

# Heterogeneous Heterobimetallic Catalysis Enabling Expeditious Access to CF<sub>3</sub>-Containing *vic*-Amino Alcohols

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## 1. General Methods

### 1-1. Reactions and purifications

Unless otherwise noted, all reactions were carried out in an oven-dried glassware fitted with a 3-way glass stopcock under an argon atmosphere with magnetically stirred chips. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Thin layer chromatography (TLC) was performed on Merck TLC plates (0.25 mm) pre-coated with silica gel 60 F254 and visualized by UV quenching and staining with KMnO<sub>4</sub> or ninhydrine. Flash column chromatography was performed on a Biotage Isolera Spektra One with a Rediseq column.

### 1-2. Characterizations

Infrared (IR) spectra were recorded on a HORIBA FT210 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL ECS-400, a Bruker AVANCE III HD400 or a Bruker AVANCE III 500. Chemical shifts ( $\delta$ ) are given in ppm relative to residual solvent peaks.<sup>1</sup> Data for <sup>1</sup>H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), q (quartet), m (multiplet), br (broad). For <sup>19</sup>F NMR, chemical shifts were reported in the scale relative to PhCF<sub>3</sub> ( $\delta$  -62.7680 ppm in CDCl<sub>3</sub>) as an external reference. High performance liquid chromatography (HPLC) analysis was performed on Jasco analytical instruments with single pump and UV detector. Optical rotation was measured using a 1 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High-resolution mass spectra were measured on a Thermo Fisher Scientific LTQ Orbitrap XL.

### 1-3. Solvents and reagents

THF, Et<sub>2</sub>O, DME and CPME were purified by passing through a solvent purification system (Glass Contour). Nitroethane (**3a**), nitropropane (**3b**) and 2-Me-THF was purchased from TCI Co. Ltd. and nitroethane was used after distillation. Amide-based ligand **1** was prepared by following the reported procedure.<sup>2</sup> NdCl<sub>3</sub>•6H<sub>2</sub>O was purchased from Wako Pure Chemical Co. Ltd. PrCl<sub>3</sub>•7H<sub>2</sub>O was purchased from Kanto Chemical Co. Ltd. All other RE reagents were purchased from Kojundo Chemical Laboratory Co. Ltd. Trifluoromethyl ketone **2a**, **2c**, **2g** and **2h** were purchased from TCI Co. Ltd. and **2b**,<sup>3</sup> **2d**,<sup>4</sup> **2e**,<sup>5</sup> **2f**,<sup>6</sup> **2i**,<sup>7</sup> and **2j**<sup>8</sup> were prepared to the known procedure with a slight modification. Difluoromethyl ketone **2k** was purchased from Aldrich. All other materials were used as supplied by commercial vendors.

## 2. Experimental Procedures

### 2-1. Representative procedure for preparation of catalyst by Method A (Table 1, entry 1-3)

To a flame dried test tube (20 mL) was charged with amide-based ligand (9.1 mg, 0.024 mmol), and dried under vacuum at room temperature at least for 5 min. Ar was backfilled (evacuation/backfill was repeated for 5 times) to the test tube, and THF (400  $\mu$ L) and 0.2 M NdO<sub>1.5</sub>(O*i*-Pr)<sub>13/5</sub>/THF (120  $\mu$ L, 0.024 mmol) were added successively by well-dried syringes and needles at 0 °C. After stirring the resulting slightly cloudy suspension at room temperature for 30 min, 1.0 M NaHMDS/THF (48  $\mu$ L, 0.048 mmol) was added dropwise at 0 °C. After stirring the resulting mixture at room temperature for 1 h (white precipitate appeared), nitroethane (172  $\mu$ L, 2.4 mmol) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 2 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube with THF washing (0.5 mL x2). The tube was centrifuged at ca. 10<sup>4</sup> rpm for 30 sec. The supernatant was decanted and THF (1.6 mL) was added. The tube was agitated using a vortex mixer for 30 sec and centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated with THF (1.6 mL) and a part of resulting suspension (240  $\mu$ L, 0.0036 mmol, 3 mol%) was used for anti-selective catalytic asymmetric nitroaldol reaction.

### 2-2. Representative procedure for preparation of catalyst by Method B (Table 1, entry 4)

To a flame dried test tube (20 mL) was charged with NdCl<sub>3</sub>•6H<sub>2</sub>O (8.6 mg, 0.024 mmol), and dried under vacuum at room temperature at least for 5 min. Ar was backfilled (evacuation/backfill was repeated for 5 times) to the test tube, and THF (200  $\mu$ L) and 0.6 M amide based ligand **1**/THF (200  $\mu$ L, 0.012 mmol) were added successively by well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy suspension at 60 °C for 30 min, 2.0 M NaO<sup>t</sup>Bu/THF (72  $\mu$ L, 0.144 mmol) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (172  $\mu$ L, 2.4

mmol) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube with THF washing (0.5 mL x2). The tube was centrifuged at ca. 10<sup>4</sup> rpm for 30 sec. The supernatant was decanted and THF (1.6 mL) was added. The tube was agitated using a vortex mixer for 30 sec and centrifuged again, then the supernatant was decanted (washing process). This washing process was repeated again. The resulting precipitate was agitated with THF (1.6 mL) and a part of resulting suspension (240  $\mu$ L, 0.0036 mmol, 3 mol%) was used for anti-selective catalytic asymmetric nitroaldol reaction.

### 2-3. Representative procedure for anti-selective catalytic asymmetric nitroaldol reaction (Table 1, entry 4)

To a flame-dried 20 mL test tube was charged with THF (960  $\mu$ L) and catalyst suspension (240  $\mu$ L, 0.0036 mmol, 3 mol%). After adding nitroethane (86  $\mu$ L, 1.2 mmol, 10 eq.) at room temperature, the mixture was cooled to -78 °C and then 0.82 M 2,2,2-trifluoroacetophenone/THF (146  $\mu$ L, 0.12 mmol) was added dropwise for 1 min. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF (500  $\mu$ L) was added slowly and warmed to room temperature. Water (1 mL) was added and the resulting mixture was extracted with EtOAc (2 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of volatiles under reduced pressure, the resulting residue was analyzed by <sup>1</sup>H NMR to determine yield and diastereomeric ratio of product (mesitylene was used as internal standard). The crude product was purified by silica gel column chromatography (EtOAc/*n*-hexane = 9:1) to give product. Enantiomeric excess was determined by chiral HPLC analysis.

### 2-4. Procedure for preparation of catalyst by Method A and anti-selective catalytic asymmetric nitroaldol reaction on gram scale (Chart 1, synthesis of 4aa, RE = Nd)

To a flame dried round-bottom flask (30 mL) were charged with NdCl<sub>3</sub>•6H<sub>2</sub>O (61.7 mg, 0.172 mmol, 3 mol%) and amide-based ligand **1** (97.7 mg, 0.172 mmol, 3 mol%), and dried under vacuum at room temperature for 5 min. Ar was backfilled (evacuation/backfill was repeated for 5 times) to the test tube, and THF (4.3 mL) was added by well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy suspension at 60 °C for 30 min, 2.0 M NaO<sup>t</sup>Bu/THF (516  $\mu$ L, 1.03 mmol, 18 mol%) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (1.23 mL, 17.2 mmol, 3.0 eq.) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to a conical tube (50 mL) with THF washing (3.5 mL x2). The tube was centrifuged at ca. 4,000 rpm for 1 min. The supernatant was decanted and THF (11 mL) was added. The tube was agitated using a vortex mixer for 1 min and centrifuged again, then the supernatant was decanted (washing process). This washing process was repeated again. The resulting precipitate was agitated with THF (11 mL) and the resulting suspension was transferred to a flame-dried round-bottom flask (200 mL). After adding THF (45 mL) and nitroethane (4.1 mL, 57.4 mmol, 10 eq.), the mixture was cooled to -78 °C and then 0.82 M 2,2,2-trifluoroacetophenone/THF (7.0 mL, 5.74 mmol) was added dropwise for 5 min. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF (25 mL) was added slowly and warmed to room temperature. Water (50 mL) was added and the resulting mixture was extracted with EtOAc (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of volatiles under reduced pressure, the resulting residue was analyzed by <sup>1</sup>H NMR to determine diastereomeric ratio of product (mesitylene was used as internal standard). The crude product was purified by silica gel column chromatography (*n*-hexane/ EtOAc = 9:1) to give (2*R*,3*S*)-1,1,1-trifluoro-3-nitro-2-phenylbutan-2-ol (**4aa**, 1.21 g, 85%) as white solid. Enantiomeric excess was determined by chiral HPLC analysis (93% *ee*).

### 2-5. Procedure for synthesis of 5 and 6

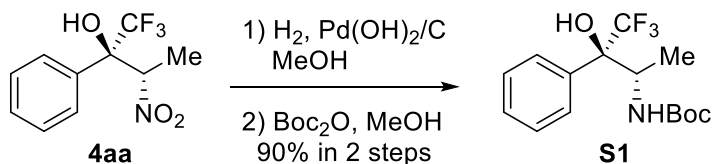
To a solution of **4aa** (250 mg, 1.00 mmol, 93% *ee*) in MeOH (10 mL) was added Pd(OH)<sub>2</sub>/C (50 mg [10 wt%Pd, 50% wet]) and resulting mixture was stirred at room temperature under H<sub>2</sub> atmosphere for 12 h. After filtration through syringe filter, the filtrate was concentrated in *vacuo* to give (2*R*,3*S*)-3-amino-1,1,1-trifluoro-2-phenylbutan-2-ol (**5**, 212.2 mg, 96%) as colorless oil.

To a solution of **5** (87.6 mg, 0.40 mmol) in MeOH (950  $\mu$ L) was added AcOH (50  $\mu$ L) and formaldehyde (35wt% in water, 37.8  $\mu$ L, 0.44 mmol, 1.1 eq.). After stirring at room temperature for 30 min, NaB(CN)<sub>3</sub>H<sub>3</sub> (50.4 mg, 0.80 mmol, 2.0 eq.) was added to reaction mixture at 0 °C. After stirring at room temperature for 12 h, reaction mixture was concentrated in *vacuo* and CHCl<sub>3</sub> (2 mL) and sat. NaHCO<sub>3</sub> aq. (2 mL) was added to the residue. After separation, the aqueous layer was extracted with CHCl<sub>3</sub> (2 mL). The combined organic layers were washed with brine (2 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane = 40:60) to give

(2*R*,3*S*)-1,1,1-trifluoro-3-(methylamino)-2-phenylbutan-2-ol (**6**, 46.7 mg, 0.20 mmol, 50%) as colorless oil.

### 2-6. Procedure for synthesis of **S1**

Enantiomeric purity after reduction of nitro group of **4aa** was determined after converting to Boc-protected **S1**.

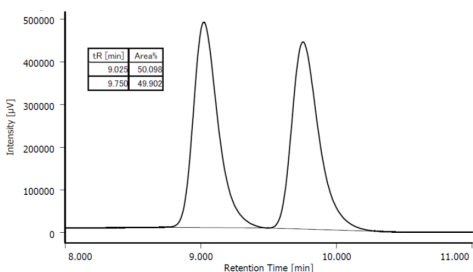


To a solution of **4aa** (100 mg, 0.40 mmol, 93% *ee*) in MeOH (3 mL) was added Pd(OH)<sub>2</sub>/C (20 mg [10 wt% Pd, 50% wet]) and resulting mixture was stirred at room temperature under H<sub>2</sub> atmosphere for 12 h. After purging with Ar, Boc<sub>2</sub>O (175 mg, 0.80 mmol, 2.0 eq.) was added to the mother liquid and stirred at room temperature for 12 h. After filtration through syringe filter, filtrate was concentrated in *vacuo*. The resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane = 10:90) to give **S1** (116 mg, 0.36 mmol, 90% in 2 steps) as white solid. Enantiomeric excess was determined by chiral HPLC analysis (93% *ee*).

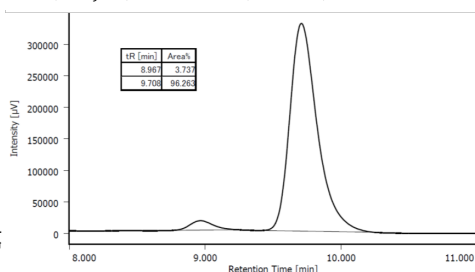
### 3. Characterization of Products

#### (2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-2-phenylbutan-2-ol (**4aa**)

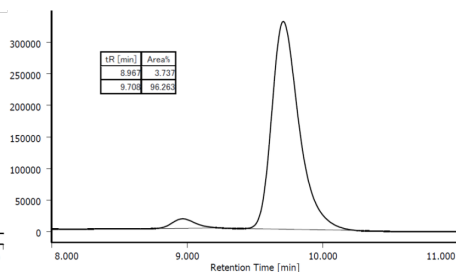
White solid; 1.21 g (85%, RE = Nd), 25.2 mg (84%, RE = Pr); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.60–7.58 (m, 2H), 7.48–7.43 (m, 3H), 5.31 (q, *J* = 6.8 Hz, 1H), 4.71 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 132.9, 129.8, 129.1, 125.8, 124.4 (q, *J* = 285.8 Hz), 83.9, 77.9 (q, *J* = 29.2 Hz), 15.0; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -76.9; IR (thin film) ν 3497, 1559, 1450, 1230, 1278, 1201, 1187, 1170, 702, 628 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>10</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>3</sub>Na *m/z* 272.0505 [M+Na]<sup>+</sup>, found 272.0501; [α]<sub>D</sub><sup>25</sup> 5.9 (*c* 0.95, CHCl<sub>3</sub>, 94% *ee*); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, *t*<sub>R</sub> = 9.7 min (major), 9.0 min (minor):



Racemic Sample



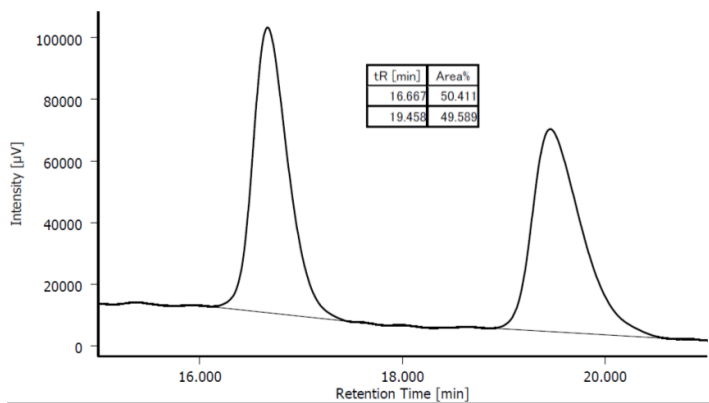
Reaction Sample (RE = Nd)



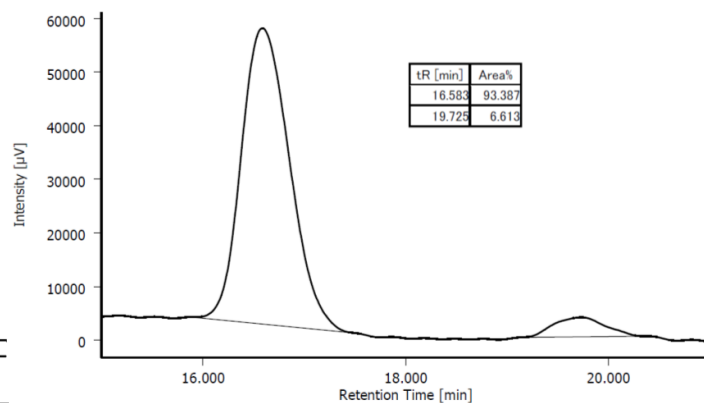
Reaction Sample (RE = Pr)

#### (2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-2-(*m*-tolyl)butan-2-ol (**4ba**)

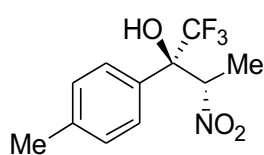
White solid; 26.6 mg (84%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40 (s, 1H), 7.36–7.31 (m, 2H), 7.24 (d, *J* = 6.6 Hz, 1H), 5.29 (q, *J* = 6.8 Hz, 1H), 4.68 (s, 1H), 2.40 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 139.0, 132.8, 130.5, 129.0, 126.4, 124.4 (q, *J* = 285.8 Hz), 122.8, 83.9, 77.6 (q, *J* = 29.2 Hz), 21.8, 15.1; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -76.8; IR (thin film) ν 3509, 1559, 1357, 1270, 1200, 1121, 1161, 1002, 969, 723 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>11</sub>H<sub>12</sub>O<sub>3</sub>NF<sub>3</sub>Na *m/z* 286.0661 [M+Na]<sup>+</sup>, found 286.0664; [α]<sub>D</sub><sup>25</sup> 4.6 (*c* 0.97, CHCl<sub>3</sub>, 87% *ee*); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99.9/0.1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, *t*<sub>R</sub> = 16.6 min (major), 19.7 min (minor):

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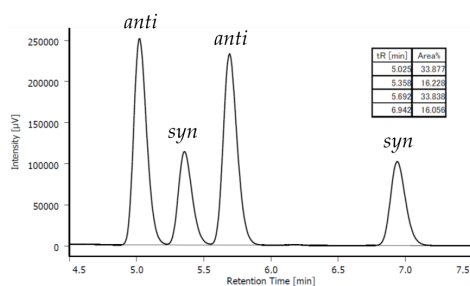
Racemic Sample



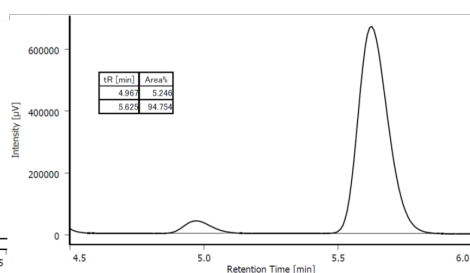
Reaction Sample

**(2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-2-(*p*-tolyl)butan-2-ol (4ca)**

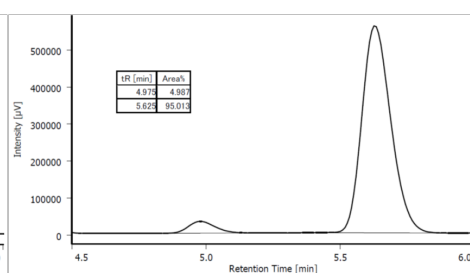
White solid; 26.6 mg (84%, RE = Nd), 25.9 mg (82%, RE = Pr); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.28 (q, *J* = 6.8 Hz, 1H), 4.66 (s, 1H), 2.38 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 139.8, 129.9, 129.8, 125.7, 124.5 (q, *J* = 285.8 Hz), 83.9, 77.6 (q, *J* = 29.1 Hz), 21.2, 15.0; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -77.0; IR (thin film) ν 3504, 1554, 1299, 1272, 1201, 1190, 1169, 1002, 920, 813 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>11</sub>H<sub>12</sub>O<sub>3</sub>NF<sub>3</sub>Na *m/z* 286.0661 [M+Na]<sup>+</sup>, found 286.0657; [α]<sub>D</sub><sup>25</sup> 5.0 (*c* 0.51, CHCl<sub>3</sub>, 90% *ee*); HPLC analysis: Daicel CHIRALPAK ID, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 5.6 min (major), 4.9 min (minor):



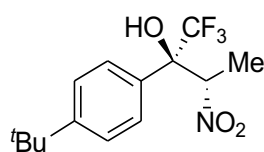
Racemic Sample



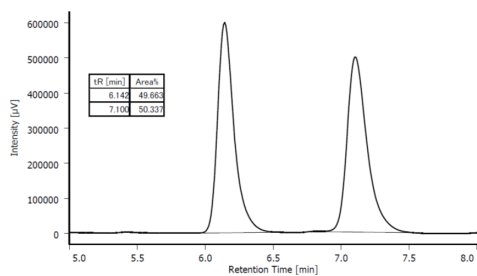
Reaction Sample (RE = Nd)



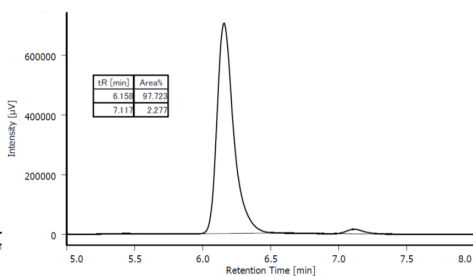
Reaction Sample (RE = Pr)

**(2*R*,3*S*)-2-(4-(*tert*-Butyl)phenyl)-1,1,1-trifluoro-3-nitrobutan-2-ol (4da)**

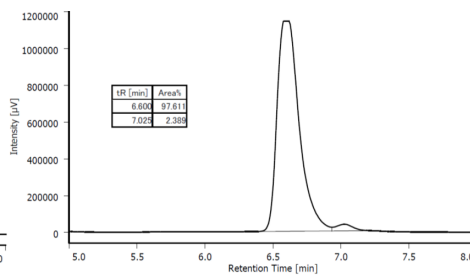
White solid; 32.8 mg (90%, RE = Nd), 27.3 mg (74%, RE = Pr); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.48 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 5.29 (q, *J* = 6.8 Hz, 1H), 4.65 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.33 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 152.9, 129.8, 126.3, 125.5, 124.5 (q, *J* = 285.8 Hz), 83.9, 77.9 (q, *J* = 29.2 Hz), 34.8, 31.3, 15.1; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -77.0; IR (thin film) ν 3510, 2964, 1559, 1355, 1273, 1198, 1164, 1122, 1109, 706 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>14</sub>H<sub>17</sub>O<sub>3</sub>NF<sub>3</sub> *m/z* 304.1166 [M-H]<sup>-</sup>, found 304.1153; [α]<sub>D</sub><sup>25</sup> 6.7 (*c* 0.81, CHCl<sub>3</sub>, 95% *ee*); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 6.2 min (major), 7.1 min (minor):



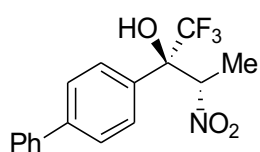
Racemic Sample



Reaction Sample (RE = Nd)

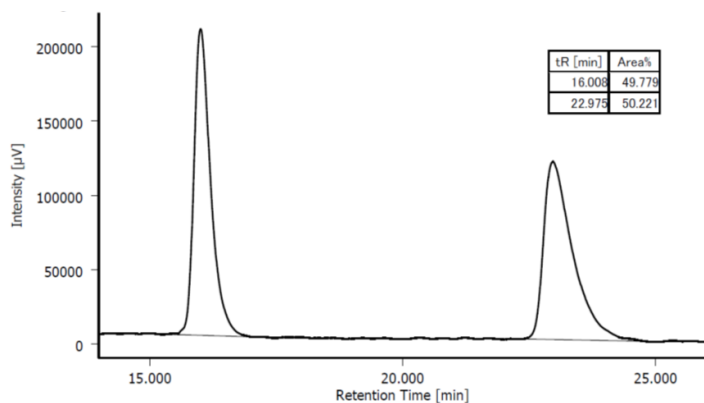


Reaction Sample (RE = Pr)

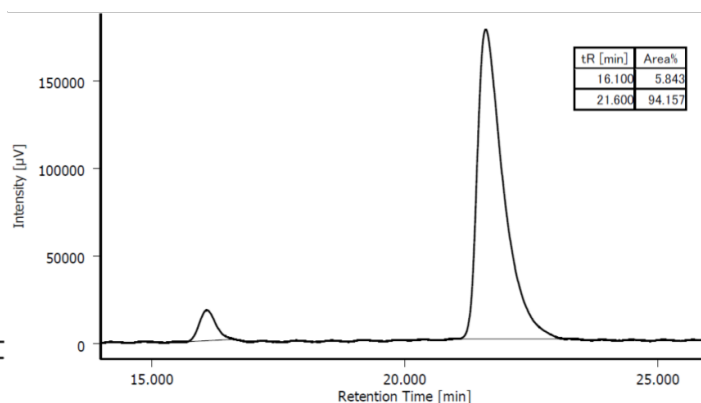
**(2R,3S)-2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoro-3-nitrobutan-2-ol (4ea)**

White solid; 32.1 mg (82%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.69–7.59 (m, 6H), 7.49–7.37 (m, 3H), 5.34 (q, *J* = 6.8 Hz, 1H), 4.74 (s, 1H), 1.42 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 142.1, 139.3, 131.1, 128.5, 127.5, 127.1, 126.7, 125.7, 123.8 (q, *J* = 286.6 Hz), 83.2, 77.3 (q, *J* = 29.2 Hz), 14.5; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -76.9; IR (thin film) ν 3500, 1557, 1300, 1271, 1199, 1170, 1002, 835, 765, 732 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>16</sub>H<sub>14</sub>O<sub>3</sub>NF<sub>3</sub>Na *m/z* 348.0818 [M+Na]<sup>+</sup>, found 348.0815; [α]<sub>D</sub><sup>25</sup>

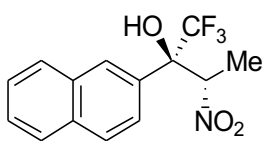
9.4 (*c* 1.23, CHCl<sub>3</sub>, 88% *ee*); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 21.6 min (major), 16.1 min (minor):



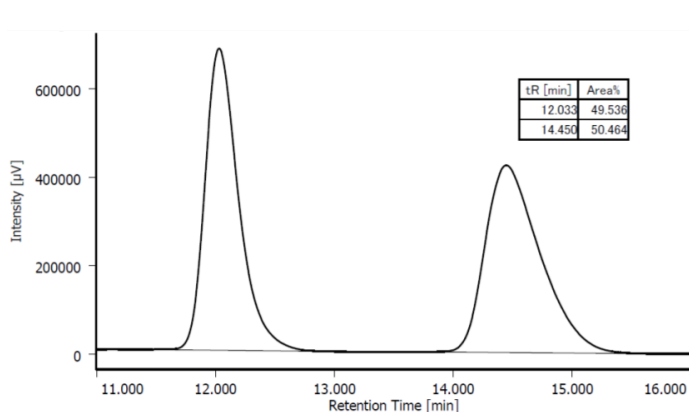
Racemic Sample



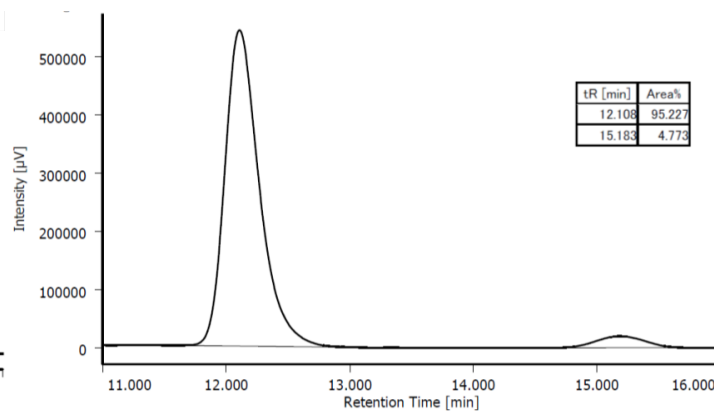
Reaction Sample

**(2R,3S)-1,1,1-Trifluoro-2-(naphthalen-2-yl)-3-nitrobutan-2-ol (4fa)**

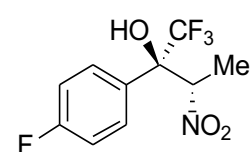
White solid; 32.4 mg (90%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.17 (s, 1H), 7.94–7.87 (m, 3H), 7.60–7.56 (m, 3H), 5.44 (q, *J* = 6.9 Hz, 1H), 4.84 (s, 1H), 1.39 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 133.6, 133.1, 130.1, 129.1, 128.8, 127.8, 127.5, 127.1, 126.4, 124.5 (q, *J* = 285.8 Hz), 122.1, 83.8, 78.1 (q, *J* = 29.2 Hz), 15.0, 14.5; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -76.5; IR (thin film) ν 3487, 1555, 1354, 1311, 1272, 1253, 1191, 1162, 822, 752 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>14</sub>H<sub>13</sub>O<sub>3</sub>NF<sub>3</sub> *m/z* 300.0842 [M+H]<sup>+</sup>, found 300.0843; [α]<sub>D</sub><sup>25</sup> 1.0 (*c* 0.76, CHCl<sub>3</sub>, 90% *ee*); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 12.1 min (major), 15.1 min (minor):



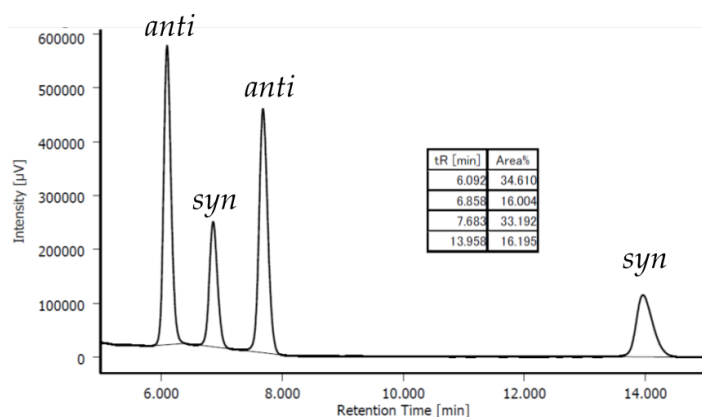
Racemic Sample



Reaction Sample

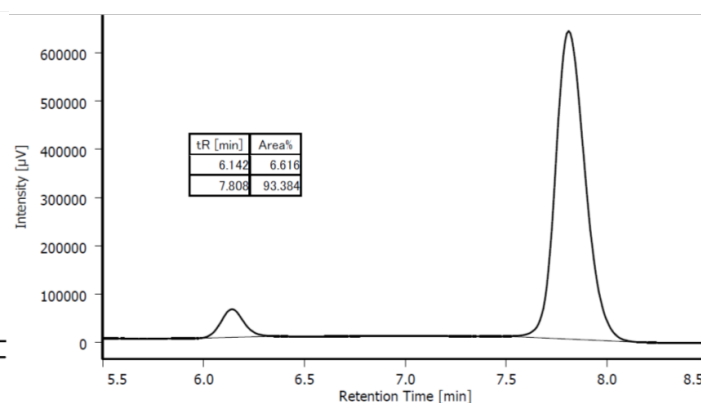
**(2*R*,3*S*)-1,1,1-Trifluoro-2-(4-fluorophenyl)-3-nitrobutan-2-ol (4ga)**

White solid; 24.7 mg (77%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.58 (dd, *J* = 5.1, 3.7 Hz, 2H), 7.15 (m, 2H), 5.27 (q, *J* = 6.8 Hz), 4.76 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.5 (d, *J* = 248.6 Hz), 128.7 (d, *J* = 3.7 Hz), 127.9 (d, *J* = 8.0 Hz), 124.3 (q, *J* = 286.5 Hz), 116.2 (d, *J* = 29.1 Hz), 83.7, 77.5 (q, *J* = 29.2 Hz), 15.0; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -77.1, -111.3; IR (thin film) ν 3504, 1560, 1514, 1392, 1357, 1274, 1241, 1201, 1164, 837 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>10</sub>H<sub>8</sub>O<sub>3</sub>NF<sub>4</sub> *m/z* 266.0446 [M-H], found 266.0437; [α]<sub>D</sub><sup>25</sup> 5.6 (*c* 0.76, CHCl<sub>3</sub>, 87% *ee*); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 7.8 min (major),

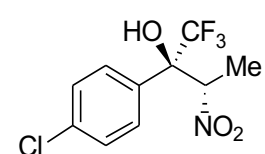


6.1 min (minor):

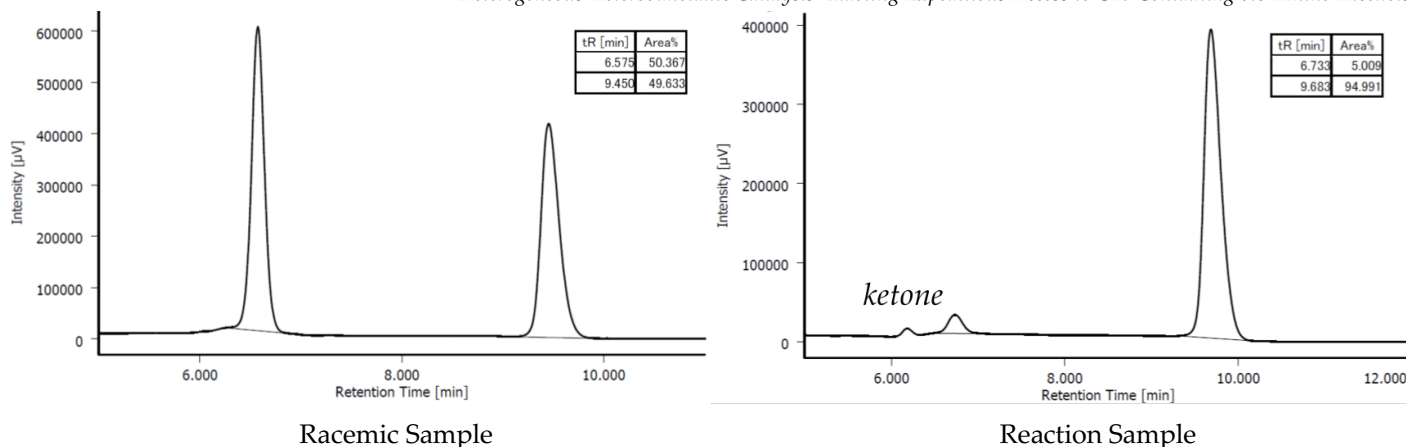
Racemic Sample



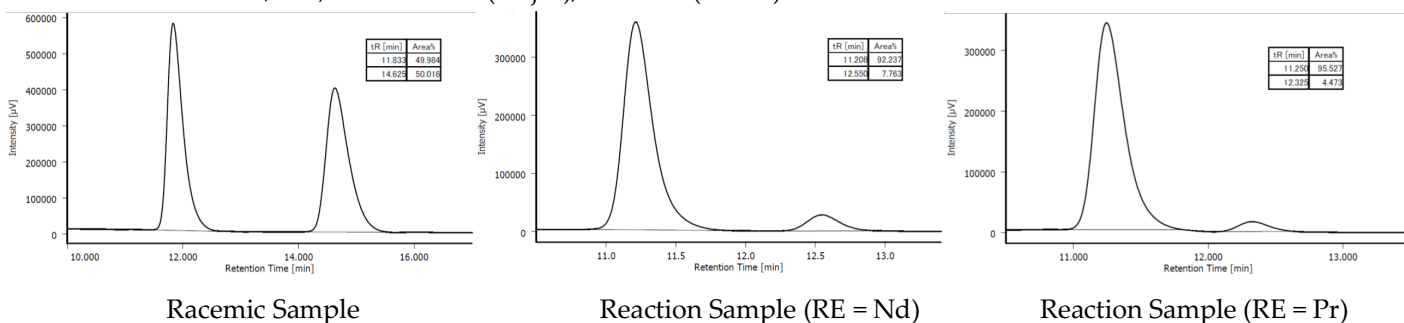
Reaction Sample

**(2*R*,3*S*)-2-(4-Chlorophenyl)-1,1,1-trifluoro-3-nitrobutan-2-ol (4ha)**

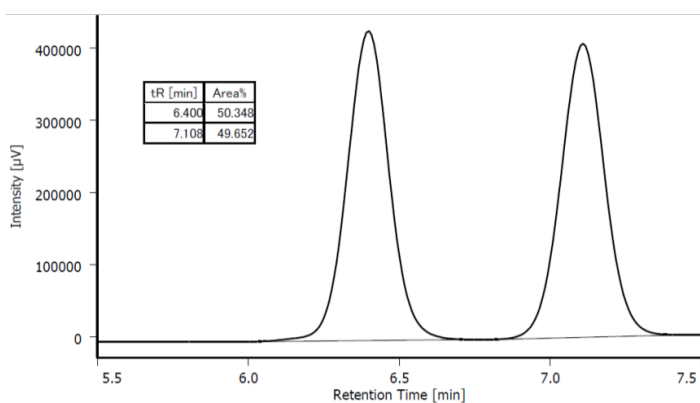
White solid; 27.2 mg (80%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.60 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 5.25 (q, *J* = 6.9 Hz, 1H), 4.76 (s, 1H), 1.37 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 132.4, 132.0, 127.6, 124.4, 124.1 (q, *J* = 285.8 Hz), 83.5, 77.7 (q, *J* = 29.2 Hz), 15.0; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -77.0; IR (thin film) ν 3503, 1559, 1496, 1357, 1271, 1202, 1166, 1096, 920, 824 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>10</sub>H<sub>8</sub>O<sub>3</sub>NCIF<sub>3</sub> *m/z* 282.0150 [M-H], found 282.0148; [α]<sub>D</sub><sup>25</sup> 10.4 (*c* 1.06, CHCl<sub>3</sub>, 90% *ee*); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 9.7 min (major), 6.7 min (minor):

Heterogeneous Heterobimetallic Catalysis Enabling Expeditious Access to CF<sub>3</sub>-Containing vic-Amino Alcohols**(2*R*,3*S*)-1,1,1-Trifluoro-2-(3-methoxyphenyl)-3-nitrobutan-2-ol (4ia)**

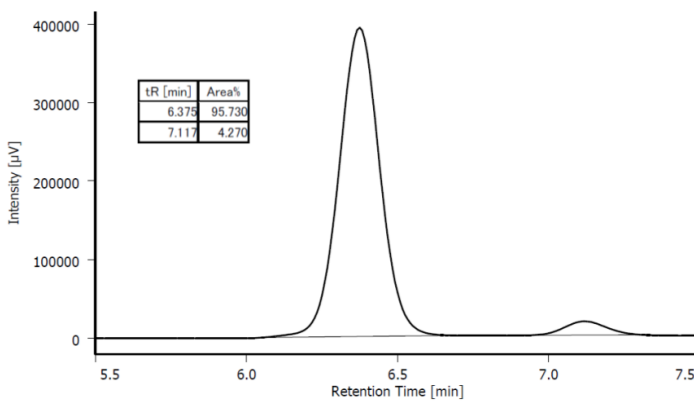
White solid; 22.4 mg (67%, RE = Nd), 26.9 mg (85%, RE = Pr); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.19 (s, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.96 (dd, *J* = 8.1, 2.7 Hz, 1H), 5.27 (q, *J* = 6.8 Hz, 1H), 4.71 (s, 1H), 3.85 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 160.2, 134.4, 130.2, 124.4 (q, *J* = 285.8 Hz), 117.7, 115.0, 112.2, 83.9, 77.8 (q, *J* = 29.2 Hz), 55.5, 15.0; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -76.8; IR (thin film) ν 3503, 2359, 1558, 1494, 1456, 1357, 1268, 1200, 1163, 724 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>11</sub>H<sub>12</sub>O<sub>3</sub>NF<sub>3</sub>Na *m/z* 302.0611 [M+Na]<sup>+</sup>, found 302.0606; [α]<sub>D</sub><sup>25</sup> 2.9 (*c* 1.13, CHCl<sub>3</sub>, 91% *ee*); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 11.2 min (major), 12.6 min (minor):

**(3*R*,4*S*)-4-Nitro-3-(trifluoromethyl)-1-(triisopropylsilyl)pent-1-yn-3-ol (4ja)**

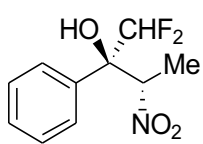
Colorless oil, 33.5 mg (79%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.94 (q, *J* = 6.8 Hz, 1H), 3.77 (s, 1H), 1.81 (d, *J* = 6.8 Hz, 3H), 1.14–1.08 (m, 21H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 122.7 (q, *J* = 284.3 Hz), 96.1, 94.5, 83.9, 73.2 (q, *J* = 32.1 Hz), 18.5, 15.9, 11.1; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -78.2; IR (thin film) ν 3491, 2947, 2869, 1567, 1357, 1264, 1204, 1062, 882, 666 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>15</sub>H<sub>26</sub>O<sub>3</sub>NF<sub>3</sub>NaSi *m/z* 376.1526 [M+Na]<sup>+</sup>, found 376.1526; [α]<sub>D</sub><sup>25</sup> -43.3 (*c* 1.34, CHCl<sub>3</sub>, 92% *ee*); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 6.4 min (major), 7.1 min (minor):



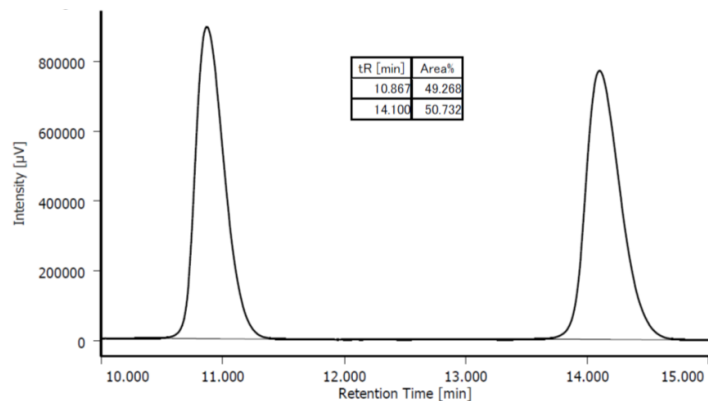
Racemic Sample



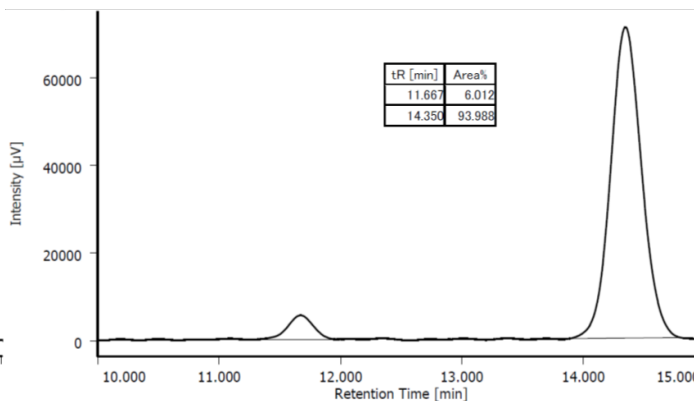
Reaction Sample

**(2R,3S)-1,1-Difluoro-3-nitro-2-phenylbutan-2-ol (4ka)**

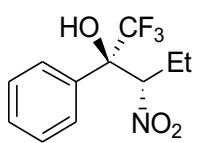
White solid; 21.4 mg (77%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.47-7.40 (m, 3H), 5.80 (t, *J* = 184.8 Hz, 1H), 5.24 (q, *J* = 6.8 Hz, 1H), 4.24 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 134.5, 129.4, 129.1, 125.9, 115.8 (t, *J* = 251.6 Hz), 83.8, 77.0 (t = 43.0 Hz), 14.7; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -126.7 (dd, *J* = 55.3, 293.5 Hz), -129.5 (dd, *J* = 55.7, 283.0 Hz); IR (thin film) ν 3525, 1556, 1451, 1390, 1356, 1195, 1126, 1075, 916, 701 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>10</sub>H<sub>10</sub>O<sub>3</sub>NF<sub>2</sub> *m/z* 230.0634 [M-H]<sup>-</sup>, found 230.0627; [α]<sub>D</sub><sup>25</sup> -2.1 (*c* 0.36, CHCl<sub>3</sub>, 87% *ee*); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 14.4 min (major), 11.7 min (minor):



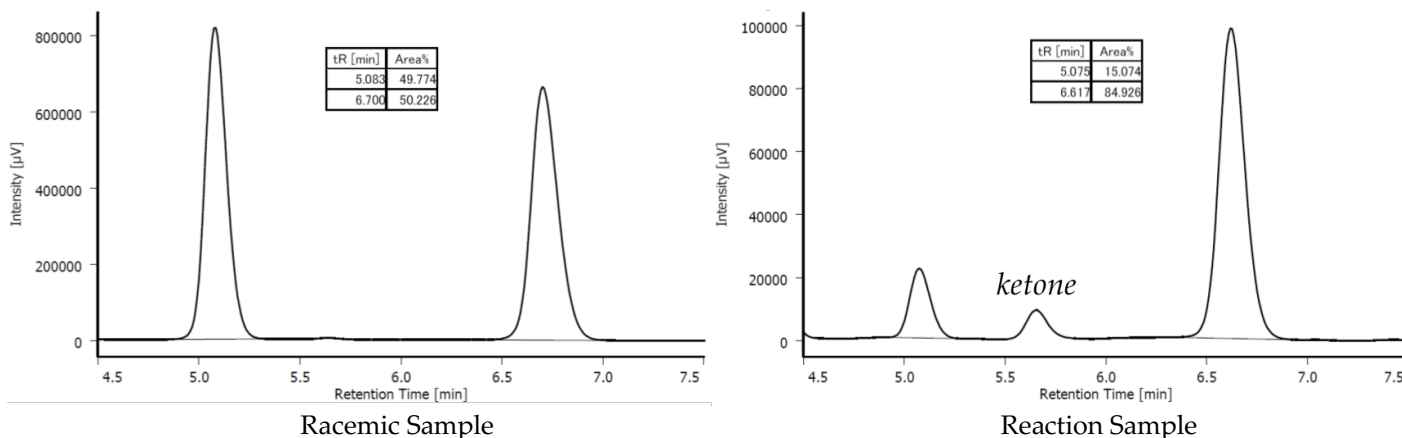
Racemic Sample



Reaction Sample

**(2R,3S)-1,1,1-Trifluoro-3-nitro-2-phenylpentan-2-ol (4ab)**

White solid; 26.0 mg (83%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.59-7.57 (m, 2H), 7.48-7.41 (m, 3H), 5.07 (dd, *J* = 3.2, 11.8 Hz, 1H), 4.73 (s, 1H), 2.05 (ddq, *J* = 3.2, 7.4, 11.8 Hz, 1H), 1.41 (ddq, *J* = 3.2, 4.4, 7.4 Hz, 1H), 0.85 (dd, *J* = 7.4, 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 133.2, 129.7, 129.1, 125.7, 124.3 (q, *J* = 285.8 Hz), 90.7, 77.9 (q, *J* = 29.2 Hz), 22.2, 10.0; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -77.0; IR (thin film) ν 3504, 1559, 1454, 1374, 1306, 1265, 1200, 1164, 723, 701 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>11</sub>H<sub>13</sub>O<sub>3</sub>NF<sub>3</sub> *m/z* 264.0842 [M+H]<sup>+</sup>, found 264.0838; [α]<sub>D</sub><sup>25</sup> 15.6 (*c* 0.56, CHCl<sub>3</sub>, 70% *ee*); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t<sub>R</sub> = 6.6 min (major), 5.1 min (minor):

**(2*R*,3*S*)-3-Amino-1,1,1-trifluoro-2-phenylbutan-2-ol (5)**

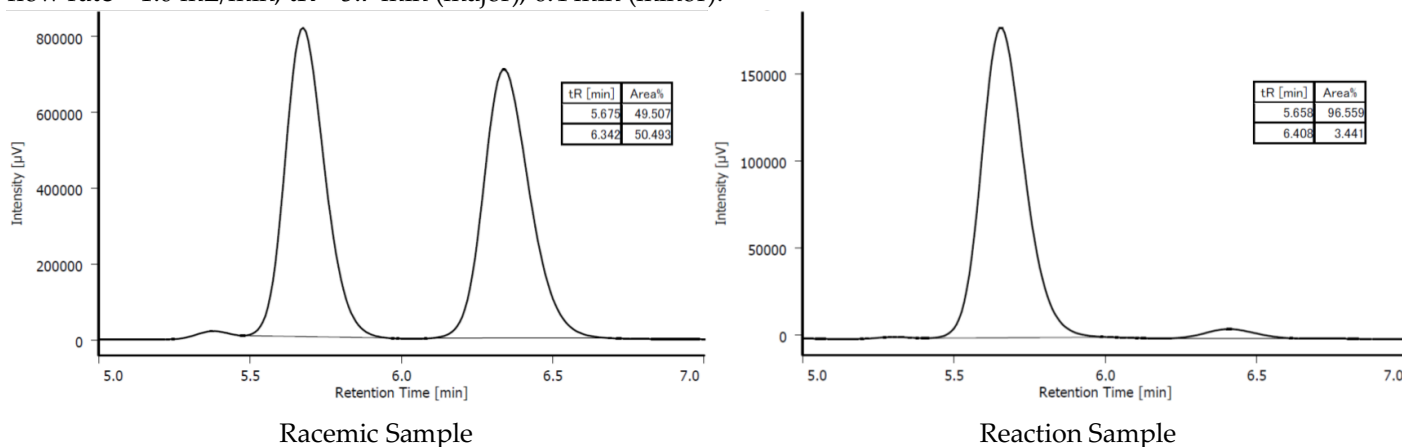
Colorless oil; 212.2 mg (96%); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.56–7.54 (m, 2H), 7.40–7.31 (m, 3H), 3.67 (q, *J* = 6.6 Hz, 1H), 0.77 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) δ 139.4, 130.1, 130.1, 128.6 (q, *J* = 285.5 Hz), 128.0, 80.4 (q, *J* = 25.5 Hz), 52.4, 18.4; <sup>19</sup>F NMR (376 MHz, CD<sub>3</sub>OD) δ -75.2; IR (thin film) ν 3416, 3352, 1452, 1385, 1269, 1153, 1075, 984, 913, 702 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>10</sub>H<sub>13</sub>ONF<sub>3</sub> *m/z* 220.0944 [M+H]<sup>+</sup>, found 220.0941; [α]<sub>D</sub><sup>25</sup> -39.5 (*c* 0.61, MeOH, 93% *ee*)

**(2*R*,3*S*)-1,1,1-Trifluoro-3-(methylamino)-2-phenylbutan-2-ol (6)**

Colorless oil; 46.7 mg (50%); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.59–7.57 (m, 2H), 7.42–7.36 (m, 3H), 3.27 (q, *J* = 6.6 Hz, 1H), 2.46 (s, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) δ 139.7, 132.8, 130.0, 130.0, 128.5 (q, *J* = 285.1 Hz), 128.2, 80.4 (q, *J* = 25.5 Hz), 60.9, 35.5, 16.0; <sup>19</sup>F NMR (376 MHz, CD<sub>3</sub>OD) δ -74.8; IR (thin film) ν 2867, 1451, 1380, 1266, 1155, 1075, 1002, 910, 761, 704 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>11</sub>H<sub>15</sub>ONF<sub>3</sub> *m/z* 234.1100 [M+H]<sup>+</sup>, found 234.1092; [α]<sub>D</sub><sup>25</sup> -25.8 (*c* 0.33, CHCl<sub>3</sub>, 93% *ee*)

***tert*-Butyl ((2*S*,3*R*)-4,4,4-trifluoro-3-hydroxy-3-phenylbutan-2-yl)carbamate (S1)**

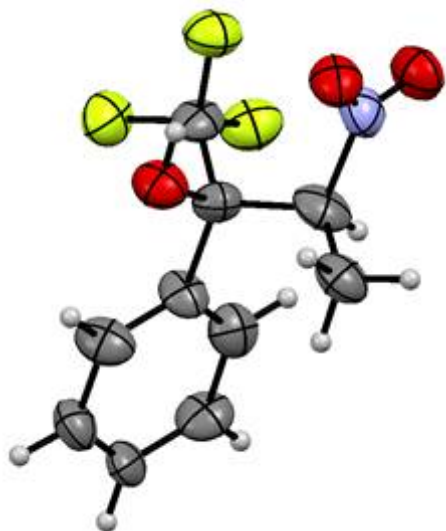
White solid; 116 mg (90%); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.60 (d, *J* = 7.6 Hz, 2H), 7.45–7.36 (m, 3H), 4.41 (q, *J* = 6.8 Hz, 1H), 1.50 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 157.9, 136.8, 128.6, 128.5, 126.1, 125.8 (q, *J* = 286.5 Hz), 81.3, 77.2 (q, *J* = 33.5 Hz), 52.6, 28.4, 14.5; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -75.7; IR (thin film) ν 3383, 2981, 1671, 1520, 1369, 1269, 1161, 1119, 1063, 702 cm<sup>-1</sup>; HRMS (ESI) calcd. for C<sub>15</sub>H<sub>21</sub>O<sub>3</sub>NF<sub>3</sub> *m/z* 320.1468 [M+H]<sup>+</sup>, found 320.1464; [α]<sub>D</sub><sup>25</sup> -22.1 (*c* 0.96, CHCl<sub>3</sub>, 93% *ee*); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, tR = 5.7 min (major), 6.4 min (minor):



#### 4. Determination of Absolute Configuration

The absolute configuration of nitroaldol product **4aa** was determined by X-ray crystallographic analysis. Single crystals of **4aa** were obtained from a solution of *n*-hexane. A suitable crystal was selected and the sample was measured on a Rigaku R-Axis RAPID diffractometer using graphite monochromated Cu-K $\alpha$  radiation. The data were collected at 93 K. Refined structure and crystallographic parameters are summarized in Figure S1 and Table S1. The ORTEP diagram was drawn by Mercury 3.8. CCDC 1587722 contains the supplementary crystallographic data for **4aa**.

Absolute configuration of other products are deduced by analogy.



**Figure S1.** ORTEP diagram of **4aa**. Color code; gray: C, white: H, blue: N, red: O, yellow: F

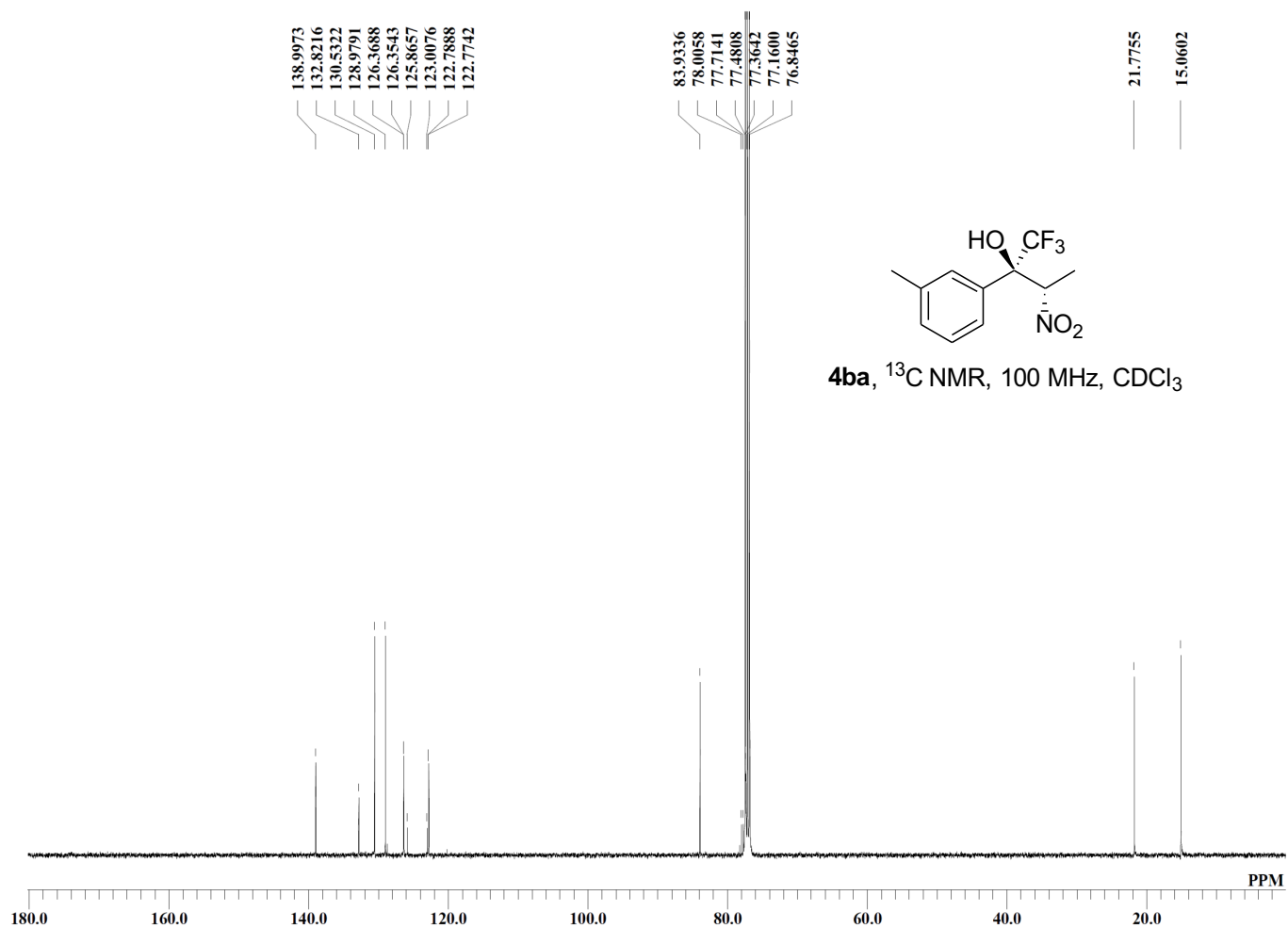
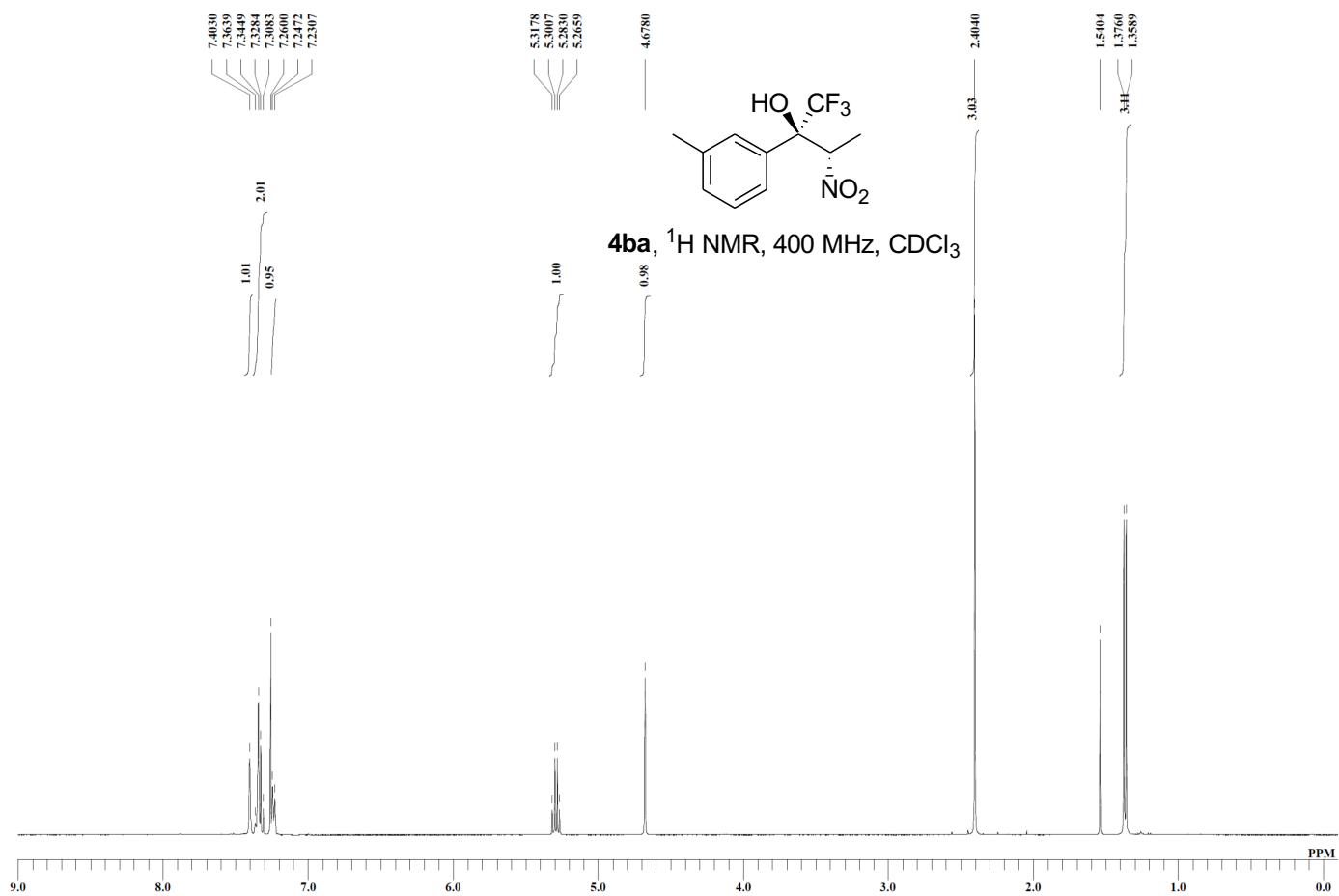
**Table S1.** Selected crystal data of **4aa**

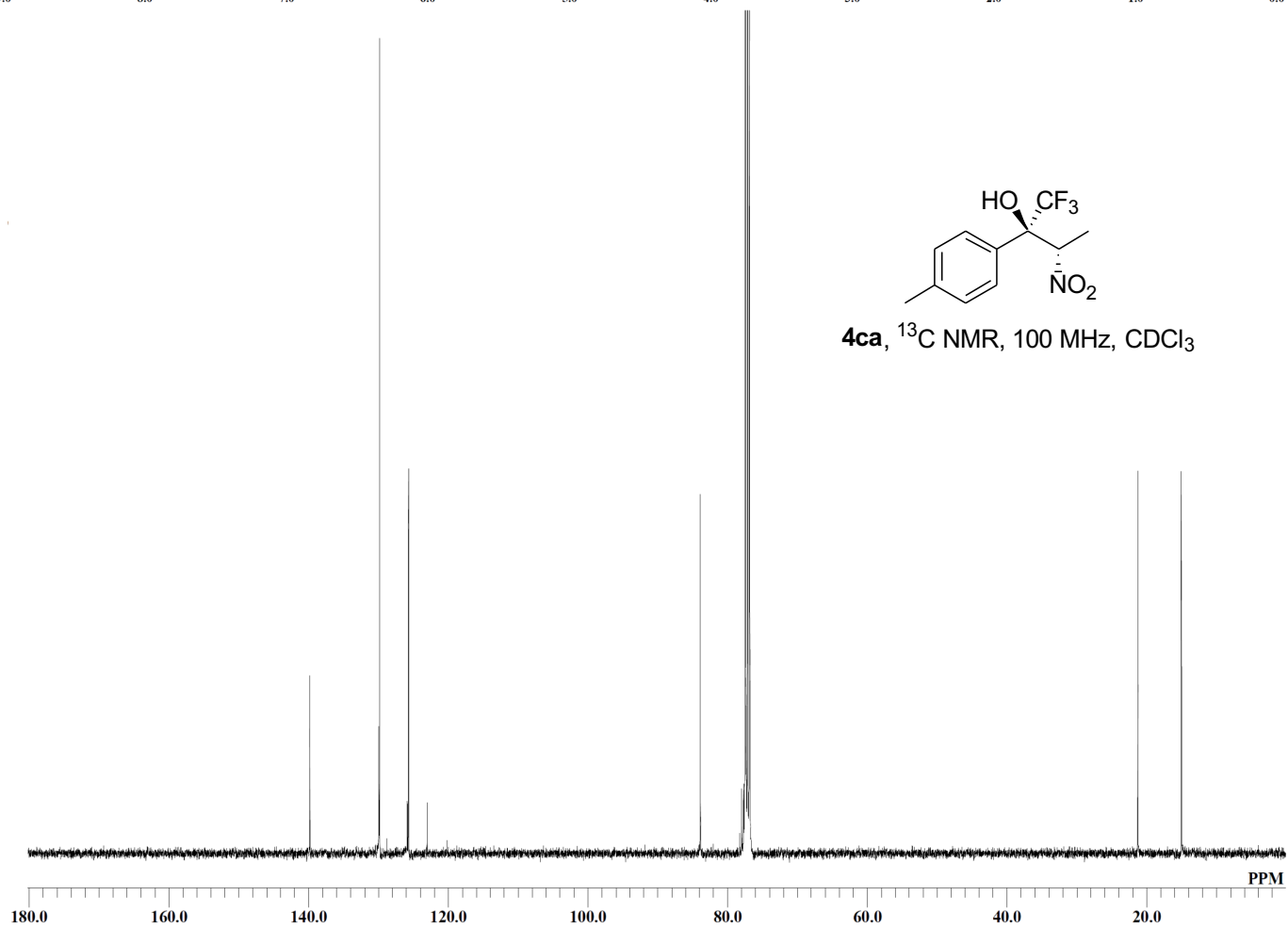
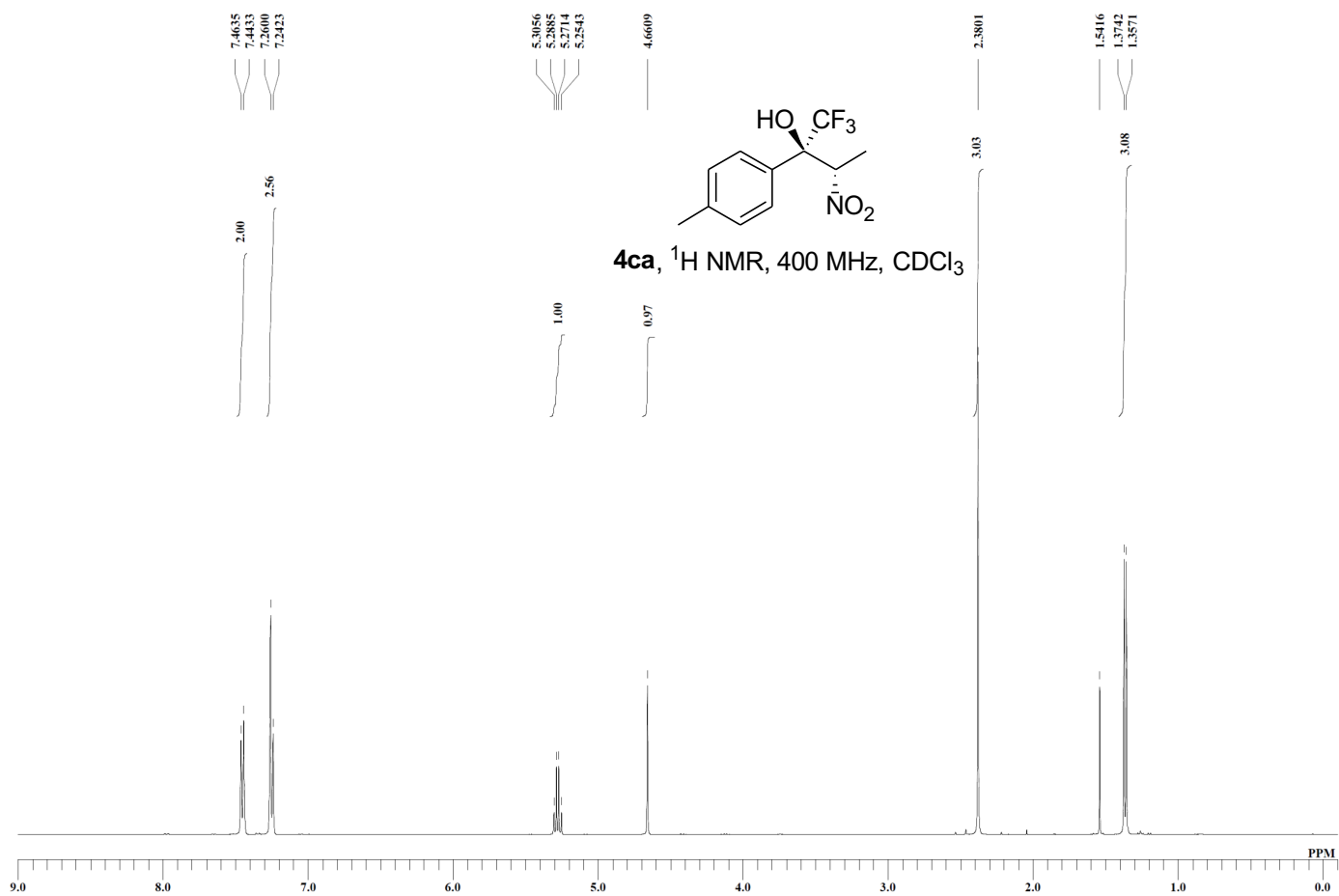
Empirical Formula	C <sub>20</sub> H <sub>20</sub> F <sub>6</sub> N <sub>2</sub> O <sub>6</sub>
Formula Weight	498.38
Crystal Color, Habit	colorless, needle
Crystal Dimensions	0.200 x 0.010 x 0.010 mm
Crystal System	monoclinic
Lattice Parameters	
a	19.267(2) Å
b	5.6798(7) Å
c	13.3285(17) Å
$\beta$	132.830(9)°
V	1069.7(3) Å <sup>3</sup>
Space Group	C2 (#5)
Z value	2
D <sub>calc</sub>	1.547 g/cm <sup>3</sup>
R <sub>1</sub>	0.0856
Flack parameter <sup>9</sup>	-0.3(6)
F <sub>000</sub>	512

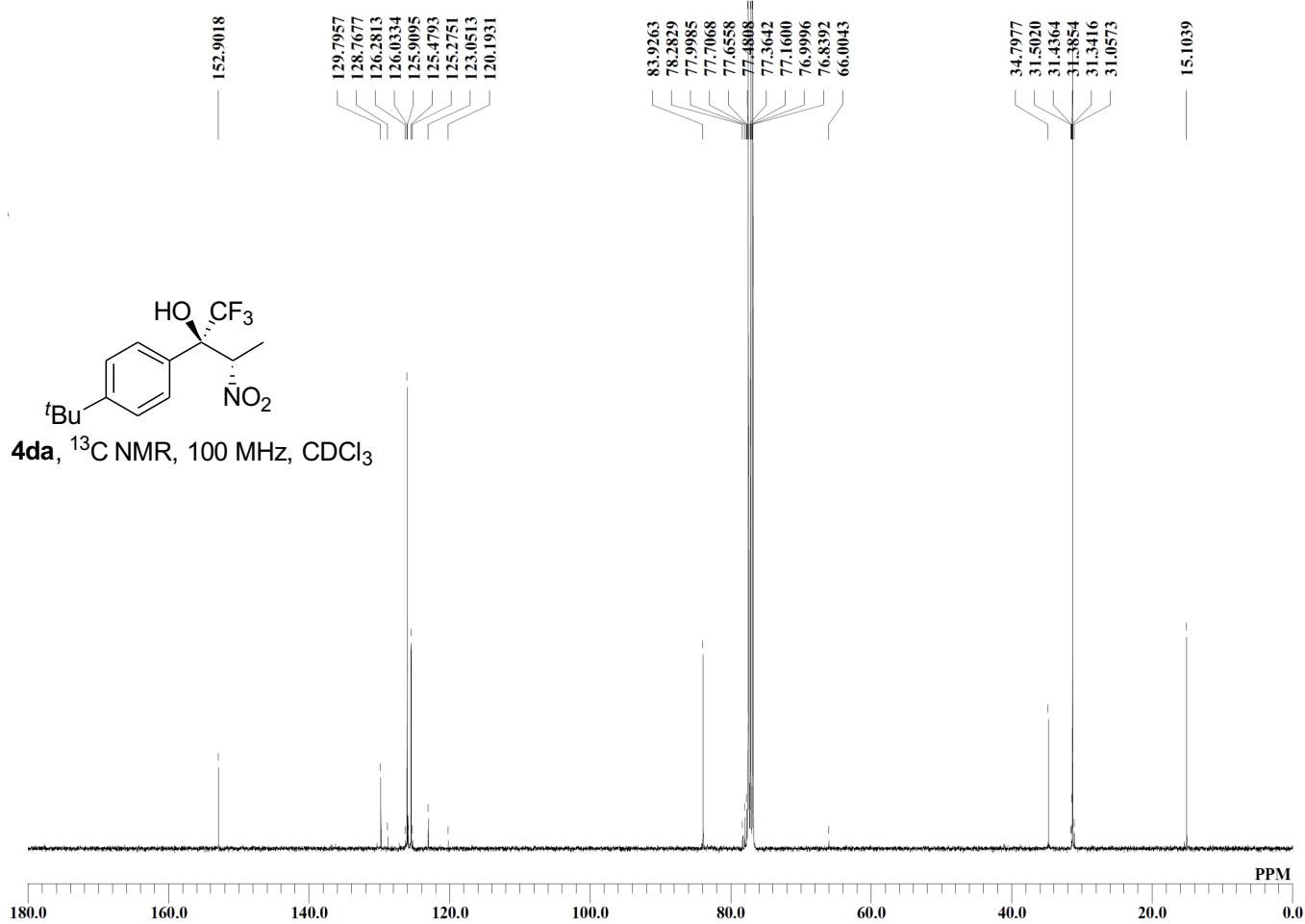
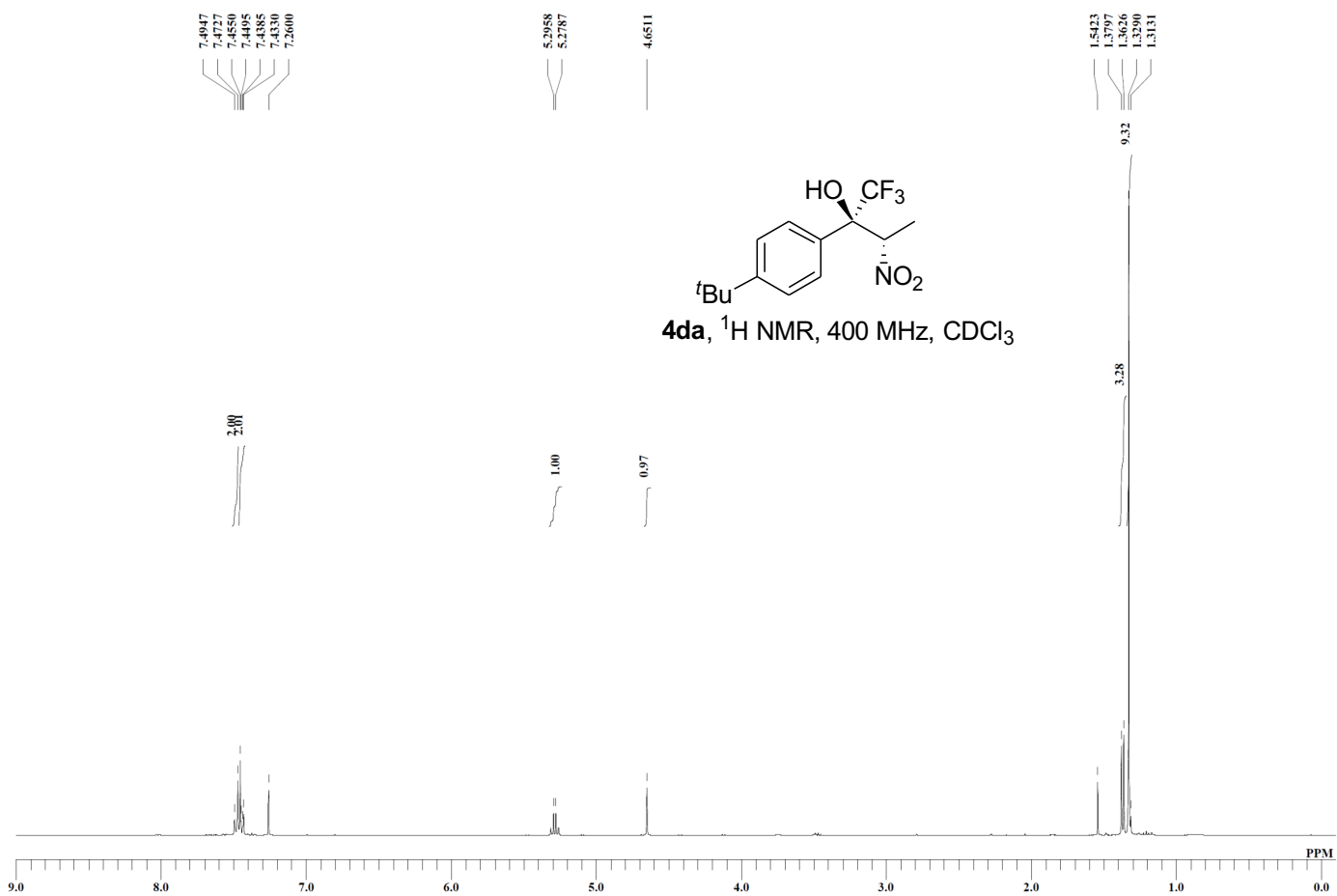
#### 6. References

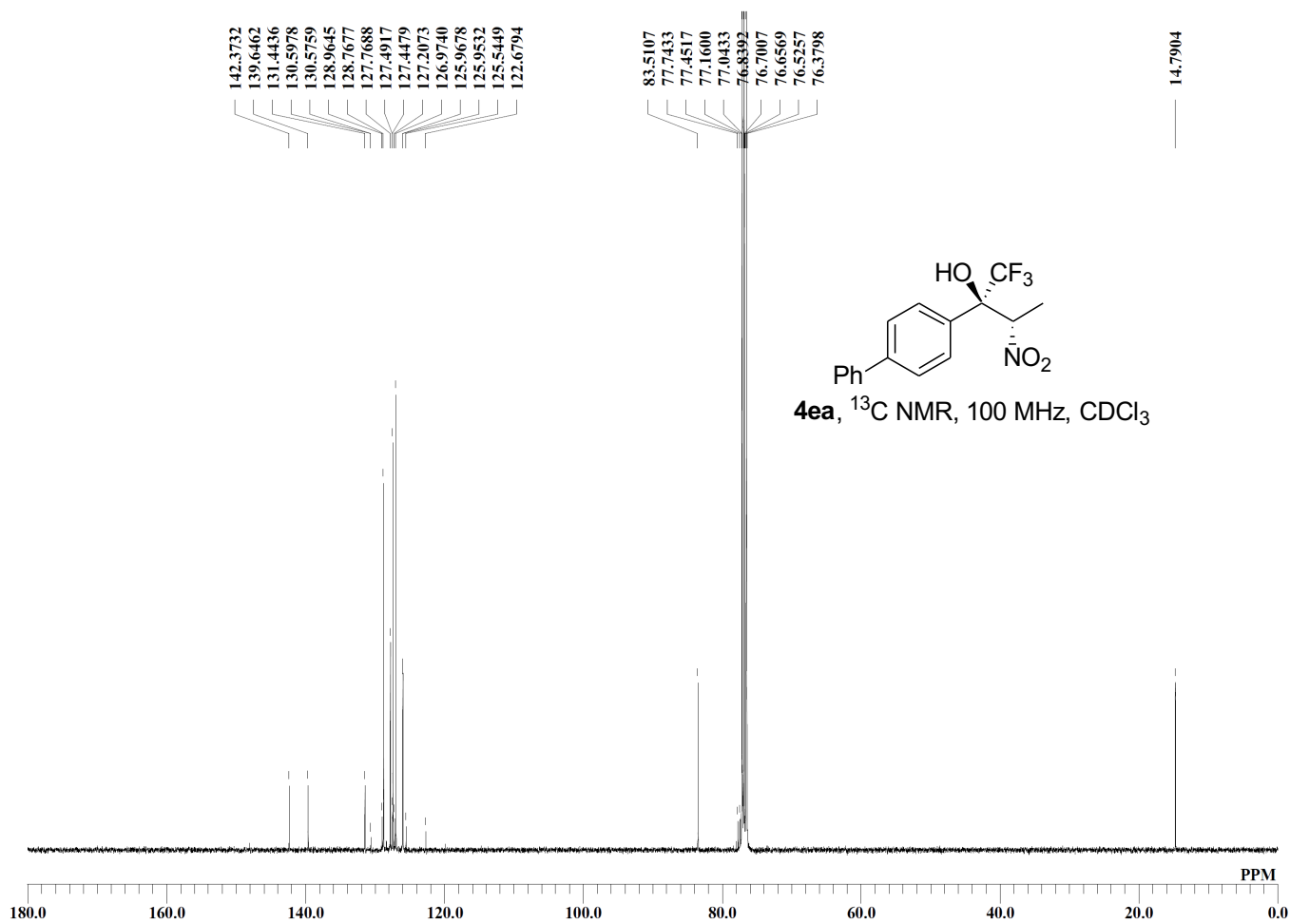
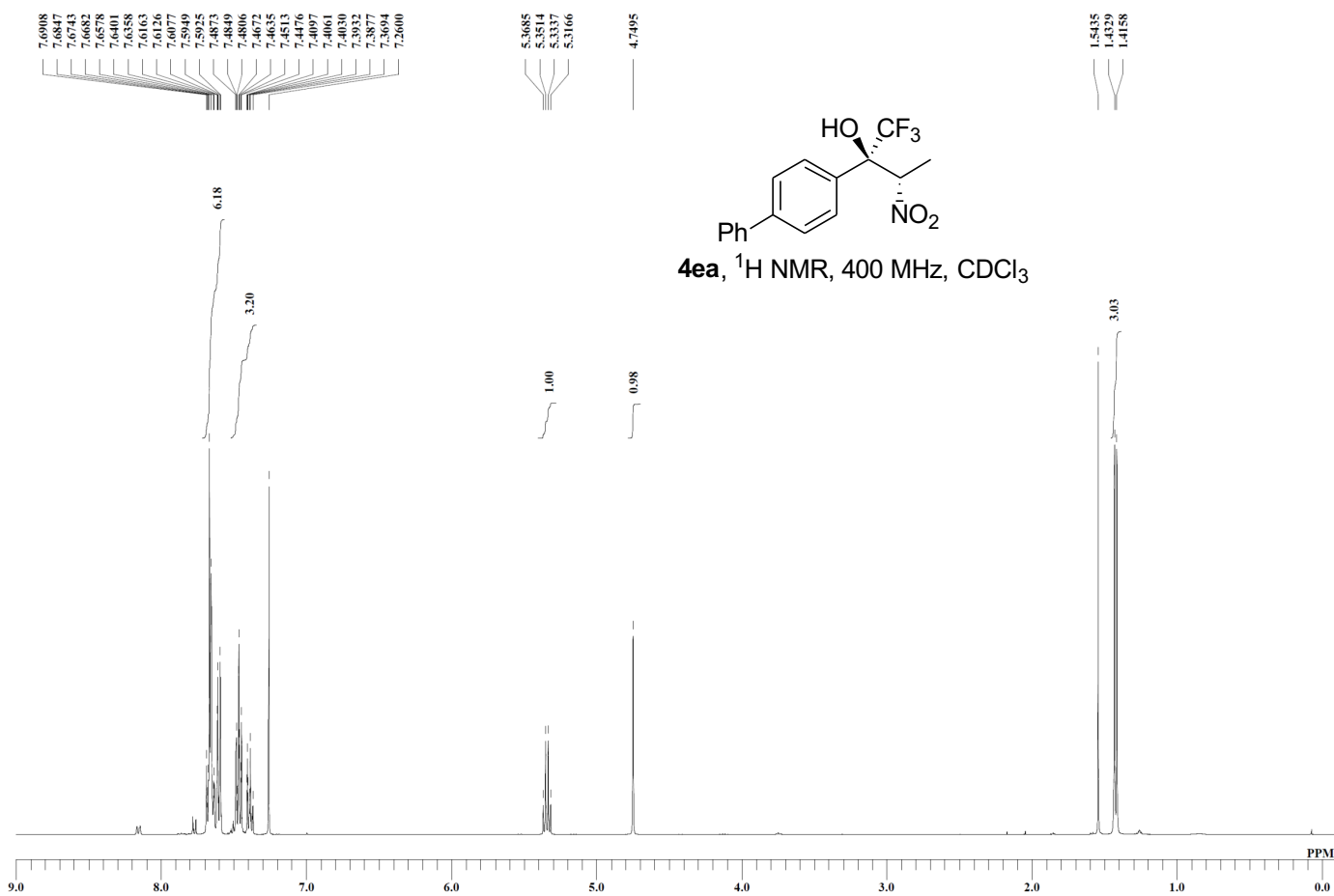
- 1 Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176.
- 2 Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860.
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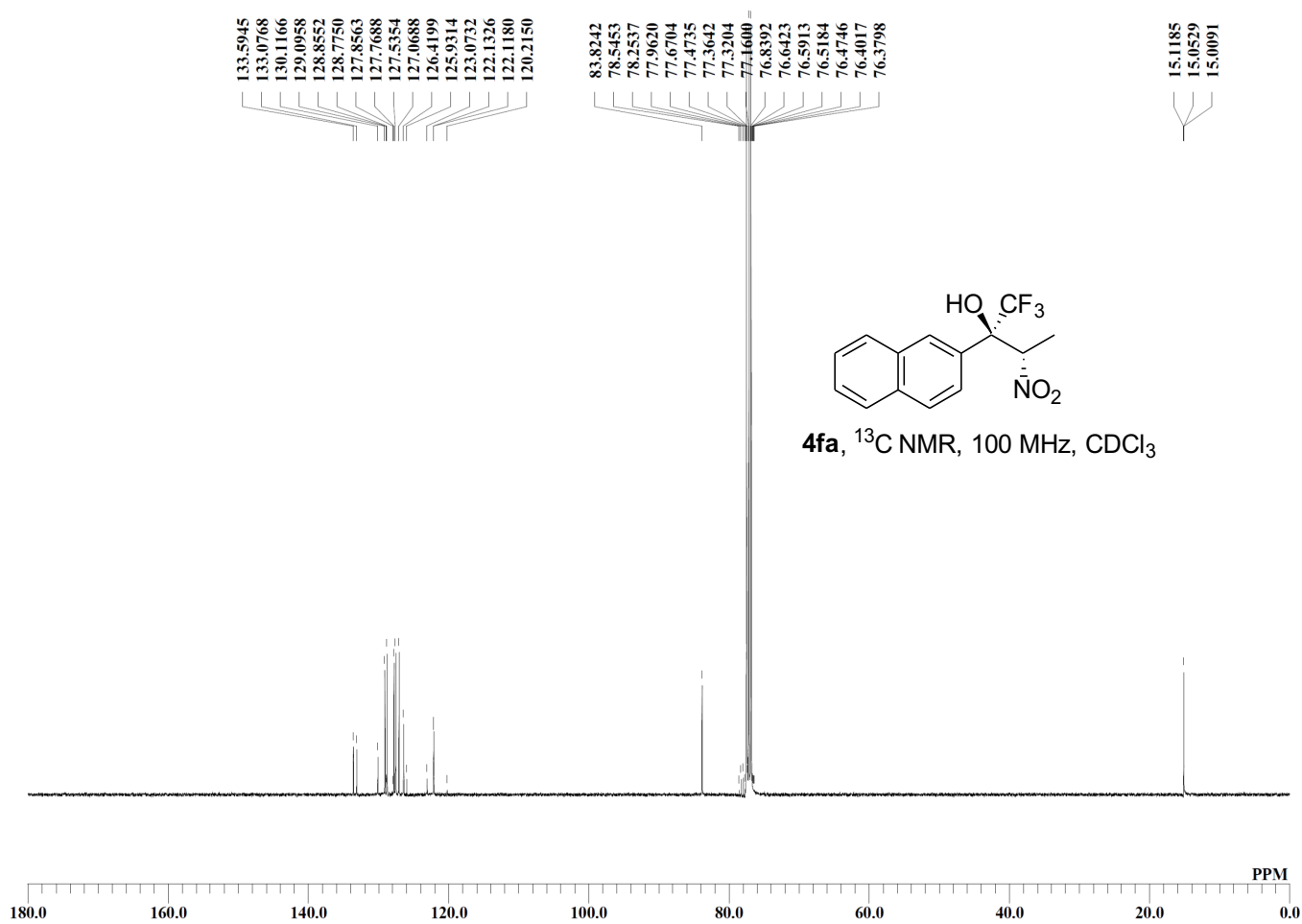
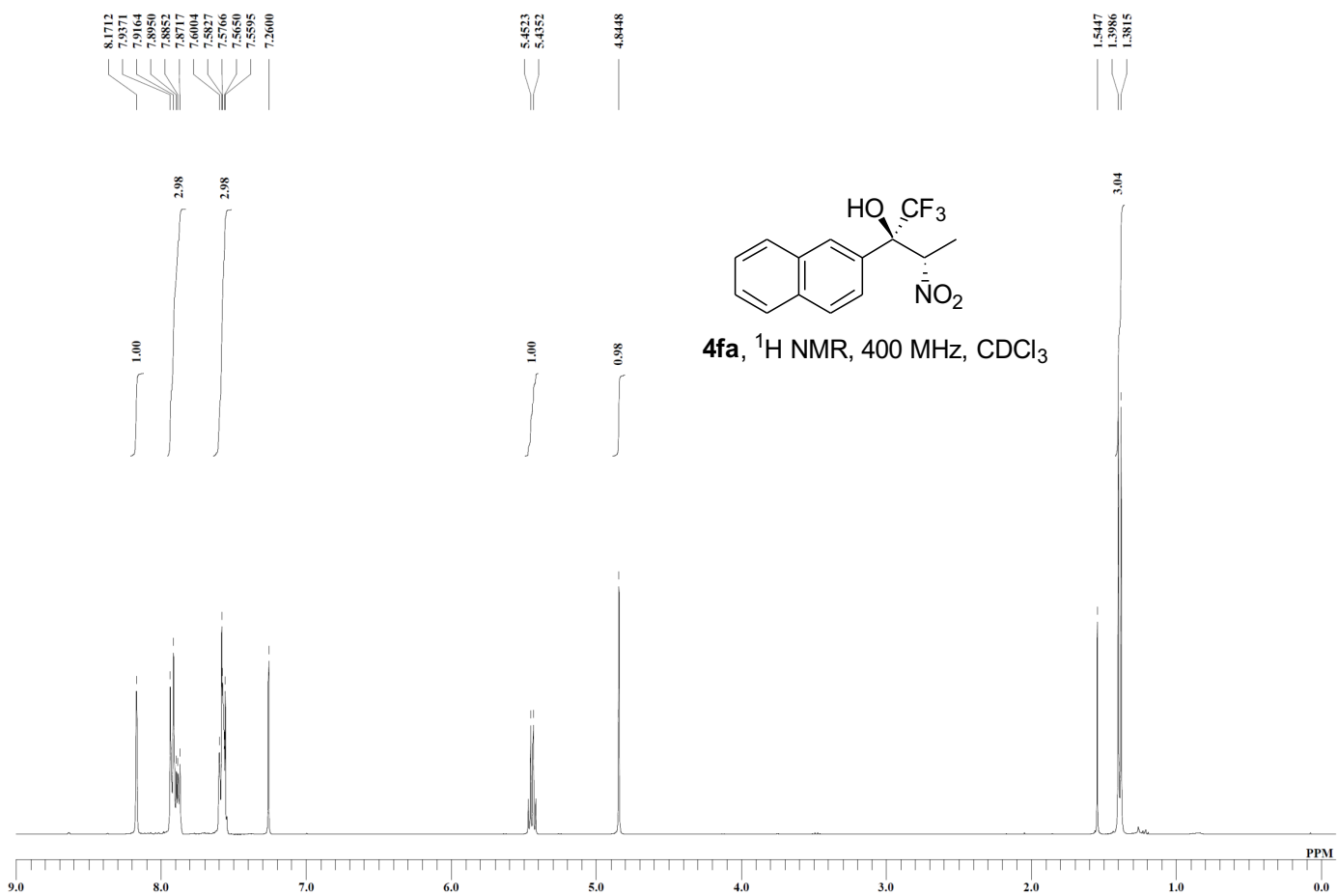
7. NMR Spectra (<sup>1</sup>H and <sup>13</sup>C NMR spectra)

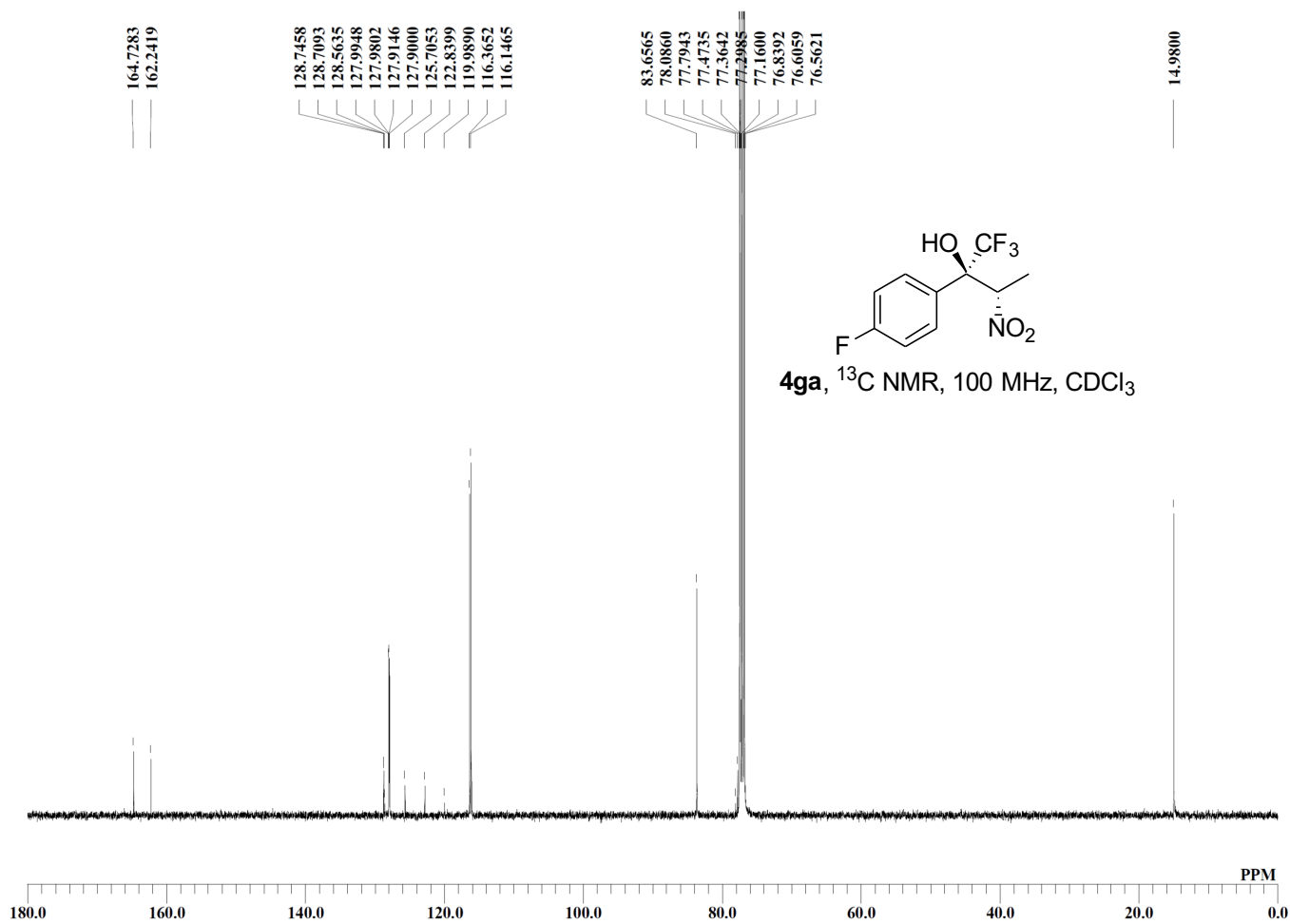
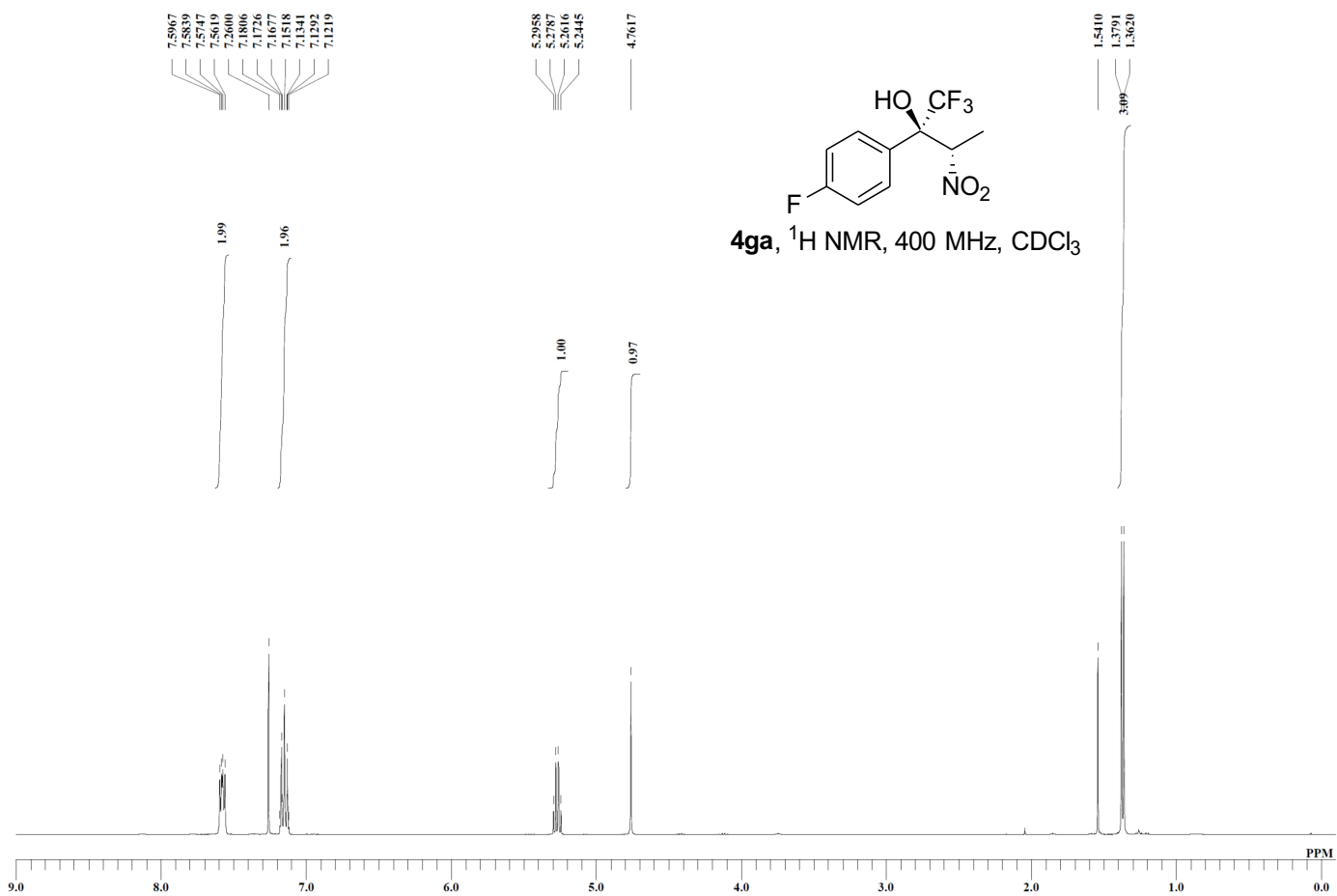
Heterogeneous Heterobimetallic Catalysis Enabling Expedient Access to CF<sub>3</sub>-Containing vic-Amino Alcohols

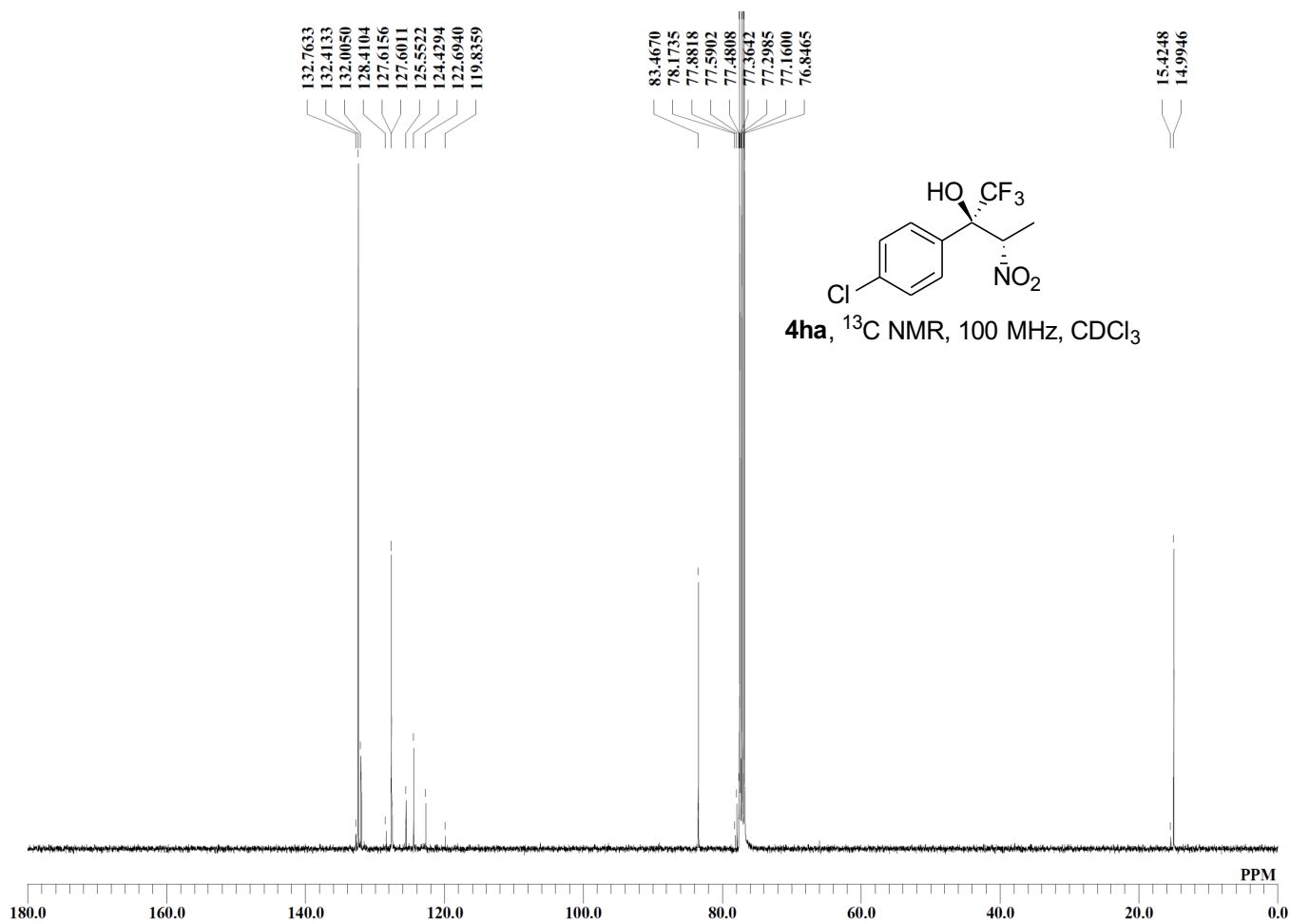
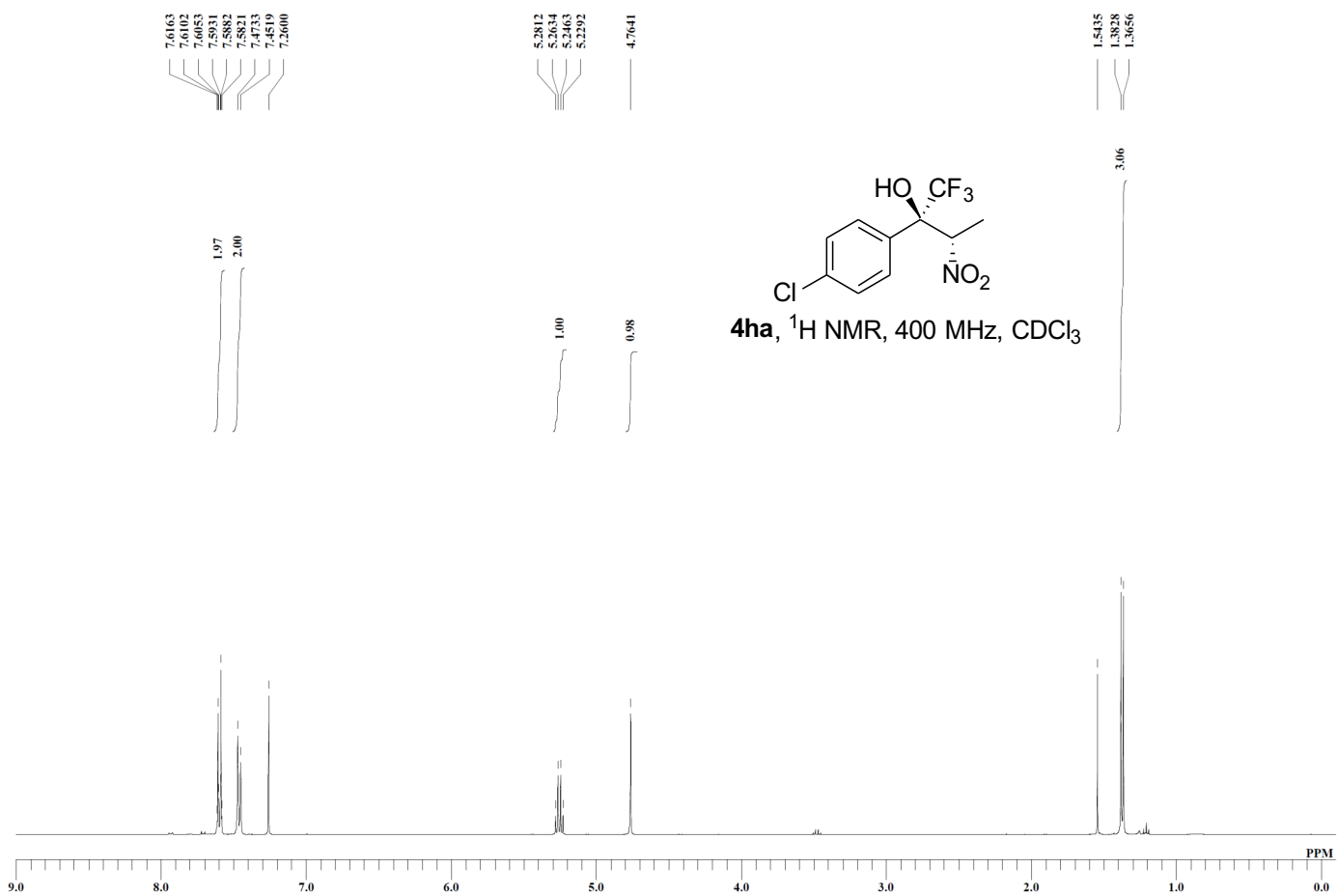


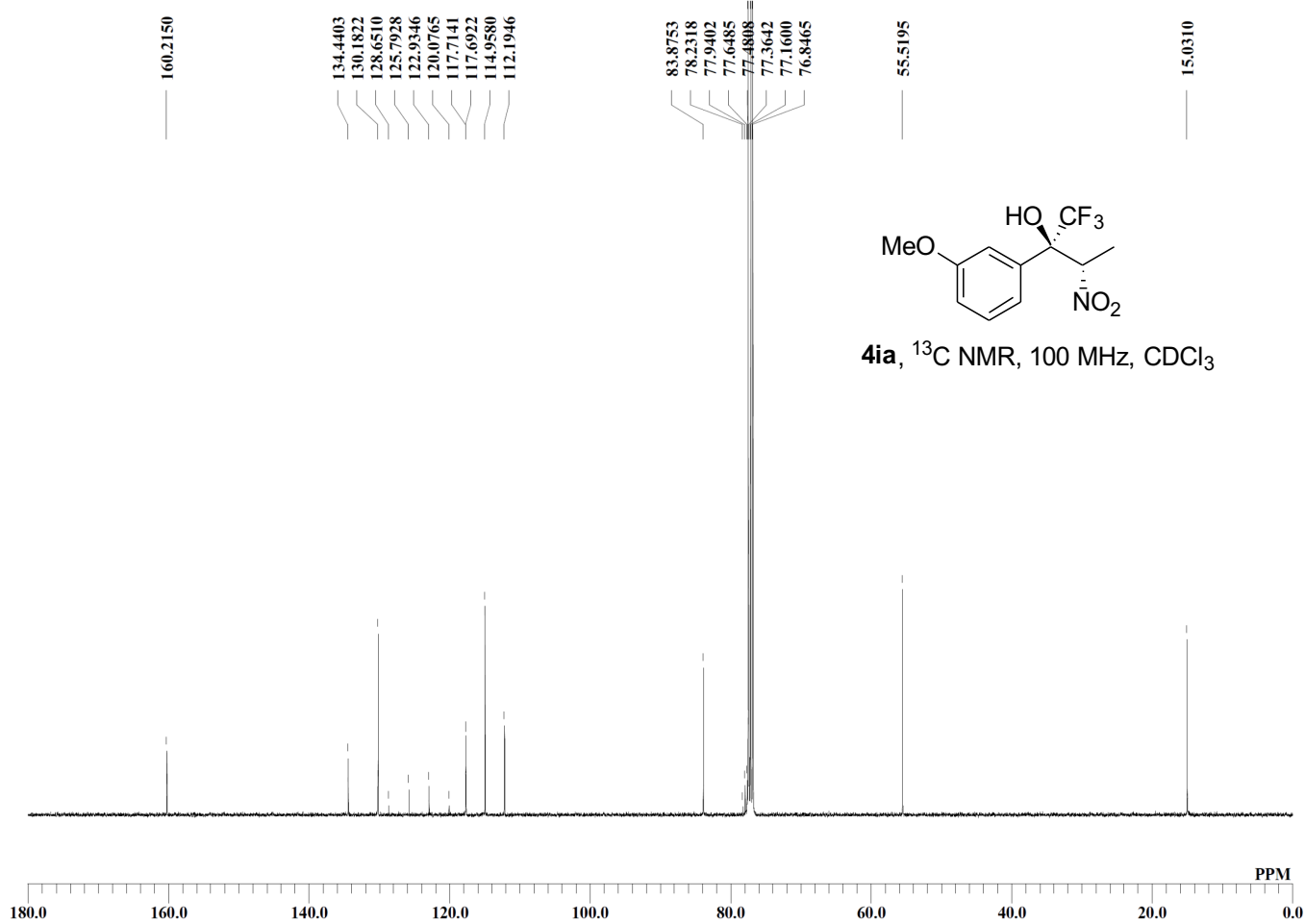
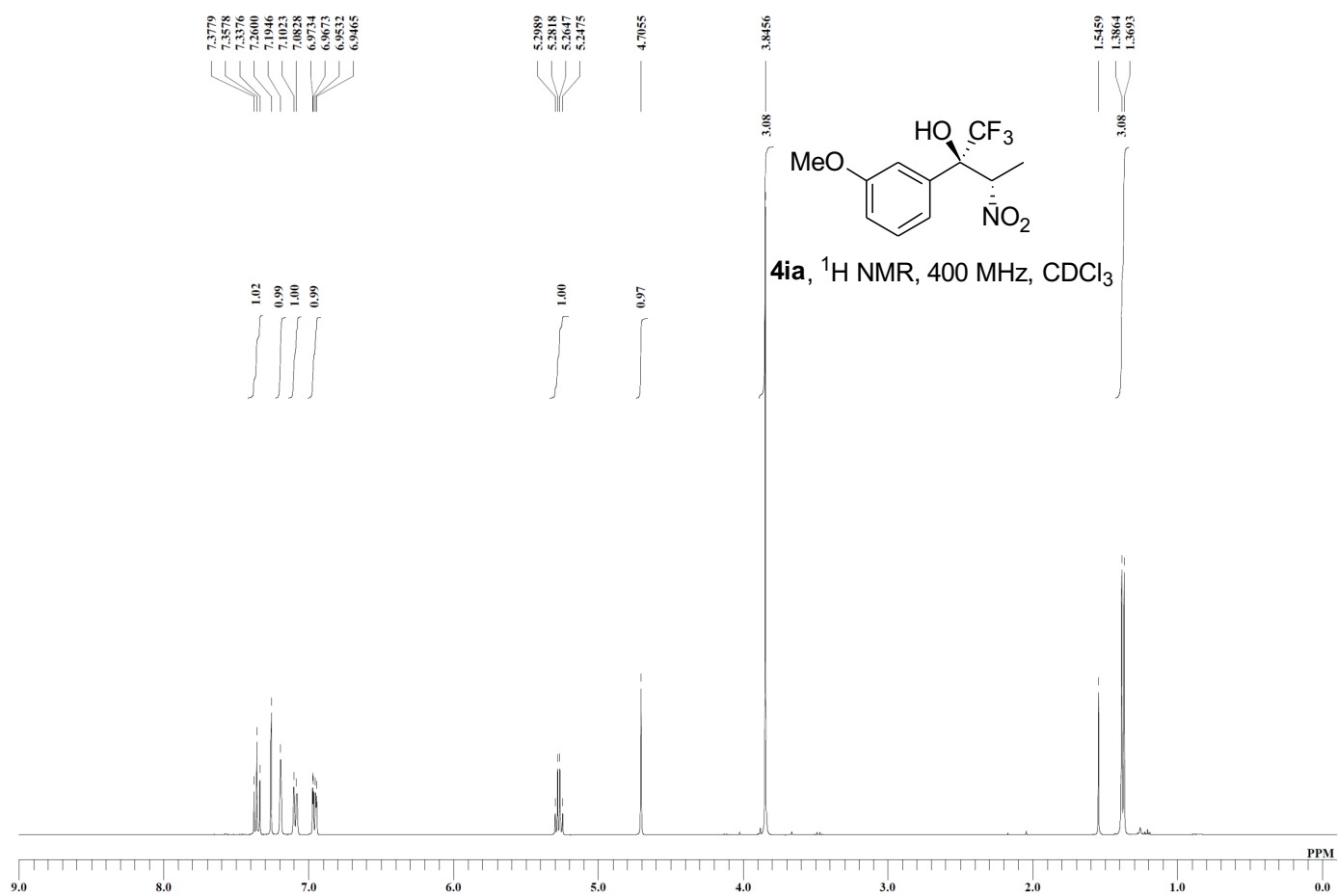
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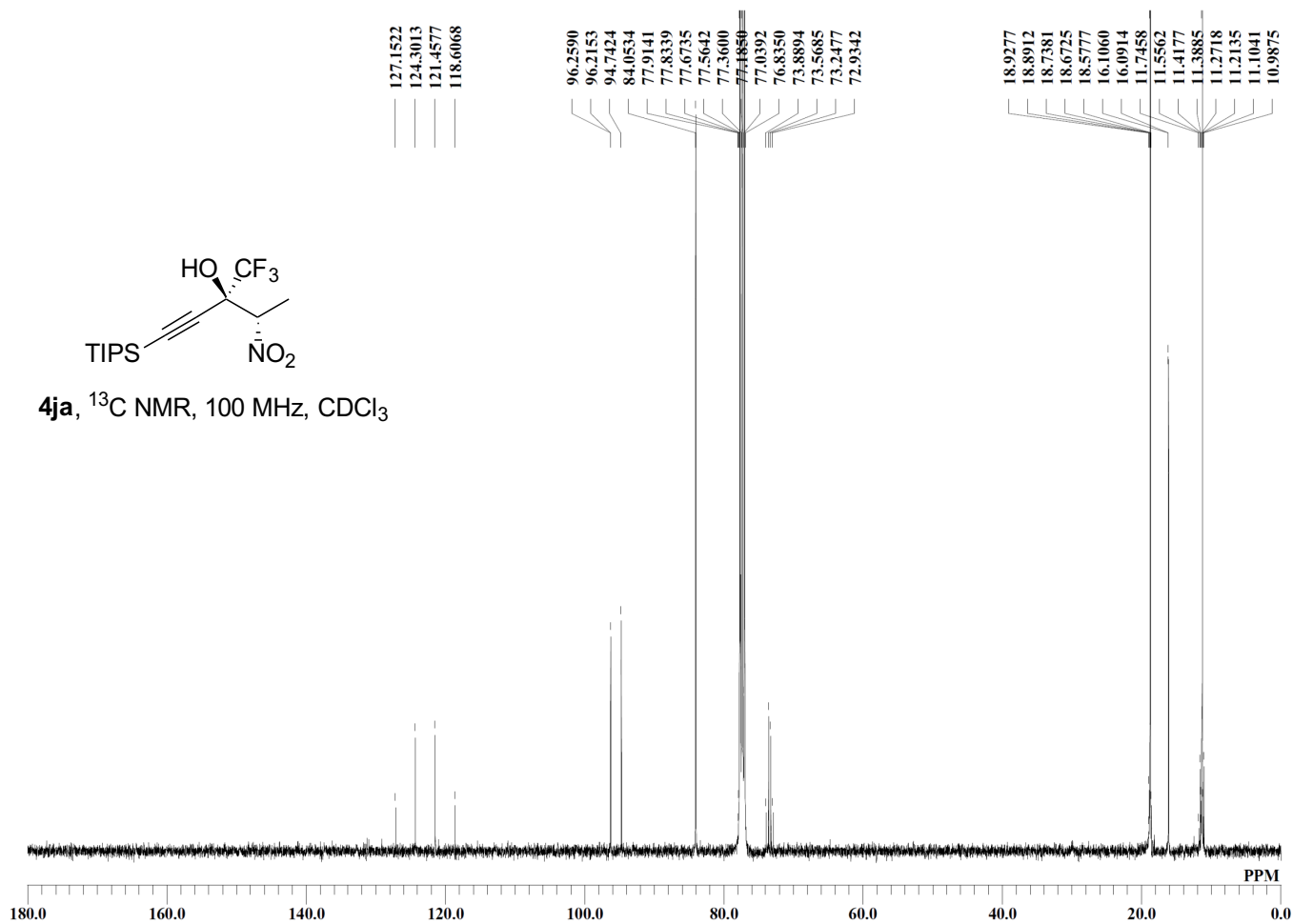
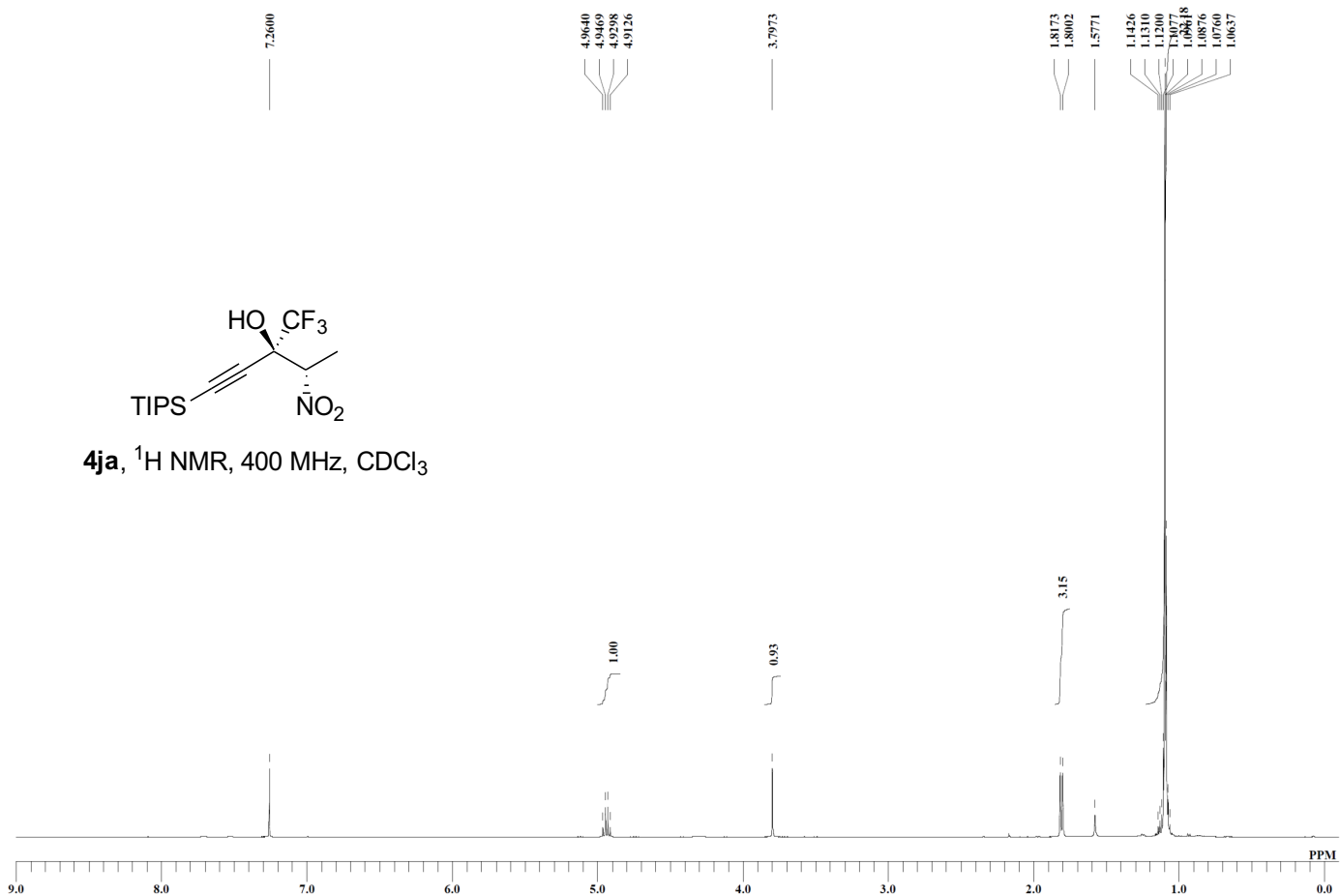


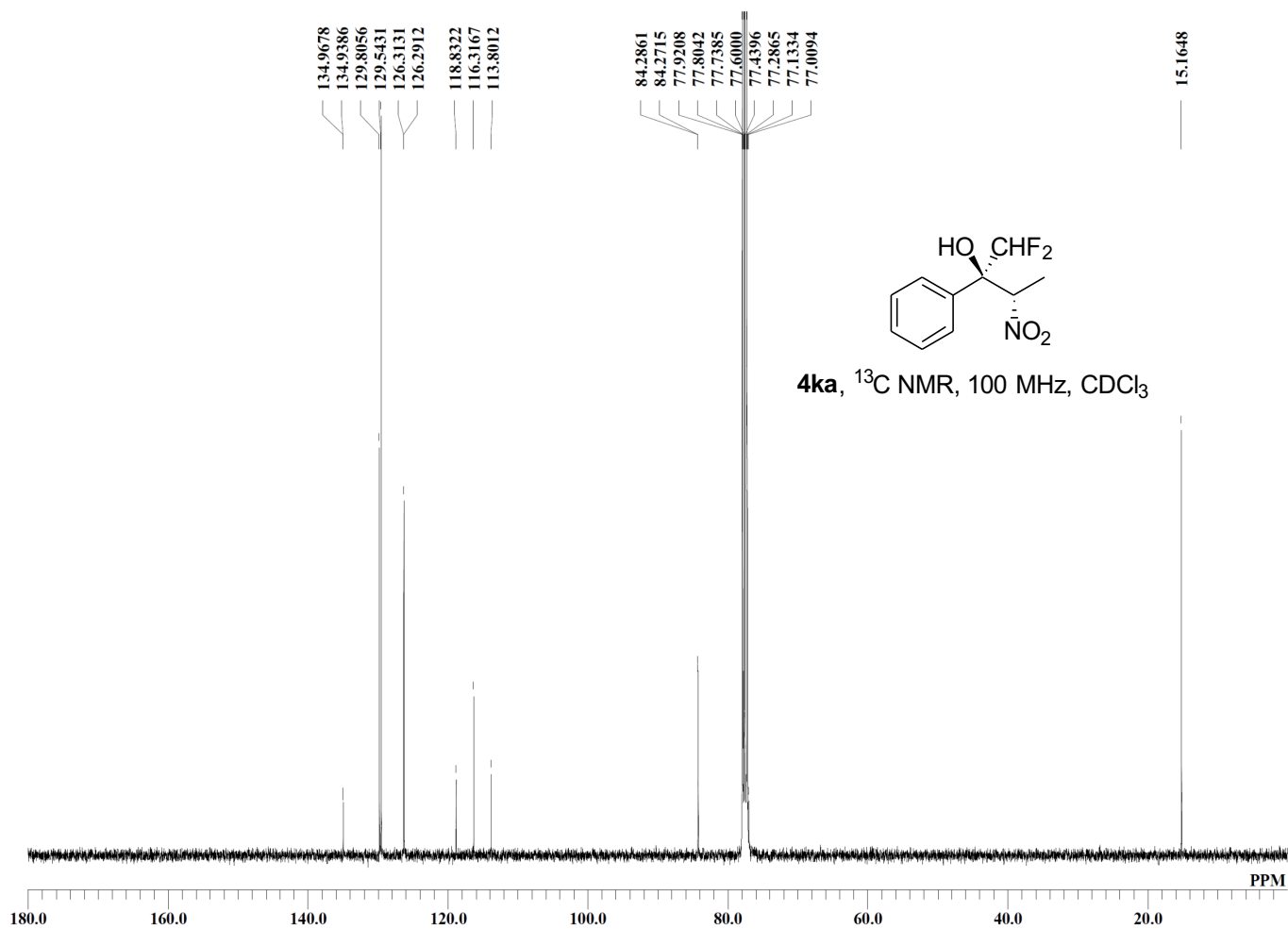
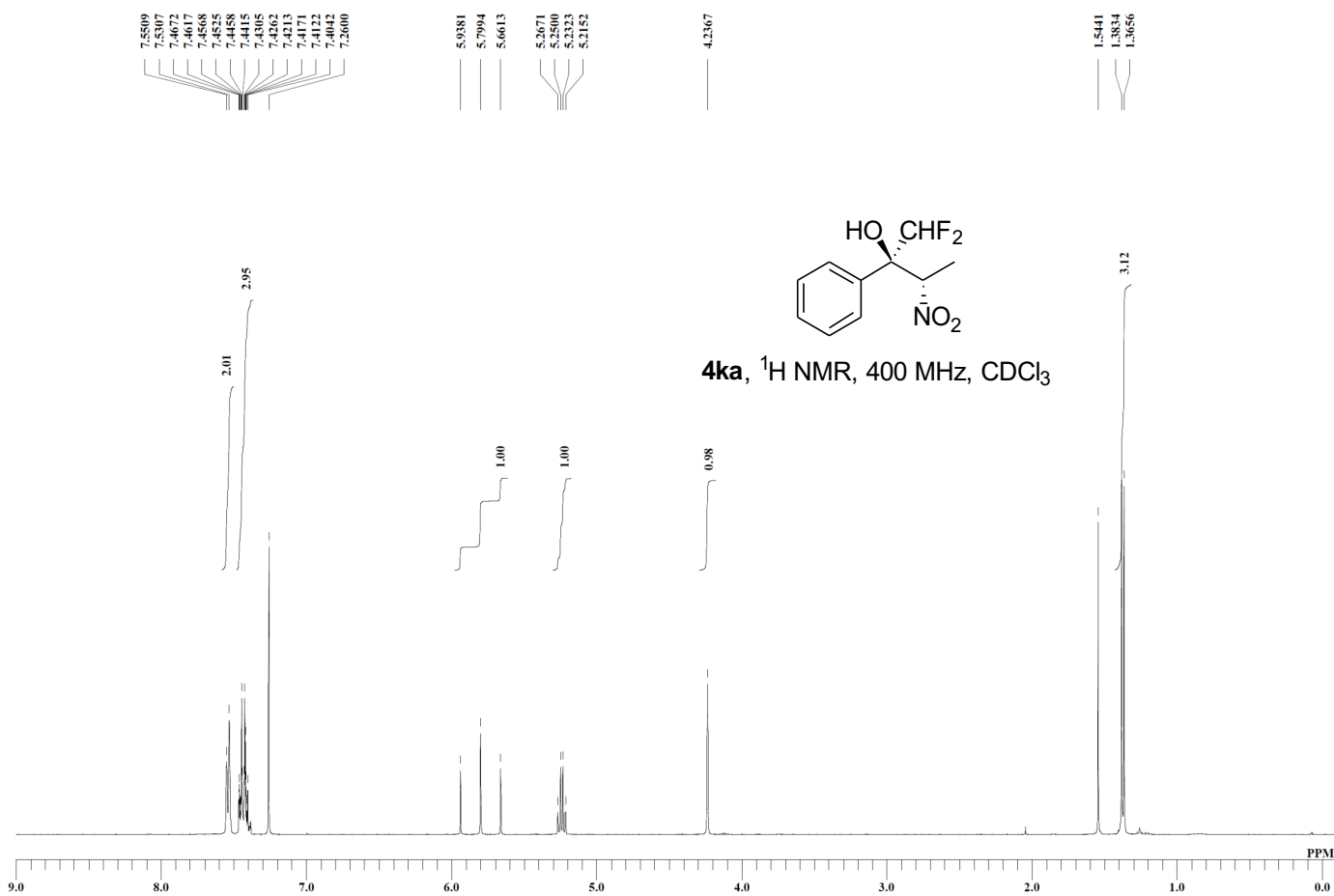
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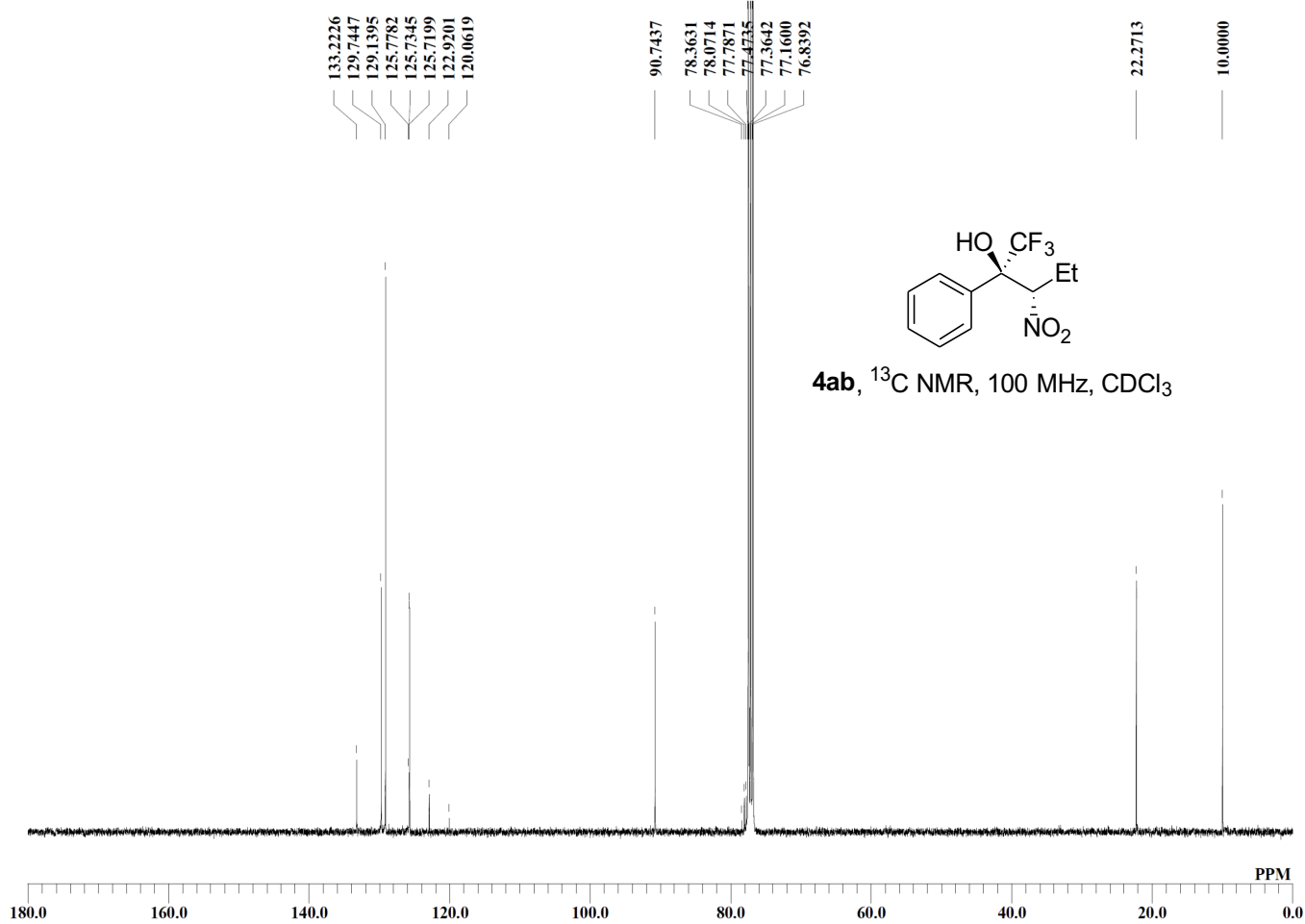
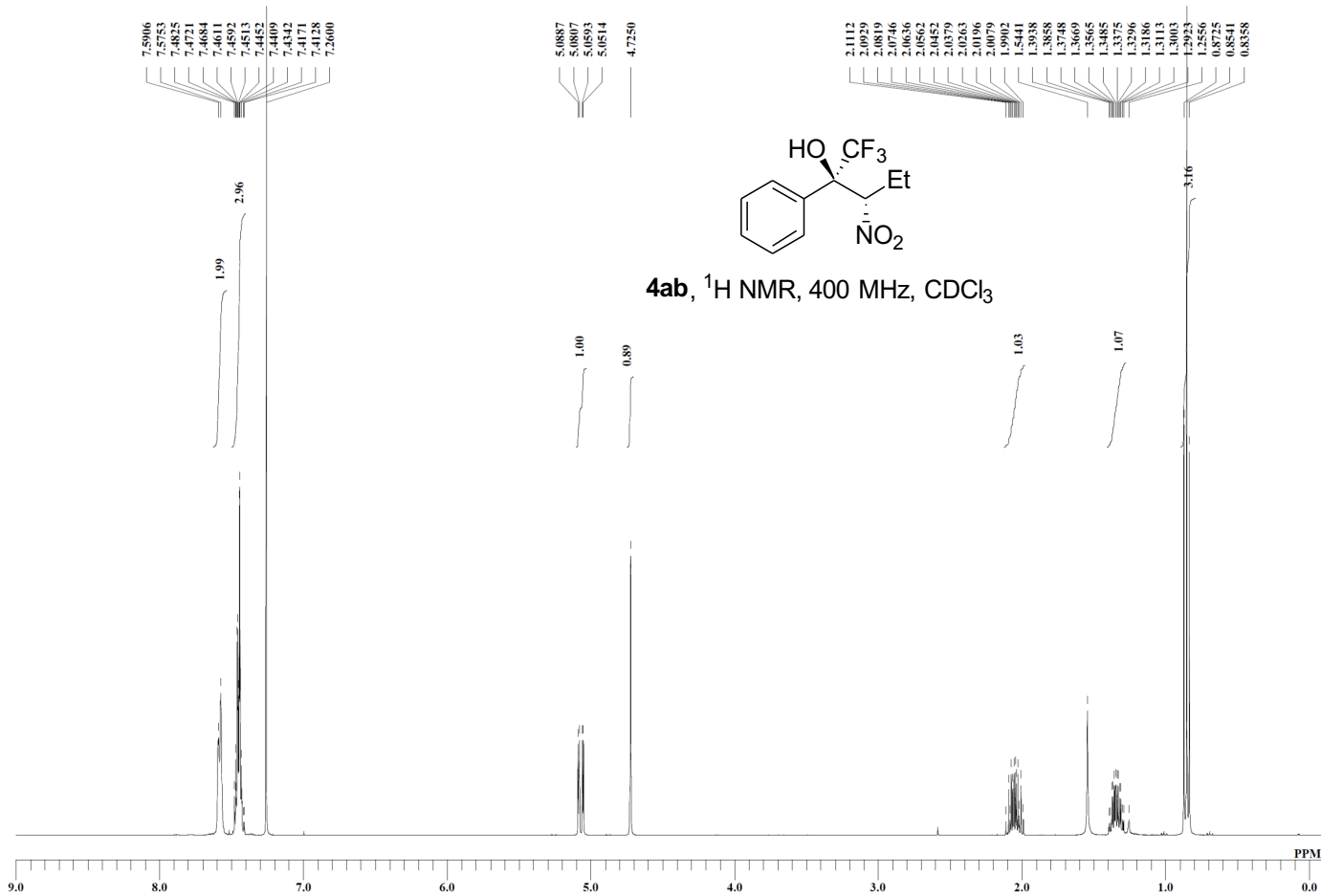


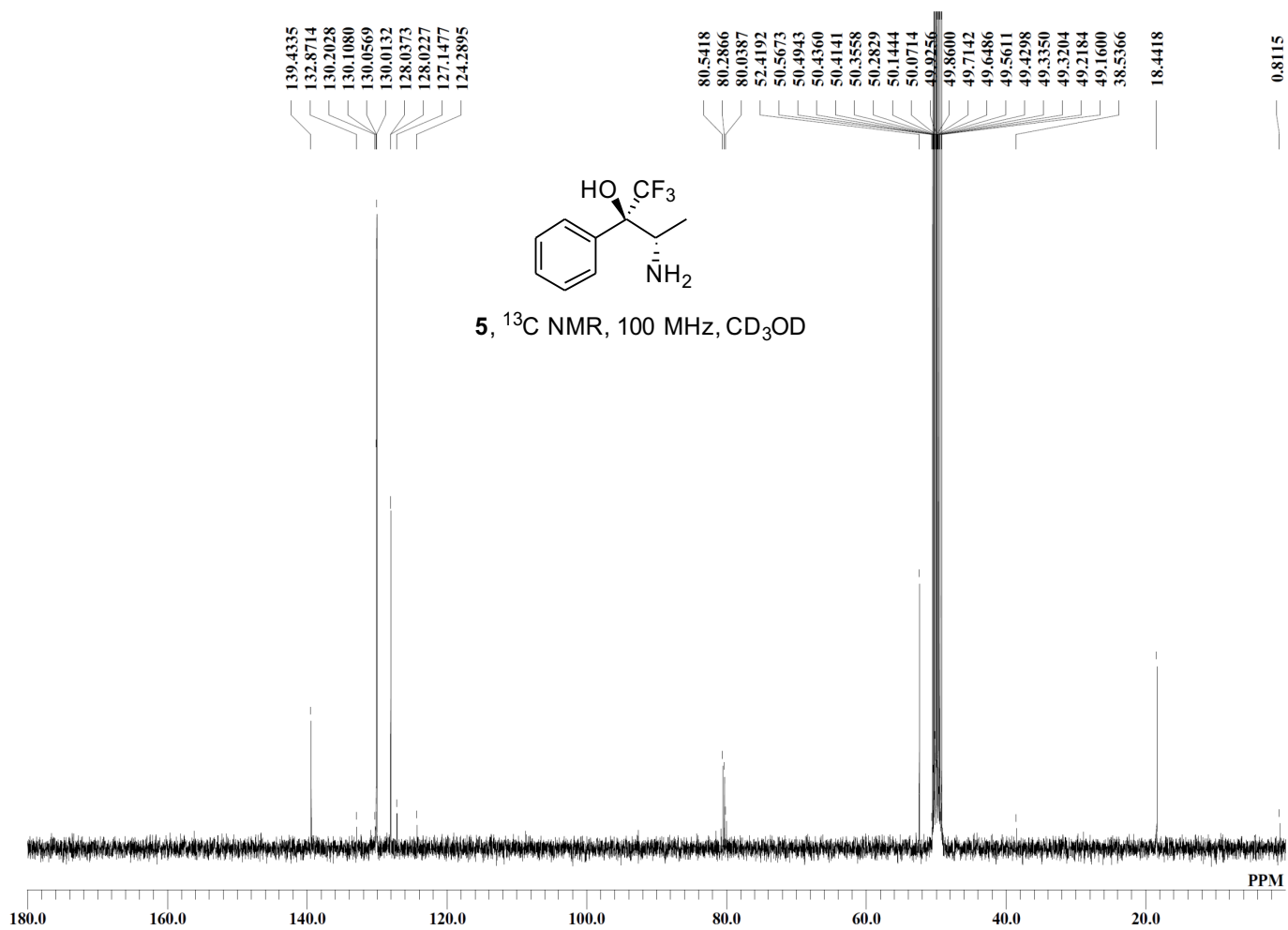
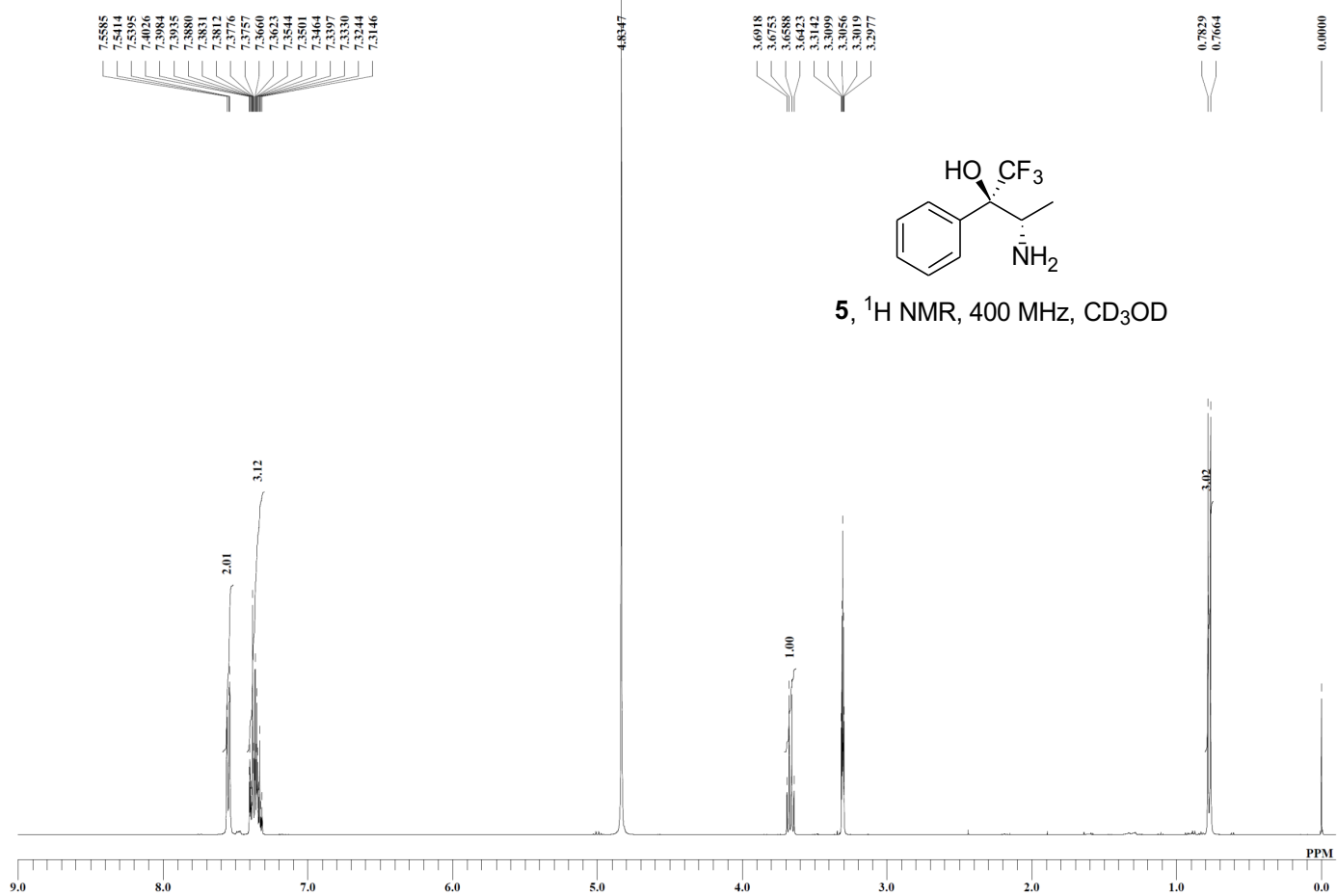
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