N-Alkyl-4-boronopyridinium Salts as Thermally Stable and Reusable Amide Condensation Catalysts

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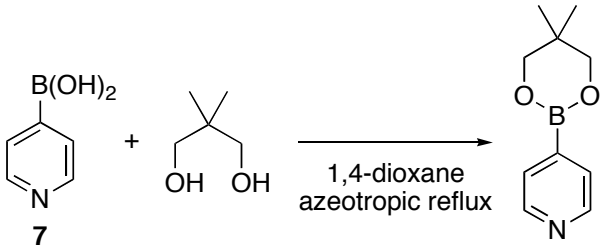
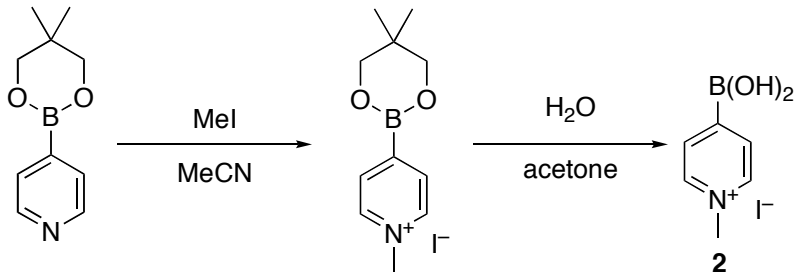
General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on Varian Gemini-2000 (75 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). All experiments were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. In experiments that required dry solvent, ether and tetrahydorofuran (THF) were purchased from Aldrich or Wako as the "anhydrous" and stored over 4A molecular sieves. Hexane and toluene were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially. 1-Ethyl-3-methylimmidazolium trifluoromethanesulfonate [emim][OTf] was purchased from Aldrich.

Preparation of 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)pyridine.



A flame-dried, 100 mL round-bottom flask fitted with a teflon-coated magnetic stirring bar was charged with 4-pyridineboronic acid (**7**) (1.23 g, 10 mmol) and neopentyl glycol (1.04 g, 10 mmol) in 1,4-dioxane (50 mL). This white suspension was brought to reflux with the removal of water with molecular sieves 4A for 12 hours to be homogeneous solution. The resulting mixture was cooled to ambient temperature and bulk solvent was removed in vacuo to afford 4-pyridineboronic acid neopentyl glycol ester (1.92 g, 10 mmol) as white solid in quantitative yield. IR (KBr) 3436, 2943, 2821, 1620, 1423, 1215, 1117, 1035, 768, 736, 674, 626 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.96 (s, 6H), 3.77 (s, 4H), 4.34 (s, 3H), 8.18 (d, J = 5.7 Hz, 2H), 8.90 (d, J = 5.7 Hz, 2H). HRMS-FAB (m/z): $[M+H]^+$ calcd for $C_{10}H_{15}NO_2$, 192.1198; Found, 192.1197.

Preparation of 4-Borono-*N*-methylpyridinium Iodide (2).



4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)pyridine (1.92 g, 10 mmol) was suspended in acetonitrile (50 mL) and added methyl iodide (3.11 mL, 50 mmol). The mixture was brought to heat at reflux for 6 h followed by removal of acetonitrile in vacuo to afford 4-borono-*N*-methylpyridinium iodide neopentyl glycol ester as yellow solid in quantitative yield. The resulting yellow solid was added to a mixture of acetone (30 mL) and water (30 mL). After this light yellow solution was stirred at room temperature for 1 day, acetone was removed in vacuo, and the aqueous solution was washed with Et_2O until neopentyl glycol was extracted completely. The aqueous solution was concentrated and resulting yellow solid was precipitated from methanol–Et_2O to give **2** (2.26 g, 9.0 mmol, 90% yield from **7**). IR (KBr) 3347, 3026, 1637, 1461, 1404, 1344, 1272, 1012, 853, 678, 627 cm^{-1}; ^1H NMR (DMSO-d_6 with 1 drop of D_2O, 300 MHz) δ

4.32 (s, 3H), 8.24 (d, J = 6 Hz, 2H), 8.88 (d, J = 6 Hz, 2H); ^{13}C NMR (DMSO-d_6 with 1 drop of D_2O, 75 MHz) δ 48.3, 132.0 (2C), 144.3 (2C), and one carbon was not observed. Anal. Calcd. for $C_6H_9O_2BNI$: C, 27.21; H, 3.43. Found: C, 27.02, H, 3.47.

Preparation of Dodecamer [2]$_{12}$. A dry, 5 mL round-bottom flask equipped with a Teflon-coated magnetic stirring bar was charged with **2** (3 mmol) and DMF (3 mL). The mixture was heated at 120 °C for 1 h to form yellow precipitate. After the resultant mixture was cooled to ambient temperature, the precipitate was collected by filtration and washed with DMF several times to obtain white solid. The white solid was recrystallized from water to get [**2**]$_{12}$ as an orange crystal. IR (KBr) 3465, 3030, 1636, 1558, 1456, 1208, 1123, 932, 843, 799, 748, 683 cm^{-1}; ^{1}H NMR (DMSO-d_6 with 1 drop of D_2O, 300 MHz) δ 4.16 (s, 3H), 7.51 (d, J = 6.3 Hz, 2H), 8.43 (d, J = 6.3 Hz, 2H); ^{13}C NMR (DMSO-d_6 with 5 drops of D_2O, 300 MHz) δ 47.9, 131.4 (2C), 143.3 (2C), and one carbon was not observed. Anal. Calcd. for $C_{72}H_{84}B_{12}I_8N_{12}O_{14}$•$10H_2O$: C, 32.43; H, 3.93; N, 6.30; I, 38.07. Found: C, 32.15; H, 3.71; N, 6.20; I, 38.44.

X-ray Crystallographic Analysis of [2]$_{12}$: Crystal data: $C_{72}H_{104}B_{12}N_{12}O_{24}I_8$, M = 2666.59, crystal dimensions 0.40×0.40×0.30 mm^3, monoclinic, space group P21/n, a = 17.136(4), b = 14.073(3), c = 21.289(5) Å, V = 5115.6(19) Å^3, Z = 2, D_c = 1.731 g/cm^3, μ = 2.495 mm^{-1}, T = 223 K. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å). The structure was solved by direct methods and expanded using Fourier techniques. 13391 reflections were independent and unique, and 10822 with $I > 2\sigma(I)$ ($2\theta_{max}$ = 29.16°) were used for the solution of the structure. R = 0.0438 and Rw = 0.1235.

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-27344 for compound [**2**]$_{12}$. Copies of the data can be obtained free of charge via http//www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

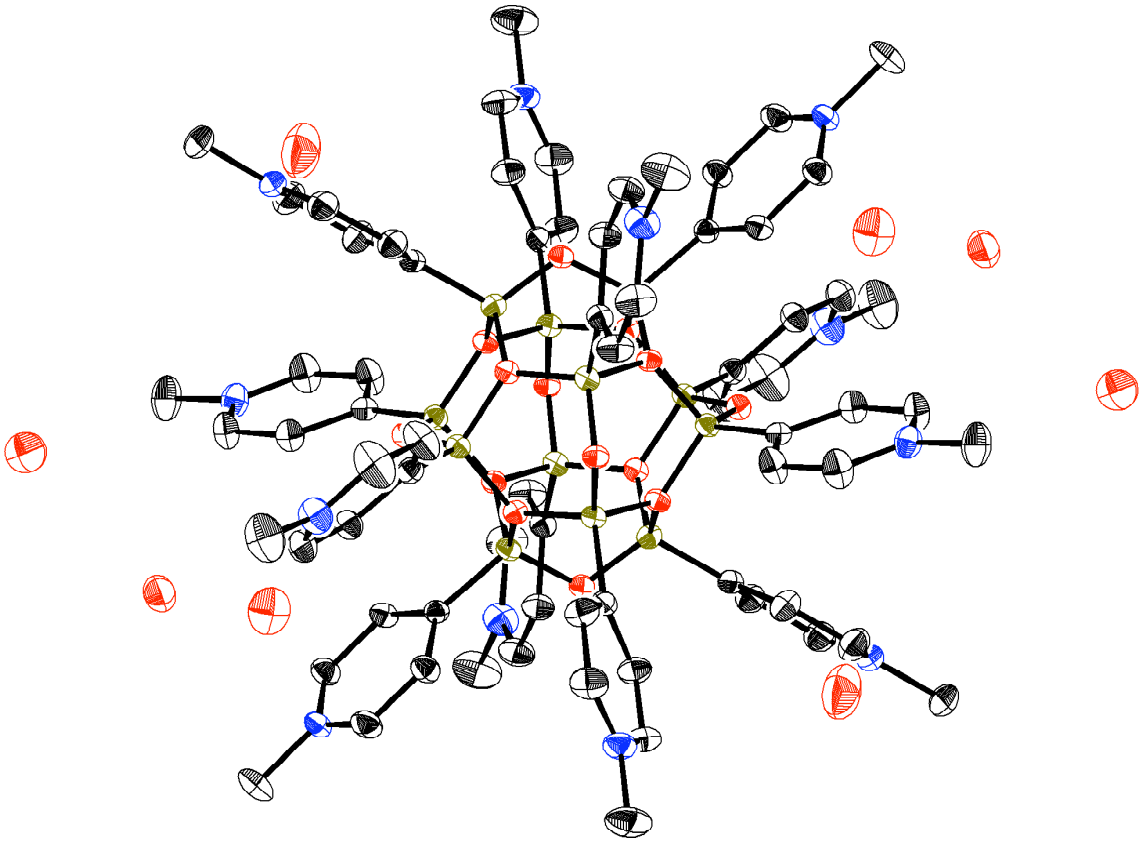
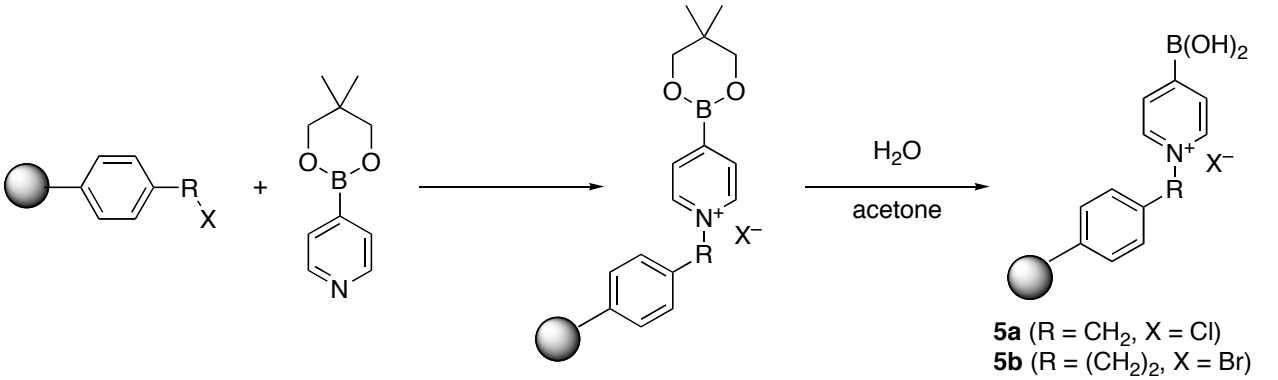


Figure. X-ray crystal structure of dodecamer [**2**]$_{12}$, $[CH_3NC_5H_4BO_{14/12}]_{12}I_8 \bullet 10H_2O$. Water was omitted for clarity.

Preparation of *N*-Polystyrene-bound 4-Boronopyridinium Salts 5.



5a (R = CH_2, X = Cl)
5b (R = $(CH_2)_2$, X = Br)
5c (R = $(CH_2)_2$, X = NTf_2)
5d (R = $(CH_2)_4$, X = Br)

A mixture of 4-(haloalkyl)polystrene resin cross-linked with divinyl benzene (2.4 mmol) and 4-pyridineboronic acid neopentyl glycol ester (990 mg, 4.8 mmol) in acetonitrile (20 mL) was heated at reflux for 2 days. After the resultant mixture was cooled to ambient temperature, the resin was collected by filtration and washed with THF, DMF, and Et_2O. The resin was added to a

mixture of THF (15 mL) and water (5 mL). This mixture was stirred at room temperature for 1 day. The resultant resin was collected by filtration and washed with THF, water, DMF, EtOAc, hexane, and Et_2O, and dried at 50 °C under reduced pressure for 12 h to give **5**.

5a: Merrifield resin (ca. 1.0 mmol-Cl/g, 400–500 μm, crosslinked with 1% divinylbenzene) purchased from Fluka was used as a polymer-support; 0.74 mmol-B/g (estimated based on nitrogen content as determined by elemental analysis); IR (KBr) 3409, 3025, 2923, 1635, 1602, 1493, 1452, 757, 698, 538 cm^{-1}. Anal. Found: C, 84.21; H, 7.51; N, 1.04.

5b: 4-(2-Bromoethyl)polystyrene resin (ca. 0.8–1.2 mmol-Br/g, 500–560 μm, crosslinked with 1% divinylbenzene) purchased from Fluka was used as a polymer-support; 0.81 mmol-B/g (estimated based on nitrogen content as determined by elemental analysis). Anal. Found: C, 82.00; H, 7.56; N, 1.14; Br, 6.52.

5c: 4-(2-Bromoethyl)polystyrene resin (ca. 0.8–1.2 mmol-Br/g, 500–560 μm, crosslinked with 1% divinylbenzene) purchased from Fluka was used as a polymer-support; 0.48 mmol-B/g (estimated from weight difference). Anal. Found: C, 77.01; H, 6.78; N, 1.47.

5d: 4-(4-Bromobutyl)polystyrene resin (2.8 mmol-Br/g, 200–400 mesh, crosslinked with 2% divinylbenzene) purchased from Novabiochem was used as a polymer-support; 1.47 mmol-B/g (estimated based on nitrogen content as determined by elemental analysis). Anal. Found: C, 65.06; H, 6.93; N, 2.06.

General Procedure for the Direct Amide Condensation of Equimolar mixtures of Carboxylic Acids and Amines Catalyzed by 2. A dry, 20 mL round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with carboxylic acid (2 mmol), amine (2 mmol), and **2** (25 mg, 0.1 mmol) in [emim][OTf] (1 mL) and toluene (5 mL). The mixture was brought to reflux with the removal of water. After several hours, the resulting mixture was cooled to ambient temperature and a colorless toluene layer was separated from a yellow ionic liquid layer by simple extraction with Et_2O, and concentrated in vacuo. The desired amide was isolated from crude products by column chromatography on silica gel. On the other hand, **2** that remained in [emim][OTf] was reused in the next reaction without further purification.

General Procedure for the Direct Amide Condensation of Equimolar Mixtures of

Carboxylic Acids and Amines Catalyzed by 5a. A dry, 5 mL round-bottom flask equipped with a Teflon-coated stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with carboxylic acid (1 mmol), amine (1 mmol), and **5a** (135 mg, 0.74 mmol-B/g, 0.1 mmol) in toluene (5 mL). The mixture was brought to reflux with the removal of water. After several hours, the resulting mixture was cooled to ambient temperature and filtered. **5a** was washed with 1 M HCl aqueous solution and ethyl acetate repeatedly, and was reused in the next reaction without further purification. On the other hand, the desired amide was isolated from the combined filtrates by column chromatography on silica gel.

***N*-Benzyl-4-phenylbutanamide:**[1] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.96–2.06 (m, 2H), 2.22 (t, *J* = 6.9 Hz, 2H), 2.67 (t, *J* = 8.0 Hz, 2H), 4.44 (d, *J* = 6.0 Hz, 2H), 5.62 (br, 1H), 7.15–7.34 (m, 10H).

***N*-Benzylcyclohexanecarboxamide:**[1] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18–1.91 (m, 10H), 2.11 (tt, *J* = 3.6 Hz, 11.4 Hz, 1H), 4.44 (d, *J* = 5.7 Hz, 1H), 5.75 (br, 1H), 7.25–7.37 (m, 5H).

***N*-Benzyl-*N*-methyl-4-phenylbutanamide (a mixture of two rotamers):**[2] IR (film) 3060, 3026, 2925, 1646, 1495, 1453, 1403, 1356, 1117, 745, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (m, 2H), 2.38 (t, *J* = 7.8 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 0.8H), 2.71 (t, *J* = 7.8 Hz, 1.2 H), 2.85 (s, 1.8 H), 2.95 (s, 1.2 H), 4.47 (s, 0.8H), 4.59 (s, 1.2 H), 7.10–7.28 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.4, 26.6, 32.1, 32.5, 33.8, 34.6, 35.1, 35.2, 50.6, 53.1, 125.7, 126.1, 127.2, 127.4, 127.9, 128.2, 128.3, 128.4, 128.8, 136.6, 137.4, 172.7, 173.0. HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{22}NO$, 268.1701; Found, 268.1692.

***N*-Benzyl-2-methoxy-2-phenylacetamide:**[3] IR (film) 3312, 3062, 3031, 2932, 2827, 1667, 1523, 1454, 1198, 1102, 741, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.35 (s, 3H), 4.47 (m, 2H), 4.68 (s, 1H), 7.07 (br, 1H), 7.25–7.43 (m, 10H).

***N*-Benzyl-2-hydrxyl-2-phenylacetamide:**[1] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.39 (dd, *J* = 14.9 Hz, 1H), 4.46 (dd, *J* = 5.7 Hz, 14.9 Hz, 1H), 5.05 (s, 1H), 6.51 (br, 1H), 7.16–7.42 (m, 5H).

2-Methoxy-*N*-phenyl-2-phenylacetamide:[4] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.42 (s, 3H), 4.72 (s, 1H), 7.07–7.60 (m, 10H), 8.57 (br, 1H).

***N*-Benzyl-1-adamantanecarboxamide:** IR (KBr) 3343, 2903, 2848, 1633, 1532, 1451, 1284, 1003, 716, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.67–1.89 (m, 12H), 2.05 (br, 3H), 4.44

(d, J = 5.7 Hz, 2H), 5.87 (br, 1H), 7.25–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 36.4, 39.2, 43.2, 127.3, 127.5, 128.6, 138.6, 177.8. HRMS-FAB (m/z): $[M+H]^+$ calcd for $C_{18}H_{24}NO$, 270.1858; Found, 270.1852.

(*E*)-*N*-Benzylcinamamide:[5] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.58 (d, J = 5.7 Hz, 2H), 5.96 (br, 1H), 6.42 (d, J = 15.6 Hz, 1H), 7.27–7.52 (m, 10H), 7.68 (d, J = 15.6 Hz, 1H).

***N*-Benzylbenzamide:**[6] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65 (d, J = 5.4 Hz, 2H), 6.48 (br, 1H), 7.28–7.82 (m, 10H).

***N*-Benzyl-*p*-cyanobenzamide:**[7] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65 (d, J = 5.7 Hz, 2H), 6.51 (br, 1H), 7.32–7.38 (m, 5H), 7.73 (dd, J = 1.8, 6.9 Hz, 2H), 7.89 (dd, J = 1.8, 6.9 Hz, 2H).

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