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Green Production of 9-Aryl-Fluoren-9-ols Achieved through Process Intensification of Grignard Reaction using Continuous Flow at Room Temperature

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Supporting Information

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General information

Unless otherwise information noted, all the solvents and reagents were purchased from commercial suppliers and used without further purification. The reaction was performed using Corning AFR®-G1 and its accompanying continuous flow system. Some products were purified via column chromatography over silica gel (200-300 mesh) (from Nanjing Wanqing Chemical Instruments Company), some were isolated by using Cycle liquid chromatography (CLC) spectrum (Agilent) and a little of them were purified by pulping filtration and column chromatography. ^{1}H NMR and ^{13}C NMR

spectra were recorded at 20 ℃ on a Varian 400 MHz and 100 MHz, respectively. Chemical shifts are exhibited as δ in units of parts per million (ppm) relative to internal standard (^{1}H NMR: TMS = 0.00 ppm) or relative residual peaks (^{1}H NMR: 7.26 for $CDCl_3$, ^{13}C NMR: 77.0 triplet for $CDCl_3$). Multiplicities in briefly were shown as: s (singlet); d (doublet); t (triplet); dd (doublet of doublets); m (multiplet).

Figure SI1: Corning AFR®-G1 and its accompanying continuous flow system

Figure SI2 Real picture of seven reactor plates in series

Table 1 Volume and division of seven reaction modules

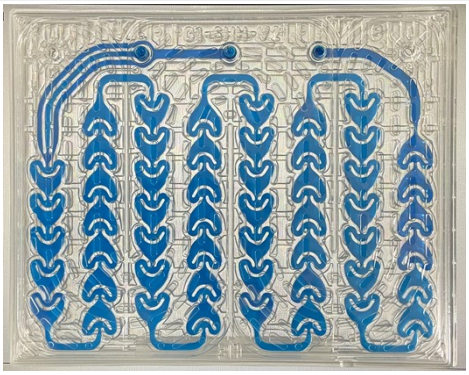
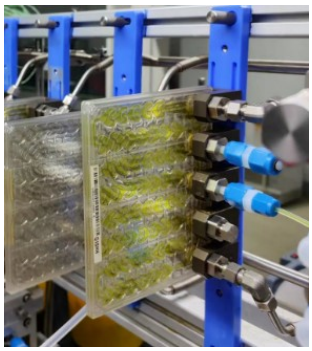
The volume of a single reactor plates (mL)	The number of preheating reactor plates	The number of reactor plates for the mixed material
Vol =8 mL	Vol ^{pre} = 8.0 mL*2=16 mL	Vol ^{R} =8*5= 40 mL
		

Table 2 Parameters of continuous flow reactor and its auxiliary equipment

Number	Instrument name	Model number	Quantity
1	Microchannel reactor	Corning AFR®-G1	1
2	Pump A	Hanban-100 ml	1
3	Pump B	Corning-PTFE	1
4	Heat exchanger	Corning-G1-A	1
5	Electronic balance	SHIMAZU	2

THF (cas: 109-99-9) was from the Energy company, 99.5%, Extra Dry, with molecular sieves, Waters50ppm (by K. F)

PhMgBr (cas: 100-58-3) was from the Energy company (1.0 Mol/l in THF).

P-Tolylmagnesium bromide (cas: 4294-57-9) was from the Energy company (1.0 Mol/l in THF).

4-Ethylphenylmagnesium bromide solution (cas: 22873-28-5) was from the Energy company (0.5 Mol/l in THF).

4-Methoxyphenylmagnesium bromide (cas: 13139-86-1) was from the Energy company (1.0 Mol/l in THF).

Unmarketed Grignard reagents were obtained according to the reported literatures[1].

Typical Procedures

The synthesis method of 9-Aryl-Fluoren-9-ols in batch can be obtained by reference[1]

Typical Procedure 1: Continuous flow system preprocessing

Since the Grignard reaction is sensitive to water and oxygen, the reaction system should be treated with no water and no oxygen first. First the heat exchanger temperature is adjusted to 100 ℃, the purpose is to turn the residual water vapor in the system into water vapor, and the nitrogen purge was then carried out at a flow rate of 50 mL/min, so that water vapor and oxygen can be replaced. The whole process lasts for 10 min and can achieve the purpose of creating an anhydrous and oxygen-free environment in the reaction system. In addition, water is also needed to calibrate the flow rate of the feed pump. The three flow rates of 10 mL/min, 30 mL/min and 50 mL/min are set for test, and the balance is used for verification. After the pump is started, click the balance to return to zero. See if the weight lost in a minute is the corresponding 10 g, 30 g, 50 g. (This involves the conversion of mass velocity and volume velocity. Mass velocity = volume velocity times density. Since the density of water is 1 g/cm3, water is often used as the calibration reagent for convenience.)

Typical Procedure 2: Preparation of 9-arylfluoren-9-alcohols starting from ketones and Grignard reagents in continuous flow

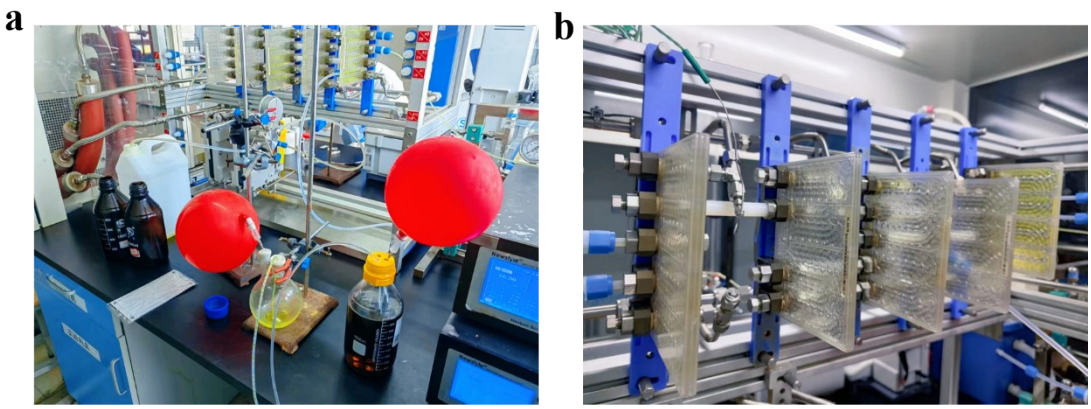


Figure SI3: (a) Flow chemistry setup for preparation of 9-aryl-fluoren-9-ols. (b) After 3 times the residence time, the color of the reaction liquid in the reaction module changed from yellow to colorless

Ketone was prepared into solution (0.25-0.4 M, 1.0 equiv) in ultra-dry THF and an Grignard reagent in ultra-dry THF (0.15 M, 1.00 M, 2.00 M, 1.2 equiv). The reagent was treated anhydrous and oxygen-free, and nitrogen balls were added. Nitrogen purge in the continuous flow system was stopped and the temperature was lowered to room temperature (30 ℃). 200mL of ultra-dry THF was injected into the reaction system to create a reaction atmosphere. Subsequently, The ketone solution was transported as the feed A at the flow rate of 34-77 $mL \cdot min^{-1}$ to the first reaction module (Vol^{pre} = 8.0 mL). Grignard reagent was transported as the feed B at the flow rate of 16-32 $mL \cdot min^{-1}$ to the second reaction module (Vol^{pre} = 8.0 mL) by PTFE pump, and the two reagents were mixed in the third reaction module and started to react, with total liquid holdup Vol^{R} = 40 mL and residence time 24-48 s. After 3 to 5 times the residence time, the reaction liquid was collected into a volume bottle filled. Finally, the reaction liquid was driven out with 200mL of ultra-dry THF and the coarse product was obtained by pulping and filtration.

Typical Procedure 3: Operation Procedure for the Production Process

Step 1: Machine Startup

1. Turn on the relevant machinery or equipment to initiate the production process. Ensure that all safety protocols and precautions are followed.

Step 2: Material Mixing and Reaction

2. In a continuous flow device, precisely introduce two separate streams of materials that need to be mixed and reacted. Maintain a controlled and steady flow of these materials throughout the reaction process.

Step 3: Reaction Time

3. Monitor the reaction closely, allowing the materials to react for a duration equal to three times the calculated residence time. This period may vary depending on the specific reaction kinetics and process requirements.

Step 4: Collection of Reaction Liquid

4. Following the designated reaction time, carefully collect the outflowing reaction liquid. Use appropriate containers or vessels for this purpose.

Step 5: Separation with Rotary Evaporator

5. Transfer the collected reaction liquid to a rotary evaporator. Employ the rotary evaporator to separate the crude products from the solvents. This separation process should be performed meticulously to obtain the desired components.

Step 6: Drying and Solvent Isolation

6. After the separation, obtain both the dry crude product and the solvent. Notably, tetrahydrofuran is used as the solvent for both of these materials. Ensure proper solvent isolation and drying procedures are followed.

Step 7: Solvent Recycling

7. Implement a solvent recycling process, to recover and reuse the solvent for future production runs. This is essential for sustainability and cost-efficiency.

Step 8: Collection of Crude Products

8. Gather the crude products, which may contain inorganic salts, into a designated container or vessel. Exercise care in handling and storing these products.

Step 9: Mixing with Water

9. Add a predetermined amount of water to the container containing the crude products. Stir and agitate the mixture thoroughly. The purpose of this step is to leverage the solubility differences between the separation products and the inorganic salts.

Step 10: Filtration

10. Transfer the agitated slurry into a specialized filtration apparatus equipped with

filter cloth and filter paper. Perform vacuum filtration to effectively remove the inorganic salts that have dissolved in the water.

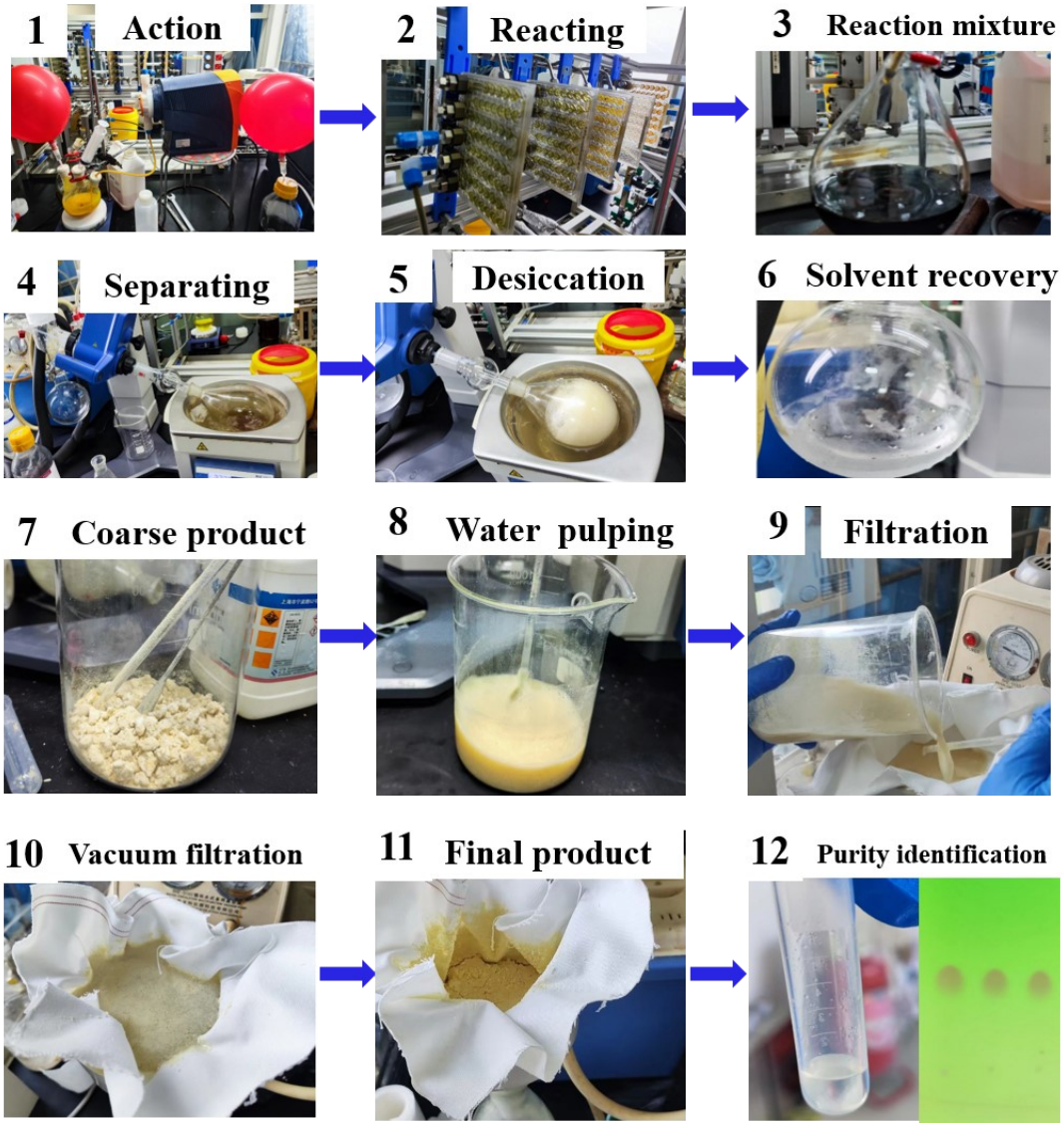
Step 11: Final Product

11. After filtration, the remaining solid material, represents the final product of the process. Ensure proper labeling and storage of the final product.

Step 12: Product Purity Verification

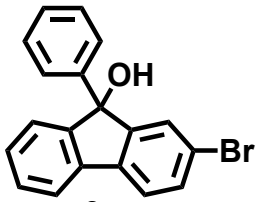
12. To assess the product's quality and purity, extract a sample for Thin Layer Chromatography (TLC) monitoring.

Operation flow chart:



Preparation of Products

2-bromo-9-phenyl-9H-fluoren-9-ol (3a)



3a

Following TP1, TP2 and TP3, THF solution of 2-bromofluorene (0.4 M, 1.0 equiv, 0.39 mol) was used as material A, and commercial phenyl magnesium bromide solution (1M, 1.2 equiv, 0.47 mol) was used as material B. A pumped into the first reaction module of the continuous flow system at a flow rate of 45 mL/min, and B pumped into the second reaction module at a flow rate of 22 mL/min. The two mixed reaction modules in the following five reaction modules (Vol ^{R} = 40 mL), the residence time was 36 s, and the reaction liquid was collected after 3 times the residence time. Employ the rotary evaporator to separate the crude products from the solvents and add a predetermined amount of water to the container containing the crude products to pulp the mixture thoroughly. Then, transfer the agitated slurry into a specialized filtration apparatus equipped with filter cloth and filter paper and 125 g final products were obtained after filtration. The >99% yield was demonstrated by Cycle liquid chromatography (CLC) spectrum.

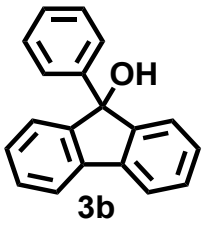
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.64 (d, *J* = 7.6 Hz, 1H), 7.55 – 7.53 (d, *J* = 8.0 Hz, 1H), 7.50 – 7.48 (dd, *J*=8 Hz,2 Hz,1H), 7.45 (s, 1H), 7.41 – 7.35(m, 3H), 7.33 – 7.26 (m, 5H), 2.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 148.1, 140.4, 136.6, 136.5, 130.2, 127.4, 126.9, 126.4, 126.2, 125.5, 123.3, 122.9, 120.1, 119.5, 118.2, 81.5. The spectra matched those of the literature.[2,3]

Upscale Experiment for Compound (3a)

THF solution of 2-bromofluorene (0.4 M, 1.0 equiv, 3.10 mol) and commercial solution of phenylmagnesium bromide (1 M, 1.2 equiv, 3.72 mol) were prepared, The THF

solution of 2-bromofluorenone was pumped into the first reaction module of the continuous flow system at the flow rate of 45 mL/min, and the solution of phenyl magnesium bromide was pumped into the second reaction module at the flow rate of 22 mL/min. The two were mixed in the following five modules (Vol ^{R} = 40 mL), and the residence time was 36 s. After 3 times residence time, the reaction liquid was collected. After 2.8 hours of continuous flow system operation, the raw materials were used up and the production was finished. Employ the rotary evaporator to separate the crude products from the solvents and add a predetermined amount of water to the container containing the crude products to pulp the mixture thoroughly. Then, transfer the agitated slurry into a specialized filtration apparatus equipped with filter cloth and filter paper and 1 kg final products were obtained after filtration. The >99% yield was demonstrated by Cycle liquid chromatography (CLC) spectrum.

9-Phenyl-9H-fluoren-9-ol (3b)



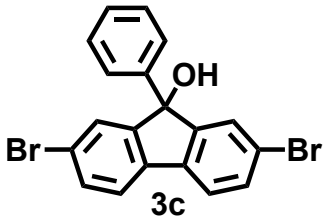
3b

Following TP1, TP2 and TP3, the THF solution of 9-fluorene (0.4 M, 1.0 equiv, 0.55 mol) was used as material A, and the commercial phenyl magnesium bromide solution (1 M, 1.2 equiv, 0.66 mol) was used as material B. A pumped into the first reaction module of the continuous flow system at a flow rate of 45 mL/min, and B pumped into the second reaction module at a flow rate of 22 mL/min. The two mixed reaction modules in the following five reaction modules (Vol ^{R} = 40 mL), the residence time was 36 s, and the reaction liquid was collected after 3 times the residence time. Employ the rotary evaporator to separate the crude products from the solvents and add a predetermined amount of water to the container containing the crude products to pulp the mixture thoroughly. Then, transfer the agitated slurry into a specialized filtration apparatus equipped with filter cloth and filter paper and 136 g final products were obtained after filtration. The >99% yield was demonstrated by Cycle liquid chromatography (CLC) spectrum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.63 (m, 2H), 7.36-7.28 (m, 7H), 7.25-7.22 (t, *J* = 5 Hz, 5H), 2.43-2.40 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 141.4, 137.8, 127.3, 126.6, 126.4, 125.4, 123.6, 123.0, 118.2, 81.8.

The spectra matched those of the literature.[2,3]

2,7-Dibromo-9-phenyl-9H-fluoren-9-ol (3c)



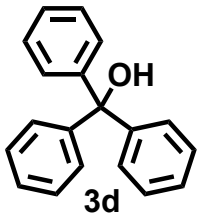
3c

Following TP1, TP2 and TP3, the THF solution of 2,7-Dibromofluorenone (0.4 M, 1.0 equiv, 0.30 mol) was used as material A, and the commercial phenyl magnesium bromide solution (1 M, 1.2 equiv, 0.36mol) was used as material B. A pumped into the first reaction module of the continuous flow system at a flow rate of 45 mL/min, and B pumped into the second reaction module at a flow rate of 22 mL/min. The two mixed reaction modules in the following five reaction modules (Vol ^{R} = 40 mL), the residence time was 36 s, and the reaction liquid was collected after 3 times the residence time. Employ the rotary evaporator to separate the crude products from the solvents and add a predetermined amount of water to the container containing the crude products to pulp the mixture thoroughly. Then, transfer the agitated slurry into a specialized filtration apparatus equipped with filter cloth and filter paper and 118 g final products were obtained after filtration. The >99% yield was demonstrated by Cycle liquid chromatography (CLC) spectrum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 4H), 7.44 (s,2H), 7.36 – 7.28(m, 4H), 2.50(s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 150.6, 140.2(d, *J* = 4.3 Hz), 136.1(d, *J* = 4.3 Hz), 131.1, 131.0, 127.1(d, *J* = 4.4 Hz), 126.9(d, *J* = 3.6 Hz), 126.4, 126.3, 123.8(d, *J* = 4.3 Hz), 121.1(d, *J* = 4.3 Hz), 120.2, 120.1, 81.9.

The spectra matched those of the literature.[2,3]

Triphenylmethanol (3d)

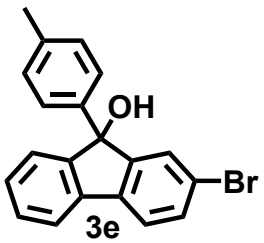


3d

Following TP1, TP2 and TP3, the THF solution of benzophenone (0.4 M, 1.0 equiv, 0.55mol) was used as material A, and the commercial phenyl magnesium bromide solution (1 M, 1.2 equiv, 0.66mol) was used as material B. A pumped into the first reaction module of the continuous flow system at a flow rate of 45 mL/min, and B pumped into the second reaction module at a flow rate of 22 mL/min. The two mixed reaction modules in the following five reaction modules (Vol^R = 40 mL), the residence time was 3 min, and the reaction liquid was collected after 3 times the residence time. Employ the rotary evaporator to separate the crude products from the solvents and add a predetermined amount of water to the container containing the crude products to pulp the mixture thoroughly. Then, transfer the agitated slurry into a specialized filtration apparatus equipped with filter cloth and filter paper and 116 g final products were obtained after filtration. (Yield:90%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.30 (m, 1H), 7.29-7.28 (m, 3H), 7.27 (s, 5H), 7.25-7.22 (m, 6H), 2.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 126.4, 125.7, 80.5.

The spectra matched those of the Chemistry Database of Shanghai Institute of Organic Chemistry of CAS.

2-bromo-9-(p-tolyl)-9H-fluoren-9-ol (3e)



3e

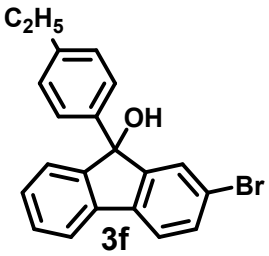
Following TP1, TP2 and TP3, the THF solution of 2-bromofluorene (0.4 M, 1.0 equiv, 0.40 mol) was used as material A, and the commercial phenyl magnesium bromide solution (1 M, 1.2 equiv, 0.48mol) was used as material B. A pumped into the first reaction module of the continuous flow system at a flow rate of 45 mL/min, and B

pumped into the second reaction module at a flow rate of 22 mL/min. The two mixed reaction modules in the following five reaction modules (Vol ^{R} = 40 mL), the residence time was 36 s, and the reaction liquid was collected after 3 times the residence time. After workup, the crude product was purified via column chromatography to give 3e 133g as a yellow viscous liquid. The >99% yield was demonstrated by Cycle liquid chromatography (CLC) spectrum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.63 (d, *J* = 7.6 Hz, 1H), 7.53 – 7.51 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.39 – 7.35 (t, *J* = 7.2 Hz, 1H), 7.32 – 7.30 (d, *J* = 6.4 Hz, 1H), 7.29-7.26 (m, 2H), 7.24 (s, 1H), 7.11 – 7.09 (d, *J* = 8.0 Hz, 2H), 2.88 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 150.3, 138.6, 138.5, 137.2, 132.1, 129.3, 129.1, 128.9, 128.2, 125.3, 124.9, 122.1, 121.5, 120.2, 83.4, 29.7, 21.1.

The spectra matched those of the literature.[4]

2-bromo-9-(4-ethylphenyl)-9H-fluoren-9-ol (3f)



3f

Following TP1, TP2 and TP3, the THF solution of 2-bromofluorene (0.4 M, 1.0 equiv, 0.40 mol) was used as material A, and the commercial phenyl magnesium bromide solution (1 M, 1.2 equiv, 0.48mol) was used as material B. A pumped into the first reaction module of the continuous flow system at a flow rate of 45 mL/min, and B pumped into the second reaction module at a flow rate of 22 mL/min. The two mixed reaction modules in the following five reaction modules (Vol ^{R} = 40 mL), the residence time was 36 s, and the reaction liquid was collected after 3 times the residence time. After workup, the crude product was purified via column chromatography to give 3f 132 g as a yellow viscous liquid. The >99% yield was demonstrated by Cycle liquid chromatography (CLC) spectrum.

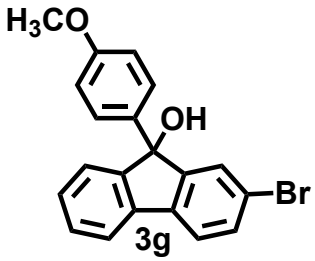
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.63 (d, *J* = 7.6 Hz, 1H), 7.53 – 7.46 (m, 3H),

7.39 – 7.35 (s, J = 7.2Hz,1H), 7.33 – 7.26 (m, 4H), 7.13 – 7.11 (d, J = 7.6Hz, 2H), 2.65-2.59 (m, 2H), 2.47 (s, 1H), 1.23 – 1.20 (t, J = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 150.2, 143.5, 139.6, 138.5, 132.1, 129.3, 128.9, 128.2, 128.0, 125.4, 124.9, 121.5, 120.2, 83.5, 28.5, 15.4.

The spectra matched those of the literature.[2]

2-bromo-9-(4-methoxyphenyl)-9H-fluoren-9-ol (3g)

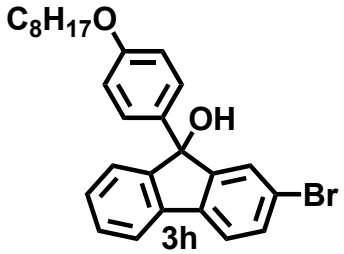


Following TP1, TP2 and TP3, the THF solution of 2-bromofluorene (0.4 M, 1.0 equiv, 0.40 mol) was used as material A, and the commercial phenyl magnesium bromide solution (1 M, 1.2 equiv, 0.48 mol) was used as material B. A pumped into the first reaction module of the continuous flow system at a flow rate of 45 mL/min, and B pumped into the second reaction module at a flow rate of 22 mL/min. The two mixed reaction modules in the following five reaction modules (Vol ^{R} = 40 mL), the residence time was 36 s, and the reaction liquid was collected after 3 times the residence time. Employ the rotary evaporator to separate the crude products from the solvents and add a predetermined amount of water to the container containing the crude products to pulp the mixture thoroughly. Then, transfer the agitated slurry into a specialized filtration apparatus equipped with filter cloth and filter paper and 139 g final products were obtained after filtration. The >99% yield was demonstrated by Cycle liquid chromatography (CLC) spectrum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.59 (d, J = 7.6 Hz, 1H), 7.49 – 7.47 (d, J = 7.6 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.36 – 7.32 (t, J = 7.2 Hz, 1H), 7.29 – 7.27 (m, 2H), 7.25 – 7.23 (m, 2H), 6.78 – 6.76 (d, J = 9.2 Hz, 2H), 3.72 (s, 3H), 1.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 152.6, 150.2, 138.5, 138.4, 134.5, 132.1, 129.3, 128.9, 128.2, 126.6, 124.8, 122.1, 121.5, 120.2, 113.7, 83.2, 55.2.

The spectra matched those of the literature.[4]

2-bromo-9-(4-(octyloxy)phenyl)-9H-fluoren-9-ol (3h)

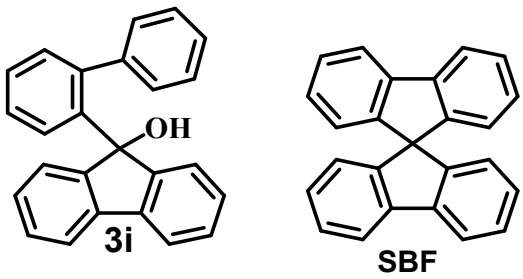


Following TP1, TP2 and TP3, the THF solution of 2-bromofluorene (0.4 M, 1.0 equiv, 0.40 mol) was used as material A, and the commercial phenyl magnesium bromide solution (1 M, 1.2 equiv, 0.48 mol) was used as material B. A pumped into the first reaction module of the continuous flow system at a flow rate of 45 mL/min, and B pumped into the second reaction module at a flow rate of 22 mL/min. The two mixed reaction modules in the following five reaction modules (Vol ^{R} = 40 mL), the residence time was 36 s, and the reaction liquid was collected after 3 times the residence time. After workup, the crude product was purified via column chromatography to give 3h (131 g, 84%) as a yellow viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$ ppm) δ 7.55-7.53 (d, *J* = 7.6 Hz, 1H), 7.43-7.37 (m, 3H), 7.30-7.26 (t, *J* = 7.2 Hz 1H), 7.24-7.21 (t, *J* = 6.8 Hz, 1H), 7.19-7.17 (d, *J* = 7.2 Hz, 3H),6.72-6.70（d, *J* = 8 Hz）,3.84-3.81 (t, *J* = 6.6 Hz, 2H), 2.39 (s, 1H), 1.70-1.63 (m, 2H), 1.35-1.19 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$ ppm) δ 152.6, 150.3, 142.6, 138.8, 138.8, 132.4, 129.6, 129.1, 128.6, 128.5, 127.7, 125.5, 125.1, 122.3, 121.7, 120.4, 68.0, 61.8, 31.8, 29.4, 29.2, 26.1, 22.7, 14.1.

The spectra matched those of the literature.[1]

9-([1,1'-biphenyl]-2-yl)-9H-fluoren-9-ol (3i) and 9,9'-spirobi[fluorene]（SBF）



Following TP1, TP2 and TP3, 9 fluorene solution (0.4 M, 1.0 equiv, 0.55mol) was prepared as material A, 2-bromobiphenyl's reagent (0.15 M, 2 equiv, 1.1 mol) prepared

via previous work was prepared as Material B (Note: The commercial 0.5 M 2-bromobiphenyl reagent has precipitate at the bottom but does not dissolve, and the reaction effect is poor. After optimization, we found that 0.15 M Grignard reagent was completely dissolved and the reaction effect was very good). A pumped into the first reaction module of the continuous flow system at the flow rate of 45 mL/min, and B pumped into the second reaction module at the flow rate of 22 mL/min. The two reaction modules were mixed in the following five reaction modules (Vol ^{R} = 40 mL), the residence time was 36 s, and the reaction liquid was collected after 5 times the residence time. In the process of reaction, the product slowly precipitates in the microchannel. Due to the small particle size, the product flows out with the reaction liquid at high flow rate. The supernatant was poured out, acetic acid and HCl were added to dissolve the solids, and the mixture was made into a material (0.1 M), which was pumped into the continuous flow reaction system at room temperature at the flow rate of 60 mL/min. The residence time was 48 s, and the reaction liquid was collected after 3 times the residence time. A large number of white solids (crude products of SBF) can be precipitated by adding water, The >99% yield was demonstrated by Cycle liquid chromatography (CLC) spectrum.

3i : ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47-8.45 (d, *J* = 8 Hz, 1H), 7.55-7.51 (t, *J* = 7.2 Hz, 1H), 7.33-7.29 (t, *J* = 7.2 Hz, 1H), 7.22-7.13 (m, 8H), 6.91-6.88 (d, *J* = 7.2 Hz, 1H), 6.83-6.79 (t, *J* = 7.6 Hz, 1H), 6.62-6.58 (t, *J* = 8 Hz, 2H), 6.0-5.98 (d, *J* = 7.2 Hz, 2H), 2.24 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ 151.6, 141.8, 140.9, 140.8, 140.5, 128.7, 128.4, 127.8, 127.4, 127.0, 126.3, 125.4, 124.7, 120.3, 81.8.

The spectra matched those of the literature[5]

SBF: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (d, *J* = 7.6 Hz, 4H), 7.39-7.35 (m, 4H), 7.13-7.09 (m, 4H), 6.75-6.73 (d, *J* = 7.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.8, 142.0, 141.8, 128.1, 127.9 (d, *J* = 8.6 Hz), 127.7, 124.3, 124.1, 120.2, 120.0, 66.2.

The spectra matched those of the literature.[5]

Calculation of raw material cost, waste and duration

Basic information :

The unit price of 2-bromo-9-fluorenone is 0.8 yuan /g (source: Pu yang Hui cheng Electronic Materials Co., LTD.), the unit price of Grignard reagent is 160 yuan /L (Source: Energy chemical), and the unit price of tetrahydrofuran is 125 yuan /L (source: Energy chemical).

The relative molecular weight of 2-bromo-9-fluorenone is 259.1g/mol, the relative molecular weight of the form reagent is 181.31g/mol, and the relative molecular weight of 2-bromo-9-phenyl-9-fluorenol is 336.9g/mol.

Take the production of one kilogram of 2-bromo-9-phenyl-9H-fluoren-9-ol as an example:

Continuous flow: no scaling effect, >99% yield: 2-bromo-9-fluorenone (3mol, 0.4mol/L, 1eq), Grignard reagent (3.6mol, 1mol/L, 1.2eq), tetrahydrofuran 7.5L.

Raw material cost: (3×259.1×0.8) + (3.6×160) + (7.5×125) =2135.34 yuan

Solid waste mass: (3×259.1+3.6×181.31) -1000=430 g

Construction period: 2 days

Batch: scaling effect, mass production yield of 65% (70 ℃): requires 2-bromo-9-fluorenone (4.6mol, 0.4mol/L, 1eq), Grignard reagent (5.52mol, 1mol/L, 1.2eq), tetrahydrofuran 11.5 L.

Raw material cost: (4.6×259.1×0.8) + (5.52×160) + (11.5×125) =3274.3 yuan

Quality of solid waste: (4.6×259.1+5.52×181.31) -1000=1192g

Construction period: 14 days

Continuous flow compared to batch:

The reduction of raw material cost is: (3274.3-2135.34) /3274.3*100%≈35%

Solid waste reduction is: (1192-430) /1192*100%=64%

The reduction of construction time is (14-2) /14*100%=86%

Calculation of Green Metrics

Table 3 Basic information on continuous flow and batch production of compound **3a**

	F. wt. of Amount of Starting Material	F. wt of Product	Amount of Starting Uesd	Amount of Product obtained	% yield
Continuous Flow	{259.1+181.32} =440.42	337.22	{0.7773+0.6528} =1.4301kg	1kg	>99%
Batch	{259.1+181.32} =440.42	337.22	{0.7773+0.6528} =1.4301kg	0.45kg	45%

It is noteworthy that Atom Economy (AE) is exclusively linked to the chemical reaction itself, and the Grignard reaction comprises only a single step. As a result, the Atom Economy (AE) value remains consistent between the continuous flow and batch methods. Furthermore, owing to the relatively diminutive molecular weight of the raw material, the substantial molecular weight contributed by a discarded bromine atom and magnesium atom during the reaction process renders the calculated Atom Economy (AE) value less than 90%.

Continuous Flow：

Due to the continuous flow production of 3a has a yield of >99%, almost no by-products are generated, and only a single solvent THF is used. As an illustrative example, 150 mL of effluent was subjected to spin steaming, yielding a crude product. It is important to note that during this process, the following quantities were involved: initial solvent volume taken =150 mL, solvent volume recovered = 136 mL, resulting in a recovery rate of 90.7%.

Amount of solvent taken = 11.1 L = (0.887*11.1) kg = 9.8457 kg

Amount of' solvent recovered = 9.99 L = (0.887*9.99) kg = 8.8611 kg

Amount of solvent waste = (11.1-9.99) L = 1.11L = (0.887*1.11) kg = 0.9846 kg

Amount of process water taken =5.6 kg

Amount of' process water recovered=5.04 kg

Amount of process water waste= (5.6-5.04) kg = 0.56 kg

Atom economy = [MW(Product)]/[Σ MW(Raw materials)+Σ MW (Reagents)] *100 % = 337.22/(259.1+181.32) *100 % = 76.57 %

Atom efficiency = yield* Atom economy/100% = 99%*76.57%/100% = 75.80 %

Reaction mass efficiency = m(Product)/Σ m(Raw materials)*100% = [1/(0.7773+0.6528)]*100%= 69.93 %

Carbon efficiency = m(Carbon in product)/[Σ m(Carbon in raw materials)]*100% = (19*12/337.22*1)/[(13*12/259.1*0.7773)+(6*12/181.32*0.6528)]*100% = 92.97 %

Chemical yield = [m(Product)*MW(Raw material)]/[m(Raw material)*MW(Product)]*100% = [1*(259.1+181.32)]/[(0.7773+0.6528)*337.22)]*100% = 91.32 %

Mass productivity = m(Product)/ Σ m(Input materials)*100% = 1/(0.7773+0.6528)*100% = 78.38%

Environmental impact factor = [Σ m(Input materials)-m(Product)]/m(Product) = (0.7773+0.6528+1.11*0.887+ 0.56 - 1)/1 = 1.9747 kg/kg

Process mass intensity = Σ m(Input materials incl. process water)/m(Product) = (0.7773+0.6528+1.11*0.887+0.56)/1 = 2.9747 kg/kg

Wastewater intensity = Σ m(Process water)/m(Product) = 0.56/1 = 0.56 kg/kg

Batch:

Due to the low yield (45%) of 3a synthesis by batch at room temperature, challenges arise in separating raw material residues, necessitating the use of numerous multi-component solvents for intricate processes. Consequently, solvent recovery becomes impractical. From the standpoint of green chemistry, employing batch production for 3a is not recommended.

Atom economy = [MW(Product)]/[Σ MW(Raw materials)+Σ MW (Reagents)] *100 % = 337.22/(259.1+181.32) *100 % = 76.57 %

Atom efficiency = yield* Atom economy/100% = 45%*76.57%/100% = 34.46 %

Reaction mass efficiency = m(Product)/Σ m(Raw materials)*100% = [0.45/(0.7773+0.6528)]*100%= 31.47 %

Carbon efficiency = m(Carbon in product)/[Σ m(Carbon in raw materials)]*100% =

(19*12/337.22*0.45)/[(13*12/259.1*0.7773)+(6*12/181.32*0.6528)]*100% = 41.83 %

Chemical yield = [m(Product)*MW(Raw material)]/[m(Raw material)*MW(Product)]*100% = [0.45*(259.1+181.32)]/[(0.7773+0.6528)*337.22)]*100% = 41.10 %

Mass productivity = m(Product)/ Σ m(Input materials)*100% = 0.45/(0.7773+0.6528)*100% =35.27%

Environmental impact factor = [Σ m(Input materials)-m(Product)]/m(Product) = (0.7773+0.6528+1.11*0.887 + 10 -0.45)/0.45 = 26.5882 kg/kg

Process mass intensity = Σ m(Input materials incl. process water)/m(Product) = (0.7773+0.6528+1.11*0.887+10)/0.45 = 27.5882 kg/kg

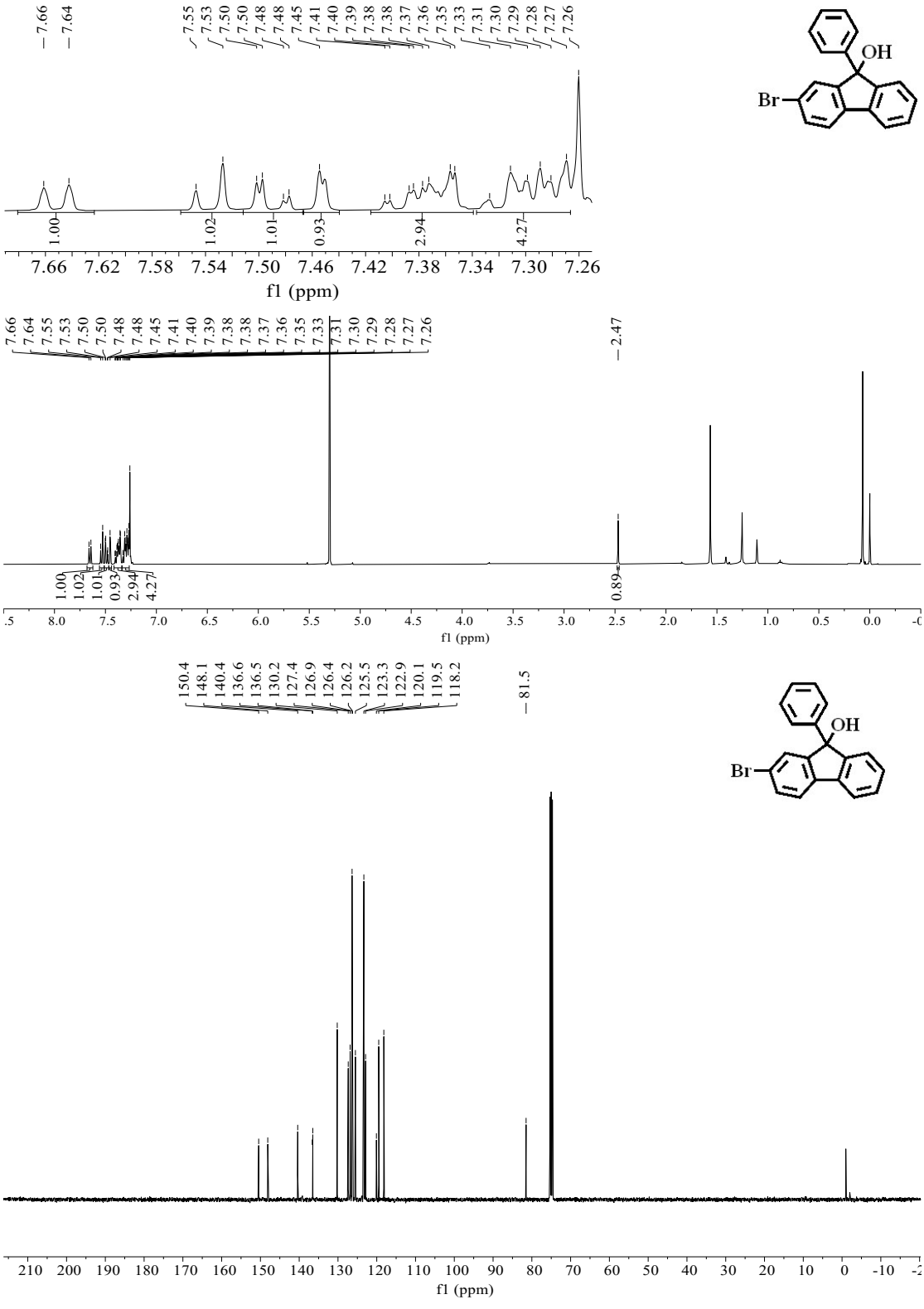
Wastewater intensity = Σ m(Process water)/m(Product) = 10/0.45 = 22.22 kg/kg

Table 4 Comparison of various green metrics of batch with the continuous flow

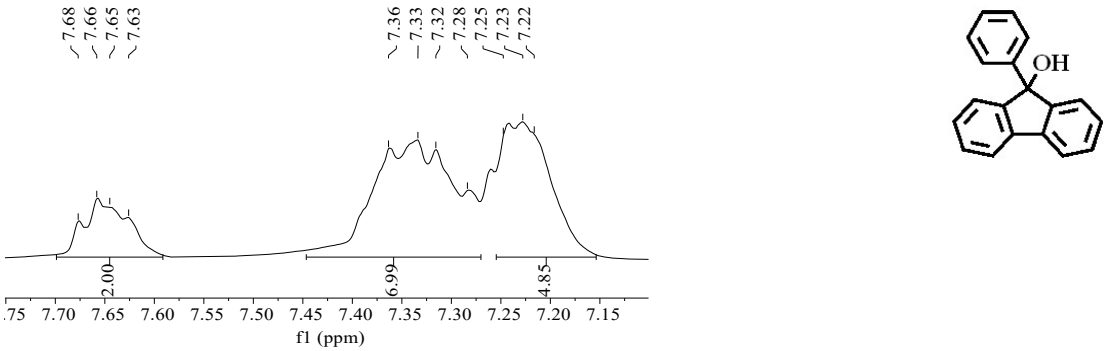
Common green chemistry process metrics	Formula	Continuous flow	Batch	Optimum value	Improved
Atom economy (AE)	$\frac{MW(Product) \times 100}{\sum MW(Raw\ material) + \sum MW(Reagents)}$	76.57%	76.57%	100%	——
Atom efficiency (Ae)	$\frac{yield \times AE}{100}$	75.80%	34.46%	100%	↑119.97%
Reaction mass efficiency (RME)	$\frac{m(Product) \times 100}{\sum m(Raw\ materials)}$	69.93%	31.47%	100%	↑ 122.21%
Carbon efficiency (CE)	$\frac{m(Carbon\ in\ product) \times 100}{\sum m(Carbon\ in\ raw\ materials)}$	92.97%	41.83%	100%	↑ 122.26%
Chemical yield (CY)	$\frac{m(Product) \times MW(Raw\ material) \times 100}{m(Raw\ material) \times MW(Product)}$	91.32%	41.10%	100%	↑ 122.19%
Mass productivity (MP)	$\frac{m(Product) \times 100}{\sum m(Input\ materials)}$	78.38%	35.27%	100%	↑ 122.23%
Environmental impact factor (E-factor)	$\frac{\sum m(Input\ materials) - m(Product)}{m(Product)}$	1.9747	26.5882	0	↓ 92.57%
Process mass intensity (PMI)	$\frac{\sum m(Input\ materials\ include\ process\ water)}{m(Product)}$	2.9747	27.5882	1	↓ 89.22%
Wastewater Intensity (WWI)	$\frac{\sum m(Process\ water)}{m(Product)}$	0.56	22.22	0	↓ 97.48%

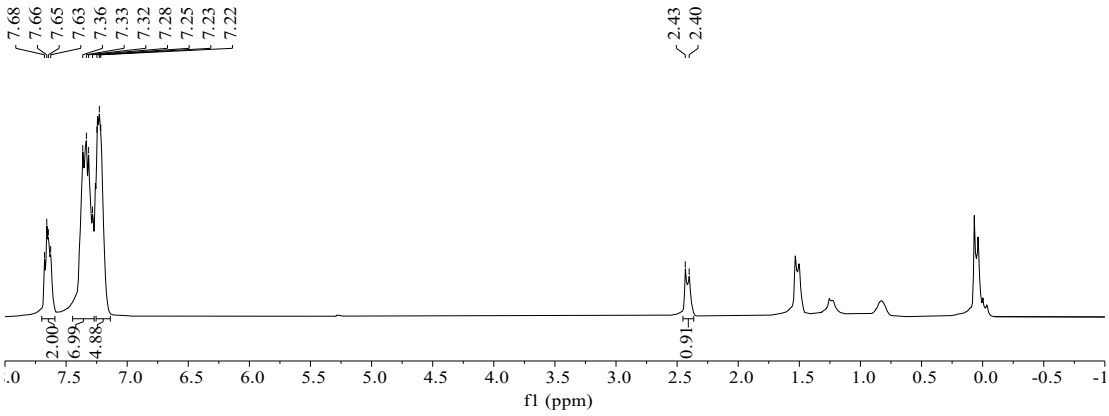
^{1}H-NMR,and ^{13}C-NMR Spectra of Products

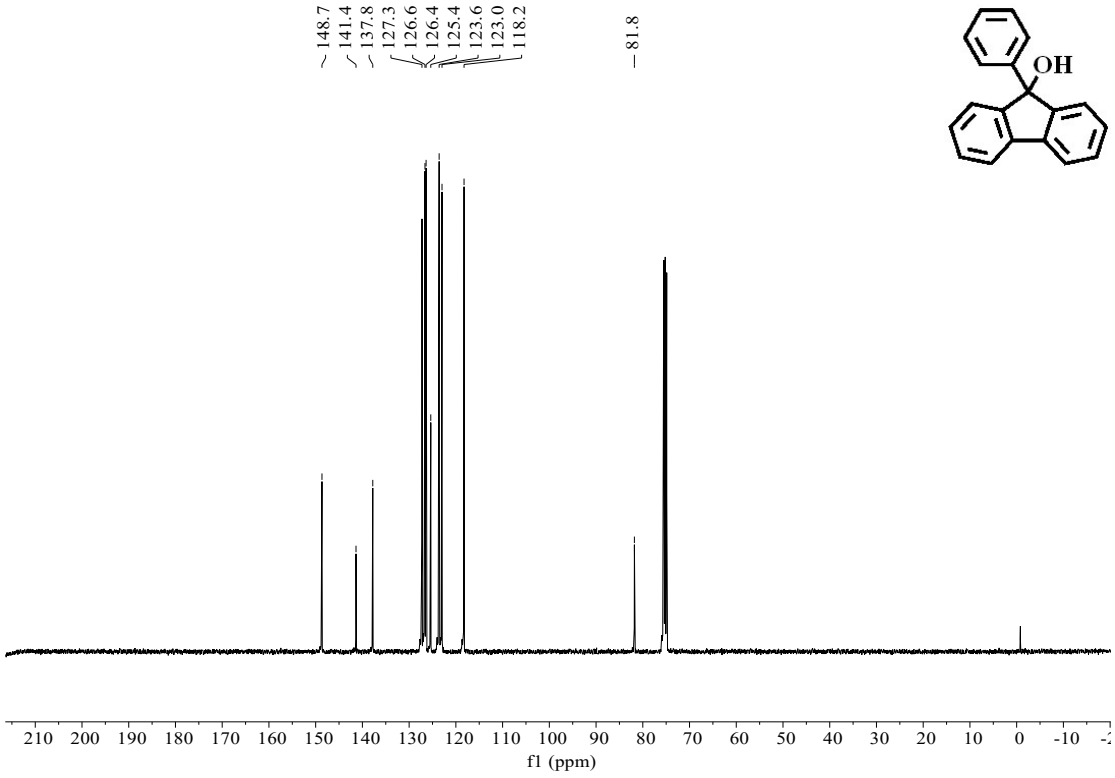
2-bromo-9-phenyl-9H-fluoren-9-ol (3a)



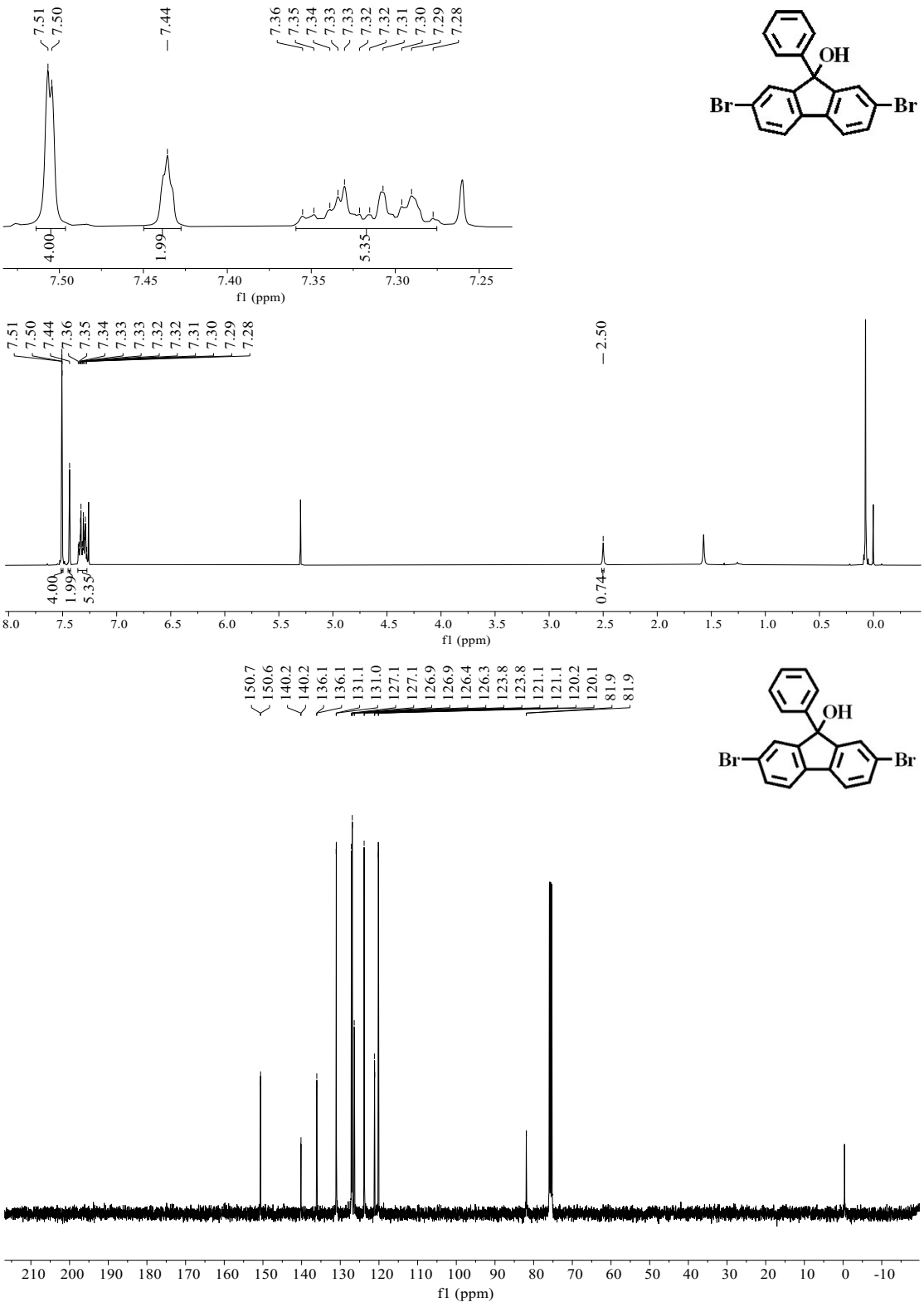
9-Phenyl-9H-fluoren-9-ol (3b)







2,7-Dibromo-9-phenyl-9H-fluoren-9-ol (3c)



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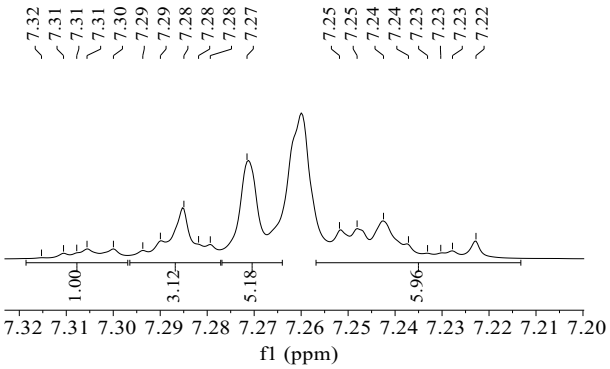
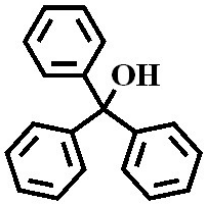
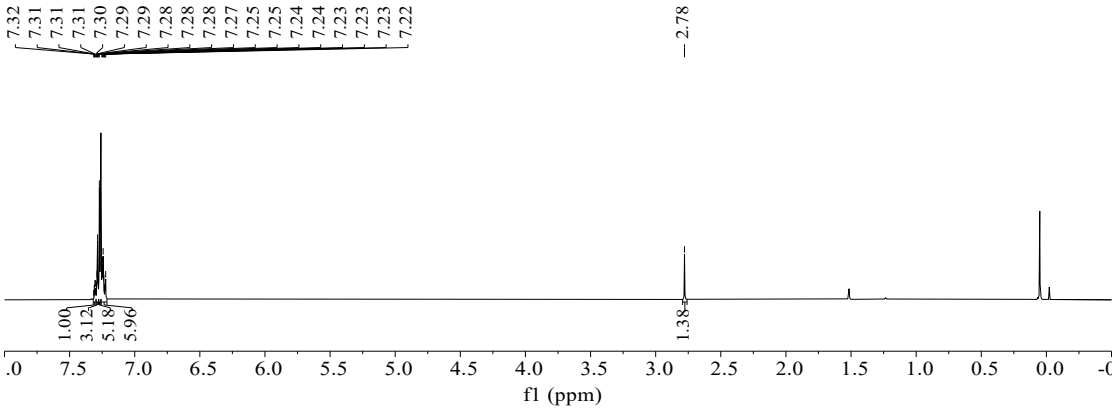
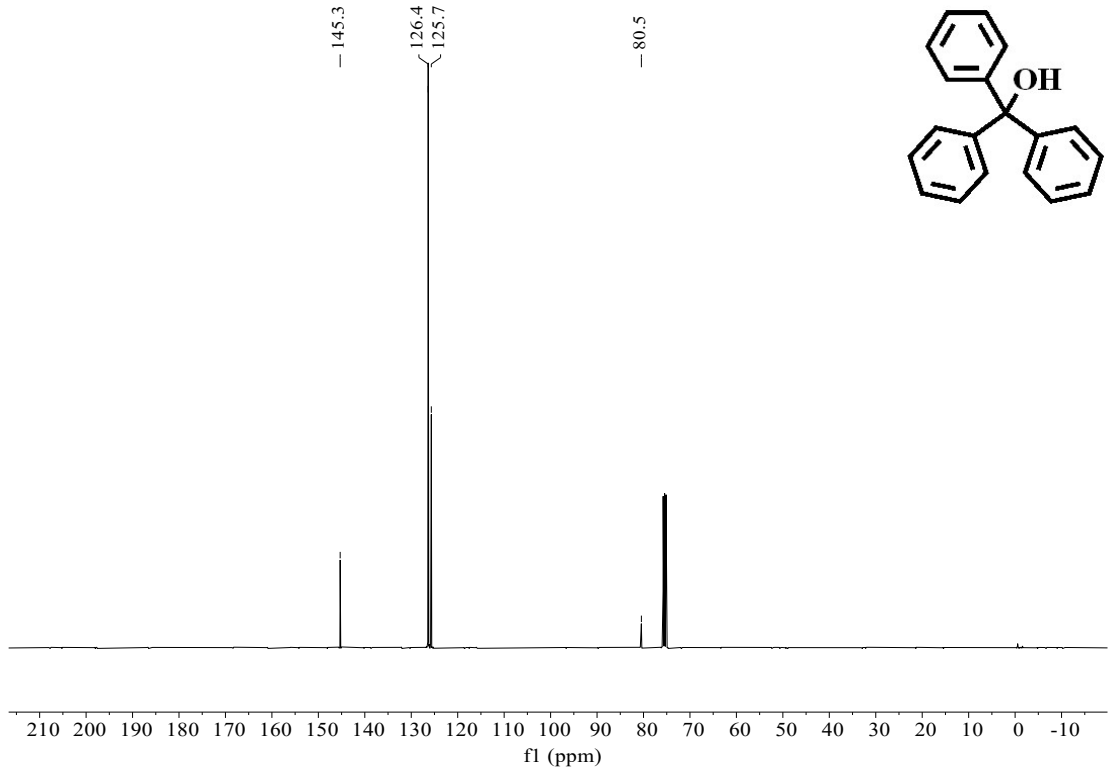
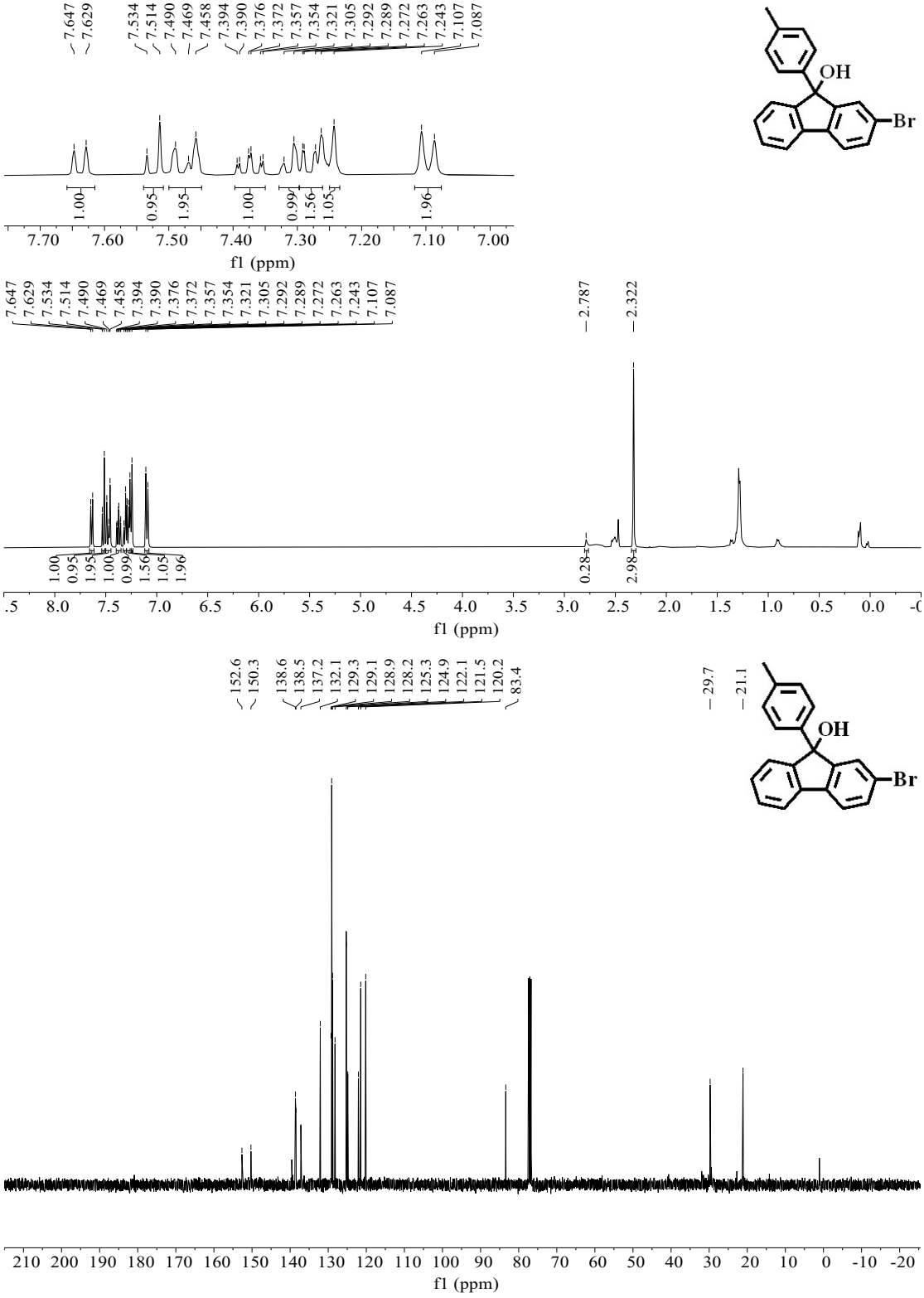




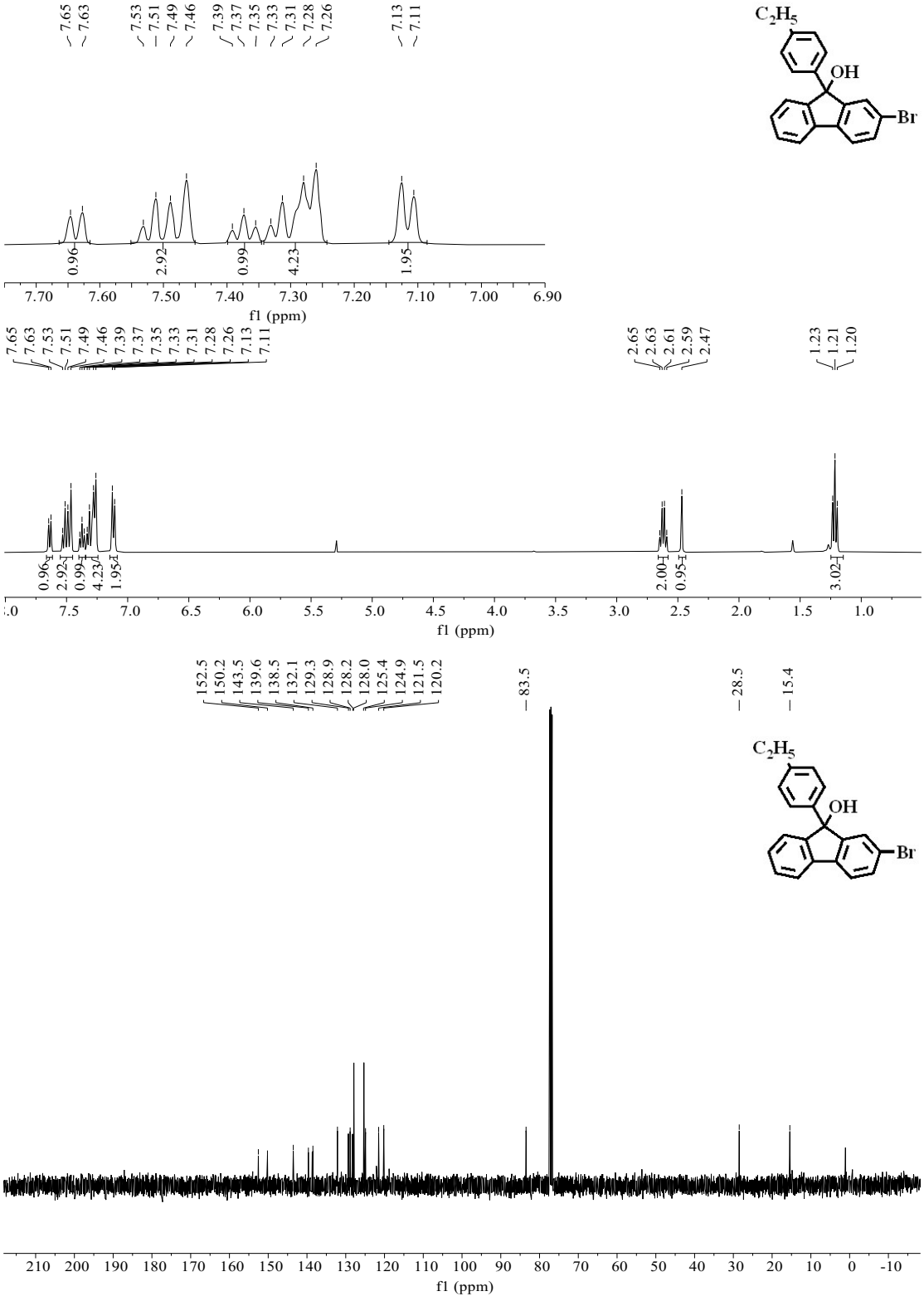




2-bromo-9-(p-tolyl)-9H-fluoren-9-ol (3e)



2-bromo-9-(4-ethylphenyl)-9H-fluoren-9-ol (3f)



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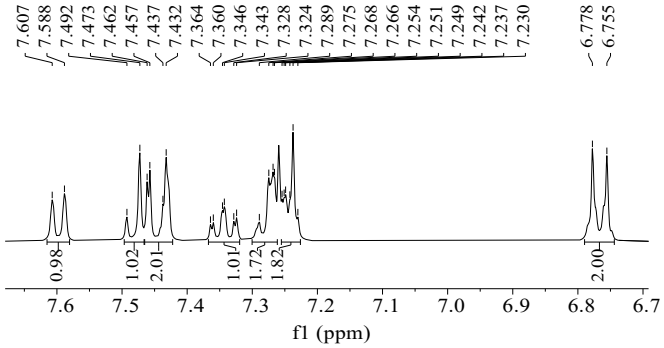
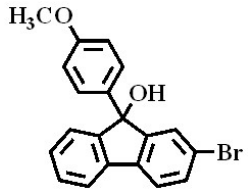
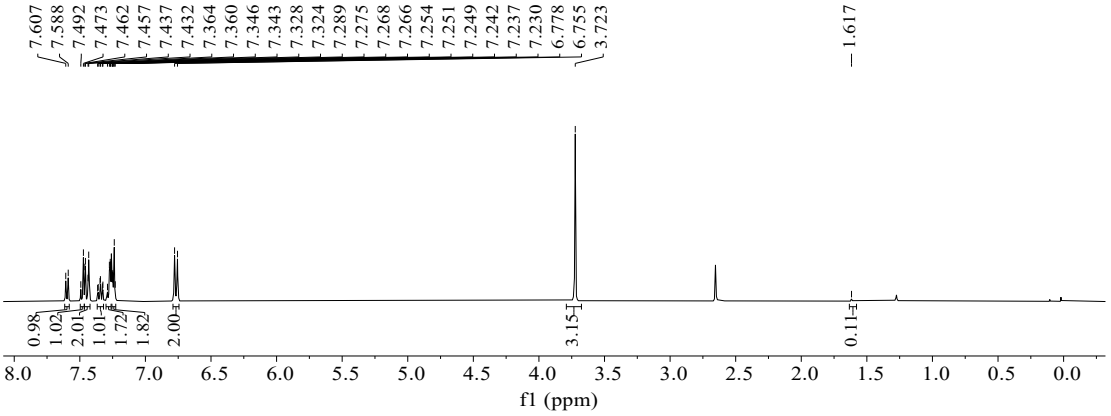
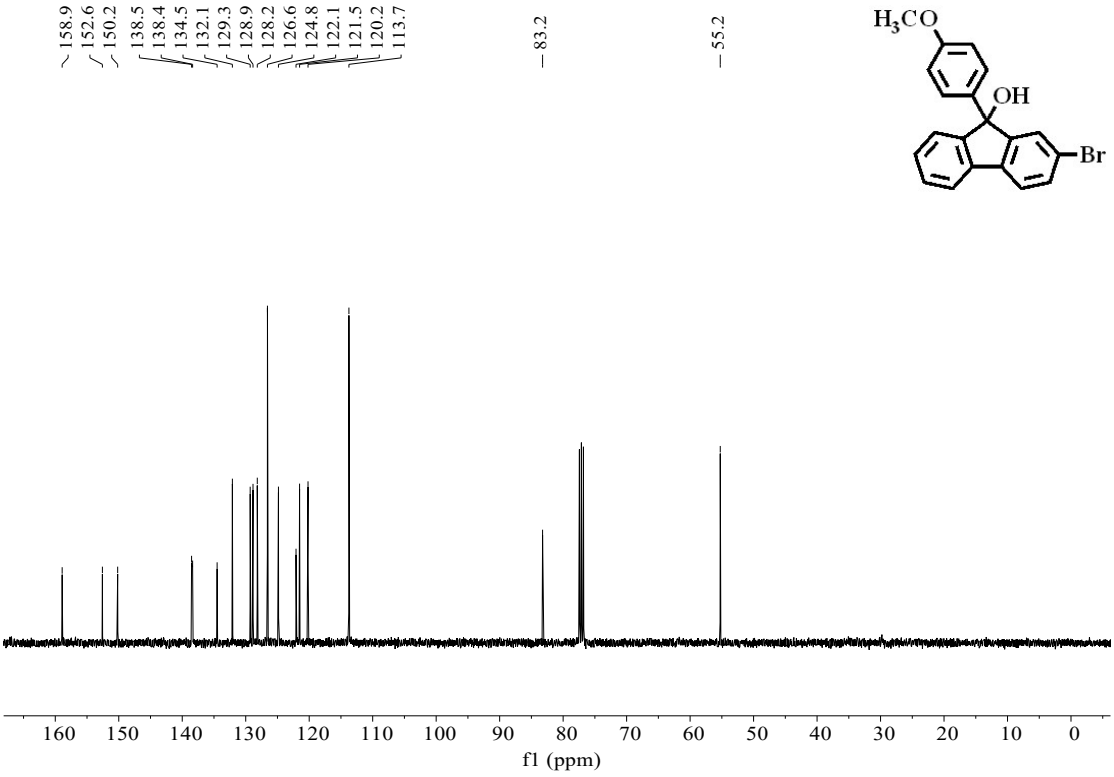
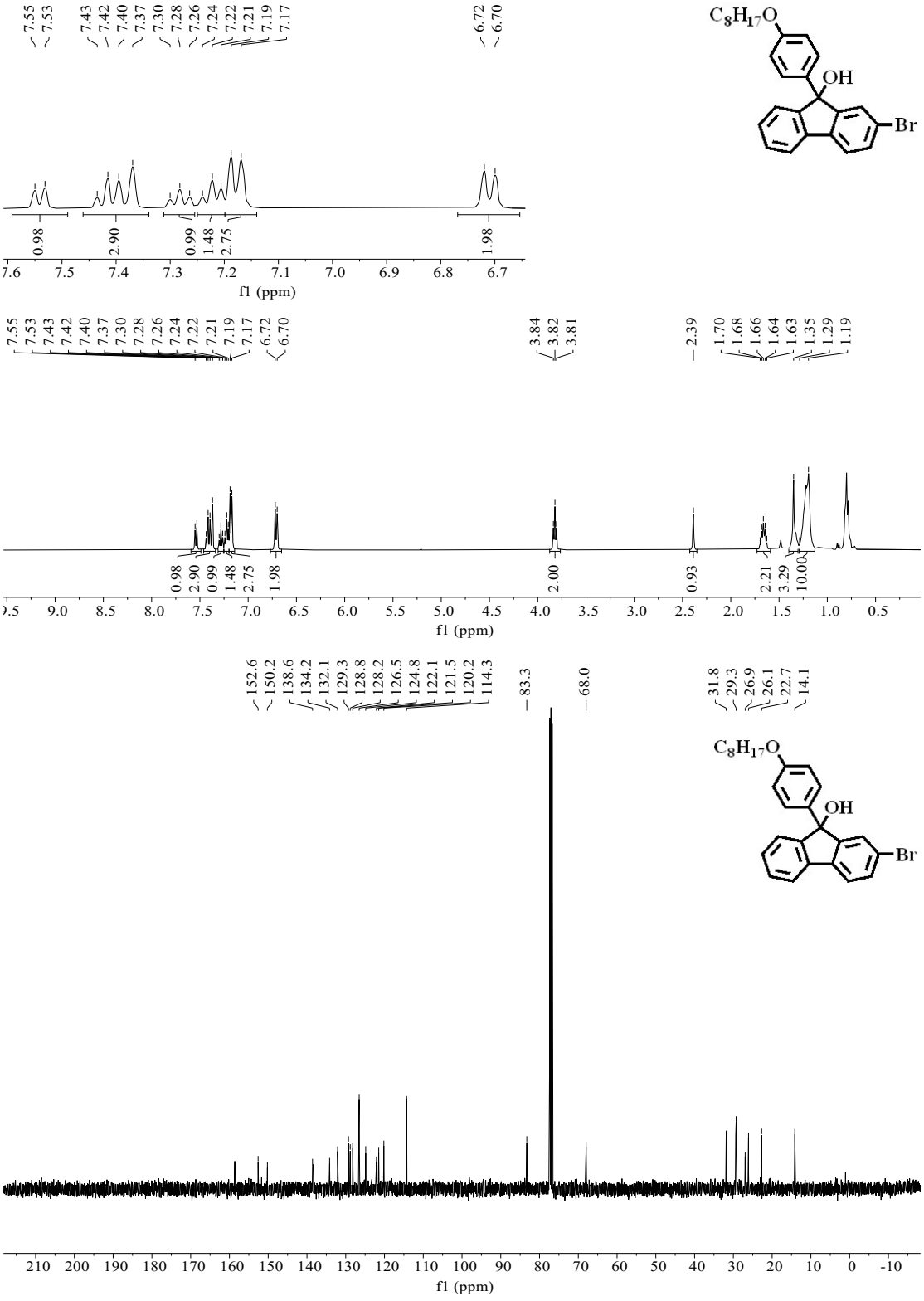




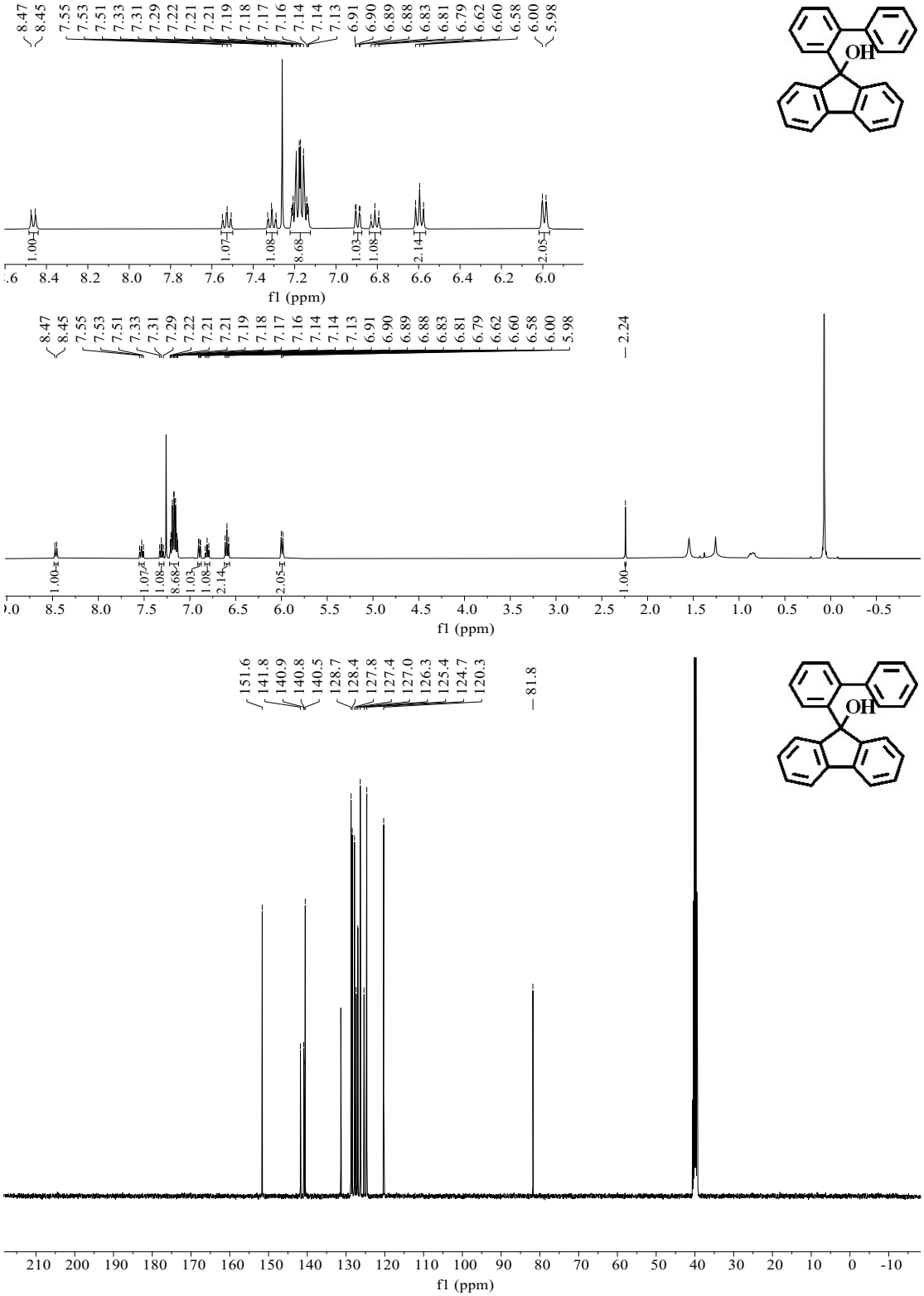




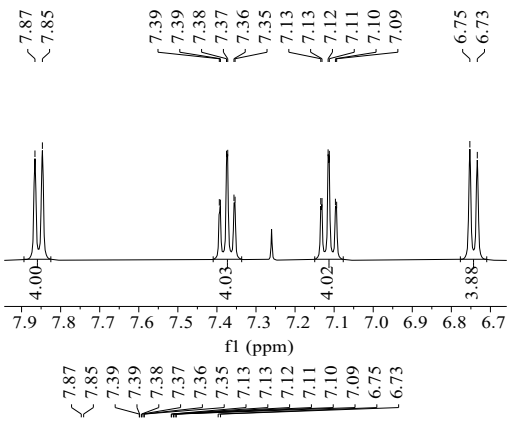
2-bromo-9-(4-(octyloxy)phenyl)-9H-fluoren-9-ol (3h)

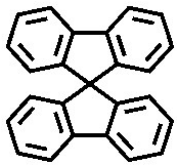


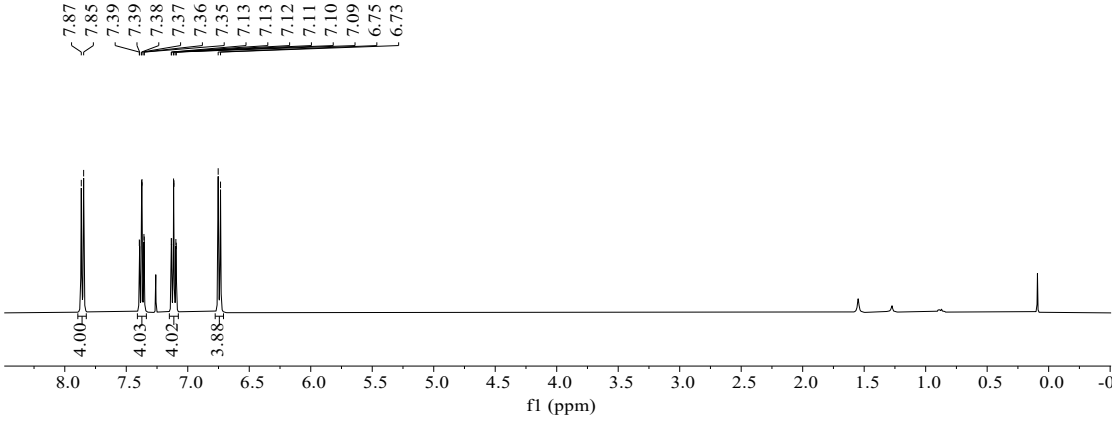
9-([1,1'-biphenyl]-2-yl)-9H-fluoren-9-ol （3i）

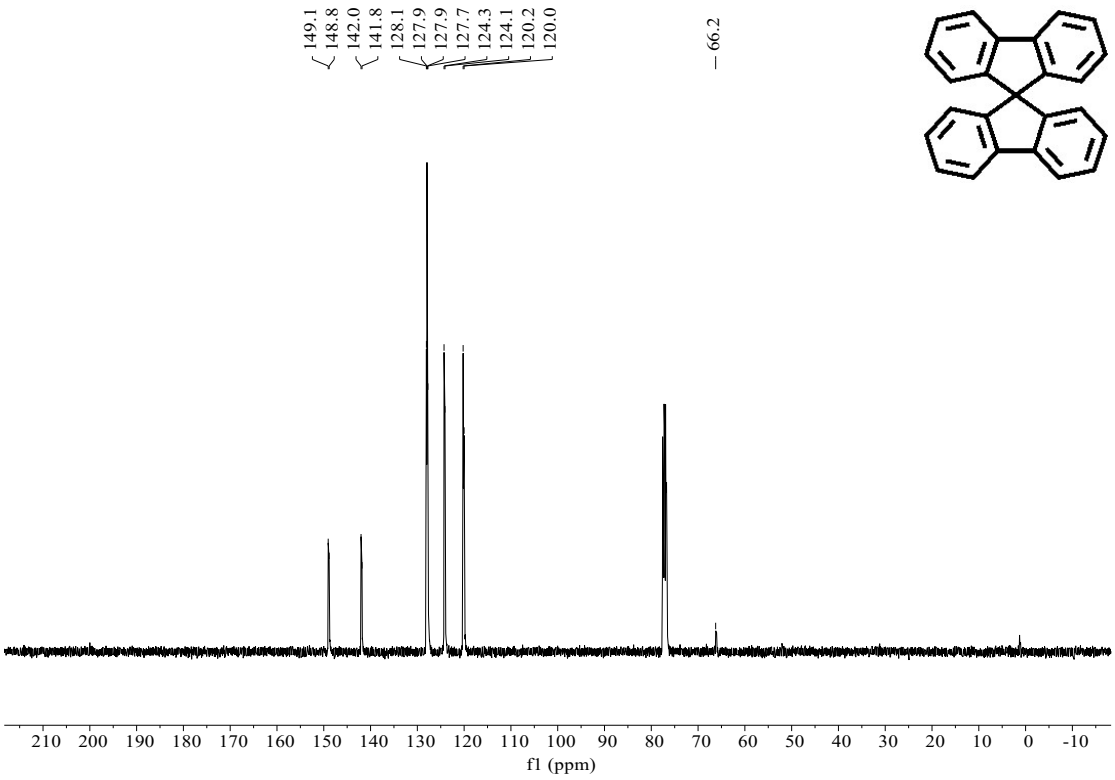


9,9'-spirobi[fluorene] （SBF）









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