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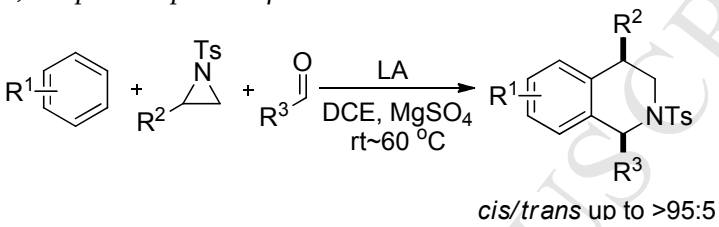

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ABSTRACT

A new Lewis acid promoted three-component reaction between the aziridine, arene and aldehyde has been developed. This reaction involves sequential ring opening of aziridine and Pictet-Splinger condensation and gives a broad range of *cis*-1,4-disubstituted tetrahydroisoquinolines in moderate yields with good diastereoselectivities under mild conditions. The methodology provides an rapid and convergent synthesis for the scaffold of tetrahydroisoquinoline and serves as a good tool for constructing the libraries of substituted tetrahydroisoquinolines.

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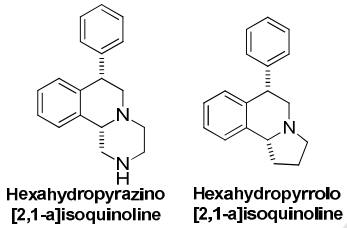
1. Introduction

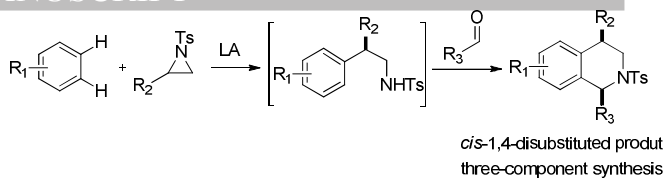
Tetrahydroisoquinoline (THIQ) derivatives are structural motifs of many pharmaceutically relevant molecules and natural products and exhibit a variety of biological activities.[1] For this reason, they have attracted continuous interest to design the synthetic methods for the construction of all kinds of substituted THIQs.[2] In particular, 1,4-disubstituted THIQs have been paid much attention along with their physiological activities investigated in recent years. For example, hexahydropyrazino [2,1-a]isoquinolines[3] and hexahydropyrrolo [2,1-a]isoquinolines[4] were found to be associated with antidepressant activities (Scheme 1). Although several reports were available for the synthesis of 1,4-disubstituted THIQs,[5, 6] most of them involved multistep syntheses employing two-component reactions. The reaction diversity and efficiency were often unsatisfactory. Moreover, the development of highly diastereoselective reactions for the synthesis of 1,4-disubstituted THIQs remains a challenging job.[6]

Because multiple chemical bonds in one-step reaction are formed, the multiple-component reaction allows an efficient and straightforward transformation from readily available materials to cyclic compounds with molecular complexity and structural diversity.[7] Due to avoiding the isolation and purification of intermediates, it saves a large number of efforts, times, and cost. Therefore, the multiple-component reaction has been widely used to the high-throughput screening in the discovery of modern new drug. Considering the continued importance of the THIQ derivatives in the field of organic and medicinal chemistry, developing efficient multiple-component reactions for the diastereoselective synthesis of THIQ derivatives is of great significance.



Scheme 1. 1,4-disubstituted tetrahydroisoquinolines

N-Sulfonylaziridine[8], an readily accessible and good reactive organic intermediate, has been utilized for the ring-opening reactions with numerous heteroatom-nucleophilic reagents[9] and carbon-nucleophilic reagents[10]. Base on these ring openings, a series of tandem cyclizations involving two-components have been developed for the construction of nitrogen-containing heterocycles.[6a,11] But tandem multiple-component reactions are seldom seen.[12] We noticed that N-sulfonyl-β-arylamines were easily provided by Lewis acid promoted ring opening of N-sulfonyl aziridines with arenes.[13] If continuing to add aldehydes, N-sulfonyl-β-arylamines would further undergo Lewis acid catalyzed Pictet-Spengler condensation[14] in a cascade fashion leading to the three-component synthesis of 1,4-disubstituted tetrahydroisoquinolines (Scheme 2). To our best knowledge, few tandem three-component reactions were designed for one-step construction of the core skeletons of tetrahydroisoquinolines up to now.[15] This new three-component reaction undoubtedly provides a good choice for the rapid and convergent synthesis of tetrahydroisoquinolines. When carrying out this three-component reaction, we find that *cis*-1,4-disubstituted THIQ is isolated as the major isomer with a good diastereoselectivity. Herein, we hope to report about the results of the new *cis*-diastereoselective three-component reactions of aziridines, arenes and aldehydes.

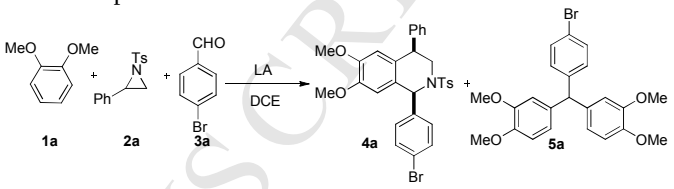


Scheme 2. Tandem three-component reactions between aziridines, arenes and aldehydes

2. Results and Discussion

Arene **1a**, aziridine **2a**, and aldehyde **3a** were selected as model substrates for optimizing the reaction conditions (Table 1). A screening of different acids was firstly carried out. $Sc(OTf)_3$, $In(OTf)_3$ and $AgPF_6$ failed to promote the three-component reaction (entries 1~3). To our delight, when $BF_3{\cdot}OEt_2$ was used

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Additive	T	Yield(**4a**)[b]	Dr[c]
1	$Sc(OTf)_3$	DCE	none	rt	0%	-
2	$In(OTf)_3$	DCE	none	rt	0%	-
3	$AgPF_6$	DCE	none	rt	0%	-
4	$BF_3.OEt_2$[d]	DCE	none	rt	32%	86:14
5	$SnCl_4$[d]	DCE	none	rt	12%	79:21
6	$BF_3.OEt_2$[d]	DCE	$MgSO_4$[h]	rt	49%	86:14
7	$BF_3.OEt_2$[d]	DCE	Na_2SO_4[i]	rt	35%	86:14
8	$BF_3.OEt_2$[d]	DCE	4Å MS	rt	40%	86:14
9	$BF_3.OEt_2$[d]	DCE	$MgSO_4$	60 °C	63%	86:14
10	$BF_3.OEt_2$[d]	DCE	$MgSO_4$	80 °C	60%	86:14
11	$BF_3.OEt_2$[e]	DCE	$MgSO_4$	60 °C	20%	86:14
12	$BF_3.OEt_2$[f]	DCE	$MgSO_4$	60 °C	63%	84:16
13	$BF_3.OEt_2$[d,g]	DCE	$MgSO_4$	60 °C	60%	84:16
14	$BF_3.OEt_2$[d]	DCM	$MgSO_4$	40 °C	38%	86:14
15	$BF_3.OEt_2$[d]	$MeNO_2$	$MgSO_4$	60 °C	0%	-
16	$BF_3.OEt_2$[d]	THF	$MgSO_4$	60 °C	0%	-
17	$BF_3.OEt_2$[d]	DMSO	$MgSO_4$	60 °C	0%	-
18	$BF_3.OEt_2$[d]	CCl_4	$MgSO_4$	60 °C	62%	86:14
19	$BF_3.OEt_2$[d]	$CHCl_3$	$MgSO_4$	60 °C	25%	84:16

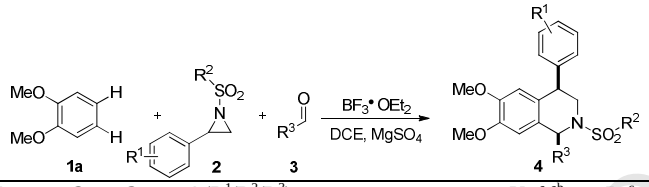
[a] Reaction conditions, unless otherwise stated: a solution of **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (0.04 mmol, 20 mol%) in solvent (2 mL) was stirred for 1h at room temperature, then **3a** (0.4 mmol) was added and the mixture was further stirred for 18 h at set temperature; [b] Combined yields of *cis*-**4a** and *trans*-**4a**; [c] Determined by NMR analysis (*cis/trans*); [d] Catalyst (300 mol%) was used; [e] Catalyst (200 mol%) was used; [f] Catalyst (400 mol%) was used; [g] **1a** (0.4mmol, 2equiv) was used; [h] Anhydrous $MgSO_4$ was used; [i] Anhydrous Na_2SO_4 was used.

as the catalyst, **4a** was obtained in 32% yield with a good diastereoselectivity (*cis:trans*=86:14) (entry 4). In the three-component reaction by-product **5a** was also obviously observed because of double arylation of aldehydes. The structure of *cis*-**4a** was unambiguously confirmed by X-ray crystal structure analysis[16]. $SnCl_4$ could also promote the three-component

reaction, but a low yield was observed (entry 5). As additives, anhydrous $MgSO_4$ was found to be more beneficial for improving the yield of the three-component reaction than anhydrous Na_2SO_4 and 4Å MS(entry 6~8). Then we attempted to raise the reaction temperature to 60 °C, the best result for the three-component reaction was obtained and **4a** was provided in 63% yield without the decrease of diastereoselectivity (entry 9). When the reaction temperature was further raised to 80 °C, a slightly low yield was observed (entry 10). Decreasing the amount of $BF_3{\cdot}OEt_2$ from 300% to 200% gave a bad result and porduct **4a** was only isolated in 20% yield (entry 11). Then we tried to increase the amount of $BF_3{\cdot}OEt_2$ to 400%, the result was similar with using 300 mol% of $BF_3{\cdot}OEt_2$ (entry 12). We also tested the reaction using an increased amount of arenes (2 equiv), a slightly decreased yield was observed (entry 13). Besides, several different solvents were selected for optimizing the reaction conditions (entries 14~19). Unsatisfied yields were detected in DCM and $CHCl_3$. In THF, $MeNO_2$ and DMSO the reaction failed to afford product **4a**. In CCl_4 the reaction gave a similar result as in DCE. Considering the high toxicity of CCl_4, we preferred DCE as the reaction solvent at last.

With the optimized reaction conditions in hand, the substrate scope of the three-component reactions was firstly investigated with a series of aldehydes and aziridines. The results were outlined in Table 2. It was found that various substituted aldehydes **2** and aziridines **3** successfully reacted with arene **1a**

Table 2 Investigation of the scope of aldehydes and aziridines[a]

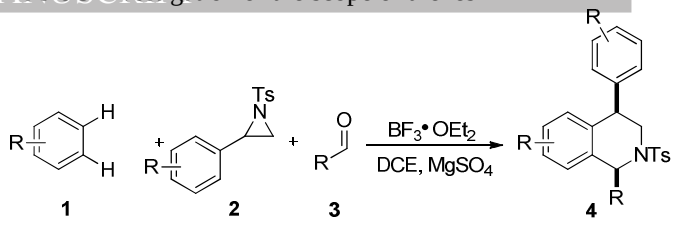


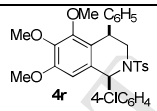
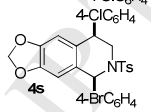
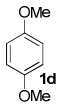
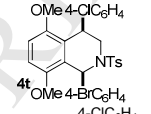
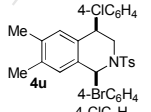
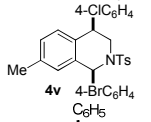
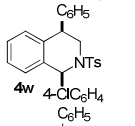
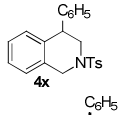
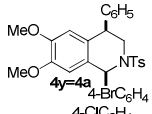
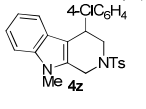
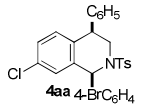
Entry	2	3	4 (R^1/R^2/R^3)	Yield[b]	Dr[c]
1	**2a**	**3a**	**4a** (H/4-MeC_6H_4/4-BrC_6H_4)	63%	86:14
2	**2a**	**3b**	**4b** (H/4-MeC_6H_4/4-ClC_6H_4)	62%	85:15
3	**2a**	**3c**	**4c** (H/4-MeC_6H_4/4-$NO_2C_6H_4$)	67%	82:18
4	**2a**	**3d**	**4d** (H/4-MeC_6H_4/4-OMeC_6H_4)	52%	86:14
5	**2a**	**3e**	**4e** (H/4-MeC_6H_4/C_6H_5)	63%	81:19
6[d]	**2a**	**3f**	**4f** (H/4-MeC_6H_4/Et)	64%	88:12
7	**2a**	**3g**	**4g** (H/4-MeC_6H_4/i-Pr)	34%	86:14
8	**2a**	**3h**	**4h** (H/4-MeC_6H_4/Bn)	50%	85:15
9[d]	**2a**	**3i**	**4i** (H/4-MeC_6H_4/H)	74%	-
10	**2b**	**3b**	**4j** (4-F/4-MeC_6H_4/4-ClCC_6H_4)	58%	83:17
11	**2c**	**3a**	**4k** (4-Cl/4-MeC_6H_4/4-BrC_6H_4)	59%	86:14
12	**2d**	**3a**	**4l** (4-Br/4-MeC_6H_4/4-BrC_6H_4)	60%	84:16
13	**2e**	**3a**	**4m** (4-Me/4-MeC_6H_4/4-BrC_6H_4)	47%	88:12
14	**2f**	**3a**	**4n** (H/4-BrC_6H_4/4-BrC_6H_4)	42%	85:15
15	**2g**	**3a**	**4o** (H/4-$NO_2C_6H_4$/4-BrC_6H_4)	25%	85:15
16	**2h**	**3e**	**4p** (2-Br/4-MeC_6H_4/C_6H_5)	65%	81:19
17	**2i**	**3a**	**4q**(H/Me/4-BrC_6H_4)	50%	71:29

[a] The reaction was run under the optimized conditions; [b] Combined yields of *cis*-**4** and *trans*-**4**; [c] Determined by NMR analysis (*cis/trans*); [d] The reaction was run at 50 °C.

affording product **4** in moderate yields and with good diastereoslectivities. *cis*-Diastereomers were isolated as the major isomers. The structures of *cis*-**4a** and *cis*-**4f** were confirmed by

Table 3 Investigation of the scope of arenes[a]



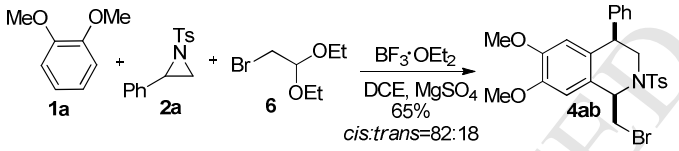
Entry	1	2	3	4	Yield[b]	Dr[c]
1		**2a**	**3b**		62%	78:22
2		**2c**	**3a**		58%	78:22
3		**2c**	**3a**		58%	33:67
4[d]		**2c**	**3a**		56%	>95:5
5[d]		**2c**	**3a**		40%	>95:5
6[d]		**2a**	**3b**		20%	>95:5
7[d]		**2a**	**3i**		39%	-
8		**2a**	**3a**		50%	86:14
9[e]		**2c**	**3i**		42%	-
10		**2a**	**3a**		0	-

[a] The reaction was run under the optimized conditions; [b] Combined yields of *cis*-**4** and *trans*-**4**; [c] Determined by NMR analysis (*cis/trans*); [d] Before the aldehyde was added, the reaction time was prolong to 5h; [e] 10% $AgPF_6$ and 100 mol% $BF_3{\cdot}OEt_2$ was used.

X-ray crystal structure analysis,[16] and the relative stereochemistry of other *cis*-diastereomers were determined by the analysis of NMR spectrum compared with *cis*-**4a** and *cis*-**4f**. Firstly, we fixed arene **1a** and aziridine **3a** as substrates to examine the scope of aldehydes. Aromatic aldehydes substituted with both electron-rich groups and electron-poor groups were suitable substrates for the three-component reaction (entries 1~5). The desired products **4a**~**4e** were obtained in moderate yields with good diastereoslectivities. The aliphatic aldehydes also reacted smoothly with arene **1a** and aziridine **3a** and led to the corresponding products **4f**~**4i** in moderate yields with good diastereoslectivities (entries 6~9). Subsequently, several aziridines were tested to react with arene **1a** and aldehyde **3** under the optimized reaction conditions. It was found that aziridines derived from aromatic alkenes could successfully undergo this reaction. Electron-withdrawing substituents on the benzene ring, such as F, Cl, Br gave similar product yields to **4a**

(entries 10~12 and entry 16). Electron-donating substituents on the benzene ring led to harmful effect on the yields of products. Aziridine **2e** underwent the three-component reaction to afford the corresponding product **4m** in 47% yield (entry 13). Besides, we examined the influence of the protecting group of the N-atom of the aziridines for the three-component reaction (entries 14~15, 17). Aziridine **2f** and **2g** gave the corresponding product with good diastereoselectivities, but along with remarkably decreased yields. When aziridine **2i** was subjected to the three-component reaction, a significantly reduced diastereoselectivity was observed.

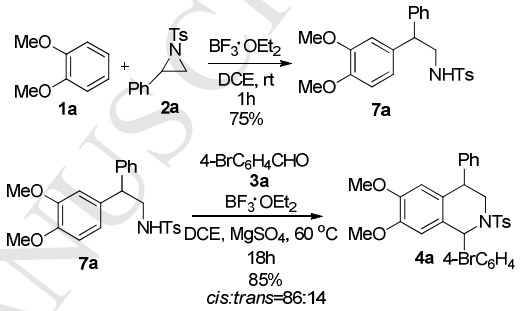
In order to further broaden the application scope of the three-component reaction, several arenes and N-methylindole were selected to react with aziridine **2** and aldehyde **3**. The results were summarized in Table 3. In most cases, *cis*-products **4** were successfully provided in moderate yields with good regioselectivities and diastereoselectivities. As the minor diastereomer, the structure of *trans*-**4r** was also confirmed by X-ray crystal structure analysis[16]. Interestingly, when benzene, o-xylene, toluene were subjected to the reaction, corresponding product *cis*-**4** were obtained as single diastereomers (*cis:trans*>95:5) (entries 4~6). For chlorobenzene **2i**, the three-component reaction failed to provide corresponding product **4z** (entry 10). As an exception, p-methoxyanisole reacted with aziridine **2b** and aldehyde **3a** to give *trans*-**4t** as the major isomer (*cis:trans*=33:67) (entry 3). Perhaps the two methoxyl groups on the benzene ring, which are close to aryl groups on the N-heterocycle, enhanced the repelling interaction between the 1-aryl group and 4-aryl group in the *cis*-isomer. It caused that *cis*-isomer was more unstable than *trans*-isomer. Moreover, arene **1h** reacted with **2a** and **3a** leading to unexpected **4a** as the exclusive product (entry 8). The reason was that Br^+ may be removed instead of proton in the process of Pictet-Spengler condensation.



Scheme 3. Three-component reaction using acetal **6**

It should be noted that acetal **6** was also a suitable substrate for the three-component reaction (Scheme 3). Product **4ab** was successfully isolated in 65% yield with a good diastereoselectivity (*cis:trans*=82:18).

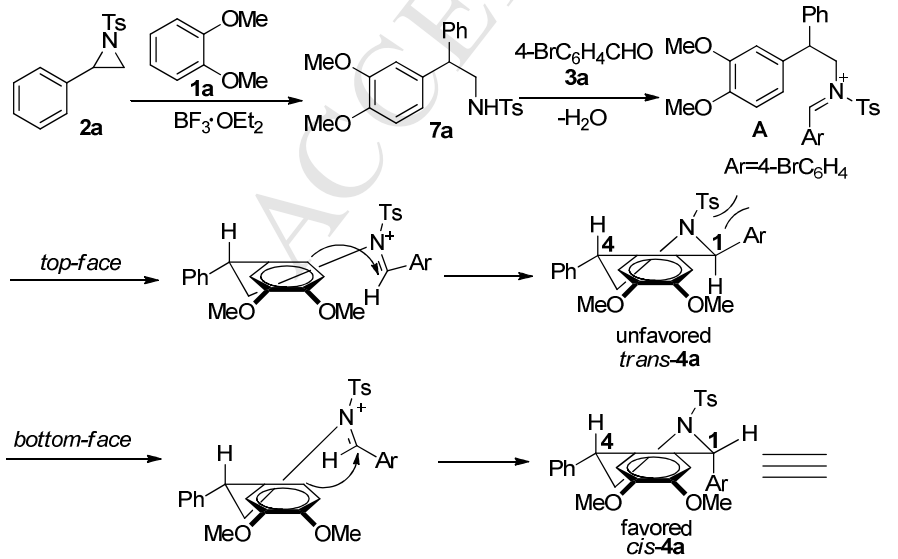
Then we investigated the mechanism of the three-component reaction (Scheme 4). As the key intermediate, amine **7a** was prepared in 75% yield by Lewis acid promoted ring opening of aziridine **2a** with arene **1a**. Then the reaction of amine **7a** with aldehyde **3a** was tested, tetrahydroisoquinoline **4a** was isolated in 85% yield with a good diastereoselectivity (*cis:trans*=86:14). According to this experiment result, a plausible mechanism for the diastereoselecctive three-component reaction was depicted in Scheme 5. In the presence of Lewis acid the ring opening of aziridine **2a** with arene **1a** afforded amine **7a**, which further reacted with aldehyde **3a** to give iminium ions **A**. A *top*-face attacking to iminium ions is unfavored. Because 1-Phenyl group occupied an equatorial position in half-chair conformation, and suffered from the gauche interaction with tosyl group which was roughly parallel on the ring of tetrahydroisoquinoline. A *bottom*-face attacking would provide a favored product *cis*-**4a**. From the X-ray crystal structure of *cis*-**4a**, we could see that the axial 1-phenyl group avoided the unfavorable interaction from tosyl group.

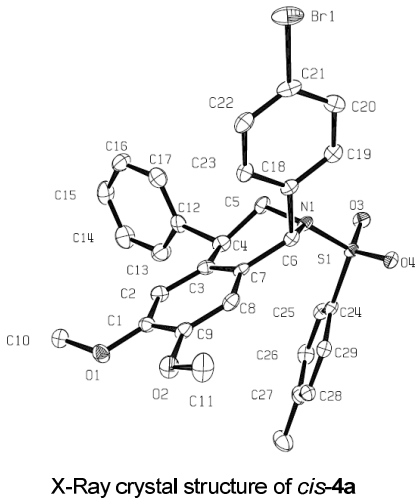


Scheme 4. Experiments for investigating the reaction mechanism

3. Conclusions

In summary, Lewis acid promoted three-component reactions of aziridines, arenes and aldehydes have been developed for the construction of 1,4-disubstituted tetrahydroisoquinolines. The presented transformation is facile, efficient and diastereoselective. In most cases, 1,4-*cis* diastereomers of tetrahydroisoquinolines were isolated as the major isomers. The application study of the three-component reaction in the synthesis of corresponding medical and bioactive molecules is in process in our laboratory.





X-Ray crystal structure of *cis*-**4a**

Scheme 5. a plausible mechanism for the three-component reaction

4. Experimental Section

4.1 General informations

The ^{1}H NMR, ^{13}C NMR spectra were recorded with Bruker 400 MHz spectrometer instruments in $CDCl_3$. The chemical shifts (δ) were measured in ppm and with the solvents as references (For $CDCl_3$, ^{1}H: δ=7.26 ppm, ^{13}C δ = 77.0 ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, br = broad. All reagents were obtained from commercial suppliers unless otherwise stated. Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under nitrogen. Purification of products was accomplished by flash chromatography using silica gel (200~300 mesh). Thin layer chromatography (TLC) was performed on Merck silica gel GF254 plates and visualized by UV-light (254 nm or 365 nm). Melting points were obtained on a Yanaco-241 apparatus and are uncorrected. IR spectra were recorded on a MAGNA-560 spectrometer made by Nicolet Company. HRMS were recorded on VG ZAB-HS mass spectrometer with ESI resource. Aziridines **2a**~**2i** in this paper are synthesized according to the literature procedures[17].

4.2 General procedure for the synthesis of tetrahydroisoquinolines

Under an argon atmosphere, $BF_3{\cdot}OEt_2$ (0.6 mmol) was added to a solution of arene **1** (0.3 mmol) and aziridine **2** (0.2 mmol) in DCE (2 mL). The mixture was stirred at room temperature for 1h and then aldehyde **3** (0.4 mmol) and anhydrous $MgSO_4$ (400 mg) were added. The mixture was stirred at 60 ^{o}C for 18h. Cooled to room temperature, water (10 mL) was added and the product was extracted with EtOAc (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate=5:1) on silica gel to afford product **4.** The physical and spectra data of the compounds **4a**~**4ab**, **5a** are shown as follows.

*4.2.1. 1-(4-Bromophenyl)-6,7-dimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4a**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 63%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=86:14). Major diastereoisomer: white solid, m.p. 190~193 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 6.8 Hz, 2H), 7.24 (d, J = 7.0 Hz, 1H), 7.17 (dd, J = 14.4, 8.2 Hz, 4H), 7.07 – 6.98 (m, 2H), 6.44 (s, 1H), 6.21 (s, 1H), 6.14 (s, 1H), 3.88 – 3.72 (m, 5H), 3.58 (s, 3H), 3.01 (dd, J = 13.9, 11.1 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.8, 143.3, 141.9, 140.5, 137.6, 131.4, 130.6, 129.7, 129.4, 128.7, 128.7, 127.2, 127.0, 125.3, 122.0, 111.7, 109.9, 58.5, 55.9, 55.7, 46.1, 42.5, 21.4. HRMS (ESI) Calcd. for $C_{30}H_{29}{}^{79}BrNO_4S$ $(M+H)^+$: 578.0995; Found: 578.0985; IR (neat): ν = 3083, 3029, 3010, 2951, 2930, 2833, 1612, 1597, 1517, 1466, 1449, 1334, 1306, 1259, 1221, 1162, 1093, 1071, 1040, 1008, 966, 846, 800, 770, 685, 664, 573, 558, 537, 504 cm^{-1}. Minor diastereoisomer: white solid, m.p. 215~218 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 2H), 7.30 (s, 2H), 7.22 – 7.17 (m, 3H), 7.13 (d, J = 8.4 Hz, 2H), 7.00 (s, 1H), 6.98 (s, 1H), 6.95 – 6.89 (m, 2H), 6.43 (d, J = 3.0 Hz, 2H), 6.12 (s, 1H), 4.12 (t, J = 3.9 Hz, 1H), 3.84 – 3.74 (m, 5H), 3.72 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 148.2, 142.8, 142.7, 140.1, 136.8, 131.3, 130.6, 129.2, 128.5, 128.3, 128.0, 127.5, 127.0, 126.6, 121.9, 111.8, 110.3, 58.8, 55.9, 55.8, 47.1, 43.7, 21.4; HRMS (ESI) Calcd. for $C_{30}H_{29}{}^{79}BrNO_4S$ $(M+H)^+$: 578.0995; Found: 578.0985; IR (neat): ν = 3728, 3674, 3526, 3295, 3030, 3009, 2961, 2933, 1770, 1714, 1592, 1517, 1486, 1467, 1453, 1342, 1323, 1161, 1110, 1092, 1008, 993, 879, 819, 797, 772, 701, 664, 556, 540, 527 cm^{-1}.

*4.2.2. 1-(4-Chlorophenyl)-6,7-dimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4b**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 62%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=85:15). Major diastereoisomer: white solid, m.p. 178~181 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.33 – 7.22 (m, 7H), 7.16 (d, J = 8.1 Hz, 2H), 7.07 – 6.98 (m, 2H), 6.45 (s, 1H), 6.24 (s, 1H), 6.14 (s, 1H), 3.92 – 3.71 (m, 5H), 3.58 (s, 3H), 3.02 (dd, J = 13.9, 11.1 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.8, 143.3, 141.9, 139.9, 137.6, 133.7, 130.2, 129.7, 129.4, 128.7, 128.7, 128.5, 127.2, 127.0, 125.4, 111.7, 109.9, 58.4, 55.9, 55.7, 46.0, 42.5, 21.4; HRMS (ESI) Calcd. for $C_{30}H_{29}ClNO_4S$ $(M+H)^+$: 534.1500; Found: 534.1493; IR (neat): ν = 3062, 3030, 3008, 2951, 2920, 2852, 1692, 1597, 1517, 1489, 1466, 1450, 1307, 1258, 1221, 1162, 1116, 1093, 1040, 1012, 965, 833, 770, 670, 652, 574, 558, 537, 507 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.3. 6,7-Dimethoxy-1-(4-nitrophenyl)-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4c**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 67%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=82:18). Major diastereoisomer: white solid, m.p. 187~190 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.32 (dt, J = 10.4, 6.9 Hz, 3H), 7.23 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 6.9 Hz, 2H), 6.51 (s, 1H), 6.38 (s, 1H), 6.23 (s, 1H), 3.95 (dd, J = 14.6, 6.4 Hz, 1H), 3.88 – 3.81 (m, 4H), 3.65 (s, 3H), 3.03 (dd, J = 14.6, 11.6 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 148.6, 147.9, 147.4, 143.6, 141.5, 137.3, 129.7, 129.5, 128.8, 128.6, 127.3, 127.0, 124.3, 123.5, 111.8, 109.8, 58.3, 55.9, 55.7, 46.3, 42.3, 21.4; one carbon resonance absent presumably due to overlap; HRMS (ESI) Calcd. for $C_{30}H_{29}N_2O_6S$ $(M+H)^+$: 545.1741; Found: 545.1737; IR (neat): ν = 3708, 3675, 3315, 2933, 1603, 1518, 1452, 1347, 1245, 1222, 1161, 1092, 1031, 956, 860, 815, 740, 702, 650, 572, 558, 542 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.4. 6,7-Dimethoxy-1-(4-methoxyphenyl)-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4d**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 52%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=86:14). Major diastereoisomer: white solid, m.p. 165-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 6.9 Hz, 2H), 7.23 (dd, J = 7.8, 4.1 Hz, 3H), 7.14 (d, J = 8.0 Hz, 2H), 7.09 – 7.03 (m, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.48 (s, 1H), 6.23 (s, 1H), 6.14 (s, 1H), 3.90 – 3.70 (m, 8H), 3.58 (s, 3H), 3.07 (dd, J = 16.3, 13.5 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 148.2, 147.7, 143.1, 142.2, 137.9, 133.5, 130.2, 129.7, 129.3, 128.8, 128.7, 127.1, 126.4, 113.6, 111.6, 110.0, 58.6, 55.9, 55.7, 55.3, 45.9, 42.7, 21.5; one carbon resonance absent presumably due to overlap; HRMS (ESI) Calcd. for $C_{31}H_{32}NO_5S$ $(M+H)^+$: 530.1996; Found: 530.1989; IR (neat): ν = 3290, 2933, 2850, 1605, 1512, 1463, 1338, 1304, 1249, 1223, 1161, 1119, 1092, 1032, 959, 862, 815, 763, 735, 703, 678, 657, 578, 561 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.5. 6,7-Dimethoxy-1,4-diphenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4e**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 63%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=81:19). Major diastereoisomer:

yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.2 Hz, 2H), 7.20 (ddd, J = 23.7, 15.3, 5.7 Hz, 8H), 7.06 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 7.0 Hz, 2H), 6.42 (s, 1H), 6.21 (s, 1H), 6.07 (s, 1H), 3.80 – 3.73 (m, 2H), 3.70 (s, 3H), 3.50 (s, 3H), 2.99 (dd, J = 16.4, 13.6 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.7, 143.1, 142.1, 141.3, 137.8, 129.7, 129.3, 128.9, 128.8, 128.7, 128.3, 127.7, 127.1, 125.9, 111.6, 110.1, 59.0, 55.9, 55.7, 46.0, 42.6, 21.4. one carbon resonance absent presumably due to overlap; HRMS (ESI) Calcd. for $C_{30}H_{30}NO_4S$ $(M+H)^+$: 500.1890; Found: 500.1900; IR (neat): *ν* = 3061, 3028, 2972, 2933, 2868, 2853, 1600, 1515, 1494, 1452, 1400, 1340, 1305, 1265, 1244, 1223, 1161, 1118, 1109, 1030, 979, 959, 865, 813, 762, 740, 681, 661, 585, 569, 540 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.6. 1-Ethyl-6,7-dimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4f**).* Compound **4f** was prepared according to a modified General Procedure. After aldehyde **3f** and $MgSO_4$ (500 mg) were added, the reaction mixture was stirred at 50 ^{o}C for 18h. Combined yield of *cis*-diastereomer and *trans*-diastereomer: 64%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=88:12). Major diastereoisomer: white solid, m.p. 138~141 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.3 Hz, 2H), 7.32 – 7.19 (m, 4H), 7.15 (s, 1H), 7.08 – 6.99 (m, 2H), 6.56 (s, 1H), 6.03 (s, 1H), 4.89 (dd, J = 9.0, 5.7 Hz, 1H), 4.08 – 3.98 (m, 1H), 3.89 (s, 3H), 3.71 – 3.61 (m, 1H), 3.53 (s, 3H), 3.23 (dd, J = 14.9, 11.8 Hz, 1H), 2.35 (s, 3H), 1.89 (ddd, J = 9.2, 6.5, 3.9 Hz, 2H), 1.06 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 147.6, 143.1, 142.5, 138.0, 129.8, 129.3, 128.8, 128.7, 127.9, 127.1, 127.0, 111.8, 108.8, 57.9, 55.9, 55.7, 45.9, 42.2, 30.3, 21.5, 11.4; HRMS (ESI) Calcd. for $C_{26}H_{30}NO_4S$ $(M+H)^+$: 452.1890; Found: 452.1893; IR (neat): *ν* = 3026, 2968, 2929, 1609, 1517, 1446, 1372, 1337, 1266, 1243, 1222, 1159, 1122, 1037, 942, 814, 766, 732, 704, 678, 653, 566, 552 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.7. 1-Isopropyl-6,7-dimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4g**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 34%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=86:14). Major diastereoisomer: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.3 Hz, 2H), 7.29 (dd, J = 8.4, 1.5 Hz, 1H), 7.24 – 7.20 (m, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.03 – 6.95 (m, 2H), 6.57 (s, 1H), 6.00 (s, 1H), 4.58 (d, J = 8.6 Hz, 1H), 4.11 – 4.03 (m, 1H), 3.89 (s, 3H), 3.61 (dd, J = 11.4, 7.7 Hz, 1H), 3.54 (s, 3H), 3.27 (dd, J = 15.2, 11.5 Hz, 1H), 2.32 (s, 3H), 2.08 (dt, J = 13.4, 6.7 Hz, 1H), 1.15 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.8, 143.1, 142.9, 137.7, 129.1, 128.7, 128.6, 128.2, 128.2, 127.1, 126.9, 111.9, 110.5, 62.1, 55.9, 55.7, 46.7, 41.9, 34.1, 21.4, 20.6, 20.1; HRMS (ESI) Calcd. for $C_{27}H_{32}NO_4S$ $(M+H)^+$: 466.2047; Found: 466.2047; IR (neat): *ν* = 3419, 2958, 2925, 2852, 1608, 1515, 1454, 1341, 1305, 1243, 1222, 1160, 1125, 1112, 1091, 870, 814, 759, 702, 660, 573, 543 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.8. 1-Benzyl-6,7-dimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4h**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 50%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=85:15). Major diastereoisomer: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.1 Hz, 2H), 7.34 – 7.27 (m, 3H), 7.25 (s, 3H), 7.11 (dd, J = 12.4, 7.9 Hz, 4H), 7.04 (d, J = 7.2 Hz, 2H), 6.19 (s, 1H), 6.14 (s, 1H), 5.29 (t, J = 6.8 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.65 (s, 3H), 3.56 (s, 3H), 3.16 (dtd, J = 20.6, 13.3, 6.9 Hz, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 147.1, 143.1, 142.5, 137.7, 137.7, 129.9, 129.5, 128.9, 128.7, 128.6, 128.5, 128.2, 127.1, 127.1, 126.7, 111.9, 109.5, 57.2, 55.7, 55.6, 46.4, 43.5, 43.2, 21.5; HRMS (ESI) Calcd. for $C_{31}H_{32}NO_4S$ $(M+H)^+$: 514.2047; Found: 514.2048; IR (neat): *ν* = 3061, 3028, 2956, 2934, 2856, 1601, 1515, 1453, 1340, 1246, 1223, 1158, 1118, 1092, 1040, 968, 912, 864, 814, 772, 734, 701, 660, 561, 550 cm^{-1}. The mixture of major diastereoisomer and minor diastereoisomer: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.0, 6.2 Hz, 3H), 7.33 – 7.26 (m, 4H), 7.26 – 7.21 (m, 3H), 7.17 – 7.07 (m, 6H), 7.04 (dd, J = 11.8, 4.9 Hz, 3H), 6.83 – 6.77 (m, 1H), 6.24 (s, 1H), 6.20 (s, 1H), 6.14 (s, 1H), 5.88 (s, 1H), 5.30 (t, J = 6.9 Hz, 1H), 5.11 (dd, J = 9.2, 3.1 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.81 (t, J = 4.4 Hz, 1H), 3.75 – 3.71 (m, 1H), 3.65 (s, 3H), 3.62 (s, 1H), 3.56 (s, 3H), 3.47 (s, 1H), 3.40 – 3.35 (m, 1H), 3.28 – 2.99 (m, 4H), 2.35 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 147.9, 147.1, 143.1, 142.9, 142.7, 142.5, 137.9, 137.7, 136.5, 130.4, 129.9, 129.4, 128.9, 128.7, 128.6, 128.5, 128.5, 128.3, 128.3, 128.2, 128.0, 127.8, 127.1, 127.1, 126.6, 126.5, 111.9, 111.5, 110.1, 109.5, 58.4, 57.2, 55.7, 55.6, 55.4, 47.8, 46.4, 44.3, 43.7, 43.5, 43.2, 21.4; HRMS (ESI) Calcd. for $C_{31}H_{32}NO_4S$ $(M+H)^+$: 514.2047; Found: 514.2048; IR (neat): *ν* = 3422, 3361, 3027, 3003, 2956, 2926, 2854, 1601, 1515, 1454, 1341, 1248, 1222, 1158, 1118, 1093, 1040, 968, 865, 814, 750, 702, 660, 561, 551 cm^{-1}.

*4.2.9. 6,7-Dimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4i**).* Compound **4i** was prepared according to a modified General Procedure. After aldehyde **3i** and $MgSO_4$ were added, the reaction mixture was stirred at 50 ^{o}C for 8h. Yield: 74%. White solid, m.p. 149~151 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 2H), 7.37 – 7.22 (m, 5H), 7.18 – 7.01 (m, 2H), 6.57 (s, 1H), 6.31 (s, 1H), 4.40 (d, J = 14.5 Hz, 1H), 4.28 – 4.18 (m, 1H), 4.12 (d, J = 14.5 Hz, 1H), 3.85 (s, 3H), 3.73 (dd, J = 11.6, 5.1 Hz, 1H), 3.63 (s, 3H), 3.03 (dd, J = 11.7, 8.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 147.9, 143.6, 142.5, 133.1, 129.6, 128.9, 128.5, 128.1, 127.7, 127.0, 124.1, 111.8, 108.4, 55.9, 55.8, 51.2, 47.7, 44.9, 21.5; The analytical data match those reported in the literature[6a].

*4.2.10. 1-(4-Chlorophenyl)-4-(4-fluorophenyl)-6,7-dimethoxy-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4j**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 58%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=83:17). Major diastereoisomer: white solid, m.p. 200~202 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2H), 7.19 (dt, J = 17.3, 8.5 Hz, 4H), 7.09 (d, J = 8.1 Hz, 2H), 6.97 – 6.85 (m, 4H), 6.38 (s, 1H), 6.15 (s, 1H), 6.04 (s, 1H), 3.80 – 3.69 (m, 5H), 3.52 (s, 3H), 2.99 – 2.82 (m, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J = 244 Hz), 148.4, 147.9, 143.4, 139.9, 137.7, 137.7, 137.6, 133.8, 130.2 (d, J = 8 Hz), 130.2, 129.4, 128.5, 127.0, 125.4, 115.7 (d, J = 21Hz), 111.5, 109.9, 58.3, 55.9, 55.7, 46.1, 41.8, 21.5; HRMS (ESI) Calcd. for $C_{30}H_{28}ClFNO_4S$ $(M+H)^+$: 552.1406; Found: 552.1397; IR (neat): *ν* =3692, 3053, 3008, 2949, 2929, 2854, 1733, 1601, 1513, 1466, 1333, 1222, 1161, 1117, 1040, 965, 868, 834, 804, 766, 650, 569, 538, 505 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.11. 1-(4-Bromophenyl)-4-(4-chlorophenyl)-6,7-dimethoxy-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4k**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 59%. The *cis/trans* ratio was determined by NMR analysis (*cis/tran*=86:14). Major diastereoisomer: white solid, m.p. 199~202 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 4.1 Hz, 2H), 7.09 (d, J = 8.3 Hz, 4H), 6.90 (d, J = 8.4 Hz, 2H), 6.38 (s, 1H), 6.13 (s, 1H), 6.03 (s, 1H), 3.77 – 3.65 (m, 5H), 3.53 (s, 3H), 2.93 – 2.84 (m, 1H), 2.29 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 148.5, 147.9, 143.5, 140.5, 140.3, 137.5, 133.0, 131.5, 130.5, 130.1, 129.5, 129.1, 129.0, 127.0, 125.4, 122.1, 111.5, 109.9, 58.4, 55.9, 55.8, 46.0, 42.1, 21.5; HRMS (ESI) Calcd. for $C_{30}H_{28}{}^{79}BrClNO_4S$ $(M+H)^+$: 612.0606; Found: 612.0595; IR (neat): *ν* = 2997, 2951, 2917, 2852, 1609, 1596, 1517, 1488, 1466, 1410, 1333, 1306, 1260, 1221, 1162, 1091, 1072, 1037, 1009, 966, 799, 767, 711, 661, 574, 562, 538 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.12. 1,4-Bis(4-bromophenyl)-6,7-dimethoxy-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4l**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 60%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=84:16). Two inseparable mixture of diastereomers,white solid, m.p. 193~198 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 1.68H), 7.47 – 7.38 (m, 3.36H), 7.36 (d, J = 8.5 Hz, 0.32H), 7.23 (d, J = 8.3 Hz, 0.32H), 7.14 (t, J = 8.8 Hz, 4H), 6.98 (d, J = 8.0 Hz, 0.32H), 6.92 (d, J = 8.4 Hz, 1.68H), 6.65 (d, J = 8.4 Hz, 0.32H), 6.45 (s, 0.84H), 6.40 (s, 0.16H), 6.38 (s, 0.16H), 6.20 (s, 0.84H), 6.17 (s, 0.16H), 6.10 (s, 0.84H), 4.05 (d, J = 3.4 Hz, 0.16H), 3.88 – 3.68 (m, 5H), 3.60 (s, 2.52H), 3.01 – 2.88 (m, 0.84H), 2.38 (s, 0.48H), 2.36 (s, 2.52H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 148.6, 148.4, 148.0, 143.5, 143.1, 142.3, 141.0, 140.3, 139.8, 137.6, 136.7, 132.0, 131.5, 131.4, 131.2, 130.9, 130.5, 130.4, 130.0, 129.5, 129.1, 129.0, 127.4, 127.0, 126.9, 125.5, 122.1, 121.1, 120.6, 111.7, 111.5, 110.2, 110.0, 58.4, 56.0, 55.9, 55.8, 46.1, 46.0, 43.1, 42.2, 21.5, 21.5; four carbon resonance absent presumably due to overlap; HRMS (ESI) Calcd. for $C_{30}H_{28}{}^{79}Br_2NO_4S$ $(M+H)^+$: 656.0100; Found: 656.0085; IR (neat): *ν* = 3673, 3294, 2953, 2933, 1595, 1515, 1486, 1466, 1448, 1408, 1333, 1306, 1220, 1163, 1110, 1009, 858, 799, 767, 657, 574, 561, 538 cm^{-1}.

*4.2.13. 1-(4-Bromophenyl)-6,7-dimethoxy-4-(p-tolyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4m**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 47%. The *cis/trans* ratio was determined by NMR analysis (*cis/tran*=88:12). Major diastereoisomer: white solid, m.p. 208~210 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.17 (dd, J = 16.5, 8.2 Hz, 4H), 7.08 (d, J = 7.8 Hz, 2H), 6.91 (d, J = 7.9 Hz, 2H), 6.43 (s, 1H), 6.20 (s, 1H), 6.16 (s, 1H), 3.87 – 3.69 (m, 5H), 3.59 (s, 3H), 2.99 (dd, J = 14.0, 11.3 Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.8, 143.3, 140.5, 138.8, 137.7, 136.8, 131.5, 130.6, 129.9, 129.4, 129.4, 128.6, 127.0, 125.3, 122.0, 111.7, 109.9, 58.5, 55.9, 55.8, 46.1, 42.2, 21.5, 21.0; HRMS (ESI) Calcd. for $C_{31}H_{31}{}^{79}BrNO_4S$ $(M+H)^+$: 592.1152; Found: 592.1147; IR (neat): *ν* = 3310, 2995, 2952, 2922, 2854, 1655, 1595, 1515, 1485, 1465, 1448, 1334, 1257, 1162, 1115, 1037, 1007, 966, 818, 799, 663, 569, 546 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.14. 1-(4-Bromophenyl)-2-((4-bromophenyl)sulfonyl)-6,7-dimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**4n**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 42%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=85:15). Major diastereoisomer: white solid, m.p. 188~191 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.7 Hz, 2H), 7.48 (dd, J = 11.8, 8.6 Hz, 4H), 7.32 – 7.27 (m, 2H), 7.25 (s, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 6.7 Hz, 2H), 6.44 (s, 1H), 6.21 (s, 1H), 6.15 (s, 1H), 3.91 – 3.71 (m, 5H), 3.60 (s, 3H), 3.05 (dd, J = 14.4, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 147.9, 141.6, 140.1, 139.7, 132.0, 131.6, 130.6, 129.4, 128.8, 128.7, 128.5, 127.5, 127.3, 125.0, 122.2, 111.7, 109.8, 58.8, 55.9, 55.8, 46.2, 42.6; HRMS (ESI) Calcd. for $C_{29}H_{26}{}^{79}Br_2NO_4S$ $(M+H)^+$: 641.9944; Found: 641.9931; IR (neat): *ν* = 3726, 3083, 3061, 3008, 2962, 2948, 2927, 2830, 1722, 1573, 1516, 1449, 1364, 1337, 1273, 1258, 1223, 1163, 1117, 1092, 1069, 1040, 1009, 964, 863, 796, 771, 736, 702, 603, 568, 543, 521, 504 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.15. 1-(4-Bromophenyl)-6,7-dimethoxy-2-((4-nitrophenyl)sulfonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**4o**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 25%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=85:15). Major diastereoisomer: white solid, m.p. 221~224 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.04 (m, 2H), 7.91 – 7.73 (m, 2H), 7.46 – 7.35 (m, 2H), 7.30 – 7.20 (m, 3H), 7.13 (d, J = 8.4 Hz, 2H), 7.01 – 6.90 (m, 2H), 6.37 (s, 1H), 6.18 (s, 1H), 6.07 (s, 1H), 3.86 – 3.67 (m, 5H), 3.50 (s, 3H), 3.06 (dd, J = 14.6, 11.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 148.7, 148.1, 146.6, 141.2, 139.7, 131.7, 130.6, 129.2, 128.9, 128.7, 128.1, 127.5, 124.8, 124.1, 122.5, 111.6, 109.7, 59.0, 56.0, 55.8, 46.3, 43.0; HRMS (ESI) Calcd. for $C_{29}H_{26}{}^{79}BrN_2O_6S$ $(M+H)^+$: 609.0690 Found: 609.0683; IR (neat): *ν* = 3101, 2963, 2948, 2928, 2909, 1610, 1531, 1517, 1484, 1464, 1404, 1346, 1306, 1259, 1224, 1164, 1117, 1093, 1011, 961, 856, 797, 735, 606, 566, 500, 491, 465 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.16. 4-(2-bromophenyl)-6,7-dimethoxy-1-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4p**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 65%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=81:19). Major diastereoisomer: white solid, m.p. 198~202 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.53 (dd, J = 8.0, 1.2 Hz, 1H), 7.38 – 7.28 (m, 5H), 7.15 (dd, J = 16.7, 7.8 Hz, 3H), 7.06 (td, J = 7.7, 1.6 Hz, 1H), 6.89 (d, J = 6.7 Hz, 1H), 6.53 (s, 1H), 6.31 (s, 1H), 6.02 (s, 1H), 4.28 (dd, J = 11.7, 6.6 Hz, 1H), 3.98 (dd, J = 14.4, 6.2 Hz, 1H), 3.81 (s, 3H), 3.59 (s, 3H), 2.93 – 2.80 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 147.9, 143.3, 141.5, 140.4, 137.5, 133.0, 131.5, 130.6, 129.7, 129.4, 128.7, 128.7, 128.0, 127.2, 125.5, 125.3, 122.0, 111.5, 110.0, 58.6, 56.0, 55.9, 44.2, 41.0, 21.5; HRMS (ESI) Calcd. for $C_{30}H_{29}{}^{79}BrNO_4S$ $(M+H)^+$: 578.0995; Found: 578.0980; IR (neat): *ν* = 2951, 2932, 2910, 2831, 1515, 1484, 1466, 1449, 1364, 1335, 1245, 1223, 1163, 1117, 1091, 1037, 965, 856, 800, 767, 743, 690, 665, 572, 561, 542 cm^{-1}. The mixture of major diastereoisomer and minor diastereoisomer: white solid, m.p. 150~156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.53 (dd, J = 8.0, 1.0 Hz, 1H), 7.45 (dd, J = 11.8, 5.0 Hz, 2.5H), 7.34 (d, J = 8.4 Hz, 1.5H), 7.26 – 7.21 (m, 3.5H), 7.15 (dd, J = 16.2, 7.6 Hz, 3H), 7.11 – 7.03 (m, 2.5H), 7.02 – 6.96 (m, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.49 (s, 1H), 6.46 (dd, J = 7.2, 2.2 Hz, 0.5H), 6.40 (d, J = 4.3 Hz, 1H), 6.24 (s, 1H), 6.19 (s, 0.5H), 6.03 (s, 1H), 4.53 (d, J = 2.8 Hz, 0.5H), 4.27 (dd, J = 11.6, 6.6 Hz, 1H), 3.99 (dd, J = 15.0, 6.7 Hz, 1H), 3.89 – 3.85 (m, 0.5H), 3.81 (s, 3H), 3.74(s, 1.5H), 3.74(s, 1.5H), 3.65 (dd, J = 13.6, 4.4 Hz, 0.5H), 3.59 (s, 3H), 2.91 – 2.84 (m, 1H), 2.33 (s, 3H), 2.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.6, 148.5, 147.9, 143.3, 142.6, 141.7, 141.5, 140.4, 139.6, 137.4, 136.8, 132.9, 132.4, 131.5, 131.3, 131.1, 130.9, 130.6, 129.6, 129.4, 129.1, 128.7, 128.7, 128.0, 128.0, 127.7, 127.2, 127.1, 126.8, 125.4, 125.3, 124.0, 122.1, 122.0, 111.7, 111.5, 110.0, 58.6, 58.2, 56.0, 55.9, 55.8, 44.2, 43.8, 43.0, 41.0, 21.4, 21.4; three carbon resonance absent presumably due to overlap; HRMS (ESI) Calcd. for $C_{30}H_{29}{}^{79}BrNO_4S$ $(M+H)^+$: 578.0995; Found: 578.0980; IR (neat): *ν* = 3053, 3007, 2952, 2932, 2832, 1597, 1515, 1485, 1466, 1363, 1306, 1274, 1245, 1162, 1118, 1092, 1038, 1009, 964, 856, 800, 761, 742, 691, 662, 572, 561, 542 cm^{-1}.

*4.2.17. 1-(4-bromophenyl)-6,7-dimethoxy-2-(methylsulfonyl)-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**4q**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 50%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=71:29). Major diastereoisomer: white solid, m.p. 172~175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.2 Hz, 2H), 7.34 – 7.23 (m, 5H), 7.15 (d, J = 7.4 Hz, 2H), 6.45 (s, 1H), 6.37 (s, 1H), 6.02 (s, 1H), 4.27 (dd, J = 11.7, 6.6 Hz, 1H), 3.89 (dd, J = 14.4, 6.6 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 3.10 – 2.99 (m, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.1, 141.7, 139.9, 131.7, 130.6, 129.5, 128.9, 128.8, 127.4, 125.4, 122.3, 112.0, 110.1, 58.3, 55.9, 55.8, 45.9, 43.6, 40.1; HRMS (ESI) Calcd. for $C_{24}H_{24}{}^{79}BrNO_4SNa$ $(M+Na)^+$: 524.0502; Found: 524.0506; IR (neat): ν = 3753, 3678, 3654, 3143, 3025, 2930, 2372, 2340, 1610, 1486, 1458, 1402, 1334, 1247, 1223, 1117, 1073, 1034, 958, 862, 804, 771, 703, 593 cm^{-1}. Minor diastereoisomer: white solid, m.p. 168~170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.3 Hz, 2H), 7.29 – 7.17 (m, 5H), 7.05 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.38 (s, 1H), 6.05 (s, 1H), 4.20 (s, 1H), 3.91 – 3.53 (m, 8H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.4, 143.6, 139.9, 131.7, 130.9, 128.7, 128.5, 127.5, 127.1, 127.0, 122.4, 112.0, 110.2, 58.3, 55.9, 55.9, 46.3, 43.6, 39.6; HRMS (ESI) Calcd. for $C_{24}H_{24}{}^{79}BrNO_4SNa$ $(M+Na)^+$: 524.0502; Found: 524.0508; IR (neat): ν = 3858, 3752, 3677, 3653, 3421, 3164, 2874, 2369, 2340, 1612, 1518, 1461, 1323, 1245, 1151, 1064, 1009, 968, 850, 786, 702, 589, 528, 460 cm^{-1}.

*4.2.18. 1-(4-Chlorophenyl)-5,6,7-trimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4r**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 62%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=78:22). Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2H), 7.34 (dd, J = 19.0, 8.5 Hz, 4H), 7.18 (d, J = 7.6 Hz, 2H), 7.11 (dd, J = 14.1, 7.6 Hz, 3H), 6.94 (d, J = 7.2 Hz, 2H), 6.35 (s, 1H), 6.15 (s, 1H), 3.99 – 3.92 (m, 1H), 3.82 – 3.76 (m, 4H), 3.69 (s, 3H), 2.99 (s, 3H), 2.91 (dd, J = 15.1, 11.3 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 152.5, 144.2, 143.1, 141.9, 139.0, 137.3, 133.8, 130.1, 129.2, 129.0, 128.5, 128.4, 127.3, 127.1, 126.4, 123.8, 106.3, 60.5, 59.3, 59.1, 56.0, 46.6, 38.6, 21.4; HRMS (ESI) Calcd. for $C_{31}H_{31}ClNO_5S$ $(M+H)^+$: 564.1606; Found: 564.1608; IR (neat): ν = 3525, 3444, 3327, 3085, 3062, 3019, 2933, 2837, 1599, 1492, 1456, 1409, 1364, 1337, 1161, 1123, 1091, 1061, 1031, 1014, 979, 812, 745, 699, 660, 576, 566, 547, 508 cm^{-1}. Minor diastereoisomer: White solid, m.p. 139~140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.05 (m, 9H), 6.96 – 6.85 (m, 4H), 6.21 (s, 2H), 4.38 (d, J = 3.3 Hz, 1H), 3.87 – 3.75 (m, 4H), 3.74 – 3.61 (m, 4H), 3.33 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 151.0, 143.7, 142.5, 141.3, 139.2, 137.0, 133.8, 130.7, 130.5, 129.0, 128.3, 128.0, 127.9, 126.8, 126.1, 122.6, 106.0, 60.6, 60.3, 58.2, 55.8, 46.0, 39.2, 21.3; HRMS (ESI) Calcd. for $C_{31}H_{31}ClNO_5S$ $(M+H)^+$: 564.1606; Found: 564.1608; IR (neat): ν = 2977, 2938, 1600, 1492, 1451, 1406, 1342, 1280, 1238, 1161, 1125, 1107, 1088, 1044, 984, 965, 870, 814, 759, 703, 655, 581, 547 cm^{-1}.

*4.2.19. 5-(4-Bromophenyl)-8-(4-chlorophenyl)-6-tosyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (**4s**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 58%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=78:22). Major diastereoisomer: white solid, m.p. 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.29 (s, 1H), 7.27 (s, 1H), 7.19 (dd, J = 10.9, 8.3 Hz, 4H), 6.98 (d, J = 8.4 Hz, 2H), 6.46 (s, 1H), 6.17 (s, 1H), 6.13 (s, 1H), 5.92 (dd, J = 3.5, 1.2 Hz, 2H), 3.93 – 3.68 (m, 2H), 3.00 (dd, J = 14.2, 11.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 146.5, 143.6, 140.3, 140.2, 137.5, 133.1, 131.6, 130.6, 130.5, 130.1, 129.5, 129.0, 127.0, 126.4, 122.1, 108.9, 107.4, 101.2, 58.6, 45.8, 42.6, 21.5; HRMS (ESI) Calcd. for$C_{29}H_{24}{}^{79}BrClNO_4S$ $(M+H)^+$: 596.0293; Found: 596.0285; IR (neat): ν = 3726, 3692, 3306, 3062, 3030, 2963, 2925, 2882, 1912, 1595, 1485, 1386, 1361, 1333, 1296, 1238, 1159, 1091, 1041, 1003, 961, 936, 856, 798, 786, 691, 656, 559, 537 cm^{-1}. Minor diastereoisomer: White solid, m.p. 180~184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 7.17 – 7.04 (m, 4H), 7.00 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.42 (s, 1H), 6.35 (s, 1H), 6.09 (s, 1H), 5.90 (dd, J = 5.5, 1.2 Hz, 2H), 4.03 (t, J = 3.6 Hz, 1H), 3.74 (dd, J = 13.1, 4.4 Hz, 1H), 3.62 (dd, J = 13.0, 3.1 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 147.0, 143.2, 141.2, 139.8, 136.5, 132.6, 131.4, 130.7, 129.7, 129.2, 128.6, 128.5, 128.4, 127.0, 122.1, 108.9, 107.6, 101.2, 58.9, 46.4, 43.4, 21.5; HRMS (ESI) Calcd. For $C_{29}H_{24}{}^{79}BrClNO_4S$ $(M+H)^+$: 596.0293; Found: 596.0285; IR (neat): ν = 3524, 3443, 3327, 2962, 2925, 2875, 1594, 1485, 1403, 1338, 1317, 1229, 1154, 1092, 1036, 1012, 960, 937, 854, 811, 692, 652, 565, 538, 506 cm^{-1}.

*4.2.20. 1-(4-Bromophenyl)-4-(4-chlorophenyl)-5,8-dimethoxy-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4t**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 58%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=33:67). Minor diastereoisomer: white solid, m.p. 166~168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 8.9 Hz, 1H), 6.35 (s, 1H), 4.01 (dd, J = 15.0, 10.0 Hz, 1H), 3.88 – 3.81 (m, 1H), 3.72 (s, 3H), 3.26 (s, 3H), 2.81 (dd, J = 15.0, 11.2 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 150.4, 143.0, 142.4, 138.8, 137.2, 131.7, 131.3, 129.9, 129.1, 128.4, 128.4, 126.9, 126.7, 124.4, 121.6, 110.7, 108.6, 55.9, 55.5, 54.7, 46.4, 38.0, 21.4; HRMS (ESI) Calcd. for $C_{30}H_{28}{}^{79}BrClNO_4S$ $(M+H)^+$: 612.0606; Found: 612.0612; IR (neat): ν = 2954, 2929, 2836, 1725, 1597, 1482, 1400, 1343, 1305, 1259, 1161, 1111, 1087, 1045, 1012, 971, 952, 813, 742, 711, 688, 666, 574, 553 cm^{-1}. Major diastereoisomer: white solid, m.p. 197~200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.72 (s, 2H), 6.63 (s, 1H), 6.61 (s, 1H), 6.47 (s, 1H), 4.28 (m, 1H), 3.62 (d, J = 2.5 Hz, 2H), 3.56 (s, 3H), 3.52 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 149.5, 142.9, 142.0, 139.3, 137.0, 131.6, 130.9, 130.7, 129.0, 128.8, 127.8, 126.9, 125.5, 125.1, 121.5, 109.7, 109.5, 100.0, 55.8, 54.3, 45.2, 38.2, 21.5; HRMS (ESI) Calcd. for $C_{30}H_{28}{}^{79}BrClNO_4S$ $(M+H)^+$: 612.0606; Found: 612.0612; IR (neat): ν = 2964, 2929, 2837, 1736, 1600, 1480, 1457, 1437, 1403, 1324, 1305, 1261, 1161, 1116, 1089, 1079, 1054, 1011, 971, 951, 929, 864, 814, 771, 735, 706.698, 673, 658, 575, 553, 543 cm^{-1}.

*4.2.21. 1-(4-bromophenyl)-4-(4-chlorophenyl)-6,7-dimethyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4u**).* Compound **4u** was prepared according to a modified General Procedure. After $BF_3{\cdot}OEt_2$ was added, the mixture was stirred at room temperature for 5h. Purification by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1). Combined yield of *cis*-diastereomer and *trans*-diastereomer: 56%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*>95:5). Major diastereoisomer: white solid, m.p. 192~195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.21 – 7.17 (m, 2H), 7.07 (dd, J = 8.2, 3.4 Hz, 4H), 6.90 (d, J = 8.3 Hz, 2H), 6.68 (s, 1H), 6.37 (s, 1H), 6.12 (s, 1H), 3.76 (dd, J = 17.4, 6.9 Hz, 2H), 3.00 – 2.90 (m, 1H), 2.29 (s, 3H), 2.09 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 140.7, 140.7, 137.6, 136.2, 135.2, 134.3, 132.9, 131.5, 130.6, 130.6, 130.3, 130.2, 129.4, 129.0, 128.9, 127.1, 122.0, 58.4, 46.1, 42.3, 21.5,

19.4, 19.4; HRMS (ESI) Calcd. For $C_{30}H_{28}{}^{79}BrClNO_2S$ $(M+H)^+$: 602.0527; Found: 602.0528; IR (neat): ν = 3678, 2975, 2939, 2883, 1596, 1487, 1452, 1405, 1358, 1336, 1162, 1095, 1071, 1012, 958, 855, 832, 810, 760, 710, 655, 561, 538 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.22. 1-(4-Bromophenyl)-4-(4-chlorophenyl)-7-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4v**).* Compound **4v** was prepared according to a modified General Procedure. After $BF_3{\cdot}OEt_2$ was added, the mixture was stirred at room temperature for 5h. Purification by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1). Combined yield of *cis*-diastereomer and *trans*-diastereomer: 40%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*>95:5). Major diastereoisomer: White solid, m.p. 186~189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.24 (m, 2H), 7.13 (dd, J = 8.1, 5.2 Hz, 4H), 6.96 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.3 Hz, 1H), 6.81 (s, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.23 (s, 1H), 3.86 (t, J = 8.0 Hz, 2H), 3.04 (dd, J = 16.1, 13.4 Hz, 1H), 2.36 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 140.6, 140.5, 137.6, 136.4, 134.1, 133.0, 133.0, 131.5, 130.6, 130.1, 129.5, 129.5, 129.0, 128.6, 128.5, 127.0, 122.1, 58.7, 46.0, 42.4, 21.5, 21.0; HRMS (ESI) Calcd. for $C_{29}H_{25}{}^{79}BrClNO_2SNa$ $(M+Na)^+$: 588.0370; Found: 588.0375; IR (neat): ν = 3648, 3524, 3443, 3327, 3212, 3045, 2922, 2874, 1653, 1631, 1594, 1489, 1450, 1408, 1343, 1306, 1160, 1090, 1012, 957, 939, 814, 772, 711, 685, 653, 572, 558, 537, 519 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.23. 1-(4-Chlorophenyl)-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4w**).* Compound **4w** was prepared according to a modified General Procedure. After $BF_3{\cdot}OEt_2$ was added, the mixture was stirred at room temperature for 5h. Purification by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1). Combined yield of *cis*-diastereomer and *trans*-diastereomer: 20%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*>95:5). Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 2H), 7.33 – 7.26 (m, 4H), 7.26 – 6.97 (m, 10H), 6.73 (d, J = 7.7 Hz, 1H), 6.31 (s, 1H), 3.97 – 3.82 (m, 2H), 3.12 (dd, J = 16.6, 13.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 141.9, 140.0, 137.6, 133.8, 133.2, 130.3, 129.8, 129.4, 128.9, 128.8, 128.5, 128.1, 127.5, 127.2, 127.0, 126.4, 58.7, 46.0, 43.1, 21.5; one carbon resonance absent presumably due to overlap; The analytical data match those reported in the literature[6a]. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.24. 4-Phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4x**).* Compound **4x** was prepared according to a modified General Procedure. After $BF_3{\cdot}OEt_2$ was added, the mixture was stirred at room temperature for 5h. Purification by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1). Yield: 39%. White solid, m.p.138~140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2H), 7.25 – 7.12 (m, 5H), 7.09 (t, J = 7.4 Hz, 1H), 7.06 – 6.95 (m, 4H), 6.78 (d, J = 7.7 Hz, 1H), 4.44 (d, J = 14.9 Hz, 1H), 4.23 (dd, J = 7.9, 5.6 Hz, 1H), 4.09 (d, J = 14.9 Hz, 1H), 3.77 – 3.64 (m, 1H), 2.96 (dd, J = 11.7, 8.4 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 142.3, 136.4, 133.0, 131.9, 129.7, 129.5, 129.0, 128.6, 127.7, 127.0, 126.9, 126.6, 126.1, 51.0, 48.0, 45.2, 21.5; HRMS (ESI) Calcd. for $C_{22}H_{22}NO_2S$ $(M+H)^+$: 364.1366; Found: 364.1373; IR (neat): ν = 3637, 3524, 3443, 3330, 3059, 3026, 294, 2921, 2883, 2845, 1953, 1920, 1883, 1656, 1597, 1492, 1452, 1343, 1326, 1164, 1090, 1052, 957, 782, 702, 663, 623, 554, 545 cm^{-1}.

*4.2.25. 1-(4-Bromophenyl)-6,7-dimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4y**=**4a**).* Compound **4y**=**4a** was prepared according to a modified General Procedure. Combined yield of *cis*-diastereomer and *trans*-diastereomer: 50%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=86:14). Major diastereoisomer: white solid, m.p. 192~195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.24 (dd, J = 6.4, 3.9 Hz, 1H), 7.22 – 7.12 (m, 4H), 7.06 – 7.00 (m, 2H), 6.44 (s, 1H), 6.21 (s, 1H), 6.14 (s, 1H), 3.90 – 3.74 (m, 5H), 3.58 (s, 3H), 3.01 (dd, J = 13.9, 11.1 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.8, 143.4, 141.9, 140.5, 137.6, 131.5, 130.6, 129.7, 129.4, 128.8, 128.7, 127.2, 127.0, 125.3, 122.0, 111.7, 109.9, 58.5, 55.9, 55.7, 46.1, 42.6, 21.5. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.26. 9-Methyl-4-phenyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**4z**).* Compound **4z** was prepared according to a modified General Procedure. $AgPF_6$ (0.02 mmol, 10 mol%) was added to a solution of indole **1i** (0.3 mmol) and aziridine **2c** (0.2 mmol) in DCE (2 mL). The mixture was stirred at room temperature for 1h and then aldehyde **3i** (0.4 mmol), $BF_3{\cdot}OEt_2$ (0.2 mmol, 1equiv) and $MgSO_4$ (400 mg) were added. The mixture was stirred at 60 °C for 18h. Purification by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1). Yield: 42%. White solid, m.p. 245~248 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.7 Hz, 2H), 7.31 – 7.25 (m, 3H), 7.20 (d, J = 7.9 Hz, 2H), 7.17 – 7.12 (m, 1H), 7.09 (d, J = 7.5 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 4.57 (d, J = 14.4 Hz, 1H), 4.37 – 4.23 (m, 2H), 3.82 (dd, J = 11.8, 4.3 Hz, 1H), 3.67 (s, 3H), 3.05 (dd, J = 11.6, 7.6 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 139.9, 137.4, 133.6, 132.7, 131.3, 129.8, 129.7, 128.6, 127.6, 125.5, 121.6, 119.4, 119.3, 109.1, 108.8, 51.9, 42.7, 39.5, 29.6, 21.5; The analytical data match those reported in the literature[6a].

*4.2.27. 1-(Bromomethyl)-6,7-dimethoxy-4-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (**4ab**).* Combined yield of *cis*-diastereomer and *trans*-diastereomer: 65%. The *cis/trans* ratio was determined by NMR analysis (*cis/trans*=82:18). Major diastereoisomer: white solid, m.p. 113~116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.30 (dd, J = 13.8, 6.4 Hz, 2H), 7.23 (d, J = 8.1 Hz, 3H), 7.11 – 7.01 (m, 2H), 6.66 (s, 1H), 6.16 (s, 1H), 5.34 (dd, J = 8.2, 4.4 Hz, 1H), 4.00 – 3.82 (m, 5H), 3.74 (qd, J = 11.2, 6.5 Hz, 2H), 3.57 (s, 3H), 3.38 (dd, J = 14.4, 11.1 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 147.8, 143.6, 141.8, 137.3, 129.5, 129.3, 128.8, 128.8, 127.4, 127.3, 125.6, 111.9, 109.1, 56.3, 56.0, 55.7, 46.3, 42.7, 35.6, 21.5; HRMS (ESI) Calcd. for $C_{25}H_{27}{}^{79}BrNO_4S$ $(M+H)^+$: 516.0839; Found: 516.0832; IR (neat): ν = 3028, 3006, 2963, 2937, 2913, 2851, 2835, 2251, 1598, 1517, 1463, 1402, 1338, 1311, 1274, 1248, 1221, 1161, 1114, 1044, 1015, 913, 880, 837, 816, 731, 701, 680, 653, 582, 559 cm^{-1}. Minor diastereoisomer could not be obtained in pure form due to trace amounts of its.

*4.2.28. 4,4'-((4-Bromophenyl)methylene)bis(1,2-dimethoxybenzene) (**5a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 6.65 (d, J = 1.8 Hz, 2H), 6.58 (dd, J = 8.2, 1.8 Hz, 2H), 5.40 (s, 1H), 3.87 (s, 6H), 3.78 (s, 6H).The analytical data match those reported in the literature[18].

4.3. Confirm the reaction mechanism of three-component reactions

*4.3.1. Synthesis of N-(2-(3,4-dimethoxyphenyl)-2-phenylethyl)-4-methylbenzenesulfonamide (**7a**).* Under an argon atmosphere,

$BF_3{\cdot}OEt_2$ (0.6 mmol, 3equiv) was added to a solution of arene **1a** (41.4mg, 0.3 mmol) and aziridine **2a** (54.4mg, 0.2 mmol) in DCE (2 mL). The mixture was stirred at room temperature for 1h. Water (10 mL) was added and the product was extracted with EtOAc (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate=2:1) on silica gel to afford product **7a** (61.6mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.3 Hz, 2H), 7.19 (dt, J = 7.5, 3.5 Hz, 4H), 7.14 – 7.10 (m, 1H), 7.05 – 6.96 (m, 2H), 6.68 (d, J = 8.2 Hz, 1H), 6.57 (dd, J = 8.2, 1.9 Hz, 1H), 6.50 (d, J = 1.9 Hz, 1H), 4.41 (t, J = 6.1 Hz, 1H), 3.94 (t, J = 7.9 Hz, 1H), 3.50 – 3.33 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.0, 143.4, 141.0, 136.6, 133.0, 129.7, 128.7, 127.7, 127.0, 127.0, 119.7, 111.3, 111.2, 55.8, 55.7, 50.0, 47.3, 21.5. The analytical data match those reported in the literature[13c].

*4.3.2. The reaction of amine (**7a**) with aldehyde (**3a**).* Under an argon atmosphere, $BF_3{\cdot}OEt_2$ (0.45 mmol, 3equiv) was added to a solution of amine **7a** (61.6mg, 0.15 mmol), aldehyde **3a** (55.5mg, 0.3 mmol) in DCE (2 mL). Then $MgSO_4$ (400 mg) were added. The mixture was stirred at 60 °C for 18h. Cooled to room temperature, water (10 mL) was added and the product was extracted with EtOAc (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate=5:1) on silica gel to afford product **4a** (73.7 mg, 85% yield, *cis:trans*=84:16).

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.xx.xxx.

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16. The crystallographic data of *cis*-**4a**, *cis*-**4f**, and *trans*-**4r** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1046206, 1046759 and 1046698, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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Lewis acid promoted three-component reactions of aziridines, arenes and aldehydes: an efficient and diastereoselective synthesis of *cis*-1,4-disubstituted tetrahydroisoquinolines

Siyang Xing*, Jing Ren, Kui Wang*, Hong Cui, Wenrui Li, Han Yan

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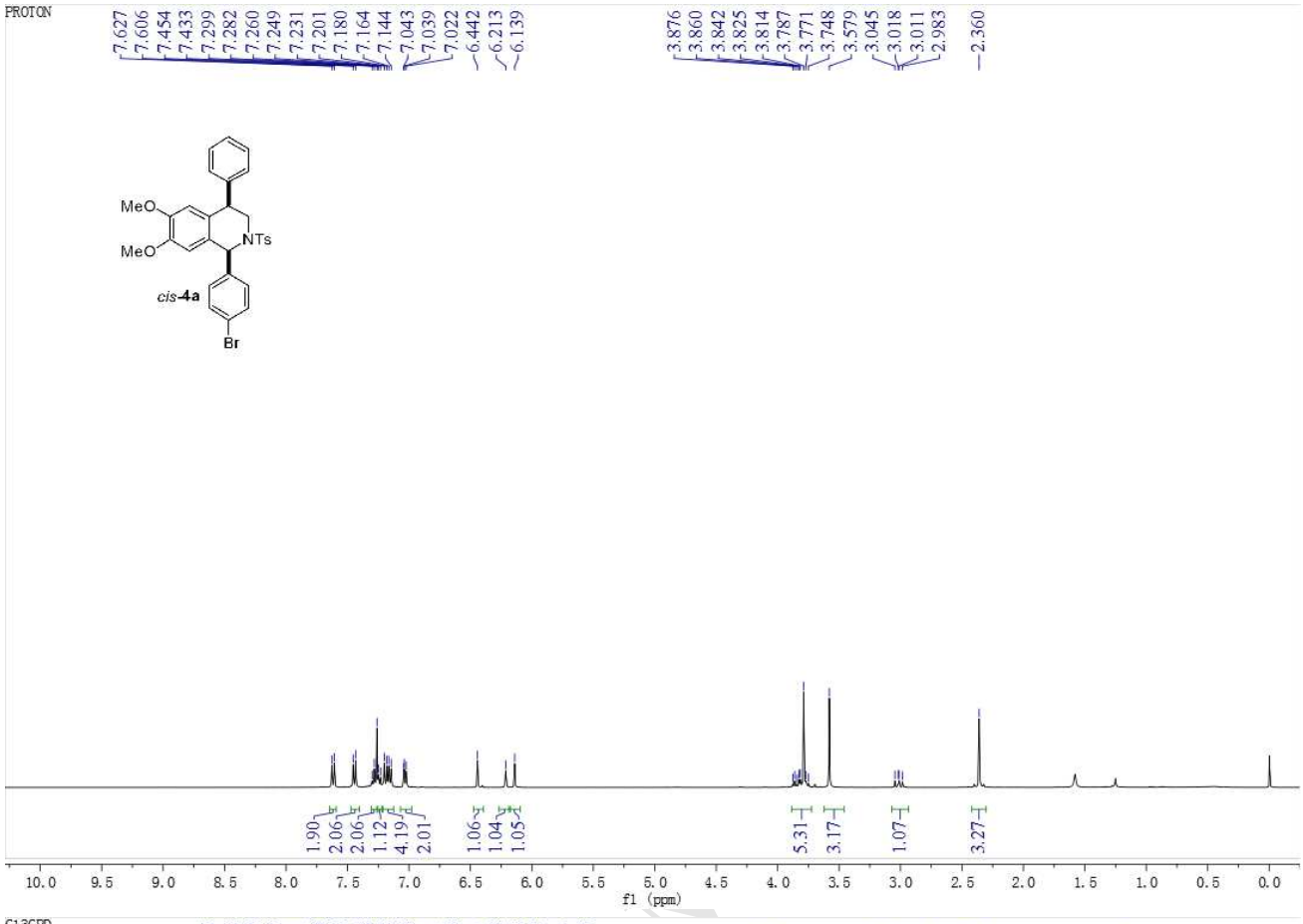
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MeO
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cis-4a
Br
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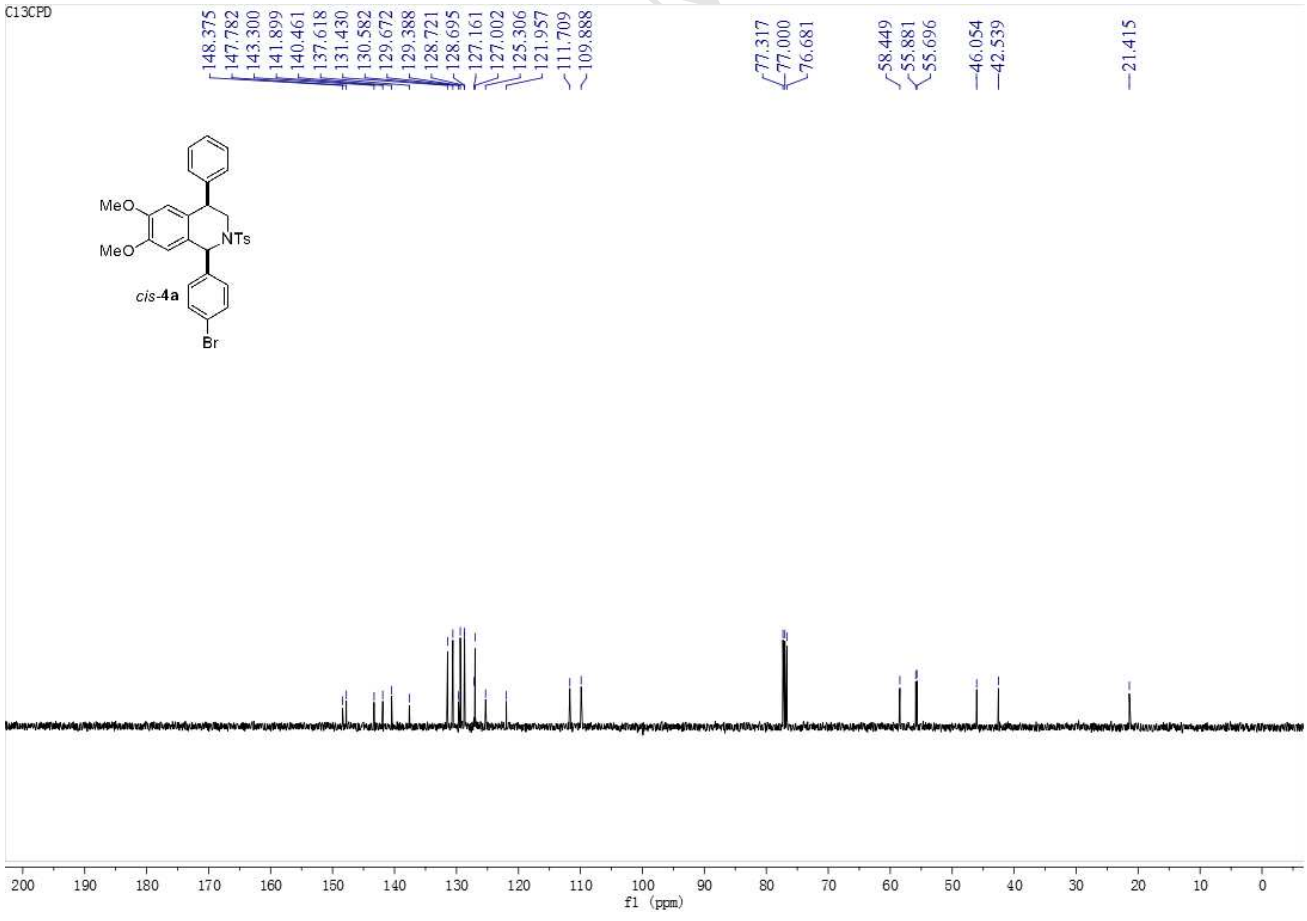
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128.695
127.161
127.002
125.306
121.957
111.709
109.888
77.317
77.000
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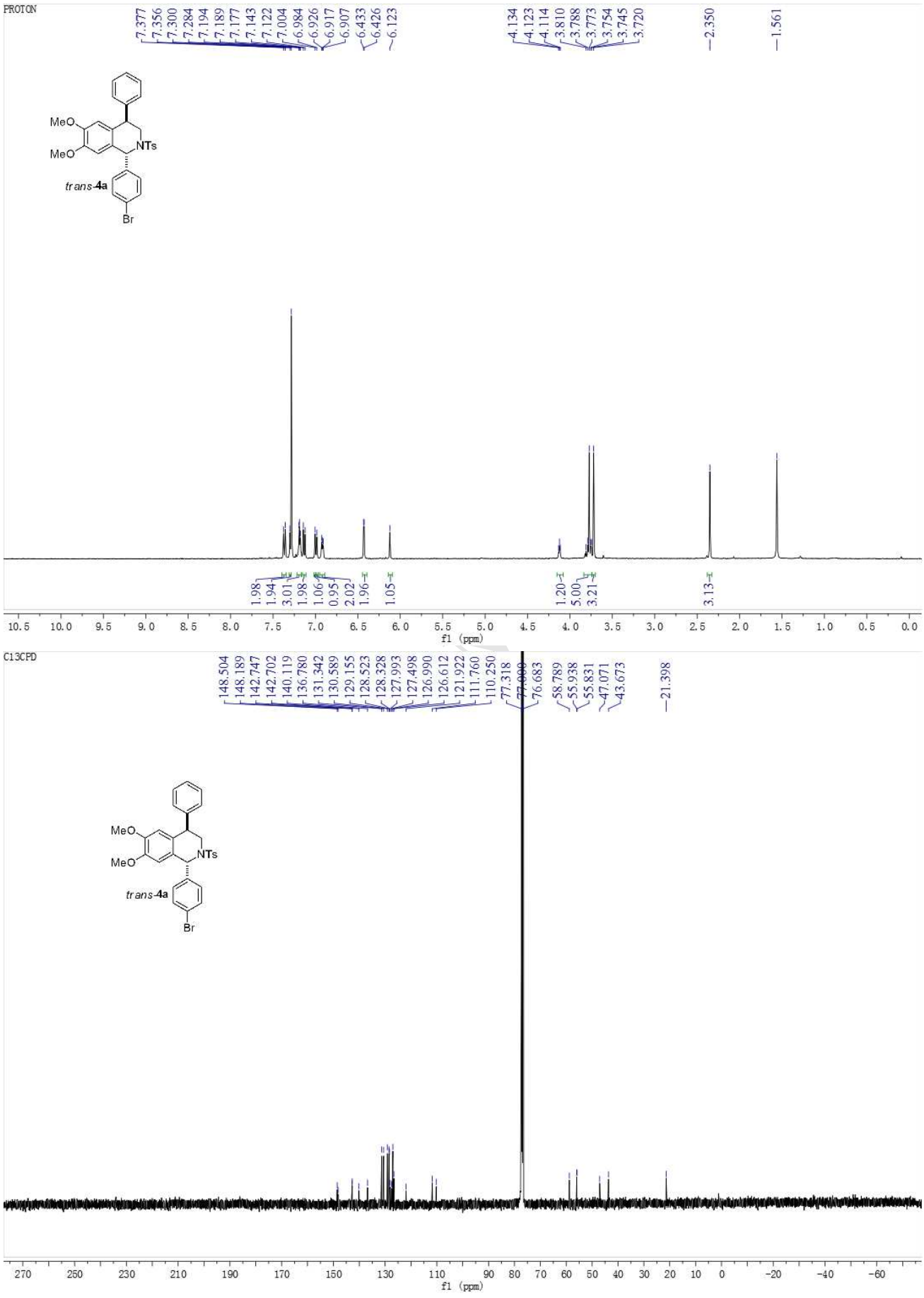
MeO
NTs
cis-4a
Br
f1 (ppm)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6.926
6.917
6.907
6.433
6.426
6.123
4.134
4.123
4.114
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3.788
3.773
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3.745
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2.350
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MeO
MeO
NTs
trans-4a
Br
1.98
1.94
3.01
1.98
1.06
0.95
2.02
1.96
1.05
1.20
5.00
3.21
3.13
f1 (ppm)
C13CPD
148.504
148.189
142.747
142.702
140.119
136.780
131.342
130.589
129.155
128.523
128.328
127.993
127.498
126.990
126.612
121.922
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77.318
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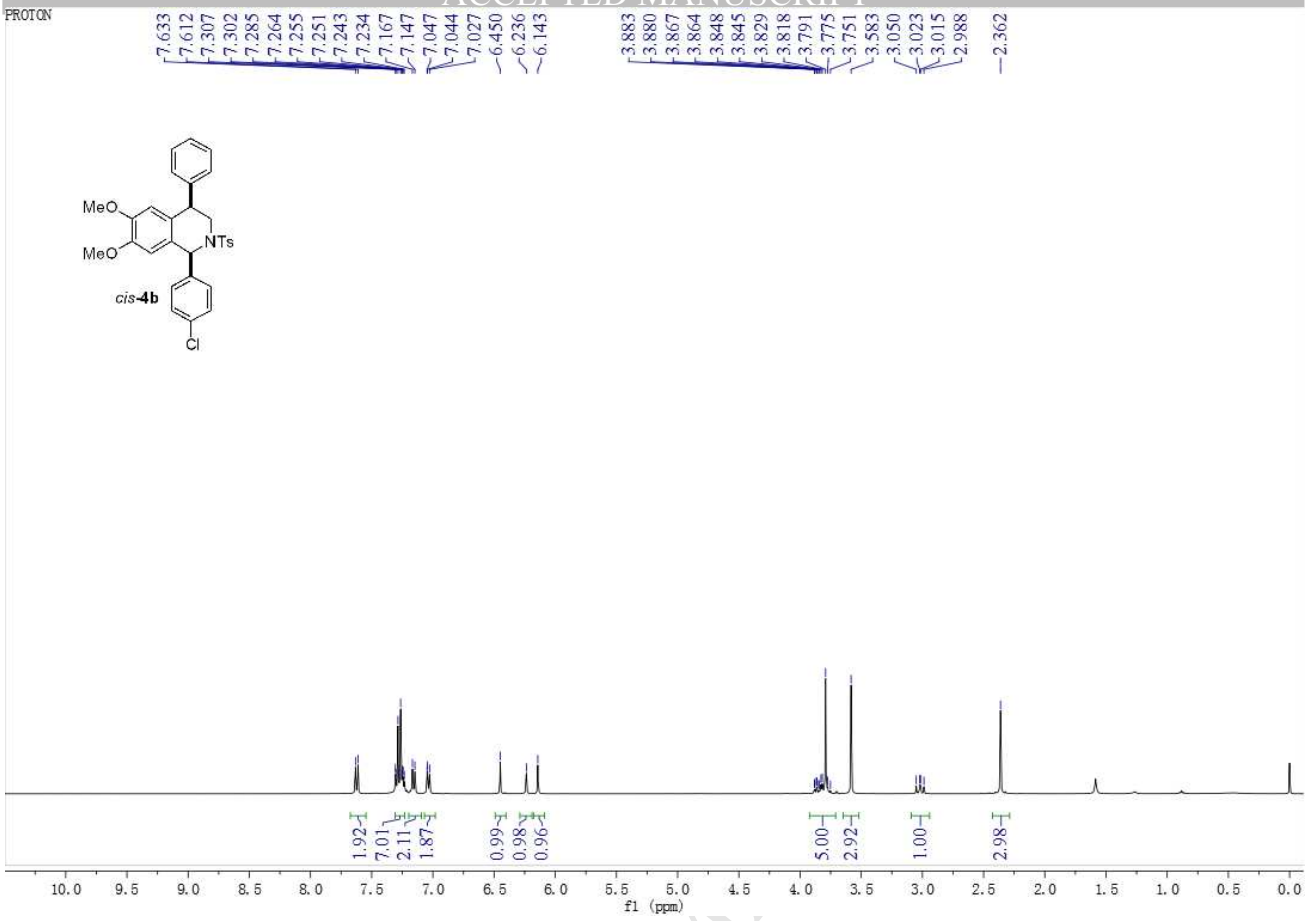
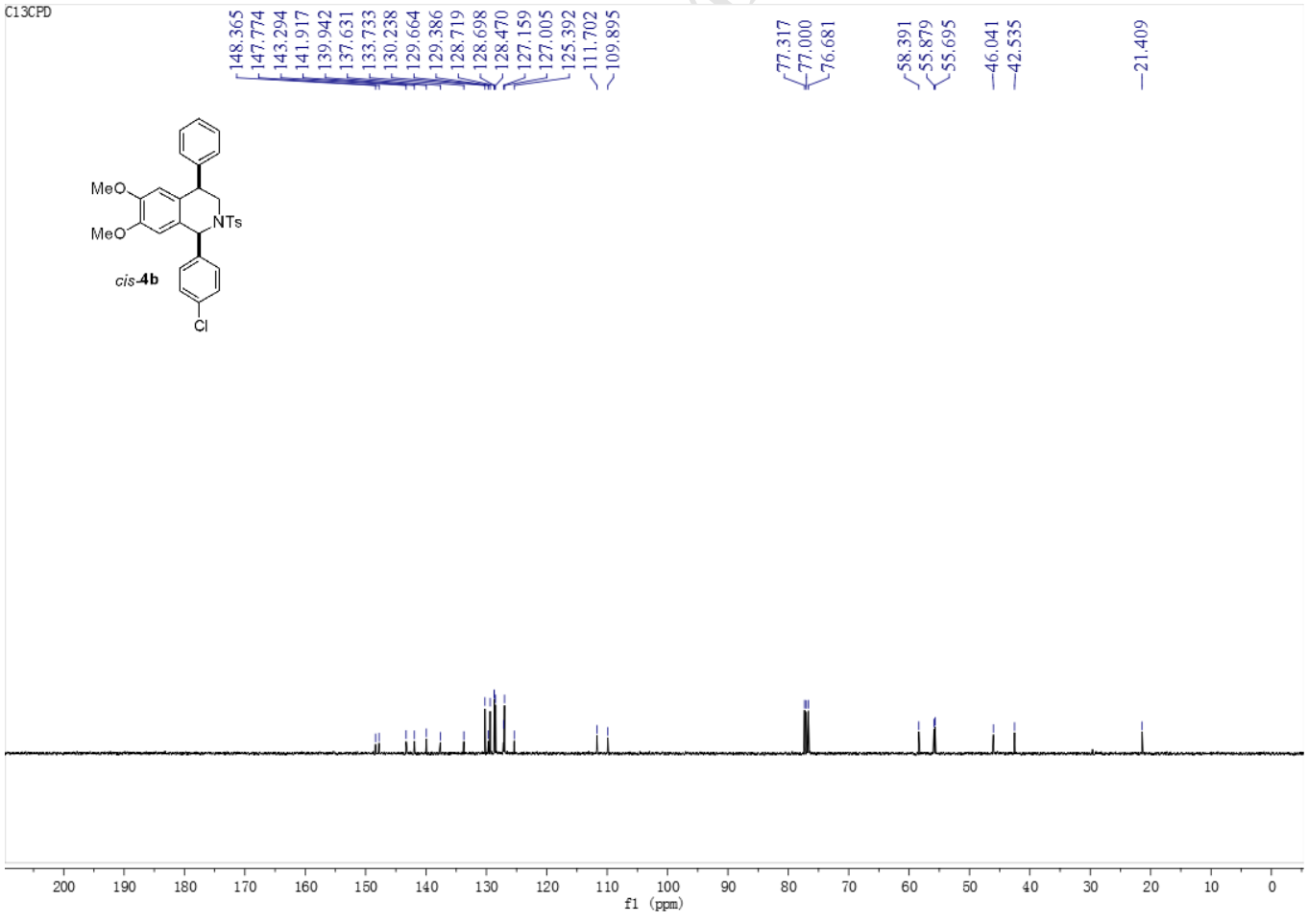
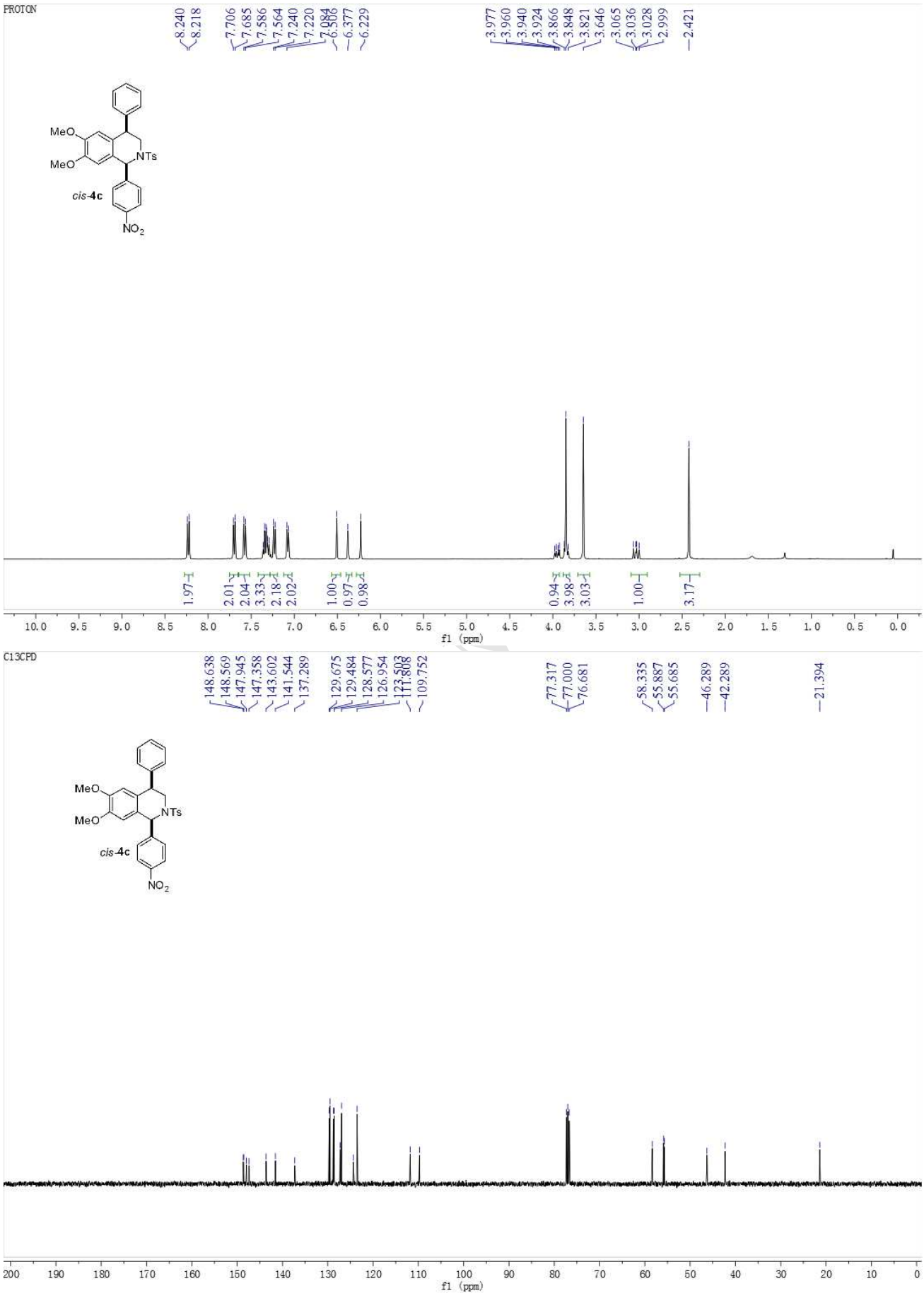
f1 (ppm)



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3.940
3.924
3.866
3.848
3.821
3.646
3.065
3.036
3.028
2.999
2.421
MeO
MeO
NTs
cis-4c
NO2
1.97
2.01
2.04
3.33
2.18
2.02
1.00
0.97
0.98
0.94
3.98
3.03
1.00
3.17
f1 (ppm)
C13CPD
148.638
148.569
147.945
147.358
143.602
141.544
137.289
129.675
129.484
128.577
126.954
111.808
109.752
77.317
77.000
76.681
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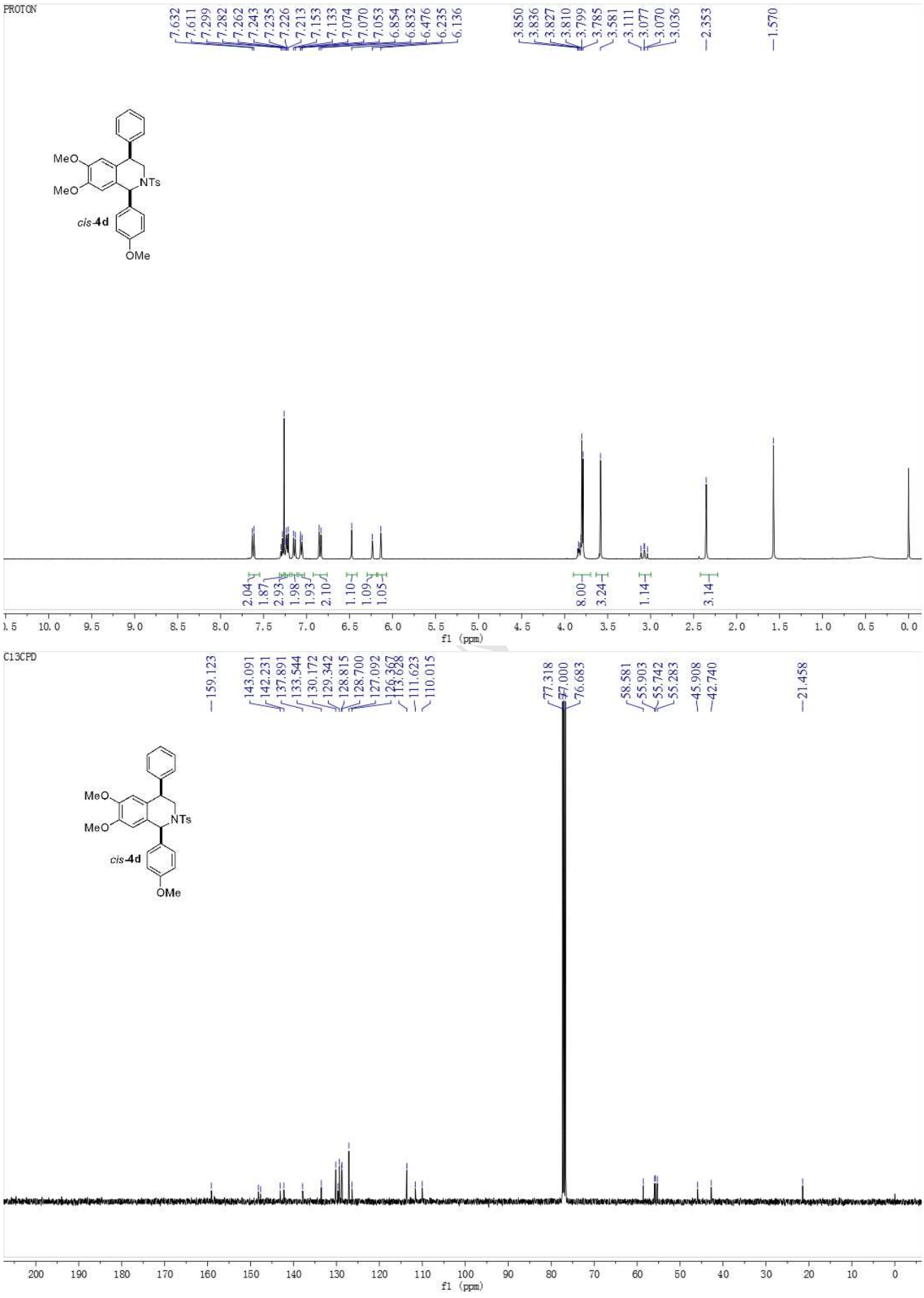
cis-4c
NO2
f1 (ppm)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7.070
7.053
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6.476
6.235
6.136
3.850
3.836
3.827
3.810
3.799
3.785
3.581
3.111
3.077
3.070
3.036
2.353
1.570
MeO
MeO
NTs
cis-4d
OMe
2.04
1.87
2.93
1.98
1.93
2.10
1.10
1.09
1.05
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3.14
f1 (ppm)
C13CPD
159.123
143.091
142.231
137.891
133.544
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129.342
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128.700
127.092
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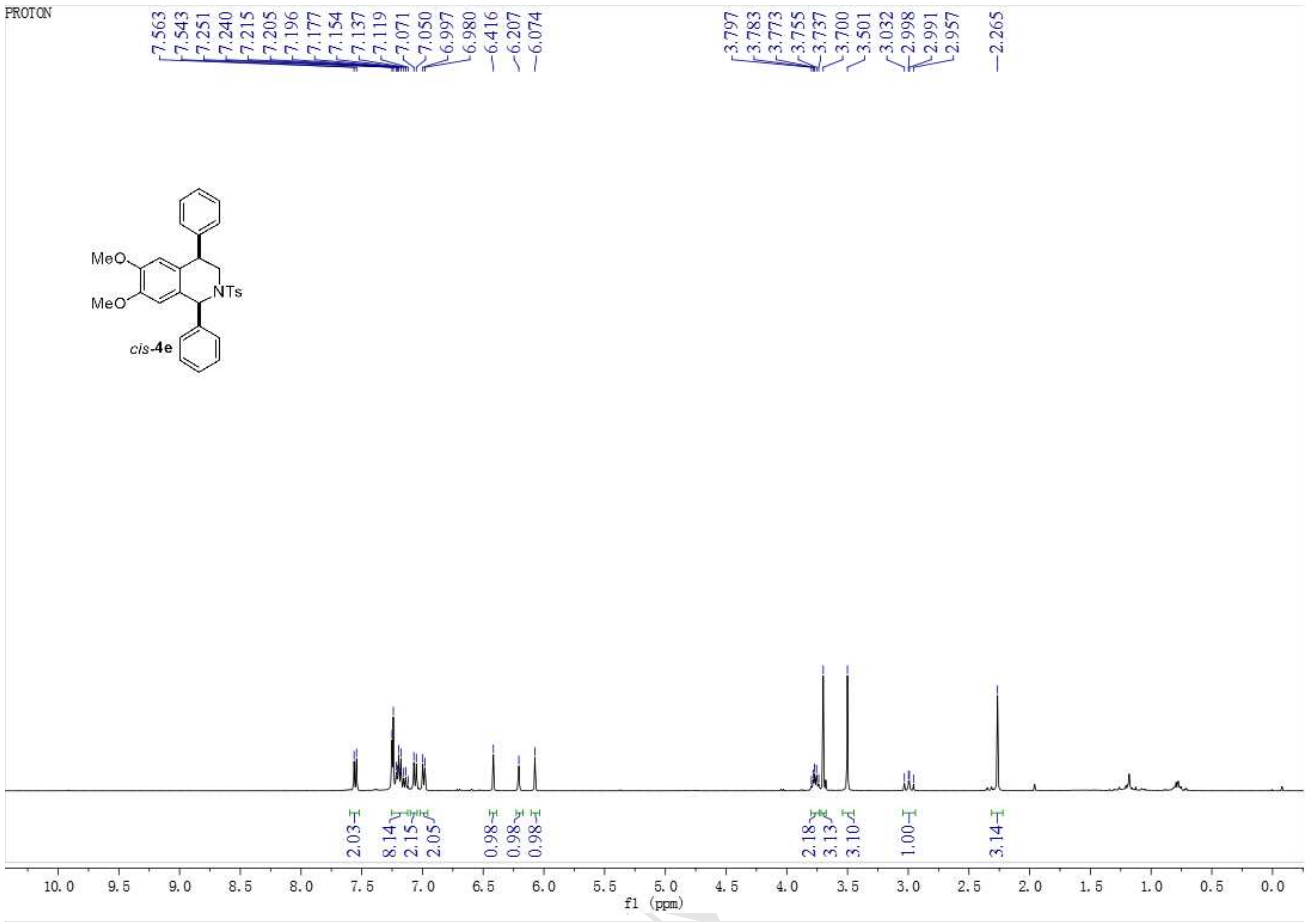
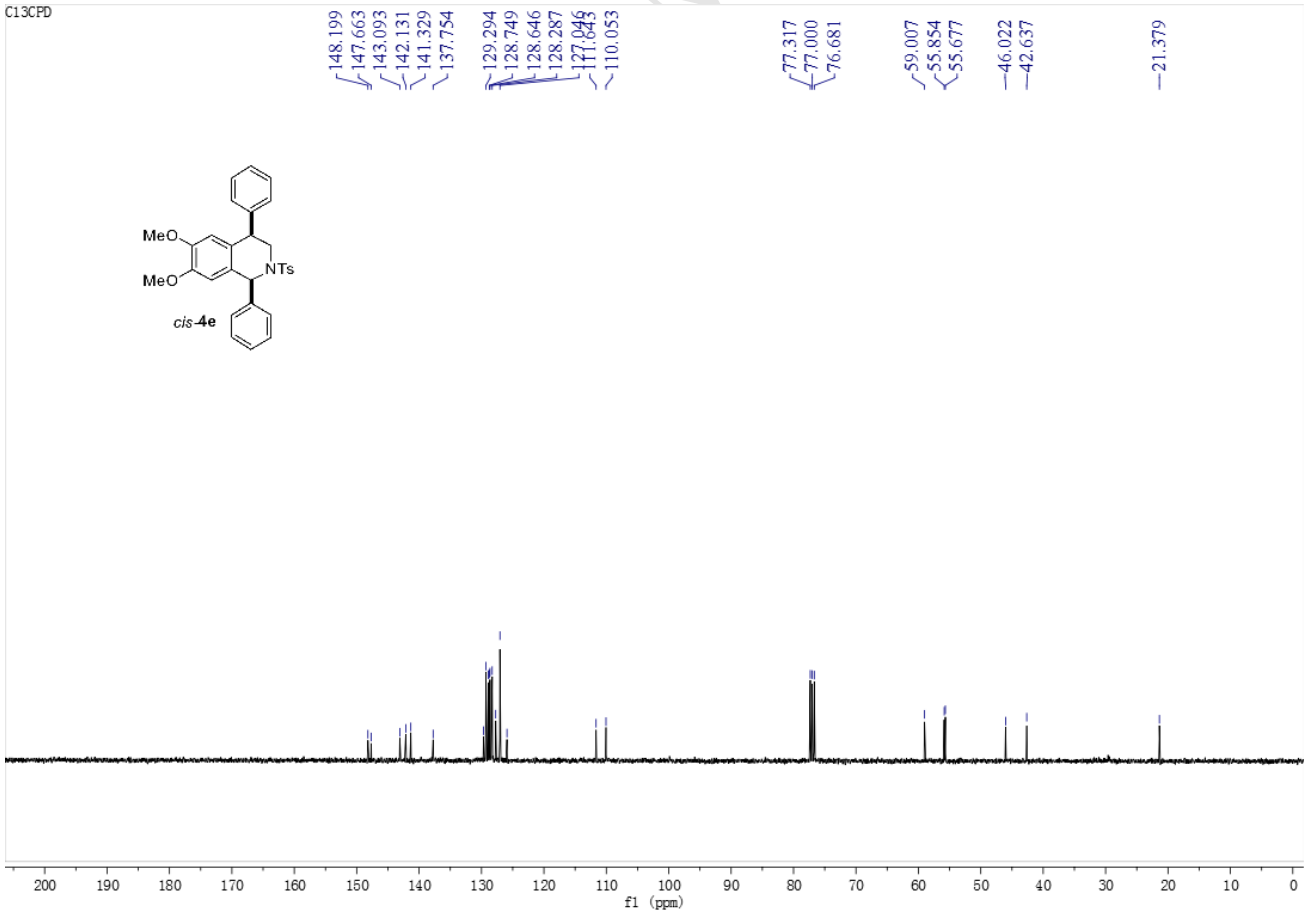
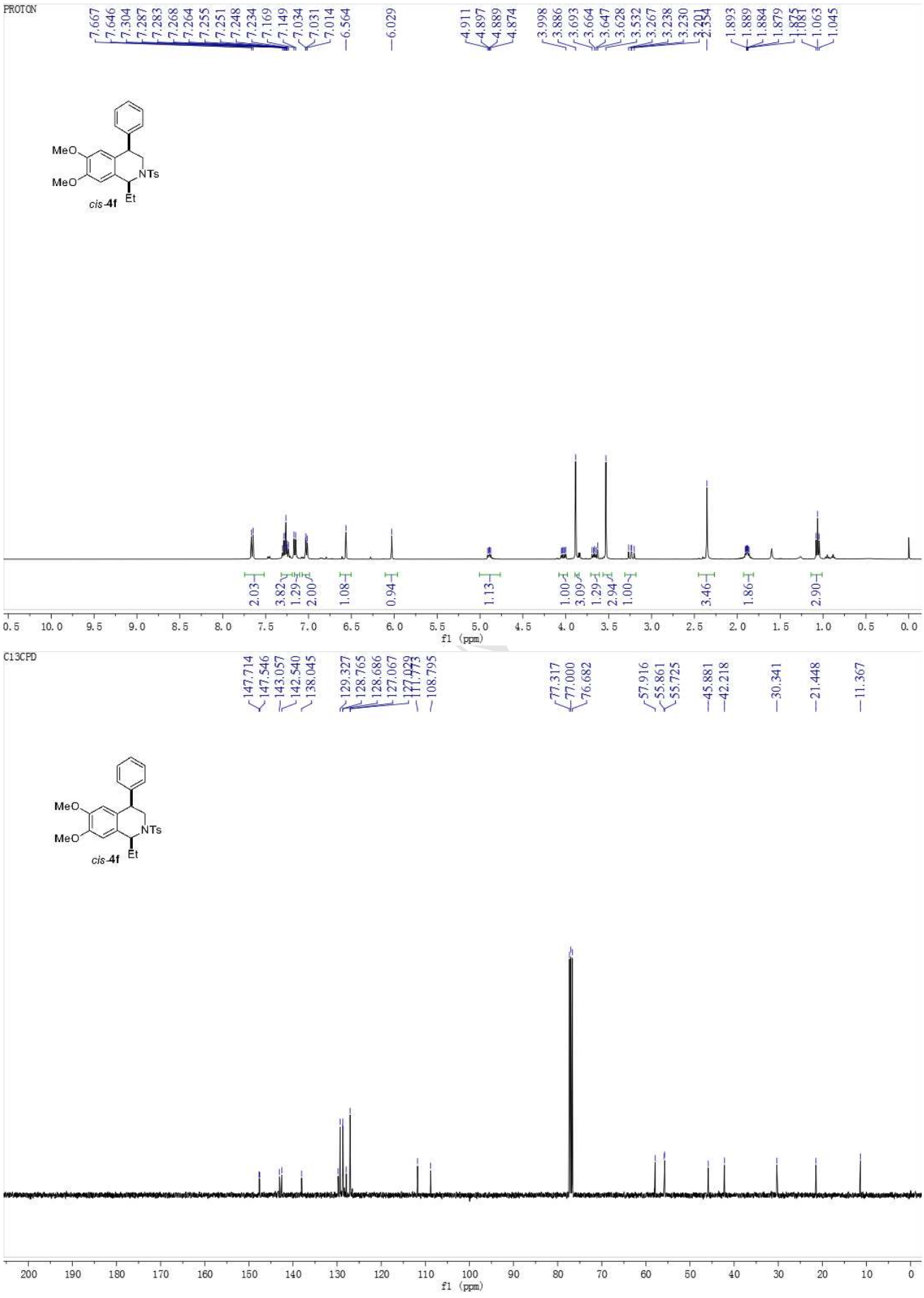
PROTON



C13CPD

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7.149
7.034
7.031
7.014
6.564
6.029
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4.897
4.889
4.874
3.998
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3.647
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1.081
1.063
1.045
MeO
MeO
NTs
Et
cis-4f
2.03
3.82
1.29
2.00
1.08
0.94
1.13
1.00
3.09
1.29
2.94
1.00
3.46
1.86
2.90
f1 (ppm)
C13CPD
147.714
147.546
143.057
142.540
138.045
129.327
128.765
128.686
127.067
127.029
111.773
108.795
77.317
77.000
76.682
57.916
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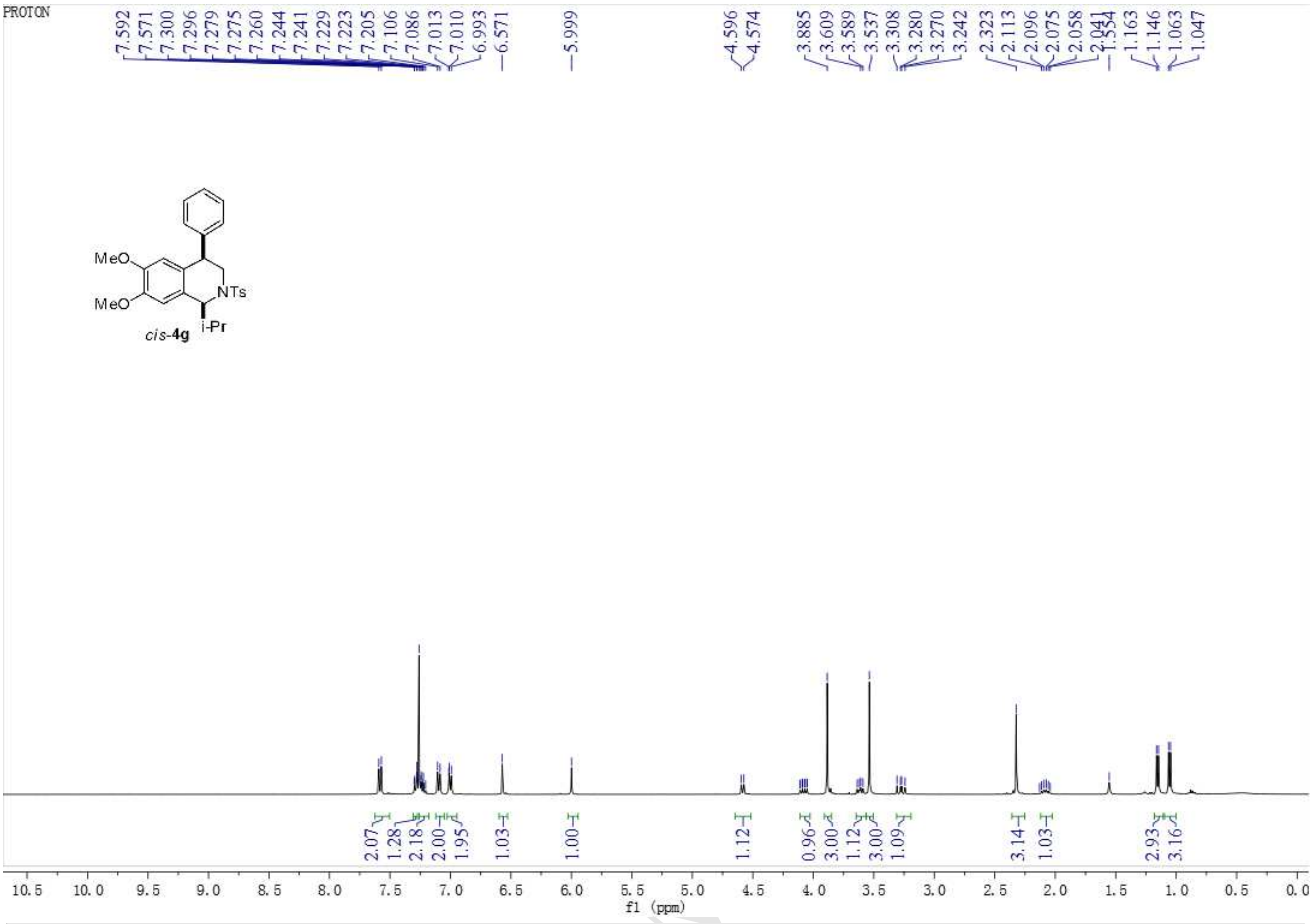
NTs
Et
cis-4f
f1 (ppm)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MeO
NTs
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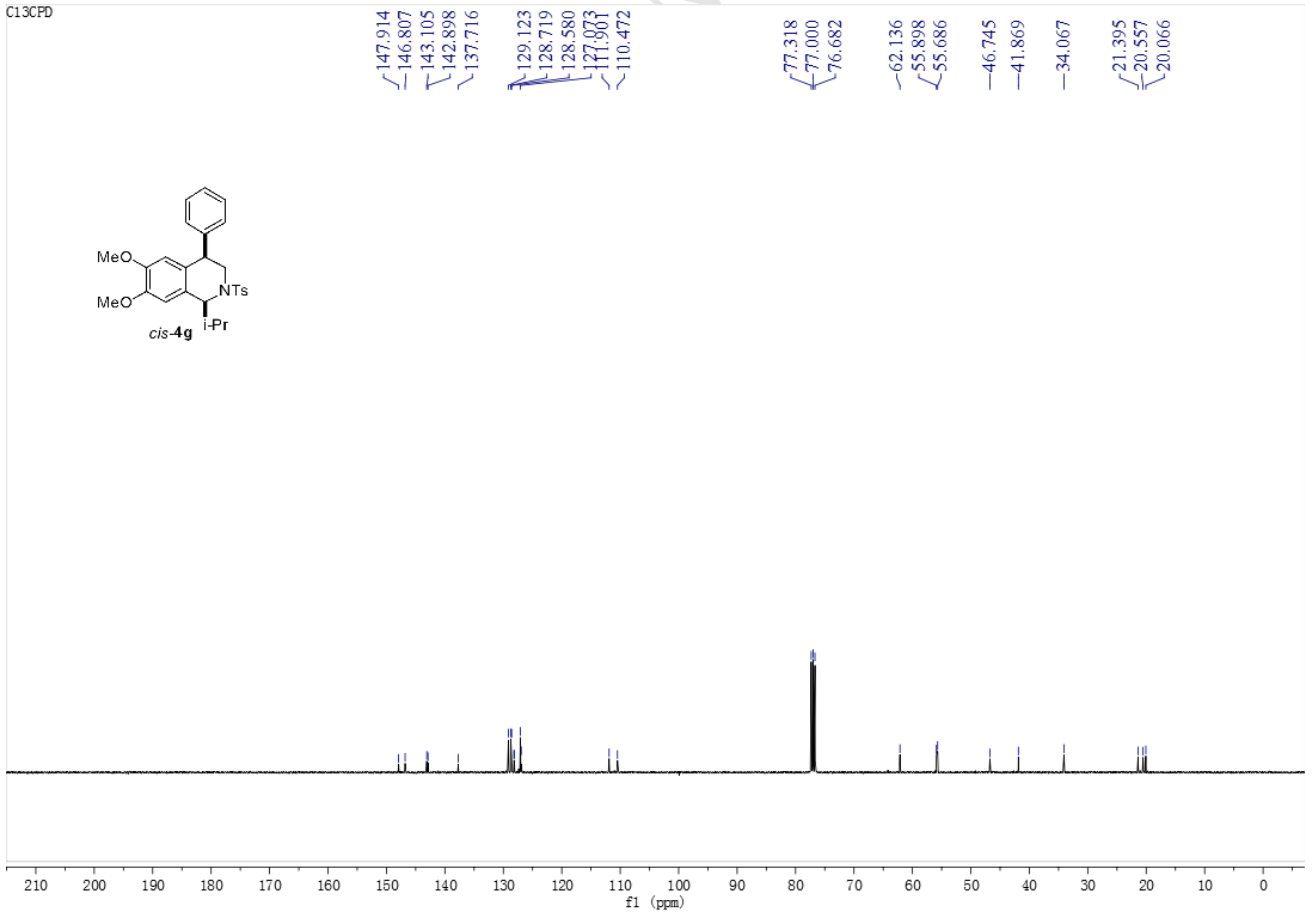
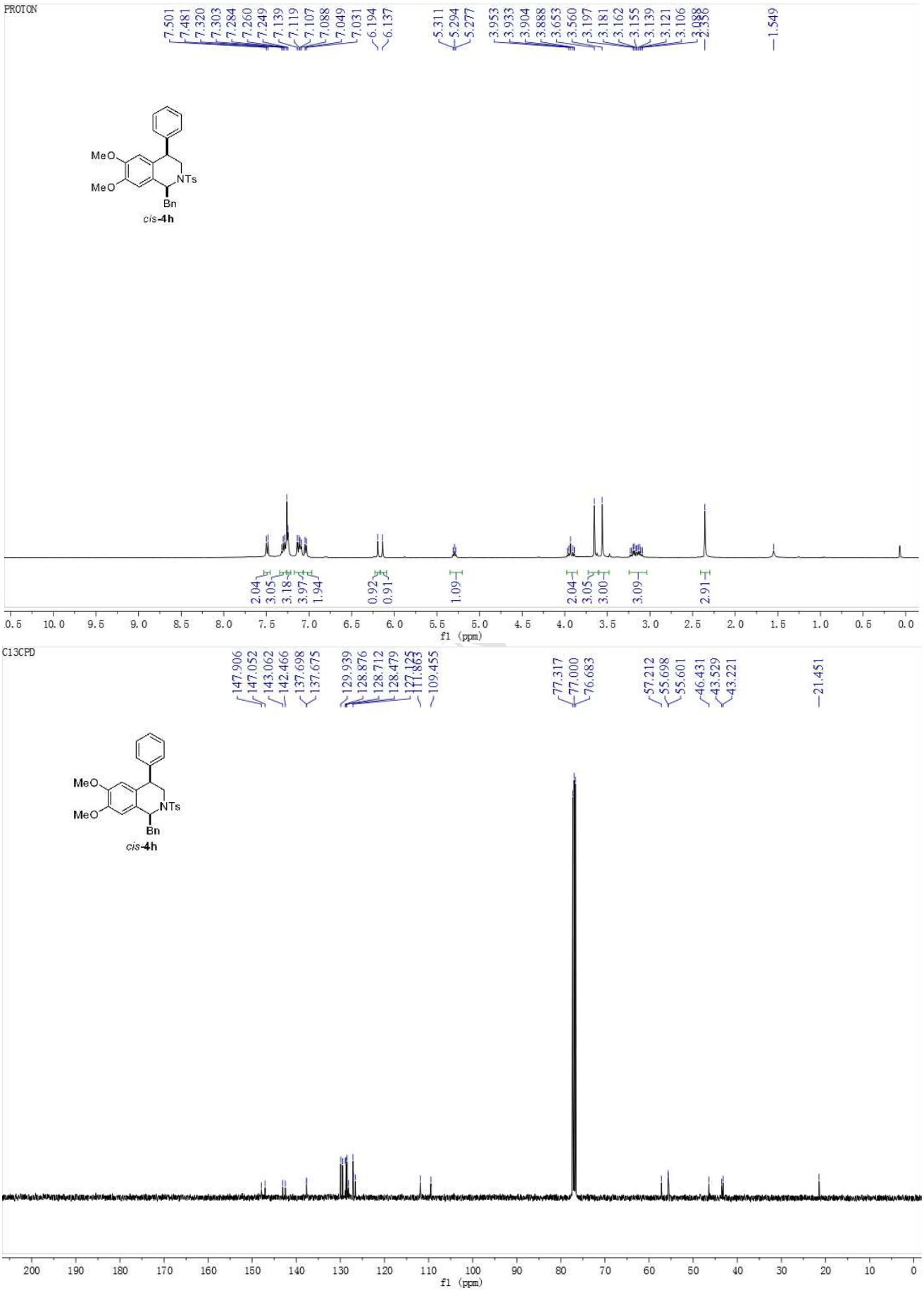
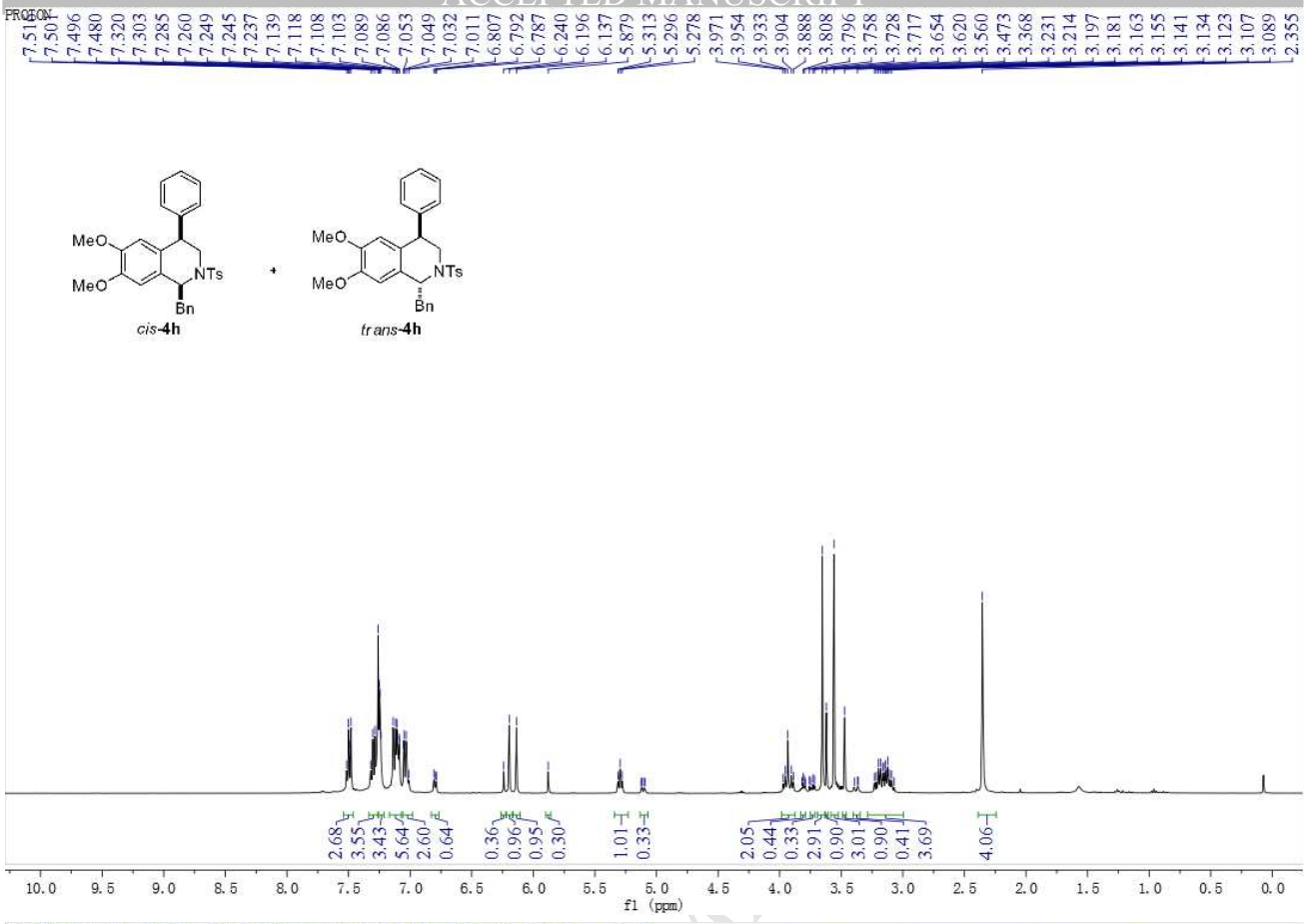
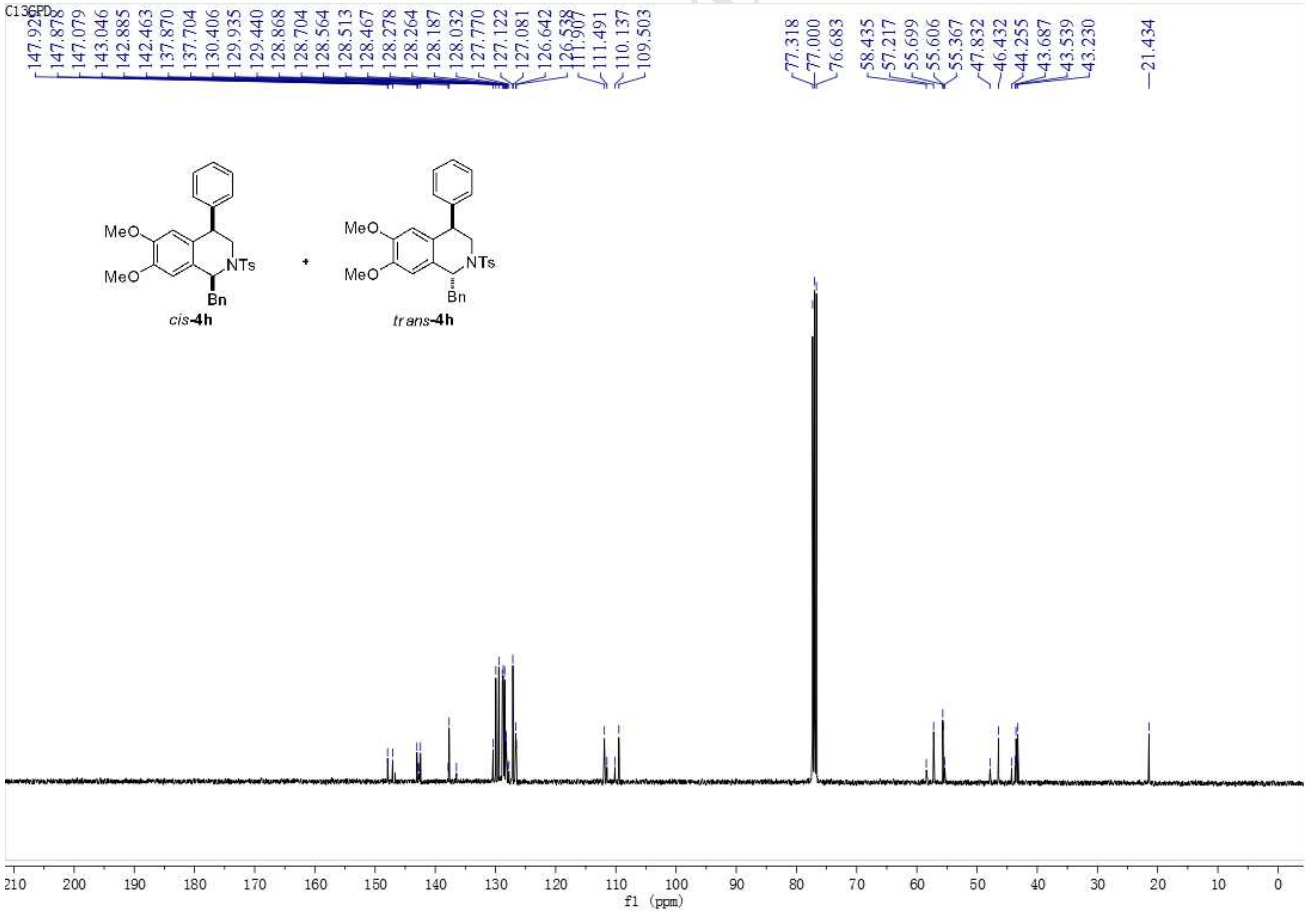
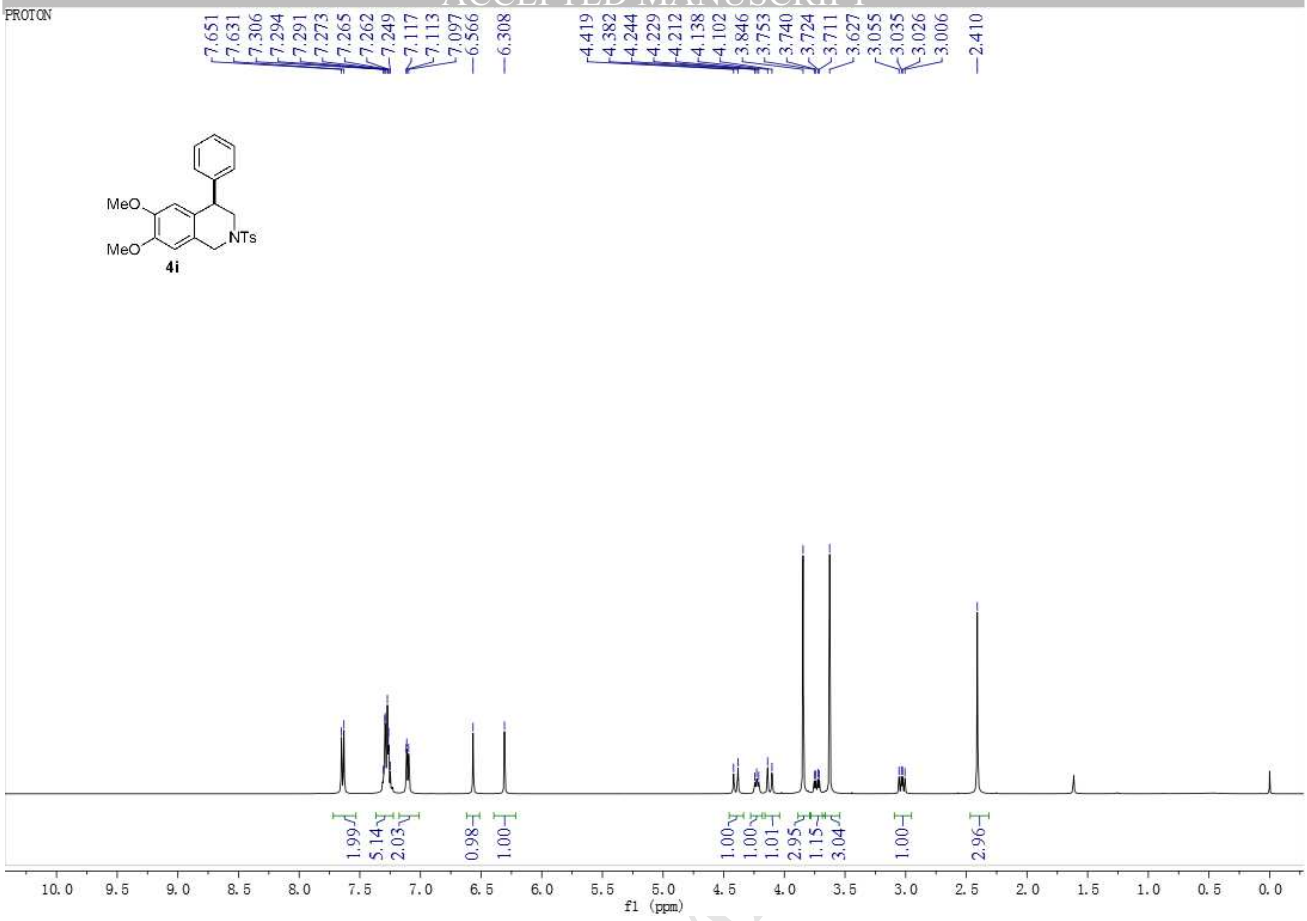
cis-4g
2.07
1.28
2.18
2.00
1.95
1.03
1.00
1.12
0.96
3.00
1.12
3.00
1.09
3.14
1.03
2.93
3.16
f1 (ppm)

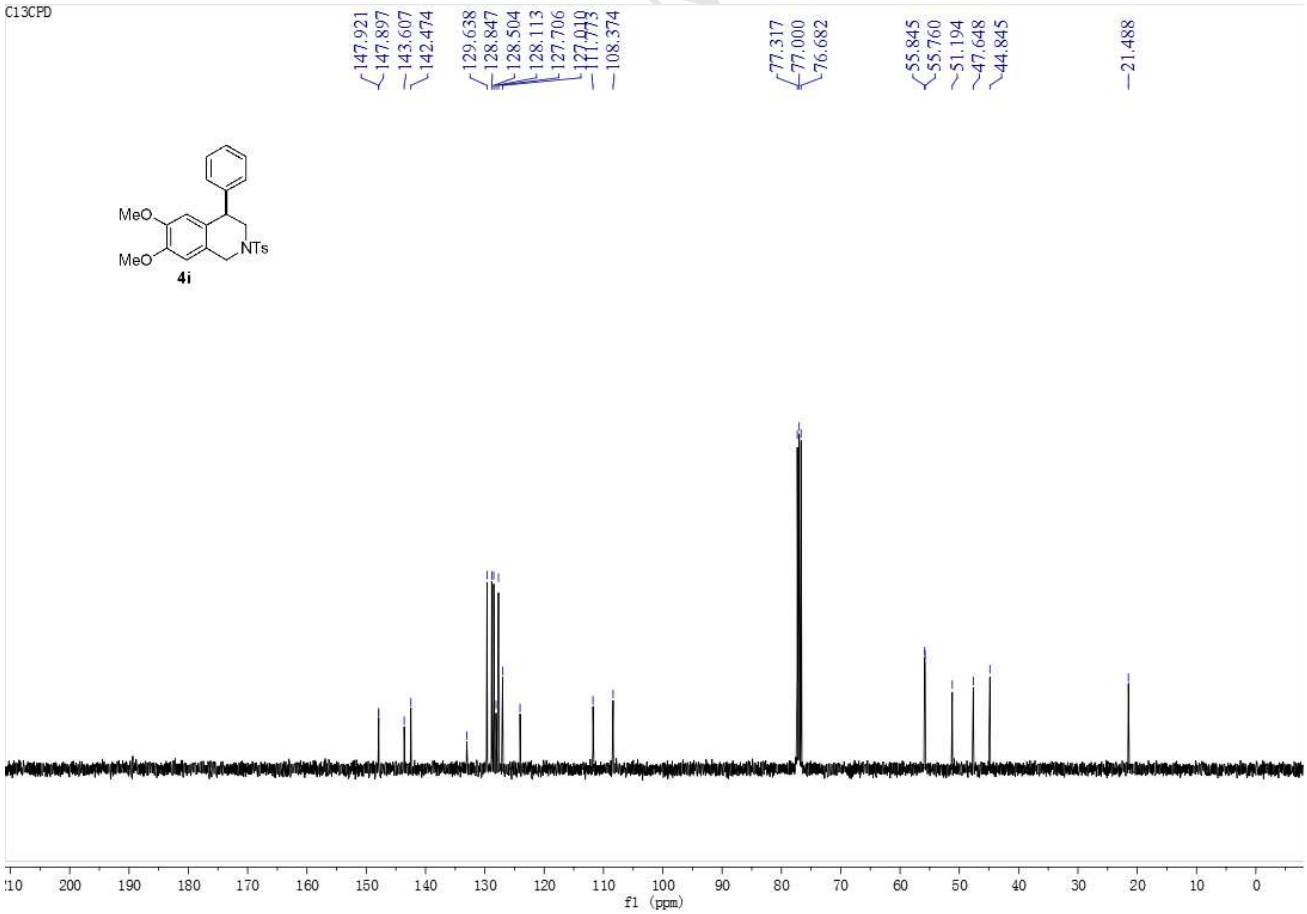

C13CPD
147.914
146.807
143.105
142.898
137.716
129.123
128.719
128.580
127.073
111.901
110.472
77.318
77.000
76.682
62.136
55.898
55.686
46.745
41.869
34.067
21.395
20.557
20.066
MeO
MeO
NTs
i-Pr
cis-4g
f1 (ppm)

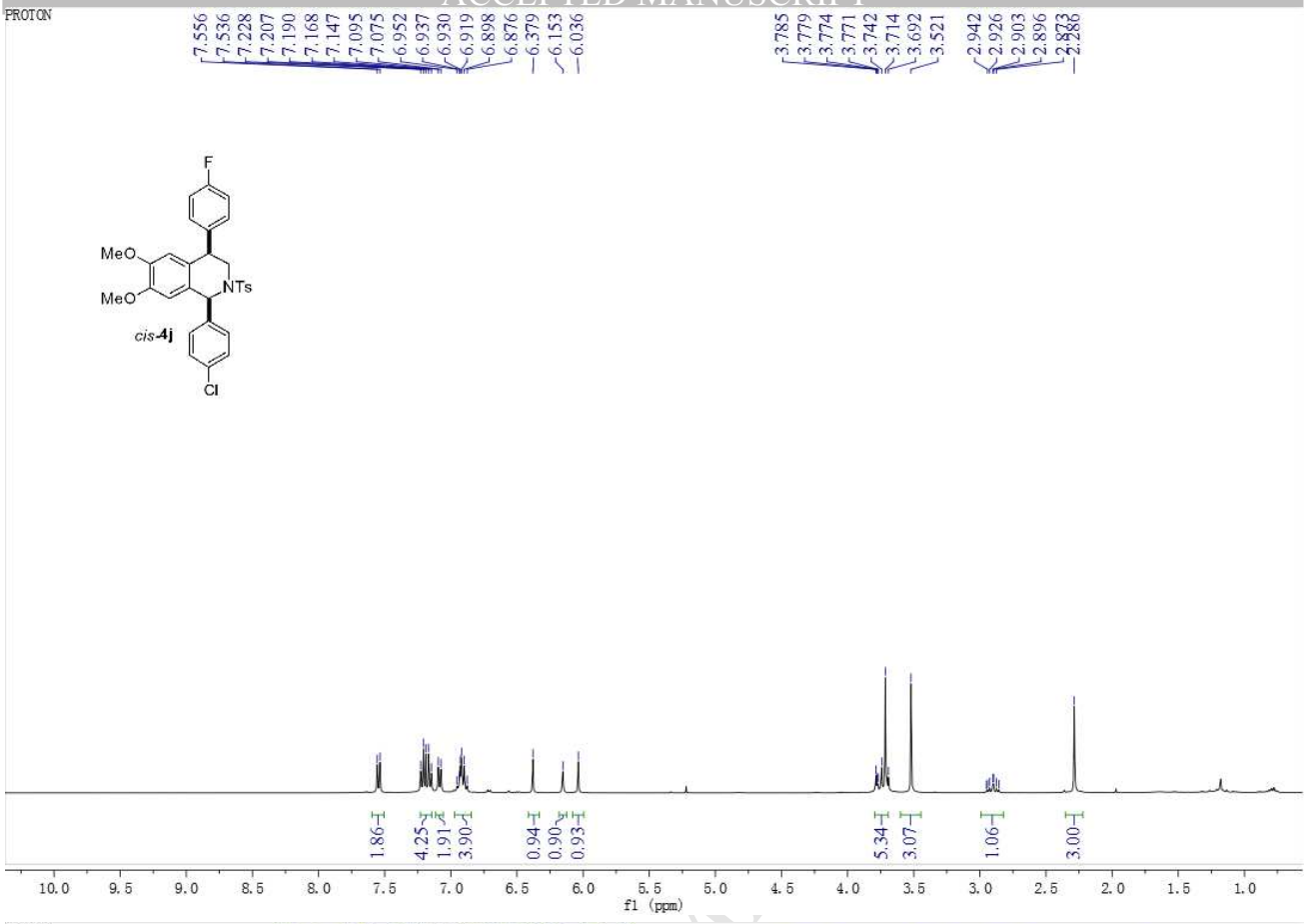

PROTON
7.501
7.481
7.320
7.303
7.284
7.260
7.249
7.139
7.119
7.107
7.088
7.049
7.031
6.194
6.137
5.311
5.294
5.277
3.953
3.933
3.904
3.888
3.653
3.560
3.197
3.181
3.162
3.155
3.139
3.121
3.106
3.088
2.356
1.549
MeO
MeO
NTs
Bn
cis-4h
2.04
3.05
3.18
3.97
1.94
0.92
0.91
1.09
2.04
3.05
3.00
3.09
2.91
f1 (ppm)
C13CPD
147.906
147.052
143.062
142.466
137.698
137.675
129.939
128.876
128.712
128.479
127.125
111.863
109.455
77.317
77.000
76.683
57.212
55.698
55.601
46.431
43.529
43.221
21.451
MeO
MeO
NTs
Bn
cis-4h
f1 (ppm)

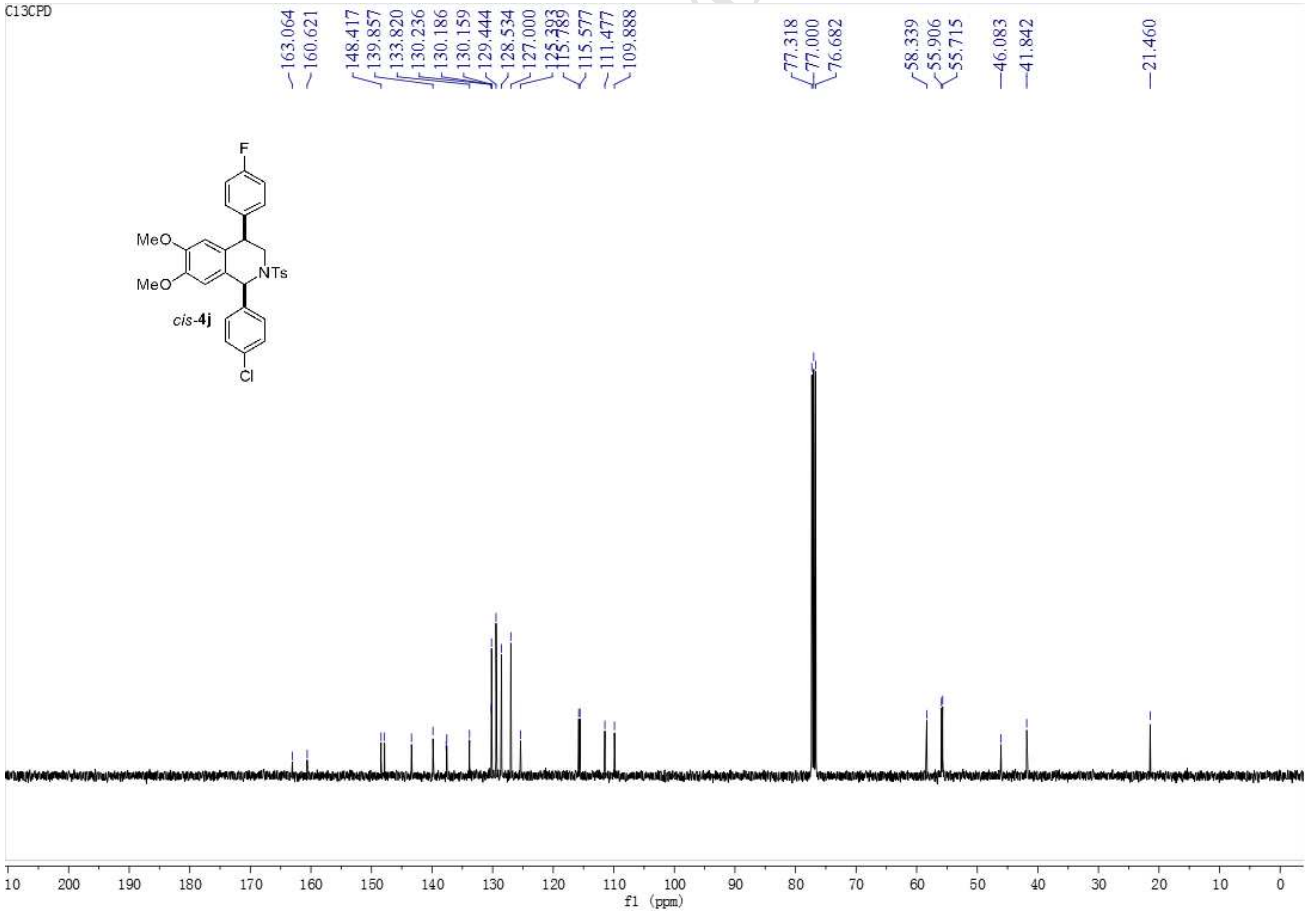

PROTON
7.514 7.507 7.496 7.480 7.320 7.303 7.285 7.260 7.249 7.245 7.237 7.139 7.118 7.108 7.103 7.089 7.086 7.053 7.049 7.032 7.011 6.807 6.792 6.787 6.240 6.196 6.137 5.879 5.313 5.296 5.278 3.971 3.954 3.933 3.904 3.888 3.808 3.796 3.758 3.728 3.717 3.654 3.620 3.560 3.473 3.368 3.231 3.214 3.197 3.181 3.163 3.155 3.141 3.134 3.123 3.107 3.089 2.355
MeO
MeO
NTs
Bn
cis-4h
+
trans-4h
2.68 3.55 3.43 5.64 2.60 0.64 0.36 0.96 0.95 0.30 1.01 0.33 2.05 0.44 0.33 2.91 0.90 3.01 0.90 0.41 3.69 4.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

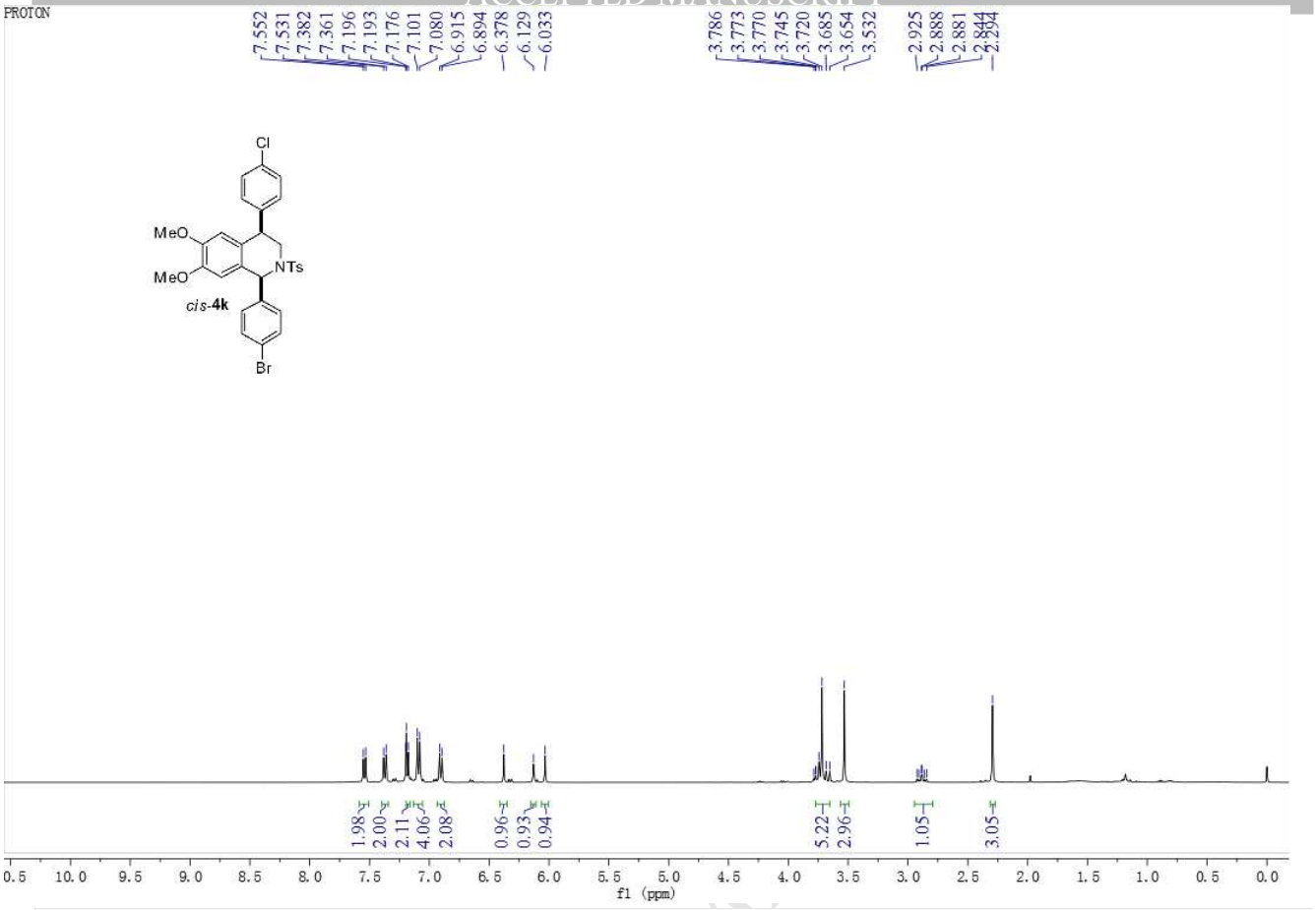

C13CPD
147.928 147.878 147.079 143.046 142.885 142.463 137.870 137.704 130.406 129.935 129.440 128.868 128.704 128.564 128.513 128.467 128.278 128.264 128.187 128.032 127.770 127.122 127.081 126.642 126.538 111.907 111.491 110.137 109.503
77.318 77.000 76.683 58.435 57.217 55.699 55.606 55.367 47.832 46.432 44.255 43.687 43.539 43.230 21.434
MeO
MeO
NTs
Bn
cis-4h
+
trans-4h
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

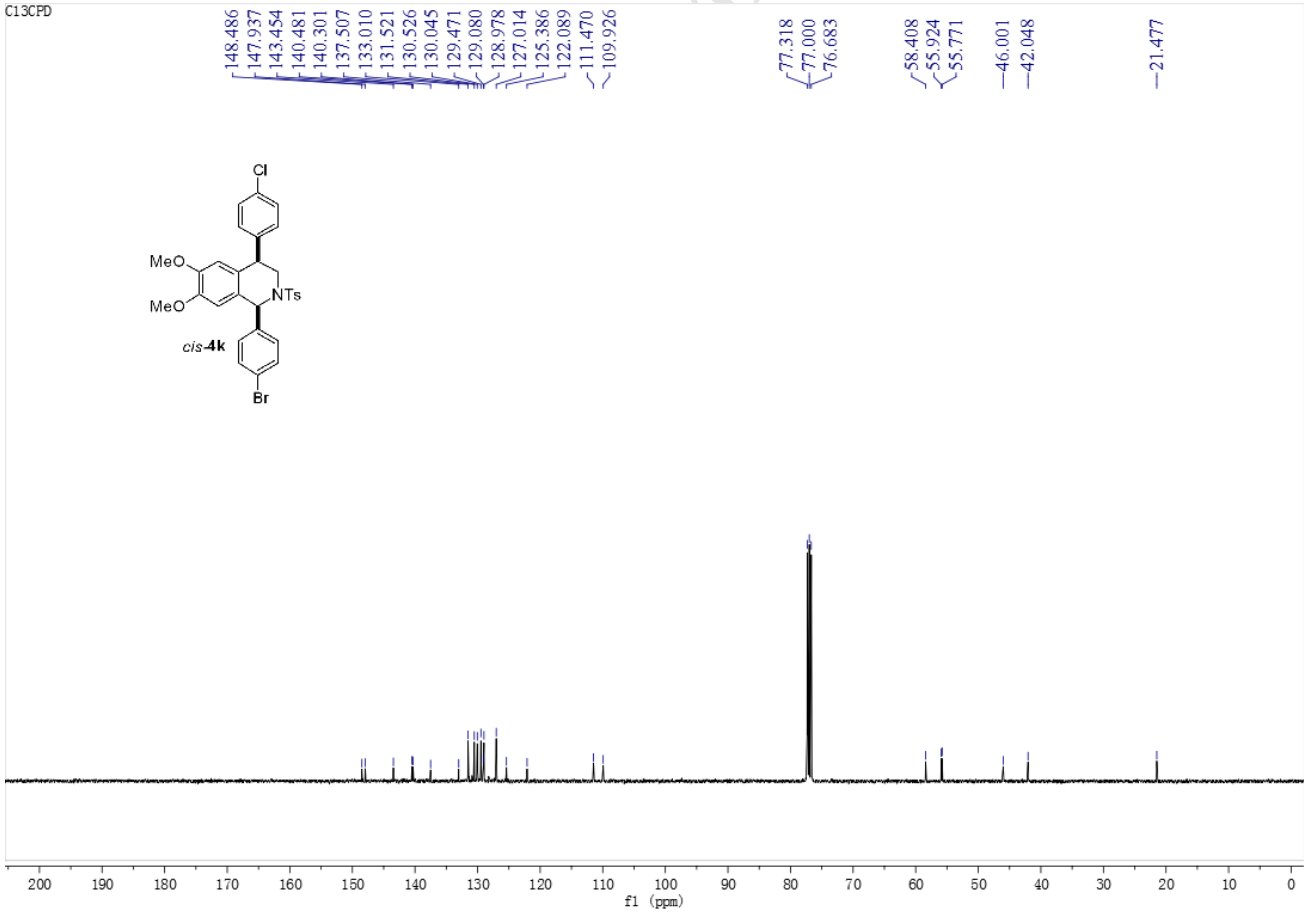

PROTON
7.651
7.631
7.306
7.294
7.291
7.273
7.265
7.262
7.249
7.117
7.113
7.097
6.566
6.308
4.419
4.382
4.244
4.229
4.212
4.138
4.102
3.846
3.753
3.740
3.724
3.711
3.627
3.055
3.035
3.026
3.006
2.410
MeO
MeO
NTs
4i
1.99
5.14
2.03
0.98
1.00
1.00
1.00
1.01
2.95
1.15
3.04
1.00
2.96
f1 (ppm)

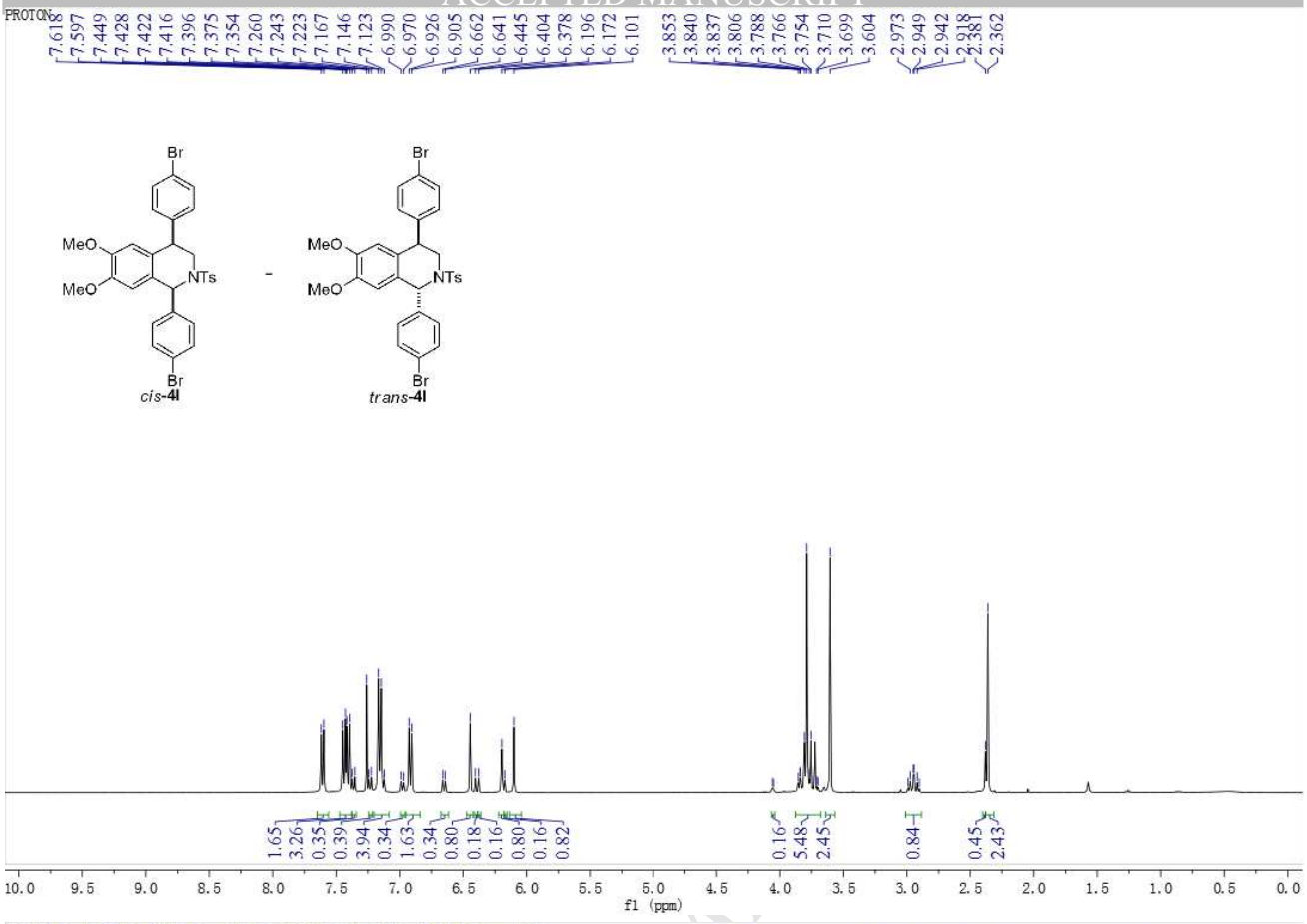

C13CPD
147.921
147.897
143.607
142.474
129.638
128.847
128.504
128.113
127.706
127.010
111.773
108.374
77.317
77.000
76.682
55.845
55.760
51.194
47.648
44.845
21.488
MeO
MeO
NTs
4i
f1 (ppm)

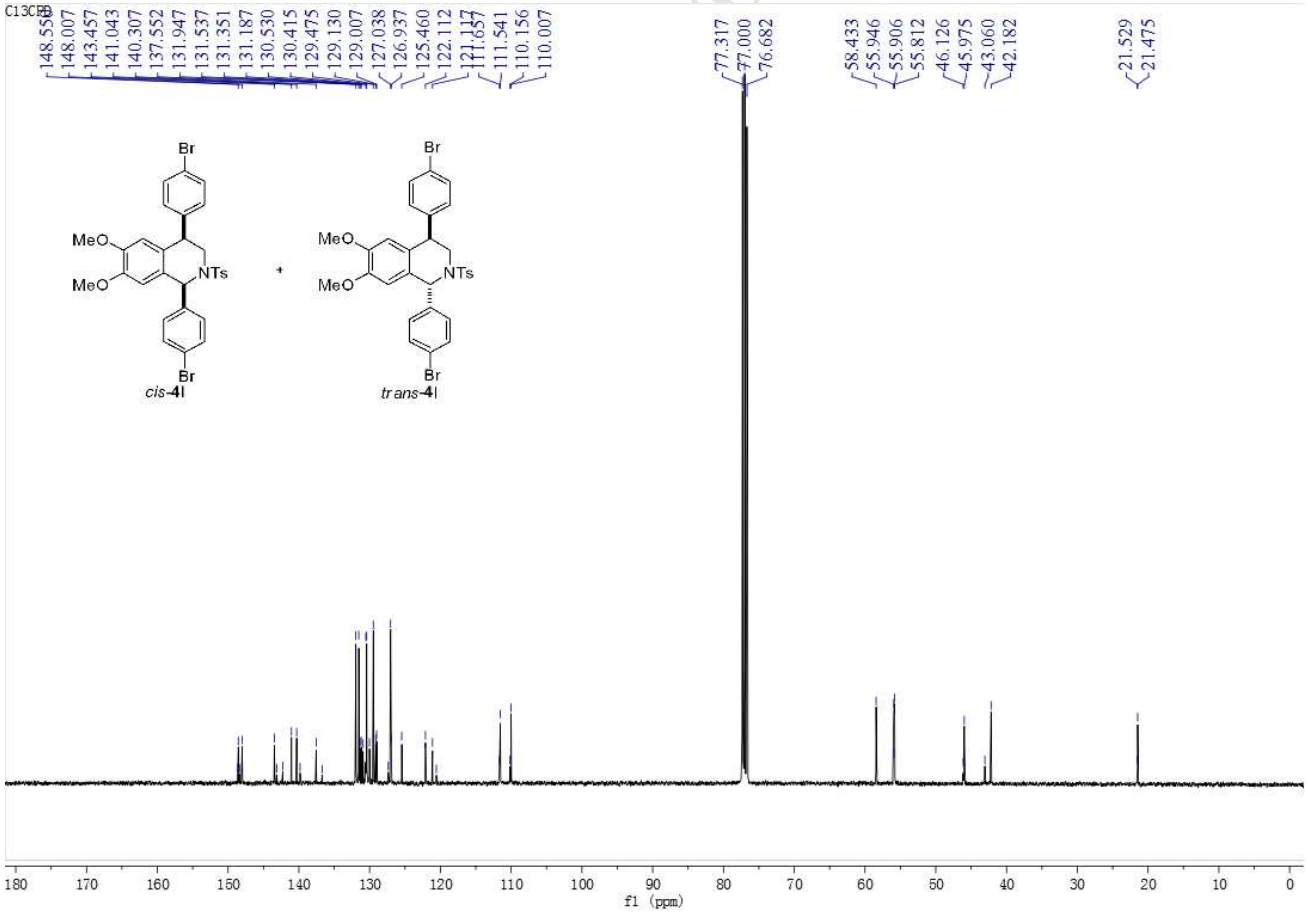

PROTON
7.556
7.536
7.228
7.207
7.190
7.168
7.147
7.095
7.075
6.952
6.937
6.930
6.919
6.898
6.876
6.379
6.153
6.036
3.785
3.779
3.774
3.771
3.742
3.714
3.692
3.521
2.942
2.926
2.903
2.896
2.873
2.286
F
MeO
MeO
NTs
cis-4j
Cl
1.86
4.25
1.91
3.90
0.94
0.90
0.93
5.34
3.07
1.06
3.00
f1 (ppm)

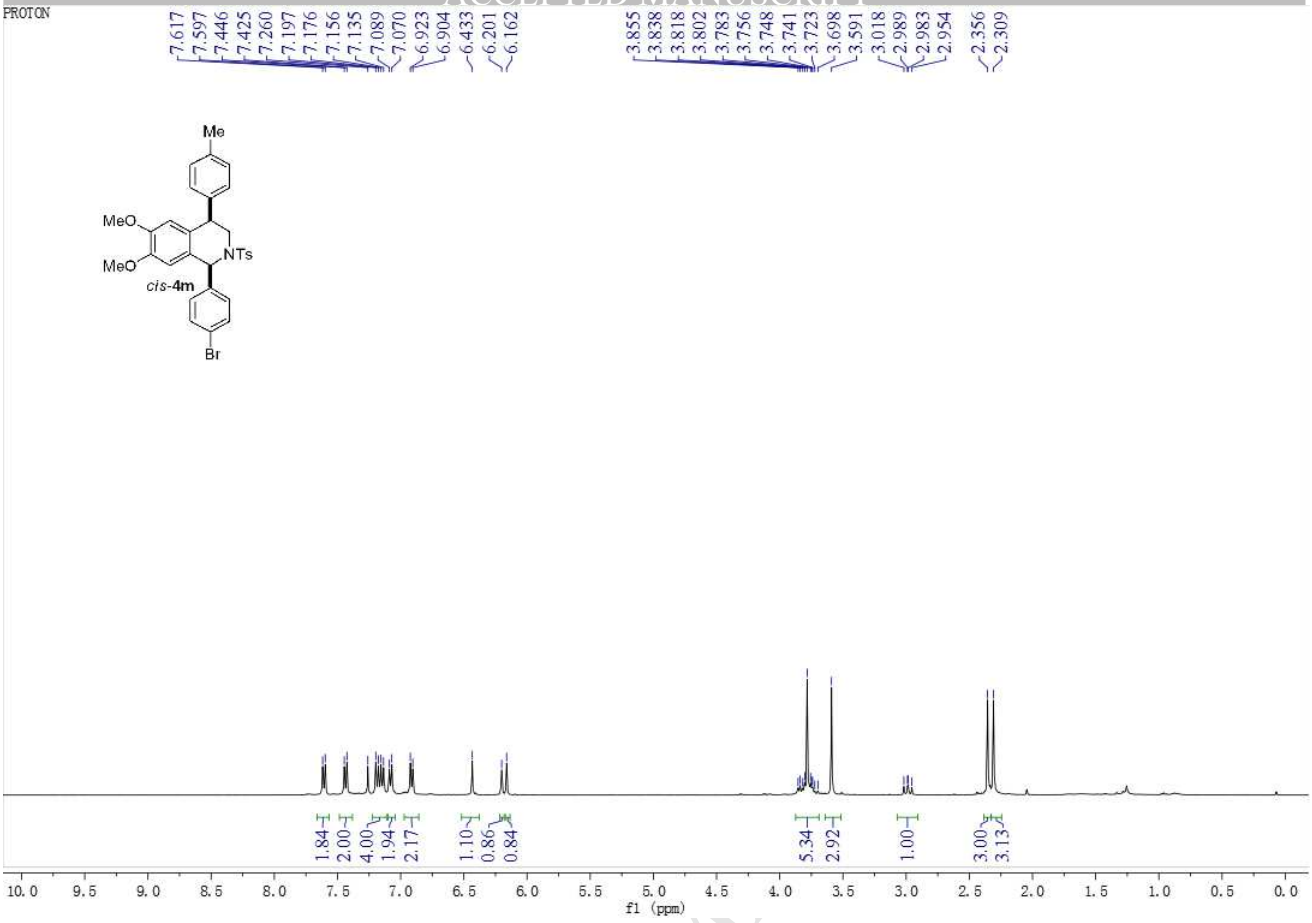

C13CPD
163.064
160.621
148.417
139.857
133.820
130.236
130.186
130.159
129.444
128.534
127.000
115.577
111.477
109.888
77.318
77.000
76.682
58.339
55.906
55.715
46.083
41.842
21.460
F
MeO
MeO
NTs
cis-4j
Cl
f1 (ppm)

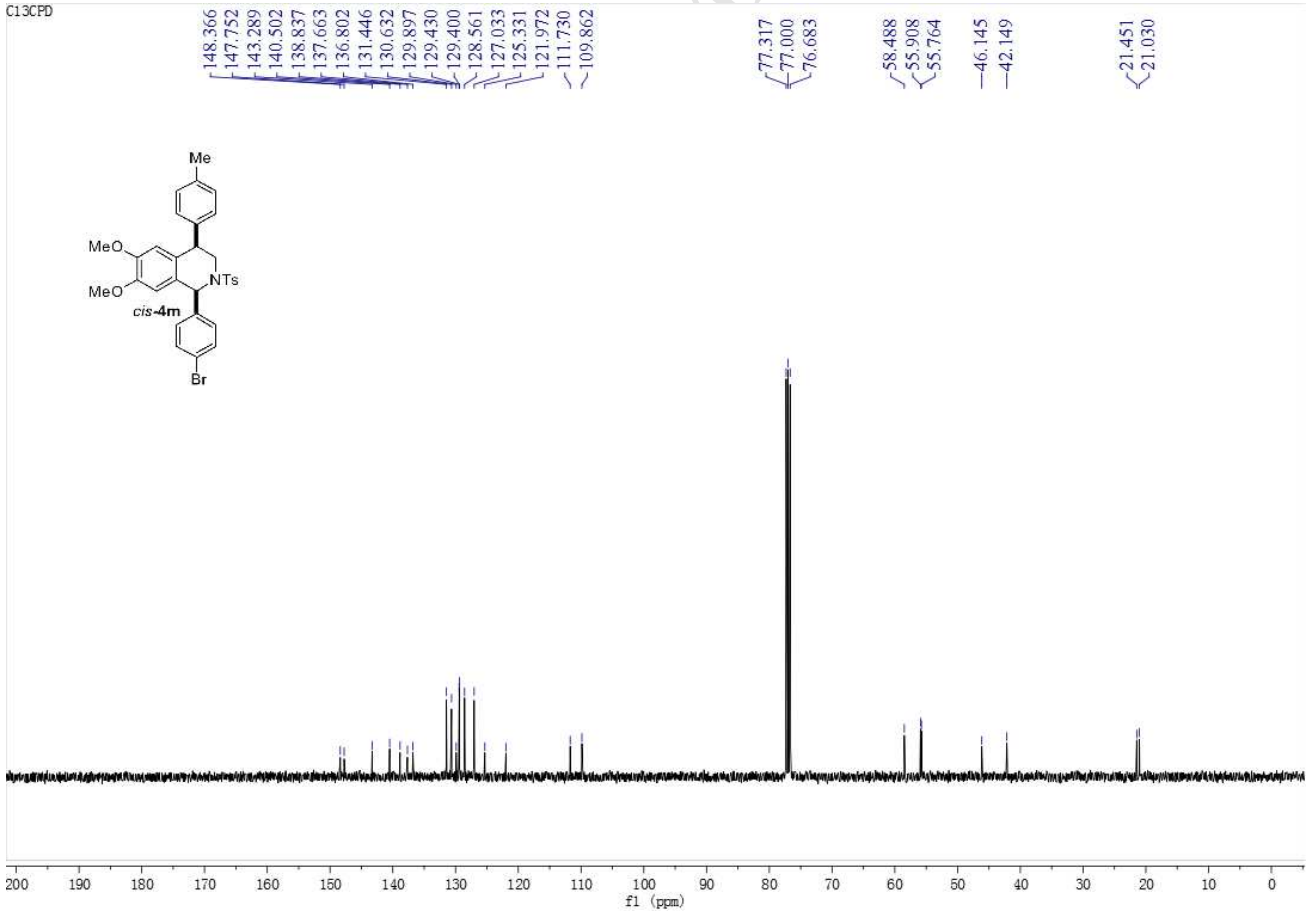




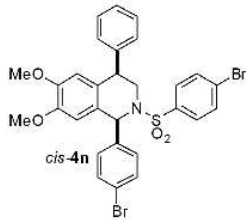

PROTON
7.618
7.597
7.449
7.428
7.422
7.416
7.396
7.375
7.354
7.260
7.243
7.223
7.167
7.146
7.123
6.990
6.970
6.926
6.905
6.662
6.641
6.445
6.404
6.378
6.196
6.172
6.101
3.853
3.840
3.837
3.806
3.788
3.766
3.754
3.710
3.699
3.604
2.973
2.949
2.942
2.918
2.381
2.362
Br
MeO
MeO
NTs
Br
cis-4l
trans-4l
1.65
3.26
0.35
0.39
3.94
0.34
1.63
0.34
0.80
0.18
0.16
0.80
0.16
0.82
0.16
5.48
2.45
0.84
0.45
2.43
f1 (ppm)

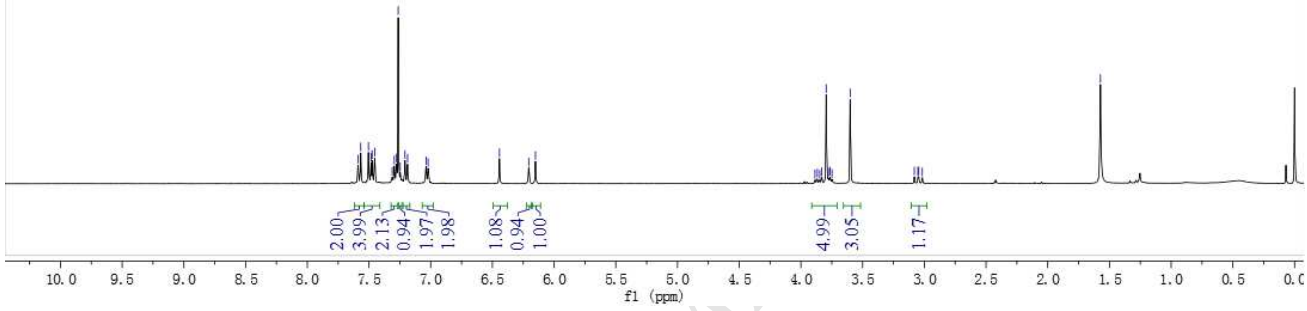

C13CPD
148.558
148.007
143.457
141.043
140.307
137.552
131.947
131.537
131.351
131.187
130.530
130.415
129.475
129.130
129.007
127.038
126.937
125.460
122.112
121.657
111.541
110.156
110.007
77.317
77.000
76.682
58.433
55.946
55.906
55.812
46.126
45.975
43.060
42.182
21.529
21.475
Br
MeO
MeO
NTs
Br
cis-4l
trans-4l
f1 (ppm)



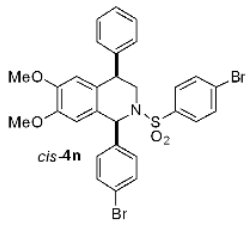


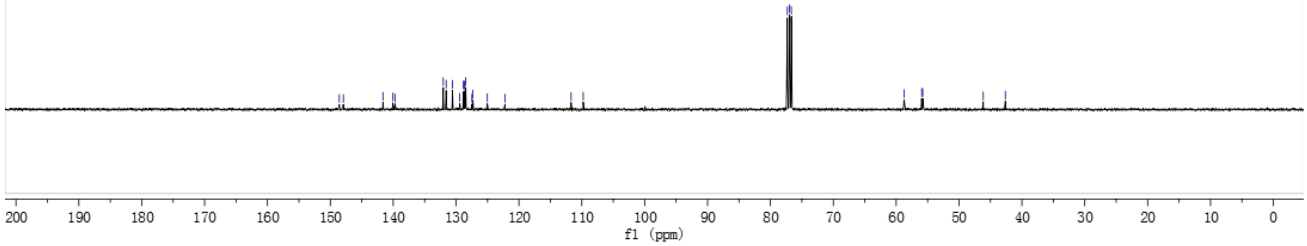
PROTON

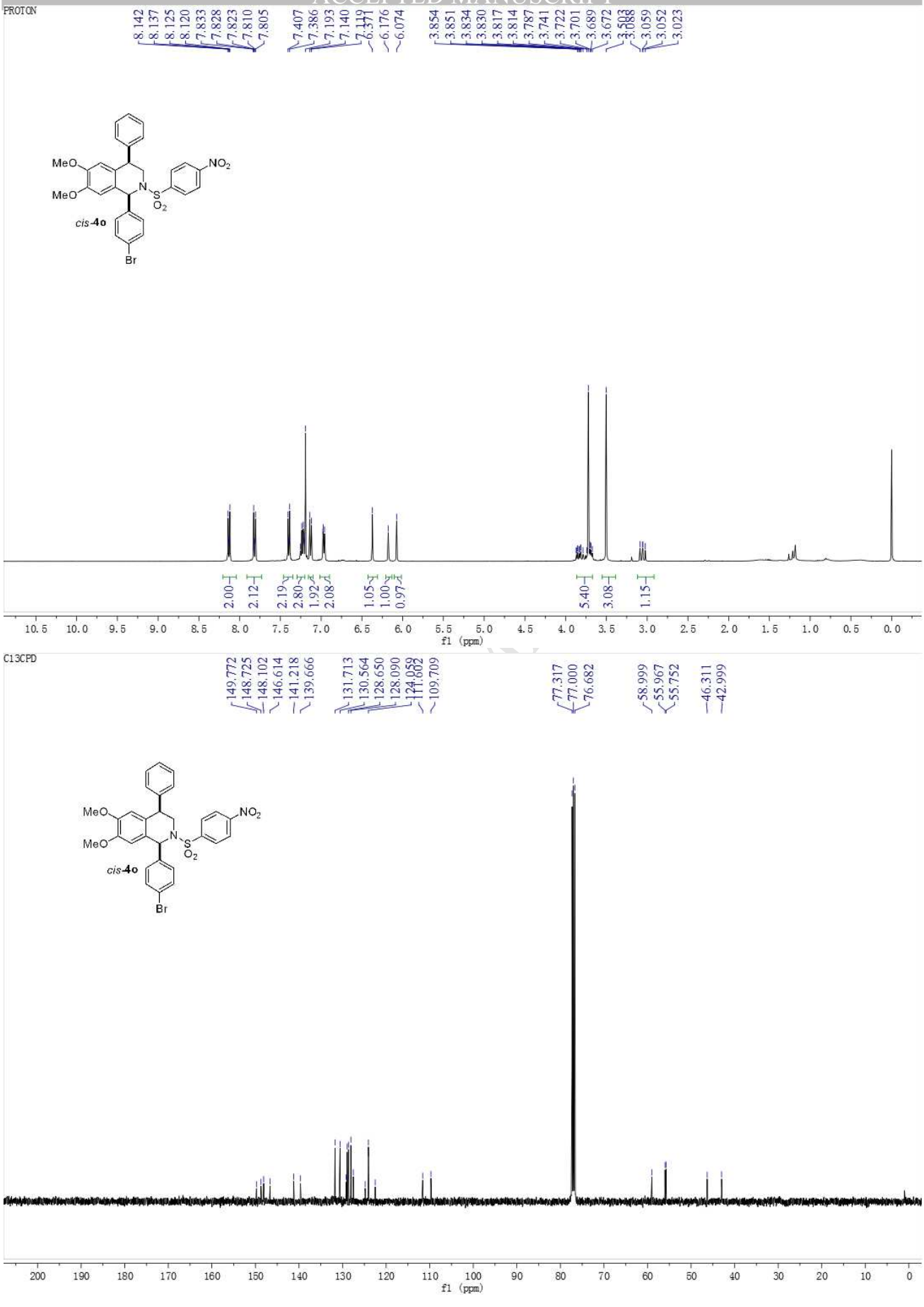


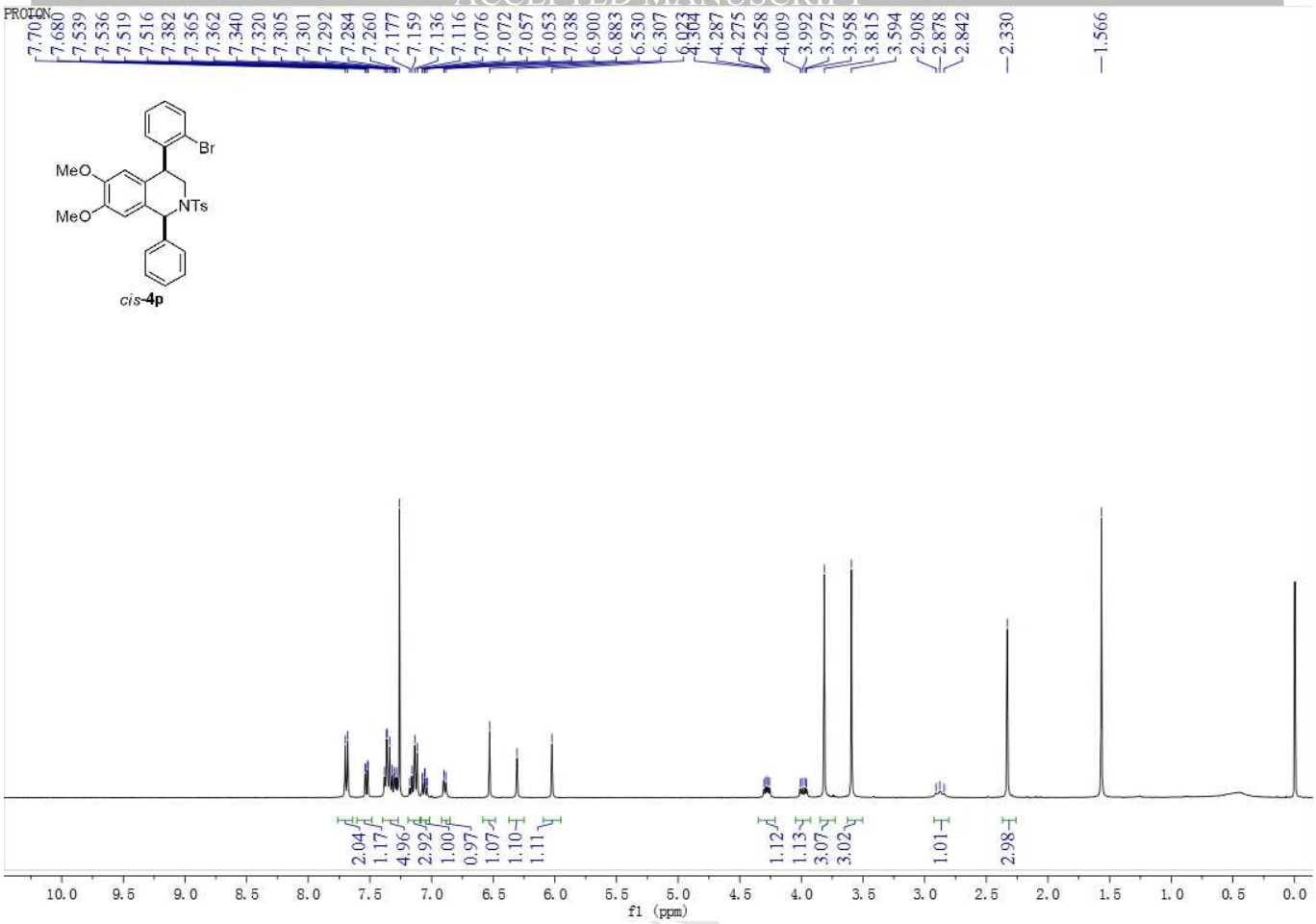


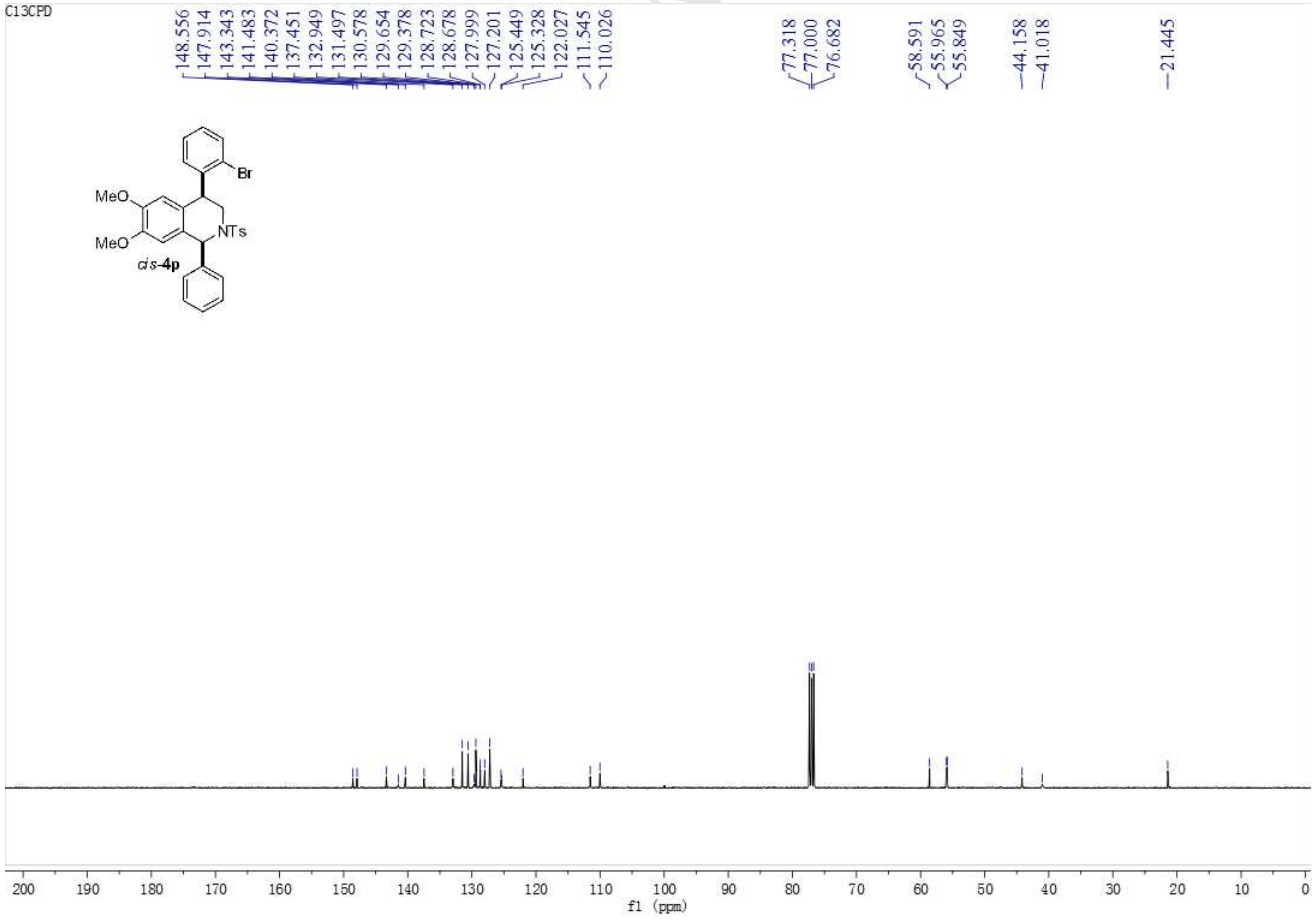
C13CPD

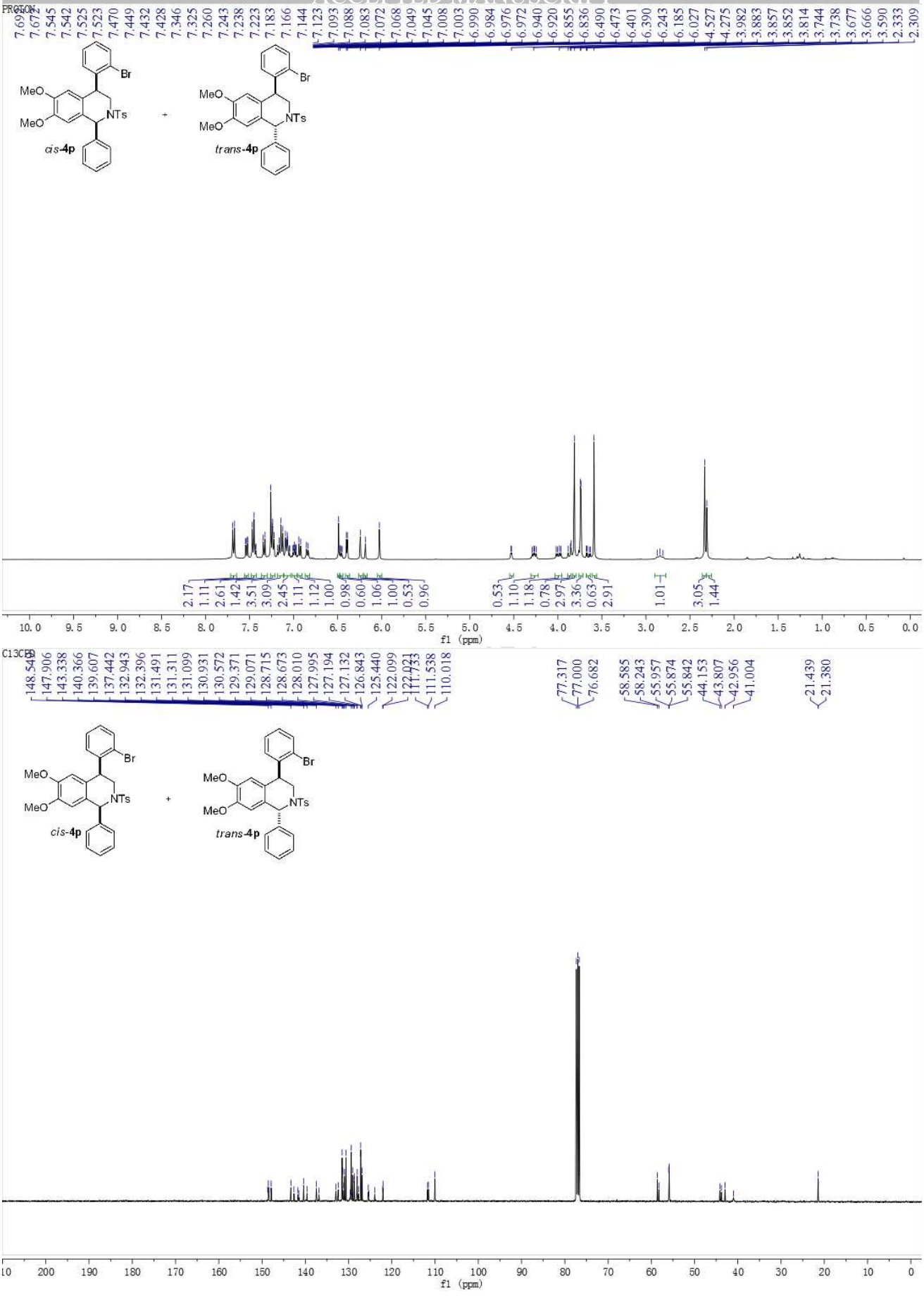


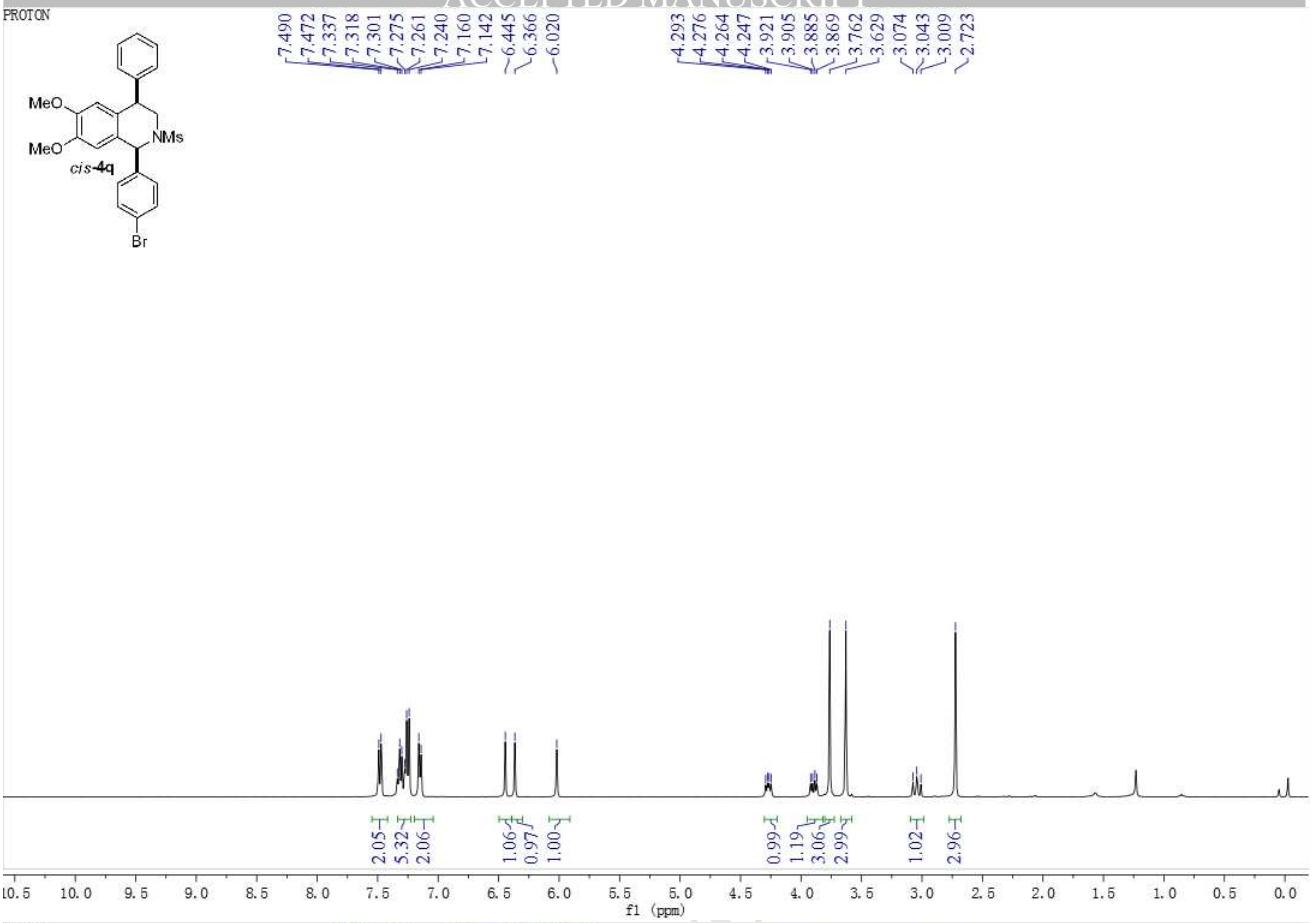


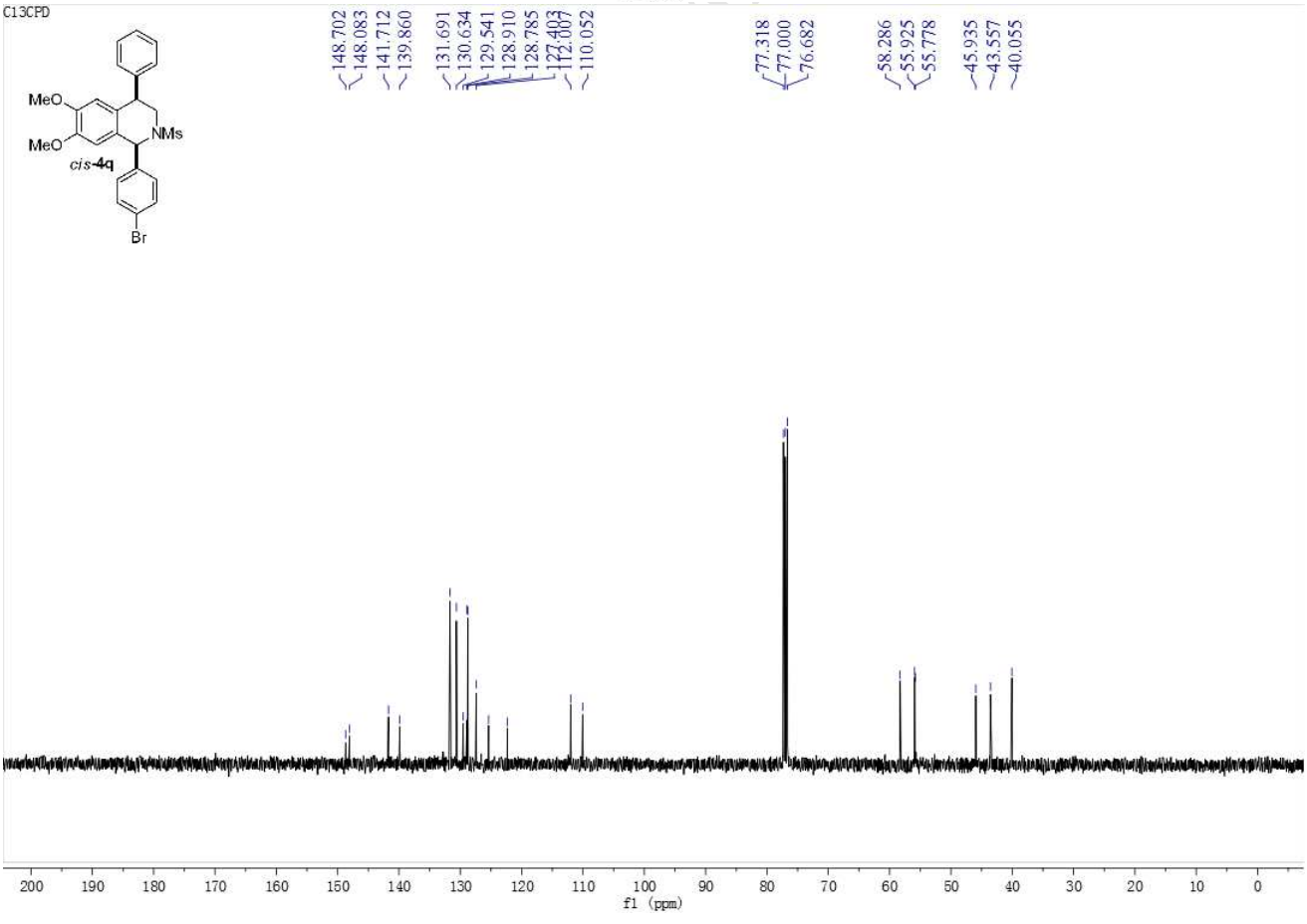

PROTON
8.142
8.137
8.125
8.120
7.833
7.828
7.823
7.810
7.805
7.407
7.386
7.193
7.140
7.119
6.371
6.176
6.074
3.854
3.851
3.834
3.830
3.817
3.814
3.787
3.741
3.722
3.701
3.689
3.672
3.503
3.088
3.059
3.052
3.023
MeO
MeO
N
S
O2
NO2
cis-4o
Br
2.00
2.12
2.19
2.80
1.92
2.08
1.05
1.00
0.97
5.40
3.08
1.15
f1 (ppm)
C13CPD
149.772
148.725
148.102
146.614
141.218
139.666
131.713
130.564
128.650
128.090
124.059
111.602
109.709
77.317
77.000
76.682
58.999
55.967
55.752
46.311
42.999
f1 (ppm)

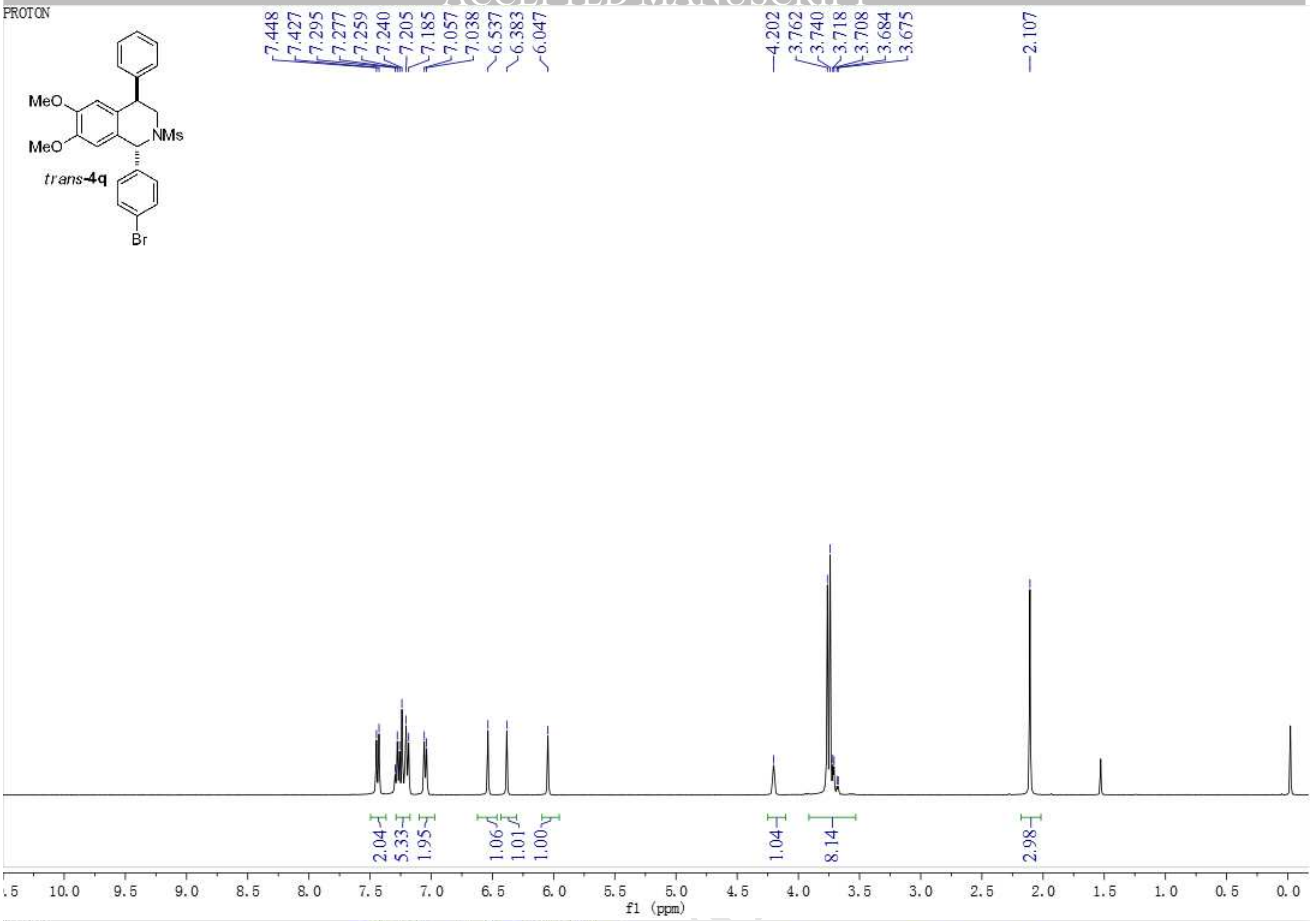


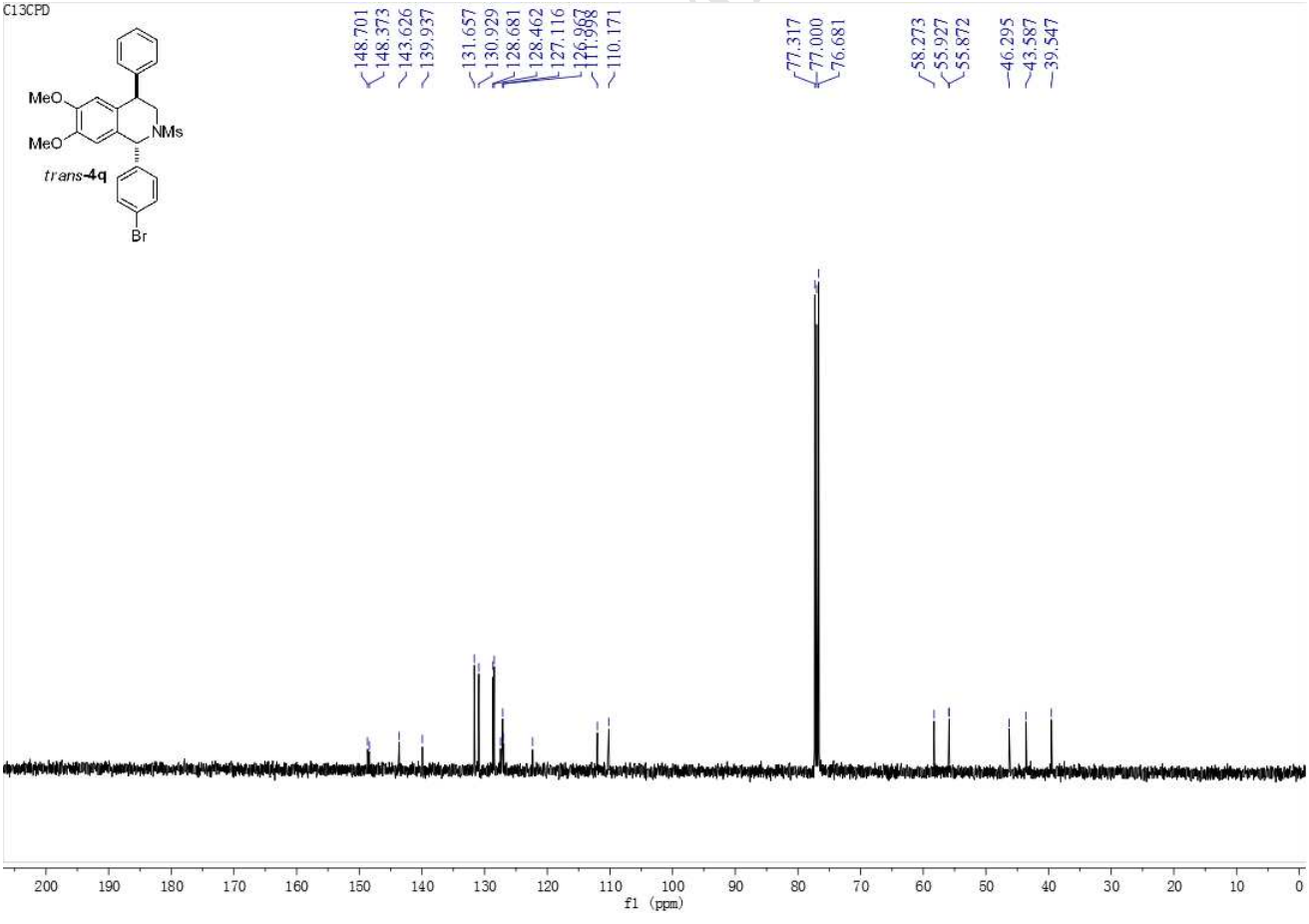



PROTON
MeO
MeO
Br
NTs
cis-4p
trans-4p
f1 (ppm)
C13CPD
f1 (ppm)

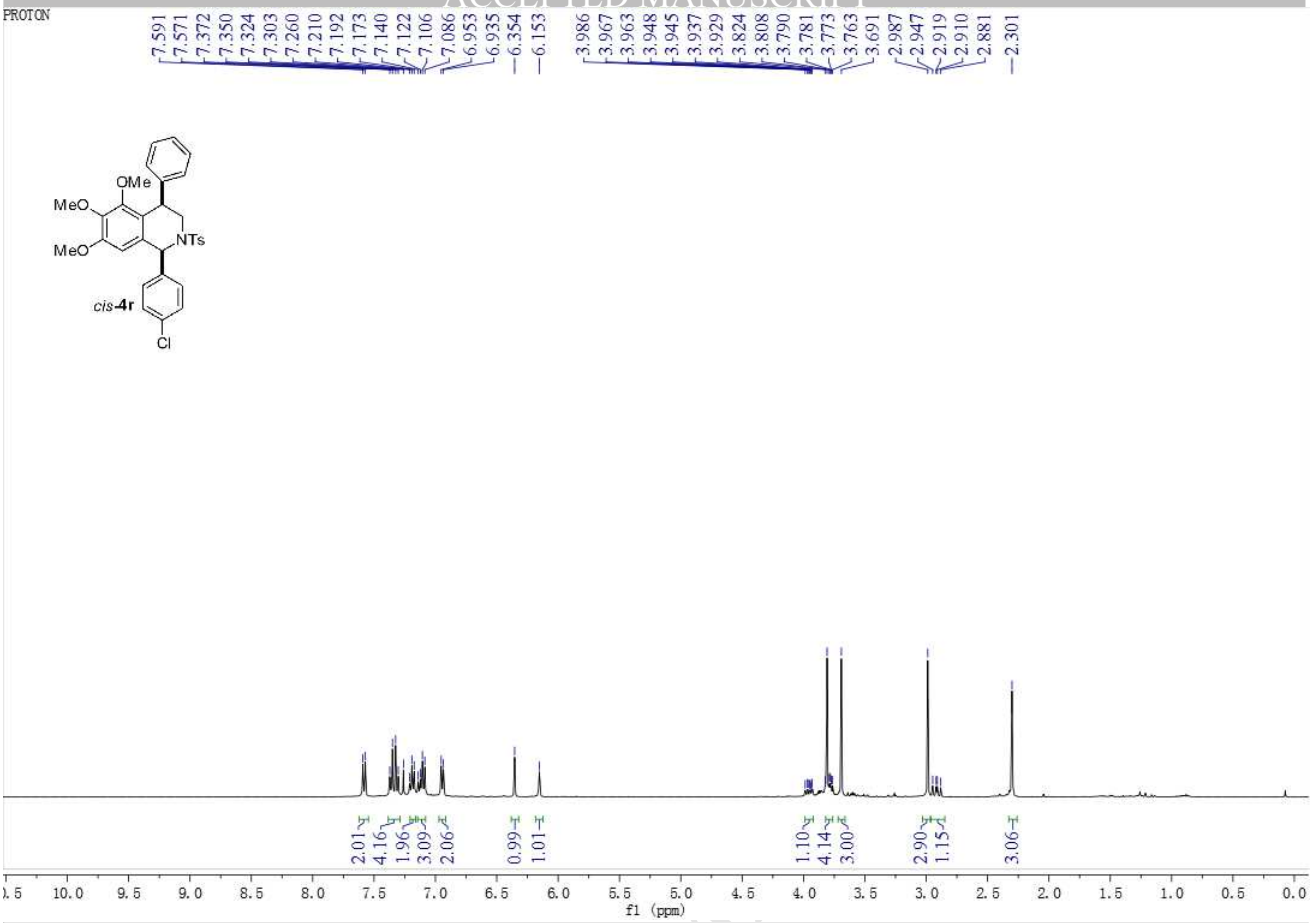

PROTON
MeO
MeO
NMs
cis-4q
Br
7.490
7.472
7.337
7.318
7.301
7.275
7.261
7.240
7.160
7.142
6.445
6.366
6.020
4.293
4.276
4.264
4.247
3.921
3.905
3.885
3.869
3.762
3.629
3.074
3.043
3.009
2.723
2.05
5.32
2.06
1.06
0.97
1.00
0.99
1.19
3.06
2.99
1.02
2.96
f1 (ppm)


C13CPD
MeO
MeO
NMs
cis-4q
Br
148.702
148.083
141.712
139.860
131.691
130.634
129.541
128.910
128.785
127.403
112.007
110.052
77.318
77.000
76.682
58.286
55.925
55.778
45.935
43.557
40.055
f1 (ppm)

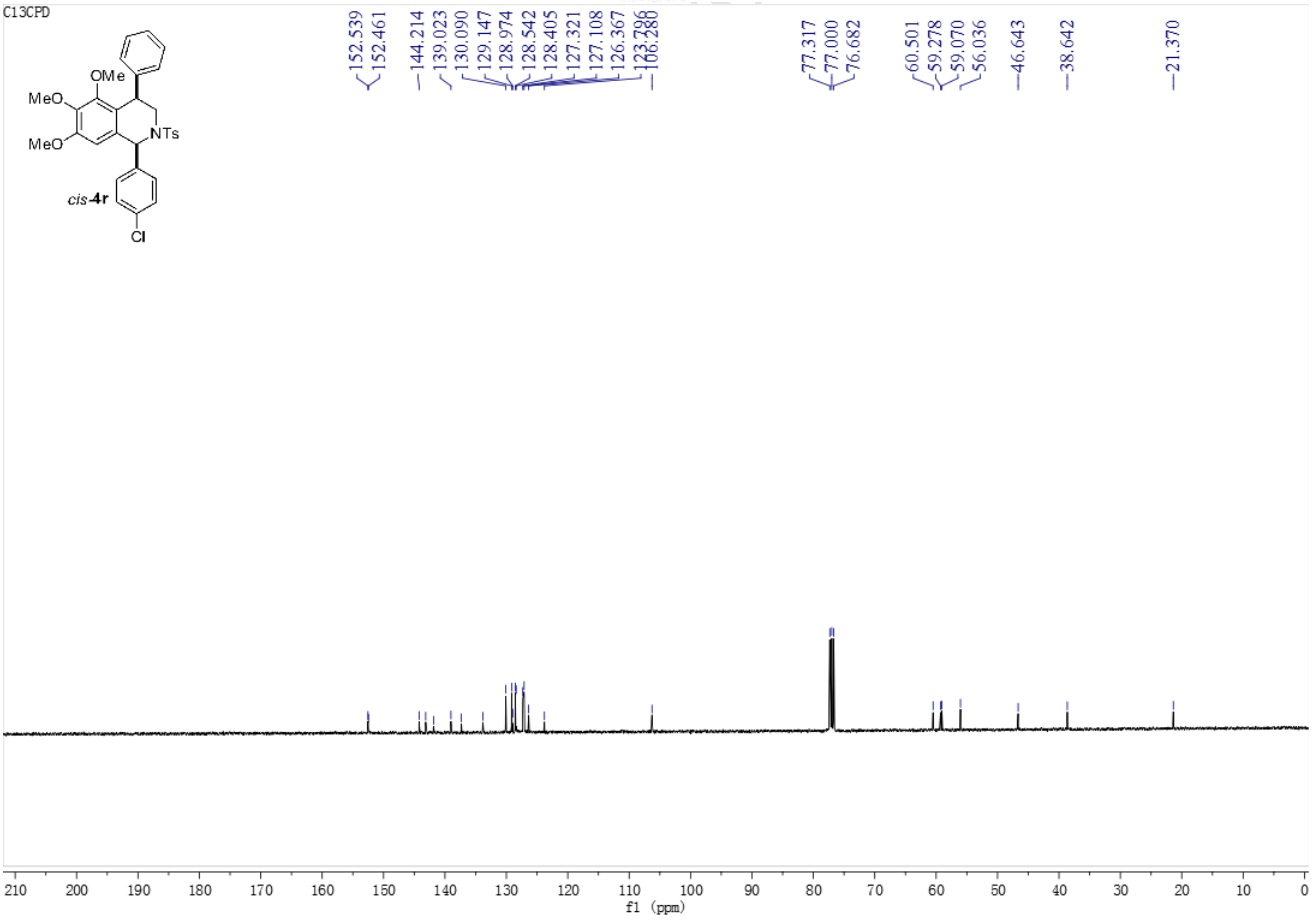

PROTON
MeO
MeO
NMs
trans-4q
Br
7.448
7.427
7.295
7.277
7.259
7.240
7.205
7.185
7.057
7.038
6.537
6.383
6.047
4.202
3.762
3.740
3.718
3.708
3.684
3.675
2.107
2.04
5.33
1.95
1.06
1.01
1.00
1.04
8.14
2.98
f1 (ppm)

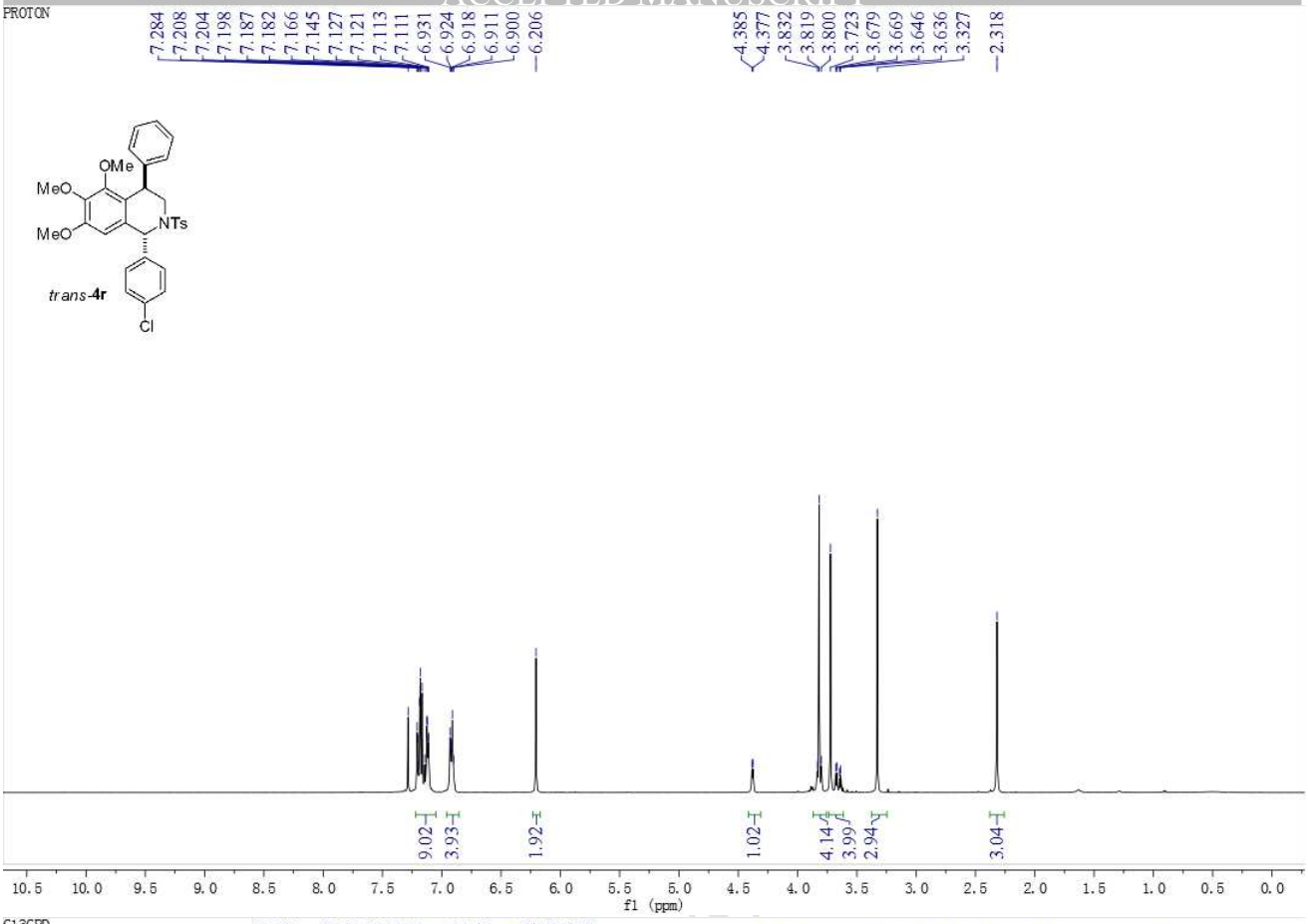

C13CPD
MeO
MeO
NMs
trans-4q
Br
148.701
148.373
143.626
139.937
131.657
130.929
128.681
128.462
127.116
111.998
110.171
77.317
77.000
76.681
58.273
55.927
55.872
46.295
43.587
39.547
f1 (ppm)

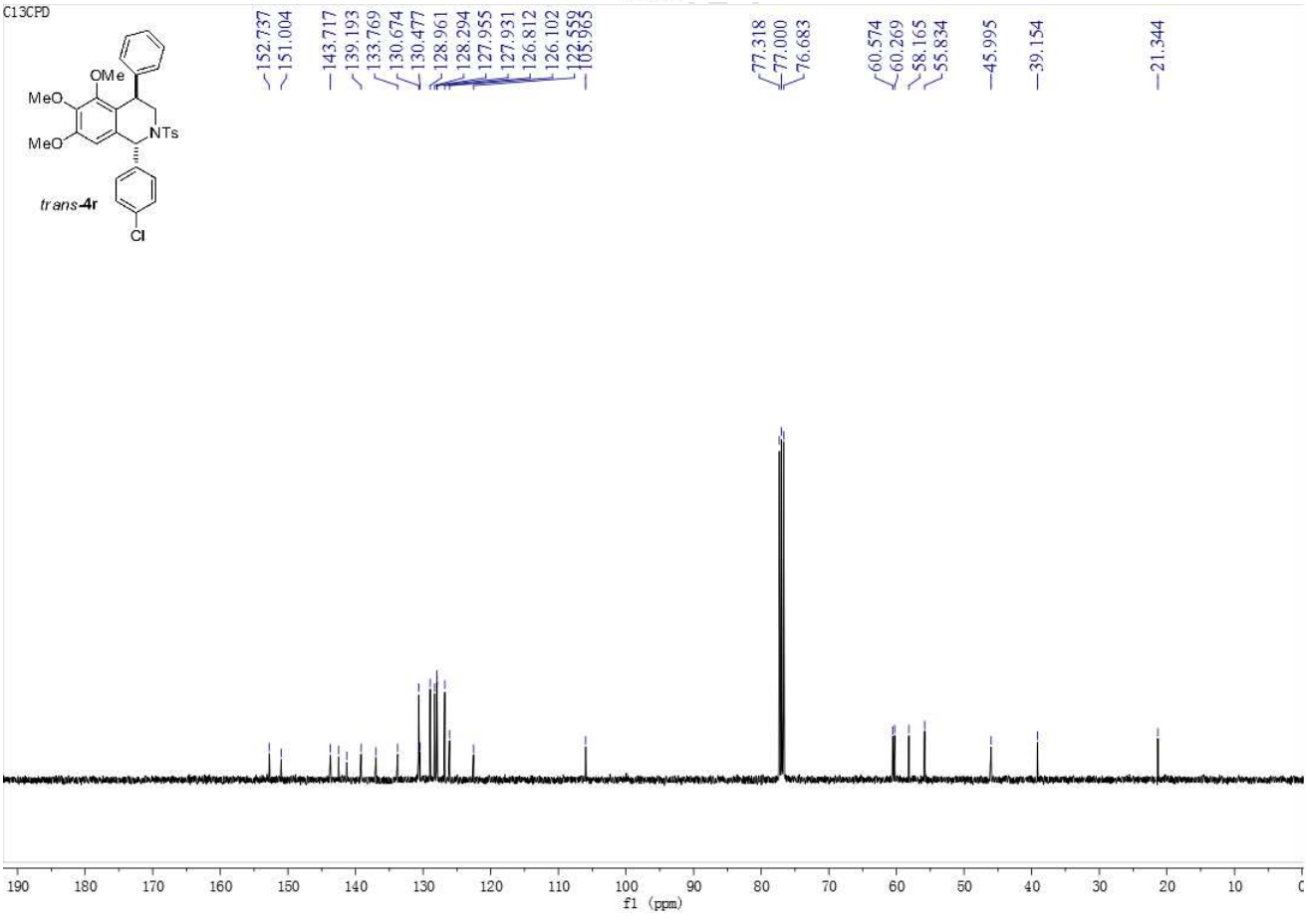
PROTON

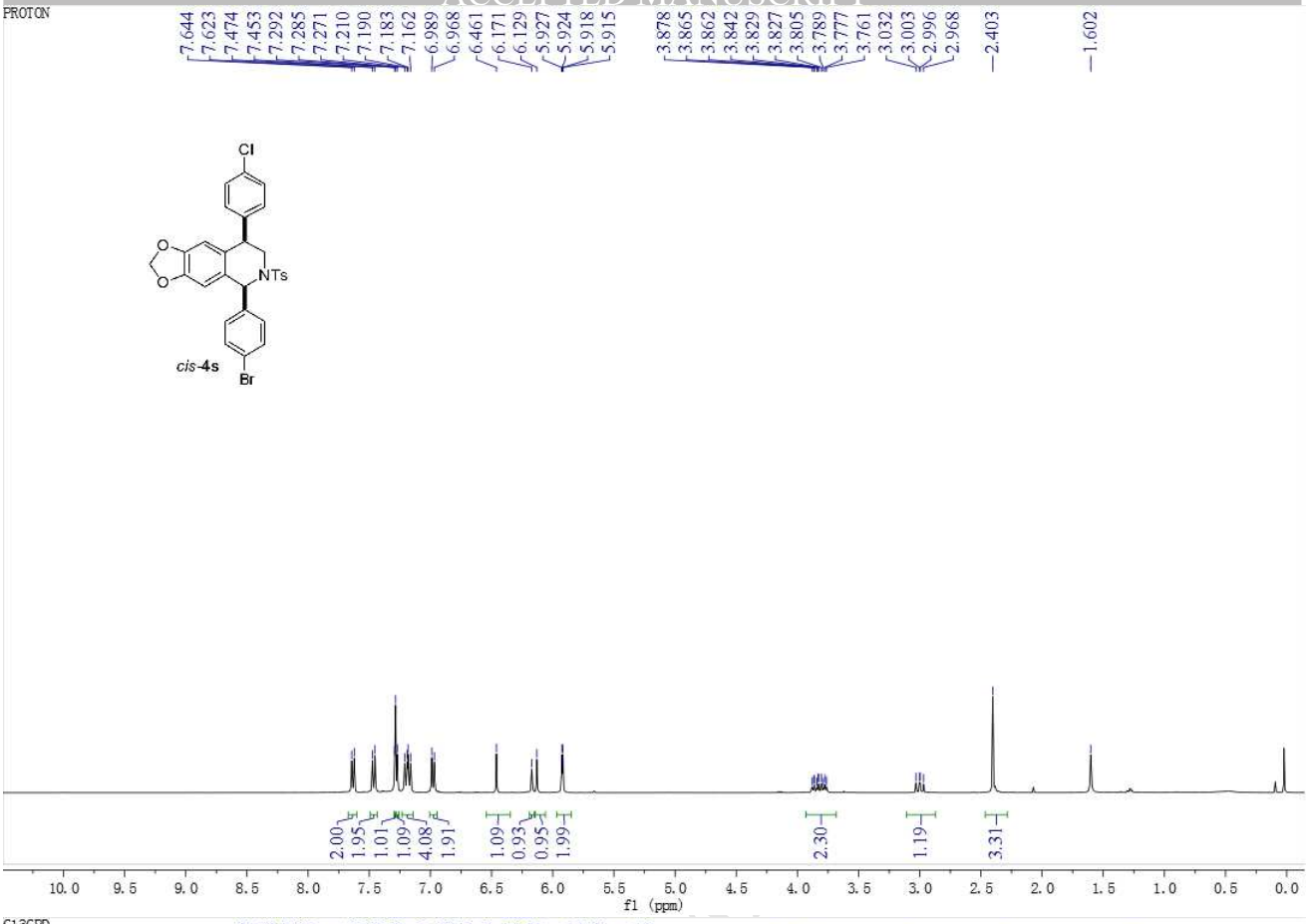


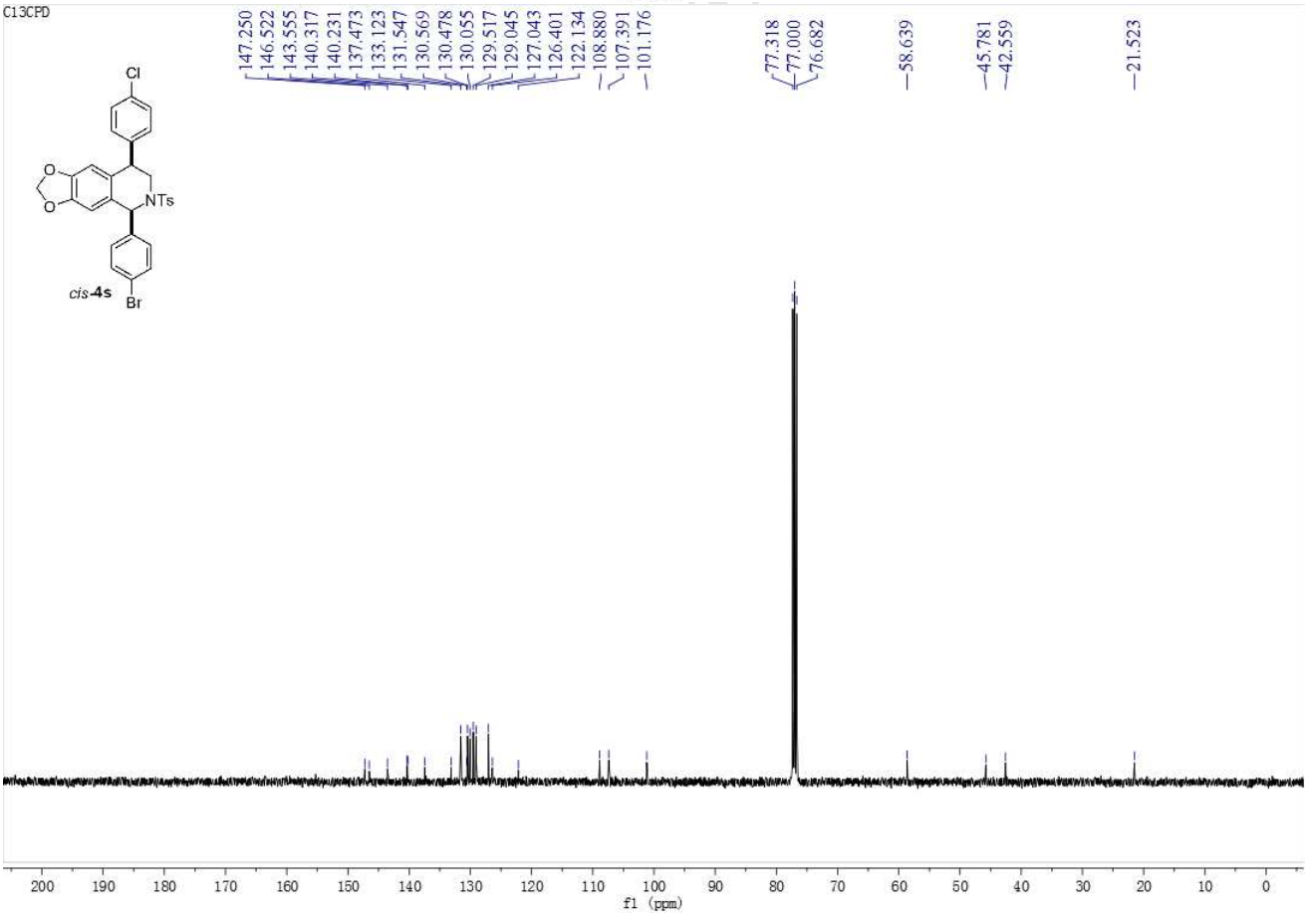
C13CPD

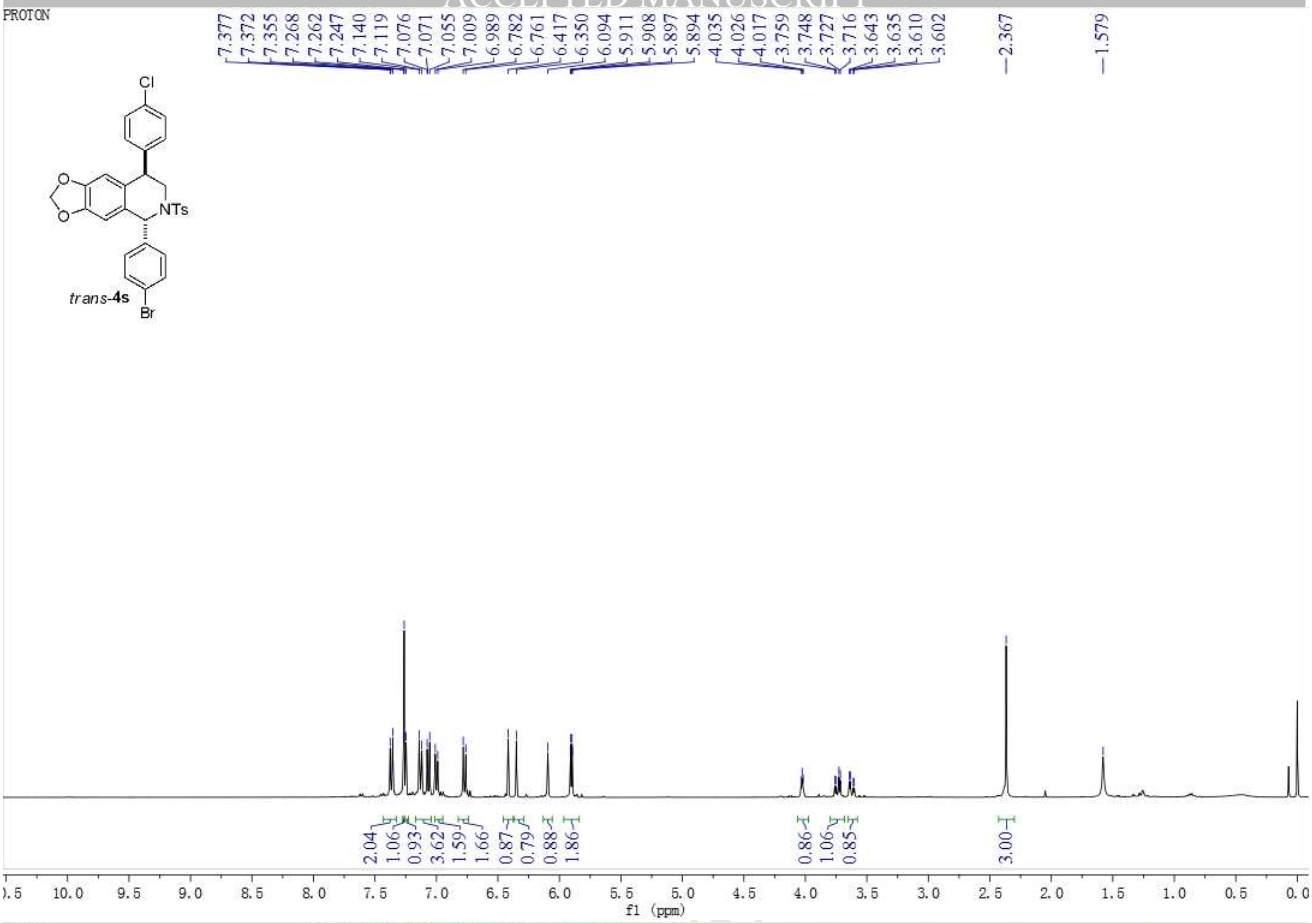


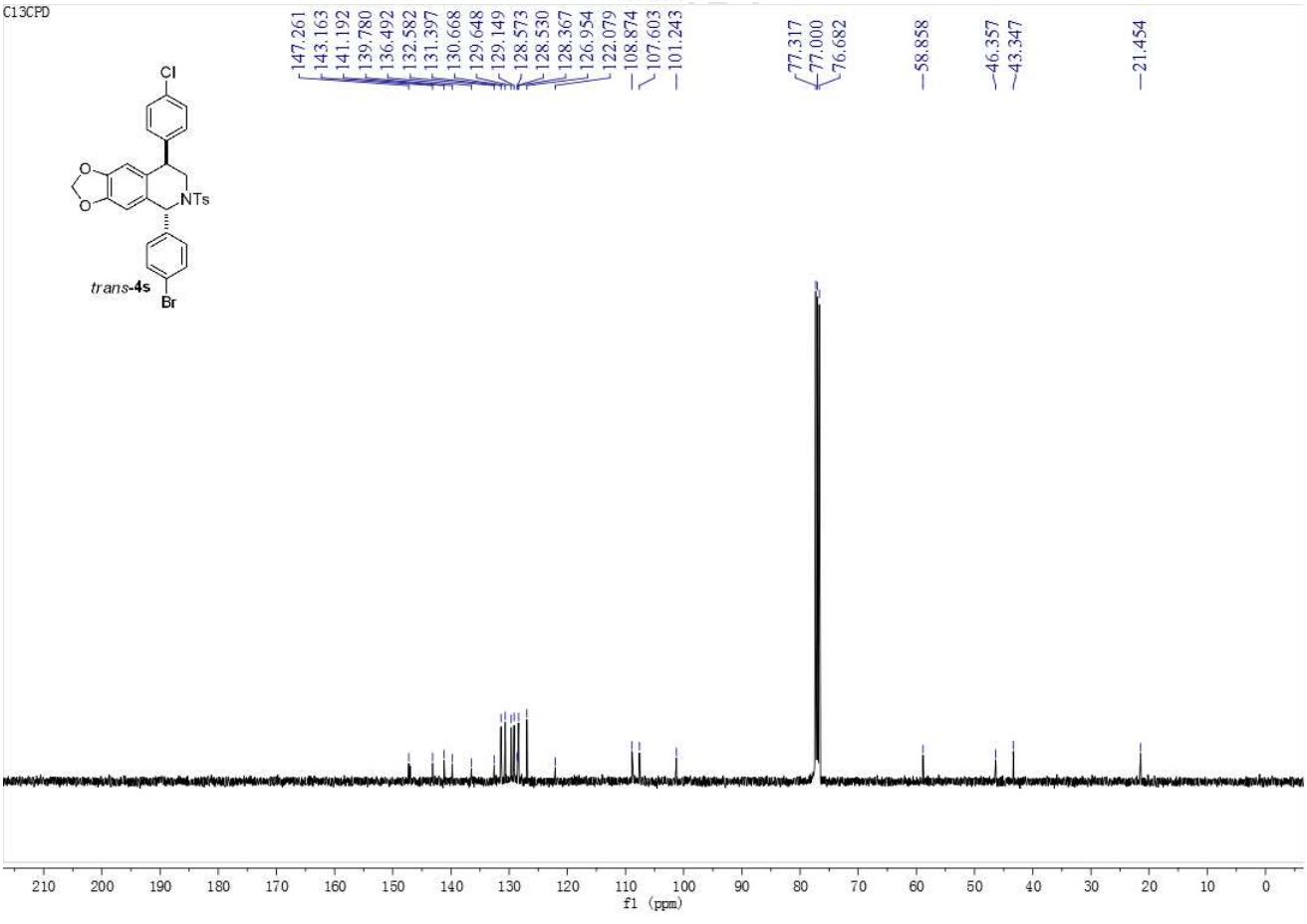

PROTON
7.284
7.208
7.204
7.198
7.187
7.182
7.166
7.145
7.127
7.121
7.113
7.111
6.931
6.924
6.918
6.911
6.900
6.206
4.385
4.377
3.832
3.819
3.800
3.723
3.679
3.669
3.646
3.636
3.327
2.318
OMe
MeO
MeO
NTs
trans-4r
Cl
9.02
3.93
1.92
1.02
4.14
3.99
2.94
3.04
f1 (ppm)

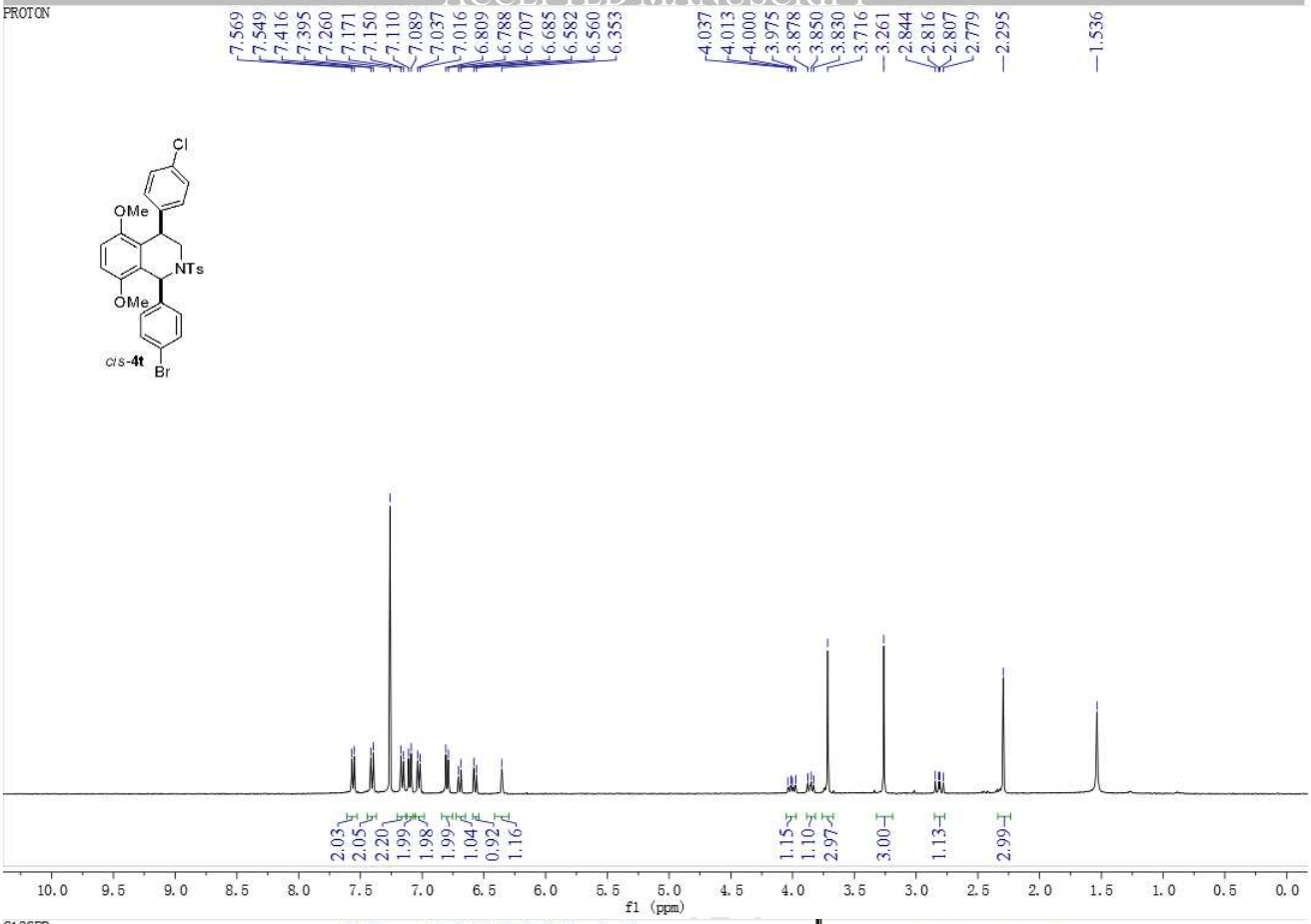

C13CPD
152.737
151.004
143.717
139.193
133.769
130.674
130.477
128.961
128.294
127.955
127.931
126.812
126.102
122.559
105.965
77.318
77.000
76.683
60.574
60.269
58.165
55.834
45.995
39.154
21.344
OMe
MeO
MeO
NTs
trans-4r
Cl
f1 (ppm)

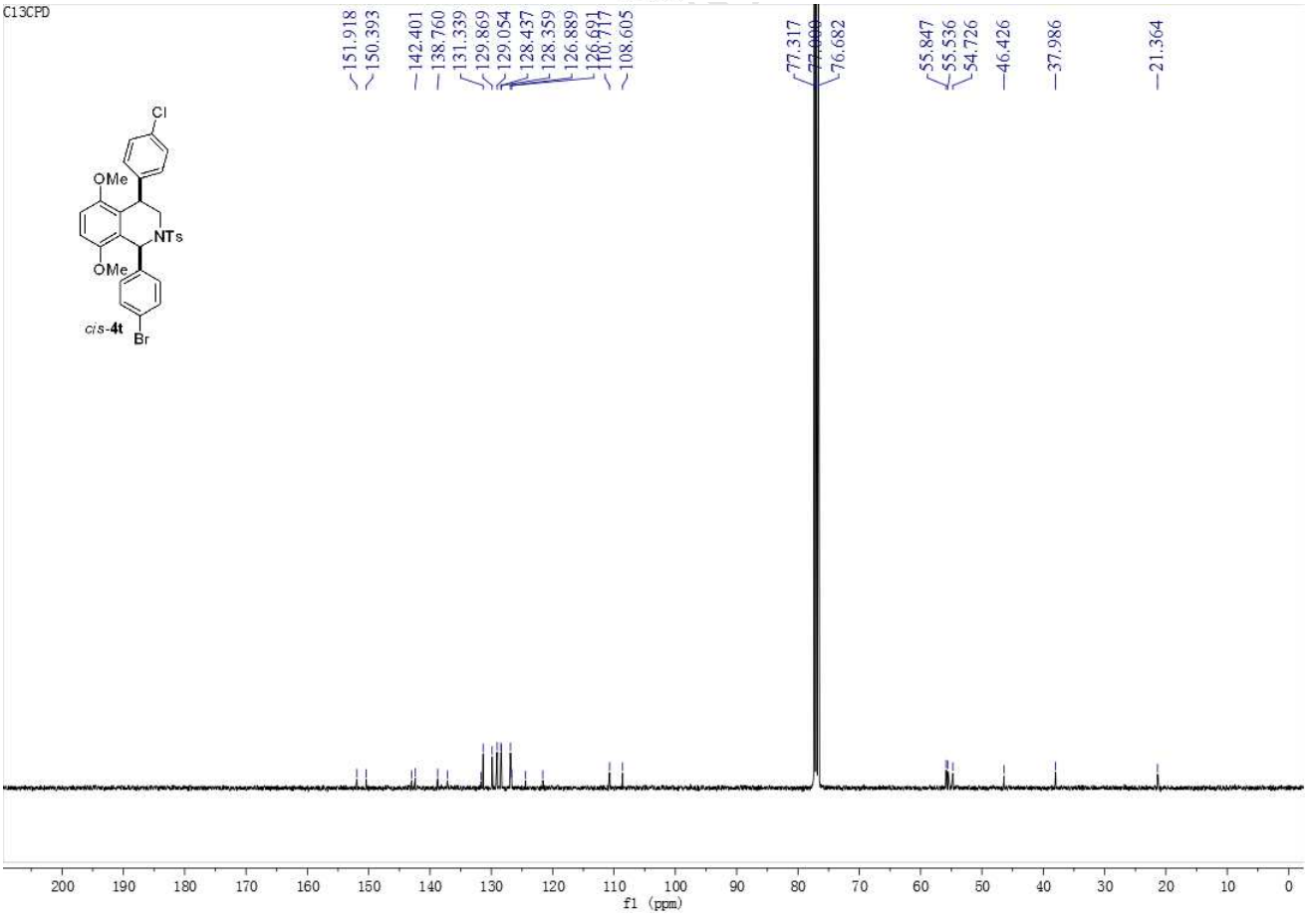

PROTON
7.644
7.623
7.474
7.453
7.292
7.285
7.271
7.210
7.190
7.183
7.162
6.989
6.968
6.461
6.171
6.129
5.927
5.924
5.918
5.915
3.878
3.865
3.862
3.842
3.829
3.827
3.805
3.789
3.777
3.761
3.032
3.003
2.996
2.968
2.403
1.602
Cl
O
O
NTs
cis-4s
Br
2.00
1.95
1.01
1.09
4.08
1.91
1.09
0.93
0.95
1.99
2.30
1.19
3.31
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

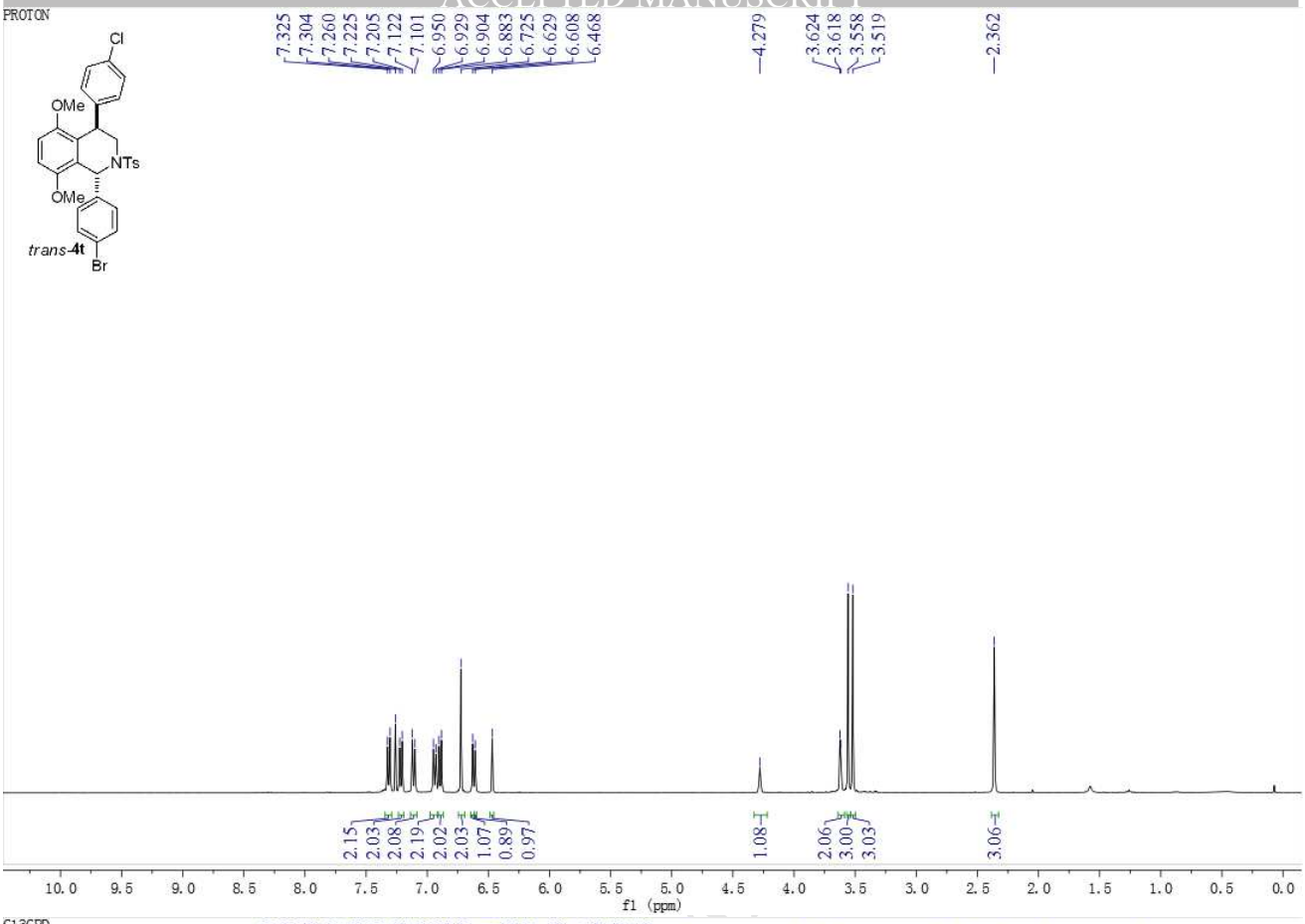

C13CPD
147.250
146.522
143.555
140.317
140.231
137.473
133.123
131.547
130.569
130.478
130.055
129.517
129.045
127.043
126.401
122.134
108.880
107.391
101.176
77.318
77.000
76.682
58.639
45.781
42.559
21.523
Cl
O
O
NTs
cis-4s
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

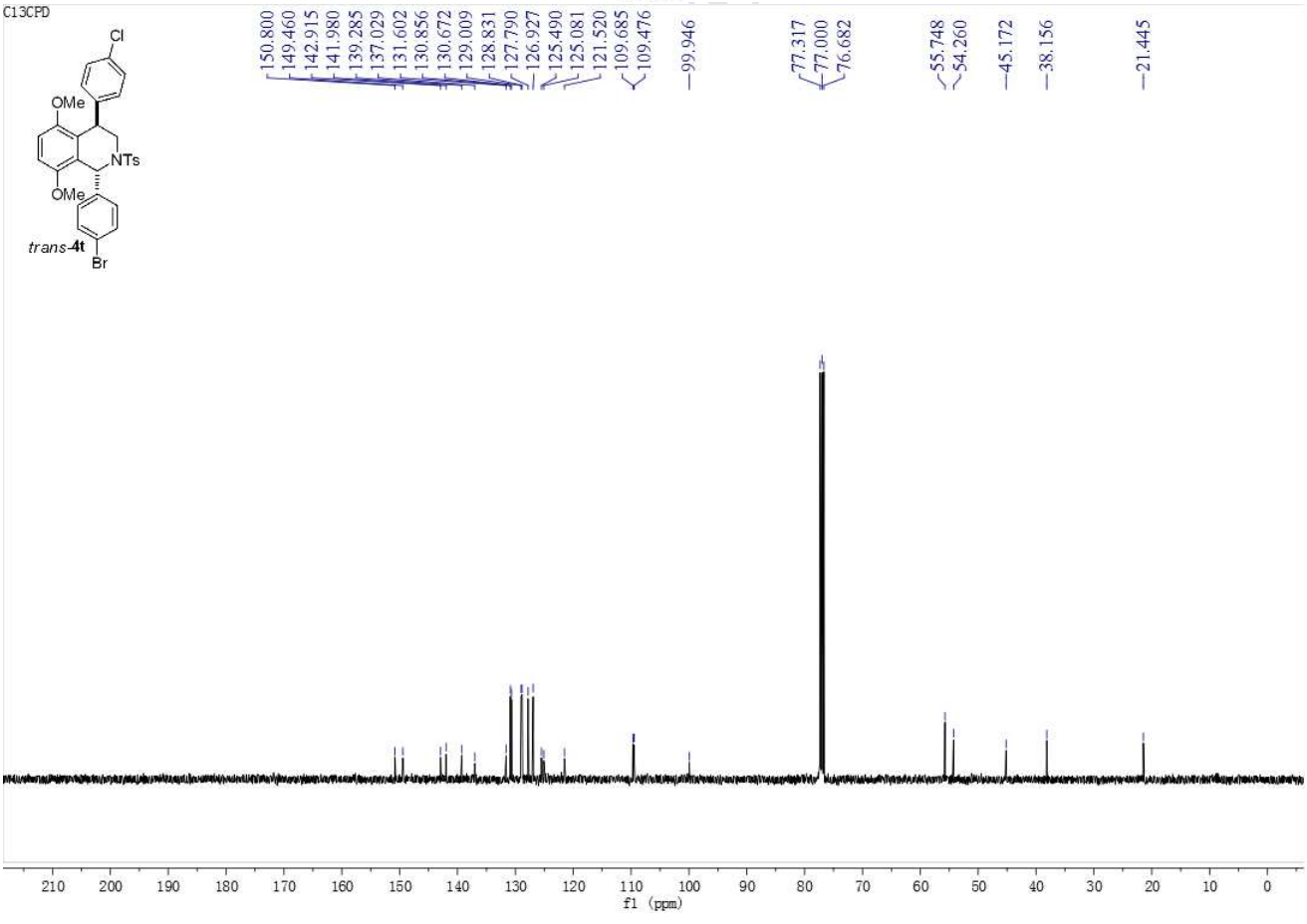

PROTON
7.377
7.372
7.355
7.268
7.262
7.247
7.140
7.119
7.076
7.071
7.055
7.009
6.989
6.782
6.761
6.417
6.350
6.094
5.911
5.908
5.897
5.894
4.035
4.026
4.017
3.759
3.748
3.727
3.716
3.643
3.635
3.610
3.602
2.367
1.579
Cl
NTs
trans-4s
Br
2.04
1.06
0.93
3.62
1.59
1.66
0.87
0.79
0.88
1.86
0.86
1.06
0.85
3.00
f1 (ppm)

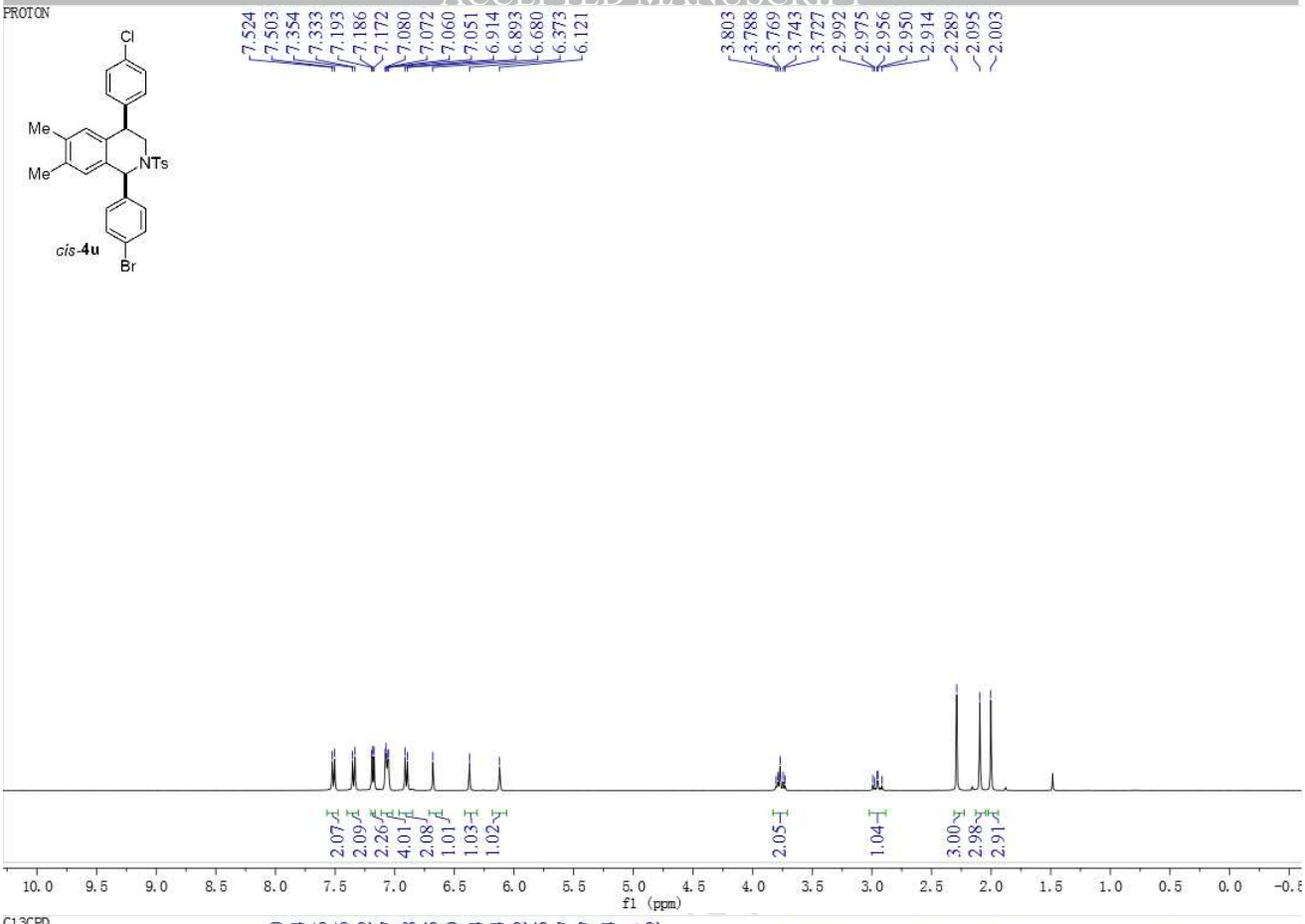

C13CPD
147.261
143.163
141.192
139.780
136.492
132.582
131.397
130.668
129.648
129.149
128.573
128.530
128.367
126.954
122.079
108.874
107.603
101.243
77.317
77.000
76.682
58.858
46.357
43.347
21.454
Cl
NTs
trans-4s
Br
f1 (ppm)

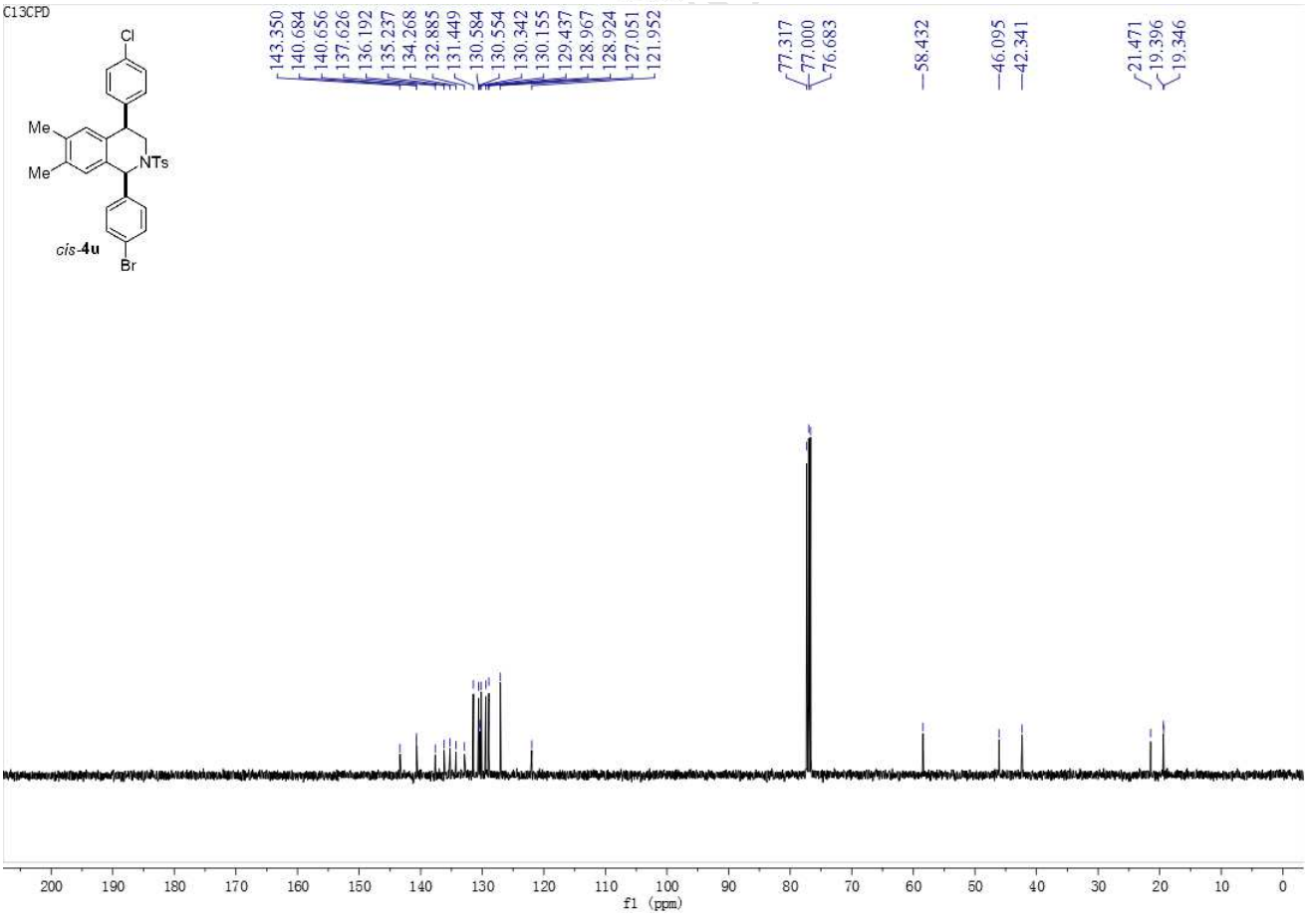

PROTON
7.569
7.549
7.416
7.395
7.260
7.171
7.150
7.110
7.089
7.037
7.016
6.809
6.788
6.707
6.685
6.582
6.560
6.353
4.037
4.013
4.000
3.975
3.878
3.850
3.830
3.716
3.261
2.844
2.816
2.807
2.779
2.295
1.536
Cl
OMe
NTs
OMe
cis-4t
Br
2.03
2.05
2.20
1.99
1.98
1.99
1.04
0.92
1.16
1.15
1.10
2.97
3.00
1.13
2.99
f1 (ppm)

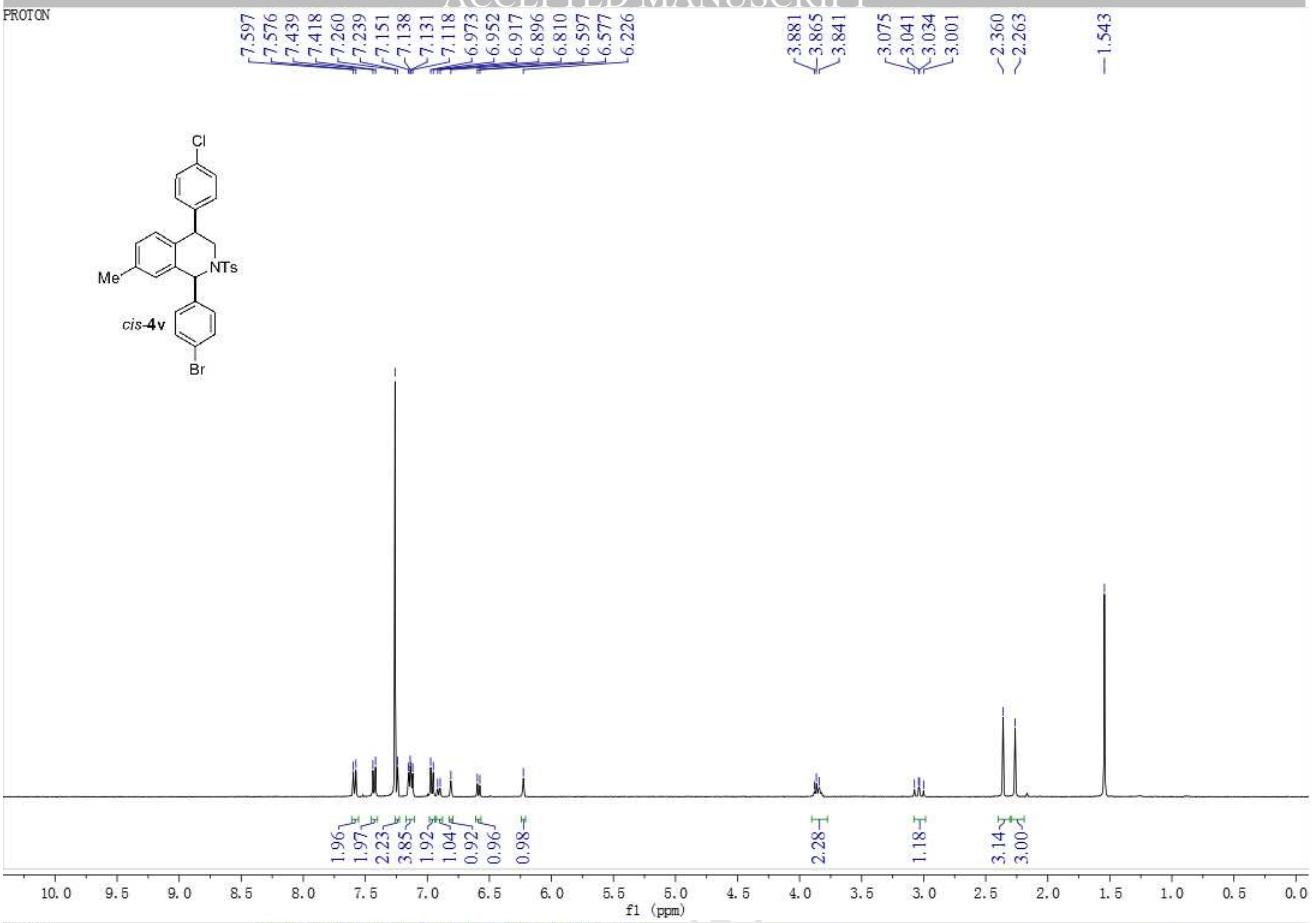

C13CPD
151.918
150.393
142.401
138.760
131.339
129.869
129.054
128.437
128.359
126.889
110.717
108.605
77.317
76.682
55.847
55.536
54.726
46.426
37.986
21.364
Cl
OMe
NTs
OMe
cis-4t
Br
f1 (ppm)

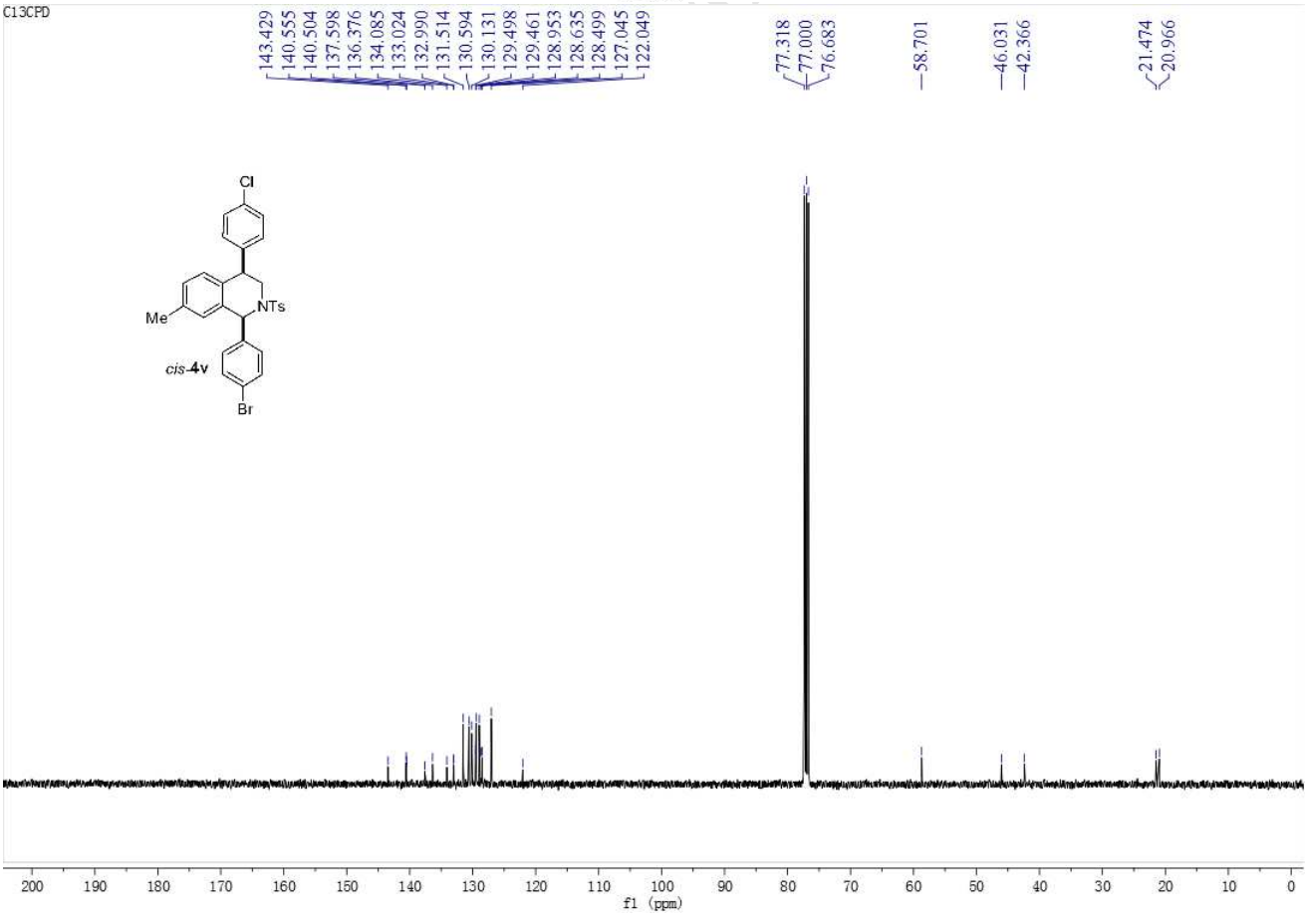


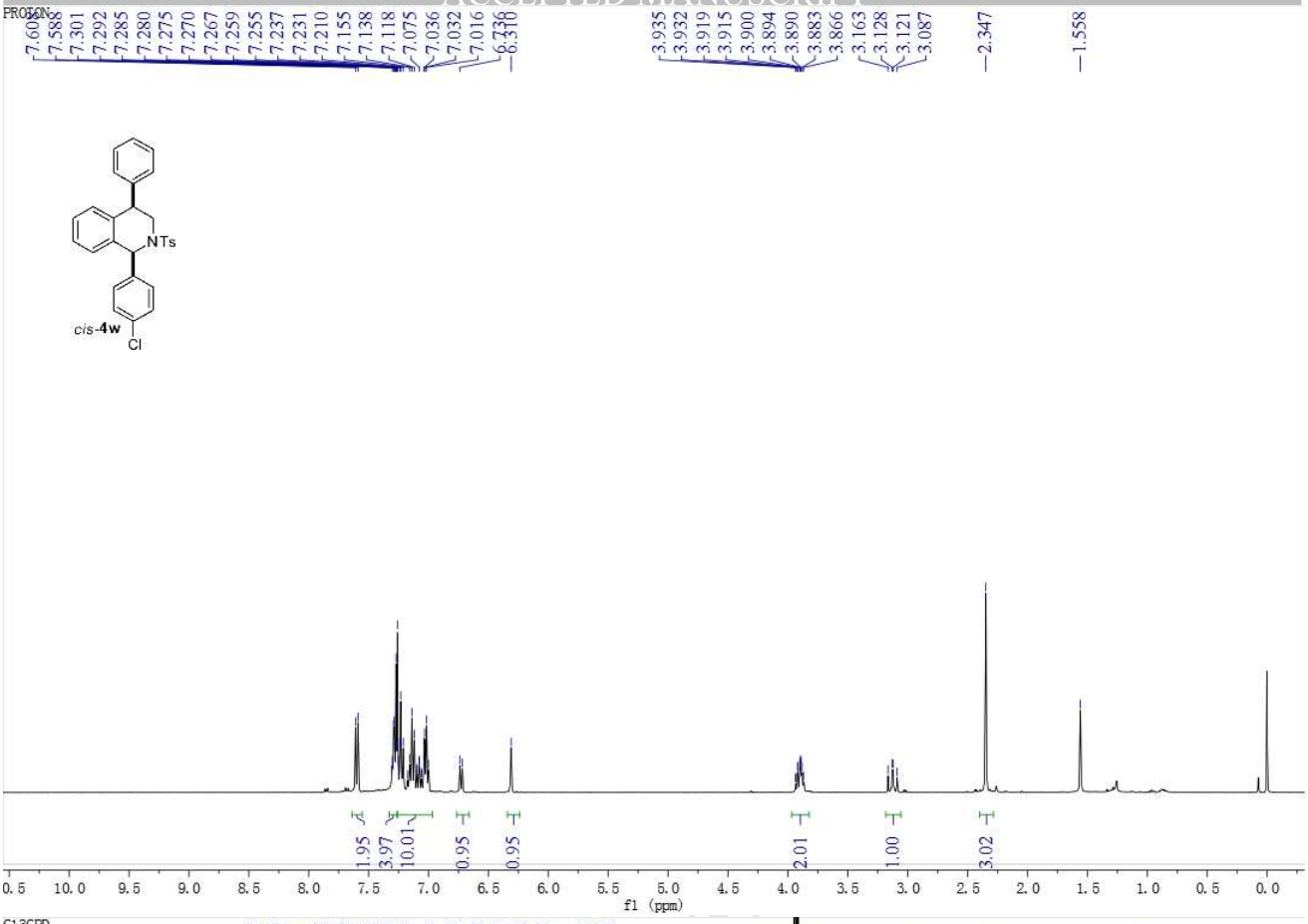


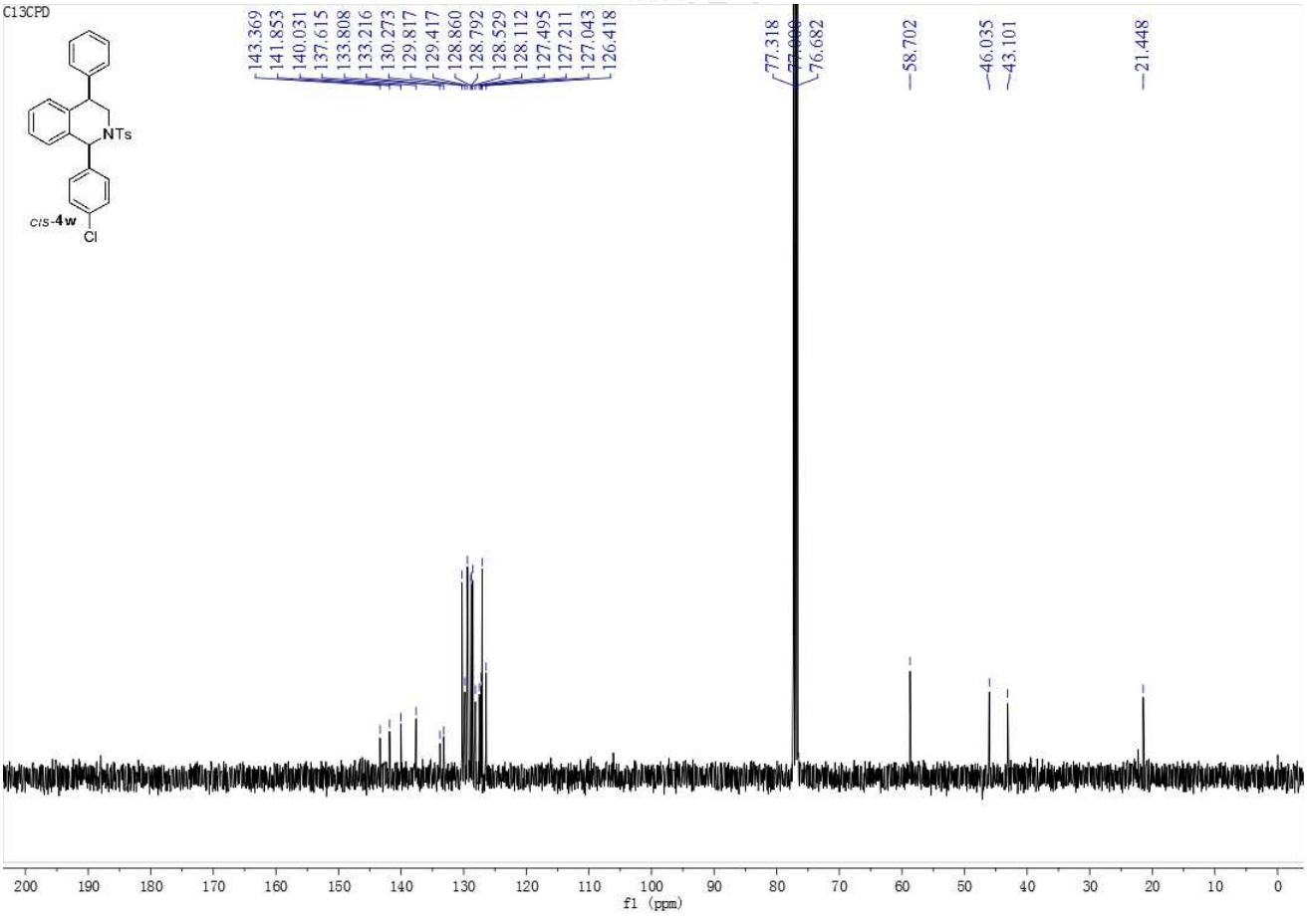


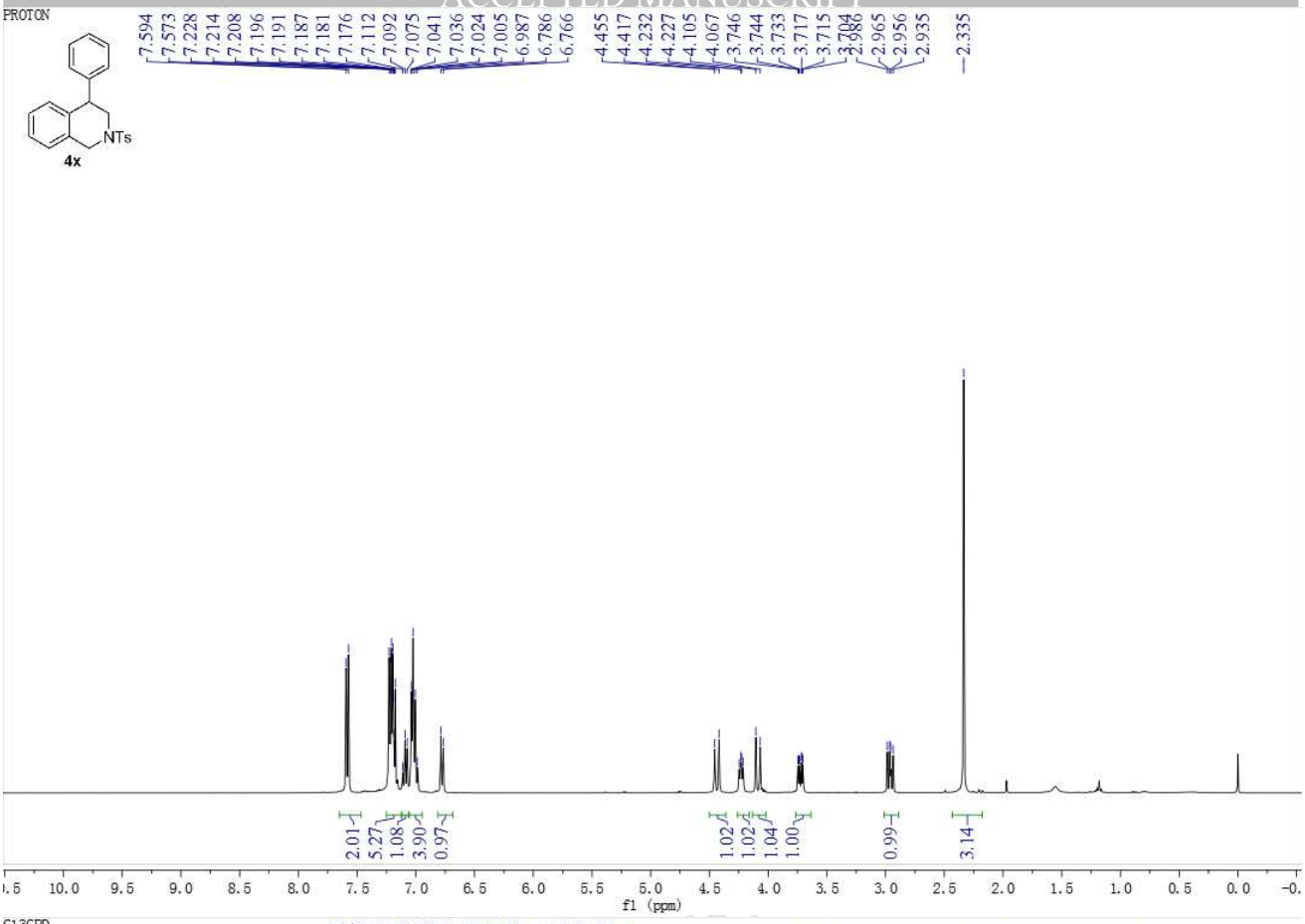


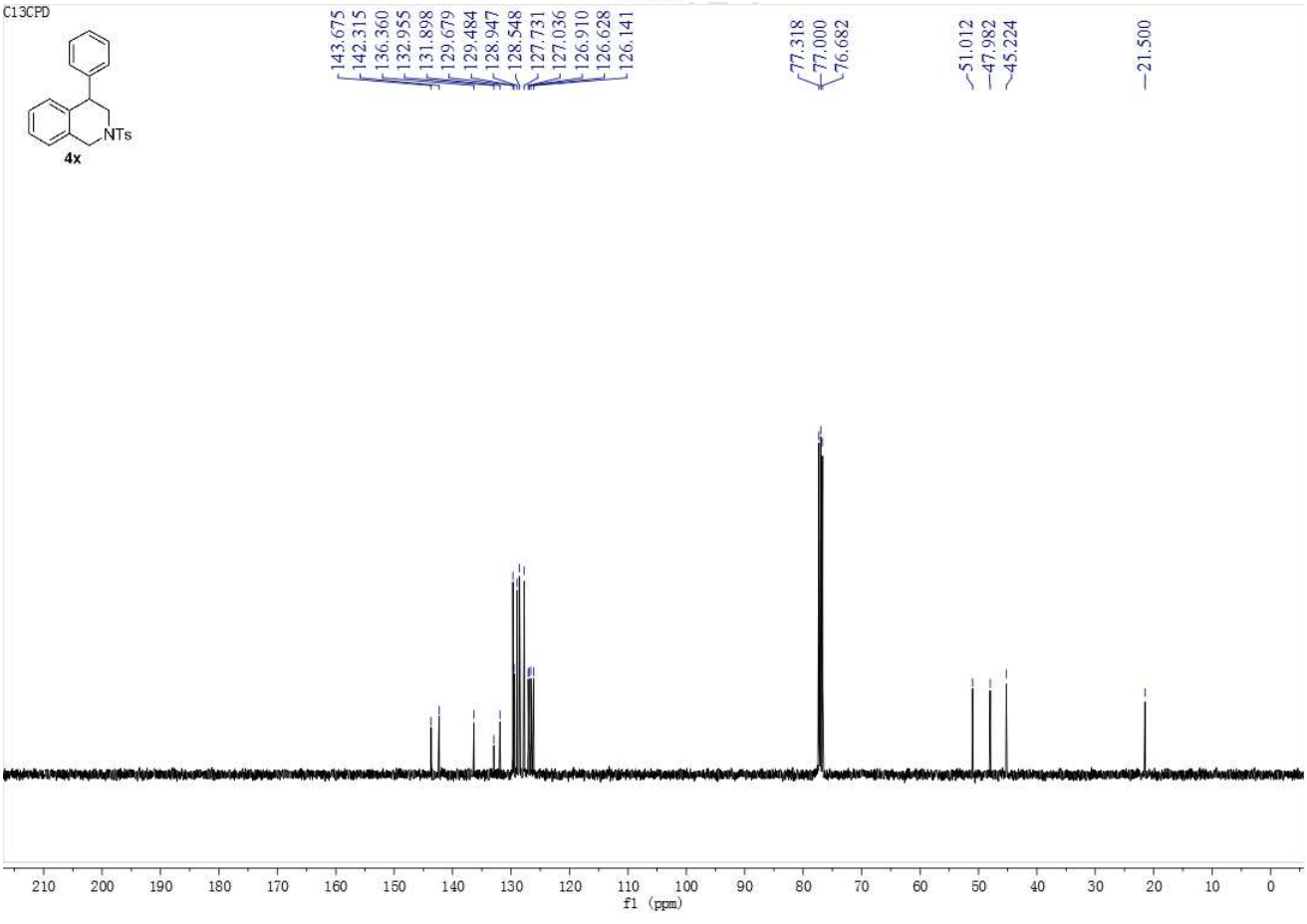


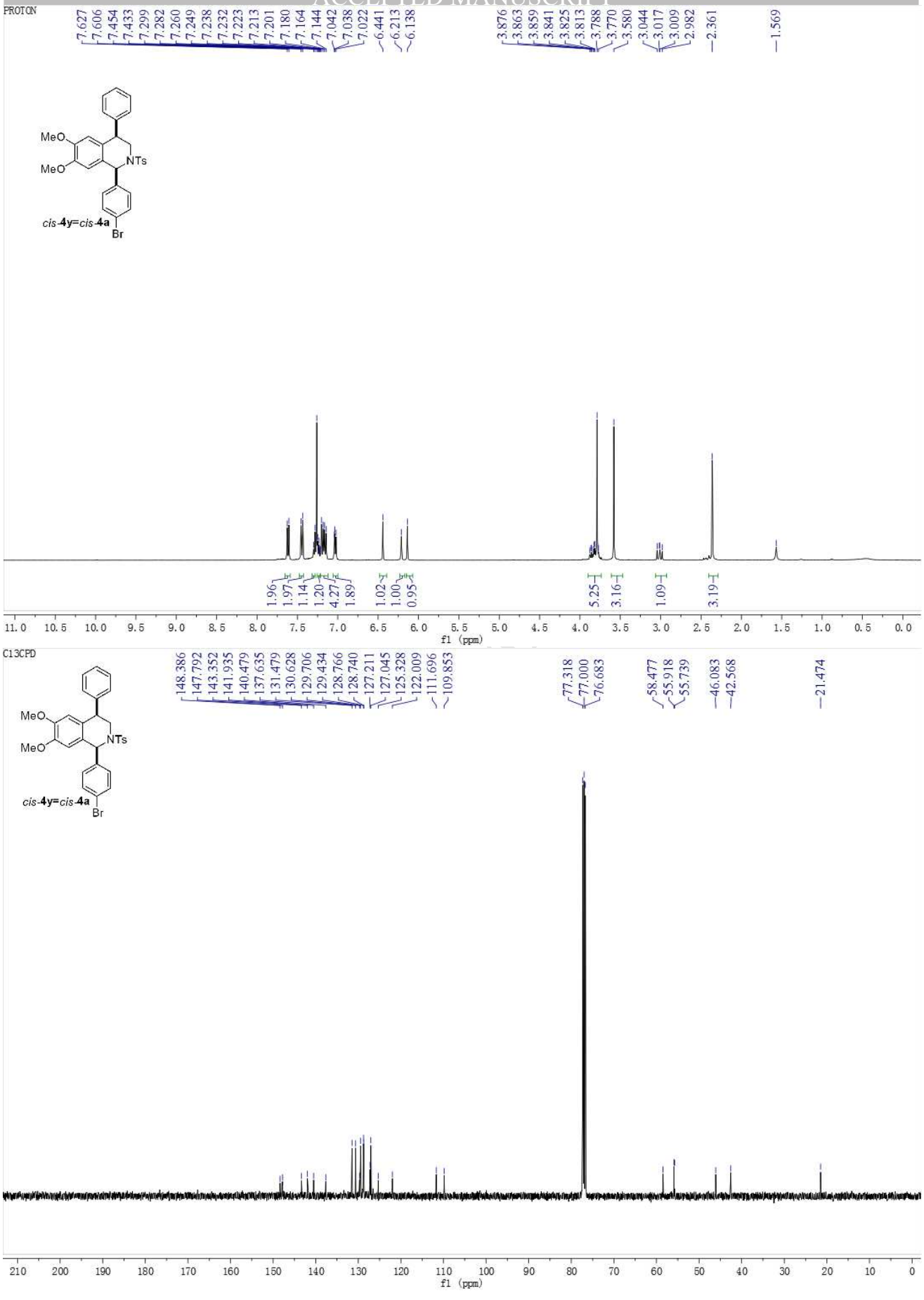


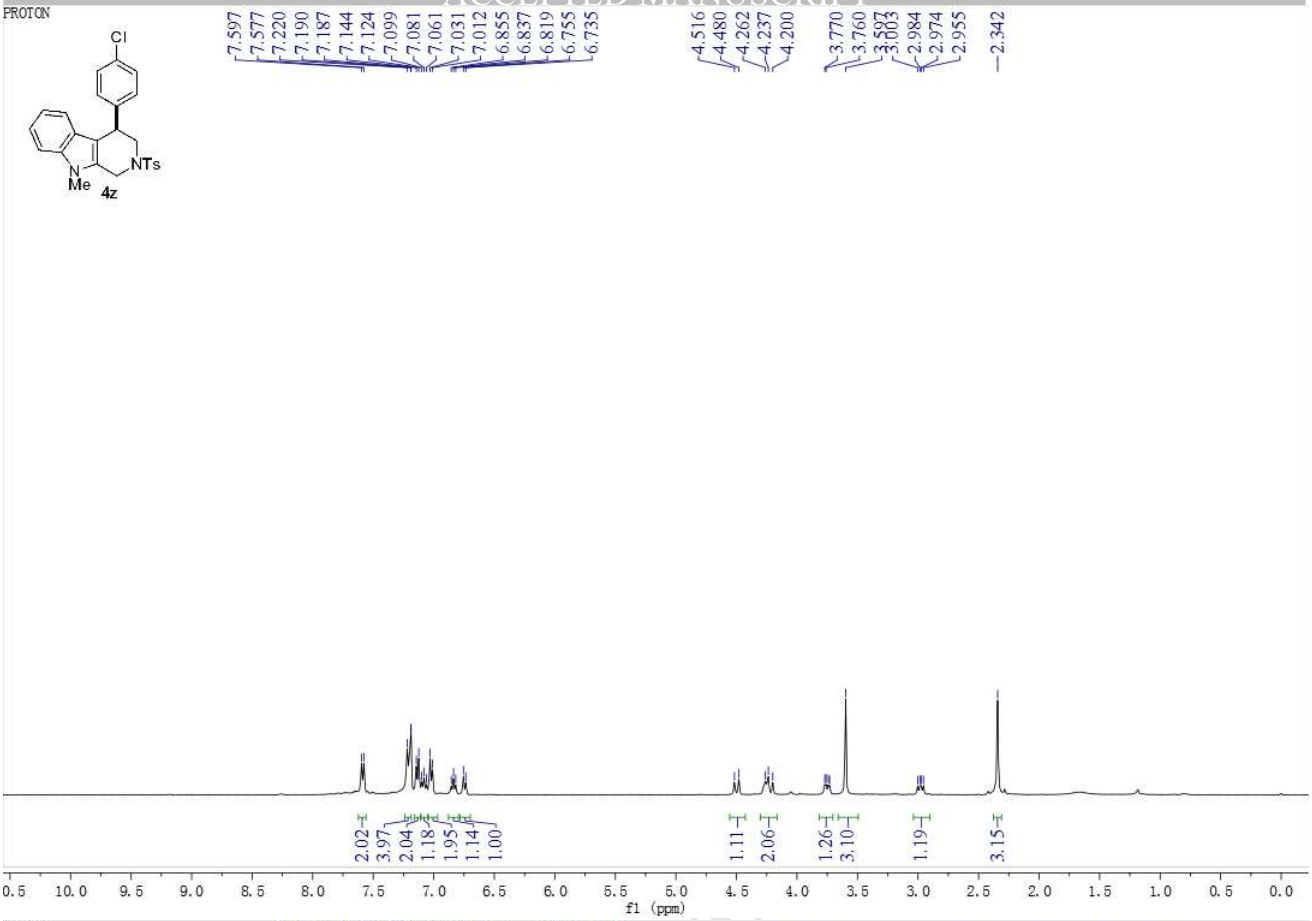


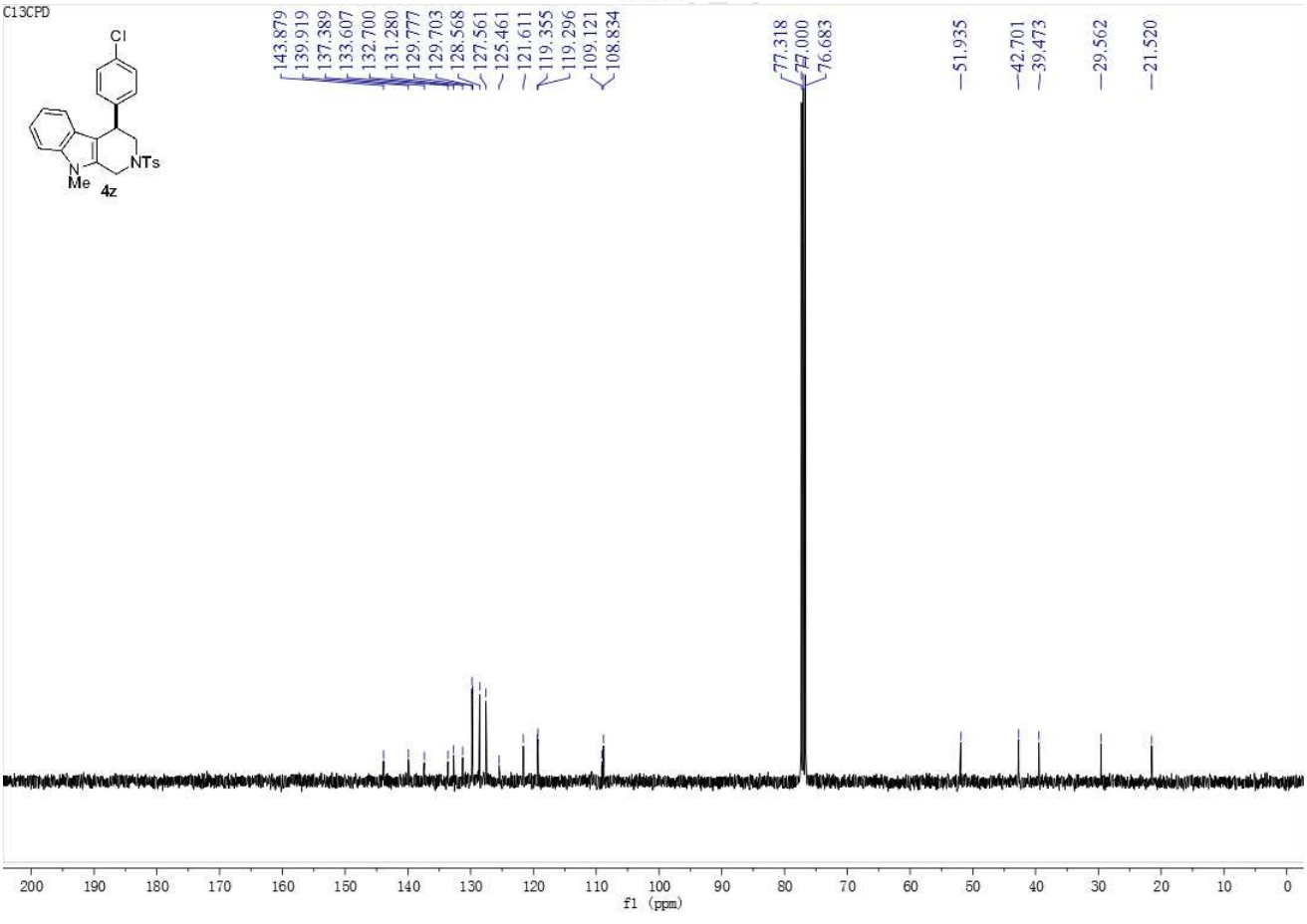


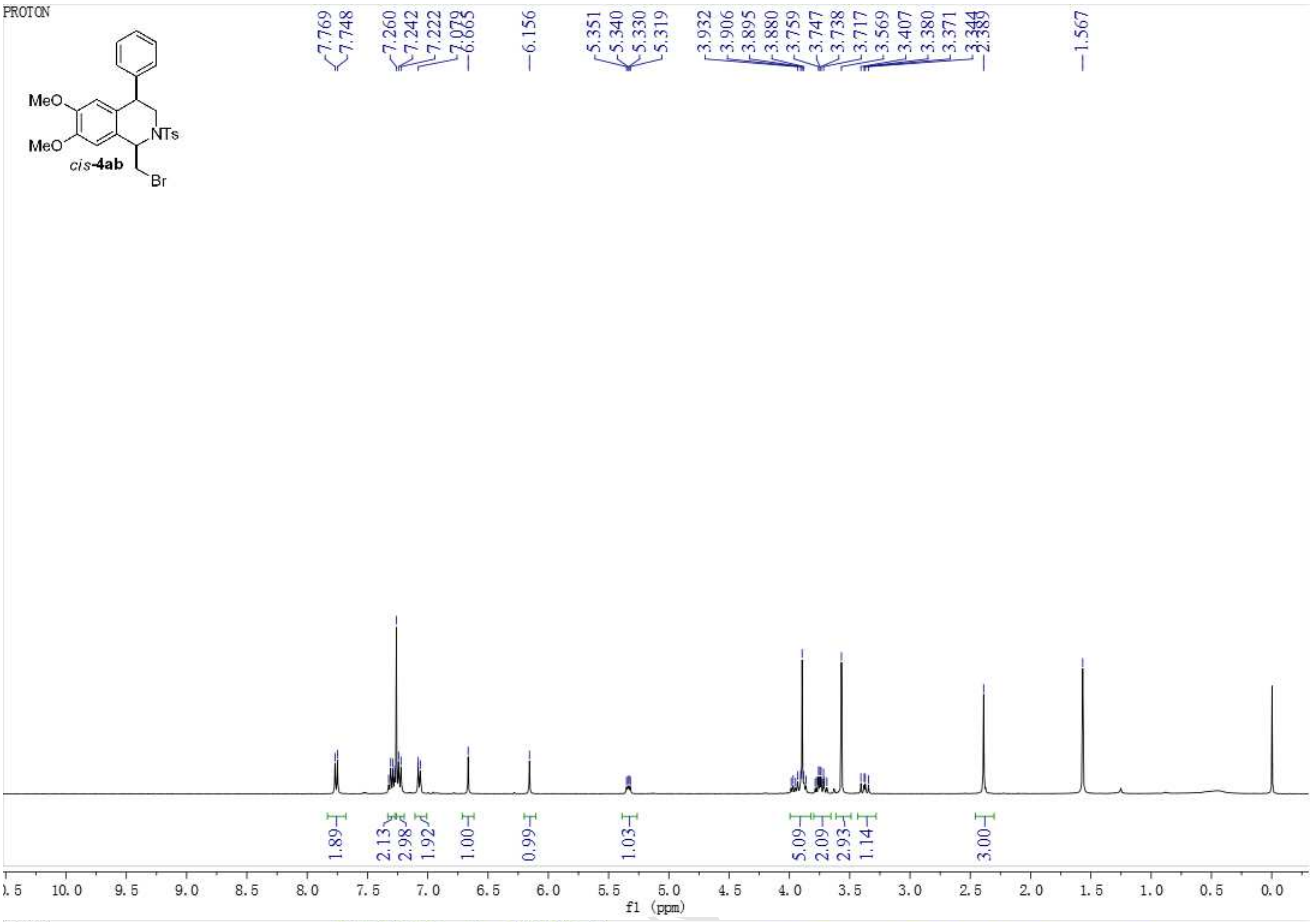


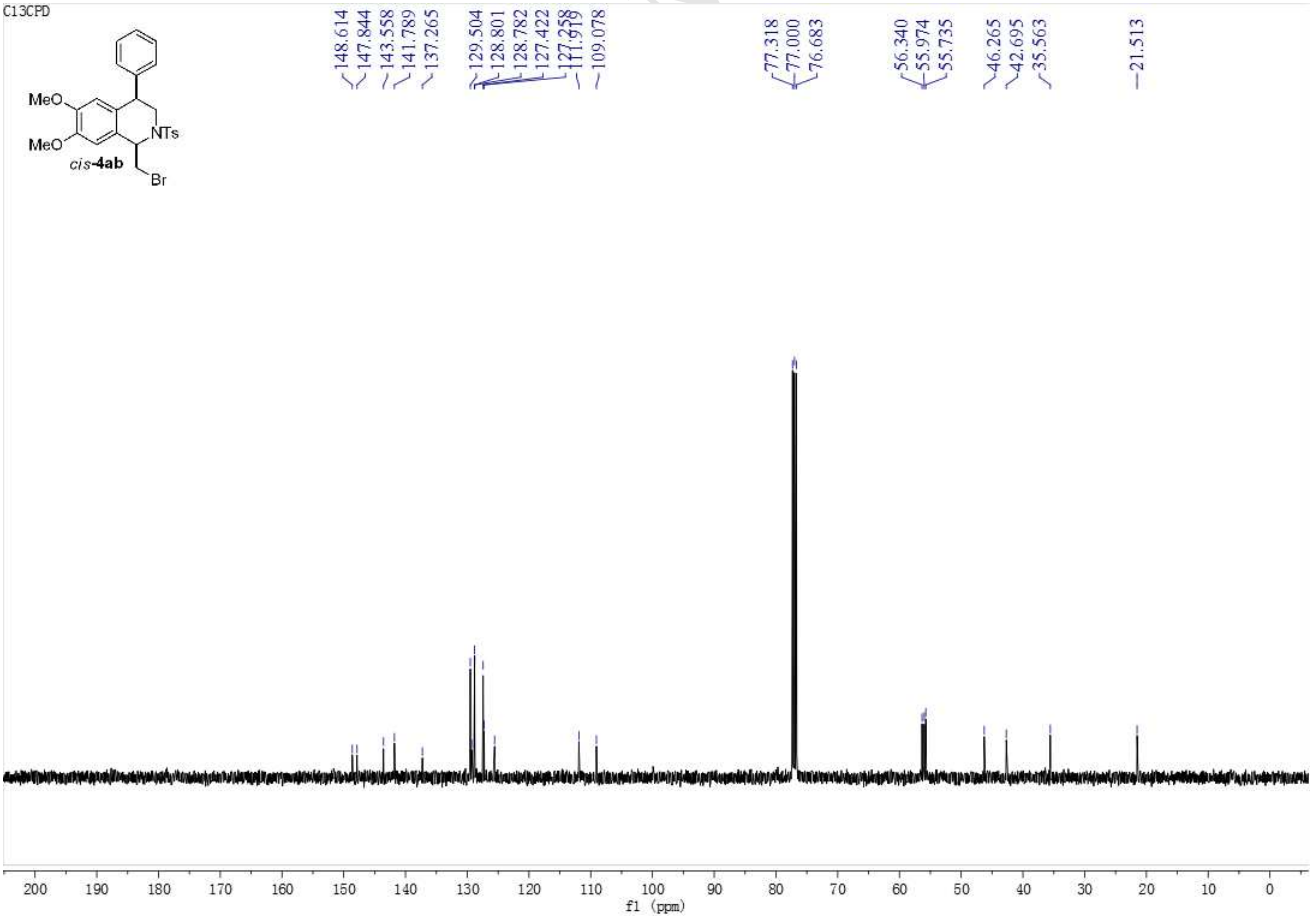


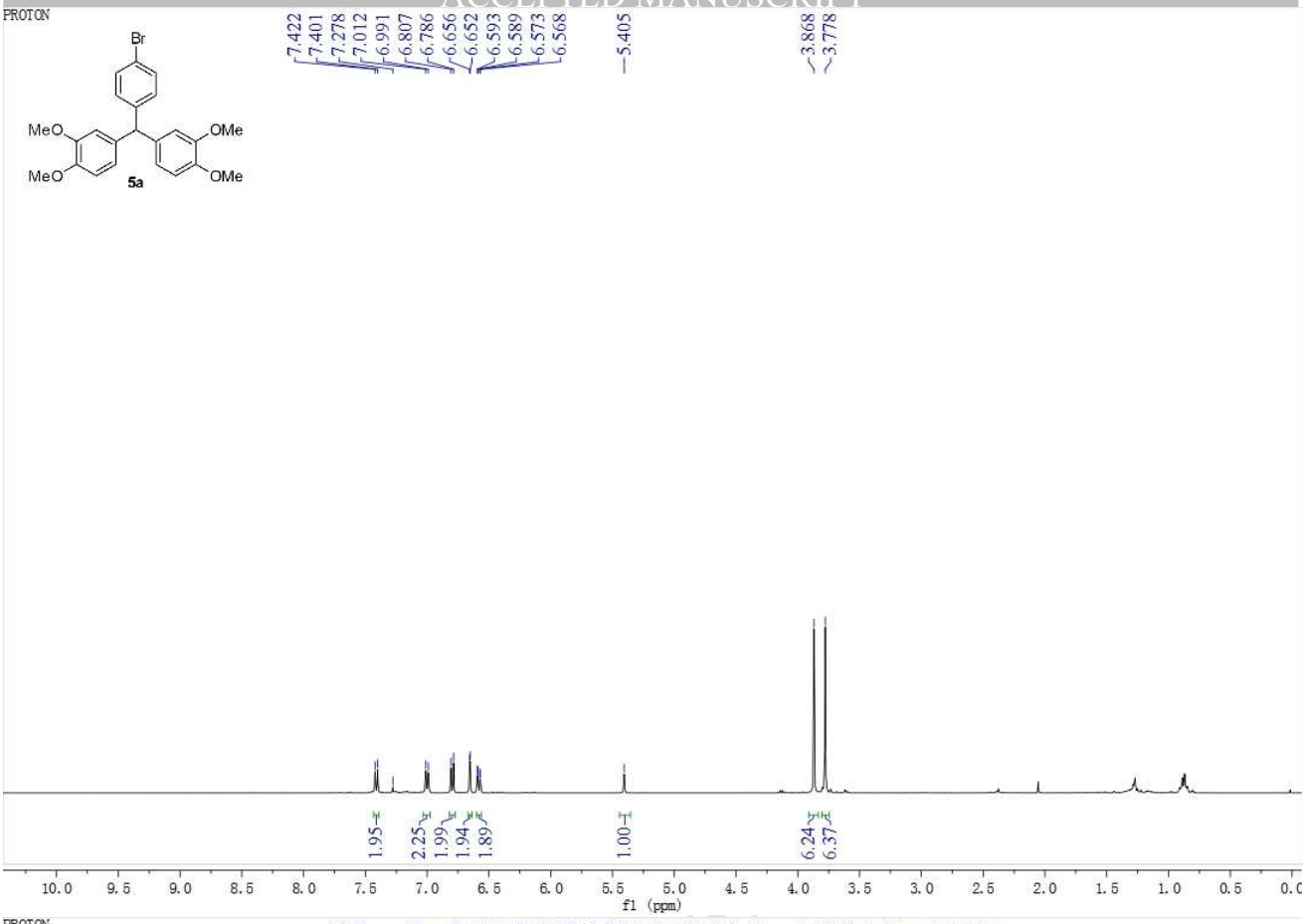

PROTON
7.627
7.606
7.454
7.433
7.299
7.282
7.260
7.249
7.238
7.232
7.223
7.213
7.201
7.180
7.164
7.144
7.042
7.038
7.022
6.441
6.213
6.138
3.876
3.863
3.859
3.841
3.825
3.813
3.788
3.770
3.580
3.044
3.017
3.009
2.982
2.361
1.569
MeO
MeO
NTs
cis-4y=cis-4a
Br
1.96
1.97
1.14
1.20
4.27
1.89
1.02
1.00
0.95
5.25
3.16
1.09
3.19
f1 (ppm)
C13CPD
148.386
147.792
143.352
141.935
140.479
137.635
131.479
130.628
129.706
129.434
128.766
128.740
127.211
127.045
125.328
122.009
111.696
109.853
77.318
77.000
76.683
58.477
55.918
55.739
46.083
42.568
21.474
f1 (ppm)

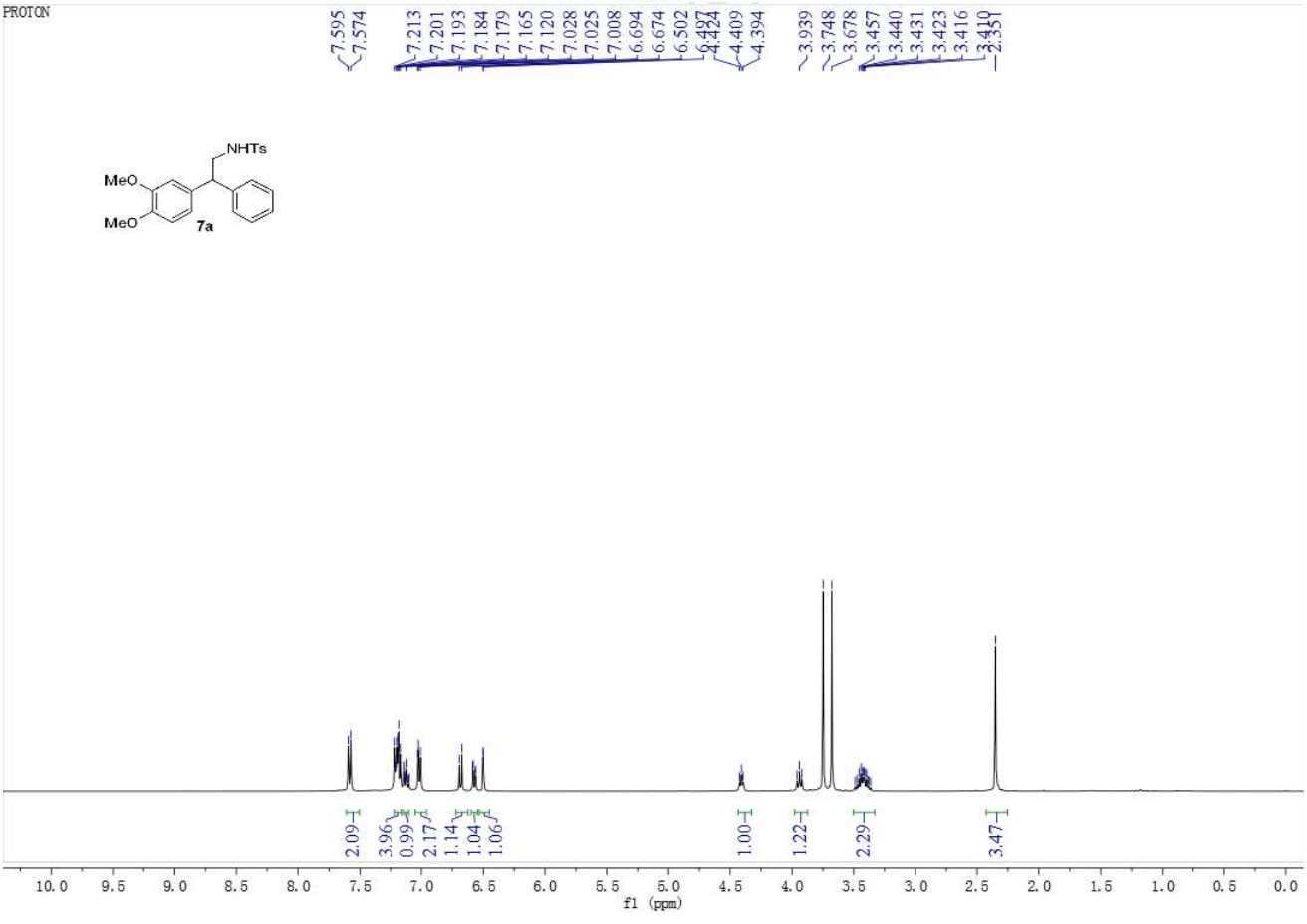

PROTON
Cl
NTs
Me
4z
7.597
7.577
7.220
7.190
7.187
7.144
7.124
7.099
7.081
7.061
7.031
7.012
6.855
6.837
6.819
6.755
6.735
4.516
4.480
4.262
4.237
4.200
3.770
3.760
3.597
3.583
2.984
2.974
2.955
2.342
2.02
3.97
2.04
1.18
1.95
1.14
1.00
1.11
2.06
1.26
3.10
1.19
3.15
f1 (ppm)

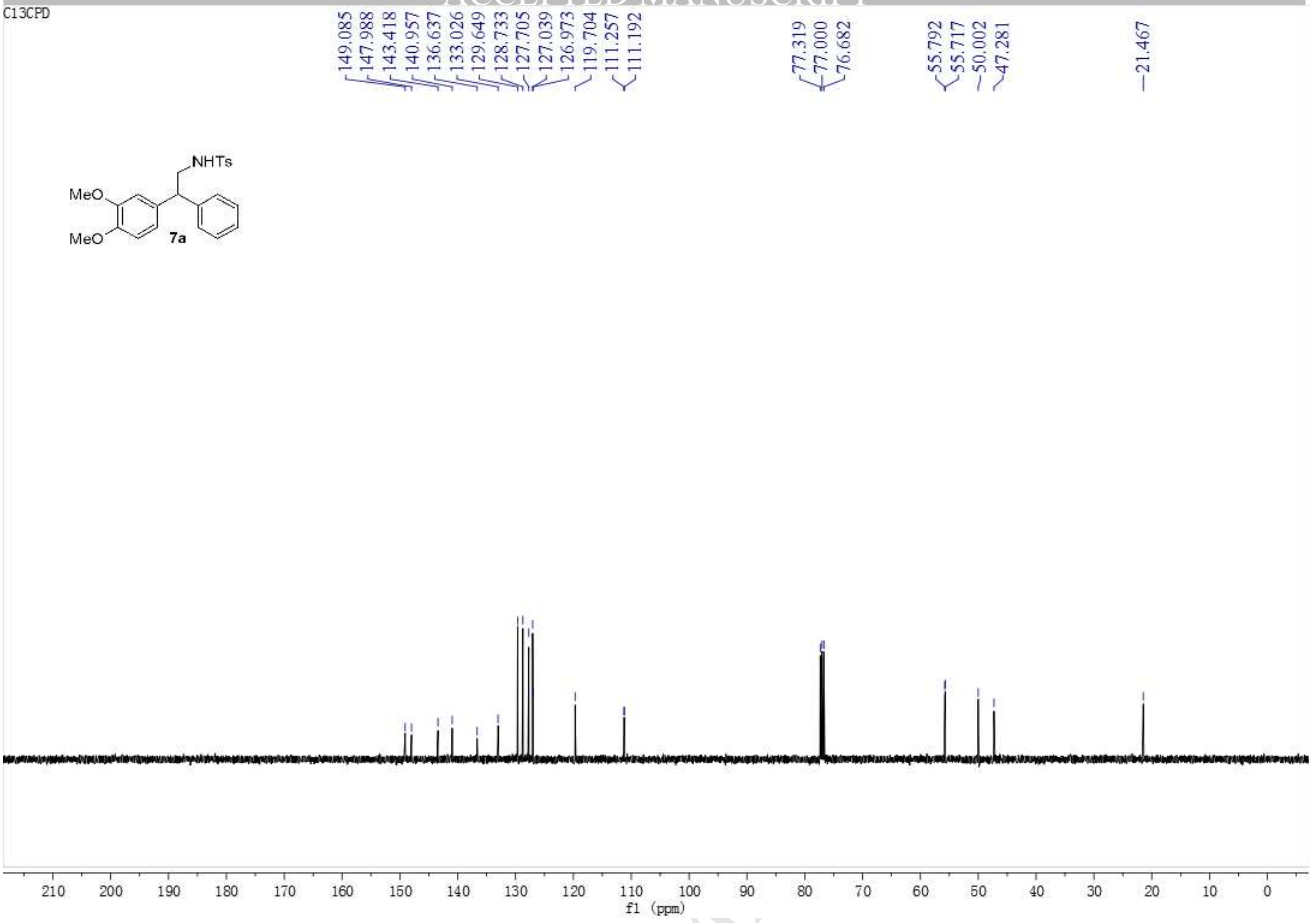

C13CPD
Cl
NTs
Me
4z
143.879
139.919
137.389
133.607
132.700
131.280
129.777
129.703
128.568
127.561
125.461
121.611
119.355
119.296
109.121
108.834
77.318
77.000
76.683
51.935
42.701
39.473
29.562
21.520
f1 (ppm)


PROTON
MeO
MeO
NTs
cis-4ab
Br
7.769
7.748
7.260
7.242
7.222
7.079
6.885
6.156
5.351
5.340
5.330
5.319
3.932
3.906
3.895
3.880
3.759
3.747
3.738
3.717
3.569
3.407
3.380
3.371
2.389
1.567
1.89
2.13
2.98
1.92
1.00
0.99
1.03
5.09
2.09
2.93
1.14
3.00
f1 (ppm)

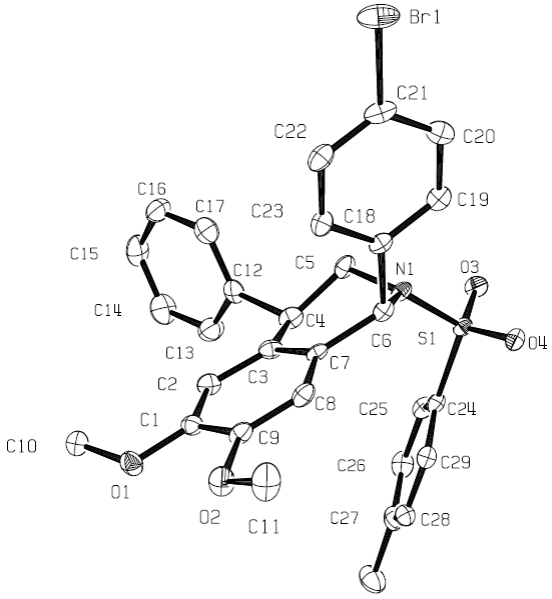

C13CPD
MeO
MeO
NTs
cis-4ab
Br
148.614
147.844
143.558
141.789
137.265
129.504
128.801
128.782
127.422
109.078
77.318
77.000
76.683
56.340
55.974
55.735
46.265
42.695
35.563
21.513
f1 (ppm)



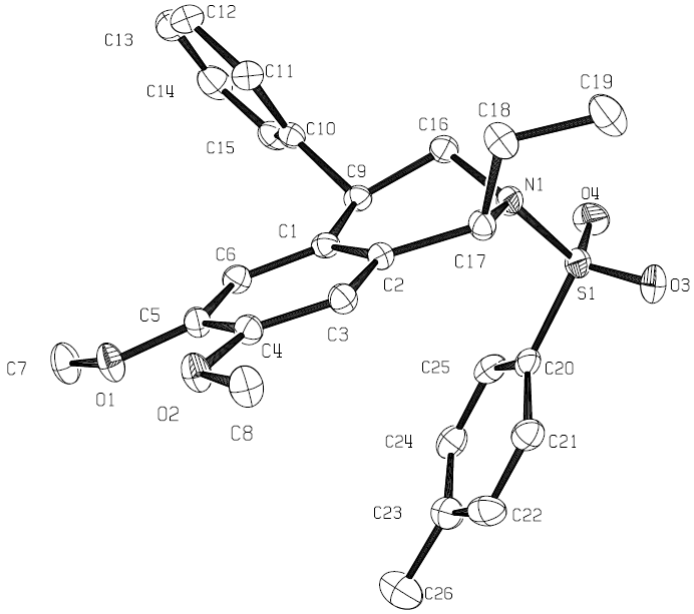




ORTEP drawing of *cis*-**4a**



ORTEP drawing of *cis*-**4f**



ORTEP drawing of *trans*-**4r**