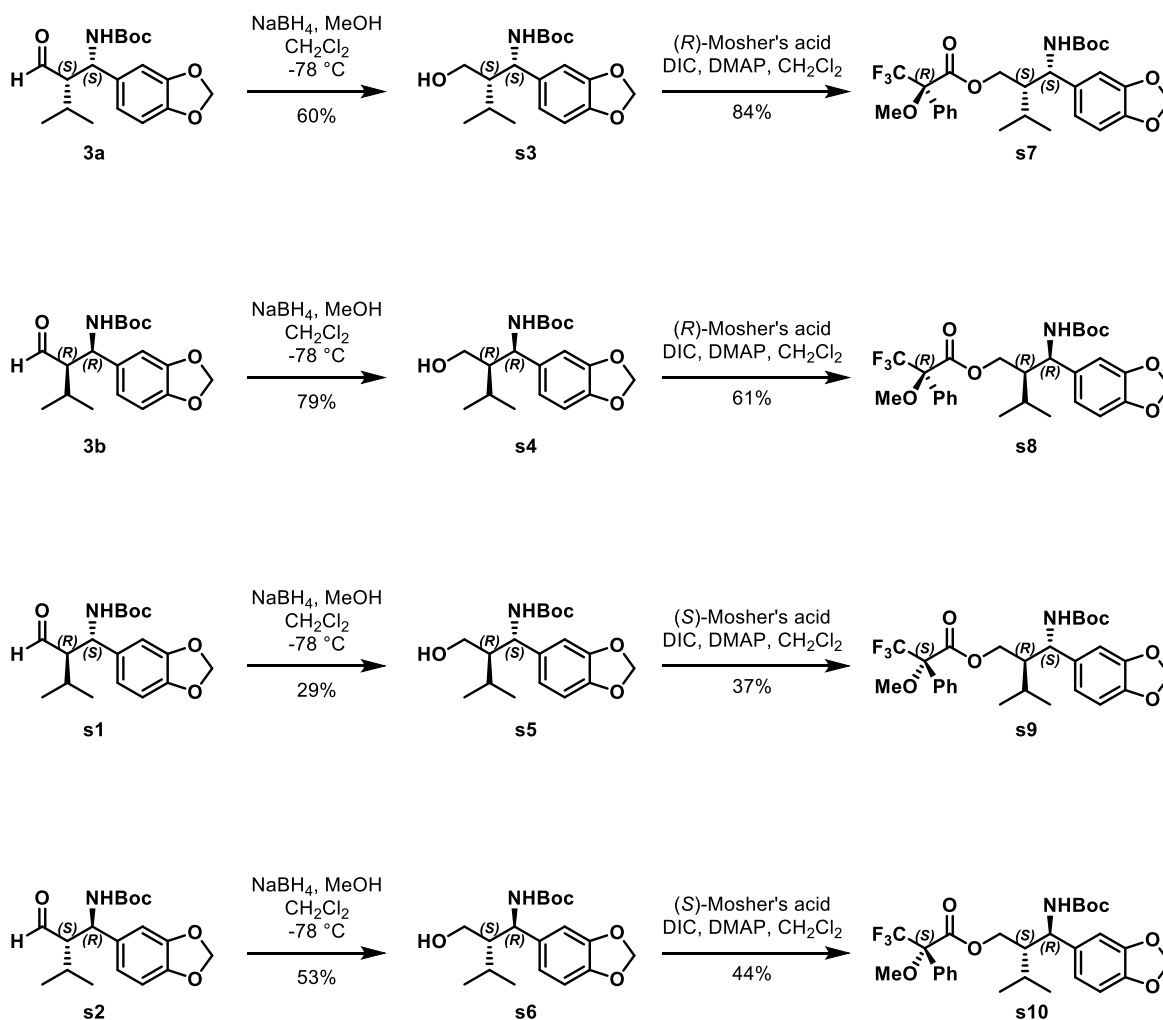


NMR (400 MHz, Chloroform-*d*) δ 6.80 – 6.65 (m, 3H), 5.92 (s, 2H), 4.91 (s, 2H), 2.67 (dd, $J = 9.6, 5.2$ Hz, 1H), 2.11 (s, 1H), 1.40 (s, 9H), 1.06 (d, $J = 7.0$ Hz, 3H), 1.01 (d, $J = 6.7$ Hz, 3H).

^{13}C NMR (101 MHz; Acetone-*d*₆): δ 173.3, 155.9, 148.3, 147.5, 137.8, 121.9, 108.7, 108.5, 101.9, 78.9, 57.0, 54.7, 28.6, 28.2, 22.0, 17.3

Retention time 9.975 min, 94.3% purity, detected at 254 nm.



Scheme S1. Enantiomeric purities of Mannich products were analyzed by the formation of Mosher ester to compare the diastereomeric peaks on NMR.

tert-butyl ((1*S*,2*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-formyl-3-methylbutyl)carbamate (s1). Isovaleraldehyde (0.24 mL, 2.27 mmol) was added to a solution of TMS-diaryl prolinol-derived **catalyst C** (74 mg, 0.23 mmol) in dichloromethane (7 mL). The reaction mixture was stirred for 5 min and amidosulfone **2a'** (461 mg, 1.14 mmol) and potassium fluoride (330 mg, 5.69 mmol) were added successively. The reaction mixture

was stirred for 20 h and the reaction was quenched with water. The reaction mixture was extracted with EtOAc and the organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 142 mg (37%) of the *anti*-Mannich adduct **s1** as pale yellow oil: ¹H NMR (400 MHz, Chloroform-*d*) δ 9.75 (dd, *J* = 3.7, 0.5 Hz, 1H), 6.78 – 6.70 (m, 3H), 5.95 (d, *J* = 1.8 Hz, 2H), 5.28 (s, 1H), 5.02 (s, 1H), 2.54 (ddd, *J* = 7.7, 5.9, 3.6 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.39 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H).

tert-butyl ((1*R*,2*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-formyl-3-methylbutyl)carbamate (s2). To a solution of *syn*-Mannich adduct **3b** (59 mg, 0.17 mmol) in tetrahydrofuran (1 mL), methanol (1 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (18 mg, 0.44 mmol). The reaction mixture was stirred for 120 h. The reaction was quenched with saturated ammonium chloride aqueous solution and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 20 mg (34%) of the *anti*-Mannich adduct **s2** as pale yellow oil: ¹H NMR (400 MHz, Chloroform-*d*) δ 9.75 (d, *J* = 3.7 Hz, 1H), 6.79 – 6.67 (m, 3H), 5.94 (s, 2H), 5.30 (d, *J* = 8.5 Hz, 1H), 5.03 (d, *J* = 8.3 Hz, 1H), 2.54 (ddd, *J* = 7.8, 6.0, 3.7 Hz, 1H), 1.86 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.39 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H).

General procedure A for preparation of reduced Mannich adducts s3 – s6. To a solution of Mannich adduct (1.0 equiv.) in dry dichloromethane and methanol was added sodium borohydride (10.0 equiv.) at -78 °C and the reaction mixture was stirred for 4 h. The reaction was quenched with water and the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane).

tert-butyl ((1*S*,2*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(hydroxymethyl)-3-methylbutyl)carbamate (s3). Alcohol **s3** was prepared from **3a** according to the general procedure A (41 mg, 60%): ¹H NMR (400 MHz, Chloroform-*d*) δ 6.82 (t, *J* = 1.1 Hz, 1H), 6.77 (d, *J* = 1.1 Hz, 2H), 5.97 – 5.92 (m, 2H), 4.87 (s, 1H), 3.68 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.50 (dd, *J* = 11.3, 8.6 Hz, 1H), 1.76 (m, 2H), 1.41 (s, 9H), 1.25 (d, *J* = 2.2 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).

tert-butyl ((1*R*,2*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(hydroxymethyl)-3-methylbutyl)carbamate (s4). Alcohol **s4** was prepared from **3b** according to the general procedure A (65 mg, 79%): ¹H NMR (400 MHz, Chloroform-*d*) δ 6.83 (s, 1H), 6.77 (s, 2H), 5.95 (s, 2H), 5.60 (br, 1H), 4.86 (s, 1H), 3.72 – 3.60 (m, 1H), 3.51 (dd, *J* =

11.0, 8.0 Hz, 1H), 1.76 (s, 2H), 1.41 (s, 9H), 1.30 – 1.20 (m, 1H), 1.02 (d, $J = 6.5$ Hz, 3H), 0.84 (d, $J = 6.6$ Hz, 3H).

tert-butyl ((1*S*,2*R*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(hydroxymethyl)-3-methylbutyl)carbamate (s5). Alcohol **s5** was prepared from **s1** according to the general procedure A (11 mg, 29%): ^1H NMR (400 MHz, Chloroform-*d*) δ 6.79 – 6.72 (m, 3H), 5.93 (s, 2H), 4.86 (d, $J = 6.3$ Hz, 1H), 3.75 (dd, $J = 11.3, 3.3$ Hz, 1H), 3.62 (dd, $J = 11.3, 2.3$ Hz, 1H), 1.87 (h, $J = 6.9$ Hz, 1H), 1.40 (s, 9H), 1.34 – 1.30 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H).

tert-butyl ((1*R*,2*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(hydroxymethyl)-3-methylbutyl)carbamate (s6). Alcohol **s6** was prepared from **s2** according to the general procedure A (11 mg, 53%): ^1H NMR (400 MHz, Chloroform-*d*) δ 6.81 – 6.72 (m, 3H), 5.94 (s, 2H), 4.86 (d, $J = 6.3$ Hz, 1H), 3.76 (dd, $J = 11.3, 3.3$ Hz, 1H), 3.62 (dd, $J = 11.3, 2.3$ Hz, 1H), 1.88 (dt, $J = 13.9, 6.9$ Hz, 1H), 1.41 (s, 9H), 1.33 (q, $J = 3.7$ Hz, 1H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H).

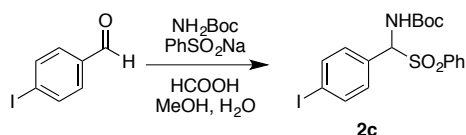
General procedure B for preparation of Mosher esters s7 – s10. To a solution of reduced Mannich adduct (1.0 equiv.) and Mosher's acid (3.1 equiv.) in dry dichloromethane were added *N,N*-diisopropylcarbodiimide (3.1 equiv.) and 4-dimethylaminopyridine (3.1 equiv.) successively. The reaction mixture was stirred overnight and the reaction was quenched with water. The mixture was extracted with dichloromethane, dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane).

(*S*)-2-((*S*)-benzo[*d*][1,3]dioxol-5-yl((*tert*-butoxycarbonyl)amino)methyl)-3-methylbutyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (s7). Mosher ester **s7** was prepared from **s3** and (*R*)-Mosher's acid according to the general procedure B (38 mg, 84%): ^1H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.36 (m, 5H), 6.67 (d, $J = 7.9$ Hz, 1H), 6.64 – 6.48 (m, 2H), 5.98 – 5.88 (m, 2H), 5.18 – 5.02 (m, 1H), 4.80 – 4.68 (m, 1H), 4.20 – 4.13 (m, 1H), 4.08 – 4.00 (m, 1H), 3.48 (d, $J = 1.4$ Hz, 3H), 1.39 (s, 9H), 1.25 – 1.20 (m, 1H), 1.01 (d, $J = 6.4$ Hz, 3H), 0.88 (d, $J = 6.7$ Hz, 3H).

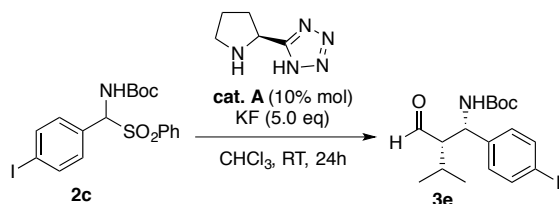
(*R*)-2-((*R*)-benzo[*d*][1,3]dioxol-5-yl((*tert*-butoxycarbonyl)amino)methyl)-3-methylbutyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (s8). Mosher ester **s8** was prepared from **s4** and (*R*)-Mosher's acid according to the general procedure B (24 mg, 61%): ^1H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.37 (m, 5H), 6.63 – 6.41 (m, 3H), 5.94 – 5.89 (m, 2H), 5.33 – 5.22 (m, 1H), 4.83 – 4.74 (m, 1H), 4.23 – 4.14 (m, 1H), 4.07 – 4.00 (m, 1H), 3.56 (s, 3H), 1.91 – 1.84 (m, 1H), 1.39 (s, 9H), 1.25 – 1.20 (m, 1H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.83 (d, $J = 6.8$ Hz, 3H).

(R)-2-((S)-benzo[d][1,3]dioxol-5-yl((tert-butoxycarbonyl)amino)methyl)-3-methylbutyl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (s9). Mosher ester **s9** was prepared from **s5** and (S)-Mosher's acid according to the general procedure B (7 mg, 37%): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.47 (m, 5H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 1.8 Hz, 1H), 6.31 – 6.25 (m, 1H), 5.91 (q, *J* = 1.5 Hz, 2H), 5.36 (d, *J* = 9.2 Hz, 1H), 4.93 (dd, *J* = 9.4, 5.7 Hz, 1H), 4.40 (dd, *J* = 11.7, 3.1 Hz, 1H), 3.83 (dd, *J* = 11.7, 2.3 Hz, 1H), 3.61 (d, *J* = 1.5 Hz, 3H), 1.80 (dp, *J* = 8.8, 6.6 Hz, 1H), 1.57 – 1.50 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

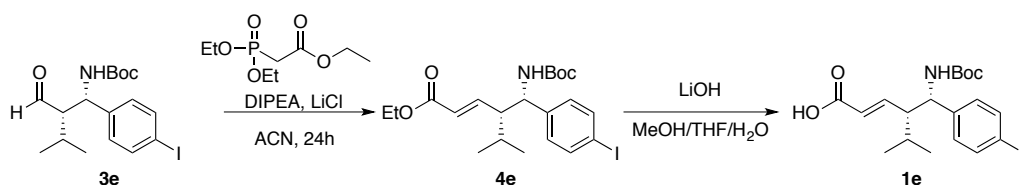
(S)-2-((R)-benzo[d][1,3]dioxol-5-yl((tert-butoxycarbonyl)amino)methyl)-3-methylbutyl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (s10). Mosher ester **s10** was prepared from **s6** and (S)-Mosher's acid according to the general procedure B (7 mg, 44%): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.46 (m, 5H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.59 – 6.48 (m, 2H), 5.98 – 5.89 (m, 2H), 5.43 (d, *J* = 9.0 Hz, 1H), 4.95 (dd, *J* = 9.0, 5.5 Hz, 1H), 4.48 (dd, *J* = 11.8, 3.2 Hz, 1H), 3.86 (dd, *J* = 11.5, 2.1 Hz, 1H), 3.54 (d, *J* = 1.4 Hz, 3H), 1.69 – 1.61 (m, 1H), 1.59 – 1.54 m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H).



tert-butyl ((4-iodophenyl)(phenylsulfonyl)methyl)carbamate (2c): White solid, 50% yield. ¹H-NMR (400 MHz; CDCl₃): δ 7.91 (d, *J* = 7.3 Hz, 2H), 7.77-7.74 (m, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.57-7.53 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 5.80 (dd, *J* = 56.1, 10.7 Hz, 2H), 1.25 (s, 9H).



tert-butyl ((1S,2S)-2-formyl-1-(4-iodophenyl)-3-methylbutyl)carbamate (3e): White solid, 78% yield. ¹H-NMR (400 MHz; CDCl₃): δ 9.49 (d, *J* = 3.9 Hz, 1H), 7.67-7.63 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 5.13 (d, *J* = 8.5 Hz, 1H), 5.02 (t, *J* = 7.6 Hz, 1H), 2.48 (q, *J* = 5.3 Hz, 1H), 2.09 (dd, *J* = 11.8, 6.6 Hz, 1H), 1.40 (s, 9H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H). HRMS (ESI+) *m/z*: [M+H]⁺ Calcd for 418.0874; Found 418.0871. [2M+H]⁺ Calcd for 835.1675; Found 835.1674. (ESI-) *m/z*: [M-H]⁻ Calcd for 416.0728; Found 416.0732. [M+FA-H]⁻ Calcd for 462.0783; Found 462.0790. For common adducts shown in Fourier transform ion cyclotron resonance mass spectrometer, see ref 5.



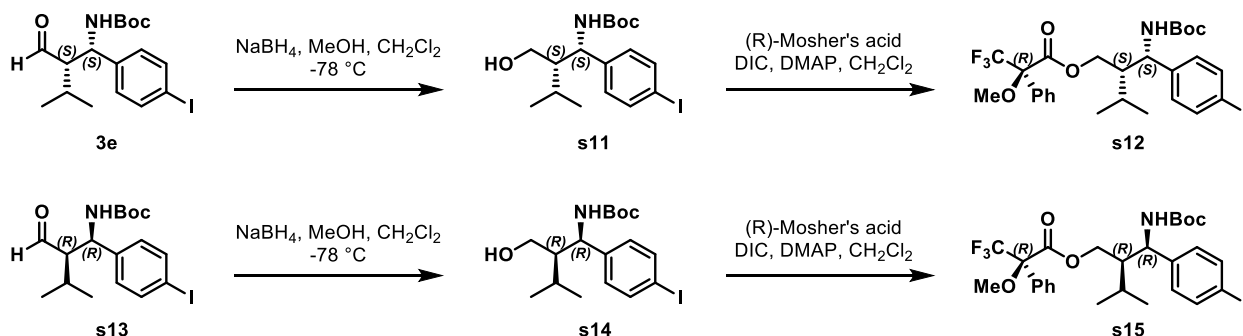
(R,E)-4-((S)-((tert-butoxycarbonyl)amino)(4-iodophenyl)methyl)-5-methylhex-2-enoic acid (1e): White solid, 90% yield, crude compound was used without further purification. ¹H-NMR (400 MHz; CDCl₃): δ 10.79 (br, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.66-6.58 (m, 1H), 5.73-5.70 (m, 1H), 4.83-4.57 (m, 1H), 2.36-2.30 (m, 1H), 1.95-1.76 (m, 1H), 1.40-1.36 (m, 9H), 1.05-1.00 (m, 3H), 0.88-0.85 (m, 3H).

For detailed characterization, the compound was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to afford 81% of vinylogous beta amino acid **1e** as white solid. Retention time 11.150 min, 98.6% purity, detected at 254 nm.

¹H NMR (400 MHz; DMSO-*d*₆): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.40 (dd, *J* = 15.1, 10.9 Hz, 1H), 5.32 (d, *J* = 15.4 Hz, 1H), 4.54 (t, *J* = 9.8 Hz, 1H), 2.45-2.38 (m, 1H), 2.09 (br, 1H), 1.34 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (101 MHz; 25 °C, DMSO-*d*₆): δ 166.4, 154.9, 145.2, 142.8, 136.7, 129.8, 125.2, 92.7, 77.9, 54.8, 52.6, 28.2, 27.5, 21.5, 16.0

HRMS (ESI+) *m/z*: [2M+H]⁺ Calcd for 919.1887; Found 919.1889. (ESI-) *m/z*: [M-H]⁻ Calcd for 458.0834; Found 458.0837. [2M-H]⁻ Calcd for 917.1741; Found 917.1752. m.p. = 196.0 – 198.3 °C



Scheme S2. Enantiomeric purities of Mannich products were analyzed by the formation of Mosher ester to compare the diastereomeric peaks on NMR.

(S)-2-((S)-((tert-butoxycarbonyl)amino)(4-iodophenyl)methyl)-3-methylbutyl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (s12) To a solution of *syn*-Mannich adduct **3e** (57.6 mg, 0.138 mmol) in dry dichloromethane (1 mL) and methanol (1 mL) was added sodium borohydride (52.2 mg, 1.380 mmol) at -78 °C and the reaction mixture was stirred for 1 h. The reaction was quenched with water and the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used for the next

reaction without further purification. To a solution of crude residue and (*R*)-Mosher's acid (100.2 mg, 0.428 mmol) in dry dichloromethane were added *N,N*-diisopropylcarbodiimide (0.067 mL, 0.428 mmol) and 4-dimethylaminopyridine (52.3 mg, 0.428 mmol) successively. The reaction mixture was stirred overnight and the reaction was quenched with water. The mixture was extracted with dichloromethane, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to give Mosher ester **s12** (73.0 mg, 83% for 2 steps) as colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.51 (m, 2H), 7.48 – 7.40 (m, 5H), 6.83 (d, *J* = 7.9 Hz, 2H), 5.18 (s, 1H), 4.80 (s, 1H), 4.14 (s, 1H), 4.02 (s, 1H), 3.66 (s, 1H), 3.48 (d, *J* = 1.3 Hz, 3H), 1.39 (s, 9H), 1.25 (d, *J* = 2.0 Hz, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

(*R*)-2-((*R*)-((*tert*-butoxycarbonyl)amino)(4-iodophenyl)methyl)-3-methylbutyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (s15**):** To a solution of *syn*-Mannich adduct **s13** (55.0 mg, 0.132 mmol) in dry dichloromethane (1 mL) and methanol (1 mL) was added sodium borohydride (50.0 mg, 1.320 mmol) at -78 °C and the reaction mixture was stirred for 1 h. The reaction was quenched with water and the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used for the next reaction without further purification. To a solution of crude residue and (*R*)-Mosher's acid (95.8 mg, 0.409 mmol) in dry dichloromethane were added *N,N*-diisopropylcarbodiimide (0.063 mL, 0.409 mmol) and 4-dimethylaminopyridine (50.0 mg, 0.409 mmol) successively. The reaction mixture was stirred overnight and the reaction was quenched with water. The mixture was extracted with dichloromethane, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane) to give Mosher ester **s15** (60.0 mg, 68% for 2 steps) as colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.50 (m, 2H), 7.48 – 7.43 (m, 5H), 6.68 (d, *J* = 7.9 Hz, 2H), 5.42 (d, *J* = 9.3 Hz, 1H), 4.85 (s, 1H), 4.22 (d, *J* = 11.6 Hz, 1H), 3.90 (t, *J* = 9.7 Hz, 1H), 3.65 (s, 1H), 3.58 (s, 3H), 1.26 (dd, *J* = 4.5, 2.5 Hz, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

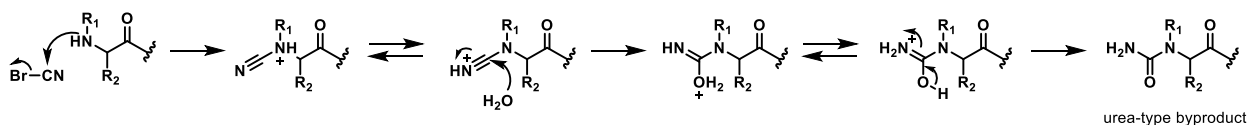
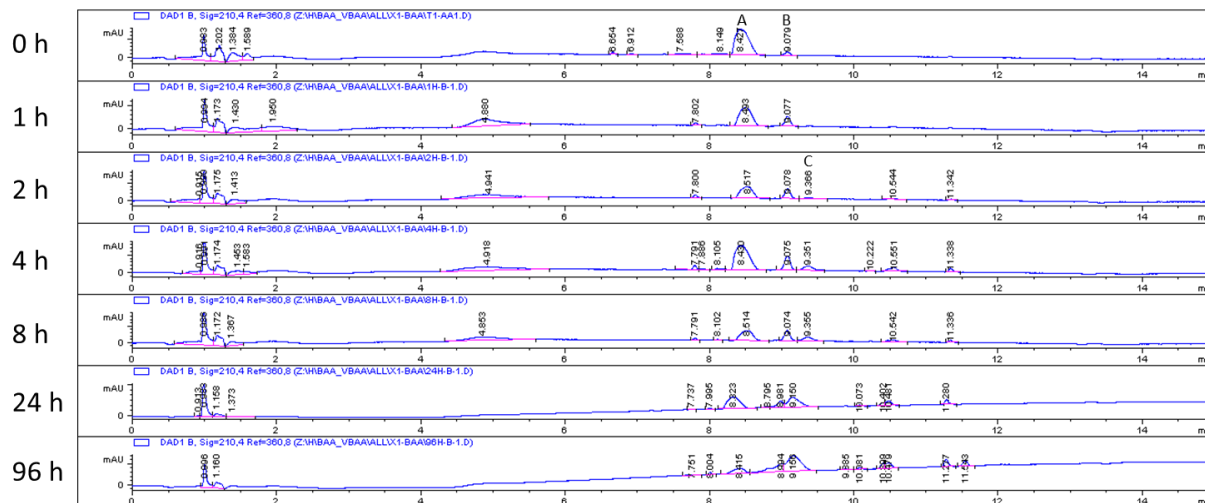


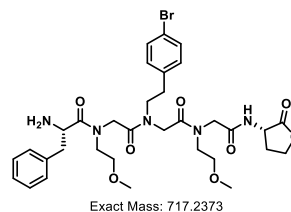
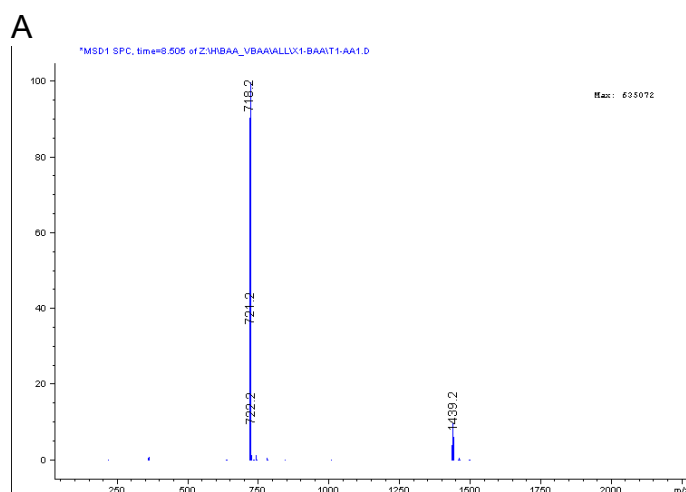
Fig. S2. A plausible mechanism of formation of urea-type byproduct with a mass of $[M+43]^+$. During CNBr cleavage, a cyano group is added to the N-terminal secondary amines ($R_2 = H$; peptoid or $R_2 = \text{alkyl}$; PTA), which lead to terminal urea formation.

LC-MS data for coupling efficiency of BAA 5b and VBAA 1b with different types of amines discussed in Table 1.

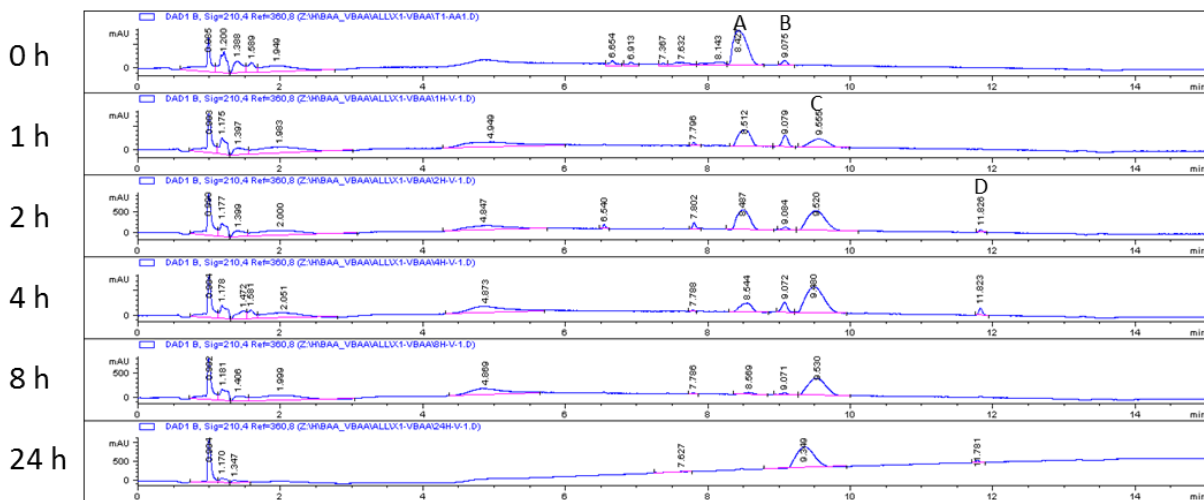
5b-X₁-Linker



time	A (area %)	B (area %)	C (area %)	conversion yield (C/A+B+C)
0 h	83	4		-
1 h	78	18		-
2 h	61	24	5	6%
4 h	60	16	9	11%
8 h	47	23	16	19%
24 h	41	6	31	40%
96 h	12		61	84%

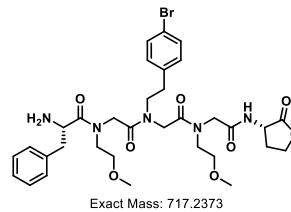
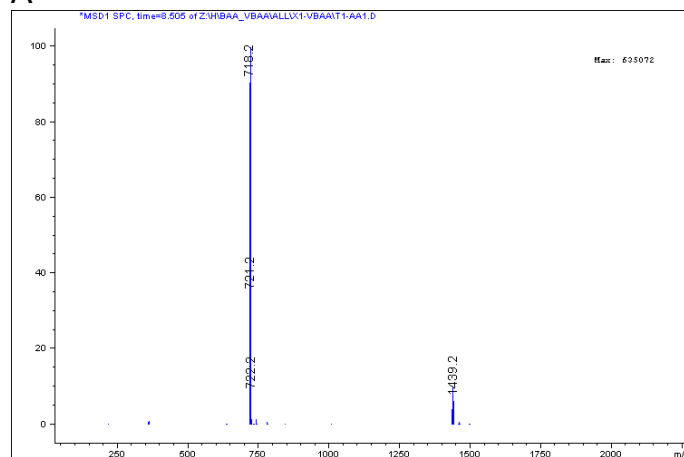


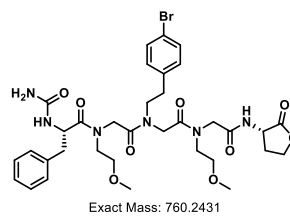
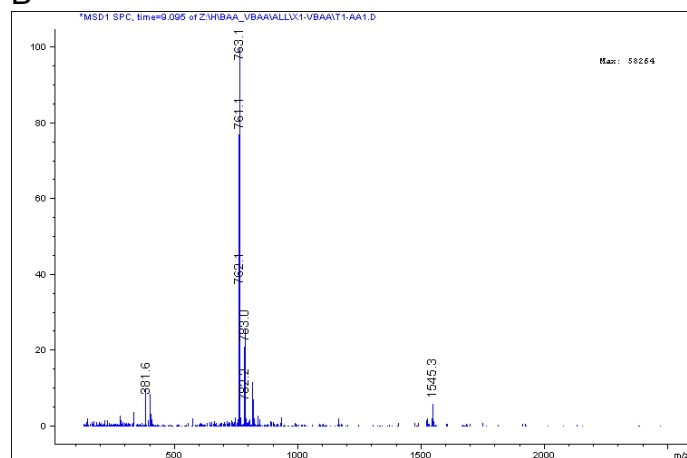
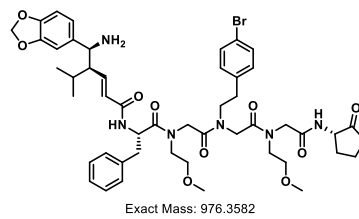
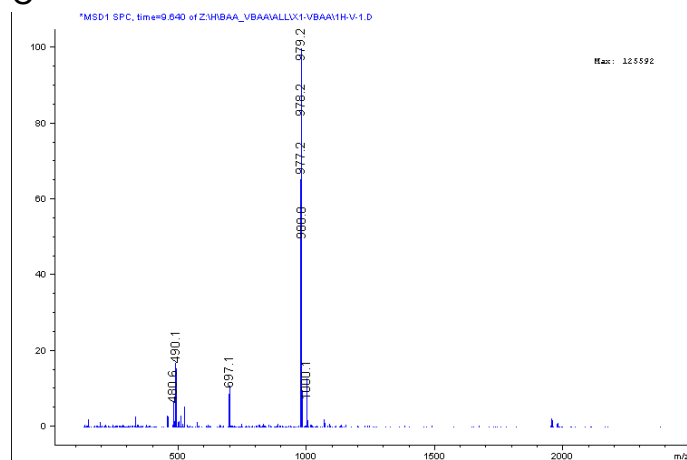
1b-X₁-Linker



time	A (area %)	B (area %)	C (area %)	D (area %)	conversion yield (C+D/A+B+C+D)
0 h	83	4			-
1 h	48	16	34		35%
2 h	38	3	53	2	57%
4 h	16	9	70	4	75%
8 h	7	4	89		89%
24 h			98	2	100%

A



B**C****D**