Highly Enantioselective Friedel-Crafts Reaction of 3,5-Dimethoxylphenol with Nitroolefins Mediated by Bifunctional Quinine Derived Thiourea Catalyst

Xiaoyu Han,*[,a] Can Ye,[a] Fenfen Chen,[a] Yongjiang Wang,*[,a] Xiaofei Zeng *[,b]

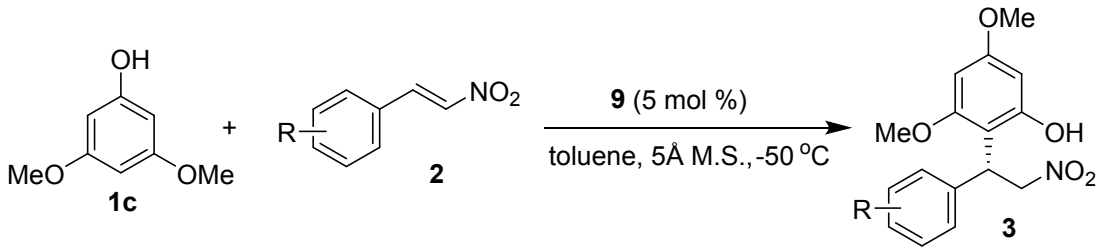
[a] *Zhejiang Provincial Key Laboratory for Chemical & Biological Processing Technology of Farm Products, School of Biological and Chemical Engineering, Zhejiang University of Science and Technolgoy, No. 318 Liuhe Road, Hangzhou, P. R. China, 310023;*
Email: chemhanxy@zust.edu.cn; yjwang@zust.edu.cn
[b] *College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, P. R. China. E-mail: chemzxf@hznu.edu.cn*

Supporting Information

A. General Information

All the starting materials were obtained from commercial sources and were used without further purification unless otherwise stated. Toluene was dried and distilled from sodium benzophenone prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. Optical rotations were measured using a Jasco DIP-1000 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (*d*-chloroform δ 7.26), carbon (*d*-chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. Enantiomeric excesses were determined by HPLC analysis on achiral stationary phase. The racemic products used to determine the ee values were synthesized by using TEA as racemic catalyst to generate racemic products.

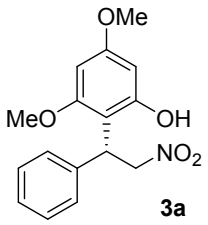
B. Representative Procedure for Quinine Derived Thiourea-mediated Friedel-Crafts Reaction



A stirred solution of 3, 5-dimethoxylphenol (0.12 mmol, 1.2 equiv.) and nitroolefin (0.1 mmol, 1.0 equiv.) in toluene 1 mL containing 5Å molecular sieves (30 mg) was cooled to -50 °C for 5 min., then catalyst **9** (0.005 mmol, 5 mol %) was added and the resulting mixture was stirred at -50 °C until the disappearance of the starting material. The mixture was directly purified by column chromatography on silica gel (hexane/EtOAc = 15:1 to 10:1) to afford the desired product **3**.

C. Analytical Data and HPLC Chromatogram of Friedel-Crafts Reaction Products

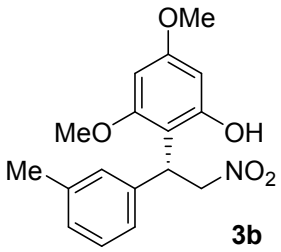
(*R*)-3,5-dimethoxy-2-(2-nitro-1-phenylethyl)phenol (**3a**)



3a

76% yield, a white solid; $[\alpha]^{20}_{D}$ = +16.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.4 Hz, 2H), 7.31–7.23 (m, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.08 (d, *J* = 2.3 Hz, 1H), 5.93 (d, *J* = 2.3 Hz, 1H), 5.45 (t, *J* = 7.9 Hz, 1H), 5.21 (dd, *J* = 7.9, 4.4 Hz, 2H), 3.78 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 159.4, 155.0, 140.1, 128.5, 127.6, 126.8, 107.3, 94.5, 91.9, 77.9, 55.8, 55.3, 38.6, 29.7; HRMS calcd for $C_{16}H_{18}NO_5$ $[M + 1]^+$ = 304.1185, found = 304.1186; the ee value was 91%, t_R (major) = 19.6 min, t_R (minor) = 16.7 min (Chiralcel IE-H, λ = 254 nm, 5%*i*PrOH/hexanes, flow rate = 1.2 mL/min).

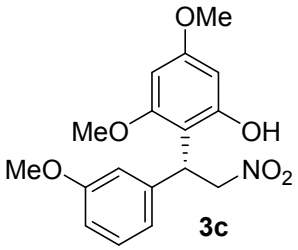
(*R)*-3,5-dimethoxy-2-(2-nitro-1-(m-tolyl)ethyl)phenol (**3b**)



3b

78% yield, a yellow oil; $[\alpha]^{20}_{D}$ = +27.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, *J* = 4.5 Hz, 3H), 7.00 (d, *J* = 6.6 Hz, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 5.90 (d, *J* = 2.3 Hz, 1H), 5.41 (t, *J* = 7.9 Hz, 1H), 5.27 (d, *J* = 6.9 Hz, 1H), 5.18 (d, *J* = 7.9 Hz, 2H), 3.76 (s, 3H), 3.69 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 159.4, 155.1, 139.9, 138.1, 128.4, 128.4, 127.7, 124.5, 107.3, 94.5, 91.9, 78.0, 55.8, 55.3, 38.6, 21.5; HRMS calcd for $C_{17}H_{20}NO_5$ $[M + H]^+$= 318.1341, found = 318.1337; the ee value was 90%, t_R (major) =16.041min, t_R (minor) = 13.671min (Chiralpak ID-H, i-PrOH/hexane = 5/95, flow rate = 1.2mL/min, λ = 254 nm).

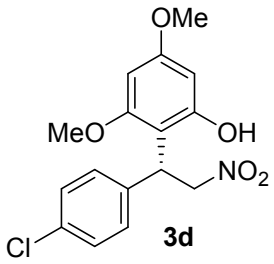
(*R*)-3,5-dimethoxy-2-(1-(3-methoxyphenyl)-2-nitroethyl)phenol (**3c**)



3c

85% yield, a yellow oil; $[\alpha]^{20}_{D}$ = +23.7(*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.9 Hz, 1H), 7.03–6.79 (m, 2H), 6.74 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.06 (d, *J* = 2.3 Hz, 1H), 5.90 (d, *J* = 2.3 Hz, 1H), 5.41 (dd, *J* = 17.0, 9.2 Hz, 2H), 5.19 (dd, *J* = 7.9, 2.8 Hz, 2H), 3.76 (d, *J* = 7.8 Hz, 6H), 3.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 159.6, 159.4, 155.2, 141.8, 129.5, 120.0, 114.0, 111.8, 107.1, 94.5, 91.9, 77.9, 55.8, 55.3, 55.2, 38.7; HRMS calcd for $C_{17}H_{20}NO_6$ $[M + 1]^+$ = 334.1291, found = 334.1288; the ee value was 98%, t_R (major) = 9.69 min, t_R (minor) = 7.39 min (Chiralcel ID-H, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

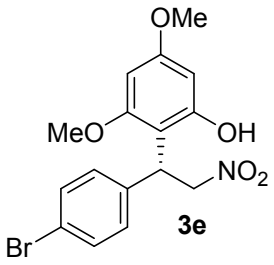
(*R*)-2-(1-(4-chlorophenyl)-2-nitroethyl)-3,5-dimethoxyphenol (**3d**)



3d

78% yield, a white solid; $[\alpha]^{20}_{D}$ = -25.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.5 Hz, 2H), 7.15–7.09 (m, 2H), 5.97 (d, *J* = 2.3 Hz, 1H), 5.84 (d, *J* = 2.3 Hz, 1H), 5.31 (t, *J* = 7.8 Hz, 1H), 5.14 (dd, *J* = 12.9, 8.2 Hz, 1H), 5.03 (dd, *J* = 12.9, 7.5 Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 159.3, 154.8, 138.8, 132.5, 129.0, 128.5, 106.9, 94.4, 91.9, 77.8, 55.8, 55.3, 38.1; HRMS calcd for $C_{16}H_{17}ClNO_5$ $[M + 1]^+$ = 338.0795,found = 338.0798; the ee value was 91%, t_R (major) = 10.48 min, t_R (minor) = 9.69 min (Chiralcel ID-H, λ = 254 nm, 5%*i*PrOH/hexanes, flow rate = 1.2 mL/min).

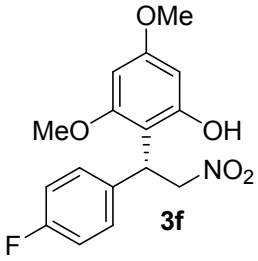
(*R*)-2-(1-(4-bromophenyl)-2-nitroethyl)-3,5-dimethoxyphenol (**3e**)



3e

81% yield, a yellow oil; $[\alpha]^{20}_{D}$ = –19.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.07 (d, *J* = 2.3 Hz, 1H), 5.93 (d, *J* = 2.3 Hz, 1H), 5.39 (t, *J* = 7.8 Hz, 2H), 5.22 (dd, *J* = 12.9, 8.2 Hz, 1H), 5.13 (dd, *J* = 12.9, 7.5 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 159.3, 154.9, 139.3, 131.5, 129.4, 120.6, 106.8, 94.4, 91.9, 77.9, 55.8, 55.3, 38.2; HRMS calcd for $C_{16}H_{17}BrNO_5$ $[M + 1]^+$ = 382.0290, found = 382.0293; the ee value was 94%, t_R (major) = 7.21 min, t_R (minor) = 6.25 min (Chiralcel ID, λ = 254 nm, 10%*i*PrOH/hexanes, flow rate = 1.2 mL/min).

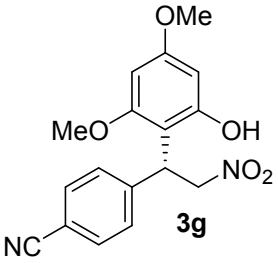
(*R*)-2-(1-(4-fluorophenyl)-2-nitroethyl)-3,5-dimethoxyphenol (**3f**)



3f

80% yield, a white solid; $[\alpha]^{20}_{D}$ = +6.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 8.6, 5.4 Hz, 2H), 6.91–6.81 (m, 2H), 5.99 (d, *J* = 2.2 Hz, 1H), 5.86 (d, *J* = 2.3 Hz, 1H), 5.33 (t, *J* = 7.9 Hz, 1H), 5.14 (dd, *J* = 12.8, 8.2 Hz, 1H), 5.06 (dd, *J* = 12.8, 7.6 Hz, 1H), 3.70 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 159.8, 159.5, 158.4, 154.0, 135.1, 135.1, 128.4, 128.3, 114.4, 114.3, 106.3, 93.6, 91.0, 77.3, 54.9, 54.4, 37.2; HRMS calcd for $C_{16}H_{17}FNO_5$ $[M + H]^+$= 322.1091, found = 322.1088; the ee value was 91%, t_R (major) = 14.46min, t_R (minor) = 12.30 min (Chiralcel ID-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.2 mL/min).

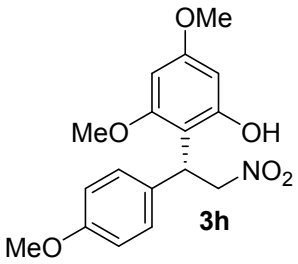
(*R*)-4-(1-(2-hydroxy-4,6-dimethoxyphenyl)-2-nitroethyl)benzonitril (**3g**)



3g

80% yield, a yellow oil; $[\alpha]^{20}_{D}$ = –23.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.50 (m, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.07 (d, *J* = 2.3 Hz, 1H), 5.97 (d, *J* = 2.3 Hz, 1H), 5.60 (s, 1H), 5.49 (dd, *J* = 8.5, 6.9 Hz, 1H), 5.33 (dd, *J* = 13.2, 8.7 Hz, 1H), 5.08 (dd, *J* = 13.2, 6.7 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 159.2, 155.0, 146.1, 132.2, 128.5, 118.9, 110.4, 106.1, 94.4, 91.8, 55.8, 55.3, 38.6, 29.7; HRMS calcd for $C_{17}H_{17}N_2O_5$ [M+ 1]$^+$ = 329.1137, found = 329.1134; the ee value was 94%, t_R (major) = 22.09 min, t_R (minor) = 17.01 min (Chiralcel ID-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1 mL/min).

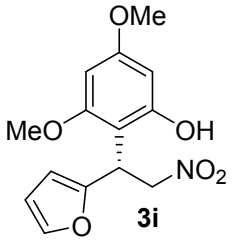
(*R*)-3,5-dimethoxy-2-(1-(4-methoxyphenyl)-2-nitroethyl)phenol (**3h**)



3h

75% yield, a yellow oil; $[\alpha]^{20}_{D}$ = +20.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 3.0 Hz, 2H), 7.19–7.17 (m, 2H), 6.74–6.71 (m, 1H), 6.71–6.68 (m, 1H), 5.97 (d, *J* = 2.3 Hz, 1H), 5.82 (d, *J* = 2.3 Hz, 1H), 5.56 (s, 1H), 5.30 (t, *J* = 7.9 Hz, 1H), 5.14–5.01 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 158.4, 157.4, 154.2, 131.4, 127.9, 113.0, 106.6, 93.6, 90.9, 77.5, 54.9, 54.4, 37.3; HRMS calcd for $C_{17}H_{20}NO_6$[M + H]$^+$ = 334.1291, found = 334.1292; the ee value was 90%, t_R (major) = 35.09 min, t_R (minor) = 29.34 min (Chiralpak ID-H, i-PrOH/hexane = 5/95, flow rate = 1.2mL/min, λ = 254 nm).

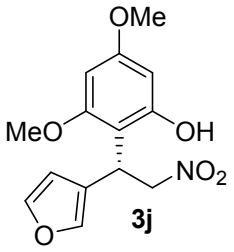
(*R*)-2-(1-(furan-2-yl)-2-nitroethyl)-3,5-dimethoxyphenol (**3i**)



3i

77% yield, a yellow oil; $[\alpha]^{20}_{D}$ = +17.68 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 1.1 Hz, 1H), 6.28 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.10 (d, *J* = 2.2 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 5.99 (d, *J* = 2.3 Hz, 1H), 5.55 (t, *J* = 7.6 Hz, 1H), 5.45 (s, 1H), 5.19 (dd, *J* = 12.9, 7.9 Hz, 1H), 4.97 (dd, *J* = 12.9, 7.4 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.8, 159.4, 155.6, 152.8, 141.7, 110.5, 106.3, 104.4, 94.7, 92.1, 76.2, 55.9, 55.3, 33.1; HRMS calcd for $C_{14}H_{16}NO_6$ $[M + H]^+$ = 294.0978, found = 294.0977; the ee value was 90%, t_R (major) = 17.99 min, t_R (minor) = 16.05 min (Chiralpak ID-H, i-PrOH/hexane = 5/95, flow rate = 1.2mL/min, λ = 254 nm).

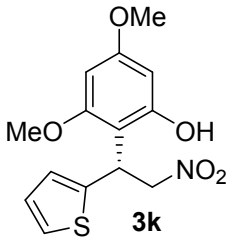
(*R*)-2-(1-(furan-3-yl)-2-nitroethyl)-3,5-dimethoxyphenol (**3j**)



3j

72% yield, a yellow oil; $[\alpha]^{20}_{D}$ = +10.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 2H), 6.35 (d, *J* = 0.5 Hz, 1H), 6.09 (d, *J* = 2.3 Hz, 1H), 5.95 (d, *J* = 2.3 Hz, 1H), 5.33 (t, *J* = 7.7 Hz, 1H), 5.07 (dd, *J* = 12.6, 8.1 Hz, 1H), 5.01 (dd, *J* = 12.6, 7.5 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 159.3, 155.2, 142.9, 139.6, 123.9, 110.4, 106.3, 94.5, 91.8, 78.1, 55.8, 55.3, 30.4; HRMS calcd for $C_{14}H_{16}NO_6$ $[M + H]^+$ = 294.0978, found = 294.0980; the ee value was 90%, t_R (major) = 11.60 min, t_R (minor) = 13.68 min, (Chiralpak IC-H, i-PrOH/hexane = 5/95, flow rate = 1.2mL/min, λ = 254 nm).

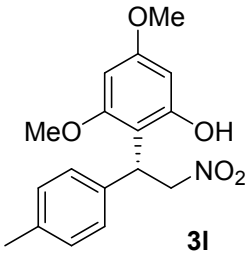
(*R*)-3,5-dimethoxy-2-(2-nitro-1-(thiophen-2-yl)ethyl)phenol (**3k**)



3k

68% yield, a yellow oil; $[\alpha]^{20}_{D}$ = –32.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.01–6.83 (m, 1H), 6.09 (d, *J* = 2.3 Hz, 1H), 5.95 (d, *J* = 2.3 Hz, 1H), 5.70 (t, *J* = 7.7 Hz, 1H), 5.16 (m, 3H), 3.81 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 159.3, 154.9, 143.1, 126.5, 124.9, 124.4, 106.8, 94.5, 91.9, 78.6, 55.8, 55.3, 34.6; HRMS calcd for $C_{14}H_{16}NO_5S$ $[M + 1]^+$ = 310.0749, found = 310.0744; the ee value was 89%, t_R (major) = 19.22min, t_R (minor) = 15.28min (Chiralpak ID-H, i-PrOH/hexane = 5/95, flow rate = 1.2 mL/min, λ = 254 nm).

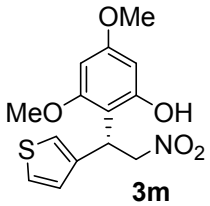
(*R*)-3,5-dimethoxy-2-(2-nitro-1-(p-tolyl)ethyl)phenol (**3l**)



3l

76% yield, a light yellow oil; $[\alpha]^{20}_{D}$ = +14.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 5.99 (d, *J* = 2.3 Hz, 1H), 5.83 (d, *J* = 2.3 Hz, 1H), 5.33 (t, *J* = 7.9 Hz, 1H), 5.10 (dd, *J* = 7.9, 2.2 Hz, 2H), 3.69 (s, 3H), 3.63 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 159.4, 155.0, 136.9, 136.5, 129.3, 127.4, 107.4, 94.5, 94.2, 91.9, 78.00, 55.78, 55.35, 55.29, 38.30, 21.01; HRMS calcd for $C_{17}H_{20}NO_5$ $[M + H]^+$ = 318.1341, found = 318.1337; the ee value was 93%, t_R (major) = 16.041 min, t_R (minor) = 13.671 min (Chiralpak ID-H, λ=254nm, 5% *i*-PrOH/hexanes, flow rate = 1.2mL/min).

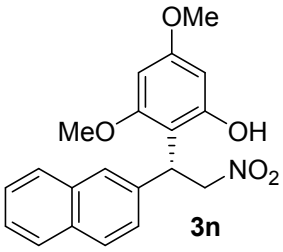
(*S*)-3,5-dimethoxy-2-(2-nitro-1-(thiophen-3-yl)ethyl)phenol (**3m**)



3m

99% yield, a white solid; $[\alpha]^{20}_{D}$ = +60.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.13–7.05 (m, 1H), 7.02 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.08 (d, *J* = 2.3 Hz, 1H), 5.94 (d, *J* = 2.3 Hz, 1H), 5.51 (t, *J* = 7.8 Hz, 1H), 5.37 (s, 1H), 5.18 (dd, *J* = 12.7, 7.9 Hz, 1H), 5.11 (dd, *J* = 12.7, 7.7 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 159.3, 155.2, 140.3, 127.6, 125.7, 121.1, 106.7, 94.5, 91.9, 78.0, 55.8, 55.3, 34.7; HRMS calcd for $C_{14}H_{16}NO_5S$ $[M + H]^+$ = 310.0749, found = 310.0749; the ee value was 90%, t_R (major)= 17.693min, t_R (minor) = 14.920min (Chiralpak ID-H, λ = 254 nm, 5% *i*-PrOH/hexanes , flow rate = 1.2mL/min).

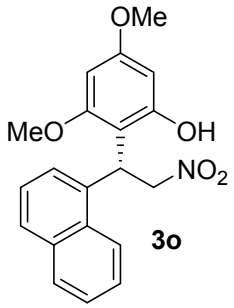
(*R*)-3,5-dimethoxy-2-(1-(naphthalen-2-yl)-2-nitroethyl)phenol (**3n**)



3n

82% yield, a light yellow oil; $[\alpha]^{20}_{D}$ = +55.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.57 (m, 4H), 7.53–7.29 (m, 3H), 6.01 (d, *J* = 2.3 Hz, 1H), 5.87 (d, *J* = 2.3 Hz, 1H), 5.53 (t, *J* = 7.8 Hz, 1H), 5.28 (dd, *J* = 12.9, 8.0 Hz, 1H), 5.18 (dd, *J* = 12.9, 7.7 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 158.6, 154.3, 136.7, 132.4, 131.5, 127.4, 126.9, 126.6, 125.4, 125.2, 124.9, 124.8, 106.3, 93.7, 91.1, 76.9, 54.9, 54.4, 37.8, 28.8; HRMS calcd for $C_{20}H_{20}NO_5$ $[M + H]^+$ = 354.1341, found = 354.1342; the ee value was 93%, t_R (major) = 26.098min, t_R (minor) = 20.281min (Chiralpak ID-H, λ = 254 nm, 5% *i*-PrOH/hexanes, flow rate = 1.2mL/min).

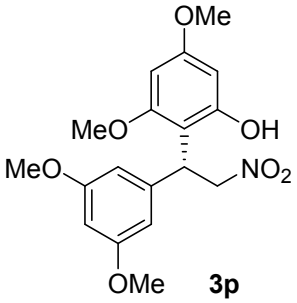
(*R*)-3,5-dimethoxy-2-(1-(naphthalen-1-yl)-2-nitroethyl)phenol (**3o**)



3o

70% yield, a yellow oil; $[\alpha]^{20}_{D}$ = –31.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.49 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.44 (dd, *J* = 10.9, 3.9 Hz, 1H), 7.41–7.35 (m, 1H), 6.16 (t, *J* = 8.0 Hz, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 5.87 (d, *J* = 2.3 Hz, 1H), 5.30 (dd, *J* = 12.8, 8.6 Hz, 1H), 5.19 (dd, *J* = 12.8, 7.3 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 159.4, 155.9, 135.1, 134.1, 131.7, 128.9, 128.1, 126.5, 125.8, 125.1, 124.9, 123.5, 106.3, 94.8, 92.1, 55.8, 55.2, 35.5; HRMS calcd for $C_{20}H_{20}NO_5$ $[M + 1]^+$ = 354.1341, found = 354.1342; the ee value was 92%, t_R (major) = 20.63 min, t_R (minor) = 17.99 min, (ChiralpakID-H, λ = 254 nm, 5% *i*-PrOH/hexanes, flow rate = 1.2 mL/min).

(*R*)-2-(1-(3,5-dimethoxyphenyl)-2-nitroethyl)-3,5-dimethoxyphenol (**3p**)



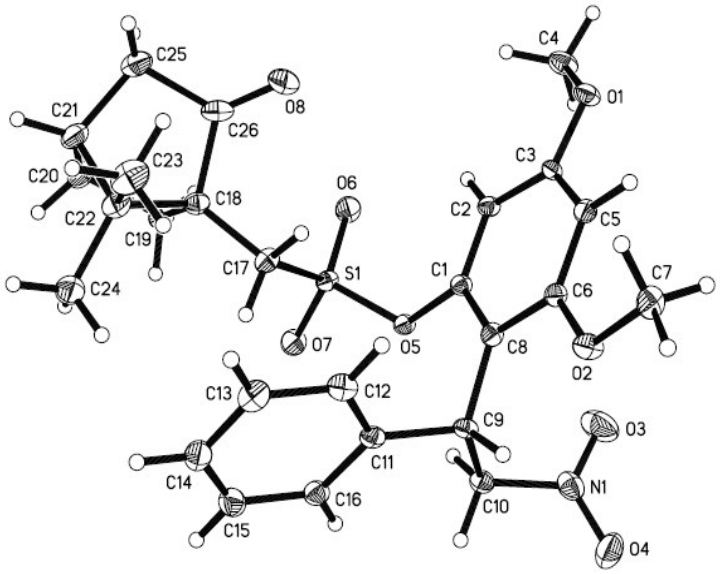
3p

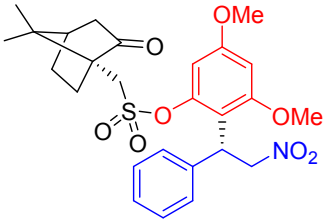
70% yield, a white solid; $[\alpha]^{20}_{D}$ = +16.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.2 Hz, 2H), 6.31 (*t*, *J* = 2.2 Hz, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 5.90 (d, *J* = 2.3 Hz, 1H), 5.45– 5.31 (m, 1H), 5.17 (dd, *J* = 7.8, 2.8 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 6H), 3.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 160.3, 159.3, 155.2, 142.5, 106.9, 106.2, 98.4, 94.5, 91.9, 77.9, 55.8, 55.3, 55.3, 38.9; HRMS calcd for $C_{18}H_{22}NO_7$ $[M + 1]^+$ = 364.1396, found = 364.1399; the ee

value was 91%, t_R (major) = 13.29 min, t_R (minor) = 11.07 min, (Chiralpak AS-H, λ = 254 nm, 10% *i*-PrOH/hexanes, flow rate = 1 mL/min).

D. Determination of Absolute Configurations of Friedel-Crafts Products

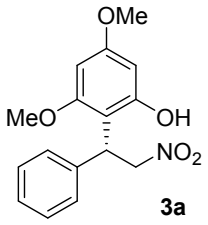
The X-ray structure of the Michael addition product derivative



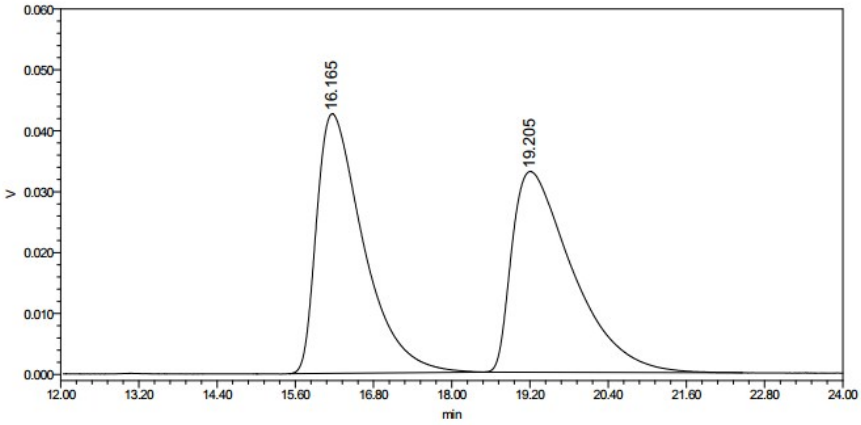


E. HPLC Chromatogram Spectra of the Friedel-Crafts Products

(*R*)-3,5-dimethoxy-2-(2-nitro-1-phenylethyl)phenol (**3a**)

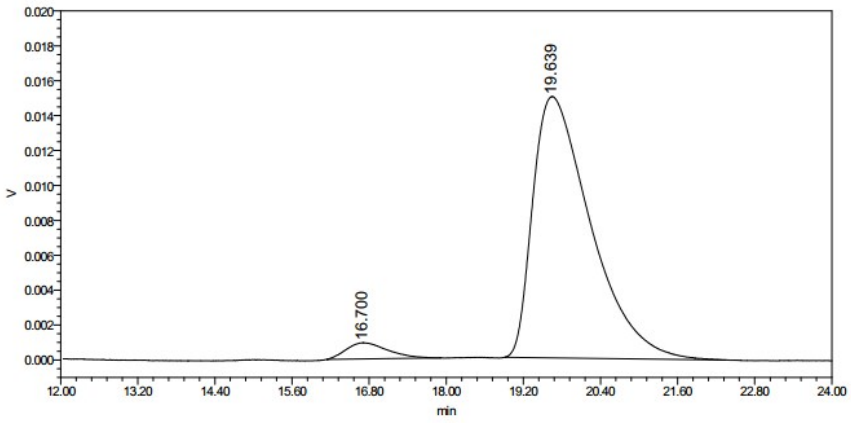


3a



	RT	Area	Height	% Area	% Height
1	16.165	2124087	42599	49.88	56.39
2	19.205	2134610	32943	50.12	43.61

Racemic **3a**

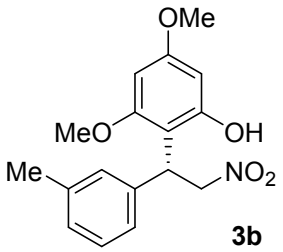


254nm

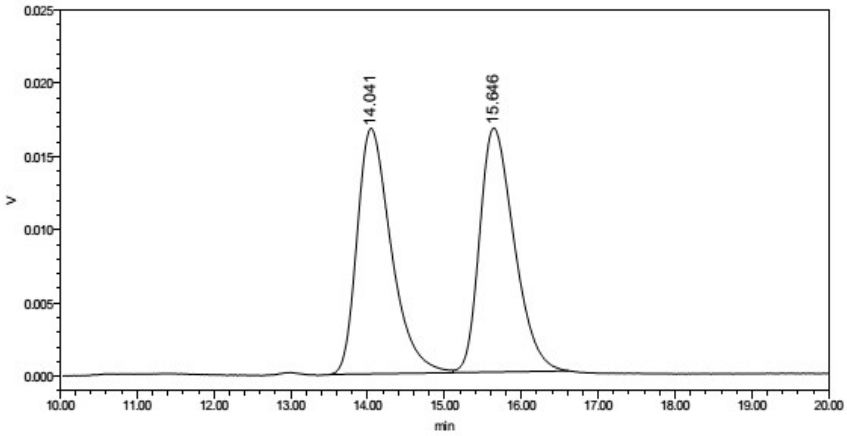
	RT	Area	Height	% Area	% Height
1	16.700	41077	922	4.20	5.80
2	19.639	937413	14977	95.80	94.20

Enantiomerically enriched **3a**

(*R*)-3,5-dimethoxy-2-(2-nitro-1-(m-tolyl)ethyl)phenol (**3b**)



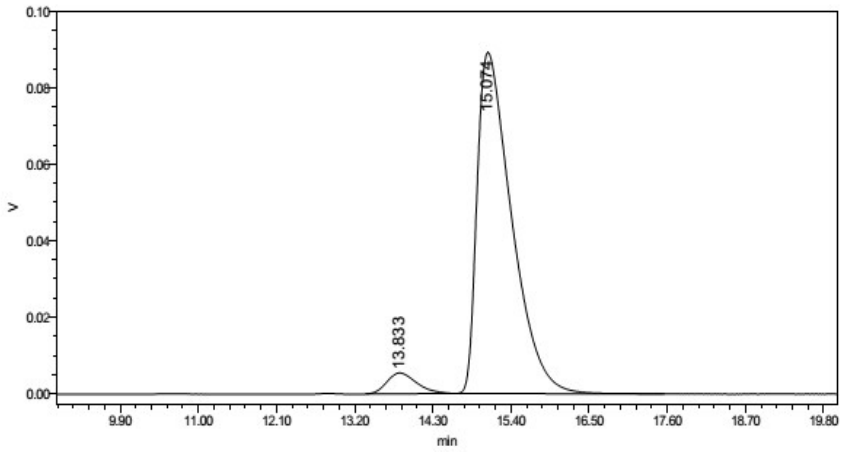
3b



254nm

	RT	Area	Height	% Area	% Height
1	14.041	516953	16762	49.90	50.15
2	15.646	519104	16659	50.10	49.85

Racemic **3b**

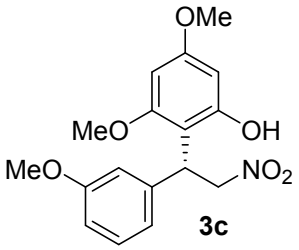


254nm

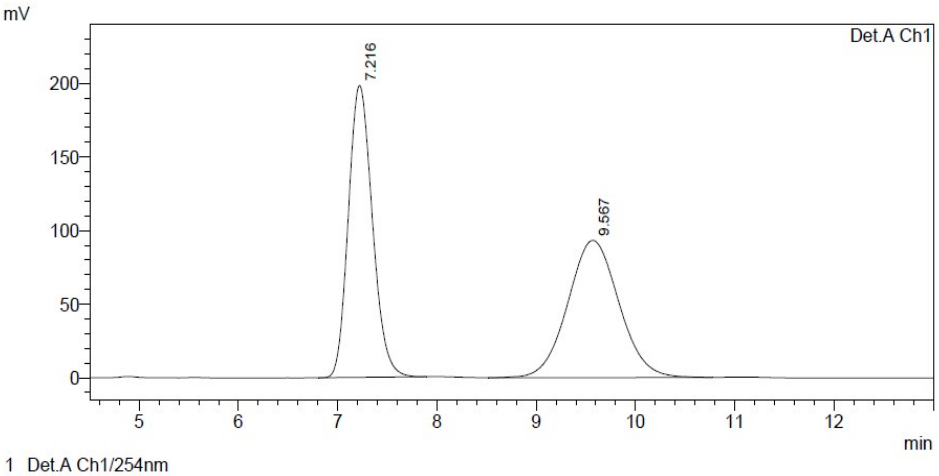
	RT	Area	Height	% Area	% Height
1	13.833	158618	5445	5.00	5.76
2	15.074	3012693	89139	95.00	94.24

Enantiomerically enriched **3b**

(*R*)-3,5-dimethoxy-2-(1-(3-methoxyphenyl)-2-nitroethyl)phenol (**3c**)



3c



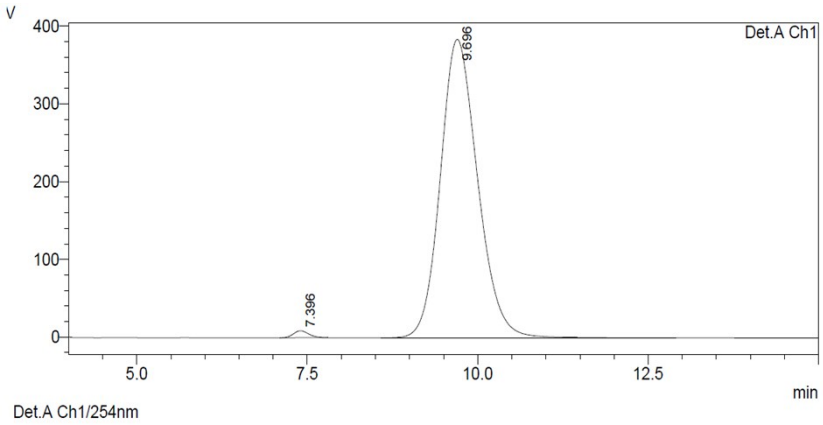
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.216	3347810	198356	49.984	68.022
2	9.567	3349924	93248	50.016	31.978
Total		6697733	291604	100.000	100.000

Racemic **3c**



Det.A Ch1/254nm

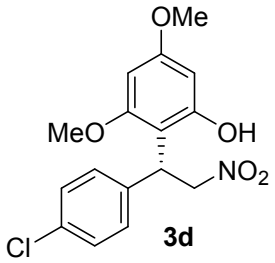
PeakTable

Detector A Ch1 254nm

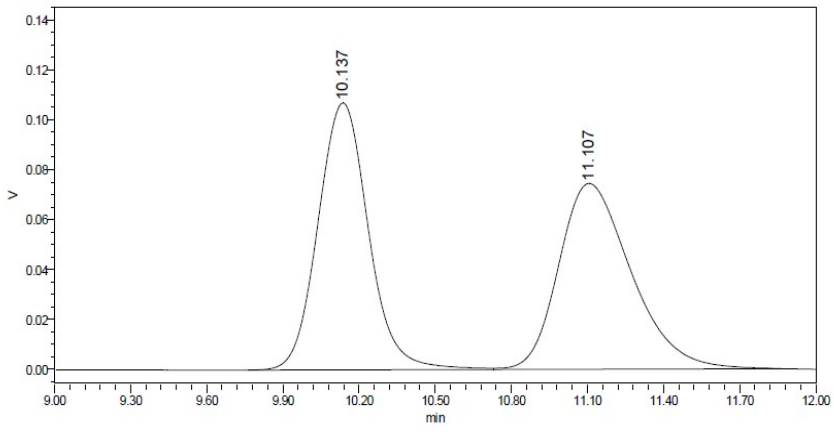
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.396	139136	8959	0.943	2.280
2	9.696	14612305	383950	99.057	97.720
Total		14751441	392909	100.000	100.000

Enantiomerically enriched **3c**

(*R*)-2-(1-(4-chlorophenyl)-2-nitroethyl)-3,5-dimethoxyphenol (**3d**)



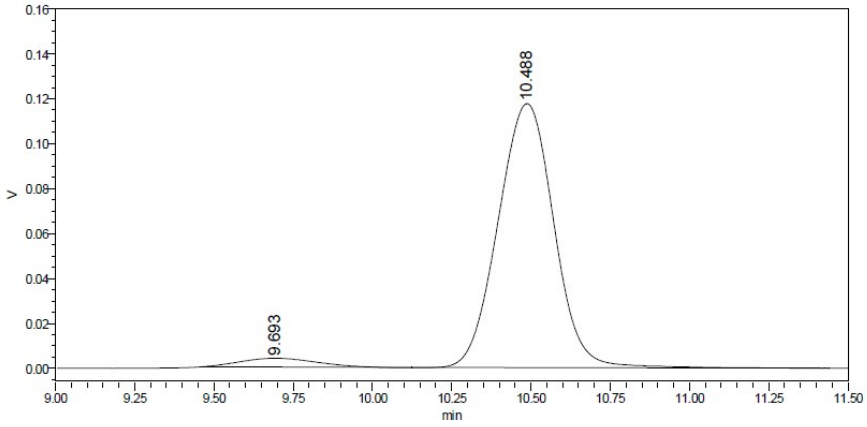
3d



254nm

	RT	Area	Height	% Area	% Height
1	10.137	1480636	106986	50.03	58.95
2	11.107	1478978	74507	49.97	41.05

Racemic **3d**

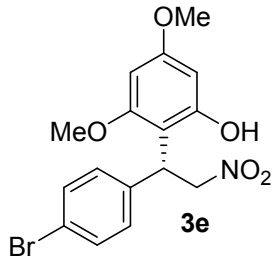


254nm

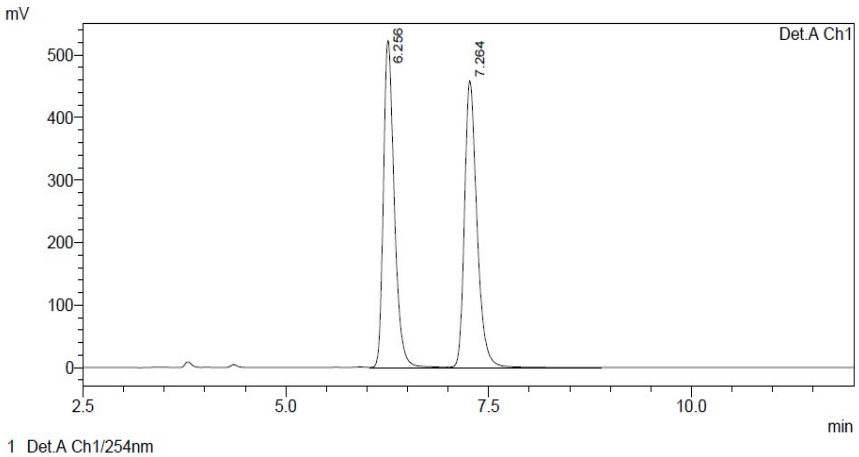
	RT	Area	Height	% Area	% Height
1	9.693	65840	3903	4.38	3.22
2	10.488	1435675	117472	95.62	96.78

Enantiomerically enriched **3d**

(*R*)-2-(1-(4-bromophenyl)-2-nitroethyl)-3,5-dimethoxyphenol (**3e**)



3e



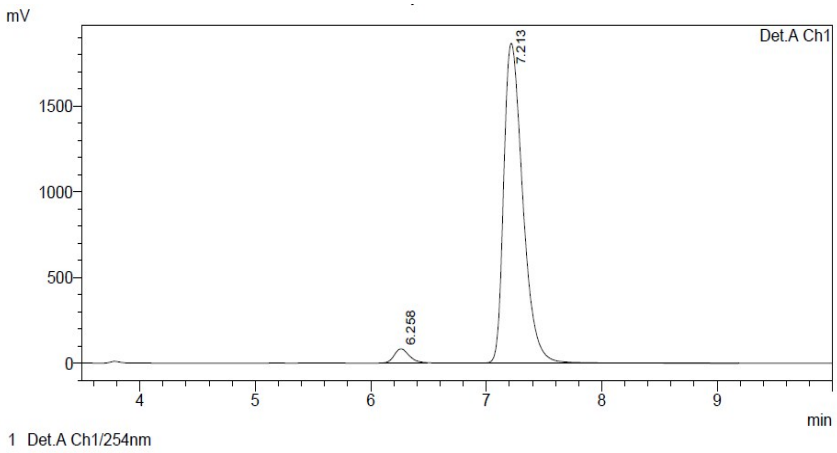
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.256	4876100	523524	49.910	53.300
2	7.264	4893734	458704	50.090	46.700
Total		9769834	982228	100.000	100.000

Racemic **3e**



1 Det.A Ch1/254nm

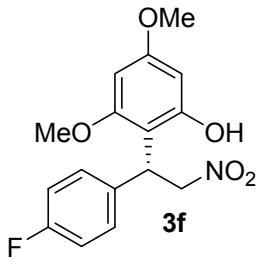
PeakTable

Detector A Ch1 254nm

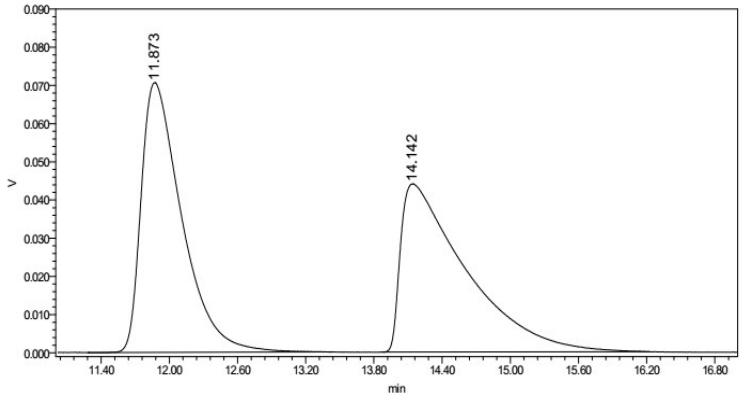
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.258	709992	81342	3.216	4.177
2	7.213	21365813	1865812	96.784	95.823
Total		22075806	1947153	100.000	100.000

Enantiomerically enriched **3e**

(*R*)-2-(1-(4-fluorophenyl)-2-nitroethyl)-3,5-dimethoxyphenol (**3f**)



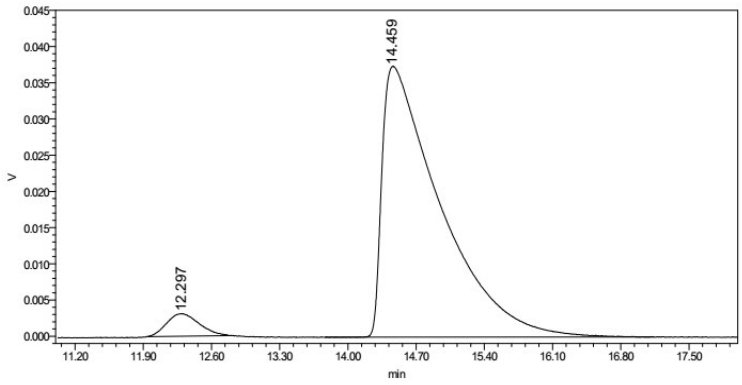
3f



254nm

	RT	Area	Height	% Area	% Height
1	11.873	1750622	70575	49.93	61.59
2	14.142	1755709	44019	50.07	38.41

Racemic **3f**

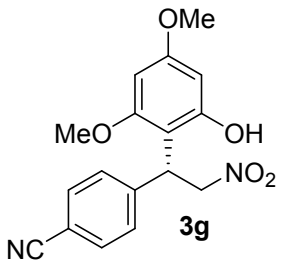


254nm

	RT	Area	Height	% Area	% Height
1	12.297	71662	3094	4.41	7.65
2	14.459	1553450	37371	95.59	92.35

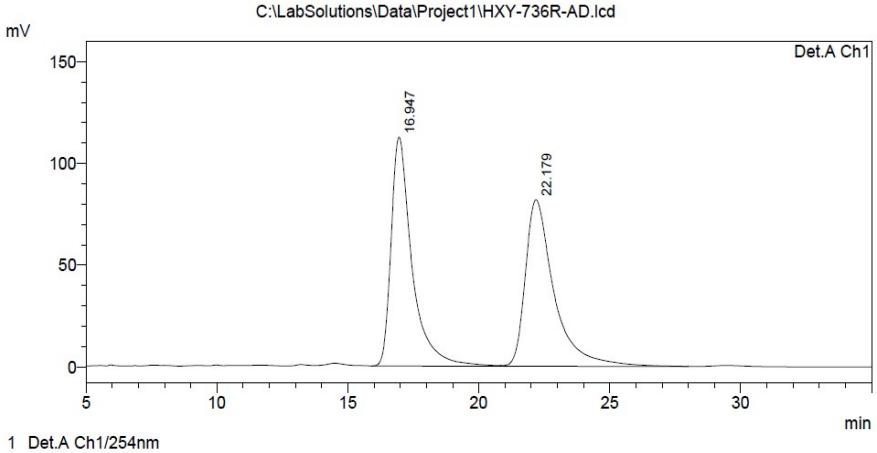
Enantiomerically enriched **3f**

(*R*)-4-(1-(2-hydroxy-4,6-dimethoxyphenyl)-2-nitroethyl)benzonitril (**3g**)



3g

C:\LabSolutions\Data\Project1\HXY-736R-AD.lcd



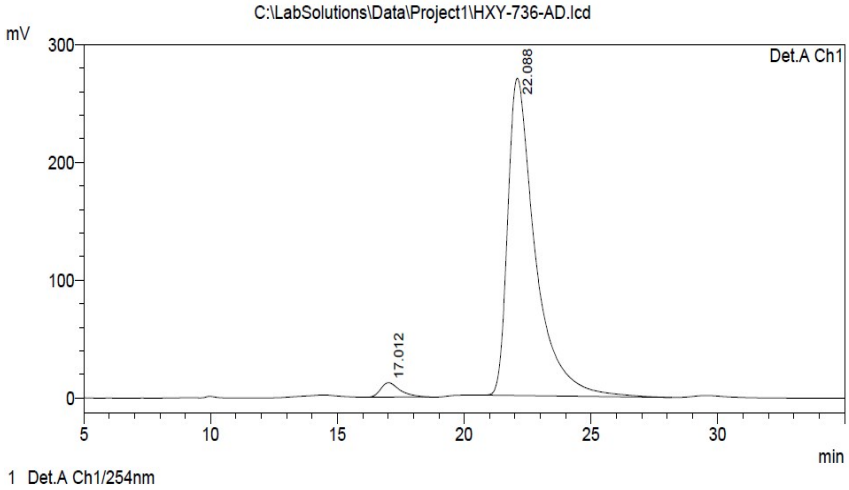
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.947	6235154	112356	49.969	57.877
2	22.179	6242767	81772	50.031	42.123
Total		12477921	194128	100.000	100.000

Racemic **3g**



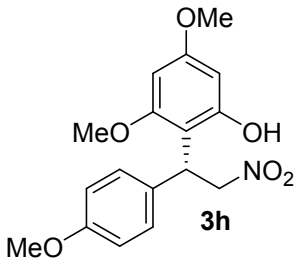
PeakTable

Detector A Ch1 254nm

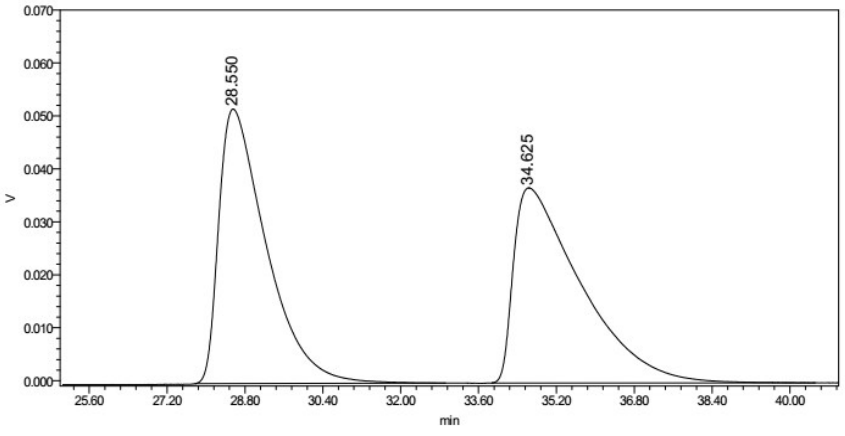
Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.012	647506	12280	3.081	4.362
2	22.088	20366756	269239	96.919	95.638
Total		21014262	281519	100.000	100.000

Enantiomerically enriched **3g**

(*R*)-3,5-dimethoxy-2-(1-(4-methoxyphenyl)-2-nitroethyl)phenol (**3h**)



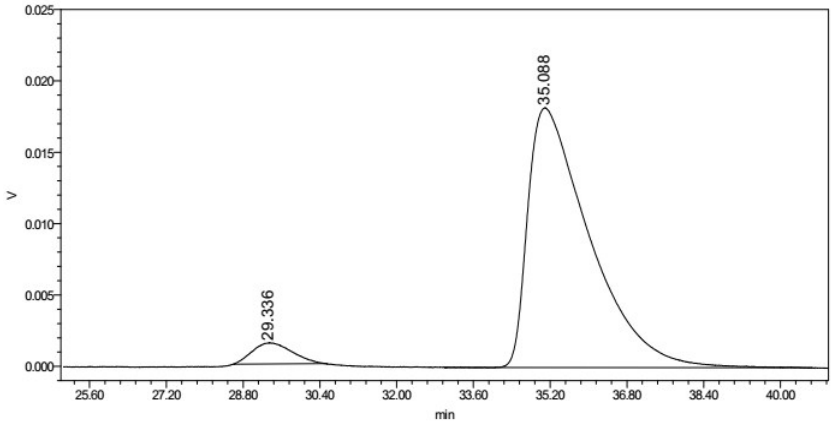
3h



254nm

	RT	Area	Height	% Area	% Height
1	28.550	3521339	51835	49.86	58.46
2	34.625	3541049	36827	50.14	41.54

Racemic **3h**

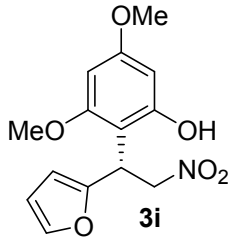


254nm

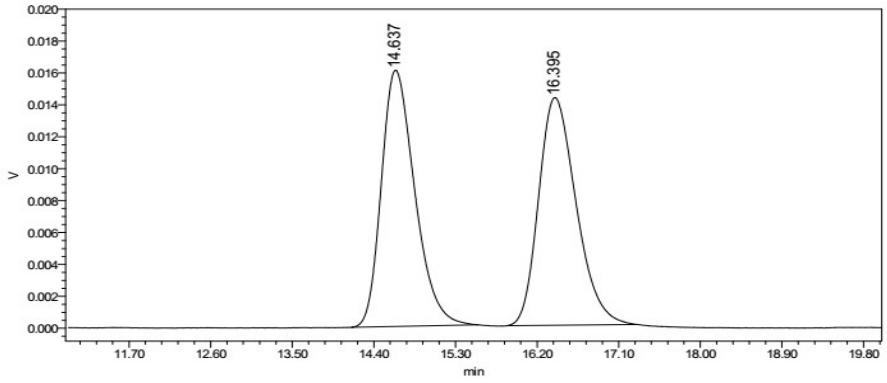
	RT	Area	Height	% Area	% Height
1	29.336	84597	1474	4.94	7.49
2	35.088	1627844	18196	95.06	92.51

Enantiomerically enriched **3h**

(*R*)-2-(1-(furan-2-yl)-2-nitroethyl)-3,5-dimethoxyphenol (**3i**)



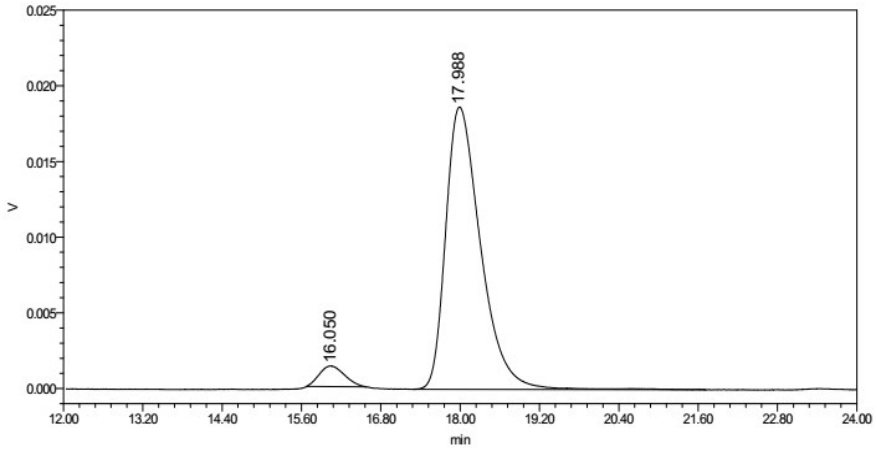
3i



254nm

	RT	Area	Height	% Area	% Height
1	14.637	411894	16055	50.09	52.96
2	16.395	410475	14262	49.91	47.04

Racemic **3i**

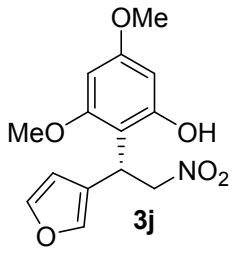


254nm

	RT	Area	Height	% Area	% Height
1	16.050	35896	1357	4.98	6.78
2	17.988	685275	18651	95.02	93.22

Enantiomerically enriched **3i**

(*R*)-2-(1-(furan-3-yl)-2-nitroethyl)-3,5-dimethoxyphenol (**3j**)

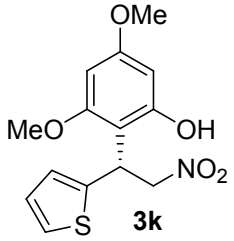


3j

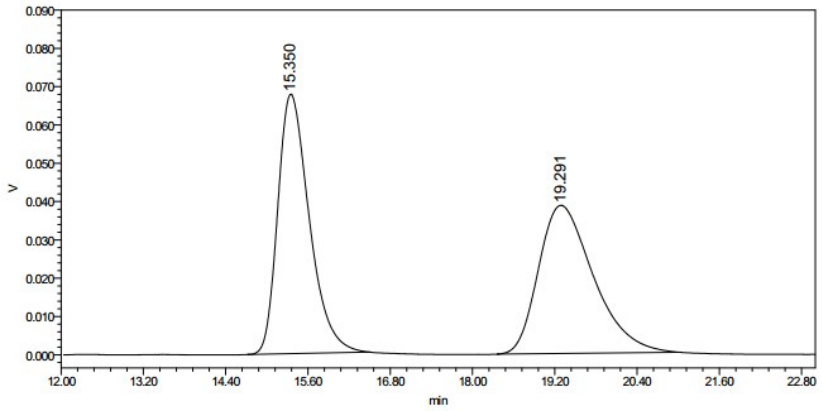
Racemic **3j**

Enantiomerically enriched **3j**

(*R*)-3,5-dimethoxy-2-(2-nitro-1-(thiophen-2-yl)ethyl)phenol (**3k**)



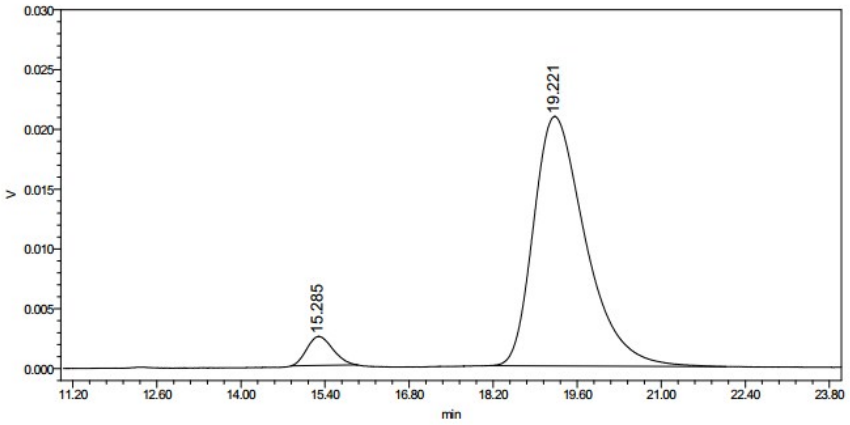
3k



254nm

	RT	Area	Height	% Area	% Height
1	15.350	2164288	67746	50.13	63.66
2	19.291	2153493	38679	49.87	36.34

Racemic **3k**

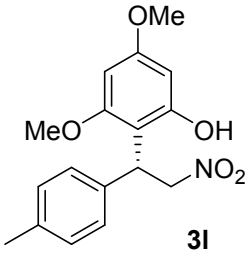


254nm

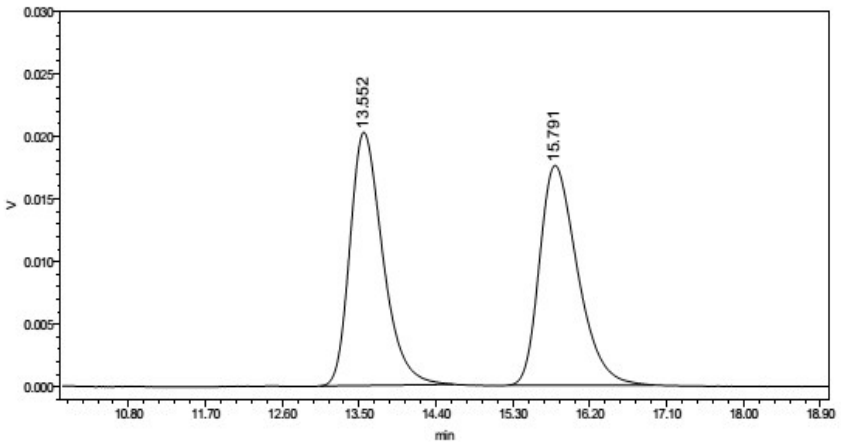
	RT	Area	Height	% Area	% Height
1	15.285	72761	2424	5.48	10.41
2	19.221	1253945	20856	94.52	89.59

Enantiomerically enriched **3k**

(*R*)-3,5-dimethoxy-2-(2-nitro-1-(p-tolyl)ethyl)phenol (**3l**)



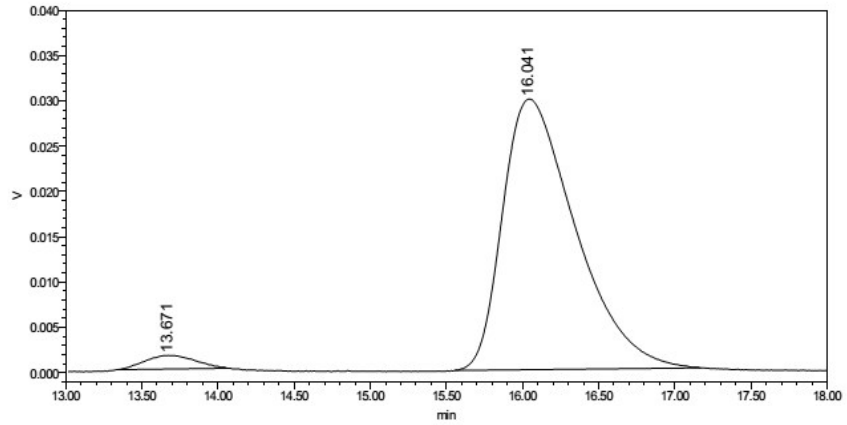
3l



254nm

	RT	Area	Height	% Area	% Height
1	13.552	540976	20230	49.93	53.56
2	15.791	542566	17541	50.07	46.44

Racemic **3l**

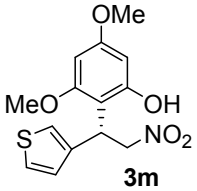


254nm

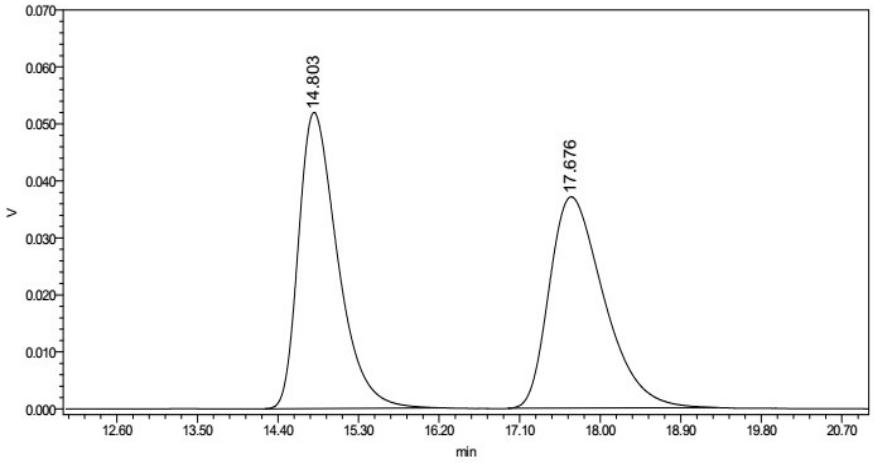
	RT	Area	Height	% Area	% Height
1	13.671	34944	1512	3.39	4.82
2	16.041	995680	29887	96.61	95.18

Enantiomerically enriched **3l**

(*S*)-3,5-dimethoxy-2-(2-nitro-1-(thiophen-3-yl)ethyl)phenol (**3m**)



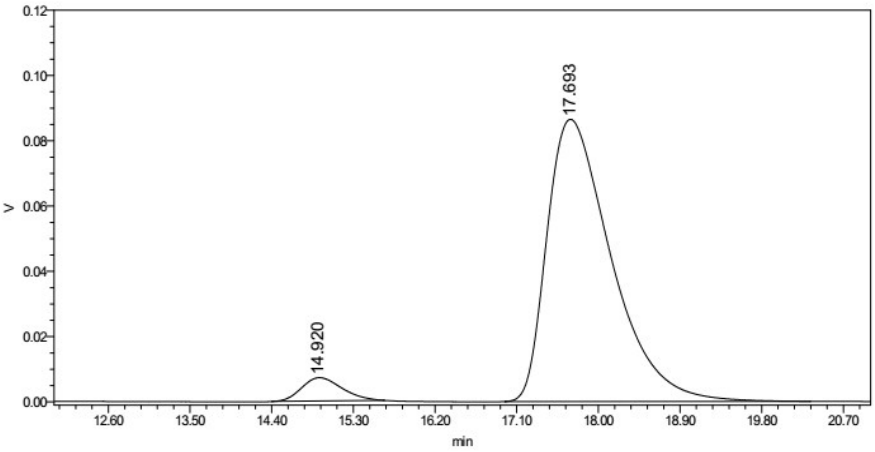
3m



254nm

	RT	Area	Height	% Area	% Height
1	14.803	1573945	51943	50.06	58.35
2	17.676	1570095	37077	49.94	41.65

Racemic **3m**

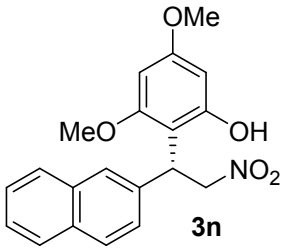


254nm

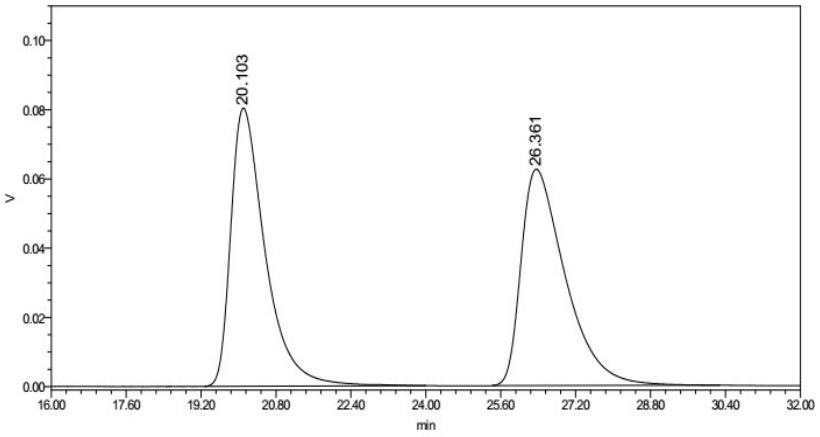
	RT	Area	Height	% Area	% Height
1	14.920	220241	7150	4.93	7.64
2	17.693	4248561	86441	95.07	92.36

Enantiomerically enriched **3m**

(*R*)-3,5-dimethoxy-2-(1-(naphthalen-2-yl)-2-nitroethyl)phenol (**3n**)



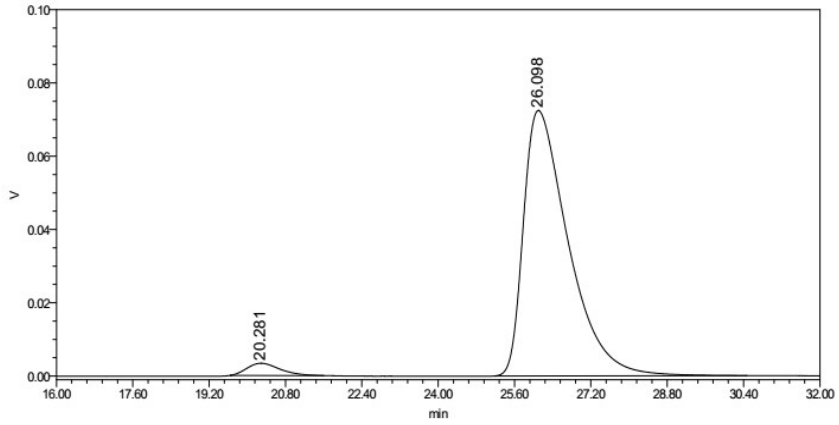
3n



254nm

	RT	Area	Height	% Area	% Height
1	20.103	4102917	80364	49.99	56.26
2	26.361	4104477	62476	50.01	43.74

Racemic **3n**

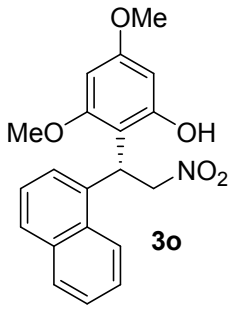


254nm

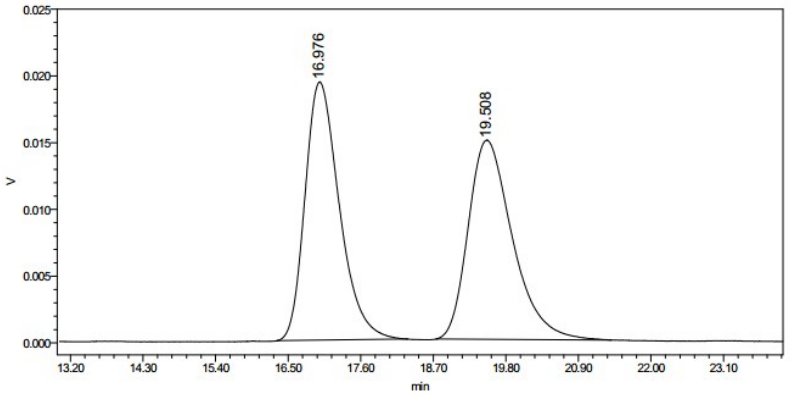
	RT	Area	Height	% Area	% Height
1	20.281	157888	3324	3.24	4.39
2	26.098	4720967	72411	96.76	95.61

Enantiomerically enriched **3n**

(*R*)-3,5-dimethoxy-2-(1-(naphthalen-1-yl)-2-nitroethyl)phenol (**3o**)



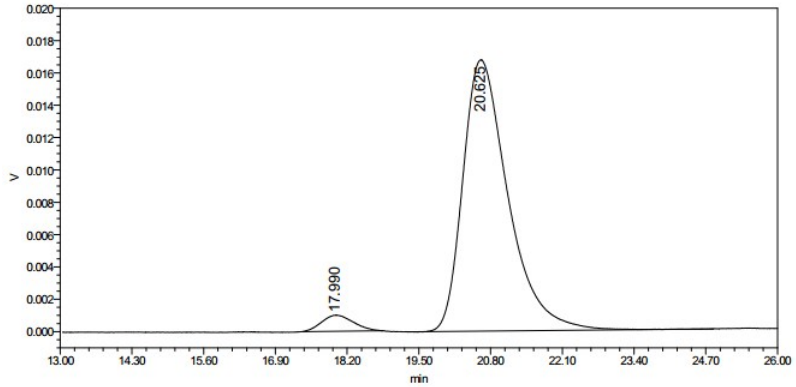
3o



254nm

	RT	Area	Height	% Area	% Height
1	16.976	698732	19329	50.14	56.44
2	19.508	694934	14917	49.86	43.56

Racemic **3o**

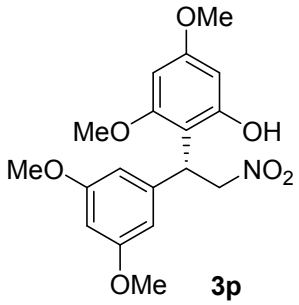


254nm

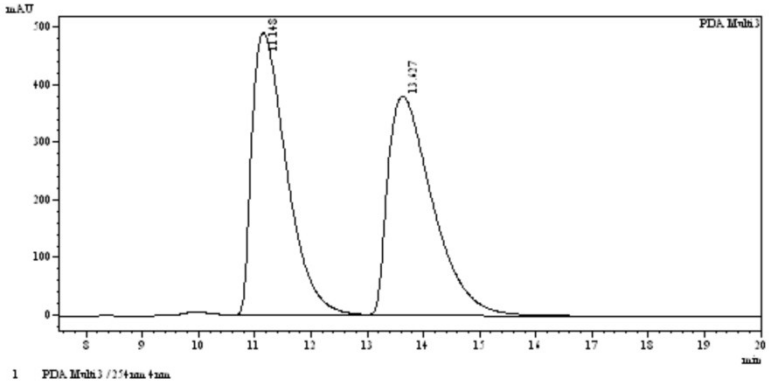
	RT	Area	Height	% Area	% Height
1	17.990	39545	996	3.98	5.61
2	20.625	954015	16775	96.02	94.39

Enantiomerically enriched **3o**

(*R*)-2-(1-(3,5-dimethoxyphenyl)-2-nitroethyl)-3,5-dimethoxyphenol (**3p**)



3p

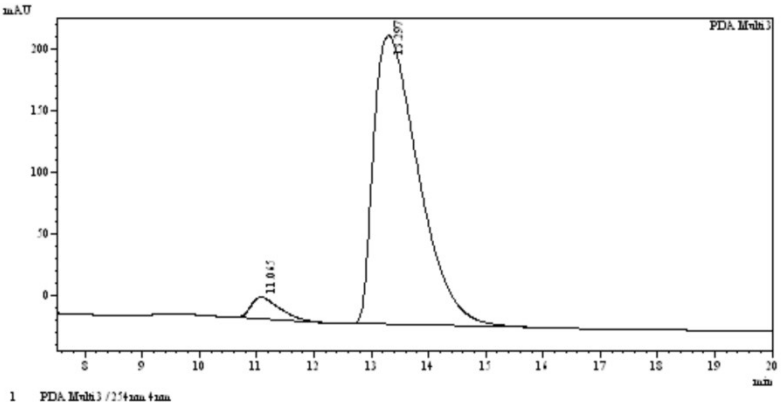


PeakTable

PDA Ch3 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.148	21100237	490326	49.961	56.297
2	13.627	21132991	380635	50.039	43.703
Total		42233228	870961	100.000	100.000

Racemic **3o**



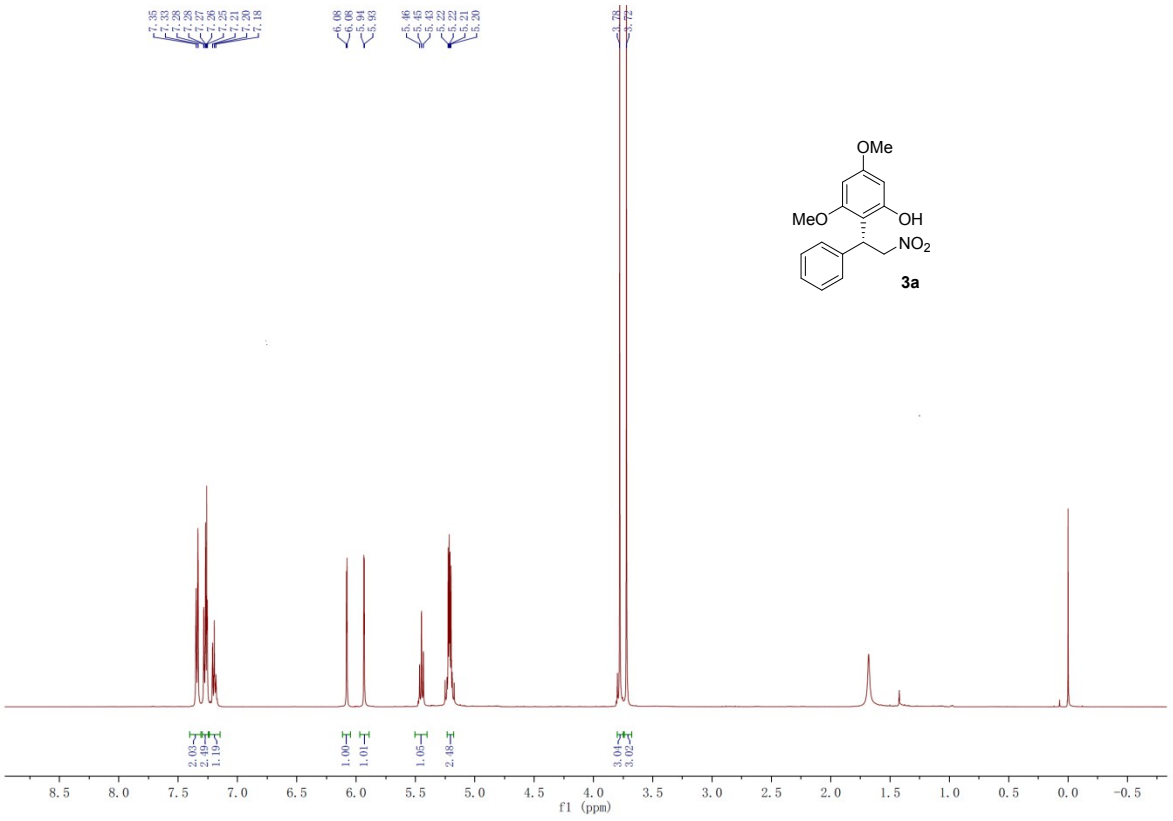
PeakTable

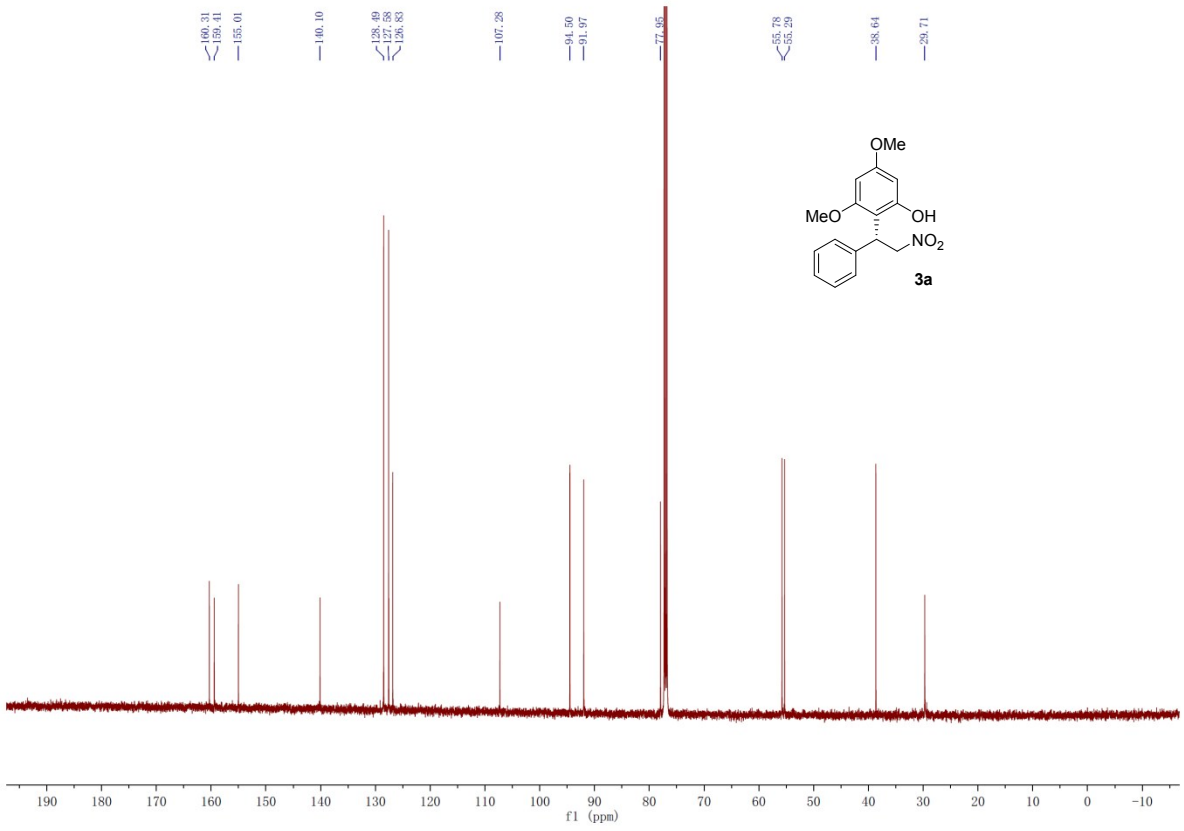
PDA Ch3 254nm 4nm

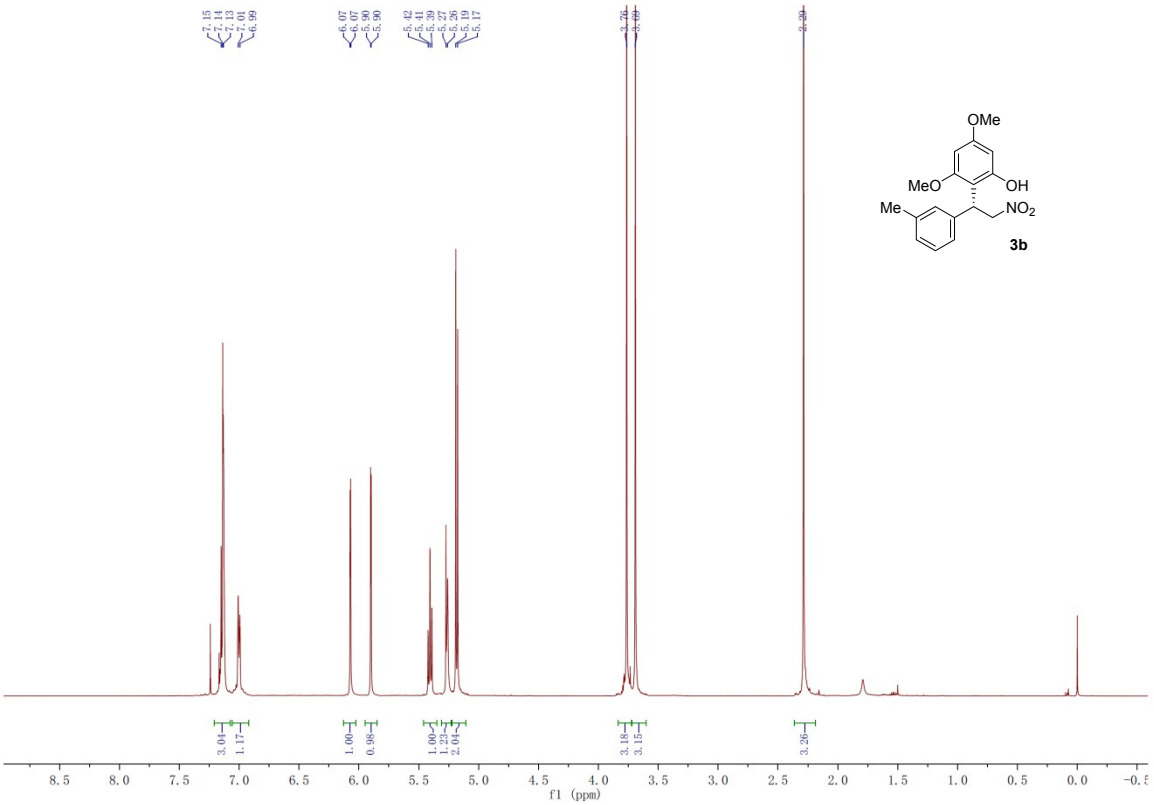
Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.065	631714	18023	4.692	7.131
2	13.297	12830946	234704	95.308	92.869
Total		13462660	252727	100.000	100.000

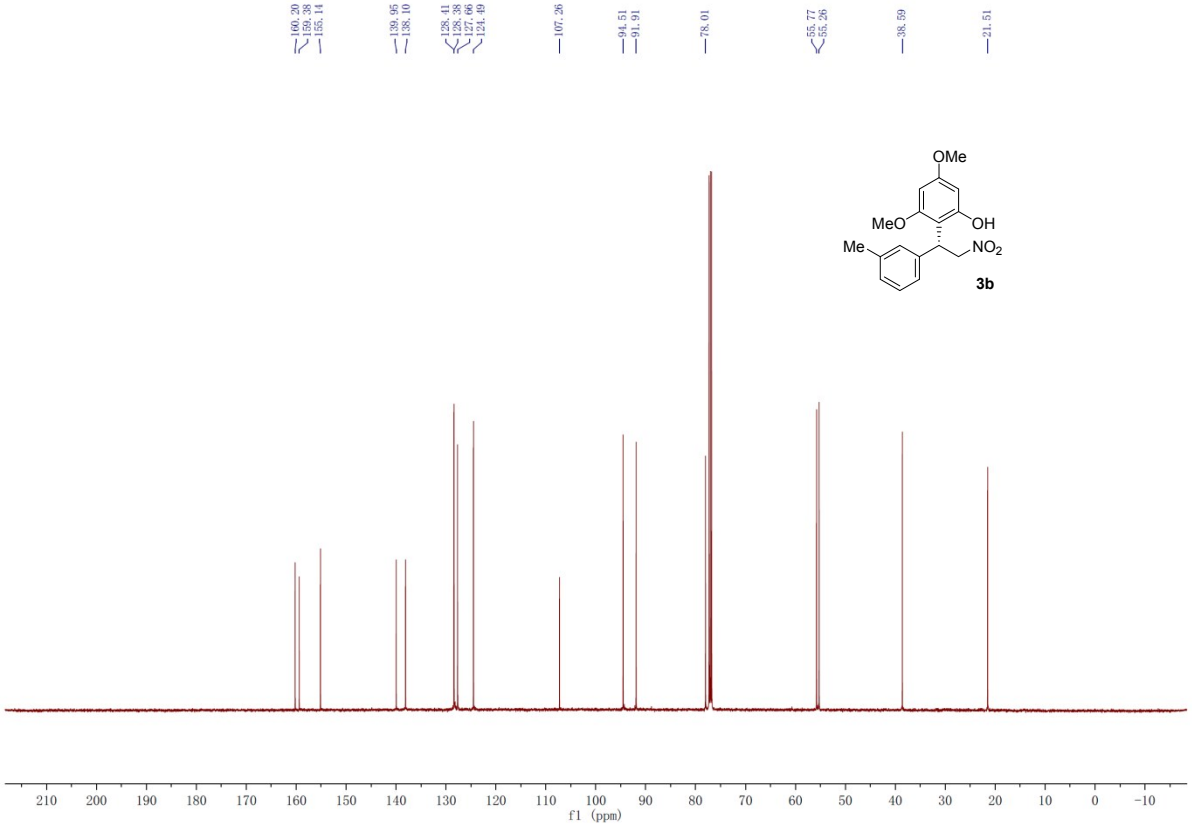
Enantiomerically enriched **3p**

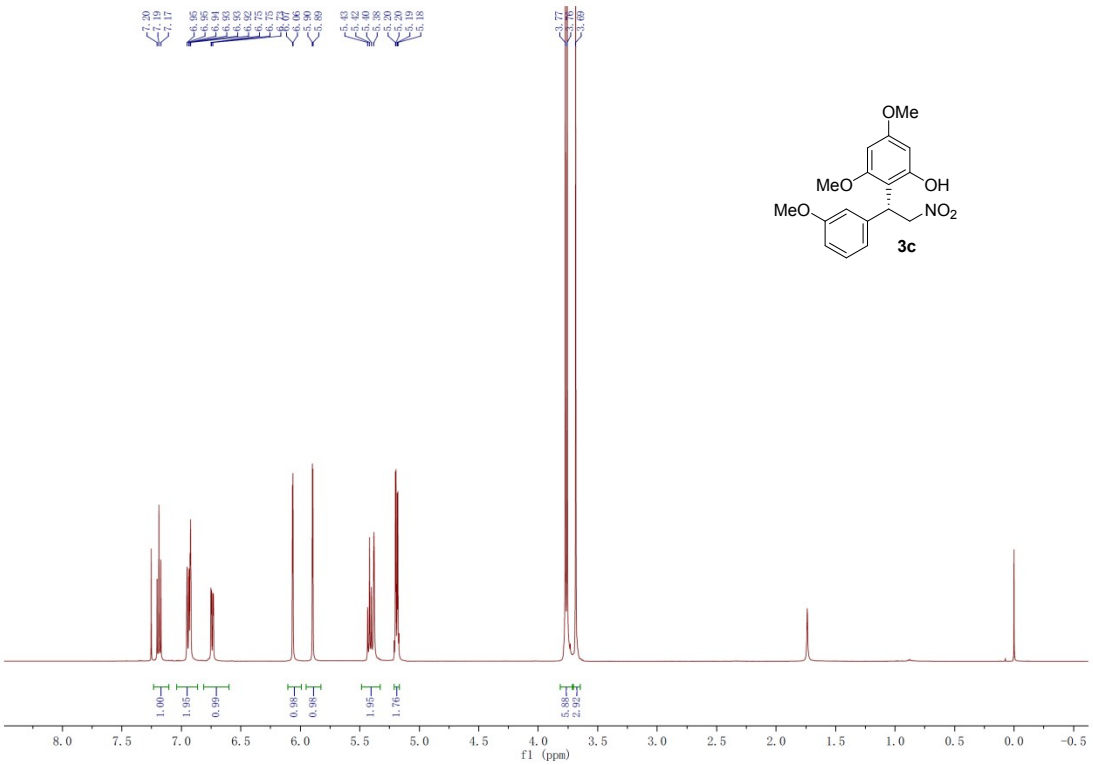
E. NMR Spectra of the Friedel-Crafts Reaction Products

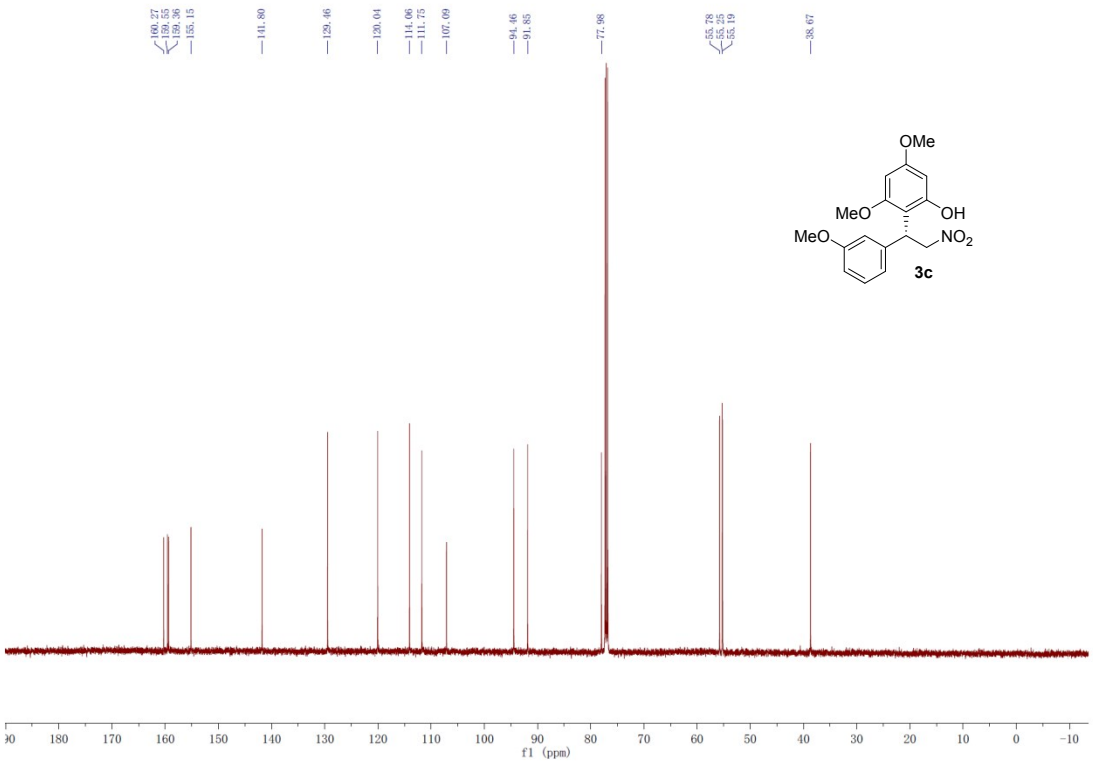

7.35
7.33
7.29
7.28
7.27
7.26
7.25
7.21
7.20
7.18
6.08
6.08
5.94
5.93
5.46
5.45
5.43
5.22
5.22
5.21
5.20
3.73
3.72
OMe
MeO
OH
NO2
3a
2.03
2.49
1.19
1.00
1.01
1.05
2.48
3.04
3.02
f1 (ppm)

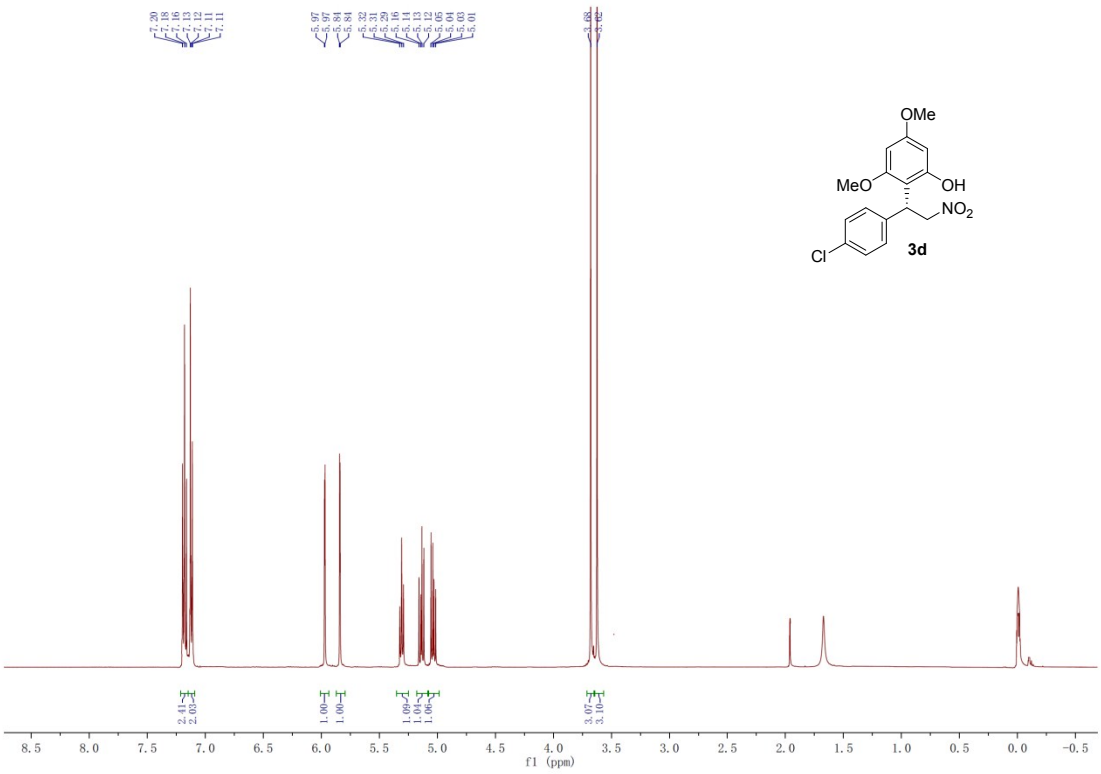

160.31
159.41
155.01
140.10
128.49
127.88
126.83
107.28
94.50
91.97
77.95
55.78
55.29
38.64
29.71
OMe
MeO
OH
NO2
3a
f1 (ppm)

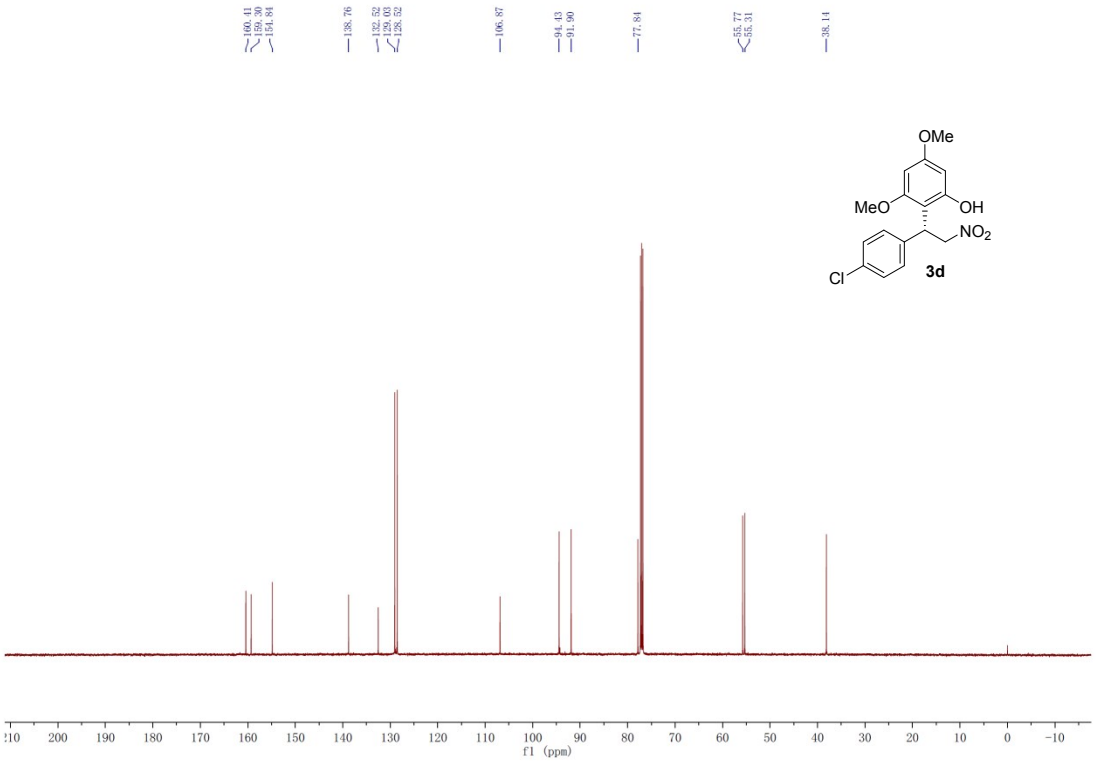

7.15
7.14
7.13
7.01
6.99
6.07
6.07
5.90
5.90
5.42
5.41
5.39
5.27
5.26
5.19
5.17
3.26
3.19
2.30
OMe
MeO
OH
Me
NO2
3b
3.04
1.17
1.00
0.98
1.00
1.23
2.04
3.18
3.15
3.26
f1 (ppm)

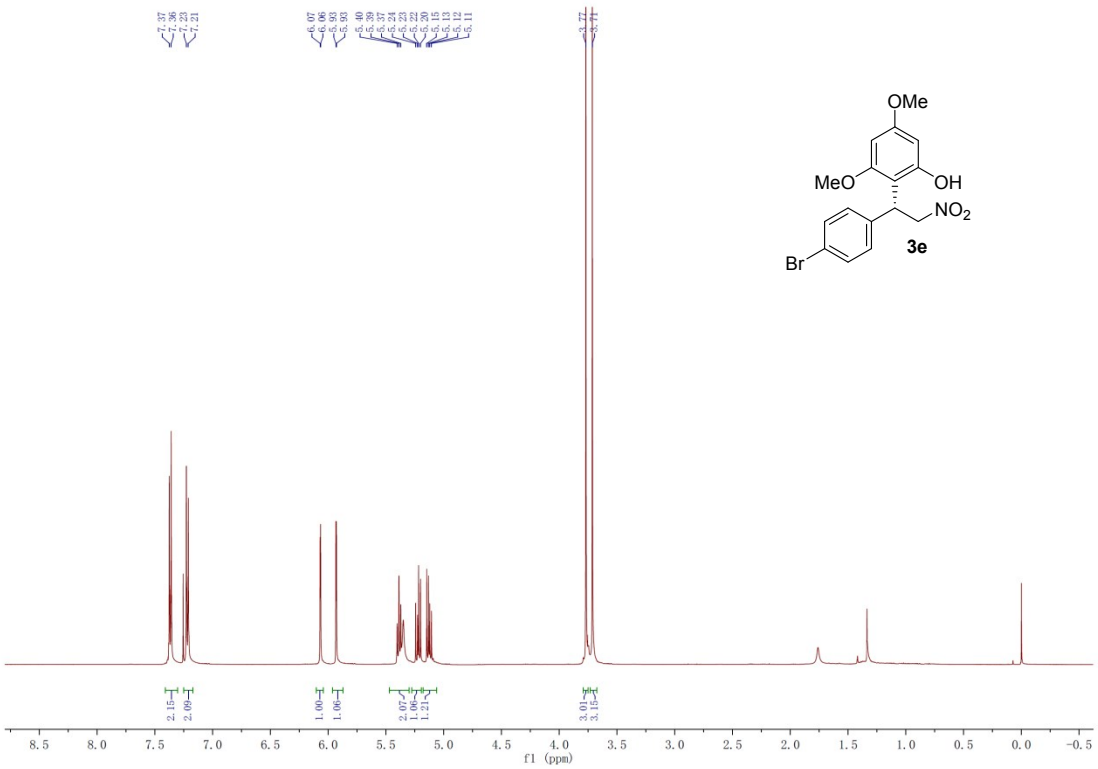

160.20
159.38
155.14
139.95
138.10
128.41
128.38
127.66
124.49
107.26
94.51
91.91
78.01
55.77
55.26
38.59
21.51
OMe
MeO
OH
Me
NO2
3b
f1 (ppm)

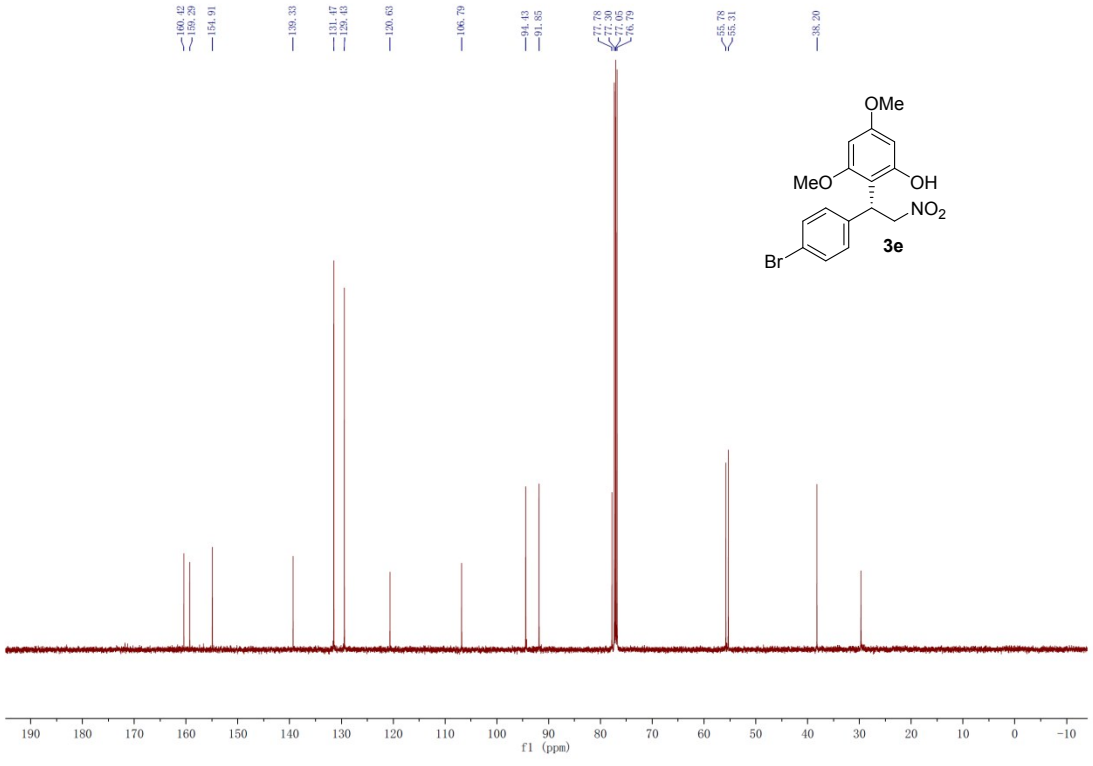

OMe
MeO
OH
MeO
NO2
3c
f1 (ppm)

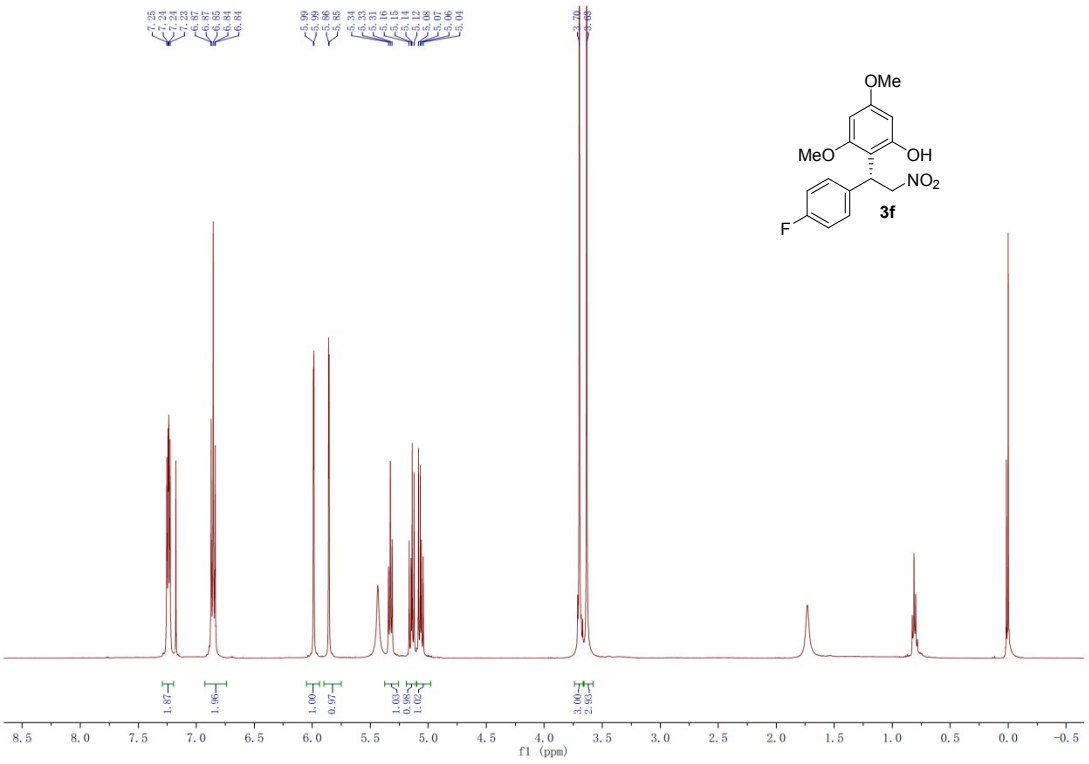

OMe
MeO
OH
MeO
NO2
3c
f1 (ppm)

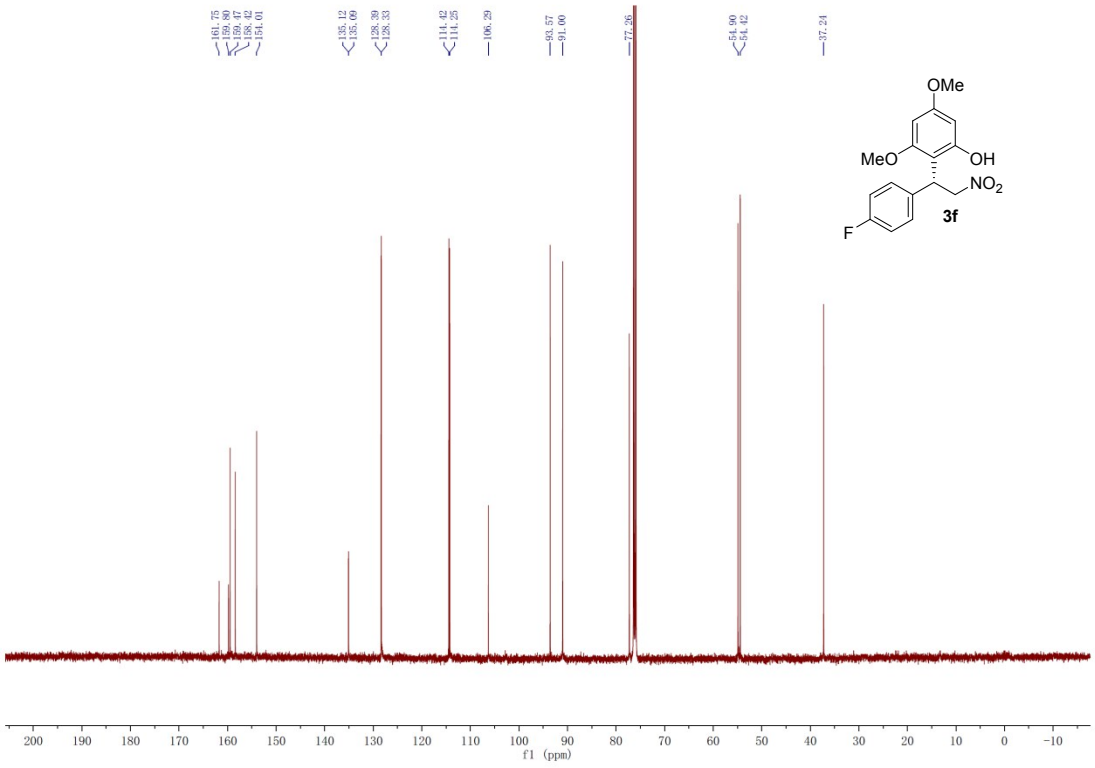

7.20
7.18
7.16
7.13
7.12
7.11
7.11
5.97
5.97
5.84
5.84
5.32
5.31
5.29
5.16
5.14
5.13
5.12
5.05
5.04
5.03
5.01
3.68
3.42
OMe
MeO
OH
NO2
Cl
3d
2.41
2.03
1.00
1.00
1.09
1.04
1.08
3.07
3.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

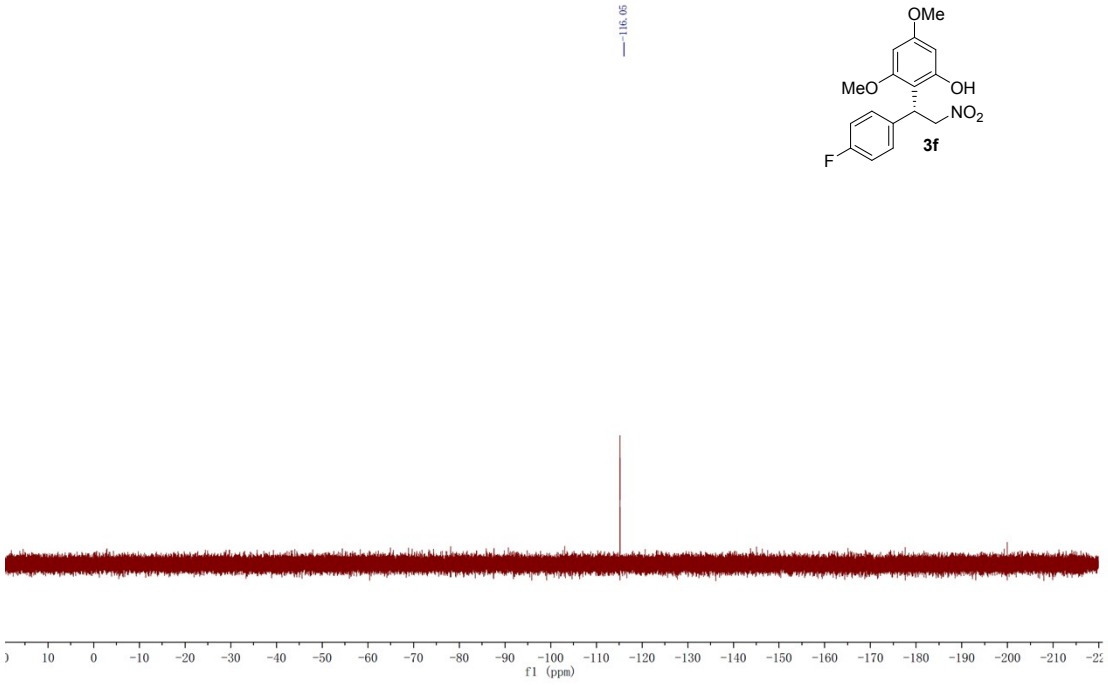

160.41
159.30
154.84
138.76
132.52
129.03
128.52
106.87
94.43
91.90
77.84
55.77
55.31
38.14
OMe
MeO
OH
NO2
Cl
3d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

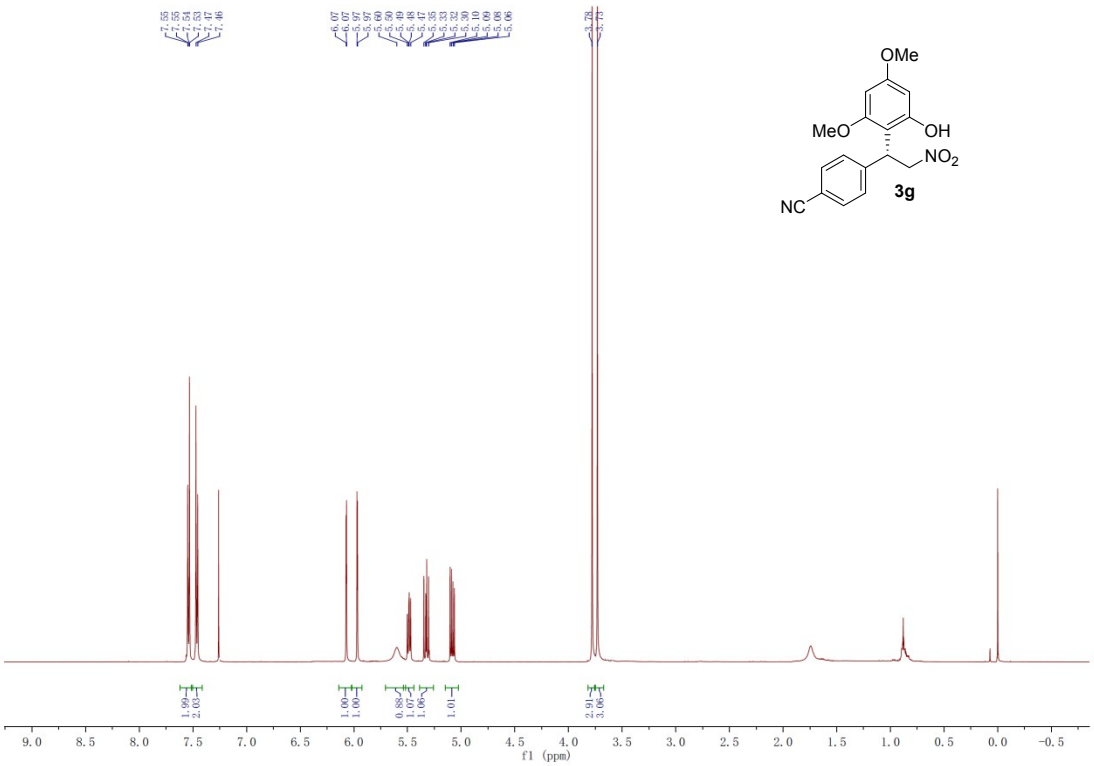

7.37
7.36
7.23
7.21
6.07
6.06
5.93
5.93
5.40
5.39
5.37
5.24
5.23
5.22
5.20
5.15
5.13
5.12
5.11
3.77
3.71
OMe
MeO
OH
NO2
Br
3e
2.15
2.09
1.00
1.06
2.07
1.04
1.21
3.01
3.15
f1 (ppm)

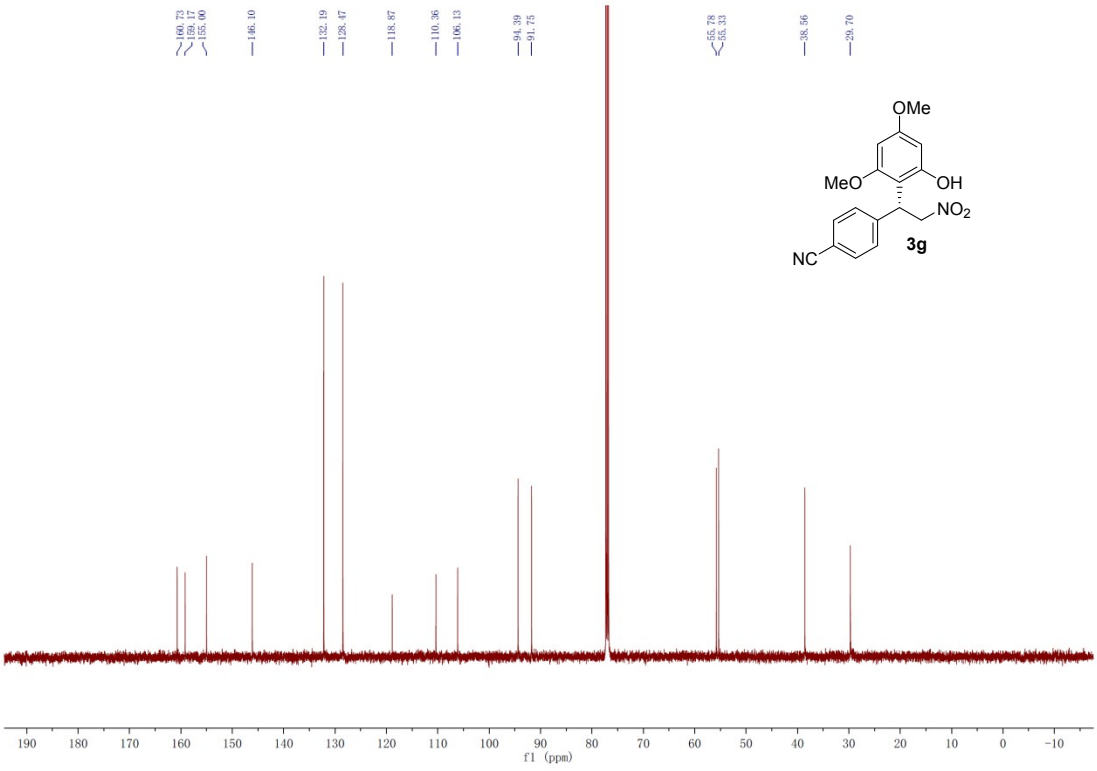

160.42
159.29
154.91
139.33
131.47
129.43
120.63
106.79
94.43
91.85
77.78
77.50
77.15
76.79
65.78
65.31
38.20
OMe
MeO
OH
NO2
Br
3e
f1 (ppm)

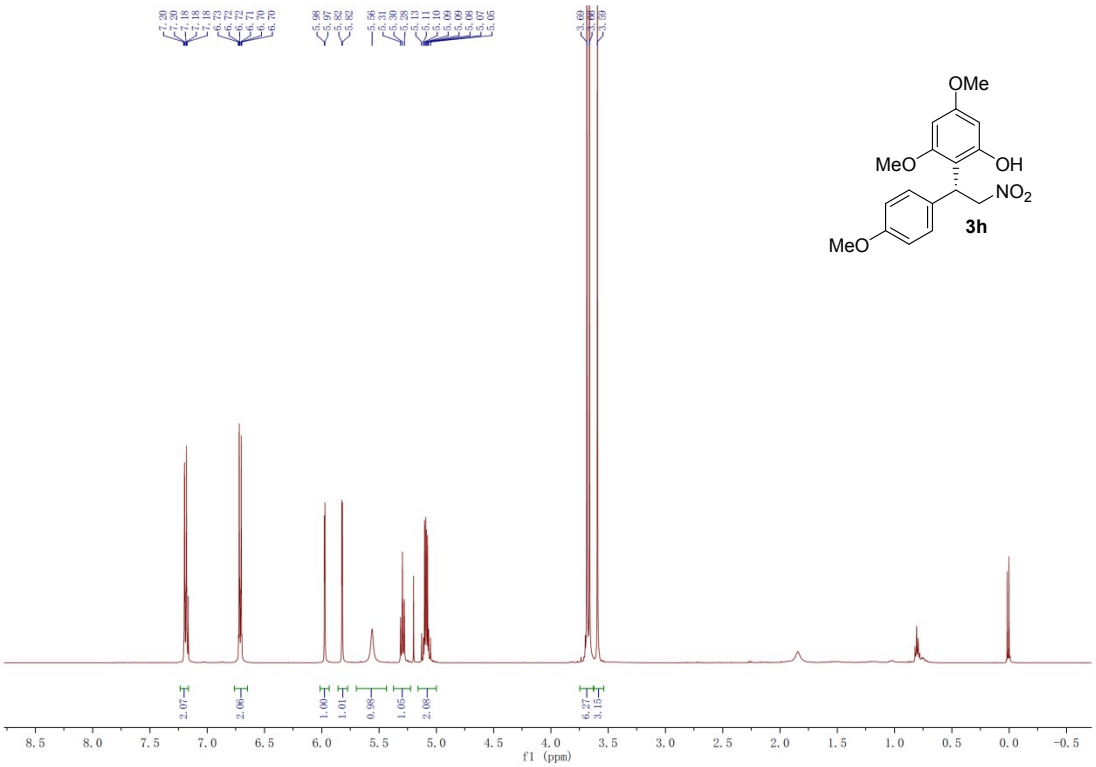

OMe
MeO
OH
NO2
F
3f
f1 (ppm)

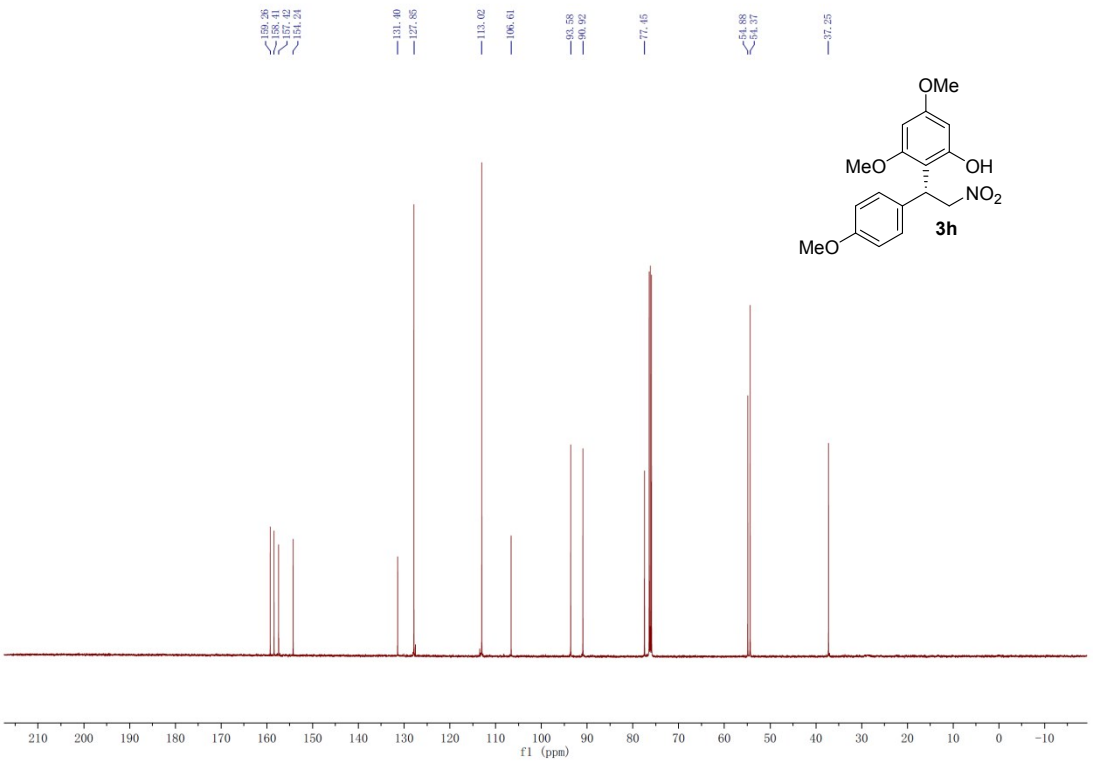

OMe
MeO
OH
NO2
F
3f
f1 (ppm)

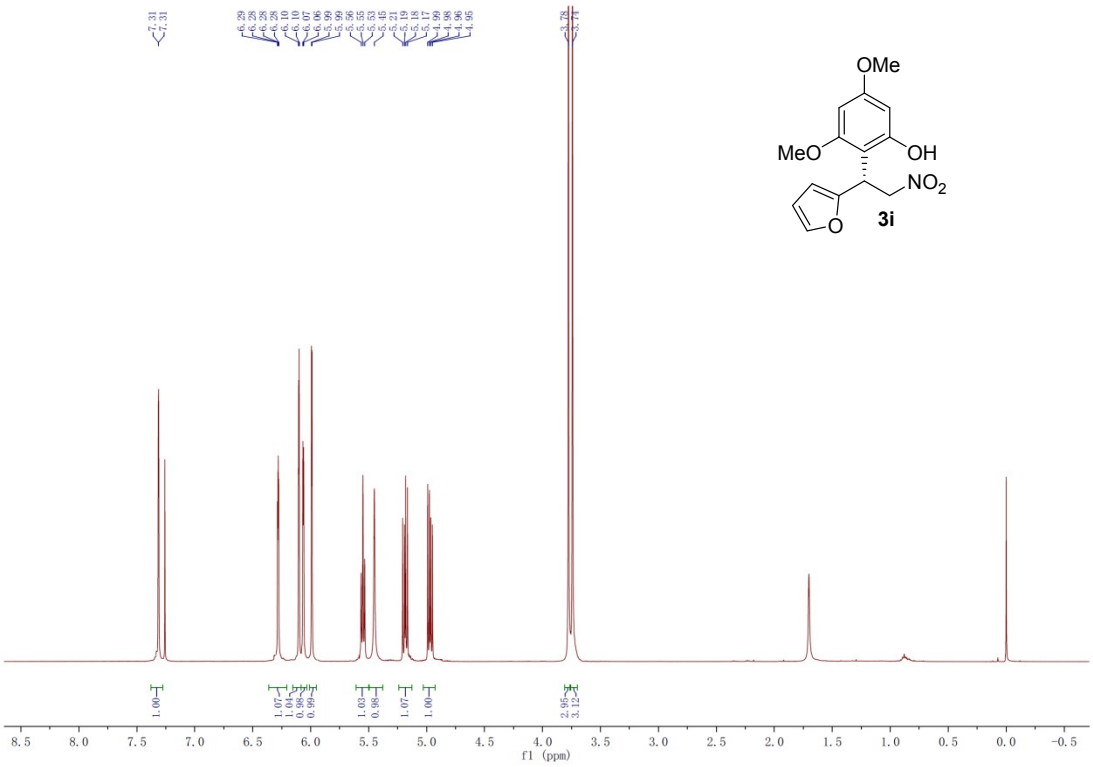

-116.05
OMe
MeO
OH
NO2
F
3f
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

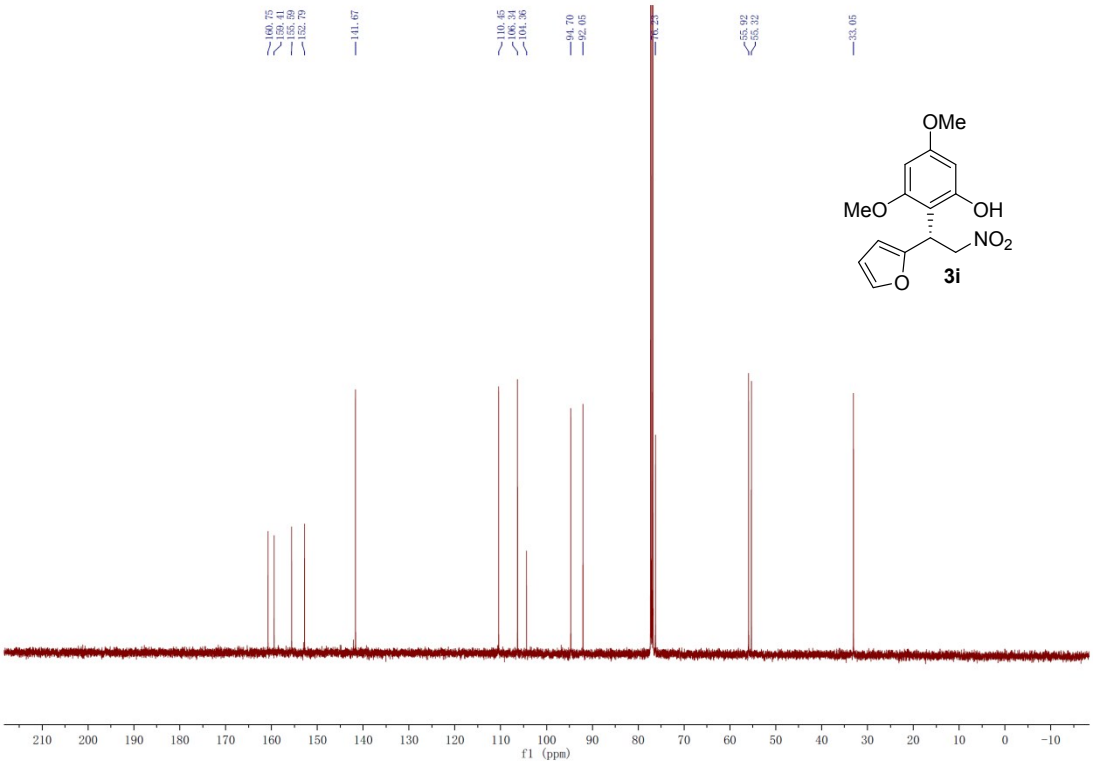

OMe
MeO
OH
NO2
NC
3g
f1 (ppm)

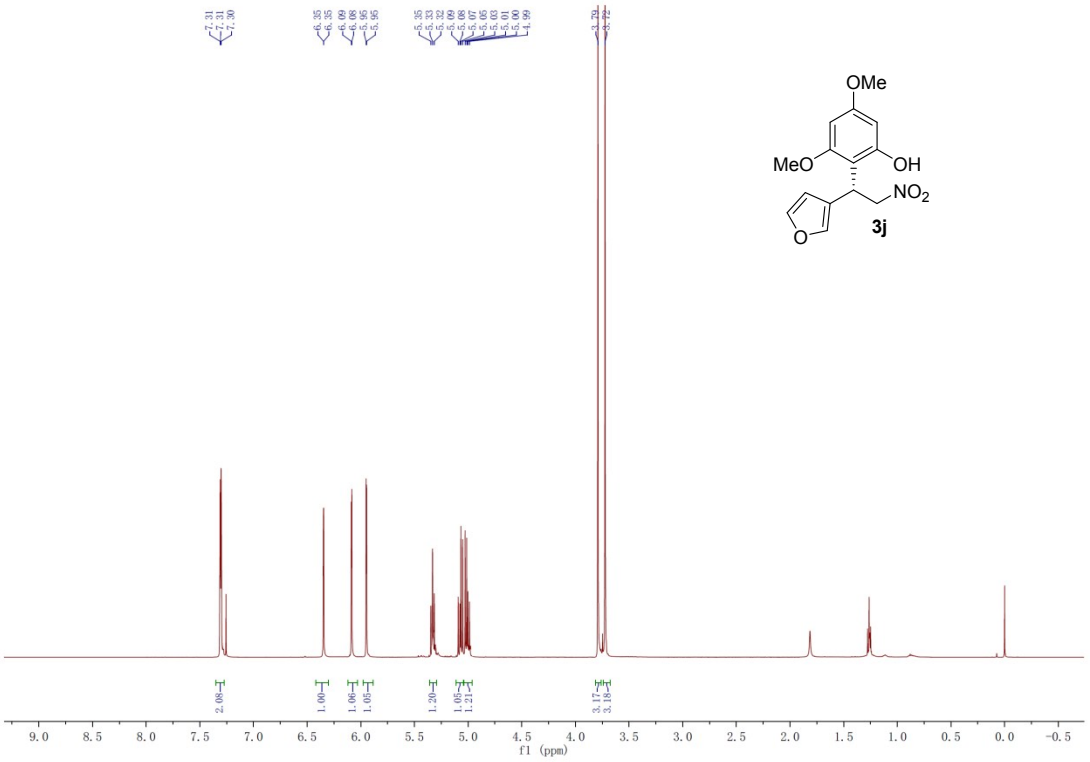

OMe
MeO
OH
NO2
NC
3g
f1 (ppm)

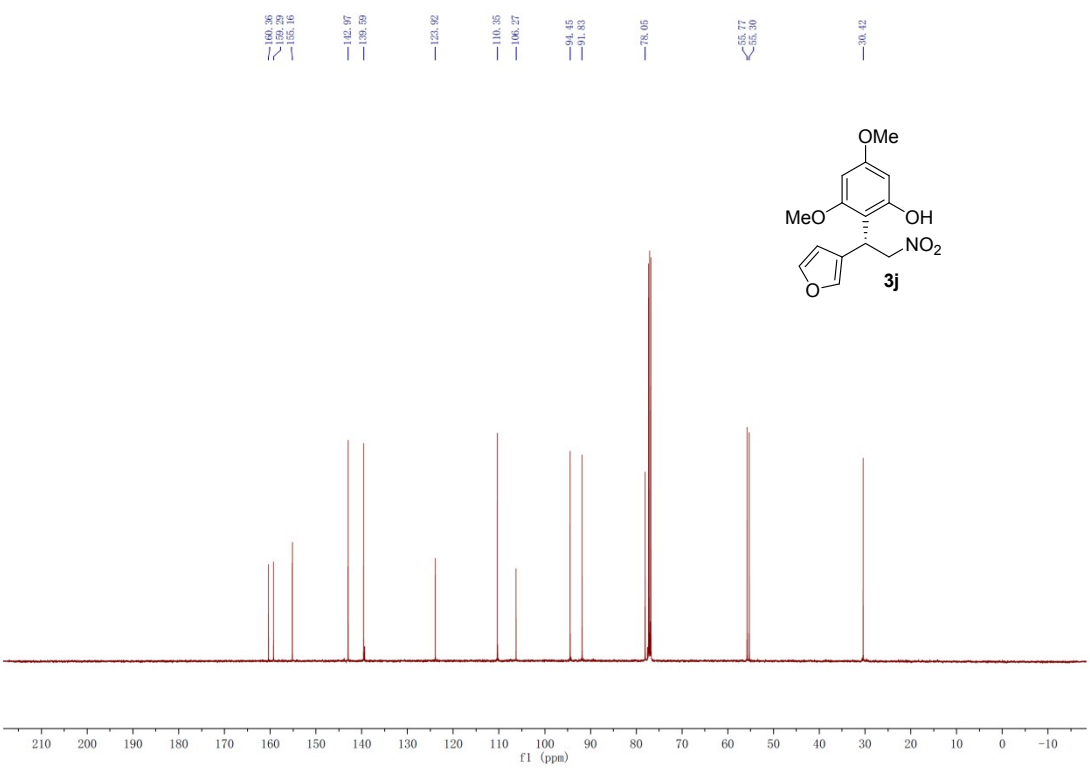

OMe
MeO
OH
NO2
MeO
3h
f1 (ppm)

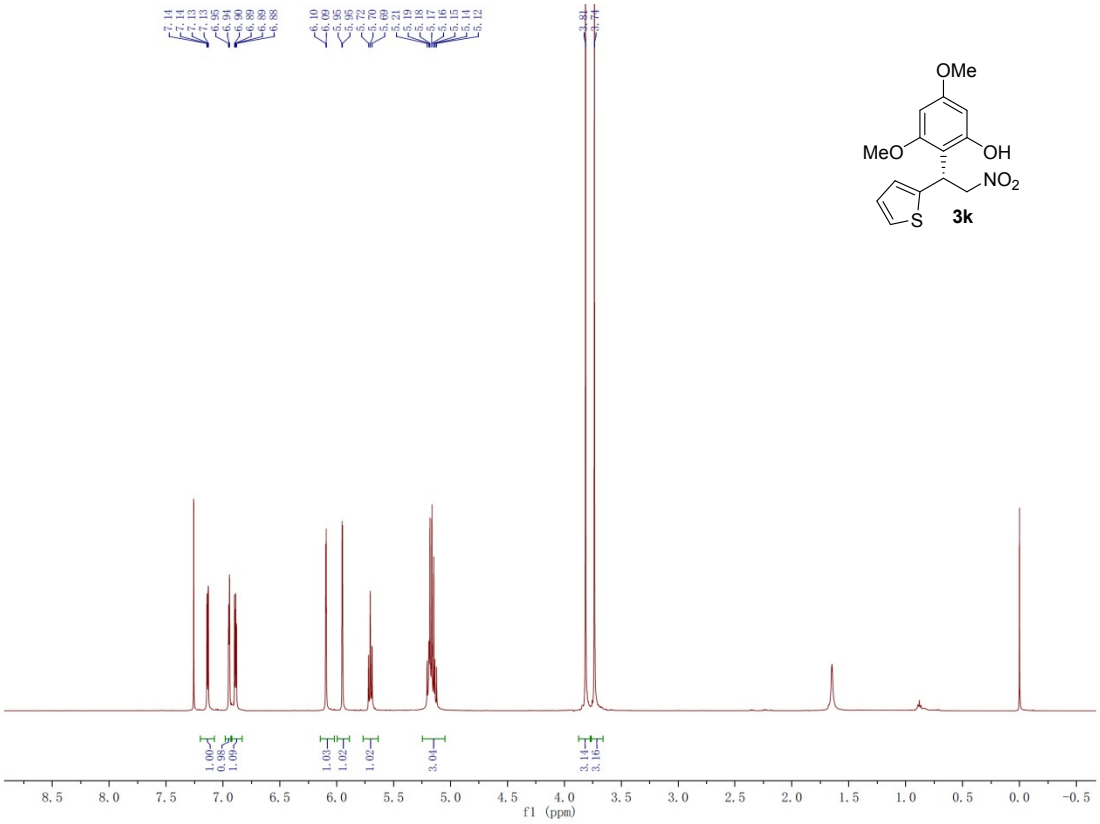

OMe
MeO
OH
NO2
MeO
3h
f1 (ppm)

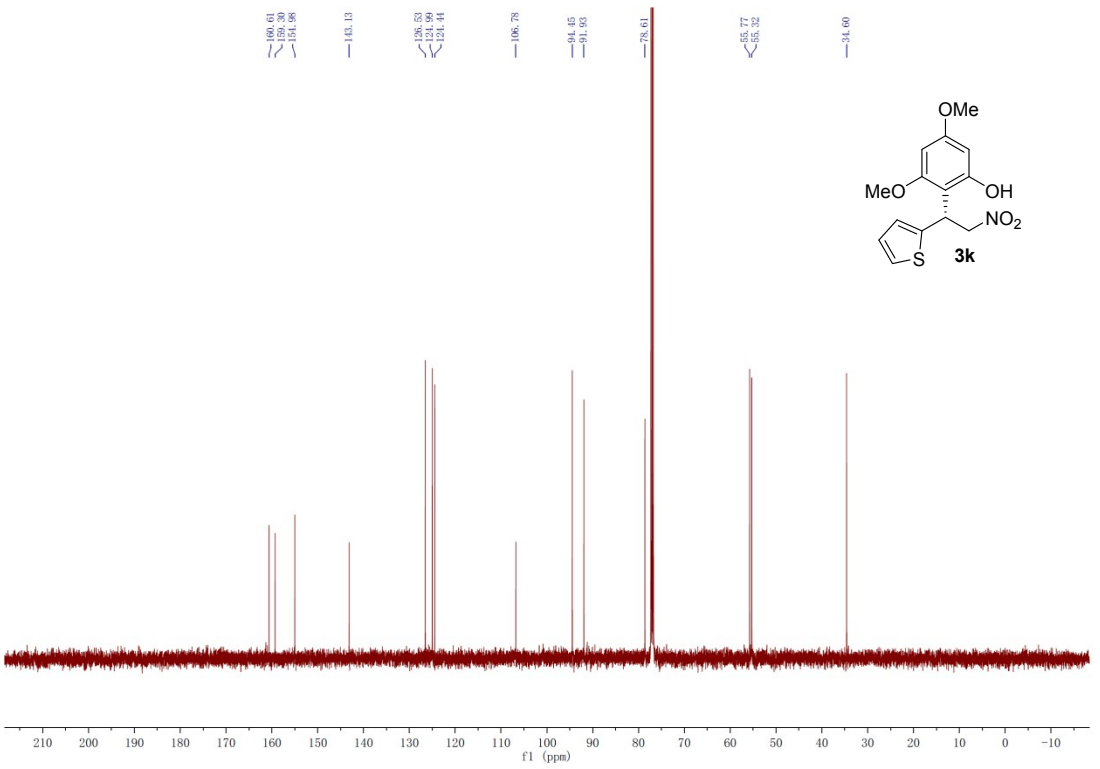

OMe
MeO
OH
NO2
O
3i
f1 (ppm)

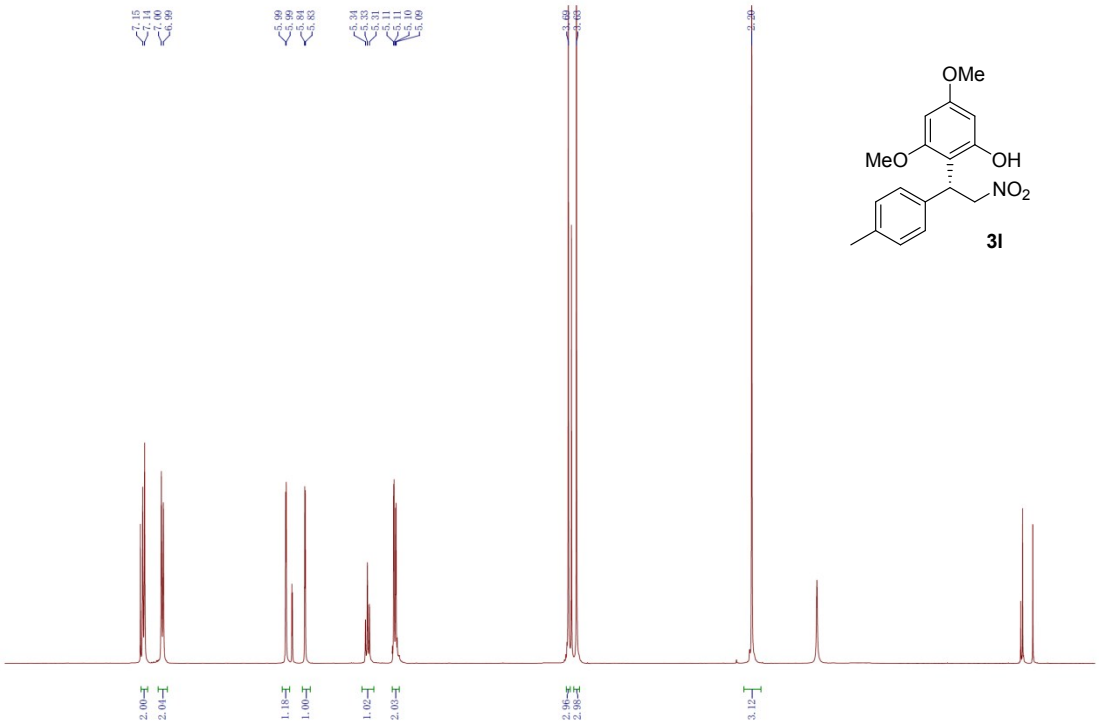

OMe
MeO
OH
NO2
O
3i
f1 (ppm)

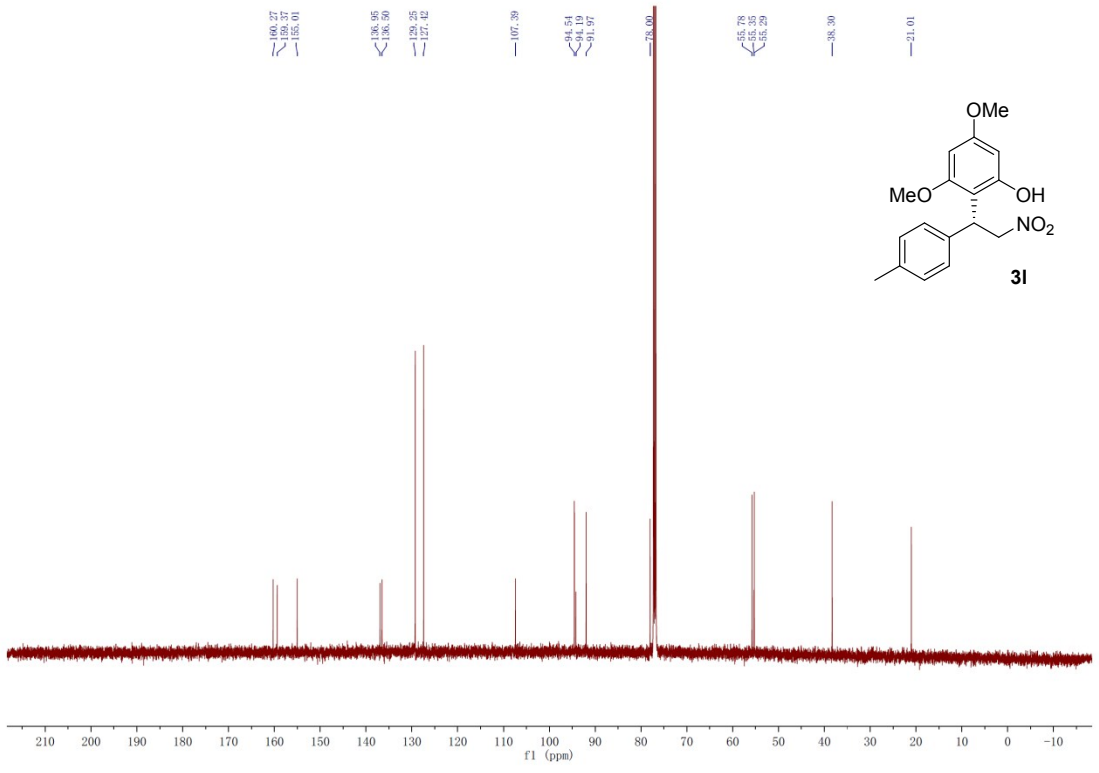

7.31
7.31
7.30
6.35
6.35
6.09
6.08
5.95
5.95
5.35
5.33
5.32
5.08
5.07
5.05
5.03
5.01
5.00
4.99
3.79
3.72
OMe
MeO
OH
NO2
O
3j
2.08
1.00
1.06
1.05
1.20
1.05
1.21
3.17
3.18
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

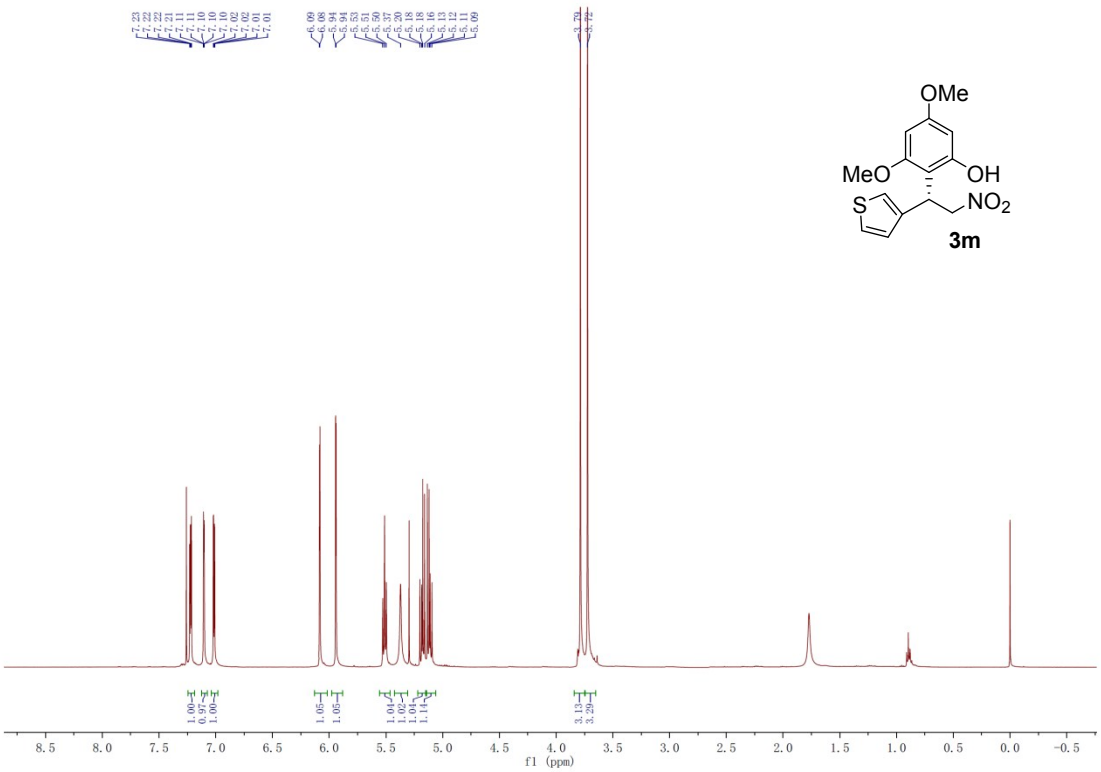

160.36
159.29
155.16
142.97
139.59
123.92
110.35
106.27
94.45
91.83
78.05
55.77
55.30
30.42
OMe
MeO
OH
NO2
O
3j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

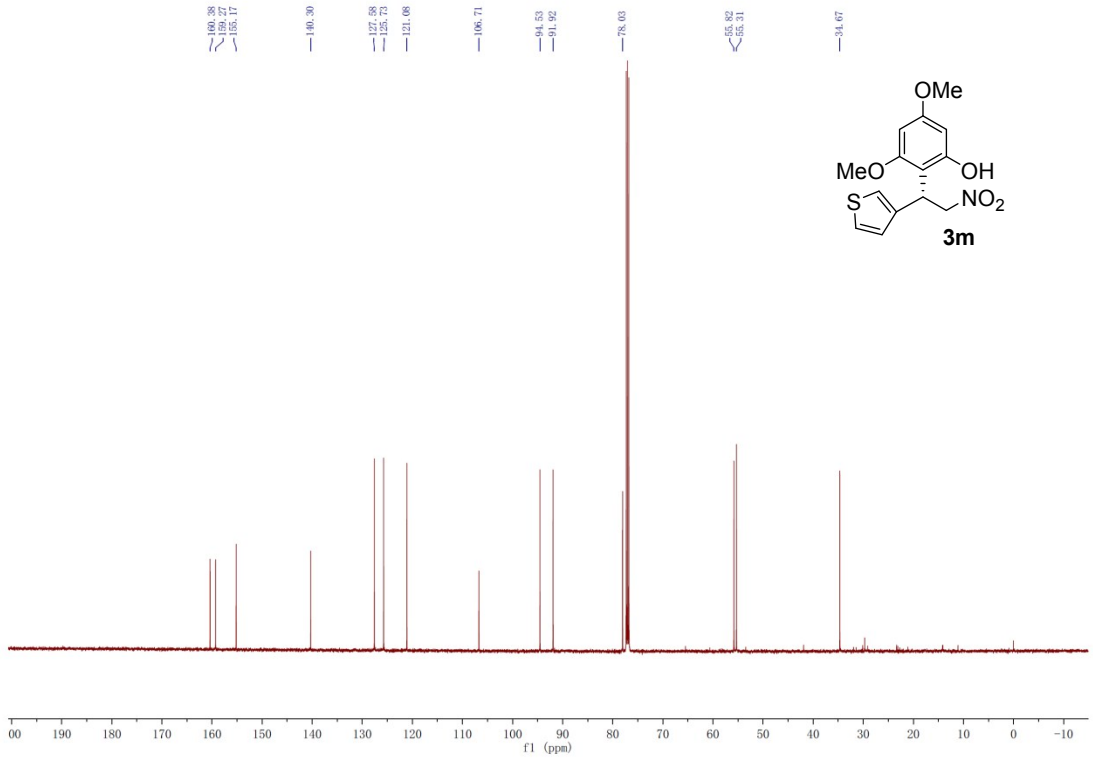

7.14
7.14
7.13
7.13
6.95
6.94
6.89
6.89
6.88
6.10
6.09
5.95
5.95
5.72
5.70
5.69
5.21
5.19
5.18
5.17
5.16
5.15
5.14
5.12
3.81
3.74
OMe
MeO
OH
NO2
S
3k
1.00
0.98
1.09
1.03
1.02
1.02
3.04
3.14
3.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

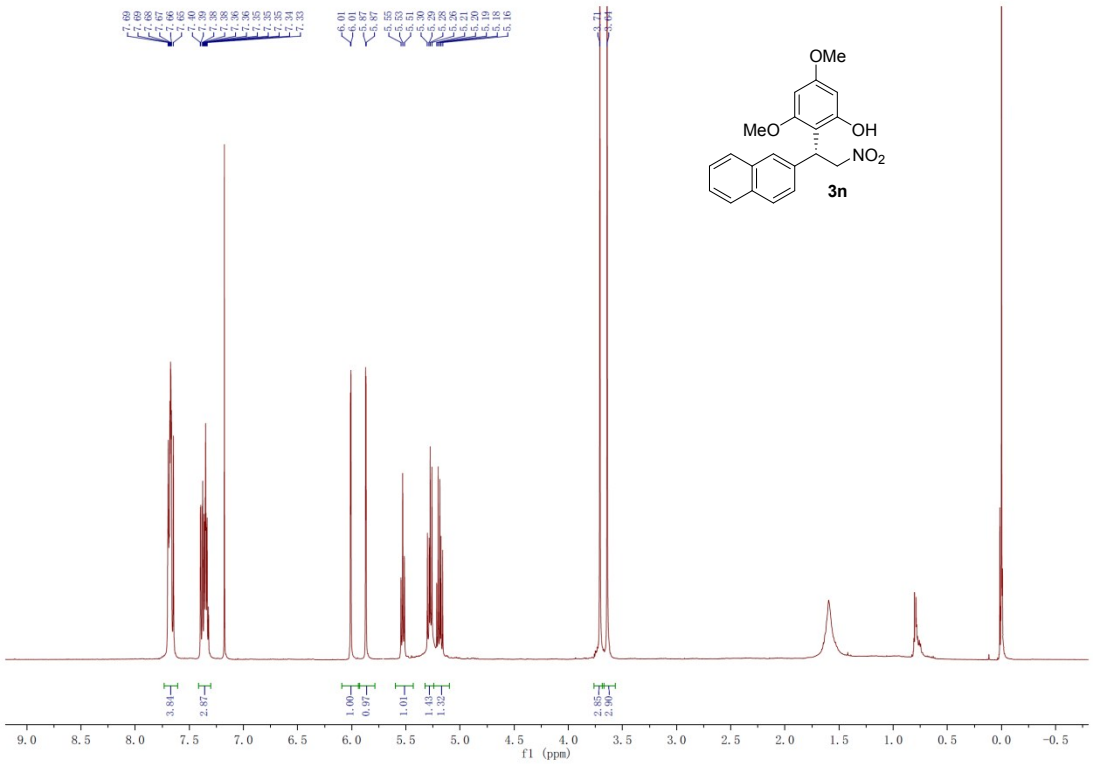

160.61
159.30
154.98
143.13
126.53
124.99
124.44
106.78
94.45
91.93
78.61
55.77
55.32
34.60
OMe
MeO
OH
NO2
S
3k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

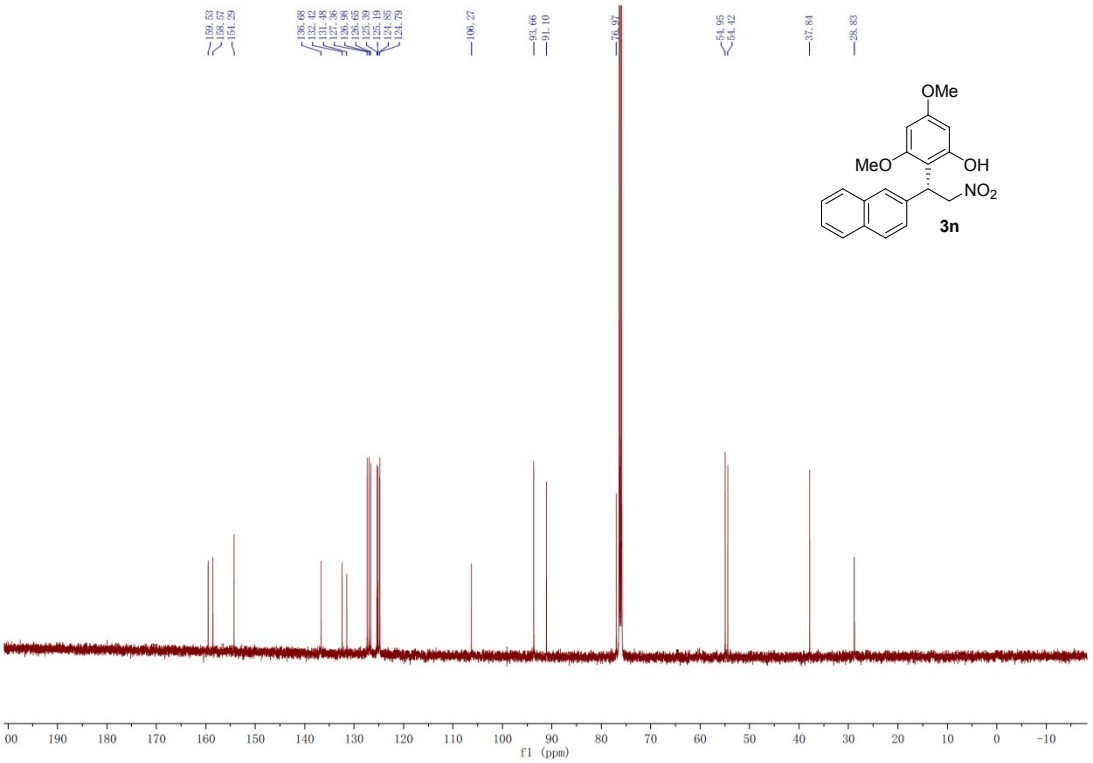

OMe
MeO
OH
NO2
3l

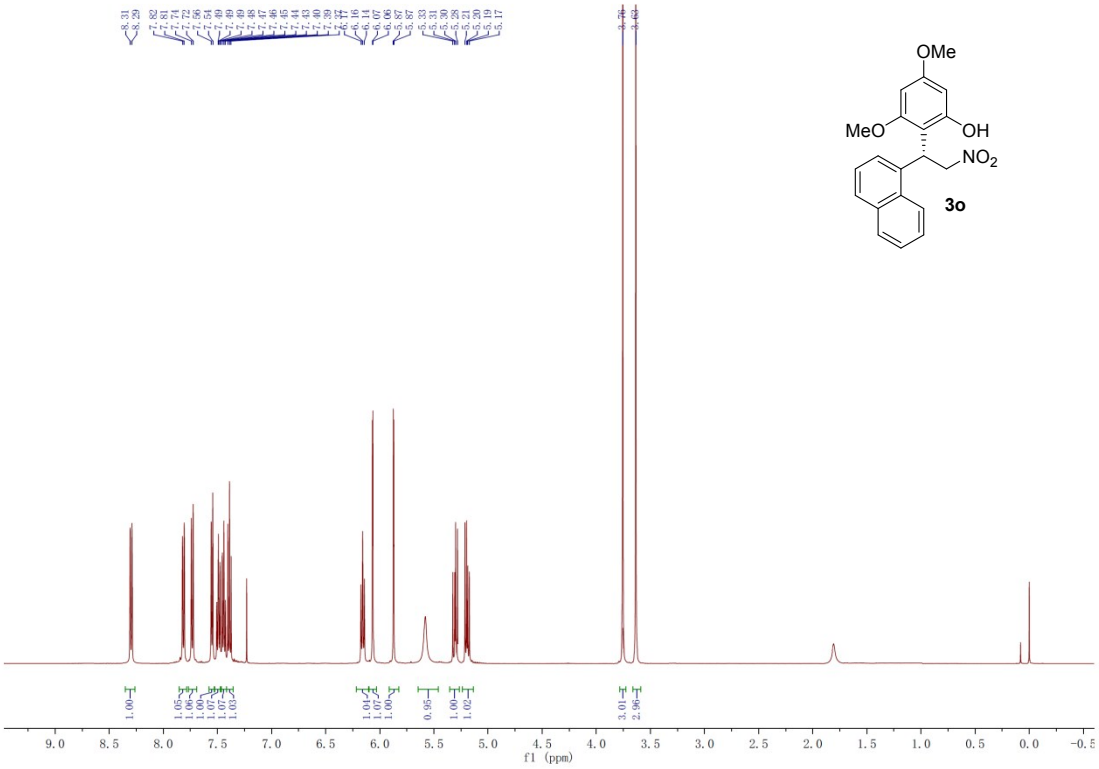

OMe
MeO
OH
NO2
3l
f1 (ppm)

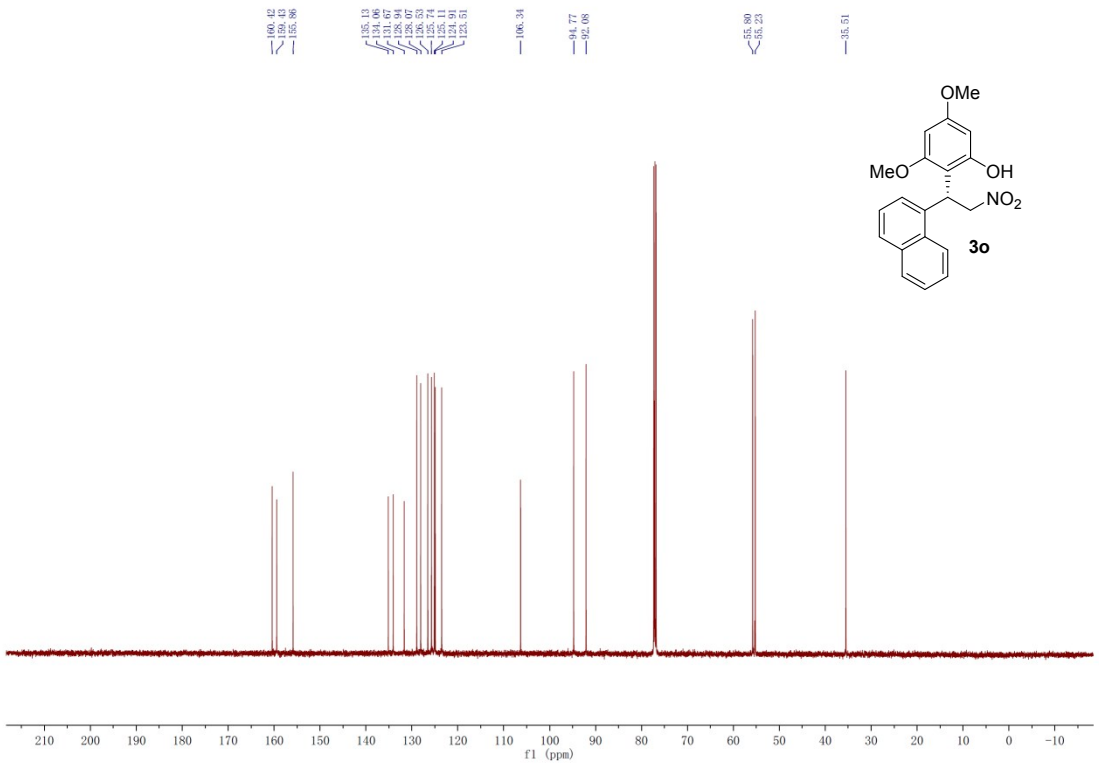

OMe
MeO
OH
S
NO2
3m
f1 (ppm)

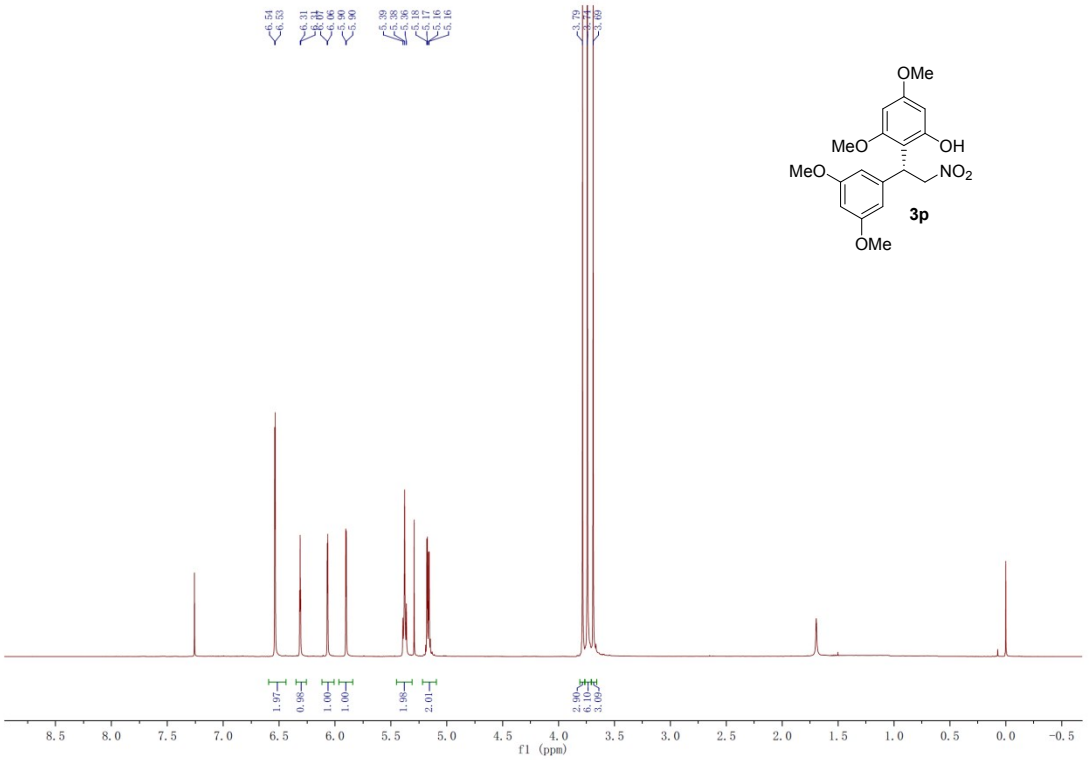

OMe
MeO
OH
S
NO2
3m
f1 (ppm)

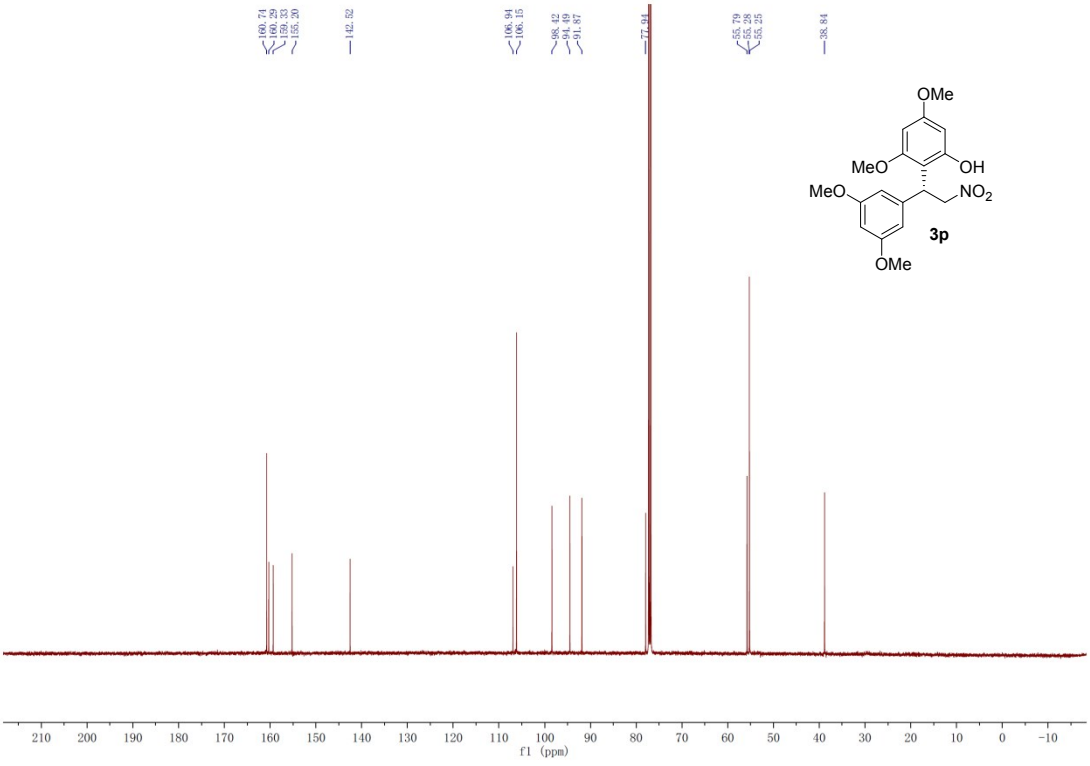

OMe
MeO
OH
NO2
3n
f1 (ppm)

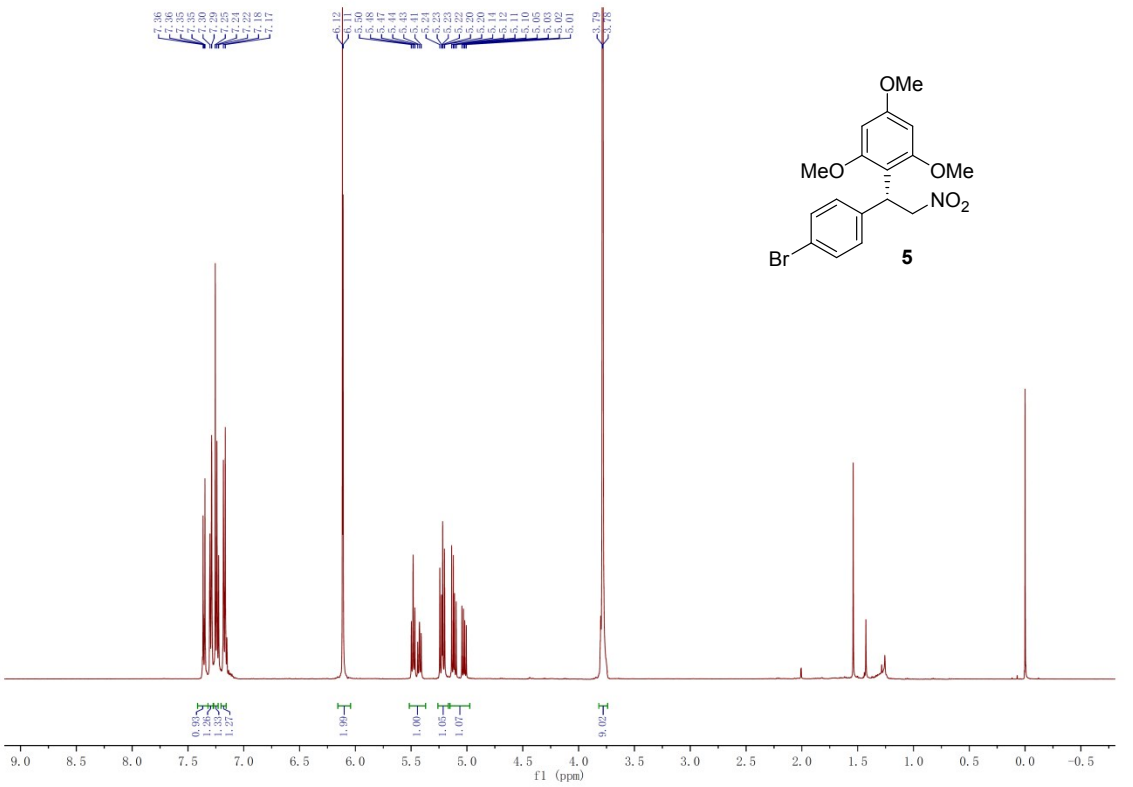

OMe
MeO
OH
NO2
3n
f1 (ppm)

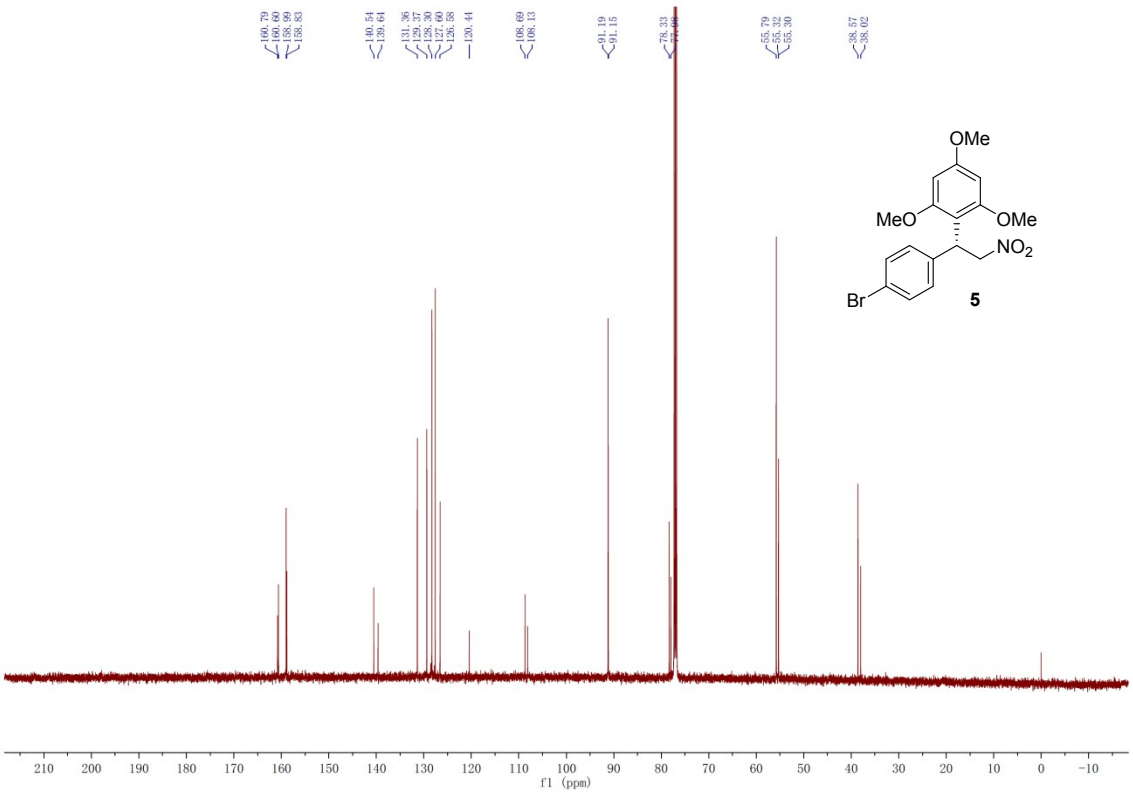

OMe
MeO
OH
NO2
3o
f1 (ppm)


OMe
MeO
OH
NO2
3o
f1 (ppm)


6.54
6.53
6.31
6.07
6.06
5.90
5.90
5.39
5.38
5.36
5.18
5.17
5.16
5.16
3.79
3.77
3.74
3.69
OMe
MeO
OH
MeO
NO2
3p
OMe
1.97
0.98
1.00
1.00
1.98
2.01
2.90
6.10
3.09
f1 (ppm)


160.74
160.29
139.33
135.20
142.52
106.94
106.15
98.42
94.49
91.87
77.94
55.79
55.28
55.25
38.84
OMe
MeO
OH
MeO
NO2
3p
OMe
f1 (ppm)


OMe
MeO
OMe
NO2
Br
5
f1 (ppm)


OMe
MeO
OMe
NO2
Br
5
f1 (ppm)