

Supporting Information

# Development of Facile and Simple Processes for the Heterogeneous Pd-Catalyzed Ligand-Free Continuous-Flow Suzuki–Miyaura Coupling

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## 1. General

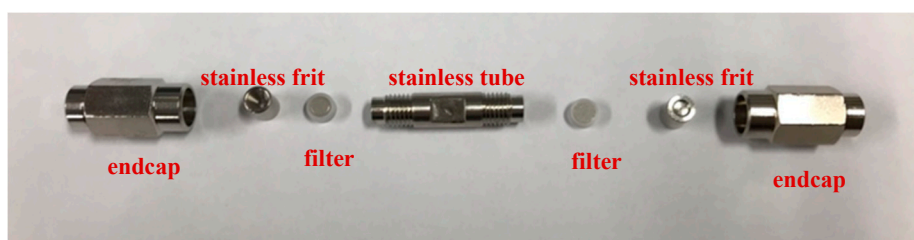
All reagents and solvents were obtained from commercial sources and used without further purification. The dimethylamine-immobilized polymer WA30 was obtained from Mitsubishi Chemical Corporation (Tokyo, Japan).  $\text{Pd}(\text{OAc})_2$  was obtained from N.E. Chemcat Corporation (Tokyo, Japan). Flash column chromatography was performed using Silica Gel 60 N (Kanto Chemical Co. Inc., 63–210  $\mu\text{m}$  spherical, neutral). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a JEOL ECA-500 (500 MHz for  $^1\text{H}$  NMR and 125 MHz for  $^{13}\text{C}$  NMR) and ECZ-400 (400 MHz for  $^1\text{H}$  NMR and 100 MHz for  $^{13}\text{C}$  NMR) spectrometers.  $\text{CDCl}_3$  was used as solvent for the NMR measurements. The chemical shifts ( $\delta$ ) are expressed in parts per million and internally referenced (0.00 ppm for tetramethylsilane). All  $^1\text{H}$  NMR spectra of known products were identical to those reported in literature.

## 2. Preparation of 7% Pd/WA30

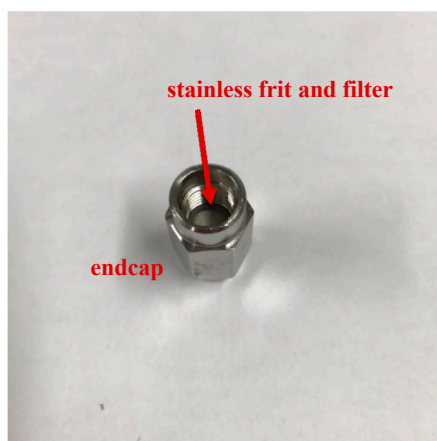
A suspension of dry WA30 (3.00 g, colorless particles) in an ethyl acetate solution (30 mL) of  $\text{Pd}(\text{OAc})_2$  [2.12 mmol (226 mg; palladium)] was stirred under argon atmosphere at 25 °C for 4 d. The resulting yellow solid was collected by filtration (1 mm filter paper), washed with  $\text{H}_2\text{O}$  (10 mL  $\times$  3), ethyl acetate (10 mL  $\times$  3), and MeOH (10 mL  $\times$  3), and dried in vacuo for 24 h. The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with MeOH. Leached Pd species were not detected (detection limit: < 1 ppm) in the diluted filtrate using atomic absorption spectrometry (SHIMADZU AA-7000). The collected solid was then stirred with hydrazine monohydrate ( $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ ) (310.0  $\mu\text{L}$ , 6.37  $\mu\text{mol}$ ) in  $\text{H}_2\text{O}$  (30 mL) for 24 h at 25 °C under argon atmosphere. A pale gray solid was collected by filtration (1 mm filter paper), washed with  $\text{H}_2\text{O}$  (10 mL  $\times$  3) and MeOH (10 mL  $\times$  3), and dried in vacuo for 24 h to generate Pd/WA30 (3.23 g). The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with MeOH. Palladium species were not observed in the diluted filtrate (detection limit: < 1 ppm). Palladium species absorbed on WA30 were not detected. Thus, the palladium content of Pd/WA30 (ethyl acetate) was estimated to be approximately 7% [(226–0)/3230  $\times$  100].

## 3. Preparation of catalyst cartridge

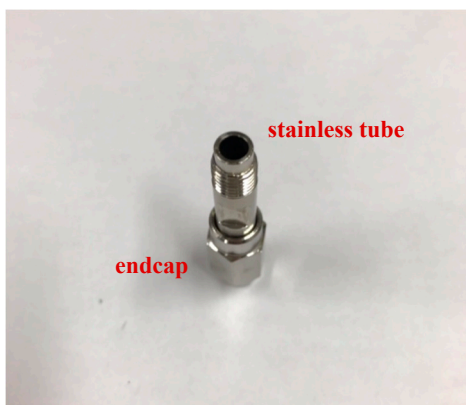
1) Prepare endcaps, stainless frits, filters, and stainless tube.



↓ Insert stainless frit and filter inside the endcap.



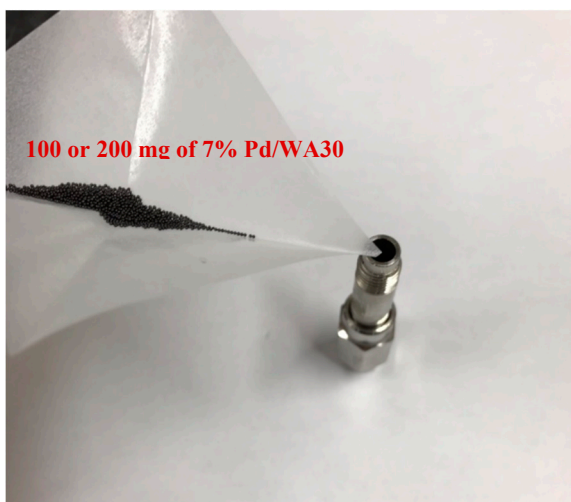
- 2) Assemble the endcap (with stainless frit and filter) and stainless tube, according to the diagram below.



- 3) Insert ca. 0.8 mL of glass wool tightly into the stainless tube.



- 4) Fill the tube with 100 or 200 mg of 7% Pd/WA30.



- 5) Fill the tube with glass wool tightly to the end of the tube to fix the catalyst.



↓



6) Tighten the end cap (with stainless frit and filter).



#### 4. Experimental procedures

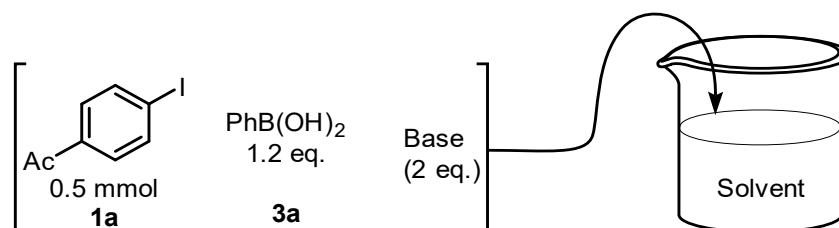
##### General Procedure A

A solution of aryl iodide or bromide (**1** or **2**, 0.50 mmol), aryl boronic acid (**3**, 0.75 mmol), and NaOH or KOH (1.0 mmol) in a mixed solvent of H<sub>2</sub>O (0.5 mL) and 1,4-dioxane (1.5 mL) was moved through the 7% Pd/WA30-packed cartridge (Ø 4.6 × 50 mm, SUS-316) by a syringe pump (YMC, YSP-101) at a flow rate of 0.05 mL/min. After transferring the entire reaction solution, the catalyst cartridge was washed with an additional mixed solvent of H<sub>2</sub>O (5 mL) and 1,4-dioxane (15 mL). The combined reaction mixture and washing solution were extracted with ethyl acetate (40 mL × 2). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to produce the corresponding coupling product **4**.

##### General Procedure B

A solution of aryl chloride (**5**, 0.25 mmol), aryl boronic acid (**3**, 0.50 mmol), and tetrabutylammonium fluoride (0.50 mmol; 1 mol/L in THF solution) was moved through the 7% Pd/WA30-packed cartridge (Ø 4.6 × 50 mm, SUS-316) by a syringe pump (YMC, YSP-101) at a flow rate of 0.05 mL/min. After transferring the entire reaction solution, the catalyst cartridge was washed with additional THF (5 mL), and then ethyl acetate (15 mL). The combined reaction mixture and washing solution were concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the corresponding coupling product **4**.

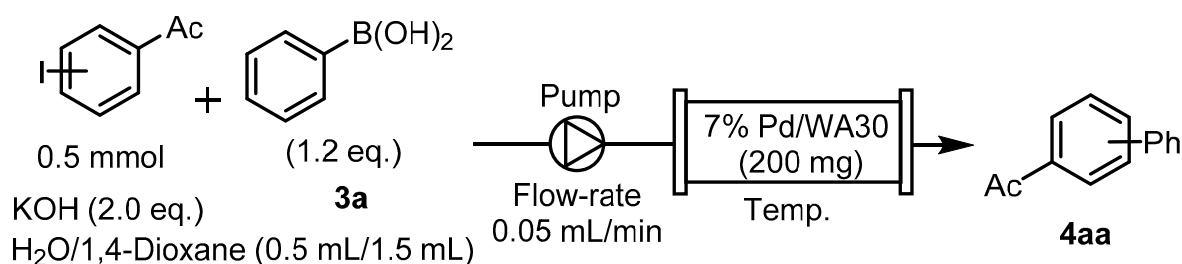
#### 5. Preliminary experiments for the solubility of the reaction solutions



Base	Solvent	Solubility
K <sub>3</sub> PO <sub>4</sub>	H <sub>2</sub> O/1,4-dioxane (0.5/1.5 mL)	Insoluble
K <sub>3</sub> PO <sub>4</sub>	H <sub>2</sub> O/1,4-dioxane (1.0/1.5 mL)	Insoluble
K <sub>3</sub> PO <sub>4</sub>	H <sub>2</sub> O/1,4-dioxane (0.5/2.5 mL)	Insoluble
K <sub>3</sub> PO <sub>4</sub>	H <sub>2</sub> O/EtOH (0.5/1.5 mL)	Insoluble
K <sub>3</sub> PO <sub>4</sub>	H <sub>2</sub> O/DMA (0.5/1.5 mL)	Insoluble
K <sub>3</sub> PO <sub>4</sub>	H <sub>2</sub> O/DMF (0.5/1.5 mL)	Insoluble
K <sub>3</sub> PO <sub>4</sub>	H <sub>2</sub> O/THF (0.5/1.5 mL)	Insoluble
NaOH	H <sub>2</sub> O/THF (0.5/1.5 mL)	Insoluble
NaOH	H <sub>2</sub> O/DMSO (0.5/1.5 mL)	Insoluble
NaOH	H <sub>2</sub> O/DMA (0.5/1.5 mL)	Insoluble
NaOH	H <sub>2</sub> O/DMF (0.5/1.5 mL)	Insoluble
NaOH	H <sub>2</sub> O/NMP (0.5/1.5 mL)	Insoluble
NaOH	H <sub>2</sub> O/2-PrOH (0.5/1.5 mL)	Insoluble
NaOH	H <sub>2</sub> O/EtOH (0.5/1.5 mL)	Insoluble <sup>1</sup>
NaOH	H <sub>2</sub> O/1,4-dioxane (0.5/1.5 mL)	Soluble
KOH	H <sub>2</sub> O/1,4-dioxane (0.5/1.5 mL)	Soluble

<sup>1</sup> Precipitation was observed after leaving to stand the solution.

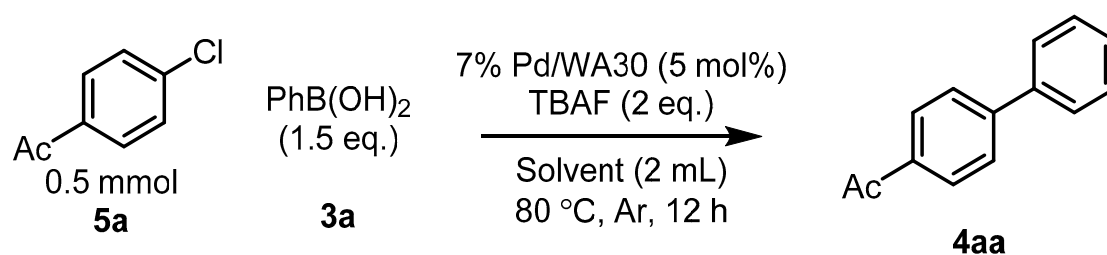
#### 6. Optimization for the continuous-flow Suzuki–Miyaura coupling of 3'-iodoacetophenone and 2'-iodoacetophenone



Entry	X	Temp.	<sup>1</sup> H NMR ratio (SM : Product)	Yield (%)
1	3-I ( <b>1b</b> )	25 °C	47 : 53	53
2	3-I ( <b>1b</b> )	40 °C	25 : 75	65 <sup>1</sup>
3	3-I ( <b>1b</b> )	80 °C	Trace : >99	Quant. <sup>1</sup>
4	2-I ( <b>1c</b> )	25 °C	45 : 55	55
5	2-I ( <b>1c</b> )	40 °C	36 : 64	64 <sup>1</sup>
6	2-I ( <b>1c</b> )	80 °C	17 : 83	83 <sup>1</sup>

<sup>1</sup> 1.5 equivalents of phenylboronic acid (**3a**) were used.

#### 7. Optimization of a reaction solvent for the continuous-flow Suzuki–Miyaura coupling of 3'-chloroacetophenone under the batch conditions



Entry	Solvent	<sup>1</sup> H NMR ratio (SM : Product)	Yield (%)
1	DMA	13 : 87	46
2	MeCN	80 : 20	15
3	toluene	19 : 81	81
4	1,4-dioxane	Trace : >99	85
5	CPME	13 : 87	87
6	THF	Trace : Quant.	Quant.

## 8. Spectroscopic data of products

### 4-Acetylbiphenyl (4aa)

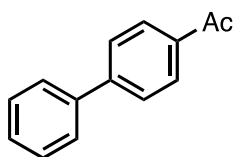


Table 1, entry 3: According to the GP-A, 4'-iodoacetophenone (**1a**, 123.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 4-Acetylbiphenyl (**4aa**, 97.1 mg, 0.5 mmol) was obtained in 99% yield as a colorless solid.

Table 1, entry 7: According to the GP-A, 4'-bromoacetophenone (**2a**, 99.5 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 4-Acetylbiphenyl (**4aa**, 93.2 mg, 0.48 mmol) was obtained in 95% yield as a colorless solid.

Table 2, entry 7: According to the GP-A, iodobenzene (**1g**, 102.0 mg, 0.50 mmol), 4-acetylphenylboronic acid (**3c**, 123.0 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol), H<sub>2</sub>O (1.0 mL), 1,4-dioxane (3.0 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 4-Acetylbiphenyl (**4aa**, 94.4 mg, 0.48 mmol) was obtained in 96% yield as a colorless solid.

Table 3, entry 6: According to the GP-B, 4'-chloroacetophenone (**5a**, 38.6 mg, 0.25 mmol), phenylboronic acid (**3a**, 61.0 mg, 0.50 mmol), tetrabutylammonium fluoride (0.5 mL, 0.50 mmol; 1 mol/L in tetrahydrofuran), tetrahydrofuran (2.0 mL), and 7% Pd/WA30 (100 mg) were used at 80 °C. 4-Acetylbiphenyl (**4aa**, 33.4 mg, 0.17 mmol) was obtained in 68% yield as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.46–7.42 (m, 2H), 7.39–7.35 (m, 1H), 2.59 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 197.6, 145.5, 139.6, 135.6, 128.8, 128.8, 128.1, 127.1, 127.0, 26.5. Spectroscopic data of <sup>1</sup>H NMR was identical to that of reference 1.

### 3-Acetylbiphenyl (4ba)

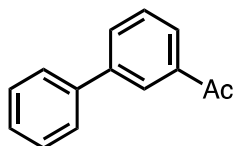


Table 2, entry 1: According to the GP-A, 3'-iodoacetophenone (**1b**, 123.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 3-Acetylbiphenyl (**4ba**, 98.1 mg, 0.50 mmol) was obtained in quantitative yield as a colorless solid.

Table 2, entry 8: According to the GP-A, 3'-bromoacetophenone (**2b**, 99.5 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.57 mmol), NaOH (40.0 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 3-Acetylbiphenyl (**4ba**, 80.0 mg, 0.41 mmol) was obtained in 81% yield as a colorless solid.



Figure 3: According to the GP-B, 3'-chloroacetophenone (**5b**, 38.6 mg, 0.25 mmol), phenylboronic acid (**3a**, 61.0 mg, 0.50 mmol), tetrabutylammonium fluoride (0.5 mL, 0.50 mmol; 1 mol/L in tetrahydrofuran), tetrahydrofuran (2.0 mL), and 7% Pd/WA30 (100 mg) were used at 80 °C. 3-Acetylbiphenyl (**4ba**, 33.4 mg, 0.17 mmol) was obtained in 68% yield as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.17 (d, *J* = 1.2 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.61–7.59 (m, 2H), 7.53–7.49 (m, 1H), 7.47–7.43 (m, 2H), 7.39–7.35 (m, 1H), 2.64 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 198.0, 141.5, 140.0, 137.5, 131.6, 128.9, 128.8, 127.7, 127.1, 126.8 (2C), 26.7. Spectroscopic data of <sup>1</sup>H NMR was identical to that of reference 1.

#### 2-Acetylbiphenyl (**4ca**)

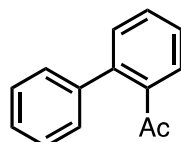


Table 2, entry 2: According to the GP-A, 2'-iodoacetophenone (**1c**, 123.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 2-Acetylbiphenyl (**4ca**, 81.4 mg, 0.42 mmol) was obtained in 83% yield as a colorless solid.

Table 2, entry 9: According to the GP-A, 2'-bromoacetophenone (**2c**, 99.5 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 2-Acetylbiphenyl (**4ca**, 55.9 mg, 0.29 mmol) was obtained in 57% yield as a colorless solid.

Figure 3: According to the GP-B, 2'-chloroacetophenone (**5c**, 38.6 mg, 0.25 mmol), phenylboronic acid (**3a**, 61.0 mg, 0.50 mmol), tetrabutylammonium fluoride (0.5 mL, 0.50 mmol; 1 mol/L in tetrahydrofuran), tetrahydrofuran (2.0 mL), and 7% Pd/WA30 (100 mg) were used at 80 °C. 2-Acetylbiphenyl (**4ca**, 31.4 mg, 0.16 mmol) was obtained in 64% yield as a colorless solid.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.53–7.50 (m, 1H), 7.45–7.38 (m, 5H), 7.36–7.34 (m, 2H), 2.00 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 205.0, 140.9, 140.7, 140.5, 130.7, 130.2, 128.8, 128.7, 127.9, 127.8, 127.4, 30.4. Spectroscopic data of <sup>1</sup>H NMR was identical to that of reference 1.

#### Ethyl biphenyl-4-carboxylate (**4da**)

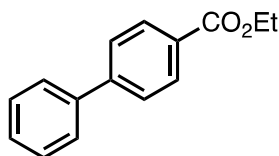


Table 2, entry 3: According to the GP-A, ethyl 4-iodobenzoate (**1d**, 138.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. Ethyl biphenyl-4-carboxylate (**4da**, 100.7 mg, 0.45 mmol) was obtained in 89% yield as a colorless solid.

Table 2, entry 10: According to the GP-A, ethyl 4-bromobenzoate (**2d**, 114.5 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. Ethyl biphenyl-4-carboxylate (**4da**, 56.6 mg, 0.25 mmol) was obtained in 50% yield as a colorless solid.

Figure 3: According to the GP-B, ethyl 4-chlorobenzoate (**5d**, 46.2 mg, 0.25 mmol), phenylboronic acid (**3a**, 61.0 mg, 0.50 mmol), tetrabutylammonium fluoride (0.5 mL, 0.50 mmol; 1 mol/L in tetrahydrofuran), tetrahydrofuran (2.0 mL), and 7% Pd/WA30 (100 mg) were used at 80 °C. Ethyl biphenyl-4-carboxylate (**4da**, 41.9 mg, 0.19 mmol) was obtained in 74% yield as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.66–7.60 (m, 4H), 7.45 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.40–7.36 (m, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ

166.4, 145.4, 139.9, 130.0, 129.1, 128.8, 128.0, 127.2, 126.9, 60.9, 14.3. Spectroscopic data of  $^1\text{H}$  NMR was identical to that of reference 1.

#### 4-Methylbiphenyl (4ea)

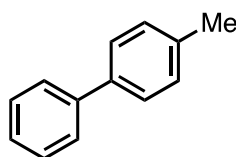


Table 2, entry 4: According to the GP-A, 4-iodotoluene (**1e**, 109.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 4-Methylbiphenyl (**4ea**, 70.4 mg, 0.42 mmol) was obtained in 84% yield as a colorless solid.

Table 2, entry 11: According to the GP-A, 4-bromotoluene (**2e**, 85.5 mg, 0.5 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 4-Methylbiphenyl (**4ea**, 67.3 mg, 0.40 mmol) was obtained in 80% yield as a colorless solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.57 (d,  $J$  = 7.1 Hz, 2H), 7.48 (d,  $J$  = 7.8 Hz, 2H), 7.41 (dd,  $J$  = 7.1, 7.1 Hz, 2H), 7.31 (dd,  $J$  = 7.1, 7.1 Hz, 1H), 7.23 (d,  $J$  = 7.8 Hz, 2H), 2.38 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  141.1, 138.2, 137.0, 129.5, 128.7, 127.0 (3C), 21.1. Spectroscopic data of  $^1\text{H}$  NMR was identical to that of reference 2.

#### 4-Methoxybiphenyl (4fa)

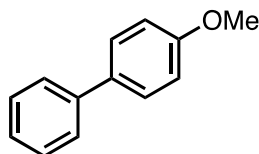


Table 2, entry 5: According to the GP-A, 4-iodoanisole (**1f**, 117.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 4-Methoxybiphenyl (**4fa**, 81.1 mg, 0.44 mmol) was obtained in 88% yield as a colorless solid.

Table 2, entry 12: According to the GP-A, 4-bromoanisole (**2f**, 93.5 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 4-Methoxybiphenyl (**4fa**, 39.6 mg, 0.22 mmol) was obtained in 43% yield as a colorless solid.

Table 2, entry 6: According to the GP-A, iodobenzene (**1g**, 102.0 mg, 0.50 mmol), 4-methoxyphenylboronic acid (**3b**, 114.0 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 4-Methoxybiphenyl (**4fa**, 66.3 mg, 0.36 mmol) was obtained in 72% yield as a colorless solid.

Table 2, entry 13: According to the GP-A, bromobenzene (**2g**, 78.5 mg, 0.50 mmol), 4-methoxyphenylboronic acid (**3b**, 114.0 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.8 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 4-Methoxybiphenyl (**4fa**, 68.8 mg, 0.38 mmol) was obtained in 75% yield as a colorless solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.55–7.50 (m, 4H), 7.39 (dd,  $J$  = 7.6, 7.6 Hz, 2H), 7.30–7.26 (m, 1H), 6.96 (d,  $J$  = 9.2 Hz, 2H), 3.81 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  159.1, 140.7, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.2. Spectroscopic data of  $^1\text{H}$  NMR was identical to that of reference 1.

#### 4-Methyl-4'-methoxybiphenyl (4eb)

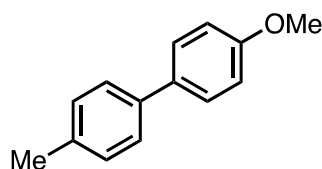


Figure 3: According to the GP-B, 4-chlorotoluene (**5e**, 31.6 mg, 0.25 mmol), 4-methoxyphenylboronic acid (**3b**, 76.0 mg, 0.50 mmol), tetrabutylammonium fluoride (0.5 mL, 0.50 mmol; 1 mol/L in tetrahydrofuran), tetrahydrofuran (2.0 mL), and 7% Pd/WA30 (100 mg) were used at 80 °C. 4-Methyl-4'-methoxybiphenyl (**4eb**, 28.3 mg, 0.14 mmol) was obtained in 57% yield as a colorless solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.51 (d,  $J$  = 9.0 Hz, 2H), 7.44 (d,  $J$  = 8.0 Hz, 2H), 7.22 (d,  $J$  = 7.5 Hz, 2H), 6.96 (d,  $J$  = 8.0 Hz, 2H), 3.84 (s, 3H), 2.38 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  158.9, 138.0, 136.3, 133.7, 129.4, 127.9, 126.6, 114.1, 55.3, 21.0. Spectroscopic data of  $^1\text{H}$  NMR was identical to that of reference 1.

#### Ethyl 4-(4-methoxyphenyl)benzoate (**4db**)

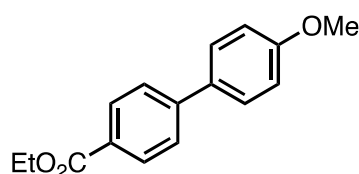


Figure 3: According to the GP-B, ethyl 4-chlorobenzoate (**5d**, 46.2 mg, 0.25 mmol), 4-methoxyphenylboronic acid (**3b**, 76.0 mg, 0.50 mmol), tetrabutylammonium fluoride (0.5 mL, 0.50 mmol; 1 mol/L in tetrahydrofuran), tetrahydrofuran (2.0 mL), and 7% Pd/WA30 (100 mg) were used at 80 °C. Ethyl 4-(4-methoxyphenyl)benzoate (**4db**, 26.9 mg, 0.11 mmol) was obtained in 42% yield as a colorless solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.08 (d,  $J$  = 8.5 Hz, 2H), 7.61 (d,  $J$  = 8.0 Hz, 2H), 7.57 (d,  $J$  = 8.5 Hz, 2H), 6.99 (d,  $J$  = 8.5 Hz, 2H), 4.42–4.37 (m, 2H), 3.86 (s, 3H), 1.41 (t,  $J$  = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.6, 159.8, 145.1, 132.4, 130.0, 128.6, 128.3, 126.4, 114.3, 60.1, 55.3, 14.3. Spectroscopic data of  $^1\text{H}$  NMR was identical to that of reference 3.

#### 4-Phenylpyridine (**4ha**)

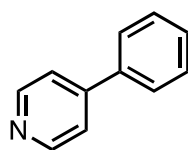


Figure 2: According to the GP-A, 4-iodopyridine (**1h**, 102.5 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 4-Phenylpyridine (**4ha**, 77.6 mg, 0.5 mmol) was obtained in quantitative yield as a colorless solid.

Figure 2: According to the GP-A, 4-bromopyridine (**2h**, 79.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 4-Phenylpyridine (**4ha**, 42.7 mg, 0.28 mmol) was obtained in 55% yield as a colorless solid.

Figure 3: According to the GP-B, 4-chloropyridine hydrochloride (**5h**, 79.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 122.9 mg, 1.0 mmol), tetrabutylammonium fluoride (0.75 mL, 0.75 mmol; 1 mol/L in tetrahydrofuran), tetrahydrofuran (1.75 mL), and 7% Pd/WA30 (100 mg) were used at 80 °C. 4-Phenylpyridine (**4ha**, 44.2 mg, 0.29 mmol) was obtained in 57% yield as a colorless solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.66 (d,  $J$  = 4.5 Hz, 2H), 7.64 (d,  $J$  = 8.5 Hz, 2H), 7.53–7.44 (m, 5H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.2, 148.3, 138.1, 129.1, 129.0, 127.0, 121.6. Spectroscopic data of  $^1\text{H}$  NMR was identical to that of reference 1.

### 3-Phenylpyridine (4ia)

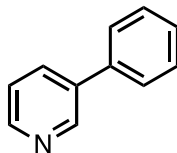


Figure 2: According to the GP-A, 3-iodopyridine (**1i**, 102.5 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 3-Phenylpyridine (**4ia**, 30.0 mg, 0.20 mmol) was obtained in 39% yield as a colorless solid.

Figure 2: According to the GP-A, 3-bromopyridine (**2i**, 79.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 3-Phenylpyridine (**4ia**, 30.3 mg, 0.20 mmol) was obtained in 39% yield as a colorless solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.85 (d,  $J$  = 1.6 Hz, 1H), 8.59 (dd,  $J$  = 1.6, 4.8 Hz, 1H), 7.87 (ddd,  $J$  = 1.6, 1.6, 8.0 Hz, 1H), 7.59–7.56 (m, 2H), 7.50–7.46 (m, 2H), 7.43–7.33 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.4, 148.2, 137.7, 136.5, 134.3, 129.0, 128.0, 127.1, 123.5. Spectroscopic data of  $^1\text{H}$  NMR was identical to that of reference 1.

### 2-Phenylpyridine (4ja)

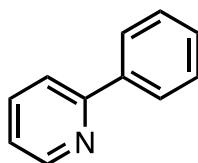


Figure 2: According to the GP-A, 2-iodopyridine (**1j**, 102.5 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 60 °C. 2-Phenylpyridine (**4ja**, 31.0 mg, 0.20 mmol) was obtained in 40% yield as a colorless solid.

Figure 2: According to the GP-A, 2-bromopyridine (**2j**, 79.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 2-Phenylpyridine (**4ja**, 26.4 mg, 0.17 mmol) was obtained in 34% yield as a colorless solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.69 (d,  $J$  = 4.8 Hz, 1H), 7.99 (dd,  $J$  = 1.6, 8.8 Hz, 2H), 7.76–7.70 (m, 2H), 7.49–7.45 (m, 2H), 7.43–7.39 (m, 1H), 7.23–7.19 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  157.4, 150.0, 139.3, 136.7, 128.9, 128.7, 126.8, 122.0, 120.5. Spectroscopic data of  $^1\text{H}$  NMR was identical to that of reference 1.

### 2-Phenylthiophene (4ka)

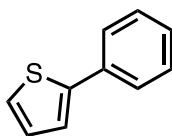


Figure 2: According to the GP-A, 2-iodothiophene (**1k**, 105.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol),  $\text{H}_2\text{O}$  (0.5 mL), 1,4-dioxane (1.5 mL), and 7%

Pd/WA30 (200 mg) were used at 40 °C. 2-Phenylthiophene (**4ka**, 66.8 mg, 0.42 mmol) was obtained in 83% yield as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.63–7.61 (m, 2H), 7.40–7.36 (m, 2H), 7.32–7.25 (m, 3H), 7.10–7.07 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 144.4, 134.4, 128.9, 128.0, 127.4, 125.9, 124.8, 123.0. Spectroscopic data of <sup>1</sup>H NMR was identical to that of reference 4.

#### 2-Formyl-5-phenylthiophene (**4la**)

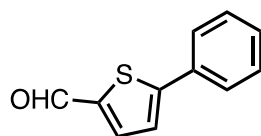


Figure 2: According to the GP-A, 5-bromo-2-flomylthiophene (**2l**, 95.5 mg, 0.5 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), NaOH (40.0 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 80 °C. 2-Formyl-5-phenylthiophene (**4la**, 49.9 mg, 0.27 mmol) was obtained in 53% yield as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.87 (s, 1H), 7.72 (d, *J* = 4.4 Hz, 1H), 7.66–7.64 (m, 2H), 7.44–7.35 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 182.8, 154.2, 142.3, 137.4, 132.9, 129.4, 129.1, 126.3, 124.0. Spectroscopic data of <sup>1</sup>H NMR was identical to that of reference 6.

#### 2-Formyl-5-phenylfuran (**4ma**)

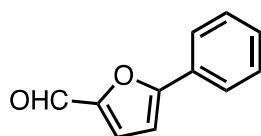


Figure 2: According to the GP-A, 5-iodo-2-flomylfuran (**1m**, 111.0 mg, 0.50 mmol), phenylboronic acid (**3a**, 91.4 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 2-Formyl-5-phenylfuran (**4ma**, 45.6 mg, 0.27 mmol) was obtained in 53% yield as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.64 (s, 1H), 7.81 (d, *J* = 6.8 Hz, 2H), 7.46–7.37 (m, 3H), 7.31 (d, *J* = 3.8 Hz, 1H), 6.83 (d, *J* = 3.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 177.1, 159.3, 151.9, 129.6, 128.9 (2C), 125.2 (2C), 107.6. Spectroscopic data of <sup>1</sup>H NMR was identical to that of reference 5.

#### 2-(3-Pyridyl)-benzofuran (**4id**)

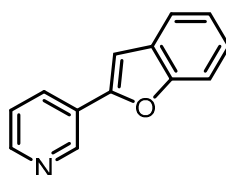


Figure 2: According to the GP-A, 3-iodopyridine (**1i**, 102.5 mg, 0.50 mmol), 2-benzofuranboronic acid (**3d**, 121.5 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 2-(3-Pyridyl)-benzofuran (**4id**, 83.2 mg, 0.43 mmol) was obtained in 85% yield as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.10 (s, 1H), 8.56 (d, *J* = 4.4 Hz, 1H), 8.10–8.07 (m, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.36–7.29 (m, 2H), 7.26–7.23 (m, 1H), 7.09 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 155.0, 152.8, 149.2, 146.3, 131.8, 128.7, 126.5, 124.9, 123.5, 123.2, 121.1, 111.2, 102.7. Spectroscopic data of <sup>1</sup>H NMR was identical to that of reference 7.

#### 3-(Dibenzo[b,d]furan-4-yl)pyridine (**4ie**)

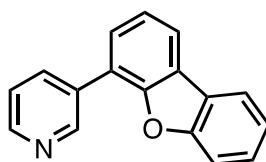
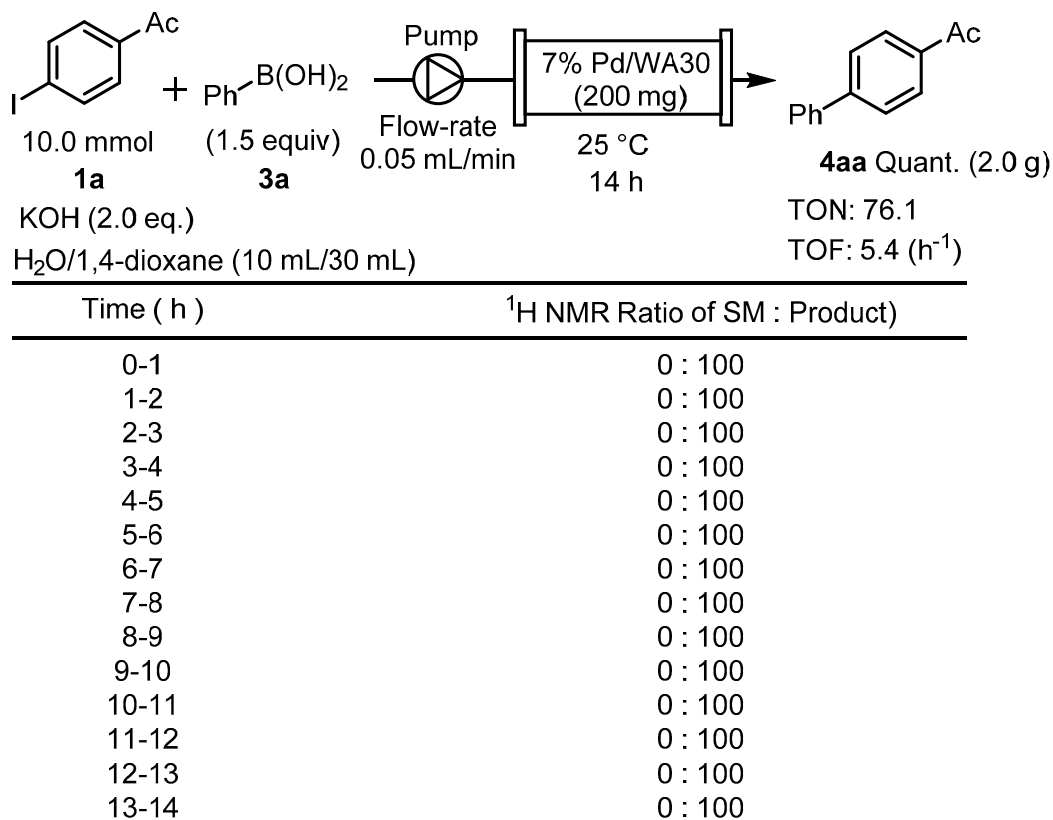


Figure 2: According to the GP-A, 3-iodopyridine (**1i**, 102.5 mg, 0.50 mmol), dibenzofuran-4-boronic acid (**3e**, 159.0 mg, 0.75 mmol), KOH (56.1 mg, 1.0 mmol), H<sub>2</sub>O (0.5 mL), 1,4-dioxane (1.5 mL), and 7% Pd/WA30 (200 mg) were used at 40 °C. 3-(Dibenzo[b,d]furan-4-yl)pyridine (**4ie**, 122.6mg, 0.50 mmol) was obtained in quantitative yield as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.17 (d, *J* = 2.4 Hz, 1H), 8.66 (d, *J* = 4.8 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.95 (dd, *J* = 6.6, 6.6 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.48–7.40 (m, 3H), 7.35 (dd, *J* = 7.2, 7.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 156.0, 153.2, 149.4, 148.6, 135.9, 132.1, 127.4, 126.4, 125.0, 123.8, 123.4, 123.3, 122.9, 122.1, 120.7, 120.5, 111.8. Spectroscopic data of <sup>1</sup>H NMR was identical to that of reference 8.

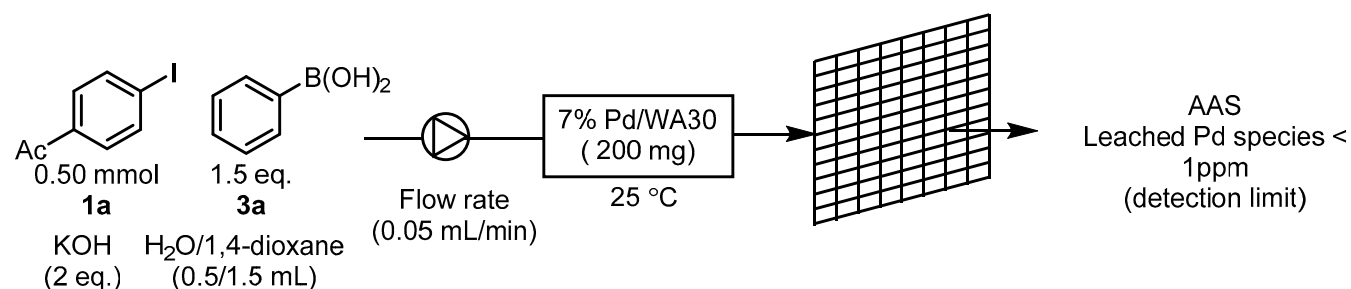
### 9. Procedure for the continuous-flow Suzuki–Miyaura coupling reaction over an extended period of time

A solution of 4'-iodoacetophenone (**1a**, 2.5 g, 10.0 mmol), phenylboronic acid (**3a**, 1.5 g, 12.0 mmol), and KOH (1.1 g, 20 mmol) in a mixed solvent of H<sub>2</sub>O (10 mL) and 1,4-dioxane (30 mL) was moved through a cartridge packed with 200 mg of 7% Pd/WA30 (Ø 4.6 × 150 mm, SUS-316) by a syringe pump (YMC, YSP-101) at a flow rate of 0.05 mL/min at 25 °C. The reaction solution was collected every 1 h changing the receiving vessel (1<sup>st</sup>: 0–1 h, 2<sup>nd</sup>: 1–2 h, 3<sup>rd</sup>: 2–3 h, 4<sup>th</sup>: 3–4 h, 5<sup>th</sup>: 4–5 h, 6<sup>th</sup>: 5–6 h, 7<sup>th</sup>: 6–7 h, 8<sup>th</sup>: 7–8 h, 9<sup>th</sup>: 8–9 h, 10<sup>th</sup>: 9–10 h, 11<sup>th</sup>: 10–11 h, 12<sup>th</sup>: 11–12 h, 13<sup>th</sup>: 12–13 h, 14<sup>th</sup>: 13–14 h). Each reaction solution was extracted separately with ethyl acetate (10 mL × 2), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. Subsequently, each residue was analyzed by <sup>1</sup>H NMR. The combined residues were purified by silica-gel column chromatography (hexane/ethyl acetate = 15/1) to obtain 4-acethylbiphenyl (**4aa**, 2.0 g, 10 mmol) in quantitative yield.



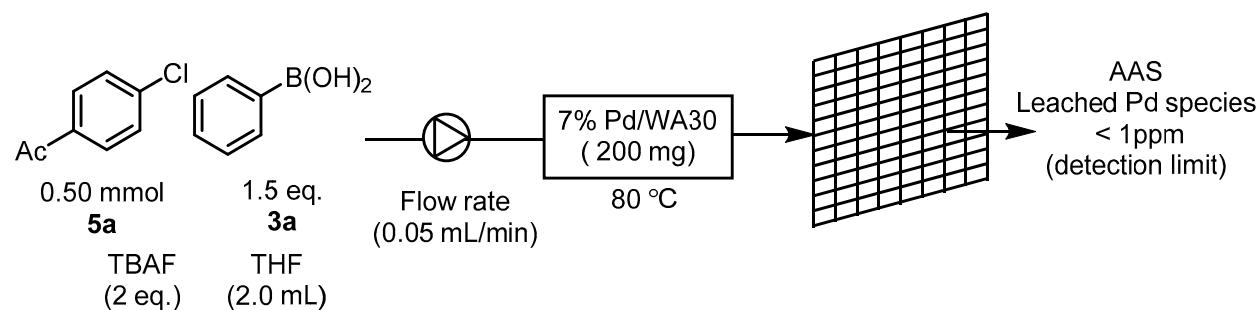
## 10. Leaching test for the continuous-flow Suzuki–Miyaura coupling of 4'-iodoacetophenone and 4'-chloroacetophenone

### 4'-iodoacetophenone



A solution of the 4'-iodoacetophenone (**1a**, 123.0 mg, 0.5 mmol), phenylboronic acid (**3a**, 94.1 mg, 0.75 mmol), and KOH (56.1 mg, 1.0 mmol) in a mixed solvent of H<sub>2</sub>O (0.5 mL) and 1,4-dioxane (1.5 mL) was moved through a 7% Pd/WA30 (200 mg)-packed cartridge (Ø 4.6 × 50 mm, SUS-316) by syringe pump (YMC, YSP-101) at a flow rate of 0.05 mL/min at room temperature. The cartridge was washed with a 15 mL of mixed solvent of H<sub>2</sub>O (0.5 mL) and 1,4-dioxane (1.5 mL). The whole reaction mixture was collected, filtered through a membrane filter (pore size: 0.45 µm). The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with MeOH and palladium species was not observed in the diluted filtrate and leached Pd species < 1 ppm in the diluted filtrate by using atomic absorption spectrometry (SHIMADZU AA-7000).

### 4'-chloroacetophenone



A solution of the 4'-chloroacetophenone (**5a**, 38.6 mg, 0.25 mmol), phenylboronic acid (**3a**, 45.7 mg, 0.375 mmol), and tetrabutylammonium fluoride (0.5 mL, 0.5 mmol; 1 mol/L in tetrahydrofuran) in tetrahydrofuran (2.0 mL) was moved through a 7% Pd/WA30 (200 mg)-packed cartridge (Ø 4.6 × 50 mm, SUS-316) by syringe pump (YMC, YSP-101) at a flow rate of 0.05 mL/min at 80 °C. The cartridge was washed with a 15 mL of tetrahydrofuran. The whole reaction mixture was collected, filtered through a membrane filter (pore size: 0.45 µm). The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with MeOH and palladium species was not observed in the diluted filtrate and leached Pd species < 1 ppm in the diluted filtrate by using atomic absorption spectrometry (SHIMADZU AA-7000).

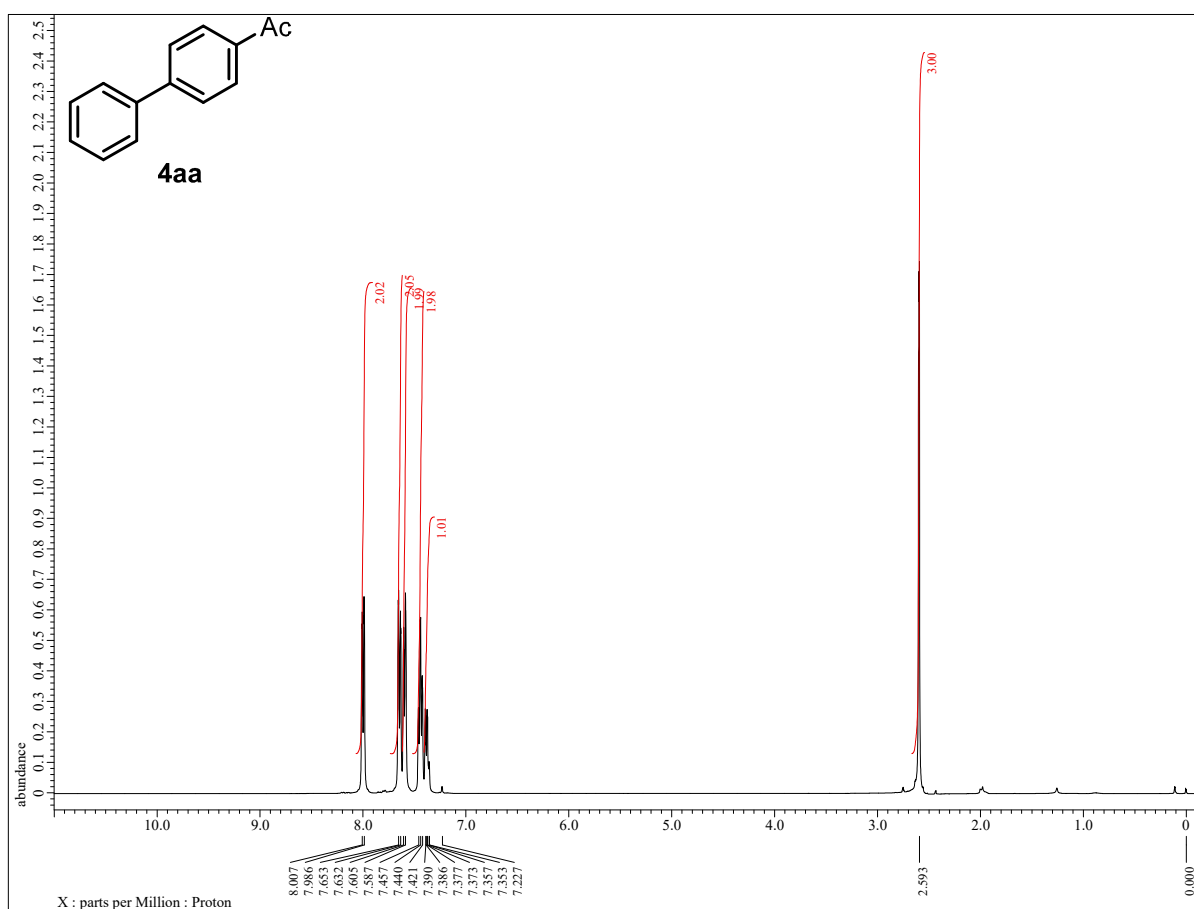
## 11. References

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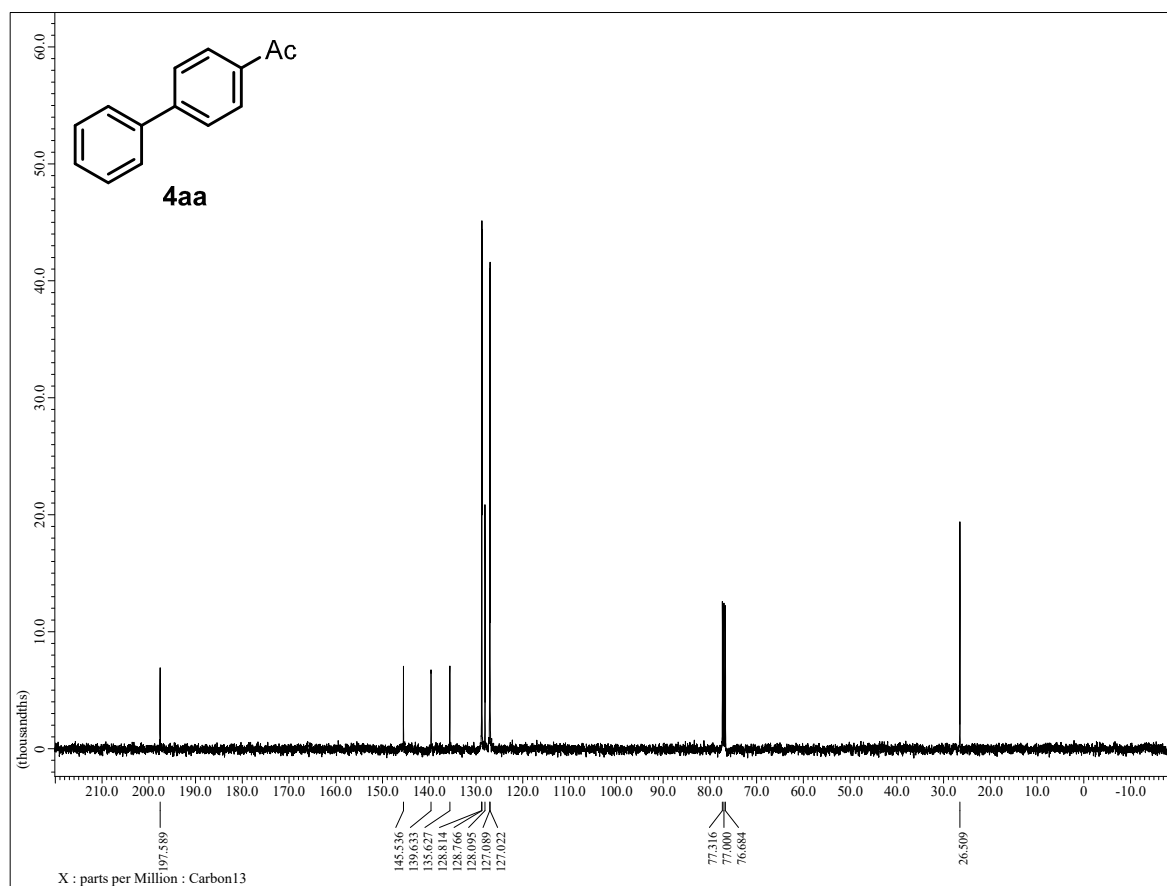
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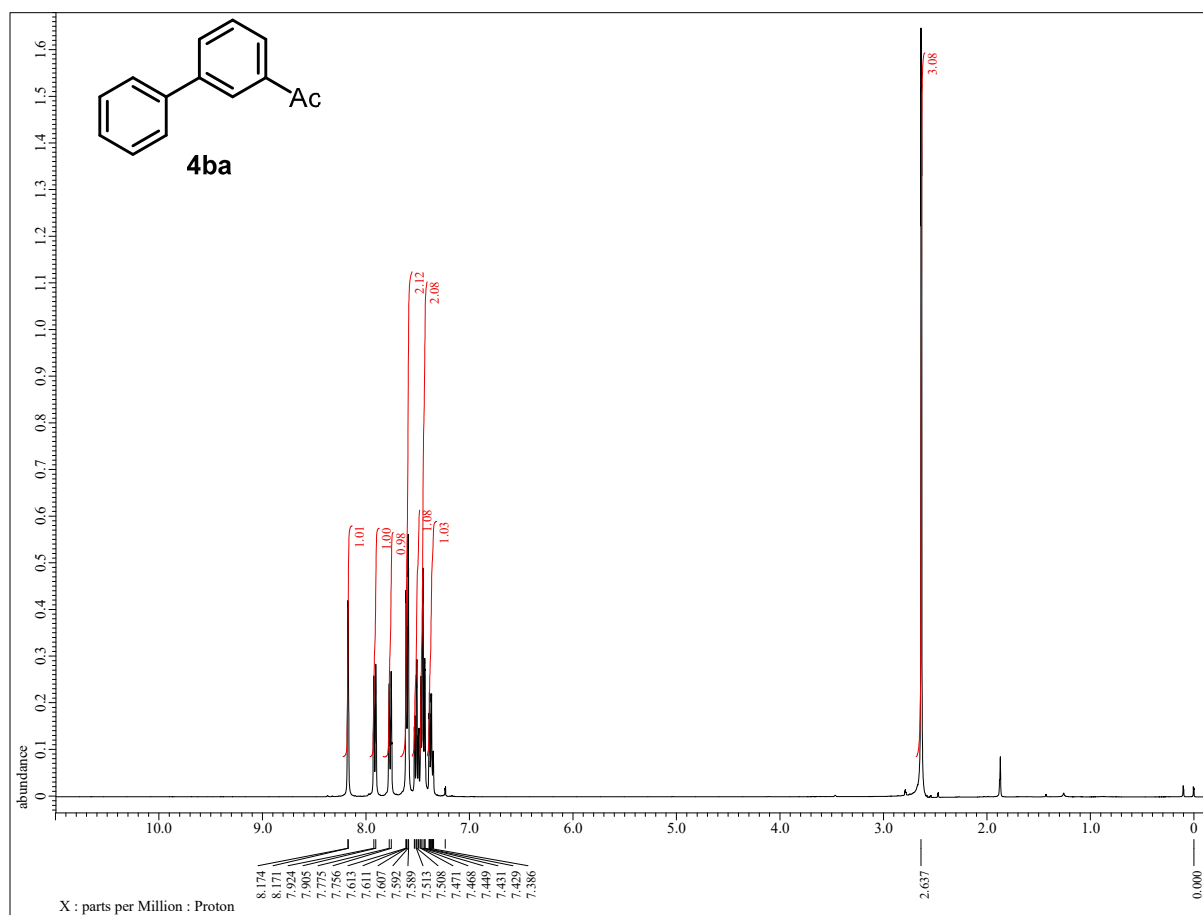
## 12. H and $^{13}\text{C}$ spectra of products

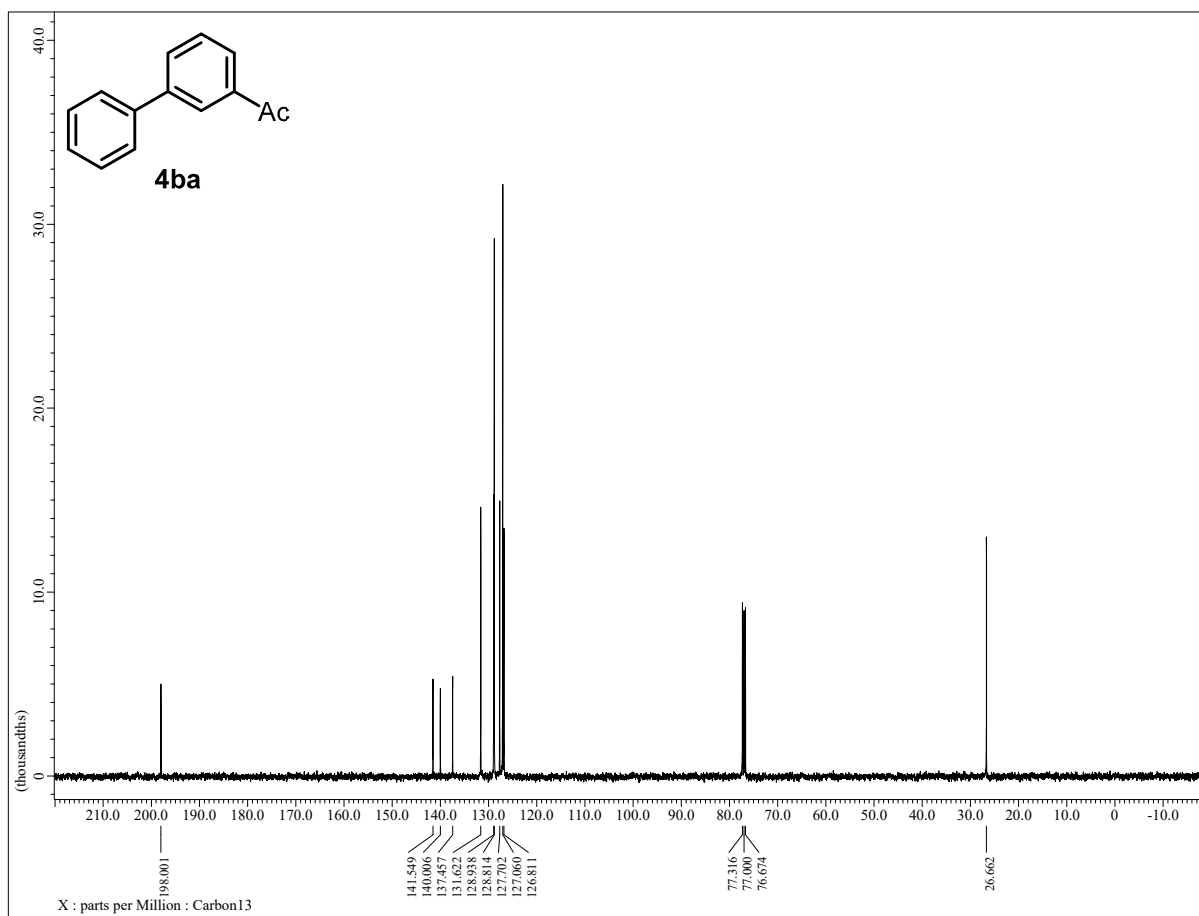
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of 4-acetylbiphenyl (4aa).

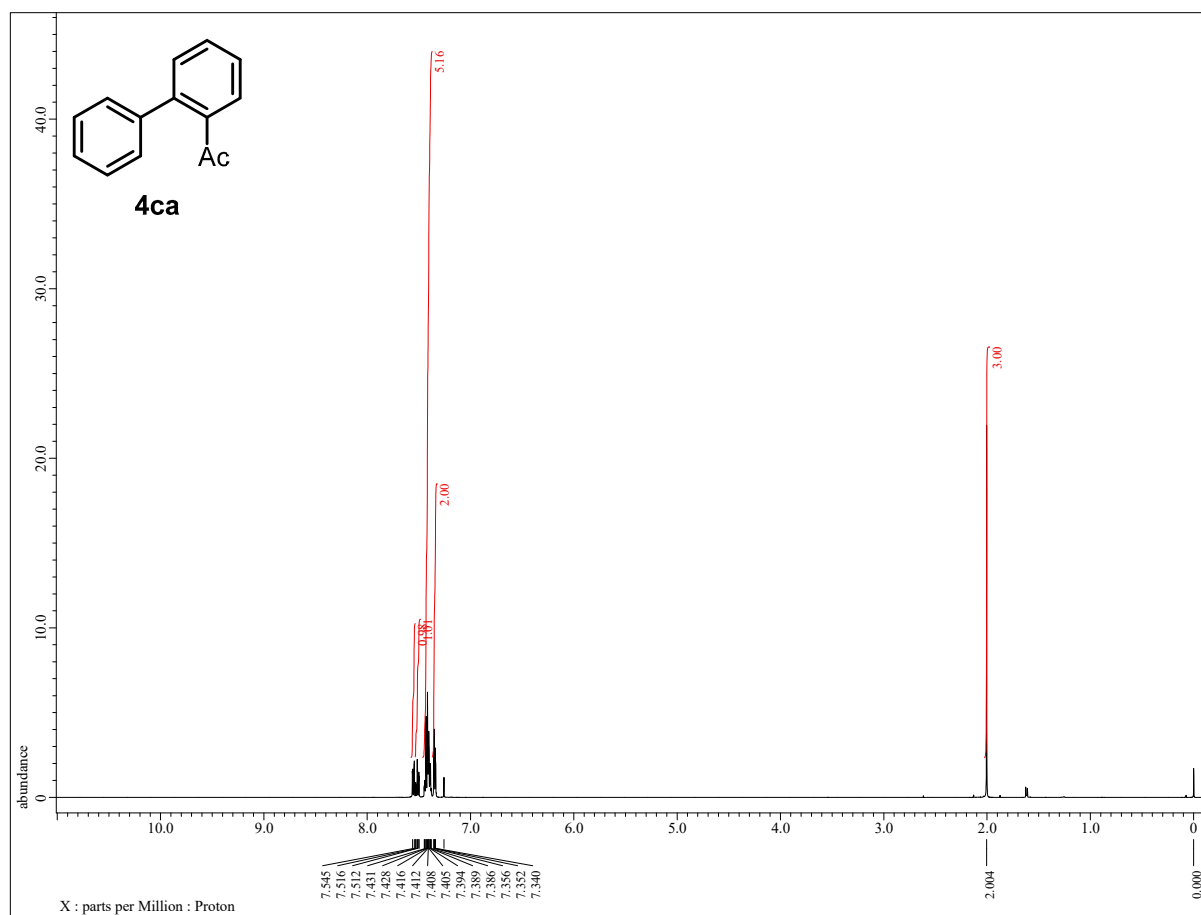


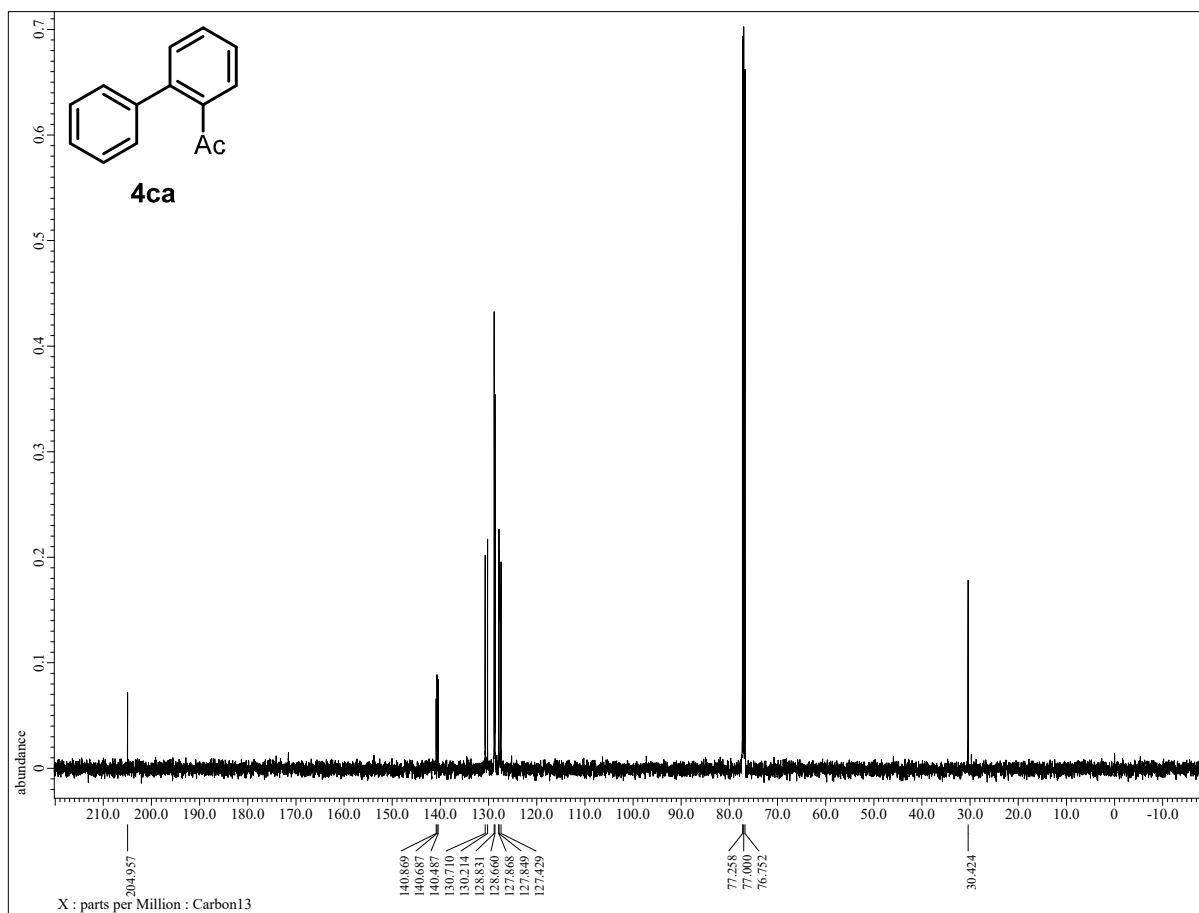


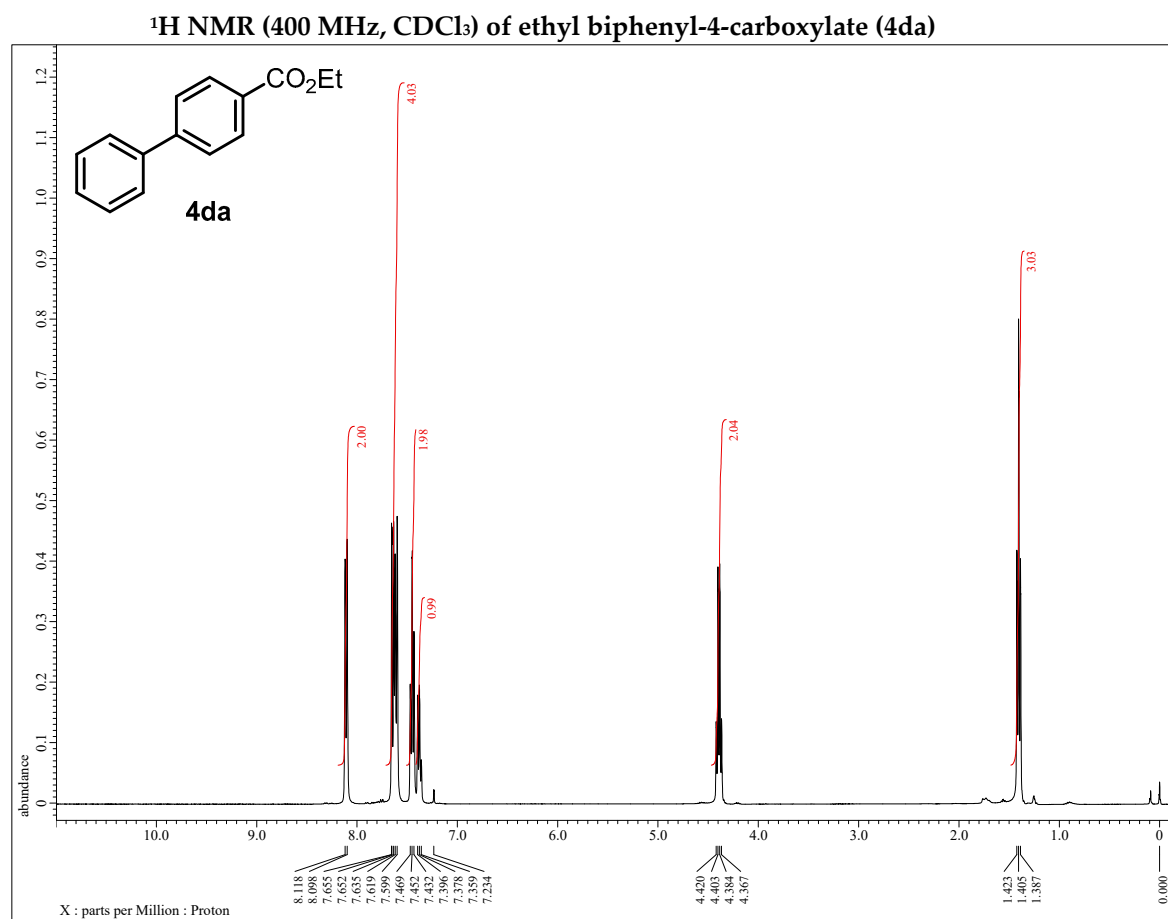
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) of 4-acetylbiphenyl (4aa).

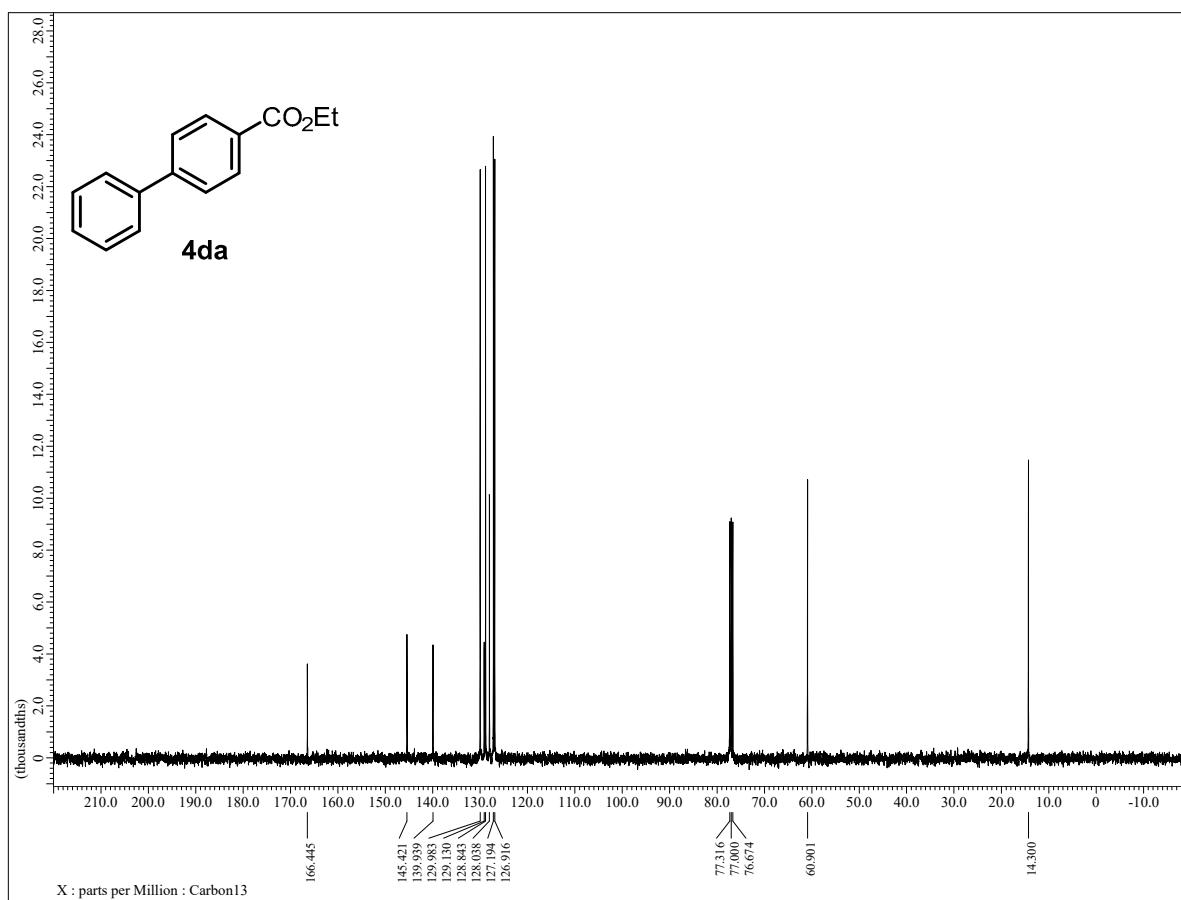
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-acetylbiphenyl (4ba)

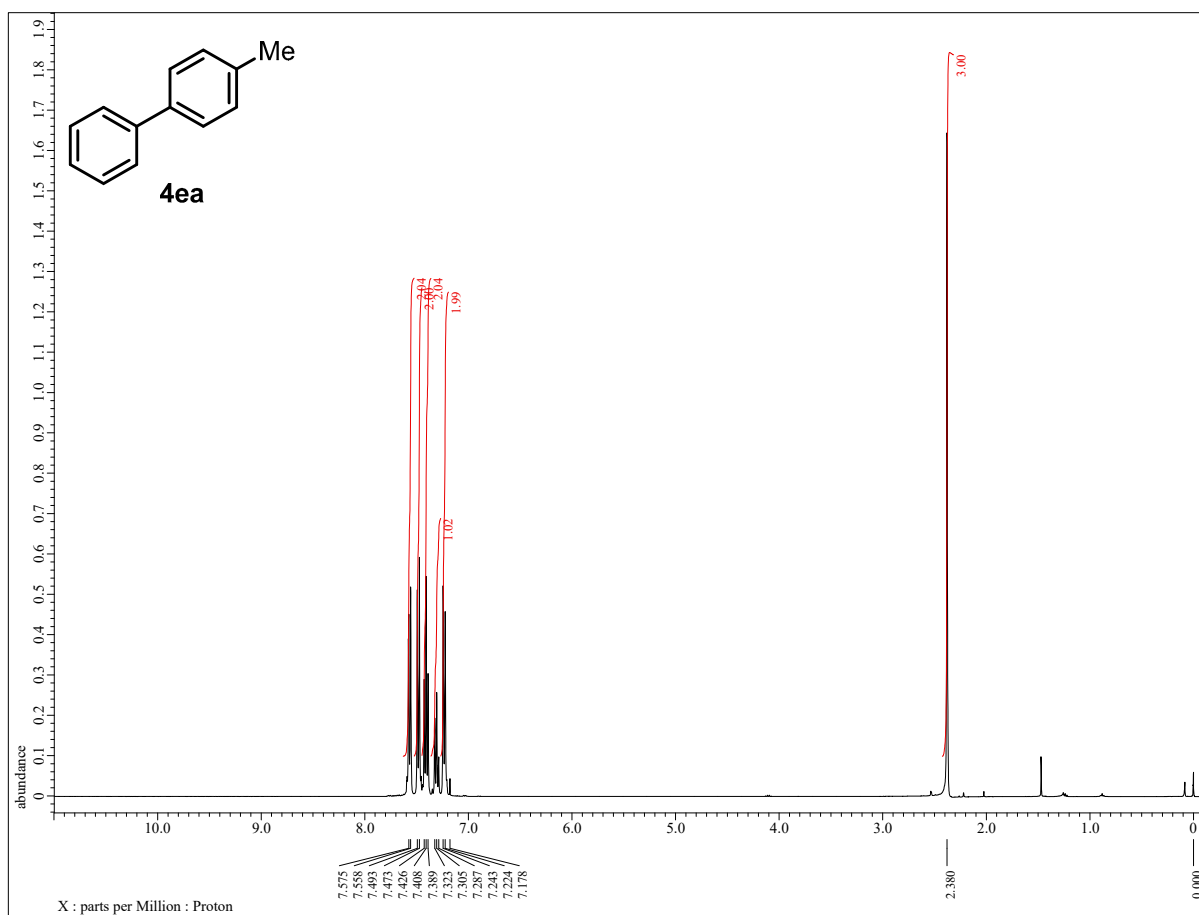
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 3-acetylbiphenyl (4ba)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of 2-acetylbiphenyl (4ca).

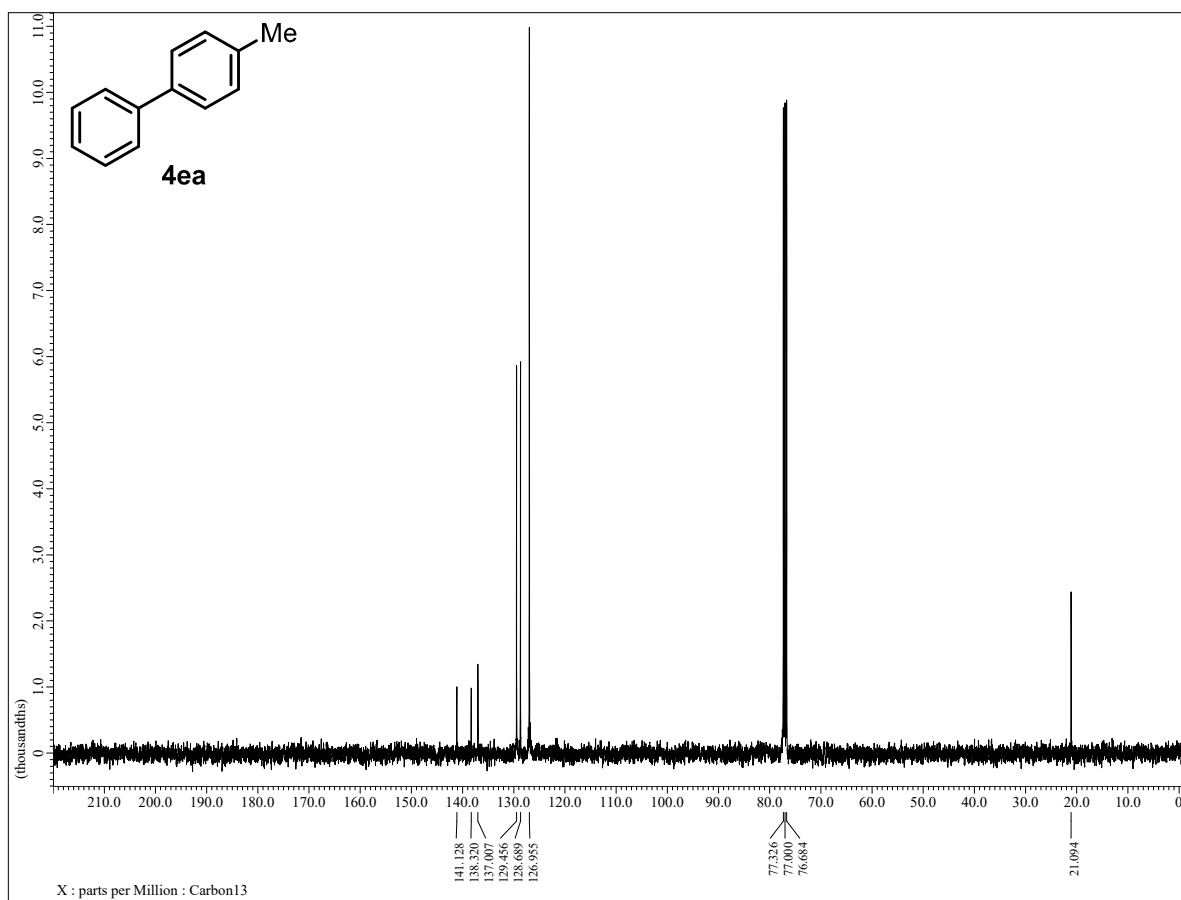
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) of 2-acetylbiphenyl (4ca)

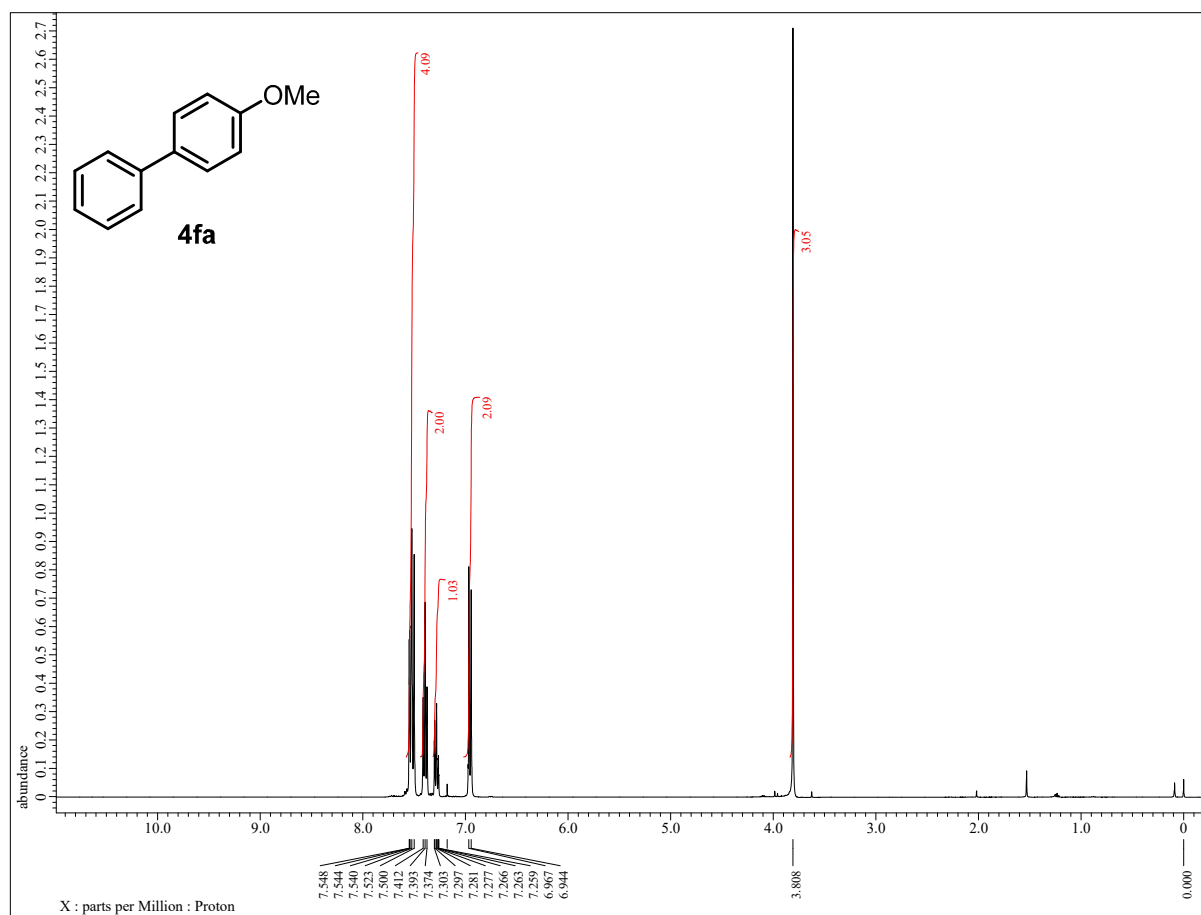


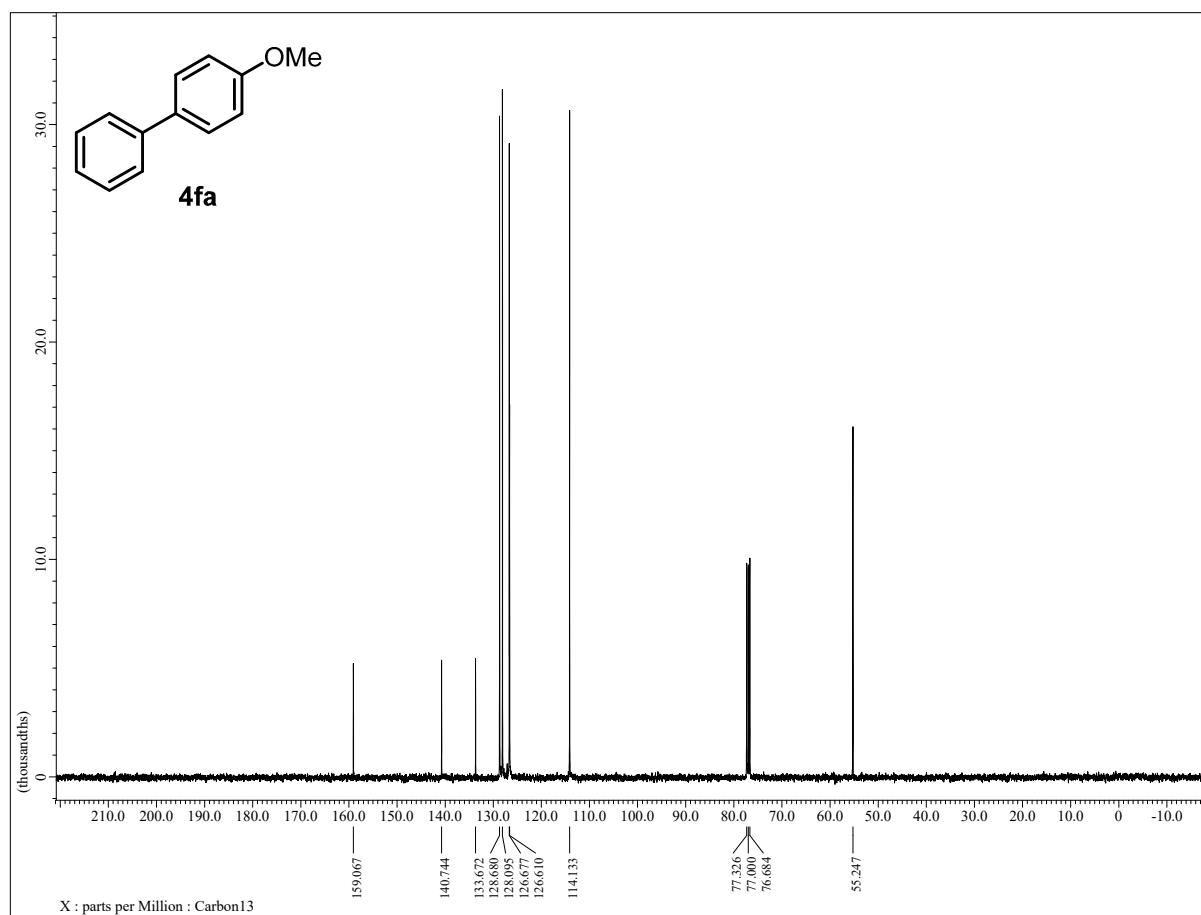
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) of ethyl biphenyl-4-carboxylate (4da).

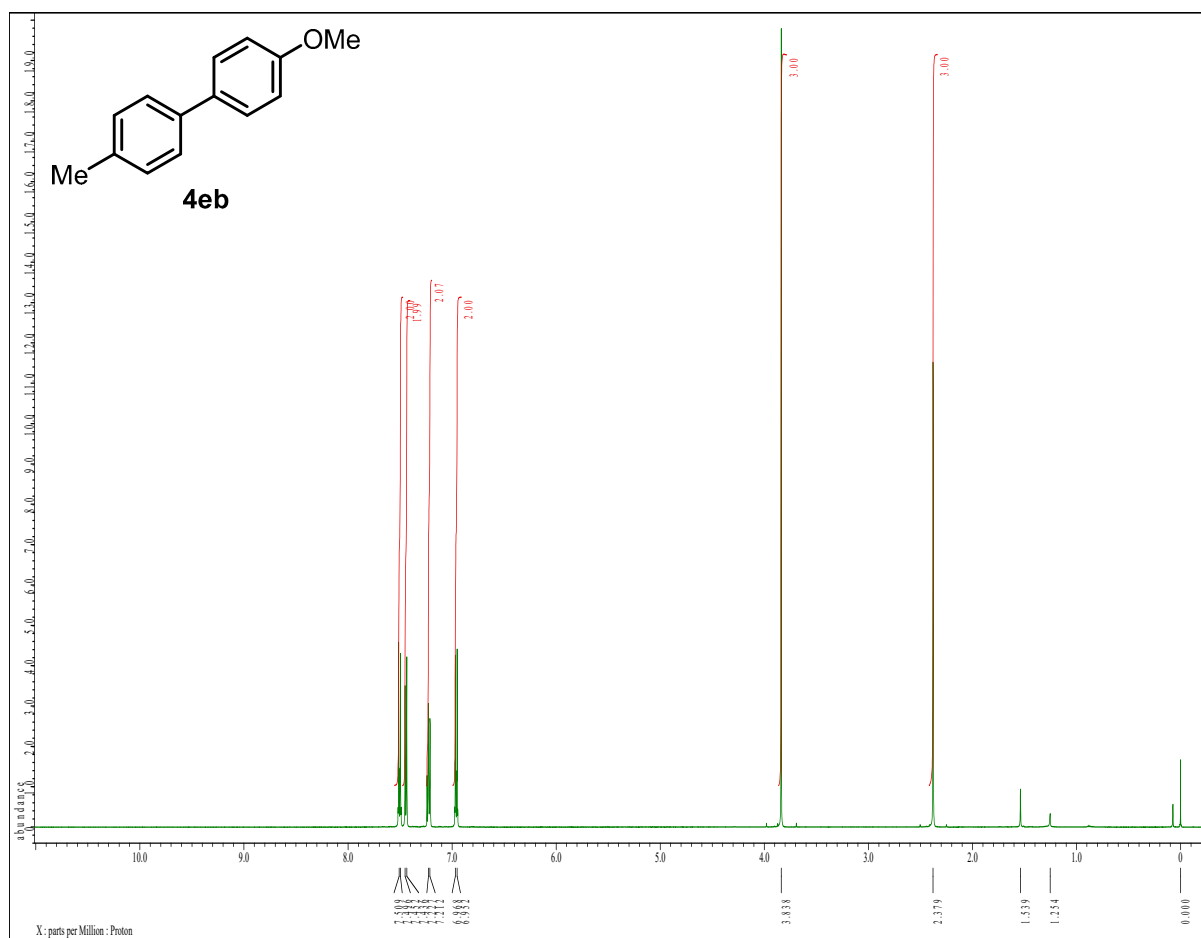
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 4-methylbiphenyl (4ea).

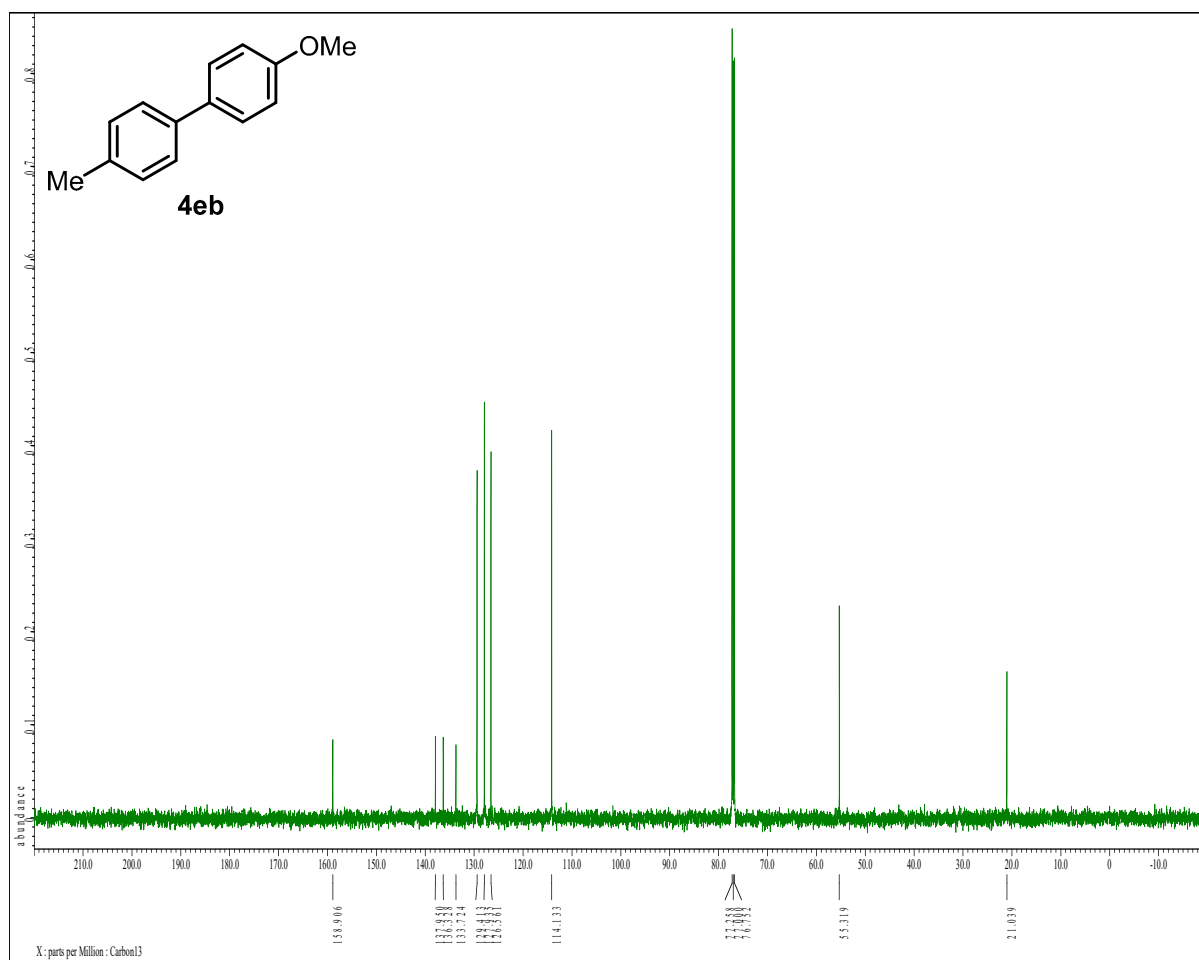


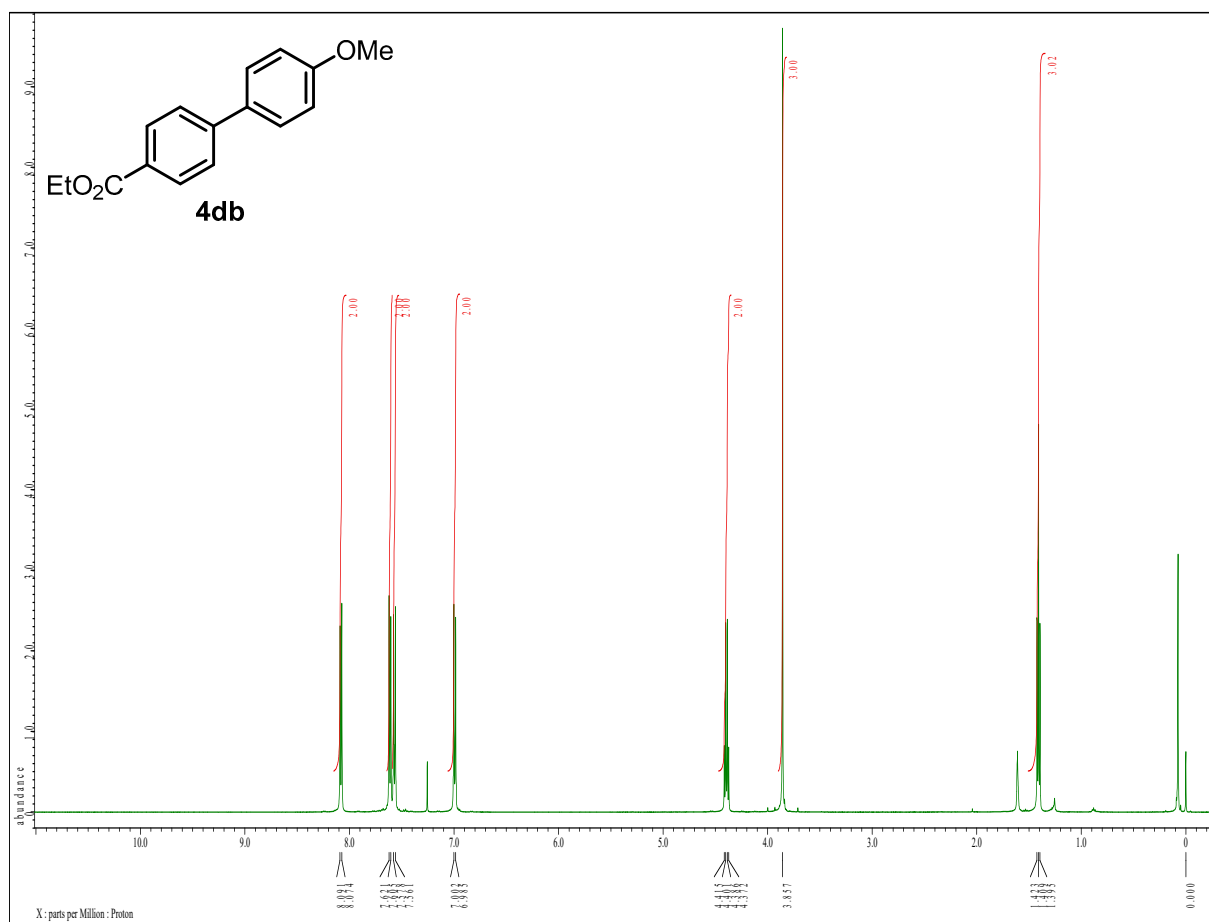
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 4-methylbiphenyl (4ea).

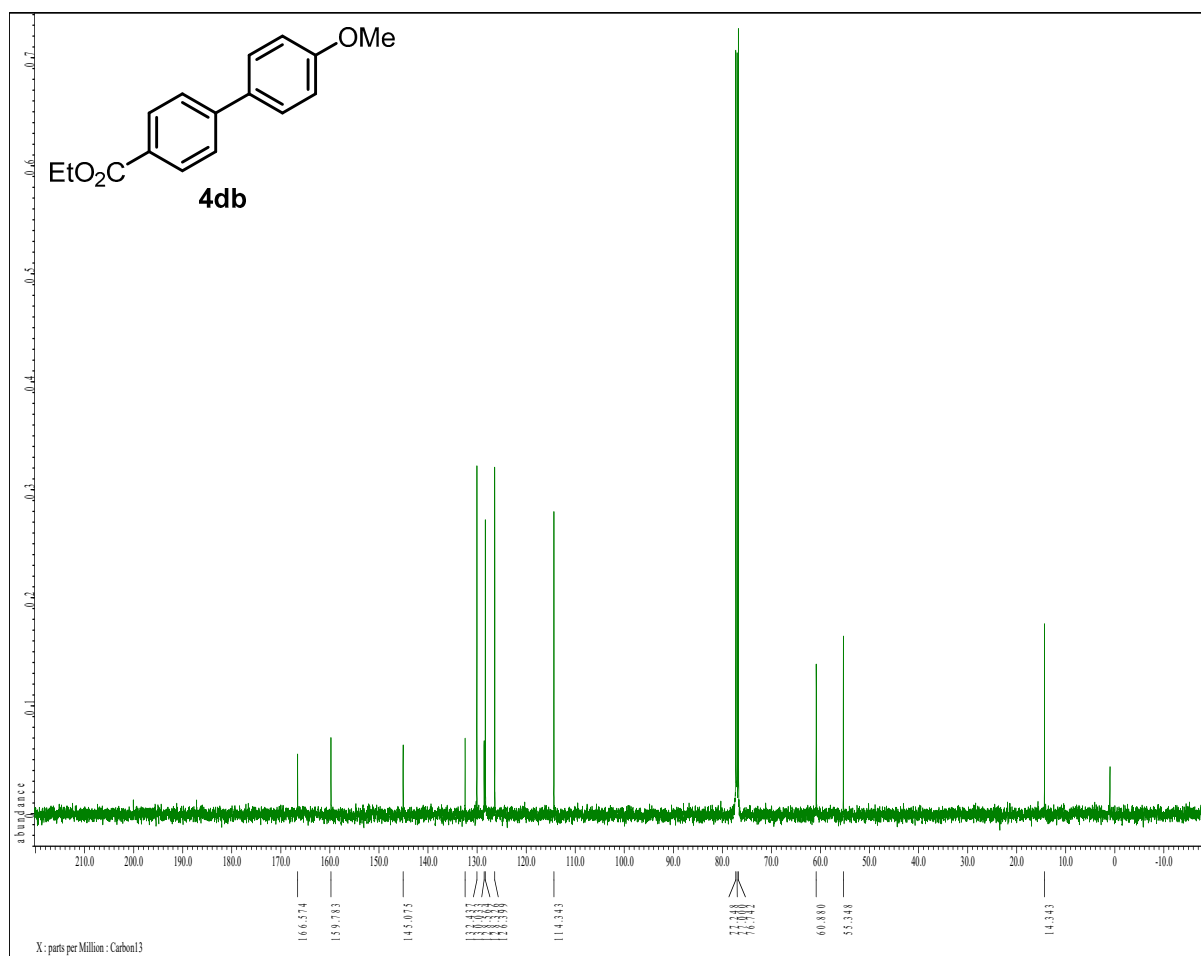
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 4-methoxybiphenyl (4fa).

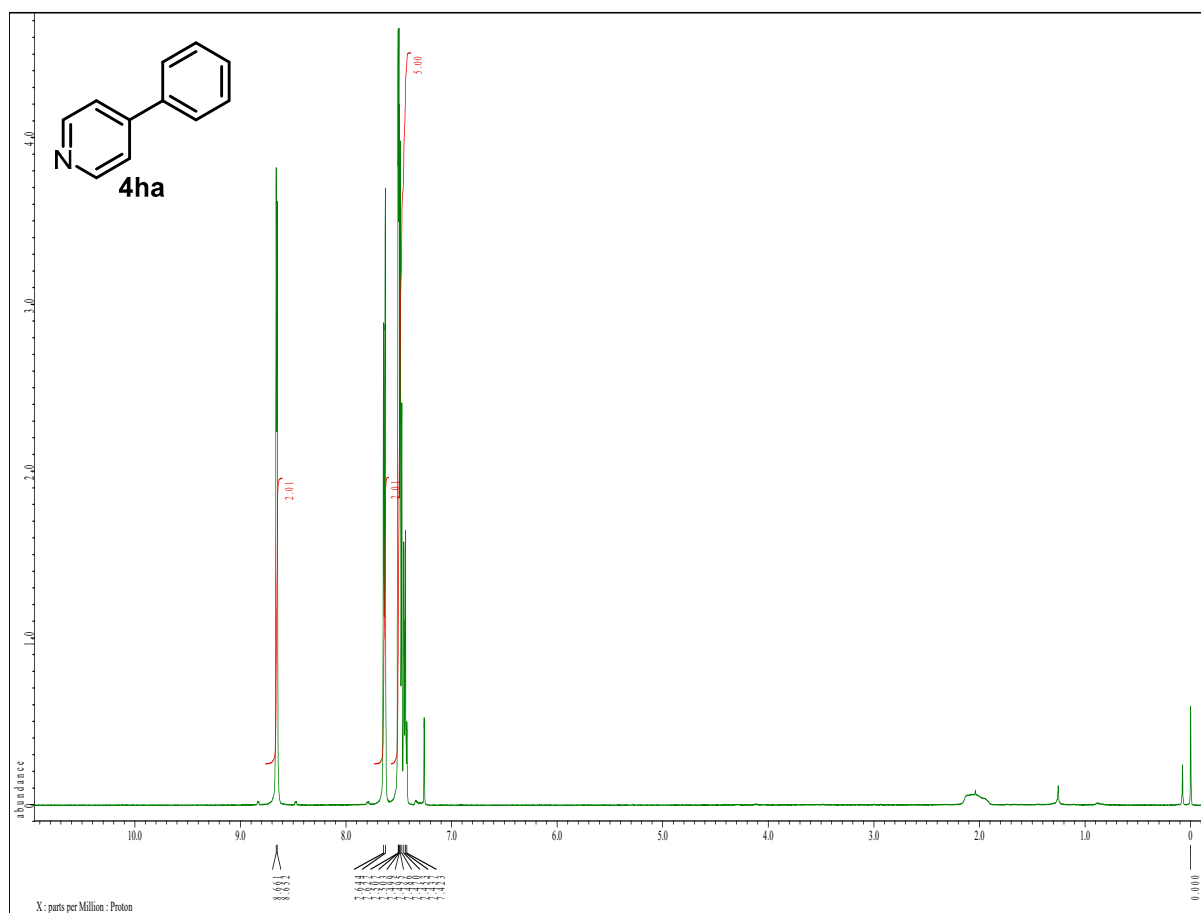
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 4-methoxybiphenyl (4fa).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of 4-methyl-4'-methoxybiphenyl (4eb).

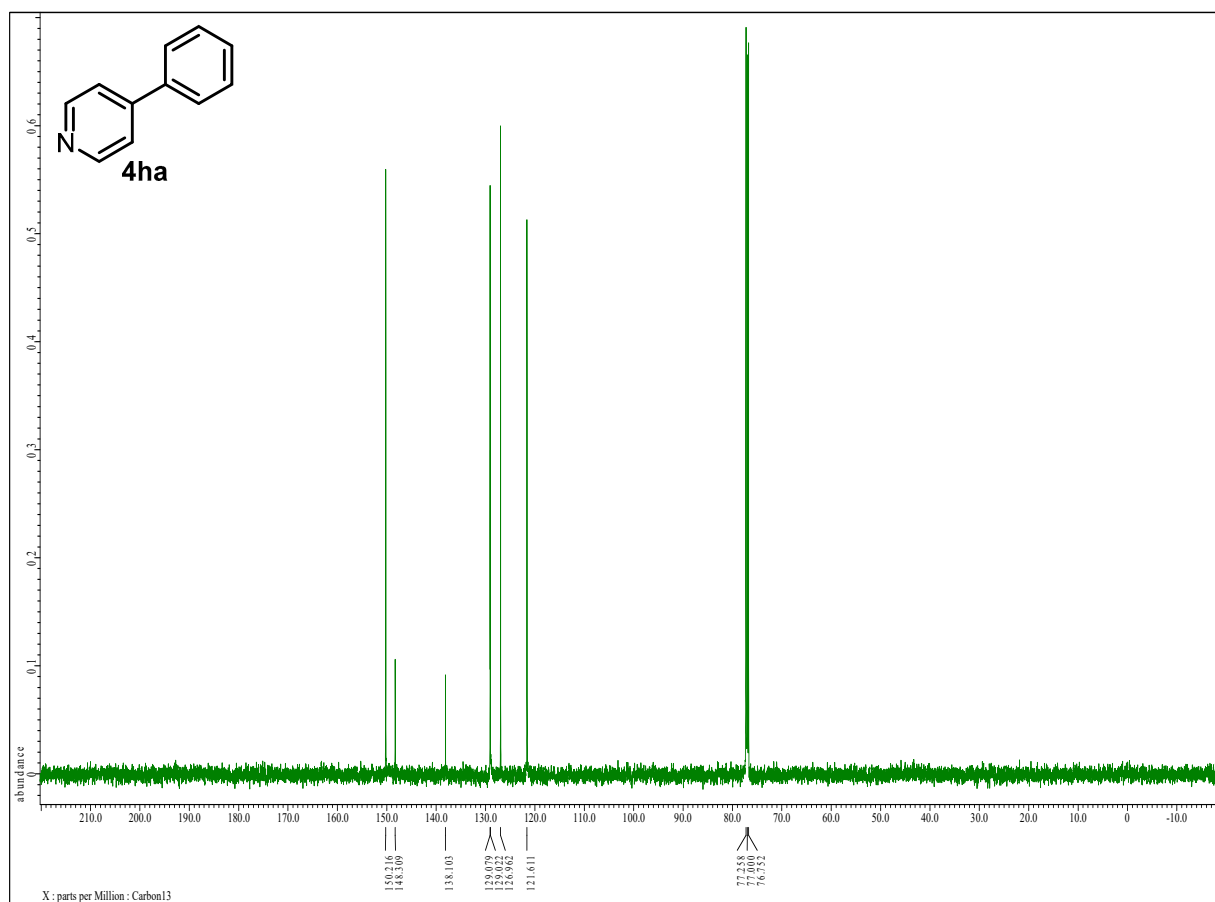
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) of 4-methyl-4'-methoxybiphenyl (4eb).

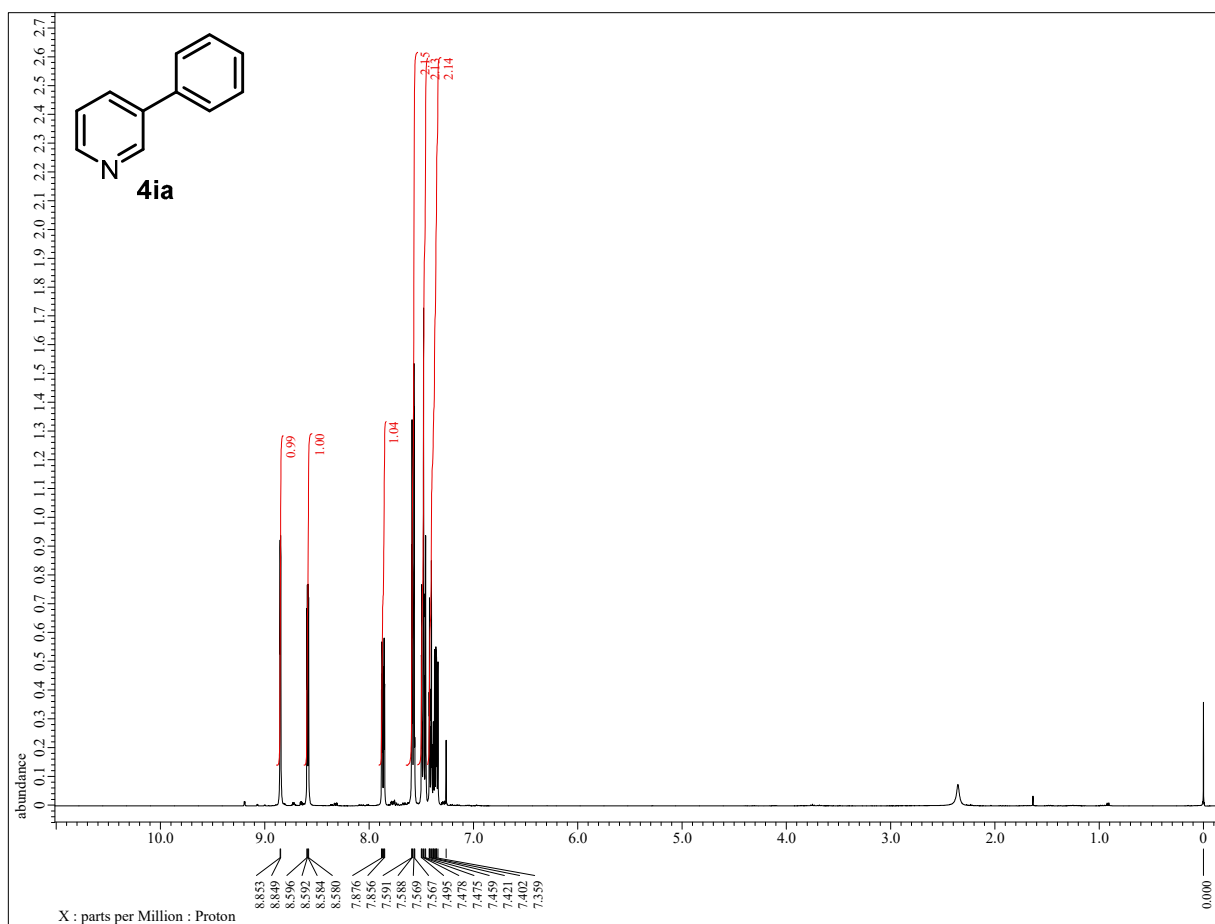
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of ethyl 4-(4-methoxyphenyl)benzoate (4db).

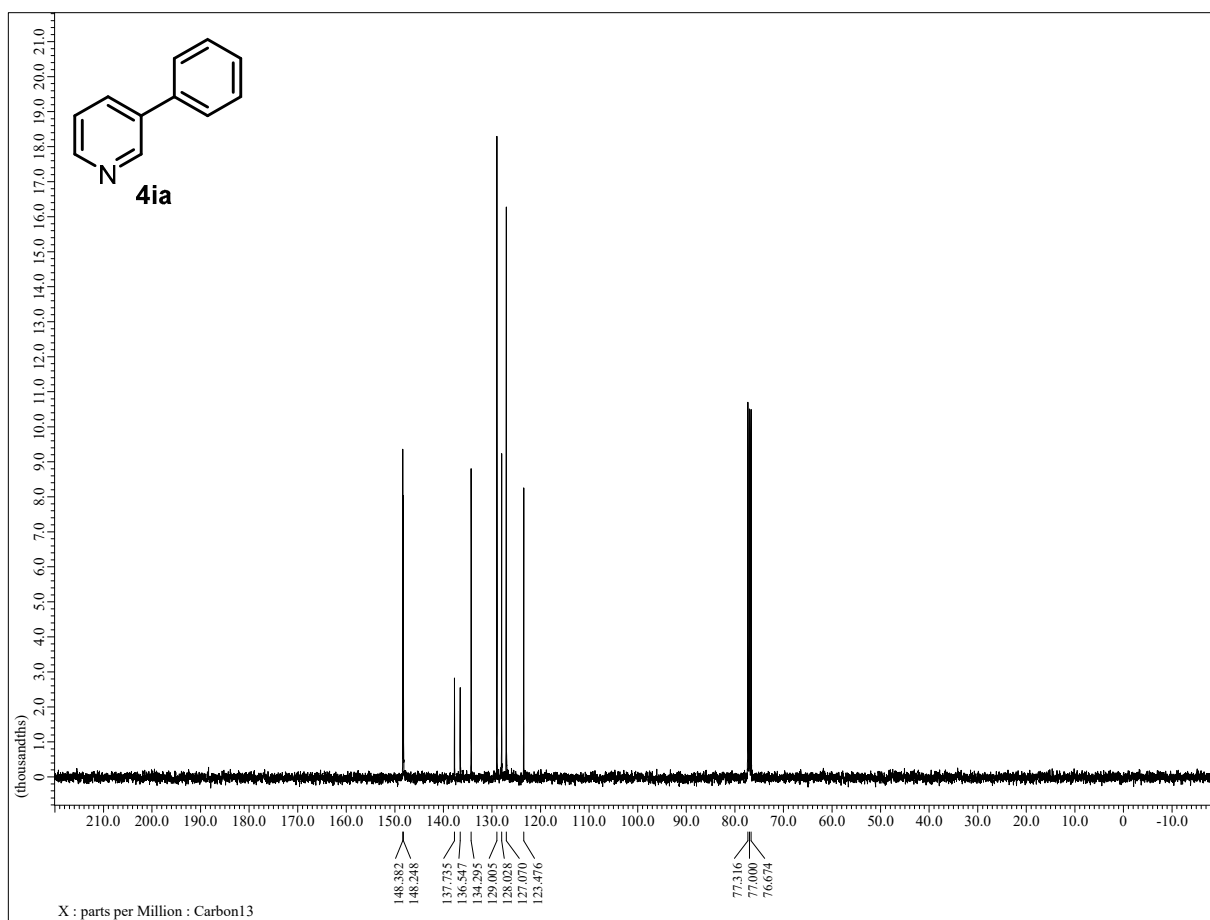
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of ethyl 4-(4-methoxyphenyl)benzoate (4db).

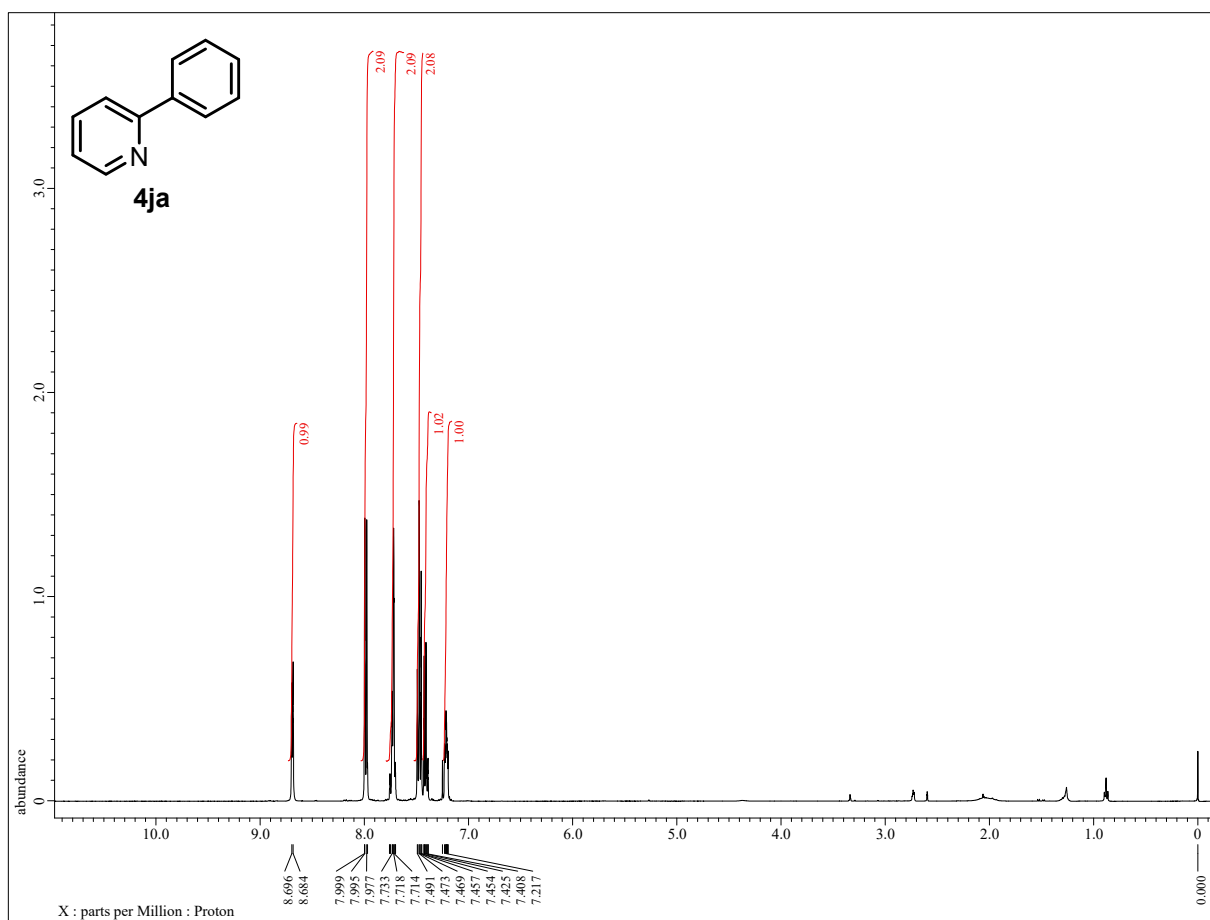
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) of 4-phenylpyridine (4ha).

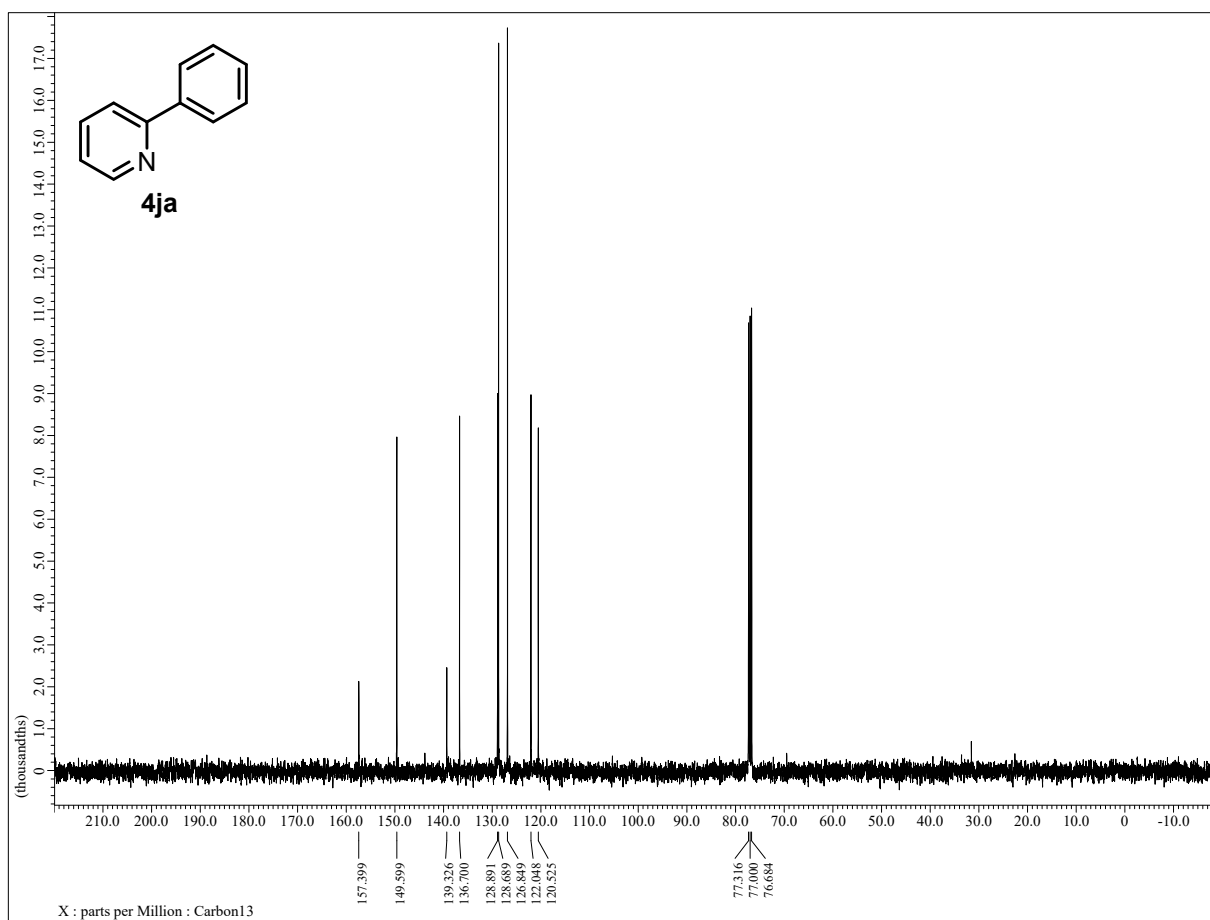


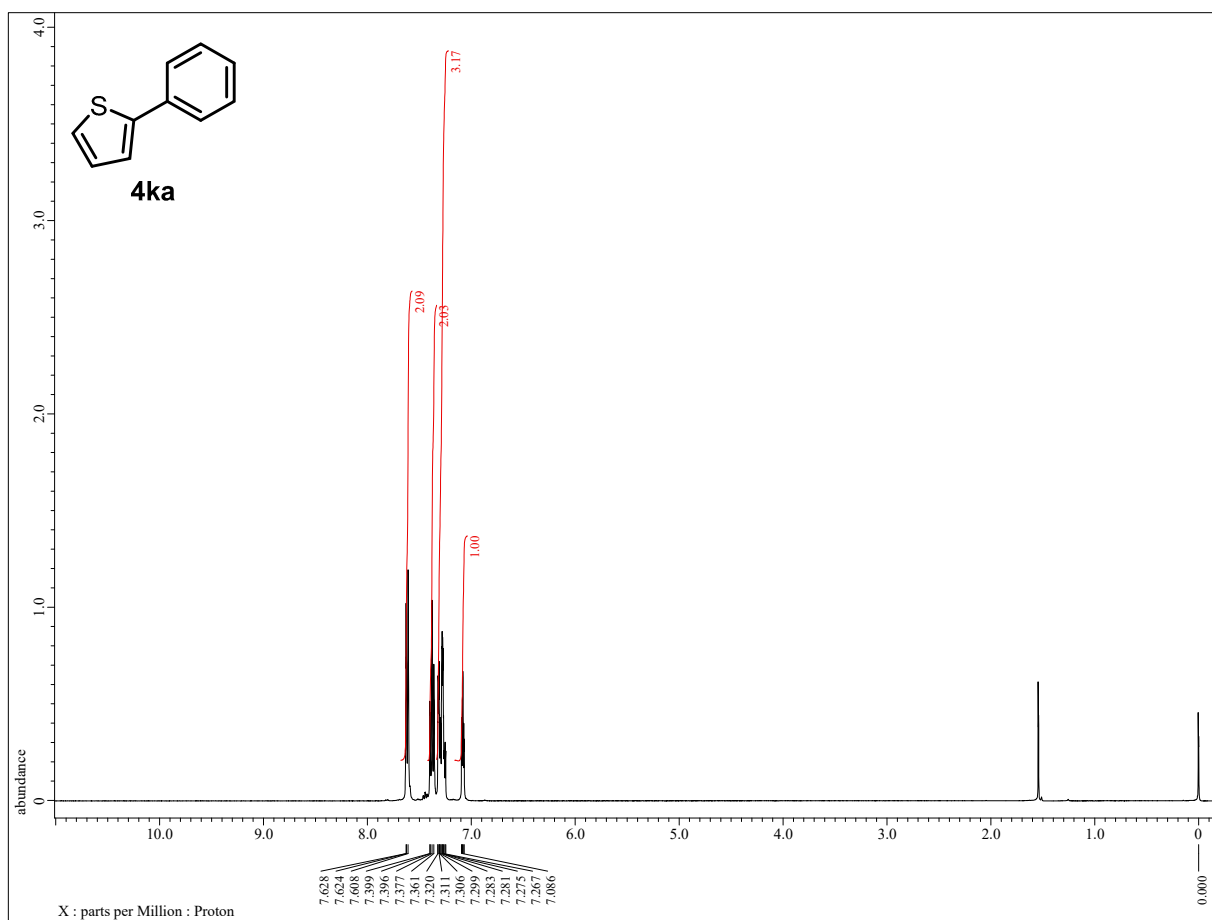
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 4-phenylpyridine (4ha).

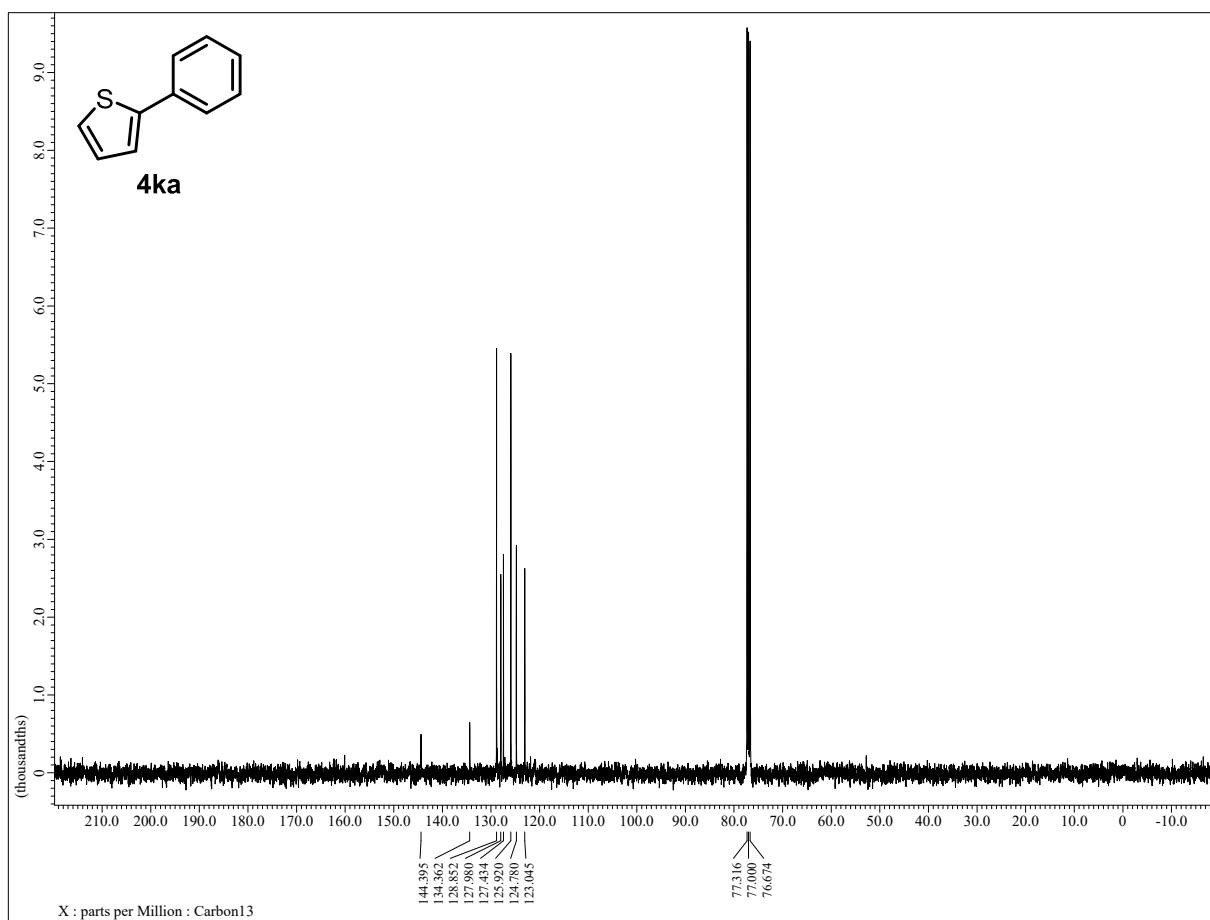
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-phenylpyridine (4ia).

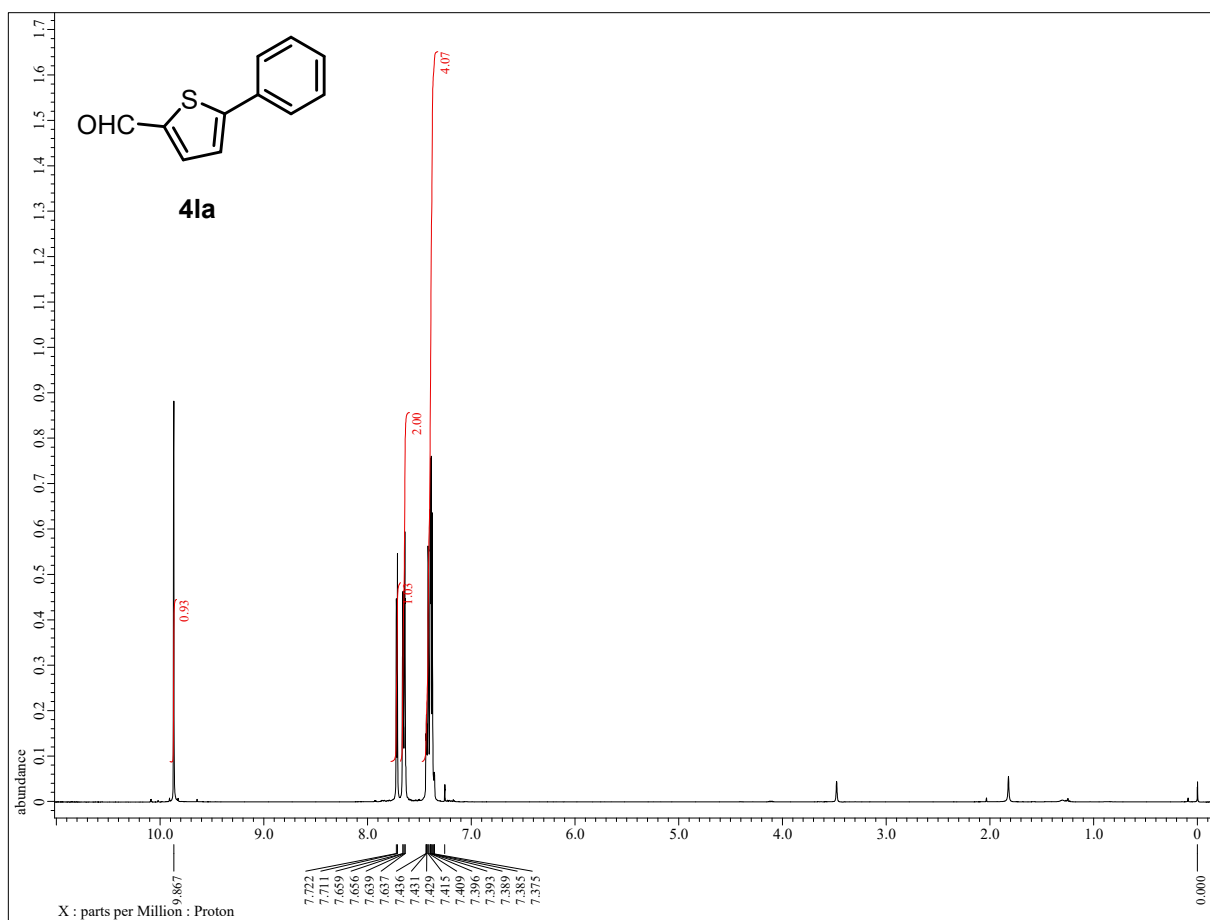
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 3-phenylpyridine (4ia).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 2-phenylpyridine (4ja).

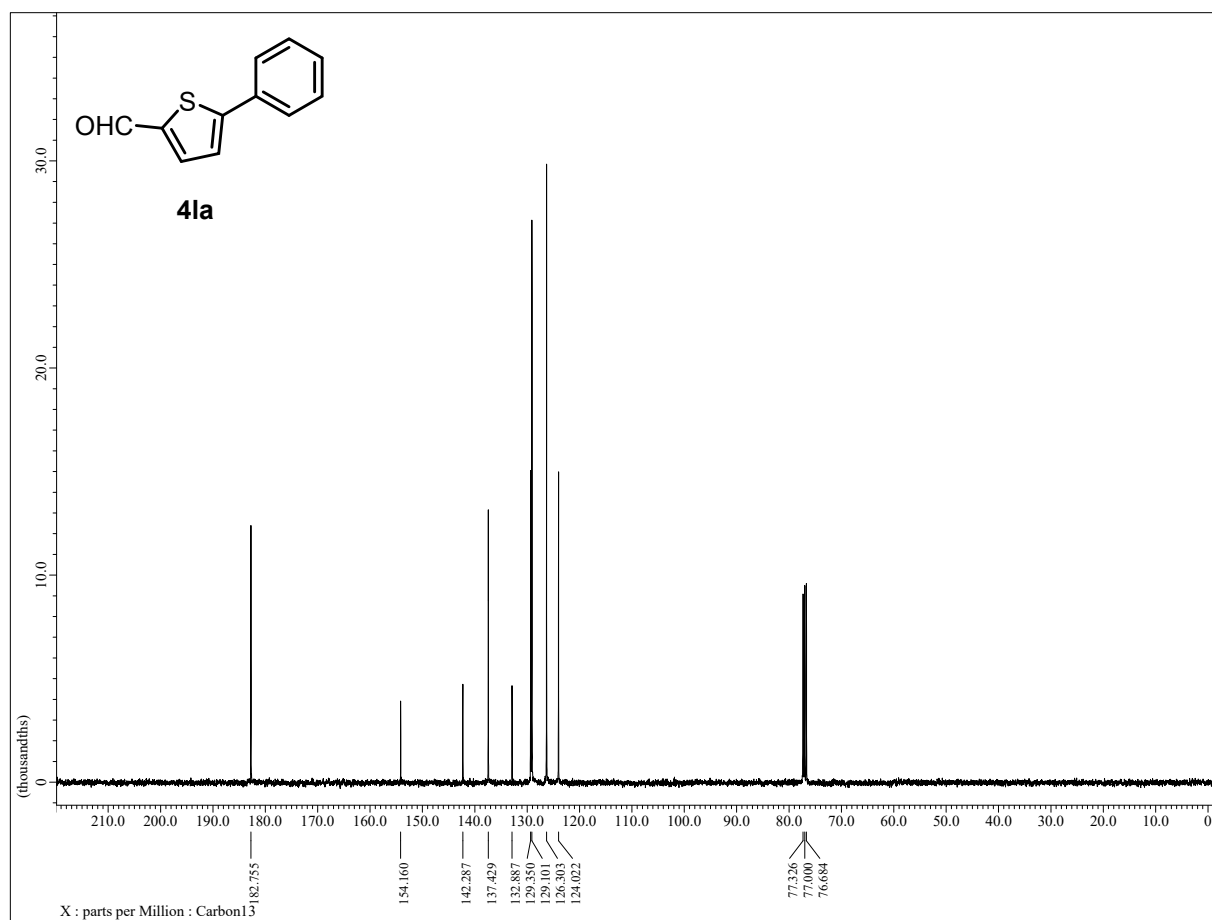
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 2-phenylpyridine (4ja).

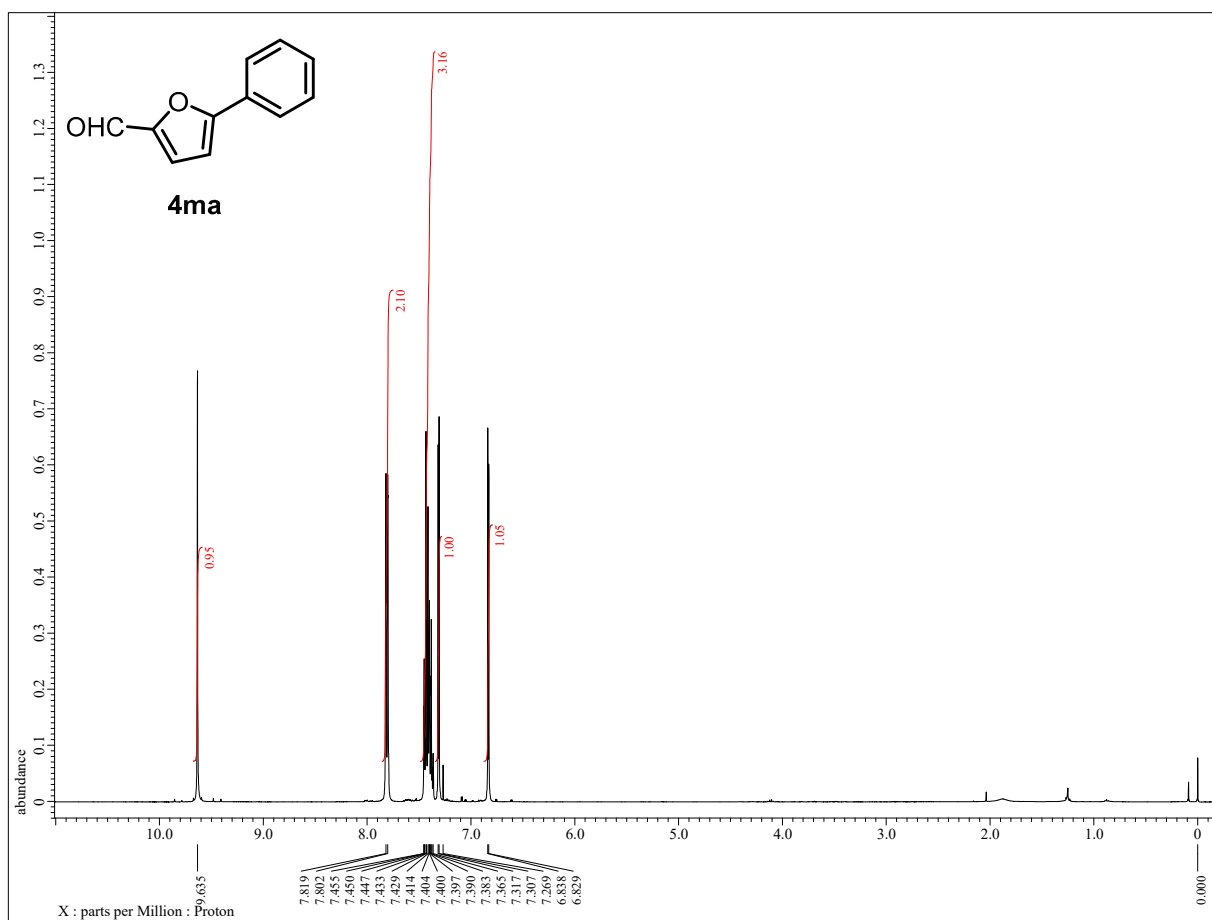
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 2-phenylthiophene (4ka).

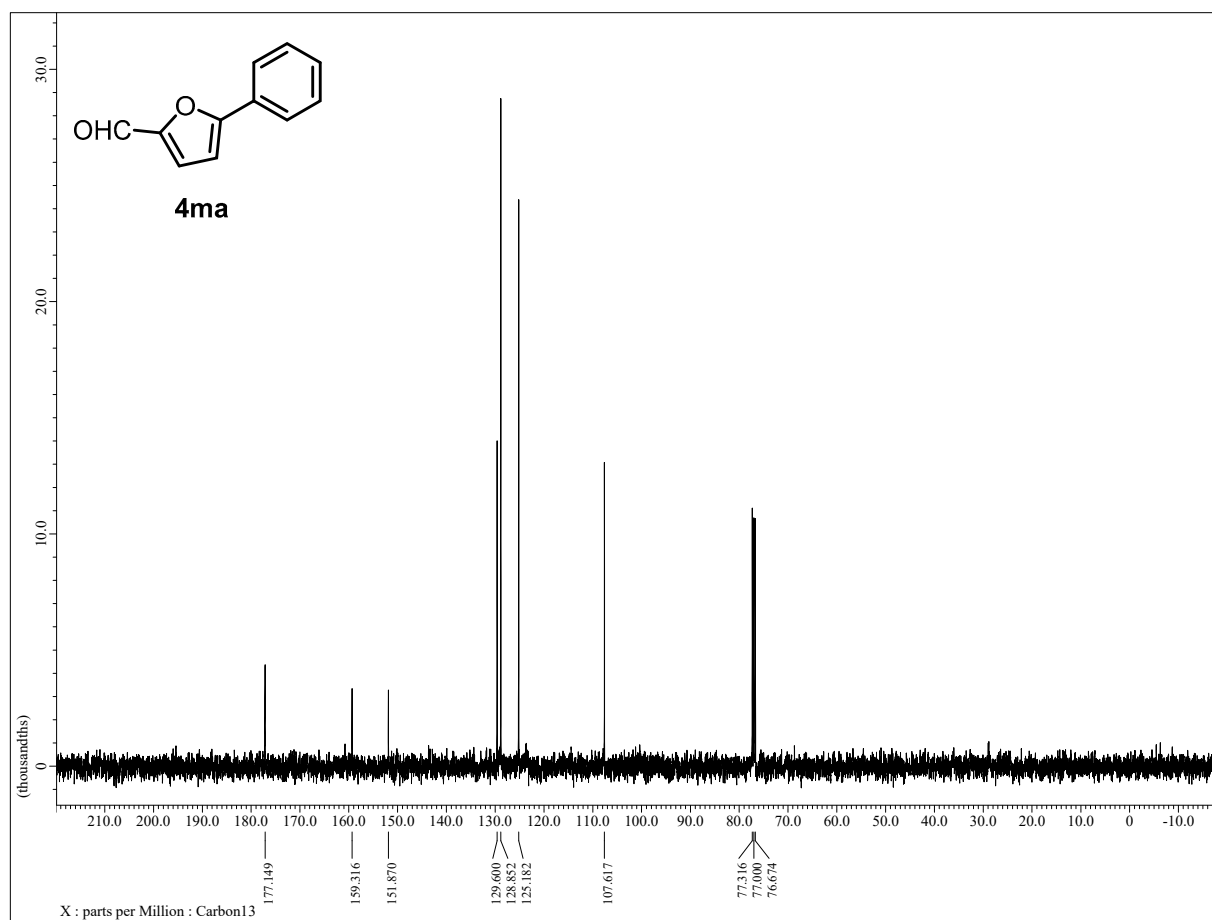
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 2-phenylthiophene (4ka).

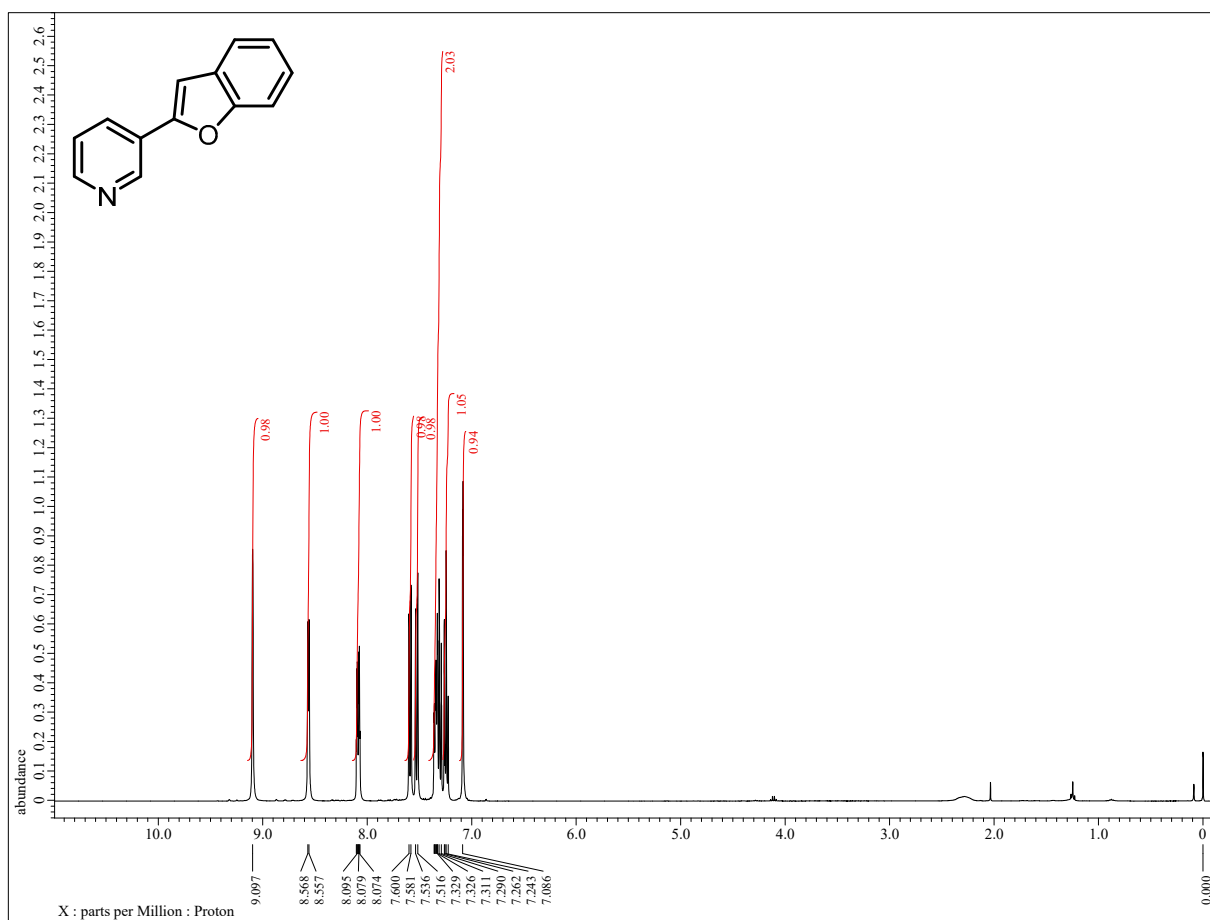
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 2-formyl-5-phenylthiophene (4la).

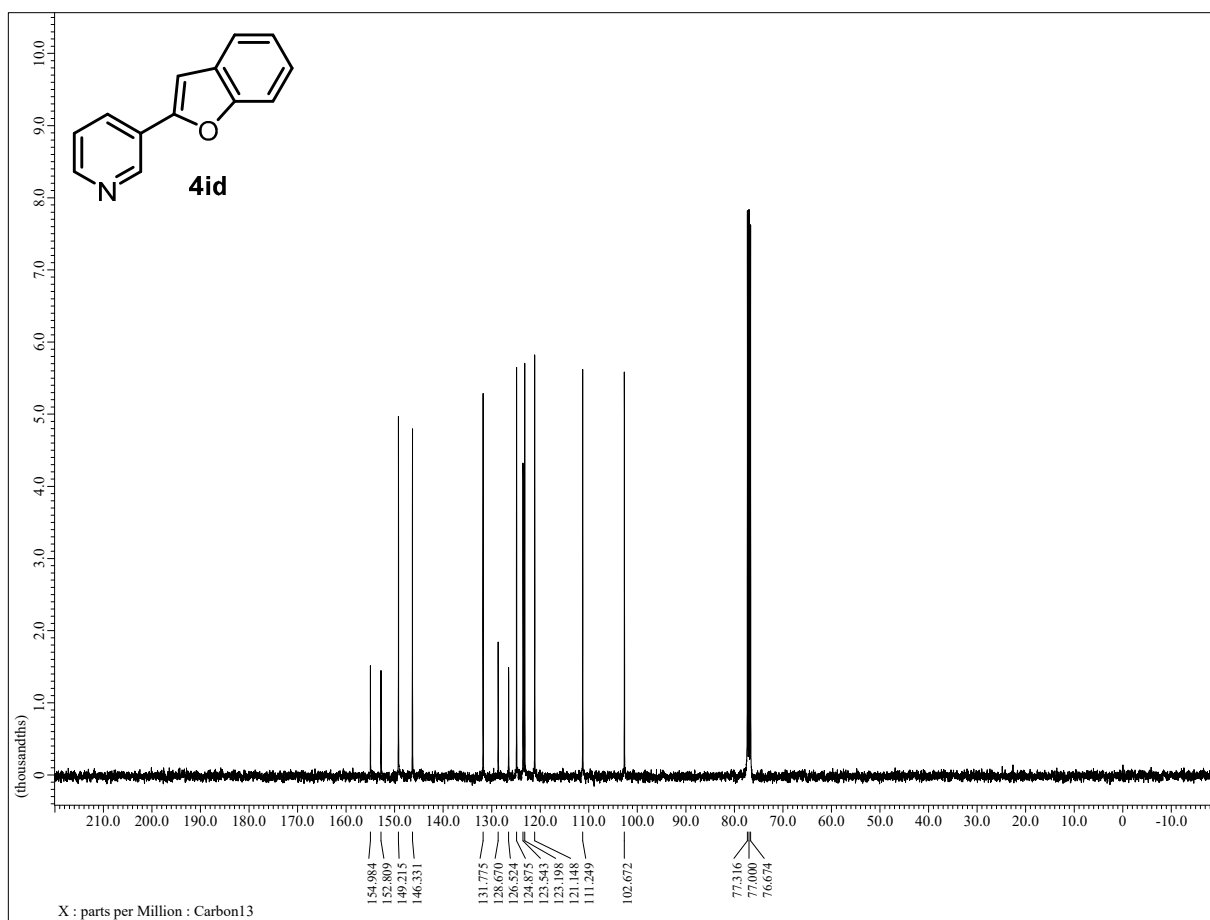


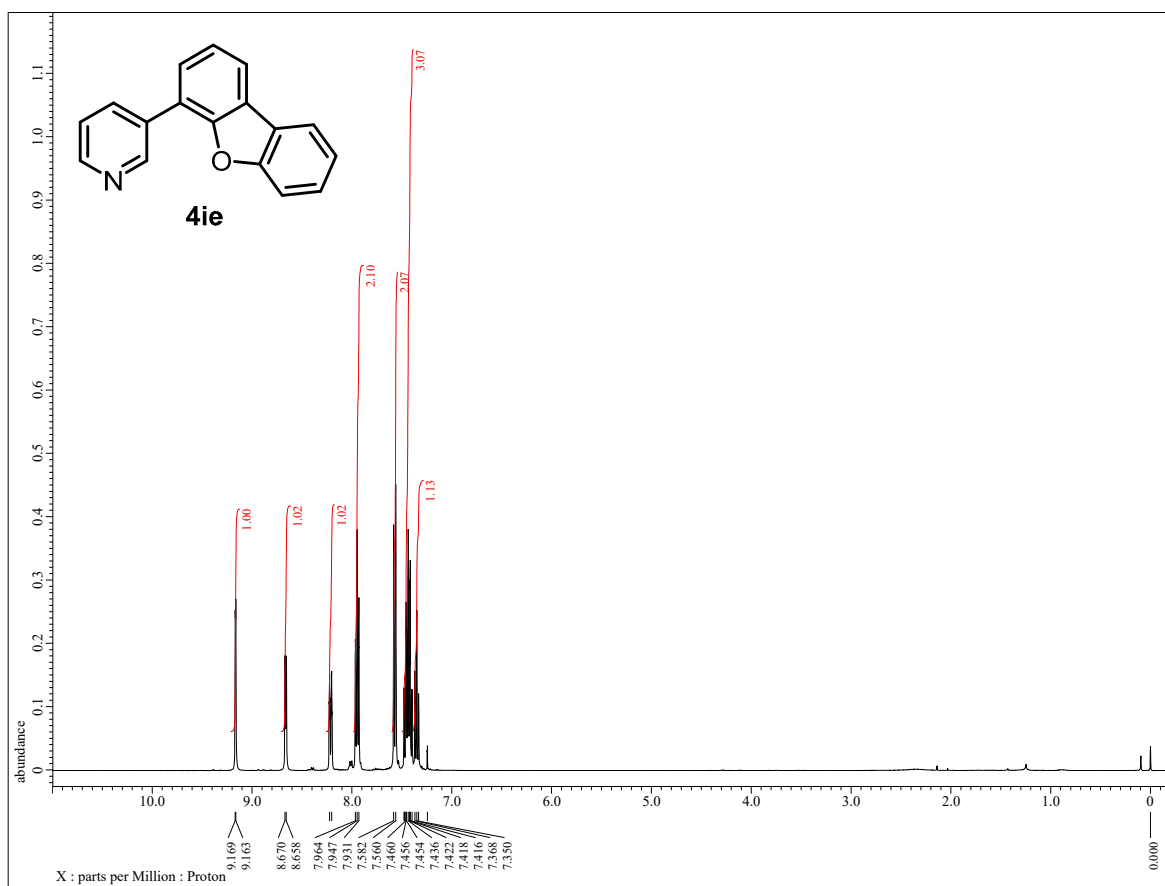
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) of 2-formyl-5-phenylthiophene (4la).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 2-formyl-5-phenylfuran (4ma).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 2-formyl-5-phenylfuran (4ma).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 2-(3-pyridyl)-benzofuran (4id).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) of 2-(3-pyridyl)-benzofuran (4id).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(dibenzo[b,d]furan-4-yl)pyridine (4ie).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) of 2-(3-pyridyl)-benzofuran (4ie).