N-Alkyl-4-boronopyridinium Halides versus Boric Acid as Catalysts for the Esterification of α-Hydroxycarboxylic Acids

Toshikatsu Maki,[†] Kazuaki Ishihara,*[,†] and Hisashi Yamamoto*[,‡]

[†]Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan

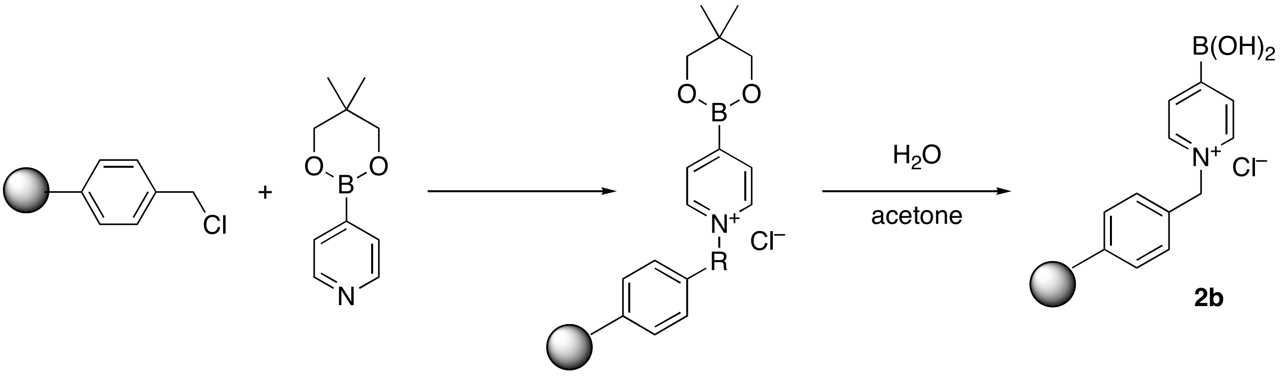
[‡]Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago, Illinois 60637

ishihara@cc.nagoya-u.ac.jp; yamamoto@uchicago.edu

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.

Preparation of 4-Borono-*N*-methylpyridinium Iodide (2a). See the supporting information of the preceding paper.

Preparation of *N*-Polystyrene-bound 4-Boronopyridinium Chloride 2b.



A mixture of 2.4 mmol of Merrifield resin (ca. 1.0 mmol-Cl/g, 400–500 μm, crosslinked with 1% divinylbenzene) purchased from Fluka 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 **2b**. 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.

General Procedure for the Esterification of Hydroxycarboxylic Acids in Alcohols Catalyzed by 2a (Table 2). To a stirring solution of hydroxycarboxylic acids (2 mmol) in alcohol (5 mL) was added **2a** (26.5 mg, 0.1 mmol) in one portion and the mixture was dissolved soon. The solution was stirred at room temperature or was heated to reflux. After the reaction was complete, excess alchol was removed in vacuo, and the residue was purified by column chromatography on silica gel to give the desired ester.

Methyl 2-Hydroxy-2-phenylacetate:[1] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.71 (s, 3H), 3.75 (d, 1H, J = 5.4 Hz), 5.16 (d, 1H, J = 5.4 Hz), 7.32–7.42 (m, 5H).

Isobutyl 2-Hydroxy-2-phenylacetate: IR (film) 3482, 2963, 2875, 1736, 1455, 1186, 1067, 733, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (d, J = 1.8 Hz, 3H), 0.82 (d, J = 1.8 Hz, 3H), 1.85 (septet, J = 6.9 Hz, 1H), 3.72 (d, J = 5.4 Hz, 1H), 3.86–3.99 (m, 2H), 5.17 (d, J = 5.4 Hz, 1H), 7.24–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.6, 18.7, 27.6, 71.9, 72.8, 126.4, 128.3, 128.4, 138.4, 173.7. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{17}O_3$, 209.1178; Found, 209.1179.

Methyl 2-Hydroxy-3-phenylpropanoate:[2] ^1H NMR ($CDCl_3$, 300 MHz) δ 12.89–3.14 (m, 3H), 3.74 (s, 3H), 4.40–4.46 (m, 1H), 7.18–7.32 (m, 5H).

Methyl 2-Hydroxy-3-methylbutanoate:[1] ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 6H), 3.32 (s, 1H), 3.79 (s, 3H).

Ethyl 2-Hydroxy-2-phenylacetate:[1] ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, *J* = 6.9 Hz, 3H), 3.67 (d, *J* = 5.7 Hz, 1H), 4.12–4.28 (m, 2H), 5.15 (d, *J* = 5.7 Hz, 1H), 7.28–7.45 (m, 5H).

Isopropyl 2-Hydroxy-2-phenylacetate:[3] ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (d, *J* = 6.3 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 3.50 (d, *J* = 5.7 Hz, 1H), 5.07 (septet, *J* = 6.3 Hz, 1H), 5.12 (d, *J* = 5.7 Hz, 1H), 7.31–7.44 (m, 5H).

2-Hydroxyethyl 2-Hydroxy-2-phenylacetate: IR (film) 3389, 2956, 1738, 1454, 1260, 1183, 1067, 733, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.38 (br, 1H), 3.68 (br, 2H), 4.10–4.28 (m, 2H), 4.55 (s, 1H), 5.21 (s, 1H), 7.31–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.3, 66.9, 73.2, 126.5 (2C), 128.5, 128.6 (2C), 138.0, 173.2. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{10}H_{13}O_4$, 197.0814; Found, 197.0816.

(*S*)-Dimethyl 2-Hydroxysuccinate:[1] ^1H NMR ($CDCl_3$, 300 MHz) δ 2.81 (dd, *J* = 6.0, 16.5 Hz, 1H), 2.89 (dd, *J* = 4.5, 16.5 Hz, 1H), 3.42 (s, 1H), 3.72 (s, 3H), 3.82 (s, 3H), 4.53 (dd, *J* = 4.5, 6.0 Hz, 1H).

(*S*)-Diethyl 2-Hydroxysuccinate:[4] ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 2.78 (dd, *J* = 6.0, 16.2 Hz, 1H), 2.86 (dd, *J* = 4.5, 16.2 Hz, 1H), 3.44 (d, *J* = 4.5 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.27 (q, *J* = 1.5, 7.2 Hz, 2H), 4.47–4.52 (m, 1H).

(2*R*,3*R*)-Diethyl 2,3-Dihydroxysuccinate:[1] ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, *J* = 6.9 Hz, 6H), 3.45 (s, 2H), 4.32 (q, *J* = 6.9 Hz, 4H), 4.56 (s, 2H).

Isobutyl 2-Hydroxybenzoate:[1] ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (d, *J* = 6.9 Hz, 6H), 2.11 (septet, *J* = 6.9 Hz, 1H), 4.14 (d, *J* = 6.9 Hz, 2H), 6.86–7.88 (m, 4H), 10.86 (s, 1H).

4-Hydroxy-3-(isobutoxycarbonyl)benzoic Acid: IR (KBr) 2968, 2626, 1696, 1592, 1445, 1357, 1291, 976, 800, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (d, *J* = 6.6 Hz, 6H), 2.15 (septet, *J* = 6.6 Hz, 1H), 4.18 (d, *J* = 6.9 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 1H), 8.19 (dd, *J* = 2.1, 8.7 Hz, 1H), 8.65 (d, *J* = 2.1 Hz, 1H), 11.43 (br, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1 (2C), 27.7, 71.8, 112.6, 118.0, 120.4, 133.2, 137.0, 166.0, 169.6, 171.2. HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{15}O_5$, 239.0919; Found, 239.0914.

(*S*)-Methyl 2-(Benzyloxycarbonylamino)-3-hydroxypropanoate:[1] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.54 (t, *J* = 6.0 Hz, 1H), 3.69 (s, 3H), 3.78–3.97 (m, 2H), 4.38–4.43 (m, 1H), 5.07 (s, 2H), 6.12 (d, *J* = 7.8 Hz, 1H), 7.20–7.38 (m, 5H).

(2*S*,3*R*)-Methyl 2-(Benzyloxycarbonylamino)-3-hydroxybutanoate:[1] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, *J* = 6.3 Hz, 3H), 2.91 (d, *J* = 5.7 Hz, 1H), 3.72 (s, 3H), 4.29–4.33 (m, 2H), 5.10 (s, 2H), 5.87 (d, *J* = 9.0 Hz, 1H), 7.26–7.40 (m, 5H).

General Procedure for the Esterification of Hydroxycarboxylic Acids in Alcohols Catalyzed by 2b (Table 3). To a sirring solution of hydroxycarboxylic acids (1 mmol) in alcohol (2.5 mL) was added **2b** (135 mg, 0.1 mmol, 0.74 mmol-B/g), and the mixture was brought to reflux. After the reaction was completed, the resulting mixture was cooled to ambient temperature and filtered. **2b** was washed with 1M HCl aqueous solution and ethyl acetate repeatedly, and was used directly in the next reaction without further purification. On the other hand, the desired ester was isolated from the combined filtrates by column chromatography on silica gel.

General Procedure for the Esterification of Equimolar Mixtures of Equimolar Mixtures of Carboxylic Acids and Alcohols Catalyzed by $B(OH)_3$ (Table 4). A dry, 10 mL round-bottom flask equipped with a Teflon-coated stirring bar and a Dean–Stark apparatus surmounted by a reflux condenser was charged with hydroxycarboxylic acids (2 mmol), alcohols (2 mmol), and $B(OH)_3$ (6.2 mg, 0.1 mmol) in toluene (5 mL). The mixture was brought to reflux with the removal of water. After the reaction was complete, the resulting mixture was cooled to ambient temperature and washed with sodium hydrogen carbonate, and the product was extracted with ethyl acetate. The organic layers were dried over magnesium sulfate. The solvents were evaporated, and the residue was purified by column chromatography on silica gel to give the desired ester.

Octyl 2-Hydroxy-2-phenylacetate: IR (film) 3502, 2927, 1735, 1261, 1184, 1067, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20–1.61 (m, 12H), 3.49 (d, *J* = 6.0 Hz, 1H), 4.15 (t, *J* = 6.3 Hz, 2H), 5.16 (d, *J* = 6.0 Hz, 1H), 7.33–7.494 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 25.5, 283, 29.0 (2C), 31.6, 66.2, 72.8, 126.4 (2C), 128.3, 128.5 (2C), 138.4, 173.7. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{25}NO3$, 265.1804; Found, 265.1796.

Octyl 2-Hydroxy-2-methylpropanoate: IR (film) 3502, 2928, 2857, 1731, 1468, 1267, 1183 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 3H), 1.26–1.609 (m, 12H), 1.43 (s, 6H), 3.13 (s, 1H), 4.17 (t, J = 6.9 Hz, 2H) ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 25.7, 27.1 (2C), 28.4, 29.1 (2C), 31.7, 65.9, 71.9, 177.6. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{25}O_3$, 217.1804; Found, 217.1795.

Octyl 2-Hydroxy-2-phenylpropanoate: IR (film) 3511, 2928, 2856, 1727, 1448, 1251, 1150, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 3H), 1.18–1.68 (m, 12H), 1.79 (s, 3H), 3.83 (s, 1H), 4.09–4.23 (m, 2H), 7.27–7.58 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.6, 25.6, 28.3, 29.0, 29.1, 31.7, 66.4, 75.6, 125.1 (2C9, 127.7, 128.2 82C), 142.8, 175.7. HRMS-FAB (*m*/*z*): $[M–OH]^+$ calcd for $C_{17}H_{25}O_2$, 261.1855; Found, 261.1855.

(+)-(2*R*,3*R*)-Dioctyl 2,3-Dihydroxysuccinate:[5] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 6H), 1.24–1.71 (m, 24H), 3.25 (d, J = 6.9 Hz, 2H), 4.26 (dt, J = 0.6, 6.8 Hz, 4H), 4.53 (d, J =6.9 Hz, 2H).

Cyclododecyl 2-Hydroxy-2-methylpropanoate: IR (film) 3526, 2936, 2864, 1723, 1470, 1267, 1183, 978, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26–1.81 (m, 2H), 1.41 (s, 6H), 3.25 (s, 1H), 5.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6 (2C), 22.9 (2C), 23.1 (2C), 2.38, 23.9 (2C), 27.0 (2C), 28.7 (2C), 71.7, 73.8, 177.1. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{31}O_3$, 271.2273; Found, 271.2271.

Octyl 2-Hydroxybenzoate: IR (film) 3183, 2927, 1676, 1486, 1302, 1214, 1158, 1091, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87–1.83 (m, 15H), 4.34 (t, J = 6.6 Hz, 2H), 6.86–7.87 (m, 4H), 10.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.7, 26.0, 28.6, 29.3 (2C), 31.9, 65.5, 112.7, 117.6, 119.1, 129.9, 135.6, 161.7, 170.3. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{23}O_3$, 251.1647; Found, 251.1641.

Other Product Data

Butyl 2-Hydroxy-2-phenylacetate: IR (film) 3482, 2960, 2874, 1735, 1455, 1184, 1067, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, J = 7.2 Hz, 3H), 1.18–1.30 (m, 2H), 1.50–1.60 (m, 2H), 3.63 (s, 1H), 4.10–4.22 (m, 2H), 5.16 (s, 1H), 7.30–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 18.8, 30.3, 65.9, 72.8, 126.4 (2C), 128.3, 128.4 (2C), 138.4, 173.7. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{17}O_3$, 209.1178; Found, 209.1178.

***N*-(5-Hydroxypentyl)-4-phenylbutanamide:**[6] IR (KBr) 3306, 2946, 1630, 1542, 1048, 1005, 730, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34–1.61 (m, 6H), 1.90–2.18 (m, 4H), 2.63 (t, J = 7.5 Hz, 2H), 3.22 (q, J = 6.6 Hz, 2H), 3.60 (t, J = 6.6 Hz, 2H), 5.85 (br, 1H), 7.15–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1, 27.3, 29.4, 32.3, 35.3, 36.0, 39.4, 62.4, 126.0, 128.5 (2C), 141.6, 173.1. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{24}NO_2$, 250.1807; Found, 250.1812.

5-(4-Phenylbutanamido)pentyl 2-Hydroxy-2-methylpropanoate: IR (film) 33.07, 2936, 1732, 1646, 1550, 1271, 1151, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33–1.74 (m, 6H), 1.42 (s, 6H), 1.94–2.19 (m, 4H), 2.65 (t, J = 7.5 Hz, 2H), 3.18 (s, 1H), 3.25 (q, J = 6.6 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 5.44 (br, 1H), 7.17–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.0, 27.0 (3C), 28.0, 29.1, 35.0, 35.7, 39.0, 65.3, 71.8, 125.8, 128.2 (2C), 128.3 (2C), 141.3, 172.7, 177.3. HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{30}NO_4$, 336.2175; Found, 336.2178.

References

1. Commercially available from Aldrich.
2. Commercially available from Fluka.
3. Houston, T. A.; Wikinson, B. L.; Blanchfield, J. T. *Org. Lett.* **2004**, *6*, 679–681.
4. Commercially available from Tokyo Kasei Kogyo Co., Ltd. (TCI).
5. van Nunen, J. L.; Folmer, B. F. B.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1997**, *119*, 283–391.
6. Günther, R.; Bordusa, F. *Chem. Eur. J.* **2000**, *6*, 463–467.