平成 29 年度

博　士　論　文

Convenient green preparation of dipeptides and primary amides via carbonic carboxylic anhydrides and asymmetric synthesis of memantine analogues as a candidate of anti-Alzheimer's medicine

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List of abbreviations

The following abbreviations are used in this paper.

Aβ	amiloyd β
Ac	acetyl
Ad	adamantyl
AD	Alzheimer's disease
Ala	alanine
ALS	amyotrophic lateral sclerosis
(+)-AMMP	(+)-*cis*-4-(*N*-adamantyl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol
aq.	aqueous
Ar	aryl
Asp	aspartic acid
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad singlet (spectral)
°C	degrees Celsius
Cbz	benzyloxycarbonyl
CDI	carbonyldiimidazole
CNS	central nervous system
COMU	*N*-[1-(cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino(morpholino)]uronium hexafluorophosphate
Cys	cysteine
D	dextro
d	doublet (spectral)
DCC	dicyclohexylcarbodiimide
DIBAL-H	diisobutylaluminium hydride
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DMT-MM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DPPA	diphenylphosphoryl azide
ee	enantiomeric excess
eq	equivalent
ER	endoplasmic reticulum
ESI	electronspray ionization
Et	ethyl

Fmoc	9-fluorenylmethyloxycarbonyl
g	gram (s)
Gln	glutamine
Glu	glutamic acid
Gly	glycine
h	hour (s)
His	histidine
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
i-Bu	*iso*-butyl
IBX	2-iodoxybenzoic acid
i-Pr	*iso*-propyl
IR	infrared
J	coupling constant (in NMR)
L	levo
L	liter (s)
Leu	leucine
Lys	lysine
m	milli, multiplet (spectral)
M	moles per liter
m/z	mass to change ratio (in mass spectrometry)
MAO	monoamine oxidase
Me	methyl
Met	methonine
mol	mole (s)
Ms	methanesulfonyl
4-NBsOXY	ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl
PB	phosphate buffer (1/15 M, pH 7.0)
Ph	phenyl
Phe	phenylalanine
Phg	phenylglycine
PPL	porcine pancreas lipase
q	quartet (spectral)
rt	room temperature

s	singlet (spectral)
Ser	serine
t	triplet (spectral)
TBPB	*tert*-butyl peroxybenzoate
t-Bu	*tert*-butyl
TCT	2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thr	threonine
TLC	thin-layer chromatography
TMS	tetramethylsilane
TOF	time-of-flight
Trp	tryptophan
Trp(5-OH)	5-hydroxytryptophan
Ts	*p*-toluenesulfonyl
Tyr	tyrosine
Tyr(3-I)	3-iodoxytyrosine
Tyr(3-OH)	3-hydroxytyrosine
Val	valine
Z	zusammen
δ	chemical shift in parts per million downfield from tetramethylsilane
μ	micro

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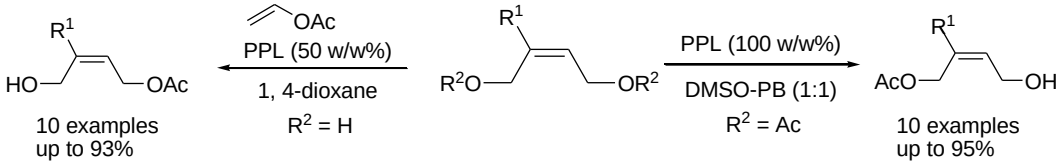
Introduction

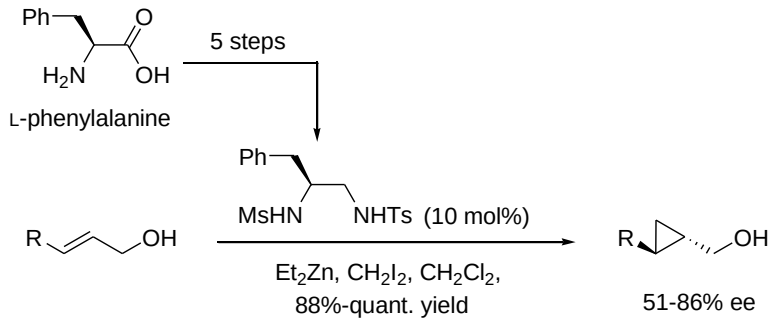
The green chemistry meaning "the environment-conscious chemistry" is an attractive topic for scientific technology because environmental pollution has become a serious global issues. Since the Nobel Prize in Chemistry was won in the areas of the catalytic enantioselective reactions that were largely seen as a green chemistry in both 2001 (Knowles,[1] Noyori,[2] Sharpless[3]) and 2005 (Chauvin,[4] Grubbs,[5] Schrock[6]), they have made remarkable progress. In particular, development of organocatalysts and their application to asymmetric syntheses are considerable efforts. The intramolecular aldol reaction catalyzed by proline as an organocatalyst was initially reported by Hajos,[7] and its intermolecular type was discovered by List.[8] Recently, effective approaches using peptide-derived organocatalyst for asymmetric reactions were also developed by many groups.[9] α-Amino acids and their derivatives are commercially available chiral catalyst and play an important role in the fields of chemical and biological reserches.[10] On the other hand, it is difficult to synthesize the catalysts prepared from α-amino acid derivatives because of the problems such as protection of functional group, racemization or epimerization, side reaction, and low solubility in organic solvent.[11] Development of catalytic synthetic method for chiral compounds has strongly been desired in terms of keeping green.

Under those background, our group is aiming at development of green organic reaction and the synthetic method of bioactive substances containing a chiral cyclopropane skeleton. As the results, the regioselective acetylation using porcine pancreas lipase (PPL) (Scheme 1),[12] and the catalytic enantioselective Simmons-Smith reaction using L-phenylalanine-derived chiral ligand (Scheme 2),[13] and preparations of dipeptides,[14d, 14e] primary amides[14c, 14a] and acetaminophen analogues[14b] via mixed carbonic carboxylic anhydrides without racemization or epimerization in the presence of water have been reported (Scheme 3). Additionally, the convenient syntheses of optically active biological substances containing a chiral cyclopropane skeleton have been also achieved via the reactions.[15]

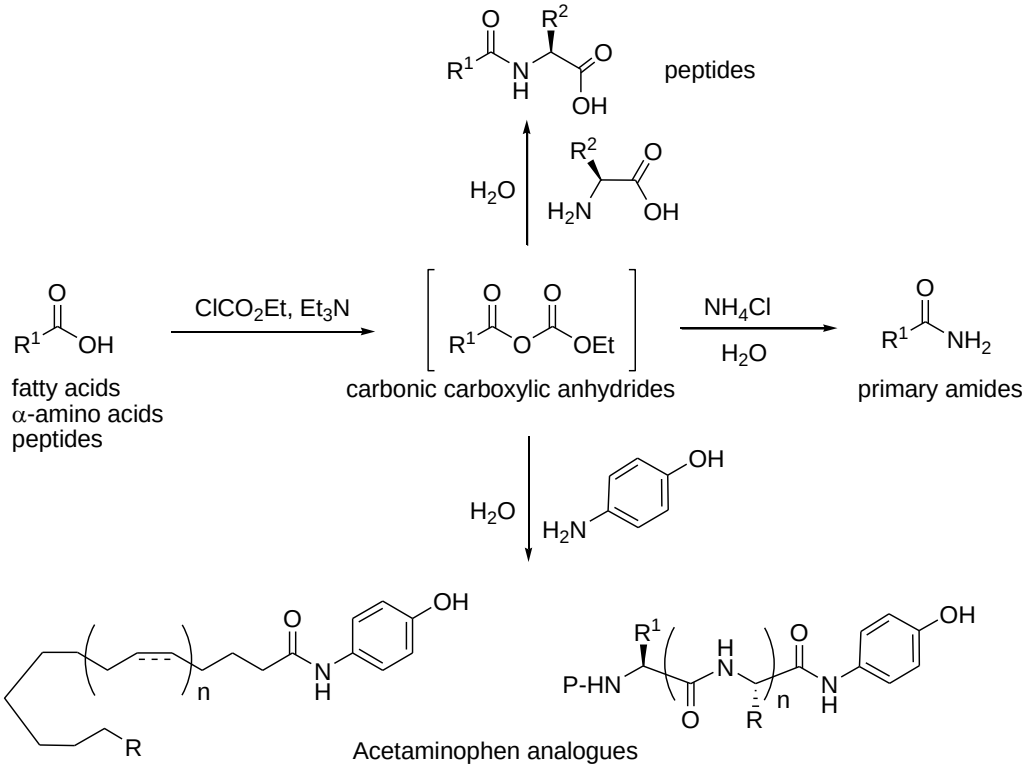
Among those reactions, the cyclopropanation and the amidation attracted my attention. Although general amidation is several limitations including expensive coupling reagents, protection of functional group and unstability of active intermediates in water, the amidation reported by my group enable to lead not only simple procedure but also utilizing hydrophilic substrate and avoiding racemization or epimerization. Then, the chiral ligands are cheaply and easily prepared from α-amino



Scheme 1. Regioselective preparation of monoacetates using PPL



Scheme 2. Catalytic enantioselective Simmons-Smith reaction of allyl alcohol in the presence of chiral lgand derived from L-phenylalanine



Scheme 3. Convenient synthesis of various amides via mixed carbonic carboxylic anhydrides

acids in five steps and are not C_2-symmetrical unlike various chiral ligands[16] used for Simmons-Smith reaction. Herein, I performed further application to synthesis of bioactive substance containing a cyclopropane skeleton using the reactions. Namely, the two contents; (I) convenient green preparation of dipeptides and primary amides via carbonic carboxylic anhydrides without racemization;[17] (II) synthesis of memantine analogues containing a sigma-1 receptor activity as a candidate of anti-Alzheimer's medicine[18] are described in this paper.

Chapter 1. Amidations of carboxylic acids via mixed carboxylic carbonic anhydrides

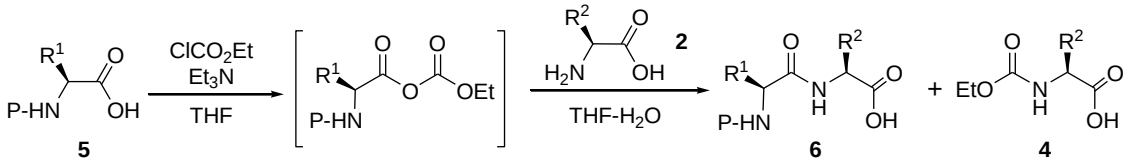
The amide group is one of the most important functional groups in organic chemistry. It is widely found in various compounds such as proteins, bioactive substances, drugs, and agrochemicals.[19] Therefore, development of convenient amidations has been a challenging subject in organic chemistry. So far, the convenient syntheses of various biological substance containing a chiral cyclopropane skeleton have been achieved in my group.[15] In the prosses on the synthesis of cyclopropane amino acids which are α-amino acid derivatives containing a cyclopropane ring, preparation of primary amides as a key intermediate was succeeded by the reaction of the mixed carbonic carboxylic anhydride of carboxylic acids with aqueous ammonia solution.

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.[20] The reagents, such as thionyl chloride,[21g] oxalyl chloride,[21d] dicyclohexylcarbodiimide (DCC),[21e, 21f] diphenylphosphoryl azide (DPPA),[21h] carbonyldiimidazole (CDI),[21i] alkyl chloroformate,[21j] 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM),[21b, 21c] and *N*-[1-(cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino(morpholino)]uronium hexafluorophosphate (COMU)[21a] have often been used for activation of carboxylic acids. In particular, the mixed carbonic carboxylic anhydrides prepared from the corresponding carboxylic acids are relatively stable and efficiently reactive with nucleophiles.[22]

Then, I focused on advantageous property of the mixed carbonic carboxylic anhydride which is chemically more reactive with amines than alcohols, stable in water at low temperature, and prepared by simple procedure. Therefore, it would be expected that the mixed carbonic carboxylic anhydrides of carboxylic acids are easily condensed with the desired hydrophilic parts by the minimal use of protecting group. Recently, we reported the convenient amidation of the mixed carbonic carboxylic anhydrides with unprotected α-amino acids under neutral or basic conditions to afford the corresponding dipeptides easily by crystallization.[14d, 14e] In addition, we have also developed an amidation using ammonium chloride or aniline derivatives as a nucleophile in the presence of water.[14a-14c] As scope of substrate tolerance, the synthesis of various amides from carboxylic acids with unprotected α-amino acids, ammonium chloride and amines in the presence of water are described in Sections 1-3 of Chapter 1.

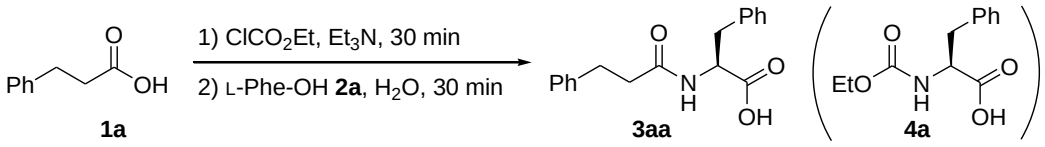
Section 1. Convenient green preparation of dipeptides using unprotected α-amino acids under neutral conditions

Peptides are one of the most important human components and induce various physiological



Scheme 4. Convenient synthetic method of dipeptides via the mixed carbonic carboxylic anhydrides

Table 1. Solvent effect on the amidation of 3-phenylpropanoic acid **1a** with L-phenylalanine **2a** in the presence of ethyl chloroformate[a]



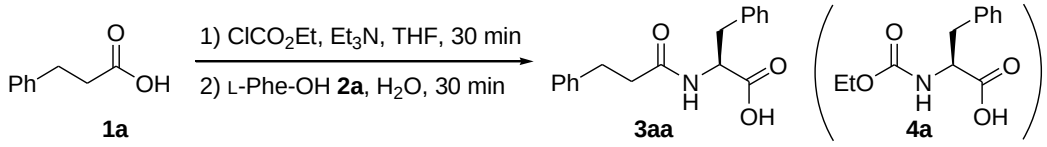
Entry	Solvent	Reaction Temp.		Yield[b]/%
		Step 1)	Step 2)	
1	ether	0 °C	rt [c]	87
2	THF	0 °C	0 °C	97
3	1,4-dioxane	rt	rt	95
4	DMSO	rt	0 °C to rt	4
5	DMF	rt	0 °C to rt	59
6	acetone	0 °C	0 °C	96
7	acetonitrile	0 °C	0 °C	93

[a] All reactions were carried out with 0.50 mmol of **1a**, 0.70 mmol of ethyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of **2a**. [b] Isolated yields. [c] The reaction time was 3 h.

activities as an element of proteins.[23] Therefore, various types of convenient peptide syntheses have been developed in chemical and biomedical research.[24] It is well known that the functional groups such as hydroxy, amino, and carboxy group on α-amino acids should be protected in order to avoid production of undesired by-products in the amidation.[11] However, the methods using protecting groups are not environmentally friendly. Herein, the condensation of carboxylic acids with unprotected α-amino acids via the corresponding mixed carbonic carboxylic anhydrides activated with ethyl chloroformate in the presence of triethylamine was described (Scheme 4).

In a preliminary investigation, the reaction of 3-phenylpropanoic acid **1a** with 1.5 equiv of L-phenylalanine **2a** in the presence of 1.4 equiv of ethyl chloroformate and 3.0 equiv of triethylamine in tetrahydrofuran (THF)-H_2O afforded the corresponding amide **3aa** in 97% yield as indicated in entry 2 of Table 1. The solvent effect of the reaction was examined as shown in Table 1. The reaction of **1a** and **2a** in ether was monitored by TLC in both steps; the second step did not proceed at 0 °C. Therefore, the second step was performed at rt to afford the corresponding amide **3aa** in 87% yield (entry 1). In the case of using dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) as the solvent, the

Table 2. Effect of the quantity of ethyl chloroformate on the amidation of 3-phenylpropanoic acid **1a** with L-phenylalanine **2a**[a]



Entry	$ClCO_2Et$	Reaction Temp.		Yield[b]/%
		Step 1)	Step 2)	
1	1.1 eq	0 °C	0 °C	96
2	1.4 eq	0 °C	0 °C	97
3	2.0 eq	0 °C	0 °C	97
4	1.4 eq	0 °C	0 °C to rt	94
5	1.4 eq	0 °C to rt	0 °C to rt	95

[a] All reactions were carried out with 0.50 mmol of **1a**, ethyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of **2a**. [b] Isolated yields.

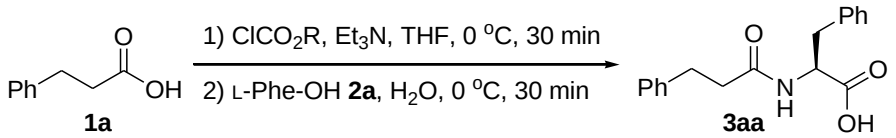
yield of **3aa** decreased to 4% and 59%, respectively (entries 4 and 5). The reactions using 1,4-dioxane, DMSO, and DMF as the solvent were carried out at rt in order to avoid freezing. Amidation of **1a** with **2a** proceeded in THF, 1,4-dioxane, acetone, and acetonitrile to give **3aa** in 93-97% yields (entries 2, 3, 6 and 7). A small amount of *N*-ethoxycarbonyl-L-phenylalanine **4a** was detected as a by-product on the basis of ^{1}H NMR analysis in all entries of Table 1. It is assumed that **4a** is mainly produced by the reaction of **2a** with the remaining ethyl chloroformate (Scheme 4).

Next, the effect of the quantity of ethyl chloroformate on the amidation was examined and the results are summarized in Table 2. Carboxylic acid **1a** was efficiently coupled with **2a** to afford **3aa** in 94-97% yields, and a small amount of the by-product **4a** was detected by ^{1}H NMR analysis in all entries of Table 2. The optimized conditions for preparing **3aa** were treatment of **1a** with 1.4 equiv of ethyl chloroformate and 3.0 equiv of triethylamine in THF at 0 °C, followed by addition of 1.5 equiv of **2a** in H_2O at 0 °C (entry 2 of Table 2).

Subsequently, I checked the effect of various activating reagents on the amidation of **1a** with **2a** and the results are shown in Table 3. The reactions of **1a** with **2a** using methyl chloroformate afforded the corresponding amide **3aa** in 82% yield (entry 1). In contrast, **2a** reacted with the mixed carbonic carboxylic anhydrides prepared from **1a** and ethyl, isopropyl or isobutyl chloroformate to give the corresponding amide **3aa** in 97%, 96%, and 94% yields, respectively (entries 2-4). I decided to use ethyl chloroformate as the activating reagent because the yield of **3aa** in the reaction with ethyl chloroformate was similar to those with isopropyl and isobutyl chloroformates, while ethyl chloroformate is cheaper than isopropyl and isobutyl chloroformates.

Then, Table 4 shows the results of the reactions of **1a** with several kinds of α-amino acids **2a**-**2j**. I selected L-Phe-OH **2a**, L-Phg-OH **2b**, L-Trp-OH **2i** and L-His-OH **2j** as aromatic α-amino acid, L-Val-

Table 3. Effect of activating reagent on the amidation of 3-phenylpropanoic acid **1a** with L-phenylalanine **2a**[a]



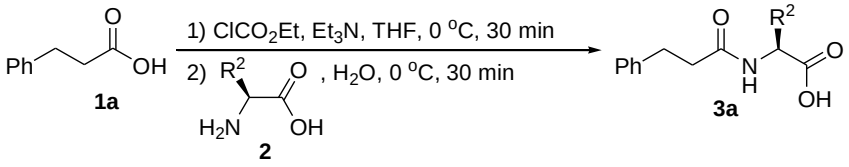
Entry	R	Yield[b]/%
1	Me	82
2	Et	97
3	*i*-Pr	96
4	*i*-Bu	94

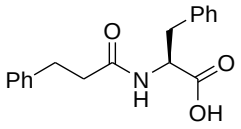
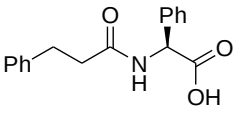
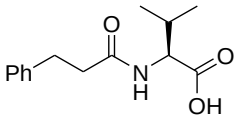
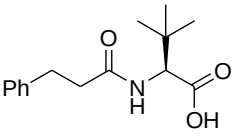
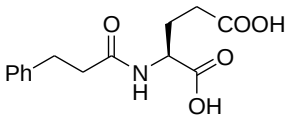
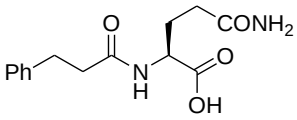
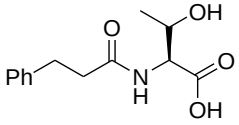
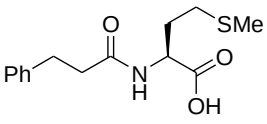
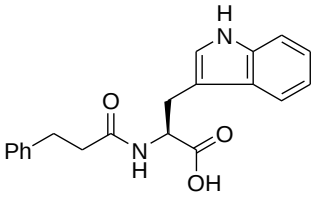
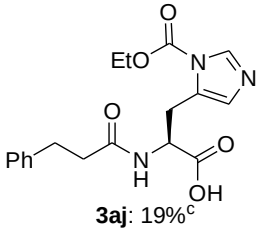
[a] All reactions were carried out with 0.50 mmol of **1a**, 0.70 mmol of alkyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of **2a**. [b] Isolated yields.

OH **2c** and L-*tert*-Leu-OH **2d** as chain-branched α-amino acid, and L-Glu-OH **2e**, L-Gln-OH **2f**, L-Thr-OH **2g** and L-Met-OH **2h** as α-amino acid containing another functional group. The amidation of **1a** with **2a** proceeded efficiently to give the corresponding amide **3aa** in excellent yield. Amide **3ab** was obtained in 89% yield by the reaction of **1a** with **2b**. Amino acids **2c** and **2d** were reacted with the activated **1a** to afford the corresponding amides **3ac** and **3ad** in excellent yields in spite of sterically hindered side-chain such as isopropyl and *tert*-butyl groups. The coupling reaction of **1a** and **2e** containing the carboxy group gave the corresponding amide **3ae** in lower yield with the recovered **1a** because of the solubility in the reaction solution. In contrast, the amidation of **1a** with **2f** containing the amide group proceeded smoothly to afford the corresponding amide **3af** in 85% yield because **2f** is highly soluble in water. Amides **3ag** and **3ah** were prepared in 85% and 87% yields from **2g** containing a hydroxyl group and **2h** containing a sulfide group, respectively. Amino acid **2i** possessing indole moiety was converted into the corresponding amide **3ai** in 86% yield. The reaction with **2j** gave *N*-ethoxycarbonylimidazolylamide **3aj** in 19% yield due to nucleophilic nitrogen atom on the imidazole moiety.

Next, the results of the condensation of *N*-protected L-phenylalanines **5a**-**5c** with several types of unprotected α-amino acids **2a** and **2c**-**2j** via the corresponding mixed carbonic carboxylic anhydrides are shown in Table 5. I examined the effect of the protecting group on the *N*-terminal of the starting α-amino acids. I selected benzyl carbamate (Cbz), *tert*-butyl carbamate (Boc), and 9-fluorenylmethyl carbamate (Fmoc) as protecting group for the starting α-amino acids **5a**, **5b**, and **5c**, respectively. The reaction of Cbz-L-Phe-OH **5a** with L-Val-OH **2c** afforded the corresponding dipeptide **6ac** in 75% yield, and Boc-L-Phe-OH **5b** was reacted with **2c** to give the corresponding dipeptide **6bc** in 82% yield. The dipeptide **6cc** was obtained by the reaction of Fmoc-L-Phe-OH **5c** with **2c** in 77% yields. Generally, Boc group is cleavaged by strong acids such as HCl, trifluoroacetic acid (TFA), or *p*-toluenesulfonic acid (TsOH), providing *t*-BuOH or isobutylene and CO_2 as the by-products. It is well known that *tert*-butylcation generated from deprotection of Boc group react readily with electron rich side-chain

Table 4. Amidation of 3-phenylpropanoic acid **1a** with α-amino acids **2** without protection of *C*-terminals[a]



Amide **3a**: Yield[b]			
 **3aa**: 97%	 **3ab**: 89%	 **3ac**: 89%	 **3ad**: Quant.
 **3ae**: 59%	 **3af**: 85%	 **3ag**: 85%	 **3ah**: 87%
 **3ai**: 86%	 **3aj**: 19%[c]		

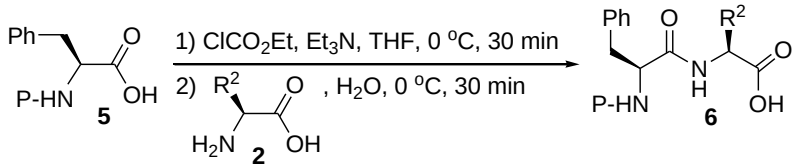
[a] All reactions were carried out with 0.50 mmol of **1a**, 0.70 mmol of ethyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of **2**. [b] Isolated yields. [c] The *N*-ethoxycarbonyl derivative was obtained.

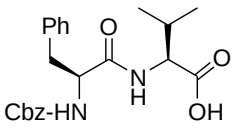
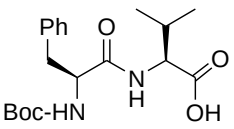
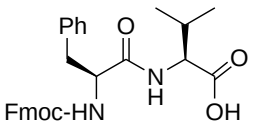
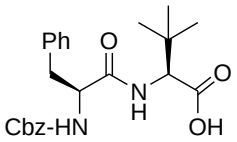
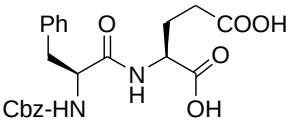
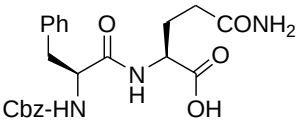
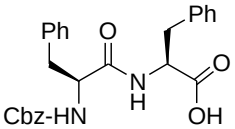
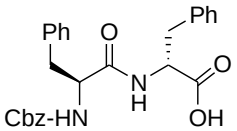
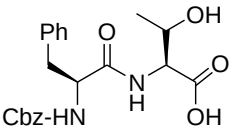
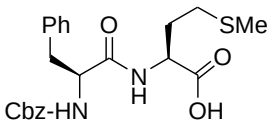
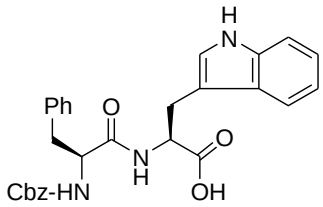
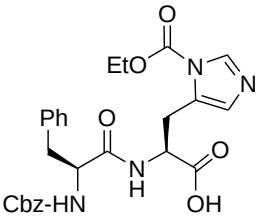
of α-amino acids (Cys, Met, Thr, Ser, and Trp).[25] I was concerned about racemization under basic conditions although Fmoc group is cleavaged by weak bases such as $NaHCO_3$, piperidine, and morpholine. On the other hand, deprotection of Cbz group is usually carried out with hydrogenation using H_2/Pd-C under mild conditions. Hence, I decided to check the variety of the reaction using Cbz group.

The yield of the dipeptide **6ad** was slightly lower due to bulky side-chain on L-*tert*-Leu **2d**. The reaction of **5a** with L-Glu-OH **2e** did not proceed well because of the solubility, while the dipeptide **6af** was synthesized from **5a** and L-Gln-OH **2f** in 87% yield. The two ^{1}H NMR spectra of the diastereomers **6aa** and **6aa'** prepared from the reactions of **5a** with the enantiomers L-Phe-OH **2a** and D-Phe-OH **2a'** in 80% and 81% yield, respectively, showed no epimerization under the optimized reaction conditions. Subsequently, I tried to run the reactions of L-Thr-OH **2g**, L-Met-OH **2h** and L-Trp-OH **2i**. Amino acid **5a** reacted with **2g** and **2i** to afford the corresponding dipeptides **6ag** and **6ai** in 81% and 78% yields, respectively. The yield of the dipeptide **6ah** synthesized from **5a** and **2h** containing sulfide group was 65%. In the case of L-His-OH **2j** containing the imidazole moiety, the reaction gave *N*-ethoxycarbonyl dipeptide **6aj** in 21% yield.

Finally, I applied this method to various *N*-Cbz α-amino acids **5d**-**5i**, and the results are shown in

Table 5. Synthesis of dipeptides **6** without protection of *C*-terminals in α-amino acids **2**[a]

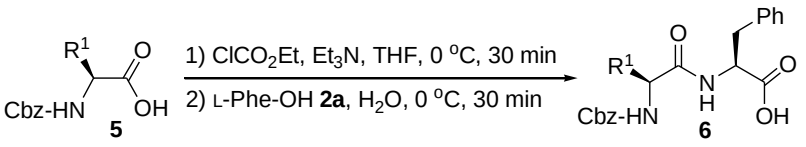


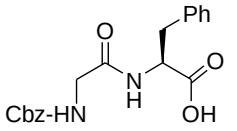
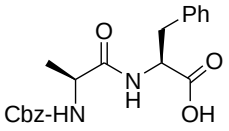
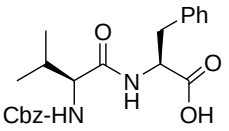
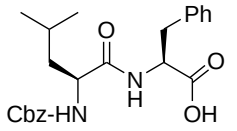
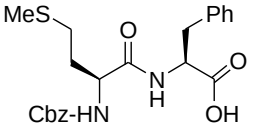
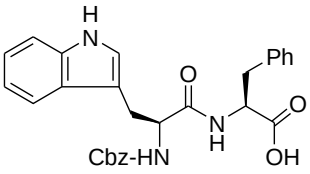
Dipeptide **6**: Yield[b]		
 **6ac**: 75%	 **6bc**: 82%	 **6cc**: 77%
 **6ad**: 68%	 **6ae**: 36%	 **6af**: 87%
 **6aa**: 80%	 **6aa'**: 81%	 **6ag**: 81%
 **6ah**: 65%	 **6ai**: 78%	 **6aj**: 21%[c]

[a] All reactions were carried out with 0.50 mmol of **5**, 0.70 mmol of ethyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of **2**. [b] Isolated yields. [c] The *N*-ethoxycarbonyl derivative was obtained.

Table 6. The reaction of Cbz-Gly-OH **5d** with L-Phe-OH **2a** proceeded to afford the corresponding dipeptide **6da** in 75% yield, and Cbz-L-Ala-OH **5e** reacted with **2a** to provide the corresponding dipeptide **6ea** in 79% yield. Cbz-L-Val-OH **5f** and Cbz-L-Leu-OH **5g** as chain-branched α-amino acids were converted to the corresponding dipeptides **6fa** and **6ga** in 71% and 76% yields, respectively. Dipeptide **6ha** was synthesized from Cbz-L-Met-OH **5h** and **2a** in 70% yield. The activated Cbz-L-Trp-OH **5i** coupled easily with **2a** to produce the dipeptide **6ia** in 85% yield because of the intramolecular π-π stacking interaction[26] between phenyl and indole moieties in **5i**.

Table 6. Application to synthesis of various dipeptides **6** with *N*-Cbz α-amino acids **5** and L-phenylalanine **2a**[a]



Dipeptide **6**: Yield[b]		
		
6da: 75%	**6ea**: 79%	**6fa**: 71%
		
6ga: 76%	**6ha**: 70%	**6ia**: 85%

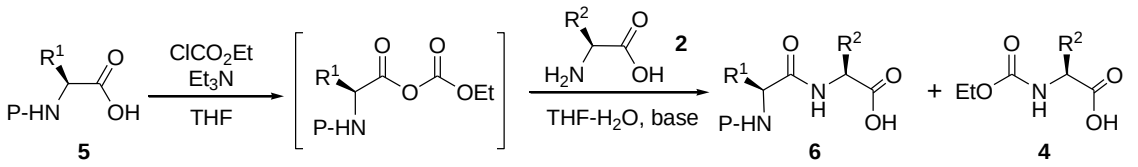
[a] All reactions were carried out with 0.50 mmol of **5**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine, and 0.75 mmol of **2a**. [b] Isolated yields.

Section 2. Ecological base-conditioned preparation of dipeptides using unprotected α-amino acids containing hydrophilic side chains

It was described that the yields of amide **3ae** and dipeptide **6ae** prepared from carboxylic acid with L-Glu-OH **2e** were decrease in low to moderate yields in Section 1. The use of L-Glu-OH as unprotected α-amino acid is not suitable in the amidation under neutral conditions because of its acidity and solubility.

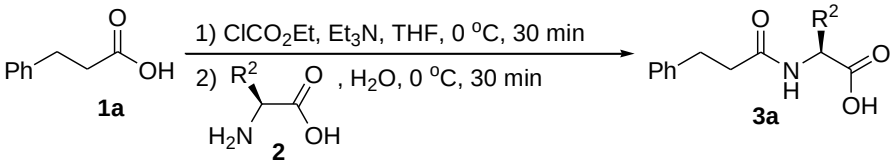
α-Amino acids containing nucleophilic side chains such as hydroxy, mercapto, and carboxy groups also react easily with electrophiles in these side chains as undesired side reactions. Therefore, it is necessary for synthesis of peptides to protect not only the *N*-terminals of α-amino acids and the *C*-terminals of the other reactants but also the nucleophilic side chains in order to avoid the undesired side reactions. In this Section, amidation of carboxylic acids with unprotected α-amino acid containing hydrophilic moiety under basic conditions was examined (Scheme 5).

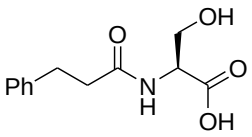
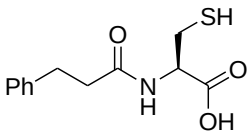
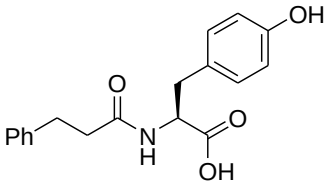
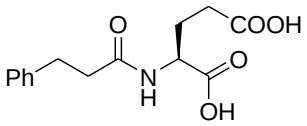
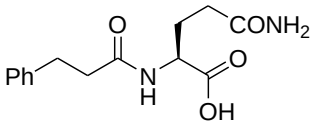
In a preliminary investigation, a clear solution of 3-phenylpropanoic acid **1a** and 1.5 equiv of unprotected α-amino acids **2e**, **2f** and **2k-2m** containing another hydrophilic moiety as a side chain in aqueous THF under neutral conditions was reacted to afford the corresponding amides **3ae**, **3af** and **3ak-3am** as indicated in Table 7. The reactions of **1a** with unprotected α-amino acids **2k** and **2l** containing hydroxy and mercapto groups gave the corresponding amides **3ak** and **3al** in 90% and 87%



Scheme 5. Convenient condensation of *N*-protected α-amino acids with unprotected α-amino acids containing hydrophilic side chains under basic conditions

Table 7. Amidation of 3-phenylpropanoic acid **1a** with unprotected α-amino acids **2**[a]



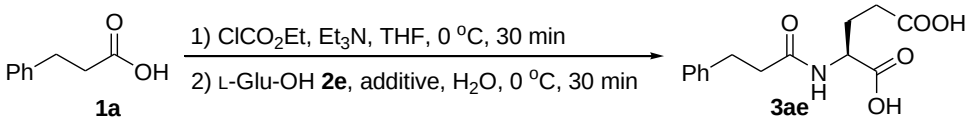
Amide **3**: Yield[b]		
 **3ak**: 90%	 **3al**: 87%	 **3am**: 19%
 **3ae**: 59%	 **3af**: 85%	

[a] All reactions were carried out with 0.50 mmol of **1a**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine, and 0.75 mmol of **2**. [b] Isolated yields.

yields, respectively. The amide **3am** was obtained by the reaction of **1a** with **2m** containing aromatic hydroxy group in 19% yield due to low solubility of **2m** in H_2O. The acid **1a** was smoothly reacted with **2f** containing amide group to give the corresponding amide **3af** in 85% yield. In contrast, the coupling reaction of **1a** with **2e** containing carboxy group gave the corresponding amide **3ae** in moderate yield. It is suggested that the amino group does not work well as a nucleophile due to protonation by the carboxy group of **2e**. Unprotected α-amino acids **2k**, **2l**, and **2f** are easily dissolved in H_2O, but the solubility of **2m** and **2e** in H_2O is low despite possession of hydrophilic side chains. A small amount of *N*-ethoxycarbonyl α-amino acids **4e**, **4f** and **4k**-**4m** were observed as a by-product on the basis of ^{1}H NMR analysis in all entries of Table 7.

Subsequently, I tried to resolve the problems in **3am** and **3ae** of Table 7. The amidation of 3-phenylpropanoic acid **1a** with L-Glu-OH **2e** was examined under acidic and basic conditions and the results are summarized in Table 8. The reaction of **1a** with **2e** in aqueous HCl gave the corresponding

Table 8. Effect of additives on the amidation of 3-phenylpropanoic acid **1a** with L-Glu-OH **2e**[a]



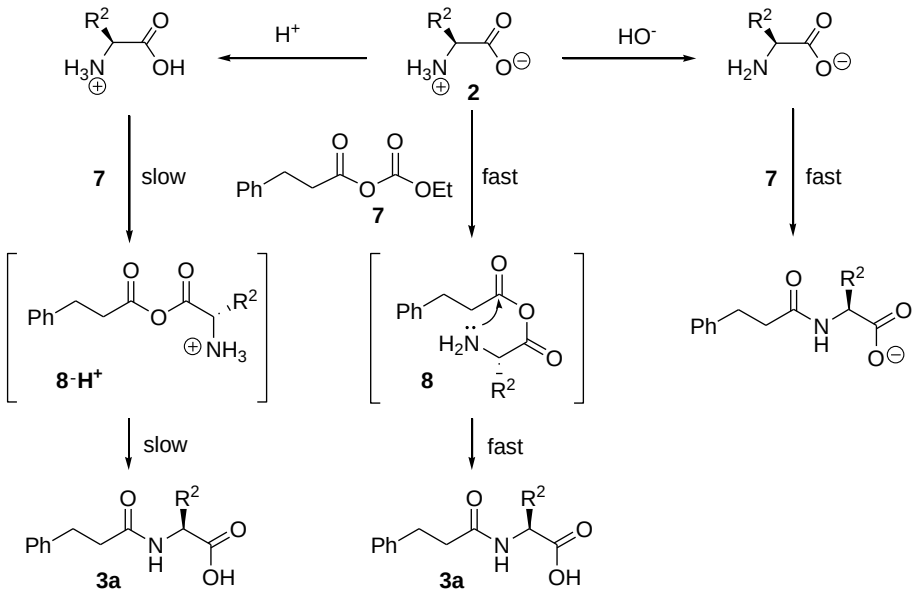
Entry	Additive	pH	Yield[b]/%
1	HCl	1.0	5
2	Free	4.5	59
3	$NaHCO_3$	6.5	90
4	NaOH	7.5	93
5	Na_2CO_3	8.0	92
6	K_2CO_3	9.0	93
7[c]	K_2CO_3	12.0	36

[a] All reactions were carried out with 0.50 mmol of **1a**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine, 0.75 mmol of **2e**, and 0.75 mmol of an additive. [b] Isolated yields. [c] The pH value of the solution of **2e** and additive in 10 ml of H_2O was measured with pH-test paper. [d] The reaction was carried out with 20 mmol of K_2CO_3.

amide **3ae** in 5% yield, which was obviously decreased (entry 1). In contrast, **1a** reacted with **2e** under the basic conditions in the presence of $NaHCO_3$ to afford **3ae** in 90% yield (entry 3). The amide **3ae** was obtained in 93% yield by the reaction using NaOH as a base (entry 4). The amidations in the presence of Na_2CO_3 and K_2CO_3, which are stronger bases than $NaHCO_3$, gave **3ae** in 92% and 93% yields, respectively (entries 5 and 6). In the presence of an excess amount of K_2CO_3, the reaction of **1a** with **2e** proceeded in 36% yield (entry 7). I judged that $NaHCO_3$ is better among these bases in the reaction by considering safety and handling.

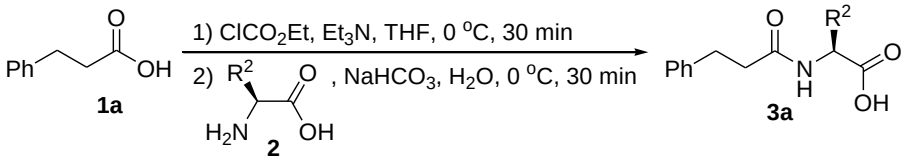
A possible pathway of the amidation via the mixed carbonic carboxylic anhydride **7** is shown in Scheme 6. The carboxylic anhydride intermediate **8** is generated under the neutral conditions from the corresponding mixed carbonic carboxylic anhydride **7** by the nucleophilic attack of α-amino acid **2**. The free amine of **8** works as a good nucleophile and the corresponding product **3a** is formed by the intramolecular reaction of **8** via the five-membered transition state (entries 3-6 in Table 8). The reaction rate is very slow under the acidic conditions due to the protonation of the nitrogen atom of **8-H**$^+$ (entry 1 in Table 8). Then, the mixed carbonic carboxylic anhydride **7** reacts directly under the basic conditions with the amine part of **2** to give the corresponding product **3a**.

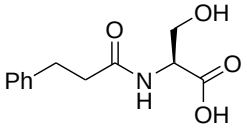
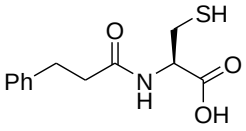
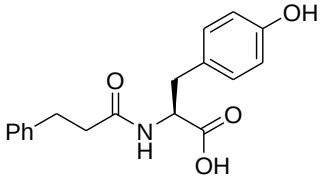
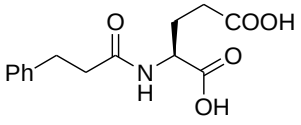
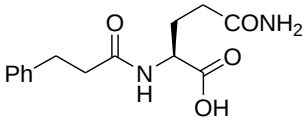
Next, I tried to synthesize the amides **3a** using 3-phenylpropanoic acid **1a** with several kinds of unprotected α-amino acids **2e**, **2f** and **2k-2m** in an aqueous $NaHCO_3$ solution as collected in Table 9. The coupling reaction of **1a** with L-Ser-OH **2k** proceeded smoothly to give the corresponding amide **3ak** in 93% yield. L-Cys-OH **2l** was converted to the corresponding amide **3al** in 96% yield. Although the amidation of **1a** with L-Tyr-OH **2m** afforded the corresponding amide **3am** in 25% yield under the basic conditions using $NaHCO_3$, **2m** reacted efficiently with **1a** to give **3am** in 86% yield under the



Scheme 6. Possible pathway of the amidation via the mixed carbonic carboxylic anhydride **7**

Table 9. Amidation of 3-phenylpropanoic acid **1a** with unprotected α-amino acids **2** under the basic conditions using $NaHCO_3$[a]

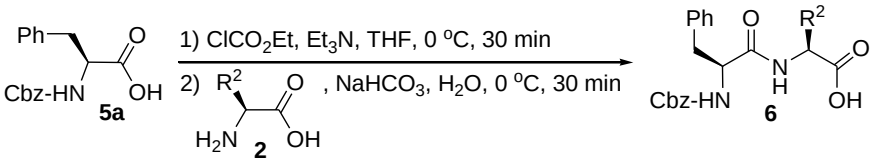


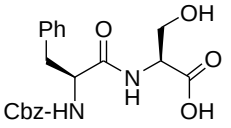
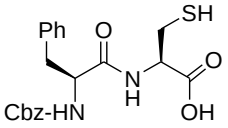
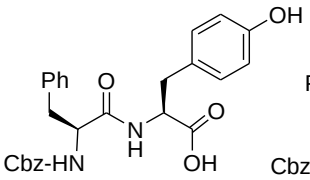
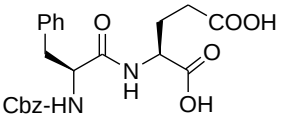
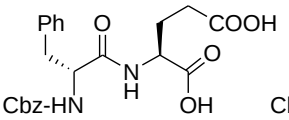
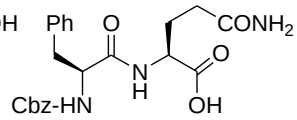
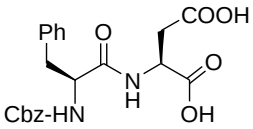
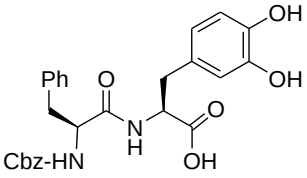
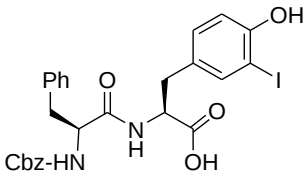
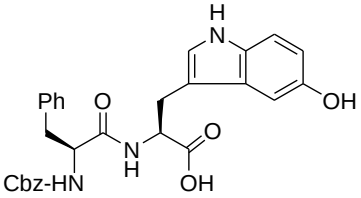
Amide **3**: Yield[b]
 **3ak**: 93%
 **3al**: 96%
 **3am**: 25% (86%)[c]
 **3ae**: 90%
 **3af**: 83%

[a] All reactions were carried out with 0.50 mmol of **1a**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine, 0.75 mmol of **2**, and 0.75 mmol of $NaHCO_3$. [b] Isolated yields. [c] NaOH was used instead of $NaHCO_3$.

basic conditions using NaOH. In the case of using $NaHCO_3$ as a base, **2m** is hardly dissolved in H_2O as well as the neutral conditions. It is suggested that the solubility of **2m** is improved by the production of sodium phenoxide in an aqueous NaOH solution, and that **2m** works as a good nucleophile in the

Table 10. Synthesis of dipeptides **6** with Cbz-L-Phe-OH **5a** and unprotected α-amino acids **2** under the basic conditions[a]



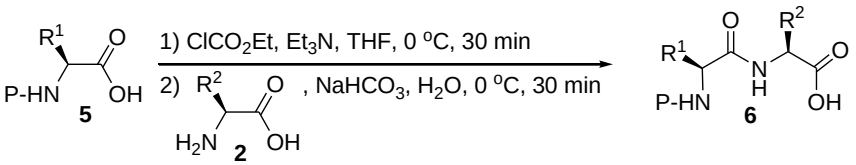
Dipeptide **6**: Yield[b]			
 **6ak**: 82%	 **6al**: 86%	 **6am**: 73%[c]	 **6ae**: 87% (81%)[d]
 **6a'e**: 85%[e]	 **6af**: 83%	 **6an**: 74%	 **6ao**: 68%[c]
 **6ap**: 74%[c, f]	 **6aq**: 76%[c, f]		

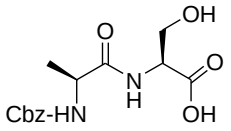
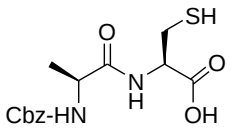
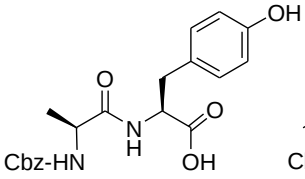
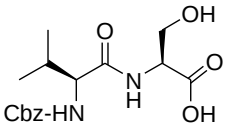
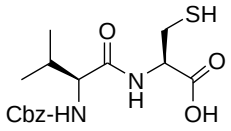
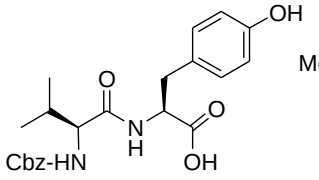
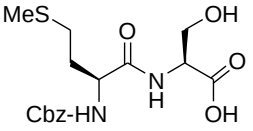
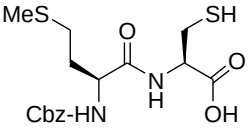
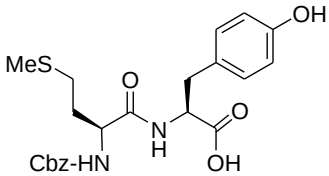
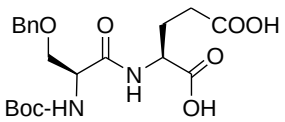
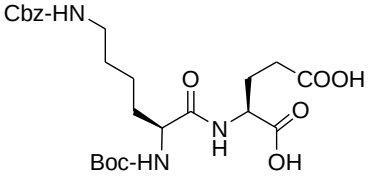
[a] All reactions were carried out with 0.50 mmol of **5a**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine, 0.75 mmol of **2**, and 0.75 mmol of $NaHCO_3$. [b] Isolated yields. [c] NaOH was used instead of $NaHCO_3$. [d] 5.0 mmol (1.5 g) of **5a** was used. [e] This reaction was carried out with Cbz-D-Phe-OH **5a'**. [f] Isobutyl chloroformate was used instead of ethyl chloroformate.

second step of the reaction. The amide **3af** was prepared from **1a** with L-Gln-OH **2f** in 83% yield, which is similar to that of the reaction under the neutral conditions.

Then, I attempted to prepare dipeptides from Cbz-L-Phe-OH **5a** and various unprotected α-amino acids **2** and these results were indicated in Table 10. L-Asp-OH **2n**, L-Tyr(3-OH)-OH **2o**, L-Tyr(3-I)-OH **2p**, and L-Trp(5-OH)-OH **2q** were added to the substrates containing aromatic alcohols as a side chain. The dipeptide **6ak** was synthesized from **5a** and L-Ser-OH **2k** containing a hydroxy group in 82% yield. The reaction of **5a** with L-Cys-OH **2l** containing a mercapto group proceeded sufficiently to give the corresponding dipeptide **6al** in 86% yield. L-Tyr-OH **2m** containing a phenolic hydroxy group reacted with the activated form of **5a** to afford **6am** in 73% yield. L-Gln-OH **2e** is most soluble in H_2O among them and was converted to produce **6af** in 83% yield. Absence of racemization under the reaction conditions was investigated using Cbz-L-Phe-OH **5a** and Cbz-D-Phe-OH **5a'** as follows. The dipeptides **6ae** and **6a'e** were synthesized as a single diastereomer by the reactions of **5a** and **5a'**

Table 11. The coupling reaction of *N*-protected α-amino acids **5** and unprotected α-amino acids **2** under the basic conditions[a]



Dipeptide **6**: Yield[b]			
 **6ek**: 79%	 **6el**: 89%	 **6em**: 71%[c]	 **6fk**: 81%
 **6fl**: 75%	 **6fm**: 71%[c]	 **6hk**: 77%	 **6hl**: 78%
 **6hm**: 66%[c]	 **6je**: 76%	 **6ke**: 84%	

[a] All reactions were carried out with 0.50 mmol of **5**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine, 0.75 mmol of **2**, and 0.75 mmol of $NaHCO_3$. [b] Isolated yields. [c] NaOH was used instead of $NaHCO_3$.

with L-Glu-OH **2e** containing a carboxy group in 87% and 85% yields, respectively. The coupling reaction of **5a** with L-Asp-OH **2n** gave the corresponding dipeptide **6an** in 74% yield, which is caused by slightly lower solubility of **2n** in H_2O than that of **2e**. Both α-amino acids **5a** and **2o** containing a 3,4-dihydroxyphenyl moiety condensed to give **6ao** in 68% yield. The formations of the dipeptides **6ap** and **6aq** by the reactions of **5a** from **2p** containing 4-hydroxy-3-iodophenyl moiety and **2q** containing 5-hydroxyindole moiety succeeded via the activation of **5a** by isobutyl chloroformate in 74% and 76% yields, respectively. The dipeptides **6ap** and **6aq** were easily separated from the *N*-isobutyloxycarbonyl by-products **4p'** and **4q'** by silica gel chromatography. In the case of using ethyl chloroformate for the activating agent, it was difficult to isolate from the mixtures of the dipeptides **6ap**, **6aq** and the *N*-ethoxycarbonyl derivatives **4p**, **4q**, respectively.

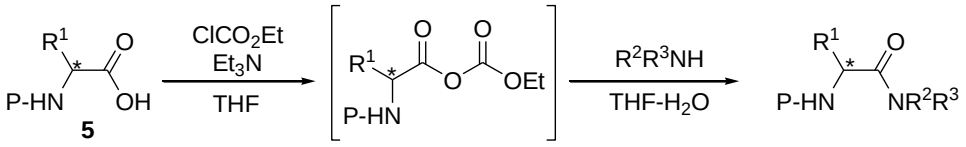
Finally, I examined application to synthesis of various dipeptides **6e**, **6f**, **6h**, **6j**, and **6k** under the reaction conditions, and the results are shown in Table 11. Cbz-L-Ala-OH **5e**, Cbz-L-Val-OH **5f** and Cbz-L-Met-OH **5h** were selected as a *N*-protected α-amino acid. The reaction of Cbz-L-Ala-OH **5e**

with L-Ser-OH **2k** was carried out to afford the corresponding dipeptide **6ek** in 79% yield. The reaction of **5e** with L-Cys-OH **2l** efficiently proceeded to give **6el** in 89% yield. The dipeptide **6em** was synthesized from **5e** and L-Tyr-OH **2m** in 71% yield, which was slightly lower than those of **6ek** and **6el**. Cbz-L-Val-OH **5f** possessing a branched side chain reacted with **2k**, **2l**, and **2m** to provide the corresponding dipeptides **6fk**, **6fl**, and **6fm** in 81%, 75%, and 71% yields, respectively. Cbz-L-Met-OH **5h** containing a mercapto group as a side chain was converted by the reactions of unprotected α-amino acids **2k**, **2l**, and **2m** to the corresponding dipeptides **6hk**, **6hl**, and **6hm** in 77%, 78%, and 66% yields, respectively. Then, I attempted to synthesize the corresponding dipeptide from *N*-protected α-amino acids containing hydrophilic side chains as the starting materials with L-Glu-OH **2e**. The dipeptide **6je** was synthesized from *N*-Boc-*O*-Bn-L-Ser-OH **5j** and **2e** under basic conditions in 76% yield. N^{α}-Boc-N^{ε}-Cbz-L-Lys-OH **5k** containing bulky side chain was effectively converted into the corresponding dipeptide **6ke** in 84% yield.

Section 3. Amidation of carboxylic acids via the mixed carbonic carboxylic anhydrides and its application to synthesis of antidepressant (1*S*,2*R*)-tranylcypromine

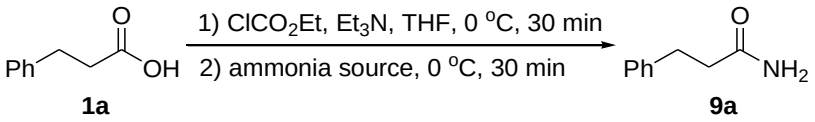
The synthesis of primary amide is limited due to disadvantages of using ammonia such as low nucleophilicity, toxicity, and gas under ordinary conditions. On the other hand, ammonium chloride is very useful as an ammonia source because it is easy to handle, inexpensive, and safe. Nezhad has reported the efficient primary amidation of carboxylic acids activated by tosyl chloride (TsCl) and 4.0 equiv of silica-supported ammonium chloride.[27] Bhanage 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.[28] Furthermore, the hydration of nitriles in the presence of acids,[29a-29c] bases,[29d, 29e] the transition metal[29f-29h] and the rearrangement of oximes using transition metal catalysts[30] have been developed as preparations for primary amides. Recently, interesting synthetic methods such as direct transformation of ethylarenes,[31] methyl ketones,[32] carbinols[32] via tandem Lieben-Haller-Bauer reaction, aminocarbonylation of aryl halides with NH_4Cl and $Co_2(CO)_8$ as a carbonyl source,[33] and amidation of ester using magnesium nitride (Mg_3N_2) as an ammonia source[34] have also been reported. Excess amounts of ammonia source, high temperatures, toxic reagents such as transition metals, and/or complicated procedures are required for synthesis of primary amides.

The synthesis of dipeptide in the presence of ethyl chloroformate and triethylamine under neutral and basic conditions were described in Sections 1 and 2 of Chapter 1. Primary amidation of the mixed carbonic carboxylic anhydrides with ammonium chloride as an ammonia source was examined in this Section. Furthermore, application to synthesis of (1*S*,2*R*)-(+)-*N*-Cbz-tranylcypromine **15** via Lossen



Scheme 7. Amidation via the mixed carbonic carboxylic anhydrides.

Table 12. Primary amidation of 3-phenylpropanoic acid **1a**[a]



Entry	Ammonia source	Yield[e]/%
1	NH_3/MeOH[b]	85
2	NH_4OH/H_2O[c]	85
3	NH_4Cl/H_2O[d]	96
4	$MeCO_2NH_4/H_2O$[d]	97

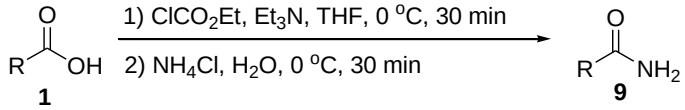
[a] All reactions were carried out with 0.50 mmol of **1a**, 0.70 mmol of ethyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of ammonia source. [b] 2.0 mol/L solution in MeOH was used. [c] 28% aqueous solution was used. [d] 1.0 M aqueous solution was used. [e] Isolated yield.

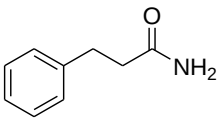
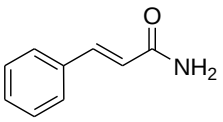
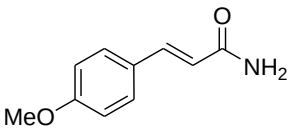
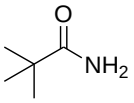
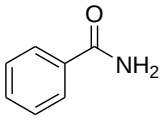
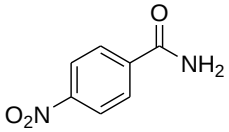
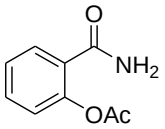
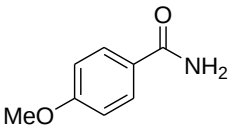
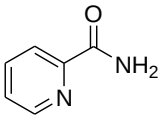
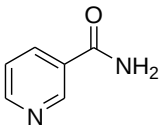
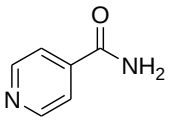
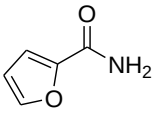
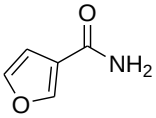
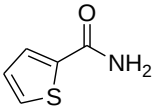
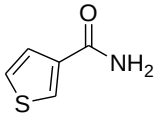
rearrangement was also presented (Scheme 7).

In a preliminary investigation, I optimized the conditions of an ammonia source (NH_3, NH_4OH, NH_4Cl, and $MeCO_2NH_4$), and the results are shown in Table 12. Primary amidation of 3-phenylpropanoic acid **1a** with NH_3/MeOH and NH_4OH/H_2O via the mixed carbonic carboxylic anhydride in THF afforded 3-phenylpropanamide **9a** in good yields (entries 1 and 2). The excellent yields were obtained by the reactions of **1a** with NH_4Cl and $MeCO_2NH_4$ (entries 3 and 4). On the basis of these results, cost, and safety, I selected NH_4Cl as the optimal ammonia source.

The results of the primary amidation of several types of carboxylic acids **1a**-**1o** with NH_4Cl in the presence of ethyl chloroformate and triethylamine are collected in Table 13. The reaction of cinnamic acid **1b** as a conjugated carboxylic acid afforded the corresponding primary amide **9b** in 79% yield. 4-Methoxycinnamic acid **1c** containing an electron donating group reacted with NH_4Cl to give the corresponding primary amide **9c** in 33% yield. The reaction of pivalic acid **1d** proceeded easily to afford the corresponding primary amide **9d** in excellent yield despite a bulky *tert*-butyl group on **1d**. Although benzamide **9e**, 4-nitrobenzamide **9f**, and acetylsalicylamide **9g** were synthesized from benzoic acid **1e**, 4-nitrobenzoic acid **1f**, and acetylsalicylic acid **1g** in 64%, 92%, and 56% yields, respectively, the yield of 4-methoxybenzamide **9h** was low. 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_4Cl via activation by isobutyl chloroformate was carried out to afford the corresponding amide **9h** in 22%

Table 13. Primary amidation of carboxylic acids **1** with ammonium chloride[a]

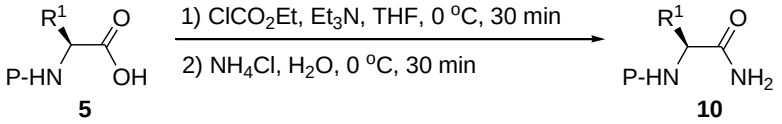


Primary amide **9**: Yield[b]			
 **9a**: 96%	 **9b**: 79%	 **9c**: 33%	 **9d**: 87%
 **9e**: 64%	 **9f**: 92%	 **9g**: 56%	 **9h**: 25% (22%)[c]
 **9i**: 97%	 **9j**: 84%	 **9k**: 95%	 **9l**: 59%
 **9m**: 45%	 **9n**: 42%	 **9o**: 45%	

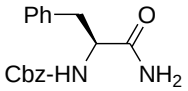
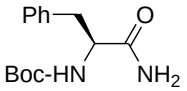
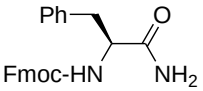
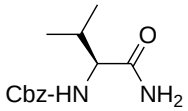
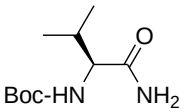
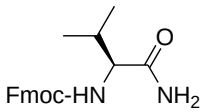
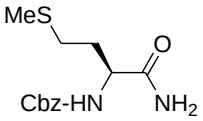
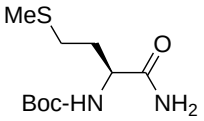
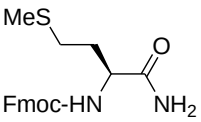
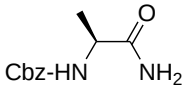
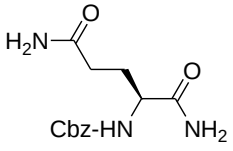
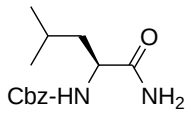
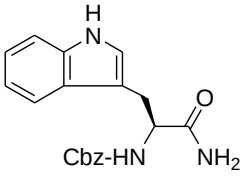
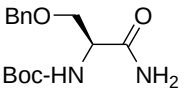
[a] All reactions were carried out with 0.50 mmol of **1**, 0.70 mmol of ethyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of a 1.0 M aqueous solution of NH_4Cl. [b] Isolated yield. [c] Isobutyl chloroformate was used instead of ethyl chloroformate.

yield. The reactions of heteroaromatic carboxylic acid **1i-1o** with NH_4Cl were also examined. Picolinic acid **1i**, nicotinic acid **1j**, and isonicotinic acid **1k** were converted into the corresponding primary amides **9i-9k** in 97%, 84%, and 95% yields, respectively. The low electron density of the pyridine ring contributes to these excellent yields. The primary amides **9l-9o** were prepared from the corresponding carboxylic acids **1l-1o** containing electron-rich heteroaromatic rings in moderate yields due to increasing electron density of the carbonyl carbons. Katritzky reported the amidation of carboxylic acid activated by 1-(methanesulfonyl)benzotriazole and triethylamine with ammonium hydroxide, in which the primary amides **9f** and **9i-9l** were obtained in quantitative yields.[20b] Moreover, syntheses of the primary amides **9a**, **9b**, **9d**, **9e**, and **9h** via the activation of carboxylic acids with DMT-MM were achieved in excellent yields by Kunishima.[21b] The yields of the primary amides **9a**, **9b**, **9d**, **9f**, and **9i-9k** by my method are similar except for the primary amides **9e**, **9h**, and **9l**. It is suggested that the electrondensity 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 primary amides **9c**, **9e**, **9g**, **9h**, and **9l-9o**.

Table 14. Synthesis of the primary amides derived from *N*-protected α-amino acids **5**[a]



5 **10**

Primary amide **10**: Yield[b], ee[c]			
 **10a**: 87%, 97% ee	 **10b**: Quant., >99% ee	 **10c**: 96%, >99% ee	 **10f**: 93%, >99% ee
 **10l**: 98%, >99% ee	 **10m**: 98%, >99% ee	 **10h**: 92%, >99% ee	 **10n**: 98%, >99% ee
 **10o**: Quant., >99% ee	 **10e**: 79%, >99% ee	 **10p**: 74%, -- ee	
 **10g**: 86%, >99% ee	 **10i**: 82%, >99% ee	 **10j**: 87%, >99% ee	

[a] All reactions were carried out with 0.50 mmol of **5**, 0.70 mmol of ethyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of a 1.0 M aqueous solution of NH_4Cl. [b] Isolated yield. [c] Determined by HPLC analysis with a mixture of hexane-isopropanol as an eluent using Chiralcel (1.0 mL/min).

Next, I synthesized the primary amides **10** from the corresponding *N*-protected α-amino acids **5** without racemization under the optimized conditions and these results are shown in Table 14. Firstly, I checked the effect of protecting groups such as Cbz, Boc, and Fmoc. The mixed carbonic carboxylic anhydrides of Cbz-L-Phe-OH **5a**, Boc-L-Phe-OH **5b**, and Fmoc-L-Phe-OH **5c** reacted with NH_4Cl to give the corresponding primary amides **10a**, **10b**, and **10c** in excellent yields, and no racemization was observed. The primary amide **10f** was prepared from Cbz-L-Val-OH **5f** in 93%. The reactions of Boc-L-Val-OH **5l** and Fmoc-L-Val-OH **5m** afforded the corresponding primary amides **10l** and **10m** in 98% and 98% yields with >99% ee under the conditions, respectively. Furthermore, the primary amides **10h**, **10n**, and **10o** were obtained in excellent yields by the reactions of Cbz-L-Met-OH **5h**, Boc-L-Met-OH **5n**, and Fmoc-L-Met-OH **5o** containing a sulfide group. Cbz-L-Ala-OH **5e** was converted to the corresponding primary amide **10e** in good yield with >99%. The amidation of Cbz-L-Gln-OH **5p** with NH_4Cl under the conditions gave the corresponding primary amide **10p** in 74% yield, but the enantiomeric excess of **10p** was not determined by HPLC analysis because of low solubility of **10p** in

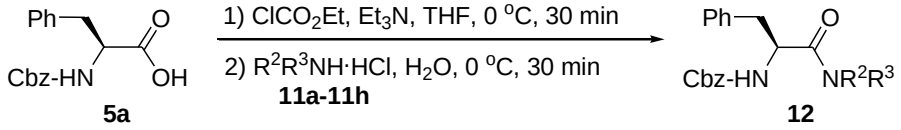
the eluent. The low solubility of **5p** possessing the hydrophilic side chain in THF gave a lower yield of **10p** compared to the other primary amides. Cbz-L-Leu-NH_2 **10g** as a branched α-amino acid was synthesized from Cbz-L-Leu-OH **5g** in good yield with >99% ee. The yield of the primary amide **10i** was slightly lower due to the bulky side chain. Boc-*O*-Bn-L-Ser-OH **5j** containing a hydrophilic side chain was condensed with NH_4Cl via the mixed carbonic carboxylic anhydride to afford the corresponding primary amide **10j** in 87% yield, and no racemization was observed in the reaction. The results of primary amidation of D-α-amino acids **5a'-5c'**, **5e'-5j'**, and **5l'-5p'** and with NH_4Cl 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 preparations of hydroxamic acids, there are a variety of reported reactions of carboxylic acids with toxic hydroxylamine using alkyl chloroformate,[35] with hydroxylamine hydrochloride in the presence of the expensive coupling reagents such as 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride, TCT)[36] and ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY),[37] and so on.[38] 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[39] and the mechanism of MAO for inhibition has also been elucidated Silverman.[40] We have recently reported synthesis of tranylcypromine via catalytic enantioselective cyclopropanation in the presence of chiral ligand derived from L-phenylalanine in five steps.[15a] The synthetic method has several disadvantages such the use of toxic, expensive, excessive reagents, and harsh conditions.

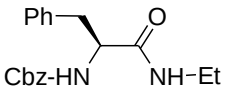
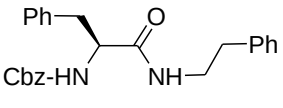
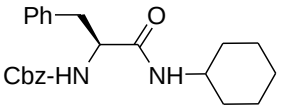
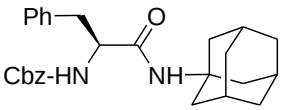
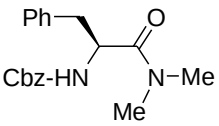
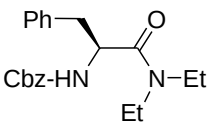
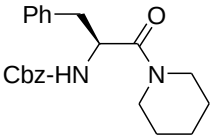
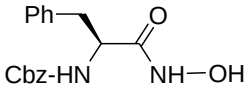
Therefore, I applied the amidation using mixed carbonic carboxylic anhydride to the synthesis of (1*S*,2*R*)-*N*-Cbz-tranylcypromine **15**. I examined the amidation of Cbz-L-Phe-OH **5a** with various amine hydrochlorides **11a-11h** for the preparation of *N*-hydroxy-2,3-methano-3-phenylpropanamide **8** and the results are indicated in Table 15. Ethylamine hydrochloride **11a** and 2-phenethylamine hydrochloride **11b** reacted with **5a** to afford the corresponding secondary amide **12aa** and **12ab** in good yields. The secondary amide **12ac** was synthesized from **5a** using cyclohexylamine hydrochloride **11c** in 84% yield. The amidation of **5a** with 1-adamantanamine hydrochloride **11d** effectively proceeded to afford the corresponding secondary amide **12ad** in 87% yield despite sterically hindered primary amine. Dimethylamine hydrochloride **11e**, diethylamine hydrochloride **11f**, and piperidine hydrochloride **11g** as a secondary amine were also examined. The amine hydrochlorides **11e**, **11f**, and **11g** worked as a good nucleophile under the conditions to give the corresponding tertiary amides **12ae**, **12af**, and **12ag** in 85%, 72%, and 84% yields, respectively. The hydroxamic acid **12ah** was synthesized by the reaction of **5a** with hydroxylamine hydrochloride **11h** in moderate yield.

Finally, I optimized the reaction conditions for the amidation of (2*S*,3*S*)-(+)-2,3-methano-3-phenylpropanoic acid **13** prepared via two oxidations from (2*S*,3*S*)-(+)-2,3-methano-3-phenylpropanol[15a] with hydroxylamine hydrochloride **11h** and for Lossen rearrangement of (2*S*,3*S*)-

Table 15. Amidation of Cbz-L-Phe-OH **5a** with primary or secondary amine hydrochlorides **11a-11h**[a]

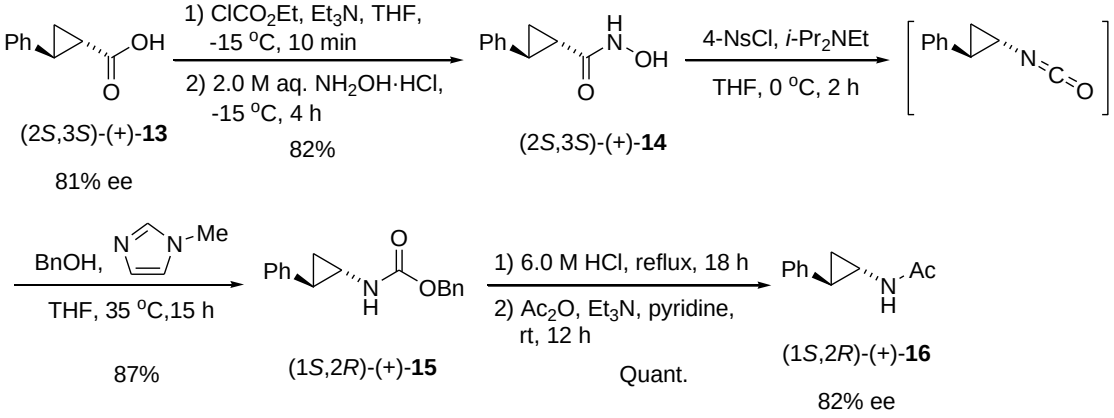


5a **11a-11h** **12**

Amide **12**: Yield[b]		
 **12aa**: 87%	 **12ab**: 84%	 **12ac**: 84%
 **12ad**: 87%	 **12ae**: 85%	 **12af**: 72%
 **12ag**: 84%	 **12ah**: 64%	

[a] All reactions were carried out with 0.50 mmol of **5a**, 0.70 mmol of ethyl chloroformate, 1.5 mmol of triethylamine, and 0.75 mmol of a 1.0 M aqueous solution of amine hydrochlorides **11**. [b] Isolated yield.

(+)-2,3-methano-3-phenylpropyl hydroxamic acid **14**. The reactions of carboxylic acids to amines, which are well known as Hofmann,[41] Curtius,[42] Schmidt,[43] and Lossen[44] rearrangements, have been widely used for syntheses of various organic compounds. The main disadvantages of Hofmann rearrangement are the use of 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 Lossen rearrangement are milder than those of the other rearrangements. As a result, (2*S*,3*S*)-(+)-**14** was obtained in 82% yield by the amidation of (2*S*,3*S*)-(+)-**13** with **11h** under the optimized conditions, followed by Lossen rearrangement of (2*S*,3*S*)-(+)-**14** under Miller's conditions[44a] to afford (1*S*,2*R*)-(+)-*N*-Cbz-tranylcypromine **15** in 87% yield (Scheme 8). I also tried to prepare (1*S*,2*R*)-(+)-**15** under the following conditions, but failed. Methanesulfonyl chloride (MsCl), TsCl, and CDI were used instead of 4-nitrobenzenesulfonyl chloride (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 (1*S*,2*R*)-(+)-**15** was not determined by HPLC analysis using general Chiralcels. Therefore, (1*S*,2*R*)-(+)-**15** was deprotected under acidic conditions, followed by acetylation to afford (1*S*,2*R*)-(+)-*N*-acetyltranylcypromine **16** in quantitative yield with 82% ee, which was determined by HPLC analysis using Chiralcel OD as indicated in Scheme 8.

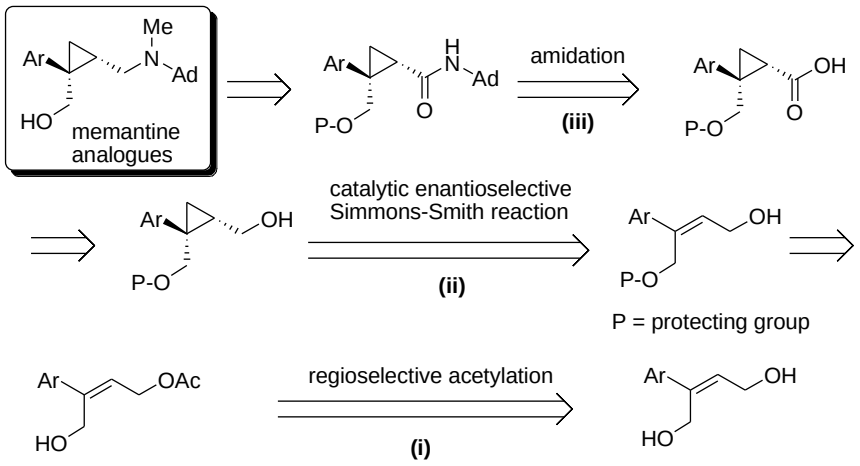


Scheme 8. Preparation of (1*S*,2*R*)-(+)-*N*-Cbz-tranylcypromine **15** via Lossen rearrangement

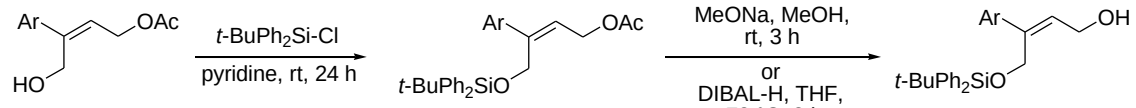
Chapter 2. Synthesis of memantine analogues containing a sigma-1 receptor activity as a candidate of anti-Alzheimer's medicine

Sigma receptor has recently attracted attention as a new action site of therapeutic medicine for several diseases such as amnesia, pain, stroke, retinal neuroprotection, HIV infection, cancer, amyotrophic lateral sclerosis (ALS), depression, and Alzheimer's disease.[45] Sigma-1 and sigma-2 receptors, as the two established subtypes, are both highly expressed in the central nervous system (CNS) and can be distinguished by their distinct pharmacological profiles and molecular characteristics.[46] It was reported that sigma-1 receptor regulates protein folding/degradation, endoplasmic reticulum (ER)/oxidative stress, and cell survival through the molecular chaperone activity.[47] Therefore, the sigma-1 receptor is significantly influential in homeostasis of tissue, which is incapable of repairing, and it is anticipated that the agonists activated by sigma-1 receptor become the therapeutic agents of diseases caused by cell damage. For instance, it has been elucidated that patients with ALS carry mutations in sigma-1 receptor gene and dysfunction of sigma-1 receptor protein.[48] It has been suggested that 1-[2-(3,4-dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazine (SA4503)[49] promotes regeneration and maturation of nerves as a selective sigma-1 receptor agonist.[50] Currently, Phase II trials for SA4503 have been carried out in Europe as a medicine against CNS disorders, which are caused by major depression and stroke.[51] The sigma agonists protect cultured neurons against amyloid β ($A\beta)_{25\text{-}35}$-induced toxicity,[52] and prevent memory deficits when $A\beta_{25\text{-}35}$ is injected intracerebroventricularly in mice.[53] Therefore, the induction or activation of sigma-1 receptor could improve clinical symptoms of Alzheimer's disease and protect against the associated neuropathologic changes. Indeed, tetrahydro-*N,N*-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73), which exhibits neuroprotective effects and prevents tau hyperphosphorylation, has been examined in Phase IIa for Alzheimer's disease trials as a sigma-1 receptor agonist since January, 2015.[54] As a part of interim studies for the planned analysis, it was announced that a positive dose-response relationship has been observed in its ongoing Phase IIa clinical trials of ANAVEX 2-73 as a potential treatment for mild-to-moderate Alzheimer's disease by November, 2015. For these reasons, sigma-1 receptor agonists have become key targets for therapeutic approaches to treat these diseases and elicited significant interest in medicinal chemistry.

Recently, (+)-(2*R,*3*S*)-4-(*N*-adamant-1-yl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol [(+)-AMMP] was reported as a high affinity probe for sigma receptors by Marrazzo.[55] However, the synthetic route of (+)-AMMP afforded 9% overall yield from 2-oxo-1-phenyl-3-oxabicyclo[3.1.0]hexane as the starting material and the reagents used for synthesis of (+)-AMMP were relatively expensive. Additionally, it was necessary to prepare various chiral lactones as the starting materials in order to synthesize the substituted aryl analogues of (+)-AMMP. Therefore, it was desirable to develop more efficient and inexpensive synthetic method for synthesis of (+)-AMMP analogues. We have just achieved convenient asymmetric synthesis of (+)-AMMP from (*Z*)-2-



Scheme 9. Retrosynthetic analysis of memantine analogues containing a chiral cyclopropane skeleton via the three key reactions.



17b (Ar = 4-$MeOC_6H_4$)
17c (Ar = 4-MeC_6H_4)
17d (Ar = 4-ClC_6H_4)
17e (Ar = 4-BrC_6H_4)

18b: Quant.
18c: Quant.
18d: Quant.
18e: 92%

19b: 90%
19c: 95%
19d: Quant.
19e: 95 %

Scheme 10. Preparation of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-arylbut-2-en-1-ols **19b-19e**.

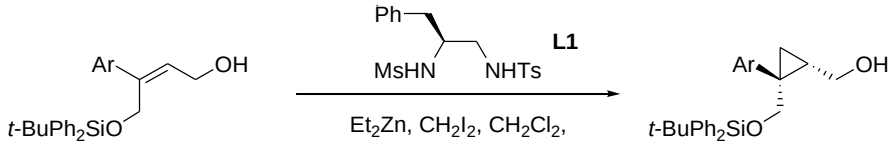
phenylbut-2-ene-1,4-diol **34a** via the following reactions[56] such as (i) the regioselective acetylation using PPL,[12] (ii) the catalytic enantioselective Simmons-Smith reaction in the presence of our developed chiral ligand which was prepared cheaply and easily from L-phenylalanine in five steps,[13] and (iii) the convenient amidation of mixed carbonic carboxylic anhydrides in aqueous organic solvent.[14] Particularly, the cyclopropane moiety with two stereogenic carbon centers was constructed in quantitative yield with 71% ee via catalytic enantioselective Simmons-Smith reaction and the sterically hindered 1-adamantanamine moiety was successfully introduced by our developed amidation.

In this Chapter, I report a convenient enantioselective synthesis of (+)-AMMP and memantine analogues containing a chiral cyclopropane skeleton, 4-substituted aryl group, and 1-adamantanamine or memantine (3,5-dimethyl-1-adamantanamine) moiety via our developed reactions as shown in Scheme 9.

As optimized our previous report,[56] *tert*-butyldiphenylsilyl group was chosen for preparation of various 4-*O*-protected (*Z*)-3-arylbut-2-en-1-ols **19b-19e**. The allyl alcohols **19b-19e** were converted from (*Z*)-3-arylbut-2-en-1-yl acetates **17b-17e** in 87%-quantitative yields in 2 steps, which were prepared by our developed regioselective acetylation (Scheme 10).

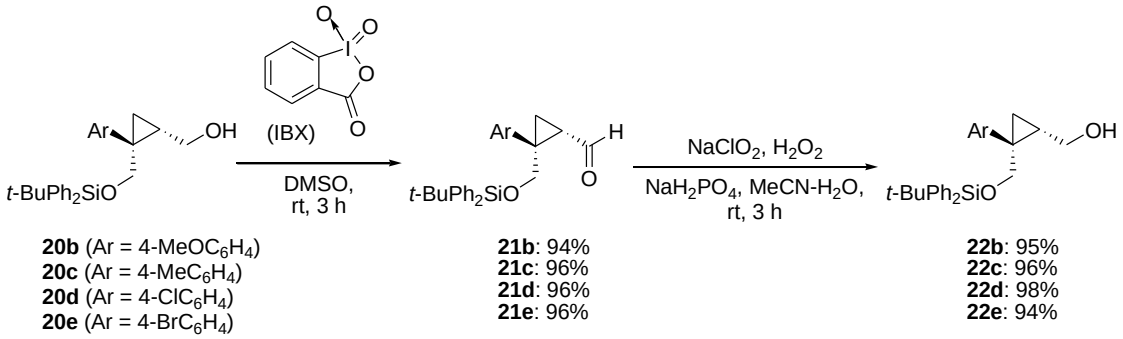
Next, I attempted cyclopropanation of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-arylbut-2-en-1-ols **19b-**

Table 16. Simmons-Smith reaction of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-arylbut-2-en-1-ols **19b-19e**[a]



Entry	Product	Ar	Yield/%	ee[b]/%
1	**20b**	4-$MeOC_6H_4$	70	36
2	**20c**	4-MeC_6H_4	Quant.	65
3	**20d**	4-ClC_6H_4	97	66[c]
4	**20e**	4-BrC_6H_4	97	73[d]

[a] All reactions were carried out with (*Z*)-4-*tert*-butyldiphenylsiloxy-3-arylbut-2-en-1-ols **19b-19e**, 2.0 equiv of Et_2Zn, and 3.0 equiv of CH_2I_2 in anhydrous CH_2Cl_2. [b] Determined by HPLC analysis with a 95:5 mixture of hexane and 2-propanol as an eluent using Chiralcel OD (1.0 mL/min). [c] Determined by HPLC analysis with hexane containing 0.1% 2-propanol as an eluent using Chiralcel OD-H after acetylation (1.0 mL/min). [d] Determined by HPLC analysis with a 99:1 mixture of hexane and 2-propanol as an eluent using Chiralcel OD (1.0 mL/min).

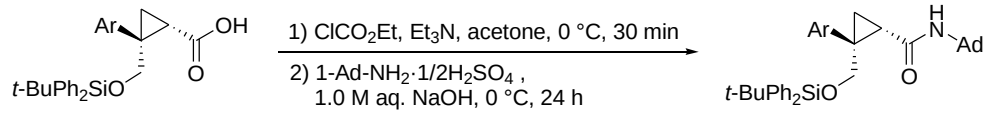


Scheme 11. Preparation of the 2,3-methano-3-arylbutanoic acids **22b-22e**.

19e as shown in Table 16. The reactions of allyl alcohols **19b-19e** with various oriented substituents on the aromatic ring worked smoothly. Methyl- and halo-substituted cinnamyl alcohols **19c-19e** gave the correspondoing cyclopropane products **20c-20e** in excellent yields with satisfactory enantioselectivities (entries 2-4). However, the reaction of methoxy-substituted cinnamyl alcohol **19b** proceeded in 70% yield with low enantioselectivity (36% ee). It was suggested that the oxygen atom of the methoxy group acts as a Lewis base to the catalyst (entry 1 of Table 16).

Subsequently, the 2,3-methano-3-arylbutan-1-ols **20b-20e** were oxidized with 2-iodoxybenzoic acid (IBX) in DMSO at rt for 3 h to afford the corresponding 2,3-methano-3-arylbutan-1-als **21b-21e** in 94-96% yields, which were converted with $NaClO_2$, H_2O_2, and NaH_2PO_4 in MeCN-H_2O at rt for 3 h to the corresponding 2,3-methano-3-arylbutanoic acids **22b-22e** in 95-98% yields as indicated in Scheme 11.

Next, the amidation of the 2,3-methano-3-arylbutanoic acids **22b-22e** with 1-adamantanamine

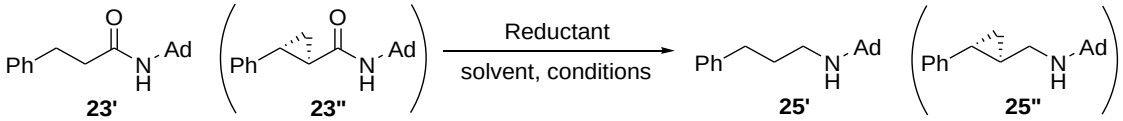


22b (Ar = 4-$MeOC_6H_4$)
22c (Ar = 4-MeC_6H_4)
22d (Ar = 4-ClC_6H_4)
22e (Ar = 4-BrC_6H_4)

23b: 84%
23c: 97%
23d: 73%
23e: 78%

Scheme 12. Preparation of the 2,3-methano-3-arylbutanamides **23b-23e**.

Table 17. Optimaization of the reaction conditions for reduction of *N*-adamant-1-yl-2,3-methano-3-phenylbutanamide (**23'**)[a]



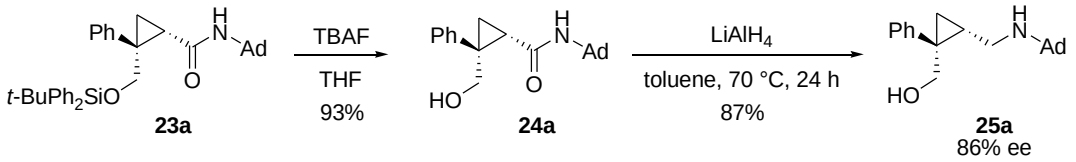
23' **23"** **25'** **25"**

Entry	Reductant	Equiv	solvent	conditions	Yield[b]/%
1	$BH_3{\cdot}SMe_2$	2.0	THF	40 °C, 49 h	6
2	$BH_3{\cdot}SMe_2$	2.0	THF	50 °C to reflux, 70 h	31
3	$BH_3{\cdot}SMe_2$	5.0	THF	rt to 40 °C, 71 h	58
4	$BH_3{\cdot}SMe_2$	5.0	toluene	rt to 70 °C, 23 h	69
5[c]	$NaBH_4$, I_2	2.5, 1.0	THF	40 °C, 72 h	20
6	$LiAlH_4$	5.0	THF	rt to reflux, 65 h	48
7	$LiAlH_4$	2.5	toluene	rt to 70 °C, 46 h	54
8	$LiAlH_4$	5.0	toluene	40 to 70 °C, 19 h	88
9[d]	$LiAlH_4$	5.0	toluene	70 °C, 13 h	92

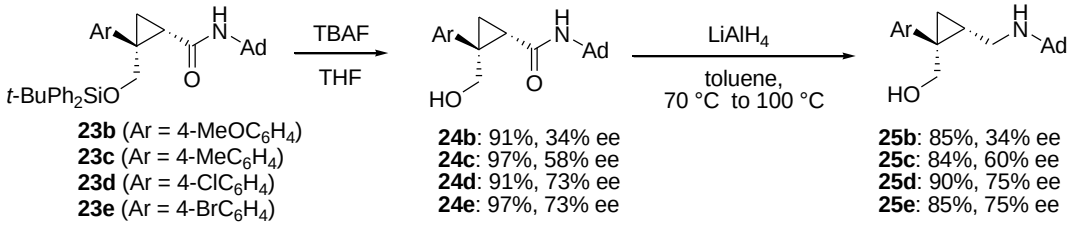
[a] All reactions were carried out with 0.18 mmol of **23'**. [b] Isolated yield. [c] The reaction was carried out with 0.18 mmol of **23'**, 2.5 equiv of $NaBH_4$, and 1.0 equiv of I_2 in anhydrous THF. [d] **23"** was used as the starting material instead of **23'**.

sulfate was performed in the optimized conditions[56] to afford the corresponding 2,3-methano-3-arylbutanamides **23b-23e** in 73-97% yields as indicated in Scheme 12.

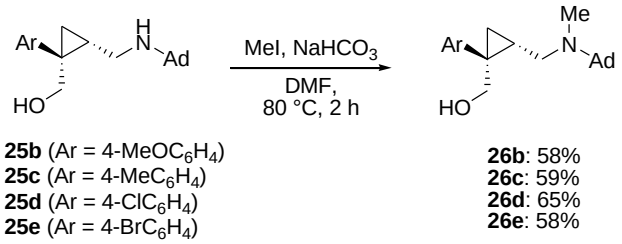
Furthermore, the conditions for the reduction of *N*-adamant-1-yl-2,3-methano-3-phenylbutanamide **23'** were optimized and the results are shown in Table 17. The reaction of **23'** with 2.0 equiv of $BH_3{\cdot}SMe_2$ in anhydrous THF at 40 °C for 49 h afforded *N*-adamant-1-yl-3-phenylpropylamine **25'** in 6% yield (entry 1). The use of 5.0 equiv of $BH_3{\cdot}SMe_2$ in anhydrous THF at rt to 40 °C for 71 h gave the desired amine **25'** in 58% yield (entry 3), and **25'** was obtained in 69% yield when the reaction was carried at rt to 70 °C for 23 h in anhydrous toluene (entry 4). The yield obtained when Meyer's method was used was 20% (entry 5).[57] The yield (88%) greatly improved under the conditions using 5.0 equiv of $LiAlH_4$ in toluene at 40 to 70 °C for 19 h (entry 8). The reduction of the chiral amide **23"** containing a cyclopropane ring with 5.0 equiv of $LiAlH_4$ proceeded smoothly at 70 °C for 13 h to afford the corresponding chiral amine **25"** in 92% yield without cleavage



Scheme 13. Optimal preparation pathway to the chiral 2,3-methano-2-pheylbutan-1-ol **25a**.



Scheme 14. Preparation of the chiral 2,3-methano-2-arylbutan-1-ols **25b-25e** in two steps from the chiral 2,3-methano-3-arylbutanamides **23b-23e**.



Scheme 15. Synthesis of (+)-AMMP analogues by methylation from the chiral 2,3-methano-2-arylbutan-1-ols **25b**-**25e**.

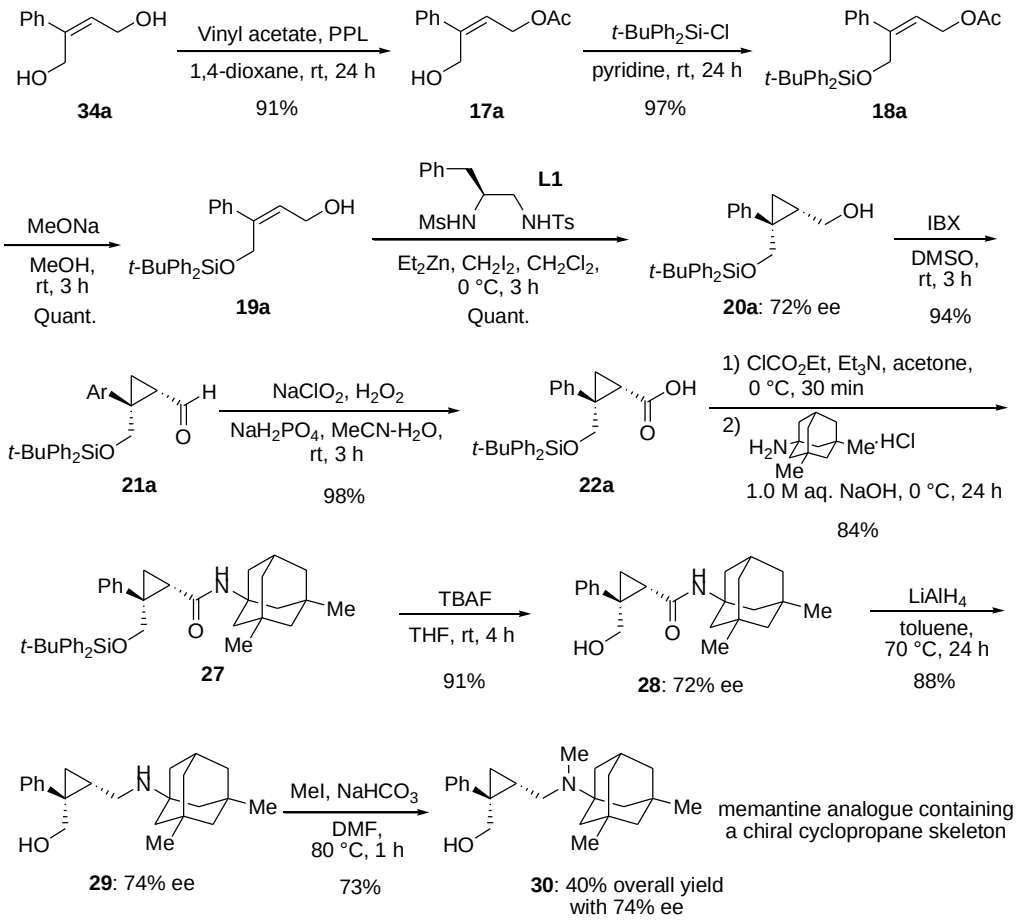
of the cyclopropane skeleton (entry 9 of Table 17).

Subsequently, the silyl group of **23a** was cleaved by tetrabutylammonium fluoride (TBAF) to give the corresponding chiral 4-hydroxyamide **24a** in 93% yield, followed by reduction with $LiAlH_4$ to afford **25a** in 87% yield with 86% ee. The overall yield in 2 steps was 81%, which is better than the yield of **25a** in our previous report (Scheme 13).[56]

The chiral 2,3-methano-2-arylbutan-1-ols **25b-25e** were prepared efficiently from the corresponding chiral amides **23b-23e** in excellent yields in two steps as described in Scheme 14. I was able to convert (+)-*cis*-4-*tert*-butyldiphenylsiloxy-2,3-methano-3-arylbutan-1-ols **20b-20e** into the corresponding chiral alcohols **25b-25e** in five steps without the significant loss of enantiomeric excess in all cases.

Additionally, (+)-AMMP analogues **26b-26e** were acquired in 58-65% yields via methylation of the amino alcohols **25b-25e** with MeI as indicated in Scheme 15.

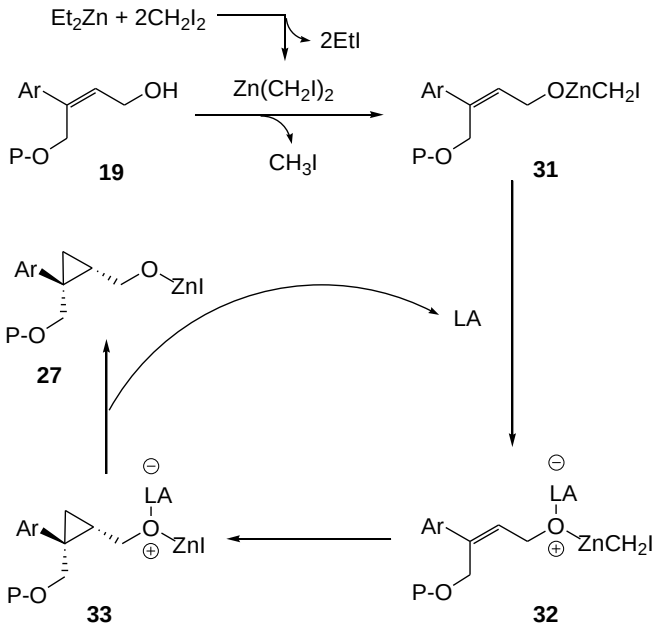
Finally, I succeeded in synthesizing memantine (3,5-dimethyl-1-adamantanamine) analogue **30** containing a chiral cyclopropane skeleton as shown in Scheme 16. The amidation of 2,3-methano-3-phenylbutanoic acid **22a** prepared from (*Z*)-2-phenylbut-2-ene-1,4-diol **34a** in six steps[56, 58] with



Scheme 16. Synthesis of memantine analogue containing a chiral cyclopropane skeleton from the **34a**.

memantine hydrochloride worked easily to give the corresponding amide in 84% yield, followed by desilylation, reduction, and methylation to afford the memantine derivative **30** in 40% overall yield with 74% ee.

We have recently reported the detail of the cyclopropanation of various allylic alcohols using L-tyrosine-derived fluorous disulfonamide as a chiral ligand and described the proposed reaction pathway (Scheme 17) and a possible transition state (Fig. 1) of the cyclopropanation.[59, 60] The iodomethylzinc alkoxide **31** is produced by the addition of $Zn(CH_2I)_2$ to the allylic alcohol **19**, and complex **32** is formed from the species **31** and Lewis acid. The cyclopropane derivative **20** is generated from the disulfonamide **L1**-zinc complex (Lewis acid) via complexes **32** and **33**. I propose a possible transition state for the enantioselective cyclopropanation with L-phenylalanine-derived disulfonamide **L1** as shown in Figure 1. I speculated that the zinc derived from the carbenoid to the double bond of allylic alcohol **19** is accelerated by the oxygen atom of the methanesulfonamide group. Allylic alcohol **19** would take the opposite side of the benzene ring derived from L-phenylalanine in order to avoid the steric hindrance, then the carbenoid approaches the allylic alcohol **19** from the opposite side of the *p*-toluenesulfonamide group.



Scheme 17. Proposed reaction pathway of the cyclopropanation

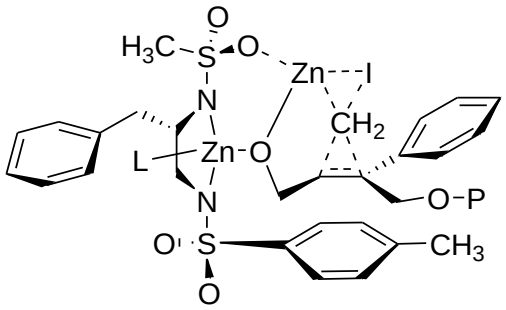
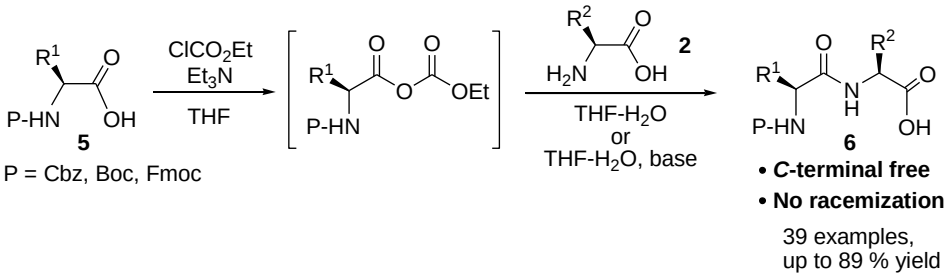


Figure 1. Possible transition state of the cyclopropanation

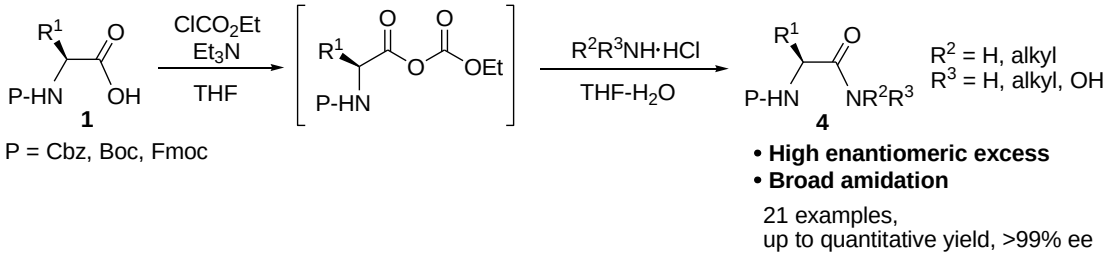
Conclusions

Chapter 1. Amidation of carboxylic acids via mixed carboxylic carbonic anhydrides

Dipeptides were obtained in high yields from the reaction of *N*-protected α-amino acids **5** with unprotected α-amino acids **2** via the corresponding mixed carbonic carboxylic anhydrides using ethyl chloroformate and triethylamine under neutral conditions. Unprotected α-amino acids **2** containing a hydrophilic side chain such as aliphatic alcohol, aromatic alcohol, thiol, carboxylic acid, and amide are also suitable as a nucleophile and were reacted with mixed carbonic carboxylic anhydrides under the basic conditions to afford the corresponding dipeptide in 66-96% yields. No racemization was observed by ^{1}H NMR analysis (Scheme 18).[17a, 17b] Next, primary amidation of *N*-protected α-amino acids **5** with NH_4Cl in the presence of ethyl chloroformate and triethylamine gave the corresponding primary amides **10** in 74% to quantitative yields with 97->99% ee (Scheme 19).[17c] Furthermore, the application to the synthesis of (1*S*,2*R*)-(+)-*N*-Cbz-tranylcypromine **15** via Lossen rearrangement have been also achieved in 71% overall yield with 82% ee in three steps from (2*S*,3*S*)-(+)-**13**. Our method is convenient and green because of inexpensive reagents, mild conditions, and safe byproducts, such as triethylamine hydrochloride, carbon dioxide, and the corresponding alcohols.



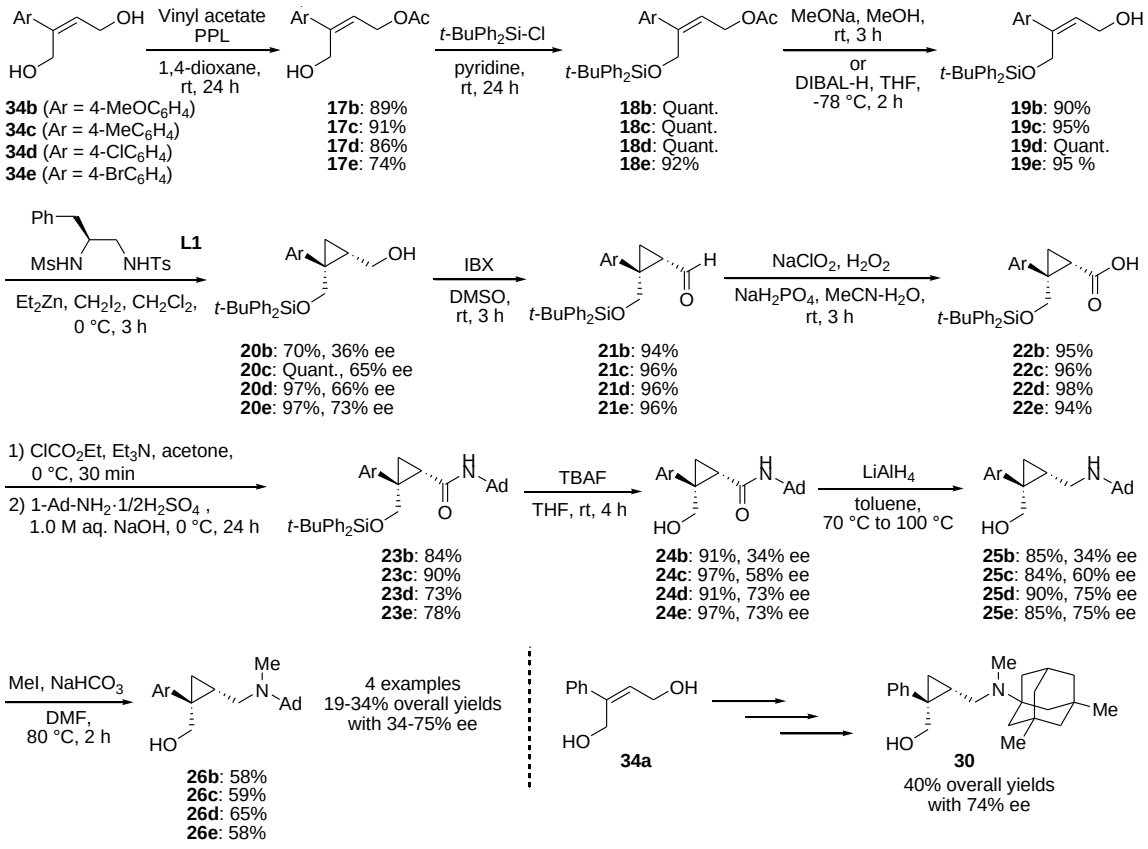
Scheme 18. Preparation of dipeptides **6** without protection of *C*-terminal under neutral or basic conditions



Scheme 19. Primary amidation of *N*-protected α-amino acids **5** via the mixed carbonic carboxylic anhydrides

Chapter 2. Synthesis of memantine analogues containing sigma-1 receptor activity as a candidate of anti-Alzheimer's medicine

I have achieved the convenient enantioselective synthesis of (+)-AMMP analogues **26b-26e** containing a chiral cyclopropane skeleton in 19-39% overall yields from the starting (*Z*)-2-arylbut-2-ene-1,4-diols **34b-34e** without the significant loss of enantiomeric excess. The reagents used in our synthetic route are relatively cheap, and the key reactions are three as follows; (i) the regioselective acetylation using PPL,[12] (ii) the catalytic enantioselective Simmons-Smith reaction in the presence of L-phenylalanine-derived disulfonamide,[13] and (iii) the convenient amidation of mixed carbonic carboxylic anhydrides in aqueous organic solvent.[14] Additionally, I have also succeeded in synthesizing memantine analogue **30** containing a chiral cyclopropane skeleton with 74% ee in 40% overall yield from (*Z*)-2-phenylbut-2-ene-1,4-diol **34a** (Scheme 20).



Scheme 20. Convenient enantioselective total synthesis of memantine analogues via the three key reactions

Experimental

1. General

All reagents were used without purification except for CH_2Cl_2. CH_2Cl_2 was washed with water twice, dried over molecular sieves 4 Å, heated at reflux for 24 h with CaH_2, and distilled before use. The ^1H NMR and ^{13}C NMR spectra were measured with a Bruker UltrashieldTM 400 Plus (400 MHz) spectrometer. The chemical shifts of ^1H NMR spectra are expressed in parts per million downfield from tetramethylsilane (= 0.00) or dimethyl sulfoxide-d^6 (= 2.50) as an internal standard. ^{13}C NMR spectra were calibrated with tetramethylsilane (= 0.00) or dimethyl sulfoxide-d^6 (= 39.5). Chemical shifts () are reported in ppm, and spin-spin coupling constants (J) are given in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), 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 thin-layer chromatography with silica gel 60 F_{254}. Purification of the reaction products was carried out by column chromatography using silica gel (64-210 mesh). HPLC analysis was carried out with Chiralcel OD, OJ, OB, OK (10 mm, 46 × 250 mm), Chiralpak AD, AS (10 mm, 46 × 250 mm), and Chiralcel OD-H (5 mm, 46 × 250 mm) coupled to a photodiode array detector or a dual λ absorbance detector, and HPLC grade solvents were used for HPLC analysis. 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.

Chapter 1. Amidation of carboxylic acids via mixed carboxylic carbonic anhydrides

Section 1. Convenient green preparation of dipeptides using unprotected α-amino acids under neutral conditions

2. Typical procedure for amidation of 3-phenylpropanoic acid 1a with L-Phe-OH 2a

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 ethyl chloroformate and 209 μL (1.5 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, a solution of 124 mg (0.75 mmol, 1.5 equiv) of L-Phe-OH **2a** in 10 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and concentrated in vacuo. To the residue was added a 1.0 M aqueous HCl solution to adjust to pH 2. The resulted suspension was extracted with 50 mL of EtOAc, washed with 10 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 2:1

mixture of hexane and EtOAc containing 1% AcOH to afford 145 mg (97% yield) of *N*-(3-phenylpropanoyl)-L-Phe-OH **3aa**.

2.1. *N*-(3-phenylpropanoyl)-L-Phe-OH 3aa

Colorless powder; mp: 167-169 °C; $[\alpha]^{23}_{D}$ = +1.42 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 2.45 (ddd, *J* = 1.0, 7.6, 7.6 Hz, 1H, CH_ACO), 2.45 (ddd, *J* = 1.0, 8.0, 8.0 Hz, 1H, CH_BCO), 2.79 (dd, *J* = 7.6, 8.0 Hz, 2H, $CH_2CH_2C_6H_5$), 2.91 (dd, *J* = 8.9, 13.8 Hz, 1H, $CHCH_AC_6H_5$), 3.15 (dd, *J* = 5.0, 13.8 Hz, 1H, $CHCH_BC_6H_5$), 4.64 (dd, *J* = 5.0, 8.9 Hz, 1H, CHCO), 7.13-7.17, 7.18-7.26 (m, m, 5H, 5H, C_6H_5 ×2); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 30.5, 36.2, 36.4, 52.9, 124.9, 125.4, 127.1, 127.1, 127.2, 128.0, 136.3, 139.9, 172.7, 172.8; HRMS (ESI-TOF): Calcd for $C_{18}H_{19}NO_3Na$ $(M+Na)^+$: 320.1257, found: 320.1283; IR (KBr, ν_{max}/cm^{-1}) = 3307 (OH), 1708 (CO_2), 1600 (CON).

2.2. *N*-(3-phenylpropanoyl)-L-Phg-OH 3ab

Colorless powder; mp: 152-153 °C; $[\alpha]^{27}_{D}$ = +108.4 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 2.57 (ddd, *J* = 1.5, 7.6, 7.6 Hz, 1H, CH_ACO), 2.57 (ddd, *J* = 1.5, 8.0, 8.0 Hz, 1H, CH_BCO), 2.90 (dd, *J* = 7.6, 8.0 Hz, 2H, $CH_2C_6H_5$), 5.41 (s, 1H, CHCO), 7.12-7.24, 7.30-7.34 (m, m, 5H, 5H, C_6H_5 ×2); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 32.8, 38.5, 58.2. 127.2, 128.8, 129.3, 129.5, 129.5, 129.8, 138.2, 142.2, 173.8, 174.8; HRMS (ESI-TOF): Calcd for $C_{17}H_{17}NO_3Na$ $(M+Na)^+$: 306.1101, found: 306.1086; IR (KBr, ν_{max}/cm^{-1}) = 3338 (OH), 1698 (CO_2), 1616 (CON).

2.3. *N*-(3-phenylpropanoyl)-L-Val-OH 3ac

Colorless powder; mp: 141-143 °C; $[\alpha]^{21}_{D}$ = –22.9 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 0.87 (d, *J* = 6.8 Hz, 6H, $(CH_3)_2$), 2.06-2.14 (m, 1H, $CH(CH_3)_2$), 2.57 (ddd, *J* = 3.9, 7.6, 7.6 Hz, 1H, CH_ACO), 2.58 (ddd, *J* = 3.9, 7.7, 7.7 Hz, 1H, CH_BCO), 2.91 (dd, *J* = 7.6, 7.7 Hz, 2H, $CH_2C_6H_5$), 4.28 (d, *J* = 5.7 Hz, 1H, CHCO), 7.13-7.17, 7.20-7.27 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 18.3, 19.6, 31.7, 32.9, 59.1, 127.2, 129.5, 129.5, 142.2, 175.1, 175.4; HRMS (ESI-TOF): Calcd for $C_{14}H_{19}NO_3Na$ $(M+Na)^+$: 272.1257, found: 272.1243; IR (KBr, ν_{max}/cm^{-1}) = 3338 (OH), 1699 (CO_2), 1616 (CON).

2.4. *N*-(3-phenylpropanoyl)-L-*tert*-Leu-OH 3ad

Colorless powder; mp: 183-185 °C; $[\alpha]^{26}_{D}$ = –9.72 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 0.94 (s, 9H, $(CH_3)_3C$), 2.59 (ddd, *J* = 6.5, 7.7, 7.7 Hz, 1H, CH_ACO), 2.59 (ddd, *J* = 6.5, 7.7, 7.7 Hz, 1H, CH_BCO), 2.91 (dd, *J* = 7.7, 7.7 Hz, 2H, $CH_2C_6H_5$), 4.25 (s, 1H, CHCO), 7.13-7.17, 7.20-7.26 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 27.2, 32.9, 34.8, 38.5, 62.2, 127.2, 129.5, 142.2, 174.4, 175.2; HRMS (ESI-TOF): Calcd for $C_{15}H_{21}NO_3Na$ $(M+Na)^+$: 286.1414, found: 286.1386; IR (KBr, ν_{max}/cm^{-1}) = 3348 (OH), 1699 (CO_2), 1610 (CON).

2.5. *N*-(3-phenylpropanoyl)-L-Glu-OH 3ae

Colorless powder; mp: 131-134 °C; $[\alpha]^{23}_{D}$ = –28.4 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.80-1.90 (m, 1H, CH_ACH), 2.07-2.15 (m, 1H, CH_BCH), 2.22-2.26 (m, 2H, CH_2CH$_2$CH), 2.54 (dd, *J* = 7.4, 8.0 Hz, 2H, CH$_2$CO), 2.91 (dd, *J* = 7.4, 8.0 Hz, 2H, CH_2C$_6$H$_5$), 4.40 (dd, *J* = 4.8, 9.8 Hz, 1H, CHCO), 7.15-7.18, 7.20-7.27 (m, m, 1H, 4H, C$_6$H$_5$); ^{13}C NMR (100MHz, MeOD-d^4): δ 27.9, 31.2, 32.8, 38.7, 53.0, 127.3, 129.5, 129.5, 142.2, 175.0, 175.4, 176.4; HRMS (ESI-TOF): Calcd for $C_{14}H_{17}NO_5Na$ $(M+Na)^+$: 302.0999, found: 302.1010; IR (KBr, ν_{max}/cm^{-1}) = 3276 (OH), 1716 (CO$_2$), 1653 (CON).

2.6. *N*-(3-phenylpropanoyl)-L-Gln-OH 3af

Colorless powder; mp: 141-144 °C; $[\alpha]^{22}_{D}$ = –19.2 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.83-1.93 (m, 1H, CH_ACH), 2.07-2.24 (m, 3H, CH_BCH, CH_2CH$_2$CH), 2.55 (dd, *J* = 7.5, 8.1 Hz, 2H, CH$_2$CO), 2.92 (dd, *J* = 7.5, 8.1 Hz, 2H, CH_2C$_6$H$_5$), 4.37 (dd, *J* = 4.5, 9.4 Hz, 1H, CHCO), 7.14-7.18, 7.21-7.28 (m, m, 1H, 4H, C$_6$H$_5$); ^{13}C NMR (100MHz, MeOD-d^4): δ 28.6, 32.7, 32.8, 38.7, 53.3, 127.3, 129.5, 129.5, 142.2, 175.0, 175.4, 177.7; HRMS (ESI-TOF): Calcd for $C_{14}H_{18}N_2O_4Na$ $(M+Na)^+$: 301.1159, found: 301.1184; IR (KBr, ν_{max}/cm^{-1}) = 3292 (OH), 1724 (CO$_2$), 1646 (CON).

2.7. *N*-(3-phenylpropanoyl)-L-Thr-OH 3ag

Colorless oil; $[\alpha]^{22}_{D}$ = –7.04 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.06 (d, *J* = 6.4 Hz, 3H, CH$_3$), 2.61 (dd, *J* = 7.4, 8.2 Hz, 2H, CH$_2$CO), 2.94 (dd, *J* = 7.4, 8.2 Hz, 2H, CH_2C$_6$H$_5$), 4.24-4.29 (m, 1H, C*H*CH$_3$), 4.41 (d, *J* = 3.0 Hz, 1H, CHCO), 7.13-7.20, 7.21-7.27 (m, m, 1H, 4H, C$_6$H$_5$); ^{13}C NMR (100MHz, MeOD-d^4): δ 20.4, 32.8, 38.7, 59.1, 68.4, 127.2, 129.5, 129.5, 142.2, 173.9, 175.7; HRMS (ESI-TOF): Calcd for $C_{13}H_{17}NO_4Na$ $(M+Na)^+$: 274.1050, found: 274.1040; IR (NaCl, ν_{max}/cm^{-1}) = 3325 (OH), 1732 (CO$_2$), 1653 (CON).

2.8. *N*-(3-phenylpropanoyl)-L-Met-OH 3ah

Yellow powder; mp: 73-75 °C; $[\alpha]^{21}_{D}$ = –28.9 (*c* 0.98, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.80-1.89 (m, 1H, CH_ACH$_2$S), 2.01-2.10 (m, 1H, CH_BCH$_2$S), 2.03 (s, 3H, CH$_3$), 2.27-2.41 (m, 2H, CH$_2$CH_2S), 2.54 (dd, *J* = 7.4, 7.9 Hz, 2H, CH$_2$CO), 2.91 (dd, *J* = 7.4, 7.7 Hz, 2H, CH_2C$_6$H$_5$), 4.48-4.51 (m, 1H, CHCO), 7.14-7.27 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100MHz, MeOD-d^4): δ 15.2, 31.2, 32.2, 32.8, 38.7, 52.6, 127.3, 129.5, 129.5, 142.2, 175.2, 175.4; HRMS (ESI-TOF): Calcd for $C_{14}H_{19}NO_3SNa$ $(M+Na)^+$: 304.0978, found: 304.0953; IR (KBr, ν_{max}/cm^{-1}) = 3302 (OH), 1705 (CO$_2$), 1647 (CON).

2.9. *N*-(3-phenylpropanoyl)-L-Trp-OH 3ai

Colorless powder; mp: 160-162 °C; $[\alpha]^{27}_{D}$ = +1.30 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.44 (dd, *J* = 7.6, 8.0 Hz, 2H, CH$_2$CO), 2.78 (ddd, *J* = 3.1, 7.6, 7.6 Hz, 1H, CH_AC$_6$H$_5$), 2.78 (ddd, *J*

= 3.1, 8.0, 8.0 Hz, 1H, CH_BC$_6$H$_5$), 3.11 (dd, *J* = 8.0, 14.8 Hz, 1H, CH_ACH), 3.30 (dd, *J* = 5.0, 14.8 Hz, 1H, CH_BCH), 4.71 (dd, *J* = 5.0, 8.0 Hz, 1H, CHCO), 6.96, 7.00, 7.06-7.21, 7.32, 7.53 (s, t, m, d, d, *J* = 7.4, 7.8, 7.8 Hz, 1H, 1H, 6H, 1H, 1H, indole, C$_6$H$_5$); ^{13}C NMR (100MHz, MeOD-d^4): δ 28.6, 32.7, 38.8, 54.7, 111.1, 112.3, 119.3, 119.8, 122.4, 124.4, 127.2, 128.9, 129.4, 129.5, 138.1, 142.2, 175.1, 175.3; HRMS (ESI-TOF): Calcd for $C_{20}H_{20}N_2O_3Na$ $(M+Na)^+$: 359.1366, found: 359.1348; IR (KBr, ν_{max}/cm^{-1}) = 3410 (OH), 1734 (CO_2), 1655 (CON).

3. Typical procedure for amidation of Cbz-L-Phe-OH 5a with L-Val-OH 2c

To a colorless solution of 150 mg (0.50 mmol) of Cbz-L-Phe-OH **5a** in 10 mL of THF were added at 0 °C 67 μL (0.70 mmol, 1.4 equiv) of ethyl chloroformate and 209 μL (1.5 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, a solution of 88 mg (0.75 mmol, 1.5 equiv) of L-Val-OH **2c** in 10 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and concentrated in vacuo. To the residue was added a 1.0 M aqueous HCl solution to adjust to pH 2. The resulted suspension was extracted with 50 mL of EtOAc, washed with 10 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc containing 1% AcOH to afford 149 mg (75% yield) of Cbz-L-Phe-L-Val-OH **6ac**.

3.1. Cbz-L-Phe-L-Val-OH 6ac

Colorless powder; mp: 140-143 °C; $[\alpha]^{25}_D$ = –7.70 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, $CDCl_3$): δ 0.84 (d, *J* = 6.8 Hz, 3H, CH_3), 0.89 (d, *J* = 6.8 Hz, 3H, CH_3), 2.13-2.21 (m, 1H, CH(CH$_3$)$_2$), 3.08 (dd, *J* = 7.0, 7.3 Hz, 2H, CHCH_2C$_6$H$_5$), 4.46-4.49 (m, 2H, CHCO ×2), 5.07 (d, *J* = 12.3 Hz, 1H, OCH_AC$_6$H$_5$), 5.11 (d, *J* = 12.3 Hz, 1H, OCH_BC$_6$H$_5$), 5.45 (br, 1H, NH), 6.36 (br, 1H, NH), 7.18-7.37 (m, 10H, C$_6$H$_5$ ×2); ^{13}C-NMR (100MHz, $CDCl_3$): δ 17.6, 18.8, 30.9, 38.2, 56.3, 57.2, 67.2, 127.1, 128.1, 128.3, 128.6, 128.8, 129.3, 136.1, 156.1, 171.2, 174.7; HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_2O_5$ $(M+H)^+$: 399.1914, found: 399.1918; IR (KBr, ν_{max} /cm^{-1}) = 3307 (OH), 1697 (CO_2), 1635 (CON).

3.2. Boc-L-Phe-L-Val-OH 6bc

Colorless powder; mp: 64-67 °C; $[\alpha]^{27}_D$ = –5.34 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 0.96 (d, *J* = 6.8 Hz, 6H, (CH$_3$)$_2$), 1.34 (s, 9H, (CH_3)$_3$C), 2.13-2.21 (m, 1H, CH(CH$_3$)$_2$), 2.80 (dd, *J* = 4.2, 13.9 Hz, 1H, CH_AC$_6$H$_5$), 3.12 (dd, *J* = 4.9, 13.9 Hz, 1H, CH_BC$_6$H$_5$), 4.32-4.37 (m, 2H, CHCO ×2), 7.17-7.26 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100MHz, MeOD-d^4): δ 18.3, 19.6, 28.7, 32.1, 39.0, 57.3, 58.9, 80.7, 127.7, 129.4, 130.4, 138.7, 157.7, 174.4, 174.5; HRMS (ESI-TOF): Calcd for $C_{19}H_{28}N_2O_5Na$ $(M+Na)^+$: 387.1890, found: 387.1901; IR (KBr, ν_{max}/cm^{-1}) = 3309 (OH), 1716 (CO_2), 1652 (CON).

3.3. Fmoc-L-Phe-L-Val-OH 6cc

Colorless powder; mp: 93-95 °C; $[\alpha]^{25}_D$ = –19.6 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 0.96 (d, *J* = 6.8 Hz, 6H, CH$_3$ ×2), 2.13-2.21 (m, 1H, CH(CH$_3$)$_2$), 2.85 (dd, *J* = 9.8, 13.9 Hz, 1H,

CH_AC$_6$H$_5$), 3.12 (dd, J = 4.9, 13.9 Hz, 1H, CH_BC$_6$H$_5$), 4.11-4.36 (m, 4H, CHCH(CH$_3$)$_2$, CH$_2$O, CHCH$_2$O), 4.45-4.51 (m, 1H, CHCH$_2$C$_6$H$_5$), 7.16-7.30, 7.37, 7.55-7.58, 7.78 (m, t, m, d, J = 7.6, 7.6 Hz, 7H, 2H, 2H, 2H, C$_6$H$_5$, fluorenyl); ^{13}C NMR (100MHz, MeOD-d^4): δ 18.3, 19.6, 32.0, 39.0, 57.7, 59.0, 59.1, 68.1, 121.0, 126.3, 126.3, 127.8, 128.2, 128.8, 129.5, 130.4, 138.7, 142.6, 145.2, 158.3, 174.3, 174.5; HRMS (ESI-TOF): Calcd for $C_{29}H_{30}N_2O_5Na$ $(M+Na)^+$: 509.2047, found: 509.2039; IR (KBr, ν_{max}/cm^{-1}) = 3301 (OH), 1718 (CO$_2$), 1691 (CON), 1656 (CON).

3.4. Cbz-L-Phe-L-*tert*-Leu-OH 6ad

Colorless powder; mp: 164-167 °C; $[\alpha]^{25}_D$ = –14.3 (c 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.00 (s, 9H, CH$_3$ ×3), 2.83 (dd, J = 9.6, 13.8 Hz, 1H, CH_AC$_6$H$_5$), 3.11 (dd, J = 5.3, 13.8 Hz, 1H, CH_BC$_6$H$_5$), 4.29 (s, 1H, CHC(CH$_3$)$_3$), 4.48 (dd, J = 5.3, 9.6 Hz, 1H, CHCH$_2$C$_6$H$_5$), 5.09 (s, 2H, OCH_2C$_6$H$_5$), 7.17-7.32 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 27.1, 35.2, 38.9, 57.8, 61.9, 67.6, 127.6, 128.7, 129.0, 129.5, 130.4, 138.2, 138.5, 158.3, 173.8, 174.0; HRMS (ESI-TOF): Calcd for $C_{23}H_{28}N_2O_5Na$ $(M+Na)^+$: 435.1890, found: 435.1890; IR (KBr, ν_{max}/cm^{-1}) = 3327 (OH), 1699 (CO$_2$), 1635 (CON).

3.5. Cbz-L-Phe-L-Glu-OH 6ae

Colorless powder; mp: 149-152 °C; $[\alpha]^{27}_D$ = –12.1 (c 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.89-1.99 (m, 1H, CH_ACH$_2$CO), 2.15-2.23 (m, 1H, CH_BCH$_2$CO), 2.39 (dd, J = 7.6, 7.8 Hz, 2H, CH$_2$CO), 2.84 (dd, J = 9.6, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.15 (dd, J = 5.0, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 4.40-4.47 (m, 2H, CH ×2), 4.99 (d, J = 13.0 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 13.0 Hz, 1H, OCH_BC$_6$H$_5$), 7.18-7.33 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 28.0, 31.1, 39.0, 53.1, 57.8, 67.6, 127.8, 128.8, 129.0, 129.5, 130.4, 138.2, 138.6, 158.3, 174.2, 174.6, 176.4; HRMS (ESI-TOF): Calcd for $C_{22}H_{25}N_2O_7$ $(M+H)^+$: 429.1656, found: 429.1672; IR (KBr, ν_{max}/cm^{-1}) = 3286 (OH), 1716 (CO$_2$), 1660 (CON).

3.6. Cbz-L-Phe-L-Gln-OH 6af

Colorless powder; mp: 179-182 °C; $[\alpha]^{28}_D$ = –10.2 (c 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.91-1.98 (m, 1H, CH_ACH$_2$CO), 2.16-2.35 (m, 3H, CH_BCH$_2$CO, CH$_2$CO), 2.85 (dd, J = 9.7, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.16 (dd, J = 4.9, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 4.38-4.43 (m, 2H, CH ×2), 4.99 (d, J = 12.7 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 12.7 Hz, 1H, OCH_BC$_6$H$_5$), 7.17-7.33 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 28.8, 32.7, 39.0, 53.2, 57.8, 67.6, 127.8, 128.7, 129.0, 129.5, 129.5, 130.4, 138.2, 138.6, 158.3, 174.3, 174.6, 177.8; HRMS (ESI-TOF): Calcd for $C_{22}H_{25}N_3O_6Na$ $(M+Na)^+$: 450.1636, found: 450.1606; IR (KBr, ν_{max}/cm^{-1}) = 3309 (OH), 1716 (CO$_2$), 1654 (CON).

3.7. Cbz-L-Phe-L-Phe-OH 6aa

Colorless powder; mp: 148-151 °C; $[\alpha]^{24}_D$ = –10.5 (c 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4):

δ 2.76 (dd, J = 9.7, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.00 (dd, J = 8.2, 13.8 Hz, 1H, CH_A·C$_6$H$_5$), 3.08 (dd, J = 5.0, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 3.19 (dd, J = 5.2, 13.8 Hz, 1H, CH_B·C$_6$H$_5$), 4.36 (dd, J = 5.0, 9.7 Hz, 1H, CH), 4.65 (dd, J = 5.2, 8.2 Hz, 1H, CH'), 4.97 (d, J = 12.6 Hz, 1H, OCH_AC$_6$H$_5$), 5.01 (d, J = 12.6 Hz, 1H, OCH_BC$_6$H$_5$), 7.15-7.33 (m, 15H, C$_6$H$_5$ ×3); ^{13}C NMR (100MHz, MeOD-d^4): δ 38.5, 39.1, 55.0, 57.7, 67.6, 127.7, 127.8, 128.7, 128.9, 129.4, 129.5, 130.4, 130.5, 138.2, 138.6, 158.2, 173.9, 174.2; HRMS (ESI-TOF): Calcd for $C_{26}H_{27}N_2O_5$ $(M+H)^+$: 447.1914, found: 447.1890; IR (KBr, ν_{max}/cm^{-1}) = 3307 (OH), 1716 (CO_2), 1695 (CON), 1660 (CON).

3.8. Cbz-L-Phe-D-Phe-OH 6aa'

Colorless powder; mp: 109-112 °C; $[\alpha]^{27}_D$ = –19.2 (c 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.67 (dd, J = 9.5, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 2.92-2.98 (m, 2H, CH_A·C$_6$H$_5$, CH_BC$_6$H$_5$), 3.16 (dd, J = 5.0, 13.6 Hz, 1H, CH_B·C$_6$H$_5$), 4.37 (dd, J = 5.4, 9.5 Hz, 1H, CH), 4.66 (dd, J = 5.0, 8.4 Hz, 1H, CH'), 4.96 (d, J = 12.8 Hz, 1H, OCH_AC$_6$H$_5$), 5.02 (d, J = 12.8 Hz, 1H, OCH_BC$_6$H$_5$), 7.08-7.33 (m, 15H, C$_6$H$_5$ ×3); ^{13}C NMR (100MHz, MeOD-d^4): δ 38.4, 39.3, 54.9, 57.7, 67.6, 127.7, 127.9, 128.7, 129.0, 129.4, 129.5, 129.6, 130.4, 130.4, 138.2, 138.5, 158.1, 173.8, 174.3; HRMS (ESI-TOF): Calcd for $C_{26}H_{26}N_2O_5Na$ $(M+Na)^+$: 469.1734, found: 469.1726; IR (KBr, ν_{max}/cm^{-1}) = 3307 (OH), 1716 (CO_2), 1652 (CON).

3.9. Cbz-L-Phe-L-Thr-OH 6ag

Colorless powder; mp: 141-143 °C; $[\alpha]^{25}_D$ = –7.70 (c 1.00, MeOH); ^{1}H NMR (400MHz, $CDCl_3$): δ 1.17 (d, J = 6.4 Hz, 3H, CH_3), 2.95 (dd, J = 8.0, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.11 (dd, J = 5.5, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 4.40-4.48 (m, 1H, CHOH), 4.60-4.69 (m, 2H, CHCH$_2$, CHCHOH), 4.92 (d, J = 12.2 Hz, 1H, OCH_AC$_6$H$_5$), 5.04 (d, J = 12.2 Hz, 1H, OCH_BC$_6$H$_5$), 5.46 (br, 1H, NH), 7.09-7.11, 7.19-7.21, 7.28-7.31 (m, m, m, 11H, NH, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, $CDCl_3$): δ 19.2, 38.6, 55.8, 57.3, 67.3, 68.6, 127.1, 128.0, 128.2, 128.5, 128.7, 129.3, 135.9, 156.4, 172.0, 172.8; HRMS (ESI-TOF): Calcd for $C_{21}H_{25}N_2O_6$ $(M+H)^+$: 401.1707, found: 401.1708; IR (KBr, ν_{max}/cm^{-1}) = 3294 (OH), 1701 (CO_2), 1658 (CON).

3.10. Cbz-L-Phe-L-Met-OH 6ah

Colorless powder; mp: 103-104 °C; $[\alpha]^{26}_D$ = –16.1 (c 1.00, MeOH); ^{1}H NMR (400MHz, $CDCl_3$): δ 1.92-2.04 (m, 1H, CH_ACH$_2$S), 2.04 (s, 3H, CH_3), 2.10-2.19 (m, 1H, CH_BCH$_2$S), 2.37-2.48 (m, 2H, CH$_2$S), 3.03-3.15 (m, 2H, CH_2C$_6$H$_5$), 4.43-4.55 (m, 1H, CHCH$_2$CH$_2$), 4.61-4.66 (m, 1H, CHCH$_2$C$_6$H$_5$), 5.08 (s, 2H, OCH_2C$_6$H$_5$), 5.39 (br, 1H, NH), 6.72 (br, 1H, NH), 7.17-7.38 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, $CDCl_3$): δ 15.3, 29.8, 30.8, 38.2, 51.7, 56.1, 67.3, 127.2, 128.1, 128.3, 128.6, 128.8, 129.3, 136.0, 156.2, 171.5, 174.4; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_5SNa$ $(M+Na)^+$: 453.1455, found: 453.1440; IR (KBr, ν_{max}/cm^{-1}) = 3301 (OH), 1712 (CO_2), 1689 (CON), 1652 (CON).

3.11. Cbz-L-Phe-L-Trp-OH 6ai

Colorless powder; mp: 141-144 °C; $[\alpha]^{27}_{D}$ = –3.30 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 2.74 (dd, *J* = 9.7, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.07 (dd, *J* = 5.0, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_5$), 3.22 (dd, *J* = 7.2, 14.7 Hz, 1H, CH$_A$-indole), 3.34 (dd, *J* = 5.2, 14.7 Hz, 1H, CH$_B$-indole), 4.37 (dd, *J* = 5.0, 9.7 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.71 (dd, *J* = 5.2, 7.2 Hz, 1H, C*H*CH$_2$-indole), 4.94 (d, *J* = 12.8 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.00 (d, *J* = 12.8 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 6.99, 7.05-7.09, 7.14-7.32, 7.55 (t, m, m, d, *J* = 7.0, 7.9 Hz, 1H, 2H, 11H, 1H, C$_6$H$_5$ ×2, indole); ^{13}C NMR (100MHz, MeOD-*d*^{4}): *δ* 28.5, 39.0, 54.7, 57.8, 67.6, 110.7, 112.3, 119.4, 119.9, 122.4, 124.6, 127.7, 128.7, 129.0, 129.4, 129.5, 130.4, 138.0, 138.2, 138.6, 158.2, 173.9, 174.9; HRMS (ESI-TOF): Calcd for $C_{28}H_{27}N_3O_5Na$ $(M+Na)^+$: 508.1843, found: 508.1836; IR (KBr, ν_{max}/cm^{-1}) = 3408 (NH), 3313 (OH), 1712 (CO_2), 1627 (CON).

3.12. Cbz-Gly-L-Phe-OH 6ba

Colorless sticky oil; $[\alpha]^{28}_{D}$ = +25.1 (*c* 0.98, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 3.00 (dd, *J* = 7.6, 14.2 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.18 (dd, *J* = 5.4, 14.2 Hz, 1H, C*H*$_B$C$_6$H$_5$), 3.72 (d, *J* = 17.0 Hz, 1H, C*H*$_A$CONH), 3.79 (d, *J* = 17.0 Hz, 1H, C*H*$_B$CONH), 4.67 (dd, *J* = 5.4, 7.6 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.09 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.16-7.27, 7.28-7.38 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-*d*^{4}): *δ* 38.4, 44.8, 54.9, 67.9, 127.9, 128.9, 129.1, 129.5, 130.4, 138.1, 159.0, 171.9, 174.4; HRMS (ESI-TOF): Calcd for $C_{19}H_{20}N_2O_5Na$ $(M+Na)^+$: 379.1264, found: 379.1250; IR (KBr, ν_{max}/cm^{-1}) = 3326 (OH), 1732 (CO_2), 1662 (CON).

3.13. Cbz-L-Ala-L-Phe-OH 6ca

Colorless powder; mp: 125-127 °C; $[\alpha]^{27}_{D}$ = +0.96 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 1.27 (d, *J* = 7.1 Hz, 3H, CH$_3$), 3.01 (dd, *J* = 7.8, 13.9 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.18 (dd, *J* = 5.2, 13.9 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.13 (q, *J* = 7.1 Hz, 1H, C*H*CH$_3$), 4.64 (dd, *J* = 5.2, 7.8 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.06 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.16-7.26, 7.28-7.38 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-*d*^{4}): *δ* 18.3, 38.4, 51.9, 54.9, 67.7, 127.8, 128.9, 129.0, 129.5, 129.5, 130.5, 138.2, 158.2, 174.3, 175.3; HRMS (ESI-TOF): Calcd for $C_{20}H_{22}N_2O_5Na$ $(M+Na)^+$: 393.1421, found: 393.1449; IR (KBr, ν_{max}/cm^{-1}) = 3330 (OH), 1736 (CO_2), 1714 (CON), 1691 (CON).

3.14. Cbz-L-Val-L-Phe-OH 6da

Colorless powder; mp: 174-177 °C; $[\alpha]^{27}_{D}$ = –0.76 (*c* 1.00, DMSO); ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 0.87 (d, *J* = 6.8 Hz, 3H, CH$_3$), 0.89 (d, *J* = 6.8 Hz, 3H, CH$_3$), 1.93-2.00 (m, 1H, C*H*(CH$_3$)$_2$), 2.97 (dd, *J* = 8.6, 13.9 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.18 (dd, *J* = 5.2, 13.9 Hz, 1H, C*H*$_B$C$_6$H$_5$), 3.90 (d, *J* = 7.3 Hz, 1H, C*H*CH(CH$_3$)$_2$), 4.66 (dd, *J* = 5.2, 8.6 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.08 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.13-7.22, 7.28-7.35 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-*d*^{4}): *δ* 18.6, 19.7, 32.1, 38.5, 54.9, 62.1, 67.7, 127.8, 128.9, 129.1, 129.5, 129.5, 130.4, 138.3, 158.5, 174.0, 174.4; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_5Na$ $(M+Na)^+$: 421.1734, found: 421.1757; IR (KBr, ν_{max}/cm^{-1}) = 3342 (OH),

1734 (CO_2), 1635 (CON).

3.15. Cbz-L-Leu-L-Phe-OH 6ea

Colorless powder; mp: 81-83 °C; $[\alpha]^{27}_D$ = –7.43 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 0.89 (d, *J* = 6.6 Hz, 3H, CH_3), 0.92 (d, *J* = 6.6 Hz, 3H, CH_3), 1.44-1.48 (m, 2H, CH_ACH(CH_3)$_2$, CH(CH_3)$_2$), 1.58-1.66 (m, 1H, CH_BCH(CH_3)$_2$), 3.00 (dd, *J* = 8.4, 13.7 Hz, 1H, C$H_A$$C_6H_5$), 3.19 (dd, *J* = 5.2, 13.7 Hz, 1H, C$H_B$$C_6H_5$), 4.14 (dd, *J* = 6.3, 6.3 Hz, 1H, C$H$$CH_2$CH), 4.65 (dd, *J* = 5.2, 8.3 Hz, 1H, C$H$$CH_2$$C_6H_5$), 5.07 (s, 2H, OC$H_2$$C_6H_5$), 7.15-7.24, 7.27-7.35 (m, m, 5H, 5H, C_6H_5 ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 22.0, 23.4, 25.9, 38.4, 42.1, 54.9, 54.9, 67.7, 127.8, 128.8, 129.0, 129.5, 129.5, 130.5, 138.2, 158.4, 174.3, 175.1; HRMS (ESI-TOF): Calcd for $C_{23}H_{28}N_2O_5Na$ $(M+Na)^+$: 435.1890, found: 435.1909; IR (KBr, ν_{max}/cm^{-1}) = 3319 (OH), 1716 (CO_2), 1697 (CON), 1664 (CON).

3.16. Cbz-L-Met-L-Phe-OH 6fa

Colorless powder; mp: 125-126 °C; $[\alpha]^{27}_D$ = –6.98 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.77-1.86 (m, 1H, C$H_A$$CH_2$S), 1.92-1.99 (m, 1H, C$H_B$$CH_2$S), 2.04 (s, 3H, CH_3), 2.40-2.53 (m, 2H, CH_2S), 3.00 (dd, *J* = 8.3, 13.9 Hz, 1H, C$H_A$$C_6H_5$), 3.19 (dd, *J* = 5.2, 13.9 Hz, 1H, C$H_B$$C_6H_5$), 4.22 (dd, *J* = 5.6, 8.5 Hz, 1H, C$H$$CH_2$$CH_2$), 4.66 (dd, *J* = 5.2, 8.3 Hz, 1H, C$H$$CH_2$$C_6H_5$), 5.07 (s, 2H, OC$H_2$$C_6H_5$), 7.15-7.26, 7.28-7.35 (m, m, 5H, 5H, C_6H_5 ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 15.2, 31.0, 32.9, 38.3, 54.9, 55.5, 67.8, 127.9, 128.9, 129.1, 129.5, 129.5, 130.4, 138.2, 158.4, 174.1, 174.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_5SNa$ $(M+Na)^+$: 453.1455, found: 453.1454; IR (KBr, ν_{max}/cm^{-1}) = 3311 (OH), 1722 (CO_2), 1695 (CON), 1660 (CON).

3.17. Cbz-L-Trp-L-Phe-OH 6ga

Colorless powder; mp: 70-72 °C; $[\alpha]^{28}_D$ = –18.1 (*c* 0.99, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.96 (dd, *J* = 7.8, 13.9 Hz, 1H, C$H_A$$C_6H_5$), 3.01 (dd, *J* = 8.4, 14.8 Hz, 1H, CH_A-indole), 3.14 (dd, *J* = 5.4, 13.9 Hz, 1H, C$H_B$$C_6H_5$), 3.20 (dd, *J* = 5.4, 14.8 Hz, 1H, CH_B-indole), 4.43 (dd, *J* = 5.4, 8.4 Hz, 1H, C$H$$CH_2$-indole), 4.64 (dd, *J* = 5.4, 7.8 Hz, 1H, C$H$$CH_2$$C_6H_5$), 5.00 (s, 2H, OC$H_2$$C_6H_5$), 6.96-7.33, 7.57 (m, d, *J* = 7.9 Hz, 14H, 1H, C_6H_5 ×2, indole); ^{13}C NMR (100MHz, MeOD-d^4): δ 29.1, 38.4, 55.0, 57.2, 67.7, 111.0, 112.3, 119.4, 119.9, 122.4, 124.7, 127.8, 128.7, 128.8, 128.9, 129.4, 129.5, 130.5, 138.1, 158.2, 174.2; HRMS (ESI-TOF): Calcd for $C_{28}H_{27}N_3O_5Na$ $(M+Na)^+$: 508.1843, found: 508.1820; IR (KBr, ν_{max}/cm^{-1}) = 3402 (NH), 3313 (OH), 1716 (CO_2), 1662 (CON).

Section 2. Ecological base-conditioned preparation of dipeptides using unprotected α-amino acids containing hydrophilic side chains

4. Typical procedure for the amidation of 3-phenylpropanoic acid 1a using ethyl chloroformate

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 ethyl chloroformate and 209 μL (1.5 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, a solution of 110 mg (0.75 mmol, 1.5 equiv) of L-Glu-OH **2e** and 63 mg (0.75 mmol, 1.5 equiv) of $NaHCO_3$ in 10 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and the resulted colorless clear solution was concentrated in vacuo. The residue was adjusted to pH 2 by addition of a 1.0 M aqueous solution of HCl. The resulted suspension was diluted with 30 mL of EtOAc. The aqueous layer was extracted with 20 mL of EtOAc. The combined organic layer was washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with EtOAc containing 1% AcOH to afford 126 mg (90% yield) of *N*-(3-phenylpropanoyl)-L-Glu-OH **3e**.

4.1. *N*-(3-phenylpropanoyl)-L-Ser-OH 3ak

Colorless powder; mp: 119-123 °C; $[\alpha]^{28}_D$ = +6.70 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.72 (ddd, *J* = 1.5, 7.6, 7.6 Hz, 1H, CH_ACO), 2.72 (ddd, *J* = 1.5, 8.3, 8.3 Hz, 1H, CH_BCO), 2.92 (dd, *J* = 7.6, 8.3 Hz, 2H, $CH_2C_6H_5$), 3.77 (dd, *J* = 4.3, 11.2 Hz, 1H, CH_AOH), 3.86 (dd, *J* = 4.8, 11.2 Hz, 1H, CH_BOH), 4.48 (dd, *J* = 4.3, 4.8 Hz, 1H, $CHCH_2OH$), 7.14-7.18, 7.21-7.28 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100MHz, MeOD-d^4): δ 32.8, 38.8, 56.1, 63.0, 127.2, 129.4, 129.5, 142.3, 173.5, 175.4; HRMS (ESI-TOF): Calcd for $C_{12}H_{15}NO_4Na$ $(M+Na)^+$: 260.0893, found: 260.0894; IR (KBr, ν_{max}/cm^{-1}): 3305 (OH), 1716 (CO_2), 1648 (CON).

4.2. *N*-(3-phenylpropanoyl)-L-Cys-OH 3al

Colorless powder; mp: 132-133 °C; $[\alpha]^{28}_D$ = –4.10 (*c* 1.01, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.58 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H, CH_ACO), 2.58 (ddd, *J* = 1.2, 7.7, 7.7 Hz, 1H, CH_BCO), 2.79 (dd, *J* = 6.6, 14.0 Hz, 1H, CH_ASH), 2.86 (dd, *J* = 4.6, 14.0 Hz, 1H, CH_BSH), 2.93 (dd, *J* = 7.6, 7.7 Hz, 2H, $CH_2C_6H_5$), 4.58 (dd, *J* = 4.6, 6.6 Hz, 1H, $CHCH_2SH$), 7.14-7.19, 7.21-7.28 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100MHz, MeOD-d^4): δ 26.8, 32.8, 38.6, 55.9, 127.3, 129.5, 129.5, 142.1, 173.1, 175.3; HRMS (ESI-TOF): Calcd for $C_{12}H_{16}NO_3S$ $(M+Na)^+$: 254.0854, found: 254.0856; IR (KBr, ν_{max}/cm^{-1}): 3353 (OH), 2563 (SH), 1720 (CO_2), 1589 (CON).

4.3. *N*-(3-phenylpropanoyl)-L-Tyr-OH 3am

Colorless powder; mp: 164-167 °C; $[\alpha]^{28}_D$ = +16.8 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.46 (ddd, *J* = 1.6, 8.1, 8.1 Hz, 1H, CH_ACO), 2.46 (ddd, *J* = 1.6, 8.2, 8.2 Hz, 1H, CH_BCO) , 2.81 (dd, *J* = 8.1, 8.2 Hz, 2H, $CH_2C_6H_5$), 2.82 (dd, *J* = 8.8, 13.9 Hz, 1H, $CH_AC_6H_4$), 3.05 (dd, *J* = 5.1, 13.9 Hz, 1H, $CH_BC_6H_4$), 4.58 (dd, *J* = 5.1, 8.8 Hz, 1H, $CHCH_2C_6H_4$), 6.67, 6.95, (d, d, *J* = 8.6, 8.6 Hz, 2H, 2H, C_6H_4), 7.13-7.16, 7.21-7.25 (m, m, 3H, 2H, C_6H_5); ^{13}C NMR (100MHz, MeOD-d^4): δ 32.8, 37.7, 38.6, 55.3, 116.2, 127.2, 129.1, 129.4, 129.5, 131.3, 142.2, 157.3, 174.9, 175.1; HRMS (ESI-TOF): Calcd

for $C_{18}H_{19}NO_4Na$ $(M+Na)^+$: 336.1206, found: 336.1187; IR (KBr, ν_{max}/cm^{-1}): 3309 (ArOH), 3197 (OH), 1745 (CO_2), 15923(CON).

4.4. *N*-(3-phenylpropanoyl)-L-Glu-OH 3ae (see Section 1 of Chapter 1 in Experimental)[16a]

Colorless powder; ^{1}H NMR (400MHz, MeOD-d^4): δ 1.80-1.90 (m, 1H, CH_ACH), 2.07-2.15 (m, 1H, CH_BCH), 2.22-2.26 (m, 2H, CH_2CH$_2$CH), 2.54 (ddd, J = 1.4, 7.4, 7.4 Hz, 1H, CH$_A$CO), 2.54 (ddd, J = 1.4, 8.0, 8.0 Hz, 1H, CH$_B$CO), 2.91 (dd, J = 7.4, 8.0 Hz, 2H, CH_2C$_6$H$_5$), 4.40 (dd, J = 4.8, 9.8 Hz, 1H, CHCO), 7.15-7.18, 7.20-7.27 (m, m, 1H, 4H, C$_6$H$_5$).

4.5. *N*-(3-phenylpropanoyl)-L-Gln-OH 3af (see Section 1 of Chapter 1 in Experimental)[16a]

Colorless powder; ^{1}H NMR (400MHz, MeOD-d^4): δ 1.83-1.93 (m, 1H, CH_ACH), 2.07-2.24 (m, 3H, CH_BCH, CH_2CH$_2$CH), 2.55 (ddd, J = 1.5, 7.5, 7.5 Hz, 1H, CH$_A$CO), 2.55 (ddd, J = 1.5, 8.1, 8.1 Hz, 1H, CH$_B$CO), 2.92 (dd, J = 7.5, 8.1 Hz, 2H, CH_2C$_6$H$_5$), 4.37 (dd, J = 4.5, 9.4 Hz, 1H, CHCO), 7.14-7.18, 7.21-7.28 (m, m, 1H, 4H, C$_6$H$_5$).

5. Typical procedure for the amidation of Cbz-L-Phe-OH 5a using ethyl chloroformate

To a colorless solution of 150 mg (0.50 mmol) of Cbz-L-Phe-OH **5a** in 10 mL of THF were added at 0 °C 67 μL (0.70 mmol, 1.4 equiv) of ethyl chloroformate and 209 μL (1.5 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, a solution of 110 mg (0.75 mmol, 1.5 equiv) of L-Glu-OH **2e** and 63 mg (0.75 mmol, 1.5 equiv) of $NaHCO_3$ in 10 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and the resulted colorless clear solution was concentrated in vacuo. The residue was adjusted to pH 2 by addition of a 1.0 M aqueous solution of HCl. The colorless suspension was diluted with 10 mL of brine, extracted with 25 mL ×3 of a 4:1 mixture of EtOAc and MeOH, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 9:1 mixture of chloroform and MeOH containing 1% AcOH to afford 187 mg (87% yield) of Cbz-L-Phe-L-Glu-OH **6ae**.

5.1. Cbz-L-Phe-L-Ser-OH 6ak

Colorless powder; mp: 156-159 °C; $[\alpha]^{30}_D$ = +4.82 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.85 (dd, J = 9.8, 13.8 Hz, 1H, CH_AC$_6$H$_5$), 3.19 (dd, J = 4.7, 13.8 Hz, 1H, CH_BC$_6$H$_5$), 3.83 (dd, J = 3.8, 11.2 Hz, 1H, CH_AOH), 3.92 (dd, J = 4.5, 11.2 Hz, 1H, CH_BOH), 4.46 (dd, J = 4.7, 9.8 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.48 (dd, J = 3.8, 4.5 Hz, 1H, CHCH$_2$OH), 4.98 (d, J = 12.6 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 12.6 Hz, 1H, OCH_BC$_6$H$_5$), 7.19-7.33 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 39.2, 56.2, 57.8, 63.0, 67.6, 127.8, 128.7, 129.0, 129.5, 129.5, 130.4, 138.2, 138.6, 158.4, 173.1, 174.2; HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_2O_6$ $(M+H)^+$: 387.1551, found: 387.1539; IR (KBr, ν_{max}/cm^{-1}): 3298 (OH), 1732 (CO_2), 1647 (CON).

5.2. Cbz-L-Phe-L-Cys-OH 6al

Colorless powder; mp: 121-122 °C; $[\alpha]^{29}_{D}$ = –9.32 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 2.87 (dd, *J* = 9.5, 13.9 Hz, 1H, C*H*$_A$C$_6$H$_5$), 2.88 (dd, *J* = 4.6, 14.0 Hz, 1H, C*H*$_A$SH), 2.97 (dd, *J* = 4.6, 14.0 Hz, 1H, C*H*$_B$SH), 3.16 (dd, *J* = 5.2, 13.9 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.44 (dd, *J* = 5.2, 9.5 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.60 (dd, *J* =4.6, 4.6 Hz, 1H, C*H*CH$_2$SH), 5.01 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.17-7.33 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-*d*^{4}): *δ* 26.8, 39.0, 56.0, 57.8, 67.6, 127.8, 128.7, 129.0, 129.5, 130.4, 138.2, 138.6, 158.3, 172.8, 174.2; HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_2O_5S$ $(M+H)^+$: 403.1322, found: 403.1296; IR (KBr, ν_{max}/cm^{-1}): 3309 (OH), 2568 (SH), 1716 (CO_2), 1656(CON).

5.3. Cbz-L-Phe-L-Tyr-OH 6am

Colorless powder; mp: 189-190 °C; $[\alpha]^{28}_{D}$ = –4.90 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 2.77 (dd, *J* = 9.9, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_4$), 2.91 (dd, *J* = 8.0, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.09 (dd, *J* = 5.0, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_4$), 3.09 (dd, *J* = 5.3, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.36 (dd, *J* = 5.0, 9.9 Hz, 1H, C*H*CH$_2$C$_6$H$_4$), 4.58 (dd, *J* = 5.3, 8.0 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.97 (d, *J* = 12.6 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.03 (d, *J* = 12.6 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 6.68, 7.02 (d, d, *J* = 8.4, 8.4 Hz, 2H, 2H, C$_6$H$_4$), 7.16-7.32 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-*d*^{4}): *δ* 37.7, 39.0, 55.3, 57.8, 67.6, 116.3, 127.7, 128.7, 128.8, 129.0, 129.4, 129.5, 130.4, 131.5, 138.2, 138.6, 157.4, 173.9, 174.4; HRMS (ESI-TOF): Calcd for $C_{26}H_{27}N_2O_6$ $(M+H)^+$: 463.1864, found: 463.1862; IR (KBr, ν_{max}/cm^{-1}): 3433 (OH), 3334 (ArOH), 1734 (CO_2), 1684 (CON), 1653 (CON).

5.4. Cbz-L-Phe-L-Glu-OH 6ae (see Section 1 of Chapter 1 in Experimental)[16a]

Colorless powder; ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 1.89-1.99 (m, 1H, C*H*$_A$CH$_2$CO), 2.15-2.23 (m, 1H, C*H*$_B$CH$_2$CO), 2.39 (dd, *J* = 7.6, 7.8 Hz, 2H, CH$_2$CO), 2.84 (dd, *J* = 9.6, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.15 (dd, *J* = 5.0, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.40-4.47 (m, 2H, CH ×2), 4.99 (d, *J* = 13.0 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.03 (d, *J* = 13.0 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 7.18-7.33 (m, 10H, C$_6$H$_5$ ×2).

5.5. Cbz-L-Phe-L-Gln-OH 6af (see Section 1 of Chapter 1 in Experimental)[16a]

Colorless powder; ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 1.91-1.98 (m, 1H, C*H*$_A$CH$_2$CO), 2.16-2.35 (m, 3H, C*H*$_B$CH$_2$CO, CH$_2$CO), 2.85 (dd, *J* = 9.7, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.16 (dd, *J* = 4.9, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.38-4.43 (m, 2H, CH ×2), 4.99 (d, *J* = 12.7 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.03 (d, *J* = 12.7 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 7.17-7.33 (m, 10H, C$_6$H$_5$ ×2).

5.6. Cbz-D-Phe-L-Glu-OH 6a'e

Colorless powder; mp: 169-172 °C; $[\alpha]^{28}_{D}$ = +0.82 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): *δ* 1.79-1.88 (m, 1H, C*H*$_A$CH$_2$CO), 2.04-2.18 (m, 3H, C*H*$_B$CH$_2$CO, CH$_2$CO), 2.88 (dd, *J* = 8.8, 13.7 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.09 (dd, *J* = 6.6, 13.7 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.38 (dd, *J* = 6.6, 8.8 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.40-4.44 (m, 1H, C*H*CH$_2$CH$_2$), 5.00 (d, *J* = 12.4 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.05 (d, *J* = 12.4 Hz, 1H,

OCH_BC$_6$H$_5$), 7.19-7.33 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 27.8, 31.0, 39.5, 53.1, 58.0, 67.7, 127.9, 128.8, 129.0, 129.5, 129.6, 130.4, 138.2, 138.4, 158.2, 174.0, 174.6, 176.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{24}N_2O_7Na$ $(M+Na)^+$: 451.1476, found: 451.1488; IR (KBr, ν_{max}/cm^{-1}): 3299 (OH), 1716 (CO_2), 1670 (CON).

5.7. Cbz-L-Phe-L-Asp-OH 6an

Colorless powder; mp: 178-179 °C; $[\alpha]^{28}_D$ = –11.7 (*c* 1.01, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.84 (dd, *J* = 9.7, 13.9 Hz, 1H, CH_AC$_6$H$_5$), 2.84 (d, *J* = 5.6 Hz, 2H, CH$_2$CO), 3.18 (dd, *J* = 4.8, 13.9 Hz, 1H, CH_BC$_6$H$_5$), 4.42 (dd, *J* = 4.8, 9.7 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.73 (t, *J* = 5.6 Hz, 1H, C*H*CH$_2$CO), 4.97 (d, *J* = 12.7 Hz, 1H, OCH_AC$_6$H$_5$), 5.02 (d, *J* = 12.7 Hz, 1H, OCH_BC$_6$H$_5$), 7.18-7.33 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 36.8, 39.1, 50.2, 57.8, 67.6, 127.7, 128.7, 128.9, 129.5, 130.4, 138.2, 138.6, 158.3, 173.7, 173.9, 174.0; HRMS (ESI-TOF): Calcd for $C_{21}H_{23}N_2O_7$ $(M+H)^+$: 415.1500, found: 415.1486; IR (KBr, ν_{max}/cm^{-1}): 3305 (OH), 1716 (CO_2), 1695 (CON), 1653 (CON).

5.8. Cbz-L-Phe-L-Tyr(3-OH)-OH 6ao

Colorless powder; mp: 132-134 °C; $[\alpha]^{28}_D$ = –7.26 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.77 (dd, *J* = 9.8, 14.0 Hz, 1H, CH_AC$_6$H$_3$), 2.87 (dd, *J* = 7.7, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.03 (dd, *J* = 5.5, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 3.09 (dd, *J* = 4.9, 14.0 Hz, 1H, CH_BC$_6$H$_3$), 4.37 (dd, *J* = 4.9, 9.8 Hz, 1H, C*H*CH$_2$C$_6$H$_3$), 4.58 (dd, *J* = 5.5, 7.7 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.96 (d, *J* = 12.7 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, *J* = 12.7 Hz, 1H, OCH_BC$_6$H$_5$), 6.53, 6.65-6.67 (d, m, *J* = 8.0 Hz, 1H, 2H, C$_6$H$_3$), 7.16-7.32 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 37.9, 39.0, 55.2, 57.8, 67.7, 116.4, 117.5, 121.9, 127.7, 128.7, 128.9, 129.4, 129.5, 130.4, 138.2, 138.6, 145.3, 146.2, 158.3, 173.9, 174.5; HRMS (ESI-TOF): Calcd for $C_{26}H_{27}N_2O_7$ $(M+H)^+$: 479.1813, found: 479.1796; IR (KBr, ν_{max}/cm^{-1}): 3487 (ArOH), 3325 (ArOH), 3033 (OH), 1724 (CO_2), 1695 (CON), 1657 (CON).

5.9. Cbz-L-Phe-L-Tyr(3-I)-OH 6ap

Colorless powder; mp: 182-185 °C; $[\alpha]^{28}_D$ = –1.08 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 2.79 (dd, *J* = 9.7, 13.9 Hz, 1H, CH_AC$_6$H$_3$), 2.88 (dd, *J* = 7.9, 13.9 Hz, 1H, CH_AC$_6$H$_5$), 3.08 (dd, *J* = 5.1, 13.9 Hz, 1H, CH_BC$_6$H$_5$), 3.08 (dd, *J* = 5.1, 13.9 Hz, 1H, CH_BC$_6$H$_3$), 4.36 (dd, *J* = 5.1, 9.7 Hz, 1H, C*H*CH$_2$C$_6$H$_3$), 4.58 (dd, *J* = 5.1, 7.9 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.97 (d, *J* = 12.6 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, *J* = 12.6 Hz, 1H, OCH_BC$_6$H$_5$), 6.74, 7.03, 7.54 (d, d, s, *J* = 8.0 Hz, 1H, 1H, 1H C$_6$H$_3$), 7.17-7.32 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-d^4): δ 37.0, 39.2, 55.1, 57.9, 67.7, 84.6, 115.7, 127.7, 128.7, 128.9, 129.5, 129.5, 130.4, 131.0, 131.6, 138.2, 138.6, 141.0, 157.0, 174.0, 174.2; HRMS (ESI-TOF): Calcd for $C_{26}H_{26}IN_2O_6$ $(M+H)^+$: 589.0830, found: 589.0835; IR (KBr, ν_{max}/cm^{-1}): 3359 (ArOH), 3280 (OH), 1735 (CO_2), 1706 (CON) 1644 (CON), 1051 (ArI).

5.10. Cbz-L-Phe-L-Trp(5-OH)-OH 6aq

Colorless powder; mp: 107-110 °C; $[\alpha]^{28}_{D}$ = –14.2 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 2.72 (dd, *J* = 10.0, 14.0 Hz, 1H, CH_A-indole), 3.08 (dd, *J* = 4.7, 14.0 Hz, 1H, CH_B-indole), 3.14 (dd, *J* = 7.2, 14.1 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.28 (dd, *J* = 5.3, 14.1 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.37 (dd, *J* = 4.7, 10.0 Hz, 1H, C*H*CH$_2$-indole), 4.69 (dd, *J* = 5.3, 7,2 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.94 (d, *J* = 12.8 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.01 (d, *J* = 12.8 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 6.66, 6.95, 7.03, 7.13-7.29 (d, s, s, m, *J* = 8.6 Hz, 1H, 1H, 1H, 11H, indole, C$_6$H$_5$ ×2); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 28.6, 39.0, 54.7, 57.8, 67.6, 103.7, 110.0, 112.5, 112.8, 125.4, 127.7, 128.7, 128.9, 129.4, 129.5, 129.7, 130.3, 133.0, 138.2, 138.6, 151.3, 158.3, 174.0, 174.9; HRMS (ESI-TOF): Calcd for $C_{28}H_{28}N_3O_6$ $(M+H)^+$: 502.1973, found: 502.1957; IR (KBr, ν_{max}/cm^{-1}): 3566 (NH), 3396 (ArOH), 3324 (OH), 1704 (CO_2), 1654 (CON).

5.11. Cbz-L-Ala-L-Ser-OH 6ek

Colorless powder; mp: 300 °C<; $[\alpha]^{28}_{D}$ = +33.9 (*c* 1.00, DMSO); ^{1}H NMR (400MHz, DMSO-*d*^{6}): δ 1.22 (d, *J* = 7.3 Hz, 3H, CH_3), 3.40 (dd, *J* = 6.2, 9.9 Hz, 1H, C*H*$_A$OH), 3.60 (dd, *J* = 5.3, 9.9 Hz, 1H, C*H*$_B$OH), 3.79 (ddd, *J* = 5.3, 6.2, 6.2 Hz, 1H, C*H*CH$_2$OH), 4.04 (dd, *J* = 7.3, 7.6 Hz, 1H, C*H*CH$_3$), 5.01 (d, *J* = 12.6 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.06 (d, *J* = 12.6 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 5.34 (br, 1H, OH), 7.31-7.38 (m, 5H, C$_6$H$_5$), 7.49 (d, *J* = 6.2 Hz, 1H, N*H*CHCH$_2$), 7.60 (d, *J* = 7.6 Hz, 1H, N*H*CHCH$_3$); ^{13}C NMR (100MHz, DMSO-*d*^{6}): δ 18.3, 50.4, 55.2, 62.5, 65.4, 127.7, 127.8, 128.4, 137.0, 155.7, 171.7, 173.9; HRMS (ESI-TOF): Calcd for $C_{14}H_{18}N_2O_6Na$ $(M+Na)^+$: 333.1057, found: 333.1073; IR (KBr, ν_{max}/cm^{-1}): 3354 (OH), 3320 (OH), 1693 (CO_2), 1666 (CON).

5.12. Cbz-L-Ala-L-Cys-OH 6el

Colorless powder; mp: 164-166 °C; $[\alpha]^{27}_{D}$ = –11.9 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 1.36 (d, *J* = 7.2 Hz, 3H, CH_3), 2.90 (dd, *J* = 5.8, 14.0 Hz, 1H, C*H*$_A$SH), 2.98 (dd, *J* = 4.6, 14.0 Hz, 1H, C*H*$_B$SH), 4.21 (q, *J* = 7.2 Hz, 1H, C*H*CH$_3$), 4.61 (dd, *J* = 4.6, 5.8 Hz, 1H, C*H*CH$_2$SH), 5.09 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.26-7.37 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 18.2, 26.8, 52.0, 55.9, 67.7, 128.9, 129.1, 129.5, 138.2, 158.3, 173.0, 175.6; HRMS (ESI-TOF): Calcd for $C_{14}H_{18}N_2O_5SNa$ $(M+Na)^+$: 349.0829, found: 349.0847; IR (KBr, ν_{max}/cm^{-1}): 3346 (OH), 2565 (SH), 1733 (CO_2), 1637 (CON).

5.13. Cbz-L-Ala-L-Tyr-OH 6em

Colorless powder; mp: 148-152 °C; $[\alpha]^{28}_{D}$ = +10.6 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 1.28 (d, *J* = 7.1 Hz, 3H, CH_3), 2.93 (dd, *J* = 7.5, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_4$), 3.07 (dd, *J* = 5.4, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_4$), 4.14 (q, *J* = 7.1 Hz, 1H, C*H*CH$_3$), 4.57 (dd, *J* = 5.4, 7.5 Hz, 1H, C*H*CH$_2$C$_6$H$_4$), 5.05 (d, *J* = 12.5 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.09 (d, *J* = 12.5 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 6.68, 7.02 (d, d, *J* = 8.3, 8.3 Hz, 2H, 2H, C$_6$H$_4$), 7.28-7.35 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 18.2, 37.6, 51.9, 55.2, 67.8, 116.2, 128.8, 128.9, 129.1, 129.5, 131.5, 138.2, 157.4, 158.2, 174.6, 175.3; HRMS (ESI-TOF):

Calcd for $C_{20}H_{22}N_2O_6Na$ $(M+Na)^+$: 409.1370, found: 409.1386; IR (KBr, ν_{max}/cm^{-1}): 3401 (ArOH), 3300 (OH), 1733 (CO_2), 1687 (CON), 1653 (CON).

5.14. Cbz-L-Val-L-Ser-OH 6fk

Colorless powder; mp: 172-175 °C; $[\alpha]^{28}_D$ = –4.24 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 0.94 (d, *J* = 6.8 Hz, 3H, CH_3), 0.99 (d, *J* = 6.8 Hz, 3H, CH_3), 2.05-2.14 (m, 1H, C*H*$(CH_3)_2$), 3.82 (dd, *J* = 4.2, 11.3 Hz, 1H, CH_AOH), 3.91 (dd, *J* = 4.5, 11.3 Hz, 1H, CH_BOH), 4.03 (d, *J* = 6.8 Hz, 1H, C*H*CH$(CH_3)_2$), 4.49 (dd, *J* = 4.2, 4.5 Hz, 1H, C*H*CH_2OH), 5.10 (s, 2H, OC$H_2C_6H_5$), 7.26-7.38 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 18.4, 19.8, 32.2, 56.1, 62.0, 63.1, 67.8, 128.9, 129.1, 129.5, 138.3, 158.7, 173.2, 174.3; HRMS (ESI-TOF): Calcd for $C_{16}H_{22}N_2O_6Na$ $(M+Na)^+$: 361.1370, found: 361.1388; IR (KBr, ν_{max}/cm^{-1}): 3546 (OH), 3307 (OH), 1733 (CO_2), 1645 (CON).

5.15. Cbz-L-Val-L-Cys-OH 6fl

Colorless powder; mp: 152-154 °C; $[\alpha]^{28}_D$ = –11.2 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 0.96 (d, *J* = 7.0 Hz, 3H, CH_3), 0.98 (d, *J* = 7.0 Hz, 3H, CH_3), 2.03-2.12 (m, 1H, C*H*$(CH_3)_2$), 2.88 (dd, *J* = 6.4, 13.9 Hz, 1H, CH_ASH), 2.96 (dd, *J* = 4.6, 13.9 Hz, 1H, CH_BSH), 3.99 (d, *J* = 7.0 Hz, 1H, C*H*CH$(CH_3)_2$), 4.62 (dd, *J* = 4.6, 6.4 Hz, 1H, C*H*CH_2SH), 5.09 (s, 2H, OC$H_2C_6H_5$), 7.26-7.37 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 18.6, 19.8, 26.7, 31.9, 55.9, 62.2, 67.8, 128.9, 129.0, 129.5, 138.3, 158.7, 172.8, 174.4; HRMS (ESI-TOF): Calcd for $C_{16}H_{22}N_2O_5SNa$ $(M+Na)^+$: 377.1142, found: 372.1144; IR (KBr, ν_{max}/cm^{-1}): 3356 (OH), 2575 (SH), 1736 (CO_2), 1643 (CON).

5.16. Cbz-L-Val-L-Tyr-OH 6fm

Colorless powder; mp: 156-157 °C; $[\alpha]^{27}_D$ = –4.70 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 0.88 (d, *J* = 7.1 Hz, 3H, CH_3), 0.89 (d, *J* = 7.1 Hz, 3H, CH_3), 1.96-2.01 (m, 1H, C*H*$(CH_3)_2$), 2.89 (dd, *J* = 8.2, 13.9 Hz, 1H, CH_AC$_6$H$_4$), 3.08 (dd, *J* = 5.3, 13.9 Hz, 1H, CH_BC$_6$H$_4$), 3.91 (d, *J* = 7.1 Hz, 1H, C*H*CH$(CH_3)_2$), 4.60 (dd, *J* = 5.3, 8.2 Hz, 1H, C*H*CH_2C$_6$H$_4$), 5.06 (d, *J* = 12.5 Hz, 1H, OCH_AC$_6$H$_5$), 5.11 (d, *J* = 12.5 Hz, 1H, OCH_BC$_6$H$_5$), 6.67, 7.03 (d, d, *J* = 8.4, 8.4 Hz, 2H, 2H, C$_6$H$_4$), 7.26-7.37 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, MeOD-*d*^{4}): δ 18.6, 19.7, 32.0, 37.8, 55.3, 62.1, 67.8, 116.2, 128.9, 129.0, 129.1, 129.6, 131.4, 138.3, 157.4, 158.6, 174.0, 174.6; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_6Na$ $(M+Na)^+$: 437.1683, found: 437.1685; IR (KBr, ν_{max}/cm^{-1}): 3301 (ArOH), 3307 (OH), 1716 (CO_2), 1695 (CON), 1654 (CON).

5.17. Cbz-L-Met-L-Ser-OH 6hk

Colorless powder; mp: 158-161 °C; $[\alpha]^{28}_D$ = +8.16 (*c* 1.00, DMSO); ^{1}H NMR (400MHz, MeOD-*d*^{4}): δ 1.87-1.96 (m, 1H, C$H_A$$CH_2$S), 2.04-2.13 (m, 1H, C$H_B$$CH_2$S), 2.08 (s, 3H, CH_3), 2.51-2.63 (m, 2H, CH_2S), 3.83 (dd, *J* = 3.9, 11.3 Hz, 1H, CH_AOH), 3.93 (dd, *J* = 4.3, 11.3 Hz, 1H, CH_BOH), 4.32 (dd, *J* = 5.3, 8.6 Hz, 1H, C*H*$CH_2$$CH_2$), 4.48 (dd, *J* = 3.9, 4.3 Hz, 1H, C*H*CH_2OH), 5.10 (s, 2H, OC$H_2C_6H_5$),

7.26-7.38 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, MeOD-d^4): δ 15.2, 31.1, 33.0, 55.5, 56.2, 62.9, 67.8, 128.9, 129.1, 129.5, 138.2, 158.5, 173.2, 174.4; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_2O_6S$ $(M+H)^+$: 371.1271, found: 371.1262; IR (KBr, ν_{max}/cm^{-1}): 3289 (OH), 1743 (CO_2), 1722 (CON), 1680 (CON).

5.18. Cbz-L-Met-L-Cys-OH 6hl

Colorless powder; mp: 142-144 °C; $[\alpha]^{28}_D$ = –7.03 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.88-1.97 (m, 1H, CH_ACH$_2$S), 2.03-2.12 (m, 1H, CH_BCH$_2$S), 2.07 (s, 3H, CH$_3$), 2.50-2.63 (m, 2H, CH$_2$CH_2S), 2.90 (dd, *J* = 6.0, 13.8 Hz, 1H, CH_ASH), 2.98 (dd, *J* = 4.5, 13.8 Hz, 1H, CH_BSH), 4.30 (dd, *J* = 5.5, 8.5 Hz, 1H, C*H*CH$_2$CH$_2$), 4.62 (dd, *J* = 4.5, 6.0 Hz, 1H, C*H*CH$_2$SH), 5.10 (s, 2H, OCH_2C$_6$H$_5$), 7.27-7.37 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, MeOD-d^4): δ 15.3, 26.7, 31.1, 32.8, 55.5, 55.9, 62.9, 67.8, 128.9, 129.1, 129.5, 138.2, 158.5, 172.8, 174.5; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_2O_5S$ $(M+H)^+$: 387.1043, found: 387.1062; IR (KBr, ν_{max}/cm^{-1}): 3313 (OH), 2584 (SH), 1736 (CO_2), 1635 (CON).

5.19. Cbz-L-Met-L-Tyr-OH 6hm

Colorless powder; mp: 133-135 °C; $[\alpha]^{28}_D$ = +0.26 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.78-1.87 (m, 1H, CH_ACH$_2$S), 1.93-2.04 (m, 1H, CH_BCH$_2$S), 2.04 (s, 3H, CH$_3$), 2.41-2.54 (m, 2H, CH$_2$S), 2.92 (dd, *J* = 8.0, 14.0 Hz, 1H, CH_AC$_6$H$_4$), 3.09 (dd, *J* = 5.1, 14.0 Hz, 1H, CH_BC$_6$H$_4$), 4.23 (dd, *J* = 5.7, 8.7 Hz, 1H, C*H*CH$_2$CH$_2$), 4.59 (dd, *J* = 5.1, 8.0 Hz, 1H, C*H*CH$_2$C$_6$H$_4$), 5.06 (d, *J* = 12.4 Hz, 1H, OCH_AC$_6$H$_5$), 5.10 (d, *J* = 12.4 Hz, 1H, OCH_BC$_6$H$_5$), 6.68, 7.03 (d, d, *J* = 8.4, 8.4 Hz, 2H, 2H, C$_6$H$_4$), 7.28-7.35 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, MeOD-d^4): δ 15.2, 31.0, 32.8, 37.5, 55.2, 55.5, 67.8, 116.3, 128.8, 128.9, 129.1, 129.5, 131.4, 138.2, 157.4, 158.4, 174.1, 174.5; HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_2O_6S$ $(M+H)^+$: 447.1584, found: 447.1569; IR (KBr, ν_{max}/cm^{-1}): 3302 (OH), 1716 (CO_2), 1691 (CON), 1649 (CON).

5.20. *N*-Boc-*O*-Bn-L-Ser-L-Glu-OH 6je

Colorless sticky oil; $[\alpha]^{19}_D$ = –1.46 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.45 (s, 9H, CH$_3$ ×3), 1.89-1.98 (m, 1H, CH_ACH$_2$CO), 2.15-2.25 (m, 1H, CH_BCH$_2$CO), 2.36-2.42 (m, 2H, CH$_2$CO), 3.67 (dd, *J* = 4.5, 9.8 Hz, 1H, CH_AOCH$_2$C$_6$H$_5$), 3.74 (dd, *J* = 5.2, 9.8 Hz, 1H, CH_BOCH$_2$C$_6$H$_5$), 4.30 (dd, *J* = 4.5, 5.2 Hz, 1H, C*H*CH$_2$O), 4.47-4.50 (m, 1H, C*H*CH$_2$CH$_2$), 4.52 (d, *J* = 11.5 Hz, 1H, OCH_AC$_6$H$_5$), 4.55 (d, *J* = 11.5 Hz, 1H, OCH_BC$_6$H$_5$), 7.26-7.33 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, MeOD-d^4): δ 28.2, 28.7, 31.0, 53.0, 56.2, 71.1, 74.3, 81.0, 128.8, 129.0, 129.5, 139.3, 157.8, 172.9, 174.4, 176.4; HRMS (ESI-TOF): Calcd for $C_{20}H_{28}N_2O_8Na$ $(M+Na)^+$: 447.1743, found: 447.1756; IR (KBr, ν_{max}/cm^{-1}): 3329 (OH), 1716 (CO_2), 1652 (CON).

5.21. N^{α}-Boc-N^{ε}-Cbz-L-Lys-L-Glu-OH 6ke

Colorless sticky oil; $[\alpha]^{18}_D$ = –11.4 (*c* 1.00, MeOH); ^{1}H NMR (400MHz, MeOD-d^4): δ 1.39-1.55 (m,

13H, CH_3 ×3, CH_2(CH_2)$_2$N, C$H_2$$CH_2$N), 1.56-1.63 (m, 1H, C$H_A$($CH_2$)$_3$N), 1.70-1.81 (m, 1H, C$H_B$($CH_2$)$_3$N), 1.91-1.98 (m, 1H, C$H_A$$CH_2$CO), 2.14-2.23 (m, 1H, C$H_B$$CH_2$CO), 2.38-2.42 (m, 2H, CH_2CO), 3.09-3.13 (m, 2H, CH_2N), 3.99-4.03 (m, 1H, CH(CH_2)$_4$N), 4.42-4.44 (m, 1H, C$H$$CH_2$$CH_2$CO), 5.06 (s, 2H, OC$H_2$$C_6H_5$), 7.28-7.34 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, MeOD-d^4): δ 24.1, 28.0, 28.8, 30.5, 31.1, 32.9, 41.5, 52.9, 56.0, 67.4, 81.0, 128.8, 129.0, 129.5, 138.5, 157.9, 159.0, 174.6, 175.4, 176.4; HRMS (ESI-TOF): Calcd for $C_{24}H_{35}N_3O_9Na$ $(M+Na)^+$: 532.2276, found: 532.2278; IR (KBr, ν_{max}/cm^{-1}): 3329 (OH), 1716 (CO_2), 1685 (CON), 1655 (CON).

6. Typical procedure for the amidation of Cbz-L-Phe-OH 5a in a glam scale

To a colorless solution of 1.50 g (5.0 mmol) of Cbz-L-Phe-OH **5a** in 100 mL of THF were added at 0 °C 0.67 mL (7.0 mmol, 1.4 equiv) of ethyl chloroformate and 2.09 mL (15 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, a solution of 1.10 g (7.5 mmol, 1.5 equiv) of L-Glu-OH **2e** and 0.63 g (7.5 mmol, 1.5 equiv) of $NaHCO_3$ in 100 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and the resulted colorless clear solution was concentrated in vacuo. The residue was adjusted to pH 2 by addition of a 1.0 M aqueous solution of HCl. The colorless suspension was diluted with 100 mL of brine, extracted with 200 mL of a 9:1 mixture of EtOAc and MeOH. The aqueous layer was extracted with 100 mL ×2 of a 9:1 mixture of EtOAc and MeOH. The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was recrystallized from 50 mL of a 1:4 mixture of toluene and hexane to afford a colorless solid, followed by recrystallization from 20 mL of a 4:1 mixture of EtOAc and hexane to afford 1.74 g (81% yield) of Cbz-L-Phe-L-Glu-OH **6ae**.

Section 3. Amidation of carboxylic acids via mixed carbonic carboxylic anhydrides and its application to synthesis of antidepressant (1*S*,2*R*)-tranylcypromine

7. Typical procedure for the primary amidation of 3-phenylpropanoic acid 1a with NH_4Cl

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 ethyl chloroformate and 209 μL (1.5 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, 0.75 ml of a 1.0 M aqueous solution of NH_4Cl (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_2O 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 $MgSO_4$. The crude product was chromatographed on silica gel with EtOAc to afford 72 mg (96% yield) of 3-phenylpropanamide **9a**.

7.1. 3-Phenylpropanamide 9a

Colorless solid; mp: 92-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (t, J = 8.0 Hz, 2H, CH_2C$_6$H$_5$), 2.98 (t, J = 8.0 Hz, 2H, CH_2CO), 5.29 (br, 2H, NH_2), 7.20-7.23, 7.26-7.32 (m, m, 3H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4, 37.5, 126.3, 128.3, 128.6, 140.8, 174.6; HRMS (ESI-TOF): Calcd for $C_9H_{11}NONa$ $(M+Na)^+$: 172.0733, found: 172.0711; IR (KBr, ν_{max}/cm^{-1}) = 3394 (CONH), 3186 (CONH), 1646 (CON), 1628 (CON).

7.2. Cinnamamide 9b

Colorless powder; mp: 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (br, 2H, NH_2), 6.46 (d, J = 15.7 Hz, 1H, CHCO), 7.37-7.40, 7.51-7.54 (m, m, 3H, 2H, C_6H_5), 7.66 (d, J = 15.7 Hz, 1H, CHC$_6$H$_5$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.7, 128.1, 129.0, 130.1, 134.6, 142.6, 167.8; HRMS (ESI-TOF): Calcd for C_9H_9NONa $(M+Na)^+$: 170.0576, found: 170.0556; IR (KBr, ν_{max}/cm^{-1}) = 3373 (CONH), 3168 (CONH), 1662 (CON).

7.3. 4-Methoxycinnamamide 9c

Colorless powder; mp: 198-201 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ 3.82 (s, 3H, CH_3), 6.49 (d, J = 15.9 Hz, 1H, CHCO), 7.50 (d, J = 15.9 Hz, 1H, CHC$_6$H$_5$), 6.94, 7.51 (d, d, J = 8.7, 8.7 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, MeOD-d^4): δ 55.9, 115.4, 118.8, 128.8, 130.6, 142.6, 162.7, 171.5; HRMS (ESI-TOF): Calcd for $C_{10}H_{11}NO_2Na$ $(M+Na)^+$: 200.0682, found: 200.0673; IR (KBr, ν_{max}/cm^{-1}) = 3361 (CONH), 3166 (CONH), 1684 (CON), 1662 (CON).

7.4. Pivalamide 9d

Colorless solid; mp: 105-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 9H, CH_3 ×3), 5.21 (br, 1H, NH_A), 5.59 (br, 1H, NH_B); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 38.7, 181.6; HRMS (ESI-TOF): Calcd for $C_5H_{11}NONa$ $(M+Na)^+$: 124.0733, found: 124.0723; IR (KBr, ν_{max}/cm^{-1}) = 3398 (CONH), 3205 (CONH), 2960 (CH_3), 1653 (CON), 1624 (CON).

7.5. Benzamide 9e

Colorless powder; mp: 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 (br, 1H, NH_A), 6.08 (br, 1H, NH_B), 7.44-7.49, 7.52-7.57, 7.81-7.84 (m, m, m, 2H, 1H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.4, 128.6, 132.0, 133.4, 169.4; HRMS (ESI-TOF): Calcd for C_7H_7NONa $(M+Na)^+$: 144.0420, found: 144.0411; IR (KBr, ν_{max}/cm^{-1}) = 3367 (CONH), 3170 (CONH), 1658 (CON), 1623 (CON).

7.6. 4-Nitrobenzamide 9f

Colorless powder; mp: 202-204 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ 8.07, 8.32 (d, d, J = 9.0, 9.0 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, MeOD-d^4): δ 124.6, 130.0, 140.9, 151.2, 170.2; HRMS (ESI-

TOF): Calcd for $C_7H_6N_2O_3Na$ $(M+Na)^+$: 189.0271, found: 189.0280; IR (KBr, ν_{max}/cm^{-1}) = 3467 (CONH), 1664 (CON), 1602 (CON), 1525 (NO_2), 1342 (NO_2).

7.7. 2-Acetoxybenzamide 9g

Colorless powder; mp: 130-132 °C; ^1H NMR (400 MHz, $CDCl_3$) : δ 2.36 (s, 3H, CH_3), 5.75 (br, 1H, NH_A), 6.27 (br, 1H, NH_B), 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_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 123.3, 126.3, 127.2, 130.1, 132.4, 148.2, 167.5, 169.1; HRMS (ESI-TOF): Calcd for $C_9H_9NO_3Na$ $(M+Na)^+$: 202.0475, found: 202.0496; IR (KBr, ν_{max}/cm^{-1}) = 3392 (CONH), 3167 (CONH), 1741 (CO_2), 1678 (CON), 1628 (CON).

7.8. 4-Methoxybenzamide 9h

Coloress solid; mp: 139-142 °C; ^1H NMR (400 MHz, MeOD-d^4): δ 3.86 (s, 3H, CH_3), 6.97, 7.84 (d, d, J = 9.0, 9.0 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, MeOD-d^4): δ 56.0, 114.7, 127.0, 130.7, 164.2, 172.1; HRMS (ESI-TOF): Calcd for $C_9H_9NO_3Na$ $(M+Na)^+$: 202.0475, found: 202.0496; IR (KBr, ν_{max}/cm^{-1}): 3392 (CONH), 3168 (CONH), 1646 (CON), 1618 (CON).

7.9. Picolinamide 9i

Colorless solid; mp: 95-97 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 5.55 (br, 1H, NH_A), 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_B); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.4, 126.5, 137.3, 148.3, 149.6, 167.0; HRMS (ESI-TOF): Calcd for $C_6H_6N_2ONa$ $(M+Na)^+$: 145.0372, found: 145.0370; IR (KBr, ν_{max}/cm^{-1}) = 3417 (CONH), 3182 (CONH), 1662 (CON).

7.10. Nicotinamide 9j

Colorless solid; mp: 122-124 °C; ^1H NMR (400 MHz, DMSO-d^6): δ 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, 1H, pyridyl), 7.61 (br, 1H, NH_A), 8.16 (br, 1H, NH_B); ^{13}C NMR (100 MHz, DMSO-d^6): δ 123.3, 129.6, 135.1, 148.6, 151.8, 166.4; HRMS (ESI-TOF): Calcd for $C_6H_6N_2ONa$ $(M+Na)^+$: 145.0372, found: 145.0370; IR (KBr, ν_{max}/cm^{-1}) = 3367 (CONH), 3159 (CONH), 1699 (CON), 1682 (CON).

7.11. Isonicotinamide 9k

Colorless solid; mp: 151-153 °C; ^1H NMR (400 MHz, DMSO-d^6): δ 7.73 (br, 1H, NH_A), 7.76, 8.72 (d, d, J = 6.0, 6.0 Hz, 2H, 2H, pyridyl), 8.25 (br, 1H, NH_B); ^{13}C NMR (100 MHz, DMSO-d^6): δ 121.3, 141.2, 150.1, 166.2; HRMS (ESI-TOF): Calcd for $C_6H_7N_2O$ $(M+H)^+$: 123.0553, found: 123.0529; IR (KBr, ν_{max}/cm^{-1}) = 3334 (CONH), 1684 (CON), 1624 (CON).

7.12. Furan-2-carboxamide 9l

Colorless powder; mp: 143-144 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 5.82 (br, 1H, NH_A), 6.26 (br, 1H,

NH_B), 6.53, 7.17, 7.47 (dd, d, d, J = 1.8, 3.5, 3.5, 1.8 Hz, 1H, 1H, 1H, furanyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.3, 115.1, 144.4, 147.5, 160.4; HRMS (ESI-TOF): Calcd for $C_5H_5NO_2Na$ $(M+Na)^+$: 134.0212, found: 134.0209; IR (KBr, ν_{max}/cm^{-1}) = 3352 (CONH), 3163 (CONH), 1664 (CON), 1624 (CON).

7.13. Furan-3-carboxamide 9m

Colorless powder; mp: 162-164 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ 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, 1H, furanyl); ^{13}C NMR (100 MHz, MeOD-d^4): δ 110.0, 123.4, 145.3, 147.1, 167.6; HRMS (ESI-TOF): Calcd for $C_5H_5NO_2Na$ $(M+Na)^+$: 134.0212, found: 134.0209; IR (KBr, ν_{max}/cm^{-1}) = 3309 (CONH), 1621 (CON).

7.14. Thiophene-2-carboxamide 9n

Colorless solid; mp: 143-145 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ 7.12, 7.66, 7.70 (dd, d, d, J = 3.9, 5.0, 5.0, 3.9 Hz, 1H, 1H 1H, thiophenyl); ^{13}C NMR (100 MHz, MeOD-d^4): δ 128.9, 130.6, 132.2, 139.9, 166.7; HRMS (ESI-TOF): Calcd for $C_5H_5NO_2Na$ $(M+Na)^+$: 134.0212, found: 134.0209; IR (KBr, ν_{max}/cm^{-1}) = 3342 (CONH), 1612 (CON).

7.15. Thiophene-3-carboxamide 9o

Colorless powder; mp: 178-180 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ 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, 1H, thiophenyl); ^{13}C NMR (100 MHz, MeOD-d^4): δ 127.5, 127.9, 130.6, 138.1, 167.8; HRMS (ESI-TOF): Calcd for C_5H_5NOSNa $(M+Na)^+$: 149.9984, found: 150.0010; IR (KBr, ν_{max}/cm^{-1}) = 3359 (CONH), 1622 (CON).

8. Typical procedure for the primary amidation of Cbz-L-Phe-OH 5a with NH_4Cl

To a colorless solution of 150 mg (0.50 mmol) of Cbz-L-Phe-OH **5a** in 10 mL of THF were added at 0 °C 67 μL (0.70 mmol, 1.4 equiv) of ethyl chloroformate and 209 μL (1.5 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, 0.75 ml of a 1.0 M aqueous solution of NH_4Cl (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_2O 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 $MgSO_4$. The crude product was chromatographed on silica gel with EtOAc to afford 129 mg (86% yield) of Cbz-L-Phe-NH_2 **10a**.

8.1. Cbz-L-Phe-NH_2 10a

Colorless solid; 97% ee; mp: 163-164 °C; $[\alpha]^{25}_D$ = –8.2 (c 1.01, MeOH); ^{1}H NMR (400 MHz, DMSO-d^6): δ 2.73 (dd, J = 10.5, 13.6 Hz, 1H, CHCH_AC$_6$H$_5$), 2.99 (dd, J = 4.1, 13.6 Hz, 1H, CHCH_BC$_6$H$_5$), 4.17 (ddd, J = 4.1, 8.7, 10.5 Hz, 1H, CH), 4.94 (s, 2H, OCH_2C$_6$H$_5$), 7.08 (br, 1H, $CONH_A$), 7.19-7.35

(m, 10H, C_6H_5 ×2), 7.43 (d, *J* = 8.7 Hz, 1H, N*H*CH), 7.48 (br, 1H, $CONH_B$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): *δ* 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; HRMS (ESI-TOF): Calcd for $C_{17}H_{18}N_2O_3Na$ $(M+Na)^+$: 321.1210, found: 321.1290; IR (KBr, ν_{max}/cm^{-1}) = 3419 (CONH), 3318 (CONH), 3199 (CONH), 1691 (CON), 1657 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 23.0 min.

8.2. Cbz-D-Phe-NH_2 10a'

Colorless solid; >99% ee; $[\alpha]^{23}_D$ = +7.9 (*c* 1.00, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 18.2 min.

8.3. Boc-L-Phe-NH_2 10b

Colorless solid; >99% ee; mp: 142-144 ºC; $[\alpha]^{23}_D$ = +12.9 (*c* 1.00, MeOH); ^1H NMR (400 MHz, DMSO-*d*^{6}): *δ* 1.30 (s, 9H, CH_3 ×3), 2.72 (dd, *J* = 10.2, 13.8 Hz, 1H, C*H*$_A$$C_6H_5$), 2.95 (dd, *J* = 4.4, 13.8 Hz, 1H, C*H*$_B$$C_6H_5$), 4.08 (ddd, *J* = 4.4, 8.8, 10.2 Hz, 1H, CH), 6.81 (d, *J* = 8.8 Hz, 1H, N*H*CH), 7.01 (br, 1H, $CONH_A$), 7.16-7.21, 7.24-7.28 (m, m, 1H, 4H, C_6H_5), 7.37 (br, 1H, $CONH_B$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): *δ* 28.1, 37.5, 55.6, 77.9, 126.1, 128.0, 129.2, 138.3, 155.2, 173.6; HRMS (ESI-TOF): Calcd for $C_{14}H_{20}N_2O_3Na$ $(M+Na)^+$: 287.1366, found: 287.1351; IR (KBr, ν_{max}/cm^{-1}) = 3390 (CONH), 3346 (CONH), 3192 (CONH), 1684 (CON), 1660 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 95/5): T_r 20.7 min.

8.4. Boc-D-Phe-NH_2 10b'

Colorless solid; >99% ee; $[\alpha]^{25}_D$ = –14.2 (*c* 0.99, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 95/5): T_r 18.3 min.

8.5. Fmoc-L-Phe-NH_2 10c

Colorless solid; >99% ee; mp: 221-224 °C; $[\alpha]^{26}_D$ = –8.4 (*c* 1.01, DMSO); ^1H NMR (400 MHz, DMSO-*d*^{6}): *δ* 2.78 (dd, *J* = 10.6, 13.6 Hz, 1H, C*H*$_A$$C_6H_5$), 3.00 (dd, *J* = 4.2, 13.6 Hz, 1H, C*H*$_B$$C_6H_5$), 4.11-4.20 (m, 4H, C*H*$CH_2C_6H_5$, CH_2O, C*H*CH_2O), 7.08 (br, 1H, $CONH_A$), 7.45 (br, 1H, $CONH_B$), 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, N*H*CH, C_6H_5, fluorenyl); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): *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; HRMS (ESI-TOF): Calcd for $C_{24}H_{22}N_2O_3Na$ $(M+Na)^+$: 409.1523, found: 409.1519; IR (KBr, ν_{max}/cm^{-1}) = 3375 (CONH), 3321 (CONH), 3207 (CONH), 1682 (CON), 1645 (CON), 1623 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 22.2 min.

8.6. Fmoc-D-Phe-NH_2 10c'

Colorless solid; >99% ee; $[\alpha]^{26}_D$ = +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.

8.7. Cbz-L-Val-NH_2 10f

Colorless solid; >99% ee; mp: 172-175 °C; $[\alpha]^{25}_D$ = +17.8 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 0.83 (d, *J* = 6.8 Hz, 3H, CH_3), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 1.94 (ddd, *J* = 6.7, 6.8, 6.8 Hz, 1H, C*H*$(CH_3)_2$), 3.80 (dd, *J* = 6.7, 8.8 Hz, 1H, CHCO), 5.03 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.03 (br, 1H, $CONH_A$), 7.16 (d, *J* = 8.8 Hz, 1H, N*H*CH), 7.29-7.39 (m, 6H, $CONH_B$, C_6H_5); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ 18.0, 19.3, 30.1, 60.0, 65.3, 127.6, 127.7, 128.3, 137.1, 156.1, 173.2; HRMS (ESI-TOF): Calcd for $C_{13}H_{18}N_2O_3Na$ $(M+Na)^+$: 273.1210, found: 273.1193; IR (KBr, ν_{max}/cm^{-1}): 3381 (CONH), 3319 (CONH), 3203 (CONH), 1654 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 11.5 min.

8.8. Cbz-D-Val-NH_2 10f'

Colorless solid; >99% ee; $[\alpha]^{26}_D$ = –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.

8.9. Boc-L-Val-NH_2 10l

Colorless solid; >99% ee; mp: 149-152 °C; $[\alpha]^{30}_D$ = –2.4 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CH), 0.99 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CH), 1.45 (s, 9H, $(CH_3)_3C$), 2.16 (ddd, *J* = 6.7, 6.8, 6.8 Hz, 1H, C*H*$(CH_3)_2$), 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_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 19.3, 28.3, 30.8, 59.5, 79.9, 156.0, 174.4; HRMS (ESI-TOF): Calcd for $C_{10}H_{20}N_2O_3Na$ $(M+Na)^+$: 239.1366, found: 239.1340; IR (KBr, ν_{max}/cm^{-1}): 3386 (CONH), 3345 (CONH), 3205 (CONH), 1680 (CON), 1641 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5): T_r 9.4 min.

8.10. Boc-D-Val-NH_2 10l'

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

8.11. Fmoc-L-Val-NH_2 10m

Colorless solid; >99% ee; mp: 204-206 °C; $[\alpha]^{25}_D$ = –3.0 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 0.87 (d, *J* = 7.0 Hz, 3H, CH_3), 1.96 (ddd, *J* = 6.8, 7.0, 8.2 Hz, 1H, C*H*$(CH_3)_2$), 3.80 (dd, *J* = 7.6, 8.2 Hz, 1H, CHCO), 4.22-4.29 (m, 3H, C*H*CH$_2$O, CHC*H*$_2$O), 7.04 (br, 1H, $CONH_A$), 7.29-7.44, 7.75, 7.90 (m, d, d, *J* = 5.9, 7.5 Hz, 6H, 2H, 2H, N*H*CH, $CONH_B$, fluorenyl); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): 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; HRMS (ESI-TOF): Calcd for $C_{20}H_{22}N_2O_3Na$ $(M+Na)^+$: 361.1523, found: 361.1509; IR (KBr, ν_{max}/cm^{-1}): 3369 (CONH), 3311 (CONH), 3197 (CONH), 1689

(CON), 1660 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 20.7 min.

8.12. Fmoc-D-Val-NH_2 10m'

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

8.13. Cbz-L-Met-NH_2 10h

Colorless solid; >99% ee; mp: 108-112 °C; $[\alpha]^{30}_D$ = –14.9 (*c* 1.01, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96-2.05 (m, 1H, CH_ACH), 2.08-2.17 (m, 1H, CH_BCH), 2.11 (s, 3H, CH_3S), 2.52-2.66 (m, 2H, CH_2S), 4.37-4.43 (m, 1H, CH), 5.12 (s, 2H, OC$H_2C_6H_5$), 5.39, 5.46, 6.08 (br, br, br, 1H, 1H, 1H, NH, NH_2), 7.31-7.40 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 30.1, 31.6, 53.5, 67.2, 128.1, 128.3, 128.6, 136.1, 156.3, 173.8; HRMS (ESI-TOF): Calcd for $C_{13}H_{18}N_2O_3SNa$ $(M+Na)^+$: 305.0930, found: 305.0908; IR (KBr, ν_{max}/cm^{-1}) = 3386 (CONH), 3315 (CONH), 3201 (CONH), 1655 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 21.2 min.

8.14. Cbz-D-Met-NH_2 10h'

Colorless solid; >99% ee; $[\alpha]^{29}_D$ = +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.

8.15. Boc-L-Met-NH_2 10n

Colorless solid; >99% ee; mp: 118-120 °C; $[\alpha]^{27}_D$ = –8.3 (*c* 1.01, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H, $(CH_3)_3C$), 1.89-1.98 (m, 1H, CH_ACH), 2.08-2.16 (m, 1H, CH_BCH), 2.12 (s, 3H, CH_3S), 2.53-2.65 (m, 2H, CH_2S), 3.99-4.02 (m, 1H, CH), 5.16, 5.46, 6.19 (br, br, br, 1H, 1H, 1H, NH, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 28.4, 30.2, 31.7, 53.1, 80.3, 155.7, 174.3; HRMS (ESI-TOF): Calcd for $C_{10}H_{20}N_2O_3SNa$ $(M+Na)^+$: 271.1087, found: 271.1095; IR (KBr, ν_{max}/cm^{-1}): 3390 (CONH), 3346 (CONH), 3188 (CONH), 1684 (CON), 1660 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5): T_r 17.4 min.

8.16. Boc-D-Met-NH_2 10n'

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

8.17. Fmoc-L-Met-NH_2 10o

Colorless solid; >99% ee; mp: 181-184 °C; $[\alpha]^{27}_D$ = –2.0 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ 1.78-1.83 (m, 1H, CH_ACH), 1.88-1.94 (m, 1H, CH_BCH), 2.04 (s, 3H, CH_3S), 2.39-2.50

(m, 2H, CH_2S), 3.99-4.02 (m, 1H, C*H*CH_2CH_2), 4.22-4.30 (m, 3H, $CHCH_2O$), 7.04 (br, 1H, $CONH_A$), 7.33-7.49, 7.72-7.75, 7.90 (m, m, d, *J* = 7.5 Hz, 6H, 2H, 2H, N*H*CH, $CONH_B$, fluorenyl); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): 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; HRMS (ESI-TOF): Calcd for $C_{13}H_{18}N_2O_3SNa$ $(M+Na)^+$: 305.0930, found: 305.0908; IR (KBr, ν_{max}/cm^{-1}): 3367 (CONH), 3319 (CONH), 3201 (CONH), 1685 (CON), 1647 (CON), 1626 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 80/20): T_r 9.9 min.

8.18. Fmoc-D-Met-NH$_2$ 10o'

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

8.19. Cbz-L-Ala-NH$_2$ 10e

Colorless solid; >99% ee; mp: 128-130 °C; $[\alpha]^{25}_D$ = –4.9 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (d, *J* = 7.1 Hz, 3H, CH_3), 4.23-4.31 (m, 1H, C*H*CH_3), 5.08 (d, *J* = 12.2 Hz, 1H, OC*H*$_A$$C_6H_5$), 5.12 (d, *J* = 12.2 Hz, 1H, OC*H*$_B$$C_6H_5$), 5.48, 5.74, 6.19 (br, br, br, 1H, 1H, 1H, NH, NH_2), 7.29-7.38 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 50.1, 67.1, 128.0, 128.2, 128.6, 136.1, 156.1, 175.1; HRMS (ESI-TOF): Calcd for $C_{11}H_{14}N_2O_3Na$ $(M+Na)^+$: 245.0897, found: 245.0916; IR (KBr, ν_{max}/cm^{-1}) = 3394 (CONH), 3311 (CONH), 3197 (CONH), 1682 (CON), 1643 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 13.6 min.

8.20. Cbz-D-Ala-NH$_2$ 10e'

Colorless solid; 99% ee; $[\alpha]^{24}_D$ = +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.

8.21. Cbz-L-Gln-NH$_2$ 10p

Colorless solid; 198-200 °C; $[\alpha]^{25}_D$ = +11.7 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 1.65-1.74 (m, 1H, C*H*$_A$CH), 1.82-1.91 (m, 1H, C*H*$_B$CH), 2.07-2.12 (m, 2H, CH_2CO), 3.86-3.92 (m, 1H, CH), 5.02 (s, 2H, OC*H*$_2$$C_6H_5$), 6.76 (br, 1H, NH_A), 7.02 (br, 1H, NH_B), 7.28-7.39 (m, 8H, NH, NH_2, C_6H_5); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ 27.7, 31.5, 54.3, 65.4, 127.7, 127.8, 128.4, 137.1, 155.9, 173.6, 173.7; HRMS (ESI-TOF): Calcd for $C_{13}H_{17}N_3O_4Na$ $(M+Na)^+$: 302.1111, found: 302.1115; IR (KBr, ν_{max}/cm^{-1}): 3446 (CONH), 3423 (CONH), 3328 (CONH), 3203 (CONH), 1658 (CON).

8.22. Cbz-D-Gln-NH$_2$ 10p'

Colorless solid; $[\alpha]^{25}_D$ = –10.5 (*c* 0.99, DMSO).

8.23. Cbz-L-Leu-NH$_2$ 10g

Colorless solid; >99% ee; mp: 123-125 °C; $[\alpha]^{27}_D$ = –11.2 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, *J* = 6.2 Hz, 6H, CH_3 ×2), 1.51-1.59 (m, 1H, C*H*$_A$CH(CH_3)$_2$), 1.66-1.74 (m, 2H, C*H*$_B$CH(CH_3)$_2$, C*H*(CH_3)$_2$), 4.19-4.25 (m, 1H, CHCO), 5.12 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.12, 5.39, 6.00 (br, br, br, 1H, 1H, 1H, NH, NH_2), 7.30-7.39 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.9, 24.7, 41.3, 53.1, 67.1, 128.0, 128.3, 128.6, 136.1, 156.4, 174.9; HRMS (ESI-TOF): Calcd for $C_{14}H_{20}N_2O_3Na$ $(M+Na)^+$: 287.1366, found: 287.1396; IR (KBr, ν_{max}/cm^{-1}) = 3392 (CONH), 3321 (CONH), 3203 (CONH), 1666 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 10.7 min.

8.24. Cbz-D-Leu-NH$_2$ 10g'

Colorless solid; >99% ee; $[\alpha]^{27}_D$ = +11.1 (*c* 1.00, MeOH); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 90/10): T_r 14.4 min.

8.25. Cbz-L-Trp-NH$_2$ 10i

Colorless solid; >99% ee; mp: 186-188 °C; $[\alpha]^{28}_D$ = –30.0 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 2.90 (dd, *J* = 9.5, 13.9 Hz, 1H, CH_A-indole), 3.10 (dd, *J* = 4.3, 13.9 Hz, 1H, CH_B-indole), 4.21 (ddd, *J* = 4.3, 8.2, 9.5 Hz, 1H, CH), 4.92 (d, *J* = 12.5 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 4.96 (d, *J* = 12.5 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 6.95-6.98, 7.04-7.08, 7.14, 7.25-7.35 (m, m, s, m, 1H, 2H, 1H, 7H, $CONH_A$, C_6H_5, indolyl), 7.47 (br, 1H, $CONH_B$), 7.64 (d, *J* = 8.2 Hz, 1H, N*H*CHCH$_2$), 10.81 (br, 1H, indoleNH); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): 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; HRMS (ESI-TOF): Calcd for $C_{19}H_{19}N_3O_3Na$ $(M+Na)^+$: 360.1319, found: 360.1329; IR (KBr, ν_{max}/cm^{-1}) = 3402 (NH), 3313 (OH), 1716 (CO_2), 1662 (CON); The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 85/15): T_r 26.1 min.

8.26. Cbz-D-Trp-NH$_2$ 10i'

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

8.27. Boc-*O*-Bn-L-Ser-NH$_2$ 10j

Colorless solid; >99% ee; mp: 86-89 °C; $[\alpha]^{27}_D$ = +13.9 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H, CH_3 ×3), 3.58 (dd, *J* = 6.9, 9.1 Hz, 1H, C*H*$_A$CH), 3.93 (dd, *J* = 3.7, 9.1 Hz, 1H, C*H*$_B$CH), 4.24-4.36 (m, 1H, CH), 4.53 (d, *J* = 11.6 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 4.61 (d, *J* = 11.6 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 5.42, 6.44 (br, br, 2H, 1H, NH, NH_2), 7.29-7.38 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 53.6, 69.8, 73.5, 80.3, 127.8, 128.0, 128.5, 137.4, 155.5, 172.8; HRMS (ESI-TOF): Calcd for $C_{15}H_{22}N_2O_4Na$ $(M+Na)^+$: 317.1472, found: 317.1490; IR (KBr, ν_{max}/cm^{-1}) = 3390 (CONH), 3346

(CONH), 3192 (CONH), 1685 (CON), 1660 (CON); The enantiomeric ratio was determined by HPLC(Chiralcel AD: hexane/2-propanol = 95/5): T_r 23.8 min.

8.28. Boc-*O*-Bn-D-Ser-NH_2 10j'

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

9. Typical procedure for the amidation of Cbz-L-Phe-OH 5a with hydroxylamine hydrochloride 11h

To a colorless solution of 150 mg (0.50 mmol) of Cbz-L-Phe-OH **5a** in 10 mL of THF were added at 0 °C 67 μL (0.70 mmol, 1.4 equiv) of ethyl chloroformate and 209 μL (1.5 mmol, 3.0 equiv) of triethylamine. 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) was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C, and 5 mL of H_2O 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 Na_2SO_4. 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 **12ah**.

9.1. Cbz-L-Phe-NHEt 12aa

Colorless solid; mp: 138-139 °C; $[\alpha]^{26}_D$ = –6.6 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.3 Hz, 3H, CH_3), 2.99 (dd, *J* = 8.1, 13.6 Hz, 1H, CHCH_AC$_6$H$_5$), 3.12-3.22 (m, 3H, CH_2CH$_3$, CHCH_BC$_6$H$_5$), 4.30 (dd, *J* = 7.6, 8.4 Hz, 1H, C*H*CH$_2$), 5.09 (s, 2H, OCH_2C$_6$H$_5$), 5.34, 5.43 (br, br, 1H, 1H, NH ×2), 7.19-7.38 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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; HRMS (ESI-TOF): Calcd for $C_{19}H_{22}N_2O_3Na$ $(M+Na)^+$: 349.1523, found: 349.1513; IR (KBr, ν_{max}/cm^{-1}) = 3315 (CONH), 1689 (CON), 1651 (CON).

9.2. Cbz-L-Phe-NHCH$_2$CH$_2$Ph 12ab

Colorless solid; mp: 118-120 °C; $[\alpha]^{25}_D$ = –6.8 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56-2.72 (m, 2H, CH$_2$CH_2C$_6$H$_5$), 2.99 (dd, *J* = 7.8, 13.5 Hz, 1H, CHCH_AC$_6$H$_5$), 3.10 (dd, *J* = 6.0, 13.5 Hz, 1H, CHCH_BC$_6$H$_5$), 3.23-3.50 (m, 2H, CH_2CH$_2$C$_6$H$_5$), 4.29 (dd, *J* = 6.0, 7.8 Hz, 1H, C*H*CH$_2$), 5.07 (s, 2H, OCH_2C$_6$H$_5$), 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$_6$H$_5$ ×3); ^{13}C NMR (100 MHz, $CDCl_3$): 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; HRMS (ESI-TOF): Calcd for $C_{25}H_{26}N_2O_3Na$ $(M+Na)^+$: 425.1836, found: 425.1827; IR (KBr, ν_{max}/cm^{-1}) = 3305 (CONH), 1687 (CON), 1651 (CON).

9.3. Cbz-L-Phe-cyclohexylNH 12ac

Colorless solid; mp: 151-153 °C; $[\alpha]^{25}_{D}$ = +16.8 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 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, 1H, 1H, 1H, 2H, 4H, 1H, CH_2 ×5 of cyclohexane), 2.95 (dd, *J* = 8.2, 13.7 Hz, 1H, CHCH_AC$_6$H$_5$), 3.15 (dd, *J* = 5.7, 13.7 Hz, 1H, CHCH_BC$_6$H$_5$), 3.61-3.69 (m, 1H, CH of cyclohexane), 4.28 (dd, *J* = 5.7, 8.2 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.10 (s, 2H, OCH_2C$_6$H$_5$), 5.25, 5.40 (br, br, 1H, 1H, NH ×2), 7.19-7.38 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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; HRMS (ESI-TOF): Calcd for $C_{23}H_{28}N_2O_3Na$ $(M+Na)^+$: 403.1992, found: 403.1972; IR (KBr, ν_{max}/cm^{-1}) = 3317 (CONH), 3275 (CONH), 1689 (CON), 1647 (CON).

9.4. Cbz-L-Phe-adamantylNH 12ad

Colorless solid; mp: 55-57 °C; $[\alpha]^{25}_{D}$ = –1.1 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59-1.64 (m, 6H, CH_2 ×3 of adamantane), 1.75-1.82 (m, 6H, CH_2 ×3 of adamantane), 1.97-2.04 (m, 3H, CH ×3 of adamantane), 2.90 (dd, *J* = 8.7, 13.4 Hz, 1H, CHCH_AC$_6$H$_5$), 3.14 (dd, *J* = 5.0, 13.4 Hz, 1H, CHCH_BC$_6$H$_5$), 4.25 (dd, *J* = 5.0, 8.7 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.00 (br, 1H, NH), 5.10 (s, 2H, OCH_2C$_6$H$_5$), 5.43 (br, 1H, NH), 7.21-7.38 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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; HRMS (ESI-TOF): Calcd for $C_{27}H_{32}N_2O_3Na$ $(M+Na)^+$: 455.2305, found: 455.2277; IR (KBr, ν_{max}/cm^{-1}): 3307 (CONH), 1705 (CON), 1655 (CON).

9.5. Cbz-L-Phe-NMe$_2$ 12ae

Colorless oil; $[\alpha]^{25}_{D}$ = +12.9 (*c* 1.21, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 2.93-3.03 (m, 2H, CHCH_2C$_6$H$_5$), 4.85-4.91 (m, 1H, C*H*CH$_2$), 5.06 (d, *J* = 12.4 Hz, 1H, OCH_AC$_6$H$_5$), 5.10 (d, *J* = 12.4 Hz, 1H, OCH_BC$_6$H$_5$), 5.69 (br, 1H, NH), 7.14-7.18, 7.21-7.38 (m, m, 2H, 8H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, $CDCl_3$) : 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; HRMS (ESI-TOF): Calcd for $C_{19}H_{23}N_2O_3$ $(M+H)^+$: 327.1703, found: 327.1726; IR (NaCl, ν_{max}/cm^{-1}) = 3280 (CONH), 1716 (CON), 1639 (CON).

9.6. Cbz-L-Phe-NEt$_2$ 12af

Colorless oil; $[\alpha]^{25}_{D}$ = –8.7 (*c* 0.99, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.1 Hz, 3H, CH_3), 1.04 (t, *J* = 7.1 Hz, 3H, CH_3), 2.88-3.11 (m, 5H, CH_2CH$_3$ ×2, CHCH_AC$_6$H$_5$), 3.49-3.58 (m, 1H, CHCH_BC$_6$H$_5$), 4.76-4.82 (m, 1H, C*H*CH$_2$), 5.05 (d, *J* = 12.3 Hz, 1H, OCH_AC$_6$H$_5$), 5.12 (d, *J* = 12.3 Hz, 1H, OCH_BC$_6$H$_5$), 5.61 (br, 1H, NH), 7.18-7.29, 7.30-7.37 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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; HRMS (ESI-TOF): Calcd for $C_{21}H_{27}N_2O_3$ $(M+H)^+$: 355.2016, found: 355.2022; IR (NaCl, ν_{max}/cm^{-1}) = 3273 (CONH), 1716 (CON), 1631 (CON).

9.7. Cbz-L-Phe-piperidyl 12ag

Pale orange oil; $[\alpha]^{25}_{D}$ = +2.5 (*c* 1.01, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97-1.04 (m, 1H, CH_ACH$_2$CH$_2$N of piperidine), 1.34-1.58 (m, 5H, CH_BCH$_2$CH$_2$N of piperidine, CH_2CH$_2$N ×2 of piperidine), 2.97 (br, 1H, CH$_A$N of piperidine) , 2.99 (br, 1H, CH$_B$N of piperidine), 3.00 (dd, *J* = 7.3, 13.3 Hz, 1H, CHCH_AC$_6$H$_5$) 3.23 (dd, *J* = 7.3, 13.3 Hz, 1H, CHCH_AC$_6$H$_5$) 3.48 (t, *J* = 5.3 Hz, 2H, CH$_2$N of piperidine), 4.91 (ddd, *J* = 7.3, 7.3, 8.2 Hz, 1H, C*H*CH$_2$), 5.06 (d, *J* = 12.4 Hz, 1H, OCH_AC$_6$H$_5$), 5.11 (d, *J* = 12.4 Hz, 1H, OCH_BC$_6$H$_5$), 5.73 (d, *J* = 8.2 Hz, 1H, NH), 7.13-7.38 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, $CDCl_3$): 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; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_3Na$ $(M+Na)^+$: 389.1836, found: 389.1808; IR (NaCl, ν_{max}/cm^{-1}) = 3280 (CONH), 1716 (CON), 1630 (CON).

9.8. Cbz-L-Phe-NHOH 12ah

Colorless solid; mp: 139-141 ºC; $[\alpha]^{29}_{D}$ = –11.8 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d^6): δ 2.78 (dd, *J* = 10.0, 13.7 Hz, 1H, CHCH_AC$_6$H$_5$), 2.89 (dd, *J* = 4.9, 13.7 Hz, 1H, CHCH_BC$_6$H$_5$), 4.10 (ddd, *J* = 4.9, 8.8, 10.0 Hz, 1H, C*H*CH$_2$), 4.92 (d, *J* = 13.3 Hz, 1H, OCH_AC$_6$H$_5$), 4.95 (d, *J* = 13.3 Hz, 1H, OCH_BC$_6$H$_5$), 7.18-7.36 (m, 10H, C$_6$H$_5$ ×2), 7.62 (d, *J* = 8.8 Hz, 1H, N*H*CH), 8.89 (s, 1H, NHO*H*), 10.73 (s, 1H, N*H*OH); ^{13}C NMR (100 MHz, DMSO-d^6): 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; HRMS (ESI-TOF): Calcd for $C_{17}H_{18}N_2O_4Na$ $(M+Na)^+$: 337.1159, found: 337.1129; IR (KBr, ν_{max}/cm^{-1}) = 3315 (OH), 3255 (CONH), 3143 (CONH), 1701 (CON), 1668 (CON).

10. Typical procedure for the amidation of (2*S*,3*S*)-(+)-2,3-methano-3-phenylpropanoic acid 13 with hydroxylamine hydrochloride 11h

To a colorless solution of 162 mg (1.0 mmol) of (2*S*,3*S*)-(+)-2,3-methano-3-phenylpropanoic acid **13** prepared from (2*S*,3*S*)-(+)-2,3-methano-3-phenylpropanol in 5 mL of THF were added at -15 °C 105 μL (1.1 mmol, 1.1 equiv) of ethyl chloroformate and 419 μL (3.0 mmol, 3.0 equiv) of triethylamine 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) **11h** was added at -15 °C to the colorless suspension. The mixture was stirred for 4 h at -15 °C and 5 mL of a 1.0 M aqueous HCl solution was 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 ×2. The organic layers were combined, washed with 5 mL of brine, and dried over anhydrous Na_2SO_4. The crude product was chromatographed on silica gel with a 15:1 mixture of $CHCl_3$ and MeOH to afford 146 mg (82% yield) of (2*S*,3*S*)-(+)-*N*-hydroxy-2,3-methano-3-phenylpropanamide **14**. (2*S*,3*S*)-(+)-**14**: colorless solid; mp: 125-127 °C; $[\alpha]^{18}_{D}$ = +338.1 (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33-1.37 (m, 1H, CH$_A$ of cyclopropane), 1.65-1.70 (m, 2H, CH$_B$ of cyclopropane, C*H*C$_6$H$_5$), 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_6H_5), 8.01 (br, 1H, NH), 8.26 (br, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, few drops of CD_3OD for solubility): δ 15.5, 23.0, 24.7, 31.3, 126.2, 126.5, 128.5, 140.3, 171.3; HRMS (ESI-TOF): Calcd for $C_{10}H_{11}NO_2Na$ $(M+Na)^+$: 200.0682, found: 200.0655; IR (KBr, ν_{max}/cm^{-1}) = 3361 (CONH), 3186 (OH), 1653 (CON).

11. Typical procedure for the Lossen rearrangment of (2*S*,3*S*)-(+)-*N*-hydroxy-2,3-methano-3-phenylpropanamide 14

To a colorless solution of 100 mg (0.565 mmol) of (2*S*,3*S*)-(+)-*N*-hydroxy-2,3-methano-3-phenylpropanamide **14** and 142 mg (0.622 mmol, 1.1 equiv) of 4-nitrobenzenesulfonyl chloride in 5 mL of anhydrous THF was added at 0 °C 250 μL (1.41 mmol, 2.5 equiv) of *i*-Pr_2NEt. 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 $MgSO_4$. 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 **15**. (1*S*,2*R*)-(+)-**15**: colorless solid; mp: 67-69 °C; $[\alpha]^{27}_D$ = +69.6 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12-1.27 (m, 1H, CH_2 of cyclopropane), 2.05-2.12 (m, 1H, CHC*H*C_6H_5), 2.72-2.81 (m, 1H, CHCO), 5.09 (br, 1H, NH), 5.12 (s, 2H, OC*H*$_2C_6H_5$), 7.10-7.41 (m, 10H, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 25.1, 32.6, 66.8, 126.1, 126.6, 128.1, 128.3, 128.5, 136.4, 140.4, 156.8; HRMS (ESI-TOF): Calcd for $C_{17}H_{17}NO_2Na$ $(M+Na)^+$: 290.1151, found: 290.1146; IR (KBr, ν_{max}/cm^{-1}) = 3342 (CONH), 1689 (CON).

12. Typical procedure for the preparation of (1*S*,2*R*)-(+)-*N*-acetyltranylcypromine 16

A colorless suspension of 30 mg (0.11 mmol) of (1*S*,2*R*)-(+)-*N*-Cbz-tranylcypromine **15** 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 ×3. The aqueous layer was concentrated in vacuo to afford a crude (1*S*,2*R*)-tranylcypromine hydrochloride. To the crude residual solid were added at rt 2 mL of pyridine, 23 μL (0.22 mmol, 2.0 equiv) of Ac_2O, and 31 μL (0.22 mmol, 2.0 equiv) of triethylamine. After stirring for 12 h at rt, the colorless solution was quenched with 5 mL of H_2O and extracted with 10 mL of EtOAc ×2. The organic layers were combined, washed with 5 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with EtOAc to afford 20 mg (quant.) of (1*S*,2*R*)-(+)-*N*-acetyltranylcypromine **16**. (1*S*,2*R*)-(+)-**16**: colorless solid; 82% ee; mp: 90-93 °C; $[\alpha]^{26}_D$ = +123.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14-1.18 (m, 1H, CH_A of cyclopropane), 1.20-1.28 (m, 1H, CH_B of cyclopropane), 1.98 (s, 3H, CH_3), 2.02-2.06 (m, 1H, C*H*C_6H_5), 2.87-2.92 (m, 1H, C*H*NH), 5.77 (br, 1H, NH), 7.12-7.32 (m, 5H, C_6H_5); ^{13}C NMR (100MHz, $CDCl_3$): δ 16.3, 23.1, 24.6, 126.1, 126.4, 128.4, 140.5, 171.3; HRMS (ESI-TOF): Calcd for $C_{11}H_{13}NONa$ $(M+Na)^+$: 198.0889, found: 198.0907; IR (KBr, ν_{max}/cm^{-1}) = 3273 (CONH), 1647 (CON); The enantiomeric ratio was determined

by HPLC (Chiralcel OD: hexane/2-propanol = 95/5): T_r(major) 54.2 min, T_r(minor) 42.6 min (er 90.9:9.1).

Chapter 3. Synthesis of memantine analogues containing a sigma-1 receptor activity as a candidate of anti-Alzheimer's medicine

13. Typical procedure for acetylation of (*Z*)-2-phenylbut-2-ene-1,4-diol 34a using PPL[12, 58]

To a pale yellow suspension of 164 mg (1.00 mmol) of (*Z*)-2-phenylbut-2-ene-1,4-diol **34a**, 0.92 mL (10.0 mmol, 10 equiv) of vinyl acetate, and 82 mg (50 w/w%) of PPL in 3 mL of 1,4-dioxane was stirred at rt for 24 h. The reaction suspension was diluted with 10 mL of EtOAc and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 1:2 mixture of EtOAc and hexane to afford 187 mg (91% yield) of (*Z*)-4-hydroxy-3-phenylbut-2-en-1-yl acetate **17a**.

13.1. (*Z*)-4-Hydroxy-3-phenylbut-2-en-1-yl acetate 17a[12, 58]

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 2.45 (br, 1H, OH), 4.60 (s, 2H, CH_2OH), 4.88 (d, J = 7.2 Hz, 2H, CH_2OAc), 5.92 (t, J = 7.2 Hz, 1H, =CH), 7.28-7.38, 7.48-7.50 (m, m, 3H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 60.1, 61.2, 124.3, 126.4, 128.0, 128.6, 140.1, 143.9, 171.5; HRMS (ESI-TOF): Calcd for $C_{12}H_{14}O_3Na$ $(M+Na)^+$: 229.0835, found: 229.0815.

13.2. (*Z*)-4-Hydroxy-3-(4-methoxyphenyl)but-2-en-1-yl acetate 17b[12, 58]

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 2.43 (t, J = 6.1 Hz, 1H, OH), 3.81 (s, 3H, OCH_3), 4.58 (d, J = 6.1 Hz, 2H, CH_2OH), 4.85 (d, J = 7.4 Hz, 2H, CH_2OAc), 5.86 (t, J = 7.4 Hz, 1H, =CH), 6.91, 7.14 (d, d, J = 8.8, 8.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 55.3, 60.0, 61.3, 113.9, 122.5, 127.6, 132.4, 143.4, 159.5, 171.5; HRMS (ESI-TOF): Calcd for $C_{13}H_{16}O_4Na$ $(M+Na)^+$: 259.0941, found: 259.0915.

13.3. (*Z*)-4-Hydroxy-3-(4-methylphenyl)but-2-en-1-yl acetate 17c[12, 58]

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 2.35 (s, br, 3H, 1H, ArCH_3, OH), 4.59 (d, J =5.4 Hz, 2H, CH_2OH), 4.87 (d, J = 7.4 Hz, 2H, CH_2OAc), 5.90 (t, J = 7.4 Hz, 1H, =CH), 7.16, 7.39 (d, d, J = 8.2, 8.2 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.1, 60.0, 61.2, 123.4, 126.3, 129.3, 137.1, 137.9, 143.8, 171.4; HRMS (ESI-TOF): Calcd for $C_{13}H_{16}O_3Na$ $(M+Na)^+$: 243.0992, found: 243.1007.

13.4. (*Z*)-3-(4-Chlorophenyl)-4-hydroxybut-2-en-1-yl acetate 17d[12, 58]

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 2.49-2.54 (m, 1H, OH), 4.56 (d, J

= 6.0 Hz, 2H, CH_2OH), 4.86 (d, J =7.2 Hz, 2H, CH_2OAc), 5.90 (t, J = 7.2 Hz, 1H, =CH), 7.31, 7.44 (d, d, J = 8.6 Hz, 8.6 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 59.9, 61.1, 124.7, 127.8, 128.7, 133.9, 138.6, 142.8, 171.5; HRMS (ESI-TOF): Calcd for $C_{12}H_{13}ClO_3Na$ $(M+Na)^+$: 263.0445, found: 263.0425.

13.5. (*Z*)-3-(4-Bromophenyl)-4-hydroxybut-2-en-1-yl acetate 17e

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H, CH_3CO), 2.50 (br, 1H, OH), 4.57 (d, J = 5.5 Hz, 2H, CH_2OH), 4.86 (d, J =7.4 Hz, 2H, CH_2OAc), 5.91 (t, J = 7.4 Hz, 1H, =CH), 7.38, 7.48 (d, d, J =8.6, 8.6 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 59.9, 61.1, 122.0, 124.7, 128.1, 131.6, 139.1, 142.8, 171.5; HRMS (ESI-TOF): Calcd for $C_{12}H_{13}BrO_3Na$ $(M+Na)^+$: 306.9940, found: 306.9964.

14. Typical procedure for preparation of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate 18a.[58]

To a colorless solution of 206 mg (1.00 mmol) of (*Z*)-4-hydroxy-3-phenylbut-2-en-1-yl acetate **17a** in 5 mL of pyridine was added 330 mg (1.20 mmol 1.2 equiv) of *t*-BuPh_2SiCl under an argon atmosphere. After stirring at rt for 24 h, the reaction mixture was quenched with 10 mL of water and extracted with 10 mL ×3 of EtOAc. The organic layers were combined, washed with 5 mL of brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 1:8 mixture of EtOAc and hexane to afford 431 mg (97 % yield) of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate **18a**.

14.1. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate 18a[58]

Reaction time: 24h; Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 2.03 (s, 3H, CH_3CO), 4.60 (s, 2H, CH_2OSi), 4.65 (d, J = 6.8 Hz, 2H, CH_2OAc), 5.84 (t, J = 6.8 Hz, 1H, =CH), 7.25-7.31, 7.34-7.44, 7.62-7.65 (m, m, m, 3H, 8H, 4H, C_6H_5 ×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 20.8, 26.6, 61.0, 61.3, 124.2, 126.8, 127.3, 127.6, 128.0, 129.7, 133.1, 135.5, 140.3, 142.8, 170.5; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_3SiNa$ $(M+Na)^+$: 467.2013, found: 467.2010.

14.2. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methoxyphenyl)but-2-en-1-yl acetate 18b

Reaction time: 24h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H, $(CH_3)_3C$), 2.03 (s, 3H, CH_3CO), 3.81 (s, 3H, CH_3O), 4.57 (s, 2H, CH_2OSi), 4.62 (d, J = 6.9 Hz, 2H, CH_2OAc), 5.78 (t, J = 6.9 Hz, 1H, =CH), 6.83, 7.31 (d, d, J = 8.8 Hz, 8.8 Hz, 2H, 2H, C_6H_4), 7.35-7.45, 7.63-7.65 (m, m, 6H, 4H, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 21.0, 26.7, 55.3, 61.2, 61.4, 113.5, 122.7, 127.7, 128.0, 129.7, 132.8, 133.3, 135.7, 142.4, 159.1, 170.8; HRMS (ESI-TOF): Calcd for $C_{29}H_{34}O_4SiNa$ $(M+Na)^+$: 497.2119, found: 497.2125.

14.3. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methylphenyl)but-2-en-1-yl acetate 18c

Reaction time: 24h; Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H, $(CH_3)_3C$), 2.03 (s, 3H, CH_3CO), 2.34 (s, 3H, CH_3), 4.57 (s, 2H, CH_2OSi), 4.65 (d, J = 6.9 Hz, 2H, CH_2OAc), 5.82 (t, J = 6.9 Hz, 1H, =CH), 7.10, 7.25-7.27, 7.34-7.45, 7.63-7.65 (d, m, m, m, J = 7.8 Hz, 2H, 2H, 6H, 4H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 21.0, 21.1, 26.7, 61.3, 61.5, 123.6, 126.7, 127.7, 128.8, 129.7, 133.3, 135.7, 137.2, 137.5, 142.7, 170.1; HRMS (ESI-TOF): Calcd for $C_{29}H_{34}O_3SiNa$ $(M+Na)^+$: 481.2175, found: 481.2178.

14.4. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)but-2-en-1-yl acetate 18d

Reaction time: 24h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H, $(CH_3)_3C$), 2.04 (s, 3H, CH_3CO), 4.56 (s, 2H, CH_2OSi), 4.59 (d, J = 6.8 Hz, 2H, CH_2OAc), 5.81 (t, J = 6.8 Hz, 1H, =CH), 7.24-7.29, 7.35-7.46, 7.60-7.63 (m, m, m, 4H, 6H, 4H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 20.9, 26.7, 61.0, 61.1, 124.6, 127.7, 128.2, 129.8, 133.1, 133.3, 135.6, 138.8, 141.9, 170.7; HRMS (ESI-TOF): Calcd for $C_{28}H_{31}ClO_3SiNa$ $(M+Na)^+$: 501.1623, found: 501.1608.

14.5. (*Z*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)but-2-en-1-yl acetate 18e

Reaction time: 24h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 2.04 (s, 3H, CH_3CO), 4.59 (s, 2H, CH_2OSi), 4.62 (d, J = 6.9 Hz, 2H, CH_2OAc), 5.81 (t, J = 6.9 Hz, 1H, =CH), 7.22, 7.35-7.46, 7.60-7.62 (d, m, m, J = 8.6 Hz, 2H, 8H, 4H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 20.9, 26.7, 61.0, 61.0, 121.5, 124.7, 127.8, 128.6, 129.8, 131.2, 133.1, 135.6, 139.3, 141.9, 170.7; HRMS (ESI-TOF): Calcd for $C_{28}H_{31}BrO_3SiNa$ $(M+Na)^+$: 545.1118, found: 545.1114.

15. Typical procedure for preparation of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-ol 19a[58]

To a colorless solution of 907 mg (2.03 mmol) of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate **18a** in 58 ml of 1:1 mixture of Et_2O-MeOH was added a catalytic amount (3 drops) of 28% MeONa solution in MeOH. The mixture was stirred at rt for 5 h and quenched with 5 mL of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with 10 mL ×2 of EtOAc. The organic layers were combined, washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 5:1 mixture of hexane and EtOAc to afford 821 mg (quantitative yield) of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-ol **19a**.

15.1. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-phenylbut-2-en-1-ol 19a[58]

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H, $(CH_3)_3C$), 1.64 (br, 1H, OH), 4.16 (dd, J = 6.4, 6.4 Hz, 2H, CH_2OH), 4.59 (s, 2H, CH_2OSi), 5.97 (t, J = 6.4 Hz, 1H, =CH), 7.23-7.46, 7.64-7.66 (m, m, 11H, 4H, C_6H_5 ×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 26.7, 59.3, 61.6, 126.8, 127.3, 127.7,

128.1, 129.7, 129.8, 133.2, 135.7, 140.8, 141.3; HRMS (ESI-TOF): Calcd for $C_{26}H_{30}O_2SiNa$ $(M+Na)^+$: 425.1907, found: 425.1915.

15.2. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)but-2-en-1-ol 19d

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 1.53 (t, J = 6.2 Hz, 1H, OH), 4.11 (dd, J = 6.2, 6.5, 2H, CH_2OH), 4.56 (s, 2H, CH_2OSi), 5.93 (t, J = 6.5 Hz, 1H, =CH), 7.24-7.29, 7.36-7.47, 7.62-7.64 (m, m, m, 4H, 6H, 4H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 26.7, 59.2, 61.2, 127.8, 128.1, 128.3, 129.9, 130.0, 133.1, 135.7, 139.1, 140.1; HRMS (ESI-TOF): Calcd for $C_{26}H_{29}ClO_2SiNa$ $(M+Na)^+$: 459.1518, found: 459.1526.

15.3. (*Z*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)but-2-en-1-ol 19e

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 1.50 (br, 1H, OH), 4.11 (dd, J = 6.3, 6.6 Hz, 2H, CH_2OH), 4.55 (s, 2H, CH_2OSi), 5.94 (t, J = 6.6 Hz, 1H, =CH), 7.21, 7.36-7.47, 7.62-7.64 (d, m, m, J = 8.6 Hz, 2H, 8H, 4H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 26.7, 59.2, 61.1, 121.3, 127.8, 128.5, 129.9, 130.0, 131.2, 133.1, 135.7, 139.6, 140.1; HRMS (ESI-TOF): Calcd for $C_{26}H_{29}BrO_2SiNa$ $(M+Na)^+$: 503.1012, found: 503.1017.

16. Typical procedure for preparation of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-(4-methoxyphenyl) but-2-en-1-ol 19b.[58]

To a colorless solution of 588 mg (1.2 mmol) of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-(4-methoxyphenyl)but-2-en-1-yl acetate **18b** in 5 mL of anhydrous THF was added dropwise at -78 °C 3.1 mL (2.6 mmol, 2.1 equiv) of a 1.03M DIBAL-H solution in hexane under an argon atmosphere. The mixture was stirred at -78 °C for 2 h and quenched at -78 °C with 2 mL of MeOH. To the reaction mixture was added a solution of 7.20 g of potassium sodium tartarate in 20 mL of water. After stirring at rt for 3 h, the reaction mixture was extracted with 20 mL ×3 of EtOAc. The EtOAc layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 5:1 mixture of hexane and EtOAc to afford 466 mg (90% yield) of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-(4-methoxyphenyl)but-2-en-1-ol **19b**.

16.1. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methoxyphenyl)but-2-en-1-ol 19b

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 9H, $(CH_3)_3C$), 1.55-1.58 (m, 1H, OH), 3.82 (s, 3H, CH_3O), 4.13 (dd, J = 6.2, 6.7 Hz, 2H, CH_2OH), 4.57 (s, 2H, CH_2OSi), 5.92 (t, J = 6.7 Hz, 1H, =CH), 6.82, 7.29 (d, d, J = 8.9, 8.9 Hz, 2H, 2H, C_6H_4), 7.36-7.46, 7.64-7.67 (m, m, 6H, 4H, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 26.7, 55.3, 59.3, 61.6, 113.5, 127.7, 127.9, 128.2, 129.8, 133.2, 135.7, 140.7, 159.0; HRMS (ESI-TOF): Calcd for $C_{27}H_{32}O_3SiNa$ $(M+Na)^+$: 455.2013, found: 455.2038.

16.2. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methylphenyl)but-2-en-1-ol 19c

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 9H, $(CH_3)_3C$), 1.63 (br, 1H, OH), 2.34 (s, 3H, CH_3), 4.15 (dd, J = 6.6, 6.6 Hz, 2H, CH_2OH), 4.57 (s, 2H, CH_2OSi), 5.96 (t, J = 6.6 Hz, 1H, =CH), 7.09, 7.24 (d, d, J = 8.2, 8.2 Hz, 2H, 2H, C_6H_4), 7.36-7.46, 7.64-7.67 (m, m, 6H, 4H, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 21.1, 26.7, 59.3, 61.7, 126.6, 127.7, 128.8, 129.0, 129.8, 133.2, 135.7, 137.0, 137.9, 141.1; HRMS (ESI-TOF): Calcd for $C_{27}H_{32}O_2SiNa$ $(M+Na)^+$: 439.2064, found: 439.2090.

17. Typical procedure for cyclopropanation of 19a in the presence of a catalytic amount of L1.[58]

To a colorless solution of 201 mg (0.50 mmol) of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-ol **19a** and 19 mg (0.05 mmol, 0.1 equiv) of the disulfonamide **L1** in 7.5 mL of anhydrous CH_2Cl_2 were added dropwise at -40 ºC under an argon atmosphere 1.0 mL (1.00 mmol, 2.0 equiv) of 1.0 M Et_2Zn solution in hexane and 121 μL (1.50 mmol, 3.0 equiv) of CH_2I_2. After stirring at 0 ºC for 3 h, the reaction mixture was quenched with 0.3 mL of triethylamine and extracted with 20 mL ×3 of EtOAc. The organic layers were combined, washed with 5 mL of brine, and dried over $MgSO_4$. The residue was chromatographed on silica gel with a 8:1 mixture of hexane and EtOAc to afford 208 mg (quantitative yield) of (2*S*,3*R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutan-1-ol **20a**.

17.1. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-phenylbutan-1-ol 20a[58]

Colorless oil; 71% ee; $[\alpha]^{28}_D$ = +51.2 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69 (dd, J = 5.3, 5.3 Hz, 1H, CH_A of cyclopropane), 0.96 (s, 9H, $(CH_3)_3C$), 0.96-0.99 (m, 1H, CH_B of cyclopropane), 1.81-1.89 (m, 1H, C*H*CH_2OH), 3.45-3.59 (m, 2H, CH_AOH, OH), 3.55 (d, J = 11.2 Hz, 1H, CH_AOSi), 4.06 (d, J = 11.2 Hz, 1H, CH_BOSi), 4.12-4.19 (m, 1H, CH_BOH), 7.05-7.07, 7.11-7.15, 7.28-7.45, 7.56-7.59 (m, m, m, m, 2H, 2H, 9H, 2H, C_6H_5 ×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 19.0, 25.8, 26.7, 32.5, 63.7, 69.2, 126.8, 127.5, 127.9, 128.2, 129.5, 129.8, 130.6, 131.7, 132.7, 135.4, 135.5, 143.9; HRMS (ESI-TOF): Calcd for $C_{27}H_{32}O_2SiNa$ $(M+Na)^+$: 439.2064, found: 439.2069; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 5.1 min, T_r(minor) 4.3 min (er 85.7:14.3).

17.2. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butan-1-ol 20b

Colorless oil; 36% ee; $[\alpha]^{23}_D$ = +34.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 (dd, J = 5.2, 5.3, Hz, 1H, CH_A of cyclopropane), 0.91-0.94 (m, 1H, CH_B of cyclopropane), 0.97 (s, 9H, $(CH_3)_3C$), 1.76-1.84 (m, 1H, C*H*CH_2OH), 3.43-3.59 (m, 3H, OH, CH_AOH, CH_AOSi), 3.85 (s, 3H, CH_3O), 4.03 (d, J = 11.0 Hz, 1H, CH_BOSi), 4.11-4.18 (m, 1H, CH_BOH), 6.85, 7.08-7.16, 7.29-7.45, 7.56-7.59 (d, m, m, m, J = 8.8 Hz, 2H, 4H, 6H, 2H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.0, 26.0, 26.7, 31.7, 55.4, 63.8, 69.4, 113.5, 127.5, 127.8, 129.5, 129.8, 131.6, 131.8, 132.8, 135.4, 135.6, 136.2, 142.3; HRMS (ESI-TOF): Calcd for $C_{28}H_{34}O_3SiNa$ $(M+Na)^+$: 469.2169, found:

469.2178; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 5.2 min, T_r(minor) 4.7 min (er 68:32).

17.3. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methylphenyl)butan-1-ol 20c

Colorless oil; 65% ee; $[\alpha]^{20}_D$ = +56.7 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.66 (dd, *J* = 5.2, 5.3 Hz, 1H, CH_A of cyclopropane), 0.93-0.96 (m, 1H, CH_B of cyclopropane), 0.97 (s, 9H, $(CH_3)_3C$), 1.78-1.86 (m, 1H, C*H*CH_2OH), 2.40 (s, 3H, CH_3), 3.44-3.60 (m, 3H, OH, CH_AOH, CH_AOSi), 4.05 (d, *J* = 11.1 Hz, 1H, CH_BOSi), 4.11-4.18 (m, 1H, CH_BOH), 7.05-7.13, 7.27-7.45, 7.56-7.59 (m, m, m, 6H, 6H, 2H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.0, 21.1, 25.9, 26.7, 32.0, 63.8, 69.3, 127.5, 127.8, 128.8, 129.5, 129.8, 130.4, 131.8, 132.8, 135.4, 135.6, 136.3, 141.0; HRMS (ESI-TOF): Calcd for $C_{28}H_{34}O_2SiNa$ $(M+Na)^+$: 453.2220, found: 453.2231; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 4.5 min, T_r(minor) 4.1 min (er 82.4:17.6).

17.4. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)-2,3-methanobutan-1-ol 20d

Colorless oil; 66% ee; $[\alpha]^{21}_D$ = +75.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (dd, *J* = 5.3, 5.4 Hz, 1H, CH_A of cyclopropane), 0.93 (dd, *J* = 5.3, 8.6 Hz, 1H, CH_B of cyclopropane), 0.97 (s, 9H, $(CH_3)_3C$), 1.76-1.83 (m, 1H, C*H*CH_2OH), 3.45-3.57 (m, 3H, OH, CH_AOH, CH_AOSi), 4.02 (d, *J* = 10.8 Hz, 1H, CH_BOSi), 4.11-4.18 (m, 1H, CH_BOH), 7.09-7.12, 7.15-7.19, 7.24-7.46, 7.54-7.56 (m, m, m, m, 2H, 2H, 8H, 2H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.0, 26.0, 26.8, 31.9, 63.6, 69.0, 127.6, 127.8, 128.3, 129.7, 129.9, 131.8, 132.6, 135.4, 135.5, 142.3; HRMS (ESI-TOF): Calcd for $C_{27}H_{31}ClO_2SiNa$ $(M+Na)^+$: 473.1674, found: 473.1676; The enantiomeric ratio was determined by HPLC (Chiralcel OD-H: hexane/2-propanol = 99.9/0.01) after acetylation T_r(major) 18.0 min, T_r(minor) 14.5 min (er 83:17).

17.5. (2*S*,3*R*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)-2,3-methanobutan-1-ol 20e

Colorless oil; 73% ee; $[\alpha]^{22}_D$ = +82.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (dd, *J* = 5.2, 5.2 Hz, 1H, CH_A of cyclopropane), 0.93 (dd, *J* = 5.2, 8.6 Hz, 1H, CH_B of cyclopropane), 0.97 (s, 9H, $(CH_3)_3C$), 1.77-1.81 (m, 1H, C*H*CH_2OH), 3.45-3.57 (m, 3H, OH, CH_AOH, CH_AOSi), 4.02 (d, *J* = 11.2 Hz, 1H, CH_BOSi), 4.11-4.18 (m, 1H, CH_BOH), 7.09-7.11, 7.16-7.24, 7.32-7.45, 7.54-7.56 (m, m, m, m, 2H, 4H, 6H, 2H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.0, 25.9, 26.8, 32.0, 63.5, 68.9, 120.7, 127.6, 127.9, 129.7, 129.9, 131.2, 131.6, 132.2, 132.6, 135.4, 135.5, 143.0; HRMS (ESI-TOF): Calcd for $C_{27}H_{31}BrO_2SiNa$ $(M+Na)^+$: 517.1169, found: 517.1159; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 99/1) T_r(major) 9.0 min, T_r(minor) 8.2 min (er 86.6:13.4).

18. Typical procedure for oxidation of the alcohol 20a into the aldehyde 21a.[58]

To a solution of 204 mg (0.46 mmol) of (*2S,3R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutan-1-ol **20a** in 5 mL of dimethylsulfoxide (DMSO) was added at rt 320 mg (1.14 mmol, 2.5 equiv) of 2-iodoxybenzoic acid (IBX). After stirring at rt for 3 h, 10 mL of EtOAc was added to the reaction mixture. The suspension was filtered through Celite. The filtrate was combined with 10 mL of half brine and extracted with 10 mL ×3 of EtOAc. The EtOAc layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The resiue was chromatographed on silica gel with a 8:1 mixture of hexane and EtOAc to afford 191 mg (94 % yield) of (2*S*,3*R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanal **21a**.

18.1. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-phenylbutanal 21a[58]

Colorless oil; 71% ee derived from **20a**; $[\alpha]^{28}_D$ = +57.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H, $(CH_3)_3C$), 1.49 (dd, *J* = 4.9, 8.1 Hz, 1H, CH_A of cyclopropane), 1.79 (dd, *J* = 4.9, 5.3 Hz, 1H, CH_B of cyclopropane), 2.30 (dt, *J* = 8.1, 5.3 Hz 1H, C*H*CHO), 3.76 (d, *J* = 11.0 Hz, 1H, CH_AOSi), 4.04 (d, *J* = 11.0 Hz, 1H, CH_BOSi), 7.19-7.43, 7.49-7.52 (m, m, 13H, 2H, C_6H_5 ×3), 9.63 (d, *J* = 5.3 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 19.1, 26.6, 34.3, 41.1, 66.5, 127.4, 127.5, 127.7, 128.4, 129.5, 129.7, 129.8, 132.8, 132.9, 135.4, 135.5, 142.0, 200.1; HRMS (ESI-TOF): Calcd for $C_{27}H_{30}O_2SiNa$ $(M+Na)^+$: 437.1907, found: 437.1900.

18.2. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butanal 21b

Colorless oil; 36% ee derived from **20b**; $[\alpha]^{20}_D$ = +29.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 1.46 (dd, *J* = 4.8, 8.1 Hz, 1H, CH_A of cyclopropane), 1.76 (dd, *J* = 4.8, 5.3 Hz, 1H, CH_B of cyclopropane), 2.24 (dt, *J* = 8.1, 5.3 Hz, 1H, C*H*CHO), 3.73 (d, *J* = 11.0 Hz, 1H, CH_AOSi), 3.83 (s, 3H, CH_3O), 4.02 (d, *J* = 11.0 Hz, 1H, CH_BOSi), 6.85, 7.20-7.43, 7.50-7.52 (d, m, m, *J* = 8.8 Hz, 2H, 10H, 2H, C_6H_4, C_6H_5 ×2), 9.61 (d, *J* = 5.3 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 19.1, 26.7, 34.7, 40.4, 55.4, 66.7, 113.7, 127.5, 127.7, 129.5, 129.7, 130.8, 132.9, 133.0, 134.3, 135.5, 135.5, 158.9, 200.2; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_3SiNa$ $(M+Na)^+$: 467.2013, found: 467.2010.

18.3. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methylphenyl)butanal 21c

Colorless oil; 65% ee derived from **20c**; $[\alpha]^{20}_D$ = +53.2 (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 1.46 (dd, *J* = 4.8, 8.1 Hz, 1H, CH_A of cyclopropane), 1.78 (dd, *J* = 4.8, 5.3 Hz, 1H, CH_B of cyclopropane), 2.26 (dt, *J* = 8.1, 5.4 Hz, 1H, C*H*CHO), 2.37 (s, 3H, CH_3), 3.75 (d, *J* = 11.0 Hz, 1H, CH_AOSi), 4.04 (d, *J* = 11.0 Hz, 1H, CH_BOSi), 7.12-7.14, 7.19-7.42, 7.50-7.52 (m, m, m, 2H, 10H, 2H, C_6H_4, C_6H_5 ×2), 9.61 (d, *J* = 5.4 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 19.1, 21.1, 26.7, 34.5, 40.8, 66.6, 127.5, 127.7, 129.0, 129.5, 129.6, 129.7, 132.9, 133.0, 135.5, 135.5, 137.1 139.1, 200.2; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_2SiNa$ $(M+Na)^+$: 451.2064, found: 451.2087.

18.4. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)-2,3-methanobutanal 21d

Colorless oil; 66% ee derived from **20d**; $[\alpha]^{20}_{D}$ = +69.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H, $(CH_3)_3C$), 1.44 (dd, *J* = 5.0, 8.2 Hz, 1H, CH_A of cyclopropane), 1.77 (dd, *J* = 5.0, 5.2 Hz, 1H, CH_B of cyclopropane), 2.25 (dt, *J* = 8.2, 5.2 Hz, 1H, C*H*CHO), 3.75 (d, *J* = 11.1 Hz, 1H, CH_AOSi), 4.00 (d, *J* = 11.1 Hz, 1H, CH_BOSi), 7.21-7.43, 7.48-7.50 (m, m, 12H, 2H, C_6H_4, C_6H_5 ×2), 9.61 (d, *J* = 5.2 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 19.1, 26.7, 34.2, 40.4, 66.3, 127.6, 127.7, 128.5, 129.6, 129.8, 131.1, 132.7, 132.8, 133.3, 135.4, 135.5, 140.5, 199.6; HRMS (ESI-TOF): Calcd for $C_{27}H_{29}ClO_2SiNa$ $(M+Na)^+$: 471.1518, found: 471.1496.

18.5. (2*S*,3*R*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)-2,3-methanobutanal 21e

Colorless oil; 73% ee derived from **20e**; $[\alpha]^{19}_{D}$ = +77.5 (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H, $(CH_3)_3C$), 1.44 (dd, *J* = 5.0, 8.2 Hz, 1H, CH_A of cyclopropane), 1.77 (dd, *J* = 5.0, 5.2 Hz, 1H, CH_B of cyclopropane), 2.25 (dt, *J* = 8.1, 5.2 Hz, 1H, C*H*CHO), 3.75 (d, *J* = 11.1 Hz, 1H, CH_AOSi), 4.00 (d, *J* = 11.1 Hz, 1H, CH_BOSi), 7.21-7.50 (m, 14H, C_6H_4, C_6H_5 ×2), 9.61 (d, *J* = 5.2 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 19.1, 26.7, 34.1, 40.5, 66.3, 121.4, 127.6, 127.7, 129.6, 129.8, 131.4, 132.7, 132.8, 135.4, 135.5, 141.1, 199.5; HRMS (ESI-TOF): Calcd for $C_{27}H_{29}BrO_2SiNa$ $(M+Na)^+$: 515.1012, found: 515.1010.

19. Typical procedure for oxidation of the aldehyde 21a into the carboxylic acid 22a.[58]

To a colorless solution of 187 mg (0.45 mmol) of (*2S,3R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanal **21a** and 16 mg (0.14 mmol, 0.3 equiv) of NaH_2PO_4 in 5.5 mL of a 10:1 mixture of MeCN and water were added at 0 °C 61 μL (0.54 mmol, 1.2 equiv) of 35% aq. H_2O_2 solution and a solution of 76 mg (0.68 mmol, 1.5 equiv.) of $NaClO_2$ in 2 mL of water. After stirring at rt for 3 h, 1 mL of sat. aq. Na_2SO_3 solution was added to the reaction mixture. The resulted mixture was adjusted to pH 3 with 1.0M aq. HCl solution and extracted with 10 mL ×3 of EtOAc. The combined EtOAc layers were washed with brine and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 5:1 mixture of hexane and EtOAc to afford 190 mg (98 % yield) of (2*S*,3*R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanoic acid **22a**.

19.1. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-phenylbutanoic acid 22a[58]

Colorless solid; 71% ee derived from **20a**; mp: 143-145 °C; $[\alpha]^{28}_{D}$ = +57.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1.38 (dd, *J* = 4.8, 8.0 Hz, 1H, CH_A of cyclopropane), 1.55 (dd, *J* = 4.8, 5.7 Hz, 1H, CH_B of cyclopropane), 2.18 (dd, *J* = 5.7, 8.0 Hz, 1H, C*H*CO_2H), 3.98 (s, 2H, CH_2OSi), 7.15-7.23, 7.28-7.38, 7.43-7.46, 7.50-7.52 (m, m, m, m, 4H, 7H, 2H, 2H, C_6H_5 ×3), 11.59 (br, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 24.5, 26.5, 39.6, 66.4, 127.2, 127.4, 127.6, 128.2, 129.3, 129.5, 130.1, 133.2, 133.4, 135.4, 135.5, 142.7, 178.2; HRMS (ESI-TOF): Calcd for $C_{27}H_{30}O_3SiNa$ $(M+Na)^+$: 453.1856, found: 453.1852.

19.2. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butanoic acid 22b

Colorless solid; 36% ee derived from **20b**; mp: 93-94 °C; $[\alpha]^{20}_D$ = +38.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H, $(CH_3)_3C$), 1,32-1.36 (m, 1H, CH_A of cyclopropane), 1.52 (dd, *J* = 4.9, 5.6 Hz, 1H, CH_B of cyclopropane), 2.11-2.16 (m, 1H, C*H*CO_2H), 3.84 (s, 3H, CH_3O), 3.95 (s, 2H, CH_2OSi), 6.86, 7.17-7.39, 7.50-7.52 (d, m, m, *J* = 8.7 Hz, 2H, 10H, 2H, C_6H_4, C_6H_5 ×2), 9.55 (br, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 19.4, 24.6, 26.6, 38.8, 55.4, 66.5, 113.5, 127.4, 127.5, 129.3, 129.5, 131.1, 133.2, 133.4, 134.9, 135.5, 135.5, 158.8, 177.1; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_4SiNa$ $(M+Na)^+$: 483.1962, found: 483.1978.

19.3. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methylphenyl)butanoic acid 22c

Colorless solid; 65% ee derived from **20c**; mp: 124-127 °C; $[\alpha]^{25}_D$ = +69.3 (*c* 0.96, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1,32-1.37 (m, 1H, CH_A of cyclopropane), 1.53 (dd, *J* = 4.8, 5.7, 1H, CH_B of cyclopropane), 2.12-2.18 (m, 1H, C*H*CO_2H), 2.39 (s, 3H, CH_3), 3.97 (s, 2H, CH_2OSi), 7.13-7.38, 7.49-7.53 (m, m, 12H, 2H, C_6H_4, C_6H_5 ×2), 11.80 (br, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 19.4, 21.1, 24.7, 26.5, 39.2, 66.5, 127.4, 127.5, 128.8, 129.2, 129.4, 129.9, 133.2, 133.4, 135.5, 135.5, 136.8, 139.7, 178.3; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_3SiNa$ $(M+Na)^+$: 467.2013, found: 467.2036.

19.4. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)-2,3-methanobutanoic acid 22d

Colorless solid; 66% ee derived from **20d**; mp: 42-44 °C; $[\alpha]^{18}_D$ = +87.8 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1,35 (dd, *J* = 4.8, 8.0 Hz, 1H, CH_A of cyclopropane), 1.54 (dd, *J* = 4.8, 5.9 Hz, 1H, CH_B of cyclpropane), 2.11 (dd, *J* = 5.9, 8.0 Hz, 1H, C*H*CO_2H), 3.93 (d, *J* = 10.7 Hz, 1H, CH_AOSi), 3.97 (d, *J* = 10.7 Hz, 1H, CH_BOSi), 7.18-7.39, 7.47-7.49 (m, m, 12H, 2H, C_6H_4, C_6H_5 ×2), 11.06 (br, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 24.5, 26.6, 38.7, 66.2, 127.5, 127.6, 128.3, 129.4, 129.6, 131.3, 133.0, 133.1, 133.2, 135.4, 135.5, 141.1, 177.0; HRMS (ESI-TOF): Calcd for $C_{27}H_{29}ClO_3SiNa$ $(M+Na)^+$: 487.1467, found: 487.1465.

19.5. (2*S*,3*R*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)-2,3-methanobutanoic acid 22e

Colorless sticky oil; 73% ee derived from **20e**; $[\alpha]^{22}_D$ = +77.9 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1,34 (dd, *J* = 4.9, 8.0 Hz, 1H, CH_A of cyclopropane), 1.55 (dd, *J* = 4.9, 5.9 Hz, 1H, CH_B of cyclpropane), 2.11 (dd, *J* = 5.9, 8.0 Hz, 1H, C*H*CO_2H), 3.94 (d, *J* = 10.7 Hz, 1H, CH_AOSi), 3.98 (d, *J* = 10.7 Hz, 1H, CH_BOSi), 7.19-7.50 (m, 14H, C_6H_4, C_6H_5 ×2), 11.71 (br, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 24.5, 26.6, 38.9, 66.2, 121.2, 127.5, 127.6, 129.4, 129.6, 131.3, 131.7, 133.0, 133.2, 135.4, 135.5, 141.6, 177.8; HRMS (ESI-TOF): Calcd for $C_{27}H_{30}BrO_3Si$ $(M+H)^+$: 509.1142, found: 509.1157.

20. Typical procedure of amidation of 22b with 1-adamantanamine sulfate.[58]

To a solution of 143 mg (0.31 mmol) of (*2S,3R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butanoic acid **22b** in 6 mL of acetone were added dropwise at 0 °C 32 μL (0.34 mmol, 1.1 equiv) of ethyl chloroformate and 47 μL (0.34 mmol, 1.1 equiv) of triethylamine. After stirring at 0 °C for 30 min, 68 mg (0.34 mmol, 1.1 equiv) of 1-adamantanamine sulfate and 0.68 mL (0.58 mmol, 2.0 equiv) of 1.0M aq. NaOH solution were added at 0 °C to the colorless suspension. The mixture was stirred at 0 °C for 24 h, diluted with 30 mL of EtOAc, washed with 5 mL of brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 6:1 mixture of hexane and EtOAc to afford 150 mg (84% yield) of (2*S*,3*R*)-*N*-adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butanamide **23b.**

20.1. (2*S*,3*R*)-*N*-Adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl) butanamide 23b

Colorless solid; 36% ee derived from **20b**; mp: 147-149 °C; $[\alpha]^{19}_D$ = +24.2 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 9H, $(CH_3)_3C$), 1.09 (dd, *J* = 4.6, 8.1 Hz, 1H, CH_A of cyclopropane), 1.39 (dd, *J* = 4.6, 5.7 Hz, 1H, CH_B of cyclopropane), 1.64-1.68 (m, 6H, CH_2 ×3 of adamantane), 1.77 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 2.01-2.07 (m, 9H, CH_2 ×3 of adamantane, CH ×3 of adamantane), 3.83 (s, 3H, CH_3O), 3.85 (d, *J* = 10.5 Hz, 1H, CH_AOSi), 4.02 (d, *J* = 10.5 Hz, 1H, CH_BOSi), 5.49 (br, 1H, NH), 6.83, 7.18-7.21, 7.25-7.38, 7.48-7.50 (d, m, m, m, *J* = 8.7 Hz, 2H, 2H, 8H, 2H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 19.2, 26.9, 28.6, 29.5, 36.1, 36.4, 41.8, 52.1, 55.4, 66.1, 113.4, 127.3, 127.4, 129.2, 129.3, 131.1, 133.5, 133.8, 135.6, 135.6, 135.9, 158.5, 169.2; HRMS (ESI-TOF): Calcd for $C_{38}H_{47}NO_3SiNa$ $(M+Na)^+$: 616.3217, found: 616.3202.

20.2. (2*S*,3*R*)-*N*-Adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-(4-methylphenyl) butanamide 23c

Colorless sticky oil; 65% ee derived from **20c**; $[\alpha]^{22}_D$ = +37.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 9H, $(CH_3)_3C$), 1.10 (dd, *J* = 4.7, 8.1 Hz, 1H, CH_A of cyclopropane), 1.41 (dd, *J* = 4.7, 5.7 Hz, 1H, CH_B of cyclopropane), 1.64-1.68 (m, 6H, CH_2 ×3 of adamantane), 1.79 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 2.01-2.08 (m, 9H, CH_2 ×3 of adamantane, CH ×3 of adamantane), 2.38 (s, 3H, CH_3), 3.87 (d, *J* = 10.5 Hz, 1H, CH_AOSi), 4.04 (d, *J* = 10.5 Hz, 1H, CH_BOSi), 5.50 (br, 1H, NH), 7.10-7.12, 7.16-7.20, 7.23-7.38, 7.46-7.49 (m, m, m, m, 2H, 2H, 8H, 2H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 19.2, 21.1, 26.9, 28.4, 29.5, 36.3, 36.4, 41.8, 52.1, 66.1, 127.3, 127.4, 128.7, 129.2, 129.3, 130.0, 133.5, 133.8, 135.6, 135.6, 136.3, 140.6, 169.2; HRMS (ESI-TOF): Calcd for $C_{38}H_{48}NO_2Si$ $(M+H)^+$: 578.3449, found: 578.3462.

20.3. (2*S*,3*R*)-*N*-Adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-3-(4-chlorophenyl)-2,3-methano butanamide 23d

Colorless solid; 66% ee from **20d**; mp: 88-89 °C; $[\alpha]^{17}_{D}$ = +57.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H, $(CH_3)_3C$), 1.09 (dd, *J* = 4.7, 8.1 Hz, 1H, CH_A of cyclopropane), 1.43 (dd, *J* =4.7, 5.7 Hz, 1H, CH_B of cyclopropane), 1.64-1.68 (m, 6H, CH_2 ×3 of adamantane), 1.76 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 2.01-2.08 (m, 9H, CH_2 ×3 of adamantane, CH ×3 of adamantane), 3.86 (d, *J* = 10.6 Hz, 1H, CH_AOSi), 4.05 (d, *J* = 10.6 Hz, 1H, CH_BOSi), 5.49 (br, 1H, NH), 7.19-7.39, 7.45-7.48 (m, m, 12H, 2H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 19.2, 26.9, 28.3, 29.5, 36.2, 36.4, 41.8, 52.2, 65.7, 127.4, 127.5, 128.1, 129.4, 129.4, 131.4, 132.5, 133.3, 133.5, 135.5, 135.5, 142.1, 168.8; HRMS (ESI-TOF): Calcd for $C_{37}H_{44}ClNO_2SiNa$ $(M+Na)^+$: 620.2722, found: 620.2724.

20.4. (2*S*,3*R*)-*N*-Adamant-1-yl-3-(4-bromophenyl)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano butanamide 23e

Colorless solid; 73% ee derived from **20e**; mp: 79-81 °C; $[\alpha]^{19}_{D}$ = +66.7 (*c* 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H, $(CH_3)_3C$), 1.08 (dd, *J* = 4.7, 8.1 Hz, 1H, CH_A of cyclopropane), 1.43 (dd, *J* = 4.7, 5.7 Hz, 1H, CH_B of cyclopropane), 1.64-1.70 (m, 6H, CH_2 ×3 of adamantane), 1.75 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 2.02-2.08 (m, 9H, CH_2 ×3 of adamantane, CH ×3 of adamantane), 3.85 (d, *J* = 10.6 Hz, 1H, CH_AOSi), 4.06 (d, *J* = 10.6 Hz, 1H, CH_BOSi), 5.49 (br, 1H, NH), 7.18-7.48 (m, 14H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.2, 26.9, 28.2, 29.5, 36.3, 36.4, 41.8, 52.2, 65.7, 120.6, 127.4, 127.5, 129.4, 129.4, 131.1, 131.8, 133.3, 133.5, 135.5, 135.5, 142.6, 168.8; HRMS (ESI-TOF): Calcd for $C_{37}H_{45}BrNO_2Si$ $(M+H)^+$: 642.2397, found: 642.2396.

20.5. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-*N*-(3,5-dimethyladamant-1-yl)-2,3-methano-3-phenyl butanamide 27

Colorless solid; 72% ee from **20a**; mp: 116-118 °C; $[\alpha]^{21}_{D}$ = +39.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 6H, CH_3 × 2), 0.91 (s, 9H, $(CH_3)_3C$), 1.10-1.18 (m, 3H, CH_2 of adamantane, CH_A of cyclopropane), 1.26-1.38 (m, 4H, CH_2 ×2 of adamantane), 1.41-1.43 (m, 1H, CH_B of cyclopropane), 1.63-1.76 (m, 4H, CH_2 ×2 of adamantane), 1.80-1.91 (m, 3H, CH_2 of adamantane, CH of adamantane), 2.11-2.14 (m, 1H, CHCO), 3.89 (d, *J* = 10.5 Hz, 1H, CH_AOSi), 4.04 (d, *J* = 10.5 Hz, 1H, CH_BOSi), 5.56 (br, 1H, NH), 7.15-7.23, 7.27-7.38, 7.48-7.50 (m, m, m, 4H, 9H, 2H, C_6H_5 ×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 19.2, 26.9, 28.2, 30.1, 30.2, 32.4, 36.9, 40.4, 42.7, 42.7, 47.6, 47.8, 50.6, 53.7, 66.0, 126.8, 127.3, 127.5, 128.1, 129.2, 129.3, 130.2, 133.4, 133.7, 135.6, 143.6, 169.2; HRMS (ESI-TOF): Calcd for $C_{39}H_{49}NO_2SiNa$ $(M+Na)^+$: 614.3425, found: 614.3445.

21. Typical procedure for desilylation of 23a with TBAF.

To a solution of 275 mg (0.49 mmol) of (*2S,3R*)-*N*-adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanamide **23a** in 5 mL of THF was added at rt 980 μL (0.98 mmol, 2.0 equiv) of a 1.0M TBAF solution in THF. After stirring at rt for 3 h, the colorless solution was diluted with 30 mL of EtOAc, washed with 5 mL of half brine, 5 mL of brine, and dried over anhydrous $MgSO_4$. The

residue was chromatographed on silica gel with a 2:1 mixture of hexane and EtOAc to afford 147 mg (93% yield) of (2*S*,3*R*)-*N*-adamant-1-yl-4-hydroxy-2,3-methano-3-phenylbutanamide **24a**.

21.1. (2*S*,3*R*)-*N*-Adamant-1-yl-4-hydroxy-2,3-methano-3-phenylbutanamide 24a

Colorless solid; 82% ee; mp 74-75 ^{o}C; $[\alpha]^{25}_{D}$ = +73.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31-1.36 (m, 1H, CH_A of cyclopropane), 1.67-1.72 (m, 8H, CH_B of cyclopropane, CH_2 ×3 of adamantine, CHCO), 2.02-2.05 (m, 6H, CH_2 ×3 of adamantane), 2.07-2.12 (m, 3H, CH ×3 of adamantane), 3.76-3.85 (m, 2H, CH_AOH, OH), 4.16 (dd, *J* = 6.4, 11.5 Hz, 1H, CH_BOH), 5.55 (br, 1H, NH), 7.21-7.35 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 29.4, 29.5, 36.3, 36.8, 41.6, 52.5, 65.5, 126.9, 128.3, 128.5, 143.3, 171.5; HRMS (ESI-TOF): Calcd for $C_{21}H_{27}NO_2Na$ $(M+Na)^+$: 348.1934, found: 348.1950; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 12.8 min, T_r(minor) 21.2 min (er 91:9).

21.2. (2*S*,3*R*)-*N*-Adamant-1-yl-4-hydroxy-2,3-methano-3-(4-methoxyphenyl)butanamide 24b

Colorless solid; 34% ee; mp: 150-152 ^{o}C; $[\alpha]^{19}_{D}$ = +42.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.31 (m, 1H, CH_A of cyclopropane), 1.63-1.66 (m, 2H, CH_B of cyclopropane, CHCO), 1.67-1.72 (m, 6H, CH_2 ×3 of adamantane), 2.02-2.06 (m, 6H, CH_2 ×3 of adamantane), 2.06-2.13 (m, 3H, CH ×3 of adamantane), 3.74-3.81 (m, 2H, CH_AOH, OH), 3.79 (s, 3H, CH_3O), 4.07-4.13 (m, 1H, CH_BOH), 5.55 (br, 1H, NH), 6.84, 7.26 (d, d, *J* = 8.8, 8.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 29.4, 29.5, 36.2, 36.3, 41.6, 52.5, 55.3, 65.7, 113.9, 129.5, 135.4, 158.5, 171.6; HRMS (ESI-TOF): Calcd for $C_{22}H_{29}NO_3Na$ $(M+Na)^+$: 378.2040, found: 378.2039; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 17.0 min, T_r(minor) 15.4 min (er 67:33).

21.3. (2*S*,3*R*)-*N*-Adamant-1-yl-4-hydroxy-2,3-methano-3-(4-methylphenyl)butanamide 24c

Colorless solid; 58% ee; mp: 161-163 ^{o}C; $[\alpha]^{25}_{D}$ = +70.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29-1.32 (m, 1H, CH_A of cyclopropane), 1.67-1.72 (m, 8H, CH_B of cyclopropane, CHCO, CH_2 ×3 of adamantane), 2.02-2.06 (m, 6H, CH_2 ×3 of adamantane), 2.06-2.12 (m, 3H, CH ×3 of adamantane), 2.32 (s, 3H, CH_3), 3.75-3.83 (m, 2H, CH_AOH, OH), 4.13 (dd, *J* = 6.5, 10.7 Hz, 1H, CH_BOH), 5.55 (br, 1H, NH), 7.12, 7.22 (d, d, *J* = 7.8, 7.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 21.0, 29.4, 29.5, 36.3, 36.5, 41.6, 52.5, 65.5, 128.2, 129.2, 136.6, 140.3, 171.5; HRMS (ESI-TOF): Calcd for $C_{22}H_{29}NO_2Na$ $(M+Na)^+$: 362.2091, found: 362.2091; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 10.7 min, T_r(minor) 9.3 min (er 79:21).

21.4. (2*S*,3*R*)-*N*-Adamant-1-yl-3-(4-chlorophenyl)-4-hydroxy-2,3-methanobutanamide 24d

Colorless solid; 73% ee; mp: 132-134 ^{o}C; $[\alpha]^{17}_{D}$ = +92.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28-1.32 (m, 1H, CH_A of cyclopropane), 1.67-1.72 (m, 8H, CH_A of cyclopropane, CHCO, CH_2 ×3

of adamantane), 2.01-2.05 (m, 6H, CH_2 ×3 of adamantane), 2.07-2.13 (m, 3H, CH ×3 of adamantane), 3.72-3.82 (m, 2H, CH_AOH, OH), 4.11 (dd, J = 6.0, 11.7 Hz, 1H, CH_BOH), 5.55 (br, 1H, NH), 7.28 (s, 4H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 29.4, 29.5, 36.1, 36.3, 41.6, 52.6, 65.5, 128.6, 129.8, 132.7, 141.8, 171.1; HRMS (ESI-TOF): Calcd for $C_{21}H_{26}ClNO_2Na$ $(M+Na)^+$: 382.1544, found: 382.1533; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 11.5 min, T_r(minor) 9.2 min (er 86.6:13.4).

21.5. (2*S*,3*R*)-*N*-Adamant-1-yl-3-(4-bromophenyl)-4-hydroxy-2,3-methanobutanamide 24e

Colorless solid; 73% ee; mp: 159-161 °C; $[\alpha]^{23}_D$ = +98.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27-1.32 (m, 1H, CH_A of cyclopropane), 1.64-1.69 (m, 2H, CH_A of cyclopropane, CHCO), 1.67-1.72 (m, 6H, CH_2 ×3 of adamantane), 2.01-2.07 (m, 6H, CH_2 ×3 of adamantane), 2.05-2.13 (m, 3H, CH ×3 of adamantane), 3.71-3.82 (m, 2H, CH_AOH, OH), 4.11 (dd, J = 5.9, 11.7 Hz, 1H, CH_BOH), 5.55 (br, 1H, NH), 7.22, 7.43 (d, d, J = 8.5, 8.5 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 29.4, 36.1, 36.3, 41.6, 52.6, 65.5, 120.8, 130.1, 131.6, 142.3, 171.1; HRMS (ESI-TOF): Calcd for $C_{21}H_{26}BrNO_2Na$ $(M+Na)^+$: 426.1039, found: 426.1034; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 13.7 min, T_r(minor) 10.2 min (er 86.6:13.4).

21.6. (2*S*,3*R*)-*N*-(3,5-Dimethyladamant-1-yl)-4-hydroxy-2,3-methano-3-phenylbutanamide 28

Colorless oil; 72% ee; $[\alpha]^{25}_D$ = +85.3 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (s, 6H, CH_3 ×2), 1.13-1.22 (m, 2H, CH of adamantane, CH_A of cyclopropane), 1.29-1.41 (m, 5H, CH_2 ×2 of adamantane, CH_B of cyclopropane), 1,66-1.71 (m, 6H, CH_2 ×3 of adamantane), 1.83-1.90 (m, 2H, CH_2 of adamantane), 2.15-2.18 (m, 1H, CHCO), 3.76-3.85 (m, 2H, CH_AOH, OH), 4.15 (dd, J = 6.4, 11.1 Hz, 1H, CH_BOH), 5.60 (br, 1H, NH), 7.21-7.26, 7.29-7.35 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 29.4, 30.1, 30.1, 32.4, 36.9, 40.2, 42.6, 47.5, 47.6, 50.5, 54.2, 65.5, 126.9, 128.4, 128.5, 143.2, 171.6; HRMS (ESI-TOF): $C_{23}H_{31}NO_2Na$ $(M+Na)^+$: 376.2247, found: 376.2247; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 10.1 min, T_r(minor) 12.7 min (er 86:14).

22. Typical procedure of reduction of 24a.

A solution of 128 mg (0.39 mmol, 1.0 equiv) of (*2S,3R*)-*N*-adamant-1-yl-4-hydroxy-2,3-methano-3-phenylbutanamide **24a** in 2 mL of anhydrous CH_2Cl_2 was added at 0 °C under an argon atmosphere to a suspension of 74 mg (1.95 mmol, 5.0 equiv) of $LiAlH_4$ in 5 mL of anhydrous toluene. After stirring at 70 °C for 24 h and at 100 °C for 3 h, the colorless suspension was treated with 246 mg (5.85 mmol, 15 equiv) of NaF, diluted at 0 °C with 15 mL of EtOAc, quenched at 0 °C with 140 μL (7.80 mmol, 20 equiv) of water, and filtered through Celite. The filtrate was evaporated and the residue was chromatographed on silica gel with a 9:1:0.2 mixture of hexane, EtOAc, and triethylamine to afford

105 mg (87% yield) of (2*R*,3*S*)-4-(adamant-1-ylamino)-2,3-methano-2-phenylbutan-1-ol **25a**.

22.1. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2,3-methano-2-phenylbutan-1-ol 25a[58]

Colorless solid; 86% ee; mp: 89-90 °C; $[\alpha]^{25}_{D}$ = +16.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (dd, *J* = 5.1, 5.1 Hz, 1H, CH_A of cyclopropane), 1.14 (dd, *J* = 5.1, 8.5 Hz, 1H, CH_B of cyclopropane), 1.27-1.34 (m, 2H, C*H*CH_2N*H*), 1.60-1.74 (m, 13H, CH_2 ×6 of adamantane, OH), 2.05-2.10 (m, 3H, CH ×3 of adamantane), 2.28 (dd, *J* = 11.7, 11.7 Hz, 1H, CH_AN), 3.39 (dd, *J* = 5.0, 11.7 Hz, 1H, CH_BN), 3.51 (d, *J* = 12.2 Hz, 1H, CH_AO), 4.15 (d, *J* = 12.2 Hz, 1H, CH_BO), 7.17-7.21, 7.27-7.33, 7.37-7.39 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 25.3, 29.5, 31.9, 36.6, 40.8, 42.4, 50.7, 67.6, 126.0, 128.1, 128.2, 145.2; HRMS (ESI-TOF): Calcd for $C_{21}H_{30}NO$ $(M+H)^+$: 312.2327, found: 312.2304; IR (NaCl, ν_{max}/cm^{-1}): 3269, 2906, 2846; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.05) T_r(major) 12.0 min, T_r(minor) 7.5 min (er 93:7).

22.2. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2,3-methano-2-(4-methoxyphenyl)butan-1-ol 25b

Reaction conditions: at 70 °C for 19h; Colorless solid; 34% ee; mp: 88-91 °C; $[\alpha]^{17}_{D}$ = +5.78 (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (dd, *J* = 5.0, 5.0 Hz, 1H, CH_A of cyclopropane), 1.08 (dd, *J* = 5.0, 8.5 Hz, 1H, CH_B of cyclopropane), 1.22-1.28 (m, 1H, C*H*CH_2N), 1.60-1.74 (m, 14H, CH_2 ×6 of adamantane, OH, NH), 2.03-2.06 (m, 3H, CH ×3 of adamantane), 2.25 (dd, *J* = 11.8, 11.8 Hz, 1H, CH_AN), 3.37 (dd, *J* = 6.8, 11.8 Hz, 1H, CH_BN), 3.48 (d, *J* = 11.9, 1H, CH_AO), 3.79 (s, 3H, CH_3O), 4.06 (d, *J* = 11.9 Hz, 1H, CH_BO), 6.84, 7.31 (d, d, *J* = 8.8, 8.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 25.0, 29.5, 31.4, 36.6, 40.8, 42.5, 50.7, 55.3, 67.9, 113.6, 129.4, 137.5, 157.9; HRMS (ESI-TOF): Calcd for $C_{22}H_{32}NO_2$ $(M+H)^+$: 342.2428, found: 342.2437; IR (KBr, ν_{max}/cm^{-1}): 3266, 2904, 2846; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 14.8 min, T_r(minor) 11.0 min (er 67:33).

22.3. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2,3-methano-2-(4-methylphenyl)butan-1-ol 25c

Reaction conditions: at 70 °C for 14h and 100 °C for 3h; Colorless solid; 60% ee; mp 128-130 °C; $[\alpha]^{21}_{D}$ = +13.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.11 (dd, *J* = 4.4, 8.5 Hz, 1H, CH_B of cyclopropane), 1.24-1.31 (m, 1H, C*H*CH_2N), 1.59-1.73 (m, 14H, CH_2 ×6 of adamantane, OH, NH), 2.04-2.10 (m, 3H, CH ×3 of adamantane), 2.26 (dd, *J* = 11.7, 11.7 Hz, 1H, CH_AN), 2.31 (s, 1H, CH_3), 3.38 (dd, *J* = 5.0, 11.7 Hz, 1H, CH_BN), 3.49 (d, *J* = 12.2, 1H, CH_AO), 4.11 (d, *J* = 12.2 Hz, 1H, CH_BO), 7.11, 7.28 (d, d, *J* = 7.8, 7.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 21.0, 25.3, 29.5, 31.5, 36.6, 40.8, 42.5, 50.6, 67.7, 128.0, 128.9, 135.5, 142.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{32}NO$ $(M+H)^+$: 326.2478, found: 326.2460; IR (KBr, ν_{max}/cm^{-1}): 3267, 2902, 2846, 2360; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 11.5 min, T_r(minor) 6.8 min (er 80:20).

22.4. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2-(4-chlorophenyl)-2,3-methanobutan-1-ol 25d

Reaction conditions: at 70 °C for 12h and 100 °C for 3h; Colorless solid; 75% ee; mp: 98-101 °C; $[\alpha]^{17}_{D}$ = +18.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.12 (dd, *J* = 4.4, 8.5 Hz, 1H, CH_B of cyclopropane), 1.23-1.29 (m, 1H, C*H*CH_2N), 1.56-1.73 (m, 14H, CH_2 ×6 of adamantane, OH, NH), 2.04-2.10 (m, 3H, CH ×3 of adamantane), 2.26 (dd, *J* = 11.8, 11.8 Hz, 1H, CH_AN), 3.39 (dd, *J* = 7.0, 11.8 Hz, 1H, CH_BN), 3.49 (d, *J* = 12.5, 1H, CH_AO), 4.08 (d, *J* = 12.5 Hz, 1H, CH_BO), 7.25, 7.31 (d, d, *J* = 8.7, 8.7 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 25.5, 29.5, 31.4, 36.6, 40.7, 42.4, 50.7, 67.4, 128.2, 129.5, 131.7, 143.8; HRMS (ESI-TOF): Calcd for $C_{21}H_{29}ClNO$ $(M+H)^+$: 346.1932, found: 346.1926; IR (KBr, ν_{max}/cm^{-1}): 3267, 2906, 2848, 2360; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 7.9 min, T_r(minor) 6.3 min (er 87.6:12.4).

22.5. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2-(4-bromophenyl)-2,3-methanobutan-1-ol 25e

Reaction conditions: at 70 °C for 12h and 100 °C for 3h; Colorless solid; 76% ee; mp: 114-117 °C; $[\alpha]^{22}_{D}$ = +19.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.12 (dd, *J* = 4.4, 8.5 Hz, 1H, CH_B of cyclopropane), 1.22-1.29 (m, 1H, C*H*CH_2N), 1.59-1.73 (m, 14H, CH_2 ×6 of adamantane, OH, NH), 2.05-2.11 (m, 3H, CH ×3 of adamantane), 2.26 (dd, *J* = 11.7, 11.7 Hz, 1H, CH_AN), 3.38 (dd, *J* = 6.9, 11.7 Hz, 1H, CH_BN), 3.48 (d, *J* = 12.4, 1H, CH_AO), 4.08 (d, *J* = 12.4 Hz, 1H, CH_BO), 7.26, 7.41 (d, d, *J* = 8.6, 8.6 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 25.6, 29.5, 31.4, 36.6, 40.7, 42.4, 50.7, 67.3, 119.8, 129.9, 131.2, 144.3; HRMS (ESI-TOF): Calcd for $C_{21}H_{29}BrNO$ $(M+H)^+$: 390.1427, found: 390.1417; IR (KBr, ν_{max}/cm^{-1}): 3269, 2902, 2846; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 8.0 min, T_r(minor) 6.8 min (er 88:12).

22.6. (2*R*,3*S*)-4-[(3,5-Dimethyladamant-1-yl)amino]-2,3-methano-2-phenylbutan-1-ol 29

Colorless oil; 74% ee; $[\alpha]^{19}_{D}$ = +13.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (dd, *J* = 5.2, 5.2 Hz, 1H, CH_A of cyclopropane), 0.85 (s, 6H, CH_3 ×2 of adamantane), 1.12-1.16 (m, 3H, CH_2 of adamantane, CH_B of cyclopropane), 1.23-1.38 (m, 10H, CH_2 ×5 of adamantane), 1.45-1.48 (m, 1H, CH of adamantane), 1.56-1.59 (m, 2H, OH, NH), 2.13-2.16 (m, 1H, C*H*CH_2N), 2.27 (t, *J* = 11.6, 11.6 Hz, 1H, CH_AN), 3.39 (dd, *J* = 6.8, 11.6 Hz, 1H, CH_BN), 3.50 (d, *J* = 12.3 Hz, 1H, CH_AO), 4.14 (d, *J* = 12.3 Hz, 1H, CH_BO), 7.17-7.21, 7.27-7.32, 7.36-7.39 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 25.4, 30.2, 31.8, 32.4, 41.0, 41.1, 42.9, 48.5, 48.7, 50.9, 52.5, 67.6, 125.9, 128.1, 128.2, 145.2; HRMS (ESI-TOF): Calcd for $C_{23}H_{34}NO$ $(M+H)^+$: 340.2635, found: 340.2650; IR (NaCl, ν_{max}/cm^{-1}): 3263, 2900, 2843, 1600; The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 10.0 min, T_r(minor) 7.7 min (er 87:13).

23. Typical procedure for methylation of 25b.[58]

To a colorless solution of 25 mg (0.073 mmol) of (2*R*,3*S*)-4-(adamant-1-ylamino)-2,3-methano-2-(4-methoxyphenyl)butan-1-ol **25b** and 9 mg (0.11 mmol, 1.5 equiv) of $NaHCO_3$ in 2 mL of anhydrous DMF was added at rt 9 μL (0.14 mmol, 2.0 equiv) of MeI. After stirring at 80 °C for 2 h, the reaction mixture was diluted with 20 mL of a 3:1 mixture of EtOAc and hexane, washed with 10 mL of water and 5 mL of half brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 9:1:0.1 mixture of hexane, EtOAc, and triethylamine to afford 15 mg (58% yield) of (+)-(2*R*,3*S*)-4-(*N*-adamant-1-yl-*N*-methylamino)-2,3-methano-2-(4-methoxyphenyl)butan-1-ol **26b**.

23.1. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2,3-methano-2-(4-methoxyphenyl)butan-1-ol 26b

Colorless oil; 34% ee derived from **25b**; $[\alpha]^{22}_D$ = +13.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (dd, *J* = 4.9, 4.9 Hz, 1H, CH_A of cyclopropane), 1.17 (dd, *J* = 3.8, 4.9 Hz, 1H, CH_B of cyclopropane), 1.35-1.41 (m, 1H, C*H*CH_2N), 1.60-1.68 (m, 6H, CH_2 ×3 of adamantane), 1.72-1.75 (m, *J* = 2.8 Hz, 6H, CH_2 ×3 of adamantane), 2.07-2.13 (m, 3H, CH ×3 of adamantane), 2.37 (s, 3H, CH_3N), 2.63 (dd, *J* = 10.5, 12.6 Hz, 1H, CH_AN), 2.79 (dd, *J* = 7.1, 12.6 Hz, 1H, CH_BN), 3.39 (d, *J* = 12.2 Hz, 1H, CH_AO), 3.79 (s, 3H, CH_3O), 4.04 (d, *J* = 12.2 Hz, 1H, CH_BO), 6.65 (br, 1H, OH), 6.84, 7.35 (d, d, *J* = 8.8, 8.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 23.7, 29.6, 31.8, 32.2, 36.7, 37.9, 48.8, 54.8, 55.3, 67.7, 113.6, 129.1, 137.7, 157.9; HRMS (ESI-TOF): Calcd for $C_{23}H_{34}NO_2$ $(M+H)^+$: 356.2584, found: 356.2571; IR (NaCl, ν_{max}/cm^{-1}): 2906, 2848, 2360, 2332.

23.2. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2,3-methano-2-(4-methylphenyl)butan-1-ol 26c

Colorless solid; 60% ee derived from **25c**; mp: 81-83 °C; $[\alpha]^{22}_D$ = +30.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.20 (dd, *J* = 4.4, 8.4 Hz, 1H, CH_B of cyclopropane), 1.37-1.42 (m, 1H, C*H*CH_2N), 1.59-1.68 (m, 6H, CH_2 ×3 of adamantane), 1.73-1.77 (m, 6H, CH_2 ×3 of adamantane), 2.07-2.12 (m, 3H, CH ×3 of adamantane), 2.31 (s, 3H, CH_3N), 2.36 (s, 3H, C*H*$_3$C$_6$H$_4$), 2.65 (dd, *J* = 12.7, 12.7 Hz, 1H, CH_AN), 2.80 (dd, *J* = 7.1, 12.7 Hz, 1H, CH_BN), 3.40 (d, *J* = 12.1 Hz, 1H, CH_AO), 4.08 (d, *J* = 12.1 Hz, 1H, CH_BO), 6.68 (br, 1H, OH), 7.11, 7.32 (d, d, *J* = 8.0, 8.0 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 21.0, 23.9, 29.6, 32.0, 32.2, 36.7, 37.9, 48.8, 54.7, 67.5, 127.8, 128.9, 135.4, 142.4; HRMS (ESI-TOF): Calcd for $C_{23}H_{34}NO$ $(M+H)^+$: 340.2635, found: 340.2614; IR (KBr, ν_{max}/cm^{-1}): 2902, 2846.

23.3. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2-(4-chlorophenyl)-2,3-methanobutan-1-ol 26d

Colorless solid; 75% ee derived from **25d**; mp: 100-102 °C; $[\alpha]^{17}_D$ = +30.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (dd, *J* = 5.0, 5.0 Hz, 1H, CH_A of cyclopropane), 1.21 (dd, *J* = 5.0, 8.5 Hz,

1H, CH_B of cyclopropane), 1.35-1.41 (m, 1H, C*H*CH_2N), 1.59-1.65 (m, 6H, CH_2 ×3 of adamantane), 1.70-1.78 (m, 6H, CH_2 ×3 of adamantane), 2.07-2.12 (m, 3H, CH ×3 of adamantane), 2.34 (s, 3H, CH_3N), 2.65 (dd, *J* = 12.6, 12.6 Hz, 1H, CH_AN), 2.80 (dd, *J* = 6.4, 12.6 Hz, 1H, CH_BN), 3.40 (d, *J* = 12.2, 1H, CH_AO), 4.07 (d, *J* = 12.2 Hz, 1H, CH_BO), 6.75 (br, 1H, OH), 7.25, 7.35 (d, d, *J* = 8.7, 8.7 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.8, 24.4, 29.5, 31.8, 32.2, 36.7, 37.9, 48.7, 54.8, 67.1, 128.2, 129.2, 131.6, 143.9; HRMS (ESI-TOF): Calcd for $C_{22}H_{31}ClNO$ $(M+H)^+$: 360.2089, found: 360.2099; IR (KBr, ν_{max}/cm^{-1}): 2910, 2848.

23.4. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2-(4-bromophenyl)-2,3-methanobutan-1-ol 26e

Colorless solid; 76% ee derived from **25e**; mp: 108-111 °C; $[\alpha]^{22}_D$ = +34.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.78 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.21 (dd, *J* = 4.4, 8.5 Hz, 1H, CH_B of cyclopropane), 1.33-1.41 (m, 1H, C*H*CH_2N), 1.59-1.68 (m, 6H, CH_2 ×3 of adamantane), 1.70-1.77 (m, *J* = 2.7 Hz, 6H, CH_2 ×3 of adamantane), 2.07-2.13 (m, 3H, CH ×3 of adamantane), 2.33 (s, 3H, CH_3N), 2.65 (dd, *J* = 10.4, 12.7 Hz, 1H, CH_AN), 2.80 (dd, *J* = 7.1, 12.7 Hz, 1H, CH_BN), 3.39 (d, *J* = 12.4, 1H, CH_AO), 4.07 (d, *J* = 12.4 Hz, 1H, CH_BO), 6.76 (br, 1H, OH), 7.29, 7.40 (d, d, *J* = 8.6, 8.6 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.8, 24.4, 29.5, 31.8, 32.2, 36.7, 37.9, 48.7, 54.8, 67.1, 119.7, 129.5, 131.2, 144.4; HRMS (ESI-TOF): Calcd for $C_{22}H_{31}BrNO$ $(M+H)^+$: 404.1584, found: 404.1582; IR (KBr, ν_{max}/cm^{-1}): 2904, 2846.

23.5. (+)-(2*R*,3*S*)-4-[*N*-(3,5-Dimethyladamant-1-yl)-*N*-methylamino]-2,3-methano-2-phenyl butan-1-ol 30

Colorless oil; 74% ee derived from **29**; $[\alpha]^{17}_D$ = +25.7 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.77 (dd, *J* = 5.1, 5.1 Hz, 1H, CH_A of cyclopropane), 0.83-0.87 (m, 6H, CH_3 ×2-adamantane), 1.08-1.16 (m, 2H, CH_2 of adamantane), 1.22-1.45 (m, 11H, CH_2 ×5 of adamantane, CH_B of cyclopropane), 1.57-1.62 (m, 1H, CH of adamantane), 2.15-2.19 (m, 1H, C*H*CH_2N), 2.36 (s, 3H, CH_3N), 2.66 (dd, *J* = 10.6, 12.5 Hz, 1H, CH_AN), 2.81 (dd, *J* = 7.0, 12.5 Hz, 1H, CH_BN), 3.41 (d, *J* = 12.2 Hz, 1H, CH_AO), 4.13 (d, *J* = 12.2 Hz, 1H, CH_BO), 6.80 (br, 1H, OH), 7.17-7.21, 7.27-7.31, 7.40-7.43 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.8, 24.2, 30.2, 30.5, 32.2, 32.4, 32.4, 32.5, 36.3, 43.0, 44.1, 44.2, 49.1, 50.8, 56.7, 67.4, 125.9, 127.7, 128.2, 145.3; HRMS (ESI-TOF): Calcd for $C_{24}H_{36}NO$ $(M+H)^+$: 354.2791, found: 354.2786; IR (NaCl, ν_{max}/cm^{-1}): 3201, 2950, 2360, 2341, 1604.

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References

1. (a) Knowles, W. S. *Angew*. *Chem. Int. Ed.* **2002**, *41*, 1998-2007; (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1997**, *99*, 5946-5952.
2. (a) Noyori, R. "*Asymmetric Catalysis In Organic Synthesis"* Wiley-Interscience. **1994**; (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1; (c) Noyori, R.; Okhuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akuragawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856-5858.
3. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976; (b) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263-4265.
4. Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3740-3747.
5. (a) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760-3765; (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953-956; (c) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250; (d) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed*. **1995**, *34*, 2039-2041.
6. (a) Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748-3759; (b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886; (c) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260-2265.
7. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615-1621.
8. List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.
9. For examples: (a) Chinn, A. J.; Kim, B.; Kwon, Y.; Miller, S. J. *J. Am. Chem. Soc*. **2017**, *139*, 18107-18114; (b) Hurtley, A. E.; Stone, E. A.; Metrano, A. J.; Miller, S. J. *J. Org. Chem.* **2017**, *82*, 11326-11336; (c) Grünenfelder, C. E.; Kisunzu, J. K.; Wennemers, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 8571-8574; (d) Gustafson, J. L.; Lim, D.; Barrett, K. T.; Miller, S. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 5125-5129; (e) Lichtor, P. A.; Miller, S. J. *ACS Comb. Sci.* **2011**, *13*, 321-326; (f) Nagano, M.; Doi, M.; Kurihara, M.; Suemune, H.; Tanaka, M. *Org. Lett*. **2010**, *12*, 3564-3566; (g) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454-16455; (h) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101-1103; (i) Berkessel, A.; Gasch, N.; Glaubitz, K.; Koch, C. *Org. Lett*. **2001**, *3*, 3839-3842; (j) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629-1630.
10. (a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601-610; (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481-2495.
11. Llobet, A. I.; Alvarez, M.; Albericio, F. *Chem. Rev*. **2009**, *109*, 2455-2504.
12. Kawashima, Y.; Ezawa, T.; Harada, T.; Noguchi, T.; Kawasaki, M.; Kirihara, M.; Imai, N. *Bull.*

Chem. Soc. Jpn. **2016**, *89*, 257-267.

13. Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett.* **1997**, *38*, 1423-1426.
14. (a) Noguchi, T.; Jung, S.; Imai, N. *Tetrahedron Lett.* **2014**, *55*, 394-396; (b) Jung, S.; Tsukuda, Y.; Kawashima, R.; Ishiki, T.; Matsumoto, A.; Nakaniwa, A.; Takagi, M.; Noguchi, T.; Imai, N. *Tetrahedron Lett.* **2013**, *54*, 5718-5720; (c) Noguchi, T.; Sekine, M.; Yokoo, Y.; Jung, S.; Imai, N. *Chem. Lett.* **2013**, *42*, 580-582; (d) Noguchi, T.; Jung, S.; Imai, N. *Chem. Lett.* **2012**, *41*, 577-579; (e) Noguchi, T.; Tehara, N.; Uesugi, Y.; Jung, S.; Imai, N. *Chem. Lett.* **2012**, *41*, 42-43.
15. (a) Ishizuka, Y.; Fujimori, H.; Noguchi, T.; Kawasaki, M.; Kishida, M.; Nagai, T.; Imai, N.; Kirihara, M. *Chem. Lett.* **2013**, *42*, 1311-1313; (b) Koyata, N.; Miura, T.; Akaiwa, Y.; Sasaki, H.; Sato, R.; Nagai, T.; Fujimori, H.; Noguchi, T.; Kirihara, M.; Imai, N. *Tetrahedron Asymmetry* **2009**, *20*, 2065-2071.
16. (a) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168-12175; (b) Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T. *Chem. Lett.* **1995**, *24*, 1113-1114; (c) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013-12026; (d) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651-2652; (e) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, *21*, 61-64.
17. (a) Ezawa, T.; Jung, S.; Kawashima, Y.; Noguchi, T.; Imai, N. *Tetrahedron: Asymmetry* **2017**, *28*, 75-83; (b) Ezawa, T.; Jung, S.; Kawashima, Y.; Noguchi, T.; Imai, N. *Bull. Chem. Soc. Japan* **2017**, *90*, 689-696; (c) Ezawa, T.; Jung, S.; Kawashima, Y.; Noguchi, T.; Imai, N. *Tetrahedron: Asymmetry* **2017**, *28*, 1690-1699.
18. Ezawa, T.; Kawashima, Y.; Noguchi, T.; Jung, S.; Imai, N. *Tetrahedron: Asymmetry* **2017**, *28*, 266-281.
19. (a) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1248-1252; (b) Bray, B. L. *Nat. Rev. Drug Discovery* **2003**, *2*, 587-593; (c) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243-2266; (d) Beckwith, A. L. J. In *The Chemistry of Amides: Synthesis of Amides*; Zabicky, J., Ed.; Wiley Interscience: New York, 1970.
20. (a) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557-6602; (b) Katritzky, A. R.; He, H. Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210-8213; (c) Ranu, B. C.; Sarkar, A.; Chakraborty, R. *J. Org. Chem.* **1994**, *59*, 4114-4116.
21. (a) El-Faham, A.; Funosas, S. R.; Prohens, R.; Albericio, F. *Chem. Eur. J.* **2009**, *15*, 9404-9416; (b) Mizuhara, T.; Hioki, K.; Yamada, M.; Sasaki, H.; Morisaki, D.; Kunishima, M. *Chem. Lett.* **2008**, *37*, 1190-1191; (c) Kunishima, M.; Kawachi, C.; Hioki, K.; Terao, K.; Tani, S. *Tetrahedron* **2001**, *57*, 1551-1558; (d) Kuwajima, I.; Urabe, H. In *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, pp 486-489; (e) Chen, S. T.; Wu, S. H; Wang, K. T. *Synthesis* **1989**, 37-38; (f) Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17*, 522-524; (g) *Synthetic Reagents*; Pizey, J. S., Ed.; Wiley: New York, 1974; Vol. 1, pp 321-357; (h) Shioiri, T.; Ninomiya, K.;

Yamada, S. Y. *J. Am. Chem. Soc*. **1972**, *94*, 6203-6205; (i) Paul, R.; Anderson, W. *J. Am. Chem. Soc.* **1960**, *82*, 4596-4600; (j) Vaughan, J.; Osato, R. L. *J. Am. Chem. Soc.* **1952**, *74*, 676-678.

22. (a) Chu, W.; Tu, Z.; McElveen, E.; Xu, J.; Taylor, M.; Luedtke, R. R.; Mach, R. H. *Bioorg. Med. Chem.* **2005**, *13*, 77-87; (b) Chaudhary, A.; Girgis, M.; Prashad, M.; Hu, B.; Har, D.; Repic, O.; Blacklock, Y. J. *Tetrahedron Lett.* **2003**, *44*, 5543-5546; (c) Shieh, W. -C.; Carlson, J. A.; Shore, M. E. *Tetrahedron Lett.* **1999**, *40*, 7167-7170; (d) Wenger, R. M. *Helv. Chim. Acta*. **1983**, *66*, 2672-2702; (e) Meienhofer, J. *in Major Methods of Peptide Bond Formation in The Peptides: Analysis, Synthesis, Biology*, ed by Gross, E.; Meienhofer, J. Academic Press, New York, 1979, *1*, 263-314.
23. (a) Puccetti, A.; Lunardi, C. *Discovery Medicine*. **2010**, *9*, 224-228; (b) Nussey, S.; Whitehead, S. *Endocrinology: An Integrated Approach*, Oxford, 2001; (c) Barrett, G. C.; Elmore, D. T. *Amino Acids and Peptides: Biological roles of amino acids and peptides*, Cambridge University Press, Cambridge, 1998.
24. For selected reviews on peptide syntheses: (a) Blaskovich, M. A. *Handbook on Syntheses of Amino Acids: General Routes for the Syntheses of Amino Acids*, Oxford University Press, New York, 2010; (b) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827-10852; (c) Gagnon, P.; Huang, X.; Therrien, E.; Keillor, J. W. *Tetrahedron Lett.* **2002**, *43*, 7717- 7719, and the references cited therein.; (d) Anuradha, M. V.; Ravindranath, B. *Tetrahedron* **1997**, *53*, 1123-1130; (e) Wieland, T.; Bodanszky, M. *The World of Peptides: A Brief History of Peptide Chemistry*, Springer-Verlag, New York, 1991, 77-102. For selected reports for peptide syntheses using unprotected α-amino acids; (f) Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *International Journal of Peptide and Protein Research* **1991**, *37*, 487-493; (g) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839-1842; (h) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.
25. Amblard, M.; Fehrentz, J. A.; Martinez, J.; Subra, G. *Mol. Biotechnol.* **2006**, *33*, 239-254.
26. McGaughey, G. B.; Gagne, M.; Rappe, A. K. *J. Biol. Chem.* **1998**, *273*, 15458-15463.
27. Nezhad, A. K.; Parhami A.; Radb, M. N. S.; Zarea, A. *Tetrahedron Lett.* **2002**, *43*, 2529-2533.
28. Yadav, D. K. T.; Bhanage, B. M. *Synlett* **2015**, *26*, 1862-1866.
29. (a) Moorthy, J. N.; Shinghal, N. *J. Org. Chem.* **2005**, *70*, 1926-1929; (b) Testa, E.; Fontanella, L.; Cristiani, G. F.; Mariani, L. *Helv. Chim. Acta* **1959**, *42*, 2370-2379; (c) Westfahl, J. C.; Gresham, T. L. *J. Am. Chem. Soc.* **1955**, *77*, 936-938; (d) Linke, S. *Synthesis* **1978**, 303; (e) Hall, J.; Gisler, M. *J. Org. Chem.* **1976**, *41*, 3769-3770; (f) Goto, A.; Endo, K.; Saito, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3607-3609; (g) Sonia I. Maffioli, S. I.; Marzorati, E.; Marazzi, A. *Org. Lett.* **2005**, *7*, 5237-5239; (h) Jiang, X.; Minnaard, A. J.; Feringa, B. L.; Vries, J. G. *J. Org. Chem.* **2004**, *69*, 2327-2331.
30. (a) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 3599-3601; (b) Park, S.; Choi, Y.; Han, H.; Yang, S. H.; Chang, S. *Chem. Commun.* **2003**, 1936-1937; (c) Smith, M. B.;

March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001 and references cited therein; (d) Gawly, R. E. *Org. React.* 1988, *35*, and references cited therein; (e) Field, L.; Hughmark, P. B.; Shumaker, S. H.; Marshall, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 1983-1987.

31. Shimokawa, S.; Kawagoe, Y.; Moriyama, K.; Togo, H. *Org. Lett*. **2016**, *18*, 784-787.
32. Cao, L.; Ding, J.; Gao, M.; Wang, Z.; Li, J.; Wu, A. *Org. Lett*. **2009**, *11*, 3810-3813.
33. Suresh, A. S.; Baburajan P.; Ahmed, M. *Tetrahedron Lett*. **2015**, *56*, 4864-4867.
34. Veitch, G. E.; Bridgwood, K. L.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3623-3625.
35. Narendra, N.; Chennakrishnareddy, G.; Sureshbabu, V. V. *Org. Biomol. Chem.* **2009**, *7*, 3520-3526.
36. Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett*. **2003**, *5*, 2715-2717.
37. Thalluri, K; Manne, S. R.; Dev, D.; Mandal, B. *J. Org. Chem*. **2014**, *79*, 3765-3775.
38. (a) Choi, J.; Park, G. J.; Pang, P. Y. *Tetrahedron Lett.* **2008**, *49*, 1103-1106; (b) Ho, C. Y.; Strobel, E.; Ralbovsky, J.; Galemmo, R. A., Jr. *J. Org. Chem.* **2005**, *70*, 4873-4875; (c) Sibi, M. P.; Hasegawa, H.; Ghorpade, S. R. *Org. Lett*. **2002**, *4*, 3343-3346; (d) Thouin, E.; Lubell, D. W. *Tetrahedron Lett*. **2000**, *41*, 457-460.
39. Burger, A.; Yost, W. L. *J. Am. Chem. Soc*. **1948**, *70*, 2198-2201.
40. (a) Silverman, R. *Acc. Chem. Res*. **1995**, *28*, 335-342; (b) Silverman, R. B. *J. Biol. Chem*. **1983**, *258*, 14766-14769.
41. (a) Matsuo, M. *J. Synth. Org. Chem. Jpn*. **1968**, *26*, 563-583; (b) Wallis, E. S.; Lane, J. F. *Organic Reactions* **1946**, *3*, 267-306; (c) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2725-2736.
42. (a) Zhang, Q.; Shi, C.; Zhang, H. R.; Wang, K. K. *J. Org. Chem.* **2000**, *65*, 7977-7983; (b) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc*. **1972**, *94*, 6203-6205; (c) Smith, P. A. S. *Organic Reactions* **1946**, *3*, 337-449; (d) Curtius, T. *Ber. Dtsch. Chem. Ges*. **1890**, *23*, 3023-3033.
43. (a) Shioiri, T. *Comp. Org. Syn*. **1991**, *6*, 817-821; (b) Wolff, H. *Organic Reactions* **1946**, *3*, 307-336; (b) Koldobskii, G. I.; (c) Schmidt, R. F. *Ber. Dtsch. Chem. Ges*. **1924**, *57*, 704-706.
44. (a) Yoganathan, S.; Miller, S. J. *Org. Lett.* **2013**, *15*, 602-605; (b) Dube, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622-5625; (c) Anilkumar, R.; Chandrasekhar, S.; Sridhar, M. *Tetrahedron Lett*. **2000**, *41*, 5291-5293; (d) Shiori, T. *Comp. Org. Syn*. **1991**, *6*, 821-825; (e) Bauer, L.; Exner, O. *Angew. Chem. Int. Ed.* **1974**, *13*, 376-384; (f) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209-256; (g) Lossen, W. *Ann*. **1872**, *161*, 347-362.
45. (a) ALS see: Mavlyutov, T. A.; Guo, L. W.; Epstein, M. L.; Ruoho, A. E. *J. Phamacol. Sci.* **2015**, *127*, 10-16; (b) Several diseases except ALS see: Maurice, T.; Su, T. P. *Phamacoogy & Therapeutics* **2009**, *124*, 195-206 and references cited therein.
46. (a) Maurice, T.; Su, T. P. *Pharmacol. Ther.* **2009**, *124*, 195-206; (b) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, M. J.; Rothman, R. B.; Su, T. P.; Tam, S. W.; Taylor, D. P. *Trends Pharmacol. Sci.* **1992**, *13*, 85-86.

47. (a) Hayashi, T. *J. Pharmacol. Sci.* **2015**, *127*, 2-5; (b) Omi, T.; Tanimukai, H.; Kanayama, D.; Sakagami, Y.; Tagami, S.; Okochi, M.; Moriha T.; Sato, M.; Yanagida, K.; Kitasyoji, A.; Hara, H.; Imaizumi, K.; Maurice, T.; Chevallier, N.; Marchal, S.; Takeda, M.; Kudo, T. *Cell Death and Disease* **2014**, *5*, e1332; (c) Hayashi, T.; Su, T. *Cell* **2007**, *131*, 596-610.
48. (a) Prause, J.; Goswami, A.; Katona, I.; Roos, A.; Schnizler, M.; Bushuven, E.; Dreier, A.; Buchkremer, S.; Johann, S.; Beyer, C.; Deschauer, M.; Troost, D.; Weis, J. H. *Mol. Genet.* **2013**, *22*, 1581-1600; (b) Al-Saif, A.; Al-Mohanna, F.; Bohlega, S. *Ann. Neurol.* **2011**, *70*, 913-919.
49. Matsuno, K.; Nakazawa, M.; Okamoto, K.; Kawashima, Y.; Mita, S. *Eur. J. Pharmaco.* **1996**, *306*, 271-279.
50. (a) Banister, S. D.; Kassiou, M. *Curr. Pharm. Des.* **2012**, *18*, 884-901; (b) Niitsu, T.; Iyo, M.; Hashimoto, K. *Curr. Pharm. Des.* **2012**, *18*, 875-883; (c) Hayashi, T.; Tsai, S. Y.; Mori, T.; Fujimoto, M.; Su, T. P. *Expert Opin. Ther. Targets* **2011**, *15*, 557-577; (d) Ishikawa, M.; Hashimoto, K. *J. Receptor Ligand Channel Res.* **2010**, *3*, 25-36.
51. (a) Urfer, R.; Moebius, H. J.; Skoloudik, D.; Santamarina, E.; Sato, W.; Mita, S.; Muir, K. W. *Stroke* **2014**, *45*, 3304-3310; (b) Simona, C.; Raffaella, G.; Annamaria, M.; Andrea, B.; Sara, N.; Francesca, N.; Daniela, R. *Expert Opinion on Therapeutic Patents* **2013**, *23*, 597-613.
52. (a) Behensky, A.; Yasny, I.; Shuster, A.; Seredenin, S.; Petrov, A.; Cuevas, J. *J Pharmacol Exp Ther.* **2013**, *347*, 468-477; (b) Marrazzo, A.; Caraci, F.; Salinaro, E.; Su, T.; Copani, A.; Ronsisvalle, G. *Neuroreport.* **2005**, *16*, 1223-1226.
53. (a) Villard, V.; Espallergues, J.; Keller, E.; Alkam, T.; Nitta, A.; Yamada, K.; Nabeshima, T.; Vamvakides, A.; Maurice, T. *Neuropsychopharmacology* **2009**, *34*, 1552-1566; (b) Meunier, J.; Ieni, J.; Maurice, T. *Br J Pharmacol*. **2006**, *149*, 998-1012; (c) Maurice, T.; Su, T.; Privat, A. *Neuroscience* **1998**, *83*, 413-428;
54. (a) Froestl, W.; Muhs, A.; Preifer, A. *Journal of Alzheimer's Disease* **2014**, *41*, 961-1019; (b) Villard, V.; Espallergues, J.; Keller, E.; Vamvakides, A.; Maurice, T. J. *Psychopharmacol.* **2011**, *25*, 1101-1117.
55. Marrazzo, A.; Prezzavento, O.; Pappalardo, M. S.; Bousquet, E.; Indanza, M.; Pike, V. W.; Ronsisvalle, G. *IL Farmaco* **2002**, *57*, 45-53.
56. Kawashima, Y.; Ezawa, T.; Yamamura, M.; Harada, T.; Noguchi, T.; Miura, T.; Imai, N. *Tetrahedron Lett.* **2016**, *57*, 668-671.
57. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568-3571.
58. Kawashima, Y. Ph.D. Thesis, Chiba Institute of Science, 2016.
59. Kawashima, Y.; Ezawa, T.; Yamamura, M.; Harada, T.; Noguchi, T.; Miura, T.; Imai, N. *Tetrahedron* **2015**, *71*, 8585-8592.
60. Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367-11368.