Highly Efficient Cu Catalyst System for the Radical Reactions of α-Bromocarboxyls

Yushi Noda, Takashi Nishikata*

Graduate School of Science and Engineering, Yamaguchi University, Ube, Yamaguchi, 755-8611, Japan

Corresponding Author: nisikata@yamaguchi-u.ac.jp

Supporting Information

Table of Contents
1. General Procedures S2
2. Spectral charts for compounds S9
1. General procedures

General Information

All reactions were carried out under nitrogen (99.95%) atmosphere. For TLC analyses precoated Kieselgel 60 F254 plates (Merck, 0.25 mm thick) were used; for column chromatography Silica Flash® P60 (SiliCycle, 40-63 μm) was used. Visualization was accomplished by UV light (254 nm), 1H and 13C NMR spectra were obtained using a JEOL 400 MHz NMR spectrometer. Chemical shifts for 1H NMR were described in parts per million (chloroform as an internal standard δ = 7.26) in CDCl₃, unless otherwise noted. Chemical shifts for 13C NMR were expressed in parts per million in CDCl₃ as an internal standard (δ = 77.16), unless otherwise noted. High resolution mass analyses were obtained using an ACQUITY UPLC/ TOF-MS for ESI. Anhydrous solvents were purchased from Kanto Chemical Co., Ltd. Other chemicals were purchased from TCI, Aldrich and Wako and directly used from the bottles.

Typical experimental procedure for radical reactions

Cu salt (5 x 10⁻⁴ M in MeCN), ligand (0.1 mmol), 1 (1.0 mmol), and 2 (0.50 mmol) [or 4 (Scheme 2) or 6 (Scheme 3)] were sequentially added under air to a dram vial equipped with a stir bar, amine (0.6 mmol), and dried solvent (0.5 mL) were added by syringe, and the resulting mixture was vigorously stirred under nitrogen atmosphere [charged by general N₂ (99.95%) gas flow] for 20 h at the temperature, as shown in the tables. After this time, the contents of the flask were filtered through a plug of silica gel and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product 3.

Table S1
Compounds 3a-3e\textsuperscript{[1]}, 3j-3n\textsuperscript{[2]} and 5\textsuperscript{[3]} are known.

[Reference]


Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2a (0.50 mmol, 59 mg), CuI solution (5 x 10\textsuperscript{-5} mmol, 5 x 10\textsuperscript{-4} M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 3a (64 mg, 55%); \textit{H} NMR (CDCl\textsubscript{3}) \(\delta\): 1.25 (t, \(J = 7.2\) Hz, 3H), 1.40 (s, 6H), 2.33 (s, 3H), 4.14 (q, \(J = 7.1\) Hz, 2H), 6.35 (d, \(J = 16.2\) Hz, 1H), 6.41 (d, \(J = 16.2\) Hz, 1H), 7.11 (d, \(J = 8.0\) Hz, 2H), 7.27 (d, \(J = 8.0\) Hz, 2H). \textit{C} NMR (CDCl\textsubscript{3}) \(\delta\): 14.20, 21.18, 30.80, 44.38, 60.80, 126.35, 127.89, 129.35, 133.62, 134.52, 137.26, 176.53.

Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2b (0.50 mmol, 67 mg), CuI solution (5 x 10\textsuperscript{-5} mmol, 5 x 10\textsuperscript{-4} M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 60 °C, yielded the product 3b (110 mg, 89%); \textit{H} NMR (CDCl\textsubscript{3}) \(\delta\): 1.25 (t, \(J = 7.2\) Hz, 3H), 1.40 (s, 6H), 3.79 (s, 3H), 4.13 (q, \(J = 7.1\) Hz, 2H), 6.26 (d, \(J = 16.1\) Hz, 1H), 6.38 (d, \(J = 16.1\) Hz, 1H), 6.84 (d, \(J = 8.8\) Hz, 2H), 7.31 (d, \(J = 8.8\) Hz, 2H). \textit{C} NMR (CDCl\textsubscript{3}) \(\delta\): 14.16, 25.11, 44.26, 55.26, 60.74, 113.90, 127.26, 127.43, 129.88, 132.33, 159.02, 176.45.

Following the general procedure above, using 1b (1.0 mmol, 207 mg), 2b (0.50 mmol, 67 mg), CuI solution (5 x 10\textsuperscript{-5} mmol, 5 x 10\textsuperscript{-4} M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 60 °C, yielded the product 3c (87 mg, 70%); \textit{H} NMR (CDCl\textsubscript{3}) \(\delta\): 1.27 (t, \(J = 7.2\) Hz, 3H), 1.90-19.4 (m, 2H), 3.79 (s, 3H), 4.13 (q, \(J = 7.1\) Hz, 2H), 6.26 (d, \(J = 16.1\) Hz, 1H), 6.38 (d, \(J = 16.1\) Hz, 1H), 6.84 (d, \(J = 8.8\) Hz, 2H), 7.31 (d, \(J = 8.8\) Hz, 2H). \textit{C} NMR (CDCl\textsubscript{3}) \(\delta\): 14.16, 25.11, 44.26, 55.26, 60.74, 113.90, 127.26, 127.43, 129.88, 132.33, 159.02, 176.45.
2.22-2.27 (m, 2H), 2.56-2.62 (m, 2H), 3.81 (s, 3H), 4.17 (q, J = 7.2 Hz, 2H), 6.15 (d, J = 16.1 Hz, 1H),
6.55 (d, J = 16.1 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H). 13C NMR (CDCl 3) δ:

Following the general procedure above, using 1c (1.0 mmol, 221 mg), 2b (0.50 mmol, 67 mg), CuI
solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg),
diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1,2-dimethoxyethane (0.5 mL) at 60 °C, yielded
the product 3d (127 mg, 88%); 1H NMR (CDCl 3) δ: 1.30-1.44 (m, 3H), 1.55-1.65 (m, 5H), 2.18 (m,
2H), 3.69 (s, 3H), 3.80 (s, 3H), 6.02 (d, J = 16.3 Hz, 1H), 6.37 (d, J = 16.3 Hz, 1H), 6.84 (d, J = 8.7
Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H). 13C NMR (CDCl 3) δ: 23.47, 25.99, 34.36, 49.24, 52.28, 55.63, 114.31,
127.80, 129.11, 130.26, 132.13, 159.54, 176.17.

Following the general procedure above, using 1d (1.0 mmol, 187 μl), 2b (0.50 mmol, 67 mg), CuI
solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg),
diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1,2-dimethoxyethane (0.5 mL) at 60 °C, yielded
the product 3e (124 mg, 81%); 1H NMR (CDCl 3) δ: 1.26 (t, J = 7.1 Hz, 6H), 1.65 (s, 3H), 3.80
(s, 3H), 4.19-4.23 (m, 4H), 6.43 (d, J = 16.2 Hz, 1H), 6.54 (d, J = 16.2 Hz, 1H), 6.58 (d, 8.7 Hz, 2H),
7.34 (d, J = 8.7 Hz, 2H). 13C NMR (CDCl 3) δ: 14.11, 20.46, 55.41, 55.71, 61.74, 114.12, 125.59, 127.98,
129.52, 130.36, 159.63, 171.51.

Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2c (0.50 mmol, 73 mg), CuI
solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg),
diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1,2-dimethoxyethane (0.5 mL) at 100 °C,
yielded the product 3f (90 mg, 69%); IR (neat) ν 1727, 1611, 973 cm⁻¹; 1H NMR (CDCl 3) δ: 1.25 (t, J
= 7.3 Hz, 3H), 1.42 (s, 6H), 2.24 (s, 6H), 2.27 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 5.82 (d, J = 16.6 Hz, 1H), 6.35 (d, J = 16.6 Hz, 1H), 6.86 (s, 2H). 13C NMR (CDCl3) δ: 14.33, 20.76, 21.06, 25.13, 44.76, 60.82, 125.62, 128.54, 134.21, 135.96, 136.13, 139.37, 176.62; HREIMS calcd. for C17H25O2 (M+H+): 261.1854; found 261.1853.

Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2e (0.50 mmol, 97 mg), CuI solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75mmol, 131μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 60 °C, yielded the product 3e (134 mg, 87%); IR (neat) ν 1722, 1236, 1120, 965 cm⁻¹; ¹H NMR (CDCl3) δ: 1.26 (t, J = 7.2 Hz, 3H), 1.40 (s, 6H), 3.83 (s, 3H), 3.88 (s, 6H), 4.15 (q, J = 7.1 Hz, 2H), 6.30 (d, J = 16.1 Hz, 1H), 6.36 (d, J = 16.1 Hz, 1H), 6.60 (s, 2H). 13C NMR (CDCl3) δ:14.24, 25.20, 44.44, 56.19, 60.94, 61.03, 103.50, 128.10, 133.04, 134.13, 153.49, 176.49; HRESIMS calcd. for C17H25O5 (M+H+): 309.1702; found 309.1707.

Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2d (0.50 mmol, 111 mg), CuI solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75mmol, 131μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 3c (102 mg, 61%); IR (neat) ν 2973, 1720, 1229, 1124, 1023 cm⁻¹; ¹H NMR (CDCl3) δ: 1.28 (t, J = 7.0 Hz, 3H), 1.42 (t, J = 7.3 Hz, 3H), 1.46 (s, 6H), 4.17 (q, J = 7.3 Hz, 2H), 4.6 (q, J = 7.2 Hz, 2H), 6.41 (d, J = 16.2 Hz, 1H), 6.62 (d, J = 16.2 Hz, 1H), 7.23-7.26 (m, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 7.9, 1H), 7.47 (dd, J = 7.1, and 8.2 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 8.11-8.12 (m, 2H) ¹³C NMR (CDCl₃) δ: 13.82, 14.26, 25.32, 37.61, 44.46, 60.83, 108.56, 108.68, 118.56, 119.01, 120.58, 123.10, 123.29, 124.36, 125.85, 128.45, 128.78, 131.91, 139.68, 140.44, 176.82; HRESIMS calcd. for C22H₂⁶NO₂ (M+H⁺): 336.1963; found 336.1964.
Following the general procedure above, using 1e (1.0 mmol, 236 mg), 2f (0.50 mmol, 59 mg), CuI solution (5 $\times$ 10^{-5} mmol, 5 $\times$ 10^{-4} M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131 µl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 3f (62 mg, 43% (exo:endo = 9:1 (the isomers are inseparable))); IR (neat) ν 1726, 1130, 1075 cm^{-1}; ^1H NMR (CDCl₃) δ: 0.71 (t, J = 7.43 Hz, 3H), 0.81 (t, J = 7.40 Hz, 3H), 0.99-1.16 (m, 4H), 1.40-1.53 (m, 2H), 1.58-1.65 (m, 2H), 2.32 (s, 3H), 2.75 (s, 2H), 3.29 (s, 3H), 4.99 (d, J = 1.7 Hz, 1H), 5.14 (d, J = 1.8 Hz, 1H), 7.08 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H). ^13C NMR (CDCl₃) δ: 8.35, 14.04, 21.14, 23.14, 26.00, 26.51, 33.09, 40.66, 49.96, 51.11, 116.56, 126.86, 128.77, 136.95, 139.96, 146.36, 177.14; HRESIMS calcd. for C₂₀H₃₁O₂ (M+H⁺): 303.2324; found 303.2324.

Following the general procedure above, using 1d (1.0 mmol, 187 µl), 2f (0.50 mmol, 59 mg), CuI solution (5 $\times$ 10^{-5} mmol, 5 $\times$ 10^{-4} M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131µl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 3a (93 mg, 61% (exo:endo = 9:1 (the isomers are inseparable))); ^1H NMR (CDCl₃) δ: 1.15 (t, J = 7.1 Hz, 6H), 1.27 (s, 3H), 2.32 (s, 3H), 3.14 (s, 2H), 3.86-3.92 (m, 2H), 3.95-4.02 (m, 2H), 5.06 (d, J = 0.8 Hz, 1H), 5.2 (d, J = 1.6 Hz, 1H), 7.08 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H). ^13C NMR (CDCl₃) δ: 13.94, 19.94, 21.14, 40.04, 53.61, 61.19, 117.59, 126.82, 128.86, 137.32, 139.00, 144.56, 172.06.

Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2a (0.50 mmol, 59 mg), CuI solution (5 $\times$ 10^{-5} mmol, 5 $\times$ 10^{-4} M in MeCN, 0.1 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131 µl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 3a (102 mg, 83% (exo:endo = 9:1 (the isomers are inseparable))); ^1H NMR (CDCl₃)
δ: 1.10 (s, 6H), 1.11-1.14 (t, J = 7.0 Hz, 3H), 2.32 (s, 3H), 2.77 (s, 2H), 3.77 (J = 7.0 Hz, 2H), 5.01 (s, 1H), 5.21 (d, J = 1.76 Hz, 1H), 7.09 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H). 13C NMR (CDCl3) δ: 14.02, 21.13, 25.57, 42.60, 45.80, 60.25, 116.36, 126.73, 128.87, 137.07, 146.12, 177.51.

Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2a (0.50 mmol, 76 mg), CuI solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.2 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 3a (65 mg, 49% (exo:endo = 93:7 (the isomers are inseparable))); IR (neat) ν 1722, 1133, 835 cm⁻¹; 1H NMR (CDCl3) δ: 1.01 (s, 6H), 1.12 (t, J = 7.1 Hz, 3H), 2.75 (s, 2H), 3.77 (q, J = 7.1 Hz, 2H), 5.07 (d, J = 1.3 Hz, 1H), 5.22 (d, J = 1.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H). 13C NMR (CDCl3) δ: 14.03, 25.57, 42.75, 45.75, 60.36, 117.73, 121.35, 128.57, 131.30, 141.41, 145.26, 177.26; HRESIMS calcd. for C15H20ClO2 (M+H⁺): 267.1151; found 267.1153.

Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2a (0.50 mmol, 98 mg), CuI solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.2 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 3a (83 mg, 54% (exo:endo = 93:7 (the isomers are inseparable))); IR (neat) ν 1722, 1193, 1008, cm⁻¹; 1H NMR (CDCl3) δ: 1.10 (s, 6H), 1.12 (t, J = 7.1 Hz, 3H), 2.75 (s, 2H), 3.76 (q, J = 7.1 Hz, 2H), 5.06 ( J = 1.3 Hz, 1H), 5.22 (d, J = 1.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H). 13C NMR (CDCl3) δ: 14.03, 25.57, 42.56, 45.81, 60.35, 117.68, 128.22, 128.33, 133.23, 140.93, 145.22, 177.27; HRESIMS calcd. for C15H20BrO2 (M+H⁺): 311.0646; found 311.0645.

Following the general procedure above, using 1a (1.0 mmol, 198 mg), 2i (0.50 mmol, 98 mg), CuI solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.2 ml), TPMA (0.02 mmol, 2.9 mg),
diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 3a (85 mg, 73%); 1H NMR (CDCl3) δ: 1.11 (t, J = 7.2 Hz, 3H), 1.11 (s, 6H), 2.80 (s, 2H), 3.72 (q, J = 7.1 Hz, 2H), 5.05 (d, J = 1.6 Hz, 1H), 5.23 (d, J = 1.7 Hz, 1H), 7.23-7.32 (m, 5H).

13C NMR (CDCl3) δ: 14.02, 25.57, 42.55, 45.91, 60.25, 117.11, 126.90, 127.40, 128.20, 142.51, 146.35, 177.43.

Following the general procedure above, using 4 (0.5 mmol, 127 mg), CuI solution (5 x 10⁻⁵ mmol, 5 x 10⁻⁴ M in MeCN, 0.2 ml), TPMA (0.02 mmol, 2.9 mg), diisopropylmethylamine (0.75 mmol, 131 μl) and dried 1, 2-dimethoxyethane (0.5 mL) at 100 °C, yielded the product 5 (88 mg, 100%); 1H NMR (CDCl3) δ: 1.37 (s, 6H), 3.21 (s, 3H), 6.85 (d, J = 7.7 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.26 (dt, J = 1.2, 7.6 Hz, 1H). 13C NMR (CDCl3) δ: 24.35, 26.16, 44.14, 108.07, 122.31, 122.54, 127.73, 135.89, 142.72, 181.46.
1H NMR

13C NMR
$^1$H NMR

$^1$C NMR

13C NMR
1H NMR

13C NMR
1H NMR

13C NMR
1H NMR

13C NMR
1H NMR

13C NMR
1H NMR

13C NMR
1H NMR

13C NMR