Supporting Information
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Supporting Information

Stereoselective synthesis of 4-substituted 2,4-dichloro-2-butenals by α- and γ-regioselective double chlorination of dienamine catalysis

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1. General information

$^1$H NMR spectra were measured on Bruker (400 or 500 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in CDCl$_3$, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet-doublet, m = multiplet, br = broad), coupling constants (Hz), and assignment. $^{13}$C NMR spectra were measured on Bruker (100 or 125 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. $^{19}$F NMR spectra were measured on Bruker (376 or 470 MHz) spectrometer. High-resolution mass spectra (HRMS) were performed on LTQ Orbitrap at Okinawa Institute of Science and Technology Graduate University and FAB at Kyoto Institute of Technology. For thin layer chromatography (TLC) analysis, TLC plates (silica gel 60 F$_{254}$) were used. The products were purified by flash column chromatography silica gel 60 (KANTO, spherical, neutral, 40-50 µm).
2. General experimental procedure.

2-1. General experimental procedure for compound 2:

To the solution of α,β-unsaturated aldehyde 1 (0.1 mmol) in DCM (0.5 mL, 0.2 M) was added L-proline (20 mol%) at room temperature, and the reaction was replaced into the ice bath. Next, NCS (2.5 equiv) was added into a solution at 0 °C and the reaction was purged with argon gas, then the whole reaction mixture was stirred for 30 mins at 0 °C. After 30 mins, the reaction was removed from the ice bath, and stirred at room temperature until TLC revealed that starting material 1 was totally consumed. Note: the reaction flask was shielded from the light by an aluminum foil during the reaction. The reaction was quenched by aqueous sat. NaHCO₃ and extracted by EtOAc (20 mL x 3). Then, the whole organic layer was washed by brine and dried over MgSO₄. The organic solution was filtered and concentrated by the rotary evaporator. NMR yield of the compound 2 was determined by ¹H NMR after dried the reaction mixture by a high vacuum pump with CH₂Br₂ as an internal standard.

2-2. General experimental procedure for compound 3: Next, the mixture of compound 2 was diluted in methanol (0.1 M), and the whole reaction mixture was heated at 60 °C until compound 2 was totally consumed monitoring with TLC. The reaction was quenched by water and extracted by Et₂O (20 mL x 3). Then, the whole organic layer was washed by brine and dried over MgSO₄. The organic solution was filtered and concentrated by the rotary evaporator. The residue was purified by a silica gel flash chromatography.

2-3. General experimental procedure for compound 4a:

After preparing the compound 2a by the procedure mentioned above, to the solution of compound 2a in DCM/EtOH (3/1, 0.1 M) was added NaBH₄ (10 equiv) at 0 °C, then the whole reaction
mixture was stirred for 1 h at 0 °C. After the consumption of the compound 2 was confirmed by TLC, the reaction was quenched by aqueous sat. NH₄Cl and extracted by Et₂O (20 mL x 3). Then, the whole organic layer was washed by brine and dried over MgSO₄. The organic solution was filtered and concentrated by the rotary evaporator. The residue was purified by a silica gel flash chromatography.

2-4. General experimental procedure for compound 5a:

After preparing the compound 2a by the procedure mentioned above, to the solution of compound 2a in dry DCM (0.2 M) was added methyl (triphenylphosphoranylidene)acetate (1.2 equiv) at 0 °C, and then the whole reaction mixture was stirred for 1 h at room temperature. After the consumption of the compound 2a was confirmed by TLC, the reaction mixture was passed through the short silica gel chromatography to remove insoluble material washed by Hex/EtOAc (7/1). Then, the collected organic solution was concentrated by the rotary evaporator and the residue was purified by a silica gel flash chromatography.

3. Screening of chlorinating reagents.

![Diagram](image)

<table>
<thead>
<tr>
<th>Chlorine Source</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl-1</td>
<td>56%</td>
<td>14 h</td>
</tr>
<tr>
<td>Cl-2</td>
<td>53%</td>
<td>48 h</td>
</tr>
<tr>
<td>Cl-3</td>
<td>0%</td>
<td>24 h</td>
</tr>
<tr>
<td>Cl-4</td>
<td>0%</td>
<td>24 h</td>
</tr>
<tr>
<td>Cl-5</td>
<td>0%</td>
<td>24 h</td>
</tr>
</tbody>
</table>

Yields were determined by ¹H NMR using CH₂Br₂ as an internal standard.
4. Characterization of compound 2 and 3

NOTE: HRMS of following compounds was not observed due to unstable nature under HRMS experiment condition: compound 2i, 2j, 2k, 2l, 2j', 2k', 4a and 5a.

[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]benzene (3a)

Purification by flash chromatography (SiO₂, Hexane/Et₂O = 15/1) afforded 3a (14.1 mg, 0.055 mmol, 55% yield): ¹H NMR (400 MHz, CDCl₃) δ 3.27 (3H, s), 3.33 (3H, s), 3.36 (3H, s), 4.74 (1H, s), 5.22 (1H, d, J = 8.5 Hz), 6.23 (1H, dd, J = 8.5, 0.6 Hz), 7.26-7.30 (1H, m), 7.32-7.40 (4H, m); ¹³C NMR (125 MHz, CDCl₃) δ 53.07, 53.14, 56.5, 79.5, 102.4, 126.5, 127.9, 128.6, 130.6, 131.4, 140.1; HRMS calculated for C₁₃H₁₆ClO₃⁺: m/z 255.0782 ([M − H]⁺), found: m/z 255.0782 ([M − H]⁺).

1-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-4-fluorobenzene (3b)

Purification by flash chromatography (SiO₂, Hexane/Et₂O = 20/1) afforded 3b (14.6 mg, 0.0531 mmol, 53% yield): ¹H NMR (500 MHz, CDCl₃) δ 3.27 (3H, s), 3.33 (3H, s), 3.35 (3H, s), 4.75 (1H, s), 5.20 (1H, d, J = 8.5 Hz), 6.20 (1H, dd, J = 8.5, 0.6 Hz), 7.01-7.05 (2H m), 7.34-7.37 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ 53.09, 53.12, 56.5, 78.8, 102.3, 115.4 (d, J = 21.7 Hz), 128.2 (d, J = 8.2 Hz), 130.4, 131.6, 135.95, 135.97, 161.4, 163.4; ¹⁹F NMR (470 MHz, CDCl₃) δ −114.3−−114.4 (1F, m); HRMS calculated for C₁₃H₁₅ClFO⁺: m/z 273.0701 ([M − H]⁺), found: m/z 273.0688 ([M − H]⁺).
1-chloro-4-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]benzene (3c)

Purification by flash chromatography (SiO₂, 20/1 Hexane/Et₂O) afforded 3c (19.3 mg, 0.0662 mmol, 66% yield): \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 3.27 (3H, s), 3.33 (3H, s), 3.35 (3H, s), 4.75 (1H, s), 5.19 (1H, d, \(J = 8.5\) Hz), 6.18 (1H, d, \(J = 8.5\) Hz), 7.32 (4H, m); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 53.08, 53.11, 56.5, 78.8, 102.3, 127.8, 128.7, 130.2, 131.8, 133.7, 138.7; HRMS calculated for C₁₃H₁₅Cl₂O₃⁺: m/z 289.0398 ([M – H]⁺), found: m/z 289.0393 ([M – H]⁺).

1-bromo-4-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]benzene (3d)

Purification by flash chromatography (SiO₂, Hexane/Et₂O = 30/1) afforded 3d (17.5 mg, 0.0521 mmol, 52% yield): \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 3.27 (3H, s), 3.33 (3H, s), 3.35 (3H, s), 4.74 (1H, s), 5.18 (1H, d, \(J = 8.5\) Hz), 6.17 (1H, d, \(J = 8.5\) Hz), 7.26 (2H d, \(J = 8.3\) Hz), 7.47 (2H, d, \(J = 8.3\) Hz); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 53.08, 53.12, 56.5, 78.9, 102.2, 121.8, 128.2, 130.1, 131.7, 131.9, 139.2; HRMS calculated for C₁₃H₁₄BrClO₃⁺: m/z 332.9884 ([M – H]⁺), found: m/z 332.9888 ([M – H]⁺).

1-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-4-methylbenzene (3e)

Purification by flash chromatography (SiO₂, Hexane/Et₂O = 30/1) afforded 3e (16.8 mg, 0.0620 mmol, 62% yield): \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 2.33 (3H, s), 3.27 (3H, s), 3.32 (3H, s), 3.34 (3H, s), 4.73 (1H, s), 5.18 (1H, d, \(J = 8.5\) Hz), 6.23 (1H, d, \(J = 8.5\) Hz), 7.15 (2H d, \(J = 7.9\) Hz), 7.27 (2H, d, \(J = 8.0\) Hz); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 21.1 53.0, 53.1, 56.4, 79.4, 102.4, 126.5, 129.2, 130.8, 131.1, 137.1, 137.6; HRMS calculated for C₁₄H₁₅ClNaO₃: m/z 293.0920
([M + Na]+), found: m/z 293.0919 ([M + Na]+).

1-(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-3-methylbenzene (3g)

Purification by flash chromatography (SiO2, Hexane/Et2O = 30/1) afforded 3g (19.5 mg, 0.0720 mmol, 72% yield): 1H NMR (500 MHz, CDCl3) δ 2.35 (3H, s), 3.28 (3H, s), 3.33 (3H, s), 3.36 (3H, s), 4.74 (1H, s), 5.18 (1H, d, J = 8.6 Hz), 6.22 (1H, d, J = 8.6 Hz), 7.09 (1H, d, J = 7.4 Hz), 7.17–7.25 (3H, m); 13C NMR (125 MHz, CDCl3) δ 21.4, 53.0, 53.2, 56.5, 79.5, 102.4, 123.6, 127.1, 128.4, 128.7, 130.6, 131.3, 138.2, 140.0; HRMS calculated for C14H19ClNaO3: m/z 293.0920 ([M + Na]+), found: m/z 293.0912 ([M + Na]+).

1-(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-2-methylbenzene (3h)

Purification by flash chromatography (SiO2, Hexane/Et2O = 30/1) afforded 3h (16.4 g, 0.0605 mmol, 61% yield): 1H NMR (400 MHz, CDCl3) δ 2.38 (3H, s), 3.29 (3H, s), 3.34 (3H, s), 3.36 (3H, s), 4.76 (1H, s), 5.36 (1H, d, J = 8.8 Hz), 6.20 (1H, d, J = 8.8 Hz), 7.13–7.23 (3H m), 7.42–7.44 (1H, m); 13C NMR (100 MHz, CDCl3) δ 19.4, 53.11, 53.13, 56.3, 76.6, 102.5, 126.2, 126.6, 127.7, 129.6, 130.5, 131.9, 135.9, 138.2; HRMS calculated for C14H19ClNaO3: m/z 293.0920 ([M + Na]+), found: m/z 293.0918 ([M + Na]+).

1-(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-naphthalene (3i)

Purification by flash chromatography (SiO2, Hexane/EtOAc = 30/1) afforded 3i (22.0 g, 0.0717 mmol, 72% yield): 1H NMR (400 MHz, CDCl3) δ 3.21 (3H, s), 3.30 (3H, s), 3.44 (3H, s), 4.75 (1H, s), 5.82 (1H,
d, $J = 8.7$ Hz), 6.39 (1H, d, $J = 8.7$ Hz), 7.45–7.54 (3H m), 7.64 (1H, d, $J = 7.1$ Hz), 7.80 (1H, d, $J = 8.2$ Hz), 7.86 (1H, d, $J = 7.6$ Hz), 8.20 (1H, d, $J = 8.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 52.9, 53.1, 56.6, 77.6, 102.3, 123.8, 124.8, 125.4, 125.7, 126.2, 128.6, 128.8, 130.0, 130.9, 132.2, 133.9, 135.8

**(2Z)-2,4-dichloro-6-phenyhex-2-enal (2j)**

Purification by flash chromatography (SiO$_2$, Hexane/Et$_2$O = 40/1) afforded 2j (6.6 mg, 0.0288 mmol, 29% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 3.20 (1H, dd, $J = 6.8$, 14.1 Hz), 3.28 (1H, ddd, $J = 7.1$, 14.1 Hz), 5.20 (1H, ddd, $J = 6.9$, 7.0, 9.5 Hz), 6.82 (1H, d, $J = 9.5$ Hz), 7.22–7.24 (2H, m), 7.28–7.35 (3H, m), 9.36 (1H, s); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 43.3, 55.6, 127.5, 128.7, 129.4, 135.22, 135.29, 146.6, 184.8

**(2Z)-2-chloro-6-phenyhex-2-enal (2j')**

Purification by flash chromatography (SiO$_2$, Hexane/Et$_2$O = 40/1) afforded 2j' (4.4 mg, 0.0226 mmol, 27% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 2.86–2.88 (4H, m, overlapping), 6.85–6.89 (1H, m), 7.21–7.24 (3H, m), 7.30–7.34 (2H, m) 9.33 (1H, s); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 30.9, 33.5, 126.6, 128.3, 128.7, 136.1, 139.9, 150.3, 185.6

**(2Z)-5-(benzyloxy)-2,4-dichloropent-2-enal (2k)**

Purification by flash chromatography (SiO$_2$, Hexane/Et$_2$O = 10/1) afforded 2k (6.1 mg, 0.0235 mmol, 24% yield): $^1$H NMR (400 MHz, CDCl$_3$) δ 3.78 (1H, dd, $J = 6.0$, 10.5 Hz), 3.83 (1H, dd, $J = 5.1$, 10.5 Hz)
Hz), 4.62 (2H, s), 5.12 (1H, ddd, $J = 5.3, 5.8, 9.4$ Hz), 6.88 (1H, d, $J = 9.4$ Hz), 7.30–7.39 (5H, m), 9.40 (1H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 53.0, 72.0, 73.6, 127.8, 128.1, 128.6, 136.5, 137.0, 144.7

(2Z)-5-(benzyloxy)-2,4-dichloropent-2-enal (2k’)

Purification by flash chromatography (SiO$_2$, Hexane/Et$_2$O = 10/1) afforded 2k’ (7.6 mg, 0.0338 mmol, 34% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.81 (1H, d, $J = 6.2$ Hz), 2.84 (1H, d, $J = 6.2$ Hz), 3.68 (2H, t, $J = 6.1$ Hz), 4.55 (2H, s), 7.00 (1H, t, $J = 6.9$ Hz), 7.30–7.38 (5H, m), 9.37 (1H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 30.2, 67.2, 73.1, 127.7, 127.9, 128.5, 136.5, 137.8, 148.7, 185.6

(2Z)-2,4-dichlorodec-2-enal (2l)

Purification by flash chromatography (SiO$_2$, Hexane/Et$_2$O = 60/1) afforded 2l (9.8 mg, 0.0439 mmol, 44% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.88–0.91 (3H, m), 1.31–1.36 (8H, m), 1.85–1.95 (2H, m), 4.97 (1H, ddd, $J = 6.6, 7.4, 9.5$ Hz), 6.81 (1H, d, $J = 9.5$ Hz), 9.41 (1H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 14.0, 22.5, 26.0, 28.6, 31.5, 37.2, 55.6, 134.7, 147.8, 185.1

(2Z)-2-chlorodec-2-enal (2l’)

Purification by flash chromatography (SiO$_2$, Hexane/Et$_2$O = 40/1) afforded 2l’ (4.2 mg, 0.0223 mmol, 22% yield): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.87–0.91 (3H, m), 1.29–1.34 (10H, m), 2.51 (1H, d, $J = 7.4$ Hz), 2.55 (1H, d, $J = 7.4$ Hz), 6.89 (1H, t, $J = 7.3$ Hz), 9.37 (1H, s); $^{13}$C NMR (100
MHz, CDCl₃) δ 14.0, 22.6, 27.6, 28.9, 29.2, 29.5, 31.7, 135.6, 152.1, 185.8; HRMS calculated for C₁₀H₁₈ClO: m/z 189.1046 ([M + H]⁺), found: m/z 189.1038 ([M + H]⁺).

(2Z)-2-chloro-4-ethoxy-4-phenylbut-2-en-1-ol (4a)

Purification by flash chromatography (SiO₂, Hexane/Et₂O = 3/1) afforded 4a (7.2 mg, 0.0317 mmol, 32% yield): ¹H NMR (400 MHz, CDCl₃) δ 1.23 (3H, t, J = 7.0 Hz), 3.44–3.58 (2H, m), 4.19 (2H, bs), 5.31 (1H, d, J = 8.5 Hz), 6.02 (1H, d, J = 8.5 Hz), 7.28–7.30 (1H, m), 7.33–7.41 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ 15.3, 64.1, 66.3, 77.8, 126.5, 127.6, 127.9, 128.6, 134.8, 140.6

methyl (2E,4Z)-4,6-dichloro-6-phenylhexa-2,4-dienoate (5a)

Purification by flash chromatography (SiO₂, Hexane/EtOAc = 3/1) afforded 5a (8.0 mg, 0.0295 mmol, 30% yield): ¹H NMR (500 MHz, CDCl₃) δ 3.76 (3H, s), 5.81 (1H, d, J = 8.0 Hz), 6.30 (1H, d, J = 15.0 Hz), 6.33 (1H, d, J = 8.0 Hz), 7.29 (1H, d, J = 15.0 Hz), 7.31–7.39 (3H, m), 7.42–7.44 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ 51.9, 71.2, 122.0, 126.1, 128.3, 128.8, 130.5, 139.5, 141.2, 141.5, 166.6
5. NMR spectra

[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]benzene (3a)
1-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-4-fluorobenzene (3b)

1H023-teru-#69 OMe introduction after CC p-fluoro
171023-tert-#69 OMe introduction after OC p-fluoro
1-chloro-4-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]benzene (3c)

1H and 13C NMR spectra are shown.
1-bromo-4-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]benzene (3d)
1-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-4-methylbenzene (3e)
1-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-3-methylbenzene (3g)

171130-teru-#91 OMe introduction after CC m-methyl
1-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]-2-methylbenzene (3h)
1-[(2Z)-3-chloro-1,4,4-trimethoxybut-2-en-1-yl]naphthalene (3i)

13C NMR check ishi-naphthal after CC 3rd-176

1H NMR check ishi-naphthal after CC 3rd-176

171005-tetu-#59 OMe introduction after CC 1-naphthyl
(2Z)-2,4-dichloro-6-phenylhex-2-enal (2j)

180603 check-ishi-PbCH2 up after CC 2nd-173,174
(2Z)-2-chloro-6-phenylhex-2-enal (2j')

180604 check-ishi-R ; PhCH2 down after CC 3rd-173,174

Bruker

[Graph with chemical shifts]

*171218-nnu-4102 add B chlorination after CC TLC down phenylmet* 20 1 "C:\Users\user\Desktop\Bruker, 2019\experiment\master\NMR data\benzyl.txt"

171218-nnu-4102 add B chlorination after CC TLC down phenylmet

[Graph with chemical shifts]
(2Z)-5-(benzyloxy)-2,4-dichloropent-2-enal (2k)

1H0517-ishi-chlorination R; BnOCH2 up-after CC=169,171
(2Z)-5-(benzyloxy)-2,4-dichloropent-2-enal (2k')

180524-ishi-chlorination R ; BnOCH2 down after CC 2nd-#169,171
(2Z)-2,4-dichlorodec-2-enal (2I)

1H NMR (CDCl₃, 400 MHz) 

Bruker spectrometer
(2Z)-2-chlorodec-2-enal (2l') Z/E = 9.4/1

1H0306-teru-#130 chlorination after CC n-Hex TLC down
(2Z)-2-chloro-4-ethoxy-4-phenylbut-2-en-1-ol (4a)

1H NMR (400 MHz, CDCl₃) δ (ppm): 7.50 (s, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 6.95 (t, J = 7.6 Hz, 1H), 4.00 (q, J = 7.1 Hz, 2H), 3.76 (t, J = 7.6 Hz, 2H), 3.69 (s, 2H), 2.39 (t, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H).
methyl (2E,4Z)-4,6-dichloro-6-phenylhexa-2,4-dienoate (5a) $Z/E = 20/1, 1/14$

1H0530-a-ari- wittig reCC up
6. HPLC data of 5a

Reaction with DL-proline (racemic sample)

Reaction with L-proline
7. Determination of stereochemistry of 3a

7-1. HSQC of 3a
7-2. DEPT of 3a
7-3. HMBC of 3a
7-3. COSY of 3a

7-3. NOESY of 3a
8. Determination of stereochemistry of 5a

8-1. COSY of 5a

8-2. NOESY of 5a