

## Supporting Information

### A Site-Specific Synthetic Route to Substituted Inda(box) Ligands

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## General Information

**General Methods:** Unless otherwise stated, all reactions were carried out open to air. Thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was accomplished using UV light and either KMnO<sub>4</sub> solution or cerium ammonium molybdate (CAM) stain. Flash chromatography was performed under positive air pressure using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Yields, regioisomeric ratios, diastereomeric ratios and enantiomeric ratios are reported for a specific experiment and as a result may differ slightly from those reported in the in-text figures, which represent averages of at least two experimental trials.

**Instrumentation and Data Acquisition:** Proton (<sup>1</sup>H), carbon (<sup>13</sup>C), and fluorine (<sup>19</sup>F) magnetic resonance spectra were obtained on Bruker Avance 400 MHz, Bruker NEO Avance 400 MHz, Bruker Avance III 500 MHz, Bruker NEO Avance 600 MHz, or a Bruker Avance III 600 instruments, using solvent resonances and/or hexafluorobenzene for internal chemical shift calibration (<sup>1</sup>H NMR: CDCl<sub>3</sub> at δ = 7.26 ppm; <sup>13</sup>C NMR: CDCl<sub>3</sub> at δ = 77.0 ppm; <sup>19</sup>F NMR: C<sub>6</sub>F<sub>6</sub> at δ = -164.90 ppm). Mass spectra were obtained using a Thermo Scientific Q Exactive HF-X mass spectrometer with electrospray introduction and external calibration. Optical rotations were measured at room temperature using a 2 mL cell with a 1 dm path length on a Jasco P-1010 polarimeter. Melting points were obtained using a Thomas Hoover Uni-Melt 6LO6-K melting point apparatus. Infrared (IR) Spectra were obtained on a Thermo Scientific Nicolet iS 5 FT-IR. Compounds were analyzed as solids on the diamond surface. Spectra are reported in frequency of absorption in cm<sup>-1</sup>. Only the most prominent and diagnostic peaks are reported.

High pressure liquid chromatography was performed using an Agilent Series 1100 HPLC system equipped with a G1314A VWD detector. Daicel Chiralpak IA (received: August 2014), Chiralpak IB (received: August 2014), Chiralpak IC (received: August 2014 and March 2020), Chiralpak ID (received: August 2014), and Chiralpak OJ-H (received: November 2018) were available for use in separations.

**Data Reporting:** The following format is used for the presentation of <sup>1</sup>H NMR spectroscopic data: magnet strength, analysis solvent, chemical shift (ppm), multiplicity (s = singlet, br s = broad singlet, app s = apparent singlet, d = doublet, bd = broad doublet, t = triplet, app t = apparent triplet, q = quartet, app q = apparent quartet, dd = doublet of doublets, td = triplet of doublets, app td = apparent triplet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, app ddt = apparent doublet of doublet of triplets, dddd = doublet of doublet of doublet of doublets, m = multiplet), *J*-coupling constants (Hz), and integration. Solvent ratios are reported as volume ratios.

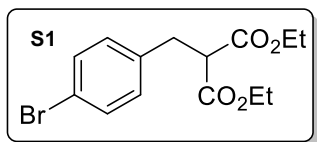
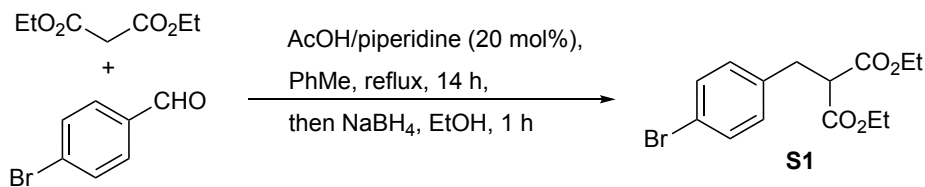
**Equipment:** Transformations requiring syringe pump addition were performed using a New Era NE-300 Just Infusion™ single channel syringe pump. Transformations requiring extended cooling were performed in an isopropanol bath maintained by a Techno Sigma UCR 150N cooling reactor [referred to as "UC reactor"].

**Materials:** Unless otherwise stated, technical grade solvents were used as received. Anhydrous tetrahydrofuran (THF), diethyl ether (Et<sub>2</sub>O), methylene chloride (CH<sub>2</sub>Cl<sub>2</sub>), toluene (PhMe), and triethylamine (TEA, NEt<sub>3</sub>) were obtained by passage of the respective solvents through a neutral alumina column under nitrogen. Solvent ratios are reported as volume ratios.

HPLC grade solvents were used for both sample preparation and analysis eluent.

4-Bromobenzaldehyde (Oakwood, Sigma), diethyl malonate (Sigma), acetic acid (Sigma), piperidine (Sigma), sodium borohydride (Sigma), aluminum trichloride (Sigma), trimethylsilyl triflate (TMSOTf, Oakwood), triflic acid (TfOH, Sigma), *p*-toluenesulfonic acid monohydrate (*p*TSA•H<sub>2</sub>O, Sigma), (*R,R*)-Jacobsen Catalyst (Sigma), sodium hypochlorite (13% free chlorine, Sigma), thionyl chloride (Sigma), boronic acids (Oakwood, Strem, Sigma), diethylmalonimidate dihydrochloride (Oakwood), sodium hydride (Sigma), lithium bis(trimethylsilyl)amide (LiHMDS, Sigma), 1,2-dibromoethane (Sigma), benzyl bromide (Sigma), 3,5-di-*tert*-butylbenzyl bromide (Sigma), 4-*tert*-butylbenzyl bromide (Oakwood), 4-trifluoromethylbenzyl bromide (Oakwood), S-Phos Palladacycle gen. 4 (Strem), Ru-Phos Palladacycle gen. 4 (Strem), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (Sigma), potassium isopropenyltrifluoroborate (Oakwood), cesium carbonate (Fisher), copper(II) acetate monohydrate (Sigma), were obtained from commercial sources.

## Preparation of Inda(box) Ligand 4.1



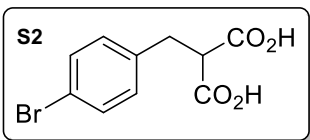
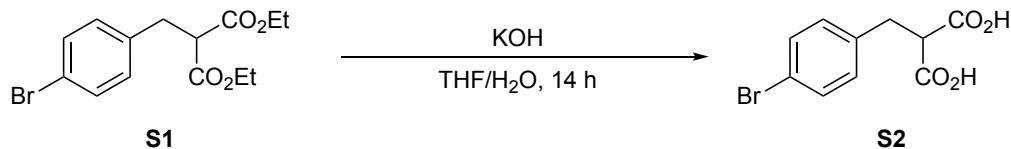
**Diethyl 2-(4-bromobenzyl)malonate (S1)** The title compound was prepared according to a literature procedure.<sup>1</sup> To a 500 mL round-bottomed flask containing a stir bar was added 4-bromobenzaldehyde (14.8 g, 80.0 mmol, 1.00 equiv) and PhMe (100 mL). Diethyl malonate (12.2 mL, d = 1.05 g/mL, 80.0 mmol, 1.00 equiv) was added, followed by dropwise addition of both acetic acid (1.58 mL, d = 0.862 g/mL, 16.0 mmol, 0.20 equiv) and piperidine (916  $\mu$ L, d = 1.05 g/mL, 16.0 mmol, 0.20 equiv). The flask containing the colorless mixture was then fitted with a reflux condenser and a Dean Stark trap. The reaction was heated to 135 °C overnight in an oil bath, during which time the mixture became dark orange. The material was cooled to room temperature, and the solvent was evaporated in vacuo. Residual toluene was removed by azeotrope (3x) with heptanes on the rotary evaporator. Completion of the condensation was assayed by disappearance of aldehyde by <sup>1</sup>H NMR spectroscopic analysis of the unpurified mixture. The material was then dissolved in absolute EtOH (100 mL) and cooled to 0 °C in an ice bath. Sodium borohydride (3.33 g, 88.0 mmol, 1.10 equiv) was added portionwise by spatula (NOTE: if the reducing agent is added too quickly, products arising from over-reduction are observed and diminished yields result). Reaction progress was monitored by disappearance of the intermediate alkylidene by <sup>1</sup>H NMR spectroscopy. The reaction was quenched with water (12.7 mL, 704 mmol, 8.8 equiv), and the organics were extracted with EtOAc (5x100 mL). (NOTE: If the layers become difficult to separate, the mixture may be concentrated on the rotary evaporator to remove EtOAc and EtOH, and the mixture can be extracted instead with DCM.) The combined organics were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The orange oil was used directly in the following step (26.3 g theoretical). The spectral data for **S1** were consistent with the prior report.<sup>1,2</sup>

### Physicochemical Properties

Orange Oil

**TLC** (10% EtOAc/Hex) R<sub>f</sub> = 0.40 (UV/KMnO<sub>4</sub>)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 – 7.38 (m, 2H), 7.15 – 7.07 (m, 2H), 4.18 (qd, *J* = 7.2, 4.0 Hz, 4H), 3.61 (t, *J* = 7.8 Hz, 1H), 3.18 (d, *J* = 7.8 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 6H).



**2-(4-bromobenzyl)malonic acid (S2)** The title compound was prepared according to a literature procedure.<sup>2</sup> To a 1 L round-bottomed flask was charged unpurified malonate **S1** and THF (150 mL) followed by water (100 mL, 3:2 THF:H<sub>2</sub>O v/v). KOH (18.0 g, 320 mmol, 4.00 equiv) was added portionwise (NOTE: slight exotherm), and the mixture was stirred at room temperature overnight. The mixture was quenched by the portionwise addition of 3 M HCl until

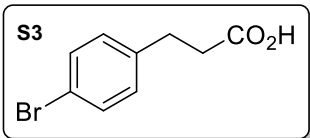
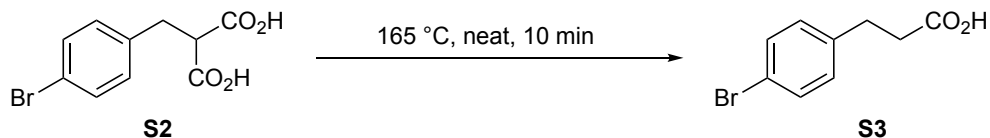
the pH reached ~1. The mixture was transferred to a separatory funnel, and the organics were extracted with EtOAc (3x 100 mL). The combined organics were washed with 1 M NaOH (2x 100 mL), taking care to keep the acidic aqueous material separate from the basic aqueous solution. The organics were then discarded (NOTE: an aliquot can be analyzed by <sup>1</sup>H NMR spectroscopy to ensure all of **S2** is in the basic aqueous solution). The aqueous basic washes were acidified to pH ~1 by addition of 3 M HCl, during which time the mixture became white and cloudy as **S2** precipitates. The aqueous material was then extracted a final time with EtOAc (3 x 100mL), and the combined organics were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The colorless solution is filtered and evaporated to give a white solid that was not purified further (7.14 g, 26.1 mmol, 33% over 2 steps). The spectral data for **S2** were consistent with the prior report.<sup>2</sup>

### Physicochemical Properties

White solid

**TLC** (30% EtOAc/Hex) R<sub>f</sub> = 0.05 (UV/KMnO<sub>4</sub>)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.43 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 3.73 (t, J = 7.5 Hz, 1H), 3.24 (d, J = 7.4 Hz, 2H).



**3-(4-bromophenyl)propanoic acid (S3)** The title compound was prepared according to a literature procedure.<sup>2</sup> To a 250 mL round-bottomed flask was charged crude malonic acid **S2** (6.64 g, 24.3 mmol, 1.00 equiv). The flask was fitted with a reflux condenser (NOTE: the purpose of the reflux condenser is to collect any material that sublimes during decarboxylation) with cooling water (open at the top to allow for gas evolution), and the mixture

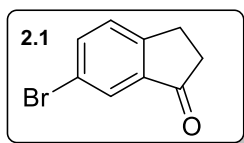
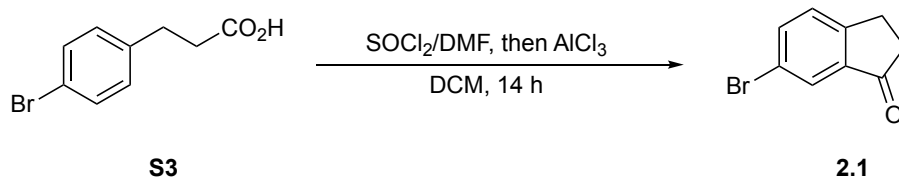
was heated gradually in a heating mantle to 165 °C to encourage decarboxylation. (NOTE: the solids generally begin to melt at 150 °C. For adequate stirring below this temperature, it is advised to break up the solids into a powder before heating is begun.) Once CO<sub>2</sub> evolution ceases (approx. 10-15 min), the flask was cooled to room temperature gradually. During this time, crystallization occurred, and the white crystals of **S3** that remain once the flask was cooled were collected and not purified further (5.48 g, 23.9 mmol, 98%). The spectral data for **S3** were consistent with the prior report.<sup>2</sup> This procedure has been used successfully on scales up to 12 g of starting material with comparable yields.

### Physicochemical Properties

White crystalline solid

**TLC** (30% EtOAc/Hex)  $R_f = 0.10$  (UV/KMnO<sub>4</sub>)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.44 – 7.39 (m, 2H), 7.11 – 7.07 (m, 2H), 2.91 (t,  $J = 7.7$  Hz, 2H), 2.67 (t,  $J = 7.7$  Hz, 2H).



**6-bromo-2,3-dihydro-1H-inden-1-one (2.1)** The title compound was prepared according to a literature procedure.<sup>2,3</sup> To a 500 mL round-bottomed flask was charged **S3** (5.83 g, 25.5 mmol, 1.00 equiv) and DCM (77 mL). Thionyl chloride (4.64 mL, d = 1.63 g/mL, 63.6 mmol, 2.50 equiv) and DMF (197  $\mu$ L, d = 0.94 g/mL, 2.55 mmol, 0.10 equiv) were added successively to the pot, and the resulting yellow mixture was stirred overnight at rt under a balloon of argon. The following day, the

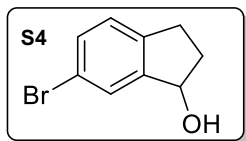
residual SOCl<sub>2</sub> and DCM were removed via rotary evaporation inside of a ventilated cabinet (NOTE: the solvent trap can be filled with saturated aqueous NaHCO<sub>3</sub> to protect the pump and prevent odors from escaping). The crude acyl chloride was then dissolved in DCM (77 mL) and cooled to 0 °C in an ice bath. The flask opening was fitted with a plastic funnel, and aluminum trichloride (4.07 g, 30.5 mmol, 1.20 equiv) was added portionwise with a spatula. The reaction mixture turned dark brown and was allowed to warm to room temperature overnight. The reaction was quenched the following day at 0 °C in an ice bath with cold water, and the quenched mixture was stirred until it warmed to room temperature. The layers were then separated, and the aqueous was extracted with DCM (3 x 50 mL). The combined organics were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford ketone **2.1** (5.12 g, 24.3 mmol, 95%). If desired, the beige solids may be purified by recrystallization with ethyl acetate, though it was found to be unnecessary for our purposes. The spectral data for **2.1** were consistent with the prior report.<sup>2</sup> This procedure has been used successfully on scales up to 12 g of starting material with comparable yields.

#### Physicochemical Properties

Beige crystalline solid

**TLC** (30% EtOAc/Hex)  $R_f$  = 0.65 (UV/KMnO<sub>4</sub>)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.91 (d,  $J$  = 2.0 Hz, 1H), 7.71 (dd,  $J$  = 8.1, 1.9 Hz, 1H), 7.43 – 7.36 (m, 1H), 3.16 – 3.09 (m, 2H), 2.79 – 2.71 (m, 2H).



**6-bromo-2,3-dihydro-1H-inden-1-ol (S4)** The title compound was prepared according to a literature procedure.<sup>2</sup> To a 250 mL round-bottomed flask was added **2.1** (5.12 g, 24.3 mmol, 1.00 equiv) and absolute EtOH (120 mL). Sodium borohydride (918 mg, 24.7 mmol, 1.00 equiv) was added portionwise at room temperature, and the mixture was stirred at room temperature for 1 h. Once TLC indicated full conversion, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and concentrated using a rotary evaporator. The crude solution was extracted with EtOAc (3 x 50 mL), and the combined organics were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The resulting white solid **S4** (4.93 g, 23.1 mmol, 95%) was used directly in the following step. The spectral data for **S4** were consistent with the prior report.<sup>2</sup> This procedure has been used successfully on scales up to 25 g of starting material with comparable yields.

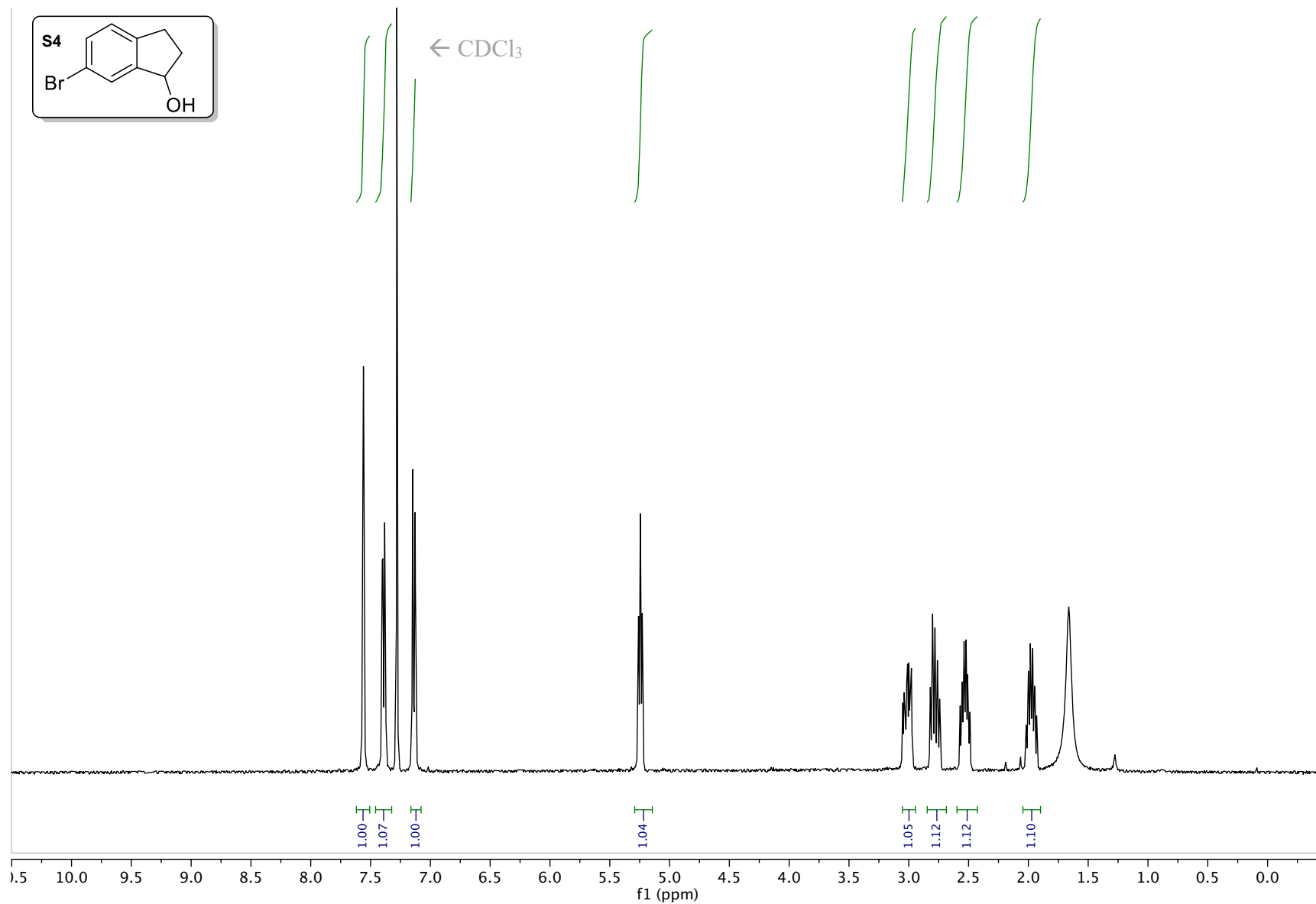
#### Physicochemical Properties

White solid

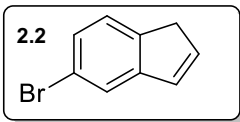
**TLC** (30% EtOAc/Hex)  $R_f = 0.55$  (UV/KMnO<sub>4</sub>)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.54 (d,  $J = 2.0$  Hz, 1H), 7.37 (dd,  $J = 8.0, 2.0$  Hz, 1H), 7.12 (d,  $J = 8.0$  Hz, 1H), 5.22 (t,  $J = 6.2$  Hz, 1H), 2.99 (ddd,  $J = 16.1, 8.5, 4.5$  Hz, 1H), 2.76 (dt,  $J = 15.8, 7.6$  Hz, 1H), 2.51 (dddd,  $J = 13.0, 8.2, 6.9, 4.5$  Hz, 1H), 1.95 (dddd,  $J = 12.9, 8.6, 6.9, 5.6$  Hz, 1H).

Compound **S4** ( $^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ )







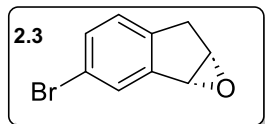
**5-bromo-1H-indene (2.2)** The title compound was prepared according to a literature procedure.<sup>2</sup> To a 250 mL round-bottomed flask was added **S4** (4.93 g, 23.1 mmol, 1.00 equiv) and benzene (165 mL). *p*-Toluenesulfonic acid monohydrate (440 mg, 2.31 mmol, 0.10 equiv) was added at room temperature, and an ethylene glycol reflux condenser was fitted to the flask. The mixture was stirred at 65 °C in an oil bath until TLC indicated the reaction was complete (typically 4-16 h; longer reaction times are required when impure indanol **S4** is used). The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> and concentrated using a rotary evaporator in a ventilated cabinet. The crude solution was extracted with EtOAc (3x 50 mL), and the combined organics were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. If necessary, the brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 40/60) to afford **2.2** (3.46 g, 17.7 mmol, 77%). NOTE: For reactions conducted on scales larger than 5 g, purification is not necessary for the following step. The spectral data for **2.2** were consistent with the prior report.<sup>2</sup> This procedure has been used successfully on scales up to 25 g of starting material with comparable yields.

### Physicochemical Properties

Beige crystalline solid

**TLC** (30% EtOAc/Hex)  $R_f = 0.70$  (UV/KMnO<sub>4</sub>)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) 7.56 (s, 1H), 7.44 – 7.29 (m, 2H), 6.85 (dd,  $J = 5.0, 2.3$  Hz, 1H), 6.63 (dd,  $J = 4.9, 2.3$  Hz, 1H), 3.38 (d,  $J = 2.1$  Hz, 2H).

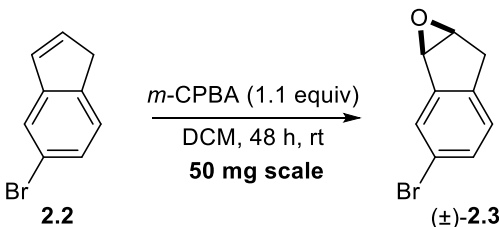


(1aR,6aS)-3-bromo-1a,6a-dihydro-6H-indeno[1,2-b]oxirene (**2.3**) The following procedure was adapted from a literature procedure.<sup>2,4</sup> Indene **2.2** (3.46 g, 17.7 mmol, 1.00 equiv) and (*R,R*)-(+)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (112 mg, 0.177 mmol, 0.01 equiv) were dissolved in 21 mL DCM in a 250 mL round-bottomed flask. 4-Phenylpyridine *N*-oxide (121 mg, 0.708 mmol, 0.04 equiv) was added, and the solution was stirred

for 10 min at room temperature before cooling to -5 °C using an ice bath or UC reactor. While vigorously stirring, 8.9 mL of a solution of half-saturated aqueous K<sub>2</sub>CO<sub>3</sub> (0.5 mL/mmol indene) was added followed by slow, dropwise addition of 22 mL aqueous NaOCl (1.25 mL/mmol indene, 13% free chlorine). The pH was monitored and adjusted to pH 11-12 as necessary by dropwise addition of an aqueous 0.1 M phosphate buffer solution (pH = 7, approximately 4 drops). The biphasic solution was continually stirred at -5 °C and monitored by TLC until complete consumption of the indene was observed (typically 2-4 h). The solution was then removed from the ice bath, and the layers were separated. The aqueous solution was extracted with DCM (2 x 25 mL), and the combined organic layers were washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (25 mL), followed by water (25 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 40/60) to afford epoxide **2.3** (2.46 g, 11.7 mmol, 65%). The off-white solid was additionally recrystallized from hot heptanes to obtain enantiomerically pure product (2.10 g, 56% yield, 85% recovery). This procedure has been used successfully on scales up to 9 g of starting material with comparable yields.

#### NOTES:

- On one occasion, this reaction was performed on 23 g scale, with the reaction stalling at 66% conversion. The starting material was isolated during the chromatography step and successfully resubjected to the reaction conditions, with full conversion to the epoxide product.
- On scales larger than 5-10 g of epoxide **2.3**, traces of the epoxidation catalyst may remain after chromatography. As a result, the recrystallization can be less efficient, typically delivering the product in enantiomeric purities ranging from 98:2 – 99.3:0.07 er. A second recrystallization is effective in purging the unwanted enantiomer with a slightly lower overall yield. For maximum recovery, large quantities of epoxide **2.3** containing traces of the epoxidation catalyst should instead be split into batches during the recrystallization step.
- The racemic epoxide was prepared by *m*-CPBA oxidation of indene **2.2**:



#### Physicochemical Properties

Off-white crystalline solid

mp: 76-79 °C

TLC (30% EtOAc/Hex) R<sub>f</sub> = 0.65 (UV/KMnO<sub>4</sub>)

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 1.9 Hz, 1H), 7.41 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 4.25 (dd, *J* = 2.9, 1.3 Hz, 1H), 4.16 (t, *J* = 2.9 Hz, 1H), 3.18 (d, *J* = 18.0 Hz, 1H), 2.94 (ddd, *J* = 18.1, 3.0, 1.1 Hz, 1H), 1.57 (s, 2H).

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 143.1, 142.4, 131.5, 128.5, 127.6, 119.8, 58.5, 57.8, 34.2.

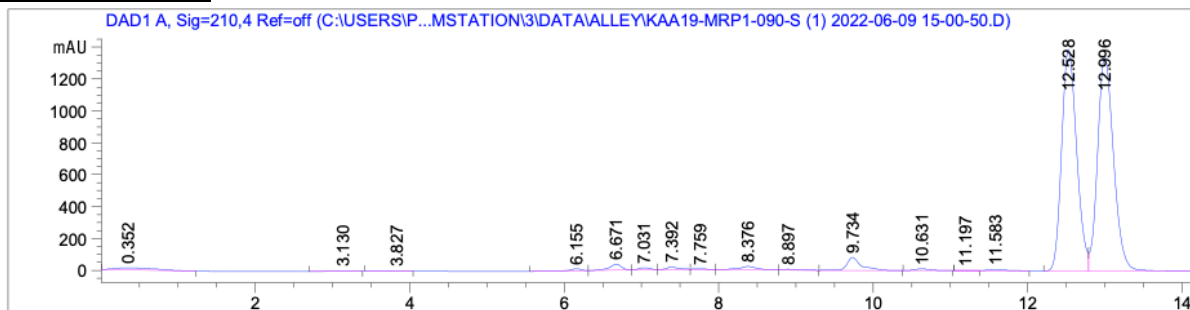
IR (ATR)  $\tilde{\nu}$  3042, 2928, 1730, 1466, 809, 446 cm<sup>-1</sup>.

HRMS (APCI): Calculated for C<sub>9</sub>H<sub>7</sub>BrO (M<sup>+</sup>): 209.9680, Found: 209.9675

$\alpha_D^{23}$  (c = 1.00, CHCl<sub>3</sub>): +8.44°

HPLC (75:25 isopropanol:hexanes, Daicel CHIRALPAK OJ-H, 210 nm, 0.5 mL/min): >99:1 er, *t<sub>R</sub>* (major) = 12.53 min, *t<sub>R</sub>* (minor) = 13.00 min

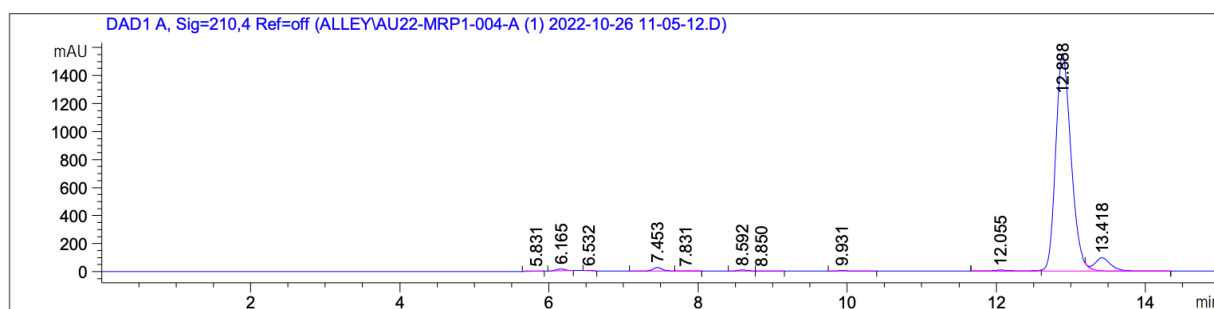
### Racemic material:



Retention Time (min)	Area (mAU•min)	Area %
12.528	1.8723x10 <sup>4</sup>	50.8
12.996	1.9364x10 <sup>4</sup>	49.2

### Before Recrystallization (Enantioenriched material):

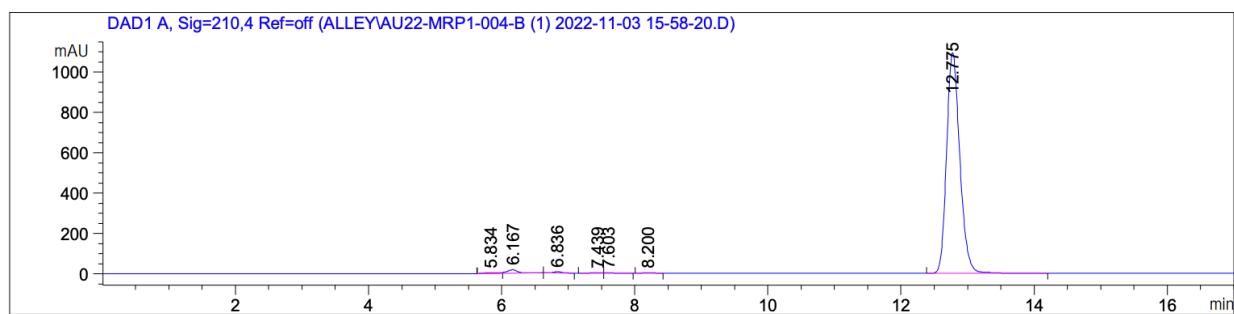
Sample Info : OJ-H, 75:25 IPA:HEX, 1 uL, 0.5 ml/min



Retention Time (min)	Area (mAU•min)	Area %
12.888	2.2336 x10 <sup>4</sup>	94.3
13.418	1346.6	5.69

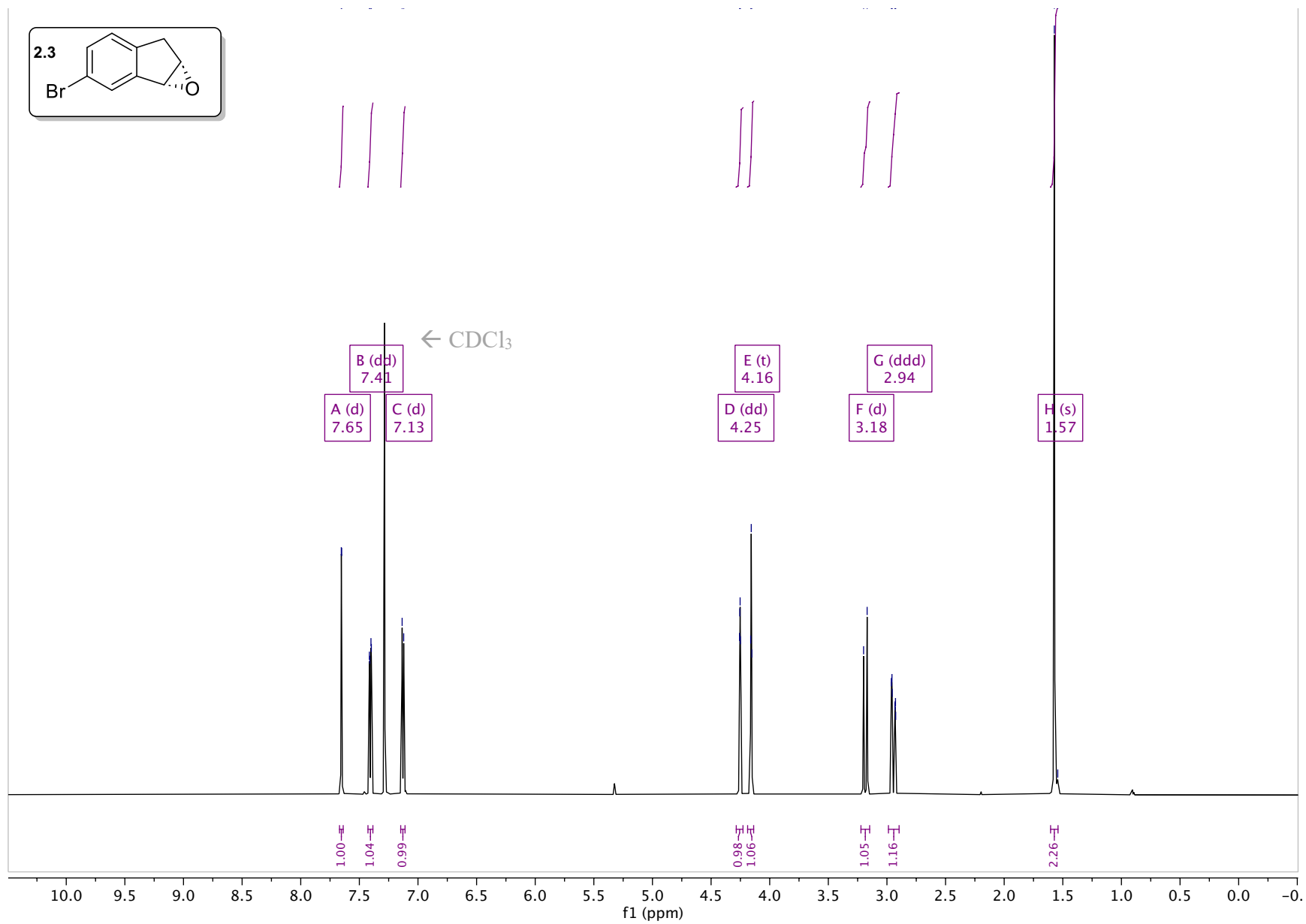
### Recrystallization 1 (Enantiopure material):

Sample Info : OJ-H, 75:25 IPA:HEX, 2.5 uL, 0.5 ml/min, RECRYST 1X

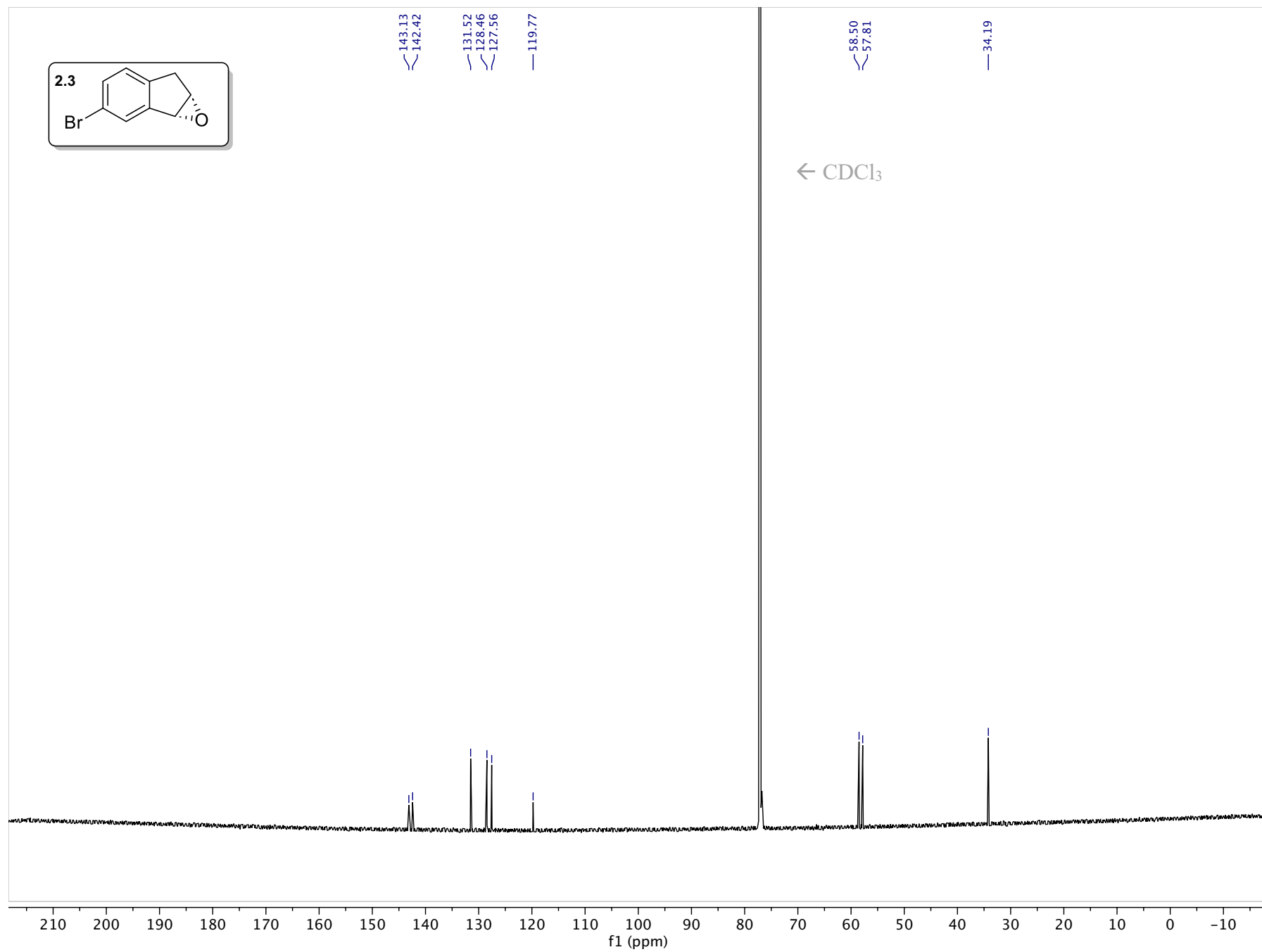


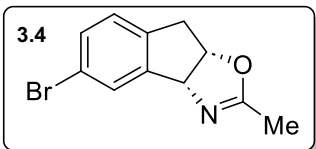
Retention Time (min)	Area (mAU•min)	Area %
12.775	1.5087x10 <sup>4</sup>	>99.9
No 2 <sup>nd</sup> peak observed		

Compound **2.3** ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )



Compound **2.3** ( $^{13}\text{C}$  NMR, 151 MHz,  $\text{CDCl}_3$ )





(3*aR*,8*aS*)-5-bromo-2-methyl-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole (**3.4**) The following procedure was adapted from a literature procedure.<sup>5,6</sup> A 100 mL flame-dried round bottomed flask was cooled under a stream of nitrogen and charged with indene oxide **2.3** (4.245 g, 20.1 mmol, 1.00 equiv). Anhydrous MeCN (33 mL, 1.65 mL per 1 mmol **2.3**) was added, and the flask was cooled to -40 °C using a MeCN/ ice bath. TMSOTf (7.27 mL, 40.2 mmol, 2.00 equiv)

was added to the solution dropwise, and the reaction mixture gradually turned orange. The reaction was allowed to warm to rt overnight under a balloon of argon, during which time the mixture became dark brown. The reaction was then opened to air and cooled to 0 °C using an ice bath. The mixture was poured into a 250 mL Erlenmeyer flask containing ice-cold saturated aqueous Na<sub>2</sub>CO<sub>3</sub>, and rapidly swirled by hand to quench the acid (Caution: exothermic). The pH was verified to be approx. 7, and the mixture was extracted with DCM (5 x 50 mL) in a separatory funnel. The combined organic layers were washed with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (50 mL), followed by water (50 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The brown crude solids were purified by silica plug (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 40/60) to afford **3.4** (2.37 g, 9.41 mmol, 47%). This procedure has been used successfully on scales up to 5.7 g of starting material with comparable yields.

### Physicochemical Properties

Tan crystalline solid

**mp:** 141-145 °C

**TLC** (30% EtOAc/Hex) *R<sub>f</sub>* = 0.40 (UV/KMnO<sub>4</sub>)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.61 – 7.58 (m, 1H), 7.37 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 5.47 (d, *J* = 7.9 Hz, 1H), 5.31 (ddd, *J* = 8.1, 6.9, 1.6 Hz, 1H), 3.36 (ddd, *J* = 18.0, 7.0, 1.1 Hz, 1H), 3.17 (dt, *J* = 18.0, 1.3 Hz, 1H), 1.96 (d, *J* = 1.2 Hz, 3H).

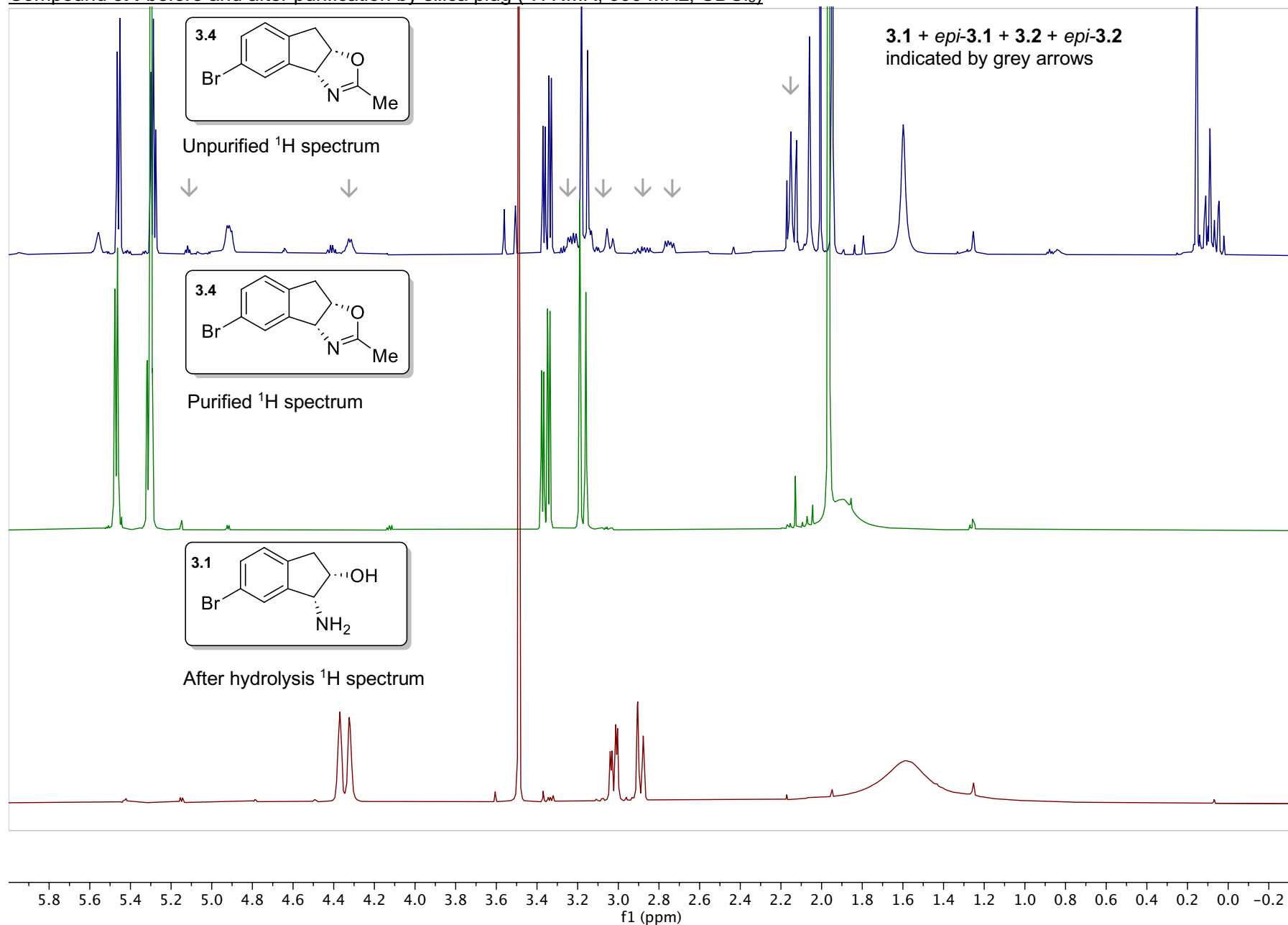
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 165.9, 144.4, 138.8, 131.7, 128.7, 126.9, 121.3, 83.4, 76.3, 39.5, 14.2.

**IR** (ATR) 3276, 1660, 1436, 1263, 841 cm<sup>-1</sup>.

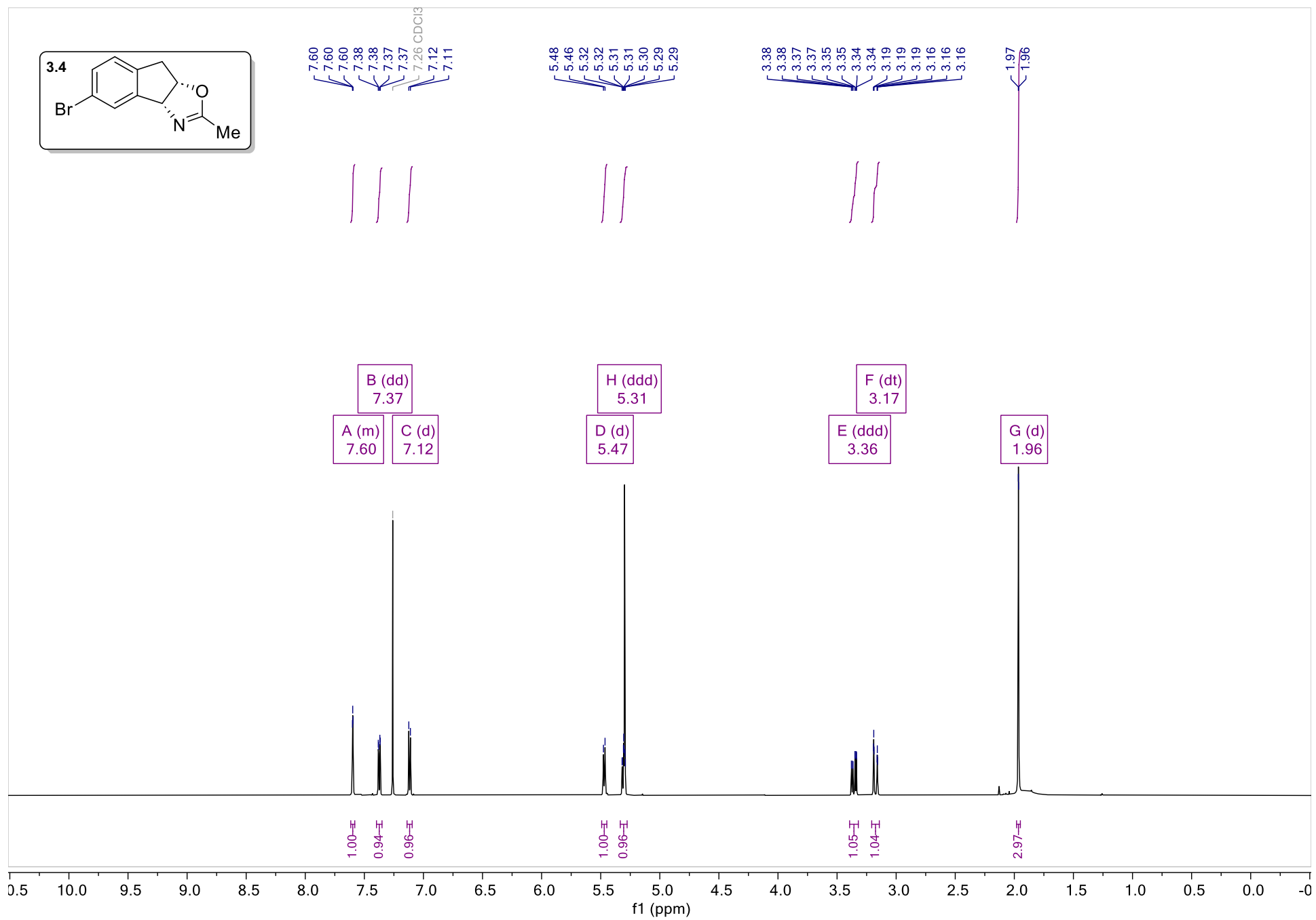
**HRMS** (ESI+): Calculated for C<sub>11</sub>H<sub>11</sub>BrON [M+H]<sup>+</sup>: 252.0024, Found: 252.0015.

**α<sub>D</sub><sup>23</sup>** (c = 1.00, CHCl<sub>3</sub>): +136.2°

Compound **3.4** before and after purification by silica plug ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )

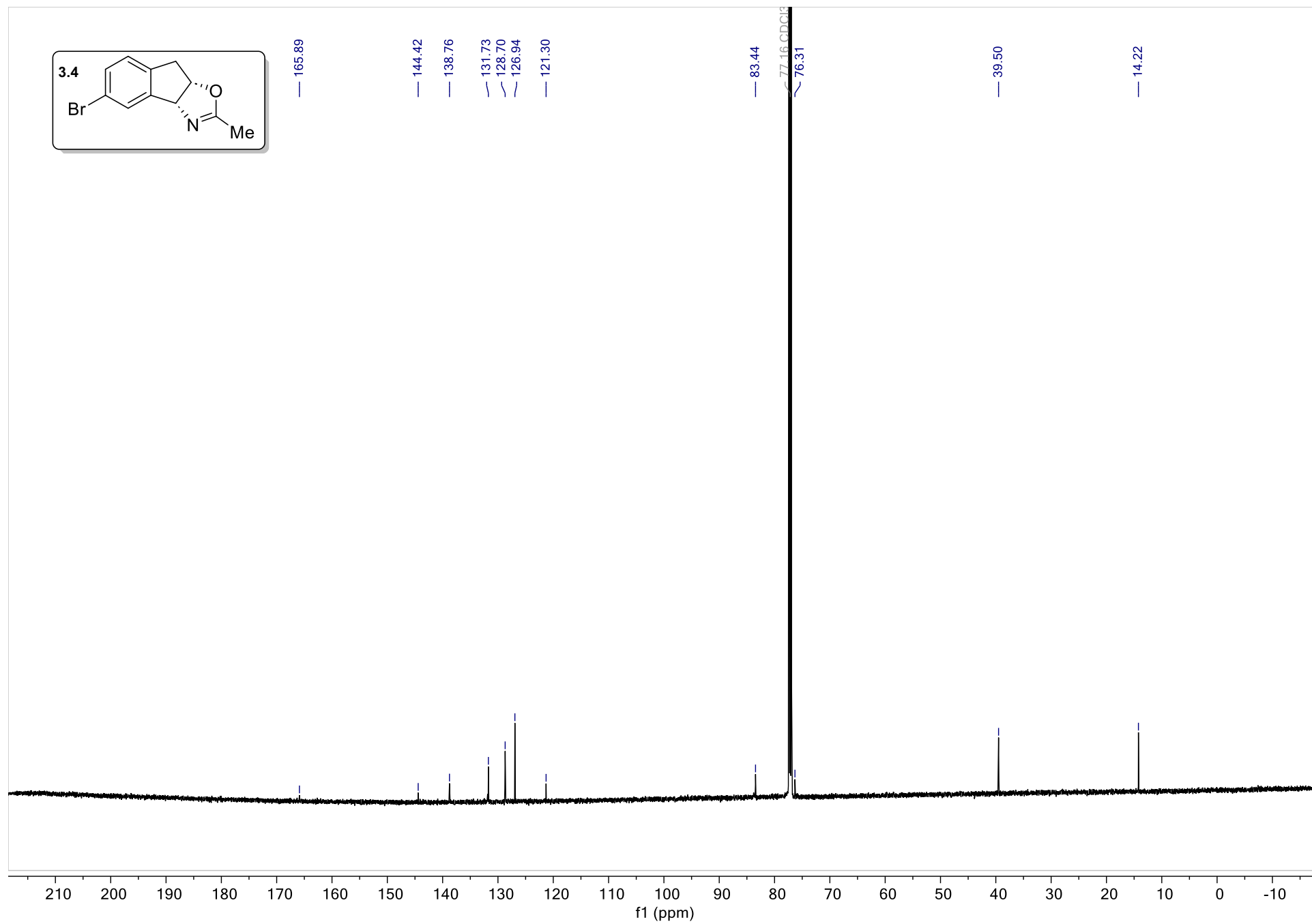


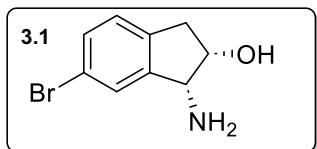
Compound **3.4** ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )





Compound **3.4** ( $^{13}\text{C}$  NMR, 151 MHz,  $\text{CDCl}_3$ )





(1*R*,2*S*)-1-amino-6-bromo-2,3-dihydro-1*H*-inden-2-ol (**3.1**) The following procedure was adapted from a literature procedure.<sup>7</sup> Oxazoline **3.4** (0.680 g, 2.70 mmol, 1.00 equiv) was dissolved in 14 mL MeOH in a 100 mL round-bottomed flask. 6 M HCl (1:1 v/v with MeOH) was added slowly, and the solution was heated in an oil bath at 60 °C for 18 h with an ethylene glycol reflux condenser. The reaction was then cooled to room temperature before being

submersed in an ice bath. The reaction was terminated by the dropwise addition of 6 M NaOH solution (approx. equal volume to that of the HCl added). Upon addition of ca. 75% of the volume of base, the free aminoindanol precipitated from the solution. After all of the base was added, the mixture was left stirring a further 10 min at 0°C before the solids were collected by vacuum filtration. The solids were washed twice with cold water and dried for 30 min under vacuum. Any residual aminoindanol was recovered from the reaction flask by rinsing with MeOH and evaporating the solution. The combined light beige solids were then dried via azeotrope with PhMe on the rotary evaporator (3x) followed by 12 h under vacuum to afford **3.1** (0.466 g, 2.04 mmol, 43% yield over two steps). The spectral data for amino alcohol **3.1** were consistent with the prior report.<sup>8</sup> This procedure has been used successfully on scales up to 3.8 g of starting material with comparable yields.

### Physicochemical Properties

Beige solid

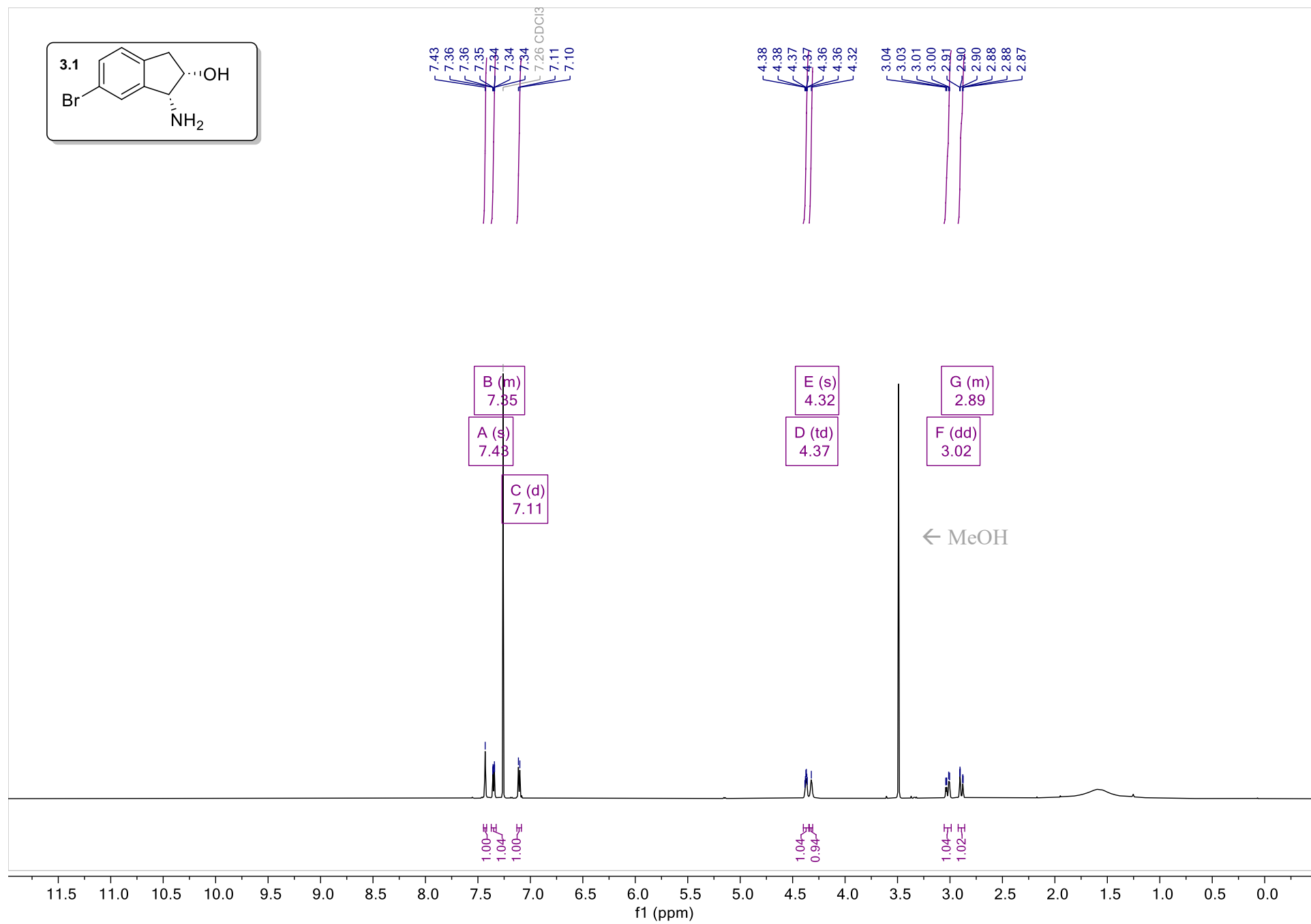
**mp**: 123-125 °C (decomposition)

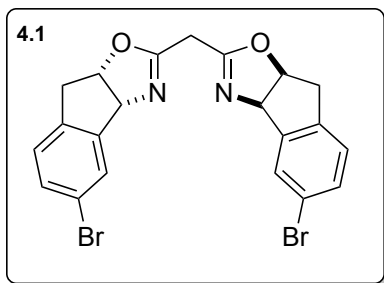
**TLC** (100% EtOAc/Hex)  $R_f = 0.05$  (UV/KMnO<sub>4</sub>)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.43 (s, 1H), 7.37 – 7.33 (m, 1H), 7.11 (d,  $J = 8.0$  Hz, 1H), 4.37 (td,  $J = 5.4, 2.6$  Hz, 1H), 4.32 (s, 1H), 3.02 (dd,  $J = 16.6, 5.4$  Hz, 1H), 2.89 (d,  $J = 16.3$  Hz, 1H). Note: The NMR sample was spiked with MeOH to aid with solubility.

$\alpha_D^{23}$  (c = 0.54, CHCl<sub>3</sub>): +10.3° [Lit., (1*S*,2*R*)-enantiomer:<sup>8</sup> (c = 0.53, CHCl<sub>3</sub>): -93.1°] NOTE: The compound is not soluble at this concentration in CHCl<sub>3</sub>. A second measurement was taken in a solvent giving a homogenous solution:  $\alpha_D^{23}$  (c = 0.57, MeOH): +48.6°

Compound **3.1** ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )





bis((3a*R*,8a*S*)-5-bromo-3a,8a-dihydro-8H-indeno[1,2-d]oxazol-2-yl)methane (**4.1**) The following procedure was adapted from a literature procedure.<sup>9</sup> A 250 mL flame-dried round-bottomed flask was cooled under a stream of nitrogen before aminoalcohol **3.1** (1.873 g, 8.21 mmol, 2.10 equiv) and diethyl malonimidate dihydrochloride (0.904 g, 3.91 mmol, 1.00 equiv) were added, followed by 85 mL DCM. The solution was heated in a sand bath at 40 °C for 18 h with an ethylene glycol reflux condenser. The reaction was then cooled to room temperature before being transferred to a separatory funnel. The reaction was terminated by the addition of 50 mL of distilled H<sub>2</sub>O, followed by 1M aqueous NaOH, and the layers were separated. (NOTE: If an insufficient quantity of base is added during the workup, the water-soluble HCl adduct of bis(oxazoline) **4.1** is

obtained.) The aqueous layer was extracted with DCM (5 x 50 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. No additional purification steps were required to afford **4.1** (1.592 g, 3.26 mmol, 84%). The spectral data for **4.1** were consistent with the prior report.<sup>8</sup> This procedure has been used successfully on scales up to 3.0 g of starting material with comparable yields.

#### Physicochemical Properties

White solid

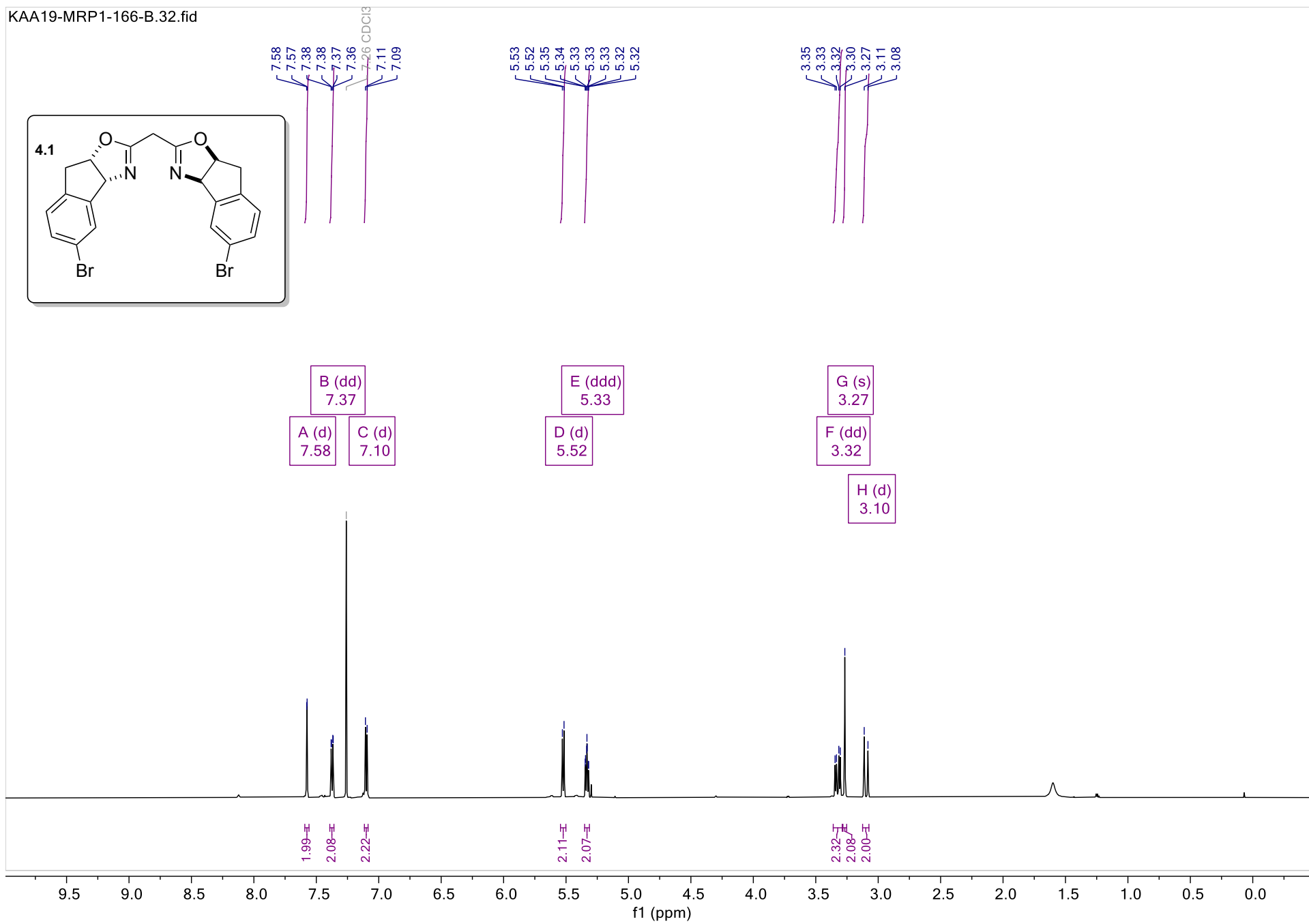
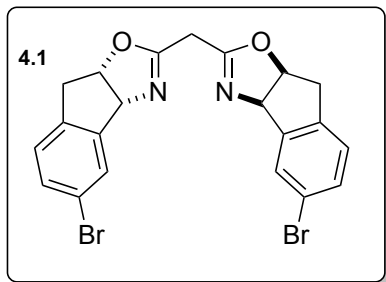
**mp:** 215-217 °C (decomposition)

**TLC** (5% MeOH/DCM) *R<sub>f</sub>* = 0.30 (UV/Magic)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.58 (d, *J* = 1.9 Hz, 2H), 7.37 (dd, *J* = 8.1, 1.9 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 5.52 (d, *J* = 7.9 Hz, 2H), 5.33 (ddd, *J* = 8.2, 7.0, 1.7 Hz, 2H), 3.32 (dd, *J* = 18.1, 7.0 Hz, 2H), 3.27 (s, 2H), 3.10 (d, *J* = 18.1 Hz, 2H).

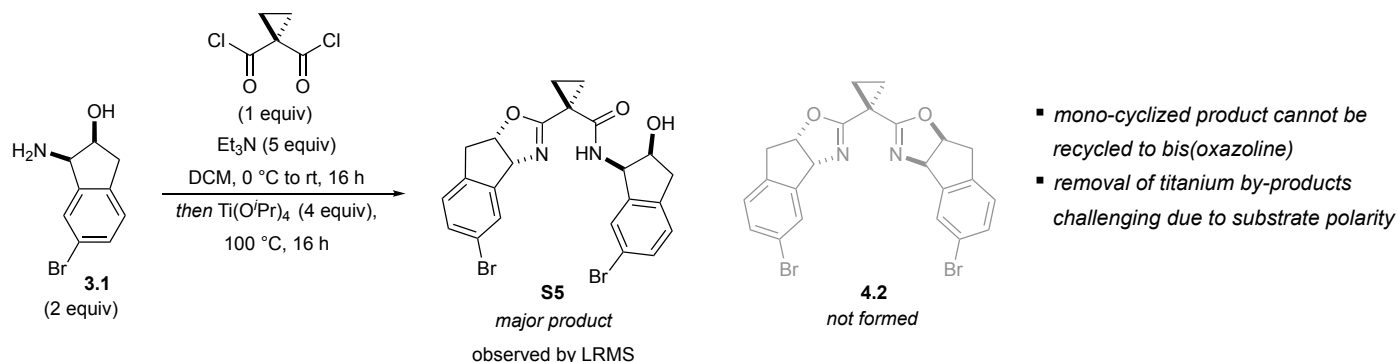
Compound **4.1** ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-166-B.32.fid



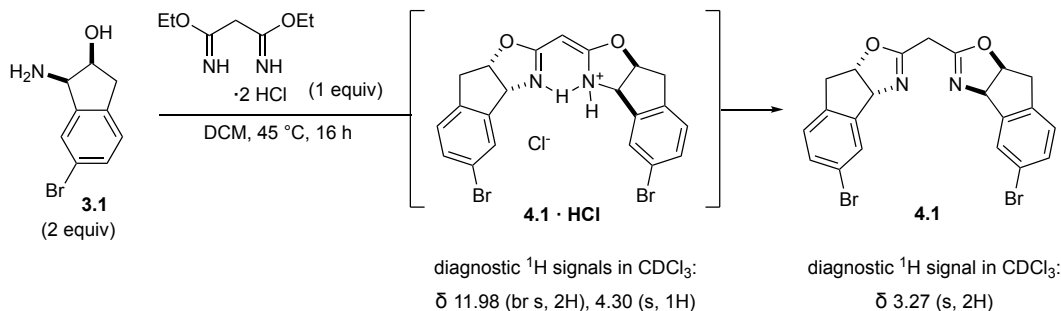
## Optimization of the Synthesis of Bis(oxazoline) Ligands via Aminoindanol 3.1

### Two-step amidation/cyclodehydration sequence:



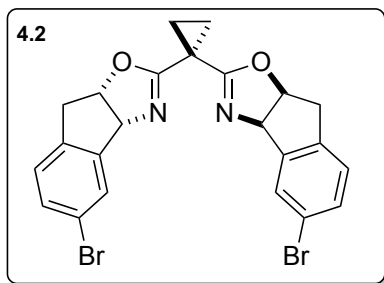
Reaction of cyclopropyl-substituted malonyl dichloride with **3.1** was used to form the bis(amide). Cyclodehydration by modification of a literature procedure using titanium (IV) isopropoxide was expected to afford the bromine-functionalized inda(box) **4.2**<sup>9-11</sup>; however, the major product obtained instead was determined to be amide **S5** (in low yield due to water solubility). Resubjection of the mono-cyclized **S5** to the reaction conditions did not result in further cyclodehydration. Further, removal of the titanium (IV) byproducts from the reaction mixture during extractive workup was complicated by the tendency for the bromine-substituted compounds to migrate into the aqueous layer. These factors prompted us to investigate an alternative two-step sequence (below).

### Imidate Condensation Optimization:



The majority of literature procedures for the condensation of aminoindanol with diethyl malonimidate dihydrochloride describe a quench with water and extractive workup with DCM.<sup>8,9,12</sup> When bromo-aminoindanol **3.1** was used in the condensation reaction, recovery of **4.1** from the reaction mixture varied especially when the reaction was scaled up. The major product isolated was the HCl adduct of **4.1**, which is a water-soluble white solid with modest solubility in DCM. It was necessary to perform an aqueous base wash to free-base the bis(oxazoline) **4.1** which improved the yield of the condensation and allowed **4.1** to be isolated without the need for additional purification steps. The presence of the bromine atoms probably contributes to the observed  $\text{pK}_a$  difference from the des-bromoinda(box).

## Preparation of Bridgehead-Substituted Inda(box) Ligands 4.2 – 4.6



(3*a**R*,3*a'**R*,8*a**S*,8*a'**S*)-2,2'-(cyclopropane-1,1-diyl)bis(5-bromo-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**4.2**) The following procedure was adapted from a literature procedure.<sup>9</sup> A 2-necked 10 mL flame-dried round-bottomed flask fitted with an ethylene glycol reflux condenser was cooled under a stream of nitrogen before bis(oxazoline) **4.1** (0.200 g, 0.410 mmol, 1.00 equiv) was added followed by 6 mL THF. The suspension was cooled to 0 °C in an ice bath, and NaH (60% dispersion in mineral oil, 32.8 mg, 0.819 mmol, 2.00 equiv) was added portionwise. The reaction mixture was stirred for 5 min at 0 °C, and 1,2-dibromoethane (53.0 μL, *d* = 2.18 g/mL, 0.615 mmol, 1.50 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 24 h (NOTE: hydrogen gas evolution occurred upon warming to room temperature). The reaction was then cooled to 0 °C in an ice bath. The reaction was terminated by the dropwise addition of 4 mL aq. saturated NH<sub>4</sub>Cl solution. The reaction was then transferred to a separatory funnel and diluted with H<sub>2</sub>O. The aqueous layer was extracted with DCM (5 x 5 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The brown solids were purified by trituration from hexane (1 mL/g solids) to give **4.2** (0.190 g, 0.370 mmol, 90% yield).

### Physicochemical Properties

Tan solid

**mp**: 160-162 °C (decomposition)

**TLC** (20% EtOAc/Hex) *R<sub>f</sub>* = 0.07 (UV/Magic)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.57 (d, *J* = 1.9 Hz, 2H), 7.36 (dd, *J* = 8.2, 1.9 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 5.49 (d, *J* = 7.9 Hz, 2H), 5.35 – 5.28 (m, 2H), 3.32 (dd, *J* = 18.1, 7.0 Hz, 2H), 3.16 – 3.09 (m, 2H), 1.38 – 1.27 (m, 4H).

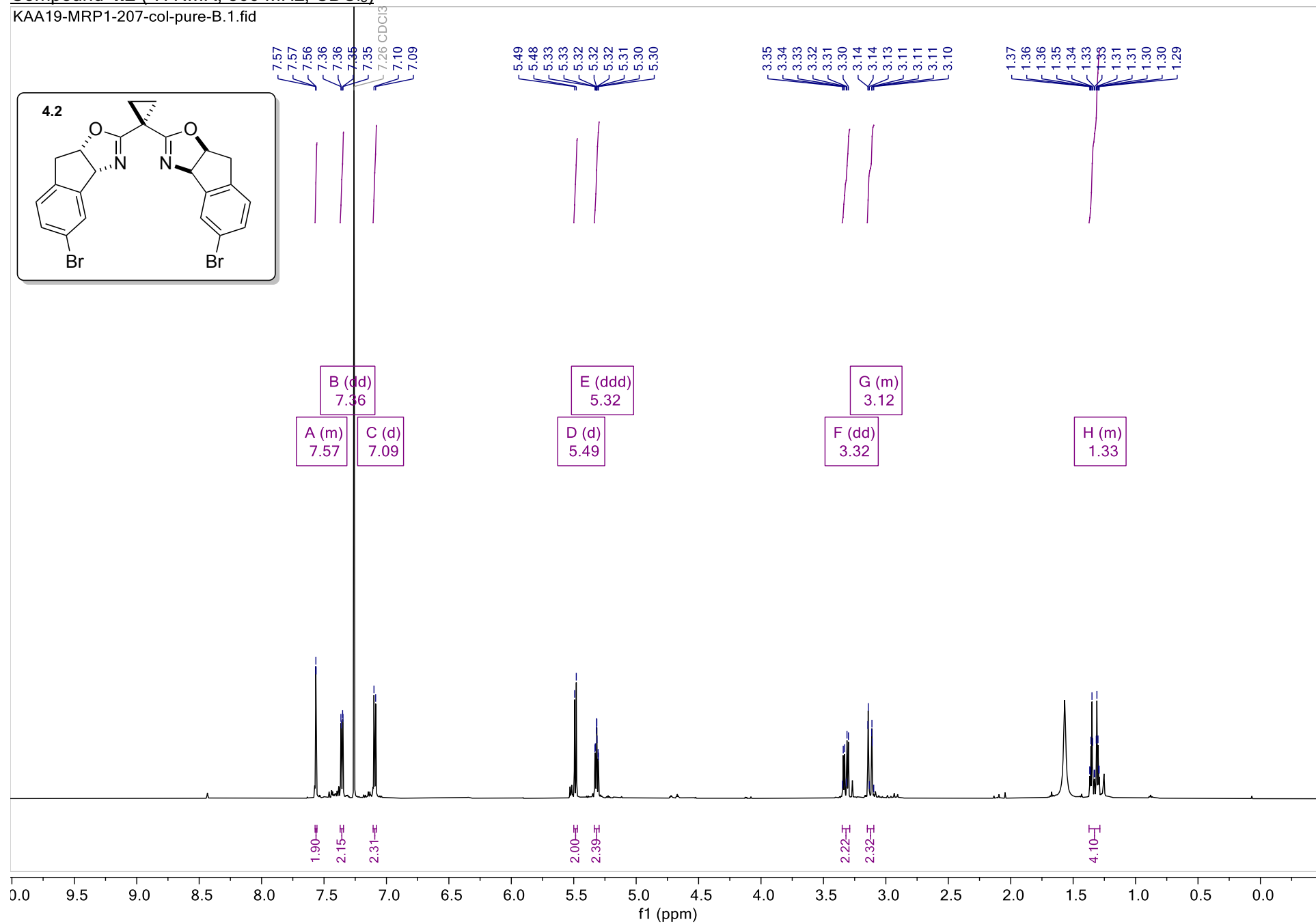
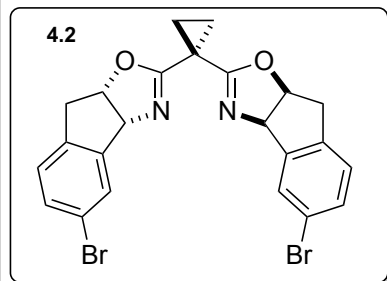
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 166.2, 144.1, 138.8, 131.7, 128.9, 126.8, 121.2, 83.6, 76.2, 39.4, 18.5, 16.0.

**HRMS** (ESI+): Calculated for C<sub>23</sub>H<sub>21</sub>Br<sub>2</sub>O<sub>3</sub>N<sub>2</sub> [M+H<sub>2</sub>O+H]<sup>+</sup>: 530.9913, Found: 530.9906.

**$\alpha_D^{23}$**  (*c* = 0.28, CHCl<sub>3</sub>): +132.0°

Compound **4.2** ( $^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$ )

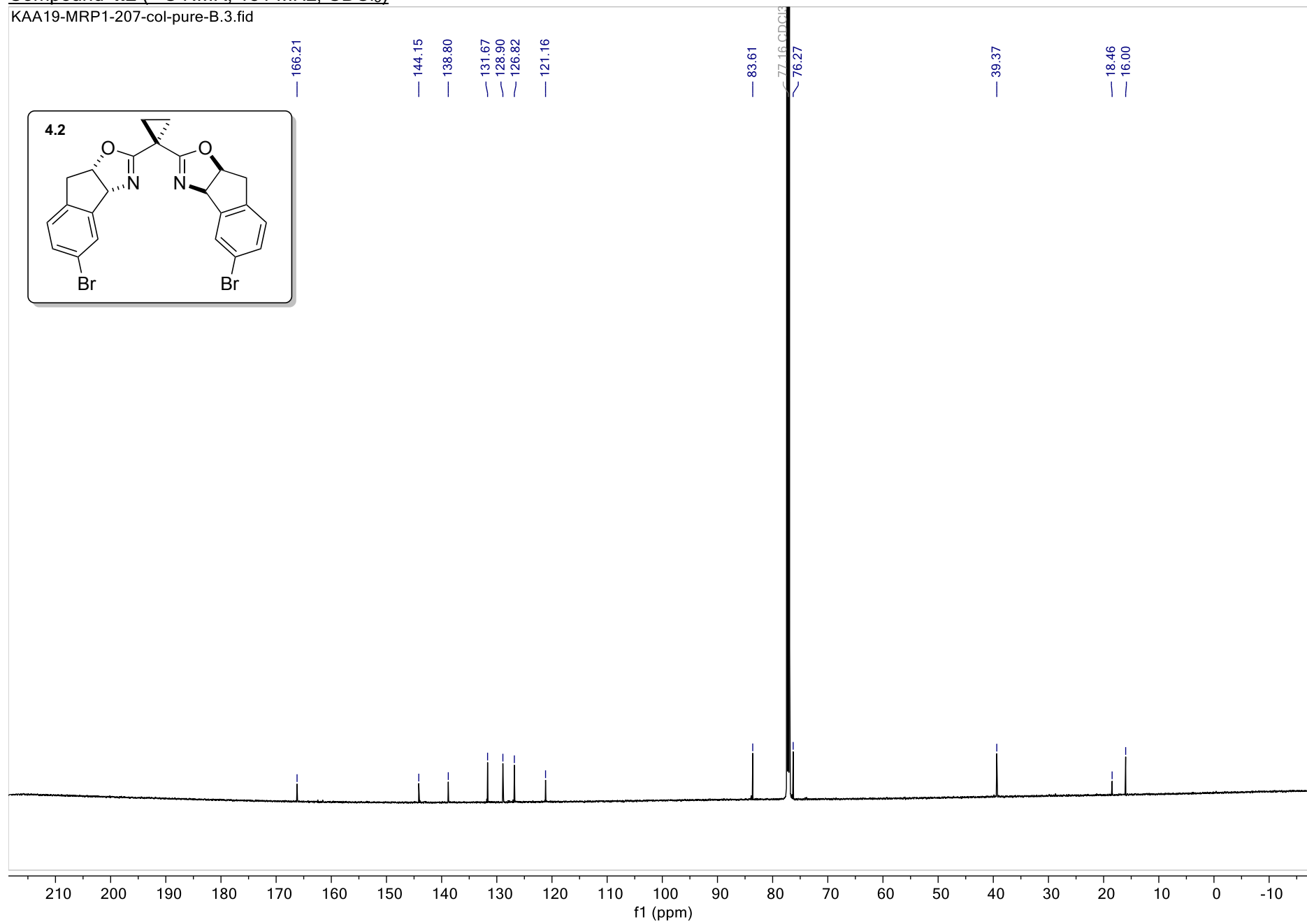
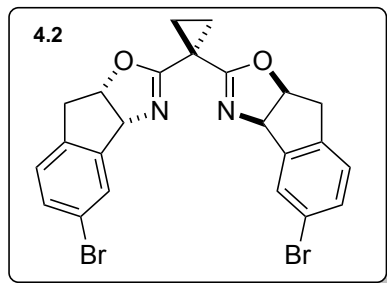
KAA19-MRP1-207-col-pure-B.1.fid

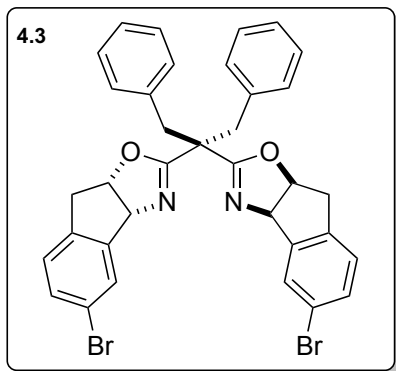




Compound **4.2** ( $^{13}\text{C}$  NMR, 151 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-207-col-pure-B.3.fid





(3aR,3a'R,8aS,8a'S)-2,2'-(1,3-diphenylpropane-2,2-diyl)bis(5-bromo-3a,8a-dihydro-8H-indeno[1,2-d]oxazole) (**4.3**) The following procedure was adapted from a literature procedure.<sup>9</sup> A 2-necked 100 mL flame-dried round-bottomed flask fitted with a reflux condenser was cooled under a stream of nitrogen before bis(oxazoline) **4.1** (0.165 g, 0.338 mmol, 1.00 equiv) was added followed by 15 mL THF. The suspension was cooled to 0 °C in an ice bath, and NaH (60% dispersion in mineral oil, 86.0 mg, 2.15 mmol, 6.36 equiv) was added portionwise. The reaction mixture was stirred for 10 min at 0 °C, and a solution of benzyl bromide (291  $\mu$ L, d = 1.44 g/mL, 2.44 mmol, 7.21 equiv) dissolved in 10 mL THF was added dropwise. The reaction mixture was warmed to room temperature and stirred for 18 h (NOTE: hydrogen gas evolution occurred upon warming to room temperature). The reaction was then cooled to 0 °C in an ice bath. The reaction was terminated by the dropwise addition of 10 mL aq. saturated NH<sub>4</sub>Cl solution. The reaction was then transferred to a separatory funnel and diluted

with H<sub>2</sub>O. The aqueous layer was extracted with DCM (5 x 5 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The brown crude solids were purified by recrystallization from EtOH to afford **4.3** (0.186 g, 0.278 mmol, 82%).

A procedure detailing the synthesis of this ligand on gram-scale is described later in the SI ([hyperlink](#))

### Physicochemical Properties

White solid

**mp:** 215-217 °C

**TLC** (30% EtOAc/Hex) R<sub>f</sub> = 0.37 (UV/Magic)

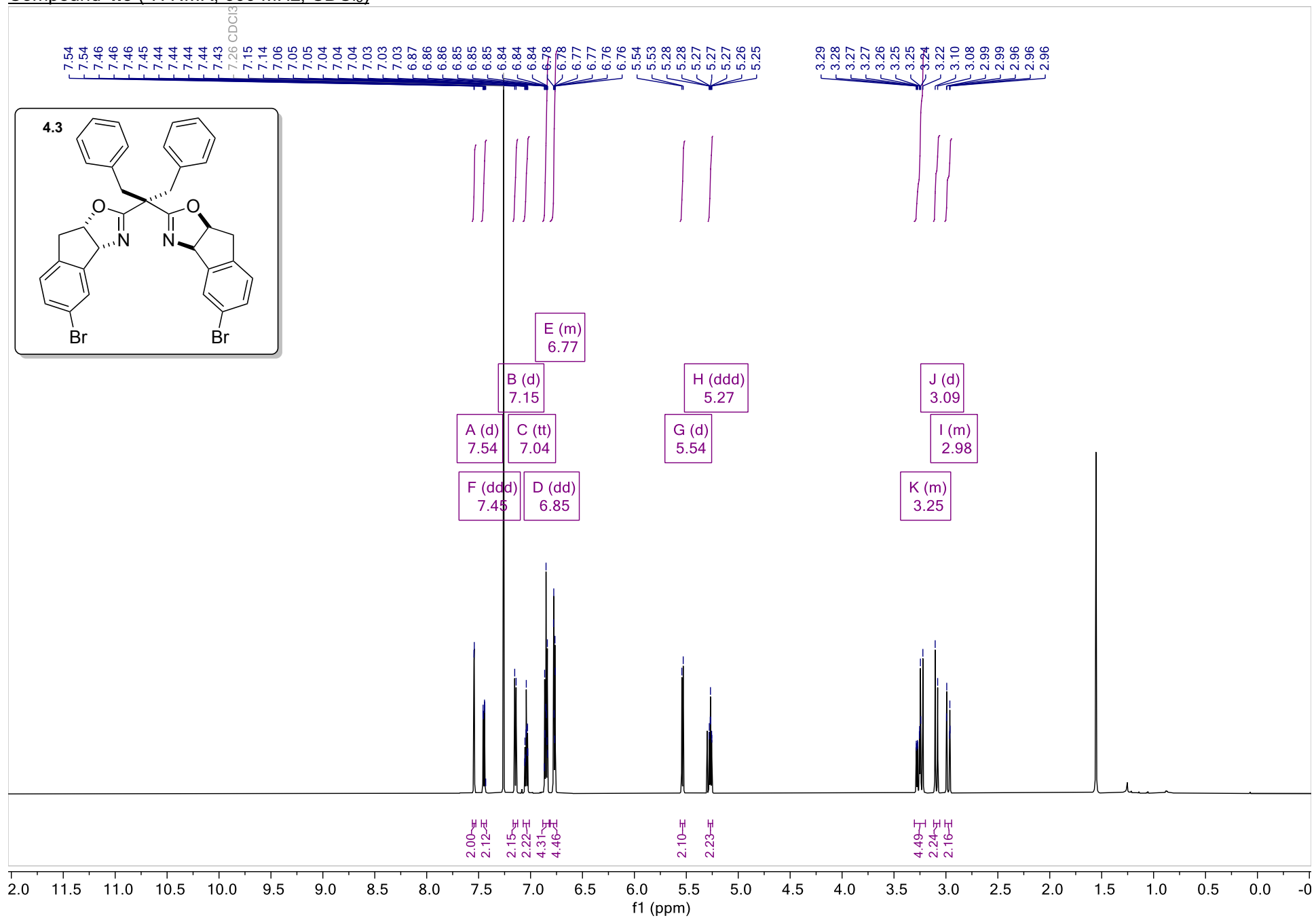
**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.54 (d, *J* = 1.9 Hz, 2H), 7.45 (ddd, *J* = 8.1, 1.9, 0.6 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.04 (tt, *J* = 7.4, 1.3 Hz, 2H), 6.85 (dd, *J* = 8.5, 7.0 Hz, 4H), 6.81 – 6.75 (m, 4H), 5.54 (d, *J* = 7.8 Hz, 2H), 5.27 (ddd, *J* = 7.9, 6.6, 1.2 Hz, 2H), 3.29 – 3.21 (m, 4H), 3.09 (d, *J* = 14.3 Hz, 2H), 3.01 – 2.95 (m, 2H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  167.80, 143.94, 138.91, 136.03, 131.66, 130.27, 129.02, 127.80, 126.78, 126.63, 121.30, 76.25, 47.68, 39.12, 38.96.

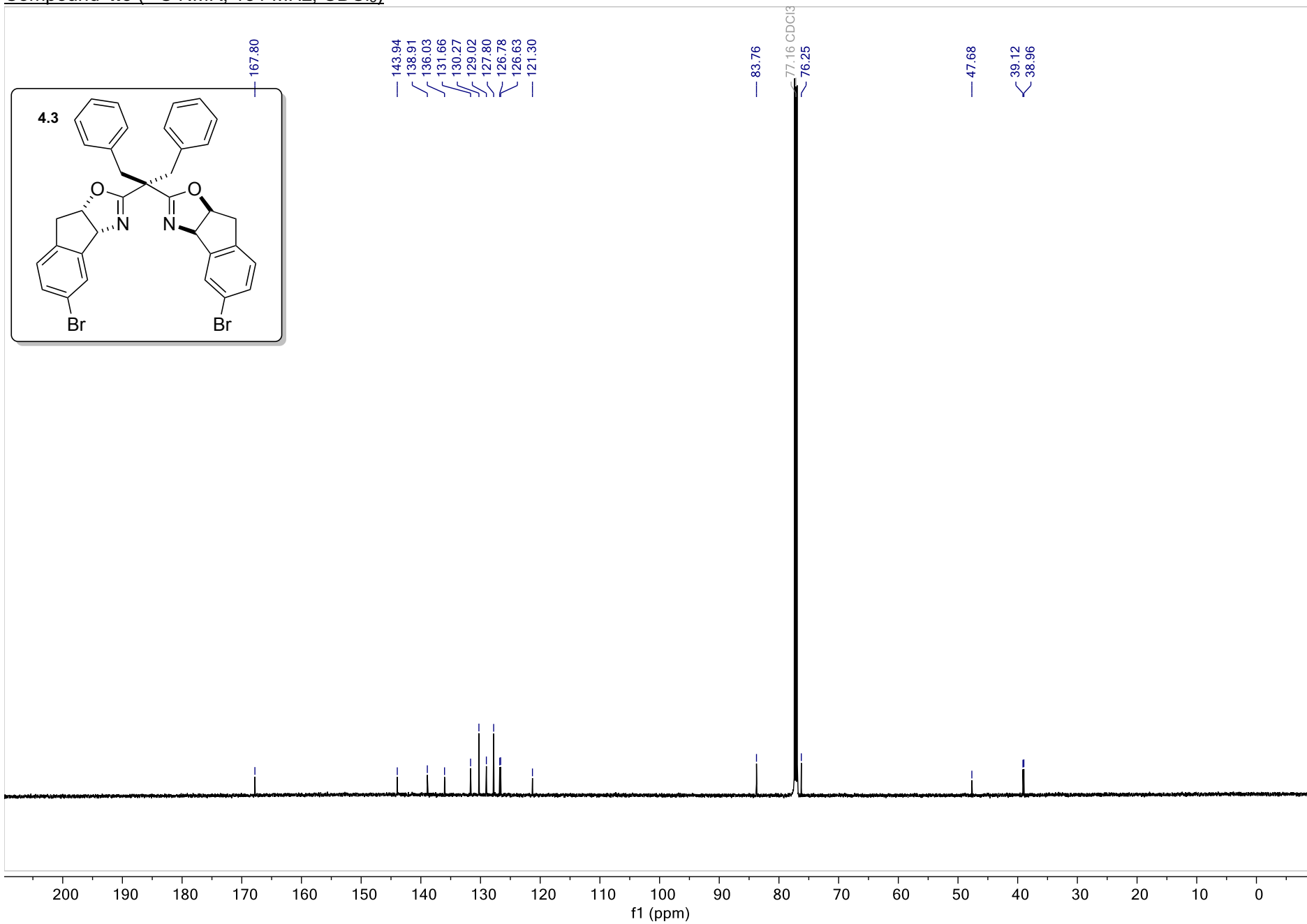
**HRMS** (ESI+): Calculated for C<sub>35</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>Br<sub>2</sub> [M+H]<sup>+</sup>: 667.0596, Found: 667.0580.

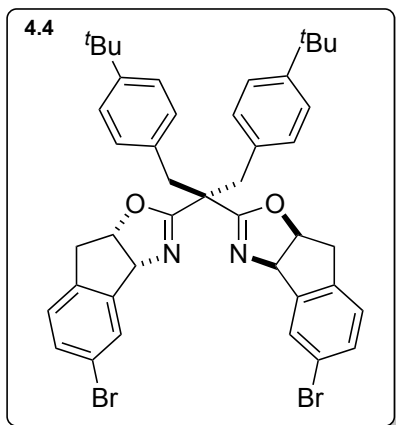
$\alpha_D^{23}$  (c = 0.41, CHCl<sub>3</sub>): +259.1°

Compound **4.3** ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )



Compound **4.3** ( $^{13}\text{C}$  NMR, 151 MHz,  $\text{CDCl}_3$ )





(3*a**R*,3*a'**R*,8*a**S*,8*a'**S*)-2,2'-(1,3-bis(4-(*tert*-butyl)phenyl)propane-2,2-diyl)bis(5-bromo-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**4.4**) The following procedure was adapted from a literature procedure.<sup>9</sup> A 2-necked 100 mL flame-dried round-bottomed flask fitted with a reflux condenser was cooled under a stream of nitrogen before bis(oxazoline) **4.1** (0.050 g, 0.102 mmol, 1.00 equiv) was added followed by 3 mL of THF. The suspension was cooled to 0 °C in an ice bath, and NaH (60% dispersion in mineral oil, 29.5 mg, 0.737 mmol, 7.2 equiv) was added portionwise. The reaction mixture was stirred for 10 min at 0 °C, and a solution of 1-(bromomethyl)-4-(*tert*-butyl)benzene (92 μL, *d* = 1.24 g/mL, 0.501 mmol, 4.89 equiv) dissolved in 2 mL THF was added dropwise. The reaction mixture was warmed to room temperature and stirred for 18 h (NOTE: hydrogen gas evolution occurred upon warming to room temperature). The reaction was then cooled to 0 °C in an ice bath. The reaction was terminated by the dropwise addition of 4 mL aq. saturated NH<sub>4</sub>Cl solution. The reaction was then transferred to a separatory funnel and diluted with H<sub>2</sub>O. The aqueous layer was extracted with DCM (5 x 5 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>,

filtered, and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 20/80) to afford **4.4** (0.048 g, 0.062 mmol, 60%).

### Physicochemical Properties

White solid

**mp**: 195-200 °C (decomposition)

**TLC** (20% EtOAc/Hex) *R<sub>f</sub>* = 0.48 (UV/Magic)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.60 (d, *J* = 1.9 Hz, 2H), 7.47 (dd, *J* = 8.1, 1.9 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.88 – 6.80 (m, 4H), 6.70 – 6.62 (m, 4H), 5.58 (d, *J* = 7.8 Hz, 2H), 5.31 (ddd, *J* = 7.9, 6.6, 1.3 Hz, 2H), 3.30 (dd, *J* = 18.2, 6.7 Hz, 2H), 3.20 (d, *J* = 14.2 Hz, 2H), 3.04 (d, *J* = 18.1 Hz, 2H), 2.96 (d, *J* = 14.3 Hz, 2H), 1.23 (s, 18H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 168.0, 149.3, 143.9, 139.0, 132.9, 131.7, 130.1, 129.1, 126.8, 124.6, 121.3, 83.7, 76.4, 47.9, 39.1, 38.2, 34.4, 31.5.

**HRMS** (ESI+): Calculated for C<sub>43</sub>H<sub>45</sub>Br<sub>2</sub>O<sub>2</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 781.1821, Found: 781.1823.

**α<sub>D</sub><sup>23</sup>** (c = 0.37, CHCl<sub>3</sub>): +263.4°

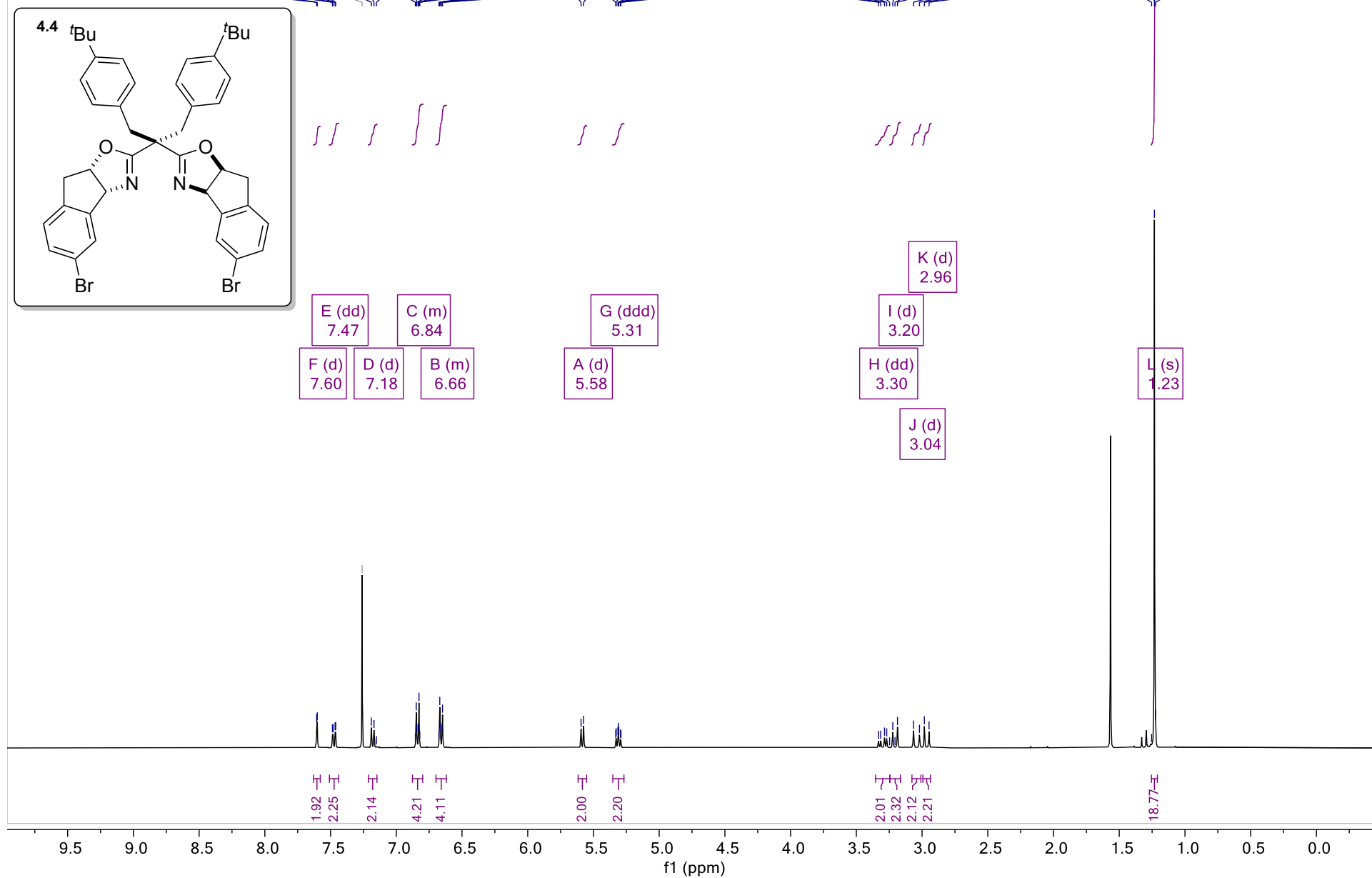
Compound 4.4 (<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>)

KAA19-MRP1-178-pure-C.1.fid

Advisor Johnson

Grant number 5120786

Onyen alleyk



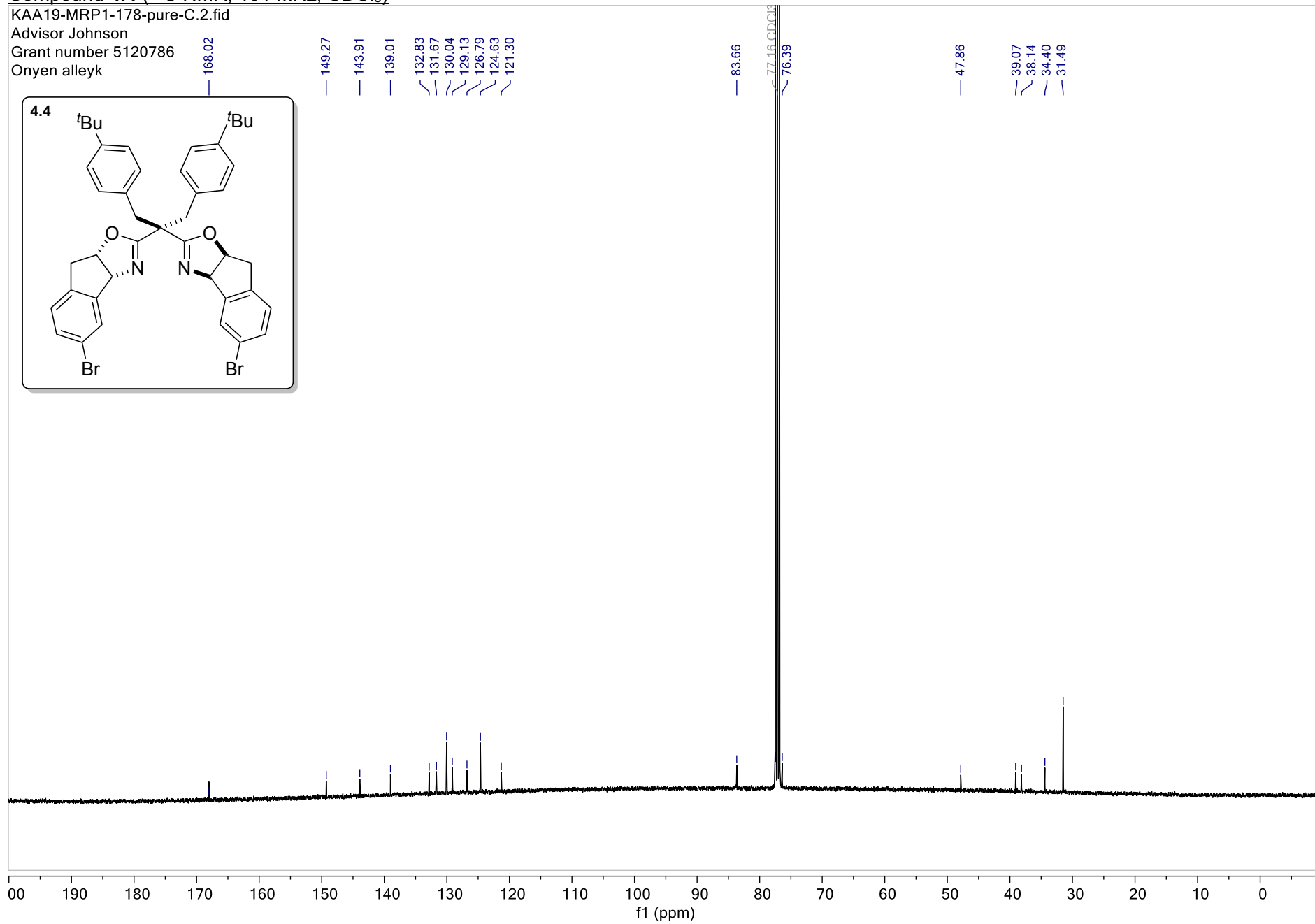
Compound **4.4** ( $^{13}\text{C}$  NMR, 101 MHz,  $\text{CDCl}_3$ )

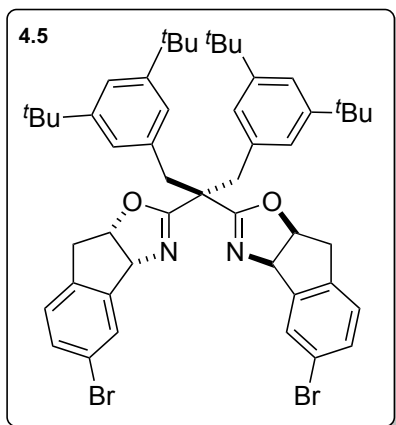
KAA19-MRP1-178-pure-C.2.fid

Advisor Johnson

Grant number 5120786

Onyen alleyk





(3*a**R*,3*a'**R*,8*a**S*,8*a'**S*)-2,2'-(1,3-bis(3,5-di-*tert*-butylphenyl)propane-2,2-diyl)bis(5-bromo-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**4.5**) The following procedure was adapted from a literature procedure.<sup>13</sup> A 2-necked 100 mL flame-dried round-bottomed flask fitted with a reflux condenser was cooled under a stream of nitrogen before bis(oxazoline) **4.1** (0.050 g, 0.102 mmol, 1.00 equiv) was added followed by 3 mL of THF. The suspension was cooled to 0 °C in an ice bath, and NaH (60% dispersion in mineral oil, 29.5 mg, 0.737 mmol, 7.2 equiv) was added portionwise. The reaction mixture was stirred for 10 min at 0 °C, and a solution of 1-(bromomethyl)-3,5-di-*tert*-butylbenzene (142 mg, 0.501 mmol, 4.89 equiv) dissolved in 2 mL THF was added dropwise. The reaction mixture was warmed to room temperature and stirred for 18 h (NOTE: hydrogen gas evolution occurred upon warming to room temperature). The reaction was then cooled to 0 °C in an ice bath. The reaction was terminated by the dropwise addition of 4 mL aq. saturated NH<sub>4</sub>Cl solution. The reaction was then transferred to a separatory funnel and diluted with H<sub>2</sub>O. The aqueous layer was

extracted with DCM (5 x 5 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 20/80) to afford **4.5** (0.049 g, 0.054 mmol, 53%). The spectral data for **4.5** were consistent with the prior report.<sup>8</sup>

### Physicochemical Properties

White solid

**mp:** 132-135 °C

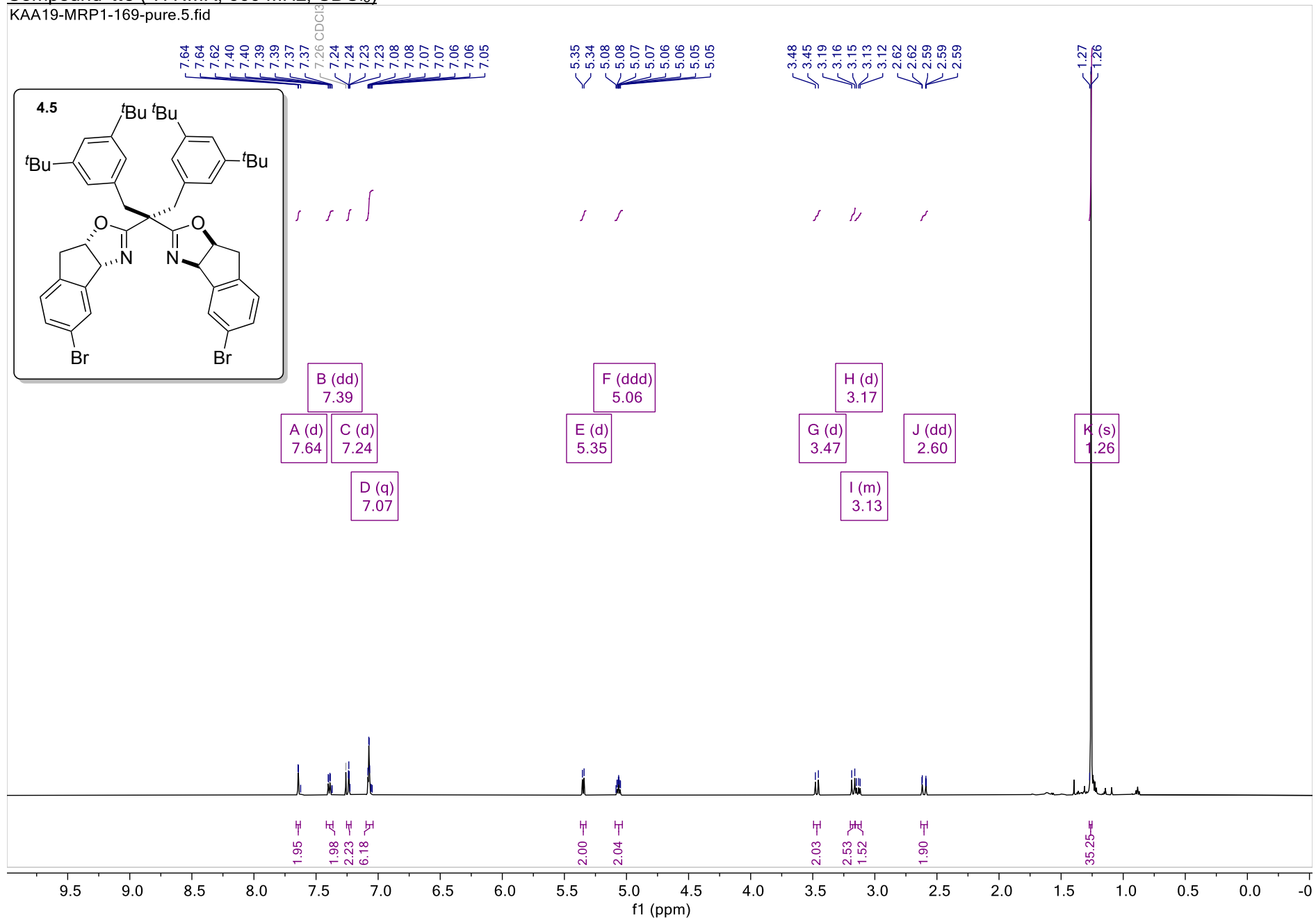
**TLC** (20% EtOAc/Hex) *R<sub>f</sub>* = 0.81 (UV/Magic)

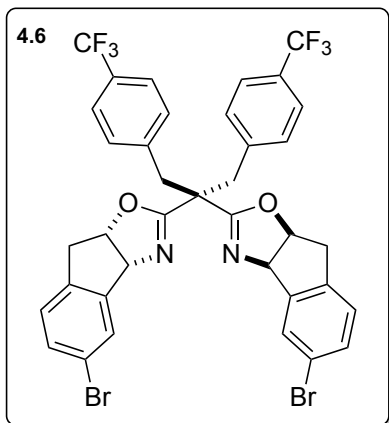
**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 1.9 Hz, 2H), 7.39 (dd, *J* = 8.1, 1.9 Hz, 2H), 7.24 (d, *J* = 1.8 Hz, 2H), 7.07 (q, *J* = 3.3, 2.4 Hz, 6H), 5.35 (d, *J* = 8.0 Hz, 2H), 5.06 (ddd, *J* = 8.7, 7.1, 1.9 Hz, 2H), 3.47 (d, *J* = 14.3 Hz, 2H), 3.17 (d, *J* = 14.8 Hz, 2H), 3.16 – 3.11 (m, 2H), 2.60 (dd, *J* = 17.7, 1.7 Hz, 2H), 1.26 (s, 36H).



Compound **4.5** ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-169-pure.5.fid





(3*a**R*,3*a'**R*,8*a**S*,8*a'**S*)-2,2'-(1,3-bis(4-(trifluoromethyl)phenyl)propane-2,2-diyl)bis(5-bromo-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**4.6**) The following procedure was adapted from a literature procedure.<sup>13</sup> A 25 mL flame-dried round-bottomed flask was cooled under a stream of nitrogen before bis(oxazoline) **4.1** (0.057 g, 0.117 mmol, 1.00 equiv) was added followed by 3 mL of THF and 4-(trifluoromethyl)benzyl bromide (0.112 g, 0.467 mmol, 4.00 equiv). The solution was cooled to 0 °C in an ice bath, and LiHMDS (1 M in THF, 0.315 mL, 0.315 mmol, 2.7 equiv) was slowly added. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction was then cooled to 0 °C in an ice bath. The reaction was terminated by the dropwise addition of 2 mL aq. saturated NH<sub>4</sub>Cl solution. The reaction was then transferred to a separatory funnel and diluted with H<sub>2</sub>O. The aqueous layer was extracted with DCM (5 x 2 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 30/70) to afford **4.6** (0.077 g, 0.096

mmol, 82%).

### Physicochemical Properties

White solid

**mp:** 58-60 °C

**TLC** (20% EtOAc/Hex) *R<sub>f</sub>* = 0.67 (UV/Magic)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.56 (d, *J* = 1.9 Hz, 2H), 7.49 (dd, *J* = 8.1, 1.9 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 4H), 6.86 (d, *J* = 8.0 Hz, 4H), 5.57 (d, *J* = 7.8 Hz, 2H), 5.31 – 5.24 (m, 2H), 3.31 (d, *J* = 13.9 Hz, 2H), 3.29 – 3.22 (m, 2H), 3.06 (d, *J* = 14.1 Hz, 2H), 2.86 (d, *J* = 18.2 Hz, 2H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.0, 143.8, 140.0, 138.7, 131.9, 130.6, 129.0 (q, *J* = 32.3 Hz), 126.9, 124.7 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 273.4 Hz), 121.4, 84.1, 76.1, 47.4, 40.2, 38.8.

**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>) δ -62.41.

**HRMS** (ESI+): Calculated for C<sub>37</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>Br<sub>2</sub>F<sub>6</sub> [M+H]<sup>+</sup>: 803.03435, Found: 803.0328.

**$\alpha_D^{23}$**  (c = 0.38, CHCl<sub>3</sub>): +250.8°

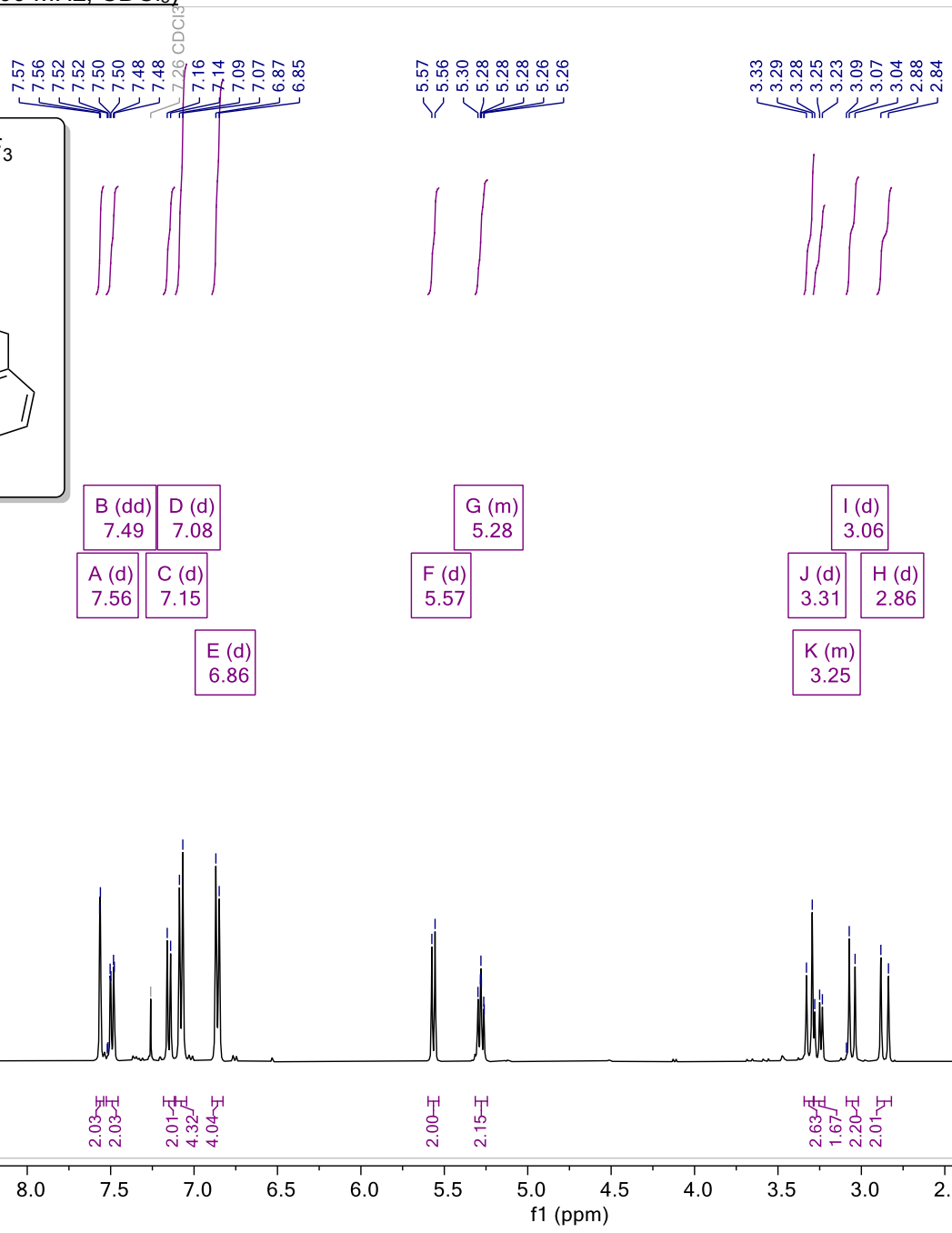
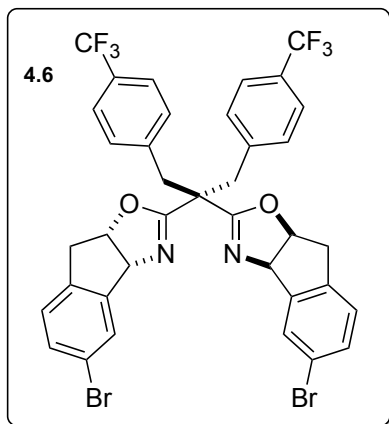
Compound **4.6** ( $^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-181-E.1.fid

Advisor Johnson

Grant number 5120786

Onyen alleyk



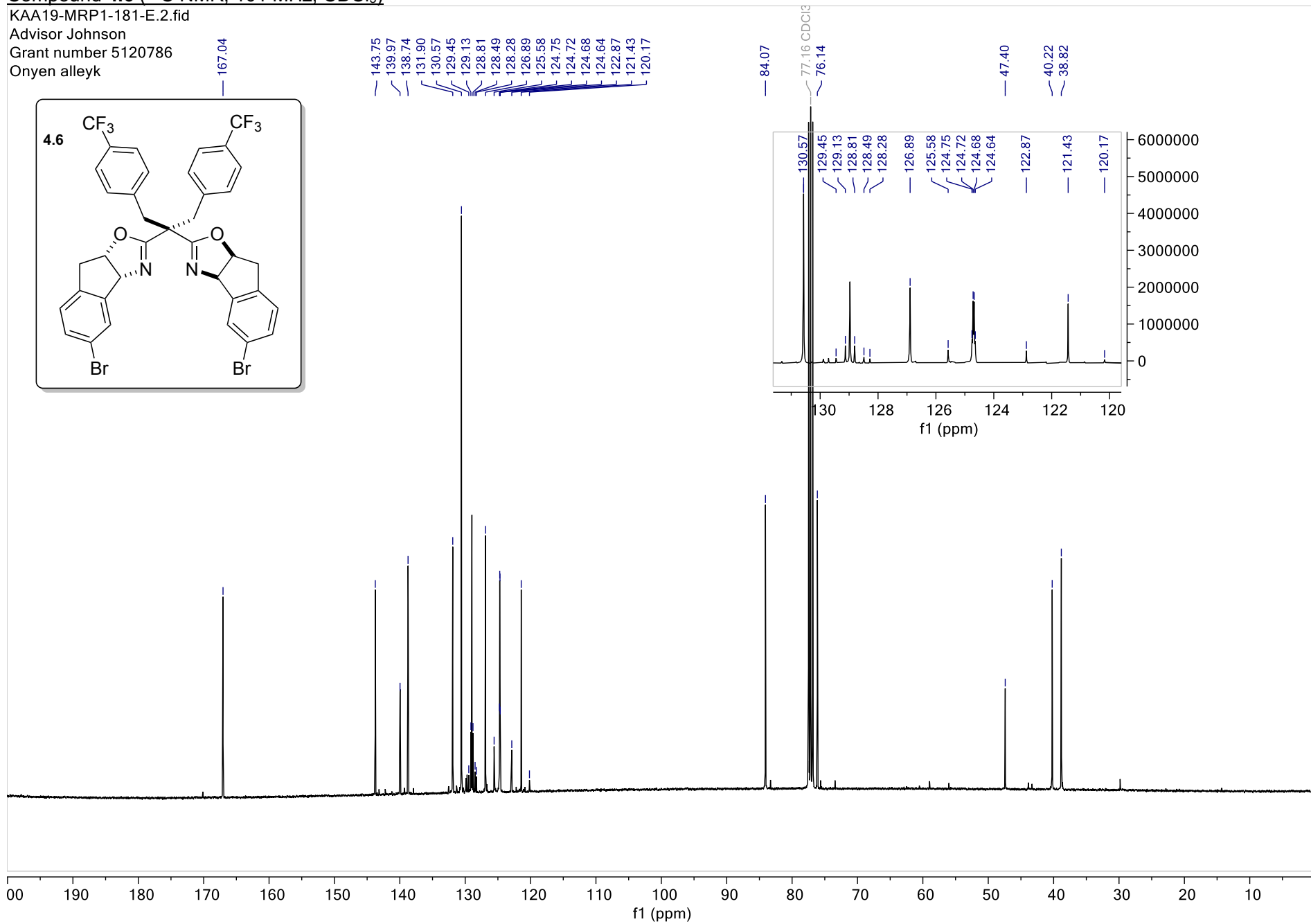
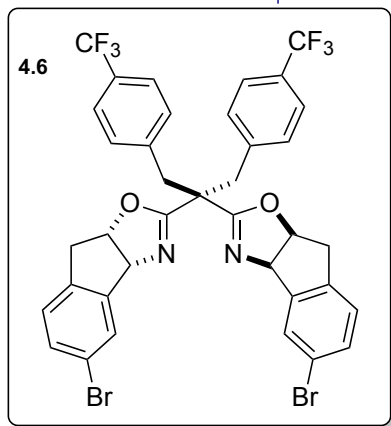
Compound **4.6** ( $^{13}\text{C}$  NMR, 101 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-181-E.2.fid

Advisor Johnson

Grant number 5120786

Onyen alleyk



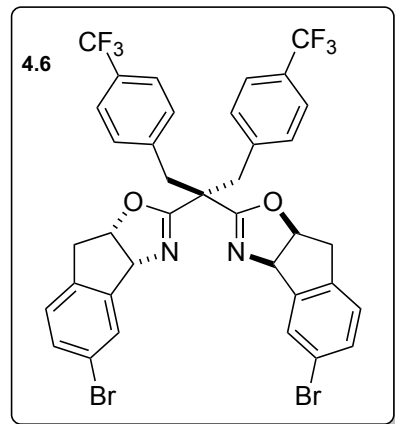
Compound **4.6** ( $^{19}\text{F}$  NMR, 377 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-181-E.5.fid

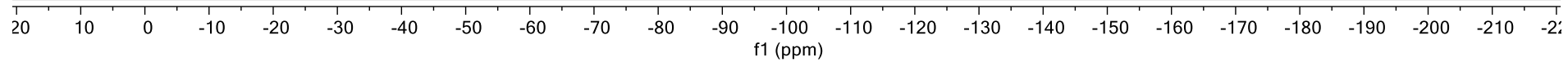
Advisor Johnson

Grant number 5120786

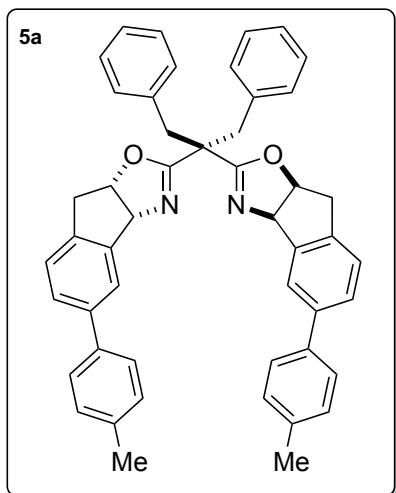
Onyen alleyk



-62.41



## Cross-Coupling Procedures: Synthesis of Inda(box) Ligands 5a – 5i



(3*aR*,3*a'R*,8*aS*,8*a'S*)-2,2'-(1,3-diphenylpropane-2,2-diyl)bis(5-(*p*-tolyl)-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**5a**) A 10 mL screw cap reaction tube was purged under a stream of nitrogen and charged with S-Phos palladacycle gen. 4 catalyst (2.0 mg, 2.5  $\mu$ mol, 0.05 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.065 g, 0.200 mmol, 4.00 equiv), (4-methylphenyl)boronic acid (0.027 g, 0.200 mmol, 4.0 equiv), bis(oxazoline) **4.3** (0.033 g, 0.050 mmol, 1.00 equiv). and 1 mL anhydrous PhMe. The tube was sparged using a balloon filled with argon for 10 min and fitted with an unpunctured PTFE screw cap. The reaction was heated in an oil bath at 100 °C for 16 h, then cooled to room temperature. The mixture was then filtered over a plug of Celite and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100  $\rightarrow$  30/70) to afford **5a** (0.028 g, 0.041 mmol, 82%).

### Physicochemical Properties

White solid

**mp:** 76-80 °C

**TLC** (30% EtOAc/Hex) *R<sub>f</sub>* = 0.46 (UV/Magic)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (d, *J* = 1.7 Hz, 2H), 7.58 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 4H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 4H), 6.92 (qt, *J* = 7.6, 4.2 Hz, 2H), 6.81 – 6.72 (m, 8H), 5.66 (d, *J* = 7.8 Hz, 2H), 5.36 (t, *J* = 7.1 Hz, 2H), 3.40 (dd, *J* = 18.2, 6.6 Hz, 2H), 3.29 (d, *J* = 14.3 Hz, 2H), 3.18 (d, *J* = 18.1 Hz, 2H), 3.10 (d, *J* = 14.3 Hz, 2H), 2.42 (s, 6H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.7, 142.3, 140.9, 138.7, 138.4, 137.1, 136.0, 130.3, 129.6, 127.7, 127.5, 127.2, 126.4, 125.5, 124.3, 84.1, 76.5, 47.6, 39.1, 38.7, 21.2.

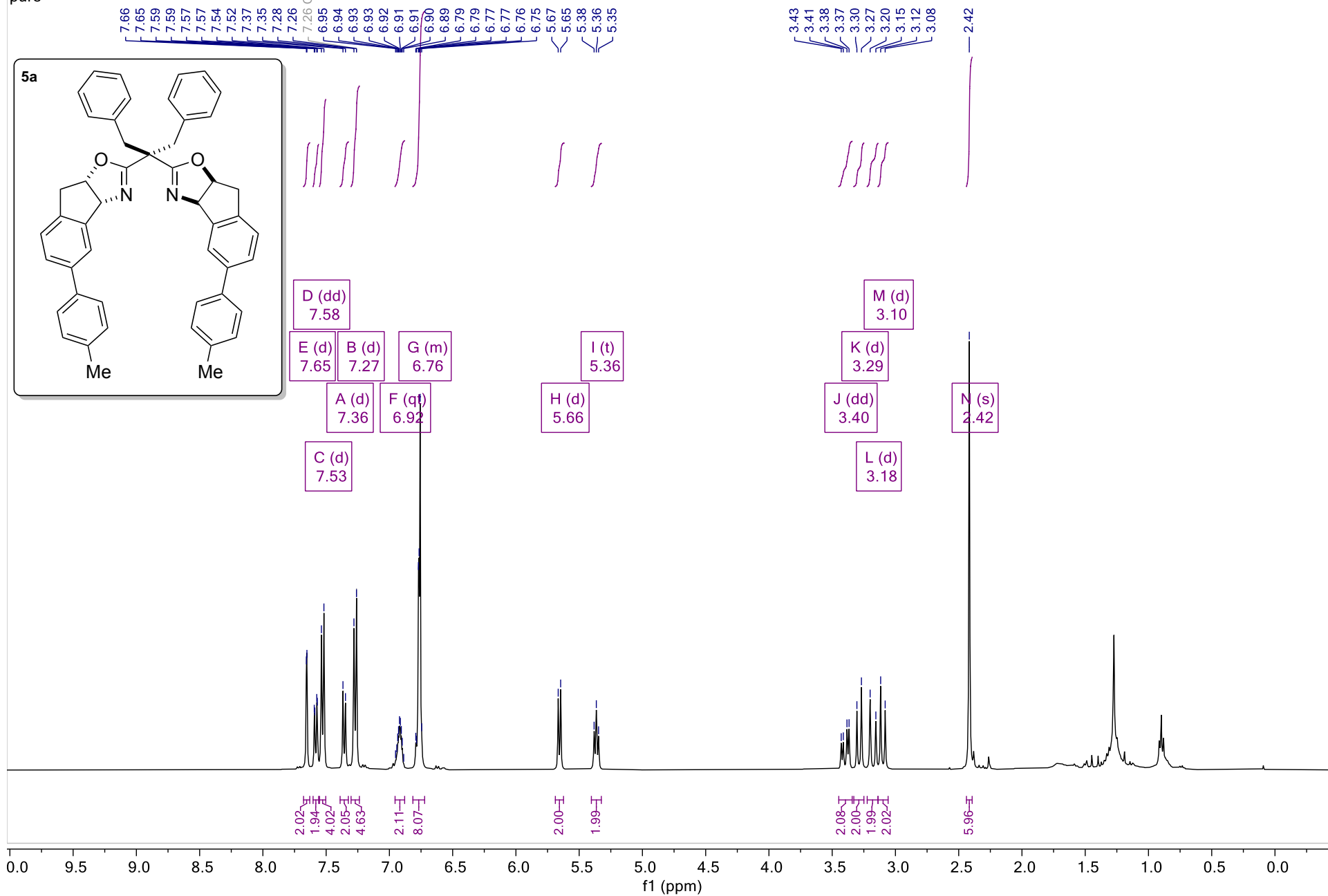
**HRMS** (ESI+): Calculated for C<sub>49</sub>H<sub>43</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 691.3325, Found: 691.3308.

$\alpha_D^{23}$  (c = 0.35, CHCl<sub>3</sub>): +238.5°

Compound **5a** (<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>)

KAA19-MRP1-189-C.5.fid

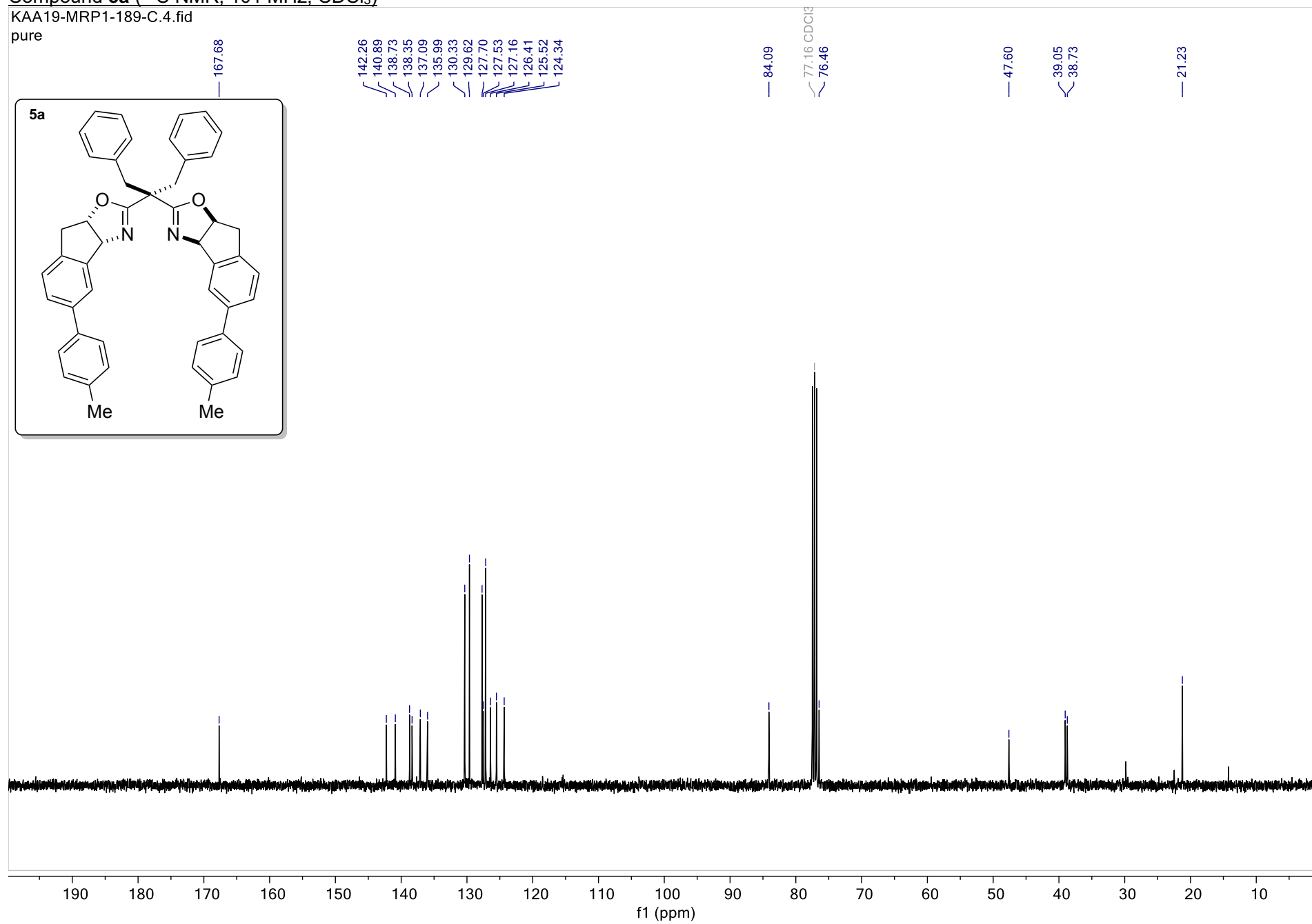
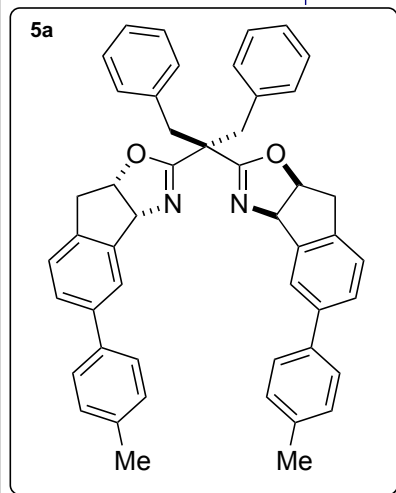
pure



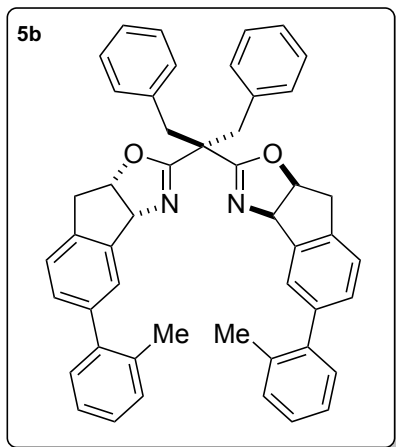
Compound **5a** ( $^{13}\text{C}$  NMR, 101 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-189-C.4.fid

pure







(3*a**R*,3*a'**R*,8*a**S*,8*a'**S*)-2,2'-(1,3-diphenylpropane-2,2-diyl)bis(5-(*o*-tolyl)-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**5b**) A 10 mL screw cap reaction tube was purged under a stream of nitrogen and charged with S-Phos palladacycle gen. 4 catalyst (2.0 mg, 2.5  $\mu$ mol, 0.05 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.065 g, 0.200 mmol, 4.00 equiv), (2-methylphenyl)boronic acid (0.027 g, 0.200 mmol, 4.0 equiv), bis(oxazoline) **4.3** (0.033 g, 0.050 mmol, 1.00 equiv). and 1 mL anhydrous PhMe. The tube was sparged using a balloon filled with argon for 10 min and fitted with an unpunctured PTFE screw cap. The reaction was heated in an oil bath at 100 °C for 16 h, then cooled to room temperature. The mixture was then filtered over a plug of Celite and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 30/70) to afford **5b** (0.035 g, 0.050 mmol, >99%).

### Physicochemical Properties

White amorphous solid

**TLC** (30% EtOAc/Hex) *R<sub>f</sub>* = 0.43 (UV/Magic)

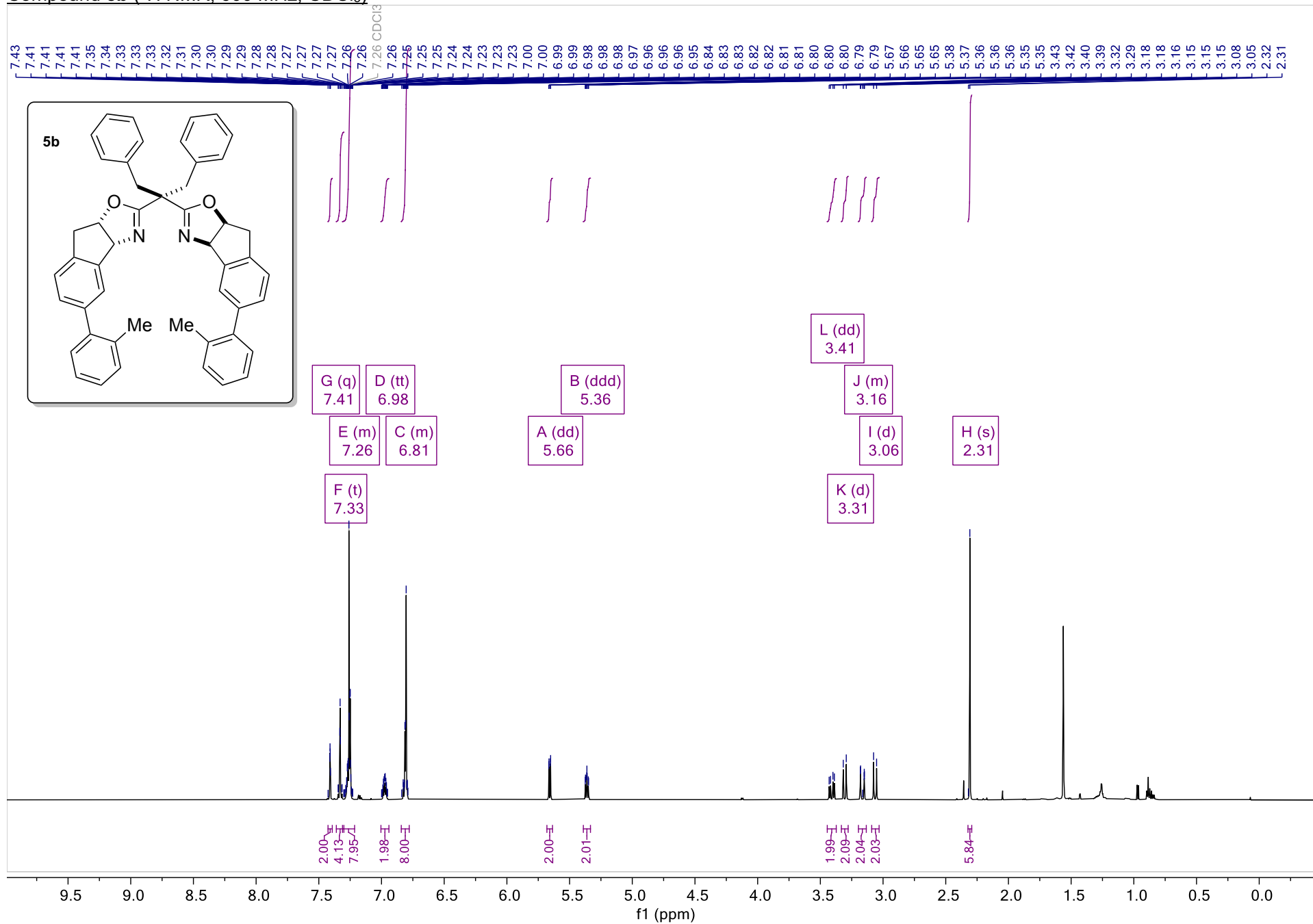
**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.41 (q, *J* = 0.9 Hz, 2H), 7.33 (t, *J* = 1.4 Hz, 4H), 7.31 – 7.21 (m, 8H), 6.98 (tt, *J* = 6.0, 2.7 Hz, 2H), 6.84 – 6.78 (m, 8H), 5.66 (dd, *J* = 7.9, 0.9 Hz, 2H), 5.36 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 2H), 3.41 (dd, *J* = 18.1, 6.8 Hz, 2H), 3.31 (d, *J* = 14.3 Hz, 2H), 3.20 – 3.13 (m, 2H), 3.06 (d, *J* = 14.3 Hz, 2H), 2.31 (s, 6H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  167.6, 141.8, 141.4, 138.5, 136.2, 135.4, 130.6, 130.4, 130.1, 129.8, 127.8, 127.4, 126.6, 126.4, 126.0, 124.9, 83.9, 76.7, 47.7, 39.3, 39.0, 20.7.

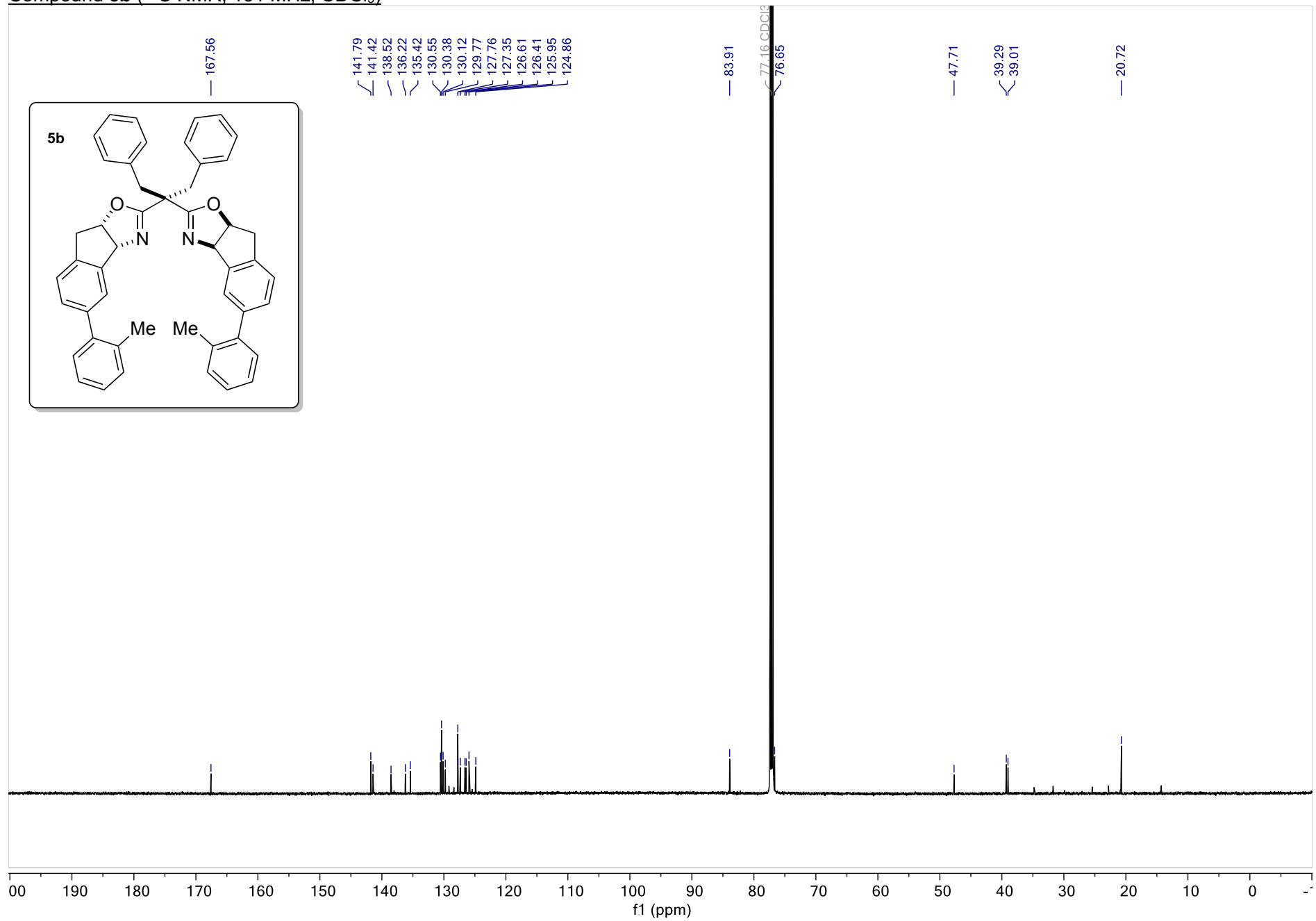
**HRMS** (ESI+): Calculated for C<sub>49</sub>H<sub>43</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 691.3325, Found: 691.3312.

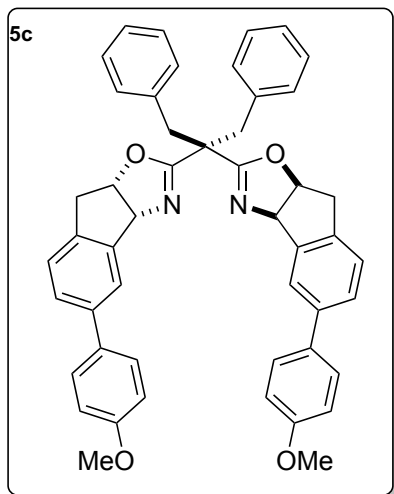
$\alpha_D^{23}$  (c = 0.52, CHCl<sub>3</sub>): +231.8°

Compound **5b** (<sup>1</sup>H NMR, 600 MHz, CDCl<sub>3</sub>)



Compound **5b** ( $^{13}\text{C}$  NMR, 151 MHz,  $\text{CDCl}_3$ )





(3*a**R*,3*a'**R*,8*a**S*,8*a'**S*)-2,2'-(1,3-diphenylpropane-2,2-diyl)bis(5-(4-methoxyphenyl)-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**5c**) A 10 mL screw cap reaction tube was charged with S-Phos palladacycle gen. 4 catalyst (2.0 mg, 2.5  $\mu$ mol, 0.05 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.065 g, 0.200 mmol, 4.00 equiv), (4-methoxyphenyl)boronic acid (0.030 g, 0.200 mmol, 4.00 equiv), and bis(oxazoline) **4.3** (0.050 g, 0.050 mmol, 1.00 equiv). The tube was purged with nitrogen for 5 min, and 1 mL PhMe was added. The reaction mixture was sparged using a balloon filled with argon for 10 min. The tube was fitted with a fresh, unpunctured PTFE screw cap and sealed with parafilm. The reaction was heated in an oil bath at 100 °C for 16 h, then cooled to room temperature. The mixture was then filtered over a plug of Celite and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 10/90 → 40/60) to afford **5c** (0.036 g, 0.050 mmol, >99%).

A procedure detailing the synthesis of this ligand on larger scale is described later in the SI ([hyperlink](#))

### Physicochemical Properties

White solid

**mp:** 172-174 °C (decomposition)

**TLC** (30% EtOAc/Hex) *R<sub>f</sub>* = 0.24 (UV/Magic)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.62 (d, *J* = 1.7 Hz, 2H), 7.55 (td, *J* = 6.8, 2.0 Hz, 6H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.02 – 6.97 (m, 4H), 6.92 (tt, *J* = 6.5, 2.1 Hz, 2H), 6.80 – 6.73 (m, 8H), 5.64 (d, *J* = 7.7 Hz, 2H), 5.36 (ddd, *J* = 7.8, 6.6, 1.2 Hz, 2H), 3.86 (s, 6H), 3.39 (dd, *J* = 18.1, 6.6 Hz, 2H), 3.28 (d, *J* = 14.3 Hz, 2H), 3.16 (d, *J* = 18.1 Hz, 2H), 3.09 (d, *J* = 14.3 Hz, 2H).

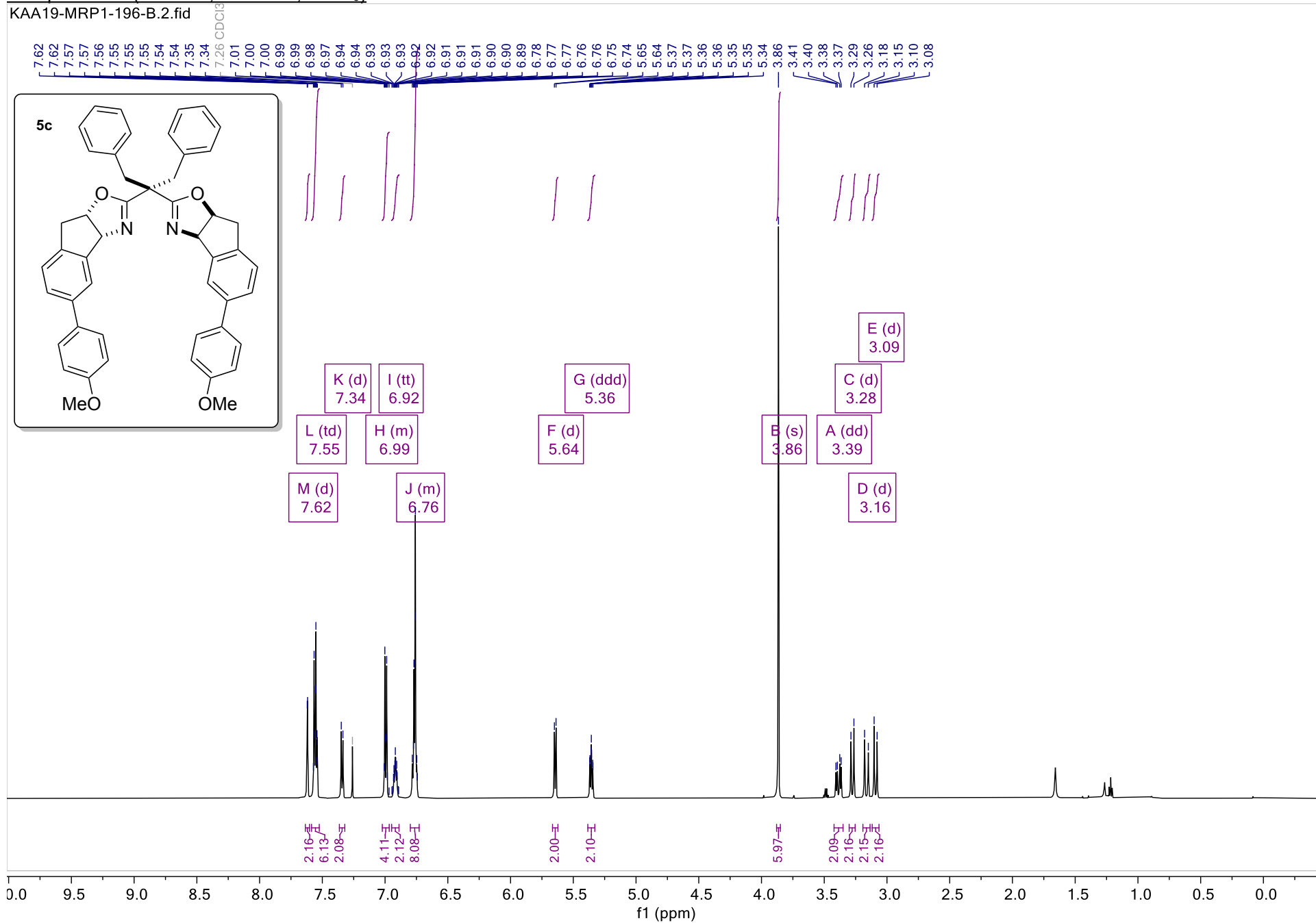
**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  167.7, 159.2, 142.3, 140.6, 138.4, 136.0, 133.8, 130.4, 128.3, 127.7, 127.3, 126.4, 125.5, 124.1, 114.3, 84.1, 76.5, 55.5, 47.6, 39.0, 38.7.

**HRMS** (ESI+): Calculated for C<sub>49</sub>H<sub>43</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 723.3223, Found: 723.3203.

$\alpha_D^{23}$  (c = 0.47, CHCl<sub>3</sub>): +312.4°

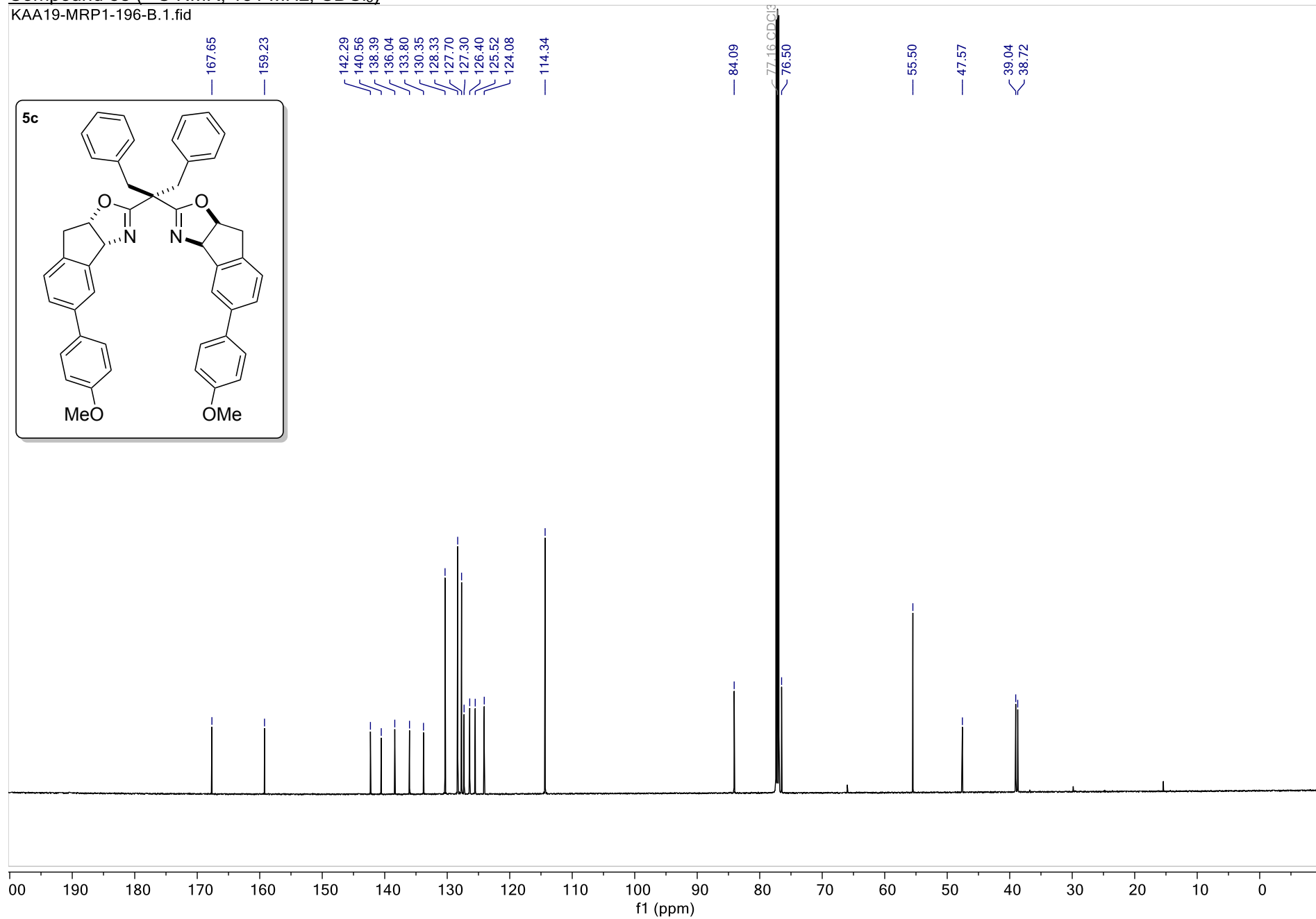
Compound **5c** ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )

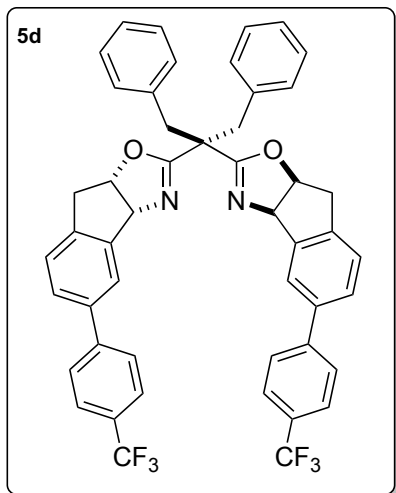
KAA19-MRP1-196-B.2.fid



Compound **5c** ( $^{13}\text{C}$  NMR, 151 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-196-B.1.fid





(3*aR*,3*a'R*,8*aS*,8*a'S*)-2,2'-(1,3-diphenylpropane-2,2-diyl)bis(5-(4-(trifluoromethyl)phenyl)-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**5d**) A 10 mL screw cap reaction tube was charged with S-Phos palladacycle gen. 4 catalyst (2.0 mg, 2.5  $\mu$ mol, 0.05 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.065 g, 0.200 mmol, 4.00 equiv), (4-(trifluoromethyl)phenyl)boronic acid (0.038 g, 0.200 mmol, 4.00 equiv), and bis(oxazoline) **4.3** (0.050 g, 0.050 mmol, 1.00 equiv). The tube was purged with nitrogen for 5 min, and 1 mL PhMe was added. The reaction mixture was sparged using a balloon filled with argon for 10 min. The tube was fitted with a fresh, unpunctured PTFE screw cap and sealed with parafilm. The reaction was heated in an oil bath at 100 °C for 16 h, then cooled to room temperature. The mixture was then filtered over a plug of Celite and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 30/70) to afford **5d** (0.035 g, 0.043 mmol, 87%).

### Physicochemical Properties

White solid

**mp:** 82-85 °C

**TLC** (30% EtOAc/Hex) *R<sub>f</sub>* = 0.21 (UV/Magic)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (s, 8H), 7.66 (d, *J* = 1.7 Hz, 2H), 7.60 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 6.91 (ddd, *J* = 8.6, 5.7, 2.4 Hz, 2H), 6.80 – 6.71 (m, 8H), 5.67 (d, *J* = 7.8 Hz, 2H), 5.38 (ddd, *J* = 7.9, 6.6, 1.2 Hz, 2H), 3.43 (dd, *J* = 18.3, 6.6 Hz, 2H), 3.29 (d, *J* = 14.2 Hz, 2H), 3.20 (d, *J* = 18.3 Hz, 2H), 3.10 (d, *J* = 14.3 Hz, 2H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.8, 144.7, 142.7, 140.2, 139.5, 136.0, 130.3, 129.4 (*J* = 32.7 Hz), 125.9 (*J* = 3.7 Hz), 124.5 (*J* = 272.7 Hz), 84.0, 76.4, 47.6, 39.1, 38.8.

**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>)  $\delta$  -62.32.

**HRMS** (ESI+): Calculated for C<sub>49</sub>H<sub>37</sub>N<sub>2</sub>O<sub>2</sub>F<sub>6</sub> [M+H]<sup>+</sup>: 799.2759, Found: 799.2734.

$\alpha_D^{23}$  (c = 0.45, CHCl<sub>3</sub>): +229.3°

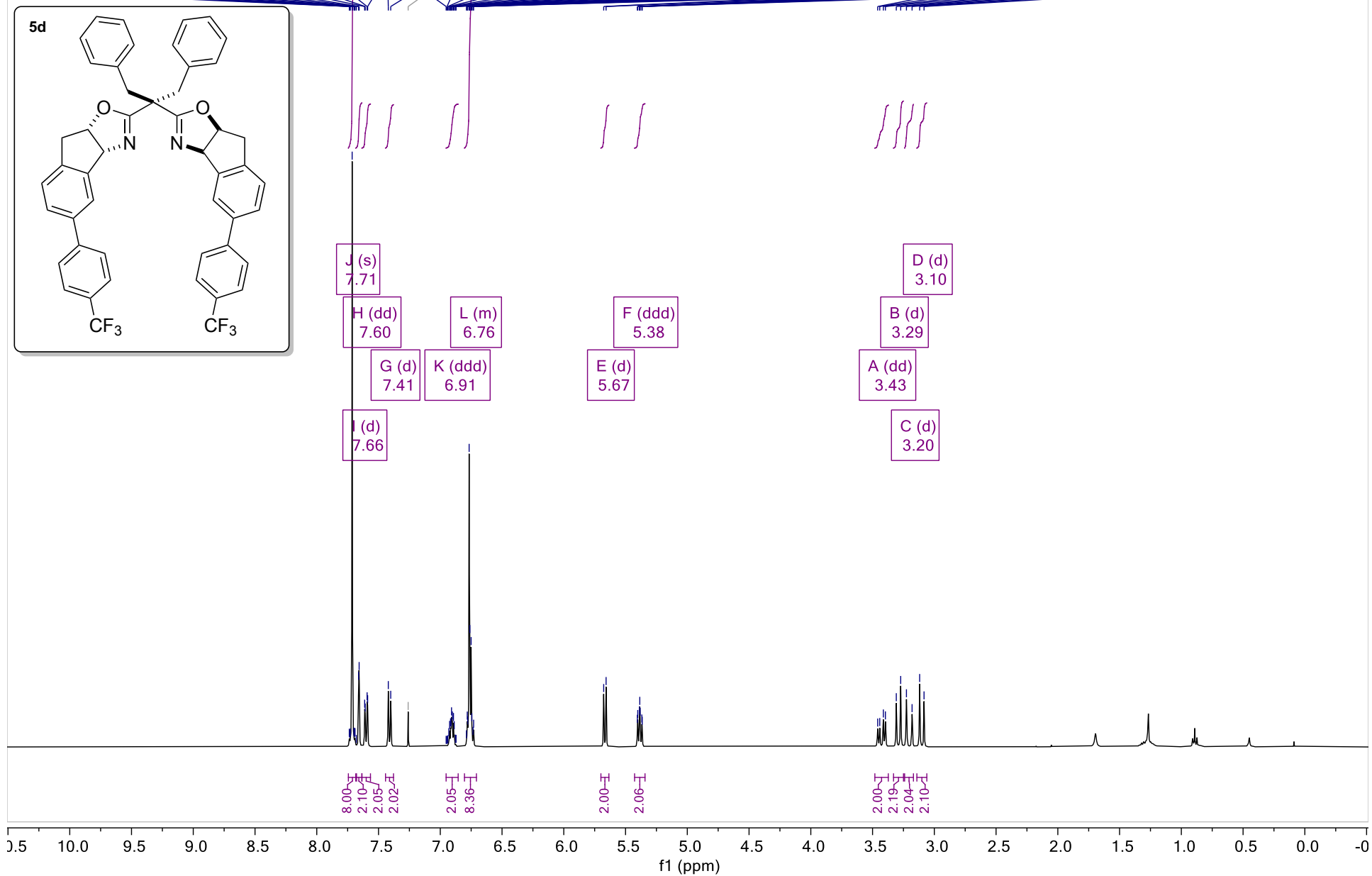
Compound **5d** (<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>)

KAA19-MRP1-197-dry-1.1.fid

Advisor Johnson

Grant number 5120786

Onyen alleyk





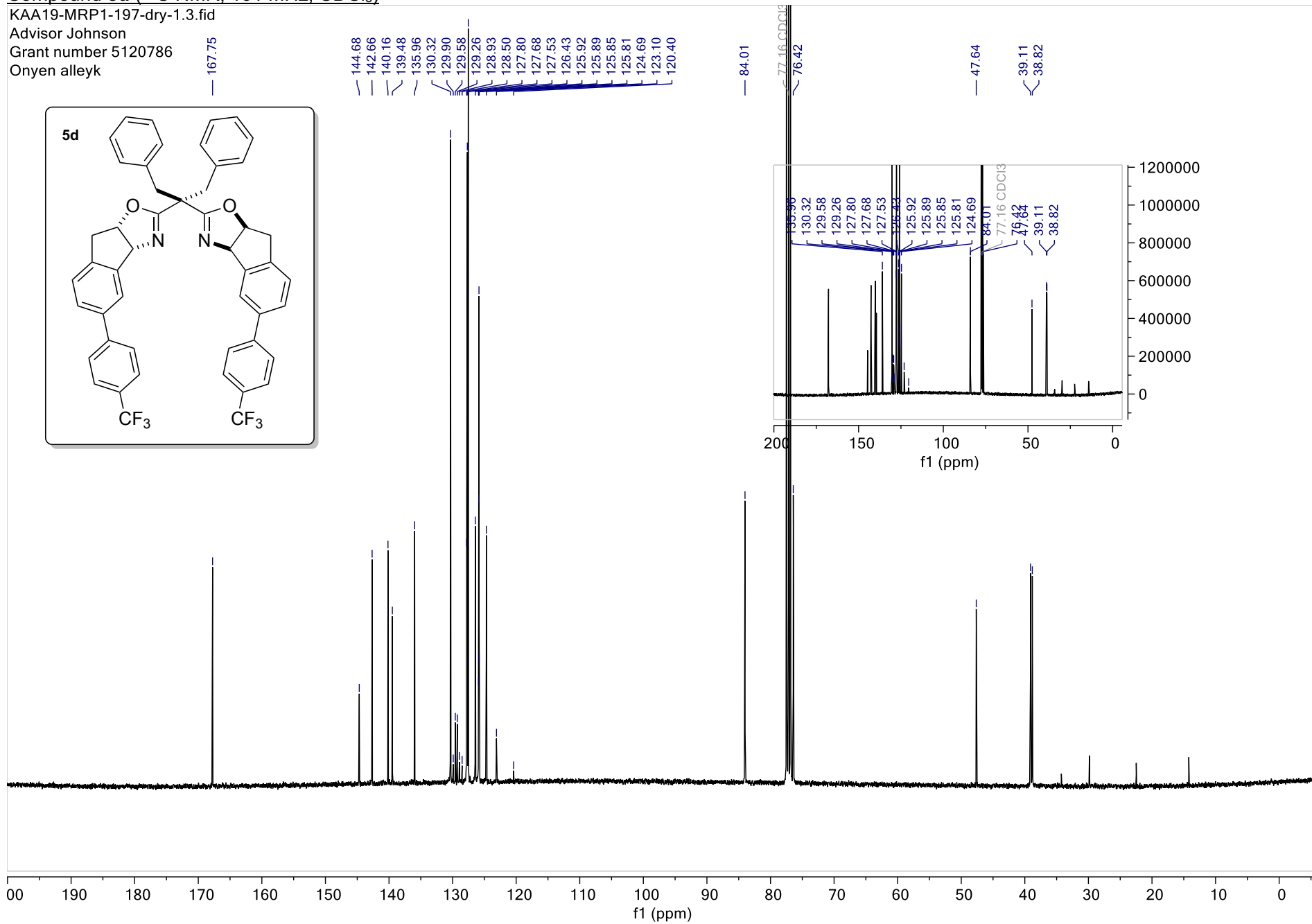
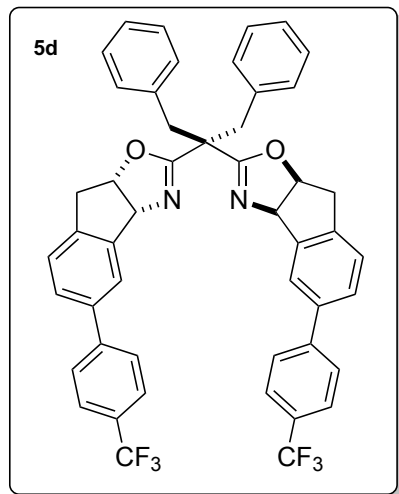
Compound **5d** ( $^{13}\text{C}$  NMR, 101 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-197-dry-1.3.fid

Advisor Johnson

Grant number 5120786

Onyen alleyk



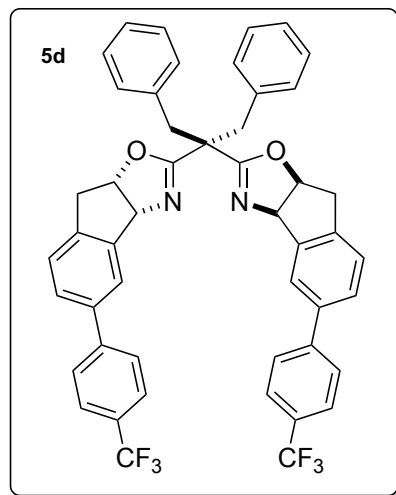
Compound **5d** ( $^{19}\text{F}$  NMR, 377 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-197-dry-1.4.fid

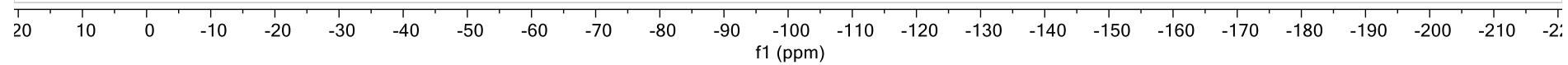
Advisor Johnson

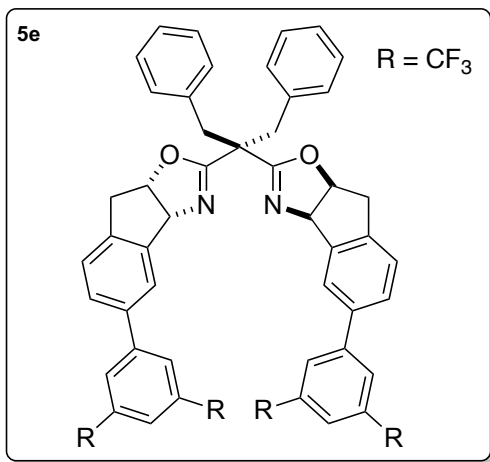
Grant number 5120786

Onyen alleyk



-62.32





(3*a**R*,3*a'**R*,8*a**S*,8*a'**S*)-2,2'-(1,3-diphenylpropane-2,2-diyl)bis(5-(3,5-bis(trifluoromethyl)phenyl)-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**5e**) A 10 mL screw cap reaction tube was purged under a stream of nitrogen and charged with S-Phos palladacycle gen. 4 catalyst (2.0 mg, 2.5 μmol, 0.05 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.065 g, 0.200 mmol, 4.00 equiv), (3,5-bis(trifluoromethyl)phenyl)boronic acid (0.052 g, 0.200 mmol, 4.0 equiv), bis(oxazoline) **4.3** (0.033 g, 0.050 mmol, 1.00 equiv) and 1 mL anhydrous PhMe. The tube was sparged using a balloon filled with argon for 10 min and fitted with an unpunctured PTFE screw cap. The reaction was heated in an oil bath at 100 °C for 16 h, then cooled to room temperature. The mixture was then filtered over a plug of Celite and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100 → 30/70) to afford **5e** (0.029 g, 0.032 mmol, 64%).

### Physicochemical Properties

White solid

**mp**: 235 °C (decomposition)

**TLC** (30% EtOAc/Hex) *R<sub>f</sub>* = 0.29 (UV/Magic)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 8.03 – 8.00 (m, 4H), 7.88 – 7.84 (m, 2H), 7.63 (d, *J* = 1.8 Hz, 2H), 7.60 (dd, *J* = 7.9, 1.9 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 6.91 – 6.85 (m, 2H), 6.82 – 6.77 (m, 4H), 6.75 (dd, *J* = 8.1, 7.2 Hz, 4H), 5.66 (d, *J* = 7.8 Hz, 2H), 5.39 (ddd, *J* = 7.8, 6.6, 1.2 Hz, 2H), 3.48 – 3.41 (m, 2H), 3.29 (d, *J* = 14.2 Hz, 2H), 3.21 (d, *J* = 18.3 Hz, 2H), 3.12 (d, *J* = 14.3 Hz, 2H).

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 167.9, 143.2, 143.1, 141.0, 138.0, 135.9, 132.3 (*J* = 33.2 Hz), 130.3, 127.72, 127.69, 127.4 (*J* = 3.5 Hz), 126.4, 126.2, 124.7, 123.5 (*J* = 272.8 Hz), 121.1-120.9 (m), 84.0, 76.3, 47.7, 39.1, 38.9.

**<sup>19</sup>F NMR** (565 MHz, CDCl<sub>3</sub>) δ -62.8.

**HRMS** (ESI+): Calculated for C<sub>51</sub>H<sub>35</sub>N<sub>2</sub>O<sub>2</sub>F<sub>12</sub> [M+H]<sup>+</sup>: 935.2507, Found: 935.2491.

**α<sub>D</sub><sup>23</sup>** (c = 0.37, CHCl<sub>3</sub>): +185.0°

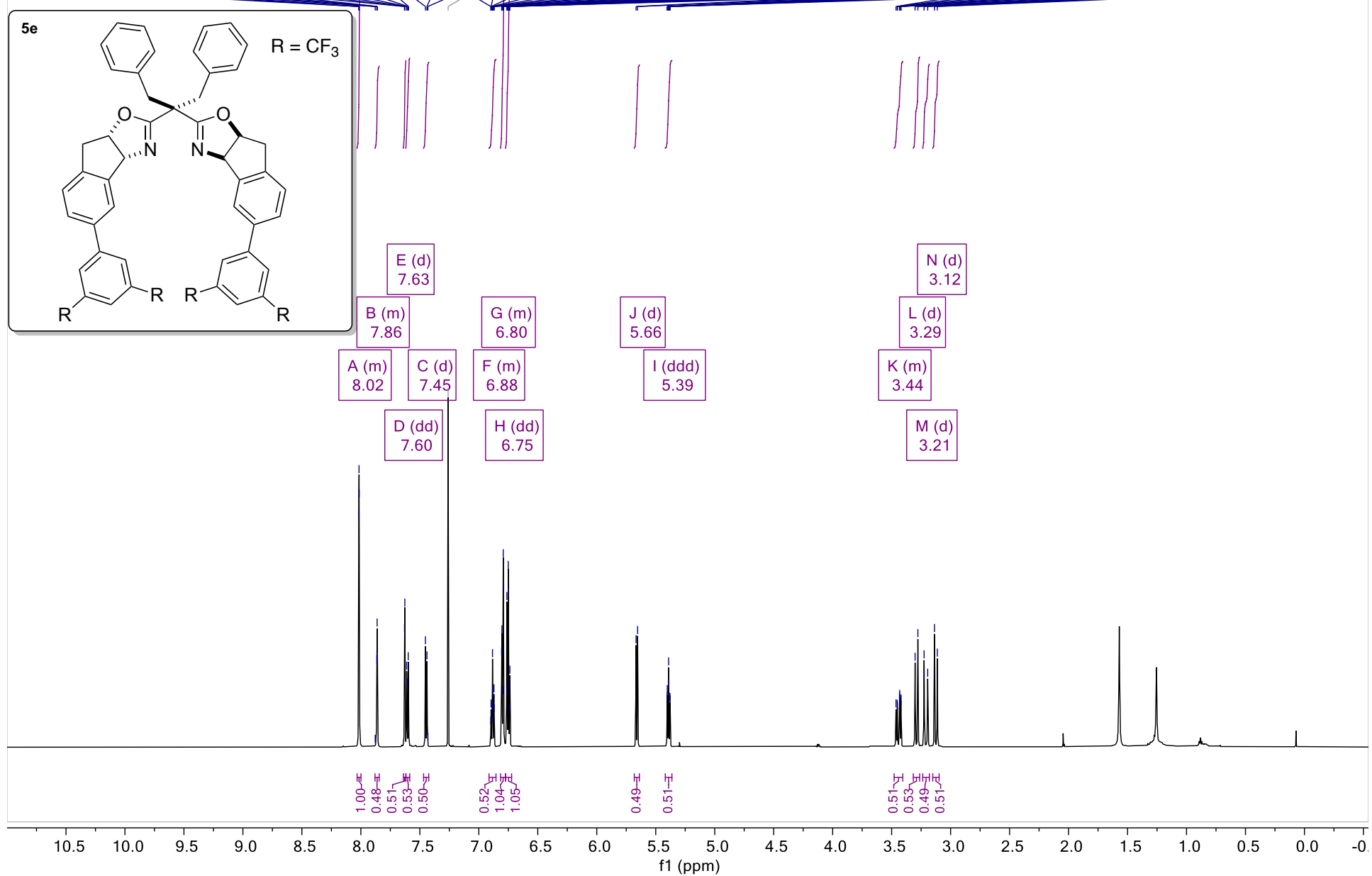
Compound **5e** ( $^1\text{H}$  NMR, 600 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-191-pure.1.fid

Advisor Johnson

Grant number 5120786

PROTON  $\text{CDCl}_3$  (C:\data\alek\K) QC1-drop-off 28



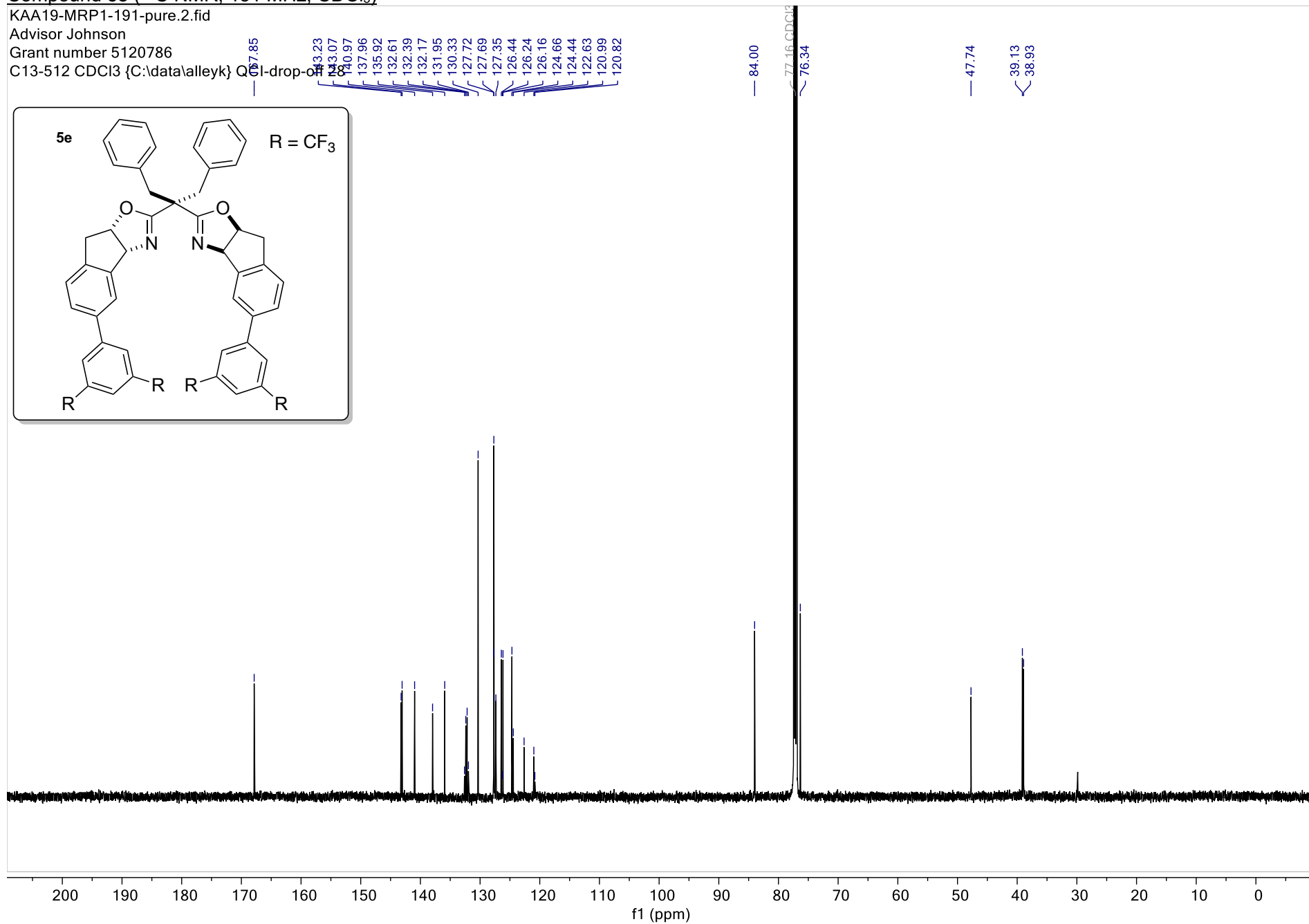
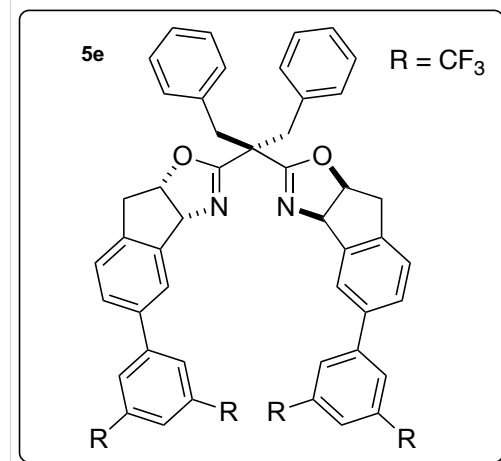
Compound **5e** ( $^{13}\text{C}$  NMR, 151 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-191-pure.2.fid

Advisor Johnson

Grant number 5120786

C13-512  $\text{CDCl}_3$  {C:\data\alleyk} QCI-drop-off 26



Compound **5e** ( $^{19}\text{F}$  NMR, 565 MHz,  $\text{CDCl}_3$ )

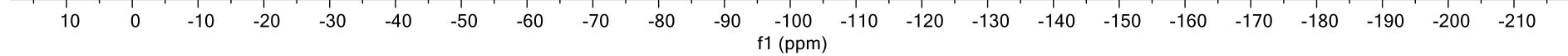
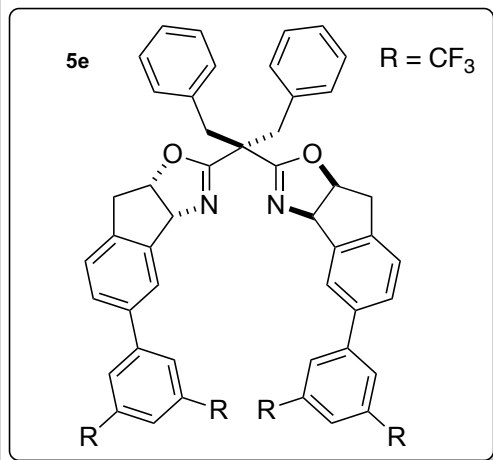
KAA19-MRP1-191-E.15.fid

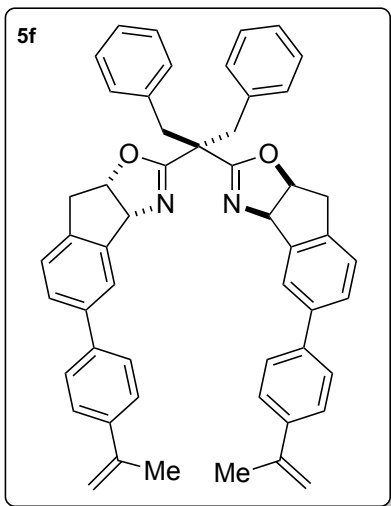
Advisor JOhnson

Grant number 5120786

F19-16  $\text{CDCl}_3$  {C:\data\alleyk} QCI-drop-off 6

— -62.78





(3*a**R*,3*a'**R*,8*a**S*,8*a'**S*)-2,2'-(1,3-diphenylpropane-2,2-diyl)bis(5-(4-(prop-1-en-2-yl)phenyl)-3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole) (**5f**) A 10 mL screw cap reaction tube was purged under a stream of nitrogen and charged with [1,1' - Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (2.0 mg, 3.0  $\mu$ mol, 0.06 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.065 g, 0.200 mmol, 4.00 equiv), potassium isopropenyltrifluoroborate (0.018 g, 0.120 mmol, 2.4 equiv), bis(oxazoline) **4.3** (0.033 g, 0.050 mmol, 1.00 equiv), 0.25 mL anhydrous THF, and 0.25 mL distilled H<sub>2</sub>O. The tube was sparged using a balloon filled with argon for 10 min and fitted with an unpunctured PTFE screw cap. The reaction was heated in an oil bath at 90 °C for 16 h, then cooled to room temperature. The mixture was quenched with 2 mL H<sub>2</sub>O. The aqueous layer was extracted with EtOAc (5 x 2 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100  $\rightarrow$  30/70) to afford **5f** (0.028 g, 0.048 mmol, 96%).

### Physicochemical Properties

White solid

**mp:** 95-98 °C

**TLC** (30% EtOAc/Hex) *R<sub>f</sub>* = 0.30 (UV/Magic)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.53 (d, *J* = 1.7 Hz, 2H), 7.47 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.25 (d, *J* = 7.4 Hz, 1H), 6.97 (tt, *J* = 7.0, 1.6 Hz, 2H), 6.83 – 6.71 (m, 8H), 5.59 (d, *J* = 7.8 Hz, 2H), 5.42 – 5.37 (m, 2H), 5.32 (ddd, *J* = 7.9, 6.7, 1.3 Hz, 2H), 5.09 (p, *J* = 1.5 Hz, 2H), 3.34 (dd, *J* = 18.2, 6.7 Hz, 2H), 3.25 (d, *J* = 14.3 Hz, 2H), 3.16 – 3.03 (m, 4H), 2.20 – 2.15 (m, 6H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.6, 143.3, 141.7, 141.1, 139.2, 136.0, 130.3, 127.7, 126.4, 126.1, 124.9, 123.0, 112.5, 84.0, 76.4, 47.5, 39.1, 38.7, 22.2.

**HRMS** (ESI<sup>+</sup>): Calculated for C<sub>41</sub>H<sub>39</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 591.3011, Found: 591.2995.

$\alpha_D^{23}$  (c = 0.45, CHCl<sub>3</sub>): +199.3°

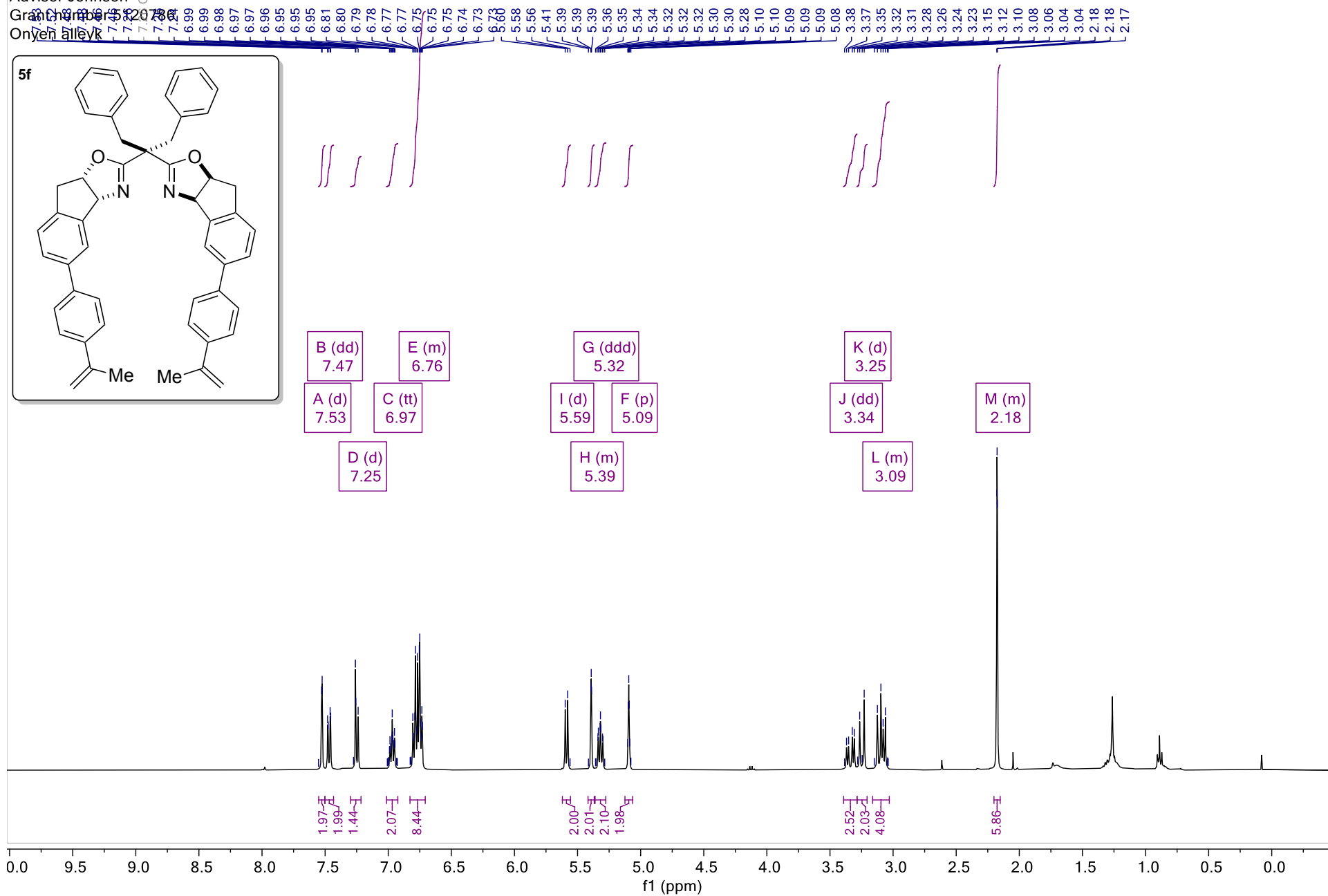
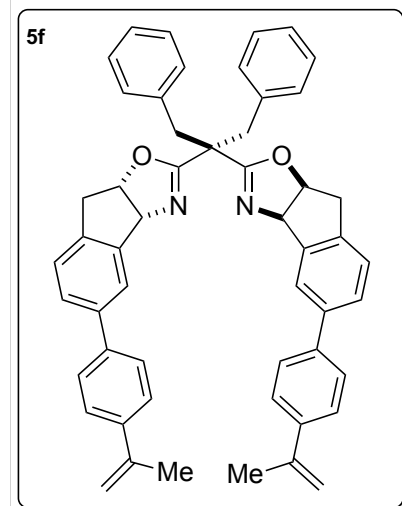
Compound **5f** (<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>)

KAA19-MRP1-199-dry-1.8.fid

Advisor Johnson

Grant number 5120736

Onyen Alek





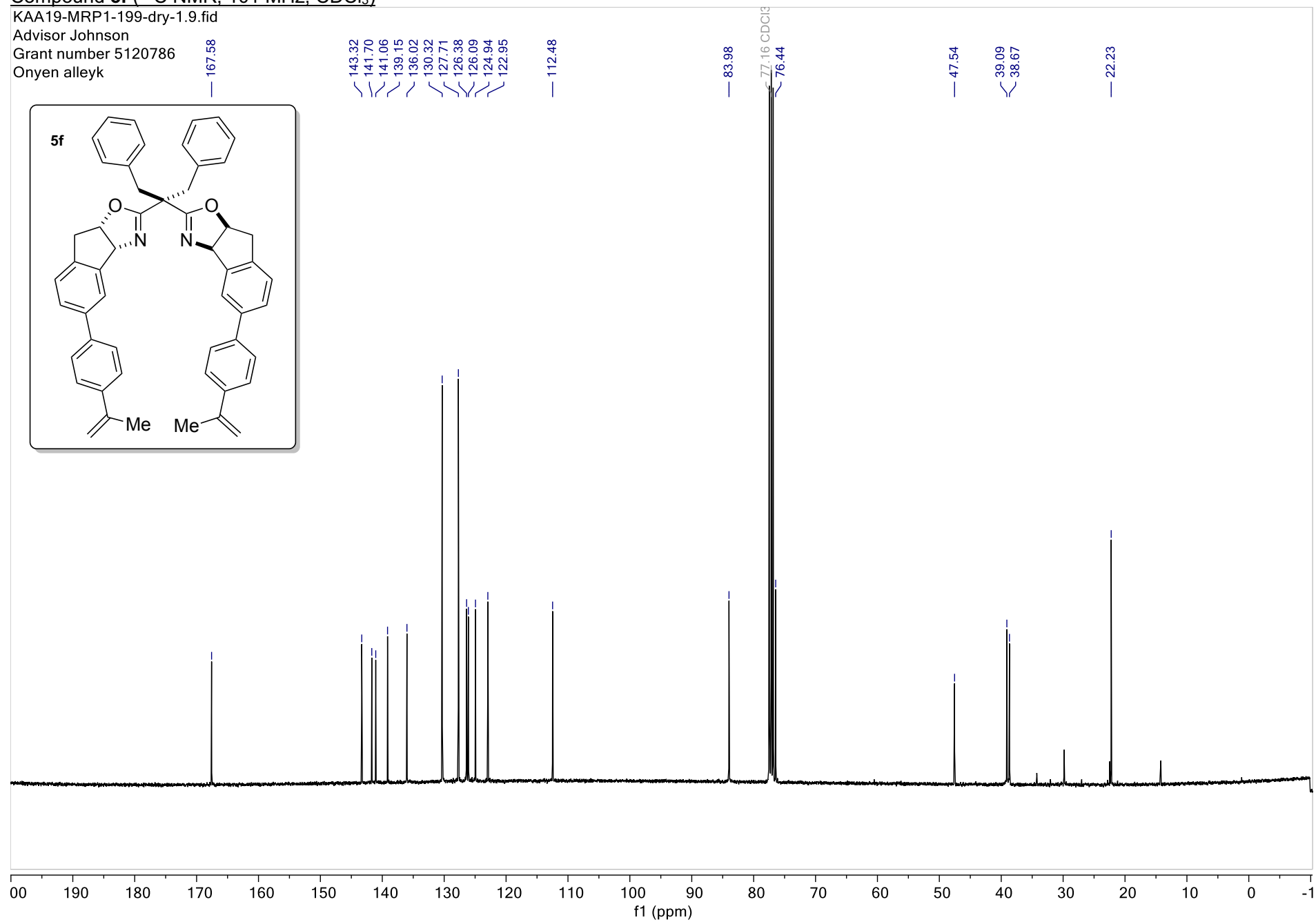
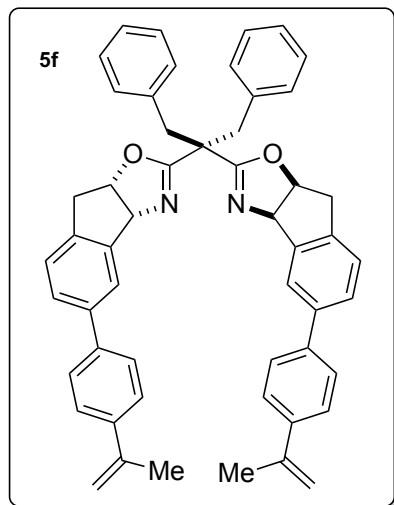
Compound **5f** ( $^{13}\text{C}$  NMR, 101 MHz,  $\text{CDCl}_3$ )

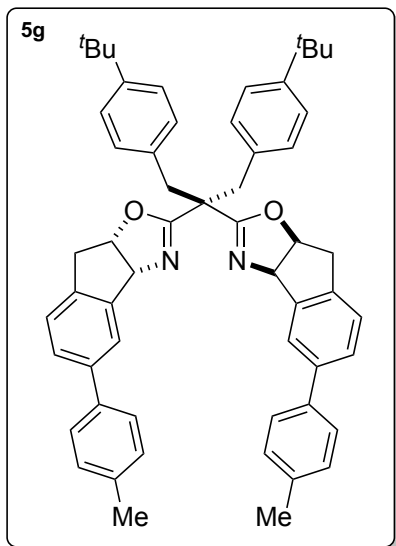
KAA19-MRP1-199-dry-1.9.fid

Advisor Johnson

Grant number 5120786

Onyen alleyk





(3a*R*,3a'*R*,8a*S*,8a'*S*)-2,2'-(1,3-bis(4-(*tert*-butyl)phenyl)propane-2,2-diyl)bis(5-(*p*-tolyl)-3a,8a-dihydro-8H-indeno[1,2-d]oxazole) (**5g**) A 10 mL screw cap reaction tube was purged under a stream of nitrogen and charged with S-Phos palladacycle gen. 4 catalyst (2.0 mg, 2.5  $\mu$ mol, 0.05 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.065 g, 0.200 mmol, 4.00 equiv), (4-methylphenyl)boronic acid (0.027 mg, 0.200 mmol, 4.00 equiv), bis(oxazoline) **4.3** (0.039 g, 0.050 mmol, 1.00 equiv) and 1 mL anhydrous PhMe. The tube was sparged using a balloon filled with argon for 10 min and fitted with an unpunctured PTFE screw cap. The reaction was heated in an oil bath at 100 °C for 16 h, then cooled to room temperature. The mixture was then filtered over a plug of Celite and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 0/100  $\rightarrow$  30/70) to afford **5g** (0.034 g, 0.042 mmol, 84%).

### Physicochemical Properties

White solid

mp: 85-89 °C

TLC (20% EtOAc/Hex) R<sub>f</sub> = 0.50 (UV/Magic)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.76 (d, *J* = 1.8 Hz, 2H), 7.62 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 4H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.3 Hz, 4H), 6.83 (d, *J* = 8.2 Hz, 4H), 6.70 (d, *J* = 8.1 Hz, 4H), 5.68 (d, *J* = 7.8 Hz, 2H), 5.42 – 5.34 (m, 2H), 3.40 (dd, *J* = 18.2, 6.8 Hz, 2H), 3.24 (d, *J* = 14.2 Hz, 2H), 3.14 (d, *J* = 18.1 Hz, 2H), 3.03 (d, *J* = 14.3 Hz, 2H), 2.40 (s, 6H), 1.13 (s, 18H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.8, 149.1, 142.3, 140.7, 138.9, 138.0, 137.1, 133.0, 130.1, 129.6, 127.3, 127.1, 125.5, 124.6, 124.3, 83.8, 76.7, 47.8, 39.2, 38.0, 34.3, 31.4, 21.2.

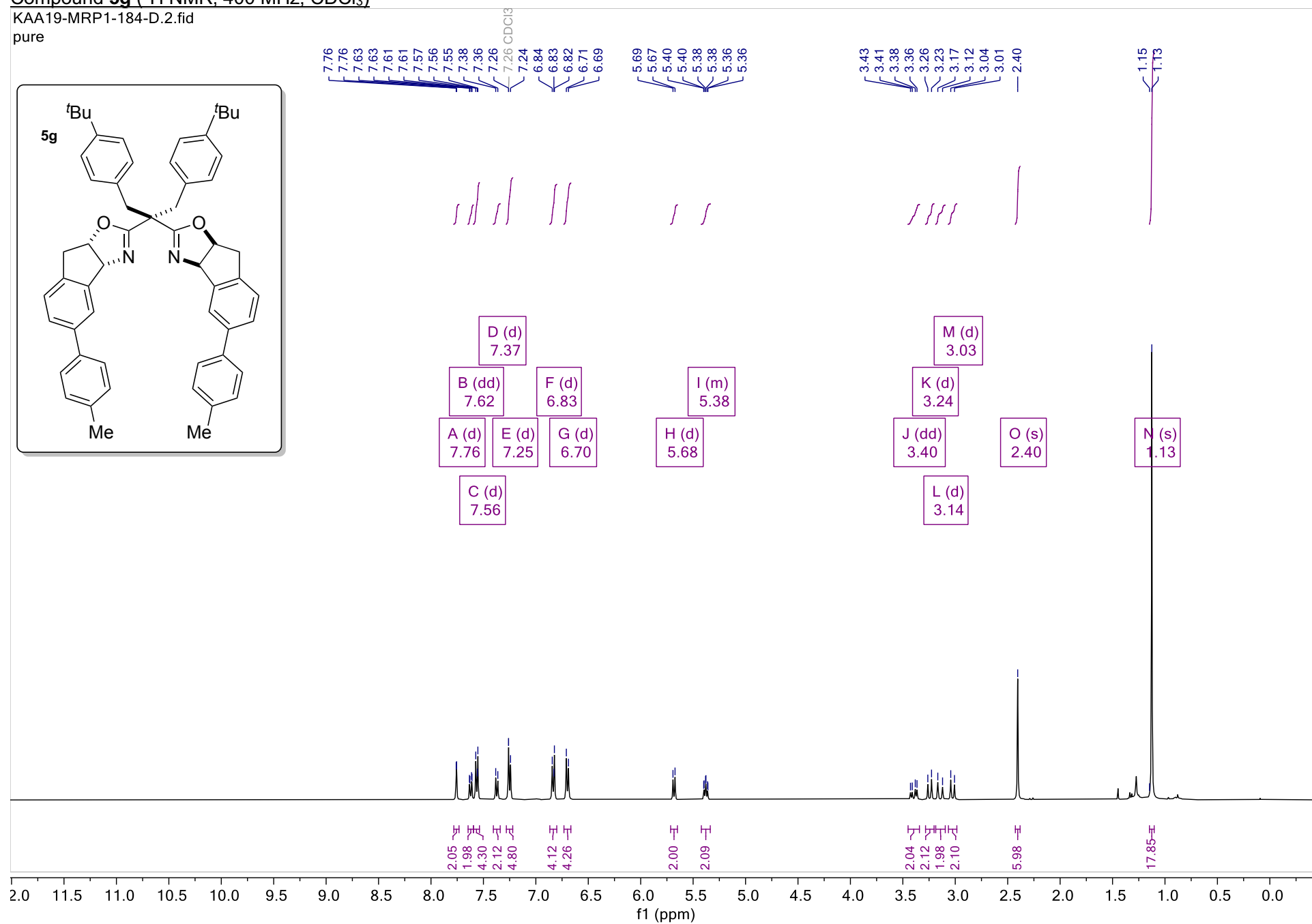
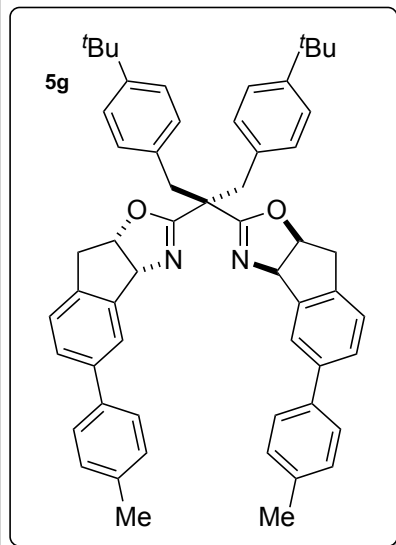
HRMS (ESI+): Calculated for C<sub>57</sub>H<sub>59</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 803.4577, Found: 803.4558.

$\alpha_D^{23}$  (c = 0.35, CHCl<sub>3</sub>): +351.5°

Compound **5g** (<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>)

KAA19-MRP1-184-D.2.fid

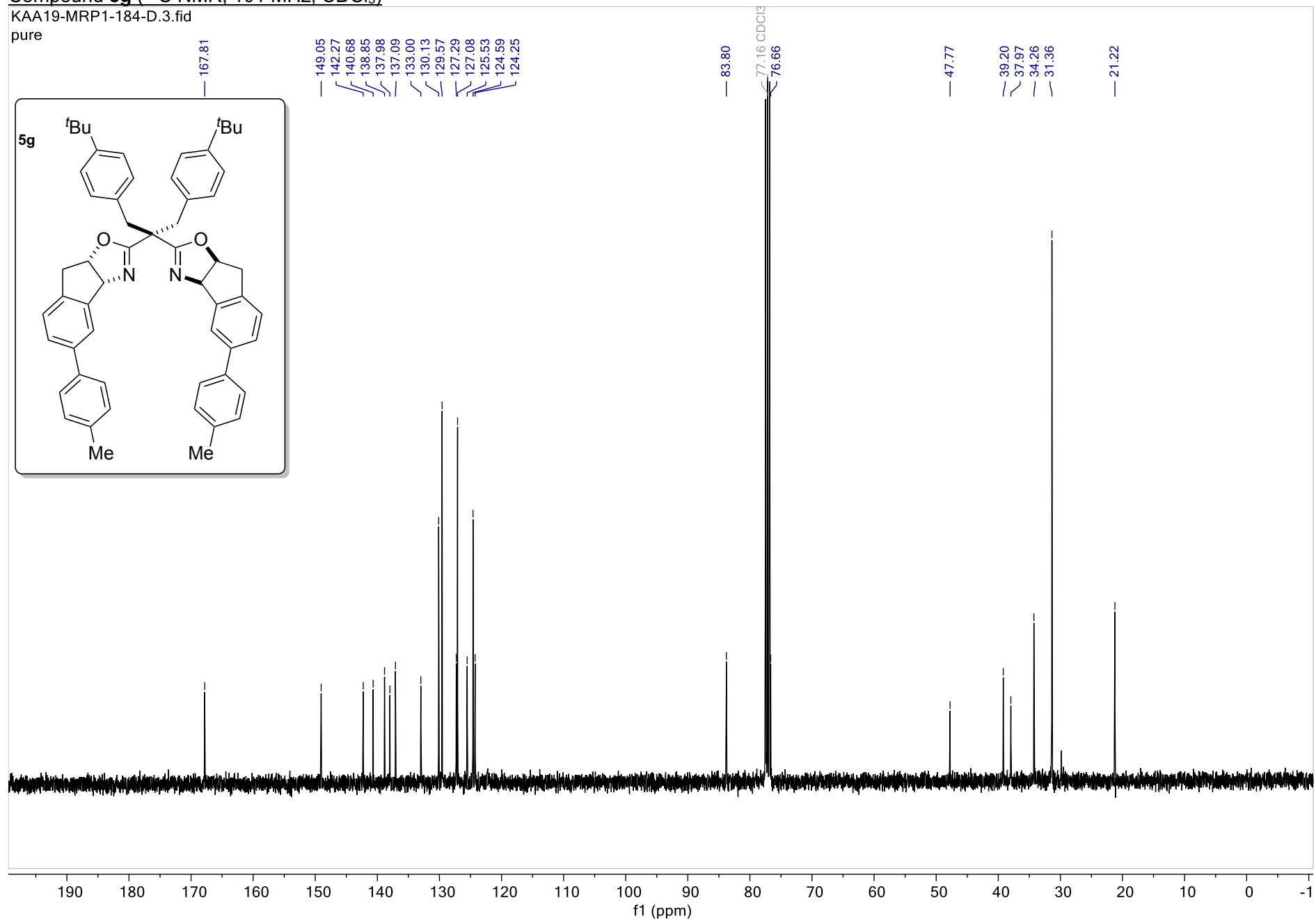
pure



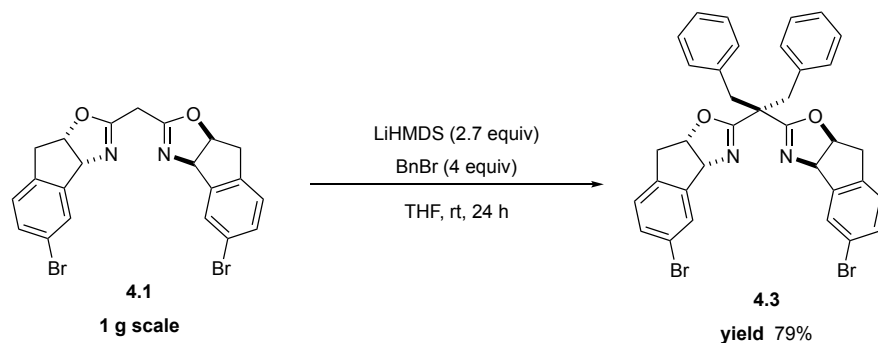
Compound **5g** ( $^{13}\text{C}$  NMR, 101 MHz,  $\text{CDCl}_3$ )

KAA19-MRP1-184-D.3.fid

pure



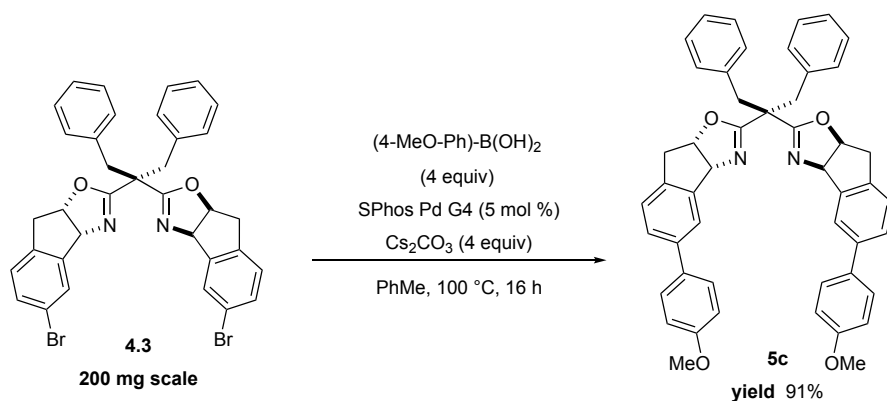
## Gram Scale Benzyl Bridge Installation



### Scale-up Procedure:<sup>13</sup>

A 250 mL flame-dried round-bottomed flask was cooled under a stream of nitrogen before bis(oxazoline) **4.1** (1.00 g, 2.05 mmol, 1.00 equiv) was added followed by 40 mL THF and benzyl bromide (0.973 mL, d = 1.44 g/mL, 8.19 mmol, 4.00 equiv). The suspension was cooled to 0 °C in an ice bath, and LiHMDS (1M in THF, 5.53 mL, 5.53 mmol, 2.70 equiv) was added dropwise over 5 min. The reaction mixture was warmed to room temperature and stirred for 24 h. Reaction progress was monitored by <sup>1</sup>H NMR analysis of an aliquot of the reaction mixture. The reaction was then cooled to 0 °C in an ice bath. The reaction was terminated by the dropwise addition of 20 mL aq. saturated NH<sub>4</sub>Cl solution. The reaction was then transferred to a separatory funnel and diluted with H<sub>2</sub>O. The aqueous layer was extracted with DCM (5 x 20 mL). The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The brown crude solids were purified by trituration from EtOH to afford **4.3** (1.080 g, 1.62 mmol, 79%). The spectral properties were consistent with the data reported above. [Characterization Data Hyperlink](#)

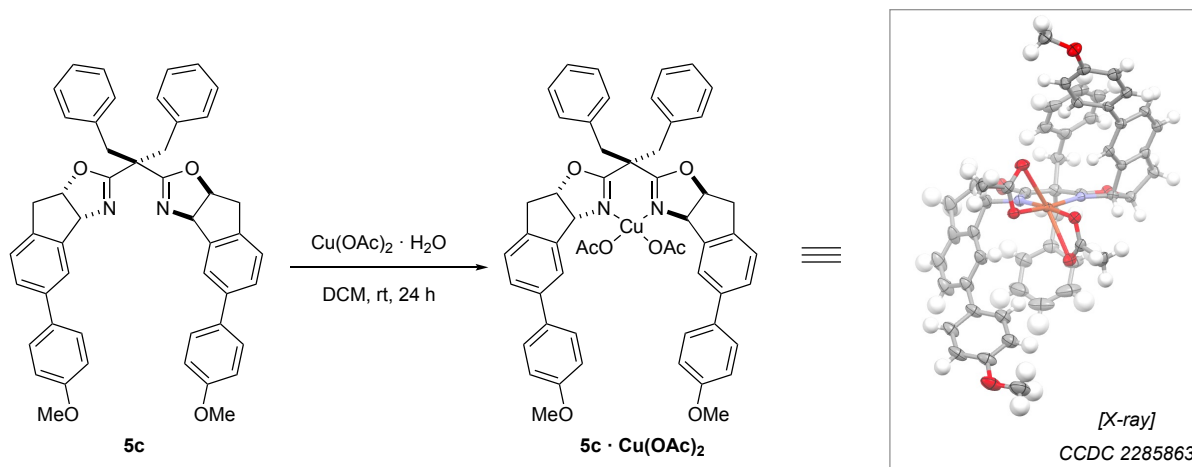
## Larger Scale Cross-Coupling



### Scale-up Procedure:

A 100 mL round-bottomed flask was charged with S-Phos palladacycle gen. 4 catalyst (15 mg, 19  $\mu$ mol, 0.06 equiv), Cs<sub>2</sub>CO<sub>3</sub> (0.350 g, 1.07 mmol, 3.60 equiv), (4-methoxyphenyl)boronic acid (0.200 g, 1.32 mmol, 4.40 equiv), and bis(oxazoline) **4.3** (0.200 g, 0.300 mmol, 1.00 equiv). The flask was purged with nitrogen for 10 min, and 7 mL PhMe was added. The reaction mixture was sparged using a balloon filled with argon for 10 min. The flask was fitted with a fresh, unpunctured rubber septum and sealed with electrical tape. The reaction was heated in an oil bath at 100 °C for 16 h, then cooled to room temperature. The mixture was then filtered over a plug of Celite and evaporated under reduced pressure. The brown crude solids were purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Hex = 10/90  $\rightarrow$  40/60) to afford **5c** (0.197 g, 0.272 mmol, 91%). The spectral properties were consistent with the data reported above. [Characterization Data Hyperlink](#)

## Copper (II) Acetate-Bis(oxazoline) Complexation and X-Ray Quality Crystallization



### Complexation:

A 1-dram vial with a stir flea was charged with bis(oxazoline) **5c** (20 mg, 27.7  $\mu\text{mol}$ , 1.00 equiv) and copper (II) acetate monohydrate ( $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ , 5.5 mg, 27.7  $\mu\text{mol}$ , 1.00 equiv). The solids were suspended in 1 mL DCM, sealed with a PTFE cap, and stirred for 24 h at rt. The resulting cloudy blue solution was used directly in the crystallization step. (NOTE: The complex is modestly soluble in DCM. Most of the ligands generated in this study do form DCM-soluble complexes with copper (II) acetate and form clear blue solutions when the complexation is complete.)

### Crystallization:

X-Ray-quality crystals were grown using a vial-in-vial vapor diffusion protocol. The 1-dram vial containing the catalyst solution was placed inside a 20 mL scintillation vial containing 5 mL pentane. The scintillation vial was capped with a plastic screw cap and the catalyst solution was allowed to precipitate. Blue crystals formed within 24 h and were allowed to continue growth over the course of 5 days. The solvent was then evaporated, and the dark blue crystals were collected for X-Ray analysis. (NOTE: A teal amorphous solid also formed on the bottom of the 1-dram vial during crystallization, which was not analyzed further.)

### **X-Ray Diffraction Data for Complex **5c** · $\text{Cu}(\text{OAc})_2$**

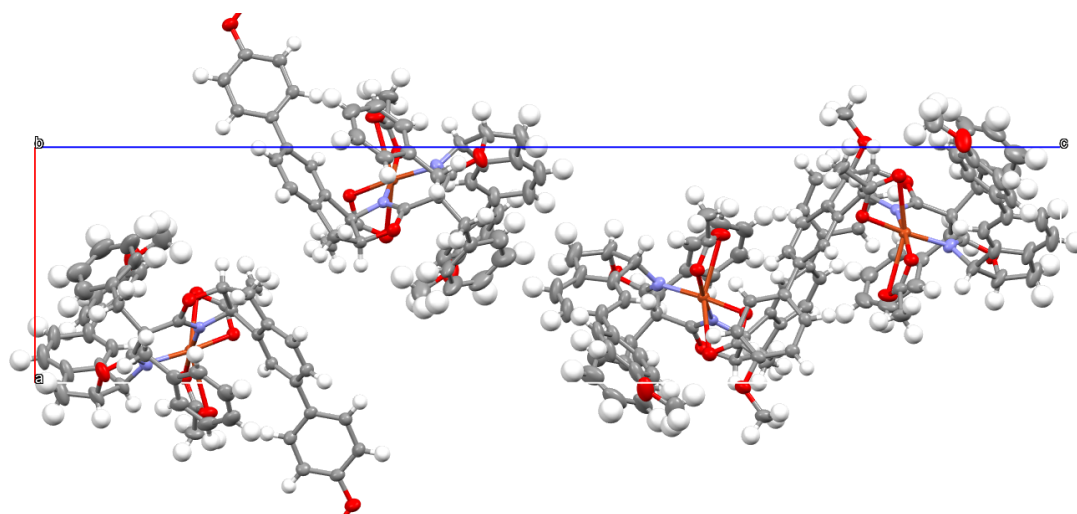
#### **Procedure:**

The above structure was crystallized by vapor diffusion (inner solvent: DCM, outer solvent: pentane) as a blue crystal (approximate dimensions 0.010 x 0.050 x 0.200 mm<sup>3</sup>) and placed on the tip of a MiTeGen using a minimal amount of Paratone. The crystal was mounted and centered on a Bruker D8 VENTURE diffractometer at 150 K. A single set of 180 scans was taken for unit cell determination using a Cu K $\alpha$  radiation source ( $\lambda = 1.54184 \text{ \AA}$ ). Data was collected using  $\omega$  and  $\phi$  scans. After integration, data to a resolution of 0.83  $\text{\AA}$  was reduced using SAINT. The space group was determined to be  $P2_12_12_1$  and the structure was solved using Superflip and refined using the Oxford University Crystals for Windows systems. The solution provided all non-hydrogen atoms, which were refined anisotropically. The hydrogen atoms were added geometrically to the existing structure and refined isotropically. The Fourier difference map showed additional electron density, likely resulting from partial occupation of  $\text{CH}_2\text{Cl}_2$  and pentane. Attempts at solvent modeling were unsuccessful, thus PLATON SQUEEZE was implemented.<sup>14</sup> SQUEEZE implementation identified 133 electrons in a solvent accessible void of 445  $\text{\AA}^3$ . This equates to the electron density of three  $\text{CH}_2\text{Cl}_2$  molecules in a void with the approximate volume of eight  $\text{CH}_2\text{Cl}_2$  molecules. The final full-matrix least squares refinement converged to  $R1 = 0.0401$  and  $wR2 = 0.1062$  ( $F^2$ , all data) with a Flack parameter of 0.00(2).

### Crystallographic Data for 23100

Molecular Formula	C <sub>53</sub> H <sub>48</sub> CuN <sub>2</sub> O <sub>8</sub>
Molecular Weight	904.52
Approximate Crystal Dimensions	0.010 x 0.050 x 0.200 mm <sup>3</sup>
Temperature	150 K
Radiation Source	Cu K $\alpha$ ( $\lambda$ = 1.54184 Å)
Crystal System	Orthorhombic
Space Group	P2(1)2(1)2(1)
a	9.3520(3) Å
b	13.3330(4) Å
c	40.7850(13) Å
$\alpha$	90°
$\beta$	90°
$\gamma$	90°
Volume	5085.5(3) Å <sup>3</sup>
Z	4
Density (calcd)	1.181 g/mL
F <sub>000</sub>	1892
Absorption coef., $\mu_{\text{abs}}$	1.026 mm <sup>-1</sup>
$\Theta$ Range	3.4875 to 68.3674°
Index Range	-11 $\leq$ h $\leq$ 11, 0 $\leq$ k $\leq$ 16, 0 $\leq$ l $\leq$ 49
Collected Reflections	66857
Independent Reflections	9285
Observed Reflections	8764
Data/Restraints/Parameters	8764/0/578
Goof on F <sup>2</sup>	1.0068
Final R indexes [ $I > 2\sigma(I)$ ]	R1 = 0.0426, wR2 = 0.1086
Final R indexes (all)	R1 = 0.0401, wR2 = 0.1062
Flack Parameter	0.00(2)
Largest Diff. peak and Hole	-0.36 and 0.23 Å

#### Cell Plot Along b-axis:







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