Copper-Catalysed Cyanoalkylative Cycloetherification of Alkenes to 1,3-Dihydroisobenzofurans: Development and Application to the Synthesis of Citalopram

Tu M. Ha, Qian Wang, Jieping Zhu*

Laboratory of Synthesis and Natural Products, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne, Switzerland

Supporting Information

Table of Contents

General Information .................................................................................................................................................. 2
Synthesis of Compounds 3 .................................................................................................................................. 3
Characterization Data of Compounds 3 ................................................................................................................ 4
Optimization of The Reaction Conditions ........................................................................................................ 12
General Procedure for The Synthesis of Dihydroisobenzofurans 4 ................................................................. 17
Characterization Data of Compounds 4 ................................................................................................................ 17
Synthesis of Citalopram (1) from Dihydrobenzofuran 4l .................................................................................. 28
Transformation of Dihydrobenzofuran 4l ........................................................................................................ 30
Copies of the $^1$H and $^{13}$C NMR Spectra .................................................................................................... 31
General Information

All reactions were carried out in oven dried glasswares. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used directly unless stated otherwise. CH$_3$CN, DCM, THF, toluene and DMF were dried by passage over activated alumina under nitrogen atmosphere (H$_2$O content < 30 ppm, Karl-Fischer titration).

Chromatographic purification was conducted with technical grade solvents and silica gel 40-63 μm. TLC was performed on Merck silica gel 60 F$_{254}$ TLC aluminium plates and visualized with UV light (254 nm), permanganate stain, phosphomolyblic acid stain, CAN stain or anisaldehyde stain.

Melting points were measured on a Stuart SMP30 melting point apparatus using open glass capillaries (uncorrected).

NMR spectra were recorded on a Bruker AvanceIII-400, Bruker Avance-400 at room temperature, $^1$H frequency is at 400.13 MHz, $^{13}$C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: CHCl$_3$ [$^1$H: 7.26, $^{13}$C: 77.2]; CD$_3$OD [$^1$H: 3.31, $^{13}$C:49.0]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. When needed, a COSY, HSQC and/or HMBC experiments were carried out to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacle™ ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra were reported in cm$^{-1}$.

Mass spectra were determined with a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionisation (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters or APPI-FT-ICR using a linear ion trap Fourier transform ion cyclotron resonance mass spectrometer from Thermo Scientific.
Synthesis of Compounds 3

Compound 3a was prepared according to the reported procedure:[1]

\[
\begin{align*}
\text{R}^1 & \quad \text{OMe} \\
\text{R}^2 & \quad \text{OTf} \\
\end{align*}
\]

1. Ph3PCH3Br, tBuOK

\[
\begin{align*}
\text{Pd}_2(\text{dba})_3 & \quad 10 \text{ mol\%} \\
\text{dpff} & \quad 12 \text{ mol\%} \\
\text{Urotropine} & \quad 2.0 \text{ equiv} \\
\text{THF} & \quad 90^\circ \text{C} \\
\end{align*}
\]

2. LAH, THF, reflux

Compounds 3b-m were prepared in 2 steps according to the following general procedure:[2,3]

\[
\begin{align*}
\text{R}^1 & \quad \text{OMe} \\
\text{R}^2 & \quad \text{R}^2 \\
\end{align*}
\]

Step 1: In the glovebox, Pd2(dba)3 and dpff were dissolved in THF (0.2 M) in a sealed tube. After stirring for 10 min at room temperature, phenol triflate (1.0 equiv), styrene (2.0 equiv) and urotropine (2.0 equiv) were successively added. The reaction mixture was heated to 90 °C and stirred overnight. After quenching with water, the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over MgSO4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/30) to give the corresponding 2-vinylbenzoate.

Step 2: To a solution of 2-vinylbenzoate (1.0 equiv) in THF (0.1 M) was added dropwise at −78 °C a solution of AlH/(Bu)2 in toluene (1.4 M, 2.5 equiv). The reaction mixture was stirred at this temperature for 1 h and then warmed up to 0 °C. After stirring for 3 h, the reaction mixture was quenched with methanol at −78 °C, then warmed up to room temperature and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over MgSO4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/10) to give the corresponding compound 3b-m.

Compound 3r was prepared from 2-(1-phenylvinyl)benzoate[2] according to the following procedure:

---

To a solution of methyl 2-(1-phenylvinyl)benzoate (170 mg, 0.71 mmol) in THF (0.1 M) was added dropwise at –78 °C a solution of MeLi in THF (1.5 M, 1.2 mL). The reaction mixture was stirred at this temperature for 1 h and then slowly warmed up to room temperature. After stirring overnight, the reaction mixture was quenched with an aqueous NH₄Cl solution, extracted with ethyl acetate. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/50) to give compound 3r as a colorless oil (121 mg, 71% yield).

**Characterization Data of Compounds 3**

*(2-(prop-1-en-2-yl)phenyl)methanol (3a)*

![3a](image)

Colorless oil;

¹H NMR (400 MHz, CDCl₃) δ 7.49 – 7.40 (m, 1H), 7.30 – 7.23 (m, 2H), 7.19 – 7.10 (m, 1H), 5.26 (p, J = 1.7 Hz, 1H), 4.90 (d, J = 1.7 Hz, 1H), 4.70 (s, 2H), 2.08 (s, 3H), 1.70 (s, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 144.9, 143.2, 137.5, 128.3, 128.2, 127.7, 127.4, 115.6, 63.4, 25.2;

ATR-IR ν 3334 (w), 3316 (w), 3304 (w), 1436 (w), 1195 (w), 1006 (m), 901 (m), 762 (s);


*(2-(oct-1-en-2-yl)phenyl)methanol (3b)*

![3b](image)
Colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 (dd, $J = 7.2, 1.8$ Hz, 1H), 7.33 – 7.23 (m, 2H), 7.12 (dd, $J = 7.2, 1.8$ Hz, 1H), 5.21 (q, $J = 1.7$ Hz, 1H), 4.91 (d, $J = 2.1$ Hz, 1H), 4.68 (s, 2H), 2.35 (t, $J = 7.6$ Hz, 2H), 1.43 – 1.19 (m, 8H), 0.87 (t, $J = 6.7$ Hz, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 149.4, 142.6, 137.8, 128.6, 128.3, 127.5, 127.3, 114.4, 63.3, 38.5, 31.8, 29.2, 27.9, 22.8, 14.2;

ATR-IR $\nu$ 3310 (w), 2956 (w), 2927 (m), 2856 (w), 2855 (w), 1458 (w), 1034 (m), 1008 (m), 902 (m), 762 (s), 727 (m);

HRMS (ESI) calcd for C$_{15}$H$_{22}$O $[M+]$ 218.1665; found 218.1668.

3-(2-(hydroxymethyl)phenyl)but-3-en-1-ol (3c)

Colorless oil;

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.50 – 7.41 (m, 1H), 7.29 – 7.21 (m, 2H), 7.16 – 7.10 (m, 1H), 5.29 (q, $J = 1.4$ Hz, 1H), 4.96 (d, $J = 1.9$ Hz, 1H), 4.63 (s, 2H), 3.55 (t, $J = 6.7$ Hz, 2H), 2.62 (td, $J = 6.8, 1.4$ Hz, 2H);

$^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 146.9, 142.8, 139.3, 129.6, 129.2, 128.2, 116.8, 62.8, 60.8, 42.5;

ATR-IR $\nu$ 3319 (w), 2933 (w), 2884 (w), 1446 (w), 1427 (w), 1197 (w), 1042 (m), 1016 (s), 761 (s);

HRMS (ESI) calcd for C$_{13}$H$_{14}$NaO$_2$ $[M+Na]^+$ 201.0886; found 201.0886.

(2-(4-(benzyloxy)but-1-en-2-yl)phenyl)methanol (3d)
Colorless oil;

\[^1\text{H NMR (400 MHz, CD}_3\text{OD)}\] δ 7.45 – 7.39 (m, 1H), 7.36 – 7.21 (m, 7H), 7.16 – 7.10 (m, 1H), 5.33 (q, \(J = 1.5\) Hz, 1H), 5.04 (d, \(J = 1.8\) Hz, 1H), 4.68 (s, 2H), 4.43 (s, 2H), 3.50 (t, \(J = 6.1\) Hz, 2H), 2.73 (t, \(J = 6.1\) Hz, 2H);

\[^{13}\text{C NMR (101 MHz, CD}_3\text{OD)}\] δ 145.4, 141.5, 138.5, 138.0, 129.4, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 116.8, 72.8, 67.9, 63.3, 38.6;

ATR-IR ν 3382 (w), 2914 (w), 2864 (w), 1454 (m), 1362 (w), 1096 (m), 1095 (m), 1078 (m), 1029 (m), 1007 (m), 736 (s), 698 (s);

HRMS (ESI) calcd for C\(_{18}\)H\(_{20}\)NaO\(_2\) \([\text{M+Na}]^+\) 291.1355; found 291.1355.

**Colorless oil;**

\[^1\text{H NMR (400 MHz, CDCl}_3\text{)}\] δ 7.49 (dd, \(J = 7.5, 1.5\) Hz, 1H), 7.40 – 7.24 (m, 8H), 5.80 (d, \(J = 1.3\) Hz, 1H), 5.25 (d, \(J = 1.4\) Hz, 1H), 4.43 (s, 2H);

\[^{13}\text{C NMR (101 MHz, CDCl}_3\text{)}\] δ 148.5, 140.8, 140.6, 138.8, 130.4, 128.7, 128.24, 128.20, 128.1, 127.8, 126.7, 115.8, 63.4;

ATR-IR ν 3422 (w), 3416 (w), 3058 (w), 3026 (w), 2924 (w), 1493 (w), 1446 (w), 1026 (m), 757 (s), 700 (s);

HRMS (ESI) calcd for C\(_{15}\)H\(_{14}\)O \([\text{M+]\)} 210.1039; found 210.1042.

**2-(1-phenylvinyl)phenyl)methanol (3e)**

\[\text{3e}\]

**Colorless oil;**

\[^1\text{H NMR (400 MHz, CDCl}_3\text{)}\] δ 7.49 (dd, \(J = 7.5, 1.5\) Hz, 1H), 7.40 – 7.24 (m, 8H), 5.80 (d, \(J = 1.3\) Hz, 1H), 5.25 (d, \(J = 1.4\) Hz, 1H), 4.43 (s, 2H);

\[^{13}\text{C NMR (101 MHz, CDCl}_3\text{)}\] δ 148.5, 140.8, 140.6, 138.8, 130.4, 128.7, 128.24, 128.20, 128.1, 127.8, 126.7, 115.8, 63.4;

ATR-IR ν 3422 (w), 3416 (w), 3058 (w), 3026 (w), 2924 (w), 1493 (w), 1446 (w), 1026 (m), 757 (s), 700 (s);

HRMS (ESI) calcd for C\(_{18}\)H\(_{14}\)O \([\text{M+]\)} 210.1039; found 210.1042.

**2-(1-(p-tolyl)vinyl)phenyl)methanol (3f)**

\[\text{3f}\]
Colorless oil;

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.54 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.36 (td, $J = 7.6, 1.4$ Hz, 1H), 7.28 (td, $J = 7.5, 1.5$ Hz, 1H), 7.17 – 7.08 (m, 5H), 5.76 (d, $J = 1.4$ Hz, 1H), 5.12 (d, $J = 1.4$ Hz, 1H), 4.37 (s, 2H), 2.31 (s, 3H);

$^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 149.8, 141.6, 140.4, 139.1, 138.8, 130.8, 130.1, 128.7, 128.0, 127.9, 127.5, 114.7, 62.6, 21.1;

ATR-IR $\nu$ 3325 (w), 2921 (w), 2886 (w), 2864 (w), 1510 (m), 1035 (m), 1019 (m), 826 (s), 770 (s), 735 (m);

HRMS (ESI) calcd for C$_{16}$H$_{16}$O [M+] 224.1196; found 224.1200.

(2-(1-(4-methoxyphenyl)vinyl)phenyl)methanol (3g)

![Structure of compound 3g](image)

Colorless oil;

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.55 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.36 (td, $J = 7.5, 1.5$ Hz, 1H), 7.28 (td, $J = 7.5, 1.4$ Hz, 1H), 7.19 – 7.15 (m, 3H), 6.83 (d, $J = 8.9$ Hz, 2H), 5.70 (d, $J = 1.4$ Hz, 1H), 5.06 (d, $J = 1.5$ Hz, 1H), 4.38 (s, 2H), 3.77 (s, 3H);

$^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 161.0, 149.3, 141.7, 140.4, 134.4, 130.8, 128.74, 128.69, 127.98, 127.96, 114.8, 113.6, 62.6, 55.7;

ATR-IR $\nu$ 3364 (w), 2934 (w), 2836 (w), 1509 (s), 1249 (s), 1180 (m), 1033 (s), 837 (s), 773 (m);

HRMS (ESI) calcd for C$_{16}$H$_{16}$NaO$_2$ $^+$ [M+Na]$^+$ 263.1042; found 263.1043.

(2-(1-(4-fluorophenyl)vinyl)phenyl)methanol (3h)

![Structure of compound 3h](image)
Colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.50 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.38 (td, $J = 7.5$, 1.6 Hz, 1H), 7.32 (td, $J = 7.4$, 1.5 Hz, 1H), 7.25 – 7.21 (m, 3H), 6.97 (t, $J = 8.7$ Hz, 2H), 5.73 (d, $J = 1.1$ Hz, 1H), 5.22 (d, $J = 1.1$ Hz, 1H), 4.43 (s, 2H);

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.7 (d, $J = 247.7$ Hz), 147.4, 140.3, 138.7, 136.8 (d, $J = 3.3$ Hz), 130.3, 128.4 (d, $J = 8.1$ Hz), 128.3, 128.1, 127.8, 115.5 (d, $J = 21.4$ Hz), 115.5, 63.3;

ATR-IR ν 3335 (w), 2953 (w), 2926 (w), 2898 (w), 2889 (w), 1508 (s), 1225 (m), 1161 (m), 842 (s), 773 (m);

HRMS (ESI) calcd for C$_{15}$H$_{13}$FO [M+] 228.0945; found 228.0949.

(4-methyl-2-(1-(p-tolyl)vinyl)phenyl)methanol (3i)

Colorless oil;

$^1$H NMR (400 MHz, CD$_3$OD) δ 7.41 (d, $J = 7.8$ Hz, 1H), 7.18 (dd, $J = 7.9$, 1.7 Hz, 1H), 7.14 – 7.07 (m, 4H), 6.98 (d, $J = 1.8$ Hz, 1H), 5.73 (d, $J = 1.5$ Hz, 1H), 5.10 (d, $J = 1.5$ Hz, 1H), 4.33 (s, 2H), 2.33 (s, 3H), 2.31 (s, 3H);

$^{13}$C NMR (101 MHz, CD$_3$OD) δ 149.8, 141.6, 139.2, 138.7, 137.7, 137.3, 131.5, 130.0, 129.3, 128.3, 127.5, 114.5, 62.6, 21.13, 21.10.;

ATR-IR ν 3383 (w), 2920 (w), 2864 (w), 1510 (w), 1206 (w), 1185 (w), 1035 (m), 1018 (s), 815 (s);

HRMS (ESI) calcd for C$_{17}$H$_{18}$O [M+] 238.1352; found 238.1353.

(4-chloro-2-(1-(p-tolyl)vinyl)phenyl)methanol (3j)
Colorless oil;

\textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}OD) \(\delta\) 7.53 (d, \(J = 8.3\) Hz, 1H), 7.37 (dd, \(J = 8.3, 2.2\) Hz, 1H), 7.18 – 7.08 (m, 5H), 5.79 (d, \(J = 1.1\) Hz, 1H), 5.15 (d, \(J = 1.2\) Hz, 1H), 4.33 (s, 2H), 2.32 (s, 3H);

\textsuperscript{13}C NMR (101 MHz, CD\textsubscript{3}OD) \(\delta\) 148.5, 143.3, 139.4, 139.2, 138.3, 133.6, 130.5, 130.2, 129.6, 128.7, 127.39, 115.5, 62.0, 21.2;

ATR-IR \(\nu\) 3312 (w), 3312 (w), 2921 (w), 2864 (w), 1511 (w), 1039 (m), 879 (m), 825 (s);

HRMS (ESI) calcd for C\textsubscript{16}H\textsubscript{15}ClO [M+] 258.0806; found 258.0807.

(5-methyl-2-(1-(p-tolyl)vinyl)phenyl)methanol (3k)

Colorless oil;

\textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}OD) \(\delta\) 7.36 (d, \(J = 1.8\) Hz, 1H), 7.17 – 7.00 (m, 6H), 5.72 (d, \(J = 1.4\) Hz, 1H), 5.10 (d, \(J = 1.4\) Hz, 1H), 4.33 (s, 2H), 2.38 (s, 3H), 2.30 (s, 3H);

\textsuperscript{13}C NMR (101 MHz, CD\textsubscript{3}OD) \(\delta\) 149.7, 140.1, 139.3, 138.74, 138.70, 138.4, 130.9, 130.0, 128.7, 128.6, 127.5, 114.6, 62.7, 21.4, 21.1;

ATR-IR \(\nu\) 3391 (w), 2920 (w), 2863 (w), 2862 (w), 1511 (w), 1033 (m), 1032 (m), 1018 (s), 818 (s);

HRMS (ESI) calcd for C\textsubscript{17}H\textsubscript{18}O [M+] 238.1352; found 238.1354.

(5-bromo-2-(1-(4-fluorophenyl)vinyl)phenyl)methanol (3l)
Colorless oil;

\(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.72 (d, \(J = 2.1\) Hz, 1H), 7.45 (dd, \(J = 8.1, 2.2\) Hz, 1H), 7.26 (dd, \(J = 8.9, 5.4\) Hz, 2H), 7.09 (d, \(J = 8.1\) Hz, 1H), 7.03 (t, \(J = 8.8\) Hz, 2H), 5.79 (d, \(J = 1.0\) Hz, 1H), 5.19 (d, \(J = 1.0\) Hz, 1H), 4.33 (s, 2H);

\(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 164.0 (d, \(J = 246.4\) Hz), 147.7, 143.2, 140.0, 137.7 (d, \(J = 3.3\) Hz), 132.6, 131.0, 130.9, 129.5 (d, \(J = 8.2\) Hz), 122.9, 116.3 (d, \(J = 22.1\) Hz), 116.3, 62.0;

ATR-IR \(\nu\) 3309 (w), 2926 (w), 2855 (w), 1507 (s), 1225 (m), 1160 (m), 1037 (m), 1014 (m), 842 (s), 825 (s);

HRMS (ESI) calcd for C\(_{15}\)H\(_{12}\)BrFO [M+] 306.0050; found 306.0054.

\((5\text{-nitro-2-(1-(p-tolyl)vinyl)phenyl)methanol (3m)}\)

Yellow oil;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.44 (d, \(J = 2.4\) Hz, 1H), 8.16 (dd, \(J = 8.3, 2.4\) Hz, 1H), 7.41 (d, \(J = 8.3\) Hz, 1H), 7.15 – 7.08 (m, 4H), 5.84 (d, \(J = 0.8\) Hz, 1H), 5.22 (d, \(J = 0.8\) Hz, 1H), 4.50 (s, 2H), 2.35 (s, 3H);

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 147.9, 147.0, 146.6, 141.0, 138.8, 136.4, 131.1, 129.6, 126.4, 122.6, 122.5, 116.0, 62.2, 21.3;

ATR-IR \(\nu\) 3324 (w), 2951 (w), 2924 (w), 2856 (w), 1519 (s), 1344 (s), 1039 (w), 905 (w), 827 (m);

HRMS (ESI) calcd for C\(_{16}\)H\(_{15}\)NO\(_3\) [M+] 269.1046; found 269.1049.

\(2\text{-}(2\text{-}(1\text{-phenylvinyl)phenyl)propan-2-ol (3r)}\)
Colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.52 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.34 – 7.24 (m, 7H), 7.11 (dd, $J = 7.5$, 1.5 Hz, 1H), 5.87 (d, $J = 1.3$ Hz, 1H), 5.23 (d, $J = 1.3$ Hz, 1H), 1.49 (s, 6H);

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.6, 146.7, 141.1, 138.5, 132.6, 128.5, 127.9, 127.6, 126.7, 126.6, 126.5, 114.4, 74.4, 32.5;

ATR-IR ν 3432 (w), 2972 (w), 2929 (w), 1494 (w), 1363 (w), 1166 (w), 902 (m), 783 (m), 761 (s), 712 (s);

HRMS (ESI) calcd for C$_{17}$H$_{18}$O [M+] 238.1352; found 238.1354.
Optimization of The Reaction Conditions

Procedure:
In the glovebox, alkene 3a (0.1 mmol, 1 equiv), copper catalyst (x equiv), ligand (y equiv), base (z equiv), and additive (t equiv) were dissolved in degassed MeCN/MeOH (0.067 M) in a sealed tube. Oxidant (u equiv) was then added and the tube was sealed and heated to 100 – 120 °C. After 2 – 24 h, the reaction mixture was cooled down to room temperature, diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound 4a.

Copper catalyst screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu source (50 mol%)</th>
<th>Solvent</th>
<th>Yield/Conversion(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(BF₄)₂·6H₂O</td>
<td>MeCN</td>
<td>24% (20%)&lt;sup&gt;(b)&lt;/sup&gt; 4a, 100% conv.</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)₂</td>
<td>MeCN</td>
<td>20% 4a, 100% conv.</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)₂</td>
<td>MeCN</td>
<td>22% 4a, 90% conv.</td>
</tr>
<tr>
<td>4</td>
<td>CuCl₂</td>
<td>MeCN</td>
<td>degradation</td>
</tr>
<tr>
<td>5</td>
<td>CuSO₄</td>
<td>MeCN</td>
<td>&lt;10% 4a, 82% conv.</td>
</tr>
<tr>
<td>6</td>
<td>CuF₂</td>
<td>MeCN</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>Cu₂O</td>
<td>MeCN</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>CuCl</td>
<td>MeCN</td>
<td>22% 4a, 100% conv.</td>
</tr>
<tr>
<td>9</td>
<td>CuBr</td>
<td>MeCN</td>
<td>&lt;10% 4a, 100% conv.</td>
</tr>
<tr>
<td>10</td>
<td>CuI</td>
<td>MeCN</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>Cu(acac)₂</td>
<td>MeCN</td>
<td>22% 4a, 73% conv.</td>
</tr>
<tr>
<td>Entry</td>
<td>Ligand (y equiv)</td>
<td>Yield/Conversion</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>L1 (0.75)</td>
<td>37% (29%) (b) 4a, 100% conv.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>L2 (0.75)</td>
<td>0% 4a, 80% conv.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>L3 (1.50)</td>
<td>&lt;10% 4a, 84% conv.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>L4 (0.75)</td>
<td>47% (40%) (b) 4a, 100% conv.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>L5 (0.75)</td>
<td>0% 4a, 63% conv.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>L6 (0.75)</td>
<td>34% 4a, 100% conv.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>L7 (0.75)</td>
<td>19% 4a, 76% conv.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>L8 (0.75)</td>
<td>53% (44%) (b) 4a, 100% conv.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>L8 (0.25)</td>
<td>42% 4a, 100% conv.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>L8 (0.50)</td>
<td>50% 4a, 100% conv.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>L8 (1.00)</td>
<td>57% (51%) (b) 4a, 100% conv.</td>
<td></td>
</tr>
</tbody>
</table>

(a) Yield determined by $^1$H NMR spectroscopy with CH$_2$Br$_2$ as internal standard
(b) Isolated yield.
(a) Yield determined by $^1$H NMR spectroscopy with CH$_2$Br$_2$ as internal standard
(b) Isolated yield.

Selected ligands used for screening

**Base screening**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(BF$_4$)$_2$6H$_2$O (x equiv)</th>
<th>Base (z equiv)</th>
<th>Yield/Conversion$^{(a)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>K$_3$PO$_4$ (0.5)</td>
<td>57% (51%)$^{(b)}$ 4a, 100% conv.</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>Na$_3$PO$_4$ (0.5)</td>
<td>43% 4a, 100% conv.</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>Na$_2$HPO$_4$ (0.5)</td>
<td>13% 4a, 60% conv.</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>K$_2$CO$_3$ (0.5)</td>
<td>45% 4a, 90% conv.</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>CsOPiv (0.5)</td>
<td>34% 4a, 83% conv.</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>KOH (0.5)</td>
<td>43% 4a, 100% conv.</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>tBuOK (0.25)</td>
<td>54% 4a, 100% conv.</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
<td>none</td>
<td>20% 4a, 64% conv.</td>
</tr>
<tr>
<td>9</td>
<td>0.3</td>
<td>K$_3$PO$_4$ (0.5)</td>
<td>50% 4a, 90% conv.</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
<td>K$_3$PO$_4$ (0.5)</td>
<td>30% 4a, 72% conv.</td>
</tr>
<tr>
<td>11</td>
<td>0.1</td>
<td>K$_3$PO$_4$ (0.5)</td>
<td>26% 4a, 72% conv.</td>
</tr>
<tr>
<td>12</td>
<td>0.3</td>
<td>K$_3$PO$_4$ (0.25)</td>
<td>52% 4a, 92% conv.</td>
</tr>
</tbody>
</table>

(a) Yield determined by $^1$H NMR spectroscopy with CH$_2$Br$_2$ as internal standard;
(b) Isolated yield.
**Solvent screening**

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents</th>
<th>Yield/Conversion&lt;sup&gt;(a)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN/MeOH (4/1)</td>
<td>52% 4a, 92% conv.</td>
</tr>
<tr>
<td>2</td>
<td>MeCN/EtOH (4/1)</td>
<td>40% 4a, 90% conv.</td>
</tr>
<tr>
<td>3</td>
<td>MeCN/iPrOH (4/1)</td>
<td>19% 4a, 96% conv.</td>
</tr>
<tr>
<td>4</td>
<td>MeCN/tBuOH (4/1)</td>
<td>28% 4a, 100% conv.</td>
</tr>
<tr>
<td>5</td>
<td>MeCN/CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH (4/1)</td>
<td>26% 4a, 100% conv.</td>
</tr>
<tr>
<td>6</td>
<td>MeCN/H&lt;sub&gt;2&lt;/sub&gt;O (4/1)</td>
<td>39% 4a, 78% conv.</td>
</tr>
<tr>
<td>7</td>
<td>MeCN/MeOH (9/1)</td>
<td>33% 4a, 99% conv.</td>
</tr>
<tr>
<td>8</td>
<td>MeCN/MeOH (7/3)</td>
<td>54% (56%)&lt;sup&gt;(b,c)&lt;/sup&gt; 4a, 90% conv.</td>
</tr>
<tr>
<td>9</td>
<td>MeCN/MeOH (6/4)</td>
<td>43% 4a, 83% conv.</td>
</tr>
</tbody>
</table>

<sup>(a)</sup> Yield determined by <sup>1</sup>H NMR spectroscopy with CH<sub>2</sub>Br<sub>2</sub> as internal standard

<sup>(b)</sup> Isolated yield

<sup>(c)</sup> Reaction time: 3.5 h

**Oxidant and Additive screening**

![Chemical reaction diagram]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (u equiv)</th>
<th>Additive (t equiv)</th>
<th>Yield/Conversion(^{(a)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O1 (4.0)</td>
<td>none</td>
<td>54% 4a, 90% conv.</td>
</tr>
<tr>
<td>2</td>
<td>O2 (4.0)</td>
<td>none</td>
<td>50% 4a, 100% conv.</td>
</tr>
<tr>
<td>3</td>
<td>O3 (4.0)</td>
<td>none</td>
<td>50% 4a, 94% conv.</td>
</tr>
<tr>
<td>4</td>
<td>O4 (4.0)</td>
<td>none</td>
<td>&lt;10% 4a, 100% conv.</td>
</tr>
<tr>
<td>5</td>
<td>O1 (3.0)</td>
<td>none</td>
<td>52% 4a, 90% conv.</td>
</tr>
<tr>
<td>6</td>
<td>O1 (2.0)</td>
<td>none</td>
<td>39% 4a, 80% conv.</td>
</tr>
<tr>
<td>7</td>
<td>O4 (4.0)</td>
<td>BnOH (2.0)</td>
<td>43% 4a, 95% conv.</td>
</tr>
<tr>
<td>8</td>
<td>O4 (4.0)</td>
<td>BnOH (1.6)</td>
<td>58% 4a, 94% conv.</td>
</tr>
<tr>
<td>9</td>
<td>O4 (4.0)</td>
<td>BnOH (1.2)</td>
<td>61% (62(^{(b,c)})) 4a, 94% conv.</td>
</tr>
<tr>
<td>10</td>
<td>O4 (4.0)</td>
<td>BnOH (0.7)</td>
<td>55% 4a, 95% conv.</td>
</tr>
<tr>
<td>11</td>
<td>O4 (4.0)</td>
<td>p-NO(_2)C(_6)H(_4)CH(_2)OH (1.2)</td>
<td>48% 4a, 90% conv.</td>
</tr>
<tr>
<td>12</td>
<td>O4 (4.0)</td>
<td>p-ClC(_6)H(_4)CH(_2)OH (1.2)</td>
<td>59% 4a, 93% conv.</td>
</tr>
<tr>
<td>13</td>
<td>O4 (4.0)</td>
<td>p-MeOC(_6)H(_4)CH(_2)OH (1.2)</td>
<td>59% 4a, 91% conv.</td>
</tr>
<tr>
<td>14</td>
<td>O4 (4.0)</td>
<td>Pinacol (1.2)</td>
<td>25% 4a, 95% conv.</td>
</tr>
<tr>
<td>15</td>
<td>O4 (4.0)</td>
<td>Benzaldehyde (1.2)</td>
<td>38% 4a, 59% conv.</td>
</tr>
<tr>
<td>16</td>
<td>O4 (4.0)</td>
<td>1-Phenylethanol (1.0)</td>
<td>52% 4a, 91% conv.</td>
</tr>
<tr>
<td>17</td>
<td>O4 (4.0)</td>
<td>Diphenylcarbinol (1.0)</td>
<td>60% 4a, 89% conv.</td>
</tr>
<tr>
<td>18</td>
<td>O4 (4.0)</td>
<td>Diphenylcarbinol (2.0)</td>
<td>61% 4a, 93% conv.</td>
</tr>
<tr>
<td>19(^{(d)})</td>
<td>O4 (4.0)</td>
<td>BnOH (1.2)</td>
<td>69% (65(^{(b)})) 4a, 100% conv.</td>
</tr>
</tbody>
</table>

(a) Yield determined by \(^1\)H NMR spectroscopy with CH\(_2\)Br\(_2\) as internal standard;
(b) Isolated yield
(c) Reaction time : 3 h
(d) Reaction was conducted at 100 °C.

\(O1 = \text{DTBP (di-tert-butyl peroxide)}\)  \(O2 = \text{Dicumyl peroxide}\)

\(O3 = \text{t-Butyl benzoyl peroxide}\)

\(O4 = \text{t-Butyl benzoyl peroxide}\)
General Procedure for The Synthesis of Dihydroisobenzofurans 4

In the glovebox, alkene 3 (0.1 mmol, 1 equiv), Cu(BF$_4$)$_2$.6H$_2$O (30 mol%), bathophenanthroline (60 mol%), BnOH (120 mol%), and K$_3$PO$_4$ (25 mol%) were dissolved in degassed MeCN/MeOH (v/v 7/3, 0.067 M) in a sealed tube. (t-BuO)$_2$ (4 equiv) was then added and the tube was sealed and heated to 100 °C. After 18 h, the reaction mixture was cooled down to room temperature, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound 4.

Characterization Data of Compounds 4

3-(1-methyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4a)

Yield: 12.2 mg (65%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.10 – 7.06 (m, 1H), 5.11 (d, $J = 12.5$ Hz, 1H), 5.05 (d, $J = 12.5$ Hz, 1H), 2.34 (ddd, $J = 16.1$, 10.0, 5.7 Hz, 1H), 2.24 (ddd, $J = 13.6$, 9.9, 5.7 Hz, 1H), 2.14 (ddd, $J = 13.7$, 9.9, 5.1 Hz, 1H), 2.10 – 1.99 (m, 1H), 1.49 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 143.1, 139.1, 128.3, 128.0, 121.5, 120.9, 120.1, 87.1, 72.0, 37.1, 27.5, 12.4;

ATR-IR ν 2970 (w), 2928 (w), 2856 (w), 2247 (w), 1454 (w), 1359 (w), 1031 (s), 1019 (s), 763 (s), 726 (s);

HRMS (ESI) calcd for C$_{12}$H$_{12}$NO [M+] 186.0913; found 186.0916.
3-(1-hexyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4b)

Yield: 16.1 mg (63%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.23 – 7.18 (m, 2H), 7.13 – 7.07 (m, 1H), 6.99 – 6.91 (m, 1H), 4.99 (s, 2H), 2.26 – 2.09 (m, 2H), 2.07 – 1.96 (m, 1H), 1.86 (ddd, $J$ = 17.0, 10.6, 5.1 Hz, 1H), 1.75 – 1.58 (m, 2H), 1.20 – 1.05 (m, 7H), 0.90 – 0.82 (m, 1H), 0.73 (t, $J$ = 6.8 Hz, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.5, 139.9, 128.2, 128.0, 121.3, 121.2, 120.2, 90.1, 73.2, 41.3, 36.5, 31.8, 29.6, 23.6, 22.7, 14.2, 12.2;

ATR-IR $\nu$ 2929 (m), 2929 (m), 2929 (m), 2856 (w), 2248 (w), 1463 (m), 999 (s), 756 (s), 701 (m);

HRMS (ESI) calcd for C$_{17}$H$_{23}$NNaO$_2$ $^{[M+Na]^+}$ 280.1672; found 280.1670.

3-(1-(2-hydroxyethyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4c)

Yield: 10.6 mg (52%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 – 7.31 (m, 2H), 7.27 – 7.25 (m, 1H), 7.09 – 7.04 (m, 1H), 5.16 (d, $J$ = 12.4 Hz, 1H), 5.13 (d, $J$ = 12.4 Hz, 1H), 3.67 (ddd, $J$ = 11.4, 6.8, 4.8 Hz, 1H), 3.58 (ddd, $J$ = 11.4, 6.8, 4.8 Hz, 1H), 2.43 – 2.23 (m, 1H), 2.18 – 1.95 (m, 4H), 1.64 (broad, s, 1H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 140.9, 139.3, 128.8, 128.4, 121.7, 121.1, 119.8, 90.6, 73.0, 59.3, 42.2, 36.2, 12.1;

ATR-IR $\nu$ 3423 (w), 2952 (w), 2923 (w), 2912 (w), 1028 (s), 1018 (s), 761 (s), 726 (m);

HRMS (ESI) calcd for C$_{13}$H$_{13}$NNaO$_2$ $^{[M+Na]^+}$ 240.0995; found 240.0994.
3-(1-(2-hydroxyethyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4d)

Yield: 15.3 mg (49%), colorless oil;

$^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 7.37 – 7.23 (m, 5H), 7.23 – 7.17 (m, 3H), 7.12 – 7.03 (m, 1H), 5.08 (d, \ J = 12.5 \text{ Hz, 1H}), 5.04 (d, \ J = 12.5 \text{ Hz, 1H}), 4.39 (d, \ J = 11.8 \text{ Hz, 1H}), 4.35 (d, \ J = 11.8 \text{ Hz, 1H}), 3.53 (ddd, \ J = 9.4, 7.3, 6.1 \text{ Hz, 1H}), 3.33 (ddd, \ J = 9.4, 7.3, 6.3 \text{ Hz, 1H}), 2.38 – 2.22 (m, 2H), 2.22 – 2.07 (m, 3H), 1.98 (ddd, \ J = 14.6, 11.0, 4.8 \text{ Hz, 1H});$

$^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \ \delta \ 141.0, 139.5, 138.2, 128.5, 128.4, 128.1, 127.8, 127.7, 121.5, 121.4, 120.0, 88.8, 73.2, 72.9, 66.2, 40.6, 36.6, 12.1;$

ATR-IR ν 2925 (w), 2856 (w), 2246 (w), 1456 (m), 1367 (m), 1366 (m), 1102 (s), 1027 (s), 730 (s), 699 (s);

HRMS (ESI) calcd for $C_{20}H_{21}NNaO_2^+$ [M+Na]$^+$ 330.1464; found 330.1464.

3-(1-phenyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4e)

Yield: 14.6 mg (58%), yellow oil;

$^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 7.53 – 7.44 (m, 2H), 7.39 – 7.15 (m, 7H), 5.20 (d, \ J = 12.5 \text{ Hz, 1H}), 5.15 (d, \ J = 12.5 \text{ Hz, 1H}), 2.59 (ddd, \ J = 13.9, 10.2, 5.9 \text{ Hz, 1H}), 2.47 (ddd, \ J = 14.0, 9.6, 5.7 \text{ Hz, 1H}), 2.37 – 2.13 (m, 2H);$}

$^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \ \delta \ 143.5, 142.4, 139.2, 128.7, 128.4, 128.0, 127.7, 125.0, 121.9, 121.6, 120.0, 89.9, 72.2, 37.3, 12.7;$

ATR-IR ν 2929 (w), 2928 (w), 2853 (w), 2853 (w), 2247 (w), 1459 (w), 1446 (w), 1018 (m), 753 (s), 753 (s), 725 (s), 700 (s);
HRMS (ESI) calcd for C_{17}H_{15}NNaO^+ [M+Na]^+ 272.1046; found 272.1048.

3-(1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4f)

Yield: 20.0 mg (76%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 (d, $J = 8.2$ Hz, 2H), 7.33 – 7.27 (m, 3H), 7.24 – 7.19 (m, 1H), 7.15 (d, $J = 8.2$ Hz, 2H), 5.19 (d, $J = 12.5$ Hz, 1H), 5.15 (d, $J = 12.5$ Hz, 1H), 2.58 (ddd, $J = 13.9$, 10.4, 5.7 Hz, 1H), 2.46 (ddd, $J = 13.9$, 9.8, 5.6 Hz, 1H), 2.37 – 2.17 (m, 2H), 2.32 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 142.6, 140.6, 139.1, 137.4, 129.4, 128.3, 128.0, 124.9, 121.8, 121.6, 120.0, 89.9, 72.2, 37.2, 21.1, 12.7;

ATR-IR ν 2953 (w), 2945 (w), 2923 (w), 2858 (w), 2247 (w), 1509 (w), 1459 (w), 1017 (s), 817 (s), 758 (s), 732 (s);

HRMS (ESI) calcd for C$_{18}$H$_{17}$NNaO$^+$ [M+Na]$^+$ 286.1202; found 286.1205.

3-(1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4g)

Yield: 22.9 mg (82%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 (d, $J = 8.8$ Hz, 2H), 7.32 – 7.27 (m, 3H), 7.23 – 7.19 (m, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.18 (d, $J = 12.5$ Hz, 1H), 5.13 (d, $J = 12.5$ Hz, 1H), 3.78 (s, 3H), 2.58 (ddd, $J = 13.8$, 10.4, 5.6 Hz, 1H), 2.45 (ddd, $J = 13.8$, 9.9, 5.4 Hz, 1H), 2.37 – 2.14 (m, 2H);

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.1, 142.6, 139.2, 135.6, 128.3, 128.0, 126.3, 121.8, 121.6, 120.0, 114.1, 89.7, 72.1, 55.4, 37.2, 12.7;
ATR-IR ν 2952 (w), 2932 (w), 2839 (w), 2246 (w), 1509 (s), 1248 (s), 1029 (s), 830 (s), 760 (s), 735 (s);

HRMS (ESI) calcd for C_{18}H_{17}NNaO_{2}+ [M+Na]^+ 302.1151; found 302.1163.

3-(1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4h)

Yield: 13.9 mg (52%), white solid, mp: 123 – 124 °C;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.49 – 7.40 (m, 2H), 7.36 – 7.28 (m, 3H), 7.25 – 7.22 (m, 1H), 7.09 – 6.92 (m, 2H), 5.19 (d, \(J = 12.5\) Hz, 1H), 5.14 (d, \(J = 12.5\) Hz, 1H), 2.56 (ddd, \(J = 13.9\), 10.2, 5.9 Hz, 1H), 2.46 (ddd, \(J = 14.0\), 9.6, 5.6 Hz, 1H), 2.38 – 2.12 (m, 2H);

\(^13\)C NMR (101 MHz, CDCl\(_3\)) δ 162.3 (d, \(J = 246.5\) Hz), 142.0, 139.4 (d, \(J = 3.1\) Hz), 139.2, 128.5, 128.1, 126.8 (d, \(J = 8.0\) Hz), 121.8, 121.7, 119.8, 115.6 (d, \(J = 21.4\) Hz), 89.6, 72.2, 37.3, 12.7;

ATR-IR ν 2934 (w), 2933 (w), 2932 (w), 2916 (w), 2863 (w), 2241 (w), 1506 (s), 1219 (m), 1158 (m), 1009 (s), 832 (s), 767 (s), 738 (s);

HRMS (ESI) calcd for C_{17}H_{14}FNNaO^+ [M+Na]^+ 290.0952; found 290.0957.

3-(6-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4i)

Yield: 21.0 mg (76%), white solid, mp: 61 – 63 °C;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.36 (d, \(J = 8.2\) Hz, 2H), 7.15 (d, \(J = 8.2\) Hz, 2H), 7.10 – 7.08 (m, 3H), 5.16 (d, \(J = 12.5\) Hz, 1H), 5.12 (d, \(J = 12.5\) Hz, 1H), 2.57 (ddd, \(J = 13.8\), 10.6, 5.6 Hz, 1H), 2.45 (ddd, \(J = 13.8\), 10.1, 5.3 Hz, 1H), 2.38 (s, 3H), 2.37 – 2.18 (m, 2H), 2.32 (s, 3H);
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 142.8, 140.8, 137.8, 137.3, 136.2, 129.4, 129.2, 124.9, 122.3, 121.2, 120.1, 89.8, 72.1, 37.1, 21.6, 21.1, 12.7;

**ATR-IR** ν 2955 (w), 2954 (w), 2920 (w), 2920 (w), 2853 (w), 2251 (w), 1437 (w), 1356 (w), 1270 (w), 1022 (s), 1011 (s), 821 (s);

**HRMS (ESI)** calcd for C$_{19}$H$_{19}$NNaO$^+$ [M+Na]$^+$ 300.1359; found 300.1365.

3-(6-chloro-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4j)

![Compound 4j](image)

Yield: 24.0 mg (81%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 (d, J = 8.2 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 7.8, 0.9 Hz, 1H), 5.16 (d, J = 12.6 Hz, 1H), 5.13 (d, J = 12.6 Hz, 1H), 2.56 (ddd, J = 13.9, 9.4, 6.6 Hz, 1H), 2.42 (ddd, J = 13.9, 8.4, 6.9 Hz, 1H), 2.33 – 2.23 (m, 2H), 2.30 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 144.9, 139.8, 137.8, 137.5, 133.9, 129.6, 128.6, 124.8, 122.8, 122.1, 119.8, 89.8, 71.8, 37.0, 21.1, 12.7;

**ATR-IR** ν 2955 (w), 2926 (w), 2925 (w), 2870 (w), 2245 (w), 1510 (w), 1476 (w), 1030 (s), 817 (s);

**HRMS (ESI)** calcd for C$_{18}$H$_{16}$ClNNaO$^+$ [M+Na]$^+$ 320.0813; found 320.0817.

3-(5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4k)

![Compound 4k](image)

Yield: 22.1 mg (80%), colorless oil;
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 7.35 (d, \(J = 8.2\) Hz, 2H), 7.20 (d, \(J = 7.8\) Hz, 1H), 7.14 (d, \(J = 8.2\) Hz, 2H), 7.13 – 7.10 (m, 1H), 7.02 (s, 1H), 5.16 (d, \(J = 12.5\) Hz, 1H), 5.11 (d, \(J = 12.5\) Hz, 1H), 2.56 (ddd, \(J = 13.8, 10.4, 5.7\) Hz, 1H), 2.44 (ddd, \(J = 13.8, 9.9, 5.4\) Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.33 – 2.19 (m, 2H); 

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta \) 140.9, 139.7, 139.5, 138.3, 137.3, 129.4, 128.8, 124.9, 124.9, 122.0, 121.5, 120.1, 89.7, 72.0, 37.2, 21.4, 21.1, 12.7; 

ATR-IR \(\nu \) 2946 (w), 2945 (w), 2924 (w), 2859 (w), 2247 (w), 1511 (w), 1441 (w), 1028 (s), 1027 (s), 1017 (s), 815 (s); 

HRMS (ESI) calcd for C\(_{19}\)H\(_{19}\)NNaO\(^+\) [M+Na]\(^+\) 300.1359; found 300.1363.

3-(5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4l)

Yield: 24.4 mg (71%), yellow oil; 

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 7.49 – 7.44 (m, 1H), 7.43 – 7.37 (m, 3H), 7.18 (d, \(J = 8.1\) Hz, 1H), 7.06 – 6.99 (m, 2H), 5.16 (d, \(J = 12.9\) Hz, 1H), 5.09 (d, \(J = 12.9\) Hz, 1H), 2.54 (ddd, \(J = 13.9, 9.9, 6.0\) Hz, 1H), 2.42 (ddd, \(J = 13.9, 9.1, 5.9\) Hz, 1H), 2.35 – 2.20 (m, 2H); 

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta \) 162.4 (d, \(J = 247.0\) Hz), 141.5, 141.3, 138.7 (d, \(J = 3.2\) Hz), 131.3, 126.7 (d, \(J = 8.1\) Hz), 125.1, 123.3, 122.6, 119.6, 115.7 (d, \(J = 21.4\) Hz), 89.5, 71.5, 37.1, 12.6; 

ATR-IR \(\nu \) 2955 (w), 2925 (w), 2862 (w), 2861 (w), 2243 (w), 1506 (s), 1222 (s), 1024 (s), 845 (s), 817 (s), 742 (m); 

HRMS (ESI) calcd for C\(_{17}\)H\(_{13}\)BrFNNaO\(^+\) [M+Na]\(^+\) 368.0057; found 368.0058.

3-(5-nitro-1-(p-toly1)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4m)
Yield: 24.3 mg (79%), yellow oil;

\[^1\text{H}\text{ NMR (400 MHz, CDCl}_3\text{)}\delta 8.21 (dd, J = 8.4, 2.0 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 5.28 (d, J = 13.1 Hz, 1H), 5.21(d, J = 13.1 Hz, 1H), 2.62 (ddd, J = 13.9, 8.6, 7.1 Hz, 1H), 2.47 (ddd, J = 14.0, 9.1, 6.3 Hz, 1H), 2.32 (s, 3H), 2.34 – 2.30 (m, 2H);

\[^13\text{C NMR (101 MHz, CDCl}_3\text{)}\delta 149.8, 148.6, 140.9, 138.7, 138.2, 129.8, 124.8, 124.0, 122.6, 119.5, 117.4, 89.8, 71.4, 36.8, 21.1, 12.6;

ATR-IR ν 2954 (w), 2953 (w), 2925 (w), 2925 (w), 2869 (w), 2859 (w), 2858 (w), 2247 (w), 1521 (s), 1345 (s), 1032 (m), 1018 (m), 816 (s), 729 (m);

HRMS (ESI) calcd for C\text{18}H\text{16}N\text{2}NaO\text{3}[M+Na]^+ 331.1053; found 331.1051.

2-methyl-3-(5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4n)

Yield: 21.5 mg (74%), colorless oil;

\[^1\text{H}\text{ NMR (400 MHz, CDCl}_3\text{)}\delta 7.38 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.25 (d, J = 7.8 Hz, 0.5H), 7.17 (d, J = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.02 (s, 0.5H), 7.01 (s, 0.5H), 5.25 – 5.05 (m, 2H), 2.72 – 2.42 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.31 – 2.19 (m, 1H), 1.29 (d, J = 7.1 Hz, 1.5H), 1.28 (d, J = 7.1 Hz, 1.5H);

\[^13\text{C NMR (101 MHz, CDCl}_3\text{)}\delta 141.6, 141.4, 140.1, 140.0, 139.8, 139.3, 138.2, 138.1, 137.14, 137.09, 129.32, 129.27, 128.63, 128.61, 124.9, 124.8, 123.5, 123.4, 122.2, 122.1, 121.9, 121.5, 90.1, 89.9, 71.9 (2C), 45.6, 45.5, 21.7, 21.4, 21.4, 21.3, 21.1, 21.0, 19.8, 19.5;

ATR-IR ν 2939 (w), 2938 (w), 2921 (w), 2858 (w), 2857 (w), 2852 (w), 2238 (w), 1510 (w), 1454 (w), 1031 (s), 1018 (s), 819 (s), 813 (s);
2-((5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)butanenitrile (4o)

Yield: 20.4 mg (67%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 – 7.35 (m, 2H), 7.28 (d, $J = 7.8$ Hz, 0.5H), 7.19 (d, $J = 7.8$ Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.04 (s, 0.53H), 7.02 (s, 0.47H), 5.25 – 5.09 (m, 2H), 2.64 – 2.52 (m, 1.5H), 2.36 (s, 1.5H), 2.35 (s, 1.5H), 2.31 (s, 3H), 2.40 – 2.22 (m, 1.5H), 1.68 – 1.58 (m, 2H), 1.02 (t, $J = 7.4$ Hz, 1.5H), 1.01 (t, $J = 7.4$ Hz, 1.5H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.6, 141.5, 140.1, 140.0, 139.9, 139.3, 138.2, 138.1, 137.1, 137.0, 129.3, 129.2, 128.63, 128.59, 124.9, 124.8, 122.6, 122.5, 122.2, 122.1, 121.9, 121.4, 90.2, 89.9, 72.0, 71.9, 43.7 (2C), 29.0, 28.6, 27.1, 26.6, 21.4, 21.3, 21.1, 21.0, 11.5, 11.4;

ATR-IR $\nu$ 2967 (w), 2926 (w), 2861 (w), 2237 (w), 1510 (w), 1459 (w), 1033 (s), 811 (s);

HRMS (ESI) calcd for C$_{21}$H$_{22}$NNaO$^+$ [M+Na]$^+$ 314.1515; found 314.1514.

2-((5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)pentanenitrile (4p)

Yield: 21.1 mg (66%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.35 (m, 2H), 7.27 (d, $J = 7.8$ Hz, 0.5H), 7.18 (d, $J = 7.8$ Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.04 (s, 0.53H), 7.02 (s, 0.47H), 5.25 – 5.09 (m, 2H), 2.64 – 2.52 (m, 1.5H), 2.45 – 2.38
(m, 0.5H), 2.36 (s, 1.5H), 2.35 (s, 1.5H), 2.31 (s, 3H), 2.33 – 2.22 (m, 1H), 1.62 – 1.50 (m, 3H), 1.44 – 1.35 (m, 1H), 0.88 (t, J = 7.3 Hz, 1.5H), 0.87 (t, J = 7.3 Hz, 1.5H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.6, 141.5, 140.1, 140.0, 139.9, 139.3, 138.2, 138.1, 137.1, 137.0, 129.3, 129.2, 128.62, 128.6, 125.0, 124.8, 122.8, 122.7, 122.2, 121.4, 121.9, 90.2, 90.0, 72.0, 71.9, 44.0 (2C), 35.8, 35.4, 27.2, 26.8, 21.4, 21.3, 21.1, 21.0, 20.2, 20.1, 13.66, 13.64;

ATR-IR $\nu$ 2959 (w), 2925 (w), 2865 (w), 2237 (w), 1510 (w), 1465 (w), 1458 (w), 1032 (s), 1018 (s), 820 (s), 813 (s);

HRMS (ESI) calcd for C$_{22}$H$_{25}$NNaO$^+$ [M+Na]$^+$ 342.1828; found 342.1830.

3-methoxy-2-((5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)propanenitrile (4q)

![Chemical Structure](image)

Yield: 21.5 mg (67%), colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.38 (m, 2H), 7.27 (d, J = 7.8 Hz, 0.5H), 7.20 (d, J = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.03 (s, 0.53H), 7.02 (s, 0.47H), 5.24 – 5.09 (m, 2H), 3.54 – 3.39 (m, 2H), 3.32 (s, 1.5H), 3.31 (s, 1.5H), 2.83 (dtd, J = 7.3, 6.1, 4.6 Hz, 0.5H), 2.69 (dtd, J = 8.4, 6.1, 4.5 Hz, 0.5H), 2.62 – 2.40 (m, 2H), 2.35 (s, 3H), 2.31 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.32, 141.29, 140.0, 139.9, 139.8, 139.3, 138.3, 138.2, 137.2, 137.1, 129.3 129.30, 128.69, 128.68, 124.92, 124.88, 122.2, 122.1, 121.2, 121.6, 121.3, 121.1, 90.0, 89.8, 72.7, 72.4, 72.0, 71.9, 59.1 (2C), 40.5, 40.4, 28.3, 28.0, 21.4, 21.3, 21.11, 21.09;

ATR-IR $\nu$ 2924 (w), 2923 (w), 2880 (w), 2865 (w), 2864 (w), 2860 (w), 2242 (w), 1448 (s), 1380 (m), 1379 (m), 1348 (s), 1121 (s), 1030 (s), 1018 (s), 813 (s), 711 (s);

HRMS (ESI) calcd for C$_{23}$H$_{23}$NNaO$_2$ [M+Na]$^+$ 344.1621; found 344.1628.

3-(3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4r)
Yield: 8.3 mg (30%), white solid, mp: 63 – 64 °C;

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 – 7.53 (m, 2H), 7.40 – 7.30 (m, 5H), 7.26 – 7.22 (m, 1H), 7.15 – 7.09 (m, 1H), 2.62 – 2.48 (m, 1H), 2.38 – 2.19 (m, 3H), 1.61 (s, 3H), 1.42 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 147.1, 144.7, 141.2, 128.7, 128.6, 128.0, 127.5, 125.3, 122.3, 121.2, 120.1, 88.3, 85.7, 39.1, 30.0, 29.9, 12.9;

ATR-IR ν 974 (w), 2924 (w), 2867 (w), 2853 (w), 2243 (w), 1440 (w), 1052 (m), 975 (m), 765 (s), 704 (s);

HRMS (ESI) calcd for C$_{19}$H$_{19}$NNaO$^+$ [M+Na]$^+$ 300.1359; found 300.1365.
Synthesis of Citalopram (1) from Dihydrobenzofuran 4l

Synthesis of 3-(5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propan-1-amine (11)

To a suspension of LiAlH₄ (14 mg, 1 equiv), and AlCl₃ (40 mg, 1 equiv) in diethyl ether (c = 0.1 M) was added dropwise a solution of 4l (102 mg, 1 equiv) in diethyl ether at 0 °C. The stirring was continued at the same temperature until the starting material was consumed. The reaction mixture was then treated by successive dropwise addition of ice-cold water (14 µL), an aqueous 15% NaOH (14 µL), and ice-cold water (42 µL). After stirring for 30 min, the mixture was filtered through a sintered glass frit. The filtrate was then concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (DCM/methanol/Et₃N 20/1/0.02) to give compound 11 as a colourless oil (73.9 mg, 70% yield).

H NMR (400 MHz, CDCl₃) δ 7.44 – 7.34 (m, 3H), 7.31 (s, 1H), 7.16 (d, J = 8.1 Hz, 1H), 6.97 (t, J = 8.5 Hz, 2H), 5.17 (d, J = 12.7 Hz, 1H), 5.03 (d, J = 12.7 Hz, 1H), 2.89 (broad, s, 2H), 2.39 – 2.27 (m, 1H), 2.22 – 2.15 (m, 1H), 1.75 – 1.71 (m, 1H), 1.62 – 1.56 (m, 1H);

C NMR (101 MHz, CDCl₃) δ 162.1 (d, J = 246.3 Hz), 142.7, 141.2, 139.7 (d, J = 3.0 Hz), 131.0, 126.9 (d, J = 8.1 Hz), 124.8, 123.5, 122.0, 115.5 (d, J = 21.4 Hz), 90.7, 71.6, 39.9, 37.8, 22.6;

ATR-IR ν 3355 (w), 2930 (w), 2856 (w), 2253 (w), 1507 (s), 1224 (s), 1031 (s), 1013 (s), 836 (s), 821 (s), 739 (m), 699 (m);


Synthesis of 3-(5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-N,N-dimethylpropan-1-amine (12)

To a solution of 11 (53 mg, 1 equiv) in MeCN (c = 0.1 M) at 0 °C was added aqueous formalin (35%, 0.4 mL) and NaBH₄CN (45 mg, 5 equiv). The resulting reaction mixture was warmed up to room temperature, occasionally treated with a drop of acetic acid to keep the pH slightly below 7. After stirring for 4 h, the reaction mixture was diluted with ethyl acetate, washed with 1 M NaOH solution, then brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (chloroform/methanol 30/1 to 20/1) to give compound 12 as a colorless oil (47.0 mg, 83% yield).

^1H NMR (400 MHz, CDCl₃) δ 7.46 – 7.36 (m, 3H), 7.34 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.09 – 6.96 (m, 2H), 5.13 (d, J = 12.7 Hz, 1H), 5.08 (d, J = 12.7 Hz, 1H), 2.37 (t, J = 7.4 Hz, 2H), 2.24 (s, 6H), 2.28 – 2.03 (m, 2H), 1.61 – 1.47 (m, 1H), 1.45 – 1.33 (m, 1H);

^13C NMR (101 MHz, CDCl₃) δ 162.0 (d, J = 245.8 Hz), 143.3, 141.5, 140.4 (d, J = 3.2 Hz), 130.8, 126.9 (d, J = 7.9 Hz), 124.7, 123.5, 121.7, 115.3 (d, J = 21.3 Hz), 90.8, 71.4, 59.4, 45.0, 39.1, 21.8;

ATR-IR ν 2944 (w), 2926 (w), 2854 (w), 2781 (w), 1507 (s), 1468 (m), 1225 (s), 1160 (m), 1033 (s), 834 (s), 820 (s);

HRMS (ESI) calcd for C_{19}H_{22}BrFNO [M+H]^+ 378.0863; found 378.0865.

Synthesis of 1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile - Citalopram (1)

In a sealed tube, compound 12 (38 mg, 1 equiv) and CuCN (36 mg, 4 equiv) was dissolved in DMF (1 mL). The reaction mixture was evacuated and filled back with N₂ three times. The resultant mixture was then heated to 150 °C for 24 hours. After cooling to room temperature, this solution was partitioned between toluene (5 mL) and aqueous NH₃ 25% (5 mL) and stirred vigorously for 10 minutes. The aqueous layer was removed and the organic layer was washed 3 times with aqueous solution of NH₃ 25% (3 x 5 mL). The organic phase was then washed with brine (10 mL) and dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by preparative thin layer chromatography (chloroform/methanol 20/1) to give compound 1 as a colorless oil (23.6 mg, 74% yield).

^1H NMR (400 MHz, CDCl₃) δ 7.60 (dd, J = 7.9, 1.4 Hz, 1H), 7.50 (s, 1H), 7.45 – 7.40 (m, 3H), 7.03 – 6.99 (m, 2H), 5.20 (d, J = 12.9 Hz, 1H), 5.15 (d, J = 12.9 Hz, 1H), 2.34 (t, J = 7.2 Hz, 2H), 2.30 – 2.11 (m, 2H), 2.22 (s, 6H), 1.57 – 1.45 (m, 1H), 1.42 – 1.35 (m, 1H);
\[^{13}\text{C} \text{NMR (101 MHz, CDCl}_3\text{)} \delta 162.2 \text{ (d, } J = 246.3 \text{ Hz), 149.5, 140.4, 139.5 \text{ (d, } J = 3.2 \text{ Hz), 132.1, 126.9 \text{ (d, } J = 8.1 \text{ Hz), 125.4, 122.9, 118.8, 115.5 \text{ (d, } J = 21.4 \text{ Hz), 111.9, 91.2, 71.5, 59.3, 45.1} \text{ (2C), 38.9, 21.9};

\text{ATR-IR } \nu 2948 \text{ (w), 2858 \text{ (w), 2782 \text{ (w), 2230 \text{ (w), 1508 (s), 1226 (s), 1226 (s), 1035 (s), 835 (s)}};

\text{HRMS (ESI) calcd for C}_{20}\text{H}_{22}\text{FN}_{2}\text{O}^+ \text{[M+H]}^+ 325.1711; \text{ found 325.1714.}

\text{Transformation of Dihydrobenzofuran 4l}

\text{Synthesis of 3-((4-fluorophenyl)-5-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (13)}

\begin{align*}
\text{[Br]} & \quad \text{Pd(PPh}_3\text{)}_4 \quad \text{Na}_2\text{CO}_3 \quad \text{DME/H}_2\text{O (3/1), 90 °C} \\
4l & \quad \text{MeCN} \\
\end{align*}

To a suspension of 4-tolylboronic acid (10.2 mg, 0.075 mmol, 1.5 equiv), 4l (17.3 mg, 0.05 mmol, 1.0 equiv) and Na\textsubscript{2}CO\textsubscript{3} (10.6 mg, 0.1 mmol, 2.0 equiv) in a mixture of DME/H\textsubscript{2}O (3/1, c = 0.1 M) was added Pd(PPh\textsubscript{3})\textsubscript{4} (5.7 mg, 10 mol\%) under N\textsubscript{2}. The resulting mixture was heated to 90 °C and stirred for 24 h. The solvent was then removed under reduced pressure, and the residue was diluted with water, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/9 to 2/8) to give compound 13 as a colourless oil (14.5 mg, 82\% yield).

\[^{1}\text{H} \text{NMR (400 MHz, CDCl}_3\text{)} \delta 7.55 – 7.38 \text{ (m, 6H), 7.35 \text{ (d, } J = 7.9 \text{ Hz, 1H), 7.26 – 7.24 \text{ (m, 2H), 7.07 – 7.01 \text{ (m, 2H), 5.23 \text{ (d, } J = 12.4 \text{ Hz, 1H), 5.17 \text{ (d, } J = 12.4 \text{ Hz, 1H), 2.59 \text{ (ddd, } J = 13.9, 10.2, 5.9 \text{ Hz, 1H), 2.49 \text{ (ddd, } J = 14.0, 9.6, 5.6 \text{ Hz, 1H), 2.40 \text{ (s, 3H), 2.38 – 2.19 \text{ (m, 2H)}};}

\[^{13}\text{C} \text{NMR (101 MHz, CDCl}_3\text{)} \delta 162.3 \text{ (d, } J = 246.4 \text{ Hz), 142.0, 140.8, 139.9, 139.4 \text{ (d, } J = 3.2 \text{ Hz), 137.68, 137.65, 129.7, 127.2, 126.8 \text{ (d, } J = 8.1 \text{ Hz), 122.0, 120.2, 119.9, 115.6 \text{ (d, } J = 21.3 \text{ Hz), 89.5, 72.2, 37.3, 21.3, 12.7;}

\text{ATR-IR } \nu 2925 \text{ (w), 2856 \text{ (w), 2249 (w), 1507 (m), 1225 (m), 908 (m), 835 (m), 813 (s), 730 (s);}

\text{HRMS (ESI) calcd for C}_{24}\text{H}_{20}\text{FNNa}^+ \text{[M+Na]}^+ 380.1421; \text{ found 380.1421.}

\text{Synthesis of 3-((4-fluorophenyl)-5-(phenylethynyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (14)}
To a solution of 4l (17.3 mg, 0.05 mmol, 1.0 equiv), phenylacetylene (20.4 mg, 0.2 mmol, 4.0 equiv), Cul (1.9 mg, 20 mol%), and Et₃N (18 µL, 0.125 mmol, 2.5 equiv) in DMF (c = 0.05 M) was added Pd(PPh₃)₄ (5.7 mg, 10 mol%) at room temperature. The resulting mixture was evacuated and filled back with N₂ three times, then warmed up to 80 °C. After stirring for 24 h, the reaction mixture was diluted with water, extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/9 to 2/8) to give compound 14 as a yellow oil (11.5 mg, 62% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.50 (m, 3H), 7.45 – 7.42 (m, 3H), 7.37 – 7.34 (m, 3H), 7.29 (d, J = 7.9 Hz, 1H), 7.07 – 7.01 (m, 2H), 5.18 (d, J = 12.6 Hz, 1H), 5.12 (d, J = 12.6 Hz, 1H), 2.57 (ddd, J = 13.9, 10.1, 5.9 Hz, 1H), 2.52 – 2.39 (m, 1H), 2.38 – 2.14 (m, 2H);

¹³C NMR (101 MHz, CDCl₃) δ 162.4 (d, J = 246.6 Hz), 142.2, 139.6, 138.9 (d, J = 3.4 Hz), 131.8, 131.7, 128.7, 128.6, 126.8 (d, J = 8.1 Hz), 124.8, 123.9, 123.0, 121.8, 119.7, 115.7 (d, J = 21.4 Hz), 90.2, 89.6, 88.7, 71.9, 37.1, 12.7;

ATR-IR ν 2955 (w), 2925 (w), 2903 (w), 2855 (w), 2248 (w), 1507 (m), 1225 (m), 836 (s), 835 (s), 757 (s), 691 (s);


Copies of the ¹H and ¹³C NMR Spectra
$\text{Me} \quad \text{Me} \quad \text{CN}$

$\text{OMe} \quad \text{OMe}$

$\text{dr} = 1.1/1.0$