Supplementary Information for

Sodium methoxide: simple but highly efficient catalyst for the direct amidation of esters

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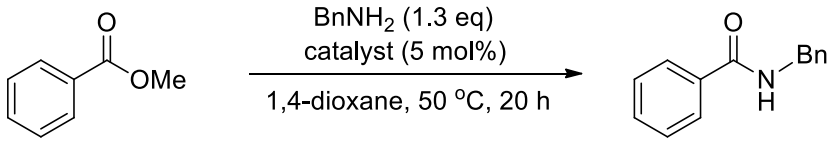
1. Additional Experimental Results

1.1. Catalyst Screening

Sodium and potassium alkoxides gave high yields of benzyl amide, whereas lithium and calcium alkoxides had almost no catalytic activities (entries 1–5). Sodium hexamethyldisilazide showed an identical result to sodium methoxide (entries 1 and 7). Because of the generation of methanol as co-product with pK_a value of 15, the most part of sodium hexamethyldisilazide should convert to sodium methoxide and hexamethyldisilazane (pK_a ≈ 26) during reaction. Lithium, sodium, potassium and calcium carbonates could not promote the reaction (entries 9–12). Alkali metal acetates, alkaline-earth metal acetates and μ-oxo bridged tetranuclear zinc cluster had no catalytic activity (entries 13–17).

Table S1. Catalyst Screening for Amidation of Ester [a]



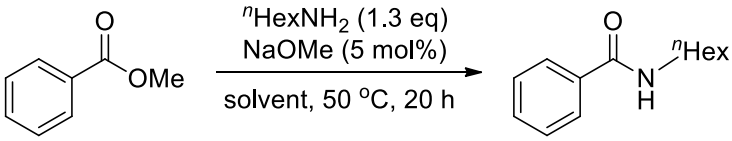
entry	catalyst	yield (%)[b]
1	NaOMe	90
2	$Ca(OMe)_2$	ND[c]
3	LiO^{t}Bu	6
4	NaO^{t}Bu	86
5	KO^{t}Bu	77
6	LiHMDS	7
7	NaHMDS	90
8	KHMDS	82
9	Li_2CO_3	ND[c]
10	Na_2CO_3	ND[c]
11	K_2CO_3	ND[c]
12	$CaCO_3$	ND[c]
13[d]	LiOAc	trace
14[d]	NaOAc	trace
15[d]	$Mg(OAc)_2$	trace
16[d]	$Ca(OAc)_2$	trace
17[d,e]	$Zn_4(OCOCF_3)_6O$	3

[a] 12.0 mmol scale, 5 mL of dioxane was used. [b] Determined by GC analysis using DB-5 column. [c] Not detected. [d] PhCl was used as a solvent. [e] Catalyst loading was 0.15 mmol (1.25 mol%).

1.2. Solvent Screening

The amidation of esters catalyzed by sodium methoxide proceeded heterogeneously in various polar and non-polar solvents, such as 1,4-dioxane, chlorobenzene, toluene, hexane, THF, diethoxymethane and NMP (entries 1–8). When using methanol, sodium methoxide promoted the reaction with only moderate activity (entry 9). Acetonitrile also inhibited the reaction (entry 10). As a result, we chose toluene as an appropriate solvent for studying about the sodium methoxide catalyzed-amidation system, considering the solubility of substrates and products in the reaction mixture.

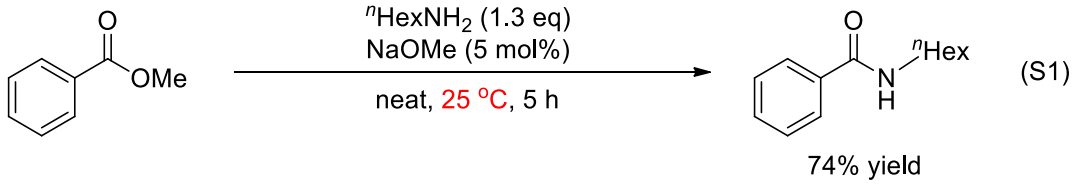
Table S2. Solvent Effects in Amidation Catalyzed by NaOMe



entry	solvent	yield (%)[b]
1	none	>99[c]
2	1,4-dioxane	>99
3	PhCl	>99
4	toluene	>99
5	hexane	>99
6	THF	91
7	diethoxymethane	91
8	*N*-methylpyrollidone	68
9	MeOH	47
10	MeCN	8

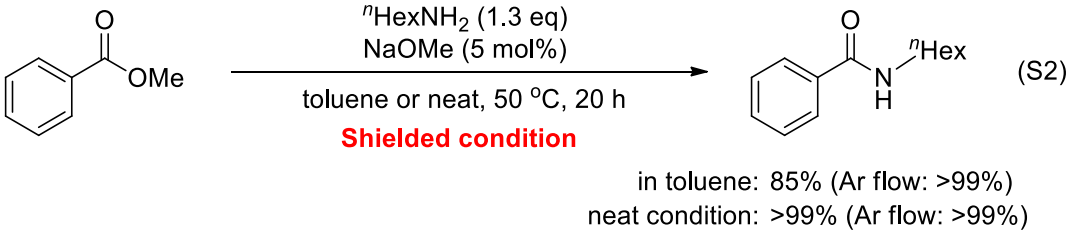
[a] 12.0 mmol scale, 5 mL of solvent was used. [b] Determined by GC analysis using DB-5 column. [c] Isolated yield.

1.3. Amidation Catalyzed by NaOMe at 25 °C



(S1)

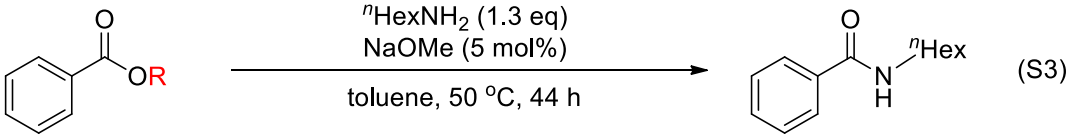
1.4. Amidation in a Shield-tube



(S2)

in toluene: 85% (Ar flow: >99%)
neat condition: >99% (Ar flow: >99%)

1.5.Amidation of Isopropyl and *tert*-Butyl Esters Catalyzed by NaOMe



(S3)

R = *i*-Pr: 54% yield
R = *t*-Bu: trace

1.6. Effects of Water in Amidation Catalyzed by NaOMe

We carried out the control experiments to investigate effects of water in the sodium methoxide catalyzed-amidation of ester. The catalytic amidation was completely inhibited in the presence of 5 mol% (1 equiv. to sodium methoxide) of water. In the water added reaction mixture, a white solid was generated and identified as sodium benzoate by FT-IR measurement. It is indicated that the existence of water cause the generation of catalytic inactive sodium benzoate via formation of sodium hydroxide by the reaction of sodium methoxide with water.

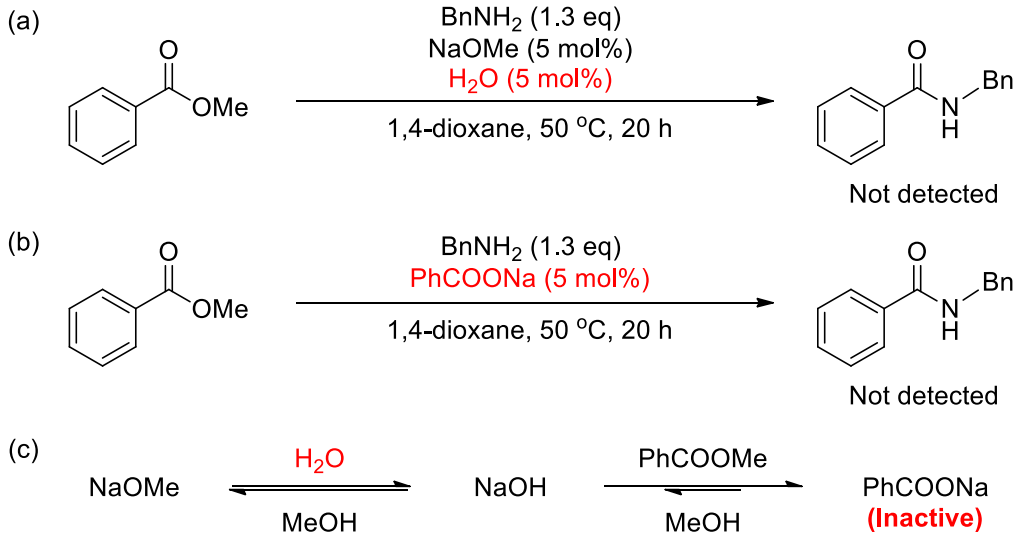


Figure S1. (a) Effects of Water in Amidation Catalyzed by NaOMe. (b) Amidation Using Sodium Benzoate as a Catalyst. (c) Generation of Sodium Benzoate by Saponification of Methyl Benzoate.

1.7. Plots for the amidation of chiral α-amino ester

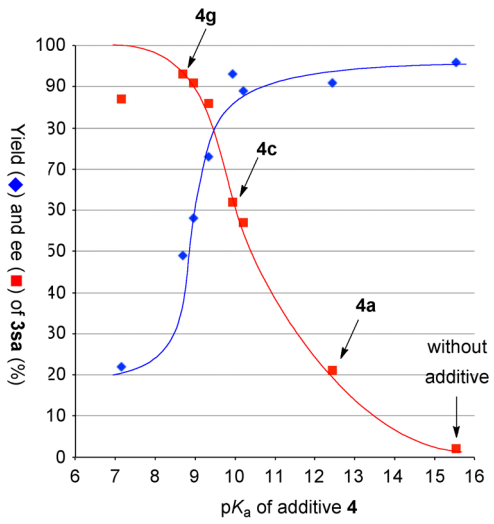


Figure S2. ◆, yield of **3sa**; ■, ee of **3sa**. Data using *ortho*-substituted phenols (Entries 5 and 9 in Table 2) were omitted to eliminate their improper steric effects.

2. Materials and methods

General: Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) spectra were measured on a VARIAN-MERCURY300-C/H spectrometer operating at 300 MHz (^{1}H NMR), 75.5 MHz (^{13}C NMR) and 282 MHz (^{19}F NMR) or on a Brucker Avance 400 spectrometer operating at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR) and 376 MHz (^{19}F NMR) in 5 mm NMR tube. All ^{1}H NMR chemical shifts were reported in ppm relative to internal references of TMS at δ 0.00. All ^{13}C NMR chemical shifts were reported in ppm relative to carbon resonance in chloroform-d_1 at δ 77.00, in dimethylsulfoxide-d_6 at δ 40.45. IR spectra were recorded on a JASCO FT/IR-230 spectrometer or on a SHIMAZU FTIR-8400 spectrometer. Low and high resolution mass spectra were recorded by JEOL JMS-700 or by LCT Premier XE mass spectrometer (Waters). Melting points of air- and moisture-sensitive compounds were measured in sealed tubes using Yanaco micro melting point apparatus. All catalytic reactions were carried out by the standard Schlenk techniques under an argon atmosphere. Toluene was distilled from benzophenone ketyl. Ester substrates were purchased at the highest commercial quality or synthesized from the corresponding carboxylic acids by standard esterification reaction with catalytic amounts of $SOCl_2$. Solid substrates were used without further purification, and liquid substrates were distilled before use.

General procedure for the amidation of esters catalyzed by sodium methoxide

A mixture of sodium methoxide (0.4 mmol, 5 mol% based on ester), ester (8.0 mmol, 1.0 eq), amine (10.4 mmol, 1.3 eq), and toluene (2.0 mL) was heated at 50 °C for periodic time under an argon flow condition. The resulting mixture was quenched with aqueous saturated NH_4Cl. After extraction with ethyl acetate, the product was purified by flash column chromatography or recrystallization.

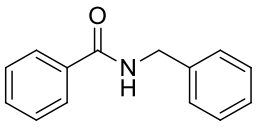
General procedure for the amidation of α-amino esters catalyzed by sodium methoxide with 4-trifluoromethylphenol

A mixture of sodium methoxide (0.2 mmol, 10 mol% based on ester), 4-trifluoromethylphenol (0.6 mmol, 30 mol% based on ester), ester (2.0 mmol, 1.0 eq), amine (2.6 mmol, 1.3 eq), MS3A (50 mg), and toluene (0.5 mL) was heated at 50 or 70 °C for periodic time under an argon flow condition. The resulting mixture was quenched with aqueous saturated NH_4Cl. After extraction with ethyl acetate, the product was purified by flash column chromatography or recrystallization.

Enantiomeric excess of the product was determined by chiral HPLC analysis.

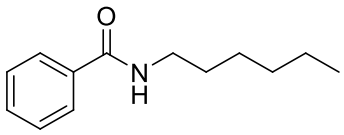
3. Characterization data for the isolated compounds

_N_-Hexylbenzamide (3aa)[S-1]



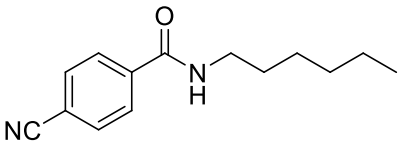
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ 7.78 (dt, *J* = 7.0, 1.7 Hz, 2H, *aromatic*), 7.45 (tt, *J* = 7.4, 1.4 Hz, 1H, *aromatic*), 7.38 (tt, *J* = 7.4, 1.4 Hz, 2H, *aromatic*), 7.32-7.24 (m, 5H, *aromatic*), 6.65 (br s, 1H, N*H*), 4.60 (d, *J* = 5.7 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C) δ 167.3, 138.2, 134.4, 131.4, 128.7, 128.5, 127.8, 127.5, 126.9, 44.0; MS (EI) *m*/*z* (relative intensity) 211 ([M^+], 23), 105 (100); HRMS (EI) *m*/*z* calcd. for $C_{14}H_{13}NO$ 211.0997, found 211.1002; Other physical measurements were previously reported in the literature.

_N_-Hexylbenzamide (3ab)[S-2]



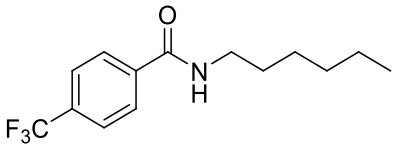
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.78-7.75 (m, 2H, *aromatic*), 7.46-7.36 (m, 3H, *aromatic*), 6.47 (br s, 1H, N*H*), 3.42 (dt, *J* = 5.8, 7.1 Hz, 2H, NHCH_2), 1.59-1.57 (m, 2H, NHCH$_2$CH_2), 1.32 (m, 6H, *methylene*), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 167.5, 134.9, 131.1, 128.4, 126.8, 40.1, 31.5, 29.6, 26.6, 22.5, 13.9; MS (EI) *m*/*z* (relative intensity) 205 ([M^+], 10), 148 (100), 105 (76), 77 (23); HRMS (EI) *m*/*z* calcd. for $C_{13}H_{19}NO$ 205.1467, found 205.1438; Other physical measurements were previously reported in the literature.

4-Cyano-_N_-hexylbenzamide (3bb)[S-3]



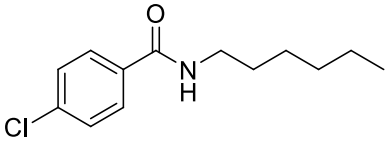
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 2/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.87-7.84 (m, 2H, *aromatic*), 7.74-7.71 (m, 2H, *aromatic*), 6.15 (br s, 1H, N*H*), 3.46 (dt, *J* = 5.8, 7.1 Hz, 2H, NHCH_2), 1.65-1.58 (m, 2H, NHCH$_2$CH_2), 1.34 (m, 6H, *methylene*), 0.90 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 165.7, 138.8, 132.4, 127.6, 118.0, 114.9, 40.4, 31.4, 29.5, 26.6, 22.5, 13.9; MS (EI) *m*/*z* (relative intensity) 230 ([M^+], 13), 173 (17), 160 (37), 130 (100), 102 (56); HRMS (EI) *m*/*z* calcd. for $C_{14}H_{18}N_2O$ 230.1419, found 230.1429; Other physical measurements were previously reported in the literature.

_N_-hexyl-4-(trifluoromethyl)benzamide (3cb)[S-4]



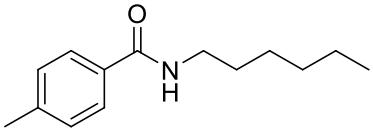
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); white solid; mp 76-77 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.87 (d, J = 8.2 Hz, 2H, *aromatic*), 7.61 (d, J = 8.2 Hz, 2H, *aromatic*), 7.01 (s, 1H, N*H*), 3.41 (q, J = 6.3 Hz, 2H, NHCH_2), 1.66-1.54 (m, 2H, $NHCH_2CH_2$), 1.41-1.21 (m, 6H, *methylene*), 0.88 (t, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 166.6, 138.1, 132.8 (q, $J_{C\text{-}F}$ = 33 Hz), 127.4, 125.2, 123.6 (q, $J_{C\text{-}F}$ = 270.8 Hz), 40.3, 31.4, 29.3, 26.6, 22.4, 13.7; MS (EI) *m*/*z* (relative intensity) 273.2 ([M^+], 8), 173 (100), 145 (33); HRMS (EI) *m*/*z* calcd. for $C_{14}H_{18}F_3NO$ 273.1340, found 273.1325; Other physical measurements were previously reported in the literature.

4-Chloro-_N_-hexylbenzamide (3db)



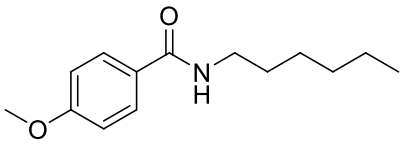
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); white solid; mp 67-68 ˚C; IR ($CHCl_3$, ν/cm^{-1}) 3457, 3356, 3009, 2931, 2862, 1659, 1597, 1520, 1481, 1296; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.72-7.60 (m, 2H, *aromatic*), 7.45-7.37 (m, 2H, *aromatic*), 6.09 (br s, 1H, N*H*), 3.43 (dt, J = 5.8, 7.1 Hz, 2H, NHCH_2), 1.68-1.49 (m, 2H, $NHCH_2CH_2$), 1.45-1.16 (m, 6H, *methylene*), 0.90 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C) δ 166.5, 137.3, 133.1, 128.5, 128.3, 40.2, 31.4, 29.5, 26.6, 22.5, 13.9; MS (EI) *m*/*z* (relative intensity) 239 ([M^+], 8), 139 (100), 111 (25); HRMS (EI) *m*/*z* calcd. for $C_{13}H_{18}ClNO$ 239.1077, found 239.1078.

_N_-hexyl-4-methylbenzamide (3eb)[S-2]



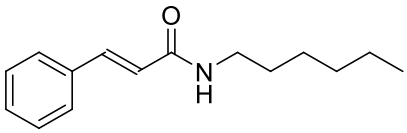
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1 to 0/1); white solid; mp 42-43 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.65 (d, J = 8.2 Hz, 2H, *aromatic*), 7.21 (d, J = 8.2 Hz, 2H, *aromatic*), 6.13 (br s, 1H, N*H*), 3.43 (dt, J = 5.8, 7.1 Hz, 2H, NHCH_2), 2.38 (s, 3H, C6H4CH_3), 1.65-1.55 (m, 2H, $NHCH_2CH_2$), 1.40-1.28 (m, 6H, *methylene*), 0.89 (t, J = 6.8 Hz, 3H, CH2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 167.4, 141.6, 132.1, 129.1, 126.8, 40.0, 31.5, 29.7, 26.7, 22.5, 21.4, 14.0; MS (EI) *m*/*z* (relative intensity) 219 ([M^+], 21), 176 (18), 148 (32), 119 (100), 91 (48); HRMS (EI) *m*/*z* calcd. for $C_{14}H_{21}NO$ 219.1623, found 219.1624; Other physical measurements were previously reported in the literature.

***N*-hexyl-4-methoxybenzamide (3fb)**



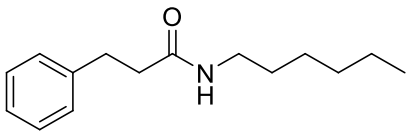
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 3/1 to 0/1); 71% yield; mp 63-64 ˚C; IR (KBr, ν/cm^{-1}) 3325, 2916, 2855, 1628, 1535, 1505, 1644, 1250, 1188, 1103, 1034, 849, 764, 610; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.72 (d, J = 9.0 Hz, 2H, *aromatic*), 6.92 (m, 2H, *aromatic*), 5.96 (br s, 1H, N*H*), 3.84 (s, 3H, CH_3O), 3.43 (dt, J = 5.8, 7.1 Hz, 2H, NHCH_2), 1.63-1.56 (m, 2H, NHCH$_2$CH_2), 1.41-1.32 (m, 6H, *methylene*), 0.90 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 167.0, 162.1, 128.6, 127.3, 113.7, 55.4, 40.1, 31.5, 29.7, 26.7, 22.5, 14.0; MS (EI) *m*/*z* (relative intensity) 235 ([M$^+$], 10), 135 (100); HRMS (EI+) *m*/*z* calcd. for $C_{14}H_{21}NO_2$ 235.1572, found 235.1582.

***N*-hexylcinnamamide (3gb)**[S-5]



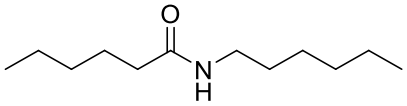
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 3/1 to 0/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.62 (d, J = 15.6 Hz, 1H, PhC*H*=CH), 7.49-7.46 (m, 2H, *aromatic*), 7.35-7.28 (m, 3H, *aromatic*), 6.42 (d, J = 15.6 Hz, 1H, PhCH=C*H*), 5.85 (br s, 1H, N*H*), 3.38 (dt, J = 5.9, 7.1 Hz, 2H, NHCH_2), 1.62-1.52 (m, 2H, NHCH$_2$CH_2), 1.38-1.30 (m, 6H, *methylene*), 0.88 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 165.0, 140.7, 135.0, 129.5, 128.7, 127.7, 121.0, 39.8, 31.5, 29.6, 26.6, 22.5, 13.5; MS (EI) *m*/*z* (relative intensity) 231 ([M$^+$], 24), 190 (75), 131 (100), 121 (75), 77 (37); HRMS (EI) *m*/*z* calcd. for $C_{15}H_{21}NO$ 231.1623, found 231.1630; Other physical measurements were previously reported in the literature.

***N*-hexyl-3-phenylpropanamide (3hb)**[S-6]



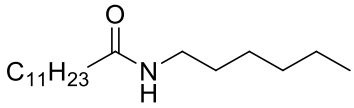
Purified by flush column chromatography (silica gel, Hexane/EtOAc = 3/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 ^{o}C) δ 7.3-7.1 (m, 5H, *Ph*), 5.52 (bs, 1H, CON*H*), 3.18 (dt, J = 7.1, 5.9 Hz, 2H, NHCH_2), 2.95 (t, J = 9.0 Hz, 2H, PhCH$_2$CH_2), 2.45 (t, J = 9.0 Hz, 2H, PhCH_2CH$_2$), 1.5-1.2 (m, 8H, *methylene*), 0.87 (t, J = 6.8 Hz, 3H, CH_3) ; ^{13}C NMR (75 MHz, DMSO-d_6, 35 ^{o}C) δ 172.0, 140.8, 128.3, 128.2, 126.0, 39.4, 38.3, 31.7, 31.3, 29.4, 26.4, 22.4, 13.8; MS (EI) *m/z* 233 [M$^+$]; HRMS (EI) *m/z* calcd for $C_{15}H_{23}NO$ 233.1780, found 233.1792; Other physical measurements were previously reported in the literature.

_N_-hexylhexanamide (3ib)



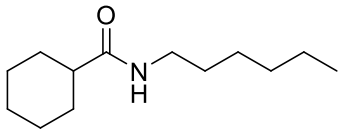
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); colorless oil; IR ($CHCl_3$, ν/cm^{-1}) 3449, 3310, 3086, 2994, 2936, 2862, 1667, 1628, 1551, 1520, 1466, 1373, 1250; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 5.44 (br s, 1H , N*H*), 3.24 (dt, *J* = 5.8, 7.1 Hz, 2H, NHCH_2), 2.15 (t, J = 5.0 Hz, 2H, COCH_2), 1.8-1.2 (m, 14H, *methylene*), 1.0-0.8 (m, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C) δ 173.1, 39.3, 36.6, 31.4, 31.4, 29.5, 26.5, 25.4, 22.4, 22.3, 13.8, 13.8; MS (ESI) *m*/*z* (relative intensity) 200 ([M+H$^+$], 100), 157 (11); HRMS (ESI) *m*/*z* calcd. for $C_{12}H_{26}NO$ 200.2014, found 200.2005.

_N_-Hexyldodecanamide (3jb)



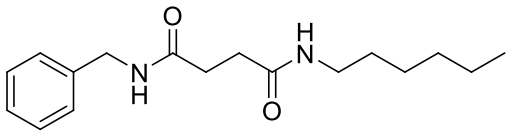
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1 to 0/1); white solid; mp 55-56 ˚C; IR ($CHCl_3$, ν/cm^{-1}) 3449, 3333, 2924, 2855, 1666, 1519, 1416, 1373, 1219; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 5.39 (br s, 1H, N*H*), 3.24 (q, *J* = 6.4 Hz, 2H, NHCH_2), 2.15 (t, *J* = 7.4 Hz, 2H, COCH_2), 1.68-1.43 (m, 4H, *methylene*), 1.40-1.16 (m, 22H, *methylene*), 0.98-0.80 (m, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 173.0, 39.5, 36.9, 31.9, 31.5, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 26.6, 25.8, 22.6, 22.5, 14.0, 13.9; MS (EI) *m*/*z* (relative intensity) 283 ([M$^+$], 19), 240 (32), 183 (18), 143 (100), 86 (30); HRMS (EI) *m*/*z* calcd. for $C_{18}H_{37}NO$ 283.2875, found 283.2893.

N-hexylcyclohexanecarboxamide (3kb)



Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); white solid; mp 69-70 ˚C; IR ($CHCl_3$, ν/cm^{-1}) 3449, 3325, 3001, 2924, 2862, 1659, 1643, 1543, 1520, 1450, 1373, 1311, 1257; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 5.38 (br s, 1H, N*H*), 3.23 (dt, *J* = 5.8, 7.0 Hz, 2H, NHCH_2), 2.05 (tt, *J* = 11.4, 3.4 Hz, 1H, C*H*), 1.90-1.05 (m, 18H, *methylene*), 0.88 (t, *J* =6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C) δ 175.9, 45.5, 39.2, 31.4, 29.7, 29.6, 29.6, 26.5, 25.7, 22.4, 13.9; MS (EI) *m*/*z* (relative intensity) 211.2 ([M$^+$], 52), 83 (100); HRMS (EI) *m*/*z* calcd. for $C_{13}H_{25}NO$ 211.1936, found 211.1909.

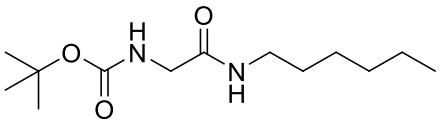
_N_^{1}-benzyl-_N_^{4}-hexylsuccinamide (3lb)



Purified by reprecipitation from $CHCl_3$ solution to EtOAc; white solid; mp 166-167

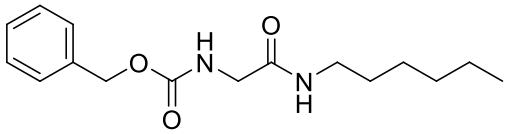
°C; IR (KBr, ν/cm^{-1}) 3302, 3086, 2924, 2855, 1636, 1551, 1427, 1343, 1211, 1080, 1026. 733, 694; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.4-7.2 (m, 5H, *aromatic*), 6.33 (bs, 1H, N*H*), 5.90 (bs, 1H, N*H*), 4.42 (d, J = 5.7 Hz, 2H, PhCH_2NH), 3.20 (td, J = 7.2, 5.8 Hz, 2H, NHCH_2CH$_2$), 2.6-2.5 (m, 4H, CO CH_2CH_2CO), 1.5-1.2 (m, 8H, *methylene*), 0.88 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, 35 °C) δ 171.3, 171.0, 139.5, 128.1, 127.0, 126.5, 42.0, 38.4, 30.9, 30.8, 30.8, 29.0, 26.0, 21.9, 13.8; MS (EI) *m/z* 290 [M$^+$]; HRMS (EI) *m/z* calcd for $C_{17}H_{26}N_2O_2$ 290.1994, found 290.1977.

tert-butyl 2-(hexylamino)-2-oxoethylcarbamate (3mb)



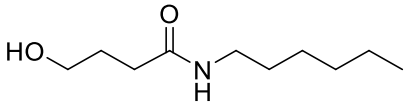
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 6.14 (br s, 1H, N*H*), 5.17 (br s, 1H, N*H*), 3.76 (d, J = 6.0 Hz, 2H, NHCH_2CO), 3.26 (dt, J = 6.0, 7.0 Hz, 2H, NHCH_2CH$_2$), 1.5-1.3 (m, 11H, NHCH$_2$CH_2 and C(CH_3)$_3$), 1.4-1.2 (m, 6H, *methylene*), 0.88 (t, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 169.3, 156.1, 80.0, 44.3, 39.4, 31.4, 29.4, 28.2, 26.4, 22.4, 13.9; MS (EI) *m/z* (relative intensity) 258 ([M$^+$], 1), 30 (100); Other physical measurements were previously reported in the literature.

benzyl 2-(hexylamino)-2-oxoethylcarbamate (3nb)[S-7]



Purified by flash column chromatography (silica gel, Hexane/EtOAc = 2/1 to 1/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.38-7.27 (m, 5H, *aromatic*), 5.89 (br s, 1H, N*H*), 5.34 (br s, 1H, N*H*), 5.13 (s, 2H, NHCH_2CO), 3.83 (d, J = 5.7 Hz, 2H, PhCH_2O), 3.29-3.21 (dt, J = 6.4, 6.8 Hz, 2H, NHCH_2CH$_2$), 1.54-1.40 (m, 2H, NHCH$_2$CH_2), 1.38-1.19 (m, 6H, *methylene*), 0.88 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C) δ 168.8, 156.6, 136.0, 128.5, 128.2, 128.0, 67.1, 44.6, 39.5, 31.4, 29.3, 26.4, 22.5, 14.0; MS (EI) *m/z* (relative intensity) 292.1 ([M$^+$], 11), 185 (17), 91 (100), 43 (44); HRMS (EI) *m/z* calcd. for $C_{16}H_{24}N_2O_3$ 292.1787, found 292.1798; Other physical measurements were previously reported in the literature.

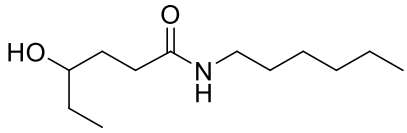
***N*-hexyl-4-hydroxybutanamide (3ob)**[S-8]



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 4/1 to EtOAc/MeOH = 99/1); white solid; IR ($CHCl_3$, ν/cm^{-1}) 3433, 3309, 3102, 3001, 2932, 2862, 1659, 1628, 1566, 1512, 1451, 1250, 1057; ^{1}H NMR

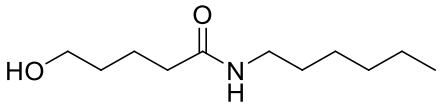
(400 MHz, $CDCl_3$, 35 °C) δ 6.51 (bs, 1H, N*H*), 4.09 (bs, 1H, O*H*), 3.65 (t, *J* = 5.8 Hz, 2H, CH_2OH), 3.21 (td, *J* = 7.1, 5.8 Hz, 2H, NHCH_2), 2.34 (t, *J* = 7.0 Hz, 2H, CH_2CO), 1.85 (tt, *J* = 7.0, 5.8 Hz, 2H, CH_2CH_2CO), 1.5-1.4 (m, 2H, NHCH_2CH_2),1.4-1.2 (m, 6H, *methylene*), 0.88 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 35 °C) δ 173.6, 61.8, 39.6, 33.7, 31.3, 29.3, 28.3, 26.5, 22.4, 13.8; MS (EI) *m/z* 187 [M^+]; HRMS (EI) *m/z* calcd for $C_{10}H_{21}NO_2$ 187.1572, found 187.1562; Other physical measurements were previously reported in the literature.

_N_-hexyl-4-hydroxyhexanamide (3pb)



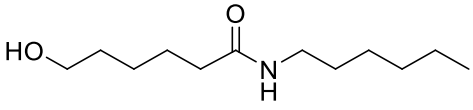
Purified by flush column chromatography (silica gel, Hexane/EtOAc = 4/1 to EtOAc/MeOH = 99/1); white solid; mp 34-35 ˚C; IR ($CHCl_3$, ν/cm^{-1}) 3441, 3318, 2932, 2862, 1659, 1643, 1528, 1458, 1234, 787; ^{1}H NMR (400 MHz, $CDCl_3$, 35 °C) δ 6.01 (bs, 1H, N*H*), 3.56 (tt, *J* = 9.0, 3.0 Hz, 1H, C*H*OH), 3.23 (td, *J* = 7.1, 4.9 Hz, 2H, NHCH_2), 3.04 (bs, 1H, O*H*), 2.4-2.3 (m, 2H, CH_2CO), 1.9-1.8 (m, 1H, CH_2CHOH), 1.7-1.6 (m, 1H, CH_2CHOH), 1.6-1.4 (m, 4H, *methylene*), 1.4-1.2 (m, 6H, *methylene*), 0.94 (t, *J* = 7.4 Hz, 3H, $CHCH_2CH_3$), 0.88 (t, *J* = 7.0 Hz, 3H, $NH(CH_2)_5CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 35 °C) δ 173.9, 72.4, 39.5, 33.0, 32.2, 31.3, 30.1, 29.3, 26.5, 22.4, 13.8, 9.8; MS (EI) *m/z* 215 [M^+]; HRMS (EI) *m/z* calcd for $C_{12}H_{25}NO_2$ 215.1885, found 215.1889.

_N_-hexyl-5-hydroxypentanamide (3qb)



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 4/1 to EtOAc/MeOH = 99/1); white solid; mp 37-38 ˚C; IR ($CHCl_3$, ν/cm^{-1}) 3449, 3325, 2947, 2932, 2862, 1667, 1636, 1528, 1458, 1373, 1234, 1057; ^{1}H NMR (400 MHz, $CDCl_3$, 35 °C) δ 5.84 (bs, 1H, N*H*), 3.64 (t, *J* = 6.2 Hz, 2H, CH_2OH), 3.22 (td, *J* = 7.1, 5.3 Hz, 2H, NHCH_2), 2.64 (bs, 1H, O*H*), 2.23 (t, *J* = 7.2 Hz, 2H, CH_2CO), 1.73 (tt, *J* = 7.5, 7.2 Hz, 2H, CH_2CH_2CO), 1.59 (tt, *J* = 7.5, 6.2 Hz, 2H, CH_2CH_2OH), 1.5-1.4 (m, 2H, NHCH_2CH_2), 1.4-1.2 (m, 6H, *methylene*), 0.87 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 35 °C) δ 173.4, 61.4, 39.3, 35.8, 31.7, 31.2, 29.2, 26.4, 22.3, 21.9, 13.7; MS (EI) *m/z* 201 [M^+]; HRMS (EI) *m/z* calcd for $C_{11}H_{23}NO_2$ 201.1729, found 201.1723.

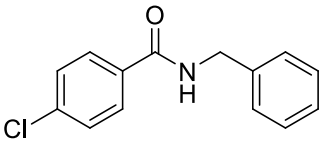
_N_-hexyl-6-hydroxyhexanamide (3rb)



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 2/1); white solid; mp 47-48 ˚C; IR ($CHCl_3$, ν/cm^{-1}) 3618, 3449, 3333, 3001, 2932, 2862, 1667, 1520, 1466, 1373, 1234, 1049; ^{1}H NMR (300 MHz,

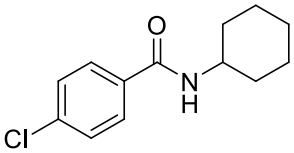
$CDCl_3$, 35 °C) δ 6.43 (bs, 1H, N*H*), 3.60 (t, *J* = 6.5 Hz, 2H, CH_2OH), 3.49 (bs, 1H, O*H*), 3.20 (td, *J* = 6.9, 6.2 Hz, 2H, NHCH_2), 2.18 (t, *J* = 7.6 Hz, 2H, CH_2CO), 1.7-1.2 (m, 14H, *methylene*), 0.89 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 173.1, 62.1, 39.4, 36.5, 32.2, 31.3, 29.4, 26.5, 25.3, 25.3, 22.4, 13.8; MS (EI) *m/z* 215 [M^+]; HRMS (EI) *m/z* calcd for $C_{12}H_{25}NO_2$ 215.1885, found 215.1857.

_N_-benzyl-4-chlorobenzamide (3ca)[S-9]



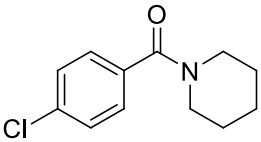
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 3/1 to 0/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.72 (d, *J* = 8.3 Hz, 2H, *aromatic*), 7.42-7.27 (m, 7H, *aromatic*), 6.42 (br s, 1H, N*H*), 4.62 (d, *J* = 5.7 Hz, 2H, CH_2); HRMS (EI) *m/z* calcd. for $C_{14}H_{12}NOCl$ 245.0607, found 245.0621; Other physical measurements were previously reported in the literature.

4-chloro-N-cyclohexylbenzamide (3cc)[S-1]



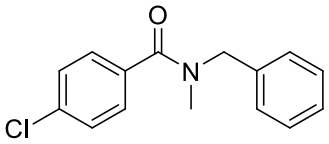
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.68 (d, 2H, *J* = 8.5 Hz, *aromatic*), 7.38 (d, *J* = 8.5 Hz, 2H, *aromatic*), 5.97 (br s, 1H, N*H*), 4.02-3.88 (m, 1H, NHC*H*), 2.07-1.96 (m, 2H, *cyclohexyl*), 1.81-1.60 (m, 3H, *cyclohexyl*), 1.50-1.34 (m, 2H, *cyclohexyl*), 1.31-1.13 (m, 3H, *cyclohexyl*); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 165.5, 137.4, 133.5, 128.7, 128.3, 48.8, 33.2, 25.5, 24.9; MS (EI) *m/z* (relative intensity) 237 ([M^+], 34), 139 (100), 111 (35); HRMS (EI) *m/z* calcd. for $C_{13}H_{16}NOCl$ 237.0920, found 237.0910; Other physical measurements were previously reported in the literature.

N-(4-chlorobenzoyl)piperidine (3cd)[S-10]



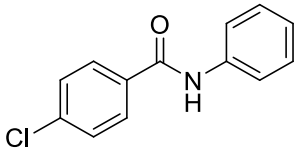
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.4-7.3 (m, 4H, *aromatic*), 3.62 (br s, 2H, *piperidyl*), 3.39 (br s, 2H, *piperidyl*), 1.7-1.5 (m, 6H, *piperidyl*); ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C) δ 169.0, 135.2, 134.7, 128.5, 128.2, 48.6, 43.0, 26.3, 25.4, 24.3; MS (EI) *m/z* (relative intensity) 222 ([M^+],100), 139 (88), 111(27); HRMS (EI) *m/z* calcd. for $C_{12}H_{14}NOCl$ 222.0686, found 222.0680; Other physical measurements were previously reported in the literature.

N-benzyl-4-chloro-N-methylbenzamide (3ce)



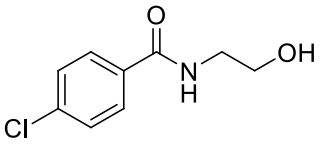
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 4/1); white solid; mp 70-71 ˚C; IR (KBr, ν/cm^{-1}) 3055, 2916, 1636, 1597, 1451, 1404, 1288, 1080, 1011, 849, 741; ^{1}H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.4-7.0 (m, 9H, *aromatic*), 4.73 and 4.50 (br s, 2H, C*H*$_2$Ph), 3.02 and 2.86 (br s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 171.1, 170.2, 136.6, 136.2, 135.5, 134.4, 128.5, 128.3, 128.0, 127.5, 126.4, 54.9, 50.7, 36.8, 33.2; MS (EI) *m*/*z* (relative intensity) 258 ([M$^+$], 47), 139 (100); HRMS (EI) *m*/*z* calcd. for $C_{15}H_{14}NOCl$ 259.0764, found 259.0735.

4-chloro-*N*-phenylbenzamide (3cf)[S-11]



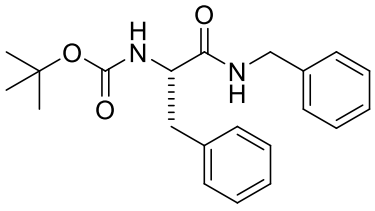
Purified by flash column chromatography (silica gel, Hexane/EtOAc = 6/1); white solid; ^{1}H NMR (300 MHz, DMSO-d_6, 35 °C) δ 10.26 (br s, 1H, N*H*), 7.99 (d, *J* = 8.3 Hz, 2H, *aromatic*), 7.76 (d, *J* = 7.8 Hz, 2H, *aromatic*), 7.60 (d, *J* = 8.3 Hz, 2H, *aromatic*), 7.36 (t, *J* = 7.5 Hz, 2H, *aromatic*), 7.11 (t, *J* = 7.5 Hz, 2H, *aromatic*); ^{13}C NMR (100 MHz, DMSO-d_6, 30 °C) δ 164.3, 138.8, 136.3, 133.5, 129.5, 128.5, 128.3, 123.7, 120.3; MS (EI) *m*/*z* (relative intensity) 231 ([M$^+$], 28), 139 (100), 111 (32); HRMS (EI) *m*/*z* calcd. for $C_{13}H_{10}NOCl$ 231.0451, found 231.0480; Other physical measurements were previously reported in the literature.

***N*-(2-hydroxyethyl)-4-chlorobenzamide (3cg)**[S-12]



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 4/1 to EtOAc/MeOH = 99/1); white solid; IR (KBr, ν/cm^{-1}) 3295, 3078, 2963, 2916, 2870, 1636, 1597, 1559, 1443, 1381, 1312, 1273, 1211, 1080, 1011, 895, 849, 756, 664; ^{1}H NMR (300 MHz, DMSO-d_6, 35 °C) δ 8.46 (bs, 1H, N*H*), 7.87 (d, *J* = 8.5 Hz, 2H, *aromatic*), 7.52 (d, *J* = 8.5 Hz, 2H, *aromatic*), 4.68 (t, *J* = 5.5 Hz, 1H, O*H*), 3.52 (td, *J* = 5.5, 5.9 Hz, 2H, C*H*$_2$OH), 3.33 (t, *J* = 5.9 Hz, 2H, NHC*H*$_2$); ^{13}C NMR (75 MHz, DMSO-d_6, 35 °C) δ 165.2, 135.7, 133.2, 129.0, 128.1, 59.6, 42.1; MS (EI) *m*/*z* 199 [M$^+$]; HRMS (EI) *m*/*z* calcd for $C_9H_{10}ClNO_2$ 199.0400, found 199.0392.

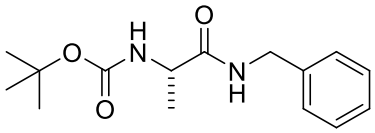
(*S*)-*tert*-butyl-1-(benzylamino)-1-oxo-3-phenylpropan-2-ylcarbamate; (*S*)-Boc-Phe-NHBn (3sa)[S-13]



Purified by recrystallization from EtOAc-hexane and flush column chromatography (silica gel, Hexane/EtOAc

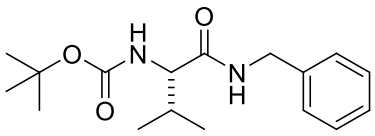
= 8/1 to 1/1); white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 21 ^{o}C) δ 7.3-7.0 (m, 10H, *aromatic*), 6.42 (br s, 1H, N*H*), 5.22 (br s, 1H, N*H*), 4.39 (br s, 2H, NHCH_2Ph), 4.30 (td, *J* = 15.5, 6.9 Hz, 1H, NHC*H*), 3.05 (d, *J* = 6.9 Hz, 2H, CHCH_2Ph), 1.36 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C) δ 171.1, 155.3, 137.7, 136.7, 129.3, 128.6, 128.5, 127.6, 127.3, 126.8, 80.0, 55.9, 43.3, 38.7, 28.2; MS (ESI) *m/z* (relative intensity) 255 (100), 299 (73), 377 ([M+Na$^+$], 30); HRMS (ESI) *m/z* calcd. for $C_{21}H_{26}N_2O_3Na$ 377.1841, found 377.1842; $[\alpha]_{589}^{22}$ +4.9 (*c* 1.05 in CH_2Cl_2); Other physical measurements were previously reported in the literature. The enantiomeric excess (%ee) was determined to be 97% by HPLC using CHIRALPAK OD-3R column (38% MeCN/ H_2O, 0.8 mL/min, 254 nm): t_R (minor, 27.8 min), t_R (major, 29.8 min).

(*S*)-*tert*-butyl-1-(benzylamino)-1-oxopropan-2-ylcarbamate; (*S*)-Boc-Ala-NHBn (3ta)[S-14]



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 10/1 to 1/1); white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 35 ^{o}C) δ 7.3-7.2 (m, 5H, *aromatic*), 6.42 (br s, 1H, N*H*), 4.91 (br s, 1H, N*H*), 4.45 (d, *J* = 5.6 Hz, 2H, NHCH_2Ph), 4.16 (td, *J* = 7.0, 7.0 Hz, 1H, C*H*), 1.42 (s, 9H, C(CH_3)$_3$), 1.38 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C) δ 172.6, 155.5, 138.1, 128.6, 127.5, 127.3, 80.0, 50.0, 43.3, 28.2, 18.4; MS (FAB) *m/z* 279 [M+H$^+$]; HRMS (EI) *m/z* calcd for $C_{15}H_{22}N_2O_3$ 278.1630, found 218.1628; $[\alpha]_{589}^{23}$ –20.0 (*c* 0.99 in CH_2Cl_2); Other physical measurements were previously reported in the literature. The enantiomeric excess (%ee) was determined to be 98% by HPLC using CHIRALPAK OD-3R column (30% MeCN/ H_2O, 0.2 mL/min, 254 nm): t_R (minor, 69.5 min), t_R (major, 74.5 min).

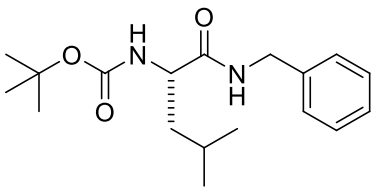
(*S*)-*tert*-butyl-1-(benzylamino)-1-oxo-3-methylbutan-2-ylcarbamate; (*S*)-Boc-Val-NHBn (3ua)



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 10/1 to 1/1); white solid; mp 125-126 °C; IR (KBr, ν/cm^{-1}) 3325, 3721, 2963, 2932, 2870, 1690, 1643, 1535, 1458, 1366, 1296, 1250, 1180. 1018, 926, 741, 694; ^{1}H NMR (400 MHz, $CDCl_3$, 35 ^{o}C) δ 7.4-7.3 (m, 5H, *aromatic*), 6.20 (br s, 1H, N*H*), 4.98 (br s, 1H, N*H*), 4.46 (d, *J* = 7.6 Hz, 2H, CH_2Ph), 3.89 (dd, *J* = 8.0, 11.6 Hz, 1H, NHC*H*), 2.19 (qd, *J* = 8.9, 8.0 Hz, 1H, $(CH_3)_2$C*H*), 1.43 (s, 9H, C(CH_3)$_3$), 0.97 (d, *J* = 8.9 Hz, 3H, CH_3), 0.93 (d, *J* = 8.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C) δ 171.7, 156.0, 138.1, 128.5, 127.6, 127.3, 60.0, 43.3, 30.9, 28.2, 19.3, 17.9; MS (ESI) *m/z* (relative intensity) 207 (25), 251 (65), 270 (100), 329 ([M+Na$^+$], 70); HRMS

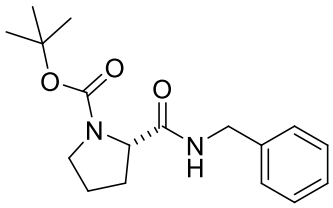
(ESI) *m*/*z* calcd. for $C_{17}H_{26}N_2O_3Na$ 329.1841, found 329.1838; $[\alpha]_{589}^{23}$ –10.12 (*c* 1.03 in CH_2Cl_2). The enantiomeric excess (%ee) was determined to be 99% by HPLC using CHIRALPAK OD-3 column (1% *i*-PrOH/ Hexane, 1.0 mL/min, 254 nm): t_R (minor, 33.9 min), t_R (major, 38.7 min).

(*S*)-*tert*-butyl-1-(benzylamino)-1-oxo-4-methylpentan -2-ylcarbamate; (*S*)-Boc-Leu-NHBn (3va)[S-15]



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 8/1 to 2/1); white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 35 ^{o}C) δ 7.2 (m, 5H, *aromatic*), 6.58 (s, 1H, N*H*CH_2), 4.93 (d, *J* = 8.0 Hz, 1H, N*H*CH), 4.34 (d, *J* = 5.7 Hz, 2H, NHCH_2), 4.06 (s, 1H, NHC*H*), 1.7-1.6 (m, 2H, CHCH_2), 1.5-1.4 (m, 1H, CH_3C*H*CH_3), 1.33 (s, 9H, ^{t}*Bu*), 0.86 (d, *J* = 6.4 Hz, 3H, CHCH_3), 0.85 (d, *J* = 6.4 Hz, 3H, CHCH_3); MS (ESI) *m/z* (relative intensity) 321 ($[M+H]^+$, 18), 265 (86), 222 (20), 212(4); HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2O_3$ 321.2178, found 321.2178; $[\alpha]_{589}^{24}$ –27.6 (*c* 1.03 in CH_2Cl_2); Other physical measurements were previously reported in the literature. The enantiomeric excess (%ee) was determined to be 98% by HPLC using CHIRALPAK OD-3 column (2% *i*-PrOH/ Hexane, 1.0 mL/min, 254 nm): t_R (minor, 13.3 min), t_R (major, 19.3 min).

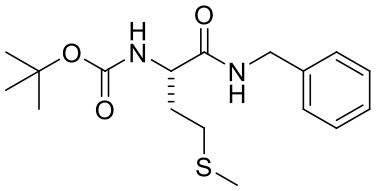
(*S*)-*tert*-butyl-2-(benzylcarbamoyl)pyrrolidine-1-carbox ylate; (*S*)-Boc-Pro-NHBn (3wa)[S-16]



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 10/1 to 1/1); white solid; ^{1}H NMR (400 MHz, DMSO-d_6, 21 ^{o}C) δ 8.40 and 8.35 (t, *J* = 5.8 Hz, 1H, CON*H*), 7.4-7.2 (m, 5H, *aromatic*), 4.33 and 4.32 (dd, *J* = 14.6, 5.8 Hz, 1H, NHC*H*HPh), 4.21 and 4.19 (dd, *J* = 14.6, 5.8 Hz, 1H, NHCH*H*Ph), 4.15-4.05 (m, 1H, α-C*H*-Pro), 3.44-3.35 (m, 1H, δ-C*H*H-Pro), 3.33-3.24 (m, 1H, δ-CH*H*-Pro), 2.18-2.04 (m, 1H, β-C*H*H-Pro), 1.9-1.7 (m, 3H, β-CH*H*-Pro, γ-CH_2-Pro), 1.41 and 1.28 (s, 9H, C(CH_3)$_3$), rotamers; ^{13}C NMR (100 MHz, DMSO-d_6, 21 °C) δ 172.4, 172.2, 153.6, 153.3, 139.6, 128.3, 128.1, 127.2, 126.8, 126.7, 126.5, 78.5, 78.4, 46.6, 46.4, 42.0, 41.7, 40.7, 31.1, 30.0, 28.1, 27.9, 23.9, 23.1, rotamers; MS (ESI) *m/z* (relative intensity) 205 (100), 327 ([M+Na$^+$], 47); HRMS (ESI) *m/z* calcd. for $C_{17}H_{24}N_2O_3Na$ 327.1685, found 327.1692; $[\alpha]_{589}^{24}$ –76.2 (*c* 1.00 in CH_2Cl_2); Other physical measurements were previously reported in the literature. The enantiomeric excess (%ee) was determined

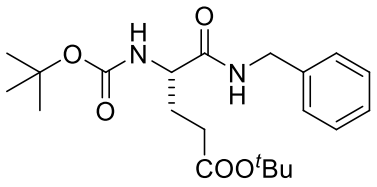
to be 99% by HPLC using SUMICHIRAL OA-4700 column (5% *i*-PrOH/ Hexane, 1.0 mL/min, 254 nm): t_R (minor, 11.2 min), t_R (major, 15.9 min).

(*S*)-*tert*-butyl-1-(benzylamino)-4-(methylthio)-1-oxobutan-2-ylcarbamate; (*S*)-Boc-Met-NHBn (3xa)



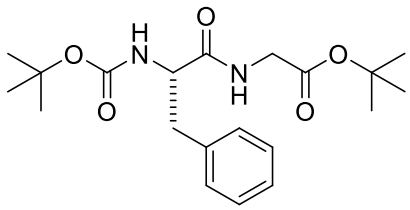
Purified by flush column chromatography (silica gel, Hexane/EtOAc = 5/1 to 2/1); white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 35 ^{o}C) δ 7.2 (m, 5H, *aromatic*), 6.77 (s, 1H, N*H*CH_2), 5.31 (d, J = 6.0 Hz, 1H, N*H*CH), 4.34 (m, 2H, NHCH_2), 4.23 (d, J = 4.6 Hz, 1H, NHC*H*), 2.5-2.4 (m, 2H, SCH_2), 2.03 (dt, J = 13.9, 7.0 Hz, 1H, CHCH_2), 1.98 (s, 3H, SCH_3), 1.85 (dt, J = 13.9, 7.0 Hz, 1H, CHCH_2), 1.32 (s, 9H, ^{t}*Bu*); MS (ESI) *m/z* (relative intensity) 339 ($[M+H]^+$, 100), 283 (91), 239 (43), 212 (34); HRMS (ESI) *m/z* calcd for $C_{17}H_{27}N_2O_3S$ 339.1742, found 339.1729; $[\alpha]_{589}^{24}$ –9.2 (*c* 1.09 in CH_2Cl_2); Other physical measurements were previously reported in the literature. The enantiomeric excess (%ee) was determined to be 99% by HPLC using CHIRALPAK OD-3 column (3% *i*-PrOH/ Hexane, 1.0 mL/min, 254 nm): t_R (minor, 17.9 min), t_R (major, 24.0 min).

(*S*)-*tert*-butyl-5-(benzylamino)-4-(tert-butoxycarbonylamino)-5-oxopentanoate; (*S*)-Boc-Glu(O*t*-Bu)-NHBn (3ya)[S-17]



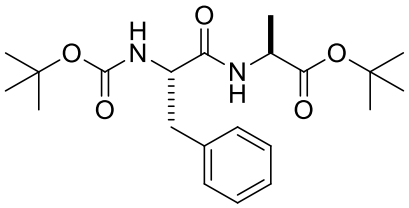
Purified by flush column chromatography (silica gel, Hexane/EtOAc = 85/15 to 1/1); white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 35 ^{o}C) δ 7.3 (m, 5H, *aromatic*), 6.58 (s, 1H, N*H*CH_2), 5.27 (d, J = 6.0 Hz, 1H, N*H*CH), 4.44 (d, J = 5.8 Hz, 2H, CHCH_2), 4.2-4.1 (m, 1H, NHC*H*), 2.41 (dt, J = 16.7, 7.0 Hz, 1H, CH_2COO^{t}Bu), 2.29 (dt, J = 16.7, 7.0 Hz, 1H, CH_2COO^{t}Bu), 2.10 (ddt, J = 14.2, 8.3, 7.0 Hz, 1H, CHCH_2CH$_2$), 1.92 (ddt, J = 14.2, 8.3, 7.0 Hz, 1H, CHCH_2CH$_2$), 1.44 (s, 9H, N*H*COO^{t}Bu), 1.41 (s, 9H, CH$_2$COO^t*Bu*); MS (ESI) *m/z* (relative intensity) 393 ($[M+H]^+$, 100), 337 (20), 281 (12), 212 (9); HRMS (ESI) *m/z* calcd for $C_{21}H_{32}N_2O_5Na$ 415.2209, found 415.2226; $[\alpha]_{589}^{24}$ –9.2 (*c* 1.09 in CH_2Cl_2); Other physical measurements were previously reported in the literature. The enantiomeric excess (%ee) was determined to be 99% by HPLC using SUMICHIRAL OA-4700 column (5% *i*-PrOH/ Hexane, 1.0 mL/min, 254 nm): t_R (minor, 3.3 min), t_R (major, 6.0 min).

(*S*)-*tert*-butyl-2-(2-(*tert*-butoxycarbonylamino)-3-phenylpropanamido)acetate; (*S*)-Boc-Phe-Gly-O*t*-Bu (3sh)[S-18]



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 10/1 to 3/1); white solid; ^{1}H NMR (400 MHz, DMSO-d_6, 21 ^{o}C) δ 8.31 (t, J = 5.6 Hz, 1H, CON*H*CH$_2$), 7.36-7.14 (m, 5H, *aromatic*), 6.94 and 6.49 (d, J = 9.0 Hz, 1H, *t*-BuOCON*H*), 4.18 and 4.11 (ddd, J = 11.2, 9.0, 4.0 Hz, 1H, C*H*), 3.79 (dd, J = 17.2, 5.6 Hz, 1H, NHC*H*H), 3.70 (dd, J = 17.2, 5.6 Hz, 1H, NHCH*H*), 3.00 (dd, J = 14.0, 4.0 Hz, 1H, C*H*HPh), 2.72 (dd, J = 14.0, 11.2 Hz, 1H, CH*H*Ph), 1.41, (s, 9H, C(C*H*$_3$)$_3$), 1.28 and 1.19 (s, 9H, C(C*H*$_3$)$_3$), rotamers; ^{13}C NMR (100 MHz, DMSO-d_6, 21 °C) δ 172.2, 168.8, 155.2, 138.2, 129.3, 129.1, 127.9, 126.1, 80.5, 77.9, 57.0, 55.5, 41.4, 38.1, 37.4, 28.1, 27.6, rotamers; MS (ESI) *m*/*z* (relative intensity) 223 (100), 267 (28), 345 (68), 401 ([M+Na$^+$], 62); HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{30}N_2O_5Na$ 401.2052, found 401.2059; $[\alpha]_{589}^{21}$ –10.7 (*c* 0.98 in MeOH); Other physical measurements were previously reported in the literature. The enantiomeric excess (%ee) was determined to be 96% by HPLC using CHIRALPAK AD-3 column (2% *i*-PrOH/ Hexane, 1.0 mL/min, 254 nm): t_R (majnor, 82.1 min), t_R (minor, 88.0 min).

(*S*)-tert-butyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)propanoate; (*S*)-Boc-Phe-Ala-O*t*-Bu (3si)



Purified by flush column chromatography (silica gel, Hexane/EtOAc = 10/1 to 4/1); white solid; mp 101-102 ˚C; IR (KBr, ν/cm^{-1}) 3302, 2978, 2932, 1736, 1659, 1535, 1451, 1381, 1250, 1157, 1049, 849; ^{1}H NMR (400 MHz, $CDCl_3$, 30 ^{o}C) δ 7.31-7.19 (m, 5H, *aromatic*), 6.39 and 6.20 (d, J = 8.0 Hz, 1H, N*H*), 4.97 (br, 1H, N*H*), 4.40-4.33 (m, 2H, NHC*H*), 3.12-3.11 (m, 2H, PhC*H*$_2$), 1.44 (s, 9H, C(C*H*$_3$)$_3$), 1.41 (s, 9H, C(C*H*$_3$)$_3$), 1.31 and 1.21 (d, J = 7.2 Hz, C*H*$_3$), rotamers; ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C) δ 171.7, 171.6, 170.6, 170.4, 155.3, 136.8, 136.6, 129.4, 129.3, 128.6, 126.9, 81.9, 80.1, 55.6, 48.7, 48.5, 38.9, 38.5, 28.2, 28.0, 27.9, 18.5, 18.3, rotamers; MS (ESI) *m*/*z* (relative intensity) 807 (100), 415 ([M+Na$^+$], 67), 393 ([M+H$^+$], 32); HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{32}N_2O_5Na$ 415.2209, found 415.2199; $[\alpha]_{589}^{29}$ –10.01 (*c* 1.00 in MeOH).

4. References for the Supplementary Information

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