Supporting Information

Brønsted acid-catalyzed Mannich reaction through dual activation of aldehydes and N-Boc-imines

Taichi Kano, Yusuke Aota, Daisuke Asakawa and Keiji Maruoka*

General information
Infrared (IR) spectra were recorded on a Thermo SCIENTIFIC NICOLET iS5. 1H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = double-doublet, td = triple-doublet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. 13C NMR spectra were measured on a JEOL JNM-FX400 (100 MHz) or a JEOL JNM-FX500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 20A instruments using Daicel Chiralpak IC and AS-H 4.6 mm x 25 cm columns. High-resolution mass spectra (HRMS) were performed on Thermo SCIENTIFIC Exactive Plus. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60N (Kanto Chemical Co. Inc., 40-50μm). N-Boc-protected aminals¹ and chiral phosphoric acid² were synthesized according to the literature procedures. Aldehydes were distilled and stored under argon atmosphere at –17 °C. 1,2-Dichloroethane (DCE), dichloromethane (DCM), ethyl acetate (EtOAc) and methanol (MeOH) were purchased from Wako Pure Chemistry Co. Inc. Molecular sieve 5A and α,α,α-trifluorotoluene (TFT) were purchased from Sigma-Aldrich Co. LLC.

General Procedure for Achiral Brønsted Acid-Catalyzed Mannich-type Reaction between aldehydes and N-Boc-protected C-Alkynyl-aminals

![Chemical reaction image]

To a solution of N-Boc-protected aminal 1 (0.10 mmol) and diphenyl phosphate (2.5 mg, 0.010 mmol) in DCM (2.0 mL) was added an aldehyde (0.30 mmol) at room temperature. After aminal was consumed, the reaction mixture was added MeOH (2.0 mL) and NaBH₄ (11 mg, 0.30 mmol) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc = 7/1, then toluene/EtOAc = 20/1) to afford the product 2.

**General Procedure for Chiral Brønsted Acid-Catalyzed Mannich-type Reaction between aldehydes and N-Boc-protected C-Alkynyl-aminals**

To a solution of N-Boc-protected aminal 1 (0.10 mmol) and (S)-3 (5.0 mg, 0.010 mmol) in solvents described above (2.0 mL) were added aldehyde (0.30 mmol) and 3,4-dihydro-2H-pyran (DHP) (18 μL, 0.20 mmol) at room temperature. After stirring for 96 h, the reaction mixture was added MeOH (2.0 mL) and NaBH₄ (11 mg, 0.30 mmol) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc = 7/1, then toluene/EtOAc = 20/1) to afford the compound 2.
tert-Butyl (3R,4S)-(4-benzyl-5-hydroxy-1-phenylpent-1-yn-3-yl)carbamate

The title compound was obtained as an inseparable diastereomixture after stirring for 7 h in the achiral condition or 96 h in the chiral condition; ^1^H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.46-7.43 (2H, m, Ar-H), 7.33-7.31 (3H, m, Ar-H), 7.30-7.25 (4H, m, Ar-H), 7.22-7.19 (1H, m, Ar-H), 5.10 (1H, d, \(J = 8.0\) Hz, NH), 4.77 (1H, app t, \(J = 8.0\) Hz, \(\text{CHNH}\)), 3.73 (1H, d, \(J = 11.6\) Hz, CH\(\text{HOH}\)), 3.51 (1H, m, CH\(\text{HOH}\)), 3.03 (1H, dd, \(J = 9.6\), 4.4 Hz, CH\(\text{HPh}\)), 2.81-2.87 (1H, m, CH\(\text{HPh}\)), 2.75 (1H, br s, OH), 1.95 (1H, m, CH\(\text{CH}_2\text{OH}\)), 1.47 (9H, s, C(CH\textsubscript{3})\textsubscript{3}); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 156.1, 140.2, 131.7, 129.3, 128.5, 128.3, 126.1, 122.5, 87.6, 84.6, 80.5, 59.8, 49.1, 45.2, 33.9, 28.3; IR (neat) 3392, 2927, 1690, 1491, 1367, 1248, 1167, 1046 cm\(^{-1}\); HRMS (ESI) Calcd. For C\textsubscript{23}H\textsubscript{27}NNaO\textsubscript{3}: 388.1883 ([M + Na\textsuperscript{+}], Found: 388.1884 ([M + Na\textsuperscript{+}]); HPLC analysis: Daicel Chiralpak IC, hexane/i-PrOH = 50/1, flow rate = 1.0 mL/min, \(\lambda = 254\) nm, retention time; t (major) = 33.6 min, t (minor) = 55.7 min.

tert-Butyl (3R*,4S*)-(4-(hydroxymethyl)-5-methyl-1-phenylhex-1-yn-3-yl)carbamate

The title compound was obtained as an inseparable diastereomixture after stirring for 12 h in the achiral condition; ^1^H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.43-7.40 (2H, m, Ar-H), 7.31-7.26 (3H, m, Ar-H), 5.47 (1H, br d, \(J = 6.4\) Hz, NH), 4.94 (1H, app br t, \(J = 8.4\) Hz, CH\(\text{NH}\)), 4.08 (1H, d, \(J = 10.8\) Hz, CH\(\text{HOH}\)), 3.88 (1H, d, \(J = 10.8\) Hz, CH\(\text{HOH}\)), 2.33 (1H, br s, OH), 2.16-2.07 (1H, m, CH(CH\textsubscript{3})\textsubscript{2}), 1.68 (1H, m, CH\(\text{CH}_2\text{OH}\)), 1.47 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.06 (3H, d, \(J = 6.4\) Hz, CH(CH\textsubscript{3})\textsubscript{2}), 1.05 (3H, d, \(J = 6.4\) Hz, CH(CH\textsubscript{3})\textsubscript{2}); \(^{13}\)C
NMR (125 MHz, CDCl$_3$) $\delta$ 155.8, 131.7, 128.2, 128.2, 122.9, 88.8, 83.7, 80.0, 60.6, 51.0, 44.3, 28.4, 26.4, 21.4, 19.7; IR (neat) 3385, 2965, 2931, 1688, 1490, 1367, 1249, 1169, 1071 cm$^{-1}$; HRMS (ESI) Calcd. For C$_{19}$H$_{27}$NNaO$_3$: 340.1883 ([M + Na]$^+$), Found: 340.1884 ([M + Na]$^+$).

**tert-Butyl (3$R$*,4$S$*)-(5-hydroxy-1,4-diphenylpent-1-yn-3-yl)carbamate**

The title compound was obtained as an inseparable diastereomixture after stirring for 10 h in the achiral condition; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42-7.27 (10H, m, Ar-H), 5.13 (1H, app br t, $J$ = 8.0 Hz, CH$_2$NH), 4.85 (1H, br d, $J$ = 8.0 Hz, NH), 4.08-3.94 (2H, m, CH$_2$OH), 3.08 (1H, m, CH$_2$OH), 2.53 (1H, br s, OH), 1.47 (9H, s, C(CH$_3$)$_3$) ; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.5, 138.6, 131.5, 129.2, 128.4, 128.4, 128.2, 127.4, 122.5, 86.8, 85.2, 80.5, 63.5, 53.2, 45.1, 28.3; IR (neat) 3420, 2977, 2929, 1695, 1491, 1367, 1249, 1166, 1046 cm$^{-1}$; HRMS (ESI) Calcd. For C$_{22}$H$_{25}$NNaO$_3$: 374.1727 ([M + Na]$^+$), Found: 374.1723 ([M + Na]$^+$).

**tert-Butyl (3$R$,4$S$)-(4-benzyl-5-hydroxy-1-(4-methoxyphenyl)pent-1-yn-3-yl)carbamate**

The title compound was obtained as an inseparable diastereomixture after stirring for 12 h in the achiral condition or 96 h in the chiral condition; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (2H, d, $J$ = 8.8 Hz, Ar-H), 7.31-7.18 (5H, m, Ar-H), 6.84 (2H, d, $J$ = 9.2Hz, Ar-H), 5.08 (1H, d, $J$ = 8.4 Hz, NH), 4.74 (1H, app t, $J$ = 8.4 Hz, CH$_2$NH), 3.81 (3H, s, OCH$_3$), 3.71 (1H, d, $J$ = 11.2 Hz, CH$_2$OH), 3.49 (1H, m, CH$_2$OH), 3.02 (1H, dd, $J$ = 13.2, 4.0 Hz, CH$_2$Ph), 2.85-2.79 (2H, m, CH$_2$Ph, OH), 1.93 (1H, m, CH$_2$OH), 1.46 (9H, s,
C(CH₃)₃; ¹³C NMR (100 MHz, CDCl₃) δ 159.8, 156.0, 140.3, 133.2, 129.3, 128.4, 126.1, 114.7, 114.0, 86.2, 84.6, 80.4, 60.1, 55.3, 49.1, 45.4, 34.0, 28.3; IR (neat) 3399, 2931, 1689, 1606, 1509, 1367, 1247, 1170, 1032 cm⁻¹; HRMS (ESI) Calcd. For C₂₄H₂₉N₆NaO₄: 418.1989 ([M + Na]⁺), Found: 418.1987 ([M + Na]⁺); HPLC analysis: Daicel Chiralpak IC, hexane/EtOH = 40/1, flow rate = 1.0 mL/min, λ = 254 nm, retention time; t (major) = 25.3 min, t (minor) = 27.2 min.

**tert-Butyl (3R*,4S*)-(4-benzyl-1-(4-bromophenyl)-5-hydroxypent-1-yn-3-yl) carbamate**

![Chemical structure](image)

The title compound was obtained as an inseparable diastereomixture after stirring for 11 h in the achiral condition; ¹H NMR (400 MHz, CDCl₃) δ 7.45 (2H, d, J = 8.0 Hz, Ar-H), 7.32-7.19 (7H, m, Ar-H), 5.12 (1H, d, J = 8.8 Hz, NH), 4.76 (1H, app t, J = 8.0 Hz, CHNH), 3.74 (1H, d, J = 10.4 Hz, CHHOH), 3.51 (1H, m, CHHOH), 2.99 (1H, dd, J = 14.0, 4.8 Hz, CHPh), 2.86-2.80 (1H, m, CHPh), 2.67 (1H, br s, OH), 1.96 (1H, m, CHCH₂OH), 1.47 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ 155.9, 140.1, 133.1, 131.6, 129.2, 128.5, 126.1, 122.7, 121.4, 88.9, 83.5, 80.6, 59.9, 48.8, 45.3, 34.0, 28.3; IR (neat) 3392, 2921, 2850, 1690, 1487, 1367, 1250, 1166, 1070, 1011 cm⁻¹; HRMS (ESI) Calcd. For C₂₃H₂₆BrNNaO₃: 466.0988 ([M + Na]⁺), Found: 466.0997 ([M + Na]⁺).

**tert-Butyl (2S*,3R*)-(2-benzyl-1-hydroxydec-4-yn-3-yl)carbamate**

![Chemical structure](image)

The title compound was obtained as an inseparable diastereomixture after stirring for 8 h in the achiral condition; ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.17 (5H, m, Ar-H), 4.93
(1H, d, J = 8.8 Hz, NH), 4.49 (1H, app t, J = 8.8 Hz, CHNH), 3.63 (1H, d, J = 11.2 Hz, CHHOH), 3.41 (1H, m, CHHOH), 2.95 (1H, dd, J = 13.6, 4.0 Hz, CHHPh), 2.82-2.72 (2H, m, CHHPh, OH), 2.22 (2H, td, J = 7.2, 2.0 Hz, CH2CC), 1.80 (1H, br s, CHCH2OH), 1.57-1.27 (6H, m, CH3C2H2C2H2), 1.45 (9H, s, C(CH3)3), 0.90 (3H, t, J = 7.2 Hz, CH3); 13C NMR (125 MHz, CDCl3) δ 156.1, 140.6, 129.2, 128.4, 126.0, 85.3, 80.3, 78.4, 59.7, 49.3, 44.9, 33.8, 31.1, 28.4, 28.3, 22.2, 18.6, 14.0; IR (neat) 3393, 2930, 2860, 1689, 1496, 1367, 1249, 1169, 1045 cm⁻¹; HRMS (ESI) Calcd. For C22H33NNaO3: 382.2353 ([M + Na]+), Found: 382.2353 ([M + Na]+).

**tert-Butyl (3R*,4S*)-(4-benzyl-5-hydroxy-1-(trimethylsilyl)pent-1-yn-3-yl) carbamate**

The title compound was obtained as an inseparable diastereomixture after stirring for 10 h in the achiral condition; 1H NMR (400 MHz, CDCl3) δ 7.31-7.19 (5H, m, Ar-H), 4.96 (1H, d, J = 8.8 Hz, NH), 4.52 (1H, app t, J = 8.4 Hz, CHNH), 3.63 (1H, d, J = 11.2 Hz, CHHOH), 3.46-3.35 (1H, m, CHHOH), 2.95 (1H, dd, J = 13.6, 4.0 Hz, CHHPh), 2.86-2.71 (2H, m, CHHPh, OH), 1.82 (1H, m, CHCH2OH), 1.45 (9H, s, C(CH3)3), 0.20 (9H, s, Si(CH3)3); 13C NMR (125 MHz, CDCl3) δ 155.9, 140.4, 129.3, 128.4, 126.0, 104.3, 89.5, 80.5, 59.4, 49.3, 45.3, 33.7, 28.3; IR (neat) 3392, 2962, 2361, 2173, 1696, 1540, 1367, 1250, 1169, 1046 cm⁻¹; HRMS (ESI) Calcd. For C22H33NNaO3Si: 384.1965 ([M + Na]+), Found: 384.1965 ([M + Na]+).

**tert-Butyl (3R,4S)-(4-(hydroxymethyl)-1-(4-methoxyphenyl)-5-methylhex-1-yn-3-yl) carbamate**

S6
The title compound was obtained as an inseparable diastereomixture after stirring for 96 h in the chiral condition; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 (2H, d, $J = 8.4$ Hz, Ar-H), 6.82 (2H, d, $J = 8.4$ Hz, Ar-H), 5.43 (1H, br d, $J = 8.4$ Hz, NH), 4.91 (1H, m, CH$_2$NH), 4.07 (1H, br d, $J = 9.2$ Hz, CHHOH), 3.95-3.85 (1H, m, CHHOH), 3.80 (3H, s, OCH$_3$), 2.35 (1H, br s, OH), 2.13-2.08 (1H, m, CH(CH$_3$)$_2$), 1.66 (1H, m, CHCH$_2$OH), 1.47 (9H, s, C(CH$_3$)$_3$), 1.06 (3H, d, $J = 6.4$ Hz, CH(CH$_3$)$_2$), 1.05 (3H, d, $J = 6.4$ Hz, CH(CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.5, 155.8, 133.1, 115.0, 113.9, 87.3, 83.5, 80.0, 60.6, 55.3, 51.1, 44.3, 28.4, 26.5, 21.4, 19.7; IR (neat) 3391, 2963, 1688, 1607, 1509, 1247, 1171 cm$^{-1}$; HRMS (ESI) Calcd. For C$_{20}$H$_{29}$NNaO$_4$: 370.1989 ([M + Na]$^+$), Found: 370.1982 ([M + Na]$^+$), HPLC analysis: Daicel Chiralpak AS-H, hexane/i-PrOH = 20/1, flow rate = 0.75 mL/min, $\lambda$ = 254 nm, retention time; t (major) = 10.8 min, t (minor) = 16.5 min.

**Determination of Absolute Configuration**

The absolute configuration of the anti-Mannich adduct, which was obtained from (S)-3 catalyzed reaction between 1a and propanal, was determined to be (3R,4S) by converting to 10 and comparison of the HPLC retention times with those obtained from the (S)-diphenylprolinol silyl ether catalyzed reaction. Absolute stereochemistry of other Mannich adducts was assigned by analogy.

![Chemical diagram](image-url)
Investigation into *In-situ* Generation of Enecarbamate

![Chemical Reaction Diagram]

To a solution of BocNH$_2$ (23 mg, 0.20 mmol) and catalyst 11 (3.5 mg, 0.010 mmol) in DCM (2.0 ml) was added a 3-phenylpropanal (26 μL, 0.20 mmol) at room temperature. After stirring for 12 h, the mixture was added MeOH (4.0 mL) and NaBH$_4$ (23 mg, 0.60 mmol) at 0 °C. After 2 h of stirring at 0 °C, the mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 20/1 to 7/1) on silica gel to provide the desired enecarbamate 5a and its derivatives such as N-Boc-aminal 12 and self Mannich adduct 13.

**Comparison of Reactivity of Aldehyde and Enecarbamate**

![Chemical Reaction Diagram]

*tert*-Butyl benzylidenecarbamate (8)$^4$ was synthesized according to the literature procedure. To a mixture of diphenyl phosphate (2.5 mg, 0.010 mmol) and molecular sieve 5A (50 mg) in DCM (2.0 mL) were added 3-phenylpropanal (40 μL, 0.30 mmol) and *tert*-butyl benzylidenecarbamate (21 mg, 0.10 mmol) at room temperature. After stirring for 5 h, the mixture was added MeOH (2.0 mL) and NaBH$_4$ (11 mg, 0.30 mmol) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$
and concentrated. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc = 7/1) to afford compound 14 with trace yield.

tert-Butyl (3-phenylprop-1-en-1-yl)carbamate (5a) was synthesized according to the literature procedure. To a mixture of diphenyl phosphate (2.5 mg, 0.010 mmol), tert-butyl (3-phenylprop-1-en-1-yl)carbamate (70 mg, 0.30 mmol) and molecular sieve 5A (50 mg) in DCM (2.0 mL) was added a tert-butyl benzylidenecarbamate (21 mg, 0.10 mmol) at room temperature. After stirring for 5 h, the mixture was added MeOH (2.0 mL) and NaBH₄ (11 mg, 0.30 mmol) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (eluting with hexane/EtOAc = 10/1) to afford compound 15 (40 mg, 0.090 mmol, 90%, E/Z = 3.5/1).

Hydrolysis of Enecarbamate 9 under Reaction Conditions

Enecarbamate 9 was prepared according to the general procedure (S1), except that molecular sieve 5A (50 mg) was added to the reaction mixture. To a solution of compound 9 (23 mg, 0.050 mmol) and diphenyl phosphate (1.3 mg, 0.0050 mmol) in DCM (1.0 mL) was added water (0.050 mmol, 0.9 μL) at room temperature. After stirring for 48 h, the reaction mixture was added MeOH (1.0 mL) and NaBH₄ (1.9 mg, 0.050 mmol) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel.
(eluting with hexane/EtOAc = 7/1,) to afford the compound 2a (14 mg, 0.039 mmol, 78%).

References
*tert*-Butyl (3R,4S)-(4-benzyl-5-hydroxy-1-phenylpent-1-yn-3-yl)carbamate
**tert-Butyl (3R*,4S*)-(4-(hydroxymethyl)-5-methyl-1-phenylhex-1-yn-3-yl) carbamate**

![Chemical structure diagram]

---

S12
tert-Butyl (3$R^*$,4$S^*$)-(5-hydroxy-1,4-diphenylpent-1-yn-3-yl)carbamate
tert-Butyl (3R,4S)-(4-benzyl-5-hydroxy-1-(4-methoxyphenyl)pent-1-yn-3-yl)carbamate
** tert-Butyl (3\(R^*, 4S^*\))-(4-benzyl -1-(4-bromophenyl)-5-hydroxypent-1-yn-3-yl) carbamate**

![Chemical Structure Diagram]

**NMR Spectra**

- Top NMR Spectrum
- Bottom NMR Spectrum
tert-Butyl (25*,3R*)-(2-benzyl-1-hydroxydec-4-yn-3-yl)carbamate
tert-Butyl (3R*,4S*)-(4-benzyl-5-hydroxy-1-(trimethylsilyl)pent-1-yn-3-yl) carbamate
tert-Butyl (3R,4S)-(4-(hydroxymethyl)-1-(4-methoxyphenyl)-5-methylhex-1-yn-3-yl) carbamate
**tert-Butyl (3R,4S)-(4-benzyl-5-hydroxy-1-phenylpent-1-yn-3-yl)carbamate**

HPLC analysis: 80% ee/ 8% ee, Daicel Chiralpak IC, hexane/i-PrOH = 50/1, flow rate = 1.0 mL/min, λ = 254 nm, retention time; t (major) = 33.6 min, t (minor) = 55.7 min.
**tert-Butyl (3R,4S)-(4-benzyl-5-hydroxy-1-(4-methoxyphenyl)pent-1-yn-3-yl)carbamate**

HPLC analysis: 85% ee/7% ee, Daicel Chiralpak IC, hexane/EtOH = 40/1, flow rate = 1.0 mL/min, λ = 254 nm, retention time; t (major) = 25.3 min, t (minor) = 27.2 min.
tert-Butyl (3R,4S)-(4-(hydroxymethyl)-1-(4-methoxyphenyl)-5-methylhex-1-yn-3-yl) carbamate

HPLC analysis: 88% ee/ 26% ee, Daicel Chiralpak AS-H, hexane/i-PrOH = 20/1, flow rate = 0.75 mL/min, λ = 254 nm, retention time; t (major) = 10.8 min, t (minor) = 16.5 min.