Supplementary Data

Asymmetric synthesis of t-butyl 3-alkyl-oxindole-3-carboxylates via chiral phosphoric acid catalyzed desymmetrization of di-t-butyl 2-alkyl-2-(2-aminophenyl)-malonates

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Contents

1. Additional experimental section  S2–S4
2. References  S5
3. 1H NMR and 13C NMR spectra of the compounds  S6–S25
4. Chiral HPLC spectra of the compounds  S26–S33
1. Additional Experimental Section

2-Fluoro-4-methoxy-1-nitrobenzene (S1)

To a solution of 2-fluoro-4-hydroxy-1-nitrobenzene (4.39 g, 27.9 mmol) in DMF 47 mL was added iodomethane (3.48 mL, 55.9 mmol) and K$_2$CO$_3$ (8.50 g, 61.5 mmol). The resultant mixture was stirred at 65 °C for 4 hours. The reaction mixture was diluted with water 100 mL and yellow precipitate was formed. The reaction mixture was filtered and washed with water. The precipitate was dried in vacuo at room temperature for 2 hours to give 4.20 g (88%) of 2-fluoro-4-methoxy-1-nitrobenzene (S1) as a pale yellow solid. mp 57–58 °C; IR (neat): 1597, 1493, 1331, 1277, 1242, 1196 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.11–8.01 (1H, m), 6.78–6.71 (2H, m), 3.90 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 165.3 (d, $J = 10.8$ Hz), 157.5 (d, $J = 263.4$ Hz), 130.8 (br), 127.9 (d, $J = 1.7$ Hz), 110.4 (d, $J = 3.3$ Hz), 103.2 (d, $J = 24.0$ H), 56.3; HRMS (ESI): m/z calcd. for C$_7$H$_7$FNO$_3$: 172.0404 [M+H]$^+$; found: 172.0406.

\[
\begin{align*}
\text{MeO} & \text{CO}_2\text{Bu} \\
\text{CO}_2\text{Bu} & \text{NO}_2
\end{align*}
\]

Di-tert-butyl 2-(2-nitrophenyl)malonate (8)

See typical procedure for malonate derivatives in experimental section.

Yield: 79%; as a pale yellow solid; mp 72–73 °C; IR (neat): 1732, 1523, 1346, 1303, 1238, 1134 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 8.09 (1H, d, $J = 8.0$ Hz), 7.79 (1H, t, $J = 8.0$ Hz), 7.63 (1H, t, $J = 8.0$ Hz), 7.50 (1H, d, $J = 8.0$ Hz), 5.09 (1H, s), 1.43 (18H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 165.8, 148.5, 133.8, 131.2, 129.4, 128.4, 125.0, 82.2, 56.3, 27.4; HRMS (ESI): m/z calcd. for C$_{17}$H$_{23}$NO$_6$Na: 360.1418 [M+Na]$^+$; found: 360.1416.

\[
\begin{align*}
\text{MeO} & \text{CO}_2\text{Bu} \\
\text{CO}_2\text{Bu} & \text{NO}_2
\end{align*}
\]

Di-tert-butyl 2-(5-methoxy-2-nitrophenyl)malonate (8c)

See typical procedure for malonate derivatives in experimental section.

Yield: 81%; as a colorless solid; mp 102–103 °C; IR (neat): 1721, 1578, 1512 1315, 1254, 1138 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 8.18 (1H, d, $J = 9.0$ Hz), 7.16 (1H, dd, $J = 9.0$, 2.9 Hz), 6.93 (1H, d, $J = 2.9$ Hz), 5.15 (1H, s), 3.89 (3H, s), 1.43 (18H, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 165.7, 162.9, 141.2, 131.5, 128.0, 116.7, 113.3, 82.1, 56.9, 56.1, 27.4; HRMS (ESI): m/z calcd. for C$_{18}$H$_{25}$NO$_7$Na: 390.1529 [M+Na]$^+$; found: 390.1528.
See typical procedure for malonate derivatives in experimental section.

Yield: 49%; as a colorless solid; mp 86–87 °C; IR (neat): 1717, 1528, 1335, 1258, 1157, 1138 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ: 8.23 (1H, dd, J = 8.8, 5.4 Hz), 7.51 (1H, ddd, J = 8.8, 7.6, 2.8 Hz), 7.32 (1H, dd, J = 9.6, 2.8 Hz), 5.19 (1H, s), 1.42 (18H, s); ¹³C NMR (100 MHz, DMSO-d₆) δ: 165.2, 163.7 (d, J = 254.1 Hz), 144.9 (d, J = 2.5 Hz), 132.1 (d, J = 9.9 Hz), 128.4 (d, J = 9.9 Hz), 118.4 (d, J = 25.7 Hz), 116.3 (d, J = 23.2 Hz), 82.4, 56.2, 27.4; HRMS (ESI): m/z calcd. for C₁₇H₂₃FNO₆Na: 378.1329 [M+Na]⁺; found: 378.1325.

See typical procedure for alkylation reaction of malonate derivatives in experimental section.

Yield: 73%; as a colorless solid; mp: 103–104 °C; IR (neat): 1736, 1528, 1358, 1142, 1111 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.97 (1H, dd, J = 8.0, 1.2 Hz), 7.55 (1H, td, J = 8.0, 1.2 Hz), 7.30 (1H, dd, J = 8.0, 1.2 Hz), 1.93 (3H, s), 1.44 (18H, s); ¹³C NMR (100 MHz, CDCl₃) δ: 168.6, 149.0, 135.5, 132.8, 129.3, 128.1, 125.7, 82.8, 61.1, 27.6, 23.7; HRMS (ESI): m/z calcd. for C₁₈H₂₅NO₆Na: 374.1580 [M+Na]⁺; found: 374.1578.

See typical procedure for alkylation reaction of malonate derivatives in experimental section.

Yield: 58%; as a yellow solid; mp: 102–103 °C; IR (neat): 1721, 1516, 1366, 1254, 1150, 1122 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ: 8.12 (1H, d, J = 9.0 Hz), 7.12 (1H, dd, J = 9.0, 2.7 Hz), 6.69 (1H, d, J = 2.7 Hz), 3.87 (3H, s), 1.80 (3H, s), 1.37 (18H, s); ¹³C NMR (100 MHz, DMSO-d₆) δ: 167.8, 162.6, 141.4, 137.3, 128.5, 115.2, 112.3, 82.1, 60.6, 56.0, 27.2, 23.5; HRMS (ESI): m/z calcd. for C₁₉H₂₇NO₇Na: 404.1685 [M+Na]⁺; found: 404.1671.

See typical procedure for alkylation reaction of malonate derivatives in experimental section.

Yield: 49%; as a yellow solid; mp: 102–103 °C; IR (neat): 1717, 1528, 1335, 1258, 1157, 1138 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ: 8.23 (1H, dd, J = 8.8, 5.4 Hz), 7.51 (1H, ddd, J = 8.8, 7.6, 2.8 Hz), 7.32 (1H, dd, J = 9.6, 2.8 Hz), 5.19 (1H, s), 1.42 (18H, s); ¹³C NMR (100 MHz, DMSO-d₆) δ: 165.2, 163.7 (d, J = 254.1 Hz), 144.9 (d, J = 2.5 Hz), 132.1 (d, J = 9.9 Hz), 128.4 (d, J = 9.9 Hz), 118.4 (d, J = 25.7 Hz), 116.3 (d, J = 23.2 Hz), 82.4, 56.2, 27.4; HRMS (ESI): m/z calcd. for C₁₇H₂₃FNO₆Na: 378.1329 [M+Na]⁺; found: 378.1325.

See typical procedure for alkylation reaction of malonate derivatives in experimental section.

Yield: 73%; as a colorless solid; mp: 103–104 °C; IR (neat): 1736, 1528, 1358, 1142, 1111 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.97 (1H, dd, J = 8.0, 1.2 Hz), 7.55 (1H, td, J = 8.0, 1.2 Hz), 7.30 (1H, dd, J = 8.0, 1.2 Hz), 1.93 (3H, s), 1.44 (18H, s); ¹³C NMR (100 MHz, CDCl₃) δ: 168.6, 149.0, 135.5, 132.8, 129.3, 128.1, 125.7, 82.8, 61.1, 27.6, 23.7; HRMS (ESI): m/z calcd. for C₁₈H₂₅NO₆Na: 374.1580 [M+Na]⁺; found: 374.1578.

See typical procedure for alkylation reaction of malonate derivatives in experimental section.

Yield: 58%; as a yellow solid; mp: 102–103 °C; IR (neat): 1721, 1516, 1366, 1254, 1150, 1122 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ: 8.12 (1H, d, J = 9.0 Hz), 7.12 (1H, dd, J = 9.0, 2.7 Hz), 6.69 (1H, d, J = 2.7 Hz), 3.87 (3H, s), 1.80 (3H, s), 1.37 (18H, s); ¹³C NMR (100 MHz, DMSO-d₆) δ: 167.8, 162.6, 141.4, 137.3, 128.5, 115.2, 112.3, 82.1, 60.6, 56.0, 27.2, 23.5; HRMS (ESI): m/z calcd. for C₁₉H₂₇NO₇Na: 404.1685 [M+Na]⁺; found: 404.1671.
See typical procedure for alkylation reaction of malonate derivatives in experimental section.

Yield: 97%; as a colorless solid; mp: 71–72 °C; IR (neat): 7.47 (1H, d, J = 9.0, 7.1, 2.7 Hz), 7.13 (1H, dd, J = 10.2, 2.7 Hz), 1.83 (3H, s), 1.36 (18H, s); 1H NMR (400 MHz, CDCl₃) δ: 8.18 (1H, dd, J = 9.0, 5.4 Hz), 7.47 (1H, d, J = 9.0, 7.1, 2.7 Hz), 7.13 (1H, dd, J = 10.2, 2.7 Hz), 1.83 (3H, s), 1.36 (18H, s); 13C NMR (100 MHz, CDCl₃) δ: 167.4, 163.7 (d, J = 251.9 Hz), 144.8 (d, J = 9.1 Hz), 128.8 (d, J = 10.7 Hz), 116.4 (d, J = 25.5 Hz), 115.6 (d, J = 23.1 Hz), 82.5, 60.0, 27.1, 23.4; HRMS (ESI): m/z calcd. for C₁₈H₂₄FNO₆Na: 392.1485 [M+Na]⁺; found: 392.1476.

Di-tert-butyl 2-ethyl-2-(2-nitrophenyl)malonate (9e)⁴

Di-tert-butyl 2-(2-nitrophenyl)malonate (8) (300 mg, 0.89 mmol) was dissolved in DMF 3 mL. NaH (55% mineral oil, 107 mg, 2.7 mmol) and iodoethane (140 μL, 1.8 mmol) were added to the reaction mixture. The resultant mixture was stirred at 70 °C for 30 min. The reaction mixture was diluted with water 80 mL and extracted with EtOAc/n-hexane = 2/1 (80 mL). The organic phase was washed with water, dried over Na₂SO₄, filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (n-hexane/EtOAc = 90/10 – 70/30) to give 316 mg (97%) of di-tert-butyl 2-ethyl-2-(2-nitrophenyl)malonate (9e) as a yellow oil. IR (neat): 7.47 (1H, d, J = 9.0, 7.1, 2.7 Hz), 7.13 (1H, dd, J = 10.2, 2.7 Hz), 1.83 (3H, s), 1.36 (18H, s); 1H NMR (400 MHz, CDCl₃) δ: 8.18 (1H, dd, J = 9.0, 5.4 Hz), 7.47 (1H, d, J = 9.0, 7.1, 2.7 Hz), 7.13 (1H, dd, J = 10.2, 2.7 Hz), 1.83 (3H, s), 1.36 (18H, s); 13C NMR (100 MHz, CDCl₃) δ: 167.4, 163.7 (d, J = 251.9 Hz), 144.8 (d, J = 9.1 Hz), 128.8 (d, J = 10.7 Hz), 116.4 (d, J = 25.5 Hz), 115.6 (d, J = 23.1 Hz), 82.5, 60.0, 27.1, 23.4; HRMS (ESI): m/z calcd. for C₁₉H₃₂NO₆Na: 388.1736 [M+Na]⁺; found: 388.1733.

Di-tert-butyl 2-(2-aminophenyl)-2-methylmalonate (2a)⁴

See typical procedure for catalytic hydrogenation in experimental section.

Yield: 81%; as a colorless solid; mp: 69–71 °C; IR (neat): 7.47 (1H, d, J = 9.0, 7.1, 2.7 Hz), 7.13 (1H, dd, J = 10.2, 2.7 Hz), 1.83 (3H, s), 1.36 (18H, s); 1H NMR (400 MHz, CDCl₃) δ: 8.18 (1H, dd, J = 9.0, 5.4 Hz), 7.47 (1H, d, J = 9.0, 7.1, 2.7 Hz), 7.13 (1H, dd, J = 10.2, 2.7 Hz), 1.83 (3H, s), 1.36 (18H, s); 13C NMR (100 MHz, CDCl₃) δ: 167.4, 163.7 (d, J = 251.9 Hz), 144.8 (d, J = 9.1 Hz), 128.8 (d, J = 10.7 Hz), 116.4 (d, J = 25.5 Hz), 115.6 (d, J = 23.1 Hz), 82.5, 60.0, 27.1, 23.4; HRMS (ESI): m/z calcd. for C₁₉H₂₅NO₄: 322.2018 [M+H]⁺; found: 322.2013.
2. References


3. ^1^H NMR and ^1^3^C NMR Spectra of The Compounds
(S)-t-Butyl 3-methyl-2-oxoindoline-3-carboxylate (1a)

\[
\text{Me} \quad \text{CO}_2\text{-Bu} \\
\text{N} \quad \text{O}
\]
(S)-t-Butyl 3,5-dimethyl-2-oxindoline-3-carboxylate (1b)
(S)-t-Butyl 5-methoxy-3-methyl-2-oxoindoline-3-carboxylate (1c)
(S)-t-Butyl 5-fluoro-3-methyl-2-oxoindoline-3-carboxylate (1d)
(S)-t-Butyl 3-ethyl-2-oxoindline-3-carboxylate (1e)
(S)-t-Butyl 2-oxo-3-propylindoline-3-carboxylate (1f)
(S)-t-Butyl 3-benzyl-2-oxoindoline-3-carboxylate (1g)
(S)-t-butyl 5-methoxy-2-oxo-3-propyliindoline-3-carboxylate (1h)
Di-t-butyl 2-(5-methyl-2-nitrophenyl)malonate (8b)
Di-t-butyl 2-methyl-2-(5-methyl-2-nitrophenyl)malonate (9b)
Di-t-butyl 2-(2-nitrophenyl)-2-(prop-2-en-1-yl)malonate (9f)
Di-t-butyl 2-benzyl-2-(2-nitrophenyl)malonate (9g)
Di-\textit{t}-butyl 2-(5-methoxy-2-nitrophenyl)-2-(prop-2-en-1-yl)malonate (9h)
Di-tert-butyl 2-(2-amino-5-methylphenyl)-2-methylmalonate (2b)
Di-\textit{t}-butyl 2-(2-amino-5-methoxyphenyl)-2-methylmalonate (2c)
Di-$t$-butyl 2-(2-amino-5-fluorophenyl)-2-methylmalonate (2d)
Di-t-butyl 2-ethyl-2-(2-aminophenyl)malonate (2e)
Di-t-butyl 2-(2-aminophenyl)-2-propylmalonate (2f)
Di-$t$-butyl 2-(2-aminophenyl)-2-benzylmalonate (2g)
Di-t-butyl 2-(2-amino-5-methoxyphenyl)-2-propylmalonate (2h)
4. Chiral HPLC Spectra of The Compounds

(S)-t-Butyl 3-methyl-2-oxoindoline-3-carboxylate (1a)

Racemic

Chiral

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(S)-t-Butyl 3,5-dimethyl-2-oxoindoline-3-carboxylate (1b)
(S)-t-Butyl 5-methoxy-3-methyl-2-oxoindoline-3-carboxylate (1c)

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(S)-t-Butyl 5-fluoro-3-methyl-2-oxoindoline-3-carboxylate (1d)

![Chemical Structure]

Racemic

![Chromatogram]

Chiral

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(S)-t-Butyl 3-ethyl-2-oxoindoline-3-carboxylate (1e)

Racemic

Chiral

Peak Report

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Peak Report

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2 | 9.202 | 4003428 | 132414 | 0.000 | 31.184
Total | | | | | 100.000
(S)-t-Butyl 2-oxo-3-propylindoline-3-carboxylate (1f)
(S)-t-Butyl 3-benzyl-2-oxoindoline-3-carboxylate (1 g)

Racemic

Chiral
(S)-Butyl 5-methoxy-2-oxo-3-propylindoline-3-carboxylate (1h)