# Efficient Palladium-Catalyzed Cross-Coupling of Highly Acidic Substrates, Nitroacetates

*Alison E. Metz, Simon Berritt, Spencer D. Dreher,* and Marisa C. Kozlowski**

**Table of Contents**

**General Methods.** Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry argon in dry glassware and all solvents and reagents were HPLC grade and used without further purification. When necessary, solvents and reagents were dried prior to use. Moisture sensitive reagents were added via syringe. Toluene was distilled from $CaH_2$ and degassed with freeze-pump-thaw cycles (3 x). THF was distilled from NaH/benzophenone prior to use. Flash column chromatography was performed on EM Reagents Silica Gel 60 (230-400). Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 254-F plates. Visualization was accomplished with UV light and/or $KMnO_4$ stain.

$^1H$ NMR and $^{13}C$ spectra were recorded on a Bruker AM-500 (500 MHz) spectrometer. Chemical shifts are reported from the solvent resonance peak ($CDCl_3$ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants, and number of protons. Mass spectra were obtained on a high resonance VG autospec with an ionization mode of either CI or ES. IR spectra were taken on an ASI ReactIR 1000FT-IR spectrometer. Melting points were obtained on a Thomas Scientific Unimelt apparatus and are uncorrected. All yields reported refer to isolated yields unless otherwise indicated, and the product purity was determined by $^1H$ NMR. Compounds described in the literature were characterized by comparison of their spectra to reported data. New compounds were also characterized by high resolution mass.

**Procedures for Parallel Microscale Experimentation. Reactions of ethyl nitroacetate with bromobenzene, *o*-bromotoluene or pyridyl halide.**

The following procedure is representative of the high-throughput experimentation reactions described in this publication. The ligands (2 μmol) were dosed into the 96-well reactor 1-mL vial as solutions (50 μL of a 0.04 M solution in THF or toluene depending on the solubility of the ligand). Plates of these ligands may be plated in advance of the screen; the solvent is removed by evacuation on a Genevac, and the plates are stored in the glovebox. Palladium source (1.0 μmol Pd, 50 μL of a 0.02 M solution in THF) was then added to the reaction vials and this was evacuated to dryness on a Genevac or JKem-blow-down block. Base (24 μmol, 25 mg/mL slurry in THF) was then added to the ligand/catalyst mixture, and this was evacuated to dryness on a Genevac or JKem-blow-down block. A parylene stir-bar was added to each reaction. The aryl halide (20 μmol/reaction), ethyl nitroacetate (40 μmol/reaction) were then dosed together in the reaction solvents (100 μL of a 0.20 M and 0.40 M solution respectively). The vials were then sealed and heated at 80 ºC for 18 h. After cooling to ambient temperature, the reaction mixtures were evacuated to dryness on a Genevac or JKem-blow-down block. The residues were diluted with a solution of internal standard and acetic acid in MeCN (2 μmol biphenyl or *tert*-butyl biphenyl, 60 μmol acetic acid, 500 μL of solution), and the contents were stirred. Into a separate 96-well plate LC block was added 750 μL of MeCN and then 20 μL of the diluted reaction mixtures. The 96-well plate LC block was then sealed with a polypropylene 1 mL cap mat. The reactions were analyzed using an Agilent Technologies 1200 series HPLC with a 96-well plate auto-sampler.

High throughput experimentation (HTE) #1 consisted of one 96-well plate in toluene and one in

1,2-dimethoxyethane (DME) and screened the variables listed below. Top leads are represented in Table 1. All table results are listed in order of least to most product formation as measured against an internal standard (IS).

Ligands

X-Phos: 2-($Cy_2P$)-2',4',6'-*i*-Pr-biphenyl
S-Phos: 2-($Cy_2P$)-2',6'-MeO-biphenyl
JohnPhos: 2-(t-$Bu_2P$)-biphenyl
DavePhos: 2-($Cy_2P$)-2'-($Me_2N$)-biphenyl
RuPhos: 2-($Cy_2P$)-2',6'-*i*-PrO-biphenyl
BrettPhos: 2-($Cy_2P$)-3,6-MeO-2',4',6'-*i*-Pr-biphenyl
cataCXium A: $Ad_2Pn$-Bu
Q-Phos: 1'-(*t*-$Bu_2P$)-1,2,3,4,5-Ph-ferrocene
[HP(*t*-Bu)$_3$]$BF_4$
AmPhos [A-$^{ta}$Phos]: 1-(*t*-$Bu_2P$)-4-($Me_2N$)-Ph
dtbpf: 1,1'-(*t*-$Bu_2P$)-ferrocene
(o-Tol)$_3$P
dppf: 1,1'-$Ph_2P$-ferrocene
dippf: 1,1'-(*i*-$Pr_2P$)-ferrocene
dppp: 1,3-($Ph_2P$)-Pr
dppb: 1,4-($Ph_2P$)-Bu
DPEPhos: (2-$Ph_2PPh)_2O$
XantPhos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
(R)-BINAP
$Me_4$ *t*-Bu XPhos: 2-(*t*-$Bu_2P$)-3,4,5,6-Me-2',4',6'-*i*-Pr-biphenyl
SL-J009-1 : (*R*)-(*S*)-$cy_2$PF-P*t*-$Bu_2$
cataCXium PtB: 2-(*t*-$Bu_2P$)-1-Ph-pyrrole
*t*-Bu XPhos: 2-(*t*-$Bu_2P$)-2',4',6'-*i*-Pr-biphenyl
[HP(Cy)$_3$]$BF_4$

Bases

$CsCO_3$, $CsHCO_3$, NaOAc, $K_3PO_4$

Palladium Sources

$[allylPdCl]_2$, $Pd_2dba_3 \bullet CHCl_3$

**Table 1.** HTE #1: Ligand screen. Selected data from conditions that gave product.

| Palladium Source | Ligand | Base | Solvent | Product/IS |
|---|---|---|---|---|
| $Pd_2dba_3 \bullet CHCl_3$ | BrettPhos | $K_3PO_4$ | toluene | 0.13 |
| $Pd_2dba_3 \bullet CHCl_3$ | $Me_4$ *t*-Bu XPhos | $K_3PO_4$ | toluene | 0.45 |
| $Pd_2dba_3 \bullet CHCl_3$ | BrettPhos | $Cs_2CO_3$ | toluene | 0.83 |
| $(PdallylCl)_2$ | $Me_4$ *t*-Bu XPhos | $CsHCO_3$ | DME | 1.04 |
| $(PdallylCl)_2$ | *t*-Bu Xphos | $Cs_2CO_3$ | DME | 1.82 |
| $(PdallylCl)_2$ | $Me_4$ *t*-Bu XPhos | $Cs_2CO_3$ | DME | 1.84 |
| $(PdallylCl)_2$ | *t*-Bu Xphos | $K_3PO_4$ | DME | 3.03 |
| $Pd_2dba_3 \bullet CHCl_3$ | $Me_4$ *t*-Bu XPhos | $CsHCO_3$ | toluene | 3.73 |
| $Pd_2dba_3 \bullet CHCl_3$ | $Me_4$ *t*-Bu XPhos | $Cs_2CO_3$ | toluene | 4.52 |
| $(PdallylCl)_2$ | *t*-Bu Xphos | $CsHCO_3$ | DME | 5.08 |
| $Pd_2dba_3 \bullet CHCl_3$ | *t*-Bu Xphos | $CsHCO_3$ | toluene | 6.91 |

High throughput experimentation (HTE) #2 consisted of 2 identical 96-well plates. One was stirred at 75 °C and the other was stirred at 110 °C to study temperature effects. Variables are listed below. Top leads are represented in Table 2 and 3. All of the reactions in the screens are represented pictorially in Figures 25. Figure 4 appears in the main text.

| Ligands | Base |
|---|---|
| *t*-Bu XPhos: 2-(*t*-$Bu_2$P)-2',4',6'-*i*-Pr-biphenyl | $Cs_2CO_3$ |
| $Me_4$ *t*-Bu XPhos: 2-(*t*-$Bu_2$P)-3,4,5,6-Me-2',4',6'-*i*-Pr-biphenyl | $CsHCO_3$ |

Palladium Sources

*t*-Bu XPhos Preformed[1]: [2-(*t*-$Bu_2$P)-2',4',6'-*i*-Pr-1,1'-biphenyl][2-(2-aminoethyl)phenyl]PdCl (only with ligand *t*-Bu XPhos)

$[PdallylCl]_2$

$Pd(OAc)_2$

$Pd_2dba_3$

Solvents

| | |
|---|---|
| toluene | tetrahydrofuran (THF) |
| *t*-amyl alcohol (*t*-AmylOH) | 1,2-dimethoxyethane (DME) |
| cyclopentyl methyl ether (CPME) | 1,4-dioxane |

**Table 2.** HTE #2: Selected data from screen at 75 °C.

| Pd | Ligand | Base | Solvent | Product/IS |
|---|---|---|---|---|
| $Pd_2dba_3$ | $Me_4$ *t*-Bu XPhos | $CsHCO_3$ | dioxane | 1.89 |
| $Pd(OAc)_2$ | $Me_4$ *t*-Bu XPhos | $Cs_2CO_3$ | *t*-AmylOH | 2.02 |
| $Pd(OAc)_2$ | *t*-Bu XPhos | $CsHCO_3$ | DME | 2.24 |
| $Pd(OAc)_2$ | *t*-Bu XPhos | $Cs_2CO_3$ | CPME | 2.28 |
| $Pd(OAc)_2$ | $Me_4$ *t*-Bu XPhos | $CsHCO_3$ | dioxane | 2.28 |
| *t*-Bu XPhos Preformed | *t*-Bu XPhos | $Cs_2CO_3$ | toluene | 2.38 |
| *t*-Bu XPhos Preformed | *t*-Bu XPhos | $Cs_2CO_3$ | *t*-AmylOH | 2.74 |

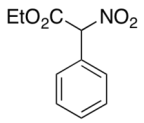
**Table 3.** HTE #2: Selected data from screen at 110 °C.

| Pd | Ligand | Base | Solvent | Product/IS |
|---|---|---|---|---|
| $Pd(OAc)_2$ | $Me_4$ *t*-Bu XPhos | $Cs_2CO_3$ | CPME | 1.28 |
| $Pd(OAc)_2$ | *t*-Bu XPhos | $CsHCO_3$ | toluene | 1.29 |
| $Pd(OAc)_2$ | $Me_4$ *t*-Bu XPhos | $CsHCO_3$ | DME | 1.34 |
| $Pd_2dba_3$ | *t*-Bu XPhos | $CsHCO_3$ | CPME | 1.39 |
| $Pd(OAc)_2$ | $Me_4$ *t*-Bu XPhos | $Cs_2CO_3$ | *t*-AmylOH | 1.51 |
| $Pd_2dba_3$ | *t*-Bu XPhos | $CsHCO_3$ | toluene | 1.57 |
| $Pd(OAc)_2$ | $Me_4$ *t*-Bu XPhos | $Cs_2CO_3$ | THF | 2.37 |

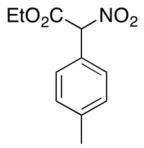
**Formation of Nitroarylacetates.**

**Method A.** In a glove-box, to an oven-dried microwave vial was added $Pd_2(dba)_3 \cdot CHCl_3$ (6.5 mg, 6.3 μmol), *t*-Bu XPhos (10.6 mg, 25.0 μmol), and $CsHCO_3$ (58.0 mg, 0.30 mmol). Next, a solution of ethyl nitroacetate (0.50 mmol, 0.63 mL of 0.80 M solution in toluene) and additional toluene (0.63 mL) were added to give a heterogenous reaction mixture. At this point, the vial was sealed using a biotag cap equipped with a septum and removed from the glovebox. Aryl bromide (0.25 mmol) was added via syringe. The solution was then heated at 75-80 °C and stirred vigorously for 18 h. After cooling, the reaction mixture was diluted with EtOAc (1 mL) and acidified with HCl (2 mL, 1 M). The layers were separated and the aqueous layer extracted with additional EtOAc (5 x 1 mL). The combined organic layers were concentrated *in vacuo*. The residue was chromatographed (5:95 EtOAc:hexanes) to afford the desired product.

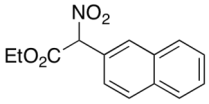
**Method B.** In a glove-box, to an oven-dried microwave vial was added $Pd_2(dba)_3 \cdot CHCl_3$ (9.8 mg, 9.50 μmol), *t*-Bu XPhos (16.1 mg, 38.0 μmol), and $CsHCO_3$ (88.0 mg, 0.427 mmol). Next, a solution of ethyl nitroacetate (0.38 mmol, 0.48 mL of 0.80 M solution in toluene) and additional toluene (1.42 mL) were added to give a heterogenous reaction mixture. At this point, the vial was sealed using a biotag cap equipped with a septum and removed from the glovebox. Aryl bromide (0.570 mmol) was added via syringe. The solution was then heated at 75-80 °C and stirred vigorously for 18 h. After cooling, the reaction mixture was diluted with EtOAc (1 mL) and acidified with HCl (2 mL, 1 M). The layers were separated and the aqueous layer extracted with additional EtOAc (5 x 1 mL). The combined organic layers were concentrated *in vacuo*. The residue was chromatographed (5:95 EtOAc:hexanes) to afford the desired product.



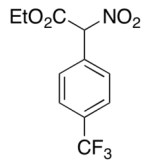

**Ethyl 2-nitro-2-phenylacetate.** Using method A of the general procedure the title compound was obtained as yellow oil (48.6 mg, 93%). In addition to the above scale, this reaction was performed on large scale using bromobenzene (379 μL, 3.60 mmol), ethyl nitroacetate (800. μL, 7.20 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (37.0 mg, 36.0 μmol, 2 mol %), *t*-Bu XPhos (61.0mg, 144 μmol), and $CsHCO_3$ (838 mg, 4.32 mmol) to yield the title compound (627 mg, 83%). Spectral data were in agreement with reported literature values.[2]



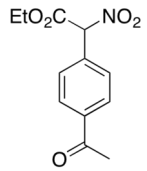

**Ethyl 2-nitro-2-(*p*-tolyl)acetate.** Using method A of the general procedure, the title compound was obtained as a yellow oil (44.1 mg, 79%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, $J$ = 8.0 Hz, 2H), 7.28 (d, $J$ = 8.0 Hz, 2H), 6.14 (s, 1H), 4.39-4.28 (m, 2H), 2.41 (s, 3H), 1.31 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 164.4, 141.3, 129.98, 129.97, 126.3, 90.9, 63.4, 21.5, 14.1; IR (film) 2989, 2927, 1746, 1568, 1367, 1259, 1205, 1020 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{11}H_{12}NO_4$, 222.0766; found, 222.0764.



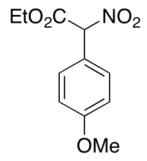
**Ethyl 2-(naphthalen-2-yl)-2-nitroacetate.** Using method A of the general procedure, the title compound was obtained as a yellow oily solid (49.9 mg, 77%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.2 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.62-7.55 (m, 3H), 6.34 (s, 1H), 4.43-4.26 (m, 2 H), 1.32 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 164.3, 134.3, 133.1, 130.8, 129.3, 128.7, 128.04, 127.98, 127.2, 126.4, 126.0, 91.2, 63.6, 14.1; IR (film) 2989, 1746, 1568, 1359, 1197, 1020 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{14}H_{12}NO_4$, 258.0766; found, 258.0757.



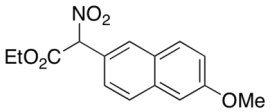
**Ethyl 2-nitro-2-(4-(trifluoromethyl)phenyl)acetate.** Using method A of the general procedure, the title compound was obtained as a yellow oil (40.3 mg, 71%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 6.23 (s, 1H), 4.41-4.29 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 163.4, 132.9 (q, *J* = 32.9 Hz), 132.5, 130.5, 126.3 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.7 Hz), 90.1, 63.8, 13.9; IR (film) 2989, 2927, 1753, 1568, 1328, 1213, 1166, 1128, 1066, 1020 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{11}H_9F_3NO_4$, 276.0472; found, 276.0475.



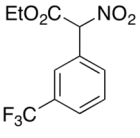
**Ethyl 2-(4-acetylphenyl)-2-nitroacetate.** Using method A of the general procedure, the title compound was obtained as a yellow oil (60.3 mg, 96%). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 6.24 (s, 1H), 4.36-4.28 (m, 2H), 2.61 (s, 3H) 1.28 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 197.4, 163.5, 138.7, 133.3, 130.3, 128.9, 90.2, 63.7, 26.8, 13.9; IR (film) 3059, 2989, 1753, 1692, 1568, 1359, 1205, 1020 cm$^{-1}$; HRMS-CI (*m/z*): $[M - H]^-$ calcd for $C_{12}H_{12}NO_5$, 250.0715; found, 250.0723.



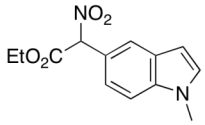
**Ethyl 2-(4-methoxyphenyl)-2-nitroacetate.** Using method B of the general procedure, the title compound was obtained as a yellow oil (44.3 mg, 74%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.23 (s, 1H), 4.37-4.29 (m, 2H), 3.85 (s, 3H) 1.31 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 164.2, 161.3, 131.3, 120.9, 114.4, 90.3, 63.1, 55.3, 13.8; IR (film) 2981, 2935, 2858, 1746, 1560, 1367, 1251, 1213, 1027 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{11}H_{12}NO_5$, 238.0715; found, 238.0715.



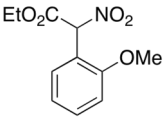

**Ethyl 2-(6-methoxynaphthalen-2-yl)-2-nitroacetate.** 2-Bromo-6-methoxynaphthalene was prepared according to literature procedure.[3] Using method B of the general procedure, the title compound was obtained as an orange oily solid (83.5 mg, 76%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.7 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.56 (dd, *J* = 1.7, 8.7 Hz, 1H), 7.22 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.17 (d, *J* = 2.5 Hz, 1H), 6.30 (s, 1H), 4.41-3.97 (m, 2 H), 3.95 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ164.6, 159.2, 135.7, 130.5, 130.1, 128.4, 128.0, 126.6, 124.1, 120.0, 105.8, 91.2, 63.5, 55.6, 14.1; IR (film) 3059, 2989, 2912, 2842, 1746, 1560, 1267, 1197, 1027 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{15}H_{14}NO_5$, 288.0872; found, 288.0862.



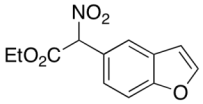

**Ethyl 2-nitro-2-(3-(trifluoromethyl)phenyl)acetate.** Using method A of the general procedure, the title compound was obtained as a yellow oil (55.4 mg, 80%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.63 (t, *J* = 7.9, 1H), 6.22 (s, 1H), 4.41-4.32 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 163.4, 133.4, 131.2 (q, *J* = 33.1 Hz), 129.90, 129.88, 127.8 (q, *J* = 3.6 Hz), 127.0 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.9 Hz), 90.2, 63.9, 14.0; IR (film) 2989, 1753, 1568, 1328, 1259, 1166, 1128,1020 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{11}H_9F_3NO_4$, 276.0484; found, 258.0494.



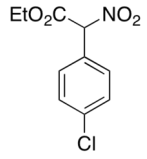

**Ethyl 2-(1-methyl-1*H*-indol-5-yl)-2-nitroacetate.** 5-Bromo-1-methylindole was prepared according to literature procedure.[4] Using method A of the general procedure, the title compound was obtained as a yellow oil (62.4 mg, 95%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 1.6 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.35 (dd, *J* = 1.6, 8.5 Hz, 1H), 7.13 (d, *J* = 3.1 Hz, 1H), 6.56 (d, *J* = 3.1 Hz, 1H), 6.29 (s, 1H), 4.41-4.28 (m, 2 H), 3.82 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 165.0, 137.7, 130.5, 128.7, 123.6, 122.9, 120.1, 110.1, 102.0, 91.9, 63.2, 33.2, 14.1; IR (film) 2981, 2927, 1746, 1560, 1359, 1189, 1020cm$^{-1}$; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{13}H_{14}N_2O_4Na$, 285.0851; found, 285.0857.



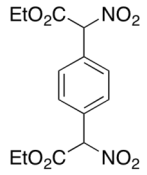

**Ethyl 2-(2-methoxyphenyl)-2-nitroacetate.** Using method A of the general procedure, the title compound was obtained as a yellow oil (41.0 mg, 69%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (dt, *J* = 1.6, 7.9 Hz, 1H), 7.36 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.64 (s, 1H), 4.40-4.33 (m, 2H), 3.87 (s, 3H) 1.33 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 164.9, 157.8, 132.4, 130.3, 121.1, 118.0, 111.2, 85.3, 63.2, 55.9, 14.1; IR (film) 2927, 2858, 1753, 1568, 1367, 1205, 1112, 1020 cm$^{-1}$; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{11}H_{13}NO_5Na$, 262.0691; found, 262.0688.



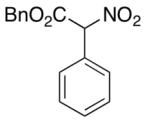
**Ethyl 2-(benzofuran-5-yl)-2-nitroacetate.** 5-Bromobenzofuran was prepared according to literature procedure.[5] Using method B of the general procedure, the title compound was obtained as a yellow oil (26.0 mg, 58%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, $J$ = 1.8 Hz, 1H), 7.71 (d, $J$ = 2.2 Hz, 1H), 7.59 (d, $J$ = 8.6 Hz, 1H), 7.44 (d, $J$ = 8.6, 1.8 Hz, 1H) 6.83 (d, $J$ = 2.2 Hz, 1H), 6.28 (s, 1H), 4.42-4.31 (m, 2H), 1.32 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 164.4, 156.0, 146.6, 128.3, 126.1, 123.8, 123.6, 112.3, 107.0, 91.1, 63.5, 14.1; IR (film) 2929, 2850, 2363, 1753, 1568, 1305, 1205, 1128, 1027 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{12}H_{10}NO_5$, 248.0559; found, 248.0563.



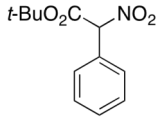
**Ethyl 2-(4-chlorophenyl)-2-nitroacetate.** Using method A of the general procedure, the title compound was obtained as a yellow oil (38.3 mg, 63%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 4H), 6.13 (s, 1H) 4.40-4.30 (m, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ163.7, 137.3, 131.4, 129.5, 127.4, 90.1, 63.7, 14.0; IR (film) 2989, 2927, 2858, 1753, 1568, 1359, 1205, 1097, 1020 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{10}H_9NO_4Cl$, 242.0220; found, 242.0211.



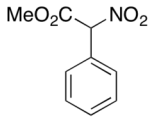
**Diethyl 2,2'-(1,4-phenylene)bis(2-nitroacetate).** In addition to the preceding desired product, the title compound was also obtained as a yellow oil (13.3 mg, 16%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 4H), 6.20 (s, 2H) 4.42-4.29 (m, 4H), 1.31 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ163.5, 131.5, 130.8, 90.3, 63.8, 14.0; IR (film) 2927, 2858, 1753, 1568, 1359, 1205, 1097, 1020 cm$^{-1}$.



**Benzyl 2-nitro-2-phenylacetate.** Method A of the general procedure was employed with benzyl nitroacetate (97.6 mg, 0.500 mmol), which was prepared according to literature procedure.[5] The title compound was obtained as a yellow oil (64.6 mg, 95%). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.49-7.43 (m, 5H), 7.40-7.30 (m, 5H), 6.22 (s, 1H), 5.33 (d, $J$ = 12.2 Hz, 1H) 5.28 (d, $J$ = 12.2 Hz, 1H) $^{13}$C NMR (125 MHz, $CDCl_3$) δ 163.9, 134.3, 130.9, 130.0, 129.2, 129.0, 128.9, 128.8, 128.5, 90.9, 68.9; IR (film) 3043, 2966, 2970, 1753, 1560, 1359, 1290, 1197 cm$^{-1}$; HRMS-ESI (*m/z*): $[M - H]^-$ calcd for $C_{15}H_{12}NO_4$, 270.0766; found, 270.0768.



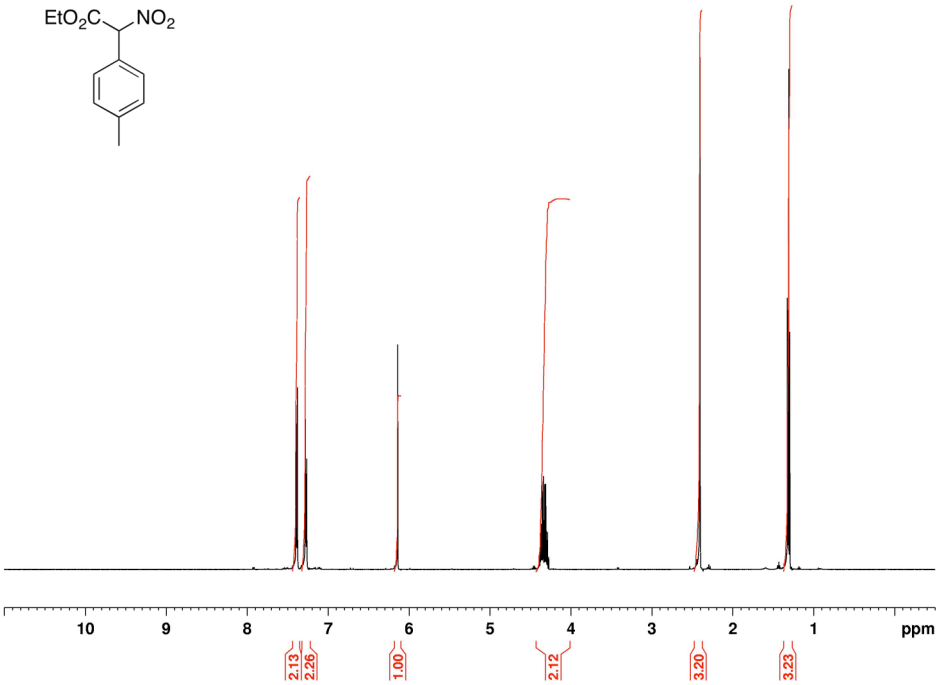

***tert*-Butyl 2-nitro-2-phenylacetate.** Method A of the general procedure was employed with *tert*-butyl nitroacetate (80.6 mg, 0.500 mmol), which was prepared according to literature procedure.[5] The title compound was obtained as a yellow oil (21.7 mg, 98%). The spectral data were in agreement with reported literature values.[6]

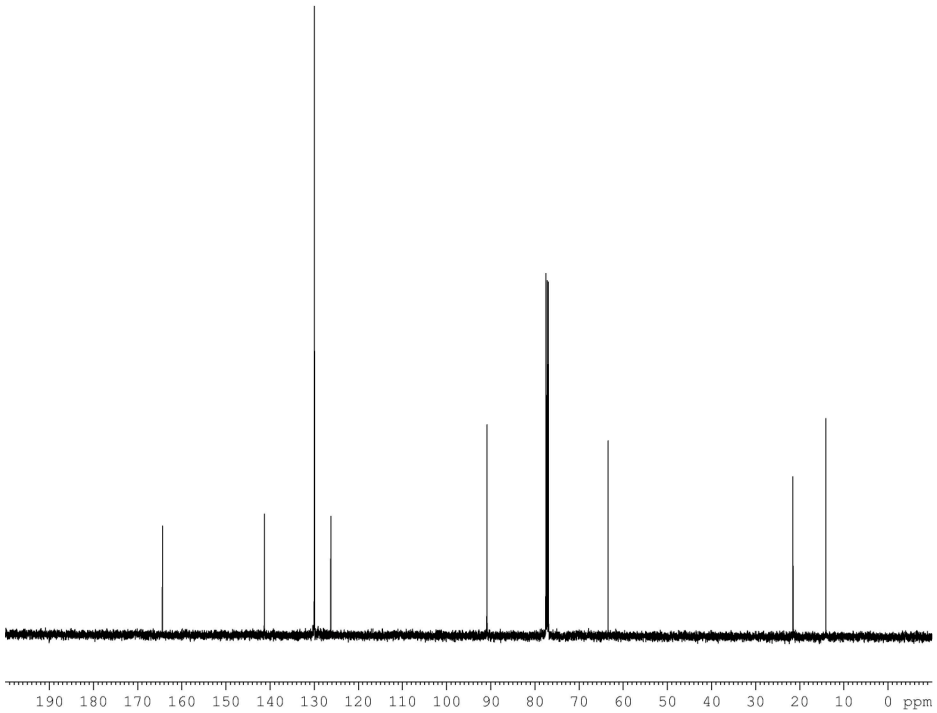


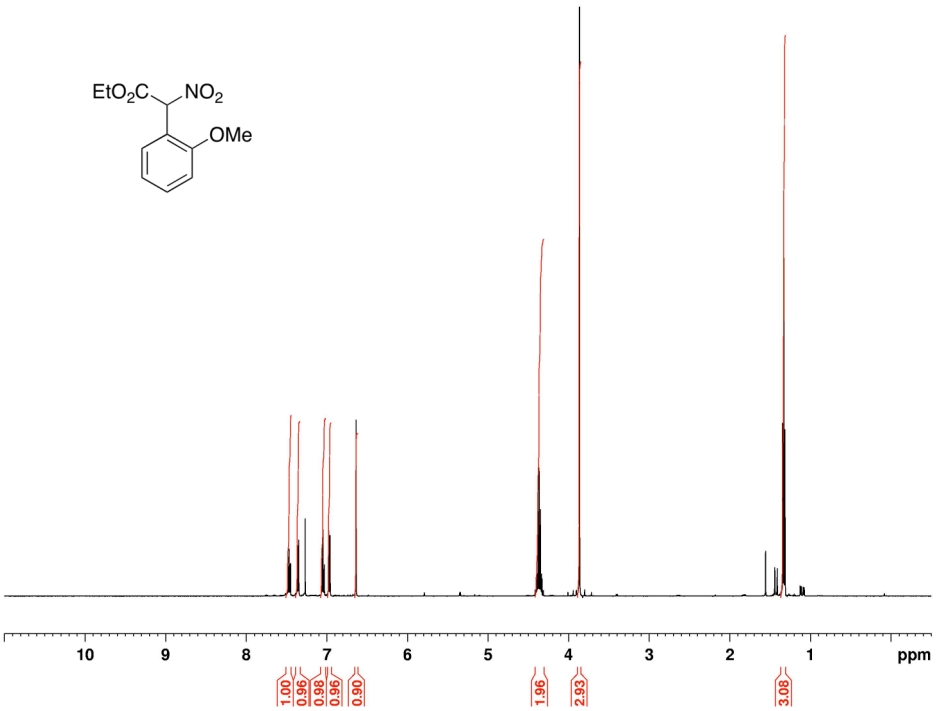

**Methyl 2-nitro-2-phenylacetate**. Method A of the general procedure was utilized with *tert*-butyl nitroacetate (59.5 mg, 0.500 mmol), which was prepared according to literature procedure.[5] The title compound was obtained as a yellow oil (25.6 mg, 53%). The spectral data were in agreement with reported literature values.[6]

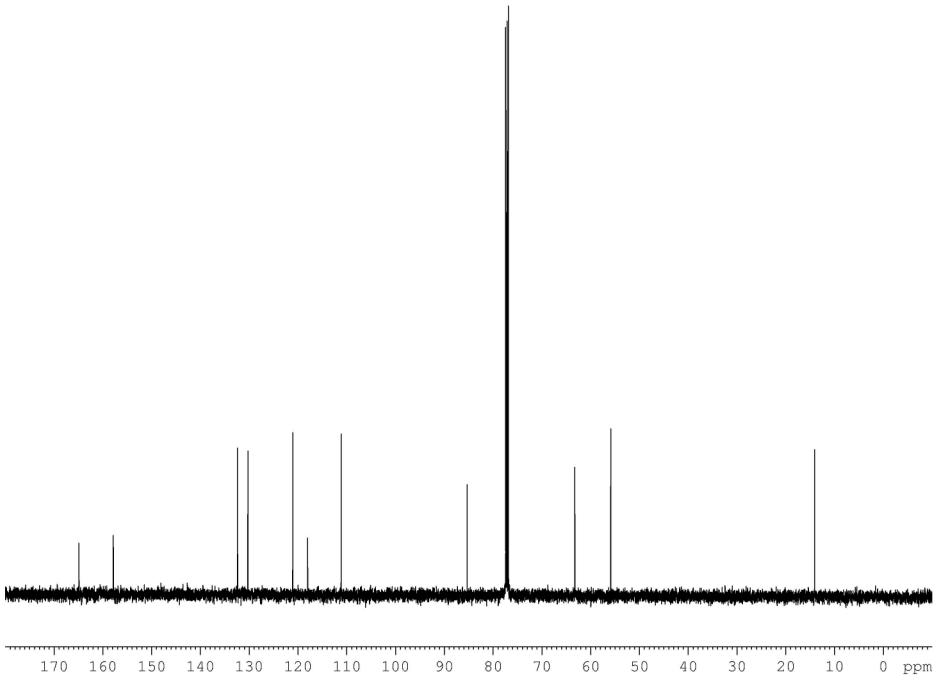
**Reference**

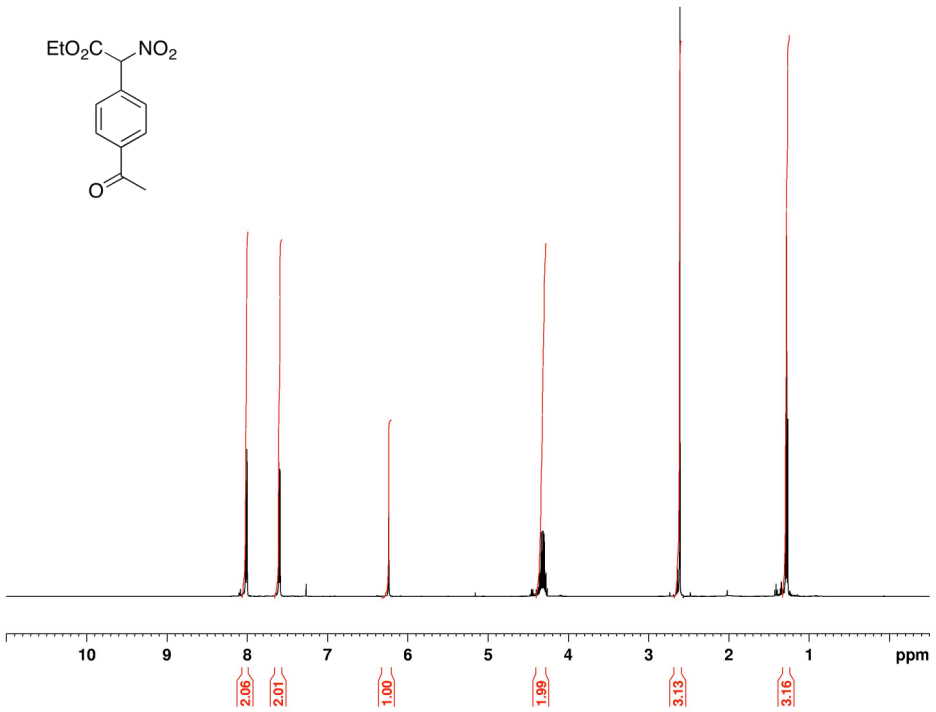
1. a) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075. b) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686-6687.
2. Lehr, F.; Gonnerman, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2258-2275.
3. Wiel, M. K. J. ter ; Feringa, B. L. *Synthesis* **2005**, *11*, 1789-1796.
4. Shieh, W.-C.; Dell, S.; Bach, A.; Repič, O.; Blacklock, T.J. *J. Org. Chem*. **2003**, *68*, 1954-1957.
5. Suzuki, H.; Tsutsui, H, Kano, A.; Katoh, S.; Morita, T.; Matsuda, K.; Iibuchi, N.; Ogawa, M. *Heterocycles* **1997**, *45*, 1657-1662.
6. González, D. F.; Brand, J. P.; Waser, J. *Chem. Eur. J.* **2010**, *16*, 9457-9461.

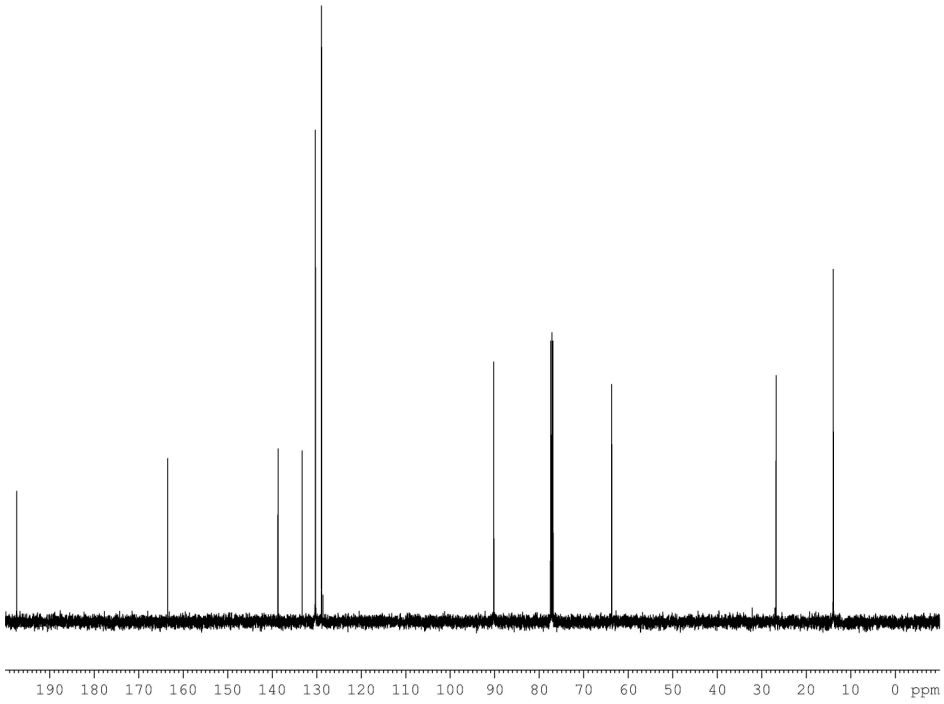

EtO2C
NO2
10
9
8
7
6
5
4
3
2
1
ppm
2.13
2.26
1.00
2.12
3.20
3.23

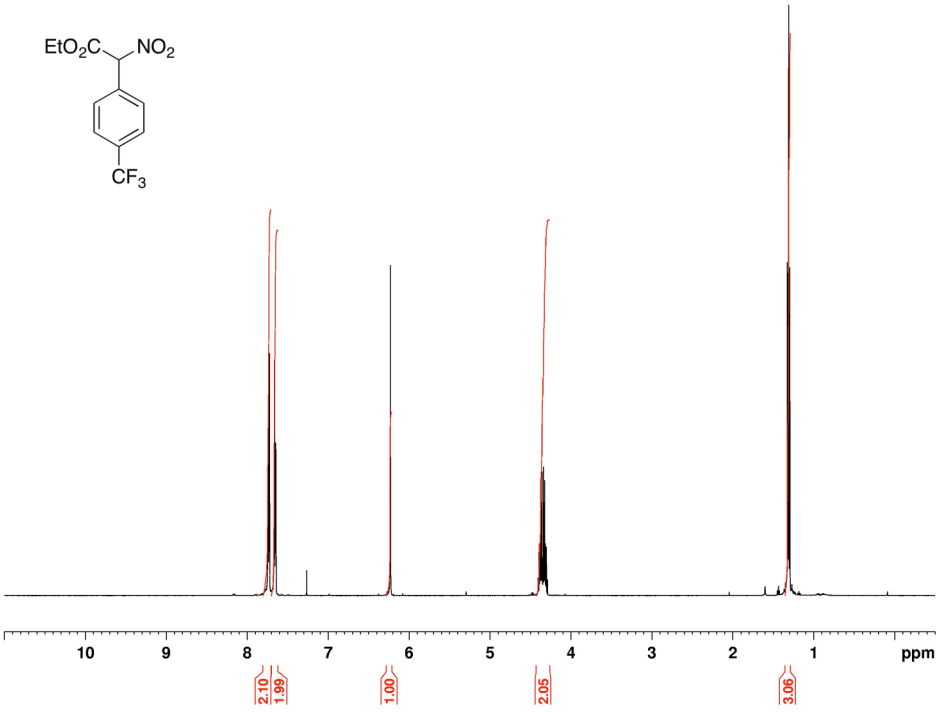

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

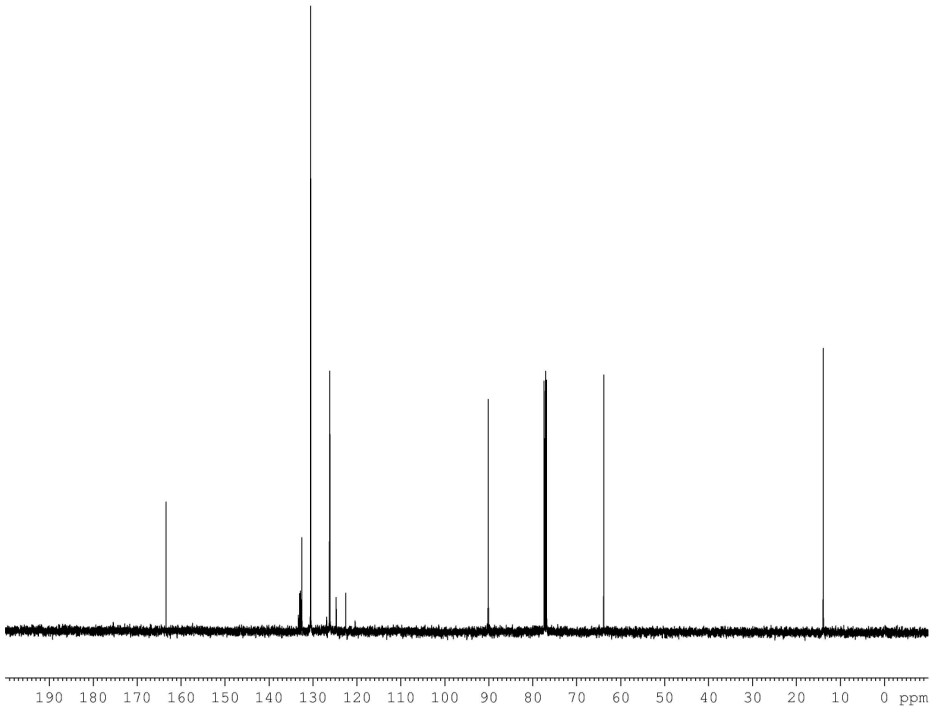

EtO2C
NO2
OMe
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.96
0.98
0.96
0.90
1.96
2.93
3.08

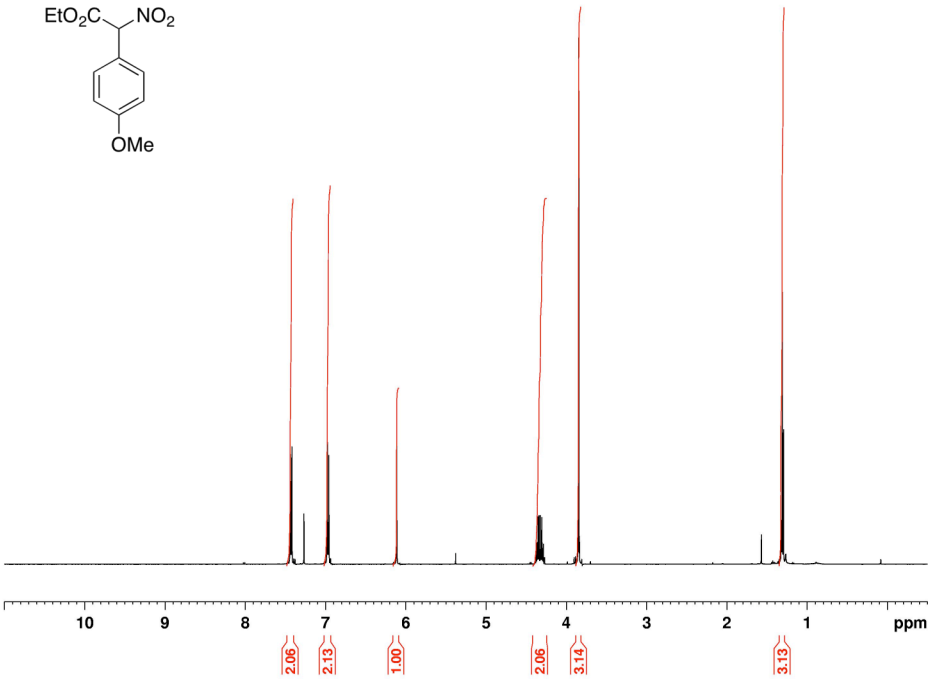

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

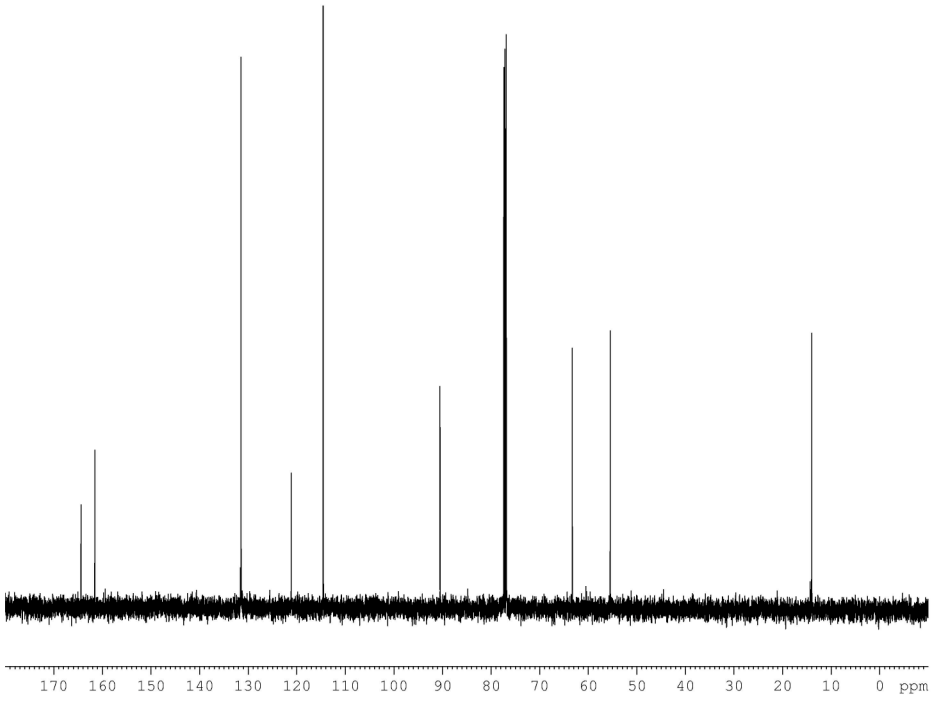

EtO2C
NO2
O
10
9
8
7
6
5
4
3
2
1
ppm
2.06
2.01
1.00
1.99
3.13
3.16

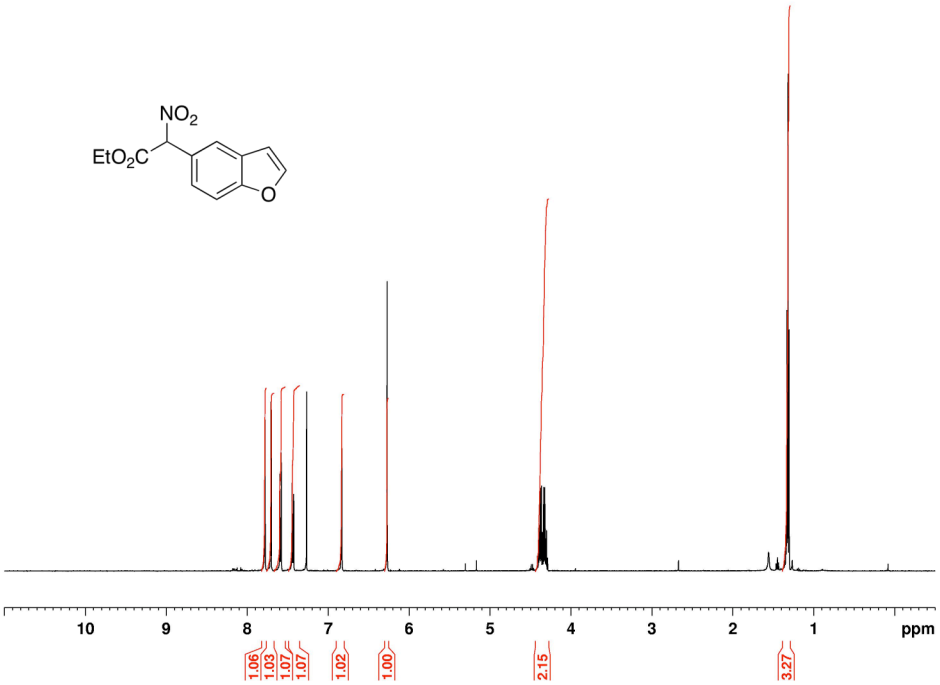

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

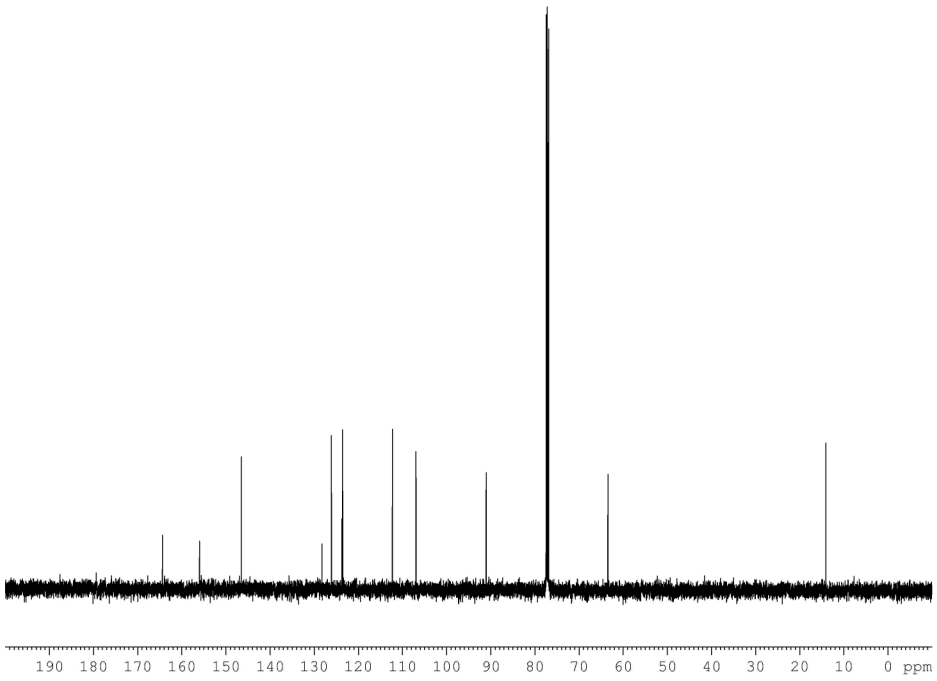

EtO2C
NO2
CF3
10
9
8
7
6
5
4
3
2
1
ppm
2.10
1.99
1.00
2.05
3.06

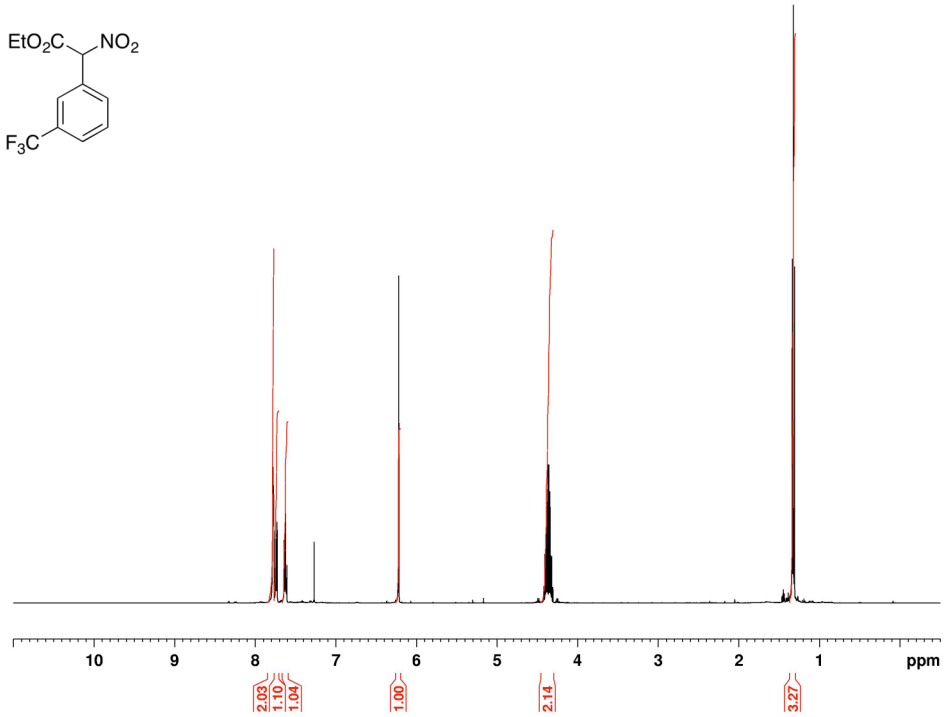

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

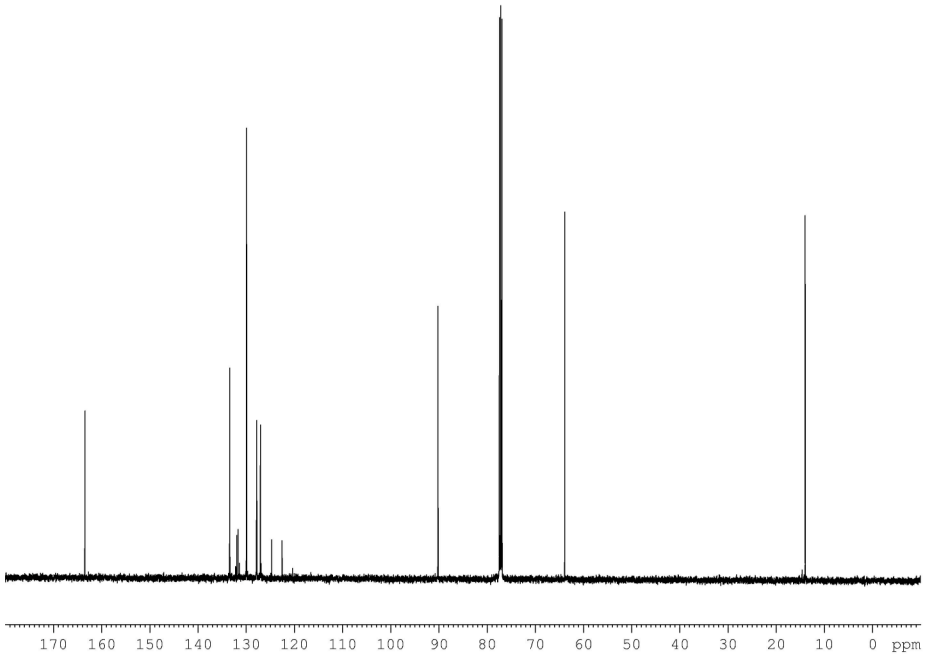

EtO2C
NO2
OMe
10
9
8
7
6
5
4
3
2
1
ppm
2.06
2.13
1.00
2.06
3.14
3.13

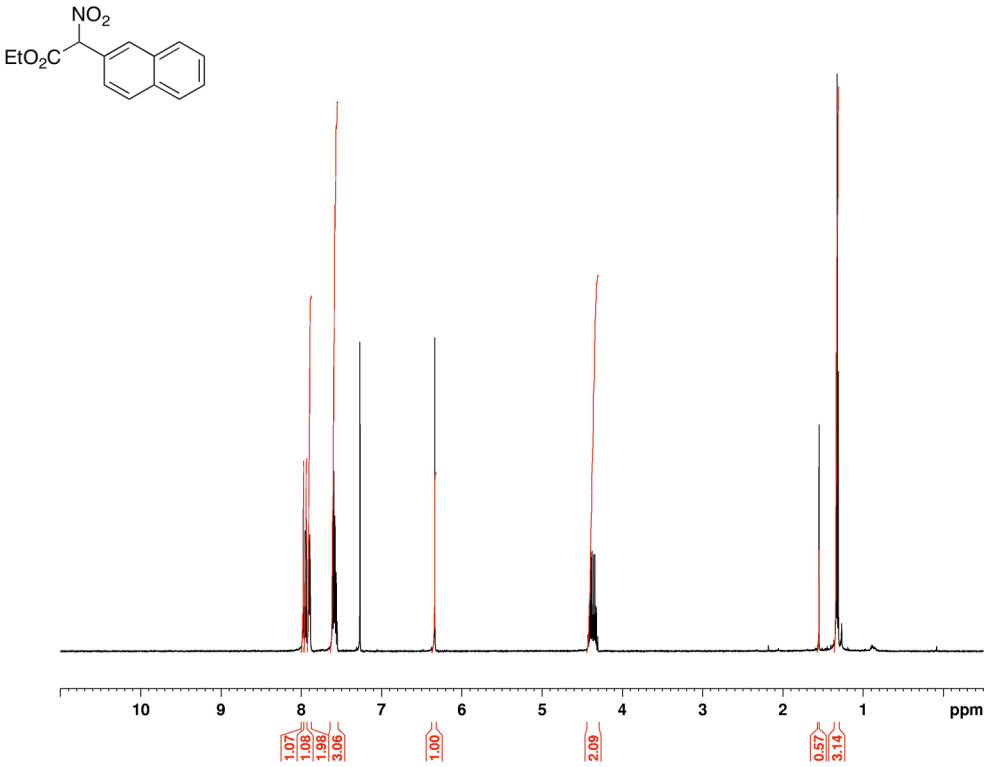

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

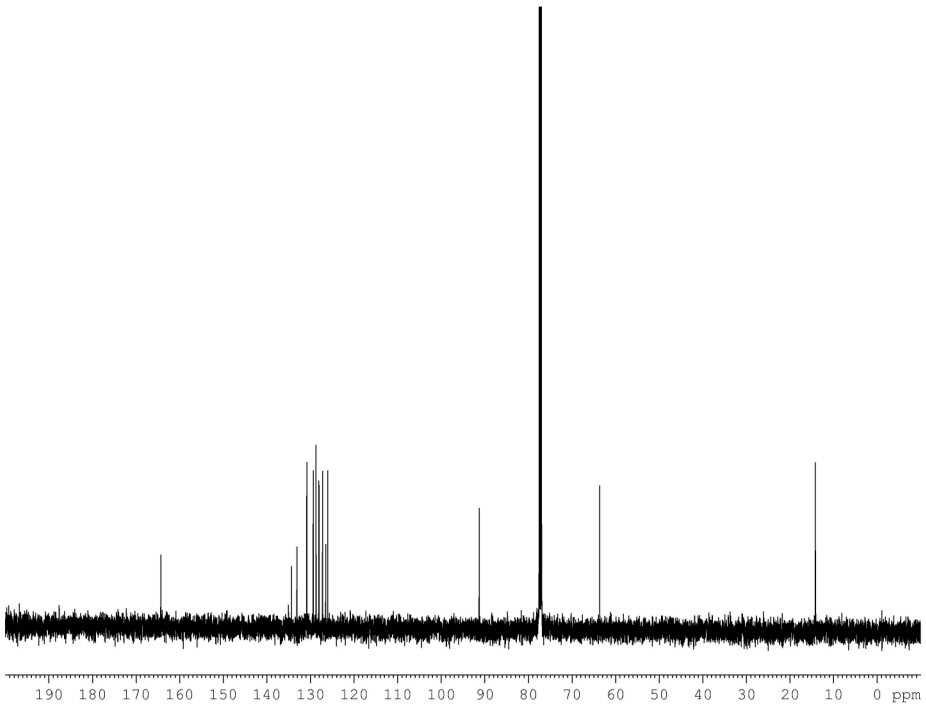

NO2
EtO2C
O
10
9
8
7
6
5
4
3
2
1
ppm
1.06
1.03
1.07
1.07
1.02
1.00
2.15
3.27

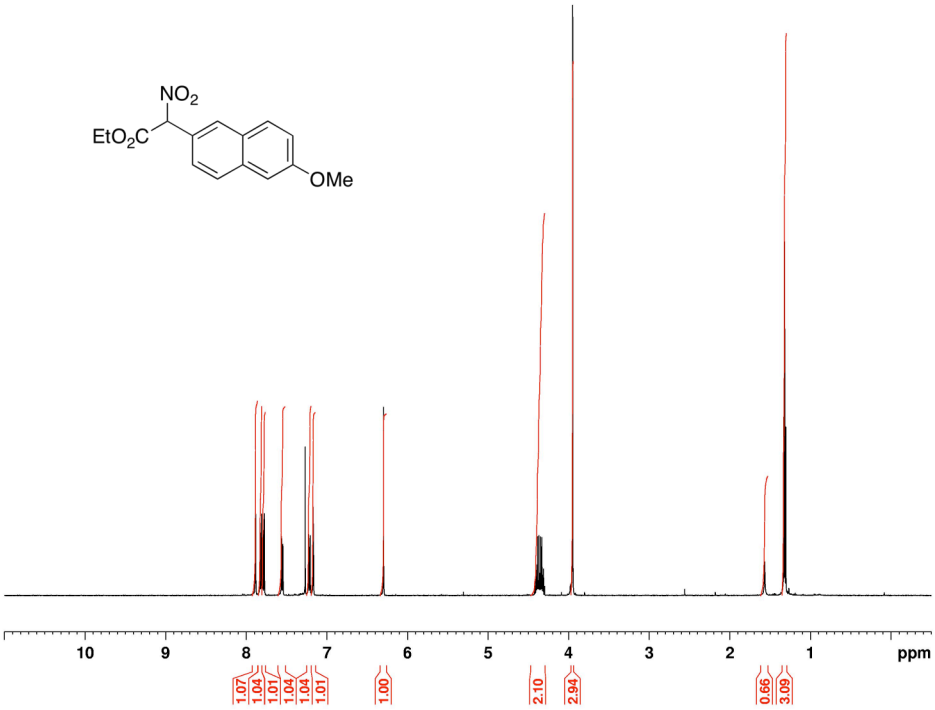

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

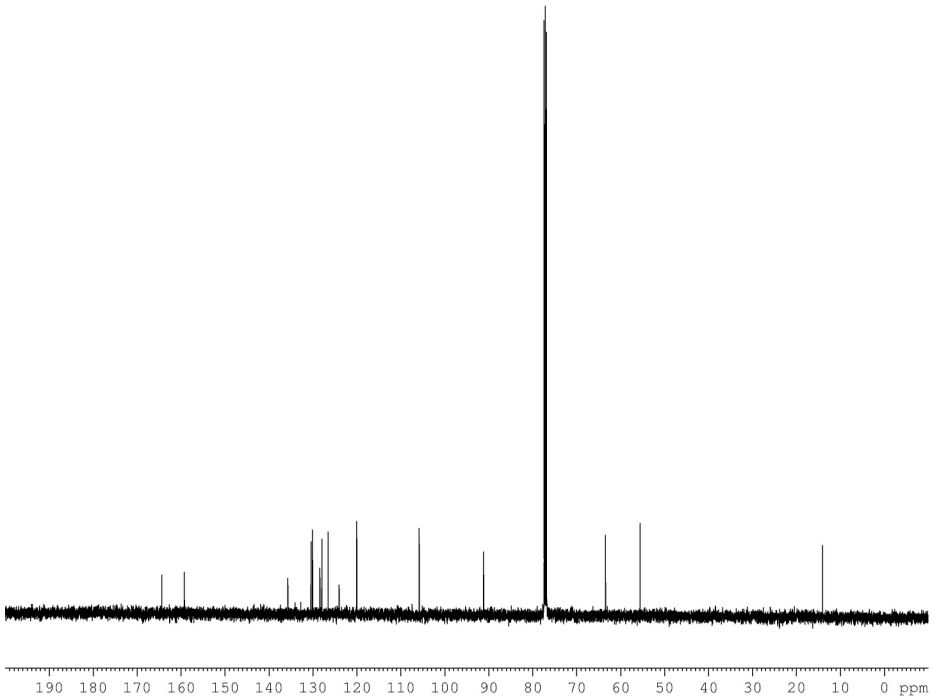

EtO2C
NO2
F3C
10
9
8
7
6
5
4
3
2
1
ppm
2.03
1.10
1.04
1.00
2.14
3.27

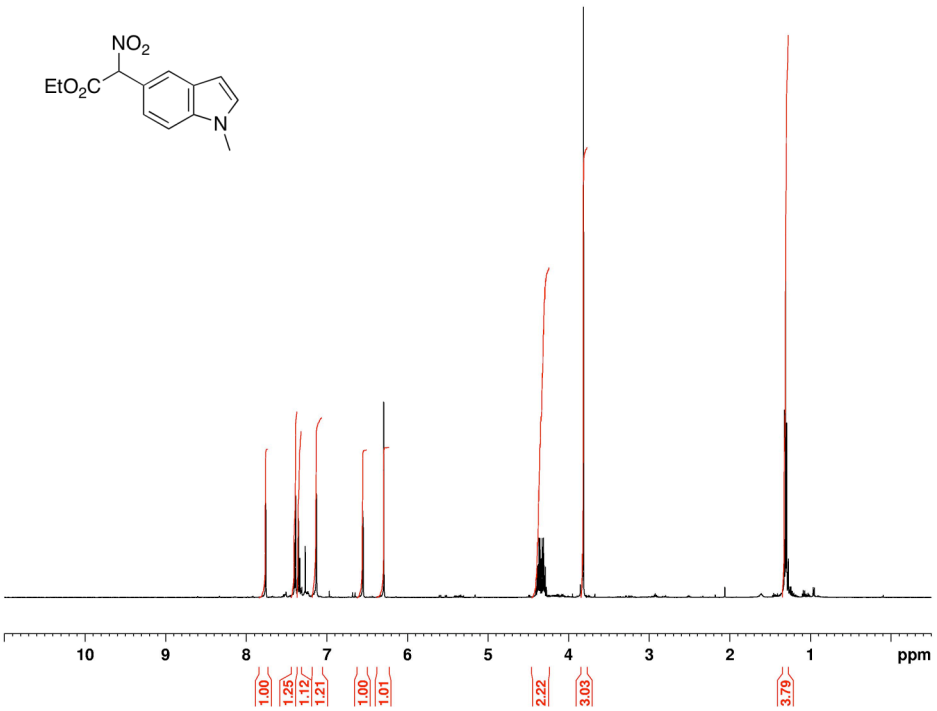

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

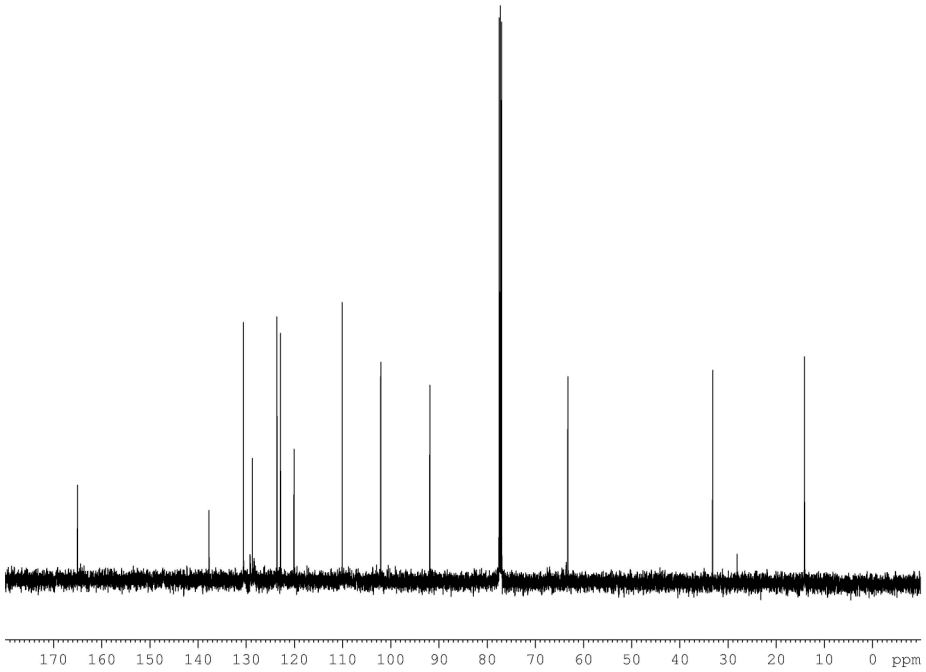

NO2
EtO2C
10
9
8
7
6
5
4
3
2
1
ppm
1.07
1.08
1.98
3.06
1.00
2.09
0.57
3.14

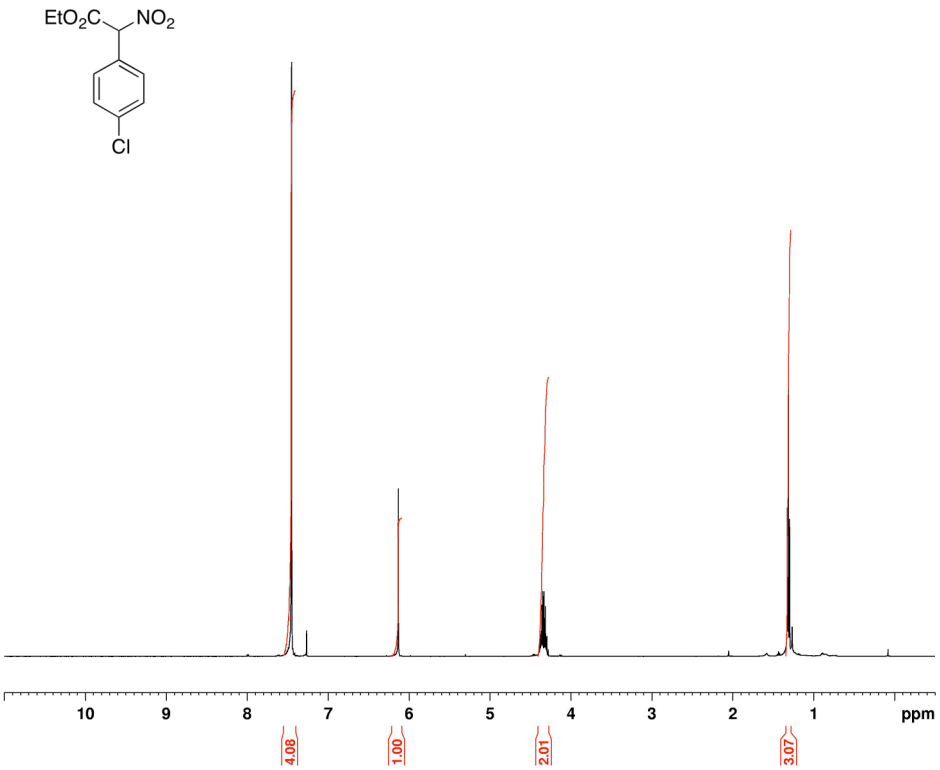

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

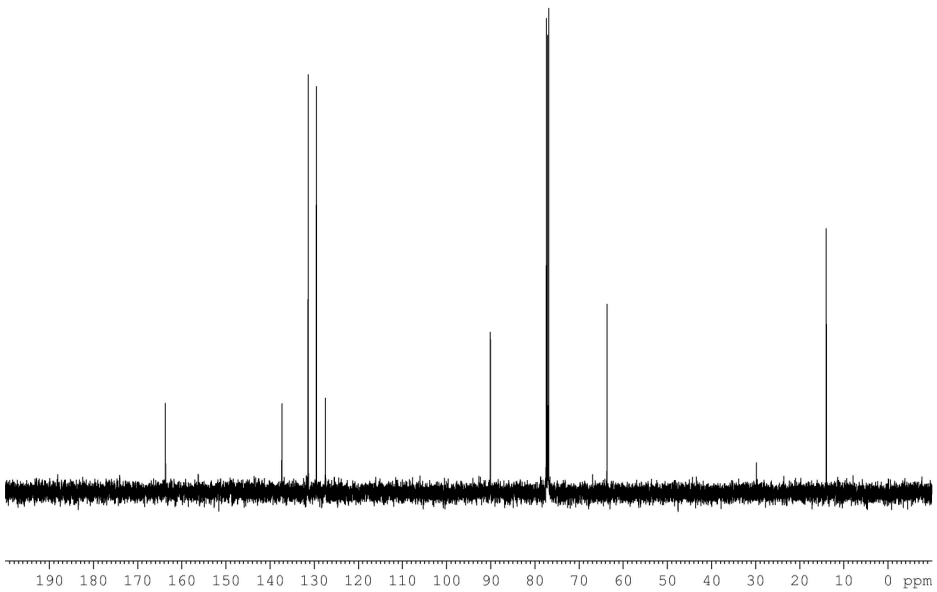

NO2
EtO2C
OMe
10
9
8
7
6
5
4
3
2
1
ppm
1.07
1.04
1.01
1.04
1.04
1.01
1.00
2.10
2.94
0.66
3.09

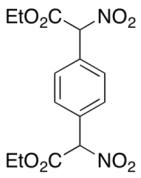

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

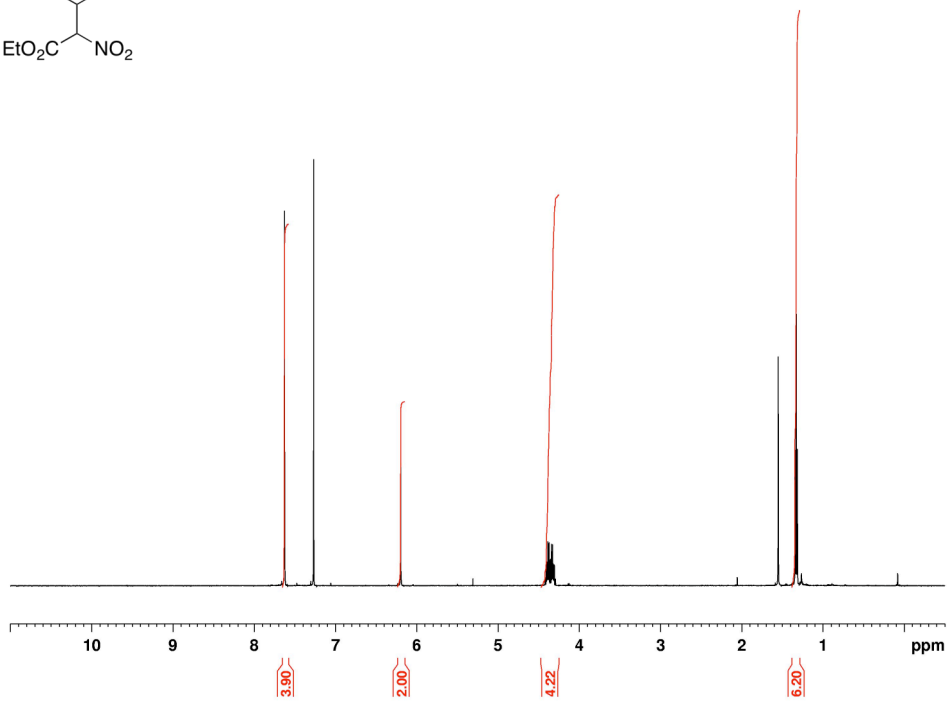

NO2
EtO2C
N
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.25
1.12
1.21
1.00
1.01
2.22
3.03
3.79

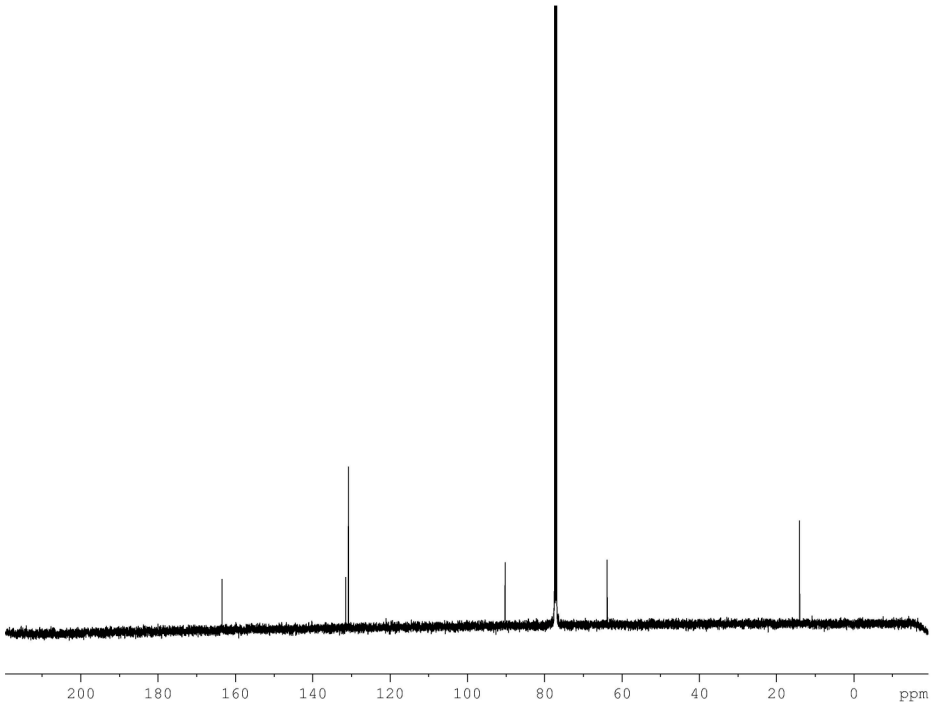

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

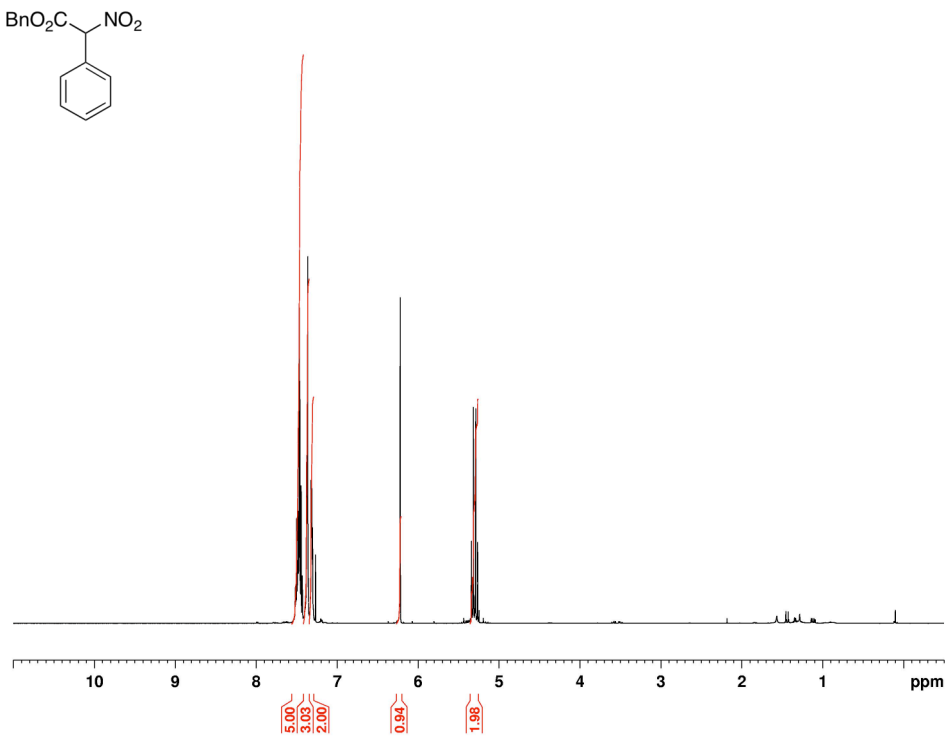

EtO2C
NO2
Cl
10
9
8
7
6
5
4
3
2
1
ppm
4.08
1.00
2.01
3.07

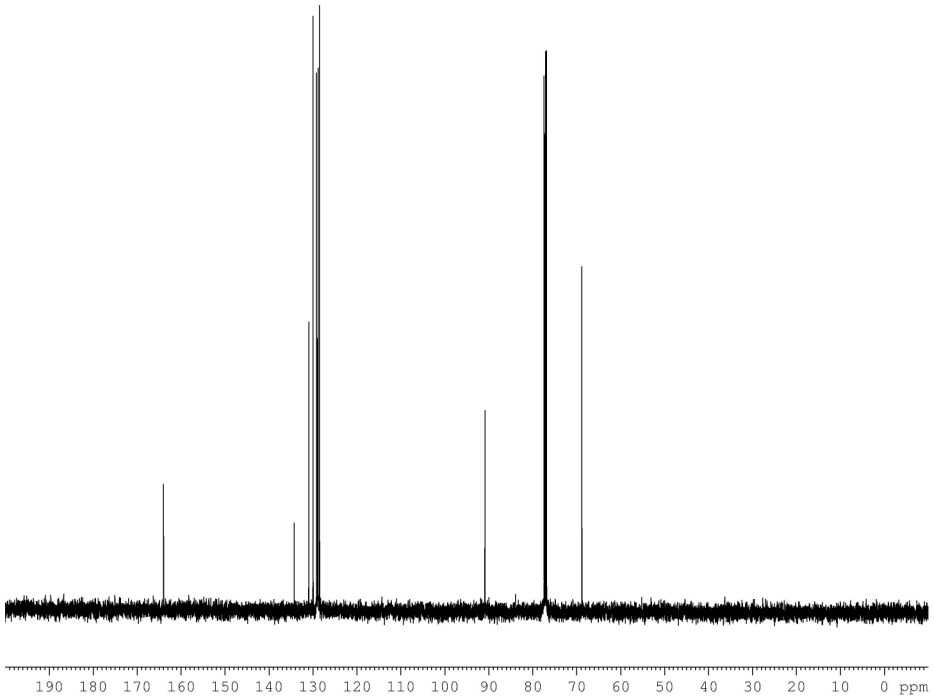

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


EtO2C
NO2
EtO2C
NO2


10
9
8
7
6
5
4
3
2
1
ppm
3.90
2.00
4.22
6.20


200
180
160
140
120
100
80
60
40
20
0
ppm


BnO2C
NO2
10
9
8
7
6
5
4
3
2
1
ppm
5.00
3.03
2.00
0.94
1.98


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