Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Flow Synthesis of Arylboronic Esters Bearing Electrophlic Functional Groups and Space Integration with Suzuki-Miyaura Coupling Without Intentionally Added Base

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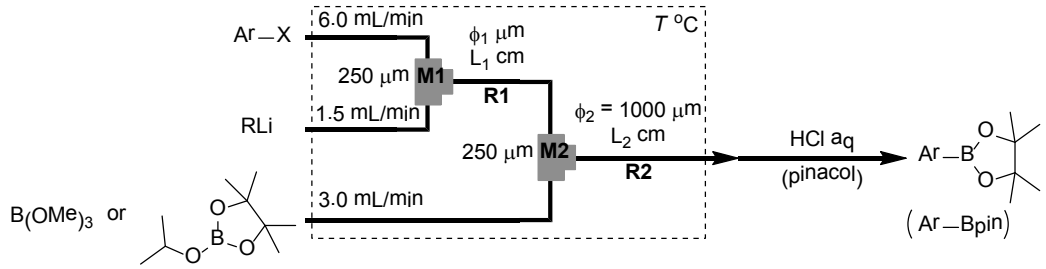
General

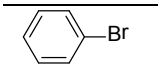
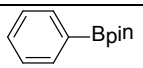
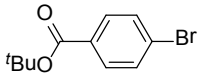
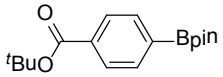
GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBPI; 0.25 mm x 25 m; initial oven temperature, 50 °C; rate of temperature increase, 10 °C/min; final oven temperature, 250 °C). ^{1}H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer with Me_4Si or $CDCl_3$ as a standard in $CDCl_3$ unless otherwise noted. Preparative gel permeation chromatography was performed on Japan Analytical Industry LC-918. THF and Et_2O were purchased from Kanto Chemical Co., Inc. as a dry solvent and used without further purification. Hexane was purchased from Wako, distilled before use, and stored over molecular sieves 4A. Bromobenzene, ethyl *p*-iodobenzoate, ethyl *o*-bromobenzoate, *p*-bromobenzonitrile, *o*-bromobenzonitrile, *p*-iodonitrobenzene, *o*-iodonitrobenzene, *p*-dibromobenzene, 2,5-dibromothiophene, 4,4'-dibromobiphenyl, 4'-bromoacetophenone, *p*-bromobenzaldehyde, *p*-bromonitrobenzene, 5-bromothiophene-2-carboxyaldehyde, trimethoxyborane, isopropoxyboronic acid pinacol ester, pinacol, palladium acetate, tri-*tert*-butylphosphine and lithium reagents were commercially available. *tert*-Butyl *p*-bromobenzoate and *tert*-butyl *o*-bromobenzoate were synthesized according to the literature.[1] *tert*-Butyl 5-bromo-2-thiophenecarboxylate and *tert*-butyl 4-bromo-2-thiophenecarboxylate were synthesized according to the literature.[2] Stainless steel (SUS304) T-shaped micromixer with inner diameter of 250 and 500 μm was manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 250, 500 and 1000 μm were purchased from GL Sciences and were cut into appropriate lengths (3.5, 12.5, 25, 50, 100, 200 and 1600 cm). The micromixer and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW) to construct the flow microreactor in the laboratory. The flow microreactor was dipped in the bath to control the temperature. Solutions were continuously introduced to the flow microreactor using syringe pumps, Harvard PHD 2000, equipped with gastight syringes purchased from SGE. After a steady state was reached, the product solution was collected for 30 s. When the collection time was longer, the product solution can be obtained in a preparative scale.

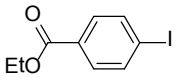
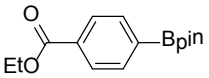
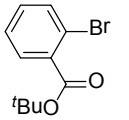
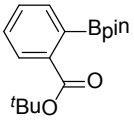
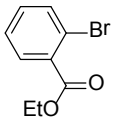
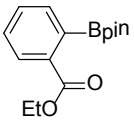
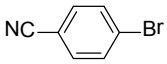
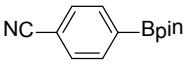
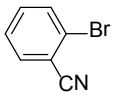
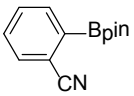
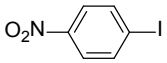
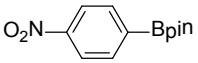
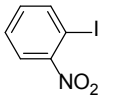
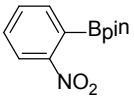
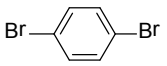
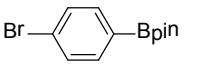
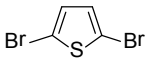
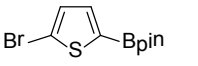
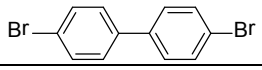
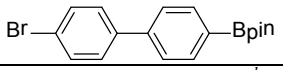
Typical Procedure for Synthesis of Phenylboronic Acid or Functionalized Boronic Esters Based on Halogen-Lithium Exchange Reaction of Aryl Halides Followed by the Borylation in a Flow Microreactor



A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 100 cm)) was used. A solution of aryl halide (0.10 M in THF, flow rate: 6.0 mL min^{-1}) and a solution of ^{n}BuLi (0.40 M in hexane) or ^{s}BuLi (0.40 M in hexane/cyclohexane (35/65)) or PhLi (0.40 M in Et_2O/cyclohexane) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, L = 50 cm, t^{R1} = 3.1 s or ϕ = 500 μm, L = 3.5 cm, t^{R1} = 0.055 s or ϕ = 250 μm, L = 3.5 cm, t^{R1} = 0.014 s) and was mixed with a solution of trimethoxyborane or isopropoxyboronic acid pinacol ester (0.20 M in THF, flow rate: 3.0 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm, t^{R2} = 2.2 s or ϕ = 1000 μm, L = 200 cm, t^{R2} = 9.0 s). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with 1 N HCl aqueous solution (1 mL). The reaction mixture was analyzed by GC using an internal standard. In the case of using trimethoxyborane for the borylation, pinacol (0.3 M in Et_2O) and 1 N HCl aqueous solution (1 mL) was added to the product solution and stirred for 5 min and the yield was determined as a pinacol ester. The results are summarized in Table S-1.

Table S-1. Halogen-Lithium Exchange Reaction of Aryl Halides Followed by the Borylation in a Flow Microreactor.

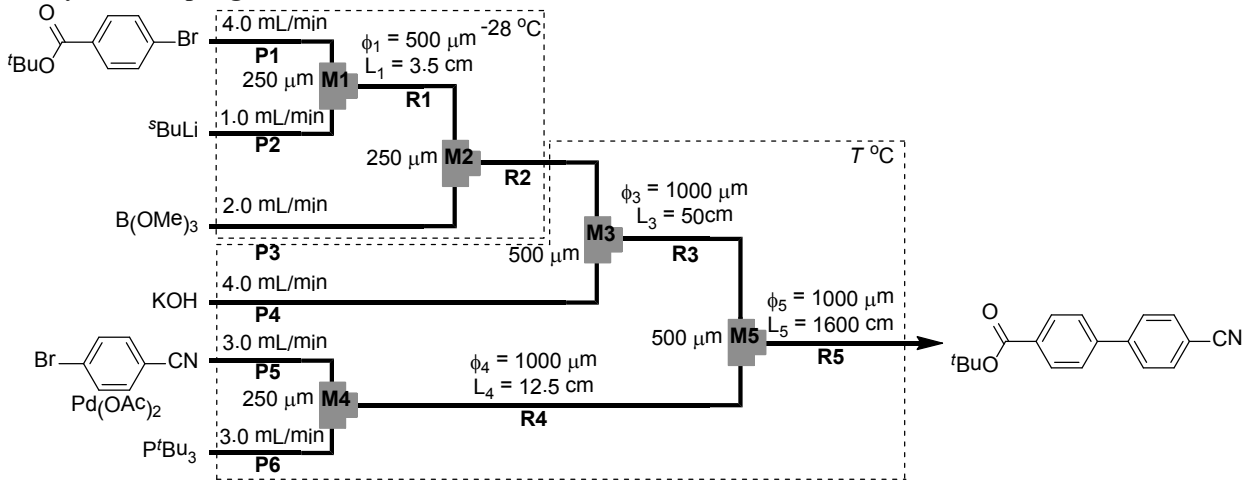
ArX	RLi	t^{R1} (s)	t^{R2} (s)	T (°C)	ArBpin	GC; ^{t}R (min)	Yield (%)[a]
	^{n}BuLi	3.1	9.0	24		16.8	92 (90[b])
	^{s}BuLi	0.055	2.2	-28		24.4	75

	PhLi	0.055	2.2	-58		23.5	69
	^{s}BuLi	0.055	9.0	-28		23.1	84
	^{s}BuLi	0.055	2.2	-48		22.2	64
	^{n}BuLi	0.055	9.0	0		21.0	85
	^{n}BuLi	0.055	2.2	24		20.8	87
	PhLi	0.055	2.2	-28		22.2	64
	PhLi	0.055	2.2	-28		21.5	80
	^{n}BuLi	0.014	2.2	24		20.6	83
	^{n}BuLi	0.014	2.2	24		20.3	73
	^{n}BuLi	0.055	9.0	0		29.4	86

[a] The yield of the products was determined by GC analysis using an internal standard. [b] Trimethoxyborane was used for borylation.

4'-Bromo-4-biphenylboronic Acid Pinacol Ester. Obtained as white solid in 86% yield (Determined by GC analysis using an internal standard) from 4,4'-dibromobiphenyl. The crude product was purified by column chromatography (hexane/ethyl acetate = 20/1) and GPC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 12H), 7.48 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 7.6 Hz, 4H), 7.88 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 83.9, 121.9, 126.2, 128.8, 131.9, 135.4, 139.9, 142.4, 142.6; HRMS (EI) calcd. For $C_{18}H_{20}BBrO_2$: 358.0740; found: 358.0735.

Crosscoupling of *tert*-Butyl *p*-Bromobenzoate and *p*-Bromobenzonitrile by the Sequence of Lithiation, Borylation and Suzuki-Miyaura Coupling Reaction in a Flow Microreactor



R2: ϕ = 1000 μm, L = 50 cm (-28 °C) + connecting teflon tube; ϕ = 1000 μm, L = 10 cm + ϕ = 1000 μm, L = 12.5 cm (T °C)

A flow microreactor system consisting of five T-shaped micromixers (**M1**, **M2**, **M3**, **M4**, and **M5**), five microtube reactors (**R1**, **R2**, **R3**, **R4**, and **R5**), and six tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 50 cm), **P2** (ϕ = 1000 μm, L = 25 cm), **P3** (ϕ = 1000 μm, L = 50 cm), **P4** (ϕ = 1000 μm, L = 50 cm), **P5** (ϕ = 1000 μm, L = 50 cm) and **P6** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of *tert*-butyl *p*-bromobenzoate (0.10 M in THF, flow rate: 4.0 mL min^{-1}) and a solution of ^{s}BuLi (0.40 M in hexane/cyclohexane (35/65), flow rate: 1.0 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 500 μm, L = 3.5 cm, t^{R1} = 0.083 s) and was mixed with a solution of

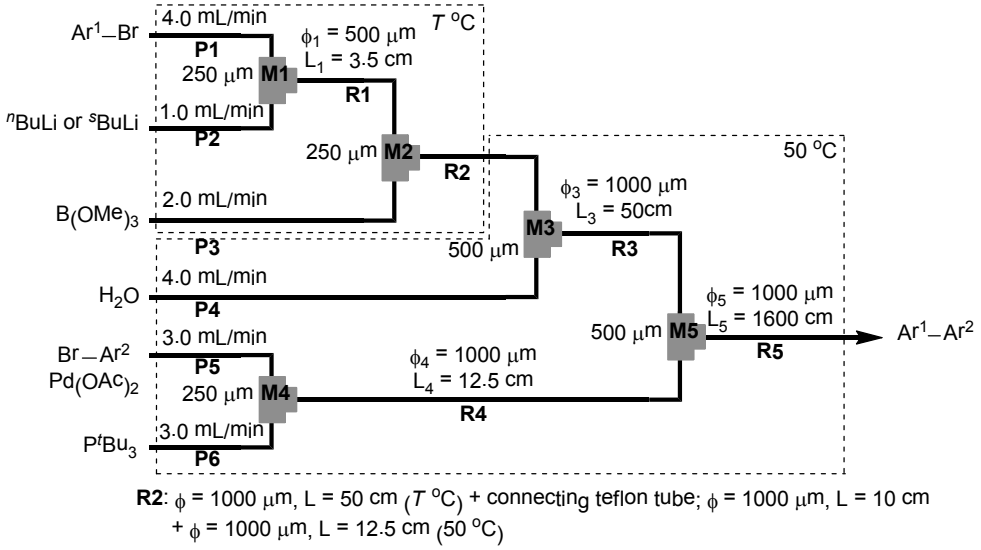
trimethoxyborane (0.20 M in THF, flow rate: 2.0 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm (-28 °C), 3.4 s + connecting teflon tube ϕ = 1000 μm, L = 10 cm, 0.67 s + ϕ = 1000 μm, L = 12.5 cm (*T* °C), 0.84 s) and mixed with a solution of potassium hydroxide (x M in H_2O, flow rate: 4.0 mL min^{-1}) in **M3** (ϕ = 500 μm). The mixture was passed through **R3** (ϕ = 1000 μm, L = 50 cm, t^{R3} = 2.1 s) and introduced to **M5** (ϕ = 500 μm). On the other hand, a solution of *p*-bromobenzonitrile (88.8 mM) and palladium acetate (4.44 mM) in THF (flow rate = 3.0 mL min^{-1}) and a solution of tri-*tert*-butylphosphine (4.44 mM in THF, flow rate = 3.0 mL min^{-1}) were introduced to **M4** (ϕ = 250 μm). The resulting solution was passed through **R4** (ϕ = 1000 μm, L = 12.5 cm, t^{R4} = 0.98 s) and introduced to **M5** (ϕ = 500 μm), where the solution was mixed a solution from **R3**. The resulting solution was passed through **R5** (ϕ = 1000 μm, L = 1600 cm, t^{R5} = 44 s). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with 1 N HCl aqueous solution (1 mL). The reaction mixture was analyzed by GC (t_R 28.8 min). The results are summarized in Table S-2.

Table S-2. Crosscoupling of *tert*-Butyl *p*-Bromobenzoate and *p*-Bromobenzonitrile by the Sequence of Lithiation, Borylation and Suzuki-Miyaura Coupling Reaction in a Flow Microreactor.

Condition	*T* (°C)	Yield (%)[a]
KOH (0.10 M) in H_2O	30	15
KOH (0.30 M) in H_2O	30	7
H_2O	30	64
H_2O	50	97

[a] The yield of the products was determined by GC analysis using an internal standard.

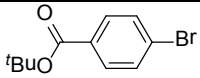
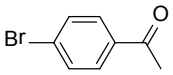
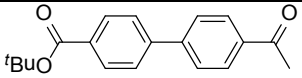
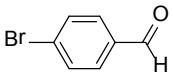
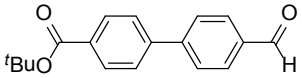
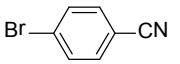
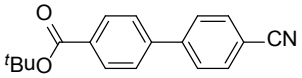
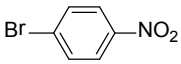
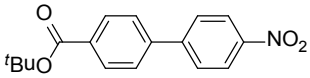
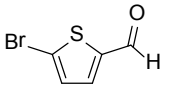
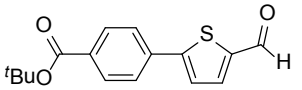
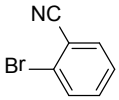
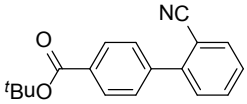
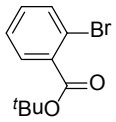
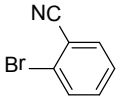
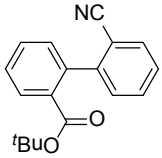
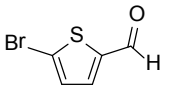
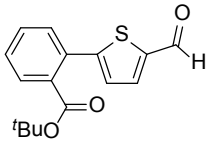
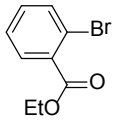
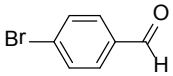
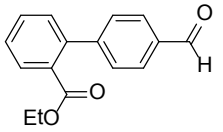
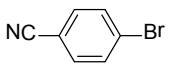
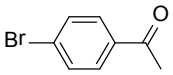
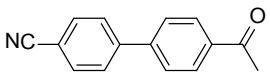
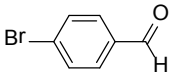
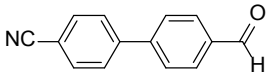
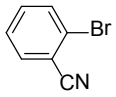
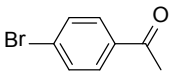
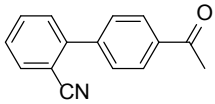
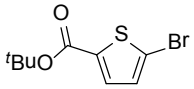
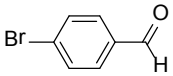
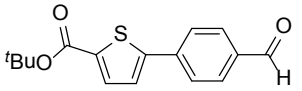
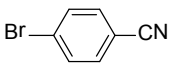
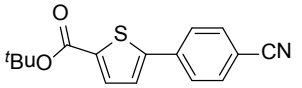
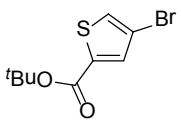
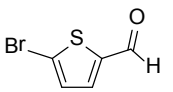
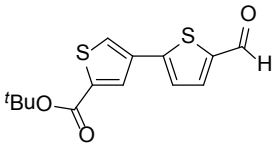
Typical Procedure for Crosscoupling of Two Aryl Bromides (Ar^1Br and $BrAr^2$) by the Sequence of Lithiation, Borylation and Suzuki-Miyaura Coupling Reaction in a Flow Microreactor



A flow microreactor system consisting of five T-shaped micromixers (**M1**, **M2**, **M3**, **M4**, and **M5**), five microtube reactors (**R1**, **R2**, **R3**, **R4**, and **R5**), and six tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 50 cm), **P2** (ϕ = 1000 μm, L = 25 cm), **P3** (ϕ = 1000 μm, L = 50 cm), **P4** (ϕ = 1000 μm, L = 50 cm), **P5** (ϕ = 1000 μm, L = 50 cm) and **P6** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of aryl bromide (Ar^1Br, 0.10 M in THF, flow rate: 4.0 mL min^{-1}) and a solution of ^{n}BuLi (0.40 M in hexane) or ^{s}BuLi (0.40 M in hexane/cyclohexane (35/65)) (flow rate: 1.0 mL min^{-1}) were introduced to **M1** (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through **R1** (ϕ = 500 μm, L = 3.5 cm, t^{R1} = 0.083 s) and was mixed with a solution of trimethoxyborane (0.20 M in THF, flow rate: 2.0 mL min^{-1}) in **M2** (ϕ = 250 μm). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm (*T* °C), 3.4 s + connecting teflon tube ϕ = 1000 μm, L = 10 cm, 0.67 s + ϕ = 1000 μm, L = 12.5 cm (50 °C), 0.84 s) and mixed with a solution of H_2O (flow rate: 4.0 mL min^{-1}) in **M3** (ϕ = 500 μm). The mixture was passed through **R3** (ϕ = 1000 μm, L = 50 cm, t^{R3} = 2.1 s) and introduced to **M5** (ϕ = 500 μm). On the other hand, a solution of aryl bromide ($BrAr^2$, 88.8 mM) and palladium acetate (4.44 mM) in THF (flow rate = 3.0 mL min^{-1}) and a solution of tri-*tert*-butylphosphine (4.44 mM in THF, flow rate = 3.0 mL min^{-1}) were introduced to **M4** (ϕ = 250 μm). The resulting solution was passed through **R4** (ϕ = 1000 μm, L = 12.5 cm, t^{R4} = 0.98 s) and introduced to **M5** (ϕ = 500 μm), where the solution was mixed a solution from **R3**. The resulting solution was passed through **R5** (ϕ = 1000 μm, L = 1600 cm, t^{R5} = 44 s). After a steady state was reached, an aliquot of the product solution was collected for 30 s and was treated with 1 N HCl aqueous solution (1 mL). After Et_2O was added, the organic layer was separated and the remaining aqueous layer was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography and GPC. The yield of product was determined by GC analysis using an internal standard or isolation. The results are summarized in Table S-3. The spectrum data of ethyl 2-(4-formylphenyl)benzoate[3] 4'-acetylbiphenyl-4-

carbonitrile[4] (GC; ^{t}R 26.5 min), 4'-formylbiphenyl-4-carbonitrile[5] (GC; ^{t}R 25.2 min) and 4'-acetylbiphenyl-2-carbonitrile[6] (GC; ^{t}R 25.4 min) were identical to those reported in the literature.

Table S-3. Crosscoupling of Ar^1Br and $BrAr^2$ by the Sequence of Lithiation, Borylation and Suzuki-Miyaura Coupling Reaction in a Flow Microreactor.

Ar^1Br	$BrAr^2$	BuLi	T (°C)	Ar^1Ar^2	Yield (%)
		^{s}BuLi	-28		62[a]
		^{s}BuLi	-28		70[a]
		^{s}BuLi	-28		97[b](91[a])
		^{s}BuLi	-28		81[a]
		^{s}BuLi	-28		80[a]
		^{s}BuLi	-28		72[a]
		^{s}BuLi	-28		87[b,c]
		^{s}BuLi	-28		69[b,d]
		^{s}BuLi	-28		52[b,e]
		^{n}BuLi	0		77[b,f]
		^{n}BuLi	0		90[b,f]
		^{n}BuLi	24		61[b,d]
		^{s}BuLi	0		81[a]
		^{s}BuLi	0		73[b]
		^{s}BuLi	0		91[a]

[a] Isolated yield. [b] Determined by GC analysis using an internal standard. [c] The resulting mixture was stirred in a flask at 50 °C for 10 min. [d] The resulting mixture was stirred in a flask at 50 °C for 5 min. [e] The resulting mixture was stirred in a flask at 50 °C for 30 min. [f] The resulting mixture was stirred in a flask at 50 °C for 2 min.

Preparation of *tert*-Butyl *p*-Bromobenzoate and *tert*-Butyl *o*-Bromobenzoate
The titled compounds were synthesized according to the literature.[1] The solution of ^{n}BuLi in hexane (1.6 M, 65.5 mL, 105 mmol) was added dropwise to the solution of *tert*-butanol (8.29 g, 115 mmol) in Et_2O (100 mL) at 0 ^{o}C. After addition, the reaction mixture was warmed to room temperature and the solution of *p*-bromobenzoyl chloride or *o*-bromobenzoyl chloride (21.9 g, 100 mmol) in Et_2O (100 mL) was added dropwise to the reaction mixture. The resulting mixture was stirred for 14 h at room temperature. After water (100 mL) was added to quench the reaction, organic layer was separated and the remaining aqueous layer was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate = 50/1).

Preparation of *tert*-Butyl 5-Bromo-2-Thiophenecarboxylate and *tert*-Butyl 4-Bromo-2-Thiophenecarboxylate
The titled compounds were synthesized according to the literature.[2] Concentrated sulfuric acid (2.7 mL, 50 mmol) was added to the suspension of anhydrous magnesium sulfate (24. 1 g, 200 mmol) in CH_2Cl_2 (200 mL) and the mixture was stirred for 15 min at room temperature. Then, 5-bromo-2-thiophenecarboxylic acid or 4-bromo-2-thiophenecarboxylic acid (10.3 g, 50 mmol) and *tert*-butanol (18.0 g, 250 mmol) were added. After the mixture was stirred for 18 h at room temperature, saturated aqueous solution of $NaHCO_3$ (350 mL) was added to quench the reaction and the resulting mixture was stirred until all magnesium sulfate had dissolved. Then, organic layer was separated and the remaining aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and organic layer was dried over Na_2SO_4. After solvent was removed under reduced pressure, the crude product was purified by column chromatography (hexane/ethyl acetate = 50/1).

***tert*-Butyl 4-(4-cyanophenyl)benzoate.** Obtained as white solid in 91% yield from *tert*-butyl *p*-bromobenzoate (Ar^1Br) and *p*-bromobenzonitrile ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 9H), 7.63 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 8.09 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.4, 111.6, 118.7, 127.0, 127.9, 130.1, 132.1, 132.6, 142.9, 144.6, 165.2; HRMS (EI) calcd. For $C_{18}H_{17}O_2N$: 279.1259; found: 279.1264.

***tert*-Butyl 4-(4-acetylphenyl)benzoate.** Obtained as white solid in 62% yield from *tert*-butyl *p*-bromobenzoate (Ar^1Br) and 4'-bromoacetophenone ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 9H), 2.65 (s, 3H), 7.65-7.73 (m, 4H), 8.04-8.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 28.2, 81.2, 127.0, 127.4, 128.9, 130.0, 131.6, 136.4, 143.7, 144.6, 165.4, 197.6; HRMS (EI) calcd. For $C_{19}H_{20}O_3$: 296.1412; found: 296.1409.

***tert*-Butyl 4-(4-formylphenyl)benzoate.** Obtained as white solid in 70% yield from *tert*-butyl *p*-bromobenzoate (Ar^1Br) and 4-bromobenzaldehyde ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9H), 7.68 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 2H), 10.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.3, 127.2, 127.9, 130.1, 130.3, 131.9, 135.6, 143.5, 146.1, 165.3, 191.8; HRMS (ESI) calcd. For $C_{18}H_{19}O_3^+$ $[M+H]^+$: 283.1334; found: 283.1321.

***tert*-Butyl 4-(4-nitrophenyl)benzoate.** Obtained as white solid in 81% yield from *tert*-butyl *p*-bromobenzoate (Ar^1Br) and 4-bromonitrobenzene ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9H), 7.67 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.4, 124.2, 127.2, 128.0, 130.2, 132.3, 142.5, 146.5, 147.5, 165.2; HRMS (EI) calcd. For $C_{17}H_{17}NO_3$: 299.1158; found: 299.1152.

5-(4-*tert*-Butoxycarbonylphenyl)thiophene-2-carbaldehyde. Obtained as colorless solid in 80% yield from *tert*-butyl *p*-bromobenzoate (Ar^1Br) and 5-bromothiophene-2-carboxyaldehyde ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 9H), 7.49 (d, J = 4.0 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 4.0 Hz, 1H), 8.04 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 81.4, 125.1, 126.0, 130.3, 132.5, 136.6, 137.2, 143.3, 152.7, 165.0, 182.8; HRMS (EI) calcd. For $C_{16}H_{16}O_3S$: 288.0820; found: 288.0815.

***tert*-Butyl 4-(2-cyanophenyl)benzoate.** Obtained as colorless solid in 72% yield from *tert*-butyl *p*-bromobenzoate (Ar^1Br) and *o*-bromobenzonitrile ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1) and GPC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 9H), 7.47-7.81 (m, 6H), 8.10-8.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.3, 111.3, 118.4, 128.1, 128.6, 129.8, 130.0, 132.2, 132.9, 133.8, 141.9, 144.5, 165.2; HRMS (ESI) calcd. For $C_{18}H_{18}O_2N^+$ $[M+H]^+$: 280.1338; found: 280.1326.

***tert*-Butyl 2-(2-cyanophenyl)benzoate.** Obtained as colorless solid in 87% yield (Determined by GC analysis using an internal standard, ^{t}R 24.8 min) from *tert*-butyl *o*-bromobenzoate (Ar^1Br) and *o*-bromobenzonitrile ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1) and GPC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 7.29 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.45-7.62 (m, 4H), 7.72 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 27.6, 81.4, 112.4, 118.0, 127.4, 128.6, 129.7, 130.7, 131.4, 132.0, 132.1, 132.3, 138.7, 146.4, 166.0 (Some carbons were overlapped.); HRMS (EI) calcd. For $C_{18}H_{17}O_2N$: 279.1259; found: 279.1254.

5-(2-*tert*-Butoxycarbonylphenyl)thiophene-2-carbaldehyde. Obtained as yellow oil in 69% yield (Determined by GC analysis using an internal standard, ^tR 25.8 min) from *tert*-butyl *o*-bromobenzoate (Ar^1Br) and 5-bromothiophene-2-carboxyaldehyde ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1). ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 7.10 (d, *J* = 2.8 Hz, 1H), 7.40-7.60 (m, 3H), 7.74 (d, *J* = 2.8 Hz, 1H), 7.80-7.83 (m, 1H), 9.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 82.0, 127.8, 129.1, 130.0, 130.9, 131.0, 132.8, 133.4, 136.3, 143.5, 153.1, 166.9, 182.9; HRMS (ESI) calcd. For $C_{16}H_{17}O_3S^+$ $[M+H]^+$: 289.0898; found: 289.0888.

***tert*-Butyl 5-(4-formylphenyl)thiophene-2-carboxylate.** Obtained as yellow solid in 81% yield from *tert*-butyl 5-bromo-2-thiophenecarboxylate (Ar^1Br) and 4'-bromoacetophenone ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 10/1). ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 9H), 7.40 (d, *J* = 3.6 Hz, 1H), 7.71 (d, *J* = 4.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 2H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 82.2, 125.1, 126.4, 130.5, 133.6, 135.8, 136.3, 139.2, 148.2, 161.1, 191.3; HRMS (ESI) calcd. For $C_{16}H_{17}O_3S^+$ $[M+H]^+$: 289.0898; found: 289.0887.

***tert*-Butyl 5-(4-cyanophenyl)thiophene-2-carboxylate.** Obtained as yellow solid in 73% yield (Determined by GC analysis using an internal standard, ^tR 27.8 min) from *tert*-butyl 5-bromo-2-thiophenecarboxylate (Ar^1Br) and *p*-bromobenzonitrile ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 20/1). ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 9H), 7.36 (d, *J* = 4.0 Hz, 1H), 7.60-7.75 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 82.2, 111.7, 118.4, 125.2, 126.3, 132.7, 133.6, 136.5, 137.7, 147.4, 161.0; HRMS (EI) calcd. For $C_{16}H_{15}NO_2S$: 285.0823; found: 285.0826.

***tert*-butyl 5-formyl-(2,3'-bithiophene)-5'-carboxylate.** Obtained as colorless solid in 91% yield from *tert*-butyl 4-bromo-2-thiophenecarboxylate (Ar^1Br) and 5-bromothiophene-2-carboxyaldehyde ($BrAr^2$). The crude product was purified by column chromatography (hexane/ethyl acetate = 5/1) and GPC. ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 9H), 7.31 (d, *J* = 4.0 Hz, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.72 (d, *J* = 4.0 Hz, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 9.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 82.6, 124.5, 127.9, 130.6, 134.8, 137.3, 137.5, 142.1, 147.5, 160.8, 182.7; HRMS (ESI) calcd. For $C_{14}H_{15}O_3S_2^+$ $[M+H]^+$: 295.0463; found: 295.0457.

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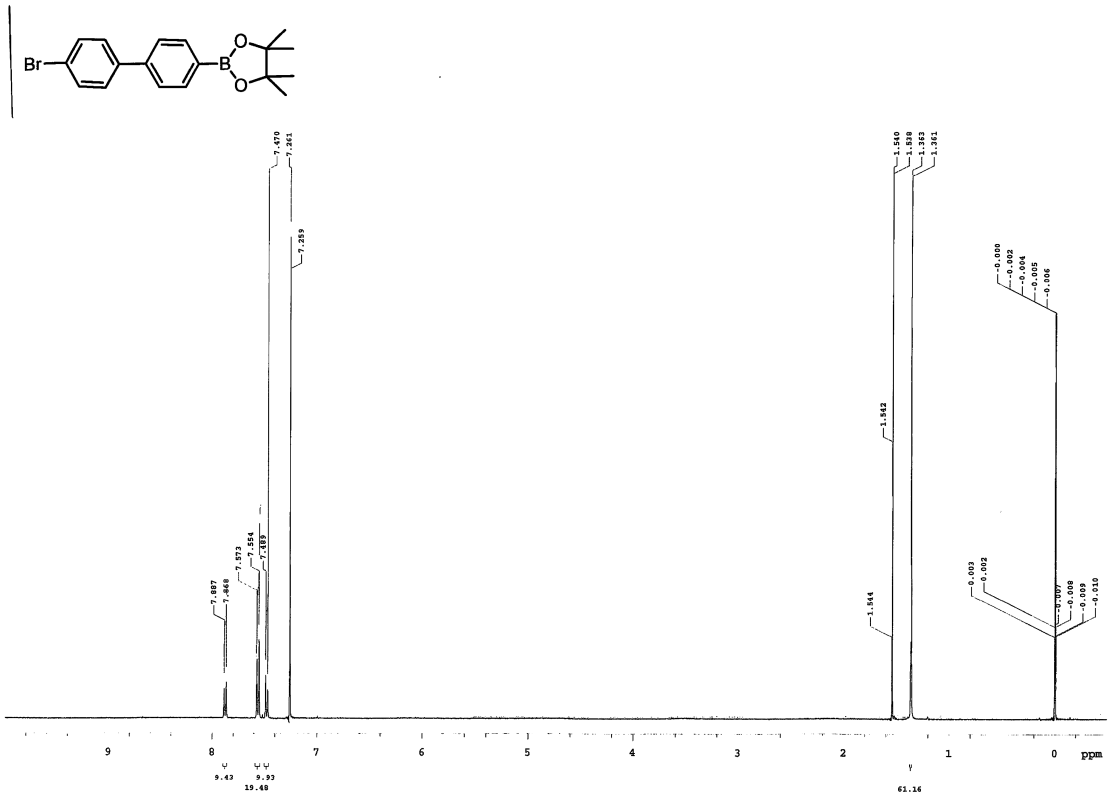
6. For the spectral data of 4'-acetylbiphenyl-2-carbonitrile: W. Li, Z. Xu, X. Jiang, M. Fang, *Org. Lett.* **2011**, *13*, 1286.



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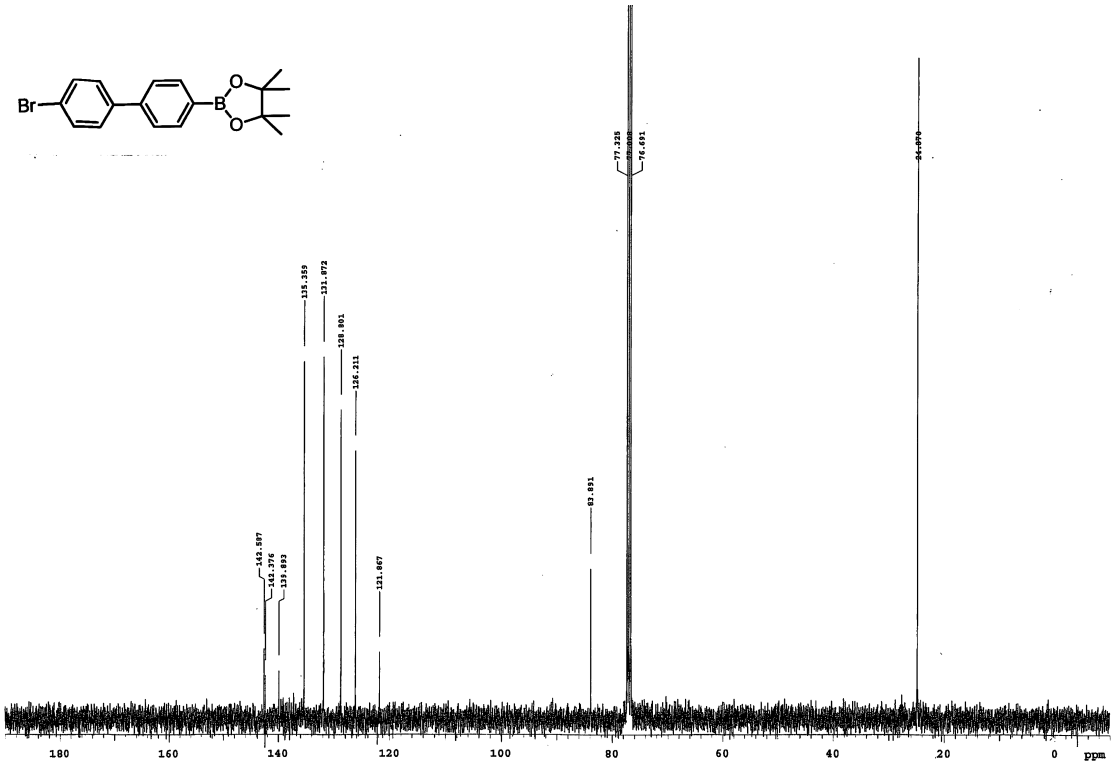

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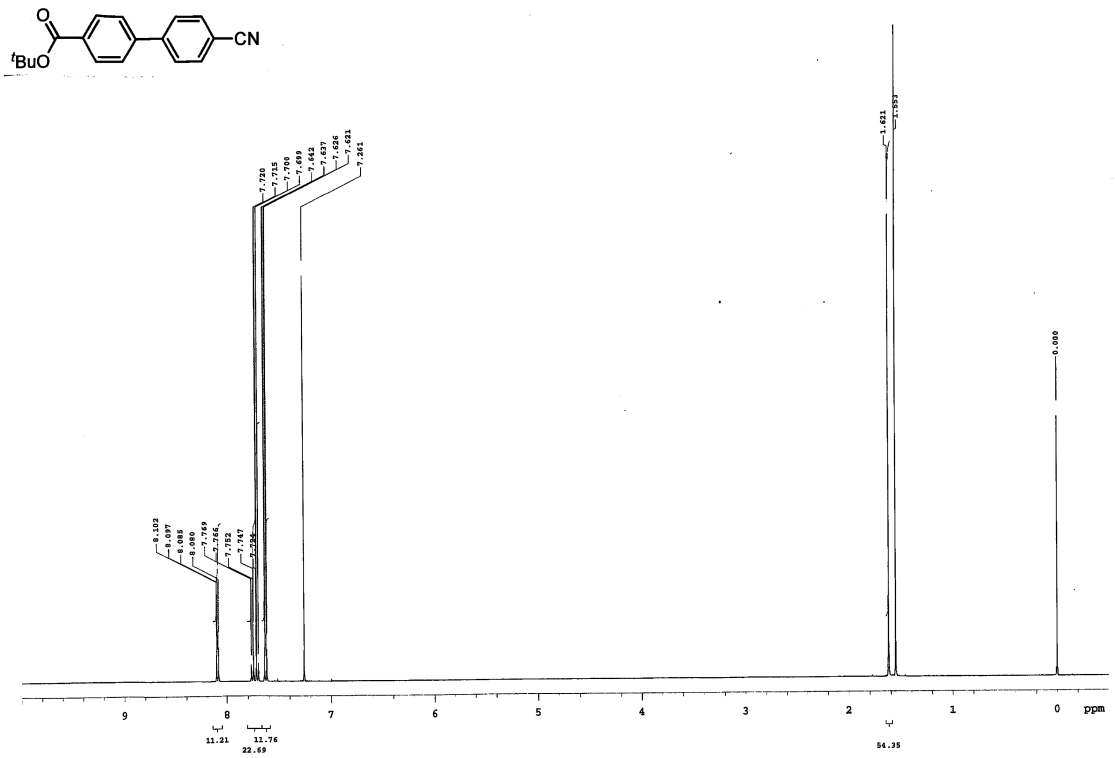

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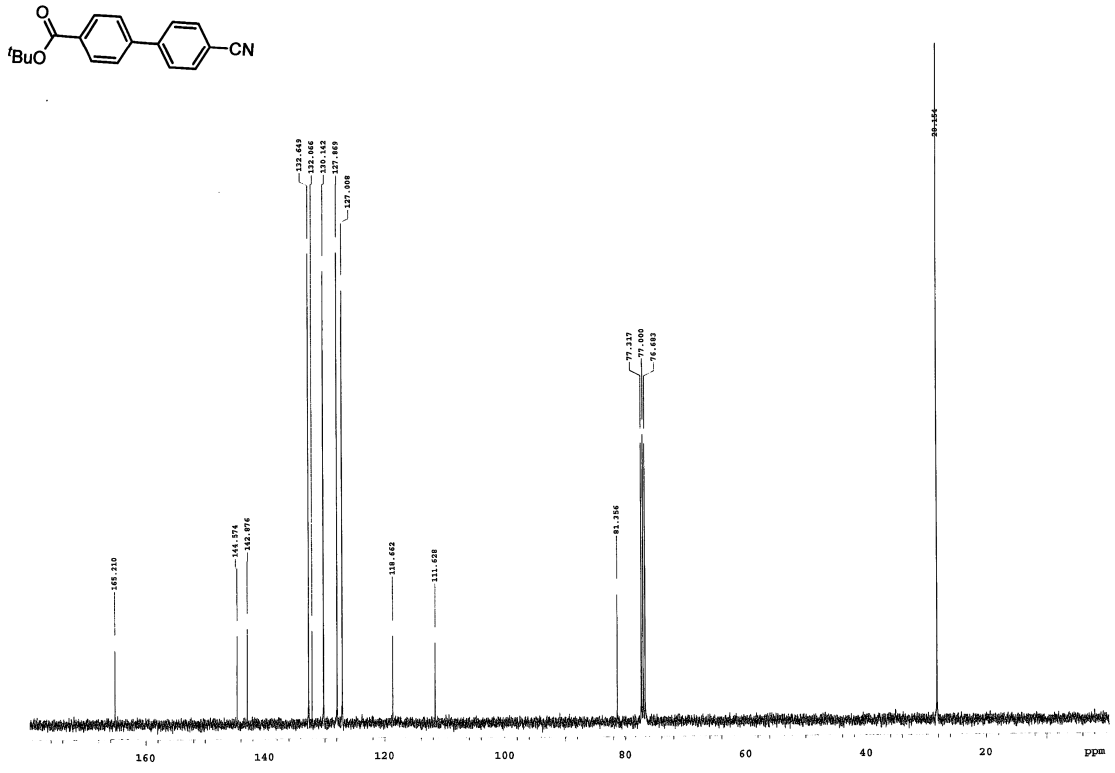

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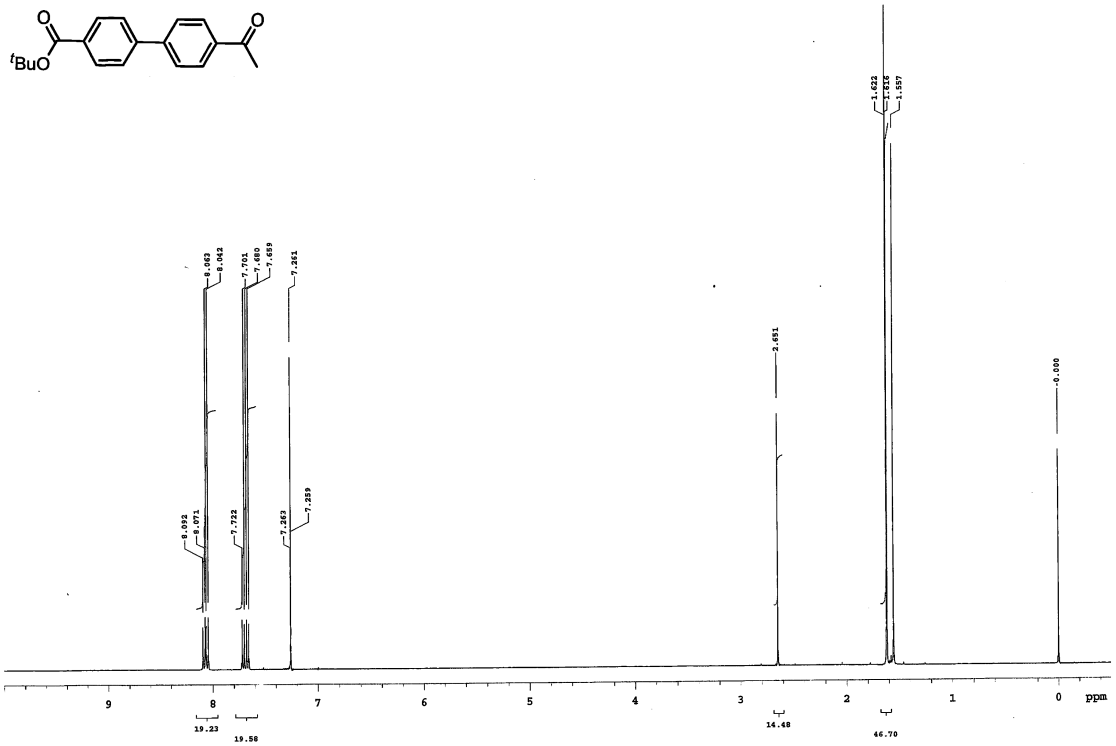

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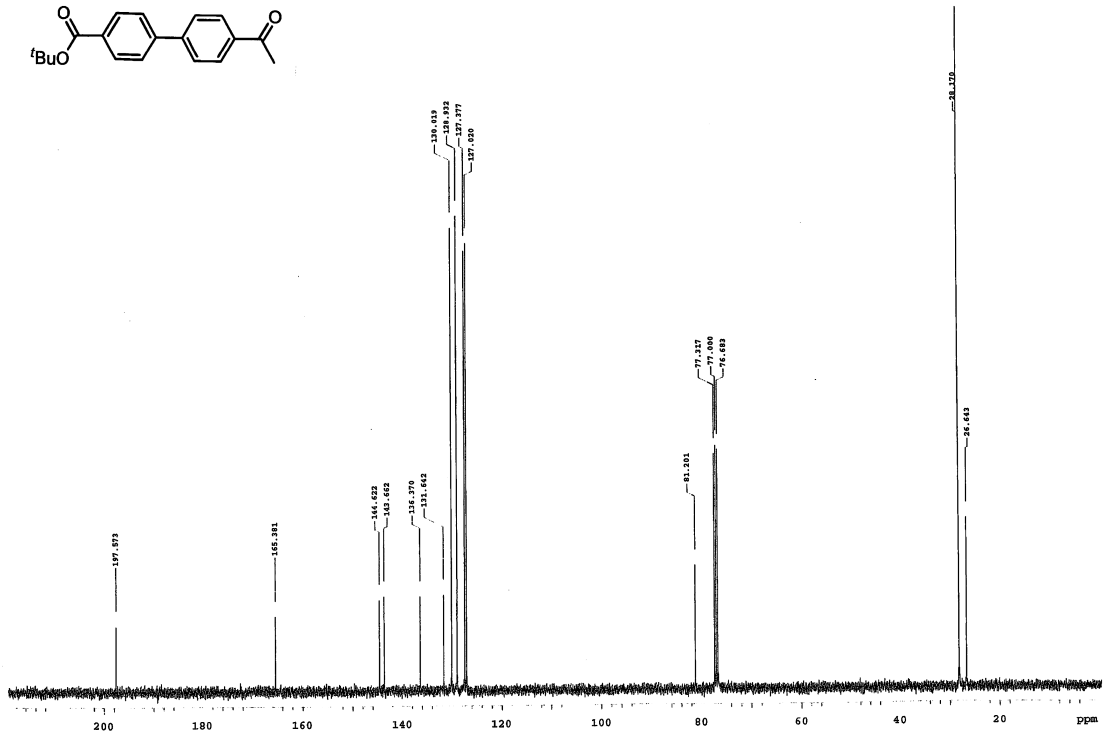

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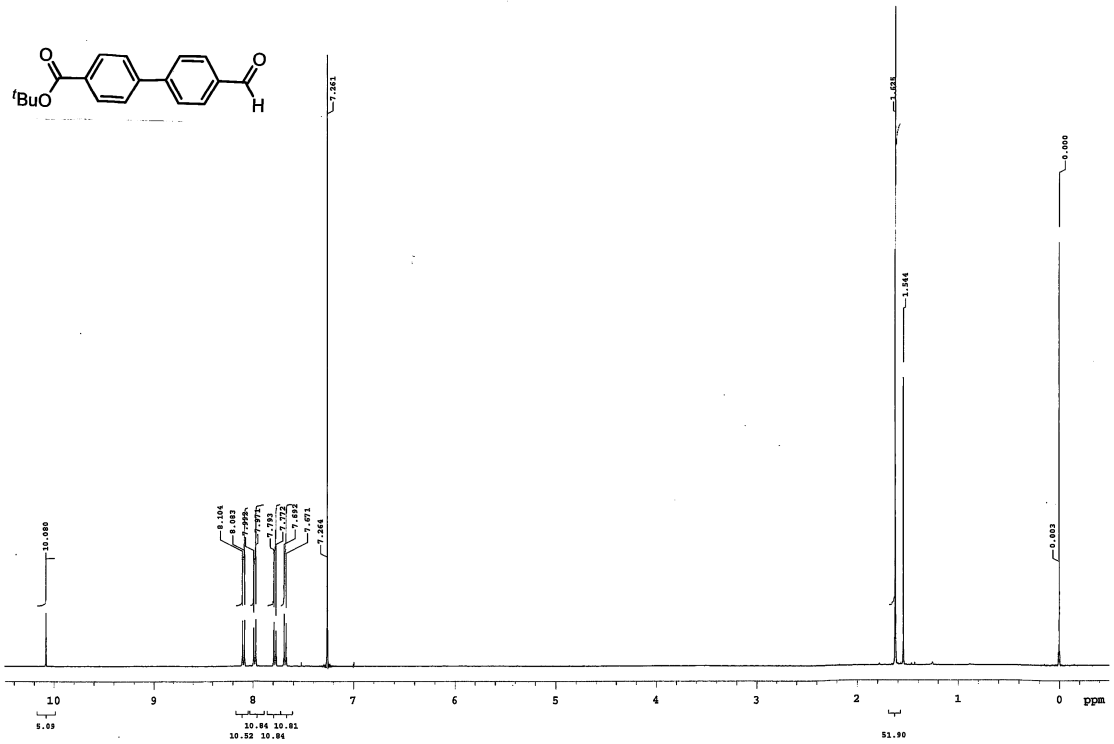

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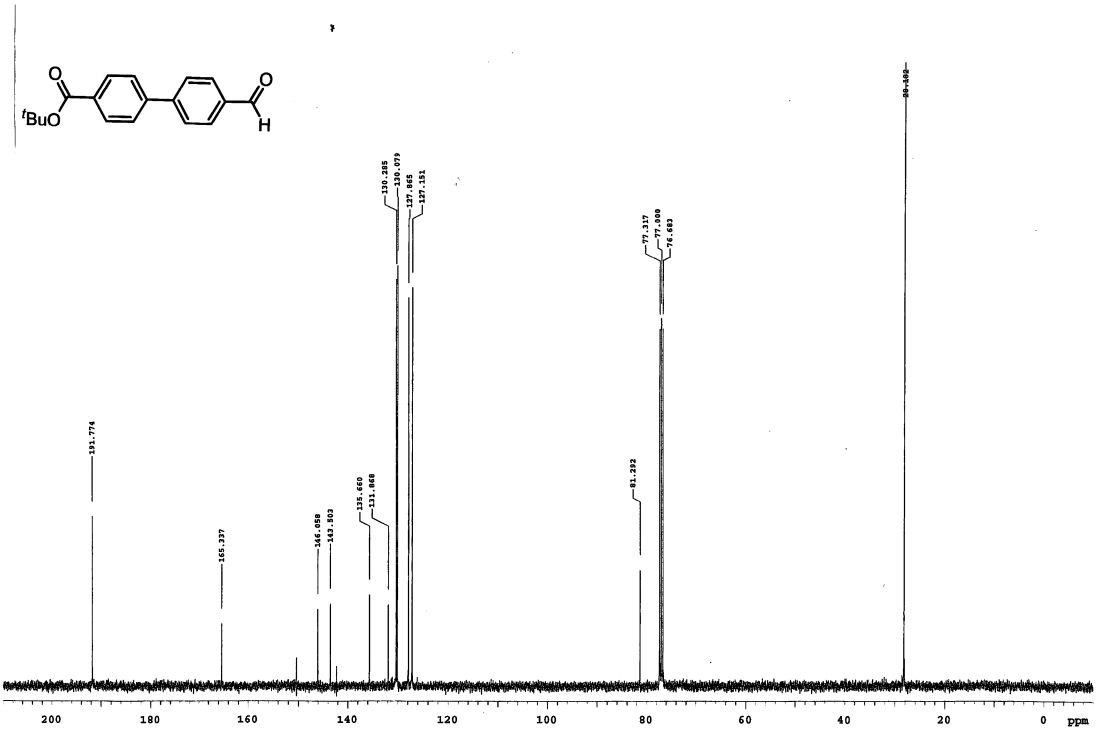

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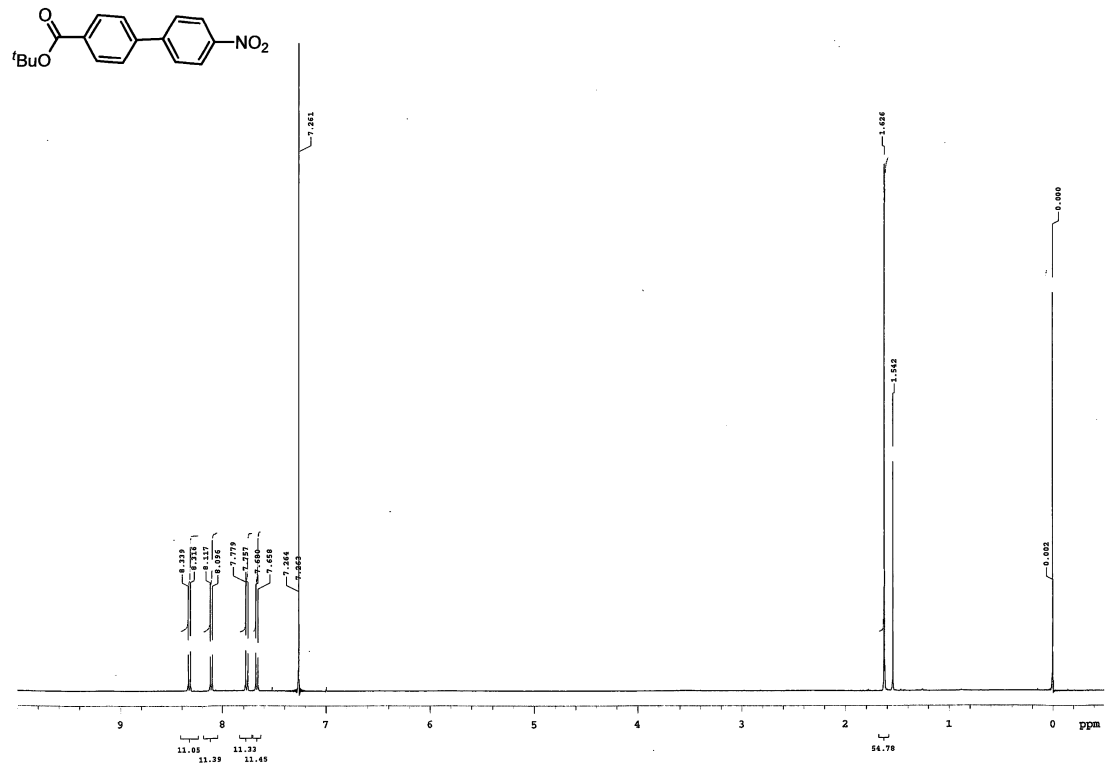

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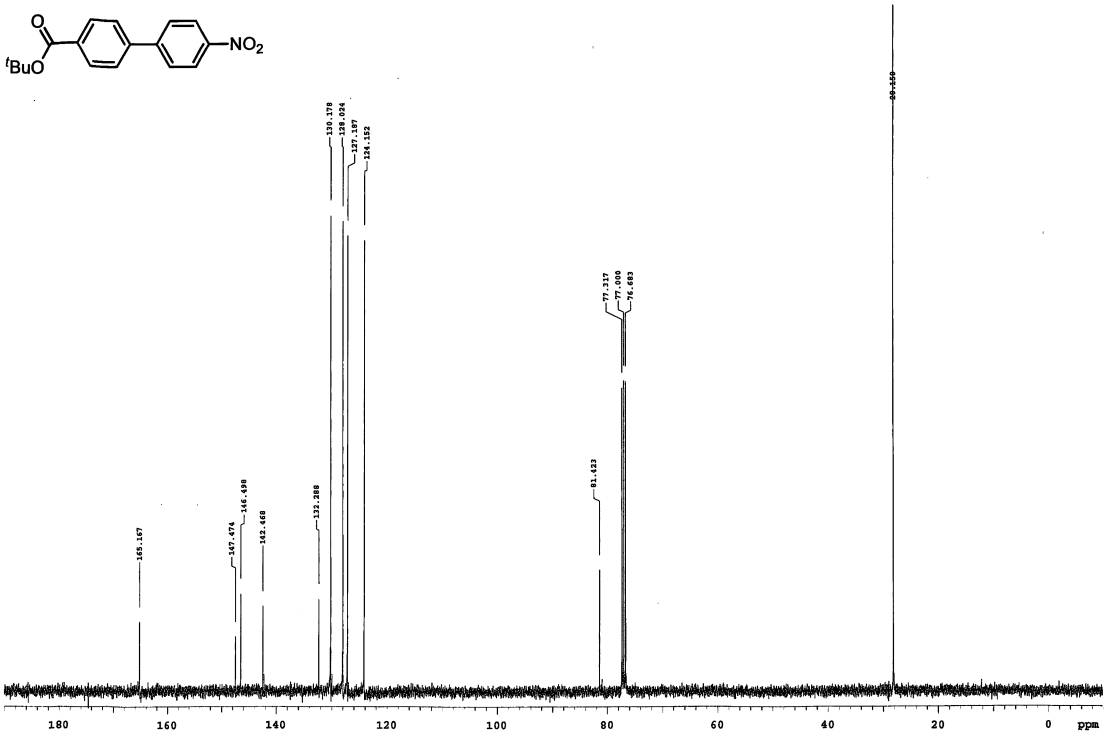

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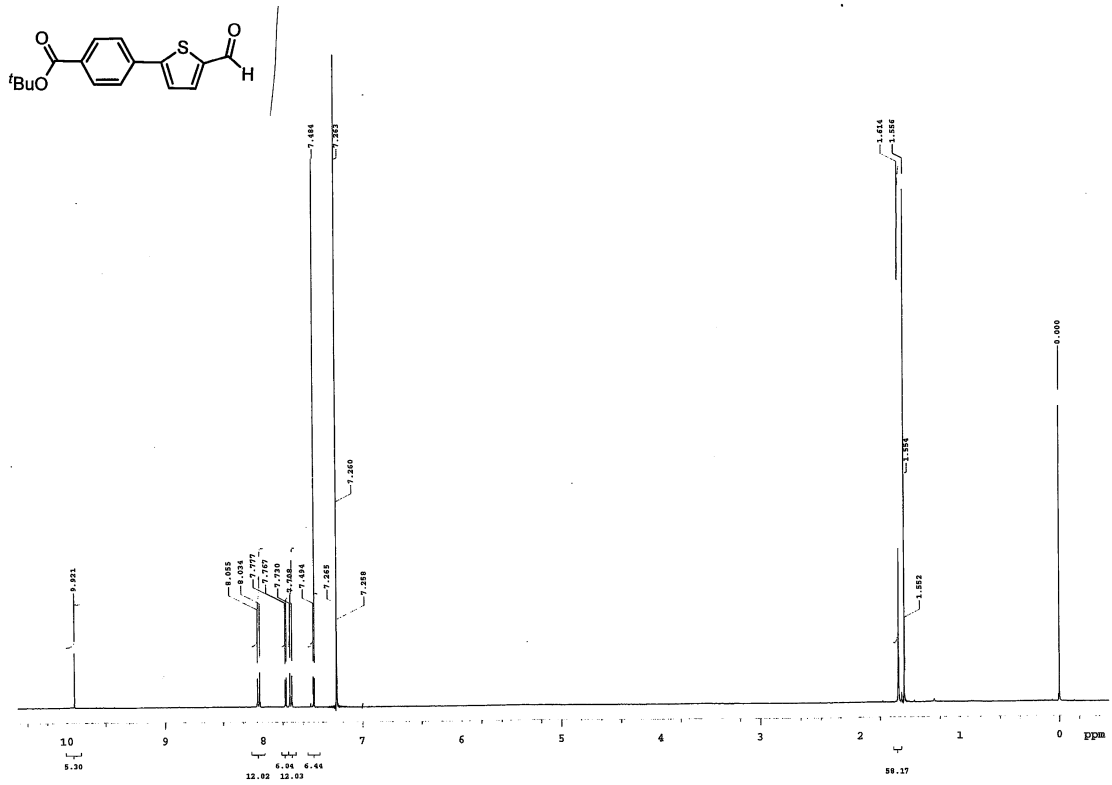

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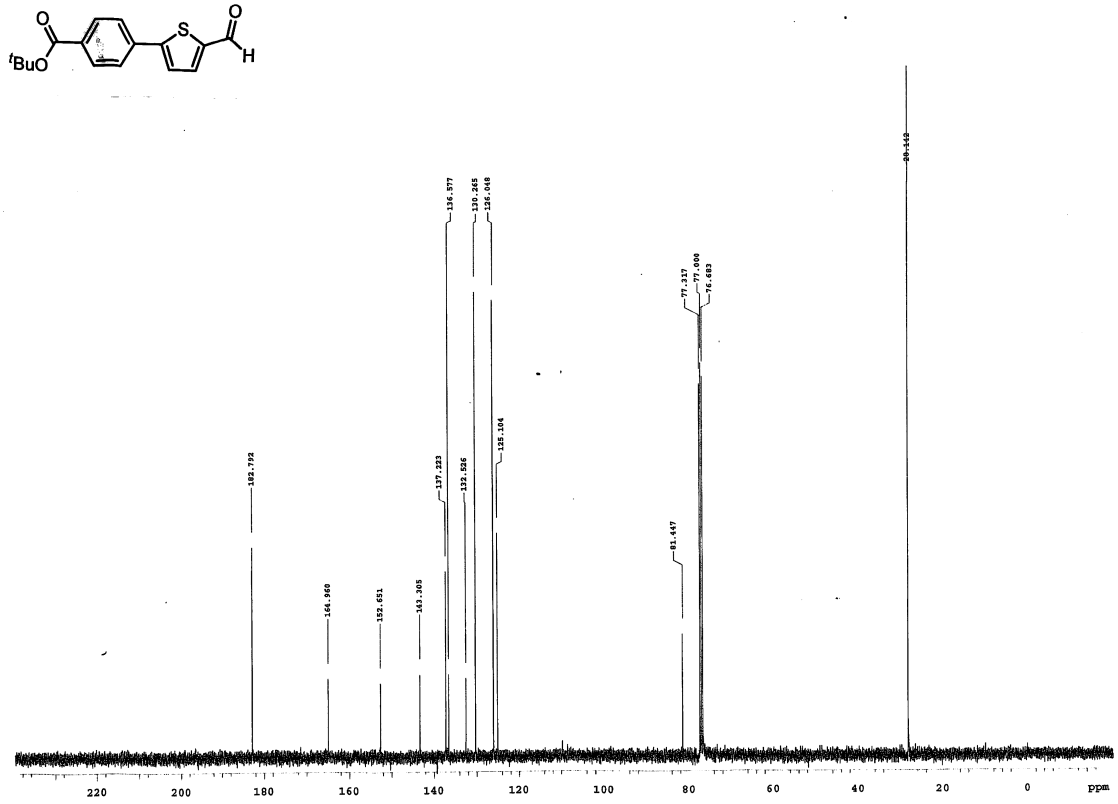

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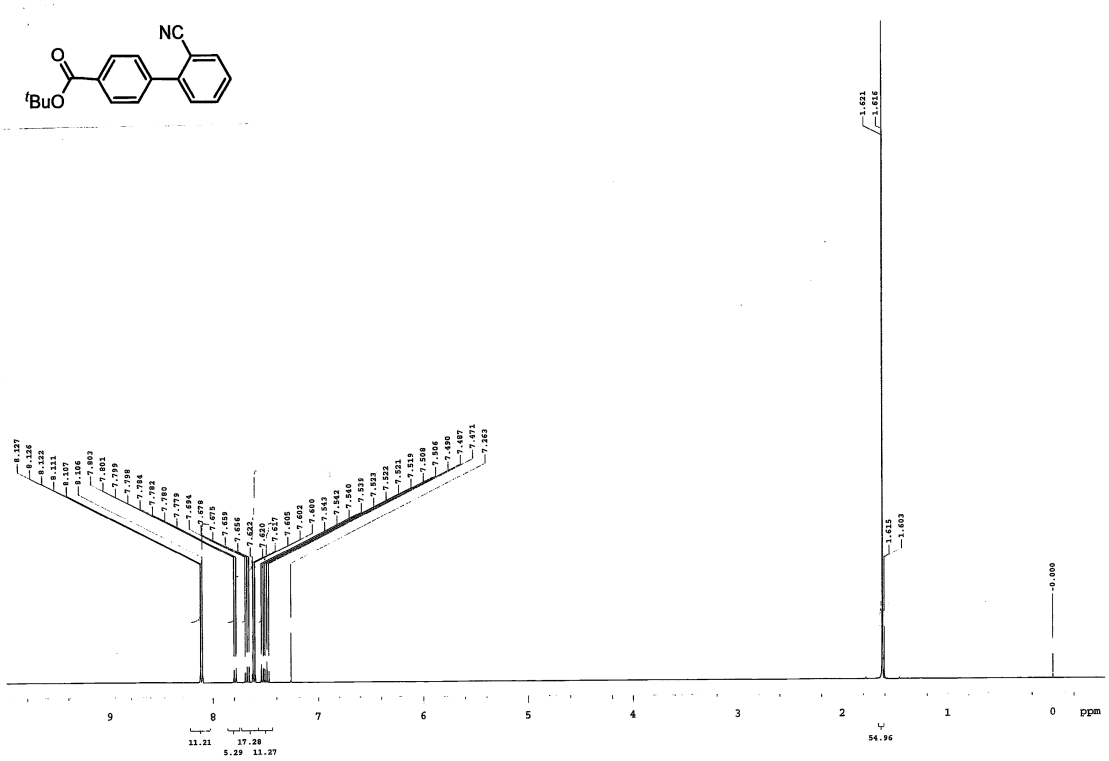

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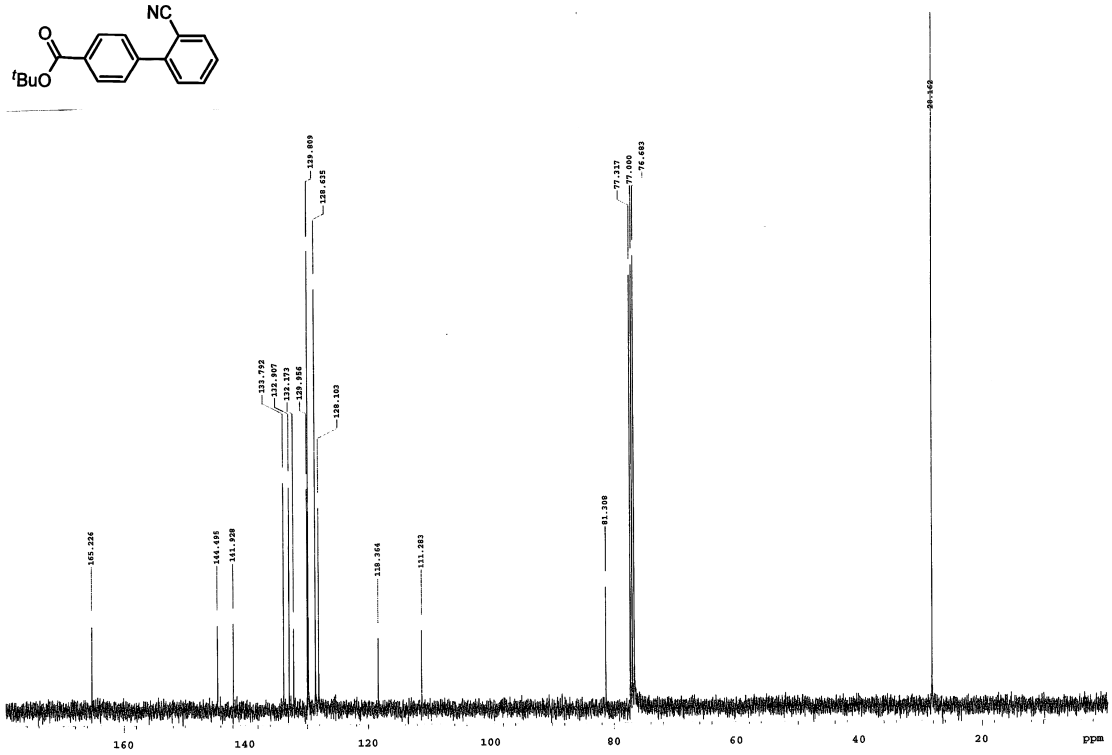

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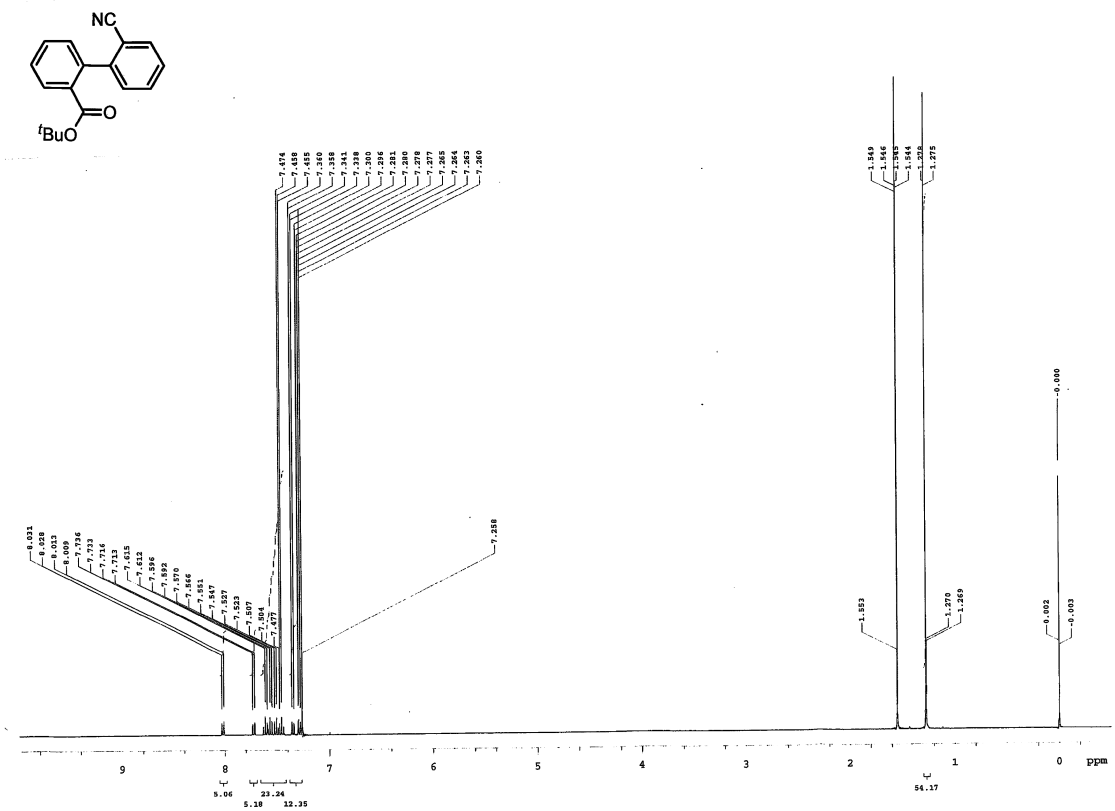

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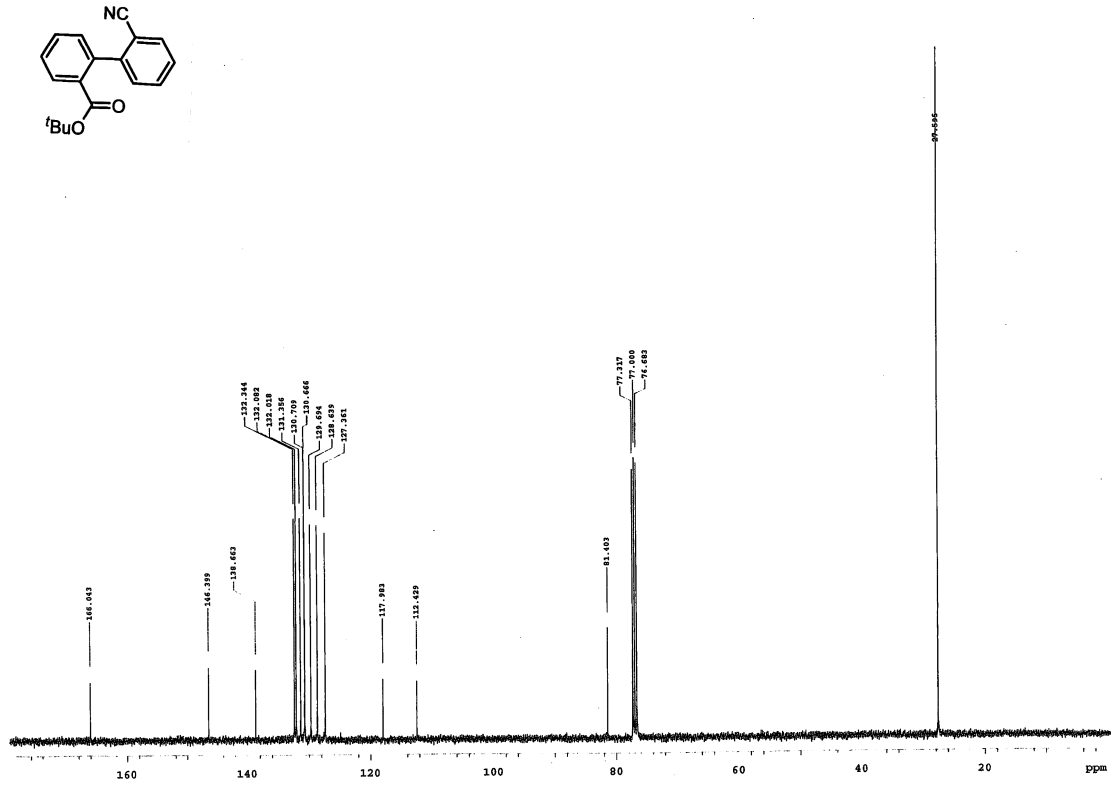

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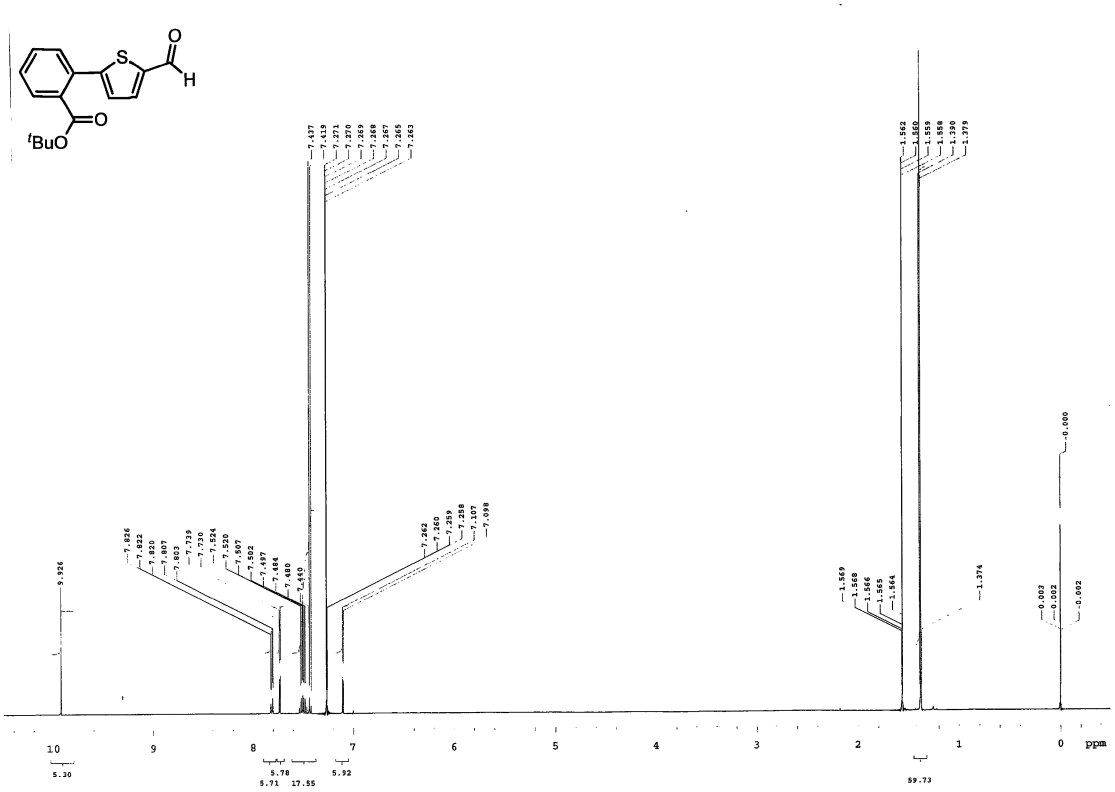

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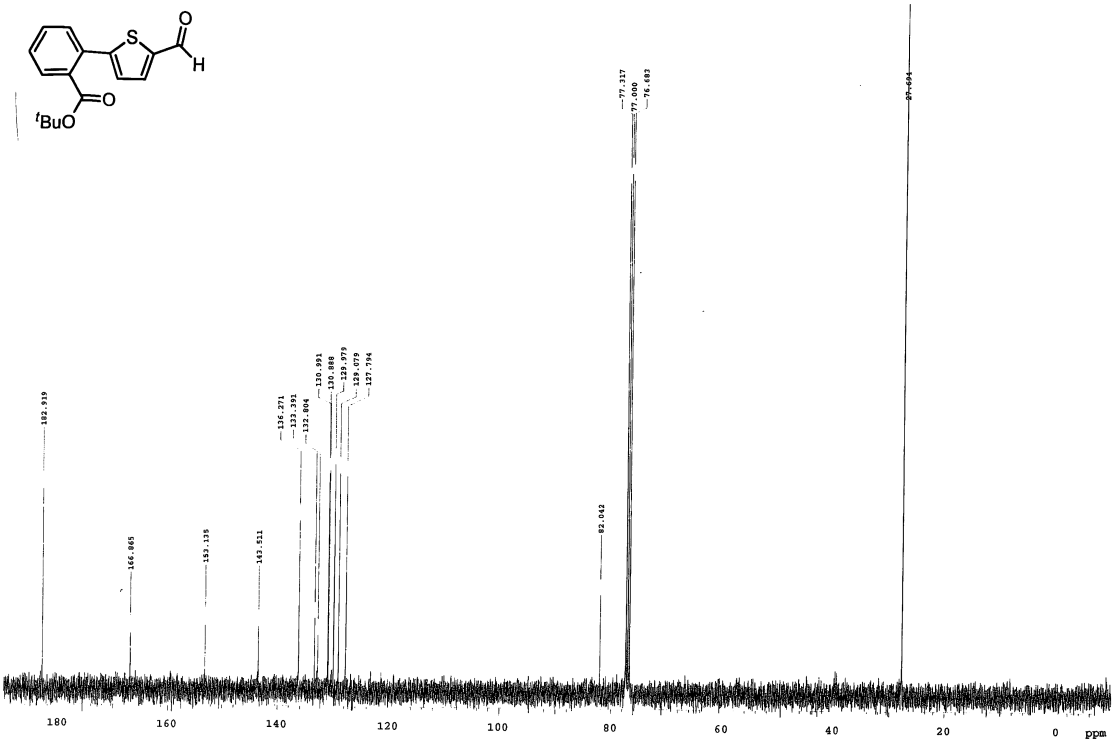

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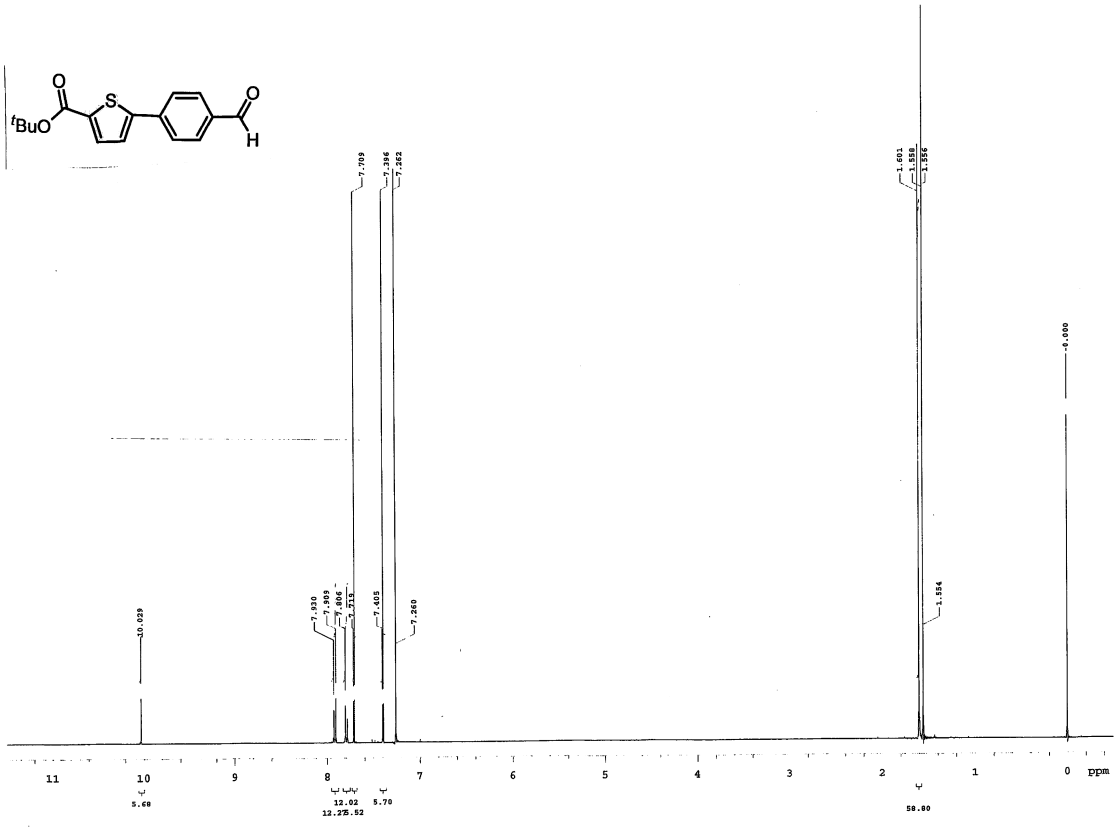

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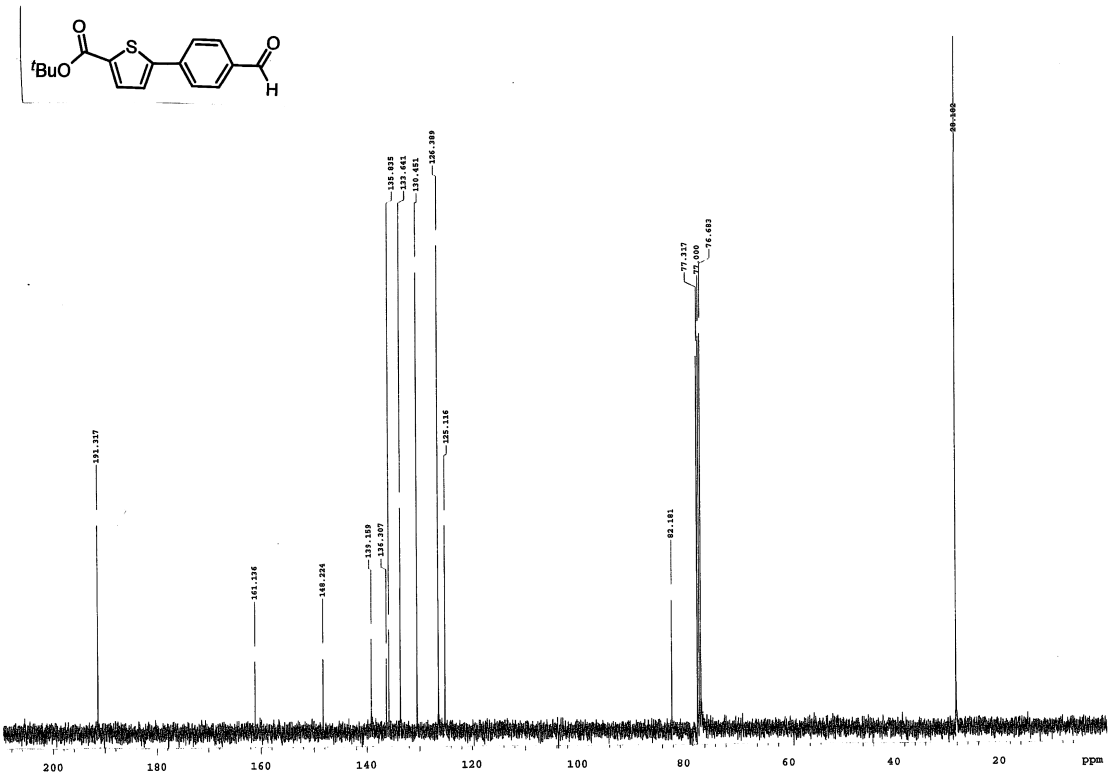

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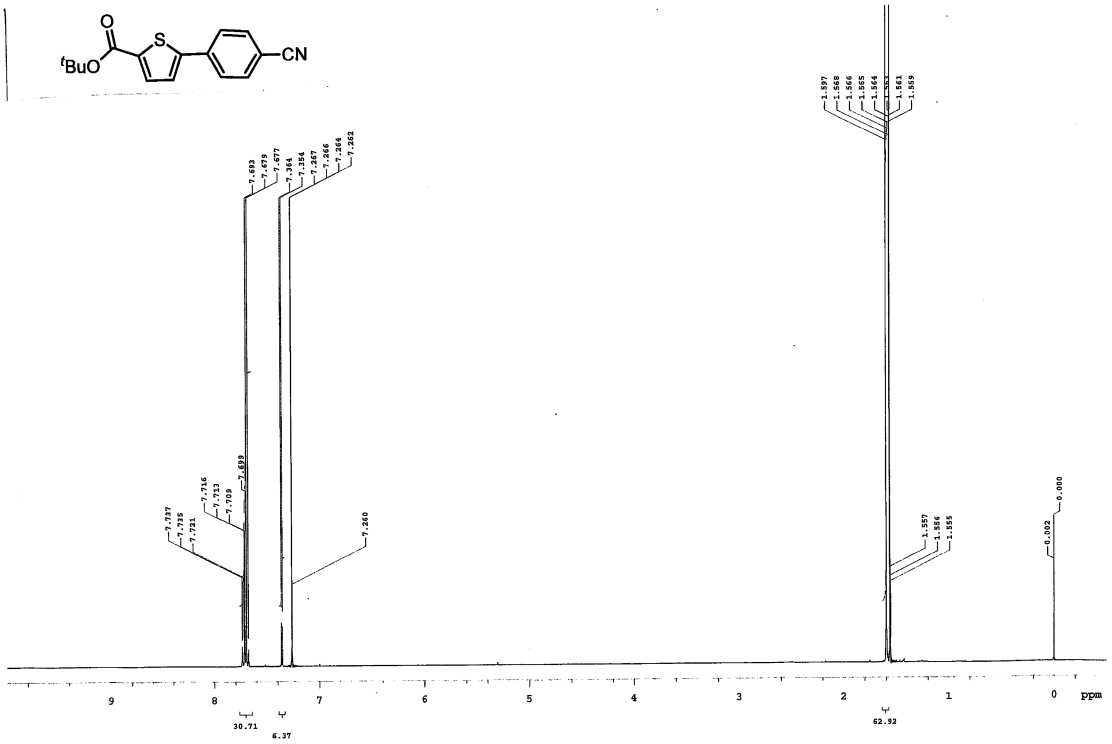

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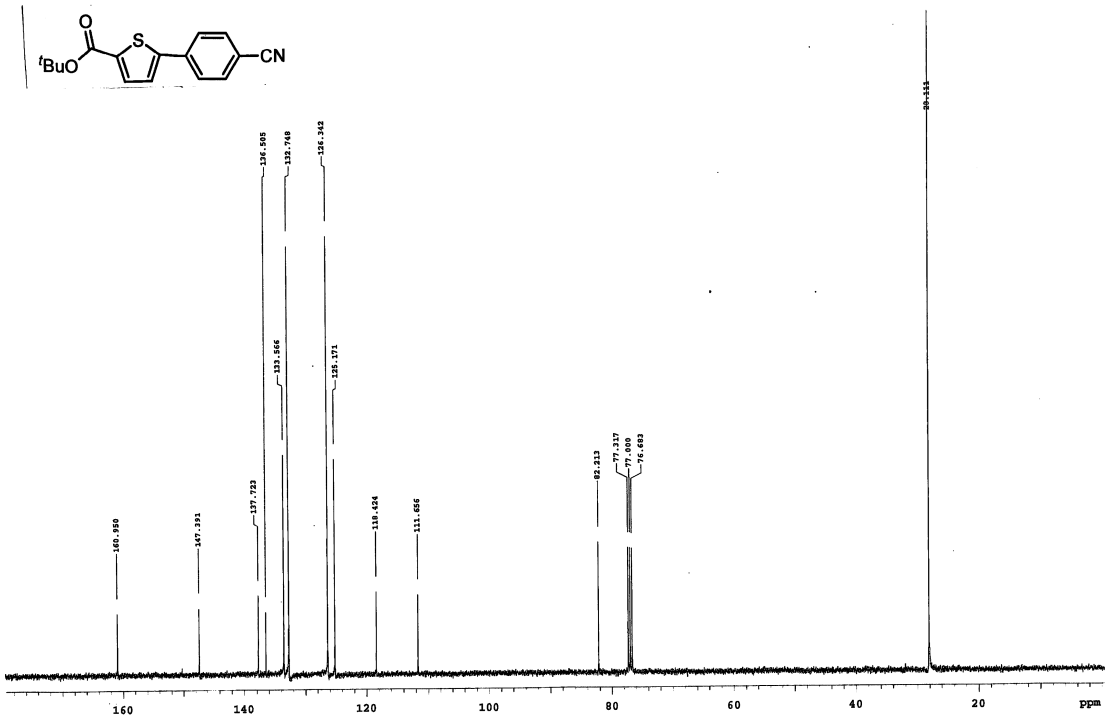

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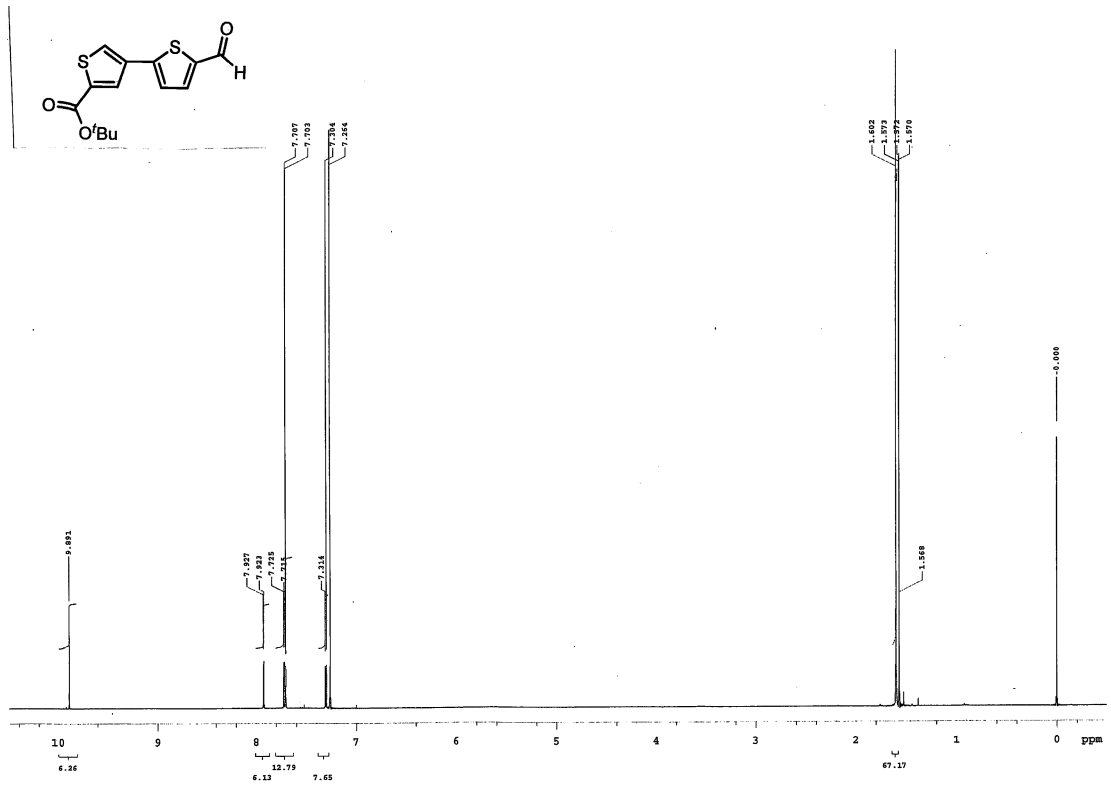

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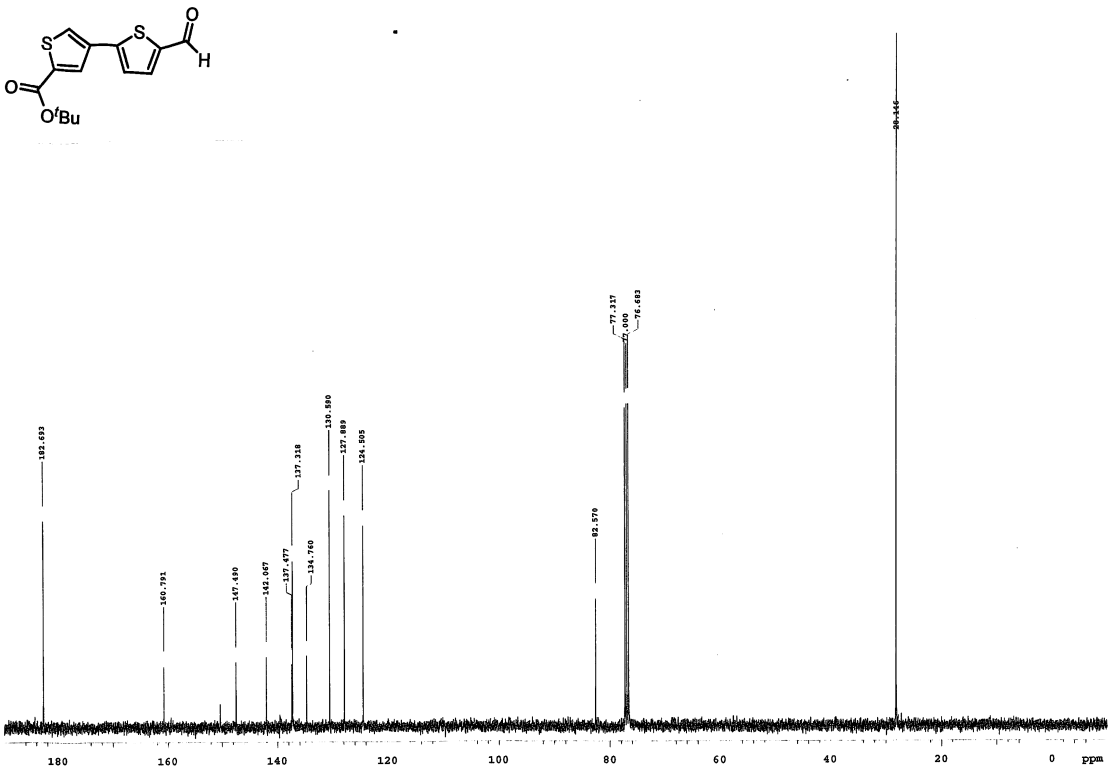

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