Electronic Supplementary Material (ESI) for ChemComm.

Dehydroxyalkylative Halogenation of C(aryl)−C Bonds of Aryl Alcohols

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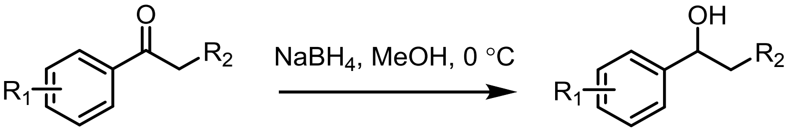
Experimental

Chemicals

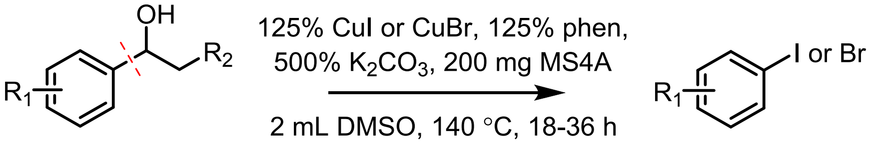
Solid chemicals including Cu salts, Ag salts, 1,10-phenanthroline, 1,10-phenanthroline monohydrate, molecular sieves 4A (MS4A), bases, butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) were purchased from Acros. Liquid chemicals including solvents, internal standards and standard samples were purchased from Sigma-Aldrich. Alcohol substrates including 1-(2-nitrophenyl)ethanol, 1-(2-methoxyphenyl)ethanol, 1-(2-chlorophenyl)ethanol, 1-(2-methoxyphenyl)propanol, 1-(o-tolyl)ethanol, (2-nitrophenyl)methanol, 2-(2-nitrophenyl)ethanol, 1-(pyridin-2-yl)ethanol, 1-(furan-2-yl)ethanol, furan-2-ylmethanol, 5-(hydroxymethyl)furancarbaldehyde are also purchased from Sigma-Aldrich. Other alcohol substrates (1**e**, 1**i-j**, 1**l-n**, 1**r**) were obtained according to the following procedure.

Synthesis of alcohol substrates[1]



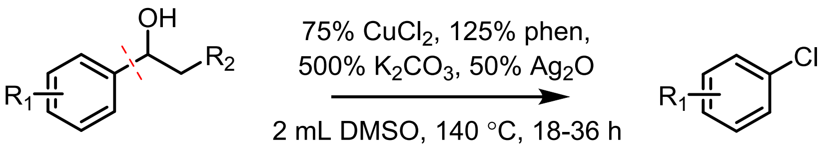
Alcohol substrates were synthesized by reduction of corresponding ketones with $NaBH_4$ in methanol. Specifically, 20 mmol ketone was dissolved in 100 mL methanol and cooled to 0 °C, to which 7 mmol $NaBH_4$ was added slowly. When the bubbles were gone, the mixture was heated to room temperature. The transformation was monitored by thin layer chromatography (TLC). After reaction, the mixture was concentrated *in vacuo* and diluted with 50 mL water. The organic products were extracted with 3×100 mL ethyl acetate, washed with saturated aqueous NH_4Cl and brine in sequence, dried with anhydrous $MgSO_4$, concentrated *in vacuo*. The alcohol products were purified by column chromatography if necessary.

General procedure for dehydroxyalkylative iodation and bromination (method **A**).



The reactions were carried out in Teflon-lined stainless-steel reactor. 0.2 mmol alcohol substrate, 0.25 mmol $CuBr/CuBr_2$ for bromination and 0.25 mmol CuI for iodation, 0.25 mmol phen, 1 mmol K_2CO_3, 200 mg MS4A, 2 mL DMSO, and internal standard (n-decane) were added into the reactor and charged with 0.5 MPa O_2. Then, the reactor was heated at 140 °C for 18 to 36 h. After reaction, the products were extracted by ethyl acetate and saturated brine of NH_4Cl for qualitative and quantitative analysis.

General procedure for dehydroxyalkylative chlorination (method **B**).



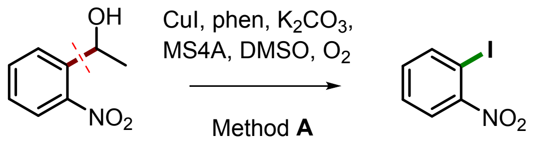
The reactions were carried out in Teflon-lined stainless-steel reactor. 0.2 mmol alcohol substrate, 0.15 mmol $CuCl_2$, 0.25 mmol phen, 1 mmol K_2CO_3, 0.1 mmol Ag_2O, 2 mL DMSO, and internal standard (n-decane) were added into the reactor and charged with 0.5 MPa O_2. Then, the reactor was heated at 140 °C for 18 to 36 h. After reaction, the products were extracted by ethyl acetate and saturated brine of NH_4Cl for qualitative and quantitative analysis.

Characterization methods

GC-MS measurement (Agilent 5975C-7890A, equipped with an electron ionization mass detector) was used for the qualitative analysis of products by comparing with authentic samples. GC (Agilent 7820, equipped with a hydrogen flame-ionization detector, full electric pneumatic control, 280 °C) was used for quantitative analysis. The conversion and yields of corresponding products were calculated based on internal standard curves and areas of integrated peak area.

Supporting results

Table S1. Optimation of reaction conditions of C(aryl)−C bond iodation.

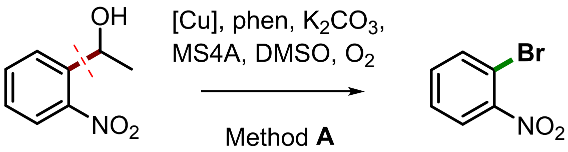


1a **4a**

Entry	CuI	Phen	Base	MS4A	Solvents	Gas	Time	Yield
1	60%	125%	500% K_2CO_3	200 mg	DMSO	O_2	18 h	**28%**
2	100%	125%	500% K_2CO_3	200 mg	DMSO	O_2	18 h	**61%**
3	**125%**	**125%**	**500% K_2CO_3**	**200 mg**	**DMSO**	**O_2**	**18 h**	**91%**
4	125%	0	500% K_2CO_3	200 mg	DMSO	O_2	18 h	**24%**
5	125%	62.5%	500% K_2CO_3	200 mg	DMSO	O_2	18 h	**59%**
6	125%	250%	500% K_2CO_3	200 mg	DMSO	O_2	18 h	**55%**
7	125%	125%	200% K_2CO_3	200 mg	DMSO	O_2	18 h	**48%**
8	125%	125%	400% K_2CO_3	200 mg	DMSO	O_2	18 h	**69%**
9	125%	125%	700% K_2CO_3	200 mg	DMSO	O_2	18 h	**39%**
10	125%	125%	500% Na_2CO_3	200 mg	DMSO	O_2	18 h	**64%**
11	125%	125%	500% Cs_2CO_3	200 mg	DMSO	O_2	18 h	**33%**
12	125%	125%	500% $NaHCO_3$	200 mg	DMSO	O_2	18 h	**50%**
13	125%	125%	500% KOH	200 mg	DMSO	O_2	18 h	**17%**
14	125%	125%	500% K_2CO_3	200 mg	DMF	O_2	18 h	**0%**
15	125%	125%	500% K_2CO_3	200 mg	DMA	O_2	18 h	**0%**
16	125%	125%	500% K_2CO_3	200 mg	Dioxane	O_2	18 h	**1%**
17	125%	125%	500% K_2CO_3	200 mg	Toluene	O_2	18 h	**2%**
18	125%	125%	500% K_2CO_3	100 mg	DMSO	O_2	18 h	**66%**
19	125%	125%	500% K_2CO_3	300 mg	DMSO	O_2	18 h	**79%**
20	125%	125%	500% K_2CO_3	200 mg	DMSO	O_2	6 h	**54%**
21	125%	125%	500% K_2CO_3	200 mg	DMSO	O_2	8 h	**80%**
22	125%	125%	500% K_2CO_3	200 mg	DMSO	O_2	12 h	**90%**
23	125%	125%	500% K_2CO_3	200 mg	DMSO	N_2	18 h	**0%**

Reaction conditions (Method **A** for iodation): Experiments were performed on 0.2 mmol scale unless otherwise noted. Yield was determined by gas chromatography (GC). CuI, 1,10-phenanthroline (phen), base, MS4A, were mixed in a sealed reaction vessel and charged with 0.5 MPa O_2 or N_2. The reaction was carried out at 140 °C.

Table S2. Optimation of reaction conditions of C(aryl)−C bond bromination.

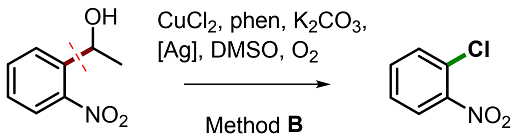


1a **3a**

Entry	[Cu]	Phen	Base	MS4A	Solvents	Gas	Time	Yield
1	**125% CuBr**	**125%**	**500% K_2CO_3**	**200 mg**	**DMSO**	**O_2**	**18 h**	**72%**
2	125% $CuBr_2$	125%	500% K_2CO_3	200 mg	DMSO	O_2	18 h	**70%**
3	125% CuBr	125%	500% K_2CO_3	200 mg	DMSO	N_2	18 h	**0%**

Reaction conditions (Method **A** for bromination): Experiments were performed on 0.2 mmol scale unless otherwise noted. Yield was determined by GC. Cu salts, phen, base, MS4A, were mixed in a sealed reaction vessel and charged with 0.5 MPa O_2 or N_2. The reaction was carried out at 140 °C.

Table S3. Optimation of reaction conditions of C(aryl)−C bond chlorination.



1a **2a**

Entry	$CuCl_2$	Phen	Base	[Ag]	Solvents	Gas	Time	Yield
1	75%	125%	250% K_2CO_3	50% Ag_2CO_3	1:1 DMSO/DMF	O_2	18 h	**65%**
2	75%	125%	250% K_2CO_3	50% Ag_2O	1:1 DMSO/DMF	O_2	18 h	**65%**
3	75%	125%	250% K_2CO_3	50% AgCl	1:1 DMSO/DMF	O_2	18 h	**42%**
4	75%	125%	250% K_2CO_3	50% AgOAc	1:1 DMSO/DMF	O_2	18 h	**21%**
5	75%	125%	250% K_2CO_3	0% Ag_2O	1:1 DMSO/DMF	O_2	18 h	**3%**
6	75%	125%	250% K_2CO_3	25% Ag_2O	1:1 DMSO/DMF	O_2	18 h	**22%**
7	75%	125%	250% K_2CO_3	100% Ag_2O	1:1 DMSO/DMF	O_2	18 h	**37%**
8	75%	125%	250% K_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**83%**
9	75%	125%	250% K_2CO_3	50% Ag_2O	DMF	O_2	18 h	**6%**
10	75%	125%	250% K_2CO_3	50% Ag_2O	DMA	O_2	18 h	**0%**
11	75%	125%	250% K_2CO_3	50% Ag_2O	Toluene	O_2	18 h	**0%**
12	75%	125%	250% KOH	50% Ag_2O	DMSO	O_2	18 h	**83%**
13	75%	125%	250% NaOH	50% Ag_2O	DMSO	O_2	18 h	**78%**
14	75%	125%	250% K_3PO_4	50% Ag_2O	DMSO	O_2	18 h	**70%**
15	75%	125%	250% Cs_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**82%**
16	75%	125%	125% K_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**70%**
17	75%	125%	375% K_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**86%**
18	75%	125%	500% K_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**86%**
19	50%	125%	500% K_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**38%**
20	100%	125%	500% K_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**84%**
21	75%	75%	500% K_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**59%**
22	**75%**	**150%**	**500% K_2CO_3**	**50% Ag_2O**	**DMSO**	**O_2**	**18 h**	**87%**
23	75%	250%	500% K_2CO_3	50% Ag_2O	DMSO	O_2	18 h	**86%**
24	75%	150%	500% K_2CO_3	50% Ag_2O	DMSO	O_2	6 h	**57%**
25	75%	150%	500% K_2CO_3	50% Ag_2O	DMSO	O_2	12 h	**72%**
26	75%	150%	500% K_2CO_3	50% Ag_2O	DMSO	N_2	18 h	**0%**

Reaction conditions (Method **B** for chlorination): Experiments were performed on 0.2 mmol scale unless otherwise noted. Yield was determined by GC. $CuCl_2$, Ag salts, phen, base, were mixed in a sealed reaction vessel and charged with 0.5 MPa O_2 or N_2. The reaction was carried out at 140 °C.

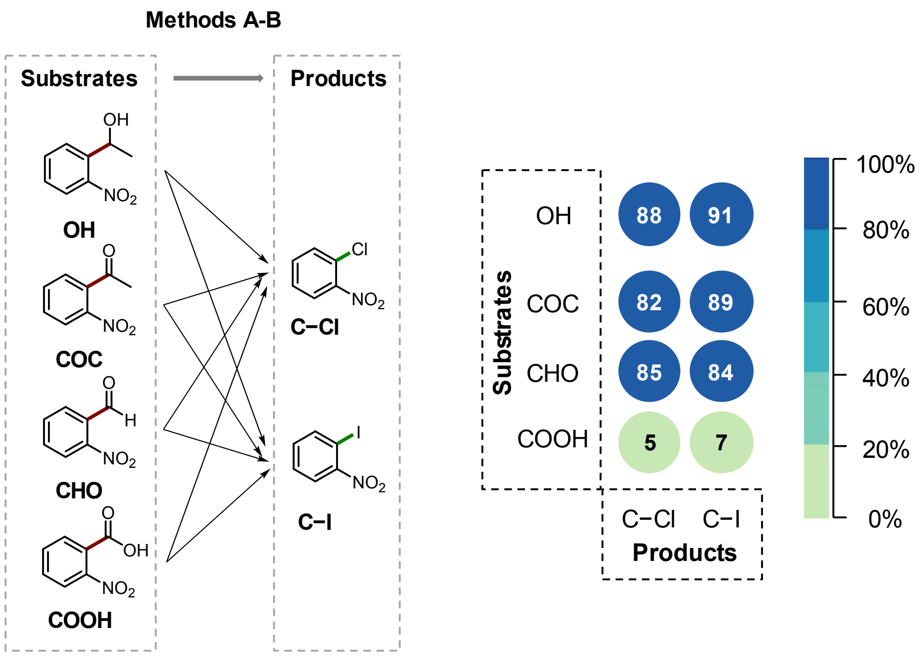


Figure S1. The transformation of possible intermediates using ketone (COC), aldehyde (CHO) and acid (COOH) derivatives of 1-(2-nitrophenyl)ethanol in the dehydroxyalkylative halogenation reactions, using the developed methods **A-B**. Yields of corresponding products are shown in the colored matrix.

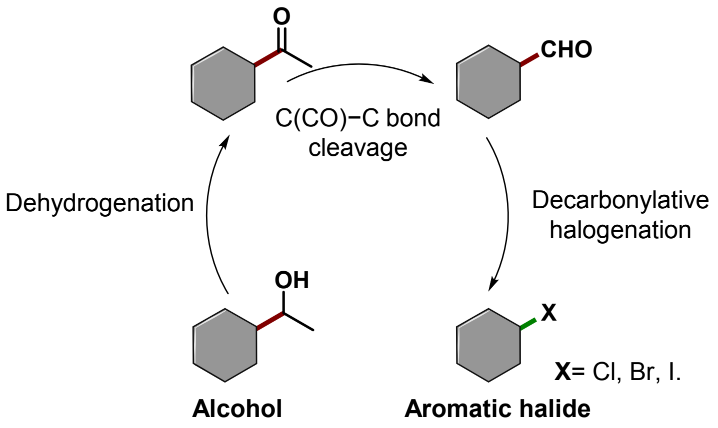


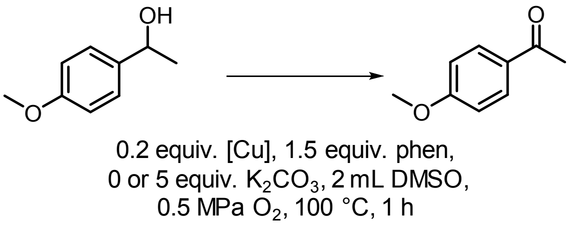
Figure S2. Probable reaction pathway of dehydroxyalkylative halogenation reactions.

Supporting mechanism study

The proposed plausible reaction pathway is illustrated in Fig. 4. During the reacion, alcohol substrate firstly reduces Cu^{II} species **1** to Cu^{I} species **2** which are subsequently oxidized back to 1 via the intermediate **3** by the terminal oxidant O_2, with the consumption of OH^-.[2] Additional experiments verified the importance of the presence of base in the reaction system (Fig. S3). Then, Cu catalyzed C(CO)−C bond cleavage of ketone leads to the generation of aldehyde intermediate *via* hydroxylation of β-H and 1,2-hydride shift.[3]

Aldehyde represents the key intermediate for halogenation. For decarbonylative iodization, The aldehyde is oxidized (single electron transfer, SET) to acyl radical **6** catalyszed by Cu, followed by the release of CO to afford aryl radical **7**. Iodide product is generated by abstracting the iodide radical came from intra-oxidation of Cu^{II}–I.[4] In this regard, aryl alcohols served as radical synthetic equivalents for dehydroxyalkylative iodation. For decarbonylative chlorination, Oxidative addition of aldehyde to Cu^{I} **8** generates Cu^{II} **9**, accompanied by the release of H_2O and CO under basic condition. Different from iodation, chlorination undergoes non-radical pathway. Extrusion of CO group of **9** generates **10**. Direct oxidation of Cu^{II} **10** by molecular oxygen is kinetically unfavored. In chlorination reactions, Ag co-catalyst transports the electrons from Cu^{II} **10** to O_2 via a low-energy pathway and promotes the reaction.[5] After oxidation to Cu^{III} **11** by Ag^{I} salt, chloride product is generated via reductive elimination.[6] In this case, aryl alcohols served as electrophilic synthetic equivalents for dehydroxyalkylative chlorination.

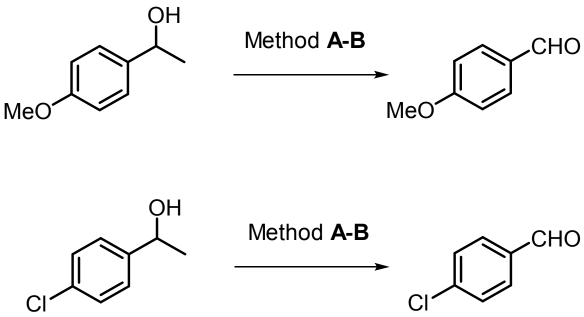
Notably, in the Cu catalyzed radical mediated iodination reaction, ionic $Cu^{(I)}$ **6** could be readily re-oxidized by O_2 to $Cu^{(II)}$ **7**. However, in chlorination reaction, electron transfer between organic Cu intermediate **10** and O_2 is difficult. Hence, additional Ag salt catalyst was required. The Ag salt catalyst acted as an electron-transfer mediator between organic Cu and O_2 and promoted the oxidation of intermediate **10** to **11**.[5, 7]



0.2 equiv. [Cu], 1.5 equiv. phen,
0 or 5 equiv. K_2CO_3, 2 mL DMSO,
0.5 MPa O_2, 100 °C, 1 h

[Cu]	With base	Without base
$CuCl_2$	78%	7%
CuBr	77%	7%
CuI	70%	10%

Figure S3. Cu catalyzed dehydrogenation of alcohol substrate to ketone. The three Cu halides used for dehydroxyalkylative halogenation reactions showed similar catalytic activities for oxidation of alcohol to ketone. In the absence of base, the reaction can hardly proceed (yiled: <10%), indicating the crucial role of base for dehydrogenation of alcohol substrates. Reaction conditions: 0.2 mmol substrate, 0.2 equiv. Cu salts,1.25 equiv. phen, 0 or 5 equiv. K_2CO_3, 2 mL DMSO, 0.5 MPa O_2, 100 °C, 1 h.



	Yield
A	91%
B	85%

A	86%
B	65%

Figure S4. The transformation of non-ortho-substituted substrates in dehydroxyalkylative reactions. The major products are aldehydes. The corresponding yields of aldehyde products are listed in the insert table. These results suggest that the developed methods are primarily effective for ortho-functionalized aryl alcohols at this stage, as decarbonylation of non-ortho-substituted substrates cannot proceed under given reaction conditions.

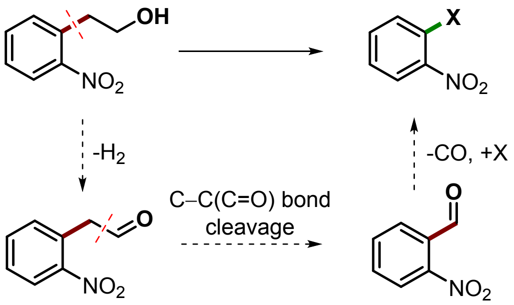


Figure S5. Transformation pathway for primary alcohol.

Reference

1. R. M. Haak, F. Berthiol, T. Jerphagnon, A. J. A. Gayet, C. Tarabiono, C. P. Postema, V. Ritleng, M. Pfeffer, D. B. Janssen, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *J. Am. Chem. Soc.*, 2008, **130**, 13508-13509.
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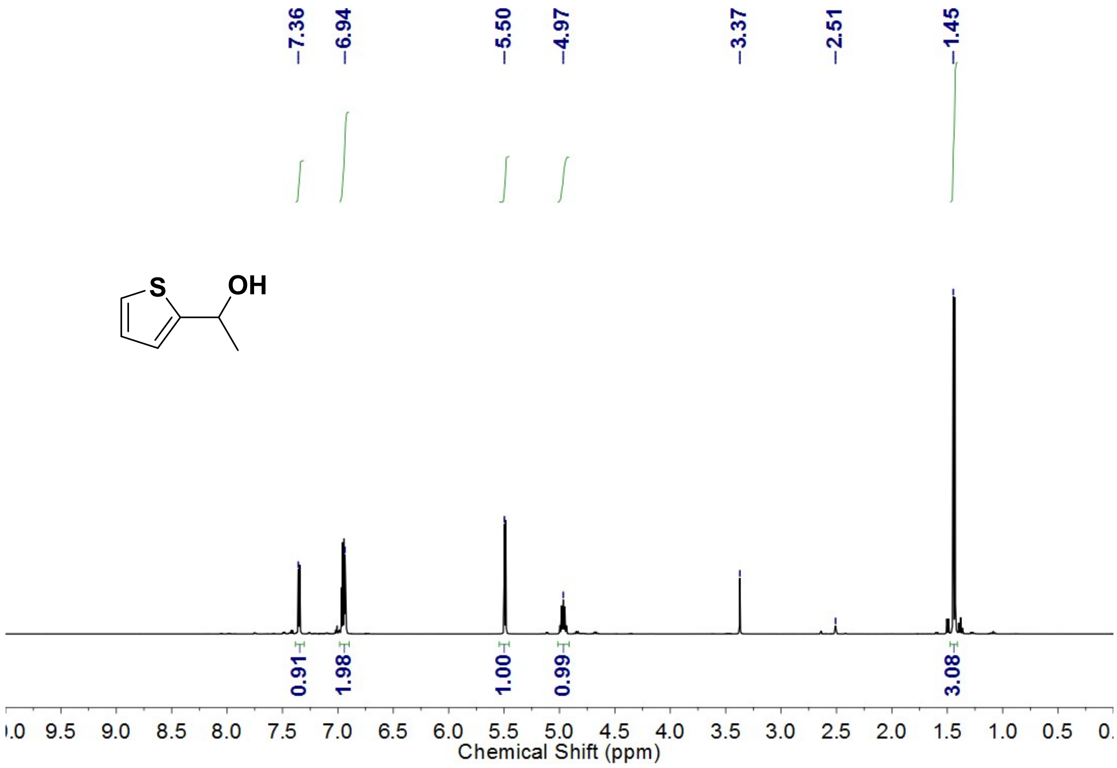
3. Y.-Y. Jiang, G. Li, D. Yang, Z. Zhang, L. Zhu, X. Fan and S. Bi, *ACS Catal.*, 2019, **9**, 1066-1080.
4. Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li and C. Li, *J. Am. Chem. Soc.*, 2012, **134**, 4258-4263.
5. J. Piera and J.-E. Bäckvall, *Angew. Chem. Int. Ed.*, 2008, **47**, 3506-3523.
6. X. Peng, X.-F. Shao and Z.-Q. Liu, *Tetrahedron Lett.*, 2013, **54**, 3079-3081.
7. B. L. Ryland and S. S. Stahl, *Angew. Chem. Int. Ed.*, 2014, **53**, 8824-8838.

NMR spectra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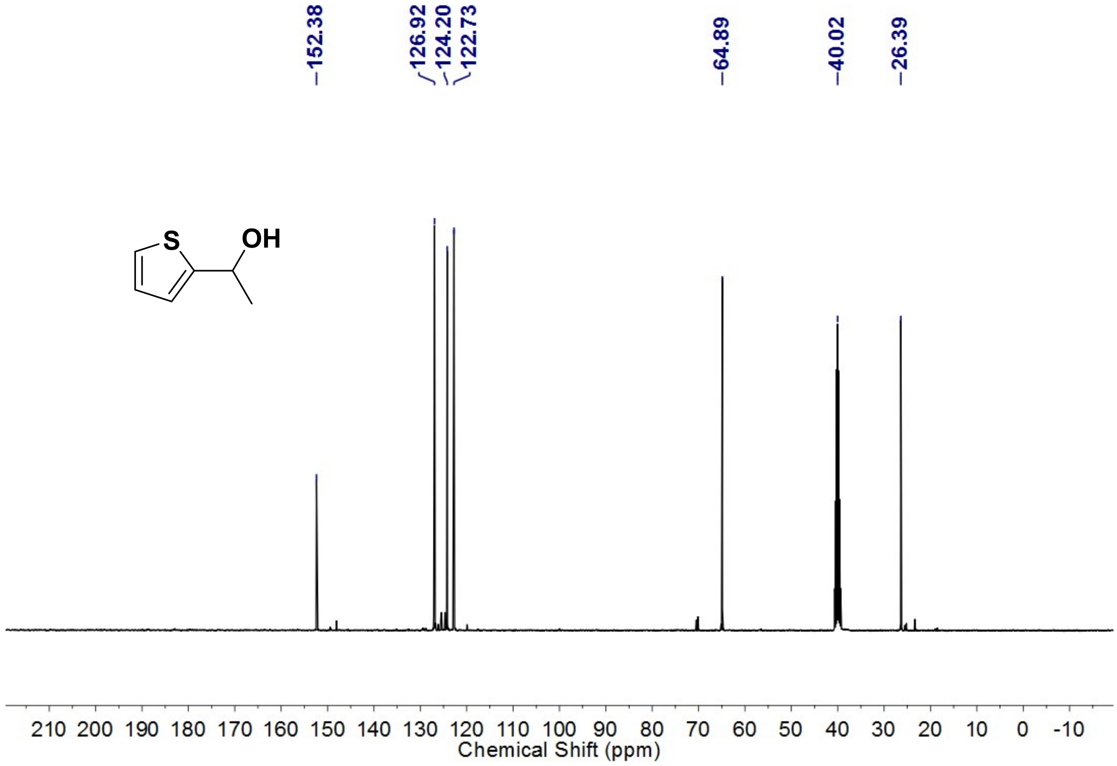
Chemical Shift (ppm)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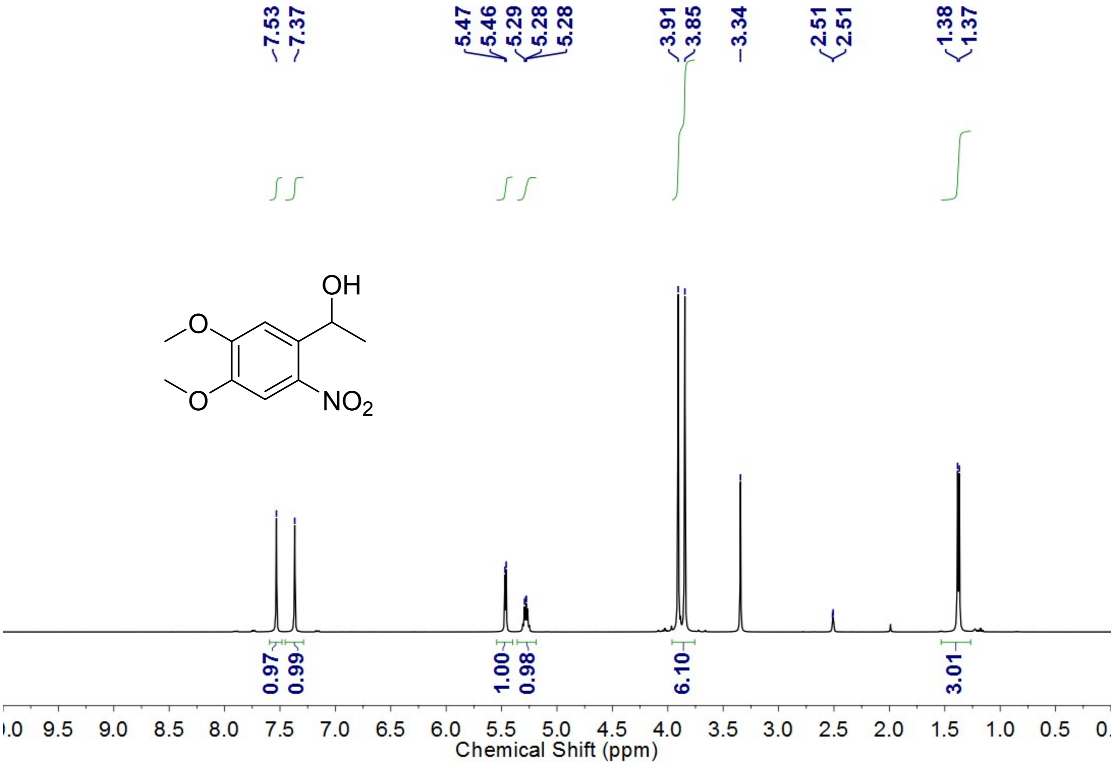
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O
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0.99
1.00
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6.10
3.01
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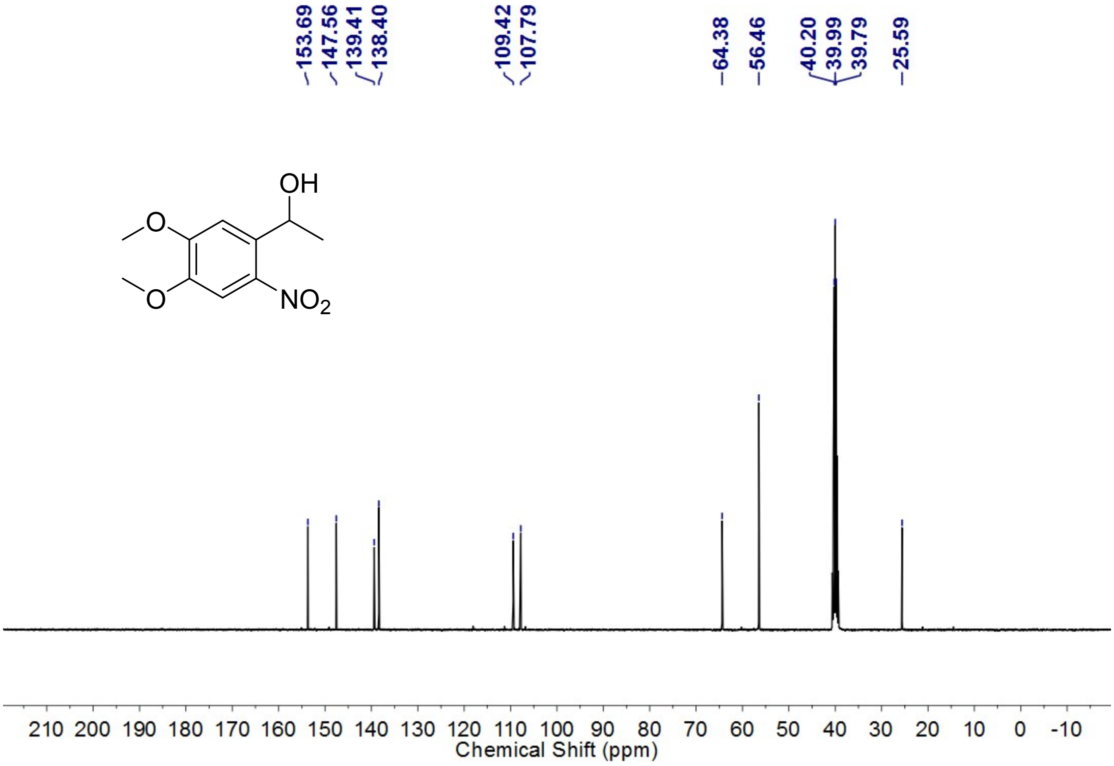
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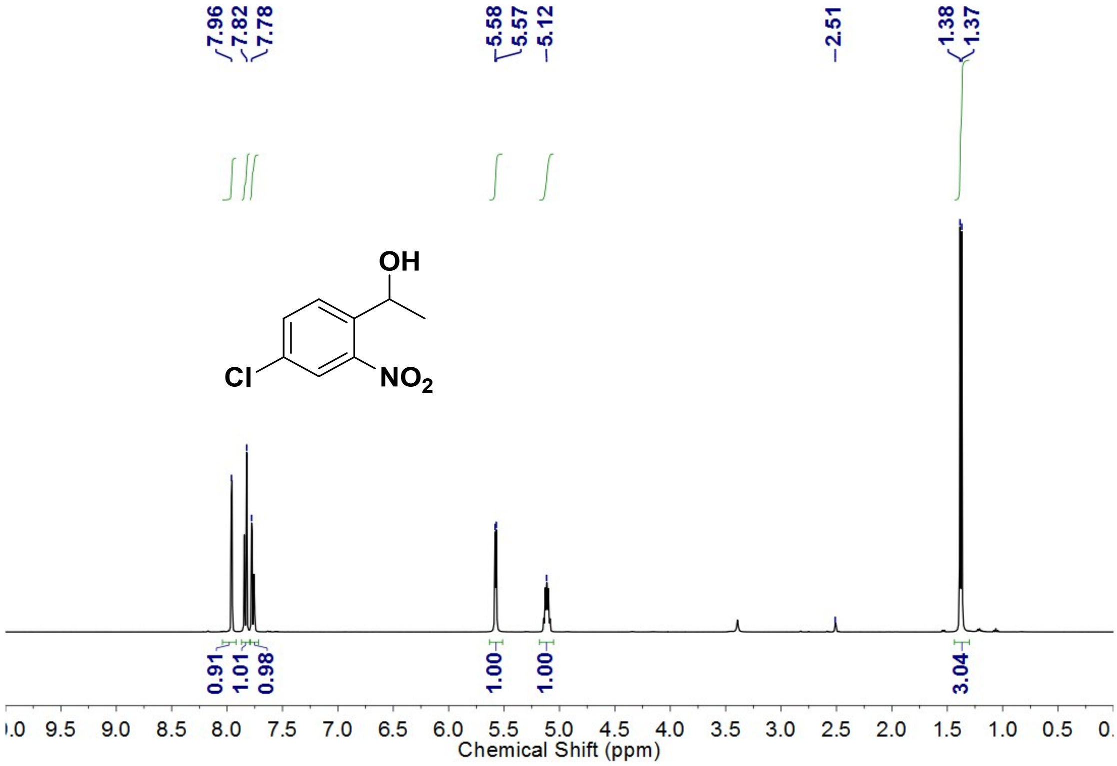
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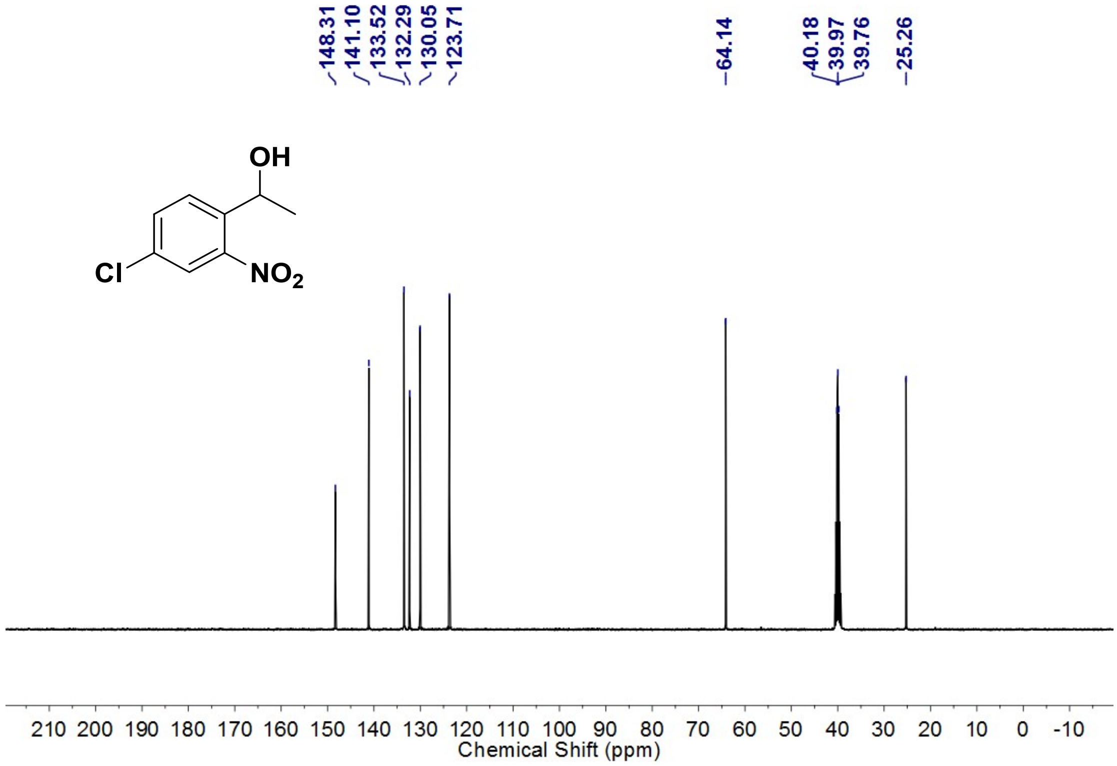
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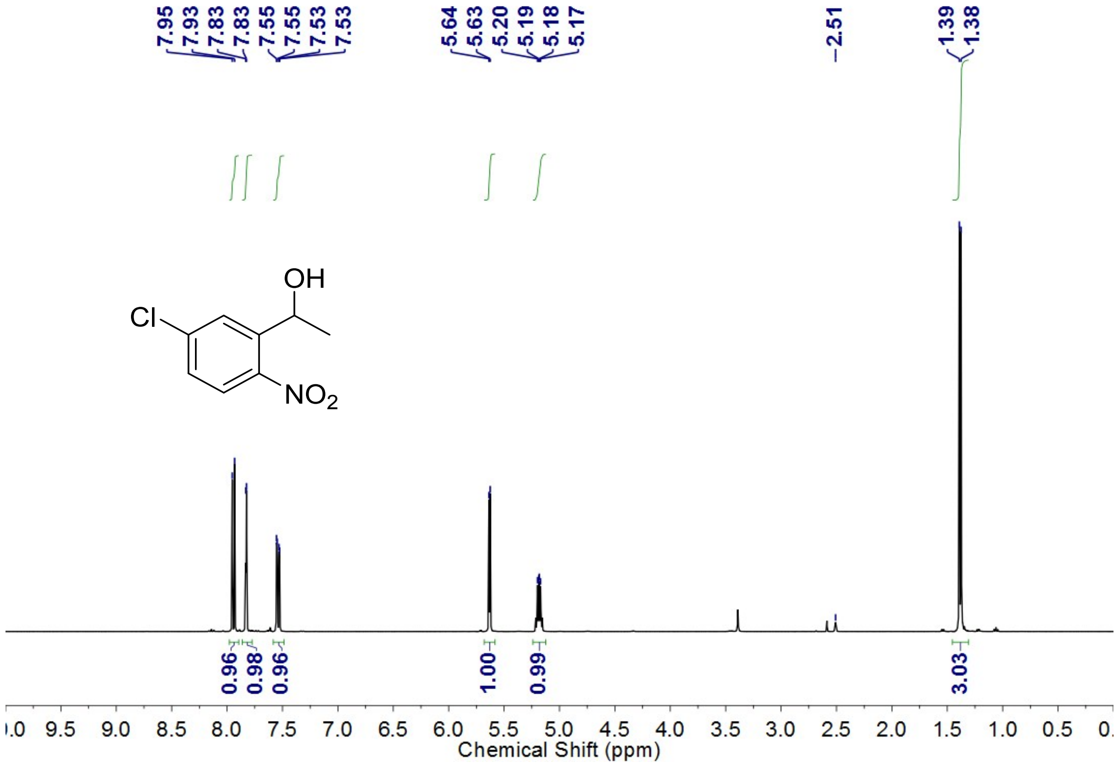
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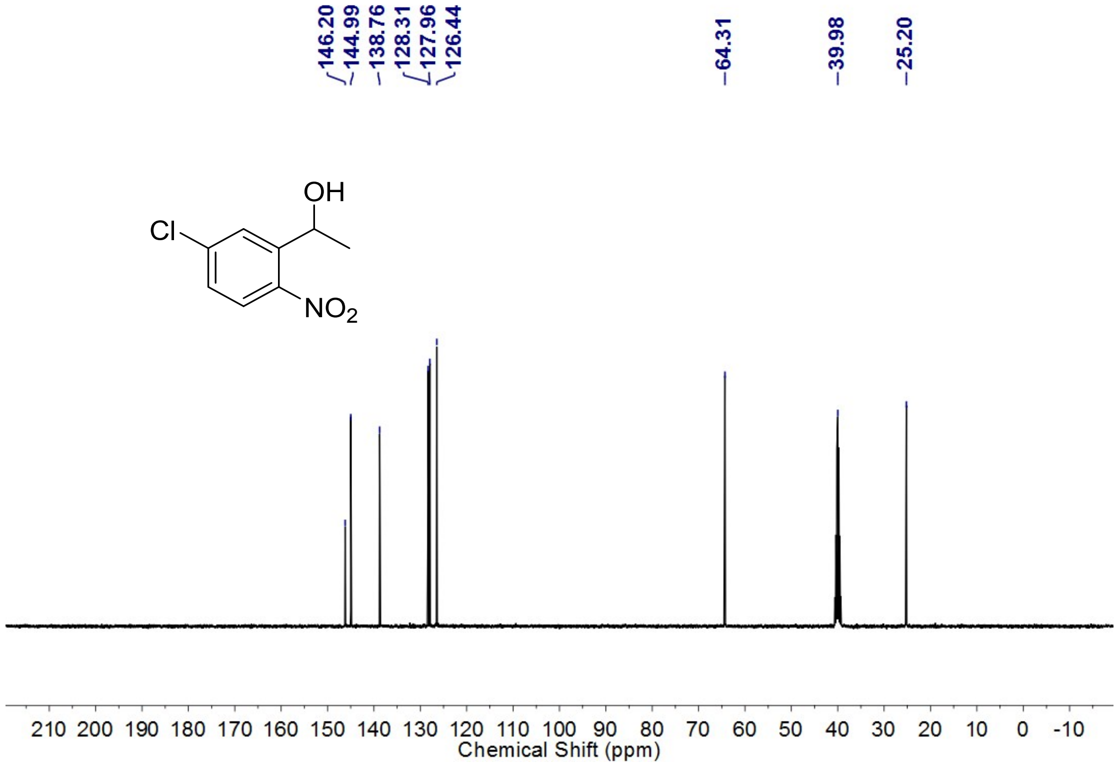
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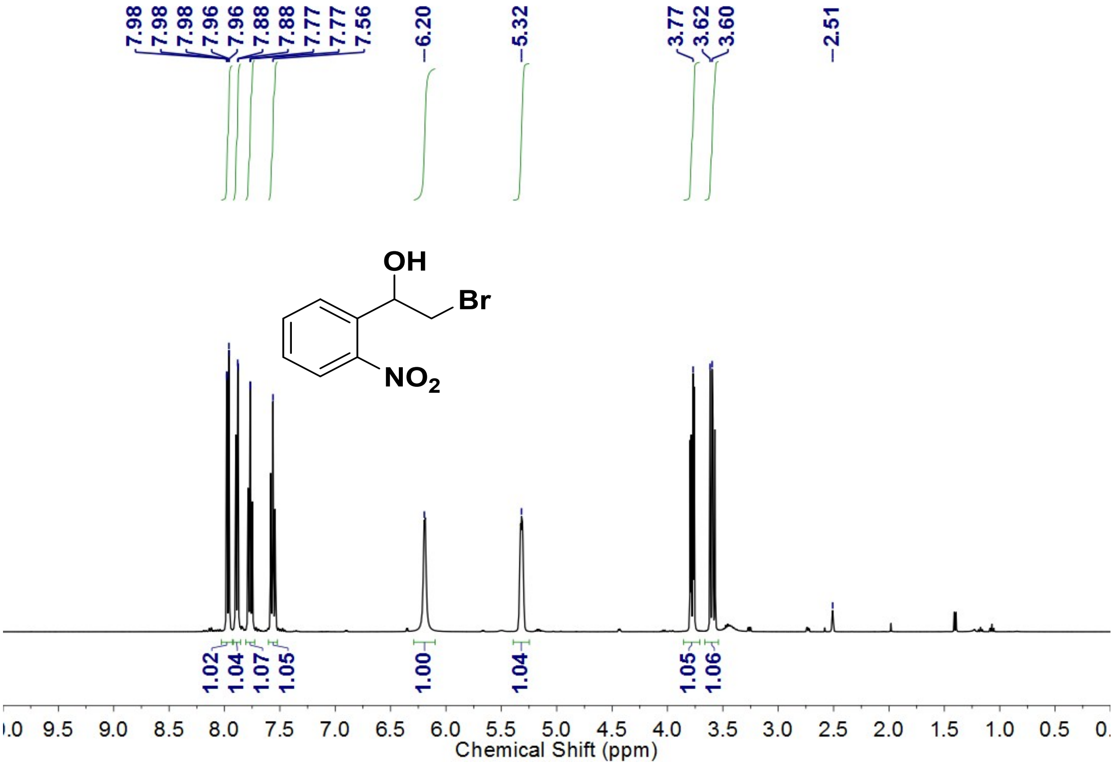
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3.62
3.60
2.51
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Br
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1.04
1.07
1.05
1.00
1.04
1.05
1.06
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9.0
8.5
8.0
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7.0
6.5
6.0
5.5
5.0
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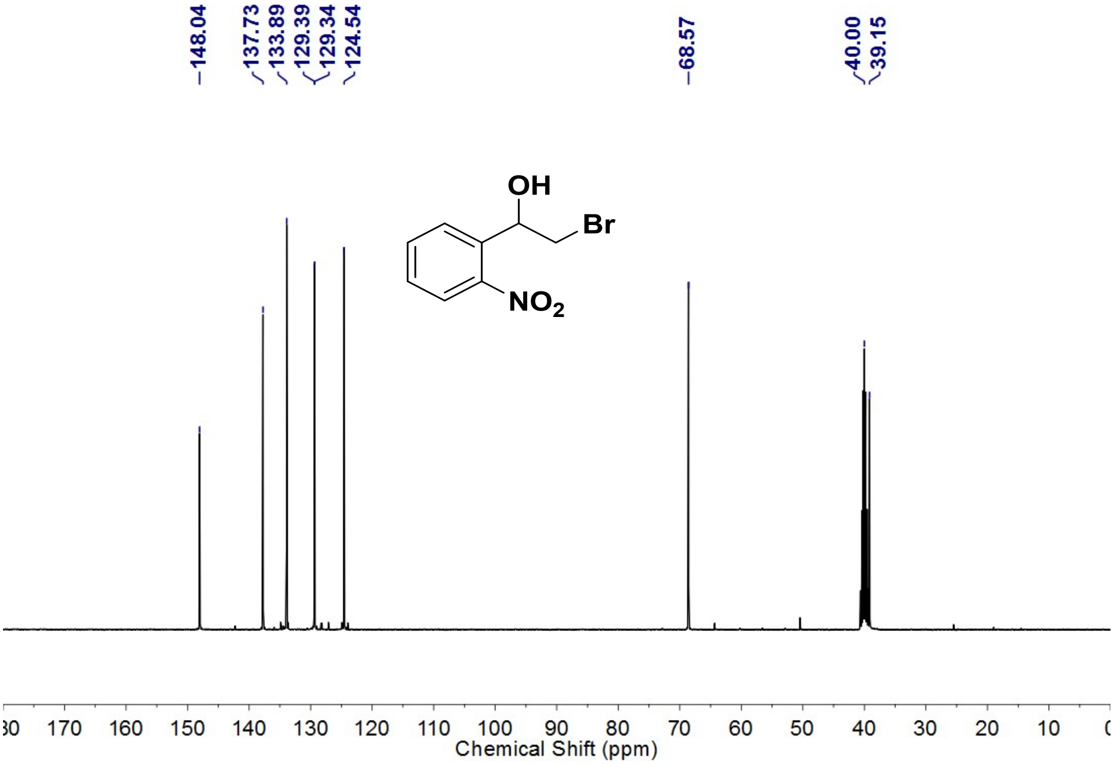
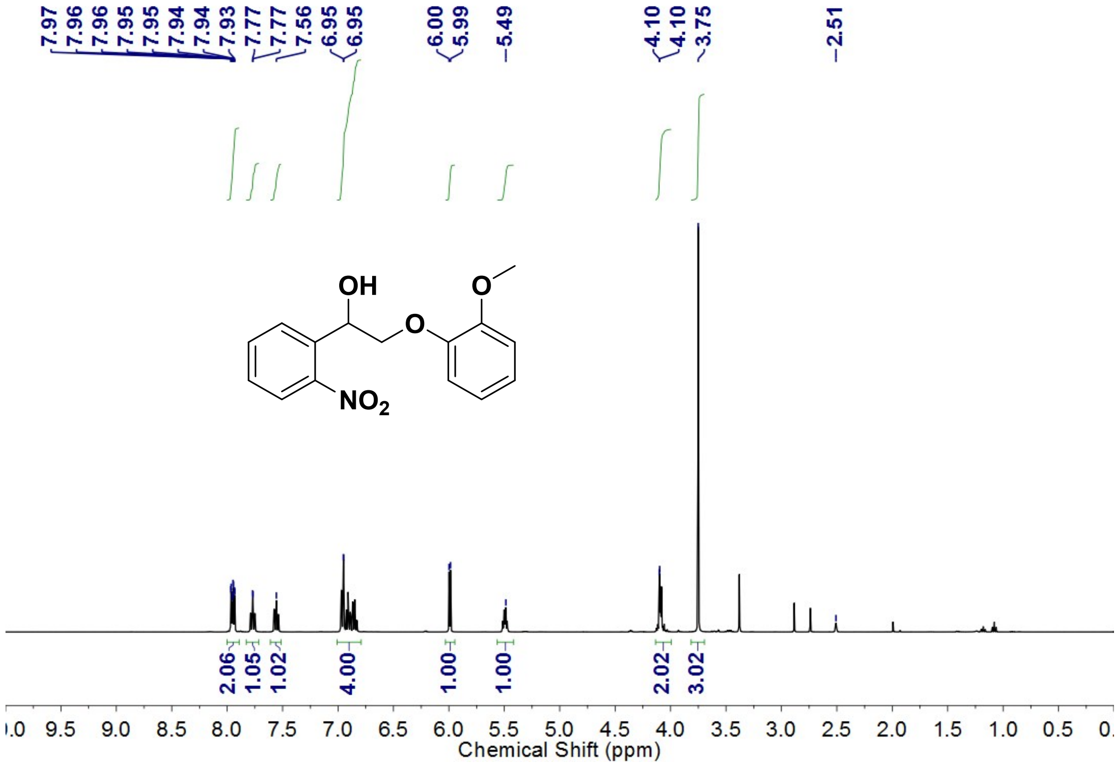
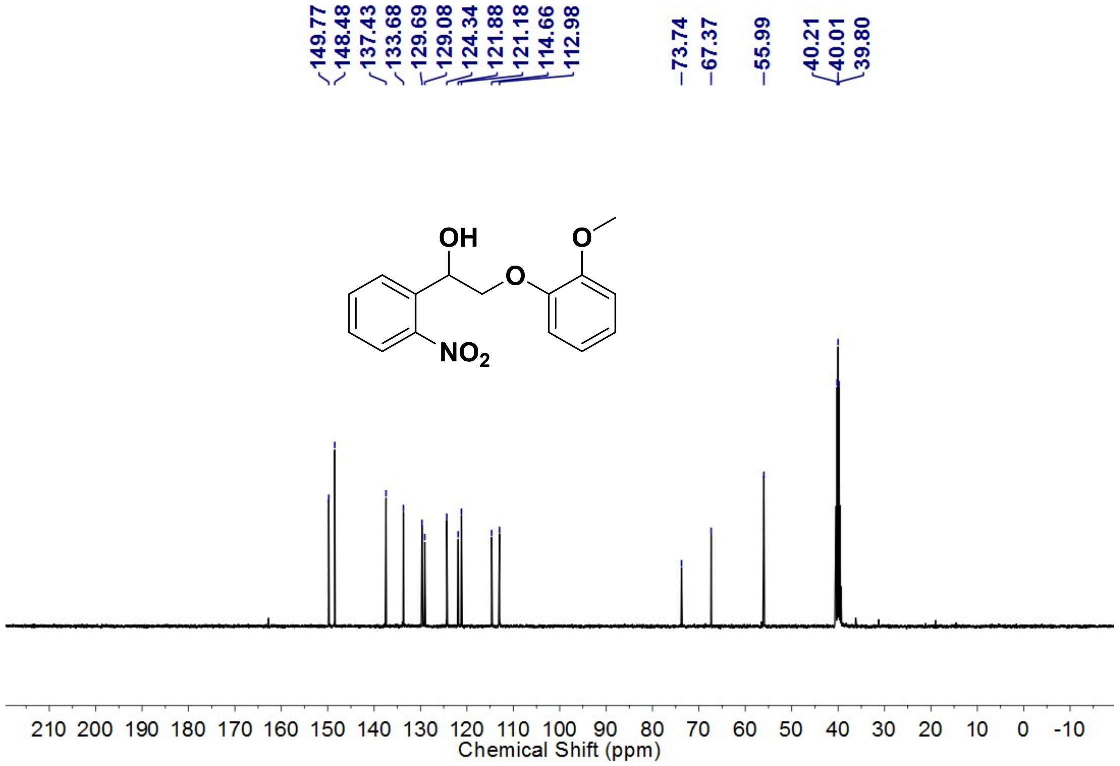
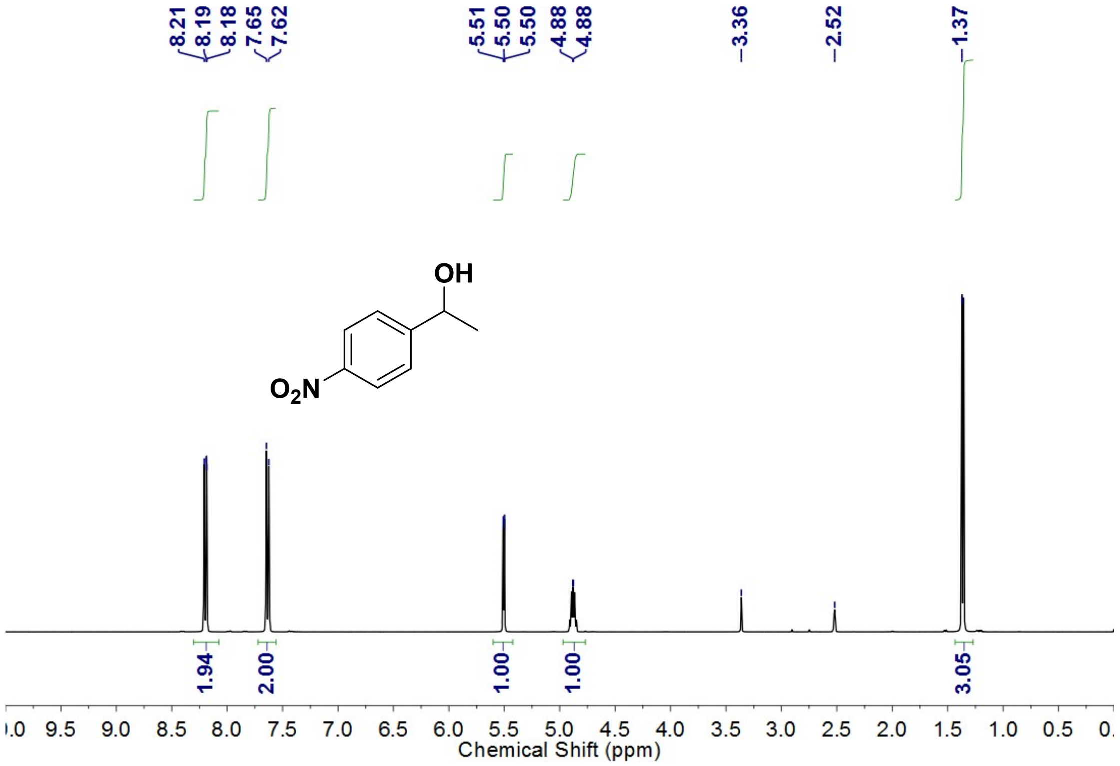
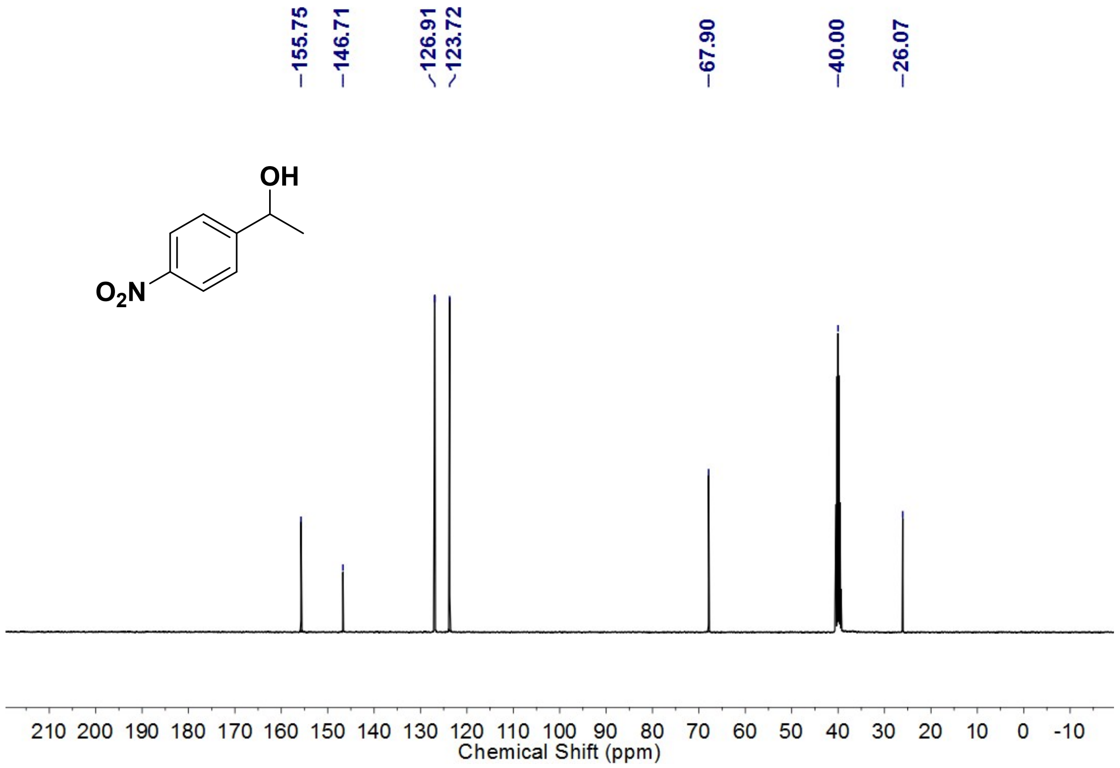
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)


148.04
137.73
133.89
129.39
129.34
124.54
68.57
40.00
39.15
OH
Br
NO_2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)


7.97
7.96
7.96
7.95
7.95
7.94
7.94
7.93
7.77
7.77
7.56
6.95
6.95
6.00
5.99
5.49
4.10
4.10
3.75
2.51
OH
O
O
NO2
2.06
1.05
1.02
4.00
1.00
1.00
2.02
3.02
.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.
Chemical Shift (ppm)


149.77
148.48
137.43
133.68
129.69
129.08
124.34
121.88
121.18
114.66
112.98
73.74
67.37
55.99
40.21
40.01
39.80
OH
O
O
NO2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


8.21
8.19
8.18
7.65
7.62
5.51
5.50
5.50
4.88
4.88
3.36
2.52
1.37
OH
O₂N
1.94
2.00
1.00
1.00
3.05
.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.
Chemical Shift (ppm)


155.75
146.71
126.91
123.72
67.90
40.00
26.07
OH
O₂N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)