Direct Asymmetric Reductive Amination of α-Keto Acetals: A Platform for Synthesizing Diverse α-Functionalized Amines

Yongjie Shi,a,b Jingxin Wang,a Feifan Yang,a Chenhan Wang,a Xumu Zhang,* a,d Pauline Chiu,b Qin Yin,* c,d

a Shenzhen Key Laboratory of Small Molecule Drug Discovery and Synthesis, Southern University of Science and Technology, Shenzhen 518055, China

b Department of Chemistry and State Key Laboratory of Synthetic Chemistry, The University of Hong Kong, Hong Kong, China

c Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China.

E-mail: qin.yin@siat.ac.cn

d Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China

Supporting Information

Contents

I. General Information ........................................................................................................... 2
II. General Procedure for the Synthesis of Substrates ............................................................ 3
III. General Procedures for Direct Asymmetric Reductive Amination of α-Keto Acetals .... 14
IV. Product Transformations ............................................................................................ 28
V. Proposed enantioinduction models .................................................................................. 36
VI. NMR spectra ................................................................................................................. 37
VII. HPLC spectra ............................................................................................................... 82
VIII. HRMS spectra ............................................................................................................. 105
IX. References ..................................................................................................................... 113
I. General Information

Unless otherwise mentioned, all experiments were carried out under an atmosphere of argon in a glovebox or using standard Schlenk techniques. Solvents were dried with standard procedures and degassed with N₂. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 300-400 mesh). NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz for ¹H NMR, 101 MHz for ¹³C NMR or 126 MHz for ¹³C NMR in CDCl₃ or CD₃OD with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in ppm and coupling constants are given in Hz. Chemical shifts were reported relative to TMS (0.00 ppm) for ¹H NMR and relative to CDCl₃ (77.16 ppm) or CD₃OD (49.00 ppm) for ¹³C NMR. Enantiomeric excesses were determined by chiral HPLC analysis on Agilent Technologies 1260 Infinity II instrument or UPLC analysis on Agilent Technologies 1290 Infinity II instrument using a chiral stationary phase in comparison with the authentic racemates. High resolution mass spectra (HRMS) were obtained on Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer at the Department of Chemistry, Southern University of Science and Technology. PE refers to petroleum ether, HEX refers to hexane, EA refers to ethyl acetate, TFE refers to 2,2,2-trifluoroethanol, and MTBE refers to methyl tert-butyl ether.
II. General Procedures for the Synthesis of Substrates

General Procedure:

To a suspension of arylglyoxal or its monohydrate\(^{[1]}\) (10.0 mmol) and PTS (\(p\)-toluenesulfonic acid, 0.1 equiv) in CH\(_2\)Cl\(_2\) (40 mL) at room temperature was added HC(OEt)\(_3\) (4.44 g, 30.0 mmol). The mixture was stirred for 2 h at 35 °C. The reaction was quenched by 30 mL saturated NaHCO\(_3\) solution and extracted by CH\(_2\)Cl\(_2\) (3 x 30 mL). The combined organic phase was dried over anhydrous Na\(_2\)SO\(_4\), filtered and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent: HEX/EA = 100/2) to afford desired keto acetals.

Characterization data of substrate

2,2-Diethoxy-1-phenylethan-1-one (1aa)

Substrate 1aa is commercially available. \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \(\delta\) 8.18 – 8.14 (m, 2H), 7.56 (t, \(J = 7.4\) Hz, 1H), 7.45 (t, \(J = 7.8\) Hz, 2H), 5.28 (s, 1H), 3.76 (dq, \(J = 9.6, 7.1\) Hz, 2H), 3.66 (dq, \(J = 9.6, 7.0\) Hz, 2H), 1.25 (t, \(J = 7.0\) Hz, 6H). \(^{13}\)C\(^{\{1\}}\) NMR (151 MHz, Chloroform-\(d\)) \(\delta\) 194.2, 133.9, 133.6, 129.8, 128.5, 102.5, 63.3, 15.3.
2,2-Dimethoxy-1-phenylethan-1-one (1ab)

Substrate 1ab was synthesized according to a reported procedure.\[1\]

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.15 – 8.08 (m, 2H), 7.58 (t, \(J = 7.4\) Hz, 1H), 7.46 (t, \(J = 7.7\) Hz, 2H), 5.23 (s, 1H), 3.48 (s, 6H). \(^{13}\)C\{\(^1\)H\} NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 193.5, 133.9, 133.8, 129.6, 128.6, 103.4, 54.7.

2,2-Diethoxy-1-(naphthalen-2-yl)ethan-1-one (1b)

Substrate 1b was synthesized according to General procedure. Light yellow oil, 5.0 mmol scale, 0.57 g, 2.2 mmol, 44% yield, \(R_f = 0.5\) (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02).

\(^1\)H NMR (600 MHz, Chloroform-\(d\)) \(\delta\) 8.78 (s, 1H), 8.15 (dd, \(J = 8.6, 1.7\) Hz, 1H), 7.99 (d, \(J = 8.1\) Hz, 1H), 7.90 – 7.85 (m, 2H), 7.62 – 7.58 (m, 1H), 7.56 – 7.52 (m, 1H), 5.41 (s, 1H), 3.81 (dq, \(J = 9.6, 7.1\) Hz, 2H), 3.71 (dq, \(J = 9.6, 7.0\) Hz, 2H), 1.27 (t, \(J = 7.1\) Hz, 6H). \(^{13}\)C\{\(^1\)H\} NMR (151 MHz, Chloroform-\(d\)) \(\delta\) 194.2, 136.0, 132.6, 132.2, 131.2, 130.1, 128.8, 128.2, 127.9, 126.7, 125.1, 102.7, 63.4, 15.4. The NMR data is consistent with that reported.\[2\]
2,2-Diethoxy-1-(o-tolyl)ethan-1-one (1c)

Substrate 1c was synthesized according to General procedure. Colorless oil, 10 mmol scale, 1.4 g, 6.3 mmol, 63% yield, \( R_f = 0.5 \) (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta \) 8.02 – 7.95 (m, 1H), 7.42 – 7.35 (m, 1H), 7.29 – 7.21 (m, 2H), 5.21 (s, 1H), 3.81 – 3.60 (m, 4H), 2.52 (s, 3H), 1.23 (t, \( J = 7.1 \) Hz, 6H). \(^{13}\)C \(^1\)H NMR (101 MHz, Chloroform-\(d\)) \( \delta \) 197.5, 139.9, 134.4, 132.0, 131.9, 130.2, 125.4, 102.5, 63.2, 21.5, 15.3. The NMR data is consistent with that reported.\(^3\)

\[
\text{Chemical Formula: } \text{C}_{13}\text{H}_{16}\text{O}_3 \\
\text{Exact Mass: } 222.1256
\]

2,2-Diethoxy-1-(m-tolyl)ethan-1-one (1d)

Substrate 1d was synthesized according to General procedure. Light yellow oil, 10 mmol scale, 1.34 g, 6.04 mmol, 60% yield, \( R_f = 0.5 \) (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \( \delta \) 8.04 – 7.91 (m, 2H), 7.40 – 7.31 (m, 2H), 5.30 (s, 1H), 3.75 (p, \( J = 7.4 \) Hz, 2H), 3.66 (p, \( J = 7.5 \) Hz, 2H), 2.41 (s, 3H), 1.25 (t, \( J = 7.0 \) Hz, 6H). \(^{13}\)C \(^1\)H NMR (151 MHz, Chloroform-\(d\)) \( \delta \) 194.3, 138.3, 134.4, 134.0, 130.2, 128.4, 127.1, 102.2, 63.2, 21.5, 15.4. The NMR data is consistent with that reported.\(^3\)

\[
\text{Chemical Formula: } \text{C}_{13}\text{H}_{16}\text{O}_3 \\
\text{Exact Mass: } 222.1256
\]

2,2-Diethoxy-1-(p-tolyl)ethan-1-one (1e)

Substrate 1e was synthesized according to General procedure. Colorless oil, 1.4 mmol scale, 0.24 g, 1.1 mmol, 76% yield, \( R_f = 0.5 \) (Hex/EA = 95/5), obtained by purification
with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.06 (d, \(J = 8.3\) Hz, 2H), 7.25 (d, \(J = 8.1\) Hz, 2H), 5.26 (s, 1H), 3.80 – 3.60 (m, 4H), 2.41 (s, 3H), 1.24 (t, \(J = 7.1\) Hz, 6H). \(^{13}\)C\(^{1}\)H NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 193.8, 144.5, 131.4, 130.0, 129.2, 102.5, 63.2, 21.9, 15.3. The NMR data is consistent with that reported.\(^{[2]}\)

1-(1,1'-Biphenyl)-4-yl)-2,2-diethoxyethan-1-one (1f)

Substrate 1f was synthesized according to General procedure. Colorless oil, 18.5 mmol scale, 4.10 g, 14.4 mmol, 78% yield, \(R_f = 0.5\) (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.25 (d, \(J = 8.5\) Hz, 2H), 7.70 – 7.60 (m, 4H), 7.51 – 7.43 (m, 2H), 7.43 – 7.37 (m, 1H), 5.29 (s, 1H), 3.79 (d q, \(J = 9.5, 7.1\) Hz, 2H), 3.68 (dq, \(J = 9.6, 7.0\) Hz, 2H), 1.27 (t, \(J = 7.1\) Hz, 6H). \(^{13}\)C\(^{1}\)H NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 193.8, 146.2, 140.1, 132.6, 130.5, 129.0, 128.4, 127.4, 127.1, 102.8, 63.40, 15.4. HRMS (ESI), m/z: [M+Na]\(^+\) Calcd for C\(_{18}\)H\(_{20}\)O\(_3\)Na\(^+\): 307.1305; Found: 307.1304.

2,2-Diethoxy-1-(3-methoxyphenyl)ethan-1-one (1g)

Substrate 1g was synthesized according to General procedure. Light yellow oil, 9.1 mmol scale, 1.94 g, 8.15 mmol, 90% yield, \(R_f = 0.5\) (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02).
1H NMR (600 MHz, Chloroform-d) δ 7.78 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.35-7.37 (t, J = 7.9 Hz, 1H), 7.12 (dd, J = 8.2, 2.0 Hz, 1H), 5.28 (s, 1H), 3.85 (s, 3H), 3.79 – 3.72 (m, 2H), 3.67 – 3.62 (m, 2H), 1.25 (t, J = 7.1 Hz, 6H). 13C{1H} NMR (151 MHz, Chloroform-d) δ 193.9, 159.7, 135.2, 129.5, 122.6, 120.3, 113.8, 102.3, 63.2, 55.5, 15.3.

The NMR data is consistent with that reported.[3]

2,2-Diethoxy-1-(4-methoxyphenyl)ethan-1-one (1h)

Substrate 1h was synthesized according to General procedure. Light yellow oil, 9.1 mmol scale, 1.99 g, 8.36 mmol, 92% yield, Rf = 0.5 (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02).

1H NMR (400 MHz, Chloroform-d) δ 8.16 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 5.23 (s, 1H), 3.87 (s, 3H), 3.75 (dq, J = 9.6, 7.1 Hz, 2H), 3.64 (dq, J = 9.6, 7.0 Hz, 2H), 1.24 (t, J = 7.0 Hz, 6H). 13C{1H} NMR (101 MHz, Chloroform-d) δ 192.8, 163.9, 132.3, 126.9, 113.7, 102.8, 63.2, 55.6, 15.3. The NMR data is consistent with that reported.[2]

1-(3,4-Dimethoxyphenyl)-2,2-diethoxyethan-1-one (1i)

Substrate 1i was synthesized according to General procedure. Light yellow oil, 5 mmol scale, 1.1 g, 4.1 mmol, 82% yield, Rf = 0.5 (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02).

1H NMR (600 MHz, Chloroform-d) δ 7.92 (dd, J = 8.5, 2.0 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 5.25 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.79 – 3.73
2,2-Diethoxy-1-(2-fluorophenyl)ethan-1-one (1j)

Substrate 1j was synthesized according to General procedure. Colorless oil, 15.5 mmol scale, 2.91 g, 12.9 mmol, 83% yield, $R_f = 0.5$ (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.93 – 7.84 (m, 1H), 7.57 – 7.48 (m, 1H), 7.26 – 7.20 (m, 1H), 7.16 – 7.09 (m, 1H), 5.39 (d, $J = 2.3$ Hz, 1H), 3.80 – 3.63 (m, 4H), 1.24 (t, $J = 7.1$ Hz, 6H). $^{13}$C{$^1$H} NMR (101 MHz, Chloroform-$d$) $\delta$ 193.5 (d, $J = 4.3$ Hz), 161.7 (d, $J = 255.4$ Hz), 134.8 (d, $J = 9.1$ Hz), 131.4 (d, $J = 2.9$ Hz), 124.5 (d, $J = 3.3$ Hz), 124.2 (d, $J = 13.7$ Hz), 116.5 (d, $J = 23.3$ Hz), 101.8 (d, $J = 5.8$ Hz), 63.2, 15.3. HRMS (ESI), m/z: [M+Na]$^+$ Calcd for C$_{12}$H$_{15}$FO$_3$Na$: 249.0897; Found: 249.0897.

2,2-Diethoxy-1-(4-fluorophenyl)ethan-1-one (1k)

Substrate 1k was synthesized according to General procedure. Light yellow oil, 3.8 mmol scale, 0.66 g, 2.9 mmol, 77% yield, $R_f = 0.5$ (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). $^1$H NMR (600 MHz, Chloroform-$d$) $\delta$ 8.22 (dd, $J = 8.7, 5.6$ Hz, 2H), 7.12 (t, $J = 8.6$ Hz, 2H), 5.18 (s, 1H), 3.82 – 3.74 (m, 2H), 3.69 – 3.60 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 6H), 3.69 – 3.63 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 6H), 3.69 – 3.63 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 6H). $^{13}$C{$^1$H} NMR (151 MHz, Chloroform-$d$) $\delta$ 192.8, 153.8, 148.9, 126.9, 125.0, 111.7, 110.1, 102.7, 63.3, 56.2, 56.1, 15.4. The NMR data is consistent with that reported.[2]
Hz, 6H). $^{13}$C{${}^1$H} NMR (151 MHz, Chloroform-$d$) δ 192.8, 166.1 (d, $J = 255.5$ Hz), 132.8 (d, $J = 9.3$ Hz), 130.1 (d, $J = 3.1$ Hz), 115.6 (d, $J = 21.7$ Hz), 103.3, 63.7, 15.3. The NMR data is consistent with that reported.[4]

![Chemical Structure of 1-(3,4-Difluorophenyl)-2,2-diethoxyethan-1-one (1l)]

Substrate 1l was synthesized according to General procedure. Colorless oil, 16.6 mmol scale, 2.55 g, 10.4 mmol, 63% yield, $R_f = 0.5$ (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). 

$^1$H NMR (600 MHz, Chloroform-$d$) δ 8.04 (ddd, $J = 11.1, 7.9, 2.1$ Hz, 1H), 8.01 – 7.96 (m, 1H), 7.23 (ddd, $J = 9.8, 8.6, 7.6$ Hz, 1H), 5.11 (s, 1H), 3.79 (dq, $J = 9.6, 7.1$ Hz, 2H), 3.63 (dq, $J = 9.6, 7.0$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 6H). $^{13}$C{${}^1$H} NMR (151 MHz, Chloroform-$d$) δ 191.9, 154.0 (dd, $J = 257.6, 13.0$ Hz), 150.2 (dd, $J = 249.6, 13.0$ Hz), 130.6 (t, $J = 4.3$ Hz), 127.3 (dd, $J = 7.4, 3.6$ Hz), 119.5 (d, $J = 19.2$ Hz), 117.4 (d, $J = 17.6$ Hz), 103.8, 64.0, 15.3. HRMS (ESI), m/z: [M+H]+ Calcd for C$_{12}$H$_{14}$F$_2$O$_3$Na+: 267.0803; Found: 267.0802.

![Chemical Structure of 1-(4-Chlorophenyl)-2,2-diethoxyethan-1-one (1m)]

Substrate 1m was synthesized according to General procedure. Colorless oil, 12 mmol scale, 1.68 g, 6.94 mmol, 58% yield, $R_f = 0.5$ (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). $^1$H NMR (600 MHz, Chloroform-$d$) δ 8.12 (d, $J = 8.7$ Hz, 2H), 7.42 (d, $J = 8.7$ Hz, 2H), 5.17 (s,
1H), 3.77 (dq, J = 9.5, 7.1 Hz, 2H), 3.64 (dq, J = 9.5, 7.0 Hz, 2H), 1.24 (t, J = 7.1 Hz, 6H). $^{13}$C{$_{^{1}H}$} NMR (151 MHz, Chloroform-$d$) $\delta$ 193.2, 140.0, 132.0, 131.5, 128.8, 103.3, 63.7, 15.3. The NMR data is consistent with that reported.[2]

1-(4-Bromophenyl)-2,2-diethoxyethan-1-one (1n)

Substrate 1n was synthesized according to General procedure. Colorless oil, 5 mmol scale, 1.20 g, 4.20 mmol, 84% yield, $R_f$ = 0.5 (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). $^1$H NMR (600 MHz, Chloroform-$d$) $\delta$ 8.04 (d, $J$ = 8.4 Hz, 2H), 7.59 (d, $J$ = 8.5 Hz, 2H), 5.17 (s, 1H), 3.77 (dq, $J$ = 9.4, 7.1 Hz, 2H), 3.64 (dq, $J$ = 9.4, 7.0 Hz, 2H), 1.24 (t, $J$ = 7.1 Hz, 6H). $^{13}$C{$_{^{1}H}$} NMR (151 MHz, Chloroform-$d$) $\delta$ 193.4, 132.4, 131.8, 131.5, 128.9, 103.2, 63.7, 15.3. The NMR data is consistent with that reported.[2]

Methyl 4-(2,2-diethoxyacetyl)benzoate (1o)

Substrate 1o was synthesized according to General procedure. Light yellow oil, 8.3 mmol scale, 1.34 g, 5.04 mmol, 61% yield, $R_f$ = 0.5 (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.22 (d, $J$ = 8.5 Hz, 2H), 8.10 (d, $J$ = 8.5 Hz, 2H), 5.23 (s, 1H), 3.95 (s, 3H), 3.78 (dq, $J$ = 9.5, 7.1 Hz, 2H), 3.66 (dq, $J$ = 9.6, 7.1 Hz, 2H), 1.25 (t, $J$ = 7.1 Hz, 6H). $^{13}$C{$_{^{1}H}$} NMR (101 MHz, Chloroform-$d$) $\delta$ 193.8, 166.4, 137.1,
134.1, 129.9, 129.6, 103.0, 63.7, 52.5, 15.3. The NMR data is consistent with that reported.\[^4\]

\[
\text{Chemical Formula: } C_{10}H_{14}O_3S
\]

\[
\text{Exact Mass: } 214.0664
\]

2,2-Diethoxy-1-(thiophen-2-yl)ethan-1-one (1p)

Substrate 1p was synthesized according to General procedure. Light yellow oil, 6.7 mmol scale, 0.97 g, 4.5 mmol, 68% yield, \( R_f = 0.6 \) (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta \) 8.07 (dd, \( J = 3.9, 1.2 \) Hz, 1H), 7.67 (dd, \( J = 4.9, 1.2 \) Hz, 1H), 7.14 (dd, \( J = 4.9, 3.8 \) Hz, 1H), 5.13 (s, 1H), 3.78 (dq, \( J = 9.5, 7.0 \) Hz, 2H), 3.67 (dq, \( J = 9.5, 7.0 \) Hz, 2H), 1.28 (t, \( J = 7.1 \) Hz, 6H). \(^13\)C\{\(^1\)H\} NMR (101 MHz, Chloroform-\(d\)) \( \delta \) 187.9, 139.8, 134.9, 134.7, 128.1, 102.4, 63.3, 15.3. HRMS (ESI), m/z: [M+Na]\(^+\) Calcd for C\(_{10}\)H\(_{14}\)O\(_3\)S\(_{Na}\): 237.0556; Found: 237.0555.

\[
\text{Chemical Formula: } C_7H_{12}O_5
\]

\[
\text{Exact Mass: } 176.0685
\]

Methyl 4,4-dimethoxy-3-oxobutanoate (1q)

Substrate 1q is commercially available. \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \( \delta \) 11.8 (s, 0.19 H), 5.44 (s, 0.18 H), 5.84 (s, 0.18 H), 4.58 (s, 1H), 3.77 (s, 0.55H), 3.74 (s, 3H), 3.60 (s, 2H), 3.43 (s, 6H), 3.38 (s, 1.17H). \(^13\)C NMR (151 MHz, Chloroform-\(d\)) \( \delta \) 198.2, 167.6, 103.7, 99.6, 90.6, 55.1, 53.5, 52.5, 51.6, 44.3.
1,1-Diethoxy-3-phenylpropan-2-one (1r)

Substrate 1r was synthesized according to a reported procedure.\[^5\]

$^1$H NMR (400 MHz, Chloroform-$d$) δ 7.35 – 7.18 (m, 6H), 4.63 (s, 1H), 3.89 (s, 2H), 3.70 (dq, $J = 9.5, 7.1$ Hz, 2H), 3.55 (dq, $J = 9.5, 7.1$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 6H).

The NMR data is consistent with that reported.\[^5\]

2,2-Dimethoxy-1,2-diphenylethan-1-one (1s)

Substrate 1s is commercially available. $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.09 – 8.01 (m, 2H), 7.64 – 7.59 (m, 2H), 7.46 – 7.40 (m, 1H), 7.37 – 7.27 (m, 5H), 3.22 (s, 6H).$^{13}$C{H$^1$} NMR (101 MHz, Chloroform-$d$) δ 195.3, 137.0, 134.4, 133.0, 130.1, 129.1, 128.7, 128.27, 127.1, 103.7, 50.2.

2,2-Diethoxy-1-(4-nitrophenyl)ethan-1-one (1t)

Substrate 1t was synthesized according to General procedure. Light yellow oil, 19.7 mmol scale, 1.04 g, 4.11 mmol, 22% yield, $R_f = 0.5$ (Hex/EA = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.02).

$^1$H NMR (400 MHz, Chloroform-$d$) δ 8.40 – 8.24 (m, 4H), 5.15 (s, 1H), 3.89 – 3.77 (m,
2H), 3.72 – 3.60 (m, 2H), 1.26 (t, $J = 7.0$ Hz, 6H). $^{13}$C{1H} NMR (101 MHz, Chloroform-$d$) δ 192.9, 150.5, 138.2, 131.2, 123.5, 104.0, 64.3, 15.3. The NMR data is consistent with that reported.[4]
III. General Procedures for Direct Asymmetric Reductive Amination of α-Keto Acetals

3.1 General Procedure for direct asymmetric reductive amination of α-keto acetals

The catalyst Ru(OAc)₂(L) was synthesized according to reported procedures.[6]

In a glovebox, Ru(OAc)₂(L) (0.002 mmol), substrate (0.2 mmol), ammonium salt (30.8 mg, 0.4 mmol) and TFE (1.0 ml) were successively added to a 5 mL vial equipped with a magnetic stirring bar. The mixture was then transferred to a stain-less autoclave and purged by three cycles of pressurization/venting with H₂. The required H₂ pressure (50 atm) was then installed, and the autoclave was placed in an oil bath preheated to 90 °C. The autoclave was cooled down to room temperature after 20 h and the pressure was slowly released in the hood. The reaction was quenched by saturated NaHCO₃ solution (2 mL) and extracted with DCM (3 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent: DCM/MeOH/Et₃N = 1/0.01/0.002) to afford desired products.

To facilitate the measurement of enantiomeric excess, the chiral primary amines obtained were all derived into their acylamides or benzylamides. Procedure: primary amine (0.2 mmol) was dissolved in dichloromethane (1 mL), followed by addition of triethylamine (80 μL) and acetic anhydride (40 μL) or BzCl (40 μL) at 0 °C. After stirred at room temperature for 2 h, saturated NaHCO₃ solution (1 mL) was added to quench the reaction. The organic phase was separated, dried, and evaporated under reduced pressure. The corresponding acetamides obtained were used for HPLC test to evaluate the ee value. For primary amine products 2ab, 2c, 2j and 2q, the yields and characterizations were determined after acetylation or benzylation due to difficulty of purification.
3.2 Determination of products’ absolute configuration

The absolute configuration of 2aa was established by converting it to a known amino alcohol. For the details, please see 4.4 Reduction to amino alcohol.

3.3 Evaluation of hydrogen pressure

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>P/bar</th>
<th>yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFE</td>
<td>50</td>
<td>87%</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>TFE</td>
<td>40</td>
<td>85%</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>TFE</td>
<td>30</td>
<td>88%</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>TFE</td>
<td>2</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Reaction conditions: 1 (0.1 mmol), Ru(OAc)$_2$(S)-L1b (0.001 mmol), NH$_4$OAc (0.2 mmol), TFE (0.5 mL), H$_2$, 90 °C, 20 h.

3.4 Characterization data of products

**Chemical Formula:** $C_{12}H_{19}NO_2$

**Exact Mass:** 209.1416

**(S)-2-Bromo-5,6-dihydro-[1,1'-biphenyl]-3(4H)-ol (2aa)**

Light yellow oil, 36.4 mg, 0.174 mmol, 87% yield (41.8 mg 1aa used), 97% ee, $[\alpha]_{27}^{27D} = +9.6$ (c=0.5, CHCl$_3$), R$_f$ = 0.3 (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et$_3$N = 1/0.01/0.002).
$^1$H NMR (600 MHz, Chloroform-$d$) $\delta$ 7.41 (d, $J$ = 7.3 Hz, 2H), 7.32 (t, $J$ = 7.5 Hz, 2H), 7.27 – 7.24 (m, 1H), 4.38 (d, $J$ = 6.1 Hz, 1H), 4.00 (d, $J$ = 6.1 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.58 – 3.52 (m, 1H), 3.52 – 3.45 (m, 1H), 3.26 – 3.18 (m, 1H), 1.22 (t, $J$ = 7.0 Hz, 3H), 1.02 (t, $J$ = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR (151 MHz, Chloroform-$d$) $\delta$ 141.6, 128.2, 127.9, 127.4, 107.1, 64.2, 63.9, 58.9, 15.4, 15.2. The ee value were determined after acylation. HPLC: Chiracel OD-3 Column (250 mm); detected at 210 nm; $n$-hexane / $i$-propanol = 90/10; flow = 0.8 mL/min; Retention time: 6.9 min (major), 8.5 min (minor). HRMS (ESI), m/z: [M+H]$^+$ Calcd for C$_{12}$H$_{20}$NO$_2$: 210.1489; Found: 210.1493.

(S)-2,2-Dimethoxy-1-phenylethan-1-amine (2ab)

Because of difficulty of purification, the yield and characterization of 2c is determined after acetylation to 2ab-Ac.

(S)-N-(2,2-Dimethoxy-1-phenylethyl)acetamide (2ab-Ac)

White solid, 40.6 mg, 0.182 mmol, 91% overall yield after acetylation (36.2 mg 1ab used), 94% ee, [$\alpha$]$^2$D = +38.6 (c=0.5, CHCl$_3$), $R_f$ = 0.4 (Hex/EA = 65/35), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.2).

$^1$H NMR (600 MHz, Chloroform-$d$) $\delta$ 7.34 – 7.30 (m, 4H), 7.28 – 7.24 (m, 1H), 6.44 – 6.27 (m, 1H), 5.18 (dd, $J$ = 8.4, 3.2 Hz, 1H), 4.42 (d, $J$ = 3.2 Hz, 1H), 3.43 (s, 3H), 3.37 (s, 3H), 2.03 (s, 3H). $^{13}$C{$^1$H} NMR (151 MHz, Chloroform-$d$) $\delta$ 169.8, 138.6, 128.5, 127.7, 127.5, 106.5, 56.2, 55.8, 54.7, 23.5. HPLC: Chiracel OD-H Column (250 mm);
detected at 210 nm; \(n\)-hexane / \(i\)-propanol = 95/5; flow = 0.8 mL/min; Retention time: 20.0 min (major), 25.1 min (minor). HRMS (ESI), m/z: \([M+Na]^+\) Calcd for \(C_{12}H_{17}NO_3Na^+\): 246.1101; Found: 246.1100.

\[
\text{Chemical Formula: } C_{12}H_{17}NO_3
\]

Exact Mass: 246.1101

\((S)-2,2\text{-Diethoxy-1-(naphthalen-2-yl)ethan-1-amine (2b)}\)

Light yellow oil, 47.1 mg, 0.182 mmol, 91% yield (51.8 mg 1b used), 98% ee, \([\alpha]^{24D} = +7.6\ (c=0.5, \text{CHCl}_3)\), \(R_f = 0.3\ (\text{DCM}/\text{MeOH} = 95/5)\), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et_3N = 1/0.01/0.002). \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \(\delta 7.89 – 7.87\ (m, 1H), 7.84 – 7.81\ (m, 2H), 7.80\ (d, \(J = 8.7\ Hz, 1H\)), 7.56\ (dd, \(J = 8.4, 1.7\ Hz, 1H\)), 7.47 – 7.43 (m, 2H), 4.48 (d, \(J = 6.2\ Hz, 1H\)), 4.18 (d, \(J = 6.1\ Hz, 1H\)), 3.84 – 3.73 (m, 1H), 3.59 – 3.48 (m, 2H), 3.26 – 3.18 (m, 1H), 1.23 (t, \(J = 7.0\ Hz, 3H\)), 1.00 (t, \(J = 7.0\ Hz, 3H\)). \(^{13}\)C\({}^{1\text{H}}\) NMR (151 MHz, Chloroform-\(d\)) \(\delta 139.2, 133.4, 133.1, 128.1, 127.8, 127.7, 126.7, 126.3, 126.0, 125.8, 107.1, 64.3, 64.0, 59.0, 15.5, 15.3\). The ee value were determined after acylation. HPLC: Chiracel ODH Column (250 mm); detected at 210 nm; \(n\)-hexane / \(i\)-propanol = 95/5; flow = 0.8 mL/min; Retention time: 16.8 min (minor), 25.8 min (major). HRMS (ESI), m/z: \([M+Na]^+\) Calcd for \(C_{16}H_{22}NO_2^+\): 260.1645; Found: 260.1644.

\[
\text{Chemical Formula: } C_{16}H_{22}NO_2
\]

Exact Mass: 260.1644

\((S)-2,2\text{-Diethoxy-1-(o-tolyl)ethan-1-amine (2c)}\)

Because of difficulty of purification, the yield and characterization of 2c is determined after acetylation to 2c-Ac.
**(S)-N-(2,2-Diethoxy-1-(o-tolyl)ethyl)acetamide (2c-Ac)**

White solid, 27.0 mg, 0.102 mmol, 52% overall yield after acetylation (44.4 mg 1c used), 78 % ee, \( [\alpha]^{27}_{D} = +6.1 \) (c=0.5, CHCl3), \( R_f = 0.3 \) (Hex/EA = 65/35), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.2).

\(^1\)H NMR (600 MHz, Chloroform-\(d\)) \( \delta 7.34 – 7.27 \) (m, 1H), \( 7.23 – 7.11 \) (m, 3H), 6.39 (d, \( J = 8.1 \) Hz, 1H), 5.39 (dd, \( J = 8.1, 2.7 \) Hz, 1H), 4.47 (d, \( J = 2.8 \) Hz, 1H), 3.73 (dq, \( J = 9.0, 7.1 \) Hz, 1H), 3.66 (dq, \( J = 8.8, 7.1 \) Hz, 1H), 3.58 (dq, \( J = 9.0, 7.1 \) Hz, 1H), 3.37 (dq, \( J = 9.2, 7.1 \) Hz, 1H), 2.45 (s, 3H), 2.02 (s, 3H), 1.21 (t, \( J = 7.0 \) Hz, 3H), 1.14 (t, \( J = 7.1 \) Hz, 3H). \(^{13}\)C{H\(^1\)} NMR (151 MHz, Chloroform-\(d\)) \( \delta 169.6, 137.4, 136.1, 130.4, 127.4, 126.9, 126.0, 103.6, 64.5, 63.7, 51.6, 23.6, 19.7, 15.3, 15.2. HPLC: Chiracel OD-3 Column (250 mm); detected at 210 nm; n-hexane / i-propanol = 95/5; flow = 0.8 mL/min; Retention time: 9.4 min (major), 10.9 min (minor). HRMS (ESI), m/z: [M+Na]\(^+\) Calcd for C\(_{15}\)H\(_{23}\)NO\(_3\)Na\(^+\): 288.1570; Found: 288.1568.

**Chemical Formula**: C\(_{15}\)H\(_{23}\)NO\(_3\)

**Exact Mass**: 265.1678

---

**Chemical Formula**: C\(_{13}\)H\(_{15}\)NO\(_2\)

**Exact Mass**: 223.1572

**Light yellow oil, 27.1 mg, 0.122 mmol, 61% yield (44.5 mg 1d used), >99% ee, [\(\alpha\)]\(^{22}\)\(D\) = +6.4 (c=0.5, CHCl3), \( R_f = 0.3 \) (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et\(_3\)N = 1/0.01/0.002).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta 7.25 – 7.17 \) (m, 3H), \( 7.10 – 7.04 \) (m, 1H), 4.39 (d, \( J = 6.1 \) Hz, 1H), 3.96 (d, \( J = 6.1 \) Hz, 1H), 3.84 – 3.71 (m, 1H), 3.61 – 3.44 (m, 2H),
3.29 – 3.18 (m, 1H), 2.35 (s, 3H), 1.22 (t, $J = 7.0$ Hz, 3H), 1.03 (t, $J = 7.0$ Hz, 3H).

$^{13}$C$\{^{1}$H$\}$ NMR (101 MHz, Chloroform-$d$) $\delta$ 141.5, 137.8, 128.6, 128.2, 128.1, 125.0, 107.1, 64.1, 63.9, 58.8, 21.6, 15.4, 15.2. The ee value were determined after acylation.

HPLC: Chiracel ODH Column (250 mm); detected at 210 nm; $n$-hexane / $i$-propanol = 95/5; flow = 0.8 mL/min; Retention time: 9.8 min (minor), 11.5 min (major). HRMS (ESI), m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{22}$NO$_2$: 224.1645; Found: 224.1643.

\[
\text{Chemical Formula: C}_{13}\text{H}_{22}\text{NO}_2 \\
\text{Exact Mass: 223.1572}
\]

(S)-2,2-Diethoxy-1-(p-tolyl)ethan-1-amine (2e)

Light yellow oil, 34.3 mg, 0.154 mmol, 77% yield (44.6 mg 1e used), 97 % ee, $[\alpha]_D^{21} = +11.8$ (c=0.5, CHCl$_3$), $R_f$ = 0.3 (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et$_3$N = 1/0.01/0.002).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.28 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 7.9$ Hz, 2H), 4.37 (d, $J = 6.1$ Hz, 1H), 3.96 (d, $J = 6.1$ Hz, 1H), 3.81 – 3.71 (m, 1H), 3.59 – 3.44 (m, 2H), 3.28 – 3.18 (m, 1H), 2.33 (s, 3H), 1.22 (t, $J = 7.0$ Hz, 3H), 1.03 (t, $J = 7.0$ Hz, 3H).

$^{13}$C$\{^{1}$H$\}$ NMR (101 MHz, Chloroform-$d$) $\delta$ 138.5, 137.0, 128.9, 127.7, 128.6, 123.7, 107.1, 64.1, 63.9, 58.6, 21.2, 15.4, 15.3. The ee value were determined after acylation. HPLC: Chiracel OD-3 Column (250 mm); detected at 210 nm; $n$-hexane / $i$-propanol = 95/5; flow = 1.0 mL/min; Retention time: 8.9 min (major), 10.6 min (minor). HRMS (ESI), m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{22}$NO$_2$: 224.1645; Found: 224.1642.

\[
\text{Chemical Formula: C}_{13}\text{H}_{22}\text{NO}_2 \\
\text{Exact Mass: 285.1729}
\]

(S)-1-([1,1'-Biphenyl]-4-yl)-2,2-diethoxyethan-1-amine (2f)
Light yellow oil, 49.6 mg, 0.174 mmol, 87% yield (57.0 mg 1f used), 94% ee, \([\alpha]^{25}_D = +21.3\) (c=0.5, CHCl3), \(R_f = 0.3\) (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et3N = 1/0.01/0.002).

\(^1\)H NMR (600 MHz, Chloroform-d) \(\delta 7.59\) (d, \(J = 8.0\) Hz, 2H), 7.56 (d, \(J = 7.9\) Hz, 2H), 7.48 (d, \(J = 7.9\) Hz, 2H), 7.42 (t, \(J = 7.5\) Hz, 2H), 7.33 (t, \(J = 7.1\) Hz, 1H), 4.45 (d, \(J = 6.0\) Hz, 1H), 4.05 (d, \(J = 6.0\) Hz, 1H), 3.83 – 3.74 (m, 1H), 3.63 – 3.48 (m, 2H), 3.33 – 3.23 (m, 1H), 1.23 (t, \(J = 7.0\) Hz, 3H), 1.05 (t, \(J = 7.0\) Hz, 3H). \(^{13}\)C\({}^{1}\)H NMR (151 MHz, Chloroform-d) \(\delta 141.0, 140.4, 140.3, 128.9, 128.3, 127.3, 127.1, 127.0, 106.8, 64.2, 64.0, 58.5, 15.4, 15.3\). The ee value were determined after acylation. HPLC: Chiracel OD-3 Column (250 mm); detected at 210 nm; n-hexane / i-propanol = 95/5; flow = 1.0 mL/min; Retention time: 11.4 min (major), 12.8 min (minor). HRMS (ESI), m/z: [M+H]+ Calcd for C\(_{18}\)H\(_{24}\)NO\(_2\): 286.1802; Found: 286.1806.

(\(S\))-2,2-Diethoxy-1-(3-methoxyphenyl)ethan-1-amine (2g)

Light yellow oil, 42.6 mg, 0.178 mmol, 89% yield (47.8 mg 1g used), 95% ee, \([\alpha]^{25}_D = +5.1\) (c=0.5, CHCl3), \(R_f = 0.3\) (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et3N = 1/0.01/0.002).

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta 7.23\) (t, \(J = 8.1\) Hz, 1H), 7.02 – 6.96 (m, 2H), 6.84 – 6.79 (m, 1H), 4.38 (d, \(J = 6.0\) Hz, 1H), 3.98 (d, \(J = 6.1\) Hz, 1H), 3.83 – 3.72 (m, 4H), 3.61 – 3.44 (m, 2H), 3.29 – 3.19 (m, 1H), 1.22 (t, \(J = 7.1\) Hz, 3H), 1.04 (t, \(J = 7.0\) Hz, 3H). \(^{13}\)C\({}^{1}\)H NMR (101 MHz, Chloroform-d) \(\delta 159.6, 143.3, 129.2, 120.3, 113.3, 113.1, 107.0, 64.3, 64.0, 58.9, 55.3, 15.4, 15.3\). The ee value were determined after acylation. HPLC: Chiracel AD-3 Column (250 mm); detected at 210 nm; n-hexane / i-propanol = 95/5; flow = 0.8 mL/min; Retention time: 16.2 min (minor), 20.2 min.
(S)-2,2-Diethoxy-1-(4-methoxyphenyl)ethan-1-amine (2h)

Light yellow oil, 34.9 mg, 0.146 mmol, 73% yield (47.8 mg 1h used), 92% ee, $[\alpha]^{22}_{D} = +12.0$ (c=0.5, CH$_2$Cl$_2$), $R_f = 0.3$ (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et$_3$N = 1/0.01/0.002).

$^1$H NMR (600 MHz, Chloroform-d) $\delta$ 7.32 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 4.34 (d, $J = 6.2$ Hz, 1H), 3.95 (d, $J = 6.1$ Hz, 1H), 3.80 (s, 3H), 3.78 – 3.73 (m, 1H), 3.58 – 3.44 (m, 2H), 3.27 – 3.18 (m, 1H), 1.22 (t, $J = 7.0$ Hz, 3H), 1.03 (t, $J = 7.0$ Hz, 3H). $^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) $\delta$ 158.9, 133.7, 128.9, 113.6, 107.2, 64.2, 63.9, 58.2, 55.3, 15.4, 15.3. The ee value were determined after acylation. HPLC: Chiral ODH Column (250 mm); detected at 210 nm; $n$-hexane / $i$-propanol = 95/5; flow = 0.8 mL/min; Retention time: 9.6 min (major). HRMS (ESI), m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{22}$NO$_3^+$: 240.1594; Found: 240.1590.

(S)-1-(3,4-Dimethoxyphenyl)-2,2-diethoxyethan-1-amine (2i)

Light yellow oil, 42.0 mg, 0.156 mmol, 78% yield (53.8 mg 1i used), 85% ee, $[\alpha]^{23}_{D} = +4.3$ (c=0.5, CHCl$_3$), $R_f = 0.3$ (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et$_3$N = 1/0.01/0.002). $^1$H NMR (600 MHz, Chloroform-d) $\delta$ 7.00 (d, $J = 1.9$ Hz, 1H), 6.95 (dd, $J = 8.2$, 1.9 Hz, 1H), 4.33 (d, $J = 6.1$ Hz, 1H), 3.93 (d, $J = 6.1$ Hz, 1H), 3.80 (s, 3H), 3.78 – 3.73 (m, 1H), 3.58 – 3.44 (m, 2H), 3.27 – 3.18 (m, 1H), 1.23 (t, $J = 7.0$ Hz, 3H), 1.03 (t, $J = 7.0$ Hz, 3H). $^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) $\delta$ 158.9, 133.7, 128.9, 113.6, 107.2, 64.2, 63.9, 58.2, 55.3, 15.4, 15.3. The ee value were determined after acylation. HPLC: Chiral ODH Column (250 mm); detected at 210 nm; $n$-hexane / $i$-propanol = 95/5; flow = 0.8 mL/min; Retention time: 9.6 min (major). HRMS (ESI), m/z: [M+H]$^+$ Calcd for C$_{14}$H$_{23}$NO$_4^+$: 269.1627; Found: 269.1627.
1H), 6.83 (d, \( J = 8.2 \) Hz, 1H), 4.35 (d, \( J = 6.2 \) Hz, 1H), 3.95 (d, \( J = 6.2 \) Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.80 – 3.74 (m, 1H), 3.57 – 3.46 (m, 2H), 3.26 – 3.17 (m, 1H), 1.23 (t, \( J = 7.1 \) Hz, 3H), 1.04 (t, \( J = 7.0 \) Hz, 3H). \(^{13}\)C\{\(^1\)H\} NMR (151 MHz, Chloroform-d) \( \delta \) 148.8, 148.4, 134.0, 120.0, 111.0, 110.9, 107.1, 64.4, 64.3, 63.9, 58.6, 56.0, 15.4, 15.3. The ee value were determined after acylation. HPLC: Chiracel OJ-3 Column (250 mm); detected at 210 nm; \( n \)-hexane / \( i \)-propanol = 90/10; flow = 0.8 mL/min; Retention time: 10.6 min (minor), 13.9 min (major). HRMS (ESI), m/z: [M+H]+ Calcd for C\(_{14}\)H\(_{24}\)NO\(_4\)+: 270.1700; Found: 270.1969.

![Chemical Structure](image)

**Chemical Formula:** C\(_{12}\)H\(_{19}\)FNO\(_2\)

**Exact Mass:** 227.1322

**(S)-2,2-Diethoxy-1-(2-fluorophenyl)ethan-1-amine (2j)**

Because of difficulty of purification, the yield and characterization of 2j is determined after acetylation to 2j-Ac.

![Chemical Structure](image)

**Chemical Formula:** C\(_{14}\)H\(_{20}\)FNO\(_3\)

**Exact Mass:** 269.1427

**(S)-N-(2,2-Diethoxy-1-(2-fluorophenyl)ethyl)acetamide (2j-Ac)**

Light yellow oil, 41.2 mg, 0.153 mmol, 77% overall yield after acetylation (45.3 mg 1j used), 99% ee, \([\alpha]\)\(^{27}\)_D = +9.6 (c=0.5, CHCl\(_3\)), \( R_f \) = 0.2 (Hex/EA = 1/0.2), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 80/20). \(^1\)H NMR (600 MHz, Chloroform-d) \( \delta \) 7.30-7.28 (td, \( J = 7.6, 1.7 \) Hz, 1H), 7.26 – 7.21 (m, 1H), 7.13 – 7.07 (m, 1H), 7.06 – 6.98 (m, 1H), 6.39 (d, 1H), 5.46 (dd, \( J = 8.4, 2.9 \) Hz, 1H), 4.59 (d, \( J = 3.0 \) Hz, 1H), 3.74 – 3.64 (m, 2H), 3.64 – 3.57 (m, 1H), 3.42 – 3.35 (m, 1H), 2.06 (s, 3H), 1.21 (t, \( J = 7.0 \) Hz, 3H), 1.09 (t, \( J = 7.1 \) Hz, 3H). \(^{13}\)C\{\(^1\)H\} NMR
(151 MHz, Chloroform-\(d\)) \(\delta\) 169.8, 160.6 (d, \(J = 245.6\) Hz), 129.1, 129.1 (d, \(J = 3.4\) Hz), 125.8 (d, \(J = 13.4\) Hz), 124.1 (d, \(J = 3.6\) Hz), 115.4 (d, \(J = 21.9\) Hz), 102.8 (d, \(J = 1.8\) Hz), 64.2, 63.7, 50.4, 23.5, 15.2, 15.1. HPLC: Chiracel OD-3 Column (250 mm); detected at 210 nm; \(n\)-hexane / \(i\)-propanol = 95/5; flow = 0.8 mL/min; Retention time: 10.3 min (minor), 10.6 min (major). HRMS (ESI), \(m/z: \ [M+Na]^+ \) Calcd for \(C_{14}H_{20}FNO_3Na^+: 292.1319\); Found: 292.1318.

\[ \text{Chemical Formula: } C_{12}H_{19}FNO_2 \]
\[ \text{Exact Mass: 227.1322} \]

(S)-2,2-Diethoxy-1-(4-fluorophenyl)ethan-1-amine (2k)

Light yellow oil, 28.6 mg, 0.126 mmol, 63% yield (45.4 mg 1k used), 98% ee, \([\alpha]^{23}_{D} = +7.0\) (c=0.5, CHCl_3), \(R_f = 0.3\) (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et_3N = 1/0.01/0.002). \(^1H\) NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.42 – 7.35 (m, 2H), 7.03 – 6.98 (m, 2H), 4.34 (d, \(J = 6.1\) Hz, 1H), 3.99 (d, \(J = 6.1\) Hz, 1H), 3.81 – 3.70 (m, 1H), 3.62 – 3.44 (m, 2H), 3.28 – 3.16 (m, 1H), 1.22 (t, \(J = 7.0\) Hz, 3H), 1.03 (t, \(J = 7.0\) Hz, 3H). \(^{13}C\)\(^{1H}\) NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 162.3 (d, \(J = 245.0\) Hz), 137.2 (d, \(J = 3.0\) Hz), 129.4 (d, \(J = 7.9\) Hz), 115.0 (d, \(J = 21.2\) Hz), 107.0, 64.4, 64.0, 58.2, 15.4, 15.2. The ee value were determined after acylation. HPLC: Chiracel AD-3 Column (250 mm); detected at 210 nm; \(n\)-hexane / \(i\)-propanol = 95/5; flow = 0.8 mL/min; Retention time: 14.4 min (minor), 16.3 min (major). HRMS (ESI), \(m/z: \ [M+H]^+ \) Calcd for \(C_{12}H_{19}FNO_2^+: 228.1394\); Found: 228.1392.

\[ \text{Chemical Formula: } C_{12}H_{17}F_2NO_2 \]
\[ \text{Exact Mass: 245.1227} \]
(S)-1-(3,4-Difluorophenyl)-2,2-diethoxyethan-1-amine (2l)

Light yellow oil, 29.9 mg, 0.122 mmol, 61% yield (49.0 mg 1l used), 98% ee, \([\alpha]^{25}_D = +3.2\) (c=0.5, CHCl3), \(R_f = 0.3\) (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et3N = 1/0.01/0.002). \(^1\)H NMR (600 MHz, Chloroform-d) \(\delta\) 7.31 (ddd, \(J = 11.5, 7.7, 2.1\) Hz, 1H), 7.17 – 7.14 (m, 1H), 7.13 – 7.07 (m, 1H), 4.40 (d, \(J = 5.9\) Hz, 1H), 4.01 (d, \(J = 5.9\) Hz, 1H), 3.79 – 3.72 (m, 1H), 3.64 – 3.57 (m, 1H), 3.52 (dq, \(J = 9.3\), 7.0 Hz, 1H), 3.33 – 3.25 (m, 1H), 1.22 (t, \(J = 7.0\) Hz, 3H), 1.06 (t, \(J = 7.0\) Hz, 3H). \(^1^3\)C\{\(^1\)H\} NMR (151 MHz, Chloroform-d) \(\delta\) 150.2 (dd, \(J = 247.6, 13.8\) Hz), 149.9 (dd, \(J = 247.6\) 12.8 Hz)137.2, 124.2 (dd, \(J = 6.2, 3.5\) Hz), 117.0 (d, \(J = 10.7\)), 116.9 (d, \(J = 9.9\)), 105.8, 64.6, 64.2, 57.9, 15.4, 15.2. The ee value were determined after acylation. HPLC: Chiracel OD-3 Column (250 mm); detected at 210 nm; \(n\)-hexane / \(i\)-propanol = 95/5; flow = 0.8 mL/min; Retention time: 10.1 min (minor), 10.7 min (major). HRMS (ESI), m/z: [M+H]\(^+\) Calcd for C\(_{12}\)H\(_{18}\)F\(_2\)NO\(_2\): 246.1300; Found: 246.1296.

\(\text{Chemical Formula: } \text{C}_{12}\text{H}_{18}\text{F}_2\text{NO}_2\)  
\text{Exact Mass: 243.1026}

(S)-1-(4-Chlorophenyl)-2,2-diethoxyethan-1-amine (2m)

Light yellow oil, 39.8 mg, 0.164 mmol, 79% yield (50.2 mg 1m used), >99% ee, \([\alpha]^{26}_D = +8.2\) (c=0.5, CHCl3), \(R_f = 0.3\) (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et3N = 1/0.01/0.002). \(^1\)H NMR (600 MHz, Chloroform-d) \(\delta\) 7.36 (d, \(J = 8.4\) Hz, 2H), 7.29 (d, \(J = 8.5\) Hz, 2H), 4.37 (d, \(J = 6.0\) Hz, 1H), 4.00 (d, \(J = 6.0\) Hz, 1H), 3.79 – 3.73 (m, 1H), 3.60 – 3.54 (m, 1H), 3.53 – 3.47 (m, 1H), 3.28 – 3.22 (m, 1H), 1.21 (t, \(J = 7.0\) Hz, 3H), 1.04 (t, \(J = 7.0\) Hz, 3H). \(^1^3\)C\{\(^1\)H\} NMR (151 MHz, Chloroform-d) \(\delta\) 139.6, 133.3, 129.4, 128.4, 106.5, 64.5, 64.1, 58.3, 15.4, 15.2. The ee value were determined after acylation. HPLC: Chiracel OJ-3 Column (250 mm); detected at 210 nm; \(n\)-hexane / \(i\)-propanol = 95/5;
flow = 0.8 mL/min; Retention time: 15.7 min (major). HRMS (ESI), m/z: [M+H]+
Calcd for C_{12}H_{19}ClNO_{2}+: 244.1099; Found: 244.1096.

(5)-1-(4-Bromophenyl)-2,2-diethoxyethan-1-amine (2n)
Light yellow oil, 43.2 mg, 0.150 mmol, 74% yield (58.4 mg 1n used), 95% ee, [α]^{21}_{D} =
+9.4 (c=0.5, CHCl_{3}), R_f = 0.3 (DCM/MeOH = 95/5), obtained by purification with flash
column chromatography on silica gel (eluent: DCM/MeOH/Et_{3}N = 1/0.01/0.002). 1H
NMR (400 MHz, Chloroform-\(d\)) δ 7.57 (d, \(J = 8.5\) Hz, 2H), 7.42 (d, \(J = 8.4\) Hz, 2H),
4.46 (d, \(J = 6.0\) Hz, 1H), 4.09 (d, \(J = 6.1\) Hz, 1H), 3.93 – 3.84 (m, 1H), 3.74 – 3.57 (m,
2H), 3.41 – 3.31 (m, 1H), 1.34 (t, \(J = 7.0\) Hz, 3H), 1.17 (t, \(J = 7.0\) Hz, 3H). 13C{1H}
NMR (101 MHz, Chloroform-\(d\)) δ 140.7, 131.3, 129.7, 121.3, 106.8, 64.4, 64.0, 58.4,
15.4, 15.2. The ee value were determined after acylation. HPLC: Chiracel AD-3
Column (250 mm); detected at 210 nm; \(n\)-hexane / \(i\)-propanol = 95/5; flow = 0.8
mL/min; Retention time: 14.8 min (minor), 16.7 min (major). HRMS (ESI), m/z:
[M+H]^+ Calcd for C_{12}H_{19}BrNO_{2}+: 288.0594; Found: 288.0598.

(5)-Methyl-4-(1-amino-2,2-diethoxyethyl)benzoate (2o)
Light yellow oil, 37.4 mg, 0.140 mmol, 70% yield (53.4 mg 1o used), 96% ee, [α]^{22}_{D} =
+2.6 (c=0.5, CHCl_{3}), R_f = 0.3 (DCM/MeOH = 95/5), obtained by purification with flash
column chromatography on silica gel (eluent: DCM/MeOH/Et_{3}N = 1/0.01/0.002). 1H
NMR (600 MHz, Chloroform-\(d\)) δ 8.00 (d, \(J = 8.4\) Hz, 2H), 7.49 (d, \(J = 8.1\) Hz, 2H),
4.38 (d, $J = 6.0$ Hz, 1H), 4.07 (d, $J = 5.9$ Hz, 1H), 3.91 (s, 3H), 3.79 – 3.71 (m, 1H),
3.60 – 3.54 (m, 1H), 3.52 – 3.45 (m, 1H), 3.26 – 3.19 (m, 1H), 1.21 (t, $J = 7.0$ Hz, 3H),
1.02 (t, $J = 7.0$ Hz, 3H). $^{13}$C $\{^1$H$\}$ NMR (151 MHz, Chloroform-d) $\delta$ 167.2, 146.9, 129.5,
129.3, 128.0, 106.7, 64.5, 64.0, 58.8, 52.2, 15.4, 15.2. The ee value were determined after acylation. HPLC: Chiracel AD-3 Column (250 mm); detected at 210 nm; n-hexane / i-propanol = 90/10; flow = 0.8 mL/min; Retention time: 12.0 min (major), 14.9 min (minor). HRMS (ESI), m/z: [M+H]$^+$ Calcd for C$_{14}$H$_{22}$NO$_4$: 268.1543; Found: 268.1539.

(R)-2,2-Diethoxy-1-(thiophen-2-yl)ethan-1-amine (2p)
Light yellow oil, 36.3 mg, 0.169 mmol, 85% yield (42.8 mg 1p used), 62% ee, $[\alpha]^{22}_D = +2.6$ (c=0.5, CHCl$_3$), $R_f = 0.3$ (DCM/MeOH = 95/5), obtained by purification with flash column chromatography on silica gel (eluent: DCM/MeOH/Et$_3$N = 1/0.01/0.002). $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.22 (dd, $J = 5.1$, 1.2 Hz, 1H), 7.04 (d, $J = 3.4$ Hz, 1H), 6.97 (dd, $J = 5.1$, 3.5 Hz, 1H), 4.39 (d, $J = 5.9$ Hz, 1H), 4.33 – 4.25 (m, 1H), 3.84 – 3.74 (m, 1H), 3.69 – 3.50 (m, 2H), 3.41 – 3.29 (m, 1H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.12 (t, $J = 7.0$ Hz, 3H). $^{13}$C $\{^1$H$\}$ NMR (101 MHz, Chloroform-d) $\delta$ 145.4, 126.6, 124.9,
124.5, 106.6, 64.4, 64.0, 55.1, 15.4, 15.3. The ee value were determined after acylation. UPLC: Chiracel OD-3 Column (250 mm); detected at 210 nm; n-hexane / i-propanol = 95/5; flow = 0.5 mL/min; Retention time: 3.9 min (major), 4.4 min (minor). HRMS (ESI), m/z: [M+H]$^+$ Calcd for C$_{10}$H$_{18}$NO$_2$S$: 216.1053; Found: 216.1056.
Methyl 3-amino-4,4-dimethoxybutanoate (2q)

For direct asymmetric reductive amination of 2q, MeOH was used as solvent instead of TFE. Because of difficulty of purification, the yield and characterization of 2q is determined after benzoylation to 2q-Bz.

Methyl 3-benzamido-4,4-dimethoxybutanoate (2q-Bz)

White solid, 46.6 mg, 0.166 mmol, 83% yield (35.4 mg 1q used), 98% ee, $[\alpha]_{D}^{24} = -2.3$ (c=1.0, CHCl₃), $R_f = 0.5$ (Hex/EA = 80/20), obtained by purification with flash column chromatography on silica gel (eluent: Hex/EA = 1/0.1). $^1$H NMR (600 MHz, Chloroform-d) $\delta$ 7.82 – 7.78 (m, 2H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.04 – 6.92 (m, 1H), 4.71 – 4.64 (m, 1H), 4.50 (d, $J = 3.9$ Hz, 1H), 3.70 (s, 3H), 3.46 (s, 3H), 3.43 (s, 3H), 2.70 (qd, $J = 15.7$, 5.8 Hz, 2H). $^{13}$C NMR (151 MHz, Chloroform-d) $\delta$ 172.7, 167.1, 134.4, 131.8, 128.7, 127.2, 104.8, 56.2, 55.6, 52.0, 48.2, 33.6. HPLC: Chiracel AD-3 Column (250 mm); detected at 230 nm; $n$-hexane / $i$-propanol = 90/10; flow = 0.8 mL/min; Retention time: 17.2 min (minor), 19.9 min (major). HRMS (ESI), m/z: [M+Na]$^+$ Calcd for C$_{14}$H$_{19}$NO$_5$Na$: 304.1155$; Found: 304.1153.
IV. Product Transformations

4.1 Gram-scale reaction:

In a glovebox, Ru(OAc)$_2$(S-L1b) (70 mg, 0.050 mmol), 1aa (1.01 g, 4.9 mmol), ammonium salt (0.77 g, 10 mmol) and TFE (20 ml) were successively added to a 50 mL reaction tube equipped with a magnetic stirring bar. The mixture was then transferred to a stain-less autoclave and purged by three cycles of pressurization/venting with H$_2$. The required H$_2$ pressure (50 atm) was then installed, and the autoclave was placed in an oil bath preheated to 90 ℃. The autoclave was cooled down to room temperature after 48 h and the pressure was slowly released in the hood. The reaction was quenched by saturated NaHCO$_3$ solution (20 mL) and extracted with DCM (30 mL x 3). The combined organic phase was dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (eluent: DCM/MeOH/Et$_3$N = 1/0.01/0.002) to afford desired products 0.81 g, 80% yield, 96% ee.

4.2 N-Alkylation:

AcOH (0.3 mmol, 18 μL) was added to the solution of 2aa (0.2 mmol, 40.8 mg) and PhCHO (0.3 mmol, 31.8 mg) in 3 mL MeOH, and the mixture was stirred for 3 h at room temperature. Then, NaBH$_3$CN (0.6 mmol, 38 mg) was added, and the reaction was stirred at 40 ℃ for 15 h. Upon completion of reaction, the reaction was quenched by 3 mL of saturated NH$_4$Cl/H$_2$O solution, followed by extraction with EA (10 mL x 3 times). The organic layer was combined, dried over anhydrous Na$_2$SO$_4$, filtered and
then evaporated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluent: Hex/EA = 1/0.1) to afford 3 as a yellow solid.

![Chemical Structure](image)

Chemical Formula: C_{19}H_{28}NO_{2}

Exact Mass: 299.1885

(S)-N-Benzyl-2,2-diethoxy-1-phenylethan-1-amine (3)

Yellow solid, 46.6 mg, 0.156 mmol, 78% yield, 95% ee, [α]_{D}^{22} = +35.0 (c=0.5, CHCl_{3}), \( R_f = 0.3 \) (Hex/EA = 95/5). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta \) 7.48 – 7.41 (m, 2H), 7.36 – 7.20 (m, 8H), 4.42 (d, \( J = 7.0 \) Hz, 1H), 3.79 – 3.60 (m, 3H), 3.53 – 3.42 (m, 3H), 3.12 – 3.03 (m, 1H), 1.21 (t, \( J = 7.1 \) Hz, 3H), 0.93 (t, \( J = 7.0 \) Hz, 3H). HPLC: Chiracel AD-3 Column (250 mm); detected at 210 nm; \( n \)-hexane / i-propanol = 95/5; flow = 0.8 mL/min; Retention time: 5.5 min (major), 6.6 min (minor). \(^{13}\)C{\(^{1}\)}H NMR (101 MHz, Chloroform-\(d\)) \( \delta \) 140.7, 139.8, 129.0, 128.4, 128.3, 128.2, 127.5, 126.9, 106.5, 65.3, 64.5, 63.0, 51.1, 15.4, 15.1. HRMS (ESI), m/z: [M+H]\(^+\) Calcd for C_{19}H_{26}NO_{2}+: 300.1958, Found: 300.1957.

4.3 N-Benzoylation:

Primary amine 2aa (41.8 mg, 0.2 mmol) was dissolved in dichloromethane (1 mL), followed by addition of triethylamine (80 \( \mu \)L) and BzCl (40 \( \mu \)L) at 0 °C. After stirred at room temperature for 2 h, saturated NaHCO\(_3\) solution (3 mL) was added to quench the reaction, followed by extraction with DCM (5 mL x 3 times). The organic phase was combined, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and then evaporated under
reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluent: Hex/EA = 1/0.1 to afford 4 as a white solid.

\[
\text{Chemical Formula: } C_{19}H_{23}NO_3 \\
\text{Exact Mass: } 313.1678
\]

(S)-N-(2,2-Diethoxy-1-phenylethyl)benzamide (4)

White solid, 58.8 mg, 0.188 mmol, 94% yield, 97% ee, [\(\alpha\)]\text{D} = -34.1 (c=0.5, CHCl3), \(R_f = 0.5 \) (Hex/EA = 80/20). \(^1\)H NMR (400 MHz, Methanol-d\(_4\)\) \(\delta\) 7.84 – 7.79 (m, 2H), 7.54 – 7.50 (m, 1H), 7.48 – 7.42 (m, 4H), 7.35 – 7.29 (m, 2H), 7.28 – 7.22 (m, 1H), 5.24 (d, \(J = 6.2\) Hz, 1H), 4.80 (d, \(J = 6.2\) Hz, 1H), 3.76 – 3.61 (m, 2H), 3.56 (dq, \(J = 9.4, 7.0\) Hz, 1H), 3.41 (dq, \(J = 9.4, 7.0\) Hz, 1H), 3.31 (p, \(J = 1.7\) Hz, 1H), 1.15 (t, \(J = 7.1\) Hz, 3H), 1.06 (t, \(J = 7.1\) Hz, 3H). \(^1\)C\(_{\{1\}}\) NMR (101 MHz, Methanol-d\(_4\)\) \(\delta\) 169.9, 140.5, 135.9, 132.7, 129.6, 129.2, 129.0, 128.4, 128.4, 105.0, 64.8, 63.5, 57.6, 15.6, 15.4. HPLC: Chiracel AS-3 Column (250 mm); detected at 230 nm; \(n\)-hexane / \(i\)-propanol = 90/10; flow = 0.8 mL/min; Retention time: 9.2 min (major), 14.2 min (minor). HRMS (ESI), \(m/z\): [M+Na]\(^+\) Calcd for C\(_{19}\)H\(_{23}\)NO\(_3\)Na\(^+\): 336.1570, Found: 336.1568.

4.4 Reduction to amino alcohol:

\[
\begin{array}{c}
\text{6 N HCl, acetone, rt, 20 min} \\
\rightarrow
\end{array}
\]

Compound 4 (31.3 mg, 0.1 mmol) was dissolved in 0.5 mL acetone at room temperature, then 0.5 mL of 6 mol/L HCl was added. The reaction was stirred at room temperature for 20 min and monitored by TLC. Upon completion of reaction, 3 mL H\(_2\)O was added, followed by extraction with EA (3 x 5 mL). The organic phase was combined, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and then evaporated under reduced pressure.
pressure to obtained crude aldehyde S2, which could be used in the next step without further purification.

The crude S2 (ca. 0.1 mmol) obtained in the last step was dissolve in 1 mL MeOH, then NaBH4 (5.5 mg) was added at 0 °C and stirred for 30 min. Upon completion of reaction, 3 mL saturated NH4Cl solution was added to quench the reaction, followed by extraction with EA (3 x 5 mL). The residue was subjected to flash column chromatography on silica gel (eluent: Hex/EA = 1/0.1) to afford 5 as white solid.

(S)-N-(2-Hydroxy-1-phenylethyl)benzamide (5)
White solid, 23.5 mg, 0.0975 mmol, 98% yield over two steps, 97% ee, [α]23D = -16.6 (c=0.5, MeOH), Rf = 0.5 (Hex/EA = 90/10). ¹H NMR (600 MHz, Methanol-d₄) δ 7.88 – 7.84 (m, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 5.20 (t, J = 6.6 Hz, 1H), 3.86 (d, J = 6.6 Hz, 2H). ¹³C{¹H} NMR (151 MHz, Methanol-d₄) δ 170.4, 141.4, 135.9, 132.7, 129.5, 129.5, 128.4, 128.4, 128.0, 66.1, 57.8. HRMS (ESI), m/z: [M+H]+ Calcd for C₁₅H₁₆NO₂+: 242.1176, Found: 242.1174. HPLC: Chiracel OJ-3 Column (250 mm); detected at 210 nm; n-hexane / i-propanol = 90/10; flow = 0.8 mL/min; Retention time: 14.9 min (major), 16.8 min (minor). The absolute configuration of 5 was determined by comparing its sign of the optical rotation with that reported in the literature.⁷ The absolute configuration of 2aa, 2ab, 2c-2p was thus determined by similarity with 5.

4.5 Oxidation to amino acid:
Jones’s reagent was added to crude S2 (0.2 mmol, see 4.4 for preparation) in 1.5 mL acetone over 0.5 h at 0 °C. The reaction was then stirred for 3 h at this temperature. Several drops of i-PrOH were added to quench the reaction and then concentrated. Water (4 mL) was then added, and the organic layers were extracted by DCM (3x 4 mL). The organic phase was combined, dried over anhydrous Na2SO4, filtered, and then evaporated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluent: DCM/MeOH = 1/0.03) to afford 6 as white solid.

(S)-2-Benzamido-2-phenylacetic acid (6)

White solid, 37.7 mg, 0.148 mmol, 74% yield over 2 steps, 91% ee, [α]23D = +48.0 (c=0.5, MeOH). Rf = 0.2 (DCM/MeOH = 95/5). 1H NMR (400 MHz, Methanol-d4) δ 7.92 – 7.82 (m, 2H), 7.56 – 7.43 (m, 5H), 7.33 – 7.19 (m, 3H), 5.44 (s, 1H). 13C NMR (151 MHz, Methanol-d4) δ 176.0, 168.9, 140.7, 135.5, 132.8, 129.6, 129.4, 128.5, 128.3, 60.4. HPLC: Chiral-NZ(2) Column (250 mm); detected at 230 nm; n-hexane / (EtOH+0.1% TEA) = 50/50; flow = 0.5 mL/min; Retention time: 7.8 min (minor), 8.7 min (major). HRMS (ESI), m/z: [M-H]- Calcd for C15H12NO3: 254.0823, Found: 254.0819. The absolute configuration of 6 was established by comparison of its sign of the optical rotation with that reported in the literature.[8]

4.6 Formal synthesis of (-)-Cytoxazone
In a glovebox, Ru(OAc)$_2$(R-L1b) (54 mg, 0.040 mmol), 2g (0.87 g, 3.7 mmol), ammonium salt (0.62 g, 8.1 mmol) and TFE (15 ml) were successively added to a 50 mL reaction tube equipped with a magnetic stirring bar. The mixture was then transferred to a stain-less autoclave and purged by three cycles of pressurization/venting with H$_2$. The required H$_2$ pressure (50 atm) was then installed, and the autoclave was placed in an oil bath preheated to 90 ℃. The autoclave was cooled down to room temperature after 48 h and the pressure was slowly released in the hood. The reaction was quenched by saturated NaHCO$_3$ solution (20 mL) and extracted with DCM (30 mL x 3). The combined organic phase was dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The residue was subjected to the next step without purification.

Primary amine obtained in the last step was dissolved in dichloromethane (20 mL) followed by addition of triethylamine (1.6 mL) and BzCl (3.2 mL) at 0 ℃. After stirred at room temperature for 2 h, saturated NaHCO$_3$ solution (20 mL) was added to quench the reaction. The organic phase was separated, dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluent: Hex/EA = 1/0.2) to afford 7 as white solid (0.76 g, 61% yield over 2 steps).

Compound 7 (34.3 mg, 0.1 mmol) was dissolved in 0.5 mL acetone at room temperature, then 6 mol/L HCl (0.5 mL) was added. The reaction was stirred at room temperature for 20 min and monitored by TLC. Upon completion of reaction, H$_2$O (3
(R)-N-(2,2-Diethoxy-1-(4-methoxyphenyl)ethyl)benzamide (7)

White solid, 0.76 g, 2.2 mmol, 61% yield over 2 steps, 92% ee, [α]$_{23}^{23D}$ = +39.7 (c=0.5, CHCl$_3$), $R_f$ = 0.6 (Hex/EA = 80/20). $^1$H NMR (600 MHz, Methanol-$d_4$) δ 7.84 – 7.78 (m, 2H), 7.55 – 7.51 (m, 1H), 7.48 – 7.44 (m, 2H), 7.37 – 7.34 (m, 2H), 6.92 – 6.85 (m, 2H), 5.19 (d, $J$ = 6.2 Hz, 1H), 4.76 (d, $J$ = 6.2 Hz, 1H), 3.77 (s, 3H), 3.74 – 3.63 (m, 2H), 3.56 (dq, $J$ = 9.4, 7.0 Hz, 1H), 3.42 (dq, $J$ = 9.5, 7.0 Hz, 1H), 3.31 (p, $J$ = 1.6 Hz, 2H), 1.16 (t, $J$ = 7.0 Hz, 3H), 1.07 (t, $J$ = 7.0 Hz, 3H). $^{13}$C{$^1$H} NMR (151 MHz, Methanol-$d_4$) δ 169.8, 160.5, 136.0, 132.7, 132.5, 130.1, 129.6, 128.4, 114.6, 105.1, 64.8 63.6, 57.0, 55.7, 15.6, 15.4. HRMS (ESI), m/z: [M+Na]$^+$ Calcd for C$_{20}$H$_{25}$NO$_4$Na$: 366.1676, Found: 366.1675. HPLC: Chiracel OJ-3 Column (250 mm); detected at 210 nm; $n$-hexane / $i$-propanol = 95/5; flow = 0.8 mL/min; Retention time: 20.4 min (major), 29.3 min (minor).

(R)-N-(1-(4-Methoxyphenyl)-2-oxoethyl)benzamide (8)

Pale yellow solid, 25.7 mg, 0.0956 mmol, 95% yield. [α]$_{27}^{27D}$ = -1.8 (c=0.5, CHCl$_3$), $R_f$ = 0.4 (Hex/EA = 80/20). $^1$H NMR (400 MHz, Chloroform-$d$) δ 9.62 (s, 1H), 7.87 – 7.81
(m, 2H), 7.55 – 7.40 (m, 4H), 7.29 (d, $J = 8.7$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H), 5.71 (d, $J = 5.8$ Hz, 1H), 3.80 (s, 3H). $^{13}$C{¹H} NMR (101 MHz, Chloroform-d) δ 195.0, 166.9, 160.2, 133.7, 132.1, 129.7, 128.8, 127.3, 125.1, 115.0, 63.4, 55.5. HRMS (ESI), m/z: [M+H]$^+$ Calcd for C$_{16}$H$_{16}$NO$_3$+: 270.1125, Found: 270.1124. The NMR data is consistent with that reported.\textsuperscript{[9]}
V. Proposed enantioinduction models

A pair of enantioinduction models for this reaction are tentatively proposed to explain the observed high enantiocontrol. As depicted in the figure, (S)-product favored transition state can avoid the steric repulsion between the aryl group on substrate and the DTBM group on P atom, while this steric hindrance repulsion is envisaged in the case of (R)-product favored transition state. The energy difference between two transition states led to S product as the major product.
VI. NMR spectra

$^1$H NMR (600 MHz, Chloroform-d) of compound 1aa

$^{13}$C$^\{^1$H$\}$ NMR (151 MHz, Chloroform-d) of compound 1aa
$^1$H NMR (400 MHz, Chloroform-d) of compound 1ab

$^{13}$C$\{^1$H$\}$ NMR (101 MHz, Chloroform-d) of compound 1ab
$^1$H NMR (600 MHz, Chloroform-d) of compound 1b

Chemical Formula: C$_7$H$_{10}$O$_2$
Exact Mass: 258.1256

$^{13}$C{$_^1$H} NMR (151 MHz, Chloroform-d) of compound 1b

Chemical Formula: C$_7$H$_{10}$O$_2$
Exact Mass: 258.1256
$^1$H NMR (400 MHz, Chloroform-d) of compound 1c

$^{13}$C$^1$H NMR (101 MHz, Chloroform-d) of compound 1c
$^1$H NMR (600 MHz, Chloroform-d) of compound 1d

Chemical Formula: C$_{12}$H$_{16}$O$_3$
Exact Mass: 222.1256

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 1d

Chemical Formula: C$_{12}$H$_{16}$O$_3$
Exact Mass: 222.1256
$^1$H NMR (400 MHz, Chloroform-d) of compound 1e

$^{13}$C\textsubscript{1H} NMR (101 MHz, Chloroform-d) of compound 1e
$^1$H NMR (400 MHz, Chloroform-d) of compound 1f

\[ \text{Chemical Formula: } \text{C}_{13}\text{H}_{20}\text{O}_3 \]

\[ \text{Exact Mass: 284.1412} \]

$^{13}$C\{1H\} NMR (101 MHz, Chloroform-d) of compound 1f

\[ \text{Chemical Formula: } \text{C}_{13}\text{H}_{20}\text{O}_3 \]

\[ \text{Exact Mass: 284.1412} \]
$^1$H NMR (600 MHz, Chloroform-d) of compound 1g

$^{13}$C{$_1^1$H} NMR (151 MHz, Chloroform-d) of compound 1g
$^{1}$H NMR (400 MHz, Chloroform-d) of compound $1h$

$^{13}$C$^{1}$H NMR (101 MHz, Chloroform-d) of compound $1h$
$^1$H NMR (600 MHz, Chloroform-d) of compound 1i

$^{13}$C$^1$H NMR (151 MHz, Chloroform-d) of compound 1i
$^1$H NMR (400 MHz, Chloroform-d) of compound 1j

$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-d) of compound 1j
$^1$H NMR (600 MHz, Chloroform-d) of compound 1k

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 1k
$^1$H NMR (600 MHz, Chloroform-d) of compound II

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound II
$^1$H NMR (600 MHz, Chloroform-d) of compound 1m

Chemical Formula: $C_{12}H_8ClO_3$
Exact Mass: 242.0710

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 1m

Chemical Formula: $C_{12}H_8ClO_3$
Exact Mass: 242.0710
$^1$H NMR (600 MHz, Chloroform-d) of compound 1n

$^{13}$C{1H} NMR (151 MHz, Chloroform-d) of compound 1n
$^1$H NMR (400 MHz, Chloroform-d) of compound 1o

$^{13}$C$\{}^1$H$\}$ NMR (101 MHz, Chloroform-d) of compound 1o
$^1$H NMR (400 MHz, Chloroform-d) of compound 1p

$^{13}$C{^1}H NMR (101 MHz, Chloroform-d) of compound 1p
$^1$H NMR (600 MHz, Chloroform-d) of compound 1q

$^{13}$C\{\textit{H}\} NMR (151 MHz, Chloroform-d) of compound 1q
$^1$H NMR (400 MHz, Chloroform-d) of compound 1r

Chemical Formula: C$_{6}$H$_{5}$O$_{3}$

Exact Mass: 222.1256
$^1$H NMR (400 MHz, Chloroform-d) of compound 1s

$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-d) of compound 1s
$^1$H NMR (400 MHz, Chloroform-d) of compound 1t

$^{13}$C ($^1$H) NMR (101 MHz, Chloroform-d) of compound 1t
$^1$H NMR (600 MHz, Chloroform-d) of compound 2aa

$^{13}$C{\text{\textsuperscript{1}H}} NMR (151 MHz, Chloroform-d) of compound 2aa
$^1$H NMR (600 MHz, Chloroform-d) of compound 2ab-Ac

$^{13}$C$^1$H NMR (151 MHz, Chloroform-d) of compound 2ab-Ac
$^1$H NMR (600 MHz, Chloroform-d) of compound 2b

Chemical Formula: C$_{14}$H$_{12}$NO$_2$
Exact Mass: 259.1572

$^{13}$C\textsuperscript{1}H NMR (151 MHz, Chloroform-d) of compound 2b

Chemical Formula: C$_{14}$H$_{12}$NO$_2$
Exact Mass: 259.1572
$^1$H NMR (600 MHz, Chloroform-d) of compound 2c-Ac

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 2c-Ac
$^1$H NMR (400 MHz, Chloroform-d) of compound 2d

Chemical Formula: C$_{10}$H$_{12}$NO$_2$
Exact Mass: 223.1572

$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-d) of compound 2d

Chemical Formula: C$_{10}$H$_{12}$NO$_2$
Exact Mass: 223.1572
$^1$H NMR (400 MHz, Chloroform-d) of compound 2e

$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-d) of compound 2a
$^1$H NMR (600 MHz, Chloroform-d) of compound 2f

Chemical Formula: C$_8$H$_{12}$NO$_2$
Exact Mass: 265.1729

$^{13}$C {$^1$H} NMR (151 MHz, Chloroform-d) of compound 2f

Chemical Formula: C$_8$H$_{12}$NO$_2$
Exact Mass: 265.1729
$^1$H NMR (400 MHz, Chloroform-d) of compound 2g

Chemical Formula: C$_7$H$_7$NO$_3$

Exact Mass: 239.1521

$^{13}$C($^1$H) NMR (101 MHz, Chloroform-d) of compound 2g

Chemical Formula: C$_7$H$_7$NO$_3$

Exact Mass: 239.1521
$^1$H NMR (600 MHz, Chloroform-d) of compound 2h

Chemical Formula: C$_7$H$_{12}$NO$_3$

Exact Mass: 239.1021

$^{13}$C{$_^1$H} NMR (151 MHz, Chloroform-d) of compound 2h

Chemical Formula: C$_7$H$_{12}$NO$_3$

Exact Mass: 239.1021

66
$^1$H NMR (600 MHz, Chloroform-d) of compound 2i

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 2i
$^1$H NMR (400 MHz, Chloroform-d) of compound 2j-Ac

$^{13}$C $^1$H NMR (101 MHz, Chloroform-d) of compound 2j-Ac
$^1$H NMR (400 MHz, Chloroform-d) of compound 2k

Chemical Formula: C$_{12}$H$_{14}$FNO$_2$
Exact Mass: 227.1322

$^{13}$C\{H\} NMR (101 MHz, Chloroform-d) of compound 2k

Chemical Formula: C$_{12}$H$_{14}$FNO$_2$
Exact Mass: 227.1322
$^1$H NMR (600 MHz, Chloroform-d) of compound 2l

Chemical Formula: $\text{C}_9\text{H}_4\text{F}_2\text{NO}_2$  
Exact Mass: 246.1227

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 2l

Chemical Formula: $\text{C}_9\text{H}_4\text{F}_2\text{NO}_2$  
Exact Mass: 246.1227
$^1$H NMR (600 MHz, Chloroform-d) of compound 2m

Chemical Formula: C$_{17}$H$_{20}$ClNO$_2$

Exact Mass: 243.1026

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 2m

Chemical Formula: C$_{17}$H$_{20}$ClNO$_2$

Exact Mass: 243.1026
$^1$H NMR (400 MHz, Chloroform-d) of compound 2n

$^{13}$C\$^1$H\$ NMR (101 MHz, Chloroform-d) of compound 2n
\( ^1\text{H} \) NMR (600 MHz, Chloroform-d) of compound 2o

\[
\text{Chemical Formula: } C_{10}H_{12}N_2O_4 \\
\text{Exact Mass: } 267.1471
\]

\( ^{13}\text{C}\{^1\text{H}\} \) NMR (151 MHz, Chloroform-d) of compound 2o

\[
\text{Chemical Formula: } C_{10}H_{12}N_2O_4 \\
\text{Exact Mass: } 267.1471
\]
$^1$H NMR (400 MHz, Chloroform-d) of compound 2p

Chemical Formula: C$_{10}$H$_7$NO$_2$S
Exact Mass: 216.0980

$^{13}$C{${}^1$H} NMR (101 MHz, Chloroform-d) of compound 2p

Chemical Formula: C$_{10}$H$_7$NO$_2$S
Exact Mass: 216.0980
$^1$H NMR (600 MHz, Chloroform-d) of compound 2q-Bz

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 2q-Bz
$^1$H NMR (400 MHz, Chloroform-d) of compound 3

$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-d) of compound 3
$^1$H NMR (400 MHz, Chloroform-d) of compound 4

$^{13}$C$\{^1$H$\}$ NMR (101 MHz, Chloroform-d) of compound 4
$^1$H NMR (600 MHz, Chloroform-d) of compound 5

$^{13}$C{$_{^1}$H} NMR (151 MHz, Chloroform-d) of compound 5
$^1$H NMR (400 MHz, Chloroform-d) of compound 6

$^{13}$C{$_H^1$} NMR (151 MHz, Chloroform-d) of compound 6
$^1$H NMR (600 MHz, Chloroform-d) of compound 7

$^{13}$C{$^1$H} NMR (151 MHz, Chloroform-d) of compound 7
$^1$H NMR (400 MHz, Chloroform-d) of compound 8

$^{13}$C{$^1$H} NMR (101 MHz, Chloroform-d) of compound 8
VII. HPLC spectra

Signal 1: DAD1 A, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>[min]</td>
<td>[min]</td>
<td>[mAU*s]</td>
<td>[mAU]</td>
</tr>
<tr>
<td>1</td>
<td>7.131</td>
<td>BV R</td>
<td>0.1702</td>
<td>1.23824e4</td>
</tr>
<tr>
<td>2</td>
<td>8.811</td>
<td>BB</td>
<td>0.2681</td>
<td>1.24117e4</td>
</tr>
</tbody>
</table>

Signal 1: DAD1 A, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>[min]</td>
<td>[min]</td>
<td>[mAU*s]</td>
<td>[mAU]</td>
</tr>
<tr>
<td>1</td>
<td>6.864</td>
<td>MM</td>
<td>0.1634</td>
<td>5296.10810</td>
</tr>
<tr>
<td>2</td>
<td>8.546</td>
<td>MM</td>
<td>0.2960</td>
<td>81.02644</td>
</tr>
</tbody>
</table>
### Signal 1: DADI C, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime [min]</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.958</td>
<td>BB</td>
<td>0.5593</td>
<td>1.44974e+4</td>
<td>395.78857</td>
<td>49.8994</td>
</tr>
<tr>
<td>2</td>
<td>25.419</td>
<td>MM</td>
<td>1.6305</td>
<td>1.45558e+4</td>
<td>148.78726</td>
<td>50.1006</td>
</tr>
</tbody>
</table>

### Signal 1: DADI C, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime [min]</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.740</td>
<td>BB</td>
<td>0.5339</td>
<td>730.16742</td>
<td>19.18851</td>
<td>3.9459</td>
</tr>
<tr>
<td>2</td>
<td>25.785</td>
<td>BB</td>
<td>1.3129</td>
<td>1.77742e+4</td>
<td>180.17317</td>
<td>96.0541</td>
</tr>
</tbody>
</table>
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.651</td>
<td>MM</td>
<td>0.3238</td>
<td>9284.31738</td>
<td>473.81577</td>
<td>49.9131</td>
</tr>
<tr>
<td>2</td>
<td>11.651</td>
<td>VB</td>
<td>0.5960</td>
<td>9236.36035</td>
<td>212.12172</td>
<td>50.0869</td>
</tr>
</tbody>
</table>

Signal 1: DAD1 C, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.751</td>
<td>BB</td>
<td>0.3307</td>
<td>4.237874</td>
<td>1987.67102</td>
<td>99.7895</td>
</tr>
<tr>
<td>2</td>
<td>11.482</td>
<td>BB</td>
<td>0.3087</td>
<td>89.38857</td>
<td>4.33246</td>
<td>0.2105</td>
</tr>
<tr>
<td>#</td>
<td>Ret Time [min]</td>
<td>Width [min]</td>
<td>Area [mAU*s]</td>
<td>Height [mAU]</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>----------------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10.554</td>
<td>0.3686</td>
<td>3271.0188</td>
<td>147.91644</td>
<td>50.5982</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12.539</td>
<td>0.7031</td>
<td>3193.67505</td>
<td>75.70998</td>
<td>49.4018</td>
<td></td>
</tr>
</tbody>
</table>

**Signal 1: DAD1 A, Sig=210,4 Ref=360,100**

---

<table>
<thead>
<tr>
<th>#</th>
<th>Ret Time [min]</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.897</td>
<td>0.2021</td>
<td>6028.88477</td>
<td>456.33356</td>
<td>98.9748</td>
</tr>
<tr>
<td>2</td>
<td>10.569</td>
<td>0.2920</td>
<td>62.44792</td>
<td>3.01062</td>
<td>1.0252</td>
</tr>
</tbody>
</table>

**Signal 1: DAD1 A, Sig=210,4 Ref=360,100**
### Signal 1: DAD1 C, Sig=228.4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.646</td>
<td>BB</td>
<td>0.4287</td>
<td>5863.24609</td>
<td>203.16783</td>
<td>96.0448</td>
</tr>
<tr>
<td>2</td>
<td>20.369</td>
<td>MM</td>
<td>0.5906</td>
<td>241.45497</td>
<td>6.81371</td>
<td>3.9552</td>
</tr>
</tbody>
</table>

### Signal 1: DAD1 C, Sig=228.4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.646</td>
<td>BB</td>
<td>0.4287</td>
<td>5863.24609</td>
<td>203.16783</td>
<td>96.0448</td>
</tr>
<tr>
<td>2</td>
<td>20.369</td>
<td>MM</td>
<td>0.5906</td>
<td>241.45497</td>
<td>6.81371</td>
<td>3.9552</td>
</tr>
</tbody>
</table>
Signal 1: DAD1 D, Sig=230,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.525</td>
<td>BB</td>
<td>0.4819</td>
<td>2658.96991</td>
<td>100.11333</td>
<td>50.5419</td>
</tr>
<tr>
<td>2</td>
<td>13.991</td>
<td>BB</td>
<td>0.6195</td>
<td>2681.89478</td>
<td>64.10281</td>
<td>49.4581</td>
</tr>
</tbody>
</table>

Signal 1: DAD1 D, Sig=230,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.651</td>
<td>BB</td>
<td>0.3955</td>
<td>173.95155</td>
<td>6.27411</td>
<td>7.6078</td>
</tr>
<tr>
<td>2</td>
<td>13.891</td>
<td>BB</td>
<td>0.5680</td>
<td>2112.53955</td>
<td>57.31940</td>
<td>92.3922</td>
</tr>
<tr>
<td>#</td>
<td>Ret Time</td>
<td>Type</td>
<td>Width</td>
<td>Area</td>
<td>Height</td>
<td>Area %</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------</td>
<td>--------</td>
<td>-------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>1</td>
<td>9.964</td>
<td>VV</td>
<td>0.2236</td>
<td>3360.1870</td>
<td>229.6709</td>
<td>49.6016</td>
</tr>
<tr>
<td>2</td>
<td>10.654</td>
<td>VB</td>
<td>0.3632</td>
<td>3414.1613</td>
<td>132.2254</td>
<td>50.3984</td>
</tr>
</tbody>
</table>

Signal 1: DAD1 A, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>#</th>
<th>Ret Time</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.389</td>
<td>BV</td>
<td>0.1767</td>
<td>67.2707</td>
<td>5.6595</td>
<td>0.3994</td>
</tr>
<tr>
<td>2</td>
<td>10.637</td>
<td>VB</td>
<td>0.2495</td>
<td>1.67752e4</td>
<td>1822.09692</td>
<td>99.6006</td>
</tr>
</tbody>
</table>

NHAc OEt
OEt
F
2j-Ac
rac
<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.721</td>
<td>0.3626</td>
<td>4904.28613</td>
<td>206.860893</td>
<td>50.2624</td>
</tr>
<tr>
<td>2</td>
<td>15.489</td>
<td>0.4161</td>
<td>4853.07178</td>
<td>175.77356</td>
<td>49.7376</td>
</tr>
</tbody>
</table>

Signal 1: DAD1 A, Sig=210,4 Ref=360,100

```
<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.733</td>
<td>0.4418</td>
<td>3395.52173</td>
<td>116.59829</td>
<td>100.0000</td>
</tr>
</tbody>
</table>
```
Signal 1: DAD1 D, Sig=230,4 Ref=360,100

<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.681</td>
<td>BB</td>
<td>0.3712</td>
<td>1897.05835</td>
<td>73.48484</td>
<td>49.5575</td>
</tr>
<tr>
<td>2</td>
<td>16.472</td>
<td>BB</td>
<td>0.4228</td>
<td>1930.93872</td>
<td>64.95163</td>
<td>50.4425</td>
</tr>
</tbody>
</table>

Signal 1: DAD1 D, Sig=230,4 Ref=360,100

<table>
<thead>
<tr>
<th>#</th>
<th>RetTime [min]</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.815</td>
<td>BB</td>
<td>0.3814</td>
<td>6202.06348</td>
<td>233.89536</td>
<td>97.6576</td>
</tr>
<tr>
<td>2</td>
<td>16.661</td>
<td>BB</td>
<td>0.4122</td>
<td>148.76442</td>
<td>5.01272</td>
<td>2.3424</td>
</tr>
</tbody>
</table>

96
Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
1 11.674 BB 0.3550 7348.78662 294.62073 49.9317
2 14.361 BB 0.4389 7368.89453 239.52878 54.0683

Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
1 11.994 BB 0.3666 2295.15405 88.48388 98.1273
2 14.898 MM 0.4385 43.80046 1.66472 1.8727
Signal 1: DAD1 D, Sig=230,4 Ref=360,100

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] |
--- | --- | --- | --- | --- |
1 4.079 MM 0.2449 2711.77124 184.55461 50.2136 100 |
2 4.695 MM 0.3374 2688.70483 132.80968 49.7864 100 |

Signal 1: DAD1 D, Sig=230,4 Ref=360,100

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] |
--- | --- | --- | --- | --- |
1 3.938 MM 0.2134 3074.28076 240.12175 81.2064 100 |
2 4.450 MM 0.2530 711.46199 46.86190 18.7936 100 |
Signal 1: DAD1 D, Sig=230.4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.119</td>
<td>BB</td>
<td>0.5108</td>
<td>4893.10986</td>
<td>131.28204</td>
</tr>
<tr>
<td>2</td>
<td>19.573</td>
<td>BB</td>
<td>0.6012</td>
<td>5020.47412</td>
<td>114.13428</td>
</tr>
</tbody>
</table>

Signal 1: DAD1 D, Sig=230.4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.250</td>
<td>BB</td>
<td>0.5141</td>
<td>165.28810</td>
<td>4.38208</td>
</tr>
<tr>
<td>2</td>
<td>19.852</td>
<td>BB</td>
<td>0.6011</td>
<td>1.35771264</td>
<td>308.71213</td>
</tr>
</tbody>
</table>
NHBN

3
rac

Signal 1: DAD 1, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.499</td>
<td>BV</td>
<td>0.1687</td>
<td>3024.60596</td>
<td>243.94107</td>
<td>50.1102</td>
</tr>
<tr>
<td>2</td>
<td>6.618</td>
<td>MF</td>
<td>0.2427</td>
<td>3011.30396</td>
<td>206.77905</td>
<td>49.8898</td>
</tr>
</tbody>
</table>

Signal 1: DAD 1, Sig=210,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.464</td>
<td>R</td>
<td>0.2291</td>
<td>1.16548e4</td>
<td>683.00140</td>
<td>97.2997</td>
</tr>
<tr>
<td>2</td>
<td>6.589</td>
<td>VBE</td>
<td>0.2249</td>
<td>323.44791</td>
<td>19.55738</td>
<td>2.7003</td>
</tr>
</tbody>
</table>
Signal 1: DAD1 D, Sig=230,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.805</td>
<td>BV</td>
<td>0.1447</td>
<td>9834.31445</td>
<td>1036.78589</td>
<td>49.8865</td>
</tr>
<tr>
<td>2</td>
<td>8.685</td>
<td>VB</td>
<td>0.1700</td>
<td>9910.74609</td>
<td>883.11548</td>
<td>50.1935</td>
</tr>
</tbody>
</table>

Signal 1: DAD1 D, Sig=230,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.808</td>
<td>BB</td>
<td>0.1412</td>
<td>403.29742</td>
<td>43.87557</td>
<td>4.5845</td>
</tr>
<tr>
<td>2</td>
<td>8.684</td>
<td>BB</td>
<td>0.1704</td>
<td>8393.61816</td>
<td>751.02795</td>
<td>95.4155</td>
</tr>
</tbody>
</table>

103
### Signal 1: DAD1 B, Sig=254,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU\times m]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.958</td>
<td>BB</td>
<td>0.9554</td>
<td>1229.65405</td>
<td>18.69534</td>
<td>49.6789</td>
</tr>
<tr>
<td>2</td>
<td>30.161</td>
<td>MM</td>
<td>1.5518</td>
<td>1245.95081</td>
<td>13.38186</td>
<td>50.3291</td>
</tr>
</tbody>
</table>

### Signal 1: DAD1 C, Sig=220,4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU\times m]</th>
<th>Height [mAU]</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.418</td>
<td>BB</td>
<td>0.9681</td>
<td>4584.30859</td>
<td>71.11302</td>
<td>95.7731</td>
</tr>
<tr>
<td>2</td>
<td>29.341</td>
<td>MM</td>
<td>1.2548</td>
<td>202.32512</td>
<td>2.68733</td>
<td>4.2269</td>
</tr>
</tbody>
</table>
VIII. HRMS spectra

1-([1,1’-biphenyl]-4-yl)-2,2-diethoxyethan-1-one (1f)

2,2-diethoxy-1-(2-fluorophenyl)ethan-1-one (1j)

1-(3,4-difluorophenyl)-2,2-diethoxyethan-1-one (1l)

2,2-diethoxy-1-(thiophen-2-yl)ethan-1-one (1p)
2-bromo-5,6-dihydro-[1,1'-biphenyl]-3(4H)-ol (2aa)

(S)-N-(2,2-dimethoxy-1-phenylethyl)acetamide (2ab-Ac)

(S)-2,2-diethoxy-1-(naphthalen-2-yl)ethan-1-amine (2b)
(S)-N-(2,2-diethoxy-1-(o-tolyl)ethyl)acetamide (2c-Ac)

(S)-2,2-diethoxy-1-(m-tolyl)ethan-1-amine (2d)

(S)-2,2-diethoxy-1-(p-tolyl)ethan-1-amine (2e)

(S)-1-[(1,1'-biphenyl]-4-yl)-2,2-dioethoxyethan-1-amine (2f)
(S)-2,2-diethoxy-1-(3-methoxyphenyl)ethan-1-amine (2g)

(S)-2,2-diethoxy-1-(4-methoxyphenyl)ethan-1-amine (2h)

(S)-1-(3,4-dimethoxyphenyl)-2,2-diethoxyethan-1-amine (2i)

(S)-N-(2,2-diethoxy-1-(2-fluorophenyl)ethyl)acetamide (2j-Ac)
(S)-2,2-diethoxy-1-(4-fluorophenyl)ethan-1-amine (2k)

(S)-1-(3,4-difluorophenyl)-2,2-diethoxyethan-1-amine (2l)

(S)-1-(4-chlorophenyl)-2,2-diethoxyethan-1-amine (2m)

(S)-1-(4-bromophenyl)-2,2-diethoxyethan-1-amine (2n)
(S)-methyl (S)-4-(1-amino-2,2-diethoxyethyl)benzoate (2o)

(R)-2,2-diethoxy-1-(thiophen-2-yl)ethan-1-amine (2p)

methyl 3-benzamido-4,4-dimethoxybutanoate (2q-Bz)

(S)-N-benzyl-2,2-diethoxy-1-phenylethan-1-amine (3)
(S)-N-(2,2-diethoxy-1-phenylethyl)benzamide (4)

(S)-N-(2-hydroxy-1-phenylethyl)benzamide (5)

(S)-2-benzamido-2-phenylacetic acid (6)
(S)-N-(2,2-diethoxy-1-(4-methoxyphenyl)ethyl)benzamide (7)

(S)-N-(1-(4-methoxyphenyl)-2-oxoethyl)benzamide (8)
IX Reference


