

Supporting Information

**Facile access to highly functionalized hydroisoquinoline derivatives via phosphine-catalyzed sequential [3 + 3]/[3 + 3] annulation**

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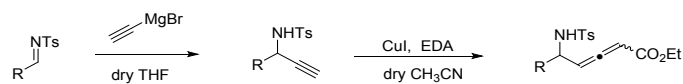
I. General Information .....	S1
II. General Procedure of $\delta$ -sulfonamido-allenoates <b>2</b> .....	S1
III. Table S1. Optimization of the Reaction Conditions.....	S3
IV. Reaction on gram Scale.....	S5
V. Table S2. Chiral phosphine catalysts catalyzed sequential [3+3]/ [3+3] annulation.....	S5
VI. Discussion about the mechanism.....	S6
VII. Spectroscopic Data and HPLC Chromatogram .....	S7
VIII. References .....	S50
IX. X-ray crystal structure of <b>3aa</b> and <b>4ba</b> .....	S50

## I. General Information

All the solvents and achiral catalysts were obtained from commercial sources and used without further purification unless otherwise stated. Dry acetonitrile were distilled over calcium hydride. Yields referred to isolated compounds were obtained through preparative TLC. NMR spectra were recorded on Varian and Bruker ARX 400 spectrometer in CDCl<sub>3</sub> solution and the chemical shifts were reported in parts per million (ppm) relative to internal standard TMS (0 ppm) for <sup>1</sup>H NMR and chloroform-d (77.0 ppm) for <sup>13</sup>C NMR. Coupling constants were given in Hertz (Hz). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), brs (broad singlet) and m (multiplet). Infrared spectra (IR) spectra were recorded on a Perkin-Elmer 983G instrument. High resolution mass spectrometry (HRMS) were obtained on an IonSpec FT-ICR mass spectrometer with ESI or MALDI resource. Melting points were measured on a RY-I apparatus and reported uncorrected.

## II. General Procedure of N-sulfonamido-allenoates 2

### 1. synthesis of $\delta$ -sulfonamido-allenoates 2



The N-sulfonyl propargylamines were prepared following the modified procedure described in the reported literature.<sup>1</sup>

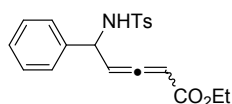
To a solution of N-Ts imine (10.0 mmol) in THF (40.0 mL) at 0 °C was added ethynylmagnesium bromide (12.0 mmol, 0.5 M in THF) and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed twice with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Recrystallization from ethyl acetate and Petroleum ether afforded N-Ts propargylamine.

The  $\delta$ -sulfonamido-allenoates were prepared following the modified procedure described in the reported literature.<sup>2,3</sup>

In a Schlenk flask filled nitrogen the corresponding propargylamine (2 mmol, 1.0 equiv) and CuI (0.4 mmol, 0.2 equiv) in dry acetonitrile (5 mL) was carefully added ethyl diazoacetate (2.2 mmol, 1.2 equiv). The reaction mixture was stirring at 40 °C for 3 h. Then the residue was quenched with saturated NH<sub>4</sub>Cl solution, extracted with ethyl acetate and dried on MgSO<sub>4</sub>. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (ethyl acetate / Petroleum ether, 1:5) to give  $\delta$ -sulfonamido-allenoates (few cases mixed with inseparable coupling products.).

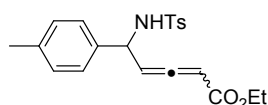
### 2. Spectroscopic Data of $\delta$ -sulfonamido-allenoates 2

### Ethyl 5-((4-methylphenyl)sulfonamido)-5-phenylpenta-2,3-dienoate 2a



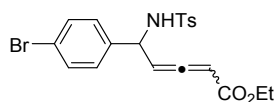
Yellow oil, 0.59 g, 79% yield, dr = 1:1. Data of single diastereomeric isomer. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.16 (m, 7H), 5.67 (t, *J* = 6.5 Hz, 1H), 5.52 (dd, *J* = 10.9, 9.0 Hz, 2H), 5.10 (t, *J* = 7.3 Hz, 1H), 4.22 – 4.08 (m, 2H), 2.40 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 211.6, 165.0, 143.5, 138.6, 137.4, 129.6, 128.6, 128.1, 127.3, 126.8, 97.5, 91.0, 61.2, 56.0, 21.6, 14.2. **HRMS (ESI)** *m/z* Calcd for [C<sub>20</sub>H<sub>22</sub>NO<sub>4</sub>S, M + H]<sup>+</sup> :372.1264, Found: 372.1262.

### Ethyl 5-((4-methylphenyl)sulfonamido)-5-(*p*-tolyl)penta-2,3-dienoate 2b



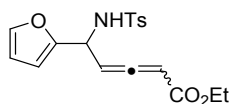
Yellow oil, 0.75 g, 95% yield, dr = 1:1. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.68 (dd, *J* = 8.2, 1.5 Hz, 4H), 7.23 (d, *J* = 8.2 Hz, 4H), 7.15 (dd, *J* = 8.1, 1.9 Hz, 4H), 7.06 (dd, *J* = 7.7, 4.8 Hz, 4H), 5.74 (dd, *J* = 5.9, 5.1 Hz, 1H), 5.68 (t, *J* = 6.5 Hz, 1H), 5.53 (dd, *J* = 6.1, 2.8 Hz, 2H), 5.47 (d, *J* = 8.0 Hz, 1H), 5.25 (d, *J* = 8.1 Hz, 1H), 5.09 (td, *J* = 8.1, 3.4 Hz, 2H), 4.25 – 4.09 (m, 4H), 2.43 (s, 6H), 2.31 (d, *J* = 2.7 Hz, 6H), 1.37 – 1.30 (t, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 211.6, 211.0, 165.2, 165.0, 143.4, 138.2, 137.9, 137.7, 137.5, 135.8, 135.7, 129.5, 129.5, 129.4, 129.2, 127.3, 127.2, 127.2, 126.7, 98.3, 97.6, 92.5, 90.9, 61.2, 61.1, 55.8, 55.2, 21.5, 21.1, 21.1, 14.2. **HRMS (ESI)** *m/z* Calcd for [C<sub>21</sub>H<sub>24</sub>NO<sub>4</sub>S, M + H]<sup>+</sup> :386.1421, Found: 386.1419.

### Ethyl 5-(4-bromophenyl)-5-((4-methylphenyl)sulfonamido)penta-2,3-dienoate 2c



Yellow oil, 0.89 g, 99% yield, dr = 1:1. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.33 (dd, *J* = 7.4, 6.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 2H), 5.68 (dt, *J* = 12.8, 5.9 Hz, 1H), 5.58 – 5.48 (m, 1H), 5.46 (d, *J* = 13.2 Hz, 1H), 5.08 (dt, *J* = 12.9, 5.9 Hz, 1H), 4.21 – 4.05 (m, 2H), 2.41 (s, 3H), 1.32 – 1.22 (m, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 211.7, 210.9, 165.0, 164.9, 143.6, 137.7, 137.6, 137.4, 137.4, 137.3, 131.7, 131.5, 129.6, 129.5, 129.1, 128.7, 127.2, 127.2, 122.3, 122.1, 100.0, 97.8, 97.2, 92.8, 91.3, 61.3, 61.3, 55.5, 54.9, 21.5, 14.2. **HRMS (ESI)** *m/z* Calcd for [C<sub>20</sub>H<sub>21</sub>BrNO<sub>4</sub>S, M + H]<sup>+</sup> :450.0369, Found: 450.0362.

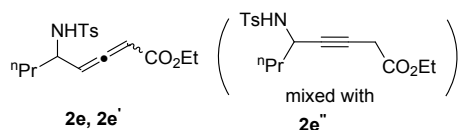
### Ethyl 5-(furan-2-yl)-5-((4-methylphenyl)sulfonamido)penta-2,3-dienoate 2d



Yellow oil, 0.43 g, 60% yield, dr = 1:1. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.69 (dd, *J* = 8.2, 5.2 Hz, 4H), 7.33 – 7.21 (m, 6H), 6.23 – 6.17 (m, 4H), 5.78 (dt, *J* = 17.3, 6.1 Hz, 2H), 5.65 (dd, *J* = 6.2, 2.5 Hz, 1H), 5.60 – 5.55 (m, 1H), 5.37 (d, *J* = 8.1 Hz, 1H), 5.26 – 5.16 (m, 3H), 4.23 – 4.13 (m, 4H), 2.41 (d, *J* = 2.2 Hz, 6H), 1.27 (dt, *J* = 9.1, 7.1 Hz, 6H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 211.7, 211.5, 164.9, 164.8, 150.8, 150.7, 143.5, 143.5, 142.8, 142.6, 137.6, 129.8, 129.6, 127.3, 127.2, 127.2, 110.4, 108.2, 107.9,

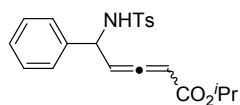
96.1, 95.7, 92.5, 91.6, 61.2, 61.2, 50.0, 49.4, 21.5, 14.2. **HRMS (ESI)**  $m/z$  Calcd for  $[C_{18}H_{19}NNaO_5S, M + Na]^+$ : 384.0876, Found: 384.0878.

### Ethyl 5-((4-methylphenyl)sulfonamido)octa-2,3-dienoate **2e**



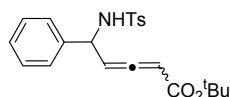
Yellow oil, 0.31 g, 46% yield. Allenoate **2e** and **2e'** were mixed with inseparable ethyl 5-((4-methylphenyl)sulfonamido)oct-3-ynoate **2e''**. **2e:2e':2e''** = 1.5:1:1. **<sup>1</sup>H NMR** (400 MHz,  $CDCl_3$ )  $\delta$  7.83 – 7.71 (m, 7H), 7.33 – 7.25 (m, 7H), 5.51 (dt,  $J = 6.7, 3.4$  Hz, 2H), 5.46 (dd,  $J = 6.2, 3.0$  Hz, 1H), 5.34 (dd,  $J = 7.2, 6.3$  Hz, 1H), 5.17 (d,  $J = 8.5$  Hz, 1H), 5.00 (d,  $J = 9.2$  Hz, 1.5H), 4.95 (d,  $J = 9.0$  Hz, 1H), 4.24 – 4.10 (m, 7H), 4.07 (ddd,  $J = 9.0, 7.0, 2.4$  Hz, 1H), 4.02 – 3.94 (m, 1H), 3.93 – 3.85 (m, 1H), 2.95 (d,  $J = 1.9$  Hz, (1.5 + 1 + 1) H), 2.43 (d,  $J = 4.1$  Hz, 10.5H), 1.68 – 1.59 (m, (1.5 + 1 + 1) H), 1.59 – 1.51 (m, (1.5 + 1 + 1) H), 1.45 (ddd,  $J = 18.3, 7.4, 3.3$  Hz, (1.5 + 1 + 1) H), 1.39 – 1.31 (m, (1.5 + 1 + 1) H), 1.30 – 1.22 (m, (4.5 + 3 + 3) H), 0.93 – 0.80 (m, (4.5 + 3 + 3) H). **<sup>13</sup>C NMR** (101 MHz,  $CDCl_3$ )  $\delta$  211.1, 210.8, 167.8, 165.3, 165.2, 143.5, 143.3, 137.9, 137.8, 137.5, 129.7, 129.4, 127.5, 127.2, 127.1, 97.9, 97.0, 91.6, 90.1, 81.5, 61.6, 61.1, 61.1, 52.3, 51.3, 45.7, 38.6, 37.7, 25.7, 21.5, 21.5, 18.6, 18.5, 18.4, 14.1, 14.1, 13.5, 13.5, 13.4. **HRMS (ESI)**  $m/z$  Calcd for  $[C_{17}H_{24}NO_4S, M + H]^+$ : 338.1421, Found: 338.1418.

### Isopropyl 5-((4-methylphenyl)sulfonamido)-5-phenylpenta-2,3-dienoate **2f**



Yellow oil, 0.44 g, 57% yield, dr = 1:1. **<sup>1</sup>H NMR** (400 MHz,  $CDCl_3$ )  $\delta$  7.65 (d,  $J = 8.2$  Hz, 4H), 7.26 – 7.18 (m, 14H), 5.72 (dd,  $J = 6.1, 4.7$  Hz, 1H), 5.69 – 5.63 (m, 1H), 5.53 – 5.47 (m, 2H), 5.38 (d,  $J = 8.0$  Hz, 1H), 5.19 – 5.08 (m, 3H), 5.02 (ddd,  $J = 18.7, 12.5, 6.2$  Hz, 2H), 2.40 (s, 6H), 1.28 (d,  $J = 6.3$  Hz, 6H), 1.23 (d,  $J = 6.3$  Hz, 6H). **<sup>13</sup>C NMR** (101 MHz,  $CDCl_3$ )  $\delta$  = 211.5, 210.8, 164.7, 143.4, 138.7, 138.6, 137.6, 137.4, 129.8, 129.6, 129.5, 128.7, 128.5, 128.3, 128.1, 127.3, 127.3, 127.2, 126.8, 98.1, 97.5, 93.1, 91.4, 68.8, 68.7, 56.1, 55.4, 21.9, 21.9, 21.8, 21.5. **HRMS (ESI)**  $m/z$  Calcd for  $[C_{21}H_{24}NO_4S, M + H]^+$ : 386.1421, Found: 386.1421.

### Tert-butyl 5-((4-methylphenyl)sulfonamido)-5-phenylpenta-2,3-dienoate **2g**

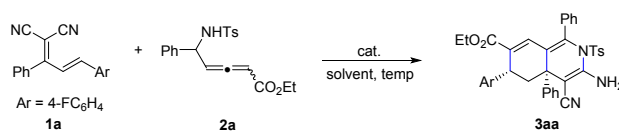


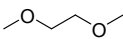
Yellow oil, 0.60 g, 75% yield, dr = 1:1. Data of single diastereomeric isomer. **<sup>1</sup>H NMR** (400 MHz,  $CDCl_3$ )  $\delta$  7.65 (d,  $J = 8.1$  Hz, 2H), 7.45 (s, 1H), 7.35 – 7.18 (m, 6H), 5.68 (t,  $J = 5.5$  Hz, 1H), 5.43 (dd,  $J = 6.0, 3.3$  Hz, 1H), 5.15 – 5.06 (m, 1H), 4.98 (s, 1H), 2.40 (s, 3H), 1.49 (s, 9H). **<sup>13</sup>C NMR** (101 MHz,  $CDCl_3$ )  $\delta$  210.3, 164.2, 143.4, 138.9, 137.7, 129.5, 128.7, 128.7, 127.5, 127.3, 127.2, 127.2, 97.8, 94.3, 81.6, 55.4, 28.1, 21.5. **HRMS (ESI)**  $m/z$  Calcd for  $[C_{22}H_{29}N_2O_4S, M + NH_4]^+$ : 417.1843, Found: 417.1841.

### III. Optimization of the Reaction Conditions

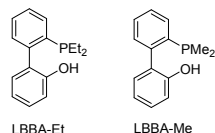
2-(1,3-diarylallylidene)malononitrile (**1**, 0.1 mmol) with  $\delta$ -sulfonamido-allenoates (**2**, 0.2 mmol), additive (1 equiv) and solvent (1.0 mL) were added to a dry flask filled with Ar. Then catalyst (40 mol %) was added. This mixture was stirred at the corresponding temperature until the complete consumption of the starting materials monitored by TLC. After the removal of the solvent, the residue was purified by preparative TLC (petroleum ether: ethyl acetate = 5:1~3:1) to afford product **3**.

**Table S1.** Optimization of the sequential [3 + 3]/[3 + 3] annulations.

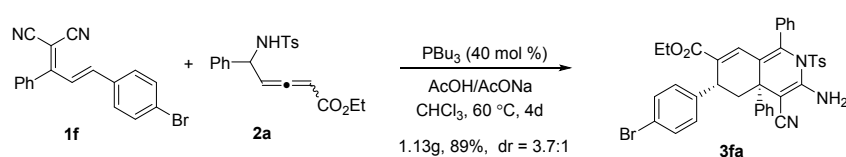


Entry	cat. (40 mol %)	solvent	temp	additive	time	yield <b>3aa</b>	dr
1	PBu <sub>3</sub>	CHCl <sub>3</sub>	60 °C	-	2d	70% <sup>b</sup>	4.3:1
2	PBu <sub>3</sub>	CHCl <sub>3</sub>	40 °C	-	2d	38% <sup>b</sup>	4:1
3	PBu <sub>3</sub>	CHCl <sub>3</sub>	25 °C	-	2d	33% <sup>b</sup>	4:1
4	PBu <sub>3</sub>	CHCl <sub>3</sub>	80 °C	-	2d	28% <sup>c</sup>	6:1
5	PBu <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	60 °C	-	3d	22% <sup>c</sup>	4.5:1
6	PBu <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	60 °C	-	3d	9% <sup>c</sup>	4:1
7	PBu <sub>3</sub>	EA	60 °C	-	3d	18% <sup>c</sup>	5:1
8	PBu <sub>3</sub>	THF	60 °C	-	2d	13% <sup>c</sup>	4:1
9	PBu <sub>3</sub>	CH <sub>3</sub> CN	60 °C	-	2d	26% <sup>c</sup>	4:1
10	PBu <sub>3</sub>	1,4-Dioxane	60 °C	-	3d	7% <sup>c</sup>	4:1
11	PBu <sub>3</sub>	tol	60 °C	-	3d	28% <sup>c</sup>	2.1:1
12	PBu <sub>3</sub>	DMSO	60 °C	-	3d	ND	-
13	PBu <sub>3</sub>		60 °C	-	3d	14% <sup>c</sup>	2.5:1
14	PBu <sub>3</sub>	CHCl <sub>3</sub>	60 °C	MS. 4A	2d	69% <sup>c</sup>	6.7:1
15	PBu <sub>3</sub>	CHCl <sub>3</sub>	60 °C	CH <sub>3</sub> CO <sub>2</sub> Na, 1eq	2d	62% <sup>c</sup>	5.9:1
16	PBu <sub>3</sub>	CHCl <sub>3</sub>	60 °C	NH <sub>2</sub> Ts, 1eq	2d	50% <sup>c</sup>	6.1:1
17	PBu <sub>3</sub>	CHCl <sub>3</sub>	60 °C	CH <sub>3</sub> COOH, 1eq	4d	59% <sup>c</sup>	5.6:1
18	PBu <sub>3</sub>	CHCl <sub>3</sub>	60 °C	PhCOOH, 1eq	4d	77% <sup>c</sup>	6:1
<b>19</b>	<b>PBu<sub>3</sub></b>	<b>CHCl<sub>3</sub></b>	<b>60 °C</b>	<b>Buffer</b>	<b>4d</b>	<b>79%<sup>c</sup></b> <b>(84%<sup>b</sup>)</b>	<b>6.2:1 (</b> <b>4.1:1)</b>
20	LBBA-Et	CHCl <sub>3</sub>	60 °C	Buffer	6d	33% <sup>b</sup>	2:1
21	LBBA-Me	CHCl <sub>3</sub>	60 °C	Buffer	4d	45% <sup>b</sup>	2.7:1
22	P(4-MeOC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	CHCl <sub>3</sub>	60 °C	Buffer	4d	48% <sup>b</sup>	4.7:1
23	PBu <sub>3</sub> (20 mol %)	CHCl <sub>3</sub>	60 °C	Buffer	4d	78% <sup>b</sup>	4.1:1
24 <sup>d</sup>	PBu <sub>3</sub>	CHCl <sub>3</sub>	60 °C	Buffer	4d	61% <sup>b</sup>	3.1:1

<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), cat (40 mol %) in solvent (1 mL) at 60 °C under an argon atmosphere. 1 eq = 1 equiv. Buffer : AcONa/AcOH = 1 eq:1 eq. <sup>b</sup>Isolated yield. Dr was determined through <sup>1</sup>H NMR spectroscopy. <sup>c</sup> The yield and dr was determined by <sup>19</sup>F NMR using 1,4-difluorobenzene as an internal standard. <sup>d</sup>2 mL CHCl<sub>3</sub> was used.

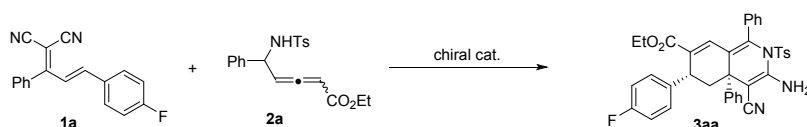


## IV. Reaction on gram Scale

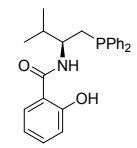
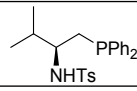
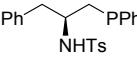
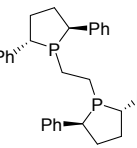
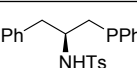
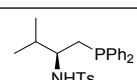


2-(1,3-diarylallylidene)malononitrile **1f** (1.8 mmol, 0.60 g) with  $\delta$ -sulfonamido-allenoates **2a** (3.6 mmol, 1.34 g), AcONa (1.8 mmol, 147.6 mg), AcOH (1.8mmol, 103  $\mu$ L) and CHCl<sub>3</sub> (18 mL) were added to a dry flask filled with Ar. Then PBU<sub>3</sub> (0.72 mmol, 153.3 mg) was added. This mixture was stirred for 4 days at 60 °C until the complete consumption of the starting materials monitored by TLC. The reaction was quenched by the addition of water and the aqueous layer was extracted with ethyl acetate and dried on MgSO<sub>4</sub>. After removal of the solvent, the crude product was purified by column chromatography (Petroleum ether/ ethyl acetate = 10:1 to 5:1) to give product **3fa** (1.13 g, 89% yield) with dr of 3.7:1.

## V. Table S2. Chiral phosphine catalysts catalyzed sequential [3 + 3]/[3 + 3] annulation



entry	Cat. (40 mol %)	conditions	yield & dr	ee
1		25 °C, 6d	31%, dr = 4.3:1	7%
2		25 °C, 4d	nd	--

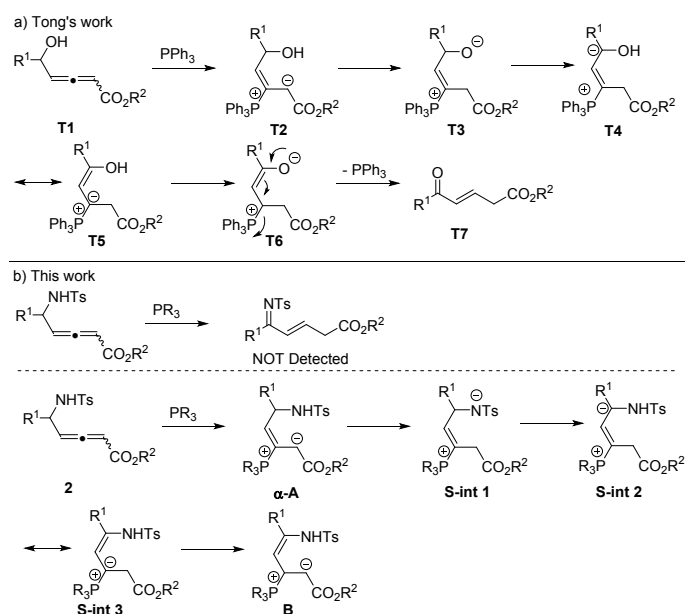
3		25 °C, 4d	nd	--
4		PhCOOH, 1eq 25 °C, 10d	nd	--
5		PhCOOH, 1eq 25 °C, 10d	nd	--
6		AcONa/AcOH=1eq:1eq 25 °C, 4d	nd	--
7		AcONa/AcOH=1eq:1eq 60 °C, 4d	80%, dr = 4.8:1	12%
8		AcONa/AcOH=1eq:1eq 60 °C, 6d	72%, dr = 5.2:1	-14%

Reaction condition: **1a** (0.1 mmol), **2a** (0.2 mmol), cat. (40 mol %) in solvent(1 mL). Dr was determined through <sup>1</sup>H NMR spectroscopy. 1eq = 1 equiv.

## VI. Discussion about the mechanism

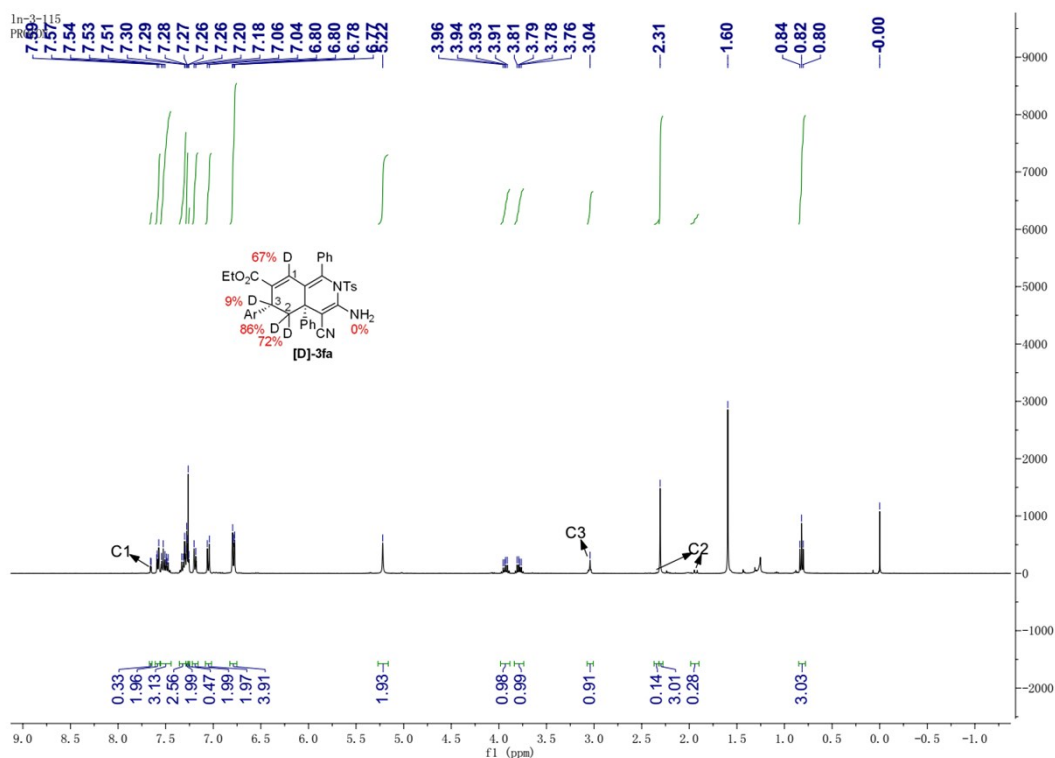
There are triple additions of  $\delta$ -sulfonamido-allenoates to 2-(1,3-Diarylallylidene)malononitrile **1** during the proposed mechanism cycle, which is quite different from any reaction mode of phosphine-catalyzed allenoates reported yet. Fortunately, the structure of side product **4aa** gave us a clue of possible pathway of how the addition initiates, as shown in Figure 3 in main text. It is still mysterious how intermediate **B** is formed through intermediate  $\alpha$ -**A**. In 2013, Tong and coworkers reported an isomerization of 5-hydroxyl-2,3-dienoate catalyzed by PPh<sub>3</sub>, leading to 5-oxohex-2(3)-enoate.<sup>3</sup> They proposed a convincing mechanism that consisted of continuous proton shifts and keto-enol tautomerism (Figure S1, a).

**Figure S1.** Possible pathway from **2** to intermediate **B**



However, in our case, none of such isomerization product was detected. In our opinion, this is the reason why  $\delta$ -sulfonamido-allenoates could participate in this [3 + 3]/[3 + 3] domino annulation. We speculated that there is a similar process when it comes to  $\delta$ -sulfonamido-allenoates (Figure S1, b), given that the enamine structure of side product **4aa** is analogous to **T5**. Generally,  $\alpha$ -A can be transformed into **S-int 2** after continuous H-shifts with the help of -NHTs. Next, intermediate **S-int 3**, which is a resonance form of **S-int 2**, undergoes 1,2-H-shift to afford key intermediate **B**, which attacks the electrophilic diene to initiate the whole annulation. **[D]-3fa** with incorporation of deuterium at the C1 position may imply the possibility of appearance of **S-int 3**. The fact that no deuterium was found at the amine position is confusing. We speculated that the imine-enamine tautomerism takes place fast and hydrogen atoms of the amine stem from starting substrates. The structure of cyano-enamine is relatively stable that excludes the possibility of hydrogen-exchanging with D<sub>2</sub>O after the reaction completes.



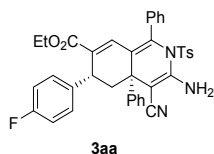


Deuterium-labelling of [D]-3fa

## VII. Spectroscopic Data and HPLC Chromatogram

Combined yields are given. Diastereomeric isomers could not be separated by flash column chromatography. Major isomers (syn-) were obtained after recrystallization in  $\text{CH}_2\text{Cl}_2/\text{n-Hexane}$  2 or 3 times. NMR and other data only for major isomers (syn-) is given below. Pure minor isomers (anti-) were not available after recrystallization. The NMR data of isomers mixture is not included because it is quite complicated. Side product **4aa** was isolated as mixture of 3 pairs of diastereomeric isomers and its analytic data is not included in this text. Fortunately, the structure of **4aa** was determined by analogy (**4ba** CCDC 1942509).

### Ethyl (4aR,6R)-3-amino-4-cyano-6-(4-fluorophenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (**3aa**)



Combined Yield: 84 % (54.0 mg), dr = 3.7:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 207-208 °C

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (d,  $J = 2.5$  Hz, 1H), 7.60 – 7.56 (m, 2H), 7.55 – 7.44 (m, 3H), 7.33 – 7.25 (m, 3H), 7.20 (d,  $J = 7.1$  Hz, 2H), 7.05 (d,  $J = 8.3$  Hz, 2H), 6.86 (d,  $J = 7.0$  Hz, 4H), 6.79 (d,  $J = 8.2$  Hz, 2H), 5.22 (s, 2H), 3.92 (dq,  $J = 10.9, 7.1$  Hz, 1H), 3.77 (dq,  $J = 10.9, 7.1$  Hz, 1H), 3.08 (ddd,  $J = 11.8, 4.3, 2.6$  Hz, 1H), 2.34 (dd,  $J = 13.1, 4.5$  Hz, 1H), 2.30 (s, 3H), 2.03 – 1.92 (m, 1H), 0.80 (t,  $J =$

7.1 Hz, 3H).

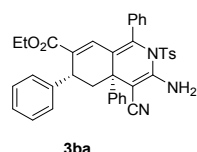
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9, 162.7, 160.2, 151.7, 146.5, 144.9, 139.7, 139.7, 135.5, 135.1, 133.6, 133.4, 129.9, 129.4, 129.3, 128.8, 128.6, 128.5, 127.9, 126.9, 125.9, 125.4, 119.1, 115.3, 115.1, 60.3, 47.4, 40.6, 38.7, 21.6, 13.6.

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -116.54.

IR (KBr,  $\text{cm}^{-1}$ ): 3483, 2923, 2850, 2188, 1710, 1638, 1510, 1366, 1250, 1170, 1102, 1086, 1014, 838, 698, 663, 583.

HRMS (ESI)  $m/z$  Calcd for  $[\text{C}_{38}\text{H}_{31}\text{FN}_3\text{O}_4\text{S}, \text{M} - \text{H}]^-$ : 644.2025, Found: 644.2022.

**Ethyl (4aR,6R)-3-amino-4-cyano-1,4a,6-triphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate(3ba)**



Combined Yield: 83% (52.1 mg), dr = 3.3:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. >220 °C

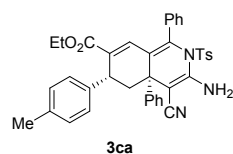
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (d,  $J$  = 2.0 Hz, 1H), 7.58 (d,  $J$  = 7.3 Hz, 2H), 7.52 (t,  $J$  = 7.3 Hz, 2H), 7.49 – 7.45 (m, 1H), 7.35 – 7.24 (m, 3H), 7.21 (d,  $J$  = 7.2 Hz, 2H), 7.13 (td,  $J$  = 13.9, 6.7 Hz, 3H), 7.05 (d,  $J$  = 8.1 Hz, 2H), 6.89 (d,  $J$  = 7.1 Hz, 2H), 6.78 (d,  $J$  = 8.0 Hz, 2H), 5.21 (s, 2H), 3.90 (tt,  $J$  = 14.2, 7.1 Hz, 1H), 3.79 – 3.68 (m, 1H), 3.08 (d,  $J$  = 10.9 Hz, 1H), 2.37 (dd,  $J$  = 13.1, 4.3 Hz, 1H), 2.30 (s, 3H), 2.01 (t,  $J$  = 12.5 Hz, 1H), 0.73 (t,  $J$  = 7.1 Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9, 162.8, 160.2, 151.7, 146.5, 144.9, 139.7, 139.7, 135.5, 135.1, 133.6, 133.4, 129.9, 129.4, 129.3, 128.8, 128.6, 128.5, 127.9, 126.9, 125.9, 125.4, 119.1, 115.3, 115.1, 60.3, 47.4, 40.6, 38.7, 21.6, 13.6.

IR (KBr,  $\text{cm}^{-1}$ ): 3468, 3392, 2188, 1711, 1637, 1393, 1251, 1169, 1086, 1029, 1012, 754, 699, 662, 608, 563.

HRMS (ESI)  $m/z$  Calcd for  $[\text{C}_{38}\text{H}_{32}\text{N}_3\text{O}_4\text{S}, \text{M} - \text{H}]^-$ : 626.2119, Found: 626.2116.

**Ethyl (4aR,6R)-3-amino-4-cyano-1,4a-diphenyl-6-(p-tolyl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ca)**



Combined Yield: 86% (55.4 mg), dr = 4:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 153-155 °C

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (dd,  $J$  = 11.4, 4.7 Hz, 3H), 7.49 (dt,  $J$  = 22.5, 7.1 Hz, 3H), 7.35 – 7.23 (m, 4H), 7.20 (d,  $J$  = 7.3 Hz, 2H), 7.05 (d,  $J$  = 8.2 Hz, 2H), 6.96 (d,  $J$  = 7.7 Hz, 2H), 6.78 (d,  $J$  = 7.9 Hz, 4H), 5.21 (s, 2H), 3.92 (dd,  $J$  = 10.7, 7.1 Hz, 1H), 3.82 – 3.71 (m, 1H), 3.05 (d,  $J$  = 10.6 Hz, 1H), 2.35 (dd,  $J$  = 13.2, 4.4 Hz, 1H), 2.30 (s, 3H), 2.24 (s, 3H), 1.99 (t,  $J$  = 12.5 Hz, 1H), 0.79 (t,  $J$  = 7.1 Hz, 3H).

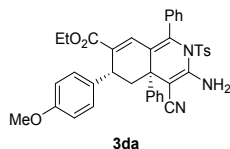
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.1, 151.7, 146.7, 144.8, 140.9, 139.3, 136.2, 135.8, 135.2, 133.6, 132.9, 129.9, 129.4, 129.2, 129.1, 128.7, 128.5, 127.9, 121.0, 126.8, 125.9, 125.7, 119.1, 60.3, 47.4,

40.7, 39.0, 21.6, 21.0, 13.6.

**IR** (KBr,  $\text{cm}^{-1}$ ): 3461, 2926, 2188, 1703, 1638, 1394, 1251, 1170, 1086, 1014, 750, 699, 663, 646.

**HRMS (ESI)**  $m/z$  Calcd for  $[\text{C}_{39}\text{H}_{36}\text{N}_3\text{O}_4\text{S}, \text{M} + \text{H}]^+$  : 642.2421, Found: 642.2425.

**Ethyl (4aR,6R)-3-amino-4-cyano-6-(4-methoxyphenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3da)**



Combined Yield: 69% (45.4 mg), dr = 3.7:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 162-163 °C

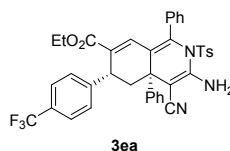
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 – 7.56 (m, 3H), 7.49 (dt,  $J = 22.2, 7.1$  Hz, 3H), 7.31 (dd,  $J = 14.2, 7.2$  Hz, 2H), 7.26 (d,  $J = 4.3$  Hz, 1H), 7.20 (d,  $J = 7.3$  Hz, 2H), 7.05 (d,  $J = 8.3$  Hz, 4H), 6.80 (dd,  $J = 10.8, 8.5$  Hz, 4H), 6.70 (d,  $J = 8.6$  Hz, 2H), 5.20 (s, 2H), 3.92 (dq,  $J = 14.3, 7.1$  Hz, 1H), 3.83 – 3.74 (m, 1H), 3.72 (s, 3H), 3.04 (d,  $J = 10.4$  Hz, 1H), 2.34 (dd,  $J = 13.2, 4.5$  Hz, 1H), 2.30 (s, 3H), 1.98 (t,  $J = 12.5$  Hz, 1H), 0.80 (t,  $J = 7.1$  Hz, 3H).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.2, 158.1, 151.7, 146.6, 144.9, 139.3, 136.3, 136.0, 135.2, 133.6, 132.7, 129.9, 129.4, 129.3, 128.7, 128.5, 128.1, 127.9, 126.8, 125.9, 125.6, 119.1, 113.8, 60.3, 55.3, 47.3, 40.7, 38.5, 21.6, 13.7.

**IR** (KBr,  $\text{cm}^{-1}$ ): 3465, 2918, 2187, 1710, 1637, 1512, 1366, 1247, 1169, 1085, 1032, 832, 812, 777, 699, 663, 562.

**HRMS (ESI)**  $m/z$  Calcd for  $[\text{C}_{39}\text{H}_{34}\text{N}_3\text{O}_5\text{S}, \text{M} - \text{H}]^-$  : 656.2225, Found: 656.2222.

**Ethyl (4aR,6R)-3-amino-4-cyano-1,4a-diphenyl-2-tosyl-6-(4-(trifluoromethyl)phenyl)-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ea)**



Combined Yield: 89% (62.1 mg), dr = 3.4:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 145-147 °C

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (s, 1H), 7.61 (d,  $J = 7.0$  Hz, 2H), 7.58 – 7.50 (m, 3H), 7.45 (d,  $J = 7.9$  Hz, 2H), 7.39 – 7.28 (m, 4H), 7.23 (d,  $J = 7.2$  Hz, 1H), 7.11 – 7.02 (m, 4H), 6.81 (d,  $J = 7.9$  Hz, 2H), 5.27 (s, 2H), 3.95 (dq,  $J = 14.1, 6.9$  Hz, 1H), 3.78 (dq,  $J = 14.4, 7.1$  Hz, 1H), 3.18 (d,  $J = 10.6$  Hz, 1H), 2.37 (dd,  $J = 13.3, 4.1$  Hz, 1H), 2.33 (s, 3H), 2.00 (t,  $J = 12.4$  Hz, 1H), 0.78 (t,  $J = 7.0$  Hz, 3H).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.5, 151.7, 148.4, 146.4, 145.0, 140.2, 135.0, 134.3, 134.2, 133.5, 129.9, 129.5, 129.4, 128.8, 128.6, 127.9, 127.4, 127.0, 125.8, 125.4, 125.4, 125.2, 119.0, 60.4, 47.1, 40.5, 39.3, 21.7, 13.5.

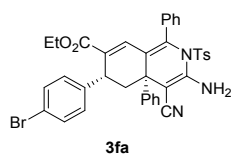
**$^{19}\text{F}$  NMR** (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.28, -62.30.

**IR** (KBr,  $\text{cm}^{-1}$ ): 3468, 2189, 1712, 1639, 1395, 1326, 1255, 1169, 1112, 1017, 751, 699, 663, 563.

**HRMS (ESI)**  $m/z$  Calcd for  $[\text{C}_{39}\text{H}_{31}\text{F}_3\text{N}_3\text{O}_4\text{S}, \text{M} - \text{H}]^-$  : 694.1993, Found: 694.1990.

**Ethyl (4aR,6R)-3-amino-6-(4-bromophenyl)-4-cyano-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydro-**

### isoquinoline-7-carboxylate (3fa)



Combined Yield: 97% (68.9 mg), dr = 3.7:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 166-167 °C

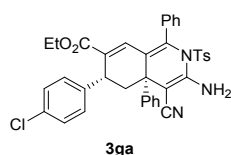
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.68 (d, *J* = 2.2 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.54 (dd, *J* = 14.1, 6.6 Hz, 3H), 7.33 (dd, *J* = 15.4, 6.9 Hz, 5H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.1 Hz, 4H), 5.24 (s, 2H), 3.96 (dq, *J* = 14.3, 7.1 Hz, 1H), 3.82 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.09 (d, *J* = 11.3 Hz, 1H), 2.41 – 2.34 (m, 1H), 2.33 (s, 3H), 1.98 (t, *J* = 12.5 Hz, 1H), 0.85 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.7, 151.7, 146.4, 144.9, 143.2, 139.9, 135.1, 134.9, 133.7, 133.5, 131.5, 129.9, 129.4, 128.9, 128.8, 128.5, 127.9, 127.0, 125.8, 125.3, 120.0, 119.0, 60.4, 47.2, 40.5, 38.9, 21.7, 13.7.

**IR** (KBr, cm<sup>-1</sup>): 3461, 2188, 1708, 1637, 1394, 1250, 1169, 1186, 1012, 233, 753, 699, 663, 544.

**HRMS (ESI)** *m/z* Calcd for [C<sub>38</sub>H<sub>31</sub>BrN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup> : 704.1224, Found: 704.1221.

### Ethyl (4aR,6R)-3-amino-6-(4-chlorophenyl)-4-cyano-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ga)



Combined Yield: 80% (52.8 mg), dr = 4.1:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 159-160 °C

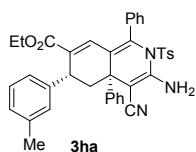
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 7.0 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.30 (dd, *J* = 14.7, 7.3 Hz, 3H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.1 Hz, 2H), 5.24 (s, 2H), 3.93 (dq, *J* = 14.3, 7.1 Hz, 1H), 3.84 – 3.73 (m, 1H), 3.07 (dd, *J* = 8.0, 2.5 Hz, 1H), 2.33 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.29 (s, 3H), 1.96 (t, *J* = 12.5 Hz, 1H), 0.81 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.7, 151.8, 146.5, 144.9, 142.7, 139.9, 135.1, 135.0, 133.7, 133.5, 132.0, 129.9, 129.4, 128.8, 128.6, 128.5, 128.5, 127.9, 127.0, 125.9, 125.4, 119.0, 60.4, 47.2, 40.6, 38.9, 21.6, 13.6.

**IR** (KBr, cm<sup>-1</sup>): 3463, 2188, 1709, 1637, 1491, 1394, 1252, 1169, 1087, 1015, 754, 699, 663, 564.

**HRMS (ESI)** *m/z* Calcd for [C<sub>38</sub>H<sub>31</sub>ClN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup> : 660.1729, Found: 660.1726.

### Ethyl (4aR,6R)-3-amino-4-cyano-1,4a-diphenyl-6-(*m*-tolyl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ha)



Combined Yield: 87% (55.6 mg), dr = 4:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. >220 °C

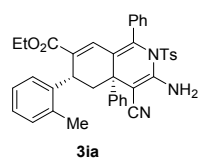
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.58 (dd, *J* = 8.7, 4.8 Hz, 3H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.20 (d, *J* = 6.9 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.99 – 6.93 (m, 3H), 6.77 (d, *J* = 8.1 Hz, 3H), 5.18 (s, 2H), 3.91 – 3.81 (m, 1H), 3.76 – 3.65 (m, 1H), 3.28 (d, *J* = 10.9 Hz, 1H), 2.28 (s, 3H), 2.26 – 2.21 (m, 1H), 1.95 – 1.86 (m, 1H), 1.84 (s, 3H), 0.69 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.1, 151.7, 146.5, 144.9, 142.1, 139.2, 136.7, 135.2, 135.0, 133.6, 132.8, 130.1, 129.9, 129.3, 129.2, 128.7, 128.5, 127.9, 126.9, 126.3, 126.1, 125.8, 125.6, 125.5, 119.1, 60.2, 46.0, 40.8, 34.4, 21.6, 18.7, 13.4.

**IR** (KBr, cm<sup>-1</sup>): 3465, 3365, 2919, 2188, 1711, 1637, 1367, 1250, 1169, 1086, 1033, 1013, 751, 699, 663, 567.

**HRMS (ESI)** *m/z* Calcd for [C<sub>39</sub>H<sub>36</sub>N<sub>3</sub>O<sub>4</sub>S, M + H]<sup>+</sup> : 642.2421, Found: 642.2424.

**Ethyl (4aR,6R)-3-amino-4-cyano-1,4a-diphenyl-6-(o-tolyl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ia)**



Combined Yield: 61% (39.2 mg), dr = 3.6:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 216-218 °C

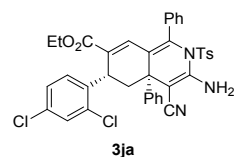
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.60 (dd, *J* = 8.5, 4.8 Hz, 3H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.49 – 7.44 (m, 1H), 7.29 (dd, *J* = 16.2, 8.5 Hz, 3H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.99 (s, 3H), 6.78 (d, *J* = 7.9 Hz, 3H), 5.22 (s, 2H), 3.87 (dt, *J* = 14.2, 7.1 Hz, 1H), 3.74 (d, *J* = 7.1 Hz, 1H), 3.31 (d, *J* = 11.3 Hz, 1H), 2.30 (s, 3H), 2.28 – 2.22 (m, 1H), 1.96 – 1.87 (m, 1H), 1.86 (s, 3H), 0.71 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.1, 151.7, 146.5, 144.9, 142.1, 139.2, 136.7, 135.2, 135.0, 133.5, 132.8, 130.1, 129.9, 129.3, 129.3, 128.7, 128.5, 127.9, 126.9, 126.3, 126.1, 125.8, 125.6, 125.5, 119.1, 60.2, 46.0, 40.8, 34.4, 21.7, 18.7, 13.4.

**IR** (KBr, cm<sup>-1</sup>): 3466, 3367, 2188, 1711, 1637, 1598, 1492, 1446, 1393, 1250, 1169, 1086, 1033, 751, 699, 663, 567, 543.

**HRMS (ESI)** *m/z* Calcd for [C<sub>39</sub>H<sub>36</sub>N<sub>3</sub>O<sub>4</sub>S, M + H]<sup>+</sup> : 642.2421, Found: 642.2425.

**Ethyl (4aR,6S)-3-amino-4-cyano-6-(2,4-dichlorophenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ja)**



Combined Yield: 88% (61.4 mg), dr = 5.5:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 184-185 °C

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.71 (d, *J* = 2.3 Hz, 1H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.50 (dt, *J* = 20.5, 7.0 Hz, 3H), 7.36 – 7.25 (m, 4H), 7.20 (d, *J* = 7.1 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 3H), 6.80 (dd, *J* = 12.5, 8.4 Hz, 3H), 5.24 (s, 2H), 4.00 – 3.88 (m, 1H), 3.85 – 3.75 (m, 1H), 3.66 (d, *J* = 10.9 Hz, 1H), 2.38 (dd, *J* = 12.9, 4.2 Hz, 1H), 2.29 (s, 3H), 1.81 (t, *J* = 12.4 Hz, 1H), 0.83 (t, *J* = 7.1 Hz, 3H).

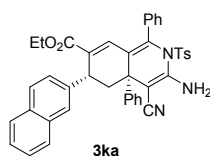
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.4, 151.7, 145.8, 145.0, 140.4, 140.1, 135.0, 134.4, 134.1, 133.9,

133.4, 132.4, 129.9, 129.4, 129.1, 128.7, 128.6, 128.0, 127.9, 127.3, 127.0, 125.8, 125.1, 119.0, 60.5, 45.3, 40.5, 35.0, 21.7, 13.6.

**IR** (KBr,  $\text{cm}^{-1}$ ): 3364, 2927, 2188, 1711, 1637, 1596, 1391, 1249, 1170, 1103, 1086, 1033, 825, 749, 699, 663, 558.

**HRMS (ESI)**  $m/z$  Calcd for  $[\text{C}_{38}\text{H}_{30}\text{Cl}_2\text{N}_3\text{O}_4\text{S}, \text{M} - \text{H}]^-$  : 694.1340, Found: 694.1338.

**Ethyl (4aR,6R)-3-amino-4-cyano-6-(naphthalen-2-yl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ka)**



Combined Yield: 94% (63.9 mg), dr = 3.2:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 174-175 °C

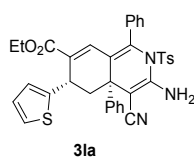
**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J$  = 8.0 Hz, 1H), 7.70 (d,  $J$  = 2.4 Hz, 1H), 7.65 – 7.59 (m, 3H), 7.57 – 7.46 (m, 3H), 7.37 (dd,  $J$  = 14.3, 6.8 Hz, 4H), 7.29 (t,  $J$  = 7.0 Hz, 5H), 7.11 (d,  $J$  = 8.2 Hz, 2H), 7.04 (d,  $J$  = 7.4 Hz, 1H), 6.81 (d,  $J$  = 8.1 Hz, 2H), 5.20 (s, 2H), 4.01 (d,  $J$  = 11.1 Hz, 1H), 3.80 (td,  $J$  = 14.1, 7.0 Hz, 1H), 3.60 (dt,  $J$  = 18.1, 7.2 Hz, 1H), 2.54 (dd,  $J$  = 13.3, 4.1 Hz, 1H), 2.31 (s, 3H), 2.07 (t,  $J$  = 12.5 Hz, 1H), 0.42 (t,  $J$  = 7.1 Hz, 3H).

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.2, 151.8, 146.4, 144.9, 140.5, 139.4, 136.6, 135.2, 133.8, 133.6, 133.1, 131.1, 129.9, 129.4, 129.3, 128.9, 128.6, 128.0, 127.1, 126.8, 126.0, 125.9, 125.6, 125.4, 125.4, 123.1, 121.9, 119.0, 60.1, 46.6, 40.9, 33.5, 21.7, 13.3.

**IR** (KBr,  $\text{cm}^{-1}$ ): 3677, 3656, 2924, 2188, 1711, 1638, 1596, 1394, 1370, 1251, 1169, 1085, 1013, 699, 663, 569, 542.

**HRMS (ESI)**  $m/z$  Calcd for  $[\text{C}_{42}\text{H}_{34}\text{N}_3\text{O}_4\text{S}, \text{M} - \text{H}]^-$  : 676.2276, Found: 676.2273.

**Ethyl (4aR,6S)-3-amino-4-cyano-1,4a-diphenyl-6-(thiophen-2-yl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3la)**



Combined Yield: 85% (54.0 mg), dr = 4.5:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 217-218 °C

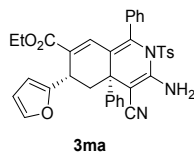
**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 (d,  $J$  = 7.0 Hz, 3H), 7.52 – 7.41 (m, 3H), 7.28 (dd,  $J$  = 14.9, 7.2 Hz, 3H), 7.18 (d,  $J$  = 7.1 Hz, 2H), 7.07 – 6.96 (m, 3H), 6.77 (d,  $J$  = 7.7 Hz, 3H), 6.61 (s, 1H), 5.20 (s, 2H), 4.02 – 3.90 (m, 1H), 3.87 – 3.75 (m, 1H), 3.41 (d,  $J$  = 10.8 Hz, 1H), 2.46 (dd,  $J$  = 12.8, 3.6 Hz, 1H), 2.28 (s, 3H), 2.11 (t,  $J$  = 12.4 Hz, 1H), 0.86 (t,  $J$  = 6.9 Hz, 3H).

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.8, 151.7, 146.6, 146.3, 144.9, 139.8, 135.4, 135.1, 133.6, 132.6, 129.9, 129.4, 128.8, 128.5, 127.9, 127.0, 126.6, 125.9, 125.2, 124.2, 123.0, 119.0, 60.4, 47.6, 40.6, 34.4, 21.6, 13.7.

**IR** (KBr,  $\text{cm}^{-1}$ ): 3750, 3112, 2931, 2187, 1712, 1638, 1394, 1249, 1169, 1085, 1013, 699, 663, 559, 543, 518, 456.

**HRMS (ESI)**  $m/z$  Calcd for  $[\text{C}_{36}\text{H}_{30}\text{N}_3\text{O}_4\text{S}_2, \text{M} - \text{H}]^-$  : 632.1683, Found: 632.1680.

**Ethyl (4aR,6S)-3-amino-4-cyano-6-(furan-2-yl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ma)**



Combined Yield: 49% (30.5 mg), dr = 3.8:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 214-215 °C

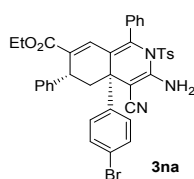
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.65 – 7.45 (m, 6H), 7.36 – 7.27 (m, 3H), 7.23 – 7.16 (m, 3H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.1 Hz, 2H), 6.22 (s, 1H), 5.88 (d, *J* = 3.0 Hz, 1H), 5.25 (s, 2H), 4.04 (tt, *J* = 14.2, 7.1 Hz, 1H), 3.95 – 3.84 (m, 1H), 3.32 – 3.24 (m, 1H), 2.37 (dd, *J* = 13.0, 4.3 Hz, 1H), 2.32 (s, 3H), 2.19 (t, *J* = 12.5 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.6, 155.8, 151.7, 146.3, 144.9, 140.5, 139.9, 135.1, 133.5, 133.2, 129.9, 129.4, 128.8, 128.5, 127.9, 127.0, 125.9, 125.2, 119.0, 110.4, 105.1, 60.5, 44.1, 40.4, 32.8, 21.6, 13.8.

**IR** (KBr, cm<sup>-1</sup>): 3742, 3468, 2188, 1711, 1369, 1366, 1251, 1170, 1086, 1016, 748, 699, 663, 569.

**HRMS (ESI)** *m/z* Calcd for [C<sub>36</sub>H<sub>32</sub>N<sub>3</sub>O<sub>5</sub>S, M + H]<sup>+</sup> : 618.2057, Found: 618.2052.

**Ethyl (4aR,6R)-3-amino-4a-(4-bromophenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3na)**



Combined Yield: 86% (61.0 mg), dr = 4:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 209-209 °C

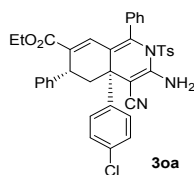
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 2.4 Hz, 1H), 7.52 (dt, *J* = 21.3, 7.0 Hz, 5H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.20 – 7.09 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.90 (t, *J* = 7.5 Hz, 4H), 5.38 (s, 2H), 3.90 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.74 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.06 (dd, *J* = 7.9, 2.5 Hz, 1H), 2.40 (s, 3H), 2.26 (dd, *J* = 13.2, 4.4 Hz, 1H), 1.99 (t, *J* = 12.5 Hz, 1H), 0.73 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.0, 152.0, 146.1, 145.5, 143.6, 139.7, 136.1, 135.2, 133.6, 133.4, 133.0, 131.6, 129.8, 129.4, 129.3, 128.6, 128.5, 127.9, 127.7, 127.1, 126.5, 125.4, 121.1, 118.9, 60.3, 47.0, 40.4, 39.3, 21.7, 13.5.

**IR** (KBr, cm<sup>-1</sup>): 3465, 3374, 2188, 1711, 1636, 1598, 1399, 1253, 1170, 1086, 1006, 825, 752, 700, 662, 538.

**HRMS (ESI)** *m/z* Calcd for [C<sub>38</sub>H<sub>31</sub>BrN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup> : 704.1224, Found: 704.1220.

**Ethyl (4aR,6R)-3-amino-4a-(4-chlorophenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3oa)**



Combined Yield: 90% (59.8 mg), dr = 3.4:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 201-202 °C

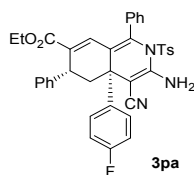
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 2.5 Hz, 1H), 7.58 – 7.44 (m, 5H), 7.20 – 7.11 (m, 7H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 7.9 Hz, 4H), 5.39 (s, 2H), 3.90 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.74 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.11 – 3.01 (m, 1H), 2.38 (s, 3H), 2.27 (dd, *J* = 13.2, 4.4 Hz, 1H), 1.99 (t, *J* = 12.5 Hz, 1H), 0.73 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.9, 152.1, 145.6, 145.5, 143.7, 139.7, 136.1, 135.2, 133.7, 133.0, 132.8, 129.8, 129.4, 129.3, 128.7, 128.6, 128.5, 127.9, 127.3, 127.1, 126.5, 125.6, 118.9, 60.3, 47.1, 40.3, 39.4, 21.7, 13.5.

**IR** (KBr, cm<sup>-1</sup>): 3462, 3363, 2188, 1712, 1636, 1599, 1492, 1400, 1253, 1171, 1089, 1010, 752, 701, 663, 564, 536.

**HRMS (ESI)** *m/z* Calcd for [C<sub>38</sub>H<sub>31</sub>ClN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup> : 660.1729, Found: 660.1727.

**Ethyl (4aR,6R)-3-amino-4-cyano-4a-(4-fluorophenyl)-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3pa)**



Combined Yield: 68% (43.8 mg), dr = 3.8:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 218-219 °C

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 2.2 Hz, 1H), 7.51 (dt, *J* = 13.0, 7.0 Hz, 5H), 7.20 – 7.07 (m, 7H), 6.89 (dd, *J* = 10.5, 5.5 Hz, 6H), 5.33 (s, 2H), 3.90 (tt, *J* = 14.3, 7.1 Hz, 1H), 3.74 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.06 (d, *J* = 11.3 Hz, 1H), 2.34 (s, 3H), 2.30 (dd, *J* = 13.2, 4.2 Hz, 1H), 1.99 (t, *J* = 12.5 Hz, 1H), 0.73 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.0, 163.0, 160.5, 152.0, 145.3, 143.7, 142.6, 139.6, 136.1, 135.2, 133.9, 133.0, 129.8, 129.3, 128.5, 128.5, 127.9, 127.5, 127.4, 127.1, 126.5, 125.9, 118.9, 115.5, 115.3, 60.3, 47.3, 40.2, 39.4, 21.6, 13.5.

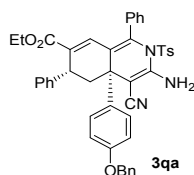
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -115.36.

**IR** (KBr, cm<sup>-1</sup>): 3462, 2188, 1711, 1637, 1600, 1505, 1393, 1254, 1188, 1086, 1012, 806, 751, 701, 663, 591, 561.

**HRMS (ESI)** *m/z* Calcd for [C<sub>38</sub>H<sub>31</sub>FN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup> : 644.2025, Found: 644.2022.

**Ethyl (4aR,6R)-3-amino-4a-(4-(benzyloxy)phenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3qa)**





Combined Yield: 53% (38.6 mg), dr = 3.7:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 192-193 °C

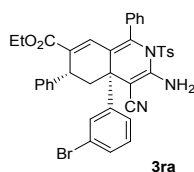
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.62 (d, *J* = 2.5 Hz, 1H), 7.54 (dt, *J* = 13.4, 7.3 Hz, 6H), 7.46 (t, *J* = 7.4 Hz, 3H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.12 (ddd, *J* = 14.5, 11.1, 6.4 Hz, 7H), 6.89 (dd, *J* = 14.7, 7.8 Hz, 4H), 6.79 (d, *J* = 8.2 Hz, 2H), 5.22 (s, 2H), 5.13 (s, 2H), 3.90 (ddd, *J* = 14.3, 9.0, 5.4 Hz, 1H), 3.74 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.15 – 3.07 (m, 1H), 2.34 (d, *J* = 4.4 Hz, 1H), 2.31 (s, 3H), 1.97 (t, *J* = 12.5 Hz, 1H), 0.74 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.1, 157.8, 151.6, 144.9, 144.0, 139.3, 138.9, 136.8, 135.9, 135.2, 133.7, 133.1, 129.9, 129.2, 129.2, 128.8, 128.5, 128.4, 128.3, 128.0, 127.7, 127.1, 127.0, 126.3, 125.9, 119.1, 114.8, 70.2, 60.2, 47.3, 40.1, 39.4, 21.7, 13.5.

**IR** (KBr, cm<sup>-1</sup>): 3455, 3378, 2925, 2187, 1709, 1637, 1602, 1507, 1391, 1246, 1170, 1085, 1026, 735, 699, 662, 560.

**HRMS (ESI)** *m/z* Calcd for [C<sub>45</sub>H<sub>38</sub>N<sub>3</sub>O<sub>5</sub>S, M - H]<sup>-</sup> : 732.2538, Found: 732.2535.

**Ethyl (4aR,6R)-3-amino-4a-(3-bromophenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ra)**



Combined Yield: 84% (59.4 mg), dr = 3.6:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 182-183 °C

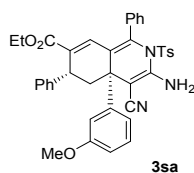
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 2.4 Hz, 1H), 7.52 (dt, *J* = 14.6, 7.0 Hz, 5H), 7.43 (d, *J* = 6.9 Hz, 1H), 7.16 (dd, *J* = 19.7, 11.1 Hz, 6H), 6.90 (dd, *J* = 7.2, 3.7 Hz, 8H), 5.35 (s, 2H), 3.91 (tt, *J* = 14.3, 7.1 Hz, 1H), 3.80 – 3.69 (m, 1H), 3.07 (d, *J* = 10.6 Hz, 1H), 2.36 (s, 3H), 2.30 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.00 (t, *J* = 12.6 Hz, 1H), 0.73 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.9, 152.0, 149.5, 145.4, 143.6, 139.8, 136.0, 135.1, 133.5, 132.9, 130.1, 129.8, 129.5, 129.4, 129.1, 128.6, 128.5, 127.9, 127.1, 126.5, 125.2, 124.5, 123.2, 118.7, 60.3, 47.1, 40.5, 39.3, 21.8, 13.5.

**IR** (KBr, cm<sup>-1</sup>): 3462, 3378, 2188, 1711, 1636, 1598, 1395, 1368, 1251, 1170, 1085, 1029, 778, 700, 663, 608, 563, 538.

**HRMS (ESI)** *m/z* Calcd for [C<sub>38</sub>H<sub>31</sub>BrN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup> : 704.1224, Found: 704.1221.

**Ethyl (4aR,6R)-3-amino-4-cyano-4a-(3-methoxyphenyl)-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3sa)**



Combined Yield: 69% (45.6 mg), dr = 3.9:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 191-193 °C

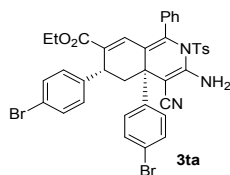
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 7.1 Hz, 2H), 7.54 – 7.43 (m, 3H), 7.15 (ddd, *J* = 19.7, 15.1, 8.0 Hz, 6H), 6.91 (d, *J* = 6.9 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 4H), 6.65 (s, 1H), 5.25 (s, 2H), 3.90 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.77 (s, 3H), 3.76 – 3.69 (m, 1H), 3.14 (dd, *J* = 7.9, 2.6 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.32 (s, 3H), 2.00 (dd, *J* = 24.7, 12.3 Hz, 1H), 0.73 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.1, 159.7, 151.7, 148.4, 144.9, 144.0, 139.4, 135.9, 135.2, 133.6, 133.1, 129.9, 129.5, 129.3, 128.5, 128.4, 128.0, 127.2, 126.3, 125.7, 119.0, 118.3, 112.6, 111.3, 77.6, 77.4, 77.1, 76.7, 60.3, 55.0, 47.1, 40.8, 39.5, 21.6, 13.5.

**IR** (KBr, cm<sup>-1</sup>): 3462, 3378, 2188, 1711, 1637, 1599, 1492, 1394, 1253, 1169, 1086, 1017, 766, 751, 700, 663, 607, 563, 537.

**HRMS (ESI)** *m/z* Calcd for [C<sub>39</sub>H<sub>34</sub>N<sub>3</sub>O<sub>5</sub>S, M - H]<sup>-</sup> : 656.2225, Found: 656.2221.

**Ethyl (4aR,6R)-3-amino-4a,6-bis(4-bromophenyl)-4-cyano-1-phenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ta)**



Combined Yield: 92% (72.4 mg), dr = 5.2:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 203-204 °C

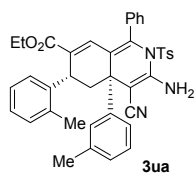
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.63 (d, *J* = 2.2 Hz, 1H), 7.53 (d, *J* = 6.7 Hz, 5H), 7.31 (dd, *J* = 12.9, 8.5 Hz, 4H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 5.39 (d, *J* = 3.5 Hz, 2H), 3.98 – 3.87 (m, 1H), 3.78 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.04 (dd, *J* = 7.9, 2.6 Hz, 1H), 2.40 (s, 3H), 2.23 (dd, *J* = 13.2, 4.4 Hz, 1H), 1.94 (t, *J* = 12.5 Hz, 1H), 0.81 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.6, 152.0, 145.9, 145.6, 142.8, 140.1, 135.1, 133.5, 131.7, 131.6, 129.8, 129.5, 129.4, 128.9, 128.6, 127.9, 127.6, 125.2, 121.2, 120.2, 118.8, 60.5, 46.9, 40.2, 38.8, 21.7, 13.6.

**IR** (KBr, cm<sup>-1</sup>): 3466, 3437, 3365, 2188, 1711, 1636, 1598, 1488, 1399, 1247, 1170, 1085, 1008, 814, 777, 739, 700, 663, 579, 563, 537.

**HRMS (ESI)** *m/z* Calcd for [C<sub>38</sub>H<sub>30</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup> : 784.0309, Found: 784.0307.

**Ethyl (4aR,6R)-3-amino-4-cyano-1-phenyl-4a-(*m*-tolyl)-6-(*o*-tolyl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ua)**



Combined Yield: 63% (41.2 mg), dr = 3.9:1

White solid with slight yellow; m.p. 200-201 °C

The major isomer was not available even after recrystallization.

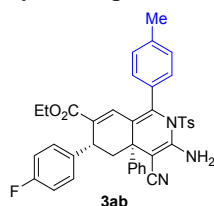
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ(major) 7.62 – 7.57 (m, 3H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.06 (dd, *J* = 13.7, 7.9 Hz, 3H), 6.98 (d, *J* = 9.7 Hz, 4H), 6.80 (d, *J* = 8.1 Hz, 3H), 5.20 (s, 2H), 3.88 (tt, *J* = 14.2, 7.1 Hz, 1H), 3.74 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.39 – 3.28 (m, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.29 – 2.23 (m, 1H), 1.92 (d, *J* = 12.4 Hz, 1H), 1.87 (s, 3H), 0.72 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ(major) 167.2, 151.6, 146.5, 144.7, 142.2, 139.1, 138.3, 136.7, 135.3, 135.0, 133.7, 132.8, 130.1, 129.9, 129.2, 128.5, 128.4, 128.0, 127.7, 126.4, 126.3, 126.1, 125.8, 125.5, 122.9, 119.2, 60.2, 45.9, 40.7, 34.4, 21.8, 21.6, 18.7, 13.4.

**IR** (KBr, cm<sup>-1</sup>): 3464, 3378, 2924, 2188, 1711, 1637, 1600, 1394, 1249, 1170, 1086, 1025, 765, 701, 663, 611, 568, 518.

**HRMS (ESI)** m/z Calcd for [C<sub>40</sub>H<sub>36</sub>N<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup>: 654.2432, Found: 654.2430.

**Ethyl (4aR,6R)-3-amino-4-cyano-6-(4-fluorophenyl)-4a-phenyl-1-(p-tolyl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ab)**



Combined Yield: 88% (58.4 mg), dr = 3.7:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 136-138 °C

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 2.6 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 3H), 7.30 – 7.26 (m, 2H), 7.22 – 7.16 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 7.0 Hz, 4H), 6.78 (d, *J* = 8.1 Hz, 2H), 5.22 (s, 2H), 3.92 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.77 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.07 (ddd, *J* = 11.8, 4.4, 2.6 Hz, 1H), 2.44 (s, 3H), 2.36 – 2.31 (m, 1H), 2.30 (s, 3H), 1.96 (dd, *J* = 12.9, 12.1 Hz, 1H), 0.79 (t, *J* = 7.1 Hz, 3H).

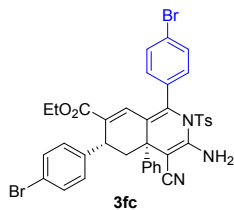
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.0, 162.6, 160.2, 151.8, 146.6, 144.8, 139.9, 139.9, 139.8, 139.4, 135.0, 133.7, 133.6, 132.2, 129.7, 129.3, 129.3, 128.8, 128.6, 128.5, 127.9, 126.9, 125.9, 125.0, 119.1, 115.3, 115.1, 60.3, 47.4, 40.6, 38.7, 21.6, 21.5, 13.6.

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -116.68, -116.70, -116.72.

**IR** (KBr, cm<sup>-1</sup>): 3464, 3375, 2188, 1710, 1637, 1600, 1509, 1394, 1250, 1170, 1102, 1086, 1015, 830, 764, 741, 699, 663, 583, 560, 535.

**HRMS (ESI)** m/z Calcd for [C<sub>39</sub>H<sub>33</sub>FN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup>: 658.2181, Found: 658.2178.

**Ethyl (4aR,6R)-3-amino-1-(4-bromophenyl)-4-cyano-6-(4-fluorophenyl)-4a-phenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3fc)**



Combined Yield: 74% (58.2 mg), dr = 2.9:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 157-159 °C

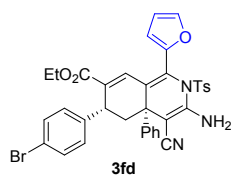
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.20 (dd, *J* = 15.3, 7.4 Hz, 5H), 7.09 (d, *J* = 7.4 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.71 (dd, *J* = 7.7, 3.8 Hz, 4H), 5.17 (s, 2H), 3.94 – 3.81 (m, 1H), 3.79 – 3.65 (m, 1H), 2.97 (d, *J* = 11.0 Hz, 1H), 2.27 (d, *J* = 4.2 Hz, 1H), 2.23 (s, 3H), 1.87 (s, 1H), 0.75 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.6, 151.5, 146.3, 145.1, 143.0, 138.5, 135.6, 134.1, 133.3, 133.0, 131.9, 131.6, 131.4, 129.5, 128.8, 127.9, 127.0, 125.8, 125.7, 123.6, 120.1, 118.9, 60.5, 47.1, 40.6, 39.0, 21.7, 13.7.

**IR** (KBr, cm<sup>-1</sup>): 3466, 3366, 2188, 1711, 1637, 1598, 1488, 1395, 1250, 1170, 1103, 1012, 835, 757, 700, 663, 564, 538.

**HRMS (ESI)** *m/z* Calcd for [C<sub>38</sub>H<sub>30</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup>: 784.0309, Found: 784.0308.

**Ethyl (4aR,6R)-3-amino-6-(4-bromophenyl)-4-cyano-1-(furan-2-yl)-4a-phenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3fd)**



Combined Yield: 87% (60.6 mg), dr = 4.2:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 146-149 °C

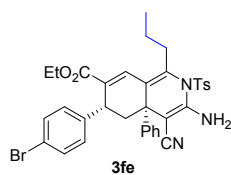
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.03 (d, *J* = 1.9 Hz, 1H), 7.65 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 3H), 7.27 – 7.21 (m, 2H), 7.15 – 7.05 (m, 4H), 6.86 – 6.72 (m, 5H), 6.62 (s, 1H), 5.21 (s, 2H), 3.98 (td, *J* = 14.2, 7.1 Hz, 1H), 3.85 (td, *J* = 14.2, 7.1 Hz, 1H), 3.04 (d, *J* = 10.9 Hz, 1H), 2.33 (d, *J* = 4.4 Hz, 1H), 2.29 (s, 3H), 1.95 (t, *J* = 12.5 Hz, 1H), 0.88 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.7, 151.2, 147.4, 146.1, 145.0, 143.6, 143.1, 135.6, 133.1, 132.9, 131.6, 129.5, 129.3, 128.9, 128.8, 128.2, 127.0, 126.1, 125.8, 120.1, 118.9, 113.5, 112.0, 60.5, 47.3, 40.9, 38.9, 21.6, 13.7.

**IR** (KBr, cm<sup>-1</sup>): 3461, 3378, 2188, 1711, 1637, 1598, 1489, 1398, 1366, 1255, 1171, 1085, 1013, 829, 747, 703, 663, 583, 563, 537.

**HRMS (ESI)** *m/z* Calcd for [C<sub>36</sub>H<sub>29</sub>BrN<sub>3</sub>O<sub>5</sub>S, M - H]<sup>-</sup>: 694.1017, Found: 694.1014.

**Ethyl (4aR,6R)-3-amino-6-(4-bromophenyl)-4-cyano-4a-phenyl-1-propyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3fe)**



Combined Yield: 15% (10.2 mg), dr = 3.4:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 208-209 °C

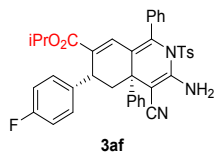
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.68 (d, *J* = 2.2 Hz, 1H), 7.23 (s, 1H), 7.19 (s, 2H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 7.5 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 2H), 4.98 (s, 2H), 3.93 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.78 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.08 (ddd, *J* = 14.5, 8.6, 5.8 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.88 (d, *J* = 9.4 Hz, 1H), 2.36 (d, *J* = 3.6 Hz, 1H), 2.29 (dd, *J* = 13.2, 4.6 Hz, 1H), 1.79 (dt, *J* = 14.4, 9.6 Hz, 2H), 1.71 – 1.63 (m, 1H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 4H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.7, 151.8, 145.4, 144.9, 143.2, 142.3, 134.2, 133.4, 132.8, 131.5, 129.3, 128.9, 128.6, 128.0, 127.5, 126.7, 125.9, 120.0, 119.2, 60.6, 47.6, 41.0, 39.2, 33.5, 23.3, 21.6, 13.7.

**IR** (KBr, cm<sup>-1</sup>): 3465, 2926, 2187, 1711, 1640, 1393, 1262, 1231, 1163, 1013, 753, 699, 665, 694, 548.

**HRMS (ESI)** *m/z* Calcd for [C<sub>35</sub>H<sub>33</sub>BrN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup>: 670.1381, Found: 670.1378.

**isopropyl (4aR,6R)-3-amino-4-cyano-6-(4-fluorophenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3af)**



Combined Yield: 64% (42.4 mg), dr = 5:1

The major isomer was not available even after recrystallization.

White solid with slight yellow; m.p. 140-142 °C

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ(major) 7.60 (d, *J* = 2.4 Hz, 1H), 7.56 (d, *J* = 7.1 Hz, 2H), 7.52 – 7.42 (m, 3H), 7.32 – 7.24 (m, 2H), 7.24 (s, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 7.0 Hz, 4H), 6.77 (d, *J* = 8.1 Hz, 2H), 5.20 (s, 2H), 4.70 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.04 (dd, *J* = 7.7, 2.6 Hz, 1H), 2.32 (dd, *J* = 13.2, 4.5 Hz, 1H), 2.28 (s, 3H), 1.94 (t, *J* = 12.5 Hz, 1H), 0.96 (d, *J* = 6.2 Hz, 3H), 0.61 (d, *J* = 6.2 Hz, 3H).

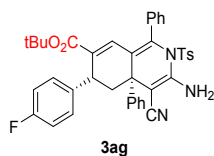
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ(major) 166.5, 162.7, 160.3, 151.7, 146.6, 144.9, 139.9, 139.9, 139.6, 135.8, 135.1, 133.6, 133.2, 129.9, 129.4, 129.3, 128.8, 128.6, 128.6, 128.5, 127.9, 126.9, 125.9, 125.5, 119.1, 115.3, 115.1, 67.9, 47.4, 40.6, 38.7, 21.6, 21.6, 20.8.

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -116.73, -116.75, -116.76.

**IR** (KBr, cm<sup>-1</sup>): 3665, 2926, 2188, 1706, 1638, 1599, 1509, 1393, 1256, 1144, 1087, 1013, 941, 839, 699, 664, 584, 560, 537.

**HRMS (ESI)** *m/z* Calcd for [C<sub>39</sub>H<sub>33</sub>FN<sub>3</sub>O<sub>4</sub>S, M - H]<sup>-</sup>: 658.2181, Found: 658.2178.

**tert-butyl (4aR,6R)-3-amino-4-cyano-6-(4-fluorophenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ag)**



Combined Yield: 53% (35.5 mg), dr = 5.8:1

The major isomer was not available even after recrystallization.

White solid with slight yellow; m.p. 129-131 °C

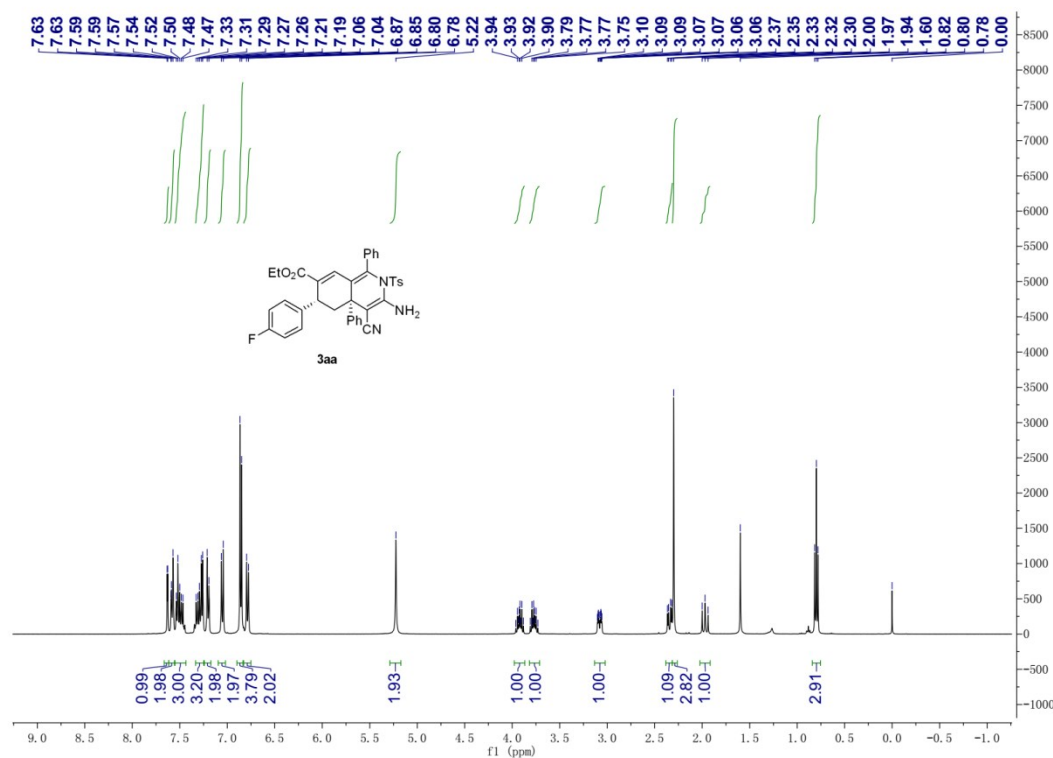
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ(major) 7.61 – 7.55 (m, 3H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.32 – 7.28 (m, 2H), 7.22 (d, *J* = 7.1 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.0 Hz, 4H), 6.79 (d, *J* = 8.1 Hz, 2H), 5.22 (s, 2H), 3.01 (dd, *J* = 7.6, 2.6 Hz, 1H), 2.36 – 2.31 (m, 1H), 2.30 (s, 3H), 1.94 (t, *J* = 12.5 Hz, 1H), 1.04 (s, 9H).

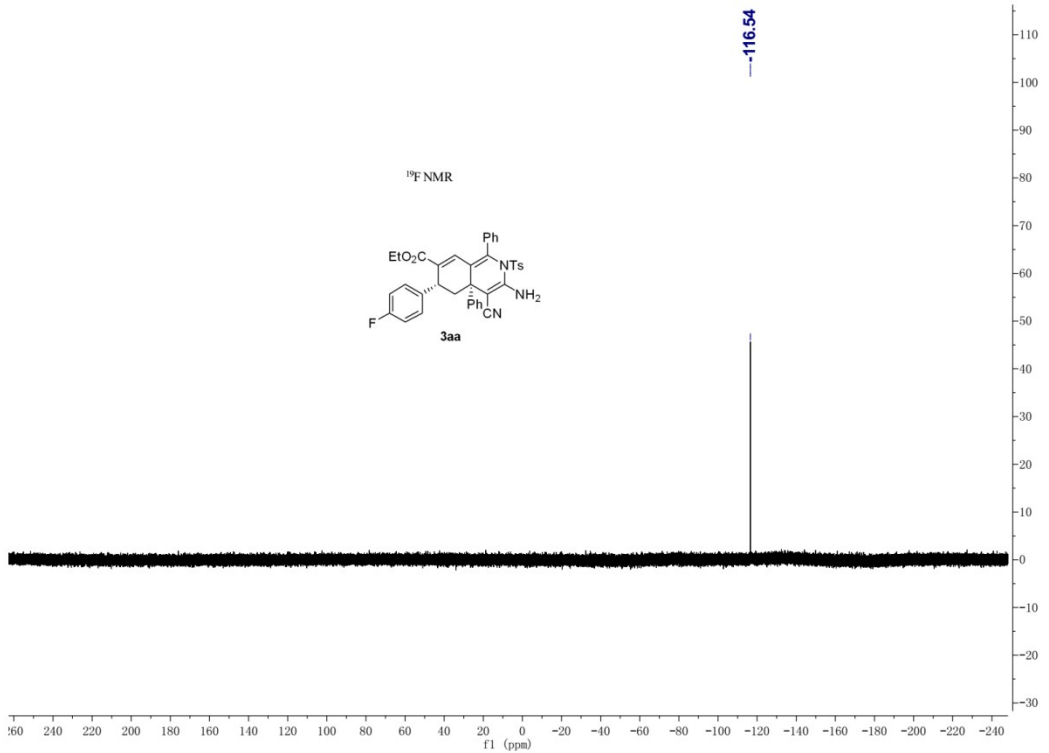
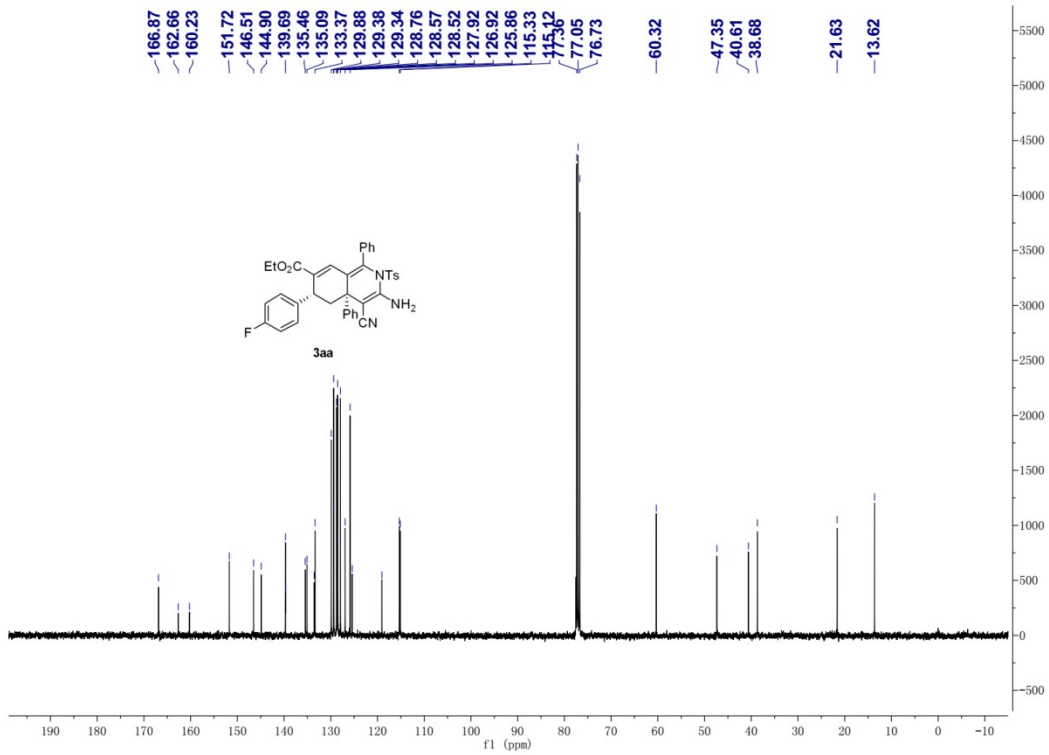
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ(major) 166.04, 162.67, 160.24, 151.79, 146.54, 144.82, 140.23, 140.20, 139.24, 136.79, 135.14, 134.07, 133.75, 132.73, 129.89, 129.37, 128.72, 128.46, 127.89, 126.81, 125.91, 119.08, 115.24, 115.03, 80.87, 47.63, 40.65, 38.87, 27.60, 21.60.

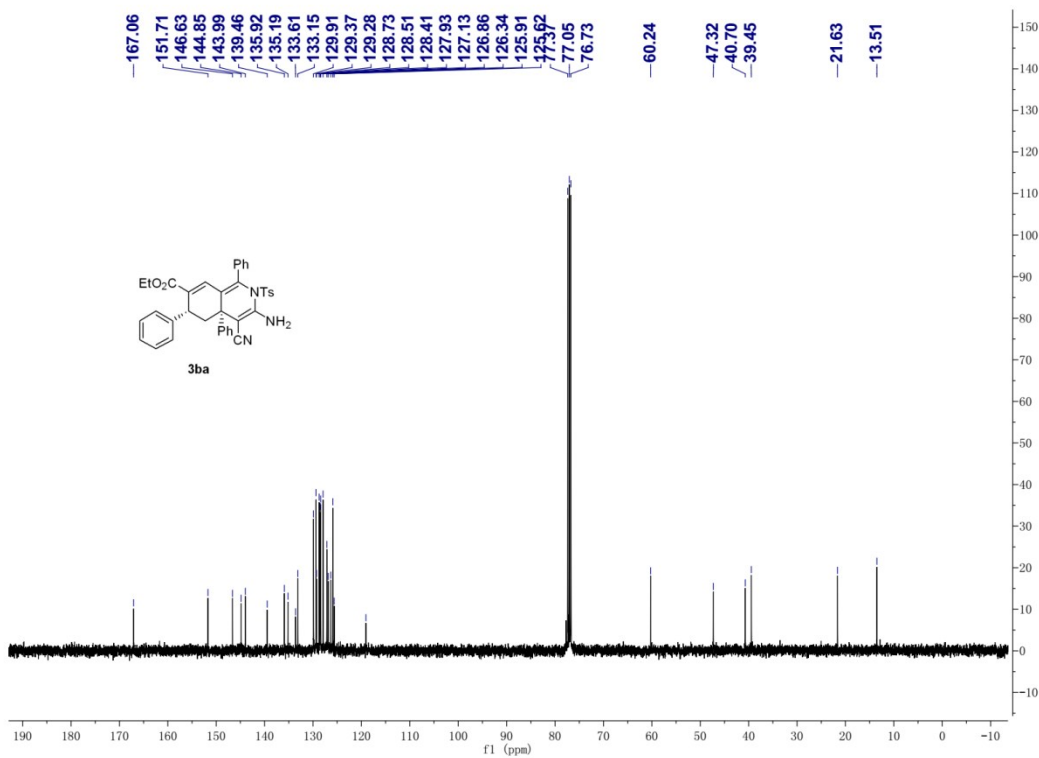
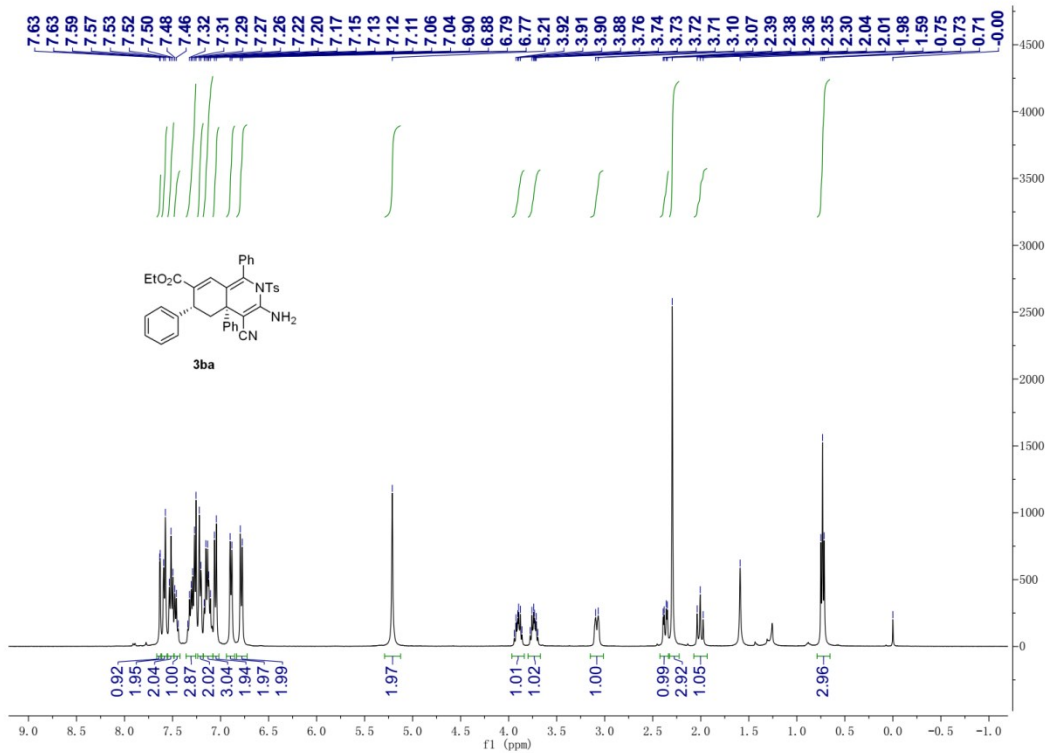
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -116.80, -116.81, -116.83, (-118.77 minor).

**IR** (KBr, cm<sup>-1</sup>): 3461, 3379, 2925, 2188, 1706, 1637, 1599, 1501, 1394, 1368, 1256, 1187, 1169, 1086, 1013, 838, 751, 700, 663, 583, 563, 539.

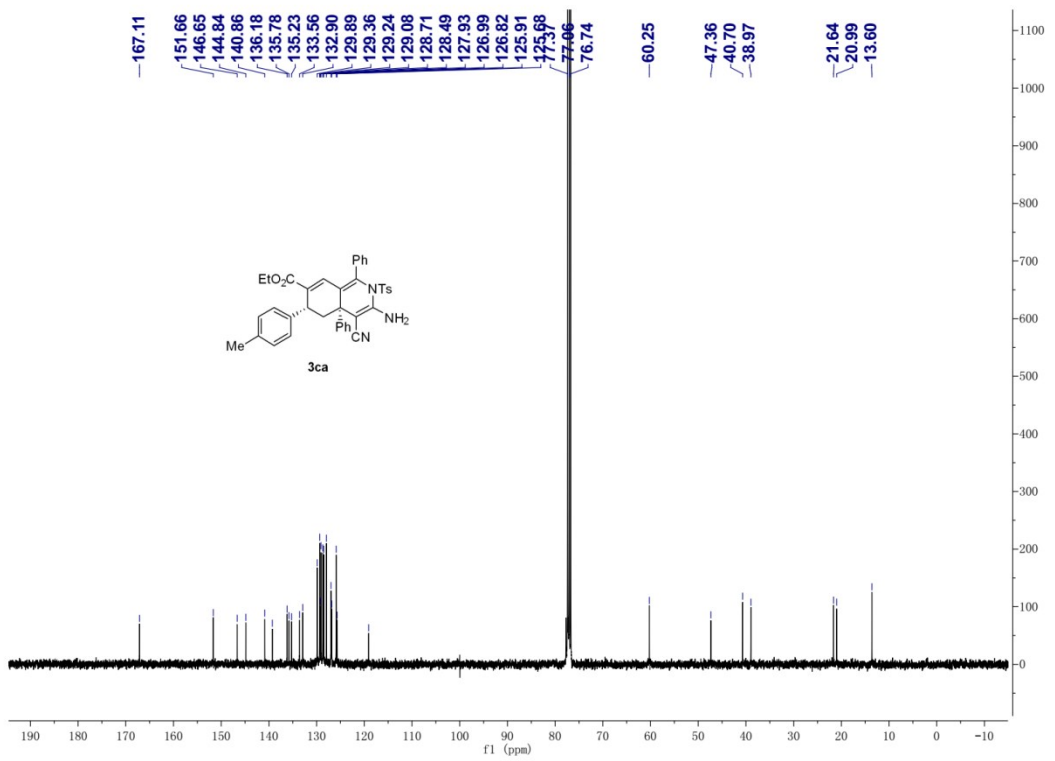
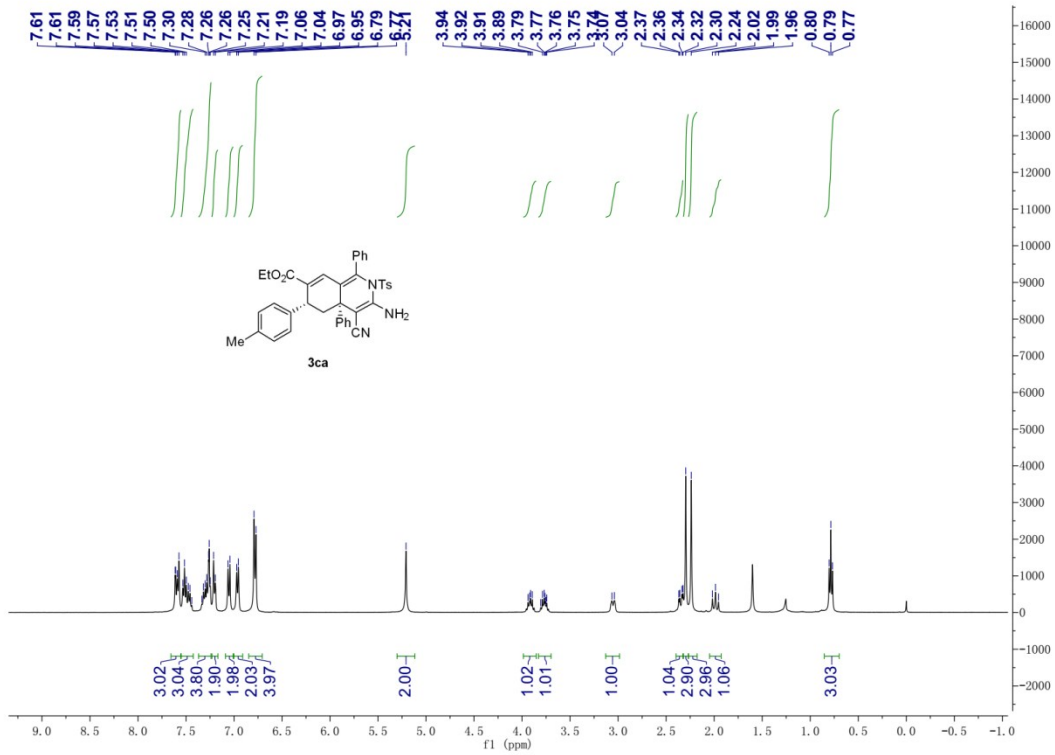
**HRMS (ESI)** m/z Calcd for [C<sub>39</sub>H<sub>33</sub>FN<sub>3</sub>O<sub>4</sub>S, M + H]<sup>+</sup> : 674.2483, Found: 674.2487.

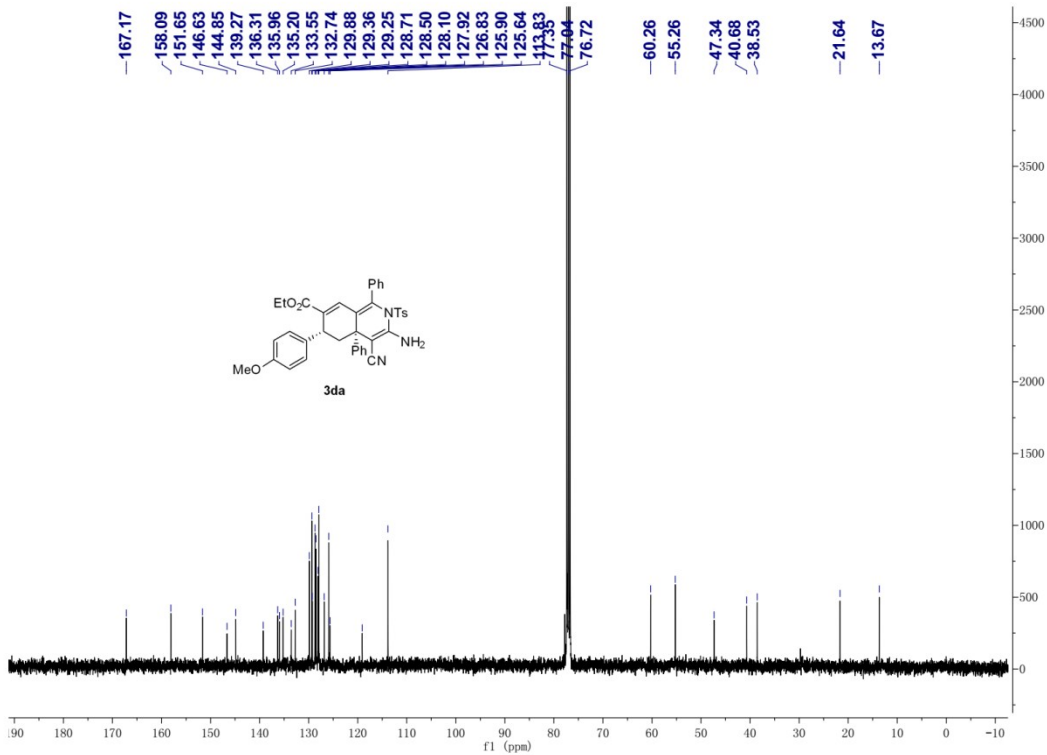
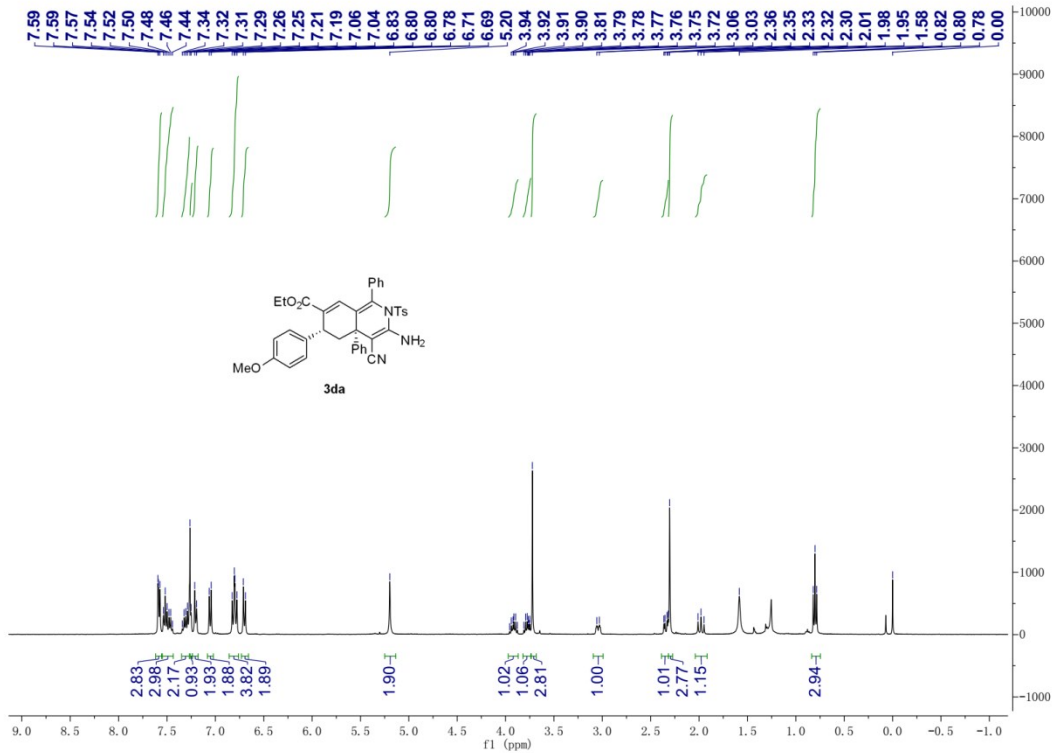


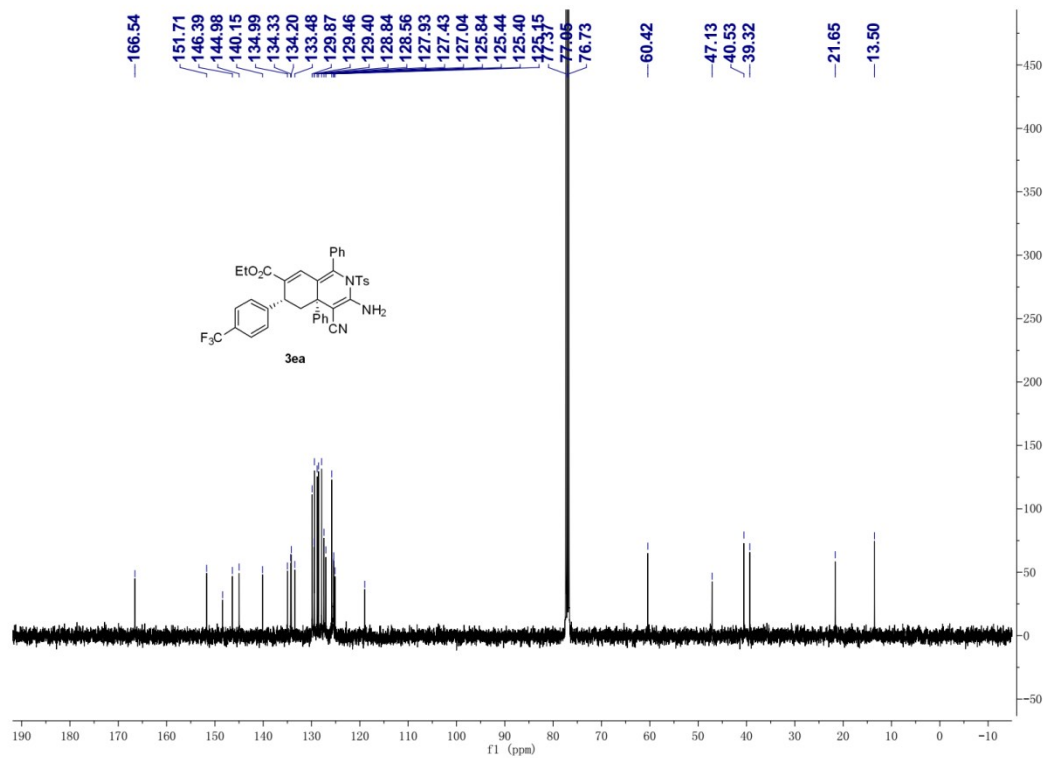
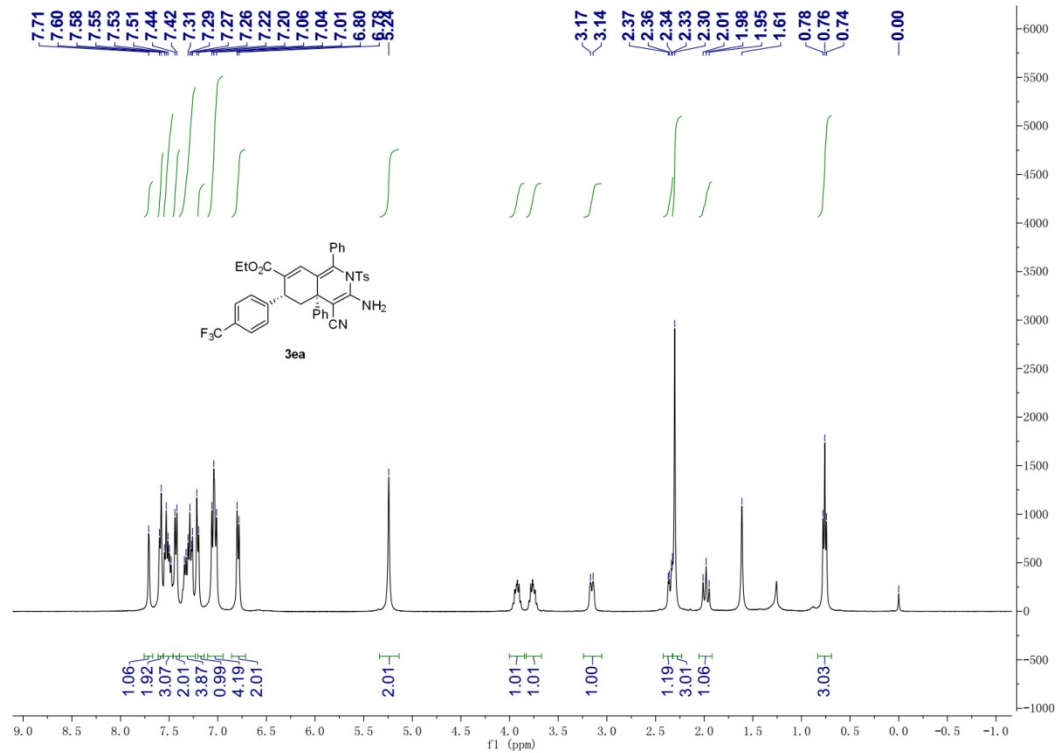


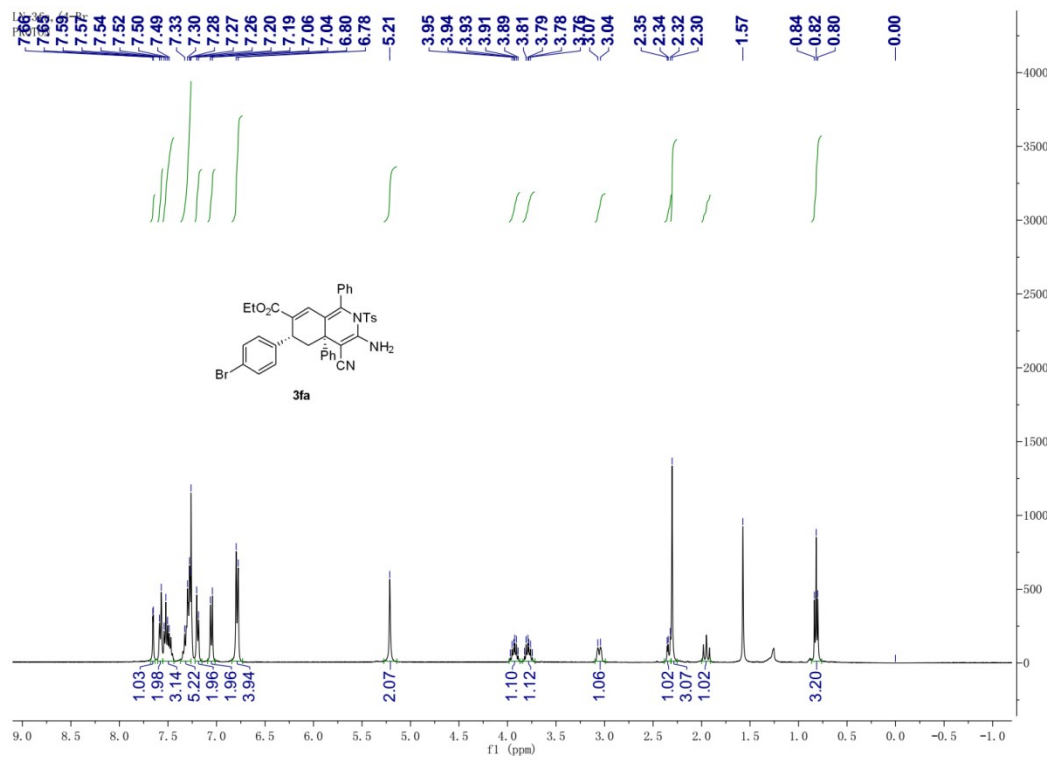
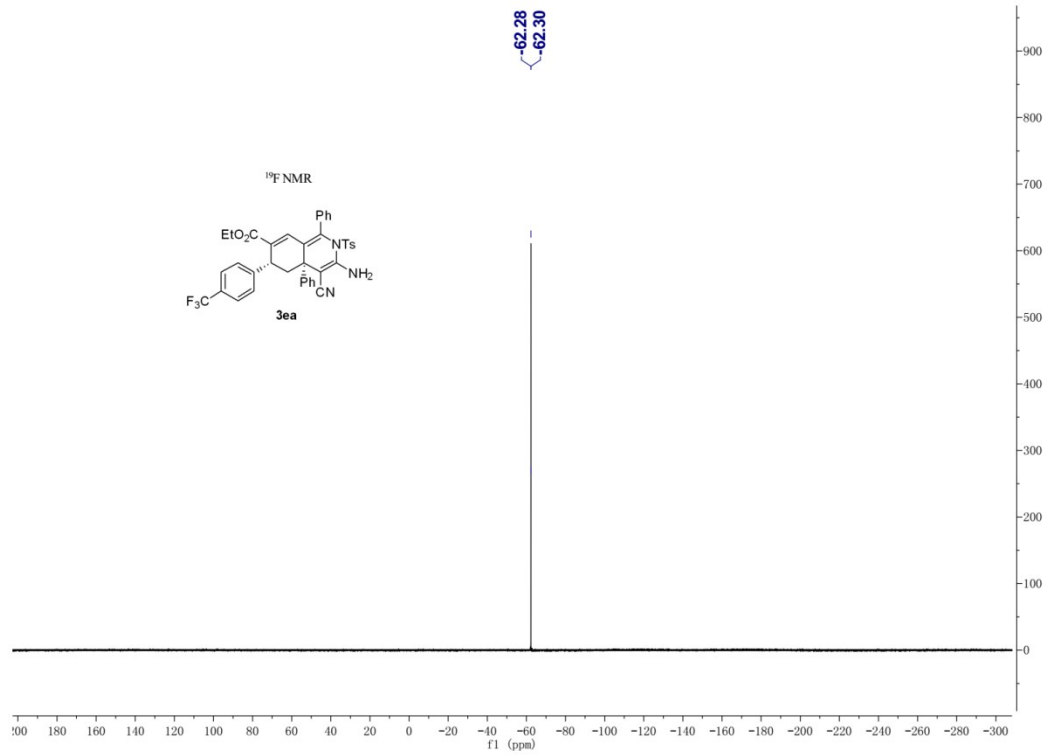


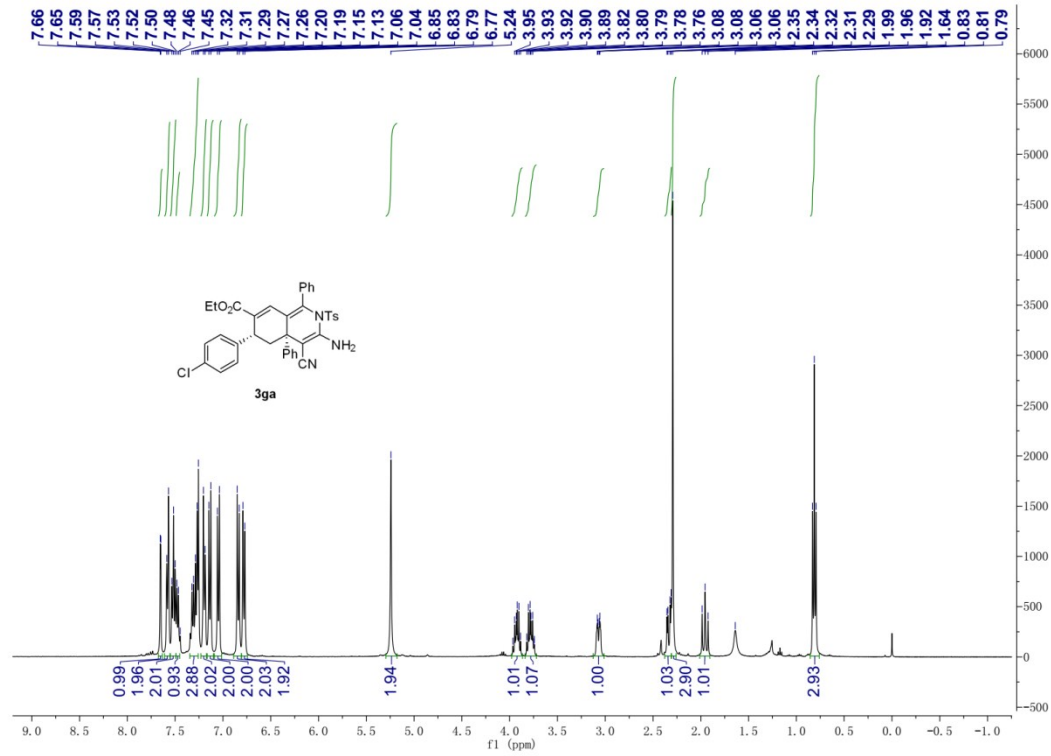
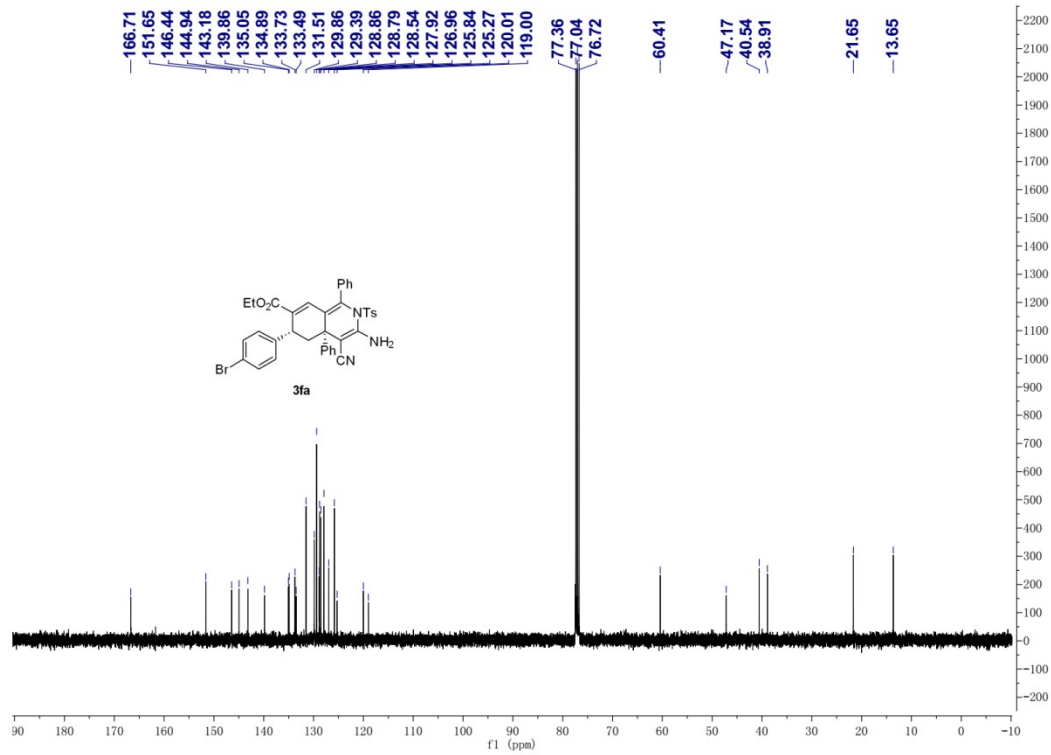


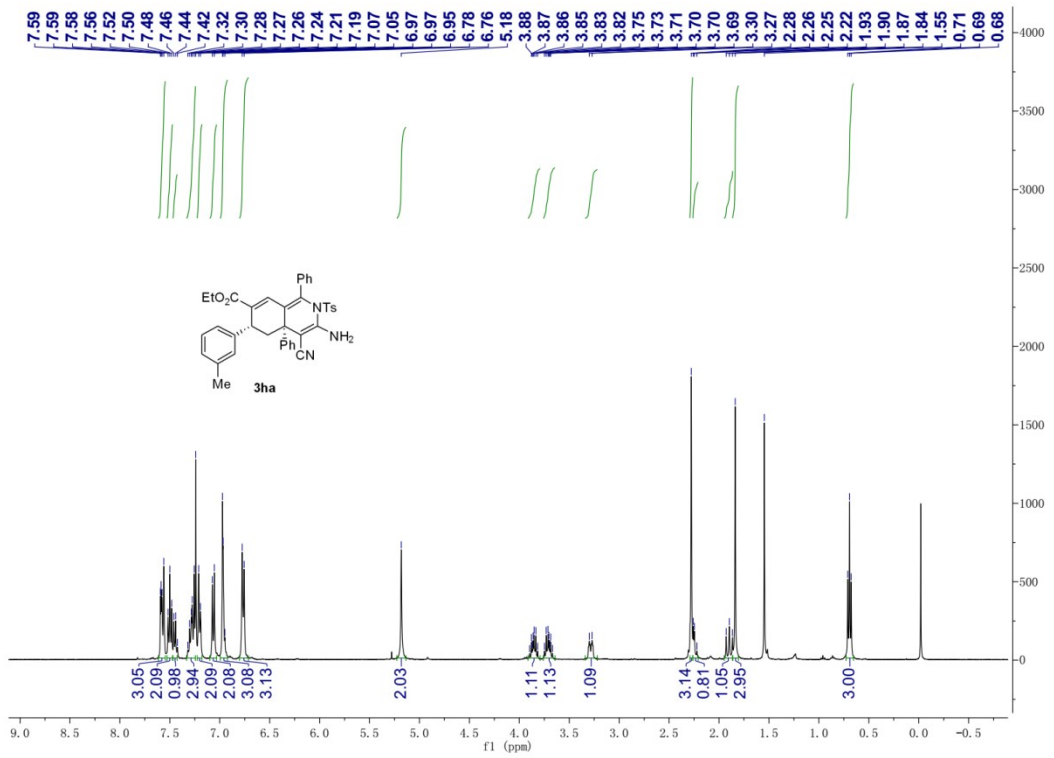
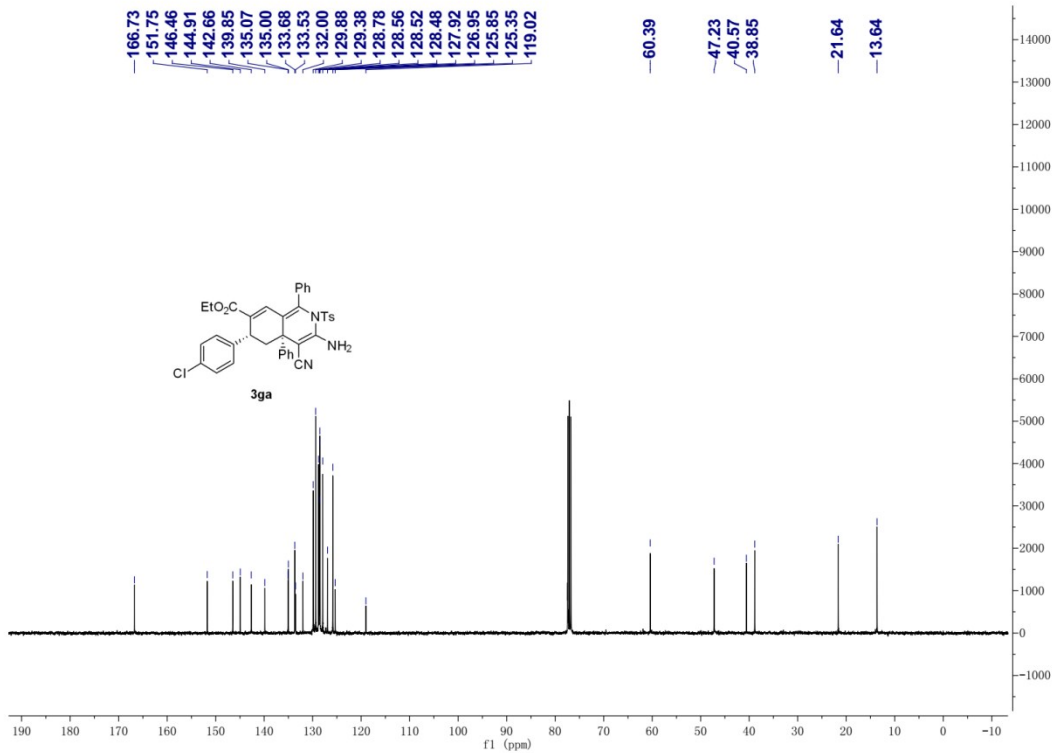




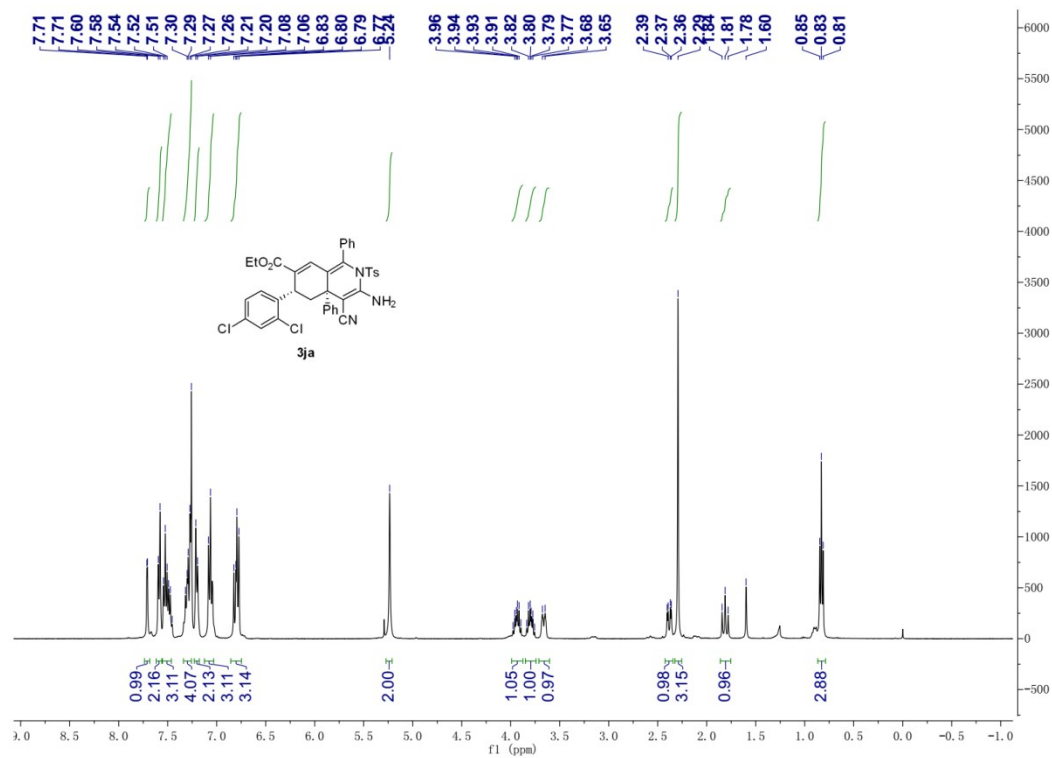
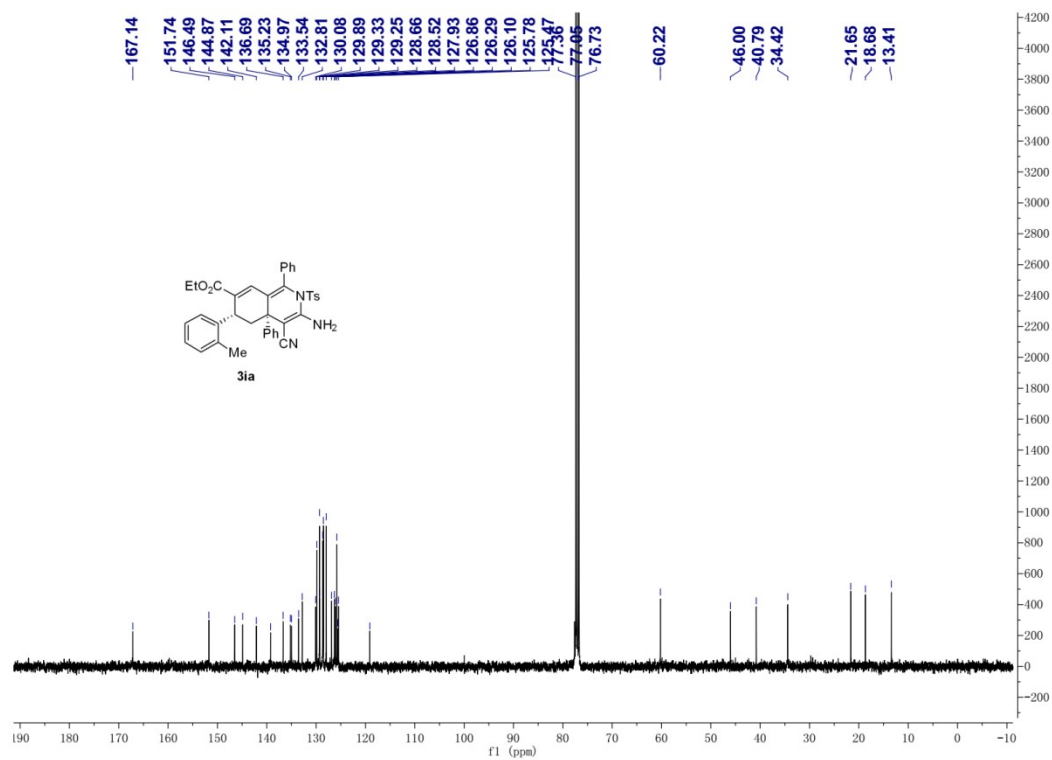




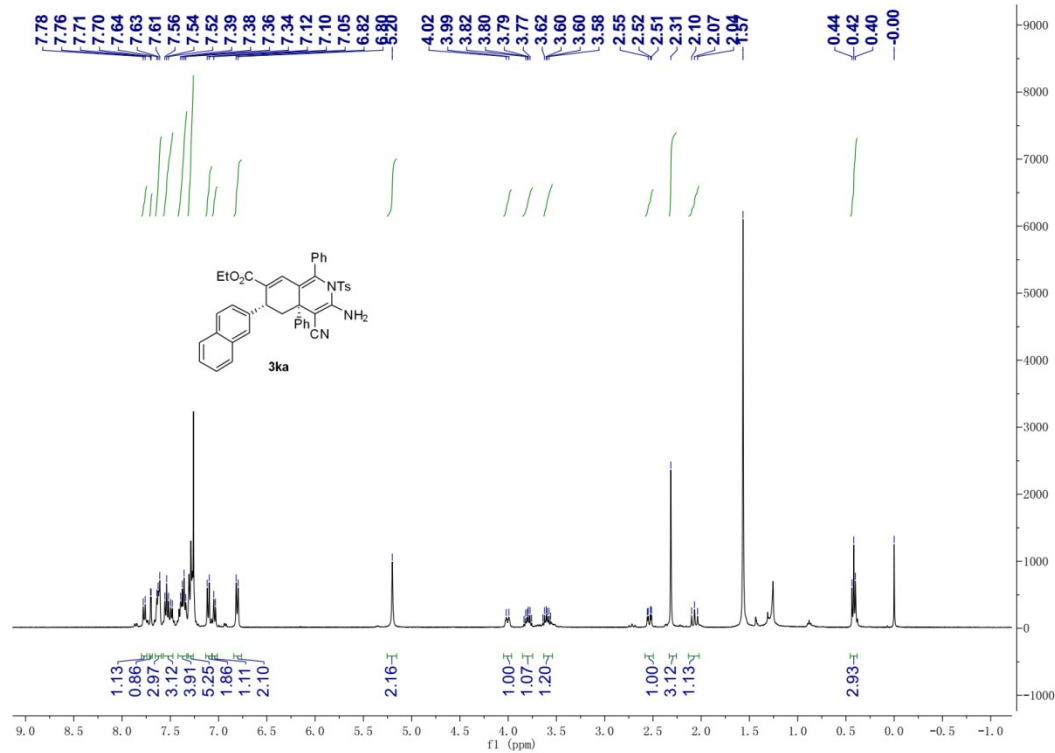
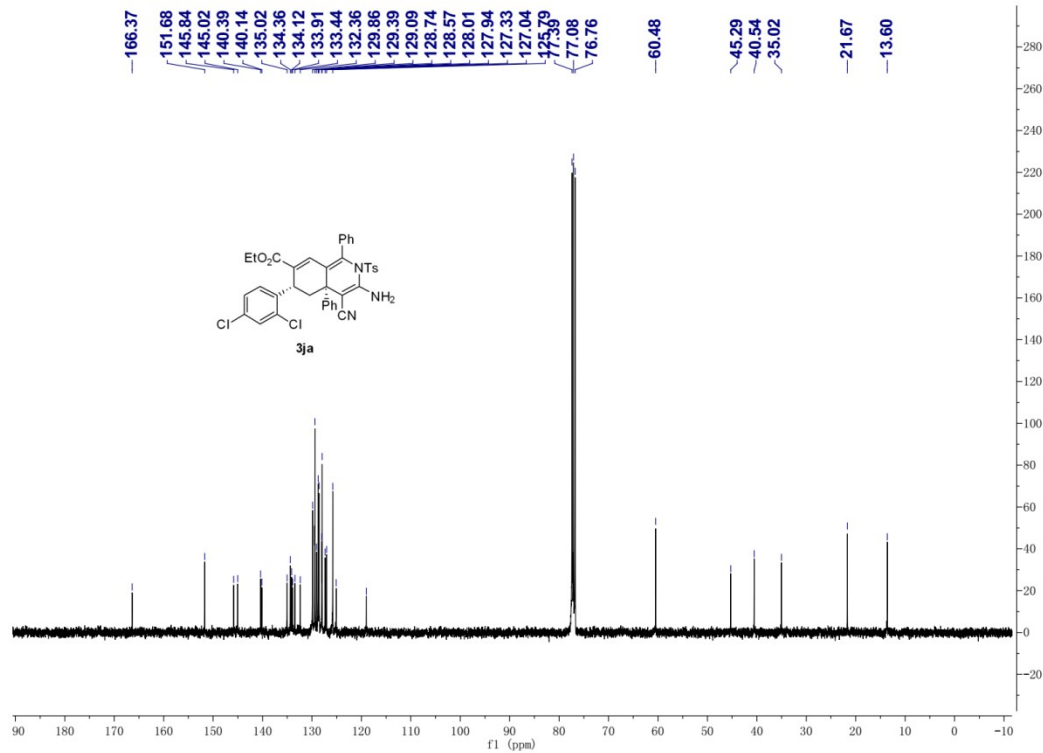


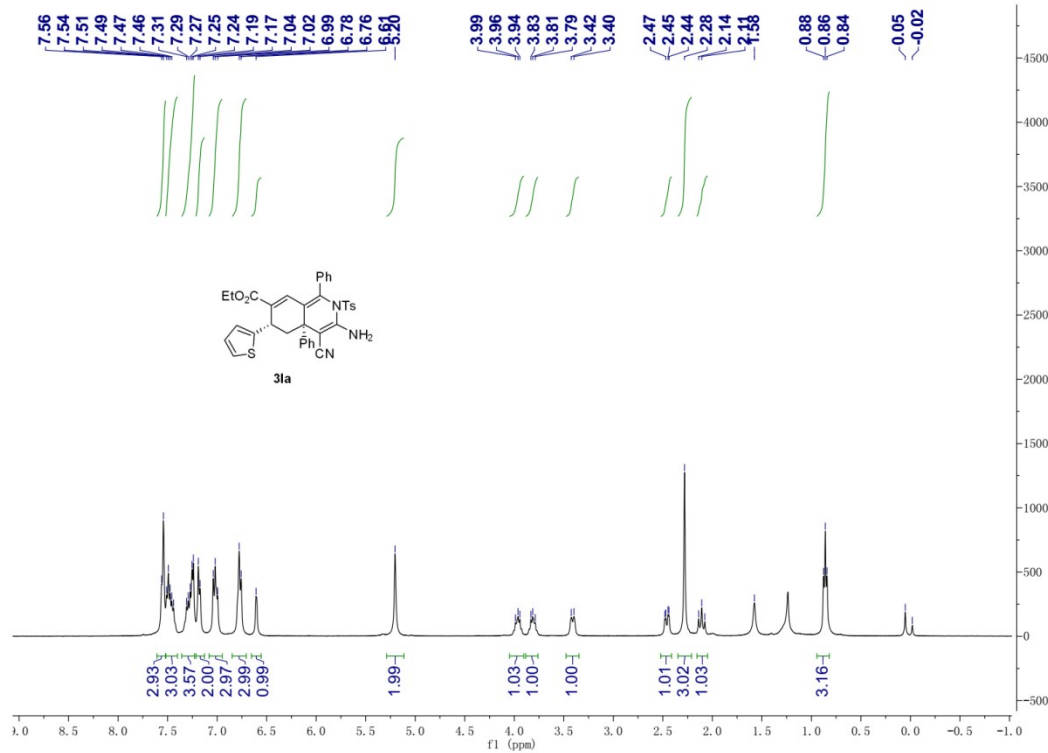
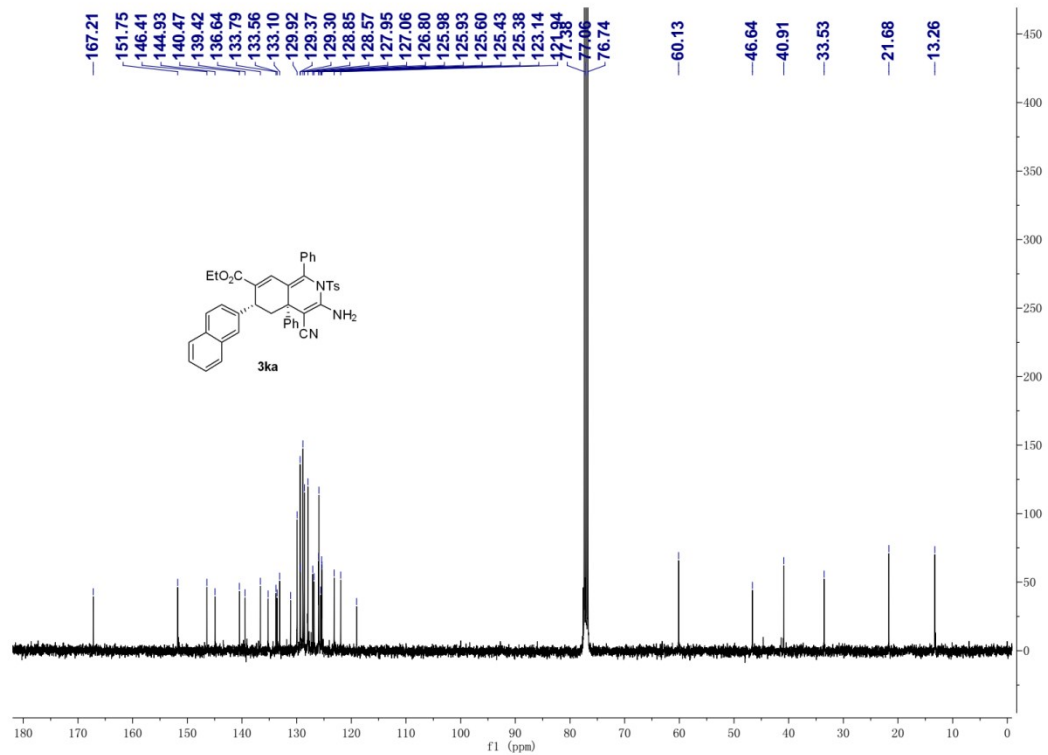


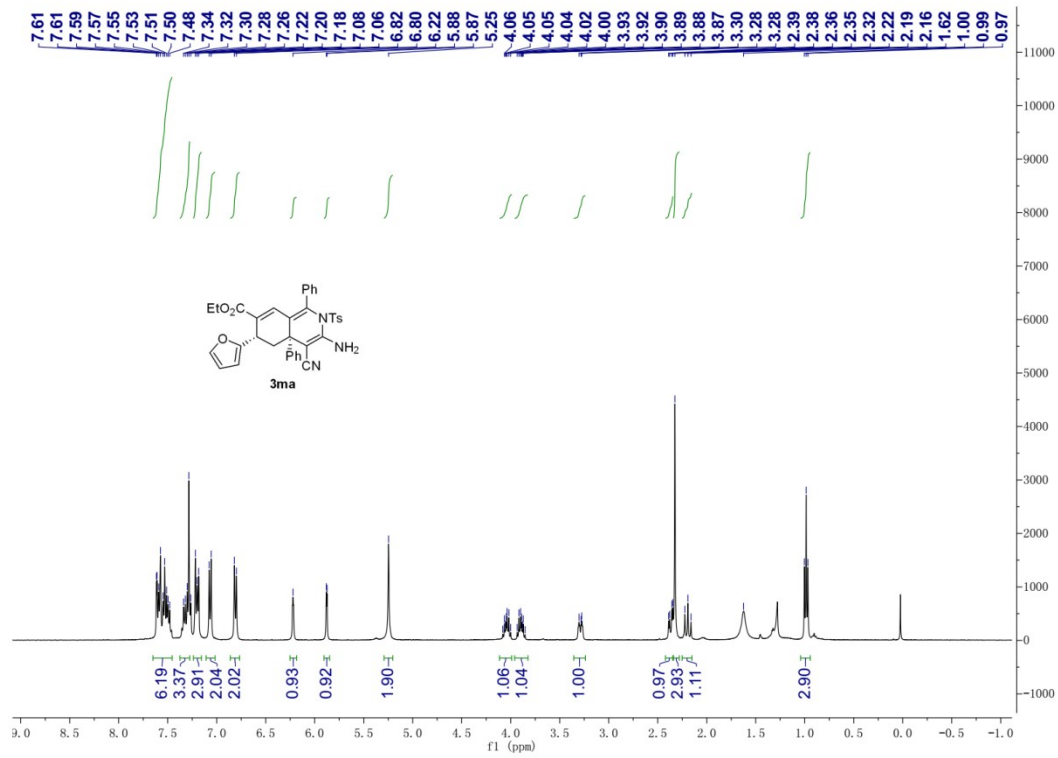
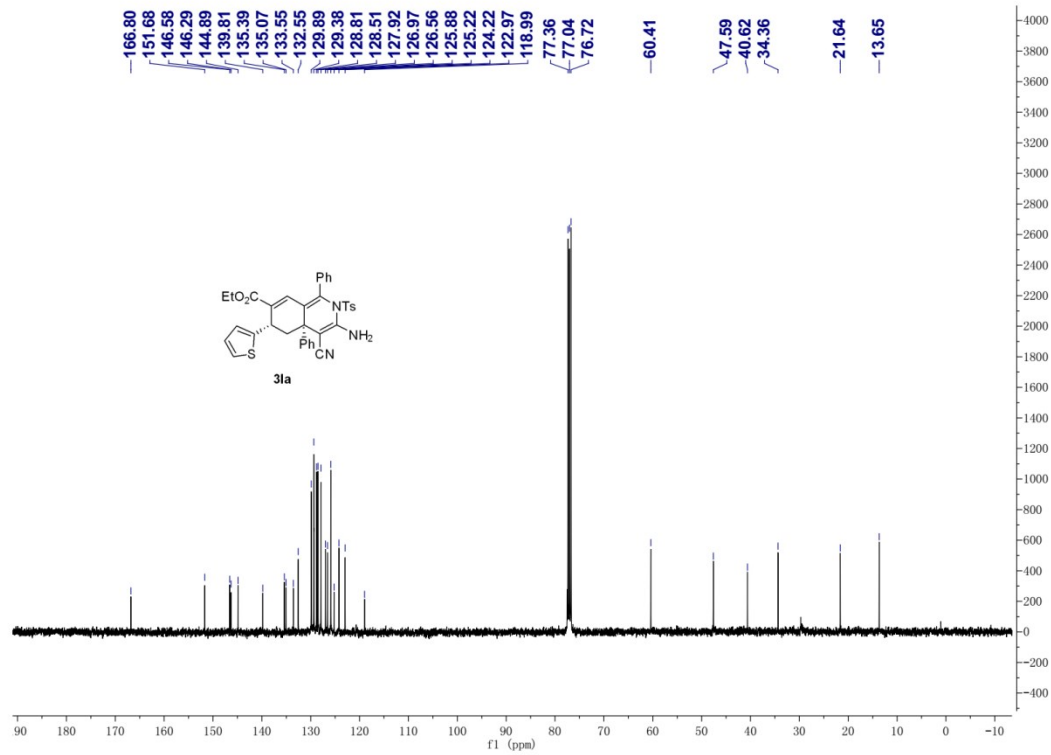


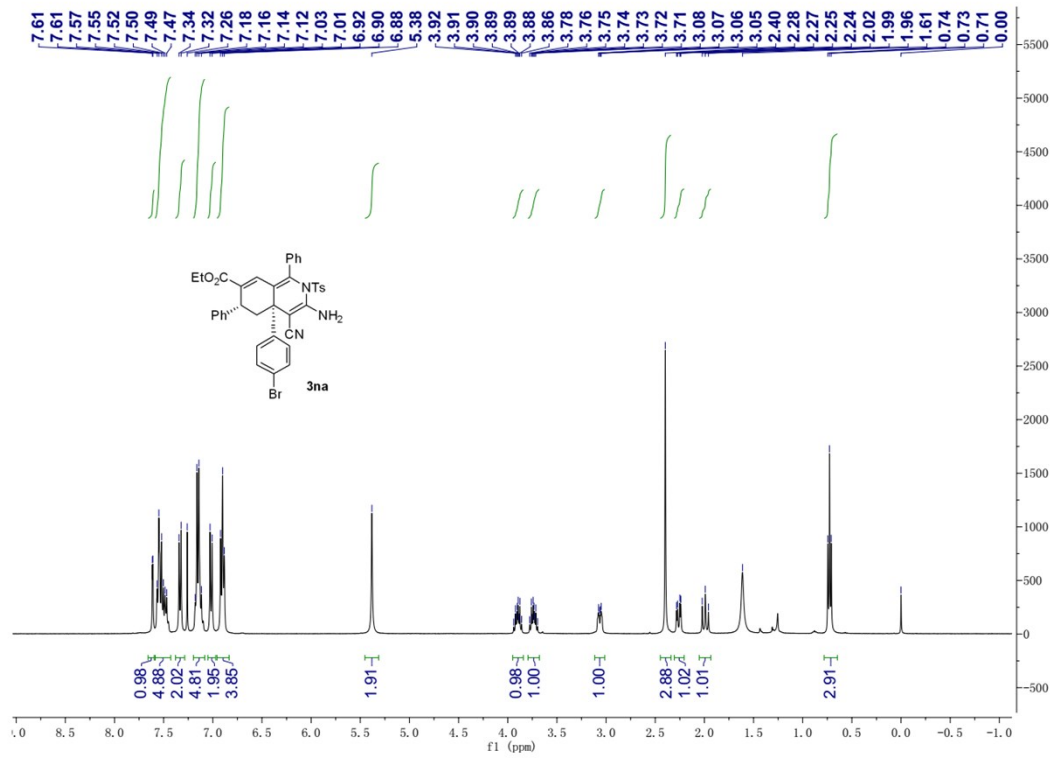
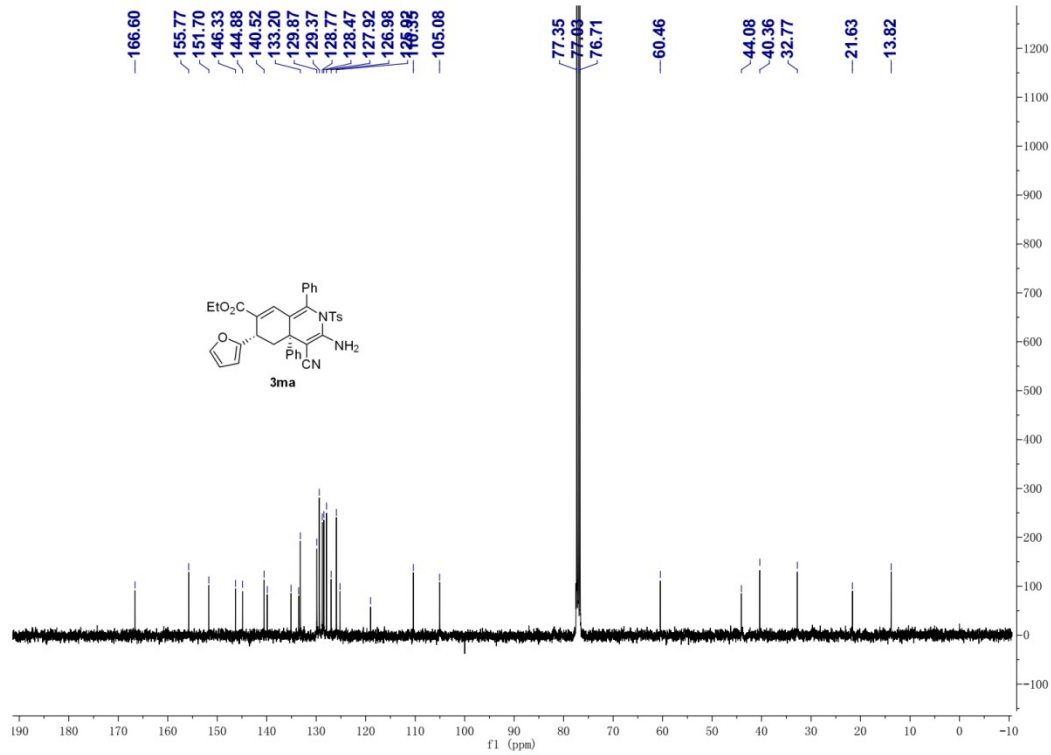


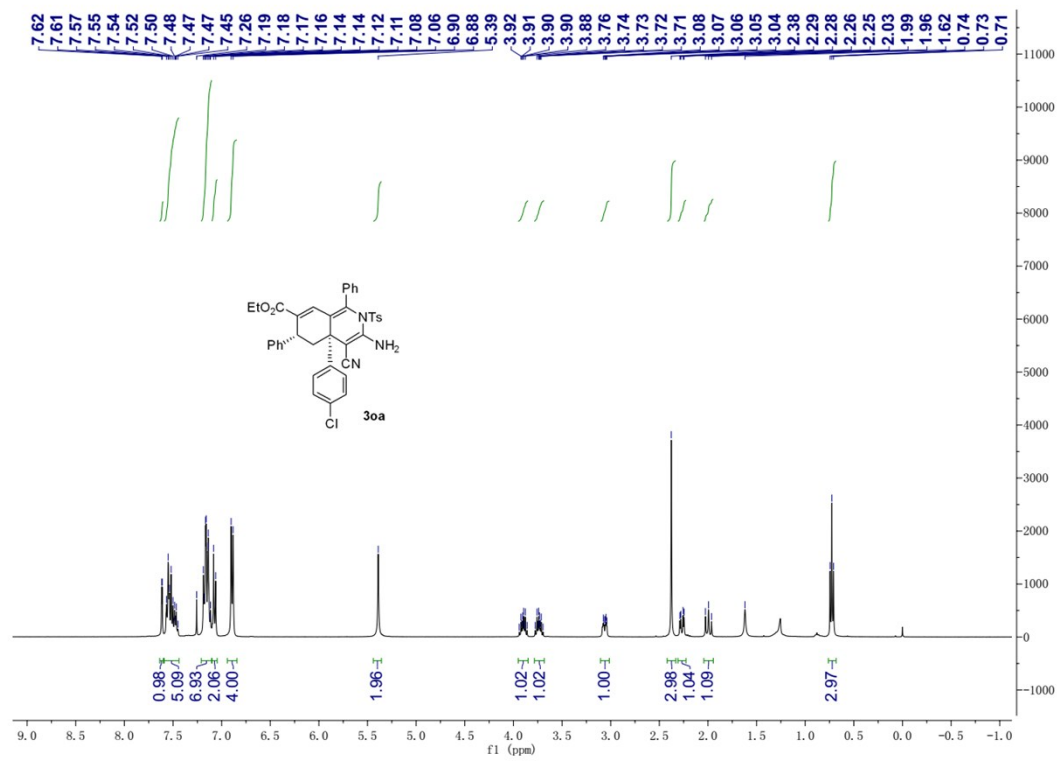
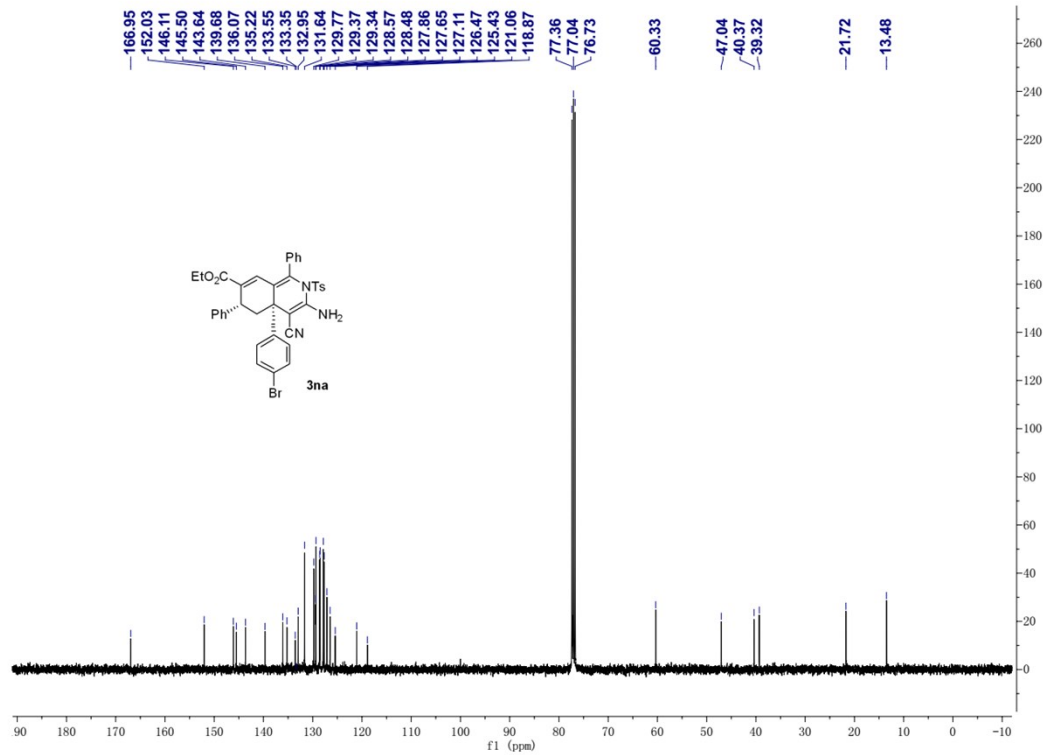


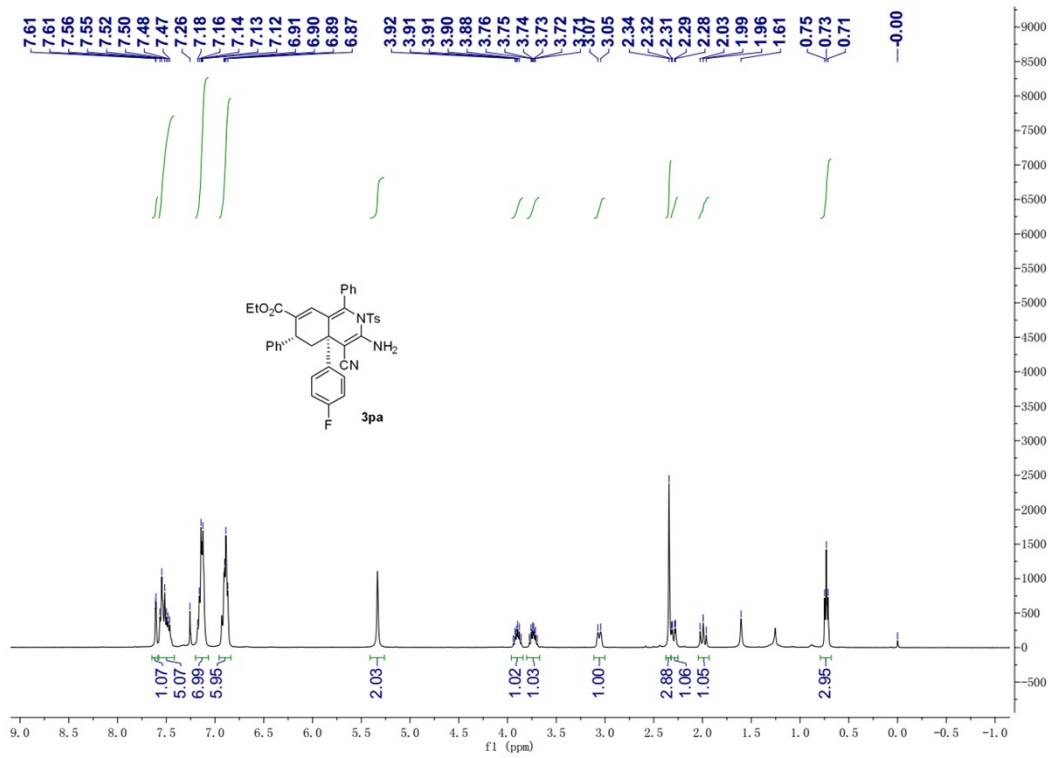
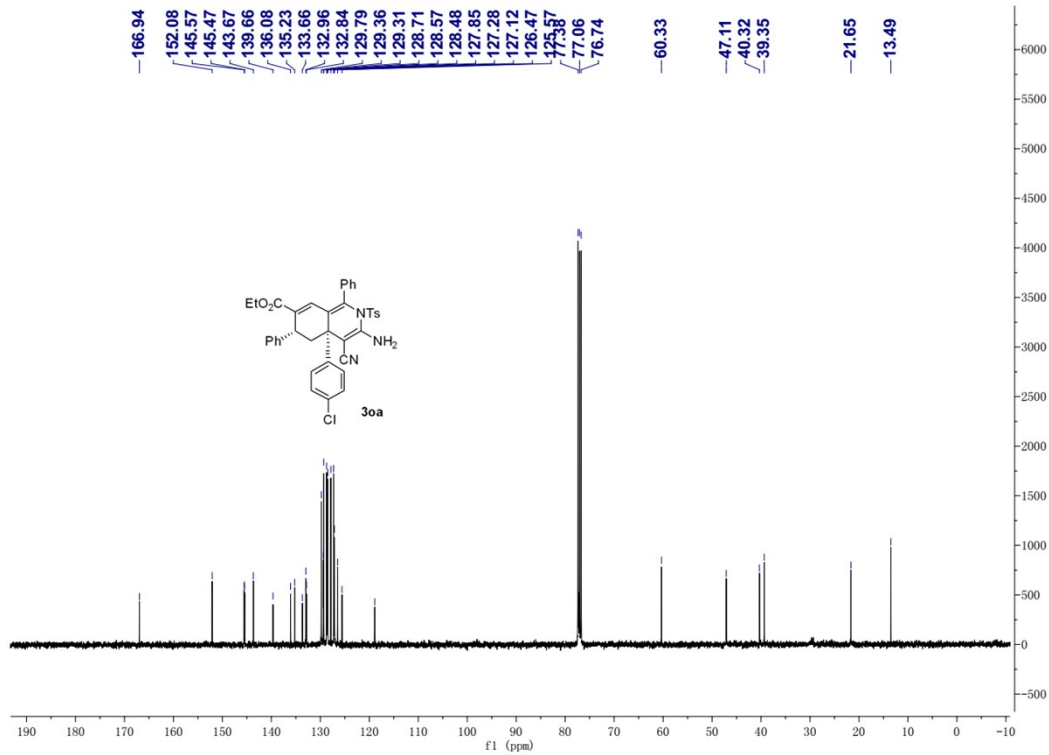


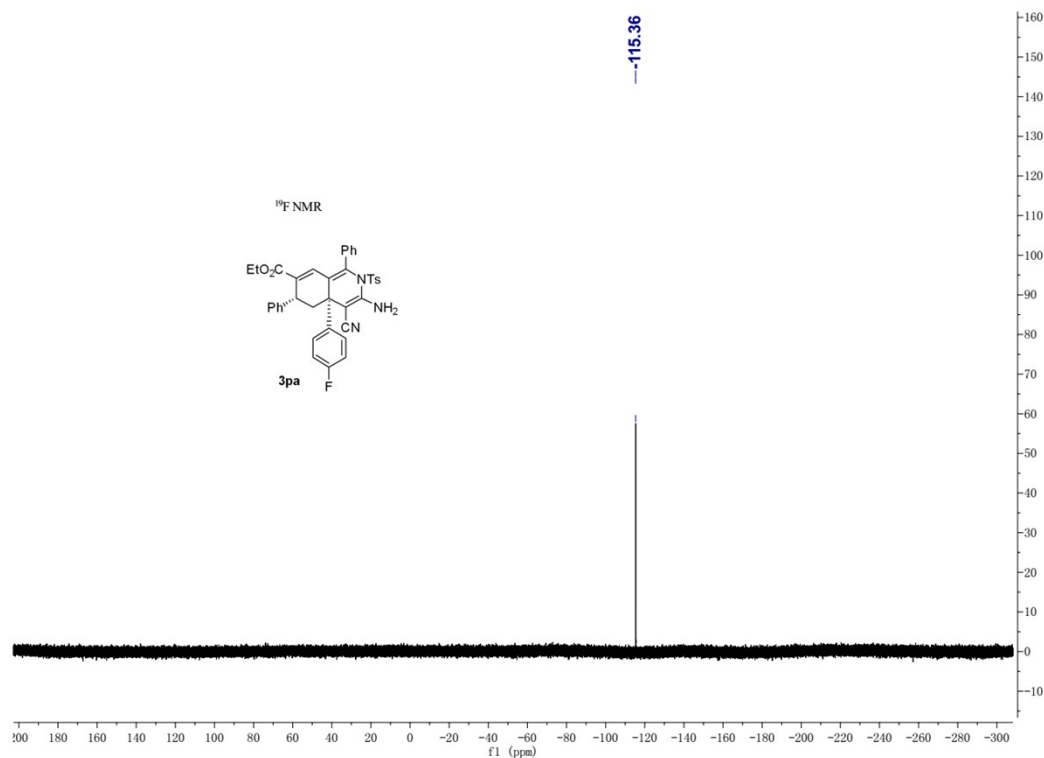
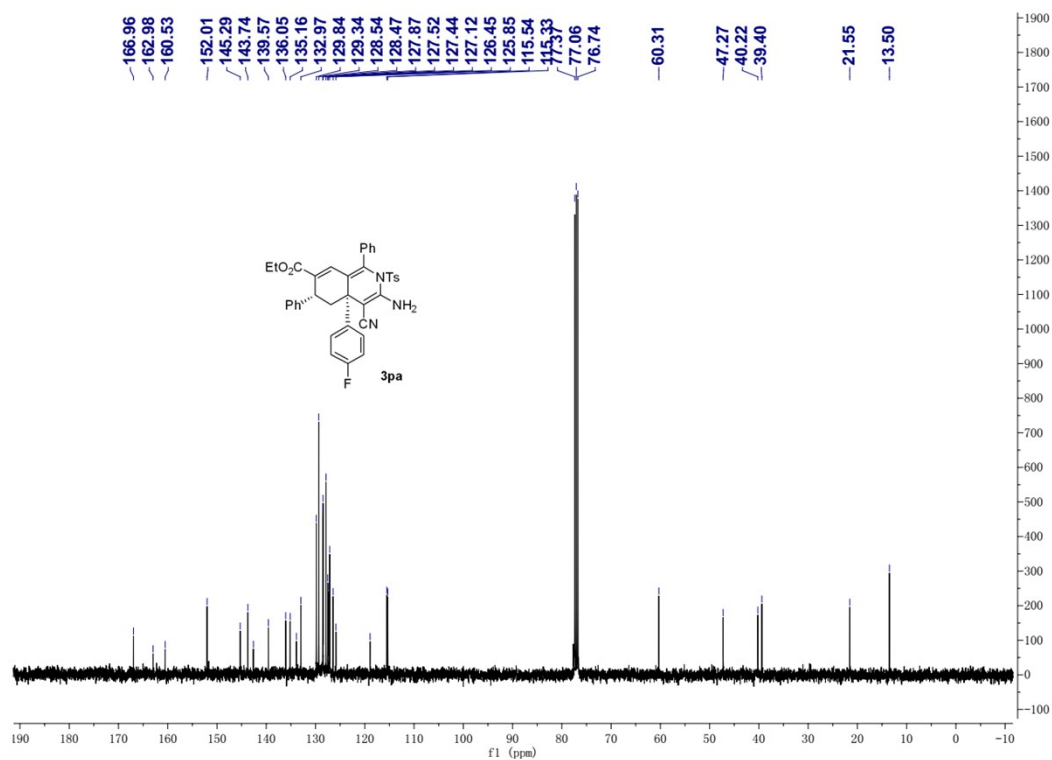


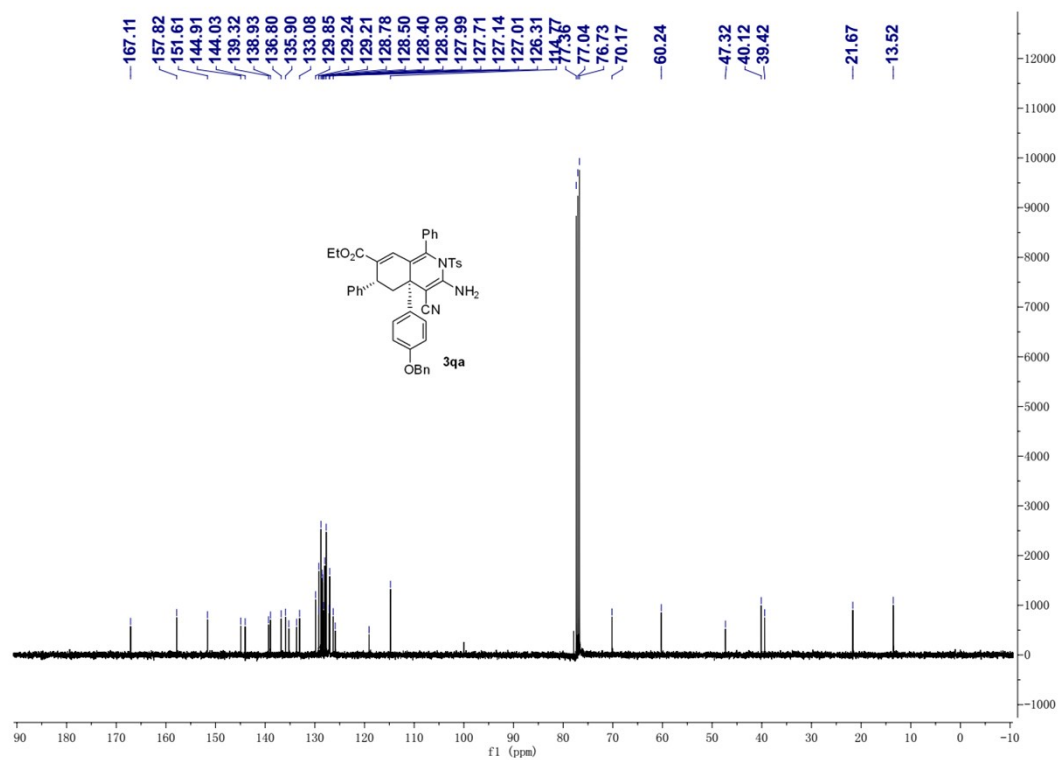
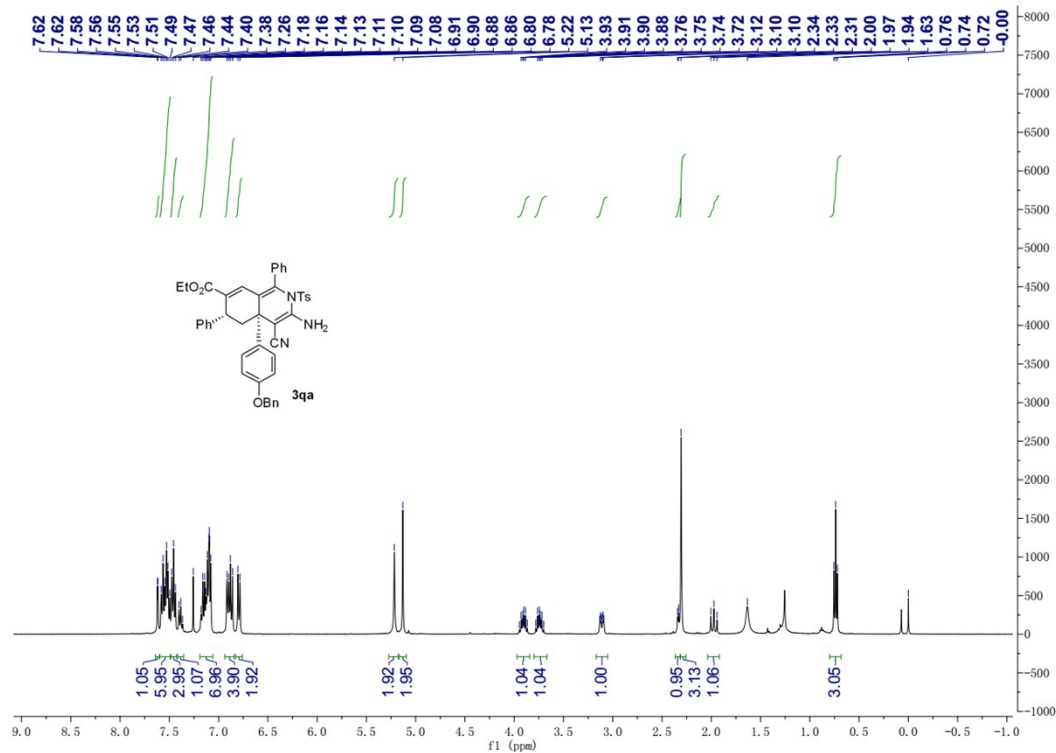




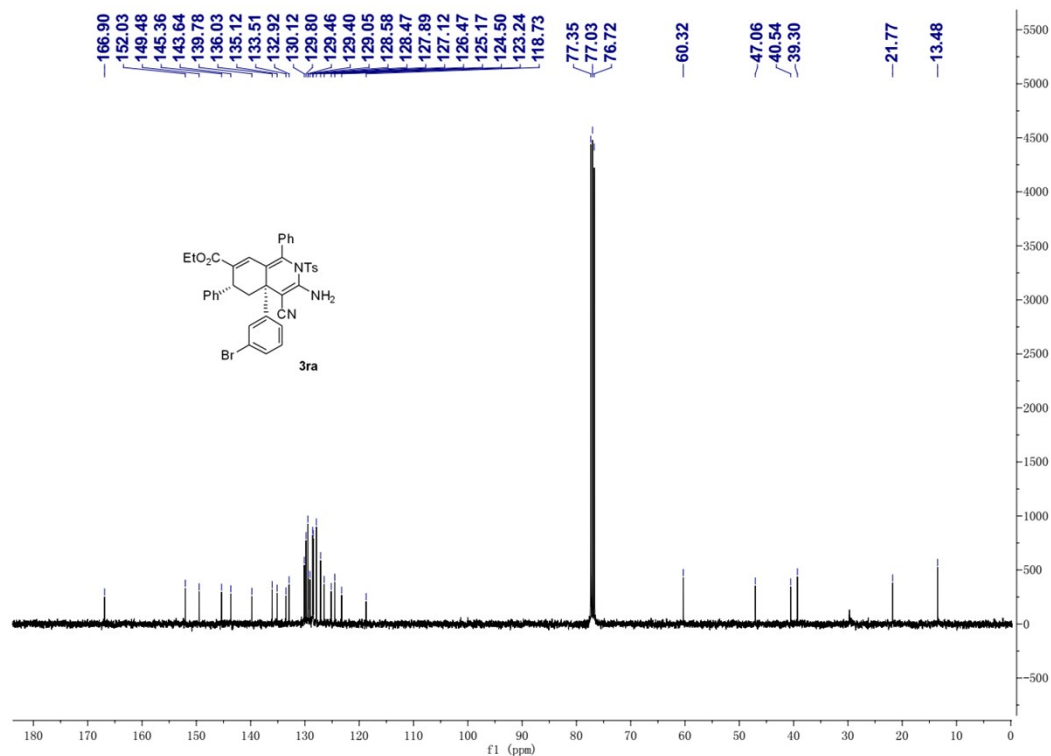
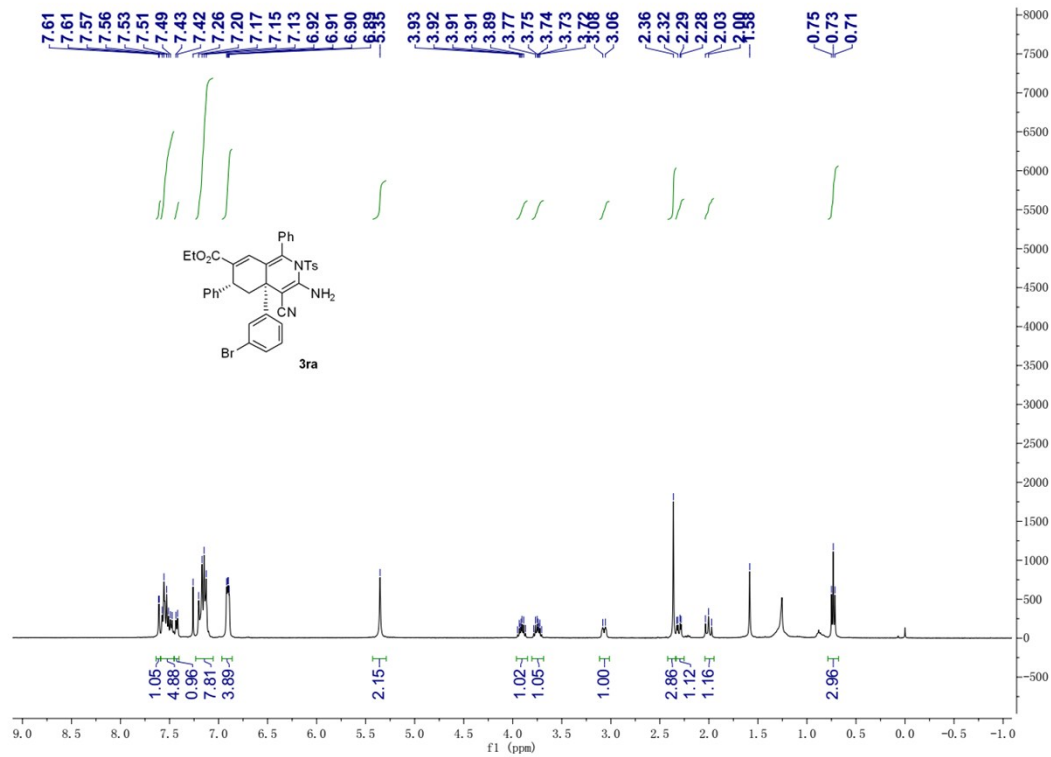


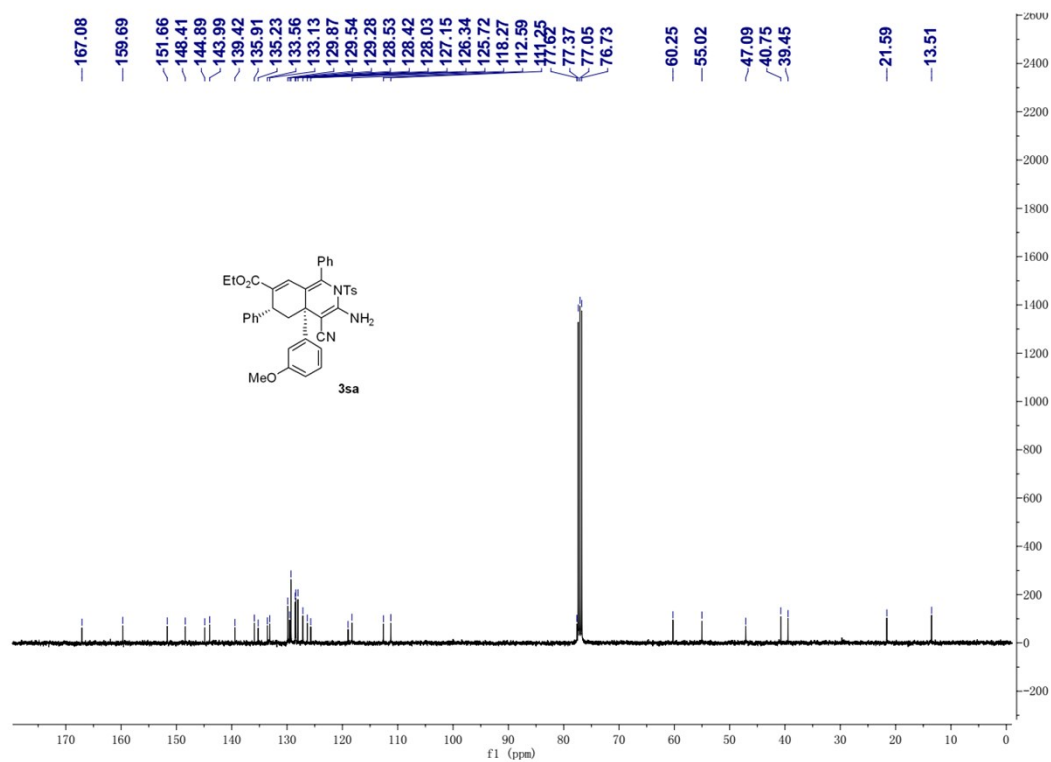
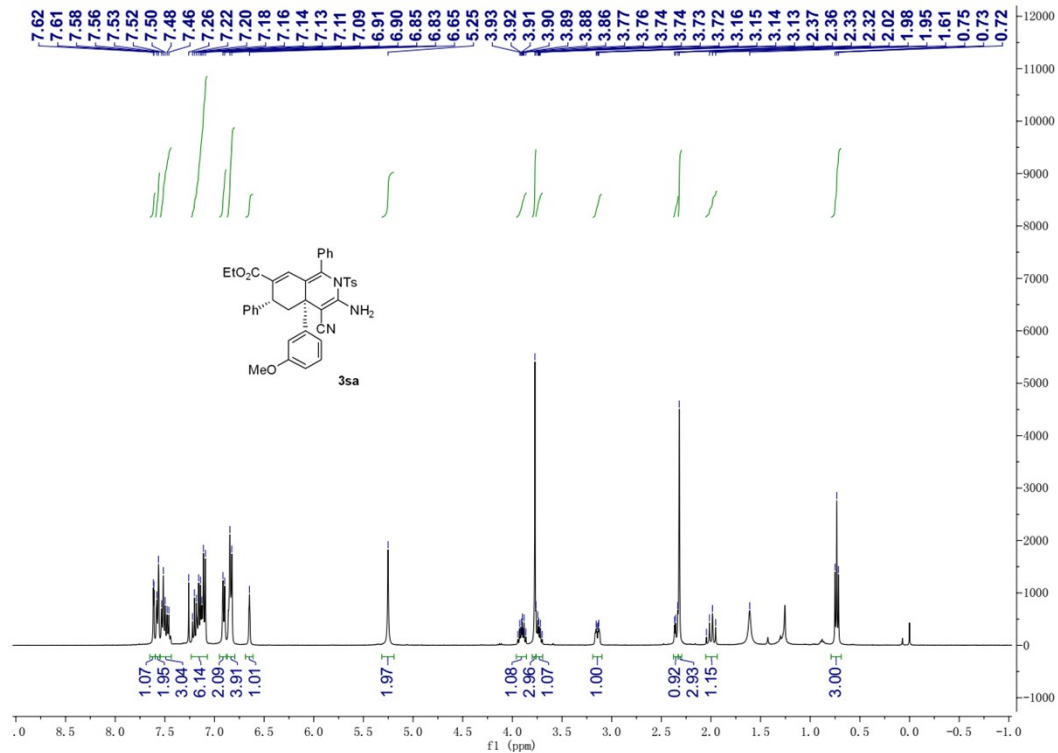


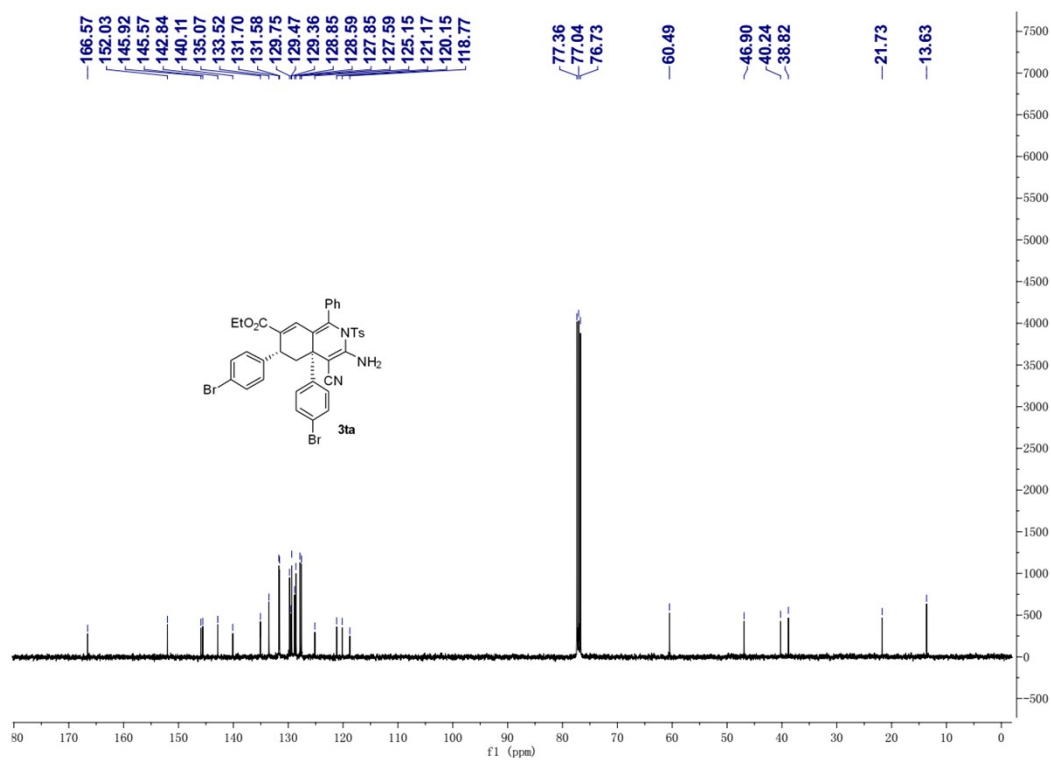
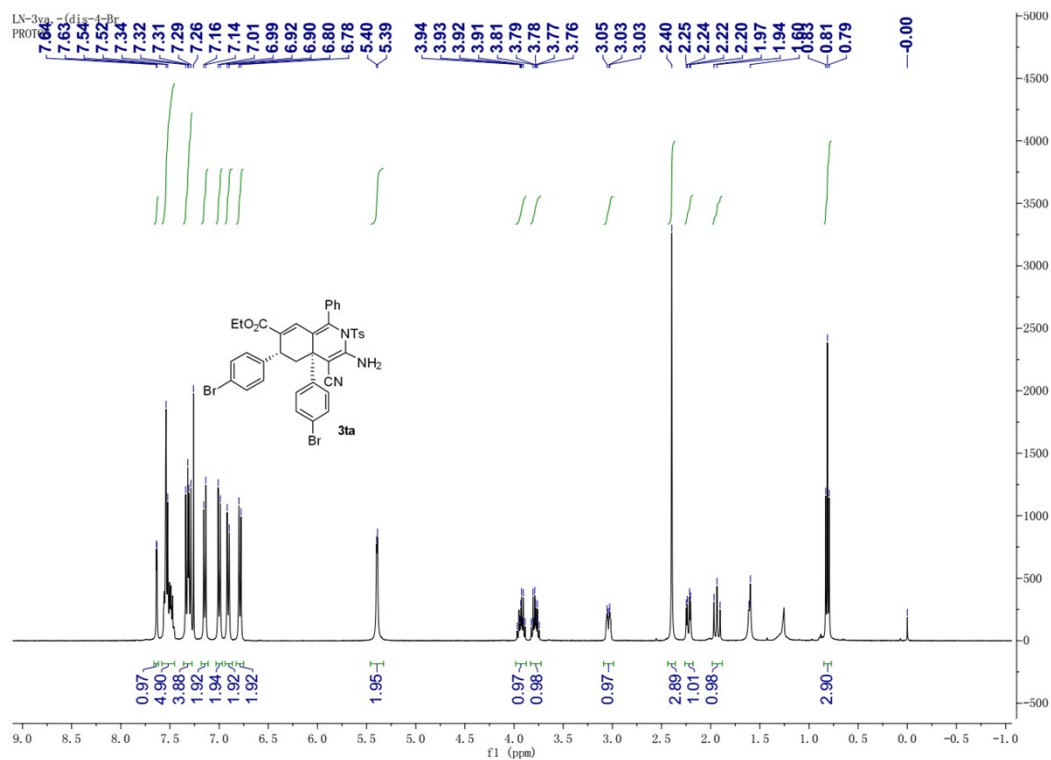


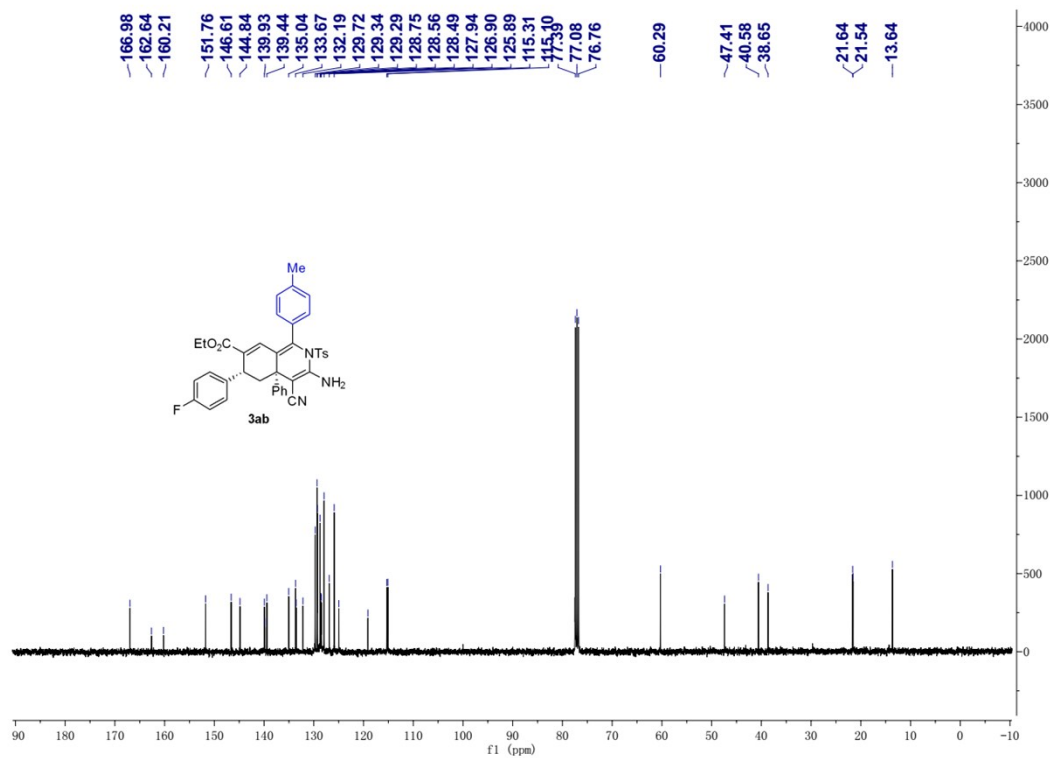
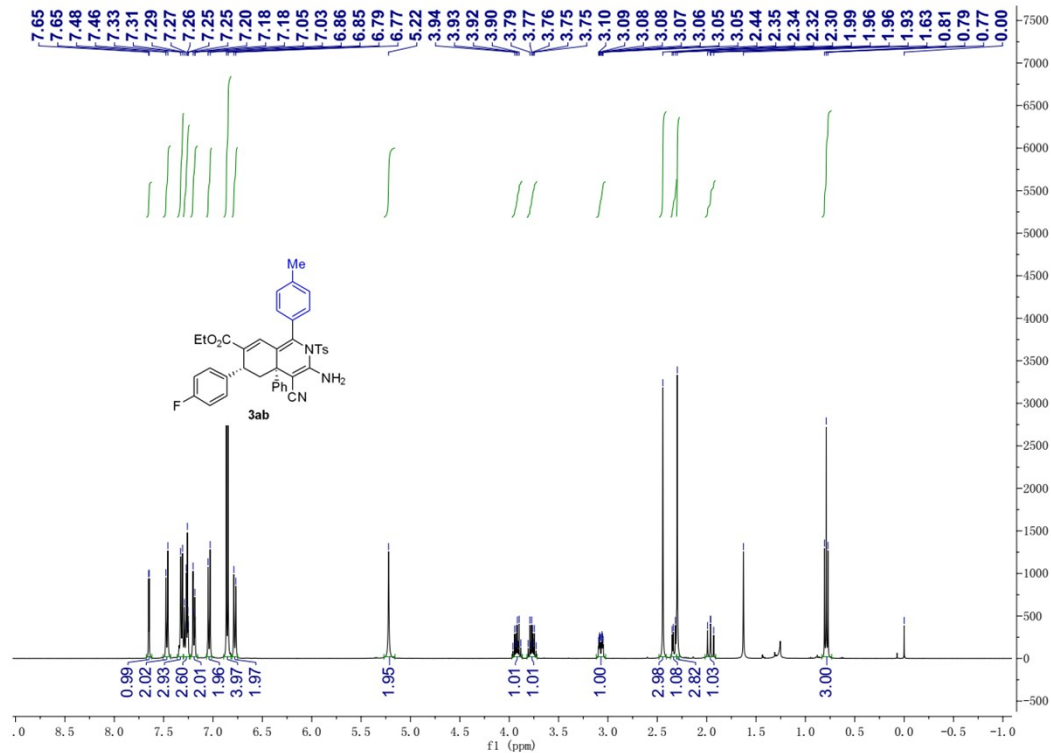


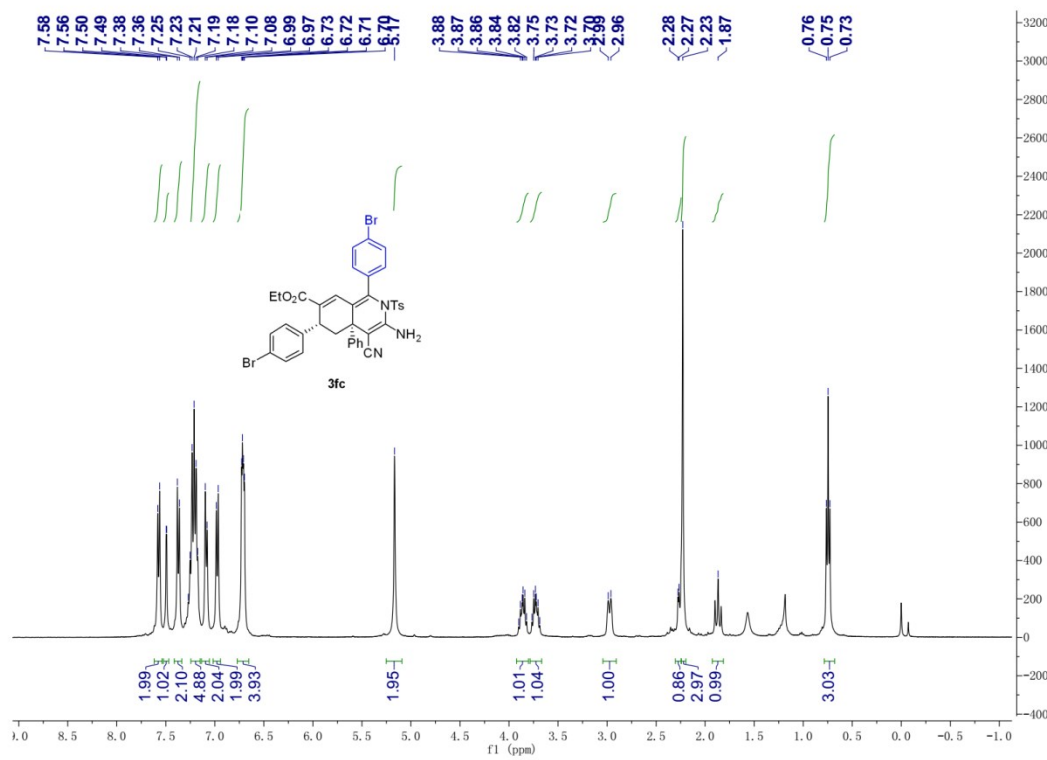
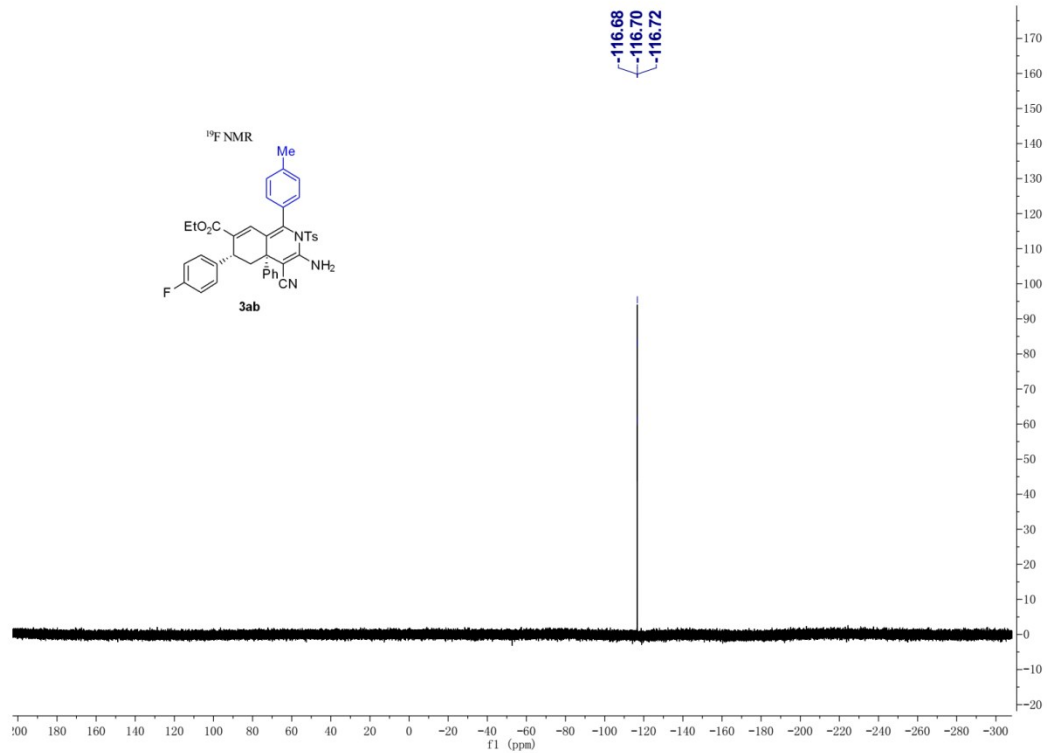


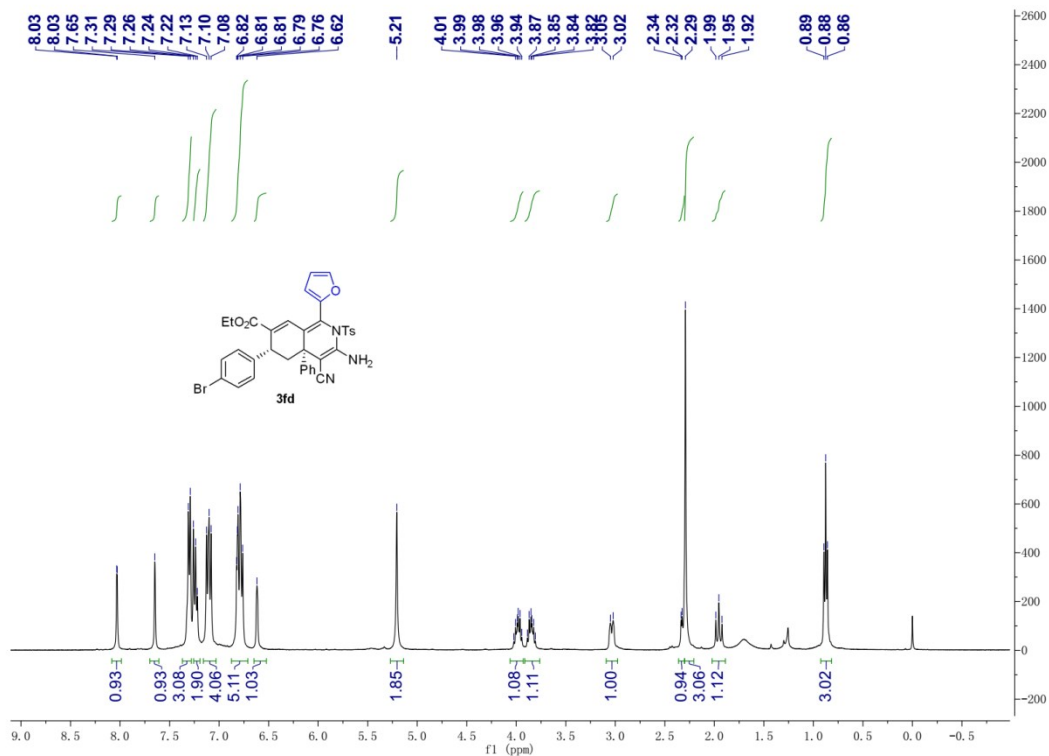
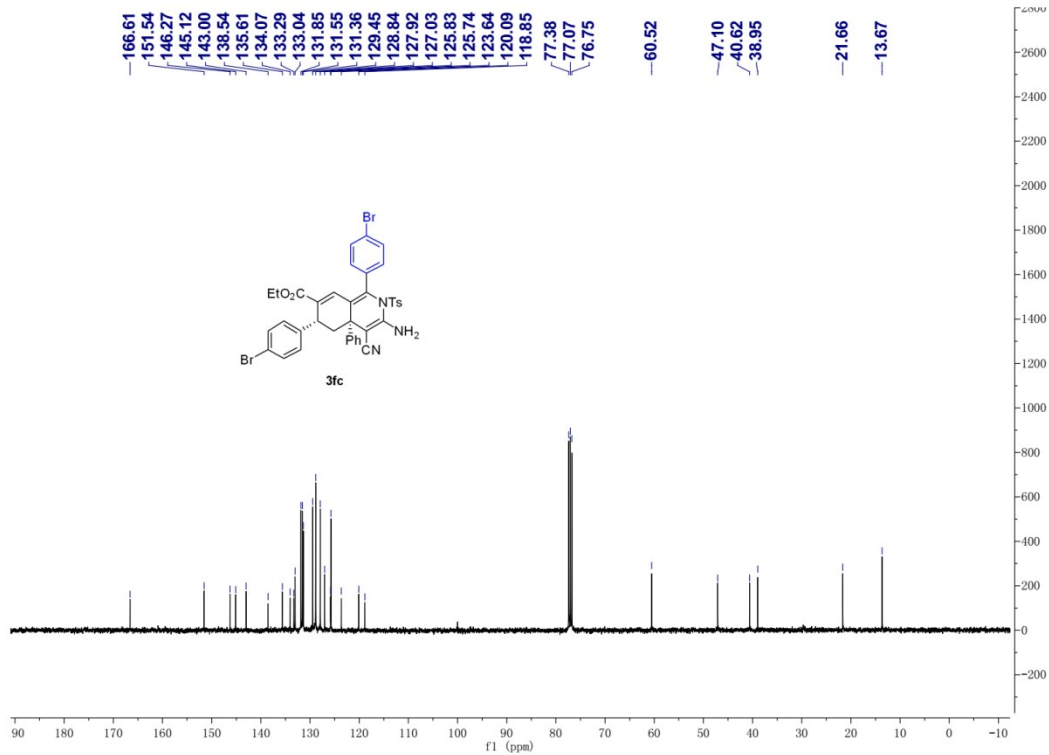


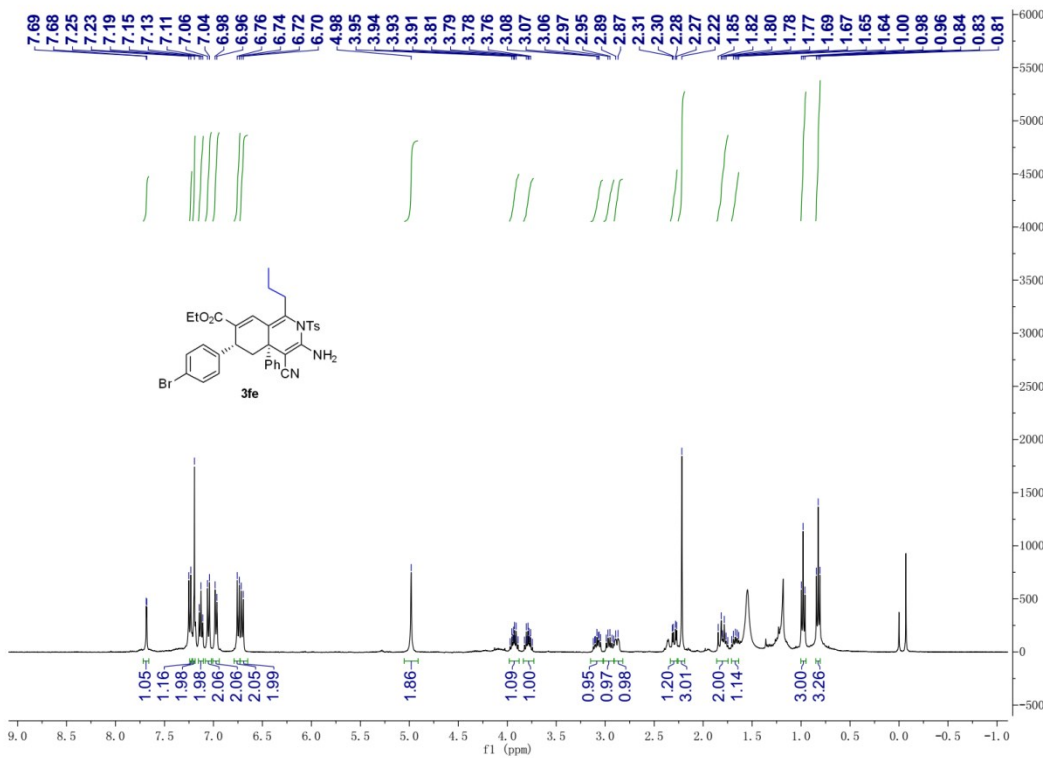
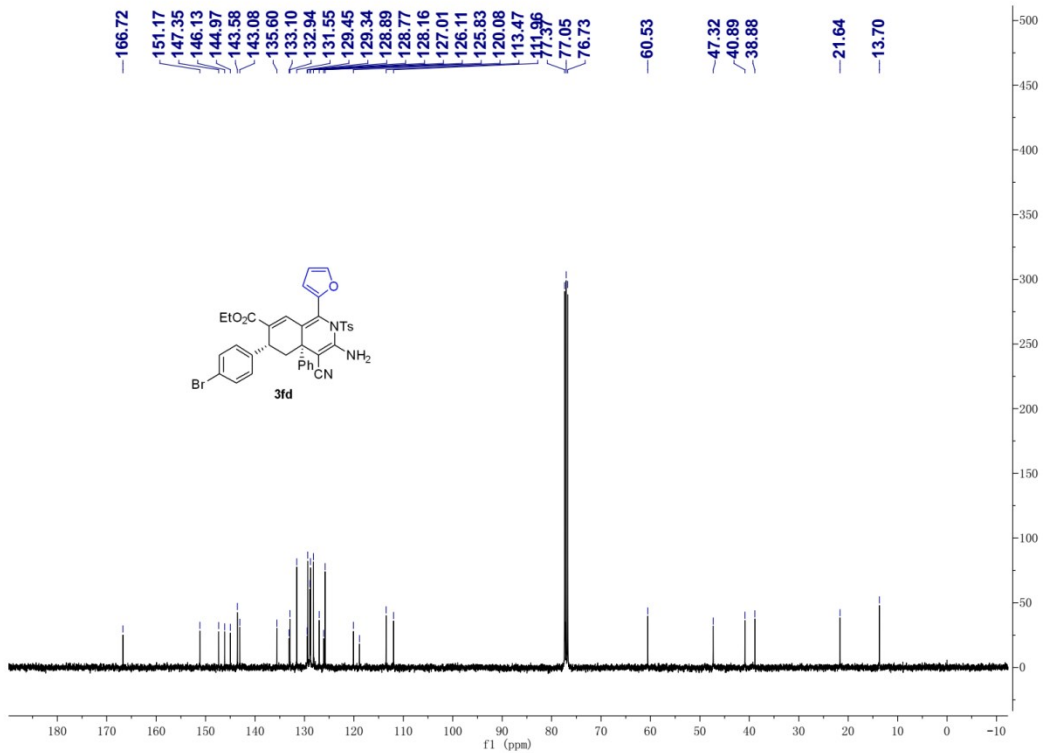


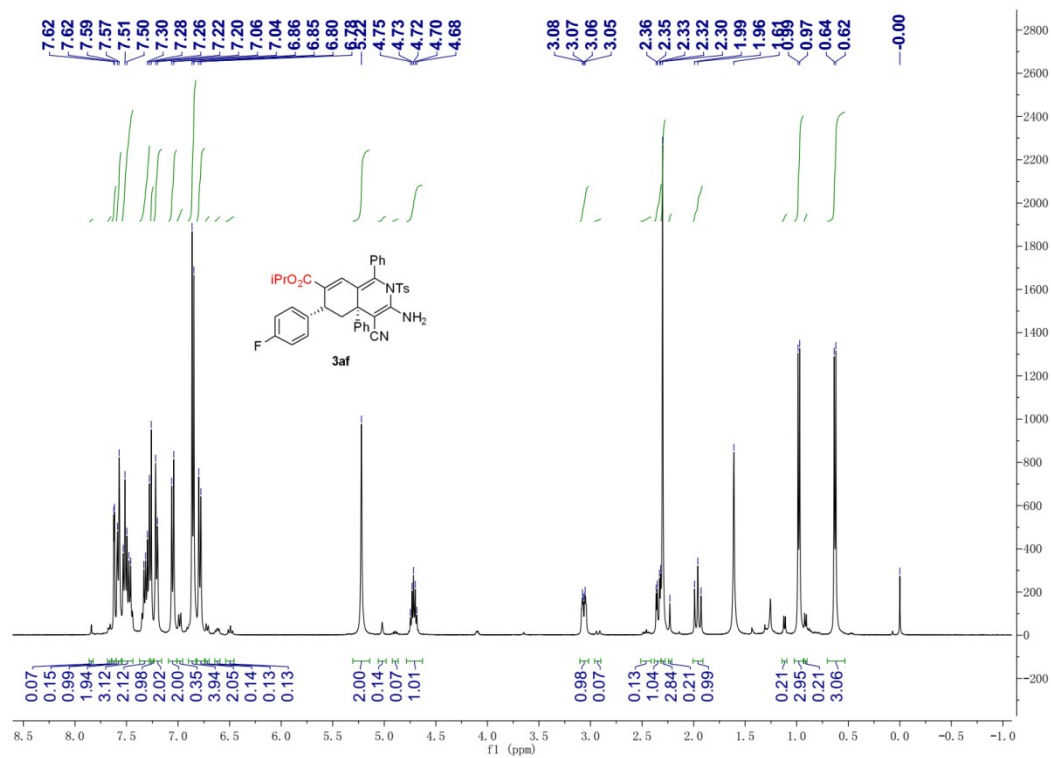
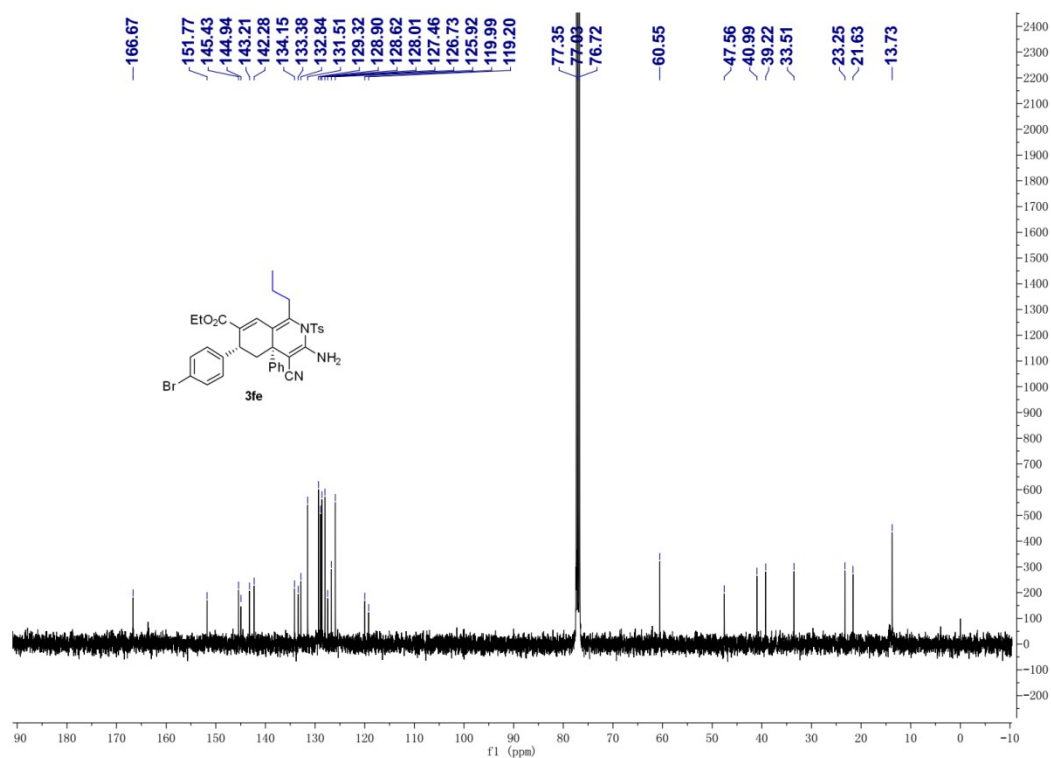




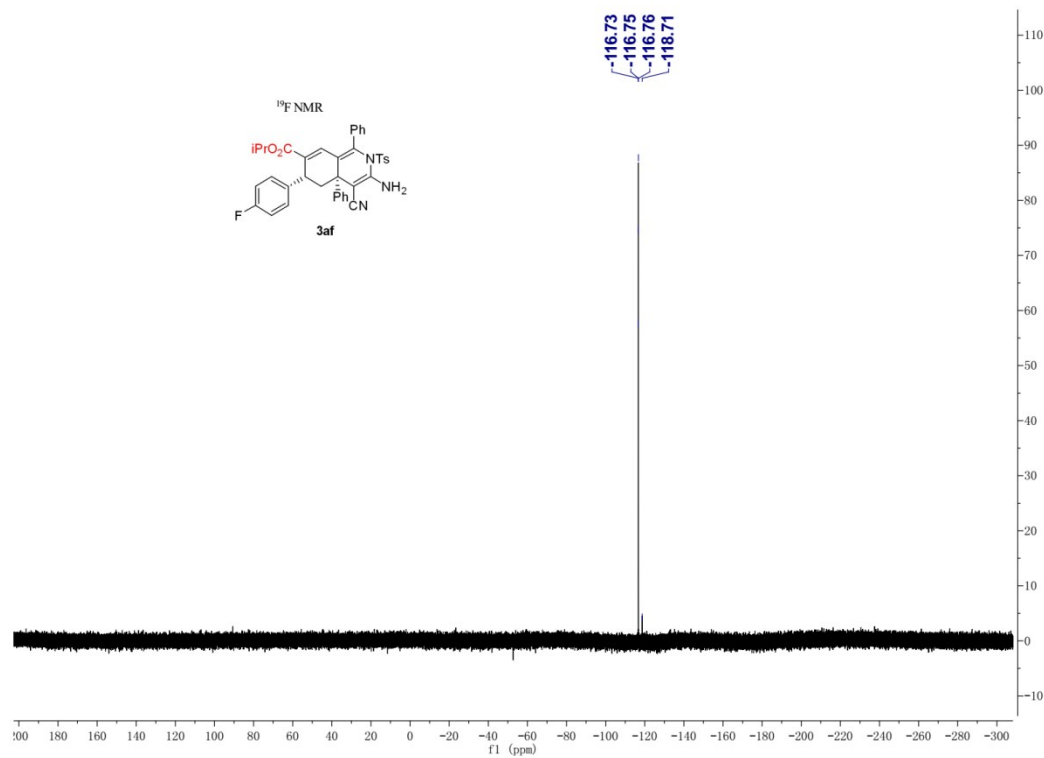
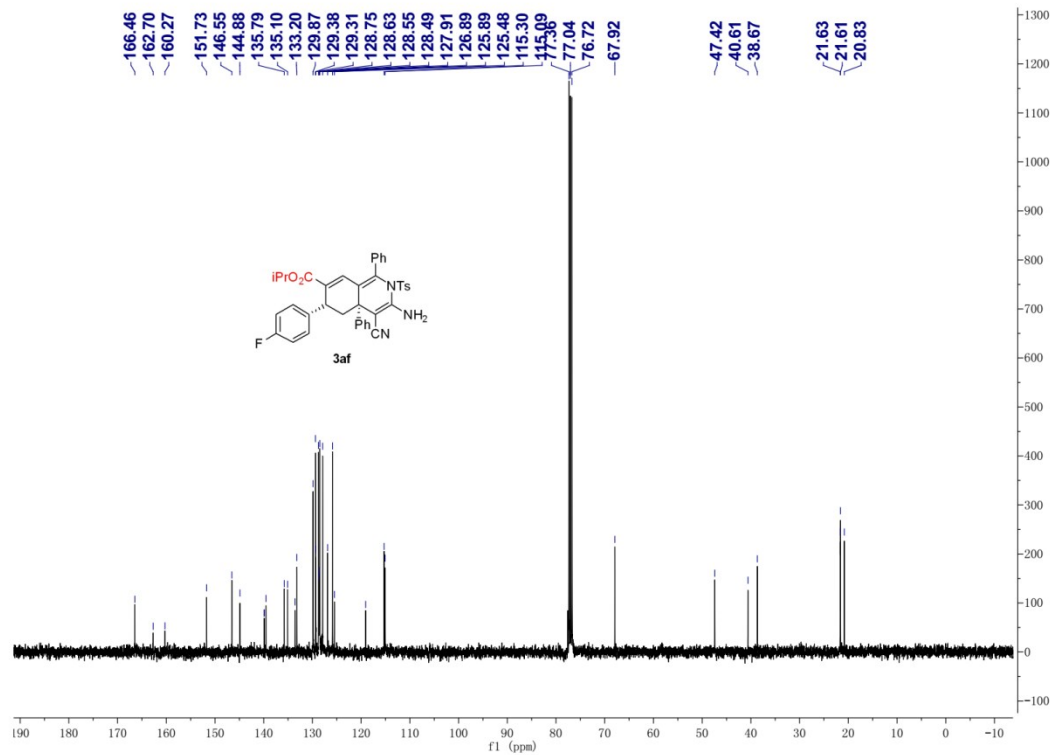


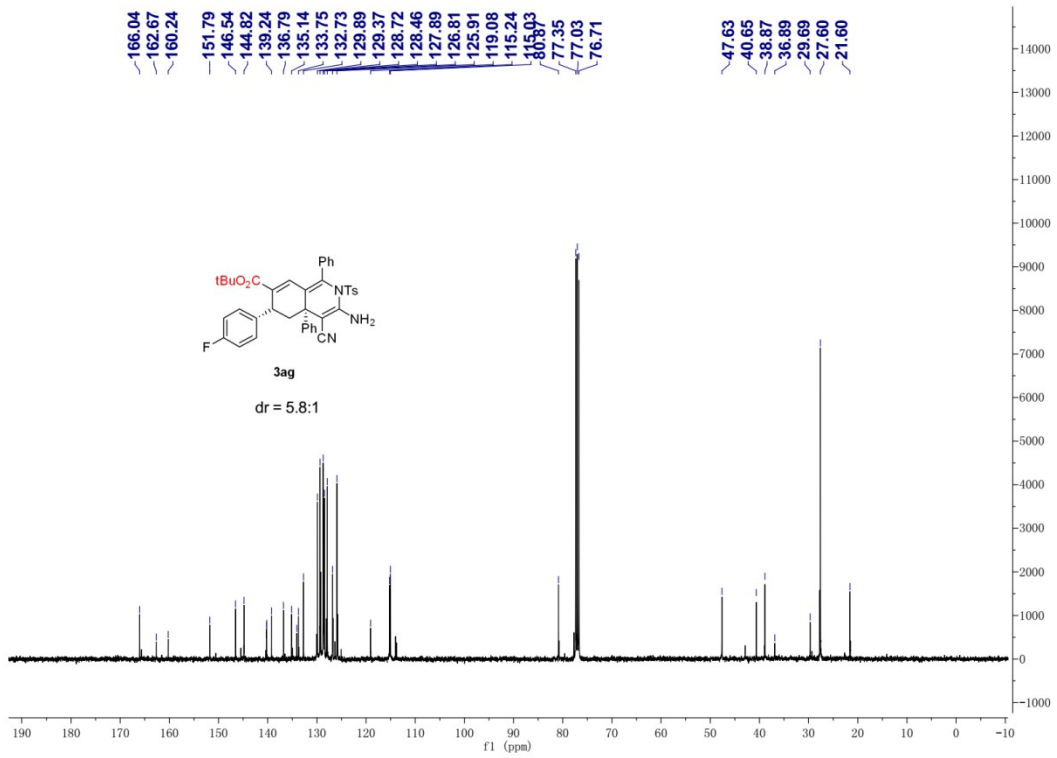
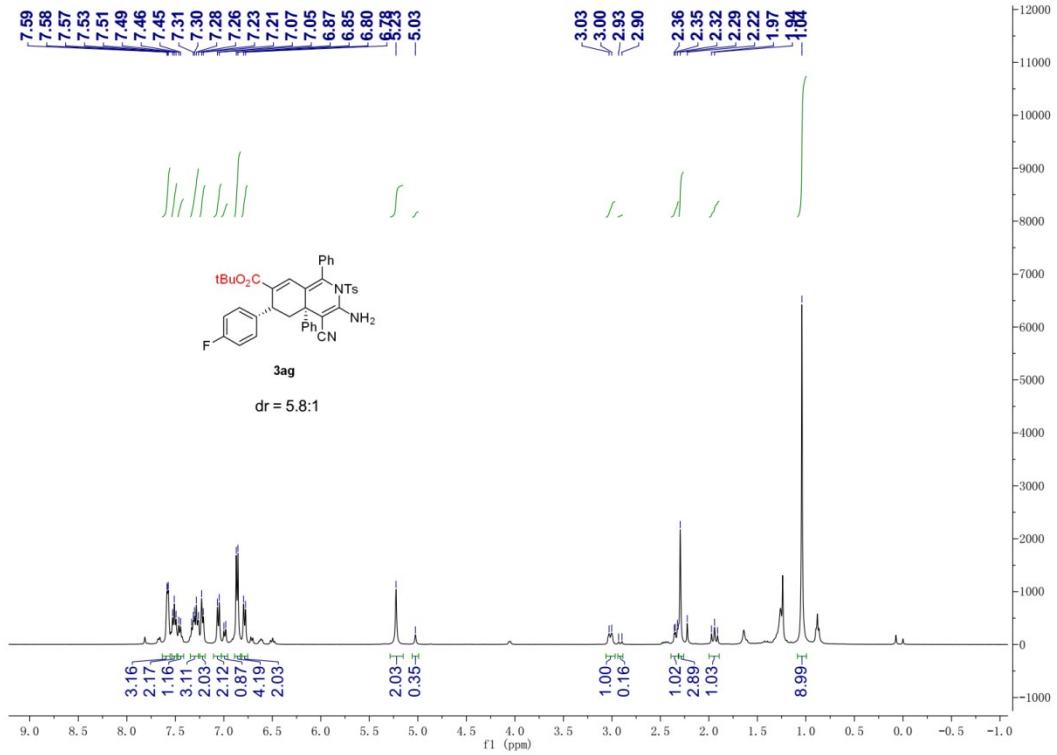


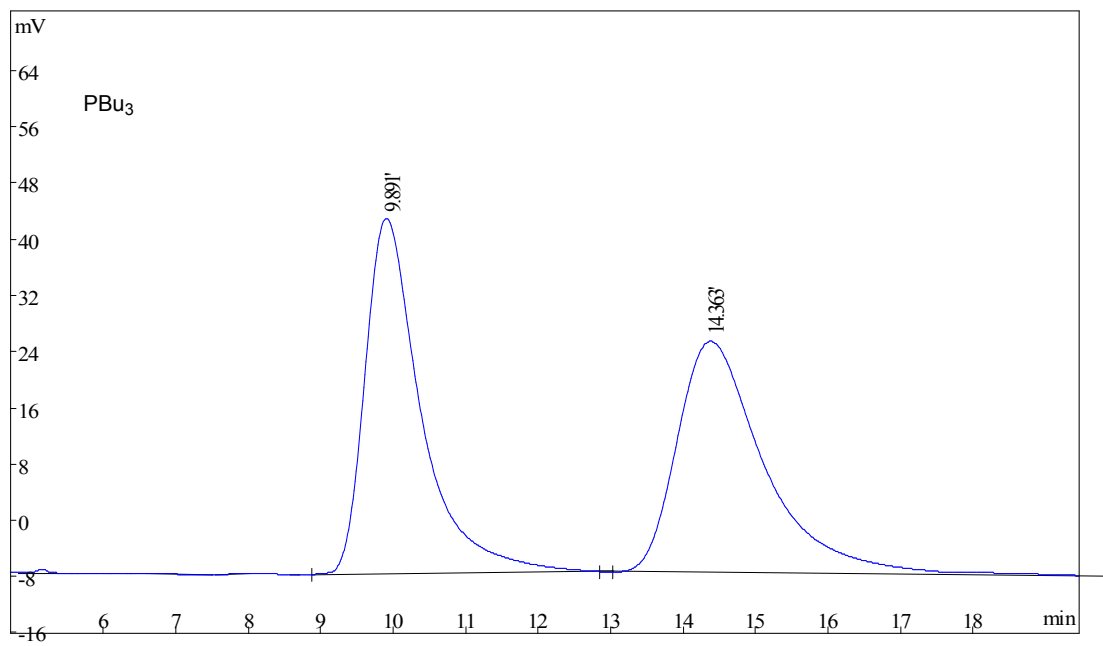
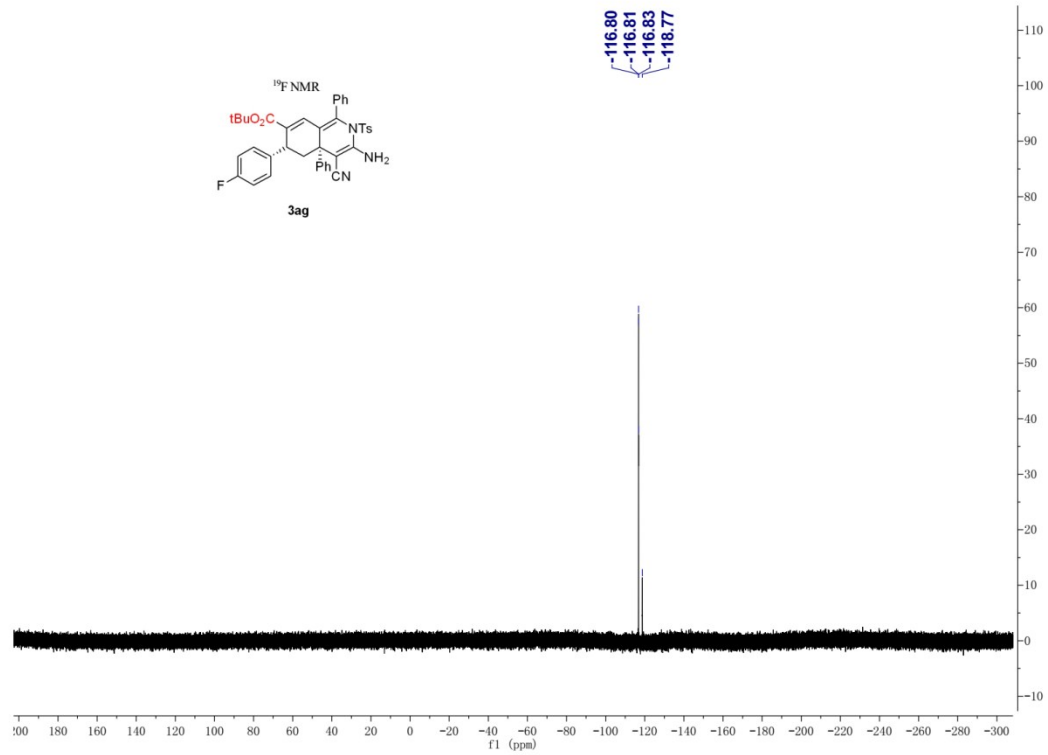




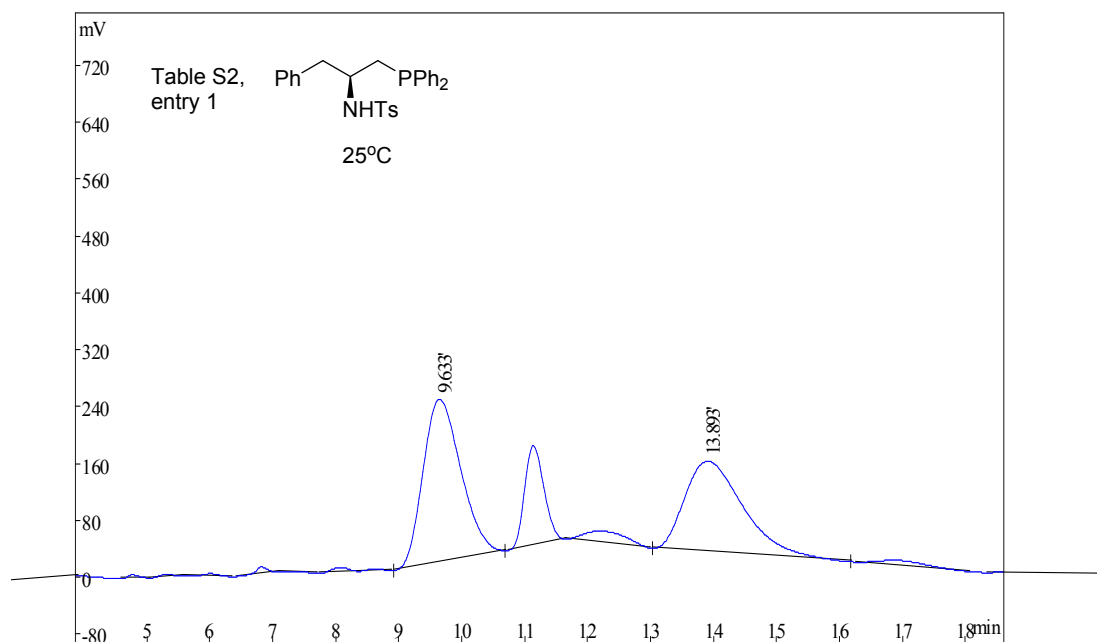




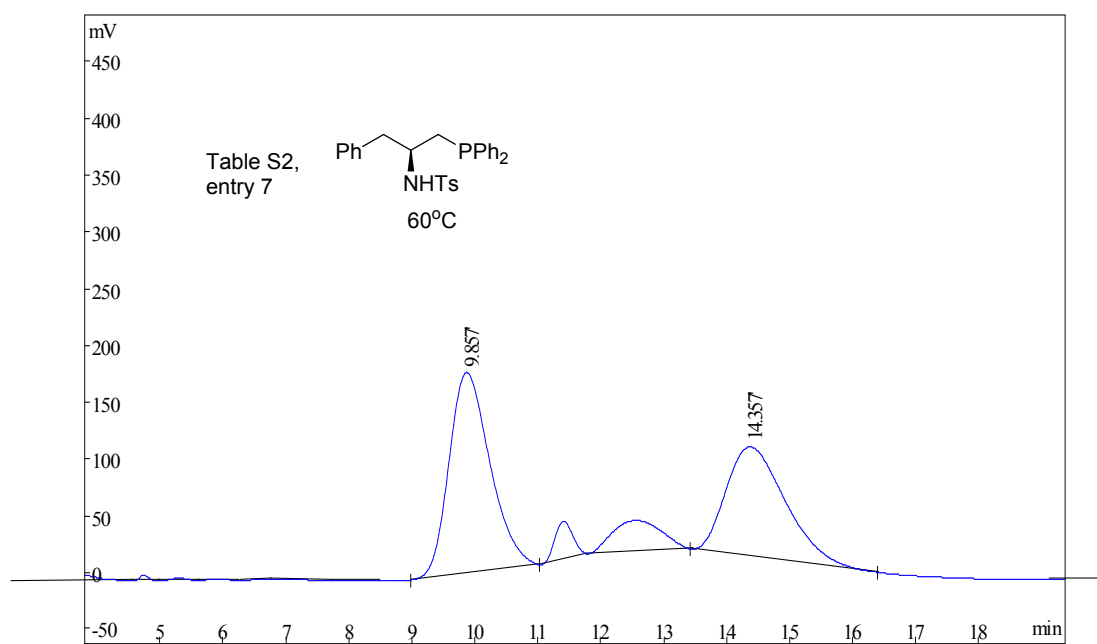




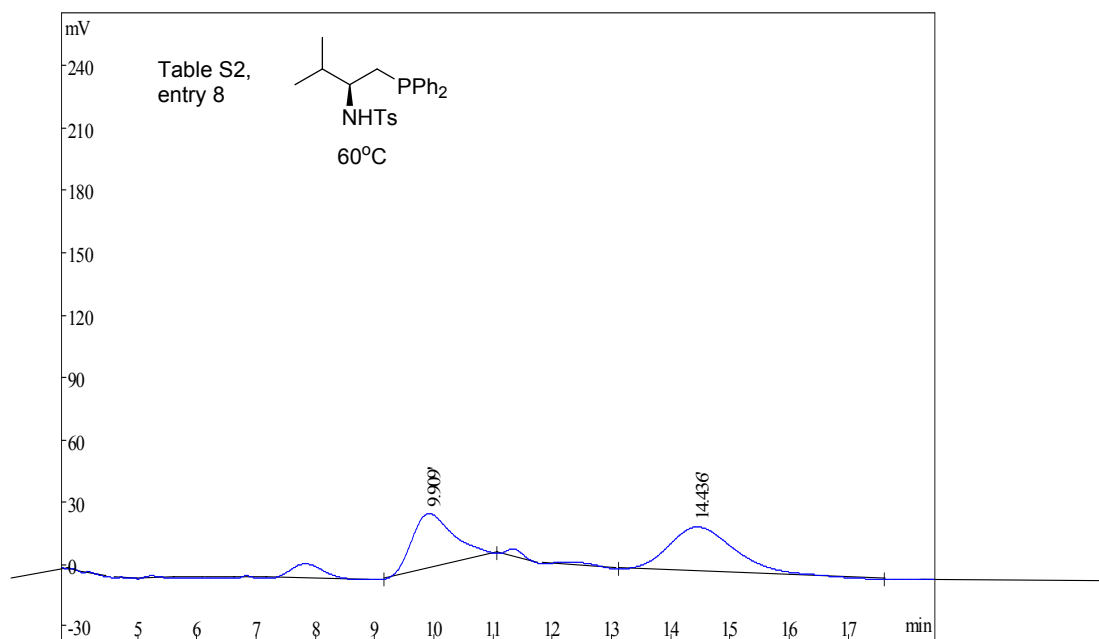
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Total		100	5529088



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1	9.633	53.55	9576240
2	13.893	46.45	8306505
Total		100	17882745



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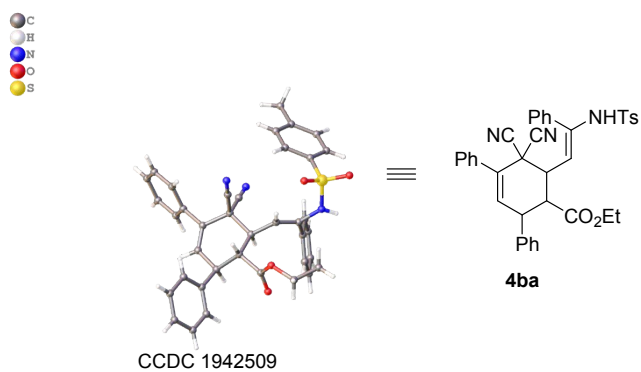
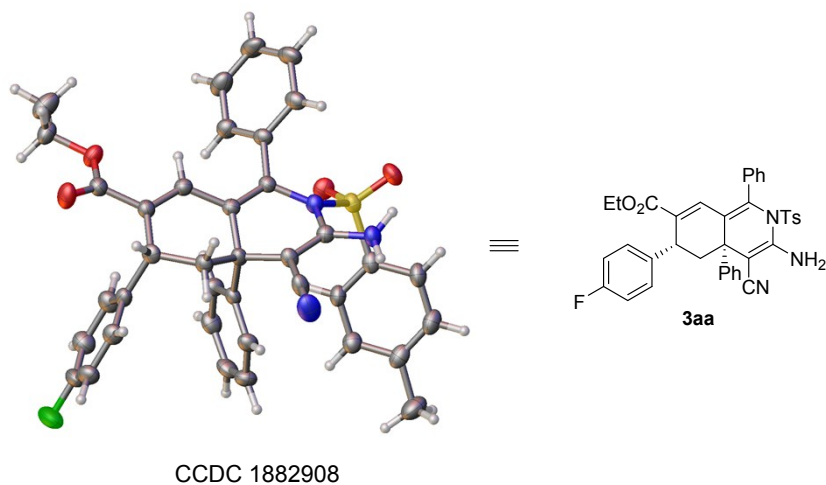


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## VIII. References

1. Y. Hu, R. Yi, X. Yu, X. Xin, C. Wang and B. Wan, *Chem. Commun.*, 2015, **51**, 15398.
2. V. R. Sabbasani, P. Mamidipalli, H. Lu, Y. Xia and D. Lee, *Org. Lett.*, 2013, **15**, 1552.
3. W. Dong, P. Hu, J. Hu and X. Tong, *Tetrahedron Lett.*, 2014, **55**, 1682.

## IX. X-ray crystal structure of 3aa and 4ba



CCDC 1882908 (**3aa**) and CCDC 1942509 (**4ba**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).