Electronic Supplementary Information for

Cleavage of unactivated amide bonds by ammonium salt-accelerated hydrazinolysis

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1. Preliminary Experiments for Understanding Steric and Electronic Effects

To understand steric and electronic effects for the hydrazinolysis of amide bonds under our reaction conditions, we performed preliminary experiments described below.

First, we performed reactions of amides with different steric hindrance (eq S1). As a result, sterically less crowded amide $1a$ reacted faster than sterically more crowded amides $1u$ and $1v$ (Fig. S1). Therefore, steric effects are important for the hydrazinolysis of amide bonds under our reaction conditions.

$$1a: R^1 = \text{Me}, R^2 = \text{H}$$

$$1u: R^1 = \text{Me}, R^2 = \text{Me}$$

$$1v: R^1 = t\text{-Bu}, R^2 = \text{H}$$

Next, we performed reactions of amides with different electronic properties (eq S2). As a result, electronically more deficient amide $1w$ (Taft’s polar substituent constant $\sigma^* = 0.60$) reacted faster than electronically more rich amide $1a$ ($\sigma^* = 0$), although steric hindrance of $1w$ (Taft’s steric substituent constant $E_s = -0.19$) is larger than that of $1a$ ($E_s = 0$) (Fig. S2). Therefore, electronic effects are also important for the hydrazinolysis of amide

Fig. S1 Time-course experiments for amides with different steric hindrance. Yields were determined by $^1$H NMR analysis of the crude mixture.

Next, we performed reactions of amides with different electronic properties (eq S2). As a result, electronically more deficient amide $1w$ (Taft’s polar substituent constant $\sigma^* = 0.60$) reacted faster than electronically more rich amide $1a$ ($\sigma^* = 0$), although steric hindrance of $1w$ (Taft’s steric substituent constant $E_s = -0.19$) is larger than that of $1a$ ($E_s = 0$) (Fig. S2). Therefore, electronic effects are also important for the hydrazinolysis of amide
bonds under our reaction conditions.

\[
\text{R}^1\text{CONHCH}_2\text{R}^2 + \text{H}_2\text{NNH}_2\cdot\text{H}_2\text{O} \xrightarrow{\text{NH}_4\text{I (1.0 equiv)}} \text{EtOH (2.0 M), 70 °C} \Rightarrow \text{H}_2\text{NCH}_2\text{R}^2
\]  
(eq S2)

**Fig. S2** Time-course experiments for amides with different electronic properties. Yields were determined by \(^1\)H NMR analysis of the crude mixture.

Taken together, these results indicate that both steric and electronic effects are important for the hydrazinolysis of amide bonds under our reaction conditions.
2. General Experimental Details

All reactions were conducted in flame-dried glassware under an argon atmosphere unless otherwise noted. Reagents and solvents were obtained from commercial sources and used as received unless otherwise stated. Microwave irradiation reactions were performed with CEM Discover LabMate. Flash silica gel column chromatography was conducted with Merck silica gel 60 (230–400 mesh ASTM) or Kanto Chemical silica gel 60N (spherical neutral, particle size 40–50 µm).

Nuclear magnetic resonance (NMR) spectra were acquired on 400 MHz Varian Unity and 500 MHz Bruker Avance III spectrometers. Chemical shifts are reported in ppm and referenced to tetramethylsilane or residual solvent peaks as internal standards (for CDCl₃, tetramethylsilane 0 ppm for ¹H and CDCl₃ 77.0 ppm for ¹³C; for DMSO-d₆, 2.50 ppm for ¹H and 39.5 ppm for ¹³C; for C₆D₆, 7.16 ppm for ¹H and 128.06 ppm for ¹³C). Coupling constants are reported in hertz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared (IR) spectra were recorded with Shimadzu FTIR-8400. High-resolution mass spectroscopy (HRMS) was obtained with Waters ACQUITY UPLC®–LCT-Premier™ XE system. High performance liquid chromatography (HPLC) was performed with JASCO PU-2089plus pump and UV-2075plus detector. Chiral HPLC analysis was performed with DAICEL CHIRALPAK AD-3 column. Optical rotation was measured with JASCO P2200 polarimeter. Melting points were measured by Yanaco Micro Melting Point System MP-J3 and are uncorrected.
3. Preparation of Substrates

Amide 1a [CAS Registry No. 588-46-5] and anilides 1j [CAS Registry No. 104-04-1], 1n [CAS Registry No. 103-90-2] and 1o [CAS Registry No. 122-80-5] were purchased from Tokyo Chemical Industry Co. Ltd. Amides 1e [CAS Registry No. 14028-67-2], If [CAS Registry No. 82342-56-1], Ig [CAS Registry No. 796053-27-5], 1i [CAS Registry No. 5464-77-7], 1t [CAS Registry No. 13343-62-9], 1u [CAS Registry No. 79649-68-6], Iv [CAS Registry No. 26209-45-0] and anilides Ih [CAS Registry No. 864424-24-8], 1l [CAS Registry No. 16375-88-5] were prepared by conventional procedure from the corresponding amines or anilines with carboxylic acid chlorides or anhydrides in the presence of base, or according to the procedure known in the literature.

Preparation Method and Characterization Data of Substrates Unknown in the Literature

N-(4-(1,3-Dioxolan-2-yl)benzyl)acetamide (1b) [CAS Registry No. 738615-92-4]

![Chemical Structure](image)

(4-(1,3-Dioxolan-2-yl)phenyl)methanamine (1.31 g, 7.30 mmol) and Et₃N (1.1 mL, 8.0 mmol) were dissolved in dichloromethane (20 mL) followed by dropwise addition of acetyl chloride (0.52 mL, 7.3 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed three times with saturated aqueous NaHCO₃. The combined organic layer was dried over Na₂SO₄, filtered and purified by flash silica gel column.
chromatography using hexane/EtOAc = 1/4 to EtOAc as eluent to give \( N-(4-(1,3\text{-dioxolan-2-yl})\text{benzyl})\text{acetamide (1b)} \) as a white solid (1.40 g, 86% yield).

mp 81–84 °C. \(^1\)H NMR (400 MHz, CDCl \(_3\)) \( \delta \) 7.45 (d, \( J = 8.0 \) Hz, 2H), 7.33–7.22 (m, 2H), 5.81 (s, 1H), 5.66 (br, 1H), 4.45 (d, \( J = 6.0 \) Hz, 2H), 4.15–4.00 (m, 4H), 2.02 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl \(_3\)) \( \delta \) 169.9, 139.3, 137.3, 127.9, 126.8, 103.4, 65.3, 43.5, 23.2. IR (KBr disc) 3310, 3063, 2886, 2808, 2762, 1651, 1551, 1435, 1397, 1366, 1296, 1250, 1227, 1080, 1026, 972, 941, 864, 826, 787, 709, 656, 617, 579, 532 cm \(^{-1}\). HRMS (ESI-TOF) \( m/z \) calcd. for C\(_{12}\)H\(_{16}\)NO\(_3\) [M + H\(^+\)] 222.1130, found 222.1122.

**tert-Butyl 4-(acetimidomethyl)benzylcarbamate (1c)** [CAS Registry No. 1257585-74-2]

\( \text{Me}^\text{\-N} \)

\( \begin{array}{c}
\text{O} \\
\text{N} \\
\text{H} \\
\text{O} \\
\text{t-}
\text{Bu}
\end{array} \)

\( 1c \)

\( \text{tert-Butyl 4-(aminomethyl)benzylcarbamate} \) \(^{11}\) (2.36 g, 10.0 mmol) and Et\(_3\)N (2.8 mL, 20 mmol) were dissolved in dichloromethane (20 mL) followed by dropwise addition of acetic anhydride (1.1 mL, 12 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The crude residue was diluted with EtOAc and washed three times with saturated aqueous NaHCO\(_3\) solution and once with brine. The combined organic layer was dried over Na\(_2\)SO\(_4\), filtered and purified by flash silica gel chromatography using EtOAc as eluent to give tert-buty 4-(acetimidomethyl)benzylcarbamate (1c) as a white solid (1.92 g, 69% yield).

mp 115–117 °C. \(^1\)H NMR (400 MHz, CDCl \(_3\)) \( \delta \) 7.32–7.19 (m, 4H), 5.67 (br, 1H), 4.82 (br, 1H), 4.42 (d, \( J = 5.6 \) Hz, 2H), 4.29 (d, \( J = 6.8 \) Hz, 2H), 2.02 (s, 3H), 1.46 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl \(_3\)) \( \delta \) 169.9, 155.9, 138.4, 137.3, 128.1, 127.7, 79.5, 44.3, 43.4, 28.4, 23.2. IR (KBr disc) 3333, 3287, 3078, 2978, 2932, 2886, 1682, 1643, 1505, 1443, 1366, 1296, 1250, 1180, 1049, 1018, 872, 826, 733, 625, 602 cm \(^{-1}\). HRMS (ESI-TOF) \( m/z \) calcd. for C\(_{15}\)H\(_{21}\)N\(_2\)O\(_3\) [M – H\(^+\)] 277.1552, found 277.1556.


Benzyl 4-(Acetamidomethyl)benzylcarbamate (1d) [CAS Registry No. N/A]

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
& \quad \text{H} \\
& \quad \text{O} \\
& \quad \text{H} \\
& \quad \text{N} \\
& \quad \text{O} \\
\end{align*}
\]

\(1d\)

\(p\)-Xylylendiamine (4.08 g, 30.0 mmol) and Et\(_3\)N (1.4 mL, 10 mmol) were dissolved in dichloromethane (80 mL) followed by dropwise addition of benzyl chloroformate (1.4 mL, 9.9 mmol) dissolved in dichloromethane (30 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was diluted with EtOAc and washed with 1 M aqueous NaOH solution. The solution was filtered and washed three times with 1 M aqueous NaOH solution and once with brine. The combined organic layer was dried over Na\(_2\)SO\(_4\), filtered and the solvent was removed under reduced pressure to give a white solid which contained benzyl 4-(aminomethyl)benzylcarbamate. \(^{12}\) The crude benzyl 4-(aminomethyl)benzylcarbamate and Et\(_3\)N (2.5 mL, 18 mmol) were dissolved in dichloromethane (30 mL) followed by dropwise addition of acetic anhydride (0.99 mL, 10 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 1 M aqueous HCl solution. The resulting mixture was filtered, and the layers were separated. The organic phase was dried over Na\(_2\)SO\(_4\), filtered and purified by flash silica gel column chromatography using EtOAc as eluent to give benzyl 4-(acetamidomethyl)benzylcarbamate (1d) as a white solid (726 mg, 23% yield for 2 steps). mp 149–155 °C. \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.38–7.10 (m, 10H), 5.68 (br, 1H), 5.13 (s, 2H), 5.05 (br, 1H), 4.42 (d, \(J = 6.0\) Hz, 2H), 4.37 (d, \(J = 6.0\) Hz, 2H), 2.02 (s, 3H). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 169.0, 156.3, 138.2, 138.1, 137.2, 128.3, 127.8, 127.7, 127.3, 127.0, 65.3, 43.6, 41.9, 22.5. IR (KBr disc) 3301, 1690, 1636, 1543, 1427, 1381, 1265, 1219, 1142, 1057, 972, 825, 748, 671, 563 cm\(^{-1}\). HRMS (ESI-TOF) \(m/z\) calcd. for C\(_{18}\)H\(_{21}\)N\(_2\)O\(_3\)[M + H\(^+\)] 313.1552, found 313.1556.

**tert-Butyl 4-(acetamido)benzoate (1k) [CAS Registry No. N/A]**

To a stirred solution of tert-butyl 4-aminobenzoate (1.93 g, 10.0 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added acetic anhydride (0.99 mL, 11 mmol) and the resulting mixture was stirred at room temperature for 8 h. The solvent was evaporated, and the crude mixture was extracted with ethyl acetate, and the organic phase was washed with 1 M aqueous HCl solution, saturated aqueous NaHCO₃ solution and brine. The organic phase was dried over Na₂SO₄, filtered and evaporated to give tert-butyl 4-(acetamido)benzoate (1k) as a white solid (2.35 g, >99% yield).

![1k](image)

mp 105–109 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, J = 8.5 Hz, 2H), 7.88 (br s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 2.19 (s, 3H), 1.58 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 168.7, 165.4, 141.8, 130.5, 127.4, 118.7, 80.9, 24.7. IR (KBr disc) 3263, 3187, 3117, 3055, 2978, 2932, 1705, 1674, 1597, 1535, 1404, 1375, 1296, 1265, 1165, 1111, 1010, 856, 772, 748, 702, 601, 579 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₃H₁₈NO₃ [M + H⁺] 236.1287, found 236.1282.

**N-(4-(((tert-Butyldimethylsilyl)oxy)methyl)phenyl)acetamide (1p) [CAS Registry No. N/A]**

To a stirred solution of 4-(acetamido)benzyl alcohol¹³ (1.65 g, 10.0 mmol) in DMF (24 mL) were added imidazole (1.00 g, 14.7 mmol) and tert-butyl(dimethyl)silyl chloride (1.50 g, 9.95 mmol) at 0 °C, and the reaction mixture was stirred at room temperature overnight. After addition of water and Et₂O, the mixture was washed trice with water. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, evaporated and purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 as eluent to give N-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)acetamide (1p) as a white solid (1.59 g, 57 % yield).

![1p](image)

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mp 98–100 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.45 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.11 (br, 1H), 4.69 (s, 2H), 2.16 (s, 3H), 0.93 (m, 9H), 0.09 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 168.2, 137.5, 136.6, 126.8, 119.7, 64.6, 25.9, 24.6, 18.4, –5.3. IR (KBr disc) 3256, 3194, 3125, 3071, 2940, 2862, 1659, 1605, 1512, 1466, 1373, 1319, 1057, 1011, 880, 810, 679 cm$^{-1}$. HRMS (ESI-TOF) $m$/z calcd. for C$_{18}$H$_{32}$NO$_2$Si [M + H$^+$] 322.2202, found 322.2196.

**(S)-2-Acetamido-N-((R)-1-phenylethyl)propanamide (1q) [CAS Registry No. N/A]**

(S)-1-oxo-1-((R)-1-phenylethylamino)propane-2-ylcarbamate (1.463 g, 5.00 mmol) was dissolved in trifluoroacetic acid (10 mL) and CH$_2$Cl$_2$ (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude TFA salt was diluted with dichloromethane and Et$_3$N (1.4 mL, 10 mmol) was added, followed by dropwise addition of acetic anhydride (0.47 mL, 5.0 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature, washed twice with 1 M aqueous HCl solution, once with saturated aqueous NaHCO$_3$ solution and once with brine. The combined organic layer was dried over Na$_2$SO$_4$, filtered and purified by flash silica gel column chromatography using dichloromethane/MeOH = 20/1 as eluent to give (S)-2-acetamido-N-((R)-1-phenylethyl)propanamide (1q) as a white solid (987.9 mg, 84% yield).

mp 180–182 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35–7.16 (m, 5H), 6.96 (d, $J = 7.0$ Hz, 1H), 6.32 (d, $J = 7.0$ Hz, 1H), 5.03 (dq, $J = 7.0$, 7.0 Hz, 1H), 4.53 (dq, $J = 7.0$, 7.0 Hz, 1H), 1.90 (s, 3H), 1.47 (d, $J = 7.0$ Hz, 3H), 1.38 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.4, 170.0, 124.1, 128.6, 127.3, 126.0, 49.1, 48.9, 23.1, 22.1, 18.5. IR (KBr disc) 3287, 3078, 2970, 2932, 2816, 2724, 2639, 1636, 1551, 1443, 1373, 1281, 1242, 1157, 1126, 1018, 926, 733, 702, 610 cm$^{-1}$. HRMS (ESI-TOF) $m$/z calcd. for C$_{13}$H$_{19}$N$_2$O$_2$ [M + H$^+$] 235.1447, found 235.1457. [$\alpha$]$^2$$_D$ –2.3 (c 1.00, CHCl$_3$).
(S)-N-(tert-Butyl)-3-phenyl-2-(2-pivalamidoacetamido)propanamide (1r) [CAS Registry No. N/A]

(S)-tert-Butyl (1-(tert-butylamino)-1-oxo-3-phenylpropan-2-yl)carbamate\(^\text{14}\) (1.03 g, 3.21 mmol) was dissolved in 20% trifluoroacetic acid in CH\(_2\)Cl\(_2\) (32 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure to give crude TFA salt (1.20 g). The crude TFA salt (1.00 g), 2-pivalamidoacetic acid\(^\text{15}\) (448 mg, 2.81 mmol) and HBTU (1.14 g, 3.01 mmol) were dissolved in dichloromethane (15 mL) followed by dropwise addition of 2,4,6-trimethylpyridine (1.2 mL, 9.1 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude residue was diluted with EtOAc and washed three times with 1 M aqueous HCl solution, three times with saturated aqueous NaHCO\(_3\) solution and once with brine. The combined organic layer was dried over Na\(_2\)SO\(_4\), filtered and purified by flash silica gel column chromatography using hexane/EtOAc = 1/4 to EtOAc as eluent to give (S)-N-(tert-butyl)-3-phenyl-2-(2-pivalamidoacetamido)propanamide (1r) as a white solid (894.6 mg, 93% yield in 2 steps). Enantiomeric excess of 1r was determined to be 99% by chiral HPLC analysis.

mp 155–158 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.35–7.20 (m, 5H), 6.56 (d, \(J = 7.5\) Hz, 1H), 6.32 (br s, 1H), 5.14 (s, 1H), 4.49–4.42 (m, 1H), 3.90 (d, \(J = 5.0\) Hz, 2H), 3.20 (dd, \(J = 5.5, 13.5\) Hz, 1H), 2.84 (dd, \(J = 9.0, 13.5\) Hz, 2H), 1.21 (s, 9H), 1.19 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 179.1, 169.2, 168.7, 136.8, 129.4, 128.7, 127.0, 55.1, 51.4, 43.3, 38.9, 38.7, 28.4, 27.4. IR (KBr disc) 3279, 3078, 2970, 2870, 1651, 1551, 1458, 1397, 1366, 1258, 1219, 1011, 941, 849, 795, 741, 702 cm\(^{-1}\). HRMS (ESI-TOF) \(m/z\) calcd. for C\(_{20}\)H\(_{32}\)N\(_3\)O\(_3\) [M + H\(^+\)] 362.2444, found 362.2429. HPLC conditions: DAICEL CHIRALCEL AD-3, eluent: Hexane/2-Propanol 9.0/1.0, flow: 1.0 mL/min, detection: 210 nm, \(t_R\): 8.8 min (minor), 11.9 min (major). \([\alpha]^{20}_D\) –4.9 (c 1.02, CHCl\(_3\)).

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(S)-N-(2-((S)-1-(tert-Butylamino)-1-oxo-3-phenylpropan-2-ylamino)-2-oxoethyl)-3-methyl-2-pivalamidobutanamide (1s) [CAS Registry No. N/A]

To a solution of (S)-tert-butyl (1-(tert-butylamino)-1-oxo-3-phenylpropan-2-yl)carbamate\(^{14}\) \((641 \text{ mg, 2.00 mmol})\) in CH\(_2\)Cl\(_2\) \((5.0 \text{ mL})\) at 0 °C was added 4 M HCl in AcOEt \((5.0 \text{ mL, 20 mmol})\). The mixture was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. The residue was diluted with CH\(_2\)Cl\(_2\) and the organic phase was washed with 1 M aqueous NaOH solution and the aqueous phase was extracted with CH\(_2\)Cl\(_2\). The combined organic phase was dried over Na\(_2\)SO\(_4\), filtered and evaporated to give crude (S)-2-amino-N-tert-butyl-3-phenylpropanamide\(^{16}\) \((459 \text{ mg})\) as pale yellow oil, which was used without further purification. The crude oil was dissolved in CH\(_2\)Cl\(_2\) \((10 \text{ mL})\) and transferred to the mixture of (S)-2-(3-methyl-2-pivalamidobutanamido)acetic acid (S\(_1\)) \((516 \text{ mg, 2.00 mmol})\) and HOBt \((297 \text{ mg, 2.20 mmol})\). To the mixture at 0 °C was added EDCI-HCl \((422 \text{ mg, 2.20 mmol})\) and Et\(_3\)N \((0.31 \text{ mL, 2.2 mmol})\), and the mixture was stirred at room temperature for 16 h. The solvent was evaporated and the crude residue was diluted with EtOAc. The organic phase was washed twice with 1 M aqueous HCl solution/brine mixture and twice with saturated aqueous NaHCO\(_3\) solution/brine mixture, dried over Na\(_2\)SO\(_4\), filtered and purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 to EtOAc only to EtOAc/MeOH = 9/1 to 2/1 as eluent to give (S)-N-(2-((S)-1-(tert-butylamino)-1-oxo-3-phenylpropan-2-ylamino)-2-oxoethyl)-3-methyl-2-pivalamidobutanamide (1s) as a white solid \((847.3 \text{ mg, 92% yield in 2 steps})\). mp 108–112 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.39–7.11 \((\text{m, 6H})\), 6.98 \((\text{d, } J = 7.5 \text{ Hz, 1H})\), 6.31 \((\text{d, } J = 8.0, \text{ Hz, 1H})\), 5.66 \((\text{s, 1H})\), 4.59 \((\text{ddd, } J = 5.5, 7.5, 8.5 \text{ Hz, 1H})\), 4.39 \((\text{dd, } J = 7.0, 8.0 \text{ Hz, 1H})\), 4.03 \((\text{dd, } J = 5.5, 17 \text{ Hz, 1H})\), 3.88 \((\text{dd, } J = 5.0, 17 \text{ Hz, 1H})\), 3.10 \((\text{dd, } J = 5.5, 17 \text{ Hz, 1H})\),

13.5 Hz, 1H), 2.94 (dd, \( J = 8.5, 13.5 \) Hz, 1H), 2.10 (qqd, \( J = 6.0, 6.5, 7.0 \) Hz, 1H), 1.22 (s, 9H), 1.17 (s, 9H), 0.95 (d, \( J = 6.0 \) Hz, 3H), 0.94 (d, \( J = 6.5 \) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 178.7, 172.0, 169.4, 168.1, 136.8, 129.5, 128.6, 126.9, 58.1, 55.1, 51.3, 42.8, 39.1, 38.9, 31.2, 28.5, 27.6, 19.3, 18.3. IR (KBr disc) 3316, 3298, 3082, 2997, 2934, 2872, 1640, 1533, 1506, 1456, 1393, 1366, 1261, 1225, 1032, 743, 698 cm⁻¹. HRMS (ESI-TOF) \( m/z \) calcd. for C₂₅H₄₁N₄O₄ \([M + H^+]\) 461.3128, found 461.3128. [\( \alpha \)]\(^{27}\)D 2.8 (c 0.99, CHCl₃).

Preparation of (S)-2-(3-Methyl-2-pivalamidobutanamido)acetic Acid (S1)
(S)-Ethyl 2-(3-methyl-2-pivalamidobutanamido)acetate (S2) [CAS Registry No. N/A]

To a solution of (S)-ethyl 2-(2-amino-3-methylbutanamido)acetate hydrochloride\(^{17}\) (2.607 g, 10.92 mmol) in CH₂Cl₂ (34 mL) at 0 °C was added Et₃N (3.4 mL, 24 mmol) and pivaloyl chloride (1.3 mL, 24 mmol) and pivaloyl chloride (1.3 mL, 11 mmol), and the mixture was stirred at room temperature for 12 h. The solvent was evaporated and the crude residue was diluted with EtOAc. The organic phase was washed twice with 1 M aqueous HCl solution/brine mixture and twice with saturated aqueous NaHCO₃ solution/brine mixture, dried over Na₂SO₄, filtered and evaporated to give (S)-ethyl 2-(3-methyl-2-pivalamidobutanamido)acetate (S2) as a white solid (2.983 g, 95% yield).

mp 103–105 °C. \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 6.53 (br s, 1H), 6.22 (d, \( J = 8.5 \) Hz, 1H), 4.32 (dd, \( J = 6.5, 8.5 \) Hz, 1H), 4.21 (q, \( J = 7.0 \) Hz, 2H), 4.10 (dd, \( J = 5.5, 18 \) Hz, 1H), 3.94 (dd, \( J = 5.0, 18 \) Hz, 1H), 2.16 (dq, \( J = 6.5, 6.5, 7.0 \) Hz, 1H), 1.28 (t, \( J = 7.0 \) Hz, 3H), 0.98 (d, \( J = 7.0 \) Hz, 3H), 0.95 (d, \( J = 6.5 \) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 178.6, 171.6, 169.5, 61.5, 58.0, 41.3, 38.9, 31.0, 27.5, 19.2, 18.1, 14.1. IR (KBr disc) 3337, 3279, 3084, 2974, 2872, 1759, 1678, 1632, 1564, 1532, 1481, 1468, 1449, 1402, 1379, 1204, 1186, 1099, 1026, 964, 930, 864, 712, 669, 559 cm⁻¹. HRMS (ESI-TOF) \( m/z \) calcd. for C₁₄H₂₇N₂O₄ \([M + H^+]\) 287.1971, found 287.1973. [\( \alpha \)]\(^{28}\)D –42.7 (c 1.00, CHCl₃).

(S)-2-(3-Methyl-2-pivalamidobutanamido)acetic acid (S1) [CAS Registry No. N/A]

To a solution of S2 (859 mg, 3.00 mmol) in MeOH (6.0 mL) at 0 °C was added 1 M aqueous NaOH solution (6.0 mL, 6.0 mmol), and the mixture was stirred at 0 °C for 1 h and acidified to pH ~ 4–5 with 1 M aqueous HCl solution (4.5 mL). The organic solvent was evaporated and the residue was further acidified to pH ~ 1 by addition of 1 M aqueous HCl solution (2.5 mL), and the aqueous phase was extracted twice with EtOAc. The combined organic phase was dried over Na2SO4, filtered and evaporated to give (S)-2-(3-methyl-2-pivalamidobutanamido)acetic acid (S1) as a white solid (750 mg, 97% yield).

mp 175–178 °C. 1H NMR (500 MHz, CDCl3) δ 7.26 (br s, 1H), 6.48 (d, J = 9.0 Hz, 1H), 4.62 (dd, J = 8.0, 9.0 Hz, 1H), 4.15 (dd, J = 5.0, 18.5 Hz, 1H), 3.99 (dd, J = 4.0, 18.5 Hz, 1H), 2.04 (qqd, J = 6.5, 6.5, 8.0 Hz, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H).

13C NMR (125 MHz, CDCl3) δ 179.6, 171.62, 171.57, 58.0, 41.4, 39.0, 31.6, 27.4, 19.3, 18.2. IR (KBr disc) 3327, 3291, 3084, 2970, 2876, 1728, 1713, 1678, 1562, 1526, 1227, 1204, 1040, 934, 889, 706 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C12H23N2O4 [M + H⁺] 259.1658, found 259.1648. [α]26D –48.7 (c 1.00, MeOH).
4. General Procedure for Deacylation of Amines (Tables 1 and 2)

Conventional heating conditions: To a 4.0 mL of a vial equipped with a magnetic stir bar, ammonium iodide (144 mg, 1.00 mmol), amide or anilide 1 (1.00 mmol) and hydrazine monohydrate (0.50 mL, 10 mmol) were added and the vial was sealed with a Teflon-lined screw cap. The vial was heated with stirring at the indicated temperature and time. The resulting mixture was purified by extraction or flush silica gel column chromatography to give amine 2.

Microwave heating conditions: To a 10 mL of a glass test tube equipped with a magnetic stir bar, ammonium iodide (144 mg, 1.00 mmol), amide or anilide 1 (1.00 mmol) and hydrazine monohydrate (0.50 mL, 10 mmol) were added and the tube was sealed with a cap. The test tube was heated with stirring at the indicated temperature and time under microwave irradiation conditions (maximum power 250 W). The crude mixture was purified by the indicated methods.

Experimental Details of Control Experiments Under Literature Conditions (Table 1)

Entry 1: Amide 1a (1.00 mmol) and hydrazine monohydrate (0.50 mL, 10 mmol) were mixed and stirred at 60 °C for 6 h. ¹H NMR analysis of the crude mixture showed that 2a was not detected.

Entry 2: Acetic acid (0.086 mL, 1.5 mmol), amide 1a (74.5 mg, 0.500 mmol) and hydrazine monohydrate (0.075 mL, 1.5 mmol) were dissolved in EtOH (0.50 mL). The resulting mixture was heated with stirring at 60 ºC for 6 h. ¹H NMR analysis of the crude mixture showed that 2a was formed in 7% yield.

Details for Each Substrate and Characterization Data of Products

Amines 2a, 2e, 2i and anilines 2h, 2j, 2k, 2l, 2n and 2o were commercially available.

Benzylamine (2a) (Table 1, entry 7) [CAS Registry No. 100-46-9]

H₂N

After the reaction, the crude mixture was diluted with dichloromethane and deprotected amine was extracted with 1 M aqueous HCl solution. The aqueous layer was basified with 1 M aqueous NaOH solution and
back-extracted with Et₂O. The organic layer was dried over Na₂SO₄, filtered and evaporated to give benzylamine (2a) as pale yellow liquid (96.3 mg, 90% yield).

1H NMR (500 MHz, CDCl₃) δ 7.40–7.25 (m, 5H), 3.87 (s, 2H), 1.55 (br, 2H); 13C NMR (125 MHz, CDCl₃) δ 143.3, 128.5, 127.1, 126.8, 46.5.

**Benzylamine (2a) (Table 1, entry 8) [CAS Registry No. 100-46-9]**

![Image of benzylamine (2a)](image)

After the reaction, the crude mixture was diluted with dichloromethane and deprotected amine was extracted with 1 M aqueous HCl solution.

The aqueous layer was basified with 1 M aqueous NaOH solution and back-extracted with Et₂O. The organic layer was dried over Na₂SO₄, filtered and evaporated to give benzylamine (2a) as pale yellow liquid (94.9 mg, 89% yield).

1H NMR (400 MHz, CDCl₃) δ 7.37–7.21 (m, 5H), 3.87 (s, 2H), 1.55 (br s, 2H). 13C NMR (100 MHz, CDCl₃) δ 143.2, 128.5, 127.0, 126.8, 46.5.

**Benzylamine (2a) (Table 1, entry 9) [CAS Registry No. 100-46-9]**

![Image of benzylamine (2a)](image)

After the reaction, the crude mixture was diluted with dichloromethane and deprotected amine was extracted with 1 M aqueous HCl solution.

The aqueous layer was basified with 1 M aqueous NaOH solution and back-extracted with Et₂O. The organic layer was dried over Na₂SO₄, filtered and evaporated to give benzylamine (2a) as pale yellow liquid (97.0 mg, 90% yield).

1H NMR (500 MHz, CDCl₃) δ 7.36–7.22 (m, 5H), 3.88 (s, 2H), 1.52 (br s, 2H). 13C NMR (125 MHz, CDCl₃) δ 143.2, 128.6, 127.1, 126.8, 46.5.

*(4-(1,3-Dioxolan-2-yl)phenyl)methanamine (2b) (Table 2, entry 1) [CAS Registry No. 104566-44-1]*

![Image of (4-(1,3-Dioxolan-2-yl)phenyl)methanamine (2b)](image)

This reaction was performed on a 0.50 mmol scale for 1b. After the reaction, the crude reaction mixture was diluted with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with AcOEt and combined organic layer was dried over Na₂SO₄, filtered and purified by flash silica gel column chromatography using
dichloromethane/MeOH = 20/1 to dichloromethane/MeOH/diethylamine = 20/1/1 as eluent. After evaporation of the solvent, the residue was washed with Et₂O and filtered to give (4-(1,3-dioxolan-2-yl)phenyl)methanamine (2b) as a white solid (69.8 mg, 78% yield).

\[
\begin{align*}
\text{H} & \text{N} \\
\text{H} & \text{O} \\
\text{t-Bu} & \\
\text{2c}
\end{align*}
\]

$^1$H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 5.81 (s, 1H), 4.17–4.00 (m, 4H), 3.88 (s, 1H), 1.48 (br s, 2H). $^{13}$C NMR (100 MHz, CDCl_3) δ 144.0, 136.5, 127.1, 126.7, 103.6, 65.2, 46.1.

Under the conditions using ethylenediamine as cleaving agent: To a 10 mL of a glass test tube equipped with a magnetic stir bar, ammonium bromide (98 mg, 1.0 mmol), amide 1b (221 mg, 1.00 mmol) and ethylenediamine (0.27 mL, 4.0 mmol) were added and the tube was sealed with a cap. The test tube was heated with stirring for 5 h at the 80 ºC under microwave irradiation conditions (maximum power 250 W). The crude mixture was diluted with saturated aqueous NaHCO₃ solution and the deprotected amine was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, evaporated and purified by flash silica gel column chromatography using dichloromethane/MeOH = 100/5 to dichloromethane/MeOH/diethylamine = 100/5/1 as eluent to give crude 2b as a yellow liquid. Yield was determined by $^1$H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard (<40% yield).

**tert-Butyl 4-(aminomethyl)benzylcarbamate (2c) (Table 2, entry 2) [CAS Registry No. 108468-00-4]**

This reaction was performed in EtOH (0.50 mL), and after the reaction the crude mixture was directly purified by flash silica gel column chromatography using dichloromethane/MeOH = 10/1 to dichloromethane/MeOH/diethylamine = 20/2/1 as eluent to give tert-butyl 4-(aminomethyl)benzylcarbamate (2c) as a white solid (200 mg, 85% yield).

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Under the conditions using ethylenediamine as cleaving agent: To a 10 mL of a glass test tube equipped with a magnetic stir bar, ammonium bromide (98 mg, 1.0 mmol), amide 1c (278 mg, 1.00 mmol) and ethylenediamine (0.27 mL, 4.0 mmol) were added and the tube was sealed with a cap. The test tube was heated with stirring for 5 h at the 80 °C under microwave irradiation conditions (maximum power 250 W). The crude mixture was diluted with saturated aqueous NaHCO₃ solution and the deprotected amine was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, evaporated and purified by flash silica gel column chromatography using dichloromethane/MeOH = 100/5 to dichloromethane/MeOH/diethylamine = 100/5/1 as eluent to give 2c containing minor impurities as a white solid (94 mg, <40% yield).

Benzyl 4-(aminomethyl)benzylcarbamate (2d) (Table 2, entry 3) [CAS Registry No. 164648-85-5]¹⁹

This reaction was performed on a 0.250 mmol scale for 1d in EtOH (0.25 mL). The crude reaction mixture was directly purified by flash silica gel column chromatography using dichloromethane/MeOH = 10/1 to dichloromethane/MeOH/diethylamine = 20/2/1 as eluent. After evaporation of the solvent, the crude 2d was dissolved in dichloromethane and 1 M aqueous NaOH solution. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na₂SO₄, filtered and evaporated to give pure 2d as a white solid (53.6 mg, 79 % yield).

¹H NMR (400 MHz, CDCl₃) δ 7.40–7.17 (m, 10H), 5.14 (s, 2H), 5.04 (br, 1H), 4.37 (d, J = 6.0 Hz, 2H), 3.85 (s, 2H), 1.45 (br s, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ 156.3, 142.7, 137.6, 137.2, 128.3, 127.8, 127.7, 126.9, 126.8, 65.3, 45.3, 43.6.

**Under the conditions using ethylenediamine as cleaving agent:** To a 10 mL of a glass test tube equipped with a magnetic stir bar, ammonium bromide (98 mg, 1.0 mmol), amide 1d (312 mg, 1.00 mmol) and ethylenediamine (0.27 mL, 4.0 mmol) were added and the tube was sealed with a cap. The test tube was heated with stirring for 5 h at the 80 °C under microwave irradiation conditions (maximum power 250 W). However, 2d was not detected on 1H NMR spectrum of the crude mixture.

1,2,3,4-Tetrahydroisoquinoline (2e) (Table 2, entry 4) [CAS Registry No. 91-21-4]

After the reaction, the crude mixture was diluted with Et2O and washed with 1 M aqueous NaOH solution. The aqueous layer was extracted with Et2O, and combined organic layers were dried over Na2SO4, filtered and evaporated to give 1,2,3,4-tetrahydroisoquinoline (2e) as pale yellow liquid (122.5 mg, 92% yield).

1H NMR (400 MHz, CDCl3) δ 7.18–6.94 (m, 4H), 4.01 (s, 2H), 3.14 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 1.58 (br s, 1H). 13C NMR (100 MHz, CDCl3) δ 136.0, 134.8, 129.3, 126.2, 126.0, 125.7, 48.3, 43.9, 29.2.

1,2,3,4-Tetrahydroisoquinoline (2e) (Table 2, entry 5) [CAS Registry No. 91-21-4]

This reaction was performed on a 0.500 mmol scale for 1f in EtOH (0.25 mL). After the reaction, the crude reaction mixture was diluted with dichloromethane and washed with 1 M aqueous NaOH solution. The aqueous layer was extracted with dichloromethane and combined organic layer was dried over Na2SO4, filtered and purified by flash silica gel column chromatography using dichloromethane/MeOH = 100/5 as eluent to give 1,2,3,4-tetrahydroisoquinoline (2e) as pale yellow liquid (55.9 mg, 84% yield).

1H NMR (500 MHz, CDCl3) δ 7.17–6.97 (m, 4H), 4.02 (s, 2H), 3.15 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 1.63 (br s, 1H). 13C NMR (125 MHz, CDCl3) δ 136.1, 134.9, 129.5, 126.4, 126.2, 125.9, 48.9, 44.1, 29.4.
1,2,3,4-Tetrahydroisoquinoline (2e) (Table 2, entry 6) [CAS Registry No. 91-21-4]

After the reaction, the crude mixture was diluted with dichloromethane and deprotected amine was extracted with 1 M aqueous HCl solution. The aqueous layer was basified with 1 M aqueous NaOH solution and back-extracted with Et₂O. The organic layer was dried over Na₂SO₄, filtered and evaporated. The residue was treated with hexane, filtered and evaporated to give 1,2,3,4-tetrahydroisoquinoline (2e) as yellow liquid (110.5 mg, 83% yield).

1H NMR (400 MHz, CDCl₃) δ 7.20–7.05 (m, 4H), 4.01 (s, 2H), 3.14 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 1.60 (br s, 1H). 13C NMR (100 MHz, CDCl₃) δ 136.0, 134.8, 129.3, 127.0, 125.7, 48.3, 43.9, 29.2.

Indoline (2h) (Table 2, entry 7) [CAS Registry No. 496-15-1]

After the reaction in EtOH (0.50 mL), the crude reaction mixture was directly purified by flash silica gel column chromatography using hexane/EtOAc = 4/1 as eluent to give indoline (2h) as colorless liquid (101.0 mg, 85% yield).

1H NMR (400 MHz, CDCl₃) δ 7.11 (d, J = 7.6 Hz, 1H), 7.03–6.92 (m, 1H), 6.74–6.77 (m, 1H), 6.64 (d, J = 7.6 Hz, 1H), 3.74 (br s, 1H), 3.55 (t, J = 8.4 Hz, 2H), 3.03 (t, J = 8.4 Hz, 2H). 13C NMR (100 MHz, CDCl₃) δ 151.6, 129.3, 127.2, 124.6, 118.6, 109.4, 47.3, 29.8.

Dibenzylamine (2i) (Table 2, entry 8) [CAS Registry No. 103-49-1]

This reaction was performed on a 0.50 mmol scale for 1i in EtOH (0.25 mL). After the reaction, the crude mixture was diluted with Et₂O and washed with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with Et₂O and combined organic layer was dried over Na₂SO₄, filtered, evaporated and purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 as eluent to give dibenzylamine (2i) as colorless liquid (90.6 mg, 92% yield).

1H NMR (400 MHz, CDCl₃) δ 7.40–7.20 (m, 10H), 3.82 (s, 4H), 1.57 (br s, 1H). 13C NMR (100 MHz, CDCl₃) δ 140.3, 128.4, 128.1, 126.9, 53.2.
The above reaction was performed without addition of ammonium iodide under identical conditions to give 2i in only 26% yield.

4-Nitroaniline (2j) (Table 2, entry 9) [CAS Registry No. 100-01-6]

This reaction was performed in EtOH (0.50 mL). After the reaction, the crude mixture was directly purified by flash silica gel column chromatography using hexane/EtOAc = 3/1 to 2/1 as eluent to give 4-nitroaniline (2j) as a yellow solid (133.7 mg, 97% yield).

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.98–7.90 (m, 2H), 6.70 (br, 2H), 6.63–6.56 (d, $J = 8.4$ Hz, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 155.7, 135.6, 126.4, 112.4.

$^t$-Butyl 4-aminobenzoate (2k) (Table 2, entry 10) [CAS Registry No. 18144-47-3]

This reaction was performed on a 0.25 mmol scale for 1l in EtOH (0.25 mL). After the reaction, the crude mixture was directly purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 to 1/4 as eluent to give $^t$-butyl 4-aminobenzoate (2k) as a white solid (80.9 mg, 84% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.77–7.83 (m, 2H), 6.59–6.65 (m, 2H), 3.82 (br s, 2H), 1.57 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.9, 150.4, 131.3, 121.8, 113.7, 80.0, 28.3.

4-Aminobenzyl alcohol (2l) (Table 2, entry 11) [CAS Registry No. 623-04-1]

After the reaction, the crude mixture was directly purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 as eluent to give 4-aminobenzyl alcohol (2l) as a pale yellow solid (115.9 mg, 94% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.20–7.10 (m, 2H), 6.72–6.62 (m, 2H), 4.55 (s, 2H), 3.67 (br s, 2H), 1.59 (br s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.0, 131.0, 128.7, 115.1, 65.3.

4-[(2-Tetrahydropyranyloxy)methyl]aniline (2m) (Table 2, entry 12) [CAS Registry No. 18484-05-4]
This reaction was performed in EtOH (0.50 mL). After the reaction, the crude mixture was directly purified by flash silica gel column chromatography using hexane/AcOEt = 1/2 as eluent to give 4-[(2-tetrahydropyranyloxy)methyl]aniline (2m) as pale yellow liquid (194.8 mg, 94% yield).

\[ ^1\text{H NMR (400 MHz, CDCl}_3 \text{)} \delta 7.19–7.13 (m, 2H), 6.69–6.64 (m, 2H), 4.70–4.65 (m, 1H), 4.66 (d, \(J = 11.2\) Hz, 2H), 4.39 (d, \(J = 11.2\) Hz, 2H), 3.96–3.84 (m, 1H), 3.64 (br, 2H), 3.58–3.50 (m, 1H), 1.90–1.45 (m, 6H). \]  
\[ ^{13}\text{C NMR (100 MHz, CDCl}_3 \text{)} \delta 145.9, 129.6, 128.0, 114.9, 97.3, 68.7, 62.1, 30.6, 25.5, 19.4. \]

4-Aminophenol (2n) (Table 2, entry 13) [CAS Registry No. 123-30-8]

After the reaction, the crude mixture was directly purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 to 1/1 as eluent to give 4-aminophenol (2n) as a white solid (106.2 mg, 97% yield).

\[ ^1\text{H NMR (400 MHz, DMSO-}d_6\text{)} \delta 8.29 (s, 1H), 6.50–6.38 (m, 4H), 4.34 (s, 2H). \]  
\[ ^{13}\text{C NMR (100 MHz, DMSO-}d_6\text{)} \delta 148.2, 140.7, 115.6, 115.3. \]

*p*-Phenylenediamine (2o) (Table 2, entry 14) [CAS Registry No. 106-50-3]

After the reaction, the crude mixture was directly purified by flash silica gel column chromatography using hexane/ EtOAc = 1/2 to EtOAc only as eluent to give *p*-phenylenediamine (2o) as a pale red solid (106.6 mg, 99% yield).

\[ ^1\text{H NMR (400 MHz, CDCl}_3 \text{)} \delta 6.57 (s, 4H), 3.32 (br s, 4H). \]  
\[ ^{13}\text{C NMR (100 MHz, CDCl}_3 \text{)} \delta 138.6, 116.7. \]
5. Comparison with Conventional Acidic/Basic Hydrolysis Conditions (Scheme 1)

Under our conditions: 4-[(tert-Butyldimethylsilyloxy)methyl]aniline (2p) [CAS Registry No. 131230-76-7][20]

According to the general procedure for Table 2, this reaction was performed in EtOH (0.50 mL), and the crude mixture was directly purified by flash silica gel column chromatography using hexane/EtOAc = 1/3 as eluent to give 4-[(tert-Butyldimethylsilyloxy)methyl]aniline (2p) as colorless liquid (210.5 mg, 89% yield).

1H NMR (400 MHz, CDCl₃) δ 7.11 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.4 Hz, 2H), 4.62 (s, 2H), 3.56 (br, 2H), 0.92 (s, 9H), 0.07 (s, 6H). 13C NMR (100 MHz, CDCl₃) δ 145.3, 131.5, 127.7, 115.0, 65.0, 26.0, 18.4, −5.2.

Under acidic conditions: 4-(Acetamido)benzyl alcohol (1l) [CAS Registry No. 16375-88-5][2]

A solution of 1p (55.9 mg, 0.200 mmol) in 1 M aqueous HCl solution (0.20 mL, 0.20 mmol) was stirred for 2.5 h at room temperature.

temperature. After the reaction, the crude mixture was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with CH₂Cl₂, and combined organic layer was dried over Na₂SO₄, filtered, evaporated and purified by silica gel column chromatography using hexane/EtOAc = 1/2 to EtOAc only as eluent to give 4-(acetamido)benzyl alcohol II as a white solid (30.0 mg, 91 % yield). The desired product 2p was not detected based on TLC analysis.

\(^1\)H NMR (400 MHz, CDCl₃) δ 7.49 (d, \(J = 8.0\) Hz, 2H), 7.32 (d, \(J = 8.0\) Hz, 2H), 4.65 (d, \(J = 5.2\) Hz, 2H), 2.18 (s, 3H), 1.63 (m, 1H).

Under basic conditions: 4-Aminobenzyl alcohol (2I) [CAS Registry No. 623-04-1]

A mixture of 1p (139.8 mg, 0.500 mmol) and NaOH (200.7 mg, 5.00 mmol) in H₂O/EtOH (1/1, 0.50 mL) was stirred for 12 h at 50 ºC. The crude mixture was diluted with EtOH, quenched with solid NH₄Cl, filtered, evaporated and purified by flash silica gel column chromatography using hexane/EtOAc = 1/1 to 1/2 to EtOAc only as eluent to give crude 4-aminobenzyl alcohol (2I) as a pale yellow solid. The yield of 2I was determined by \(^1\)H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard (63% yield). 4-[(tert-Butyldimethylsilyloxy)methyl]aniline (2p) was also obtained as yellow liquid (18.9 mg, 16% yield).
6. Application to Peptide And Amino Sugar Derivatives (Scheme 2)

(S)-2-Amino-N-((R)-1-phenylethyl)propanamide (2q) [CAS Registry No. N/A]

According to the general procedure for Table 2, this reaction was performed on a 0.250 mmol scale for 1q (58.6 mg) in EtOH (0.25 mL). After the reaction, the crude mixture was first directly purified by flash silica gel column chromatography using dichloromethane/MeOH = 100/5, and the crude product was further purified by flash silica gel column chromatography using dichloromethane/MeOH = 100/3 to dichloromethane/MeOH/Et3NH = 100/10/1 as eluent to give (S)-2-amino-N-((R)-1-phenylethyl)propanamide (2q) as yellow liquid (39.6 mg, 82% yield).

1H NMR (500 MHz, CDCl3) \(\delta\) 7.54 (br s, 1H), 7.36–7.23 (m, 5H), 5.10 (dq, \(J = 7.0, 7.0\) Hz, 1H), 3.51 (q, \(J = 7.0\) Hz, 1H), 1.53 (br s, 2H), 1.49 (d, \(J = 7.0\) Hz, 3H), 1.32 (d, \(J = 7.0\) Hz, 3H). 13C NMR (125 MHz, CDCl3) \(\delta\) 174.6, 143.5, 128.6, 127.2, 126.0, 50.8, 48.1, 22.1, 21.8. \([\alpha]^{27}_D +112.4\) (c 1.00, CHCl3).

Determination of diastereomeric purity of 2q: Diastereomeric purity of 2q was determined by 1H NMR analysis of 2q and its diastereomer 2q’ in C6D6 based on the peaks of \(\alpha\)-Me (underlined below). Peaks corresponding to 2q’ were well below the detection limit (>20/1) on 1H NMR chart of 2q (Fig. S3).

HRMS (ESI-TOF) \(m/z\) calcd. C11H17N2O [M + H+] 193.1341, found 193.1337.

Data for 2q: 1H NMR (500 MHz, C6D6) \(\delta\) 7.35 (br s, 1H), 7.25–7.09 (m, 4H), 7.09–7.01 (m, 1H), 5.27 (qd, \(J = 7.0, 7.5\) Hz, 1H), 3.07 (br q, \(J = 7.0\) Hz, 1H), 1.28 (d, \(J = 7.0\) Hz, 3H), 1.04 (d, \(J = 7.0\) Hz, 3H), 0.63 (br s, 2H). 13C NMR (125 MHz, C6D6) \(\delta\) 173.8, 144.6, 128.8, 127.3, 126.4, 50.9, 48.3, 22.23, 21.7.
HRMS (ESI-TOF) $m/z$ calcd. for C$_{11}$H$_{17}$N$_2$O [M + H$^+$] 193.1341, found 193.1336.

Fig. S3 Diastereomeric purity of 2q.

(S)-2-Amino-N-(tert-butyl)-3-phenylpropanamide (2r) [CAS Registry No. 40847-05-0]$^{21}$

According to the general procedure for Table 2, this reaction was performed on a 0.250 mmol scale for 1r (90.4 mg) in EtOH (0.13 mL). After the reaction, the crude mixture was directly purified by flash silica gel column chromatography using EtOAc only to EtOAc/MeOH =10/1 as eluent. After evaporation of the solvent, the residue was diluted with dichloromethane and deprotected amine was extracted with 1 M aqueous HCl solution. The aqueous layer was basified with 1 M aqueous NaOH solution and back-extracted with Et$_2$O. The organic layer was dried over

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Na$_2$SO$_4$, filtered and evaporated to give (S)-2-amino-$N$-(tert-butyl)-3-phenylpropanamide (2r) as yellow liquid (46.2 mg, 84% yield).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34–7.18 (m, 5H), 7.01 (br s, 1H), 3.47 (dd, $J = 4.5$, 9.0 Hz, 1H), 3.21 (dd, $J = 4.5$, 13.8 Hz, 1H), 2.71 (dd, $J = 9.0$, 13.8 Hz, 1H), 1.34 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.3, 138.2, 129.3, 128.6, 126.7, 56.9, 50.4, 41.1, 28.7. [α]$^2$D −64.4 (c 1.01, CHCl$_3$).

Enantiomeric excess of 2r was determined to be 99% after conversion of 2r as shown below:

![Chemical Structure](image)

HPLC conditions of 3 [CAS Registry No. N/A]$^{22}$: DAICEL CHIRALCEL AD-3, eluent: Hexane/2-Propanol = 9.0/1.0, flow: 1.0 mL/min, detection: 220 nm, $t_R$: 5.4 min (minor), 7.7 min (major).

(S)-2-Amino-$N$-(tert-butyl)-3-phenylpropanamide (2r) [CAS Registry No. 40847-05-0]$^{21}$

According to the general procedure for Table 2, this reaction was performed on a 0.200 mmol scale for 1s (92.3 mg) in EtOH (0.20 mL). After the reaction, the crude mixture was directly purified by flash silica gel column chromatography using EtOAc only to EtOAc/MeOH =100/5 to 100/7 as eluent. After evaporation of the solvent, the residue was diluted with Et$_2$O and washed with 1 M aqueous NaOH solution. The aqueous layer was extracted with Et$_2$O and combined organic layer was dried over Na$_2$SO$_4$ and evaporated to give (S)-2-amino-$N$-(tert-butyl)-3-phenylpropanamide (2r) as yellow liquid (32.6 mg, 74% isolated yield; 92% yield based on recovered starting material described below).

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \& \delta 7.36–7.18 (m, 5H), 7.04 (br s, 1H), 3.48 (dd, \(J = 4.5, 9.0\) Hz, 1H), 3.22 (dd, \(J = 4.5, 14.0\) Hz, 1H), 2.70 (dd, \(J = 9.0, 14.0\) Hz, 2H), 1.34 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}) \& \delta 173.5, 138.3, 129.5, 128.8, 126.8, 57.1, 50.6, 41.2, 28.8. [\(\alpha\)]\textsubscript{24}^D – 63.5 (c 0.94, CHCl\textsubscript{3}).

Enantiomeric excess of 2\(r\) was determined to be 99% after conversion of 2\(r\) as shown below:

HPLC conditions of 3 [CAS Registry No. N/A]: DAICEL CHIRALCEL AD-3, eluent: Hexane/2-Propanol = 9.0/1.0, flow: 1.0 mL/min, detection: 210 nm, \(t_R\): 5.2 min (minor), 7.4 min (major).

Recovery of starting material 1\(s\): After purification of the crude mixture by flash silica gel column chromatography as described above, fractions containing 1\(s\) were collected and the solvent was evaporated. The residue was diluted with EtOAc and washed with 1 M aqueous HCl solution, saturated aqueous NaHCO\textsubscript{3} solution and brine. The organic phase was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and evaporated to give 1\(s\) (18.4 mg, 0.040 mmol, 20% recovery).

Determination of site-selectivity: To clarify site-selectivity of hydrazinolysis of 1\(s\), a time-course experiment was performed. \(^1\)H NMR analysis of the crude mixture showed that 2\(r\), product after cleavage of Gly-Phe bond, was observed as major species, while (S)-2-(2-aminoacetamido)-N-tert-butyl-3-phenylpropanamide (S3), product after cleavage of Val-Gly bond, was not observed as major species throughout the experiment (Fig. S4). These results suggest that Gly-Phe bond was selectively cleaved over Val-Gly bond.
Preparation of (S)-2-(2-Aminoacetamido)-N-tert-butyl-3-phenylpropanamide (S3)

(S)-Benzyl 2-(1-(tert-butylamino)-1-oxo-3-phenylpropan-2-ylamino)-2-oxoethyl carbamate (S4) [CAS Registry No. N/A]

To a solution of (S)-tert-butyl (1-(tert-butylamino)-1-oxo-3-phenylpropan-2-yl)carbamate\(^1\) (160 mg, 0.500 mmol) in CH\(_2\)Cl\(_2\) (2.5 mL) at 0 °C was added 4 M HCl in AcOEt (2.5 mL, 10 mmol). The mixture was stirred at room temperature for 1.5 h, and the solvent was removed under reduced pressure. To the crude HCl salt was added N-carbobenzy oxycarbonylglycine (115 mg, 0.550 mmol), HOBut (74 mg, 0.55 mmol) and CH\(_2\)Cl\(_2\) (2.5 mL). To the mixture at 0 °C was added EDCI-HCl (105 mg, 0.550 mmol) and Et\(_3\)N (0.15 mL, 1.1 mmol). The mixture was stirred at room temperature for 17 h and the solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed twice.

\(^1\)Calcium chloride dicyano malonate
with 1 M aqueous HCl solution/brine mixture and twice with saturated aqueous NaHCO₃ solution/brine mixture, dried over Na₂SO₄, filtered, evaporated and purified by flash silica gel column chromatography using hexane/EtOAc = 2/1 to 1/4 to give (S)-benzyl 2-(1-(tert-butylamino)-1-oxo-3-phenylpropan-2-ylamino)-2-oxoethyl carbamate (S4) as a white solid (156 mg, 76% yield in 2 steps).

mp 146–148 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.10 (m, 5H), 6.68 (br s, 1H), 5.33 (br s, 1H), 5.13 (s, 2H), 5.09 (br s, 1H), 4.45 (ddd, J = 4.0, 8.0, 9.0 Hz, 1H), 3.90 (dd, J = 5.5, 17 Hz, 1H), 3.85 (dd, J = 6.5, 17 Hz, 1H), 3.14 (dd, J = 4.0, 13 Hz, 1H), 2.86 (dd, J = 9.0, 13 Hz, 1H), 1.17 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 169.0, 168.3, 156.5, 136.7, 136.1, 129.4, 128.7, 128.6, 128.3, 128.1, 127.1, 67.3, 55.1, 51.5, 44.5, 39.1, 28.4. IR (KBr disc) 3343, 3291, 3065, 2967, 1707, 1649, 1528, 1456, 1393, 1366, 1234, 1101, 1057, 735, 698 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₂₅H₃₀N₃O₄ [M + H⁺] 412.2236, found 412.2232. [α]₂⁰D −0.5 (c 1.00, CHCl₃).

(S)-2-(2-Aminoacetamido)-N-tert-butyl-3-phenylpropanamide (S3) [CAS Registry No. N/A]

A mixture of S4 (112.3 mg, 0.273 mmol) and 10% Pd/C (12.4 mg, 0.0117 mmol) in EtOH (2.7 mL) was stirred under H₂ atmosphere (1 atm) at room temperature for 2 h. The mixture was filtered through a pad of Celite, and the filtrate was evaporated and purified by flash silica gel column chromatography using EtOAc/MeOH = 4/1 to 1/1 as eluent to give (S)-2-(2-aminoacetamido)-N-tert-butyl-3-phenylpropanamide (S3) as colorless oil (55.3 mg, 73% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 8.0 Hz, 1H), 7.37–7.18 (m, 5H), 5.28 (br s, 1H), 4.45 (ddd, J = 6.0, 8.0, 9.0 Hz, 1H), 3.35 (s, 2H), 3.11 (dd, J = 6.0, 13.5 Hz, 1H), 2.95 (dd, J = 9.0, 13.5 Hz, 1H), 1.55 (br s, 2H), 1.19 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 172.6, 169.5, 137.1, 129.4, 128.6, 126.9, 54.9, 51.3, 44.8, 38.9, 28.5. IR (neat, NaCl) 3291, 2969, 1651, 1557, 1454, 1362, 1225, 745, 700 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₅H₂₉N₃O₄ [M + H⁺] 278.1869, found 278.1862. [α]₁⁰D −8.6 (c 0.98, CHCl₃).
Benzyl 2-amino-2-deoxy-α-D-glucopyranoside (2t) [CAS Registry No. 50692-69-8]²³

To a 10 mL of a glass test tube equipped with a magnetic stir bar, ammonium iodide (36.2 mg, 0.250 mmol), 1t (0.250 mmol) and hydrazine monohydrate (0.25 mL, 2.5 mmol) were added and the tube was sealed with a cap. The test tube was heated with stirring at the indicated temperature and time under microwave irradiation conditions. The crude mixture was directly purified by flash silica gel column chromatography using dichloromethane/MeOH/diethylamine = 270/30/1 to 240/60/1 as eluent. After evaporation of the solvent, the residue was treated with Et₂O and filtered to give benzyl 2-amino-2-deoxy-α-D-glucopyranoside (2t) as a white solid (54.3 mg, 81% yield).

$^1$H NMR (500 MHz, DMSO-$_d_6$) δ 4.93–4.82 (m, 2H), 4.75 (d, $J = 4.0$ Hz, 1H), 4.68 (d, $J = 12.0$ Hz, 1H), 3.70 (t, $J = 6.0$ Hz, 1H), 4.43 (d, $J = 12.0$ Hz, 1H), 3.65 (ddd, $J = 6.0, 6.0, 6.0$ Hz, 1H), 3.52–3.41 (m, 2H), 3.24 (ddd, $J = 4.0, 9.5, 9.5$ Hz, 1H), 3.07 (ddd, $J = 5.0, 9.5, 9.5$ Hz, 1H), 2.43 (dd, $J = 4.0, 9.5$ Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$_d_6$) δ 151.5, 129.3, 127.2, 124.6, 118.6, 109.4, 47.3, 29.8. [α]$^{27}_D$ +142.9 (c 1.00, MeOH).

C NMR

Table 1 Entry 8
H NMR
$^1$H NMR (CDCl$_3$)
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**Scheme: C6D6**

(Scheme C6D6)

Current DMS parameters:

E137 - May 2009
Scheme 2

C6D6

1H NMR

0.00 ppm

0.30 H2

2.32 ppm

S92

Sucravirine CDP6
HPLC

チャネル情報+ピーク情報
クロマトグラム名
サンプル名
チャンネル名
チャンネル名

131015-NSM201-AD-9-1-220nm-CH1

131015-NSM201-rac-AD-9-1-220nm-CH1

3

(Scheme2_from
PivGlyLpHeNHtBu)
HPLC

140508-5y095-AD3-9-1-210nm-2 - CH1

140508-5y095-rac-AD3-9-1-210nm-2 - CH1

(Scheme2_from PivLValGlyLpheNhtBu)