Supporting Information

Catalytic and Diastereoselective Cascade Reaction for the Preparation of *cis*-1,3-Disubstituted Isoindoline-Aminal Hybrid Compounds.

Tetsuya Tsujihara,[1]* Takeyuki Suzuki,[2] and Tomikazu Kawano[1]*

[1]School of Pharmacy, Iwate Medical University, 1-1-1 Idaidori, Yahaba, Iwate 028-3694, Japan; [2]Comprehensive Analysis Center, Institute of Scientific and Industrial Research, Osaka University, 8-1 Mihogaoka, Ibaraki, Osaka 567-0047, Japan; E-mail: ttsujiha@iwate-med.ac.jp; tkawano@iwate-med.ac.jp

Contents

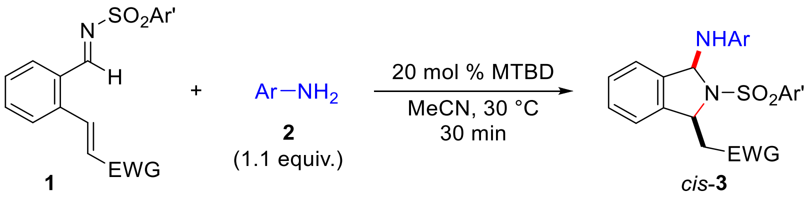
1. General methods and materials

General. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ500R (500 MHz for ^{1}H and 126 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm referenced to tetramethylsilane as internal standard ($CDCl_3$: $\delta = 0$ ppm for ^{1}H) and residual solvent signal ($CDCl_3$: $\delta = 77.0$ ppm for ^{13}C). *J*-values are given in Hz. For the correct assignment of both ^{1}H and ^{13}C NMR spectra of **3aa**, ^{1}H–^{1}H COSY HMQC, HMBC, and NOESY experiments were performed. The high-resolution mass spectra (HRMS) were obtained with a Shimadzu LCMS-IT-TOF mass spectrometer. All melting points were determined on a BÜCHI melting apparatus B-540 and are uncorrected. All manipulations were carried out with standard Schlenk technique under an argon atmosphere. Reactions were monitored by TLC (silica gel 60 F_{254}, 0.25 mm) analysis. Flash column chromatography was performed on flash silica gel 60N (spherical neutral, particle size 40–50 μm).

Materials. Anhydrous toluene, THF, 1,4-dioxane, DME, MeCN, DMF, and CH_2Cl_2 were purchased and used without any purification. (*E*)-**S1**[1] and Imines **1a-1k**[2] were prepared according to the procedure described in the literature.

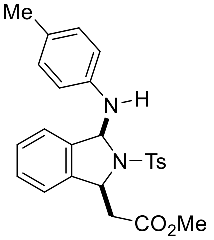
2. Experimental procedures

General procedure for aminalization/IMAMR Cascade reaction of 1.



To a solution of **1** (0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere was added a solution of MTBD (1.5 μL, 0.010 mmol, 20 mol %) and aniline **2** (0.055 mmol, 1.1 equiv.) in dry MeCN (1.0 mL) at 30 °C. The mixture was stirred at 30 °C for 30 min. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in *vacuo* and the residue was purified by flash column chromatography on silica gel (hexane/$CHCl_3$/EtOAc = 6/6/1 to 3/3/1) to afford **3**.

(1S*,3S*)-Methyl 2-{3-(4-methylphenylamino)-2-tosylisoindolin-1-yl}acetate (3aa).



3aa

According to the **general procedure**, **1a** (17.2 mg, 0.050 mmol) and *p*-toluidine **2a** (6.0 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3aa** was obtained in 89% yield (20.0 mg, 0.0444 mmol) as pale yellow foam.

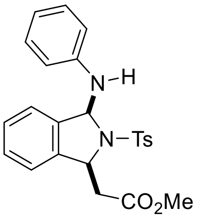
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.35 (s, 3H), 2.43 (dd, *J* = 7.7, 16.8 Hz, 1H), 2.93 (dd, *J* = 3.7, 16.8 Hz, 1H), 3.64 (s, 3H), 4.65 (brs, 1H, N*H*), 5.11 (dd, *J* = 3.6, 7.7 Hz, 1H), 6.31 (s, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 7.11–7.13 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.28–7.32 (m, 2H), 7.39–7.41 (m, 1H), 7.72 (d, *J* = 8.2 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 20.5 (CH_3), 21.5 (CH_3), 41.4 (CH_2), 51.7 (CH_3), 60.0 (*C*H), 78.1 (*C*H), 119.1 (*C*H), 122.6 (*C*H), 124.2 (*C*H), 127.4 (*C*H), 128.5 (*C*H), 129.3 (*C*H), 129.4 (*C*H), 129.8 (*C*H), 130.4 (*C*), 135.3 (*C*), 137.8 (*C*), 139.1 (*C*), 141.9 (*C*), 143.7 (*C*), 171.5 (*C*).

IR (KBr) ν: 3385, 3028, 2951, 2917, 2867, 1735, 1520, 1344, 1300, 1163, 1011, 814 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{25}H_{26}N_2NaO_4S$ 473.1505; Found 473.1508.

(1S*,3S*)-Methyl 2-(3-phenylamino-2-tosylisoindolin-1-yl)acetate (3ab).



3ab

According to the **general procedure**, **1a** (17.2 mg, 0.050 mmol) and aniline **2b** (5.0 μL, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3ab** was obtained in 83% yield (18.2 mg, 0.0417 mmol) as colorless oil.

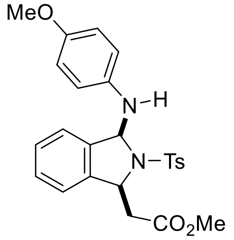
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.56 (dd, *J* = 7.4, 16.8 Hz, 1H), 2.95 (dd, *J* = 3.6, 16.8 Hz, 1H), 3.63 (s, 3H), 4.75 (brs, 1H, N*H*), 5.15 (dd, *J* = 3.6, 7.4 Hz, 1H), 6.39 (s, 1H), 6.66 (d, *J* = 8.3 Hz, 2H), 6.85 (t, *J* = 7.3 Hz, 1H), 7.12–7.15 (m, 3H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.30–7.33 (m, 2H), 7.38–7.40 (m, 1H), 7.71 (d, *J* = 8.2 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 21.5 (CH_3), 41.2 (CH_2), 51.6 (CH_3), 60.0 (*C*H), 77.4 (*C*H), 118.0 (*C*H), 120.6 (*C*H), 122.5 (*C*H), 124.1 (*C*H), 127.4 (*C*H), 128.6 (*C*H), 128.9 (*C*H), 129.3 (*C*H), 129.8 (*C*H), 135.5 (*C*), 137.9 (*C*), 139.0 (*C*), 143.7 (*C*), 144.7 (*C*), 171.4 (*C*).

IR (KBr) ν: 3388, 3032, 2952, 2927, 2850, 1735, 1601, 1510, 1340, 1161, 1092, 909, 814 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{24}H_{24}N_2NaO_4S$ 459.1349; Found 459.1351.

(1*S,3*S**)-Methyl 2-{3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl}acetate (3ac).**



3ac

According to the **general procedure**, **1a** (17.2 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3ac** was obtained in 91% yield (21.2 mg, 0.0454 mmol) as pale yellow oil.

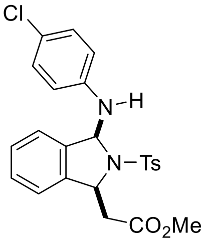
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.09 (dd, J = 8.2, 16.8 Hz, 1H), 2.36 (s, 3H), 2.82 (dd, J = 3.8, 16.8 Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 4.52 (brs, 1H, N*H*), 5.03 (dd, J = 3.8, 8.2 Hz, 1H), 6.19 (s, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.29 (dd, J = 7.6, 7.6 Hz, 1H), 7.34 (dd, J = 7.4, 7.4 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 21.5 (*C*H$_3$), 41.8 (*C*H$_2$), 51.6 (*C*H$_3$), 55.5 (*C*H$_3$), 60.0 (*C*H), 79.3 (*C*H), 114.1 (*C*H), 122.7 (*C*H), 123.0 (*C*H), 124.5 (*C*H), 127.3 (*C*H), 128.4 (*C*H), 129.3 (*C*H), 129.9 (*C*H), 135.1 (*C*), 137.2 (*C*), 137.3 (*C*), 139.6 (*C*), 143.8 (*C*), 155.2 (*C*), 171.6 (*C*).

IR (KBr) ν: 3371, 3029, 2952, 2927, 2835, 1735, 1511, 1340, 1236, 1160, 1035, 818 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{25}$H$_{26}$N$_2$NaO$_5$S 489.1455; Found 489.1458.

(1*S,3*S**)-Methyl 2-{3-(4-chlorophenylamino)-2-tosylisoindolin-1-yl}acetate (3ad).**



3ad

According to the **general procedure**, **1a** (17.2 mg, 0.050 mmol) and *p*-chloroaniline **2d** (7.2 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3ad** was obtained in 86% yield (20.3 mg, 0.0431 mmol) as pale yellow oil.

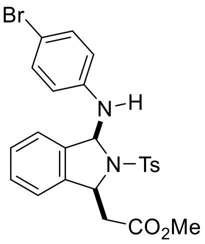
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.36 (s, 3H), 2.69 (dd, J = 7.0, 16.9 Hz, 1H), 3.00 (dd, J = 3.5, 16.9 Hz, 1H), 3.63 (s, 3H), 4.83 (brd, J = 6.2 Hz, 1H, N*H*), 5.15 (dd, J = 3.5, 7.0 Hz, 1H), 6.36 (d, J = 5.3 Hz, 1H), 6.60 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 7.13–7.15 (m, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.31–7.37 (m, 3H), 7.70 (d, J = 8.3 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 21.5 (*C*H$_3$), 41.0 (*C*H$_2$), 51.7 (*C*H$_3$), 60.0 (*C*H), 77.1 (*C*H), 118.7 (*C*H), 122.5 (*C*H), 123.9 (*C*H), 125.1 (*C*), 127.4 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 129.4 (*C*H), 129.8 (*C*H), 135.3 (*C*), 137.6 (*C*), 138.8 (*C*), 143.5 (*C*), 143.9 (*C*), 171.3 (*C*).

IR (KBr) ν: 3383, 3029, 2952, 2923, 2853, 1737, 1598, 1510, 1339, 1159, 1093, 814 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{23}$ClN$_2$NaO$_4$S 493.0959; Found 493.0961.

(1*S**,3*S**)-Methyl 2-{3-(4-bromophenylamino)-2-tosylisoindolin-1-yl}acetate (3ae).



3ae

According to the **general procedure**, **1a** (17.2 mg, 0.050 mmol) and 4-bromoaniline **2e** (9.6 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3ae** was obtained in 82% yield (21.1 mg, 0.0409 mmol) as pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.74 (dd, *J* = 6.9, 16.9 Hz, 1H), 3.01 (dd, *J* = 3.5, 16.9 Hz, 1H), 3.63 (s, 3H), 4.85 (brd, *J* = 6.9 Hz, 1H, N*H*), 5.17 (dd, *J* = 3.5, 6.9 Hz, 1H), 6.38 (d, *J* = 5.9 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 7.14–7.15 (m, 1H), 7.21–7.23 (m, 4H), 7.31–7.35 (m, 3H), 7.69 (d, *J* = 8.2 Hz, 2H).

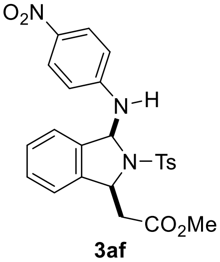
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 21.5 (CH_3), 40.9 (CH_2), 51.7 (CH_3), 60.1 (*C*H), 76.8 (*C*H), 112.2 (*C*), 118.7 (*C*H), 122.5 (*C*H), 123.9 (*C*H), 127.4 (*C*H), 128.7 (*C*H), 129.5 (*C*H), 129.8 (*C*H), 131.7 (*C*H), 135.4 (*C*), 137.7 (*C*), 138.7 (*C*), 143.9 (*C*), 144.1 (*C*), 171.3 (*C*).

IR (KBr) ν: 3384, 3033, 2952, 2923, 2850, 1737, 1594, 1510, 1460, 1338, 1159, 812 cm^{-1}.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{23}{}^{79}BrN_2NaO_4S$ 537.0454; Found 537.0455.

m/z: $[M+Na]^+$ Calcd for $C_{24}H_{23}{}^{81}BrN_2NaO_4S$ 539.0436; Found 539.0450.

(1*S**,3*S**)-Methyl 2-{3-(4-nitrophenylamino)-2-tosylisoindolin-1-yl}acetate (3af).



3af

According to the **general procedure**, **1a** (17.2 mg, 0.050 mmol) and *p*-nitroaniline **2f** (7.7 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3af** was obtained in 63% yield (15.2 mg, 0.0316 mmol) as dark yellow amorphous solid.

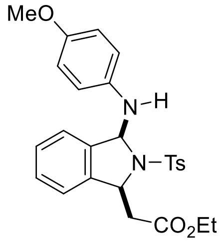
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.08 (dd, *J* = 3.2, 17.3 Hz, 1H), 3.20 (dd, *J* = 5.4, 17.3 Hz, 1H), 3.57 (s, 3H), 5.22 (dd, *J* = 3.2, 5.1 Hz, 1H), 5.86 (brd, *J* = 9.7 Hz, 1H, N*H*), 6.66 (d, *J* = 9.7 Hz, 1H), 6.73 (d, *J* = 9.2 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.33 (dd, *J* = 7.1, 7.1 Hz, 1H), 7.37 (ddd, *J* = 1.2, 7.4, 7.4 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 8.09 (d, *J* = 9.2 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 21.5 (CH_3), 39.5 (CH_2), 51.7 (CH_3), 60.2 (*C*H), 74.1 (*C*H), 112.6 (*C*H), 122.1 (*C*H), 123.5 (*C*H), 126.1 (*C*H), 127.4 (*C*H), 128.9 (*C*H), 129.7 (*C*H), 129.8 (*C*H), 135.6 (*C*), 137.4 (*C*), 138.1 (*C*), 139.1 (*C*), 144.2 (*C*), 151.0 (*C*), 171.1 (*C*).

IR (KBr) ν: 3366, 3078, 3012, 2952, 2923, 2855, 1738, 1599, 1503, 1343, 1320, 1163, 1112, 816 cm^{-1}.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{23}N_3NaO_6S$ 504.1200; Found 504.1202.

(1*S**,3*S**)-Ethyl 2-{3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl}acetate (3bc).



3bc

According to the **general procedure**, **1b** (17.9 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3bc** was obtained in 90% yield (21.6 mg, 0.0450 mmol) as pale yellow oil.

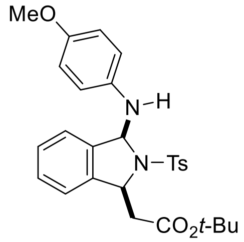
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.1 Hz, 3H), 2.12 (dd, *J* = 8.2, 16.8 Hz, 1H), 2.36 (s, 3H), 2.83 (dd, *J* = 3.8, 16.8 Hz, 1H), 3.73 (s, 3H), 4.10 (qd, *J* = 7.1, 10.8 Hz, 1H), 4.13 (qd, *J* = 7.2, 10.8 Hz, 1H), 4.59 (brs, 1H, N*H*), 5.05 (dd, *J* = 3.7, 8.1 Hz, 1H), 6.20 (s, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.29 (ddd, *J* = 1.0, 7.5, 7.5 Hz, 1H), 7.33 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 14.1 (CH_3), 21.5 (CH_3), 41.9 (CH_2), 55.5 (CH_3), 60.0 (CH), 60.6 (CH_2), 79.2 (CH), 114.1 (CH), 122.66 (CH), 122.72 (CH), 124.4 (CH), 127.3 (CH), 128.3 (CH), 129.3 (CH), 129.8 (CH), 135.2 (C), 137.3 (C), 137.4 (C), 139.7 (C), 143.7 (C), 155.1 (C), 171.1 (C).

IR (KBr) ν: 3367, 3033, 2983, 2930, 2835, 1730, 1598, 1511, 1461, 1340, 1236, 1160, 1034, 819 cm^{-1}.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{28}N_2NaO_5S$ 503.1611; Found 503.1615.

(1*S**,3*S**)-*tert*-Butyl 2-{3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl}acetate (3cc).



3cc

According to the **general procedure**, **1c** (19.3 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3cc** was obtained in 44% yield (11.3 mg, 0.0222 mmol) as pale yellow oil.

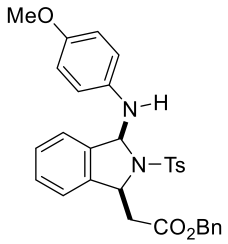
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.02 (dd, *J* = 8.5, 16.6 Hz, 1H), 2.36 (s, 3H), 2.84 (dd, *J* = 3.5, 16.5 Hz, 1H), 3.73 (s, 3H), 4.53 (brs, 1H, N*H*), 5.04 (dd, *J* = 3.4, 8.5 Hz, 1H), 6.21 (s, 1H), 6.61 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.29 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.32 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 21.5 (CH_3), 28.0 (CH_3), 43.0 (CH_2), 55.5 (CH_3), 60.2 (CH), 79.0 (CH), 80.9 (C), 114.1 (CH), 122.3 (CH), 122.7 (CH), 124.4 (CH), 127.4 (CH), 128.3 (CH), 129.2 (CH), 129.8 (CH), 135.3 (C), 137.4 (C), 137.5 (C), 139.9 (C), 143.7 (C), 155.0 (C), 170.4 (C).

IR (KBr) ν: 3367, 2978, 2933, 2833, 1719, 1598, 1510, 1460, 1340, 1236, 1158, 819 cm^{-1}.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{32}N_2NaO_5S$ 531.1924; Found 531.1926.

(1*S**,3*S**)-Benzyl 2-{3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl}acetate (3dc).



3dc

According to the **general procedure**, **1d** (21.0 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3dc** was obtained in 92% yield (25.0 mg, 0.0461 mmol) as dark orange foam.

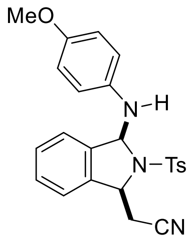
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.15 (dd, J = 7.9, 16.5 Hz, 1H), 2.35 (s, 3H), 2.82 (dd, J = 4.0, 16.6 Hz, 1H), 3.68 (s, 3H), 4.53 (brs, 1H, N*H*), 5.05 (dd, J = 4.0, 7.9 Hz, 1H), 5.10 (s, 2H), 6.20 (s, 1H), 6.59 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 7.7 Hz, 1H), 7.20–7.26 (m, 3H), 7.31–7.38 (m, 6H), 7.45 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 8.1 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 21.5 (*C*H$_3$), 42.0 (*C*H$_2$), 55.4 (*C*H$_3$), 60.0 (*C*H), 66.4 (*C*H$_2$), 79.3 (*C*H), 114.1 (*C*H), 122.7 (*C*H), 122.9 (*C*H), 124.5 (*C*H), 127.3 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 128.5 (*C*H), 129.3 (*C*H), 129.8 (*C*H), 135.1 (*C*), 135.6 (*C*), 137.2 (*C*), 137.4 (*C*), 139.5 (*C*), 143.7 (*C*), 155.2 (*C*), 170.9 (*C*). One aromatic carbon (CH) was not observed due to overlap.

IR (KBr) ν: 3379, 3033, 2932, 2833, 1731, 1512, 1343, 1296, 1238, 1163, 1095, 818 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{31}H_{30}N_2NaO_5S$ 565.1768; Found 565.1770.

(1*S**,3*S**)-[3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl]acetonitrile (3ec).



3ec

According to the **general procedure**, **1e** (15.5 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3ec** was obtained in 93% yield (20.2 mg, 0.0466 mmol) as pale yellow oil.

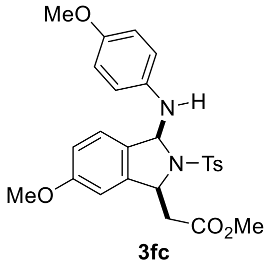
^{1}H NMR (500 MHz, CDCl$_3$): δ 1.86 (dd, J = 8.9, 16.8 Hz, 1H), 2.38 (s, 3H), 2.92 (dd, J = 2.9, 16.8 Hz, 1H), 3.73 (s, 3H), 4.43 (brs, 1H, N*H*), 4.83 (dd, J = 3.2, 9.0 Hz, 1H), 6.25 (s, 1H), 6.63 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.39–7.44 (m, 3H), 7.52 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 21.5 (*C*H$_3$), 25.7 (*C*H$_2$), 55.4 (*C*H$_3$), 59.2 (*C*H), 79.3 (*C*H), 114.1 (*C*H), 117.5 (*C*), 122.9 (*C*H), 123.0 (*C*H), 124.8 (*C*H), 127.1 (*C*H), 129.3 (*C*H), 129.7 (*C*H), 130.1 (*C*H), 135.0 (*C*), 136.9 (*C*), 137.1 (*C*), 137.6 (*C*), 144.3 (*C*), 155.4 (*C*).

IR (KBr) ν: 3379, 3021, 2929, 2854, 2833, 2250, 1510, 1339, 1234, 1160, 1033, 820 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{24}H_{23}N_3NaO_3S$ 456.1352; Found 456.1355.

(1*S,3*S**)-Methyl 2-{6-methoxy-3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl}acetate (3fc).**


3fc

According to the **general procedure**, **1f** (18.7 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3fc** was obtained in 84% yield (20.9 mg, 0.0421 mmol) as pale orange oil.

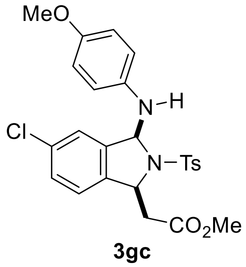
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.00 (dd, J = 8.4, 16.9 Hz, 1H), 2.37 (s, 3H), 2.78 (dd, J = 3.8, 16.9 Hz, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 4.56 (brs, 1H, N*H*), 4.96 (dd, J = 3.8, 8.3 Hz, 1H), 6.10 (s, 1H), 6.60 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 8.9 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 6.88 (dd, J = 2.4, 8.4 Hz, 1H), 7.26 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 21.5 (CH$_3$), 41.8 (CH$_2$), 51.7 (CH$_3$), 55.4 (CH$_3$), 55.5 (CH$_3$), 59.9 (CH), 79.1 (CH), 107.2 (CH), 114.0 (CH), 115.1 (CH), 123.5 (CH), 125.4 (CH), 127.3 (CH), 129.1 (C), 129.9 (CH), 135.0 (C), 137.0 (C), 141.3 (C), 143.8 (C), 155.3 (C), 160.7 (C), 171.8 (C).

IR (KBr) ν: 3381, 3000, 2950, 2924, 2836, 1734, 1512, 1340, 1240, 1162, 1034, 818 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{26}H_{28}N_2NaO_6S$ 519.1560; Found 519.1554.

(1*S,3*S**)-Methyl 2-{5-chloro-3-(4-methoxyphenylamino)-2-tosylisoindolin-1-yl}acetate (3gc).**


3gc

According to the **general procedure**, **1g** (18.9 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3gc** was obtained in 90% yield (22.6 mg, 0.0451 mmol) as pale yellow foam.

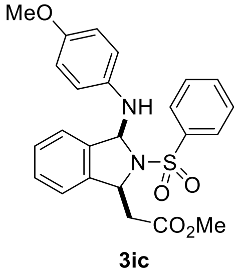
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.04 (dd, J = 8.3, 17.0 Hz, 1H), 2.38 (s, 3H), 2.82 (dd, J = 3.7, 17.0 Hz, 1H), 3.65 (s, 3H), 3.74 (s, 3H), 4.57 (brs, 1H, N*H*), 4.97 (dd, J = 3.5, 8.3 Hz, 1H), 6.13 (s, 1H), 6.64 (d, J = 8.9 Hz, 2H), 6.71 (d, J = 8.9 Hz, 2H), 7.04 (d, J = 8.2 Hz, 1H), 7.24–7.27 (m, 3H), 7.45 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 21.5 (CH$_3$), 41.5 (CH$_2$), 51.7 (CH$_3$), 55.5 (CH$_3$), 59.6 (CH), 78.8 (CH), 114.1 (CH), 123.2 (CH), 124.1 (CH), 124.6 (CH), 127.2 (CH), 129.7 (CH), 130.0 (CH), 134.4 (C), 134.8 (C), 136.8 (C), 138.0 (C), 139.3 (C), 144.0 (C), 155.4 (C), 171.5 (C).

IR (KBr) ν: 3375, 3000, 2952, 2925, 2835, 1734, 1512, 1344, 1238, 1163, 1087, 1036, 822 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{25}H_{25}ClN_2NaO_5S$ 523.1065; Found 523.1061.

(1*S,3*S**)-Methyl 2-{3-(4-methoxyphenylamino)-2-benzenesulfonylisoindolin-1-yl}acetate (3ic).**



3ic

According to the **general procedure**, **1i** (16.5 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3ic** was obtained in 87% yield (19.7 mg, 0.0435 mmol) as pale yellow oil.

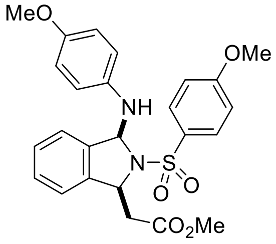
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.11 (dd, J = 8.1, 16.8 Hz, 1H), 2.82 (dd, J = 3.8, 16.8 Hz, 1H), 3.65 (s, 3H), 3.73 (s, 3H), 4.58 (brs, 1H, N*H*), 5.06 (dd, J = 3.8, 8.0 Hz, 1H), 6.23 (s, 1H), 6.63 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 7.6 Hz, 1H), 7.29 (dd, J = 7.2, 7.2 Hz, 1H), 7.34 (dd, J = 7.2, 7.2 Hz, 1H), 7.45–7.48 (m, 3H), 7.53 (dd, J = 7.4, 7.4 Hz, 1H), 7.84–7.86 (m, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 41.7 (*C*H$_2$), 51.7 (*C*H$_3$), 55.5 (*C*H$_3$), 60.0 (*C*H), 79.4 (*C*H), 114.1 (*C*H), 122.7 (*C*H), 122.9 (*C*H), 124.5 (*C*H), 127.3 (*C*H), 128.4 (*C*H), 129.2 (*C*H), 129.4 (*C*H), 132.9 (*C*H), 137.2 (*C*), 137.3 (*C*), 138.2 (*C*), 139.5 (*C*), 155.2 (*C*), 171.5 (*C*).

IR (KBr) ν: 3367, 3029, 2952, 2836, 1745, 1510, 1460, 1338, 1233, 1160, 1032, 828 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{24}$N$_2$NaO$_5$S 475.1298; Found 475.1302.

(1*S,3*S**)-Methyl 2-{3-(4-methoxyphenylamino)-2-(4-methoxybenzenesulfonyl)isoindolin-1-yl}acetate (3jc).**



3jc

According to the **general procedure**, **1j** (18.0 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3jc** was obtained in 91% yield (21.9 mg, 0.0454 mmol) as pale yellow oil.

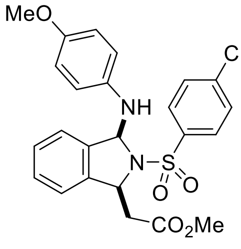
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.12 (dd, J = 8.1, 16.8 Hz, 1H), 2.82 (dd, J = 3.9, 16.8 Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 4.51 (brs, 1H, N*H*), 5.03 (dd, J = 3.8, 8.1 Hz, 1H), 6.18 (s, 1H), 6.61 (d, J = 8.9 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 7.5 Hz, 1H), 7.29 (dd, J = 7.2, 7.2 Hz, 1H), 7.34 (dd, J = 7.4, 7.4 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 9.0 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 41.7 (*C*H$_2$), 51.7 (*C*H$_3$), 55.51 (*C*H$_3$), 55.53 (*C*H$_3$), 60.0 (*C*H), 79.2 (*C*H), 114.1 (*C*H), 114.4 (*C*H), 122.7 (*C*H), 122.8 (*C*H), 124.5 (*C*H), 128.4 (*C*H), 129.3 (*C*H), 129.4 (*C*H), 129.8 (*C*), 137.3 (*C*), 137.4 (*C*), 139.6 (*C*), 155.2 (*C*), 163.1 (*C*), 171.7 (*C*).

IR (KBr) ν: 3369, 3013, 2952, 2838, 1737, 1596, 1510, 1340, 1236, 1157, 1029, 833 cm^{-1}.

HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for C$_{25}$H$_{26}$N$_2$NaO$_6$S 505.1404; Found 505.1408.

(1*S**,3*S**)-Methyl 2-{3-(4-methoxyphenylamino)-2-(4-chlorobenzenesulfonyl)isoindolin-1-yl}acetate (3kc).



3kc

According to the **general procedure**, **1k** (18.2 mg, 0.050 mmol) and *p*-anisidine **2c** (6.8 mg, 0.055 mmol) were used. After a reaction time of 30 min, *cis*-**3kc** was obtained in 52% yield (12.7 mg, 0.0261 mmol) as yellow oil.

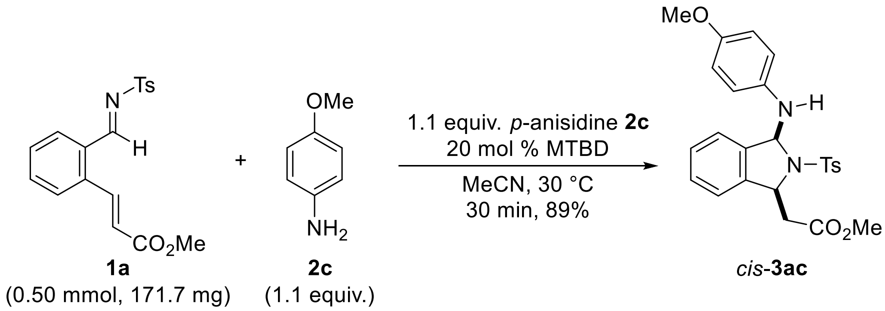
^{1}H NMR (500 MHz, CDCl$_3$): δ 2.19 (dd, J = 7.7, 16.8 Hz, 1H), 2.79 (dd, J = 3.9, 16.8 Hz, 1H), 3.64 (s, 3H), 3.74 (s, 3H), 4.56 (brs, 1H, N*H*), 5.07 (dd, J = 3.9, 7.6 Hz, 1H), 6.25 (s, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 7.11 (d, J = 7.5 Hz, 1H), 7.30–7.37 (m, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 7.3 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$): δ 41.4 (CH$_2$), 51.7 (CH$_3$), 55.5 (CH$_3$), 60.0 (CH), 79.4 (CH), 114.2 (CH), 122.4 (CH), 122.6 (CH), 124.4 (CH), 128.6 (CH), 128.7 (CH), 129.5 (2CH), 137.0 (C), 137.20 (C), 137.23 (C), 139.2 (C), 139.4 (C), 155.2 (C), 171.4 (C).

IR (KBr) ν: 3368, 3028, 3006, 2950, 2927, 2852, 1737, 1511, 1340, 1235, 1162, 1033, 828 cm^{-1}.

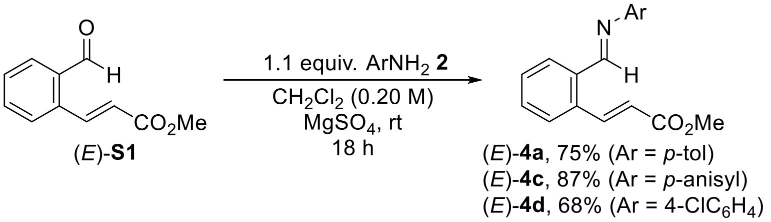
HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{24}H_{23}ClN_2NaO_5S$ 509.0908; Found 509.0909.

Aminalization/IMAMR cascade reaction of 1a on a 0.50 mmol scale (Table 2, entry 7).



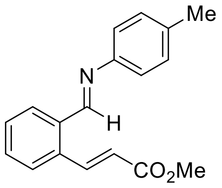
To a solution of **1a** (0.50 mmol, 171.7 mg) in dry MeCN (5.0 mL) under an argon atmosphere was added a solution of MTBD (15.2 μL, 0.10 mmol, 20 mol %) and *p*-anisidine **2c** (68.4 mg, 0.55 mmol, 1.1 equiv.) in dry MeCN (7.0 mL) at 30 °C. The mixture was stirred at 30 °C for 30 min. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in *vacuo* and the residue was purified by flash column chromatography on silica gel (hexane/CHCl$_3$/EtOAc = 4/4/1) to afford *cis*-**3ac** (207.2 mg, 0.444 mmol, 89%). The data of NMR, HRMS, IR, and HRMS were matched with the case of the reaction on a 0.050 mmol scale.

General procedure for the preparation of imine 4a, 4c, and 4d.



According to the reported procedure for preparation of imines,[3] imines (*E*)-**4a**, (*E*)-**4c**, and (*E*)-**4d** were prepared. To a mixture of (*E*)-**S1** (38.0 mg, 0.20 mmol), **2** (1.1 equiv.), and $MgSO_4$ (80 mg) was added dry CH_2Cl_2 (1.0 mL) at rt under Ar atmosphere. After being stirred the mixture at rt for 18 h, the reaction mixture was filtered. The filtrate was evaporated to dryness and the residue was purified by recrystallization from hexane and CH_2Cl_2 at rt to –10 °C. In the case of (*E*)-**4a**, the purification was carried out by flash column chromatography on silica gel (hexane/EtOAc = 10/1).

(*E*)-Methyl 3-(2-{[(4-methylphenyl)imino]methyl}phenyl)prop-2-enoate (*E*)**-4a.**



4a

According to the **general procedure**, (*E*)-**S1** (38.0 mg, 0.20 mmol) and *p*-toluidine **2a** (23.8 mg, 0.22 mmol) were used. (*E*)-**4a** was obtained in 75% yield (42.1 mg, 0.151 mmol) as dark yellow amorphous solid.

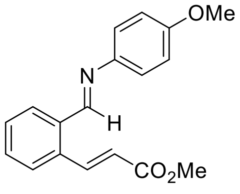
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.82 (s, 3H), 6.38 (d, J = 15.8 Hz, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.46–7.50 (m, 2H), 7.59–7.61 (m, 1H), 8.08–8.10 (m, 1H), 8.41 (d, J = 15.8 Hz, 1H), 8.83 (s, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 21.0 (CH_3), 51.8 (CH_3), 120.9 (*C*H), 121.2 (*C*H), 127.5 (*C*H), 128.9 (*C*H), 129.8 (*C*H), 130.0 (*C*H), 130.9 (*C*H), 134.6 (*C*), 135.2 (*C*), 136.3 (*C*), 141.8 (*C*H), 149.2 (*C*), 156.8 (*C*H), 167.0 (*C*).

IR (KBr) ν: 3023, 2983, 2944, 2911, 1721, 1631, 1505, 1319, 1277, 1196, 1171, 982, 820 cm^{-1}.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{17}NNaO_2$ 302.1152; Found 302.1148.

(*E*)-Methyl 3-(2-{[(4-methoxylphenyl)imino]methyl}phenyl)prop-2-enoate (*E*)**-4c.**



4c

According to the **general procedure**, (*E*)-**S1** (38.0 mg, 0.20 mmol) and *p*-anisidine **2c** (27.4 mg, 0.22 mmol) were used. (*E*)-**4c** was obtained in 87% yield (51.4 mg, 0.174 mmol) as yellow solid.

Mp: 72.8–73.7 °C

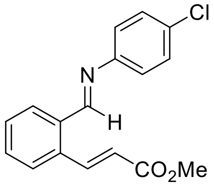
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.85 (s, 3H), 6.39 (d, J = 15.8 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.45–7.50 (m, 2H), 7.59–7.61 (m, 1H), 8.07–8.09 (m, 1H), 8.43 (d, J = 15.8 Hz, 1H), 8.84 (s, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 51.8 (*C*H$_3$), 55.5 (*C*H$_3$), 114.4 (*C*H), 121.1 (*C*H), 122.4 (*C*H), 127.5 (*C*H), 128.8 (*C*H), 130.0 (*C*H), 130.7 (*C*H), 134.8 (*C*), 135.0 (*C*), 142.0 (*C*H), 144.7 (*C*), 155.5 (*C*H), 158.6 (*C*), 167.1 (*C*).

IR (KBr) ν: 2985, 2946, 2900, 2839, 1720, 1627, 1505, 1318, 1248, 1195, 1166, 1031, 986, 830 cm^{-1}.

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{17}NNaO_3$ 318.1101; Found 318.1098.

(*E*)-Methyl 3-(2-{[(4-chlorophenyl)imino]methyl}phenyl)prop-2-enoate (*E*)-4d.



4d

According to the **general procedure**, (*E*)-**S1** (38.0 mg, 0.20 mmol) and *p*-chloroaniline **2d** (28.6 mg, 0.22 mmol) were used. (*E*)-**4d** was obtained in 68% yield (40.8 mg, 0.136 mmol) as pale yellow solid.

Mp: 88.4–88.8 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.39 (d, J = 15.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.48–7.52 (m, 2H), 7.60–7.63 (m, 1H), 8.06–8.09 (m, 1H), 8.41 (d, J = 15.8 Hz, 1H), 8.79 (s, 1H).

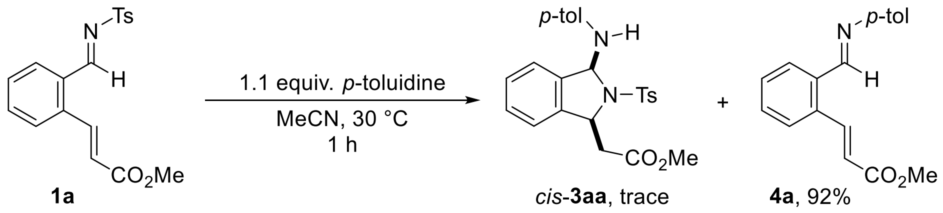
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 51.9 (*C*H$_3$), 121.5 (*C*H), 122.3 (*C*H), 127.6 (*C*H), 129.1 (*C*H), 129.3 (*C*H), 130.0 (*C*H), 131.3 (*C*H), 131.9 (*C*), 134.2 (*C*), 135.4 (*C*), 141.7 (*C*H), 150.2 (*C*), 158.1 (*C*H), 167.0 (*C*).

IR (KBr) ν: 2998, 2952, 2917, 2867, 1714, 1631, 1486, 1432, 1320, 1284, 1198, 1174, 1089, 827 cm^{-1}.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}ClNO_2$ 300.0786; Found 300.0787.

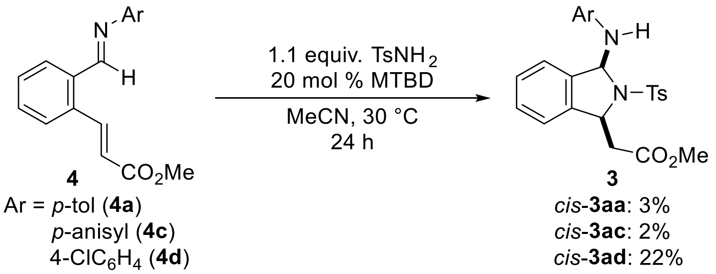
Mechanistic Study

The Cascade Reaction of 1a in the absence of MTBD (Scheme 2a).



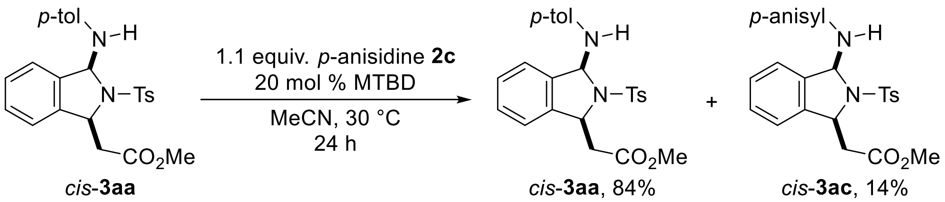
To a solution of **1a** (17.2 mg, 0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere was added a solution of *p*-toluidine **2** (6.0 mg, 0.055 mmol, 1.1 equiv.) in dry MeCN (1.0 mL) at 30 °C. The mixture was stirred at 30 °C for 1 h. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in *vacuo*. The yield of *cis*-**3aa** and **4a** were determined by NMR spectroscopy on the basis of benzyl 4-hydroxybenzoate as an internal standard.

The Cascade Reaction of 4 with *p*-Toluenesulfonamide (Scheme 2b).



To a solution of **4** (0.050 mmol) in dry MeCN (1.0 mL) under an argon atmosphere was added a solution of *p*-toluenesulfonamide (9.6 mg, 0.055 mmol, 1.1 equiv.) and MTBD (1.5 μL, 0.010 mmol, 20 mol %) in dry MeCN (1.0 mL) at 30 °C. The mixture was stirred at 30 °C for 24 h. The reaction mixture was filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in *vacuo*. The yields of *cis*-**3aa**, *cis*-**3ac**, and *cis*-**3ad** were determined by NMR spectroscopy on the basis of benzyl 4-hydroxybenzoate as an internal standard, respectively.

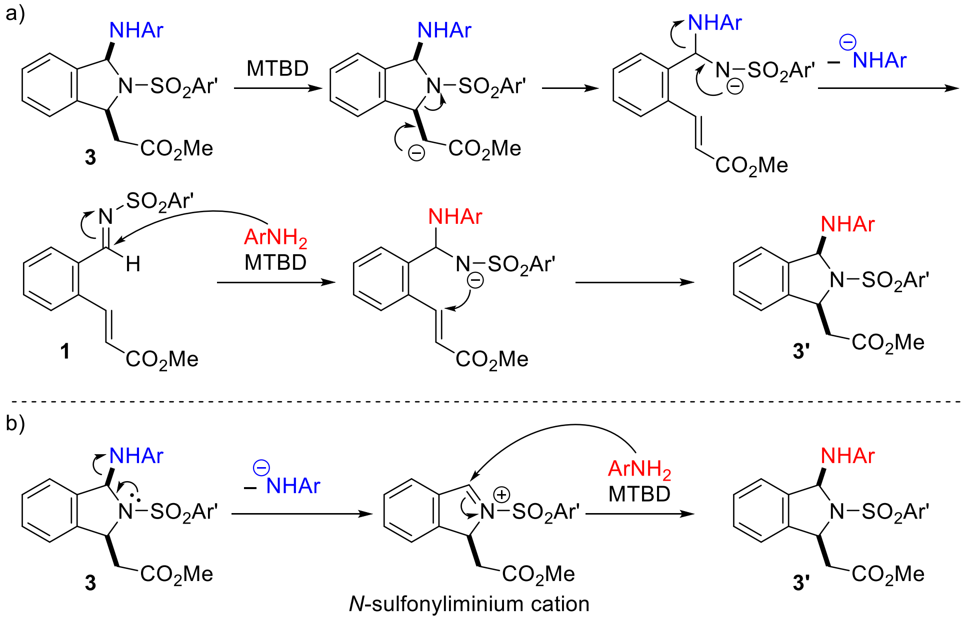
The Aminal Exchange of *cis*-3aa with *p*-Anisidine 2c (Scheme 2c).



To a solution of *cis*-**3aa** (11.3 mg, 0.025 mmol) and *p*-anisidine (3.4 mg, 0.028 mmol, 1.1 equiv.) in dry MeCN (0.50 mL) under an argon atmosphere was added a solution of MTBD (0.80 µL, 0.0050 mmol, 20 mol %) in dry MeCN (0.50 mL) at 30 °C. The mixture was stirred at 30 °C for 24 h and filtered through a short plug of silica gel, which was rinsed with hexane/EtOAc = 4/3. The filtrate was concentrated in *vacuo*. The yield of *cis*-**3aa** and *cis*-**3ac** were determined by NMR spectroscopy on the basis of benzyl 4-hydroxybenzoate as an internal standard.

3. Plausible Reaction Mechanisms of the Aminal Exchange of Cascade Reaction Product 3

The aminal exchanges of *cis*-**3** might have proceeded through a *retro*-Michael reaction or the formation of an *N*-sulfonyliminium cation as shown in Scheme S1.

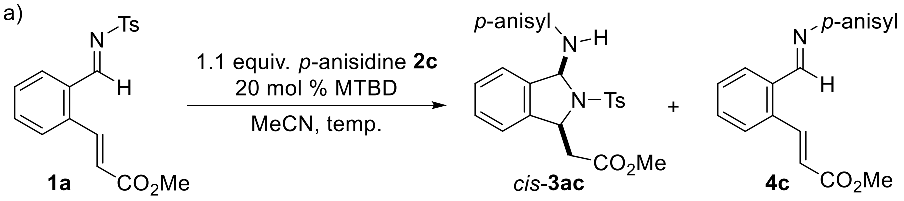


Scheme S1. Plausible reaction mechanisms of aminal exchange of product **3** through (a) a *retro*-Michael reaction or (b) the formation of an *N*-sulfonyliminium cation.

4. The effects of reaction temperature and the reaction of *cis*-3ac under reflux conditions.

To gain some insight into the selective formation of *cis*-**3ac**, which is thermodynamic products or kinetic products, the effects of reaction temperature were examined (Scheme S2a). In all case, *cis*-**3ac** was formed as the main product, and *trans*-**3ac** was not observed at all. Furthermore, the isomerization of *cis*-**3ac** to *trans*-**3ac** was not observed under reflux conditions in MeCN (Scheme S2b).

a)



temp./°C	time	yield of *cis*-**3ac**[a]	yield of **4c**[a]
50 °C	15 min	86%	10%
0 °C	40 min	89%	6%
–35 °C	8 h	81%	15%

[a] Yields determined by NMR spectroscopy on the basis of benzyl 4-hydroxybenzoate as an internal standard.

b)

$$cis\text{-}\mathbf{3ac} \xrightarrow[\text{MeCN, reflux, 24 h}]{\text{1.1 equiv. }p\text{-anisidine }\mathbf{2c}\text{, 20 mol \% MTBD}} \underset{23\%}{cis\text{-}\mathbf{3ac}} + \underset{33\%}{\mathbf{4c}}$$

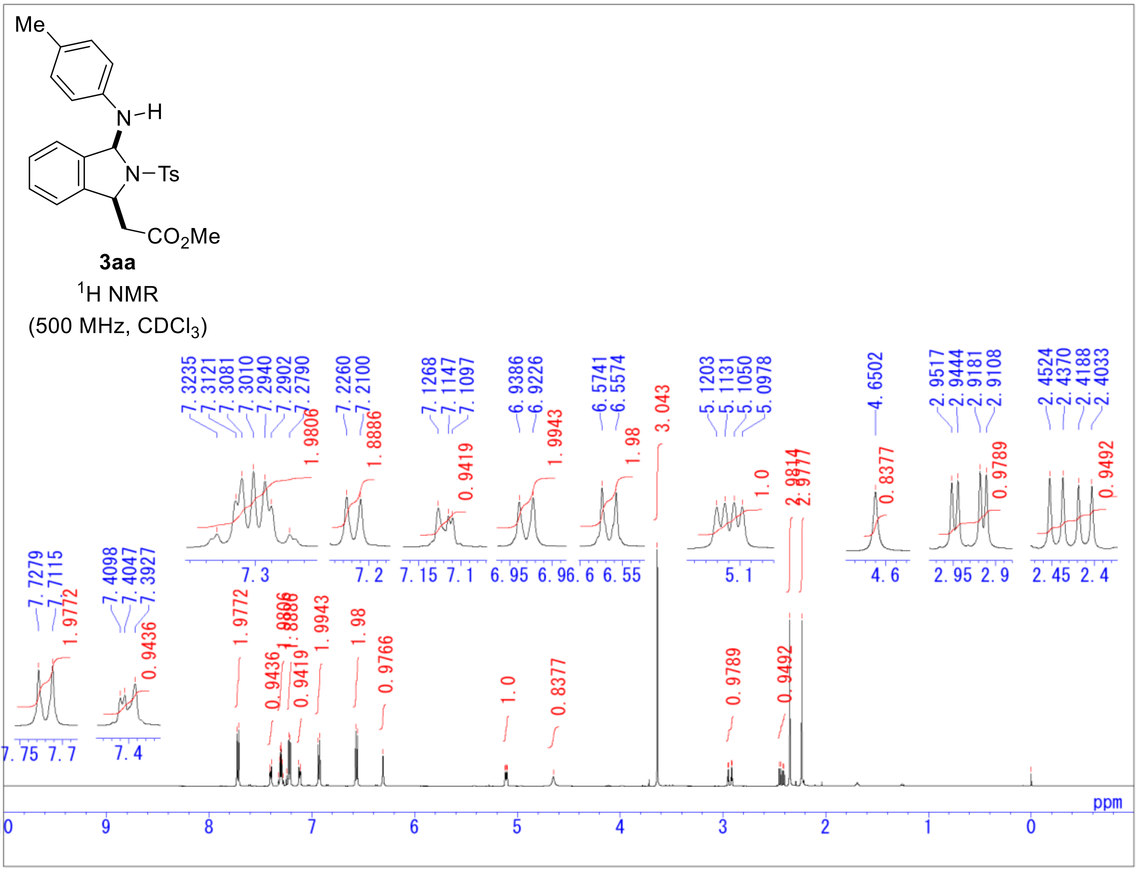
Scheme S2. (a) the effect of reaction temperature and (b) the reaction of *cis*-**3ac** under reflux conditions.

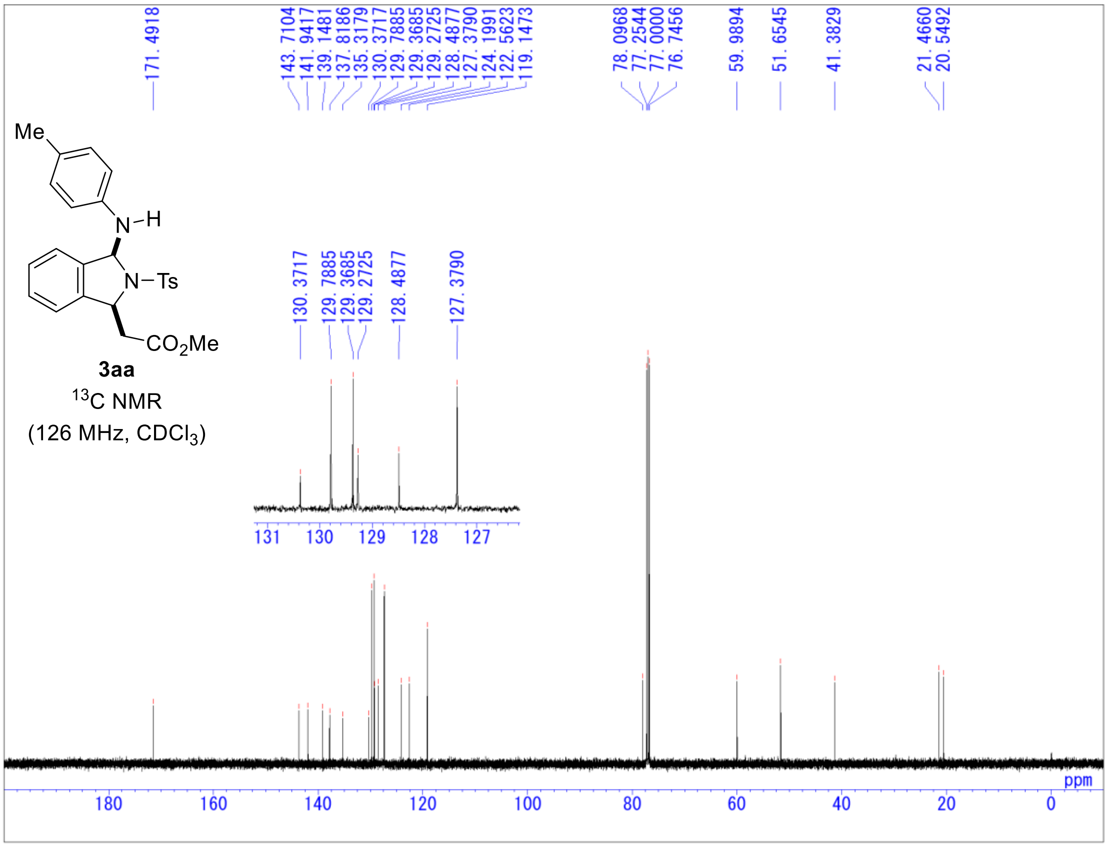
5. References

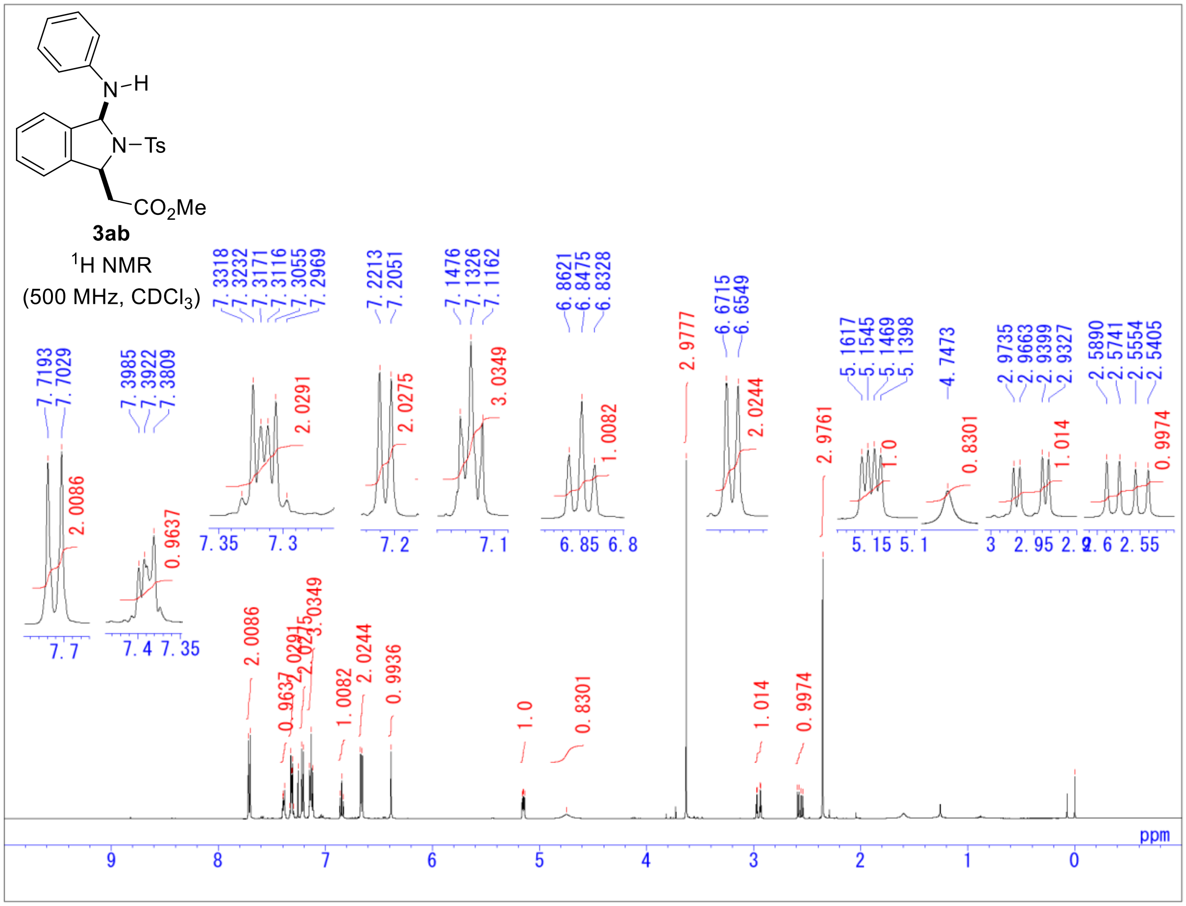
1. Bryan, C. S.; Lautens, M., *Org. Lett.* **2010**, *12*, 2754-2757.
2. (a) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T., *Angew. Chem. Int. Ed.* **2008**, *47*, 5661-5665. (b) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H., *Angew. Chem. Int. Ed.* **2010**, *49*, 9725-9729. (c) Takizawa, S.; Sako, M.; Abozeid, M. A.; Kishi, K.; Wathsala, H. D. P.; Hirata, S.; Murai, K.; Fujioka, H.; Sasai, H., *Org. Lett.* **2017**, *19*, 5426-5429. (d) Tsujihara, T.; Yamauchi, H.; Tamura, S.; Takehara, T.; Suzuki, T.; Kawano, T., *Tetrahedron Letters* **2020**, *61*, 152122.
3. Hong, X.; Wang, H.; Liu, B.; Xu, B., *Chem. Commun.* **2014**, *50*, 14129-14132.

6. Copy of ^{1}H and ^{13}C NMR spectra

cis-1,3-disubstituted isoindolines **3**



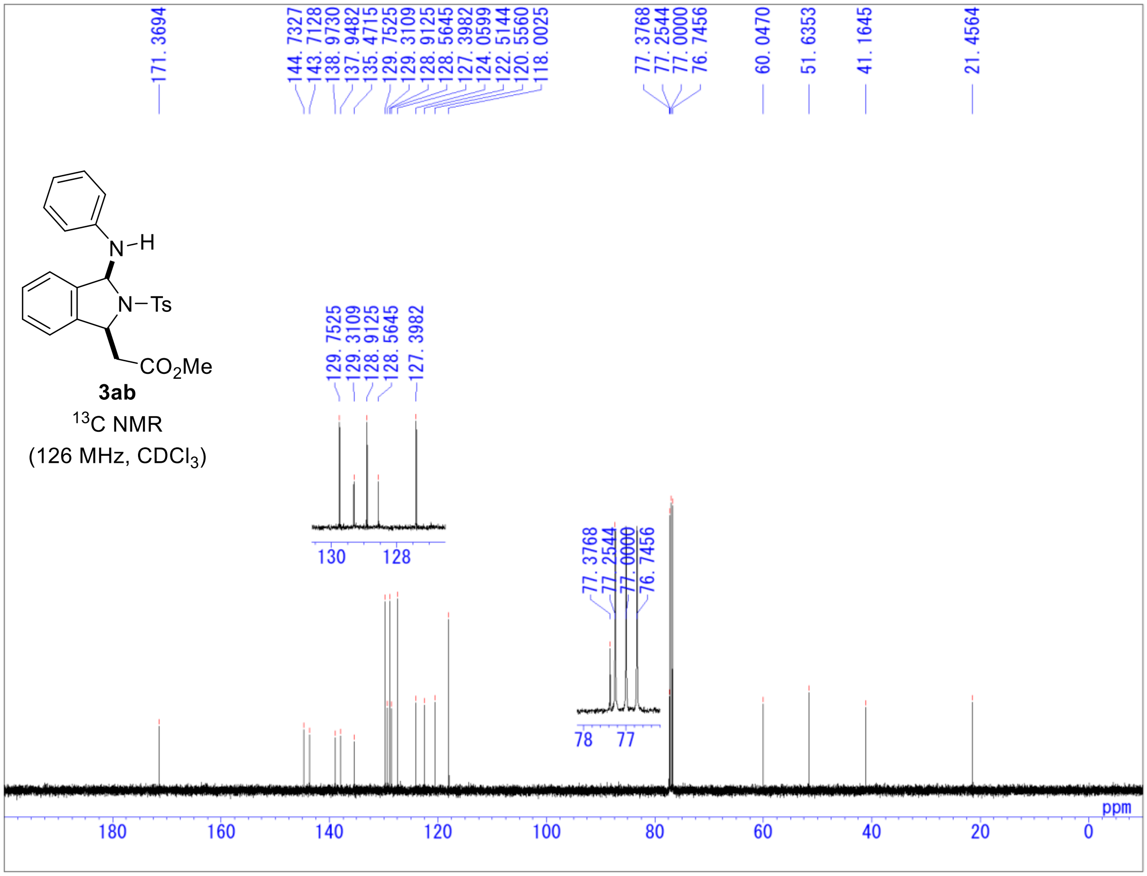




3ab

^{1}H NMR

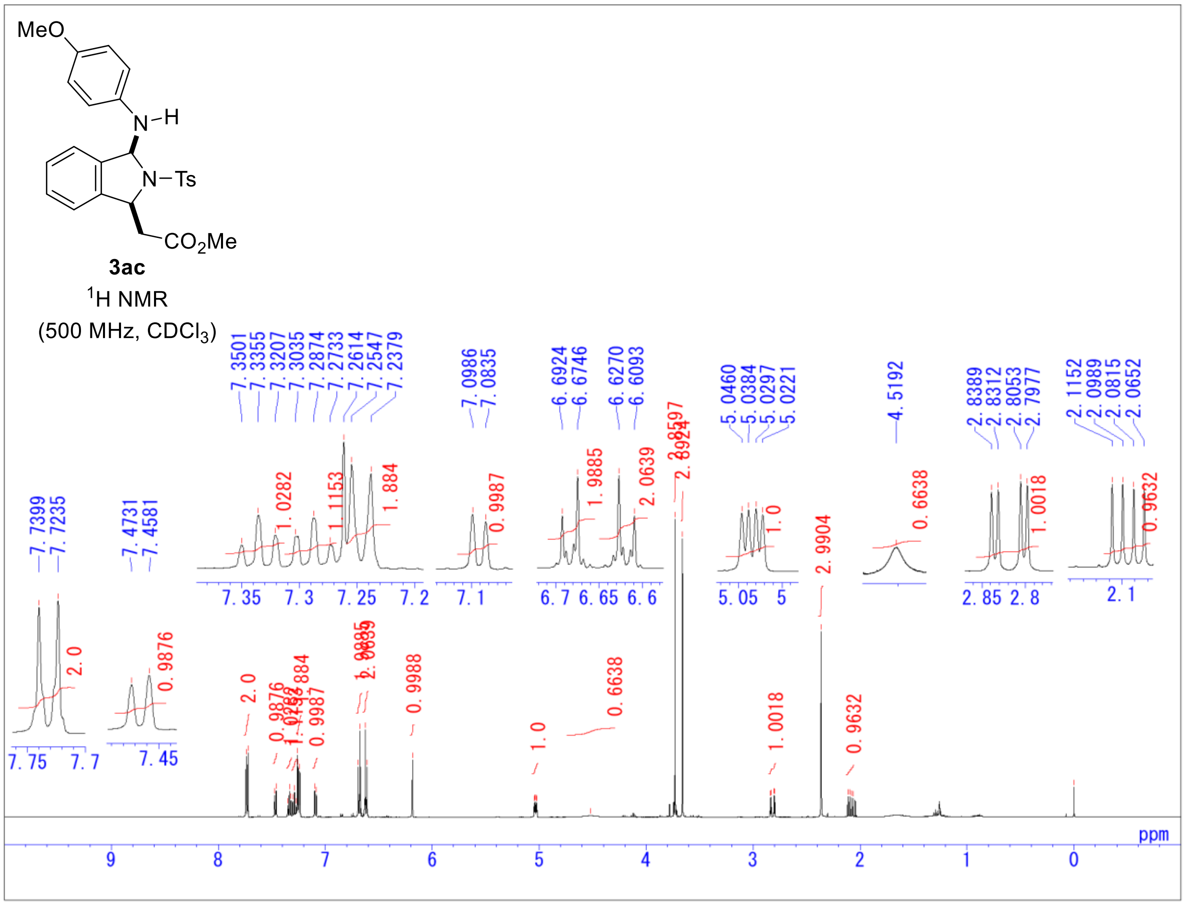
(500 MHz, $CDCl_3$)



3ab

^{13}C NMR

(126 MHz, $CDCl_3$)


MeO
N–H
N–Ts
CO2Me
3ac
1H NMR
(500 MHz, CDCl3)
7.7399
7.7235
7.4731
7.4581
7.3501
7.3355
7.3207
7.3035
7.2874
7.2733
7.2614
7.2547
7.2379
7.0986
7.0835
6.6924
6.6746
6.6270
6.6093
5.0460
5.0384
5.0297
5.0221
4.5192
2.8389
2.8312
2.8053
2.7977
2.1152
2.0989
2.0815
2.0652
2.0
0.9876
1.0282
1.1153
1.884
0.9987
1.9885
2.0639
1.0
0.6638
2.9904
1.0018
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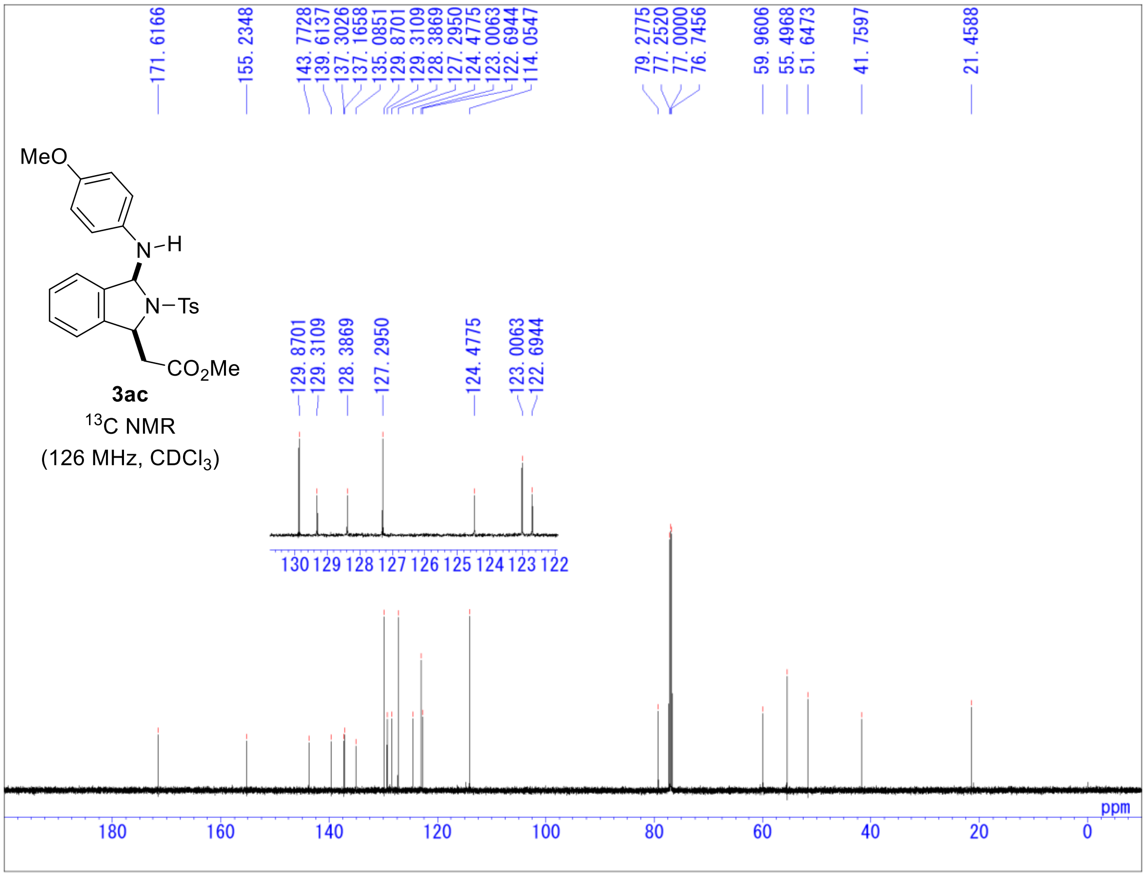
ppm
9
8
7
6
5
4
3
2
1
0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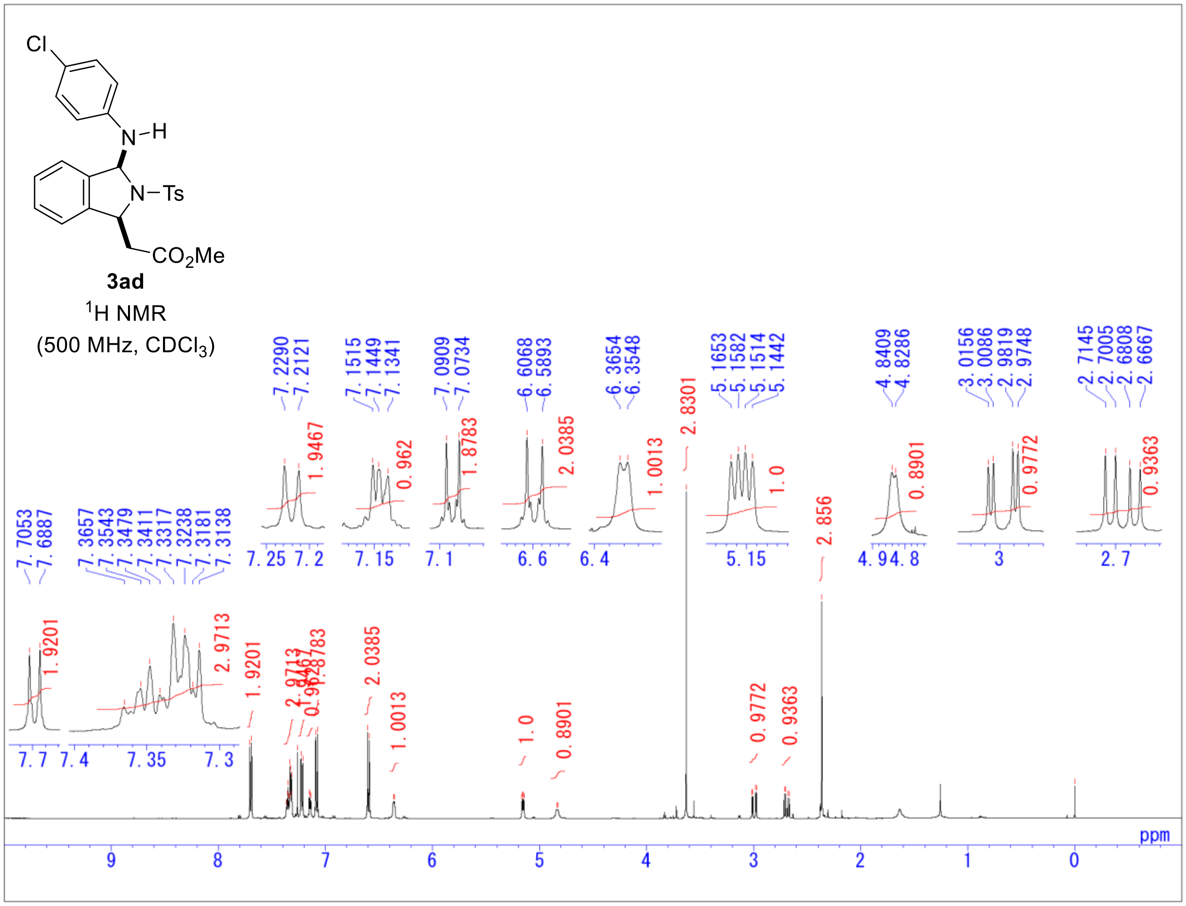
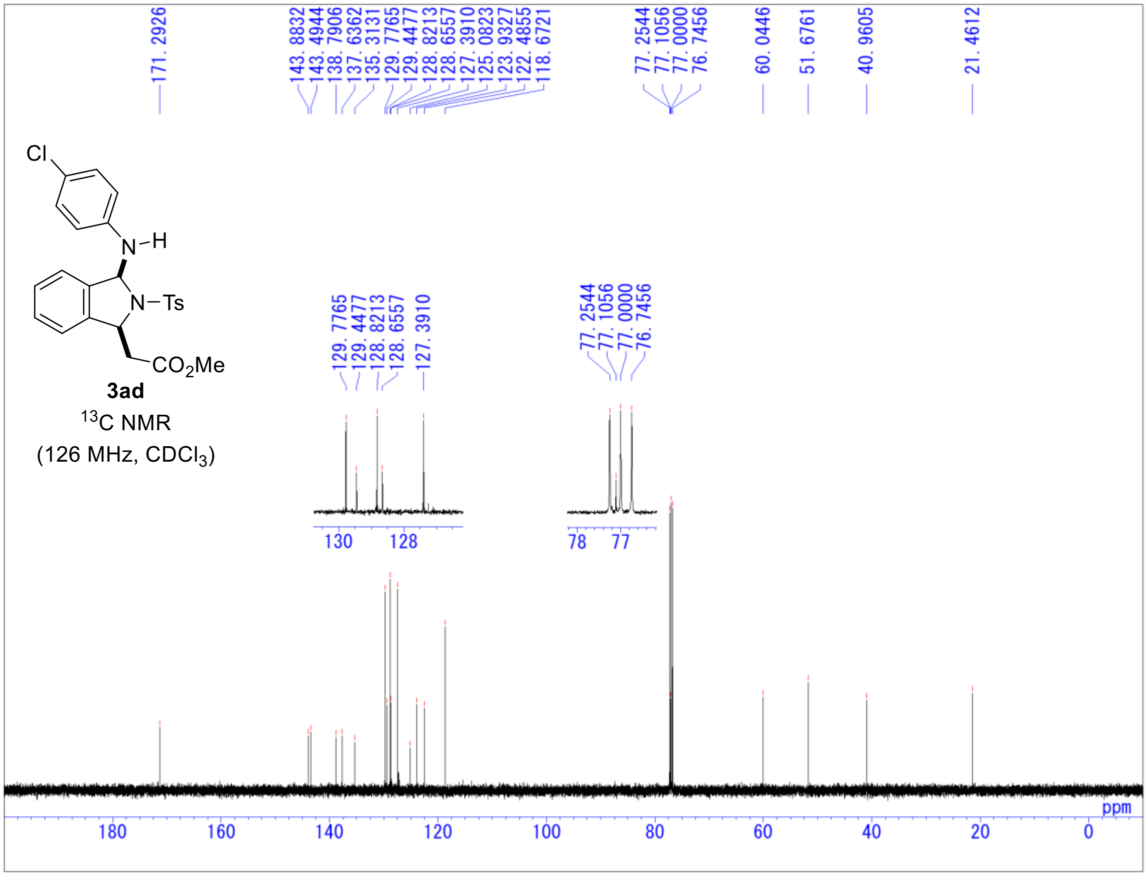
139.6137
137.3026
137.1658
135.0851
129.8701
129.3109
128.3869
127.2950
124.4775
123.0063
122.6944
114.0547
79.2775
77.2520
77.0000
76.7456
59.9606
55.4968
51.6473
41.7597
21.4588
MeO
N–H
N–Ts
CO2Me
3ac
13C NMR
(126 MHz, CDCl3)
ppm
180
160
140
120
100
80
60
40
20
0



3ad

^{1}H NMR

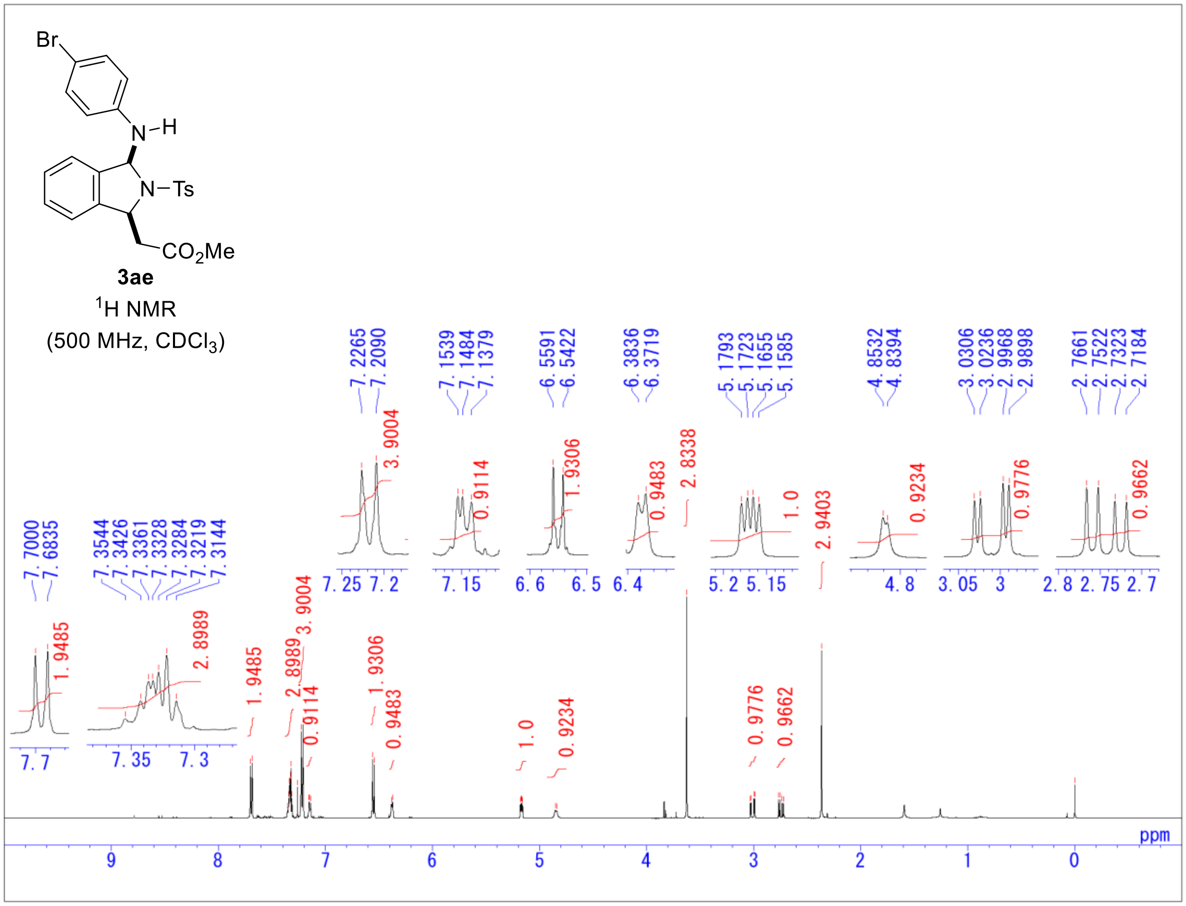
(500 MHz, $CDCl_3$)



3ad

^{13}C NMR

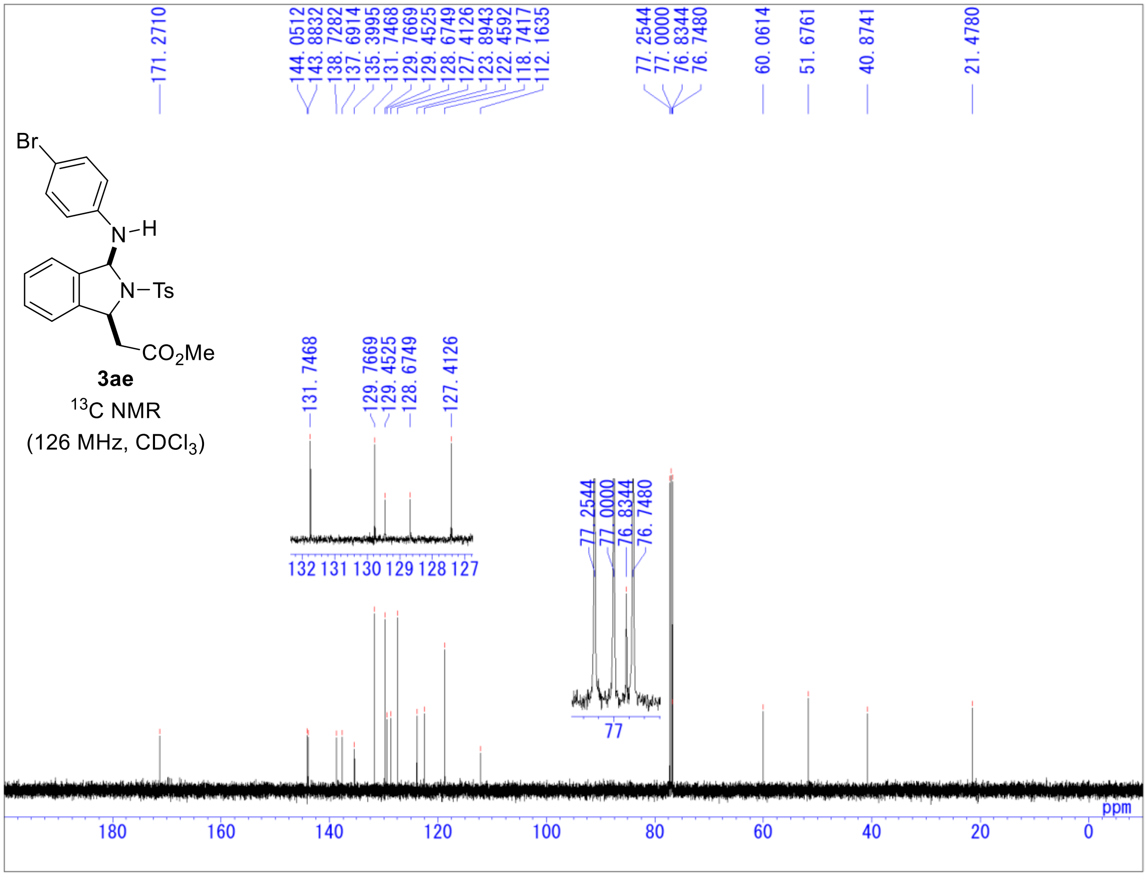
(126 MHz, $CDCl_3$)



3ae

^{1}H NMR

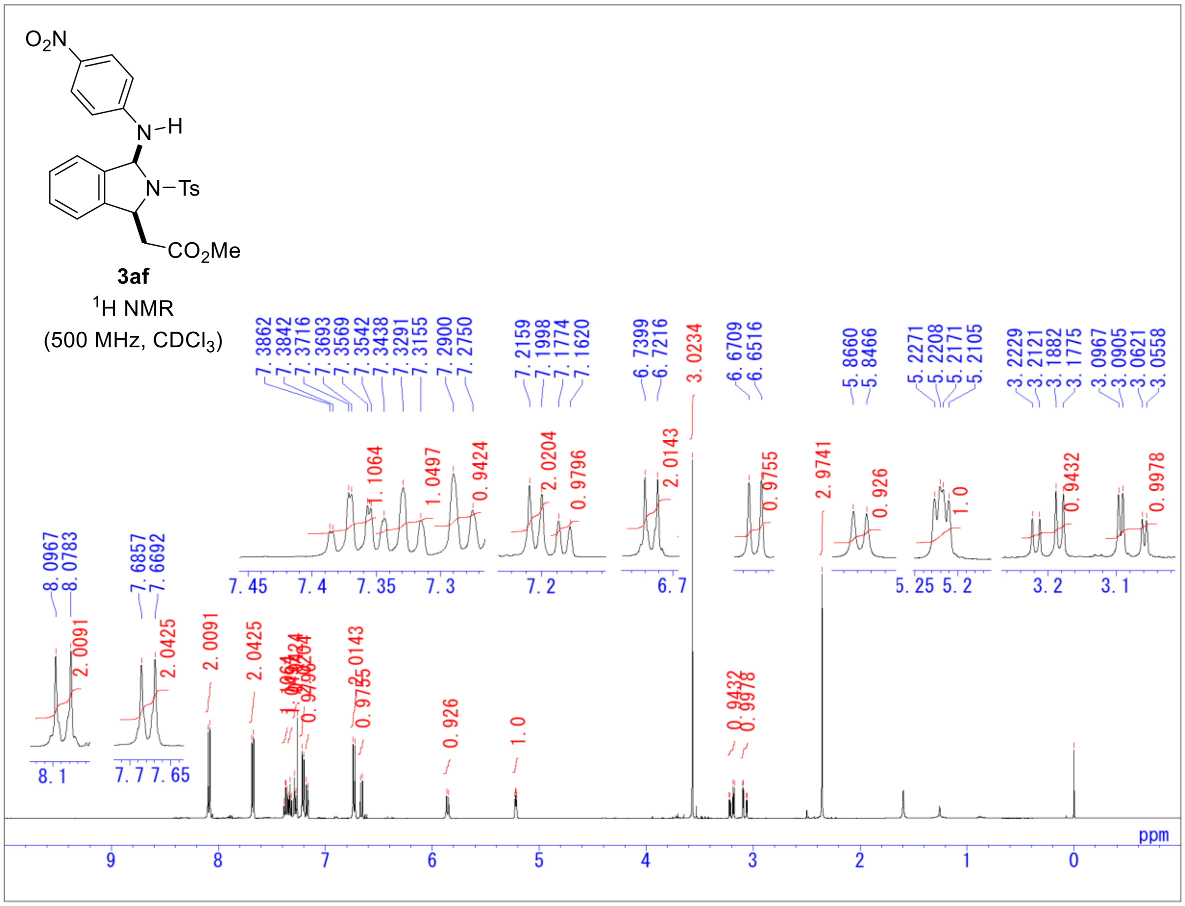
(500 MHz, $CDCl_3$)

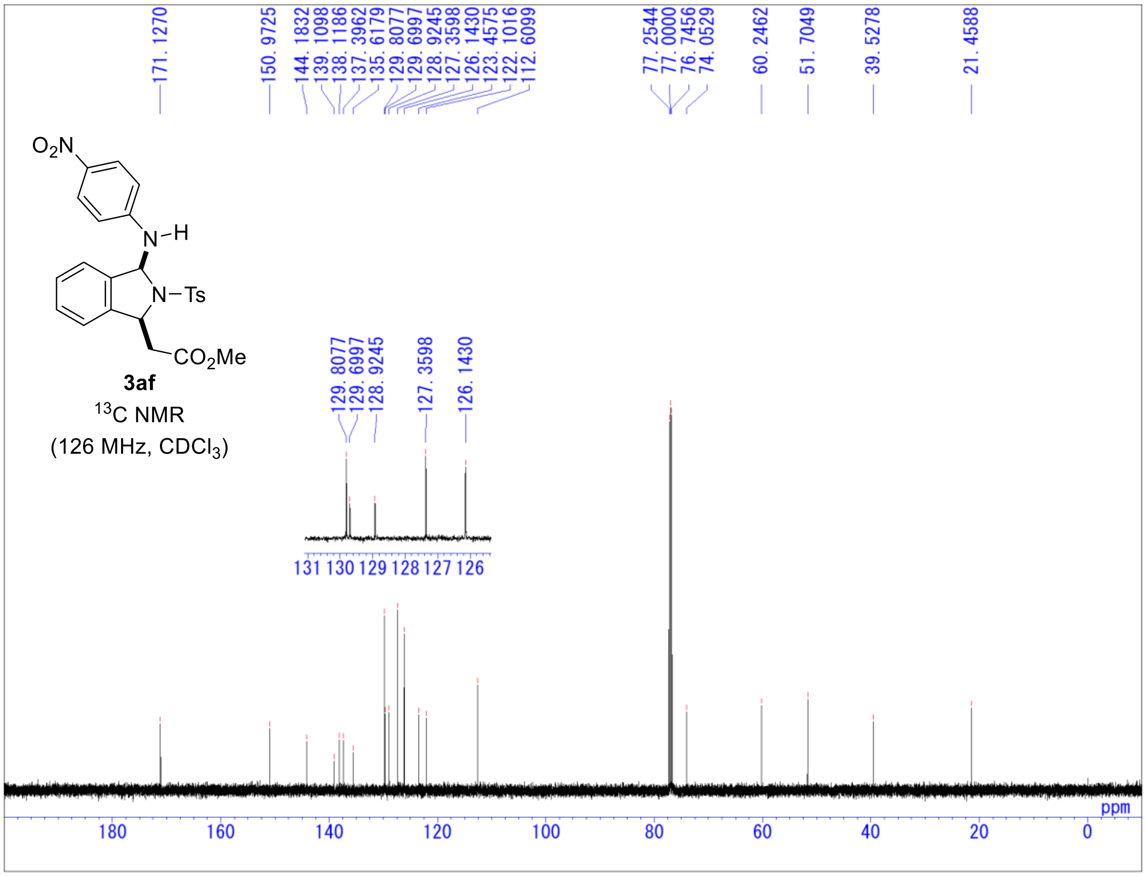


3ae

^{13}C NMR

(126 MHz, $CDCl_3$)


O2N
N–H
N–Ts
CO2Me
3af
1H NMR
(500 MHz, CDCl3)
8.0967
8.0783
7.6857
7.6692
7.3862
7.3842
7.3716
7.3693
7.3569
7.3542
7.3438
7.3291
7.3155
7.2900
7.2750
7.2159
7.1998
7.1774
7.1620
6.7399
6.7216
3.0234
6.6709
6.6516
5.8660
5.8466
5.2271
5.2208
5.2171
5.2105
3.2229
3.2121
3.1882
3.1775
3.0967
3.0905
3.0621
3.0558
2.0091
2.0425
1.1064
1.0497
0.9424
2.0204
0.9796
2.0143
0.9755
2.9741
0.926
1.0
0.9432
0.9978
8.1
7.7
7.65
7.45
7.4
7.35
7.3
7.2
6.7
5.25
5.2
3.2
3.1
ppm
9
8
7
6
5
4
3
2
1
0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144.1832
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135.6179
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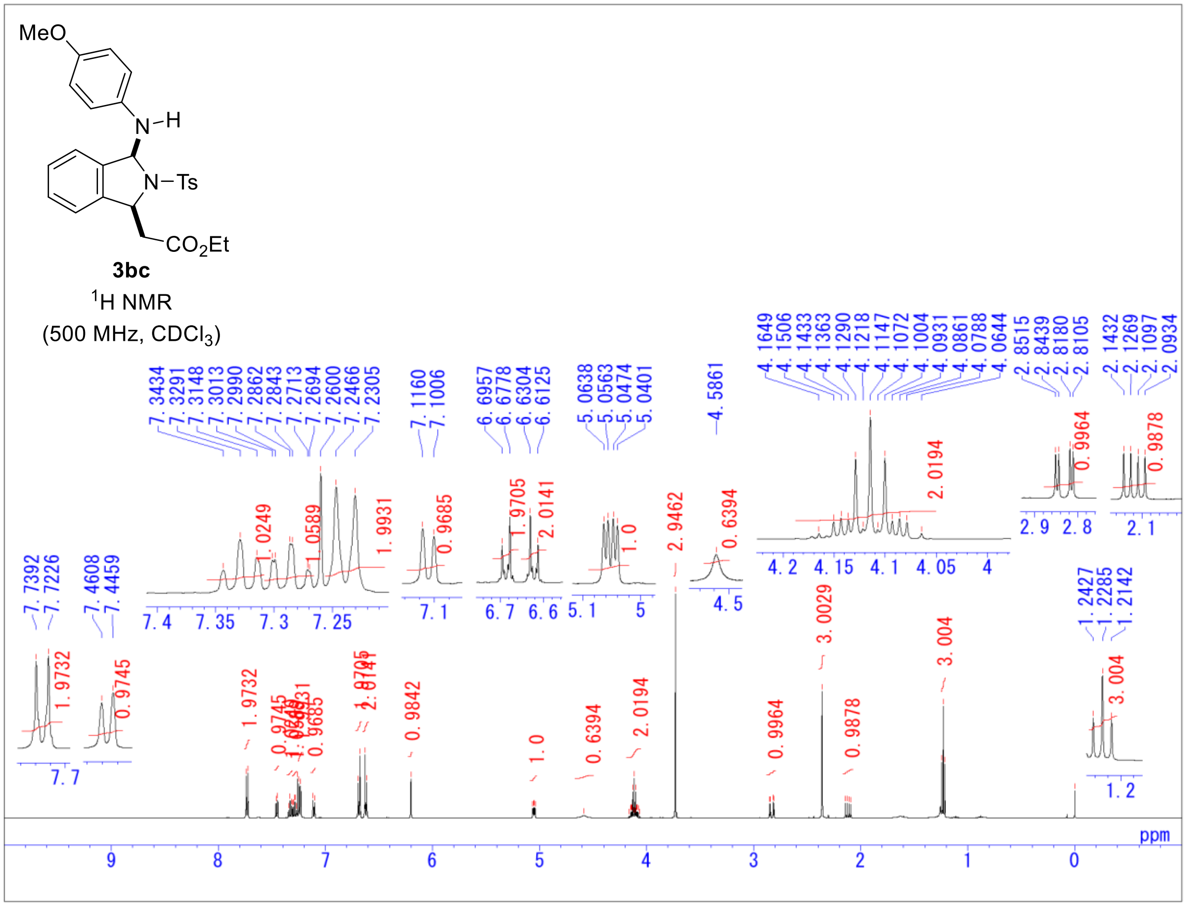
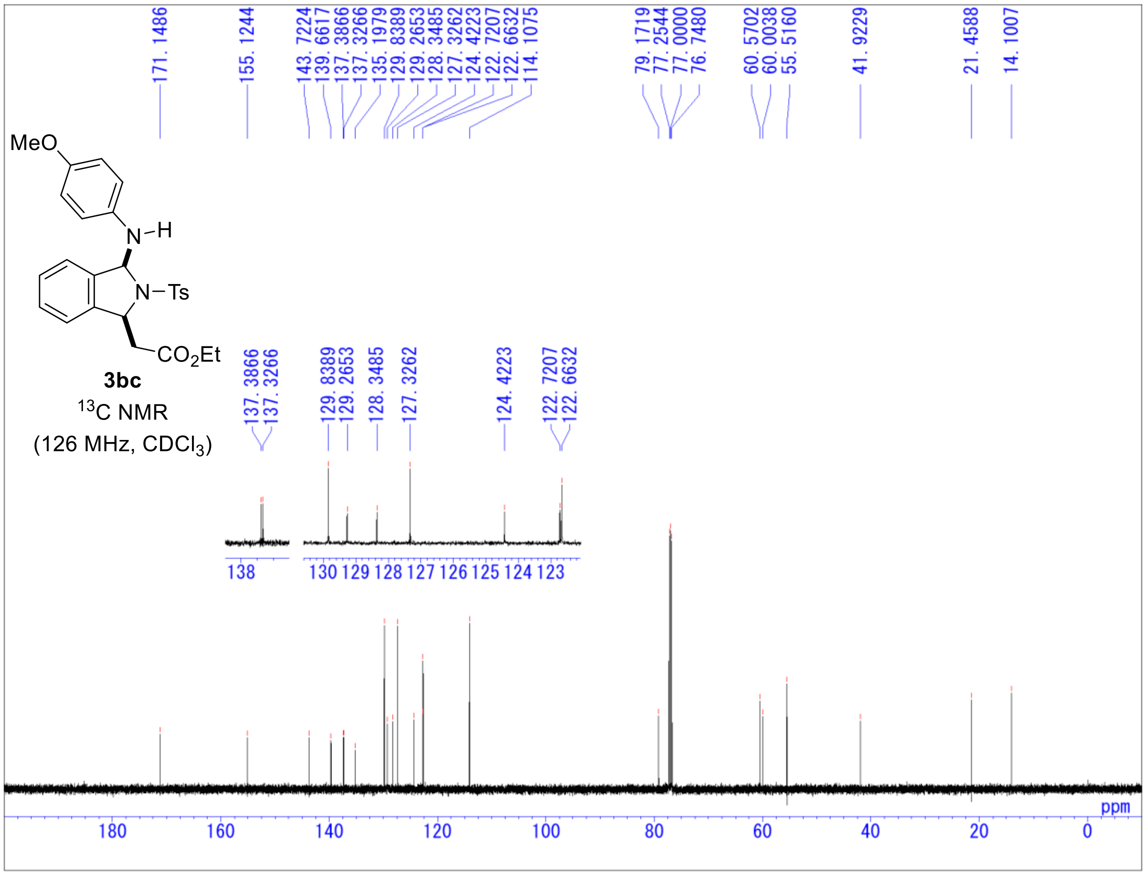
127.3598
126.1430
123.4575
122.1016
112.6099
77.2544
77.0000
76.7456
74.0529
60.2462
51.7049
39.5278
21.4588
O2N
N–H
N–Ts
CO2Me
3af
13C NMR
(126 MHz, CDCl3)
131
130
129
128
127
126
ppm
180
160
140
120
100
80
60
40
20
0



3bc

^{1}H NMR

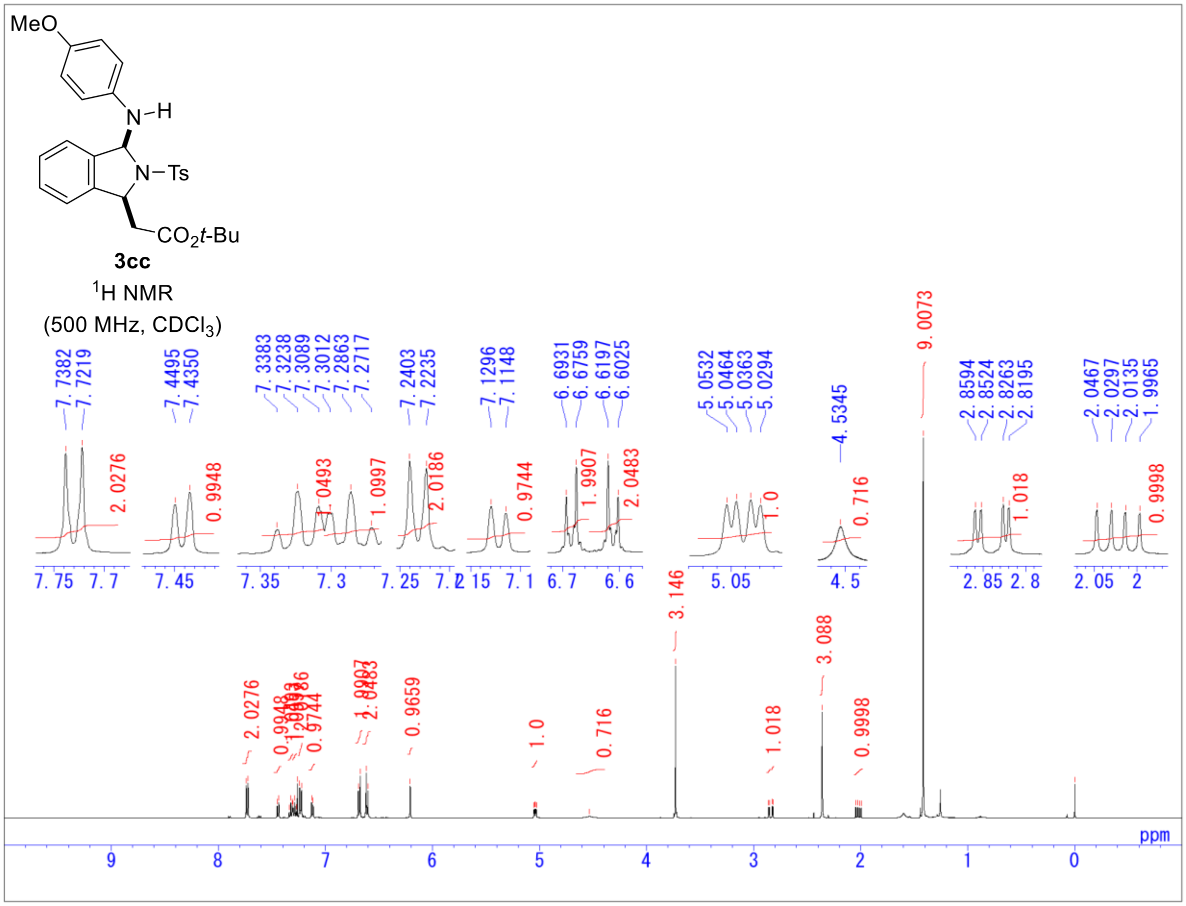
(500 MHz, $CDCl_3$)



3bc

^{13}C NMR

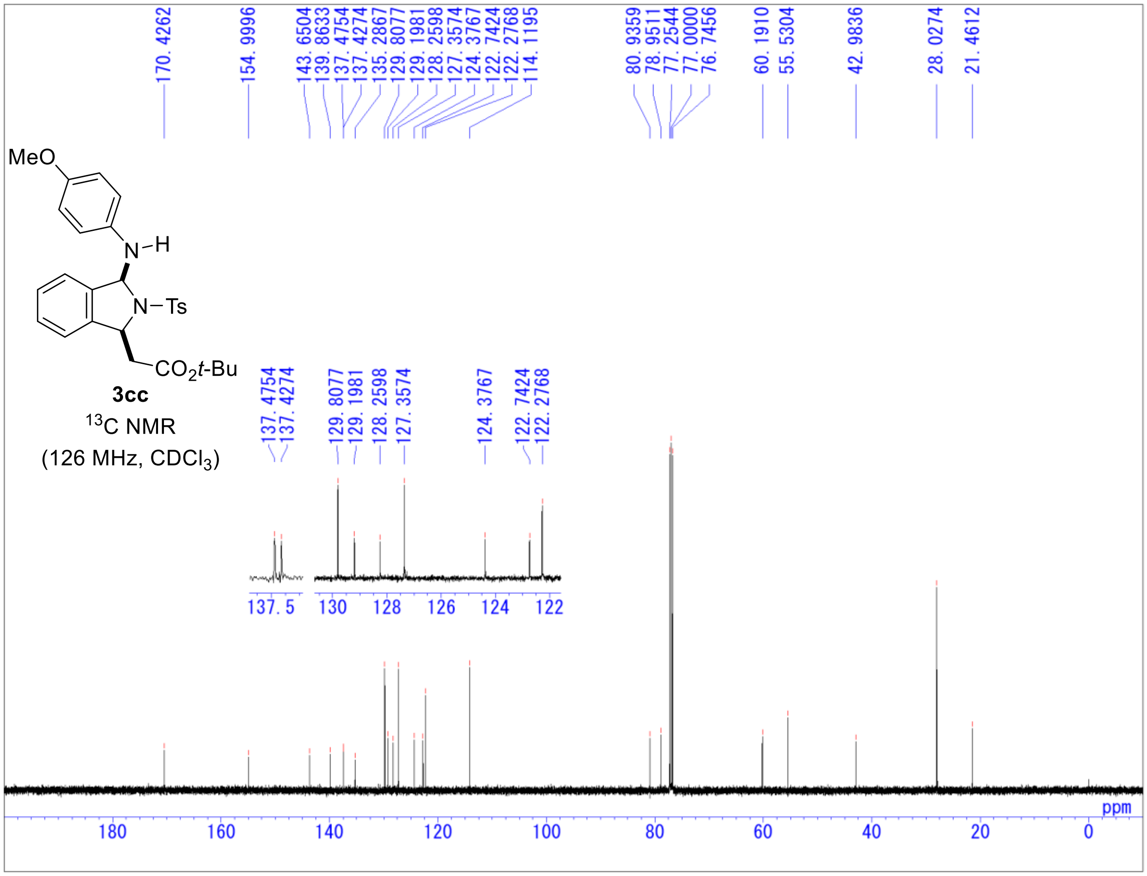
(126 MHz, $CDCl_3$)



3cc

^{1}H NMR

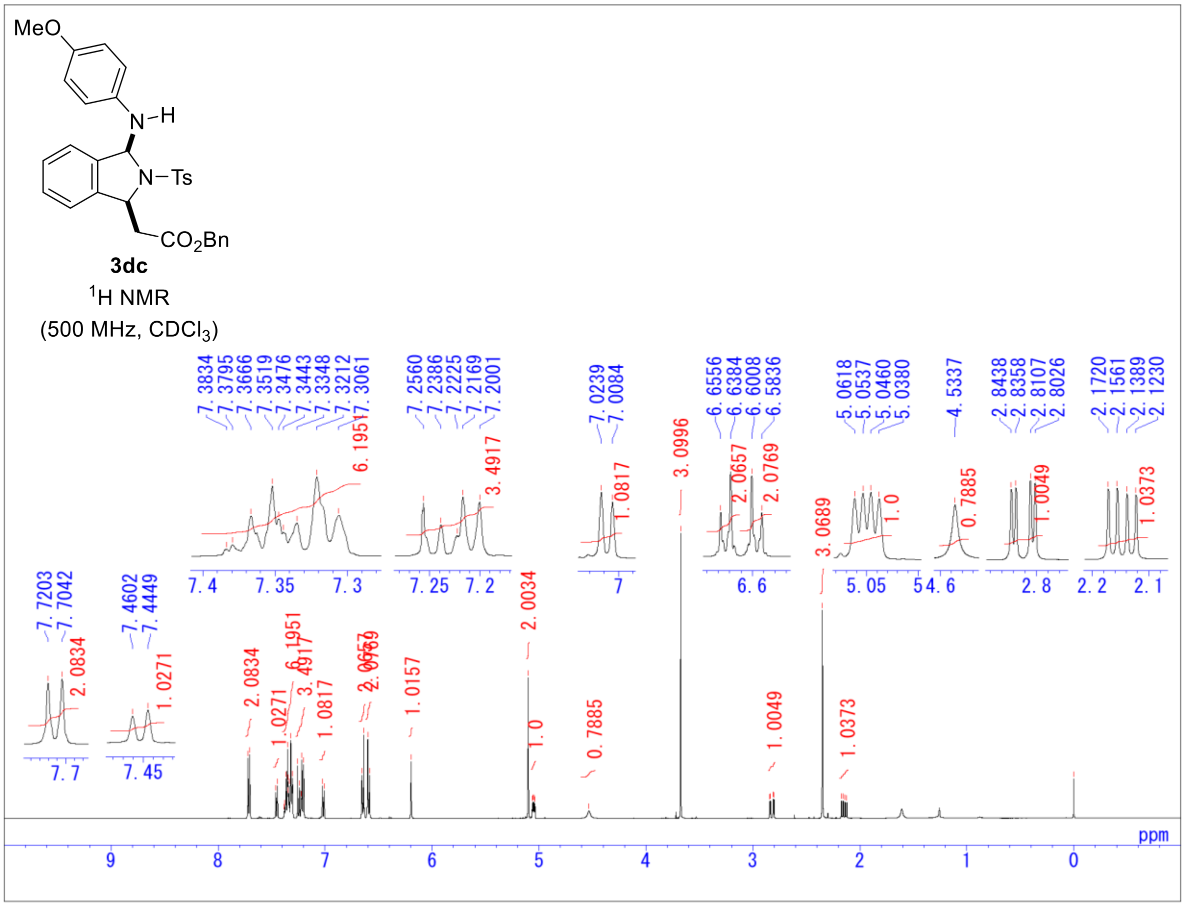
(500 MHz, $CDCl_3$)



3cc

^{13}C NMR

(126 MHz, $CDCl_3$)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N–H
N–Ts
CO2Bn
3dc
1H NMR
(500 MHz, CDCl3)
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7.4449
7.3834
7.3795
7.3666
7.3519
7.3476
7.3443
7.3348
7.3212
7.3061
7.2560
7.2386
7.2225
7.2169
7.2001
7.0239
7.0084
6.6556
6.6384
6.6008
6.5836
5.0618
5.0537
5.0460
5.0380
4.5337
2.8438
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2.8026
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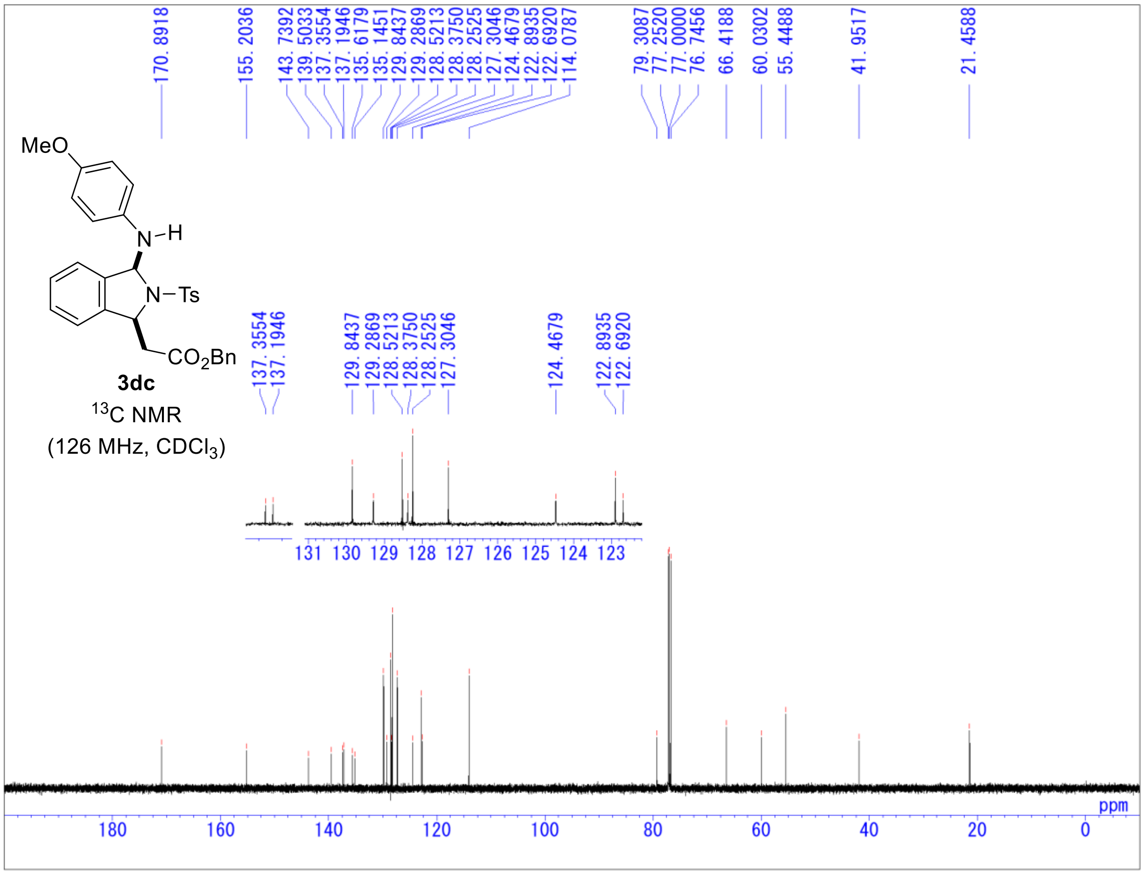
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137.1946
135.6179
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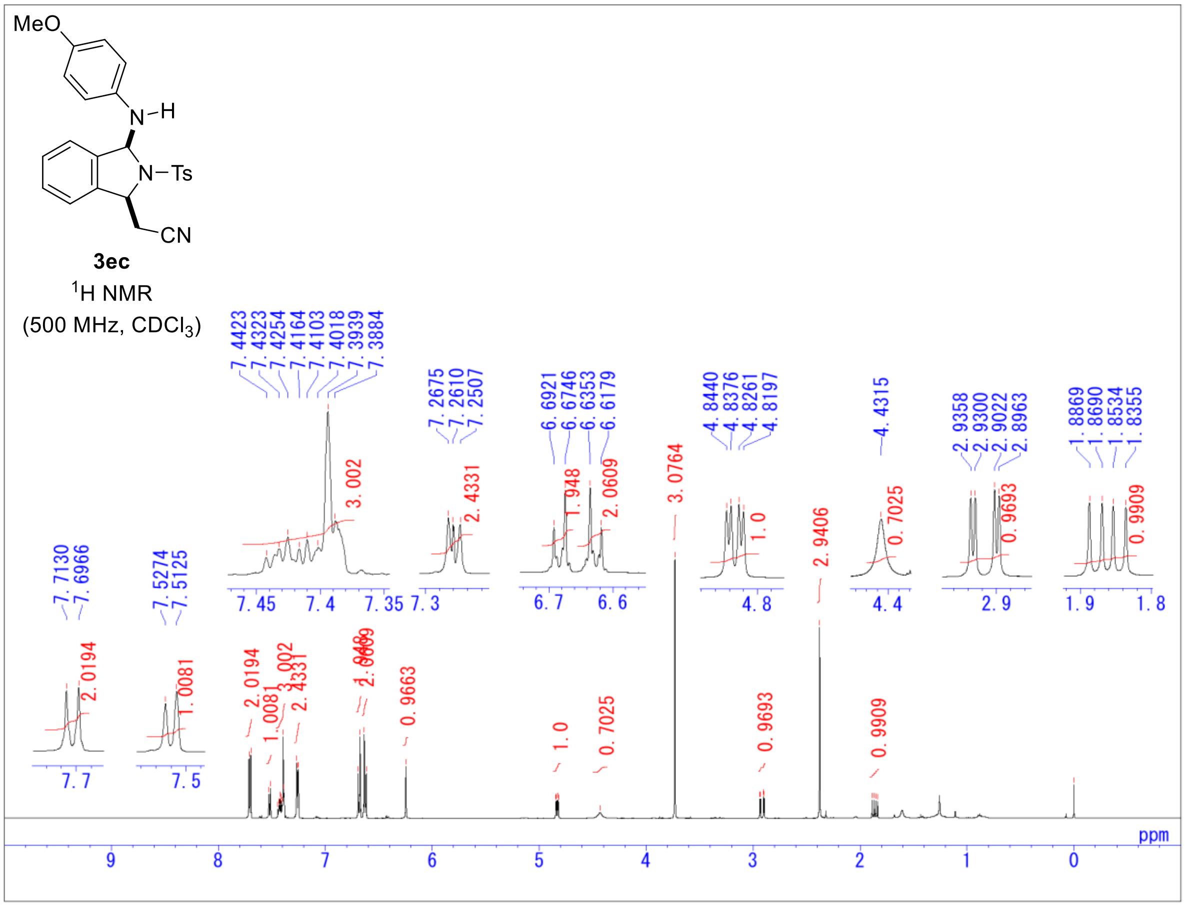
129.2869
128.5213
128.3750
128.2525
127.3046
124.4679
122.8935
122.6920
114.0787
79.3087
77.2520
77.0000
76.7456
66.4188
60.0302
55.4488
41.9517
21.4588
MeO
N–H
N–Ts
CO2Bn
3dc
13C NMR
(126 MHz, CDCl3)
131
130
129
128
127
126
125
124
123
ppm
180
160
140
120
100
80
60
40
20
0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N–H
N–Ts
CN
3ec
^{1}H NMR
(500 MHz, CDCl$_3$)
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7.5125
7.4423
7.4323
7.4254
7.4164
7.4103
7.4018
7.3939
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7.2675
7.2610
7.2507
6.6921
6.6746
6.6353
6.6179
4.8440
4.8376
4.8261
4.8197
4.4315
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2.9022
2.8963
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1.8690
1.8534
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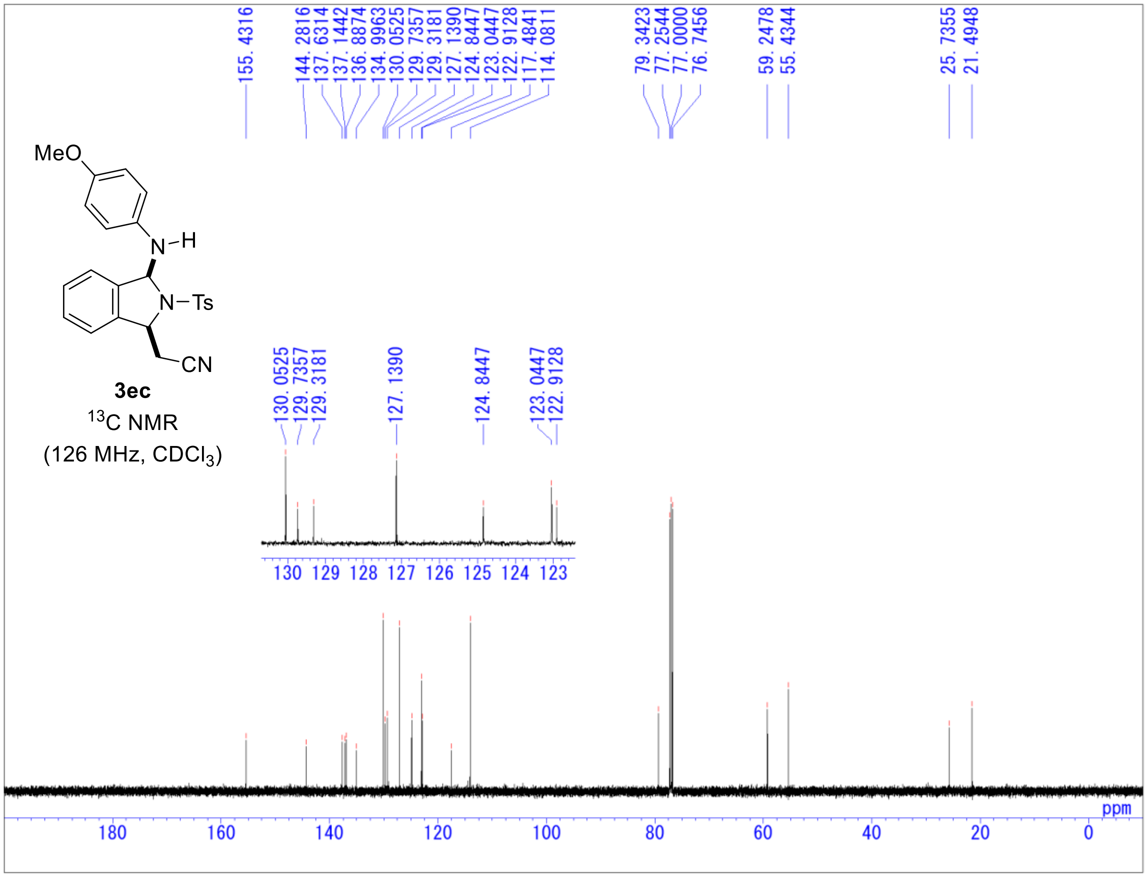
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114.0811
79.3423
77.2544
77.0000
76.7456
59.2478
55.4344
25.7355
21.4948
MeO
N–H
N–Ts
CN
3ec
^{13}C NMR
(126 MHz, CDCl$_3$)
130.0525
129.7357
129.3181
127.1390
124.8447
123.0447
122.9128
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128
127
126
125
124
123
ppm
180
160
140
120
100
80
60
40
20
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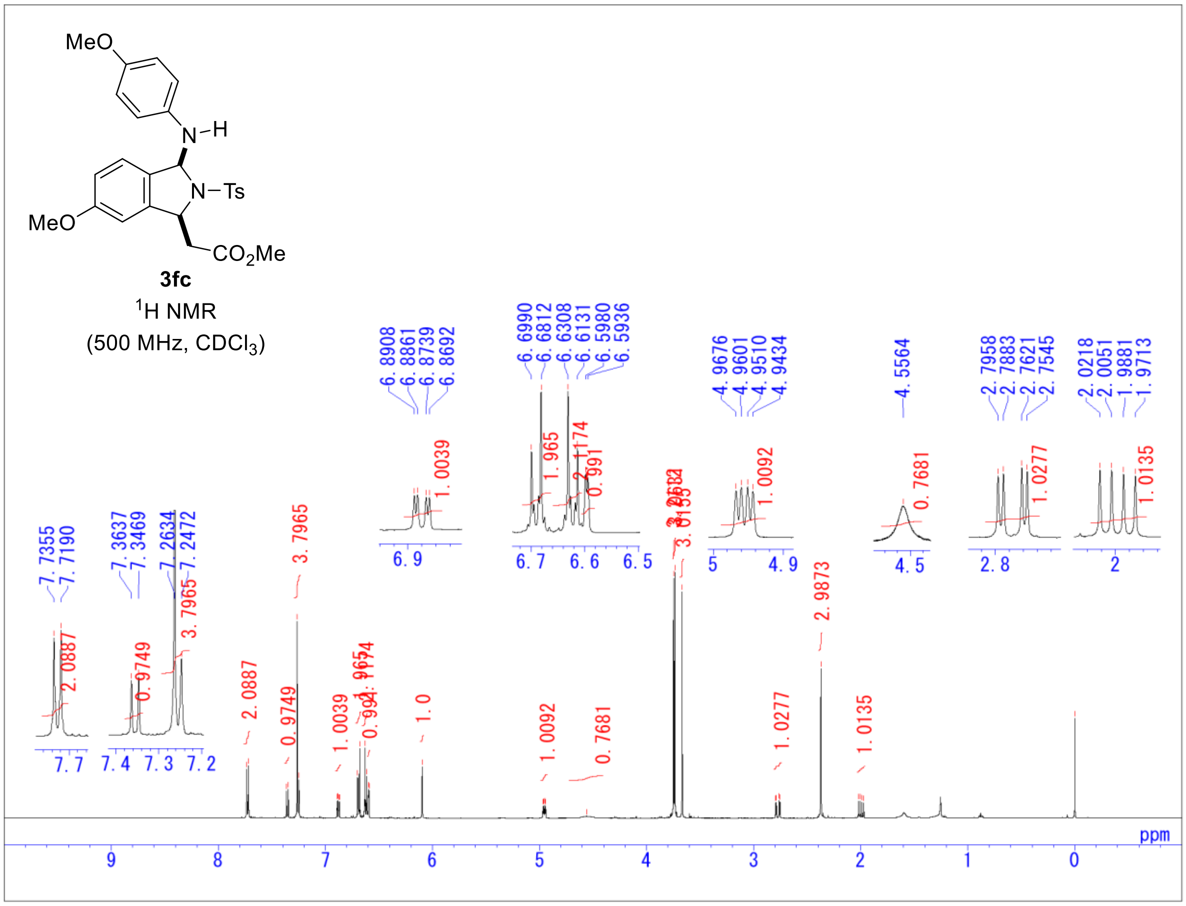
MeO
N–H
N–Ts
MeO
CO$_2$Me
3fc
^{1}H NMR
(500 MHz, CDCl$_3$)
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7.3637
7.3469
7.2634
7.2472
6.8908
6.8861
6.8739
6.8692
6.6990
6.6812
6.6308
6.6131
6.5980
6.5936
4.9676
4.9601
4.9510
4.9434
4.5564
2.7958
2.7883
2.7621
2.7545
2.0218
2.0051
1.9881
1.9713
2.0887
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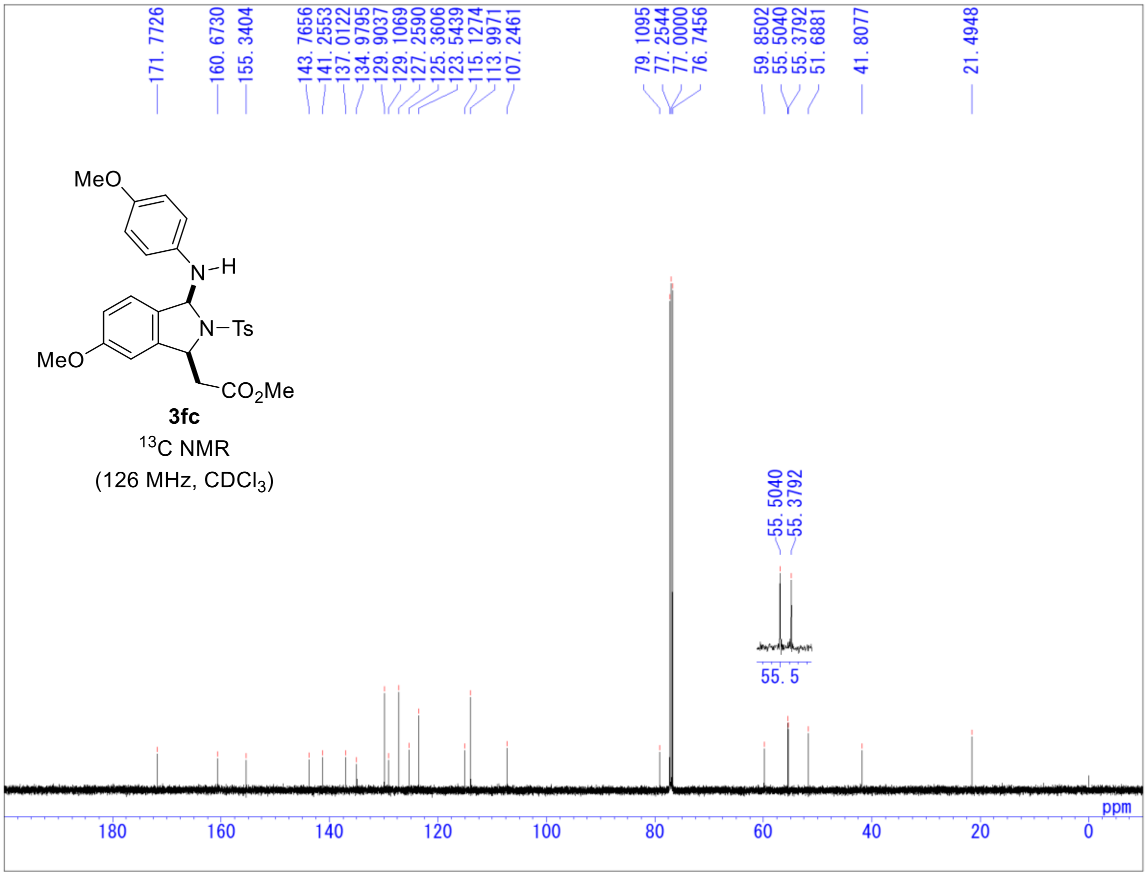
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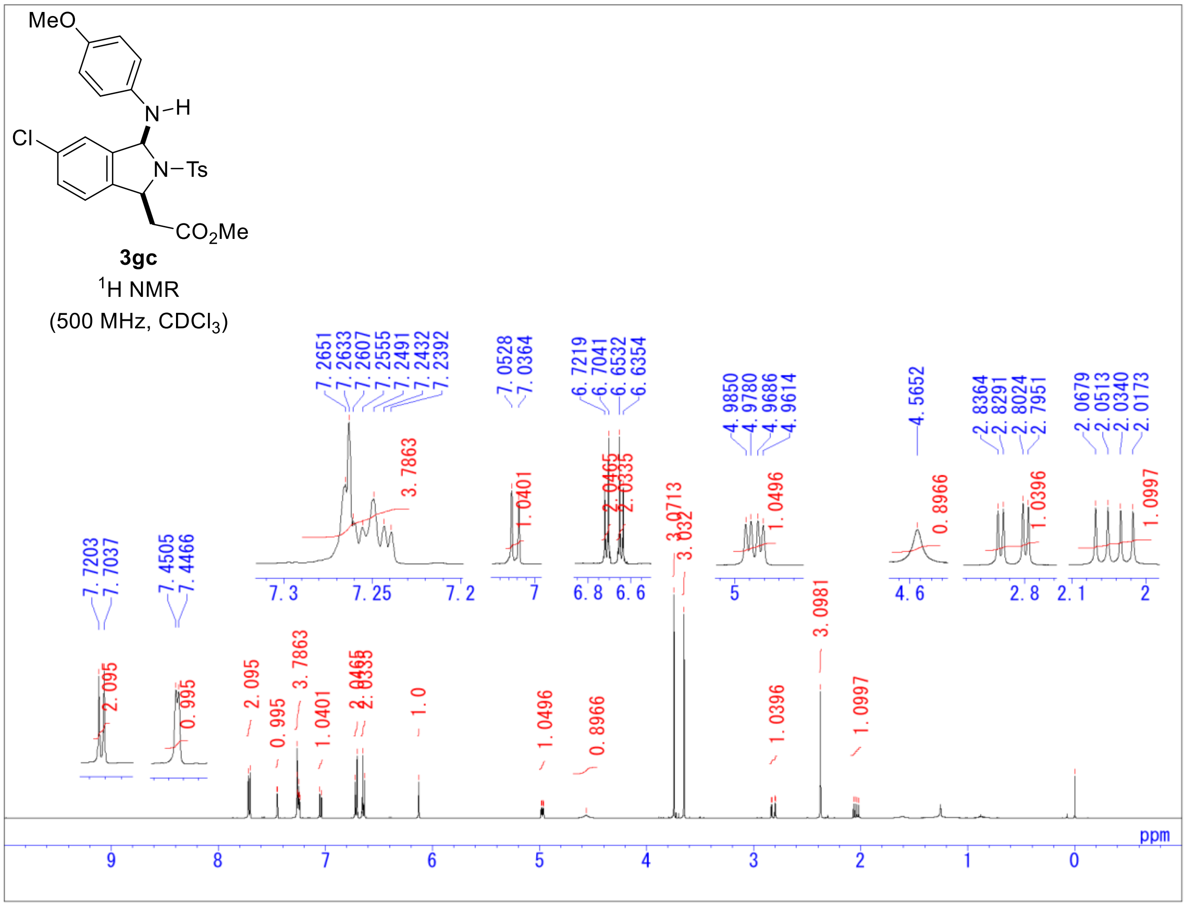
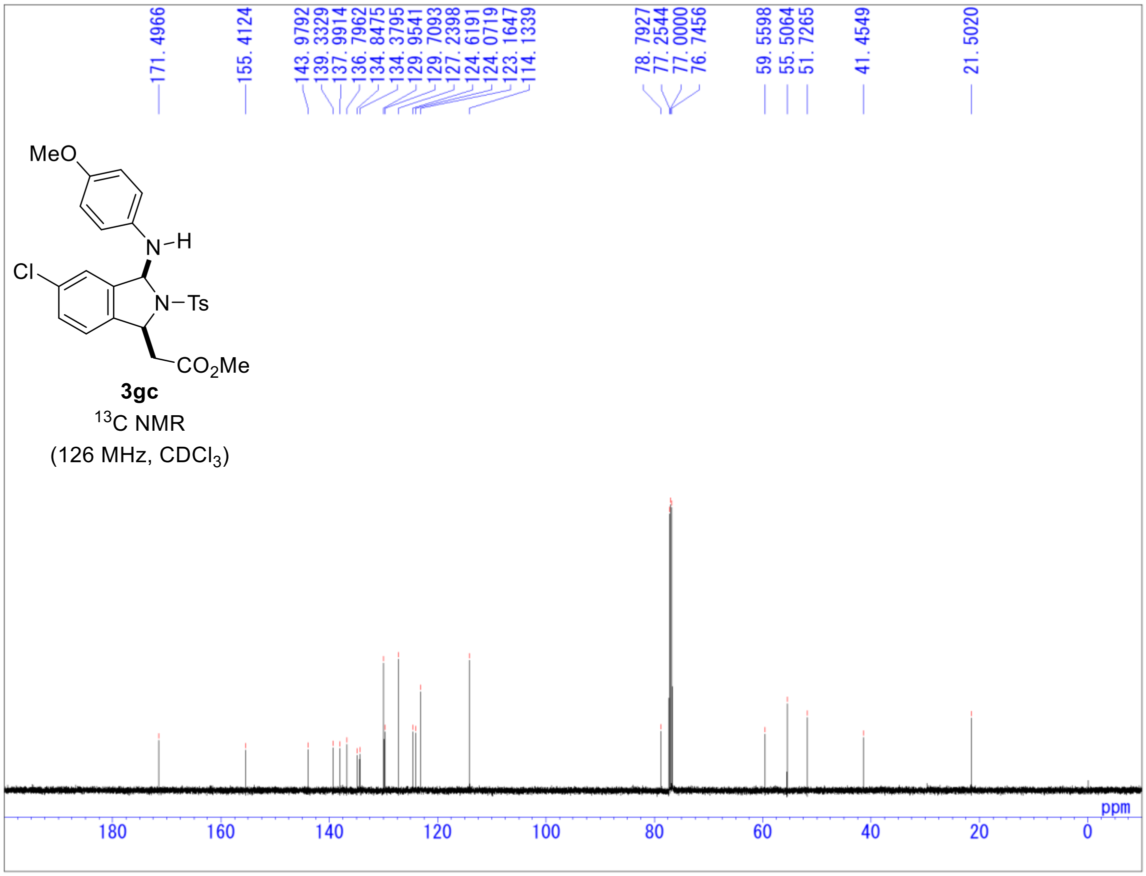
127.2590
125.3606
123.5439
115.1274
113.9971
107.2461
79.1095
77.2544
77.0000
76.7456
59.8502
55.5040
55.3792
51.6881
41.8077
21.4948
MeO
N–H
N–Ts
MeO
CO$_2$Me
3fc
^{13}C NMR
(126 MHz, CDCl$_3$)
55.5040
55.3792
55.5
ppm
180
160
140
120
100
80
60
40
20
0



3gc

^{1}H NMR

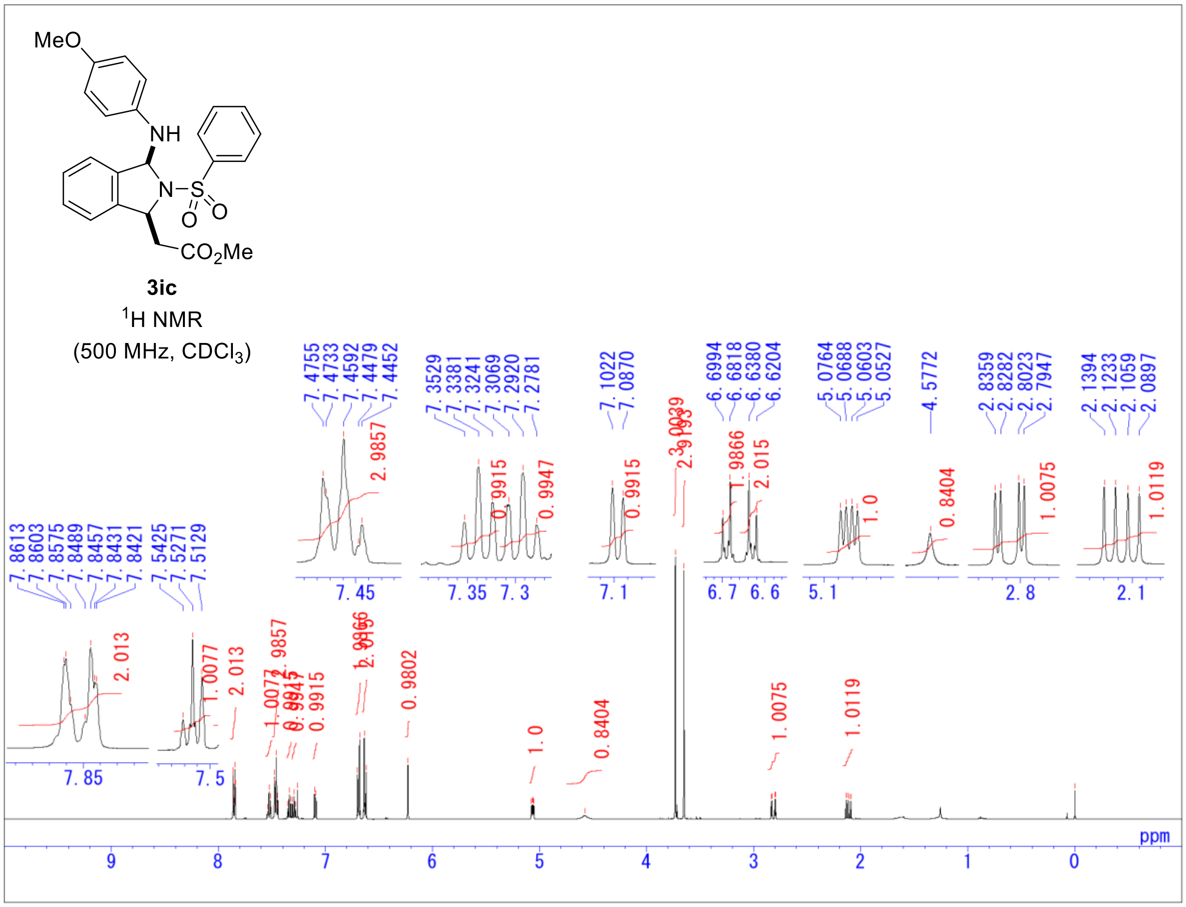
(500 MHz, $CDCl_3$)



3gc

^{13}C NMR

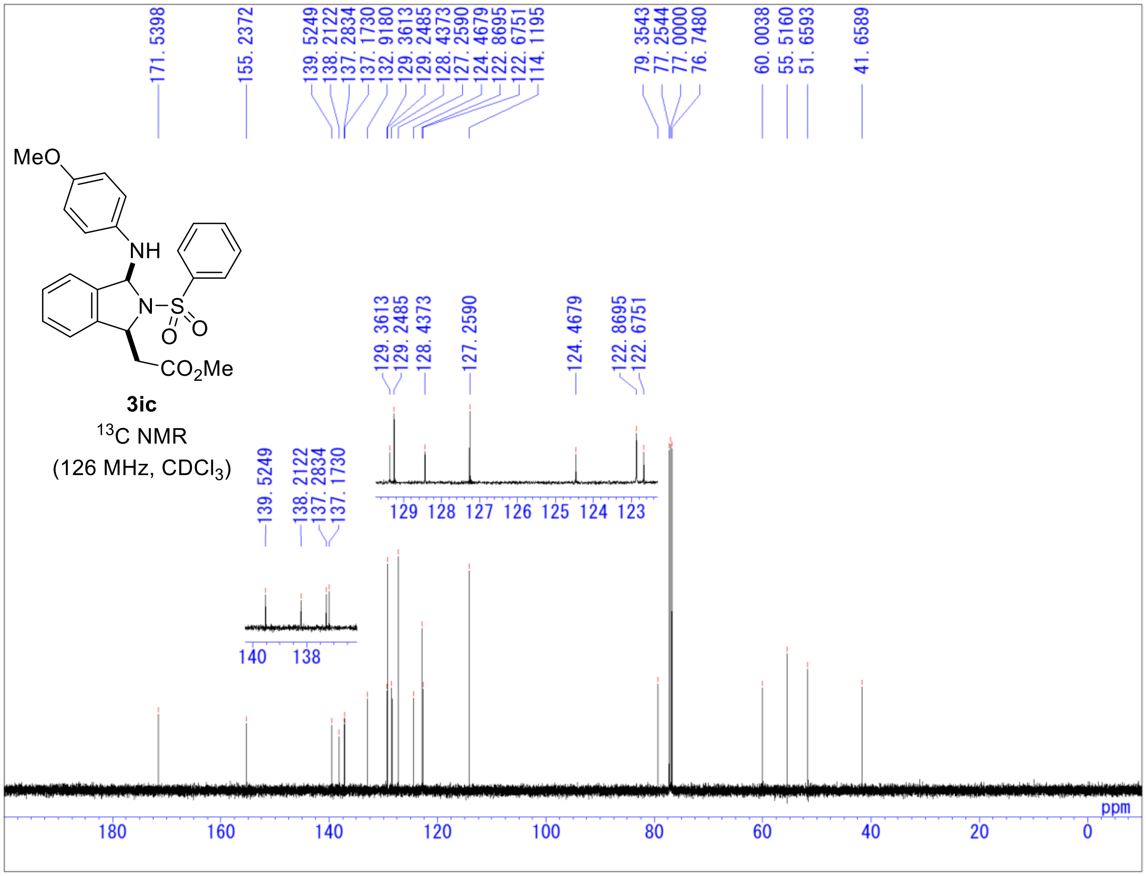
(126 MHz, $CDCl_3$)



3ic

^{1}H NMR

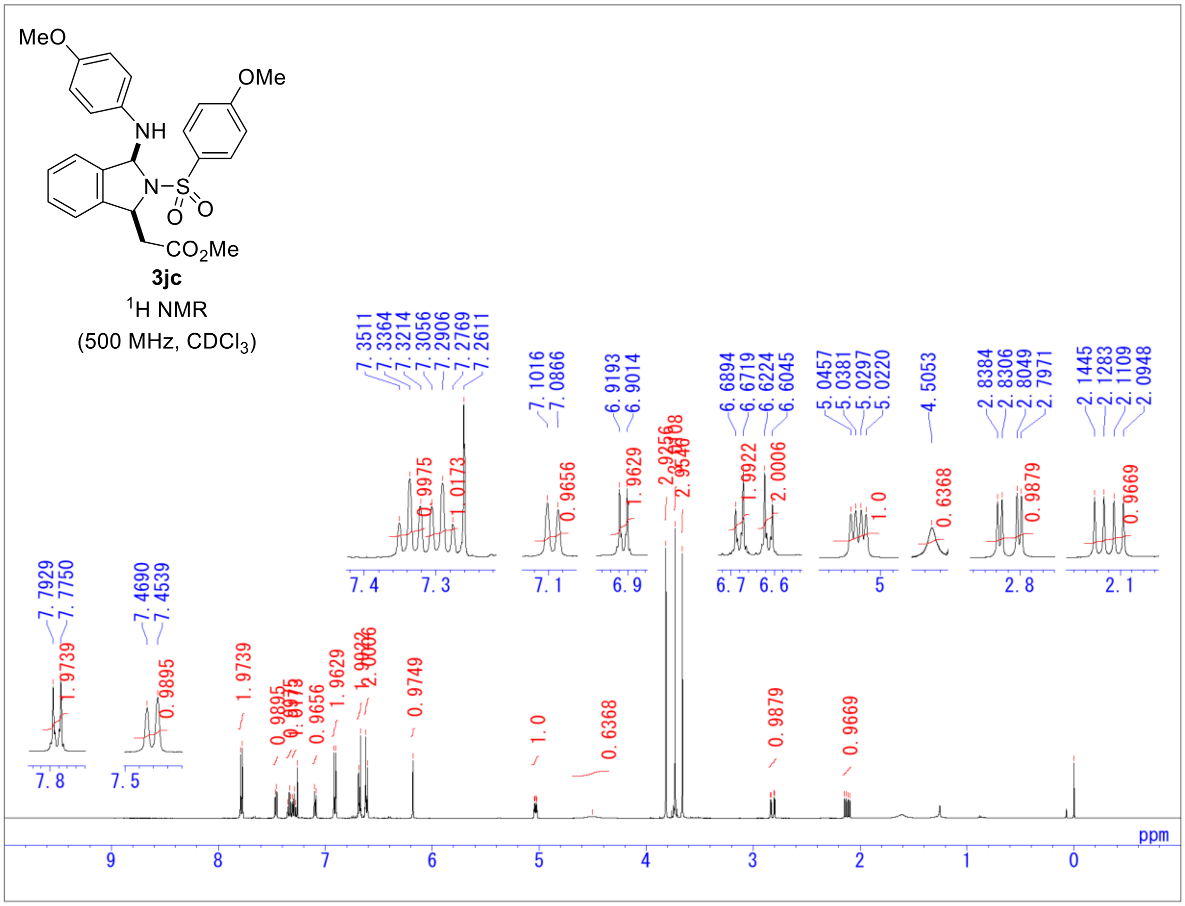
(500 MHz, CDCl$_3$)



3ic

^{13}C NMR

(126 MHz, CDCl$_3$)


MeO
OMe
NH
N
S
O
O
CO2Me
3jc
1H NMR
(500 MHz, CDCl3)
7.7929
7.7750
7.4690
7.4539
7.3511
7.3364
7.3214
7.3056
7.2906
7.2769
7.2611
7.1016
7.0866
6.9193
6.9014
6.6894
6.6719
6.6224
6.6045
5.0457
5.0381
5.0297
5.0220
4.5053
2.8384
2.8306
2.8049
2.7971
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1.9922
2.0006
0.9749
1.0
0.6368
2.9256
2.9408
2.9540
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0.9669
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7.5
7.4
7.3
7.1
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2.1
ppm
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8
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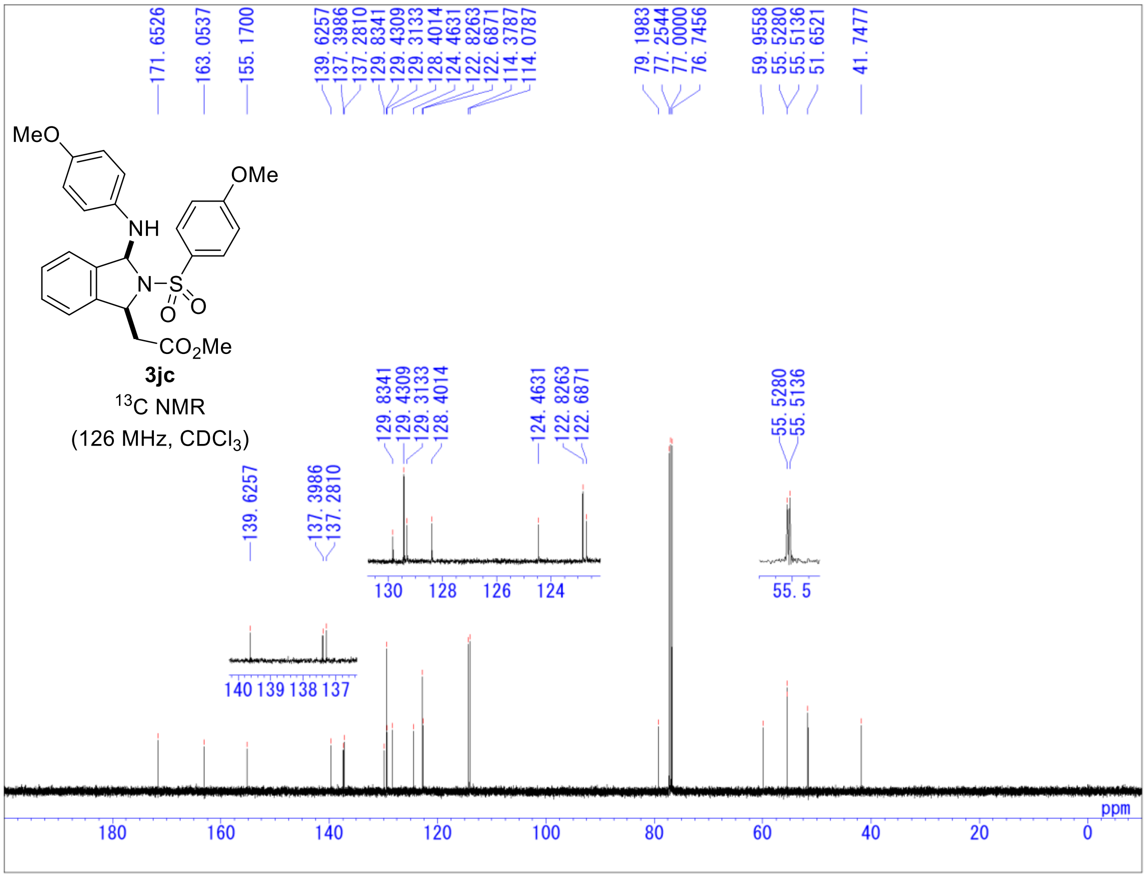
5
4
3
2
1
0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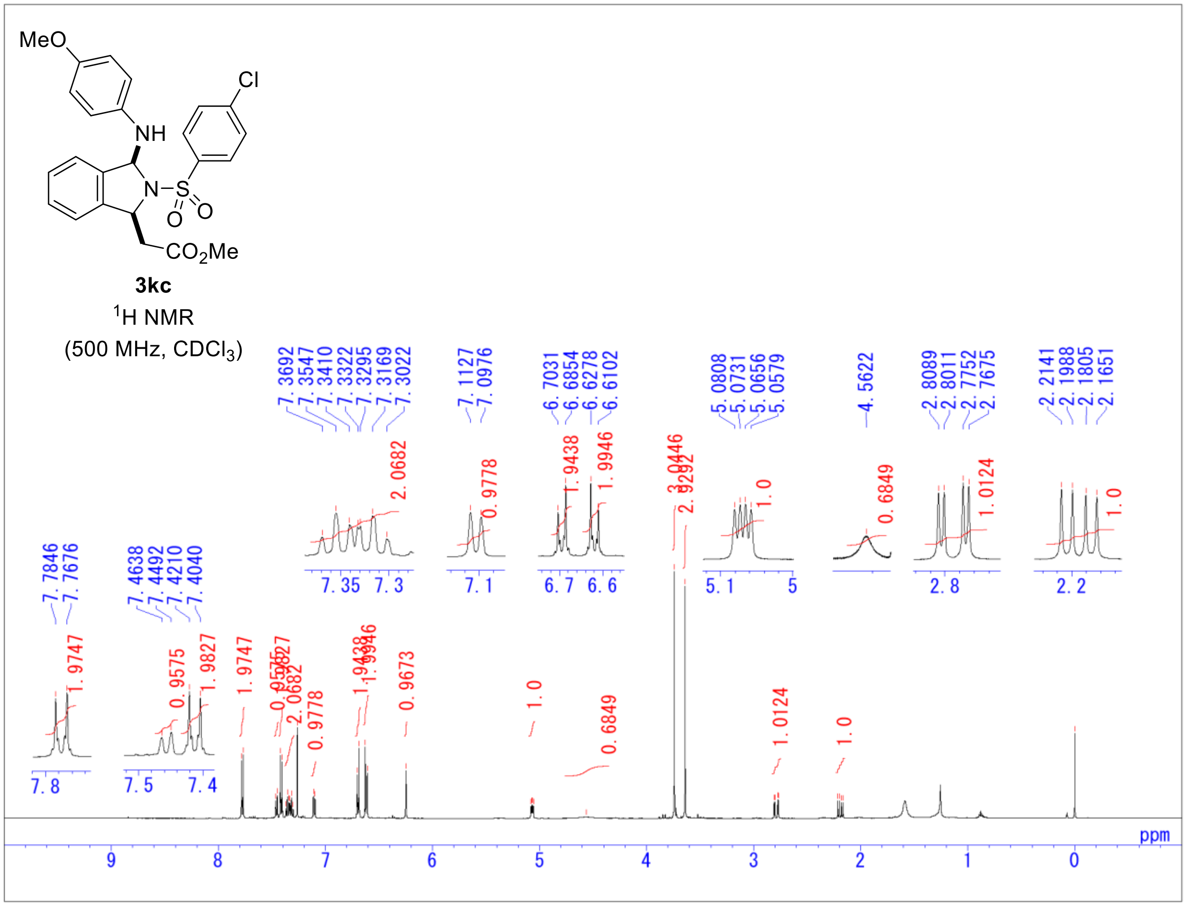
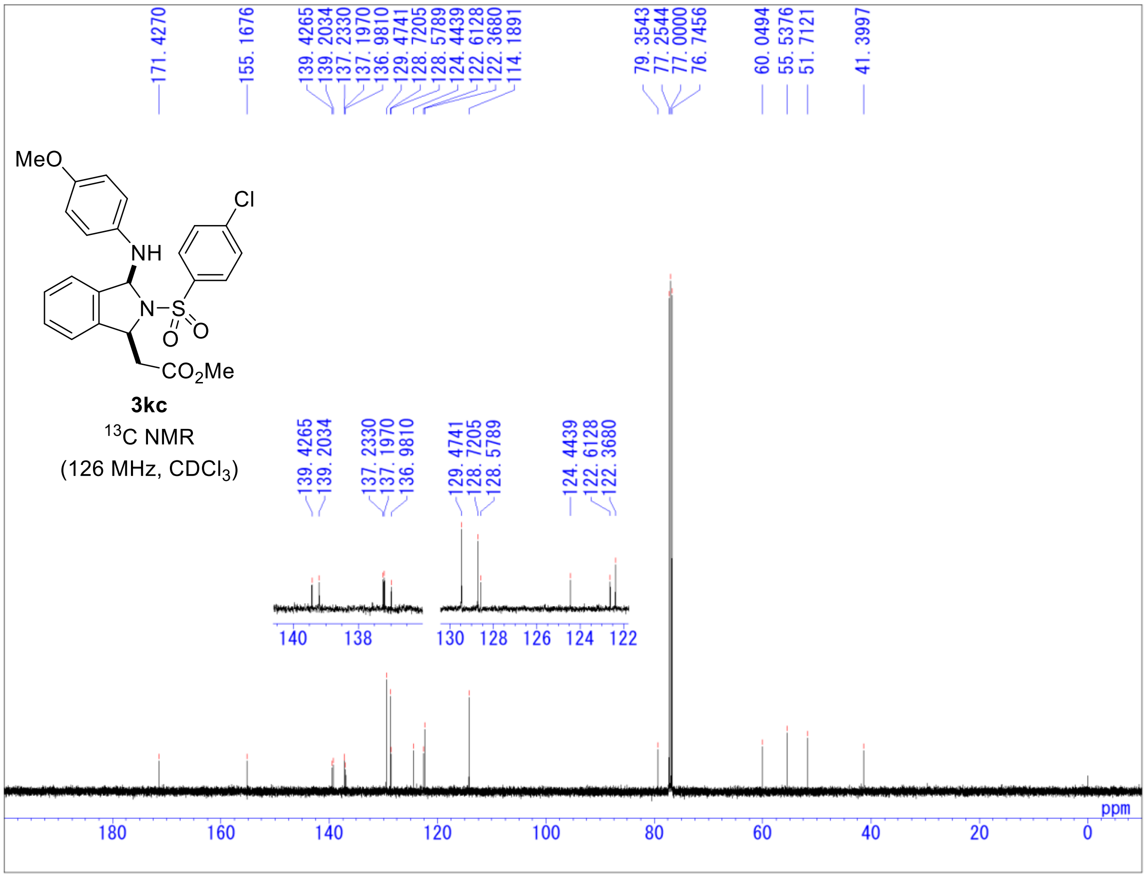
155.1700
139.6257
137.3986
137.2810
129.8341
129.4309
129.3133
128.4014
124.4631
122.8263
122.6871
114.3787
114.0787
79.1983
77.2544
77.0000
76.7456
59.9558
55.5280
55.5136
51.6521
41.7477
MeO
OMe
NH
N
S
O
O
CO2Me
3jc
13C NMR
(126 MHz, CDCl3)
140
139
138
137
130
128
126
124
55.5
ppm
180
160
140
120
100
80
60
40
20
0



3kc

^{1}H NMR

(500 MHz, $CDCl_3$)

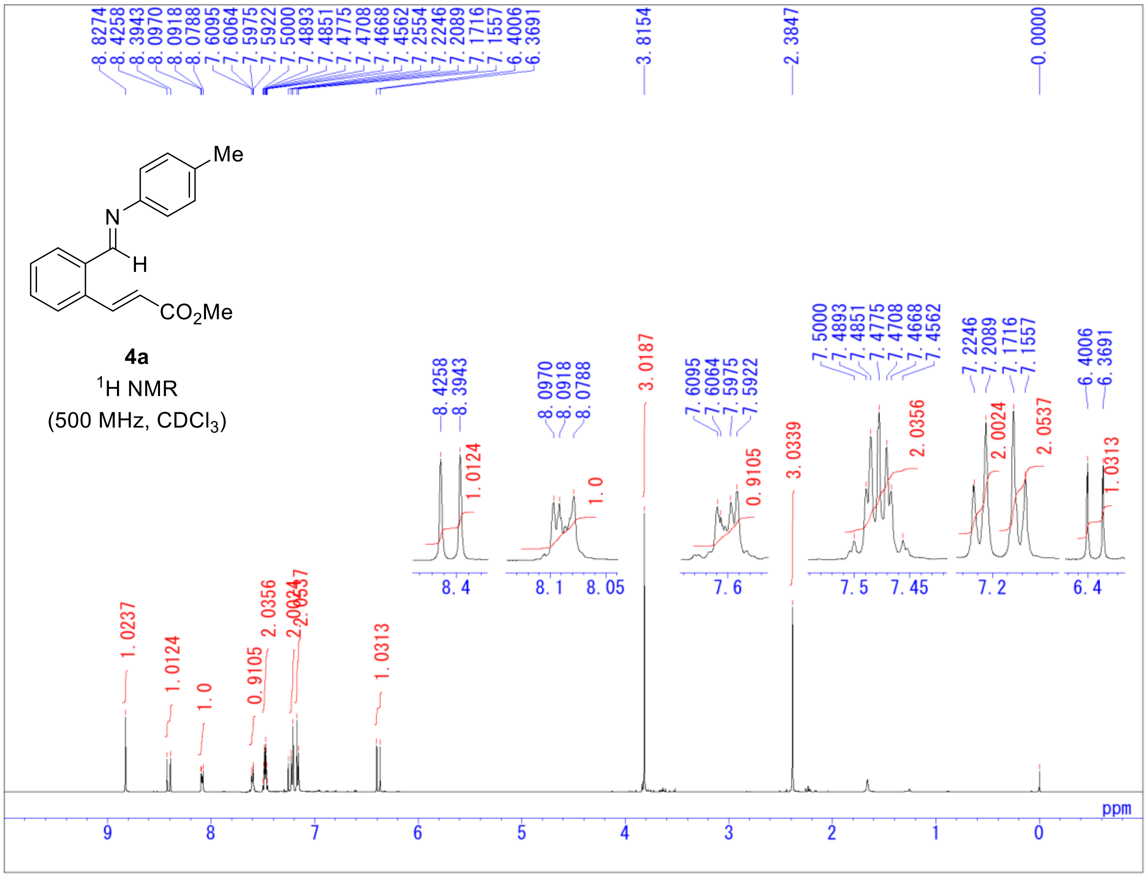


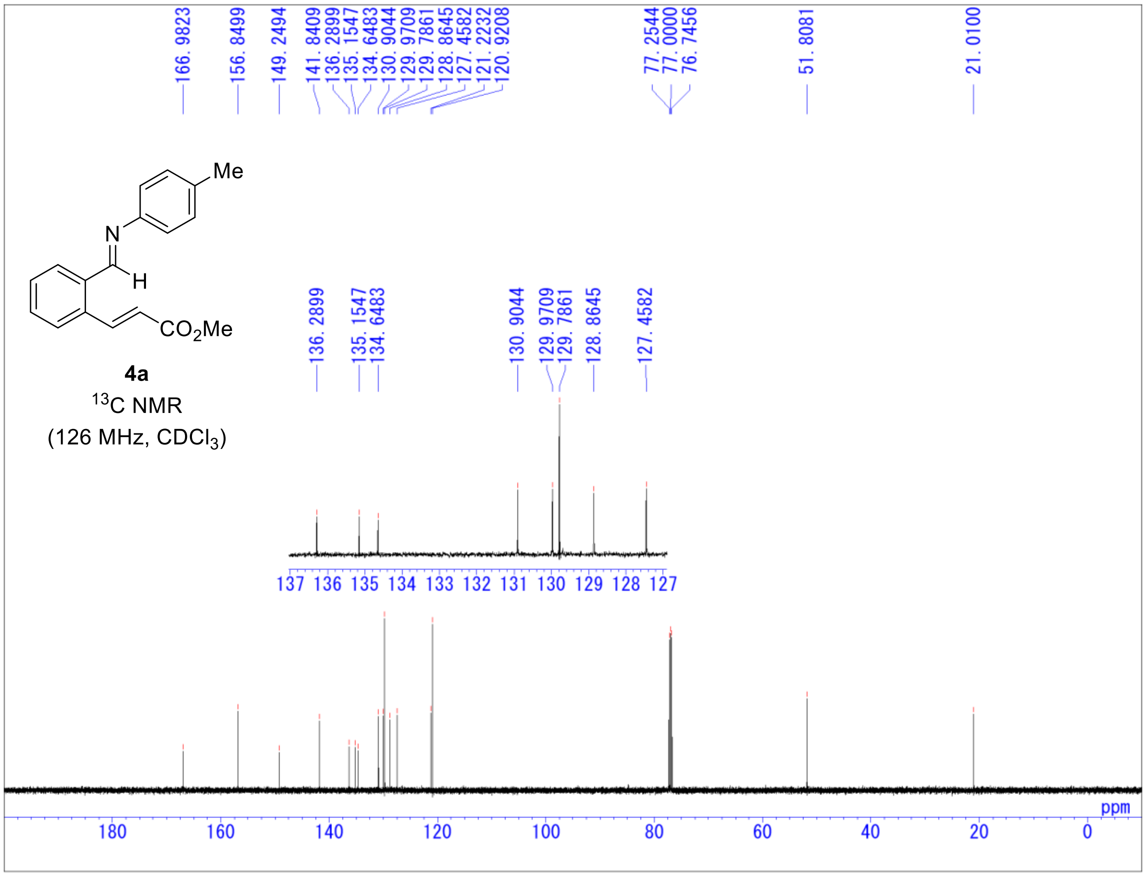
3kc

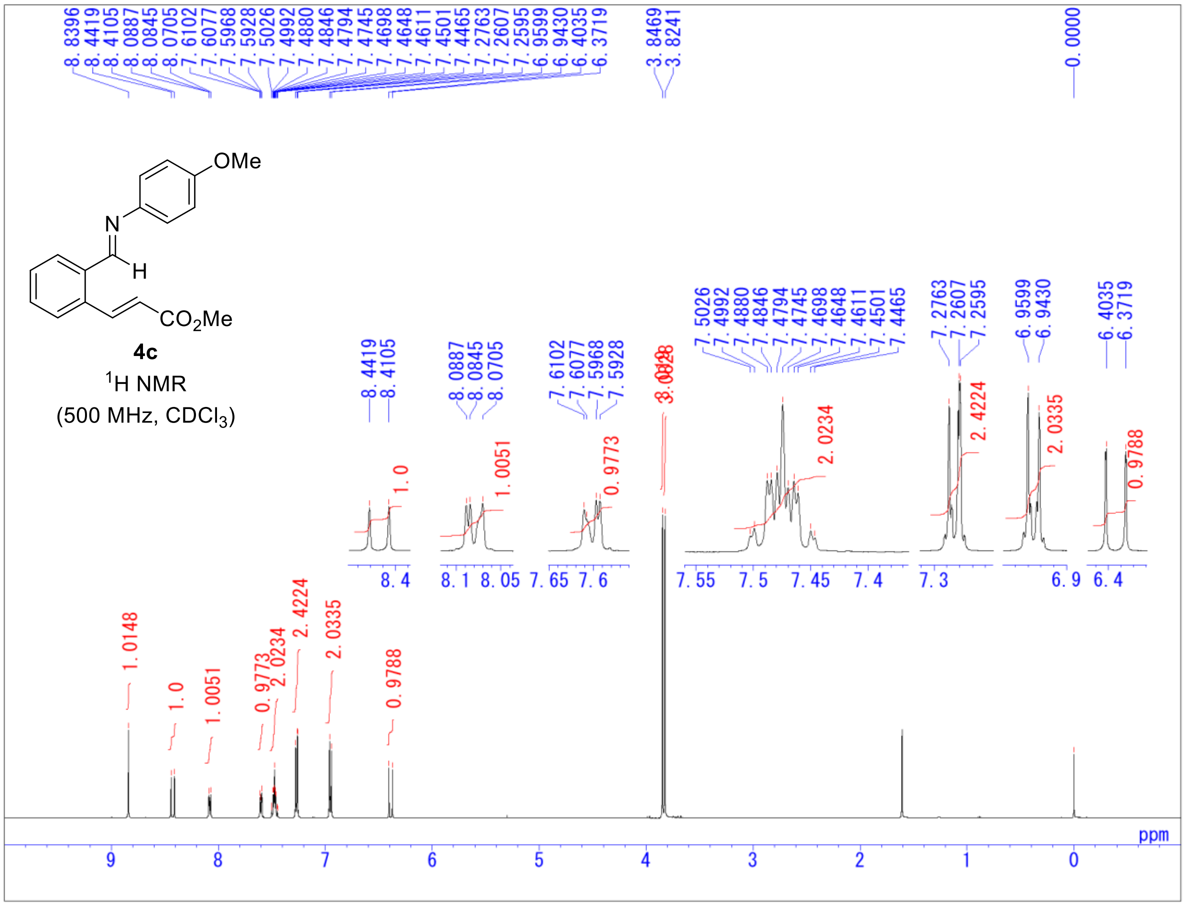
^{13}C NMR

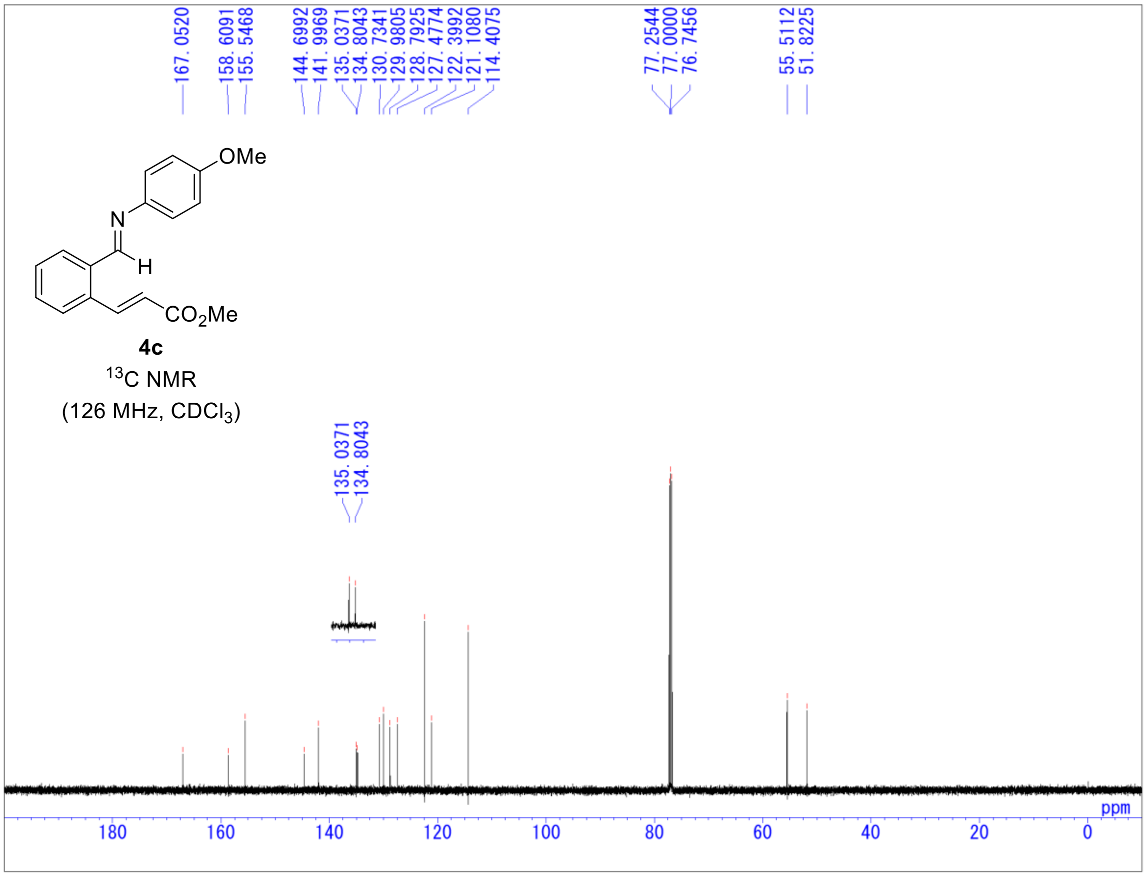
(126 MHz, $CDCl_3$)

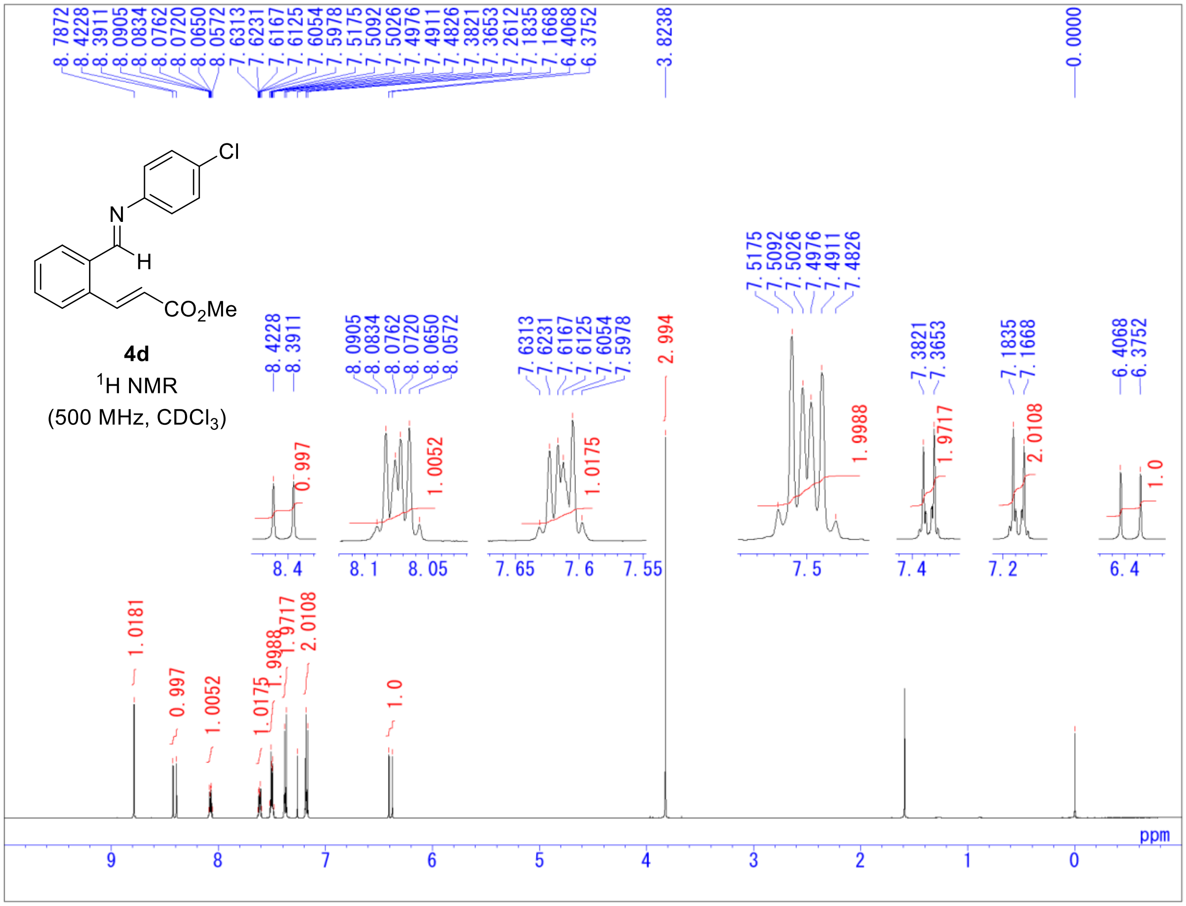
Imines **4**

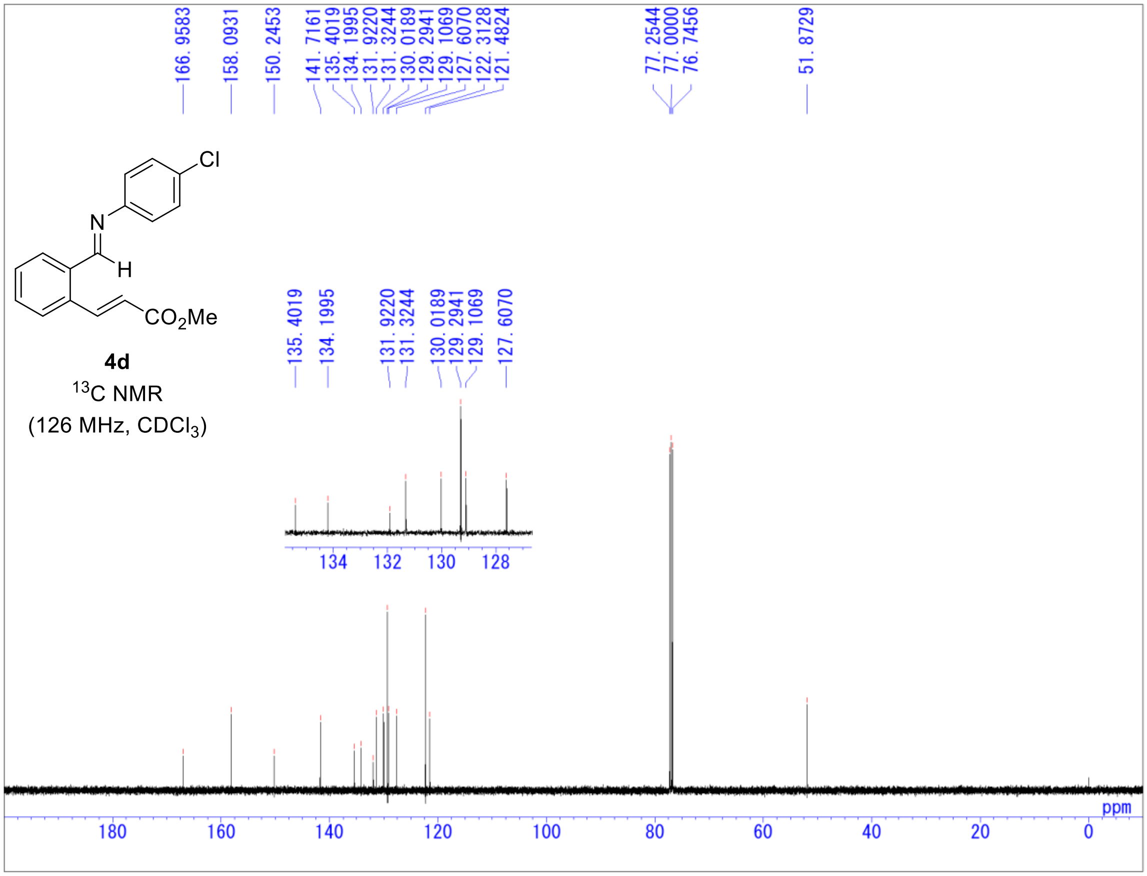

Me
N
H
CO2Me
4a
1H NMR
(500 MHz, CDCl3)
8.8274
8.4258
8.3943
8.0970
8.0918
8.0788
7.6095
7.6064
7.5975
7.5922
7.5000
7.4893
7.4851
7.4775
7.4708
7.4668
7.4562
7.2554
7.2246
7.2089
7.1716
7.1557
6.4006
6.3691
3.8154
2.3847
0.0000
1.0237
1.0124
1.0
0.9105
2.0356
2.0024
2.0537
1.0313
3.0187
3.0339
8.4
8.1
8.05
7.6
7.5
7.45
7.2
6.4
ppm
9
8
7
6
5
4
3
2
1
0


Me
N
H
CO2Me
4a
13C NMR
(126 MHz, CDCl3)
166.9823
156.8499
149.2494
141.8409
136.2899
135.1547
134.6483
130.9044
129.9709
129.7861
128.8645
127.4582
121.2232
120.9208
77.2544
77.0000
76.7456
51.8081
21.0100
137
136
135
134
133
132
131
130
129
128
127
ppm
180
160
140
120
100
80
60
40
20
0

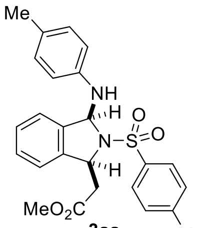

8.8396 8.4419 8.4105 8.0887 8.0845 8.0705 7.6102 7.6077 7.5968 7.5928 7.5026 7.4992 7.4880 7.4846 7.4794 7.4745 7.4698 7.4648 7.4611 7.4501 7.4465 7.2763 7.2607 7.2595 6.9599 6.9430 6.4035 6.3719
3.8469 3.8241
0.0000
OMe
N
H
CO2Me
4c
1H NMR
(500 MHz, CDCl3)
1.0148
1.0
1.0051
0.9773
2.0234
2.4224
2.0335
0.9788
ppm
9 8 7 6 5 4 3 2 1 0


167.0520
158.6091 155.5468
144.6992 141.9969 135.0371 134.8043 130.7341 129.9805 128.7925 127.4774 122.3992 121.1080 114.4075
77.2544 77.0000 76.7456
55.5112 51.8225
OMe
N
H
CO2Me
4c
13C NMR
(126 MHz, CDCl3)
135.0371
134.8043
ppm
180 160 140 120 100 80 60 40 20 0

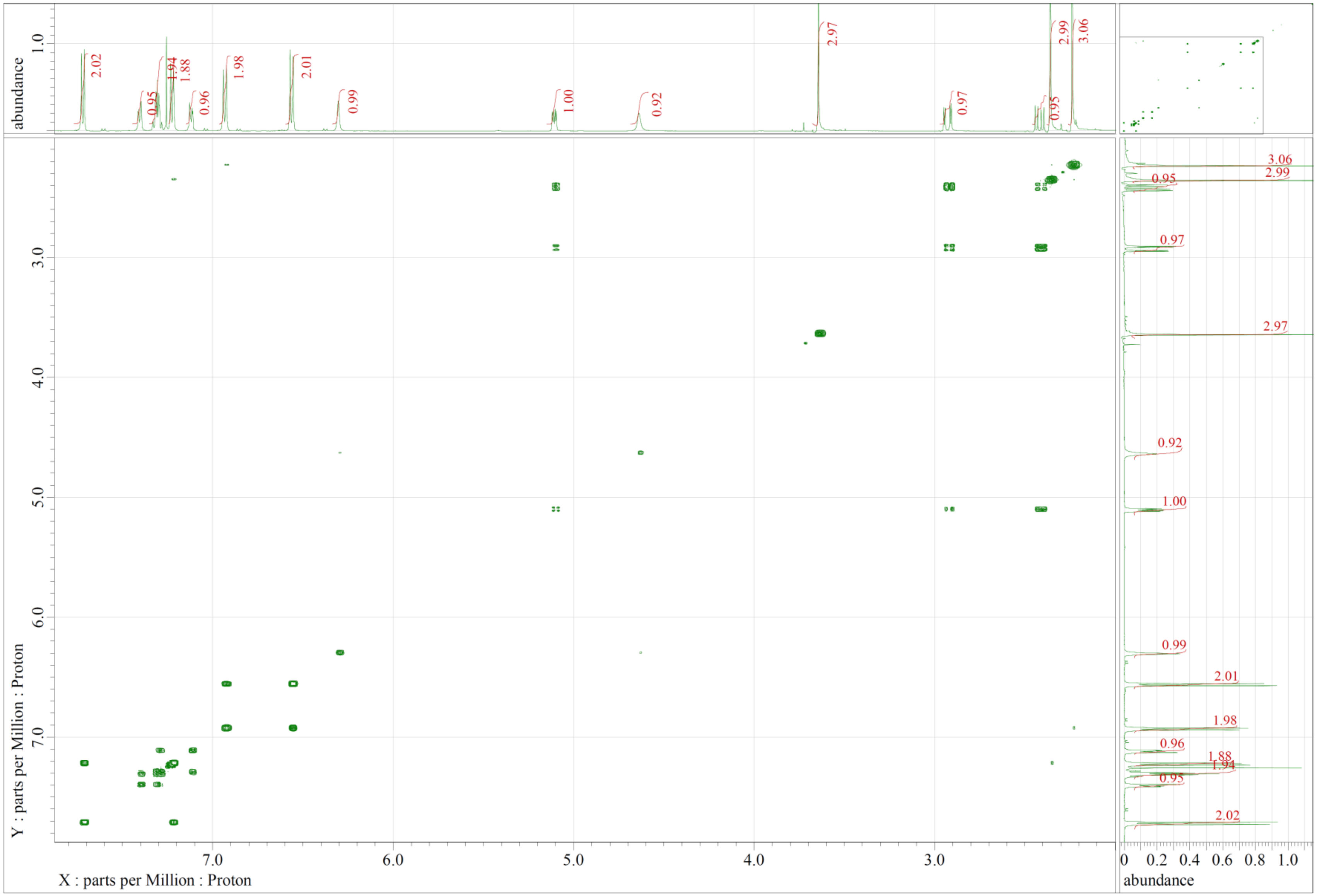

8.7872
8.4228
8.3911
8.0905
8.0834
8.0762
8.0720
8.0650
8.0572
7.6313
7.6231
7.6167
7.6125
7.6054
7.5978
7.5175
7.5092
7.5026
7.4976
7.4911
7.4826
7.3821
7.3653
7.2612
7.1835
7.1668
6.4068
6.3752
3.8238
0.0000
Cl
N
H
CO2Me
4d
1H NMR
(500 MHz, CDCl3)
1.0181
0.997
1.0052
1.0175
1.9988
1.9717
2.0108
1.0
2.994
8.4
8.1
8.05
7.65
7.6
7.55
7.5
7.4
7.2
6.4
ppm
9
8
7
6
5
4
3
2
1
0

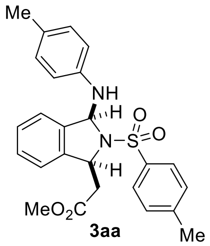

166.9583
158.0931
150.2453
141.7161
135.4019
134.1995
131.9220
131.3244
130.0189
129.2941
129.1069
127.6070
122.3128
121.4824
77.2544
77.0000
76.7456
51.8729
Cl
N
H
CO2Me
4d
13C NMR
(126 MHz, CDCl3)
134
132
130
128
ppm
180
160
140
120
100
80
60
40
20
0

7. Copy of 2D NMR spectra



3aa
COSY
(500 MHz, CDCl$_3$)

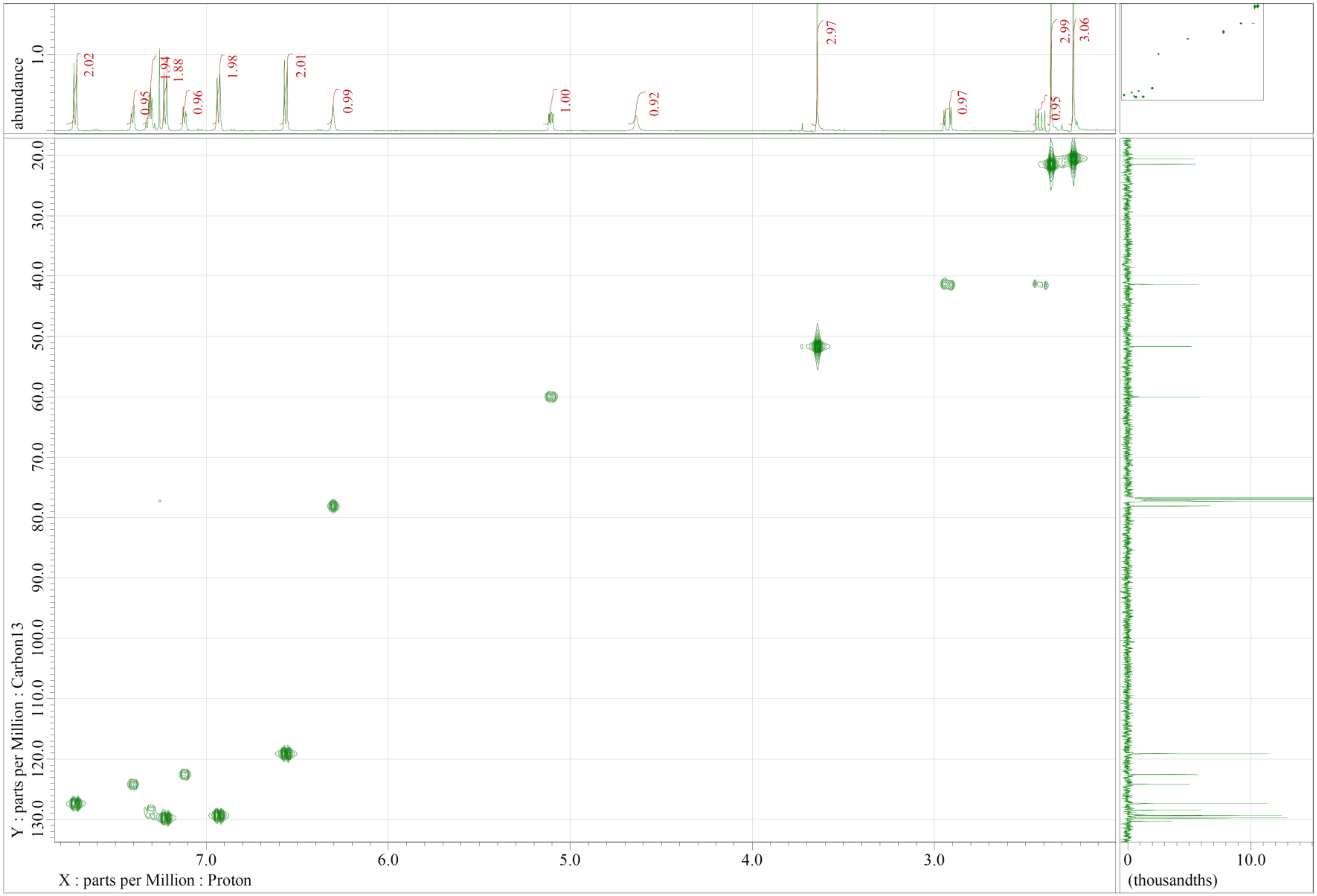


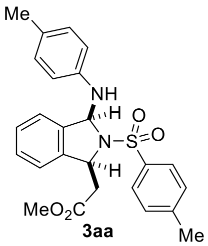


3aa

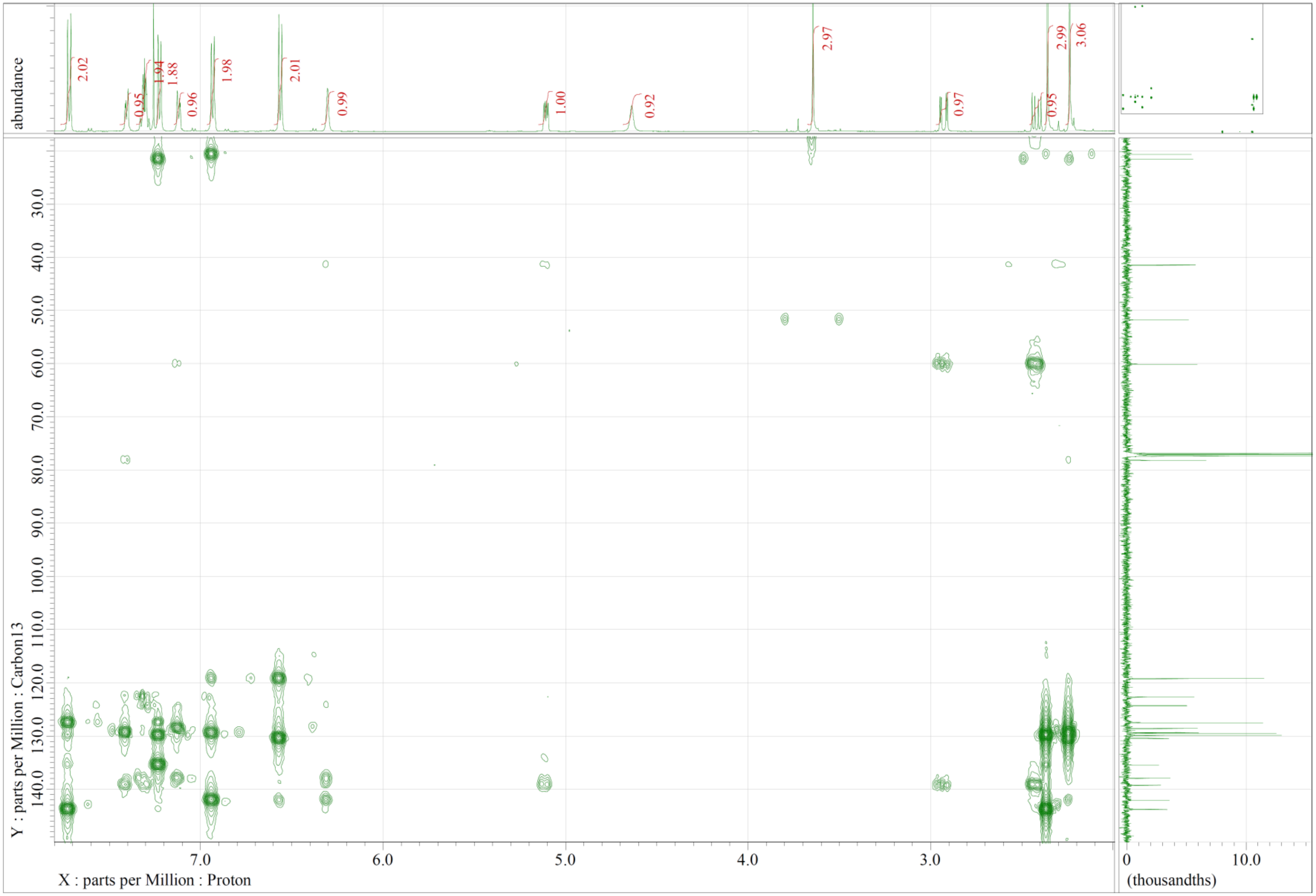
HMQC

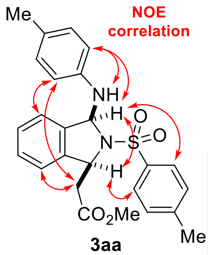
(500 MHz, CDCl$_3$)





3aa
HMBC
(500 MHz, $CDCl_3$)





3aa

NOESY

(500 MHz, $CDCl_3$)