Supplemental Information

Biocatalytic atroposelective synthesis of heterobiaryls and heterobiaryl *N*-oxides via dynamic kinetic resolution

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1. General information

General

Unless otherwise noted, all chemicals and reagents for chemical reactions were obtained from commercial suppliers and used as received (Sigma-Aldrich, TCI, Admas, Innochem, Bidepharm). Silica gel chromatography purifications were carried out using Santai SepaFlash columns (40 ~ 63 μm, 60 Å). ^{1}H and ^{13}C NMR spectra were recorded on JEOL ECZ-400S (400 MHz), Quantum-1 Plus (500 MHz), Bruker UltraShield Plus (600 MHz) instruments, and are internally referenced to residual proton signals in $CDCl_3$ (7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR), DMSO-d_6 (2.50 ppm for ^{1}H NMR and 39.52 ppm for ^{13}C NMR) or CD_3OD (3.31 ppm for ^{1}H NMR and 49.00 ppm for ^{13}C NMR).^{19}F NMR spectra were reported unreferenced. ^{1}H NMR data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet), coupling constant (Hz), and integration. High-resolution mass spectra (HRMS) were obtained on a Waters XEVO G2-XS using electrospray ionization time-of-flight (ESI-TOF).

Chromatography

Analytical high-performance liquid chromatography (HPLC) and Electron Spray Ionization (ESI) mass spectrometry were carried out using an Agilent 1200-6120 LCMS System. Yields and conversions were determined on a Poroshell C18 column (4.6 x 100 mm, 4.0 μm) against an internal standard 1,3,5-tribromobenzene (TBB) at 210 nm. Analytical chiral HPLC was carried out using an Agilent 1260 Infinity instrument equipped with ChiralPak AS-H, AD-H, OD-H, OJ-H (4.6 x 250 mm, 5.0 μm) columns with isopropanol and hexane as the mobile phase.

Cloning

pET28a (+) was used as a cloning and expression vector for all enzymes described in this study. Genes of imine-reductases were codon optimized for expression in *E. coli* and purchased from Sangon (Shanghai, China). All constructs were cloned directly in pET28a (+) between the *NdeI* and *XhoI* restriction sites. Cloned plasmids were transformed into *E. coli* DH5α cells for cell storage, and *E. coli* BL21 (DE3) chemically competent cells for protein expression.

Protein and DNA Sequence

(*S*)-Selective imine reductase from *Streptomyces sp*. GF3546 (***S*-IRED-*Ss***)

GenBank accession number: WP_319684944.1

Wide-type *S*-IRED-*Ss* protein sequence

MSKQSVTVIGLGPMGQAMVNTFLDNGHEVTVWNRTASKAEALVARGAVLAPTVEDALSANELIVLSL
TDYDAVYAILEPVTGSLSGKVIANLSSDTPDKAREAAKWAAKHGAKHLTGGVQVPPPLIGKPESSTYY
SGPKDVFDAHEDTLKVLTNADYRGEDAGLAAMYYQAQMTIFWTTMLSYYQTLALGQANGVSAKELL
PYATMMTSMMPHFLELYAQHVDSADYPGDVDRLAMGAASVDHVLHTHQDAGVSTVLPAAVAEIFKA
GMEKGFAENSFSSLIEVLKKPAV

Wide-type *S*-IRED-*Ss* DNA sequence

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TGATTGAAGTCCTGAAAAAACCGGCAGTGTAA

S-IRED-*Ss*-M9 protein sequence[1]

MSKQSVTVIGLGPMGQAMVNTFLDNGHEVTVWNRTASKAEPLVARGATLAPTVEDALSANELIVLSL
TDYDAVYAILEPVTGSLSGKTIVNLSSDTPDKAREMAKWAAKHGAKHLTGGVQVPPPLIGKPESSTYY
SGPKDVFDAHEDTLKVLTNADYLGEDPGLAAMYYQAQMTIFWTTMLSYYQTLALGQANGVSAKELLP
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MEKGFAENSFSSLIEVLKKPAV

S-IRED-*Ss*-M9 DNA sequence

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TCTTTCAGCAGCCTGATCGAAGTTCTGAAAAAACCGGCGGTTTAA

S-IRED-*Ss*-M12 protein sequence

MSKQSVTVIGLGPMGQAMVNTFLDNGHEVTVWNRTASKAEPLVARGATLAPTVEDALSANELIVLSL
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SGPKDVFDAHEDTLKVLTNADYLGEDPGLAAMYYQAQMTIFWTTMLSYYQTLALGQANGVSAKELLP
YATMTTRMMPHFLELYAQHVDSADYPGDVDRLA**A**GAASVDHVLHTHQDAGVSTVLPAAVAEIFKAG
MEKGFAENSFSSLIEVLKKPAV

S-IRED-*Ss*-M12 DNA sequence

ATGTCTAAACAGAGCGTTACCGTTATCGGCCTGGGTCCGATGGGTCAGGCGATGGTTAACACCTT
CCTGGATAACGGCCACGAAGTTACCGTTTGGAACCGTACCGCGTCTAAAGCGGAACCGCTGGTT
GCTCGTGGCGCGACCCTGGCGCCTACCGTTGAAGATGCGCTGAGCGCTAACGAACTGATCGTTC
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S-IRED-*Ss*-M13 protein sequence

MSKQSVTVIGLGPMGQAMVNTFLDNGHEVTVWNRTASKAEPLVARGATLAPTVEDALSANELIVLSL
TDYDAVYAILEPVTGSLSGKTIVNLSSDTPDKAREMAKWAAKHGAKHLTGGVQVPPPLIGKPESSTYY
SGPKDVFDAHEDTLKVLTNADYLGEDPGLAAMYYQAQMTIFWTTMLSYYQTLALGQANGVSAKELLP
YATMTTRMMPH**W**LELYAQHVDSADYPGDVDRLA**A**GAASVDHVLHTHQDAGVSTVLPAAVAEIFKAG
MEKGFAENSFSSLIEVLKKPAV

S-IRED-*Ss*-M13 DNA sequence

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S-IRED-*Ss*-M14 protein sequence

MSKQSVTVIGLGPMGQAMVNTFLDNGHEVTVWNRTASKAEPLVARGATLAPTVEDALSANELIVLSL
TDYDAVYAILEPVTGSLSGKTIVNLSSDTPDKAREMAKWAAKHGAKHLTGGVQV**H**PPLIGKPESSTYY
SGPKDVFDAHEDTLKVLTNADYLGEDPGLAAMYYQAQMTIFWTTMLSYYQTLALGQANGVSAKELLP
YATMTTRMMPH**W**LELYAQHVDSADYPGDVDRLA**A**GAASVDHVLHTHQDAGVSTVLPAAVAEIFKAG
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S-IRED-*Ss*-M14 DNA sequence

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S-IRED-*Ss*-M15 protein sequence

MSKQSVTVIGLGPMGQAMVNTFLDNGHEVTVWNRTASKAEPLVARGATLAPTVEDALSANELIVLSL
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SGPKDVFDAHEDTLKVLTNADYLGEDPGLAAMYYQAQMTIFWTTMLSYYQTLALGQANGVSAKELLP
YATMTTRMMPHFLELYAQHVDSADYPGDVDRLAAGAASVDHVLHTHQDAGVSTVLPAAVAEIFKAG
MEKGFAENSFSSLIEVLKKPAV

S-IRED-*Ss*-M15 DNA sequence

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S-IRED-*Ss*-M16 protein sequence

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SGPKDVFDAHEDTLKVLTNADYLGEDPGLAAMYYQAQMTIFWTTMLSYYQTLALGQANGVSAKELLP
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S-IRED-*Ss*-M16 DNA sequence

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IREDs Protein Expression and Purification

(*S*)-Selective imine reductase from *Streptomyces sp.* GF3546 (*S*-IRED-*Ss*) was produced in *E. coli* BL21 with a pET28a-*S*-IRED-*Ss* plasmid. Transformed glycerol stocks were used to initiate a 5 mL Luria-Bertani (LB) media with kanamycin (50 μg/mL) at 37 °C and 250 rpm overnight. Expression culture (500 mL in a 2 L baffled shake flask) containing kanamycin (50 μg/mL) was inoculated with 3 mL of the overnight culture and grown until the culture reached an OD_{600} of 0.5 ~ 0.7 at 37 °C and 250 rpm. Flasks were chilled on ice for 10 min and protein expression was induced with 0.2 mM IPTG (20 °C, 24 h, 250 rpm). The cells were harvested by centrifugation (7,100 x *g*, 20 min, 4 °C), and frozen at -80 °C for further purification.

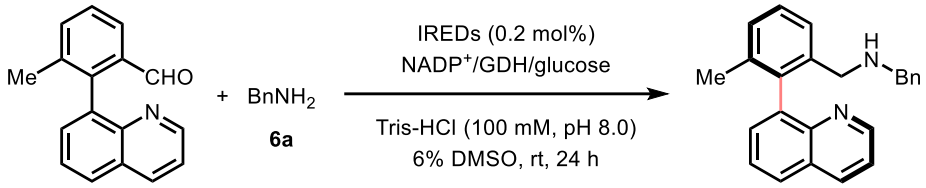
Frozen cells were thawed on ice and resuspended in buffer A (20 mM KPi, pH 7.0, 250 mM NaCl, 25 mM imidazole, with 1 mg/mL lysozyme, 0.1 mg/mL DNase I, 1 mM phenylmethylsulfonyl fluoride) to a final concentration of 2 mL/g of wet cells. The cells were disrupted by sonication (20 min, output 30 W, Ultrasonic Homogenizer JY92-IIN) under an ice bath. Lysates were centrifuged (24,200 x *g*, 1 h, 4 °C) to pellet insoluble materials. Proteins were purified by affinity chromatography with a nickel-NTA column. After washing with 10 column volumes of buffer A, enzymes were eluted with buffer B (20 mM KPi, pH 7.0, 250 mM NaCl, 250 mM imidazole) over 5 column volumes. Fractions containing IRED enzymes were pooled, concentrated, and subjected to three buffer exchanges into an imidazole-free storage buffer (100 mM KPi, pH 8.0). Concentrated enzymes were aliquoted, flash-frozen in liquid N_2, and then stored at -20 °C until later use. Protein purity was assessed with SDS-PAGE. Protein concentrations were determined using absorbance at 280 nm with an extinction coefficient of 34,380 mM^{-1} cm^{-1}.

For the preparation of lyophilized cell-free extracts (CFE), frozen cells were thawed on ice and resuspended in Tris-HCl buffer (50 mM, pH 8.0) to a final concentration of 5 mL/g of wet cells. The cells were disrupted by sonication (20 min, output 30 W, Ultrasonic Homogenizer JY92-IIN) under an ice bath. Lysates were centrifuged (24,200 x *g*, 1 h, 4 °C) to pellet insoluble materials. The supernatant was transferred to a clean centrifuge tube, and then frozen instantly by liquid N_2. Lyophilization was carried out on Alpha 1-2 LDplus (Christ, Germany).

The glucose dehydrogenase (GDH) used in this study was an engineered variant of glucose dehydrogenase from *Bacillus megaterium* (*Bm*GDH_{M6}), which was obtained from published work by Zheng *et. al*.[2] The specific activity (69 U/mg) of the *Bm*GDH_{M6} lyophilized CFE (thereafter named as *Bm*GDH) was assayed at 25 °C by monitoring the increase of the absorbance of NADPH at 340 nm using Agilent Cary 60 UV-Vis (Agilent, America).

2. Supplemental experimental procedures

Table S1. The initial panel of enzymes screened for synthesis of 8-aryl quinoline **7**.

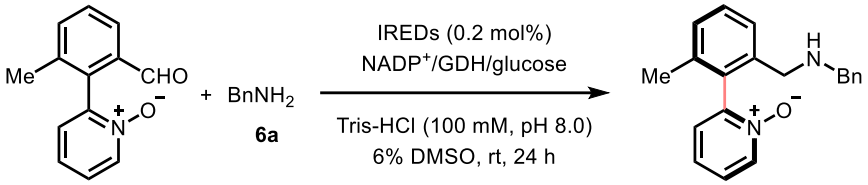


rac-**5a** **7**

Entry	Enzymes	Accession number	Source	Yield[a]	er[b]
1	IRED-1	WP_166633080	*Streptomyces sp.* GC420	4	n.d.[c]
2	IRED-2	WP_150514620.1	*Streptomyces spectabilis*	3	n.d.
3	IRED-3	WP_205760981.1	*Luteolibacter luteus*	3	n.d.
4	IRED-4	WP_088993565.1	*Micromonospora echinaurantiaca*	4	n.d.
5	IRED-5	WP_179754454.1	*Microlunatus parietis*	1	n.d.
6	*S*-IRED-*Ss*	WP_319684944.1	*Streptomyces sp.*	20	65:35
7	*S*-IRED-*Ss*-M9[d]	---	*Streptomyces sp.*	30	93:7
8	*R-IRED-Ss*	WP_015610874.1	*Streptomyces sp.*	0	n.d.
9	IRED-8	WP_189823582	*Streptomyces finlayi*	4	n.d.
10	IRED-9	WP_011731218	*Mycolicibacterium smegmatis*	16	82:18
11	IRED-10	WP_207513941	*Longitalea luteola*	3	n.d.
12	*Ad*RedAm	XP_045278909.1	*Ajellomyces dermatitidis*	0	n.d.
13	*Af*RedAm	XP_748217.1	*Aspergillus fumigatus*	5	n.d.
14	No IRED			0	n.d.
15	No turnover system			0	n.d.

Reaction conditions: substrate **5a** (5 μmol, 1 equiv), benzylamine **6a** (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), purified IREDs (entry 1~11) or reductive aminases (entry 12~13) (0.2 mol% based on **5a**) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature (rt) for 24 h, the final total volume is 1000 μL. [a] Yield (average of duplicate) determined *via* LCMS relative to an internal standard 1,3,5-tribromobenzene (TBB). [b] Enantiomeric ratio (er, *S*:*R*) determined by HPLC on a chiral stationary phase. [c] n.d., not determined. [d] *S*-IRED-*Ss*-M9 is an engineered variant with nine mutations (A41P/V48T/V88T/A90V/A103M/R158L/A162P/M207T/S209R) based on *S*-IRED-*Ss*.

Table S2. The initial panel of enzymes screened for synthesis of biaryl pyridine *N*-oxide **29**.



rac-**28a** **29**

Entry	Enzymes	Accession number	Source	Yield[a]	er[b]
1	IRED-1	WP_166633080	*Streptomyces sp.* GC420	0	n.d.[c]
2	IRED-2	WP_150514620.1	*Streptomyces spectabilis*	6	n.d.
3	IRED-3	WP_205760981.1	*Luteolibacter luteus*	0	n.d.
4	IRED-4	WP_088993565.1	*Micromonospora echinaurantiaca*	0	n.d.
5	IRED-5	WP_179754454.1	*Microlunatus parietis*	0	n.d.
6	*S*-IRED-*Ss*	WP_319684944.1	*Streptomyces sp.*	12	99:1
7	*S*-IRED-*Ss*-M9[d]	---	*Streptomyces sp.*	11	99:1
8	R-IRED-*Ss*	WP_015610874.1	*Streptomyces sp.*	0	n.d.
9	IRED-8	WP_189823582	*Streptomyces finlayi*	0	n.d.
10	IRED-9	WP_011731218	*Mycolicibacterium smegmatis*	0	n.d.
11	IRED-10	WP_207513941	*Longitalea luteola*	0	n.d.
12	*Ad*RedAm	XP_045278909.1	*Ajellomyces dermatitidis*	0	n.d.
13	*Af*RedAm	XP_748217.1	*Aspergillus fumigatus*	0	n.d.
14	No IRED			0	n.d.
15	No turnover system			0	n.d.

Reaction conditions: substrate **28a** (5 μmol, 1 equiv), benzylamine **6a** (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), purified IREDs (entry 1~11) or reductive aminases (entry 12~13) (0.2 mol% based on **28a**) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature (rt) for 24 h, the final total volume is 1000 μL. [a] Yield (average of duplicate) determined *via* LCMS relative to an internal standard 1,3,5-tribromobenzene. [b] Enantiomeric ratio (er, *S*:*R*) determined by HPLC on a chiral stationary phase. [c] n.d., not determined. [d] *S*-IRED-*Ss*-M9 is an engineered variant with nine mutations (A41P/V48T/V88T/A90V/A103M/R158L/A162P/M207T/S209R) based on *S*-IRED-*Ss*.

Directed evolution of *S*-IRED-*Ss*-M9

Site Saturation Mutagenesis of *S*-IRED-*Ss*-M9

Site saturation mutagenesis primers were designed using the PCR protocol from Kille *et al*.[3] Plasmid encoding *S*-IRED-*Ss*-M9 was used as the template, and PCR products were digested with *DpnI*, and then used to directly transform *E. coli* BL21 (DE3) chemically competent cells and plated on LB agar plates containing kanamycin (50 μg/mL). Sites examined based on *S*-IRED-*Ss*-M9 were V119, P122, P123, Y169, Q172, M173, F176, W177, M210, F214, V231, and M236 (Fig. S1).

Site Saturation Library Construction and Protein Expression.

Single colonies were picked with sterile toothpicks and used to inoculate 400 μL of Luria-Bertani (LB) media containing kanamycin (50 μg/mL) in deep-well 96-well plates, and cultured overnight (37 °C, 250 rpm). Wells A2, B4, C6, D8, E10, F12, G2, and H4 were embedded controls of the parent protein for engineering. Well H12 was used as blank control. A glycerol stock plate of the library was prepared by mixing sterilized glycerol solution (30% *v*/*v*, 50 μL/well) with the overnight cell cultures (50 μL/well). The library was sealed and stored at -80 °C. The expression cultures (1000 μL of LB media containing 50 μg/mL of kanamycin) in 96-well plates were inoculated by adding 50 μL of the overnight cultures, and grown for 4 hours (37 ºC, 250 rpm). Protein expression was induced with 0.2 mM IPTG (20 °C, 24 h, 250 rpm) in the 96-well plate. Cells were harvested by centrifugation at 7,100 x *g*, 20 min, 4 °C, and frozen at -20 ºC overnight for later screening.

General procedure for screening in 96-well plates.

The cell libraries were thawed and resuspended with lysis buffer (150 μL/well) and allowed to shake for 1 hour at 30 ºC. The crude cell lysates were centrifuged (7,100 x *g*, 20 min, 4 °C) and the supernatants (50 μL/well) were transferred into an optical 96-well plate with clear flat bottom for screening assay immediately, 130 μL/well of Tris-HCl buffer (100 mM, pH 8.0) and 20 μL/well of reaction mixture containing NADPH (0.3 mM), substrates (0.63 mM of **5a** or **28a** and 1.9 mM of benzylamine **6a**) and 6% DMSO. The reaction progress was monitored by measuring the depletion of the NADPH absorption at 340 nm for 30 min by Microplate Reader (Biotek Synergy HTX, America). *Recipe for lysis buffer*: Tris-HCl buffer (100 mM, pH 8.0) containing DNase I (0.1 mg/mL), lysozyme (1 mg/mL), and PMSF (2 mM).

Mutations that displayed an improved initial rate of consuming NADPH than that of the parent enzyme were selected for further confirmation. Promising mutations were subjected to cultivation in shaking flasks and purified *S*-IRED-*Ss* mutants were used in the standard reaction condition for further confirmation of yield and er. The DNA plasmids of hits were identified by gene sequencing.

Standard reaction condition to confirm hits: substrate **5a or 28a** (5 μmol, 1 equiv), benzylamine **6a** (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), purified *S*-IRED-*Ss* variants (0.2 mol%) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature for 24 h, the final total volume is 1000 μL. For yield determination, the reaction was quenched with 3 mL of acetonitrile and 100 μL of 5 mg/mL 1,3,5-tribromobenzene (TBB) in acetonitrile

as the internal standard. The mixture was shaken for 30 min, centrifuged at 13,400 x g for 5 min, and the supernatant was filtered and retained for LCMS analysis (30-95% ACN/H_2O with 0.1% formic acid, 8 minutes) for yield calculation. After LCMS analysis, the supernatant was concentrated under reduced pressure, extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was dissolved in 30% isopropanol/hexanes (*v*/*v*) for chiral HPLC analysis.

For the first part of protein engineering, we focused on 8-aryl quinoline aldehyde **5a** as substrate, three rounds of iterative site-saturation mutagenesis (ISM) have been conducted using *S*-IRED-*Ss*-M9 as the starting point, yielding a mutant ***S*-IRED-*Ss*-M14 (M236A/F214W/P122H)** as the final biocatalyst for efficient and asymmetric synthesis of 8-aryl quinoline amine **7**.

For the second part of protein engineering, we focused on biaryl pyridine *N*-oxide aldehyde **28a** as substrate, three rounds of ISM have been conducted using *S*-IRED-*Ss*-M9 as the starting point, yielding a mutant ***S*-IRED-*Ss*-M16 (M236A/P122V/V231T)** as the final biocatalyst for efficient and asymmetric synthesis of biaryl pyridine *N*-oxide amine **29**.

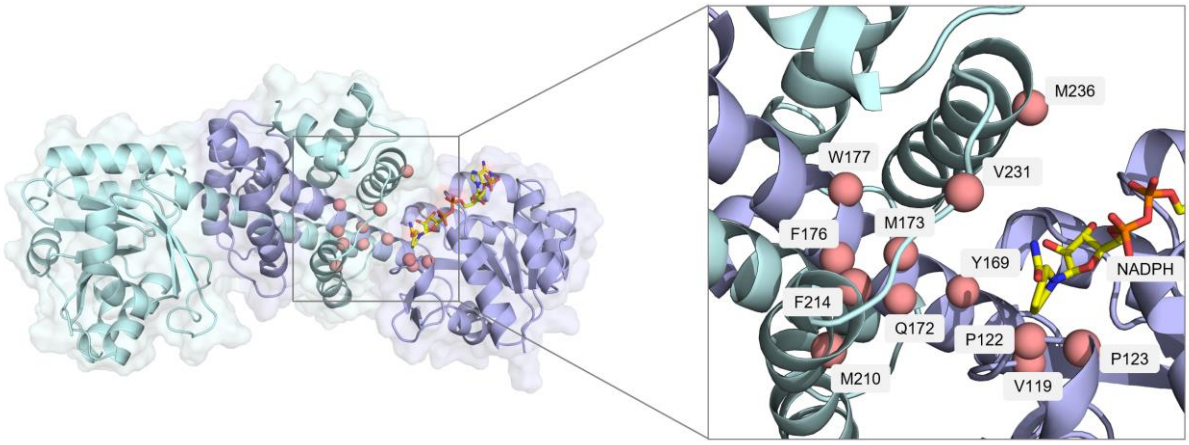
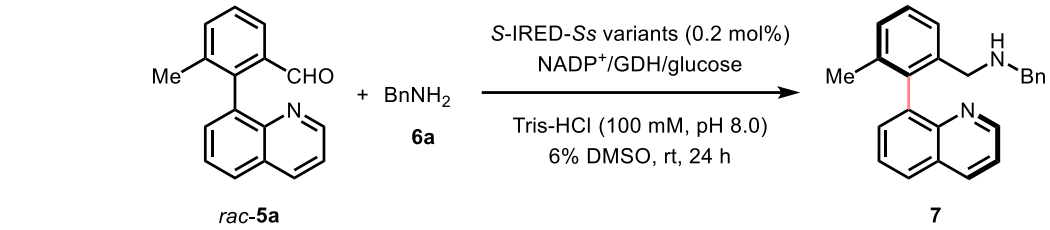


Fig. S1. Structure of *S*-IRED-*Ss*-WT (PDB:4OQY) and twelve amino acid residues (V119, P122, P123, Y169, Q172, M173, F176, W177, M210, F214, V231, and M236.) were examined during directed evolution. Pymol was used for graph preparation.



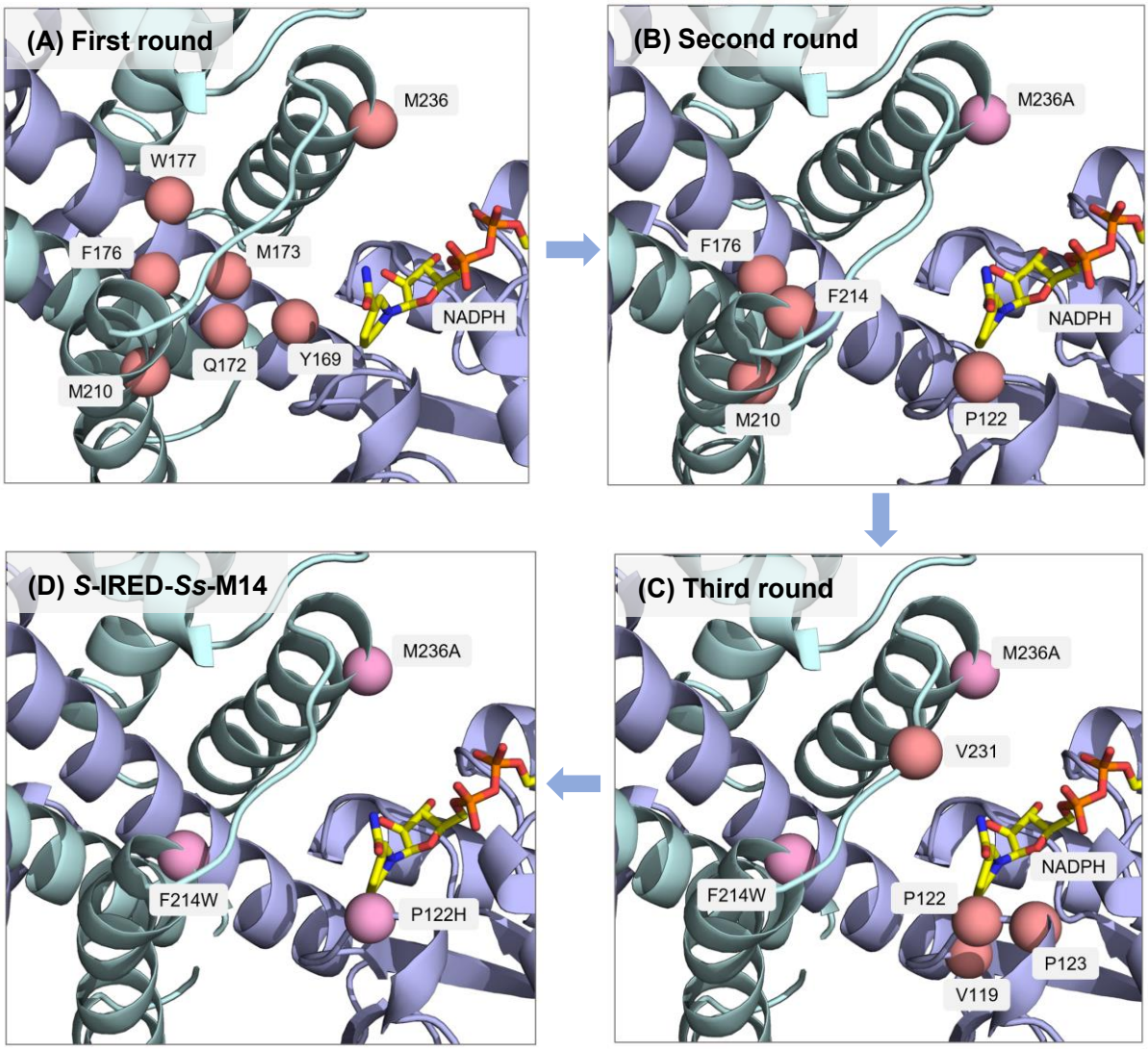
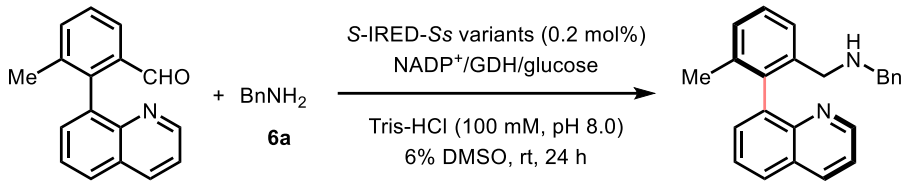


Fig. S2. Iterative site-saturation mutagenesis of *S*-IRED-*Ss*-M9 for the synthesis of *N*-heterobiaryl amine **7**. (A) The first round of site-saturation mutagenesis of *S*-IRED-*Ss*-M9. Sites Y169, Q172, M173, F176, W177, M210, and M236 were examined (Salmon balls). (B) The second round of engineering of *S*-IRED-*Ss*-M9. Sites P122, F176, M210 and F214 were examined (Salmon balls) using *S*-IRED-*Ss*-M12 (M236A, purple ball) as parent protein. (C) The third round of engineering of *S*-IRED-*Ss*-M9. Sites V119, P122, P123, and V231 were examined (Salmon balls) using *S*-IRED-*Ss*-M13 (M236A/F214W, purple balls) as parent protein. (D) Final engineered *S*-IRED-*Ss*-M14 variant (M236A/F214W/P122H, purple balls) based on *S*-IRED-*Ss*-M9.

Table S3. Summary of the site-saturation mutagenesis results for heterobiaryl amine **7**.

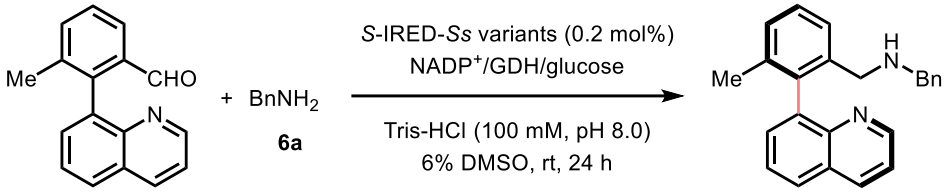


rac-**5a** **7**

Entry	*S*-IRED variants	Mutations	Yield[a]	er[b]
1	*S*-IRED-*Ss*-WT	none	20%	65:35
2	*S*-IRED-*Ss*-M9	A41P/V48T/V88T/A90V/A103M/R158L/A162P/M207T/S209R	30%	93:7
3	*S*-IRED-*Ss*-M12	M9+M236A	37%	99:1
4	*S*-IRED-*Ss*-M13	M12+F214W	82%	99:1
5	*S*-IRED-*Ss*-M14	M13+P122H	98%	99:1

Reaction conditions: **5a** (5 μmol, 1 equiv), benzylamine **6a** (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), purified *S*-IRED variants (0.2 mol%) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature (rt) for 24 h, the final total volume is 1000 μL. [a] Yield (average of duplicate) determined *via* LCMS relative to an internal standard 1,3,5-tribromobenzene. [b] Enantiomeric ratio (er, *S*:*R*) determined by HPLC on a chiral stationary phase.

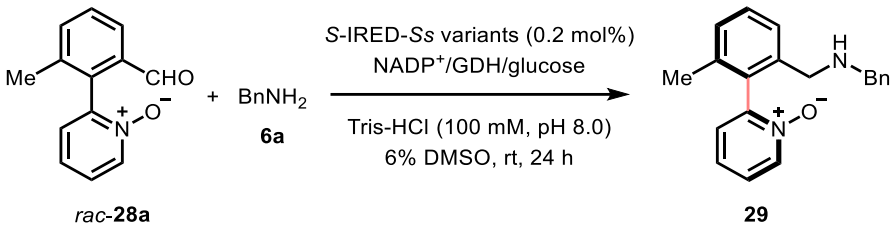
Table S4. The specific activity of *S*-IRED-*Ss* variants for the model reaction of heterobiaryl amine **7**.



rac-**5a** **7**

Entry	*S*-IRED-*Ss* variants	Initial velocity[a] (μmol/min)	Specific activity[b] (U/mg)
1	*S*-IRED-*Ss*-WT	0.0022 ± 0.0007	0.0070 ± 0.0023
2	*S*-IRED-*Ss*-M9	0.0014 ± 0.0005	0.0050 ± 0.0018
3	*S*-IRED-*Ss*-M12	0.0048 ± 0.0005	0.0155 ± 0.0019
4	*S*-IRED-*Ss*-M13	0.0101 ± 0.0001	0.0325 ± 0.0003
5	*S*-IRED-*Ss*-M14	0.0667 ± 0.0022	0.2150 ± 0.0073
6	M14 lyophilized CFE	0.0466 ± 0.0020	0.0116 ± 0.0005

Reaction conditions: **5a** (5 μmol, 1 equiv), benzylamine **6a** (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), *S*-IRED-*Ss* variants (0.2 mol%) or lyophilized CFE of *S*-IRED-*Ss*-M14 (4.0 mg/mL) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature, the final total volume is 1000 μL. Yield (triplicate) of **7** was determined *via* LCMS relative to an internal standard (TBB). **Note**: [a] Initial rate of the enzymatic reaction was calculated over the period of 0–90 min for the purified *S*-IRED-*Ss*-WT, *S*-IRED-*Ss*-M9, M12, and M13 variants or the period of 0–60 min for the purified *S*-IRED-*Ss*-M14 and its lyophilized CFE. [b] For calculation of specific activity, one unit (μmol/min) was defined as the amount of biocatalyst required for forming 1 μmol of product **7** per minute.



rac-**28a** **29**

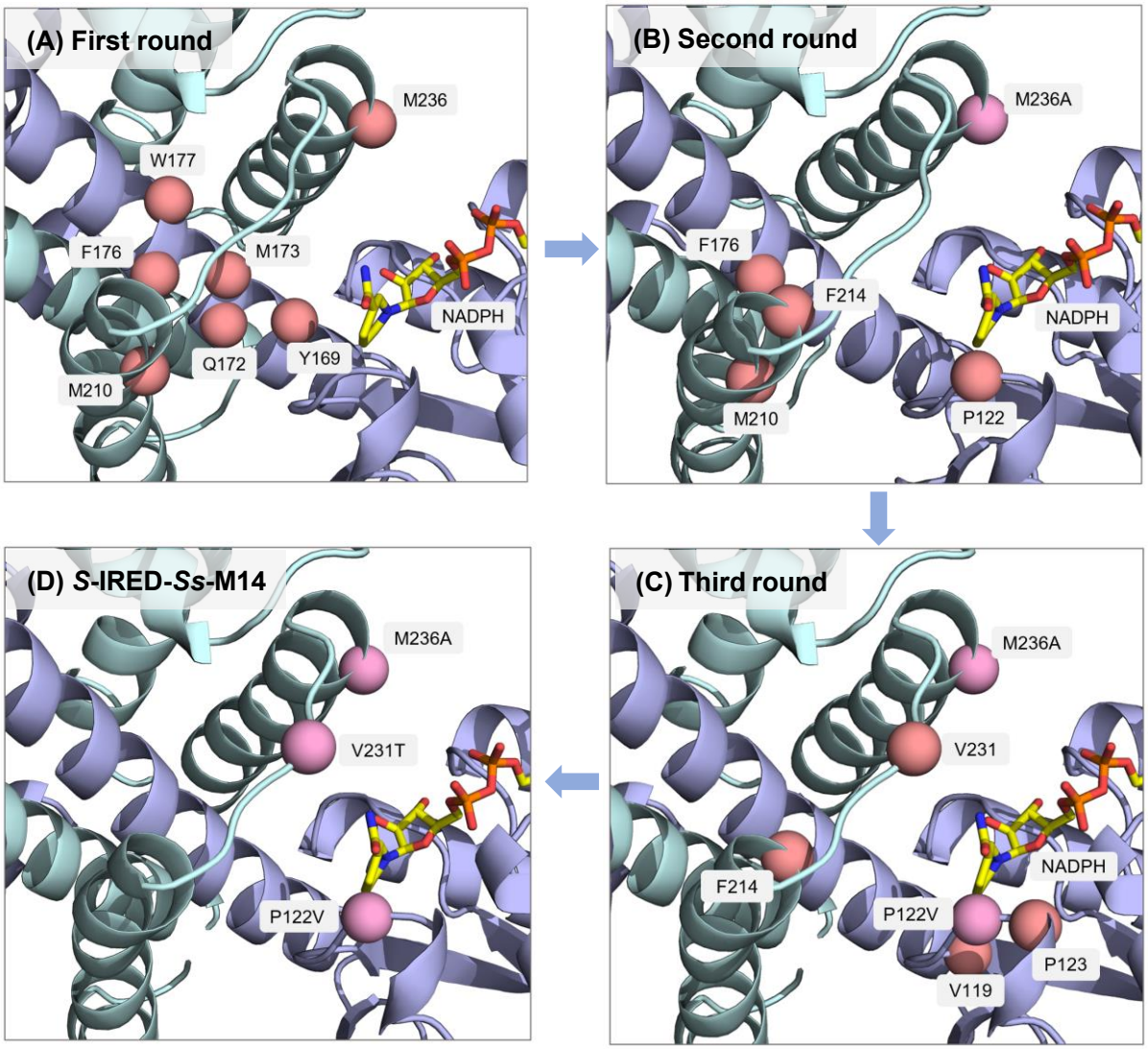
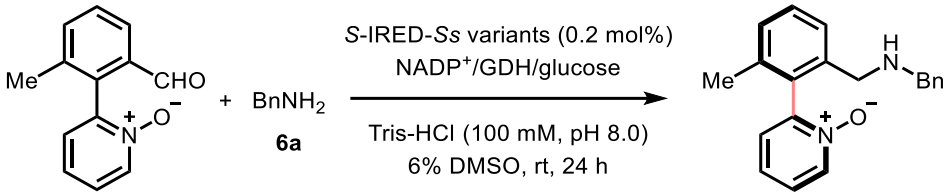


Fig. S3. Iterative site-saturation mutagenesis of *S*-IRED-*Ss*-M9 for the synthesis of biaryl pyridine *N*-oxide **29**. (A) The first round of site-saturation mutagenesis of *S*-IRED-*Ss*-M9. Sites Y169, Q172, M173, F176, W177, M210, and M236 were examined (Salmon balls). (B) The second round of engineering of *S*-IRED-*Ss*-M9. Sites P122, F176, M210 and F214 were examined (Salmon balls) using *S*-IRED-*Ss*-M12 (M236A, purple ball) as parent protein. (C) The third round of engineering of *S*-IRED-*Ss*-M9. Sites V119, P123, F214 and V231 were examined (Salmon balls) using *S*-IRED-*Ss*-M15 (M236A/P122V, purple balls) as parent protein. (D) Final engineered *S*-IRED-*Ss*-M16 variant (M236A/P122V/V231T, purple balls) based on *S*-IRED-*Ss*-M9.

Table S5. Summary of site-saturation mutagenesis results for synthesis of biaryl pyridine *N*-oxide **29**.

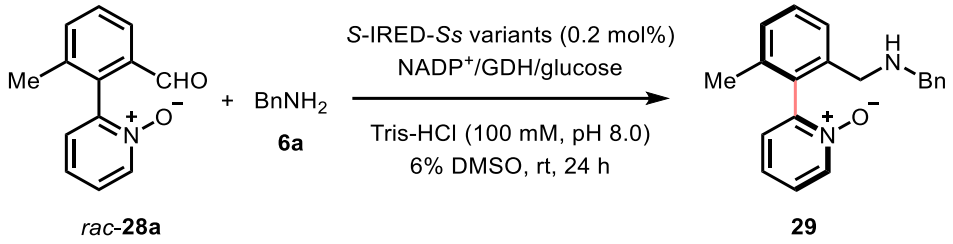


rac-**28a** **29**

Entry	*S*-IRED variants	Mutations	Yield[a]	er[b]
1	*S*-IRED-*Ss*-WT	none	12%	99:1
2	*S*-IRED-*Ss*-M9	A41P/V48T/V88T/A90V/A103M/R158L/A162P/M207T/S209R	11%	99:1
3	*S*-IRED-*Ss*-M12	M9+M236A	32%	99:1
4	*S*-IRED-*Ss*-M15	M12+P122V	92%	99:1
5	*S*-IRED-*Ss*-M16	M15+V231T	98%	99:1

Reaction conditions: **28a** (5 μmol, 1 equiv), benzylamine **6a** (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), purified *S*-IRED variants (0.2 mol%) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature (rt) for 24 h, the final total volume is 1000 μL. [a] Yield (average of duplicate) determined *via* LCMS relative to an internal standard 1,3,5-tribromobenzene. [b] Enantiomeric ratio (er, *S*:*R*) determined by HPLC on a chiral stationary phase.

Table S6. The specific activity of *S*-IRED-*Ss* variants for the model reaction of pyridine *N*-oxide **29**.



rac-**28a** **29**

Entry	*S*-IRED-*Ss* variants	Initial velocity[a] (μmol/min)	Specific activity[b] (U/mg)
1	*S*-IRED-*Ss*-WT	0.0006± 0.0002	0.0020 ± 0.0007
2	*S*-IRED-*Ss*-M9	0.0004 ± 0.0005	0.0013 ± 0.0002
3	*S*-IRED-*Ss*-M12	0.0010 ± 0.0001	0.0031 ± 0.0004
4	*S*-IRED-*Ss*-M15	0.0126 ± 0.0009	0.0408 ± 0.0030
5	*S*-IRED-*Ss*-M16	0.0237 ± 0.0011	0.0764 ± 0.0035
6	M16 lyophilized CFE	0.0158 ± 0.0013	0.0511 ± 0.0003

Reaction conditions: **28a** (5 μmol, 1 equiv), benzylamine **6a** (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), purified *S*-IRED-*Ss* variants (0.2 mol%) or lyophilized CFE of *S*-IRED-*Ss*-M16 (4.5 mg/mL) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature, the final total volume is 1000 μL. Yield (triplicate) of **29** was determined *via* LCMS relative to an internal standard (TBB). **Note**: [a] Initial rate of the enzymatic reaction was calculated over the period of 0–120 min for the purified *S*-IRED-*Ss*-WT and *S*-IRED-*Ss*-M9, the period of 0–90 min for *S*-IRED-*Ss*-M12 and M15 variants or the period of 0–60 min for the purified *S*-IRED-*Ss*-M16 and its lyophilized CFE. [b] For calculation of specific activity, one unit (μmol/min) was defined as the amount of biocatalyst required for forming 1 μmol of product **29** per minute.

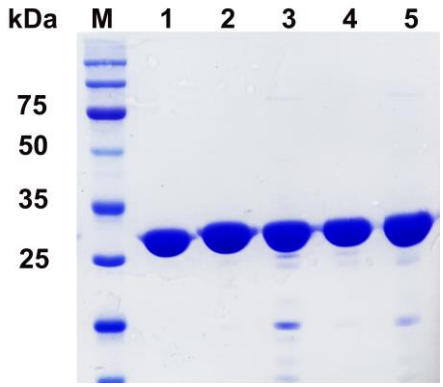


Fig. S4. SDS-PAGE analysis of the purified *S*-IRED-*Ss* variants for the synthesis of 8-aryl quinoline. M: protein marker; lane 1, *S*-IRED-*Ss*-WT; lane 2, *S*-IRED-*Ss*-M9; lane 3, *S*-IRED-*Ss*-M12; lane 4, *S*-IRED-*Ss*-M13; lane 5, *S*-IRED-*Ss*-M14.

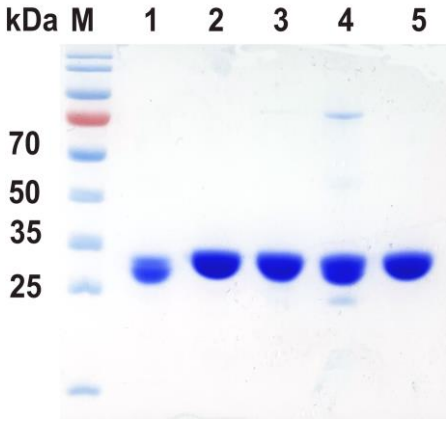
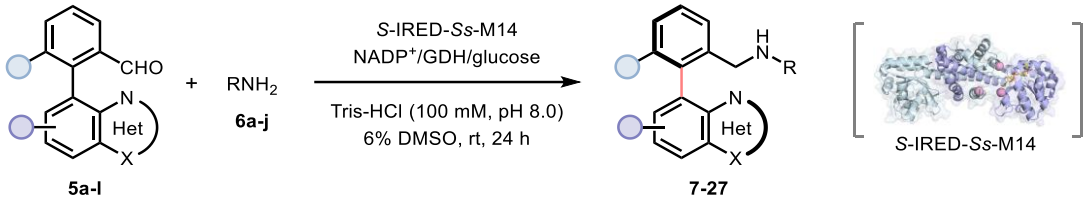


Fig. S5. SDS-PAGE analysis of the purified *S*-IRED-*Ss* variants for the synthesis of biaryl pyridine *N*-oxide. M: protein marker; lane 1, *S*-IRED-*Ss*-WT; lane 2, *S*-IRED-*Ss*-M9; lane 3, *S*-IRED-*Ss*-M12; lane 4, *S*-IRED-*Ss*-M15; lane 5, *S*-IRED-*Ss*-M16.

Enzymatic atroposelective DKR for the synthesis of *N*-heterobiaryl amines



General procedure 1 for analytical scale reaction

A screw vial (4 mL) was charged with *Bm*GDH (200 μL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), glucose (54 μL, 50 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), $NADP^+$ (15 μL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), *S*-IRED-*Ss*-M14 (0.2 mol% or 0.4 mol% catalyst loading), aldehyde (30 μL, 167 mM stock in DMSO, 5 μmol, 1 equiv) and amine (30 μL, 500 mM stock in DMSO, 15 μmol, 3 equiv). Tris-HCl buffer (100 mM pH 8.0) was added to bring the total volume to 1000 μL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed and placed on a shaker at 200 rpm at room temperature for 24 hours. Upon completion, the reaction was quenched with 3 mL of acetonitrile and 100 μL of 5 mg/mL 1,3,5-tribromobenzene (TBB) in acetonitrile as the internal standard. The mixture was shaken for 30 min, centrifuged (13,400 x g, 5 mins), and the supernatant was filtered and retained for LCMS analysis for yield calculation. After LCMS analysis, the supernatant was concentrated under reduced pressure, extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was dissolved in 10% isopropanol/hexanes (*v*/*v*) for chiral HPLC analysis.

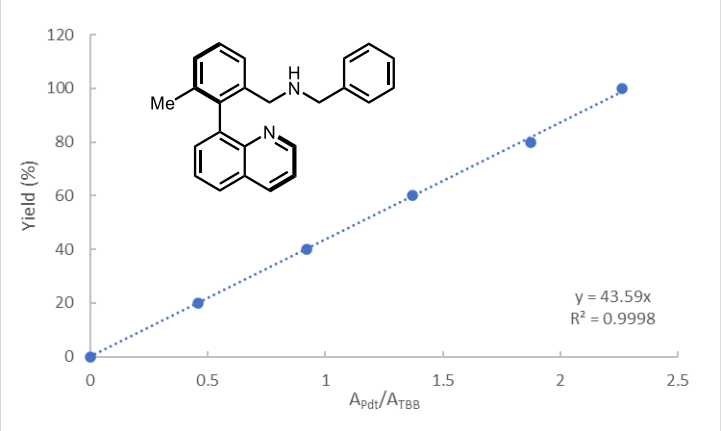
General procedure 2 for preparative scale reaction using purified enzyme

A round bottle (100 mL) was charged with *Bm*GDH (4 mL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), glucose (1.08 mL, 50 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), $NADP^+$ (0.3 mL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), *S*-IRED-*Ss*-M14 protein (0.2 mol% catalyst loading), aldehyde (0.6 mL, 167 mM stock in DMSO, 0.1 mmol, 1 equiv) and amine (0.6 mL, 500 mM stock in DMSO, 0.3 mmol, 3 equiv). Tris-HCl buffer (100 mM pH 8.0) was added to bring the total volume to 20 mL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed and placed on a shaker at 200 rpm at room temperature for 24 hours. Upon completion, the reaction was quenched with 20 mL of acetonitrile. The mixture was shaken for 30 min, filtered, concentrated, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by Flash chromatography (EtOAc/Petroleum ether, 10~20%, *v*/*v*).

General procedure 3 for preparative scale reaction using lyophilized CFE

A round bottle (250 mL) was charged with *BmGDH* (40 mL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), glucose (10.8 mL, 50 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), $NADP^+$ (3 mL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), lyophilized *S*-IRED-*Ss*-M16 CFE (800 mg), aldehyde substrate (6 mL, 167 mM stock in DMSO, 1 mmol, 1 equiv) and amine substrate (6 mL, 500 mM stock in DMSO, 3 mmol, 3 equiv). Tris-HCl buffer (100 mM pH 8.0) was added to bring the total volume to 200 mL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed and placed on a shaker at 200 rpm at room temperature for 24 hours. Upon completion, the reaction was quenched with 200 mL of acetonitrile. The mixture was shaken for 30 min, filtered, concentrated, and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by Flash chromatography (EtOAc/Petroleum ether, 10~20%, *v*/*v*).

(*S*)-*N*-benzyl-1-[3-methyl-2-(quinolin-8-yl)phenyl]methanamine (**7**)

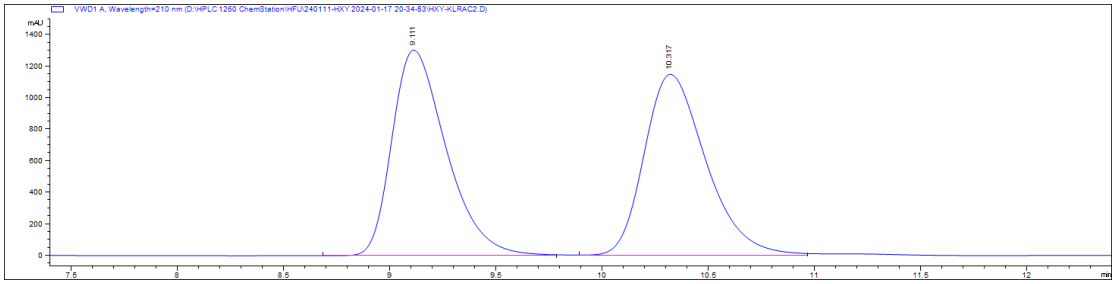


Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%). **Yields**: run 1: 98%, run 2: 99%, average yield 98%.

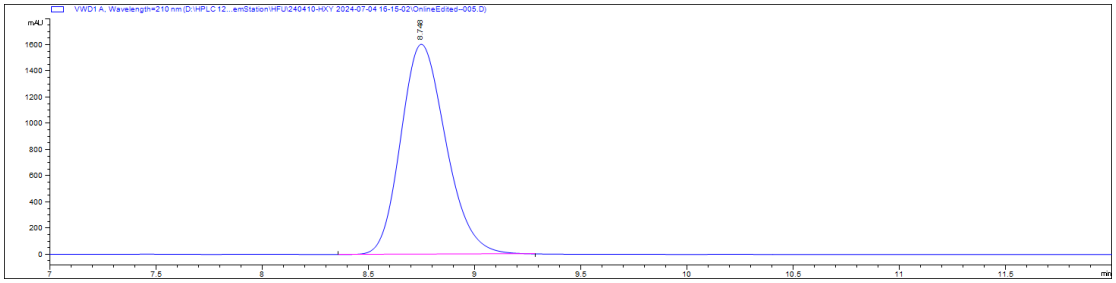
0.1-mmol-scale preparative reaction was conducted according to the general procedure 2 using **5a** (0.1 mmol, 1 equiv) and **6a** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%). **Isolated yield**: 89% (colorless amorphous, 30 mg).

1.0-mmol-scale preparative reaction was conducted according to the general procedure 3 using **5a** (1 mmol, 1 equiv) and **6a** (3 mmol, 3 equiv) catalyzed by lyophilized *S*-IRED-*Ss*-M14 CFE (4 mg/mL). **Isolated yield**: 65% (colorless amorphous, 220 mg).

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 8.75 min. **Absolute configuration** of the enzymatic product **7** was assigned as ***S*** by X-ray crystallography.

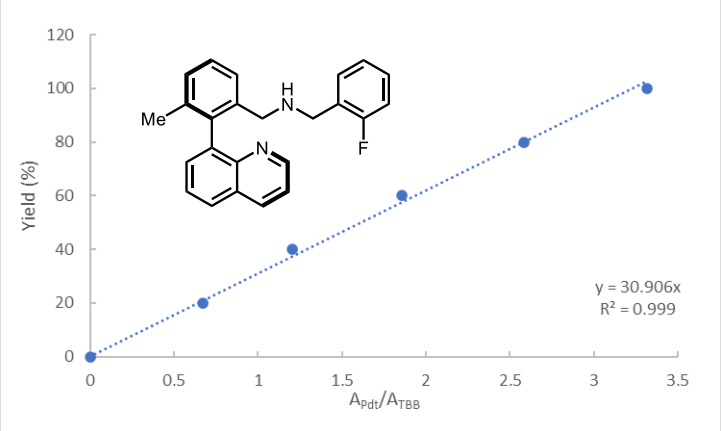


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.111	MF	23228.9	1309.2	0.2957	49.848	0.646
2	10.317	MF	23370.3	1154.5	0.3374	50.152	0.715



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.748	MF	23772.2	1608.7	0.2463	100.000	0.804

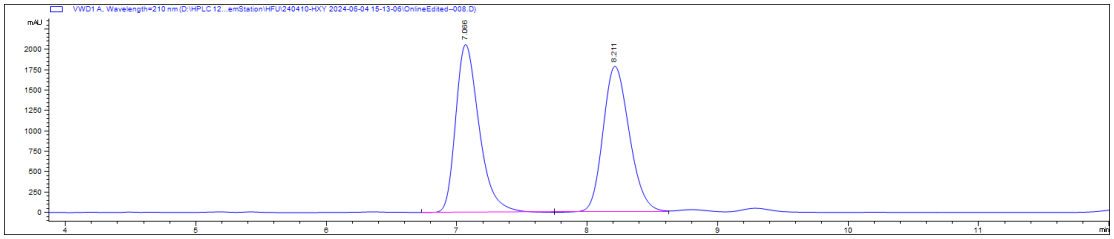
(*S*)-*N*-(2-Fluorobenzyl)-1-[3-methyl-2-(quinolin-8-yl)phenyl]methanamine (**8**)



Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and (2-fluorophenyl)methanamine **6b** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 95%, run 2: 98%, average yield 96%.

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 7.15 min, t_R (minor) = 8.37 min.



#	Time	Type	Area	Height	Width	Area%	Symmetry
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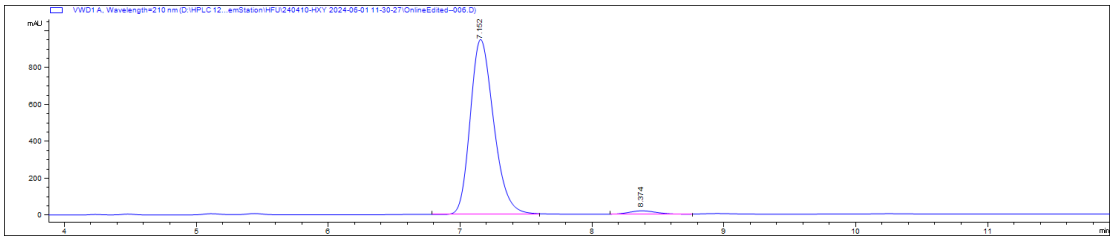
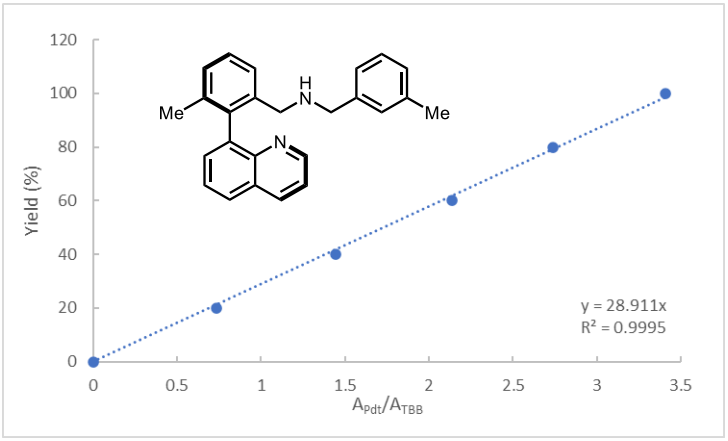


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.152	MF	11714.1	947.1	0.2061	97.822	0.765
2	8.374	FM	260.8	18.2	0.2385	2.178	0.861

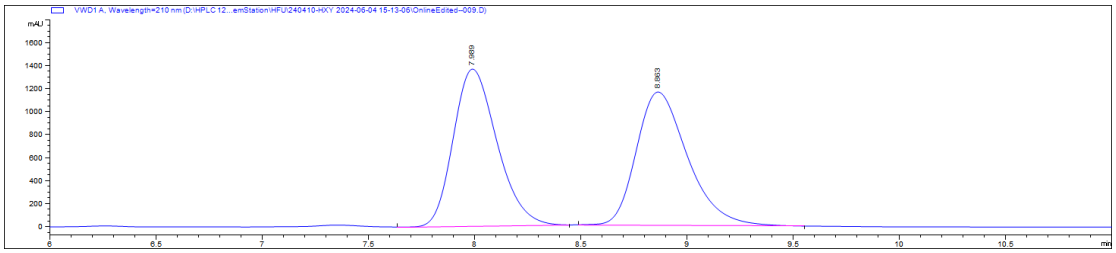
(*S*)-*N*-(3-Methyl-2-(quinolin-8-yl)benzyl)-1-(*m*-tolyl)methanamine (**9**)



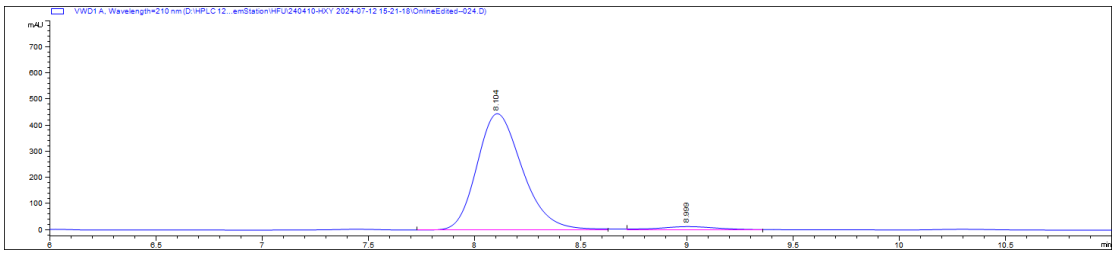
Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and *m*-tolylmethanamine **6c** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 97%, run 2: 97%, average yield 97%.

Enantioselectivity: 96:4 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 8.10 min, t_R (minor) = 9.00 min.

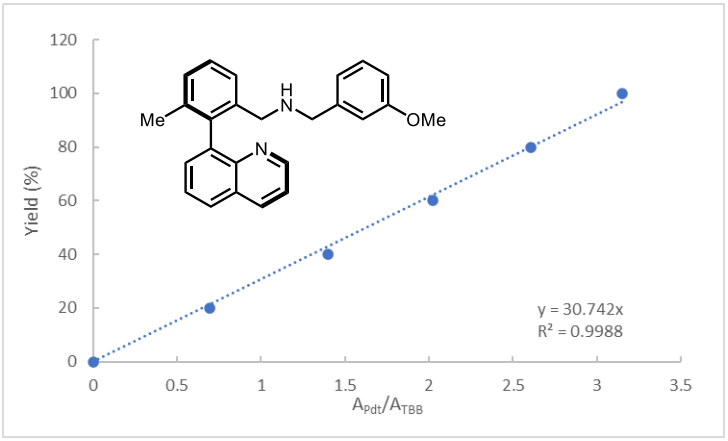


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.989	MM	19703.2	1368.7	0.2399	49.983	0.764
2	8.863	MM	19716.5	1162.9	0.2826	50.017	0.714



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.104	MF	6600.8	443.8	0.2479	96.198	0.779
2	8.999	FM	260.9	12.9	0.3371	3.802	0.942

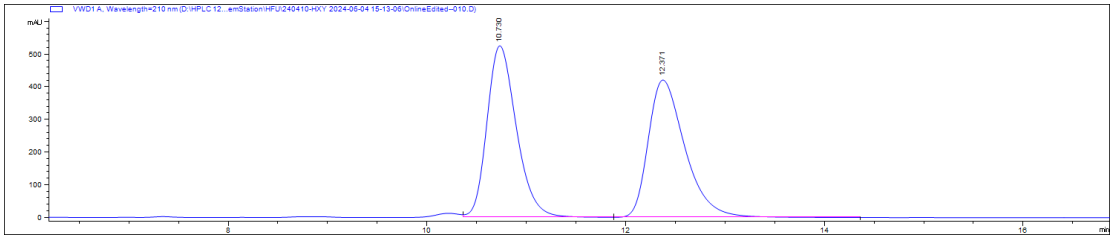
(*S*)-*N*-(3-Methoxybenzyl)-1-[3-methyl-2-(quinolin-8-yl)phenyl]methanamine (**10**)



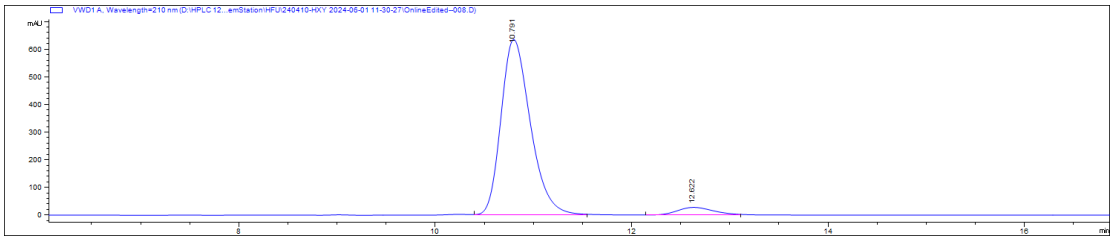
Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and (3-methoxyphenyl)methanamine **6d** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 91%, run 2: 83%, average yield 87%.

Enantioselectivity: 95:5 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 10.79 min, t_R (minor) = 12.62 min.

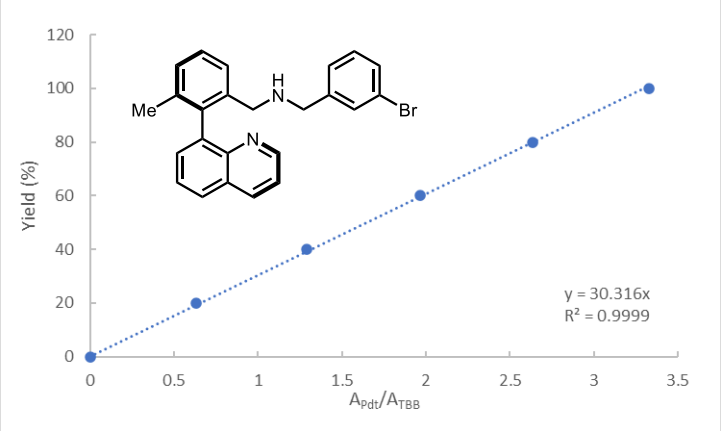


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.73	FM	10880.3	528.4	0.3432	50.081	0.75
2	12.371	BB	10845.2	422.6	0.3914	49.919	0.621



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.791	FM	13173.7	633.6	0.3465	94.845	0.737
2	12.622	MF	715.9	27.7	0.43	5.155	0.779

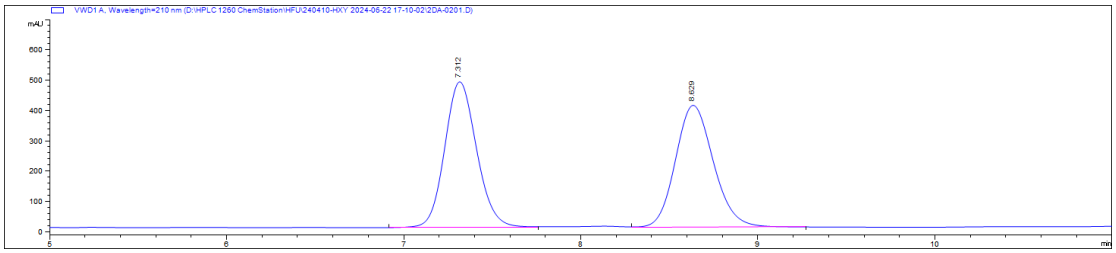
(*S*)-*N*-(3-Bromobenzyl)-1-(3-methyl-2-(quinolin-8-yl)phenyl)methanamine (**11**)



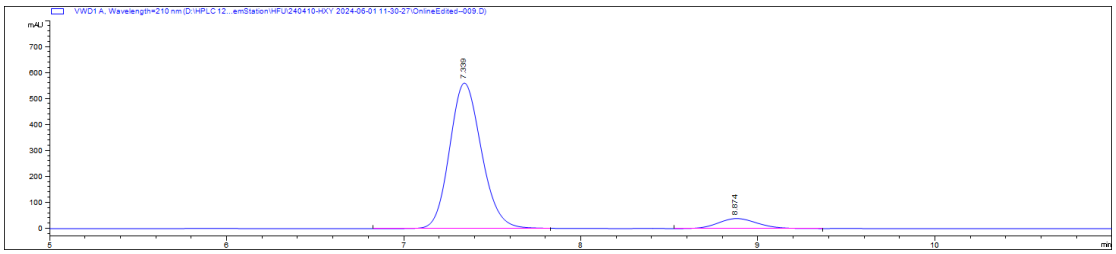
Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and (3-bromophenyl)methanamine **6e** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 97%, run 2: 99%, average yield 98%.

Enantioselectivity: 92:8 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 7.34 min, t_R (minor) = 8.87 min.

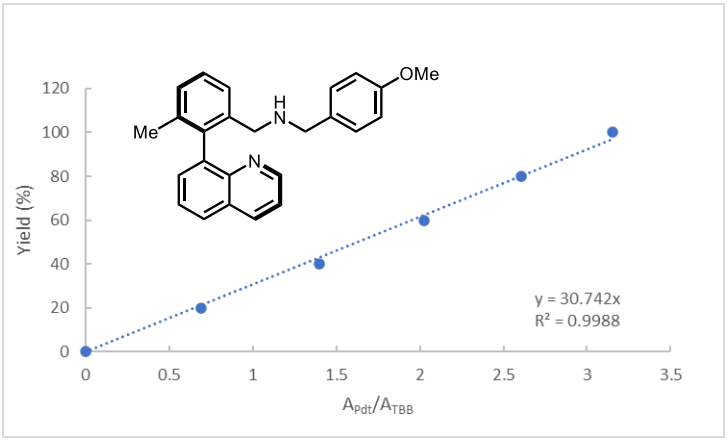


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.312	MF	6060.3	482.9	0.2092	50.027	0.862
2	8.629	MF	6053.7	404.4	0.2495	49.973	0.842



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.339	MF	7022.2	561.9	0.2083	92.164	0.844
2	8.874	VB	597	38.7	0.2399	7.836	0.865

(*S*)-*N*-(4-Methoxybenzyl)-1-(3-methyl-2-(quinolin-8-yl)phenyl)methanamine (**12**)

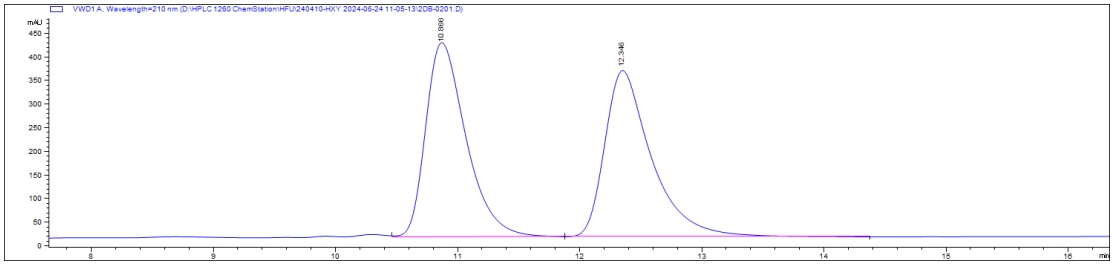


Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and (4-methoxyphenyl)methanamine **6f** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

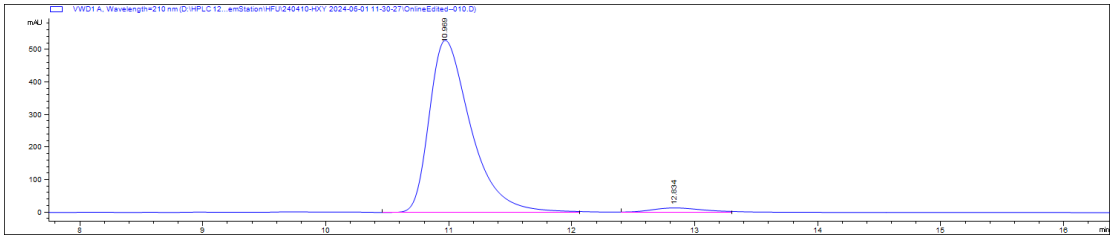
Yields: run 1: 91%, run 2: 95%, average yield 93%.

Preparative enzymatic reaction was conducted according to the general procedure 2 using **5a** (0.1 mmol, 1 equiv), (4-methoxyphenyl)methanamine **6f** (0.3 mmol, 3 equiv) catalyzed by lyophilized *S*-IRED-*Ss*-M14 (0.2 mol%). **Isolated yield**: 68% (colorless amorphous, 25 mg).

Enantioselectivity: 97:3 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 10.97 min, t_R (minor) = 12.83 min.

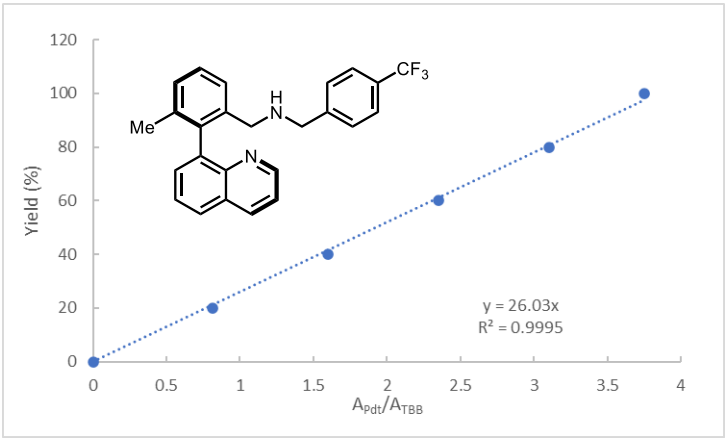


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.866	FM	9445.7	411.7	0.3824	50.178	0.645
2	12.346	BB	9378.6	351.8	0.393	49.822	0.569



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.969	MF	12450.9	529.7	0.3918	96.804	0.604
2	12.834	MF	411.1	13.8	0.4972	3.196	0.784

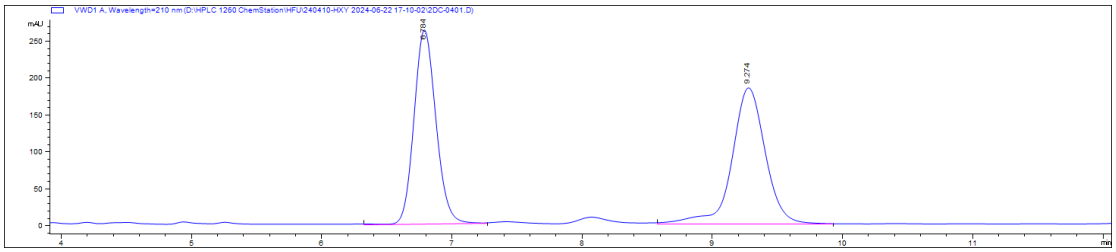
(*S*)-*N*-[3-Methyl-2-(quinolin-8-yl)benzyl]-1-[4-(trifluoromethyl)phenyl]methanamine (**13**)



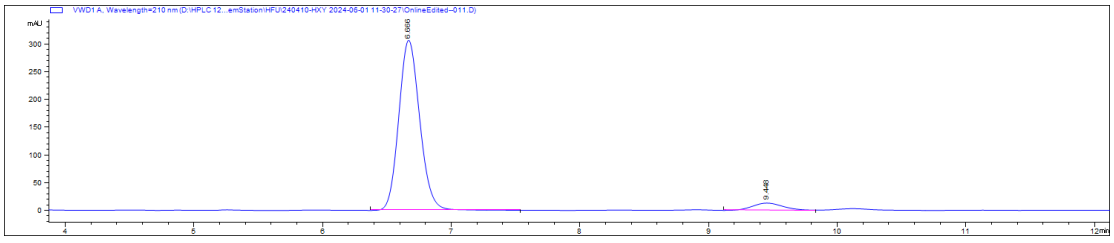
Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and (4-(trifluoromethyl)phenyl)methanamine **6g** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.4 mol%).

Yields: run 1: 80%, run 2: 82%, average yield 81%.

Enantioselectivity: 94:6 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 6.67 min, t_R (minor) = 9.45 min.

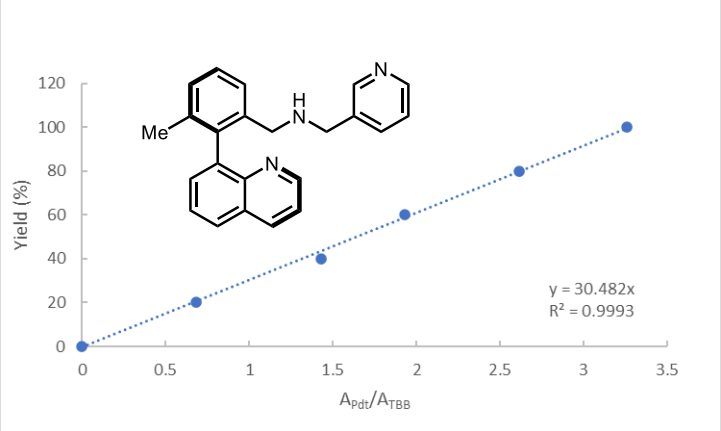


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.784	MM	3108.9	263.8	0.1964	48.244	0.875
2	9.274	MM	3335.2	185.2	0.3001	51.756	0.99



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.666	BB	3480.5	306.9	0.1743	94.015	0.841
2	9.448	BV	221.6	13.1	0.2607	5.985	0.845

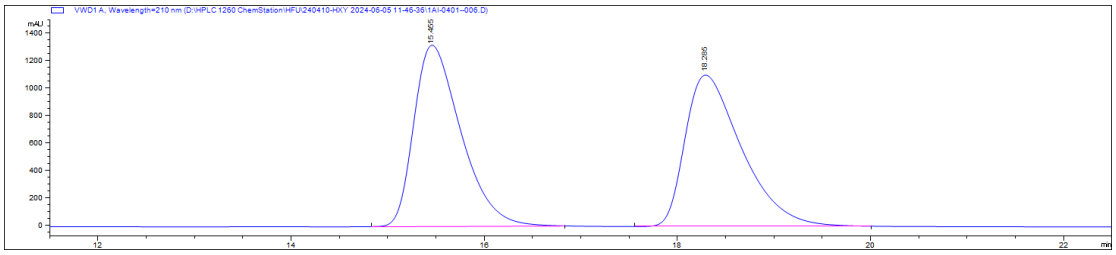
(*S*)-*N*-[3-Methyl-2-(quinolin-8-yl)benzyl)-1-(pyridin-3-yl)methanamine (**14**)



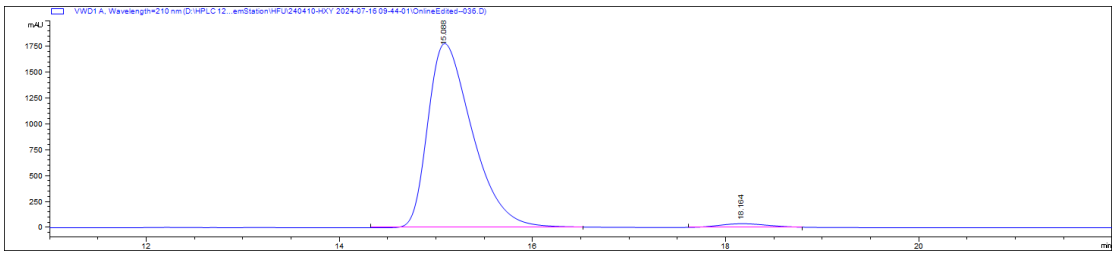
Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and pyridin-3-ylmethanamine **6h** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 88%, run 2: 89%, average yield 88%.

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 15.09 min, t_R (minor) = 18.16 min.

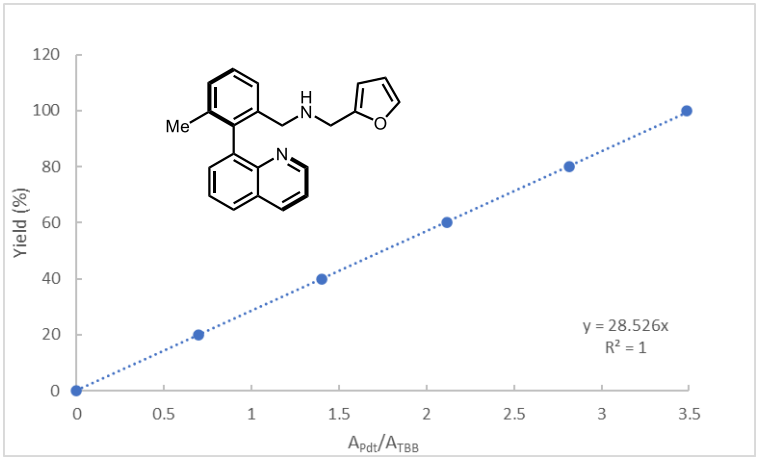


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.455	FM	44979	1321.7	0.5672	49.920	0.608
2	18.285	MF	45124	1102.7	0.682	50.080	0.546



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.088	MF	57285.9	1786.9	0.5343	97.682	0.59
2	18.164	MF	1359.5	37.2	0.6099	2.318	0.819

(*S*)-1-(Furan-3-yl)-*N*-[3-methyl-2-(quinolin-8-yl)benzyl]methanamine (**15**)

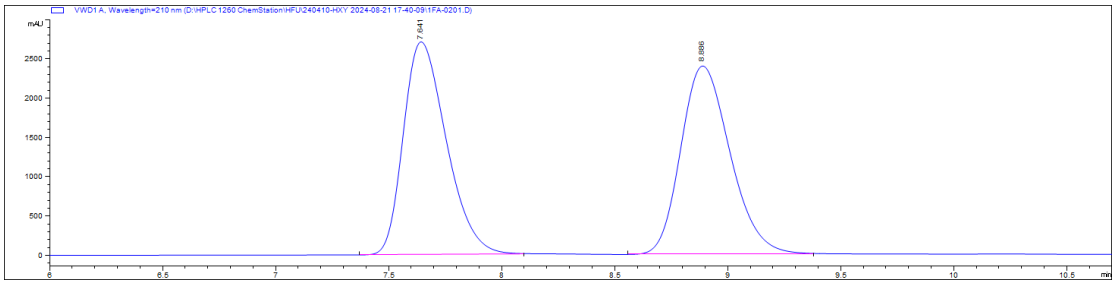


Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and furan-2-ylmethanamine **6i** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

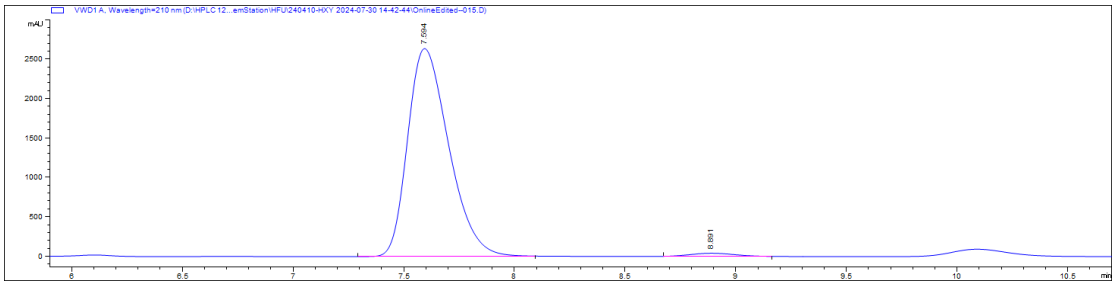
Yields: run 1: 94%, run 2: 97%, average yield 96%.

Preparative enzymatic reaction was conducted according to the general procedure 2 using **5a** (0.1 mmol, 1 equiv) and furan-2-ylmethanamine **6i** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%). **Isolated yield**: 82% (yellow amorphous, 27 mg).

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 7.59 min, t_R (minor) = 8.89 min.

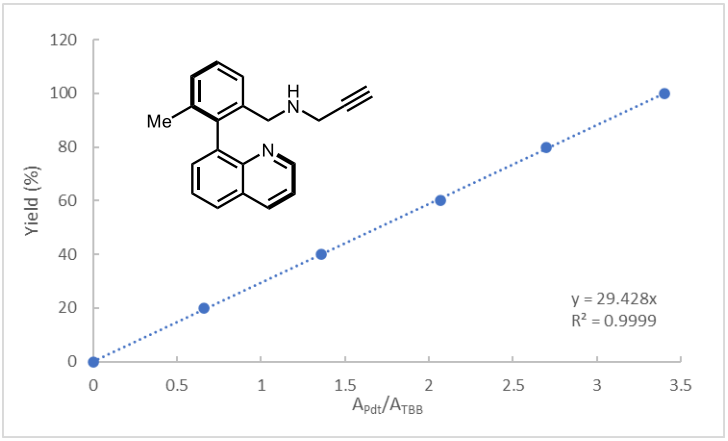


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.641	FM	36103.6	2723.4	0.2209	49.662	0.679
2	8.886	MF	36595.6	2408.3	0.2533	50.338	0.776



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.594	MF	34254.2	2649.9	0.2154	98.185	0.677
2	8.891	FM	633.2	42.7	0.2469	1.815	0.897

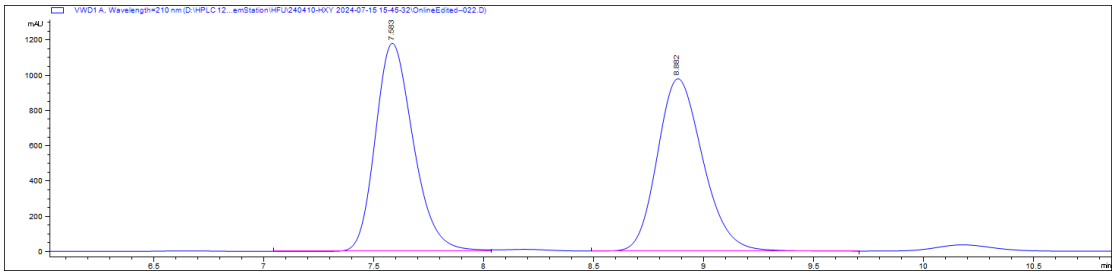
(*S*)-*N*-[3-Methyl-2-(quinolin-8-yl)benzyl]prop-2-yn-1-amine (**16**)



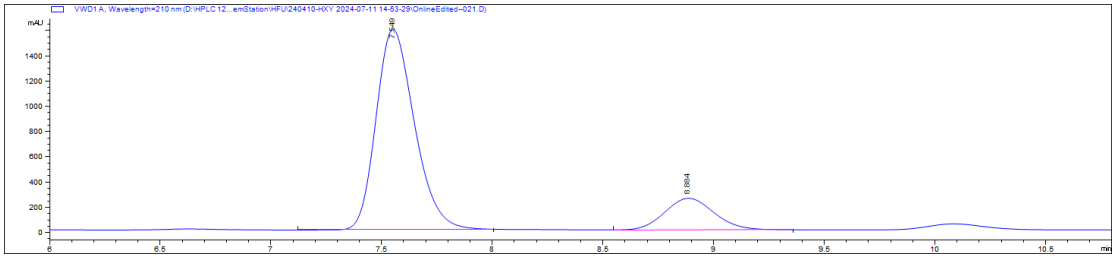
Prepared according to the general procedure 1 using substrate **5a** (5 μmol, 1 equiv) and prop-2-yn-1-amine **6j** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.4 mol%).

Yields: run 1: 70%, run 2: 72%, average yield 71%.

Enantioselectivity: 82:18 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 7.55 min, t_R (minor) = 8.88 min.

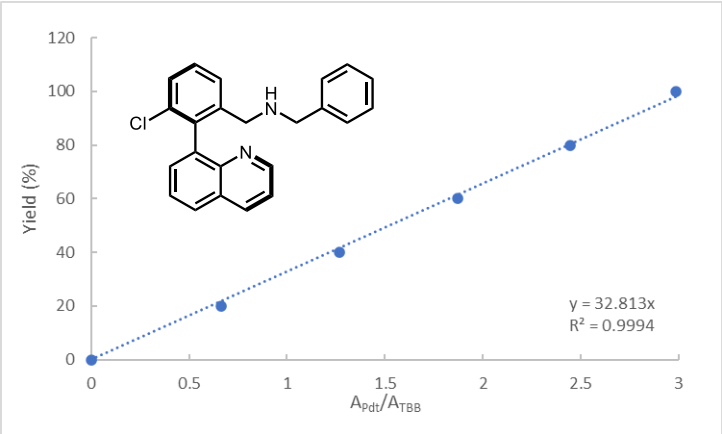


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.583	MF	14158.9	1177.6	0.2004	50.081	0.773
2	8.882	VV	14113.4	976.4	0.2246	49.919	0.785



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.549	MF	19258.1	1592.7	0.2015	82.442	0.754
2	8.884	MM	4101.5	255.5	0.2675	17.558	0.926

(*R*)-*N*-Benzyl-1-[3-chloro-2-(quinolin-8-yl)phenyl]methanamine (**17**)



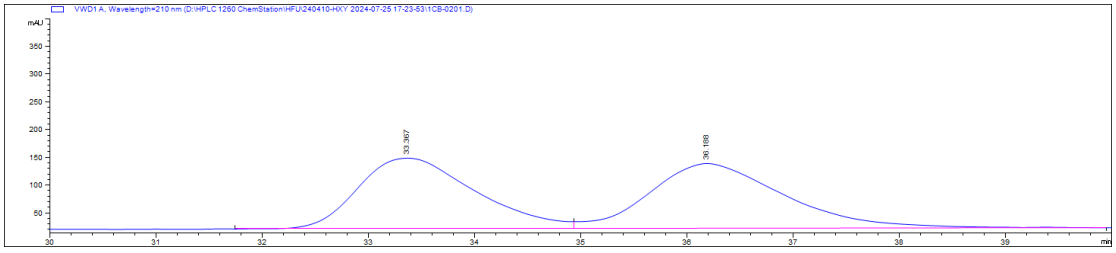
Prepared according to the general procedure 1 using substrate **5b** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 98%, run 2: 99%, average yield 98%.

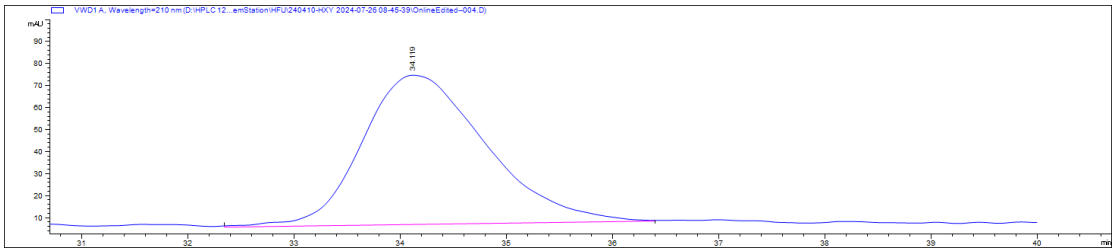
Preparative enzymatic reaction was conducted according to the general procedure 2 using **5b** (0.1 mmol, 1 equiv) and benzylamine **6a** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Isolated yield: 86% (yellow solid, 31 mg).

Enantioselectivity: 99:1 er. Obtained from acetylated derivatives of racemic reference and the enzymatic product, respectively. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 34.12 min.

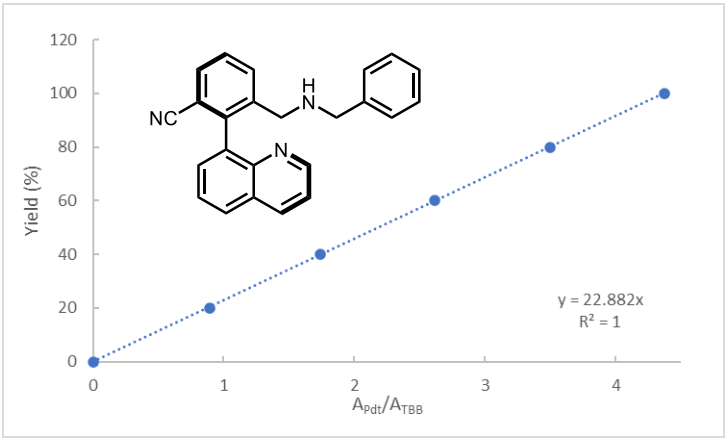


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	33.367	BV	9770.6	127.3	1.1491	48.618	0.694
2	36.188	VV R	10326	116.8	1.3212	51.382	0.709



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	34.119	MM	5569.7	68.2	1.3604	100.000	0.693

(*R*)-3-[(benzylamino)methyl]-2-(quinolin-8-yl)benzonitrile (**18**)



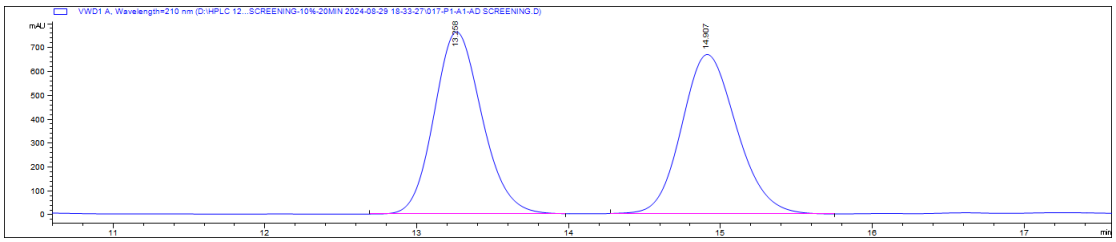
Prepared according to the general procedure 1 using substrate **5c** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 97%, run 2: 98%, average yield 98%.

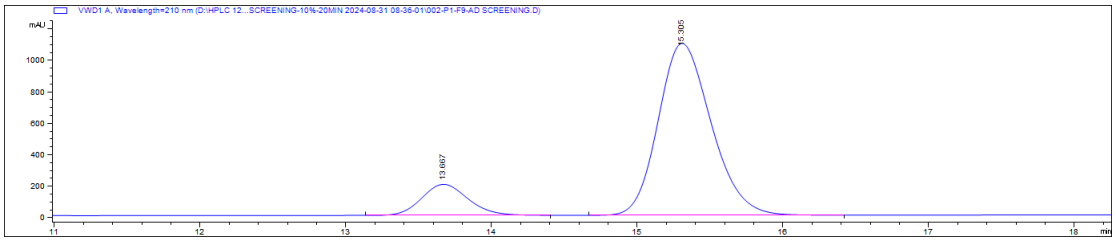
Preparative enzymatic reaction was conducted according to the general procedure 2 using **5c** (0.1 mmol, 1 equiv) and benzylamine **6a** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Isolated yield: 88% (yellow solid, 31 mg).

Enantioselectivity: 86:14 er. Obtained from *N*-Boc protected derivatives of racemic reference and the enzymatic product, respectively. Chiral HPLC method: AD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 13.67 min, t_R (major) = 15.31 min.

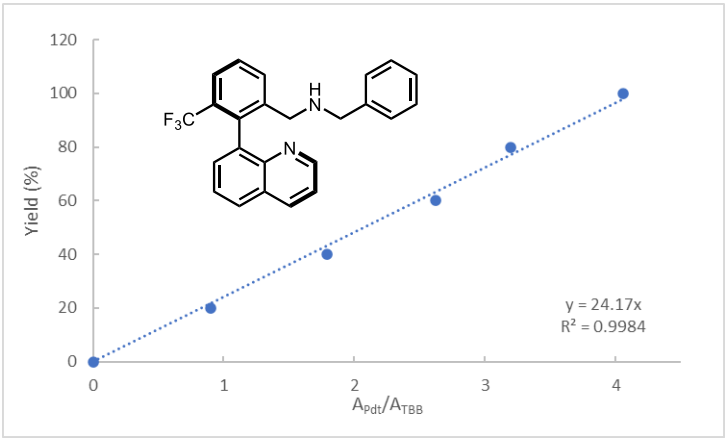


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.258	MF	16771.7	766.7	0.3646	49.801	0.855
2	14.907	FM	16905.9	670.7	0.4201	50.199	0.85



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.667	FM	4365.5	197.3	0.3689	13.674	0.87
2	15.305	BB	27559.9	1092.8	0.3882	86.326	0.783

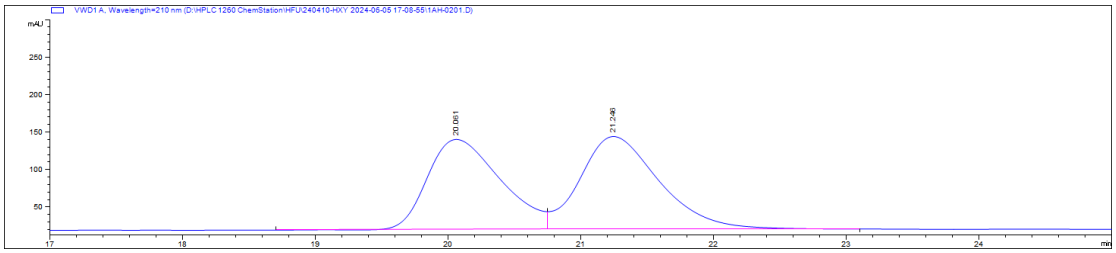
(*R*)-*N*-Benzyl-1-[2-(quinolin-8-yl)-3-(trifluoromethyl)phenyl]methanamine (**19**)



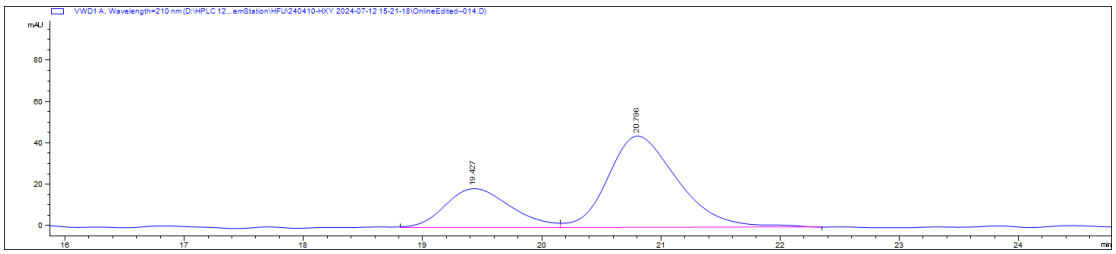
Prepared according to the general procedure 1 using substrate **5d** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 91%, run 2: 89%, average yield 90%.

Enantioselectivity: 71:29 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 19.43 min, t_R (major) = 20.80 min.

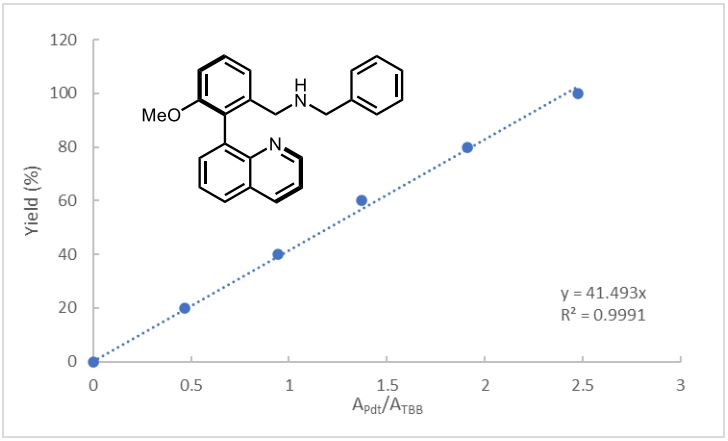


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	20.061	BV	4634.1	120.4	0.5911	47.364	0.631
2	21.246	VB	5150	123.9	0.6309	52.636	0.687



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.427	FM	730.8	18.9	0.6437	28.959	0.781
2	20.796	VB	1792.8	44.1	0.6164	71.041	0.704

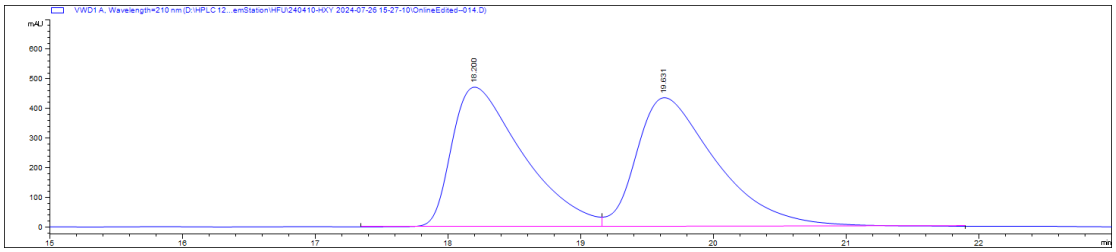
(*R*)-*N*-Benzyl-1-[3-methoxy-2-(quinolin-8-yl)phenyl]methanamine (**20**)



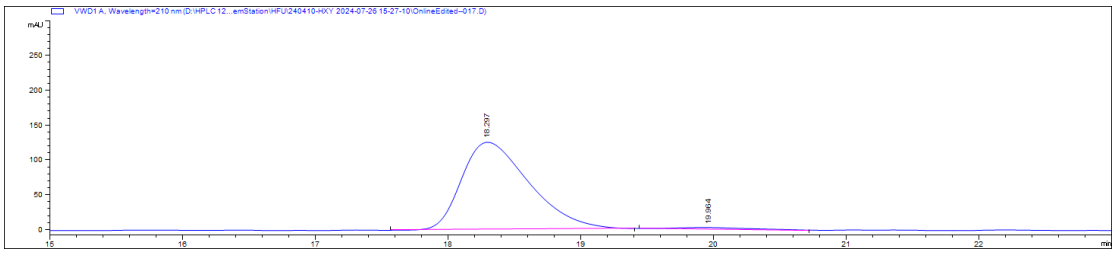
Prepared according to the general procedure 1 using substrate **5e** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 74%, run 2: 76%, average yield 75%.

Enantioselectivity: 97:3 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 18.30 min, t_R (minor) = 19.96 min.

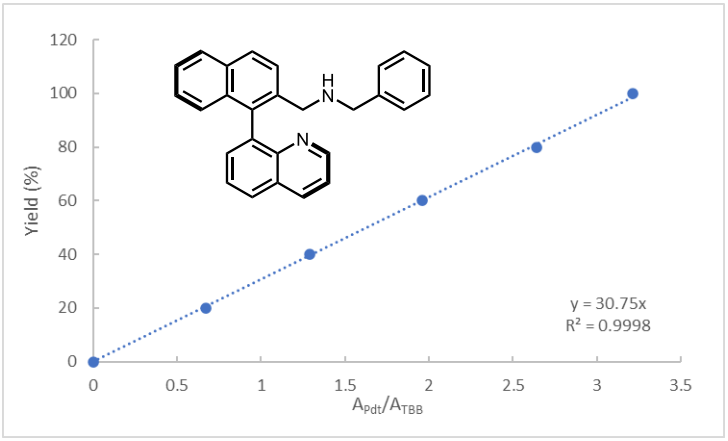


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.2	BV	17559.4	472.2	0.5559	49.009	0.439
2	19.631	VB	18269.3	436	0.6229	50.991	0.503



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.297	MM	4445.2	125.6	0.5899	97.383	0.613
2	19.964	MM	119.5	2.7	0.7399	2.617	0.378

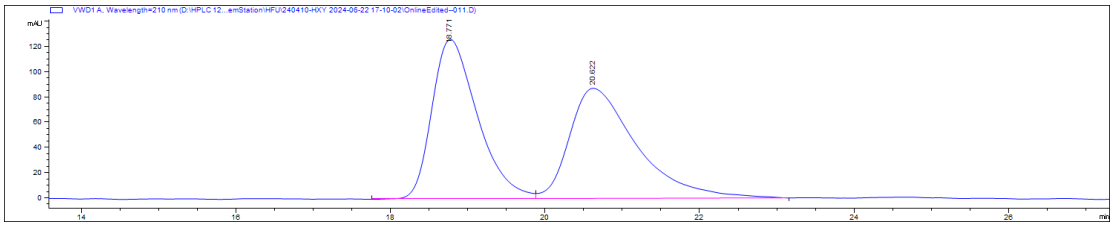
(*S*)-*N*-Benzyl-1-[1-(quinolin-8-yl)naphthalen-2-yl]methanamine (**21**)



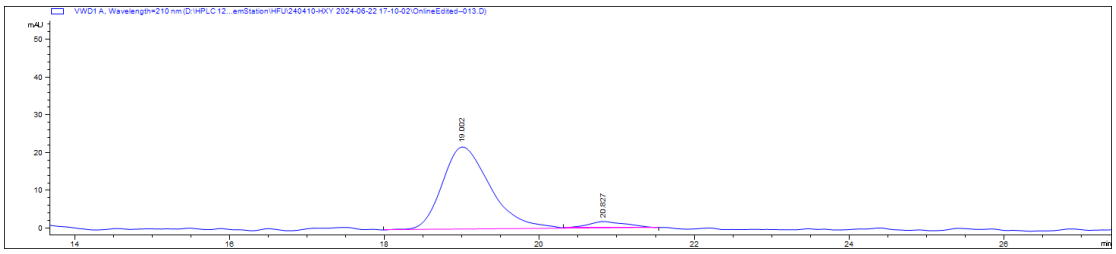
Prepared according to the general procedure 1 using substrate **5f** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 60%, run 2: 61%, average yield 60%.

Enantioselectivity: 94:6 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 19.00 min, t_R (minor) = 20.83min.

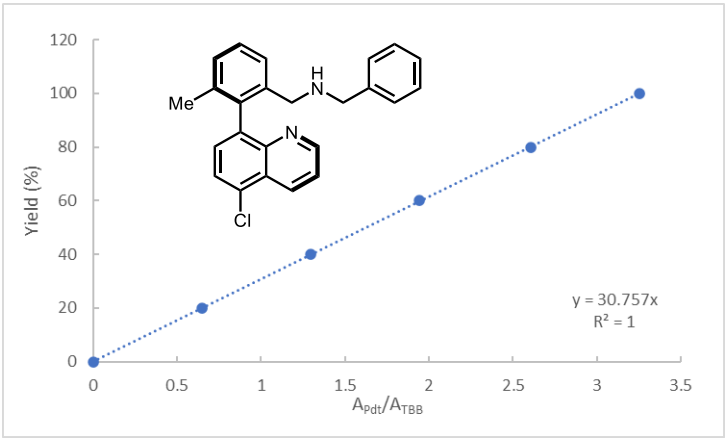


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.771	BV	5191.2	126.4	0.6293	49.597	0.638
2	20.622	VB	5275.6	87.2	0.8957	50.403	0.515



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.002	BV R	951.6	21.9	0.6526	94.018	0.7
2	20.827	VB E	60.6	1.7	0.4814	5.982	0.709

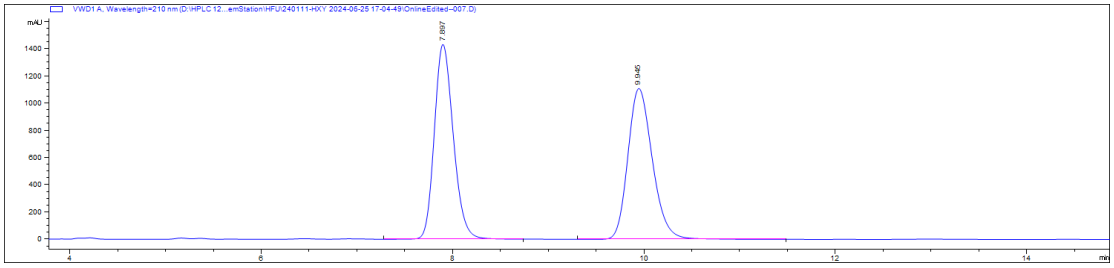
(*S*)-*N*-Benzyl-1-[2-(5-chloroquinolin-8-yl)-3-methylphenyl]methanamine (**22**)



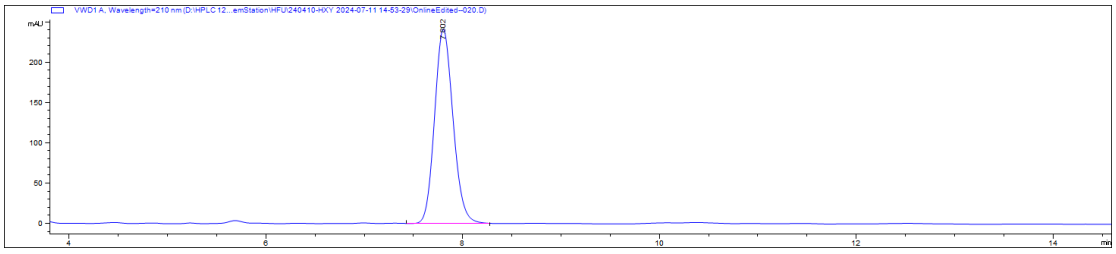
Prepared according to the general procedure 1 using substrate **5g** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 75%, run 2: 81%, average yield 78%.

Enantioselectivity: >99:1 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 7.80 min.

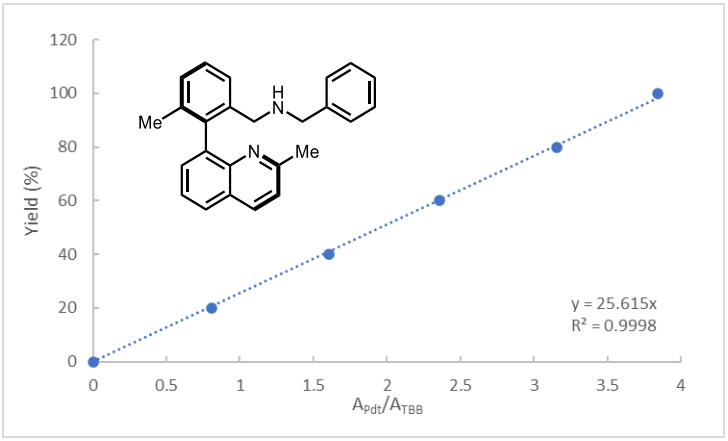


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.897	BB	19741.3	1433.5	0.2127	50.004	0.789
2	9.945	VB R	19737.9	1109.7	0.2735	49.996	0.766



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.802	MF	3151.4	240.6	0.2183	100.000	0.859

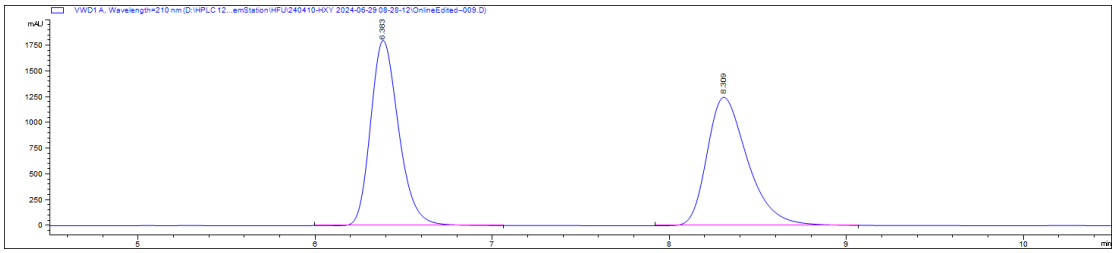
(*S*)-*N*-Benzyl-1-[3-methyl-2-(2-methylquinolin-8-yl)phenyl]methanamine (**23**)



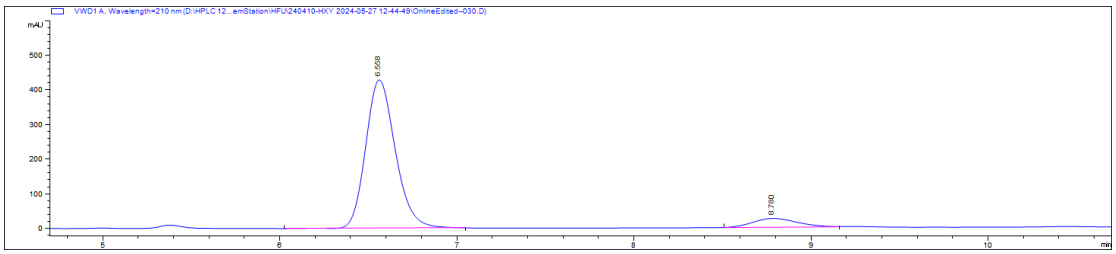
Prepared according to the general procedure 1 using substrate **5h** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 78%, run 2: 79%, average yield 78%.

Enantioselectivity: 91:9 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 6.56 min, t_R (minor) = 8.78 min.

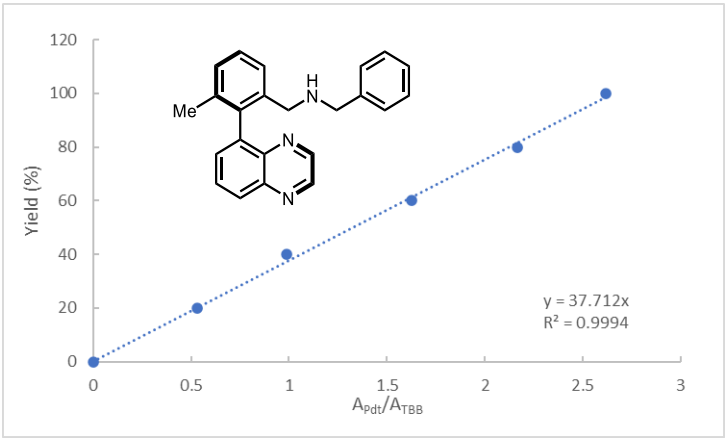


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.383	FM	19893.3	1801	0.1841	49.899	0.777
2	8.309	MF	19973.9	1247.1	0.2669	50.101	0.676



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.558	MF	4985	427.4	0.1944	91.067	0.812
2	8.78	MF	489	26.4	0.3082	8.933	0.786

(*S*)-*N*-Benzyl-1-[3-methyl-2-(quinoxalin-5-yl)phenyl]methanamine (**24**)

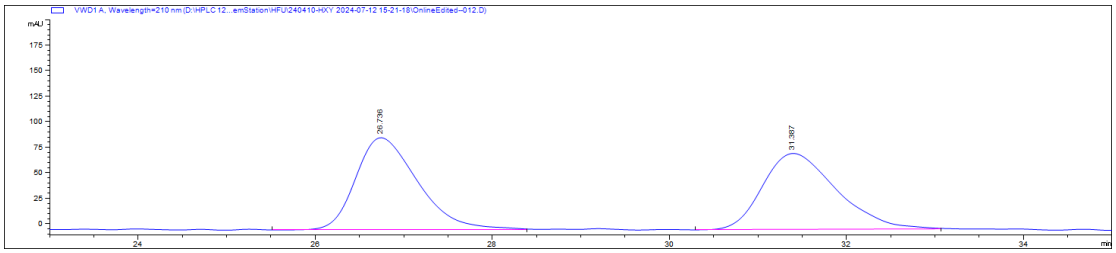


Prepared according to the general procedure 1 using substrate **5i** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

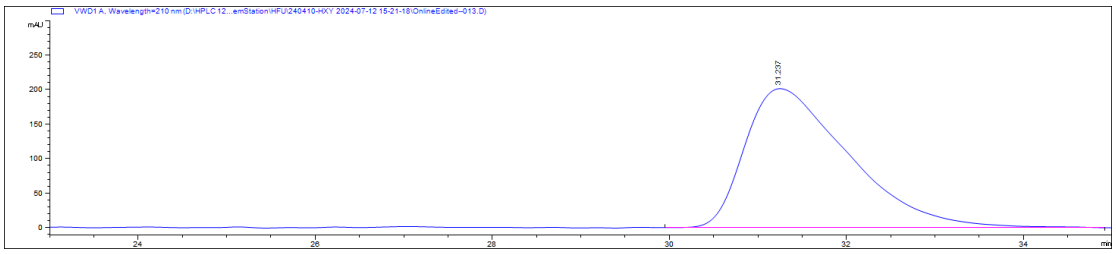
Yields: run 1: 94%, run 2: 93%, average yield 94%.

Preparative enzymatic reaction was conducted according to the general procedure 2 using **5i** (0.1 mmol, 1 equiv) and benzylamine **6a** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%). **Isolated yield**: 81% (yellow amorphous, 27 mg).

Enantioselectivity: >99:1 er. Chiral HPLC method: OD-H column, 210 nm, 2% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 31.24 min.

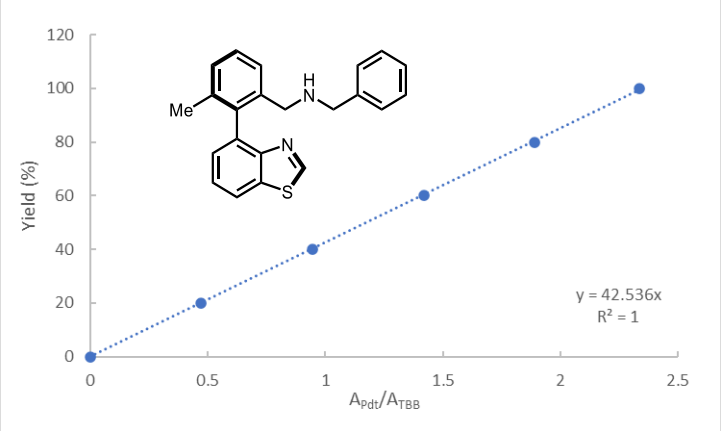


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.736	MF	4400.6	90	0.8149	50.524	0.666
2	31.387	MF	4309.3	74.3	0.9667	49.476	0.695



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	31.237	BB	16366.5	200.7	1.1893	100.000	0.481

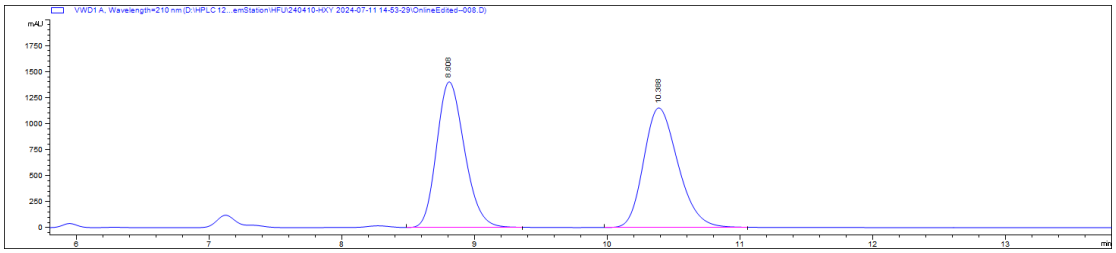
(*S*)-*N*-[2-(Benzo[*d*]thiazol-4-yl)-3-methylbenzyl]-1-phenylmethanamine (**25**)



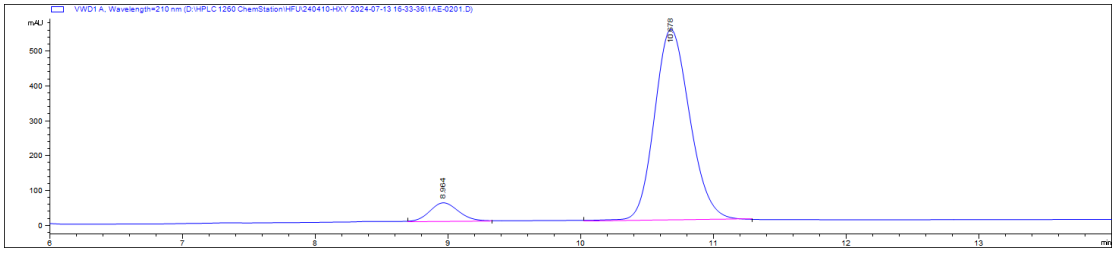
Prepared according to the general procedure 1 using substrate **5j** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 85%, run 2: 84%, average yield 84%.

Enantioselectivity: 92:8 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 8.96 min, t_R (major) = 10.68 min.

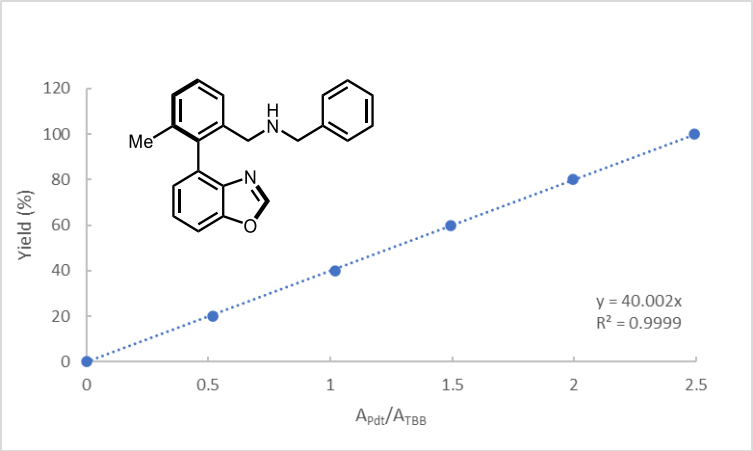


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.808	MF	20559.6	1405.8	0.2437	49.678	0.793
2	10.388	MF	20826.4	1153.8	0.3008	50.322	0.766



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.964	MF	872.8	55.1	0.2641	7.895	0.86
2	10.678	MM	10183.5	549.3	0.309	92.105	0.844

(*S*)-*N*-[2-(Benzo[*d*]oxazol-4-yl)-3-methylbenzyl]-1-phenylmethanamine (**26**)



Prepared according to the general procedure 1 using substrate **5k** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%) or *S*-IRED-*Ss*-C8 (0.2 mol%).

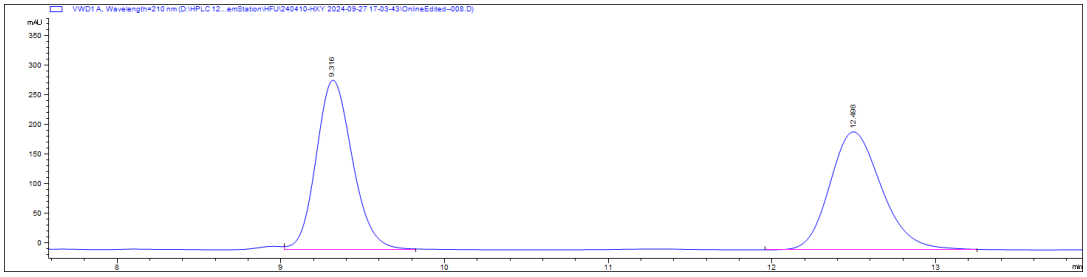
S-IRED-*Ss*-M14

Yields: run 1: 68%, run 2: 69%, average yield 68%. **Enantioselectivity**: 60:40 er.

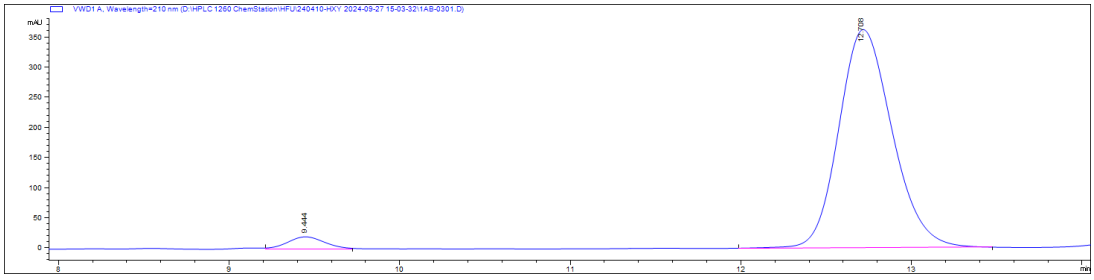
S-IRED-*Ss*-C8 (M236A/P122Y/F214W based on *S*-IRED-*Ss*-M9)

Yields: run 1: 78%, run 2: 85%, average yield 82%. **Enantioselectivity**: 96:4 er.

Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.44 min, t_R (major) = 12.71 min.

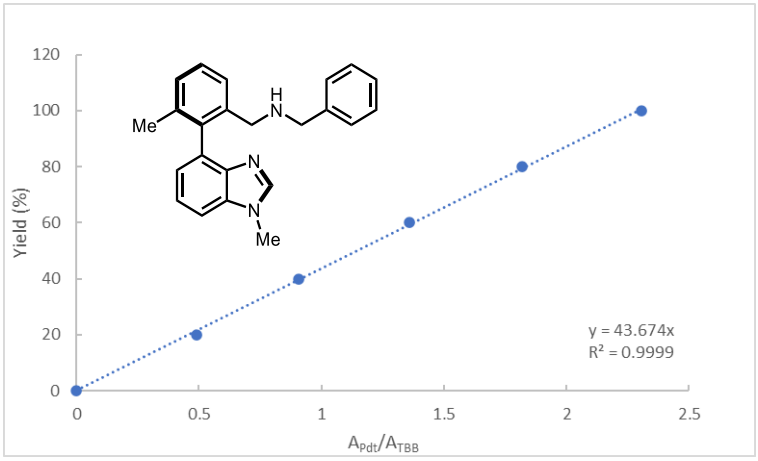


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.316	FM	4423.4	286.4	0.2574	50.223	0.837
2	12.498	MF	4384.1	199.3	0.3667	49.777	0.812



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.444	MF	313	20.5	0.2548	3.815	0.904
2	12.708	MF	7893.1	362.5	0.3629	96.185	0.821

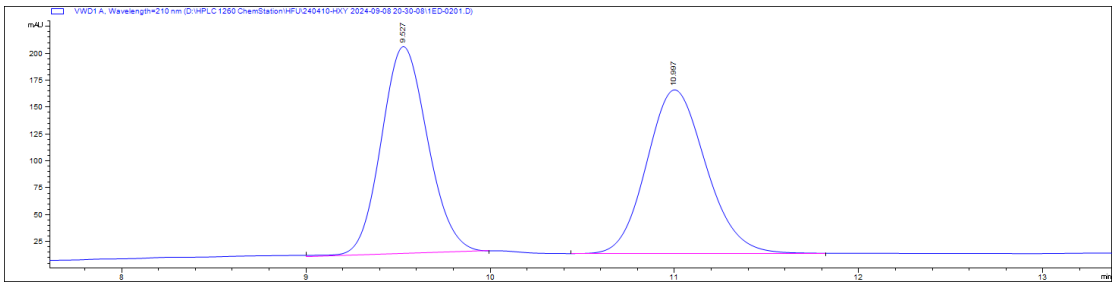
(*S*)-*N*-Benzyl-1-[3-methyl-2-(1-methyl-1H-benzo[*d*]imidazol-4-yl)phenyl]methanamine (**27**)



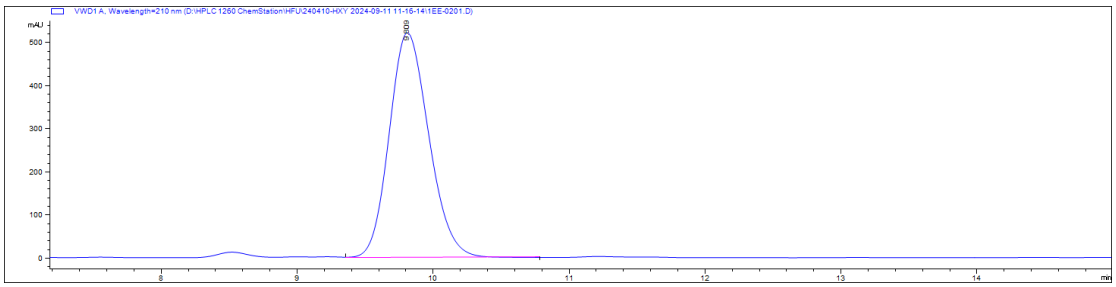
Prepared according to the general procedure 1 using substrate **5l** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M14 (0.2 mol%).

Yields: run 1: 93%, run 2: 94%, average yield 93%.

Enantioselectivity: 99:1 er. Obtained from *N*-Boc protected derivatives of racemic reference and the enzymatic product, respectively. Chiral HPLC method: AD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 9.81 min.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.527	MM	3363.4	192.3	0.2915	49.466	0.898
2	10.997	MM	3436	152.4	0.3757	50.534	0.861



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.809	VB	10595.7	522.4	0.3167	100.000	0.807

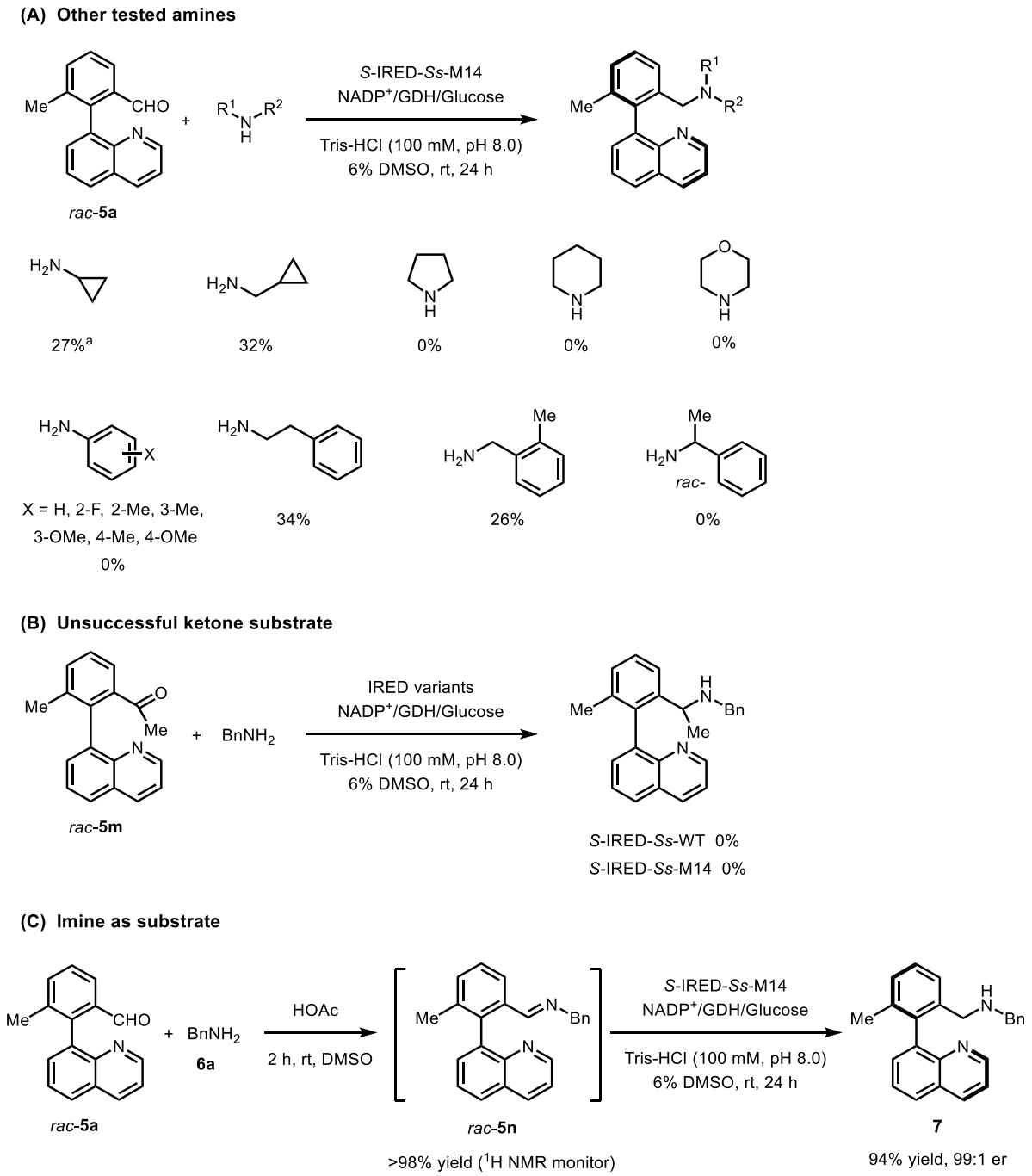
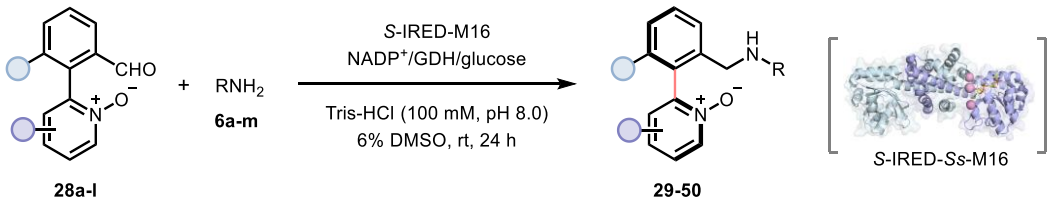


Fig. S6. (A) Amines not well accepted by *S*-IRED-*Ss*-M14. (B) Unsuccessful ketone substrate. Reaction conditions: **5a** (5 μmol, 1 equiv), amines (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), *S*-IRED-*Ss*-M14 (0.2 mol%) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature (rt) for 24 h, the final total volume is 1000 μL. [a] Conversion (average of duplicate) determined *via* LCMS relative to an internal standard 1,3,5-tribromobenzene. (C) Imine as substrate. The imine (>98% yield, monitored by NMR) was formed in situ over 2 hour from **5a** (1 equiv), $BnNH_2$ (3 equiv), and HOAc (0.5 equiv), then directly used in the enzymatic reaction.

Enzymatic atroposelective DKR for the synthesis of heterobiaryl *N*-oxide amines



28a-l **29-50**

General procedure 4 for analytical scale reaction

A screw vial (4 mL) was charged with *Bm*GDH (200 μL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), glucose (54 μL, 50 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), $NADP^+$ (15 μL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), *S*-IRED-*Ss*-M16 protein (0.2 mol% or 0.4 mol% catalyst loading), aldehyde (30 μL, 167 mM stock in DMSO, 5 μmol, 1 equiv) and amine (30 μL, 500 mM stock in DMSO, 15 μmol, 3 equiv). Tris-HCl buffer (100 mM pH 8.0) was added to bring the total volume to 1000 μL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed and placed on a shaker at 200 rpm at room temperature for 24 hours. Upon completion, the reaction was quenched with 3 mL of acetonitrile and 100 μL of 5 mg/mL 1,3,5-tribromobenzene (TBB) in acetonitrile as the internal standard. The mixture was shaken for 30 min, centrifuged (13,400 x g, 5 mins), and the supernatant was filtered and retained for LCMS analysis for yield calculation. After LCMS analysis, the supernatant was concentrated under reduced pressure, extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was dissolved in 30% isopropanol/hexanes (*v*/*v*) for chiral HPLC analysis.

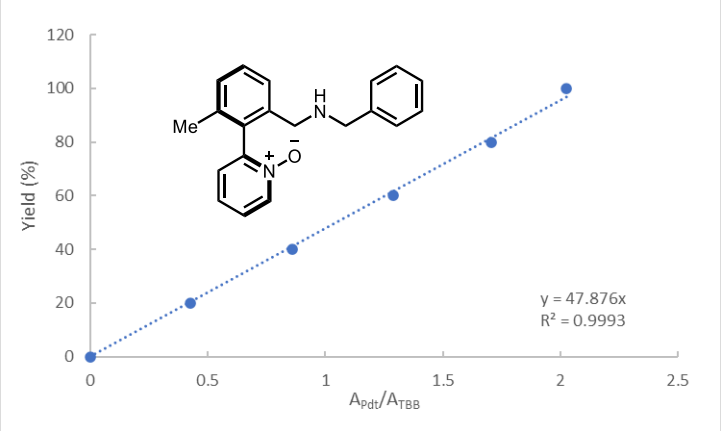
General procedure 5 for preparative scale reaction using purified enzyme

A round bottle (100 mL) was charged with *Bm*GDH (4 mL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), glucose (1.08 mL, 50 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), $NADP^+$ (0.3 mL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), *S*-IRED-*Ss*-M16 protein (0.2 mol% catalyst loading), aldehyde (0.6 mL, 167 mM stock in DMSO, 0.1 mmol, 1 equiv) and amine (0.6 mL, 500 mM stock in DMSO, 0.3 mmol, 3 equiv). Tris-HCl buffer (100 mM pH 8.0) was added to bring the total volume to 20 mL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed and placed on a shaker at 200 rpm at room temperature for 24 hours. Upon completion, the reaction was quenched with 20 mL of acetonitrile. The mixture was shaken for 30 min, filtered, concentrated, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by Flash chromatography (MeOH/DCM, 5~10%, *v*/*v*).

General procedure 6 for preparative scale reaction using lyophilized CFE

A round bottle (250 mL) was charged with *BmGDH* (40 mL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), glucose (10.8 mL, 50 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), $NADP^+$ (3 mL, 5 mg/mL stock solution in 100 mM Tris-HCl buffer pH 8.0), lyophilized *S*-IRED-*Ss*-M16 CFE (800 mg), aldehyde substrate (6 mL, 167 mM stock in DMSO, 1 mmol, 1 equiv) and amine substrate (6 mL, 500 mM stock in DMSO, 3 mmol, 3 equiv). Tris-HCl buffer (100 mM pH 8.0) was added to bring the total volume to 200 mL with 6% DMSO (*v*/*v*) as cosolvent. The vial was sealed and placed on a shaker at 200 rpm at room temperature for 24 hours. Upon completion, the reaction was quenched with 200 mL of acetonitrile. The mixture was shaken for 30 min, filtered, concentrated, and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by Flash chromatography (MeOH/DCM, 5~10%, *v*/*v*).

(*S*)-2-{2-[(Benzylamino)methyl]-6-methylphenyl}pyridine 1-oxide (**29**)

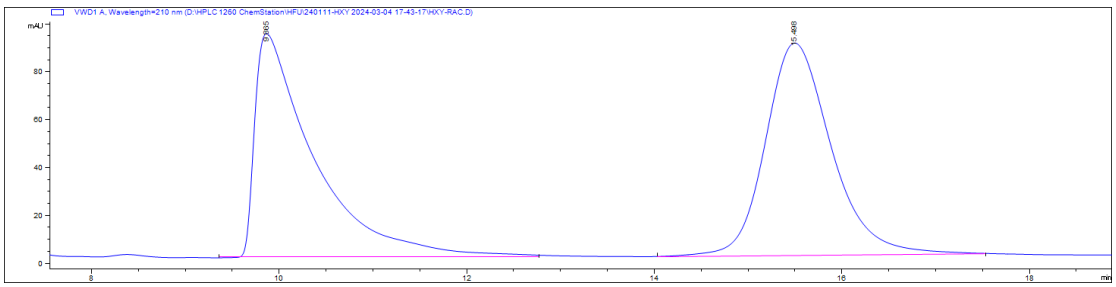


Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%). **Yields**: run 1: 98%, run 2: 97%, average yield 98%.

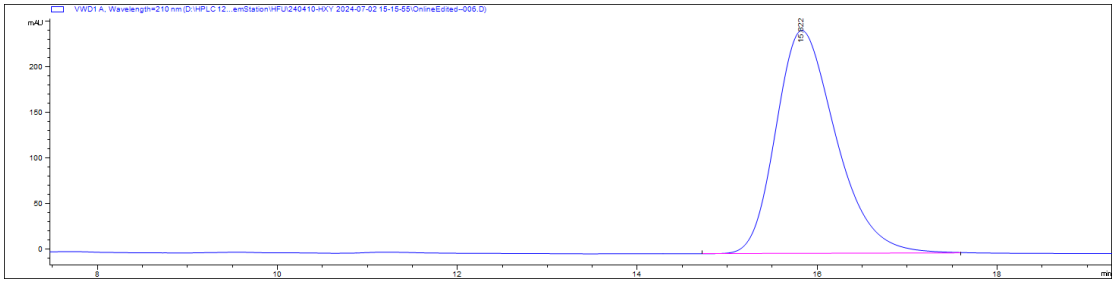
0.1-mmol-scale reaction was conducted according to the general procedure 5 using **28a** (0.1 mmol, 1 equiv) and **6a** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%). **Isolated yield**: 86% (white solid, 26 mg).

1.0-mmol-scale preparative reaction was conducted according to the general procedure 6 using **28a** (1 mmol, 1 equiv) and **6a** (3 mmol, 3 equiv) catalyzed by lyophilized *S*-IRED-*Ss*-M16 CFE (4 mg/mL). **Isolated yield**:76% (white solid, 231 mg).

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 15.82 min. **Absolute configuration** of the enzymatic product **29** was assigned as ***S*** by X-ray crystallography.

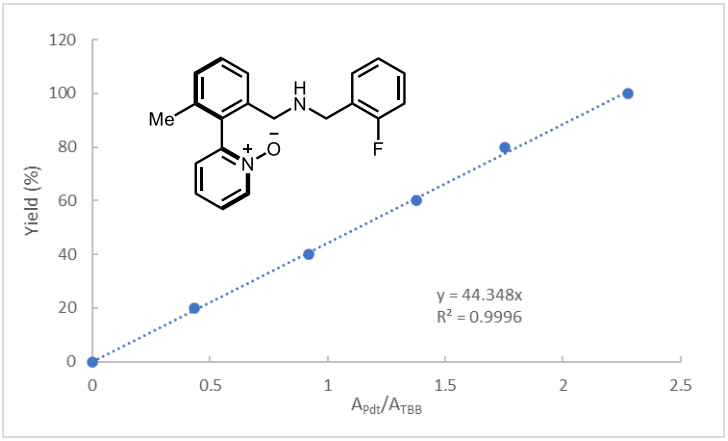


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.865	MF	4127.4	93.8	0.7337	48.313	0.239
2	15.498	MF	4415.7	89.1	0.8257	51.687	0.767



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.822	BB	11450.8	244.9	0.7195	100.000	0.704

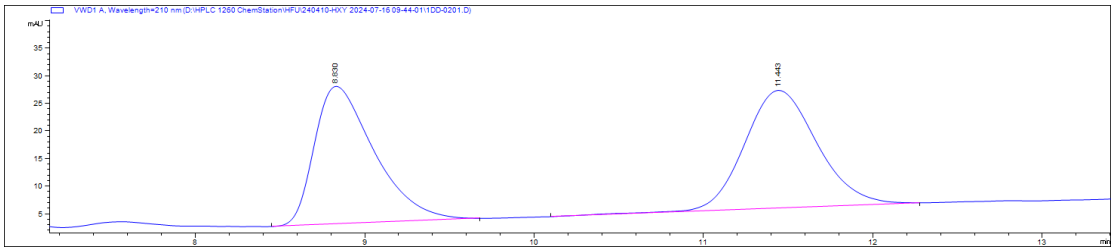
(*S*)-2-{2-{[(2-Fluorobenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**30**)



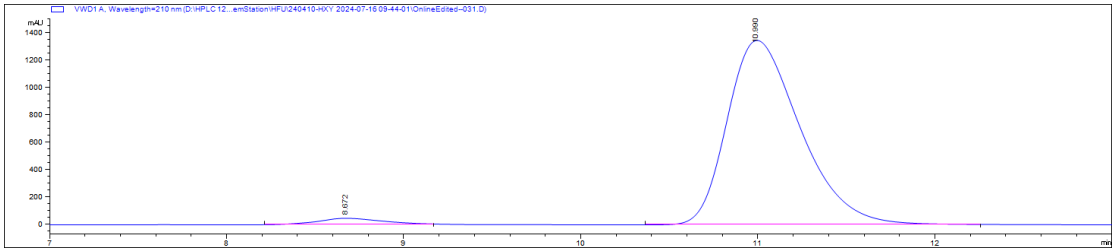
Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and (2-fluorophenyl)methanamine **6b** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1:89%, run 2: 95%, average yield 92%.

Enantioselectivity: 97:3 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 8.67 min, t_R (major) = 10.99 min.

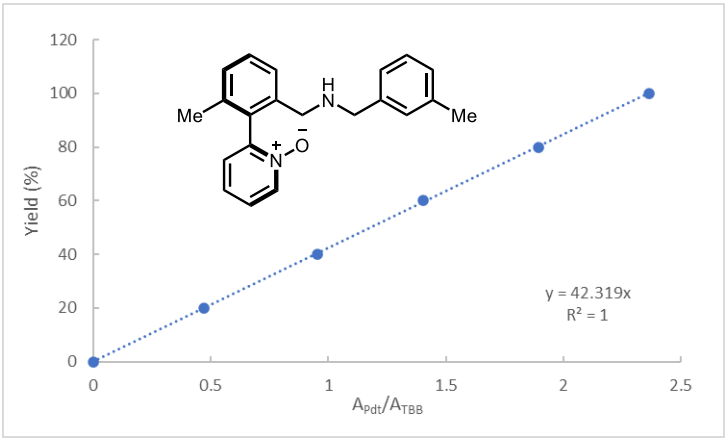


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.83	BB	611.9	24.9	0.3731	49.212	0.539
2	11.443	FM	631.5	21.3	0.4946	50.788	0.865



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.672	FM	1253.9	47.4	0.441	3.138	0.739
2	10.99	MF	38704.4	1348	0.4785	96.862	0.667

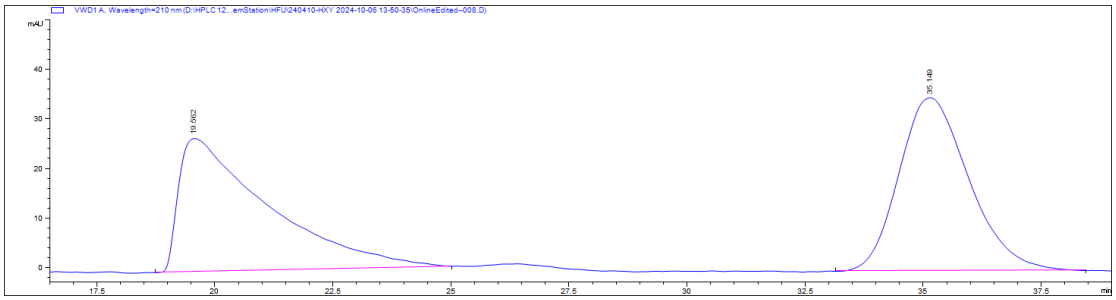
(*S*)-2-{2-Methyl-6-{[(3-methylbenzyl)amino]methyl}phenyl}pyridine 1-oxide (**31**)



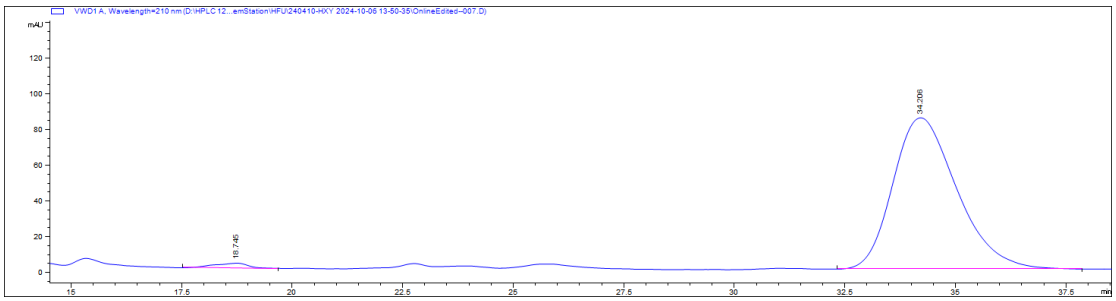
Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and *m*-tolylmethanamine **6c** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 64%, run 2: 64%, average yield 64%.

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 18.75 min, t_R (major) = 34.21 min.

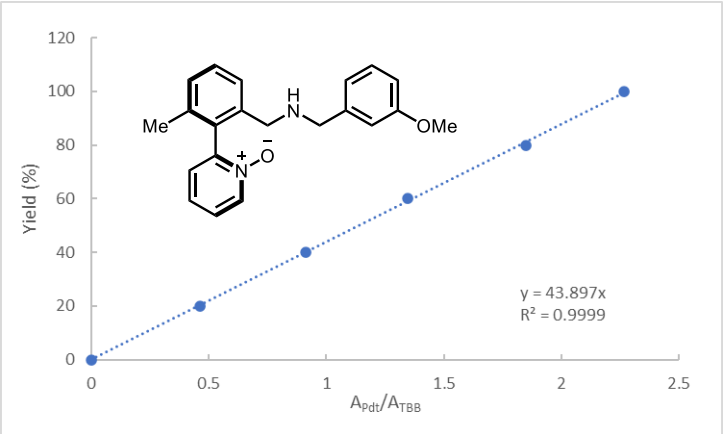


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.562	BB	3525.1	26.9	1.7551	49.461	0.199
2	35.149	BB	3601.9	34.9	1.557	50.539	0.773



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.745	MM	175.2	3	0.9722	2.011	1.631
2	34.206	BB	8536.3	84.7	1.5541	97.989	0.729

(*S*)-2-{2-{[(3-Methoxybenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**32**)

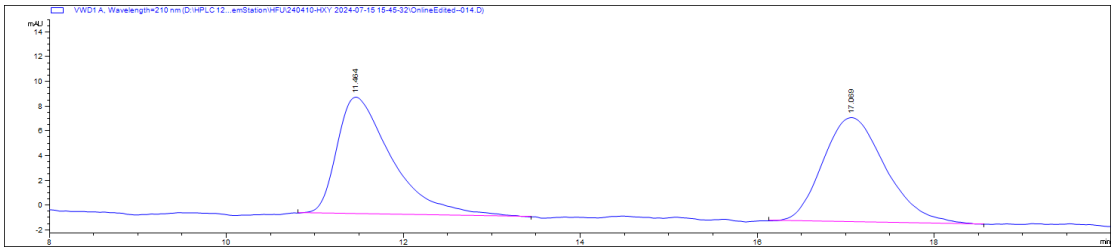


Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and (3-methoxyphenyl)methanamine **6d** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

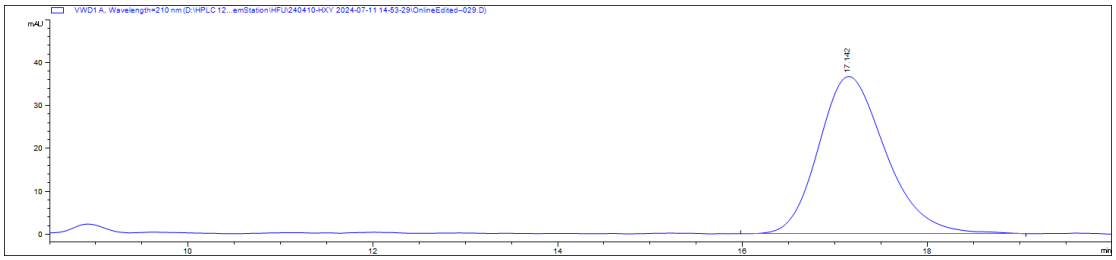
Yields: run 1: 90%, run 2: 89%, average yield 90%.

Preparative enzymatic reaction was conducted according to the general procedure 5 using **28a** (0.1 mmol, 1 equiv) and **6d** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%). **Isolated yield**: 75% (yellow solid, 25 mg).

Enantioselectivity: >99:1 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 17.14 min.

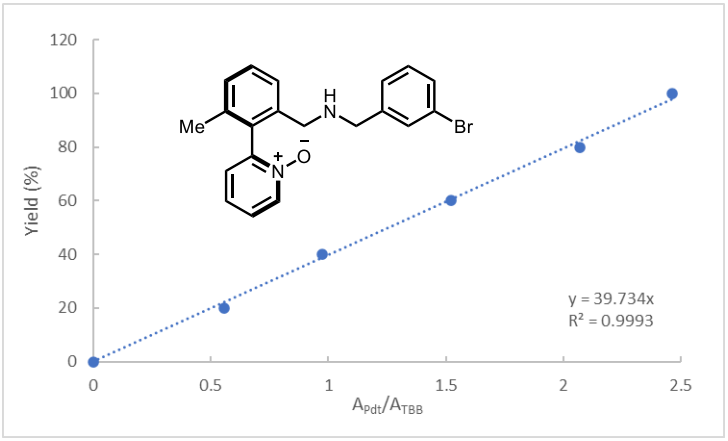


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.464	BB	410.4	9.5	0.6493	49.471	0.485
2	17.069	BB	419.2	8.5	0.7733	50.529	0.804



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.142	BB	1845.9	36.6	0.7745	100.000	0.779

(*S*)-2-{2-{[(3-Bromobenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**33**)

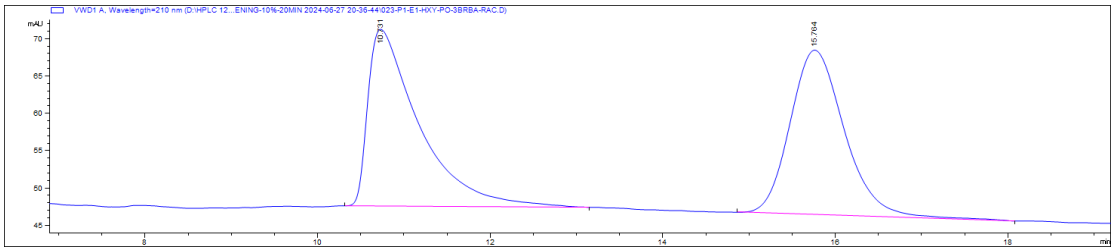


Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and (3-bromophenyl)methanamine **6e** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

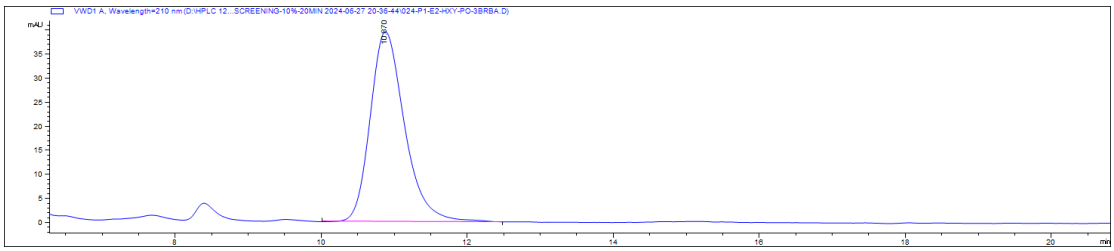
Yields: run 1: 81%, run 2: 84, average yield 82%.

Preparative enzymatic reaction was conducted according to the general procedure 5 using **28a** (0.1 mmol, 1 equiv) and **6e** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%). **Isolated yield**: 65% (yellow solid, 25 mg).

Enantioselectivity: >99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 10.87 min.

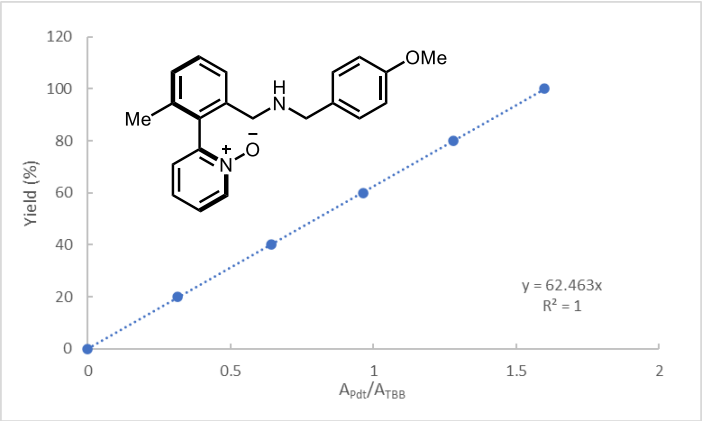


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.731	BB	973.5	23.6	0.5985	50.151	0.302
2	15.764	BB	967.7	22	0.6787	49.849	0.77



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.87	BB	1301.9	39.7	0.5002	100.000	0.742

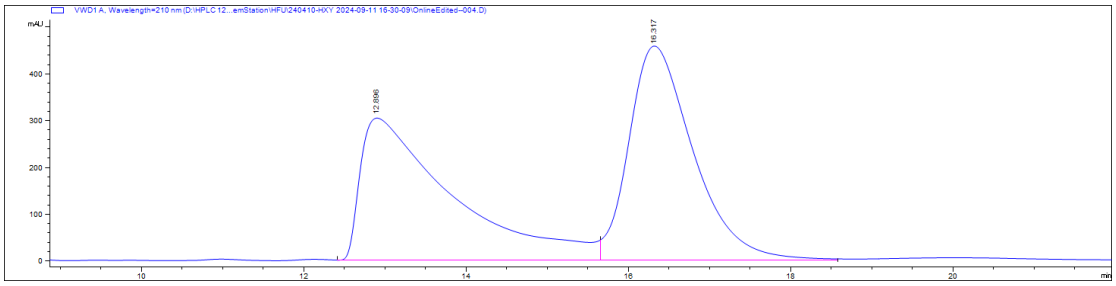
(*S*)-2-{2-{[(4-Methoxybenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**34**)



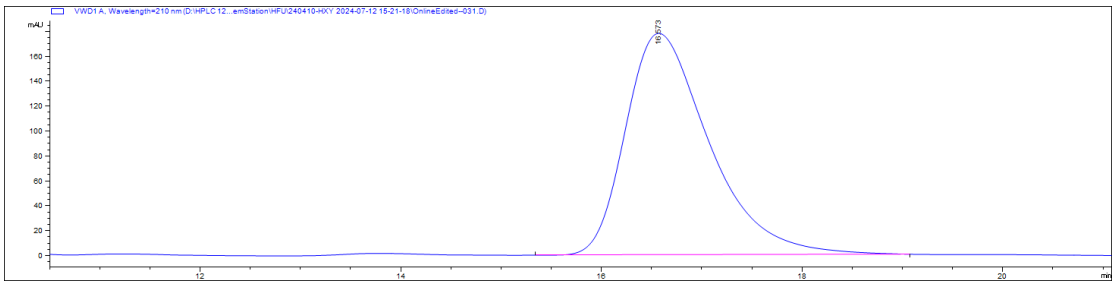
Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and (4-methoxyphenyl)methanamine **6f** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 59%, run 2: 62%, average yield 61%.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 16.57 min.

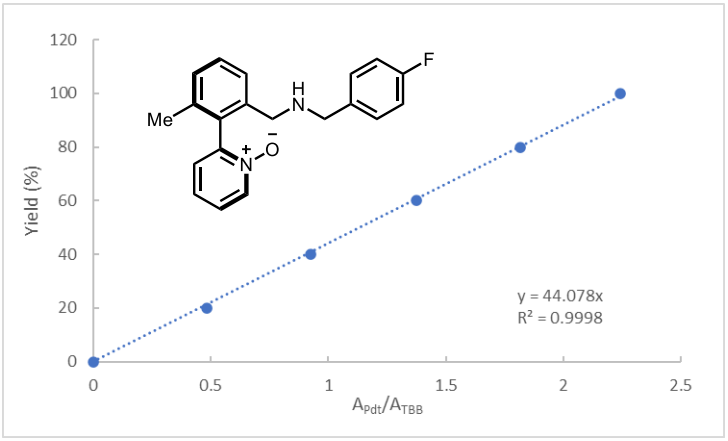


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.896	MF	24174.5	305.8	1.3178	48.715	0
2	16.317	FM	25449.8	460.2	0.9218	51.285	0.627



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	16.573	MF	10422.5	178.8	0.9713	100.000	0.634

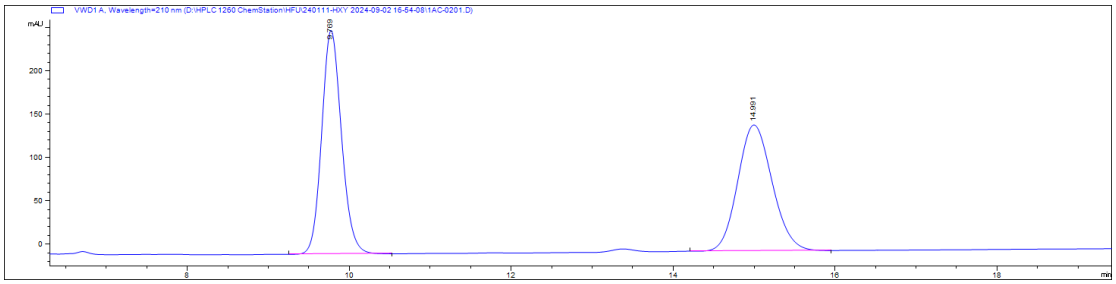
(*S*)-2-{2-{[(4-Fluorobenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**35**)



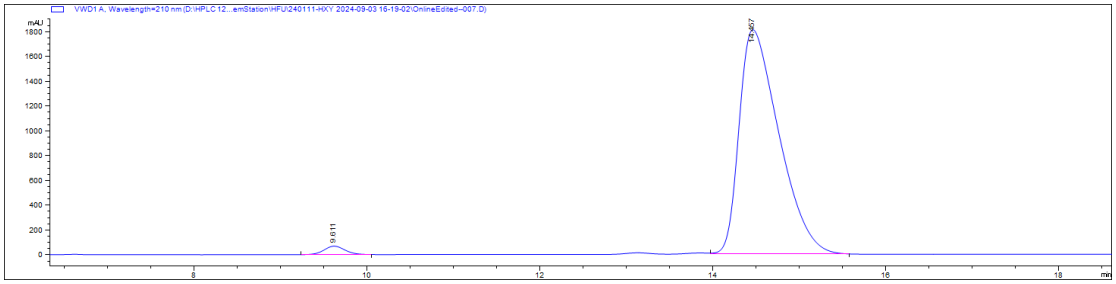
Prepared according to the general procedure 4 using substrate **28a** (5 µmol, 1 equiv) and (4-fluorophenyl)methanamine **6k** (15 µmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 88%, run 2: 82, average yield 85%.

Enantioselectivity: 98:2 er. Obtained from *N*-Boc protected derivatives of racemic reference and the enzymatic product, respectively Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.61 min, t_R (major) = 14.46 min.

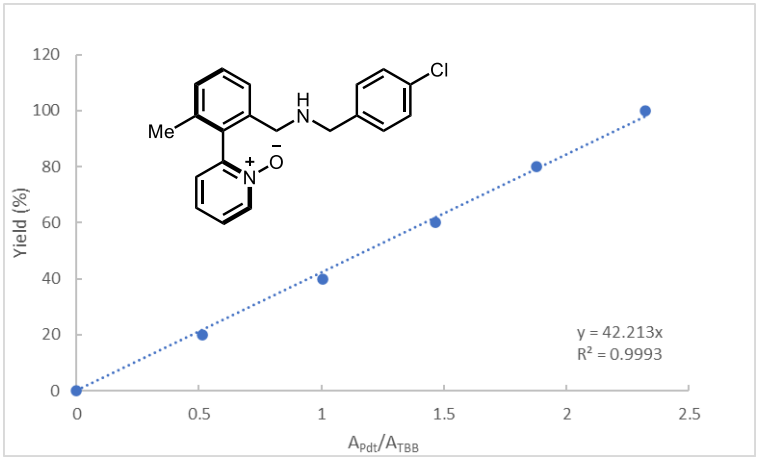


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.769	BB	4372.7	257.4	0.2622	50.425	0.85
2	14.991	FM	4299	145.1	0.4937	49.575	0.869



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.611	FM	1167.3	68.5	0.2841	1.974	0.906
2	14.457	MF	57975.8	1808.5	0.5343	98.026	0.514

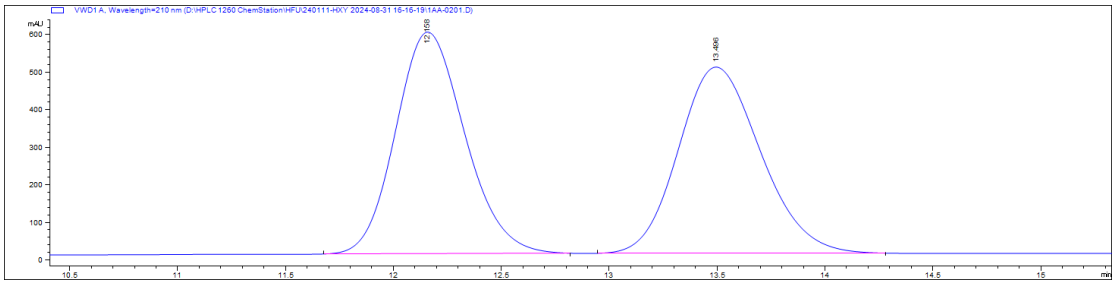
(*S*)-2-{2-{[4-Chlorobenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**36**)



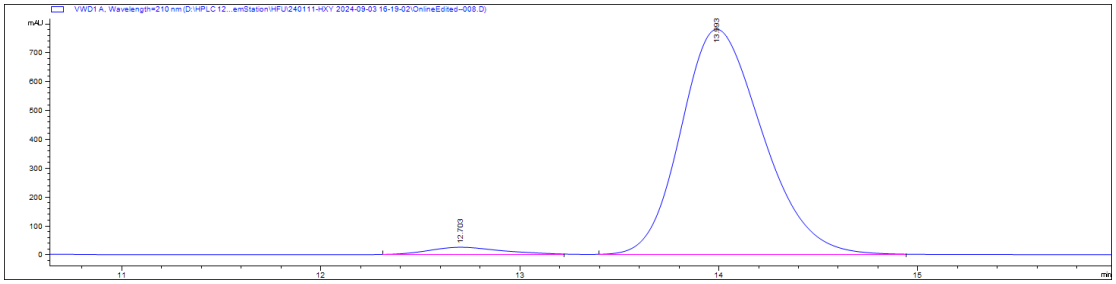
Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and (4-chlorophenyl)methanamine **6l** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.4 mol%).

Yields: run 1: 71%, run 2: 74%, average yield 72%.

Enantioselectivity: 97:3 er. Obtained from *N*-Boc protected derivatives of racemic reference and the enzymatic product, respectively Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 12.70 min, t_R (major) = 13.99 min.

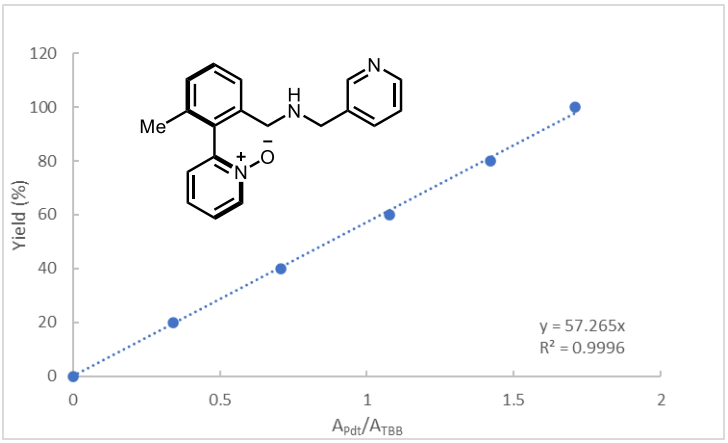


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.158	MF	13247.9	593.3	0.3721	49.973	0.841
2	13.496	MF	13262.4	498.7	0.4432	50.027	0.822



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.703	MF	682.4	25.6	0.4446	2.986	0.755
2	13.993	MF	22175.1	777.7	0.4752	97.014	0.766

(*S*)-2-{2-Methyl-6-{[(pyridin-3-ylmethyl)amino]methyl}phenyl}pyridine 1-oxide (**37**)

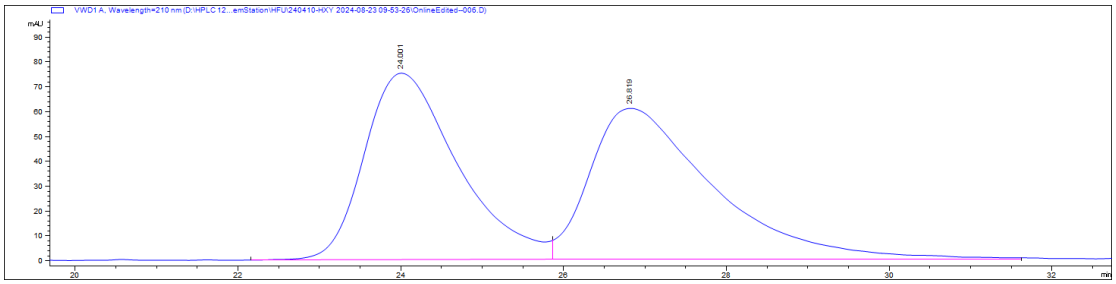


Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and pyridin-3-ylmethanamine **6h** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

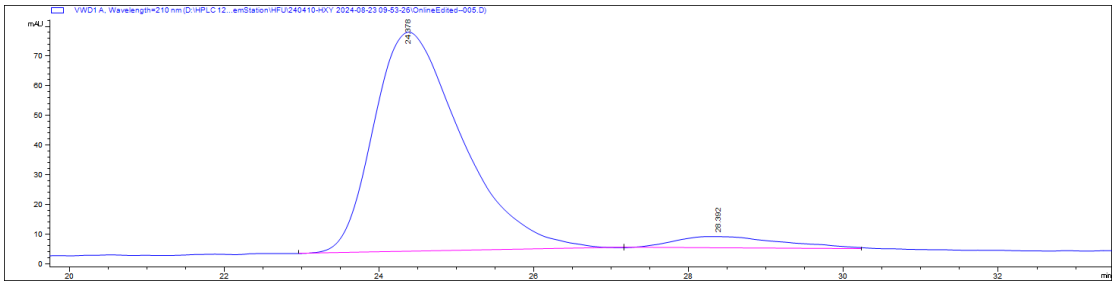
Yields: run 1: 90%, run 2: 83%, average yield 86%.

Preparative enzymatic reaction was conducted according to the general procedure 5 using **28a** (0.1 mmol, 1 equiv) and **6h** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%). **Isolated yield**: 79% (yellow solid, 25 mg).

Enantioselectivity: 94:6 er. Chiral HPLC method: OD-H column, 210 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 24.38 min, t_R (minor) = 28.39 min.

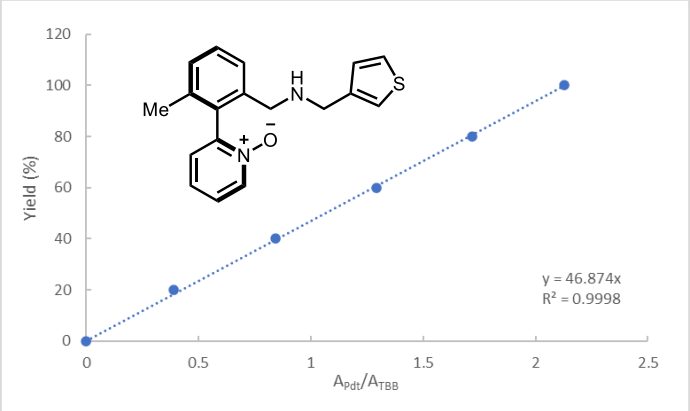


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	24.001	MF	6042.2	75.4	1.3363	48.360	0
2	26.819	FM	6452	61.1	1.7613	51.640	0.477



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	24.378	BB	5887.6	74.3	1.1981	93.609	0.621
2	28.392	MF	401.9	4	1.6904	6.391	0.536

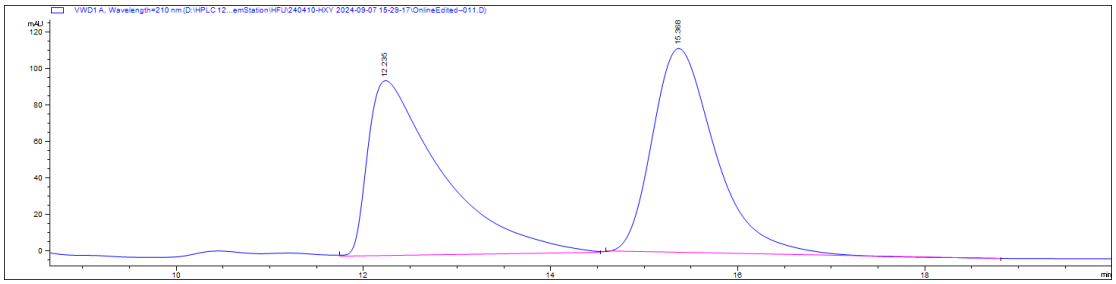
(*S*)-2-{2-methyl-6-{[(thiophen-3-ylmethyl)amino]methyl}phenyl}pyridine 1-oxide (**38**)



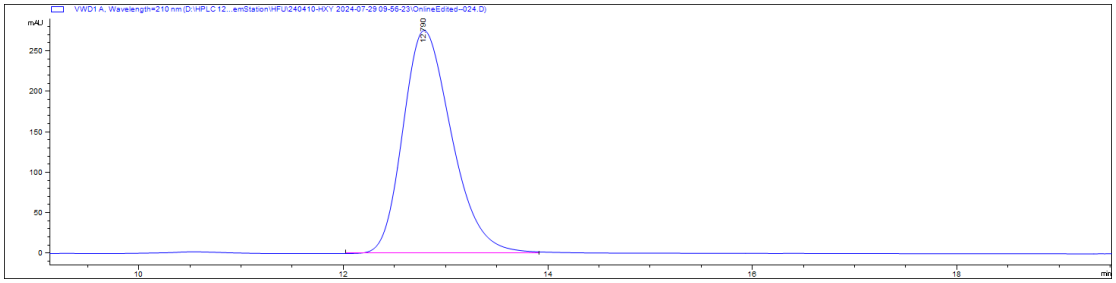
Prepared according to the general procedure 4 using substrate **28a** (5 μmol, 1 equiv) and thiophen-3-ylmethanamine **6m** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 90%, run 2: 83%, average yield 87%.

Enantioselectivity: >99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 12.79 min.

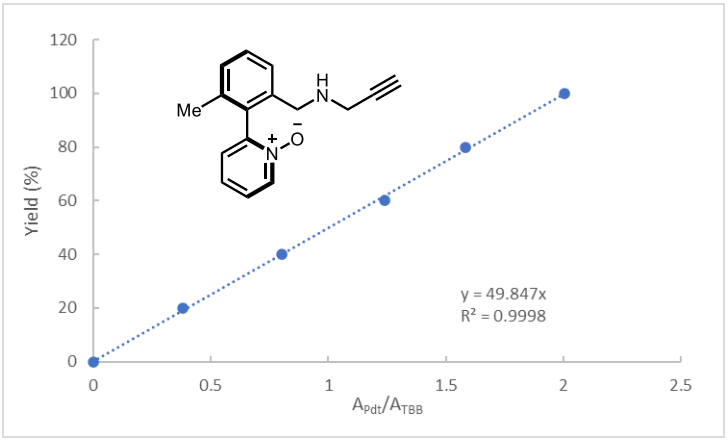


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.235	MM	5280.1	96.1	0.9159	49.898	0.305
2	15.368	MM	5301.7	112.1	0.788	50.102	0.676



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.79	MF	9146.8	275.8	0.5528	100.000	0.742

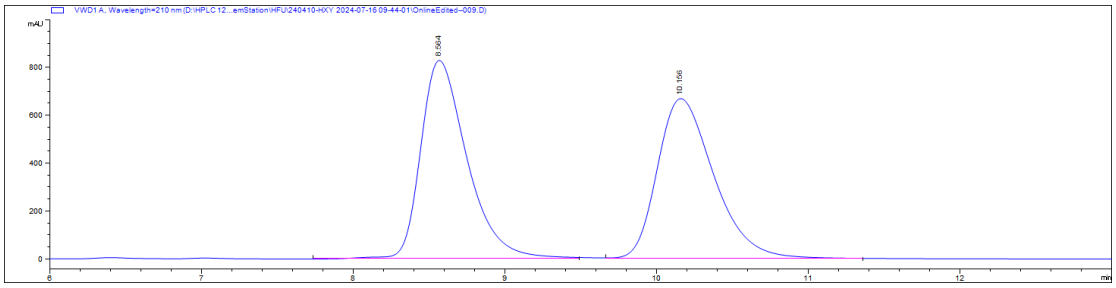
(*S*)-2-{2-Methyl-6-[(prop-2-yn-1-ylamino)methyl]phenyl}pyridine 1-oxide (**39**)



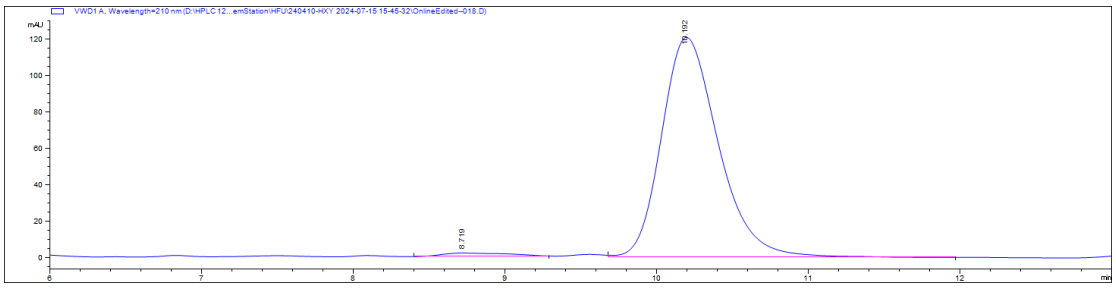
Prepared according to the general procedure 4 using substrate **28a** (5 µmol, 1 equiv) and prop-2-yn-1-amine **6j** (15 µmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.4 mol%).

Yields: run 1: 79%, run 2: 72%, average yield 76%.

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 8.72 min, t_R (major) = 10.19 min.

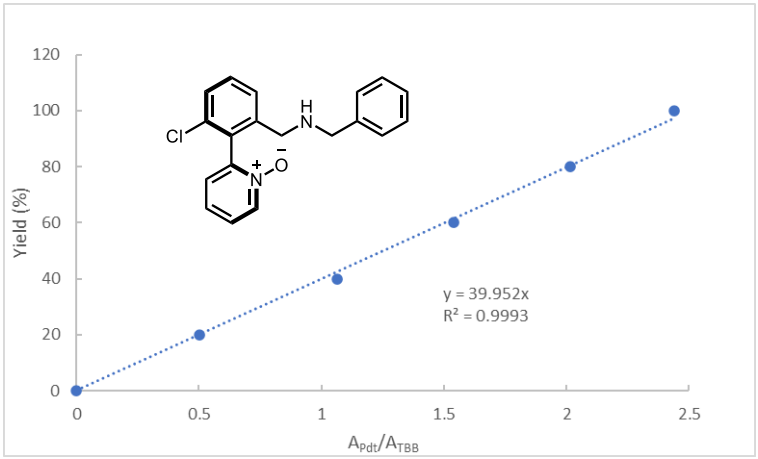


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.564	MF	17720.8	830.2	0.3558	50.296	0.648
2	10.156	MF	17512.1	670.7	0.4352	49.704	0.681



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.719	MM	72.8	2.1	0.5722	2.267	0.426
2	10.192	FM	3140.3	120.7	0.4338	97.733	0.751

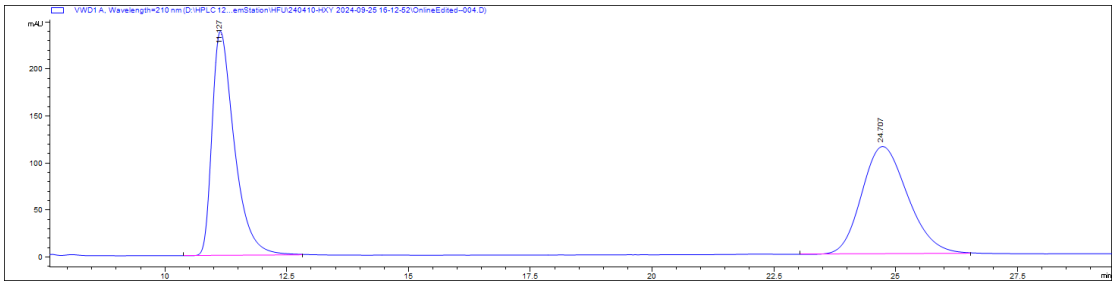
(*R*)-2-{2-[(benzylamino)methyl]-6-chlorophenyl}pyridine 1-oxide (**40**)



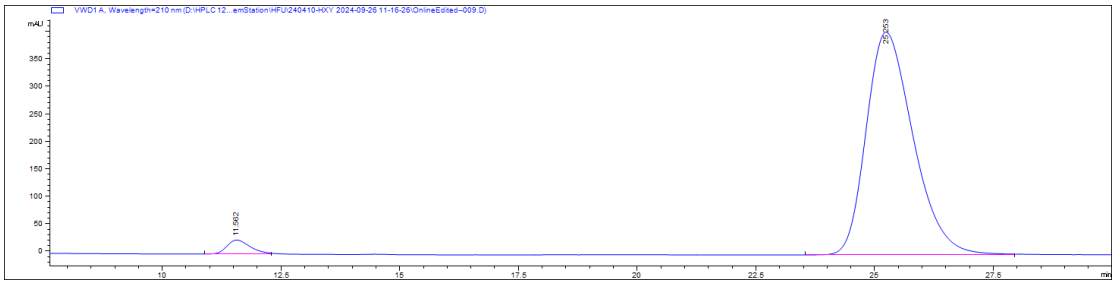
Prepared according to the general procedure 1 using substrate **28b** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 78%, run 2: 79%, average yield 78%.

Enantioselectivity: 97:3 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 11.56 min, t_R (major) = 25.25 min.

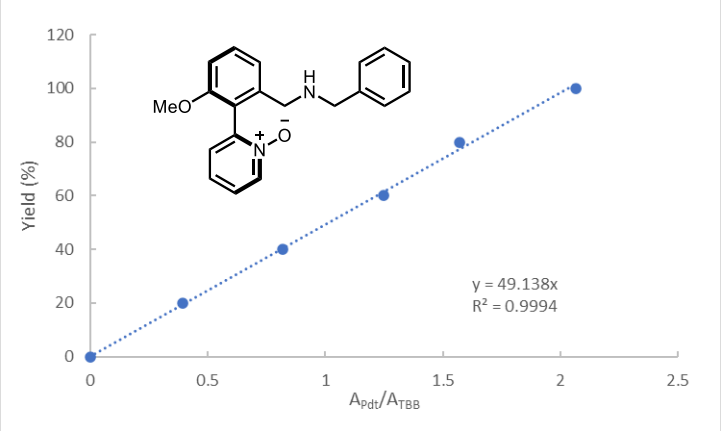


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.127	MF	7606	238.7	0.531	50.136	0.57
2	24.707	MF	7564.8	114.6	1.1002	49.864	0.805



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.562	MF	880.8	25.7	0.5721	3.051	0.69
2	25.253	MF	27991	407.1	1.1459	96.949	0.708

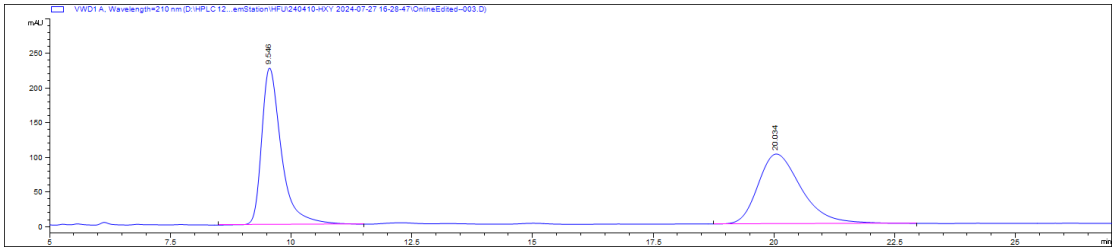
(*R*)-2-{2-[(Benzylamino)methyl]-6-methoxyphenyl}pyridine 1-oxide (**41**)



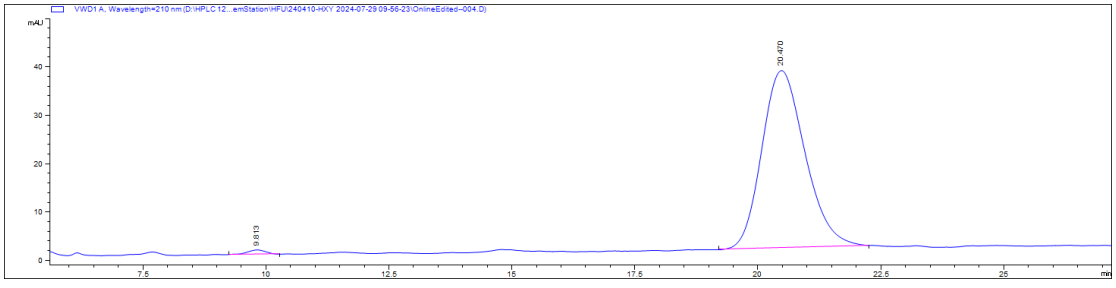
Prepared according to the general procedure 4 using substrate **28c** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 88%, run 2: 90%, average yield 89%.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.81 min, t_R (major) = 20.47 min.

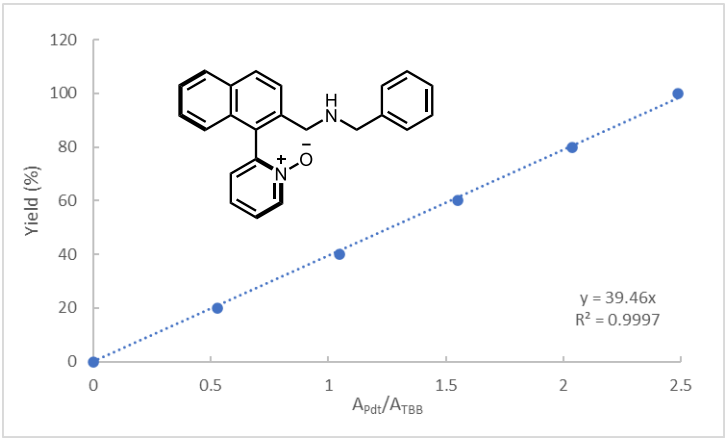


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.546	BB	6414.6	225.6	0.4277	50.692	0.609
2	20.034	BB	6239.5	100.5	0.9587	49.308	0.687



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.813	MM	29.6	1	0.4886	1.300	1.235
2	20.47	BB	2249.5	36.9	0.9382	98.700	0.811

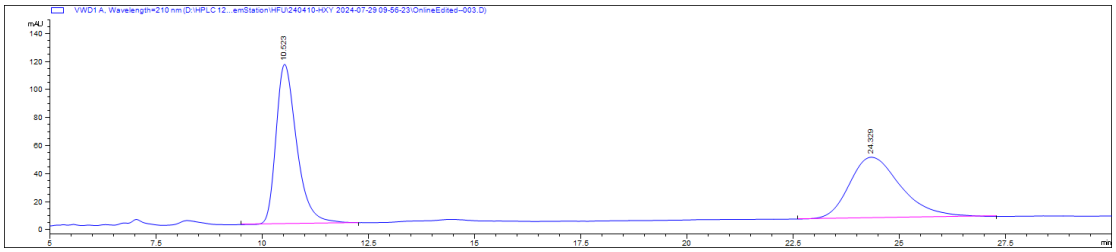
(*S*)-2-{2-[(Benzylamino)methyl]naphthalen-1-yl}pyridine 1-oxide (**42**)



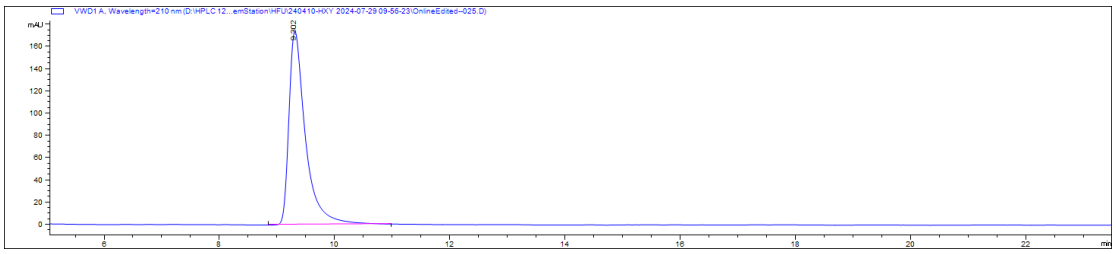
Prepared according to the general procedure 4 using substrate **28d** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 78%, run 2: 79%, average yield 78%.

Enantioselectivity: >99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 9.30 min.

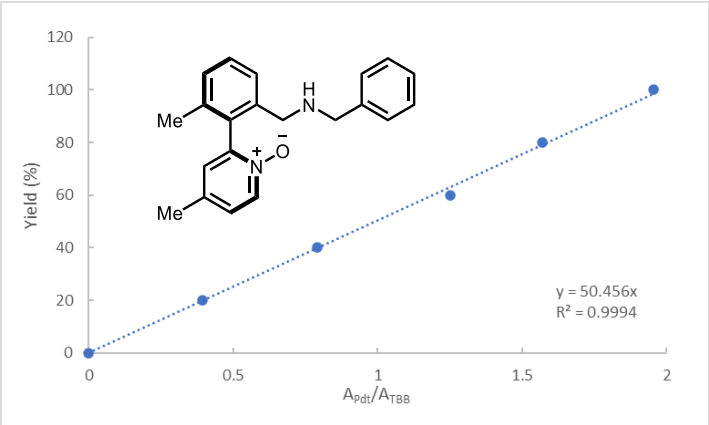


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.523	BB	3855	113.8	0.5173	51.106	0.663
2	24.329	BB	3688.2	43.4	1.2826	48.894	0.692



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.302	BB	3486	174.7	0.2949	100.000	0.507

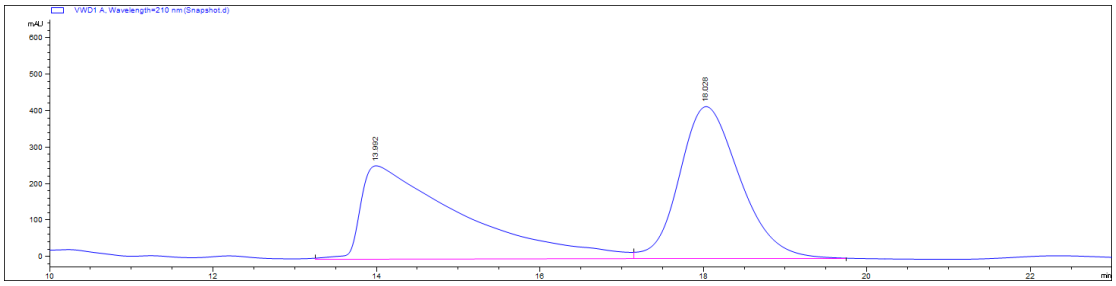
(*S*)-2-{2-[(benzylamino)methyl]-6-methylphenyl}-4-methylpyridine 1-oxide (**43**)



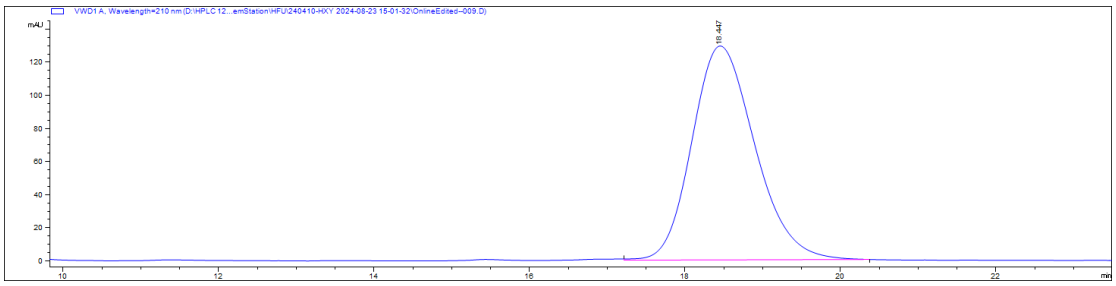
Prepared according to the general procedure 4 using substrate **28e** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 70%, run 2: 82%, average yield 76%.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 18.45 min.

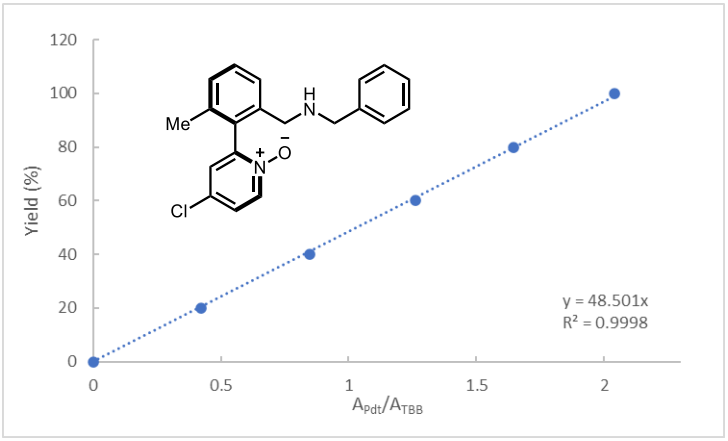


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.992	MF	22415	258.4	1.4457	50.800	0
2	18.028	FM	21709	419.8	0.8618	49.200	0.768



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.447	MF	7335.1	129.7	0.9427	100.000	0.789

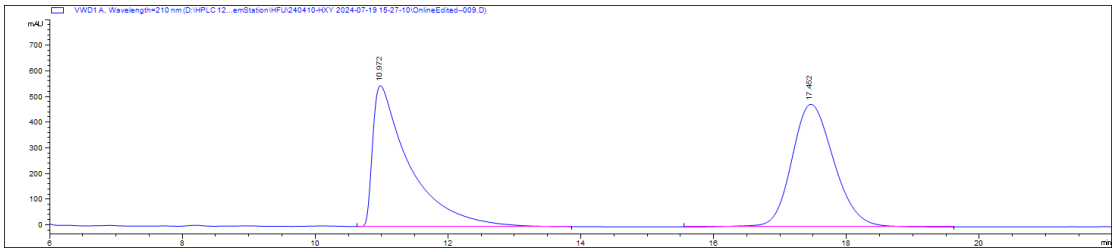
(*S*)-2-{2-[(benzylamino)methyl]-6-methylphenyl}-4-chloropyridine 1-oxide (**44**)



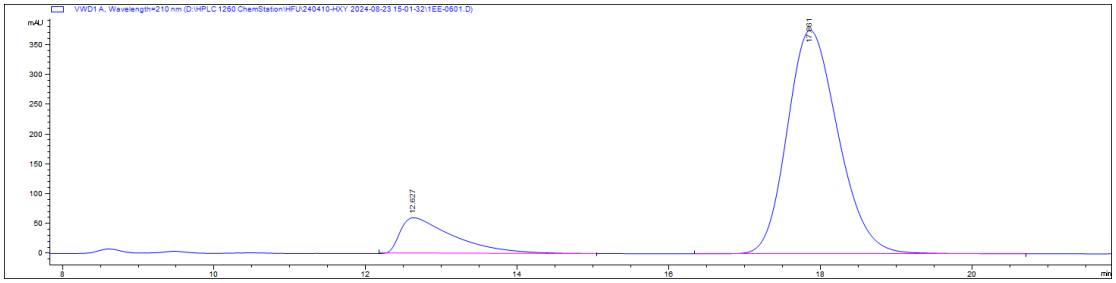
Prepared according to the general procedure 4 using substrate **28f** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.4 mol%).

Yields: run 1: 60%, run 2: 60%, average yield 60%.

Enantioselectivity: 86:14 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 12.63 min, t_R (major) = 17.86 min.

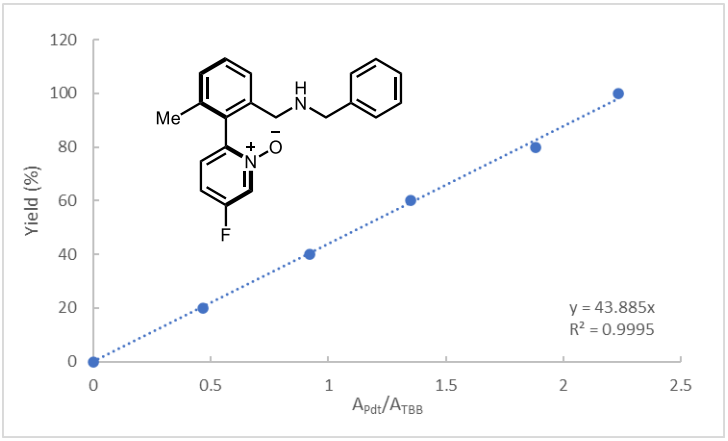


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.972	BB	21151.8	550.4	0.5304	50.024	0.237
2	17.452	BB	21131.4	479	0.6827	49.976	0.805



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.627	MM	2970.2	60.2	0.8226	14.420	0.323
2	17.861	MM	17626.9	375.8	0.7818	85.580	0.792

(*S*)-2-{2-[(Benzylamino)methyl]-6-methylphenyl}-5-fluoropyridine 1-oxide (**45**)



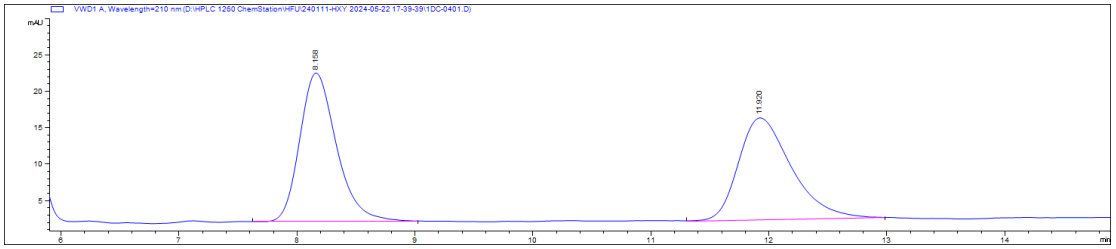
Prepared according to the general procedure 4 using substrate **28g** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 91%, run 2: 93%, average yield 92%.

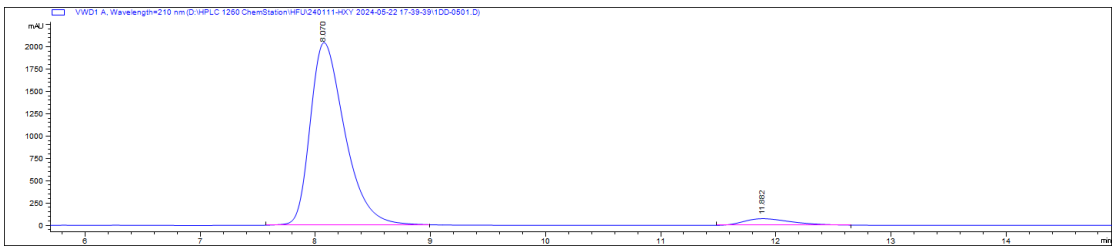
Preparative enzymatic reaction was conducted according to the general procedure 2 using **28g** (0.1 mmol, 1 equiv) and **6a** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%). **Isolated yield**: 75% (white solid, 24 mg).

Enantioselectivity: 95:5 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 8.07 min, t_R (minor) = 11.88 min.

Absolute configuration of the enzymatic product **45** was assigned as ***S*** by X-ray crystallography.

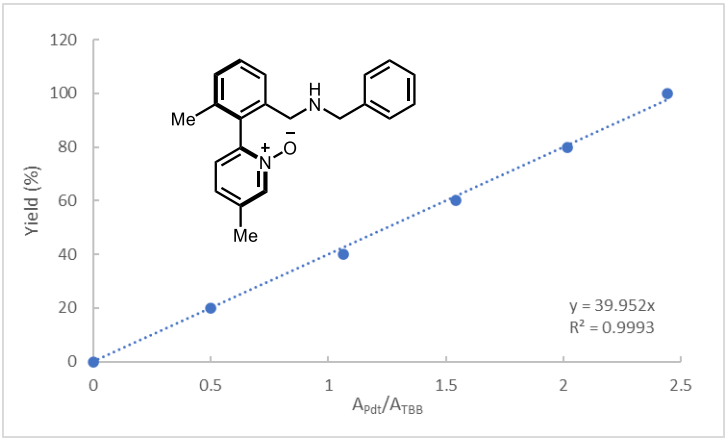


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.158	MF	435.9	20.3	0.3571	50.123	0.781
2	11.92	MF	433.8	14	0.5167	49.877	0.677



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.07	MF	42919.7	2044.5	0.3499	94.955	0.644
2	11.882	MF	2280.3	75.6	0.5028	5.045	0.612

(*S*)-2-{2-[(Benzylamino)methyl]-6-methylphenyl}-5-methylpyridine 1-oxide (**46**)

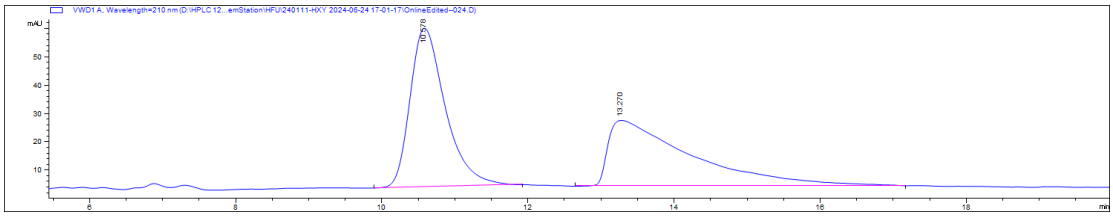


Prepared according to the general procedure 4 using substrate **28h** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

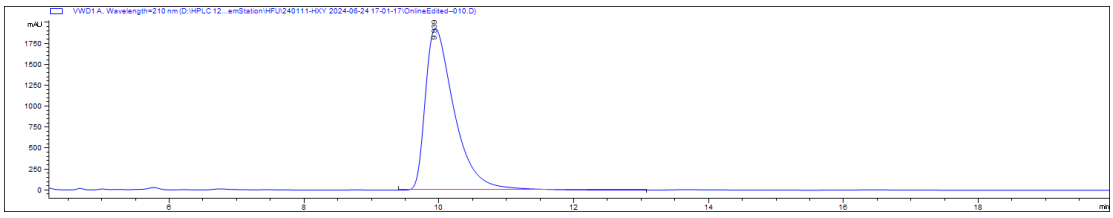
Yields: run 1: 78%, run 2: 78%, average yield 78%.

Preparative enzymatic reaction was conducted according to the general procedure 2 using **28h** (0.1 mmol, 1 equiv) and **6a** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%). **Isolated yield**: 69% (white solid, 22 mg).

Enantioselectivity: >99:1 er. Chiral HPLC method: OD-H column, 210 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 9.94 min.

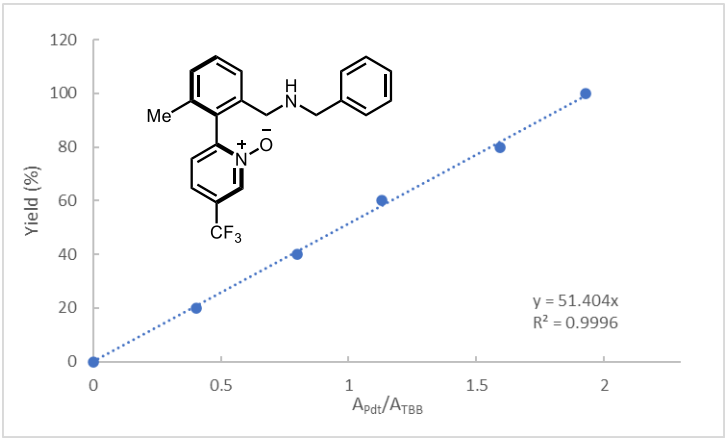


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.578	BB	1888.1	56.2	0.5097	50.638	0.65
2	13.27	BB	1840.5	23.3	1.0474	49.362	0.173



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.939	BB	57489.3	1925.4	0.4503	100.000	0.485

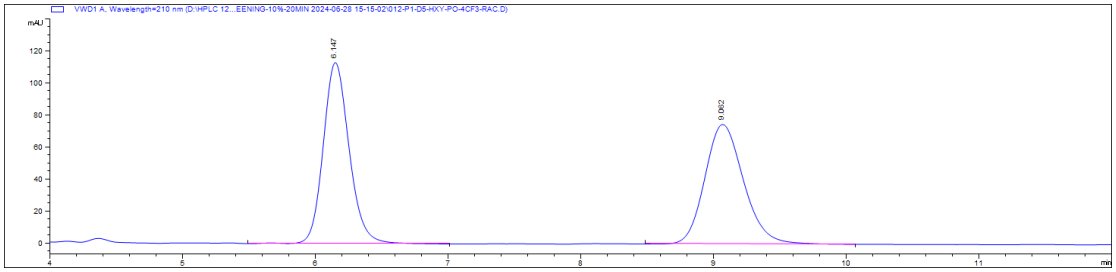
(*S*)-2-{2-[(Benzylamino)methyl]-6-methylphenyl}-5-(trifluoromethyl)pyridine 1-oxide (**47**)



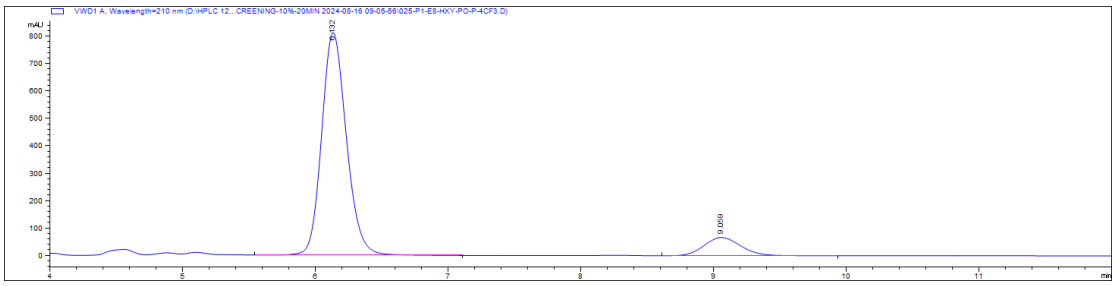
Prepared according to the general procedure 4 using substrate **28i** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 75%, run 2: 82%, average yield 78%.

Enantioselectivity: 89:11 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 6.13 min, t_R (minor) = 9.06 min.

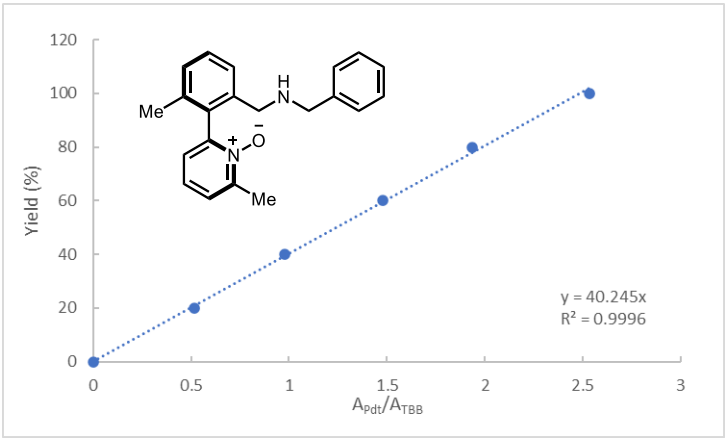


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.147	VB R	1542	113.3	0.2088	50.311	0.83
2	9.062	BB	1522.9	74.8	0.3134	49.689	0.808



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.132	VB R	10537.7	814.4	0.199	89.103	0.812
2	9.059	BB	1288.8	66.7	0.2995	10.897	0.86

(*S*)-2-{2-[(Benzylamino)methyl]-6-methylphenyl}-6-methylpyridine 1-oxide (**48**)



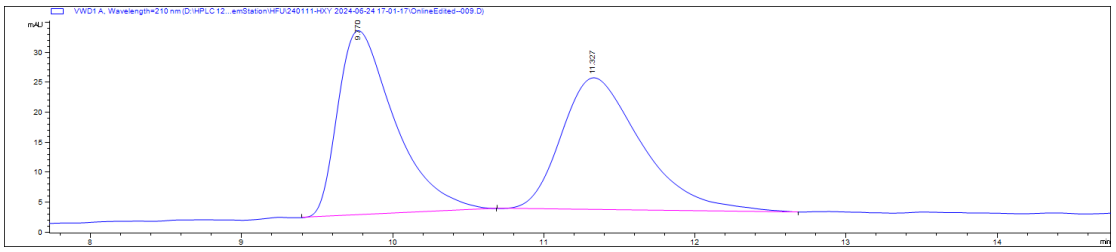
Prepared according to the general procedure 4 using substrate **28j** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 85%, run 2: 89%, average yield 87%.

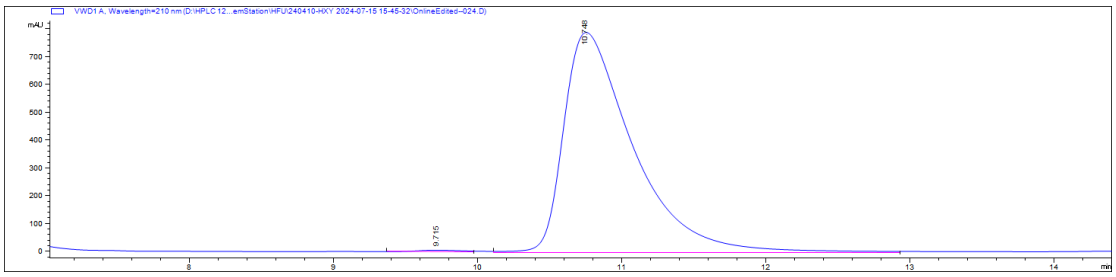
Preparative enzymatic reaction was conducted according to the general procedure 5 using **28j** (0.1 mmol, 1 equiv) and **6a** (0.3 mmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%). **Isolated yield**: 69% (white solid, 22 mg).

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 20% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.72 min, t_R (major) = 10.75 min.

Absolute configuration of the enzymatic product **48** was assigned as ***S*** by X-ray crystallography.

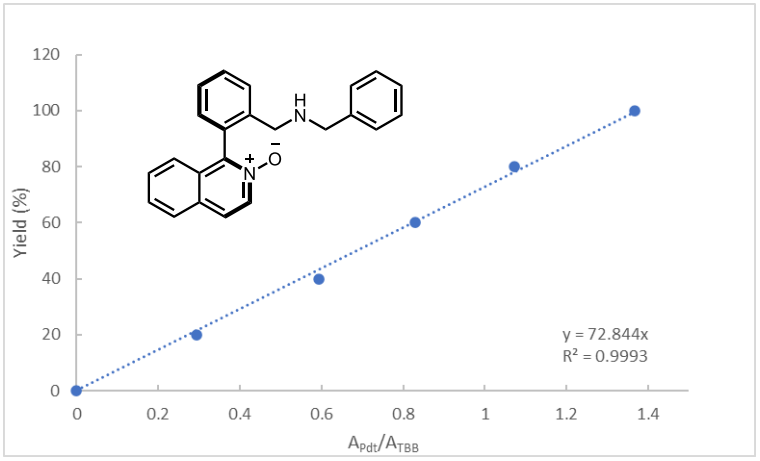


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.77	BB	805.2	30.8	0.3934	49.844	0.523
2	11.327	BB	810.2	22	0.5639	50.156	0.638



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.715	FM	132.7	6	0.3706	0.494	0.775
2	10.748	MM	26739.4	794	0.5613	99.506	0.461

(*S*)-1-{2-[(Benzylamino)methyl]phenyl}isoquinoline 2-oxide (**49**)

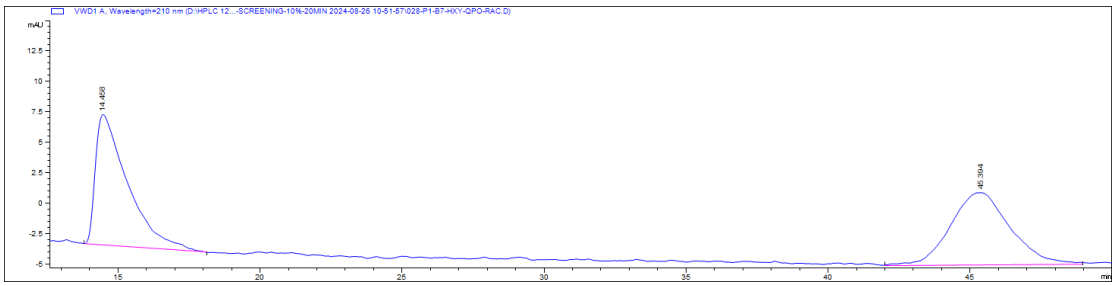


Prepared according to the general procedure 4 using substrate **28k** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.4 mol%).

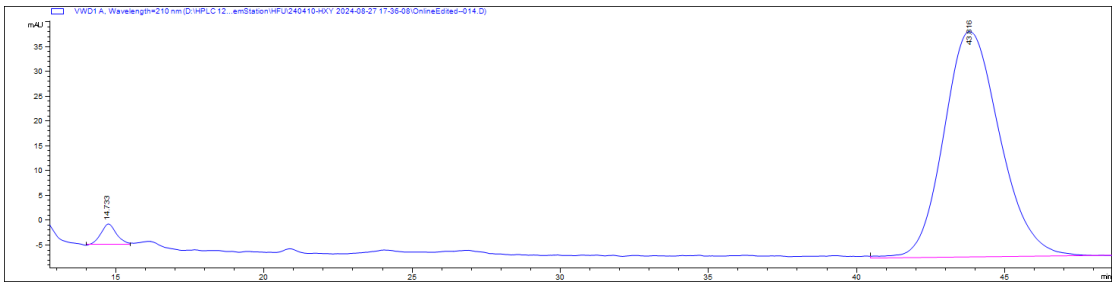
Yields: run 1: 36%, run 2: 41%, average yield 39%.

Note: Waters symmetry silica C18 column (4.6 x 250 mm, 5.0 μm) was used.

Enantioselectivity: 98:2 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 14.73 min, t_R (major) = 43.82 min.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.458	BB	846.4	10.7	1.0784	49.023	0.29
2	45.394	MM	880.2	6	2.4616	50.977	1.018



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.733	MM	149	4.1	0.6077	2.421	0.881
2	43.816	MM	6004	45.4	2.2061	97.579	0.82

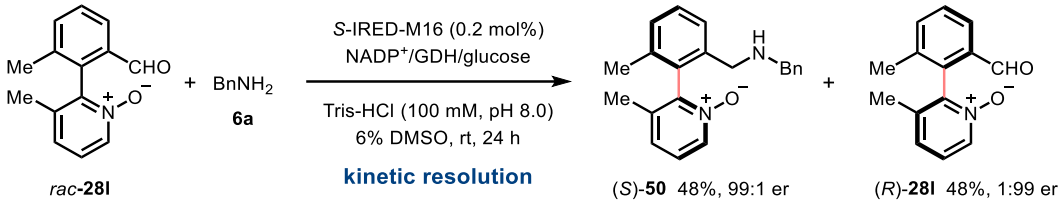
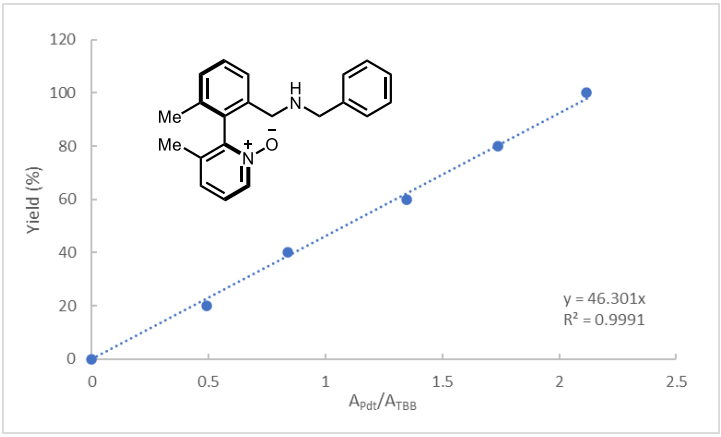


Fig. S7. Kinetic resolution of the *ortho*-tetrasubstituted substrate *rac*-**28l** using *S*-IRED-*Ss*-M16.

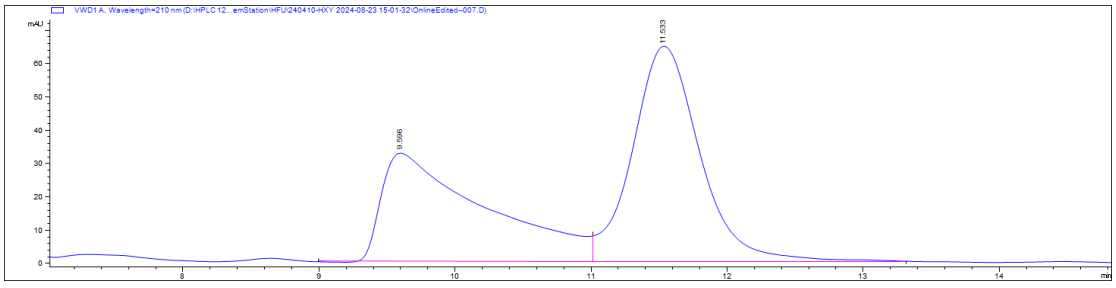
(*S*)-2-{2-[(Benzylamino)methyl]-6-methylphenyl}-3-methylpyridine 1-oxide (**50**)



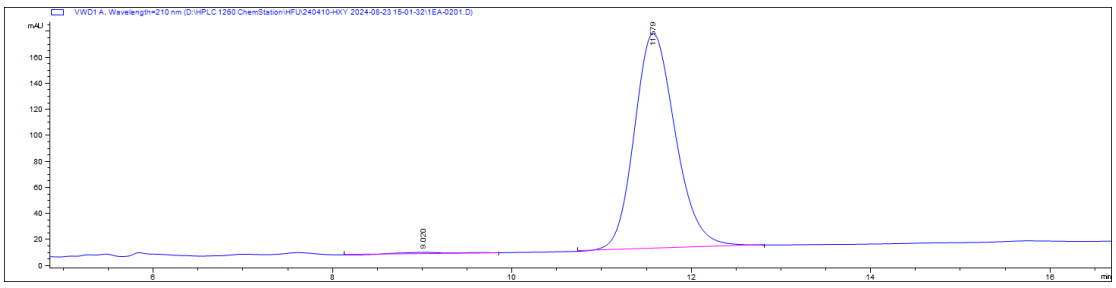
Prepared according to the general procedure 4 using substrate ***rac*-28l** (5 µmol, 1 equiv) and benzylamine **6a** (15 µmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 49%, run 2: 48%, average yield 48%.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 9.02 min, t_R (major) = 11.58 min.

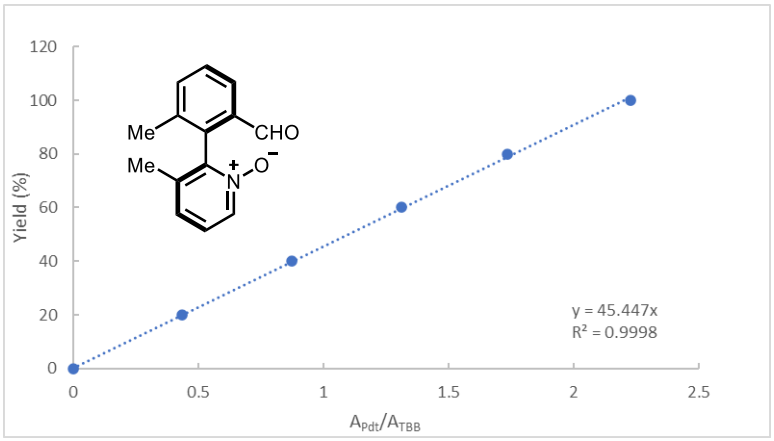


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.596	MF	1737.2	32.7	0.885	43.509	0
2	11.533	MF	2255.5	65	0.5781	56.491	0.824



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.02	MM	54.9	1.2	0.789	1.028	0.896
2	11.579	BB	5286.5	165.7	0.4922	98.972	0.807

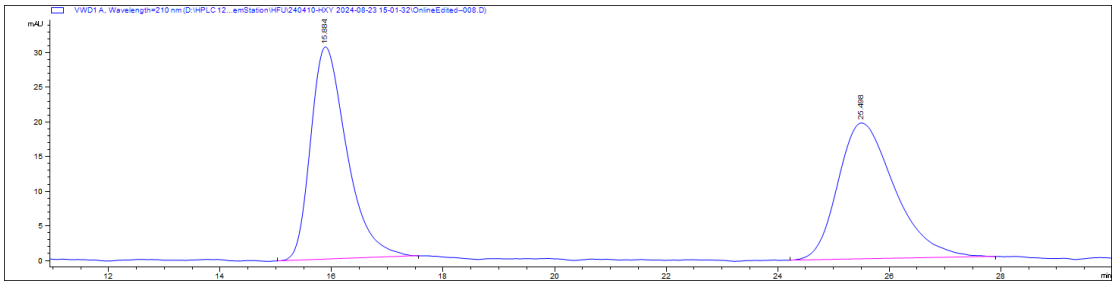
(*R*)-2-(2-Formyl-6-methylphenyl)-3-methylpyridine 1-oxide (**28l**)



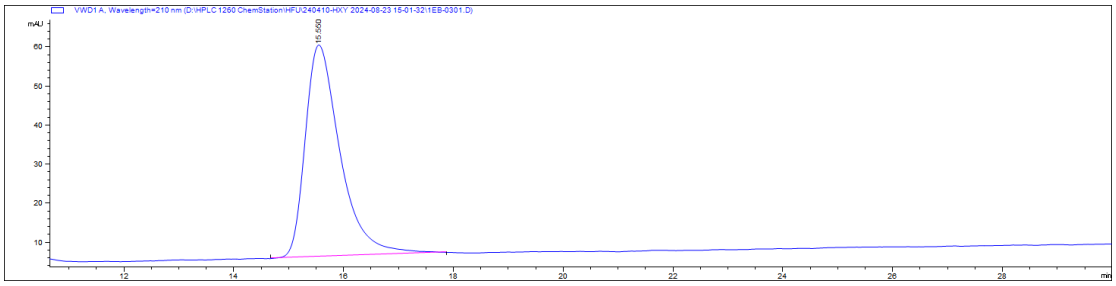
Prepared according to the general procedure 4 using substrate **28l** (5 μmol, 1 equiv) and benzylamine **6a** (15 μmol, 3 equiv) catalyzed by *S*-IRED-*Ss*-M16 (0.2 mol%).

Yields: run 1: 49%, run 2: 48%, average yield 48%.

Substrate enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 30% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 15.55 min.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.884	BB	1380.8	30.6	0.6819	49.891	0.651
2	25.498	BB	1386.9	19.6	1.0471	50.109	0.687



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.55	BB	2403.5	54.3	0.6666	100.000	0.591

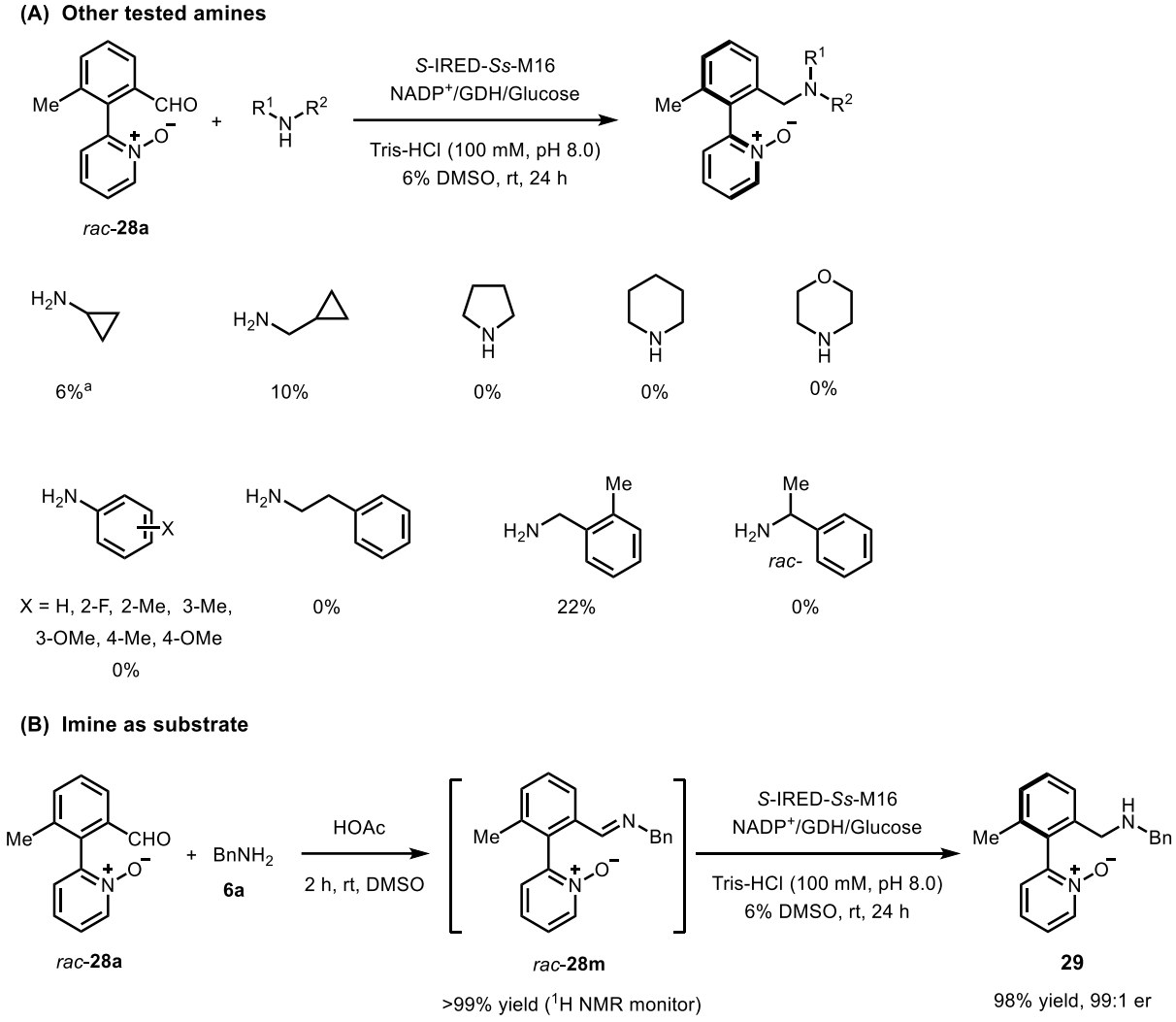
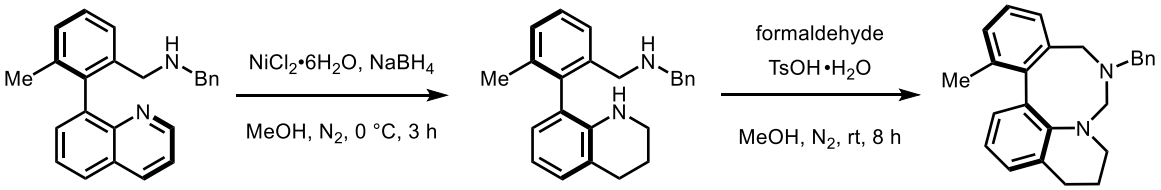


Fig. S8. (A) Amines not well accepted by *S*-IRED-*Ss*-M16. Reaction conditions: **28a** (5 μmol, 1 equiv), amines (15 μmol, 3 equiv), $NADP^+$ (0.1 μmol, 2 mol%), glucose (15 μmol, 3 equiv), *Bm*GDH (1 mg/mL), *S*-IRED-*Ss*-M16 (0.2 mol%) in Tris-HCl buffer (100 mM, pH 8.0) with 6% DMSO as cosolvent at room temperature (rt) for 24 h, the final total volume is 1000 μL. [a] Conversion (average of duplicate) determined *via* LCMS relative to an internal standard 1,3,5-tribromobenzene. (B) Imine as substrate. The imine *rac*-**28m** (>99% yield, monitored by NMR) was formed in situ over 2 hour from **28a** (1 equiv), $BnNH_2$ (3 equiv), and HOAc (0.5 equiv), then directly used in the enzymatic reaction.

Derivatization and application of enzymatic products

Derivatization of enzymatic product (*S*)-7



7
99:1 er

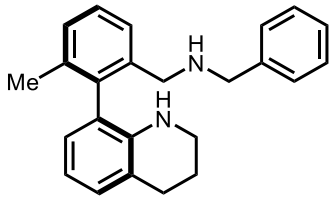
51
60% yield, 99:1 er

52
72% yield, 97:3 er

To a solution of (*S*)-**7** (obtained from enzymatic reaction catalyzed by *S*-IRED-*Ss*-M14, 200 mg, 0.6 mmol, 1.0 equiv) in MeOH/DCM (6 mL, 2:1) under N_2 atmosphere was added $NiCl_2$•$6H_2O$ (56 mg, 0.24 mmol, 0.4 equiv) and $NaBH_4$ (179 mg, 4.8 mmol, 8.0 equiv) at 0 ℃, and the reaction was stirred for another 3 hours until (*S*)-**7** was consumed. Then the reaction was quenched with H_2O (7 mL) and extracted with DCM (7 mL × 3), the organic phase was washed with brine, dried over Na_2SO_4, concentrated under vacuum, and purified through chromatography (PE/EA= 2:1) to give the axially chiral diamine product **51** (yellow oil, 122 mg, 60% yield, 99:1 er).

To a solution of **51** (60 mg, 0.18 mmol, 1.0 equiv) in MeOH (2 mL) was added *p*-toluenesulfonic acid monohydrate (0.1 mg, 5.3 μmol, 0.03 equiv) and a solution of formaldehyde (37% in water, 17 μL, 0.21 mmol, 1.2 equiv) under N_2 atmosphere at room temperature, and the mixture was stirred vigorously for 8 hours. Then the reaction was concentrated and purified through chromatography (PE/EA= 20:1) to give the product **52** (yellow oil, 45 mg, 72% yield, 97:3 er).

(*S*)-*N*-Benzyl-1-[3-methyl-2-(1,2,3,4-tetrahydroquinolin-8-yl)phenyl]methanamine (**51**)



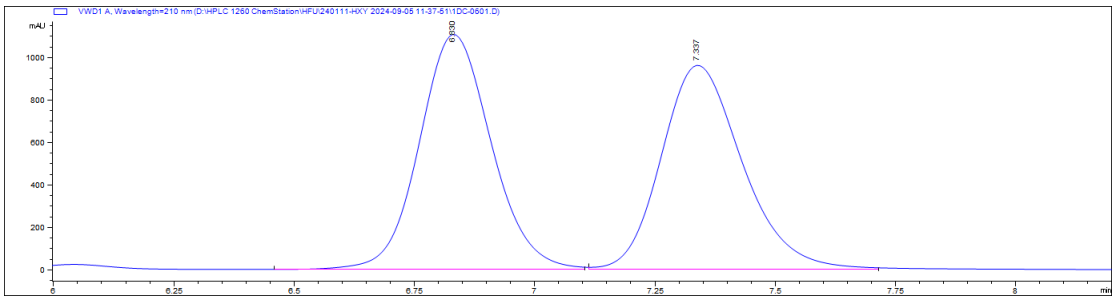
Yellow oil, 122 mg, 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 7.5, 1.5 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.24 – 7.22 (m, 2H), 7.22 – 7.19 (m, 1H), 7.17 (dd, J = 8.0, 1.5 Hz, 2H), 6.98 (m, 1H), 6.72 (dd, J = 7.5, 2.0 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 3.68 (d, J = 13.2 Hz, 1H), 3.62 – 3.58 (m, 2H), 3.52 (d, J = 12.8 Hz, 1H), 3.12 (m, 1H), 3.02 (m, 1H), 2.84 – 2.73 (m, 3H), 2.03 (s, 3H), 1.87 – 1.78 (m, 1H), 1.78 – 1.69 (m, 1H).

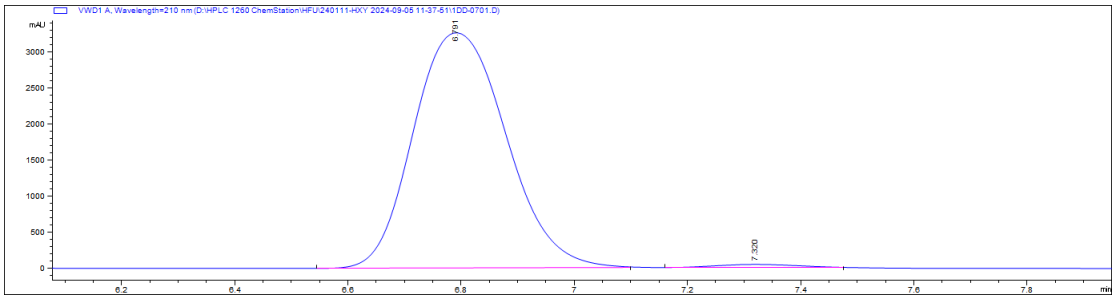
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 139.7, 138.8, 138.0, 137.8, 129.4, 128.9, 128.4, 128.2, 127.9, 127.8, 127.2, 127.0, 124.2, 121.7, 117.0, 53.4, 52.0, 42.0, 27.5, 22.1, 20.3.

HRMS: m/z calcd for $C_{24}H_{27}N_2$ $[M+H]^+$: 343.2174, found 343.2178.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 6.79 min, t_R (minor) = 7.32 min.

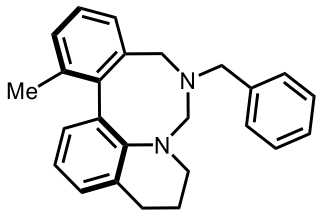


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.83	MF	11550.6	1111.7	0.1732	50.532	0.897
2	7.337	MF	11307.4	965.6	0.1952	49.468	0.791



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.791	MF	37241.3	3266.2	0.19	98.661	0.836
2	7.32	MF	505.6	47.2	0.1784	1.339	0.812

(*S*)-6-Benzyl-11-methyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[5,6][1,3]diazocino[7,8,1-*ij*]quinoline (**52**)



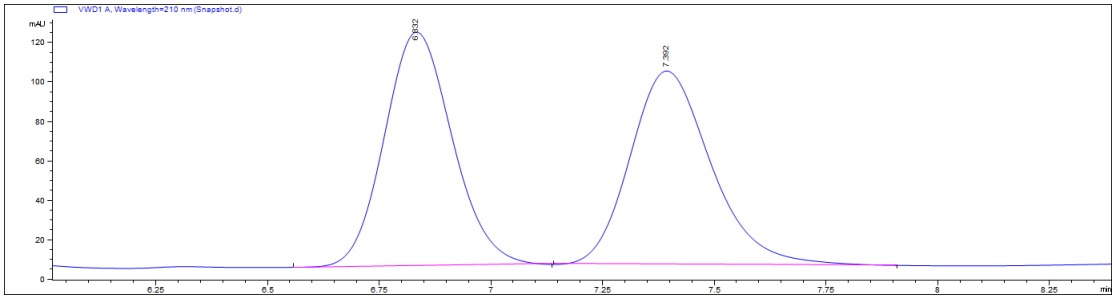
Yellow oil, 45 mg, 72% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.33 (m, 2H), 7.28 (m, 1H), 7.23 (m, 2H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.96 (m, 1H), 6.67 – 6.60 (m, 2H), 4.37 (d, *J* = 13.5 Hz, 1H), 3.96 (d, *J* = 12.0 Hz, 1H), 3.76 (d, *J* = 13.5 Hz, 1H), 3.66 (d, *J* = 12.0 Hz, 1H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.35 (m, 2H), 3.20 – 3.15 (m, 1H), 2.88 (m, 1H), 2.82 (m, 1H), 2.23 (s, 3H), 2.04 (d, *J* = 14.5 Hz, 1H), 2.01 – 1.95 (m, 1H).

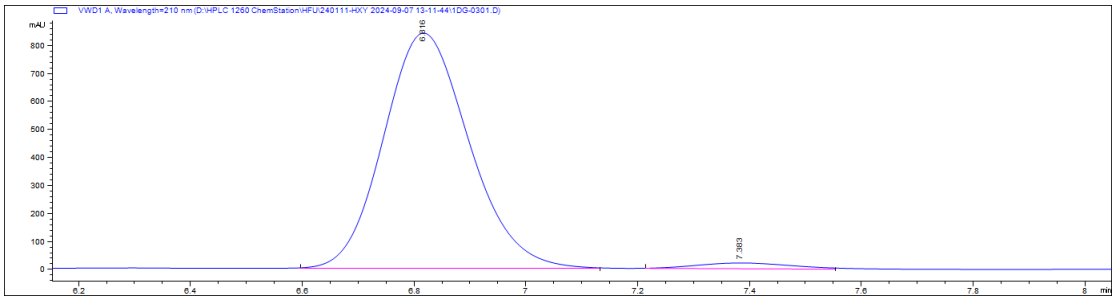
^{13}C NMR (150 MHz, $CDCl_3$) δ 145.7, 144.1, 139.5, 135.9, 132.7, 130.5, 129.0, 128.8, 128.7, 128.6, 128.4, 128.3, 127.0, 127.0, 126.5, 56.7, 55.4, 52.4, 29.4, 22.8, 22.2.

HRMS: m/z calcd for $C_{25}H_{27}N_2$ $[M+H]^+$: 355.2174, found 355.2174.

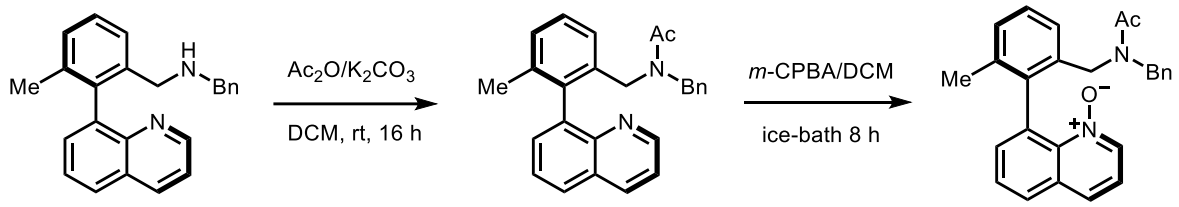
Enantioselectivity: 97:3 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 6.82 min, t_R (minor) = 7.38 min.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.832	MM	1259.4	119	0.1764	50.360	0.883
2	7.392	MM	1241.4	98.4	0.2102	49.640	0.796



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.816	MF	8987.9	843.1	0.1777	97.162	0.854
2	7.383	MF	262.5	21.8	0.2004	2.838	0.895



7
99:1 er

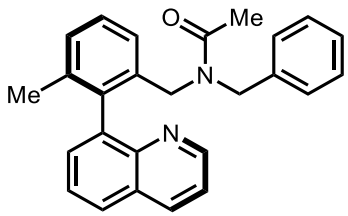
53
75% yield, 99:1 er

54
60% yield, 99:1 er

To a stirred solution of enzymatic product (*S*)**-7** (50 mg, 0.15 mmol, 1.0 equiv) in DCM (10 mL) was added Ac_2O (0.75 mmol, 5 equiv) and K_2CO_3 (207 mg, 1.5 mmol, 10 equiv), the reaction mixture was stirred over 16 hours at room temperature (rt). After completion of the reaction, the reaction mixture was quenched by saturated $NaHCO_3$ solution (20 mL), then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to provide a crude product, which was further purified by flash chromatography (EtOAc/ Hexanes, 5%, *v*/*v*) to provide the pure acetamide product **53** (white solid, 43 mg, 75% yield, 99:1 er).

To a stirred solution of acetamide **53** (40 mg, 0.11 mmol, 1.0 equiv) in dry DCM (5 mL) under ice-bath was added the *meta*-chloroperbenzoic acid (*m*-CPBA, 57 mg, 0.33 mmol, 3 equiv) and then stirred at 0 °C for 8 hours. After completion of the reaction, the reaction mixture was quenched by saturated $Na_2S_2O_3$ solution (5 mL). The resulting reaction mixture was concentrated under reduced pressure and diluted with water (10 mL), then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to provide a crude product, which was further purified by flash chromatography (EtOAc/Petroleum ether, 10%, *v*/*v*) to provide the pure *N*-oxide product **54** (yellow amorphous, 25 mg, 60% yield, 99:1 er).

(*S*)-*N*-Benzyl-*N*-(3-methyl-2-(quinolin-8-yl)benzyl)acetamide (**53**)



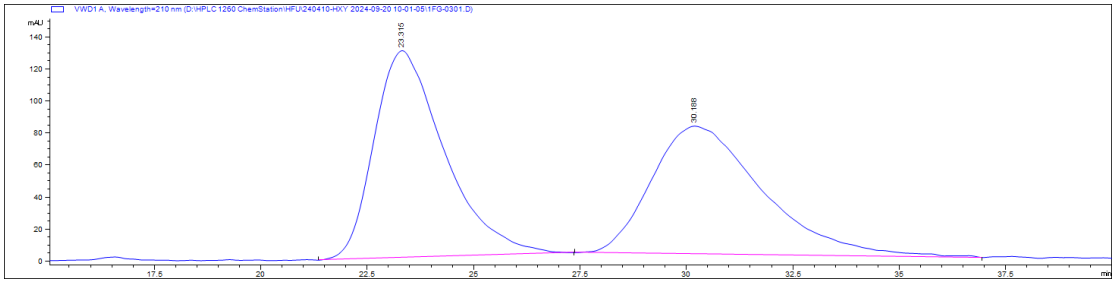
White solid, 43 mg, 75% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.79 (dd, *J* = 4.4, 1.8 Hz, 0.54H*), 8.20 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 0.58H*), 7.84 (d, *J* = 6.7 Hz, 1H), 7.80 (d, *J* = 6.7 Hz, 0.52H*), 7.60 – 7.56 (m, 1H), 7.54 (d, *J* = 7.7 Hz, 0.65H*), 7.49 – 7.43 (m, 1.6H*), 7.43 – 7.36 (m, 2H), 7.36 – 7.31 (m, 2H), 7.29 (d, *J* = 7.5 Hz, 0.77H*),7.14 (dd, *J* = 13.8, 6.7 Hz, 4H+2H*), 7.05 – 7.01 (m, 2H), 6.80 – 6.76 (m, 1H*), 4.56 (d, *J* = 14.6 Hz, 1H), 4.48 (d, *J* = 14.6 Hz, 1H), 4.39 (d, *J* = 15.1 Hz, 0.59H*), 4.30 (d, *J* = 17.1 Hz, 0.59H*), 4.23 (d, *J* = 15.1 Hz, 0.56H*), 4.17 (d, *J* = 17.1 Hz, 0.61H*), 3.96 (s, 2H), 1.94 (s, 3H), 1.91 (s, 1.55H*), 1.89 (s, 3H), 1.75 (s, 1.75H*). *Indicates the peaks of rotamer (2:1).

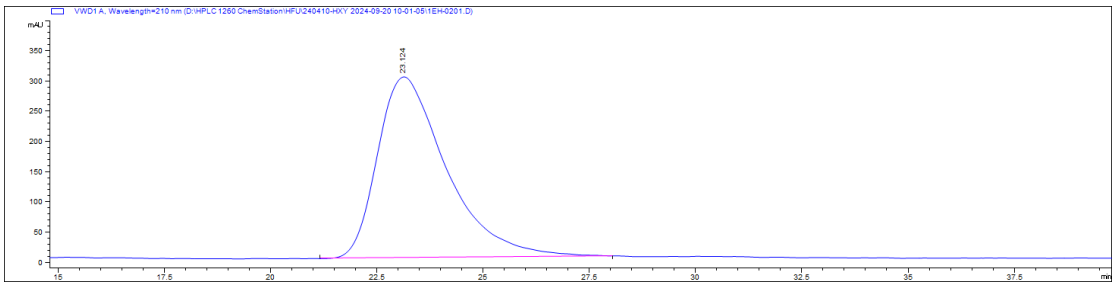
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 150.8, 137.6, 137.5, 136.6, 135.6, 134.9, 130.3, 129.3, 128.6, 128.5, 128.3, 128.3, 128.2, 127.2, 126.6, 126.1, 123.0, 121.4, 121.0, 49.8, 48.2, 21.4, 20.5.

HRMS: m/z calcd for $C_{26}H_{25}N_2O$ $[M+H]^+$: 381.1967, found 381.1972.

Enantioselectivity: 99:1 er. Chiral HPLC method: OJ-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 23.12 min.

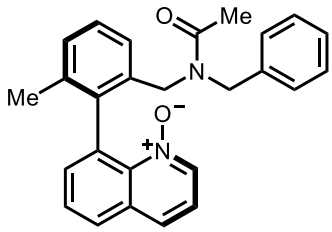


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	23.315	BB	14867	129	1.6166	50.472	0.632
2	30.188	MM	14588.9	79.9	3.0447	49.528	0.62



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	23.124	BB	33832.5	299.7	1.7011	100.000	0.575

(*S*)-8-{2-[(*N*-Benzylacetamido)methyl]-6-methylphenyl}quinoline 2-oxide (**54**)



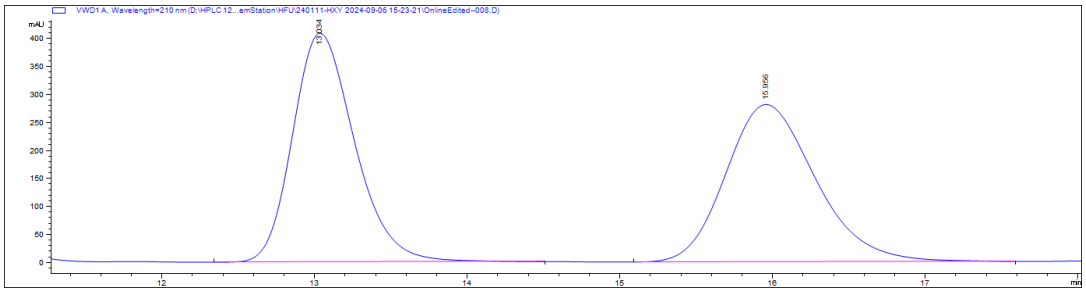
Yellow amorphous, 25 mg, 60% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (dt, *J* = 4.1, 1.8 Hz, 1H), 8.94 – 8.90 (m, 0.5H*), 8.34 (dt, *J* = 8.3, 1.8 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 0.53H*), 7.98 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.93 (dt, *J* = 8.2, 1.6 Hz, 0.64H*), 7.85 – 7.78 (m, 2H+1H*), 7.74 – 7.65 (m, 2H+1H*), 7.62 (dd, *J* = 3.1, 1.6 Hz, 1H*), 7.60 (dd, *J* = 3.1, 1.6 Hz, 2H), 7.59 (t, *J* = 2.5 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 0.48H*), 7.56 – 7.51 (m, 1H+1H*), 7.46 (d, *J* = 7.8 Hz, 2H), 7.44 – 7.41 (m, 0.7H), 7.41 – 7.38 (m, 0.42H*), 7.19 – 7.15 (m, 2H), 6.91 (dd, *J* = 5.1, 2.8 Hz, 1H*), 4.70 (d, *J* = 14.6 Hz, 1H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.53 (d, *J* = 15.1 Hz, 0.62H*), 4.44 (d, *J* = 17.2 Hz, 0.61H*), 4.37 (d, *J* = 15.1 Hz, 0.65H*), 4.30 (d, *J* = 17.2 Hz, 0.58H*), 4.10 (s, 2H), 2.07 (s, 3H), 2.05 (d, *J* = 1.6 Hz, 1.77H*), 2.02 (s, 3H), 1.88 (s, 1.77H). *Indicates the peaks of rotamer (2:1).

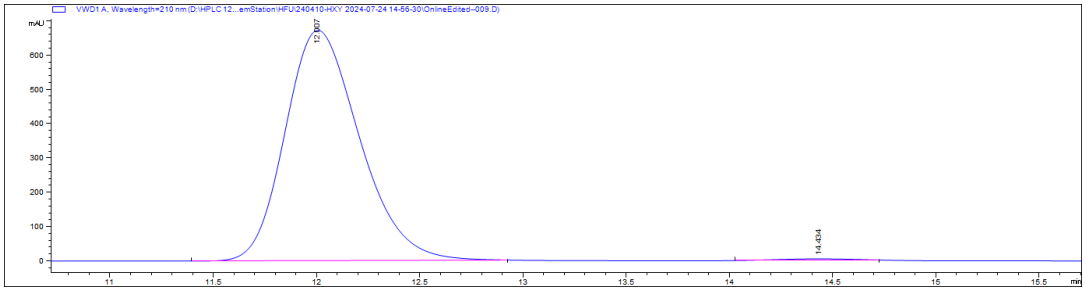
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.58, 150.80, 137.54, 136.61, 134.87, 132.26, 132.18, 130.31, 129.31, 128.68, 128.58, 128.45, 128.33, 128.25, 128.16, 127.18, 126.62, 126.08, 123.00, 121.45, 49.77, 48.22, 21.34, 20.50.

HRMS: m/z calcd for $C_{26}H_{25}N_2O_2$ $[M+H]^+$: 397.1916, found 397.1917.

Enantioselectivity: 99:1 er. Chiral HPLC method: OD-H column, 210 nm, 10% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (major) = 12.01 min, t_R (minor) = 14.43 min.

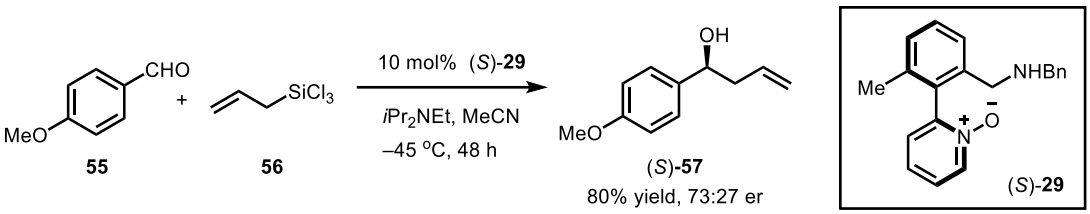


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.034	BB	11595.1	410.9	0.4372	50.083	0.75
2	15.956	BB	11556.9	282.5	0.6332	49.917	0.78



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.007	MF	16891.9	670.9	0.4196	99.032	0.761
2	14.434	MF	165.1	5.7	0.4829	0.968	1.106

Asymmetric allylation of *p*-anisaldehyde catalyzed by enzymatic product (*S*)-29

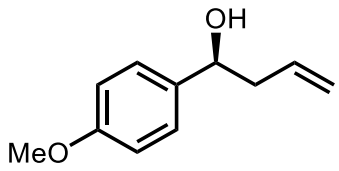


General procedure: Adapted from the method by Hayashi *et al*.[4] To a solution of *p*-anisaldehyde (**55**, 30 mg, 0.22 mmol, 1 equiv) and heterobiaryl *N*-oxide amine (**29**) in anhydrous acetonitrile (1 mL) was added *N*,*N*-diisopropylethylamine (0.12 mL, 0.66 mmol, 3.0 equiv) under N_2 atmosphere. The solution was cooled to -45℃ before allyl trichlorosilane **56** was added dropwise. The reaction was stirred at -45℃ for 48 h before quenched with 1 M NaOH aqueous solution (2 mL), and stirred for another 30 mins at room temperature. Then the reaction mixture was extracted with EtOAc (2 mL x 3), washed with brine, dried with Na_2SO_4, and concentrated for further HPLC analysis. The final product was purified through chromatography (PE/EA=10:1) to give a yellow oil.

Entry	Catalyst	Allyl trichlorosilane	Yield	er[b]
1	1 mol% *rac*-**29**	1.2 equiv	9%[a]	n.d.
2	5 mol% *rac*-**29**	1.2 equiv	58%[a]	n.d.
3	10 mol% *rac*-**29**	1.2 equiv	72%[a]	n.d.
4	10 mol% *rac*-**29**	1.6 equiv	82%[c]	50:50
5	10 mol% (*S*)-**29**	1.6 equiv	80%[c]	73:27

Table S7. Allylation of *p*-anisaldehyde catalyzed by heterobiaryl *N*-oxide **29**. [a] Yield (average of duplicate) determined *via* LCMS relative to an internal standard 1,3,5-tribromobenzene. [b] Enantiomeric ratio determined by HPLC on a chiral stationary phase. [c] Isolated yield after chromatography.

(*S*)-1-(4-Methoxyphenyl)but-3-en-1-ol (**57**)



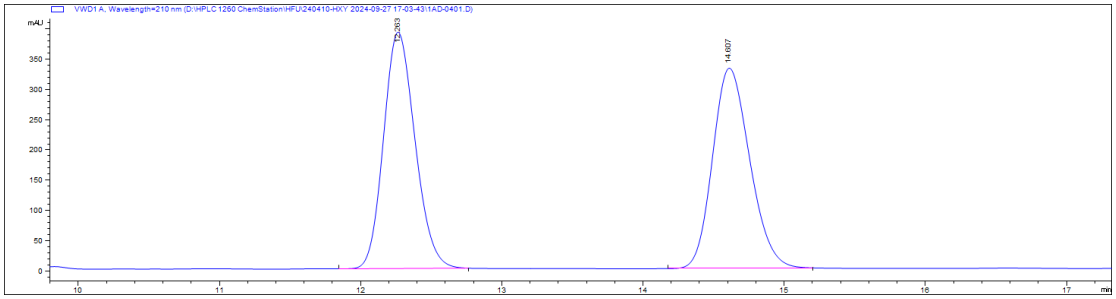
Yellow oil, 31 mg, 80% isolated yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.85 – 5.74 (m, 1H), 5.19 – 5.09 (m, 2H), 4.68 (t, J = 6.6 Hz, 1H), 3.80 (s, 3H), 2.53 – 2.46 (m, 2H), 2.10 (brs, 1H).

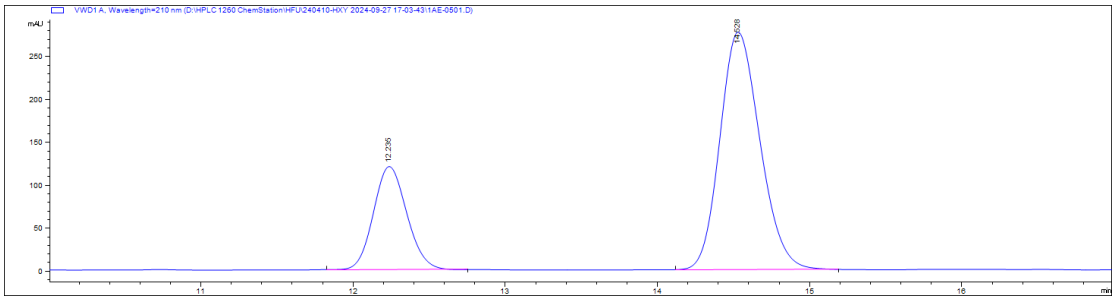
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 136.2, 134.7, 127.2, 118.3, 113.9, 73.1, 55.4, 43.9.

The NMR spectra is in agreement with published data.[4]

Enantioselectivity: 73:27 er. Chiral HPLC method: OD-H column, 210 nm, 5% isopropanol/hexanes, flow rate 1.0 mL/min, room temperature, t_R (minor) = 12.24 min, t_R (major) = 14.53 min. **Absolute configuration** of the major product of **57** is assigned as ***S*** by comparison with the previously reported chiral HPLC data.[5]

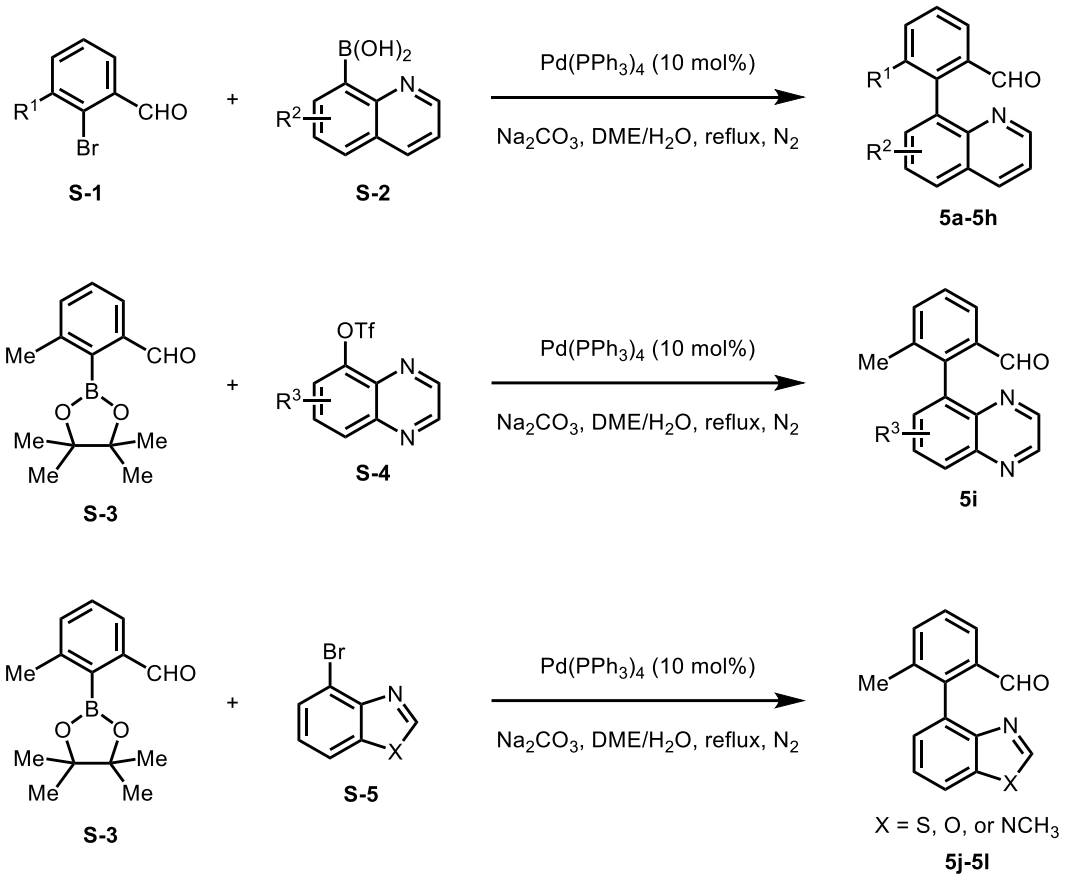


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.263	FM	6109.6	393.5	0.2587	49.969	0.827
2	14.607	MF	6117.2	333.2	0.3059	50.031	0.794



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.235	FM	1842.3	120.5	0.2547	26.571	0.88
2	14.528	MF	5091.1	277.6	0.3057	73.429	0.808

Synthesis of racemic heterobiaryl substrates



General procedure A

To a stirred solution of aldehyde **S-1** (5 mmol, 1.0 equiv) in 1,2-dimethoxyethane (DME, 20 mL) and H_2O (10 mL) was added boronic acid **S**-**2** (7.5 mmol, 1.5 equiv), Na_2CO_3 (1.59 g, 15 mmol, 3.0 equiv) and $Pd(PPh_3)_4$ (577 mg, 0.5 mmol, 0.1 equiv), the reaction mixture was heated at reflux overnight. After completion of the reaction, the solvent was removed under reduced pressure. The resulting mixture was extracted with EtOAc (25 mL × 3), and then organic layers were collected and dried over Na_2SO_4, and concentrated to provide the crude product, which was purified by flash chromatography (EtOAc/Petroleum ether, 5~10%, *v*/*v*) to give products **5a**-**5h**.

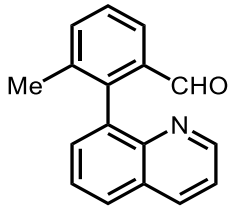
General procedure B

To a stirred solution of **S-3** (5 mmol, 1.0 equiv) in 1,2-dimethoxyethane (DME, 20 mL) and H_2O (10 mL) was added trifluoromethanesulfonate **S-4** (4 mmol, 0.8 equiv), Na_2CO_3 (1.59 g, 15 mmol, 3.0 equiv.) and $Pd(PPh_3)_4$ (577 mg, 0.5 mmol, 0.1 equiv), the reaction mixture was heated at reflux overnight. After completion of the reaction, the solvent was removed under reduced pressure. The resulting mixture was extracted with EtOAc (25 mL × 3), and then organic layers were collected and dried over Na_2SO_4, and concentrated to provide the crude product, which was purified by flash chromatography (EtOAc/Petroleum ether, 5~10%, *v*/*v*) to give products **5i**.

General procedure C

To a stirred solution of **S-3** (5 mmol, 1.0 equiv) in 1,2-dimethoxyethane (DME, 20 mL) and H_2O (10 mL) was added **S-5** (7.5 mmol, 1.5 equiv.), Na_2CO_3 (1.59 g, 15 mmol, 3.0 equiv.) and $Pd(PPh_3)_4$ (577 mg, 0.5 mmol, 0.1 equiv.), the reaction mixture was heated at reflux overnight. After completion of the reaction, the solvent was removed under reduced pressure. The resulting mixture was extracted with EtOAc (25 mL × 3), and then organic layers were collected and dried over Na_2SO_4, and concentrated to provide the crude product, which was further purified by flash chromatography (EtOAc/Petroleum ether, 5~10%, *v*/*v*) to give products **5j-5l**.

3-Methyl-2-(quinolin-8-yl)benzaldehyde (**5a**)



Yellow solid. 1087 mg, 88% yield.

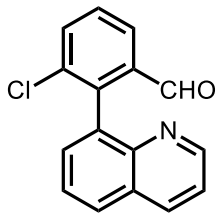
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.87 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.24 (d, *J* = 8.3 Hz, 1H), 7.94 (t, *J* = 8.8 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.01 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.7, 150.9, 146.9, 143.3, 138.1, 136.4, 135.5, 135.0, 131.6, 128.6, 128.5, 128.0, 126.1, 124.8, 121.4, 20.1.

The NMR spectra is in agreement with published data.[6]

HRMS: m/z calcd for $C_{17}H_{14}NO$ $[M+H]^+$: 248.1075, found 248.1076.

3-Chloro-2-(quinolin-8-yl)benzaldehyde (**5b**)



White solid. 1161 mg, 87% yield.

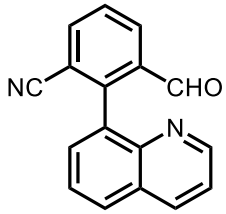
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (d, *J* = 5.1 Hz, 1H), 8.87 (s, 1H), 8.26 (t, *J* = 6.8 Hz, 1H), 8.05 – 7.96 (m, 2H), 7.79 (t, *J* = 6.7 Hz, 1H), 7.71 – 7.67 (m, 2H), 7.54 (q, *J* = 7.2 Hz, 1H), 7.47 – 7.43 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.4, 151.1, 146.9, 142.0, 136.7, 136.4, 135.4, 134.8, 134.1, 132.1, 129.4, 129.3, 128.4, 126.0, 125.7, 121.7.

The NMR spectra is in agreement with published data.[6]

HRMS: m/z calcd for $C_{16}H_{11}ClNO$ $[M+H]^+$: 268.0529, found 268.0531.

3-Formyl-2-(quinolin-8-yl)-benzonitrile (**5c**)



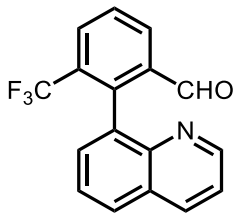
Yellow solid. 464 mg, 36% yield.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (d, J = 3.4 Hz, 1H), 8.87 – 8.82 (m, 1H), 8.58 – 8.54 (m, 1H), 8.32 (dd, J = 7.9, 3.7 Hz, 1H), 8.27 – 8.22 (m, 2H), 8.05 – 7.94 (m, 1H), 7.89 – 7.80 (m, 2H), 7.67 – 7.61 (m, 1H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 190.2, 151.1, 145.9, 145.7, 137.8, 136.7, 135.3, 132.6, 131.9, 131.2, 130.2, 129.1, 127.9, 126.2, 122.0, 117.3, 114.8.

HRMS: m/z calcd for $C_{17}H_{11}N_2O$ $[M+H]^+$: 259.0871, found 259.0869.

2-(Quinolin-8-yl)-3-(trifluoromethyl)benzaldehyde (**5d**)



White solid. 400 mg, 27% yield.

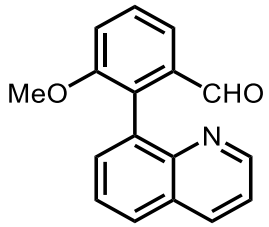
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.73 (dd, J = 4.2, 1.8 Hz, 1H), 8.44 (dd, J = 8.3, 1.8 Hz, 1H), 8.19 – 8.13 (m, 2H), 8.12 (dd, J = 8.1, 1.6 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.77 – 7.73 (m, 1H), 7.72 – 7.61 (m, 1H), 7.52 (dd, J = 8.3, 4.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 191.0, 151.0, 147.5, 142.1, 136.3, 136.2, 133.3, 131.7, 131.4 (q, J = 5.1 Hz), 130.7 (q, J = 29.8 Hz), 130.3, 129.5, 128.4, 128.0, 125.6, 123.7 (q, J = 274.3 Hz), 121.6, 121.0.

^{19}F NMR (565 MHz, $CDCl_3$) δ -58.1.

HRMS: m/z calcd for $C_{17}H_{11}F_3NO$ $[M+H]^+$: 302.0793, found 302.0798.

3-Methoxy-2-(quinolin-8-yl)benzaldehyde (**5e**)



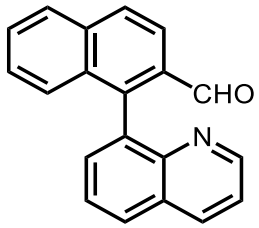
Yellow solid. 750 mg, 57% yield.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.81 – 8.76 (m, 1H), 8.46 (dd, J = 8.3, 2.0 Hz, 1H), 8.10 (dd, J = 7.4, 2.3 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.66 – 7.58 (m, 1H), 7.59 – 7.53 (m, 2H), 7.48 (d, J = 8.2 Hz, 1H), 3.67 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.2, 157.4, 150.6, 147.2, 136.2, 135.8, 132.9, 132.4, 132.3, 129.0, 128.5, 128.2, 125.8, 121.1, 118.9, 116.3, 56.0.

HRMS: m/z calcd for $C_{17}H_{14}NO_2$ $[M+H]^+$: 259.0871, found 259.0869.

1-(Quinolin-8-yl)-2-naphthaldehyde (**5f**)



Yellow solid. 1288 mg, 91% yield.

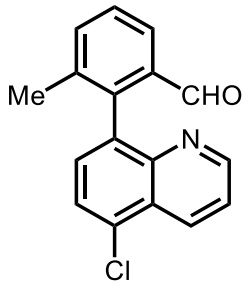
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.78 (s, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 7.0 Hz, 1H), 7.69 (t, J = 7.6 Hz,1H), 7.56 (t, J = 7.5 Hz, 1H), 7.40 (q, J = 7.4, 5.4 Hz, 2H), 7.33 (t, J = 7.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.6, 151.0, 147.8, 144.5, 136.3, 134.9, 133.0, 132.6, 131.9, 129.0, 128.7, 128.6, 128.4, 128.3, 127.7, 126.7, 125.8, 122.2, 121.6.

The NMR spectra is in agreement with published data.[6]

HRMS: m/z calcd for $C_{20}H_{14}NO$ $[M+H]^+$: 284.1075, found 284.1072.

2-(5-Chloroquinolin-8-yl)-3-methylbenzaldehyde (**5g**)



Yellow solid. 829 mg, 59% yield.

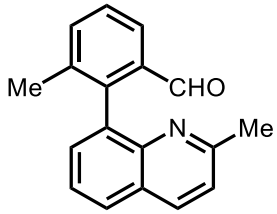
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.90 (dd, J = 4.3, 1.7 Hz, 1H), 8.68 (dd, J = 8.6, 1.7 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.56 – 7.45 (m, 3H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 151.4, 147.5, 142.3, 138.1, 136.0, 135.6, 135.1, 133.3, 131.9, 131.1, 128.3, 126.6, 126.3, 125.3, 122.3, 20.1.

The NMR spectra is in agreement with published data.[6]

HRMS: m/z calcd for $C_{17}H_{13}ClNO$ $[M+H]^+$: 282.0686, found 282.0694.

3-Methyl-2-(2-methylquinolin-8-yl)-benzaldehyde (**5h**)



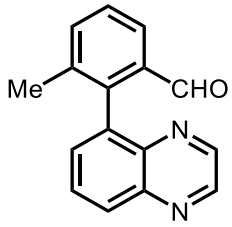
Yellow solid. 692 mg, 53% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.59 – 7.51 (m, 3H), 7.45 (s, 1H), 7.28 (s, 1H), 2.54 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 159.5, 146.6, 143.8, 138.2, 136.1, 135.6, 135.3, 135.2, 131.6, 128.3, 127.5, 126.6, 125.0, 124.3, 122.3, 25.7, 20.3.

HRMS: m/z calcd for $C_{18}H_{16}NO$ $[M+H]^+$: 262.1232, found 262.1236.

3-Methyl-2-(quinoxalin-5-yl)benzaldehyde (**5i**)



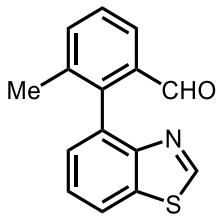
Yellow amorphous. 460 mg, 74% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.88 (d, J = 1.8 Hz, 1H), 8.79 (d, J = 1.8 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 1.98 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.1, 145.4, 145.3, 143.2, 142.0, 141.5, 138.2, 137.1, 135.6, 135.2, 131.9, 130.2, 129.7, 128.5, 125.6, 20.1.

HRMS: m/z calcd for $C_{16}H_{13}N_2O$ $[M+H]^+$: 249.1028, found 249.1029.

2-(Benzo[*d*]thiazol-4-yl)-3-methylbenzaldehyde (**5j**)



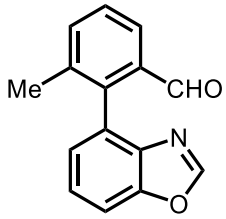
Colorless amorphous. 405 mg, 32% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.97 (s, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.48 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.3 Hz, 1H), 2.07 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.4, 154.7, 152.0, 142.2, 137.8, 135.7, 134.6, 134.4, 132.2, 128.4, 128.2, 125.4, 125.1, 122.2, 20.1.

HRMS: m/z calcd for $C_{15}H_{12}NOS$ $[M+H]^+$: 254.0640, found 254.0652.

2-(Benzo[*d*]oxazol-4-yl)-3-methylbenzaldehyde (**5k**)



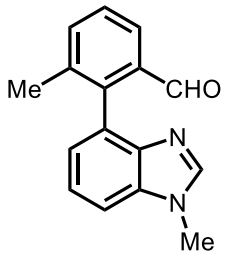
Colorless amorphous. 436 mg, 37% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.09 (s, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.68 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.25 (d, *J* = 7.4 Hz, 1H), 2.11 (s, 3H)

^{13}C NMR (126 MHz, CDCl3) δ 192.3, 153.1, 149.9, 140.2, 139.3, 138.0, 135.7, 134.7, 129.6, 128.5, 126.7, 125.6, 125.3, 111.0, 20.1.

HRMS: m/z calcd for $C_{15}H_{12}NO_2$ $[M+H]^+$: 238.0868, found 238.0868.

3-Methyl-2-(1-methyl-1*H*-benzo[*d*]imidazol-4-yl)benzaldehyde (**5l**)

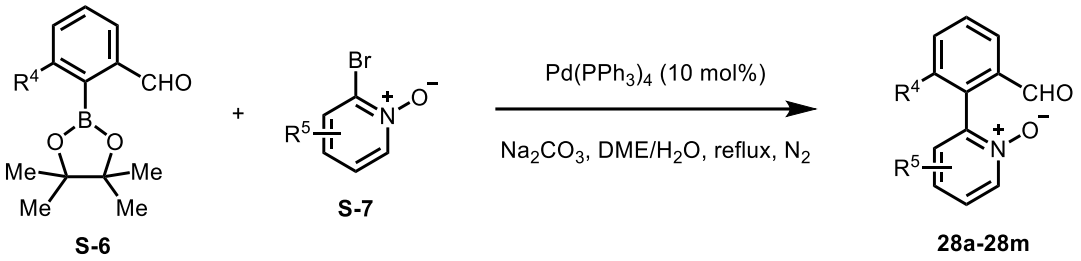


White solid. 543 mg, 53% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.85 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.41 (dt, *J* = 15.4, 7.7 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 3.89 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 144.1, 142.8, 142.1, 138.1, 135.6, 134.8, 134.6, 128.6, 128.0, 124.7, 124.23, 122.8, 109.6, 31.3, 20.1.

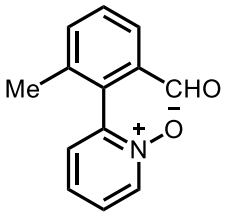
HRMS: m/z calcd for $C_{16}H_{15}N_2O$ $[M+H]^+$: 254.1184, found 254.1187.



General procedure

To a stirred solution of **S-6** (5 mmol, 1.0 equiv.) in 1,2-dimethoxyethane (DME, 20 mL) and H_2O (10 mL) was added 2-bromopyridine 1-oxide **S**-**7** (4 mmol, 0.8 equiv.), Na_2CO_3 (1.59 g, 15 mmol, 3.0 equiv.) and $Pd(PPh_3)_4$ (577 mg, 0.5 mmol, 0.1 equiv.), the reaction mixture was heated at reflux overnight. After completion of the reaction, the solvent was removed under reduced pressure. The resulting mixture was extracted with Dichloromethane (DCM) (25 mL × 3), and then organic layers were collected and dried over Na_2SO_4, concentrated to provide the crude product, which was further purified by flash chromatography (MeOH/DCM, 5%, *v*/*v*) to give products **28a**-**28m**.

2-(2-Formyl-6-methylphenyl)-pyridine 1-oxide (**28a**)



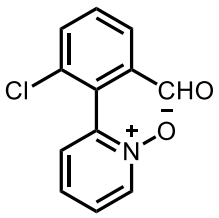
White solid. 650 mg, 61% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.40 – 8.36 (m, 1H), 7.84 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.38 – 7.32 (m, 2H), 7.26 – 7.23 (m, 1H), 2.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 147.2, 140.3, 138.4, 136.0, 134.7, 134.1, 129.9, 128.2, 128.2, 125.7, 125.4, 19.2.

HRMS: m/z calcd for $C_{13}H_{10}NO_2$ $[M+H]^+$: 214.0868, found 214.0862.

2-(2-Chloro-6-formylphenyl)pyridine 1-oxide (**28b**)



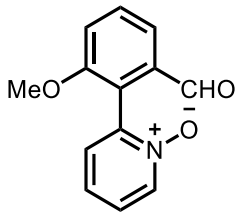
White solid. 950 mg, 41% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.40 – 8.35 (m, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.44 – 7.37 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 189.3, 144.9, 140.3, 136.6, 135.2, 135.1, 132.9, 131.2, 130.1, 128.7, 128.4, 126.4, 125.9.

HRMS: m/z calcd for $C_{12}H_9ClNO_2$ $[M+H]^+$: 234.0322, found 234.0327.

2-(2-Formyl-6-methoxyphenyl)-pyridine 1-oxide (**28c**)



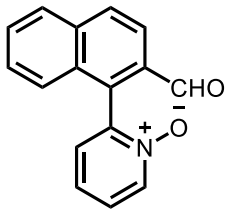
Yellow solid. 954 mg, 83% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H) 8.38 – 8.33 (m, 1H), 7.65 – 7.57 (m, 2H), 7.40 – 7.32 (m, 3H), 7.32 – 7.24 (m, 1H), 3.82 (s, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 190.5, 157.4, 144.4, 140.1, 135.9, 131.3, 129.4, 125.6, 125.3, 123.0, 121.5, 116.8, 56.3.

HRMS: m/z calcd for $C_{13}H_{12}NO_3$ $[M+H]^+$: 230.0817, found 230.0802.

2-(2-Formylnaphthalen-1-yl)-pyridine 1-oxide (**28d**)



White solid. 710 mg, 57% yield.

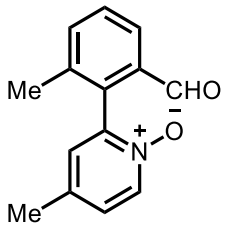
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.43 (d, J = 6.3 Hz, 1H), 8.09 – 8.01 (m, 2H), 7.93 (d, J = 8.2 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.53 – 7.36 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.7, 145.4, 140.5, 136.3, 135.4, 131.9, 131.1, 130.5, 129.6, 129.2, 128.7, 127.9, 126.3, 125.8, 125.3, 123.1.

The NMR spectra is in agreement with published data.[5]

HRMS: m/z calcd for $C_{16}H_{12}NO_2$ $[M-H]^-$: 250.0868, found 250.0871.

2-(2-Formyl-6-methylphenyl)-4-methylpyridine 1-oxide (**28e**)



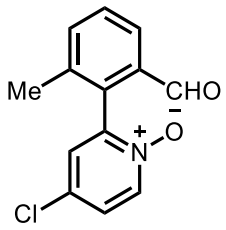
Yellow solid. 420 mg, 37% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.27 (d, J = 6.6 Hz, 1H), 7.83 (dd, J = 7.5, 1.7 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.16 (dd, J = 6.7, 2.6 Hz, 1H), 7.05 (d, J = 2.6 Hz, 1H), 2.38 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 191.1, 146.3, 139.6, 138.4, 137.0, 136.0, 134.7, 134.4, 129.8, 128.7, 127.8, 126.5, 20.5, 19.3.

HRMS: m/z calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1025, found 228.1033.

4-Chloro-2-(2-formyl-6-methylphenyl)-4-chloro-pyridine 1-oxide (**28f)**



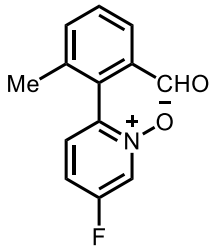
White solid. 327 mg, 26% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, J = 1.3 Hz, 1H), 8.25 (d, J = 7.0 Hz, 1H), 7.79 (dd, J = 6.5, 2.5 Hz, 1H), 7.61 – 7.47 (m, 2H), 7.30 (dd, J = 7.0, 3.0 Hz, 1H), 7.20 (d, J = 3.0 Hz, 1H), 2.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 148.5, 140.7, 138.4, 136.1, 134.6, 132.2, 131.2, 130.2, 129.5, 127.6, 125.8, 19.2.

HRMS: m/z calcd for $C_{13}H_{11}ClNO_2$ $[M+H]^+$: 248.0748, found 248.0783.

4-Fluoro-2-(2-formyl-6-methylphenyl) pyridine 2-oxide (**28g)**



White solid. 693 mg, 60% yield.

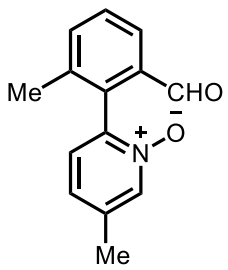
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.35 (dd, J = 5.0, 2.3 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.7 Hz, 2H), 7.26 – 7.20 (m, 1H), 7.18 – 7.11 (m, 1H), 1.75 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 197.0, 165.0 (d, J = 249.5 Hz), 148.4 (d, J = 3.9 Hz), 143.6, 141.0, 139.9, 138.6, 136.8 (d, J = 9.7 Hz), 134.9, 134.1 (d, J = 11.6 Hz), 133.5 (d, J = 9.6 Hz), 133.0, 118.8 (d, J = 20.1 Hz), 23.9.

^{19}F NMR (565 MHz, $CDCl_3$) δ -114.8.

HRMS: m/z calcd for $C_{13}H_{11}FNO_2$ $[M+H]^+$: 232.0774, found 232.0769.

2-(2-Formyl-6-methylphenyl)-5-methylpyridine 2-oxide (**28h**)



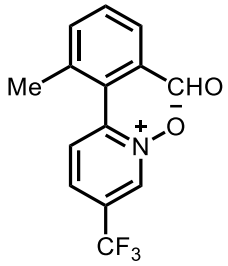
White solid. 590 mg, 52% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.22 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 2.37 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1, 144.0, 140.1, 138.5, 136.4, 135.9, 134.7, 134.3, 129.7, 127.7, 127.5, 126.8, 19.2, 18.3.

HRMS: m/z calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$: , found 228.1025, found 228.1028.

2-(2-Formyl-6-methylphenyl)-5-(trifluoromethyl)-pyridine 1-oxide (**28i)**



Yellow solid. 717 mg, 51% yield.

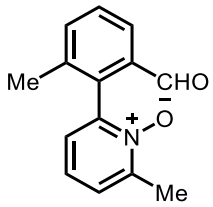
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.61 (s, 1H), 7.85 – 7.77 (m, 1H), 7.63 – 7.57 (m, 2H), 7.52 (dd, J = 8.3, 1.6 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 2.18 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.9, 151.0, 138.4, 137.7 (q, J = 3.8 Hz), 136.3, 134.6, 131.6, 130.43, 129.7 (q, J = 34.9 Hz), 128.02, 122.0 (q, J = 273.0 Hz), 121.4, 19.2.

^{19}F NMR (565 MHz, $CDCl_3$) δ -63.1.

HRMS: m/z calcd for $C_{14}H_{11}F_3NO_2$ $[M+H]^+$: 282.0742, found 282.0745.

2-(2-Formyl-6-methylphenyl)-6-methylpyridine 2-oxide (**28j**)



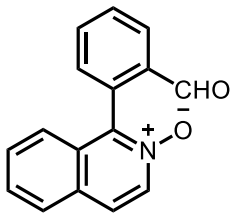
White solid. 545 mg, 48% yield.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 8.4 Hz, 1H), 2.41 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 191.4, 148.6, 145.2, 137.8, 135.7, 135.5, 134.3, 129.2, 126.5, 126.3, 126.0, 124.2, 18.8, 17.7.

HRMS: m/z calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1025, found 228.1028.

1-(2-Formylphenyl)isoquinoline 1-oxide (**28k**)



Red solid. 988 mg, 79% yield.

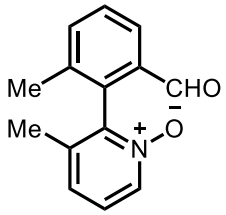
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.23 (d, J = 7.2 Hz, 1H), 8.10 (dd, J = 7.7, 1.4 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.78 (td, J = 7.5, 1.4 Hz, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.55 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.46 (td, J = 7.7, 7.0, 1.3 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 9.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.4, 143.8, 136.9, 135.3, 134.2, 132.6, 131.2, 130.2, 130.1, 129.6, 129.5, 129.0, 128.6, 127.2, 124.8, 124.1.

The NMR spectra is in agreement with published data.[5]

HRMS: m/z calcd for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0868, found 250.0873.

2-(2-formyl-6-methylphenyl)-3-methylpyridine 1-oxide (**28l**)



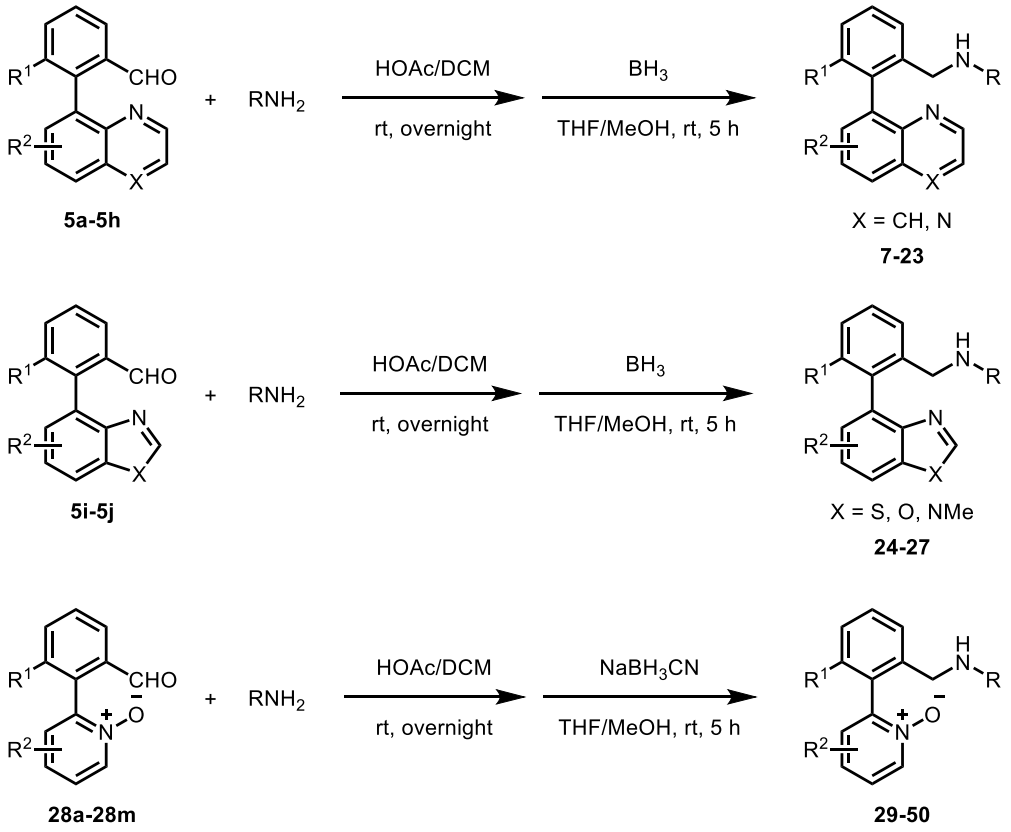
White solid. 864 mg, 76% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.26 (d, J = 6.2 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.29 – 7.19 (m, 2H), 2.12 (s, 3H), 1.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.2, 147.1, 138.0, 137.7, 136.5, 136.4, 134.1, 133.4, 129.8, 129.2, 127.5, 124.6, 19.0, 18.7.

HRMS: m/z calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1033, found 228.1025.

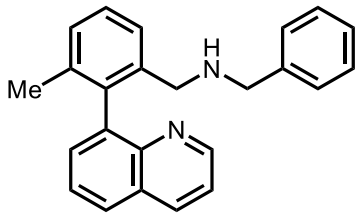
Synthesis of heterobiaryl reference compounds



General procedure

To a stirred solution of aldehyde **5a**–**5j** and **28a**–**28m** (0.4 mmol, 1.0 equiv) in dry DCM (10 mL) was added amine (0.5 mmol, 1.2 equiv) and HOAc (0.04 mmol, 0.1 equiv), the reaction mixture was stirred overnight. After completion of the reaction, the solvent was removed under reduced pressure to give the crude product (Schiff base) which was used for the next step without further purification. To the solution of Schiff base in THF/MeOH (2:1, 15 mL) under ice-bath was added BH_3 (1 M in THF, 0.8 mmol, 2.0 equiv) or $NaBH_3CN$ (4 mmol, 10 equiv), and then the reaction mixture was stirred for at 0 °C for 5 hours. After completion of the reaction, the reaction mixture was quenched by saturated NH_4Cl solution (20 mL). The resulting reaction mixture was concentrated under reduced pressure and diluted with water (20 mL), then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to provide a crude product, which was further purified by flash chromatography to provide the racemic heterobiaryl amine products (**7–27** and **29–50**).

N-Benzyl-1-[3-methyl-2-(quinolin-8-yl)phenyl]methanamine (**7**)



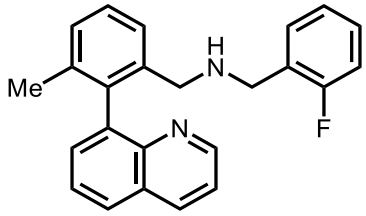
Colorless amorphous. 64 mg, 47% yield.

^{13}C NMR (101 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 6.9 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.15 (dd, *J* = 4.9, 1.9 Hz, 3H), 6.99 – 6.94 (m, 2H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.49 – 3.44 (m, 2H), 3.42 (d, *J* = 13.2 Hz, 1H), 2.37 (s, 1H), 1.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 146.8, 140.3, 139.6, 139.3, 138.4, 136.9, 136.3, 130.5, 128.6, 128.6, 128.1, 127.9, 127.7, 127.7, 126.7, 126.6, 126.3, 121.1, 53.1, 51.0, 20.7.

HRMS: m/z calcd for $C_{24}H_{23}N_2$ $[M+H]^+$: 339.1861, found 339.1861.

N-(2-Fluorobenzyl)-1-[3-methyl-2-(quinolin-8-yl)phenyl]methanamine (**8**)



White solid. 16 mg, 10% yield.

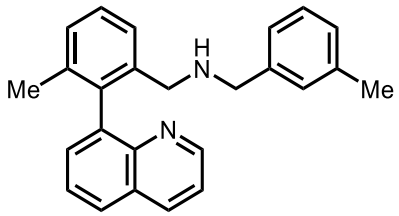
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 5.2 Hz, 1H), 8.15 – 8.08 (m, 1H), 7.76 (t, *J* = 6.6 Hz, 1H), 7.50 (q, *J* = 7.4 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.32 – 7.26 (m, 2H), 7.19 (t, *J* = 6.4 Hz, 1H), 7.07 – 6.98 (m, 1H), 6.97 – 6.89 (m, 1H), 6.86 – 6.74 (m, 2H), 3.51 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.43 (dd, *J* = 13.8, 4.9 Hz, 1H), 3.39 – 3.34 (m, 2H), 2.35 (brs, 1H), 1.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 146.8, 139.8, 139.3, 137.6 (d, *J* = 1.26 Hz, 1H), 137.1, 136.5, 130.7, 130.2, 129.0, 128.7, 128.5 (d, *J* = 2.52 Hz, 1H), 128.4, 128.0, 127.8 (d, *J* = 2.52 Hz, 1H), 127.0, 126.4, 123.9, 121.2, 115.1 (d, *J* =3.78 Hz, 1H), 115.0, 51.8, 46.2, 20.8.

^{19}F NMR (565 MHz, $CDCl_3$) δ -116.4.

HRMS: m/z calcd for $C_{24}H_{22}FN_2$ $[M+H]^+$: 357.1767 , found 357.1783.

N-(3-Methyl-2-(quinolin-8-yl)benzyl)-1-(*m*-tolyl)methanamine (**9**)



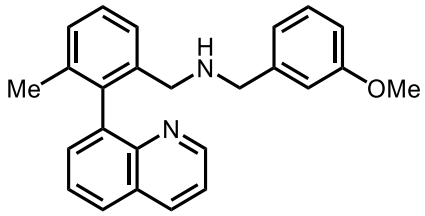
White solid. 16 mg, 10% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.52 (dd, *J* = 7.0, 1.6 Hz, 1H), 7.42 (d, *J* = 6.3 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.30 – 7.23 (m, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.83 (s, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 3.49 – 3.41 (m, 3H), 3.37 (d, *J* = 13.1 Hz, 1H), 2.25 (s, 3H), 1.90 (s, 3H), 1.83 (brs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 146.8, 140.2, 139.6, 139.3, 138.4, 137.7, 137.0, 136.4, 130.6, 128.8, 128.7, 128.7, 128.1, 127.8, 127.8, 127.4, 126.8, 126.4, 125.0, 121.2, 53.1, 52.0, 21.4, 20.7.

HRMS: m/z calcd for $C_{25}H_{25}N_2$ $[M+H]^+$: 353.2018 , found 353.2014.

N-(3-Methoxybenzyl)-1-[3-methyl-2-(quinolin-8-yl)phenyl]methanamine (**10**)



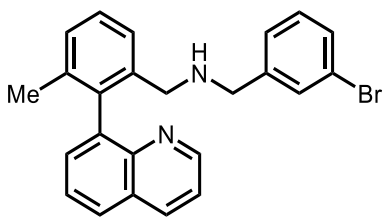
Colorless amorphous. 76 mg, 52% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.84 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.50 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.24 (s, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.68 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.63 (s, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 3.73 (s, 3H), 3.50 (d, *J* = 13.3 Hz, 1H), 3.43 (s, 2H), 3.38 (d, *J* = 13.2 Hz, 1H), 1.87 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 150.8, 146.6, 139.4, 139.0, 137.2, 136.7, 131.0, 129.5, 129.3, 128.7, 128.0, 128.0, 127.4, 126.6, 121.4, 120.8, 113.8, 113.3, 55.4, 52.4, 51.3, 20.8.

HRMS: m/z calcd for $C_{25}H_{25}N_2O$ $[M+H]^+$: 369.1967 , found 369.1967.

N-(3-Bromobenzyl)-1-[3-methyl-2-(quinolin-8-yl)phenyl]methanamine (**11**)



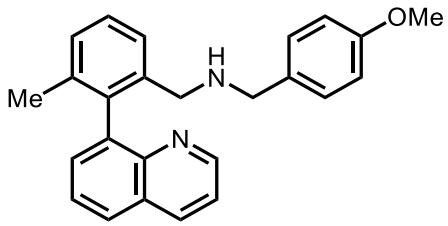
Yellow amorphous. 21 mg, 13% yield.

^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (dd, J = 4.1, 2.2 Hz, 1H), 7.68 – 7.54 (m, 2H), 7.54 – 7.51 (m, 3H), 7.50 – 7.47 (m, 1H), 7.47 – 7.39 (m, 6H), 4.26 (d, J = 13.0 Hz, 1H), 4.14 – 4.08 (m, 2H), 4.09 (d, J = 10.0 Hz, 1H), 3.68 (d, J = 13.1 Hz, 1H), 2.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 141.2, 137.5, 132.9, 132.8, 132.8, 132.6, 132.3, 131.1, 130.9, 130.9, 130.4, 129.9, 129.1, 128.9, 126.9, 123.1, 50.1, 50.1, 20.4.

HRMS: m/z calcd for $C_{24}H_{22}BrN_2$ $[M+H]^+$: 417.0966 , found 417.0940.

N-(4-Methoxybenzyl)-1-[3-methyl-2-(quinolin-8-yl)phenyl]methanamine (**12**)



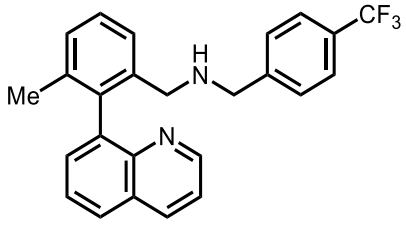
Yellow amorphous. 15 mg, 10% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 4.2 Hz, 1H), 8.30 (d, J = 6.5 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.44 – 7.37 (m, 2H), 7.32 (d, J = 7.6 Hz, 1H), 6.87 (d, J = 8.2 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 5.35 (brs, 1H), 3.76 (s, 3H), 3.75 (d, J = 6.1 Hz, 1H), 3.72 (d, J = 4.4 Hz, 1H), 3.58 (d, J = 12.6 Hz, 1H), 3.36 (d, J = 13.0 Hz, 1H), 1.78 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 150.9, 146.1, 139.5, 138.1, 137.8, 137.7, 132.4, 131.8, 131.1, 130.4, 129.0, 128.7, 128.6, 128.0, 127.1, 125.5, 121.8, 114.3, 55.4, 51.2, 51.0, 20.9.

HRMS: m/z calcd for $C_{25}H_{25}N_2O$ $[M+H]^+$: 369.1967 , found 369.1968.

N-[3-methyl-2-(quinolin-8-yl)benzyl]-1-[4-(trifluoromethyl)phenyl]methanamine (**13**)



Yellow amorphous. 17 mg, 10% yield.

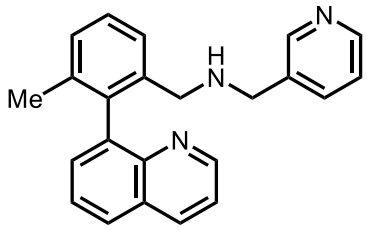
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 4.1 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 6.9 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.29 – 7.24 (m, 4H), 7.18 (d, J = 11.3 Hz, 2H), 6.93 (d, J = 7.9 Hz, 2H), 3.50 (d, J = 13.9 Hz, 1H), 3.41 – 3.29 (m, 3H), 1.98 (brs, 1H), 1.78 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.6, 146.8, 143.8, 139.4 (2), 137.3, 136.6, 130.7, 129.2, 128.7, 128.2, 128.0, 127.9, 127.1, 126.5, 125.1 (q, J = 3.7 Hz), 124.4 (q, J = 277.8 Hz), 121.3, 52.4, 51.7, 20.7.

^{19}F NMR (565 MHz, $CDCl_3$) δ -58.1.

HRMS: m/z calcd for $C_{25}H_{22}F_3N_2$ $[M+H]^+$: 407.1735 , found 407.1750.

N-(pyridin-3-ylmethyl)-1-[2-(quinolin-8-yl)-3-methylphenyl]methanamine (**14**)



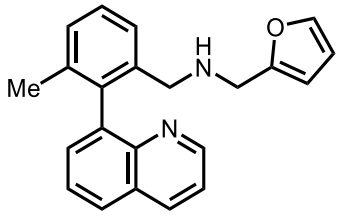
White amorphous. 72 mg, 53% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 3.7 Hz, 1H), 8.18 (d, J = 5.3 Hz, 1H), 7.83 (d, J = 6.5 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.0 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.25 (d, J = 5.3 Hz, 1H), 7.09 (q, J = 6.9 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.92 – 6.80 (m, 2H), 3.55 (d, J = 13.8 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 3.43 – 3.37 (m, 2H), 1.95 (brs, 1H), 1.88 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 149.6, 148.4, 146.7, 139.4, 139.3, 137.5, 137.3, 136.6, 135.8, 135.0, 130.6, 129.1, 128.7, 127.9, 127.0, 126.5, 123.3, 121.3, 51.9, 50.2, 20.7.

HRMS: m/z calcd for $C_{23}H_{22}N_3$ $[M+H]^+$: 340.1814, found 340.1812.

1-(Furan-2-yl)-*N*-(3-methyl-2-(quinolin-8-yl)benzyl)methanamine (**15**)



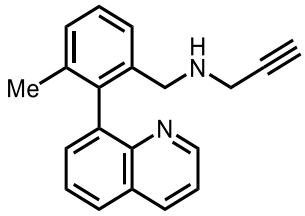
Yellow amorphous. 16 mg, 10% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.21 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 7.1 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.13 (s, 1H), 6.12 (s, 1H), 5.82 (s, 1H), 3.48 (d, J = 14.3 Hz, 1H), 3.43 – 3.33 (m, 3H), 1.93 (brs, 1H), 1.89 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 150.7, 146.8, 141.5, 139.4, 139.3, 138.1, 137.0, 136.4, 130.6, 128.8, 128.7, 127.8, 127.8, 126.8, 126.4, 121.2, 109.9, 106.6, 51.5, 45.4, 20.8.

HRMS: m/z calcd for $C_{22}H_{21}N_2O$ $[M+H]^+$: 329.1654, found 329.1655.

N-(prop-2-yn-1-yl)-1-[2-(quinolin-8-yl)-3-methylphenyl]methanamine (**16**)



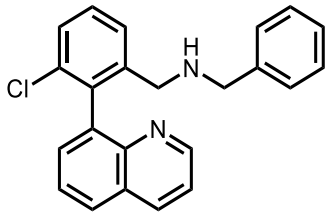
Yellow amorphous. 94 mg, 33% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (dd, J = 4.2, 1.8 Hz, 1H), 8.43 (dd, J = 8.3, 1.8 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.75 (dd, J = 7.0, 1.5 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.50 – 7.47 (m, 1H), 3.69 (d, J = 12.5 Hz, 1H), 3.61 (d, J = 12.5 Hz, 1H), 3.36 (dd, J = 16.9, 2.5 Hz, 1H), 3.29 (dd, J = 16.9, 2.4 Hz, 1H), 2.12 (s, 3H), 1.98 (t, J = 2.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 146.9, 139.4, 139.4, 137.8, 137.1, 136.5, 130.7, 128.9, 128.8, 127.9, 127.7, 126.9, 126.4, 121.3, 81.6, 70.7, 50.9, 37.4, 20.8.

HRMS: m/z calcd for $C_{20}H_{19}N_2$ $[M+H]^+$: 287.1548, found 287.1553.

N-Benzyl-1-[3-chloro-2-(quinolin-8-yl)phenyl]methanamine (**17**)



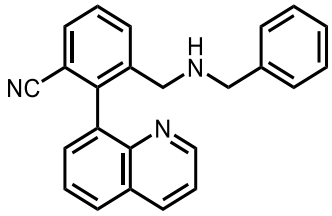
Yellow amorphous. 104 mg, 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, J = 4.2, 1.8 Hz, 1H), 8.21 (dd, J = 8.2, 1.8 Hz, 1H), 7.90 (dd, J = 7.9, 1.7 Hz, 1H), 7.66 – 7.51 (m, 3H), 7.49 (dd, J = 8.0, 1.3 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.23 – 7.12 (m, 3H), 7.05 – 6.96 (m, 2H), 3.53 (d, J = 13.2 Hz, 1H), 3.50 – 3.39 (m, 3H), 1.82 (brs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 146.6, 141.0, 140.0, 138.3, 137.4, 136.4, 134.4, 130.9, 128.9, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 126.7, 126.2, 121.3, 53.1, 51.7.

HRMS: m/z calcd for $C_{23}H_{20}ClN_2$ $[M+H]^+$: 359.1315, found 359.1302.

N-Benzyl-1-[2-(quinolin-8-yl)-3-(trifluoromethyl)phenyl]methanamine (**18**)



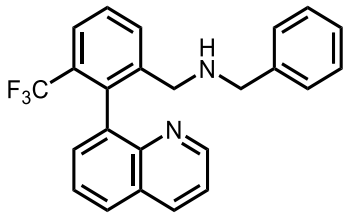
Yellow amorphous. 85 mg, 54% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, J = 4.2, 1.8 Hz, 1H), 8.24 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (dd, J = 6.1, 3.6 Hz, 1H), 7.90 (d, J = 6.5 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.54 (t, J = 7.8 Hz, 1H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.23 – 7.13 (m, 3H), 7.01 (dd, J = 7.2, 2.4 Hz, 2H), 3.54 (d, J = 13.3 Hz, 1H), 3.52 – 3.44 (m, 3H), 2.08 (brs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 146.5, 143.3, 140.5, 139.7, 136.6, 136.3, 133.5, 131.6, 131.0, 129.4, 128.7, 128.4, 128.4, 128.0, 127.0, 126.3, 121.6, 118.5, 114.3, 53.3, 51.0.

HRMS: m/z calcd for $C_{24}H_{20}N_3$ $[M+H]^+$: 350.1657, found 350.1669.

N-Benzyl-1-[2-(quinolin-8-yl)-3-(trifluoromethyl)phenyl]methanamine (**19**)



Yellow amorphous. 105 mg, 54% yield.

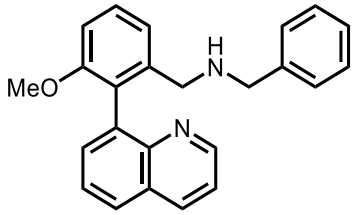
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.89 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 9.3 Hz, 1H), 7.57 (qd, *J* = 7.5, 3.1 Hz, 3H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 – 7.11 (m, 3H), 7.03 – 6.95 (m, 2H), 3.50 (d, *J* = 13.3 Hz, 1H), 3.45 – 3.29 (m, 3H), 2.04 (brs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 147.2, 140.8, 140.0, 138.1, 136.4 (×2), 132.5, 131.1, 129.7 (q, *J* = 29.2 Hz), 128.6, 128.3, 128.2, 128.0 127.9, 126.8, 125.8, 124.94 (q, *J* = 5.2 Hz), 124.2 (d, *J* = 274.3 Hz), 121.2, 53.3, 51.1.

^{19}F NMR (565 MHz, $CDCl_3$) δ -58.4.

HRMS: m/z calcd for $C_{24}H_{20}F_3N_2$ $[M+H]^+$: 393.1579, found 393.1582.

N-Benzyl-1-[3-methoxy-2-(quinolin-8-yl)phenyl]methanamine (**20**)



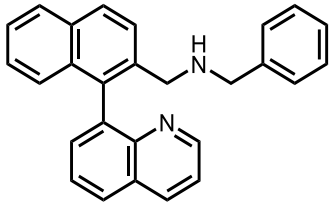
Yellow solid. 120 mg, 34% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.85 (dd, *J* = 7.3, 2.4 Hz, 1H), 7.59 (q, *J* = 6.5, 5.9 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.16 (q, *J* = 5.3 Hz, 3H), 7.00 (dd, *J* = 5.3, 3.0 Hz, 3H), 3.64 (s, 3H), 3.53 (d, *J* = 13.2 Hz, 1H), 3.48 – 3.40 (m, 3H), 1.94 (brs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 150.4, 147.2, 140.2, 140.1, 136.6, 136.4, 131.3, 128.8, 128.6, 128.6, 128.2, 128.0, 127.8, 126.7, 126.2, 121.7, 121.0, 110.0, 56.0, 53.1, 51.4.

HRMS: m/z calcd for $C_{24}H_{23}N_2O$ $[M+H]^+$: 355.1810, found 355.1829.

N-Benzyl-1-[1-(quinolin-8-yl)naphthalen-2-yl]methanamine (**21)**



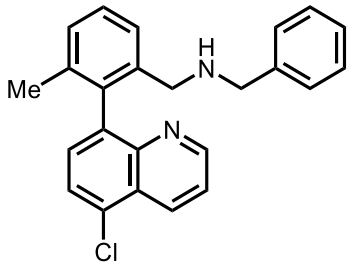
Yellow amorphous. 67 mg, 46 % yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (dd, J = 4.2, 1.8 Hz, 1H), 8.26 (dd, J = 8.3, 1.8 Hz, 1H), 7.96 (t, J = 7.6 Hz, 2H), 7.90 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.38 (dd, J = 8.3, 4.1 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.17 (h, J = 3.5 Hz, 3H), 7.11 (d, J = 8.5 Hz, 1H), 7.04 – 6.98 (m, 2H), 3.64 – 3.58 (m, 3H), 3.50 (d, J = 13.3 Hz, 1H), 2.29 (brs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 147.6, 140.3, 138.4, 136.4, 136.3, 136.2, 133.5, 132.9, 131.8, 128.6, 128.2, 128.1, 127.9, 127.5, 126.7, 126.6, 126.3, 125.8, 125.3, 121.3, 53.4, 51.9.

HRMS: m/z calcd for $C_{27}H_{23}N_2$ $[M+H]^+$: 375.1861, found 375.1862.

N-Benzyl-1-[2-(5-chloroquinolin-8-yl)-3-methylphenyl]methanamine (**22**)



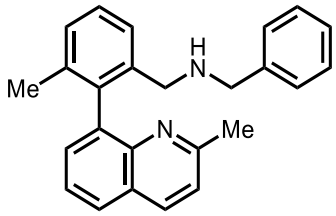
Yellow amorphous. 108 mg, 86% yield .

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (dd, J = 4.2, 1.7 Hz, 1H), 8.74 (dd, J = 8.6, 1.8 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.57 (dd, J = 8.6, 4.2 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.39 – 7.29 (m, 1H), 7.26 – 7.20 (m, 3H), 7.06 – 6.99 (m, 2H), 3.55 (d, J = 13.4 Hz, 1H), 3.51 (d, J = 12.8 Hz, 1H), 3.45 (d, J = 12.9 Hz, 1H), 1.99 (s, 3H), 1.69 (brs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 147.4, 140.2, 138.9, 138.5, 136.9, 133.1, 130.8, 130.2, 128.7, 128.2, 128.0, 127.9, 126.8, 126.7, 126.5, 121.9, 53.2, 51.6, 20.7.

HRMS: m/z calcd for $C_{24}H_{22}ClN_2$ $[M+H]^+$: 373.1472, found 373.1458.

N-Benzyl-1-[3-methyl-2-(2-methylquinolin-8-yl)phenyl]methanamine (**23**)



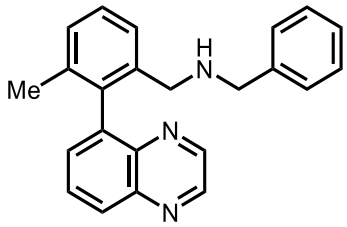
Yellow amorphous. 92 mg, 65 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 7.9, 1.7 Hz, 1H), 7.63 – 7.48 (m, 3H), 7.43 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.27 – 7.18 (m, 3H), 7.07 – 7.00 (m, 2H), 3.60 (d, J = 13.1 Hz, 1H), 3.56 – 3.51 (m, 2H), 3.42 (d, J = 13.1 Hz, 1H), 2.49 (s, 3H), 2.04 (brs, 1H), 2.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 146.4, 140.4, 139.9, 139.0, 138.6, 137.1, 136.2, 130.5, 128.4, 128.1, 127.9, 127.3, 127.2, 126.8, 126.8, 126.5, 125.3, 122.0, 53.3, 52.4, 25.4, 20.8.

HRMS: m/z calcd for $C_{25}H_{25}N_2$ $[M+H]^+$: 353.2018, found 353.2029.

N-Benzyl-1-[3-methyl-2-(quinoxalin-5-yl)phenyl]methanamine (**24**)



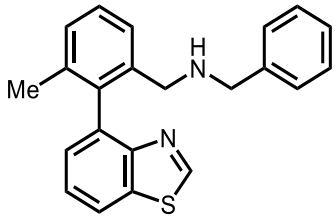
Yellow amorphous. 52 mg, 38% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, J = 1.7 Hz, 1H), 8.67 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.60 (d, J = 7.1 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.14 (dd, J = 5.0, 1.9 Hz, 3H), 6.97 (dd, J = 6.5, 2.9 Hz, 2H), 3.58 (d, J = 13.3 Hz, 1H), 3.49 (d, J = 13.3 Hz, 1H), 3.44 – 3.41 (m, 2H), 1.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.071, 145.0, 143.2, 141.6, 139.7, 138.7, 137.9, 137.4, 137.2, 131.3, 130.0, 129.4, 129.1, 128.4, 128.3, 128. 1, 127.1, 126.9, 52.8, 51.1, 20.8.

HRMS: m/z calcd for $C_{23}H_{22}N_3$ $[M+H]^+$: 340.1814, found 340.1842.

N-benzyl-1-[2-(Benzo[d]thiazol-4-yl) 3-methylbenzyl]methanamine (**25**)



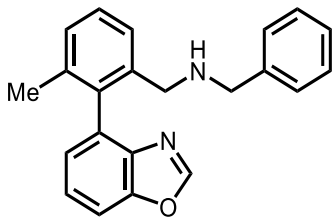
White solid. 16 mg, 10% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.38 – 7.30 (m, 2H), 7.27 (d, J = 7.4 Hz, 1H), 7.23 – 7.14 (m, 3H), 7.07 (d, J = 9.4 Hz, 2H), 3.63 (d, J = 13.2 Hz, 1H), 3.54 (d, J = 13.1 Hz, 1H), 3.51 – 3.48 (m, 2H), 1.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 151.8, 138.5, 138.1, 136.8, 135.4, 134.3, 129.0, 128.3, 128.2, 128.0, 127.3, 127.0, 126.8, 126.0, 125.8, 121.3, 53.1, 51.7, 20.8.

HRMS: m/z calcd for $C_{22}H_{21}N_2S$ $[M+H]^+$: 345.1425, found 345.1440.

N-[2-(benzo[*d*]oxazol-4-yl)-3-methylbenzyl]-1-phenylmethanamine (**26**)



Yellow amorphous. 108 mg, 82% yield.

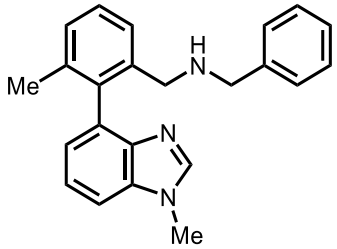
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.1, 3.4 Hz, 1H), 7.44 (q, J = 2.0 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.17 (t, J = 5.5 Hz, 2H), 7.15 – 7.05 (m, 3H), 7.01 (dd, J = 7.2, 3.4 Hz, 1H), 6.98 (t, J = 5.3 Hz, 2H),

6.73 (q, *J* = 2.2 Hz, 1H), 3.73 (d, *J* = 3.6 Hz, 1H), 3.43 (dd, *J* = 17.4, 3.6 Hz, 3H), 1.92 (s, 3H), 1.69 (brs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) *δ* 152.6, 145.2, 140.3, 139.0, 137.4, 135.7, 128.8, 128.5, 128.3, 128.2, 128.0, 127.7, 127.1, 126.78, 125.4, 123.8, 123.2, 120.6, 106.9, 53.1, 51.6, 20.5.

HRMS: m/z calcd for $C_{22}H_{21}N_2O$ $[M+H]^+$:329.1654, found 329.1668.

N-Benzyl-1-[3-methyl-2-(1-methyl-1*H*-benzo[*d*]imidazol-4-yl]phenylmethanamine (**27**)



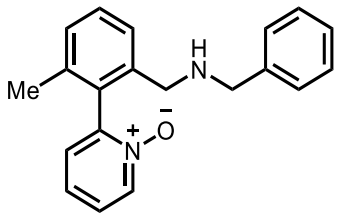
Yellow amorphous. 63 mg, 10% yield.

^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.58 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.40 – 7.33 (m, 1H), 7.33 (d, *J* = 9.6 Hz, 2H), 7.31 – 7.25 (m, 4H), 7.10 (dd, *J* = 7.0, 1.3 Hz, 1H), 4.13 (brs, 1H), 3.94 (d, *J* = 13.0 Hz, 1H), 3.85 (s, 3H), 3.79 (d, *J* = 13.0 Hz, 1H), 3.64 (d, *J* = 5.0 Hz, 1H), 3.62 (d, *J* = 5.0 Hz, 1H), 2.00 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) *δ* 144.0, 141.8, 138.4, 137.9, 134.8, 130.8, 129.2, 128.8, 128.7, 128.6, 128.1, 128.1, 127.4, 127.1, 124.1, 123.6, 109.4, 51.2, 51.0, 31.5, 21.0.

HRMS: m/z calcd for $C_{23}H_{24}N_3$ $[M+H]^+$: 342.1970, found 342.1971.

2-{2-[(Benzylamino)methyl]-6-methylphenyl}pyridine 2-oxide (**29**)



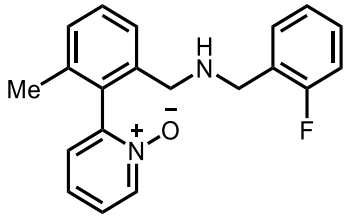
Colorless amorphous. 87 mg, 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.21 (d, *J* = 5.2 Hz, 1H), 7.65 – 7.52 (m, 3H), 7.50 – 7.43 (m, 2H), 7.40 – 7.30 (m, 4H), 7.24 – 7.19 (m, 2H), 4.08 (d, *J* = 13.1 Hz, 1H), 3.95 (d, *J* = 12.9 Hz, 1H), 3.80 (d, *J* = 13.1 Hz, 1H), 3.61 (d, *J* = 12.9 Hz, 1H), 2.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ* 148.1, 141.3, 137.6, 132.9, 132.6, 130.9, 130.7, 130.3, 130.2, 130.1, 129.8, 129.5, 128.9, 127.0, 50.8, 49.8, 20.4.

HRMS: m/z calcd for $C_{20}H_{21}N_2O$ $[M+H]^+$: 305.1654, found 305.1628.

2-{2-{[(2-Fluorobenzyl)amino]methyl}-6-methylphenyl}pyridine 2-oxide (**30**)



Colorless amorphous. 84 mg, 79% yield.

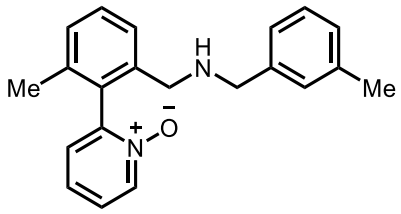
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, J = 6.9, 3.3 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.46 (q, J = 7.5 Hz, 2H), 7.38 – 7.26 (m, 4H), 7.14 (t, J = 6.9 Hz, 1H), 7.01 (t, J = 9.1 Hz, 1H), 4.15 – 4.07 (m, 1H), 4.01 – 3.92 (m, 2H), 3.60 (d, J = 12.8 Hz, 1H), 2.06 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.9, 160.3, 148.2, 141.2, 137.3, 132.5, 132.4, 132.4, 131.7 (d, J = 8.2 Hz), 131.1, 130.7, 130.0 (d, J = 2.6 Hz), 132.9, 128.6, 126.6, 125.4 (d, J = 3.7 Hz), 118.6 (d, J = 14.5 Hz), 115.8 (d, J = 21.4 Hz), 50.1, 44.0, 20.3.

^{19}F NMR (565 MHz, $CDCl_3$) δ -116.4.

HRMS: m/z calcd for $C_{20}H_{20}N_2OF$ $[M+H]^+$: 323.1560, found 323.1569.

2-{2-Methyl-6-{[(3-methylbenzyl)amino]methyl}phenyl}pyridine 2-oxide (**31**)



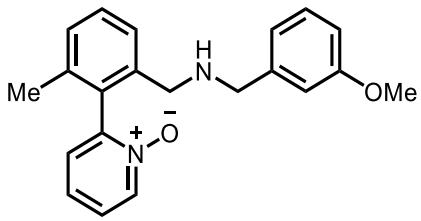
Yellow amorphous. 92 mg, 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 5.2, 2.5 Hz, 1H), 7.32 (q, J = 7.7, 7.2 Hz, 2H), 7.28 – 7.13 (m, 4H), 7.16 – 7.06 (m, 1H), 7.04 – 6.93 (m, 3H), 3.65 (d, J = 13.3 Hz, 1H), 3.59 (d, J = 13.2 Hz, 1H), 3.52 (d, J = 12.8 Hz, 1H), 3.43 (d, J = 13.1 Hz, 1H), 2.44 (brs, 1H), 2.27 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 140.3, 139.7, 138.5, 138.0, 137.2, 132.5, 129.6, 129.4, 129.2, 128.3, 128.2, 127.8, 127.3, 125.6, 125.4, 125.2, 53.3, 51.4, 21.5, 19.8.

HRMS: m/z calcd for $C_{21}H_{23}N_2O$ $[M+H]^+$: 319.1810, found 319.1805.

2-{2-{[(3-methoxybenzyl)amino]methyl}-6-methylphenyl}pyridine 2-oxide (**32**)



Colorless amorphous. 120 mg, 90% yield.

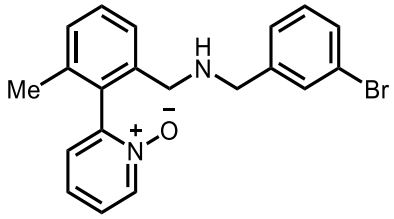
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 6.5 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.41 (d, J = 7.6 Hz, 1H), 7.30 (dd, J = 7.9, 2.0 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 6.89 – 6.82 (m, 2H), 6.80 (d,

J = 7.5 Hz, 1H), 4.02 (d, *J* = 13.0 Hz, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.80 (d, *J* = 8.3 Hz, 1H), 3.77 (s, 3H), 3.56 (d, *J* = 12.8 Hz, 1H), 2.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) *δ* 160.1, 148.1, 141.3, 137.5, 132.8, 132.4, 131.6, 130.9, 130.6, 130.3, 130.0, 129.1, 126.9, 122.0, 115.3, 115.3, 55.6, 50.7, 50.0, 20.4.

HRMS: m/z calcd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1807, found 334.1815.

2-{2-{[(3-Bromobenzyl)amino]methyl}-6-methylphenyl}pyridine 2-oxide (**33**)



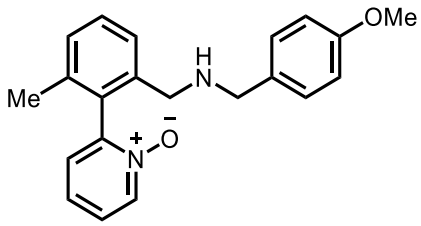
Colorless amorphous. 79 mg, 52% yield.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.25 (d, *J* = 6.4 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 4.7 Hz, 2H), 7.52 – 7.43 (m, 2H), 7.40 – 7.30 (m, 4H), 7.25 – 7.21 (m, 2H), 4.06 (d, *J* = 13.1 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.64 (d, *J* = 12.8 Hz, 1H), 2.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) *δ* 148.0, 141.2, 137.5, 132.9, 132.8, 132.8, 132.6, 132.3, 131.1, 130.9, 130.9, 130.4, 129.9, 129.1, 128.9, 126.9, 123.2, 50.1, 50.1, 20.4.

HRMS: m/z calcd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1807, found 334.1815.

2-{2-{[(4-methoxybenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**34**)



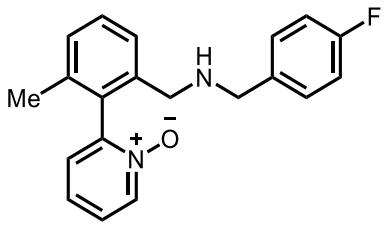
Colorless amorphous. 78 mg, 58% yield.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.26 (d, *J* = 6.5 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 11.3, 7.9 Hz, 2H), 7.30 (d, *J* = 9.9 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.06 (d, *J* = 13.0 Hz, 1H), 3.96 (d, *J* = 12.9 Hz, 1 H), 3.81 (s, 3H), 3.77 (d, *J* = 12.1 Hz, 1H), 3.59 (d, *J* = 13.0 Hz, 1H), 2.07 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) *δ* 160.5, 148.2, 141.6, 137.6, 132.8, 132.6, 131.6, 130.8, 130.5, 130.2, 128.8, 126.7, 122.3, 114.8, 114.3, 55.6, 50.2, 49.5, 20.5.

HRMS: m/z calcd for $C_{21}H_{23}N_2O_2$ $[M+H]^+$: 335.1760, found 335.1763.

2-{2-{[(4-Fluorobenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**35**)



Colorless amorphous. 44 mg, 34% yield.

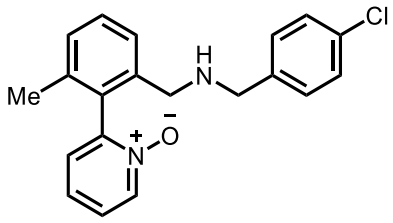
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 – 8.38 (m, 1H) , 8.16 (d, J = 6.4 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.22 – 7.15 (m, 2H), 6.91 (t, J = 8.4 Hz, 2H), 3.96 – 3.87 (m, 2H), 3.76 (d, J = 13.1 Hz, 1H), 3.50 (d, J = 12.7 Hz, 1H), 1.96 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 162.1, 147.9, 141.0, 137.4, 132.7, 132.3, 132.1 (d, J = 8.5 Hz), 130.8 (d, J = 21.2 Hz), 130.2, 129.8, 129.2, 129.1, 126.8, 126.4 (d, J = 3.3 Hz), 116.2 (d, J = 21.7 Hz), 49.9, 20.3.

^{19}F NMR (565 MHz, $CDCl_3$) δ -111.0.

HRMS: m/z calcd for $C_{20}H_{20}N_2OF$ $[M+H]^+$: 323.1560, found 323.1565.

2-{2-{[(4-Chlorobenzyl)amino]methyl}-6-methylphenyl}pyridine 1-oxide (**36**)



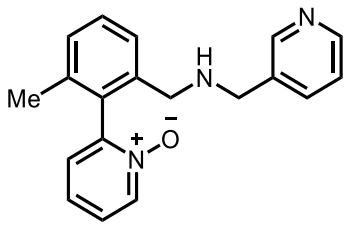
Colorless amorphous. 69 mg, 51% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 – 8.38 (m, 1H), 7.46 (d, J = 4.6 Hz, 2H), 7.40 (dd, J = 5.7, 3.1 Hz, 2H), 7.36 (d, J = 5.2 Hz, 2H), 7.31 (d, J = 8.5 Hz, 3H), 1H NMR (500 MHz, Chloroform-d) δ 8.44 – 8.38 (m, 1H), 7.46 (d, J = 4.6 Hz, 2H), 7.29 – 7.27 (m, 2H), 3.82 (d, J = 13.5 Hz, 1H), 7.27 (d, J = 8.2 Hz, 2H), 3.82 (d, J = 13.5 Hz, 1H), 3.74 (d, J = 13.4 Hz, 1H), 3.62 (d, J = 12.8 Hz, 1H), 3.57 (d, J = 13.0 Hz, 1H), 2.62 (brs, 1H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 148.1, 141.0, 137.7, 135.3, 132.7, 132.2, 131.5, 131.4, 130.8, 130.4, 130.1, 129.6, 129.2, 129.0, 126.9, 49.7, 49.6, 19.0.

HRMS: m/z calcd for $C_{20}H_{20}N_2OCl$ $[M+H]^+$: 339.1246, found 339.1277.

2-{2-Methyl-6-{[(pyridin-3-ylmethyl)amino]methyl}phenyl}pyridine 2-oxide (**37**)



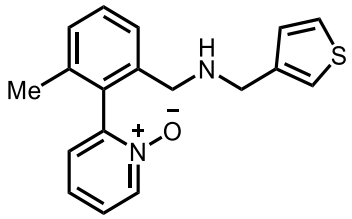
Colorless amorphous. 84 mg, 69% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 6.6 Hz, 2H), 8.27 – 8.22 (m, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.32 – 7.19 (m, 5H), 7.16 – 7.07 (m, 2H), 4.11 (brs, 1H), 3.69 (d, J = 13.5 Hz, 1H), 3.62 (d, J = 13.5 Hz, 1H), 3.51 – 3.43 (m, 2H), 2.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 149.2, 148.8, 140.5, 137.3, 137.0, 136.3, 134.1, 132.6, 130.0, 129.7, 128.3, 127.7, 126.3, 125.5, 123.5, 51.4, 50.2, 19.9.

HRMS: m/z calcd for $C_{19}H_{20}N_3O$ $[M+H]^+$:360.1606, found 360.1613.

2-{2-Methyl-6-{[(thiophen-3-ylmethyl)amino]methyl}phenyl}pyridine 1-oxide (**38**)



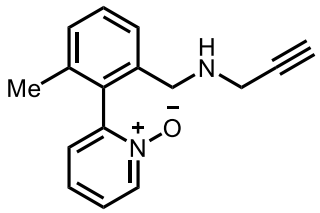
Colorless amorphous. 32 mg, 26% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 – 8.31 (m, 1H), 7.42 – 7.34 (m, 2H), 7.29 (dd, J = 5.9, 2.8 Hz, 2H), 7.25 – 7.18 (m, 3H), 7.08 – 7.04 (m, 1H), 6.97 (d, J = 4.9 Hz, 1H), 3.73 (d, J = 13.6 Hz, 1H), 3.68 (d, J = 13.7 Hz, 1H), 3.55 (d, J = 12.9 Hz, 1H), 3.48 (d, J = 12.9 Hz, 1H), 2.42 (brs, 1H), 2.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 141.4, 137.5, 132.7, 132.5, 131.0, 130.8, 130.6, 130.4, 130.1, 128.9, 128.3, 127.6, 127.5, 126.9, 49.8, 44.9, 20.4.

HRMS: m/z calcd for $C_{18}H_{19}N_2OS$ $[M+H]^+$:311.1218, found 311.1210.

2-{2-Methyl-6-[(prop-2-yn-1-ylamino)methyl]phenyl}pyridine 2-oxide (**39**)



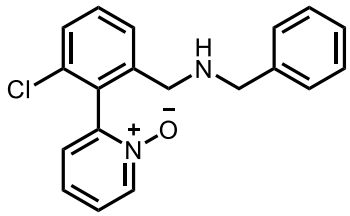
White solid. 31 mg, 31% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, J = 6.5, 1.3 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.53 (ddd, J = 7.7, 6.4, 2.1 Hz, 1H), 7.42 (d, J = 4.6 Hz, 2H), 7.39 – 7.33 (m, 2H), 6.41 (brs, 1H), 3.75 (d, J = 12.6 Hz, 1H), 3.70 (d, J = 12.6 Hz, 1H), 3.45 (dd, J = 16.9, 2.5 Hz, 1H), 3.35 (dd, J = 17.0, 2.5 Hz, 1H), 2.27 (t, J = 2.4 Hz, 1H), 2.08 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 141.3, 137.5, 133.8, 132.5, 131.4, 130.4, 129.2, 128.9, 128.8, 126.3, 75.2, 50.0, 36.5, 20.2.

HRMS: m/z calcd for $C_{16}H_{17}N_2O$ $[M+H]^+$: 253.1341, found 253.1349.

2-{2-[(benzylamino)methyl]-6-chlorophenyl}pyridine 2-oxide (**40**)



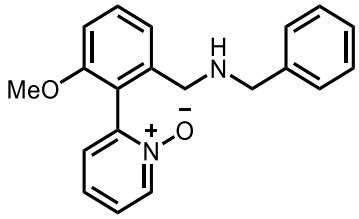
Colorless amorphous. 48 mg, 32% yield.

^{1}H NMR (500 MHz, CD_3OD) δ 8.45 (d, J = 6.5 Hz, 1H), 7.81 – 7.70 (m, 3H), 7.69 – 7.58 (m, 3H), 7.49 – 7.41 (m, 5H), 4.29 (d, J = 13.0 Hz, 1H), 4.25 (d, J = 13.0 Hz, 1H), 4.13 (d, J = 13.0 Hz, 1H), 3.74 (d, J = 13.1 Hz, 1H).

^{13}C NMR (126 MHz, CD_3OD) δ 146.1, 140.9, 134.1, 133.2, 132.1, 131.9, 131.4, 131.0, 130.9, 130.4, 130.1, 129.9, 129.4, 129.1, 127.6, 50.6, 49.1.

HRMS: m/z calcd for $C_{19}H_{18}ClN_2O$ $[M+H]^+$:325.1108 found 325.1129.

2-{2-[(Benzylamino)methyl]-6-methoxyphenyl}pyridine 2-oxide (**41**)



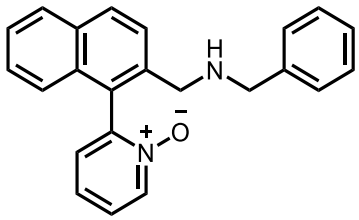
Colorless amorphous. 32 mg, 25% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 6.5 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.47 – 7.41 (m, 1H), 7.39 – 7.31 (m, 4H), 7.28 (dd, J = 9.7, 5.0 Hz, 3H), 7.13 (d, J = 8.5 Hz, 1H), 4.09 (d, J = 13.0 Hz, 1H), 3.94 (d, J = 12.8 Hz, 1H), 3.85 (d, J = 12.9 Hz, 1H), 3.72 (s, 3H), 3.58 (d, J = 12.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 145.8, 141.0, 132.5, 131.5, 130.7, 130.5, 130.3, 130.0, 129.8, 129.5, 126.7, 124.4, 121.4, 113.6, 56.2, 50.8, 49.6.

HRMS: m/z calcd for $C_{20}H_{21}N_2O_2$ $[M+H]^+$:321.1603, found 321.1605.

2-{2-[(Benzylamino)methyl]naphthalen-1-yl}pyridine 2-oxide (**42**)



White solid. 87 mg, 64% yield.

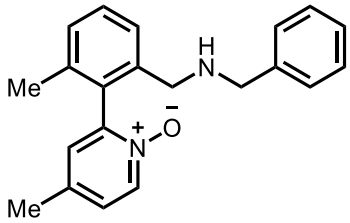
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (dd, J = 4.2, 1.8 Hz, 1H), 8.26 (dd, J = 8.3, 1.8 Hz, 1H), 7.99 – 7.93 (m, 2H), 7.90 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.69 – 7.59 (m, 2H), 7.44 – 7.35 (m, 2H),

7.23 (t, *J* = 7.7 Hz, 1H), 7.19 – 7.13 (m, 3H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.01 (dd, *J* = 7.0, 2.5 Hz, 2H), 3.64 – 3.58 (m, 3H), 3.50 (d, *J* = 13.3 Hz, 1H), 2.29 (brs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ* 150.7, 147.6, 140.3, 138.4, 136.4, 136.3, 136.2, 133.5, 132.9, 131.8, 128.6, 128.2, 128.1, 127.9, 127.5, 126.7, 126.6, 126.3, 125.8, 125.3, 121.3, 53.4, 51.9.

HRMS: m/z calcd for $C_{23}H_{21}N_2O$ $[M+H]^+$: 341.1654, found 341.1658.

2-(2-((Benzylamino)methyl)-6-methylphenyl)-4-methylpyridine 1-oxide (**43**)



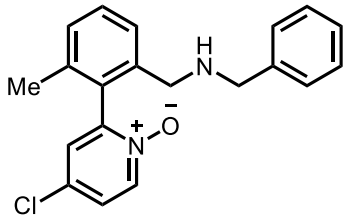
White solid. 31 mg, 24 % yield.

^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.22 (d, *J* = 6.6 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.30 – 7.22 (m, 5H), 7.24 – 7.18 (m, 1H), 7.08 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.02 (d, *J* = 2.6 Hz, 1H), 3.76 (d, *J* = 13.3 Hz, 1H), 3.69 (d, *J* = 13.3 Hz, 1H), 3.58 (d, *J* = 13.0 Hz, 1H), 3.50 (d, *J* = 12.9 Hz, 1H), 2.35 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) *δ* 148.6, 139.7, 139.3, 137.9, 137.6, 137.2, 132.7, 129.6, 129.6, 128.7, 128.5, 128.5, 127.5, 127.2, 126.1, 53.1, 51.4, 20.5, 19.9.

HRMS: m/z calcd for $C_{21}H_{23}N_2O$ $[M+H]^+$: 319.1810, found 319.1810.

2-{2-[(Benzylamino)methyl]-6-methylphenyl}-4-chloropyridine 1-oxide (**44**)



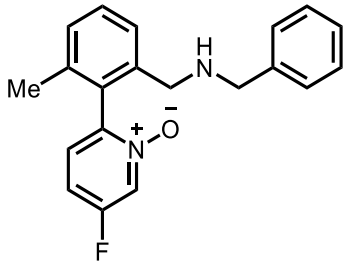
White solid. 38 mg, 28 % yield.

^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.18 (d, *J* = 6.9 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.27 – 7.14 (m, 8H), 3.69 (d, *J* = 13.3 Hz, 1H), 3.64 (d, *J* = 13.3 Hz, 1H), 3.54 (d, *J* = 12.8 Hz, 1H), 3.42 (d, *J* = 12.7 Hz, 1H), 2.17 (brs, 1H), 2.08 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) *δ* 150.3, 140.7, 139.8, 138.6, 137.2, 131.5, 131.3, 129.9, 129.4, 128.4, 128.3, 128.1, 127.4, 127.0, 125.4, 53.5, 51.5, 19.7.

HRMS: m/z calcd for $C_{20}H_{20}ClN_2O$ $[M+H]^+$:339.1264, found 339.1271.

2-{2-[(benzylamino)methyl]-6-methylphenyl}-5-fluoropyridine 1-oxide (**45**)



White solid. 33 mg, 26 % yield.

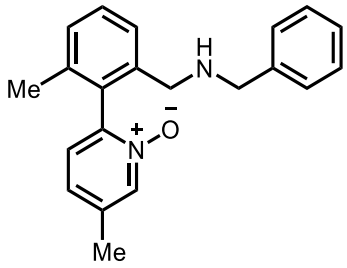
^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (dd, J = 4.2, 2.3 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.57 – 7.49 (m, 4H), 7.51 – 7.41 (m, 5H), 4.29 (d, J = 13.0 Hz, 1H), 4.15 (d, J = 8.7 Hz, 1H), 4.12 (d, J = 8.9 Hz, 1H), 3.71 (d, J = 12.9 Hz, 1H), 2.08 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 160.9, 159.2, 144.8, 138.1, 132.2, 132.0, 131.3 (d, J = 36.5 Hz), 130.9, 130.4, 130.0, 129.5 (d, J = 9.1 Hz), 129.3, 129.1, 129.0, 118.4 (d, J = 19.8 Hz), 50.5, 49.0, 18.8.

^{19}F NMR (565 MHz, $CDCl_3$) δ -119.1.

HRMS: m/z calcd for $C_{20}H_{20}N_2OF$ $[M+H]^+$: 323.1560, found 323.1534.

2-{2-[(Benzylamino)methyl]-6-methylphenyl}-5-methylpyridine 2-oxide (**46**)



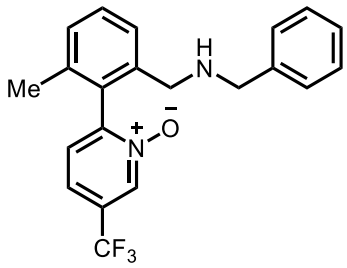
White solid. 89 mg, 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.44 (d, J = 6.4 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.33 – 7.26 (m, 3H), 7.25 – 7.21 (m, 3H), 7.17 – 7.14 (m, 1H), 7.10 (d, J = 7.9 Hz, 1H), 5.14 (brs, 1H), 3.85 (d, J = 13.3 Hz, 1H), 3.72 (d, J = 13.3 Hz, 1H), 3.59 (d, J = 2.6 Hz, 2H), 2.35 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 140.5, 137.3, 136.5, 136.3, 132.6, 130.2, 129.7, 128.9, 128.6, 128.2, 128.1, 127.6, 127.5, 52.5, 50.9, 20.0, 18.3.

HRMS: m/z calcd for $C_{21}H_{23}N_2O$ $[M+H]^+$: 319.1810, found 319.1810.

2-{2-[(Benzylamino)methyl]-6-methylphenyl}-5-(trifluoromethyl)pyridine 2-oxide (**47**)



Colorless amorphous. 65 mg, 44% yield.

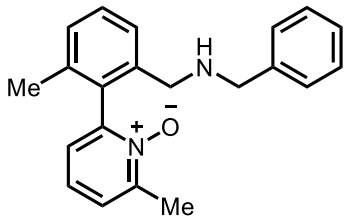
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.58 – 7.51 (m, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.32 – 7.26 (m, 3H), 7.24 – 7.22 (m, 1H), 3.98 (d, J = 13.2 Hz, 1H), 3.79 (d, J = 4.5 Hz, 1H), 3.76 (d, J = 4.0 Hz, 1H), 3.54 (d, J = 12.8 Hz, 1H), 2.07 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 154.3, 145.4, 138.3, 138.2, 124.8 (q, J = 3.9 Hz), 136.2, 130.4, 128.4 (2), 128.0, 127.2 (q, J = 31.5 Hz), 126.9, 126.6, 125.9, 124.8 (q, J = 3.9 Hz), 124.2 (q, J = 271.8 Hz), 119.1, 116.1, 51.7, 50.5, 20.2.

^{19}F NMR (565 MHz, CD_3OD) δ -64.4.

HRMS: m/z calcd for $C_{21}H_{20}F_3N_2O$ $[M+H]^+$: 373.1528, found 373.1536.

2-{2-[(Benzylamino)methyl]-6-methylphenyl}-6-methylpyridine 2-oxide (**48**)



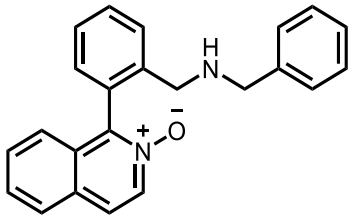
White solid. 63 mg, 61% yield.

^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (d, J = 5.0 Hz, 2H), 7.56 – 7.51 (m, 3H), 7.47 – 7.39 (m, 5H), 4.24 – 4.10 (m, 3H), 3.79 (d, J = 12.9 Hz, 1H), 2.60 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD) δ 151.9, 148.7, 138.2, 134.0, 132.7, 131.9, 131.1, 131.0, 130.6, 129.8, 129.5, 129.5, 128.1, 127.6, 50.8, 50.5, 19.5, 17.7.

HRMS: m/z calcd for $C_{21}H_{23}N_2O$ $[M+H]^+$: 319.1810, found 319.1815.

1-{2-[(Benzylamino)methyl]phenyl}isoquinoline 1-oxide (**49**)



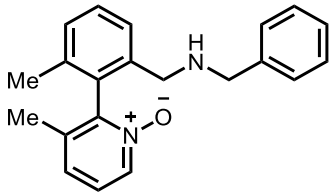
White solid. 63 mg, 46% yield.

^{1}H NMR (500 MHz, CD_3OD) δ 8.38 (d, J = 7.2 Hz, 1H), 8.15 (dd, J = 13.5, 7.7 Hz, 2H), 7.89 – 7.84 (m, 2H), 7.80 – 7.65 (m, 3H), 7.41 (d, J = 8.1 Hz, 2H), 7.28 – 7.24 (m, 3H), 7.17 – 7.12 (m, 2H), 3.78 (d, J = 13.2 Hz, 1H), 3.63 (d, J = 13.2 Hz, 1H), 3.59 (d, J = 12.8 Hz, 1H), 3.56 (d, J = 12.8 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 147.0, 136.5, 133.5, 131.5, 131.2, 131.1, 131.1,131.0, 130.9, 130.8, 130.5, 130.4, 130.2, 129.7, 129.5, 129.1, 127.5, 126.2, 125.3, 50.8, 49.8.

HRMS: m/z calcd for $C_{23}H_{21}N_2O$ $[M+H]^+$: 341.1654, found 341.1671.

2-{2-[(Benzylamino)methyl]-6-methylphenyl}-3-methylpyridine 1-oxide (**50**)



White solid. 66 mg, 52% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 6.3 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 19.3 Hz, 4H), 7.25 – 7.16 (m, 4H), 3.86 (d, J = 13.3 Hz, 1H), 3.73 (d, J = 13.2 Hz, 1H), 3.63 (d, J = 13.0 Hz, 1H), 3.52 (d, J = 12.9 Hz, 1H), 1.99 (s, 3H), 1.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 138.3, 136.9, 136.7, 134.9, 131.8, 130.8, 129.8, 129.1 (2), 128.8, 128.7, 127.9, 124.8, 115.0, 52.1, 50.9, 19.4, 19.0.

HRMS: m/z calcd for $C_{21}H_{23}N_2O$ $[M+H]^+$: 319.1810, found 319.1816.

Evaluation of Barriers to Rotation

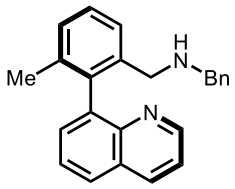
The racemization study for atropisomer (*S*)-**7** (6 mg/ mL) was performed at 100 °C in toluene heated with an oil bath. Aliquots were taken at different time intervals and the decay in enantiomeric excess (*ee*) was monitored by chiral HPLC analysis. The slope of the first-order kinetic line (plot of ln(*ee*) vs time) gives the racemization constant (k_{rac} = 2 x k_{enant}). Eyring equation gives the enantiomerization barrier from the enantiomerization constant (k_{enant}).

k_{rac} = 2.30 x 10^{-7} s^{-1} (at 100 °C);

k_{enant} = k_{rac}/2 = 1.15 x 10^{-7} s^{-1} (at 100 °C);

$\Delta G^{\neq}_{enant}$ = 141.7 kJ/mol = 33.8 kcal/mol (at 100 °C);

Half-life time $t_{1/2}$ = ln2/k_{rac} = 3013683 s = 837.1 h (at 100 °C).



(*S*)-**7**

Solvent: Toluene

Temperature: 100 °C

Time (s)	*ee* (%)
2820	96.4
7860	96.5
22440	95.9
71220	94.8
93720	94.3
172260	92.8
256080	91.1
341460	89.1
363840	88.7

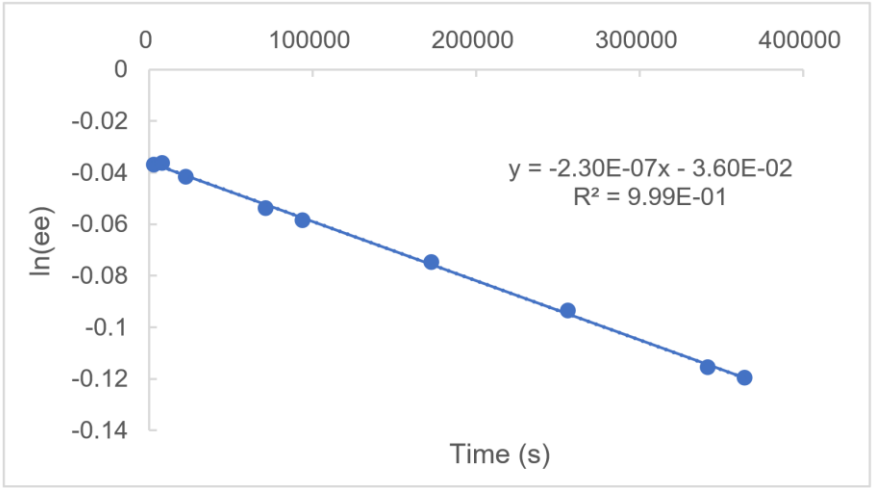


Fig. S9. The plot of ln(*ee*) v T (s) for the decay in *ee* of compound (*S*)-**7.**

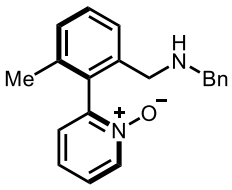
The racemization study for atropisomer (*S*)-**29** (6 mg/ mL) was performed at 100 °C in toluene heated with an oil bath. Aliquots were taken at different time intervals and the decay in enantiomeric excess (*ee*) was monitored by chiral HPLC analysis.

k_{rac} = 5.01 x 10^{-6} s^{-1} (at 100 °C);

k_{enant} = k_{rac}/2 = 2.51 x 10^{-6} s^{-1} (at 100 °C);

$\Delta G^{\neq}_{enant}$ = 132.1 kJ/mol = 31.6 kcal/mol (at 100 °C);

Half-life time $t_{1/2}$ = ln2/k_{rac} = 138353 s = 38.4 h (at 100 °C).



(*S*)-**29**

Solvent: Toluene

Temperature: 100 °C

Time (s)	*ee* (%)
0	100.0
3240	96.0
7500	93.9
11220	92.3
14460	91.3
22980	86.4
52680	77.6
67080	70.0
89580	62.1

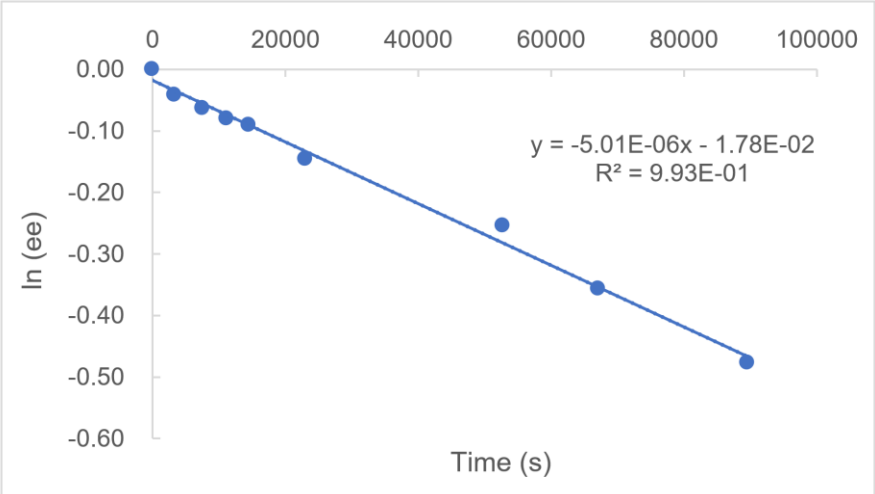
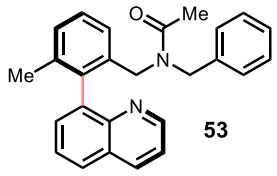


Fig. S10. The plot of ln(*ee*) v T (s) for the decay in *ee* of compound (*S*)-**29.**

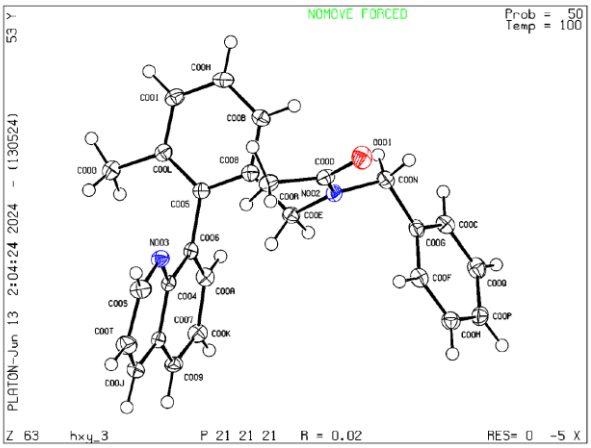
X-ray Crystallography

Experiment details. Low-temperature X-ray diffraction data was collected on a Rigaku XtaLAB Synergy diffractometer coupled to a Rigaku Hypix detector with Cu Kα radiation (λ = 1.54184 Å), from a PhotonJet micro-focus X-ray source at 173 K. The diffraction images were processed and scaled using the CrysAlisPro software. Using Olex2, the structure was solved with the SHELXT structure solution program using Direct Methods and refined with the SHELXL. The residual values of the refinements are listed in Table S8-11. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers 2381733 (**29**), 2381730 (**45**), 2381732 (**48**), 2381731 (**53**). Copies of these data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.



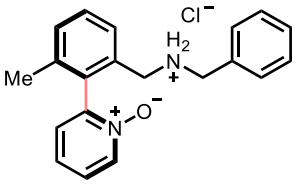
53

N-acylated (*S*)-**7**

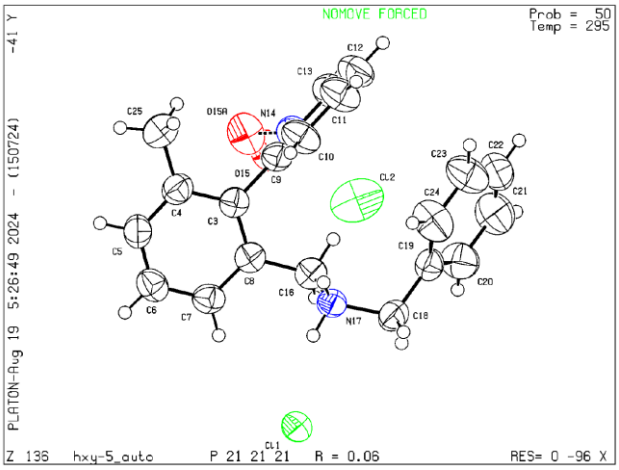


Identification code	hxy_3
Empirical formula	$C_{26}H_{24}N_2O$
Formula weight	380.47
Temperature/K	100.02(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.50530 (10)
b/Å	11.21780 (10)
c/Å	18.29070 (10)
α/°	90
β/°	90
γ/°	90
Volume/Å	1950.31 (3)
Z	4
ρcalcg/cm^3	1.296
μ/mm-1	0.616
F(000)	808.0
Crystal size/mm^3	0.16 × 0.14 × 0.13
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.248 to 155.172
Index ranges	-11 ≤ h ≤ 12, -13 ≤ k ≤ 14, -22 ≤ l ≤ 23
Reflections collected	30036
Independent reflections	4013 [R_{int} = 0.0215, R_{sigma} = 0.0101]
Data/restraints/parameters	4013/0/265
Goodness-of-fit on F2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0249, wR_2 = 0.0652
Final R indexes [all data]	R_1 = 0.0250, wR_2 = 0.0652
Largest diff. peak/hole / e Å^{-3}	0.18/-0.14
Flack parameter	0.04 (4)

Table S8. Crystal data and structure refinement for **53** (CCDC: 2381731).

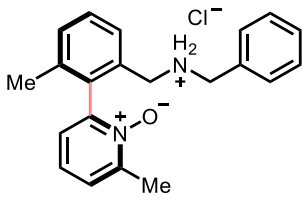


(*S*)-**29** HCl salt

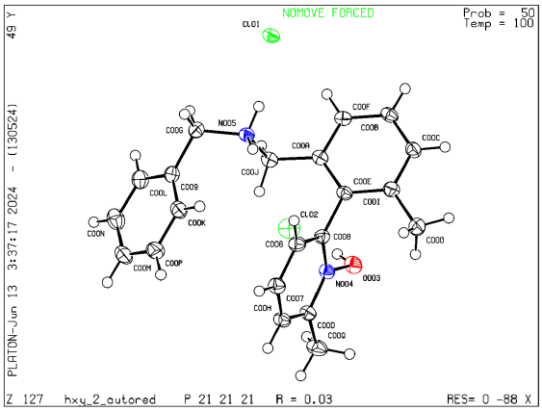


Identification code	hxy-5_auto
Empirical formula	$C_{20}H_{22}Cl_2N_2O$
Formula weight	377.29
Temperature/K	295.24 (10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.8488 (3)
b/Å	15.7366 (5)
c/Å	15.8854 (6)
α/°	90
β/°	90
γ/°	90
Volume/Å	1962.06 (12)
Z	4
ρcalcg/cm^3	1.277
μ/mm-1	3.046
F(000)	792.0
Crystal size/mm3	0.14 × 0.1 × 0.08
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.908 to 150.468
Index ranges	-7 ≤ h ≤ 9, -17 ≤ k ≤ 19, -19 ≤ l ≤ 18
Reflections collected	10412
Independent reflections	3909 [Rint = 0.0352, Rsigma = 0.0405]
Data/restraints/parameters	3909/0/231
Goodness-of-fit on F2	1.063
Final R indexes [I>=2σ (I)]	R1 = 0.0573, wR2 = 0.1673
Final R indexes [all data]	R1 = 0.0653, wR2 = 0.1754
Largest diff. peak/hole / e Å^{-3}	0.83/-0.57
Flack parameter	-0.022 (9)

Table S9. Crystal data and structure refinement for (*S*)-**29** HCl salt (CCDC: 2381733).

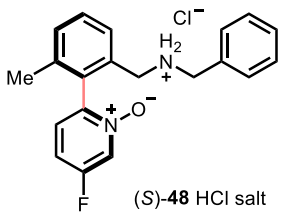


(*S*)-**45** HCl salt

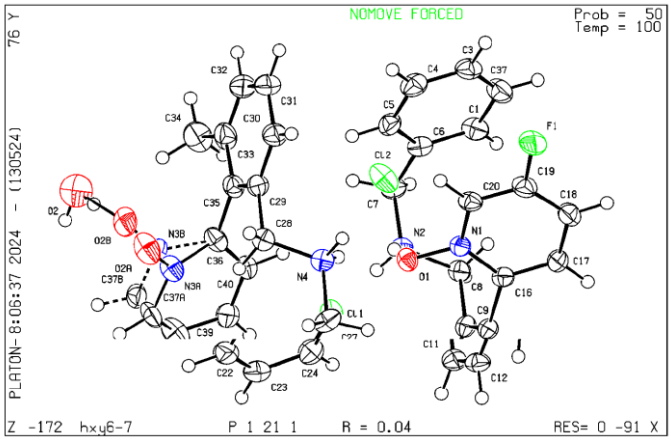


Identification code	HXY_2_autored
Empirical formula	$C_{21}H_{24}Cl_2N_2O$
Formula weight	391.32
Temperature/K	100.00 (10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.90220 (10)
b/Å	15.1936 (2)
c/Å	16.9727 (2)
α/°	90
β/°	90
γ/°	90
Volume/Å	2037.79 (4)
Z	4
ρcalcg/cm^3	1.276
μ/mm-1	2.951
F(000)	824.0
Crystal size/mm3	0.13 × 0.09 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.81 to 155.222
Index ranges	-9 ≤ h ≤ 9, -19 ≤ k ≤ 19, -21 ≤ l ≤ 15
Reflections collected	27542
Independent reflections	4146 [R_{int} = 0.0373, R_{sigma} = 0.0175]
Data/restraints/parameters	4146/0/238
Goodness-of-fit on F2	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0289, wR_2 = 0.0803
Final R indexes [all data]	R_1 = 0.0292, wR_2 = 0.0806
Largest diff. peak/hole / e Å^{-3}	0.38/-0.29
Flack parameter	-0.002 (4)

Table S10. Crystal data and structure refinement for (*S*)-**45** HCl salt (CCDC: 2381730).



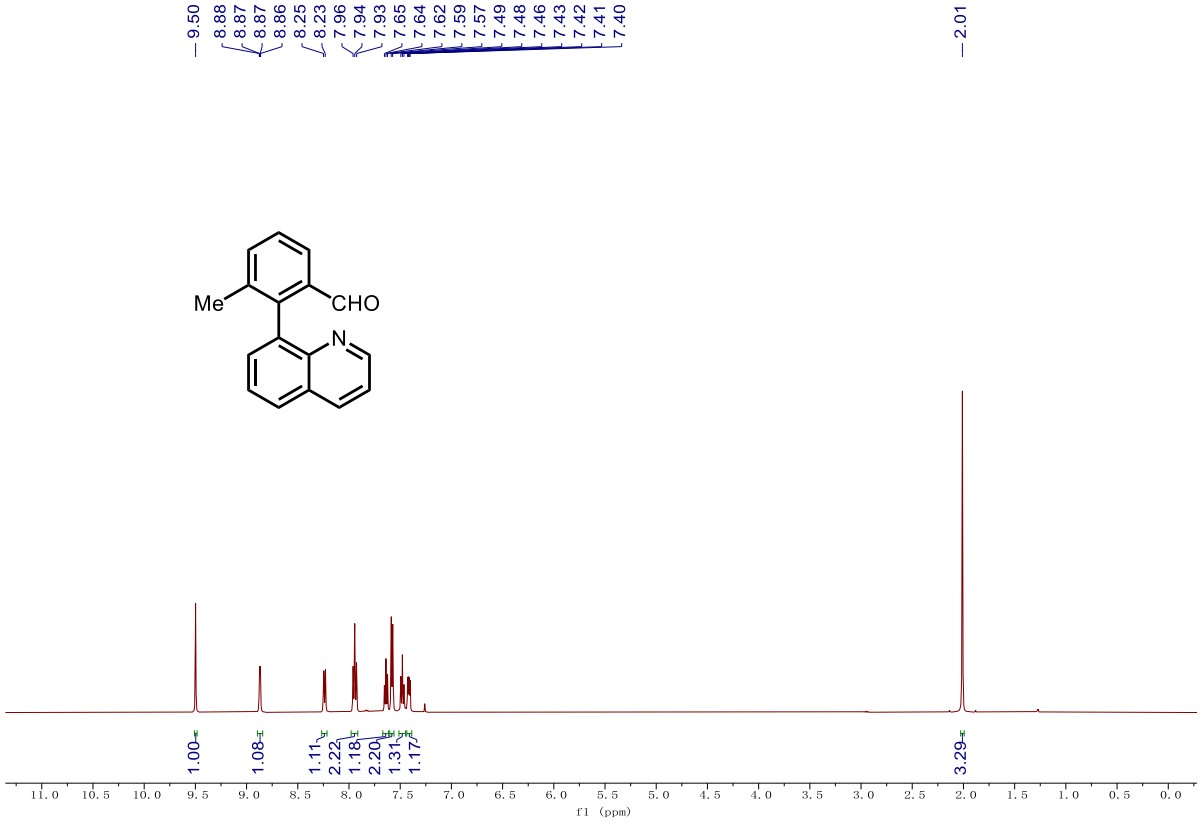
(*S*)-**48** HCl salt

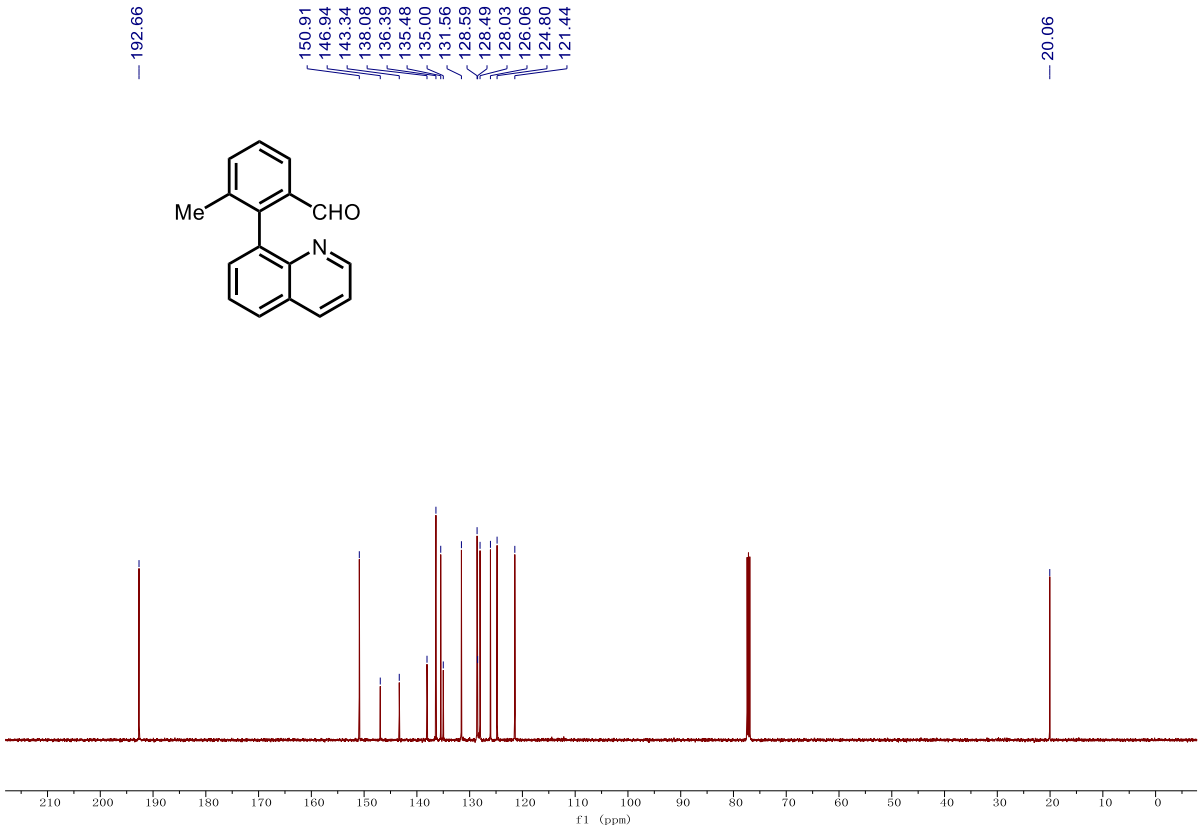


Identification code	hxy6-7
Empirical formula	$C_{20}H_{20.5}ClFN_2O_{1.25}$
Formula weight	363.33
Temperature/K	100.00 (10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.2259 (2)
b/Å	19.4327 (3)
c/Å	10.2890 (3)
α/°	90
β/°	117.079 (3)
γ/°	90
Volume/Å	1820.47 (8)
Z	4
ρcalcg/cm^3	1.326
μ/mm-1	2.038
F(000)	762.0
Crystal size/mm3	0.1 × 0.07 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.102 to 149.978
Index ranges	-12 ≤ h ≤ 7, -24 ≤ k ≤ 23, -12 ≤ l ≤ 12
Reflections collected	17287
Independent reflections	6613 [Rint = 0.0377, Rsigma = 0.0410]
Data/restraints/parameters	6613/1/488
Goodness-of-fit on F2	1.030
Final R indexes [I>=2σ (I)]	R1 = 0.0372, wR2 = 0.0974
Final R indexes [all data]	R1 = 0.0391, wR2 = 0.0987
Largest diff. peak/hole / e Å^{-3}	0.37/-0.27
Flack parameter	-0.001 (7)

Table 11. Crystal data and structure refinement for (*S*)-**48** HCl salt (CCDC: 2381732)**.**

3. NMR spectra






9.46
9.45
8.87
8.27
8.25
8.24
8.03
8.02
8.01
7.99
7.98
7.80
7.79
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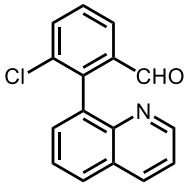
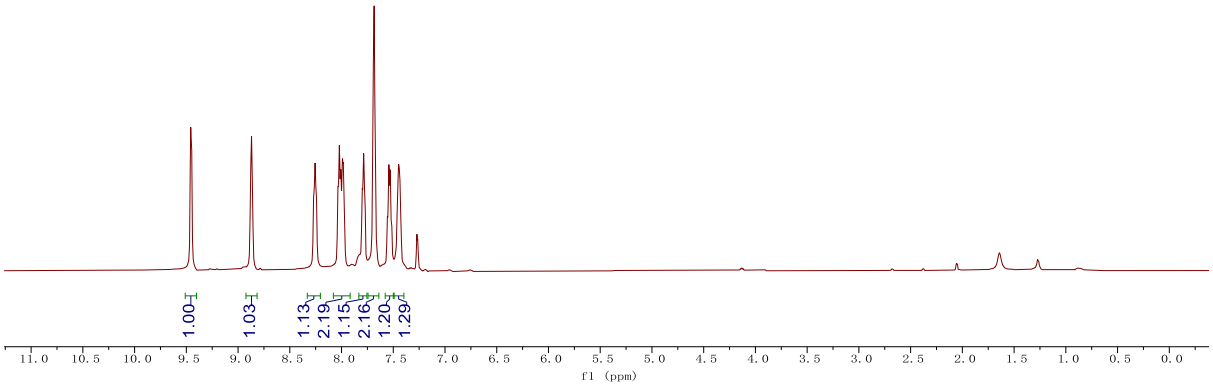
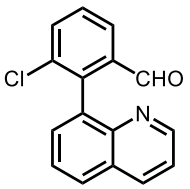
7.53
7.51
7.46
7.45
7.44
7.42


Cl
CHO
N


1.00
1.03
1.13
2.19
1.15
2.16
1.20
1.29
f1 (ppm)


191.39
151.09
146.90
141.99
136.71
136.43
135.45
134.83
134.09
132.11
129.35
129.27
128.45
126.03
125.67
121.67


Cl
CHO
N

f1 (ppm)


9.45
9.44
8.85
8.84
8.57
8.56
8.55
8.54
8.33
8.32
8.31
8.30
8.27
8.26
8.25
8.24
7.99
7.99
7.98
7.97
7.89
7.88
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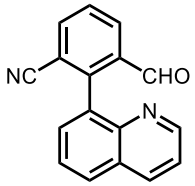
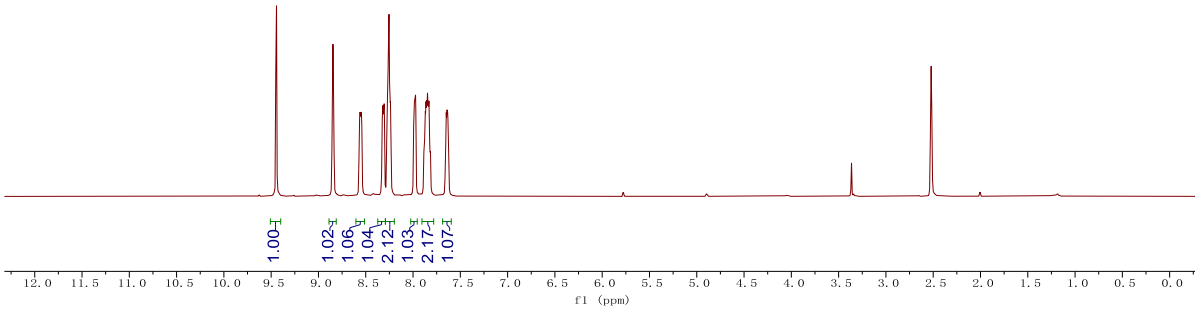
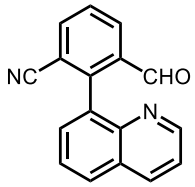
7.84
7.83
7.82
7.65
7.64
7.63


NC
CHO
N

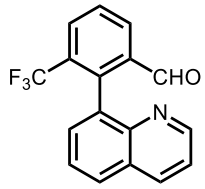

1.00
1.02
1.06
1.04
2.12
1.03
2.17
1.07
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

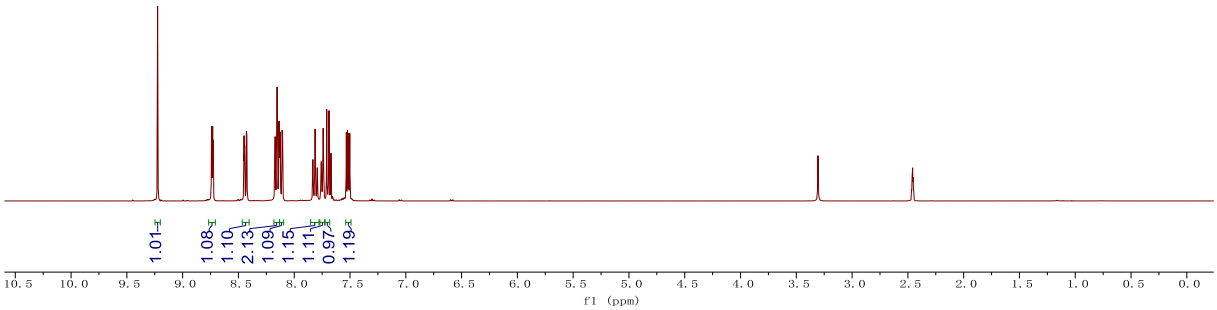

190.22
151.07
145.94
145.73
137.76
136.72
135.25
132.57
131.89
131.17
130.22
129.14
127.90
126.18
122.04
117.33
114.75


NC
CHO
N

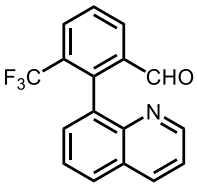
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

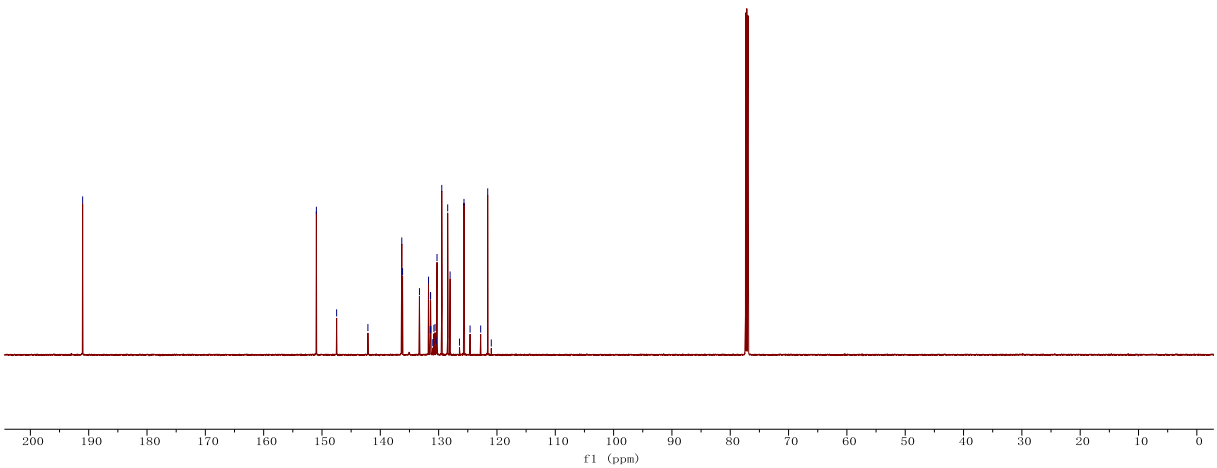

9.22
8.74
8.74
8.73
8.73
8.45
8.45
8.43
8.42
8.17
8.15
8.14
8.13
8.13
8.12
8.11
8.10
7.83
7.81
7.79
7.76
7.76
7.74
7.74
7.71
7.69
7.69
7.67
7.53
7.52
7.51
7.50


F3C
CHO
N


1.01
1.08
1.10
2.13
1.09
1.15
1.11
0.97
1.19
10.5
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)

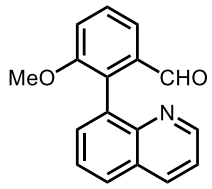

191.04
150.96
147.49
142.12
136.32
136.18
133.29
131.73
131.44
131.41
131.38
131.34
131.01
130.81
130.61
130.41
130.28
129.46
128.45
128.03
126.43
125.65
124.61
122.79
121.59
120.97

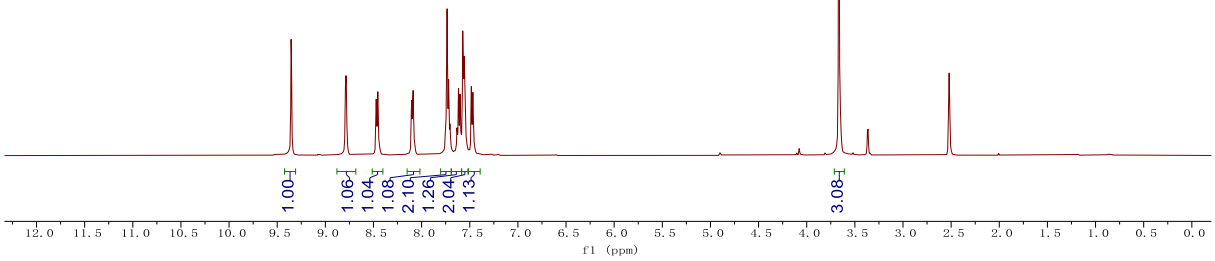

F3C
CHO
N


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

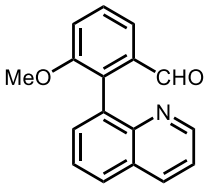

-58.10
F3C
CHO
N
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

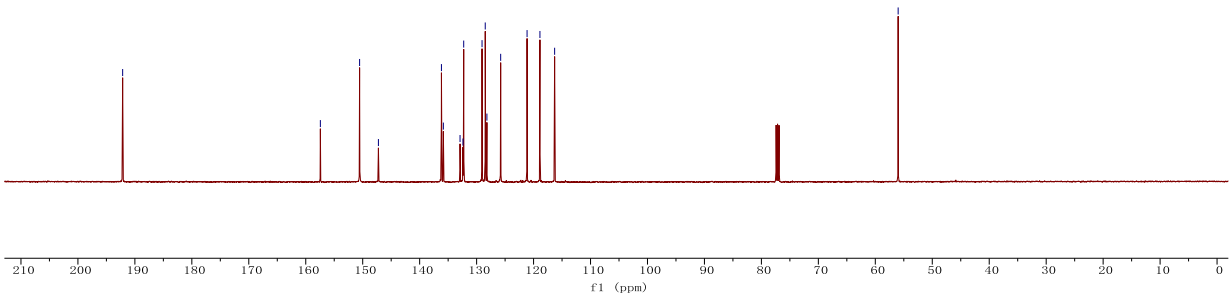

9.35
8.80
8.79
8.79
8.78
8.48
8.47
8.46
8.45
8.11
8.10
8.09
8.09
7.75
7.74
7.74
7.73
7.72
7.70
7.69
7.63
7.62
7.61
7.60
7.57
7.57
7.56
7.55
7.54
7.48
7.47
3.67


MeO
CHO
N


1.00
1.06
1.04
1.08
2.10
1.26
2.04
1.13
3.08
12.0
11.5
11.0
10.5
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)


192.15
157.43
150.55
147.24
136.18
135.84
132.91
132.40
132.27
129.05
128.48
128.20
125.78
121.14
118.88
116.30
55.99


MeO
CHO
N


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.71
8.78
8.27
8.25
8.20
8.19
8.02
8.01
7.95
7.93
7.75
7.73
7.71
7.69
7.68
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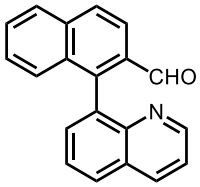
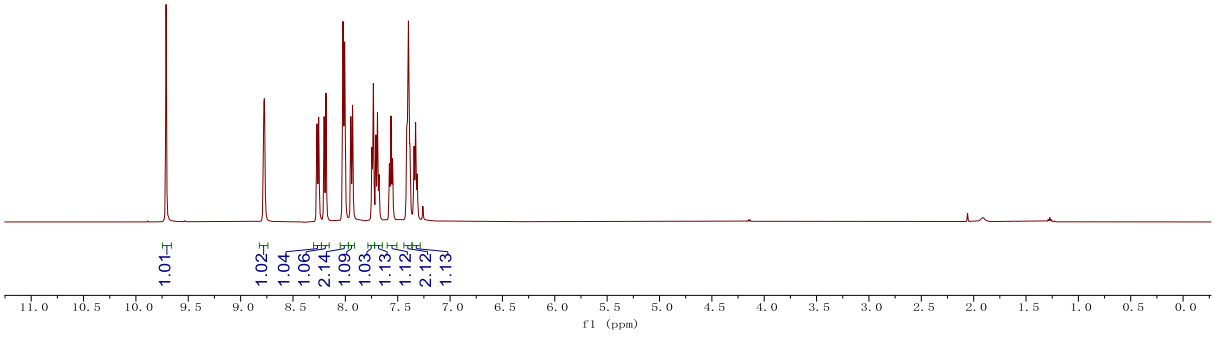
7.40
7.38
7.34
7.33
7.31
7.26


CHO
N


1.01
1.02
1.04
1.06
2.14
1.09
1.03
1.13
1.12
2.12
1.13
11.0
10.5
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)


192.56
151.01
147.79
144.46
136.30
134.94
133.05
132.65
131.93
129.04
128.65
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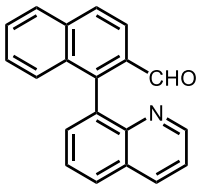
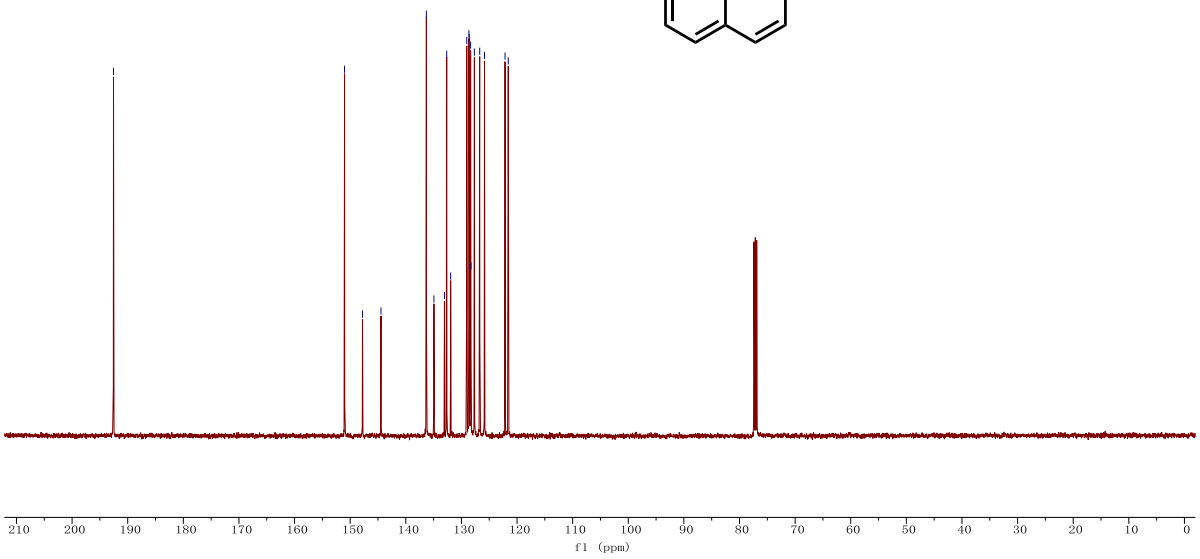
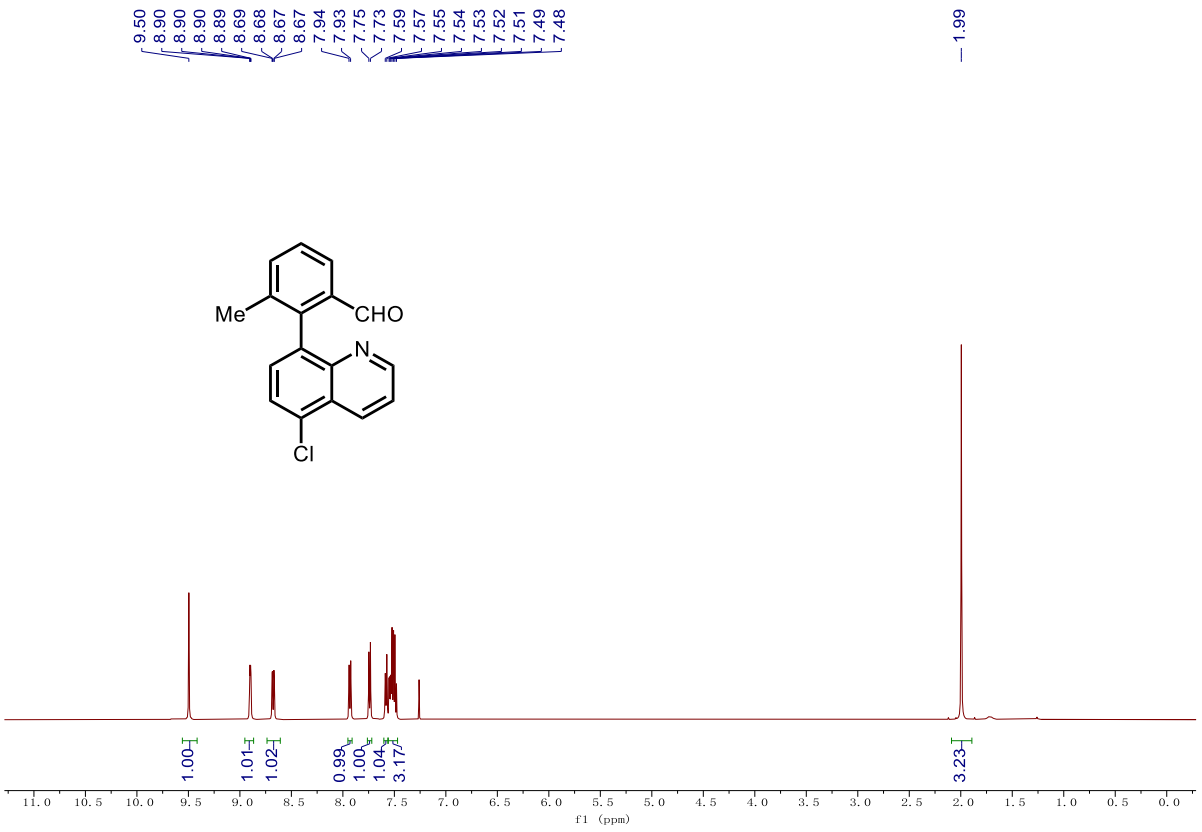
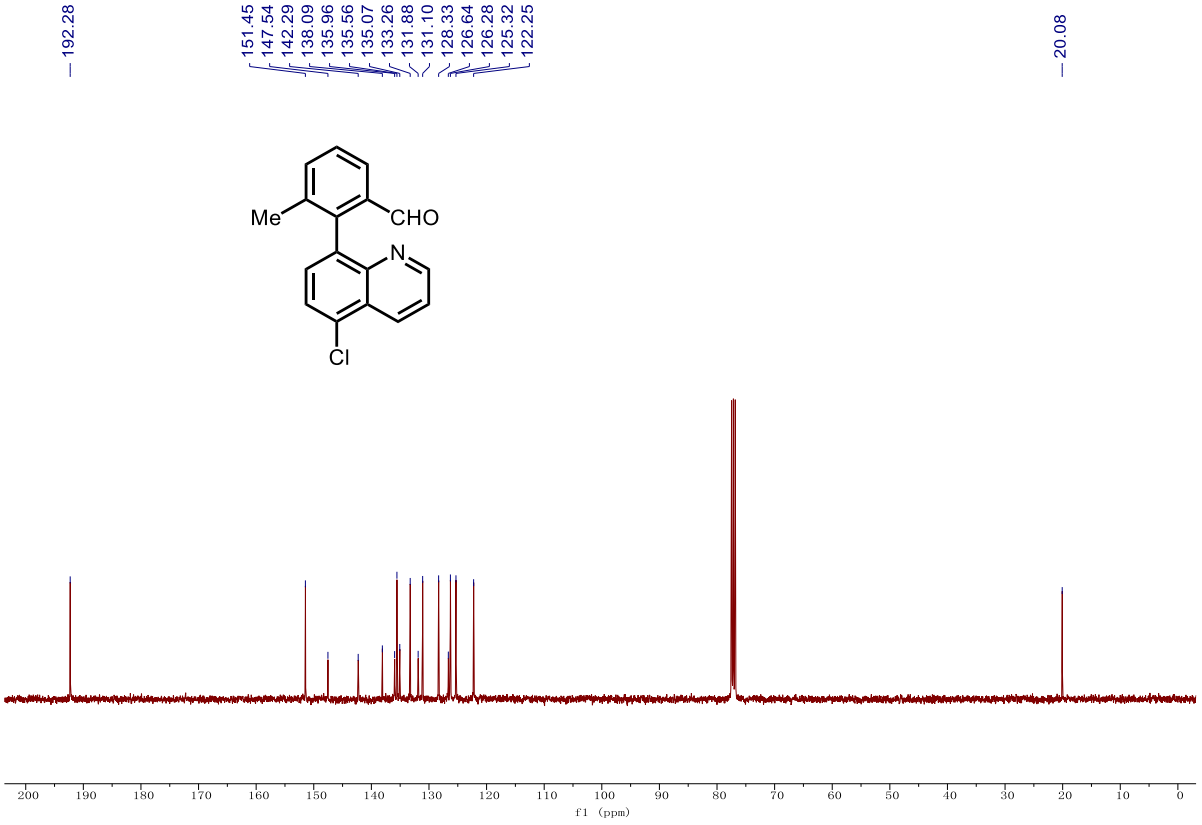
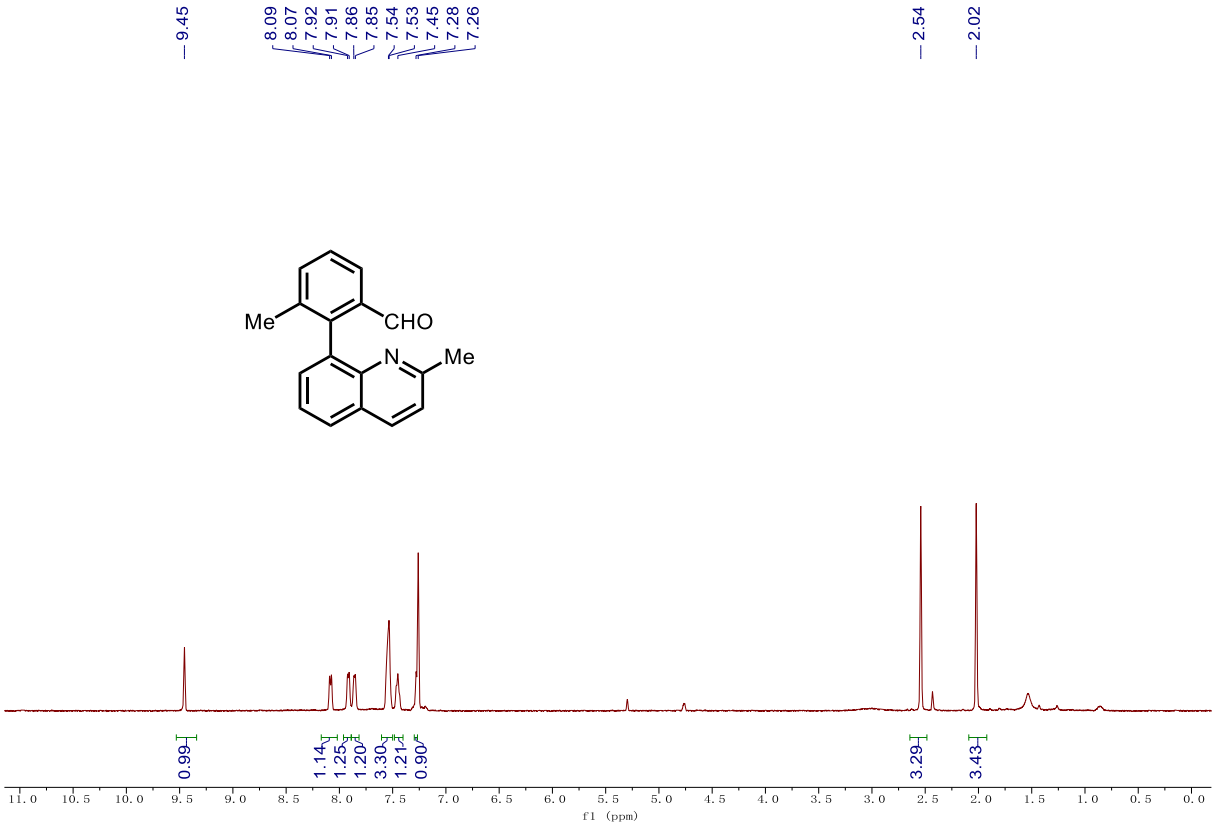
128.35
128.28
127.67
126.71
125.85
122.15
121.58

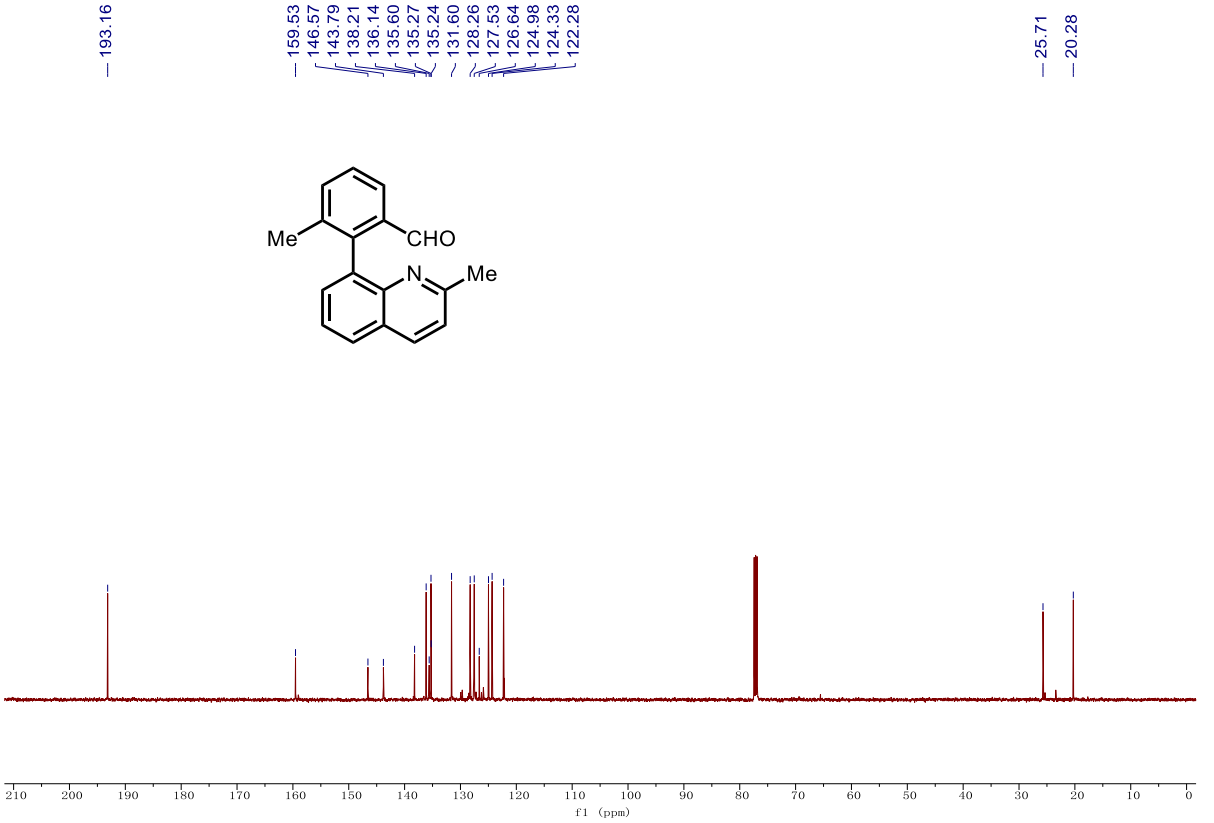

CHO
N

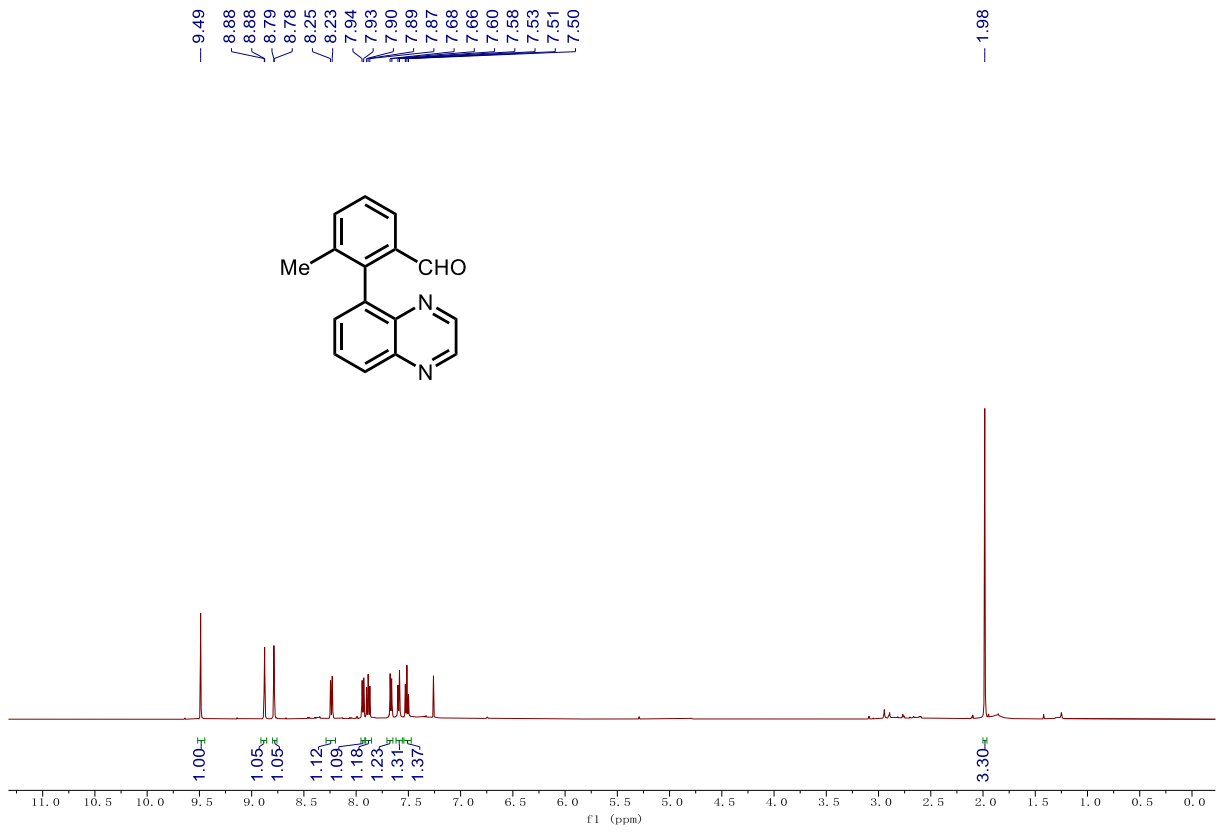

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

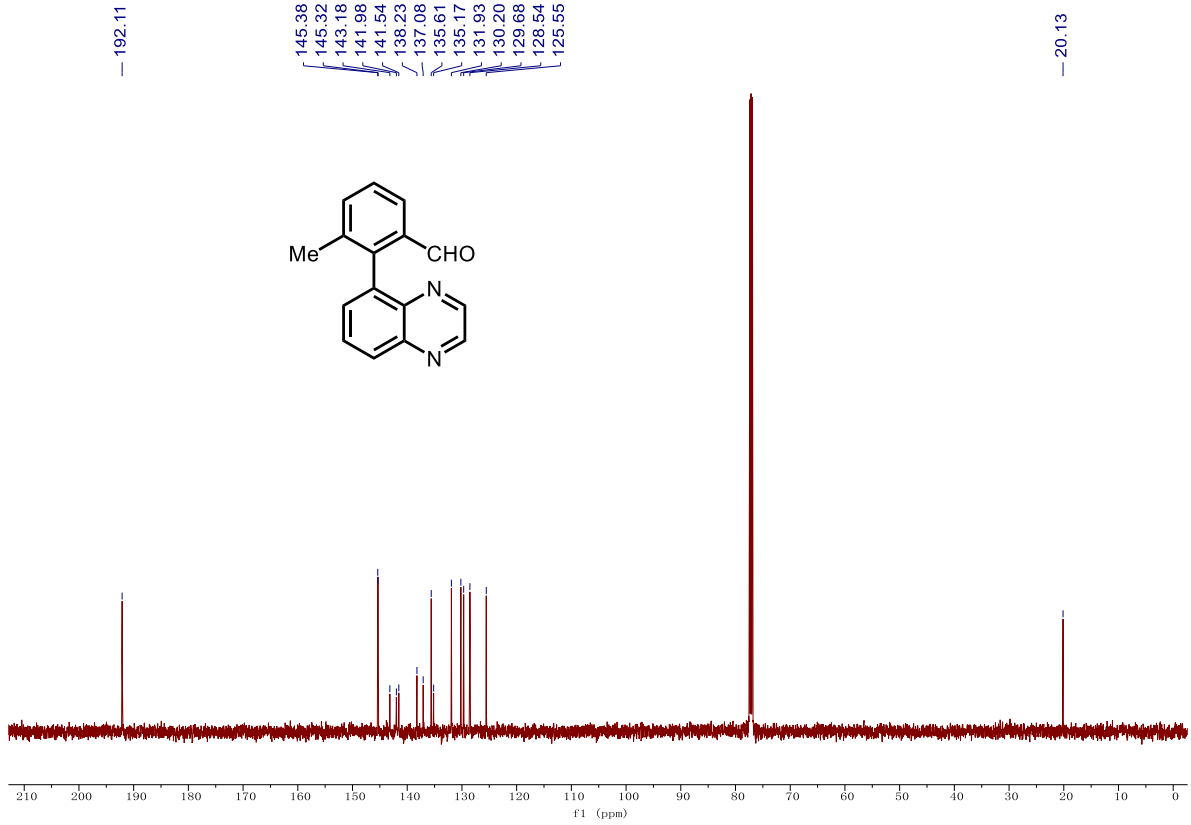

9.50
8.90
8.90
8.90
8.89
8.69
8.68
8.67
8.67
7.94
7.93
7.75
7.73
7.59
7.57
7.55
7.54
7.53
7.52
7.51
7.49
7.48
1.99
Me
CHO
N
Cl
1.00
1.01
1.02
0.99
1.00
1.04
3.17
3.23
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


192.28
151.45
147.54
142.29
138.09
135.96
135.56
135.07
133.26
131.88
131.10
128.33
126.64
126.28
125.32
122.25
20.08
Me
CHO
N
Cl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.45
8.09
8.07
7.92
7.91
7.86
7.85
7.54
7.53
7.45
7.28
7.26
2.54
2.02
Me
CHO
N
Me
0.99
1.14
1.25
1.20
3.30
1.21
0.90
3.29
3.43
f1 (ppm)


193.16
159.53
146.57
143.79
138.21
136.14
135.60
135.27
135.24
131.60
128.26
127.53
126.64
124.98
124.33
122.28
25.71
20.28
Me
CHO
N
Me
f1 (ppm)


9.49
8.88
8.88
8.79
8.78
8.25
8.23
7.94
7.93
7.90
7.89
7.87
7.68
7.66
7.60
7.58
7.53
7.51
7.50
1.98
Me
CHO
N
N
1.00
1.05
1.05
1.12
1.09
1.18
1.23
1.31
1.37
3.30
f1 (ppm)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145.38
145.32
143.18
141.98
141.54
138.23
137.08
135.61
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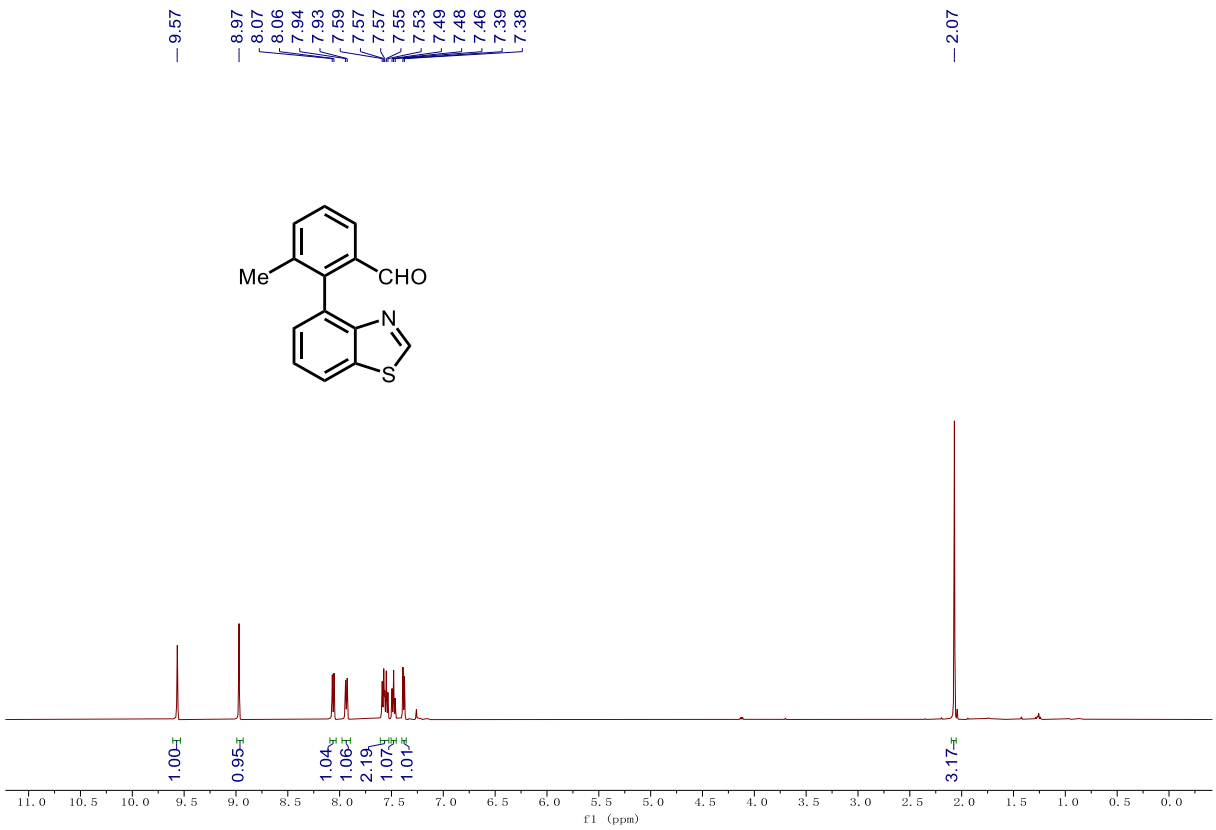
131.93
130.20
129.68
128.54
125.55
20.13
Me
CHO
N
N
f1 (ppm)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8.07
8.06
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7.93
7.59
7.57
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7.55
7.53
7.49
7.48
7.46
7.39
7.38
2.07
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S
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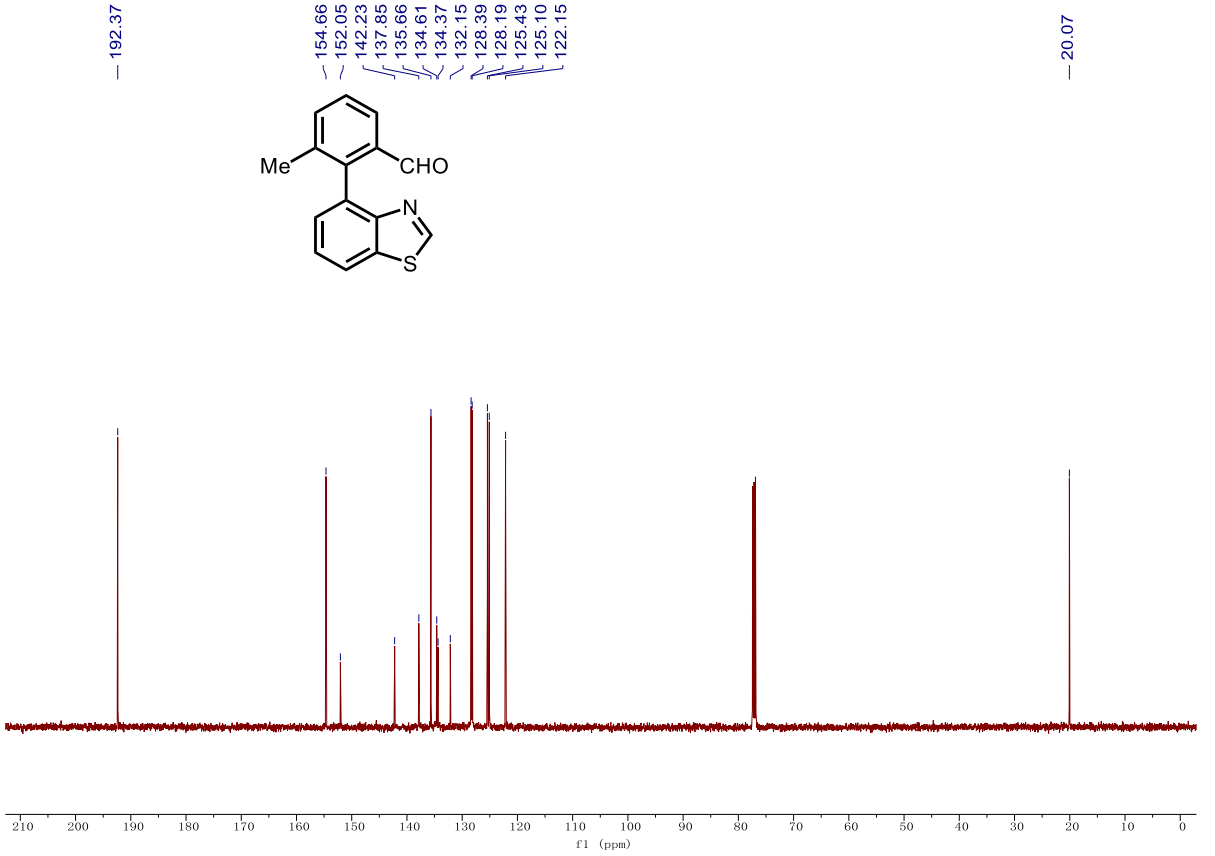
0.95
1.04
1.06
2.19
1.07
1.01
3.17
f1 (ppm)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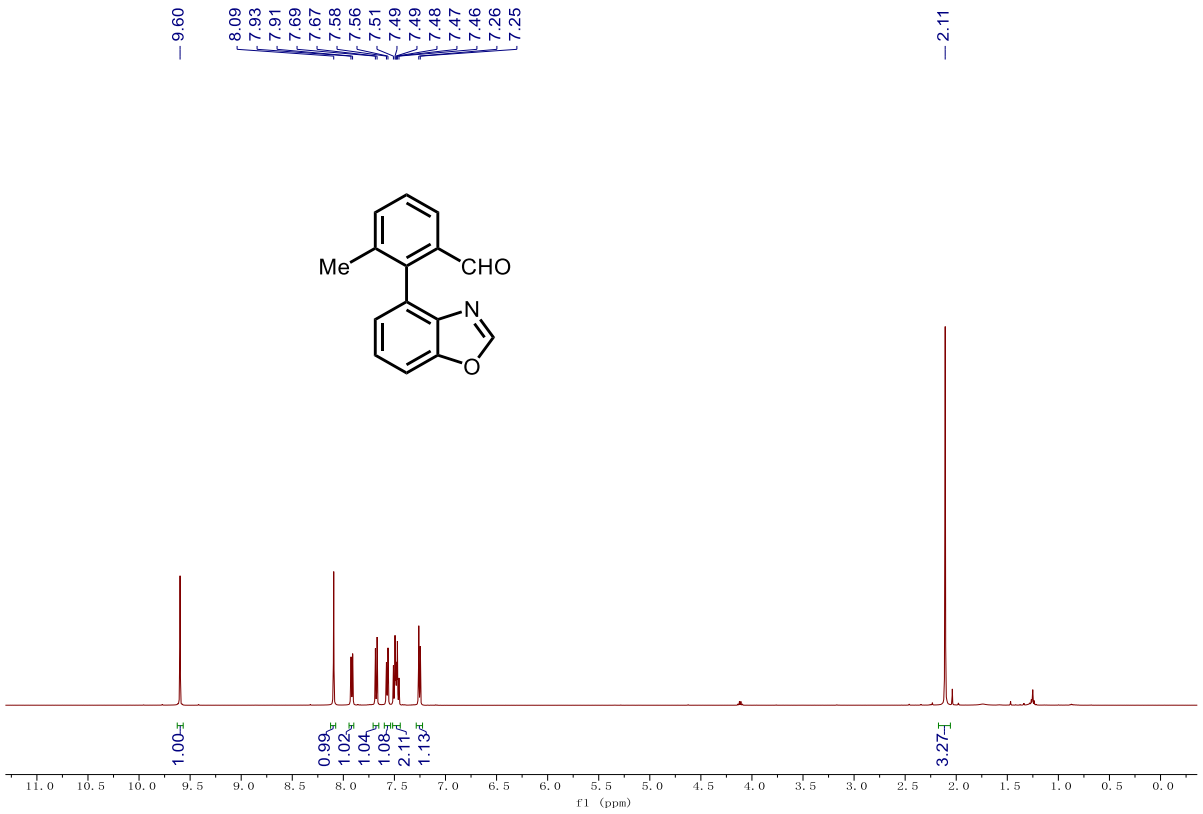
154.66
152.05
142.23
137.85
135.66
134.61
134.37
132.15
128.39
128.19
125.43
125.10
122.15
20.07
Me
CHO
N
S
f1 (ppm)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7.93
7.91
7.69
7.67
7.58
7.56
7.51
7.49
7.49
7.48
7.47
7.46
7.26
7.25
2.11
Me
CHO
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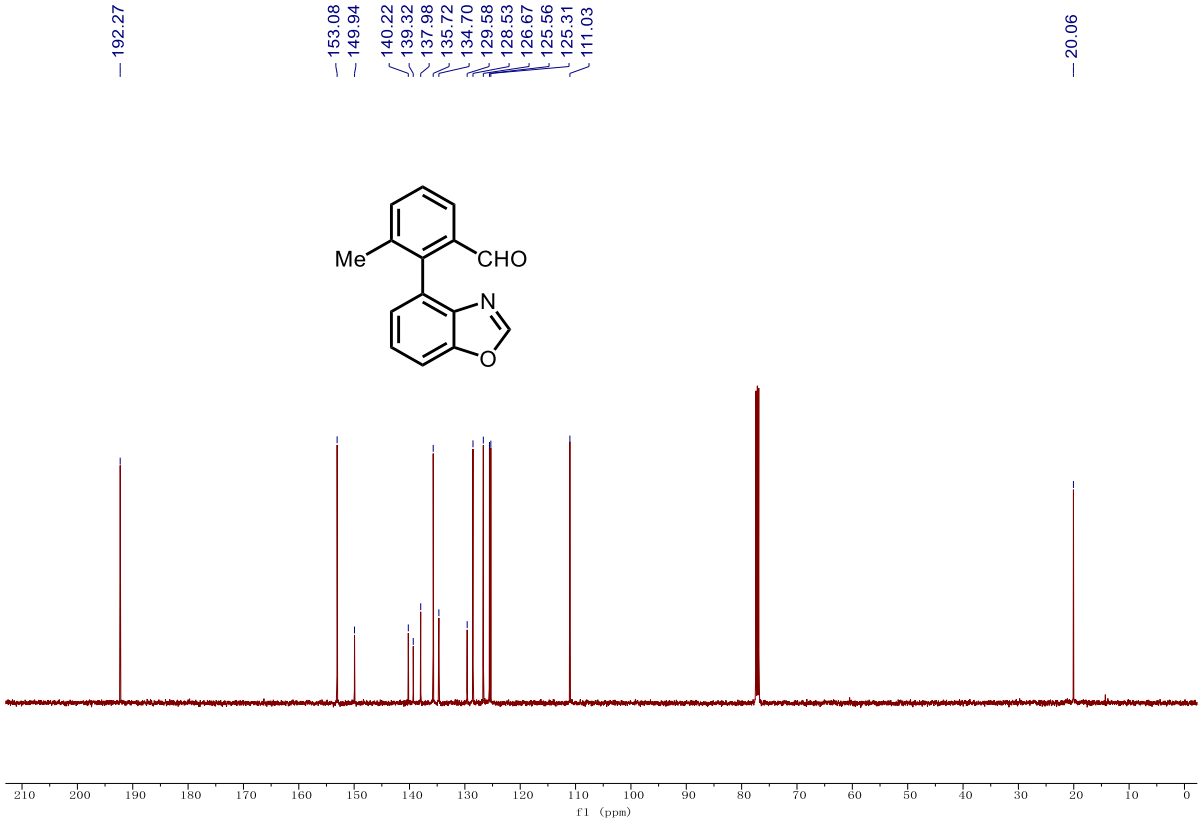
O
1.00
0.99
1.02
1.04
1.08
2.11
1.13
3.27
f1 (ppm)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153.08
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140.22
139.32
137.98
135.72
134.70
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128.53
126.67
125.56
125.31
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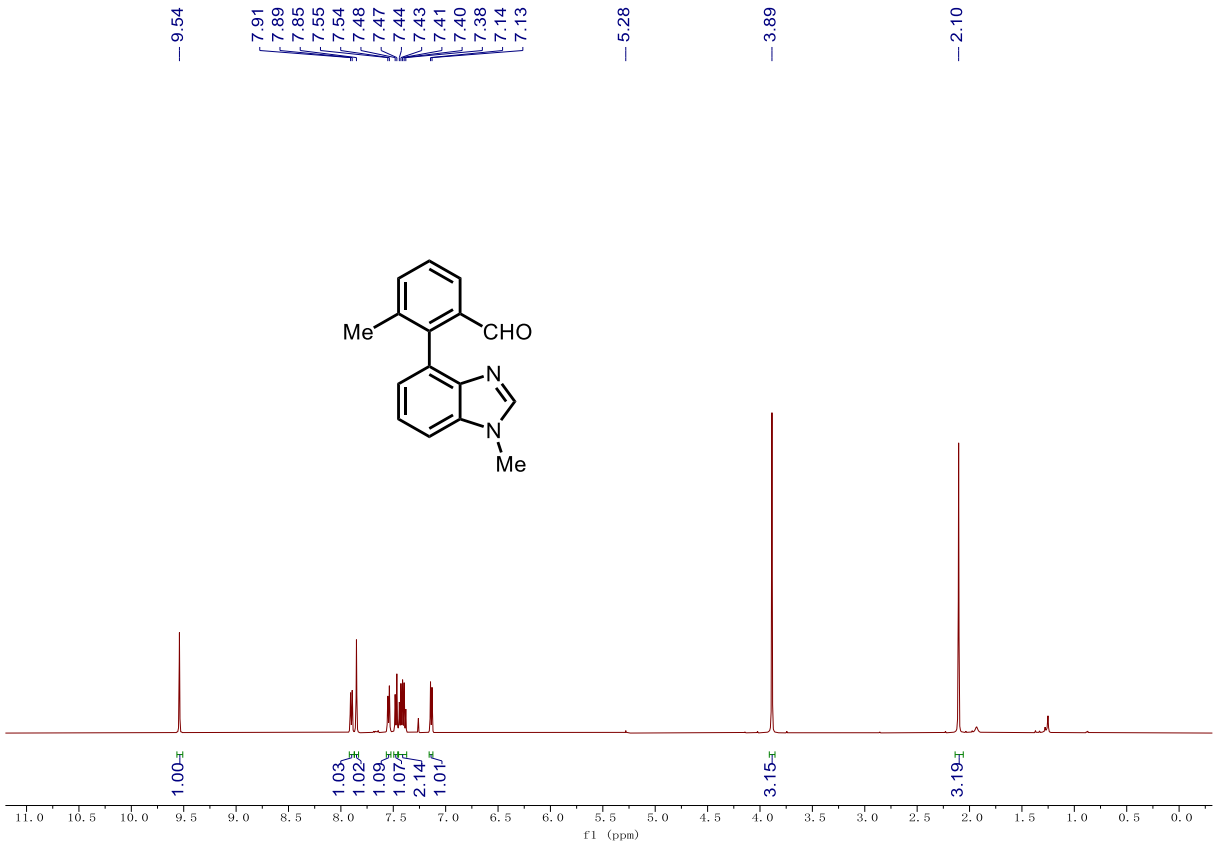
20.06
Me
CHO
N
O
f1 (ppm)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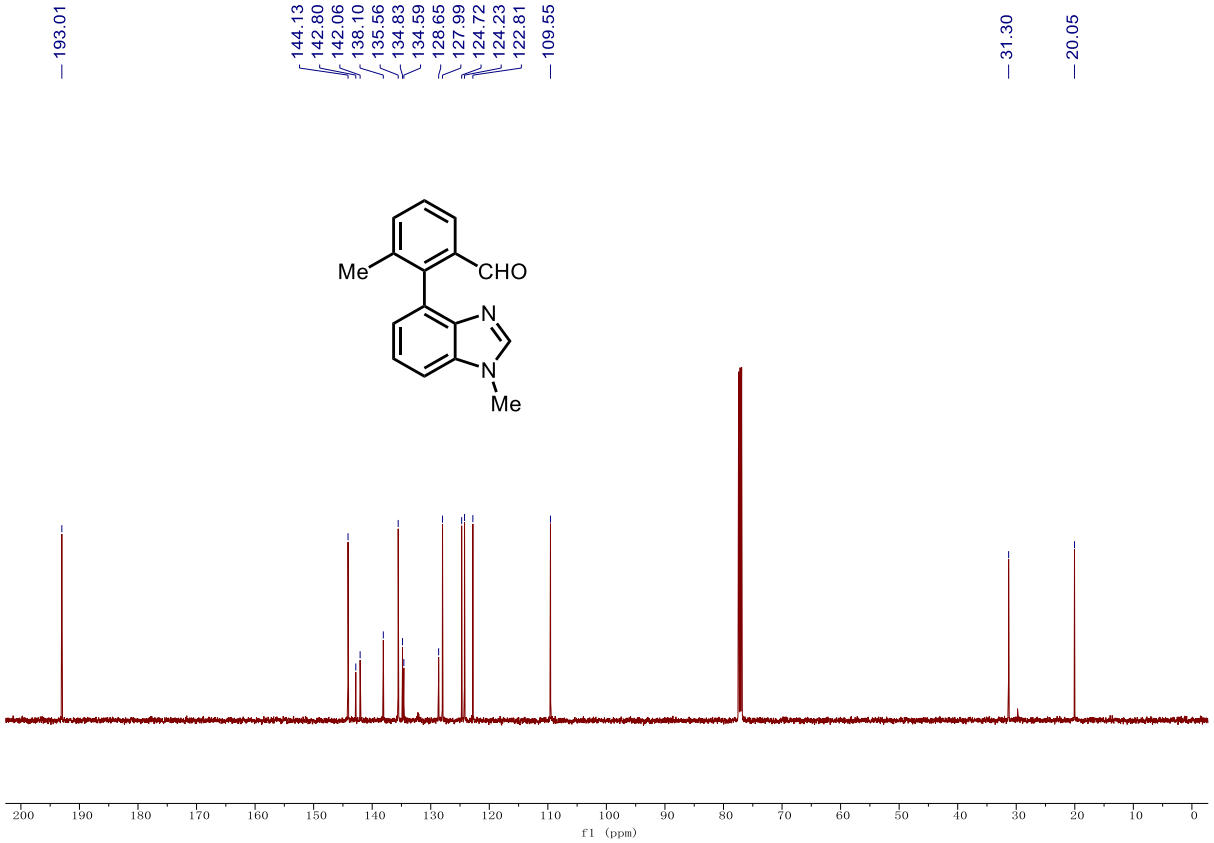
7.89
7.85
7.55
7.54
7.48
7.47
7.44
7.43
7.41
7.40
7.38
7.14
7.13
5.28
3.89
2.10
Me
CHO
N
N
Me
1.00
1.03
1.02
1.09
1.07
2.14
1.01
3.15
3.19
f1 (ppm)


193.01
144.13
142.80
142.06
138.10
135.56
134.83
134.59
128.65
127.99
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124.23
122.81
109.55
31.30
20.05
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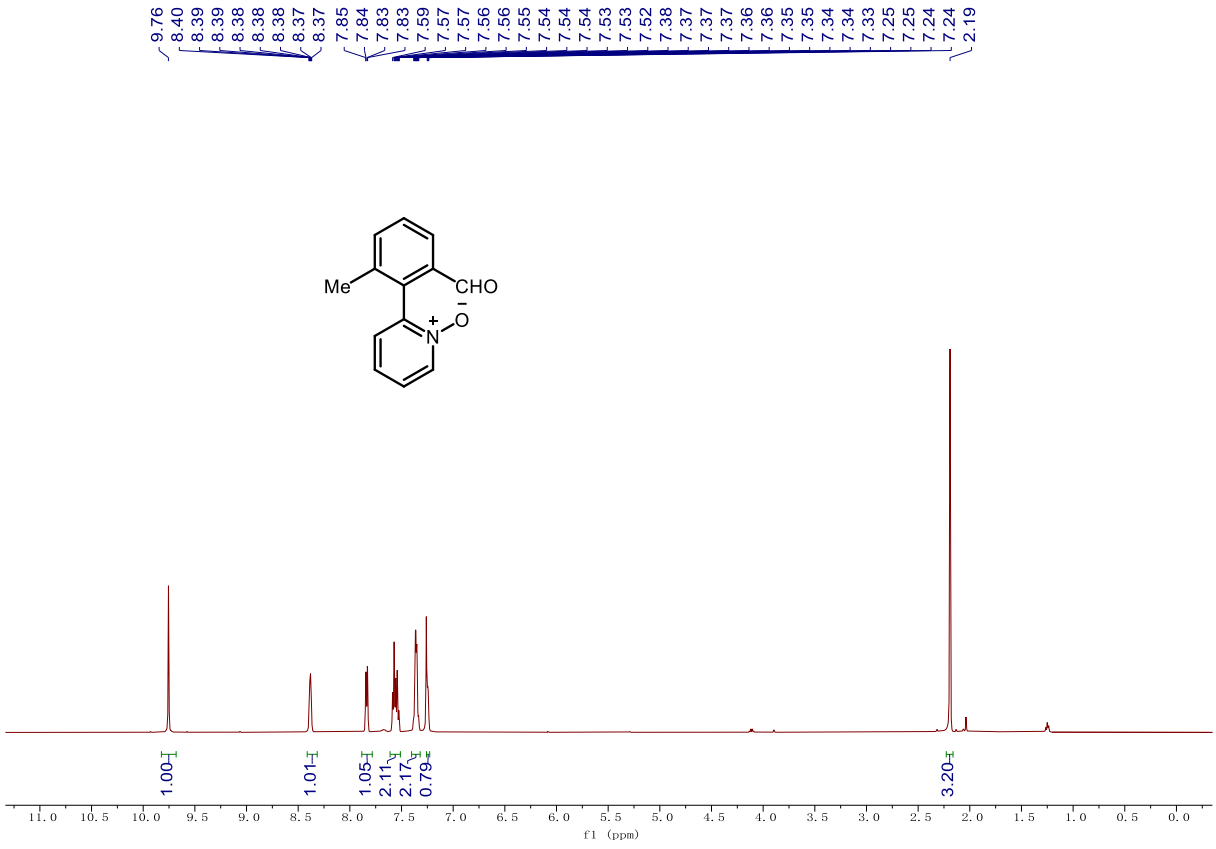
CHO
N
N
Me
f1 (ppm)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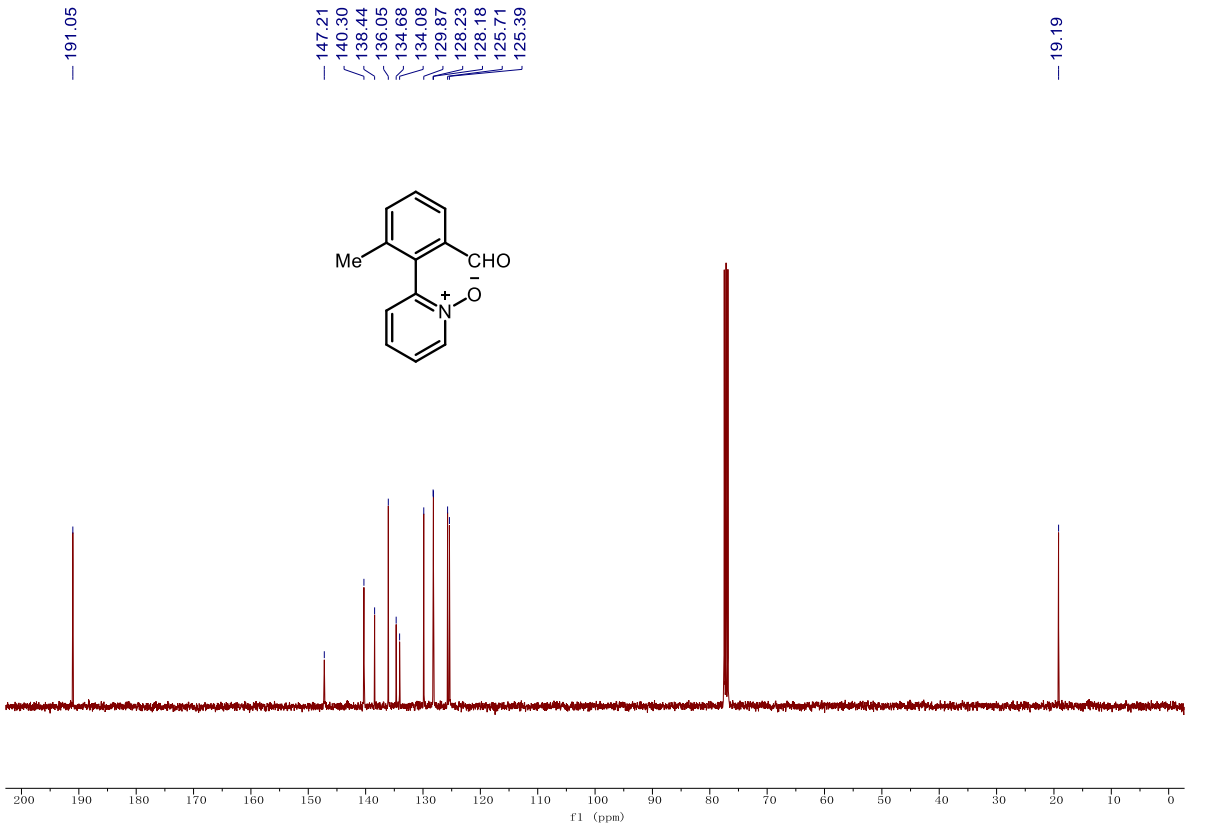
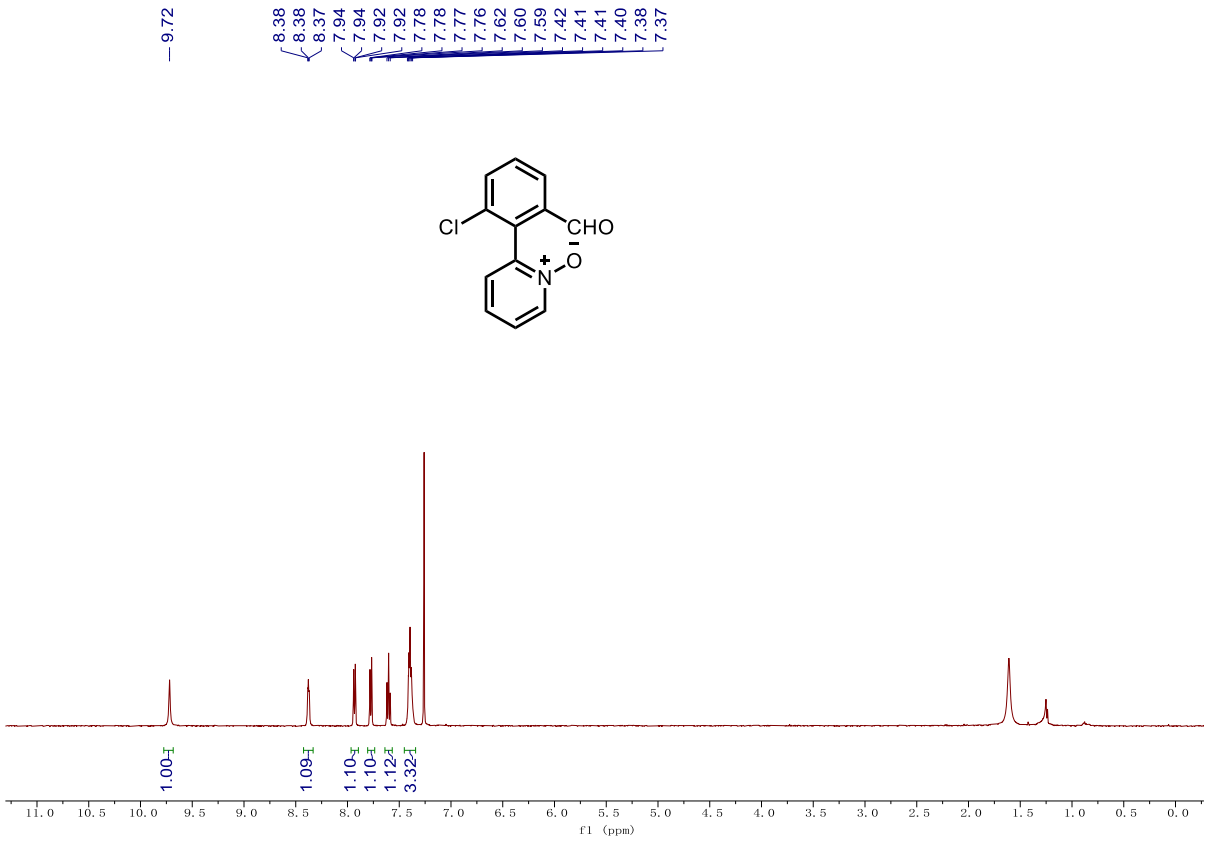
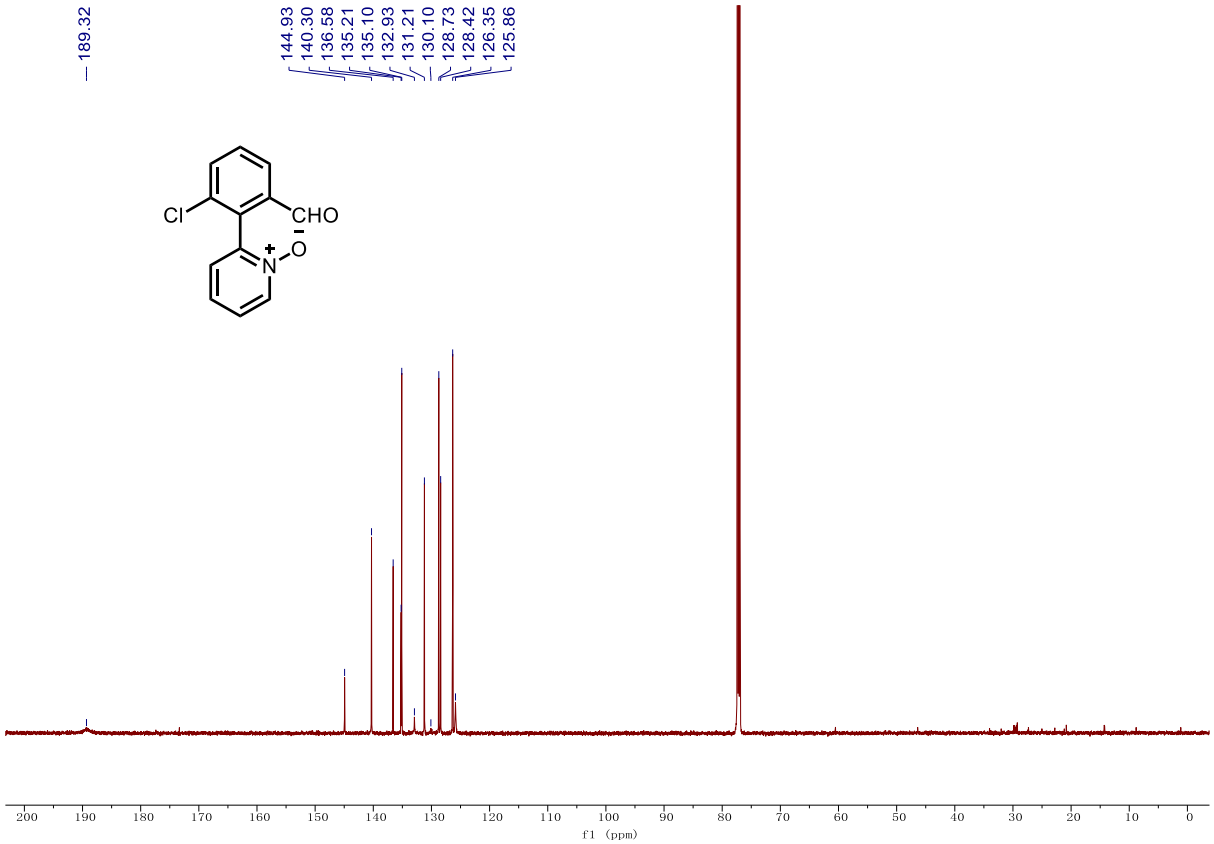
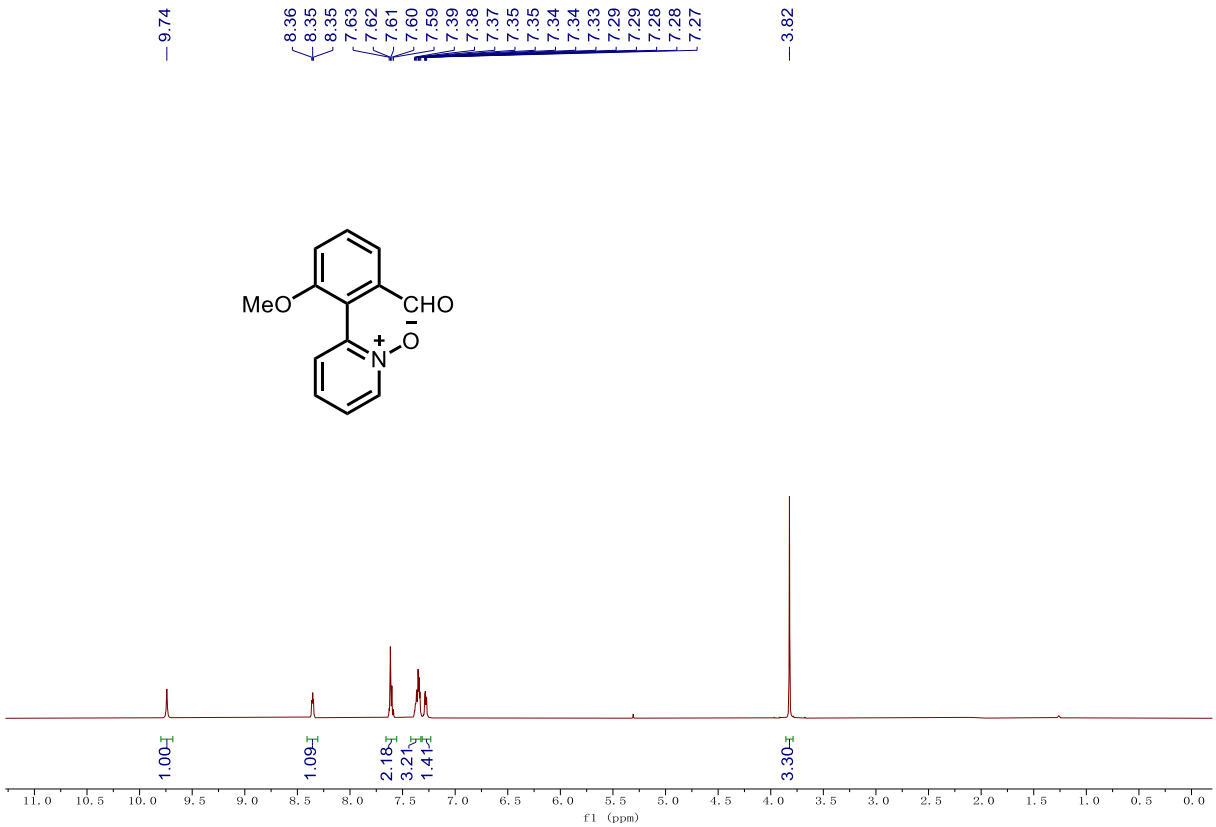
8.39
8.39
8.38
8.38
8.38
8.37
8.37
7.85
7.84
7.83
7.83
7.59
7.57
7.57
7.56
7.56
7.55
7.54
7.54
7.54
7.53
7.53
7.52
7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.25
7.25
7.24
7.24
2.19
Me
CHO
O
N
1.00
1.01
1.05
2.11
2.17
0.79
3.20
f1 (ppm)


191.05
147.21
140.30
138.44
136.05
134.68
134.08
129.87
128.23
128.18
125.71
125.39
19.19
Me
CHO
O
N
f1 (ppm)


9.72
8.38
8.38
8.37
7.94
7.94
7.92
7.92
7.78
7.78
7.77
7.76
7.62
7.60
7.59
7.42
7.41
7.41
7.40
7.38
7.37
Cl
CHO
O
N
1.00
1.09
1.10
1.10
1.12
3.32
f1 (ppm)


189.32
144.93
140.30
136.58
135.21
135.10
132.93
131.21
130.10
128.73
128.42
126.35
125.86
Cl
CHO
O
N
f1 (ppm)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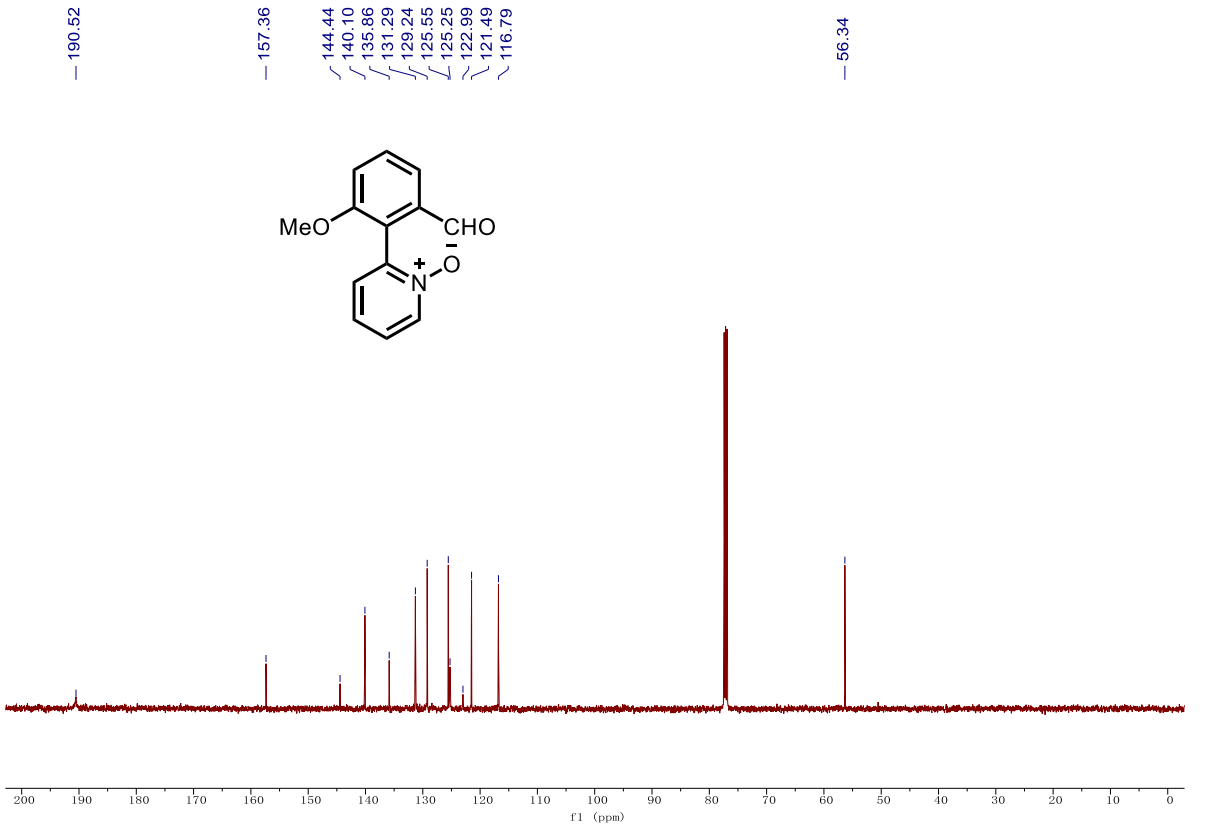
8.36
8.35
8.35
7.63
7.62
7.61
7.60
7.59
7.39
7.38
7.37
7.35
7.35
7.34
7.34
7.33
7.29
7.29
7.28
7.28
7.27
3.82
MeO
CHO
O
N
1.00
1.09
2.18
3.21
1.41
3.30
f1 (ppm)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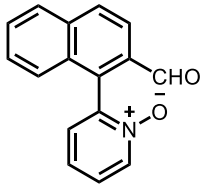
157.36
144.44
140.10
135.86
131.29
129.24
125.55
125.25
122.99
121.49
116.79
56.34
MeO
CHO
O
N
f1 (ppm)


9.87
8.44
8.42
8.08
8.06
8.05
8.03
7.93
7.92
7.63
7.61
7.60
7.51
7.49
7.48
7.46
7.45
7.44
7.43
7.43
7.42
7.40
7.39
7.37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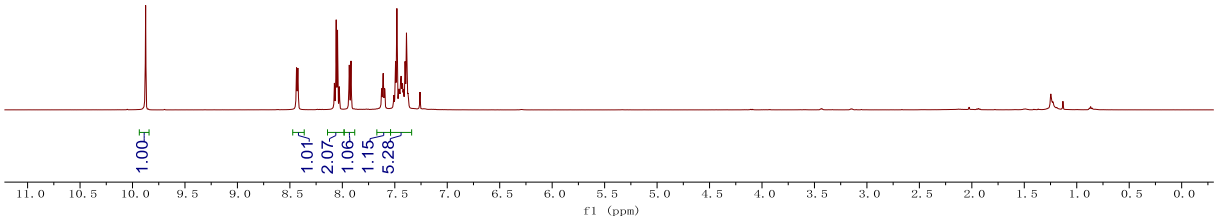
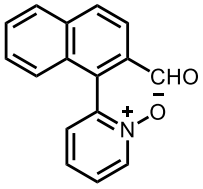
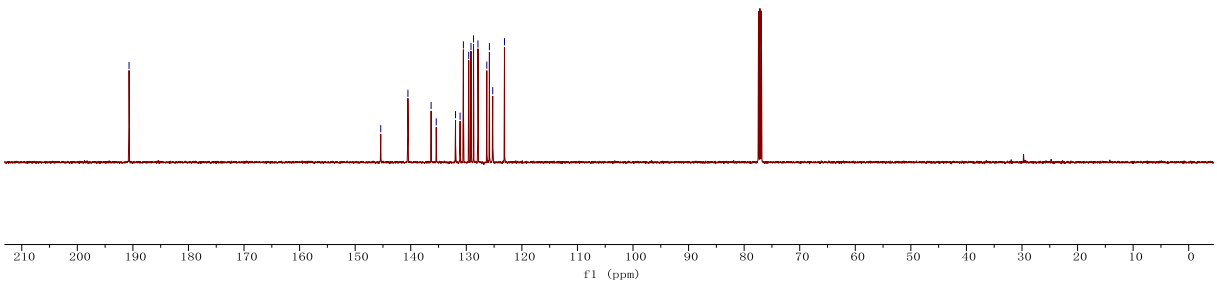
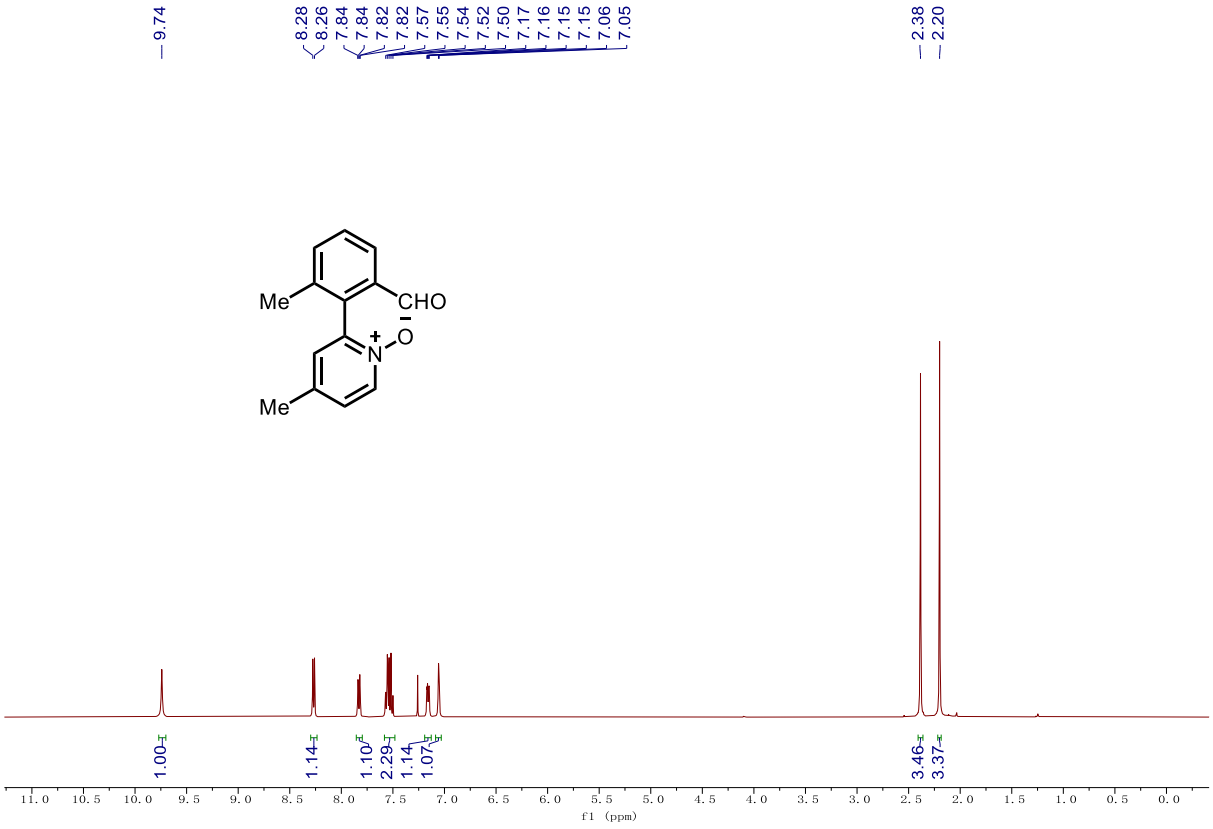
O
N
O


1.00
1.01
2.07
1.06
1.15
5.28
11.0 10.5 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)


190.69
145.40
140.50
136.33
135.41
131.94
131.12
130.52
129.57
129.16
128.70
127.90
126.31
125.84
125.25
123.13


CHO
O
N
O


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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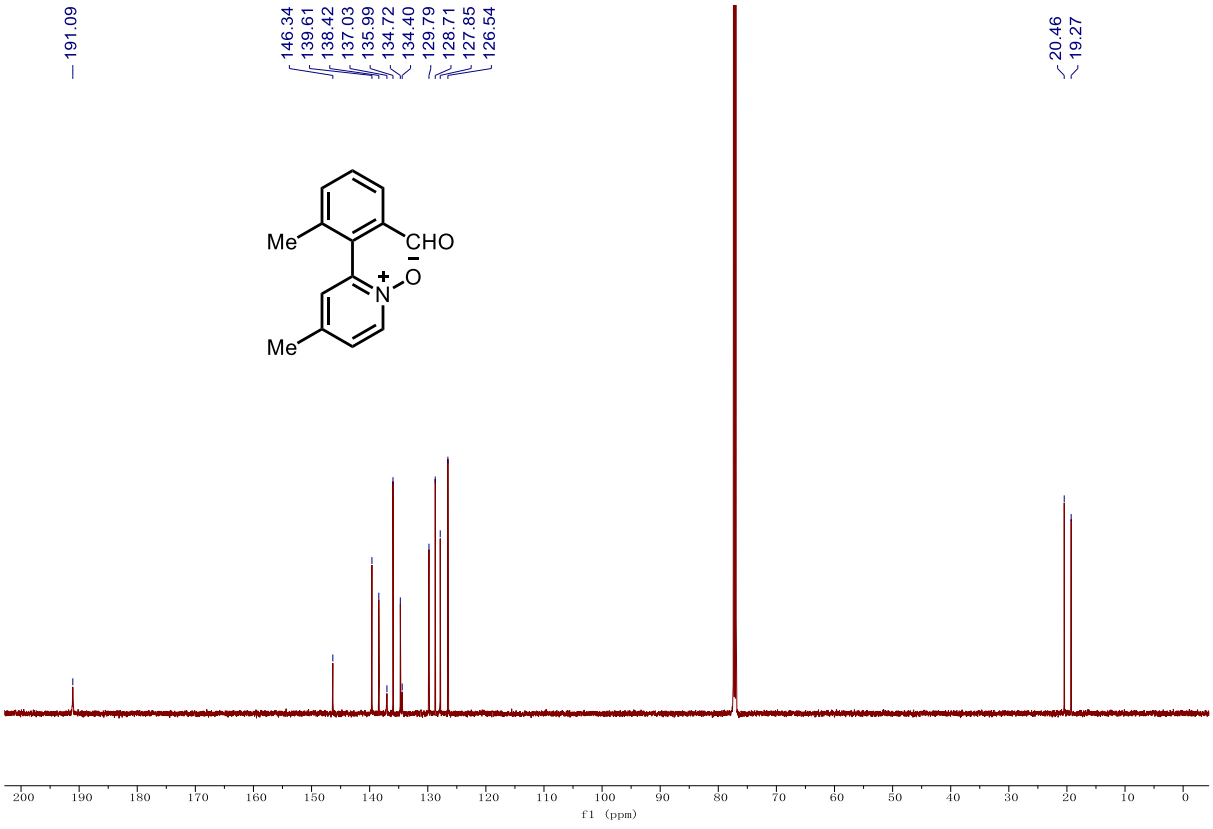
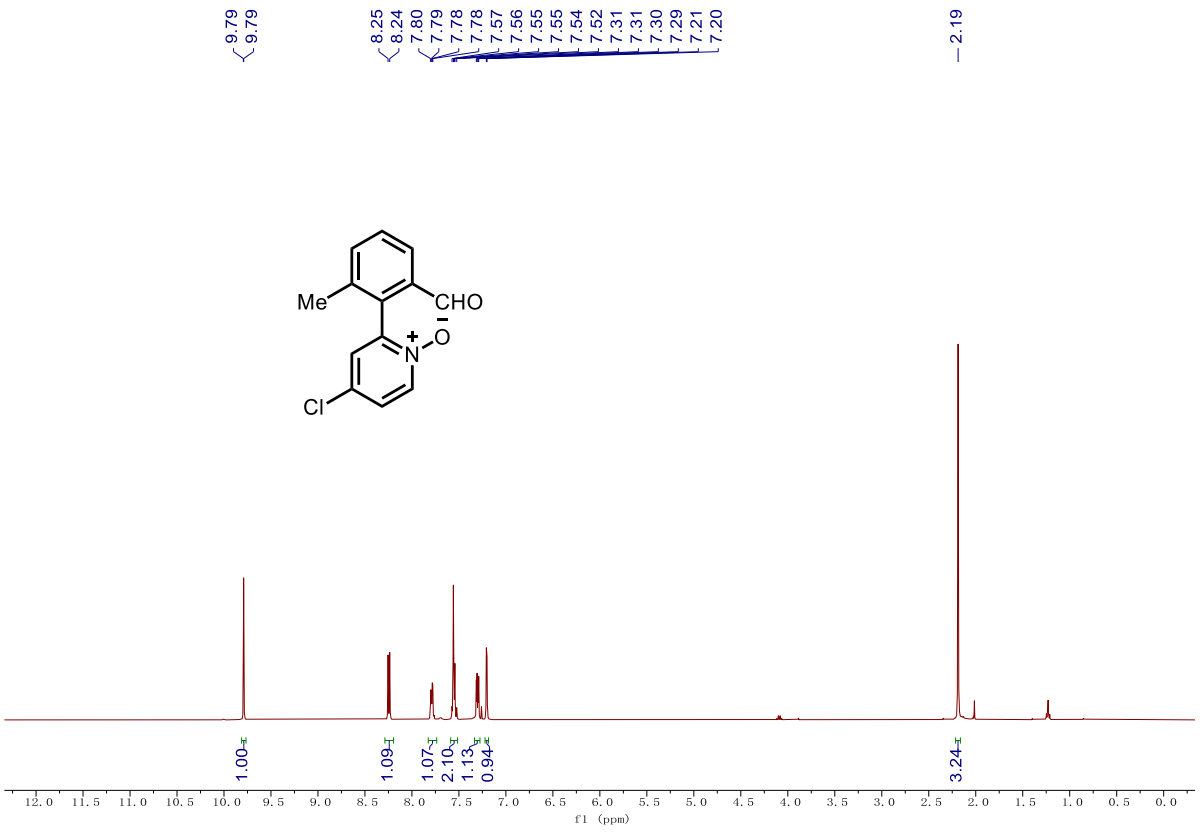
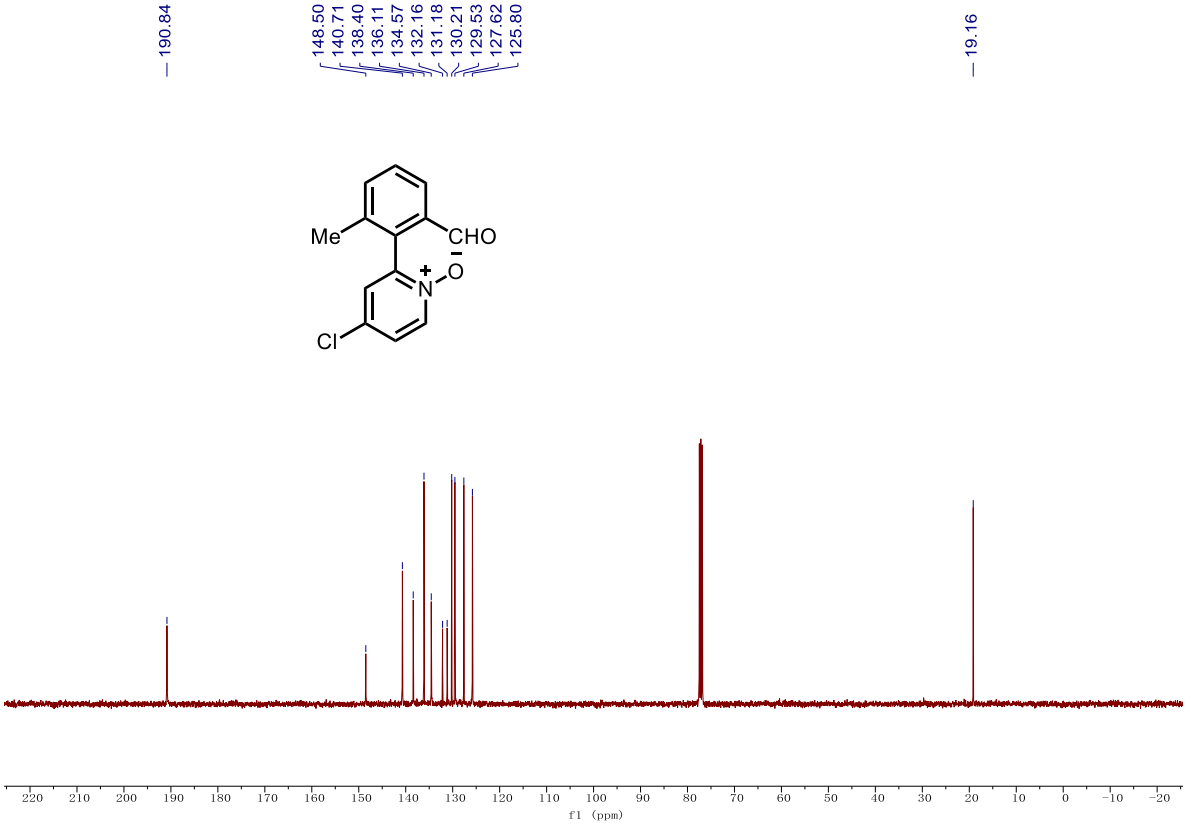
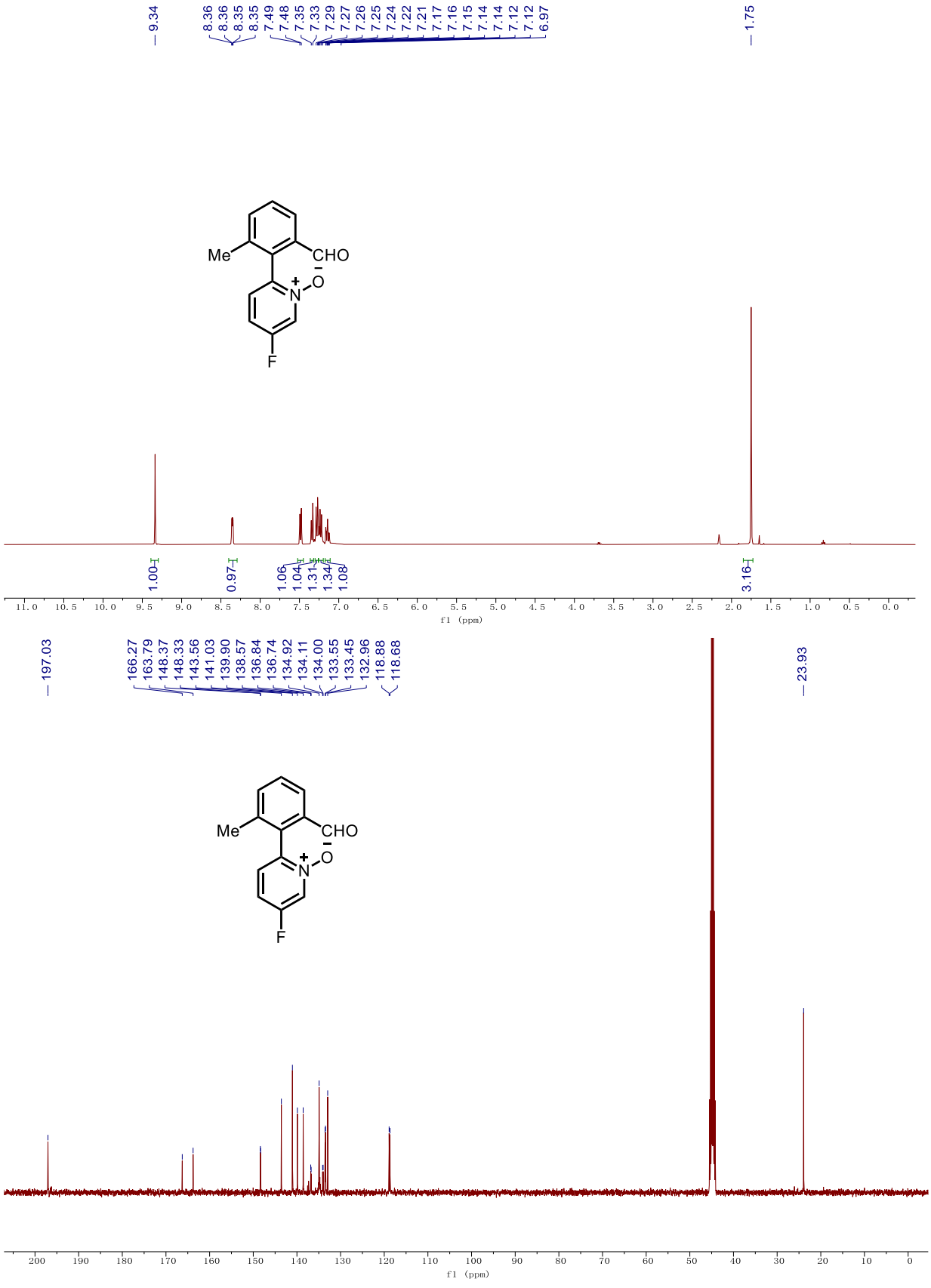
8.28
8.26
7.84
7.84
7.82
7.82
7.57
7.55
7.54
7.52
7.50
7.17
7.16
7.15
7.15
7.06
7.05
2.38
2.20
Me
CHO
O
N
Me
1.00
1.14
1.10
2.29
1.14
1.07
3.46
3.37
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


191.09
146.34
139.61
138.42
137.03
135.99
134.72
134.40
129.79
128.71
127.85
126.54
20.46
19.27
Me
CHO
O
N
Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


9.79
9.79
8.25
8.24
7.80
7.79
7.78
7.78
7.57
7.56
7.55
7.55
7.54
7.52
7.31
7.31
7.30
7.29
7.21
7.20
2.19
Me
CHO
N
O
Cl
1.00
1.09
1.07
2.10
1.13
0.94
3.24
f1 (ppm)


190.84
148.50
140.71
138.40
136.11
134.57
132.16
131.18
130.21
129.53
127.62
125.80
19.16
Me
CHO
N
O
Cl
f1 (ppm)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8.36
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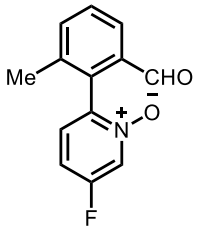
8.35
8.35
7.49
7.48
7.35
7.33
7.29
7.27
7.26
7.25
7.24
7.22
7.21
7.17
7.16
7.15
7.14
7.14
7.12
7.12
6.97
1.75
Me
CHO
N
O
F
1.00
0.97
1.06
1.04
1.31
1.34
1.08
3.16
f1 (ppm)
197.03
166.27
163.79
148.37
148.33
143.56
141.03
139.90
138.57
136.84
136.74
134.92
134.11
134.00
133.55
133.45
132.96
118.88
118.68
23.93
f1 (ppm)


Me
CHO
O
N
F

-114.81
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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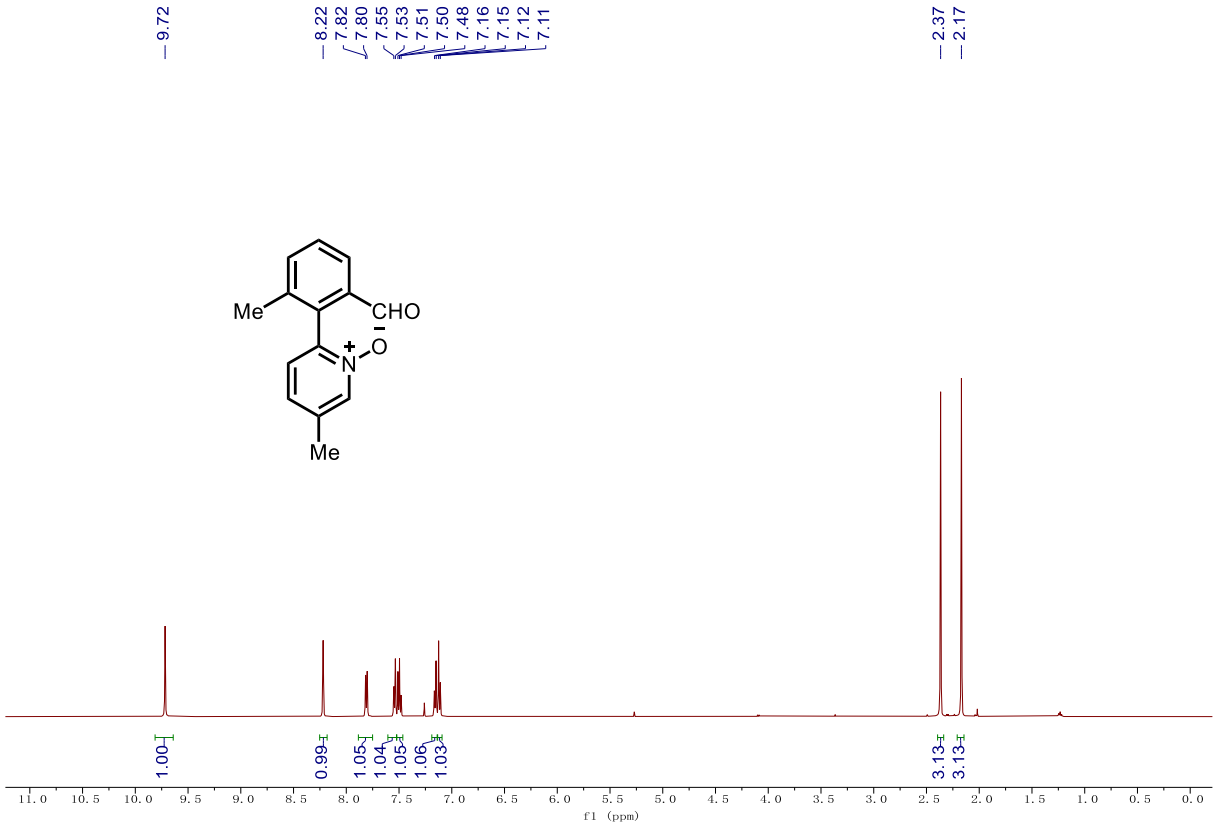
-110
-120
-130
-140
-150
-160
f1 (ppm)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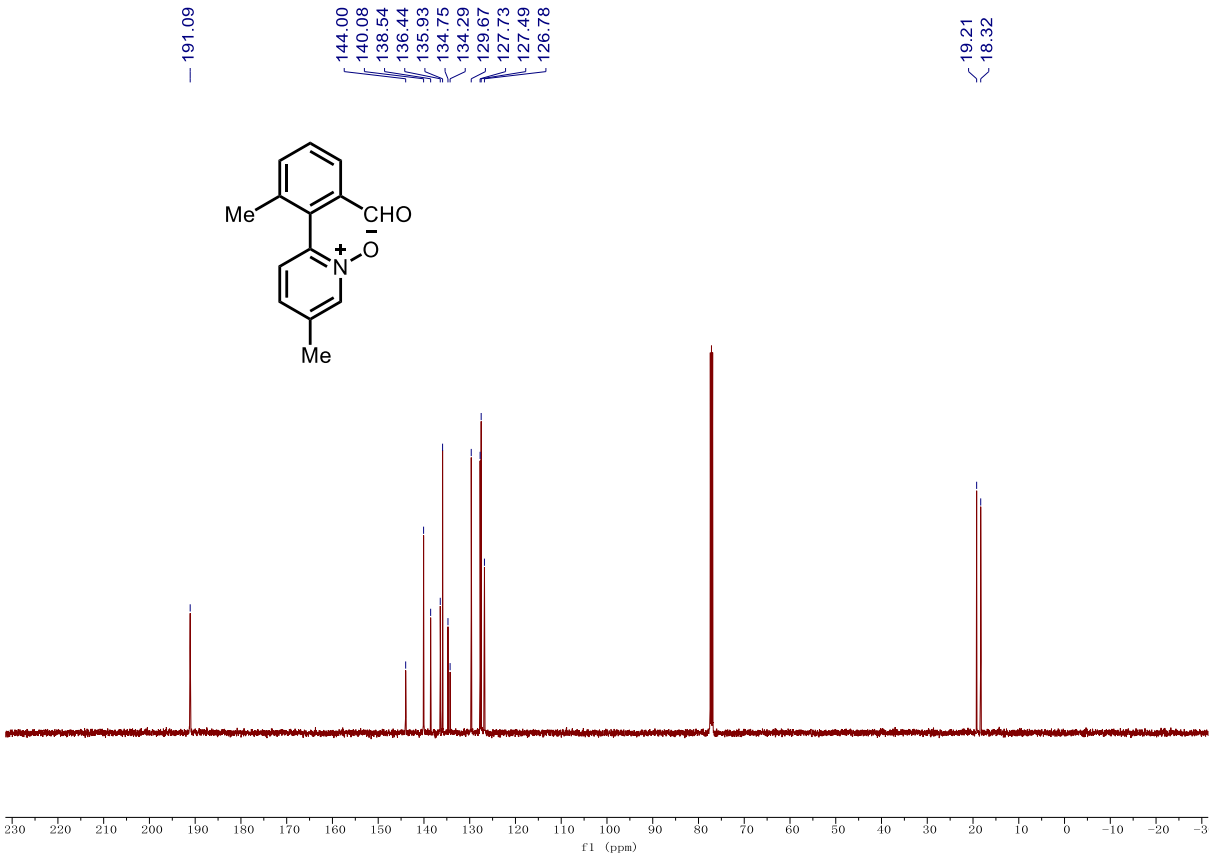
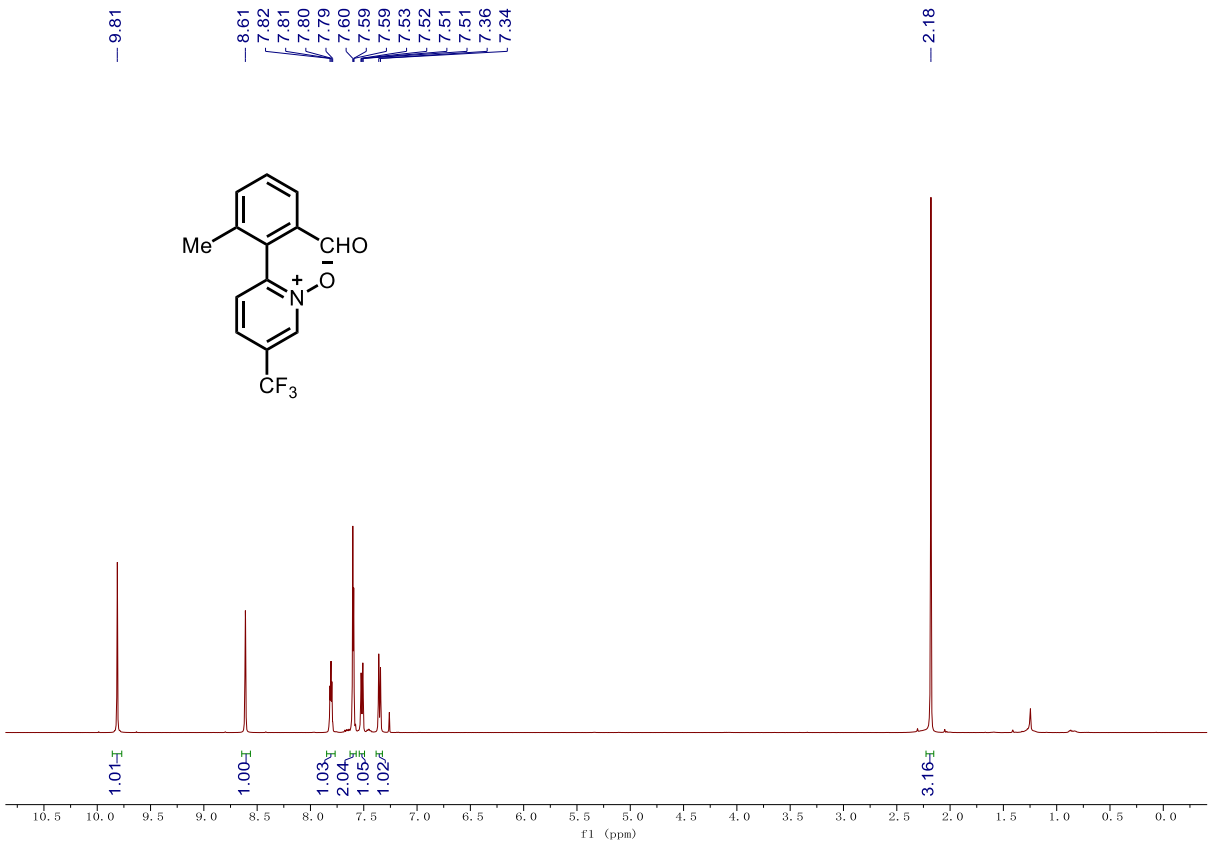
7.80
7.55
7.53
7.51
7.50
7.48
7.16
7.15
7.12
7.11
2.37
2.17
Me
CHO
N
O
Me
1.00
0.99
1.05
1.04
1.05
1.06
1.03
3.13
3.13
f1 (ppm)


191.09
144.00
140.08
138.54
136.44
135.93
134.75
134.29
129.67
127.73
127.49
126.78
19.21
18.32
Me
CHO
N
O
Me
f1 (ppm)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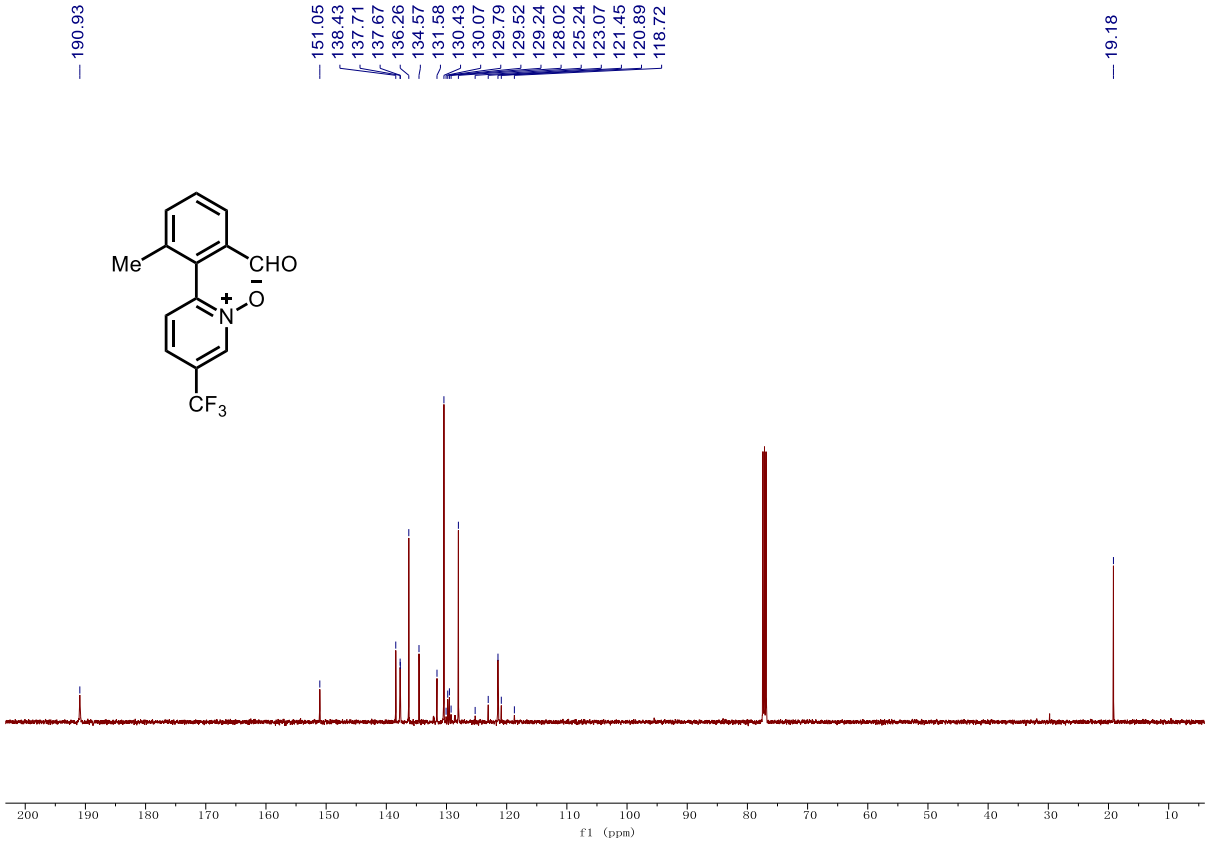
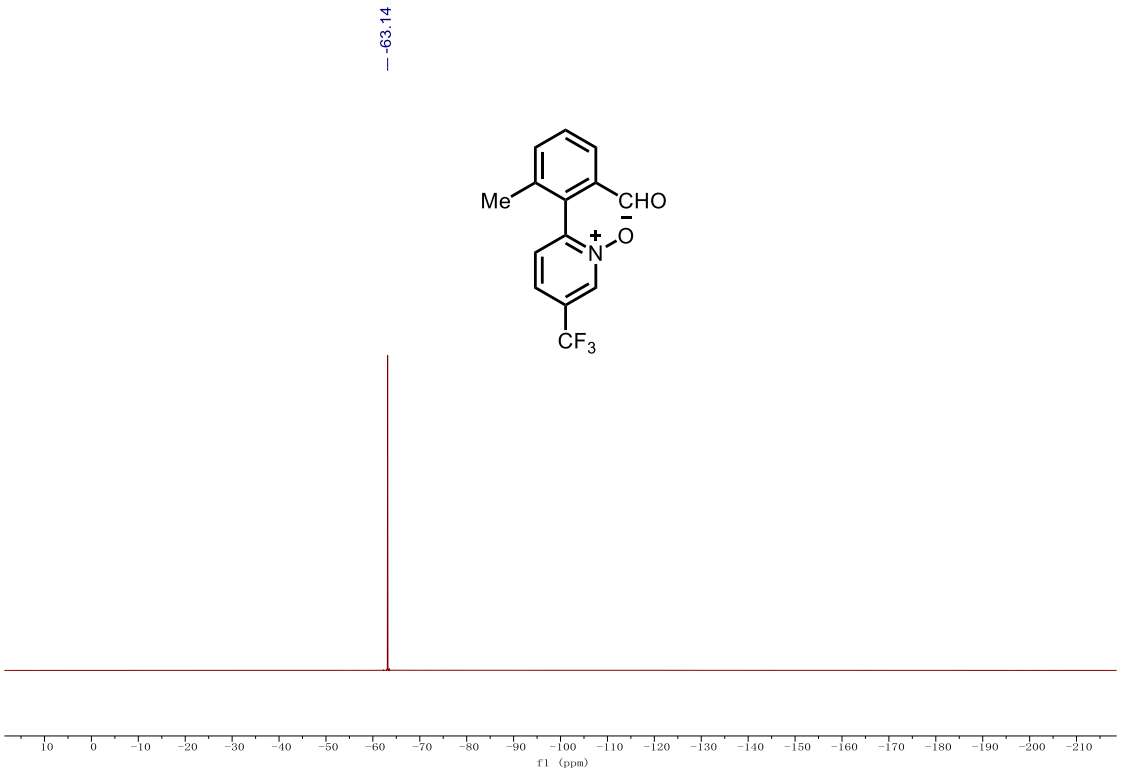
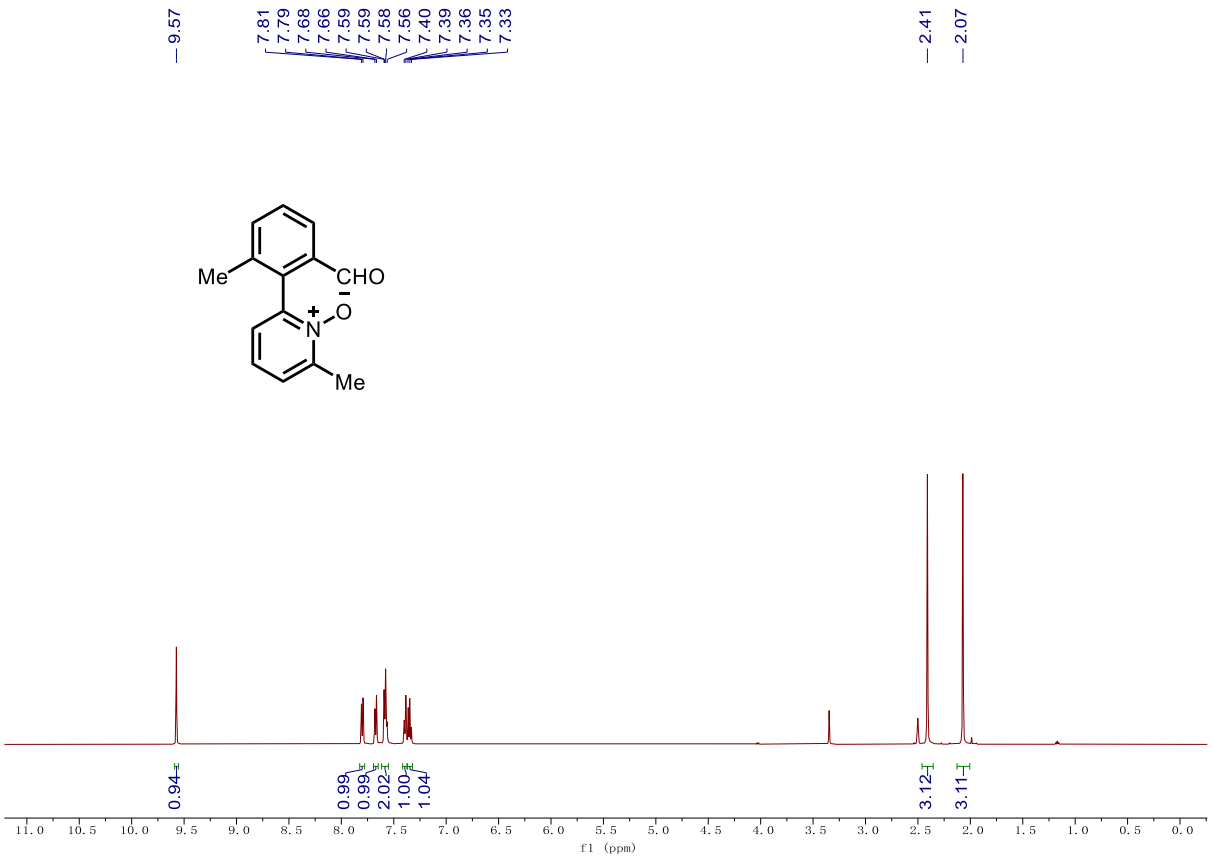
8.61
7.82
7.81
7.80
7.79
7.60
7.59
7.59
7.53
7.52
7.51
7.51
7.36
7.34
2.18
Me
CHO
O
N
CF3
1.01
1.00
1.03
2.04
1.05
1.02
3.16
f1 (ppm)


190.93
151.05
138.43
137.71
137.67
136.26
134.57
131.58
130.43
130.07
129.79
129.52
129.24
128.02
125.24
123.07
121.45
120.89
118.72
19.18
Me
CHO
O
N
CF3
f1 (ppm)


-63.14
Me
CHO
O
N
CF3
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)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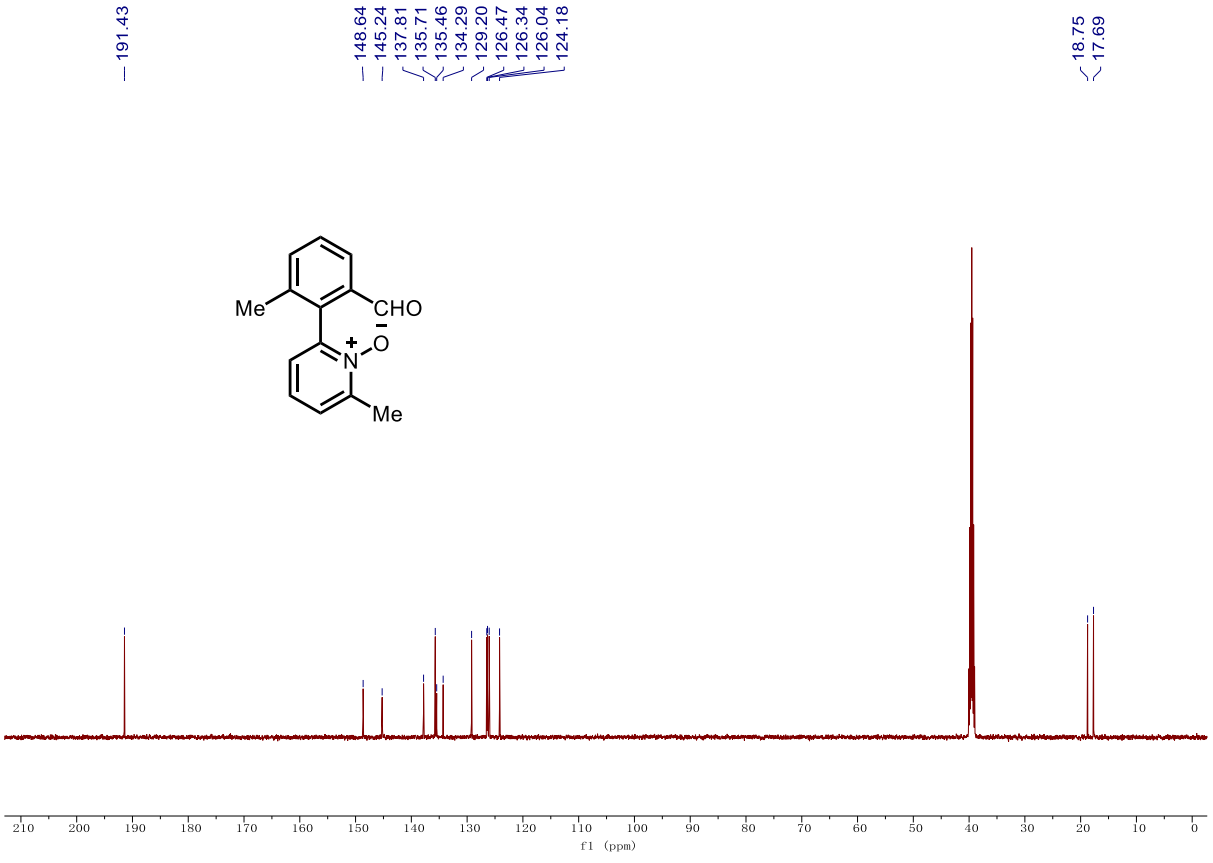
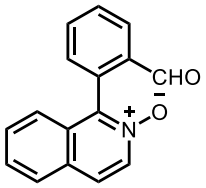
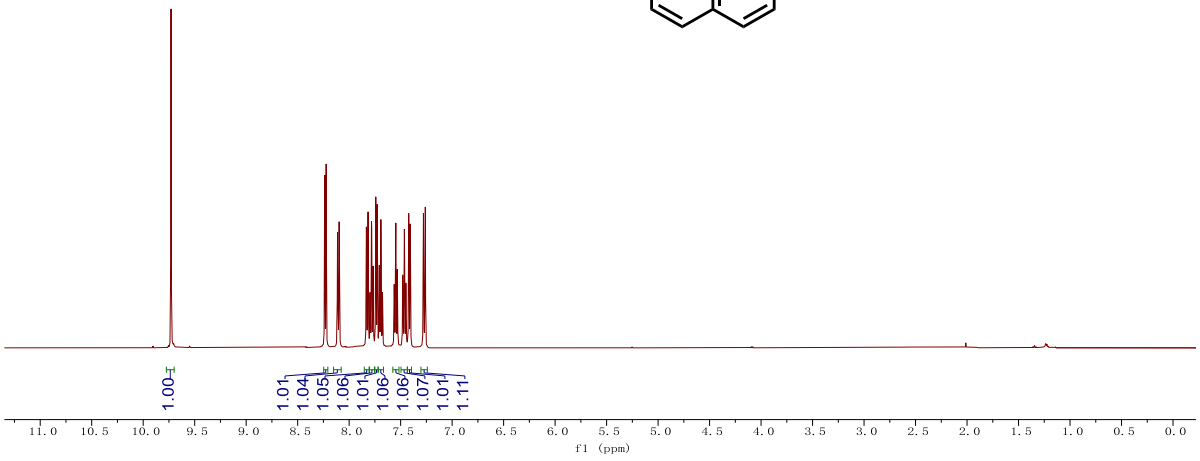
7.81
7.79
7.68
7.66
7.59
7.59
7.58
7.56
7.40
7.39
7.36
7.35
7.33
2.41
2.07
Me
CHO
O
N
Me
0.94
0.99
0.99
2.02
1.00
1.04
3.12
3.11
f1 (ppm)


191.43
148.64
145.24
137.81
135.71
135.46
134.29
129.20
126.47
126.34
126.04
124.18
18.75
17.69
Me
CHO
O
N
Me
f1 (ppm)


9.73
8.24
8.22
8.11
8.11
8.10
8.10
7.83
7.82
7.80
7.80
7.78
7.78
7.77
7.77
7.74
7.73
7.71
7.69
7.68
7.56
7.56
7.55
7.55
7.54
7.53
7.53
7.48
7.48
7.46
7.46
7.45
7.45
7.42
7.41
7.28
7.26


CHO
O
N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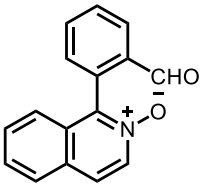
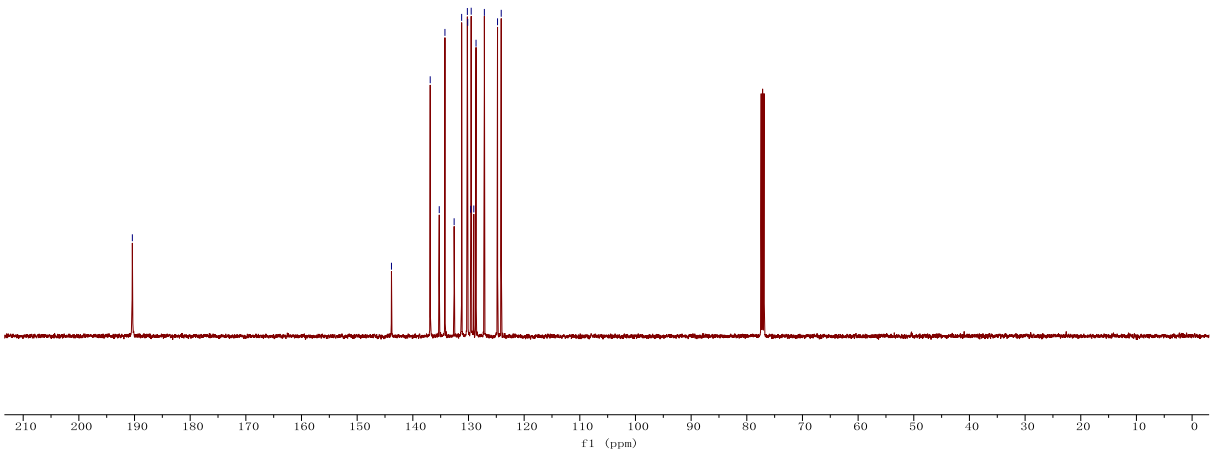
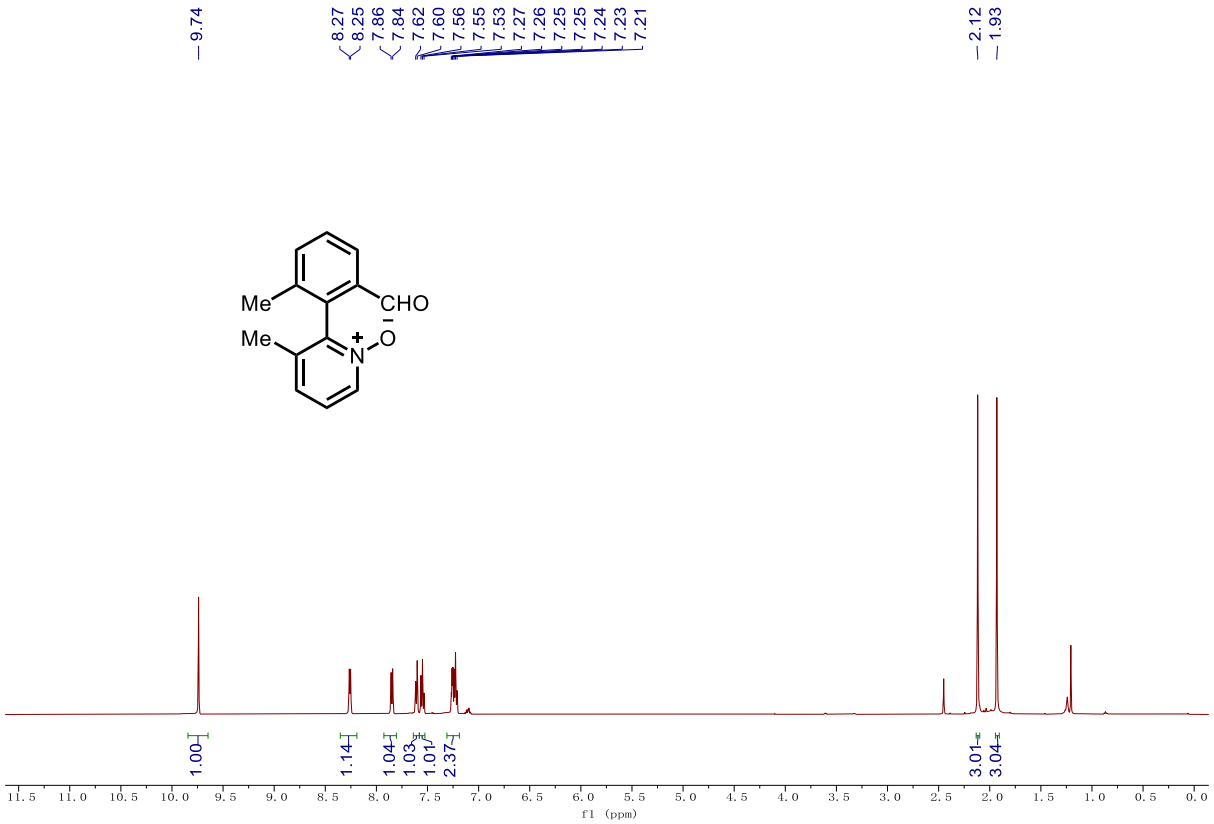
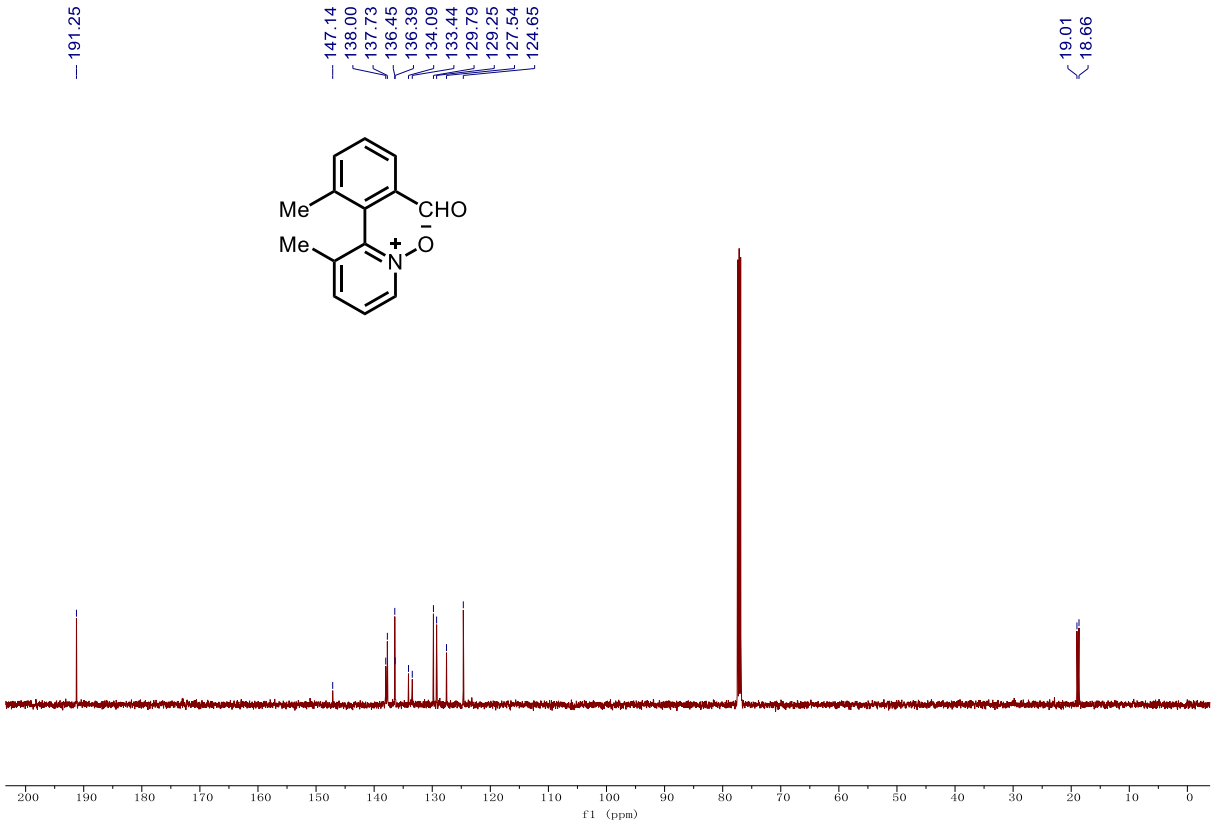
1.01
1.04
1.05
1.06
1.01
1.06
1.06
1.07
1.01
1.11
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190.39
143.84
136.88
135.25
134.23
132.58
131.23
130.20
130.14
129.60
129.51
129.04
128.64
127.15
124.78
124.12

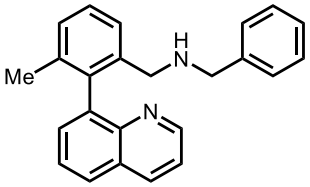

CHO
O
N

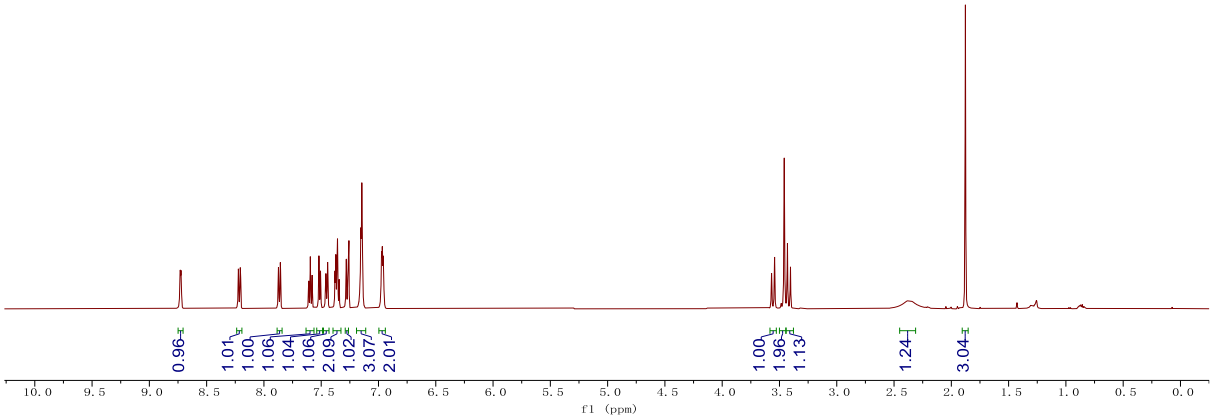

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.74
8.27
8.25
7.86
7.84
7.62
7.60
7.56
7.55
7.53
7.27
7.26
7.25
7.25
7.24
7.23
7.21
2.12
1.93
Me
Me
CHO
O
N
1.00
1.14
1.04
1.03
1.01
2.37
3.01
3.04
f1 (ppm)

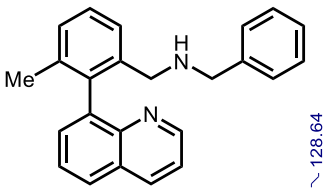

191.25
147.14
138.00
137.73
136.45
136.39
134.09
133.44
129.79
129.25
127.54
124.65
19.01
18.66
Me
Me
CHO
O
N
f1 (ppm)


8.73
8.73
8.72
8.72
8.22
8.22
8.21
8.20
7.87
7.87
7.86
7.85
7.61
7.59
7.58
7.52
7.51
7.46
7.44
7.38
7.37
7.37
7.36
7.36
7.35
7.34
7.28
7.27
7.17
7.16
7.15
7.15
7.15
7.14
6.97
6.97
6.96
6.95
3.57
3.54
3.46
3.43
3.40
2.37
1.88

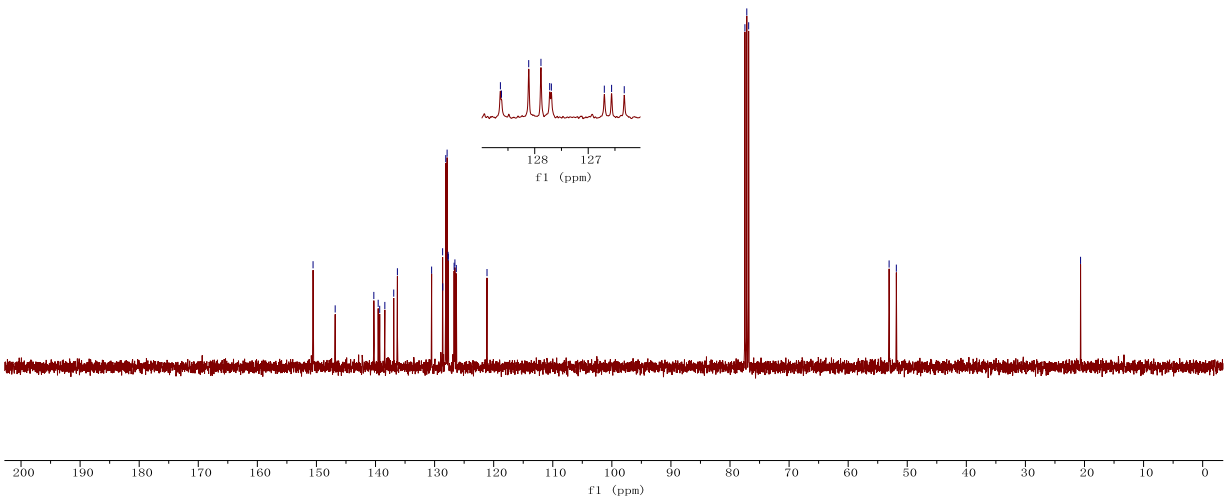

H
N
Me
N


0.96
1.01
1.00
1.06
1.04
1.06
2.09
1.02
3.07
2.01
1.00
1.96
1.13
1.24
3.04
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)

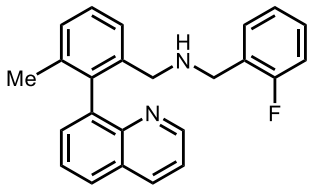

150.57
146.83
140.29
139.55
139.29
138.42
136.92
136.30
130.50
128.64
128.62
128.11
127.88
127.72
127.69
126.70
126.56
126.33
121.13
77.48
77.16
76.84
53.07
51.85
20.67

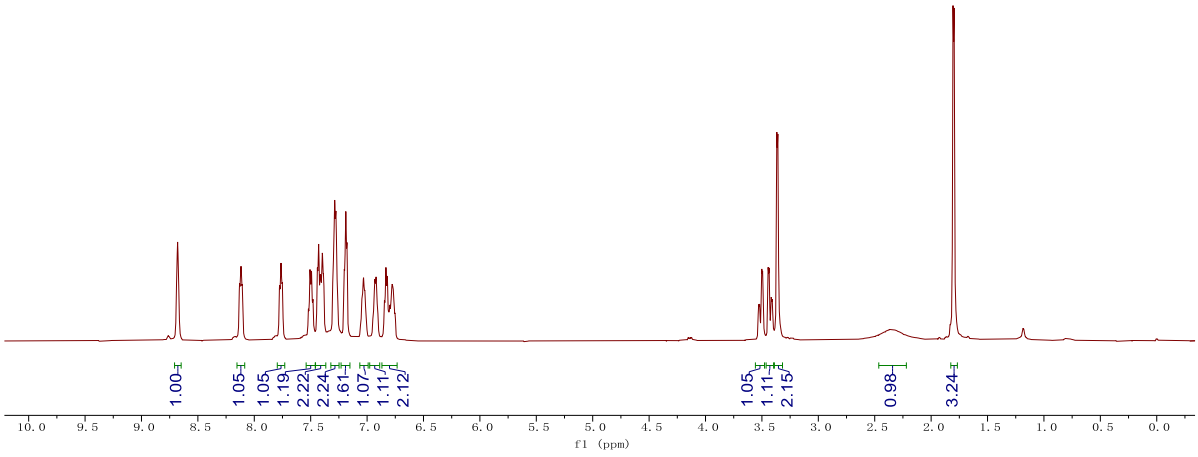

H
N
Me
N


128.64
128.11
127.88
127.72
127.69
126.70
126.56

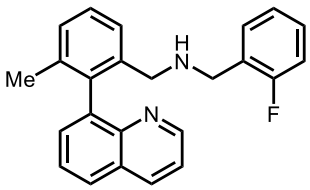

128
127
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.69
8.68
8.67
8.13
8.12
8.11
7.78
7.76
7.75
7.52
7.51
7.49
7.48
7.44
7.43
7.41
7.40
7.38
7.30
7.29
7.28
7.20
7.19
7.18
7.05
7.03
7.02
7.01
6.95
6.93
6.92
6.91
6.85
6.83
6.82
6.80
6.79
6.78
6.77
6.76
6.75
3.53
3.52
3.50
3.49
3.45
3.44
3.42
3.41
3.37
3.36

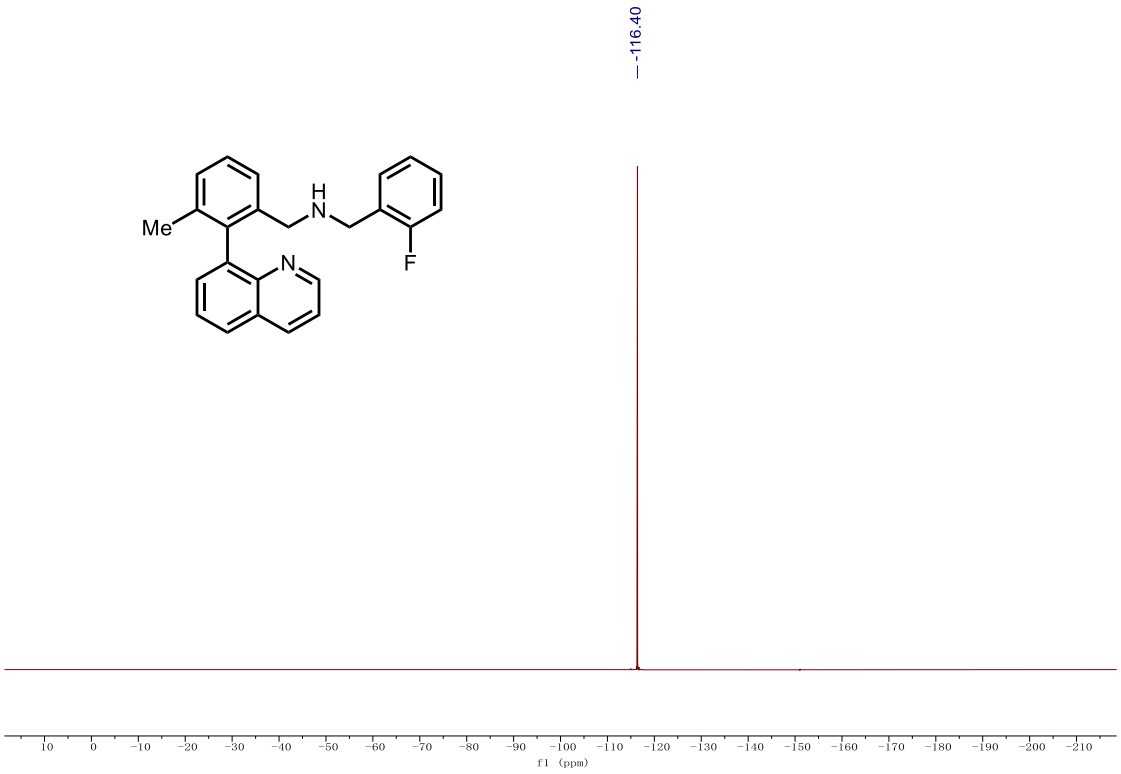

Me
H
N
N
F

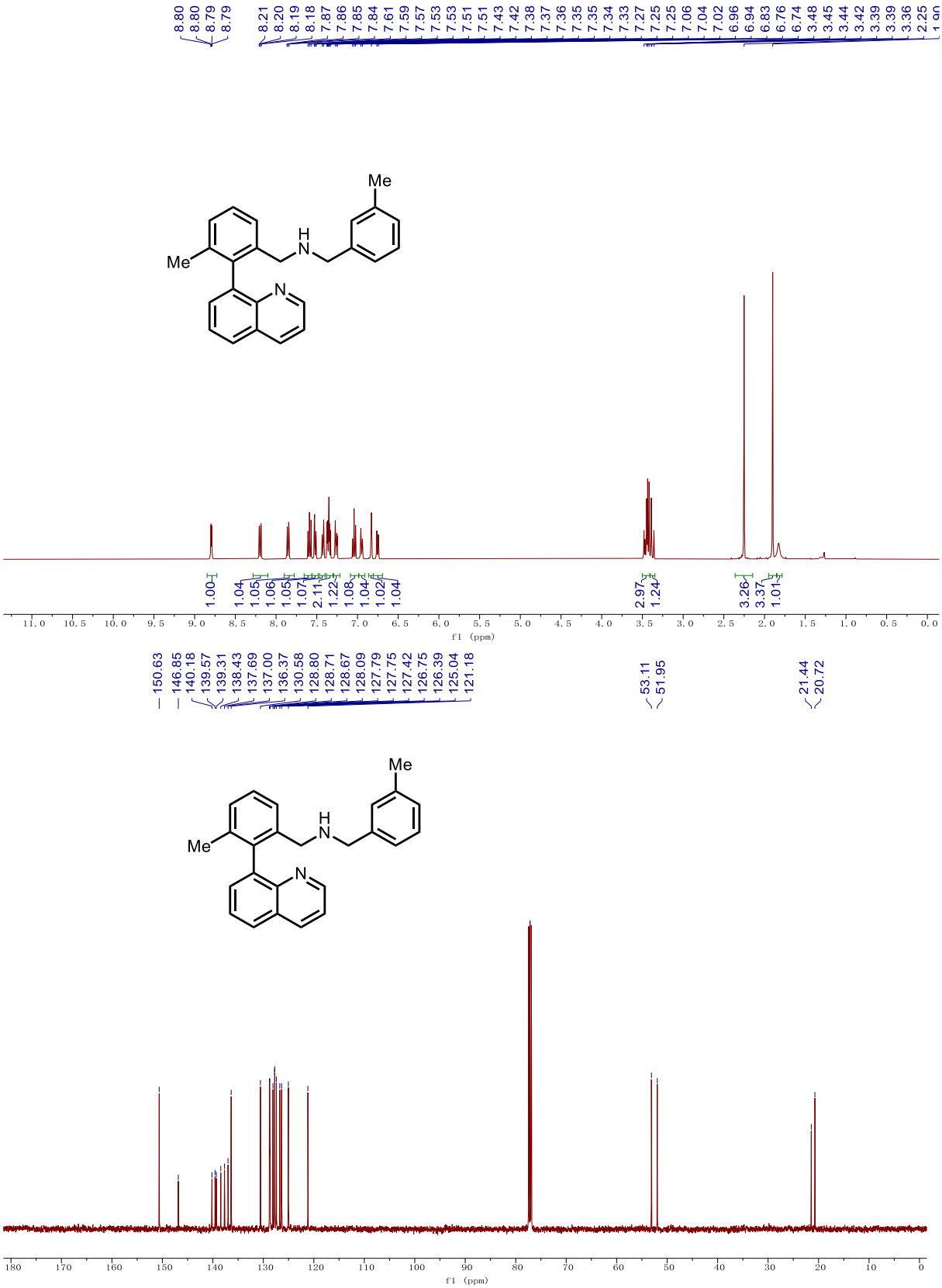

1.00
1.05
1.05
1.19
2.22
2.24
1.61
1.07
1.11
2.12
1.05
1.11
2.15
0.98
3.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

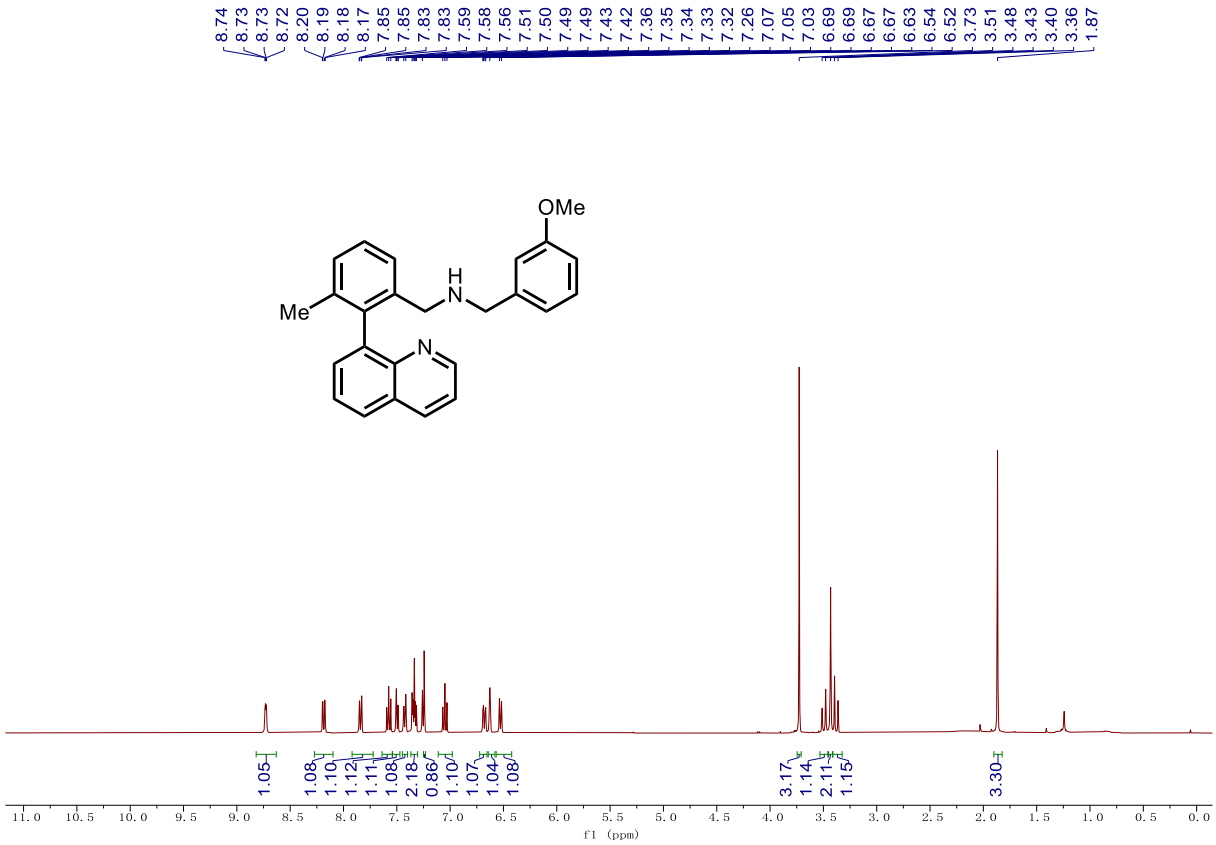

150.66
146.77
139.83
139.34
137.62
137.07
136.50
130.70
130.21
129.04
128.68
128.51
127.95
127.84
126.98
126.42
123.92
121.23
115.14
114.98
51.80
46.20
20.76

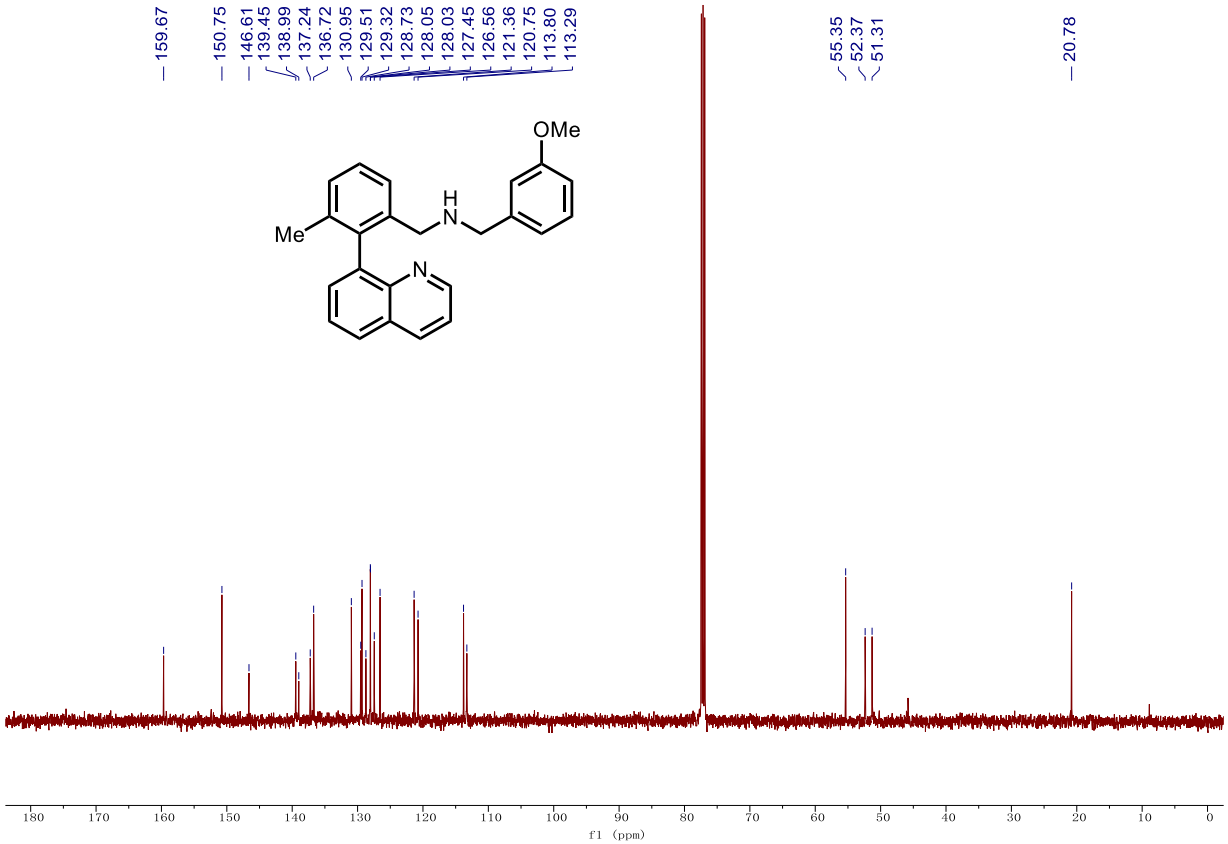

Me
H
N
N
F

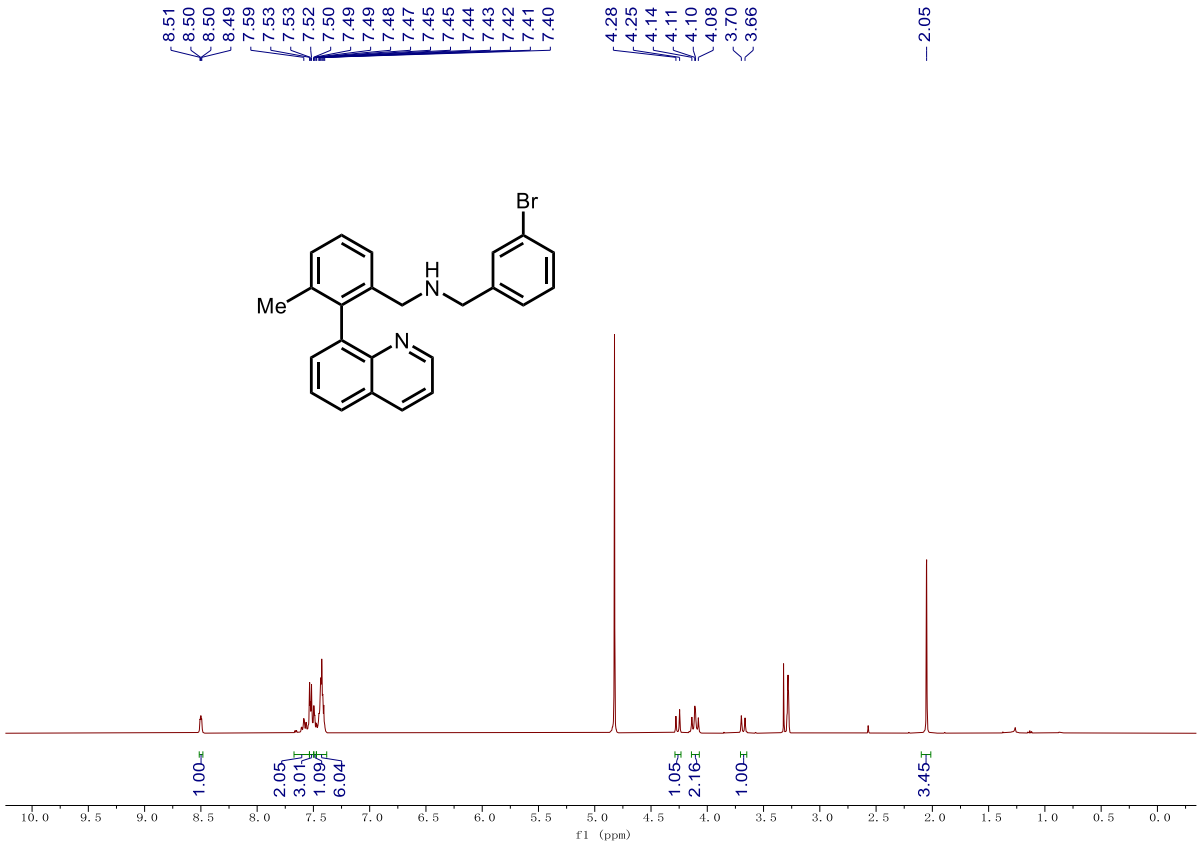
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

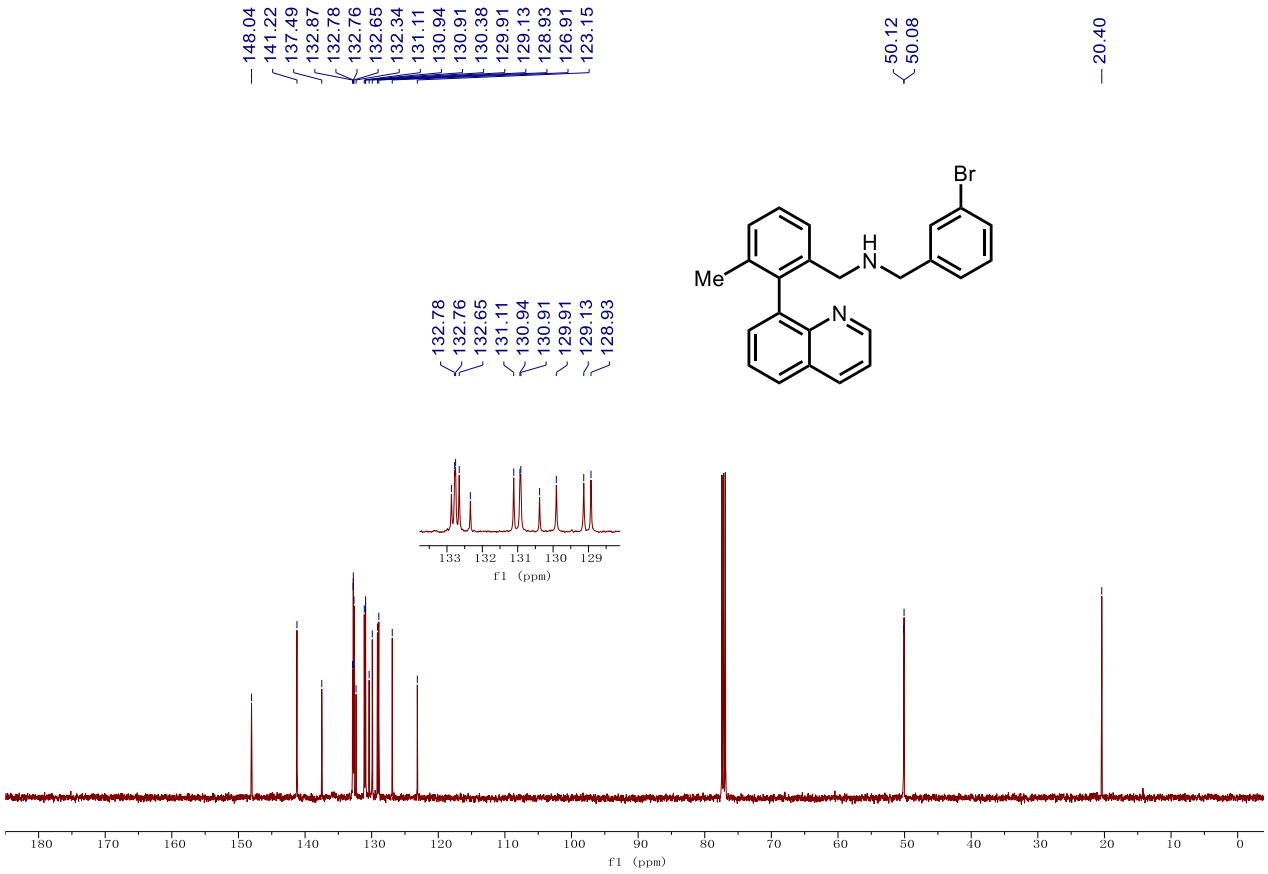

-116.40
Me
H
N
N
F
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
f1 (ppm)

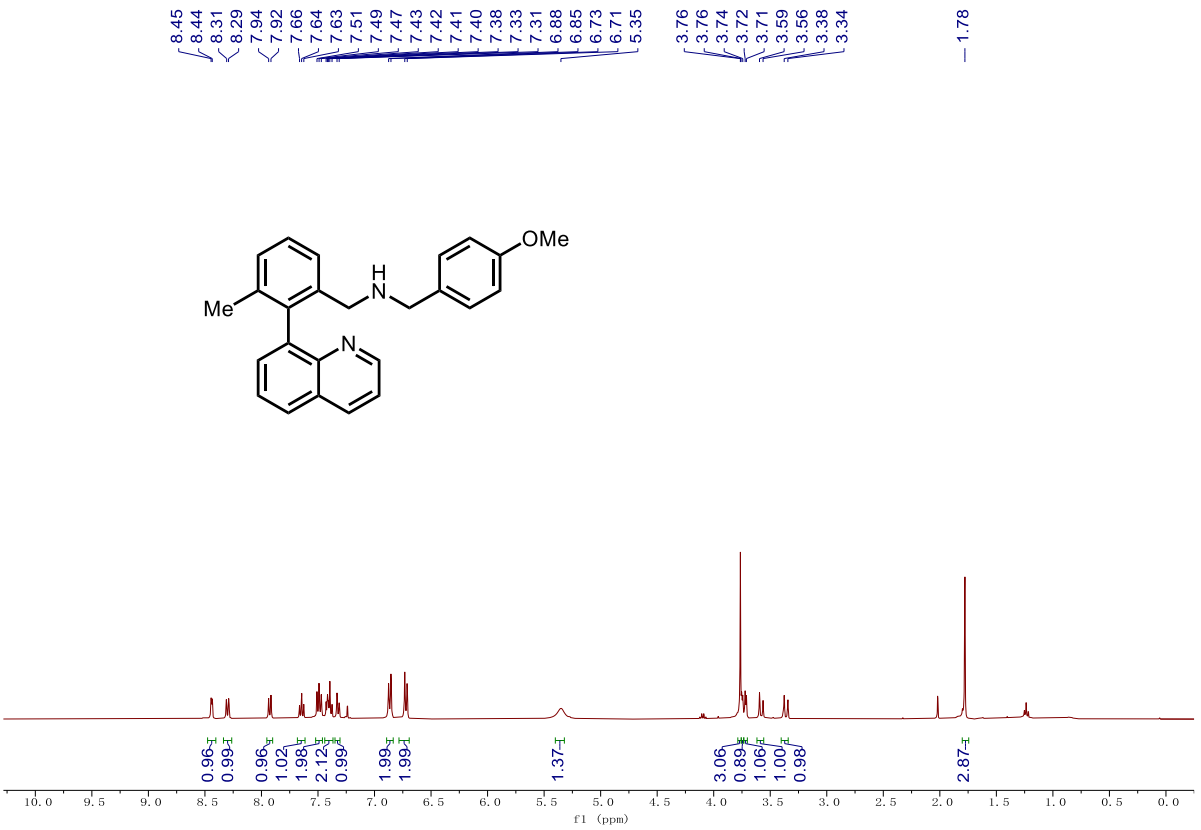

8.80 8.80 8.79 8.79 8.21 8.20 8.19 8.18 7.87 7.86 7.85 7.84 7.61 7.59 7.57 7.53 7.53 7.51 7.51 7.43 7.42 7.38 7.37 7.36 7.35 7.35 7.34 7.33 7.27 7.25 7.25 7.06 7.04 7.02 6.96 6.94 6.83 6.76 6.74 3.48 3.45 3.44 3.42 3.39 3.39 3.36 2.25
Me
H
N
Me
N
1.00 1.04 1.05 1.06 1.05 1.07 2.11 1.22 1.08 1.04 1.02 1.04 2.97 1.24 3.26 3.37 1.01
11.0 10.5 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)
150.63 146.85 140.18 139.57 139.31 138.43 137.69 137.00 136.37 130.58 128.80 128.71 128.67 128.09 127.79 127.75 127.42 126.75 126.39 125.04 121.18
53.11 51.95
21.44 20.72
Me
H
N
Me
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

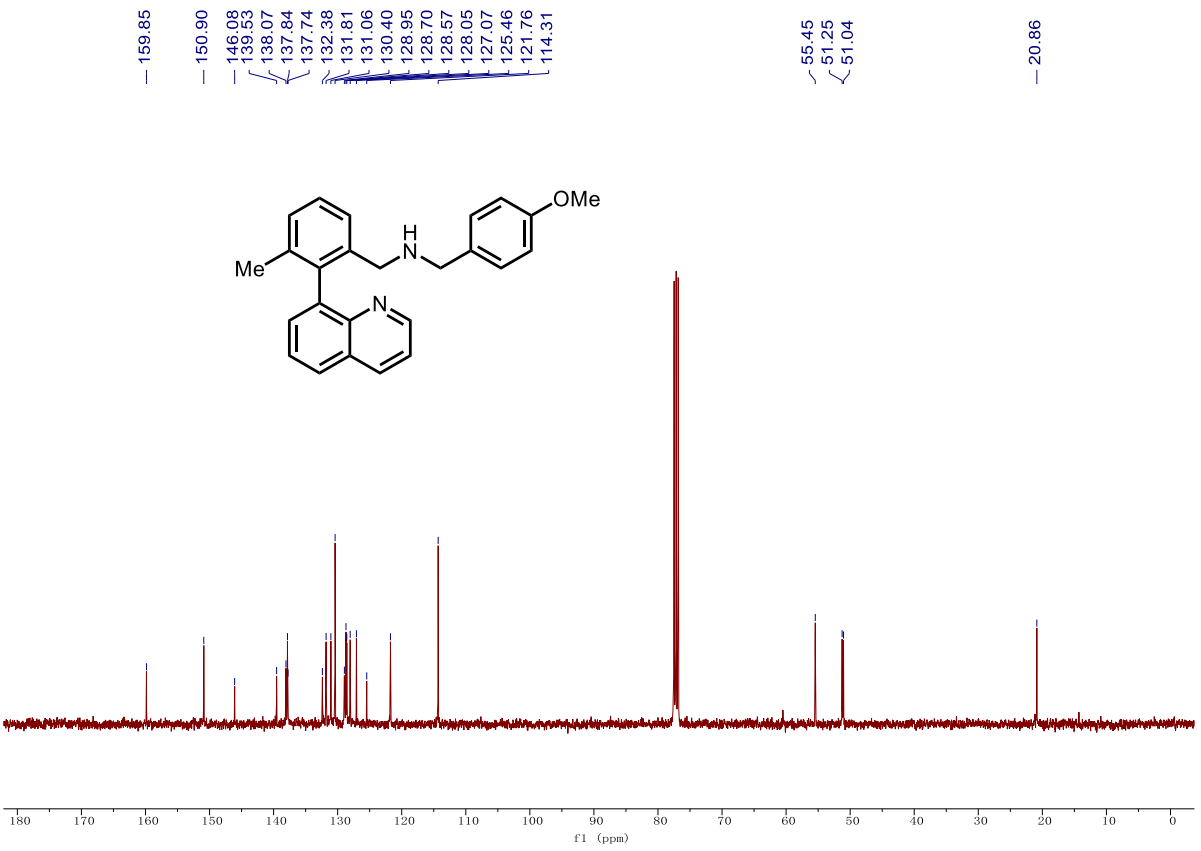

8.74
8.73
8.73
8.72
8.20
8.19
8.18
8.17
7.85
7.85
7.83
7.83
7.59
7.58
7.56
7.51
7.50
7.49
7.49
7.43
7.42
7.36
7.35
7.34
7.33
7.32
7.26
7.07
7.05
7.03
6.69
6.69
6.67
6.67
6.63
6.54
6.52
3.73
3.51
3.48
3.43
3.40
3.36
1.87
OMe
H
N
Me
N
1.05
1.08
1.10
1.12
1.11
1.08
2.18
0.86
1.10
1.07
1.04
1.08
3.17
1.14
2.11
1.15
3.30
f1 (ppm)

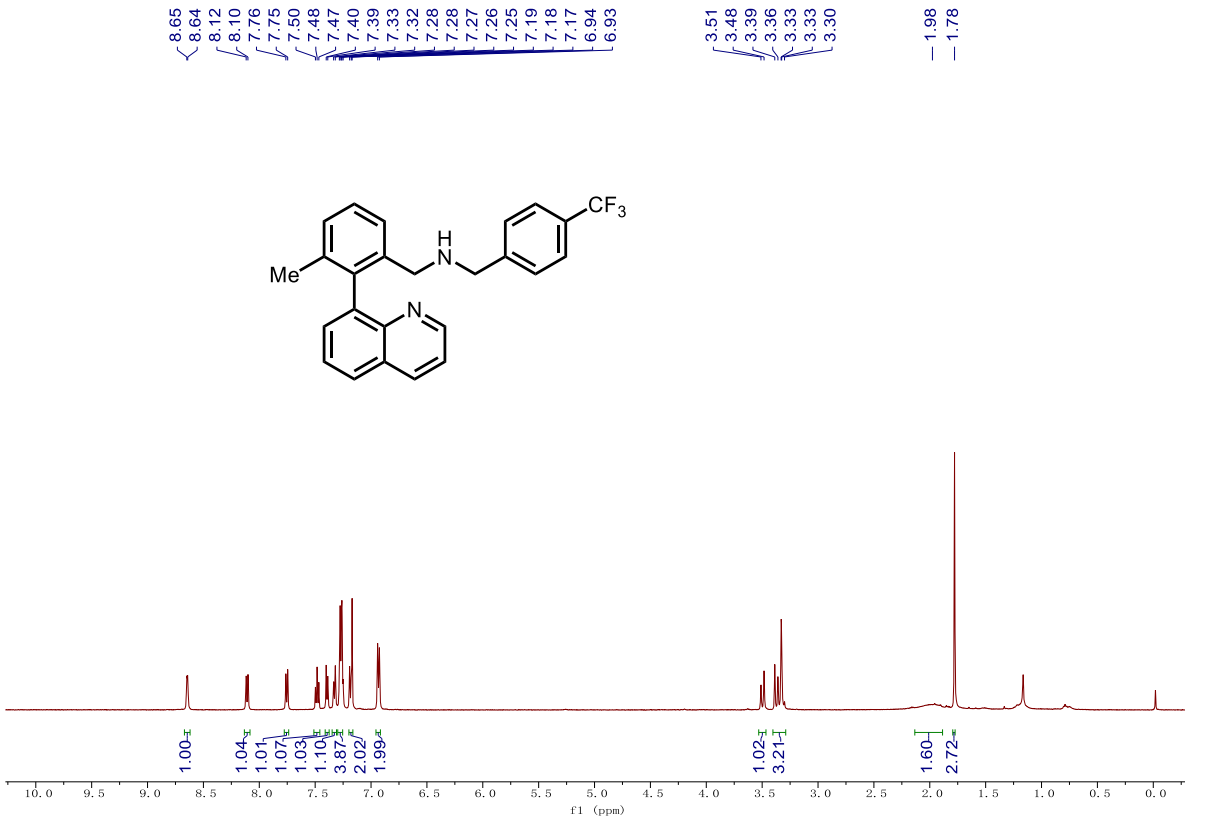

159.67
150.75
146.61
139.45
138.99
137.24
136.72
130.95
129.51
129.32
128.73
128.05
128.03
127.45
126.56
121.36
120.75
113.80
113.29
55.35
52.37
51.31
20.78
OMe
H
N
Me
N
f1 (ppm)

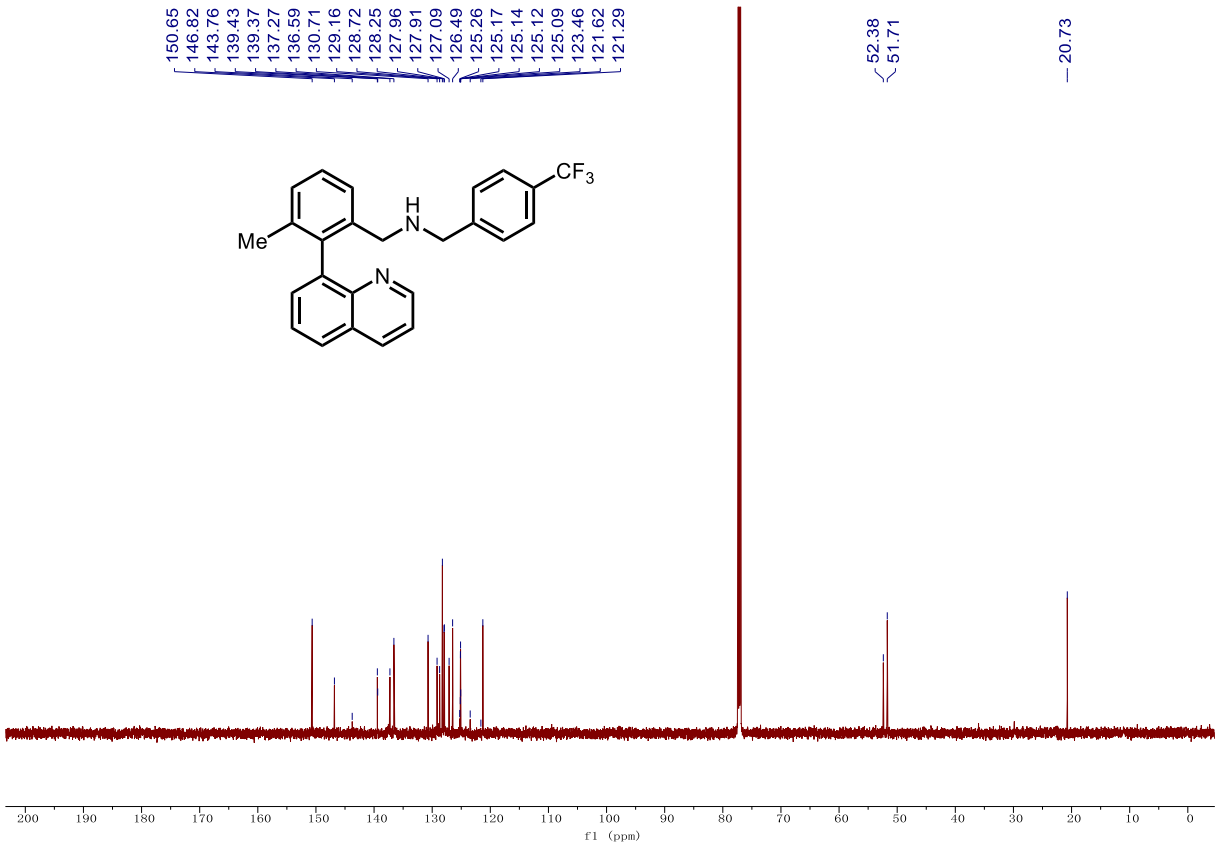

8.51
8.50
8.50
8.49
7.59
7.53
7.53
7.52
7.50
7.49
7.49
7.48
7.47
7.45
7.45
7.44
7.43
7.42
7.41
7.40
4.28
4.25
4.14
4.11
4.10
4.08
3.70
3.66
2.05
Br
Me
H
N
N
1.00
2.05
3.01
1.09
6.04
1.05
2.16
1.00
3.45
f1 (ppm)

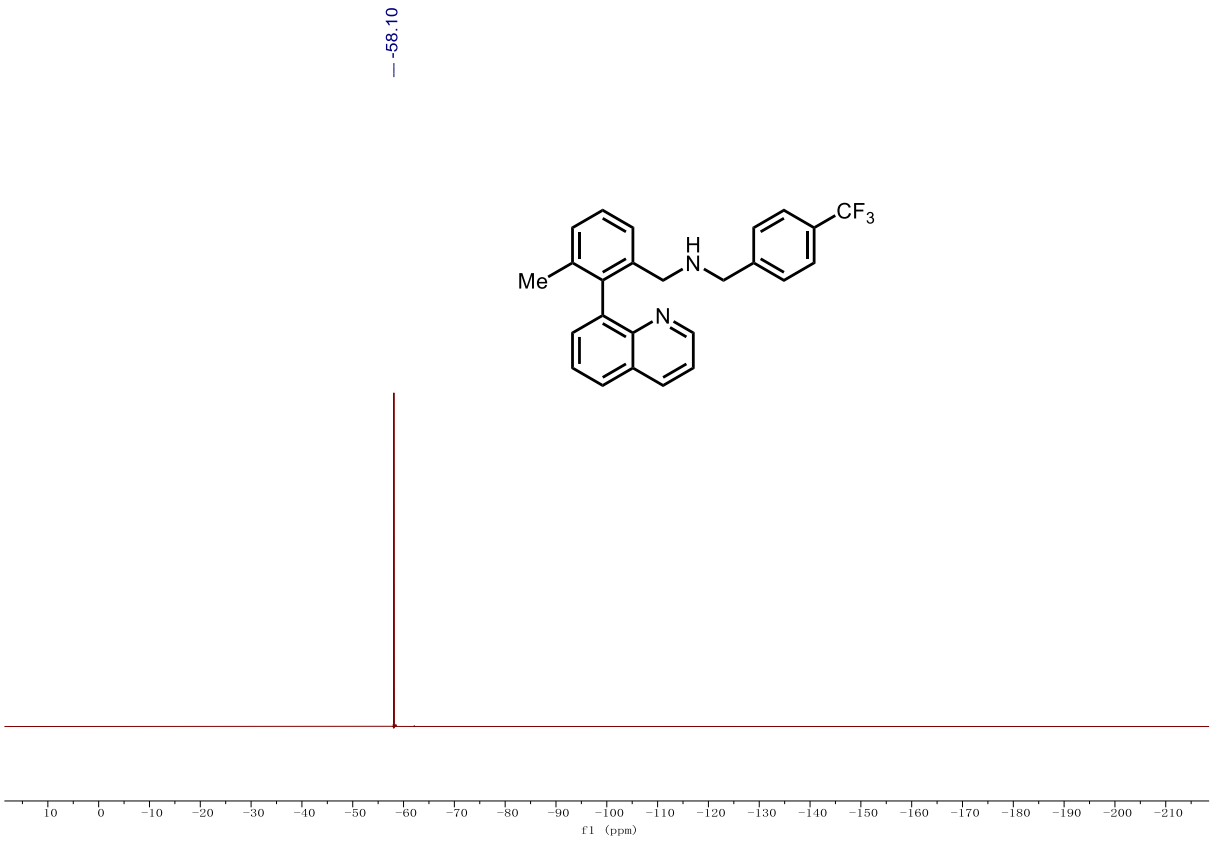

148.04
141.22
137.49
132.87
132.78
132.76
132.65
132.34
131.11
130.94
130.91
130.38
129.91
129.13
128.93
126.91
123.15
50.12
50.08
20.40
Br
Me
H
N
N
132.78
132.76
132.65
131.11
130.94
130.91
129.91
129.13
128.93
133
132
131
130
129
f1 (ppm)
f1 (ppm)


8.45
8.44
8.31
8.29
7.94
7.92
7.66
7.64
7.63
7.51
7.49
7.47
7.43
7.42
7.41
7.40
7.38
7.33
7.31
6.88
6.85
6.73
6.71
5.35
3.76
3.76
3.74
3.72
3.71
3.59
3.56
3.38
3.34
1.78
OMe
H
N
Me
N
0.96
0.99
0.96
1.02
1.98
2.12
0.99
1.99
1.99
1.37
3.06
0.89
1.06
1.00
0.98
2.87
f1 (ppm)

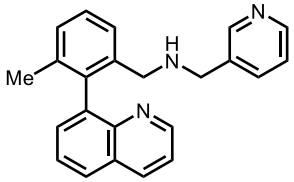

159.85
150.90
146.08
139.53
138.07
137.84
137.74
132.38
131.81
131.06
130.40
128.95
128.70
128.57
128.05
127.07
125.46
121.76
114.31
55.45
51.25
51.04
20.86
OMe
H
N
Me
N
f1 (ppm)

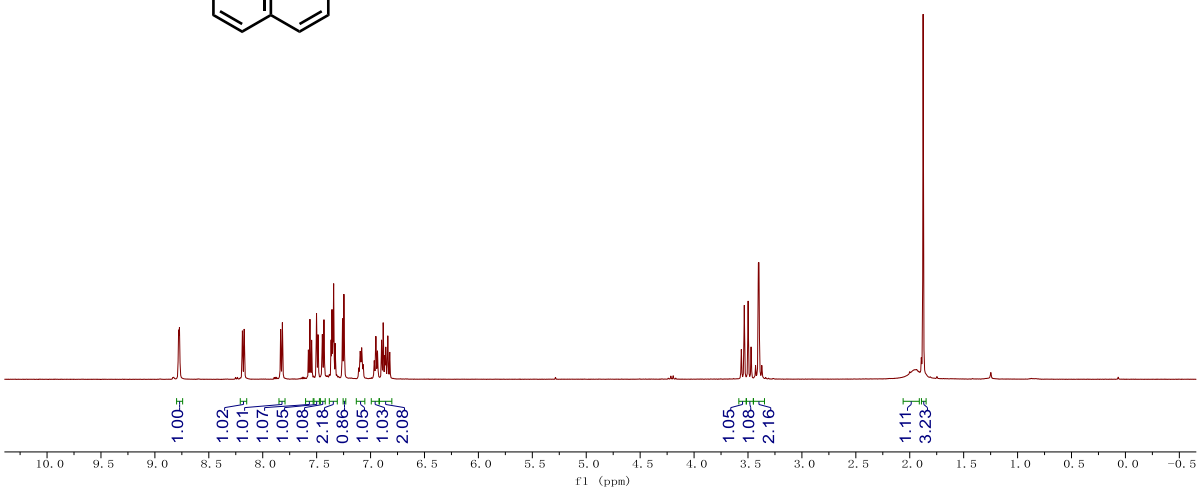

8.65
8.64
8.12
8.10
7.76
7.75
7.50
7.48
7.47
7.40
7.39
7.33
7.32
7.28
7.28
7.27
7.26
7.25
7.19
7.18
7.17
6.94
6.93
3.51
3.48
3.39
3.36
3.33
3.33
3.30
1.98
1.78
CF3
H
N
Me
N
1.00
1.04
1.01
1.07
1.03
1.10
3.87
2.02
1.99
1.02
3.21
1.60
2.72
f1 (ppm)

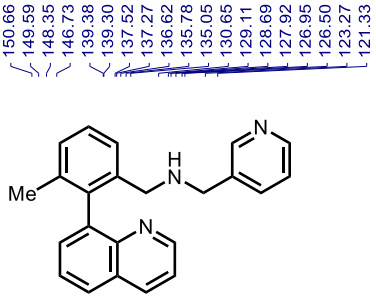

150.65
146.82
143.76
139.43
139.37
137.27
136.59
130.71
129.16
128.72
128.25
127.96
127.91
127.09
126.49
125.26
125.17
125.14
125.12
125.09
123.46
121.62
121.29
52.38
51.71
20.73
CF3
H
N
Me
N
f1 (ppm)


-58.10
CF3
H
N
Me
N
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
f1 (ppm)

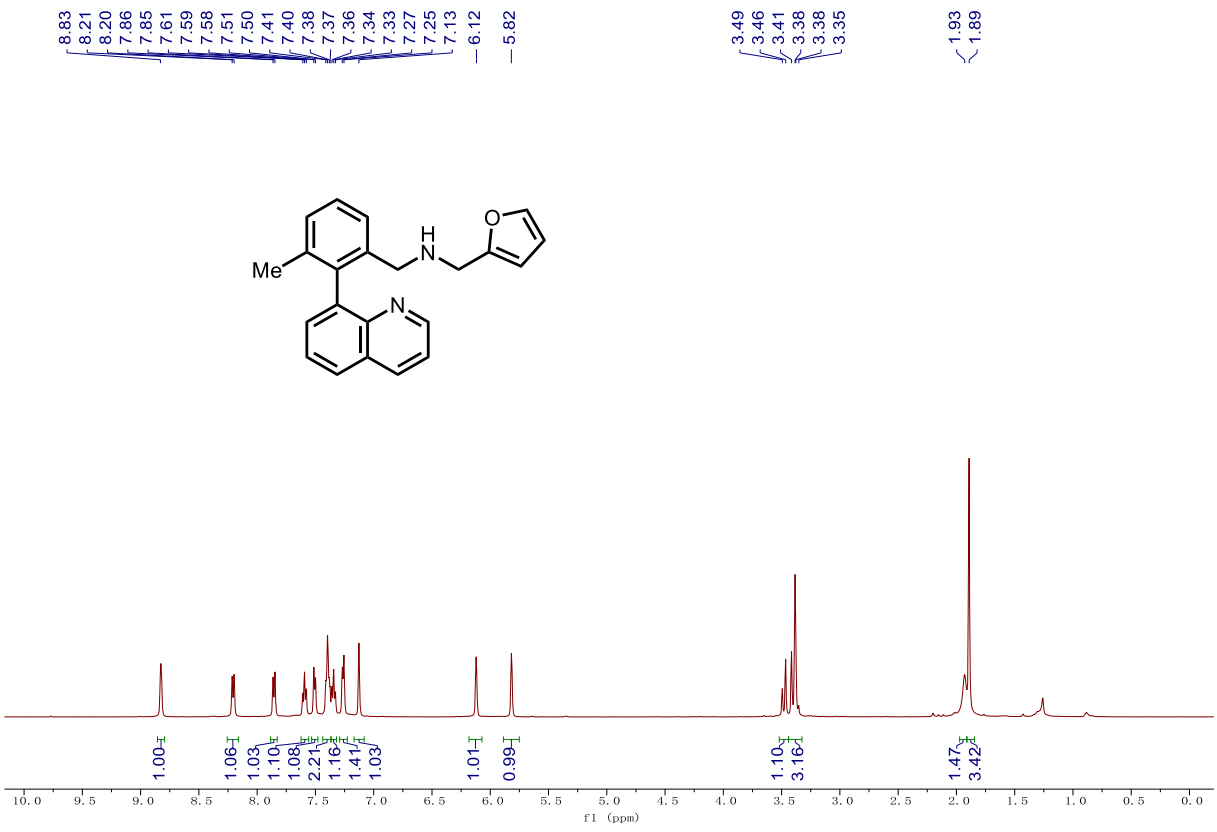

8.78
8.77
8.19
8.17
7.83
7.82
7.58
7.56
7.55
7.50
7.49
7.45
7.43
7.37
7.36
7.35
7.34
7.33
7.26
7.25
7.11
7.11
7.10
7.08
7.07
6.97
6.95
6.94
6.90
6.88
6.87
6.86
6.84
6.82
3.56
3.53
3.50
3.47
3.43
3.40
3.40
3.37
1.95
1.88

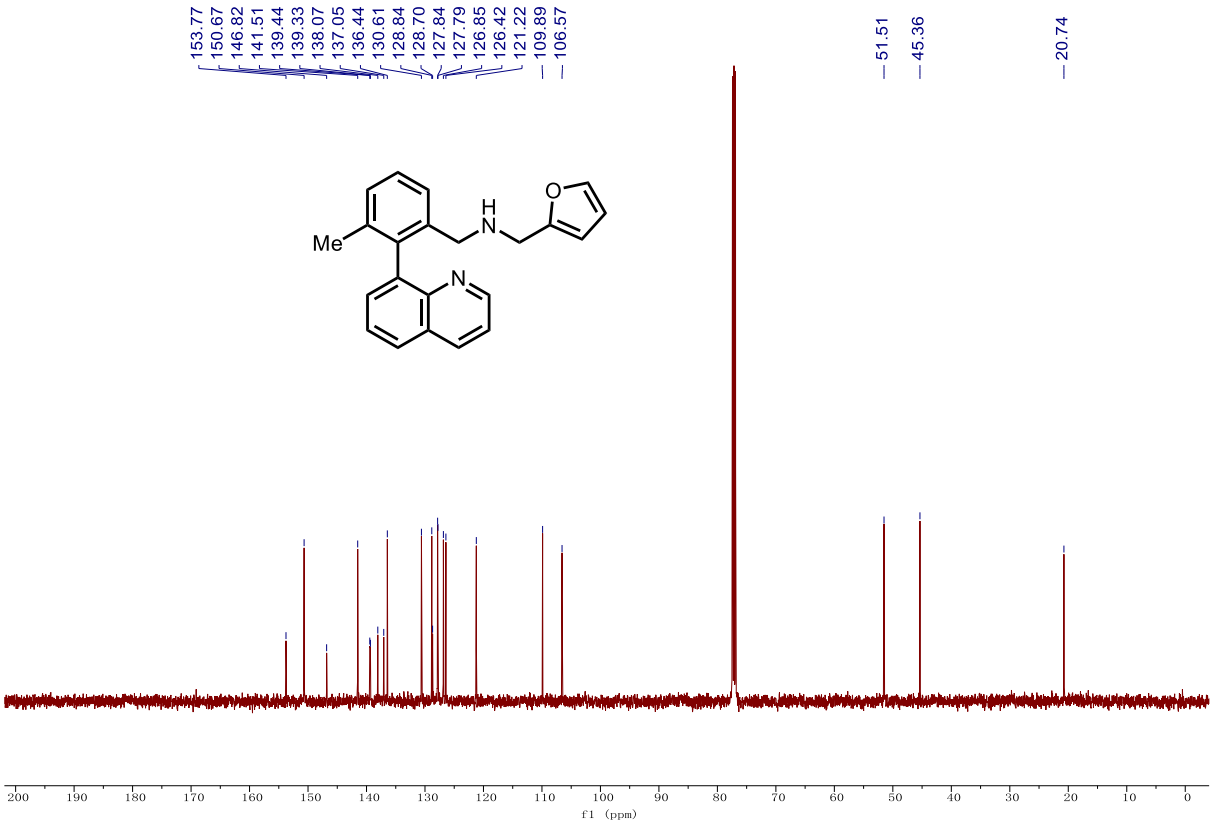

Me
H
N
N
N


1.00
1.02
1.01
1.07
1.05
1.08
2.18
0.86
1.05
1.03
2.08
1.05
1.08
2.16
1.11
3.23
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
-0.5
f1 (ppm)

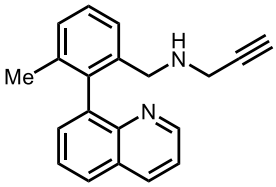

150.66
149.59
148.35
146.73
139.38
139.30
137.52
137.27
136.62
135.78
135.05
130.65
129.11
128.69
127.92
126.95
126.50
123.27
121.33
51.92
50.24
20.71
Me
H
N
N
N

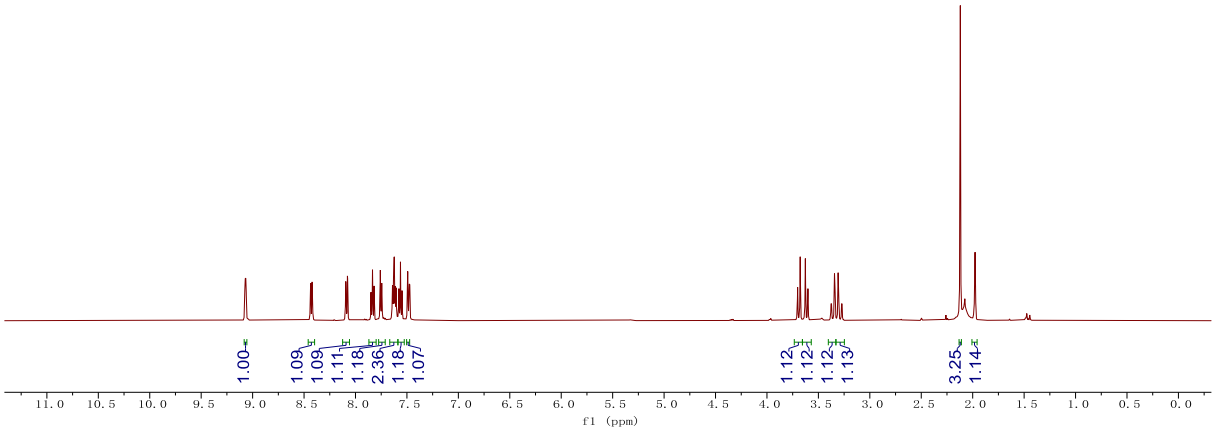
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.83
8.21
8.20
7.86
7.85
7.61
7.59
7.58
7.51
7.50
7.41
7.40
7.38
7.37
7.36
7.34
7.33
7.27
7.25
7.13
6.12
5.82
3.49
3.46
3.41
3.38
3.38
3.35
1.93
1.89
Me
H
N
O
N
1.00
1.06
1.03
1.10
1.08
2.21
1.16
1.41
1.03
1.01
0.99
1.10
3.16
1.47
3.42
f1 (ppm)

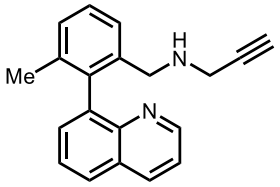

153.77
150.67
146.82
141.51
139.44
139.33
138.07
137.05
136.44
130.61
128.84
128.70
127.84
127.79
126.85
126.42
121.22
109.89
106.57
51.51
45.36
20.74
Me
H
N
O
N
f1 (ppm)

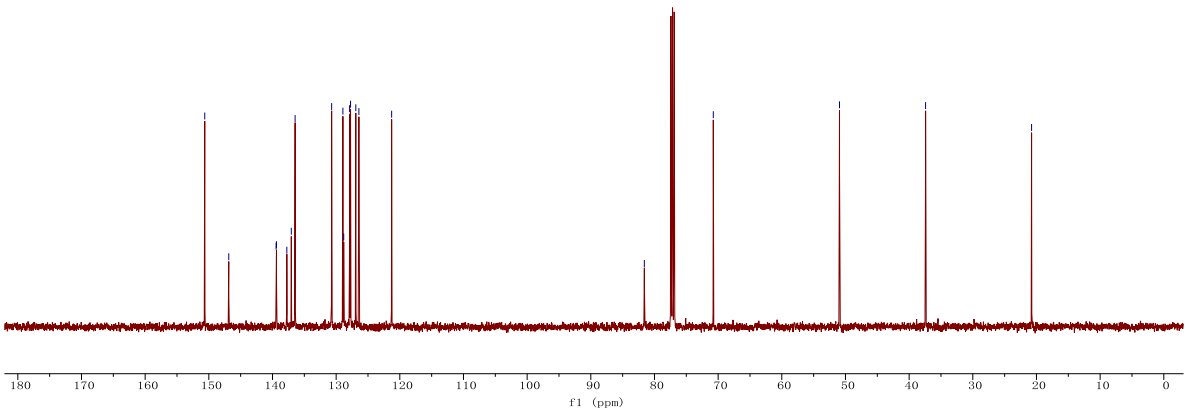

9.07
9.07
9.07
9.06
8.44
8.44
8.42
8.42
8.10
8.08
7.85
7.83
7.82
7.76
7.76
7.75
7.74
7.64
7.62
7.61
7.60
7.58
7.56
7.55
7.49
7.48
7.47
3.70
3.68
3.63
3.60
3.38
3.37
3.34
3.34
3.31
3.30
3.27
3.27
2.12
1.98
1.98
1.97


Me
H
N
N

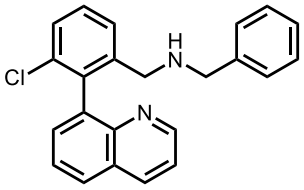

1.00
1.09
1.09
1.11
1.18
2.36
1.18
1.07
1.12
1.12
1.12
1.13
3.25
1.14
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

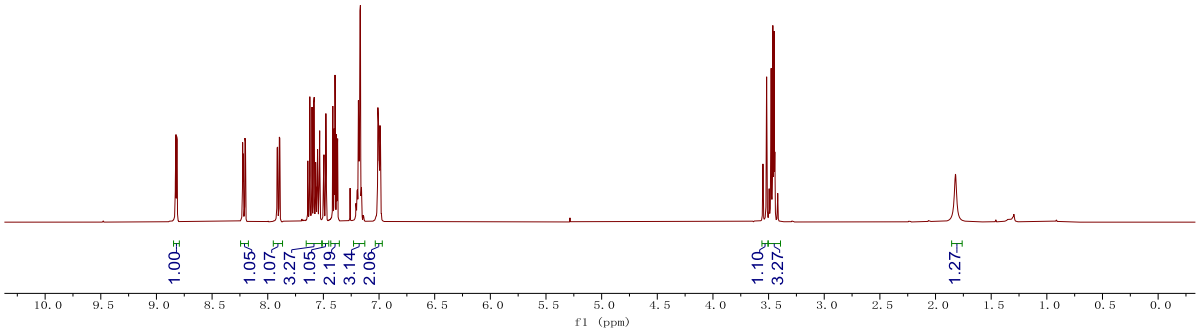

150.64
146.87
139.43
139.37
137.75
137.05
136.45
130.71
128.94
128.81
127.89
127.74
126.91
126.43
121.28
81.59
70.76
50.94
37.42
20.77

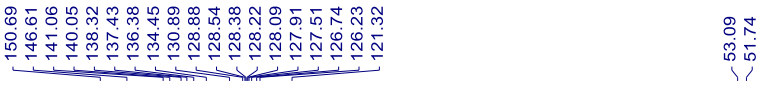

Me
H
N
N


180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

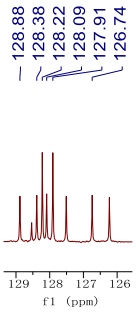

8.83
8.82
8.82
8.81
8.23
8.22
8.20
8.20
7.92
7.91
7.90
7.89
7.64
7.62
7.60
7.59
7.58
7.57
7.57
7.56
7.55
7.54
7.53
7.50
7.49
7.48
7.47
7.42
7.40
7.40
7.39
7.38
7.38
7.37
7.20
7.19
7.19
7.18
7.18
7.17
7.17
7.17
7.16
7.15
7.01
7.00
7.00
7.00
6.99
6.99
3.55
3.52
3.49
3.48
3.46
3.45
3.44
3.42
1.82

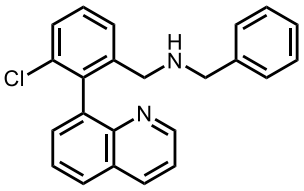

Cl
H
N
N

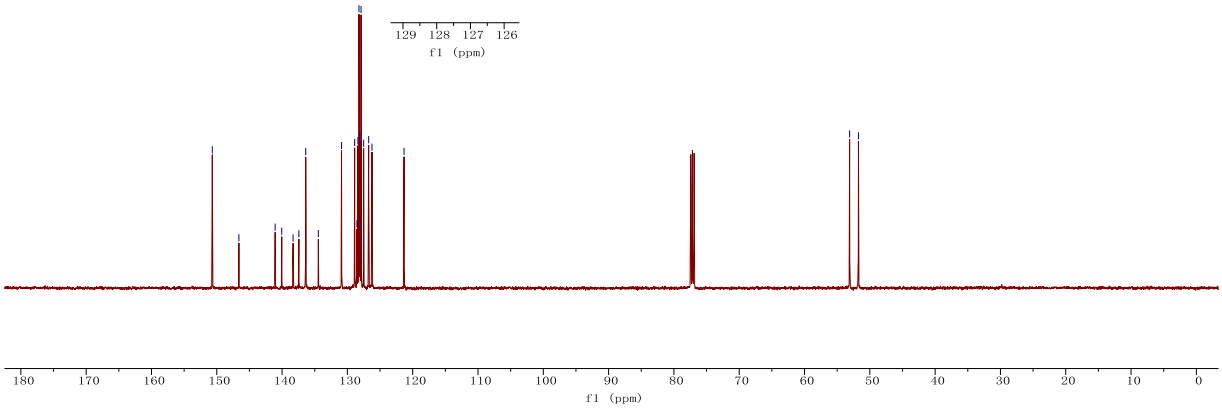

1.00
1.05
1.07
3.27
1.05
2.19
3.14
2.06
1.10
3.27
1.27
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


150.69
146.61
141.06
140.05
138.32
137.43
136.38
134.45
130.89
128.88
128.54
128.38
128.22
128.09
127.91
127.51
126.74
126.23
121.32

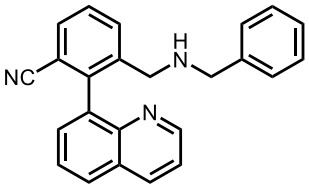
53.09
51.74

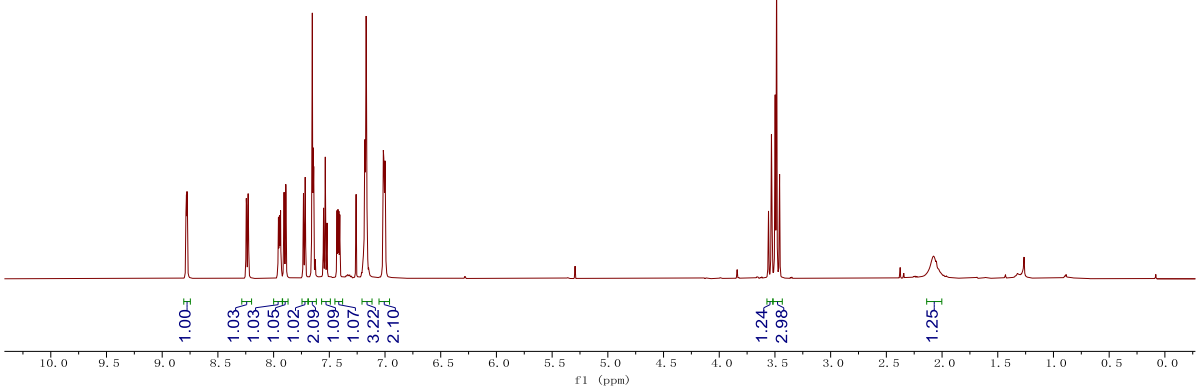

128.88
128.38
128.22
128.09
127.91
126.74
129
128
127
126
f1 (ppm)


Cl
H
N
N


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

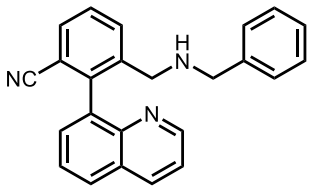

8.79
8.78
8.78
8.77
8.25
8.24
8.23
8.23
7.96
7.95
7.94
7.94
7.90
7.89
7.73
7.72
7.66
7.65
7.65
7.64
7.63
7.55
7.54
7.52
7.43
7.42
7.41
7.41
7.20
7.20
7.19
7.18
7.17
7.17
7.17
7.16
7.16
7.15
7.14
7.02
7.01
7.00
7.00
3.56
3.53
3.52
3.50
3.49
3.46
2.08


NC
H
N
N


1.00
1.03
1.03
1.05
1.02
2.09
1.09
1.07
3.22
2.10
1.24
2.98
1.25
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)


150.86
146.46
143.33
140.52
139.66
136.60
136.30
133.47
131.58
131.05
129.38
128.66
128.40
128.36
127.99
127.00
126.32
121.64
118.51
114.33


53.26
50.98


NC
H
N
N

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.77
8.77
8.76
8.76
8.21
8.21
8.19
8.19
7.90
7.90
7.89
7.88
7.84
7.82
7.77
7.75
7.60
7.59
7.58
7.58
7.57
7.56
7.55
7.54
7.38
7.37
7.36
7.35
7.20
7.20
7.19
7.19
7.18
7.18
7.17
7.17
7.16
7.15
7.15
6.99
6.99
6.98
6.97
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6.96
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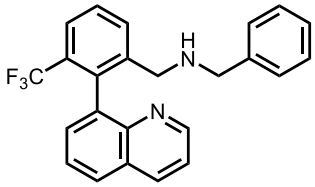
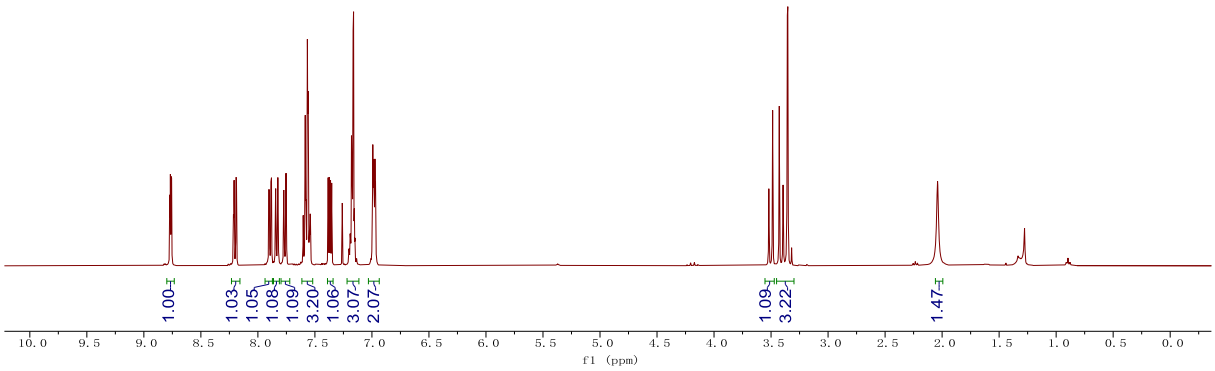
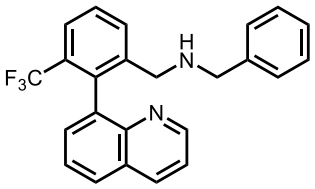
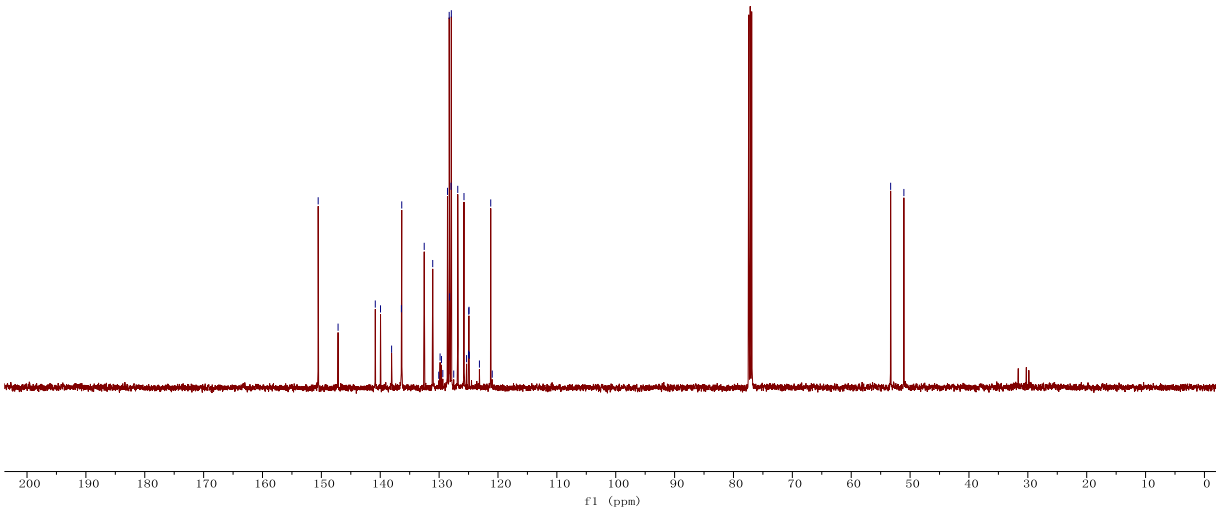
3.43
3.39
3.36
3.35
3.32
2.04

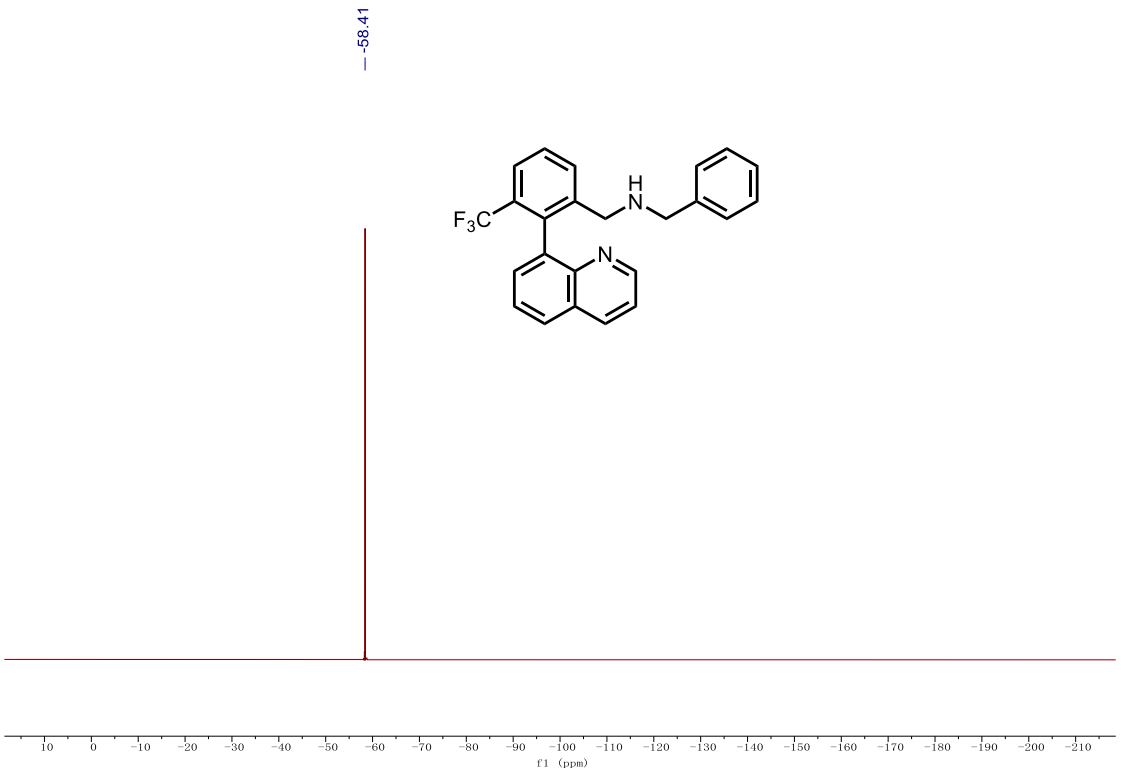

F3C
H
N
N

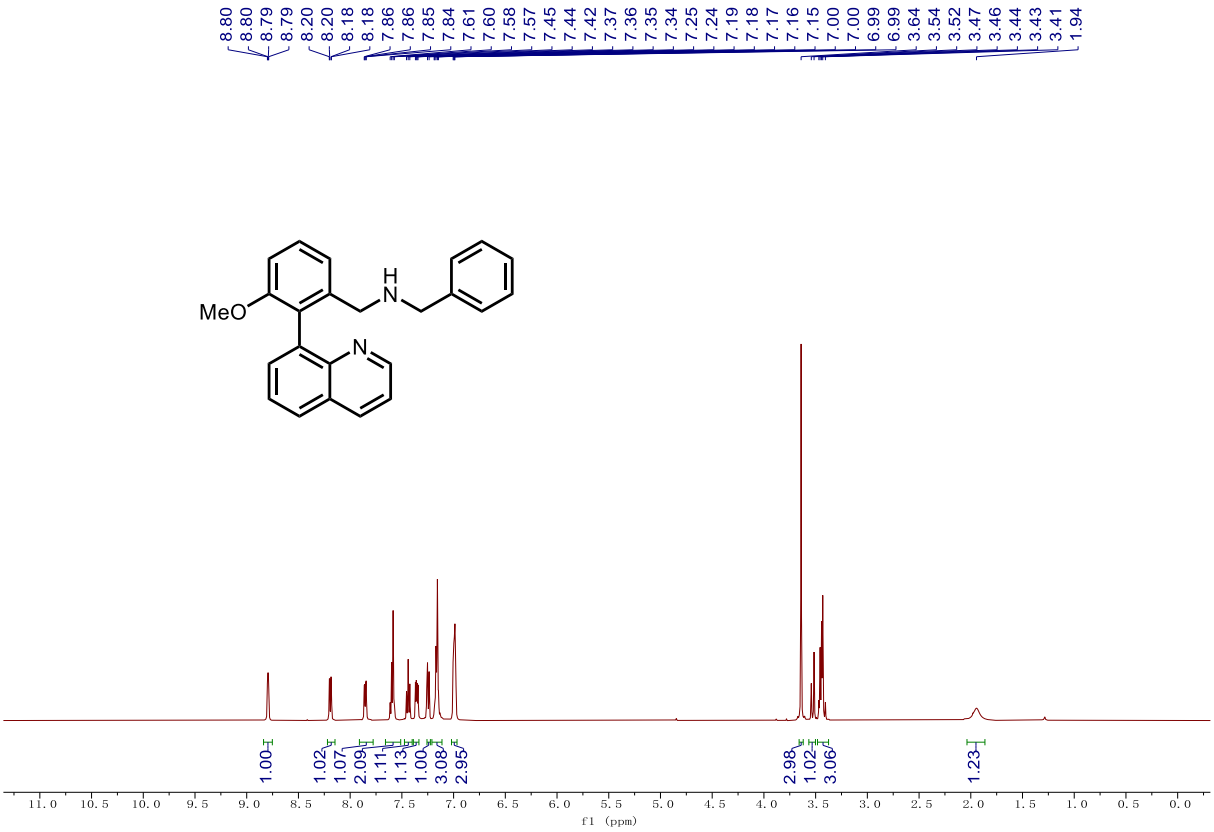

1.00
1.03
1.05
1.08
1.09
3.20
1.06
3.07
2.07
1.09
3.22
1.47
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

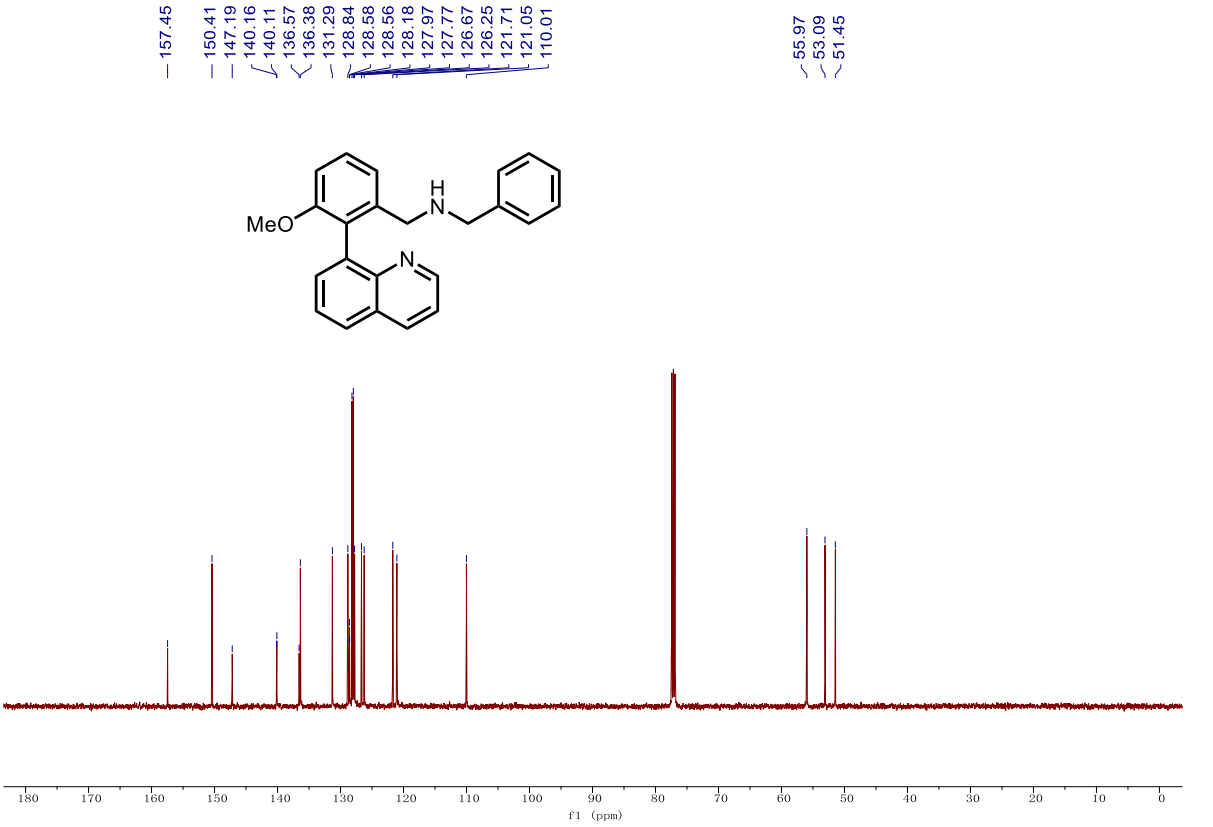

150.54
147.16
140.84
139.95
138.07
136.40
136.35
132.53
131.09
130.06
129.83
129.60
129.37
128.58
128.29
128.21
127.97
127.93
127.52
126.83
125.78
125.34
125.00
124.96
124.92
124.88
123.15
121.23
120.97
53.30
51.05


F3C
H
N
N

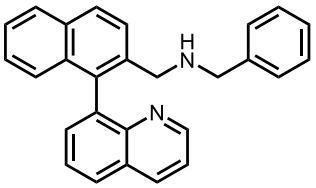

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

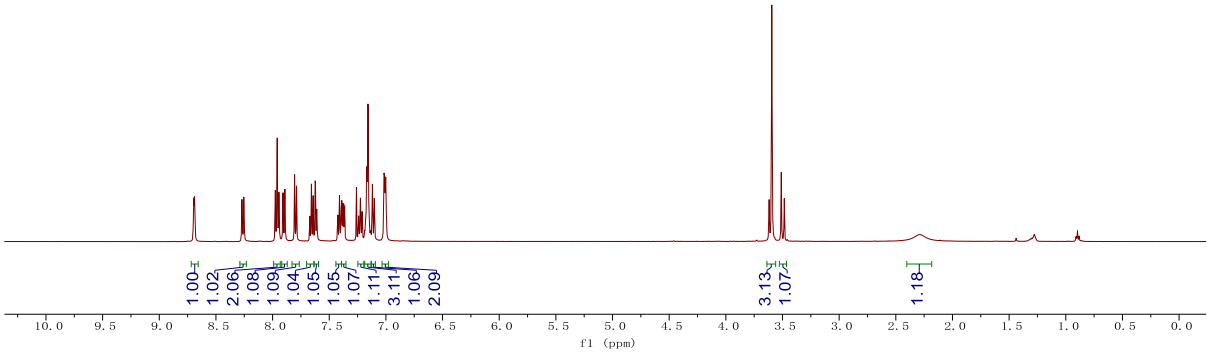

-58.41
F3C
H
N
N
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


8.80
8.80
8.79
8.79
8.20
8.20
8.18
8.18
7.86
7.86
7.85
7.84
7.61
7.60
7.58
7.57
7.45
7.44
7.42
7.37
7.36
7.35
7.34
7.25
7.24
7.19
7.18
7.17
7.16
7.15
7.00
7.00
6.99
6.99
3.64
3.54
3.52
3.47
3.46
3.44
3.43
3.41
1.94
MeO
H
N
N
1.00
1.02
1.07
2.09
1.11
1.13
1.00
3.08
2.95
2.98
1.02
3.06
1.23
f1 (ppm)

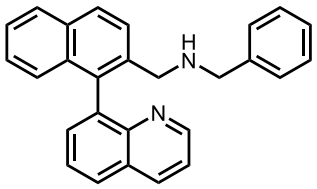

157.45
150.41
147.19
140.16
140.11
136.57
136.38
131.29
128.84
128.58
128.56
128.18
127.97
127.77
126.67
126.25
121.71
121.05
110.01
55.97
53.09
51.45
MeO
H
N
N
f1 (ppm)

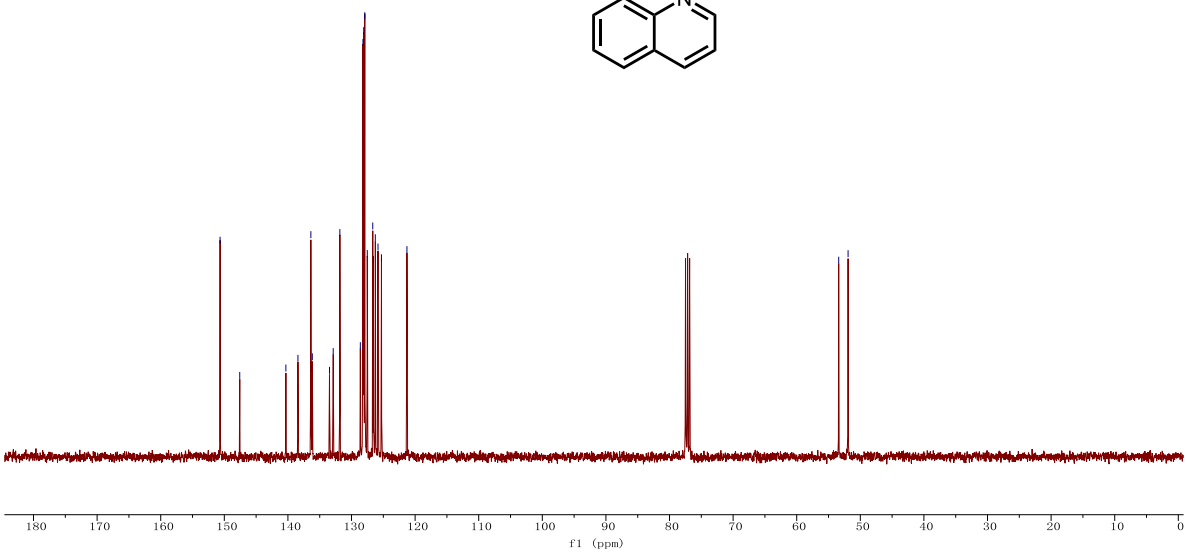

8.70
8.69
8.69
8.69
8.27
8.27
8.25
8.25
7.98
7.96
7.95
7.91
7.89
7.81
7.79
7.67
7.66
7.64
7.62
7.62
7.61
7.61
7.42
7.41
7.39
7.39
7.38
7.37
7.36
7.24
7.23
7.22
7.22
7.21
7.19
7.18
7.17
7.16
7.16
7.15
7.15
7.14
7.12
7.10
7.02
7.01
7.00
3.62
3.59
3.51
3.48
2.29

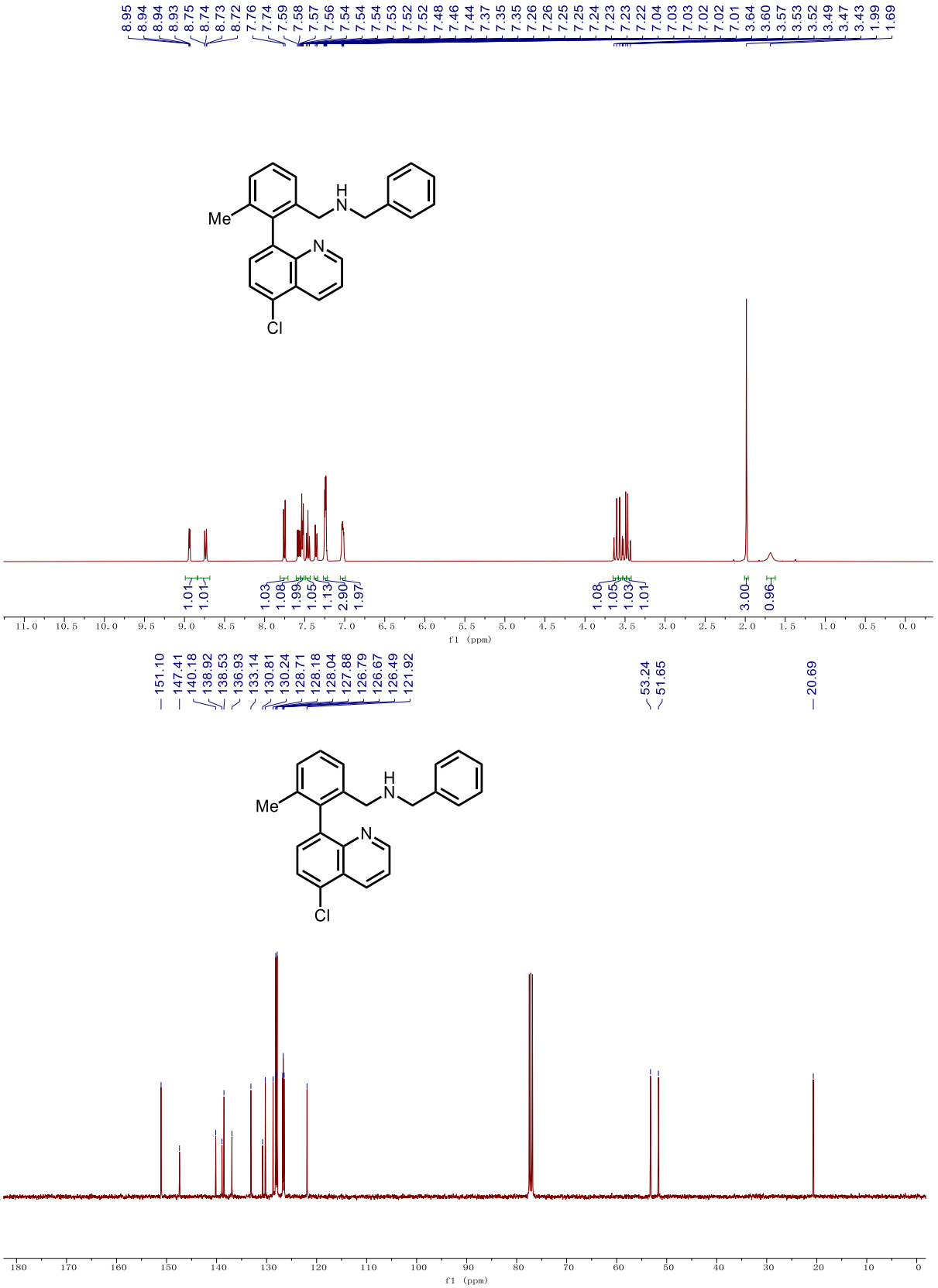

H
N
N

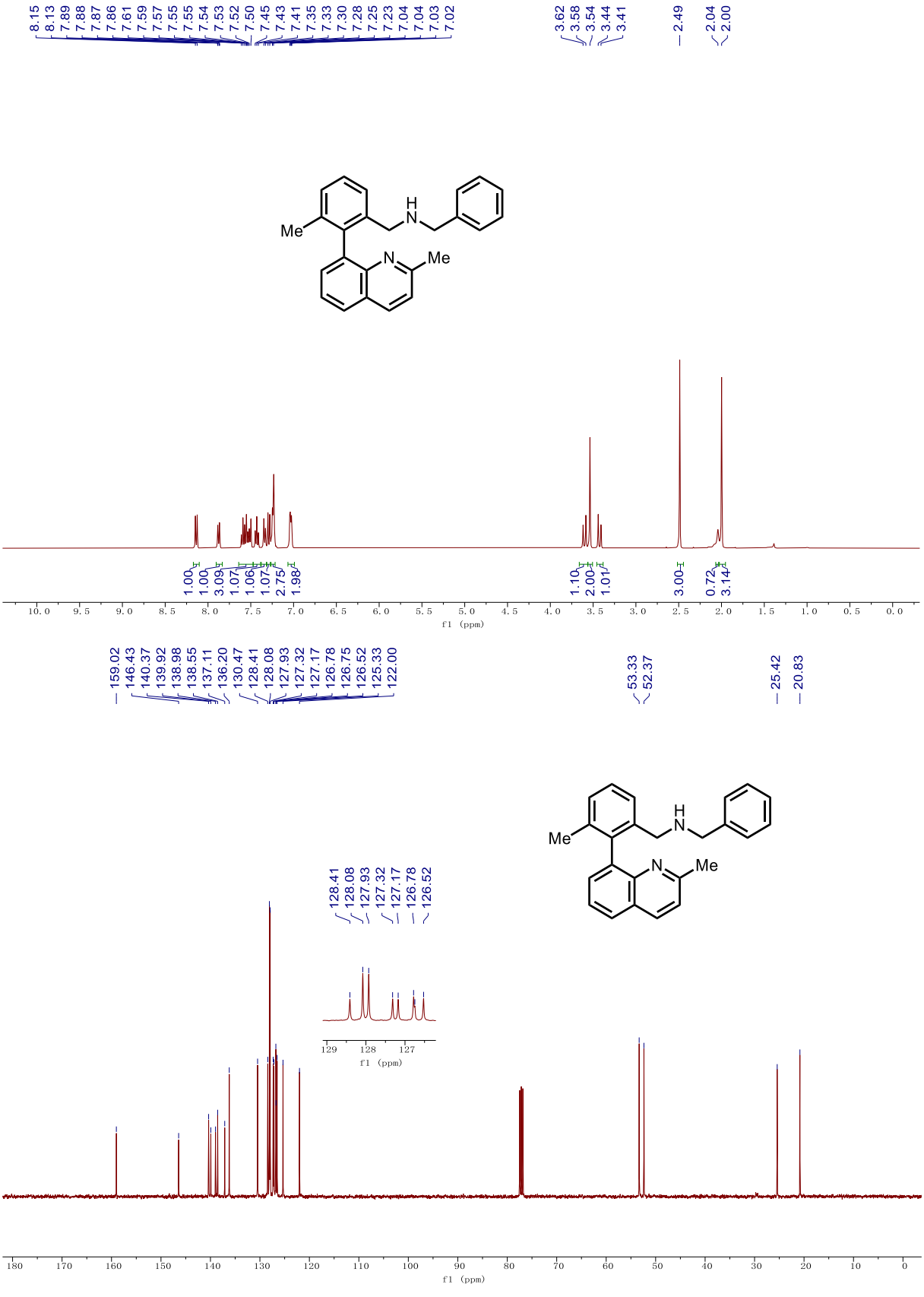

1.00
1.02
2.06
1.08
1.09
1.04
1.05
1.05
1.07
1.11
3.11
1.06
2.09
3.13
1.07
1.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


150.67
147.57
140.32
138.42
136.39
136.30
136.16
133.46
132.88
131.83
128.61
128.20
128.08
127.91
127.52
126.66
126.55
126.26
125.84
125.29
121.29
53.39
51.92


H
N
N


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.95 8.94 8.94 8.93 8.75 8.74 8.73 8.72 7.76 7.74 7.59 7.58 7.57 7.56 7.54 7.54 7.54 7.53 7.52 7.52 7.48 7.46 7.44 7.37 7.35 7.35 7.26 7.25 7.25 7.24 7.23 7.23 7.22 7.04 7.03 7.03 7.02 7.02 7.01 3.64 3.60 3.57 3.53 3.52 3.49 3.47 3.43 1.99 1.69
Me
H
N
N
Cl
1.01 1.01 1.03 1.08 1.99 1.05 1.13 2.90 1.97 1.08 1.05 1.03 1.01 3.00 0.96
f1 (ppm)
151.10 147.41 140.18 138.92 138.53 136.93 133.14 130.81 130.24 128.71 128.18 128.04 127.88 126.79 126.67 126.49 121.92 53.24 51.65 20.69
Me
H
N
N
Cl
f1 (ppm)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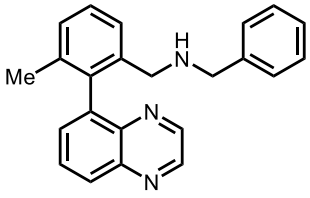
8.13
7.89
7.88
7.87
7.86
7.61
7.59
7.57
7.55
7.55
7.54
7.53
7.52
7.50
7.45
7.43
7.41
7.35
7.33
7.30
7.28
7.25
7.23
7.04
7.04
7.03
7.02
3.62
3.58
3.54
3.44
3.41
2.49
2.04
2.00
Me
H
N
N
Me
1.00
1.00
3.09
1.07
1.06
1.07
2.75
1.98
1.10
2.00
1.01
3.00
0.72
3.14
f1 (ppm)
159.02
146.43
140.37
139.92
138.98
138.55
137.11
136.20
130.47
128.41
128.08
127.93
127.32
127.17
126.78
126.75
126.52
125.33
122.00
53.33
52.37
25.42
20.83
128.41
128.08
127.93
127.32
127.17
126.78
126.52
129
128
127
f1 (ppm)
Me
H
N
N
Me
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.82
8.81
8.68
8.67
8.15
8.14
7.83
7.82
7.80
7.61
7.60
7.54
7.53
7.39
7.38
7.36
7.28
7.27
7.15
7.15
7.14
7.14
7.13
7.13
7.12
7.11
6.97
6.97
6.96
6.96
3.60
3.57
3.54
3.50
3.48
3.43
3.40
1.85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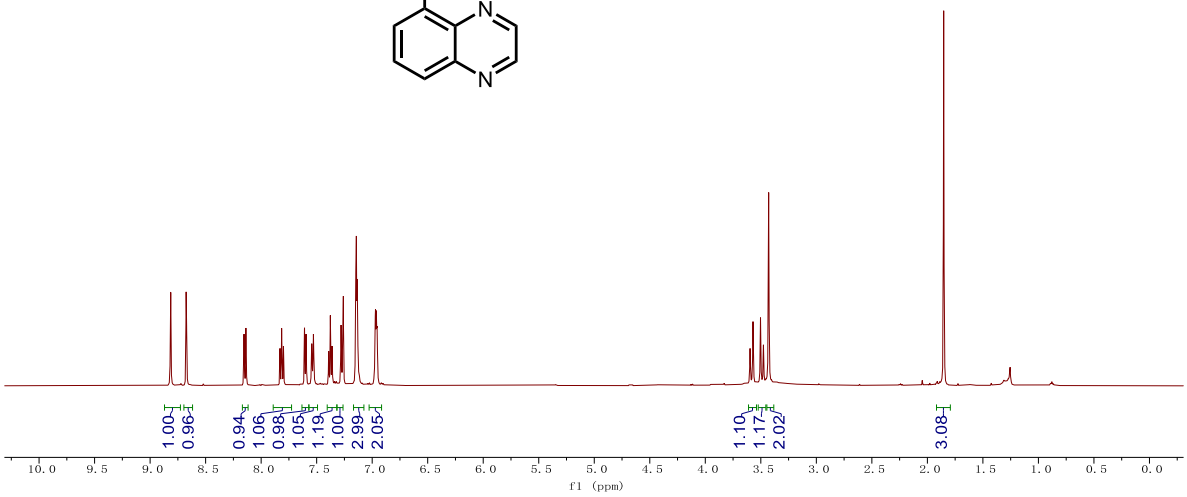
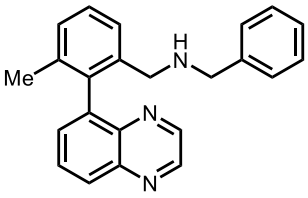
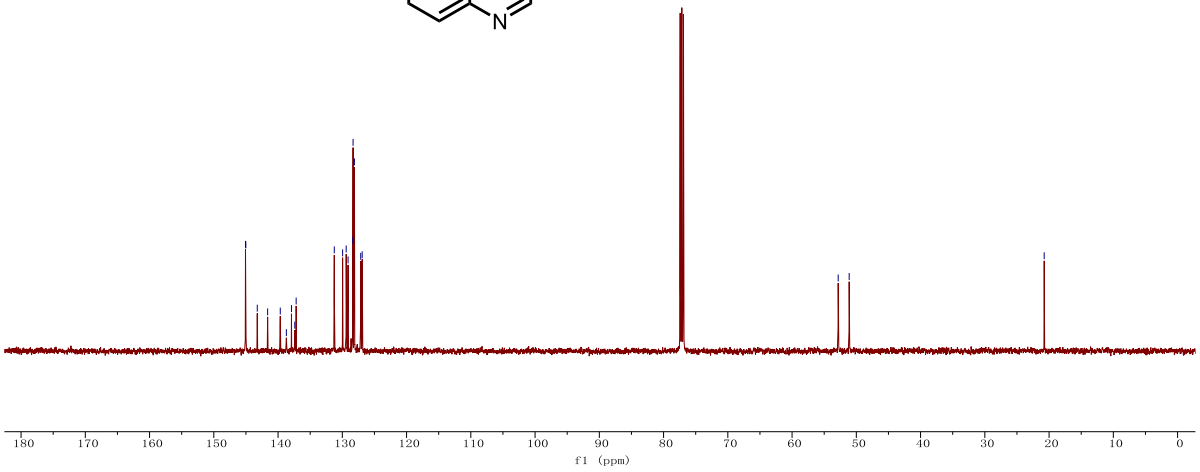
H
N
N
N

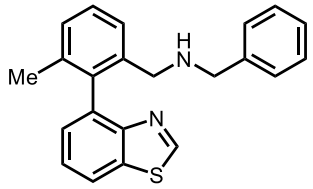

1.00
0.96
0.94
1.06
0.98
1.05
1.19
1.00
2.99
2.05
1.10
1.17
2.02
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

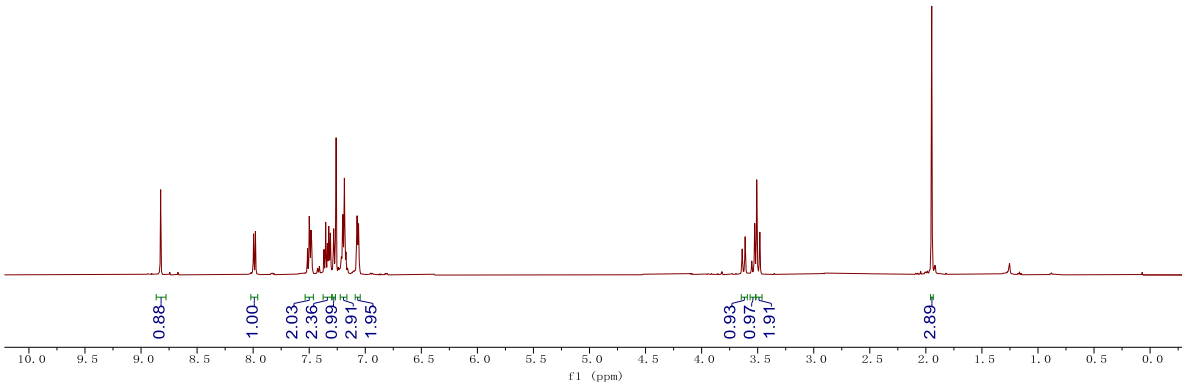

145.07
145.02
143.23
141.62
139.66
138.71
137.91
137.40
137.18
131.25
129.95
129.40
129.10
128.36
128.33
128.11
127.13
126.90
52.82
51.11
20.76


Me
H
N
N
N


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.83
8.00
7.98
7.52
7.50
7.49
7.48
7.48
7.37
7.35
7.34
7.33
7.33
7.31
7.28
7.27
7.26
7.21
7.20
7.19
7.17
7.08
7.06
3.64
3.61
3.55
3.53
3.51
3.48
1.95


Me
H
N
N
S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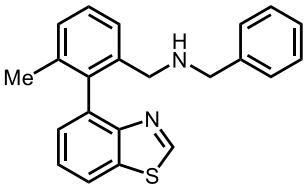
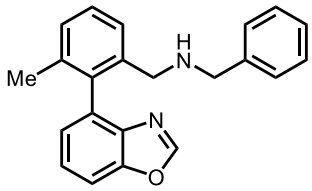
1.00
2.03
2.36
0.99
2.91
1.95
0.93
0.97
1.91
2.89
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

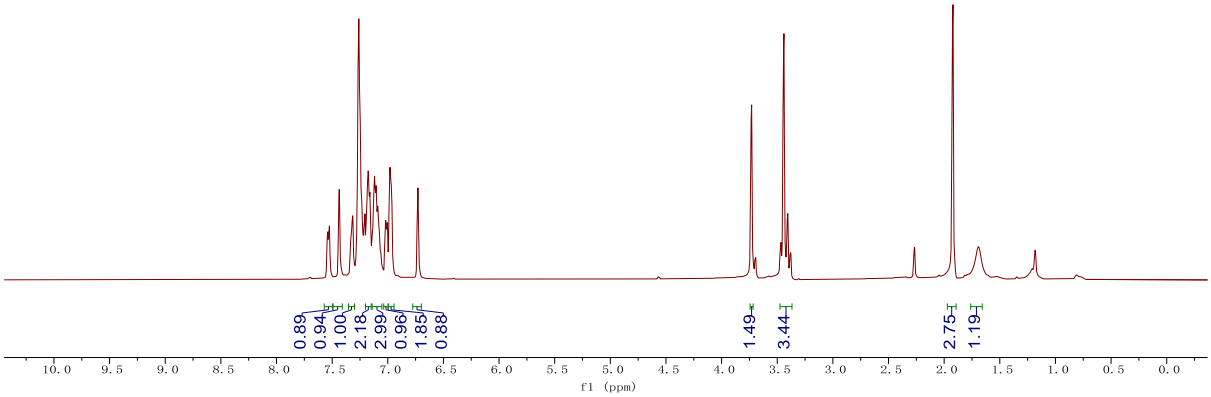

154.07
151.83
138.45
138.13
136.82
135.44
134.29
128.98
128.29
128.16
128.03
127.32
127.00
126.81
125.96
125.75
121.31
53.06
51.68
20.77


Me
H
N
N
S

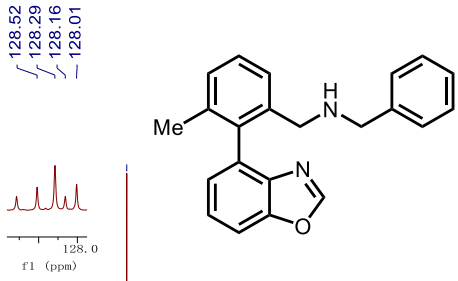
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

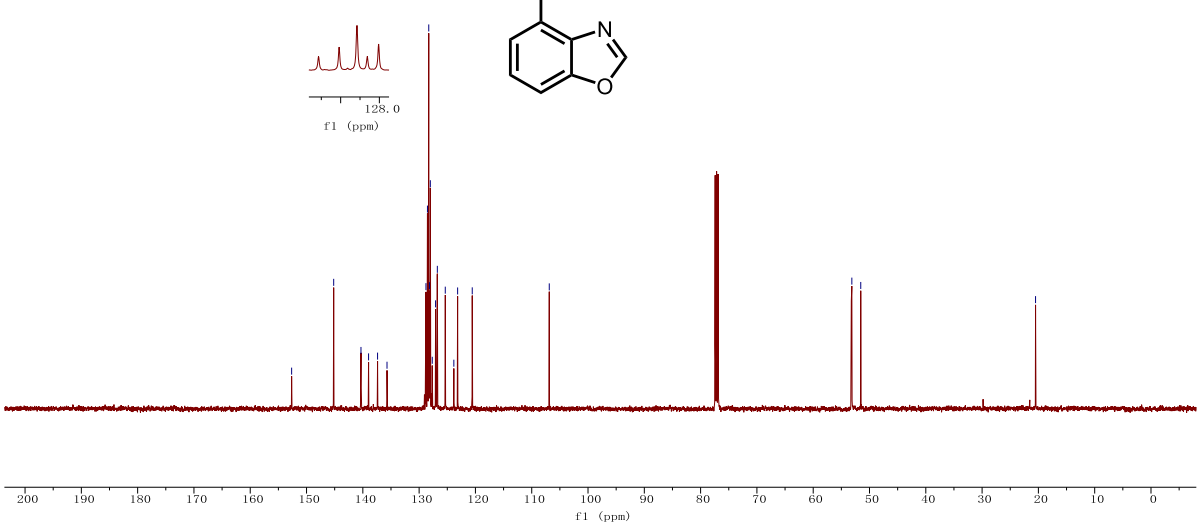

7.54
7.53
7.52
7.44
7.44
7.44
7.43
7.32
7.31
7.19
7.18
7.18
7.16
7.13
7.12
7.12
7.11
7.10
7.09
7.08
7.08
7.08
7.08
7.02
7.01
7.00
6.99
6.98
6.97
6.74
6.73
6.73
6.72
3.74
3.73
3.47
3.45
3.44
3.41
3.40
3.38
3.38
1.92
1.69


Me
H
N
N
O

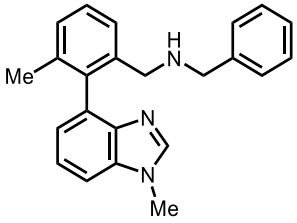

0.89
0.94
1.00
2.18
2.99
0.96
1.85
0.88
1.49
3.44
2.75
1.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

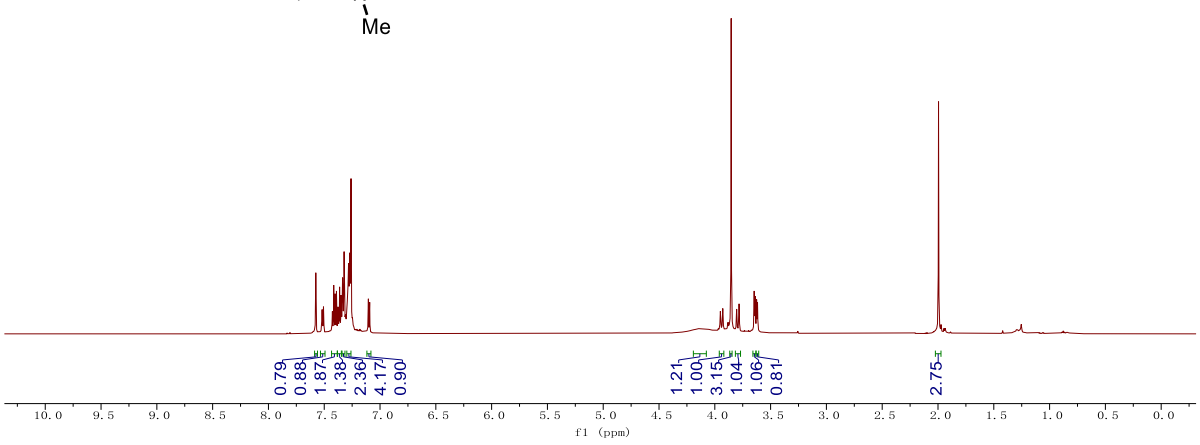

152.65
145.18
140.33
138.98
137.38
135.71
128.79
128.52
128.29
128.16
128.01
127.67
127.08
126.77
125.36
123.83
123.16
120.57
106.88
53.14
51.56
20.51

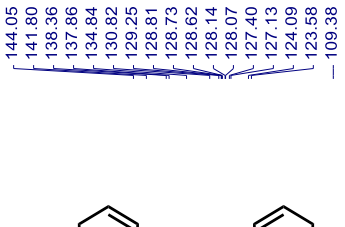

128.52
128.29
128.16
128.01
128.0
f1 (ppm)
Me
H
N
N
O

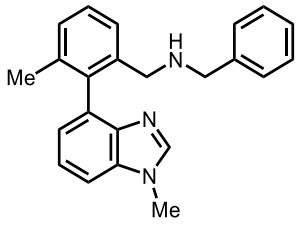

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.58
7.52
7.51
7.43
7.43
7.42
7.41
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.34
7.32
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.11
7.10
7.09
7.09
7.08
4.13
3.95
3.93
3.85
3.80
3.78
3.65
3.64
3.63
3.62
2.00


H
N
Me
N
N
Me

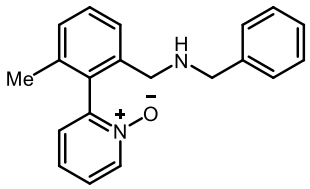

0.79
0.88
1.87
1.38
2.36
4.17
0.90
1.21
1.00
3.15
1.04
1.06
0.81
2.75
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

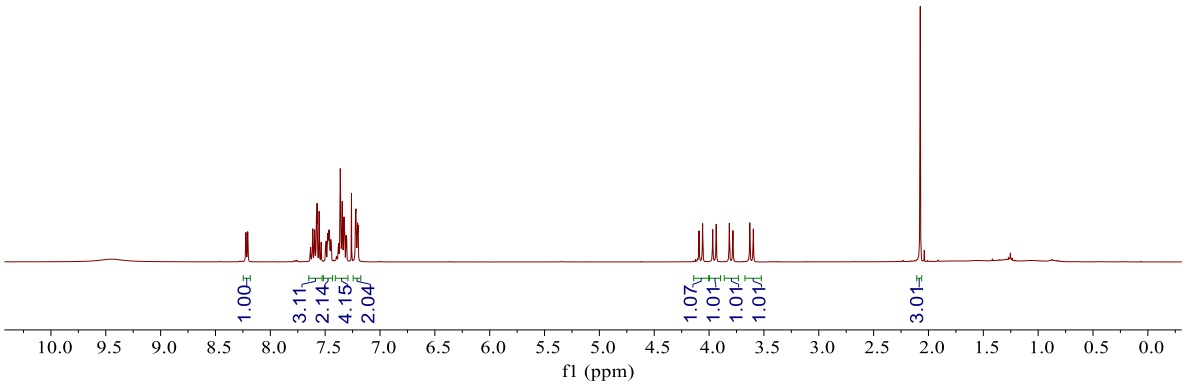

144.05
141.80
138.36
137.86
134.84
130.82
129.25
128.81
128.73
128.62
128.14
128.07
127.40
127.13
124.09
123.58
109.38
51.25
51.02
31.51
21.04


H
N
Me
N
N
Me

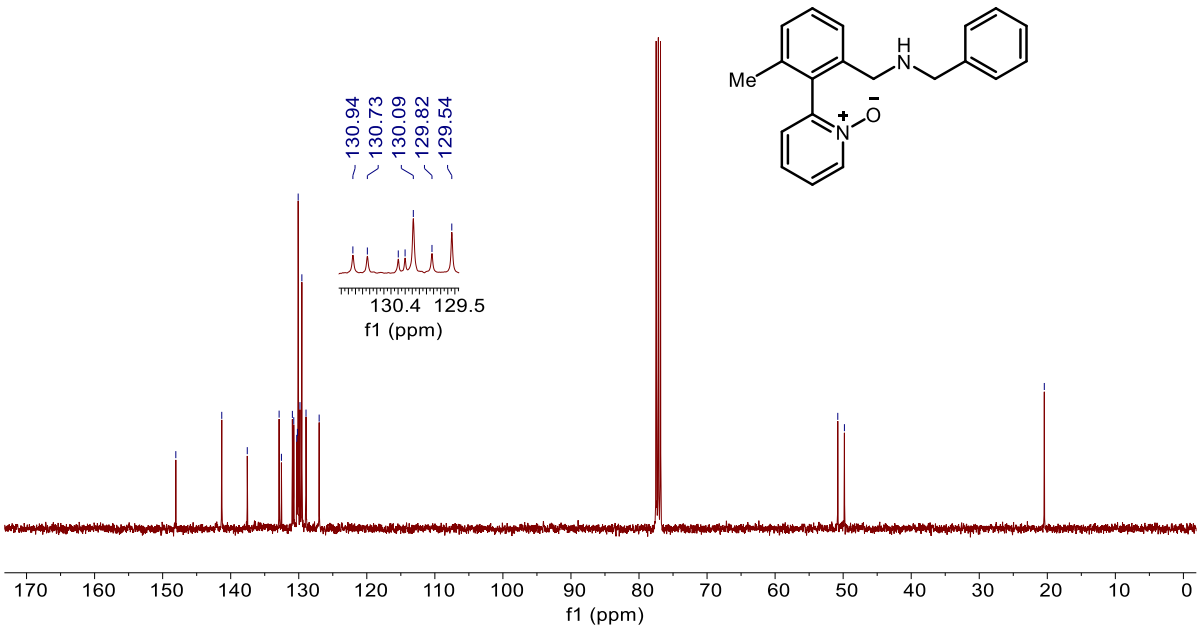
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.22
8.21
7.62
7.61
7.60
7.59
7.58
7.57
7.55
7.54
7.50
7.49
7.48
7.48
7.47
7.47
7.47
7.47
7.46
7.46
7.46
7.45
7.44
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.32
7.32
7.31
7.30
7.22
7.22
7.22
7.21
7.20
7.20
4.09
4.06
3.97
3.93
3.82
3.78
3.63
3.60
2.07


Me
H
N
O
N


1.00
3.11
2.14
4.15
2.04
1.07
1.01
1.01
1.01
3.01
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)


148.07
141.31
137.57
132.89
132.55
130.94
130.73
130.30
130.20
130.09
129.82
129.54
128.93
127.00
50.79
49.82
20.44


Me
H
N
O
N
130.94
130.73
130.09
129.82
129.54
130.4 129.5
f1 (ppm)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.29
8.28
8.28
8.27
8.05
7.64
7.63
7.57
7.55
7.54
7.48
7.46
7.45
7.43
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.27
7.27
7.15
7.14
7.13
7.03
7.01
6.99
4.14
4.14
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4.12
4.11
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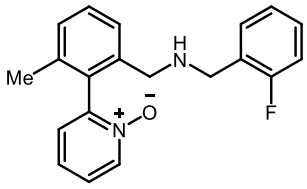
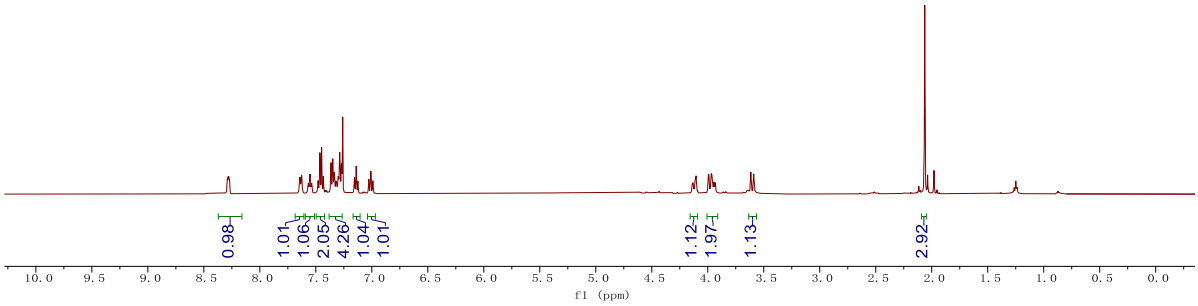
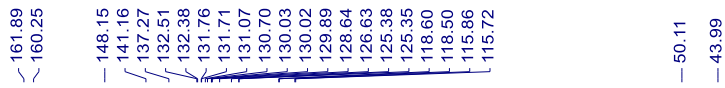
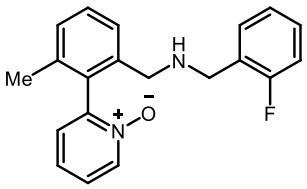
3.99
3.97
3.95
3.93
3.62
3.59
2.06

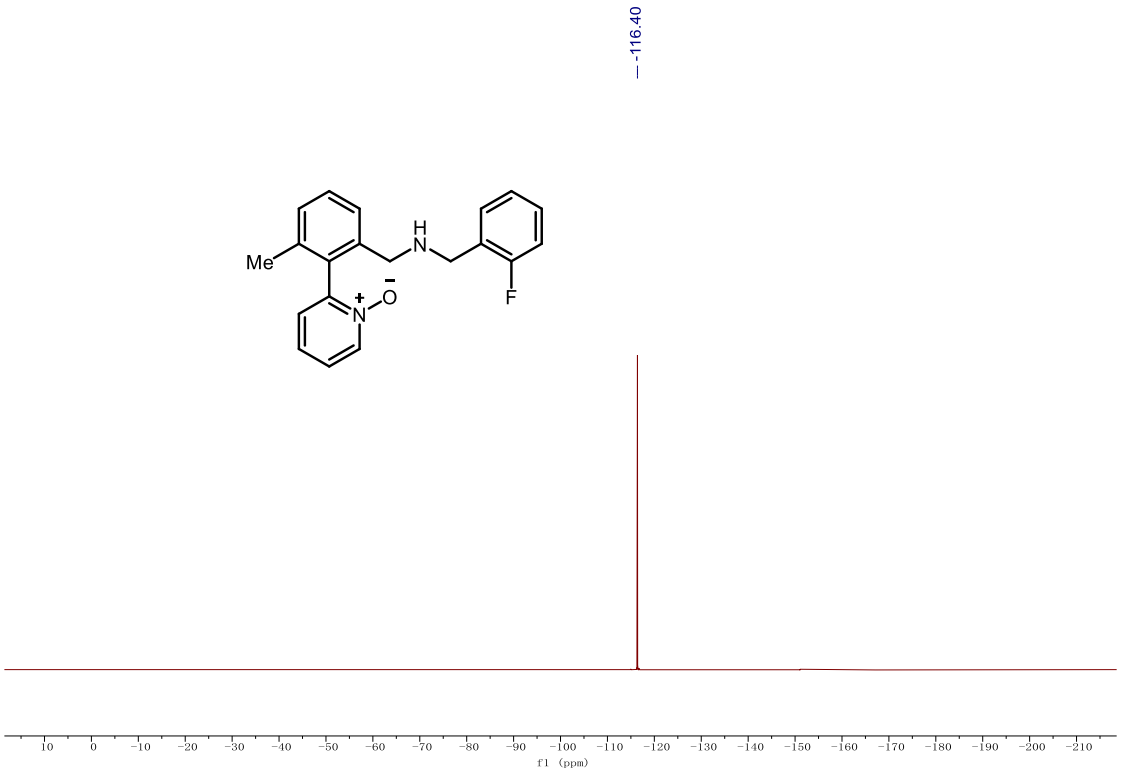

Me
H
N
O
N
F

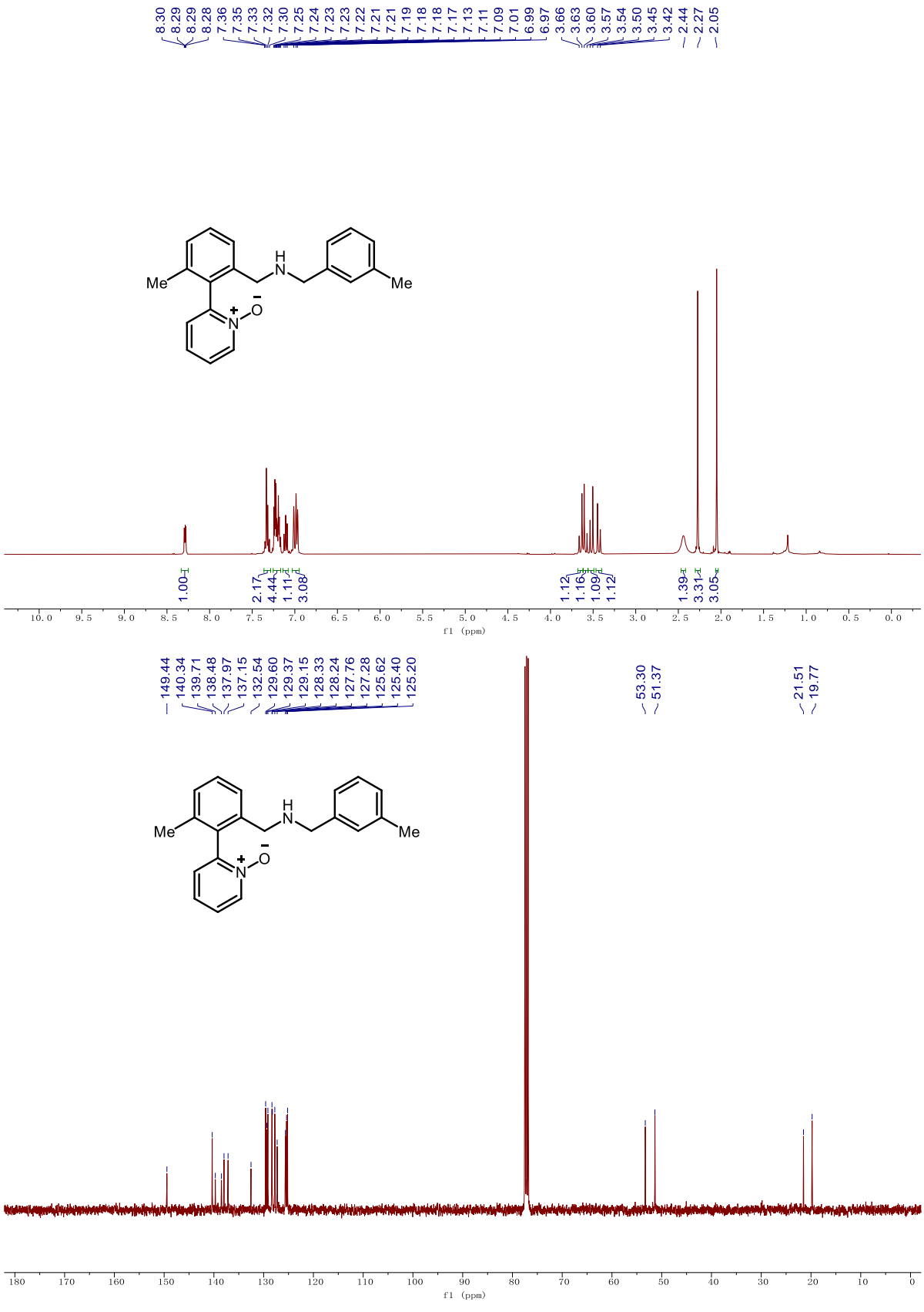

0.98
1.01
1.06
2.05
4.26
1.04
1.01
1.12
1.97
1.13
2.92
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


161.89
160.25
148.15
141.16
137.27
132.51
132.38
131.76
131.71
131.07
130.70
130.03
130.02
129.89
128.64
126.63
125.38
125.35
118.60
118.50
115.86
115.72
50.11
43.99
20.29


Me
H
N
O
N
F

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-116.40
Me
H
N
F
O
10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210
f1 (ppm)


8.30
8.29
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8.28
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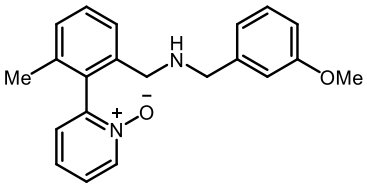
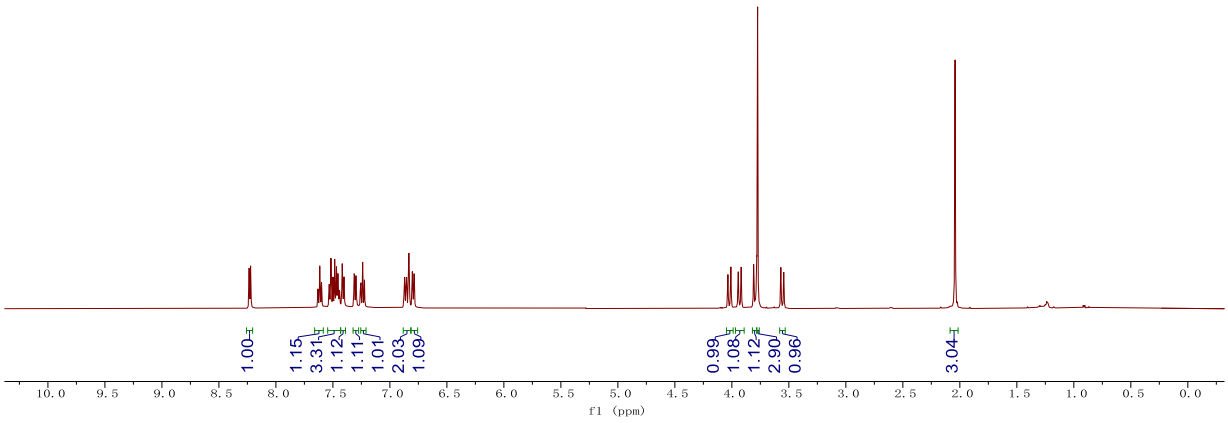
7.35
7.33
7.32
7.30
7.25
7.24
7.23
7.23
7.22
7.21
7.21
7.19
7.18
7.18
7.17
7.13
7.11
7.09
7.01
6.99
6.97
3.66
3.63
3.60
3.57
3.54
3.50
3.45
3.42
2.44
2.27
2.05
Me
H
N
Me
O
1.00
2.17
4.44
1.11
3.08
1.12
1.16
1.09
1.12
1.39
3.31
3.05
f1 (ppm)
149.44
140.34
139.71
138.48
137.97
137.15
132.54
129.60
129.37
129.15
128.33
128.24
127.76
127.28
125.62
125.40
125.20
53.30
51.37
21.51
19.77
Me
H
N
Me
O
f1 (ppm)


8.23
8.22
7.63
7.62
7.60
7.53
7.52
7.50
7.48
7.47
7.46
7.44
7.44
7.42
7.40
7.31
7.31
7.30
7.29
7.24
7.22
6.87
6.87
6.86
6.85
6.84
6.83
6.80
6.79
4.03
4.01
3.94
3.92
3.81
3.79
3.77
3.57
3.54
2.04


Me
H
N
OMe
N
O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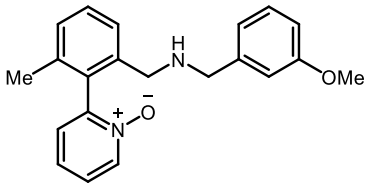
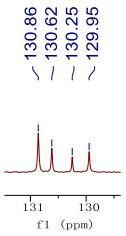
1.15
3.31
1.12
1.11
1.01
2.03
1.09
0.99
1.08
1.12
2.90
0.96
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

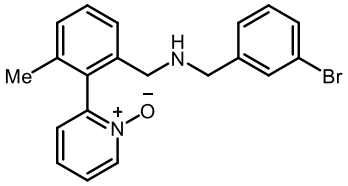

160.13
148.10
141.33
137.51
132.83
132.43
131.64
130.86
130.62
130.25
129.95
129.06
126.90
122.03
115.30
115.27
55.55
50.74
49.98
20.43

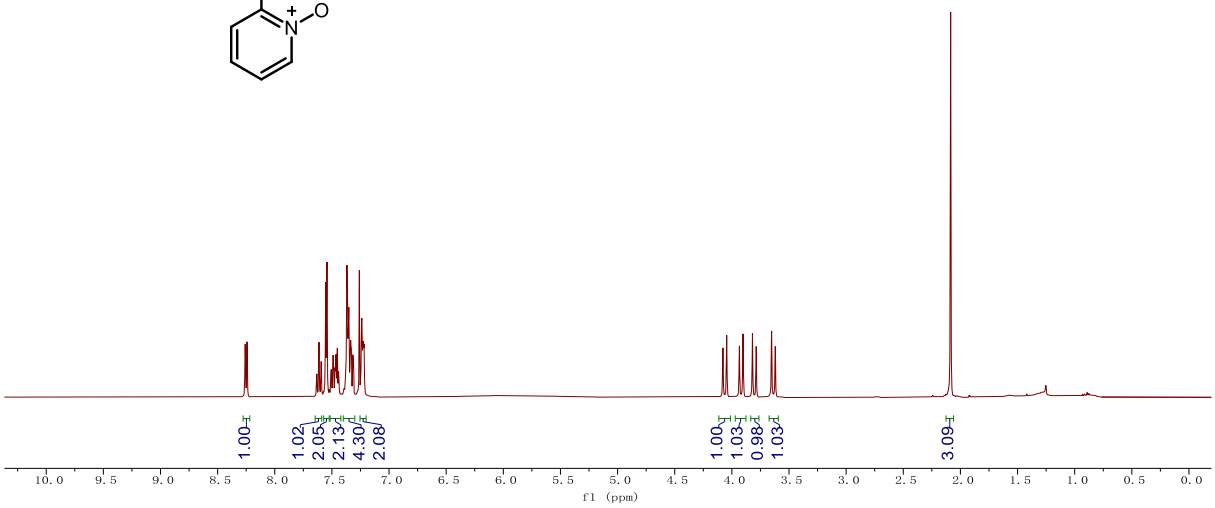

Me
H
N
OMe
N
O


130.86
130.62
130.25
129.95
131
130
f1 (ppm)

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−3
f1 (ppm)


8.26
8.24
7.63
7.61
7.59
7.55
7.54
7.51
7.50
7.49
7.47
7.46
7.45
7.44
7.40
7.38
7.37
7.36
7.36
7.35
7.34
7.33
7.32
7.31
7.24
7.24
7.23
7.22
4.08
4.05
3.93
3.90
3.82
3.79
3.65
3.62
2.09


Me
H
N
Br
O
N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2.08
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1.03
0.98
1.03
3.09
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)


148.04
141.22
137.49
132.87
132.78
132.76
132.65
132.34
131.11
130.94
130.91
130.38
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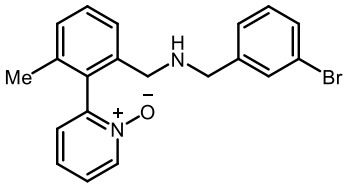
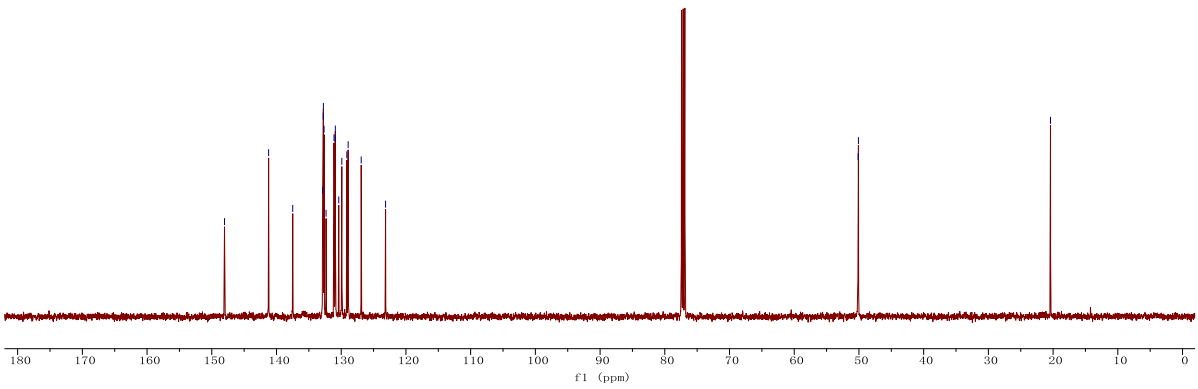
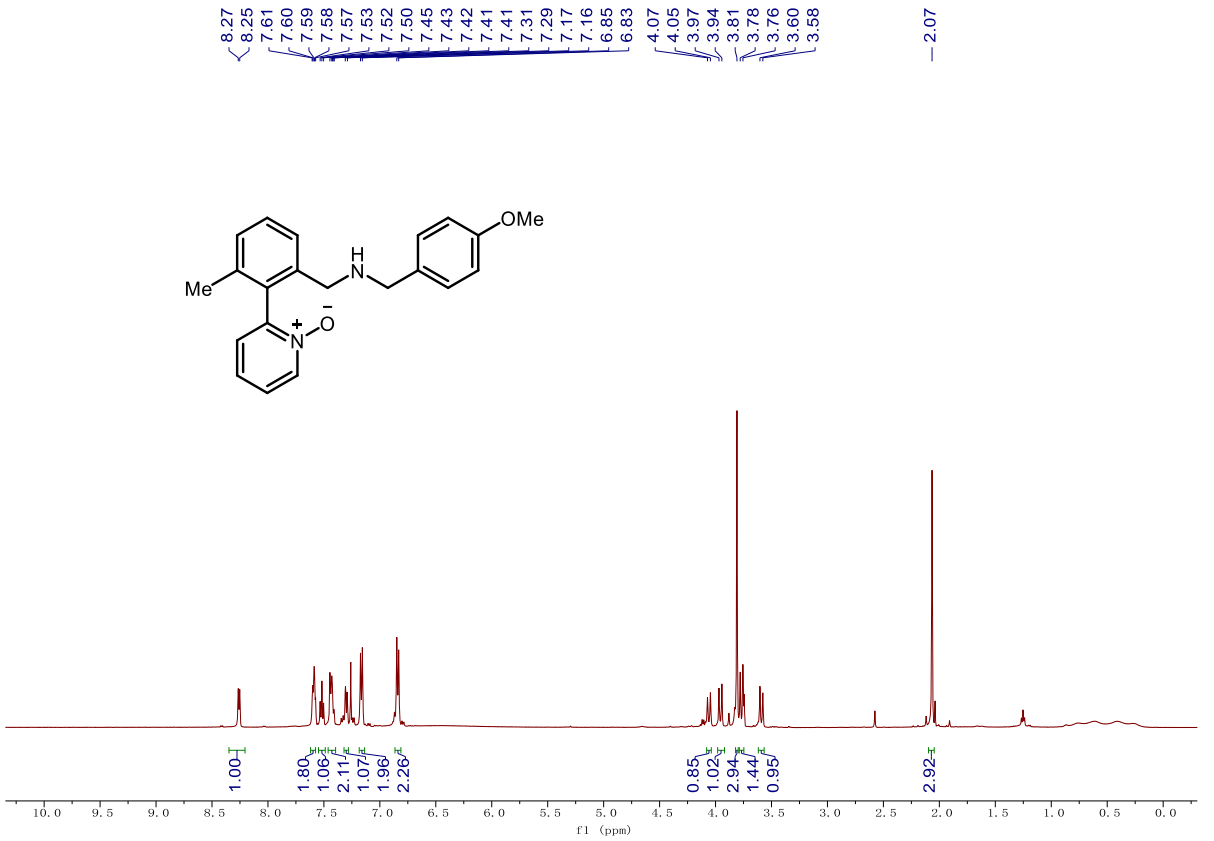
128.93
126.91
123.15
50.12
50.08
20.40


Me
H
N
Br
O
N


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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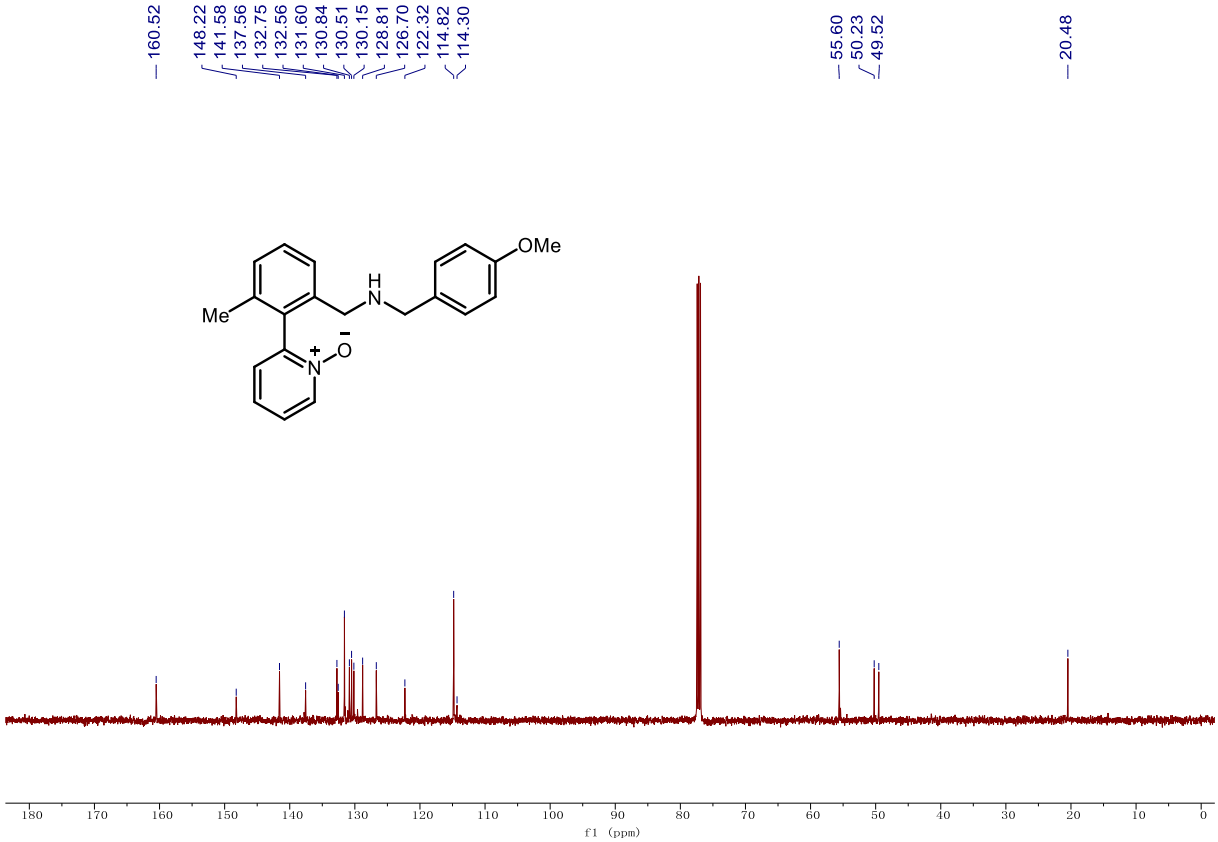
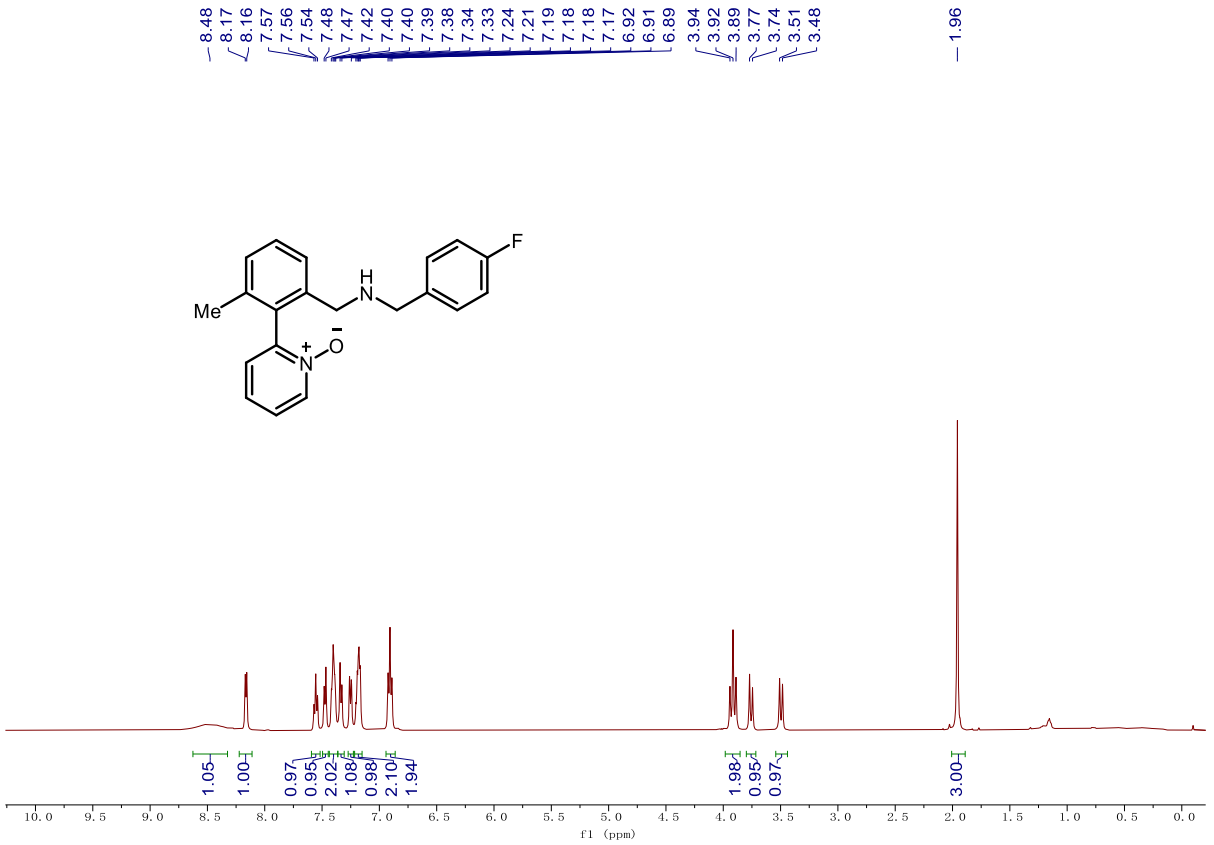
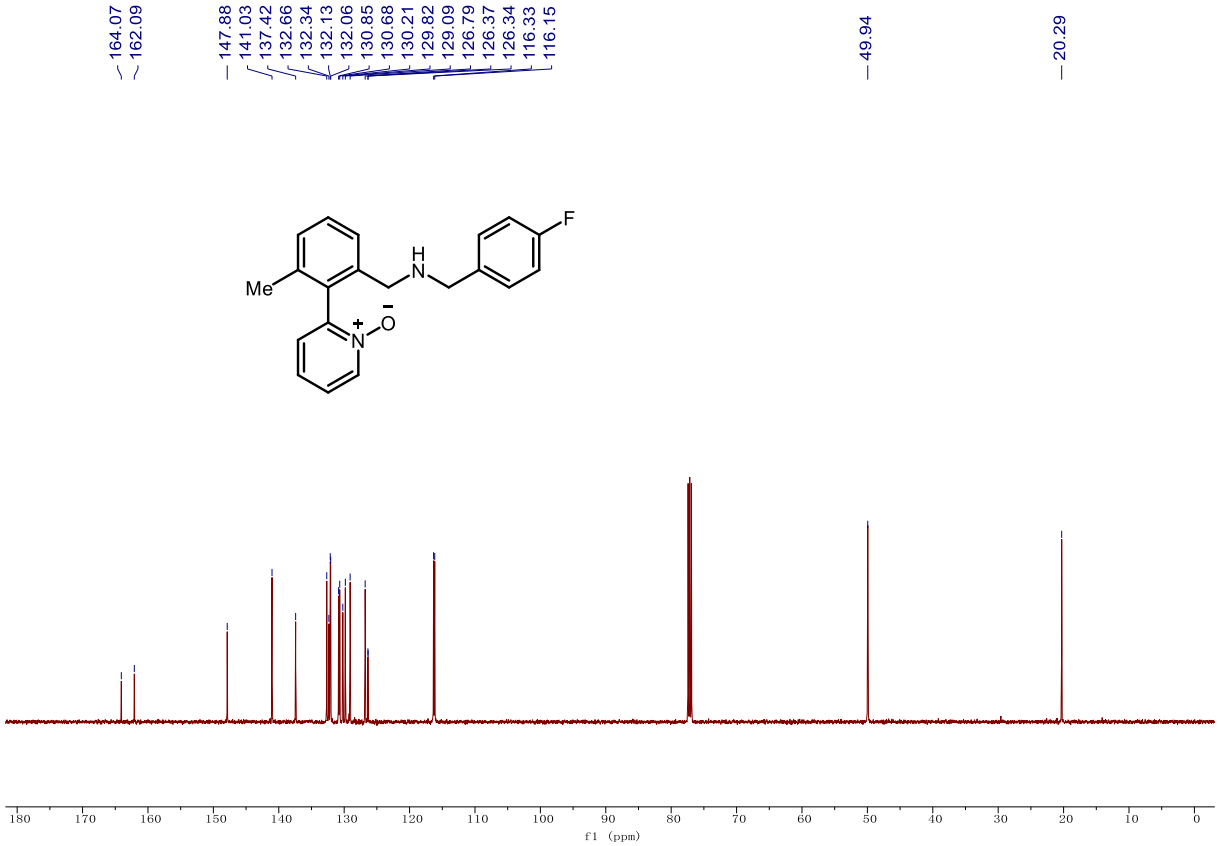
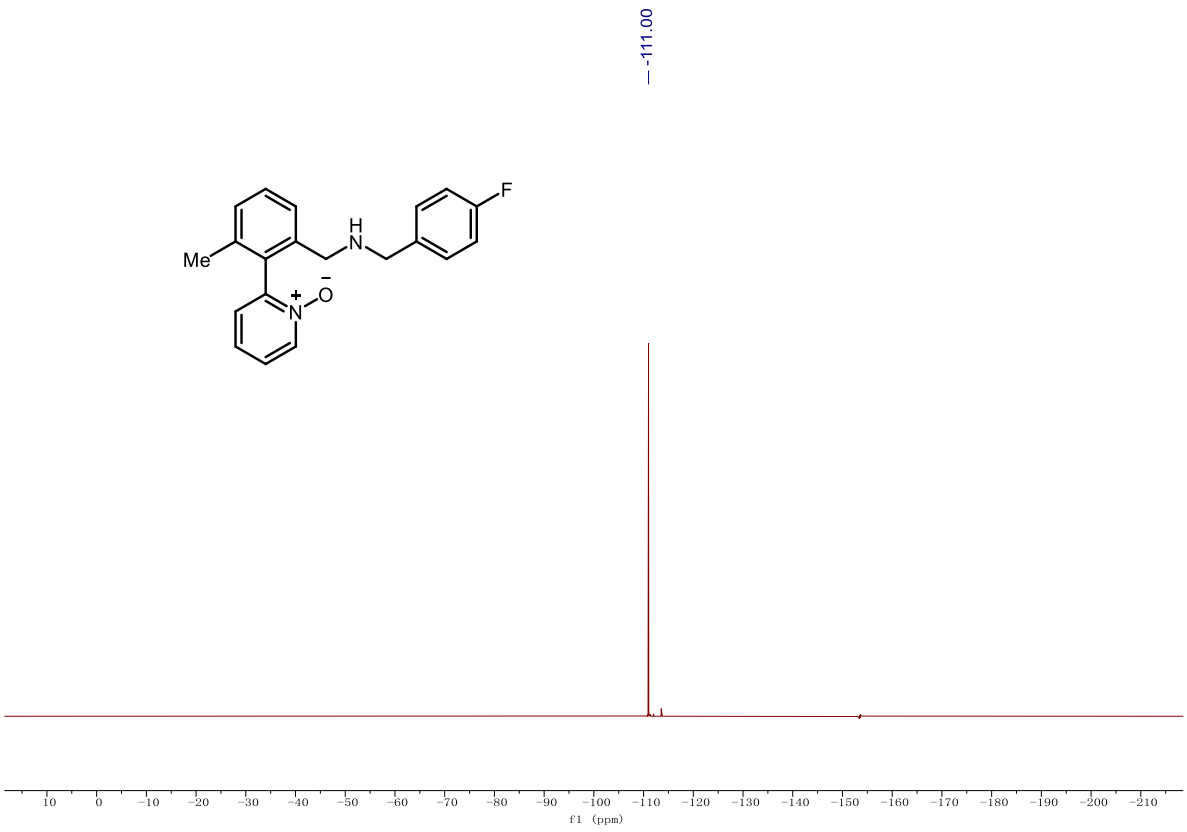
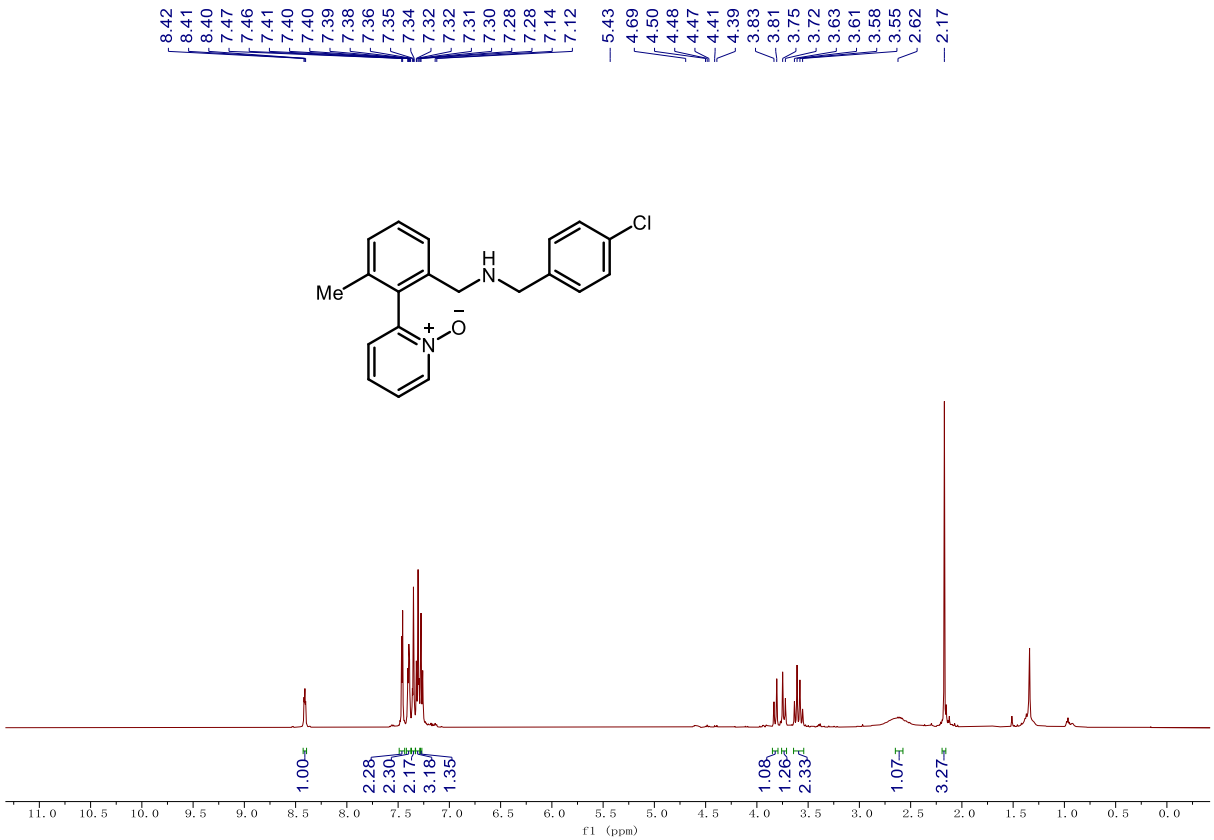
7.59
7.58
7.57
7.53
7.52
7.50
7.45
7.43
7.42
7.41
7.41
7.31
7.29
7.17
7.16
6.85
6.83
4.07
4.05
3.97
3.94
3.81
3.78
3.76
3.60
3.58
2.07
OMe
H
N
Me
O
1.00
1.80
1.06
2.11
1.07
1.96
2.26
0.85
1.02
2.94
1.44
0.95
2.92
f1 (ppm)


160.52
148.22
141.58
137.56
132.75
132.56
131.60
130.84
130.51
130.15
128.81
126.70
122.32
114.82
114.30
55.60
50.23
49.52
20.48
OMe
H
N
Me
O
f1 (ppm)


8.48
8.17
8.16
7.57
7.56
7.54
7.48
7.47
7.42
7.40
7.40
7.39
7.38
7.34
7.33
7.24
7.21
7.19
7.18
7.18
7.17
6.92
6.91
6.89
3.94
3.92
3.89
3.77
3.74
3.51
3.48
1.96
F
H
N
Me
O
1.05
1.00
0.97
0.95
2.02
1.08
0.98
2.10
1.94
1.98
0.95
0.97
3.00
f1 (ppm)


164.07
162.09
147.88
141.03
137.42
132.66
132.34
132.13
132.06
130.85
130.68
130.21
129.82
129.09
126.79
126.37
126.34
116.33
116.15
49.94
20.29
F
H
N
Me
O
f1 (ppm)


-111.00
F
H
N
Me
O
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
f1 (ppm)


8.42
8.41
8.40
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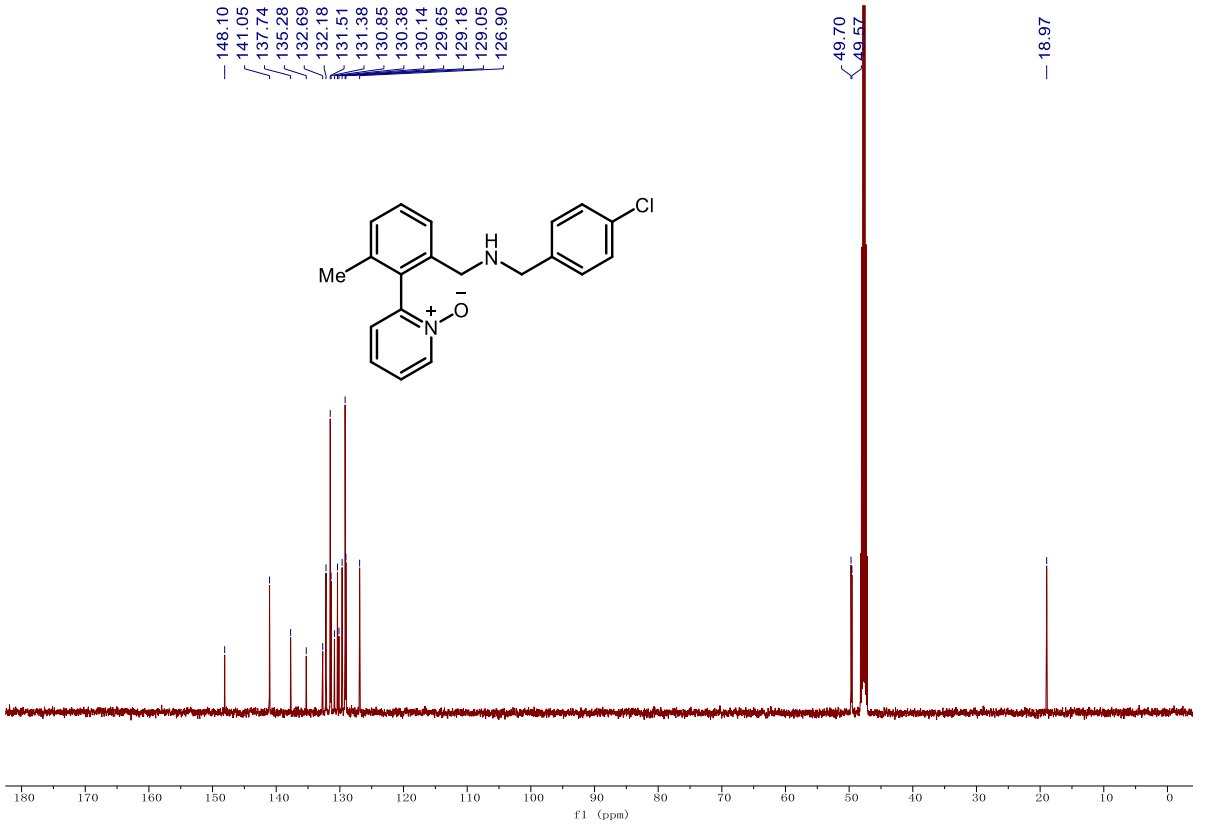
7.46
7.41
7.40
7.40
7.39
7.38
7.36
7.35
7.34
7.32
7.32
7.31
7.30
7.28
7.28
7.14
7.12
5.43
4.69
4.50
4.48
4.47
4.41
4.39
3.83
3.81
3.75
3.72
3.63
3.61
3.58
3.55
2.62
2.17
Cl
H
N
Me
O
1.00
2.28
2.30
2.17
3.18
1.35
1.08
1.26
2.33
1.07
3.27
f1 (ppm)


148.10
141.05
137.74
135.28
132.69
132.18
131.51
131.38
130.85
130.38
130.14
129.65
129.18
129.05
126.90
49.70
49.57
18.97
Cl
H
N
Me
O
f1 (ppm)


8.38
8.37
8.25
8.24
8.24
8.23
7.55
7.53
7.29
7.28
7.25
7.25
7.24
7.23
7.23
7.22
7.19
7.19
7.18
7.18
7.17
7.15
7.14
7.13
7.13
7.12
7.11
7.10
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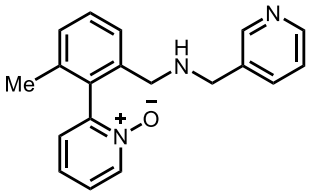
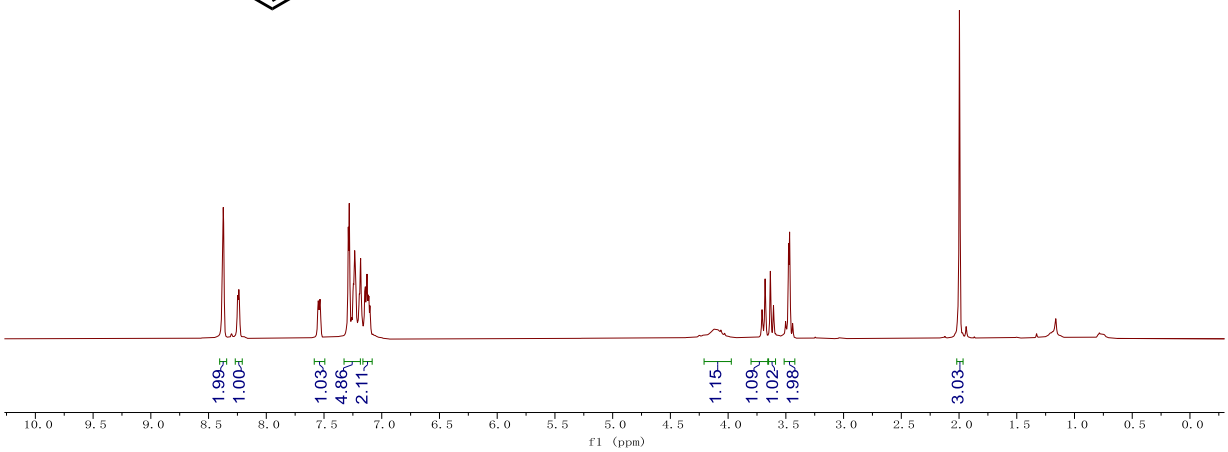
3.50
3.48
3.47
3.46
3.44
2.00


N
H
N
Me
N
O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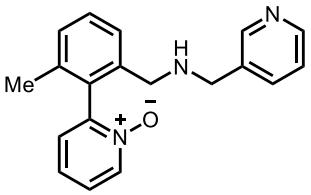
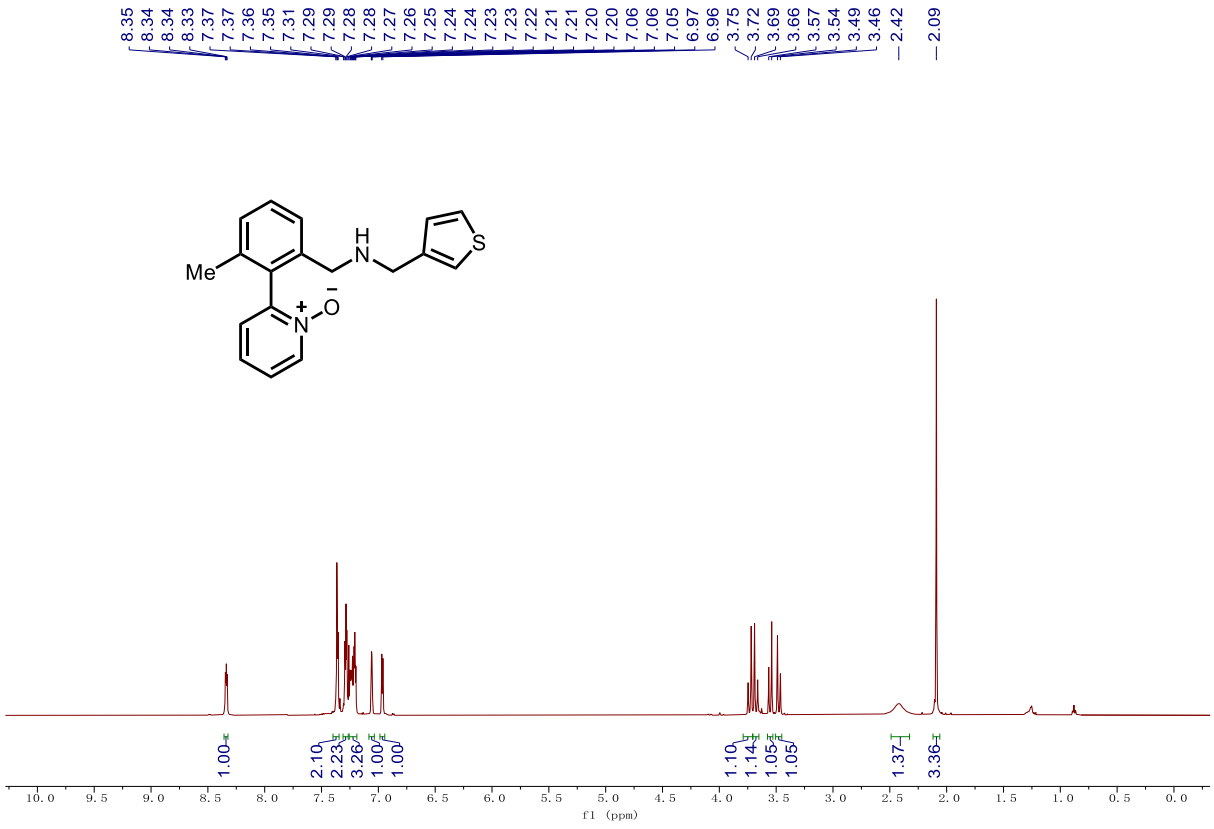
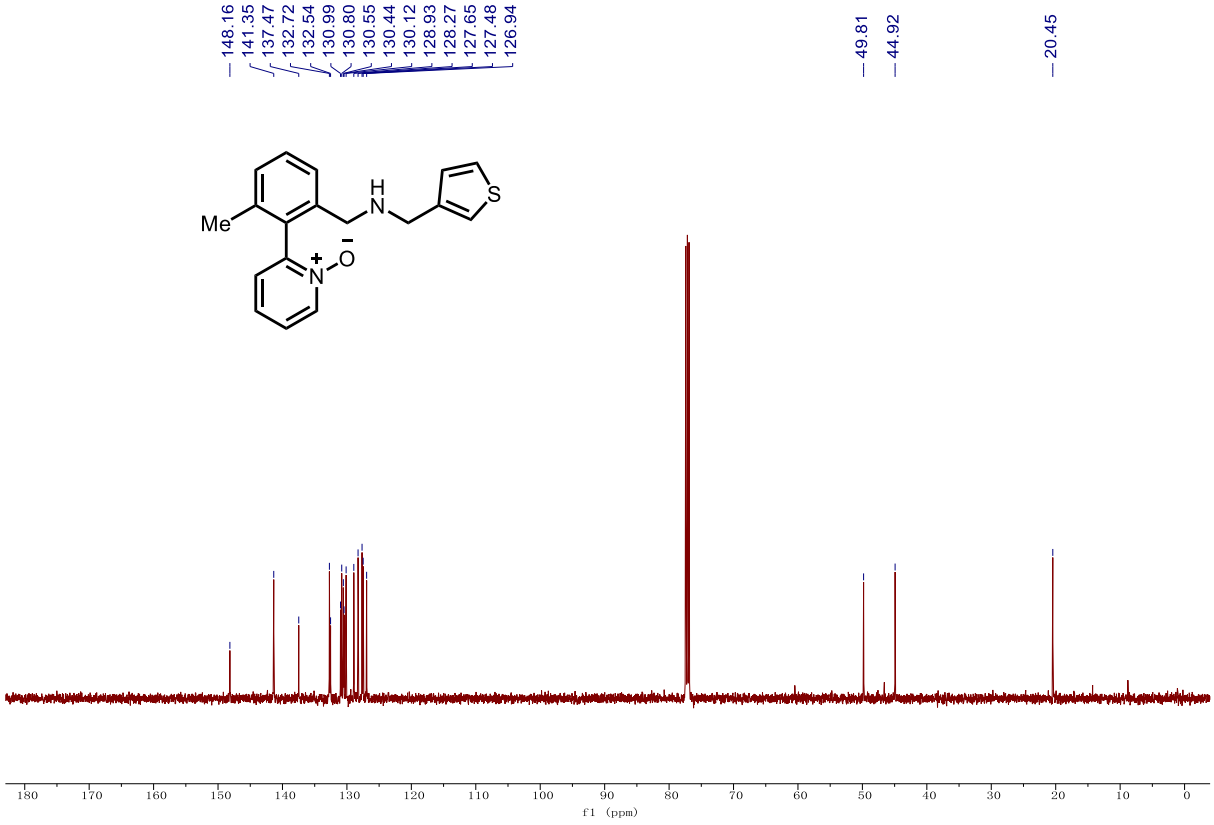
1.00
1.03
4.86
2.11
1.15
1.09
1.02
1.98
3.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


150.00
149.22
148.76
140.48
137.29
137.05
136.29
134.10
132.61
129.99
129.74
128.28
127.69
126.29
125.51
123.51
51.40
50.18
19.85


N
H
N
Me
N
O

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.35
8.34
8.34
8.33
7.37
7.37
7.36
7.35
7.31
7.29
7.29
7.28
7.28
7.27
7.26
7.25
7.24
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.20
7.06
7.06
7.05
6.97
6.96
3.75
3.72
3.69
3.66
3.57
3.54
3.49
3.46
2.42
2.09
Me
H
N
S
N
O
1.00
2.10
2.23
3.26
1.00
1.00
1.10
1.14
1.05
1.05
1.37
3.36
f1 (ppm)


148.16
141.35
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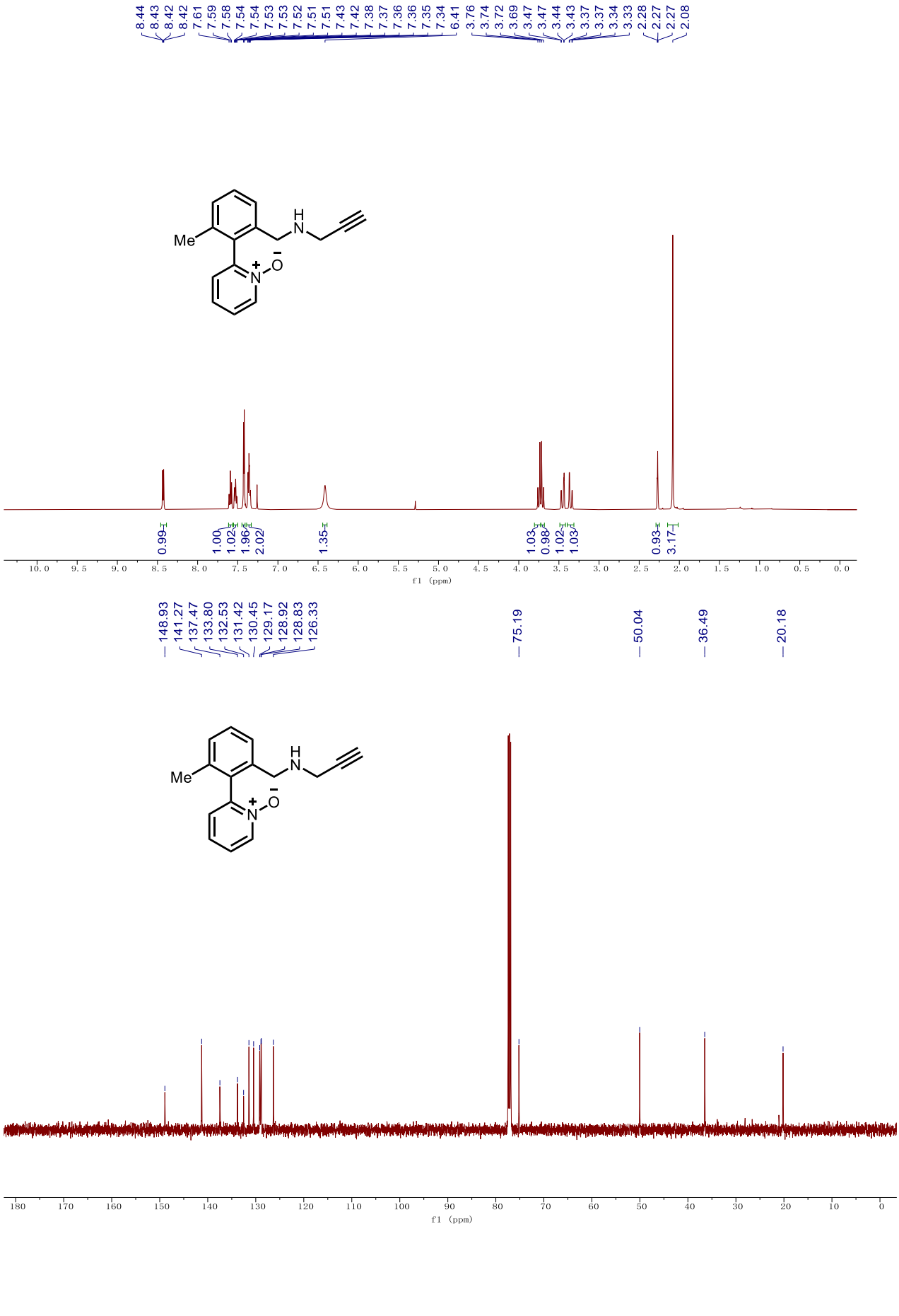
132.54
130.99
130.80
130.55
130.44
130.12
128.93
128.27
127.65
127.48
126.94
49.81
44.92
20.45
Me
H
N
S
N
O
f1 (ppm)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8.42
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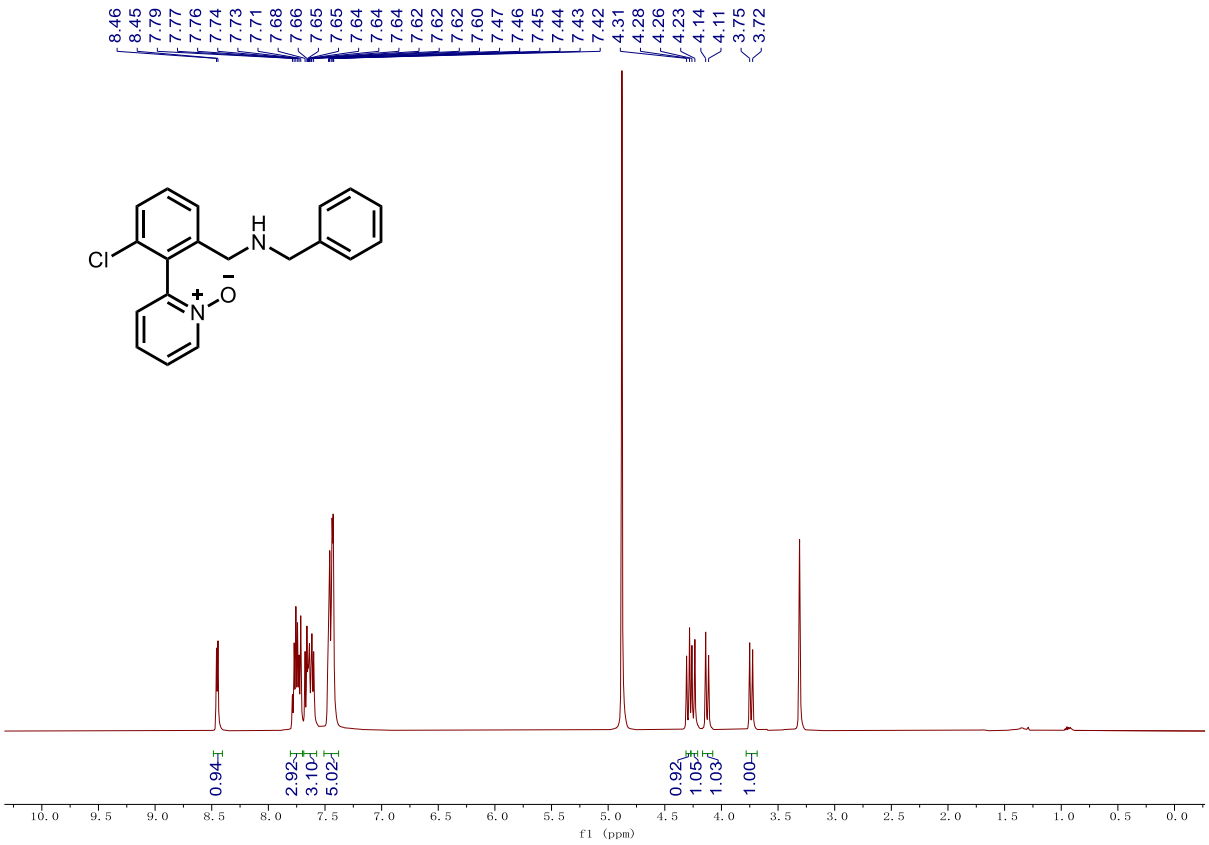
7.59
7.58
7.54
7.54
7.53
7.53
7.52
7.51
7.51
7.43
7.42
7.38
7.37
7.36
7.36
7.35
7.34
6.41
3.76
3.74
3.72
3.69
3.47
3.47
3.44
3.43
3.37
3.37
3.34
3.33
2.28
2.27
2.27
2.08
Me
H
N
O
0.99
1.00
1.02
1.96
2.02
1.35
1.03
0.98
1.02
1.03
0.93
3.17
f1 (ppm)
148.93
141.27
137.47
133.80
132.53
131.42
130.45
129.17
128.92
128.83
126.33
75.19
50.04
36.49
20.18
Me
H
N
O
f1 (ppm)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8.45
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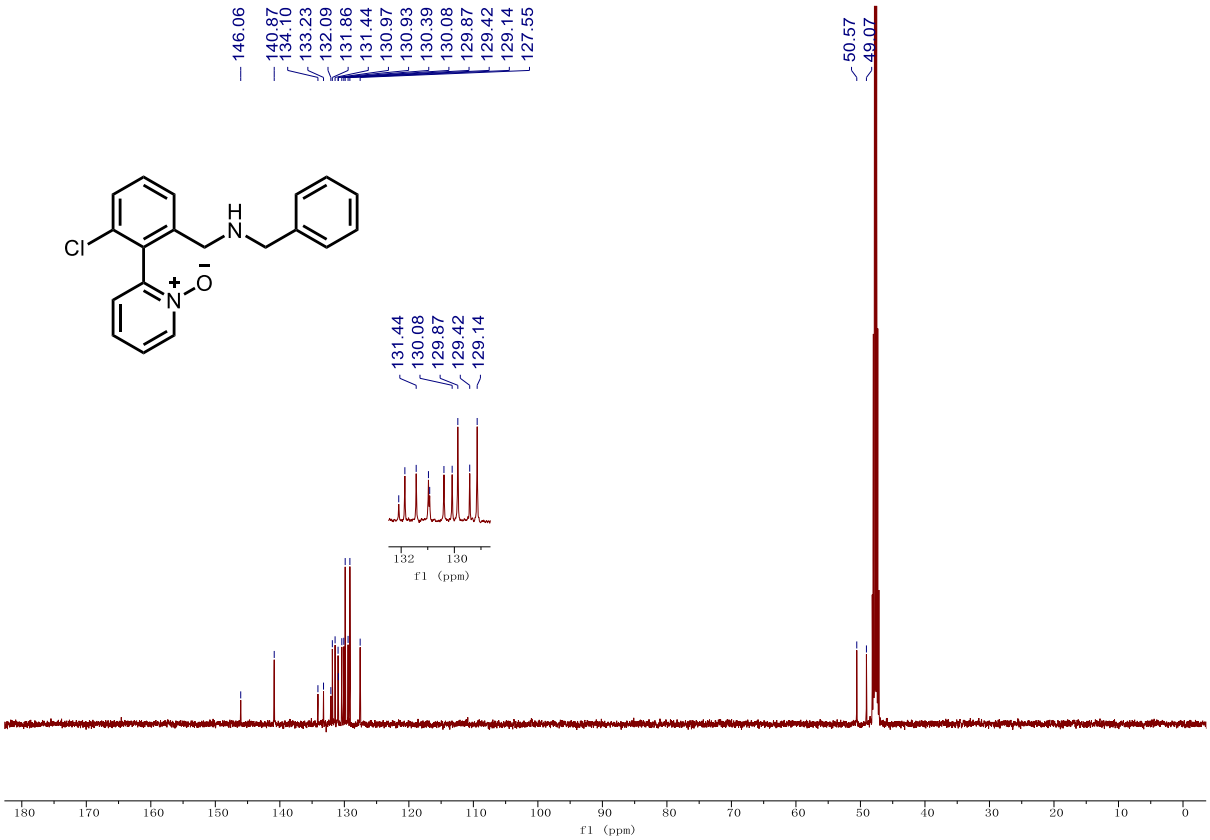
7.76
7.74
7.73
7.71
7.68
7.66
7.65
7.65
7.64
7.64
7.64
7.62
7.62
7.62
7.60
7.47
7.46
7.45
7.44
7.43
7.42
4.31
4.28
4.26
4.23
4.14
4.11
3.75
3.72
Cl
H
N
O
0.94
2.92
3.10
5.02
0.92
1.05
1.03
1.00
f1 (ppm)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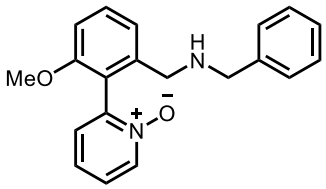
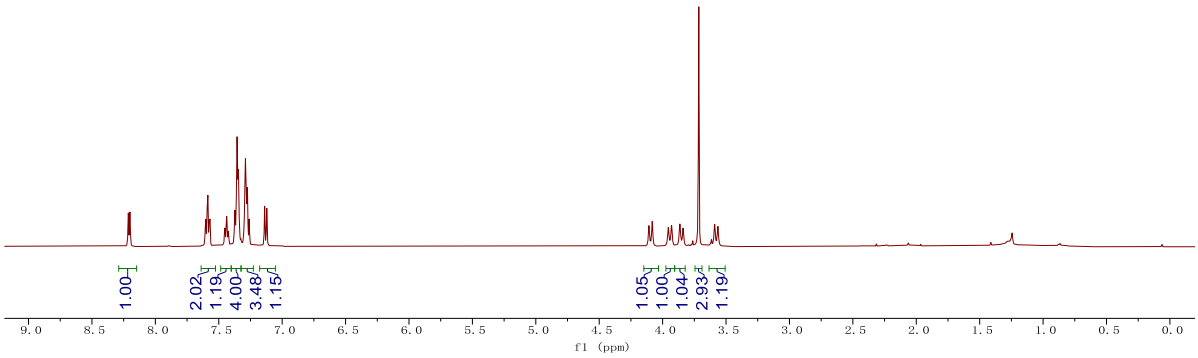
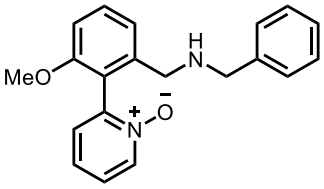
133.23
132.09
131.86
131.44
130.97
130.93
130.39
130.08
129.87
129.42
129.14
127.55
50.57
49.07
Cl
H
N
O
131.44
130.08
129.87
129.42
129.14
132
130
f1 (ppm)
f1 (ppm)


8.21
8.20
7.61
7.60
7.59
7.57
7.57
7.45
7.44
7.42
7.42
7.37
7.35
7.34
7.34
7.32
7.29
7.29
7.28
7.27
7.26
7.14
7.12
4.11
4.08
3.96
3.93
3.86
3.84
3.72
3.59
3.56

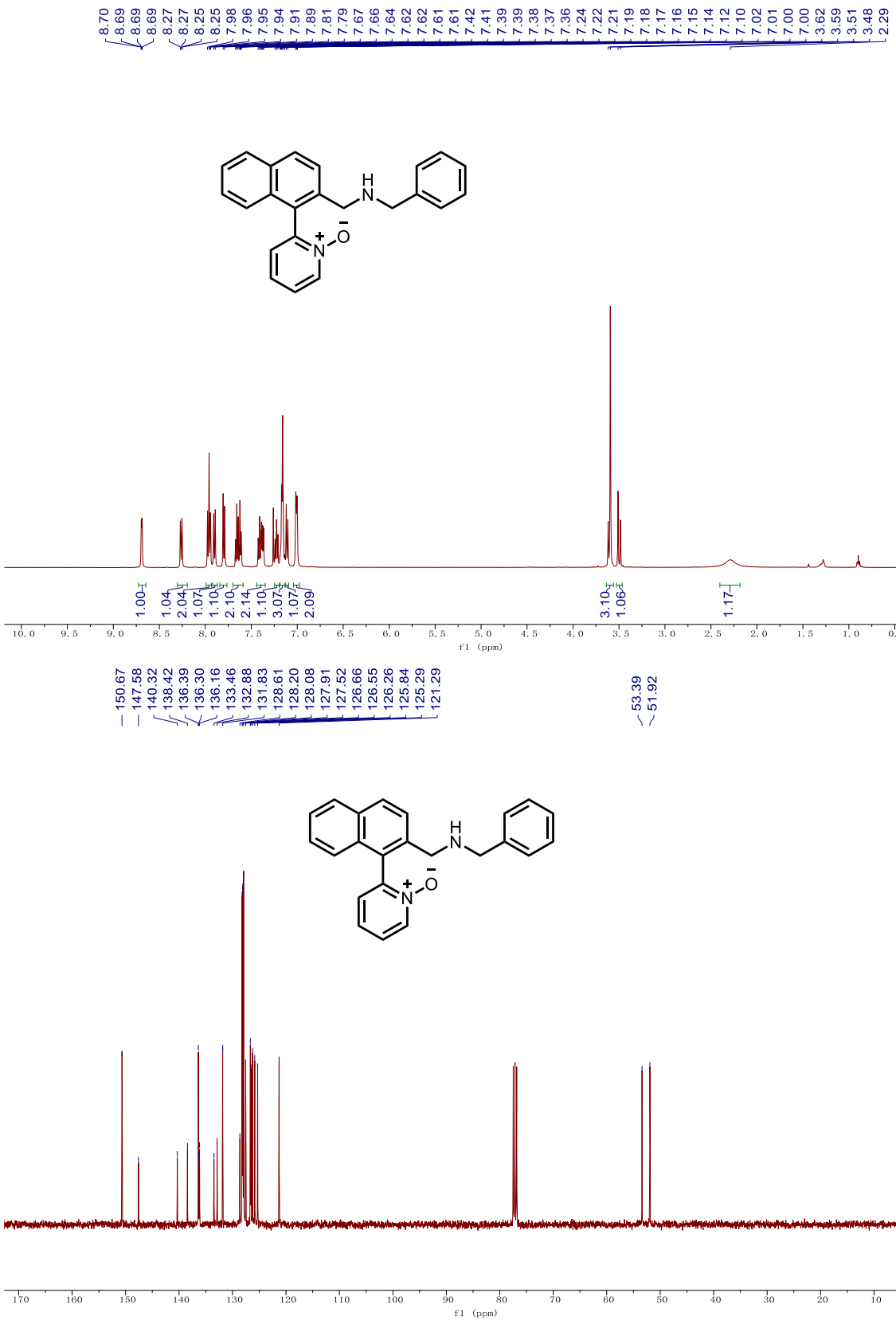

MeO
H
N
O
N


1.00
2.02
1.19
4.00
3.48
1.15
1.05
1.00
1.04
2.93
1.19
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)

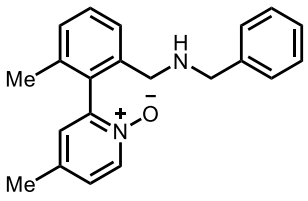

157.40
145.81
140.96
132.53
131.48
130.67
130.52
130.27
130.01
129.82
129.53
126.74
124.35
121.37
113.57
56.16
50.84
49.62

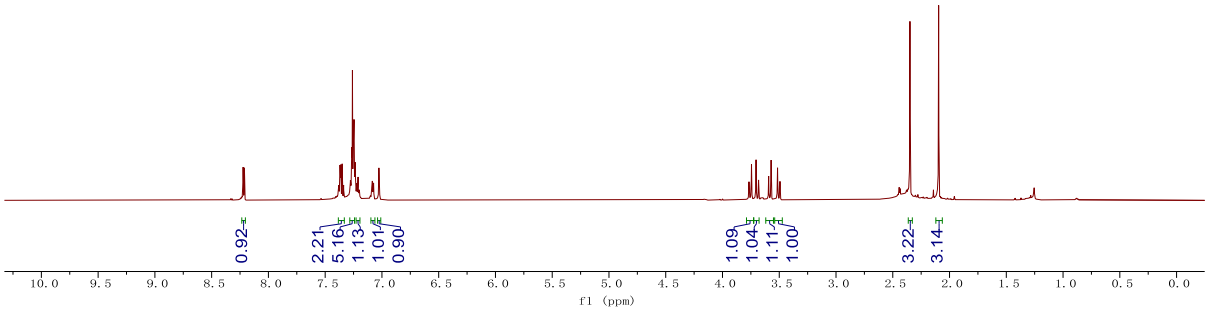

MeO
H
N
O
N

130.52
130.01
129.82
129.53
130.5
129.6
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.70
8.69
8.69
8.69
8.27
8.27
8.25
8.25
7.98
7.96
7.95
7.94
7.91
7.89
7.81
7.79
7.67
7.66
7.64
7.62
7.62
7.61
7.61
7.42
7.41
7.39
7.39
7.38
7.37
7.36
7.24
7.22
7.21
7.19
7.18
7.17
7.16
7.15
7.14
7.12
7.10
7.02
7.01
7.00
7.00
3.62
3.59
3.51
3.48
2.29
H
N
O
1.00
1.04
2.04
1.07
1.10
2.10
2.14
1.10
3.07
1.07
2.09
3.10
1.06
1.17
f1 (ppm)
150.67
147.58
140.32
138.42
136.39
136.30
136.16
133.46
132.88
131.83
128.61
128.20
128.08
127.91
127.52
126.66
126.55
126.26
125.84
125.29
121.29
53.39
51.92
f1 (ppm)


8.22
8.21
7.38
7.37
7.37
7.36
7.35
7.34
7.28
7.28
7.28
7.27
7.27
7.27
7.26
7.26
7.25
7.25
7.25
7.24
7.23
7.23
7.22
7.22
7.22
7.21
7.21
7.21
7.20
7.20
7.20
7.09
7.08
7.08
7.07
7.03
7.02
3.77
3.74
3.70
3.68
3.59
3.57
3.52
3.49
2.35
2.10


Me
H
N
O
N
Me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2.21
5.16
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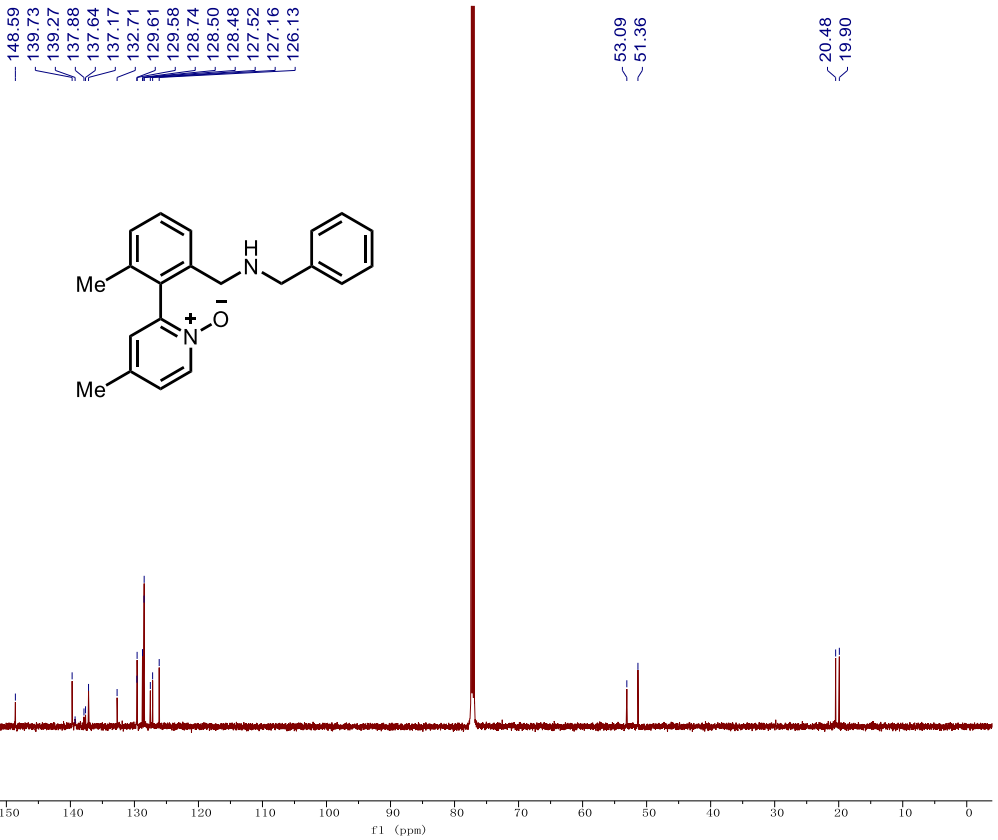
1.01
0.90
1.09
1.04
1.11
1.00
3.22
3.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


148.59
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137.88
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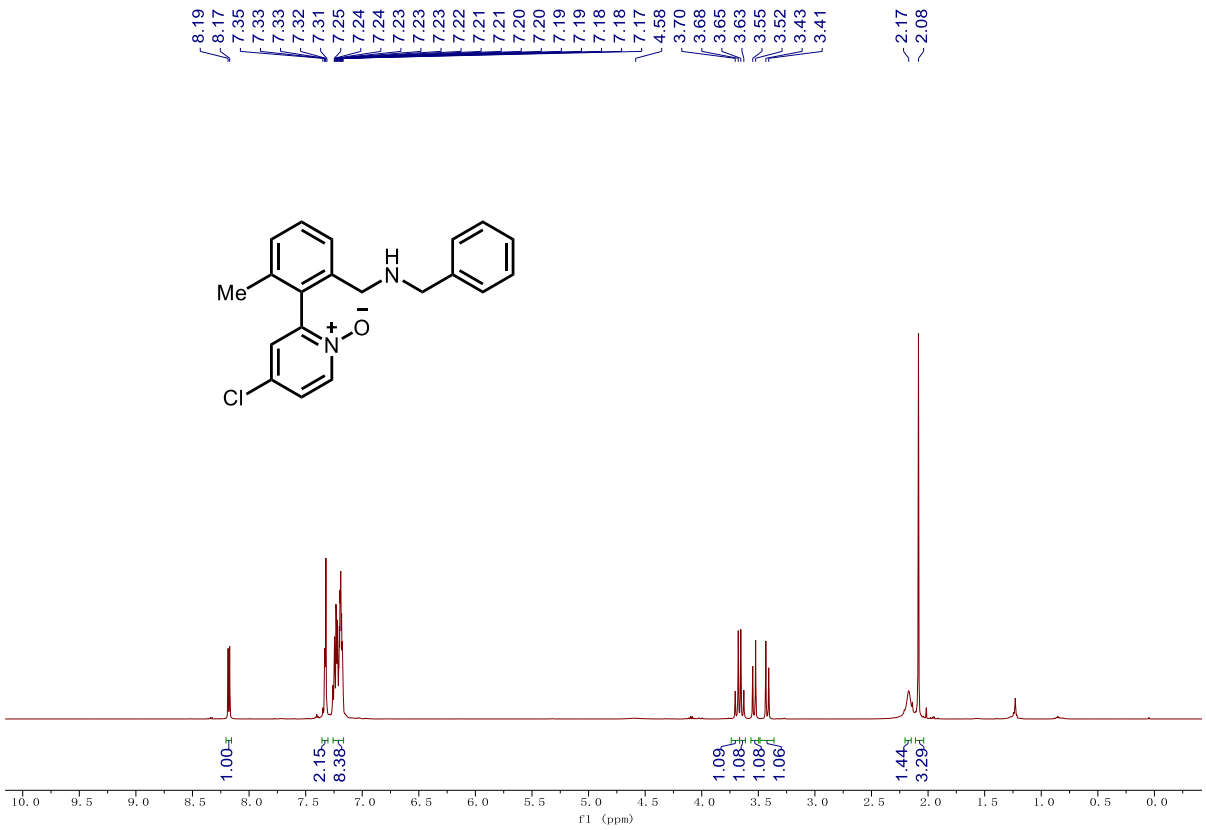
137.17
132.71
129.61
129.58
128.74
128.50
128.48
127.52
127.16
126.13
53.09
51.36
20.48
19.90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Me
H
N
O
N
Me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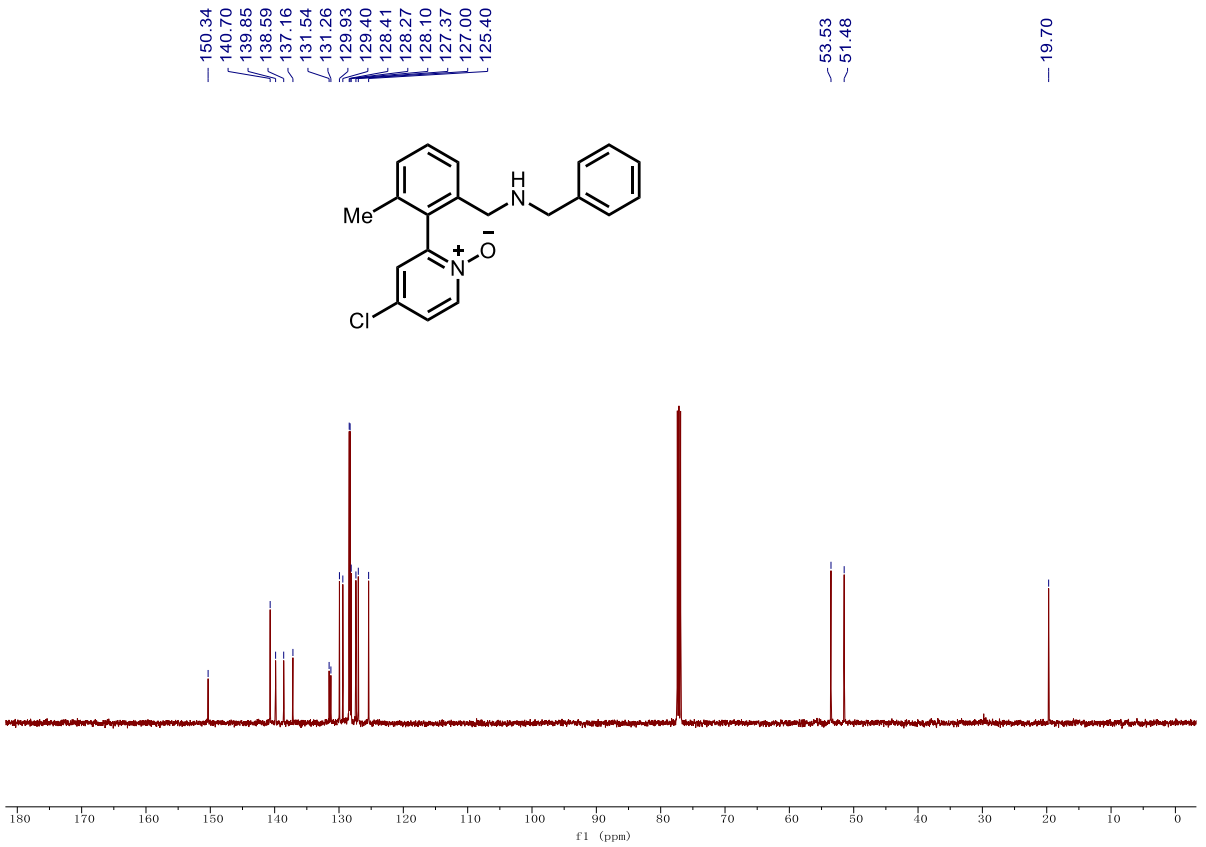
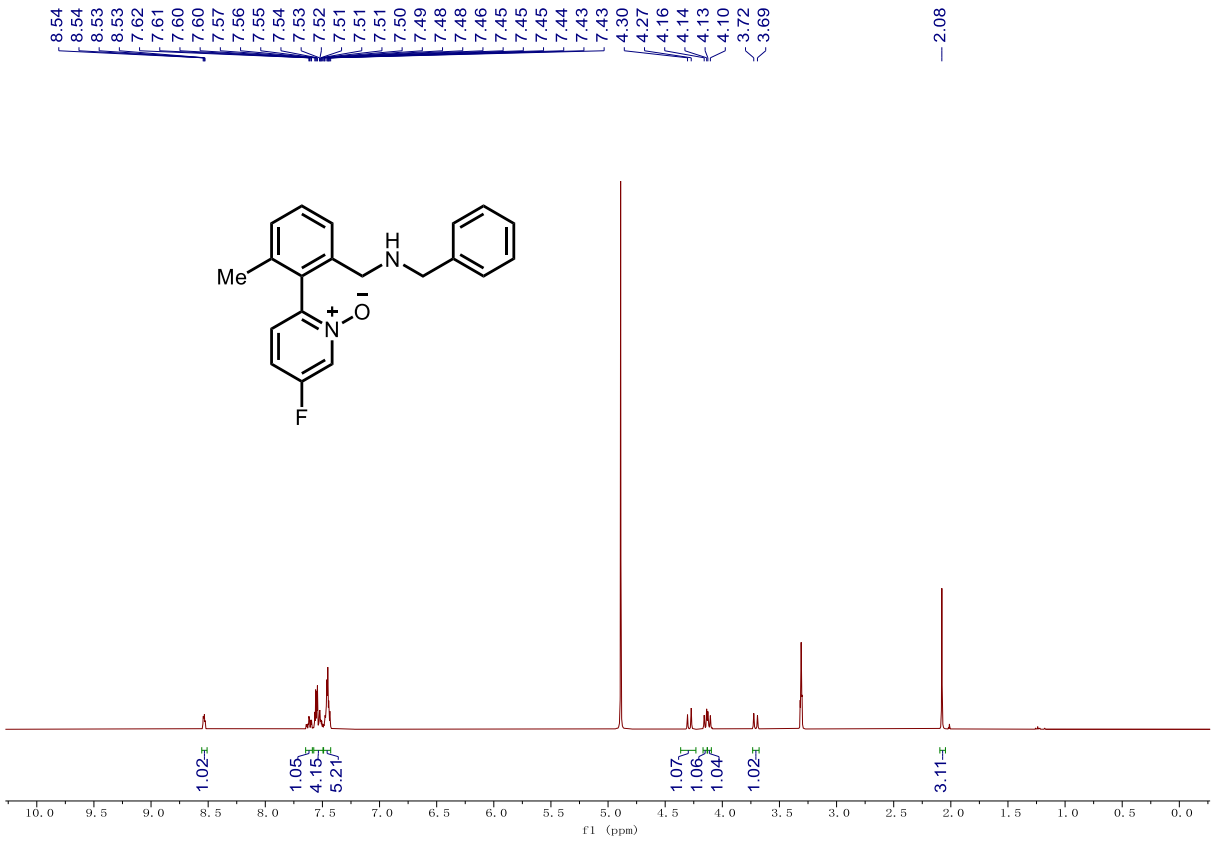
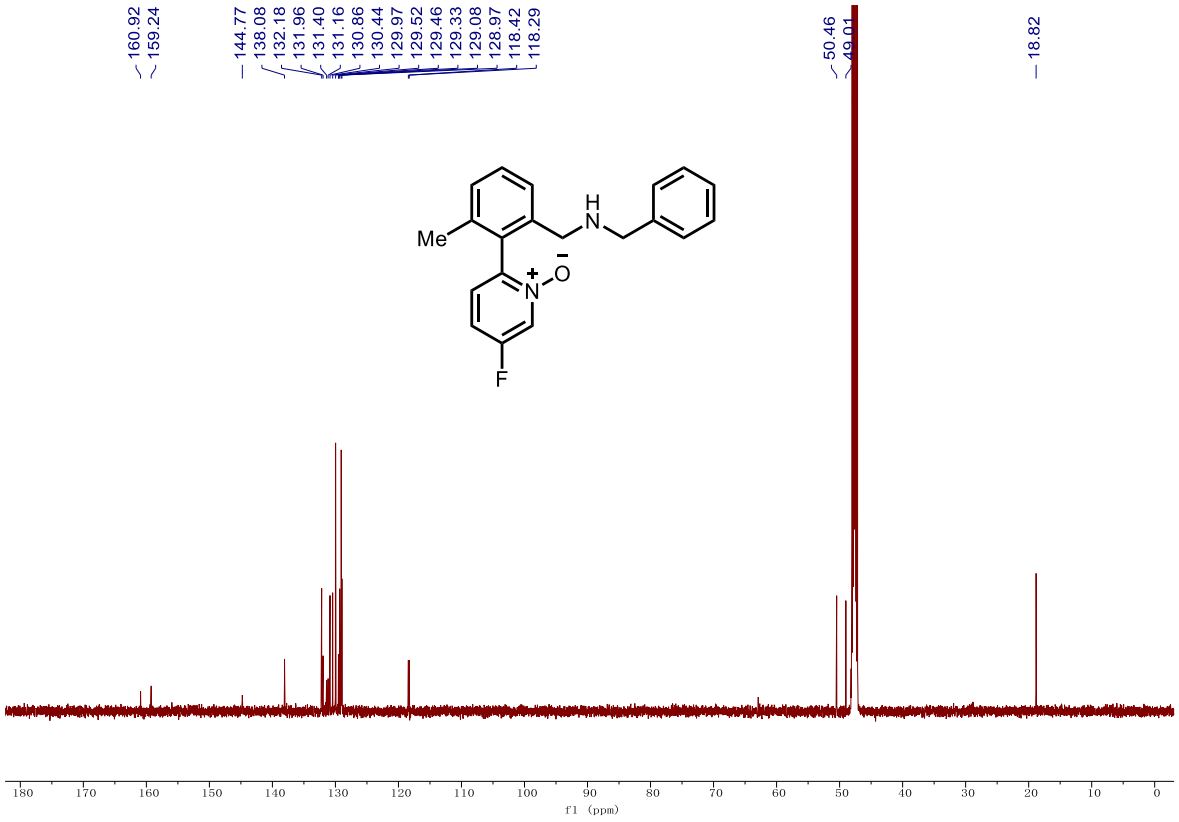
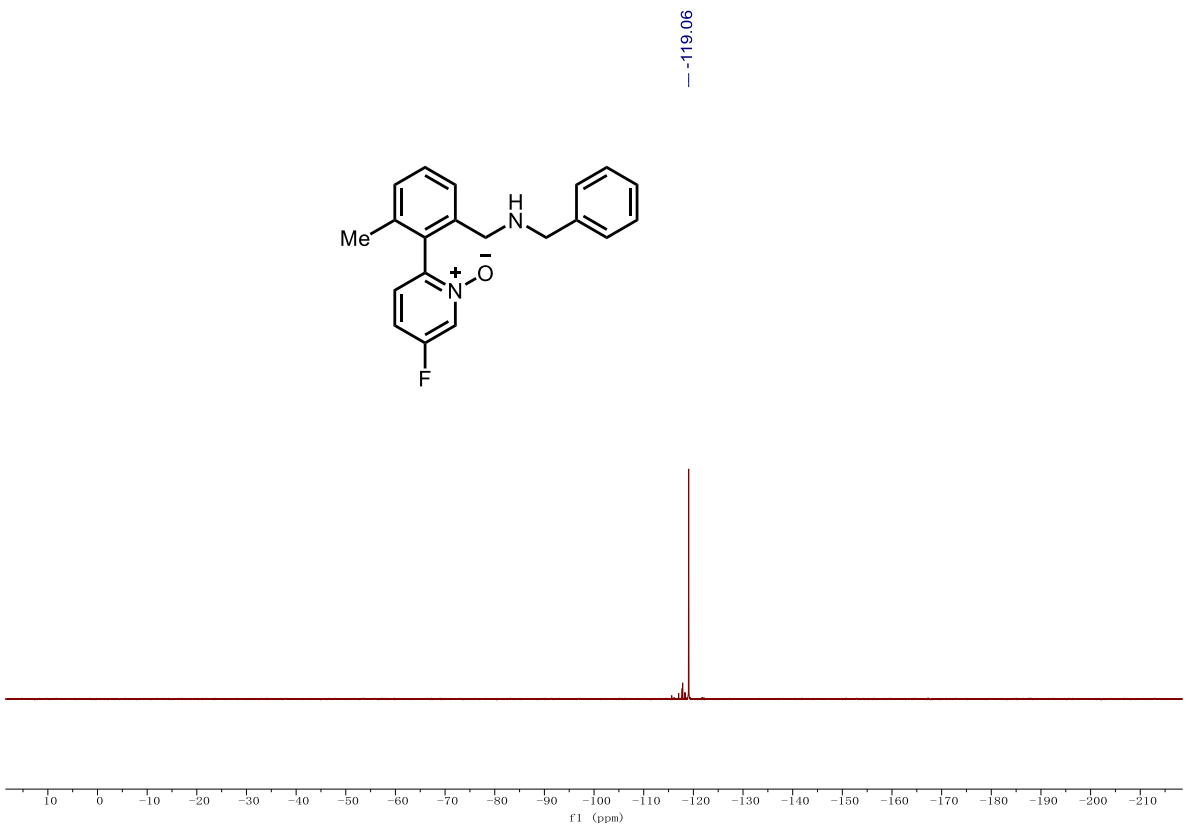
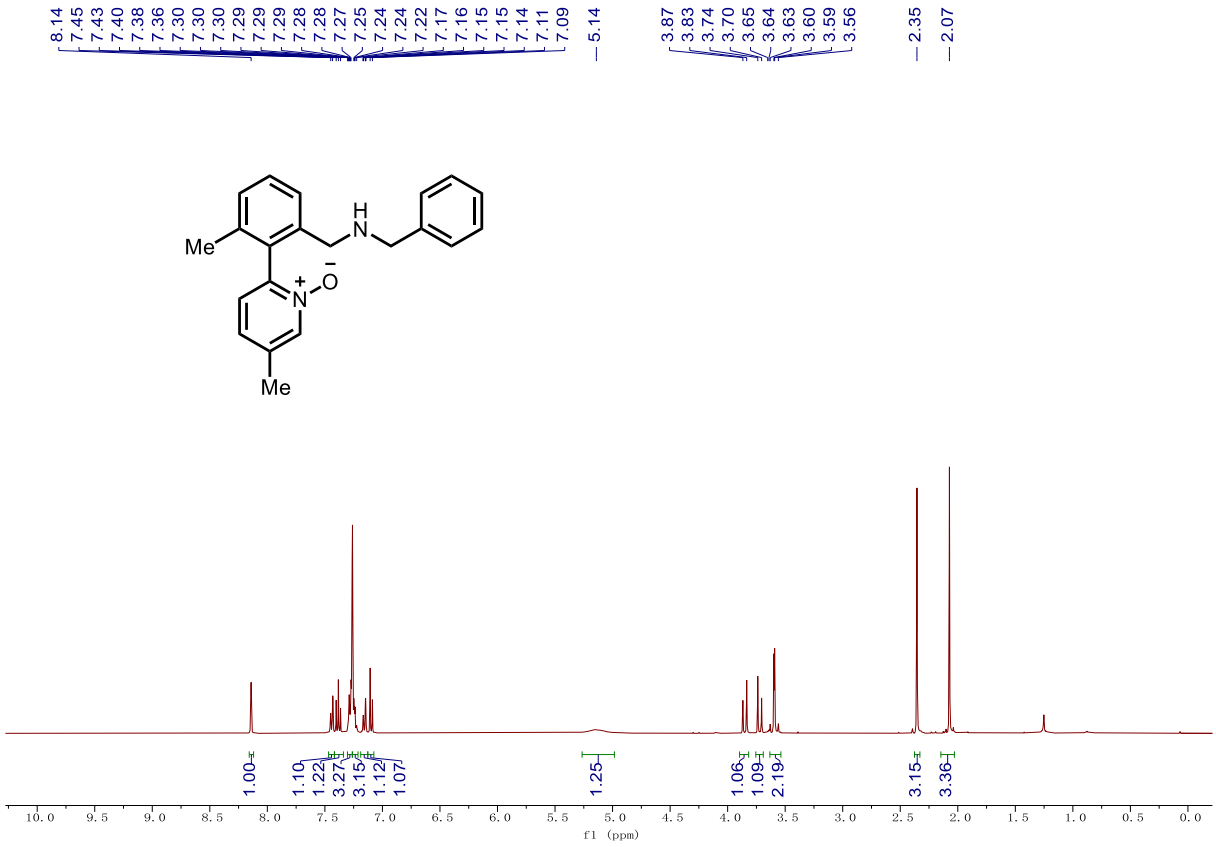
8.17
7.35
7.33
7.33
7.32
7.31
7.25
7.24
7.24
7.23
7.23
7.23
7.22
7.21
7.21
7.20
7.20
7.19
7.19
7.18
7.18
7.17
4.58
3.70
3.68
3.65
3.63
3.55
3.52
3.43
3.41
2.17
2.08
Me
H
N
O
N
Cl
1.00
2.15
8.38
1.09
1.08
1.08
1.06
1.44
3.29
f1 (ppm)

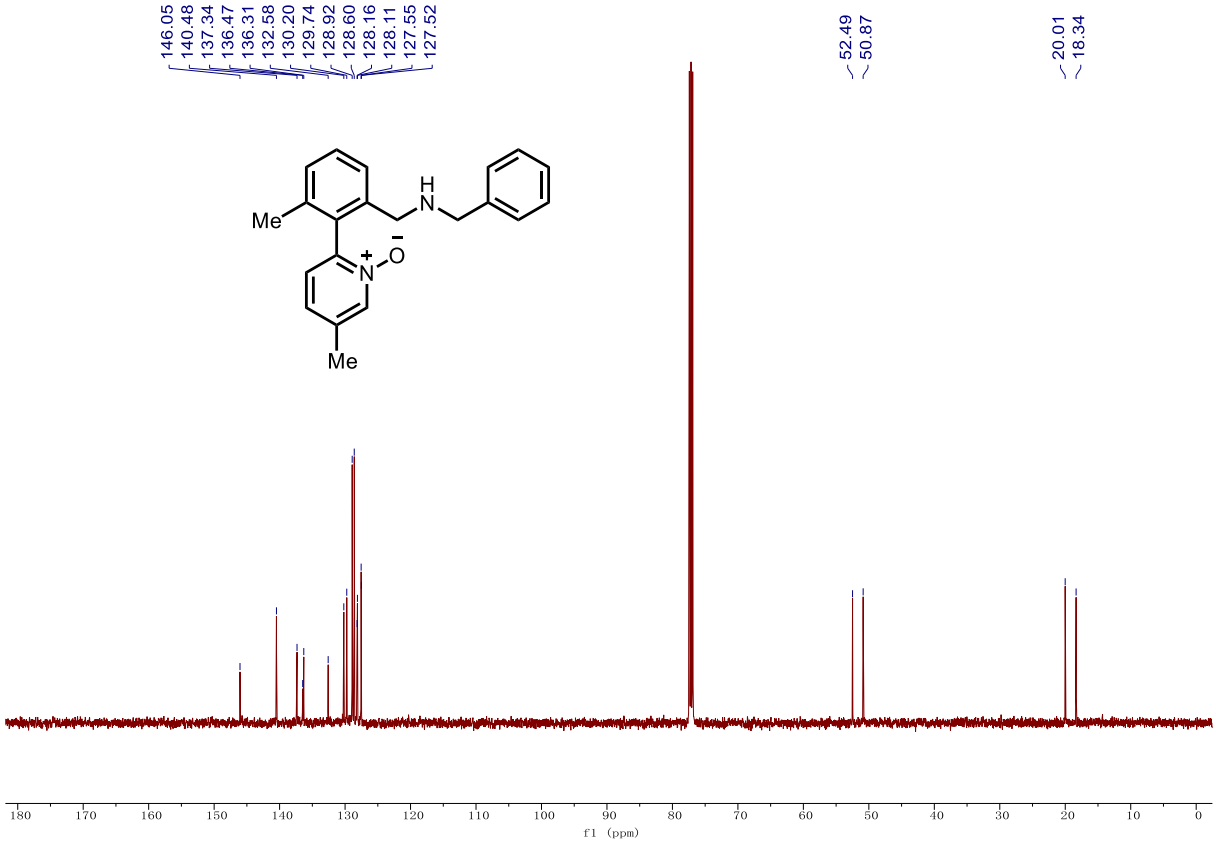

150.34
140.70
139.85
138.59
137.16
131.54
131.26
129.93
129.40
128.41
128.27
128.10
127.37
127.00
125.40
53.53
51.48
19.70
Me
H
N
O
N
Cl
f1 (ppm)


8.54
8.54
8.53
8.53
7.62
7.61
7.60
7.60
7.57
7.56
7.55
7.54
7.53
7.52
7.51
7.51
7.51
7.50
7.49
7.48
7.48
7.46
7.45
7.45
7.45
7.44
7.43
7.43
4.30
4.27
4.16
4.14
4.13
4.10
3.72
3.69
2.08
Me
H
N
O
F
1.02
1.05
4.15
5.21
1.07
1.06
1.04
1.02
3.11
f1 (ppm)

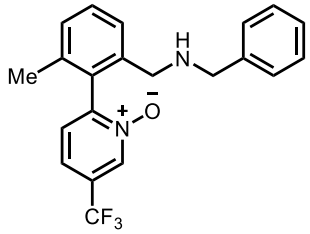

160.92
159.24
144.77
138.08
132.18
131.96
131.40
131.16
130.86
130.44
129.97
129.52
129.46
129.33
129.08
128.97
118.42
118.29
50.46
49.01
18.82
Me
H
N
O
F
f1 (ppm)

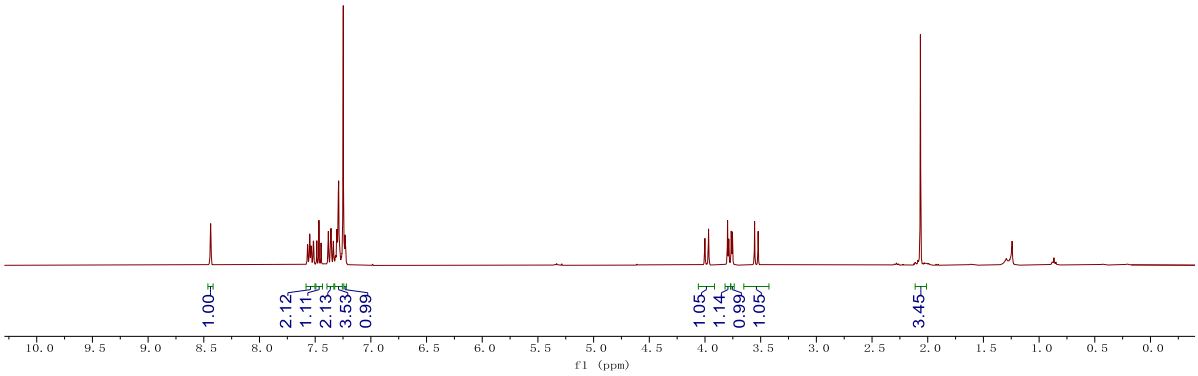

-119.06
Me
H
N
O
F
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
f1 (ppm)

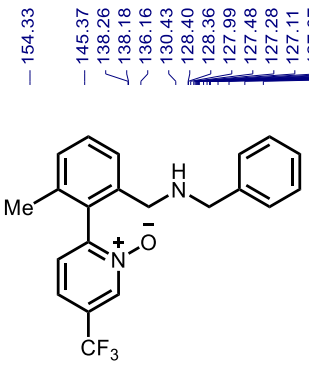

8.14
7.45
7.43
7.40
7.38
7.36
7.30
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.27
7.25
7.24
7.24
7.22
7.17
7.16
7.15
7.15
7.14
7.11
7.09
5.14
3.87
3.83
3.74
3.70
3.65
3.64
3.63
3.60
3.59
3.56
2.35
2.07
Me
H
N
O
Me
1.00
1.10
1.22
3.27
3.15
1.12
1.07
1.25
1.06
1.09
2.19
3.15
3.36
f1 (ppm)


146.05
140.48
137.34
136.47
136.31
132.58
130.20
129.74
128.92
128.60
128.16
128.11
127.55
127.52
52.49
50.87
20.01
18.34
Me
H
N
O
Me
f1 (ppm)

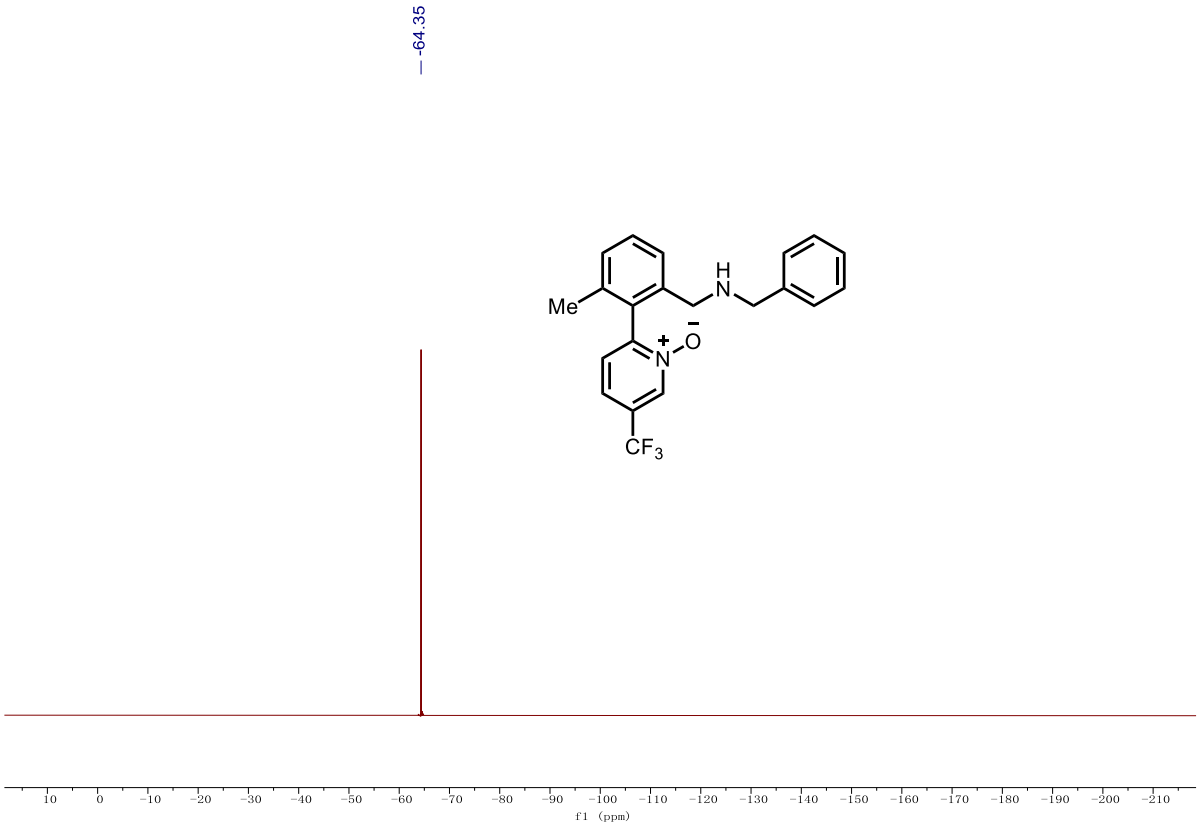

8.44
7.57
7.55
7.54
7.53
7.52
7.51
7.49
7.47
7.45
7.38
7.36
7.34
7.32
7.32
7.31
7.30
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.24
7.23
7.23
5.33
4.00
3.97
3.80
3.79
3.76
3.75
3.55
3.52
2.07

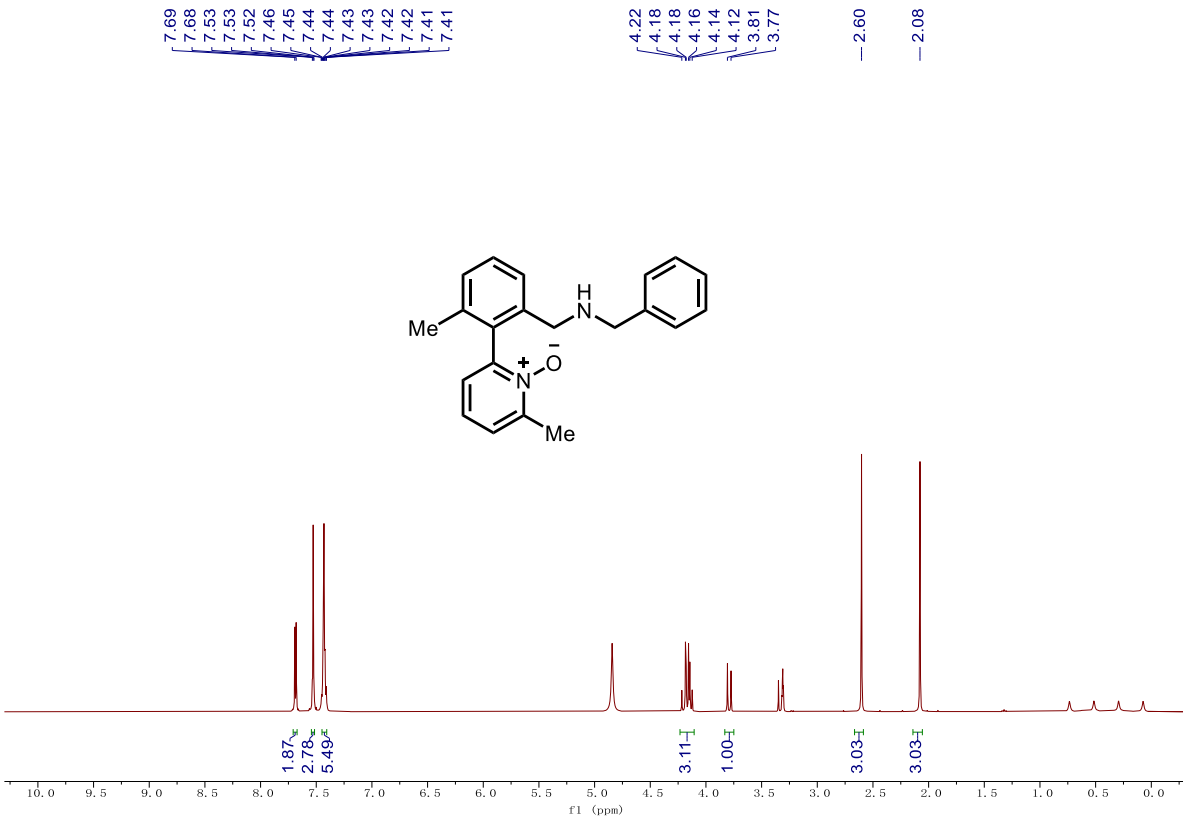

Me
H
N
O
N
CF3

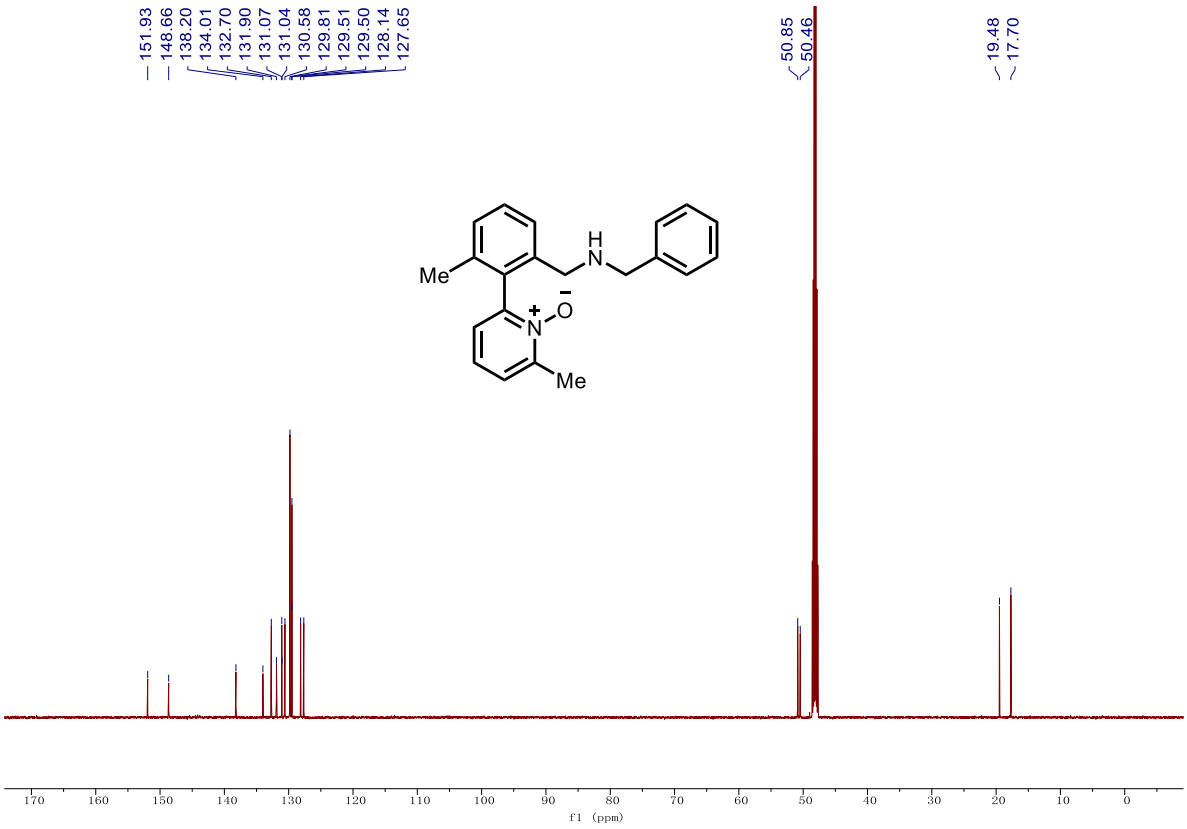

1.00
2.12
1.11
2.13
3.53
0.99
1.05
1.14
0.99
1.05
3.45
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
H
N
O
N
CF3

154.33
145.37
138.26
138.18
136.16
130.43
128.40
128.36
127.99
127.48
127.28
127.11
127.07
126.86
126.72
126.56
125.88
125.30
124.87
124.85
124.82
124.79
123.50
121.70
119.11
116.07
51.70
50.53
20.16
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-64.35
Me
H
N
O
CF3
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
f1 (ppm)


7.69
7.68
7.53
7.53
7.52
7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.41
7.41
4.22
4.18
4.18
4.16
4.14
4.12
3.81
3.77
2.60
2.08
Me
H
N
O
N
Me
1.87
2.78
5.49
3.11
1.00
3.03
3.03
f1 (ppm)


151.93
148.66
138.20
134.01
132.70
131.90
131.07
131.04
130.58
129.81
129.51
129.50
128.14
127.65
50.85
50.46
19.48
17.70
Me
H
N
O
N
Me
f1 (ppm)


8.27
8.26
8.06
8.04
8.03
8.01
7.77
7.76
7.76
7.75
7.74
7.67
7.66
7.64
7.63
7.62
7.60
7.59
7.57
7.56
7.31
7.29
7.16
7.15
7.14
7.14
7.04
7.03
7.02
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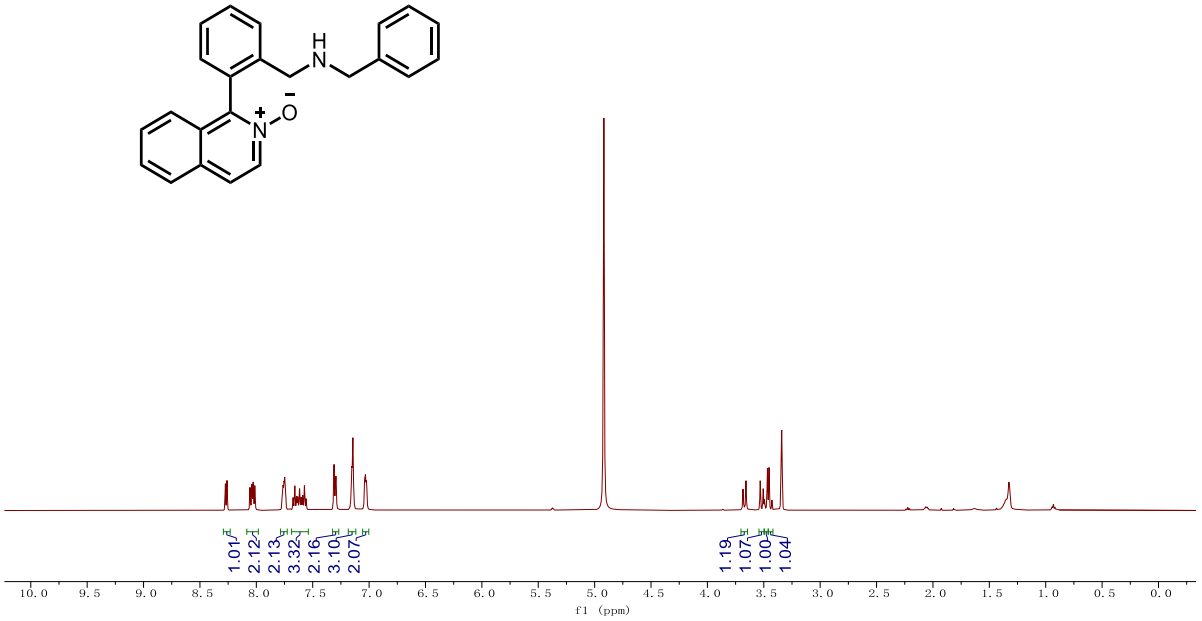
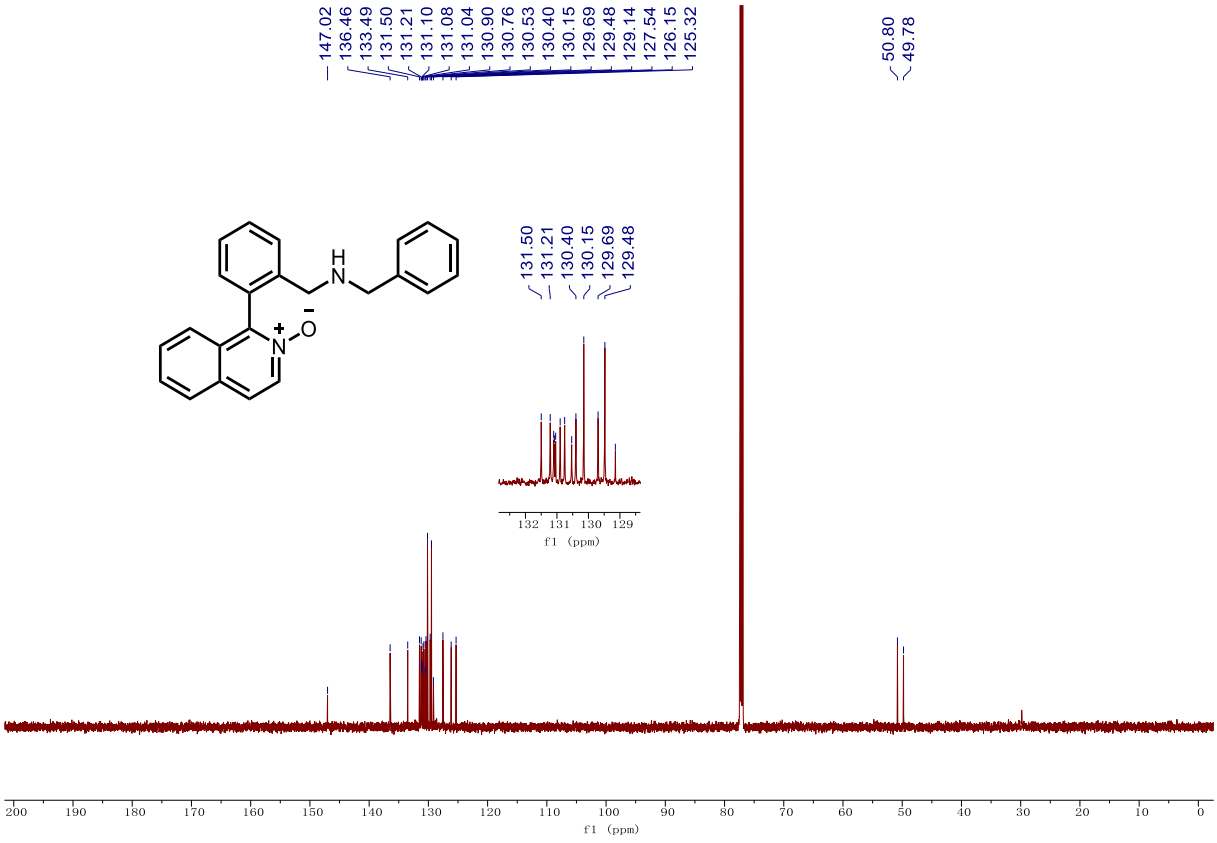
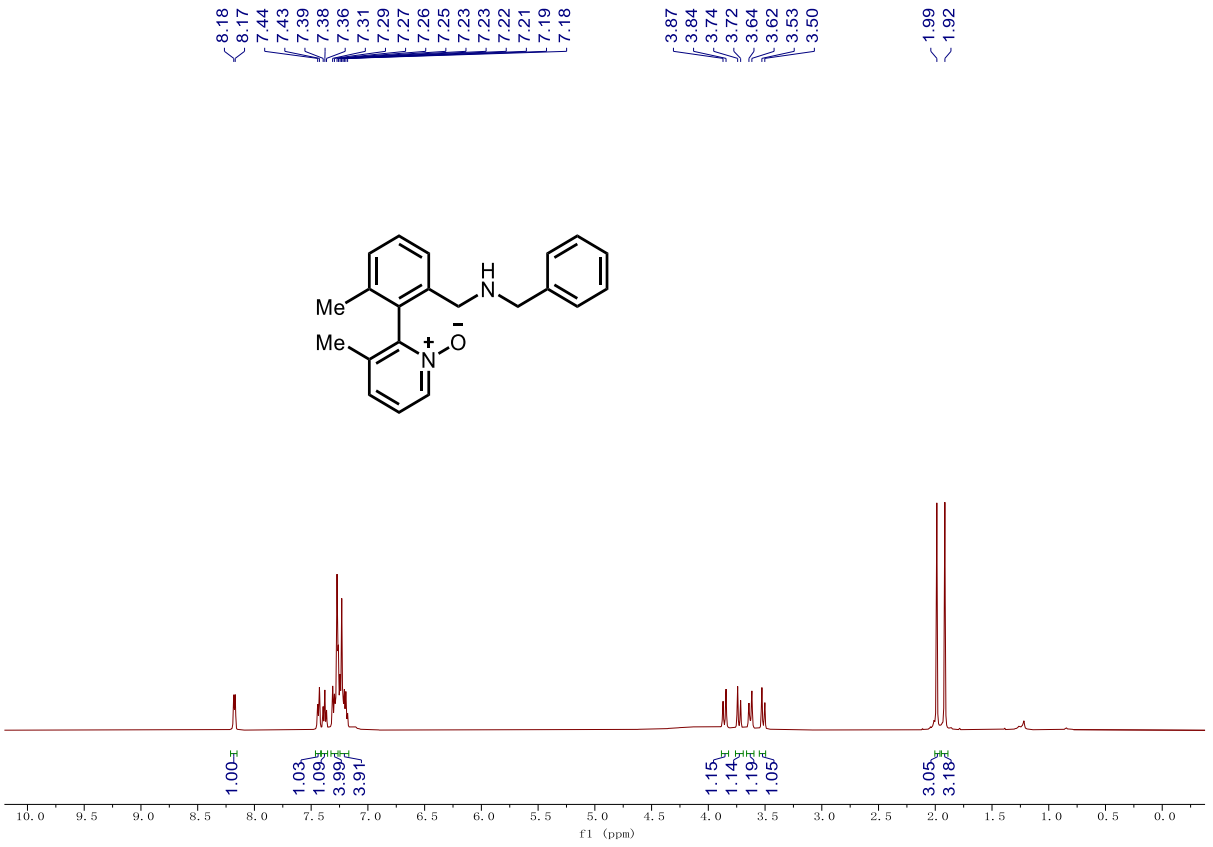
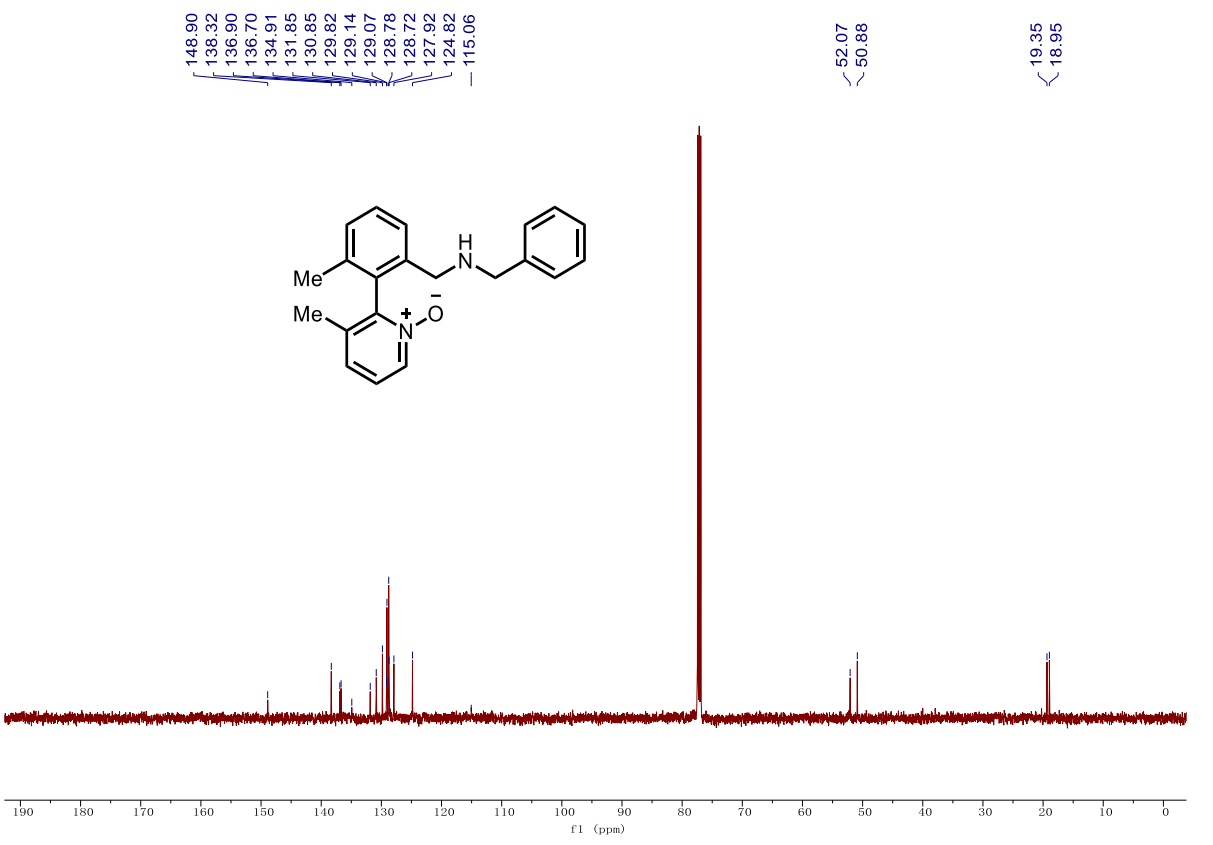
3.66
3.53
3.51
3.49
3.47
3.45
3.43


1.01
2.12
2.13
3.32
2.16
3.10
2.07
1.19
1.07
1.00
1.04
f1 (ppm)


147.02
136.46
133.49
131.50
131.21
131.10
131.08
131.04
130.90
130.76
130.53
130.40
130.15
129.69
129.48
129.14
127.54
126.15
125.32
50.80
49.78
131.50
131.21
130.40
130.15
129.69
129.48
f1 (ppm)


8.18
8.17
7.44
7.43
7.39
7.38
7.36
7.31
7.29
7.27
7.26
7.25
7.23
7.23
7.22
7.21
7.19
7.18
3.87
3.84
3.74
3.72
3.64
3.62
3.53
3.50
1.99
1.92
Me
Me
H
N
O
1.00
1.03
1.09
3.99
3.91
1.15
1.14
1.19
1.05
3.05
3.18
f1 (ppm)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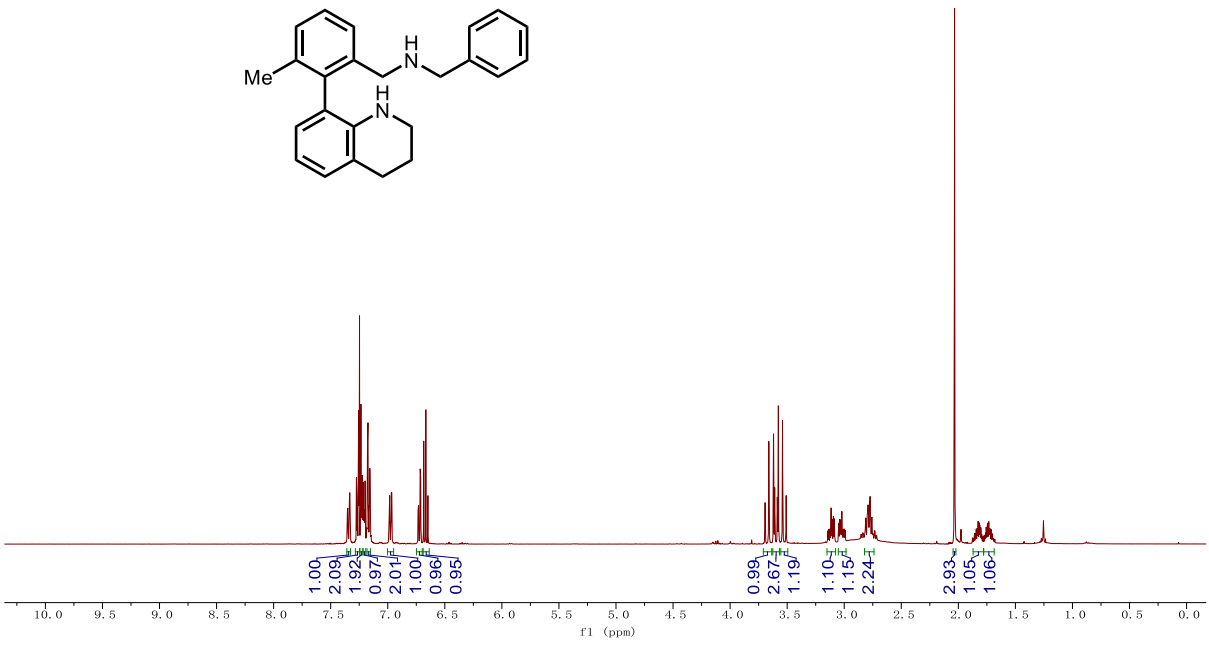
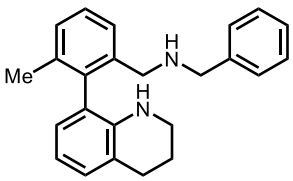
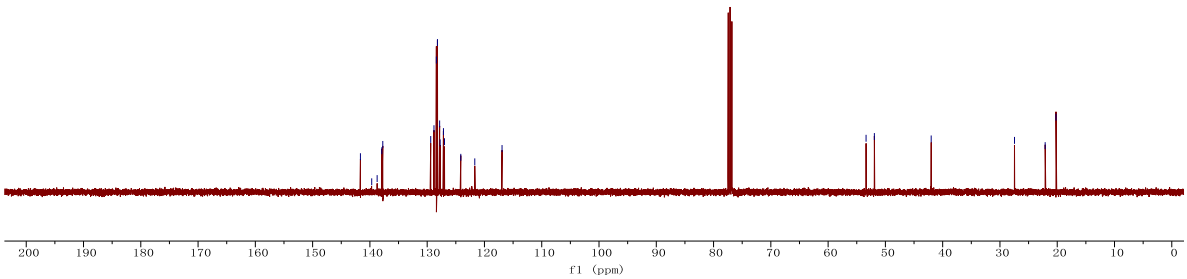
138.32
136.90
136.70
134.91
131.85
130.85
129.82
129.14
129.07
128.78
128.72
127.92
124.82
115.06
52.07
50.88
19.35
18.95
Me
Me
H
N
O
f1 (ppm)


7.35
7.35
7.34
7.33
7.27
7.27
7.26
7.25
7.25
7.24
7.23
7.23
7.23
7.23
7.22
7.22
7.22
7.21
7.21
7.20
7.20
7.18
7.17
7.16
7.16
7.15
6.99
6.99
6.98
6.97
6.97
6.96
6.96
6.73
6.72
6.71
6.68
6.67
6.65
3.69
3.66
3.62
3.61
3.59
3.58
3.54
3.51
3.11
3.11
3.10
3.09
3.04
3.02
2.81
2.79
2.77
2.76
2.03


Me
H
N
H
N
1.00
2.09
1.92
0.97
2.01
1.00
0.96
0.95
0.99
2.67
1.19
1.10
1.15
2.24
2.93
1.05
1.06
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)

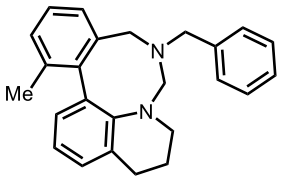

141.65
139.68
138.74
137.93
137.75
129.38
128.81
128.39
128.20
127.83
127.74
127.16
126.98
124.13
121.69
116.93
53.37
51.92
42.00
27.46
22.10
20.22

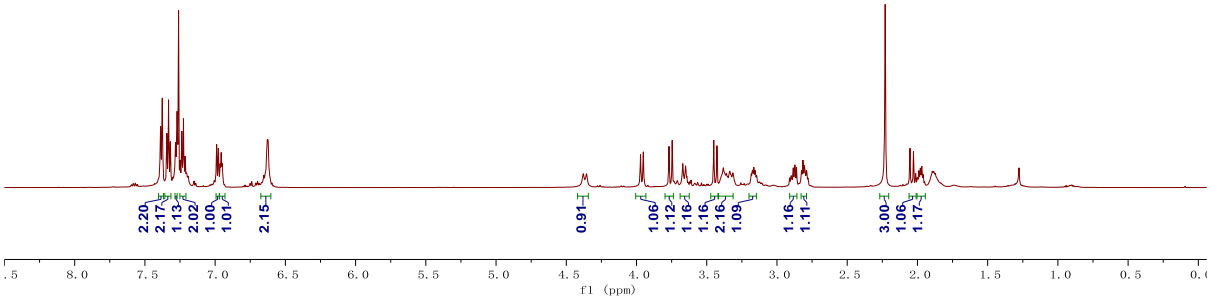

Me
H
N
H
N

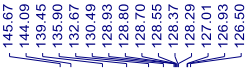

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.39
7.38
7.34
7.33
7.32
7.28
7.27
7.26
7.24
7.23
7.21
6.99
6.98
6.96
6.95
6.63
6.62


4.38
4.36
3.97
3.95
3.77
3.75
3.67
3.65
3.45
3.43
3.38
3.36
3.34
3.31
3.17
3.16
3.16
3.15
2.91
2.90
2.88
2.87
2.86
2.83
2.82
2.79
2.23
2.05
2.03
2.01
2.00
1.99
1.98
1.97
1.96
1.95


Me
N
N


2.20
2.17
1.13
2.02
1.00
1.01
2.15
0.91
1.06
1.12
1.16
1.16
2.16
1.09
1.16
1.11
3.00
1.06
1.17
f1 (ppm)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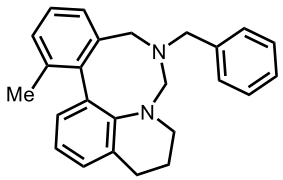
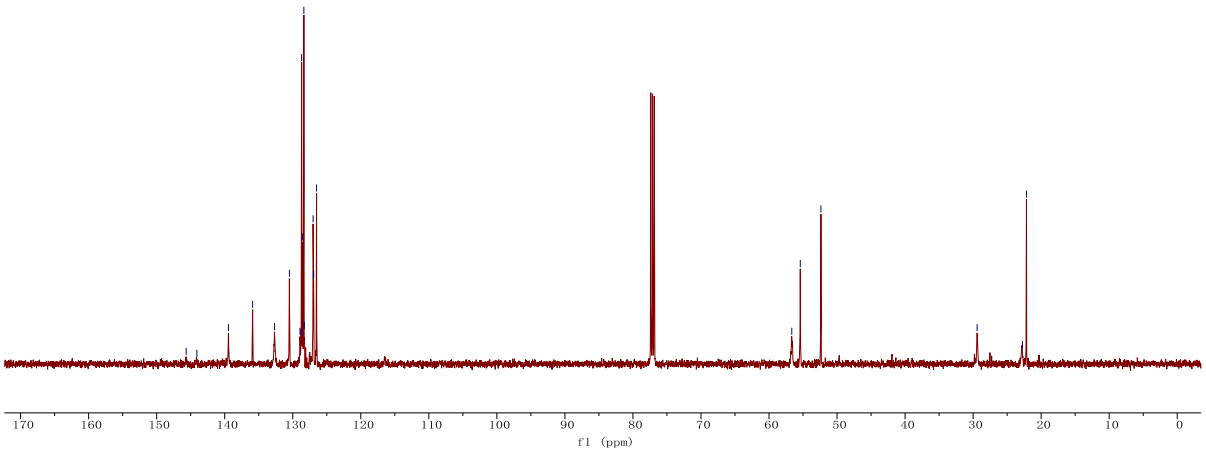
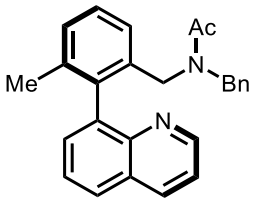
144.09
139.45
135.90
132.67
130.49
128.93
128.80
128.70
128.55
128.37
128.29
127.01
126.93
126.50

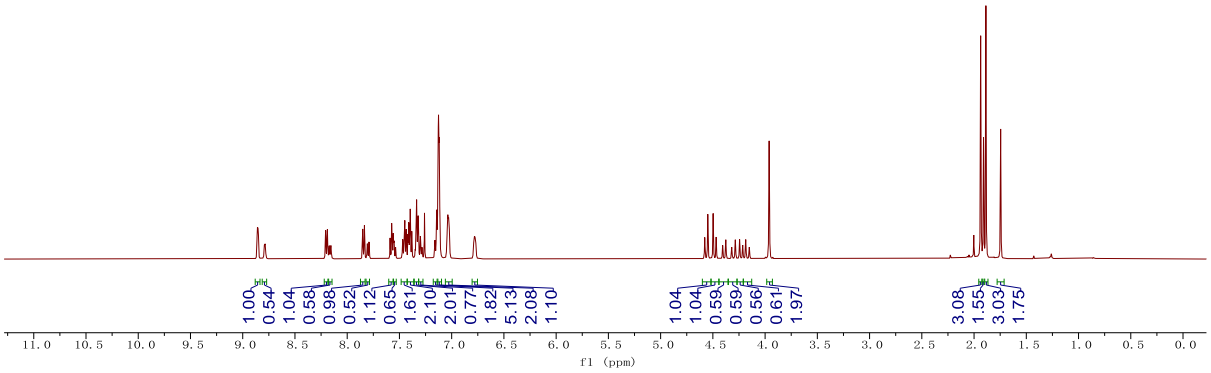

56.65
55.41
52.37
29.41
22.75
22.16

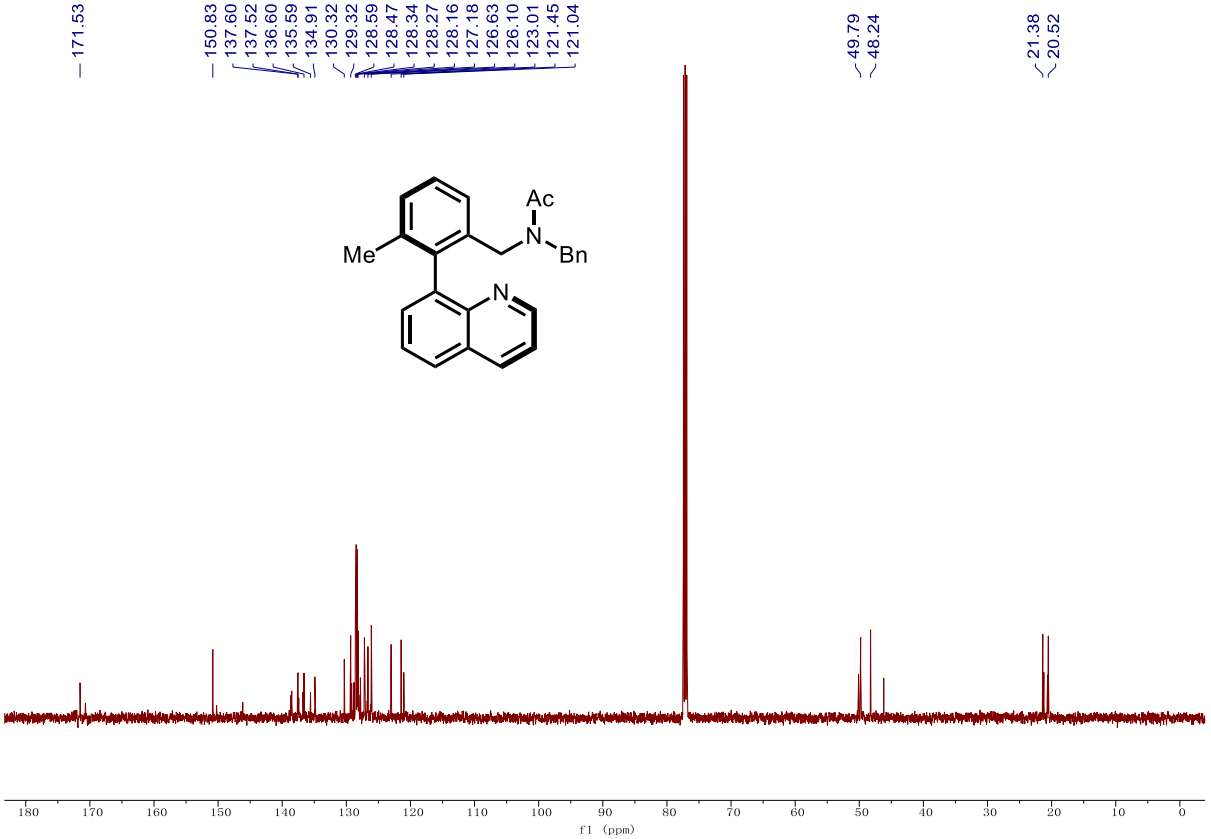

Me
N
N


f1 (ppm)


8.86
8.86
8.85
8.85
8.79
8.79
8.21
8.21
8.19
8.19
7.85
7.84
7.81
7.79
7.59
7.58
7.57
7.57
7.56
7.55
7.47
7.45
7.45
7.44
7.43
7.42
7.41
7.40
7.40
7.38
7.34
7.32
7.32
7.30
7.26
7.16
7.14
7.13
7.12
7.04
7.04
7.03
7.02
6.79
6.78
6.77
4.58
4.55
4.50
4.47
4.38
4.28
4.24
4.19
3.96
1.94
1.91
1.89
1.75

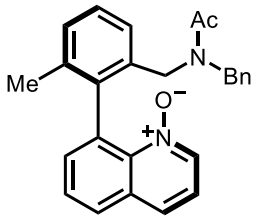

Ac
N
Me
Bn
N

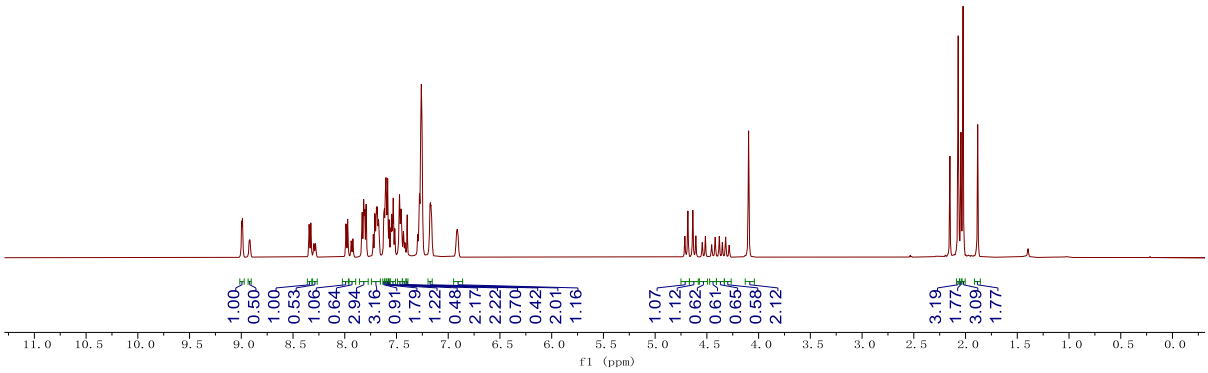

1.00
0.54
1.04
0.58
0.98
0.52
1.12
0.65
1.61
2.10
2.01
0.77
1.82
5.13
2.08
1.10
1.04
1.04
0.59
0.59
0.56
0.61
1.97
3.08
1.55
3.03
1.75
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


171.53
150.83
137.60
137.52
136.60
135.59
134.91
130.32
129.32
128.59
128.47
128.34
128.27
128.16
127.18
126.63
126.10
123.01
121.45
121.04
49.79
48.24
21.38
20.52
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

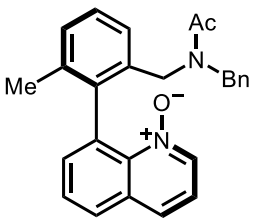
Ac
N
Me
Bn
N

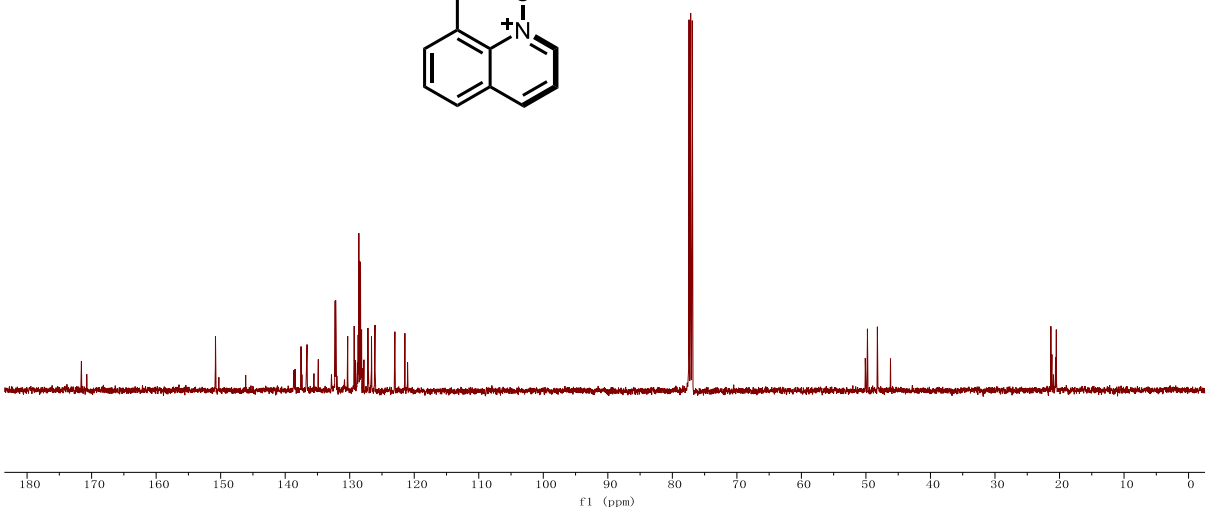

9.00
8.99
8.99
8.33
7.99
7.97
7.83
7.83
7.82
7.82
7.81
7.81
7.81
7.80
7.79
7.79
7.71
7.71
7.70
7.69
7.69
7.69
7.68
7.68
7.67
7.67
7.62
7.62
7.62
7.61
7.61
7.60
7.60
7.59
7.59
7.59
7.58
7.57
7.55
7.54
7.53
7.53
7.47
7.46
7.40
7.18
7.17
7.17
7.16
7.16
4.68
4.64
4.10
2.15
2.07
2.05
2.04
2.02
1.88


Ac
N
Bn
Me
O
N

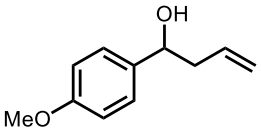

1.00
0.50
1.00
0.53
1.06
0.64
2.94
3.16
0.91
1.79
1.22
0.48
2.17
2.22
0.70
0.42
2.01
1.16
1.07
1.12
0.62
0.61
0.65
0.58
2.12
3.19
1.77
3.09
1.77
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

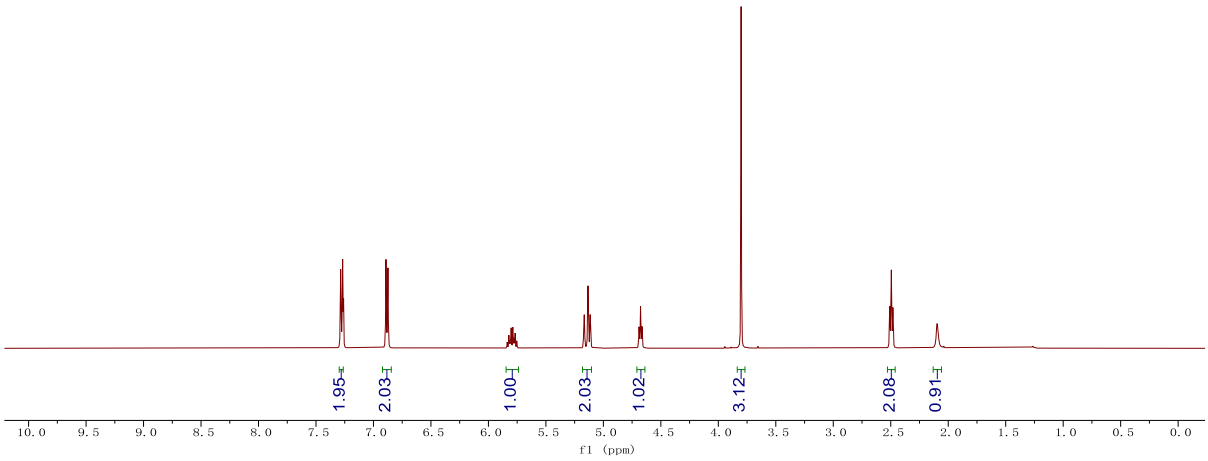

171.58
150.80
137.54
136.61
134.87
132.26
132.18
130.31
129.31
128.68
128.58
128.45
128.33
128.25
128.16
128.00
127.18
126.62
126.08
123.00
121.45
49.77
48.22
21.34
20.50


Ac
N
Bn
Me
O
N

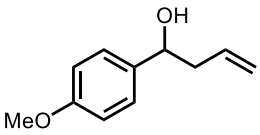

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

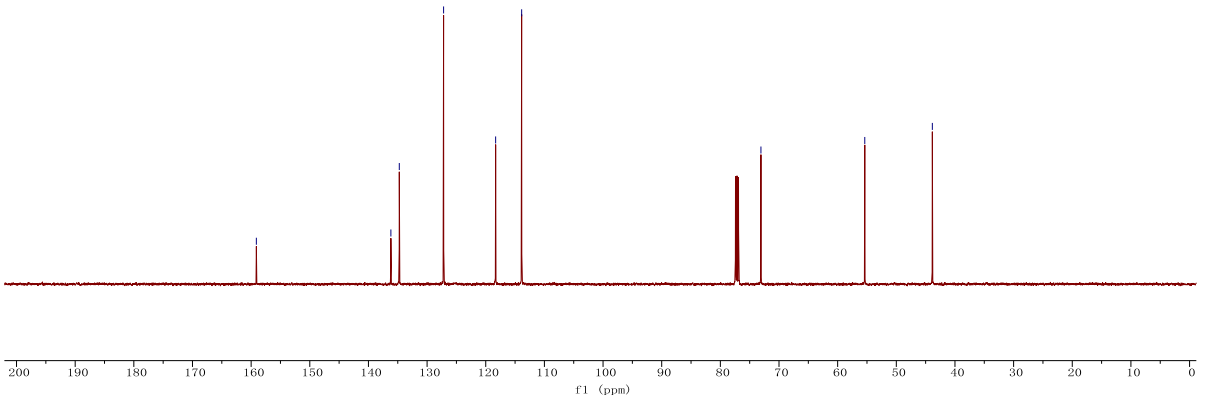

7.29
7.27
6.89
6.87
5.84
5.82
5.82
5.81
5.80
5.79
5.78
5.77
5.77
5.75
5.17
5.17
5.17
5.16
5.14
5.13
5.13
5.11
5.11
5.11
4.69
4.68
4.66
3.80
2.51
2.49
2.48
2.10


OH
MeO


1.95
2.03
1.00
2.03
1.02
3.12
2.08
0.91
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)


159.11
136.17
134.74
127.19
118.31
113.88
73.08
55.38
43.86


OH
MeO


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

4. Supplemental references

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