

**Part 1: Transition Metal Catalyzed Functionalization of Aromatic
C-H Bonds**

Part 2: New Methods in Enantioselective Synthesis

By

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To my wife...

Abstract

Part 1:

Transition-metal-catalyzed direct transformations of aromatic C-H bonds are emerging as valuable tools in organic synthesis. These reactions are attractive because they allow for inherently efficient construction of organic building blocks by minimizing the pre-activation of substrates. Of these processes, direct arylation has recently received much attention due to the importance of the biaryl core in medicinal and materials chemistry. Also, alkyne hydroarylation has garnered interest because it allows for the atom-economical synthesis of functionalized alkenes directly from simple arenes and alkynes. Described in this thesis are number of advancements in these areas.

First, palladium catalyzed direct arylation of azine *N*-oxides using synthetically important aryl triflates is described. Interesting reactivity of aryl triflates compared to aryl bromides was uncovered and exploited in the synthesis of a compound that exhibits antimalarial and antimicrobial activity. Also reported is the efficient, direct arylation enabled (formal) synthesis of six thiophene based organic electronic materials in high yields using simple starting materials. Additionally, the site-selective direct arylation of both sp^2 and sp^3 sites on azine *N*-oxide substrates is described. The arylation reactions are carried out in either a divergent manner or a sequential manner and is applied to the synthesis of the natural products, Papaverine and Crykonisine. Mechanistic investigations point towards the intimate involvement of the base in the mechanism of these reactions.

Next, the rhodium(III)-catalyzed hydroarylation of internal alkynes is described. Good yields are obtained for a variety of alkynes and arenes with excellent regioselectivity for

unsymmetrically substituted alkynes. Mechanistic investigations suggest that this reaction proceeds through arene metalation with the cationic rhodium catalyst, which enables challenging intermolecular reactivity.

Part 2:

Access to single enantiomer compounds is a fundamental goal in organic chemistry and despite remarkable advances in enantioselective synthesis, their preparation remains a challenge. Kinetic resolution of racemic products is an important method to access enantioenriched compounds, especially when alternative methods are scarce. Described in this thesis is the resolution of tertiary and secondary alcohols, which arise from ketone and aldehyde aldol additions. The method is technically simple, easily scalable, and provides tertiary and secondary alcohols in high enantiomeric ratios. A rationale for the unique reactivity/selectivity associated with (1*S*,2*R*)-*N*-methylephedrine in the resolution is proposed.

Organocatalysis is a rapidly developing, powerful field for the construction of enantioenriched organic molecules. Described here is a complimentary class of organocatalysis using simple aldehydes as temporary tethers to perform challenging formally intermolecular reactions at room temperature. This strategy allows for the enantioselective, intermolecular cope-type hydroamination of allylic amines with hydroxyl amines. Also, interesting catalytic reactivity for dichloromethane is revealed.

Acknowledgements

Firstly, I would like to thank my beautiful and loving wife Christina. I met Christina my first week here in Ottawa and is the only person who has been there for the entire duration of my PhD. She has put up with my many late nights and weekends in the lab as well as seemingly endless chemistry discussions when together with other chemists. I could not have done it without your tireless love and support. Also, thank you for your help with putting this thesis together.

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Thank you to family and friends. To my parents, brothers and sisters thank you for your support and interest even when my explanations of what I did didn't make much sense.

Finally I would like to thank Keith. I count myself lucky to be one of the few people Keith had the chance to mentor during his short time. His mentorship, attitude, passion for science and dedication to his family have shaped not only who I am as scientist but also as a person.

List of Abbreviations

Ac – Acetyl	L _n – Generic ligand set
Acac – Acetylacetyl	M – Generic Metal
<i>t</i> AmOH – <i>tert</i> -Amyl alcohol	MeCN – Acetonitrile
Ar – Generic aromatic ring	Mol sieves –Molecular sieves
Bn – Benzyl	MOM – Methoxymethyl
Boc – Tert-butyloxy carbamate	MW – Microwave
Bu – Butyl	NMP – <i>N</i> -methylpyrrolidinone
<i>t</i> Bu – Tertbutyl	Nu – Generic nucleophile
CMD – Concerted metalation-deprotonation	PCC – Pyridinium chlorochromate
Cod – 1,5-Cyclooctadiene	Ph –Phenyl
Cp* – Pentamethylcyclopentadienyl	PhH – Benzene
Cy – Cyclohexyl	PhMe – Toluene
dba – Dibenzylideneacetone	PG – Generic protecting group
DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene	Piv – Pivaloyl
DCE – 1,2-Dichloroethane	<i>i</i> Pr – isopropyl
DMA – <i>N,N</i> -dimethylacetamide	Py – Pyridine
DMF – <i>N,N</i> -dimethylformamide	R – Generic organic fragment
dppf – 1,1'- <i>bis</i> (diphenylphosphino)ferrocene	ref – Reference
dppp – 1,3- <i>bis</i> (diphenylphosphino)propane	R _L – Generic large organic fragment
<i>d-i</i> -Prpf – 1,1'-	R _S – Generic small organic fragment
<i>bis</i> (diisopropylphosphino)ferrocene	rt – Room temperature
dtbpy – 4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine	S _E Ar – Electrophilic aromatic substitution
<i>E</i> _{dist} – Energy of distortion	TBS – <i>tert</i> -butyldimethylsilyl
edg – Generic electron-donating group	Tf – Trifluoromethanesulfonyl
<i>E</i> _{int} – Energy of interaction	TFA – Trifluoroacetic acid
ewd – Generic electron-withdrawing group	THF – Tetrahydrofuran
Eq – Equivalents	THP – 2-Tetrahydropyranyl
FG – Generic functional group	Tol – Tollyl
Hex – Hexyl	Ts – <i>p</i> -toluenesulfonyl
HMPA – Hexamethylphosphoramide	μw – Microwave
IMes –1,3-(2,4,6-Mesityl)-imidazol-2-	X – Generic heteroatom
ylidene	°C – Degree Celsius

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Direct Arylation in Biaryl Synthesis

1.1 Introduction

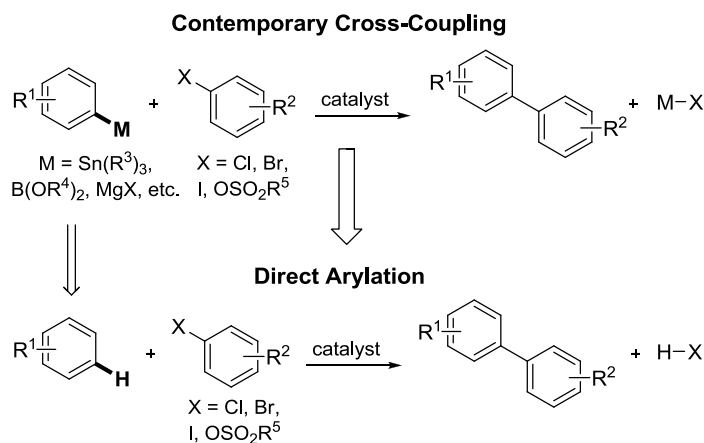
The biaryl motif is featured prominently in a variety of chemistries including pharmaceutical and materials chemistry.¹ The synthesis of biaryls was revolutionized in the 70's and 80's, which saw significant advances in the area of palladium catalyzed cross-coupling reactions.² These reactions involve the coupling of aryl organometallic reagents (Ar-MgX, Ar-ZnX, Ar-SnR₃, Ar-B(OR)₂, Ar-SiR₃) with aryl halides. This work was recently recognized with a Nobel Prize, which was awarded to Richard Heck, Ei-ichi Negishi and Akira Suzuki for “palladium-catalyzed cross couplings in organic synthesis.” With these advances, biaryls can now be prepared routinely in high yields under mild conditions with broad functional group tolerance. One might think that the field of biaryl synthesis is mature and there is little work left to be done. However, when evaluating the

¹ (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, 4, 2337. (b) Dugger, R. W.; Radan, J. A.; Ripin, D. H. B. *Org. Proc. Res. Rev.* **2005**, 9, 253. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, 103, 893. (d) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, 102, 1359. (e) Grimsdale, A. C.; Chan, K. L.; Martin, R. E.; Jokisz, P. G. Holmes, A. B. *Chem. Rev.* **2009**, 109, 897. (f) Mas-Torrent, M.; Rovira, C. *Chem. Soc. Rev.* **2008**, 37, 827.

² (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457. (b) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 508. (c) Kiso, Y.; Yamamoto, K.; Tamao, K.; Kumada M. *J. Am. Chem. Soc.* **1972**, 94, 4373. (d) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, 219, 61. (e) Negishi, E. *Acc. Chem. Res.* **1982**, 15, 340.

overall efficiency of reactions, one must not only consider the yield of the product, but also the availability and the synthetic steps required to produce the starting materials. In particular, the use of any functional group which does not appear in the final product can be considered inefficient. It is clear then that even state-of-the-art coupling reactions, which employ two pre-activated components, have inefficiencies inherent in the reaction design. Primarily the organometallic component is particularly problematic because it requires several synthetic steps to prepare, generates a stoichiometric amount of metal waste, is often toxic, difficult to handle, expensive or unavailable.

An emerging alternative to these cross-coupling methods which has received increased attention in recent years is direct arylation, in which one of the pre-activated components, usually the organometallic, is replaced by a simple arene (Scheme 1.1).³ This strategy



Scheme 1.1 – Contemporary Cross-Coupling vs. Direct Arylation

³ For recent reviews on direct arylation see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (f) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (g) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (h) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727. (i) Catellani, M.; Motti, E.; Della Ca', N.; Ferraccioli, R. *Eur. J. Org. Chem.* **2007**, 4153. (j) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (k) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

provides a more efficient synthetic route to biaryl molecules as it eliminates the need for an organometallic reagent and gives a halo-acid as its only stoichiometric by-product.

1.2 Direct Arylation of Heterocycles

Since the first examples of direct arylation the scope, utility and understanding of the reaction has increased dramatically. These advances have been extensively reviewed³ and therefore will not be discussed here. However, relevant to the chemistry in this thesis is a discussion of palladium-catalyzed intermolecular direct arylation reactions of heterocycles and the mechanism of the transformation which will be presented in the sections to follow.

1.2.1 Direct Arylation of Electron-Rich Heterocycles

For many years electron-rich heterocycles have been at the forefront of direct arylation research. Contributing to this is the high regioselectivities typically observed with electron-rich heterocycles which was originally attributed to the nucleophilicity of the arenes. Although, a concerted metalation-deprotonation mechanism can also explain the observed regioselectivities (*vide infra*).

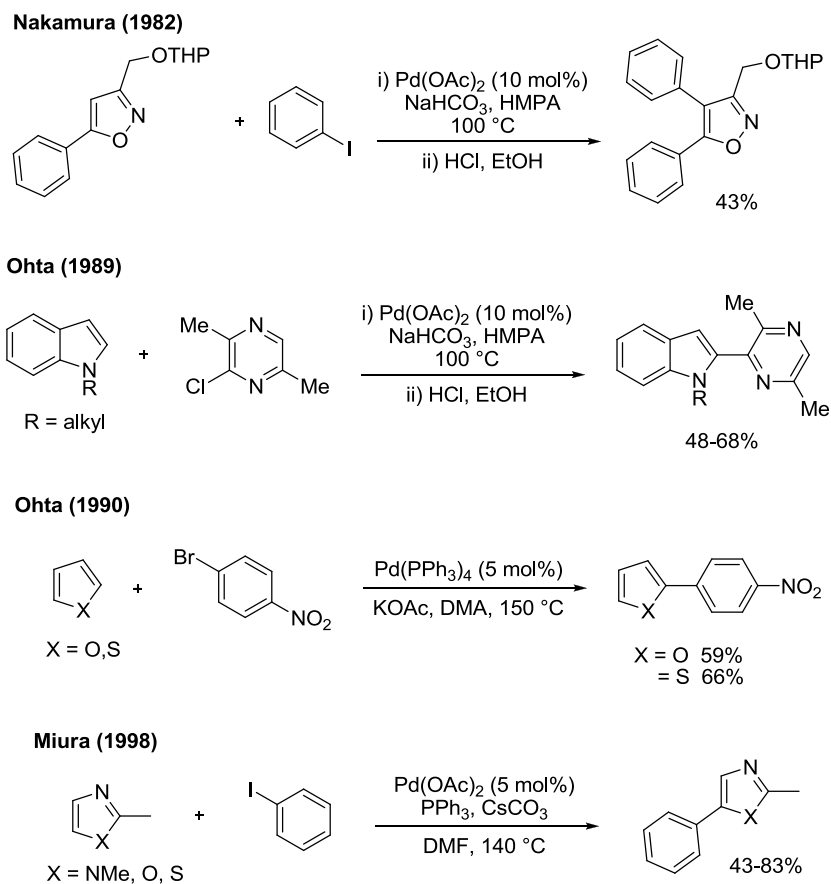
The first catalytic example of a palladium-catalyzed intermolecular direct arylation reaction was reported in 1982 by Nakamura.⁴ The reported conditions use 10 mol% of palladium acetate to accomplish the direct arylation of an isoxazole with iodobenzene under basic conditions (Scheme 1.2). Following other early examples,⁵ Ohta and co-workers described the arylation of indoles with chloropyrazines in 1989.⁶ Then, in 1990, Ohta published a second report on the direct arylation of thiophenes and furans in

⁴ Nakamura, N.; Tajima, Y.; Sakai, K. *Heterocycles* **1982**, *17*, 235.

⁵ (a) Akita, Y.; Inoue, A.; Yamamoto, K.; Ohta, A.; Kurihara, T.; Shimizu, M. *Heterocycles* **1985**, *23*, 2327. (b) Catellani, M.; Chiusoli, G. P.; Ricotti, S. J. *J. Organomet. Chem.* **1985**, *296*, c11.

⁶ Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477.

synthetically useful yields.⁷ Also, Miura has made significant contributions by describing the direct arylation of other electron-rich heterocycles. In 1998, he reported the arylation of imidazoles, oxazoles and thiazoles with yields varying from 43-83%.⁸

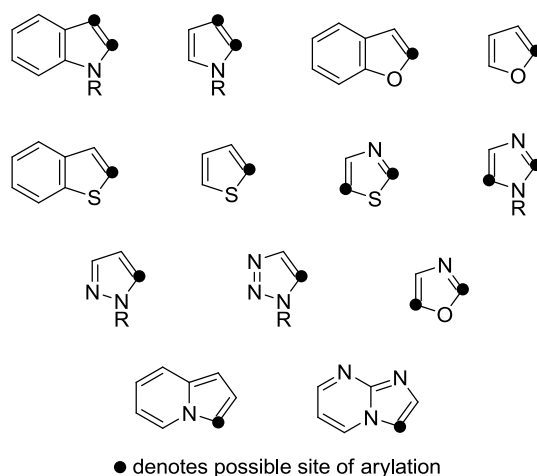


Scheme 1.2 – Early Reports of Palladium-Catalyzed Intermolecular Direct Arylation

Since these early reports, the scope of this reaction has been expanded to include many types of electron-rich heterocycles such as indoles, indolazenes, pyrroles, (benz)oxazoles, (benzo)thiazoles, (benzo)thiophenes, (benz)imidazoles, (benzo)furans among others (Scheme 1.3). Additional advancements have also been made with respect to improving the scope of aryl halides employed, the reaction yields and selectivities.

⁷ Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, 31, 1951.

⁸ Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, 71, 467.



Scheme 1.3 – Examples of Electron-Rich Heteroarenes Employed in Direct Arylation

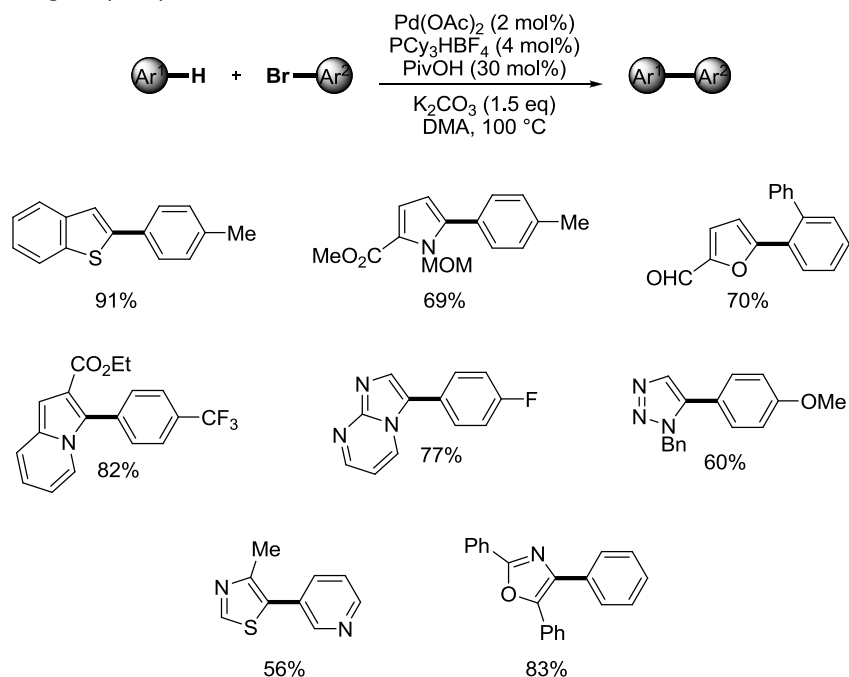
Reaction conditions vary widely but generally include: catalytic palladium acetate, carbonate base (K_2CO_3 , $NaHCO_3$, Cs_2CO_3 etc.) and a high boiling solvent (DMF, DMA, PhMe, dioxane etc.). Phosphine ligands (PCy_3 , $PtBu_2Me$, biaryl phosphines, PPh_3 etc.) are often used but not necessarily in all cases. A pivalic acid additive, which was pioneered by our group⁹ and others¹⁰ has proved to be beneficial in many cases. Given the wide range of conditions reported, our group has also pursued a set of reaction conditions that would be applicable across a wide range of heterocycles. This would simplify the reaction screening/literature search process when trying a direct arylation reaction on a new heterocycle. The reported conditions feature low catalyst loading (1-2 mol% $Pd(OAc)_2$), a 1:1 stoichiometry and applicability to a wide range of heterocycles.¹¹ The reported conditions applied to the direct arylation of a range of heterocycles are outlined in Scheme 1.4.

⁹ Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 1649.

¹⁰ Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, 126, 7460.

¹¹ Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, 74, 1826.

Fagnou (2009)

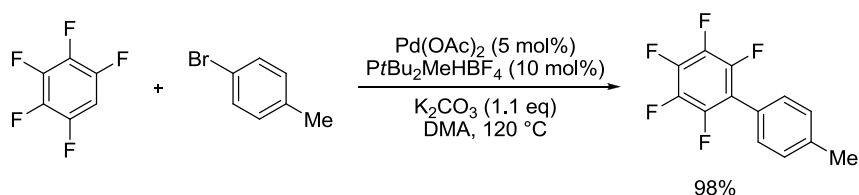


Scheme 1.4 – General Conditions for the Direct Arylation of Heterocycles

1.2.2 Direct Arylation of Electron-Poor Heterocycles

The mechanistic proposal put forth for most direct arylation reactions attributed the reactivity of electron-rich heteroarenes to their inherent nucleophilicity. With this mechanistic proposal came the assumption that electron-poor arenes would be poor substrates due to their lack of nucleophilicity. However, in 2006 our group reported the direct arylation of highly electron deficient pentafluorobenzenes (Scheme 1.5).¹²

Fagnou (2006)

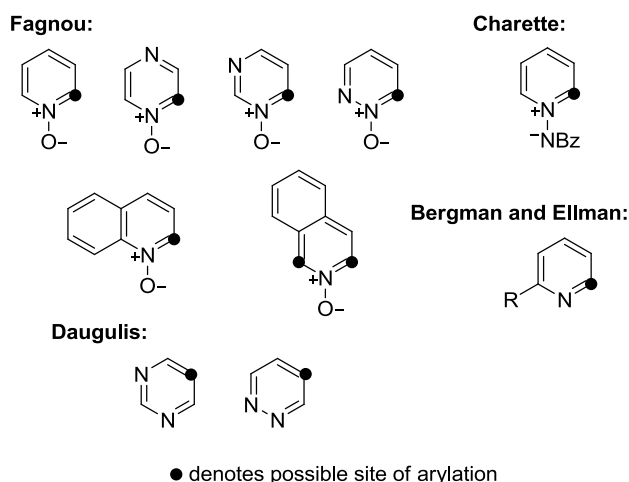


Scheme 1.5 –Direct Arylation of Pentafluorobenzene

¹² Lafrance, M.; Rowley, C.N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.

This work was related to earlier independent work by the Echavarren group who reported that an intramolecular direct arylation was actually faster with more electron withdrawing substituents. The effectiveness of electron-deficient arenes as substrates for direct arylation lead to a re-evaluation of the mechanism and a proton abstraction (also called concerted metalation-deprotonation) mechanism was proposed which will be discussed in the following section.

This concept has also been applied to the direct arylation of various electron-poor heterocycles. Examples of compatible electron-poor heterocycles are outlined in Scheme 1.6. Our group has reported a series of azine *N*-oxide substrates that are suitable for direct arylation.¹³ Charette and co-workers have described a similar strategy which employs *N*-iminopyridinium ylides.¹⁴ Unactivated pyridine substrates have been arylated under rhodium catalysis as reported by Bergman and Ellman.¹⁵ While this method avoids



Scheme 1.6 – Examples of Electron-Poor Heteroarenes Employed in Direct Arylation

¹³ (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem Int. Ed.* **2006**, *45*, 7781. (c) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

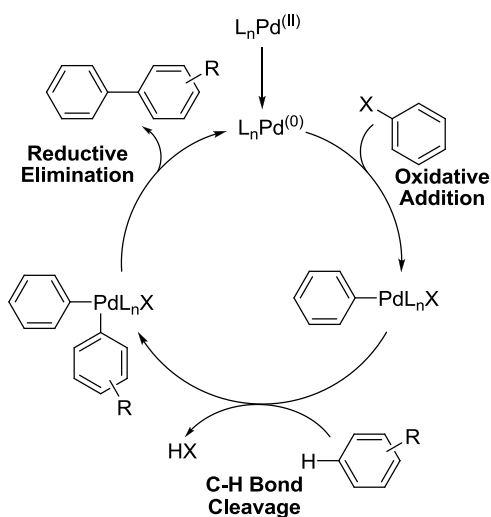
¹⁴ Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52.

¹⁵ Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926.

preactivation of the pyridine component, it also requires substitution at the 2 position of pyridine. Finally the Daugulis group has reported the copper-catalyzed direct arylation of acidic substrates including free diazines and pyridine *N*-oxide.¹⁶

1.2.3 Mechanistic Considerations for Direct Arylation

Pertinent the chemistry reported in the following three chapters of this thesis is a discussion of the mechanism of direct arylation. A general catalytic cycle is outlined in Scheme 1.7. Following catalyst initiation, the first step of the catalytic cycle is oxidative insertion of Pd(0) catalyst into the aryl halide bond. The next step is cleavage of the C-H of the simple arene with loss of HX. Finally, reductive elimination yields the biaryl product and regenerated the active Pd(0) catalyst. Of these steps in the catalytic cycle the oxidative insertion and reductive elimination steps are relatively well understood. Conversely, the C-H bond cleavage step is less understood and has been the subject of debate in recent years and warrants further discussion.



Scheme 1.7 – General Catalytic Cycle for Direct Arylation

¹⁶ Do, H.-Q.; Khan, R. K. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

There are four main possibilities that have been put forward as a mechanistic possibility for the C-H bond cleaving step (Scheme 1.8). The carbo-palladation (also called Heck-type) pathway involves the *syn*-addition of the aryl-palladium bond across the arene to be functionalized.¹⁷ Although the subsequent *anti*- β -hydride elimination is unlikely, an isomerisation through a π -allyl intermediate followed by *syn*- β -hydride elimination is possible. Also, in rare cases, the oxidative insertion of a Pd(II) species into a C-H bond of an arene has been proposed.¹⁸ A double reductive elimination would follow to yield the biaryl product and regenerate the catalytically active Pd(0) species. The most common mechanism that is proposed, especially for electron-rich heterocycles, is electrophilic palladation.^{8,19} An electrophilic palladation or electrophilic aromatic substitution (S_EAr) type process involves the nucleophilic attack of an electron-rich arene on an electrophilic Pd(II) species forming a Wheland intermediate. Deprotonation followed by reductive elimination would give the biaryl product and regenerate the active catalyst. The last mechanism, which has received increased attention in recent years, is concerted metalation-deprotonation (CMD).²⁰ This pathway was initially used to

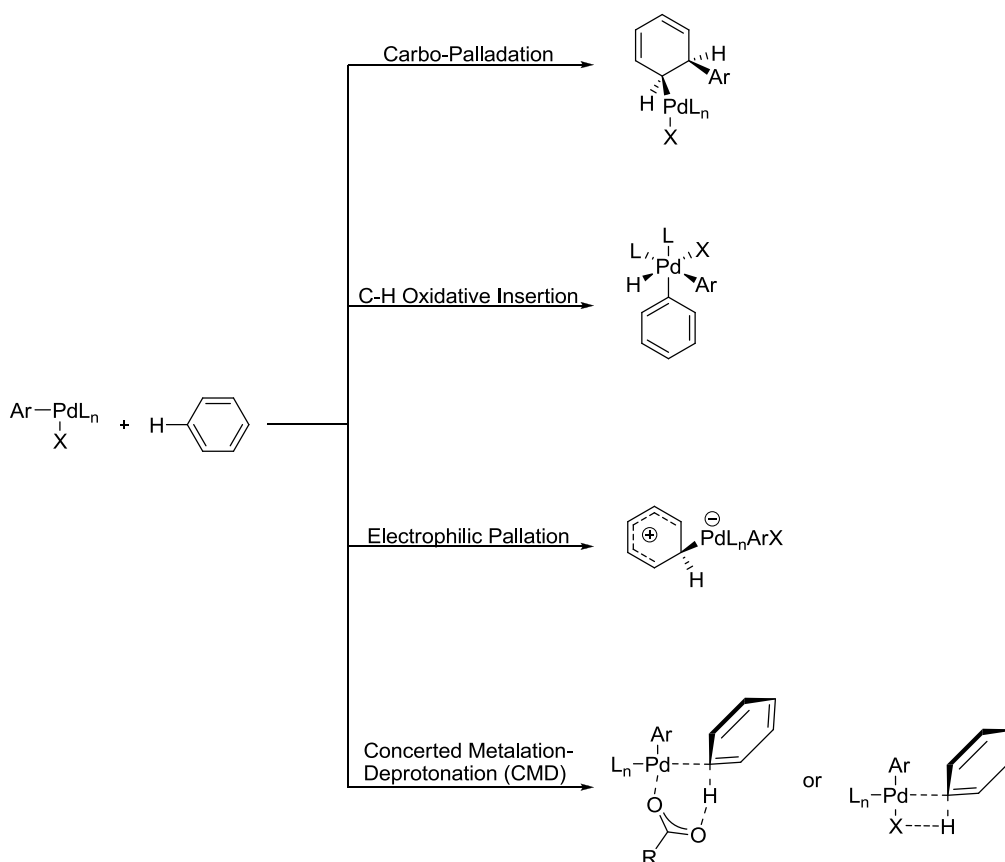
¹⁷ (a) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschinger, F. *Org. Lett.* **2001**, 3, 1677. (b) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, 5, 301. (c) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, 5, 4835. (d) Wang, J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, 10, 2923 and references cited therein.

¹⁸ Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, 125, 11506.

¹⁹ (a) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, 5, 4835. (b) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2007**, 2, 1430. (c) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, 5, 301. (d) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, 6, 1159. (e) Lane, B. S.; Brown, M. A.; Sames, D. J. *Am. Chem. Soc.* **2005**, 127, 8050. (f) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, 8, 1979. (g) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, 9, 2333.

²⁰ (a) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, 127, 7171. (b) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, 64, 6015. (c) Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, 64, 6021. (d) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, 10, 2299. (e) Ozdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.;

rationalize the reactivity of electron deficient substrates where it was thought that an electrophilic palladation reaction was not possible.^{12,21} However CMD has also been used to validate experimental outcomes from a wide range of arenes including electron-rich substrates.²² The CMD occurs with simultaneous cleavage of the C-H bond and formation of the new C-Pd bond with loss of HX. While the CMD pathway may resemble an interrupted Wheland intermediate, there is little build-up of carbocation character or loss of aromaticity in the CMD transition state.



Scheme 1.8 – Mechanistic Possibilities for C-H Bond Cleavage

Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (f) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

²¹ (a) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (c) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.

²² Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

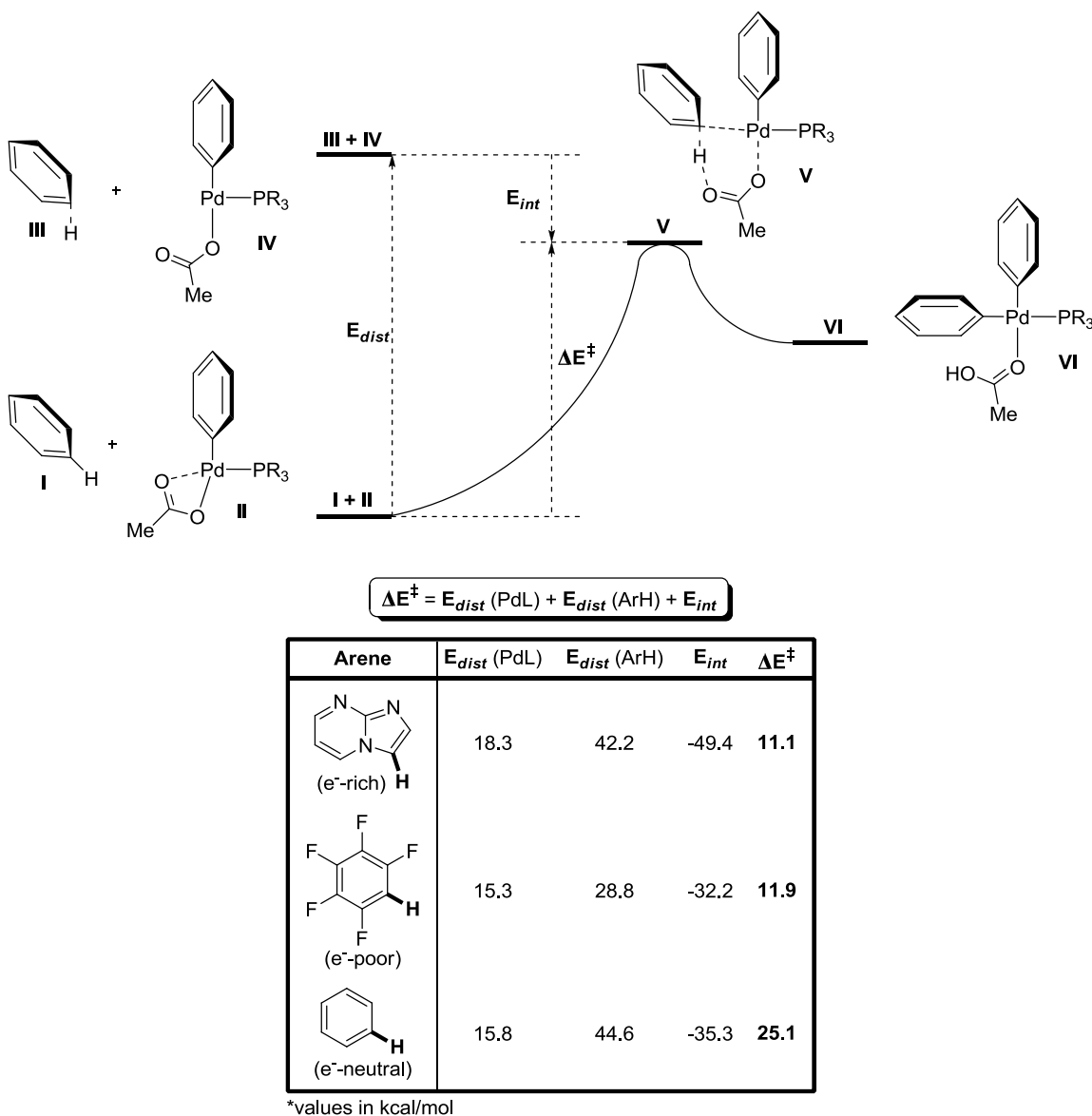
The concerted metalation-deprotonation mechanism for arene C-H bond cleavage has been applied to stoichiometric systems dating as far back as 1955.²³ With the increasing utility of direct arylation as a synthetic tool has come a re-evaluation of CMD in this catalytic context. Our group among others have proposed the CMD pathway for catalytic C-H bond functionalization reactions.^{9,11,12,13,20,21,22,24} Some of these reports suggest that C-H bond acidity may be the governing factor in determining reactivity and selectivity. However, it has been demonstrated that both nucleophilicity and C-H bond acidity may play an important role.²²

The ambiguity of the role of nucleophilicity and C-H acidity prompted our group to carry out a distortion/interaction analysis using DFT calculations (Scheme 1.9).²² In this analysis, the individual energies of distortion ($E_{dist}(\text{PdL})$ and $E_{dist}(\text{ArH})$) represents the energetic cost associated with distorting the ground state conformation of reactants to the conformation required for the CMD transition state ($\text{I} \rightarrow \text{III}$ and $\text{II} \rightarrow \text{IV}$). The energy of interaction (E_{int}) represents the energy gained from bringing the two distorted components together ($\text{III} + \text{IV} \rightarrow \text{V}$). The overall activation energy ($\Delta E^\ddagger$) is obtained by simply summing the energy loss (E_{dist}) and energy gain (E_{int}). The analysis allows the contribution of each variable to be obtained for an electronically diverse set of arenes. E_{int} values seem to correlate well electron density and therefore nucleophilicity of the

²³ (a) Brown, H. C.; McGary, Jr., C. W. *J. Am. Chem. Soc.* **1955**, 77, 2306. (b) Winstein, S.; Traylor, T. G. *J. Am. Chem. Soc.* **1955**, 77, 3747. (c) de la Mare, P. B. D.; Hilton, I. C.; Varma, S. *J. Chem. Soc.* **1960**, 4044. (d) Kresge, A. J.; Dubeck, M.; Brown, H. C. *J. Org. Chem.* **1966**, 32, 645. (e) Kresge, A. J.; Brennan, J. F. *J. Org. Chem.* **1966**, 32, 752. (f) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629. (g) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, 127, 13754. (h) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Pölleth, M. *J. Am. Chem. Soc.* **2006**, 128, 4210. For an overview of the mechanistic work on the CMD pathway see: (i) Lapointe D.; Fagnou, K. *Chem. Lett.* **2010**, 39, 1118.

²⁴ (a) Gonzalez, J. J.; Garcia, N.; Gomez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, 62, 1286. (b) Martin-Matute, B.; Mateo, C.; Cardenas, D. J.; Echavarren, A. M. *Chem.; Eur. J.* **2001**, 7, 2341.

arene. While E_{dist} (ArH) correlate often, but is not necessarily governed by, C-H bond acidity. Representative examples are shown in scheme 1.9. The electron-rich imidazopyrimidine suffers from a high energy loss from the E_{dist} (ArH) value (42.2 kcal/mol). This is offset by a large energy gain from the E_{int} value (-49.4 kcal/mol) which is expected from a nucleophilic arene. Pentafluorobenzene is, in contrast, a relatively electron-poor arene and yet has very similar $\Delta E^\ddagger$ value to the



Scheme 1.9 –Distortion/Interaction Analysis for CMD Transition State

electron rich arene (11.1 vs. 11.9 kcal/mol). While pentafluorobenzene has a lower energy gain from the E_{int} value (-32.2 kcal/mol), due to poor electron density, it also requires less energy to distort the C-H bond of the arene (28.8 kcal/mol). Therefore, these arenes have similar $\Delta E^\ddagger$ values, but for different reasons: imidazopyrimidine benefits from a large energy of interaction gain and pentafluorobenzene benefits from a low energy of distortion. Simple benzene, a challenging direct arylation substrate, suffers both a high energy of distortion (44.6 kcal/mol) and low energy of interaction gain (-35.3 kcal/mol).

Direct Arylation of Azine N-Oxides With Aryl Triflates

2.1 Introduction²⁵

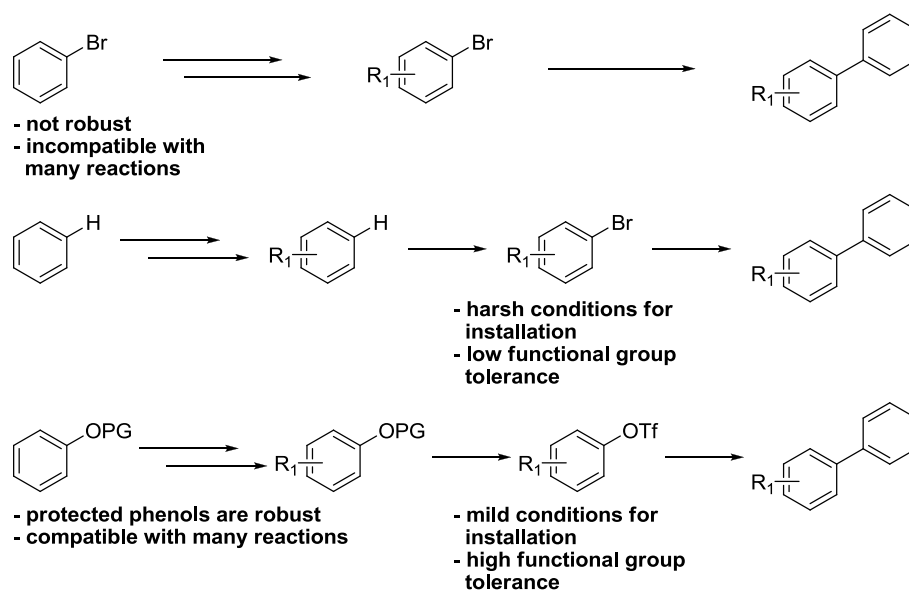
As mentioned previously, biaryl compounds represent an important class of molecule.²⁶ Specifically, the 2-aryl azine motif features prominently in ligand, medicinal and materials chemistry.²⁷ Transition metal catalyzed cross coupling reactions of aryl halides with aryl organometallics such as Suzuki, Stille and Negishi reactions represent some of the most important methods for synthesizing biaryl compounds.²⁶ However, the requirement for substrate pre-activation renders the overall process inefficient and uneconomical. An emerging alternative to these methods which has received increased attention in recent years is direct arylation, in which one of the pre-activated components,

²⁵ A significant portion of the work described in this chapter has been published in the form of an article, see: Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, 65, 4977.

²⁶ Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, 102, 1359.

²⁷ (a) Pozharski, A. F.; Soldatenko, A. T.; Katritsky, A. *Heterocycles in Life and Society*, Wiley, New York, 1997. (b) Chelucci, G.; Orru, G.; Pinna, G. A. *Tetrahedron*, **2003**, 59, 9471. (c) Pestka, S. in *Antibiotics*, ed. Corcoran, J. W.; Hahn, F. E. Springer-Verlag, New York, 1975, Vol. 3, p 480. (d) Lewis, A. M.; Ough, M.; Hinkhouse, M. M.; Tsao, M.-S.; Oberley L. W.; Cullen, J. J. *Mol. Carcinogenesis* **2005**, 43, 215. (e) Ken, W. R.; Soti, R.; Rittschof, D. *Biomol. Eng.* **2003**, 20, 355. (f) Friesen, R.W.; Brideau, C.; Chan, C. C.; Charleson, S.; Desche[^]nes, D.; Dube', D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y.; Gordon, R.; Greig, G. M.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, L. J.; Young, R. N. *Biorg. Med. Chem. Lett.* **1998**, 8, 2777. (g) Quirk, J.; Thornton, M.; Kirkpatrick, P. *Nature* **2003**, 2, 769.

usually the organometallic, is replaced by a simple arene.²⁸ Although direct arylation reactions have been investigated thoroughly with use of halides, there are few reports employing the use of aryl triflates.²⁹ Triflates, while often too expensive and impractical for large scale synthesis, are still an important class of electrophile because they provide unique advantages over the more traditional bromides or iodides (Scheme 2.1). The aryl halide bond is relatively weak and therefore labile under many reaction conditions,



Scheme 2.1 – Advantages of Aryl Triflates

²⁸ Recent reviews on direct arylation: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, *12*, 1253. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (f) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (g) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2007**, 3382. (h) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727. (i) Catellani, M.; Motti, E.; Della Ca', N.; Ferraccioli, R. *Eur J. Org. Chem.* **2007**, *25*, 4153. (j) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058. (k) Ackermann, L. *Synlett* **2007**, 507. (l) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (m) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (n) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (o) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, 1147.

²⁹ (a) Wang, L.; Shevlin, P. B. *Tetrahedron Lett.* **2000**, *41*, 285. (b) Nishioka, H.; Shoujiguchi, Y.; Abe, H.; Takeuchi, Y.; Harayama, T.; *Heterocycles* **2004**, *64*, 463. (c) (d) Hara, O.; Nakamura, T.; Sato, F.; Makino, K.; Hamada, Y. *Heterocycles* **2006**, *68*, 1. (e) Cruz, A. C. F.; Miller, N. D.; Willis M. C. *Org. Lett.* **2007**, *9*, 4391.

rendering them difficult to carry through multiple synthetic steps. Moreover, installation of halides usually requires harsh conditions which may not be compatible with a complex molecule in the late stages of a synthesis. Conversely, protected phenols are robust and conditions for triflate installation are mild. Thus, aryl triflates are ideally suited for introduction in the late stage of a synthetic sequence.

Applications of aryl triflates in the context of direct arylation are illustrated in Scheme 2.2. The first report came from the Rice group who described a palladium-catalyzed intramolecular direct arylation to form fluoranthenes and benzofluoranthenes.³⁰ Other intramolecular examples include a report from the Suzuki group who used direct arylation as a key step in the synthesis of gilvocarcin V.³¹ Steglich and co-workers described the synthesis arcyriacyanin A, which required the use of an aryl triflate because the analogous bromo derivative could not be synthesized.³² Bringmann *et al.* employed direct arylation to synthesize lactone-bridged ternaphthyl.³³ Again, when the bromo derivative failed, the triflate gave adequate results. The Harayama group used aryl triflate to cyclize amide derivatives using direct arylation to form the corresponding phenanthridone.³⁴

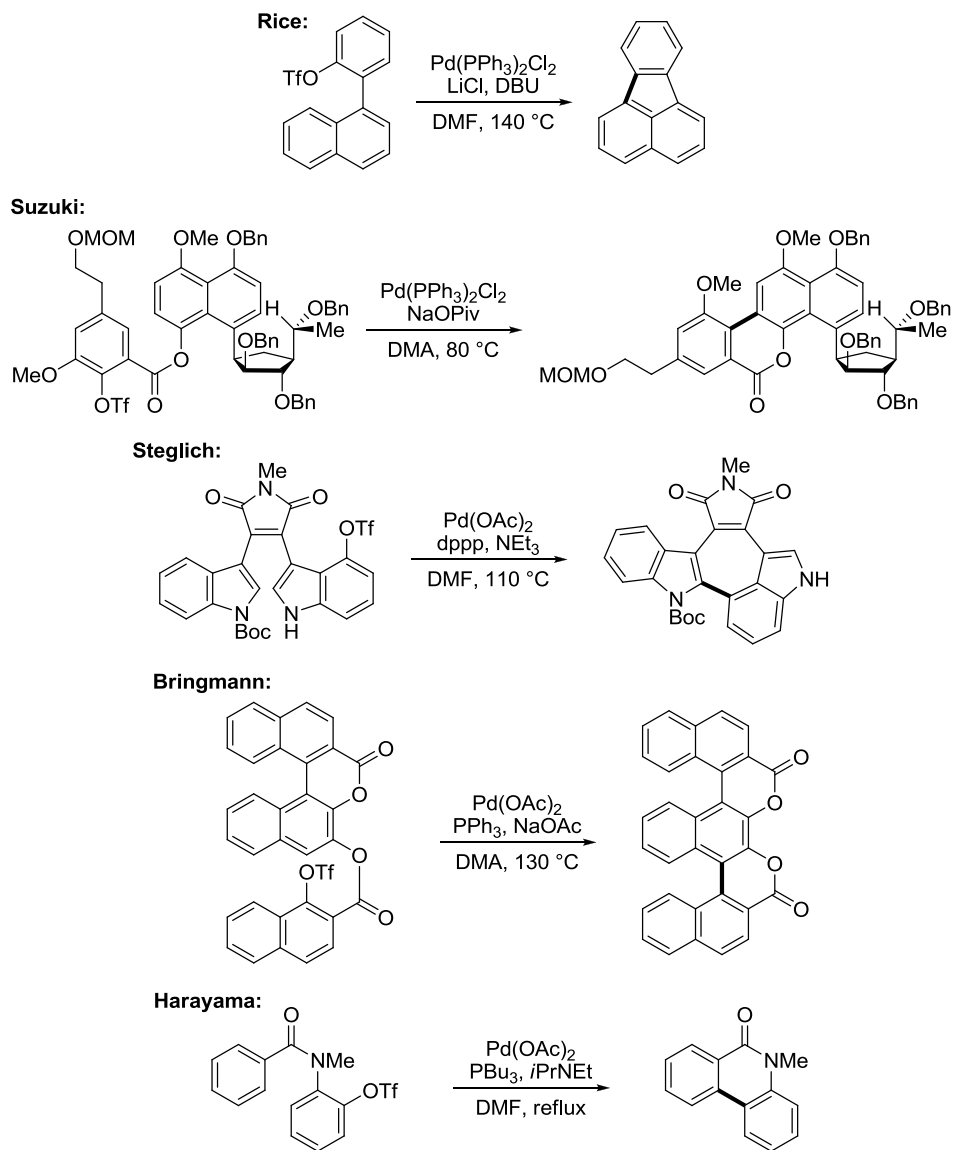
³⁰ (a) Rice, J. E.; Cai, Z.-W. *Tetrahedron Lett.* **1992**, 33, 1675. (b) Rice, J. E.; Cai, Z.-W. *J. Org. Chem.* **1993**, 58, 1415.

³¹ Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, 116, 1004.

³² Brenner, M.; Mayer, G.; Terpin, A.; Steglich, W. *Chem. Eur. J.* **1997**, 3, 70.

³³ Bringmann, G.; Wuzik, A.; Kraus, J.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, 39, 1545.

³⁴ (a) Harayama, T.; Akiyama, T.; Nakano, Y.; Nishioka, H.; Abe, H.; Takeuchi, Y. *Chem. Pharm. Bull.* **2002**, 50, 519 (b) Harayama, T.; Hori, A.; Nakano, Y.; Akiyama, T.; Abe, H.; Takeuchi, Y. *Heterocycles* **2002**, 58, 159.

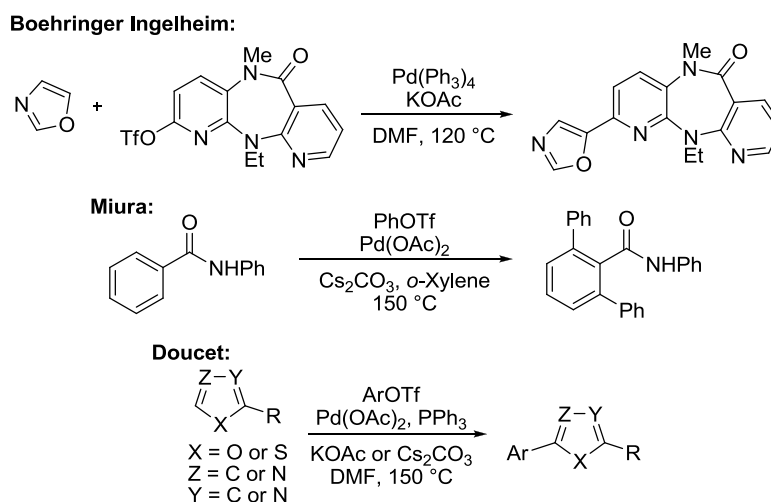


Scheme 2.2 – Intramolecular Direct Arylation with Aryl Triflates

Examples of intermolecular direct arylation which employ aryl triflates are outlined in Scheme 2.3. A group at Boehringer Ingelheim used an aryl triflate for the direct arylation of oxazole to make an HIV-1 reverse transcriptase inhibitor.³⁵ Miura has

³⁵ Proudfoot, J. R.; Hargrave, K. D.; Kapadia, S. R.; Patel, U. R.; Grozinger, K. G.; McNeil, D.W.; Cullen, E.; Cardozo, M.; Tong, L.; Kelly, T. A.; Rose, J.; David, E.; Mauldin, S. C.; Fuchs, V. U.; Vitous, J.; Hoermann, M.; Klunder, J. M.; Raghavan, P.; Skiles, J. W.; Mui, P.; Richman, D. D.; Sullivan, J. L.; Shih, C.-K.; Grob, P. M.; Adams, J.; *J. Med. Chem.* **1995**, *38*, 4830.

established arylation conditions for benzamides using triflates.³⁶ Also, the Doucet group has reported arylation of a range of electron rich heterocycles with aryl triflates.³⁷



Scheme 2.3 – Intermolecular Direct Arylation with Aryl Triflates

Our group has previously reported the palladium catalyzed direct arylation of pyridine and diazine *N*-oxides using a wide range of aryl halides.³⁸ Described in this chapter is: (1) an operationally simple catalyst system for the direct arylation of azine *N*-oxide substrates employing aryl triflates, (2) a sequential arylation to yield differentially di-arylated products that takes advantage of the increased propensity of aryl triflates to induce diarylation, (3) the scope and regioselectivity of arylation on a range of 3-substituted azine *N*-oxides, and (4) the application of this method to the synthesis of an antimalarial and antimicrobial compound.

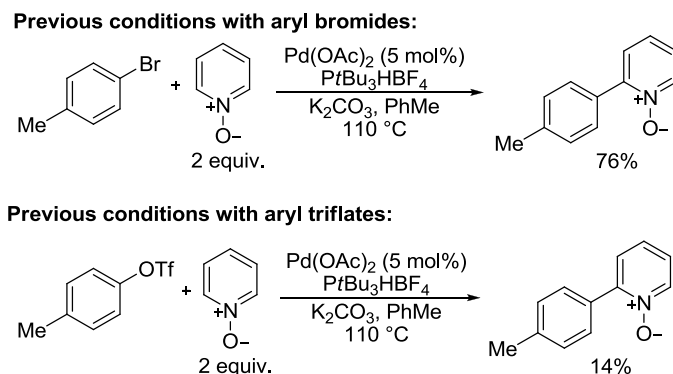
³⁶ (a) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, 41, 2655. (b) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, 124, 5286.

³⁷ Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, 6, 169.

³⁸ (a) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, 131, 3291. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron*, **2009**, 65, 3155. (c) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, 130, 3266. (d) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, 45, 7781. (e) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, 127, 18020. (f) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, 11, 1357.

2.2 Results and Discussion

We began our study by comparing the reactivity of aryl bromides to aryl triflates under our previously established conditions (Scheme 2.4).^{38e} The aryl bromide gave a 76% yield while the aryl triflate resulted in only 14% yield of the desired product. The diminished yields with triflates prompted us to reinvestigate the reaction conditions.

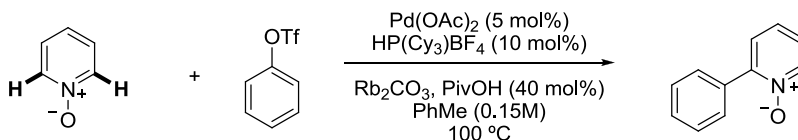


Scheme 2.4 – Comparison of Aryl Bromides with Aryl Triflates

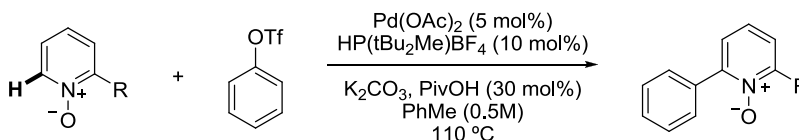
An optimization study commenced using pyridine *N*-oxide and *p*-tolyl trifluoromethanesulfonate. This study revealed that, unlike reactions employing aryl bromide substrates, diarylation of the *N*-oxide substrate was a significant challenge with aryl triflates, leading to diminished yields. An evaluation of the various reaction variables lead to two optimized reaction conditions (Scheme 2.5). The first set of conditions was found to minimize diarylation side products thus maximizing the yield of the monoarylation product. This method employs the use of tricyclohexylphosphine as the ligand, Rb₂CO₃ as the base, and 40 mol% pivalic acid in toluene (0.15 M) at 100 °C for 15 hours (Conditions A). The second set of conditions, which result in increased reactivity, were developed to maximize yields with substrates for which diarylation is not problematic. This method makes use of di-*tert*-butylmethylphosphine as the ligand, K₂CO₃ as the base, with 30 mol% pivalic acid in toluene (0.5 M) at 110 °C for 15 hours

(Conditions B). The increased reactivity of this system could be partially due to the less sterically demanding nature of the P(*t*Bu₂)Me compared to that of the PCy₃ ligand.

Conditions A - gives highest yields of mono-arylated product:



Conditions B - gives highest yield when only one arylation is possible:

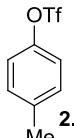
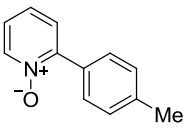
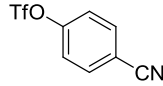
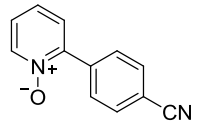
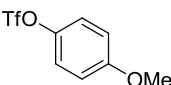
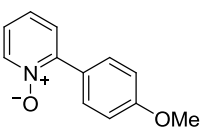
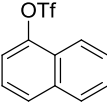
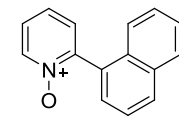
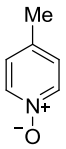
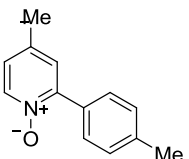
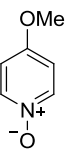
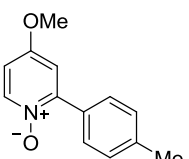
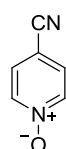
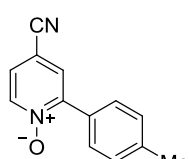
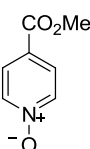
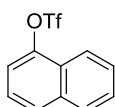
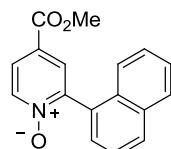
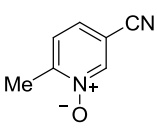
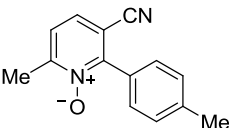
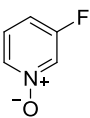
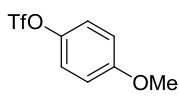
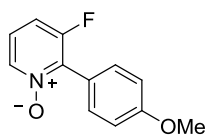


Scheme 2.5 – Optimized Arylation Conditions for Aryl Triflates

Illustrative examples for reaction with aryl triflates under the two different reaction conditions are outlined in Table 2.1. The arylation proceeds with 89 to 91% yield with 2 to 2.5 equivalents of pyridine *N*-oxide respectively (Table 2.1, entries 3-4). If less pyridine *N*-oxide is used diminished yields of 51 to 65% are noted (Table 2.1, entries 1-2). Lower yields of 38 to 59% are obtained with substitution of electron-donating or electron-withdrawing groups at the 4-position (Table 2.1, entries 9-11), although low solubility of these substrates could explain diminished yields. Also, the reaction proceeds well with electron rich aryl triflates (Table 2.1, entries 6, 13 and 26).

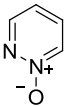
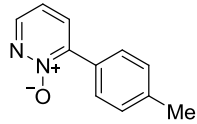
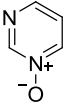
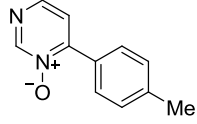
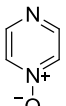
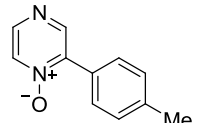
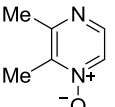
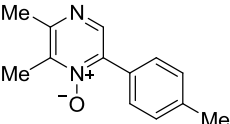
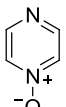
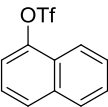
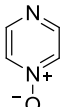
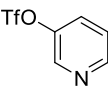
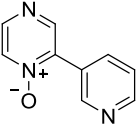
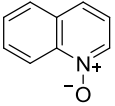
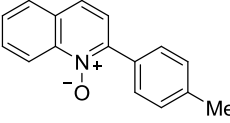
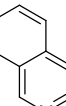
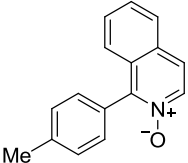
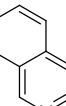
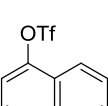
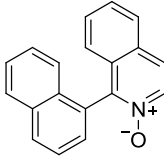
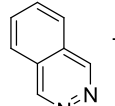
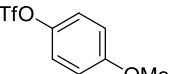
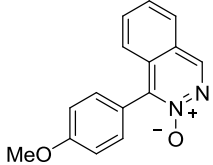
Diazine *N*-oxides are also compatible with the arylation. Pyridazine *N*-oxide is arylated in 99% when using Conditions B (Table 2.1, entry 15). Pyrazine *N*-oxide gives 43-99% yield (Table 2.1, entries 18-21). Pyrimidine *N*-oxide is less suitable, resulting in 20% yield when employing Conditions B and a 10% CuCN additive (Table 2.1, entry 17).^{38d} Quinoline (Table 2.1, entry 23) and isoquinoline (Table 2.1, entry 24) substrates are also suitable for the arylation.

Table 2.1 – Azine Arylation Scope^{a,39}

Entry	N-Oxide	Aryl Triflate	Product	Cond. ^a	Yield ^b
1	 2.1	 2.2		A	51 % ^c
2				A	65 % ^d
3				A	89 %
4				A	91 % ^e
5	2.1			A	49 %
6	2.1			A	75 %
7	2.1			A	75 %
8		2.2		A	71 %
9		2.2		A	39 %
10		2.2		A	38 %
11				A	59 %
12		2.2		B	74 %
13				A	90 %

³⁹ The scope was carried out with the assistance of undergraduate student Mohamed El-Salfiti.

Table 2.1 – Continued

Entry	<i>N</i> -Oxide	Aryl Triflate	Product	Cond. ^a	Yield ^b
14 15		2.2		A B	51 % 99 %
16 17		2.2		A B	0 % 20 % ^f
18		2.2		A	80 %
19		2.2		B	99 % ^g
20				A	60 %
21				A	43 %
22 23		2.2		A B	68 % 81 %
24		2.2		A	82 %
25				A	27 %
26				B	85 % ^g

^a Conditions A: *N*-Oxide (2 eq), Triflate (1 eq), Pd(OAc)₂ (0.05 eq), HP(Cy₃)BF₄ (0.10 eq), Rb₂CO₃ (2 eq), PivOH (0.4 eq), PhMe (0.15 M), 100° C, 15 hrs. Conditions B: *N*-Oxide (2 eq), Triflate (1 eq), Pd(OAc)₂ (0.05 eq), HP(*t*Bu₂)MeBF₄ (0.10 eq), K₂CO₃ (2 eq), PivOH (0.3 eq), PhMe (0.5 M), 110° C, 15 hrs.

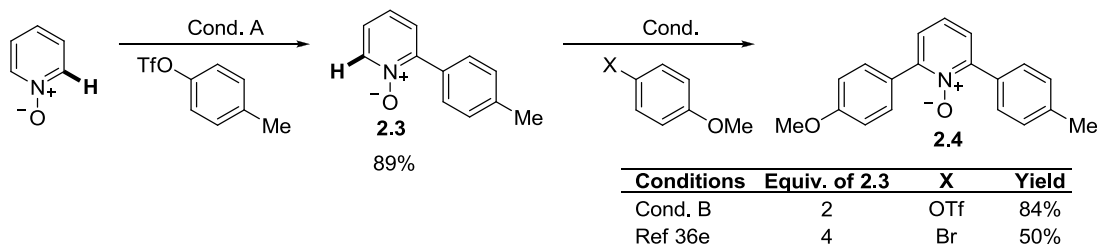
^b Isolated yields. ^c Using 1.0 equivalents of *N*-Oxide. ^d Using 1.5 equivalents of *N*-Oxide. ^e Using 2.5 equivalents of *N*-Oxide. ^f 10 mol % CuCN added. ^g Using 1.1 equivalents of *N*-Oxide.

The more active nature of Conditions B compared to Conditions A is illustrated by two examples. Pyridazine *N*-oxide, which may undergo reaction at only one position, is arylated in 51% yield under Conditions A (Table 2.1, entry 14), but the yield increases to 99% when using Conditions B (Table 2.1, entry 15). Also, quinoline *N*-oxide is arylated in 68% yield under Conditions A (Table 2.1, entry 22) but in 81% yield under Conditions B (Table 2.1, entry 23). High yields can be obtained even when using 1 equivalent of *N*-oxide by utilizing Conditions B in conjunction with an *N*-oxide substrate where diarylation is not problematic as exemplified by the arylation of phthalazine *N*-oxide (Table 2.1, entry 26).

The arylation proceeds with a range of aryl triflates. Electron deficient aryl triflates result in somewhat diminished yields (Table 2.1, entries 5 and 21). Sterically demanding aryl triflates undergo reaction in 59 to 75% yield (Table 2.1, entries 7, 11, and 20); however, lower yields are obtained when used in combination with a sterically demanding *N*-oxide (Table 2.1, entry 25). Heterocyclic aryl triflates can also be employed as illustrated by the use of 3-pyridyl trifluoromethanesulfonate (Table 2.1, entry 21).

Differentially diarylated products can be obtained by carrying out the arylation reactions in sequence as shown in Scheme 2.6. Pyridine *N*-oxide is arylated with *p*-tolyl trifluoromethanesulfonate in 89% yield under Conditions A. This product can then be resubmitted to arylation conditions with 4-methoxyphenyl trifluoromethanesulfonate under the more active Conditions B to generate the differentially diarylated compound **2.4** in 84% yield. Previously reported conditions for the arylation of pyridine *N*-oxide with aryl bromides resulted in 50% yield of the desired product.^{38e} These conditions also

require 4 equivalents of the *N*-oxide to obtain satisfactory yields. Conditions B, which employs aryl triflates, results in not only higher yield than the previously reported conditions but also requires less equivalents of intermediate **2.3**. Therefore it can be advantageous to employ aryl triflates when low yields are obtained with aryl bromides or when *N*-oxide substrates are precious.



Scheme 2.6 – Differential Di-arylation

To further investigate the reactivity and selectivity for reaction with aryl triflates, the arylation was carried out on a series of 3-substituted azine *N*-oxides (Table 2.2), affording a mixture of 2, 6 and disubstituted products. Alkyl substitution favors arylation at the 2-position, but diarylation is a significant by-product (Table 2.2, entries 1-2). Electron donating groups give more favorable selectivities for the 2-position and diarylation is not as problematic (Table 2.2, entries 3-4). Electron withdrawing substituents are the most selective substituents for the 2-position as only trace amounts of the 6-arylated product are observed (Table 2.2, entries 6 and 7). The only substitution that results in preferential arylation at the 6-position is a diethylamide substituent, which gives the 6-arylated product as the major regioisomer, which is possibly due to the increased steric requirements of this group (Table 2.2, entry 5).

Table 2.2 – Scope of 3-Substituted Azine *N*-oxides⁴⁰

Entry	N-Oxide	Cond. ^a	Yield (A:B:C) ^b
1		Conditions A ^c	94 (28:55:11)
2		Conditions B	92 (16:32:44)
3		Conditions A	85 (11:67:7)
4		Conditions B	81 (9:64:8)
5		Conditions A ^c	97 (73:14:10)
6		Conditions B	68 (trace:61:7)
7		Conditions A	90 (trace:90:trace)

^aConditions A: *N*-Oxide (2 eq), Triflate (1 eq), Pd(OAc)₂ (0.05 eq), HP(Cy₃)BF₄ (0.10 eq), Rb₂CO₃ (2 eq), PivOH (0.4 eq), PhMe (0.15 M), 100° C, 15 hrs. Conditions B: *N*-Oxide (2 eq), Triflate (1 eq), Pd(OAc)₂ (0.05 eq), HP(*t*Bu₂)MeBF₄ (0.10 eq), K₂CO₃ (2 eq), PivOH (0.3 eq), PhMe (0.5 M), 110° C, 15 hrs.

^bIsolated yields. ^cUsing 4 equivalents of *N*-Oxide.

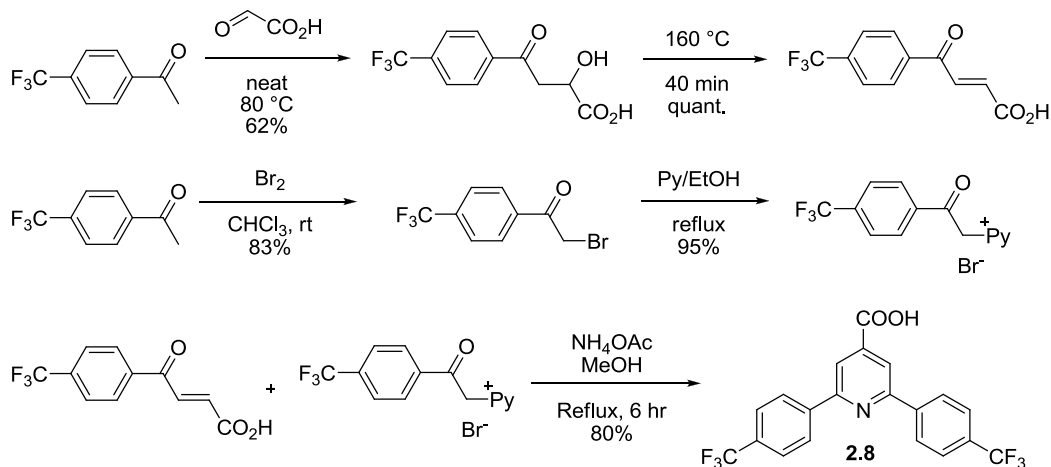
The methodology for the direct arylation of azine *N*-oxides using aryl triflates was also evaluated in the context of the synthesis of key intermediate **2.8** for the synthesis of diarylpyridine **2.5**,^{41d} which exhibits both antimalarial⁴¹ and antimicrobial⁴² activity. A

⁴⁰ This work was carried out by graduate student Christopher Whipp.

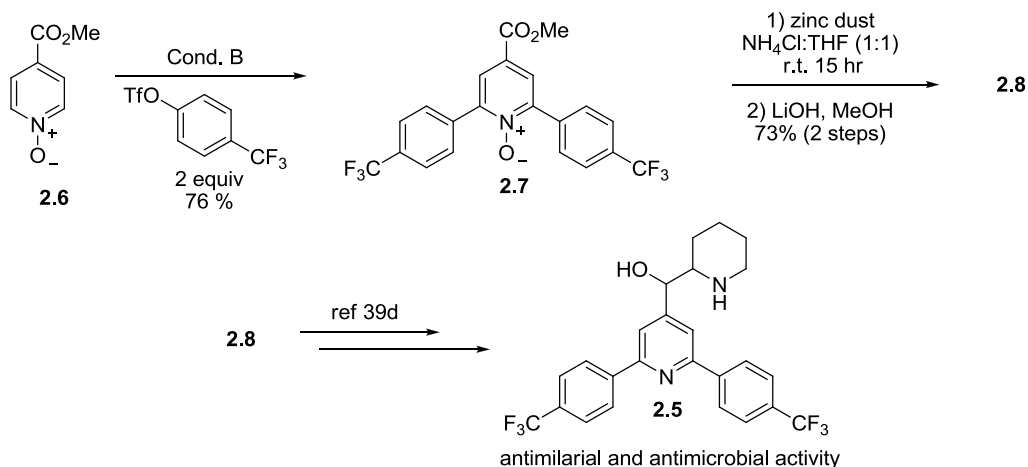
⁴¹ (a) Franke, R.; Streich, W. J. *QSAR*. **1985**, 4, 51. (b) Kim, K. H.; Hansch, C.; Fukunaga, J. Y.; Steller, E. E.; Jow, P. Y. C.; Craig, P. N.; Page, J. J. *Med. Chem.* **1979**, **22**, 366. (c) Schmidt, L. H.; Crosby, R.; Rasco, J.; Vaughan, D. *Antimicrob. Agents Chemother.* **1978**, 14, 420. (d) LaMontagne, M. P.; Markovac, A.; Blumbergs, J. *Med. Chem.* **1974**, 17, 519.

previous synthesis of **2.8**, shown in Scheme 2.7, involves the assembly of the pyridine core with aryl groups already attached.⁴³ We envisioned that, given that **2.8** is symmetrically bis-arylated, the greater propensity of aryl triflates to undergo bis-arylation compared to aryl halides may be capitalized upon. Consequently, methyl isonicotinate *N*-

Previous synthesis:⁴¹



Synthesis employing aryl triflates:



Scheme 2.7 – Formal Synthesis of 2.5

⁴² (a) Martin-Galiano, A. J.; Gorgojo, B.; Kunin, C. M.; De la Campa, A. G. *Antimicrob. Agents Chemother.* **2002**, 46, 1680. (b) Kunin, C. M.; Ellis, W. Y. *Antimicrob. Agents Chemother.* **2000**, 44, 848.

⁴³ Markovac, A.; LaMontagne, M. P.; Blumbergs, P.; Ash, A. B.; Stevens, C. L. *J. Med. Chem.* **1972**, 15, 918.

oxide was subjected to Conditions B with two equivalents of 4-(trifluoromethyl)phenyl trifluoromethanesulfonate to yield 76% of the bis-arylated product **2.7**. Compound **2.7** was then subsequently reduced and saponified to give **2.8** in 73% yield over two steps. Compared to the previous synthesis of **2.7**, the direct arylation approach saves several chemical steps and is more amenable to the synthesis of derivatives.

2.3 Conclusions

In conclusion, a method was developed for the arylation of azine *N*-oxides with aryl triflates. The reaction is broadly applicable to a wide range of both azine *N*-oxides and aryl triflates. The arylation can be carried out in sequence to afford diarylated products. The method was applied to the formal synthesis of a medically relevant compound.

Direct Arylation as a Synthetic Tool for the Synthesis of Thiophene-based Organic Electronic Materials

3.1 Introduction⁴⁴

Organic materials have been studied intensively in recent years and are making significant contributions to the fields of light-emitting diodes,⁴⁵ field-effect transistors,⁴⁶ and photovoltaics⁴⁷ among others. However, as these technologies become commercialized, the active compounds will be required in larger quantities. Therefore, developing efficient syntheses of these compounds is of paramount importance. State of the art syntheses usually rely on traditional cross-coupling reactions (Suzuki, Stille, Negishi, Kumada etc.). However, as mentioned in chapter 1, these methods have several drawbacks due to the use of an organometallic reagent which generates a stoichiometric

⁴⁴ The work described in this chapter has been published in the form of an article, see: Schipper, D. J.; Fagnou, K. *Chem. Mater.* **2011**, 23, 1594.

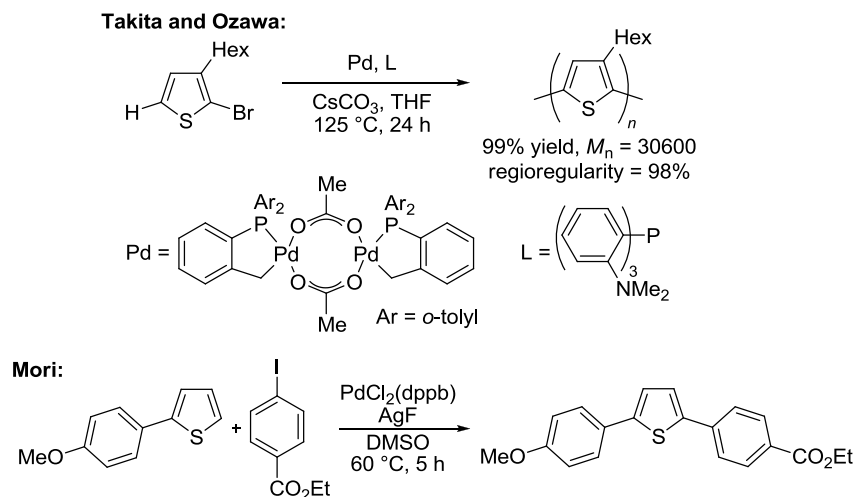
⁴⁵ (a) Tang, C. W.; VanSlyke, S. A.; Chen, C. H. *J. Appl. Phys.* **1989**, 65, 3610. (b) Grimsdale, A. C.; Chan, K. L.; Martin, R. E.; Jokisz, P. G.; Holmes, A. B. *Chem. Rev.* **2009**, 109, 897. (c) Mullen, K.; Scherf, U. *Organic Light-Emitting Devices: Synthesis, Properties and Applications*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006.

⁴⁶ (a) Coropceanu, V.; Cornil, J.; da Silva Filho, D. A.; Olivier, Y.; Silbey, R.; Bredas, J.-L. *Chem. Rev.* **2007**, 107, 926. (b) Mas-Torrent, M.; Rovira, C. *Chem. Soc. Rev.* **2008**, 37, 827. (c) Allard, S.; Forster, M.; Souharce, B.; Thiem, H.; Scherf, U. *Angew. Chem. Int. Ed.* **2008**, 47, 4070. (d) Wu, W.; Liu, Y.; Zhu, D. *Chem. Soc. Rev.* **2010**, 39, 1489.

⁴⁷ (a) Ooyama, Y.; Harima, Y. *Eur. J. Org. Chem.* **2009**, 2903. (b) Mishra, A.; Fischer, M. K. R.; Bauerle, P. *Angew. Chem. Int. Ed.* **2009**, 48, 2474. (c) Ning, Z.; Tian, H. *Chem. Commun.* **2009**, 5483.

al. have also described thiophene direct arylation under phase transfer conditions which proceeded at 80 °C and with improved yields.^{49b,c} Additionally, Doucet has reported thiophene arylation conditions that employ low catalyst loadings while being performed at 150 °C.^{49l,p,s} While the mechanism of the C-H bond cleavage step in direct arylation has been debated, several research groups, including our own, have provided evidence for the concerted metalation deprotonation pathway. This mechanistic understanding lead to the development of pivalate as a proton shuttle⁵⁰/internal base⁵¹ additive which we have found gives superior reactivity under our reported conditions.^{49r}

While direct arylation should be widely applicable, there is a paucity of examples of its utilization for the construction of organic materials. Takita and Ozawa have disclosed the use of palladium-catalyzed direct arylation for the synthesis of poly(3-alkylthiophene)s,⁵² which represents one of the most promising classes of π -conjugated



Scheme 3.2 – Synthesis of Organic Materials Using Direct Arylation

⁵⁰ Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

⁵¹ Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015.

⁵² Wang, Q.; Takita, R.; Kikuzaki, Y.; Ozawa, F. *J. Am. Chem. Soc.* **2010**, *132*, 11420.

polymers.⁵³ Mori has reported the synthesis of donor-acceptor type π -conjugated materials using direct arylation (Scheme 3.2).⁵⁴

In this chapter, we report the application of the direct arylation method to the (formal) synthesis of broad range of thiophene-based molecules which have exhibited promise for

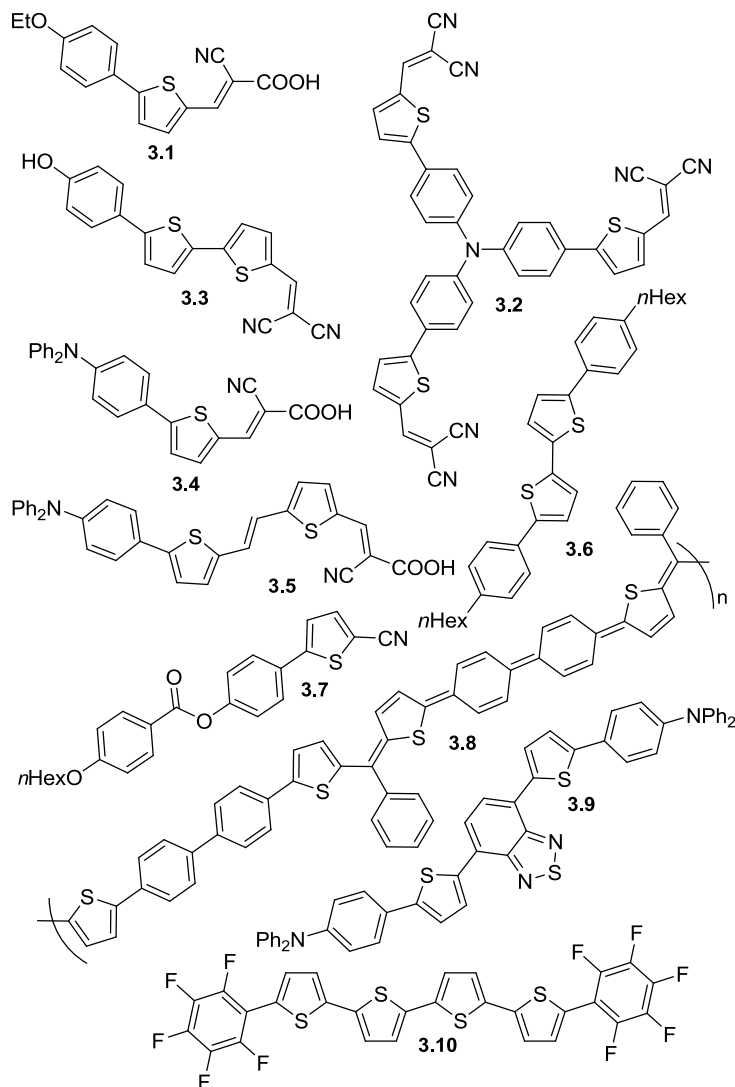


Figure 3.1 – Thiophene Based Organic Materials

⁵³ (a) Roncali, J. *Chem. Rev.* **1997**, 97, 173. (b) McCullough, R. D. *Adv. Mater.* **1998**, 10, 93. (c) Arias, A. C.; MacKenzie, J. D.; McCulloch, I.; Rivnay, J.; Salleo, A. *Chem. Rev.* **2010**, 110, 3. (d) Perepichka, I. F.; Perepichka, D. F.; Meng, H.; Wudl, F. *Adv. Mater.* **2005**, 17, 2281. (e) Grimsdale, A. C.; Chan, K. L.; Martin, R. E.; Jokisz, P. G.; Holmes, A. B. *Chem. Rev.* **2009**, 109, 897. (f) Cheng, Y.-J.; Yang, S.-H.; Hsu, C.-S. *Chem. Rev.* **2009**, 109, 5868.

⁵⁴ Masui, K.; Mori, A.; Takamura, K.; Okano, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, 6, 2011.

applications as optoelectronic materials (Figure 3.1). These syntheses require less synthetic operations than previously reported syntheses, are high yielding and avoid the use of organometallic reagents.

In the course of a research program dedicated to the development of direct arylation reactions, we became interested in organic electronic materials based on the thiophene moiety because they represent an important class of materials.⁵⁵ In addition, thiophenes are ideal substrates for direct arylation due to the facile palladation through a CMD pathway which renders the reaction generally highly selective for the 2/5-position on thiophenes.⁵⁶ We surmised that the application of the direct arylation reaction to the synthesis of known organic electronic molecules would result in shorter syntheses, and therefore higher yields, while avoiding organometallic intermediates and superfluous waste.

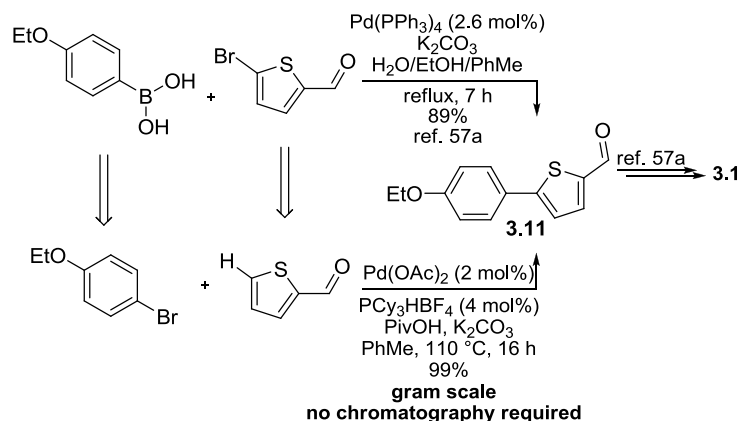
3.2 Results and Discussion

Park and co-workers have reported compound **3.1** for application in organic dye sensitized solar cells.⁵⁷ In a previous report, **3.1** was synthesized from key intermediate **3.11** which was produced in 89% yield from a Suzuki coupling of 4-ethoxyphenylboronic acid with 5-bromo-2-thiophenecarboxaldehyde (Scheme 3.3). Using direct arylation, the boronic acid and aryl bromide could be replaced with an aryl bromide and a simple arene respectively. This would provide a more direct route using simpler and cheaper starting materials. Gratifyingly, the direct arylation proceeds using catalytic Pd(OAc)₂/PCy₃ with

⁵⁵ Perepichka, I. F.; Perepichka, D. F.; *Handbook of Thiophene-Based Materials*; John Wiley & Sons Ltd.: Chichester, 2009.

⁵⁶ Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

⁵⁷ (a) Park, S. W.; Son, K.-I.; Ko, M. J.; Kim, K.; Park, N.-G. *Synth. Met.* **2009**, *159*, 2571. (b) Lee, K.; Park, S. W.; Ko, M. J.; Kim, K.; Park, N.-G. *Nat. Mater.* **2009**, *8*, 665.

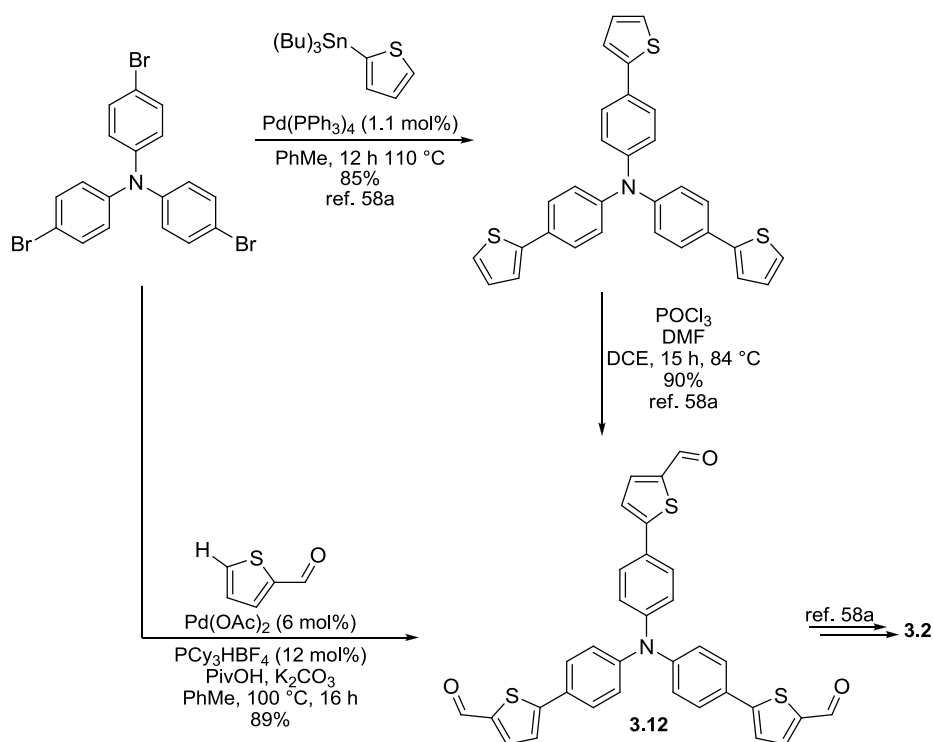


Scheme 3.3 – Formal Synthesis of **3.1**

30 mol% pivalic acid and K_2CO_3 in PhMe at 110 °C for 16 hours to give key intermediate **3.11**. To demonstrate synthetic utility, this reaction was carried out on gram scale to afford **3.11** in quantitative yield, highlighting the excellent selectivity of the reaction. Another advantage of this synthesis is that it does not require chromatographic purification which becomes less practical as the scale of the reaction is increased.

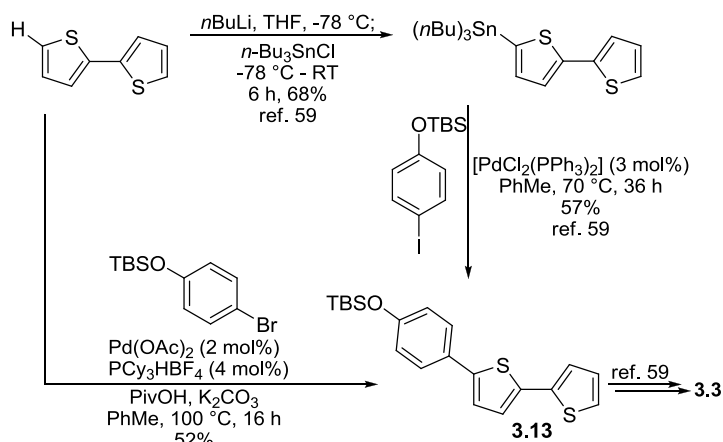
The effectiveness of star shaped molecule **3.2** as a donor material in heterojunction solar cells has been shown by Roncali, Leriche and co-workers.⁵⁸ The star-shaped molecule **3.2** was prepared from key intermediate **3.12** which was assembled in 77% overall yield via the Stille coupling of 2-(tributylstannyl)thiophene with tris(4-bromophenyl)amine followed by a Vilsmeier-Haack formylation (Scheme 3.4). Application of a direct arylation protocol gives **3.12** in one step and 89% yield using the same aryl bromide and 2-thiophenecarboxaldehyde in place of 2-(tributylstannyl)thiophene.

⁵⁸ (a) Roquet, S.; Cravino, A.; Leriche, P.; Aleveque, O.; Frere, P.; Roncali, J. *J. Am. Chem. Soc.* **2006**, 128, 3459. (b) Cravino, A.; Roquet, S.; Leriche, P.; Aleveque, O.; Frere, P.; Roncali, J.; *Chem. Commun.* **2006**, 1416. (c) Leriche, P.; Frere, P.; Cravino, A.; Aleveque, O.; Roncali, J. *J. Org. Chem.* **2007**, 72, 8332.



Scheme 3.4 – Formal Synthesis of **3.2**

The Swager group has reported the use of compound **3.3** as a fluorescent marker for *in vivo* optical imaging.⁵⁹ The synthesis of **3.3** proceeds with the deprotonation of 2,2'-bithiophene followed by quench with $\text{ClSn}(n\text{Bu})_3$ to install the requisite stannane for the

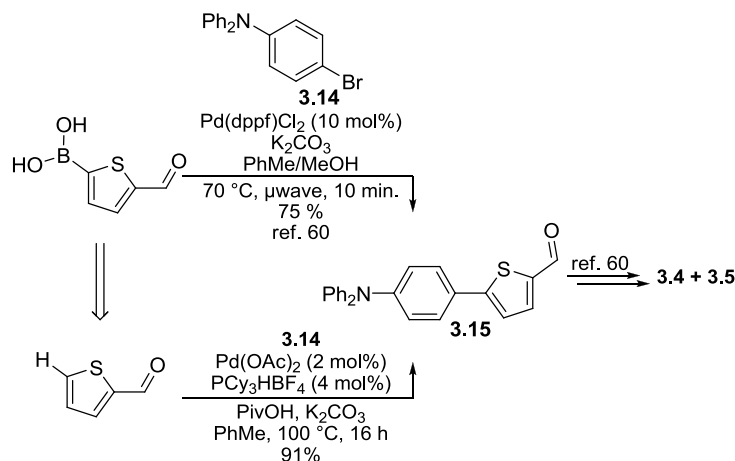


Scheme 3.5 – Formal Synthesis of **3.3**

⁵⁹ Nesterov, E. E.; Skoch, J.; Hyman, B. T.; Klunk, W. E.; Bacskai, B. J.; Swager, T. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5452.

subsequent Stille coupling which proceeds to give key intermediate **3.13** in 39% overall yield (Scheme 3.5). Alternatively, **3.13** can be prepared in one step from 2,2'-bithiophene using direct arylation under similar conditions as described above in 52% yield while avoiding organotin intermediates.

Hagfeldt and Sun described the application of **3.4** and **3.5** as chromophores for dye sensitized solar cells.⁶⁰ Both were synthesized through common intermediate **3.15**, which was prepared in 75% yield via a Suzuki reaction using 10 mol% catalyst (Scheme 3.6). The direct arylation route to **3.15** proceeds in 91% yield at 2 mol% catalyst loading and allows 5-formylthiophene-2-boronic acid to be replaced with the cheaper 2-thiophenecarboxaldehyde.



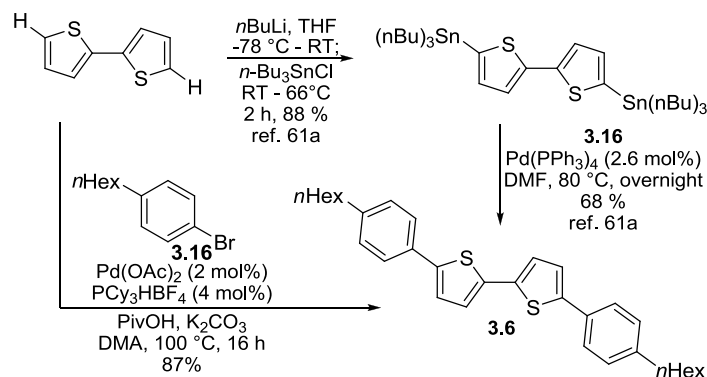
Scheme 3.6 – Formal Synthesis of **3.4** and **3.5**

Marks has pioneered the use of **6** in organic field-effect transistors.⁶¹ Bithiophene **3.6** was constructed via the functionalization of 2,2'-bithiophene to the appropriate bisstannane followed by the Stille coupling with **3.16** to afford **3.6** in 60% overall yield

⁶⁰ Hagberg, D. P.; Marinado, T.; Karlsson, K. M.; Nonomura, K.; Qin, P.; Boschloo, G.; Brinck, T.; Hagfeldt, A.; Sun, L. *J. Org. Chem.* **2007**, 72, 9550.

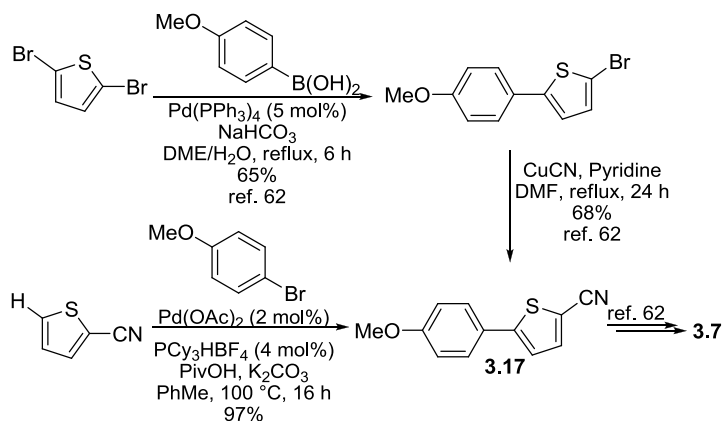
⁶¹ (a) Mushrush, M.; Facchetti, A.; Lefenfeld, M.; Katz, H. E.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, 125, 9414. (b) Yoon, M.-H.; Facchetti, A.; Marks, T. J. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, 102, 4678. (c) Yoon, M.-H.; Yan, H.; Facchetti, A.; Marks, T. J.; *J. Am. Chem. Soc.* **2005**, 127, 10388.

(Scheme 3.7). Conversely, **3.6** can be made in one step and 87% yield from commercially available starting materials using direct arylation while avoiding organometallic intermediates.



Scheme 3.7 – Synthesis of **3.6**

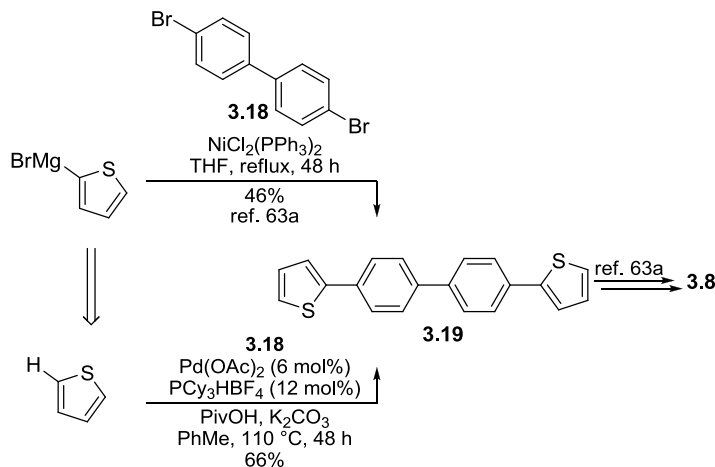
Cheng et. al. have reported **3.7** as a liquid crystalline material.⁶² Their synthesis began with a Suzuki coupling with 2,5-dibromothiophene followed by a cyanation reaction using CuCN to give key intermediate **3.17** in two steps and 44% yield (Scheme 3.8). Using the direct arylation protocol **3.17** was synthesized in a single step and 97% yield using lower palladium loading and cheaper starting materials.



Scheme 3.8 – Formal Synthesis of **3.7**

⁶² Huang, Y.; Luo, Z.; Cheng, X.; Tschierske, C. *Liq. Cryst.* **2009**, 36, 61.

The group of Yang has described **3.8** as a soluble low band gap conducting polymer.⁶³ The monomer **3.19** was assembled via a Kumada coupling in 46% yield (Scheme 3.9). By employing direct arylation, the Grignard reagent, which must be preformed and can be difficult to handle, can be replaced with an excess of simple thiophene to afford the same product in 66% yield.

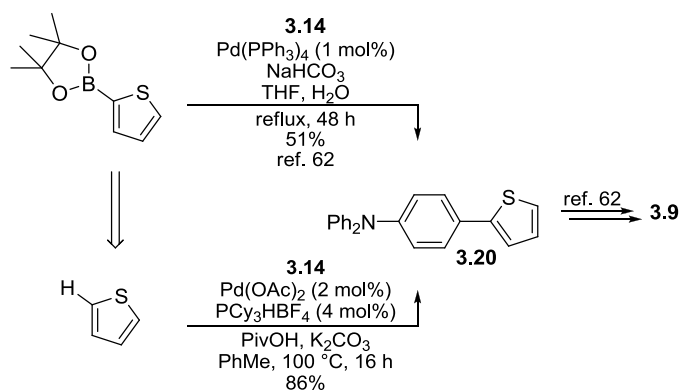


Scheme 3.9 – Formal Synthesis of **3.8**

Bo, Zhang and co-workers have shown that benzothiadiazole-based molecules such as **3.9** can be employed in efficient bulk heterojunction solar cells.⁶⁴ **3.9** can be prepared from **3.20** which was synthesized via a Suzuki coupling between 2-thiopheneboronic acid pinacol ester and **3.14** in 51% yield (Scheme 3.10). Conversely, **3.20** can also be prepared in 86% yield by employing the same aryl bromide and using an excess of thiophene in place of 2-thiopheneboronic acid pinacol ester.

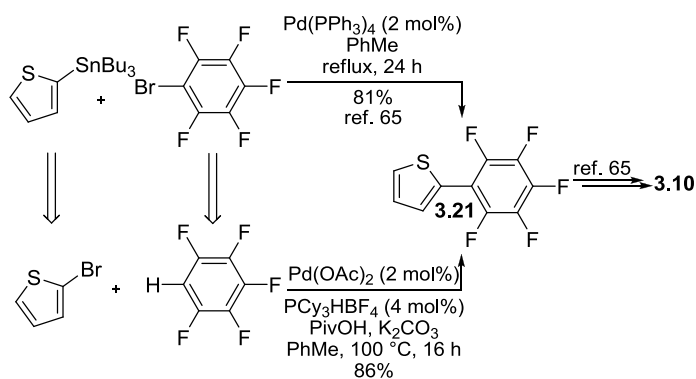
⁶³ (a) Zhang, Q.; Li, Y.; Yang, M. *J. Mater. Sci.* **2004**, 39, 6089. (b) Yang, M.; Zhang, Q.; Wu, P.; Ye, H.; Liu, X. *Polymer* **2005**, 46, 6266.

⁶⁴ Li, W.; Du, C.; Li, F.; Zhou, Y.; Fahlman, M.; Bo, Z.; Zhang, F. *Chem. Mater.* **2009**, 21, 5327.



Scheme 3.10 – Formal Synthesis of **3.9**

Marks has also demonstrated perfluorobenzene substituted oligothiophenes such as **3.10** for use as n-type organic semiconductors.⁶⁵ **3.10** was synthesized from **3.21** which had been prepared in 81% yield using a Stille coupling between 2-(tributylstannyl)thiophene and bromopentafluorobenzene (Scheme 3.11). Using direct arylation, organotin compounds can be avoided and **3.21** can be obtained in 86% yield using 2-bromothiophene and pentafluorobenzene. This example demonstrates that in cases where both arenes have been shown to undergo direct arylation, such as with



Scheme 3.11 – Formal Synthesis of **3.10**

⁶⁵ Facchetti, A.; Yoon, M.-H.; Stern, C. L.; Katz, H. E.; Marks, T. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 3900.

thiophenes⁴⁹ and pentafluorobenzene,^{66,49u} it is possible to switch the bromine substitution such that bromothiophenes and a simple arene are utilized as coupling partners.

The direct arylation method is not without limitations. In the formal synthesis of **3.1**, **3.2**, **3.4**, **3.5** and **3.7**, two equivalents of the thiophene coupling partner per aryl bromide are required to achieve desirable product yields. However, the use of this excess is mitigated because it is readily available and relatively inexpensive. Additionally, it can be recovered from the reaction mixture by distillation if desired.

It is worth noting that under the conditions reported here, arylation always occurs selectively at the 2/5-position on thiophene⁶⁷ with no byproducts arising from arylation of other positions detectable by spectroscopic methods. However, in cases where there are two possible reactive sites, as with thiophene and 2,2'-bithiophene, after arylation of one position the second position becomes more reactive towards direct arylation.⁶⁸ This renders diarylation a significant reaction product. This is disadvantageous for the formal synthesis of **3.3**, **3.8**, and **3.9** in which only one arylation is desired. In those cases five equivalents of thiophene coupling partner are required to avoid diarylation and gives **3.13** and **3.20** in 52% and 86% yield respectively. Also, six equivalents are required to isolate **3.19** in 66% yield. Again, the use of excess thiophene is mitigated because it is

⁶⁶ (a) Lafrance, M.; Rowley, C.N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

⁶⁷ The effects of substituents have not been studied in detail. However competition experiments have been conducted. See: (a) González, J. J.; García, N.; Gómez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, *62*, 1286. (b) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (c) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (d) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (e) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. See also refs 49j, 51, 52, 66a.

⁶⁸ Lapointe, D.; Gorelsky, S. I.; Fagnou, K. *Unpublished Results*.

inexpensive,⁶⁹ easily handled and less toxic compared to organometallic coupling partners. As recently demonstrated in our group, one potential solution to this problem would be to employ a chlorine atom as an activating/blocking group.^{49t} Conversely, the tendency to undergo diarylation can also be advantageous if diarylation is desired, such as with **3.6**. The ideal mol ratio of 2:1 aryl bromide to 2,2'-bithiophene can be employed to give **3.6** in 87% yield.

3.3 Conclusion

In conclusion, we have demonstrated the viability of direct arylation for the (formal) synthesis of a broad range of thiophene based organic electronic materials. Direct arylation has several advantages to traditional cross-coupling methods currently used for the construction of organic electronic materials and should be added to the “synthetic toolbox” of organic materials chemists. Direct arylation should be useful for the rapid and atom economical synthesis of an ever growing quantity of organic electronic materials, as well as streamline the synthesis of new thiophene-based organic electronic materials.

⁶⁹ Thiophene is \$10/mol, whereas 2-(tributylstannyl)thiophene is \$1702/mol and 2-thienylboronic acid is \$2323/mol (base on prices as of April 30, 2011 from Sigma-Aldrich).

Site Selective Site-Selective sp^2 and sp^3 Direct Arylation of Azine N-oxides

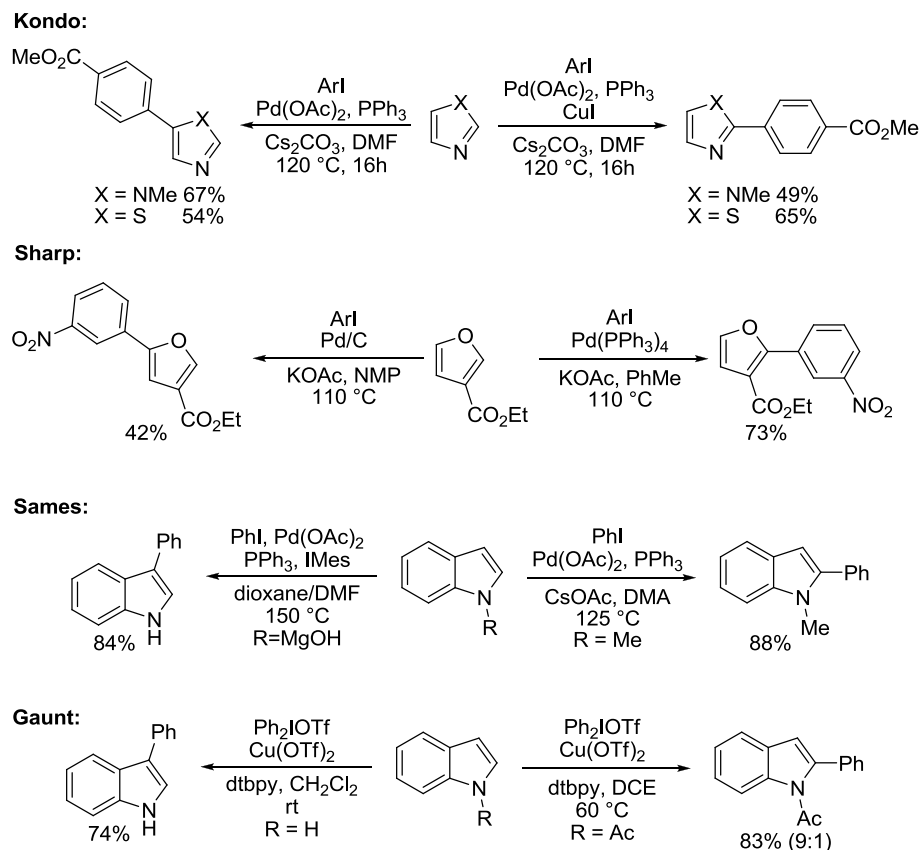
4.1 Introduction⁷⁰

While rare even just a decade ago, direct arylation of heterocycles has become a valuable tool in the transformation of otherwise chemically inert C-H bonds into a number of functional groups.⁷¹ A particularly appealing and frequently discussed aspect of this chemistry involves the ubiquity of the C-H bond as a “functional group” and the potential to strategically transform these with high site selectivity.⁷² In practice, the challenge associated with achieving a high yielding reaction at even just one position makes the realization of controlled multi-site selectivity rare. Important advances have

⁷⁰ A significant portion of the work described in this chapter has been published in the forms of a communication and a full article, see: (a) Campeau, L.-C.; Schipper, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155.

⁷¹ For general reviews on direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

⁷² For reviews on C-H activation, see: (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Ritleng, V.; Silin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (f) Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008**, *64*, 6979. (g) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987.



Scheme 4.1 – Site Selective Direct Arylations

been made with some classes of electron-rich heteroaromatics (Scheme 4.1).⁷³ For example, the inherent bias of azoles to undergo C5 direct arylation can be overridden through the use of copper additives which induce reaction at C2.⁷⁴ 3-Carboxy furan and thiophene can be selectively arylated at either the C2 or C5 position.⁷⁵ Sames has also

⁷³ For reviews, see refs 71c and 71d. For recent examples, see: (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, 6, 2897. (b) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, 5, 4835. (c) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, 125, 1700. (d) Wang, 4.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, 127, 4996. (e) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, 9, 1449. (f) Turner, G. L.; Morris, J. A.; Greany, M. F. *Angew. Chem., Int. Ed.* **2007**, 46, 7996. (g) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, 72, 8543. (h) Poz'gan, F.; Rogerm, J.; Doucet, H. *ChemSusChem* **2008**, 1, 404.

⁷⁴ (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, 71, 467. (b) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, 2, 3111.

⁷⁵ Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, 5, 301.

reported examples of C2/C3 site selectivity in indole arylations.⁷⁶ Gaunt has demonstrated that regiocontrol can be achieved in indole and pyrrole alkenylation and arylation reactions through the choice of the solvent and the azole *N*-substituent.⁷⁷ We have recently demonstrated that the choice of oxidant as well as the nature of the *N*-acyl substituent can reverse the site selectivity of the oxidative coupling of benzene with indole.⁷⁸ Significantly, these reactions all involve selectivity at aromatic sp^2 C-H bonds.

In contrast to direct arylation at sp^2 centers, which has received much attention in recent years, direct arylation at sp^3 centers has received much less. This is likely due to the inherent difficulty in cleaving an sp^3 C-H bond. However, recently several reports of palladium catalyzed direct arylation at an sp^3 center have appeared. The first examples involved reaction of activated C-H bonds such as those α to carbonyl groups. In 1997 the groups of Buchwald,⁷⁹ Hartwig⁸⁰ and Miura⁸¹ independently reported the α -arylation of ketones (equation 4.1). Since that time this method has been expanded to include many other types of carbonyl functionalities.⁸²

⁷⁶ Lane, B. S.; Brown, M. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

⁷⁷ (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. Importantly copper is not always required for these types of arylations, see: Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358 and references therein.

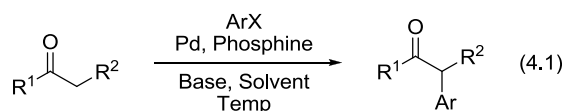
⁷⁸ (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *317*, 1172. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072.

⁷⁹ Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

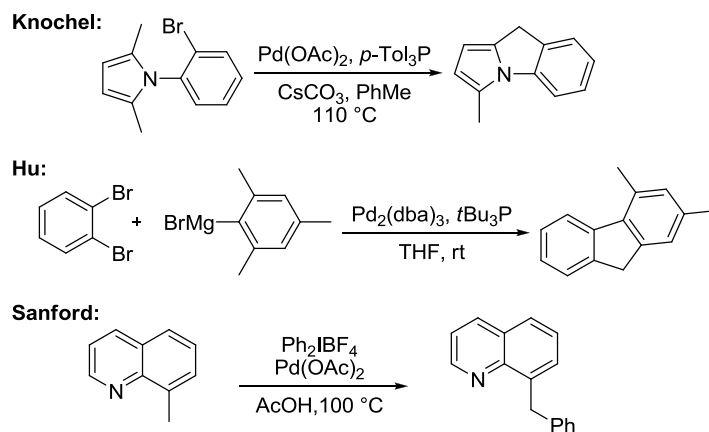
⁸⁰ Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

⁸¹ Satoh, T.; Kawamura, T.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1740.

⁸² (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345. (c) Fox, J. M.; Huang, 4.; Chieffi, A.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2000**, *122*, 1360. (d) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M.; *Tetrahedron* **2001**, *57*, 5967-5974. (e) Ehrentraut, A.; Zapf, A.; Beller, M.; *Adv. Synth. Catal.* **2002**, *344*, 209. (f) Satoh, T.; Jones, W. D.; *Organometallics* **2001**, *20*, 2916. (g) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F.; *J. Org. Chem.* **1998**, *63*, 6546. (h) Lee, S.; Hartwig, J. F.; *J. Org. Chem.* **2001**, *66*, 3402. (i) Moradi, W. A.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2001**, *123*, 7996. (j) Gaertzen, O.; Buchwald, S. L.; *J. Org. Chem.* **2002**, *67*, 465. (k) Jørgensen, M.; Lee, S.; Liu, 4.; Wolkowski, J. P.; Hartwig, J. F.; *J. Am. Chem. Soc.* **2002**, *124*, 12557. (l) Terao, Y.; Fukuoka, Y.; Satoh,



In addition to the examples of intramolecular arylation of unactivated sp^3 C-H bonds,⁸³ there have also been several recent reports on the intramolecular and intermolecular direct arylation of benzylic sp^3 C-H bonds (Scheme 4.2). Ren and Knochel have described the intramolecular direct arylation of benzylic pyrrole derivatives to form N-heterocycles.⁸⁴ Hu and co-workers reported a tandem Kumada coupling/direct arylation which proceeded through benzylic C-H bond functionalization.⁸⁵ The group of Sanford has achieved the chelation assisted arylation of a benzylic position using diaryliodonium salts.⁸⁶



Scheme 4.2 – Benzylic Direct Arylations

T.; Miura, M.; Nomura, M.; *Tetrahedron Lett.* **2002**, 43, 101. (m) Spielvogel, D. J.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2002**, 124, 3500.

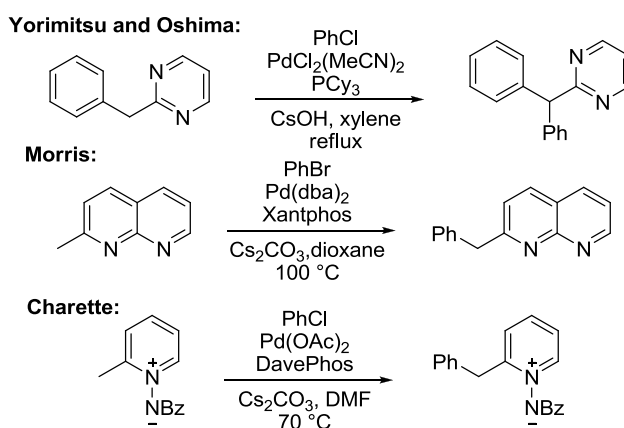
⁸³ For a review on catalytic C(sp^3)-H activation: (a) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, 16, 2654. For recent examples see: (b) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, 132, 10706. (c) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, 132, 10692. (d) Renaudat, A.; Jean-Gerard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem. Int. Ed.* **2010**, 49, 7261.

⁸⁴ Ren, H.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, 45, 3462.

⁸⁵ Dong, C.-G.; Hu, Q.-G. *Angew. Chem. Int. Ed.* **2006**, 45, 2289.

⁸⁶ Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, 127, 7330.

Of greater relevance to the chemistry presented in this chapter is direct arylation of azaaryl benzylic derivatives; of which there are several examples (Scheme 4.3). Yorimitsu and Oshima demonstrated the palladium-catalyzed direct arylation of aryl(azaaryl)methanes.⁸⁷ Morris and Burton recently reported the benzylic arylation of 2-methyl azaarenes.⁸⁸ Concurrently with our work Charette and co-workers published on the arylation of 2-methyl *N*-iminopyridinium ylides.⁸⁹ Importantly, no products arising from sp^2 arylation are detected under these conditions.



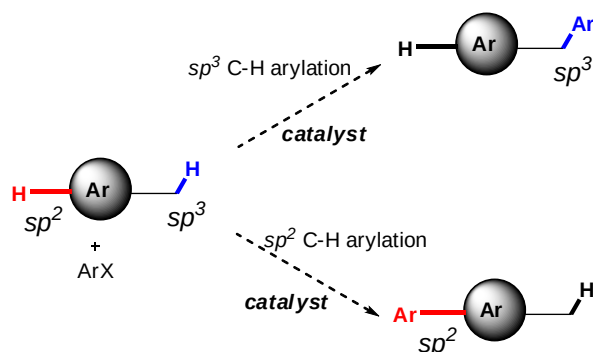
Scheme 4.3 – Direct Arylation of Azaaryl Benzylic Derivatives

As a greater appreciation of the possible mechanisms of C-H bond cleavage/functionalization is gained, and particularly as transformations and mechanisms which exhibit complimentary and orthogonal reactivity are discovered, this long-term goal of chemo- and site selective direct functionalization should become increasingly achievable. Described in this chapter is: (1) operationally simple catalyst systems for the site selective direct arylation of sp^2 and sp^3 carbons of azine *N*-oxide substrates and several new examples, exhibiting broad scope for aryl chlorides, bromides, and iodides;

⁸⁷ Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, 9, 2373.

⁸⁸ Burton, P. M.; Morris, J. A. *Org. Lett.* **2010**, 12, 5359.

⁸⁹ Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, 10, 1641.



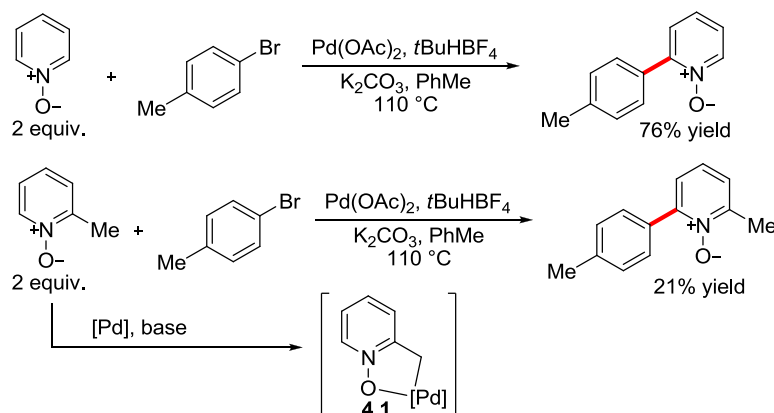
Scheme 4.4 – Catalyst controlled site selective sp^2/sp^3 arylation.

(2) that the arylation reactions can be carried out in either a divergent manner or a sequential manner in which either the sp^2 or the sp^3 arylation can be carried out first; (3) the application of the novel sp^3 arylation process to the synthesis of the natural products, Papaverine and Crykonisine, in three steps from simple starting materials; (4) insight into catalyst poisoning with electron deficient aryl halides leading to new mechanistic insights; (5) mechanistic studies pointing towards the intimate involvement of the base in the mechanism of the reactions.

4.2 Results and Discussion

Our group has described the use of *N*-oxides in direct arylation reactions as a means of avoiding the use of problematic organometallics in the formation of biaryl molecules.⁹⁰ Ongoing studies revealed that lower yields were encountered with substrates bearing methyl substituents adjacent to the *N*-oxide moiety (Scheme 4.5). This prompted a re-evaluation of the sp^2 arylation conditions during which superior yields and selectivities were observed when using a 1:1 Pd(OAc)₂ to P^tBu₃ stoichiometry compared to a 1:3 ratio (Table 4.1, entries 1 and 2). Pertinent to the chemistry that follows, the selection of the

⁹⁰ (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem Int. Ed.* **2006**, *45*, 7781.



Scheme 4.5 – Compared Reactivity of Pyridine *N*-oxide to Picoline *N*-oxide

base is crucial, with carbonates providing the optimal outcomes. Under these conditions, no other products are detected in ^1H NMR analysis of the crude reaction mixture. High yields of the azine/diazine biaryl compounds can also be achieved as illustrated by Table 4.4.

The challenges associated with these substrates lead us to question whether competing palladacycle formation (such as **4.1**) might be responsible for the challenging reactivity.⁹¹ A corollary to this hypothesis is that intermediates such as **4.1** might also enable sp^3 arylation under appropriate conditions. Towards this goal, every aspect of the reaction was reinvestigated. A promising lead involved the combination of **4.3** with 1.5 equivalents of **4.2**, 2.5 mol% $\text{Pd}_2(\text{dba})_3$, 6 mol% S-Phos and 1.05 equivalents of NaO^tBu in toluene at 70 °C which provides 31% conversion to a 4.3:1 mixture of **4.5** and **4.6** (Table 4.1, entry 3).

⁹¹ Reaction of 4-Picoline *N*-oxide under Conditions B yields only sp^2 arylation

Table 4.1 – Optimization of Picoline *N*-Oxide sp^3 -Arylation^a

Entry	Pd Source	Ligand (L:Pd)	Base (equiv.)	Equiv. 1	Temp (°C)	Ratio 4.4:4.5:4.6	Yield
1	Pd(OAc) ₂	^t Bu ₃ PBHF ₄ (3:1)	K ₂ CO ₃ (1.05)	2	110	1:0:0	21%
2	Pd(OAc) ₂	^t Bu ₃ PBHF ₄ (1:1)	K ₂ CO ₃ (1.05)	2	110	1:0:0	56%
3	Pd ₂ (dba) ₃	S-Phos (1:1)	NaO ^t Bu (1.05)	1.5	70	0:4.3:1	31%
4	Pd ₂ (dba) ₃	S-Phos (1:1)	NaO ^t Bu (1.05)	4	70	0:20:1	48%
5	Pd ₂ (dba) ₃	S-Phos (1:1)	NaO ^t Bu (3)	2	70	0:6.7:1	77% ^b
6	Pd ₂ (dba) ₃	X-Phos (1:1)	NaO ^t Bu (3)	2	70	0:20:1	41%
7	Pd ₂ (dba) ₃	Ru-Phos (1:1)	NaO ^t Bu (3)	2	70	0:8:1	78%
8	Pd ₂ (dba) ₃	X-Phos (1:1)	NaO ^t Bu (3)	1.5	110 (mw)	0:20:1	89% ^b
9	Pd ₂ (dba) ₃	X-Phos (1:1)	NaO ^t Bu (3)	1.5	110 (mw)	0:20:1	84% ^{b,c}

S-Phos

Ru-Phos

X-Phos

Conditions: Substrates, Pd, ligand and base dissolved in PhMe and heated in an oil bath or microwave reactor. ¹H NMR yield of the major product. ^b Isolated yield of the major product. ^c Using 1 mol% Pd.

While increasing the amount of *N*-oxide improves selectivity (entry 4), we also found that use of three equivalents of NaO^tBu could also increase conversion and selectivity for **4.5** with two equivalents of *N*-oxide (entry 5). A survey of other ligands revealed that X-Phos provides **4.5** as the only product, albeit with only 41% conversion (entry 6). We were gratified to find that employing X-Phos and microwave heating at 110 °C provides an 89% isolated yield of **4.5** with no drop in selectivity (entry 8). With these conditions, 1 mol% palladium and 1.5 equivalents of **4.2** can be used to provide an 84% isolated yield of **4.5** (entry 9). Importantly, *no products arising from arylation at the sp^2 position are detected by ¹H NMR analysis of the crude reaction mixture, indicating that a complete inversion in catalyst selectivity can be achieved.*

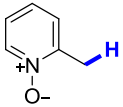
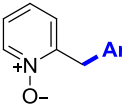
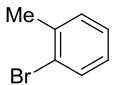
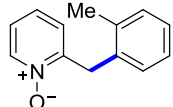
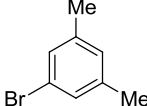
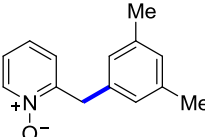
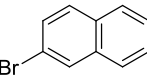
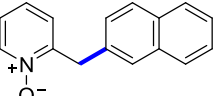
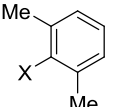
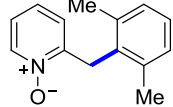
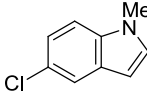
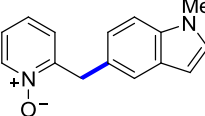
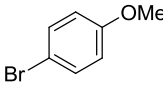
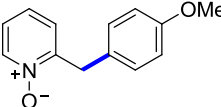
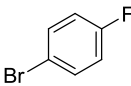
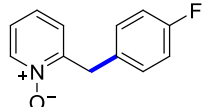
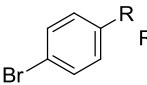
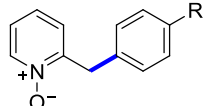
4.2.1 Reaction Scope

A scope of the sp^3 arylation reaction with respect to the aryl halides is outlined in Table 4.2. Different aryl halides are tolerated including cheap and readily available chlorides (Table 4.2, entries 1, 10 and 12) as well as more commonly used bromides (Table 4.2, entries 2-5, 7-9, 11 and 13-14 and Table 4.3 entries 1-7) and iodides (Table 4.2, entry 6). Arylation can be carried out using catalyst loadings as low as 1 mol % Pd (Table 4.2, entry 3). Also near equimolar amounts of the *N*-oxide and aryl halide can be employed (Table 4.2, entry 4). Thermal heating conditions were also developed utilizing Ru-Phos as the ligand although this method resulted in slightly diminished yields (Table 4.2, entry 5 and Table 4.3 entry 3).

A variety of substitution patterns including *ortho*, *meta* and *para* are tolerated on the aryl halide (Table 4.2). Very sterically demanding substrates require the use of S-Phos as the ligand (Table 4.2, entries 10 and 11). While electron-rich aryl halides are broadly applicable (Table 4.2, entry 13 and Table 4.3, entry 1), electron-poor aryl halides are not compatible with this catalyst system (Table 4.2, entry 15). Heterocyclic aryl halides can also be employed as illustrated by the use of an indole halide (Table 4.2, entry 12).

We have determined that a broad range of *N*-oxide substrates can be used in sp^3 arylation reactions (Table 4.3). *Meta* and *para* methyl substituted aryl bromides participate in high yield and complete selectivity (Table 4.3, entries 1-3). Quinoline (Table 4.3, entry 4) and isoquinoline (Table 4.3, entry 5) *N*-oxides are also competent substrates, although 3 equivalents of 2-methylquinoline *N*-oxide must be used due to increased amounts of diarylation. Diazine *N*-oxides can be employed in the reaction as illustrated by the use of 2,3-dimethyldiazine *N*-oxide (Table 4.3, entry 6). Other alkyl

Table 4.2 – sp^3 Arylation of Picoline *N*-Oxide^{a,92}

$ \begin{array}{c} \text{Picoline } N\text{-oxide} + \text{ArX} \xrightarrow[\text{MW, 110 } ^\circ\text{C, 45min}]{\text{Pd}_2\text{dba}_3 \text{ (2.5 mol \%)} \\ \text{X-Phos (5 mol \%)} \\ \text{NaOtBu, PhMe}} \\ \text{Product} \end{array} $				
Entry	<i>N</i> -Oxide	Aryl Halide	Product	Yield ^b
1		X=Cl		91
2		X=Br		89
3		X=Br		84 ^c
4		X=Br		77 ^d
5		X=Br		78 ^e
6		X=I		85
7	4.2			92
8	4.2			93
9	4.2			72
10	4.2			84 ^f
11				90 ^f
12	4.2			90
13	4.2			72
14	4.2			72
15	4.2	 R=CN, CO ₂ Et, CPh, NO ₂		Trace

^aConditions: Picoline *N*-oxide (1.5 eq.), Aryl Halide (1 eq.), Pd₂dba₃ (0.025 eq.), X-Phos (0.05 eq.) and NaO^tBu (3 eq.) in PhMe (0.5-1M), MW, 110 °C for 45min. ^bIsolated yield. ^cUsing 1 mol% Pd. ^dUsing 1.1 equiv. *N*-oxide. ^eUsing: Picoline *N*-oxide (2 eq.), Aryl Halide (1 eq.), Pd₂dba₃ (0.025 eq.), Ru-Phos (0.1 eq.) and NaO^tBu (3 eq.) in PhMe (0.3M), thermal heating, 70 °C overnight. ^fUsing S-Phos.

⁹² This work was carried out jointly with graduate student Louis-Charles Campeau.

Table 4.3 – sp^3 Arylation of Azine *N*-Oxides^{a,92}

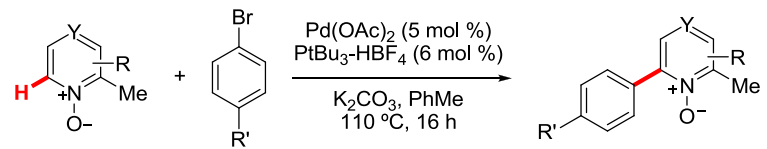
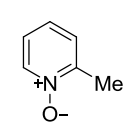
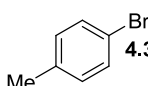
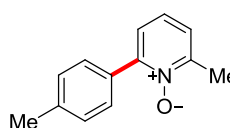
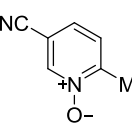
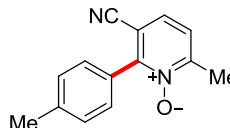
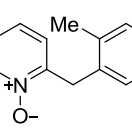
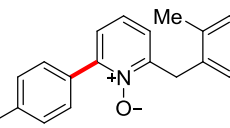
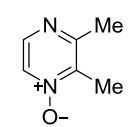
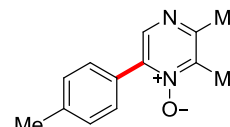
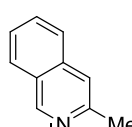
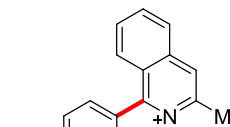
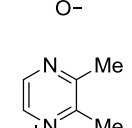
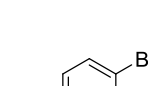
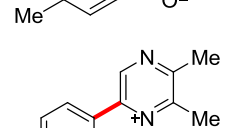
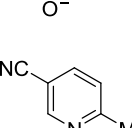
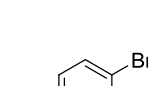
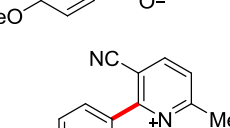
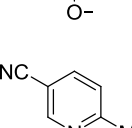
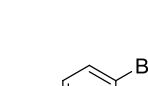
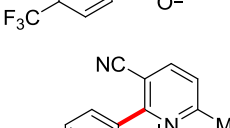
$ \begin{array}{c} \text{R} \text{---} \text{C}_5\text{H}_4\text{N}^+\text{O}^- \text{---} \text{H} + \text{ArX} \xrightarrow[\text{NaOtBu, PhMe, MW, 110 }^\circ\text{C, 45min}]{\text{Pd}_2\text{dba}_3 \text{ (2.5 mol \%), X-Phos (5 mol \%)}} \text{R} \text{---} \text{C}_5\text{H}_4\text{N}^+\text{O}^- \text{---} \text{Ar} \end{array} $				
Entry	<i>N</i> -Oxide	Aryl Halide	Product	Yield ^b
1				70
2				90
3				76 ^c
4		4.3		73 ^d
5		4.3		60
6		4.3		79
7		4.3		64 ^{d,e}

^aConditions: Picoline *N*-oxide (1.5 eq.), Aryl Halide (1 eq.), Pd₂dba₃ (0.025 eq.), X-Phos (0.05 eq.) and NaO^tBu (3 eq.) in PhMe (0.5-1M), MW, 110 °C for 45min. ^bIsolated yield. ^cUsing: Picoline *N*-oxide (2 eq.), Aryl Halide (1 eq.), Pd₂dba₃ (0.025 eq.), Ru-Phos (0.1 eq.) and NaO^tBu (3 eq.) in PhMe (0.3M), thermal heating, 70 °C overnight. ^dUsing 3 equiv. *N*-oxide. ^eUsing S-Phos.

groups can also be arylated under the reaction conditions with no products arising from a potentially competitive β -hydride elimination (Table 4.3, entry 7). Additionally, these products are readily deoxygenated.⁹³

⁹³ See supporting information for details.

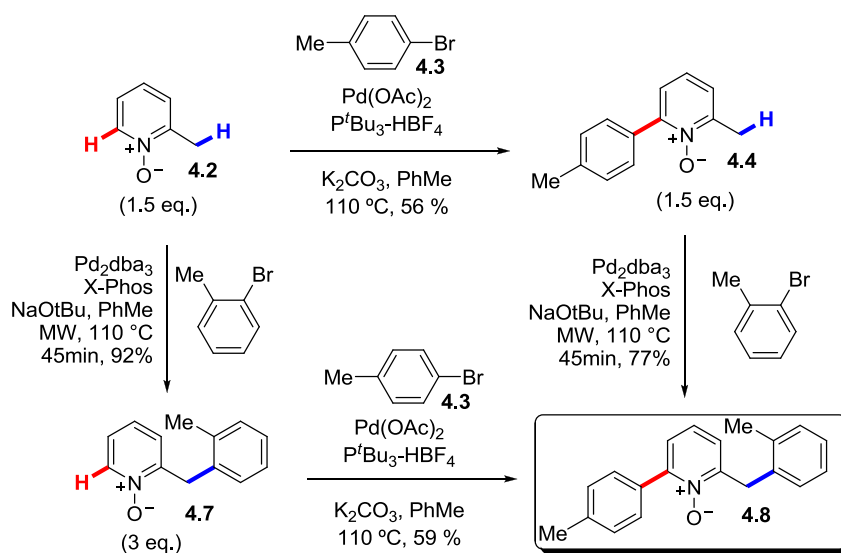
Table 4.4 – sp^2 Arylation Azine *N*-Oxides.⁹²

				
Entry	<i>N</i> -Oxide	Aryl Halide	Product	Yield ^b
1				21 ^c
2				56
3		4.3		74
4		4.3		59 ^d
5		4.3		89
6		4.3		90 ^e
7				86
8				48
9				73

^aConditions: *N*-oxide (2 eq.), Aryl Halide (1 eq.), Pd(OAc)₂ (0.05 eq.), P^tBu₃-HBF₄ (0.06 eq.) and K₂CO₃ (1.5 eq.) in PhMe (0.15 M), 110 °C, 16 h. ^bIsolated yield. ^cUsing 0.15 eq. of P^tBu₃-HBF₄. ^dUsing 3 equiv. *N*-oxide. ^eUsing 1.1 equiv. *N*-oxide.

The scope of the sp^2 arylation of 2-methyl azine *N*-oxides is outlined in Table 4.4. The sp^2 arylation reaction is compatible with electron-neutral (Table 4.4, entries 1-6), electron-rich (Table 4.4, entries 7 and 9) and electron-poor (Table 4.4, entry 8) aryl bromides. A range of *N*-oxides, including substituted pyridines (Table 4.4, entries 1-4, 8 and 9), isoquinoline (Table 4.4, entry 6) and diazines (Table 4.4, entries 5 and 7) are suitable to be employed in the sp^2 arylation reaction.

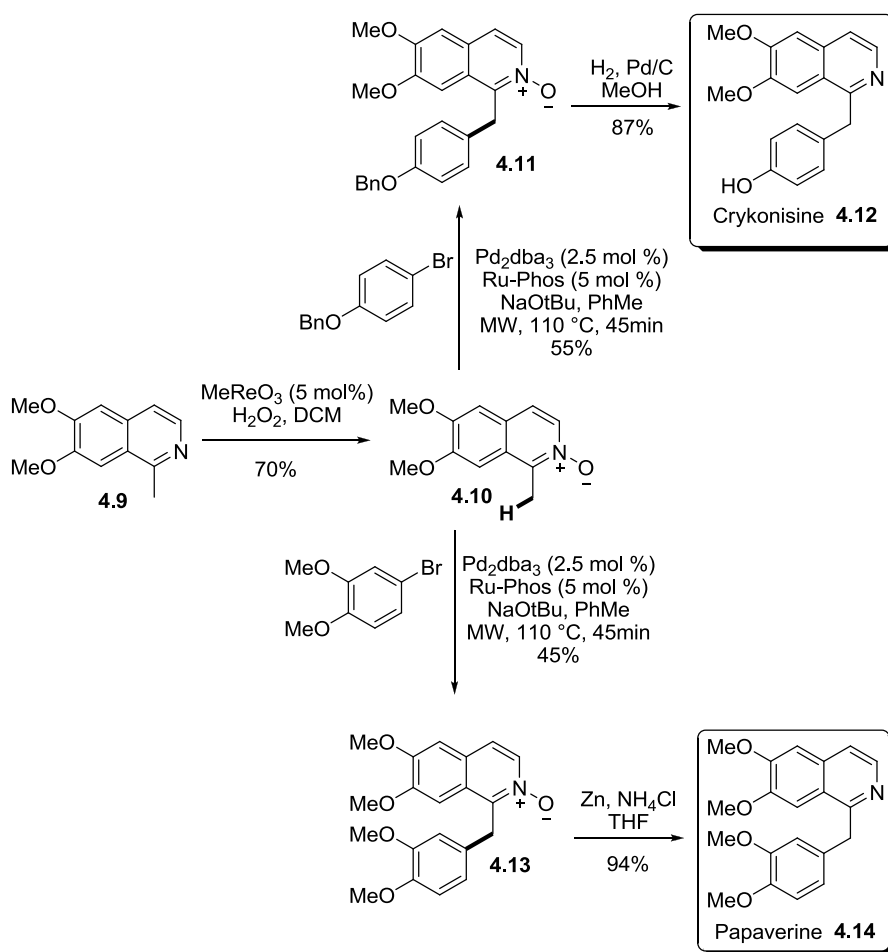
To further demonstrate the utility of these methods for the functionalization of heterocycles, we have established that the sp^2/sp^3 arylations can be carried out in both a divergent and sequential manner (Scheme 4.6). Reaction of 2-picoline *N*-oxide (**4.2**) with bromotoluene was chosen as a model reaction. 2-Picoline *N*-oxide is arylated with 4-bromotoluene (**4.3**) under the sp^2 arylation conditions to give a 56% yield of product **4.4**. *N*-oxide **4.4** is then subjected to the sp^3 arylation conditions with 2-bromotoluene to give a 77% yield of the differentially diarylated product **4.8**. Alternatively, **4.2** could be first subjected to the sp^3 arylation conditions with 2-bromotoluene to give a 92% yield of product **4.7**, demonstrating the divergent reactivity of a single substrate under different



Scheme 4.6 – Divergent and sequential sp^2/sp^3 arylation.

catalytic conditions. Compound **4.7** can then be arylated under the sp^2 conditions with 4-bromotoluene to give the same differentially diarylated product as the previous route in 59% yield.

The method for the sp^3 direct arylation of 2-methyl pyridine *N*-oxides was further validated in an efficient synthesis of natural products Papaverine (**4.14**) and Crykonisine (**4.12**) (Scheme 4.7). Papaverine is one of the four major components of opium and is used as a non-narcotic antispasmodic agent.⁹⁴ Crykonisine is a natural product isolated



Scheme 4.7 – Synthesis of Crykonisine and Papaverine.

⁹⁴ (a) Bentley, K. W. In *The Isoquinoline Alkaloids*; Ravindranath, B., Ed.; Harwood Academic Publishers: Amsterdam, 1998; pp 107-122. (b) Bentley, K. W. *Nat. Prod. Rep.* **2005**, 22, 249-268. (c) Isolation of papaverine: Merck, G. *Ann.* **1848**, 66, 125- 128.

from the plant *Papaver Triniifolium* and the stem bark of *Cryptocarya Chinensis Hemsl.*⁹⁵ To begin the syntheses compound **4.9** is oxidized to the *N*-oxide (**4.10**) by treatment with methyltrioxorhenium and aqueous hydrogen peroxide in CH₂Cl₂.⁹⁶ Compound **4.10** is then subjected to *sp*³ arylation conditions with 4-benzyloxybromobenzene which affords the arylated product **4.11**. Simultaneous removal of the benzyl group and reduction of the *N*-oxide takes place under hydrogenation conditions with Pd/C in methanol to yield the natural product Cykonisine in 3 steps and 34% overall yield from commercially available starting materials. Papeverin can also be synthesized from the common intermediate **4.10**, which is again subjected to *sp*³ arylation conditions with 4-bromoveratrole to yield **4.13**. The *N*-oxide (**4.13**) is subsequently reduced with zinc in saturated NH₄Cl/THF to yield the natural product Papaverine in 3 steps and 30% overall yield.⁹⁷ The syntheses of these two natural products from a common intermediate demonstrate the potential utility of this method for the generation of a large family of related compounds rapidly from common intermediates.

4.2.2 Limitations

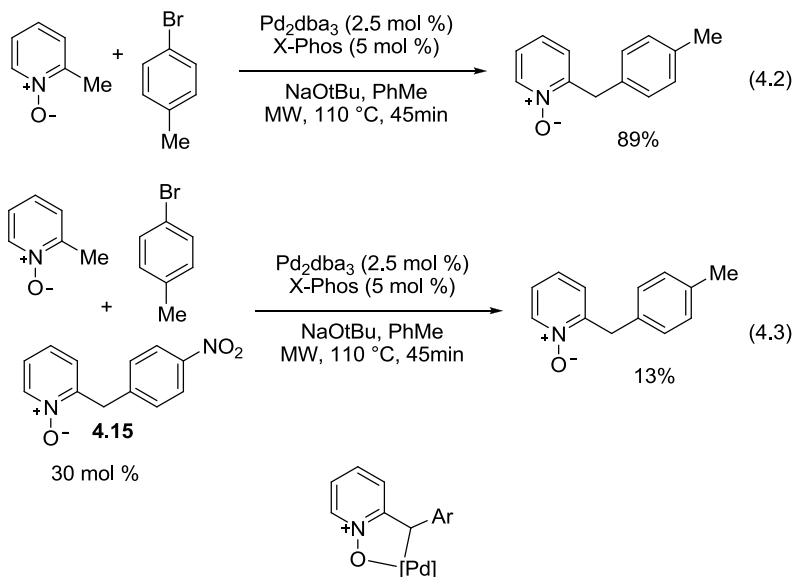
While evaluating the scope of *sp*³ arylation, it was noticed that severely reduced yields were obtained for most electron-poor aryl halides (Table 4.2, entry 15). Since electron-deficient aryl halides undergo oxidative addition more readily than electron-rich aryl

⁹⁵ (a) Sar, A.; Saryar, G. *Pharmazie* **2000**, 55, 471 (b) Lin, F. W.; Wang, J. J.; Wu, T. S. *Chem. Pharm. Bull.* **2002**, 50, 157.

⁹⁶ Coperet, C.; Adolffsson, H.; Khovong, T. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, 63, 1740.

⁹⁷ For previous syntheses of papaverine, see: (a) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, 130, 1558. (b) Pictet, A.; Finkelstein, M. *Ber. Dtsch. Chem. Ges.* **1909**, 42, 1979-1989. (c) Rosenmund, K. W.; Nothnagel, M.; Riesenfeldt, H. *Ber. Dtsch. Chem. Ges.* **1927**, 60, 392-398. (d) Mannich, C.; Walther, O. *Arch. Pharm.* **1927**, 265, 1-11. (e) Galat, A. *J. Am. Chem. Soc.* **1951**, 73, 3654-3656. (f) Wahl, H. *Bull. Soc. Chim. Fr.* **1950**, 17, 680. (g) Popp, F. D.; McEwen, W. E. *J. Am. Chem. Soc.* **1957**, 79, 3773-3777. (h) Hirsenkorn, R. *Tetrahedron Lett.* **1991**, 32, 1775-1778.

halides, we hypothesized that the attenuated reactivity of electron-poor aryl halides might be explained by product inhibition of the catalyst. Upon arylation of the sp^3 position with an electron-deficient arene the benzylic protons become more acidic, which may lead to the formation of a stable palladacycle that is unable to participate in the reaction (Scheme 4.8). To test this hypothesis a poisoning experiment was carried out in which two



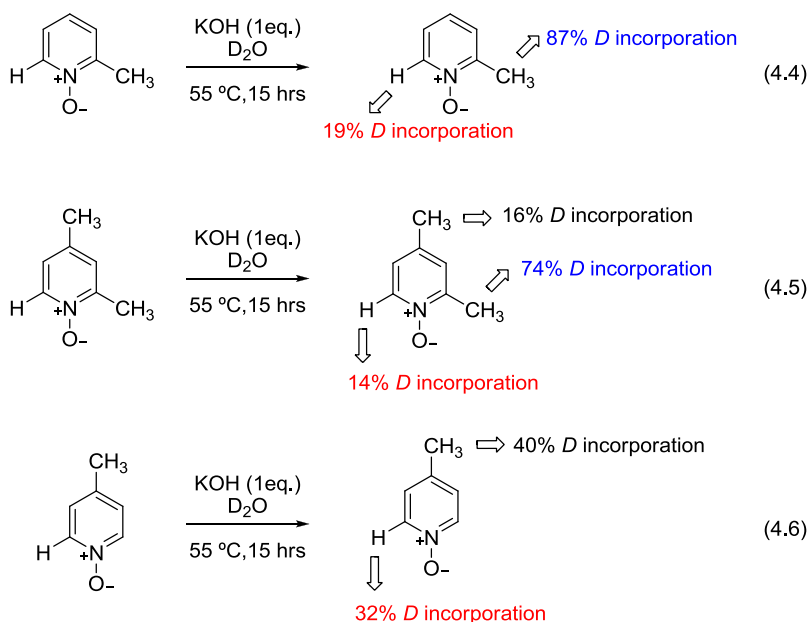
Scheme 4.8 – Poisoning Experiment

reactions were performed; one without additive (Scheme 4.8, eq. 4.2) and one with 30 mol % **4.15** (Scheme 4.8, eq. 4.3). The reaction with no additive resulted in an 89% yield of the desired product, while the reaction with 30 mol % **4.15** added resulted in only 13% yield of the desired product. These results imply product inhibition may account for the diminished yields associated with electron deficient aryl halides.

4.2.3 Mechanistic Investigations

To investigate the role that C-H bond acidity at various sites plays in the site selectivity of these reactions, deuterium incorporation experiments were carried out (Scheme 4.9). Deuterium exchange of 2-picolone *N*-oxide by treatment with KOH in D₂O reveals that

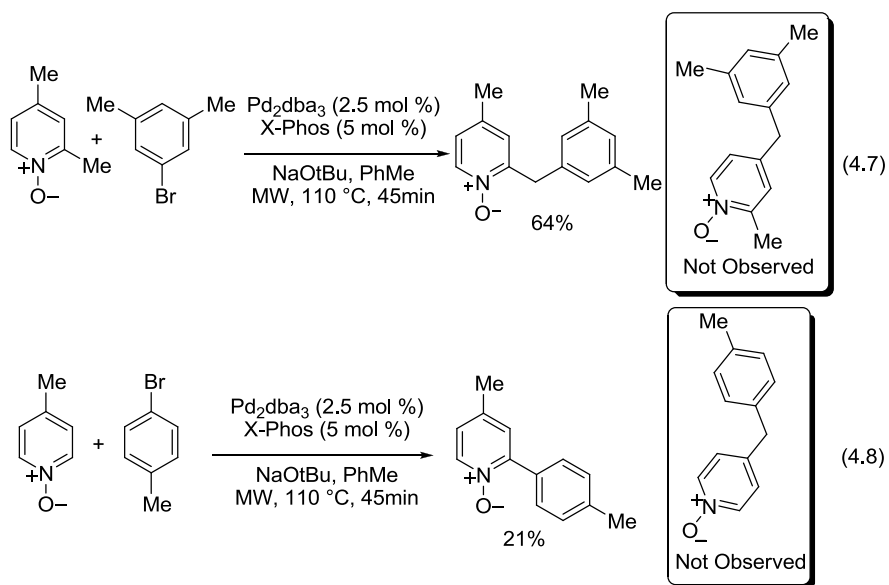
the methyl sp^3 site exchanges at a significantly faster rate than the sp^2 site adjacent to the nitrogen (eq. 4.4). Exchange on 2,4-lutidine *N*-oxide shows that the 2-methyl position undergoes exchange faster than the 4-methyl position and that the sp^2 position undergoes exchange at the slowest rate of the three positions (eq. 4.5). Exchange on 4-picoline *N*-oxide shows that in the absence of a 2-methyl substituent the 4-methyl position undergoes exchange faster than the sp^2 positions (eq. 4.6).



Scheme 4.9 – Deuterium Exchange Experiments

A series of experiments were also performed to determine if the *N*-oxide moiety influences regioselectivity (Scheme 4.10). Arylation of 2,4-lutidine *N*-oxide under the sp^3 arylation conditions results in exclusive reaction at the 2-methyl position (eq. 4.7). Arylation of 4-picoline *N*-oxide under the sp^3 arylation protocol results in exclusive arylation of the sp^2 center adjacent to the *N*-oxide (eq. 4.8). No product arising from arylation of the sp^3 center is observed (even though the sp^2 and sp^3 positions undergo deuterium exchange at a similar rate) (eq. 4.6). Given that arylation only occurs adjacent

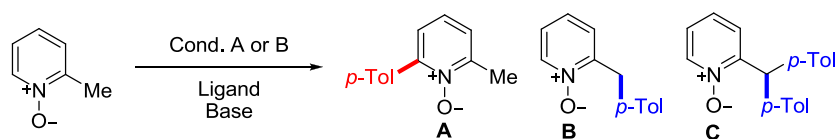
to the *N*-oxide, it is plausible that *N*-oxide interactions with the palladium catalyst could play an important role in governing the selectivity of these reactions.



Scheme 4.10 – Effect of *N*-oxide Proximity on Regioselectivity

A series of experiments were also carried out to determine the role of the base in site selectivity (Table 4.5). Arylation of 2-picoline *N*-oxide with 4-bromotoluene under conditions similar to those used for sp^2 arylation (Condition A) using K_2CO_3 as the base yields 56% of the sp^2 arylated product with complete sp^2 selectivity (entry 1). Under identical conditions, but with NaOtBu instead of K_2CO_3 , a complete inversion of the sp^2/sp^3 selectivity is observed (entry 2). Similarly, under conditions analogous to those employed for sp^3 arylation (condition B) using NaOtBu as the base, a 94% yield of sp^3 arylated product is obtained with complete selectivity for the sp^3 position (entry 3). Again if the base is changed under otherwise identical conditions from NaOtBu to K_2CO_3 , a complete inversion of the sp^2/sp^3 selectivity is observed (entry 4). These results indicate that it is the nature of the base that is of primary importance in determining sp^2/sp^3 site selectivity pointing towards its intimate involvement in the catalytic cycle.

Table 4.5 – Origin of Site Selectivity.

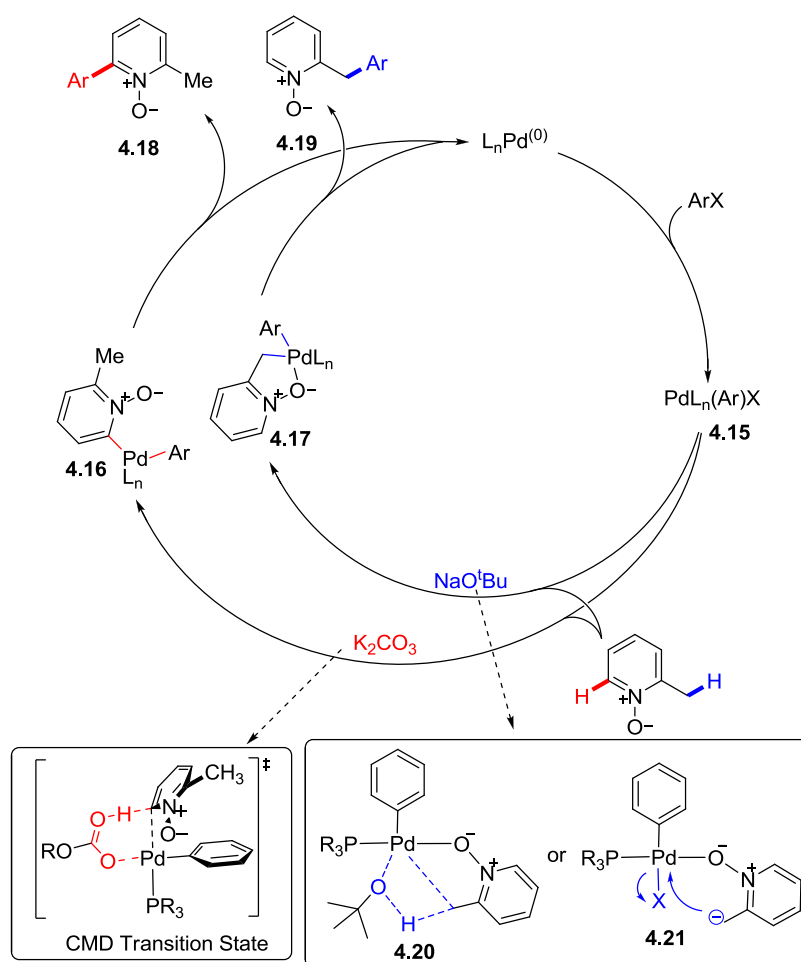


Entry	Conditions ^{a,b}	Base	Ratio A:B:C	Yield ^c
1	A	K ₂ CO ₃	1:0:0	56%
2	A	NaOtBu	0:1:1.5	45%
3	B	NaOtBu	0:20:1	94%
4	B	K ₂ CO ₃	1:0:0	2%

^aCondition A: 2-Picoline *N*-oxide (2 eq.), 4-bromotoluene (1 eq.), Pd(OAc)₂ (0.05 eq.), P^tBuHBF₄ (0.06 eq.) Base (1.5 eq.) in PhMe (0.15 M), 110 °C overnight. ^bCondition B: 2-Picoline *N*-oxide (1.5 eq.), 4-bromotoluene (1 eq.), Pd₂dba₃ (0.025 eq.), X-Phos (0.05 eq.) Base (3 eq.) in PhMe (1 M), MW, 110 °C for 45min. ^cNMR Yield using 1,3,5-trimethoxybenzene as standard.

A catalytic cycle for these transformations is proposed in Scheme 4.11. The active Pd(0) catalyst oxidatively inserts into the aryl halide bond to generate intermediate **4.15**. The next step, palladation of the *N*-oxide, determines site selectivity and is base dependant. With the strong base NaO^tBu, the most acid *sp*³ 2-methyl position may be deprotonated and proceeds through an intermediate similar to **4.21** to yield **4.17**. This pathway would be analogous to the α -arylation of carbonyls.⁹⁸ Alternatively, the deprotonation of the *sp*³ C-H bond could occur intramolecularly through a palladium alkoxide intermediate **4.20**. K₂CO₃ is not a strong enough base to deprotonate the 2-methyl position, but it does allow for the 6-membered transition state of a concerted metallation-deprotonation (CMD) pathway to activate the *sp*² position as depicted in Scheme 4.11, which gives rise to **4.16**. We and others have evaluated this pathway for the C-H activation

⁹⁸ (a) J. M. Fox, 4. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, 122, 1360. (b) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, 36, 234.



Scheme 4.11— Catalytic cycle for sp^2/sp^3 arylation.

of arenes.⁹⁹ Both intermediates **4.16** and **4.17** then undergo reductive elimination to form products **4.18** and **4.19** respectively.

4.3 Conclusions

⁹⁹ (a) Ozdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (b) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (c) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Polleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210. (d) D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (e) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (f) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (g) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (h) Pascual, S.; Mendoza, P. d.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021.

In conclusion, we have developed completely site selective arylation reactions on both sp^2 and sp^3 positions compatible with a broad range of azine *N*-oxides and aryl halides. The reactions are carried out in both a divergent and sequential manner. The efficacy of sp^3 arylation is demonstrated by the rapid synthesis of the natural products Papaverine and Crykonisine in three steps. Mechanistic studies reveal the importance of the nature of the base for catalyst controlled site selectivity. These reactions should find use for the rapid functionalization of azine derivatives and the mechanistic insights should lead to investigations of similar reactivity to other substrate classes.

Rhodium(III)-Catalyzed Intermolecular Hydroarylation of Alkynes

5.1 Introduction¹⁰⁰

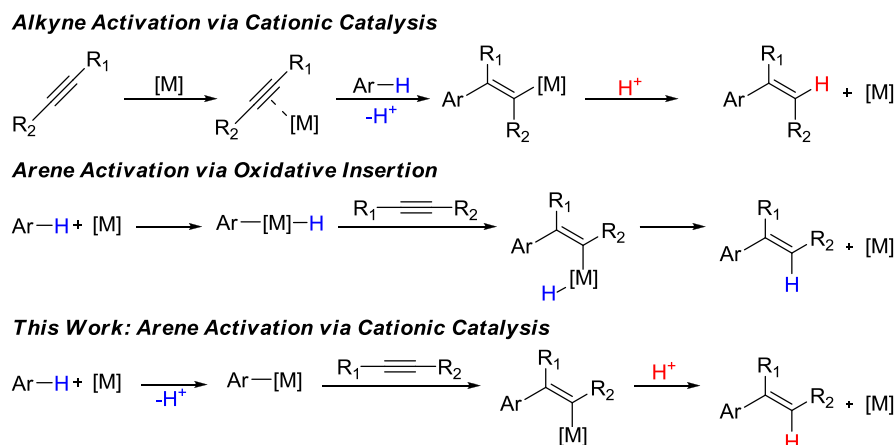
Transition metal catalyzed direct transformations of aromatic C-H bonds is a burgeoning field in organic chemistry owing to its inherently efficient construction of organic building blocks.¹⁰¹ Of these processes, alkyne hydroarylation has received much attention in recent years because it allows for the atom economical synthesis of functionalized alkenes directly from simple arenes and alkynes.¹⁰² Hydroarylation of alkynes typically occurs by one of two pathways (Scheme 5.1). The first proceeds

¹⁰⁰ A significant portion of the work described in this chapter has been published in the form of a communication, see: (a) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910.

¹⁰¹ For reviews, see: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (d) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Seregin, I. V.; Gevorgyan, V. *J. Chem. Soc., Chem. Rev.* **2007**, *36*, 1173. (h) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrich. Chim. Acta.* **2007**, *40*, 35. (h) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (i) Ackermann, L. In *Topics in Organometallic Chemistry*; Springer Berlin: Heidelberg, 2007; pp 35-60. (j) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.

¹⁰² (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (c) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (d) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111. and references therein.

through activation of the alkyne by a cationic metal complex.^{102,103} The second proceeds via activation of the arene by oxidative insertion of a nucleophilic metal into a C-H bond.^{102,104} Although many intra- and intermolecular examples have been reported, these pathways have limited scope and utility since they usually necessitate the use of electron rich arenes, electron deficient alkynes or synthetically restricted directing groups. Moreover, the products are often obtained as regio- or stereoisomeric mixtures.



Scheme 5.1 – Alkyne Hydroarylation Pathways

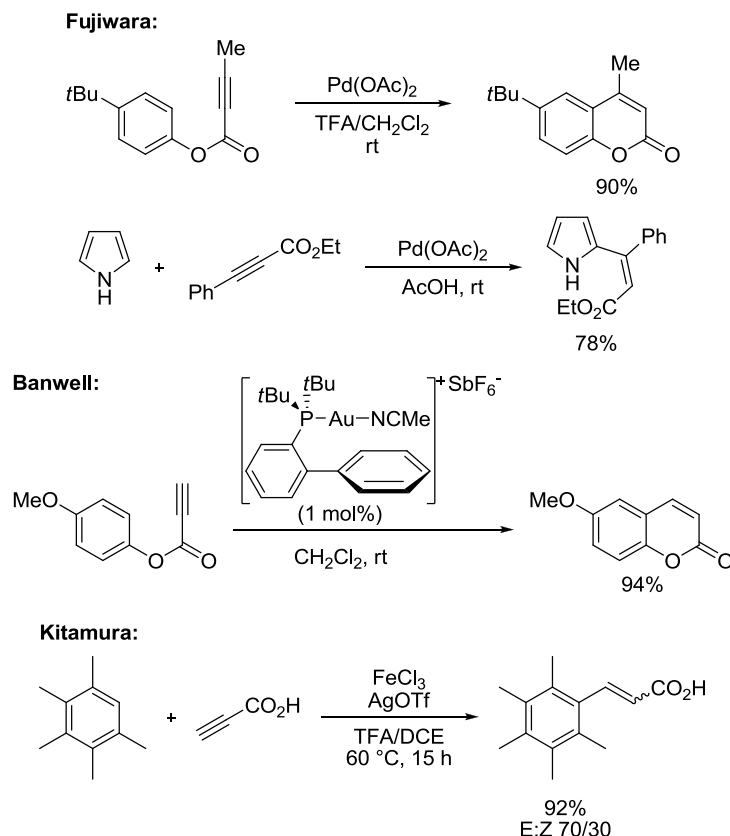
Some recent examples of hydroarylation via Lewis acid activation of the alkyne are highlighted in Scheme 5.2. Fujiwara's group has made seminal contributions to the field by describing palladium catalyzed intra and intermolecular hydroarylation of electron deficient alkynes.¹⁰⁵ This hydroarylation was initially thought to proceed through arene metallation, but further mechanistic studies suggests the reaction proceeds

¹⁰³ For recent examples see: (a) Suarez-Pantiga, S.; Palomas, D.; Rubio, E.; Gonzalez, J. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 7857. (b) Zhang, X.; Teo, W. T.; Chan, P. W. H. *Org. Lett.* **2009**, *11*, 4990.

¹⁰⁴ For recent examples see: (a) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102. (b) Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M.; *Chem. Lett.* **1999**, 615. (c) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202.

¹⁰⁵ (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927.

through a Friedel-Crafts-type reaction of a metal-activated alkyne.¹⁰⁶ A recent report from Banwell and co-workers demonstrated that Au(I) is a competent catalyst for the intramolecular hydroarylation, resulting in a range of heterocycles.¹⁰⁷ Also, Kitamura *et al.* have shown that the hydroarylation of propiolic acid with electron rich arenes provides a mixture of E/Z alkenes under iron(III) catalysis.¹⁰⁸



Scheme 5.2 –Hydroarylation Via Alkyne Activation

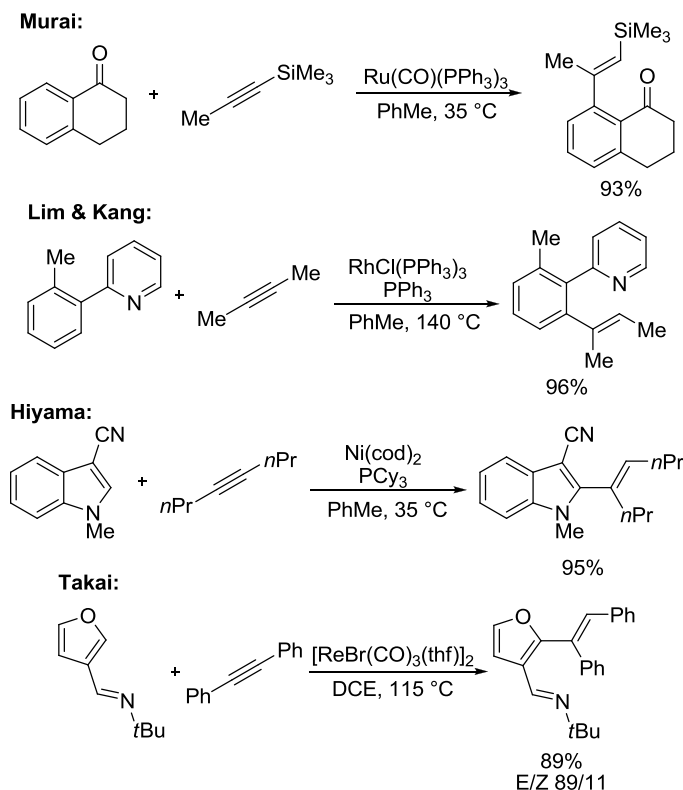
Some recent examples of hydroarylation which proceed through oxidative insertion of a metal complex into a C-H bond are shown in Scheme 5.3. The regioselective hydroarylation of alkynes with aromatic ketones has been shown by Murai

¹⁰⁶ (a) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, 24, 6440. (b) Soriano, E.; Marco-Contelles, J.; *Organometallics* **2006**, 25, 4542.

¹⁰⁷ Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, 74, 8901.

¹⁰⁸ Hashimoto, T.; Izumi, T.; Kutubi, M. S.; Kitamura, T. *Tetrahedron Lett.* **2010**, 51, 761.

and co-workers.¹⁰⁹ Also, Lim and Kang have used rhodium catalysis to accomplish the 2-pyridyl directed hydroarylation of alkynes.¹¹⁰ In addition, the Hiyama group have demonstrated the competency of Ni(0) as a catalyst for the hydroheteroarylation of alkynes.¹¹¹ Finally, the Rhenium-catalyzed hydroarylation has been reported by the Takai group.¹¹²



Scheme 5.3 – Arene Activation Via Oxidative Insertion

An alternative pathway is the activation of the arene with an electrophilic metal which could then undergo migratory insertion of the alkyne followed by protodemetallation (Scheme 5.1). Although this pathway holds promise to overcome

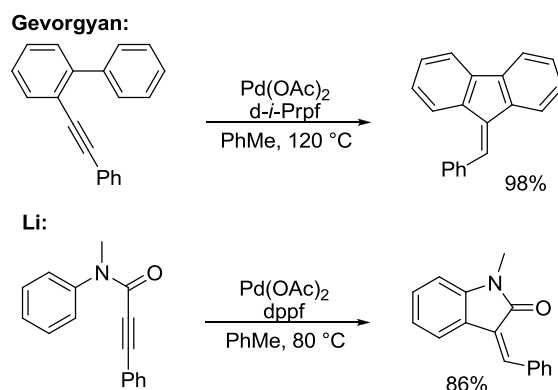
¹⁰⁹ Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681.

¹¹⁰ Lim, Y.-G.; Lee, K.-H.; Koo, B. T.; Kang, J.-B. *Tetrahedron Lett.* **2001**, 42, 7609.

¹¹¹ (a) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, 128, 8146. (b) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, 130, 2448. (c) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2007**, 46, 8872.

¹¹² Kuninobu, Y.; Kikuchi, K.; Tokunaga, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2008**, 64, 5974.

some of the limitations of hydroarylation, only Pd(II) catalysis has shown efficacy with two intramolecular examples (Scheme 5.4). In an elegant example Gevorgyan reported the hydroarylation of *o*-alkynyl biaryls.¹¹³ Under similar conditions Li has reported the hydroarylation of *N*-arylpropiolamides.¹¹⁴



Scheme 5.4 – Arene Activation Via Cationic Catalysis

Although these examples represent important advancements, development of novel catalysts is still required to achieve elusive intermolecular reactivity. Described in this chapter is the Rh(III)-catalyzed intermolecular hydroarylation of alkynes. Mechanistic investigations suggest the reaction proceeds through arene activation by the cationic metal catalyst. This relatively unexplored pathway allows intermolecular hydroarylation to proceed in high yields for a range of arenes and internal alkynes and is highly regio- and stereoselective.

5.2 Results and Discussion

5.2.1 Reaction Optimization

¹¹³ (a) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636. (b) Chernyak, N.; Gevorgyan, V. *Adv. Synth. Catal.* **2009**, *351*, 1101.

¹¹⁴ Jiang, T.-S.; Tang, R.-Y.; Zhang, X.-G.; Li, X.-H.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 8834.

Our group, among others, has recently reported Rh(III) catalyzed transformations at aromatic C-H bonds.¹¹⁵ Because they are an important medicinal chemistry, the indole motif was selected along with Cp*Rh(MeCN)₃(SbF₆)₂ and 1-phenyl-1-propyne for reaction development. The choice of the protecting/directing group on indole was found to be crucial with *N,N*-dimethylcarbamoyl being optimal (Table 5.1). The increased reactivity of the *N,N*-dimethylcarbamoyl group is likely due to its increased basicity and therefore enhanced ability to direct a metalation event.¹¹⁶

Table 5.1 – Effect of Protecting/Directing Group on Hydroarylation Activity^a

Entry	R	GC Yield (%) ^b
1	Me	Trace
2	Piv	Trace
3	Ts	Trace
4	Boc	Trace
5	Ac	14
6	CONMe ₂	49

^aConditions: Indole (1 equiv.), 1-phenyl-1-propyne (1.1 equiv.), Cp*Rh(MeCN)₃(SbF₆)₂ (5 mol%) and pivalic acid (5 equiv.) dissolved in the *t*AmOH and heated at 100 °C for 15 hrs. ^bUsing 1,3,5-trimethoxy benzene as an internal standard.

The optimization of the reaction conditions are outlined in Table 5.2. We were pleased to find that heating the coupling partners in toluene with the catalyst afforded the

¹¹⁵ (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (b) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (c) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (d) Chen, J.; Song, G.; Pan, C.-L.; Li, X. *Org. Lett.* **2010**, *12*, 5426. (e) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (f) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (g) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068. (h) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (i) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744. (j) Guoyong, S.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487. (k) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (l) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462. (m) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449.

¹¹⁶ Kondo, Y.; Morey, J. V.; Morgan, J. C.; Naka, H.; Nobuto, D.; Raithby, P. R.; Uchiyama, M.; Wheatley, A. E. H. *J. Am. Chem. Soc.* **2007**, *129*, 12734.

desired product, albeit without catalyst turnover (entry 1). Superior catalytic efficiency was obtained when 5 equivalents of acetic acid was added to the reaction (entry 2) and again upon the use of pivalic acid (entry 3). The use of the related non-cationic catalyst, $[\text{Cp}^*\text{RhCl}_2]_2$,¹¹⁷ lead to no reactivity in this reaction (entry 4). A screen of solvents revealed isopropylacetate to be superior to toluene (entry 5). Finally lowering the temperature to 90 °C gave **5.3a** in near quantitative yield (entry 6).

Table 5.2 – Optimization of Hydroarylation Conditions^a

Entry	Solvent	Acid	Temp	%Yield ^b
1	PhMe	None	100 °C	5
2	PhMe	AcOH	100 °C	76
3	PhMe	PivOH	100 °C	90
4	PhMe	PivOH	100 °C	0 ^c
5	<i>i</i> PrOAc	PivOH	100 °C	93
6	<i>i</i>PrOAc	PivOH	90 °C	99 (99)

^aConditions: Arene (0.3 mmol), 1-phenyl-propyne (1.1 equiv.) and $\text{Cp}^*\text{Rh}(\text{MeCN})_3(\text{SbF}_6)_2$ (5 mol%) in solvent (0.4 M) at 90 °C for 15 hrs. ^b¹H NMR yield of the major product using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in brackets. ^c Using $[\text{Cp}^*\text{RhCl}_2]_2$ as catalyst.

5.2.2 Reaction Scope

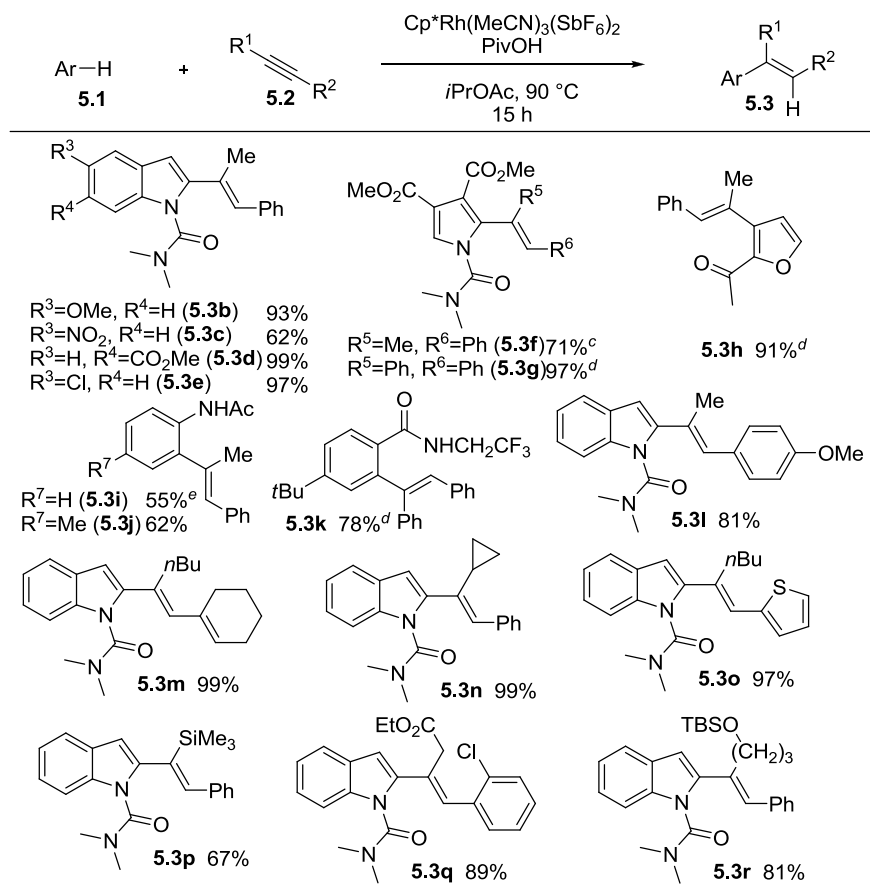
Table 5.3 outlines the scope of the hydroarylation under our optimized reaction conditions. Both electron-donating (**5.3b**) and electron-withdrawing (**5.3c,d**) groups are tolerated on the indole, as is a chloro substituted substrate (**5.3e**). This catalyst system also allows for the use of other heterocycles (**5.3f-h**), a range of different types of directing groups (**5.3h-k**) as well as electron rich (**5.3i,j**)¹¹⁸ and electron poor (**5.3k**) simple substituted benzenes in hydroarylation. A range of alkynes are also compatible with the reaction including diaryl (**5.3g,k**), electron-rich arenes (**5.3l**), alkenyl (**5.3m**),

¹¹⁷ Satoh and Miura have shown $[\text{Cp}^*\text{RhCl}_2]_2$ to be a useful for the reaction of alkynes with a range of arenes: (a) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (b) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, 72, 5362.

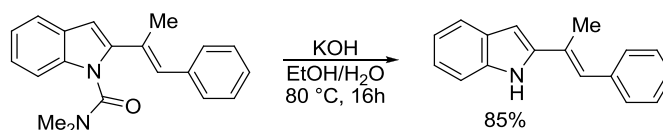
¹¹⁸ Use of the dimethylcarbamoyl protecting group in this case lead to poor conversion to product.

cyclopropyl (**5.3n**), heterocyclic (**5.3o**) trimethylsilyl (**5.3p**) as well as ester (**5.3q**) and protected alcohol (**5.3r**) moieties. The dimethyl carbamoyl group can be easily removed using KOH in EtOH/H₂O at 90 °C (Scheme 5.5).

Table 5.3 – Scope in the Rhodium Catalyzed Hydroarylation^{a,b}



^aConditions: Arene (1 equiv.), alkyne (1.1 equiv.), $\text{Cp}^*\text{Rh}(\text{MeCN})_3(\text{SbF}_6)_2$ (5 mol%) and pivalic acid (5 equiv.) in *i*PrOAc (0.4 M) at 90 °C for 15 hrs. ^b Isolated yields. ^c In 1,2-dichloroethane for 24 hrs. ^d Using arene (2 equiv.), alkyne (1 equiv.). ^e Using $\text{Cp}^*\text{Rh}(\text{MeCN})_3(\text{SbF}_6)_2$ (2.5 mol%) in *t*AmOH (0.2M) at 70 °C.



Scheme 5.5 – Removal of Dimethyl Carbamoyl Group

5.2.3 Limitations

When indole is employed in the reaction, the scope with respect to the alkyne partner is limited. Dialkyl, diaryl and propiolate-type alkynes failed to give appreciable yields under our reaction conditions. We investigated if these alkynes were merely unreactive or if they were shutting down catalytic reactivity by conducting poisoning experiments (Table 5.4). With no additive hydroarylation of **5.2a** with **5.1a** gives **5.3a** in 85% ¹H NMR yield. However, in the presence of dialkyl, diaryl and propiolate-type alkynes the reaction yields are severely reduced.

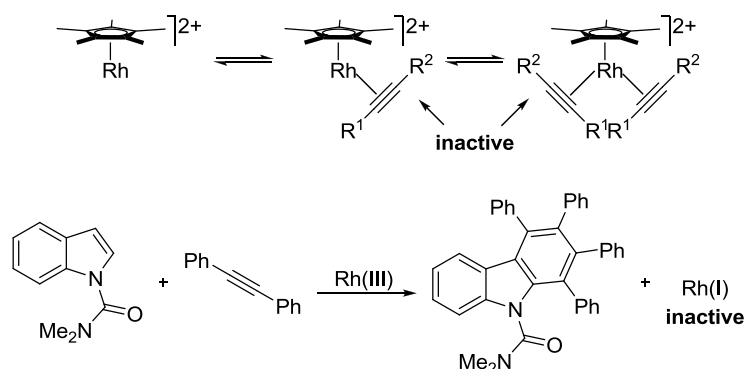
Table 5.4 – Alkyne Poisoning Experiments^a

Entry	Additive	%Yield ^b
1	none	85%
2		10%
3		0%
4		20%

^aConditions: Indole (1 equiv.), alkyne (1.1 equiv.), additive (1.1 equiv.), Cp*Rh(MeCN)₃(SbF₆)₂ (5 mol%) and acetic acid (5 equiv.) in *i*PrOAc (0.4 M) at 90 °C for 15 hrs. ^b¹H NMR yields.

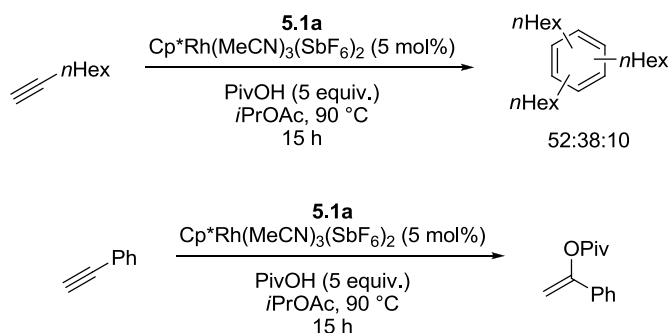
Dialkyl and propiolate-type alkynes likely reduce catalytic activity by binding relatively strongly to the rhodium catalyst (Scheme 5.6). Rate inhibition by alkynes (especially dialkyl alkynes) in a similar catalytic system has been demonstrated by our group.^{115b} Diaryl alkynes may undergo migratory insertion at increased rates allowing a second alkyne to do a migratory insertion. A subsequent cyclization/reductive

elimination step would afford an inactive Rh(I) species. This type of double alkyne addition has been demonstrated in similar catalytic systems.¹¹⁹



Scheme 5.6 – Reasoning for Catalyst Inhibition

Terminal alkynes also failed to yield the desired product (Scheme 5.7). Instead, terminal alkyl alkynes gave only a regioisomeric mixture of alkyne trimerization products. Also, terminal aryl alkynes yielded only Markovnikov addition of pivalic acid to the alkyne. However, this problem can be avoided by employing silyl protected terminal alkynes (**5.3p**).



Scheme 5.7 – Reactivity of Terminal Alkynes

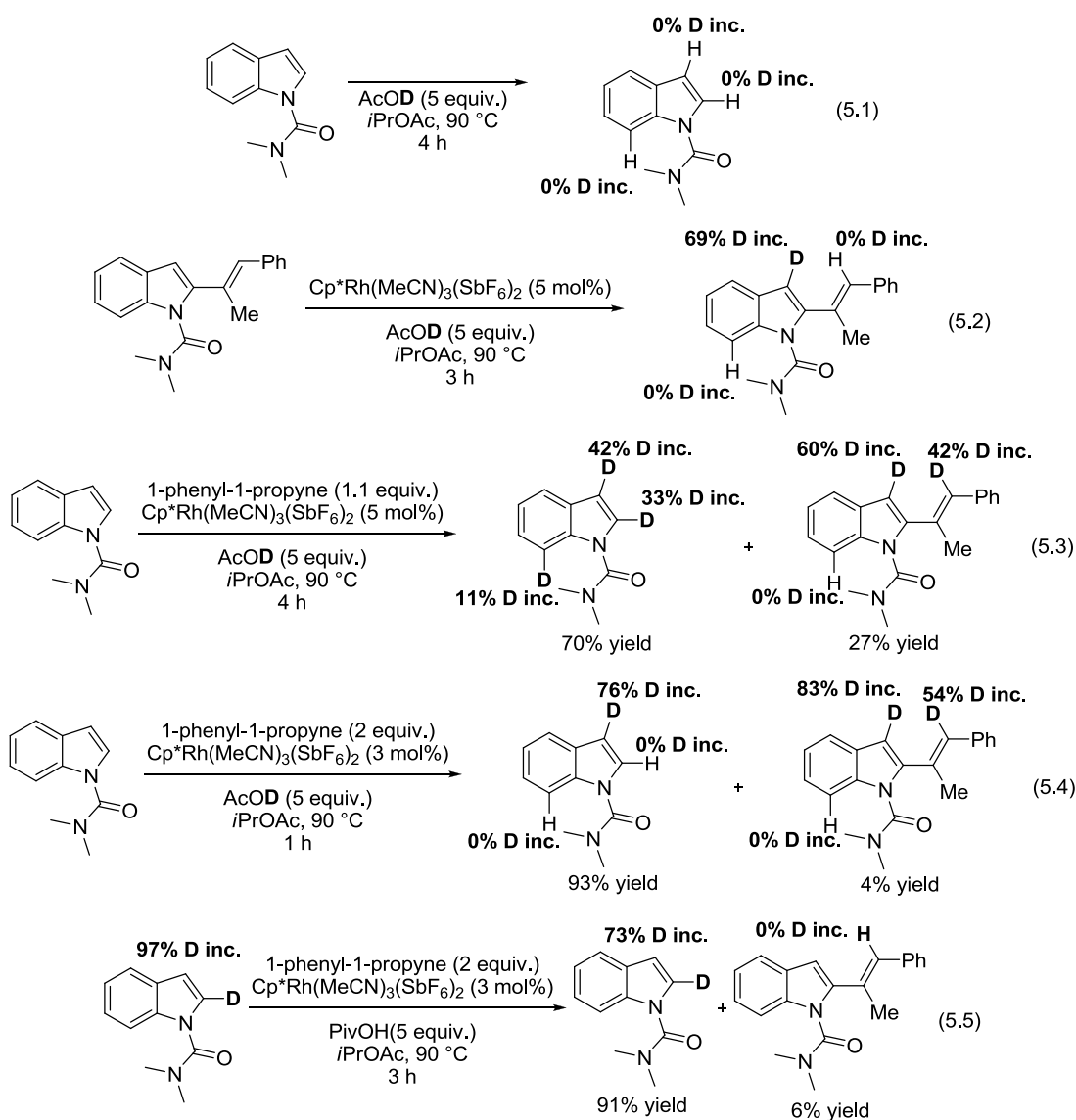
¹¹⁹ (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4019. (b) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13.

5.2.4 Mechanistic Investigations

In order to investigate the mechanism of the transformation, a series of deuterium incorporation experiments were performed. These experiments are outlined in Scheme 5.8. First, a background experiment was conducted which involved heating indole **5.1a** in the presence of AcOD (eq. 5.1). No deuterium incorporation was observed in the absence of the catalyst which allowed us to conclude that any incorporation in subsequent reactions would be the result of a metalation/deuterodemetalation sequence. Therefore, deuterium incorporation can act as a “tracer” and observed incorporation would mean that the catalyst has spent time at that position. Another background experiment was conducted in which the reaction product **5.3a** was heated at 90 °C in *i*PrOAc in with 5 mol% of the rhodium catalyst and 5 equivalents of AcOD for 3 hours (eq. 5.2). 69% Deuterium incorporation was observed at the C3 indole position which suggests reversible metalation at that position. More importantly, no deuterium incorporation was observed at the alkene position of the product, which established that any incorporation observed here would arise from a reaction intermediate and not from post-reaction incorporation.

A mechanism which involves a C-H oxidative insertion/reductive elimination sequence should not result in any incorporation at the alkene position (Scheme 5.1). To test this possibility, a reaction was conducted with AcOD in place of PivOH but taken only to 27% conversion with a 4 hour reaction time (eq. 5.3). 42% deuterium incorporation was observed at the alkene position of the product. However, a C-H bond oxidative insertion pathway could not be ruled out since 33% deuterium incorporation was also observed at the C2 indole position in the recovered starting material, which could conceivably explain incorporation at the alkene position.

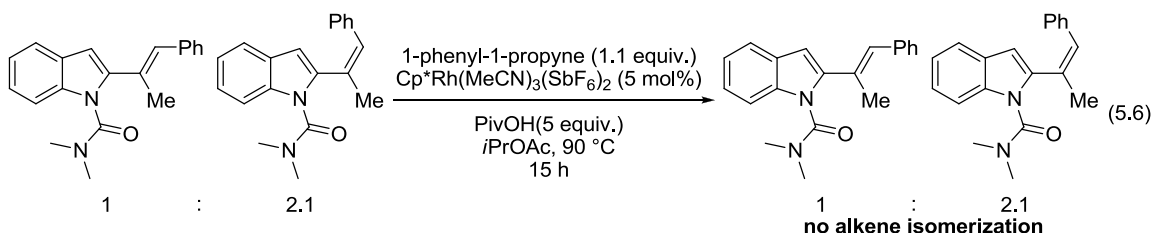
Additionally, deuterium incorporation at the C3 and C7 indole positions in the recovered starting material may suggest that hydroarylation might take place at these positions; however, none of these products were observed. In order to definitively rule out the C-H bond oxidative insertion pathway the background deuterium incorporation at the indole C2 position would have to be reduced. This was accomplished by reducing the catalyst loading to 3 mol%, the reaction time to 1 hour and increasing the amount of alkyne used to 2 equivalents (eq. 5.4). In this case there is 54% deuterium



Scheme 5.8 – Deuterium Incorporation Experiments

incorporation at the alkene position and no deuterium incorporation at the C2 indole position. Additionally, C2-deuterated **5.1a** was subjected to reaction conditions and deuterium incorporation was observed in the product (eq. 5.5). These results prove that the hydrogen at the alkene position of the product comes from the acid additive in the reaction and not from the substrate and rules out the possibility of a C-H bond oxidative insertion pathway.

The high selectivity for *syn*-addition renders the possibility of alkyne activation improbable (Scheme 5.1).^{103,120} However it is conceivable that *syn*-addition arises from isomerization of *trans*-addition product. A control experiment where a 1:2.2 mixture of *E:Z* isomers is exposed to the standard hydroarylation conditions shows no alkene isomerization (eq. 5.6), ruling out the possibility of alkene isomerization under reaction conditions or alkyne activation as the operative mechanistic pathway.



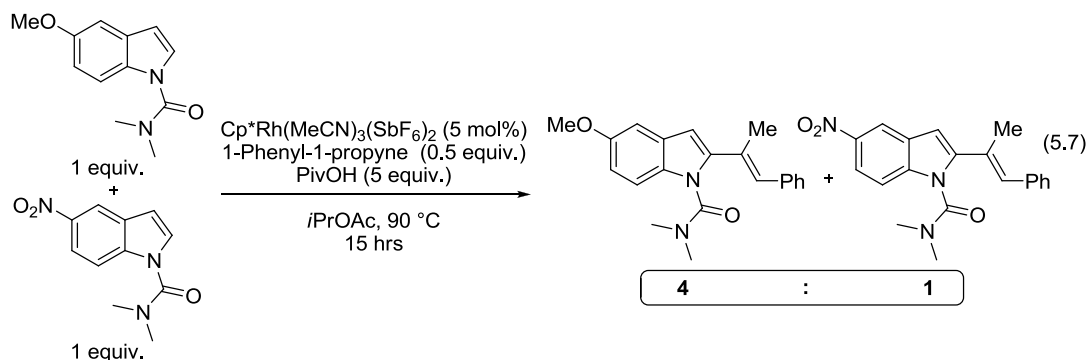
To gain insight into the nature of the C-H bond cleavage event, a competition between methoxyindole **5.1b** and nitroindole **5.1c** (eq. 5.7) which revealed a preference for the more electron rich arene (4:1 ratio). This outcome is consistent with results or related catalyst systems from our group¹²¹ and other groups¹²² in which the C-H bond

¹²⁰ For an example of reactivity of a cationic metal with alkynes see: Burns, R. M.; Hubbard, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9514.

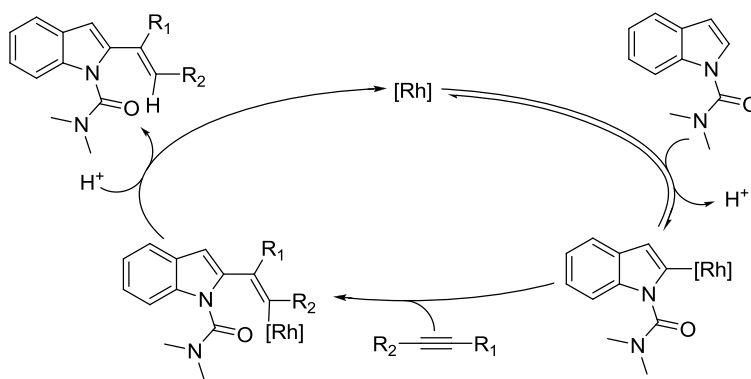
¹²¹ Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326.

¹²² (a) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492. (b) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Polleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210. (c) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.

cleavage was determined to proceed though at concerted metalation-deprotonation type mechanism. However, an electrophilic rhodation mechanism cannot be ruled out.



A proposed catalytic cycle which would explain both the decrease in deuterium incorporation and the observed alkene geometry is shown in Scheme 5.9. First reversible directed metallation with the rhodium(III) catalyst occurs with concomitant loss of a proton. The alkyne can then coordinate to the rhodium center followed by migratory insertion. Finally protonolysis yields the product and regenerates the catalyst. An off-cycle fast and reversible metallation at the C-3 position of indole could explain the observed deuterium incorporation at that position.



Scheme 5.9 – Proposed Catalytic Cycle

5.3 Conclusions

In conclusion we have developed an intermolecular rhodium(III) catalyzed hydroarylation of alkynes. The reaction is applicable across a range of both arenes and alkynes. Consequently, this reaction should be useful for the rapid and atom economical preparation of organic building blocks. Furthermore, this novel reactivity for the intermolecular hydroarylation of alkynes should have broader implications for the development of related transformations.

Kinetic Resolution of β -Hydroxy Esters

6.1 Introduction¹²³

Despite remarkable advances in enantioselective synthesis, the preparation of single enantiomer quaternary stereocenters remains a challenging and important goal in organic chemistry.¹²⁴ The difficulties associated with the use of ketone electrophiles are illustrative, where attenuated reactivity, challenging carbonyl enantiofacial differentiation and diminished stability towards retro-aldol decomposition can explain, in part, the wealth of techniques for enantioselective aldol additions to aldehydes¹²⁵ compared to

¹²³ A significant portion of the work described in this chapter has been published in the form of a communication, see: Schipper, D. J.; Rousseaux, S.; Fagnou, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 8343.

¹²⁴ (a) Marek, I. *Chem. Eur. J.* **2008**, *14*, 7460. (b) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, *17*, 1683. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, *3*, 369. (d) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (e) Christoffers, J. *Chem. Eur. J.* **2003**, *9*, 4862. (f) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591.

¹²⁵ (a) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J.* **2002**, *8*, 36. (c) Arya, P.; Quin, H. *Tetrahedron* **2000**, *56*, 917. (d) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (e) Bach, T. *Angew. Chem. Int. Ed.* **1994**, *33*, 417. (f) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (g) Braun, M. in *Stereoselective Synthesis, Houben-Weyl*, Helmchen, G.; Hoffmann, R.; Mulzer, J.; Schaumann, E. Eds. Thieme: Stuttgart, 1996; vol. E21/3, pp. 1603. (h) Heathcock, C. H.; in *Asymmetric Synthesis*, Morrison, J. D. Ed. Pergamon Press: New

ketones.¹²⁶ In such instances, kinetic resolution of a racemic product may be an attractive alternative to enantioselective synthesis, which remains an important method of accessing enantiopure material.^{127,128}

York, 1984; vol. 3, pp. 111. (i) Mahrwald, R. *Chem. Rev.* **1999**, 99, 1095. (j) Mukaiyama, T. *Org. React.* **1994**, 46, 1. (k) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, 39, 1352. (l) Carreira, E. M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Eds. Springer: Heidelberg, 1999; vol. 3, pp. 997. (m) Groger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, 4, 1137. (n) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, 9, 357. (o) Narasaka, K. *Synthesis* **1991**, 1, 1-11. (p) Alcaide, B.; Almendros, P. *Angew. Chem. Int. Ed.* **2003**, 42, 858. (q) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (r) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Etxebarria, J. *Curr. Org. Chem.* **2005**, 9, 219. (s) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, 103, 2127.

¹²⁶ (a) Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J.; *Tetrahedron* **2007**, 63, 10437. (b) Adachi, S.; Harada, T. *Org. Lett.* **2008**, 10, 4999. (c) Sedelmeier, J.; Hammerer, T.; Bolm, C. *Org. Lett.* **2008**, 10, 917. (d) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, 121, 686. (e) Langner, M.; Remy, P.; Bolm, C.; *Chem. Eur. J.* **2005**, 11, 6254. (f) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, 128, 6532. (g) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A.; *Chem. Commun.* **2002**, 620. (h) Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, 130, 5654. (i) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, 124, 4233. (j) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, 70, 5235. (k) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, 128, 7164. (l) Moreau, X.; Bazan-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, 127, 7288.

¹²⁷ For reviews on kinetic resolution see: (a) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, 44, 3974. (b) Somfai, P.; *Angew. Chem. Int. Ed.* **1997**, 36, 2731. (c) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, 18, 249. For some recent examples see: (d) Minato, D.; Nagasue, Y.; Demizu, Y.; Onomura, O. *Angew. Chem. Int. Ed.* **2008**, 47, 9458. (e) Muller, C. E.; Wanka, L.; Jewell, K.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2008**, 47, 6180. (f) Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, 130, 15957. (g) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Angew. Chem. Int. Ed.* **2008**, 47, 2447. (h) Radosevich, A. T.; Chan, V. S.; Shih, H.-W.; Toste, F. D. *Angew. Chem. Int. Ed.* **2008**, 47, 3755. (i) Coldham, I.; Patel, J. J.; Raimbault, S.; Whittaker, D. T. E. *Chem. Comm.* **2007**, 43, 4534. (j) Klare, H. F. T.; Oestreich, M. *Angew. Chem. Int. Ed.* **2007**, 46, 9335. (k) Driver, T. G.; Harris, J. R.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, 129, 3836. (l) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem. Int. Ed.* **2007**, 46, 3918. (m) Nechab, M.; Kumar, D. N.; Philouze, C.; Einhorn, C.; Einhorn, J. *Angew. Chem. Int. Ed.* **2007**, 46, 3080. (n) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J. J.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2006**, 128, 10943.

While kinetic resolution of secondary alcohols has been studied extensively,^{127,128} there are few examples of tertiary alcohol resolutions (Scheme 6.1). In addition to enzymatic processes¹²⁹ that have limited substrate scope, Miller has described a peptide based catalyst for the acylation of α -amino alcohols.¹³⁰ Hoveyda and Snapper also used a peptide based catalyst for selective silylation of 1,2-diols including 3 examples of tertiary alcohols,^{131a} as well as the desymmetrization of triols.^{131b} Oestreich has shown that stereogenic silanes can be used to resolve chiral donor functionalized tertiary alcohols.¹³¹ Matsunaga and Shibasaki also developed a resolution of tertiary nitroaldols through a retro-nitroaldol reaction catalyzed by mixed La-Li heterobimetallic complexes.¹³² Recently, Shintani and Hayashi reported a rhodium catalyzed resolution of tertiary homoallylic alcohols.¹³³

¹²⁸ (a) Spivey, A. C.; Maddaford, A.; Redgrave, A.; *J. Org. Prep. Proced. Int.* **2000**, 32, 331. (b) Jarvo, E. R.; Miller, S. J.; Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2004; Chapter 43. (c) Denmark, S. E.; Beutner, G. L.; *Angew. Chem., Int. Ed.* **2008**, 47, 1560. (d) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, 43, 5138. (e) Robinson, D. E. J. E.; Bull, S. D.; *Tetrahedron: Asymmetry* **2003**, 14, 1407. (f) Fu, G. C. *Acc. Chem. Res.* **2000**, 33, 412. (g) Rendler, S.; Auer, G.; Oestreich, M. *Angew. Chem. Int. Ed.* **2005**, 44, 7620. (h) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, 62, 285. (i) MacKay, J. A.; Vedejs, E. *J. Org. Chem.* **2006**, 71, 498. (j) Mazet, C.; Roseblade, S.; Kohler, V.; Pfaltz, A.; *Org. Lett.* **2006**, 8, 1879. (k) Li, Y.-Y.; Zhang, X.-Q.; Dong, Z.-R.; Shen, W.-Y.; Chen, G.; Gao, J.-X. *Org. Lett.* **2006**, 8, 5565.

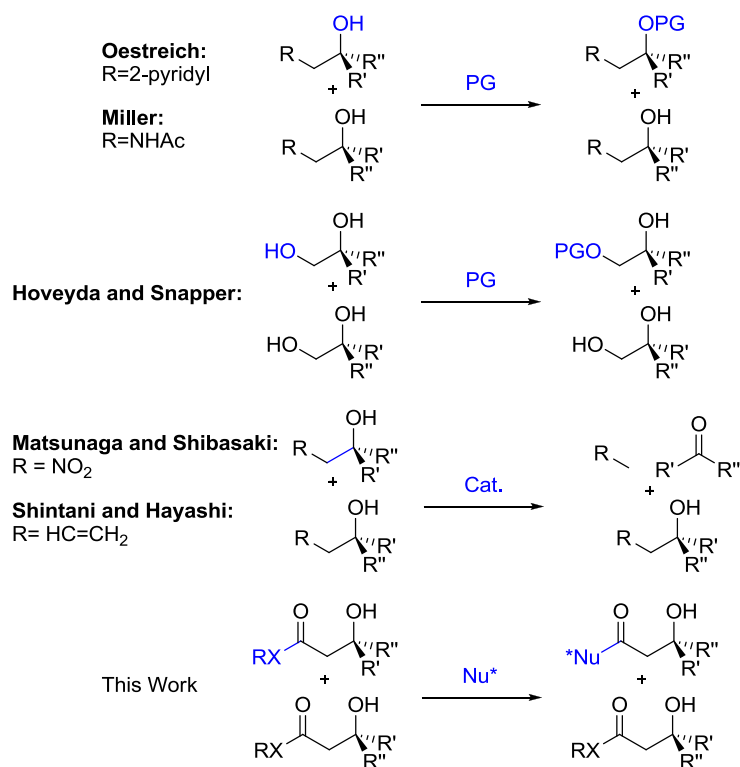
¹²⁹ (a) O'Hagan, D.; Zaidi, N. A.; *J. Chem. Soc., Perkin Trans. 1*, **1992**, 947. (b) O'Hagan, D.; Zaidi, N. A. *Tetrahedron: Asymmetry* **1994**, 5, 1111. (c) Brackenridge, I.; McCague, R.; Roberts, S. M.; Turner, N. J.; *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1093. (d) Hari Krishna, S.; Persson M.; Bornscheuer, U. T.; *Tetrahedron: Asymmetry* **2002**, 13, 2693. (e) Heinze, B.; Kourist, R.; Fransson, L.; Hult, K.; Bornscheuer, U. T.; *Protein Eng. Des. Sel.* **2007**, 20, 125. (f) Kourist, R.; Bartsch, S.; Bornscheuer, U. T.; *Adv. Synth. Catal.* **2007**, 349, 1393. (g) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **1999**, 121, 7283. (h) Kourist, R.; Nguyen, G.-S.; Struebing, D.; Boettcher, D.; Liebeton, K.; Naumer, C.; Eck, J.; Bornscheuer, U. T. *Tetrahedron: Asymmetry* **2008**, 19, 1839.

¹³⁰ Angione, M. C.; Miller, S. J. *Tetrahedron* **2006**, 62, 5254.

¹³¹ Karatas, B.; Rendler, S.; Frohlich, R.; Oestreich, M.; *Org. Biomol. Chem.* **2008**, 6, 1435.

¹³² Tosaki, S.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, 128, 11776.

¹³³ Shintani, R.; Takatsu, K.; Hayashi, T. *Org. Lett.* **2008**, 10, 1191.



Scheme 6.1 – Methods for the Non-Enzymatic Kinetic Resolution of Tertiary Alcohols

Described in this chapter is the unique reactivity/selectivity associated with (1*S*,2*R*)-*N*-methylephedrine in the resolution of tertiary alcohols arising from ketone aldol reactions. Even though the tertiary stereogenic center is three atoms removed from the reactive site, high selectivities are observed – with *s*-factors in excess of 20 in many instances. The method is technically simple to perform, and employs a cheap and readily available¹³⁴ resolving agent (1*S*,2*R*)-*N*-methylephedrine (a chiral compound that is commonly used as a stoichiometric chiral auxiliary in diastereoselective carbon-carbon bond forming processes).¹³⁵ Given the ease with which these racemic aldol processes may be performed, and the ease with which the products may be resolved, this chemistry

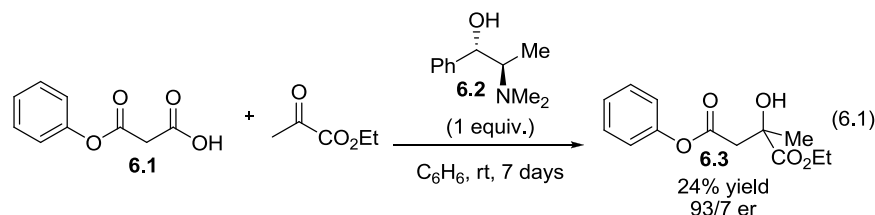
¹³⁴ (1*S*,2*R*)-*N*-methylephedrine is available from Sh-Icon Inc. for ~\$3/g.

¹³⁵ (a) Gennari, C.; Molinari, F.; Cozzi, P.; Oliva, A. *Tetrahedron Lett.* **1989**, 30, 5163. (b) Laurent, F.; Sebastien, R.; Patrice, C.; Janine, C. *Org. Lett.* **2006**, 8, 3441.

should find application in the preparation of a wide array of natural and synthetic organic molecules.

6.2 Results and Discussion

The unique reactivity of *N*-methylephedrine was inadvertently discovered while evaluating the feasibility of amine catalyzed asymmetric decarboxylative ketone aldol reactions (Equation 6.1).¹³⁶ While performing the addition of **6.1** to ethyl pyruvate in the presence of (1*S*,2*R*)-*N*-methylephedrine (**6.2**) as a chiral base, product was obtained with low yield but significant levels of enantiomeric excess when the reaction was allowed to proceed to completion over several days.¹³⁷ Further analysis of the reaction, such as isolation of phenol as well as a transesterified product, indicated that the enantiomeric excess had arisen from a kinetic resolution of racemic product.



6.2.1 Reaction Optimization

¹³⁶ Blaquiere, N.; Shore, D. G.; Rousseaux, S.; Fagnou, K. *J. Org. Chem.* **2009**, 74, 6190.

¹³⁷ This reaction was carried out by graduate student Sophie Rousseaux.

Following the initial discovery, a broad range of readily available chiral nucleophiles was evaluated for the kinetic resolution of **6.3** (Figure 6.1). With chiral alcohols such as **6.5** to **6.9**, no reaction was observed at room temperature in the absence of other additives. In these cases, improved outcomes could be obtained by addition of one equivalent of triethylamine and heating to 60 °C (Table 6.1, entries 2-6). From these screens, (*R*)-(-)-pantolactone (**6.7**) (entry 4) and (1*S*,2*R*)-*N*-methylephedrine (**6.2**) (entry 14) provided promising *s*-factors of 3.7 and 3.5 respectively. While further optimization with **6.7** failed to produce superior results, continued evaluation of *N*-methylephedrine (**6.2**) revealed that by increasing the reaction temperature to 60 °C, the selectivity factor could be dramatically improved from 3.5 to 21 (entry 16). This can be further enhanced to a selectivity factor of 38 by using 2 equivalents of **6.2** (entry 17). The reaction progress occurs over several hours and may be monitored by HPLC over chiral support. Conveniently, the reaction may be performed in ACS grade toluene without necessitating the exclusion of air or moisture.

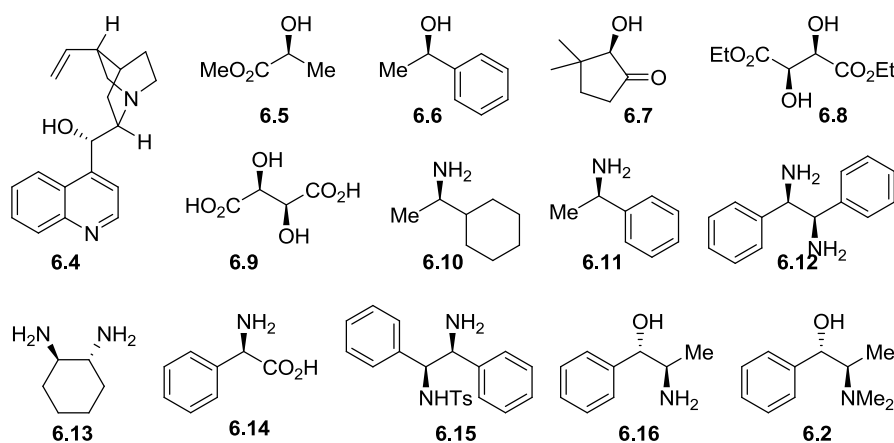


Figure 6.1 – Nucleophiles Screened for Kinetic Resolution

Table 6.1 – Nucleophiles Screened for Kinetic Resolution^a

(±)-**6.3** Nucleophile (+) or (-)-**6.3**
 PhMe, 48 hrs

Entry	Nucleophile	Temp	% conv ^[b]	er of 6.3 ^[b]	S ^[c]
1	(+)-Cinchonine (6.4)	RT	22	51.5/48.5	1.3
2	(S)-Methyl lactate (6.5)	60	0	50/50	... ^[d]
3	(R)-Phenylethanol (6.6)	60	0	50/50	... ^[d]
4	(R)-(-)-Pantolactone (6.7)	RT	34	62.5/37.5	3.7 ^[d]
5	(2R,3R)-Tartaric acid diethyl ester (6.8)	60	0	50/50	... ^[d]
6	(2S,3S)-Tartaric acid (6.9)	60	0	50/50	... ^[d]
7	(R)-1-cyclohexylethanamine (6.10)	RT	30	52/48	1.3
8	(R)-1-phenylethanamine (6.11)	RT	10	51/49	1.5
9	(1S,2S)-DPEN (6.12)	60	12	50/50	1.0
10	(1R,2R)-1,2-cyclohexanediamine (6.13)	RT	31	55/45	1.7
11	(R)2-Phenylglycine (6.14)	RT	9	51.5/48.5	1.9
12	(1S,2S)-TsDPEN (6.15)	RT	23	51/49	1.2
13	(1S,2R)-Norephedrine (6.16)	RT	33	58.5/41.5	2.4
14	(1S,2R)-N-Methylephedrine (6.2)	RT	42	66/34	3.5
15	(R)-(-)-Pantolactone (6.7)	60	12	53/47	2.7 ^[d] ^[e]
16	(1S,2R)-N-Methylephedrine (6.2)	60	49	88.5/11.5	21 ^[e]
17	(1S,2R)-N-Methylephedrine (6.2)	60	51	94.5/5.5	38 ^[f] ^[g]

^a Conditions: Substrate and nucleophile are dissolved in toluene and heated in an oil bath. ^b Conversion and er were determined by HPLC analysis using a Chiracel AS-H column and 1,3,5-trimethoxybenzene as an internal standard. ^c S-factors determined following the procedure of Kagan and Fiaud.^{127c} ^d With 1 equivalent of triethylamine. ^e 24 hour reaction time. ^f Using 2 equivalents of **6.2**. ^g 18 hour reaction time.

6.2.2 Reaction Scope

These optimized conditions were applied to a variety of compounds as illustrated in Table 6.2. In addition to **6.3**, which may be isolated in 49% yield and 94/6 enantiomeric ratio (er), other tertiary alcohol compounds may be effectively resolved. A number of functionalities at the quaternary center may be present, including alkyl (Table 6.2, entries 1 and 5), aryl (Table 6.2, entries 2 and 4), ester (Table 6.2, entries 1-3), trifluoromethyl (Table 6.2, entries 3 and 4), and ketone (Table 6.2, entry 5) substituents. While optimized for tertiary alcohol compounds, this method may also be applied to aldehyde aldol products. Under standard conditions, the selectivity is lower with these

substrates. We were pleased to find, however, that the selectivity with secondary alcohols can be improved by modifying the aryloxy substituent of the ester. For example, by changing the leaving group from an oxy-ester (Table 6.2, entry 6) to a thio-ester (Table 6.2, entry 7), the *s*-factor is doubled from 8 to 16. Synthetically useful

Table 6.2 – Kinetic Resolution Scope^a

Ph X C=O OH CH R₁ R₂ Racemic Ph CH OH CH Me NMe₂ 6.2 Temp PhMe Ph X C=O OH CH R₁ R₂ Enantioenriched								
Entry	Substrate	equiv of 6.2	Temp	% conv ^[b]	% er ^[b]	S ^[c]	Yield ^[d]	% er ^[b]
1	Ph C=O OH CH Me CO₂Et 6.3 2 60 51 94.5/5.5 38 49 94/6							
2	Ph C=O OH CH Ph CO₂Et 6.17 2 80 58 98/2 21 41 98/2							
3	Ph C=O OH CH CF₃ CO₂Et 6.18 0.8 60 46 87.5/12.5 35 41 >99/1							
4	Ph C=O OH CH CF₃ Ph 6.19 1 RT 28 67/33 21 31 97/3							
5	Ph C=O OH CH Me COMe 6.20 1 60 51^[e] 85/15 10 41 85/15							
6	Ph C=O OH CH Ph 6.21 0.6 RT 22^[f] 60.5/39.5 8.4 27 95/5							
7	Ph C=O OH CH Ph 6.22 0.7 60 38 75/25 16 42 92/8							
8	Ph C=O OH CH Cy 6.23 2 60 48^[e] 90/10 34 52 90/10							
9	Ph C=O OH CH nPr 6.24 2 60 56^[e] 88/12 9 44 88/12							
10	Ph C=O OH CH Me CO₂Et 6.25 0.7 60 46 54/46 1.3 -- --							

^a Conditions: Substrate and **6.2** are dissolved in toluene and heated in an oil bath. ^b Conversion and er determined by HPLC analysis using Chiracel columns and 1,3,5-trimethoxybenzene as an internal standard. ^c *S*-factors determined following the procedure of Kagan and Fiaud.^{127c} ^d Isolated Yield. ^e Conversion determined by isolating remaining substrate. ^f Conversion determined by ¹H NMR.

selectivities are also attained with aliphatic aldehyde products (Table 6.2, entries 8 and 9). In contrast, low selectivities are obtained when the stereogenic center is directly adjacent to the reaction site (Table 6.2, entry 10).

Encouraged by the ability to modulate selectivity through modification of the leaving group (Table 6.2, entries 6 and 7), we also investigated this influence in reactions performed at room temperature employing only 0.6 equivalents of the resolving agent **6.2** (Table 6.3). Under these conditions, reaction of the unsubstituted phenol ester **6.3** results in only 10% conversion and an *s*-factor of 3.6 (Table 6.3, entry 1). Gratifyingly, this can be significantly improved through the use of a 4-cyano substituted aryl ester. In this case, 42% conversion is observed over the same time period and with an *s*-factor of 29.3 (Table 6.3, entry 3).

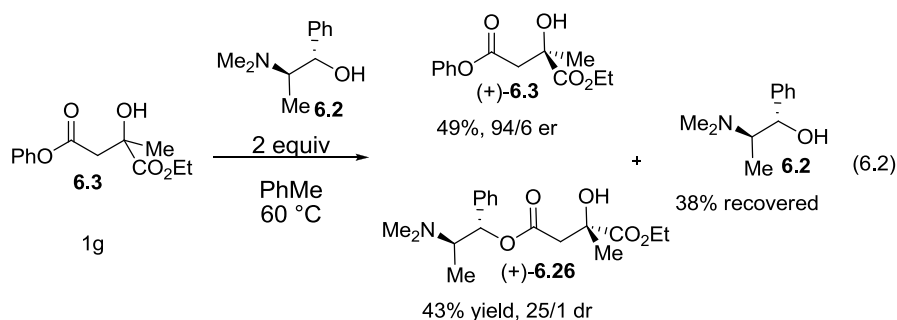
Table 6.3 – Effect of Leaving Group Modification in the Establishment of a Room Temperature Protocol Employing 0.6 Equivalents of **6.2**^a

Entry	R	% conv ^[b]	er ^[c]	<i>S</i> ^[d]
1	H	9.9	53/47	3.6
2	OMe	8.3	53/47	5.2
3	CN	42.2	82/18	29.3

^a Conditions: Substrate and **6.2** are dissolved in toluene and allowed to stir at room temperature for 48 hours. ^b Conversion determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^c er was determined by HPLC analysis using Chiracel columns. ^d *S*-factors determined following the procedure of Kagan and Fiaud.^{127c}

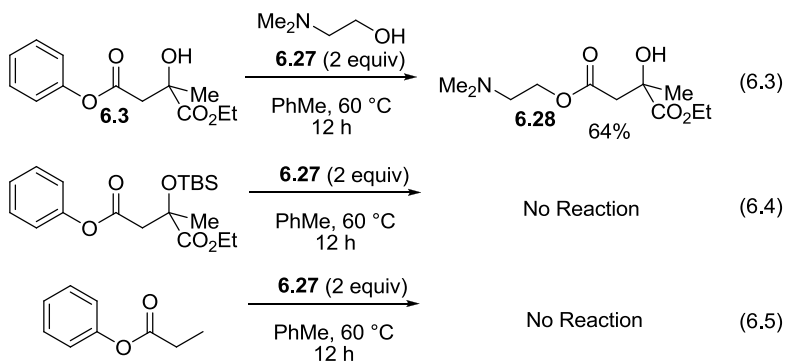
This chemistry may also be performed on larger scale (Equation 6.2). For example, treatment of one gram of **6.3** under the standard conditions results in the isolation of (+)-**6.3** in 49% yield and 94/6 er. The other enantiomer of **6.3** can be isolated as the transesterified product (+)-**6.26** as one major diastereomer (25/1 dr) in 43% yield along with 38% of unreacted **6.2**. The overall yield of the reaction is 92% when

considering the recovery of both enantiomers. Moreover, the use of excess **6.2** is mitigated by its subsequent recovery from the reaction.



6.2.3 Mechanistic Insights

To gain mechanistic insights into the reactivity and high selectivity associated with the use of **6.2**, a variety of experiments were carried out (Scheme 6.2). In these studies, a simplified system was employed by conducting the reaction with achiral 2-(dimethylamino)ethanol (**6.27**) instead of **6.2**. To establish baseline reactivity, **3** was treated with 2 equivalents of **6.27** in toluene at 60 °C. After 12 hours, 64% conversion to ester **6.28** was obtained (Equation 6.3). In contrast, if the alcohol of **3** is protected as a *tert*-butyldimethylsilyl (TBS) ether, or if it is absent as in the case of phenylpropionate, no reaction is observed after the same reaction time (Equations 6.4 and 6.5). These results, in conjunction with the inferior outcomes associated with the use of α -

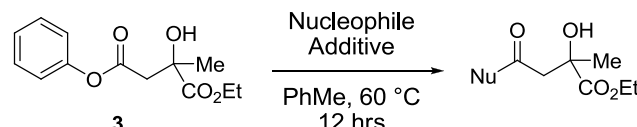
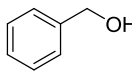
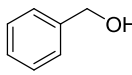
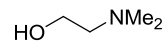
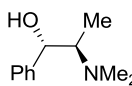
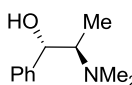


Scheme 6.2 – Importance of Alcohol Functionality

hydroxyesters (Table 6.2, entry 10), point to a key role of the β -hydroxyl moiety in establishing high reactivity and selectivity with these nucleophiles.

In a similar fashion, the role of the dimethylamine functionality of **6.2** and **6.27** on reactivity was evaluated. For example, no reaction is observed with benzyl alcohol as the nucleophile under standard conditions established for the resolution of **6.3** with **6.2** (Table 6.4, entry 1). Upon addition of one equivalent of triethylamine, up to 21% conversion is observed after 12 hours indicating that the base can accelerate the transesterification process (entry 2). When the amine base is attached to the alcohol nucleophile, as with **6.27**, a further increase in conversion is observed (entry 3). When the more sterically encumbered **6.2** is employed, a drop in conversion is noted over the same reaction time (entry 4) and this conversion is not influenced by the addition of an

Table 6.4 – Effect of Nucleophile on Rate^a

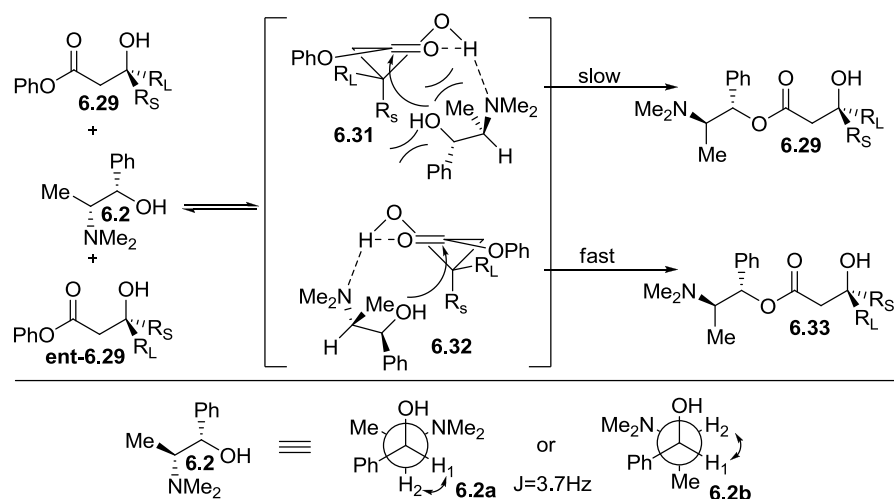
			
Entry	Nucleophile	Additive	% Conversion ^[b]
1		None	0
2		NEt ₃	21
3		None	64
4		None	35
5		NEt ₃	36

^a Conditions: Nucleophile, **6.2** and 1,3,5-trimethoxybenzene are dissolved in C₆D₆ and allowed to stir at 60 °C for 12 hours. ^b % conversion determined by measuring consumption of **6.3** by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

extra equivalent of triethylamine to the reaction mixture (entry 5). These results indicate that the presence of base is a key element in enhancing the reactivity of the alcohol nucleophile through H-bonding interactions and that this property is enhanced when the alcohol and the amine are tethered as in **6.2** and **6.27**.

A proposal for the origin of selectivity in these reactions is shown in Scheme 6.3. Since no reactivity is observed when the alcohol of the substrate is protected or removed (Scheme 6.2), H-bonding of the alcohol to the carbonyl of the phenyl ester may be a key element of electrophilic activation (Scheme 6.3). Conformational and NMR analysis of **6.2** support **6.2a** as the predominant conformer in solution. A $J_{\text{H1-H2}}$ coupling constant of 3.7 Hz that changes only slightly with heating or changing solvents indicates a gauche relationship, which is consistent with previous reports.¹³⁸ Both conformations **6.2a** and **6.2b** should give rise to the same selectivity based upon the current analysis. Given the rate acceleration associated with **6.27** and **6.2** compared to the combined use of an alcohol nucleophile and an amine base, we propose that H-bonding of the substrate alcohol to the amine of **6.2** may be important for reactivity/selectivity. If nucleophilic attack of **6.2** on **6.29** or **ent-6.29** occurs from the bottom face on stereoelectronic grounds, more severe steric interactions between the substituents of **6.29** and **6.2** should occur at **6.31** compared to reaction via **6.32**. Under these circumstances, **6.29** remains unreacted but **ent-6.29** undergoes transesterification to give **6.33**.

¹³⁸ Tsai, H.; Roberts, J. D. *Magn. Reson. Chem.* **1992**, *30*, 828 and references therein.



Scheme 6.3 – Proposed Origin of Selectivity

6.3 Conclusions

In conclusion, we have developed a method for the kinetic resolution of tertiary alcohols arising from ketone aldol reactions and extended this reactivity to other aldol products. These reactions employ commercially available (1*S*,2*R*)-*N*-methylephedrine as the resolving agent and are technically simple to perform. Given the challenge associated with the generation of quaternary stereocenters, this methodology should contribute meaningfully to the repertoire of techniques available to chemists for the preparation of single enantiomer tertiary alcohols of this type.

Enantioselective Organocatalysis Using Simple Aldehydes Temporary Tethers

7.1 Introduction

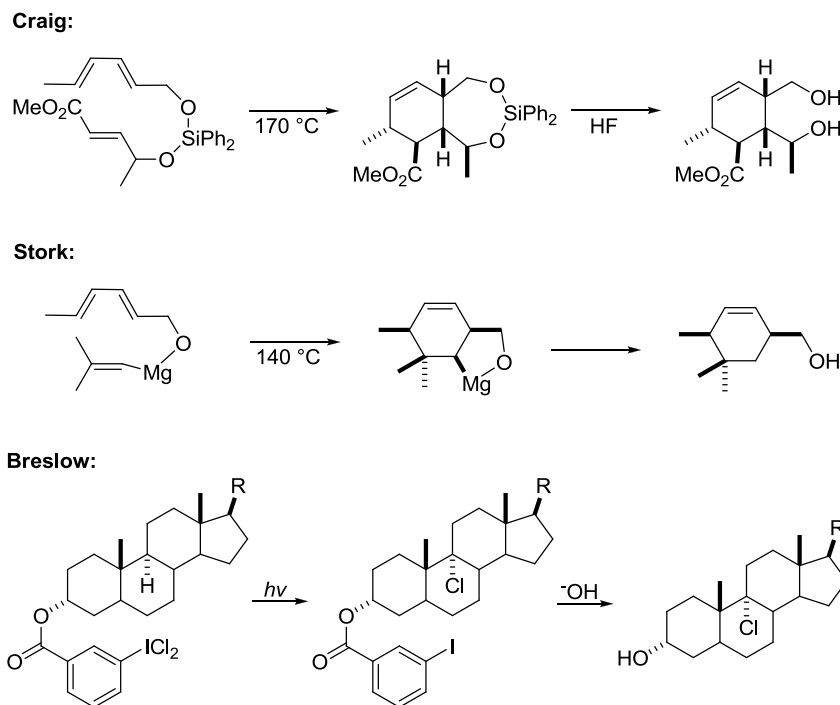
The enzymes' ability to promote preassociation is an important feature to rationalize their remarkable efficiency in catalyzing intermolecular reactions.¹³⁹ In organic synthesis, the use of directing or tethering groups allowing preassociation with a reagent or catalyst is a common strategy to achieve temporary intramolecularity which often leads to increases in reactivity, rate, regio- and stereoselectivity of formally intermolecular reactions.¹⁴⁰ Typically, such interaction involves hydrogen bonds, coordination to a metal catalyst or stepwise installation of a temporary tether.

While these methods have proven advantageous in many cases they suffer from a drawback of auxiliary-type approaches: additional steps are required for its formation and cleavage. Some tethering strategies are highlighted in Scheme 7.1. Craig has demonstrated the use of silicon based tethers to achieve challenging Diels-Alder

¹³⁹ (a) Fersht, A. *Enzyme Structure and Mechanism*; W. H. Freeman and Company. 1985; 47-97. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York. 1969.

¹⁴⁰ (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307. (b) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, 95, 1253. (c) Fensterbank, L.; Malacria, M.; Sieburt, S. *MCN. Synthesis* **1997**, 813. (d) Gauthier, Jr., D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, 54, 2289. (e) *Templated Organic Synthesis*; Diederich, F.; Stang, P. J.; Eds; Wiley-VCH, 2000.

reactions.¹⁴¹ Also, Stork has made several contributions including silicon, magnesium and aluminum reagents for Diels-Alder reactions and radical cyclizations.¹⁴² Finally, Breslow has established the efficacy of a templated, biomimetic approach to functionalization of steroid derivatives including chlorination and dehydrogenation.¹⁴³



Scheme 7.1 – Examples of Tethered Reactions

Given the effectiveness and drawbacks of a tethering approach we envisioned an alternative strategy. This approach would involve the use of a simple organic molecule that could temporarily and *catalytically* covalently link to reactants allowing a formally intermolecular reaction to take place in an intramolecular fashion (Figure 7.1). We

¹⁴¹ Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, 33, 6165.

¹⁴² (a) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, 107, 500. (b) Stork, G.; Sofia, M. *J. Am. Chem. Soc.* **1986**, 108, 6826. (c) Stork, G.; Suk, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, 113, 7054. (d) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, 117, 6595.

¹⁴³ Breslow, R. *Acc. Chem. Res.* **1995**, 28, 146.

reasoned that this strategy should increase reactions rates or allow for intermolecular reactivity that is otherwise impossible.

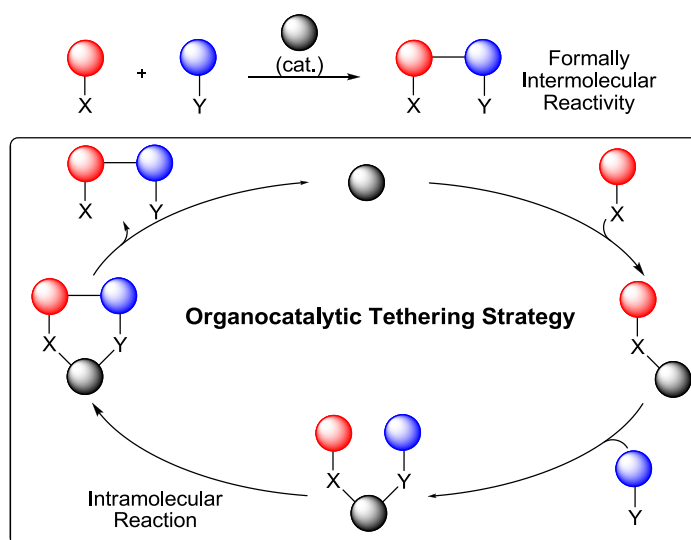


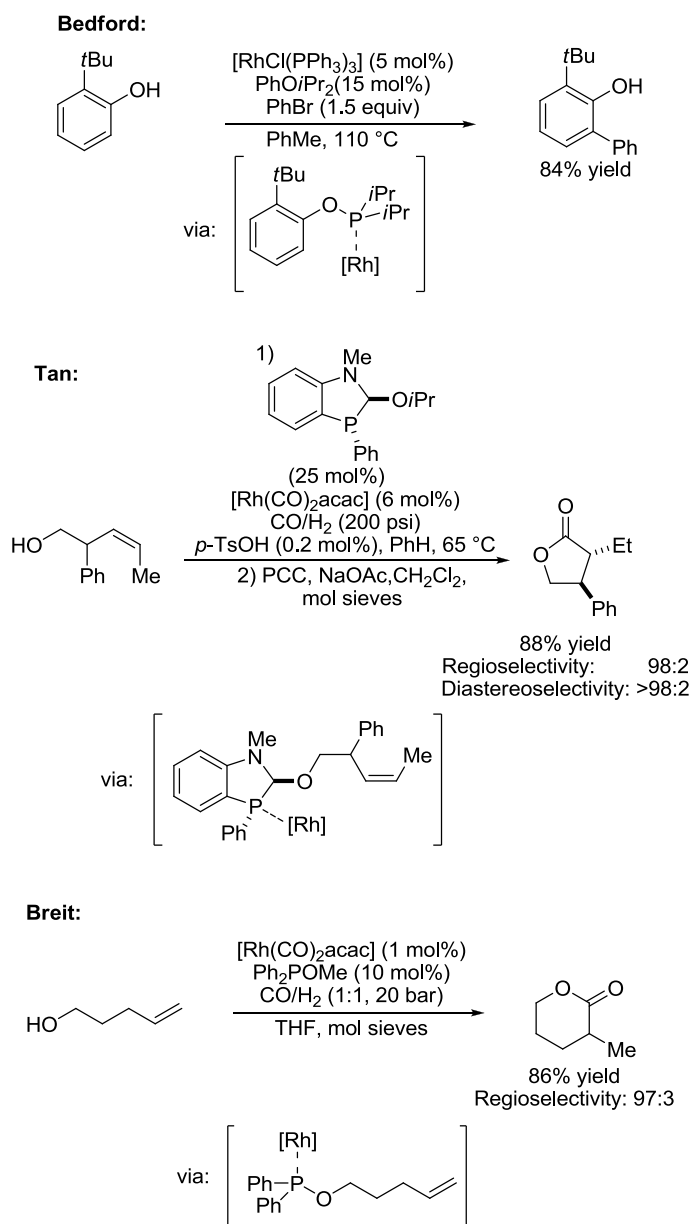
Figure 7.1 – Proposed Catalytic Tethering Strategy

A related strategy, which has received increased attention recently, is the catalytic and transient covalent attachment of a substrate, which is to undergo a transition metal mediated reaction, to the ligand, which is to bind to the metal (Scheme 7.2).^{144,145,146,147} For example, the Bedford group has exploited the exchange of phenols on phosphinite-type ligands for the *ortho*-arylation of phenols.¹⁴⁵ Also, Tan and co-workers have used a scaffolding ligand to achieve the selective, rhodium-catalyzed hydroformylation of

¹⁴⁴ (a) Grünanger, C. U.; Breit, B. *Angew. Chem. Int. Ed.* **2008**, 47, 7346. (b) Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, 11, 2764. (c) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, 41, 222; (d) Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Lewis-Alleyne, L. C.; Long, P. D.; Polo-Cerón, D.; Prashar, S. *Chem. Commun.* **2008**, 990; (e) Carrión, M. C.; Cole-Hamilton, D. J. *Chem. Commun.* **2006**, 4527.

¹⁴⁵ Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, 42, 112.

homoallylic alcohols.¹⁴⁶ Breit and Grünanger have reported a similar strategy for the hydroformylation of bishomoallylic alcohols.¹⁴⁷

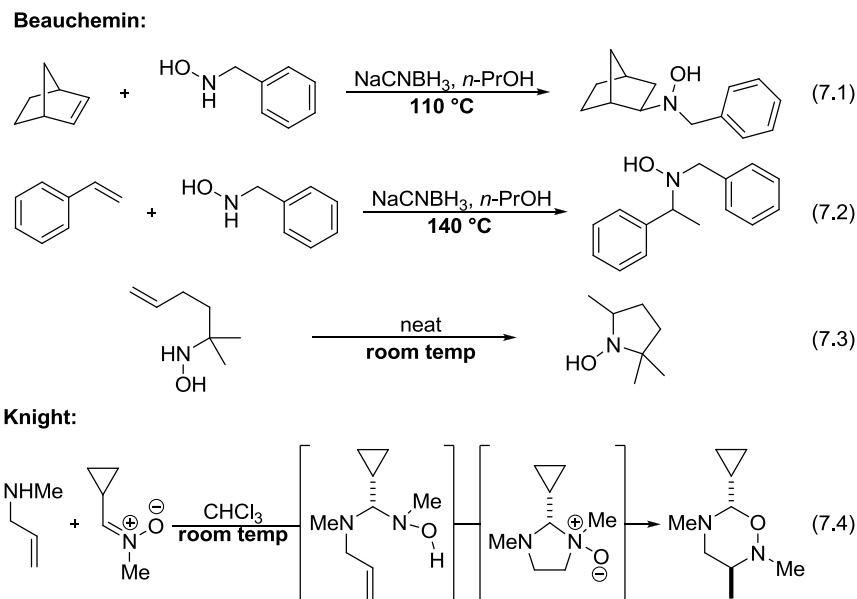


Scheme 7.2 – Scaffolding Ligands as a Strategy for Directing Reactions

¹⁴⁶ (a) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210. (b) Worthy, A.D.; Joe, C.L.; Lightburn, T.E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757. (c) Sun, X.; Frimpong, K.; Tan, K.L. *J. Am. Chem. Soc.* **2010**, *132*, 11841.

¹⁴⁷ Grünanger, C. U.; Breit, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 967.

Previous work from the Beauchemin group saw the development of Cope-type hydroaminations of alkenes and alkynes.¹⁴⁸ While the intermolecular hydroamination of alkynes is broad in scope, the hydroarylation of alkenes is more challenging. In fact, intermolecular hydroaminations proceed only at elevated temperatures with strained and/or biased alkenes such as norbornene and styrene (Scheme 7.3, eq. 7.1 and 7.2). Interestingly, when the alkene and hydroxylamine are tethered (Scheme 7.3, eq. 7.3), the subsequent intramolecular hydroamination of the unbiased alkene proceeds at room temperature (Scheme 7.3, eq. 7.3). This reactivity highlights favourable reactivity obtained with intramolecular reactions when compared to related intermolecular reactions.



Scheme 7.3 – Cope-Type Hydroamination of Alkenes

¹⁴⁸ (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, 47, 1410. (b) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, 130, 17893. (c) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, 131, 874. (d) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, 11, 1895. (e) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Whipp, C. J.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, 131, 8740.

Knight has also described some elegant work on the synthesis of 1,2,5-oxadiazinanes via addition of allyl amines to nitrones leading to the *in situ* generation of hydroxylamines as reaction intermediates (Scheme 7.3, eq. 7.4).¹⁴⁹

Building on this work it was hypothesized that the equivalent of an aldehyde tether in Knight's system might be rendered catalytic under certain conditions. Therefore, the intermolecular Cope-type hydroamination of alkenes would be an ideal setting in which to investigate an organocatalytic tethering strategy.

7.2 Results and Discussion

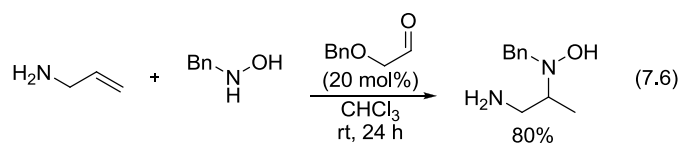
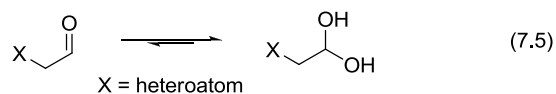
7.2.1 Reaction Discovery

α -Heteroatom substituted aldehydes are known to undergo facile hydrate formation because they are both kinetically and thermodynamically more reactive due to the inductive substituent (Scheme 7.4, eq. 7.5).¹⁵⁰ This suggested that α -heteroatom substituted aldehydes may be successful catalysts in related acetal/aminal based-tethering strategies. Indeed, upon extensive screening of aldehydes and other parameters, the reaction conditions shown in scheme 7.4, eq. 7.6 were developed.¹⁵¹ 2-(Benzyloxy)acetaldehyde proved to be the optimal catalyst for the hydroamination of allylamine with *N*-benzylhydroxylamine.

¹⁴⁹ (a) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169. (b) Bell, K. E.; Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, 38, 8545. (c) Gravestock, M. B.; Knight, D. W.; Abdul Malik, K. M.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3292.

¹⁵⁰ (a) Schulman, E. M.; Bonner, O. D.; Schulman, D. R.; Laskovics, F. M. *J. Am. Chem. Soc.* **1976**, 98, 3793. (b) Hilal, S. H.; Bornander, L. L.; Carreira, L. A. *QSAR Comb. Sci.* **2005**, 24, 631. (c) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, 4, 1.

¹⁵¹ Reaction discovery was performed by graduate student Joseph Moran. Reaction optimization was performed by graduate students Peter Ng and Melissa Macdonald.

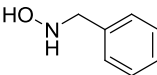
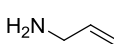
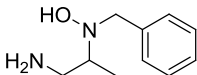
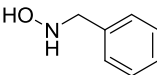
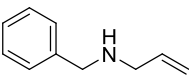
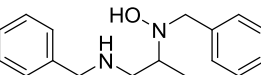
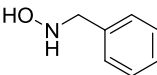
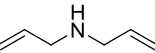
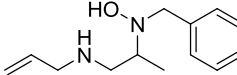
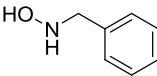
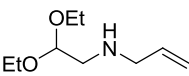
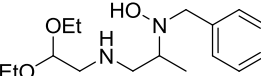
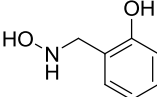
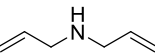
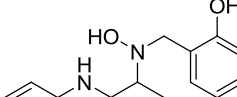
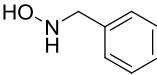
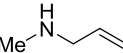
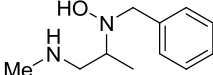
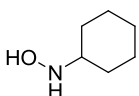
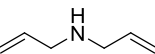
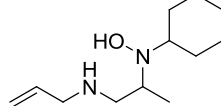


Scheme 7.4 – Organocatalyzed Hydroamination of Alkenes

7.2.2 Reaction Scope

With optimized reaction conditions in hand the reaction scope was investigated

Table 7.1 – Scope of the Organocatalyzed Hydroamination of Alkenes^a

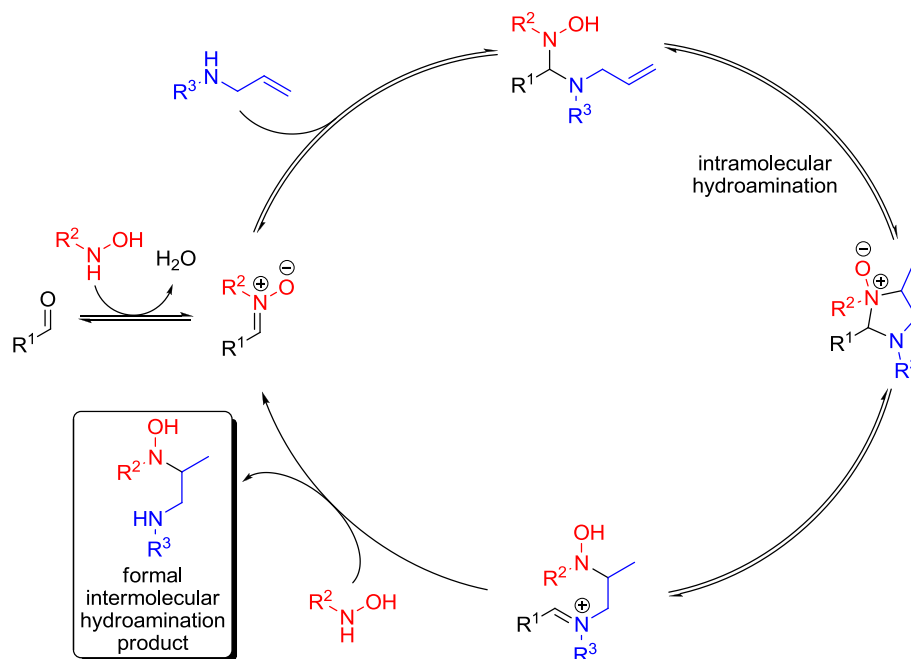
Entry	Hydroxylamine	Allylamine	Product	Solvent	% Yield ^b
1				CHCl ₃	83
2				C ₆ H ₆	62
3				C ₆ H ₆	69
4				C ₆ H ₆	56
5				CHCl ₃	61
6				C ₆ H ₆	80
7				CHCl ₃	55

^a Conditions: Hydroxylamine (1 equiv.), allylamine (1.5 equiv.), α -benzyloxyacetaldehyde (20 mol%) and solvent (1 mL) were charged to a vial and stirred at room temperature for 24 hours. ^b Isolated yield

and is shown in Table 7.1.¹⁵² The organocatalytic reaction is compatible with allyl amine (entry 1) as well as *N*-substituted allyl amines (entries 2-7). A range of hydroxylamines are also suitable substrates including benzyl (entries 1-4 and 6), substituted benzyl (entry 5) and aliphatic (entry 7) groups as substituents on the nitrogen atom.

7.2.3 Mechanistic Discussion

A proposed catalytic cycle is shown in Scheme 7.5. First, the condensation of the hydroxylamine onto the aldehyde forms a nitron. Attack of the allylamine onto the nitron leads to an aminor intermediate which can undergo a facile intramolecular Cope-type hydroamination. The resultant charged intermediate can undergo aminor cleavage to yield an iminium intermediate. Finally, condensation of a second molecule of



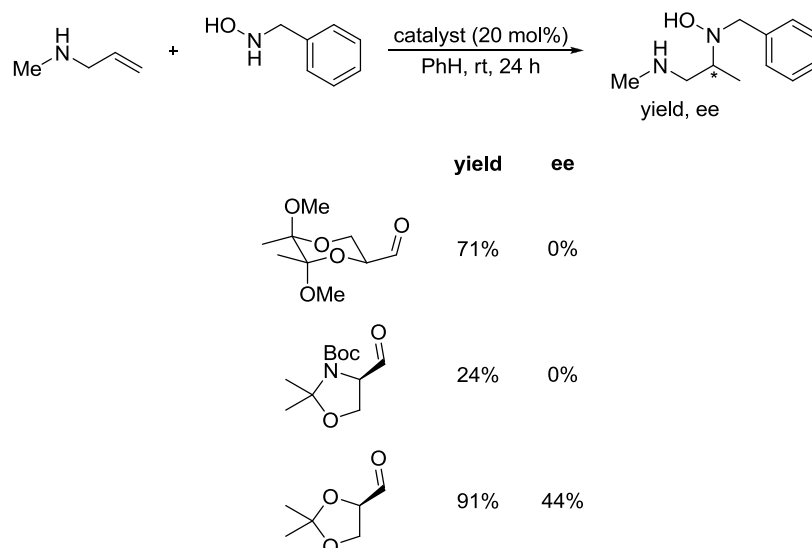
Scheme 7.5 – Proposed Catalytic Cycle

¹⁵² Reaction scope was performed by graduate students Peter Ng and Melissa Macdonald.

hydroxylamine completes the catalytic cycle and releases the product which is the result of a formal intermolecular hydroamination.

7.2.4 Enantioselectivity

One of the hallmarks of successful organocatalysis methods is the ability for the transformations in an enantioselective manner. Therefore, encouraged by the success of this novel temporary tethering strategy and the importance of the chiral 1,2-diamine motif,¹⁵³ we sought validation in the context of enantioselective catalysis. Efforts began with the screening of commercially available or easily prepared chiral aldehydes with α -heteroatoms as catalysts for the intramolecular hydroamination of *N*-methylallylamine with *N*-benzylhydroxylamine (Scheme 7.6). A chiral aldehyde reported by the Ley group¹⁵⁴ resulted in 71% isolated yield but racemic product. Garner's aldehyde gave both



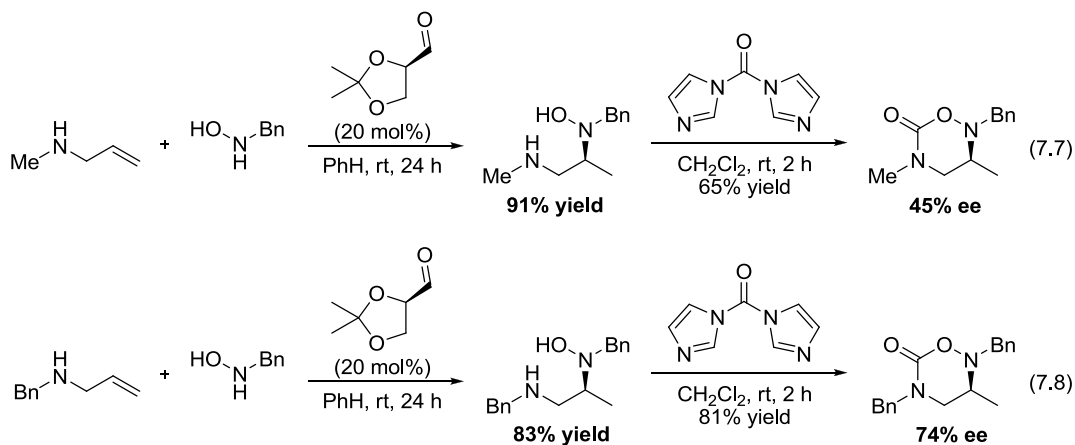
Scheme 7.6 – Catalyst Screen for Enantioselective Hydroamination

¹⁵³ (a) Anaya de Parrodi, C.; Juaristi, E. *Synlett* **2006**, 2699. (b) Martelli, G.; Savoia, D.; *Curr. Org. Chem.* **2003**, 7, 1049. (c) Mortensen, M. S.; O'Doherty, G. A. *Chemtracts* **2005**, 18, 555. (d) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, 67, 101.

¹⁵⁴ Michel, P.; Ley, S. V. *Angew. Chem. Int. Ed.* **2002**, 41, 3898.

poor yield and enantioselectivity. However, D-glyceraldehyde acetonide gave the desired product in 91% isolated yield and 44% enantiomeric excess.

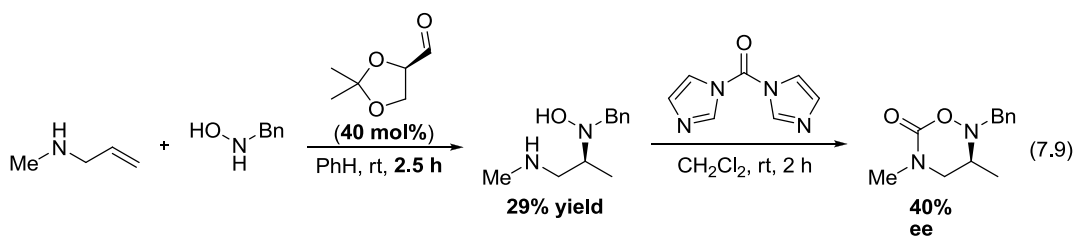
The enantioselective reaction can also be applied to other substrates as demonstrated by the reaction of *N*-benzylallylamine with *N*-benzylhydroxylamine (Scheme 7.7, eq 7.8). It is worth noting that the products of the hydroamination reactions are quite polar and not amenable to chiral HPLC analysis. Therefore a simple derivatization with carbodiimidazole is required to obtain compounds that can be analyzed by chiral HPLC. Additionally, the absolute stereochemistry was determined by optical rotation.¹⁵⁵ Hydroamination of *N*-benzylallylamine with *N*-benzylhydroxylamine with D-glyceraldehyde acetonide, resulted in not only a superior yield to α -benzyloxyacetaldehyde (62%) but also an enantiomeric excess of 74%, which represents the highest ee obtained for intermolecular hydroamination of unactivated alkenes by any method, including metal catalyzed reactions.¹⁵⁶



¹⁵⁵ Determination of absolute stereochemistry was conducted by graduate student Melissa Macdonald.

¹⁵⁶ Reznichenko, A. L.; Nguyen, H. N.; Hultsch, K. C. *Angew. Chem. Int. Ed.* **2010**, 49, 8984.

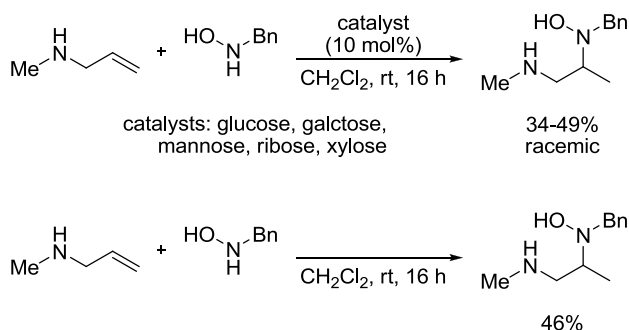
An experiment was carried out to determine if the suboptimal ee's obtained were due to catalyst epimerization under the reaction conditions. If this were the case one would expect the ee's to be higher at lower conversion and decrease at higher conversions as more time is given for catalyst epimerization. Also, an increased catalyst loading would give enough product, at early conversions, to be characterized. However, hydroamination of *N*-methylallylamine with *N*-benzylhydroxylamine using 40 mol% D-glyceraldehyde acetonide as catalyst and 2.5 hour reaction time actually gave a lower ee value of 40% (eq 7.9) when compared to optimized reaction conditions (eq 7.7). These results demonstrate reduced ee's are not likely the result of catalyst epimerization.



7.2.5 Dichloromethane as a Catalyst

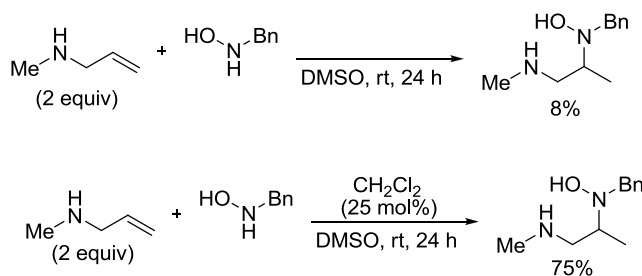
In their open form simple aldose sugars, such as glucose, contain an α -oxyaldehyde. Therefore we considered that they may be operative organocatalysts for the Cope-type hydroamination of allylamines. Indeed, we were delighted to see that the employment of a range of simple sugars as catalyst in dichloromethane at room temperature for 16 hours gave NMR yields from 34-49% as the racemate (Scheme 7.8). A solvent screen revealed that dichloromethane to be the only suitable solvent with all other solvents tested (PhMe, MeOH, acetone, EtOAc, Et₂O, THF, CH₃CN, *i*PrOH, H₂O and CH₃NO₂) giving 0-7% NMR yield. Additionally, catalyst loading seemed to have little effect as 5, 10 or 20 mol% of glucose all gave between 73-76% yield over a 20 hour reaction time. Given the lack of enantioselectivity and effect from the type of sugar used

as the catalyst and the catalyst loading, we began to wonder if the sugar was acting as a catalyst at all. A control experiment confirmed that indeed the reaction proceeds at room temperature in the absence of catalyst to give 46% NMR yield (Scheme 7.9).



Scheme 7.8 – Control Experiment

We were curious about unique reactivity of dichloromethane compared to that of other solvents. One possible explanation is the nucleophilic displacement of the chlorines on dichloromethane with the amine or hydroxylamine to yield a formaldehyde equivalent.¹⁵⁷ This formaldehyde equivalent could act then as a temporary tether similar to 2-(benzyloxy)acetaldehyde. To test this hypothesis a reaction carried in DMSO as a



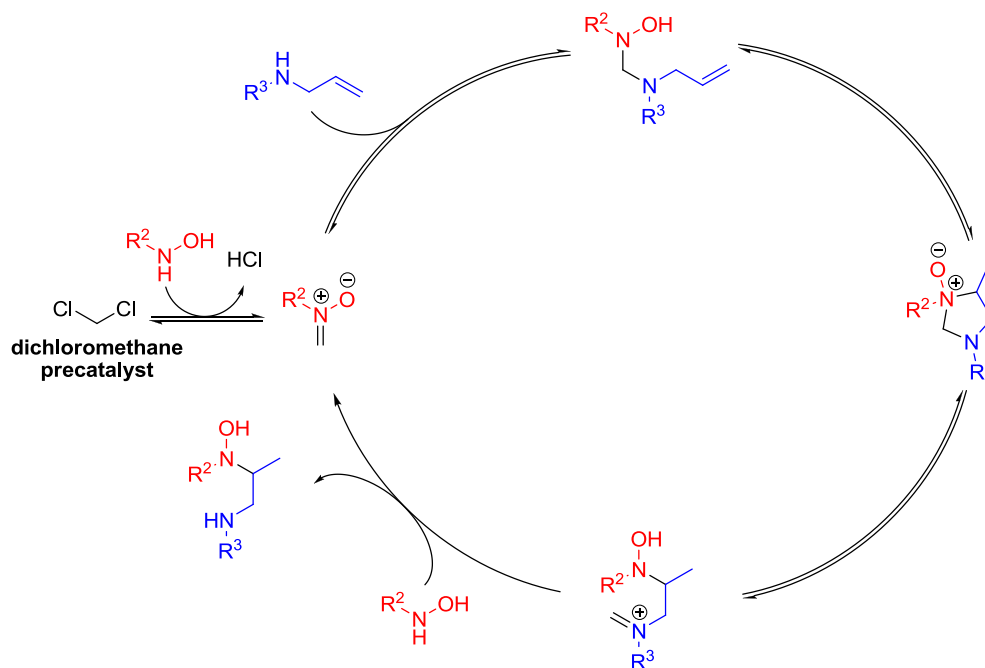
Scheme 7.9 – Dichloromethane Control Experiments¹⁵⁸

¹⁵⁷ (a) Davies, W.C.; Evans, G.B.; Hubert, F.L. *J. Chem. Soc.* **1939**, 412. (b) Wright, D.; Wulff, C. *J. Org. Chem.* **1970**, 35, 4252. (c) Hansen, S. H.; Nordholm, L. *J. Chromatogr., A* **1981**, 204, 97. (d) Beckett, A. H.; Ali, H. M. *J. Chromatogr., A* **1979**, 177, 255. (e) Nevstad, G. O.; Songstad, J. *Acta Chem. Scand.* **1984**, 38, 469. (f) Mills, J. E.; Maryanoff, C. A.; McComsey, D. F.; Stanzione, R. C.; Scott, L. *J. Org. Chem.* **1987**, 52, 1857.

¹⁵⁸ These reactions were carried out by undergraduate Eric Bilodeau: Bilodeau, E. Honours Thesis, University of Ottawa, 2011.

solvent and gave only 8% yield of the product (Scheme 7.9). However when a *catalytic* amount of dichloromethane is added to the reaction mixture to product in produced in 75% NMR yield. This experiment confirmed that, while not responsible for all of the reactivity, CH_2Cl_2 was playing a unique and catalytic role.

The catalytic cycle for the proposed reaction is outlined in Scheme 7.10. First, the displacement of the chlorines on the dichloromethane precatalyst generate a nitron. Attack of the allylamine onto the nitron leads to an aminal intermediate which can undergo a facile intramolecular Cope-type hydroamination. The resultant charged intermediate can undergo aminal cleavage to yield an iminium intermediate. Finally, condensation of a second molecule of hydroxylamine completes the catalytic cycle and releases the product.



Scheme 7.10 – Proposed Dichloromethane Catalytic Cycle

7.3 Conclusion

In conclusion, we have reported the validation of organocatalytic tethering strategy to achieve challenging intermolecular reactions. The method's potential for enantioselective reactivity has been demonstrated. Also, a unique and catalytic role for dichloromethane was uncovered. This approach represents a new paradigm in organocatalysis and we expect this advancement will prompt the investigation and development of a broad range transformations using this concept.

Supporting Information

8.1 General Methods

All palladium catalyzed direct arylation were carried out under Argon atmosphere. ^1H , ^{13}C , and DEPT-135 NMR spectra were recorded on a Bruker AVANCE 400 MHz, Bruker AVANCE 300 MHz or Varian INOVA 500 MHz spectrometers. Fourier-transform infra-red (FTIR) spectra were obtained as thin films on sodium chloride plates. High resolution mass spectra were obtained with a Kratos Concept IIH mass spectrometer. Melting points were recorded using a Gallenkamp Melting Point Apparatus and are reported uncorrected. All spectra of compounds completely characterized in this thesis are provided as electronic supporting information (attached CD). All other compounds have been reported in the literature or are commercially available.

8.2 Palladium-Catalyzed Direct Arylation with Aryl Triflates

General Triflation Procedures:

Transformation of Alcohols to Triflates: To a cooled (0 °C) biphasic mixture of toluene (30 mL), 30% (w/v) aqueous K_3PO_4 (30 mL), and the phenol (15 mmol, commercially available) was added dropwise Tf_2O (18 mmol) at a rate to maintain the reaction temperature <10 °C. The reaction was allowed to warm to ambient temperature and stirred for 30 min. The layers were separated, and the toluene layer was washed with water (30 mL) and extracted with EtOAc. The organics were combined, dried with anhydrous magnesium sulphate then concentrated in vacuo to give a liquid. The crude was subjected to flash chromatography to elute the corresponding triflate (15% Ether: 85% Pet Ether).

Transformation of Phenols with EWG to Triflates: To a stirred solution of para-trifluoromethyl phenol (1.0 g, 6.18 mmol) in anhydrous pyridine (3 cm³) at 0° C was added trifluoromethanesulfonic anhydride (1.12 mL, 6.79 mmol) dropwise over 5 min.

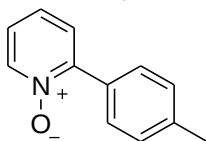
The clear colourless solution changed to a dark orange colour and was allowed to return slowly to room temperature. After 48 h the reaction was quenched with water, extracted into CH₂Cl₂ (5 x 15 cm³) and the organic phase washed with 1 M hydrochloric acid (20 cm³), water (20 cm³) and brine (10 cm³). The organic phase was dried over anhydrous magnesium sulphate, filtered and the solvent removed in vacuo to give a pale yellow liquid. After purification by flash chromatography, eluting with 10% ethyl acetate in pet ether, para-trifluoromethylphenyl triflate (1.50 g, 74% yield) was obtained as a clear colourless liquid.

General Direct Arylation Procedures:

Condition A: Pd(OAc)₂ (5 mol%), PCy₃·HBF₄ (10 mol%), rubidium carbonate powder (Rb₂CO₃, 2 equiv.), pivalic acid solid (PivOH, 0.4 equiv.) and azine *N*-oxide (1.1-2 equiv.) are weighed to air and placed inside a Radley test tube. The tube is then flushed with Argon and capped with a rubber septum. The whole setup is then evacuated under vacuum and refilled with Argon five times. In a solution of Toluene (0.15M), the aryl triflate (1 equiv.) is then added under a steady flow of argon. After addition, the cap is sealed with parafilm wax and reaction is immersed in an oil bath. Stirring is commenced and the heating source is turned on (set to 100°C). The reaction is left stirring for 12-18 hours (overnight), then allowed to cool, diluted with DCM and filtered over celite. The residues are then purified using silica gel chromatography.

Condition B: Pd(OAc)₂ (5 mol%), P^tBu₂Me·HBF₄ (10 mol%), potassium carbonate powder (K₂CO₃, 2 equiv.), pivalic acid solid (PivOH, 0.3 equiv.) and azine *N*-oxide (1.1-2 equiv.) are weighed to air and placed inside a Radley test tube. The tube is then flushed with Argon and capped with a rubber septum. The whole setup is then evacuated under vacuum and refilled with Argon five times. In a solution of Toluene (0.5M), the aryl triflate (1 equiv.) is then added under a steady flow of argon. After addition, the cap is sealed with parafilm wax and reaction is immersed in an oil bath. Stirring is commenced and the heating source is turned on (set to 110°C). The reaction is left stirring for 12-18 hours (overnight), then allowed to cool, diluted with DCM and filtered over celite. The residues are then purified using silica gel chromatography.

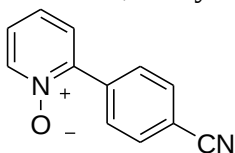
Table 2.1, Entries 1-4



This compound was obtained in 51-91% yield as a beige solid by following the general direct arylation procedure (Conditions A). Spectral data corresponds to that previously described in the literature.¹⁵⁹

¹⁵⁹ Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

Table 2.1, Entry 5



This compound was obtained in 49% yield as a white solid by following the general direct arylation procedure (Conditions A).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 7.30-7.34 (1H, m), 7.36 (1H, td, J=7.6Hz and 1.4Hz), 7.45 (1H, dd, J=7.7Hz and 2.2Hz), 7.78 (2H, d, J=8.4Hz), 7.96 (2H, d, J=8.4Hz), 8.35 (1H, dd, J=6.4Hz and 1.1Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 113.2, 118.4, 125.7, 125.8, 127.3, 130.0, 132.1, 136.9, 140.7;

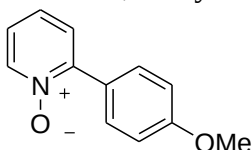
IR (ν_{max} /cm⁻¹): 2950, 2217, 1481, 1246, 835;

HRMS calculated for C₁₂H₈N₂O (M⁺) 196.0637; Found: 196.0659;

m.p. : 162-168 °C (DCM)

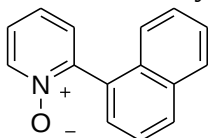
Rf: 0.32 (3:10:87 MeOH:Acetone:DCM)

Table 2.1, Entry 6



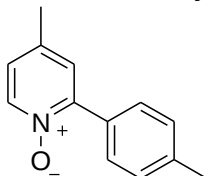
This compound was obtained in 75% yield as a light yellow solid by following the general direct arylation procedure (Conditions A). Spectral data corresponds to that previously described in the literature.¹⁵⁹

Table 2.1, Entry 7



This compound was obtained in 75% yield as a beige solid by following the general direct arylation procedure (Conditions A). Spectral data corresponds to that previously described in the literature.¹⁵⁹

Table 2.1, Entry 8



This compound was obtained in 71% yield as a light green solid by following the general direct arylation procedure (Conditions A).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.35 (3H, s), 2.39 (3H, s), 7.00 (1H, dd, J=6.6Hz and 2.1Hz), 7.20 (1H, d, J=2.5Hz), 7.26 (2H, d, J=7.9Hz), 7.70 (2H, d, J=8.2Hz), 8.20 (1H, d, J=6.6Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 20.3, 21.4, 125.1, 127.8, 128.9, 129.2, 129.8, 137.6, 139.6, 139.7, 148.5;

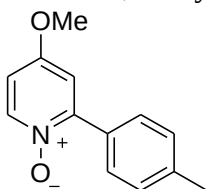
IR (ν_{max} /cm⁻¹): 2922, 1623, 1480, 1224, 784;

HRMS calculated for C₁₃H₁₃NO (M⁺) 199.0997; Found: 199.1012;

m.p. : N/A (pasty oil)

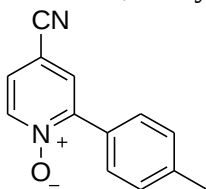
Rf: 0.35 (4:6:90, MeOH:Acetone:DCM)

Table 2.1, Entry 9



This compound was obtained in 39% yield as a green solid by following the general direct arylation procedure (Conditions A). Spectral data corresponds to that previously described in the literature.¹⁵⁹

Table 2.1, Entry 10



This compound was obtained in 38% yield as a light green solid by following the general direct arylation procedure (Conditions A).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.42 (3H, s), 7.30 (2H, d, J=8.0Hz), 7.41 (1H, dd, J=6.8Hz and 2.5Hz), 7.66 (3H, dd, J=5.5Hz and 2.7Hz), 8.31 (1H, d, J=6.8Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 21.5, 107.6, 116.1, 126.3, 127.7, 129.0, 129.3, 129.8, 141.0, 141.4, 150.6;

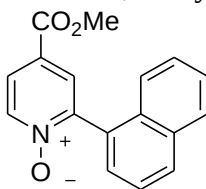
IR (ν_{max} /cm⁻¹): 3050, 2217, 1272, 896, 828;

HRMS calculated for C₁₃H₁₀N₂O (M⁺) 210.0793; Found: 210.0790;

m.p. : 192-194 °C (DCM)

Rf: 0.42 (5:95 Acetone:DCM)

Table 2.1, Entry 11



This compound was obtained in 59% yield as a yellow solid by following the general direct arylation procedure (Conditions A).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.91 (3H, s), 7.42-7.58 (5H, m), 7.90-7.98 (3H, m), 8.06 (1H, d, J=2.5Hz), 8.40 (1H, J=6.8Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 52.7, 125.0, 125.3, 125.3, 125.8, 126.4, 127.0, 127.9, 128.6, 129.0, 130.2, 130.5, 130.7, 133.4, 140.4, 149.9, 164.1;

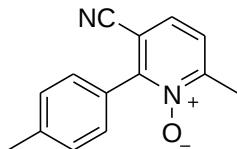
IR (ν_{max} /cm⁻¹): 2950, 1722, 1271, 1241, 770;

HRMS calculated for C₁₇H₁₃NO₃ (M⁺) 279.0895; Found: 279.0895;

m.p. : 138-140 °C (DCM)

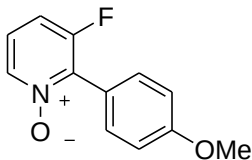
Rf: 0.32 (5:95 Acetone:DCM)

Table 2.1, Entry 12



This compound was obtained in 74% yield as an orange solid by following the general direct arylation procedure (Conditions B). Spectral data corresponds to that previously described in the literature.¹⁶⁰

Table 2.1, Entry 13



This compound was obtained in 90% yield as a tan solid by following the general direct arylation procedure (Conditions A).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.84 (3H, s), 7.02 (2H, dd, J=6.9Hz and 2.0Hz), 7.08-7.17 (2H, m), 7.61 (2H, dt, J=7.4Hz and 2.1Hz), 8.19 (1H, d, J=6.2Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): ¹³C NMR (100MHz, CDCl₃, 293K, TMS): 55.3, 113.4 (d, J=23.0Hz), 113.8, 118.4 (d, J=1.8Hz), 123.1 (d, J=10.5Hz), 131.7 (d, J=2.4Hz), 136.7 (d, J=3.6Hz), 140.4 (d, J=24.5), 158.3 (d, J=250.5), 160.7;

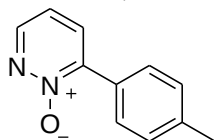
IR (ν_{max} /cm⁻¹): 2966, 1432, 1227, 1024, 842;

HRMS calculated for C₁₂H₁₀FNO₂ (M⁺) 219.0696; Found: 219.0700;

m.p. : 132-134 °C (DCM)

Rf: 0.32 (2:6:92 MeOH:Acetone:DCM)

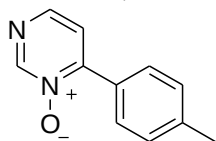
Table 2.1, Entries 14 and 15



This compound was obtained in 51-100% yield as a beige solid by following the general direct arylation procedure (Conditions B). Spectral data corresponds to that previously described in the literature.¹⁶¹

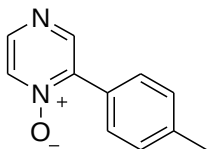
¹⁶⁰ Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, 65, 3155.

Table 2.1, Entries 16 and 17



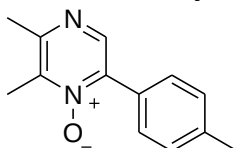
This compound was obtained in 20% yield as a brown solid by following the general direct arylation procedure (Conditions B). Spectral data corresponds to that previously described in the literature.¹⁶¹

Table 2.1, Entry 18



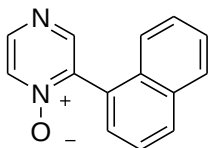
This compound was obtained in 80% yield as a tan solid by following the general direct arylation procedure (Conditions A). Spectral data corresponds to that previously described in the literature.¹⁶¹

Table 2.1, Entry 19



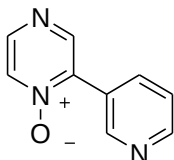
This compound was obtained in 99% yield as a light yellow solid by following the general direct arylation procedure (Conditions B). Spectral data corresponds to that previously described in the literature.¹⁶²

Table 2.1, Entry 20



This compound was obtained in 60% yield as a tan paste by following the general direct arylation procedure (Conditions A). Spectral data corresponds to that previously described in the literature.¹⁶¹

Table 2.1, Entry 21



¹⁶¹ Leclerc, J.-P.; Fagnou, K. *Angew. Chem Int. Ed.* **2006**, 45, 7781.

¹⁶² Campeau, L.-C.; Schipper, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, 130, 3266.

This compound was obtained in 43% yield as a white solid by following the general direct arylation procedure (Conditions A).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 7.47 (1H, ddd, J=8.0Hz, 4.9Hz, and 0.8Hz), 8.24 (1H, dd, J=4.1Hz and 0.6Hz), 8.30 (1H, dt, J=8.0Hz and 2.0Hz), 8.46 (1H, d, J=4.1Hz), 8.68 (1H, s), 8.74 (1H, dd, J=4.8Hz and 1.6Hz), 9.0 (1H, dd, J=2.3Hz and 0.6Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 123.2, 125.4, 134.5, 136.8, 142.0, 146.6, 148.0, 149.4, 151.3;

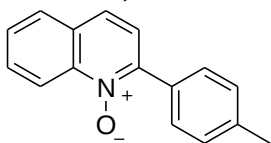
IR (ν_{max}/cm⁻¹): 3175, 1287, 1005, 813, 703;

HRMS calculated for C₉H₇N₃O (M⁺) 173.0589; Found: 173.0574;

m.p. : 188-189 °C (DCM)

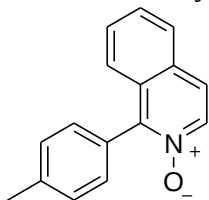
Rf: 0.23 (3:15:82 MeOH:Acetone:DCM)

Table 2.1, Entries 22 and 23



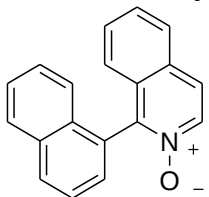
This compound was obtained in 68-81% yield as a tan solid by following the general direct arylation procedure (Conditions A or B). Spectral data corresponds to that previously described in the literature.¹⁶¹

Table 2.1, Entry 24



This compound was obtained in 69-82% yield as a brown solid by following the general direct arylation procedure. Spectral data corresponds to that previously described in the literature (Conditions A).¹⁶³

Table 2.1, Entry 25



This compound was obtained in 27% yield as a beige solid by following the general direct arylation procedure (Conditions A).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 7.20 (1H, d, J=8.5Hz), 7.27 (1H, d, J=8.4Hz), 7.38 (2H, t, J=7.5Hz), 7.48-7.55 (3H, m), 7.66 (1H, t, J=7.6Hz), 7.77 (1H, d, J=7.2Hz),

¹⁶³ Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

7.84 (1H, d, J=8.2Hz), 7.96 (1H, d, J=8.2Hz), 8.04 (1H, d, J=8.3Hz), 8.36 (1H, d, J=7.2Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 123.7, 125.1, 125.5, 125.6, 126.4, 126.8, 127.0, 128.3, 128.4, 128.7, 128.8, 128.9, 129.2, 130.0, 130.3, 131.3, 133.8, 137.5, 145.5;

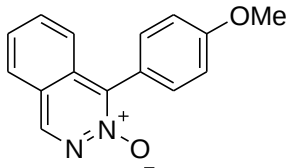
IR (ν_{max} /cm⁻¹): 3058, 1320, 1224, 945, 777;

HRMS calculated for C₁₉H₁₃NO (M⁺) 271.0997; Found: 271.0992;

m.p. : 160-162 °C (DCM)

Rf: 0.30 (2:6:92 MeOH:Acetone:DCM)

Table 2.1, Entry 26



This compound was obtained in 85% yield as a tan solid by following the general direct arylation procedure (Conditions B).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.91 (3H, s), 7.11 (2H, dd, J=6.7Hz and 2.1Hz), 7.53-7.57 (3H, m), 7.63-7.67 (1H, m), 7.69-7.74 (1H, m), 7.93 (1H, d, J=7.7Hz), 9.07 (1H, s);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 55.4, 114.4, 121.3, 121.6, 124.6, 127.2, 128.7, 131.7, 132.9, 133.5, 151.5, 160.6, 1 overlapping signal as one peak is missing even with prolonged scans;

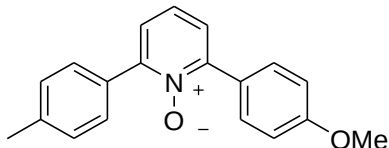
IR (ν_{max} /cm⁻¹): 3428, 1609, 1352, 1249, 829;

HRMS calculated for C₁₅H₁₂N₂O₂ (M⁺) 252.0899; Found: 252.0905;

m.p. : decomp. 216 °C (DCM), liquefies at 262 °C

Rf: 0.37 (2:10:88 MeOH:Acetone:DCM)

Scheme 2.5 (Compound 2.4)



This compound was obtained in 68-84% yield as a tan solid by following the general direct arylation procedure (Conditions B).

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.40 (3H, s), 3.85 (3H, s), 6.98 (2H, dd, J=6.8Hz and 2.1Hz), 7.26-7.30 (3H, m), 7.33-7.38 (2H, m), 7.74 (2H, dd, J=6.5Hz and 1.7Hz), 7.84 (2H, dd, J=6.8Hz and 2.1Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 21.4, 55.3, 113.4, 124.9, 125.4, 125.5, 125.6, 128.7, 129.4, 130.6, 131.1, 139.3, 149.5, 149.9, 160.3;

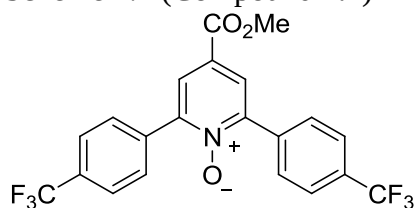
IR (ν_{max} /cm⁻¹): 2933, 1609, 1476, 1180, 782;

HRMS calculated for C₁₉H₁₇NO₂ (M⁺) 291.1259; Found: 291.1286;

m.p. : 170-173 °C (DCM)

Rf: 0.45 (10:90 EtOAc:DCM)

Scheme 2.7 (Compound 2.7)



This compound was obtained in 76% yield as a yellow solid by following conditions B with the exception of using 2 equiv of the triflate and 1 equiv of the N-oxide.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.98 (3H, s), 7.76 (4H, d, J=8.2 Hz), 7.95 (4H, d, J=8.1 Hz), 8.08 (2H, s);

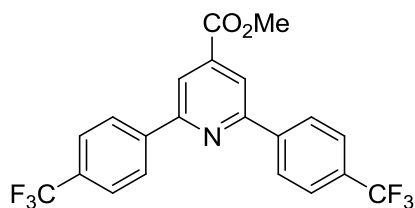
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 53.0, 123.8 (q, J=272.4 Hz), 125.4 (q, J=3.7 Hz), 125.9, 130.0, 131.8 (q, J=32.7 Hz), 135.7, 149.1, 164.0;

IR (ν_{max}/cm⁻¹): 2957, 1726, 1620, 1562, 1325, 1251, 1169, 1125, 1067, 846, 818, 764;

HRMS calculated for C₂₁H₁₃F₆NO₃ (M⁺) 441.0800; Found: 441.0776;

m.p. : 152-153 °C (CHCl₃)

Rf: 0.66 (CH₂Cl₂)



A solution of 4-(methoxycarbonyl)-2,6-bis(4-(trifluoromethyl)-phenyl)pyridine 1-oxide (148 mg, 0.335 mmol, 1 equiv) and zinc dust (99 mg, 1.509 mmol, 4.5 equiv) in THF:NH₄Cl satd 1:1 (3.5 ml) is stirred at room temperature overnight. The reaction is diluted with ether, dried over MgSO₄, and filtered over Celite. The crude product is purified by column chromatography (10–15% ether/pet. ether) to give a white solid in 87% yield.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 4.05 (3H, s), 7.79 (4H, d, J=8.2 Hz), 8.31 (4H, d, J=8.1 Hz), 8.34 (2H, s);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 53.0, 119.0, 124.10 (q, J=272.2 Hz), 125.83 (q, J=3.7 Hz), 131.51 (q, J=32.6 Hz), 139.7, 141.5, 156.6, 165.4;

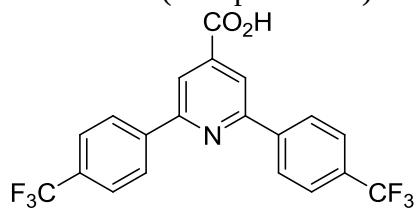
IR (ν_{max}/cm⁻¹): 2957, 1730, 1563, 1325, 1254, 1123, 1067, 847;

HRMS calculated for C₂₁H₁₃F₆NO₂ (M⁺) 425.0850; Found: 425.0835;

m.p. : 143-145 °C (CHCl₃)

Rf: 0.33 (10% ether/pet. ether)

Scheme 2.7 (Compound 2.8)



A solution of methyl 2,6-bis(4-(trifluoromethyl)phenyl)isonicotinate (75 mg, 0.176 mmol, 1 equiv) and lithium hydroxide (37 mg, 0.882 mmol, 5 equiv) in MeOH (1 ml) is

stirred at room temperature overnight. The reaction is diluted with water and the methanol is removed under reduced pressure. The solution is acidified with 10% HCl and extracted with EtOAc (3x20 ml). The combined organic extracts were dried over MgSO₄. The crude product is purified by flash chromatography (5% MeOH, 7% acetone, CHCl₃) to afford a white solid in 84% yield.

¹H NMR (400MHz, (CD₃)₂CO, 293K, TMS): 4.05 (3H, s), 7.84 (4H, d, J=7.3 Hz), 8.45 (4H, d, J=7.3 Hz), 8.46 (2H, s);

¹³C NMR (100MHz, (CD₃)₂CO, 293K, TMS): 119.4, 124.5 (q, J=271.4 Hz), 125.7 (q, J=7.3 Hz), 127.7, 130.7 (q, J=32.1 Hz), 142.0, 156.0, 165.9;

IR (ν_{max}/cm⁻¹): 3088, 2940, 1709, 1327, 1167, 1123, 1068, 1017, 847;

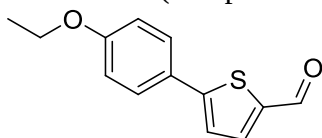
HRMS calculated for C₂₀H₁₁F₆NO₂ (M⁺) 411.0694; Found: 411.0683;

m.p. : 274-277 °C (CHCl₃)

Rf: 0.53 (5% MeOH/7% Me₂CO/CHCl₃)

8.3 Direct Arylation as a Synthetic Tool for the Synthesis of Organic Electronic Materials

Scheme 3.3 (compound **3.11**)

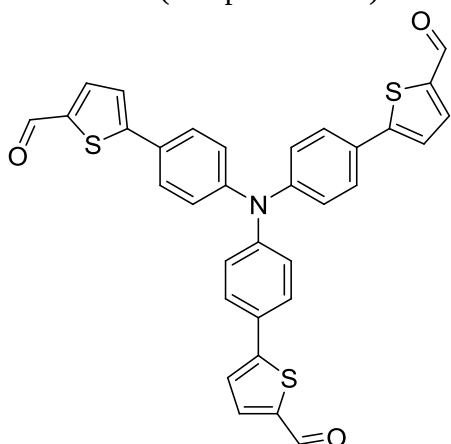


K₂CO₃ (1.5 equiv), Pd(OAc)₂ (2 mol %), PCy₃·HBF₄ (4 mol %), and PivOH (30 mol %) were weighed to air and placed in a 50 mL round bottomed pressure vessel equipped with a magnetic stir bar. The tube was purged with argon, and toluene (20 mL, 0.3 M), 2-thiophenecarboxaldehyde (2 equiv) and 1-bromo-4-ethoxybenzene (6 mmol) were then added. The reaction mixture was then vigorously stirred at 110 °C for 16 hours. The solution was then cooled to rt, diluted with CH₂Cl₂ and H₂O. The aqueous phase was extracted with CH₂Cl₂ (3X). The organics were combined and dried over MgSO₄, filtered, and evaporated under reduced pressure. Excess 2-thiophenecarboxaldehyde was then removed using Kugelrohr distillation to give **3.11** in 99% yield (1.35 g). Spectral data corresponded to that previously described in the literature.¹⁶⁴ Alternatively the reaction was also carried out in a similar manner to **3.15** and gave an 84% yield.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.44 (3H, t, J=7.0Hz), 4.08 (2H, q, J=7.0Hz), 6.94 (2H, d, J=8.9Hz), 7.29 (1H, J=4.0Hz), 7.60 (2H, d, J=8.9Hz), 7.71 (1H, d, J=4.0Hz), 9.86 (1H, s).

¹⁶⁴ Park, S. W.; Son, K.-I.; Ko, M. J.; Kim, K.; Park, N.-G.; *Synth. Met.*, **2009**, 159, 2571.

Scheme 3.4 (compound **3.12**)

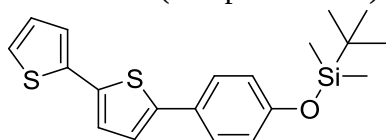


K_2CO_3 (1.5 equiv), $\text{Pd}(\text{OAc})_2$ (6 mol %), $\text{PCy}_3 \cdot \text{HBF}_4$ (12 mol %), PivOH (30 mol %) and $\text{tris}(4\text{-bromophenyl})\text{amine}$ (0.3 mmol) were weighed to air and placed in a screw-capped vial equipped with a magnetic stir bar. The vial was purged with argon then toluene (1.3 mL) and 2-thiophenecarboxaldehyde (6 equiv) were then added. The reaction mixture was then vigorously stirred at 100 °C for 16 hours. The solution was then cooled to rt, diluted with CH_2Cl_2 and H_2O . The aqueous phase was extracted with CH_2Cl_2 (3X). The organics were combined and dried over MgSO_4 , filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **3.12** in 89% yield. Spectral data corresponded to that previously described in the literature.¹⁶⁵

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 7.19 (6H, d, $J=8.7\text{Hz}$), 7.36 (3H, d, $J=4.0\text{Hz}$), 7.61 (6H, d, $J=8.7\text{Hz}$), 7.74 (3H, d, $J=4.0\text{Hz}$), 9.89 (3H, s);

^{13}C NMR (100MHz, CDCl_3 , 293K, CHCl_3): 123.6, 124.6, 127.6, 128.4, 137.6, 142.0, 147.5, 153.6, 182.7.

Scheme 3.5 (compound **3.13**)



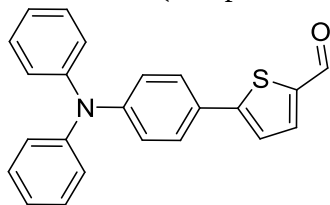
K_2CO_3 (1.5 equiv), $\text{Pd}(\text{OAc})_2$ (2 mol %), $\text{PCy}_3 \cdot \text{HBF}_4$ (4 mol %), PivOH (30 mol %) and 2,2'-bithiophene (5 equiv to avoid diarylation) were weighed to air and placed in a screw-capped vial equipped with a magnetic stir bar. The vial was purged with argon then toluene (1 mL, 0.3 M) and (4-bromophenoxy)(*tert*-butyl)dimethylsilane (0.3 mmol) were then added. The reaction mixture was then vigorously stirred at 100 °C for 16 hours. The solution was then cooled to rt, diluted with CH_2Cl_2 and H_2O . The aqueous phase was extracted with CH_2Cl_2 (3X). The organics were combined and dried over MgSO_4 , filtered, and evaporated under reduced pressure. The crude product was purified by silica

¹⁶⁵ Roquet, S.; Cravino, A.; Leriche, P.; Aleveque, O.; Frere, P.; Roncali, J. *J. Am. Chem. Soc.* **2006**, 128, 3459.

gel column chromatography to afford **3.13** in 52% yield. Spectral data corresponded to that previously described in the literature.¹⁶⁶

¹H NMR (400MHz, CDCl₃, 293K, TMS): 0.22 (s, 6H), 1.00 (s, 9H), 6.85 (2H, d, J=8.7Hz), 7.02 (1H, dd, J=5.1, 3.6Hz), 7.10 (1H, d, J=3.8Hz), 7.12 (1H, d, J=3.8Hz), 7.17 (1H, dd, J=3.6, 1.1Hz), 7.20 (1H, dd, J=5.1, 1.1Hz) 7.46 (2H, d, J=8.7Hz).

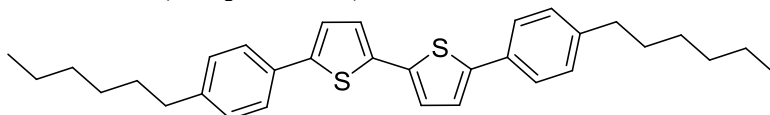
Scheme 3.6 (compound **3.15**)



K₂CO₃ (1.5 equiv), Pd(OAc)₂ (2 mol %), PCy₃·HBF₄ (4 mol %), PivOH (30 mol %) and 4-bromo-N,N-diphenylaniline (0.5 mmol) were weighed to air and placed in a screw-capped vial equipped with a magnetic stir bar. The vial was purged with argon then toluene (1.7 mL, 0.3 M) and 2-thiophenecarboxaldehyde (2 equiv) were then added. The reaction mixture was then vigorously stirred at 100 °C for 16 hours. The solution was then cooled to rt, diluted with CH₂Cl₂ and H₂O. The aqueous phase was extracted with CH₂Cl₂ (3X). The organics were combined and dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **3.15** in 91% yield. Spectral data corresponded to that previously described in the literature.¹⁶⁷

¹H NMR (400MHz, CDCl₃, 293K, TMS): 7.03-7.16 (8H, m), 7.26-7.32 (5H, m), 7.51 (2H, d, J=8.8Hz), 7.70 (1H, d, J=4.0Hz), 9.85 (1H, s).

Scheme 3.7 (compound **3.6**)



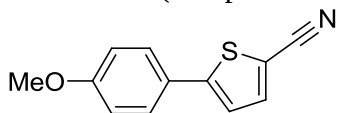
K₂CO₃ (1.5 equiv), Pd(OAc)₂ (2 mol %), PCy₃·HBF₄ (4 mol %), PivOH (30 mol %) and 2,2'-bithiophene (0.3 mmol) were weighed to air and placed in a screw-capped vial equipped with a magnetic stir bar. The vial was purged with argon then dimethylacetamide (1 mL, 0.3 M) and 1-bromo-4-hexylbenzene (2 equiv) were then added. The reaction mixture was then vigorously stirred at 100 °C for 16 hours. The solution was then cooled to rt, diluted with CH₂Cl₂ and H₂O. The aqueous phase was extracted with CH₂Cl₂ (3X). The organics were combined and dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **3.6** in 87% yield. Spectral data corresponded to that previously described in the literature.¹⁶⁸

¹⁶⁶ Nesterov, E. E.; Skoch, J.; Hyman, B. T.; Klunk, W. E.; Bacsikai, B. J.; Swager, T. M. *Angew. Chem. Int. Ed.* **2005**, 44, 5452.

¹⁶⁷ Hagberg, D. P.; Marinado, T.; Karlsson, K. M.; Nonomura, K.; Qin, P.; Boschloo, G.; Brinck, T.; Hagfeldt, A.; Sun, L. *J. Org. Chem.* **2007**, 72, 9550.

¹⁶⁸ Mushrush, M.; Facchetti, A.; Lefenfeld, M.; Katz, H. E.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, 125, 9414.

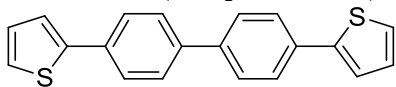
Scheme 3.8 (compound **3.17**)



K_2CO_3 (1.5 equiv, 0.75 mmol, 103.7 mg), $\text{Pd}(\text{OAc})_2$ (2 mol %, 0.01 mmol, 2.2 mg), $\text{PCy}_3 \cdot \text{HBF}_4$ (4 mol %, 0.02 mmol, 7.4 mg) and pivalic acid (30 mol %, 0.15 mmol, 15.3 mg) were weighed to air and placed in a screw-capped vial equipped with a magnetic stir bar. The vial was purged with argon then toluene (1.7 mL, 0.3 M), 2-thiophenecarbonitrile (2 equiv, 1 mmol, 93 μL) and 4-bromoanisole (1 equiv, 0.5 mmol, 62 μL) were then added. The reaction mixture was then vigorously stirred at 100 °C for 16 hours. The solution was then cooled to rt, diluted with CH_2Cl_2 and H_2O . The aqueous phase was extracted with CH_2Cl_2 (3X). The organics were combined and dried over MgSO_4 , filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **17** in 97% yield (104.9 mg). Spectral data corresponded to that previously described in the literature.¹⁶⁹

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 3.85 (3H, s), 6.95 (2H, d, $J=8.9\text{Hz}$), 7.16 (1H, d, $J=3.9\text{Hz}$), 7.53 (2H, d, $J=8.9\text{Hz}$), 7.56 (1H, d, $J=3.9\text{Hz}$).

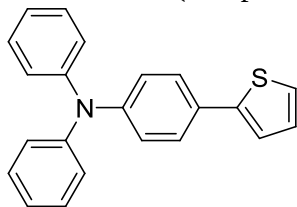
Scheme 3.9 (compound **3.19**)



K_2CO_3 (1.5 equiv, 3 mmol, 414.6 mg), $\text{Pd}(\text{OAc})_2$ (6 mol %, 0.12 mmol, 26.9 mg), $\text{PCy}_3 \cdot \text{HBF}_4$ (12 mol %, 0.24 mmol, 88.4 mg), pivalic acid (30 mol %, 0.6 mmol, 61.3 mg) and 4,4'-dibromobiphenyl (1 equiv, 2 mmol, 624.0 mg) were weighed to air and placed in a round bottomed pressure vessel equipped with a magnetic stir bar. The tube was purged with argon, and toluene (6.7 mL, 0.3 M) and thiophene (6 equiv, 12 mmol, 960 μL) were then added. The reaction mixture was then vigorously stirred at 110 °C for 48 hours. The solution was then cooled to rt and diluted with CH_2Cl_2 and 2M HCl. The aqueous phase was extracted with CH_2Cl_2 (3X). The organics were combined and dried over MgSO_4 , filtered while hot, and evaporated under reduced pressure. The crude product was purified by recrystallization from toluene afford **19** in 66% yield (421.5 mg). Spectral data corresponded to that previously described in the literature.¹⁷⁰

^1H NMR (400MHz, Pyridine d_5 , 293K, Pyridine- H): 7.05 (2H, dd, $J=5.1, 3.6\text{Hz}$), 7.36 (2H, dd, $J=5.1, 1.1\text{Hz}$), 7.44 (2H, dd, $J=3.6\text{Hz}, 1.1\text{Hz}$), 7.64 (4H, d, $J=8.6\text{Hz}$), 7.71 (4H, d, $J=8.5\text{Hz}$).

Scheme 3.10 (compound **3.20**)



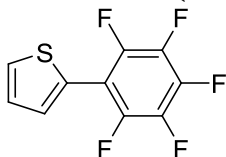
¹⁶⁹ Huang, Y.; Luo, Z.; Cheng, X.; Tschierske, C. *Liq. Cryst.* **2009**, 36, 61.

¹⁷⁰ Estrada, L. A.; Montes, V. A.; Zyryanov, G.; Anzenbacher, P., Jr. *J. Phys. Chem. B.* **2007**, 111, 6983.

K₂CO₃ (1.5 equiv, 0.75 mmol, 103.7 mg), Pd(OAc)₂ (2 mol %, 0.01 mmol, 2.2 mg), PCy₃·HBF₄ (4 mol %, 0.02 mmol, 7.4 mg), pivalic acid (30 mol %, 0.15 mmol, 15.3 mg) and 4-bromo-*N,N*-diphenylaniline (0.5 mmol, 162.1 mg) were weighed to air and placed in a screw-capped vial equipped with a magnetic stir bar. The vial was purged with argon then toluene (1.7 mL, 0.3 M) and thiophene (5 equiv, 2.5 mmol, 180 µL) were then added. The reaction mixture was then vigorously stirred at 100 °C for 16 hours. The solution was then cooled to rt, diluted with CH₂Cl₂ and H₂O. The aqueous phase was extracted with CH₂Cl₂ (3X). The organics were combined and dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **20** in 86% yield (141.1 mg). Spectral data corresponded to that previously described in the literature.¹⁷¹

¹H NMR (400MHz, CDCl₃, 293K, TMS): 6.99-7.14 (9H, m), 7.20-7.29 (6H, m), 7.47 (2H, d, J=8.5Hz).

Scheme 3.11 (compound **3.21**)



K₂CO₃ (1.5 equiv, 3 mmol, 414.6 mg), Pd(OAc)₂ (2 mol %, 0.04 mmol, 9.0 mg), PCy₃·HBF₄ (4 mol %, 0.08 mmol, 29.5 mg) and pivalic acid (30 mol %, 0.6 mmol, 61.3 mg) were weighed to air and placed in a round bottomed pressure vessel equipped with a magnetic stir bar. The tube was purged with argon, and toluene (6.7 mL, 0.3 M) pentafluorobenzene (2 equiv, 4 mmol, 444 µL) and 2-bromothiophene (1 equiv, 2 mmol, 194 µL) were then added. The reaction mixture was then vigorously stirred at 100 °C for 16 hours. The solution was then cooled to rt and diluted with CH₂Cl₂ and filtered over celite. The filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to afford **21** in 86% yield (430 mg). Spectral data corresponded to that previously described in the literature.¹⁷²

¹H NMR (400MHz, CDCl₃, 293K, TMS): 7.17-7.21 (1H, m), 7.51-7.54 (1H, m), 7.55 (1H, dd, J=5.2, 1.1Hz)

8.4 Site Selective *sp*² and *sp*³ Palladium-Catalyzed Direct Arylation

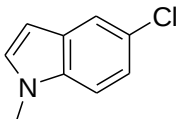
General Methods:

Picoline *N*-oxide was purchased from Aldrich and used without further purification. Reagent grade dichloromethan and HPLC grade toluene were used without further purification. Palladium sources and ligands were purchased from Strem and stored in a dessicator and were weighed out to air unless otherwise specified. All other reagents and solvents were used as is from commercial sources. All reactions were performed in air-dried glassware. Coupling reactions were performed with regard for

¹⁷¹ Li, W.; Du, C.; Li, F.; Zhou, Y.; Fahlman, M.; Bo, Z.; Zhang, F. *Chem. Mater.* **2009**, *21*, 5327.

¹⁷² Facchetti, A.; Yoon, M.-H.; Stern, C. L.; Katz, H. E.; Marks, T. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 3900.

exclusion of ambient air. Microwave heating was performed using a CEM Discover Microwave (specific reaction conditions are described below). Analysis of crude reaction mixture was done using TLC or NMR. Reactions were purified by flash chromatography on silica gel.



5-Chloroindole (755mg, 1 equiv.) and crushed KOH (1.12g, 4 equiv.) were placed in a round bottom flask equipped with a magnetic stir bar. DMSO was added (17mL, 0.5M) and the reaction was left stirring at room temperature for 120 minutes. Methyl iodide was then added in one portion (710mg, 1 equiv.) and the reaction was left stirring at room temperature for 8 hours. The reaction mixture was then diluted with NH₄Cl and extracted with Et₂O:EtOAc (1:1). The organics were washed with H₂O and Brine and re-extracted with Et₂O and the organic residue was dried over MgSO₄ and evaporated under reduced pressure. The product was purified by silica gel column chromatography using 10% Ether in Hexanes to afford the compound in 79% yield as a yellow oil.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.77 (3H, s), 6.41 (1H, dd, J=3.1, 0.6Hz), 7.06 (1H, d, J=3.1Hz), 7.16 (1H, dd, J=8.7, 2.0Hz), 7.22 (1H, d, J=8.7Hz), 7.58 (1H, d, J=1.9Hz)

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 33.0, 100.6, 110.2, 120.2, 121.8, 125.1, 129.4, 130.1, 135.1

IR (ν_{max} /cm⁻¹): 2942, 1512, 1476, 1277, 1062, 751

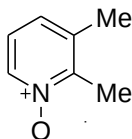
HRMS calculated for C₉H₈ClN (M⁺) 165.0345 Found: 165.0345;

Rf: 0.35 (10%Et₂O, 90% Hexanes)

Oxidation Procedure: All *N*-oxides were prepared using an adapted methyltrioxorhenium oxidation protocol first reported by Sharpless and co-workers.¹⁷³ The azine is dissolved in reagent grade CH₂Cl₂ (2.5M). This mixture is added MeReO₃ (1-4mol%) which usually results in a significant color change to deep yellow. This solution is then capped with a rubber septa which is pierced with a small needle as a vent and placed in an ice bath. To the cold solution is added dropwise a 50w% aqueous solution of H₂O₂ (2 equiv.). Once all peroxyde has been added, the reaction is allowed to warm to room temperature where it is stirred for 12-24h. After consumption of starting material, a small amount of MnO₂ (5-10mg) is added to destroy unreacted peroxide. After stirring this solution of 1-2 hours (until bubbling stops) the mixture is poured into an extraction funnel where the phases are separated. The aqueous phase is washed with two volumes of CH₂Cl₂ and the organic are combined, dried with MgSO₄, filtered and concentrated under reduced pressure. The *N*-oxides were then purified via silica gel column chromatography using 5%MeOH/CH₂Cl₂ as the eluent to afford the corresponding *N*-oxide in 60-90% yield.

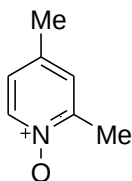
¹⁷³ Coperet, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, B. *J. Org. Chem.* **1998**, 63, 1740.

!!Caution: Pyridine *N*-oxides have been shown to exothermically decompose at very high temperature.¹⁷⁴ Uncontrolled heating of the reaction media should be avoided!!



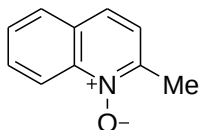
Obtained in 80% yield as a white solid.

Commercially available: CAS# 22710-07-2



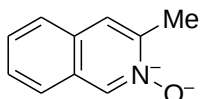
Obtained in 86% yield as a clear oil.

Commercially available: CAS# 1122-45-8



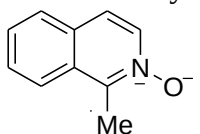
Obtained in 61% yield as an orange solid.

Previously reported: Bjorsvik, H.-R.; Gambarotti, C.; Jensen, V. R.; Gonzales, R. R.; *J. Org. Chem.* **2005**, 70, 3218



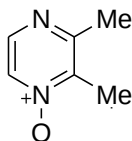
Obtained in 90% yield as a white solid.

Commercially available: CAS# 14548-00-6



Obtained in 86% yield as a yellow solid.

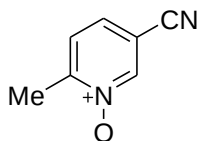
Commercially available: CAS# 14548-00-6



Obtained in 85% yield as a white solid.

¹⁷⁴ Examples of exothermic onset temperatures (*T*_o) for pyridine *N*-oxide, 288 °C; 2,6-lutidine *N*-oxide, 288 °C; nicotinic acid *N*-oxide, 302 °C; γ -picoline *N*-oxide, 285 °C; picolinic acid *N*-oxide, 307 °C, from: Ando, T.; Fujimoto, Y.; Morisaki, S. *J. Haz. Mater.* **1991**, 28, 251.

Previously reported: Leclerc, J.-P.; Fagnou, K.; *Angew. Chem. Int. Ed.* **2006**, 45, 7781



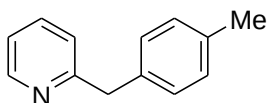
¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.58 (3H, s), 7.42 (2H, s, br), 8.51 (1H, s);
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 18.2, 110.4, 114.3, 127.0, 127.1, 141.6, 154.3;

IR (ν_{max} /cm⁻¹): 3117, 2249, 1271, 1005, 831;

HRMS calculated for C₇H₆N₂O₁ (M⁺) 134.0480; Found: 134.04730;

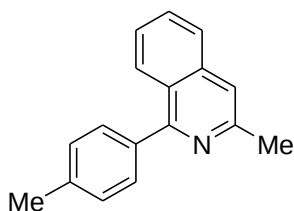
m.p. (CH₂Cl₂): 136-138 °C

Reduction Procedure: All *N*-oxide reductions were carried out using a procedure described by Ohta and co-workers.¹⁷⁵



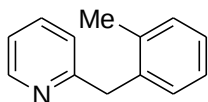
Obtained in 99% yield as a colorless oil.

Previously reported: Agai, B.; Prosenyak, A.; Tarkanyi, G.; Vida, L.; Faigl, F.; *Eur. J. Org. Chem.* **2004**, 3623.



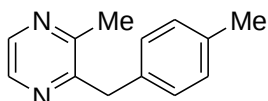
Obtained in 99% yield as a white solid.

Previously reported: Huang, Y.-T.; Chuang, T.-H.; Shu, Y.-L.; Kuo, Y.-C.; Wu, P.-L.; Yang, C.-H.; Sun, I.-W.; *Organometallics*, **2005**, 24, 6230.



Obtained in 95% yield as a colorless oil.

Previously reported: Niwa, T.; Yorimitsu, H.; Oshima, K.; *Angew. Chem. Int. Ed.* **2007**, 46, 2643.



Obtained in 80% yield as a colorless oil.

¹⁷⁵ Aoyagi, Y.; Tomomitsu, A.; Ohta, A. *Synthesis*. **1997**, 8, 891.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.24 (3H, s), 2.29 (3H, s), 4.14 (2H, s), 7.04-7.29 (4H, m), 7.39 (1H, dd, J=7.5Hz and 0.8Hz) 8.41 (1H, dd, J=4.8Hz, and 0.9 Hz)s

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 19.0, 21.0, 41.8, 121.6, 128.6, 129.1, 131.7, 135.6, 135.9, 138.0, 146.8, 159.1

IR (ν_{max} /cm⁻¹): 2922, 1573, 1513, 1449, 1106

HRMS calculated for C₁₃H₁₄N₂ (M⁺) 198.1157; Found: 199.1218;

Rf: 0.16 (20%Et₂O, 80% Pet. Ether)

sp³ Direct Arylation Procedures:

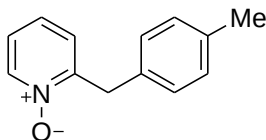
Procedure A : Using Microwave Irridiation

All reactions were performed on 0.6 mmol scale: Pd₂dba₃ (0.025 equiv.), X-Phos (0.05 equiv.), NaO^tBu (3 equiv.), and azine *N*-oxide (1.5 equiv.) are weighed to air and placed in a microwave tube with a magnetic stir bar (if the aryl halide is a solid, it is also added). The flask is capped with a rubber septa and purged with argon. The aryl halide (1 equiv.) is then added via syringe followed by degassed (with Argon) ACS grade toluene (0.5-1.0M). The rubber septa is then replace by a microwave tube cap and the mixture is then placed in the a CEM Discover microwave reactor at 110°C for 30-45 minutes (conditions: max. power: 200W; T°: 110°C; max. pressure: 250 psi). The reaction is then diluted with 50mL of DCM and filtered through celite then evaporated under reduced pressure. The residue is then loaded onto a silica gel column for chromatography typically using DCM/Acetone/MeOH mixtures.

Procedure B: Using Conventional Heating

All reactions were performed on 0.6 mmol scale: Pd₂dba₃ (0.025 equiv.), S-Phos or Ru-Phos (0.1 equiv.), NaO^tBu (3 equiv.), and Azine *N*-oxide (2 equiv.) are weighed to air and placed in a test-tube with a magnetic stir bar (if the aryl halide is a solid, it is also added). The flask is capped with a rubber septa and purged with argon. The aryl halide (1 equiv.) is then added via syringe followed by degassed (with Argon) ACS grade toluene (0.3M). The mixture is then placed in an oil bath and the heat source is set to 69°C. Reactions were left stirring at this temprature for 12-15hours (overnight, reaction times were not optimized). The reaction is then diluted with 50mL of DCM and filtered through celite then evaporated under reduced pressure. The residu is then loaded onto a silica gel column for chromatography typically using DCM/Acetone/MeOH mixtures.

Table 4.2, Entry 1-6



Obtained in 89% yield as a yellow oil.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.35 (3H, s), 4.22 (2H, s), 6.92-6.95 (1H, m), 7.10-7.17 (6H, m), 8.28-8.30 (1H, m);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 21.1, 36.1, 123.4, 125.5, 125.7, 129.6, 129.6, 133.1, 136.7, 139.4, 152.3.

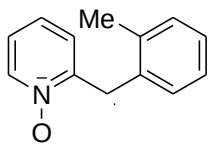
IR (ν_{max} / cm^{-1}): 2922, 1436, 1245, 766

HRMS calculated for $\text{C}_{13}\text{H}_{13}\text{NO}$ (M^+) 199.0997; Found: 199.1010;

M.P.: 47-49 °C (Chloroform)

Rf: 0.18 (1%MeOH, 15% Me_2CO , DCM)

Table 4.2, Entry 7



Obtained in 92% yield as a yellow oil.

^1H NMR (300MHz, CDCl_3 , 293K, TMS): 2.20 (3H, s), 4.25 (2H, s), 6.71 (1H, d, $J=7.5\text{Hz}$), 7.10-7.25 (6H, m), 8.33 (1H, d, $J=6.0\text{Hz}$)

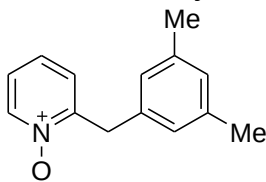
^{13}C NMR (75MHz, CDCl_3 , 293K, TMS): 19.3, 34.4, 123.4, 125.0, 125.6, 126.5, 127.5, 130.6, 134.4, 137.2, 139.4, 151.3. There is an overlapping peak.

IR (ν_{max} / cm^{-1}): 3019, 1489, 1435, 1244, 745

HRMS calculated for $\text{C}_{13}\text{H}_{13}\text{NO}$ (M^+) 199.0997; Found: 199.0987;

Rf: 0.22 (1%MeOH, 20% Me_2CO , DCM)

Table 4.2, Entry 8



Obtained in 93% yield as a yellow oil.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 2.30 (6H, s), 4.20 (2H, s), 6.88-7.14 (6H, m), 8.28 (1H, s)

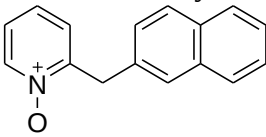
^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 21.3, 36.3, 123.4, 125.8, 127.5, 128.7, 136.1, 138.4, 139.5, 152.4 There is an overlapping peak

IR (ν_{max} / cm^{-1}): 2923, 1604, 1487, 1435, 1239, 848

HRMS calculated for $\text{C}_{14}\text{H}_{15}\text{NO}$ (M^+) 213.1154; Found: 213.1175;

Rf: 0.17 (1%MeOH, 20% Me_2CO , DCM)

Table 4.2, Entry 9



Obtained in 72% yield as a yellow oil.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 4.44 (2H, s), 6.95 (1H, d, $J=7.1\text{Hz}$), 7.05-7.17 (2H, m), 7.38 (1H, d, $J=8.4\text{Hz}$), 7.44-7.50 (2H, m), 7.74 (1H, s), 7.79-7.84 (3H, m), 8.30 (1H, s)

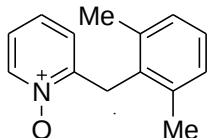
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 123.5, 125.6, 125.9, 126.3, 127.6, 127.7, 127.8, 128.4, 128.6, 128.8, 132.5, 133.6, 133.8, 139.5,

IR (ν_{max} /cm⁻¹):3054, 2927, 1487, 1434, 1241

HRMS calculated for C₁₆H₁₃NO (M⁺) 235.0997 Found: 235.0987;

Rf: 0.18 (1%MeOH, 20% Me₂CO, DCM)

Table 4.2, Entry 10 and 11



Obtained in 90% yield as a yellow oil.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.18 (6H, s), 4.26 (2H, s), 6.56 (1H, d, J=7.7 Hz), 7.07-7.18 (5H, m), 8.36 (1H, d, J=6.3Hz)

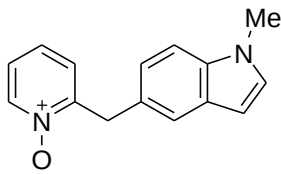
¹³C NMR (100MHz, CDCl₃, 293K, TMS):20.0, 30.6, 123.3, 123.9, 125.7, 127.2, 128.4, 133.0, 137.5, 139.4, 150.5

IR (ν_{max} /cm⁻¹):3072, 2921, 1488, 1433, 1242

HRMS calculated for C₁₄H₁₅NO (M⁺) 213.1154 Found: 213.1155;

Rf: 0.21 (1%MeOH, 20% Me₂CO, DCM)

Table 4.2, Entry 12



Obtained in 90% yield as a yellow oil.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.79 (3H, s), 4.36 (2H, s), 6.45 (1H, d, J=2.9Hz), 6.88 (1H, d, J=7.4Hz), 7.04-7.12 (4H, m), 7.31 (1H, d, J=8.3Hz), 7.52 (1H, s), 8.28 (1H, s)

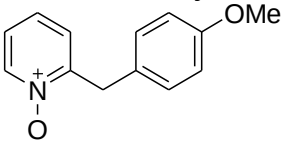
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 32.9, 36.5, 100.7, 109.6, 121.9, 123.1, 123.4, 125.6, 125.8, 126.8, 128.9, 129.4, 135.9, 139.2, 153.4

IR (ν_{max} /cm⁻¹): 3091, 1488, 1435, 1245, 763;

HRMS calculated for C₁₅H₁₄N₂O (M⁺) 238.1106; Found: 238.1116;

Rf: 0.17 (1%MeOH, 20% Me₂CO, DCM)

Table 4.2, Entry 13



Obtained in 72% yield as a white solid.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.81 (3H, s), 4.20 (2H, s), 6.88-6.91 (2H, m), 6.93-6.96 (1H, m), 7.10-7.16 (2H, m), 7.18-7.22 (2H, m), 8.28 (1H, s)

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 35.7, 55.3, 114.3, 123.4, 125.5, 125.7, 128.2, 130.8, 139.4, 152.4, 158.7

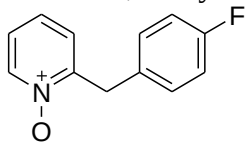
IR ($\nu_{\max}$ / cm^{-1}): 2931, 1512, 1436, 1247, 1031

HRMS calculated for $\text{C}_{13}\text{H}_{13}\text{NO}_2$ (M^+) 215.0946 Found: 215.0948;

M.P.: 94-96 °C (Chloroform)

Rf: 0.16 (1%MeOH, 20% Me_2CO , DCM)

Table 4.2, Entry 14



Obtained in 72% yield as a yellow solid.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 4.24 (2H, s), 6.95-7.00 (1H,m), 7.01-7.06 (2H, m), 7.14-7.19 (2H, m), 7.23-7.28 (2H, m), 8.27-8.31 (1H, m)

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 35.8, 115.7 (d, $J=21.3\text{Hz}$), 123.8, 125.5, 125.7, 131.2 (d, $J=8.1\text{Hz}$), 132.0 (d, $J=3.3\text{Hz}$), 139.5, 151.7, 162.0 (d, $J=245.4\text{Hz}$);

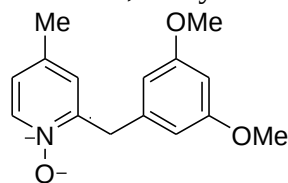
IR ($\nu_{\max}$ / cm^{-1}): 3075, 2928, 1508, 1222, 770

HRMS calculated for $\text{C}_{12}\text{H}_{10}\text{FNO}$ (M^+) 203.0746 Found: 203.0753;

M.P.: 79-81 °C (Chloroform)

Rf: 0.17 (1%MeOH, 20% Me_2CO , DCM)

Table 4.3, Entry 1



Obtained in 70% yield as a yellow solid.

^1H NMR (400MHz, CDCl_3 , 293K, TMS: 2.24 (3H, s), 3.75 (6H, s), 4.10 (2H, s), 6.38 (1H, t, $J=2.3\text{Hz}$), 6.55 (2H, d, $J=2.3\text{Hz}$), 7.02-7.09 (2H, m), 8.09 (1H, d, $J=6.7$);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 20.1, 36.7, 55.5, 99.2, 108.3, 125.6, 127.4, 136.3, 139.2, 140.7, 150.9, 162.0;

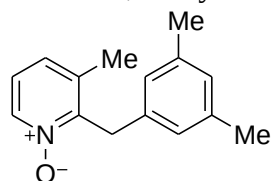
IR ($\nu_{\max}$ / cm^{-1}): 2938, 1595, 1495, 1205, 1064;

HRMS calculated for $\text{C}_{15}\text{H}_{17}\text{NO}_3$ (M^+) 259.1208; Found: 259.1195;

m.p. : 109-111 °C (CHCl_3)

Rf: 0.21 (3%MeOH, 15% Me_2CO , DCM)

Table 4.3, Entry 2



Obtained in 90% yield as a orange solid.

^1H NMR (400MHz, CDCl_3 , 293K, TMS: 2.24 (6H, s), 2.32 (3H, s), 4.36 (2H, s), 6.82 (1H, s, br), 6.86 (2H, s, br), 7.05 (2H, d, $J=4.1\text{Hz}$), 8.19 (1H, d, $J=3.9\text{Hz}$)

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 19.3, 21.3, 32.5, 122.8, 126.1, 127.4, 128.2, 135.9, 136.6, 137.5, 138.0, 150.4;

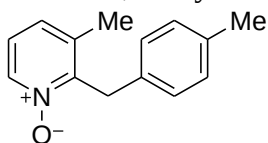
IR (ν_{max} / cm^{-1}): 2915, 1603, 1422, 1248, 822;

HRMS calculated for $\text{C}_{15}\text{H}_{17}\text{NO}$ (M^+) 227.1310; Found: 227.1297;

m.p. : 108-110 $^{\circ}\text{C}$ (CHCl_3)

Rf: 0.16 (1.5%MeOH, 15% Me_2CO , DCM)

Table 4.3, Entry 3



Obtained in 90% yield as a yellow solid.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 2.28 (3H, s), 2.32 (3H, s), 4.38 (2H, s), 7.04-7.07 (4H, m), 7.17 (2H, d, $J=7.84\text{Hz}$), 8.18 (1H, s);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 19.3, 21.0, 32.3, 122.8, 127.7, 128.3, 129.2, 133.7, 135.7, 136.0, 137.5, 150.6;

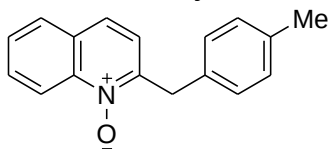
IR (ν_{max} / cm^{-1}): 3049, 1429, 1250, 809;

HRMS calculated for $\text{C}_{14}\text{H}_{15}\text{NO}$ (M^+) 213.1154; Found: 213.1143;

m.p. : 100-102 $^{\circ}\text{C}$ (CHCl_3)

Rf: 0.18 (1.5%MeOH, 15% Me_2CO , DCM)

Table 4.3, Entry 4



Obtained in 73% yield as a yellow oil.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 2.35 (3H, s), 4.44, (2H, s), 7.06 (1H, d, $J=8.7\text{Hz}$), 7.16 (2H, d, $J=7.9\text{Hz}$), 7.22 (2H, d, $J=8.0\text{Hz}$), 7.57-7.61 (2H, m), 7.75 (1H, ddd, $J=7.2\text{Hz}$ & 7.0Hz & 1.18Hz), 7.80 (1H, d, $J=8.1\text{Hz}$), 8.81 (1H, d, $J=8.8\text{Hz}$)

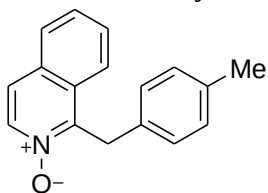
^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 21.1, 37.0, 119.8, 121.9, 125.1, 127.9, 128.0, 129.1, 129.6, 129.6, 130.4, 133.4, 136.6, 141.6;

IR (ν_{max} / cm^{-1}): 2922, 1513, 1349, 1240, 807

HRMS calculated for $\text{C}_{17}\text{H}_{15}\text{NO}$ (M^+) 249.1154; Found: 249.1151;

Rf: 0.19 (1%MeOH, 1% Me_2CO , DCM)

Table 4.3, Entry 5



Obtained in 60% yield as a light yellow solid.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.26 (3H, s), 4.77, (2H, s), 7.05 (2H, d, J=7.8Hz), 7.24 (2H, d, J=8.0Hz), 7.51-7.56 (2H, m), 7.59 (1H, ddd, J=7.0Hz & 7.0Hz & 1.3Hz), 7.75 (1H, d, J=7.9Hz), 8.00 (1H, d, J=8.0Hz), 8.22 (1H, d, J=7.0Hz)

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 21.0, 31.3, 122.5, 124.0, 127.4, 128.1, 128.5, 128.9, 128.9, 129.3, 133.9, 136.1, 136.9 (br), 147.1;

1 overlapping signal as one peak is missing even with prolonged scans.

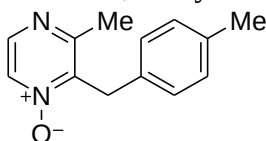
IR (ν_{max} /cm⁻¹): 3051, 1513, 1336, 1219, 749

HRMS calculated for C₁₇H₁₅NO (M⁺) 249.1154; Found: 249.1133;

m.p. : 170-172°C (CHCl₃)

Rf: 0.20 (1%MeOH, 15% Me₂CO, DCM)

Table 4.3, Entry 6



Obtained in 79% yield as a yellow oil.

¹H NMR (300MHz, CDCl₃, 293K, TMS): 2.30 (3H, s), 2.60 (3H, s), 4.31 (2H,s), 7.08 (2H, d, J=8.1Hz), 7.14 (2H, d, J=8.1Hz), 8.04 (1H, d, J=4.3Hz), 8.21 (1H, d, J=4.3Hz);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 21.0, 22.4, 31.4, 128.2, 129.4, 132.0, 132.6, 136.6, 143.6, 145.2, 157.0;

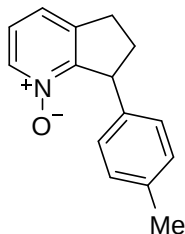
IR (ν_{max} /cm⁻¹): 2923, 1513, 1423, 1251, 791;

HRMS calculated for C₁₅H₁₇NO (M⁺) 214.1166; Found: 214.1166;

m.p. : 95-97 °C (CHCl₃)

Rf: 0.20 (2%MeOH, 10% Me₂CO, DCM)

Table 4.3, Entry 7



This compound was obtained in 64% yield as a light yellow oil by following the general *sp*³ direct arylation procedure with the exception of using 3 eq. of the *N*-oxide and S-Phos.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.14-2.22 (1H, m), 2.28 (3H, s), 2.59-2.69 (1H, m), 2.99, (1H, ddd, J=16.4, 9.2, 2.1Hz), 3.15-3.24 (1H, m), 4.71 (1H, dd, J=9.2, 1.3Hz), 6.69-7.19 (6H, m), 8.01, (1H, d, J=6.2Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 21.0, 30.3, 32.9, 47.0, 122.2, 124.5, 127.0, 129.3, 136.2, 138.0, 138.4, 142.5, 154.1;

IR (ν_{max} /cm⁻¹): 3083, 2843, 1603, 1444, 1257, 1013

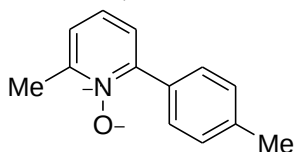
HRMS calculated for C₁₅H₁₅NO (M⁺) 225.1159; Found: 225.1140;

Rf: 0.10 (1%MeOH, 10% Me₂CO, DCM)

*sp*² Direct Arylation Procedures:

$\text{Pd}(\text{OAc})_2$ (5 mol%), $\text{P}^t\text{Bu}_3\cdot\text{HBF}_4$ (6 mol%), potassium carbonate powder (K_2CO_3 , 1.5 equiv.), aryl halide (1 equiv.) and proper azine *N*-oxide (1.1-4 equiv.) are weighed to air and placed inside the flask. The flask is then fitted with a reflux condenser which is capped with a rubber septum. The whole setup is then evacuated under vacuum and refilled with Argon four times. Toluene (0.15M) is then added under a steady flow of argon. After addition, the reaction is immersed in the oil bath. Stirring is commenced and the heating source is turned on (set to 125°C). The reaction is left stirring for 12-18 hours (overnight), then allowed to cool, diluted with DCM and filtered over celite. The residues are then purified using silica gel chromatography.

Table 4.4, Entries 1 and 2



Obtained in 54% yield as a tan solid.

^1H NMR (500MHz, CDCl_3 , 293K, TMS): 2.41 (3H, s), 2.57 (3H, s), 7.18 (1H, t, $J=7.8\text{Hz}$), 7.22 (1H, dd, $J=7.8\text{Hz}$ and 1.9Hz), 7.26-7.31 (3H, m), 7.70 (2H, d, $J=8.3\text{Hz}$);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 18.7, 21.4, 124.6, 124.8 (br), 128.8, 129.3, 130.5, 139.3, 149.5, 149.8;

1 overlapping signal as one peak is missing even with prolonged scans.

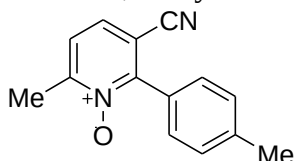
IR (ν_{max} / cm^{-1}): 3040, 1729, 1374, 1225, 757;

HRMS calculated for $\text{C}_{13}\text{H}_{13}\text{NO}$ (M^+) 199.0997; Found: 199.0982;

m.p. : 102-104 °C (CHCl_3)

Rf: 0.21 (2%MeOH, 10% Me_2CO , DCM)

Table 4.4, Entry 3



Obtained in 74% yield as a white solid.

^1H NMR (500MHz, CDCl_3 , 293K, TMS): 2.42 (3H, s), 2.59 (3H, s), 7.33-7.36 (3H, m), 7.47 (1H, d, $J=8.1\text{Hz}$), 7.53 (2H, d, $J=8.2\text{Hz}$);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 19.0, 21.6, 110.9, 115.4, 125.1, 126.7, 127.4, 129.3, 129.6, 141.0, 152.5, 154.6, ;

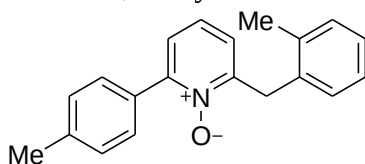
IR (ν_{max} / cm^{-1}): 2919, 2231, 1348, 1269, 815;

HRMS calculated for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$ (M^+) 224.0950; Found: 224.0943;

m.p. : 137-139 °C (CH_2Cl_2)

Rf: 0.20 (1%MeOH, 5% Me_2CO , DCM)

Table 4.4, Entry 4



Obtained in 77% yield as a yellow solid.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.23 (3H, s), 2.41 (3H, s), 4.29 (2H, s), 6.63 (1H, dd, J=7.1Hz & 2.1Hz), 7.10 (1H, t, J=7.8Hz), 7.19-7.26 (4H, m), 7.27-7.31 (3H, m), 7.73 (2H, d, J=8.2Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 19.4, 21.4, 35.0, 123.4, 124.6, 124.7, 126.5, 127.4, 128.8, 129.4, 130.4, 130.6, 130.7, 135.1, 137.3, 139.4, 149.4, 151.9;

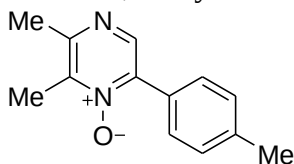
IR (ν_{max} /cm⁻¹): 3019, 2921, 1479, 1378, 1254, 770;

HRMS calculated for C₂₀H₁₉NO (M⁺) 289.1467; Found: 289.1445;

m.p. : 99-100°C (CHCl₃)

Rf: 0.2 (20% EtOAc, Petroleum Ether)

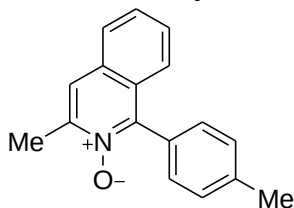
Table 4.4, Entry 5



Obtained in 89% yield as a light yellow solid.

Previously reported: Leclerc, J.-P.; Fagnou, K.; *Angew. Chem. Int. Ed.* **2006**, 45, 7781

Table 4.4, Entry 6



Obtained in 98% yield as a white solid. Using only 1.1 eq. of the N-oxide.

¹H NMR (500MHz, CDCl₃, 293K, TMS): 2.47 (3H, s), 2.68 (3H, s), 7.37-7.41 (5H, m), 7.44 (1H, d, J=8.3Hz), 7.50 (1H, td, J=7.3Hz & J=1.2Hz), 7.67 (1H, s), 7.72 (1H, d, J=7.8Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 18.3, 21.5, 122.2, 125.6, 126.0, 127.7, 127.9, 128.5, 128.7, 128.9, 129.4, 130.0, 139.0, 146.2, 146.4;

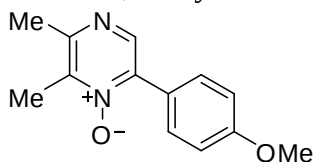
IR (ν_{max} /cm⁻¹): 3050, 1329, 1292, 1212, 1109, 811;

HRMS calculated for C₁₇H₁₅NO (M⁺) 249.1154; Found: 249.1146;

m.p. : 168-170 °C (CHCl₃)

Rf: 0.20 (1.5% MeOH, 8.5% Me₂CO, DCM)

Table 4.4, Entry 7



This compound was obtained in 86% yield as a light yellow solid by following the general sp^2 direct arylation procedure.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 2.53 (3H, s), 2.61 (3H, s), 3.86 (3H, s), 7.01 (2H, d, $J=8.6\text{Hz}$), 7.75 (2H d, 8.7 Hz), 8.36, (1H, s);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 13.5, 22.5, 55.4, 113.9, 122.2, 130.8, 141.7, 142.8, 143.1, 153.2, 160.8;

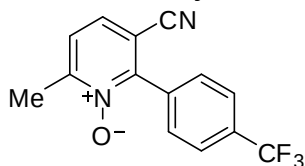
IR (ν_{max} / cm^{-1}): 3004, 2873, 1610, 1467, 1302, 1251, 832;

HRMS calculated for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$ (M^+) 230.1055; Found: 230.1042;

m.p. : 104-106 $^\circ\text{C}$ (CH_2Cl_2)

Rf: 0.51 (2%MeOH, 8% Me_2CO , DCM)

Table 4.4, Entry 8



This compound was obtained in 48% yield as a clear oil by following the general sp^2 direct arylation procedure.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 2.61 (3H, s), 7.43 (1H, d, $J=8.1\text{Hz}$), 7.53 (1H, d, $J=8.1\text{Hz}$), 7.77 (2H, d, 8.4Hz) 7.82 (2H, d, 8.4Hz);

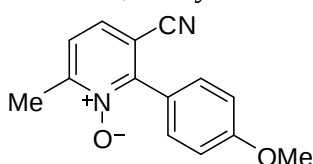
^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 18.9, 111.0, 114.8, 125.7 (q, $J=3.7\text{Hz}$), 126.0, 127.5, 130.4, 132.4, 132.7, 133.2, 150.8, 155.0;

IR (ν_{max} / cm^{-1}): 3038, 2921, 1353, 1325, 1169, 1135, 1065, 839;

HRMS calculated for $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_1\text{F}_3$ (M^+) 278.0667; Found: 278.0672;

Rf: 0.61 (30% Me_2CO , DCM)

Table 4.4, Entry 9



This compound was obtained in 73% yield as a light yellow solid by following the general sp^2 direct arylation procedure.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 2.59 (3H, s), 3.88 (3H, s), 7.04 (2H, d, $J=8.9\text{Hz}$), 7.33 (1H, d, $J=8.1\text{Hz}$), 7.47 (1H, d, $J=8.1\text{Hz}$), 7.63 (2H, d, $J=8.9\text{Hz}$);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 19.2, 55.5, 110.8, 114.1, 115.7, 121.7, 124.9, 127.7, 131.6, 152.3, 154.7, 161.5;

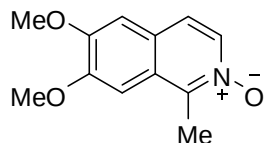
IR (ν_{max} / cm^{-1}): 2912, 2235, 1614, 1272, 1260, 1017;

HRMS calculated for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$ (M^+) 240.0899; Found: 240.08825;

m.p. : 193-195 $^\circ\text{C}$ (CH_2Cl_2)

Rf: 0.14 (1%MeOH, 3% Me₂CO, DCM)

Scheme 4.7 (compound **4.10**)



This compound was obtained in 64% yield as a light yellow oil by following the general *sp*³ direct arylation procedure with the exception of using 3 eq. of the *N*-oxide and S-Phos.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.87 (3H, s), 4.02 (3H, s), 4.05 (3H, s), 7.04 (1H, s), 7.13 (1H, s), 7.39 (1H, d, J=7.0), 8.13 (1H, d, J=7.0);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 13.2, 56.1, 56.2, 102.8, 106.0, 120.3, 124.7, 125.2, 135.0, 143.8, 151.2, 151.5, ;

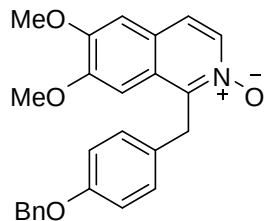
IR (ν_{max} /cm⁻¹): 2842, 1619, 1517, 1433, 1270, 1201, 1058, 805;

HRMS calculated for C₁₂H₁₃NO₃ (M⁺) 219.0895; Found: 219.0876;

m.p. : 84-86 °C (CH₂Cl₂)

Rf: 0.18 (5% MeOH, 10% Me₂CO, DCM)

Scheme 4.7 (compound **4.11**)



This compound was obtained in 64% yield as a light yellow oil by following the general *sp*³ direct arylation procedure with the exception of using 3 eq. of the *N*-oxide and S-Phos.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.93 (3H, s), 3.98 (3H, s), 4.73 (2H, s), 4.99 (2H, s), 6.87 (2H, d, J=8.6Hz), 7.02 (1H, s), 7.18 (1H, s), 7.26-7.41 (8H, m), 8.15 (1H, d, J=7.0Hz);

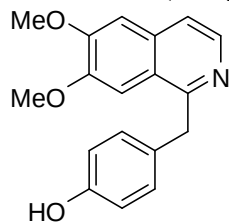
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 31.3, 56.0, 56.1, 70.0, 103.0, 106.0, 115.1, 120.9, 124.7, 125.5, 127.4, 127.9, 128.5, 129.6, 129.7, 135.2, 137.0, 145.8, 151.1, 151.6, 157.5;

IR (ν_{max} /cm⁻¹): 3036, 2932, 1612, 1267, 1235, 803;

HRMS calculated for C₂₅H₂₃NO₄ (M⁺) 401.1627; Found: 401.1643;

Rf: 0.31 (5% MeOH, 10% Me₂CO, DCM)

Scheme 4.7 (compound **4.12**)



This compound was obtained in 64% yield as a light yellow oil by following the general sp^3 direct arylation procedure with the exception of using 3 eq. of the *N*-oxide and S-Phos.

^1H NMR (400MHz, DMSO- d_6 , 293K, TMS): 3.86 (3H, s), 3.89 (3H, s), 4.42 (2H, s), 6.63 (2H, d, $J=8.5\text{Hz}$), 7.11 (2H, d, $J=8.5\text{Hz}$), 7.31 (1H, s), 7.47 (1H, s), 7.52 (1H, d, $J=5.6\text{Hz}$), 8.24 (1H, d, $J=5.6\text{Hz}$), 9.16 (1H, s);

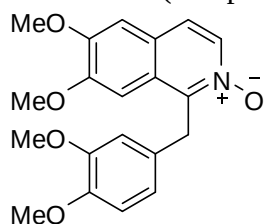
^{13}C NMR (100MHz, DMSO- d_6 , 293K, TMS): 40.3, 55.5, 55.6, 104.2, 105.5, 115.0, 118.2, 121.9, 129.4, 129.8, 132.7, 140.4, 149.4, 152.0, 155.4, 158.1;

IR (ν_{max} / cm^{-1}): 2923, 1595, 1233, 1157, 835;

HRMS calculated for $\text{C}_{15}\text{H}_{15}\text{NO}$ (M^+) 225.1159; Found: 225.1140;

Rf: 0.38 (30% Me_2CO , DCM)

Scheme 4.7 (compound **4.13**)



This compound was obtained in 64% yield as a light yellow oil by following the general sp^3 direct arylation procedure with the exception of using 3 eq. of the *N*-oxide and S-Phos.

^1H NMR (400MHz, DMSO- d_6 , 293K, DMSO- d_6): 3.66 (3H, s), 3.68 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 4.66 (2H, s), 6.79 (1H, d, $J=8.2\text{Hz}$), 6.84 (1H, dd, $J=8.2, 1.5\text{Hz}$), 7.15 (1H, d, $J=1.5\text{Hz}$), 7.37 (1H, s), 7.39 (1H, s), 7.66 (1H, d, $J=7.0\text{Hz}$), 8.12 (1H, d, $J=7.0\text{Hz}$);

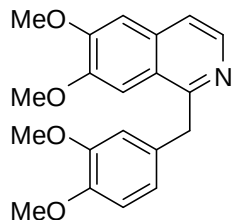
^{13}C NMR (100MHz, DMSO- d_6 , 293K, DMSO- d_6): 30.2, 55.3, 55.4, 55.7, 55.8, 102.9, 106.5, 111.9, 112.7, 115.1, 120.3, 121.2, 124.0, 124.5, 130.6, 134.7, 147.3, 148.5, 150.4, 151.2;

IR (ν_{max} / cm^{-1}): 2933, 1517, 1265, 1026, 806;

HRMS calculated for $\text{C}_{20}\text{H}_{21}\text{NO}_5$ (M^+) 355.1420; Found: 355.1415;

Rf: 0.33 (5% MeOH, 10% Me_2CO , DCM)

Scheme 4.7 (compound **4.14**)

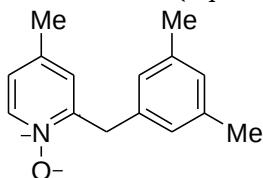


This compound was obtained in 64% yield as a light yellow oil by following the general sp^3 direct arylation procedure with the exception of using 3 eq. of the *N*-oxide and S-Phos.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 3.77 (3H, s), 3.82 (3H, s), 3.90 (3H, s), 4.00 (3H, s), 4.54 (2H, s), 6.76 (1H, d, $J=8.4\text{Hz}$), 6.80-6.84 (2H, m), 7.05, (1H, s), 7.35 (1H, s), 7.43 (1H, d, $J=5.6\text{Hz}$), 8.37 (1H, d, $J=5.7\text{Hz}$);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 42.2, 55.81, 55.86, 55.87, 56.0, 104.2, 105.3, 111.2, 111.9, 118.7, 120.5, 122.9, 132.2, 133.5, 140.9, 147.5, 149.1, 149.8, 152.5, 157.8;
IR (ν_{max} / cm^{-1}): 3083, 2843, 1603, 1444, 1257, 1013;
HRMS calculated for $\text{C}_{15}\text{H}_{15}\text{NO}$ (M^+) 225.1159; Found: 225.1140;
Rf: 0.10 (1%MeOH, 10% Me_2CO , DCM)

Scheme 4.10 (equation 4.7)



Obtained in 64% yield as a yellow oil.

^1H NMR (500MHz, CDCl_3 , 293K, TMS): 2.25 (3H, s), 2.31 (6H, s), 4.17 (2H, s), 6.74 (1H, s, br), 6.89 (2H, s), 6.92-6.95 (2H, m), 8.17 (1H, d, $J=6.4\text{Hz}$)
 ^{13}C NMR (125MHz, CDCl_3 , 293K, TMS): 20.4, 21.3, 36.2, 124.2, 126.3, 127.4, 128.6, 137.1, 138.3, 138.6, 151.2;
IR (ν_{max} / cm^{-1}): 2918, 1605, 1477, 1234, 852;
HRMS calculated for $\text{C}_{15}\text{H}_{17}\text{NO}$ (M^+) 227.1310; Found: 227.1298;
Rf: 0.20 (4%MeOH, 20% Me_2CO , DCM)

8.5 Rhodium(III)-Catalyzed Intermolecular Hydroarylation of Alkynes

General Methods:

All rhodium catalyzed hydroarylations of alkynes were carried out with no precautions to exclude ambient oxygen or moisture. The compounds: $\text{Cp}^*\text{Rh}(\text{MeCN})_3(\text{SbF}_6)_2$,¹⁷⁶ cyclopropylethynyl)benzene,¹⁷⁷ 2-(hex-1-ynyl)thiophene,¹⁷⁸ 1-(hex-1-ynyl)cyclohex-1-ene,¹⁷⁹ *tert*-butyldimethyl(5-phenylpent-4-ynyloxy)silane,¹⁸⁰ dimethyl 1H-pyrrole-3,4-dicarboxylate,¹⁸¹ 1-methoxy-4-(prop-1-ynyl)benzene,¹⁸² were prepared via literature procedures. All other reagents and solvents were used as received from commercial sources. Unless noted below, all other compounds have been reported in the literature or are commercially available.

¹⁷⁶ White, C.; Thompson S. J.; Maitlis P. M. *J. Chem. Soc., Dalton Trans.* **1977**, 1654.

¹⁷⁷ Ma, S.; He, Q. *Tetrahedron* **2006**, 62, 2769.

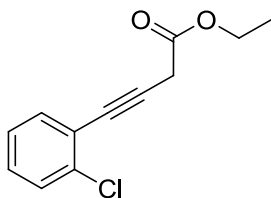
¹⁷⁸ Van den Hoven, B. G.; Alper, H. *J. Org. Chem.* **1999**, 64, 9640.

¹⁷⁹ Yoshida, M.; Hayashi, M.; Shishido, K. *Org. Lett.* **2007**, 9, 1643.

¹⁸⁰ Six, Y. *Eur. J. Org. Chem.* **2003**, 7, 1157.

¹⁸¹ Dijkstra, H. P.; Ten Have, R.; Van Leusen, A. M. *J. Org. Chem.* **1998**, 63, 5332.

¹⁸² Zhang, W.; Kraft, S.; Moore, J. S. *J. Am. Chem. Soc.* **2004**, 126, 329.



Prepared according to the procedure of Suárez and Fu¹⁸³ to afford the product in 45% yield as a yellow oil. 1.0 equivalent of pyridinium tribromide was used to eliminate the allene isomer. Crude product was purified by chromatography on silica gel (6-9% Et₂O/Petroleum Ether).

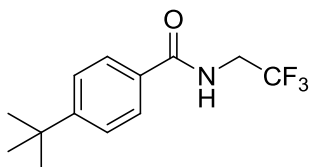
¹H NMR (400MHz, CDCl₃, 293K, CHCl₃): 1.32 (3H, t, *J*=7.1Hz), 3.57 (2H, s), 4.24 (2H, q, *J*=7.1Hz), 7.16-7.26 (2H, m), 7.38 (1H, dd, *J*=1.5, 8.0Hz), 7.48 (1H, dd, *J*=2.0, 7.4Hz);

¹³C NMR (100MHz, CDCl₃, 293K, CHCl₃): 14.1, 26.9, 61.7, 80.3, 86.7, 122.9, 126.3, 129.2, 129.2, 133.5, 136.0, 167.9;

IR (*v*_{max} /cm⁻¹): 2984, 1744, 1474, 1181, 1034, 756;

HRMS calculated for C₁₂H₁₁ClO₂ (M⁺) 222.0448; Found: 222.0448;

Rf: 0.28 (5:95, Et₂O:Petroleum Ether)



A 50 mL round bottomed flask was charged with 2,2,2-Trifluoroethylamine Hydrochloride (3 mmol). The flask was then flushed with argon. CH₂Cl₂ (15 mL), triethylamine (6.6 mmol) and 4-*tert*-Butylbenzoyl chloride (3.6 mmol) were added to the flask and the resulting solution was allowed to stir at room temperature. After 4 hours the reaction was diluted with CH₂Cl₂ and washed with 1 M HCl. The organics were dried (MgSO₄), concentrated and the residue was purified by flash chromatography on silica gel (15% EtOAc/Petroleum Ether) gave the title compound in 97% yield as a white solid.

¹H NMR (400MHz, CDCl₃, 293K, CHCl₃): 1.33 (9H, s), 4.05-4.16 (2H, m), 6.53 (1H, br s), 7.46 (2H, d, *J*=8.0Hz), 7.74 (2H, d, *J*=8.4Hz);

¹³C NMR (100MHz, CDCl₃, 293K, CHCl₃): 31.1, 35.0, 41.0 (q, *J*_F=34.7Hz), 124.2 (q, *J*_F=278.5Hz), 125.7, 127.0, 130.3, 155.9, 167.5;

IR (*v*_{max} /cm⁻¹): 3311, 2969, 1655, 1503, 1262, 1158;

HRMS calculated for C₁₃H₁₆NOF₃ (M⁺) 259.1184; Found: 259.1192;

m.p.: 114-116 °C (CH₂Cl₂)

Rf: 0.38 (15:85, EtOAc:Petroleum Ether)

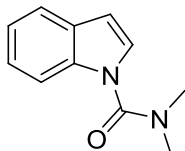
General Procedure for installation of *N,N*-dimethylcarbamoyl moiety: This procedure has been previously described.¹⁸⁴ A 100 mL round bottomed flask was charged the indole (10 mmol), NBu₄HSO₄ (1 mmol) and NaOH (25 mmol). The flask was then fitted with a reflux condenser and flushed with argon. CH₂Cl₂ (40 mL) and

¹⁸³ Suárez, A.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, 43, 3580.

¹⁸⁴ Illi, V. O. *Synthesis* **1979**, 387.

dimethylcarbamyldichloride (15 mmol) were added to the flask and the resulting solution was refluxed for 2-3 hours until the reaction was complete as judged by TLC. The reaction was quenched with saturated NH_4Cl solution. The layers were separated and the aqueous phase was extracted (2x) with CH_2Cl_2 . The organics were combined, dried (MgSO_4), concentrated and the residue was purified by flash chromatography.

Compound 5.1a



This compound was obtained in 99% yield as a white solid by following the general procedure for installation of CONMe_2 .

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 3.09 (6H, s), 6.59 (1H, dd, $J=0.6, 3.5\text{Hz}$), 7.19 (1H, ddd, $J=1.0, 7.4, 7.6\text{Hz}$), 7.29 (1H, ddd, $J=1.2, 7.7, 7.9\text{Hz}$), 7.31 (1H, d, $J=3.5\text{Hz}$), 7.59 (1H, d, $J=7.8\text{Hz}$), 7.64 (1H, d, $J=8.3\text{Hz}$);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 38.4, 105.7, 113.4, 121.0, 121.7, 123.5, 126.2, 129.4, 135.4, 155.1;

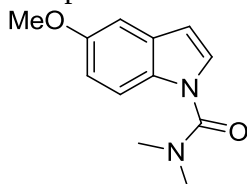
IR (ν_{max} / cm^{-1}): 2931, 1678, 1454, 1391, 749;

HRMS calculated for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$ (M^+) 188.0950; Found: 188.0933;

m.p.: 69-70 $^\circ\text{C}$ (CH_2Cl_2)

Rf: 0.31 (20:80, EtOAc:Petroleum Ether)

Compound 5.1b



This compound was obtained in 95% yield as a red oil by following the general procedure for installation of CONMe_2 .

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 3.06 (6H, s), 3.83 (3H, s), 6.51 (1H, dd, $J=0.7, 3.5\text{Hz}$), 6.92 (1H, dd, $J=2.3, 9.0\text{Hz}$), 7.05 (1H, d, $J=2.5\text{Hz}$), 7.28 (1H, d, $J=3.5\text{Hz}$), 7.56 (1H, d, $J=9.0\text{Hz}$);

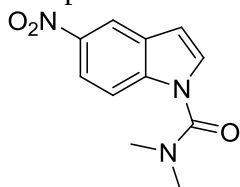
^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 38.5, 55.7, 103.0, 105.5, 113.0, 114.3, 126.8, 130.1, 130.5, 155.2, 155.4;

IR (ν_{max} / cm^{-1}): 2936, 1688, 1470, 1441, 1390, 1252, 1022;

HRMS calculated for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$ (M^+) 218.1055; Found: 218.1047;

Rf: 0.33 (30:70, EtOAc:Hexanes)

Compound **5.1c**



This compound was obtained in 97% yield as a yellow solid by following the general procedure for installation of CONMe₂.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.13 (6H, s), 6.77 (1H, d, J=3.5Hz), 7.46 (1H, d, J=3.5Hz), 7.74 (1H, d, J=9.1Hz), 8.19 (1H, dd, J=2.2, 9.1Hz), 8.55 (1H, d, J=2.2Hz), ;

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 38.5, 106.8, 113.6, 117.7, 119.0, 128.8, 129.0, 138.6, 143.2, 153.9;

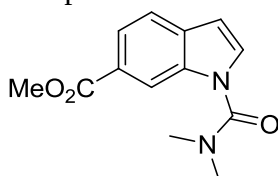
IR (ν_{max} /cm⁻¹): 3113, 2932, 1693, 1515, 1316, 744;

HRMS calculated for C₁₁H₁₁N₃O₃ (M⁺) 233.0800; Found: 233.0818;

m.p.: 106-108 °C (CH₂Cl₂)

Rf: 0.27 (50:50, EtOAc:Petroleum Ether)

Compound **5.1d**



This compound was obtained in 71% yield as a white solid by following the general procedure for installation of CONMe₂.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.11 (6H, s), 3.93 (3H, s), 6.64 (1H, dd, J=0.8, 3.5Hz), 7.47 (1H, d, J=3.5Hz), 7.63 (1H, dd, J=0.5, 8.3Hz), 7.90 (1H, dd, J=1.5, 8.3Hz), 8.33-8.35 (1H, m);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 38.5, 52.1, 105.7, 115.3, 120.7, 122.9, 125.4, 129.3, 133.1, 134.8, 154.4, 167.7;

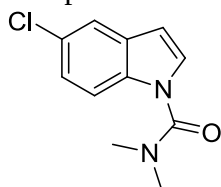
IR (ν_{max} /cm⁻¹): 2952, 1712, 1684, 1440, 1392, 1247;

HRMS calculated for C₁₃H₁₅NO₂ (M⁺) 246.1004; Found: 246.1005;

m.p.: 103-105 °C (CH₂Cl₂)

Rf: 0.17 (30:70, EtOAc:Hexanes)

Compound **5.1e**



This compound was obtained in 98% yield as a white solid by following the general procedure for installation of CONMe₂.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.09 (6H, s), 6.54 (1H, dd, J=0.7, 3.5Hz), 7.24 (1H, ddd, 0.2, 2.1, 8.8Hz), 7.33 (1H, d, J=3.5Hz), 7.56 (1H, dd, J=0.3, 2.1Hz), 7.59 (1H, d, J=8.8Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 38.5, 105.1, 114.5, 120.5, 123.8, 127.4, 130.5, 133.9, 154.7 1 overlapping signal as one peak is missing even with prolonged scans;

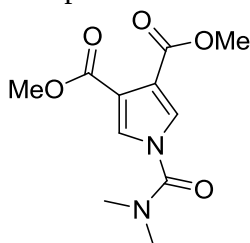
IR ($\nu_{\max}$ /cm⁻¹): 3115, 2931, 1685, 1489, 1450, 1389, 1209, 1023, 791;

HRMS calculated for C₁₁H₁₁N₂OCl (M⁺) 222.0560; Found: 222.0539;

m.p.: 83-85 °C (CH₂Cl₂)

Rf: 0.33 (20:80, EtOAc:Petroleum Ether)

Compound 5.1f



This compound was obtained in 99% yield as a white solid by following the general procedure for installation of CONMe₂.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.11 (6H, s), 3.85 (6H, s), 7.57 (2H, s);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 38.7, 51.8, 117.2, 126.8, 152.4, 163.3;

IR ($\nu_{\max}$ /cm⁻¹): 3136, 2956, 1710, 1493, 1394, 1276, 1179, 1070, 790;

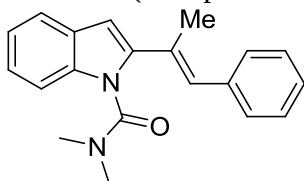
HRMS calculated for C₁₁H₁₄N₂O₅ (M⁺) 254.0903; Found: 254.0876;

m.p.: 79-81 °C (CH₂Cl₂)

Rf: 0.30 (70:30, EtOAc:Petroleum Ether)

General hydroarylation procedure: Reactions are run without exclusion of ambient air or moisture. A 2 mL screw cap vial was charged with the indole (0.3 mmol), PivOH (5 equiv.), Cp^{*}Rh(MeCN)₃(SbF₆)₂ (5 mol%) and alkyne (1.1 equiv.) if it is a solid. To the vial is added *i*PrOAc (0.75 mL) and alkyne if it is a liquid. The vial is sealed with a cap and heated at 90 °C for 16 hours. The reaction mixture is loaded onto silica gel and is purified using silica gel chromatography.

Table 5.2 (Compound 5.3a)



This compound was obtained in 99% yield as a white solid by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.22 (3H, d, *J*=1.1Hz), 2.76 (3H, br s), 3.05 (3H, br s), 6.63 (1H, s), 6.80 (1H, s), 7.12 (1H, ddd, *J*=0.8, 7.4, 7.4Hz), 7.20 (1H, ddd, *J*=1.0, 7.6, 7.6Hz), 7.23-7.33 (2H, m), 7.34-7.41 (4H, m), 7.57 (1H, d, 7.7Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 17.2, 36.1 (br s), 37.4 (br s), 104.3, 110.8, 120.6, 121.3, 123.3, 127.0, 127.8, 128.1, 128.3, 128.9, 136.2, 136.7, 142.1, 153.5, 1 overlapping signal as one peak is missing even with prolonged scans;

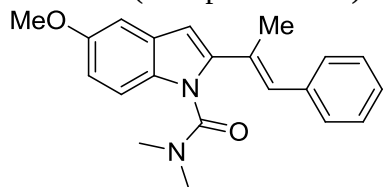
IR ($\nu_{\max}$ /cm⁻¹): 3056, 2924, 1684, 1489, 1305, 1182, 753;

HRMS calculated for $C_{20}H_{20}N_2O$ (M^+) 304.1576; Found: 304.1559;

m.p.: 98-102 °C (CH_2Cl_2)

Rf: 0.50 (15:85 EtOAc:Petroleum Ether)

Table 5.3 (Compound **5.3b**)



This compound was obtained in 93% yield as an orange oil by following the general hydroarylation procedure.

1H NMR (400MHz, $CDCl_3$, 293K, $CHCl_3$): 2.30 (3H, d, $J=2.3$ Hz), 2.81 (3H, br s), 3.02 (3H, br s), 3.85 (3H, s), 6.60 (1H, s), 6.74 (1H, s), 6.90 (1H, dd, $J=2.5, 8.9$ Hz), 7.03 (1H, d, $J=2.4$ Hz), 7.23-7.29 (1H, m), 7.30-7.41 (1H, m);

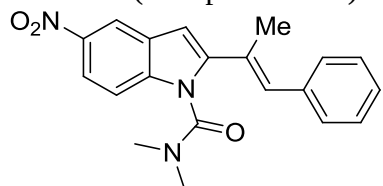
^{13}C NMR (100MHz, 100MHz, $CDCl_3$, 293K, $CHCl_3$): 17.6, 37.6 (br s), 55.8, 102.5, 104.4, 112.1, 113.2, 126.9, 128.3, 128.5, 128.9, 129.1, 129.2, 131.9, 137.3, 143.0, 154.7, 155.3;

IR (ν_{max} / cm^{-1}): 2928, 2856, 1684, 1468, 1389, 1222, 1215, 1033;

HRMS calculated for $C_{21}H_{22}N_2O_2$ (M^+) 334.1681; Found: 334.1686;

Rf: 0.32 (20:80 EtOAc:Hexanes)

Table 5.3 (Compound **5.3c**)



This compound was obtained in 62% yield as a yellow solid by following the general hydroarylation procedure.

1H NMR (400MHz, $CDCl_3$, 293K, $CHCl_3$): 2.34 (3H, s), 2.74 (3H, br s), 3.19 (3H, br s), 6.81 (1H, s), 6.83 (1H, s), 7.27-7.44 (5H, m), 7.48 (1H, d, $J=9.0$ Hz), 8.16 (1H, dd, $J=1.8, 9.0$ Hz), 8.53 (1H, d, $J=1.7$ Hz);

^{13}C NMR (100MHz, 100MHz, $CDCl_3$, 293K, $CHCl_3$): 17.6, 37.0 (br s), 38.0 (br s), 105.1, 111.3, 117.4, 118.9, 127.4, 127.5, 127.7, 128.5, 129.1, 130.9, 136.6, 139.4, 143.1, 145.3, 153.3;

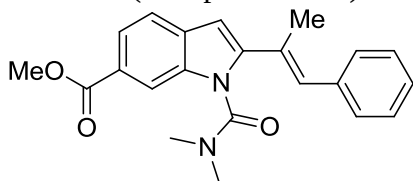
IR (ν_{max} / cm^{-1}): 3085, 2927, 1695, 1514, 1341, 1178;

HRMS calculated for $C_{20}H_{19}N_3O_3$ (M^+) 349.1426; Found: 349.1443;

m.p.: 135-138 °C (CH_2Cl_2)

Rf: 0.28 (20:80 EtOAc:Petroleum Ether)

Table 5.3 (Compound **5.3d**)



This compound was obtained in 99% yield as a yellow oil by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.32 (3H, d, *J*= 1.3Hz), 2.76 (3H, br s), 3.19 (3H, br s), 3.94 (1H, s), 6.71 (1H, d, *J*=0.5Hz), 6.83 (1H, s), 7.26-7.31 (1H, m), 7.34-7.42 (4H, m), 7.60 (1H, dd, *J*=0.4, 8.3Hz), 7.87 (1H, dd, *J*=1.4, 8.3Hz), 8.12 (1H, s);

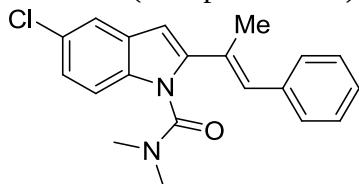
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 17.6, 37.0 (br s), 39.0 (br s), 52.0, 104.3, 113.2, 120.2, 122.8, 125.0, 127.3, 128.0, 128.4, 129.2, 130.5, 132.0, 136.0, 136.9, 145.4, 153.9, 167.7;

IR (ν_{max} /cm⁻¹): 2925, 1695, 1435, 1319, 1242;

HRMS calculated for C₂₂H₂₂N₂O₃ (M⁺) 362.1630; Found: 362.1638;

Rf: 0.31(30:70, EtOAc:Hexanes)

Table 5.3 (Compound **5.3e**)



This compound was obtained in 99% yield as a yellow oil by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, CHCl₃): 2.31 (3H, d, *J*=1.3Hz), 2.73 (3H, br s), 3.14 (3H, br s), 6.61 (1H, s), 6.78 (1H, s), 7.20 (1H, dd, *J*=2.0, 8.7Hz), 7.26-7.31 (1H, m), 7.33-7.42 (5H, m), 7.55 (1H, d, *J*=1.9Hz);

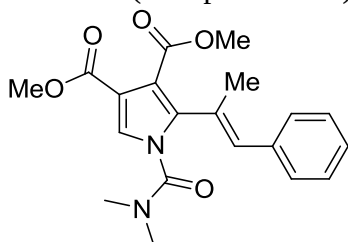
¹³C NMR (100MHz, CDCl₃, 293K, CHCl₃): 17.5, 36.9, 37.7, 103.7, 112.2, 120.0, 123.6, 127.0, 127.1, 128.0, 128.3, 129.1, 129.3, 129.8, 135.0, 137.0, 143.5, 154.1;

IR (ν_{max} /cm⁻¹): 2924, 1690, 1444, 1390, 1180;

HRMS calculated for C₂₀H₁₉N₂OCl (M⁺) 338.1186; Found: 338.1176;

Rf: 0.39 (20:80 EtOAc:Hexanes)

Table 5.3 (Compound **5.3f**)



This compound was obtained in 71% yield as yellow oil by following the general hydroarylation procedure except 1,2 dichloroethane was used as a solvent for a 24 hour reaction time.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.16 (3H, d, *J*=1.14Hz), 2.96 (6H, br s), 3.82 (3H, s), 3.85 (3H, s), 6.65 (1H, s), 7.24-7.33 (3H, m), 7.34-7.40 (3H, m);

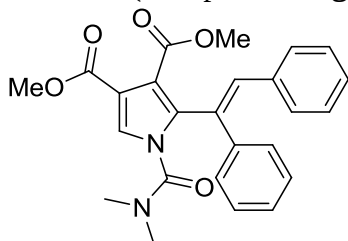
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 18.4, 37.8 (br s), 51.7, 52.3, 115.7, 115.9, 124.4, 127.0, 127.4, 128.3, 129.0, 132.9, 136.6, 138.3, 152.5, 163.5, 165.6;

IR (ν_{max} /cm⁻¹): 3030, 2952, 1716, 1437, 1392, 1206, 1176, 1070;

HRMS calculated for C₂₀H₂₂N₂O₅ (M⁺) 370.1529; Found: 370.1515;

Rf: 0.37 (50:50 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3g)



This compound was obtained in 97% yield as a colorless oil by following the general hydroarylation procedure except using 2 equivalents of arene and 1 equivalent of alkyne.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.60 (6H, br s), 3.72 (3H, s), 3.82 (3H, s), 6.92 (1H, s), 7.04-7.10 (2H, m), 7.10-7.15 (3H, m), 7.16-7.21, (2H, m), 7.21-7.26 (3H, m), 7.34 (1H, s);

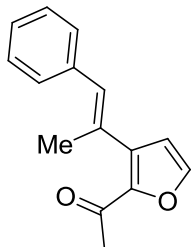
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 36.4 (br s), 38.6 (br s), 51.6, 52.3, 115.4, 118.3, 125.0, 127.6, 128.0, 128.1, 128.2, 129.5, 130.1, 130.4, 132.7, 136.0, 136.6, 137.3, 151.6, 163.3, 165.7;

IR (ν_{max} /cm⁻¹): 3023, 2950, 2360, 2336, 1716, 1221, 1087, 759;

HRMS calculated for C₂₅H₂₄N₂O₅ (M⁺) 432.1685; Found: 432.1701;

Rf: 0.50 (50:50 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3h)



This compound was obtained in 91% yield as colorless oil by following the general hydroarylation procedure except 1 equivalent of alkyne and 2 equivalents of 2-acetylfuran was used.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.24 (3H, d, *J*=1.4Hz), 2.52 (3H, s), 6.57 (1H, d, *J*=1.7Hz), 6.80 (1H, d, *J*=1.4Hz), 7.23-7.28 (1H, m), 7.36-7.39 (4H, m), 7.48 (1H, d, *J*=1.7Hz);

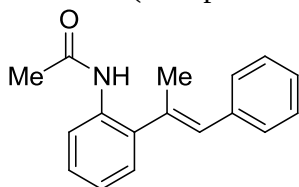
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 18.6, 27.5, 114.3, 126.9, 128.2, 129.2, 129.8, 131.6, 137.2, 137.3, 144.3, 147.6, 187.8;

IR (ν_{max} /cm⁻¹): 3029, 2924, 1675, 1560, 1356, 887;

HRMS calculated for C₁₅H₁₄O₂ (M⁺) 226.0994; Found: 226.0978;

Rf: 0.32 (10:90 Et₂O:Petroleum Ether)

Table 5.3 (Compound 5.3i)



This compound was obtained in 55% yield as white solid by following the general hydroarylation procedure except using $\text{Cp}^*\text{Rh}(\text{MeCN})_3(\text{SbF}_6)_2$ (2.5 mol%) in *t*AmOH (0.2M) at 70 °C.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 2.07 (3H, s), 2.21 (3H, d, $J=1.5\text{Hz}$), 6.48 (1H, br s), 7.14 (1H, dd, $J=7.4$, 7.4Hz), 7.23-7.30 (3H, m), 7.38-7.45 (4H, m), 7.94 (1H, d, $J=7.6\text{Hz}$), 8.52 (1H, br s);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 20.7, 25.0, 125.6, 126.1, 128.5, 129.0, 130.0, 130.3, 130.9, 132.3, 137.0, 138.0, 139.6, 140.0, 169.9;

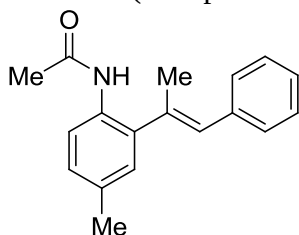
IR (ν_{max} / cm^{-1}): 3056, 1667, 1522, 1439, 756, 699;

HRMS calculated for $\text{C}_{17}\text{H}_{17}\text{NO}$ (M^+) 251.1310; Found: 251.1304;

m.p.: 62-65 °C (CH_2Cl_2)

Rf: 0.35 (40:60 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3j)



This compound was obtained in 62% yield as yellow oil by following the general hydroarylation procedure.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 2.12 (3H, s), 2.21 (3H, d, $J=1.1\text{Hz}$), 2.33 (3H, s), 6.49 (1H, s), 7.04 (1H, s), 7.10 (1H, d, $J=8.2\text{Hz}$), 7.27-7.43 (5H, m), 8.02 (1H, d, $J=8.3\text{Hz}$);

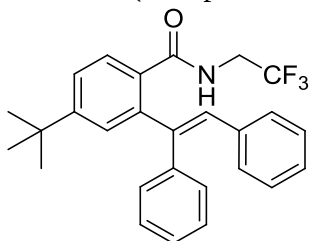
^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 19.8, 20.9, 24.6, 121.9, 127.1, 128.4, 128.8, 128.9, 129.0, 131.0, 131.5, 133.9, 135.7, 136.2, 137.1, 168.1;

IR (ν_{max} / cm^{-1}): 3263, 2927, 1662, 1520, 1299, 698;

HRMS calculated for $\text{C}_{18}\text{H}_{19}\text{NO}$ (M^+) 265.1467; Found: 265.1470;

Rf: 0.28 (30:70 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3k)



This compound was obtained in 78% yield as yellow oil by following the general hydroarylation procedure except using 2 equivalents of arene and 1 equivalent of alkyne.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.23 (9H, s), 3.54-3.86 (2H, m), 6.15-6.21 (1H, m), 6.94 (1H, d, *J*=2.1Hz), 6.96 (1H, d, *J*=3.8Hz), 7.11-7.15 (3H, m), 7.18 (1H, s), 7.22 (1H, d, *J*=2.0Hz), 7.27-7.33 (4H, m), 7.47 (1H, dd, *J*=2.0, 8.2Hz), 7.79 (1H, d, *J*=8.2Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 31.0, 34.8, 40.9 (q, *J*_F=34.6Hz), 123.9 (q, *J*_F=278.6Hz), 125.0, 126.7, 127.4, 128.0, 128.2, 128.6, 129.2, 129.2, 129.3, 129.6, 131.6, 136.5, 137.7, 141.2, 141.4, 155.2, 168.1;

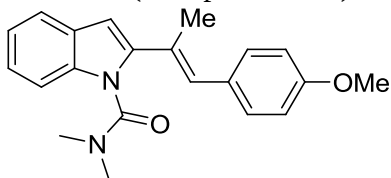
IR (ν_{max} /cm⁻¹): 3323, 2964, 1662, 1517, 1260, 1160, 696;

HRMS calculated for C₂₇H₂₆NOF₃ (M⁺) 437.1966; Found: 437.1958;

m.p.: 132-134 °C (CH₂Cl₂)

Rf: 0.24 (5:95 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3l)



This compound was obtained in 81% yield as white solid by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.30 (3H, d, *J*=1.3Hz), 2.74 (3H, br s), 3.12 (3H, br s), 3.82 (3H, s), 6.63 (3H, s), 6.70 (3H, s), 6.91 (2H, d, *J*=8.9Hz), 7.15 (1H, ddd, *J*=1.0, 7.4, 7.5Hz), 7.20-7.26 (1H, m), 7.30 (2H, d, 8.6Hz), 7.41 (1H, dd, *J*=0.7, 8.1Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 17.6, 29.7, 38.4, 55.3, 104.2, 111.2, 113.7, 120.5, 121.5, 123.3, 126.7, 128.4, 128.8, 129.9, 130.4, 136.7, 142.7, 154.7, 158.5;

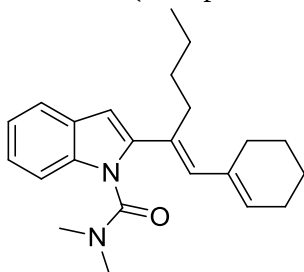
IR (ν_{max} /cm⁻¹): 3058, 2972, 1687, 1508, 1391, 1252, 753;

HRMS calculated for C₂₁H₂₂N₂O₂ (M⁺) 334.1681; Found: 334.1682;

m.p. : 120-124 °C (CH₂Cl₂)

Rf: 0.23 (20:80 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3m)



This compound was obtained in 99% yield as yellow oil by following the general hydroarylation procedure.

¹H NMR (400MHz, DMSO-d₆, 293K, DMSO): 0.84 (3H, t, *J*=7.1Hz), 1.14-1.66 (10H, m), 2.10-2.16 (4H, m), 2.77 (3H, br s), 3.07 (3H, br s), 5.71 (1H, s), 5.95 (1H, s), 6.63 (1H, s), 7.11 (1H, dd, *J*=7.3, 7.3Hz), 7.19 (1H, dd, *J*=7.1, 7.7Hz), 7.26 (1H, d, *J*=8.1Hz), 7.54 (1H, d, *J*=7.7Hz);

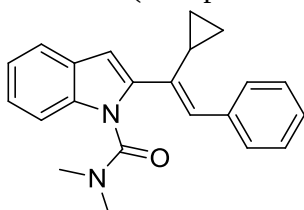
¹³C NMR (100MHz, DMSO-d₆, 293K, DMSO): 13.6, 21.5, 22.1, 22.3, 25.1, 28.4, 30.0, 31.6, 36.0 (br s), 37.5 (br s), 103.7, 110.6, 120.3, 121.0, 122.8, 127.6, 127.9, 130.4, 131.6, 134.5, 136.0, 141.8, 153.4;

IR ($\nu_{\max}$ /cm⁻¹): 3052, 2933, 1695, 1453, 1183, 739;

HRMS calculated for C₂₃H₃₀N₂O (M⁺) 350.2358; Found: 350.2369;

Rf: 0.42 (10:90 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3n)



This compound was obtained in 99% yield as yellow oil by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 0.44-0.50 (2H, m), 0.85-0.92 (2H, m), 1.88-1.97 (1H, m), 3.00 (6H, br s), 6.63 (1H, d, *J*=0.7Hz), 6.83 (1H, d, *J*=1.5Hz), 7.16 (1H, ddd, *J*=7.6, 7.3, 1.0Hz), 7.21-7.29 (2H, m), 7.34-7.40 (3H, m), 7.56 (1H, d, *J*=7.8Hz), 7.60 (2H, d, 7.3Hz);

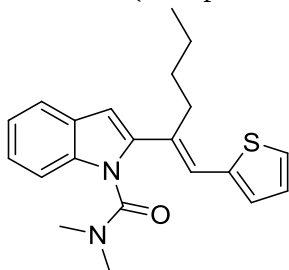
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 8.9, 13.1, 37.7, 105.4, 111.5, 120.6, 121.4, 123.2, 127.1, 128.0, 128.2, 129.5, 132.1, 134.3, 136.3, 136.9, 141.8, 154.5;

IR ($\nu_{\max}$ /cm⁻¹): 3061, 2926, 1701, 1450, 1181, 741;

HRMS calculated for C₂₂H₂₂N₂O (M⁺) 330.1732; Found: 330.1741;

Rf: 0.38 (20:80 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3o)



This compound was obtained in 97% yield as yellow oil by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 0.95 (3H, t, *J*=7.3Hz), 1.49 (2H, sex, *J*=7.3Hz), 1.55-1.66 (2H, m), 2.64-2.96 (5H, m), 3.13 (3H, br s), 6.67 (1H, s), 6.87 (1H, s), 7.03-7.08 (2H, m), 7.16 (1H, ddd, *J*=1.0, 7.4, 7.5Hz), 7.24 (1H, ddd, *J*=1.2, 7.6, 7.7Hz), 7.31 (1H, d, *J*=5.0Hz), 7.38 (1H, d, *J*=8.2Hz), 7.57 (1H, d, *J*=7.7Hz);

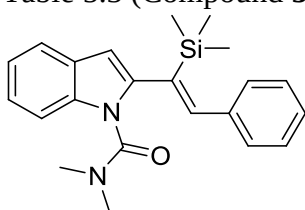
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 13.9, 23.2, 31.0, 31.7, 36.9, 37.9, 105.0, 111.1, 120.6, 121.5, 121.8, 123.5, 125.8, 127.0, 128.4, 128.6, 131.7, 136.9, 140.0, 141.5, 154.6;

IR ($\nu_{\max}$ /cm⁻¹): 3070, 2956, 1689, 1391, 1181, 739;

HRMS calculated for C₂₁H₂₄N₂OS (M⁺) 352.1609; Found: 352.1587;

Rf: 0.38 (15:85 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3p)



This compound was obtained in 67% yield as yellow oil by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 0.09 (9H, s), 3.10 (6H, br s), 6.47 (1H, d, *J*=0.69Hz), 7.20-7.32 (2H, m), 7.35-7.39 (2H, m), 7.40-7.48 (4H, m), 7.56 (1H, s), 7.64 (1H, d, *J*=7.6Hz);

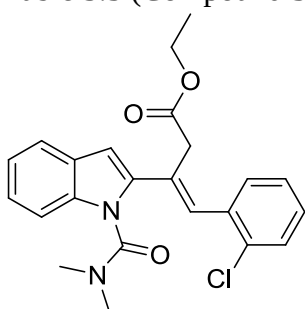
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 2.0, 39.0, 105.0, 112.8, 121.5, 122.6, 123.8, 129.0, 129.3, 129.7, 130.0, 137.1, 138.7, 140.6, 145.1, 148.4, 155.6;

IR (*v*_{max} /cm⁻¹): 3028, 2957, 1691, 1452, 1304, 1181, 840;

HRMS calculated for C₂₂H₂₆N₂OSi (M⁺) 362.1814; Found: 362.1841;

Rf: 0.33 (10:90 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3q)



This compound was obtained in 89% yield as a yellow oil by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.20 (3H, t, *J*=7.1Hz), 2.87 (3H, br s), 3.15 (3H, br s), 3.60 (2H, s), 4.12 (2H, q, *J*=7.1Hz), 6.73 (1H, s), 7.01 (1H, s), 7.12 (1H, ddd, *J*=1.0, 7.4, 7.5Hz), 7.24-7.29 (3H, m), 7.36 (1H, dd, *J*=0.8, 8.2Hz), 7.40-7.44 (1H, m), 7.50-7.53 (1H, m), 7.58 (1H, d, *J*=7.8Hz);

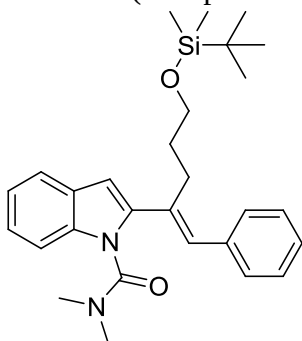
¹³C NMR (100MHz, CDCl₃, 293K, TMS): 14.1, 36.9, 37.2 (br s), 37.9 (br s), 61.0, 105.8, 111.0, 121.0, 121.6, 124.0, 126.7, 127.2, 128.0, 128.9, 129.0, 129.5, 130.2, 134.1, 135.0, 137.0, 138.9, 154.4, 171.1;

IR (*v*_{max} /cm⁻¹): 3066, 2935, 1735, 1685, 1451, 1391, 1182, 752;

HRMS calculated for C₂₃H₂₃N₂O₃Cl (M⁺) 410.1397; Found: 410.1422;

Rf: 0.29 (20:80 EtOAc:Petroleum Ether)

Table 5.3 (Compound 5.3r)



This compound was obtained in 81% yield as colorless oil by following the general hydroarylation procedure.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 0.03 (6H, s), 0.89 (9H, s), 1.75-1.86 (2H, m), 2.77 (2H, t, *J*=8.2Hz), 2.83 (3H, br s), 3.11 (3H, br s), 3.66 (2H, t, *J*=6.0Hz), 6.70 (1H, d, *J*=0.5Hz), 6.73 (1H, s), 7.17 (1H, ddd, *J*=1.1, 7.3, 7.6Hz), 7.22-7.28 (2H, m), 7.34-7.40 (5H, m), 7.57 (1H, d, *J*=7.6Hz);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): -5.34, 18.3, 26.0, 27.5, 32.5, 36.8 (br s), 38.0 (br s), 62.9, 104.9, 111.1, 120.6, 121.5, 123.4, 127.0, 128.3, 128.4, 128.8, 129.4, 133.6, 136.8, 137.2, 141.3, 154.6;

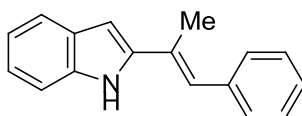
IR ($\nu_{\max}$ /cm⁻¹): 3056, 2928, 1694, 1390, 1097, 836;

HRMS calculated for C₂₈H₃₈N₂O₂Si (M⁺) 462.2703; Found: 462.2725;

Rf: 0.39 (10:90 EtOAc:Petroleum Ether)

Procedure for removal of dimethylcarbamoyl moiety

Scheme 5.4



(E)-N,N-dimethyl-2-(1-phenylprop-1-en-2-yl)-1H-indole-1-carboxamide (0.164 mmol) was charged to a 4 mL screw capped vial. To the vial was then added 2.8 mL of Ethanol (99%) and 0.9 mL of saturated aqueous KOH solution. The vial was then capped and the mixture stirred at 80 °C for 16 hours. The solution was then diluted with NH₄Cl solution and EtOAc. The phases were separated and the aqueous phase was reextracted with EtOAc. The organics were combined, dried (brine, MgSO₄) and concentrated. The residue was purified via flash chromatography over silica gel to give the above compound in 85% yield as white solid.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 2.34 (3H, d, *J*=1.3Hz), 6.67 (1H, dd, *J*=0.7, 2.0Hz), 6.91 (1H, d, *J*=1.1Hz), 7.10 (1H, ddd, *J*=1.0, 7.4, 7.5Hz), 7.19 (1H, ddd, *J*=1.2, 7.6, 7.6Hz), 7.24-7.30 (1H, m), 7.34-7.41 (5H, m), 7.59 (1H, d, *J*=7.9Hz), 8.27 (1H, br s);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 16.2, 101.6, 110.6, 120.0, 120.6, 122.7, 124.5, 126.8, 128.3, 128.8, 128.9, 129.2, 136.7, 137.3, 140.2;

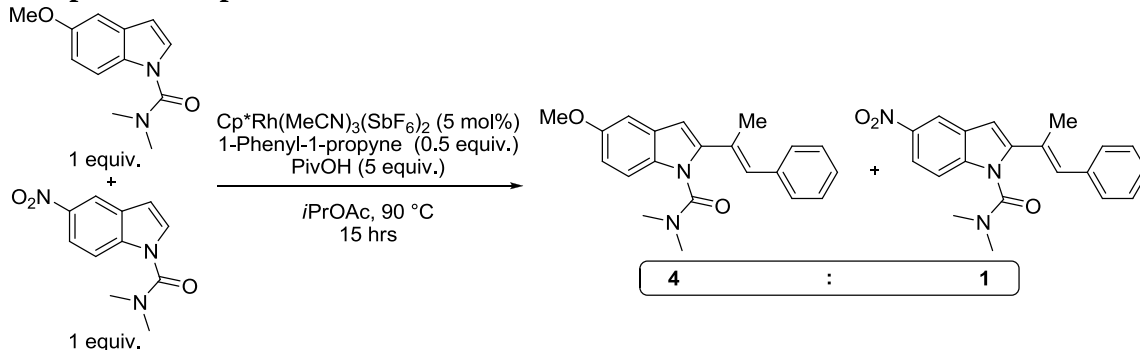
IR ($\nu_{\max}$ /cm⁻¹): 3421, 1443, 1299, 796, 753;

HRMS calculated for C₁₇H₁₅N (M⁺) 233.1204; Found: 233.1210;

m.p. : 135-140 °C (CH₂Cl₂)

Rf: 0.39 (20:80 CH₂Cl₂:Petroleum Ether)

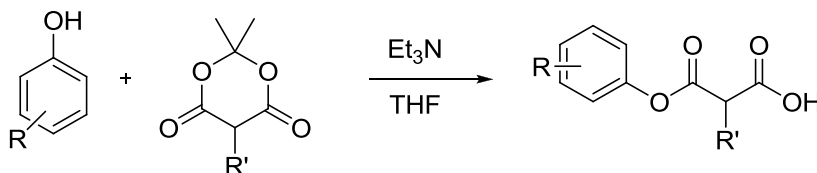
Competition Experiment



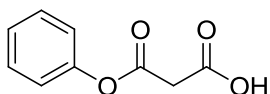
A 2 mL screw cap vial was charged with 5-Methoxy-*N,N*-dimethyl-1H-indole-1-carboxamide (0.2 mmol), *N,N*-dimethyl-5-nitro-1H-indole-1-carboxamide (0.2 mmol), PivOH (1 mmol) and $\text{Cp}^*\text{Rh}(\text{MeCN})_3(\text{SbF}_6)_2$ (0.01 mmol). To the vial was then added *i*PrOAc (0.75 mL) and 1-Phenyl-1-propyne (0.1 mmol). The vial is sealed with a cap and heated at 90 °C for 16 hours. ^1H NMR of the crude reaction mixture revealed a 4:1 ratio in favor of the OMe product.

8.6 Kinetic Resolution of β -Hydroxy Esters

General Procedure for the Preparation of Aryl Malonic Acids:



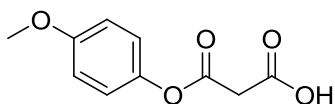
A neat solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (1.0 equiv.) and phenol (1.0 equiv.) was refluxed at 120°C for 2 hours, and then cooled to room temperature. The reaction mixture was placed under reduced pressure, and loaded directly on a silica gel column (30% EtOAc in hexanes) for purification.



3-oxo-3-phenoxypropanoic acid

This compound was obtained in 75% yield as a white solid by following the general procedure for the preparation of phenyl malonic acid. Spectral data corresponds to that previously described in the literature.¹⁸⁵

¹⁸⁵ Ryu, Y.; Scott, A.I. *Tetrahedron Lett.* **2003**, 44, 7499.



3-(4-methoxyphenoxy)-3-oxopropanoic acid

This compound was obtained in 81% yield as a beige solid by following the general procedure for the preparation of phenyl malonic acid.

¹H NMR (300MHz, CDCl₃, 293K, TMS): 3.68 (2H, s), 3.81 (3H, s), 6.87-6.93 (2H, m), 7.03-7.08 (2H, m), 8.40 (1H, b);

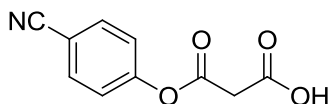
¹³C NMR (75MHz, CDCl₃, 293K, TMS) : 41.0, 55.6, 114.6, 122.1, 143.8, 157.6, 165.4, 171.4;

IR (ν_{max} /cm⁻¹): 3113, 3056, 2988, 2962, 2951, 2839, 1751, 1715, 1515, 1436, 1277, 1186, 1100, 1033, 845, 657;

HRMS calculated for C₁₀H₁₀O₅ (M⁺) 210.0528; Found : 210.0511.

M.P. = 88-90 °C

R_f = 0.09 on silica gel (30% EtOAc in hexanes)



3-(4-cyanophenoxy)-3-oxopropanoic acid

This compound was obtained in 27% yield as a white solid by following the general procedure for the preparation of phenyl malonic acids.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.72 (2H, s), 7.26-7.31 (2H, m), 7.71-7.74 (2H, m), 9.15 (1H, b);

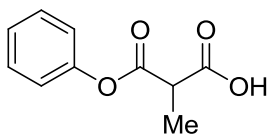
¹³C NMR (100MHz, CDCl₃, 293K, TMS) : 41.05, 110.41, 117.97, 122.56, 133.84, 153.38, 163.78, 171.09;

IR (ν_{max} /cm⁻¹): 3004, 2900, 2229, 1773, 1708, 1205, 1142, 866;

HRMS calculated for C₁₀H₇N₁O₄ (M⁺) 205.0375; Found : 205.0376.

M.P. = 76-80 °C

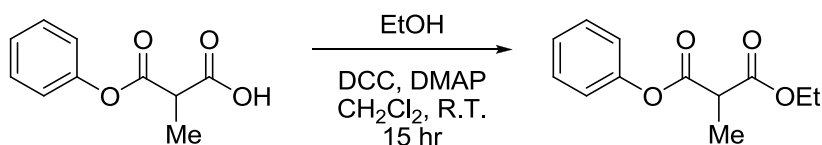
R_f = 0.06 on silica gel (30% EtOAc in hexanes)



2-methyl-3-oxo-3-phenoxypropanoic acid

2,2,5-Trimethyl-1,3-dioxane-4,6-dione (2.0 g, 12.6 mmol, 1.0 equiv.) and phenol (1.19 g, 12.6 mmol, 1.0 equiv.) were weighed into a round bottom flask equipped with a magnetic stir bar and a condenser. The flask was purged with nitrogen and the reaction mixture was heated to 120 °C for 2 h, and then cooled to room temperature. The crude reaction mixture was then loaded directly on a silica gel column for purification (40% EtOAc in hexanes) to give the product as a white solid in 81% yield. Spectral data corresponds to that previously described in the literature.¹⁸⁶

¹⁸⁶ Junek, H.; Ziegler, E.; Herzog, U.; Kroboth, H. *Synthesis*, **1976**, 332.



1-ethyl 3-phenyl 2-methylmalonate

A 100 mL round bottom flask was charged with 2-methyl-3-oxo-3-phenoxypropanoic acid (1.94 g, 10 mmol), CH₂Cl₂ (35 mL) and EtOH (584 μ L, 10 mmol) under argon atmosphere. N,N'-dicyclohexylcarbodiimide (3.09 g, 15 mmol) and 4-dimethylaminopyridine (122 mg, 1 mmol) were then added to the solution. The resulting solution was allowed to stir at room temperature for 15 hours. The reaction was then filtered through celite and washed with CH₂Cl₂. The filtrate was then concentrated and the resulting residue was purified *via* silica gel chromatography (5% EtOAc in petroleum ether) to afford the title compound in 84% yield as a clear oil.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.32 (3H, t, J=7.1Hz), 1.55 (3H, d, J=7.3), 3.68 (1H, q, J=7.3Hz), 4.26 (2H, q, 7.1Hz), 7.08-7.12 (2H, m), 7.25 (1H, d, J=7.3Hz), 7.36-7.41 (2H, m);

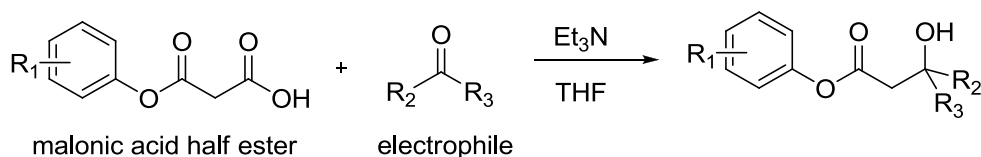
¹³C NMR (100MHz, CDCl₃, 293K, TMS) : 13.5, 14.1, 46.2, 61.6, 121.2, 126.0, 129.4, 150.5, 168.7, 169.7;

IR (v_{max} /cm⁻¹): 2987, 1767, 1739, 1594, 1194, 755;

HRMS calculated for C₁₂H₁₄O₄ (M⁺) 222.0892; Found: 222.0884.

R_f = 0.9 on silica gel (5% EtOAc in petroleum ether);

General Procedure for the Decarboxylative Addition of Aryl Malonic Acids to Ketones:

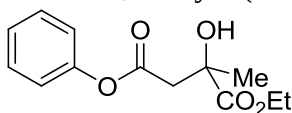


A round bottom flask is charged with the malonic acid half ester (1.0 equiv.), to which THF (0.5 M with respect to the malonic acid half ester) is added. Triethylamine (1.0 equiv.) and the electrophile (1.0 equiv.) are added *via* syringe. The resulting mixture is stirred at RT-50 °C for 4-6 hours. Upon completion, the solvent was evaporated *in vacuo* and the reaction mixture was loaded directly on a silica gel column for purification.

General Procedure for the Kinetic Resolution of Aldol Products:

A round bottom flask is charged with substrate (0.5 mmol), (1S,2R)-N-Methylephedrine (0.3-1 mmol), and toluene (2.5 mL). The reaction vessel was then sealed and the resulting solution was stirred at RT-60 °C for 15-30 hours. Solvent was then removed *in vacuo* and the resulting residue was purified *via* column chromatography.

Table 6.2, Entry 1 (Compound **6.3**)



This compound was obtained in 81% yield as a clear oil by following the general procedure for the decarboxylative addition of aryl malonic acids to ketones. Racemic mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.30 (3H, t, *J*=7.5Hz), 1.52 (3H, s), 2.93 (1H, d, *J*=16.0Hz), 3.22 (1H, d, *J*=16.6Hz), 3.77 (1H, b), 4.22-4.33 (2H, m), 7.05-7.09 (2H, m), 7.20-7.26 (1H, m), 7.35-7.39 (2H, m);

¹³C NMR (100MHz, CDCl₃, 293K, TMS) : 14.14, 26.51, 44.37, 62.25, 72.54, 121.46, 126.06, 129.46, 150.29, 169.35, 175.40;

IR (ν_{max} /cm⁻¹): 3192, 3075, 2936, 1755, 1742, 1592, 1459, 1195, 1115, 759;

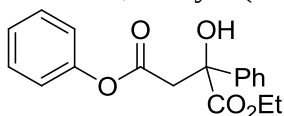
HRMS calculated for C₁₃H₁₆O₅ (M⁺) 252.0998; Found: 252.0984;

R_f = 0.40 on silica gel (20% EtOAc in hexanes);

[α]_D²⁰ = +10.1 (*c* = 1.69, CHCl₃, 94/6 er);

Chiral HPLC: Chiralcel AS-H, *i*PrOH/hexane = 10/90, 0.8 mL/min, 210 nm, *t*_{major} = 12.45 min, *t*_{minor} = 15.33 min;

Table 6.2, Entry 2 (Compound **6.17**)



This compound was obtained in 46% yield as an off-white solid by following the general procedure for the decarboxylative addition of aryl malonic acids to ketones. Racemic mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.27 (3H, t, *J*=7.2Hz), 3.16 (1H, d, *J*=16.4Hz), 3.70 (1H, d, *J*=16.4Hz), 4.23-4.33 (2H, m), 4.32 (1H, b), 7.07-7.10 (2H, m), 7.22-7.26 (1H, m), 7.32-7.42 (5H, m), 7.63-7.66 (2H, m);

¹³C NMR (100MHz, CDCl₃, 293K, TMS) : 14.00, 44.76, 62.74, 76.17, 121.44, 125.13, 126.07, 128.28, 128.54, 129.46, 140.20, 150.30, 169.39, 173.54;

IR (ν_{max} /cm⁻¹): 3487, 3062, 2991, 2939, 1750, 1728, 1589, 1490, 1185, 1121, 726, 693;

HRMS calculated for C₁₈H₁₈O₅ (M-93) 314.1154; Found : 314.1103.

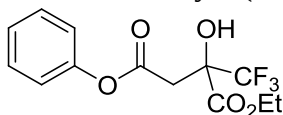
R_f = 0.30 on silica gel (15% EtOAc in hexanes);

M.P. = 94-96 °C;

[α]_D²⁰ = -15.4 (*c* = 1.1, CHCl₃, 96% ee);

Chiral HPLC: Chiralcel OD-H, *i*PrOH/hexane = 10/90, 0.8 mL/min, 210 nm, *t*_{major} = 11.33 min, *t*_{minor} = 13.83 min;

Table 6.2, Entry 3 (Compound **6.18**)



This compound was obtained in 84% yield as a white solid by following the general procedure for the decarboxylative addition of aryl malonic acids to ketones. Racemic mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.30 (3H, t, *J* = 7.1Hz), 3.20 (1H, d, *J*=16.6Hz) 3.43 (1H, d, *J*=16.6Hz), 4.32 (1H, br), 4.37 (2H, q, *J*=7.1), 7.01-7.11 (2H, m), 7.19-7.26 (1H, m), 7.32-7.41 (2H, m);

¹³C NMR (100MHz, CDCl₃, 293K, TMS) : 13.81, 37.21, 64.12, 75.23 (q, *J_F*= 30.0Hz), 121.23, 122.9 (q, *J_F*= 286.5Hz), 126.27, 129.50, 150.05, 166.96, 168.16;

IR (ν_{max} /cm⁻¹): 3475 (br), 2988, 1765, 1593, 1493, 1378, 1239, 1138, 1198, 1074, 1011, 935, 755, 689;

HRMS calculated for C₁₃H₁₃O₅F₃ (M⁺) 306.0715; Found : 306.0732;

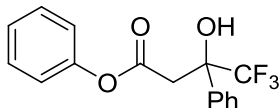
M.P. = 54-56°C;

R_f = 0.40 on silica gel (20% Et₂O in hexanes);

[α]²⁰_D = +19.3 (*c* = 1.26, CHCl₃, >99% ee);

Chiral HPLC: Chiralcel OJ-H, *i*PrOH/hexane = 10/90, 0.8 mL/min, 210 nm, *t_{major}* = 16.39 min, *t_{minor}* = 14.10 min;

Table 6.2, Entry 4 (Compound **6.19**)



This compound was obtained in 70% yield as a white solid by following the general procedure for the decarboxylative addition of aryl malonic acids to ketones. Racemic mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 3.39 (1H, d, *J*=16.0), 3.48 (1H, d, *J*=16.0), 4.87 (1H, s), 6.83 (2H, d, *J*=8.5Hz), 7.20-7.24 (1H, m), 7.30-7.35 (2H, m), 7.41-7.47 (3H, m), 7.67 (2H, d, *J*=7.30);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 39.0, 75.6 (q, *J_F*= 29.6Hz), 121.1, 125.5 (q, *J_F*= 284.9Hz), 126.5, 126.6, 128.6, 129.2, 129.6, 136.6, 149.7, 170.0;

IR (ν_{max} /cm⁻¹): 3427, 3063, 1720, 1498, 1226, 1169, 706;

HRMS calculated for C₁₆H₁₃O₃F₃ (M⁺) 310.0817; Found : 310.0801;

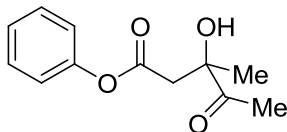
M.P. = 103-105 °C;

R_f = 0.3 on silica gel (15%Et₂O in petroleum ether);

[α]²⁰_D = +23.7 (*c* = 0.86, CHCl₃, 97/3 er);

Chiral HPLC: Chiralcel AS-H, *i*PrOH/hexane = 5/95, 0.8 mL/min, 210 nm, *t_{major}* = 9.88 min, *t_{minor}* = 12.09 min;

Table 6.2, Entry 5 (Compound **6.20**)



This compound was obtained in 43% yield as a colorless oil by following the general procedure for the decarboxylative addition of aryl malonic acids to ketones. Racemic

mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.39 (3H, s), 2.32 (3H, s), 2.89 (1H, d, J=16.5Hz), 3.24 (1H, d, 16.5Hz), 4.24 (1H, s), 7.04-7.08 (2H, m), 7.20-7.25 (1H, m), 7.33-7.39 (2H, m);

¹³C NMR (100MHz, CDCl₃, 293K, TMS) : 23.9, 25.2, 43.4, 77.5, 121.4, 126.2, 129.5, 150.2, 170.6, 211.4;

IR (ν_{max} /cm⁻¹): 3473, 2981, 1757, 1713, 1592, 1491, 1358, 1193, 1149;

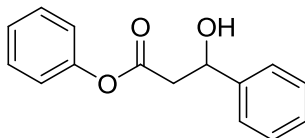
HRMS calculated for C₁₄H₁₅NO₅ (M⁺) 222.0892; Found: 222.0863.

R_f = 0.18 on silica gel (15% EtOAc in hexanes);

[α]²⁰_D = -12.5 (c = 1.0, CHCl₃, 96/4 er);

Chiral HPLC: Chiralcel OD-H, iPrOH/hexane = 10/90, 0.8 mL/min, 210 nm, *t*_{major} = 13.34 min, *t*_{minor} = 14.29 min;

Table 6.2, Entry 6 (Compound **6.21**)

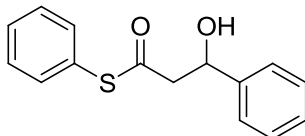


This compound was prepared as previously described in the literature.¹⁸⁷ Spectral data corresponded to that previously described in the literature.¹⁸⁶ Racemic mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

[α]²⁰_D = -23.6 (c = 1.11, CHCl₃, 95/5 er);

Chiral HPLC: Chiralcel AS-H, iPrOH/hexane = 5/95, 0.8 mL/min, 210 nm, *t*_{major} = 23.67 min, *t*_{minor} = 22.41 min;

Table 6.2, Entry 7 (Compound **6.22**)

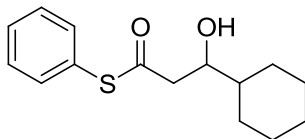


This compound was prepared as previously described in the literature.¹⁸⁸ Spectral data corresponded to that previously described in the literature.¹⁸⁷ Racemic mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

[α]²⁰_D = -18.5 (c = 0.9, CHCl₃, 92/8 er);

Chiral HPLC: Chiralcel OD-H, iPrOH/hexane = 3/97, 0.8 mL/min, 210 nm, *t*_{major} = 30.81 min, *t*_{minor} = 25.82 min;

Table 6.2, Entry 8 (Compound **6.23**)



¹⁸⁷ Wei, H.-X.; Hu, K. J.; Jasoni, R. L.; Li, G.; Pare, P. W. *Helvetica Chimica Acta*, **2004**, 87, 2354

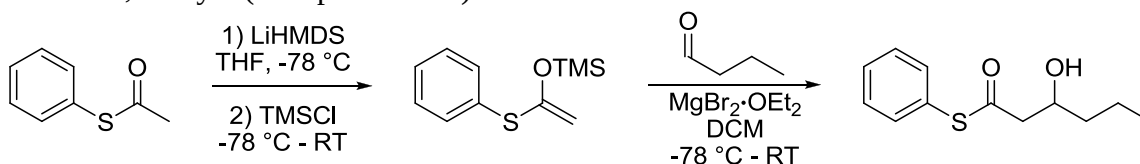
¹⁸⁸ Yost, J. M.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2006**, 8, 1503.

This compound was prepared as previously described in the literature.¹⁸⁷ Spectral data corresponded to that previously described in the literature.¹⁸⁷ Racemic mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

$[\alpha]_D^{20} = -11.8$ ($c = 1.07$, CHCl_3 , 90/10 er);

Chiral HPLC: Chiralcel OD-H, $i\text{PrOH}/\text{hexane} = 10/90$, 0.8 mL/min, 210 nm, $t_{\text{major}} = 13.35$ min, $t_{\text{minor}} = 11.73$ min;

Table 6.2, Entry 9 (Compound **6.24**)

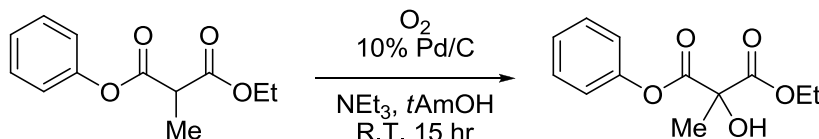


7.7 mL of a LiHMDS (7.7 mmol) solution (1M in THF) was cooled to $-78\text{ }^{\circ}\text{C}$ in a 25 mL round bottom flask under argon atmosphere. S-Phenyl thioacetate (948 μL , 7 mmol) was added to the solution dropwise and allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1 hour. TMSCl (974 μL , 7.7 mmol) was then added and the resulting mixture was allowed to warm to room temperature over the course of 1 hour. The reaction was then quenched with 8 mL of 0.1M HCl. The organic layer was separated and washed with 10 mL of 0.1M HCl. The aqueous extracts were combined and extracted with petroleum ether (2x). The organics were combined, dried (MgSO_4) and concentrated. The resulting residue was used directly in the next step. A 100 mL round bottom flask was charged with magnesium bromide etherate (3.9 g, 15 mmol), butyraldehyde (448 μL , 5 mmol) and CH_2Cl_2 (30mL). The resulting suspension was allowed to stir for 5 minutes, then it was cooled to $-78\text{ }^{\circ}\text{C}$. Trimethyl(1-(phenylthio)vinyl)oxy)silane (1.57g) in CH_2Cl_2 (20 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ and then added to the reaction. The reaction was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1 hr 40 min, then warmed to room temperature and allowed to stir for 2 hours. The reaction was then quenched with a saturated NaHCO_3 solution. The layers were separated and the aqueous phase was extracted with EtOAc. The organics were combined, washed with brine and dried (MgSO_4). The resulting residue was purified via silica gel chromatography (10% EtOAc in petroleum ether) to afford the title compound in 52% yield as a light yellow oil. Spectral data corresponded to that previously described in the literature.¹⁸⁹ Racemic mixture was resolved by following the general procedure for the kinetic resolution of aldol products.

$[\alpha]_D^{20} = -19.4$ ($c = 1.21$, CHCl_3 , 88/12 er);

Chiral HPLC: Chiralcel OJ-H, $i\text{PrOH}/\text{hexane} = 10/90$, 0.8 mL/min, 210 nm, $t_{\text{major}} = 24.72$ min, $t_{\text{minor}} = 26.71$ min;

Table 6.2, Entry 10 (Compound **6.25**)

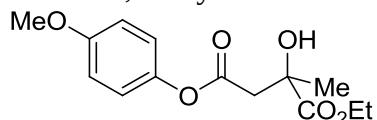


¹⁸⁹ Yuan, W.; Jia, Y.; Tian, J.; Snell, K. D.; Muh, U.; Sinskey, A. J.; Lambalot, R. H.; Walsh, C. T.; Stubbe, J. *Arch. Biochem. Biophys.* **2001**, 394, 87.

The title compound was prepared by a modification of a previously reported procedure.¹⁹⁰ A 100 mL round bottom flask was charged with 1-ethyl 3-phenyl 2-methylmalonate (1.11 g, 5 mmol), 10% Pd/C (333 mg, 30% by weight of the substrate). The flask was then capped with a septum and purged with O₂. *tert*-Amyl alcohol (20 mL) and NEt₃ (766 μ L 5.5 mmol) were then syringed into the flask. The resulting solution was allowed to stir at room temperature for 15 hours. The reaction was then filtered through celite and washed with EtOAc. The filtrate was washed with saturated NH₄Cl solution. The aqueous phase was then extracted with EtOAc (2x). The organics were combined, dried (MgSO₄) and concentrated. The resulting residue was purified *via* silica gel chromatography (10% EtOAc in petroleum ether) to afford the title compound in 48% yield as a clear oil. Spectral data corresponded to that previously described in the literature.¹⁹¹

Chiral HPLC: Chiralcel OJ-H, *i*PrOH/hexane = 10/90, 0.8 mL/min, 210 nm, t_{major} = 26.10 min, t_{minor} = 21.13 min;

Table 6.3, Entry 2



This compound was obtained in 73% yield as a clear oil by following the general procedure for the decarboxylative addition of aryl malonic acids to ketones.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.29 (3H, t, J =7.1Hz), 1.50 (3H, s), 2.90 (1H, d, J =16.3Hz), 3.19 (1H, d, J =16.3Hz), 3.77 (3H, s), 3.82 (1H, b), 4.19-4.32 (2H, m), 6.84-6.88 (2H, m), 6.96-7.00 (2H, m);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 14.14, 26.51, 44.37, 55.58 62.25, 72.54, 121.46, 126.06, 129.46, 150.29, 169.35, 175.40;

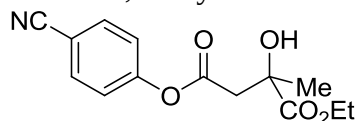
IR (ν_{max} /cm⁻¹): 3503, 2983, 2938, 2838, 1756, 1507, 1195, 1031, 840;

HRMS calculated for C₁₄H₁₈O₆ (M⁺) 282.1103; Found: 282.1085.

Rf = 0.41 on silica gel (20% EtOAc in hexanes);

Chiral HPLC: Chiralcel OD-H, *i*PrOH/hexane = 10/90, 0.8 mL/min, 210 nm, t_{major} = 11.16 min, t_{minor} = 13.51 min;

Table 6.3, Entry 3



2-Hydroxy-2-methyl-succinic acid 4-(4-cyano-phenyl) ester 1-ethyl ester

This compound was obtained in 42% yield as a clear oil by following the general procedure for the decarboxylative addition of aryl malonic acids to ketones.

¹⁹⁰ Monguchi, Y.; Takahashi, T.; Iida, Y.; Fujiwara, Y.; Inagaki, Y.; Maegawa, T.; Sajiki, H. *Synlett*. **2008**, 15, 2291.

¹⁹¹ Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T. *Angew. Chem. Int. Ed.* **2009**, 48, 803.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.30 (3H, t, J=7.1Hz), 1.52 (3H, s), 2.96 (1H, d, J=16.2Hz), 3.23 (1H, d, J=16.2Hz), 3.69 (1H, b), 4.29 (2H, qd, J=2.0Hz, 7.1Hz), 7.21-7.24 (2H, m), 7.66-7.70 (2H, m);

¹³C NMR (100MHz, CDCl₃, 293K, TMS) : 14.13, 26.65, 44.27, 62.44, 72.48, 110.01, 118.13, 122.67, 133.69, 153.51, 168.29, 175.28;

IR (ν_{max} /cm⁻¹): 3484 (br), 2985, 2945, 2231, 1761, 1735, 1604, 1502, 1207, 1170, 1141, 1014, 858;

HRMS calculated for C₁₄H₁₅NO₅ (M⁺) 277.0950; Found: 277.1001.

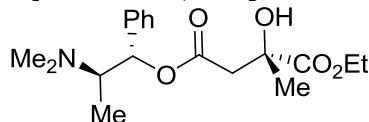
R_f = 0.45 on silica gel (20% EtOAc in hexanes);

Chiral HPLC: Chiralcel OJ-H, iPrOH/hexane = 10/90, 0.8 mL/min, 210 nm, *t*_{major} = 47.41 min, *t*_{minor} = 36.61 min;

Procedure for Kinetic Resolution on Gram Scale:

A 50 mL round bottom flask was charged with **15** (1 g, 3.96 mmol), (1S,2R)-N-Methylephedrine (**14**, 1.42 g, 7.92 mmol), and toluene (20 mL). The reaction vessel was then sealed and the resulting solution was stirred at 60 °C for 29 hours. Solvent was then removed *in vacuo* and the resulting residue was purified *via* column chromatography (10% EtOAc in hexanes to 50% EtOAc in Acetone) to yield 49% of (+)-**15** (94/6 er), 43% **24** (25/1 dr) and 37.5% **14**.

Equation 6.2 (Compound **6.26**)



Recovered in 43% yield and 25/1 dr as a light yellow oil by following the procedure for kinetic resolution on gram scale.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.03 (3H, d, J=6.7Hz), 1.18 (3H, t, J=7.1Hz), 1.46 (3H, s), 2.31 (6H, s), 2.72-2.81 (2H, m), 3.01 (1H, d, J=15.3Hz), 4.16 (2H, q, J=7.1Hz) 6.05 (1H, d, J=4.7Hz), 7.23-7.28 (3H, m), 7.30-7.35 (2H, m);

¹³C NMR (100MHz, CDCl₃, 293K, TMS): 9.9, 14.0, 26.5, 41.9, 45.0, 61.8, 64.2, 72.7, 75.6, 126.2, 127.6, 128.3, 139.3, 170.0, 175.2;

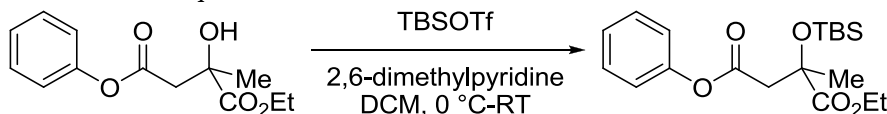
IR (ν_{max} /cm⁻¹): 3067, 2978, 1735, 1596, 1454, 1381, 1292, 1188, 1111, 999, 701;

HRMS calculated for C₁₈H₂₇NO₅ (M⁺) 337.1889; Found: 337.1847.

R_f = 0.3 on silica gel (50% EtOAc in acetone);

[α]_D²⁰ = +58.3 (*c* = 0.78, CHCl₃, 63/1 dr);

Scheme 6.2, Equation 6.4



1-ethyl 4-phenyl 2-(tert-butyldimethylsilyloxy)-2-methylsuccinate

A 10 mL round bottom flask was charged with 1-ethyl 4-phenyl 2-hydroxy-2-methylsuccinate (252 mg, 1 mmol), 2,6-dimethylpyridine (128 μL, 1.1 mmol) and CH₂Cl₂ (2mL) under argon atmosphere. The solution was cooled to 0 °C. TBSOTf (253 μL, 1.1 mmol) was then added. The solution was allowed to warm to room temperature

and then stirred for 4.5 hours. The reaction was then quenched with saturated NH_4Cl solution. The mixture was then extracted with CH_2Cl_2 . The organics were combined, dried (MgSO_4) and concentrated. The resulting residue was purified *via* silica gel chromatography (5-8% Et_2O in petroleum ether) to afford the title compound in 60% yield as a clear oil.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 0.16 (6H, d, $J=5.6\text{Hz}$), 0.89 (9H, s), 1.28 (3H, t, $J=7.1\text{Hz}$), 1.58 (3H, s), 2.89 (1H, d, $J=14.7\text{Hz}$), 3.15 (1H, d, $J=14.7\text{Hz}$), 4.16-4.27 (2H, m), 7.06 (2H, d, $J=8.3\text{Hz}$), 7.21 (1H, t, $J=7.4\text{Hz}$), 7.35 (2H, t, $J=7.9\text{Hz}$);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS) : -2.9, -2.7, 14.2, 18.3, 25.7, 27.0, 47.0, 61.4, 75.8, 121.5, 125.7, 129.3, 150.5, 168.3, 174.0;

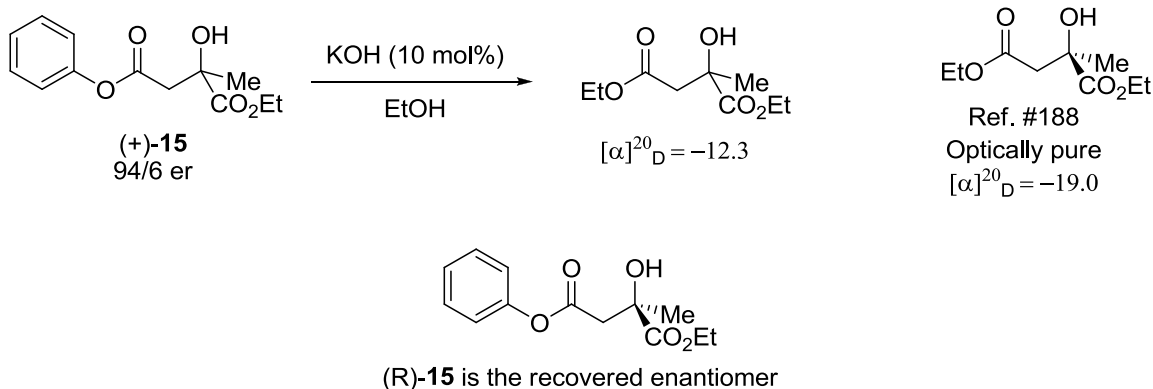
IR (ν_{max} / cm^{-1}): 2956, 2857, 1764, 1493, 1202, 1153, 1025, 838;

HRMS calculated for $\text{C}_{15}\text{H}_{21}\text{O}_5\text{Si}$ ($\text{M}^+ - t\text{Bu}$) 309.1153; Found: 309.1157.

Rf = 0.28 on silica gel (5% Et_2O in petroleum ether);

Identification of Absolute Stereochemistry

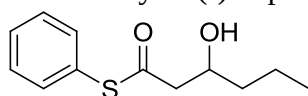
Absolute stereochemistry of (+)-2-hydroxy-2-methyl-succinic acid 1-ethyl ester 4-phenyl ester (**6.15**)



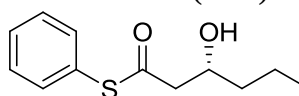
2-Hydroxy-2-methyl-succinic acid 1-ethyl ester 4-phenyl ester (0.4 mmol, 94/6 er) and KOH (0.04 mmol) was stirred in 1 mL of ethanol for 2 hours. The solvent was removed in vacuo and the product was isolated using preparatory TLC (20% EtOAc in hexanes) in 34% yield. Spectral data corresponded to that previously described in the literature.¹⁸⁹ Comparison of the optical rotation data to literature values¹⁹² show the R enantiomer to be in excess.

¹⁹² Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S. Goti, A.; *Eur. J. Org. Chem.* **2004**, 776.

Absolute stereochemistry of (-)-S-phenyl 3-hydroxyhexanethioate (**6.24**)



(-)-**6.24**
88/12 er
[α]_D²⁰ = -19.4

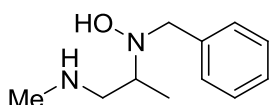


Ref. #184
Optically pure
[α]_D²⁰ = -27.4

(R)-**6.24** is the recovered enantiomer

Comparison of the optical rotation data for enantioenriched (-)-**6.24** to literature values¹⁸⁸ show the R enantiomer to be in excess.

8.7 Enantioselective Organocatalysis Using Simple Aldehydes Temporary Tethers



A 2 mL vial was charged with D-glyceraldehyde acetone (0.2 mmol, 26 mg). Benzene (1 mL), *N*-benzylhydroxylamine (1 mmol, 123 mg) and *N*-methylallylamine (1.5 mmol, 107 mg) were then added. The mixture was allowed to stir at room temperature for 24 hours. The solvent was then removed *in vacuo*. The residue was purified by flash chromatography (1% NEt₃/10% MeOH in CH₂Cl₂) to give the product in 91% yield as a pale yellow oil.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.12 (3H, d, J=6.5 Hz), 2.35 (3H, s), 2.56 (1H, dd, J=12.2, 4.0 Hz), 2.78 (1H, dd, J=12.2, 8.5 Hz), 2.97-3.08 (1H, m), 3.72 (1H, d, J=13.2 Hz), 3.97 (1H, d, J=13.2 Hz), 7.26-7.39 (5H, m);

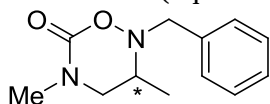
¹³C NMR (100 MHz, CDCl₃, 293K, TMS): 11.5; 35.6, 55.1, 59.0, 60.4, 127.1, 128.2, 129.3, 138.6;

IR (ν_{max} /cm⁻¹): 3397, 2926, 2854, 1641, 1447, 1371;

HRMS calculated for C₁₁H₁₈N₂O (M⁺) 194.1419; Not found. HRMS m/z (relative intensity): 150.0896 (16.5%), 91.0545 (100%), 44.0503 (24.2%), 30.0349 (57.2%).

Rf: 0.19 (85:15, CH₂Cl₂:MeOH)

Scheme 7.7 (equation 7.7)



N-benzyl-*N*-hydroxy-1-(methylamino)propan-2-amine (0.14 g) was dissolved in CH₂Cl₂ (2 mL). 1,1'-Carbonyldiimidazole (0.17 g, 1.5 equiv.) was then added to the solution. After stirring at room temperature for 3 hours under argon atmosphere the solvent was then removed *in vacuo* and the residue purified by flash chromatography over silica gel. The title compound was obtained as a white solid in 75% yield (0.12 g) and 72/28 enantiomeric ratio.

¹H NMR (400MHz, CDCl₃, 293K, TMS): 1.20 (3H, d, J=6.20 Hz), 3.10-26 (3H, m), 3.89 (1H, d, J=14.0 Hz), 4.27 (1H, d, J=14.0 Hz), 7.28-7.36 (5H, m);

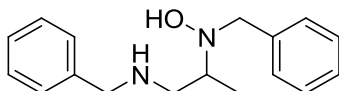
¹³C NMR (100 MHz, CDCl₃, 293K, TMS): 54.3, 58.9, 127.7, 128.4, 129.3, 135.3, 154.4;

IR ($\nu_{\max}$ / cm^{-1}): 3119, 2925, 2857, 1690, 1322, 1067, 784;

HRMS calculated for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ (M^+) 220.1212; Found: 220.1198;

Rf: 0.6 (95:5, CH_2Cl_2 :MeOH)

Chiral HPLC: ChiralPak OJ-H, *i*PrOH/hexane = 10/90, 1.0 mL/min, 210 nm, t_{major} = 28.3 min, t_{minor} = 31.7 min.



A 2 mL vial was charged with D-glyceraldehyde acetone (0.2 mmol, 26 mg). Benzene (1 mL), *N*-benzylhydroxylamine (1 mmol, 123 mg) and *N*-benzylallylamine (1.5 mmol, 221 mg) were then added. The mixture was allowed to stir at room temperature for 24 hours. The solvent was then removed *in vacuo*. The residue was purified by flash chromatography (1% NEt_3 /2% MeOH in CH_2Cl_2) to give the product in 83% yield as a yellow oil.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 1.11 (3H, d, $J=6.5$ Hz), 2.64 (1H, dd, $J=12.2$, 4.0 Hz), 2.80 (1H, dd, $J=12.2$, 8.5 Hz), 3.02-3.08 (1H, m), 3.67 (1H, d, $J=13.2$ Hz), 3.72 (d, $J=13.3$ Hz, 1H), 3.73 (1H, d, $J=13.1$ Hz), 3.93 (d, $J = 13.2$ Hz, 1H), 7.24-7.37 (10H, m,);

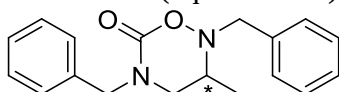
^{13}C NMR (100 MHz, CDCl_3 , 293K, TMS): 11.3, 51.8, 53.0, 58.9, 60.1, 126.9, 127.0, 128.1, 128.2, 128.3, 129.4, 138.5, 139.5;

IR ($\nu_{\max}$ / cm^{-1}): 3063, 3032, 2926, 2850, 1497, 1451, 1364, 1155, 1026, 733, 698;

HRMS calculated for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$ (M^+) 270.1732; Not found. HRMS m/z (relative intensity): 253.1662 (2.3%), 150.0929 (16.0%), 134.0954 (24.4%), 91.0539 (100%) 83.9507 (12.3%), 82.9445 (14.2%), 65.0412 (9.9%);

Rf: 0.25 (90:10, CH_2Cl_2 :MeOH)

Scheme 7.7 (equation 7.8)



N-benzyl-2-(benzyl(hydroxy)amino)propan-1-amine (88.0 mg) was dissolved in CH_2Cl_2 (2 mL). 1,1'-Carbonyldiimidazole (53.0 mg, 1.5 equiv.) was then added to the solution. After stirring at room temperature for 2 hours under argon atmosphere the solvent was then removed *in vacuo* and the residue purified by flash chromatography over silica gel. The title compound was obtained as a white solid in 93% yield (90.0 mg) and 87/13 enantiomeric ratio.

^1H NMR (400MHz, CDCl_3 , 293K, TMS): 1.14 (3H, d, $J=6.2$ Hz), 2.95-3.05 (1H, m), 3.14-3.25 (2H, m), 3.91 (1H, d, $J=14.0$ Hz), 4.29 (1H, d, $J=14.0$ Hz), 4.48 (1H, d, $J=15.2$ Hz), 4.59 (1H, d, $J=14.8$ Hz) 7.24-7.36 (8H, m), 7.37-7.42 (2H, m);

^{13}C NMR (100MHz, CDCl_3 , 293K, TMS): 14.0 (br), 51.3, 51.6, 54.2 (br), 58.9, 127.7, 127.8, 128.2, 128.4, 128.7, 129.3, 135.3, 136.2, 154.6;

IR ($\nu_{\max}$ / cm^{-1}): 3034, 2920, 1700, 1487, 1238, 707;

HRMS calculated for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$ (M^+) 296.1525; Found: 296.1527;

m.p.: 98-102 °C (CHCl_3);

Rf: 0.28 (30:70, EtOAc:Petroleum Ether);

Chiral HPLC: ChiralPak AD-H, *i*PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, t_{major} = 41.0 min, t_{minor} = 43.5 min;

Spectral Data

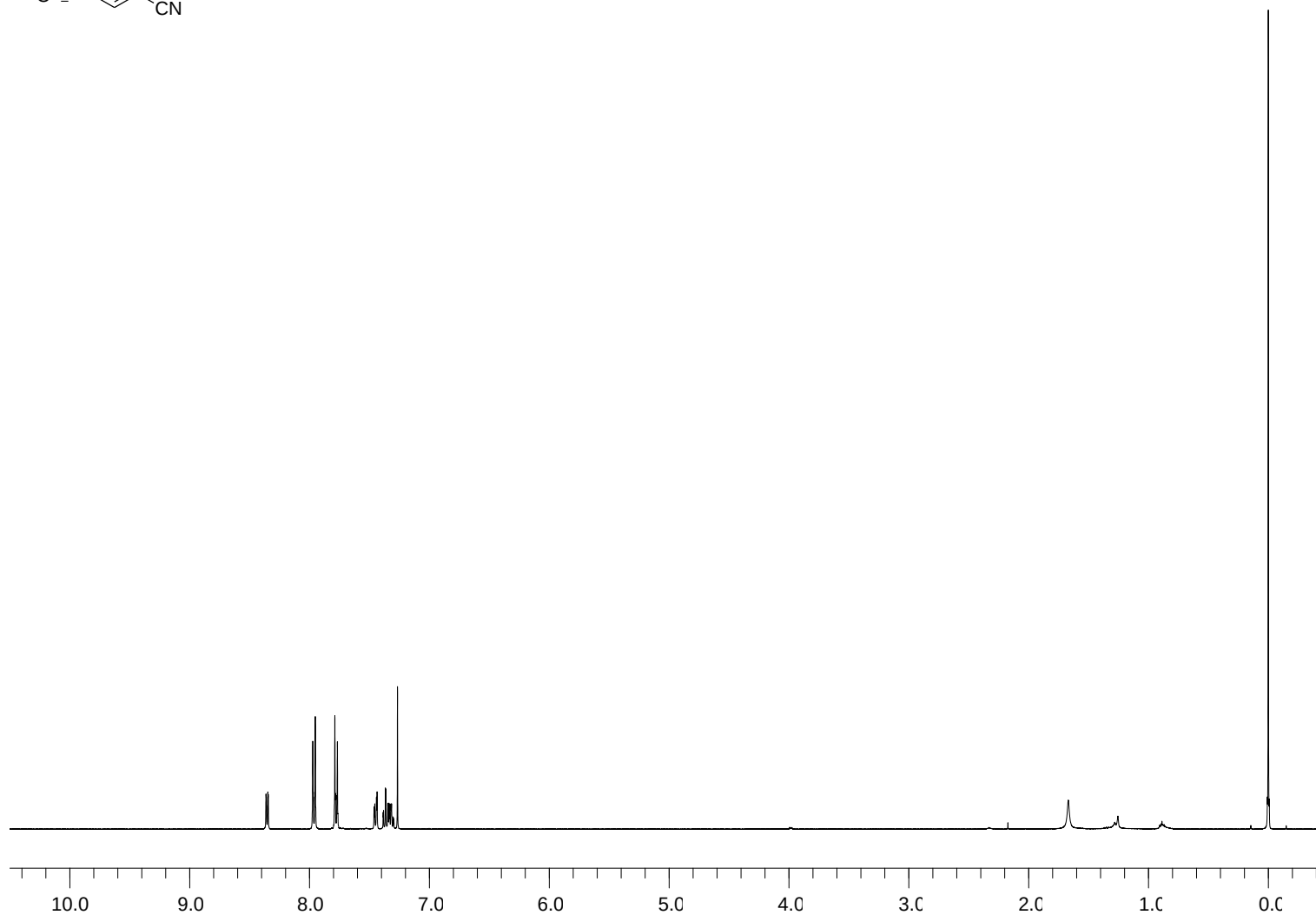
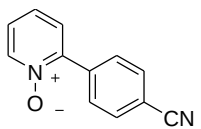
Derek Schipper

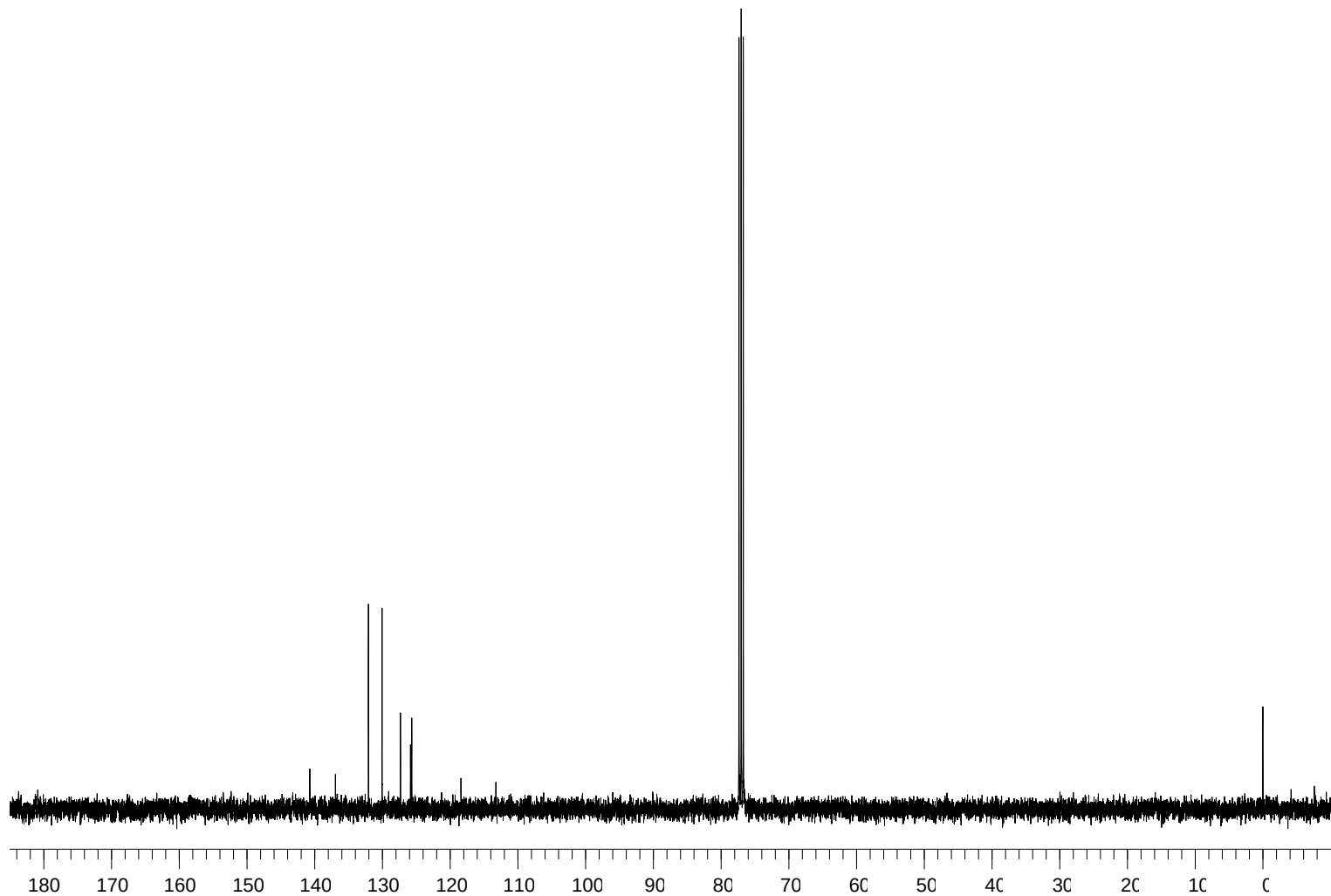
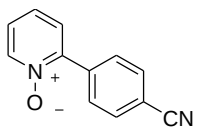
(to accompany a thesis in partial fulfillment of the degree of Ph.D in chemistry)

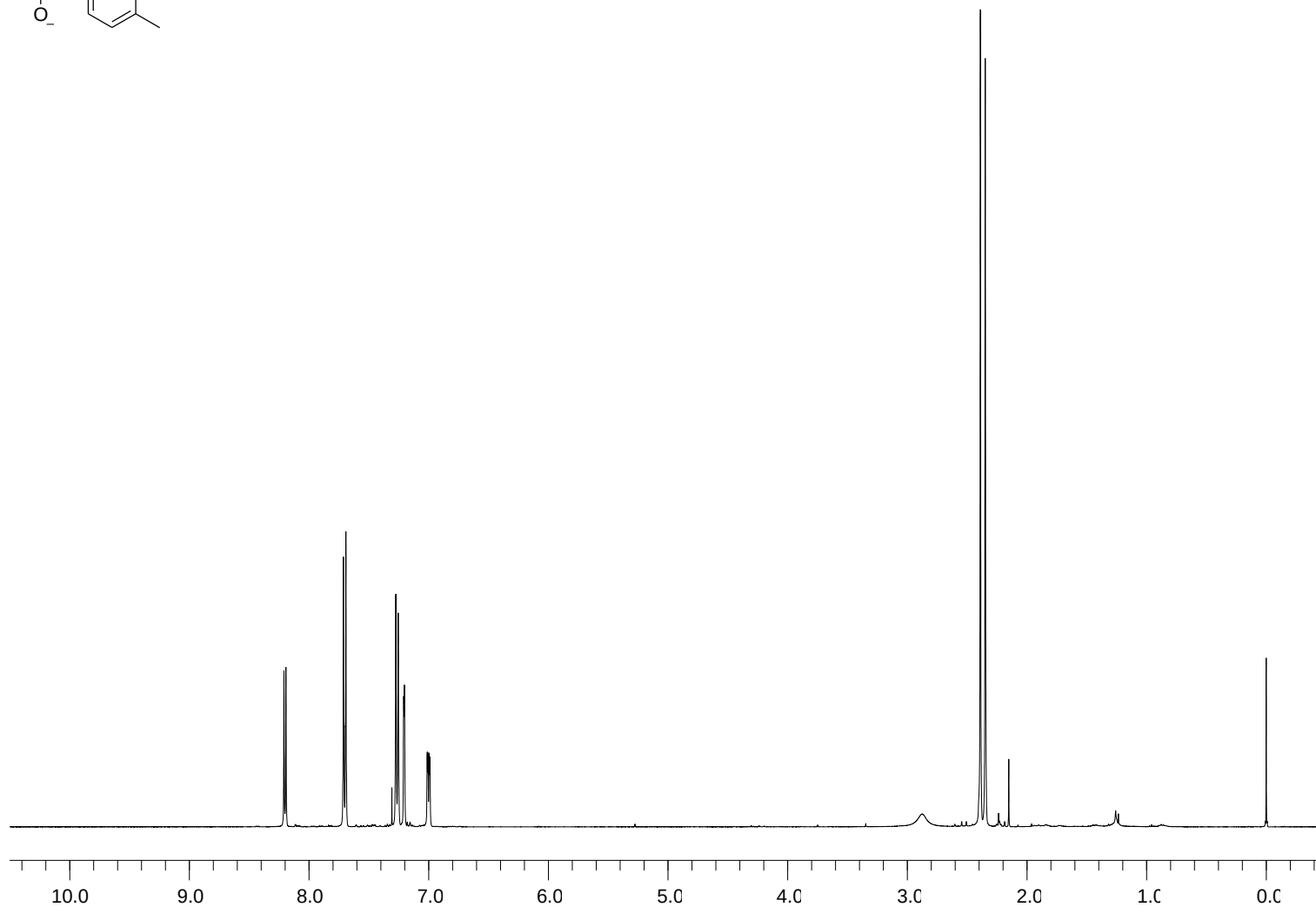
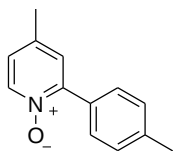
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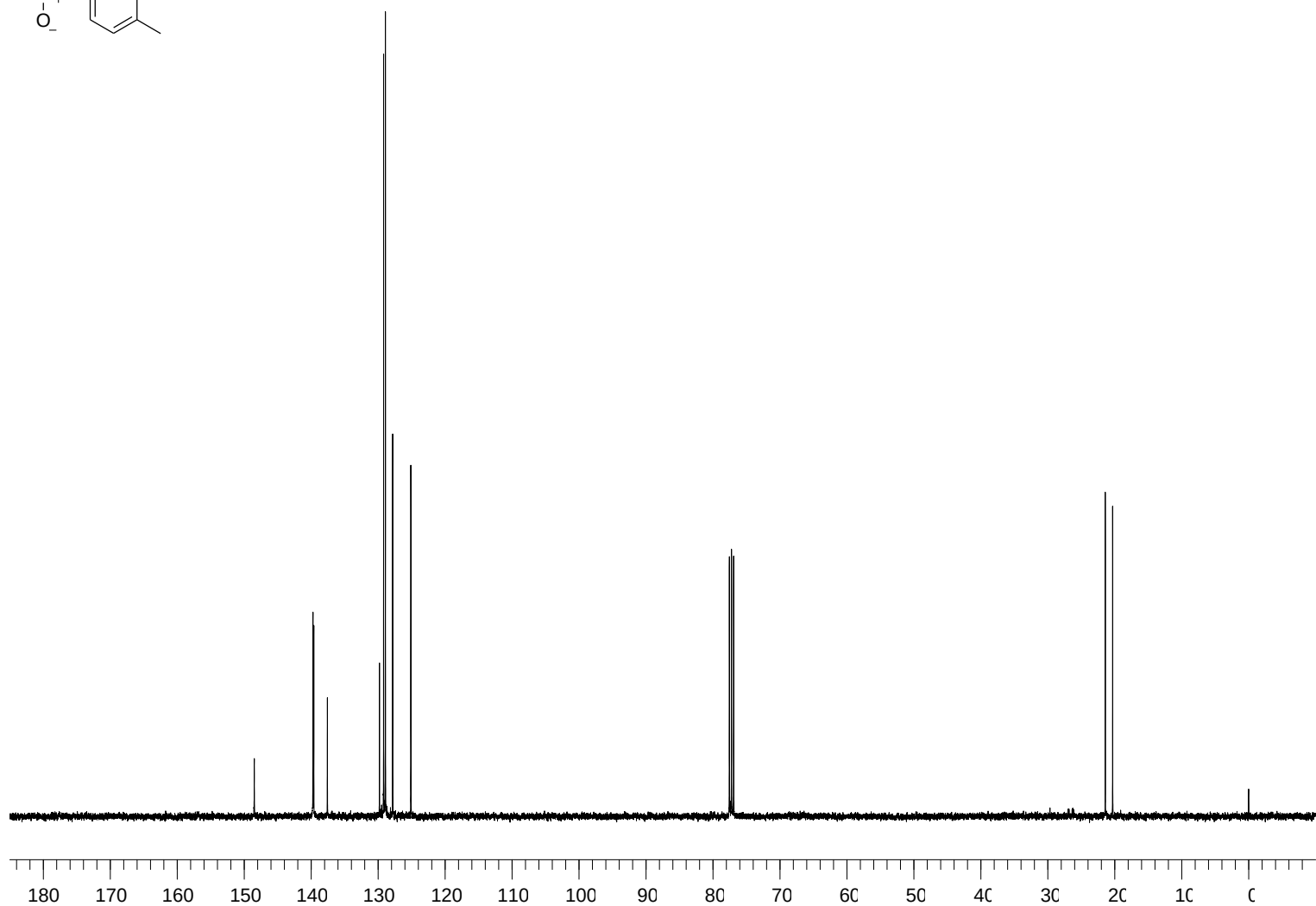
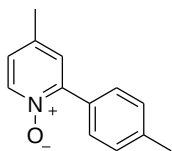
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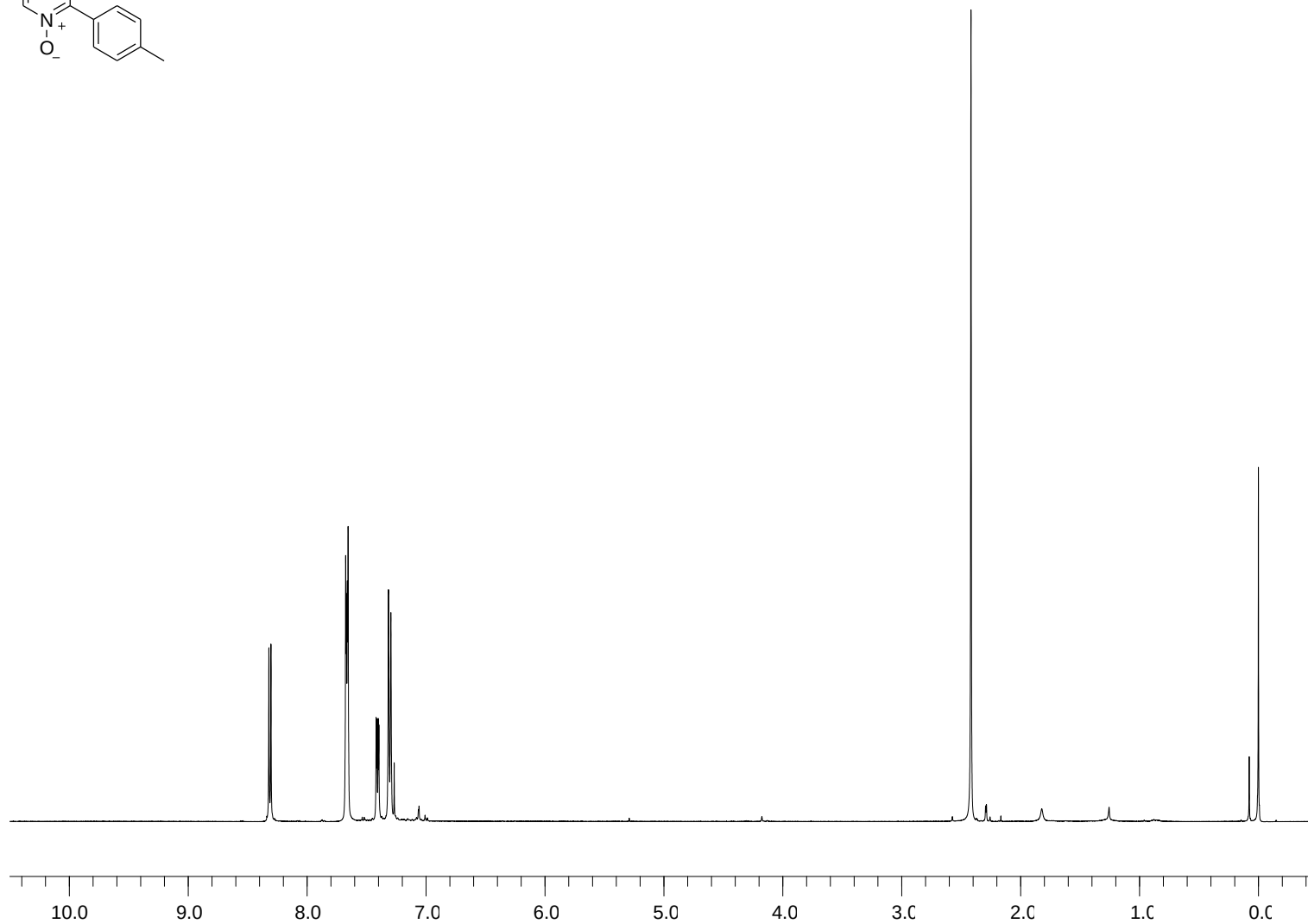
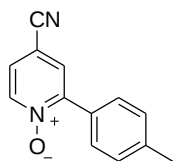
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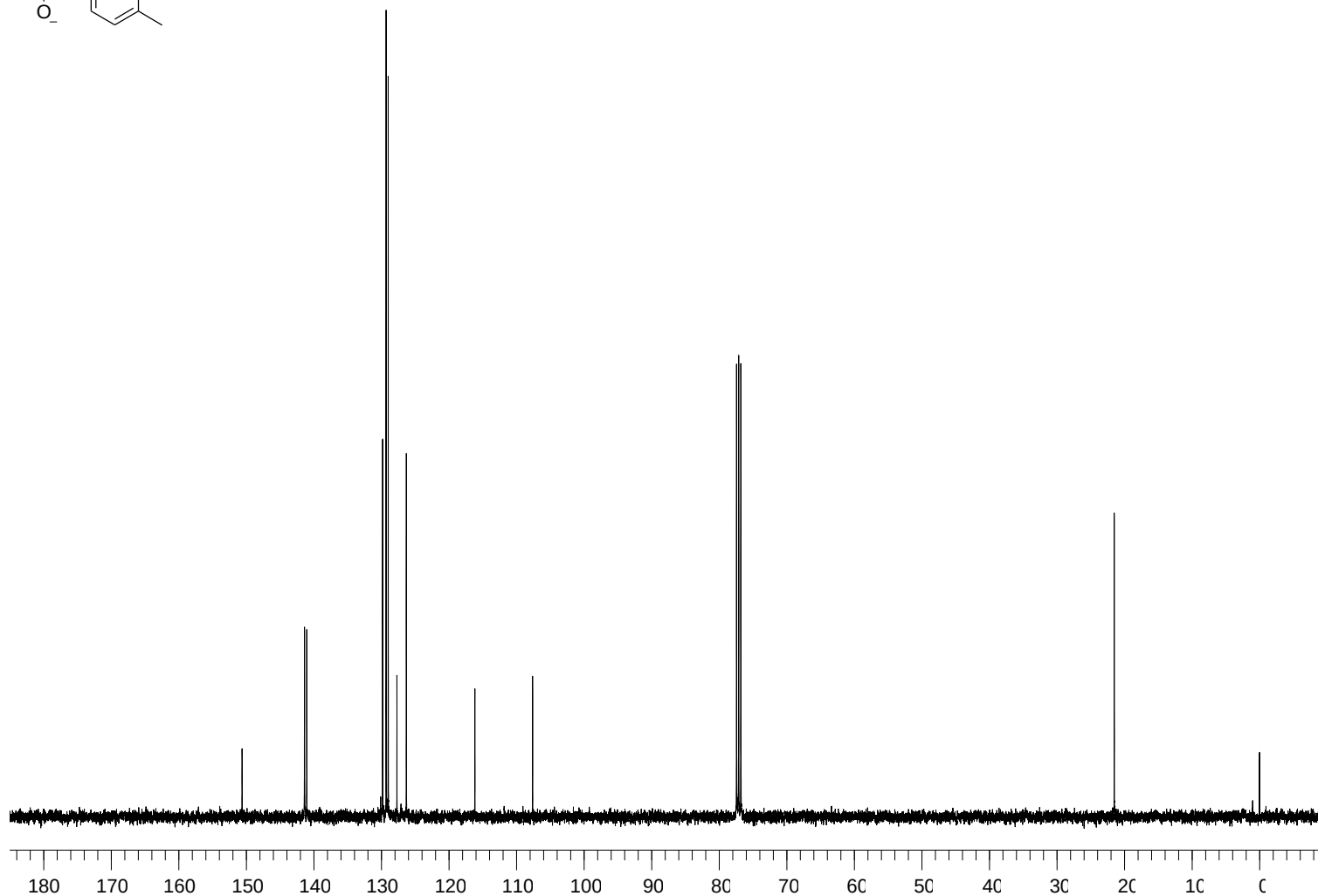
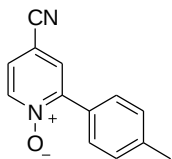


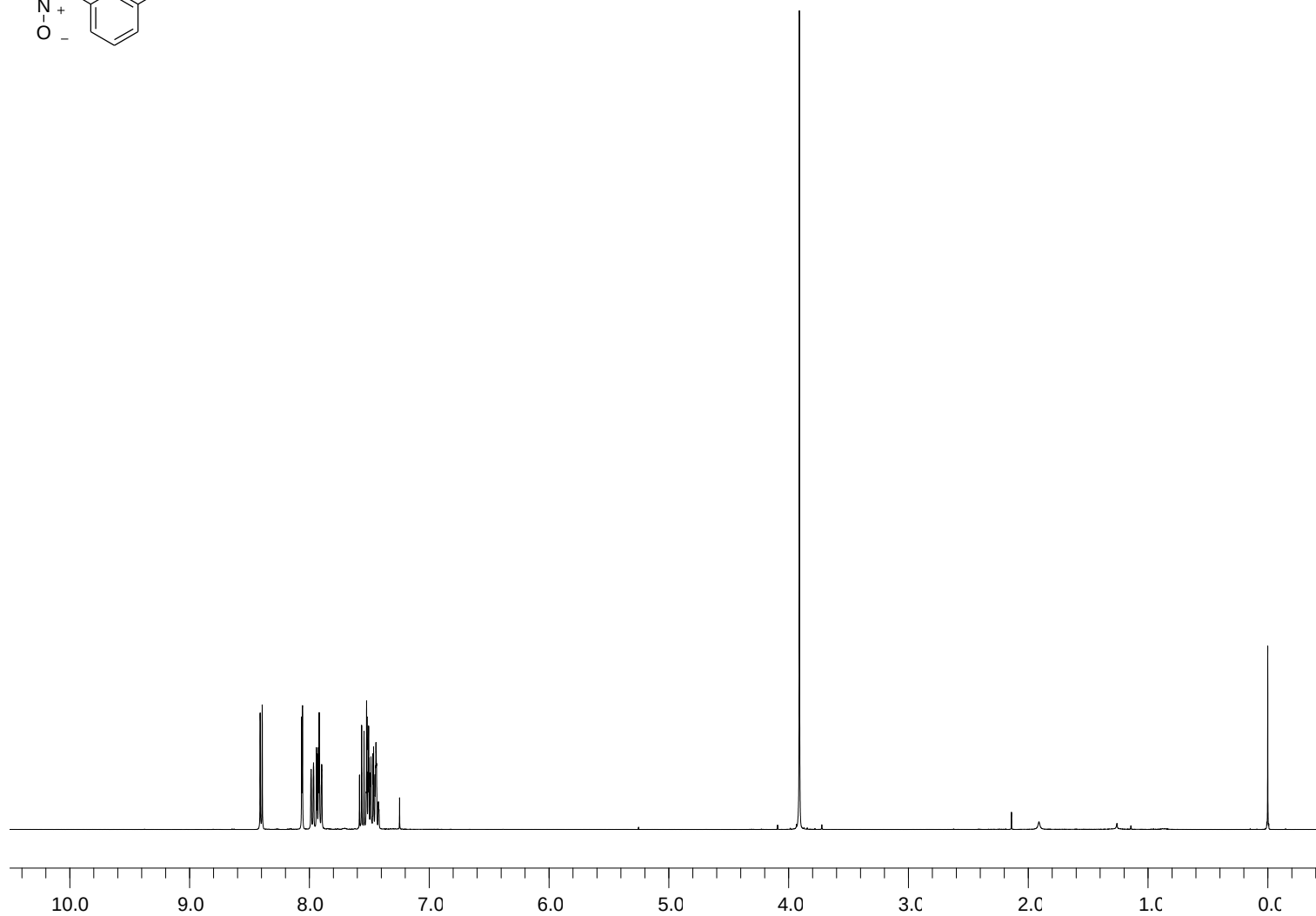
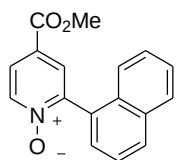


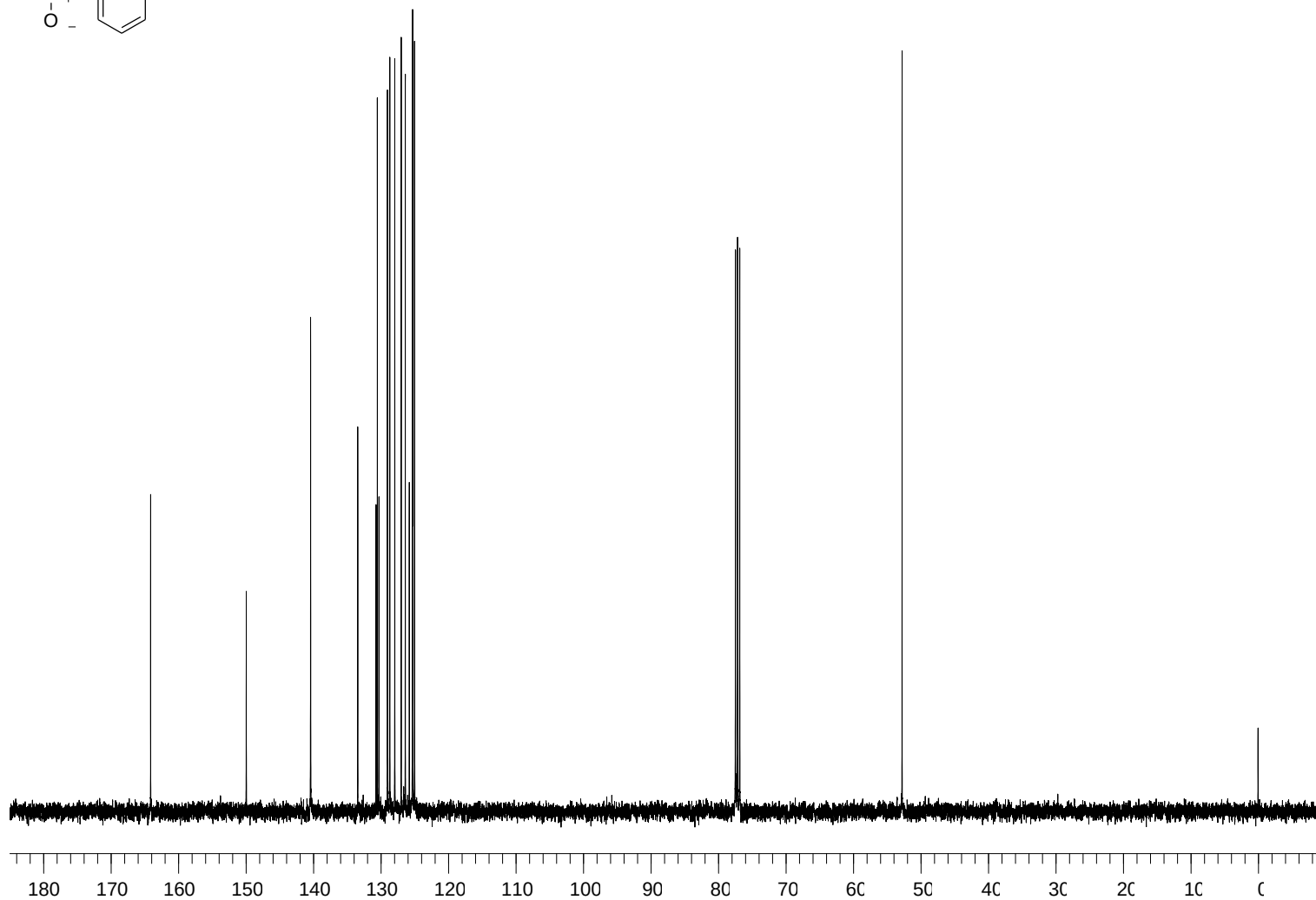
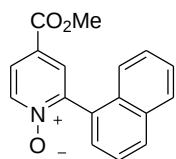


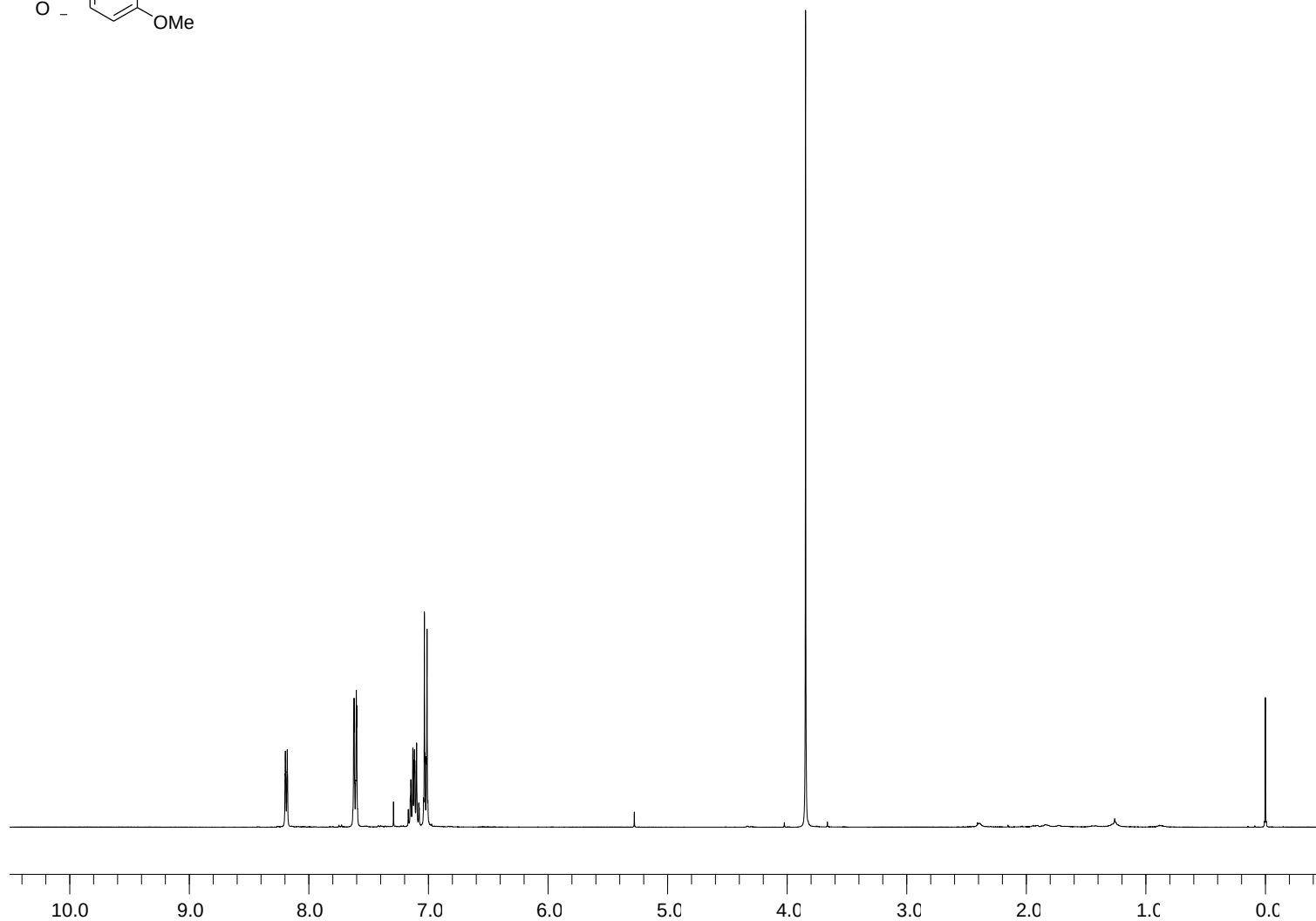
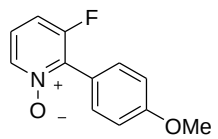


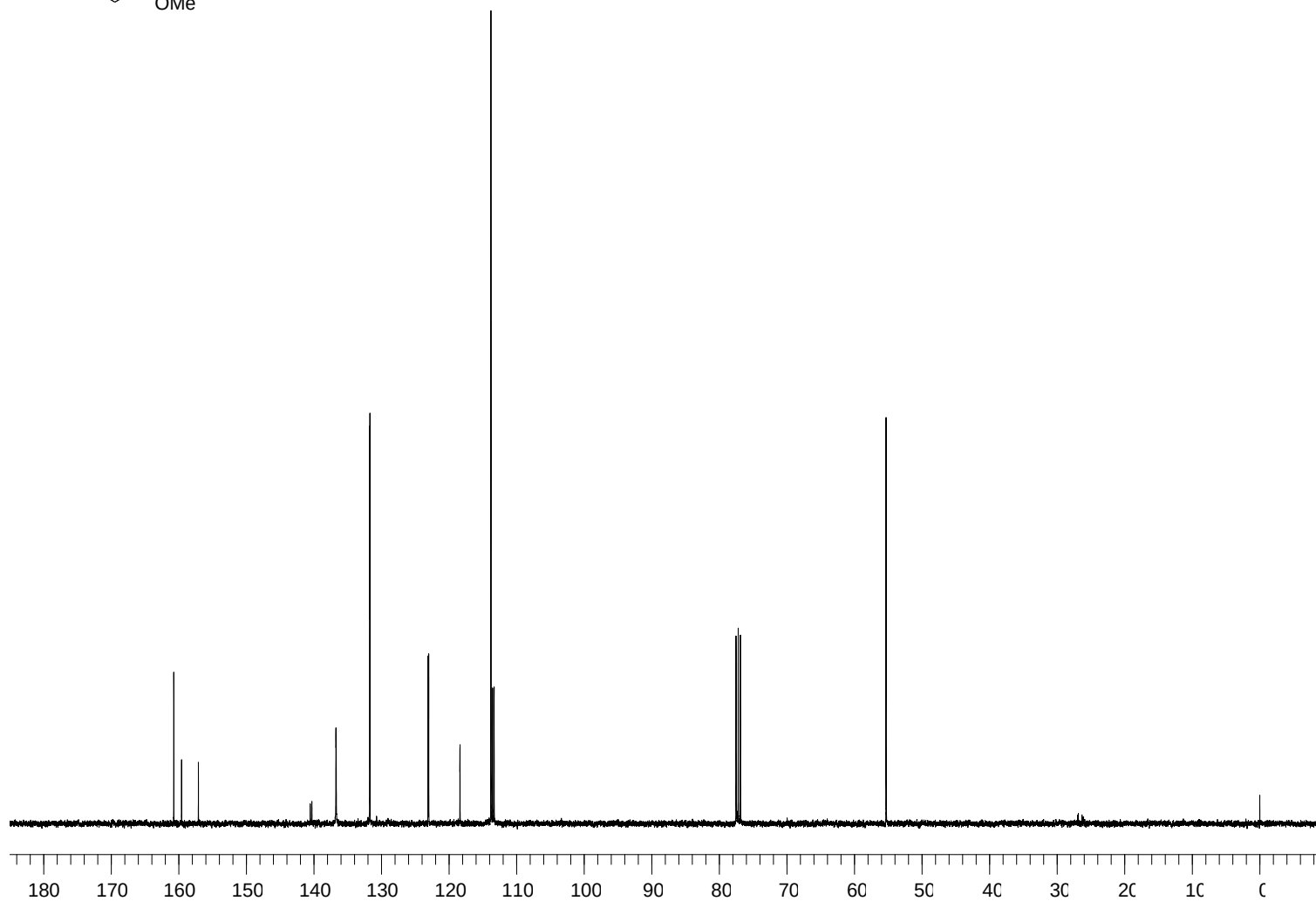
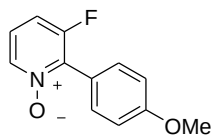


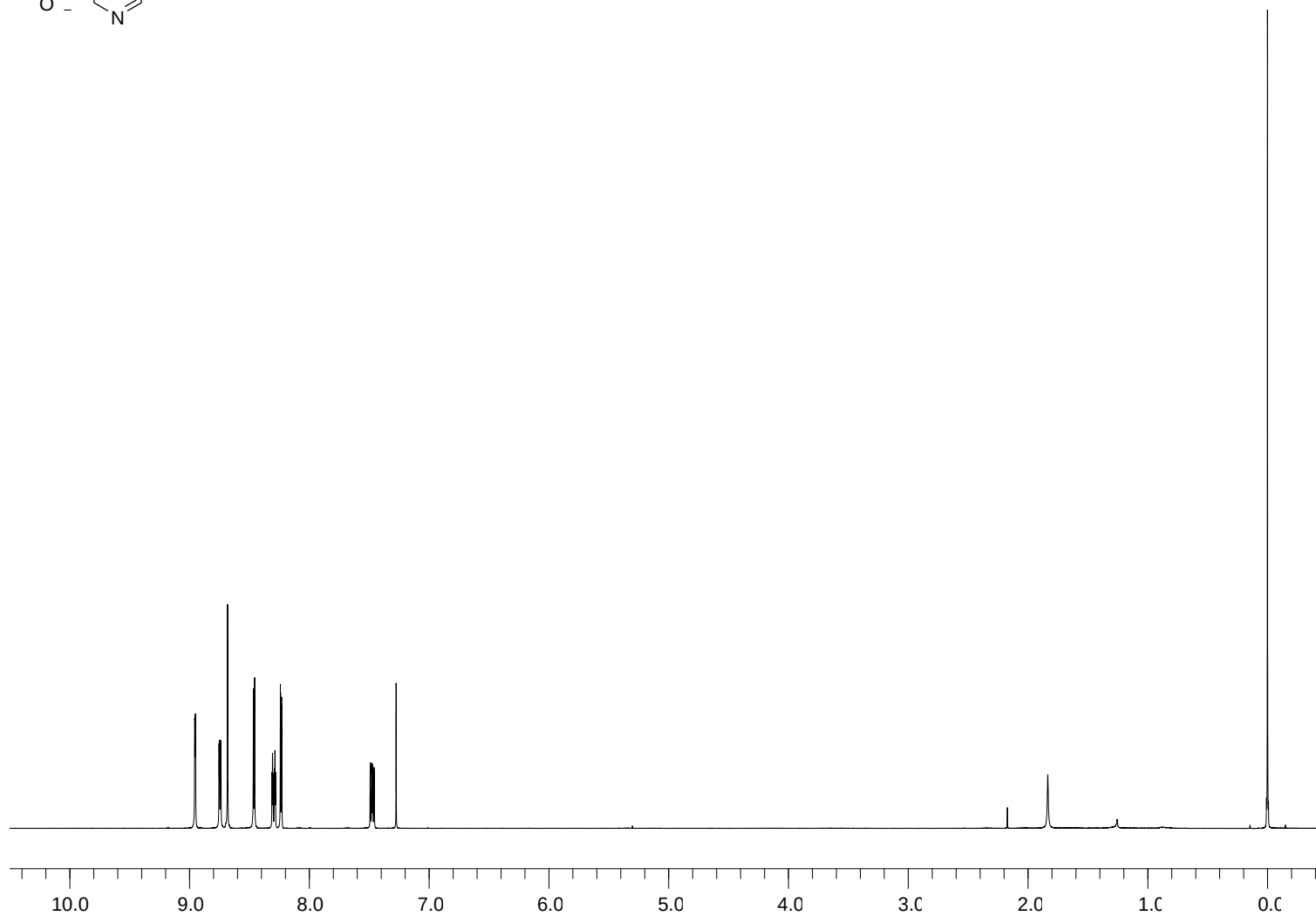
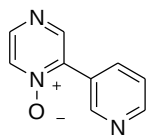


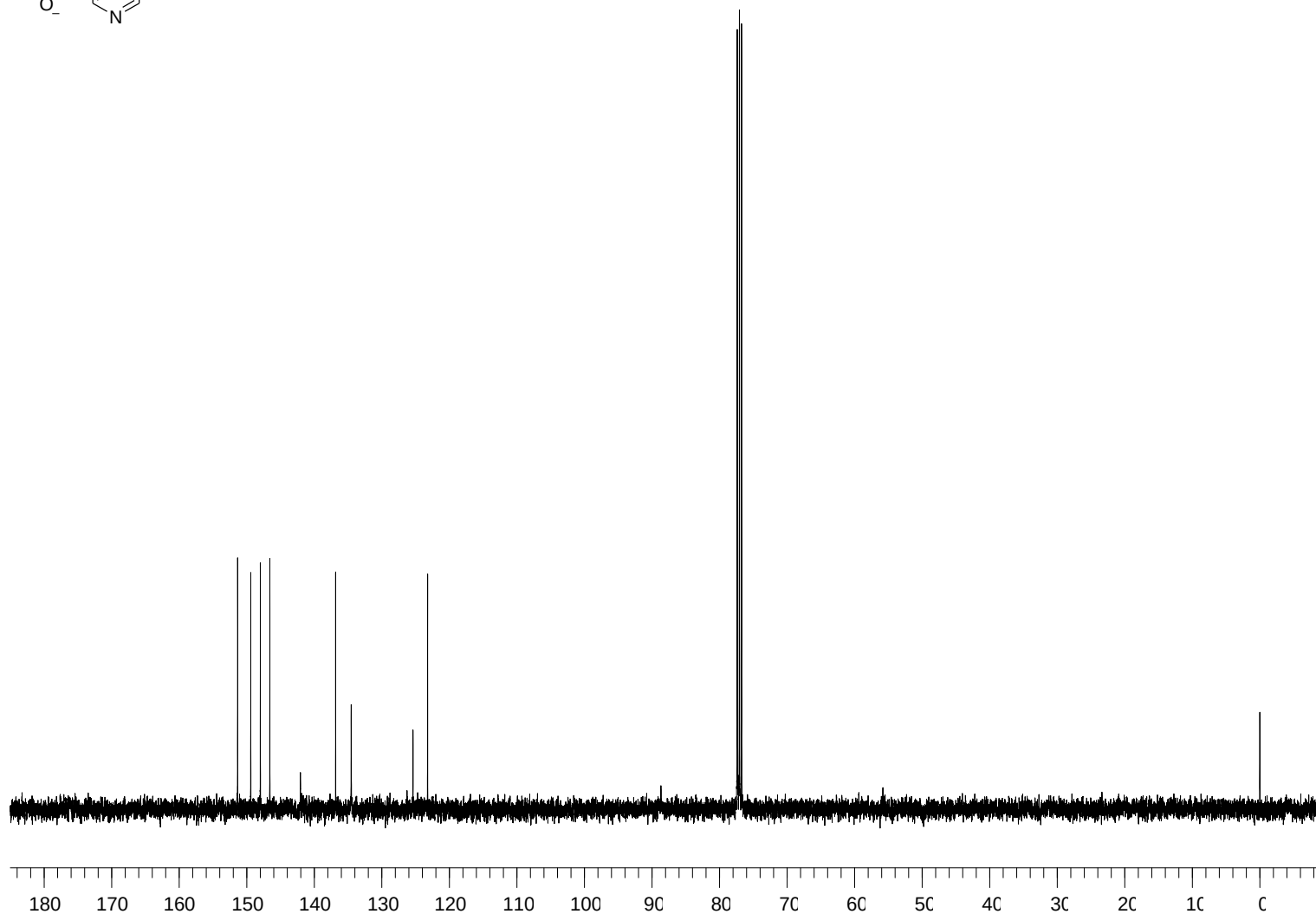
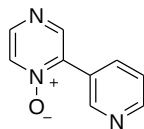


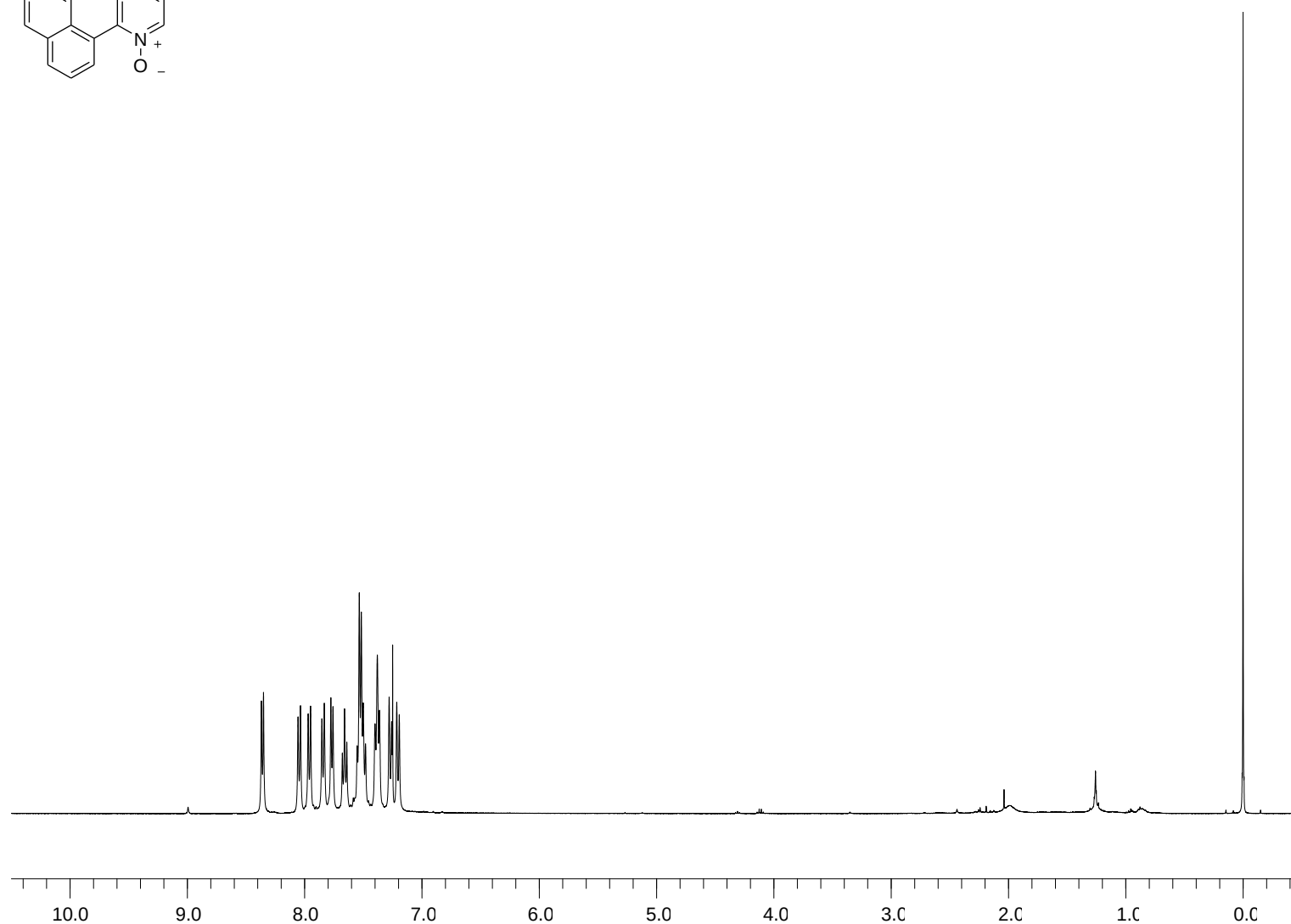
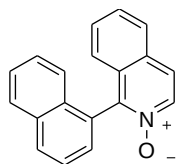


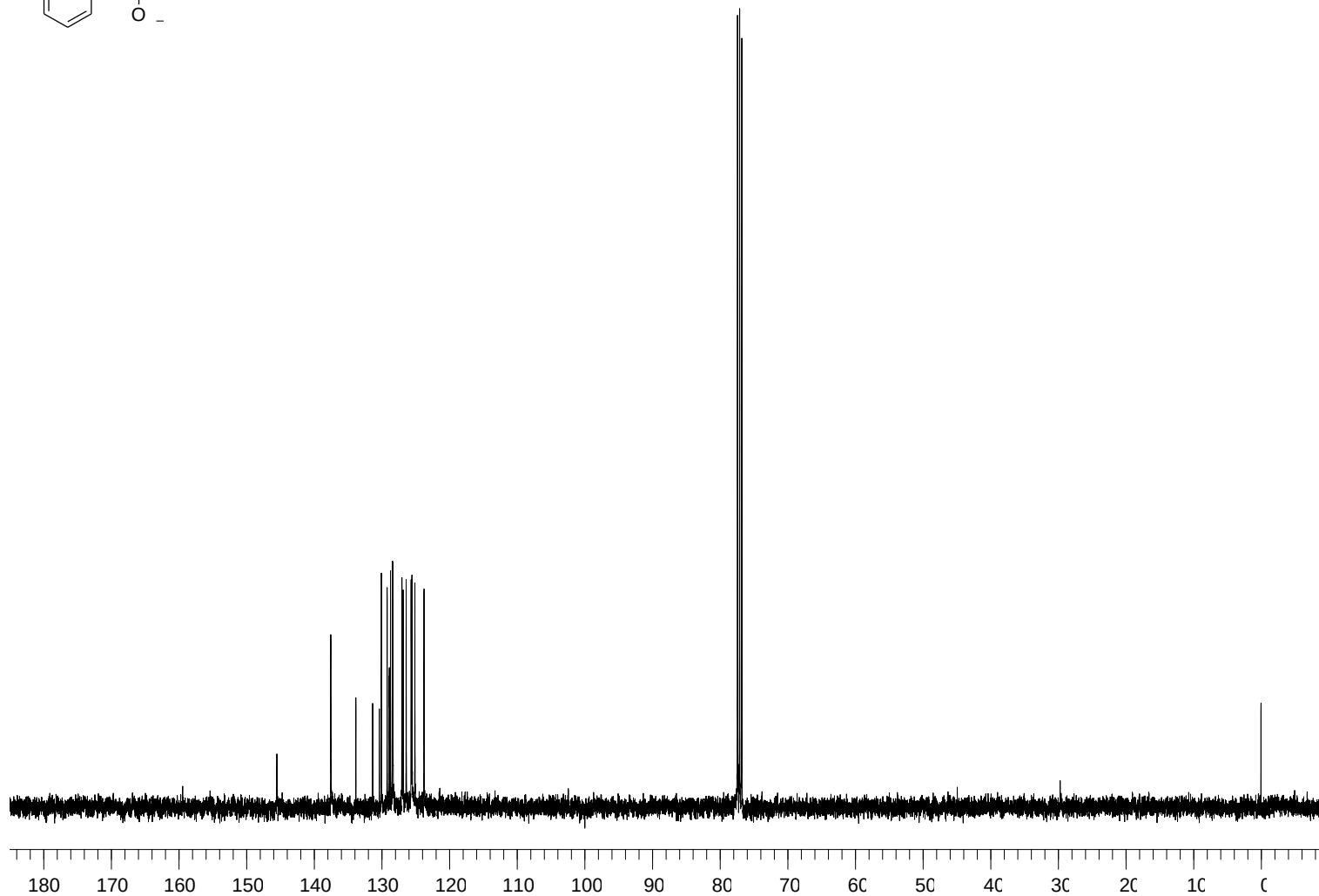
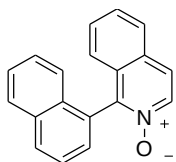


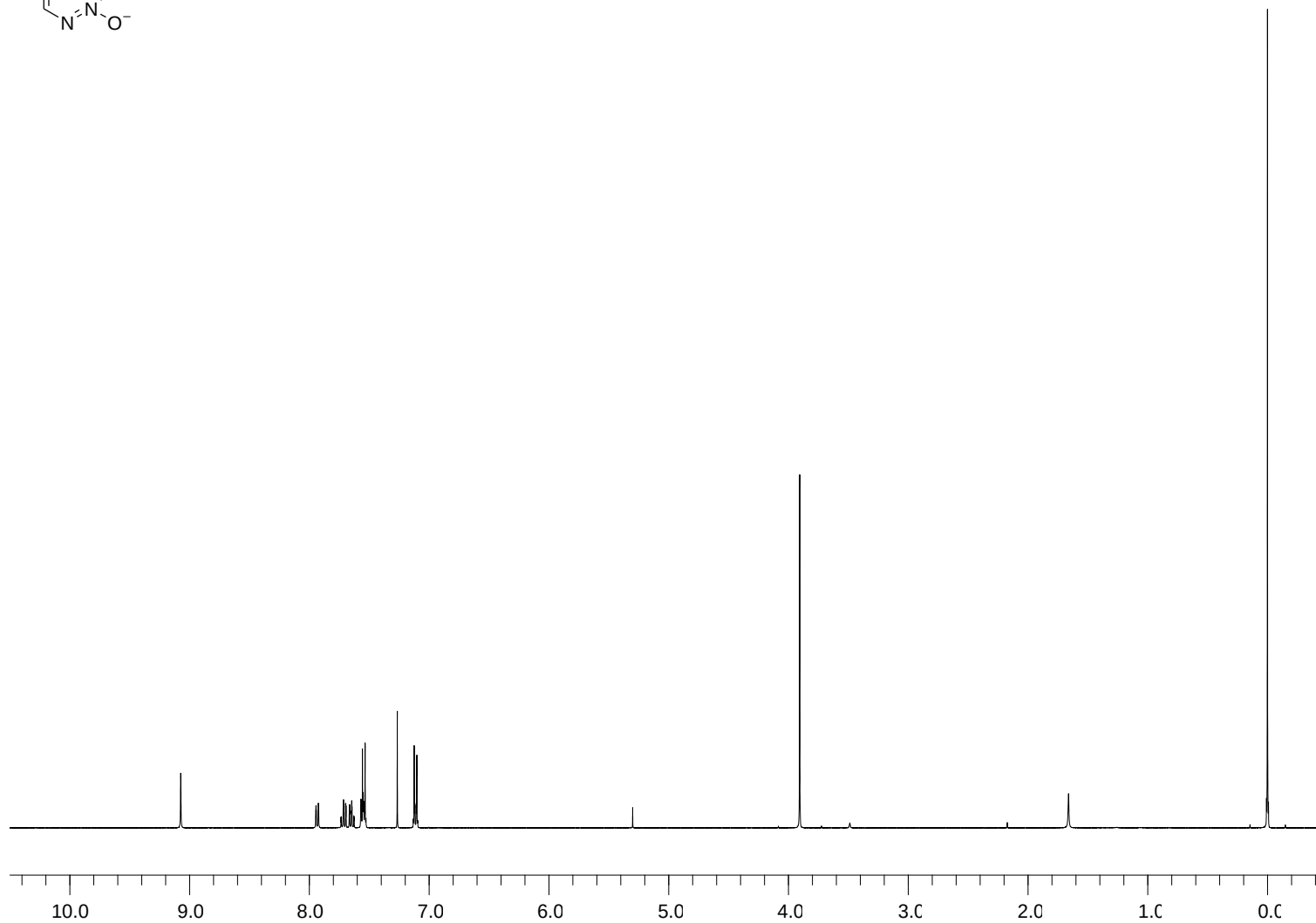
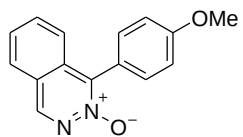


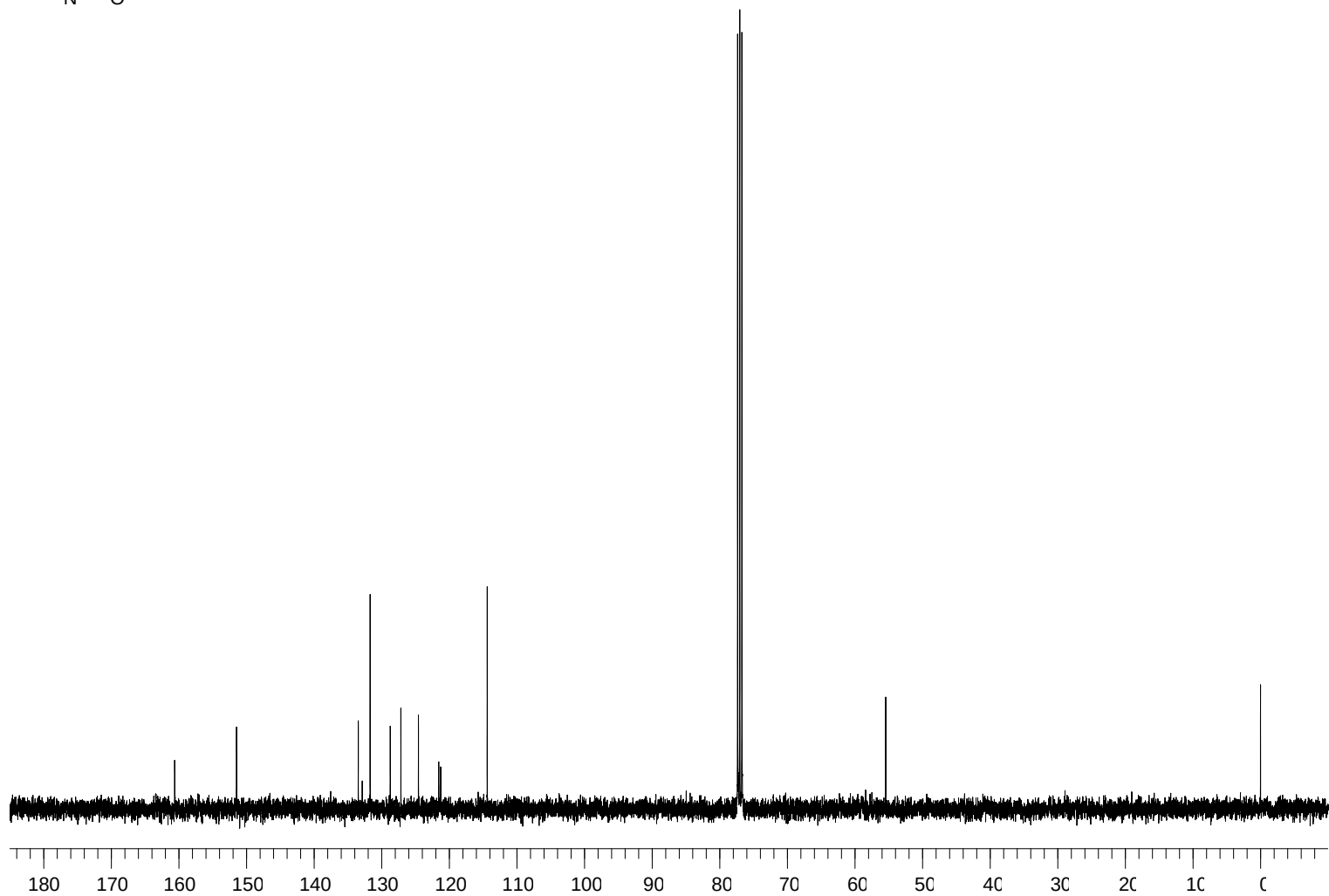
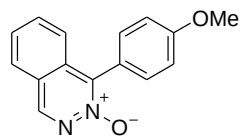


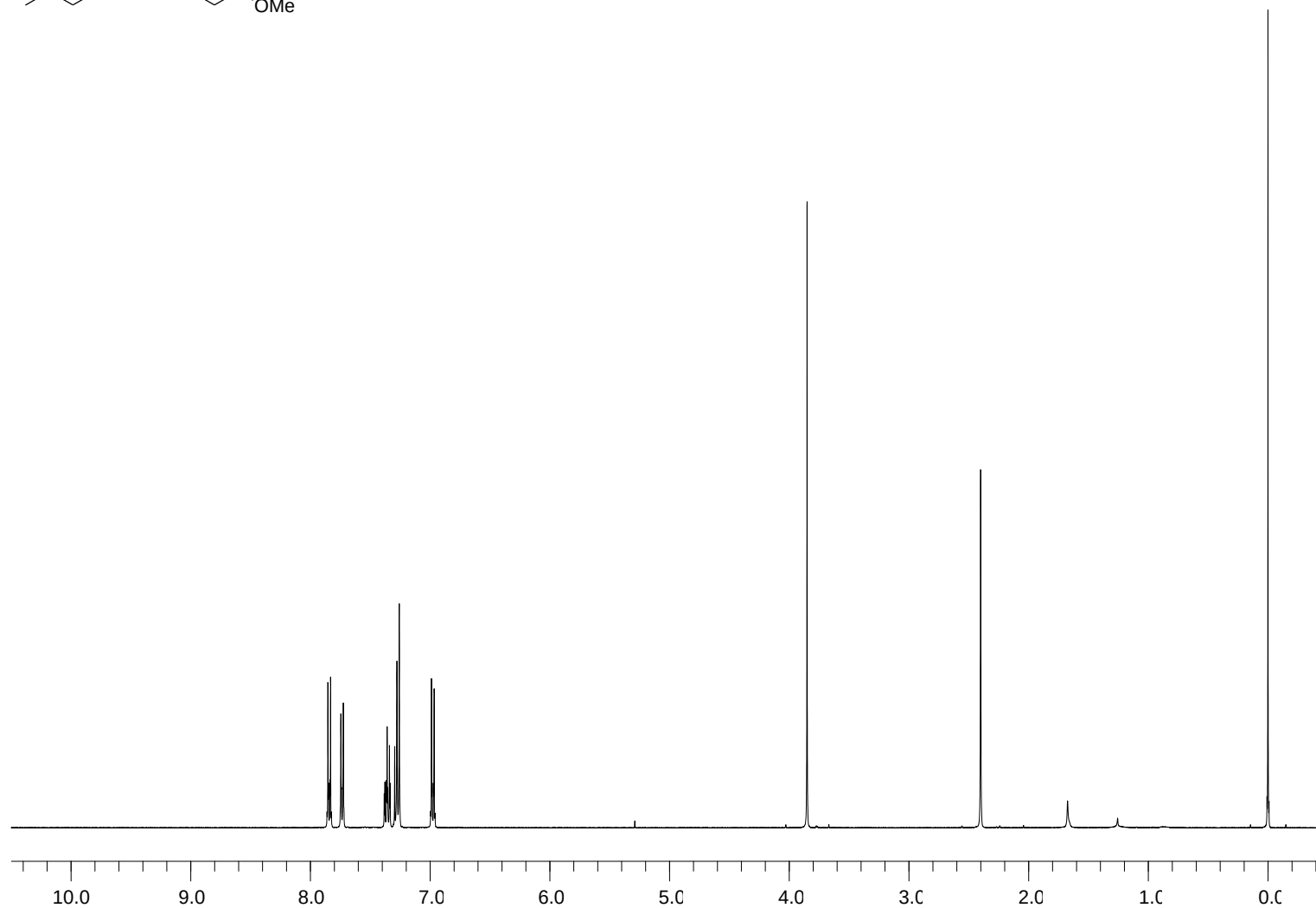
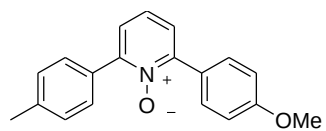


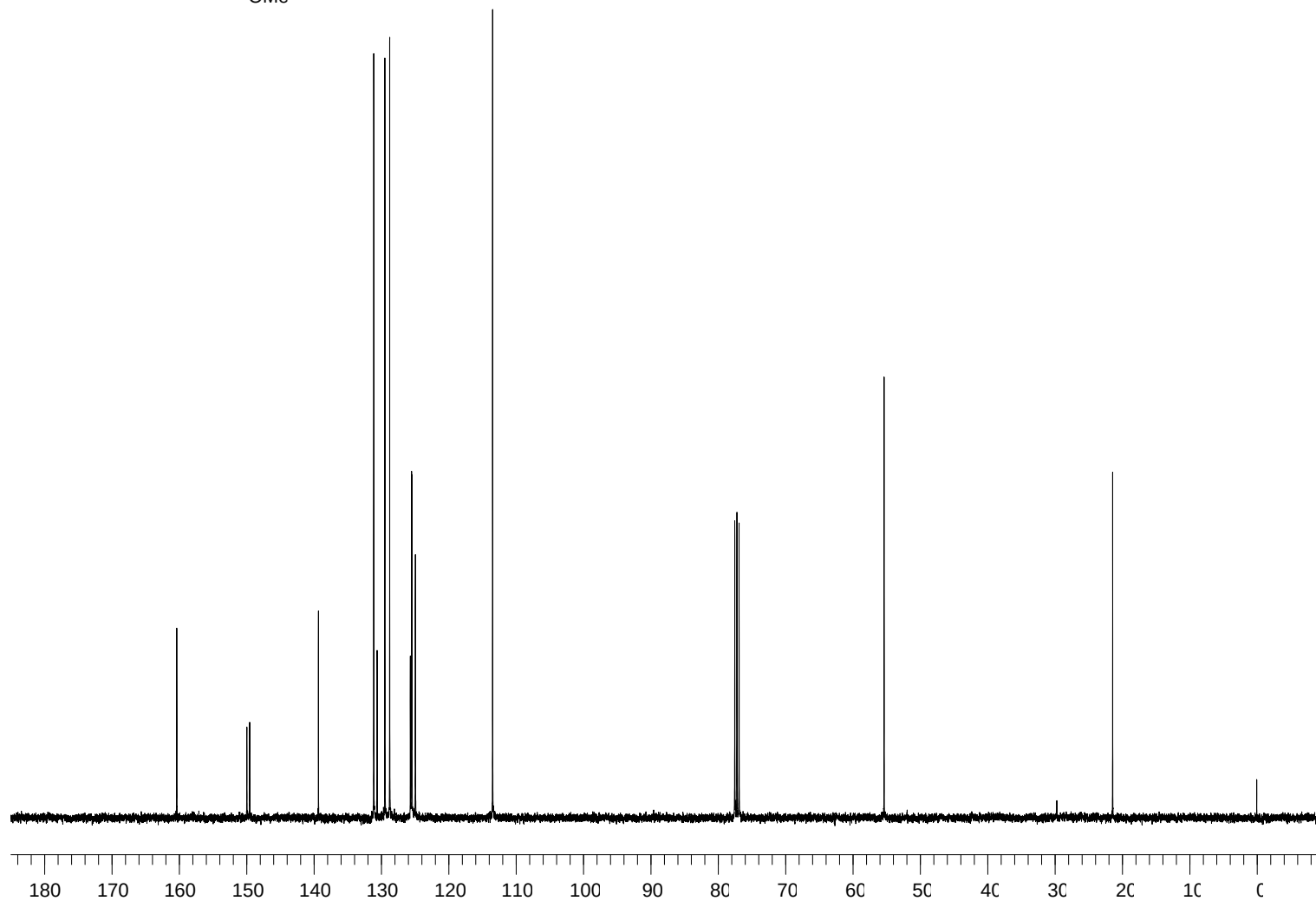
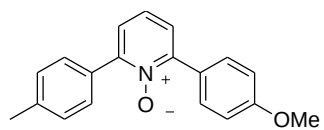


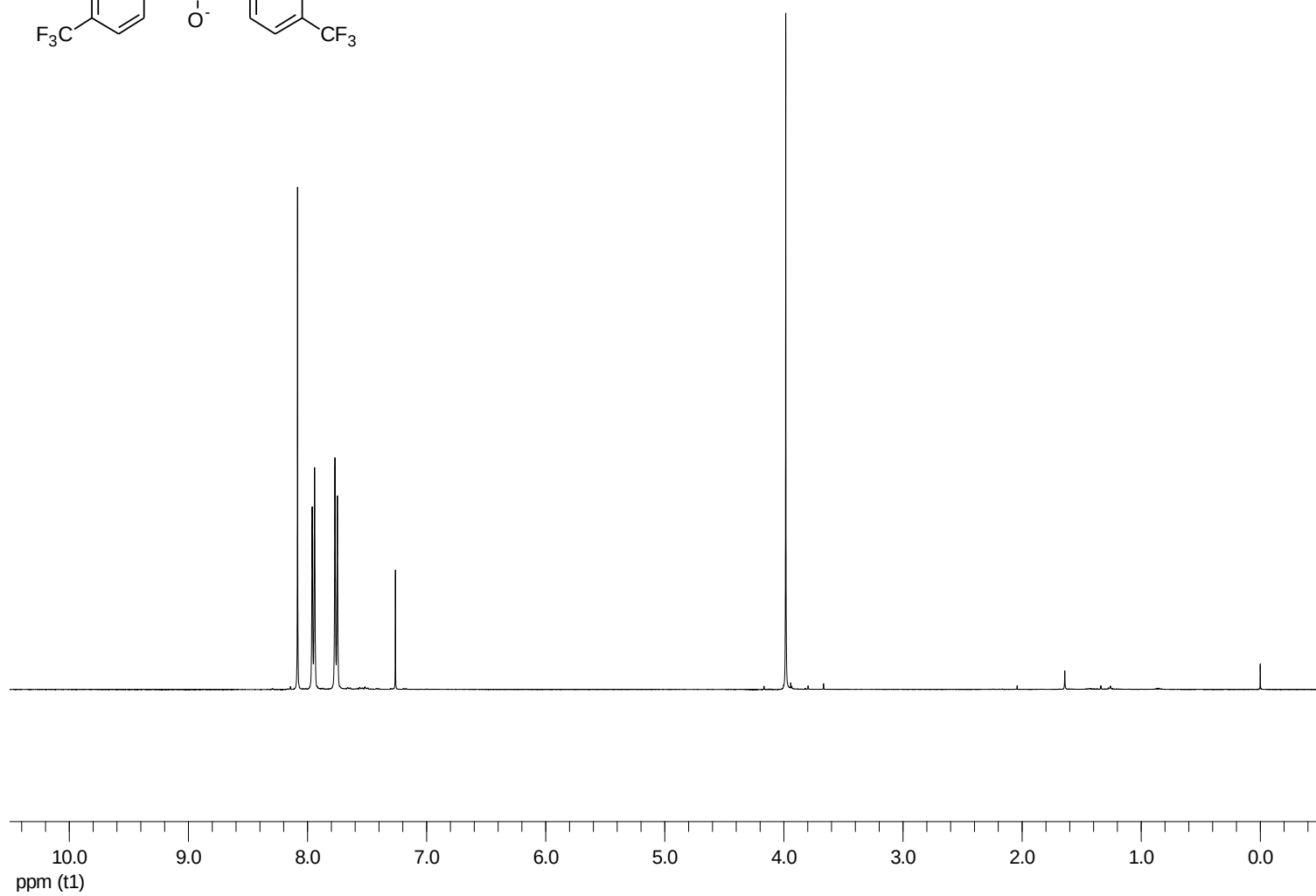
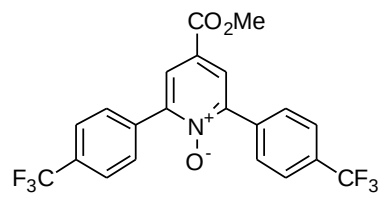


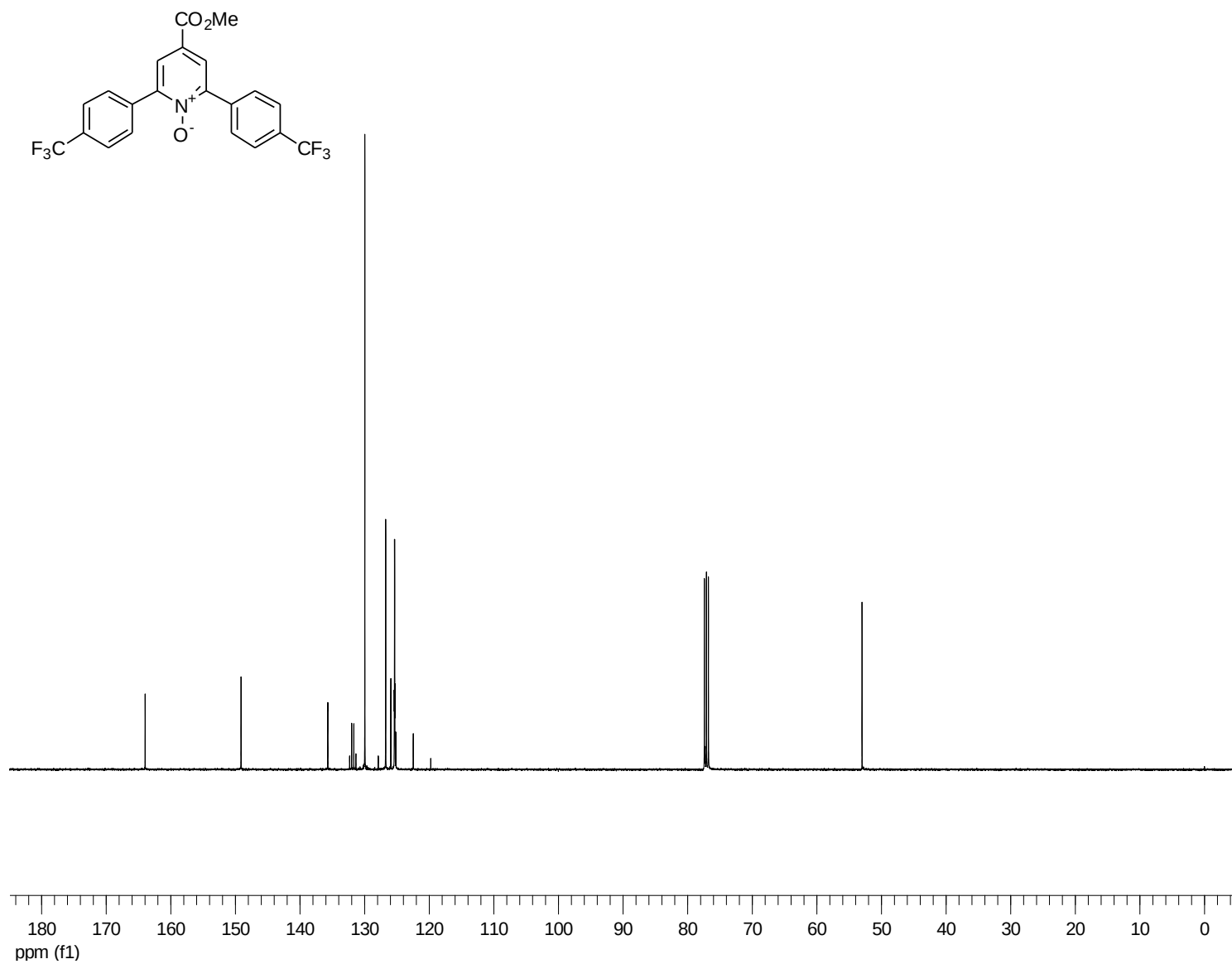


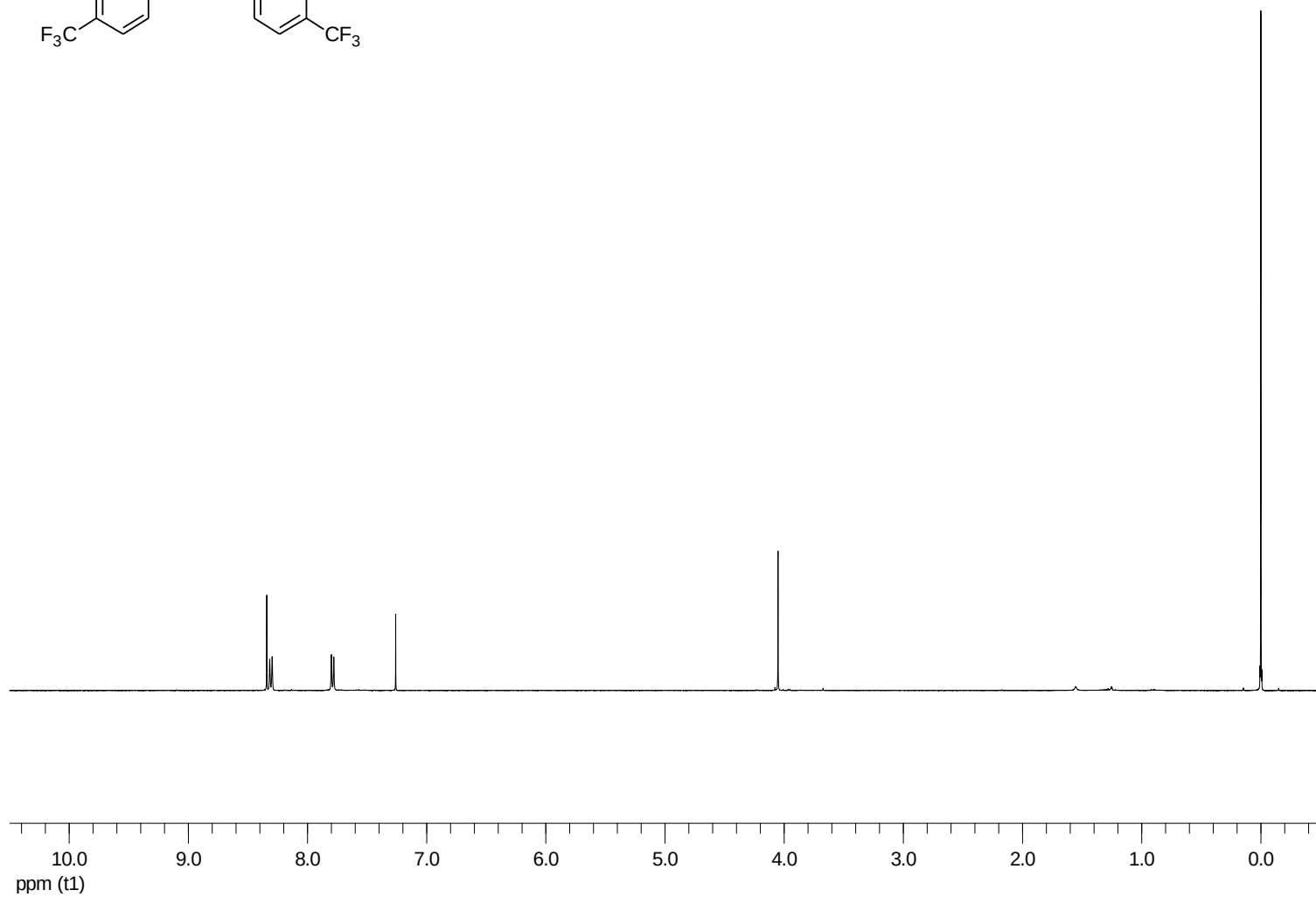
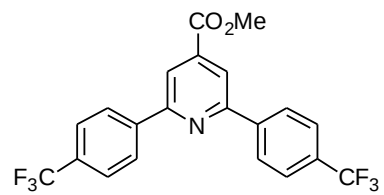


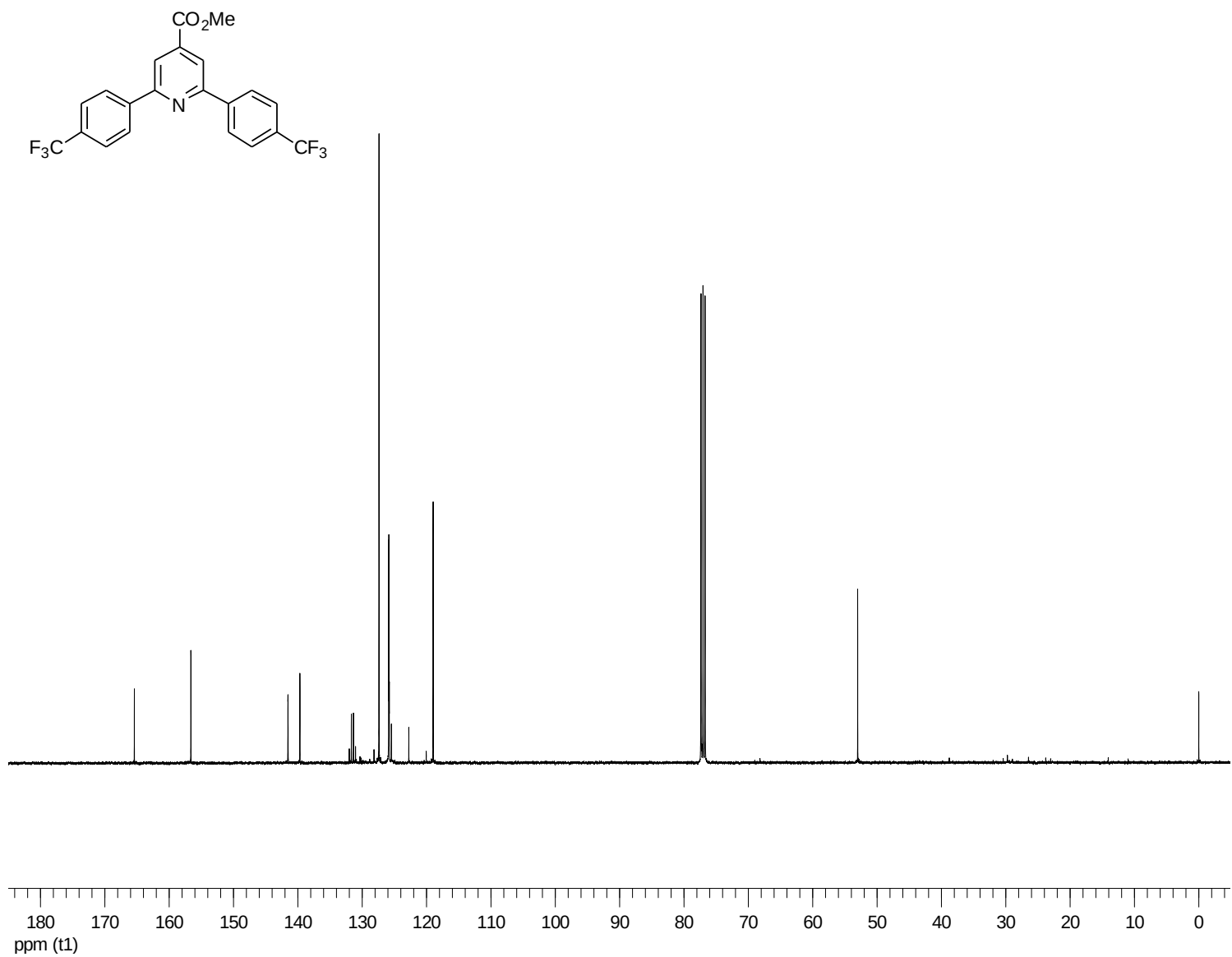


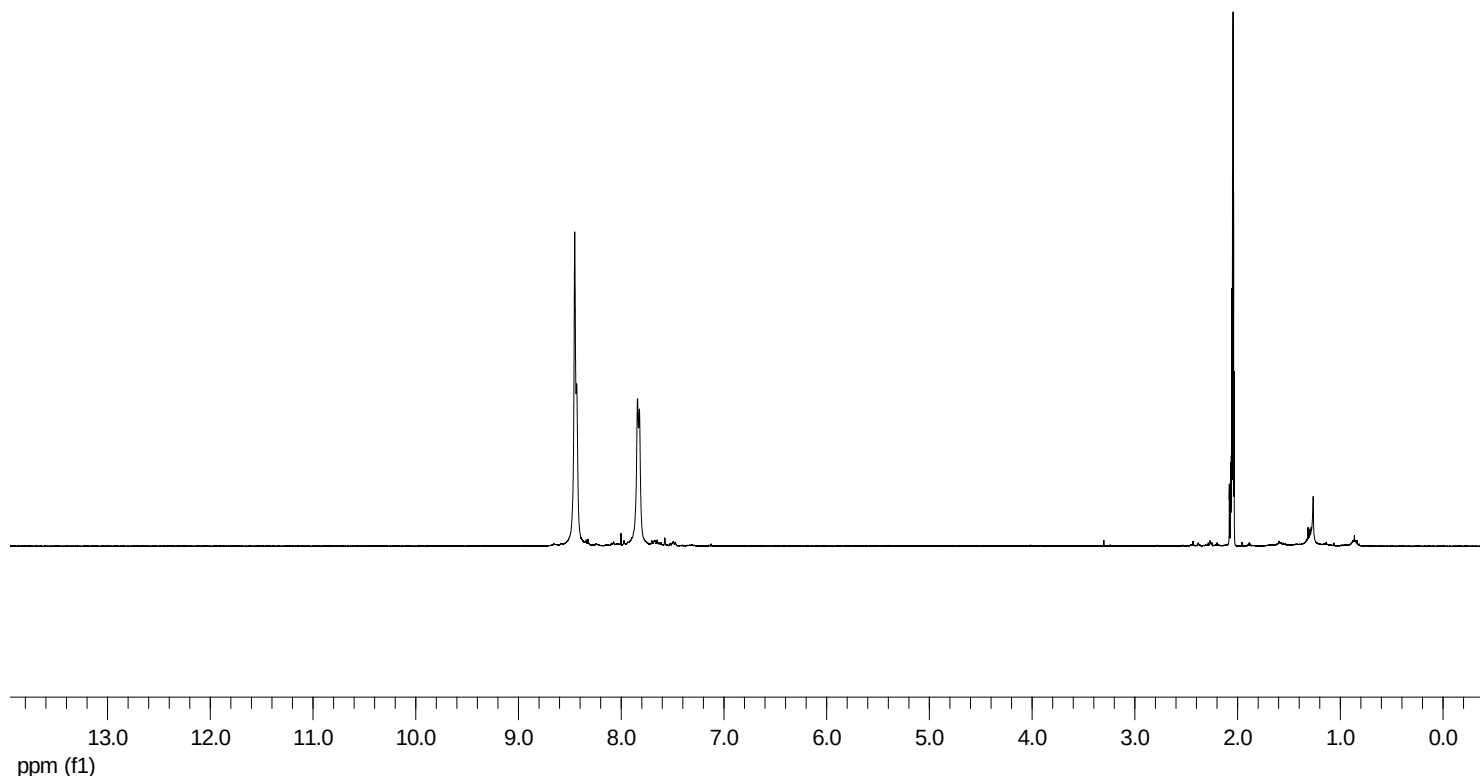
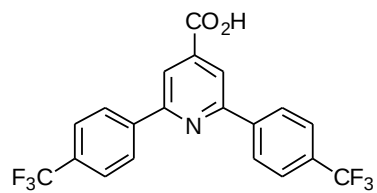


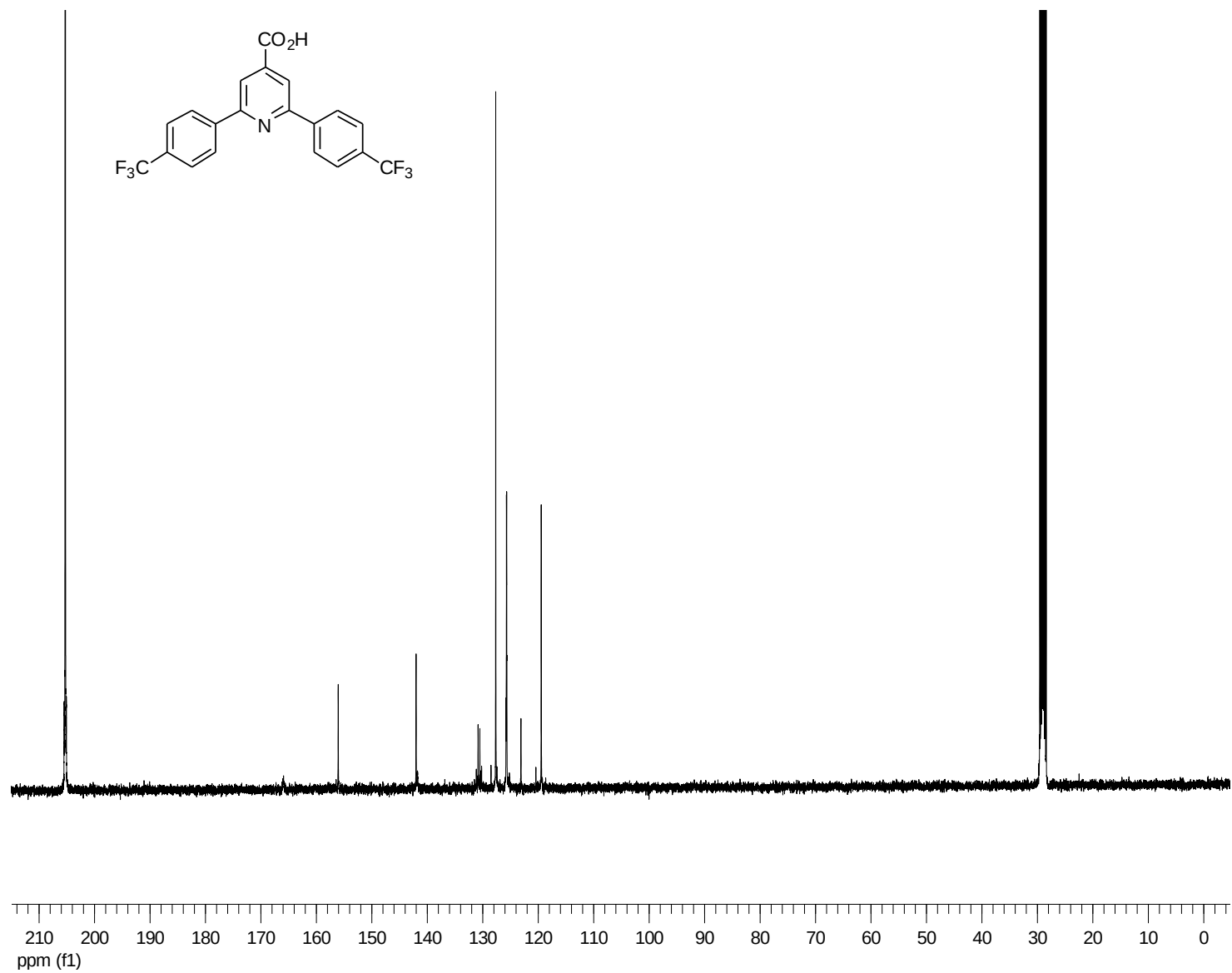




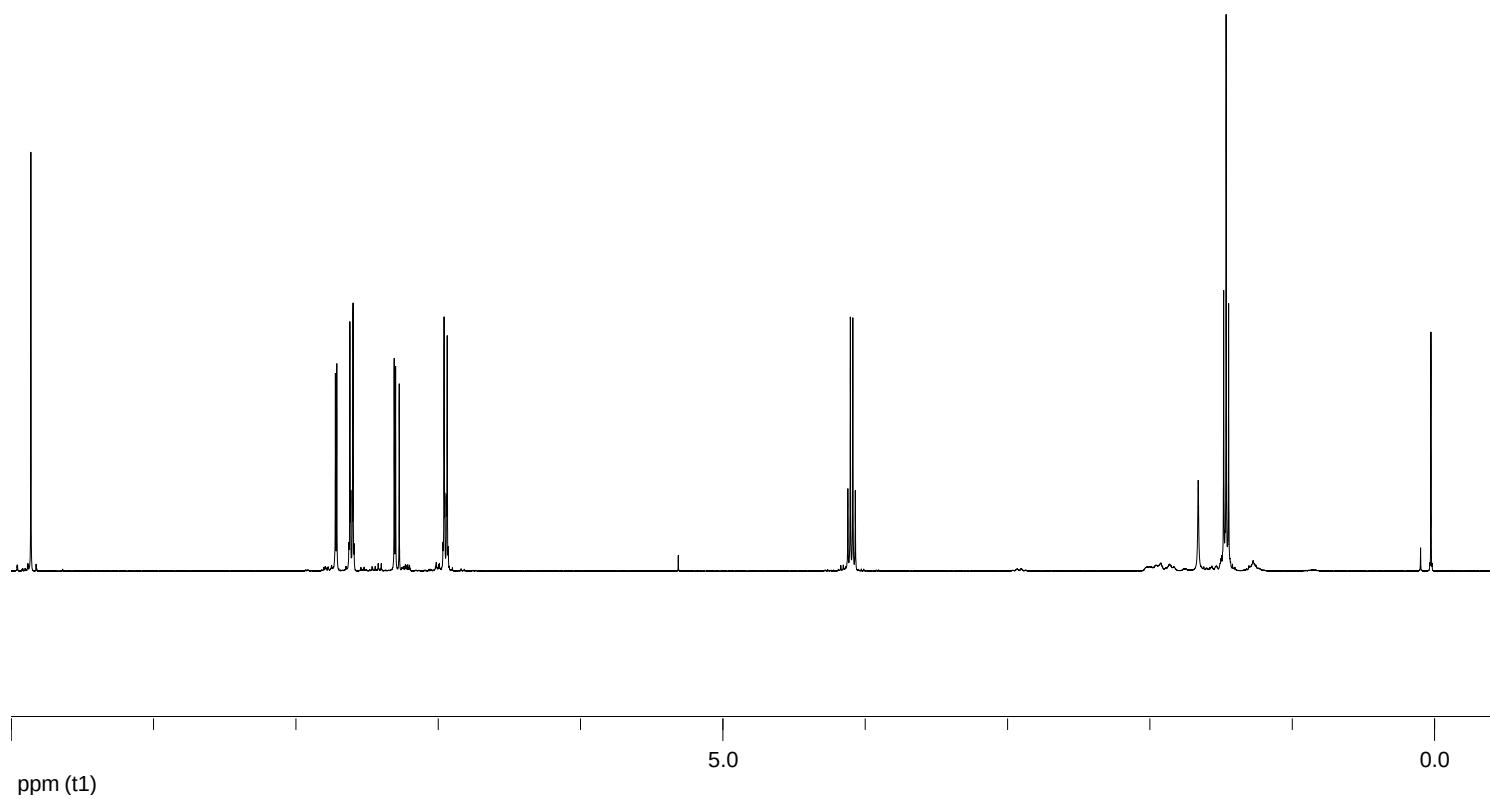
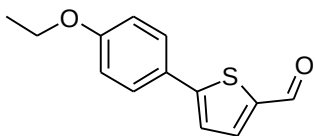


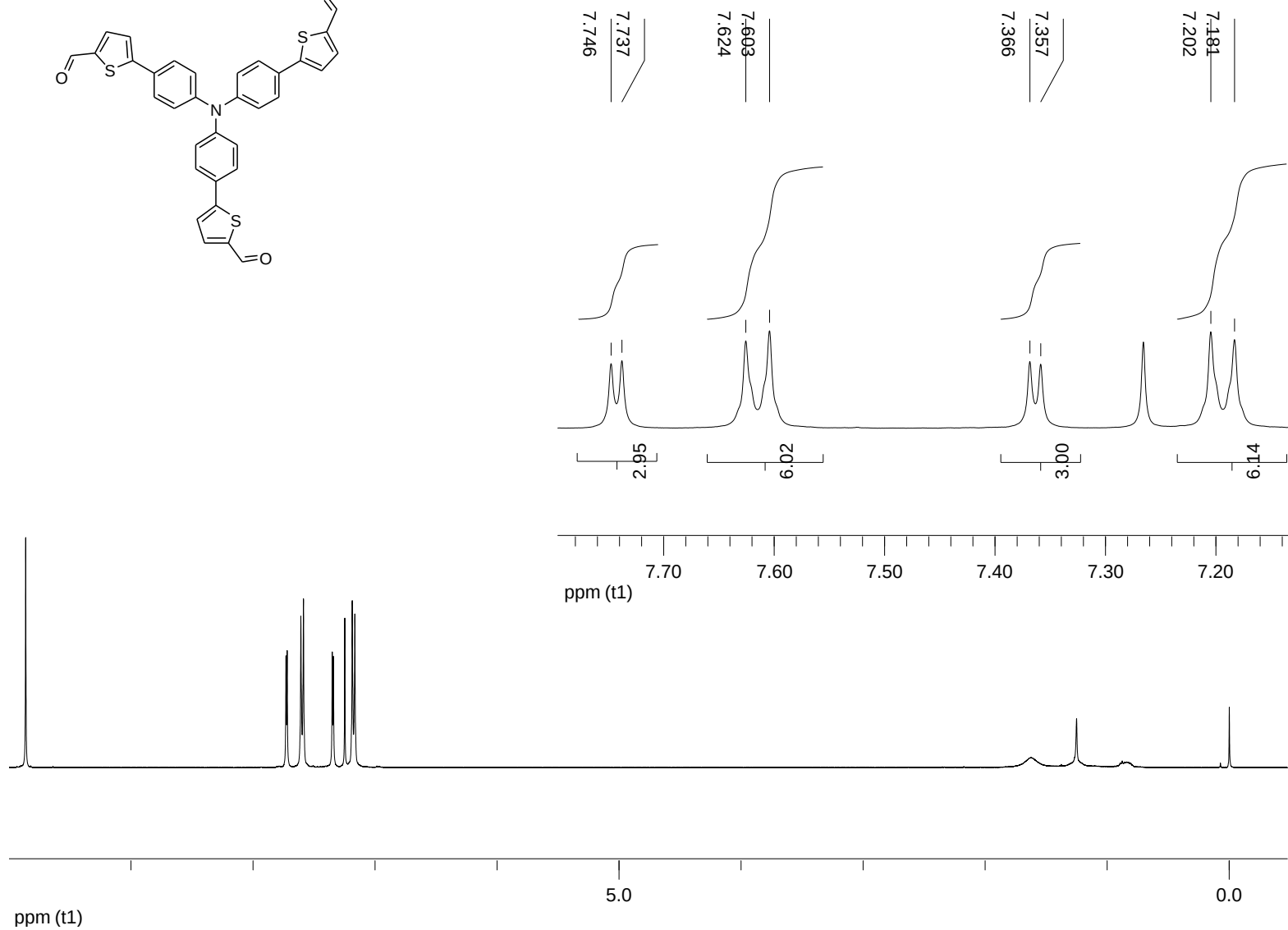
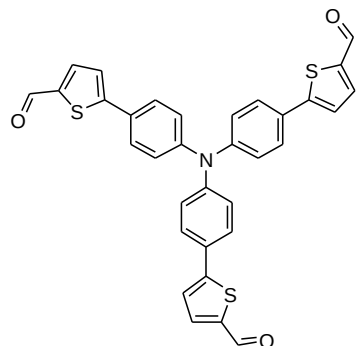


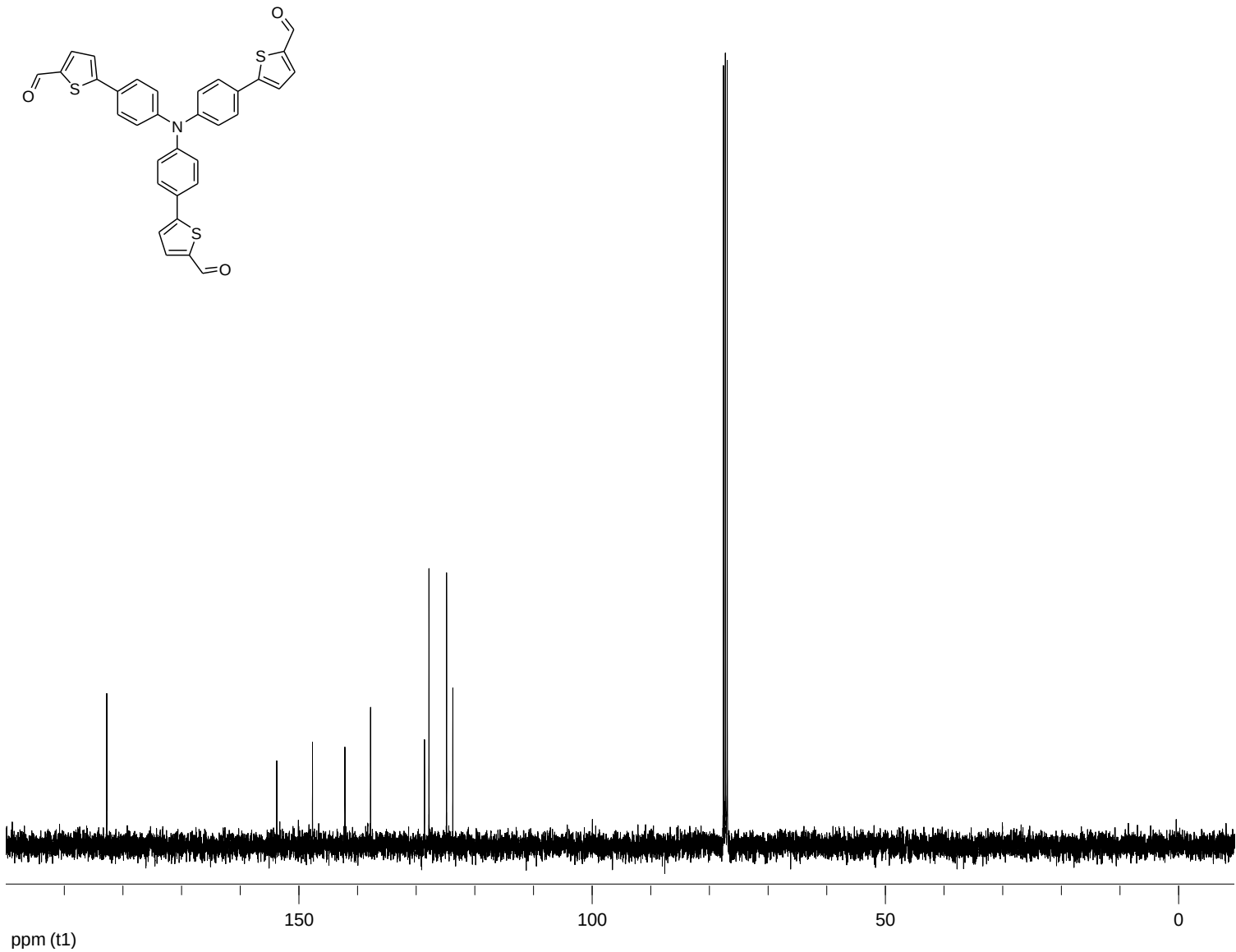


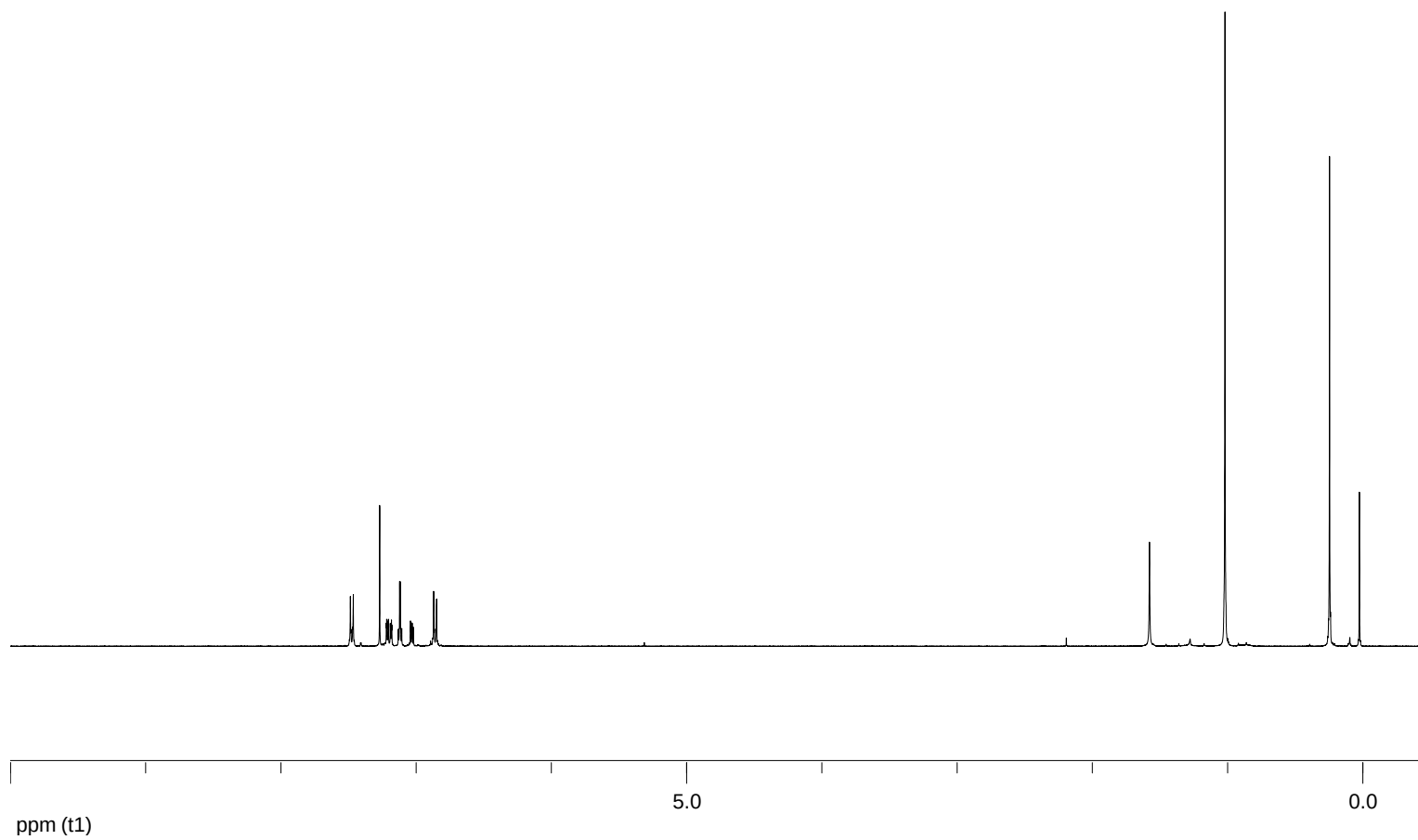
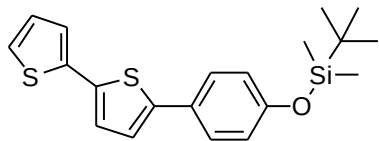


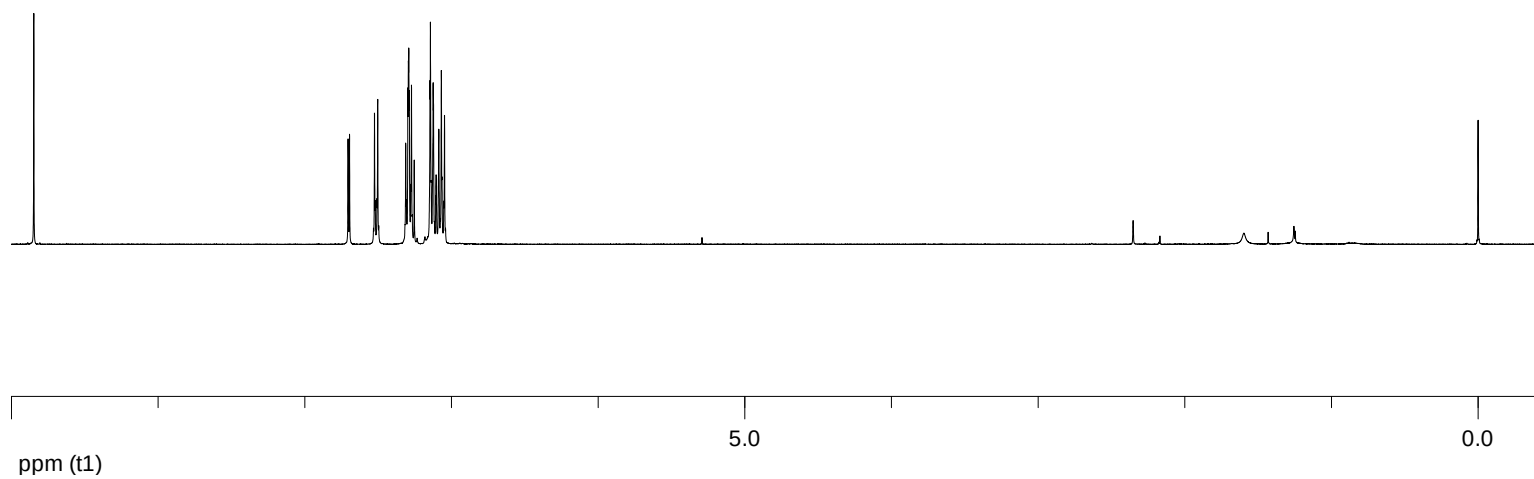
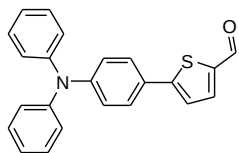
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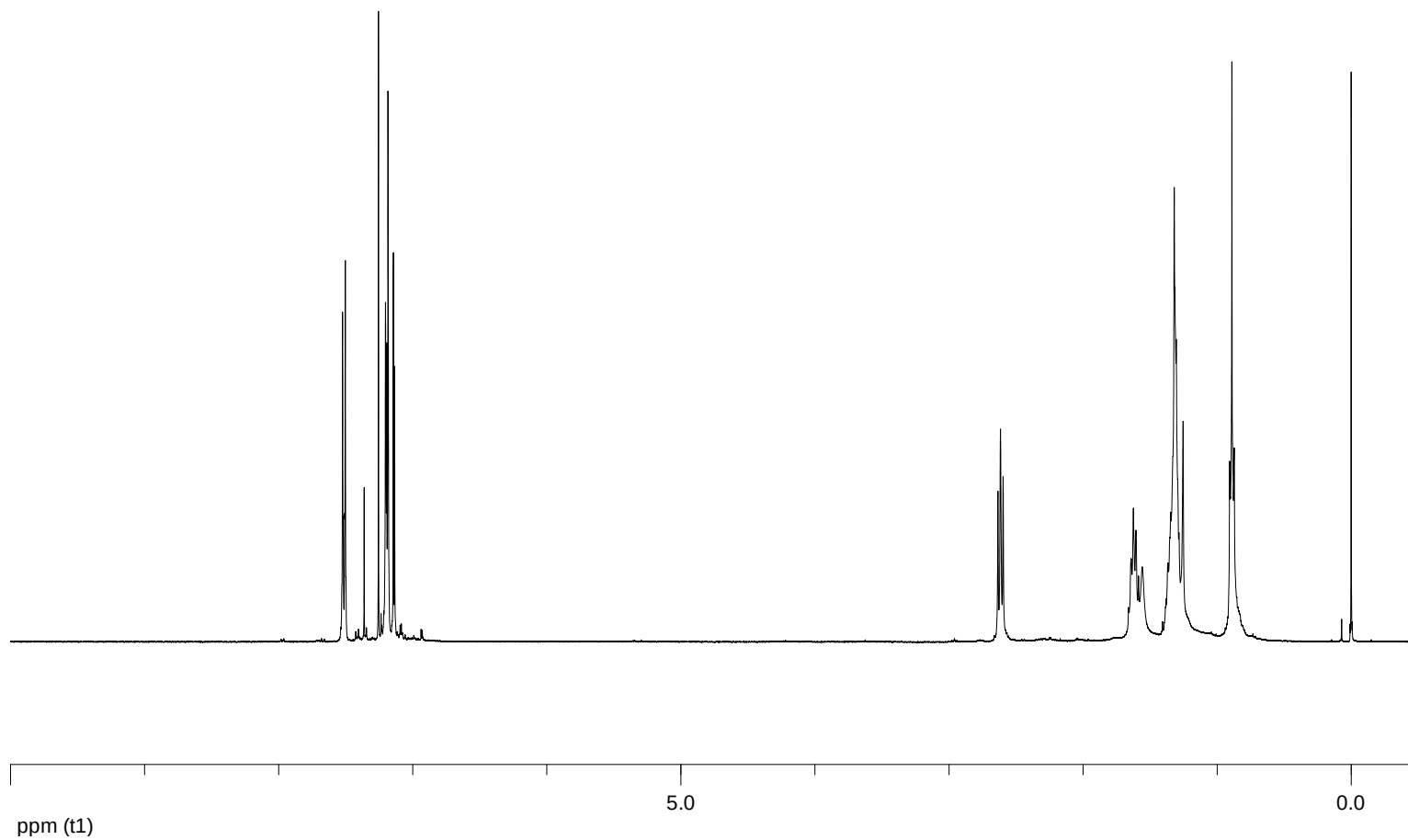
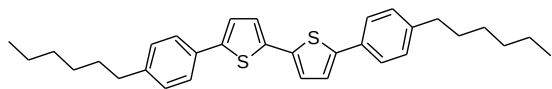


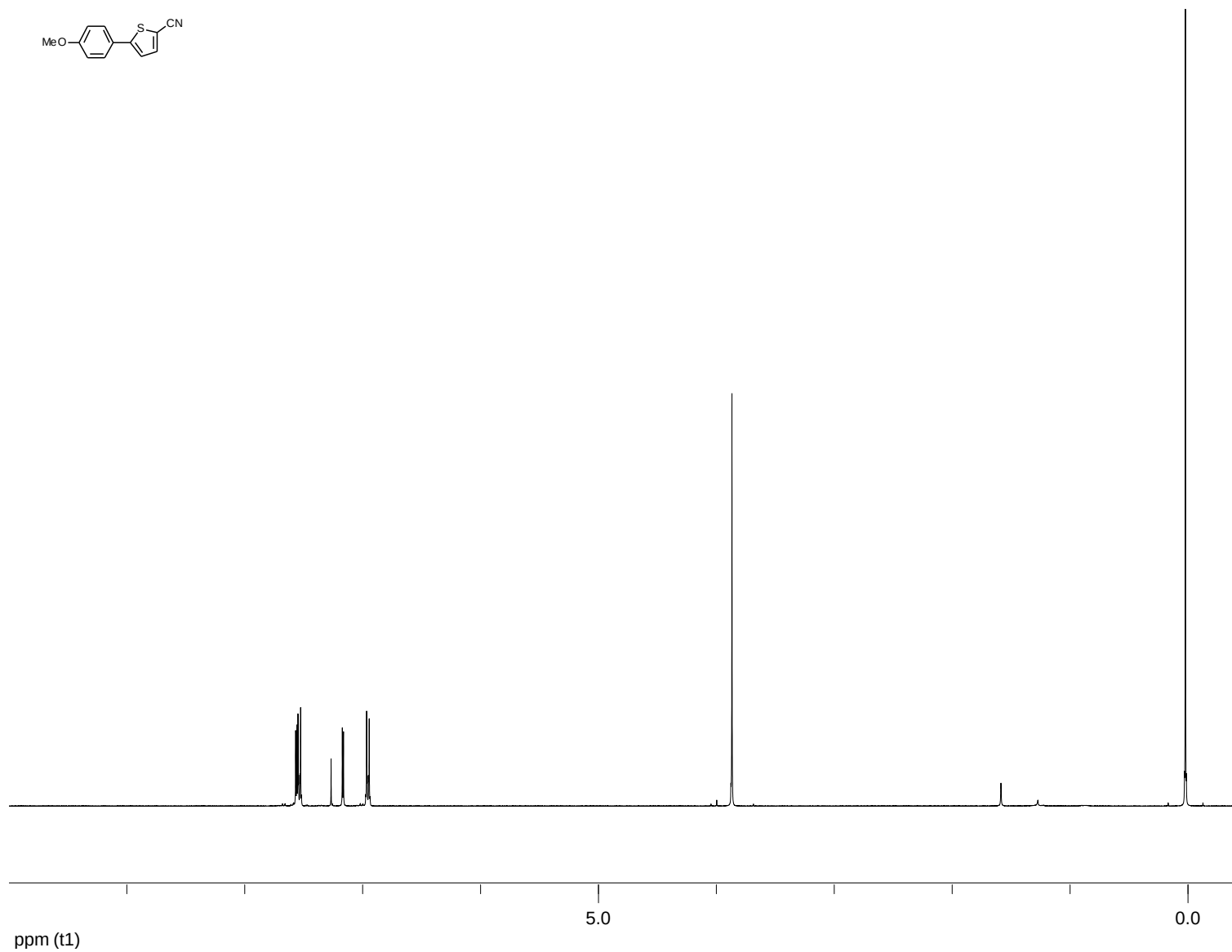
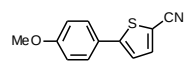


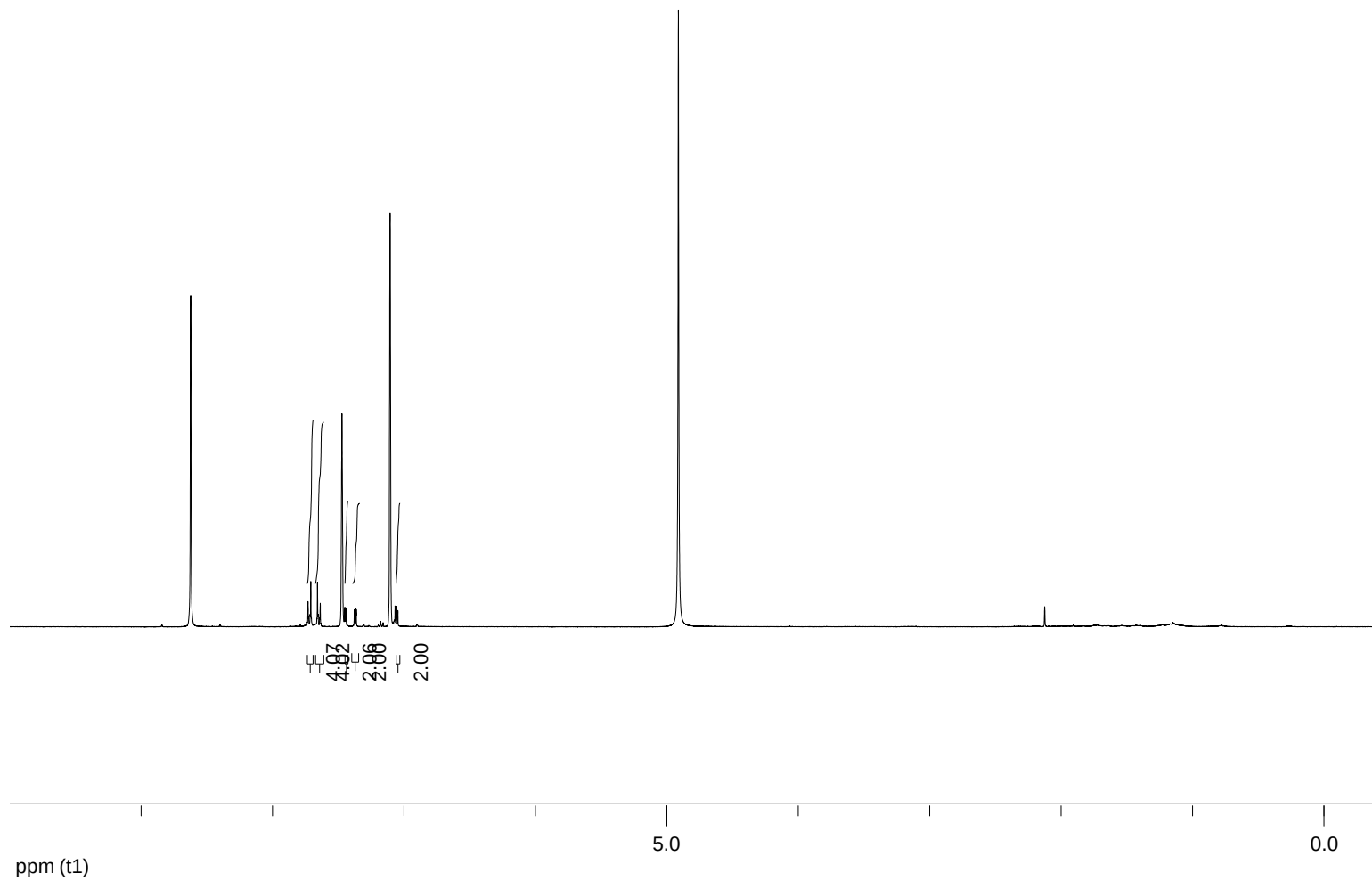
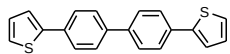


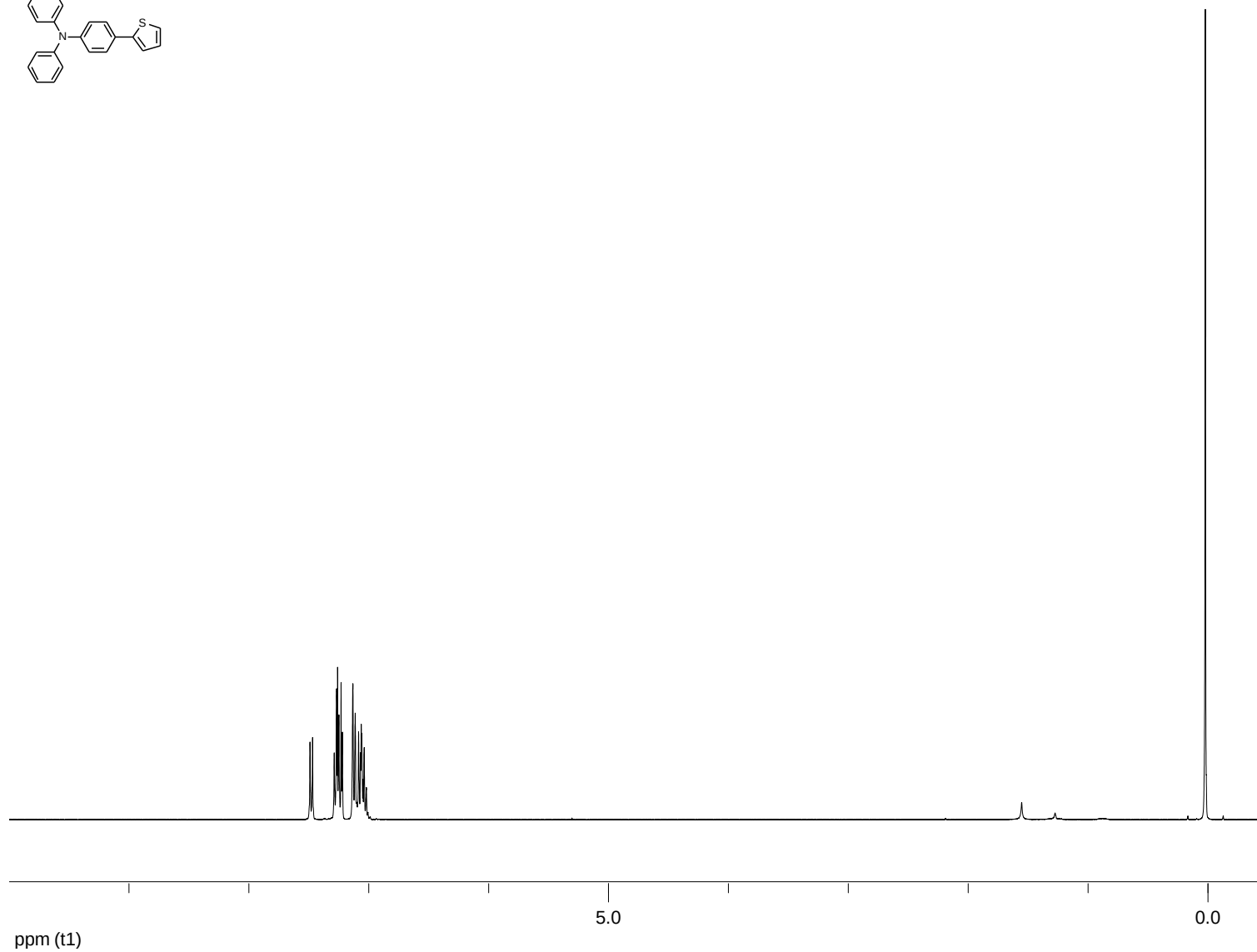
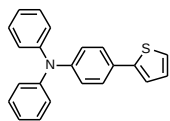


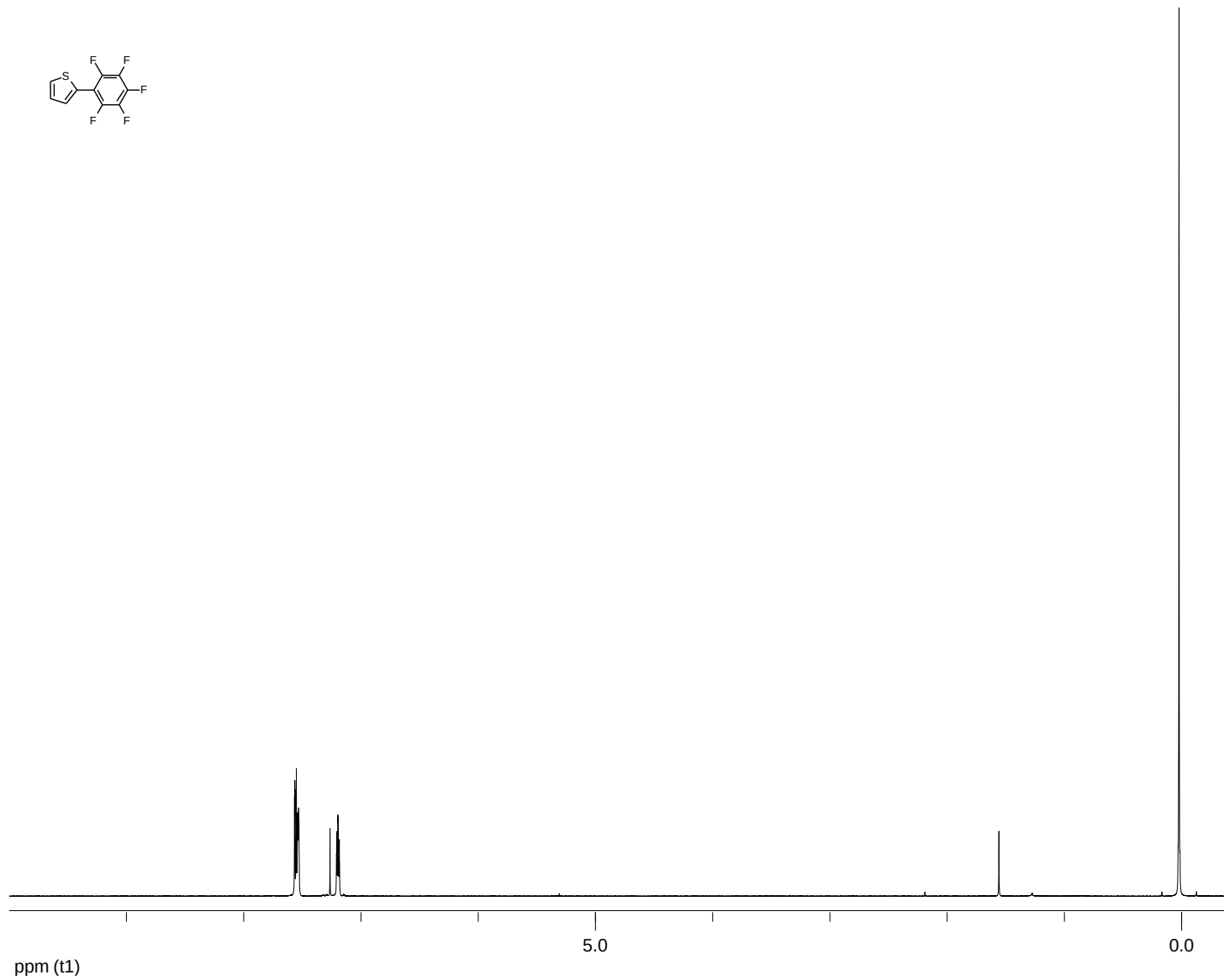
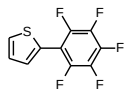




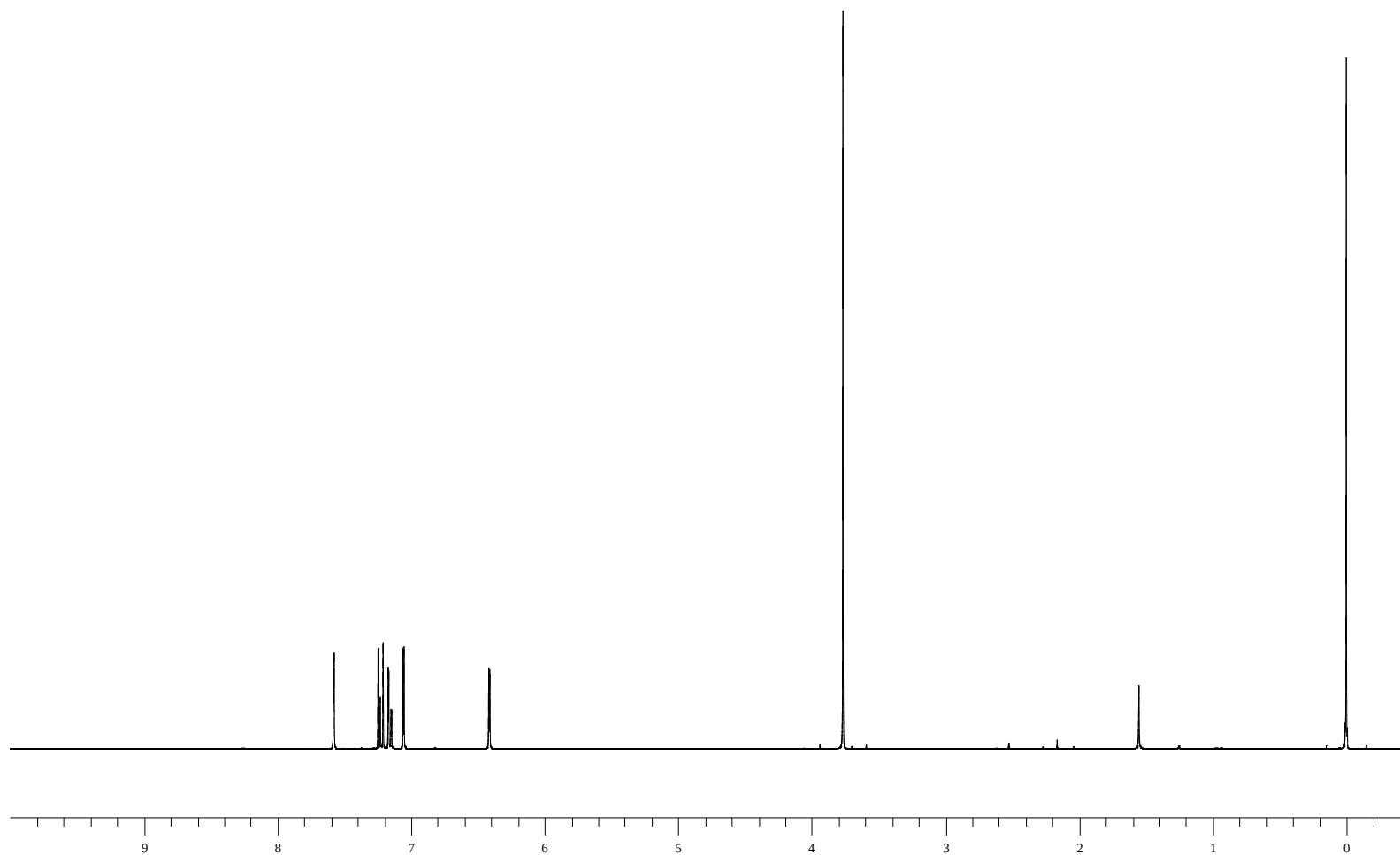
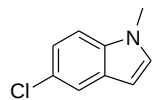


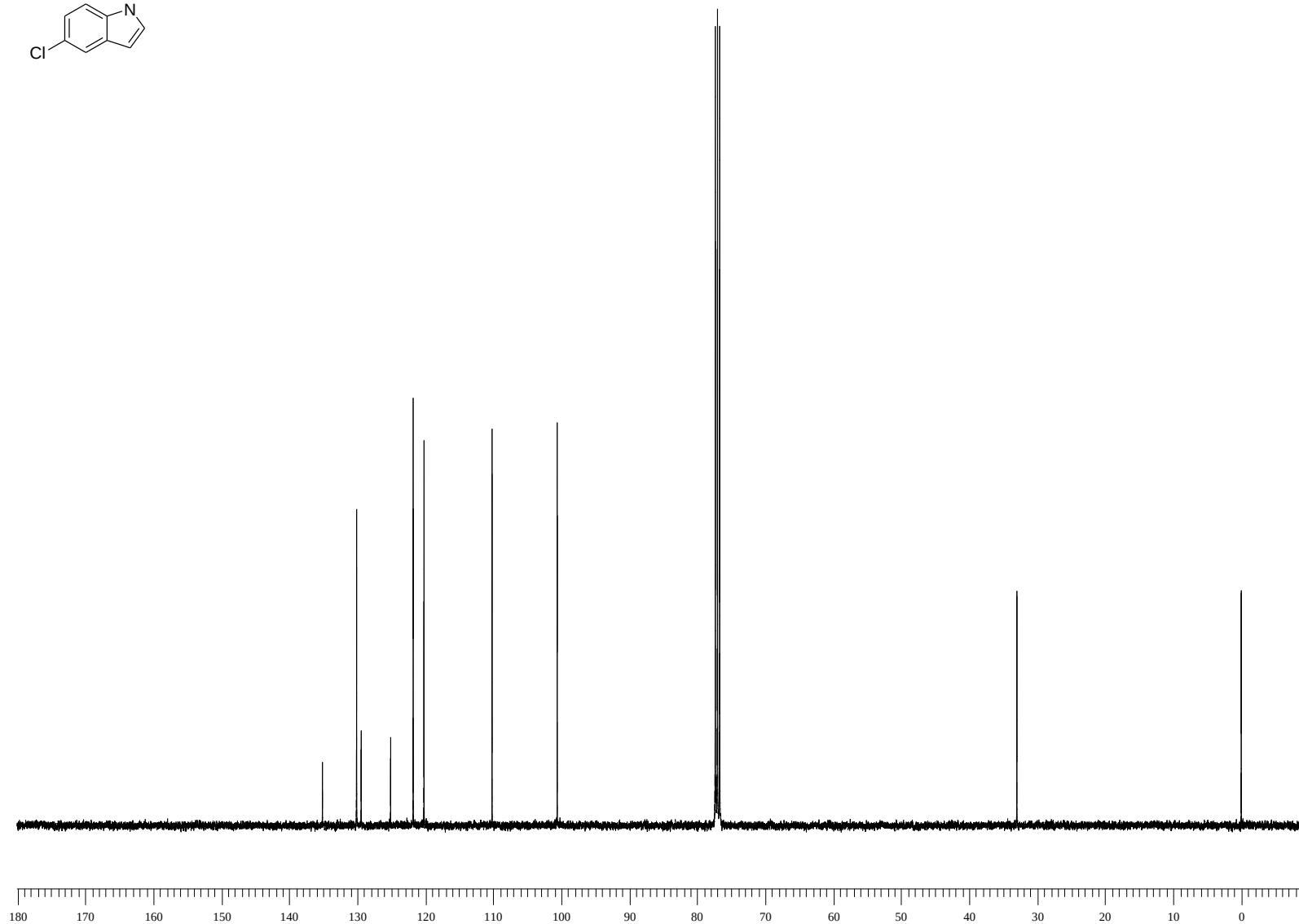
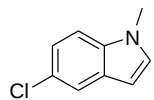


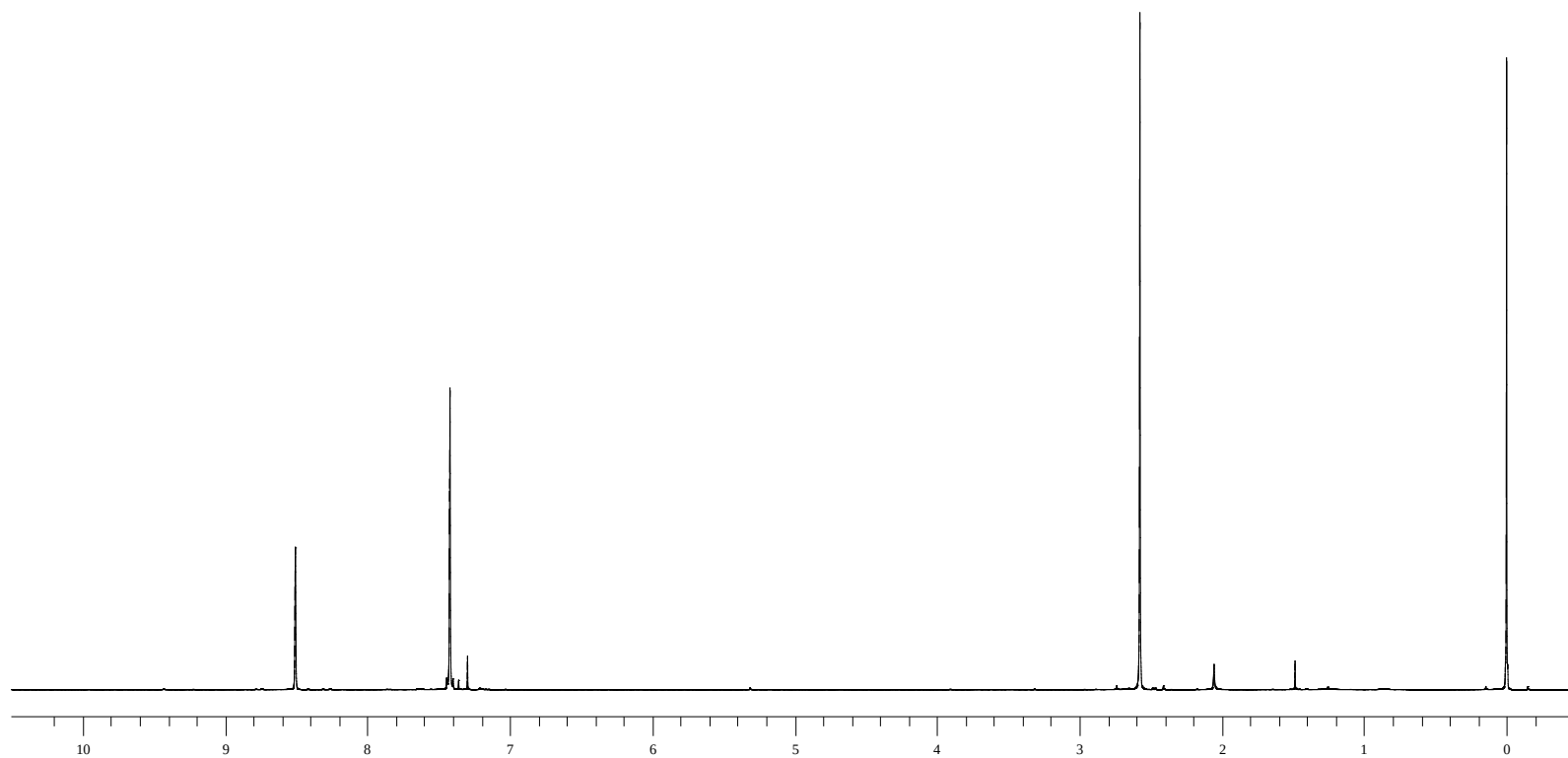
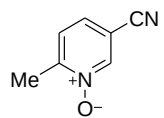


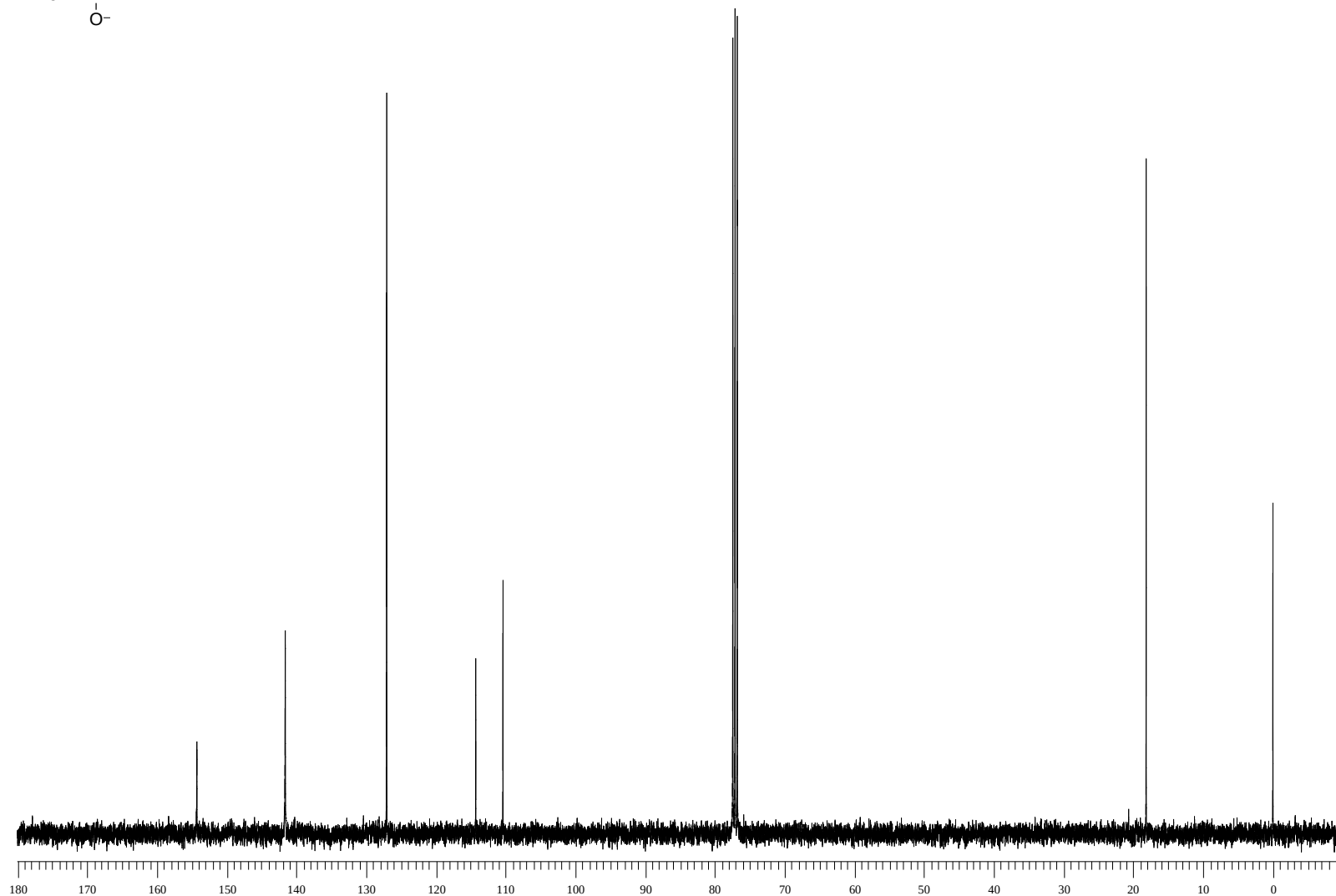
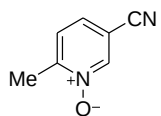


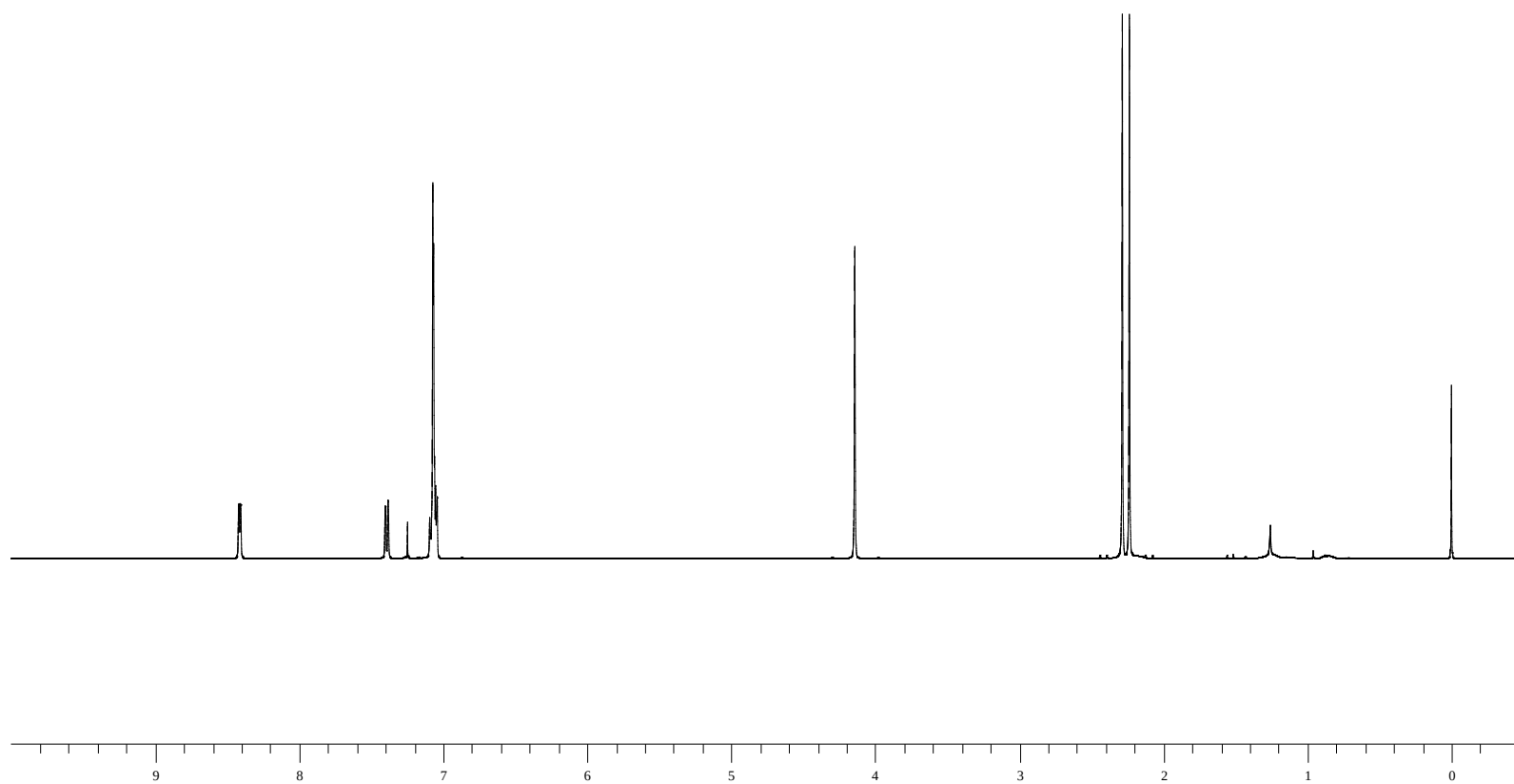
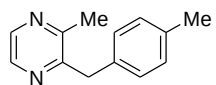
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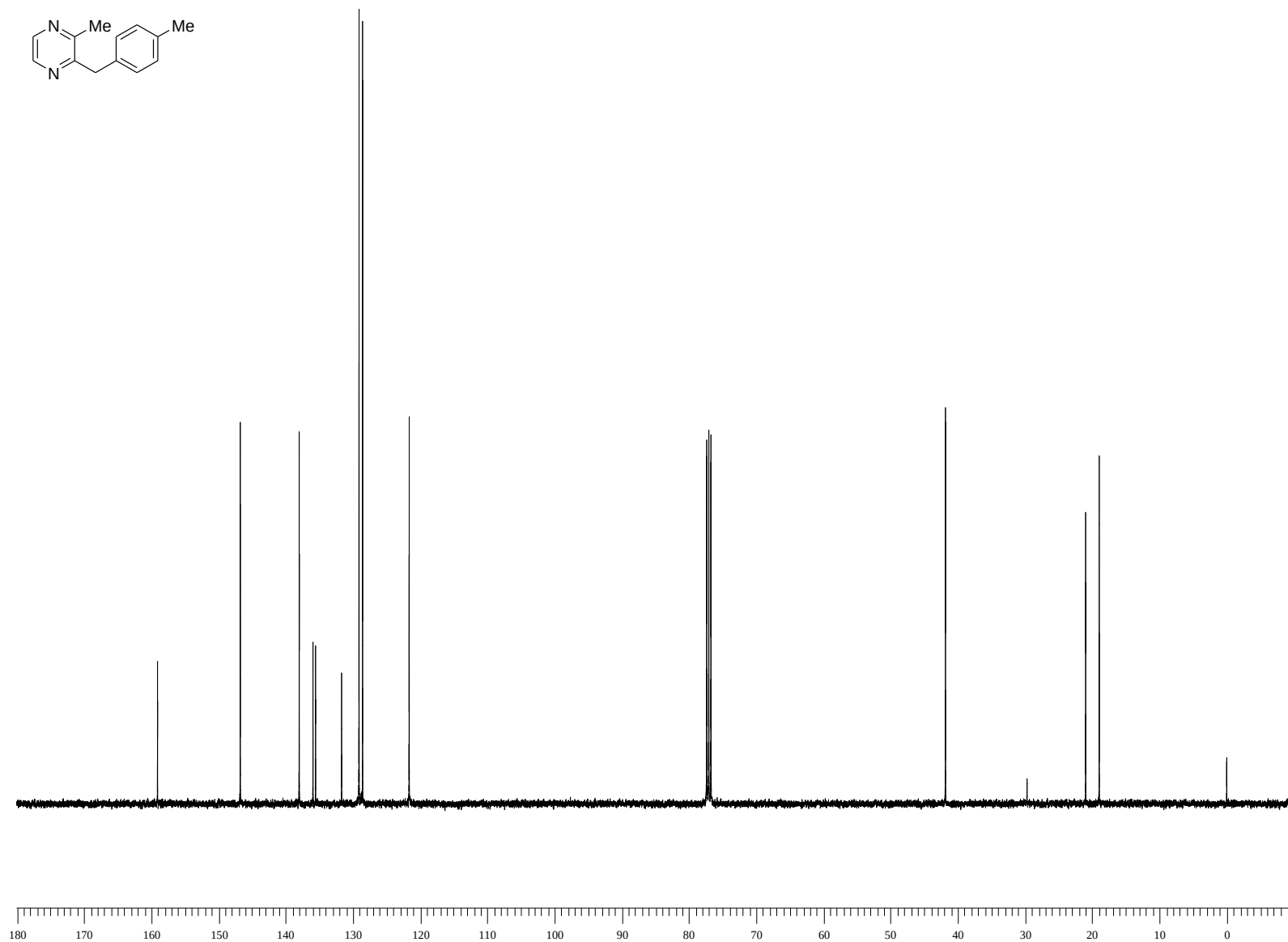
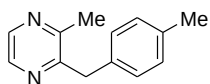


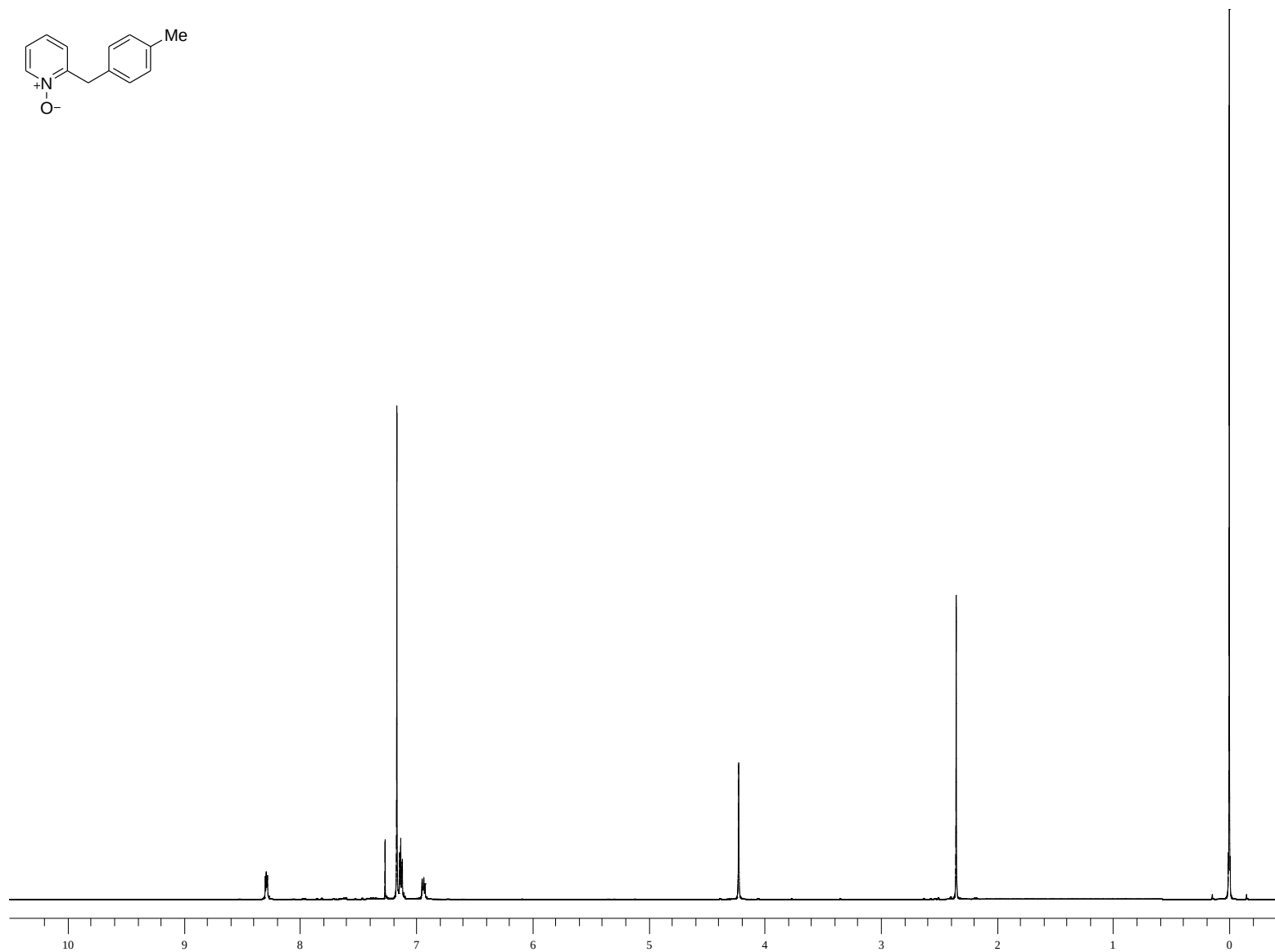
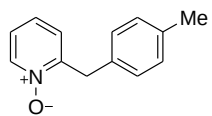


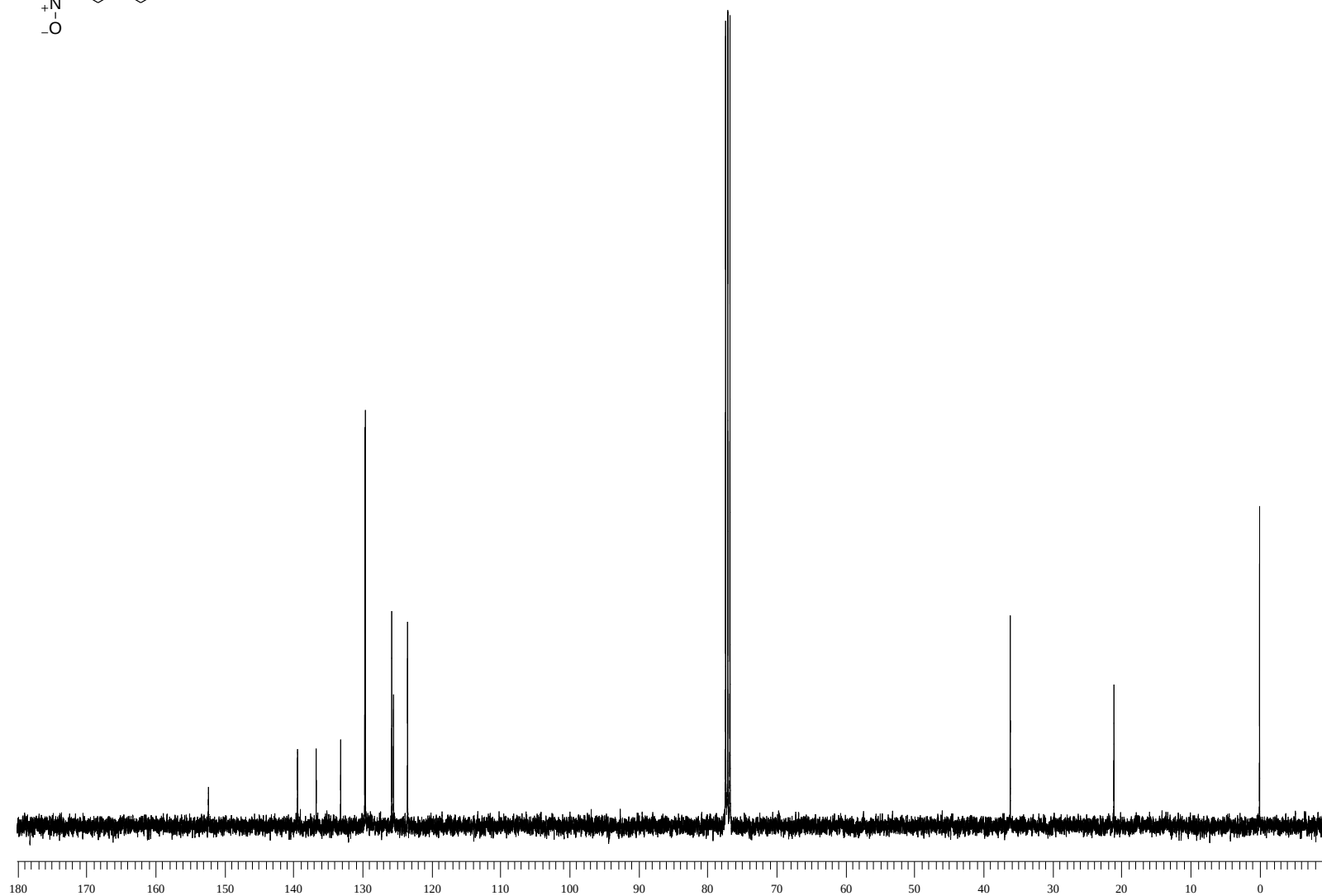
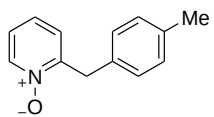


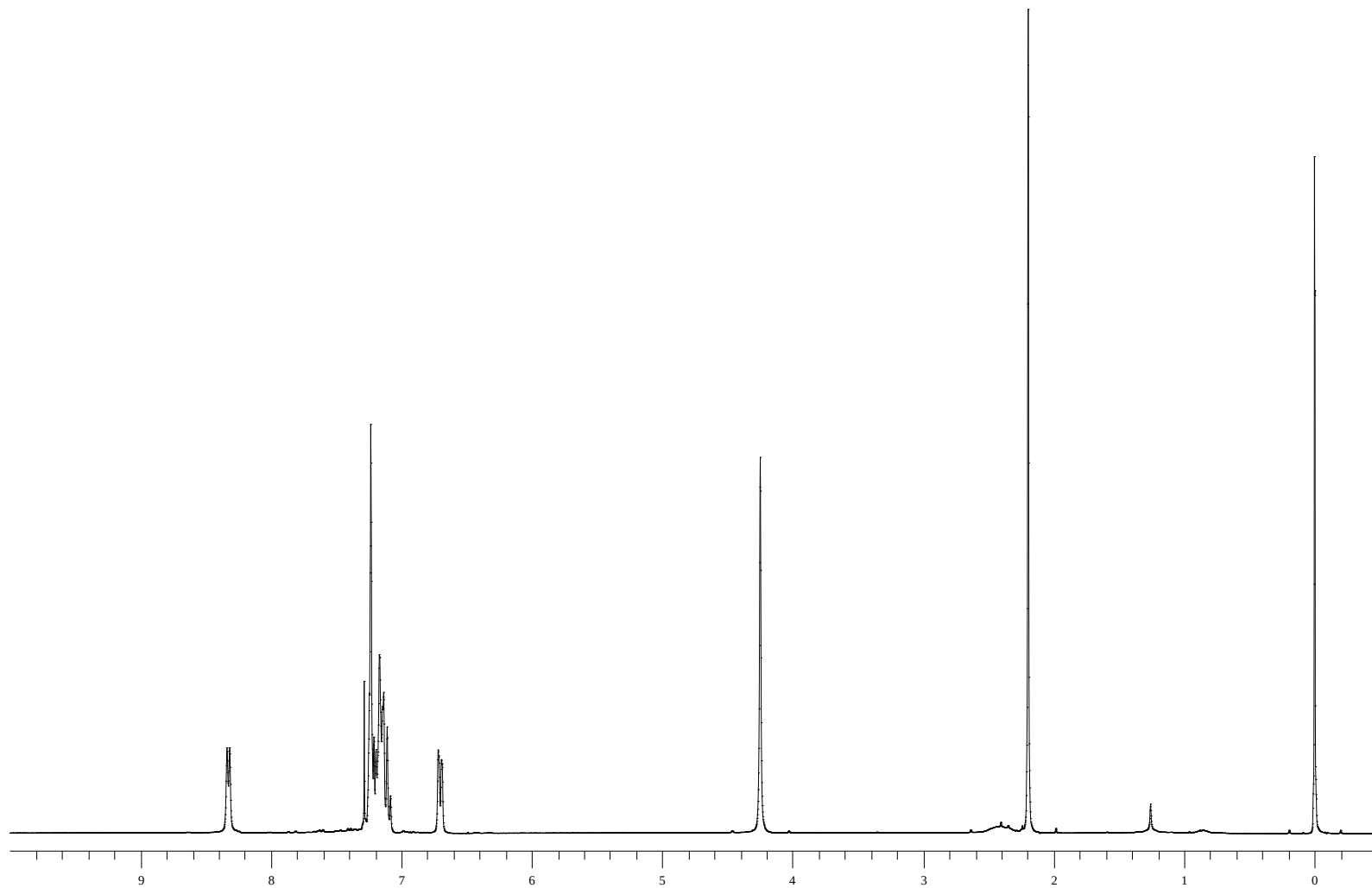
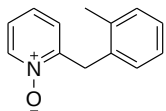


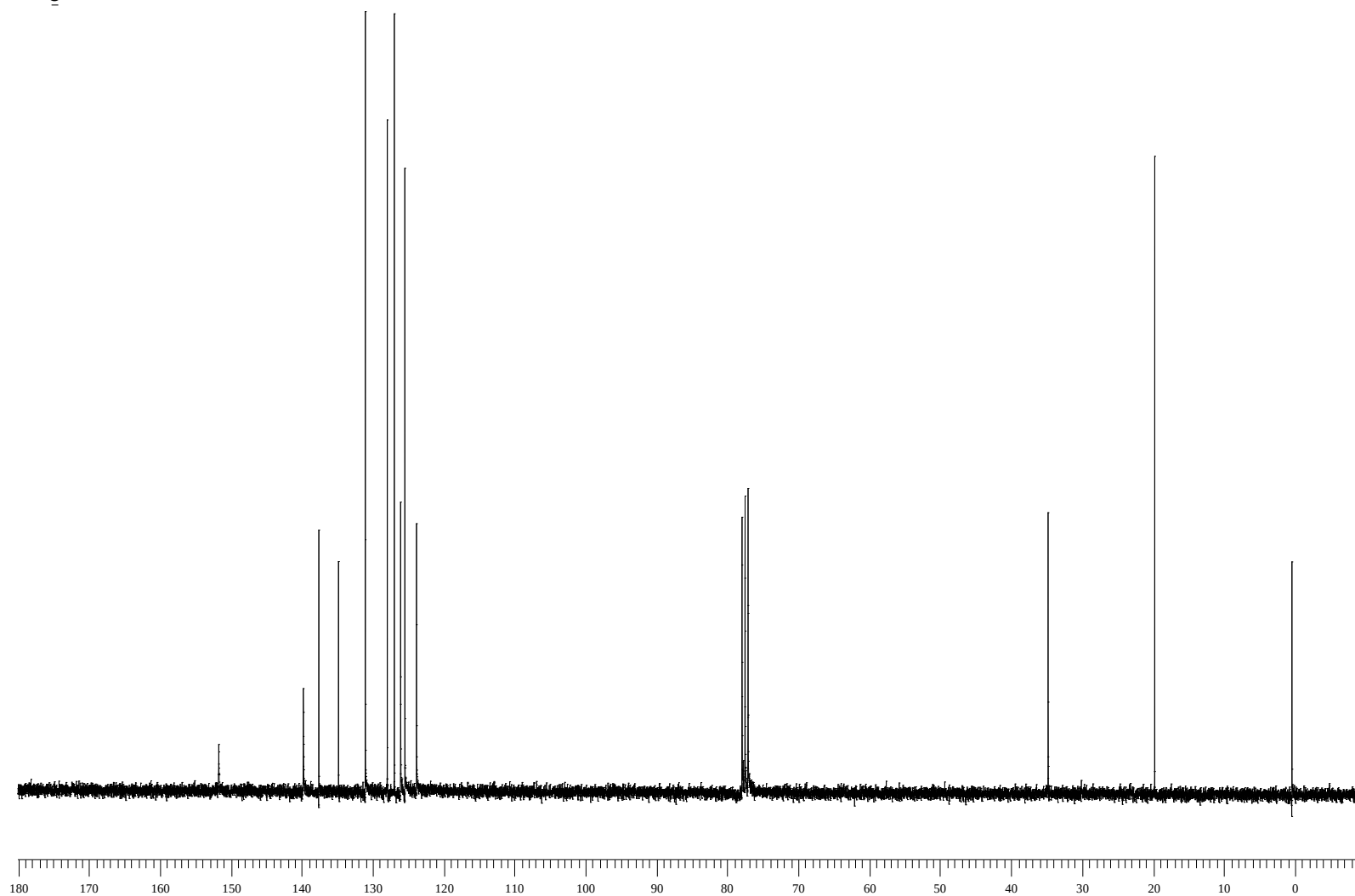
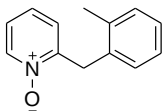


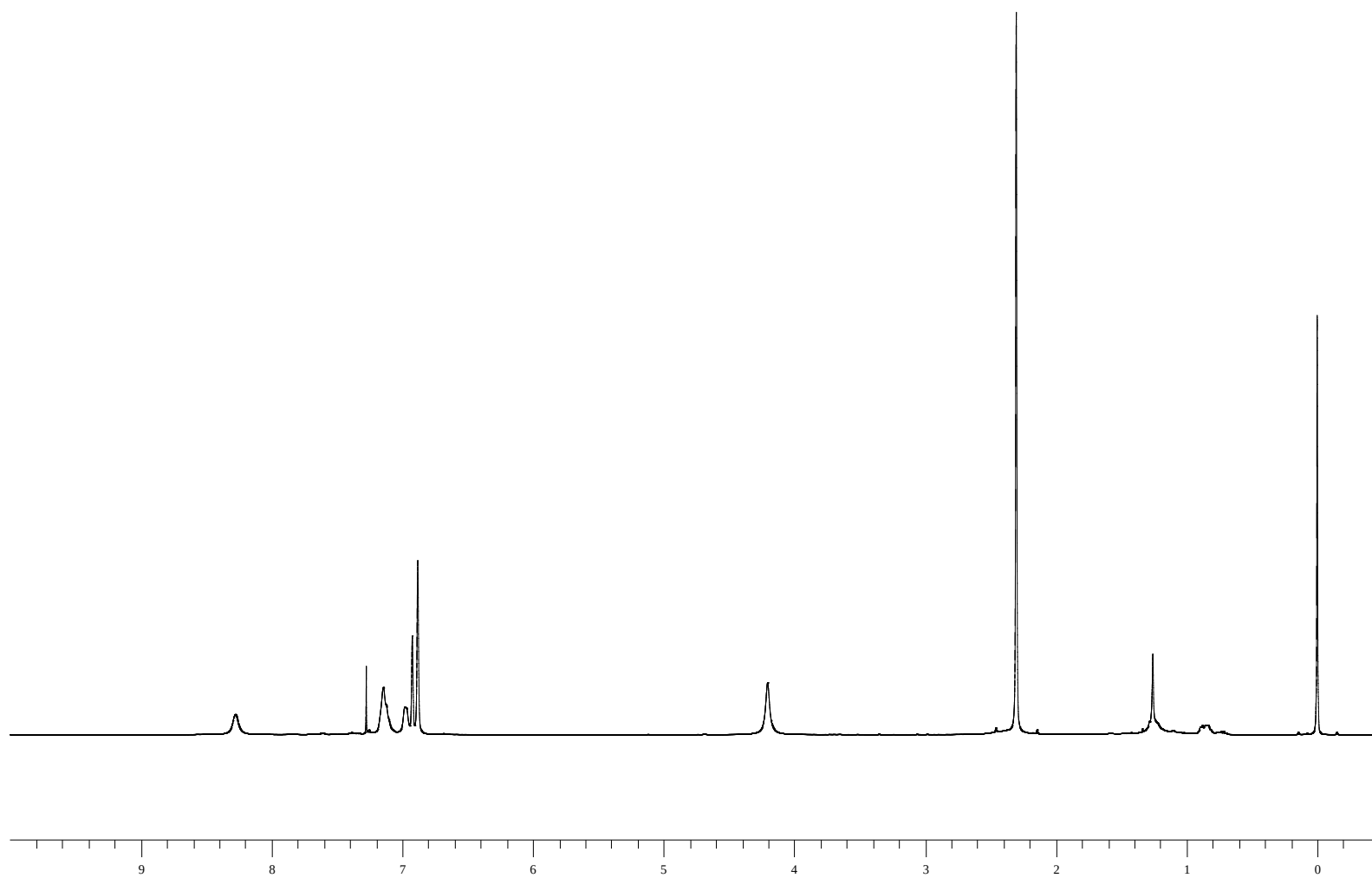
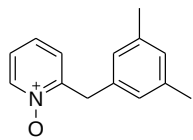


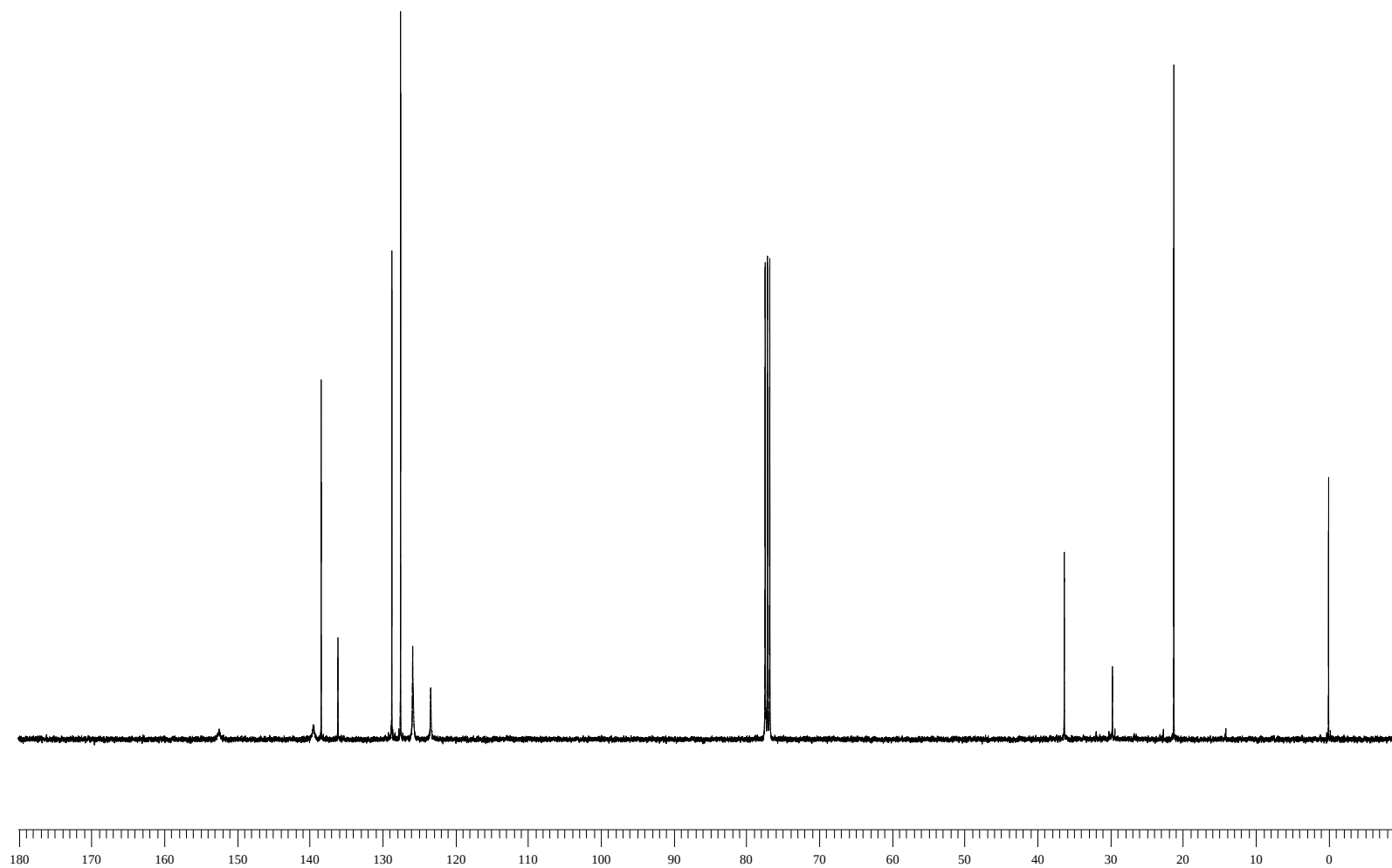
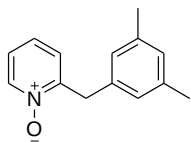


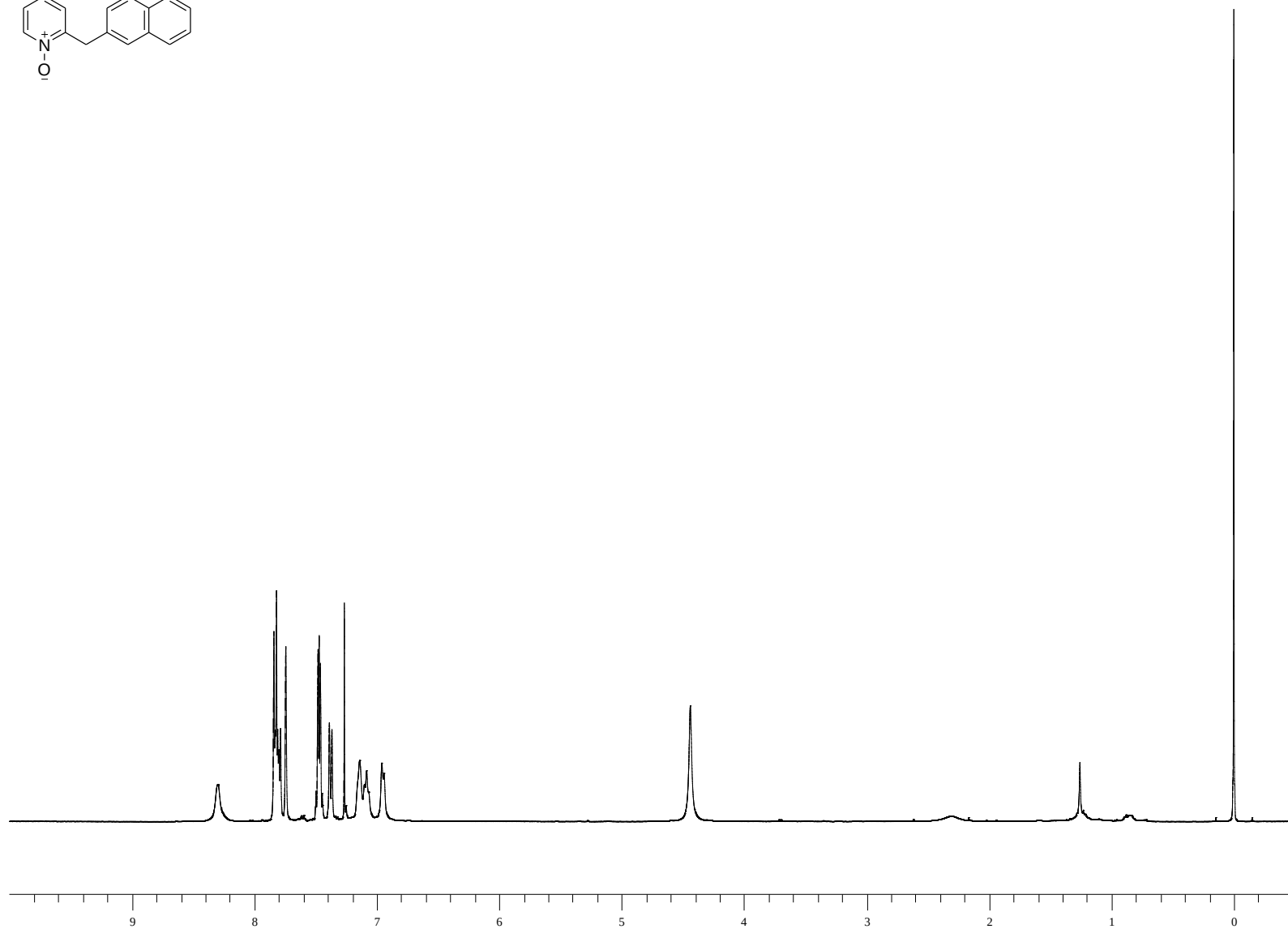
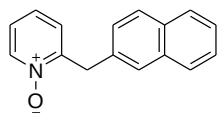


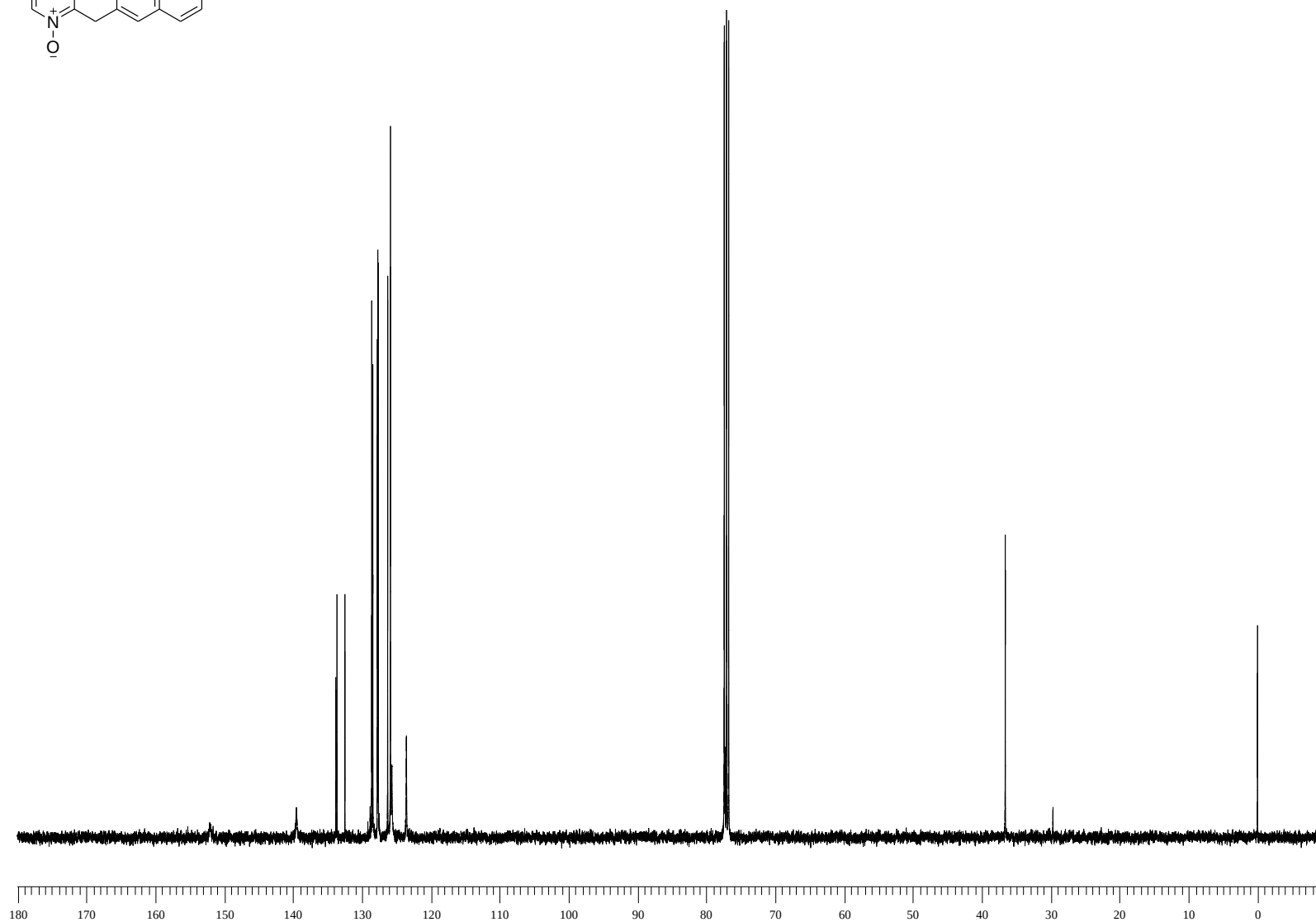
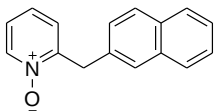


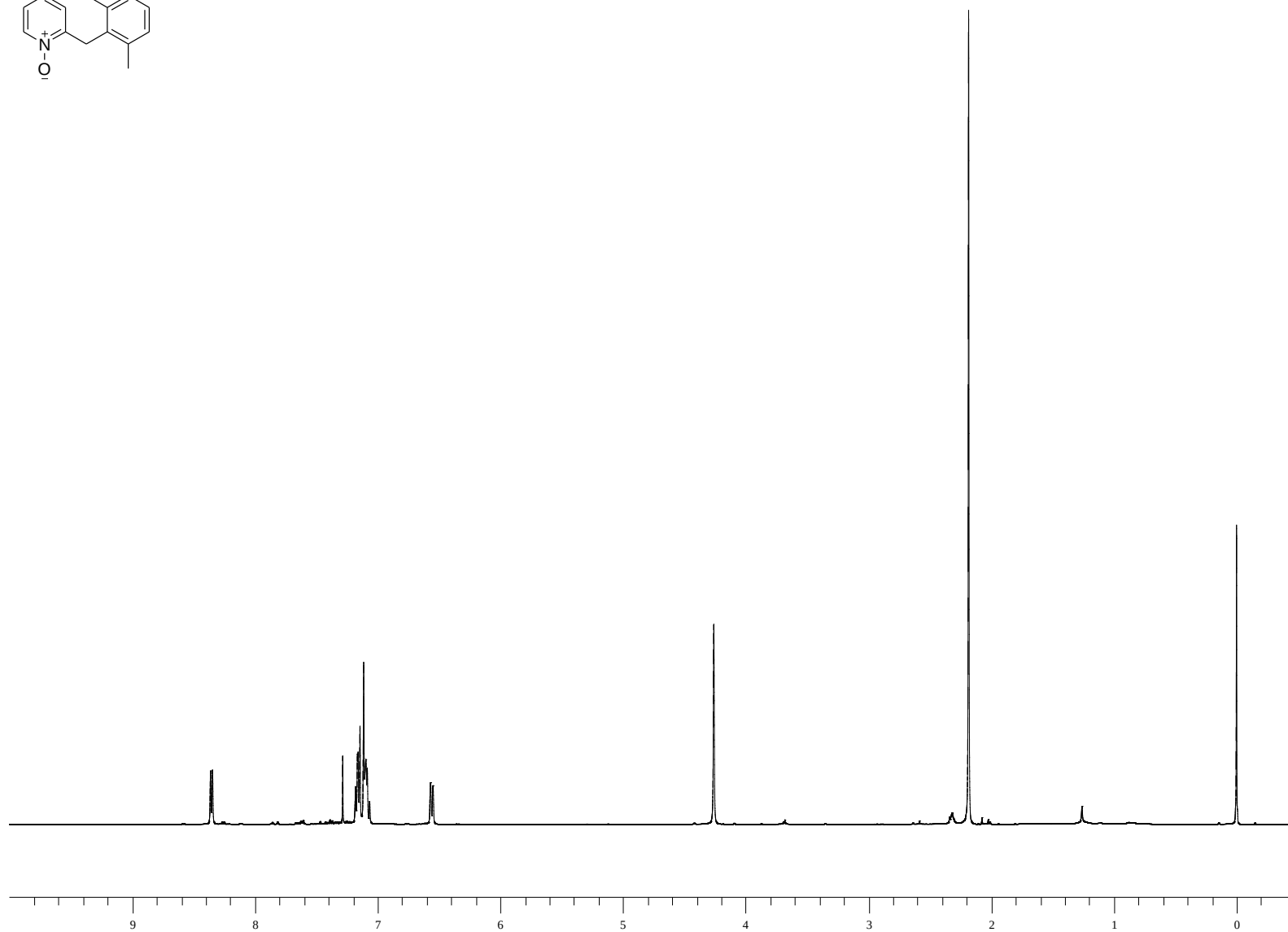
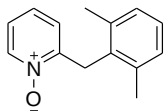


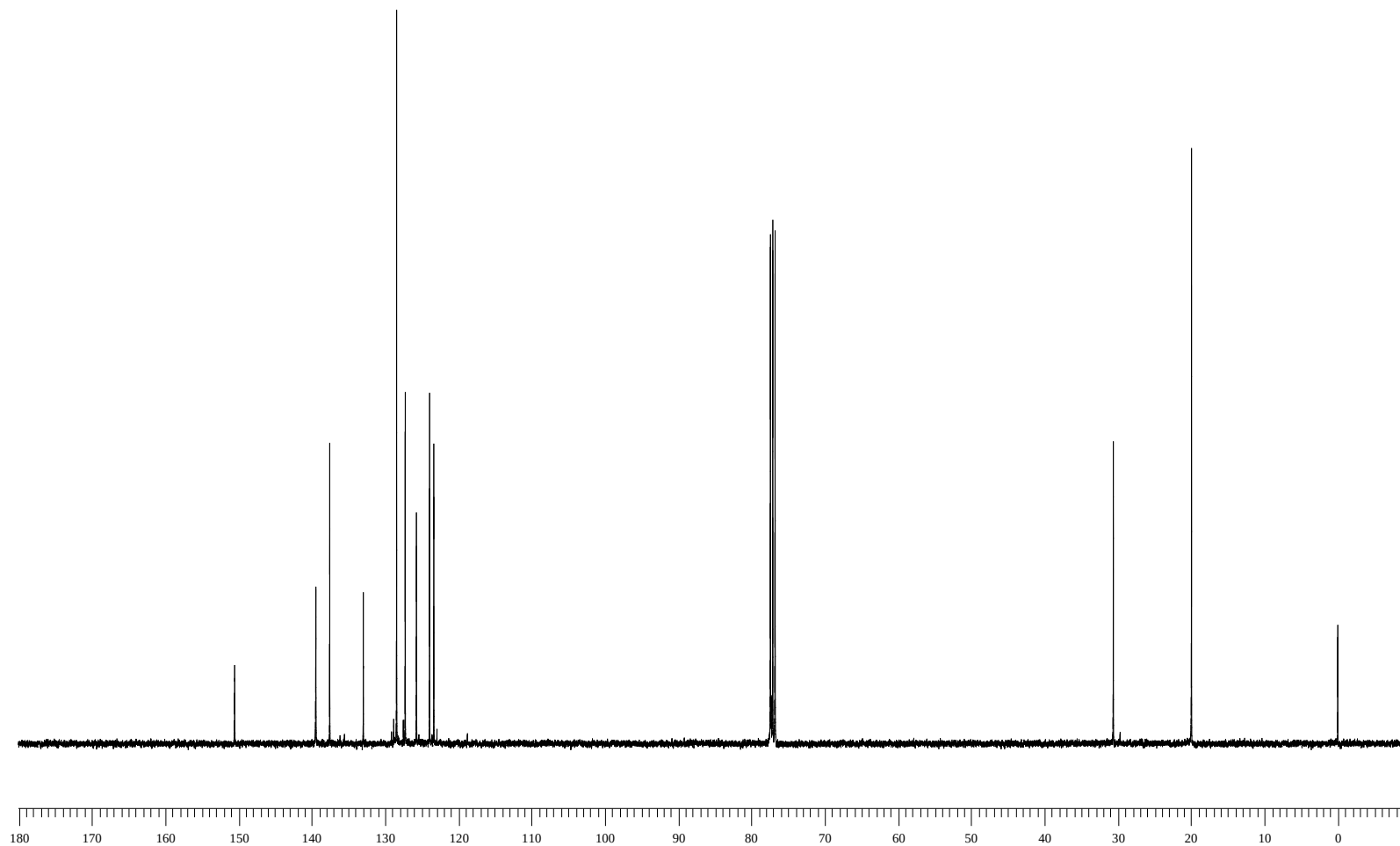
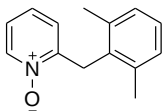


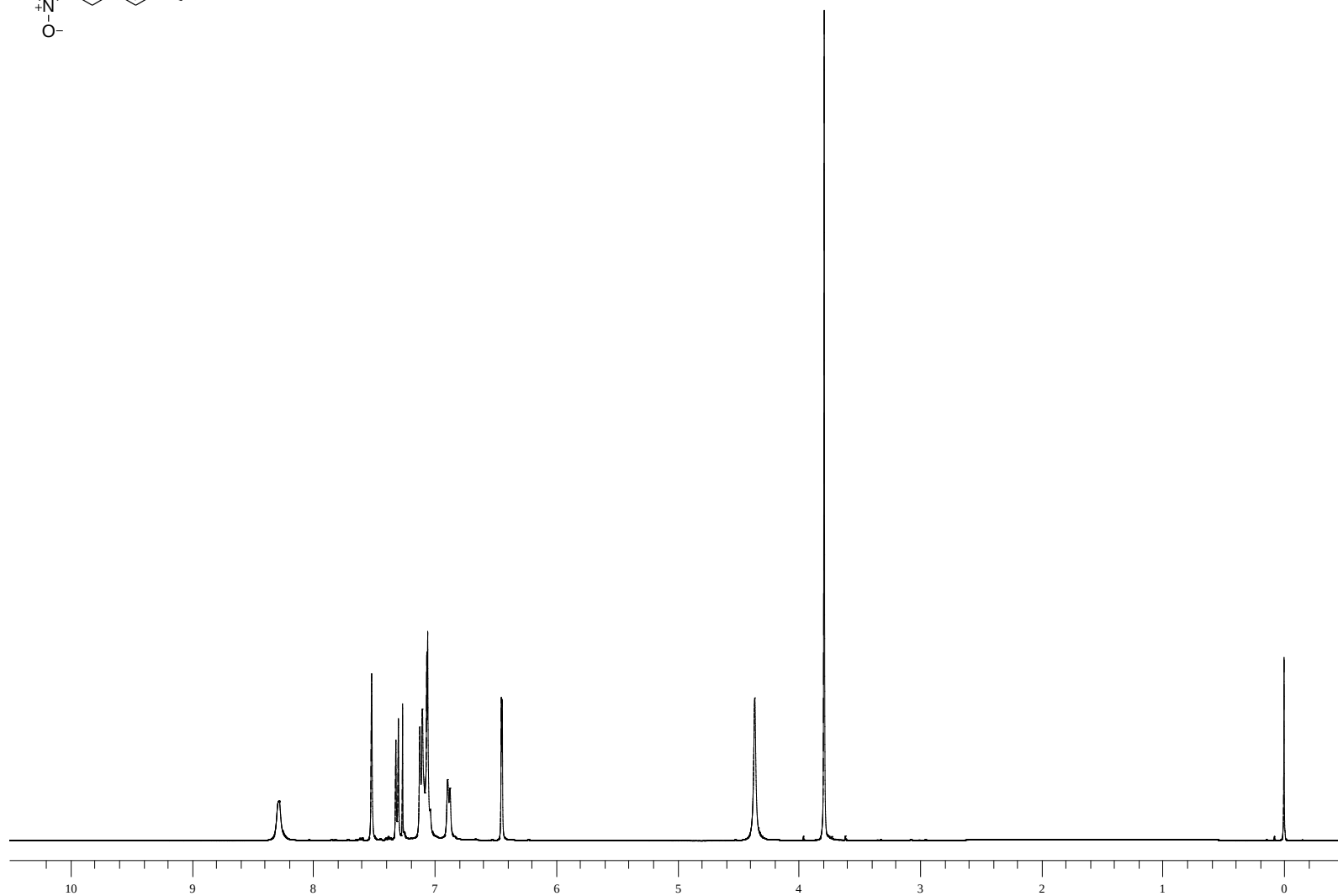
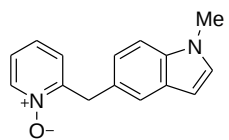


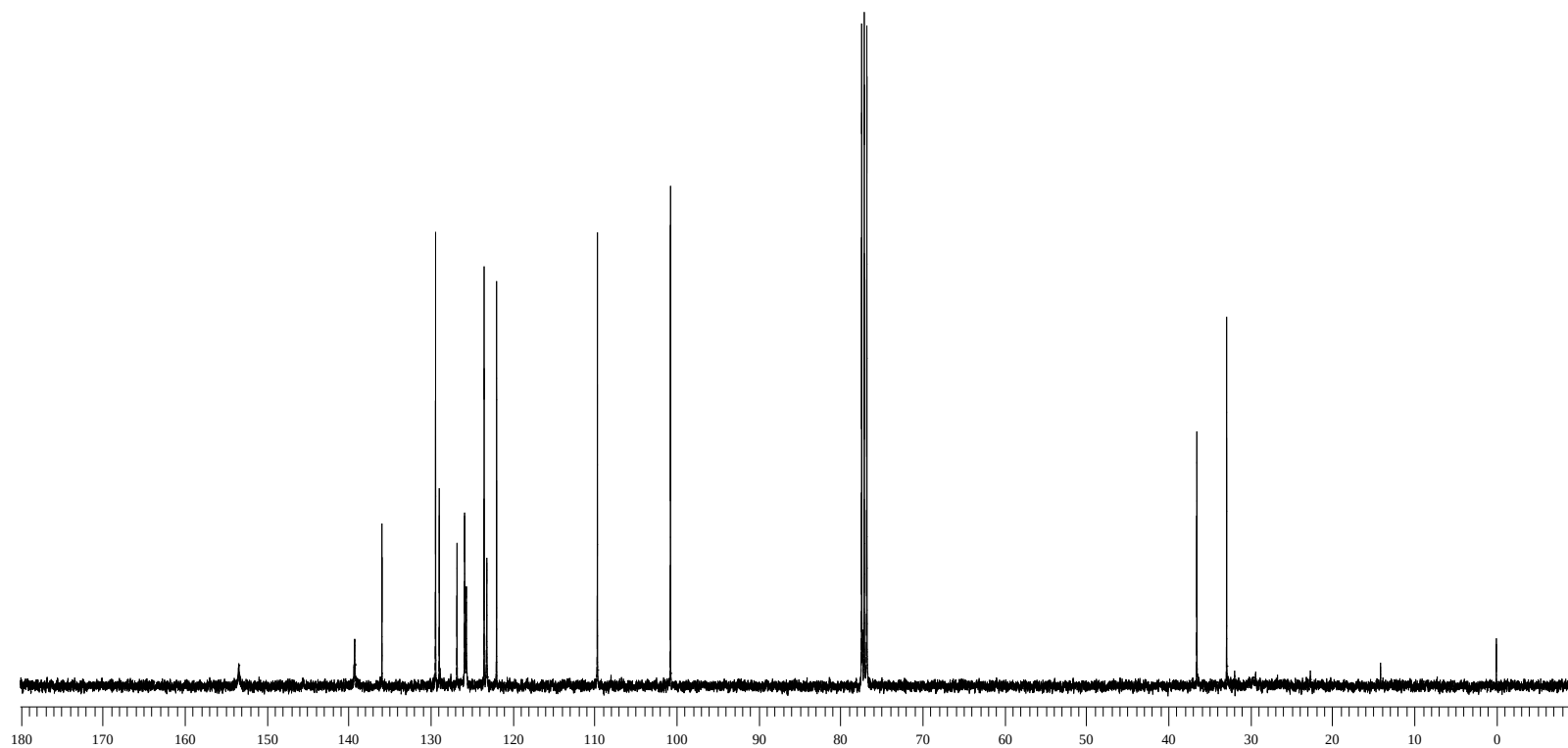
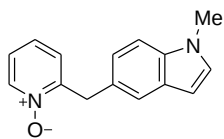


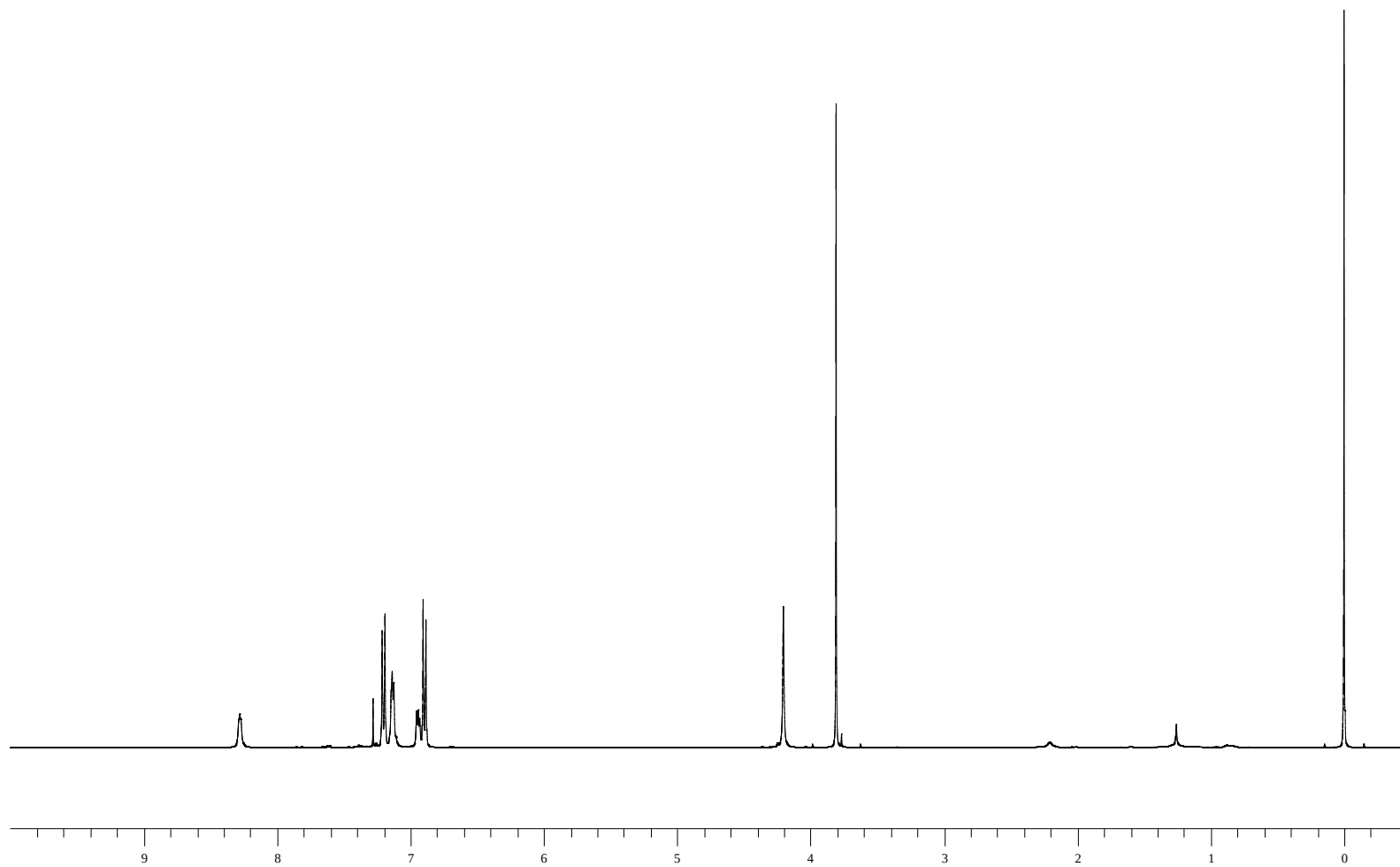
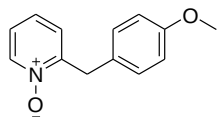


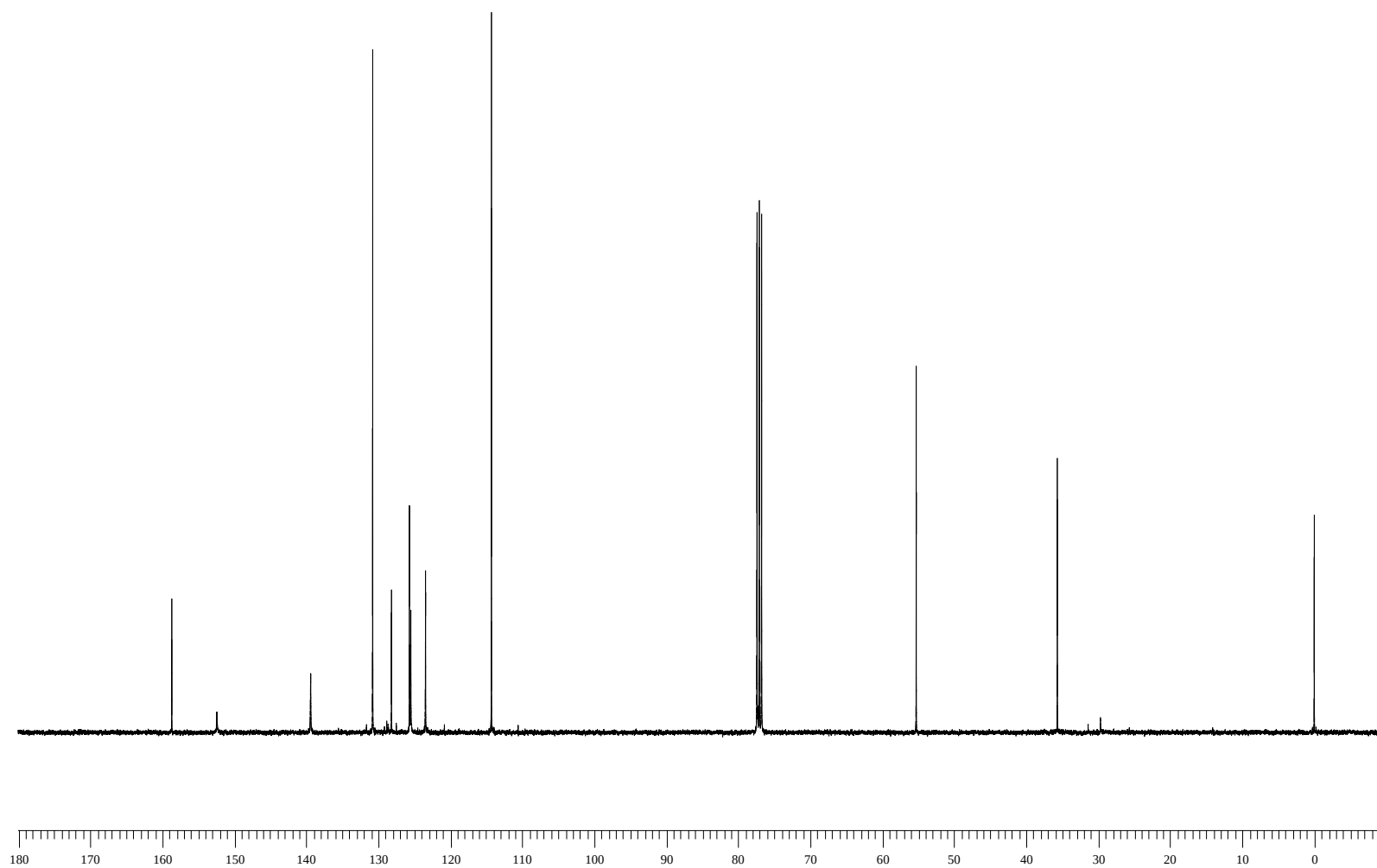
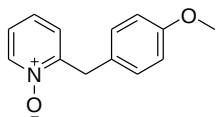


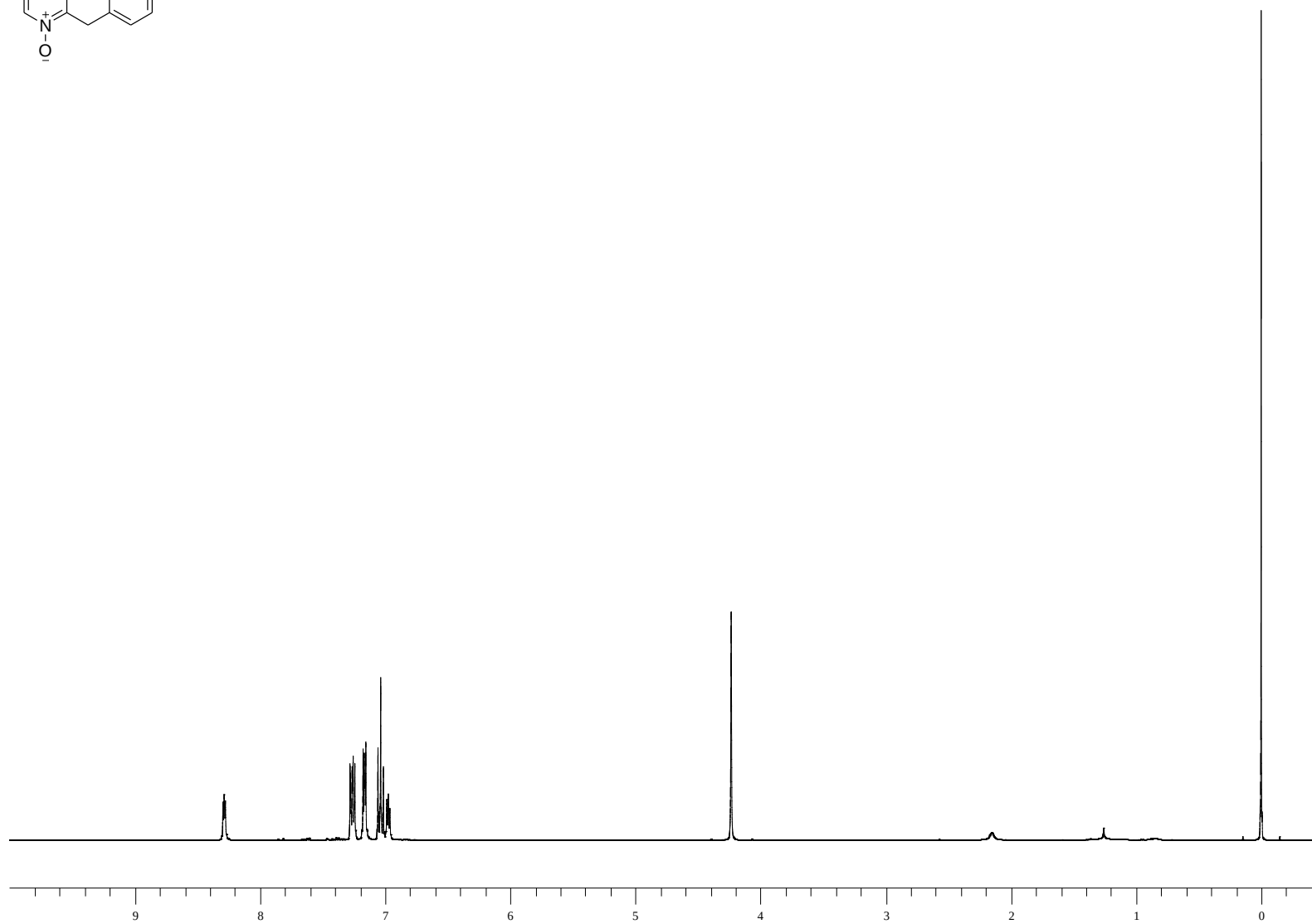
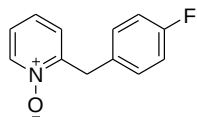


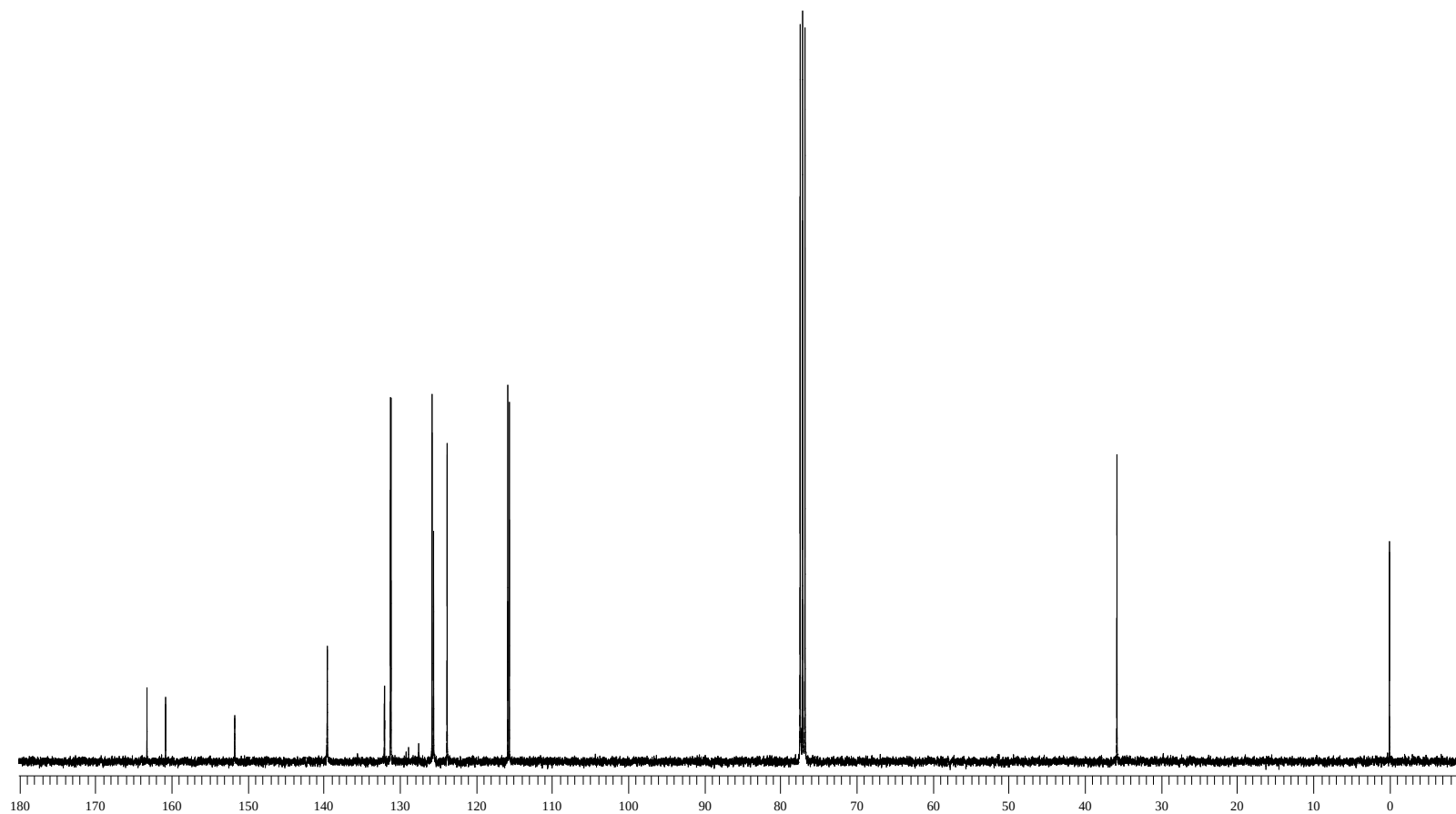
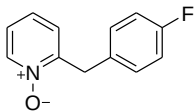


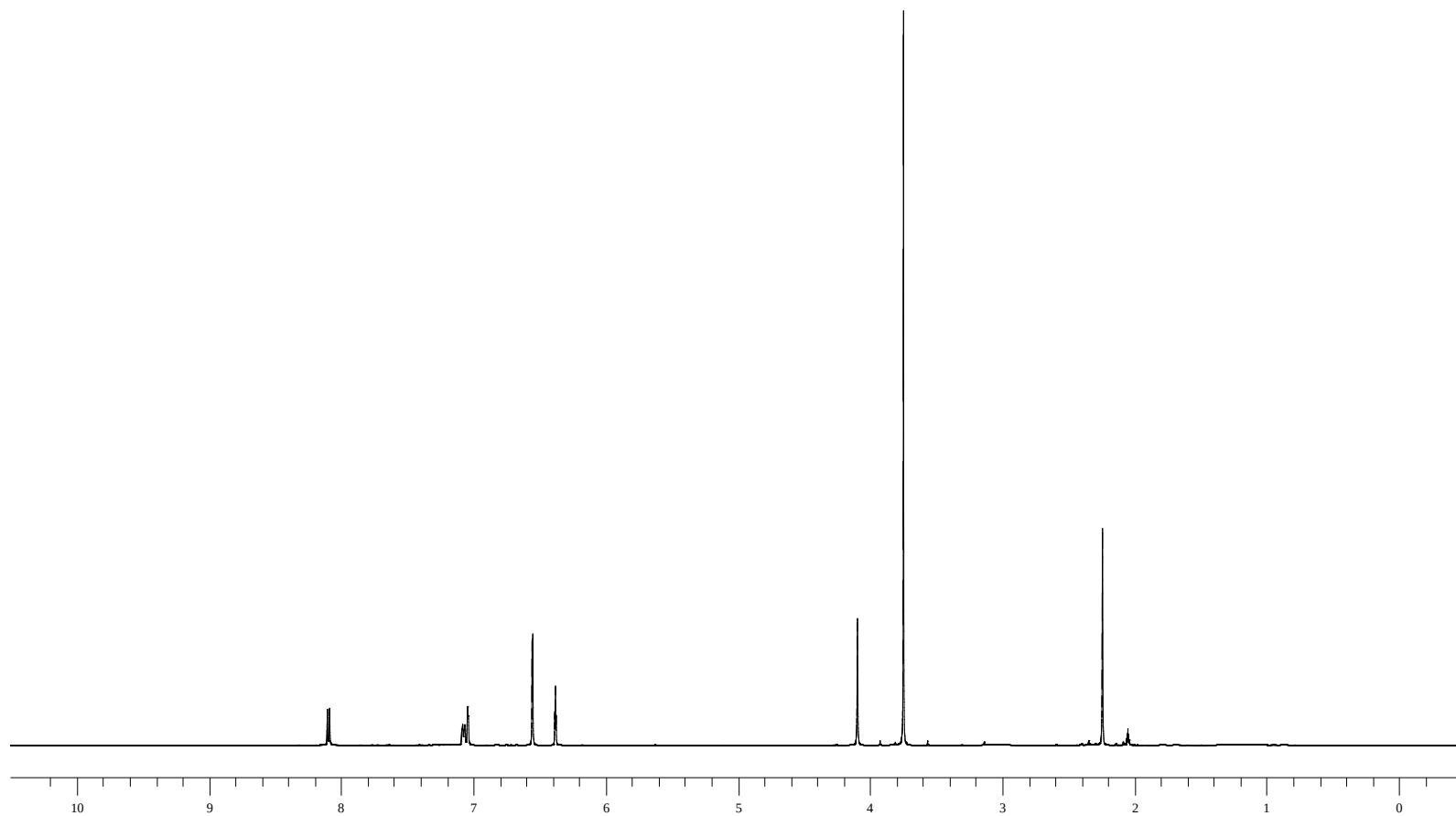
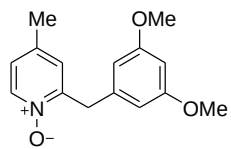


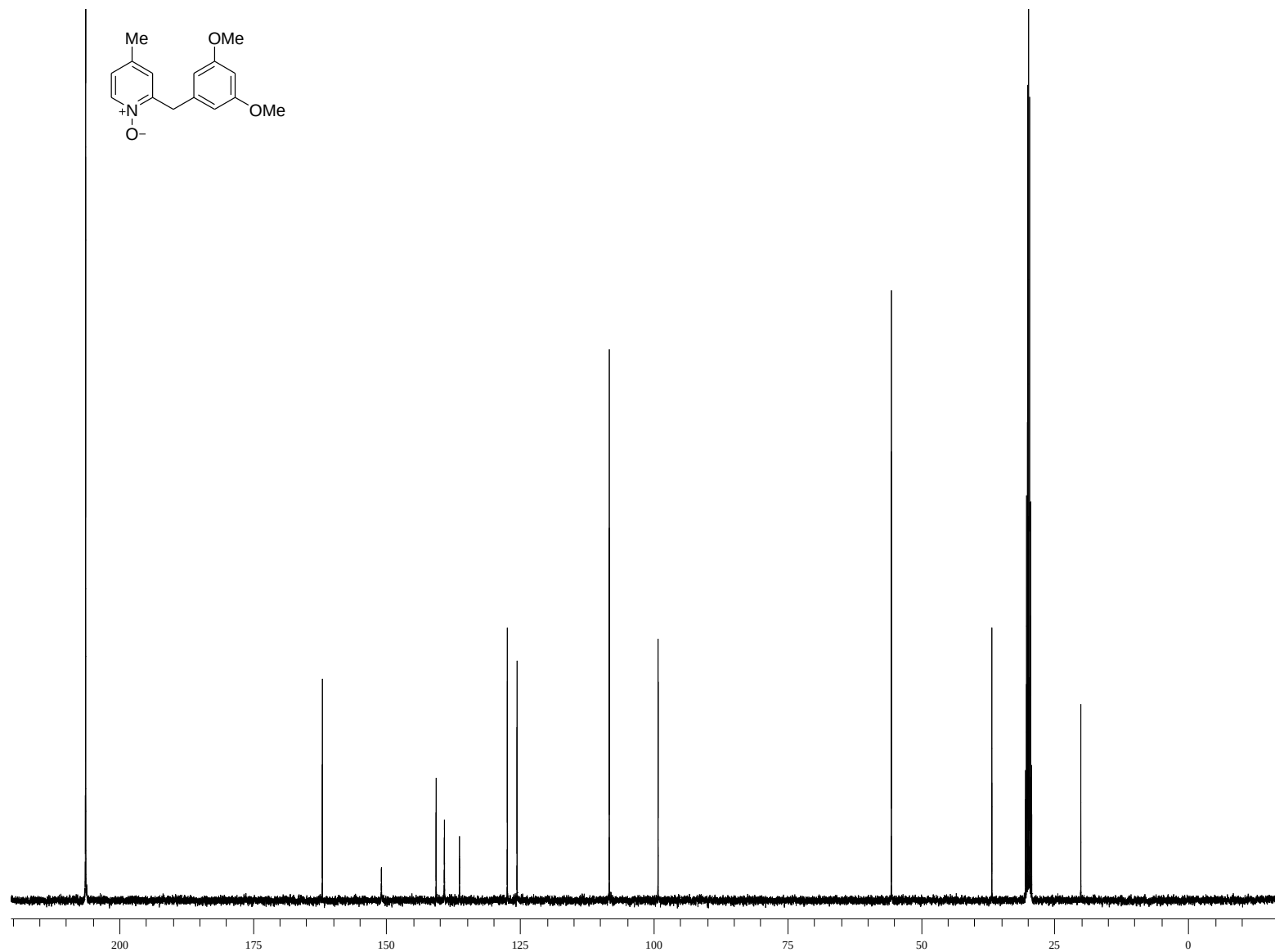


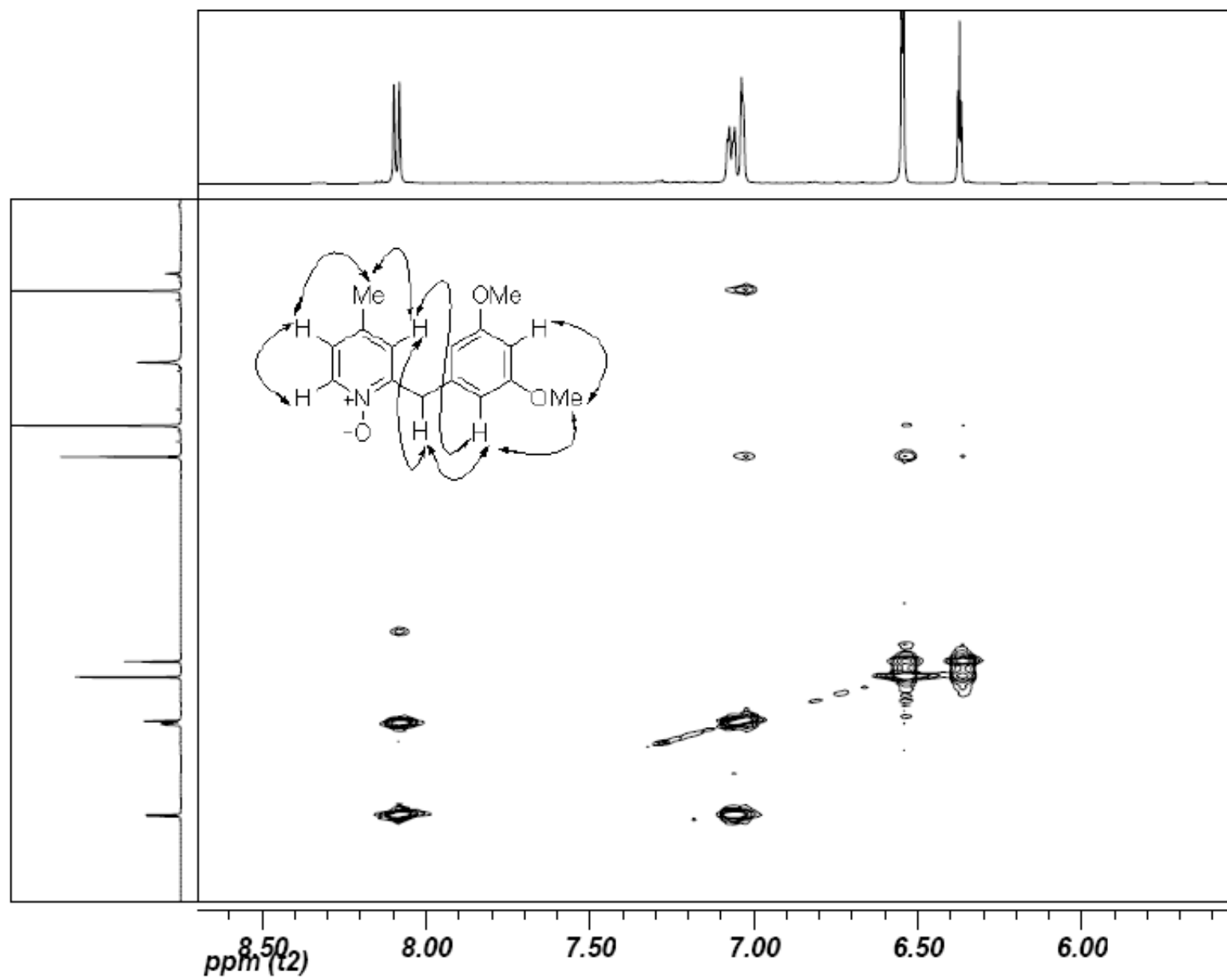


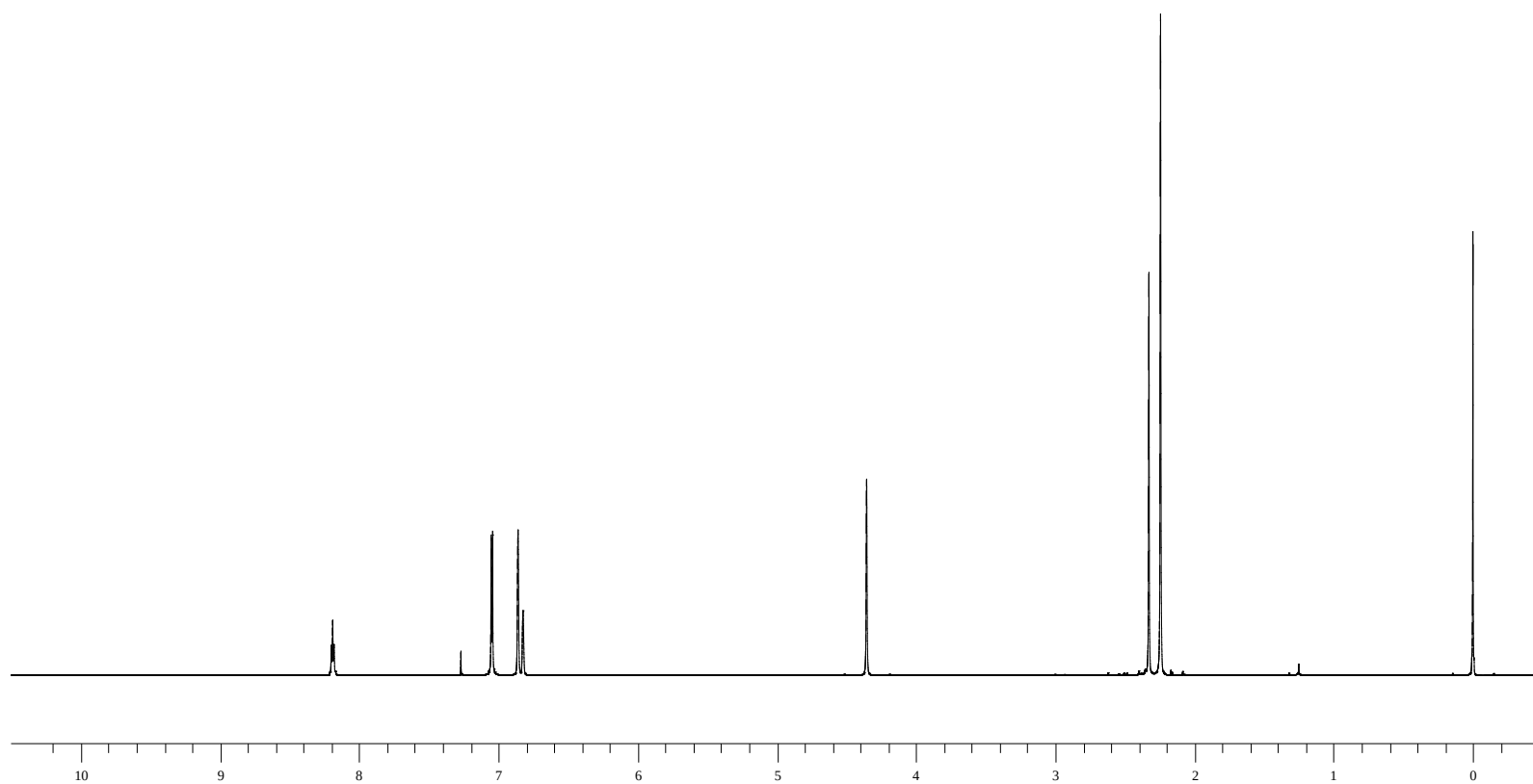
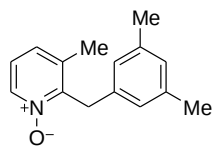


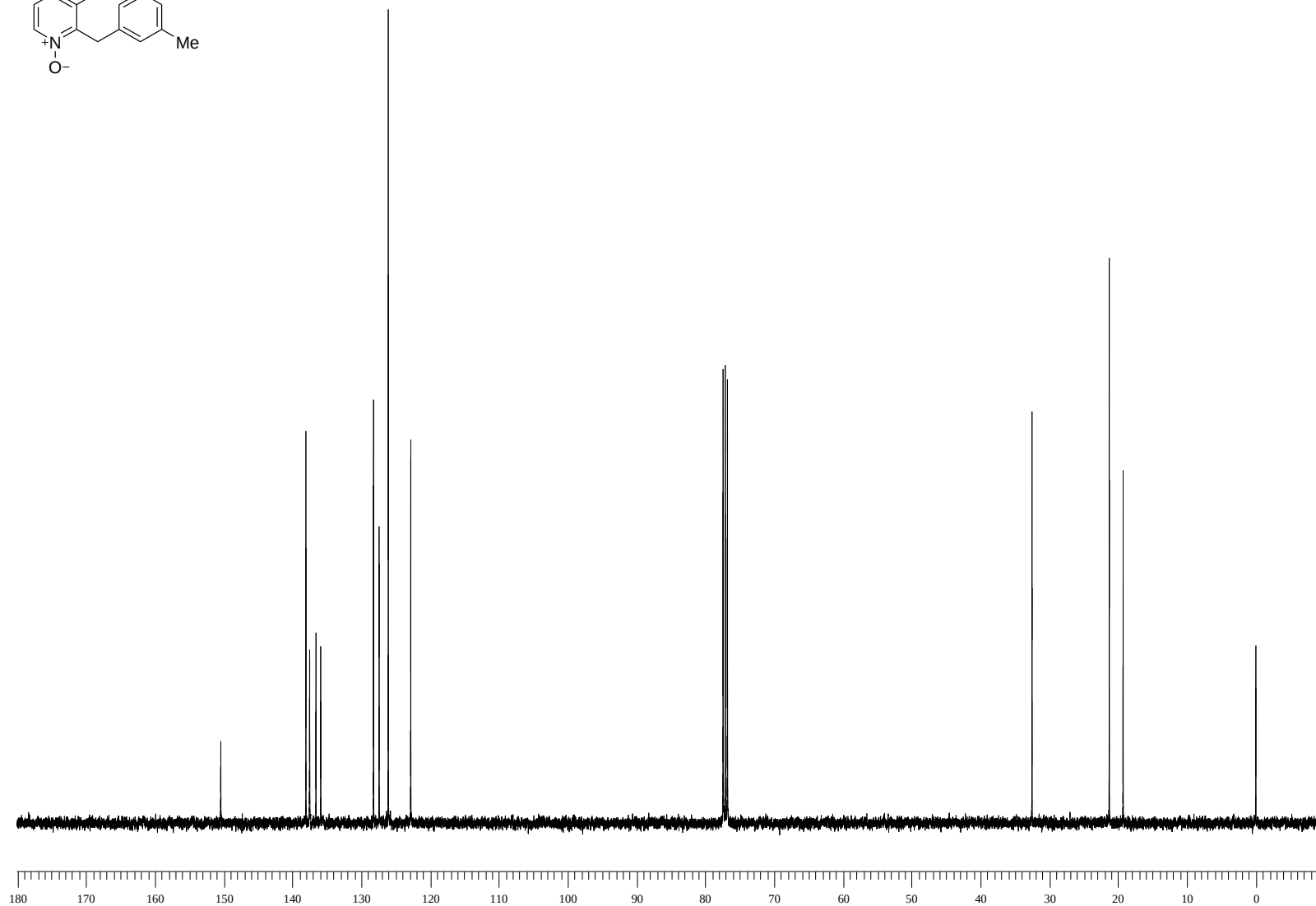
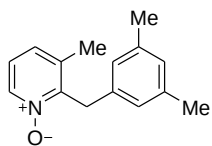


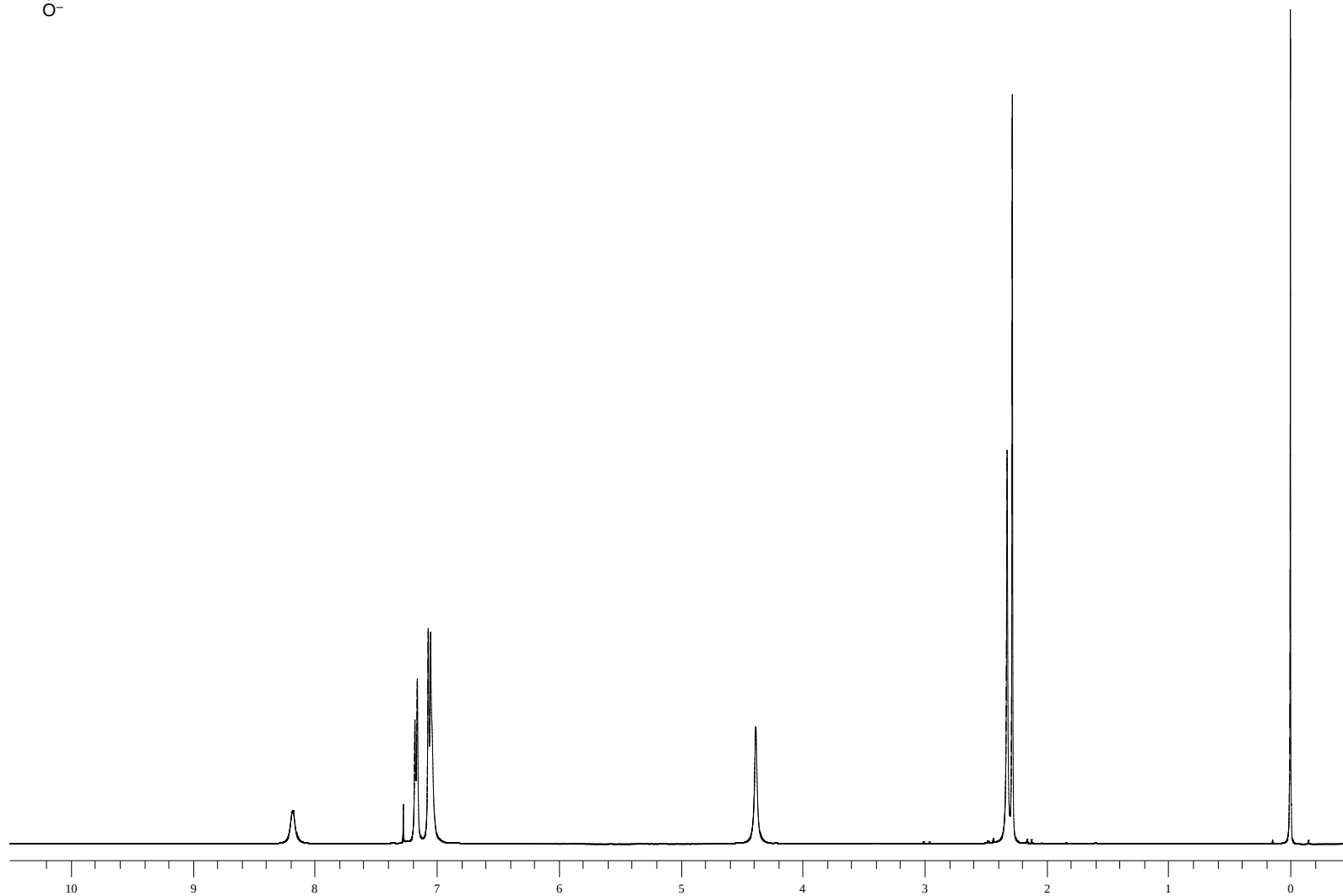
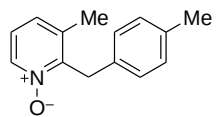


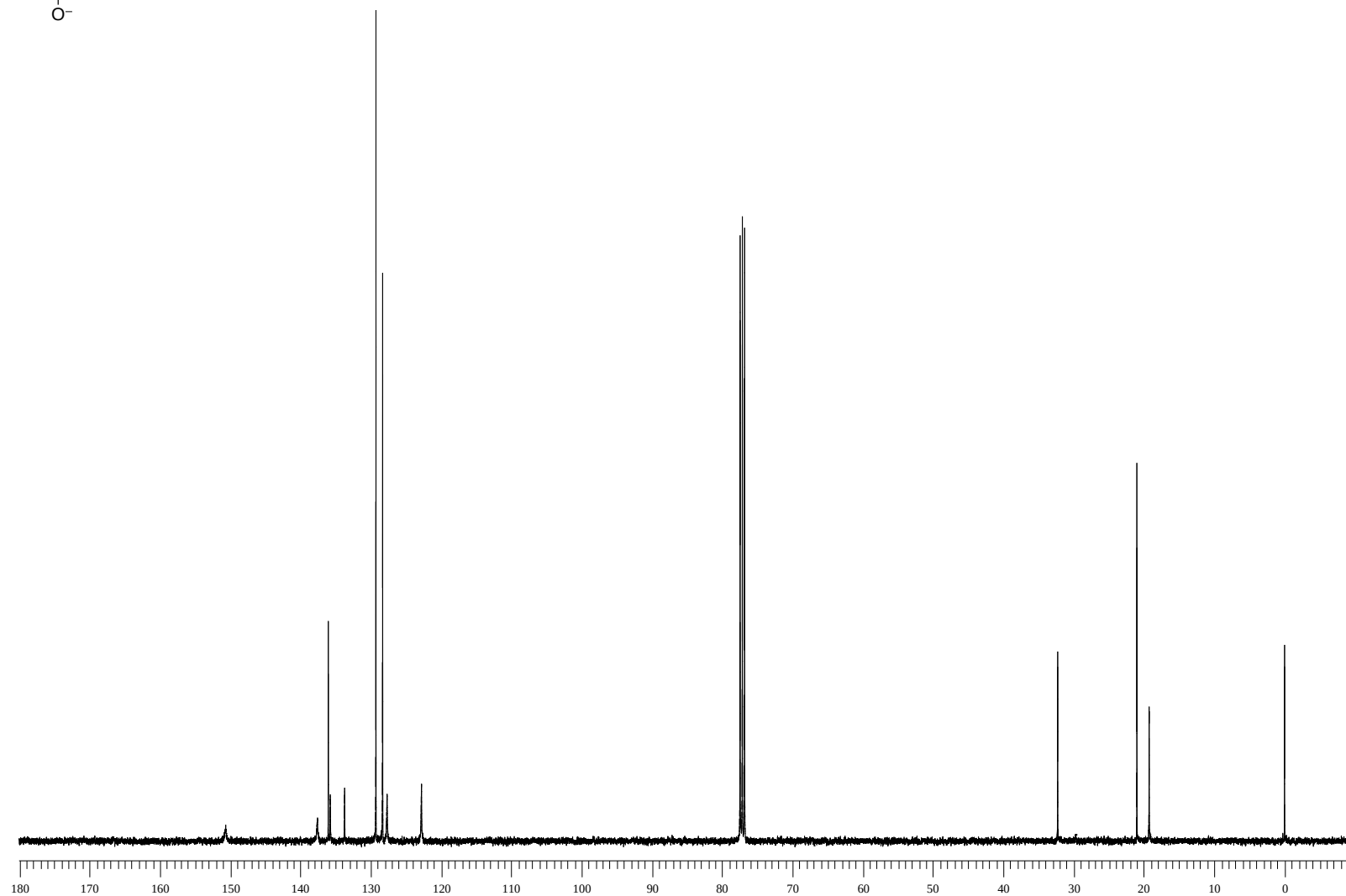
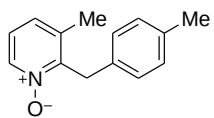


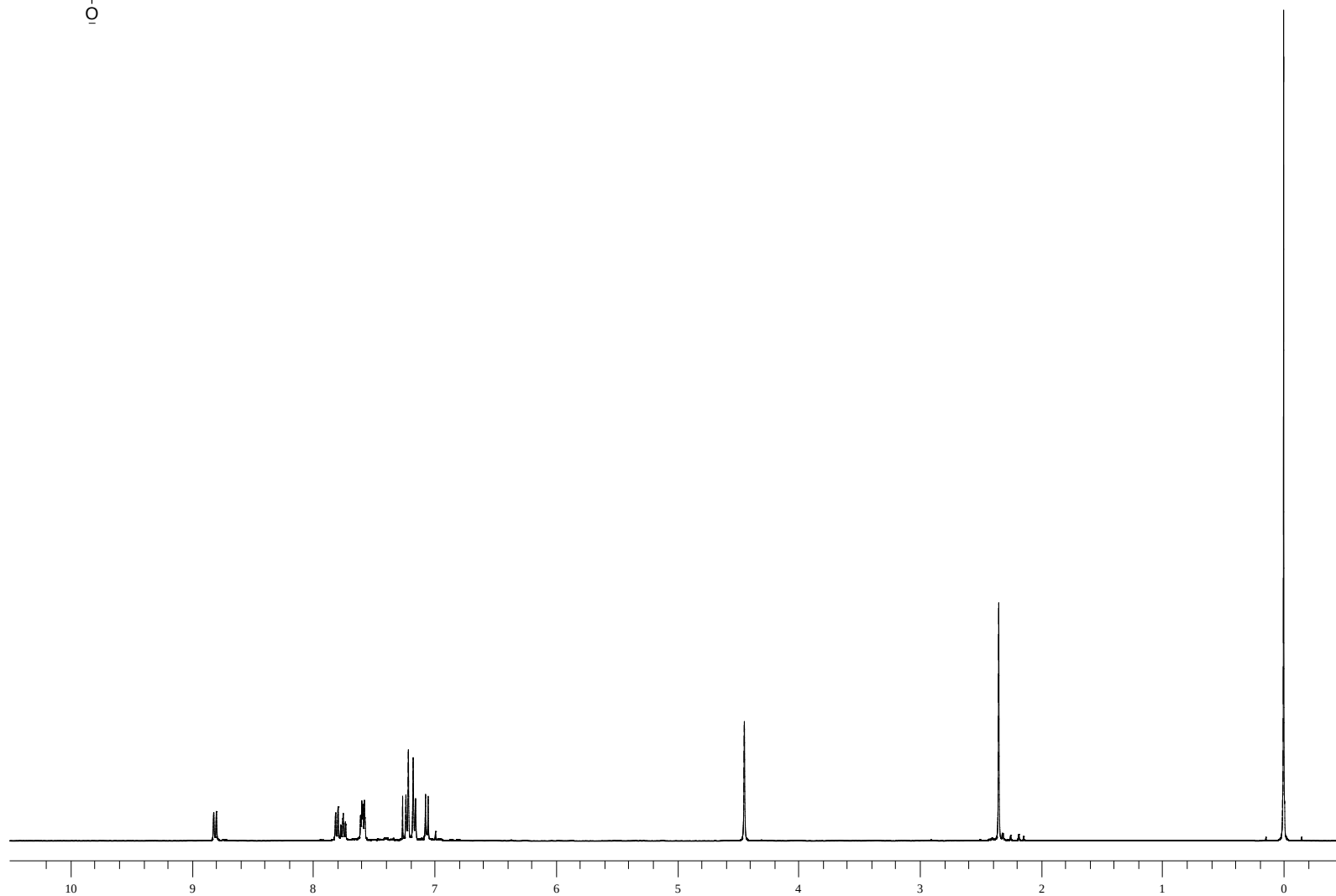
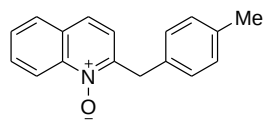


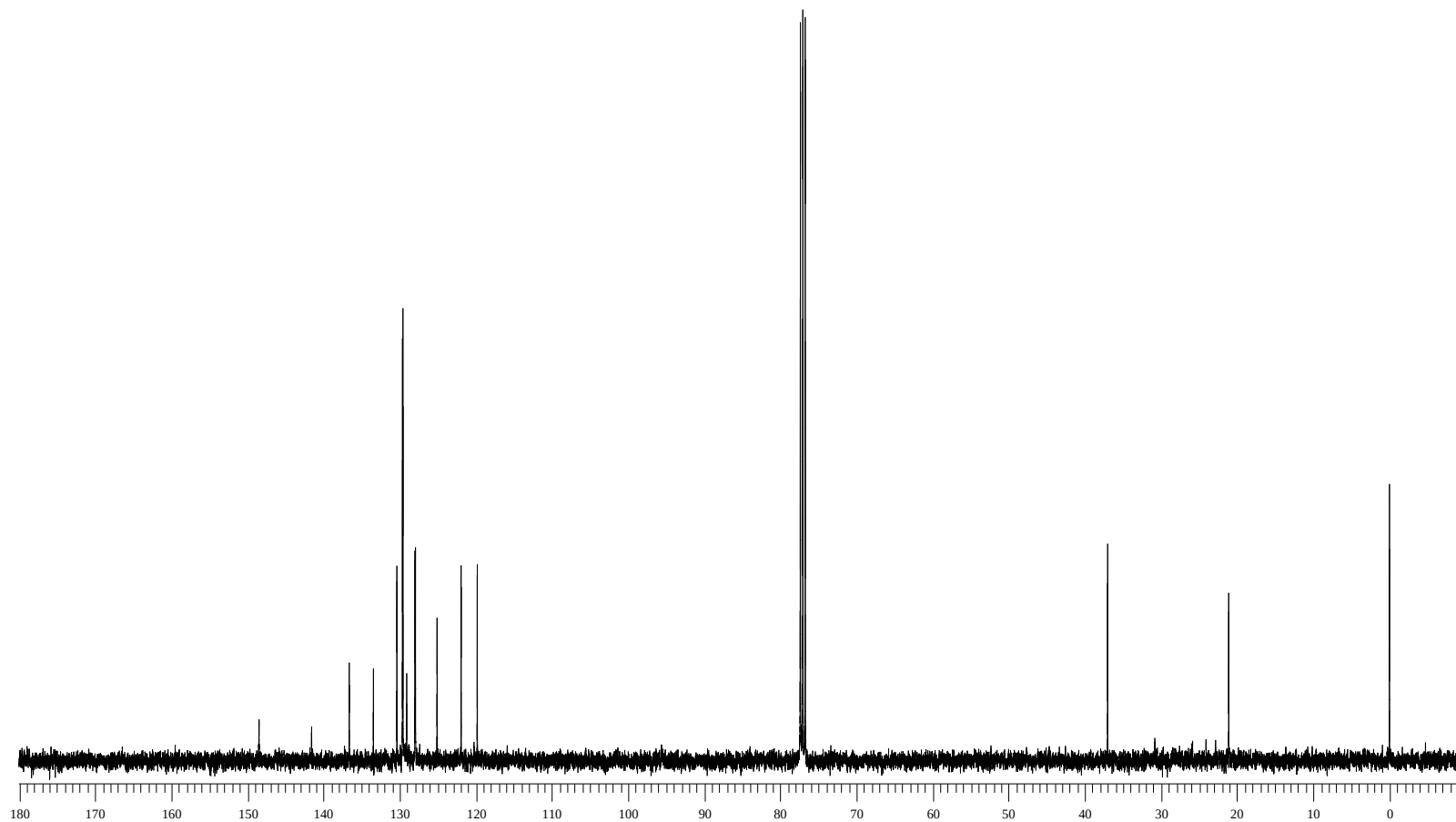
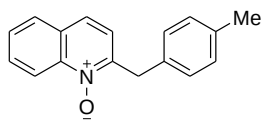


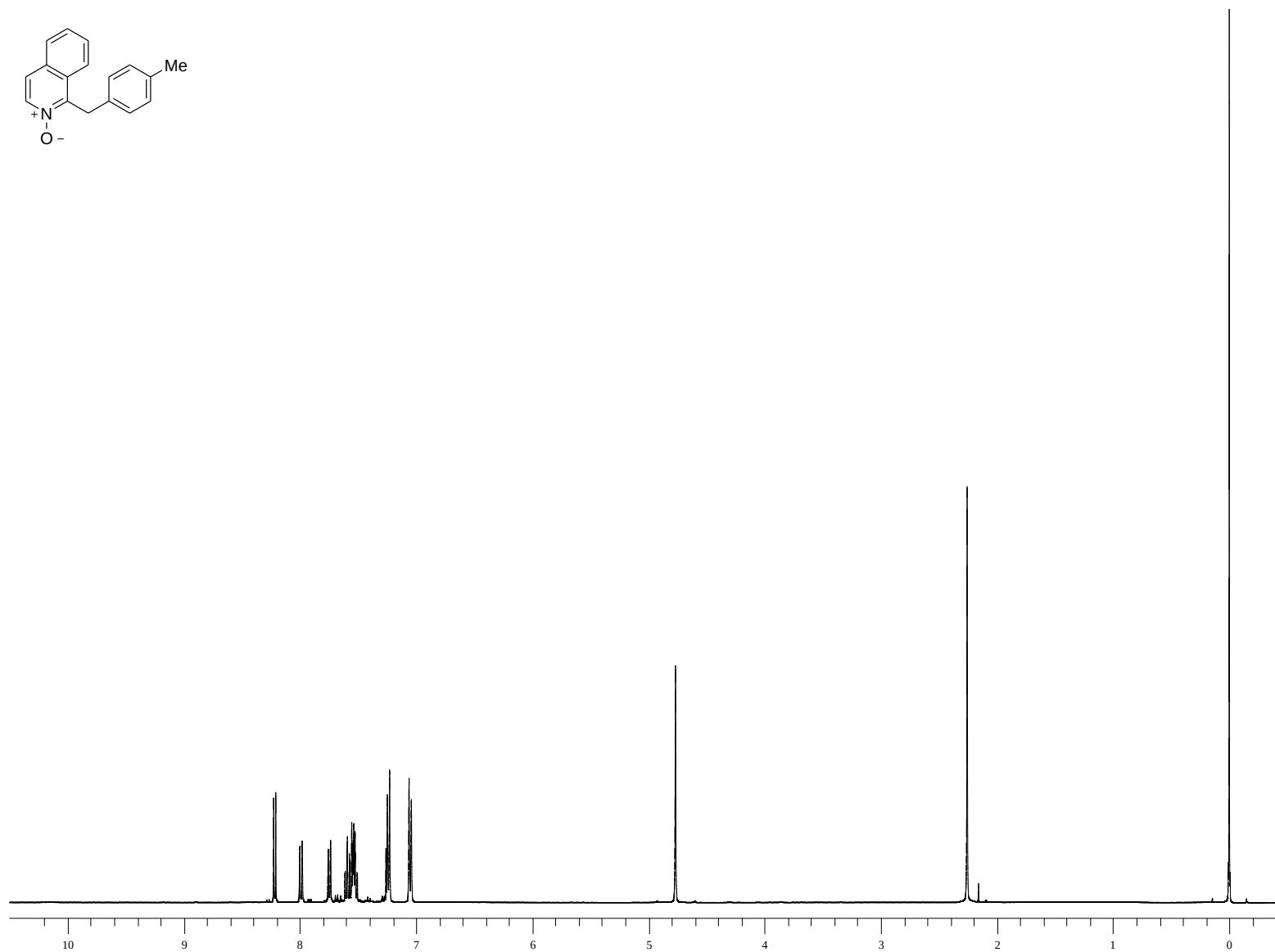
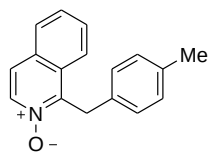


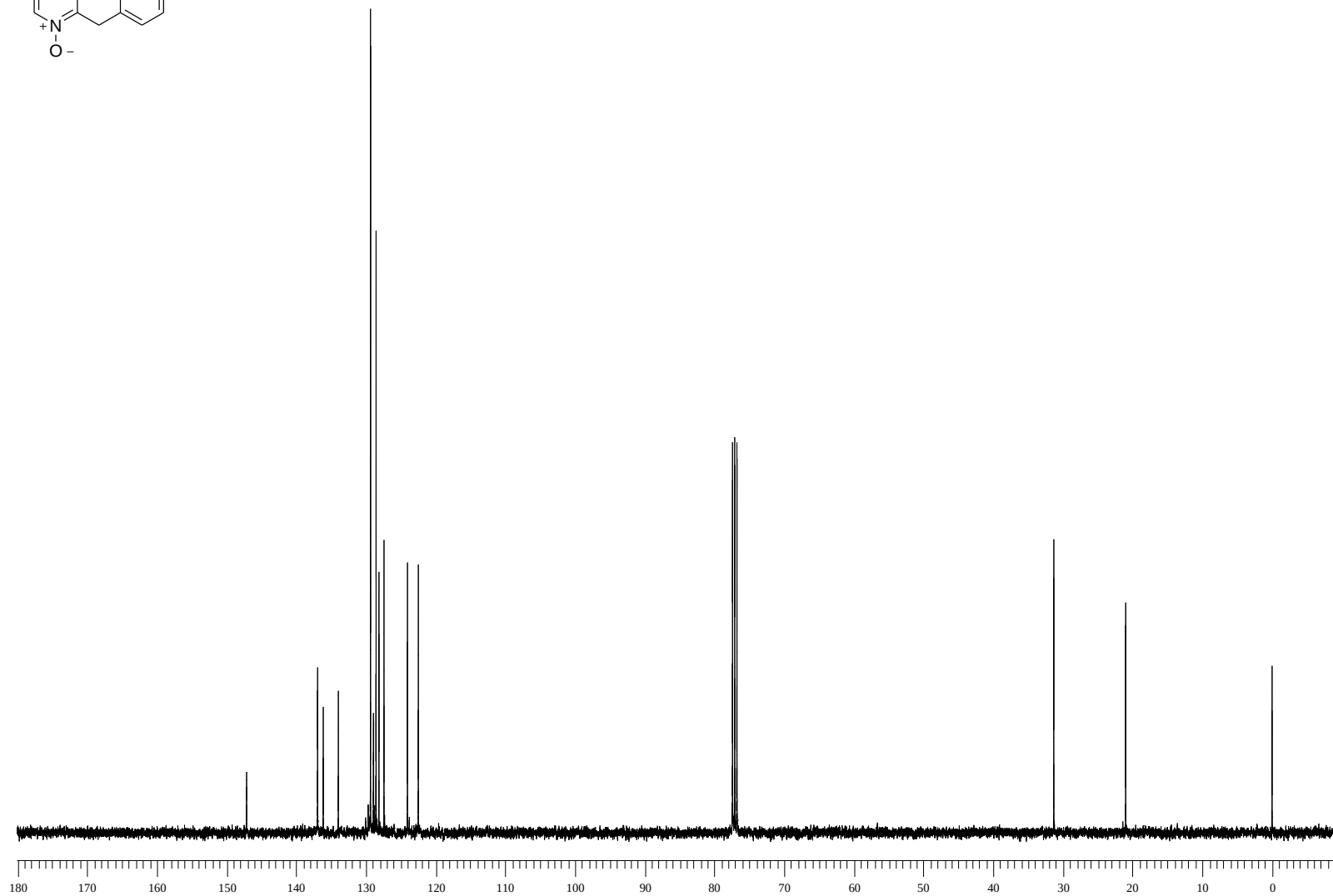
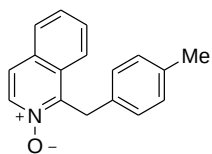


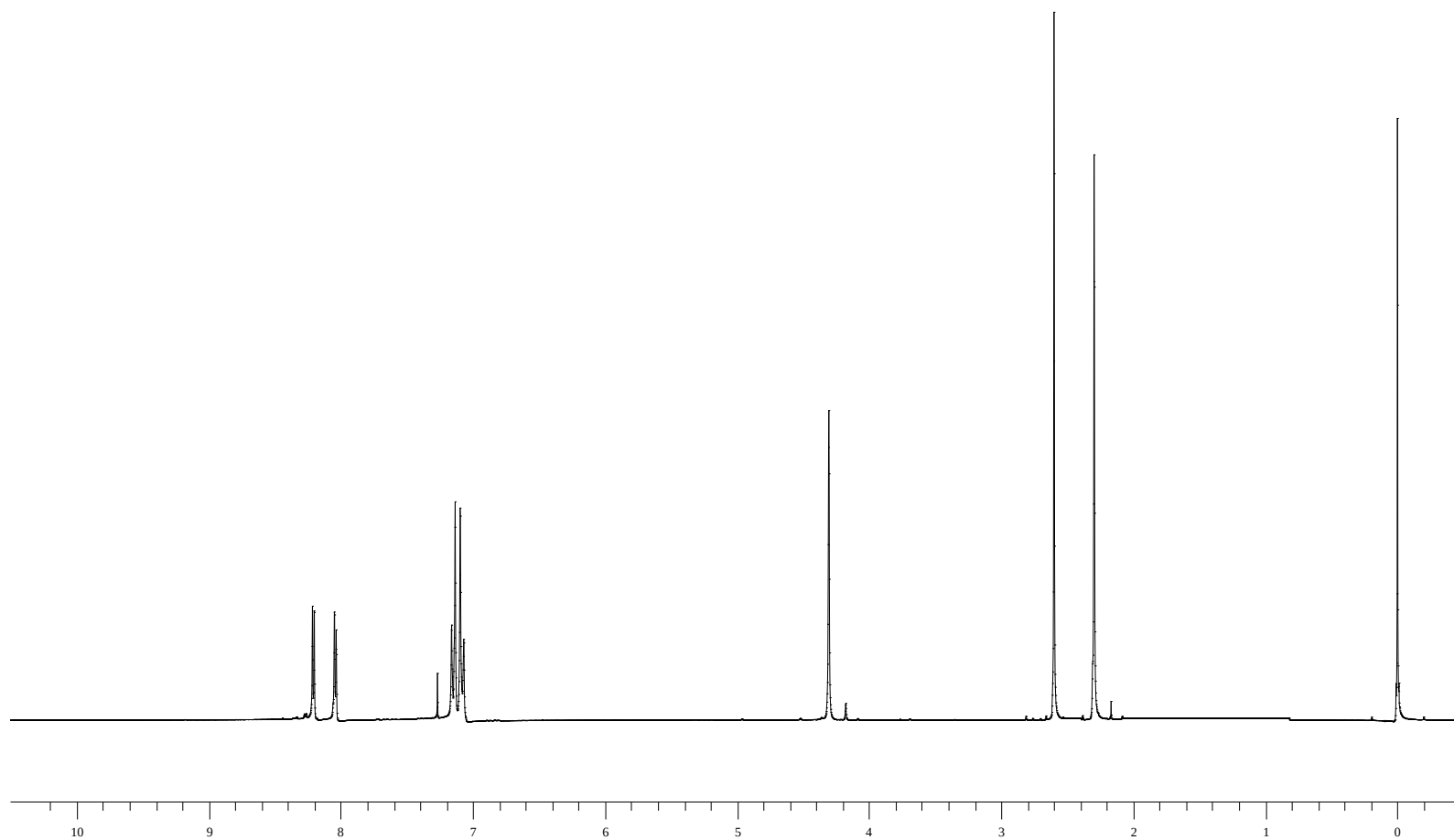
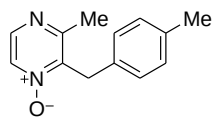


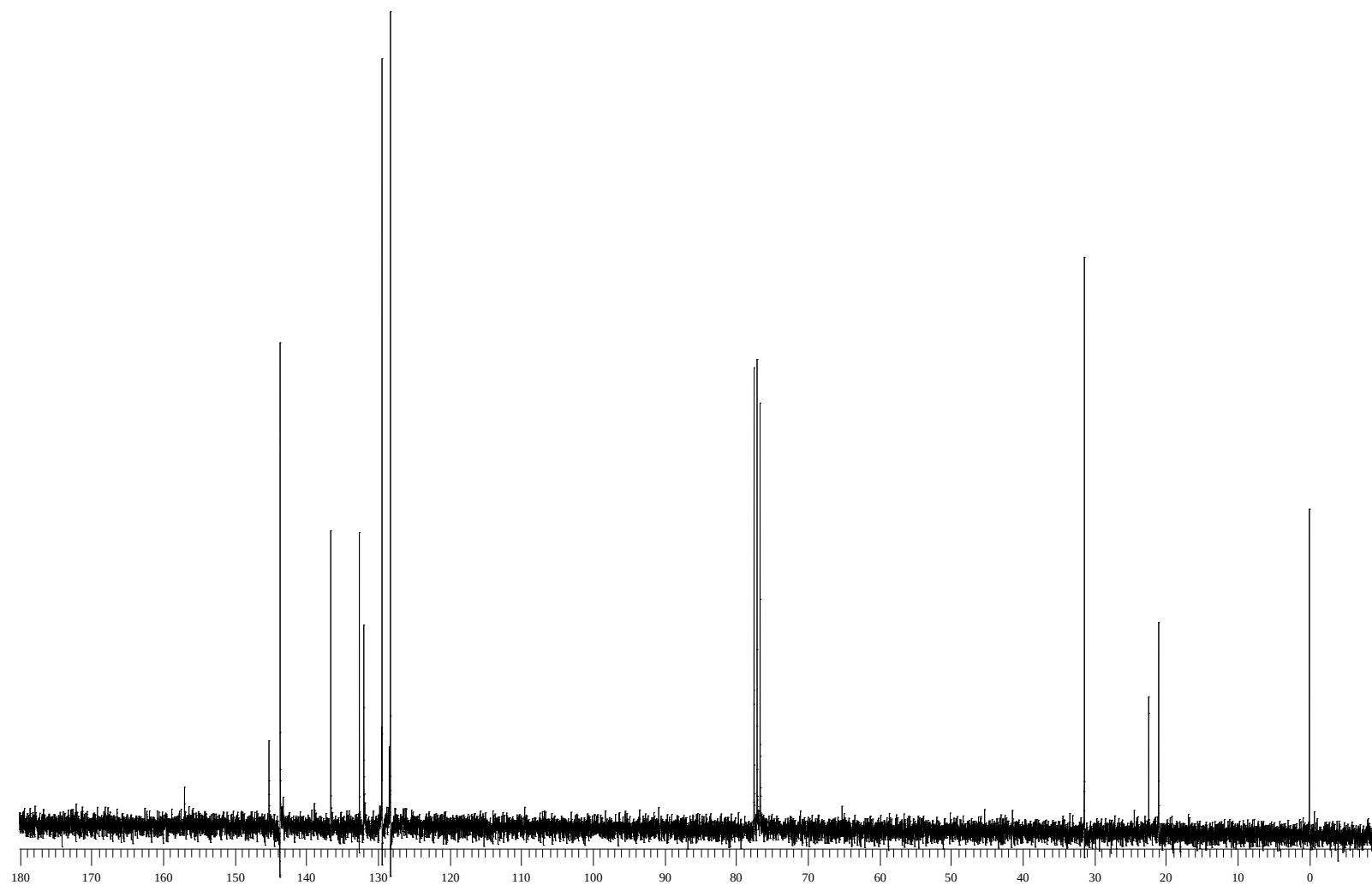
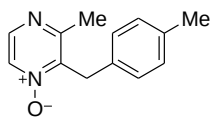


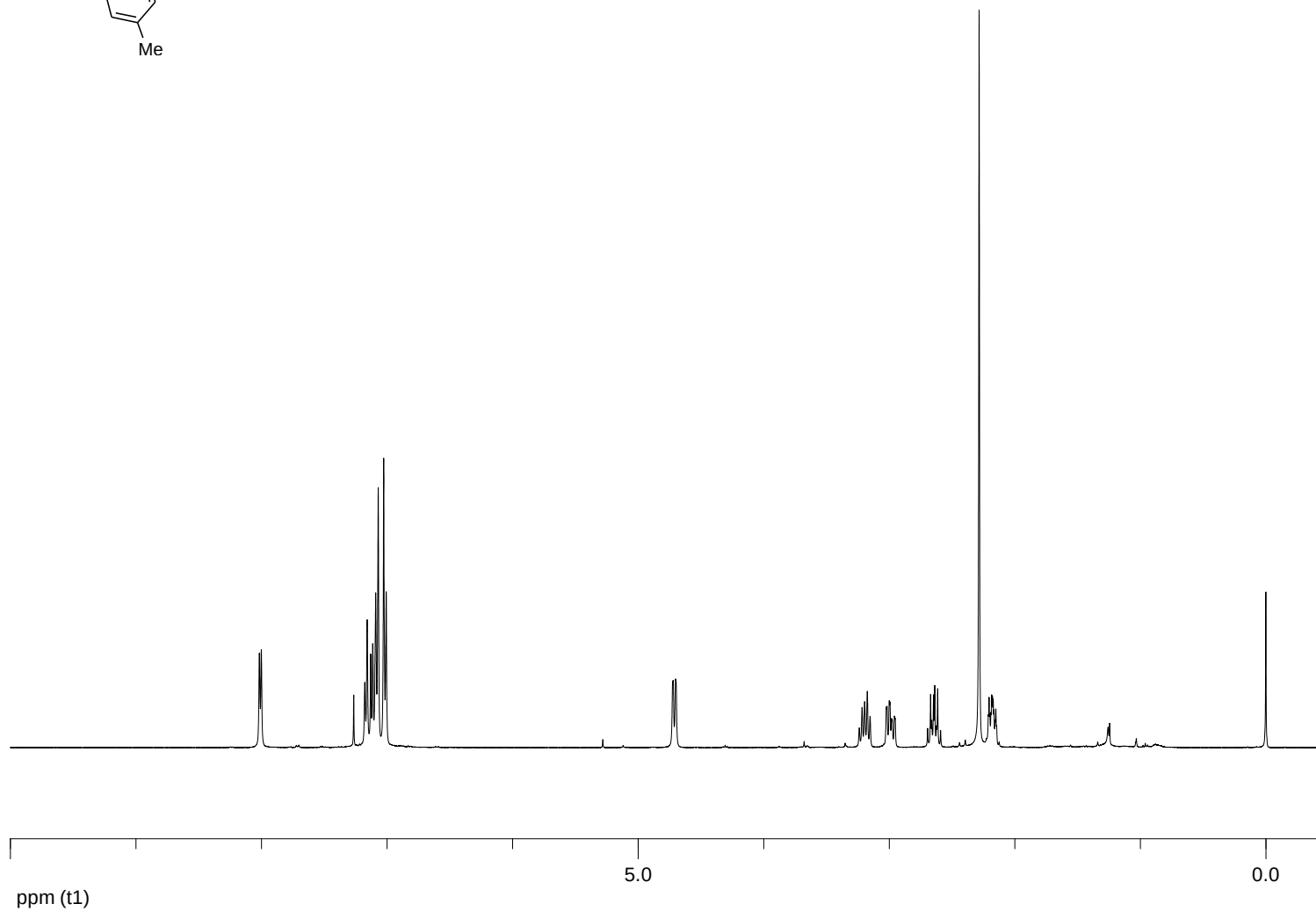
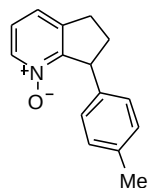


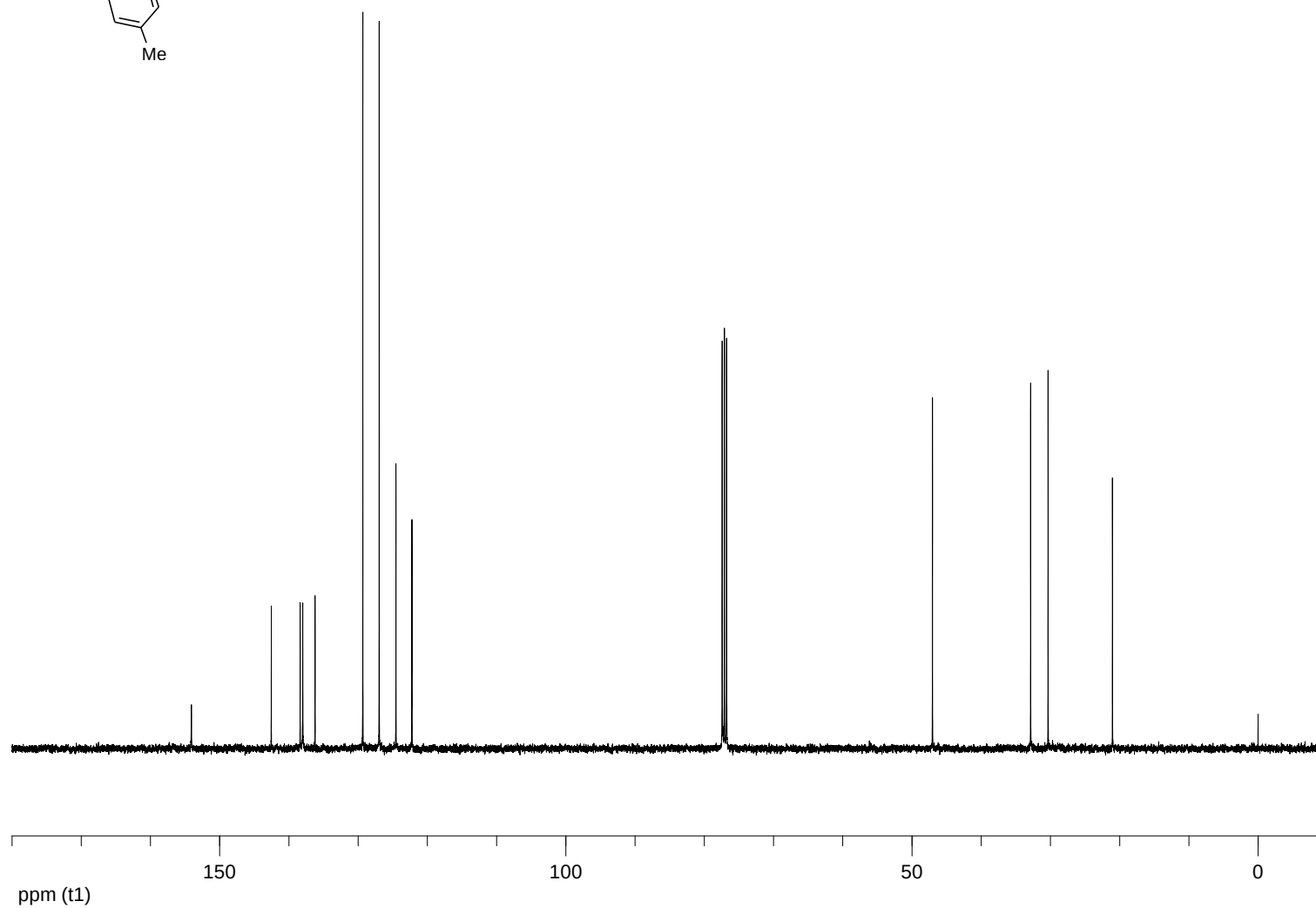
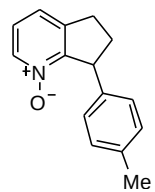


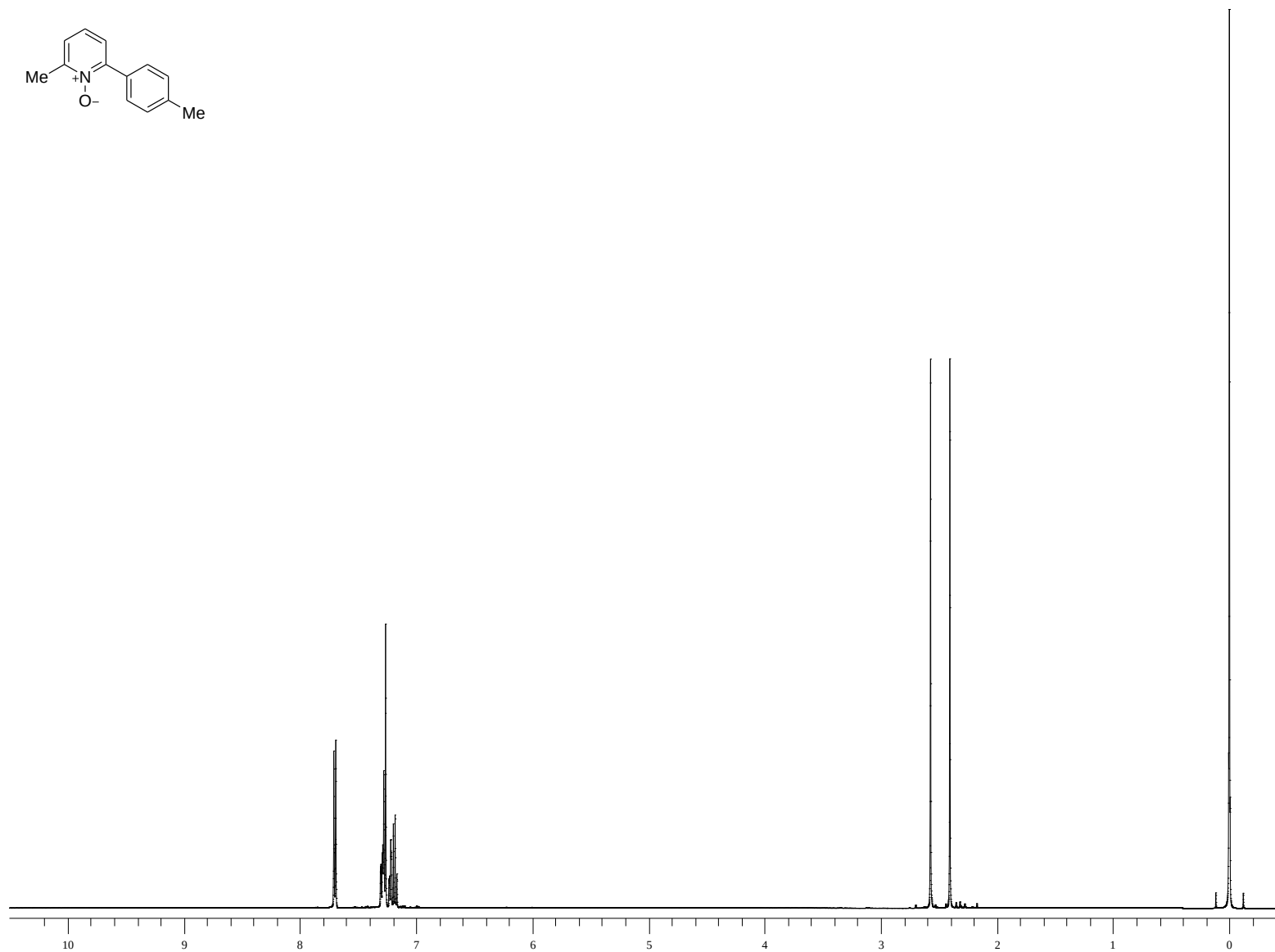
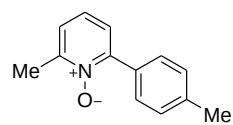


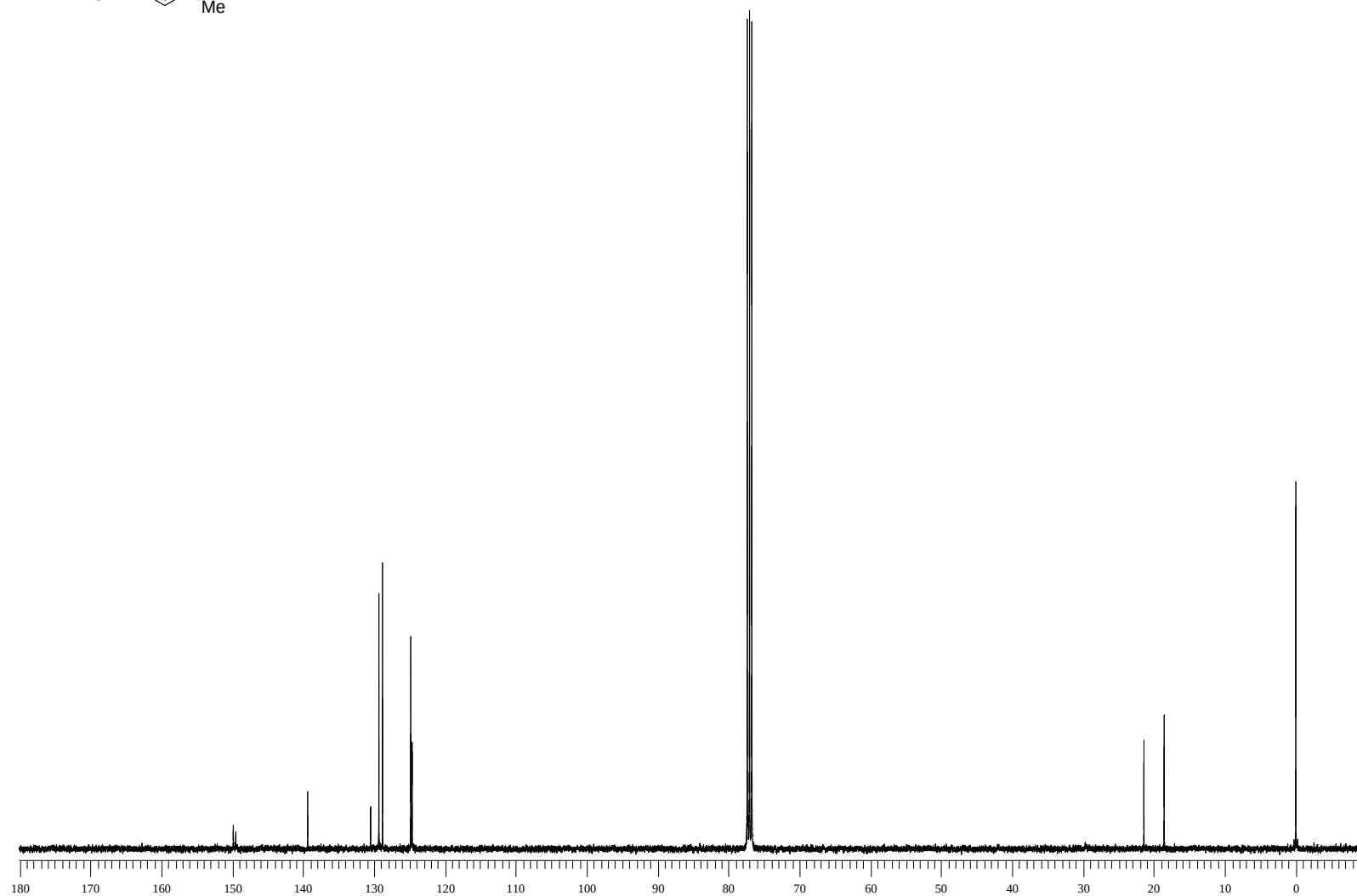
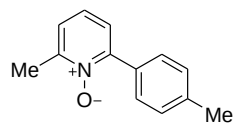


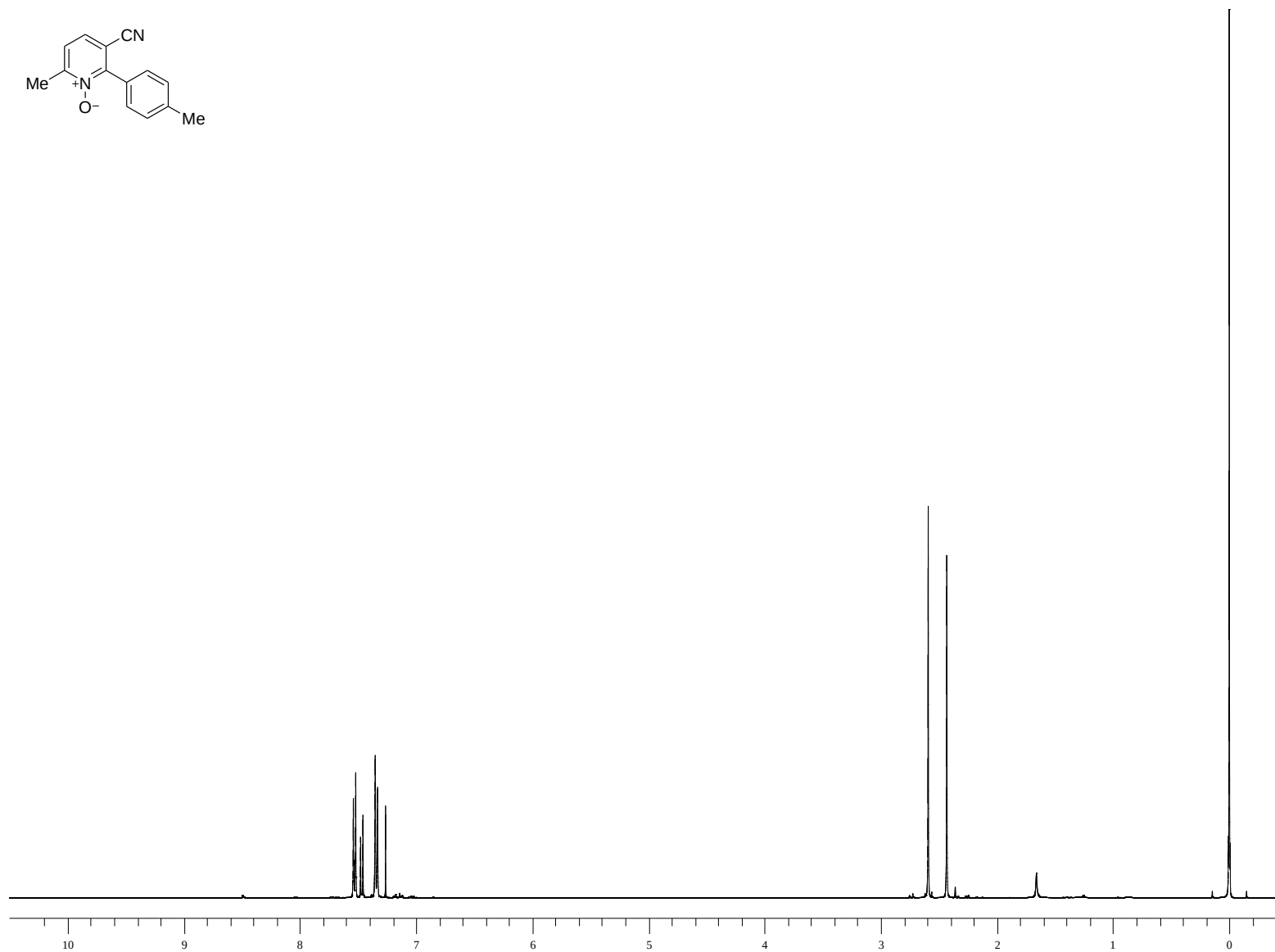
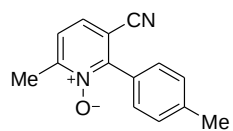


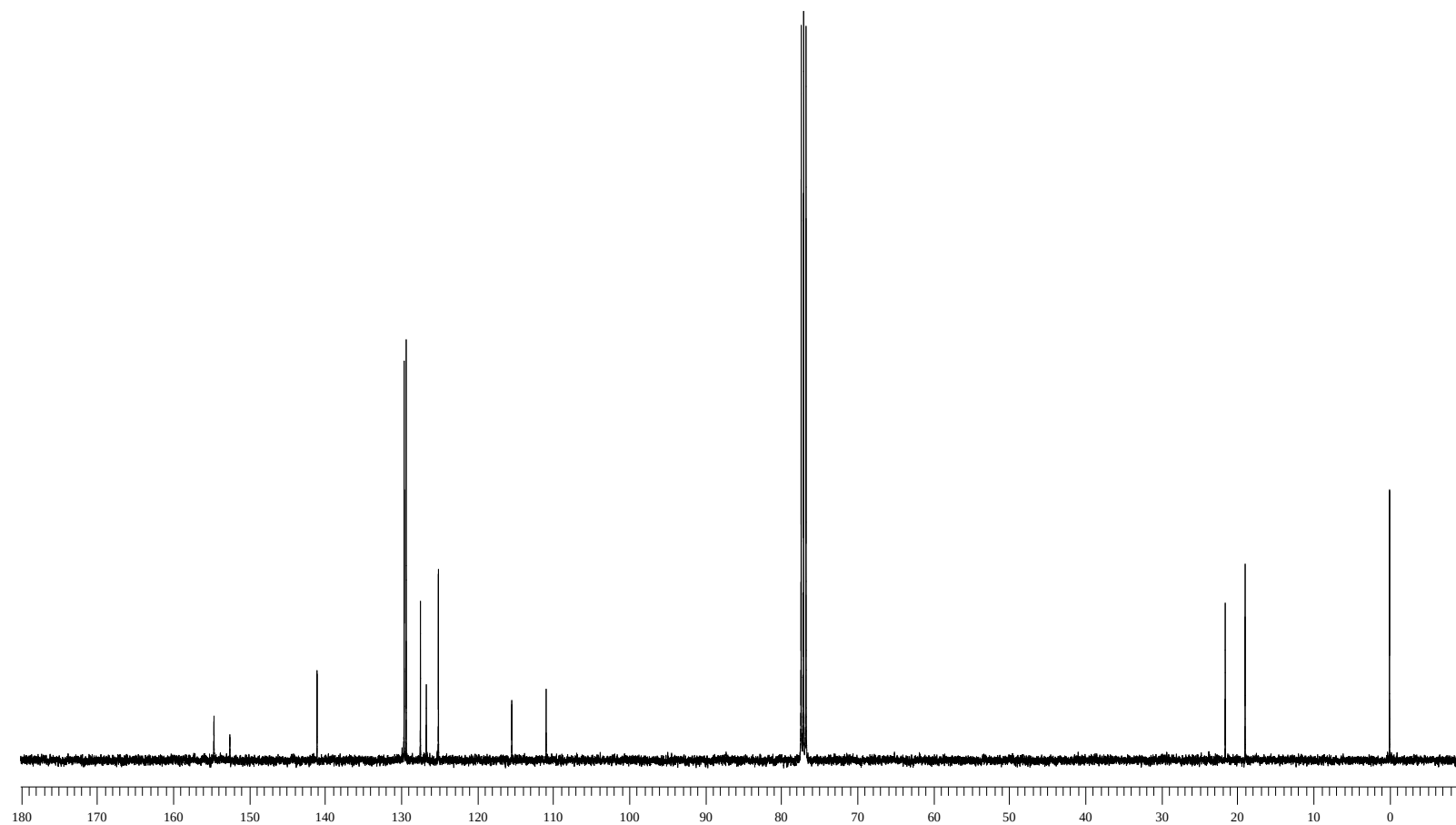
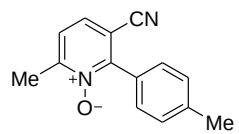


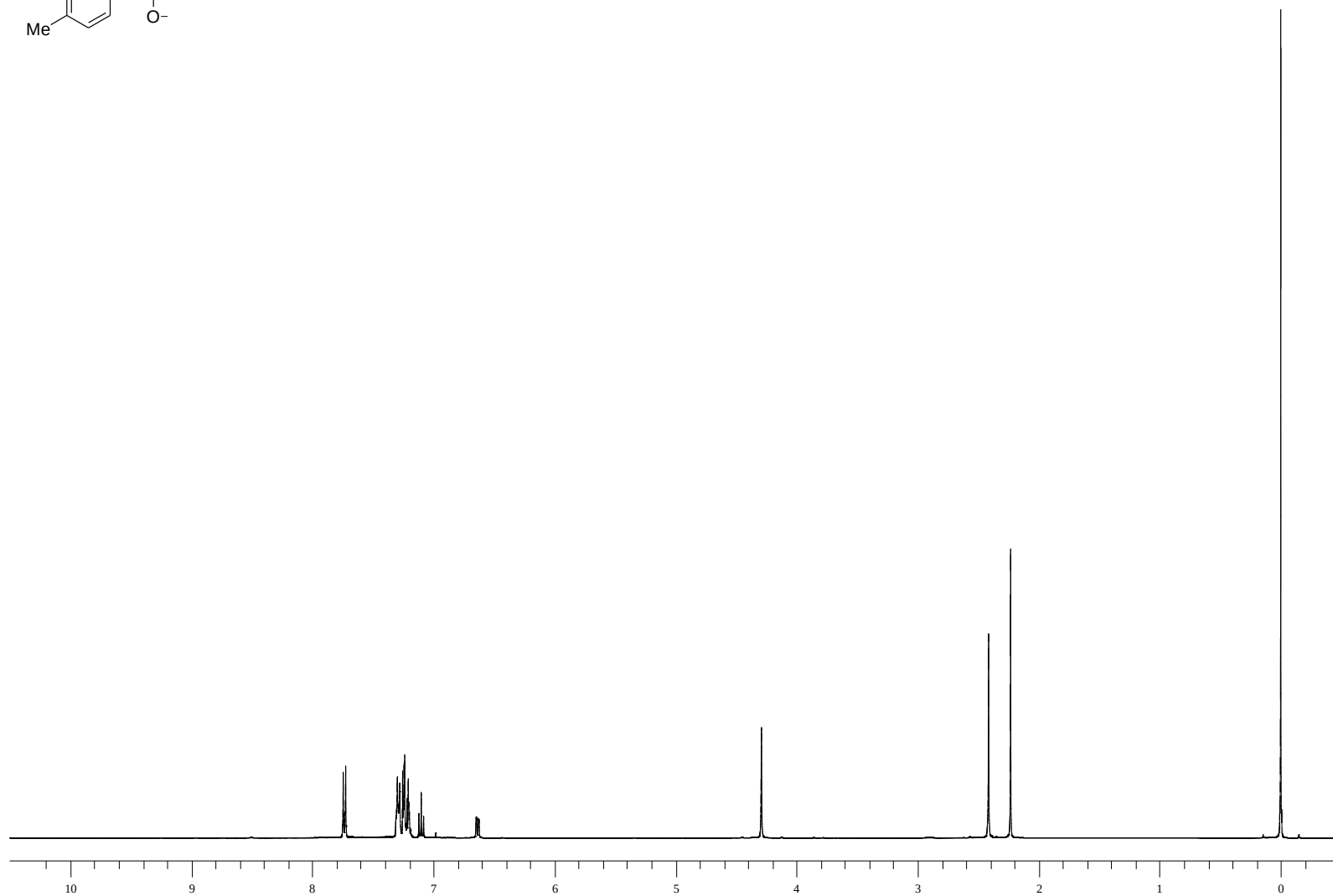
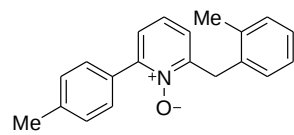


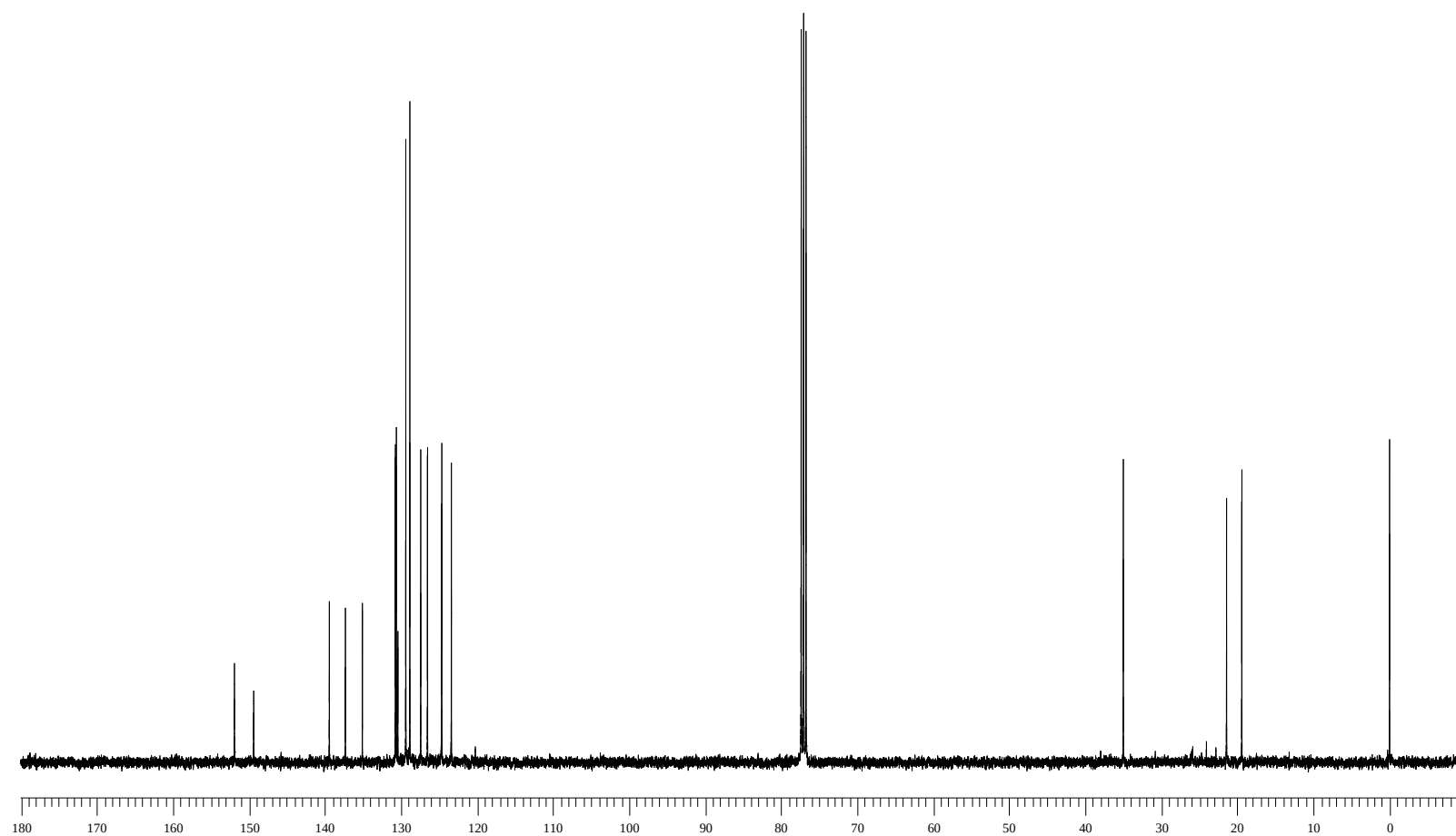
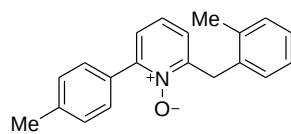


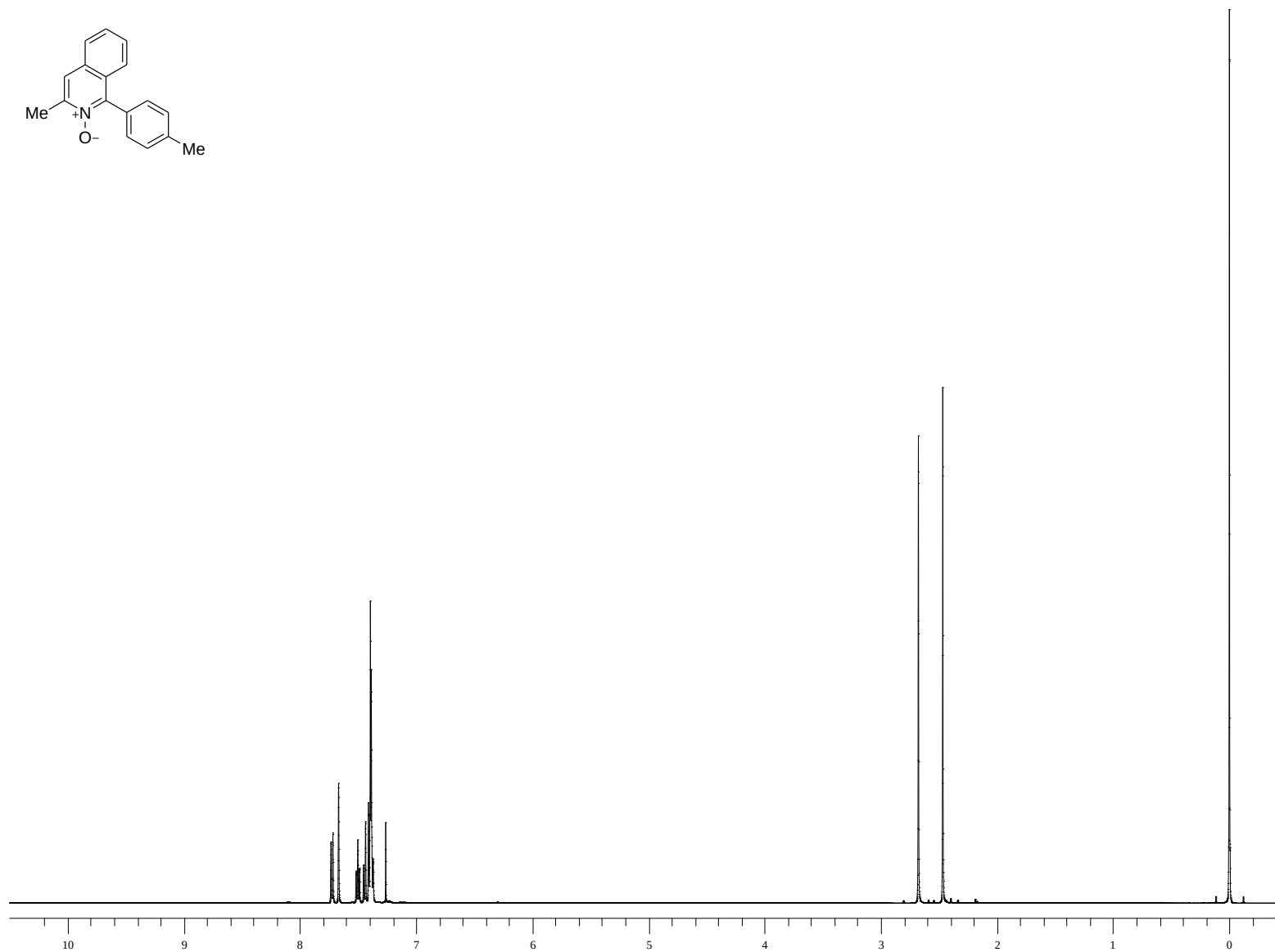
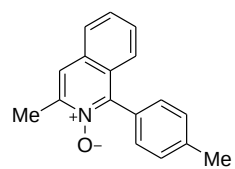


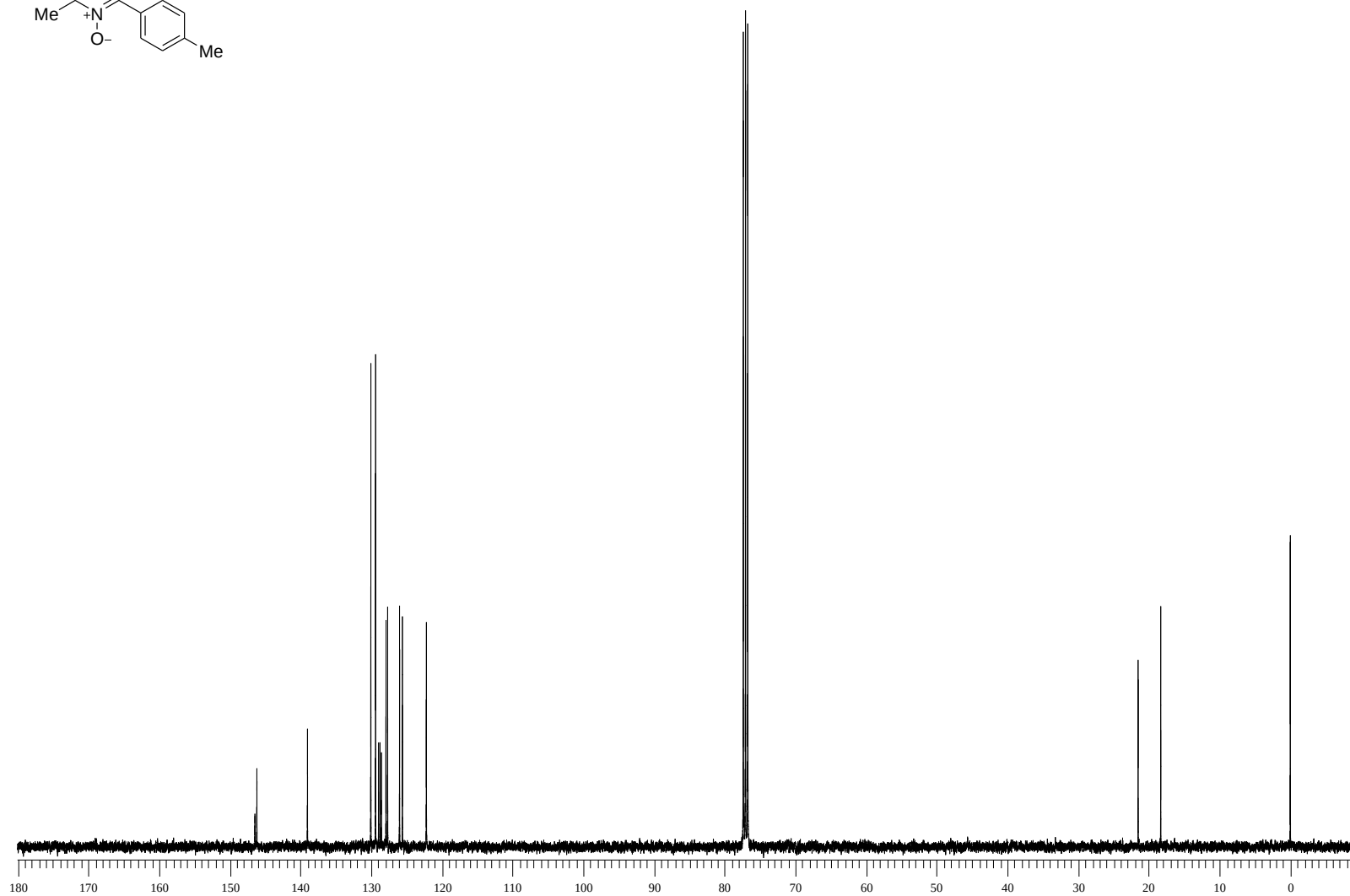
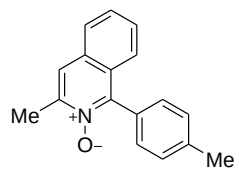


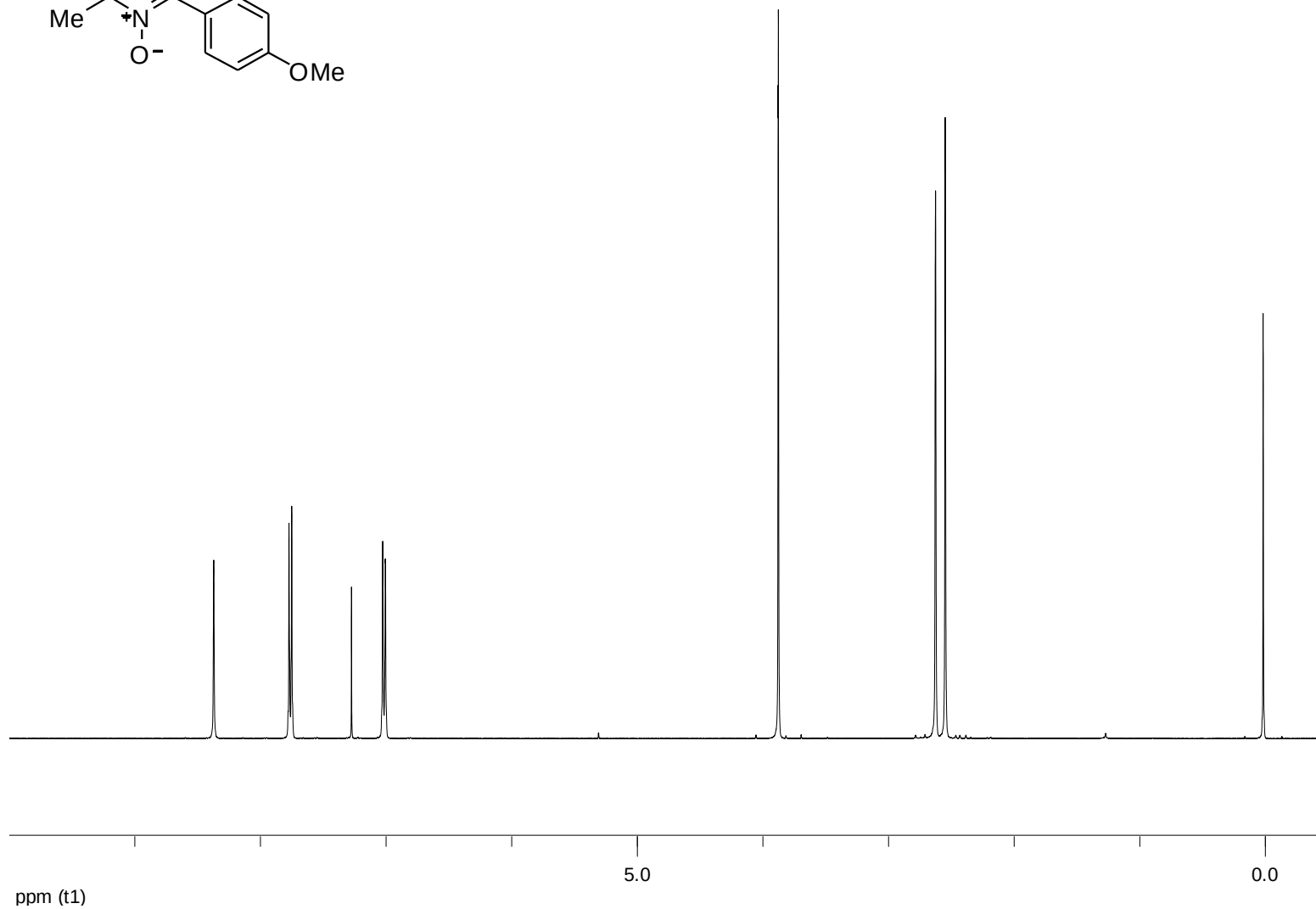
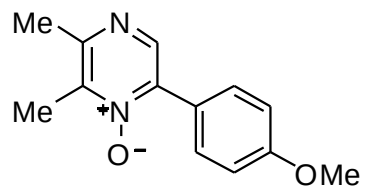


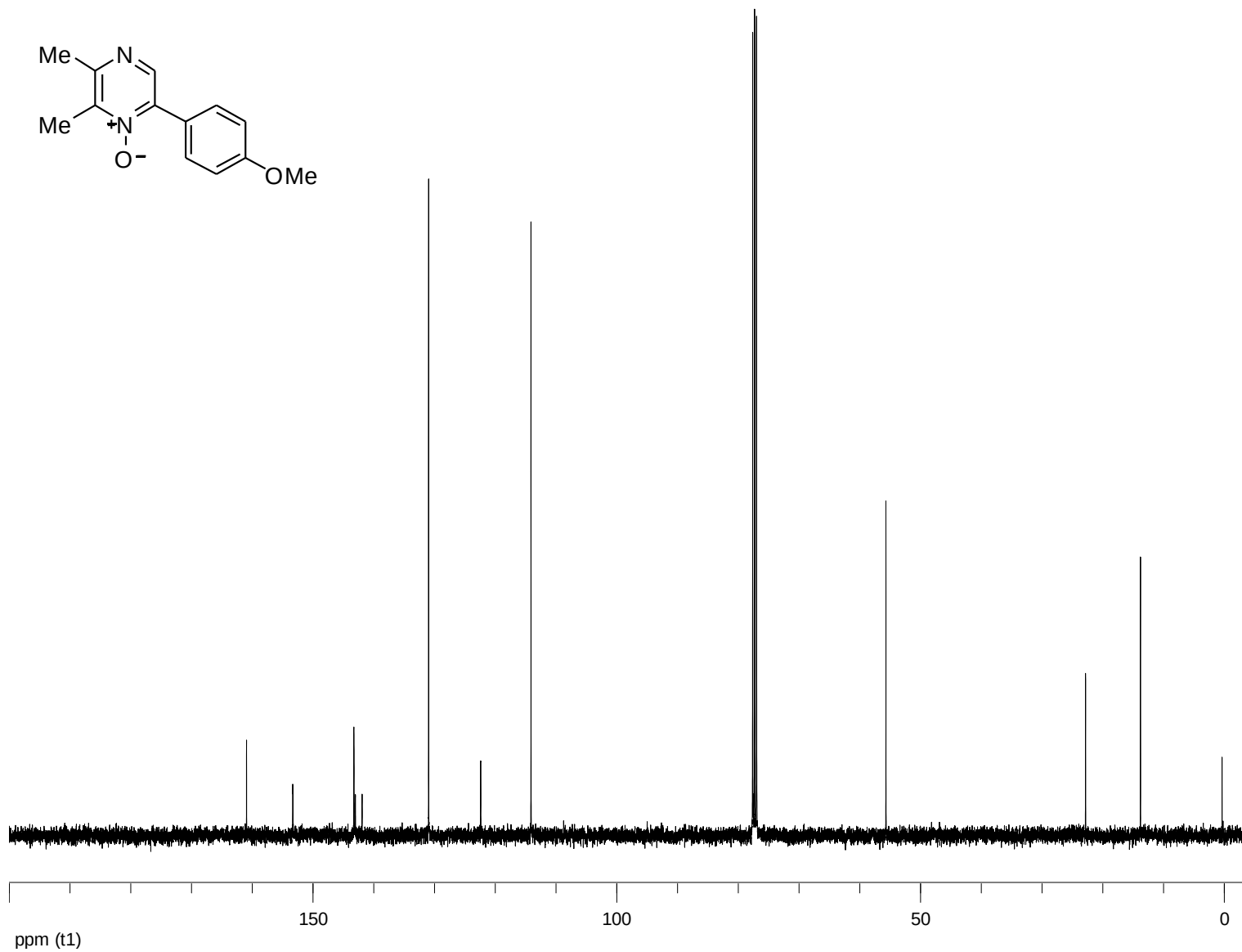
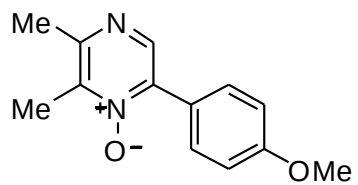


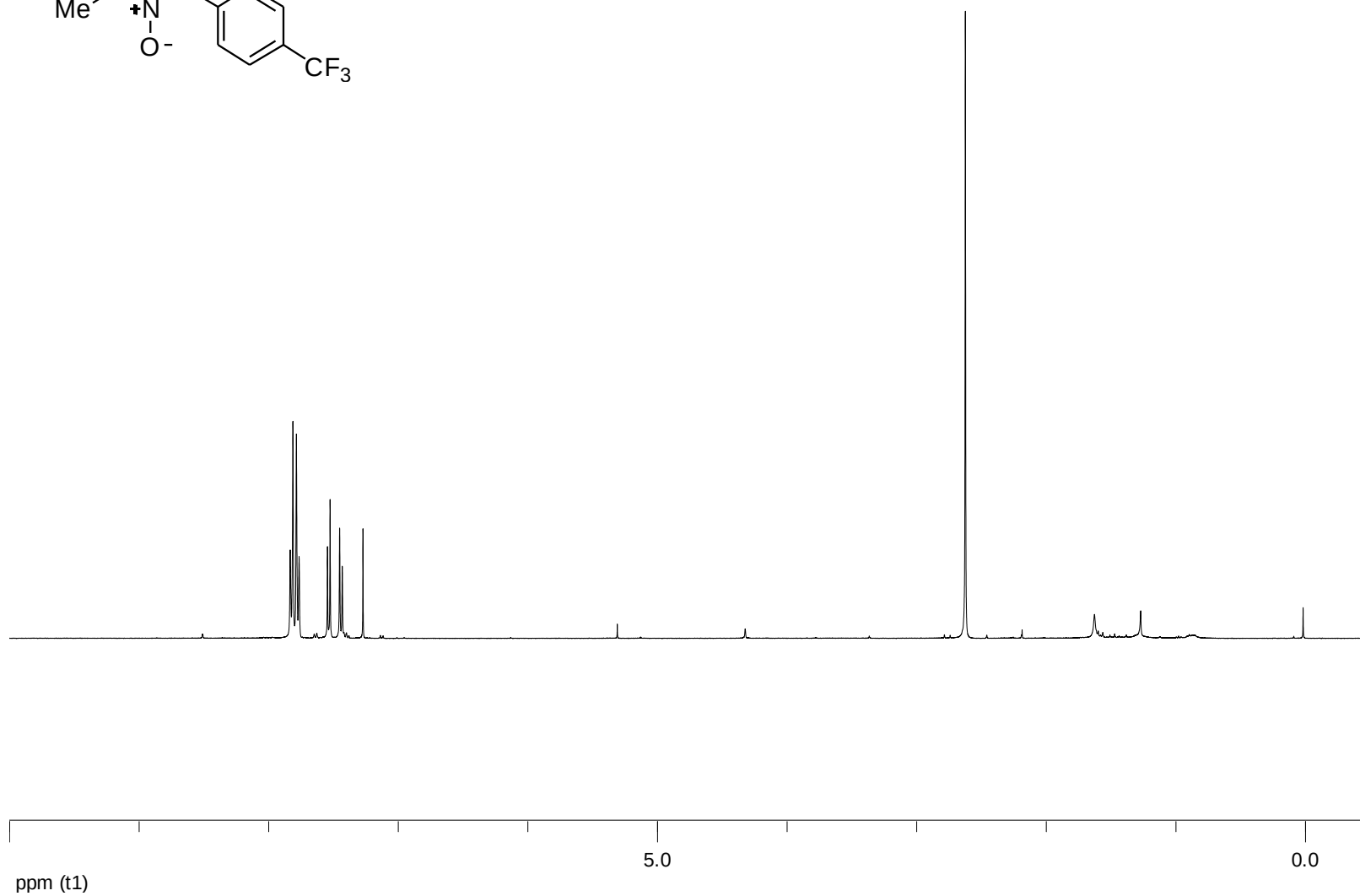
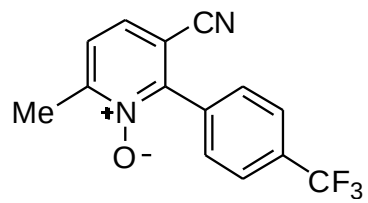


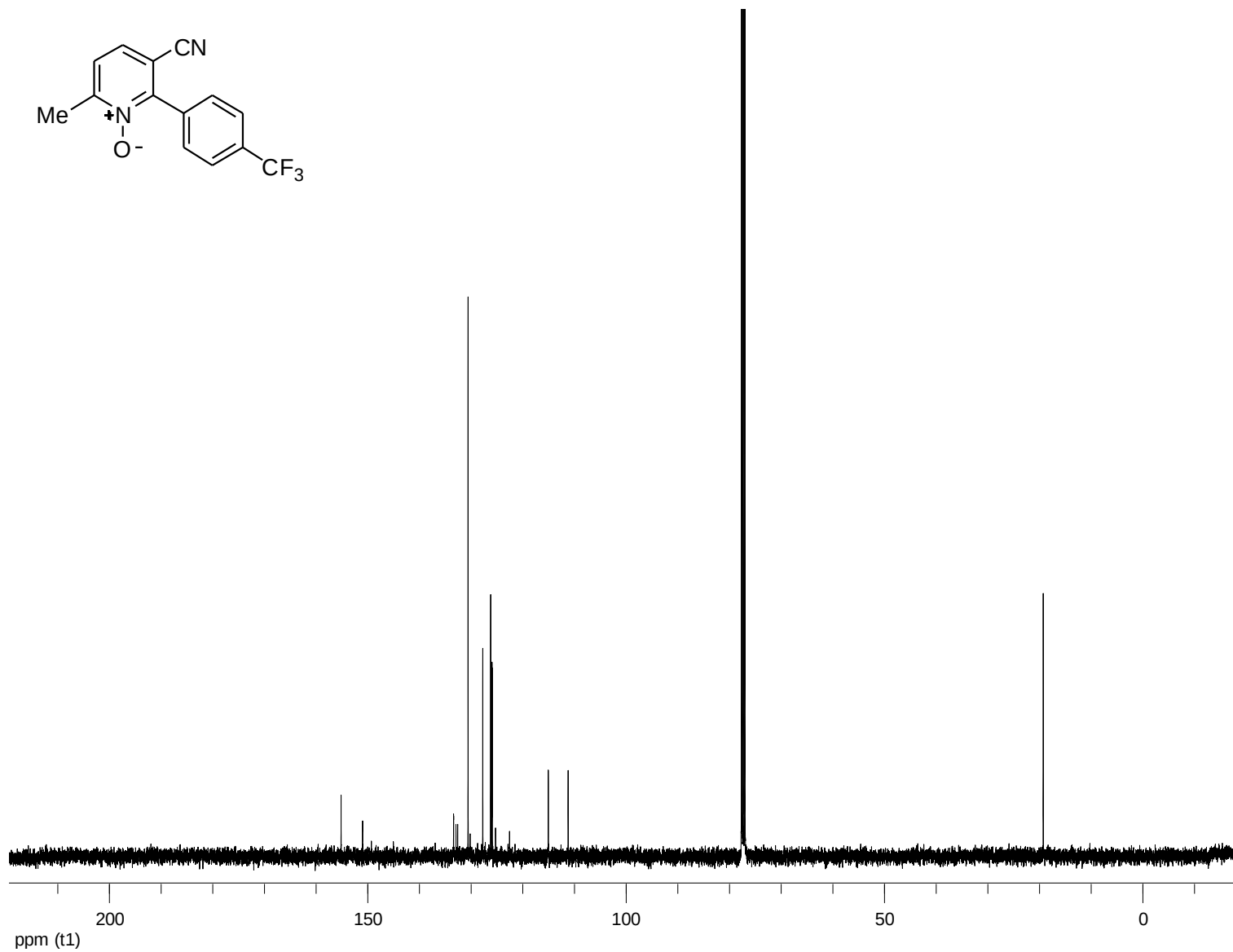
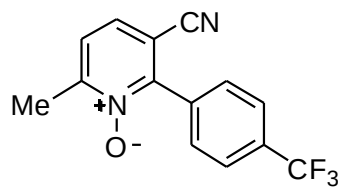


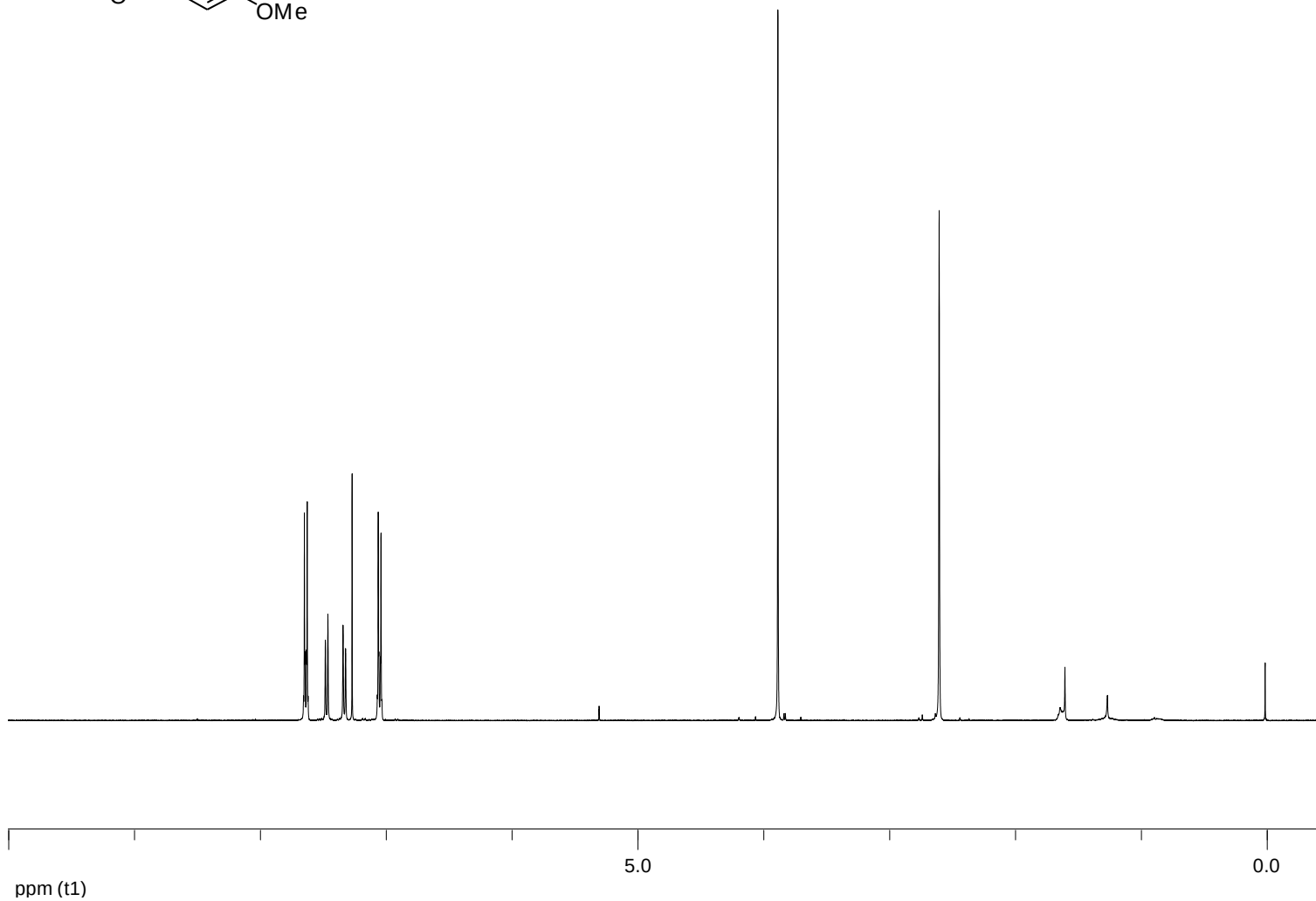


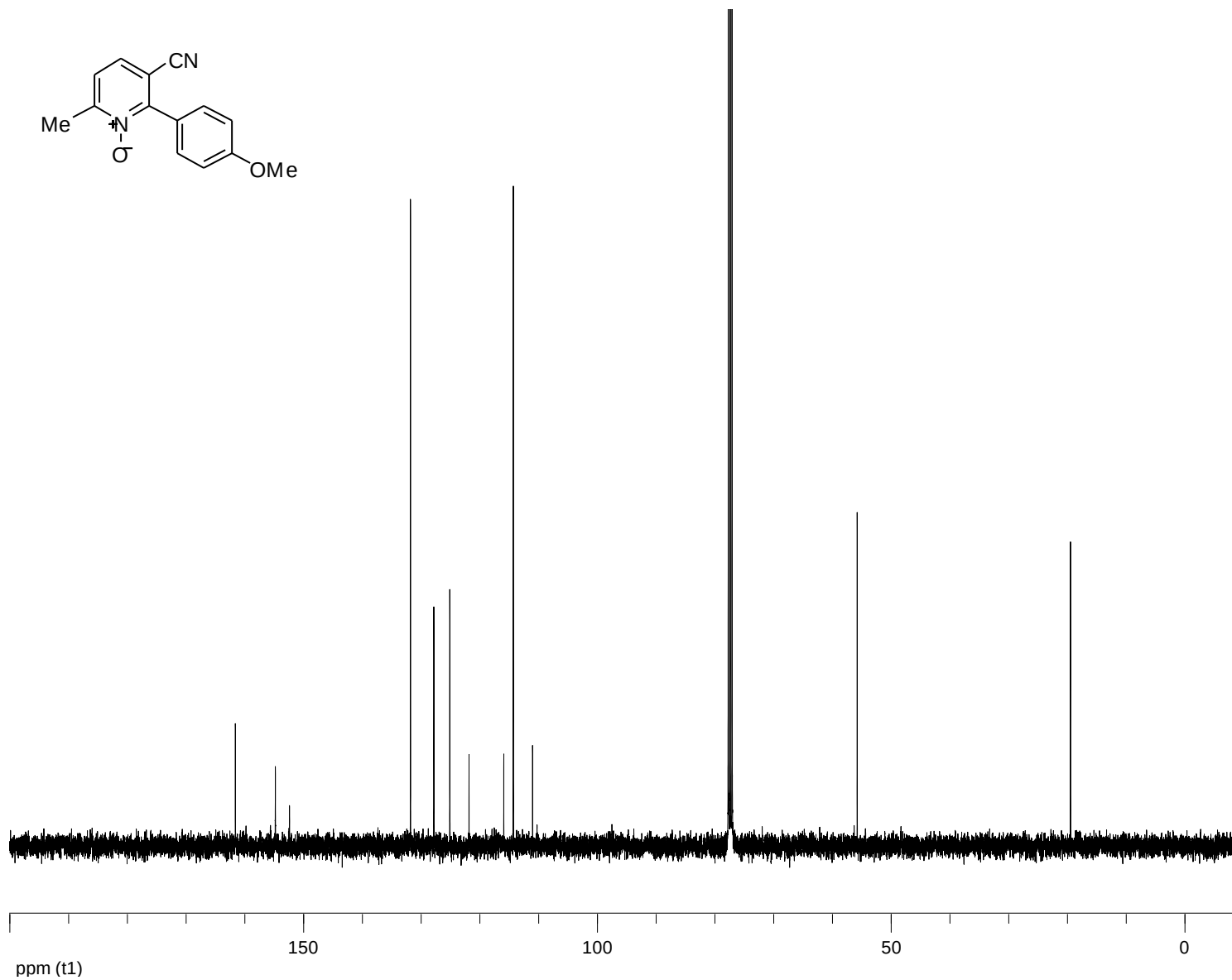
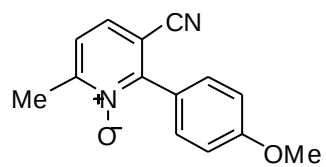


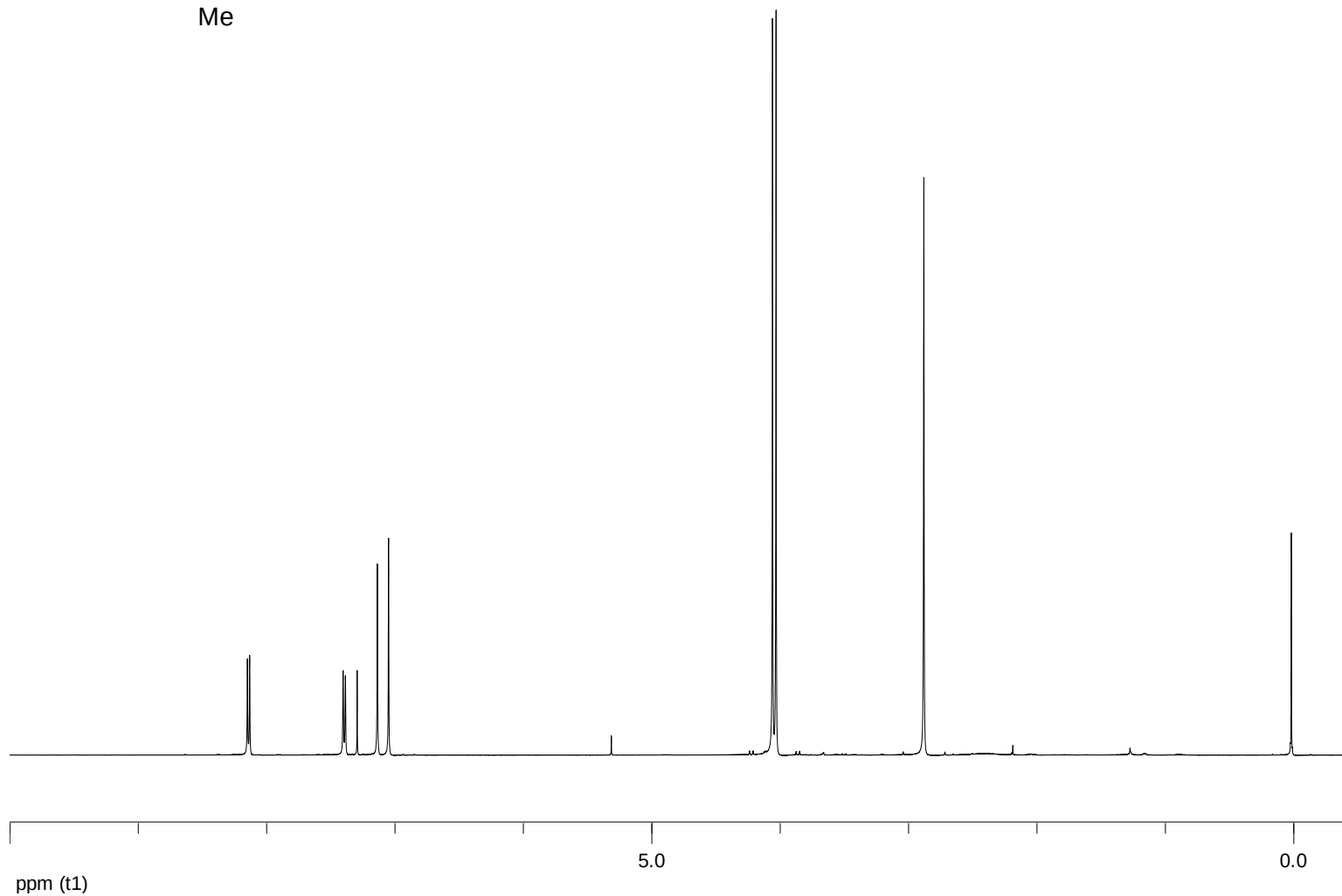
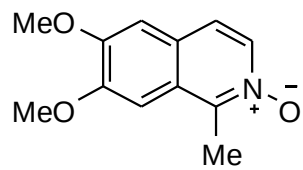


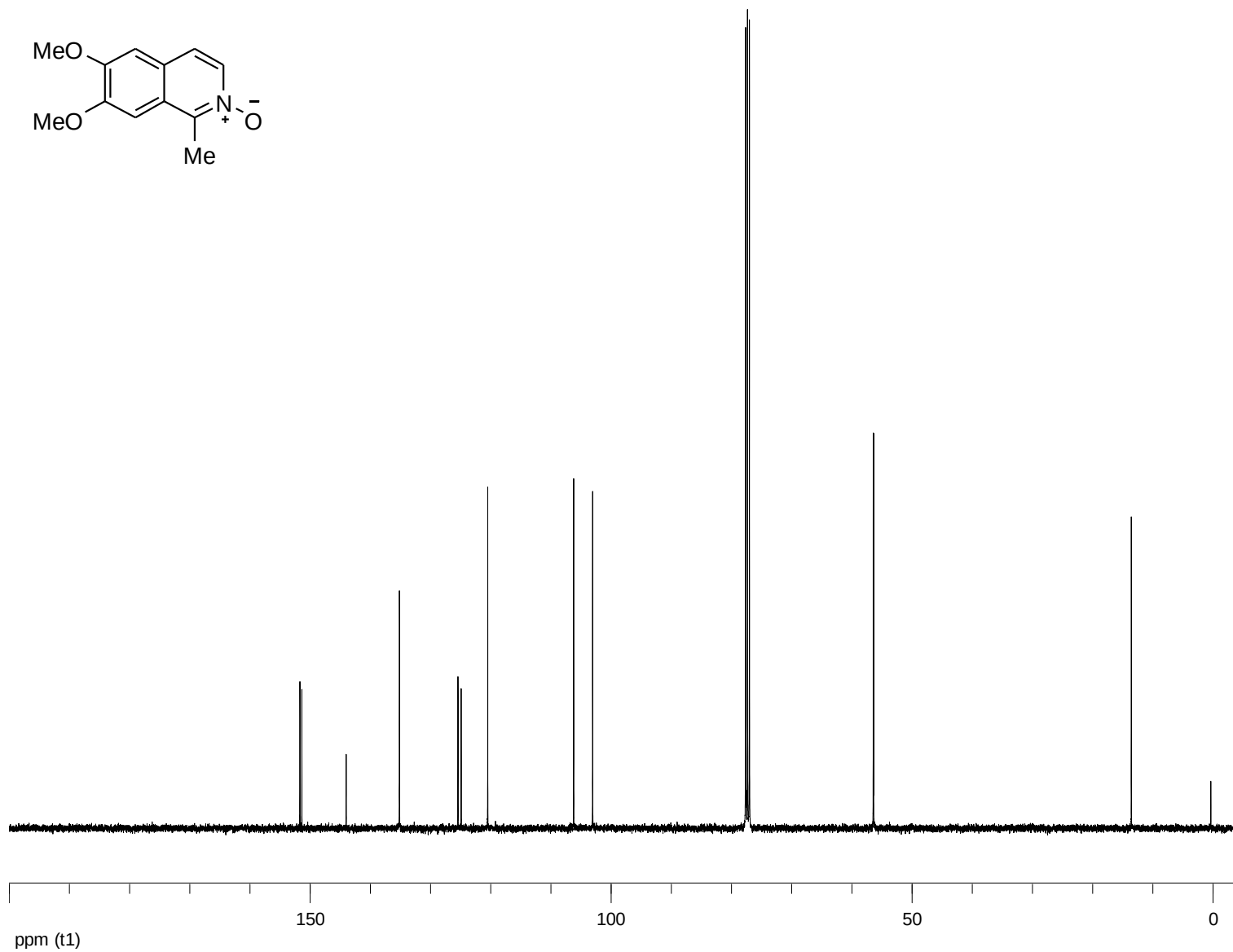
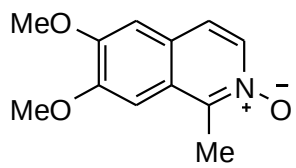


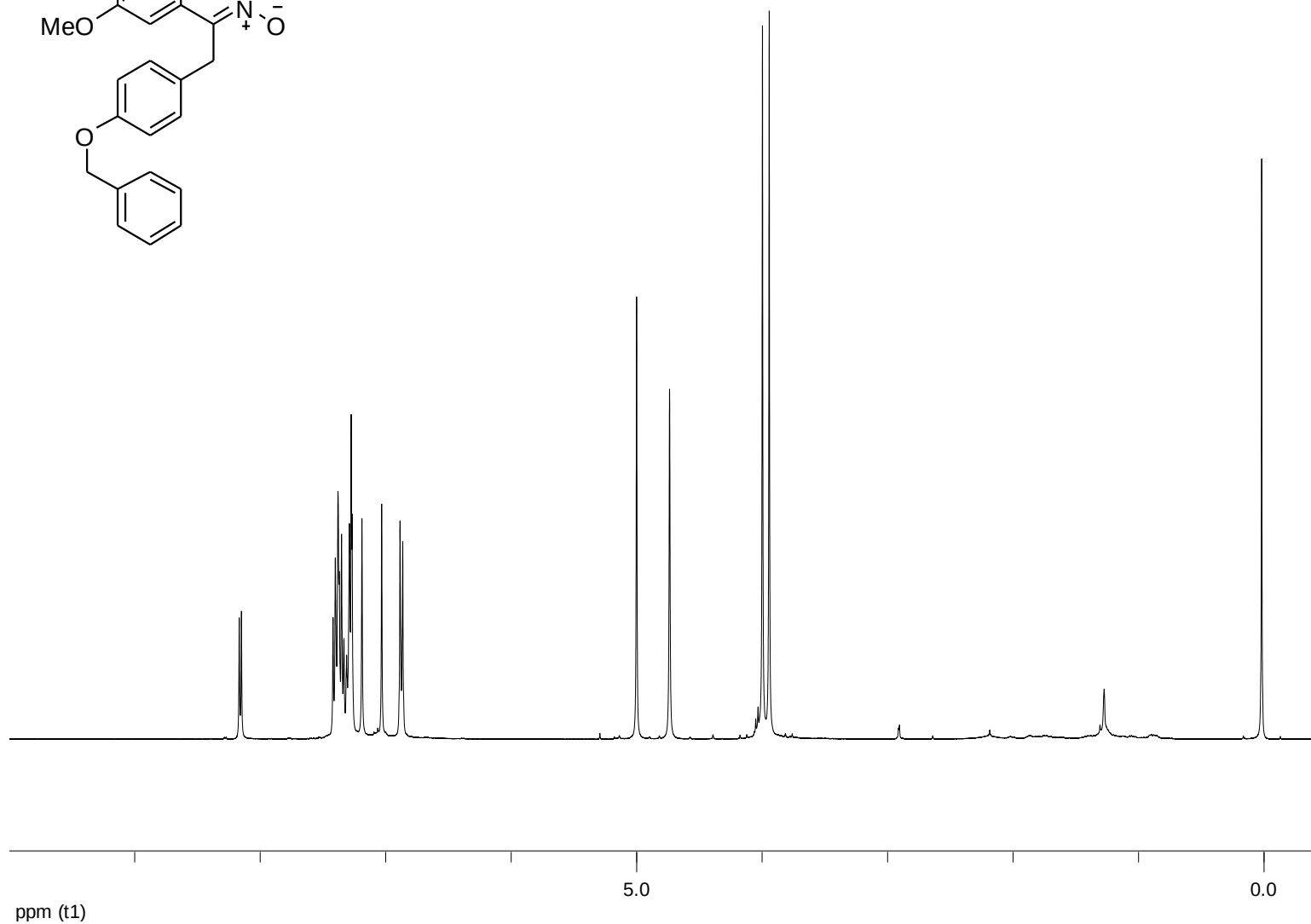
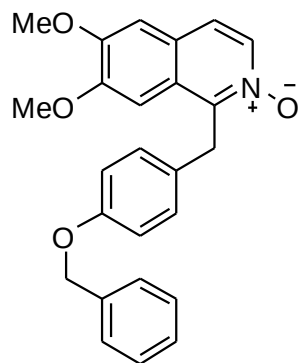


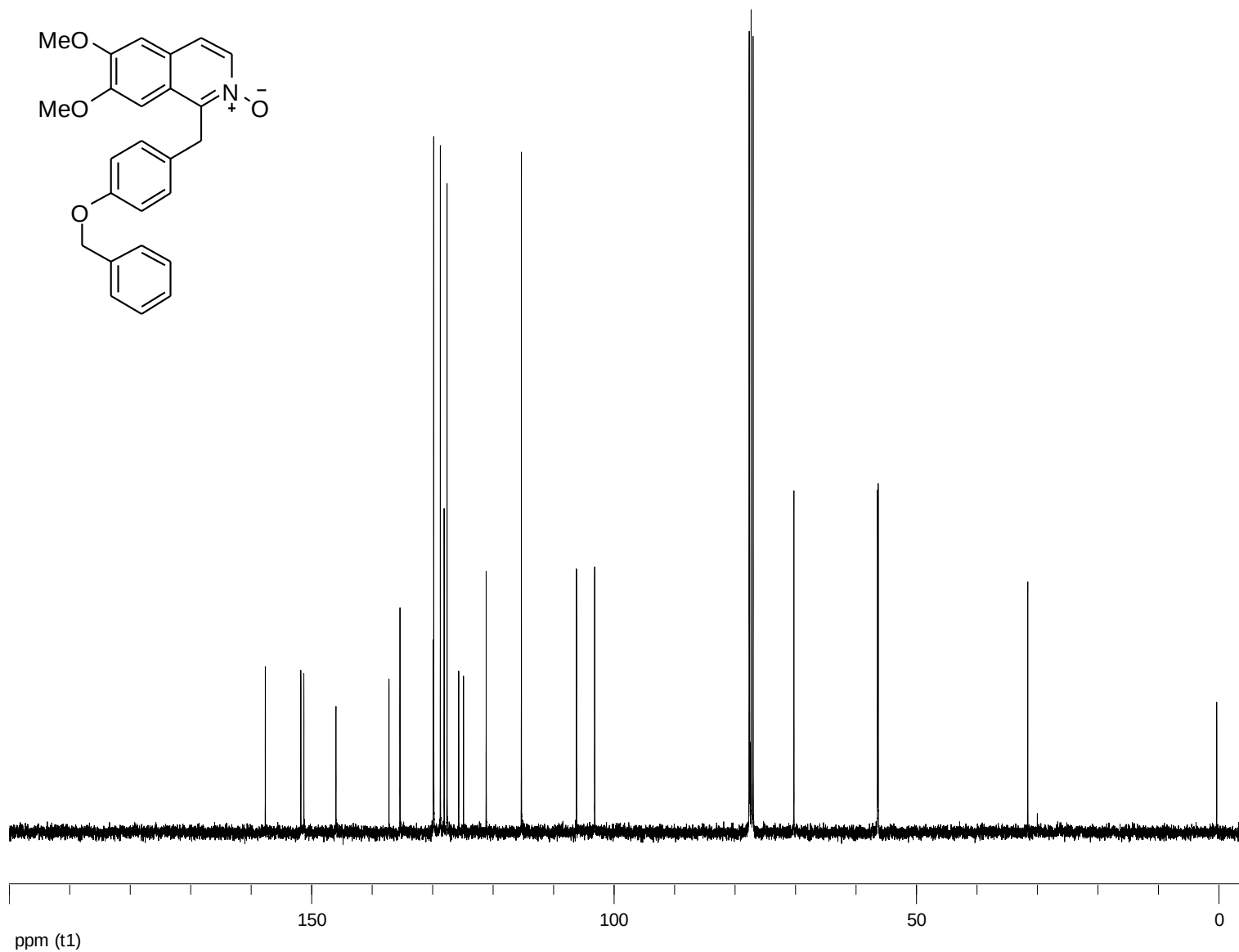
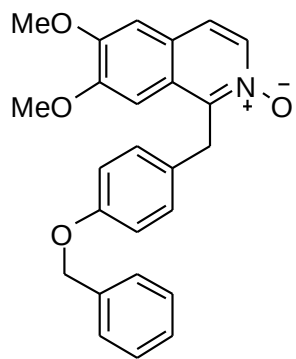


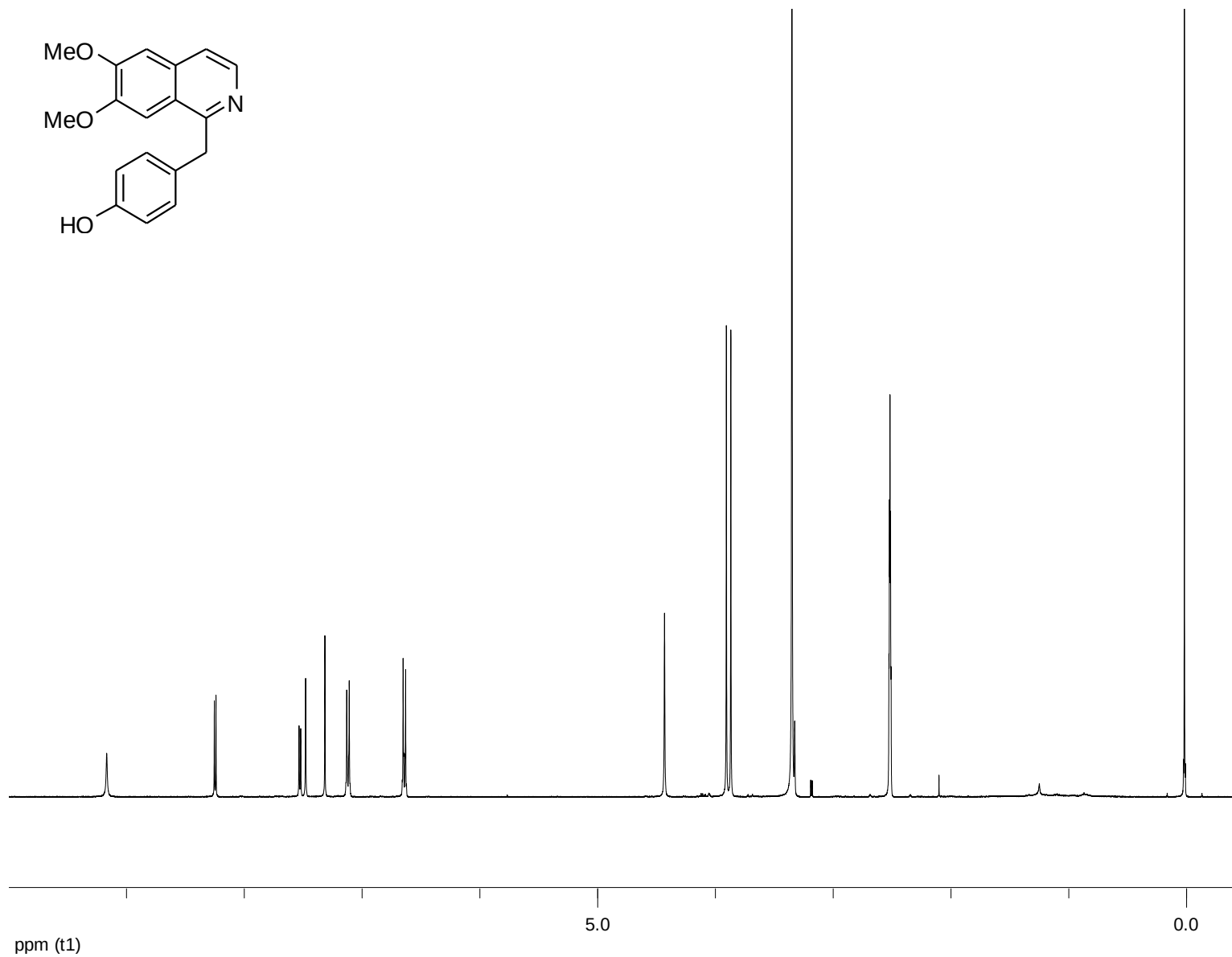
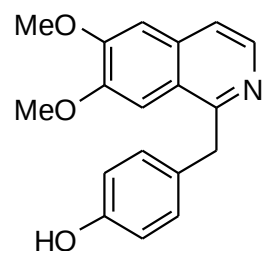


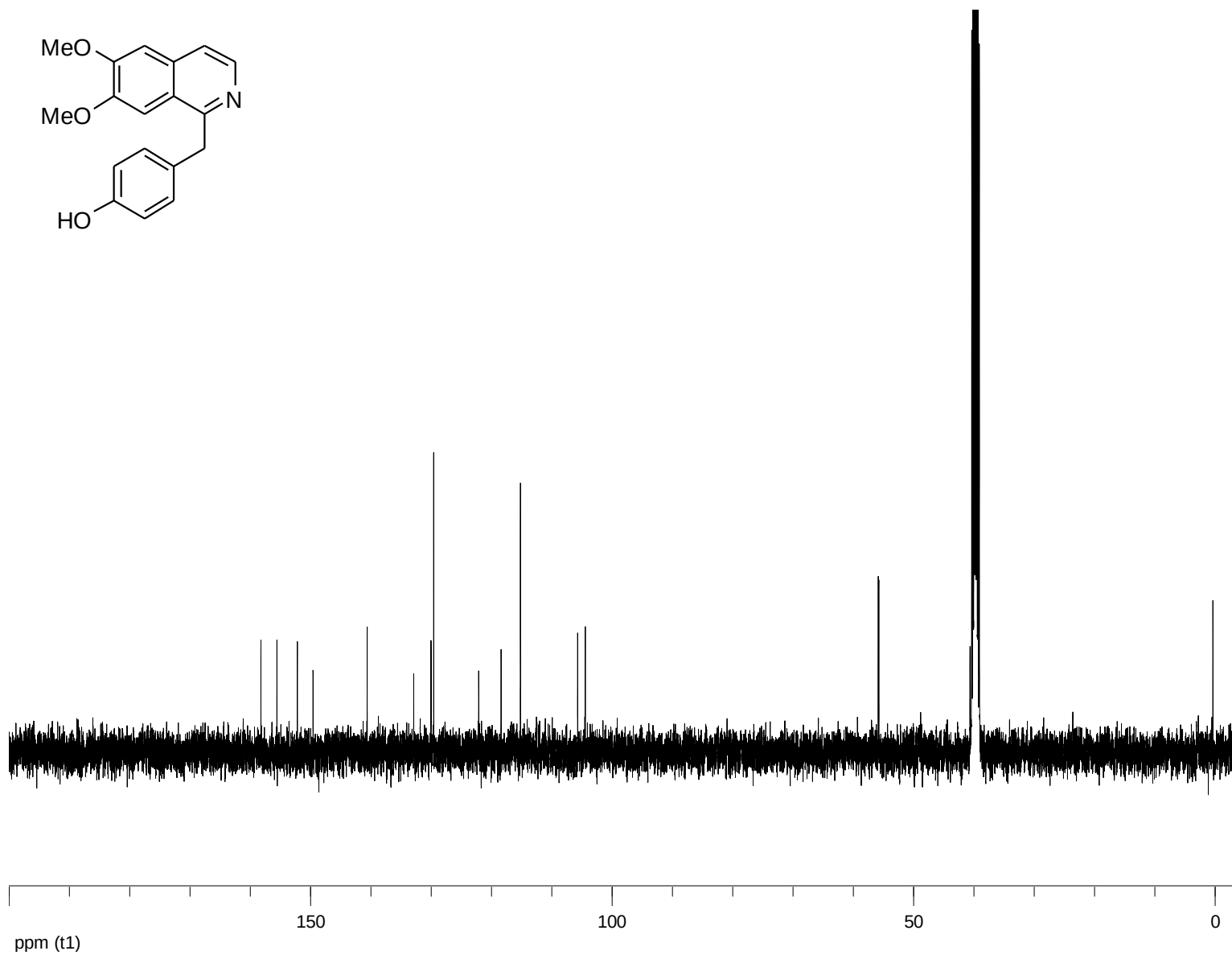
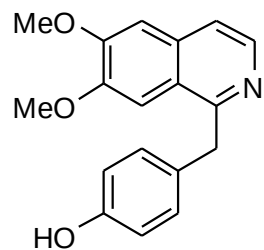


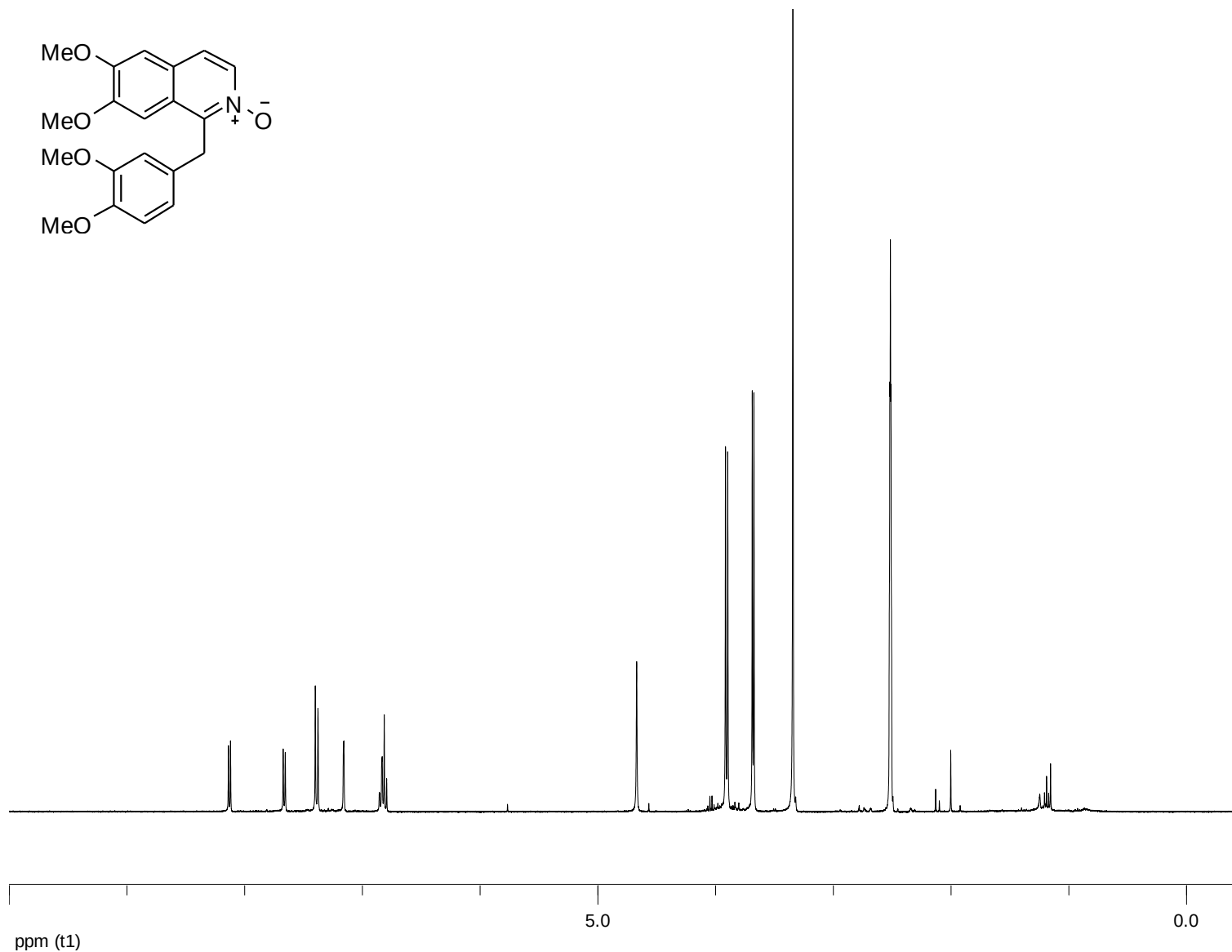


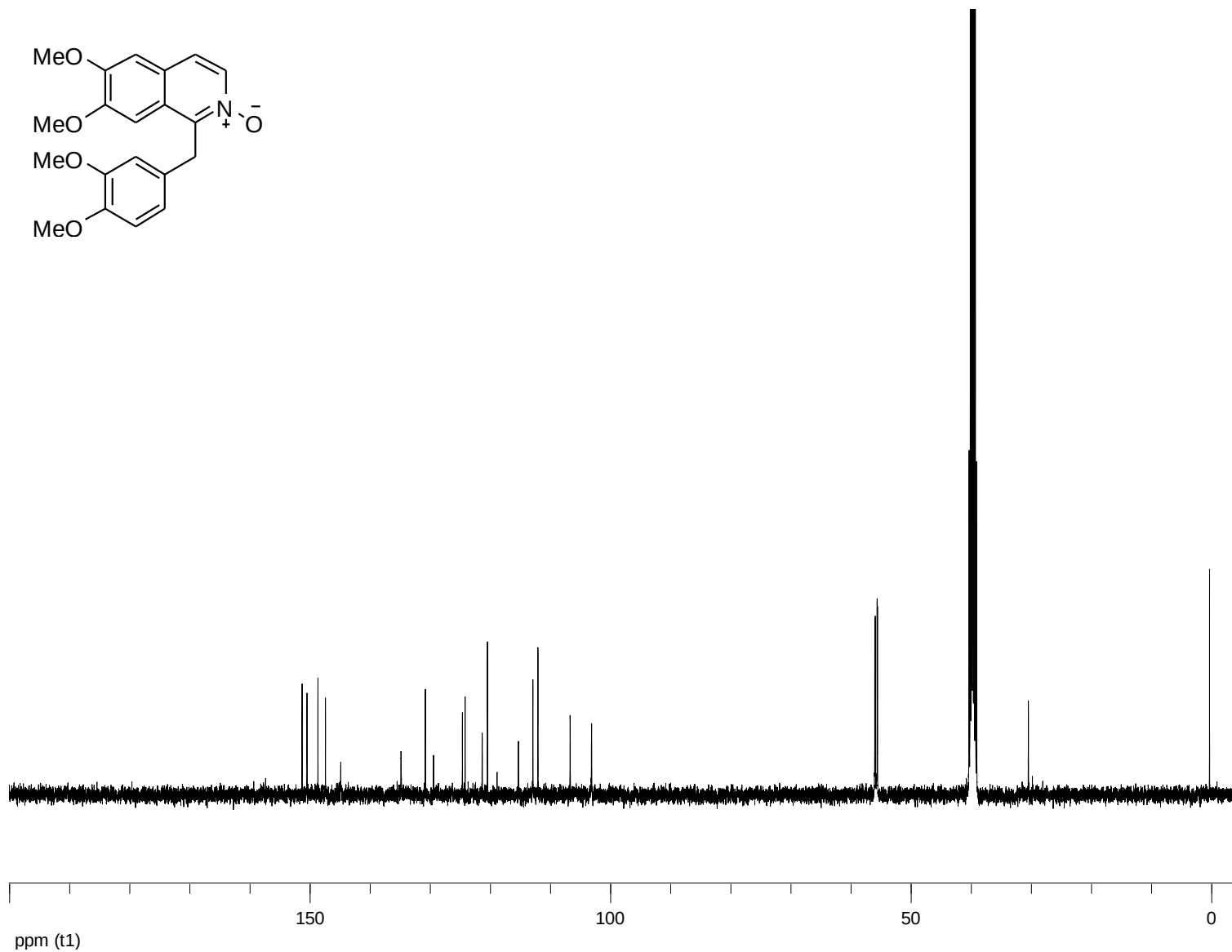
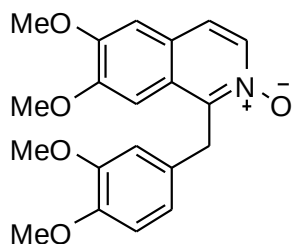


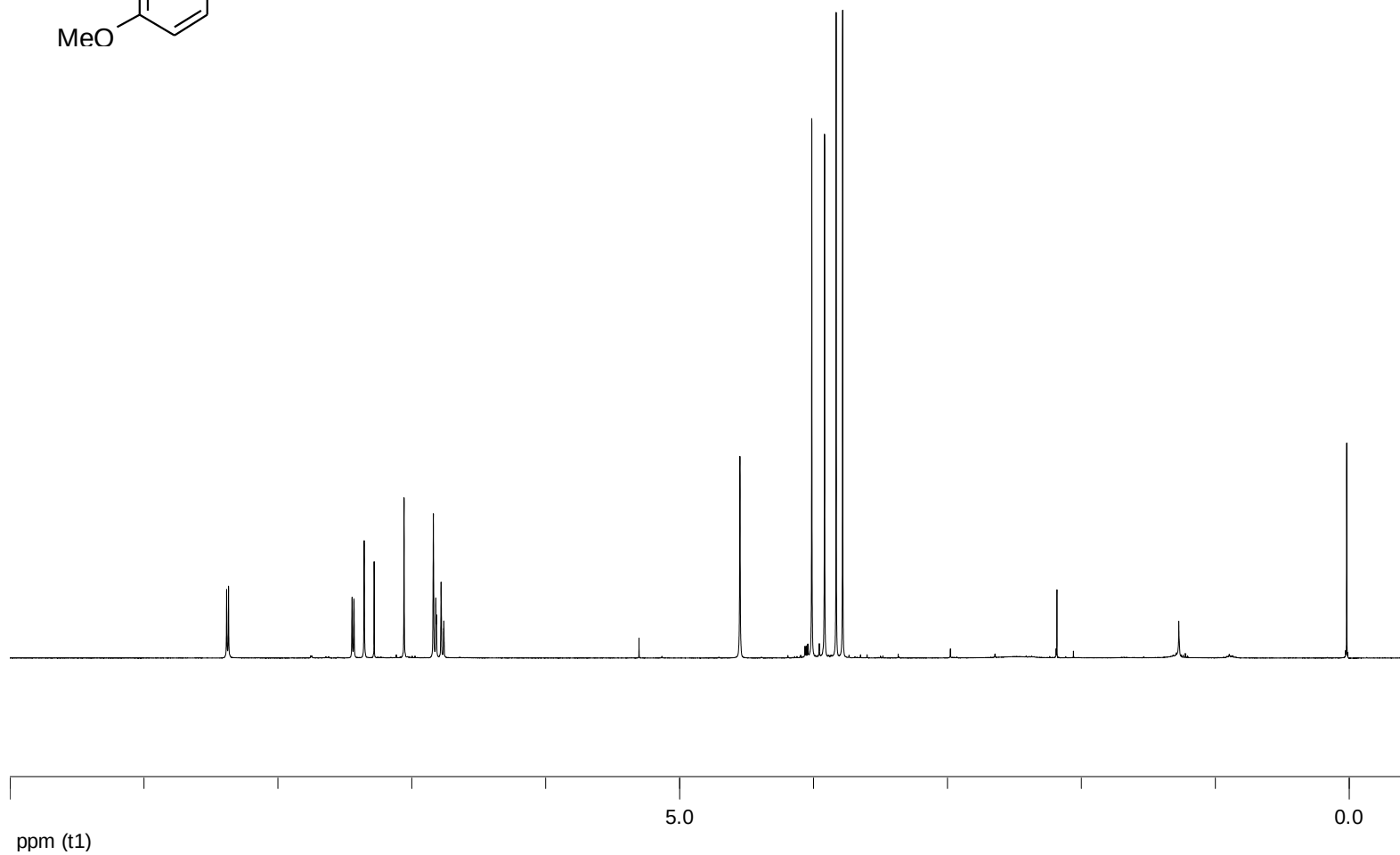
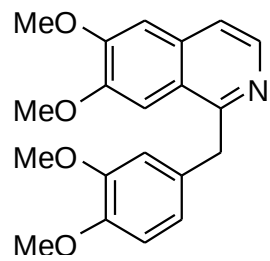


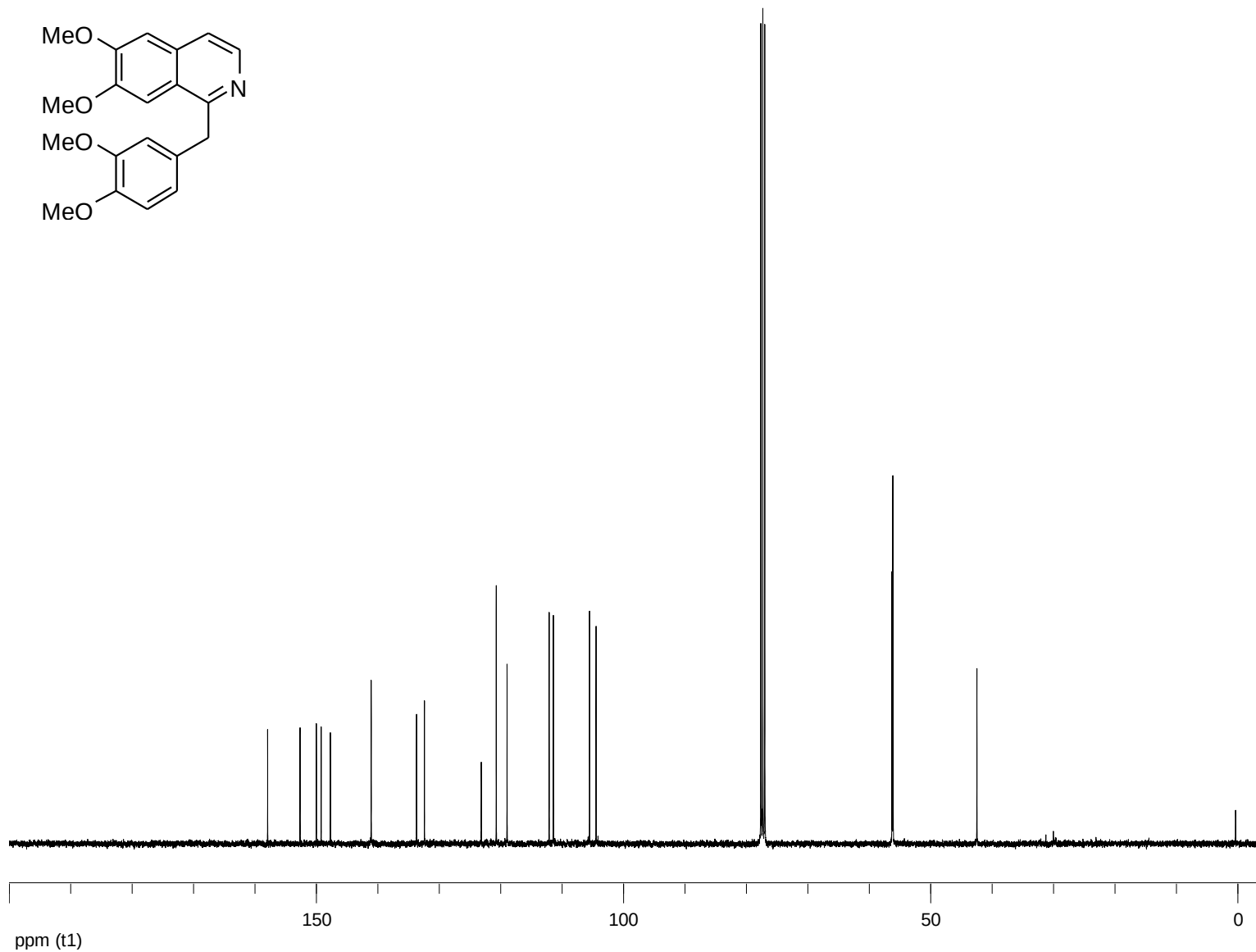
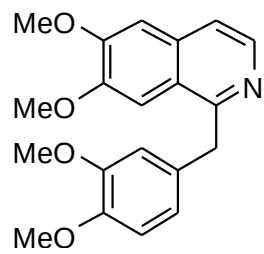


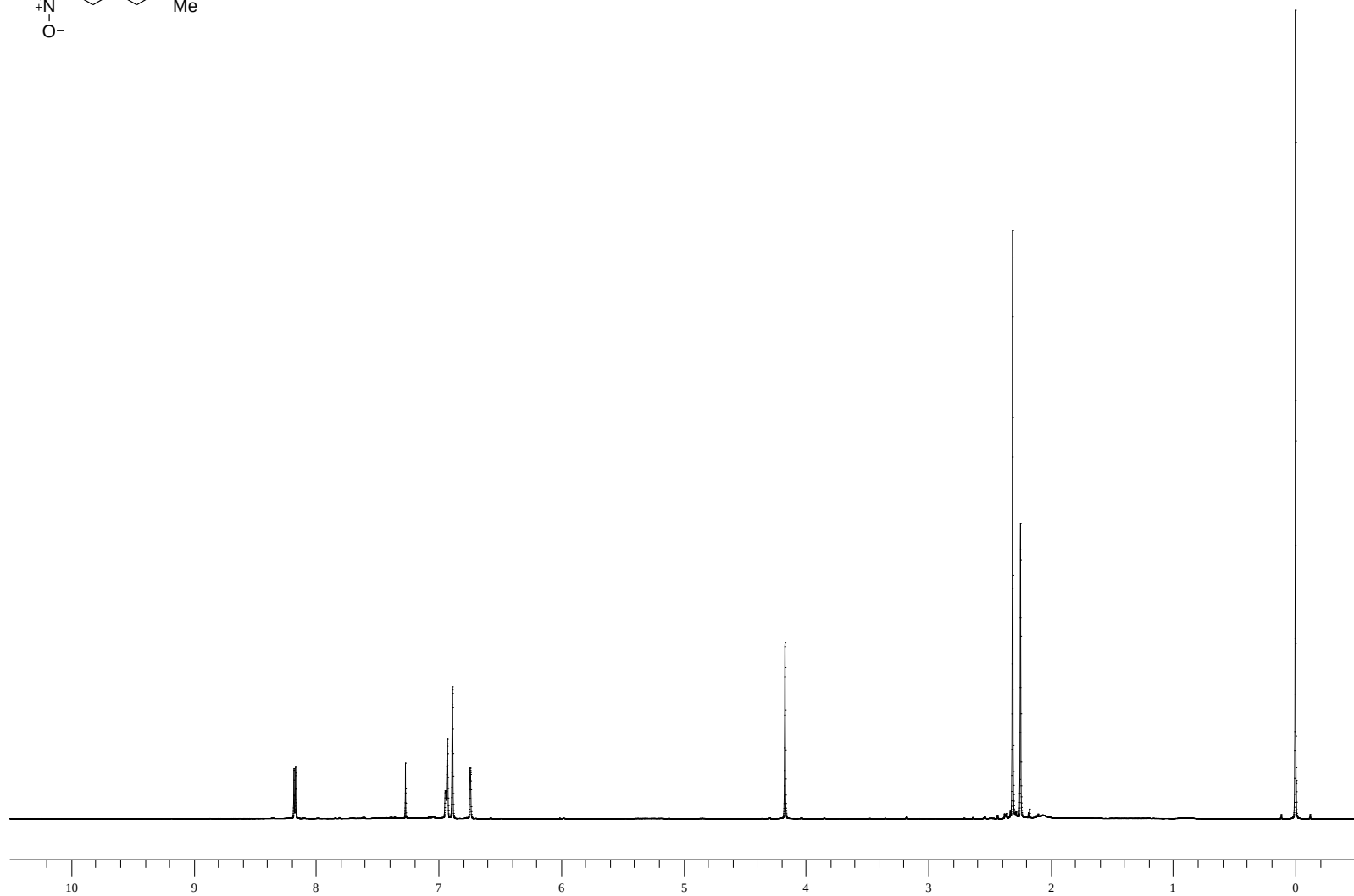
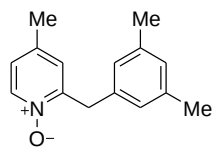


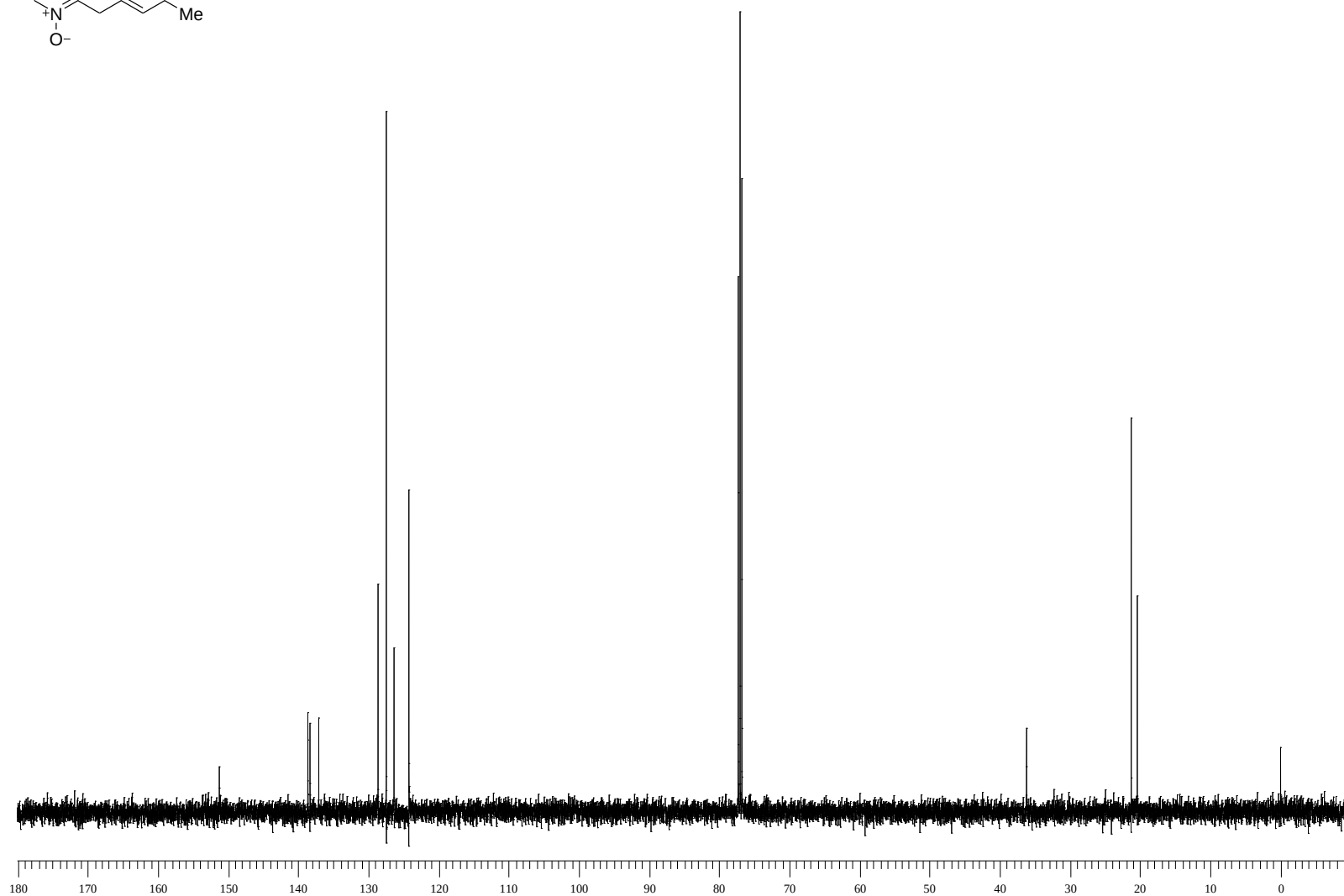
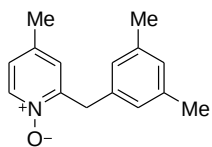




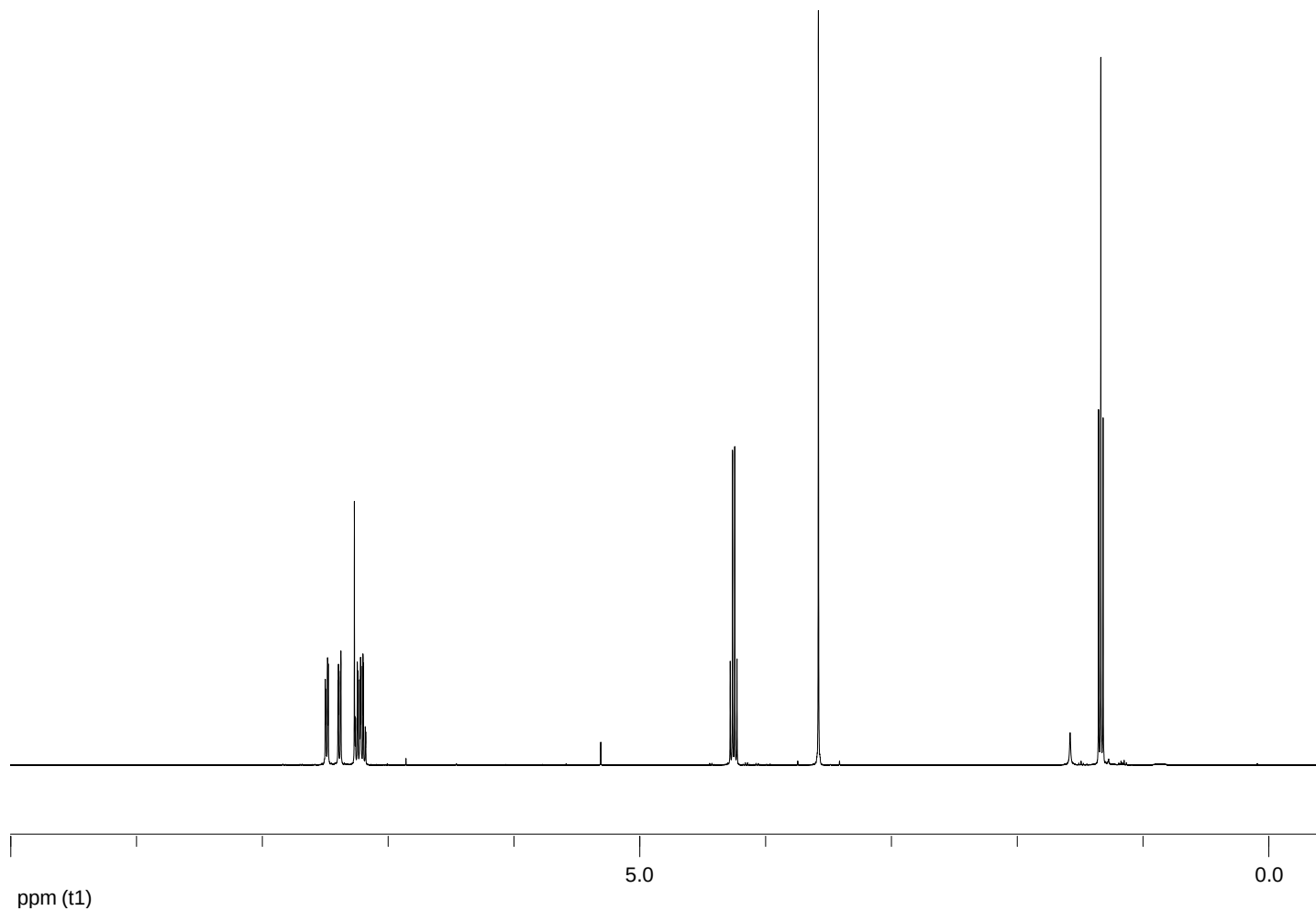
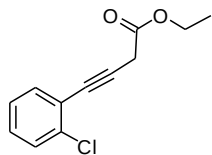


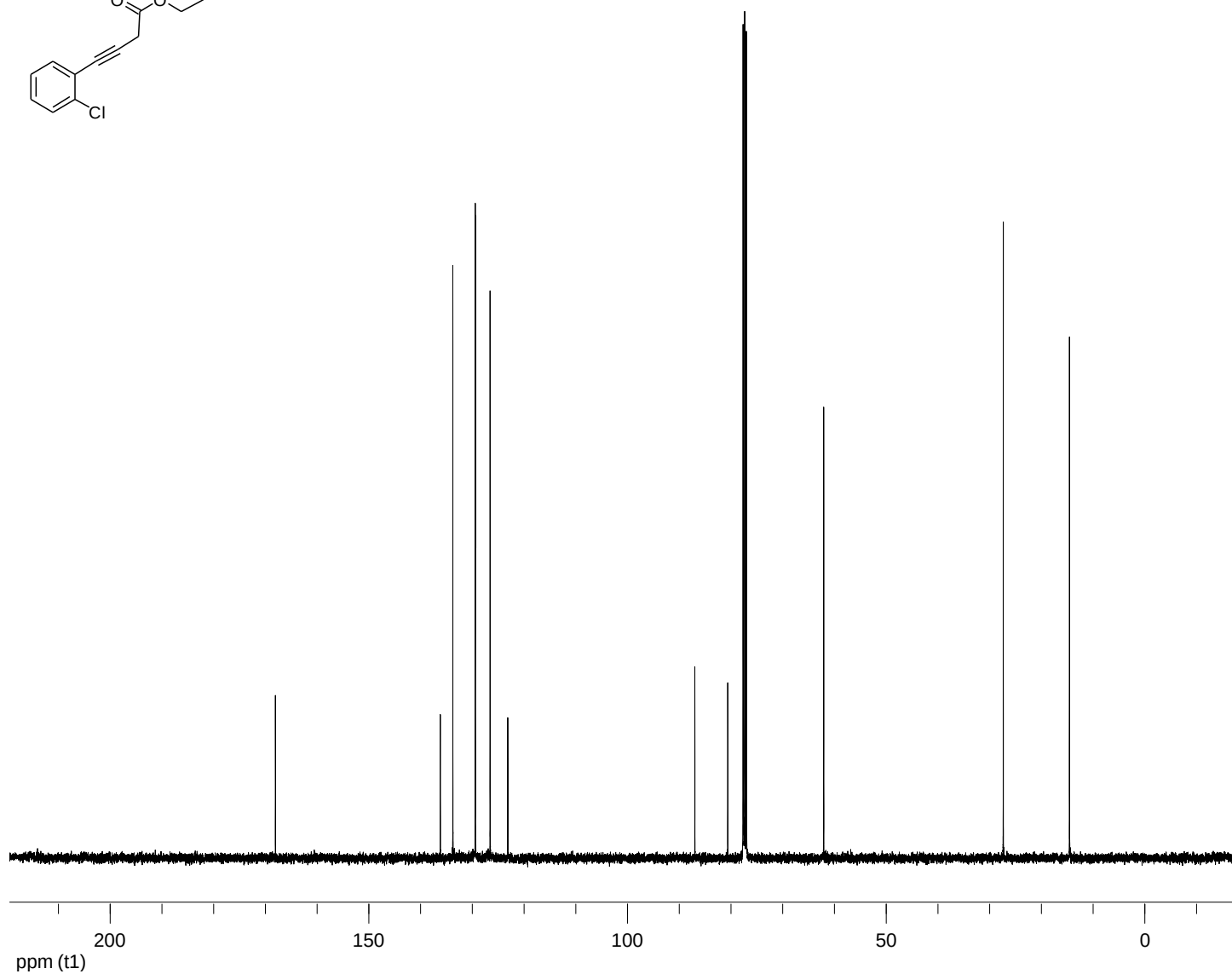
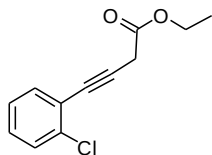


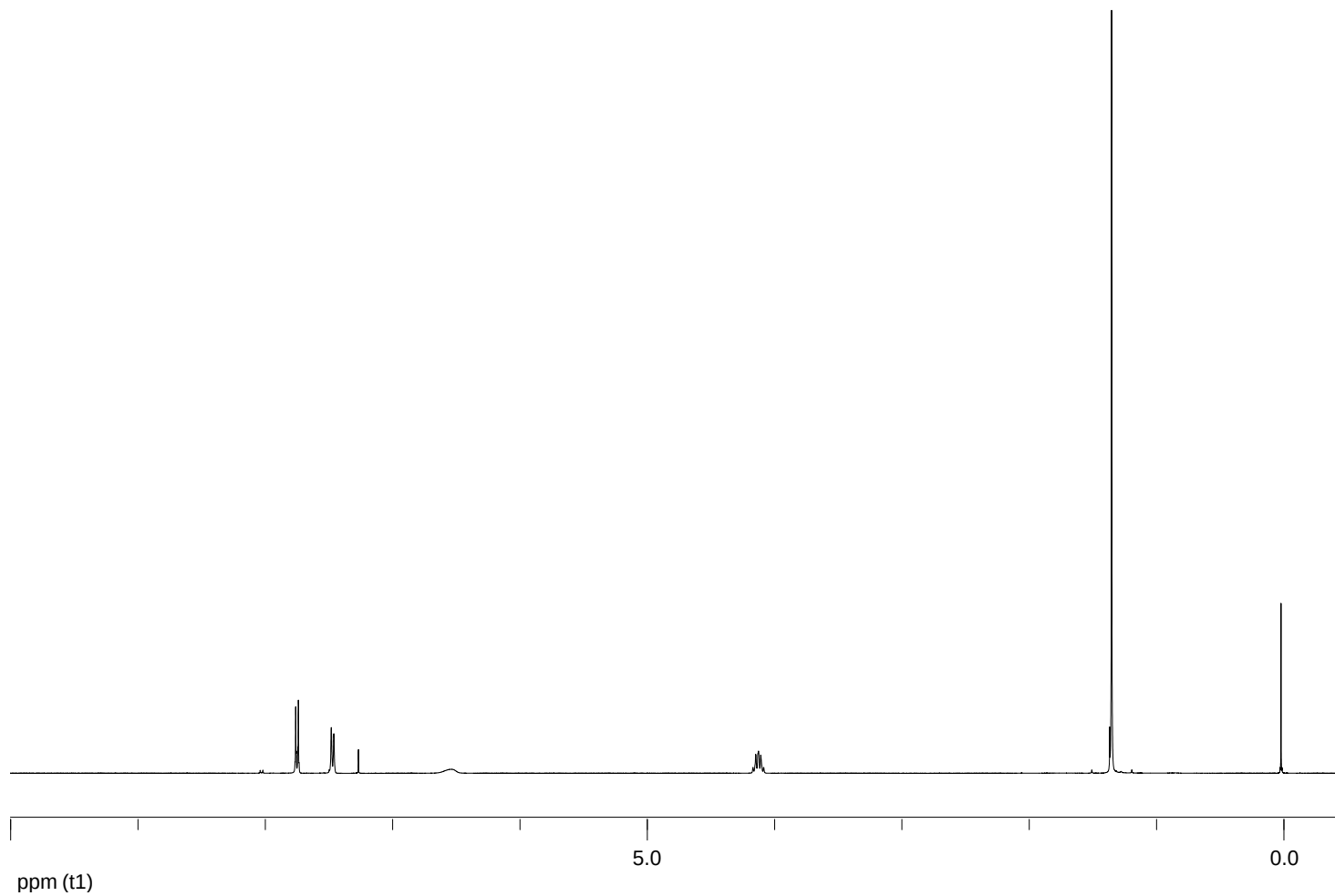
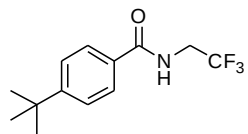


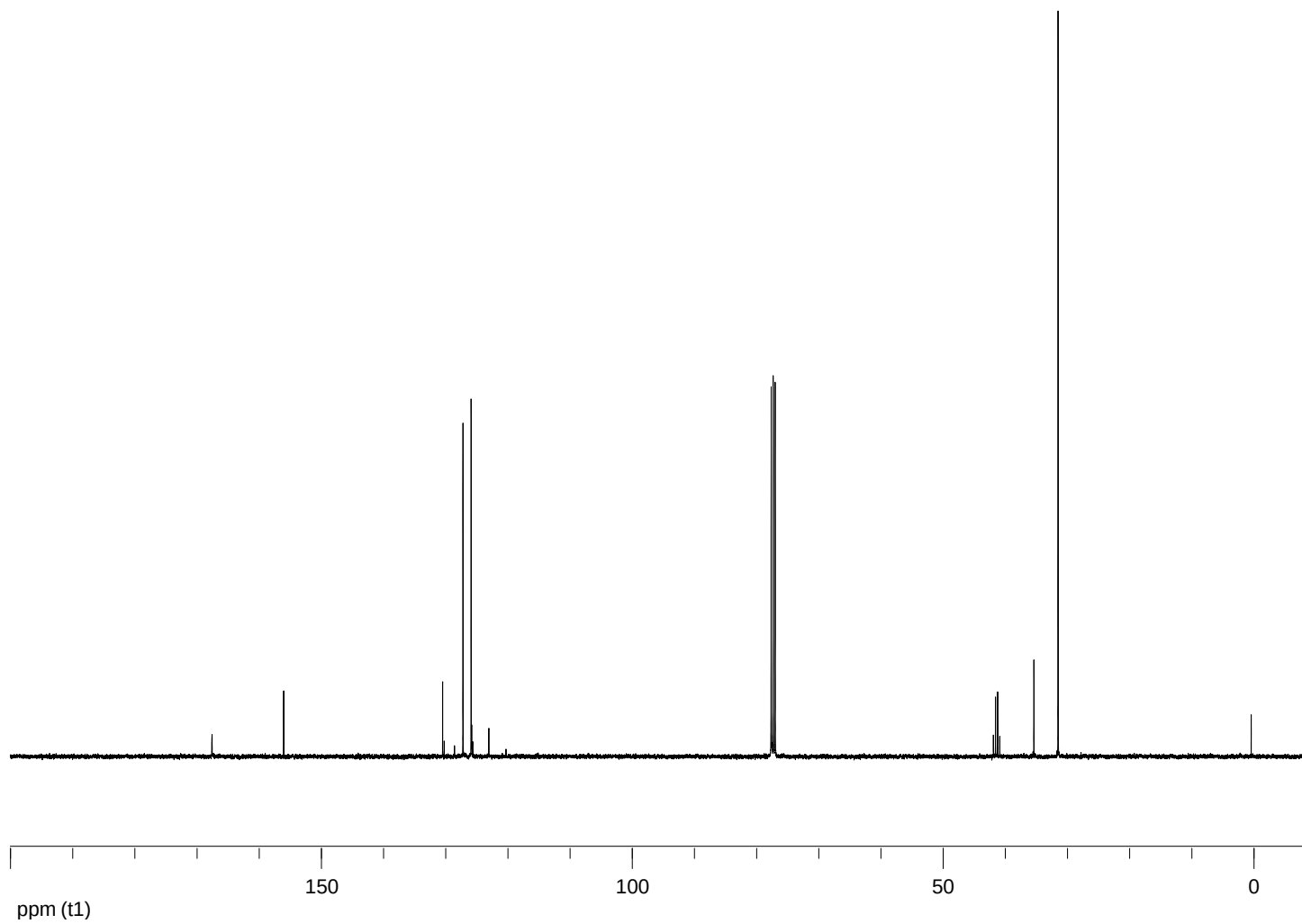
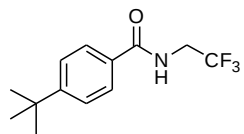


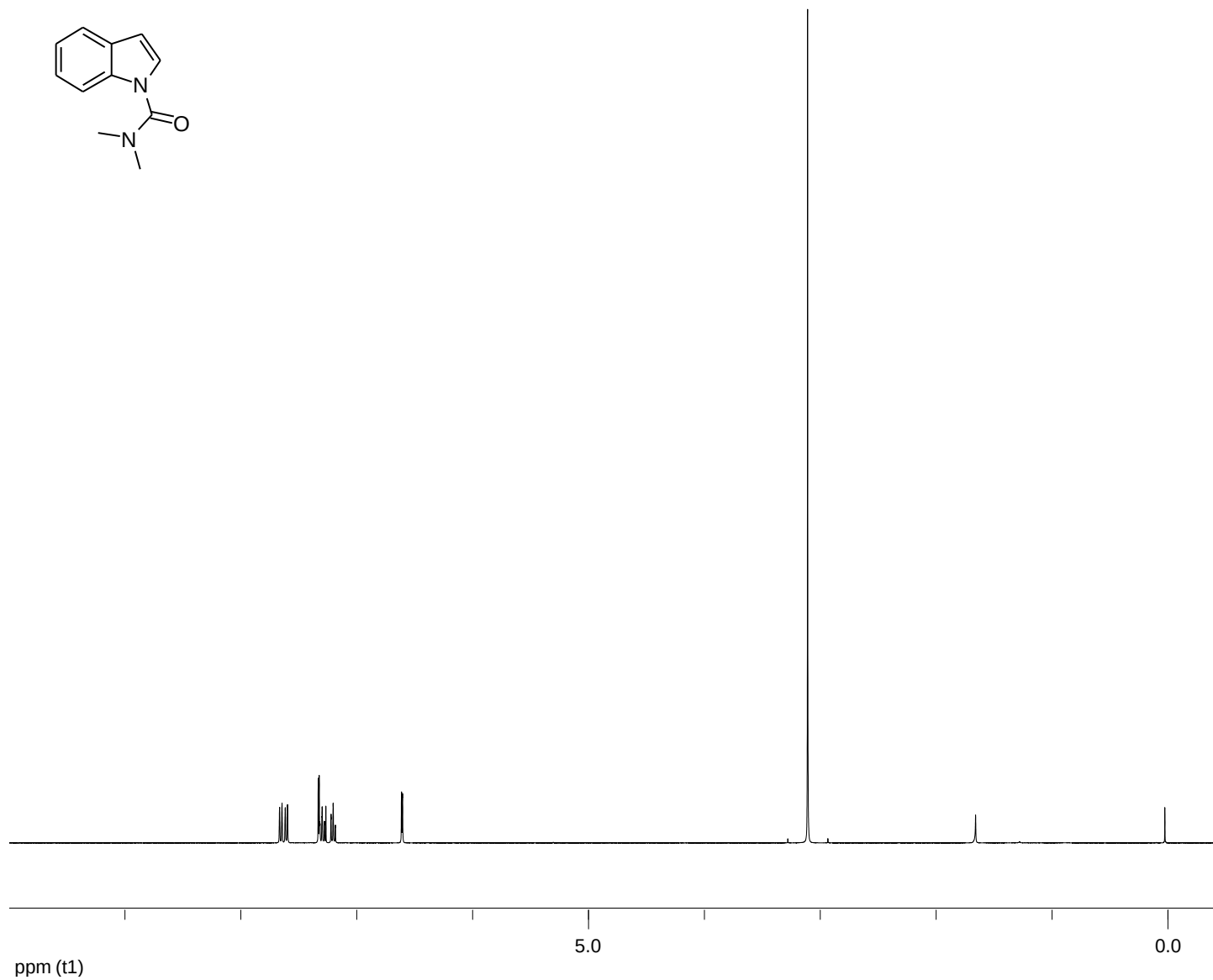
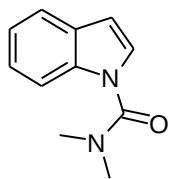
Chapter 5 – Spectral Data

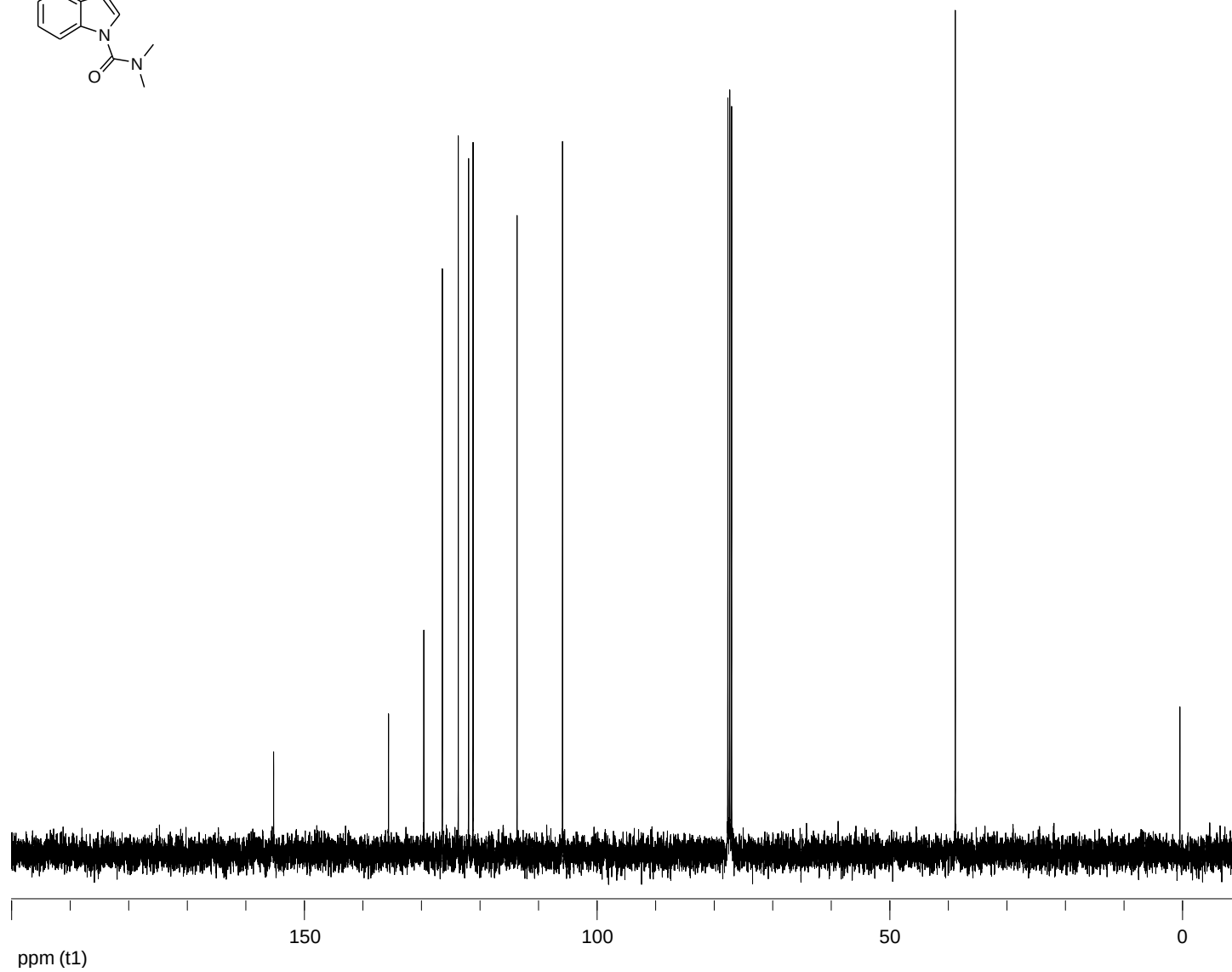
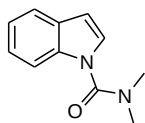


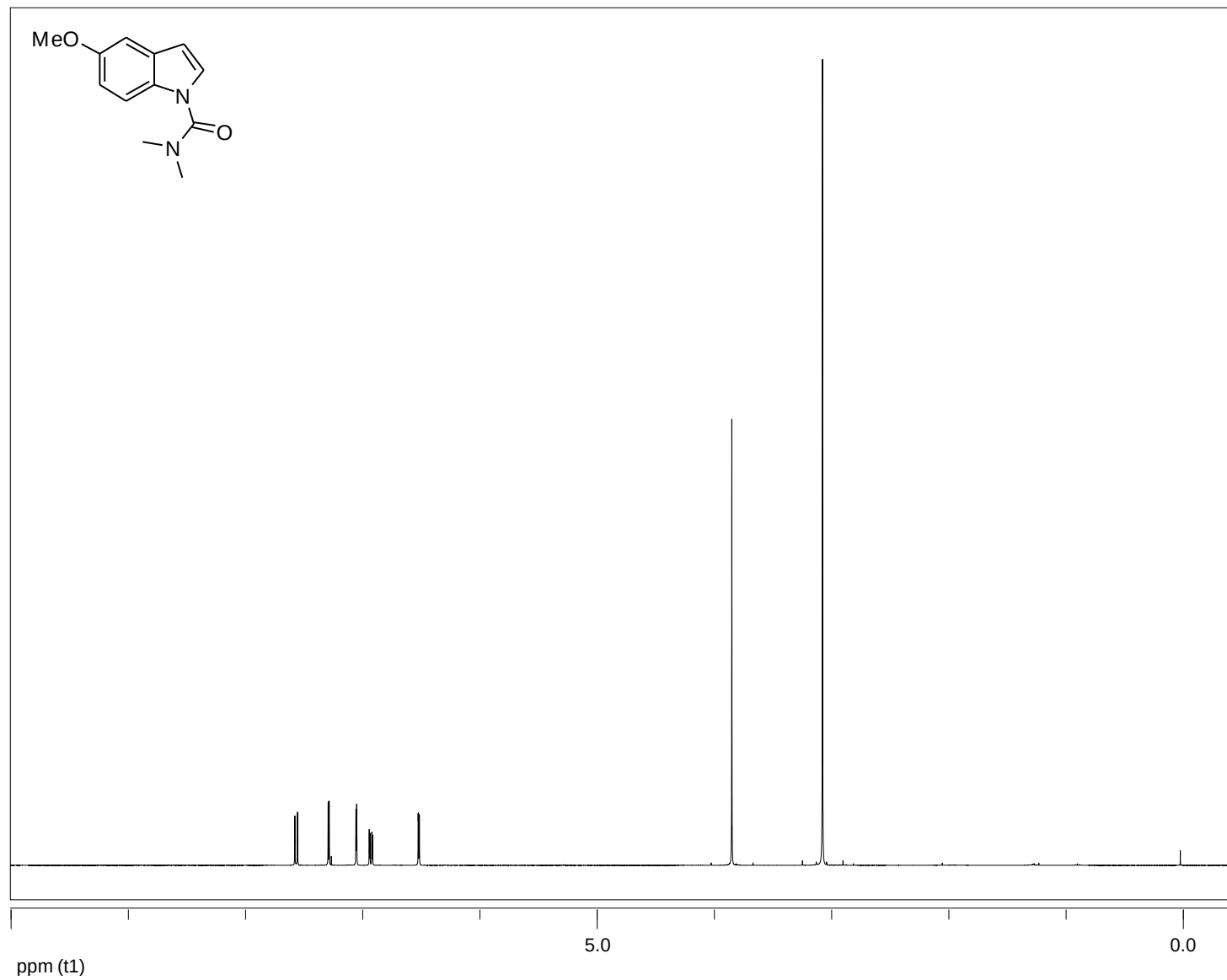


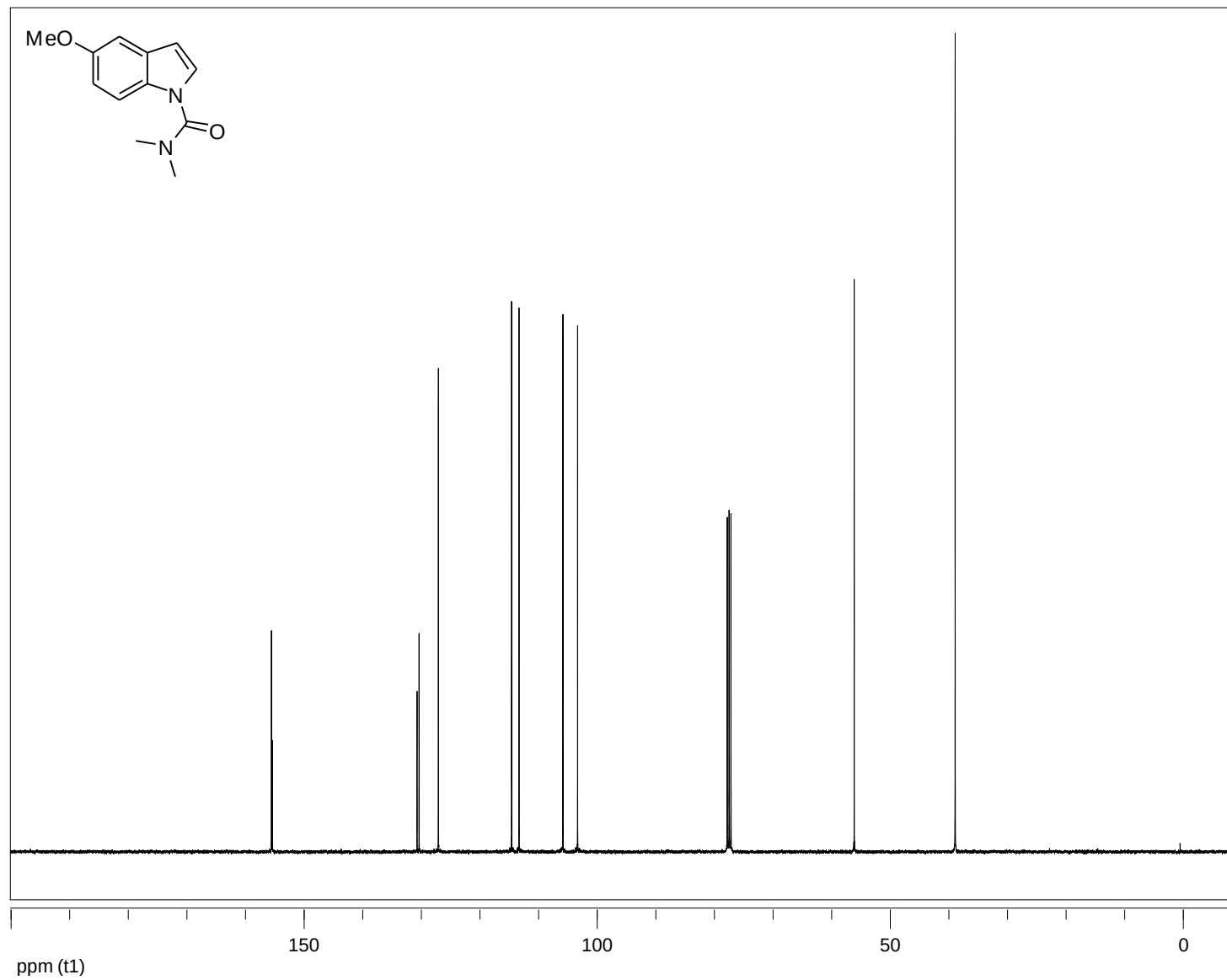


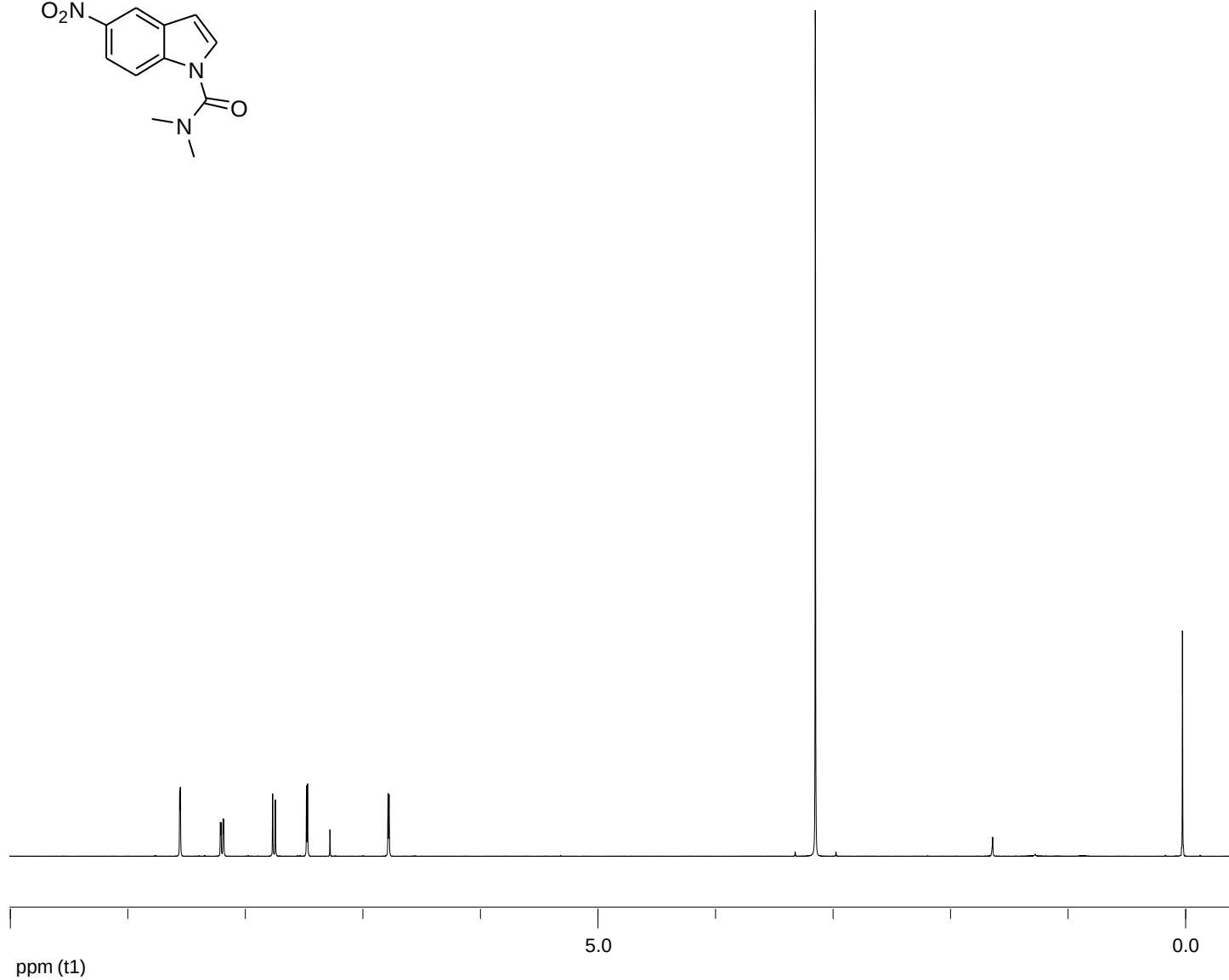
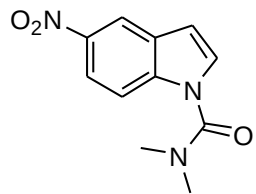


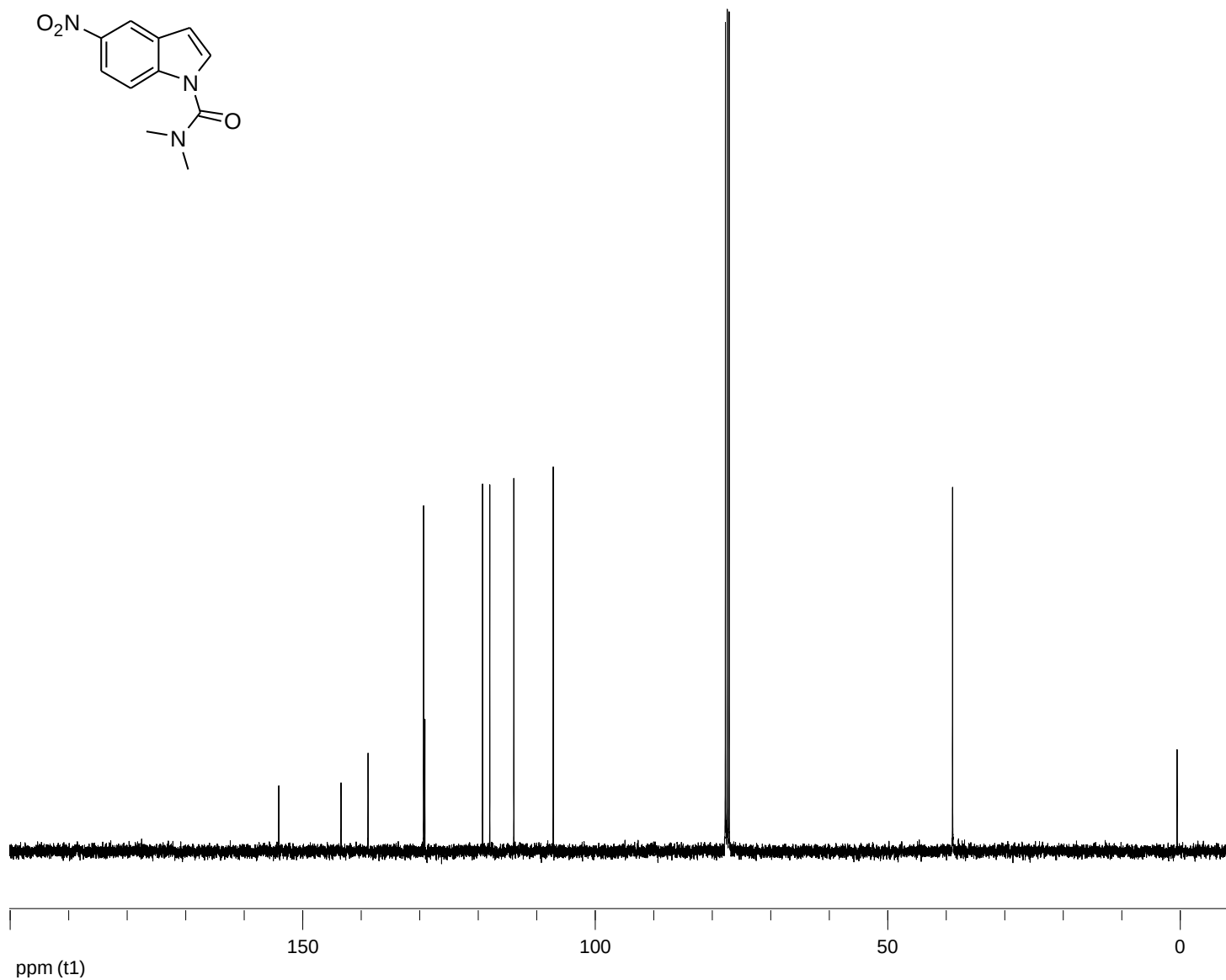
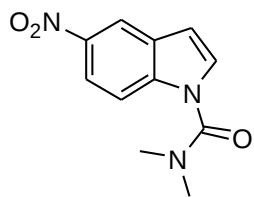


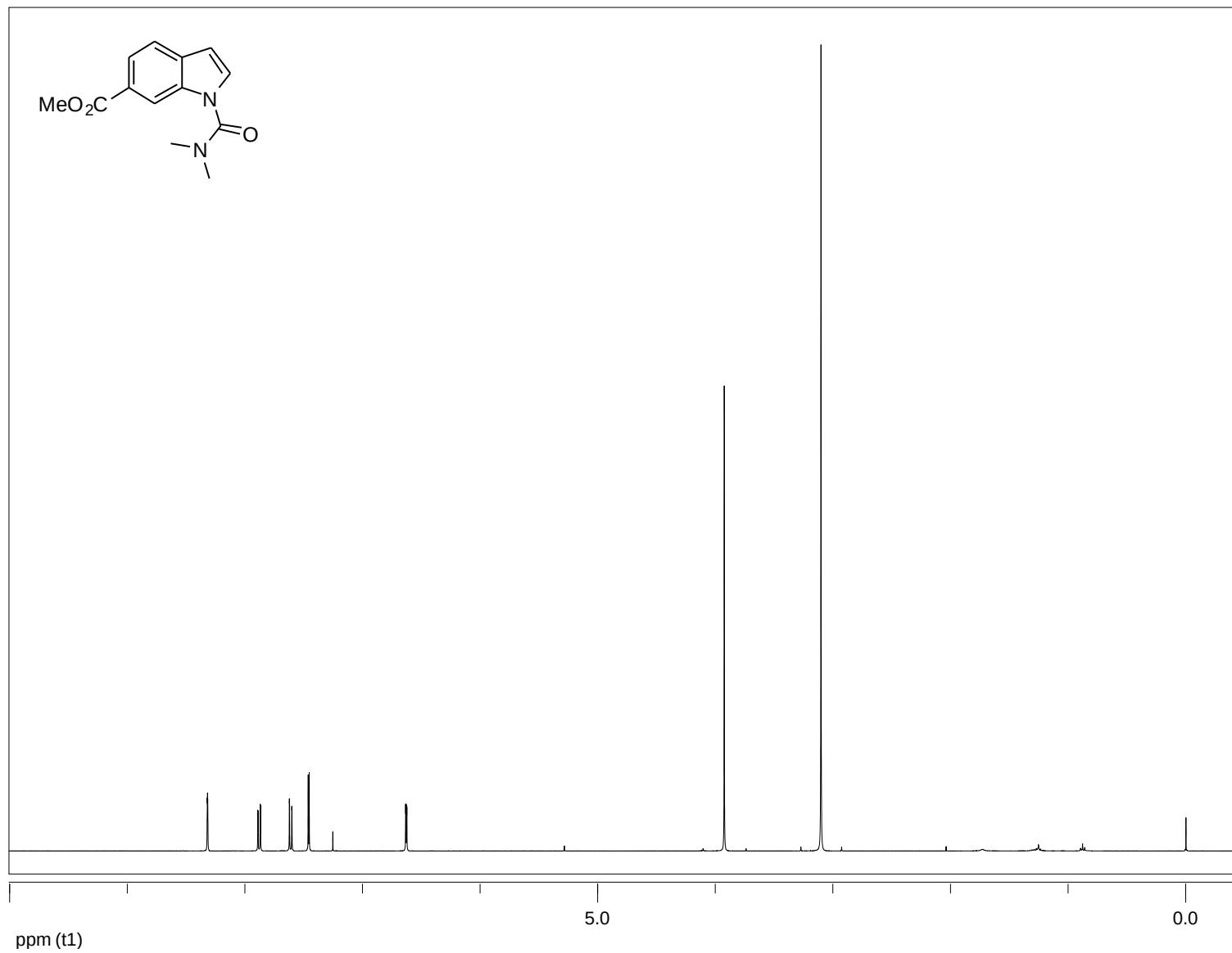


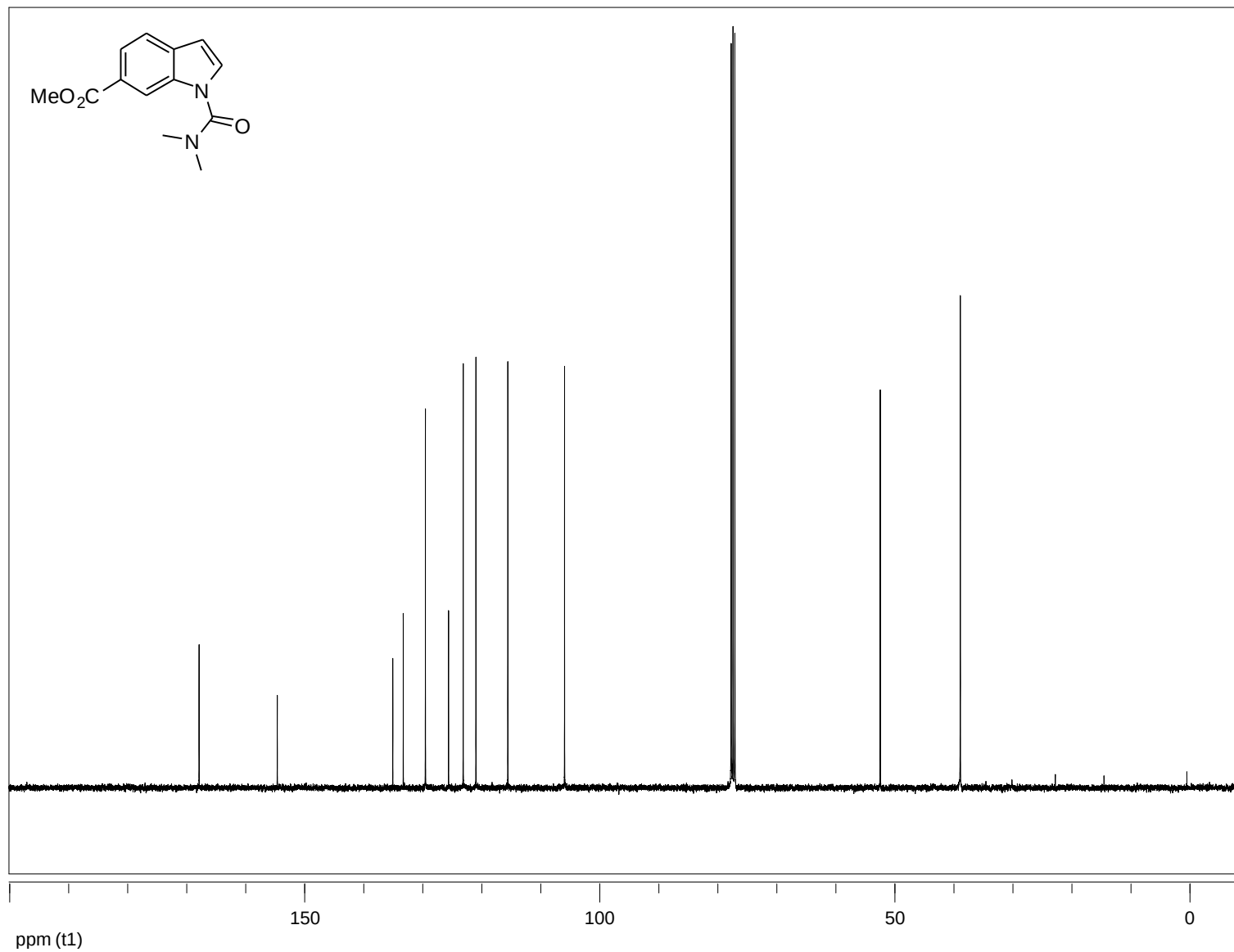


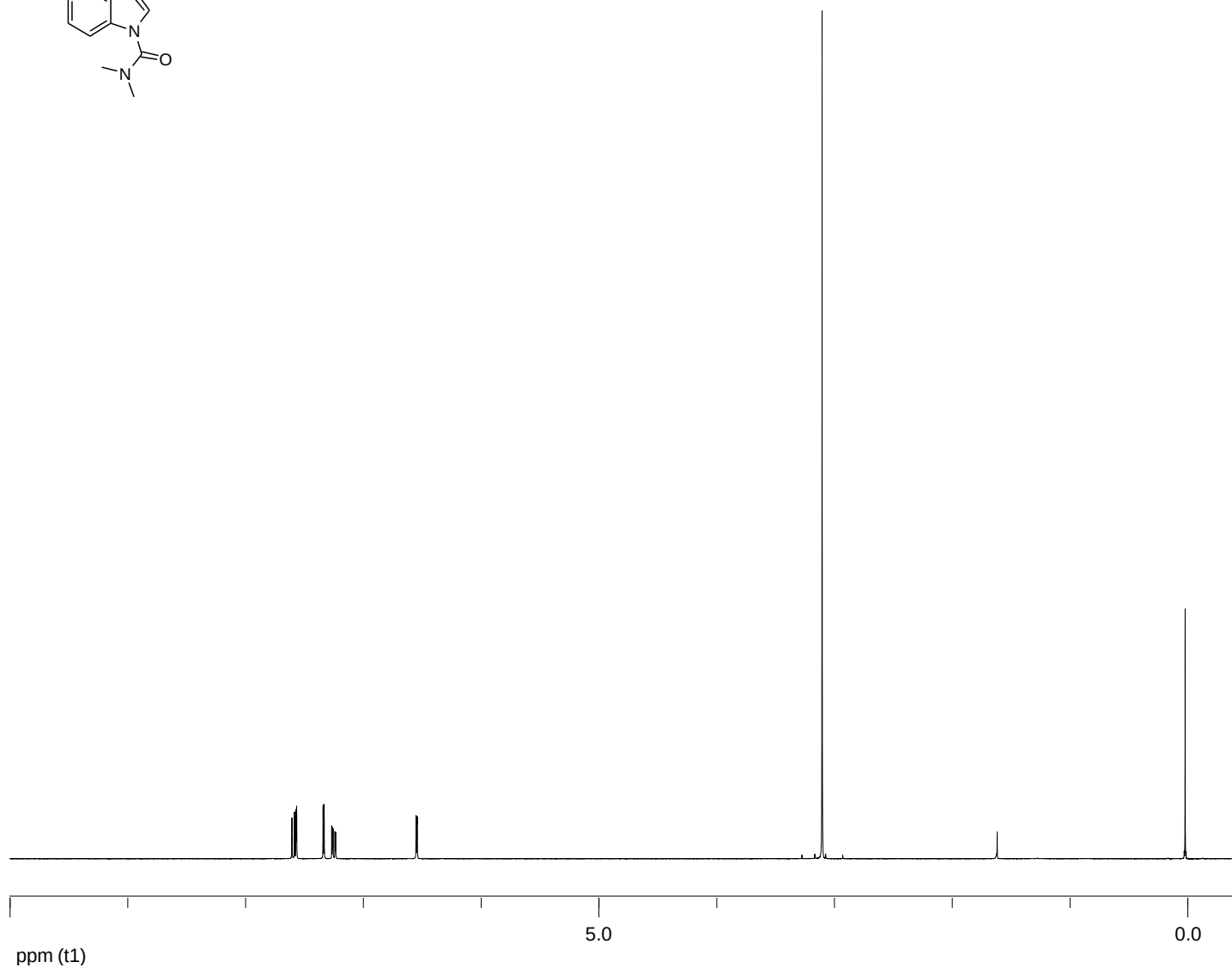
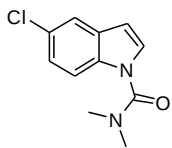


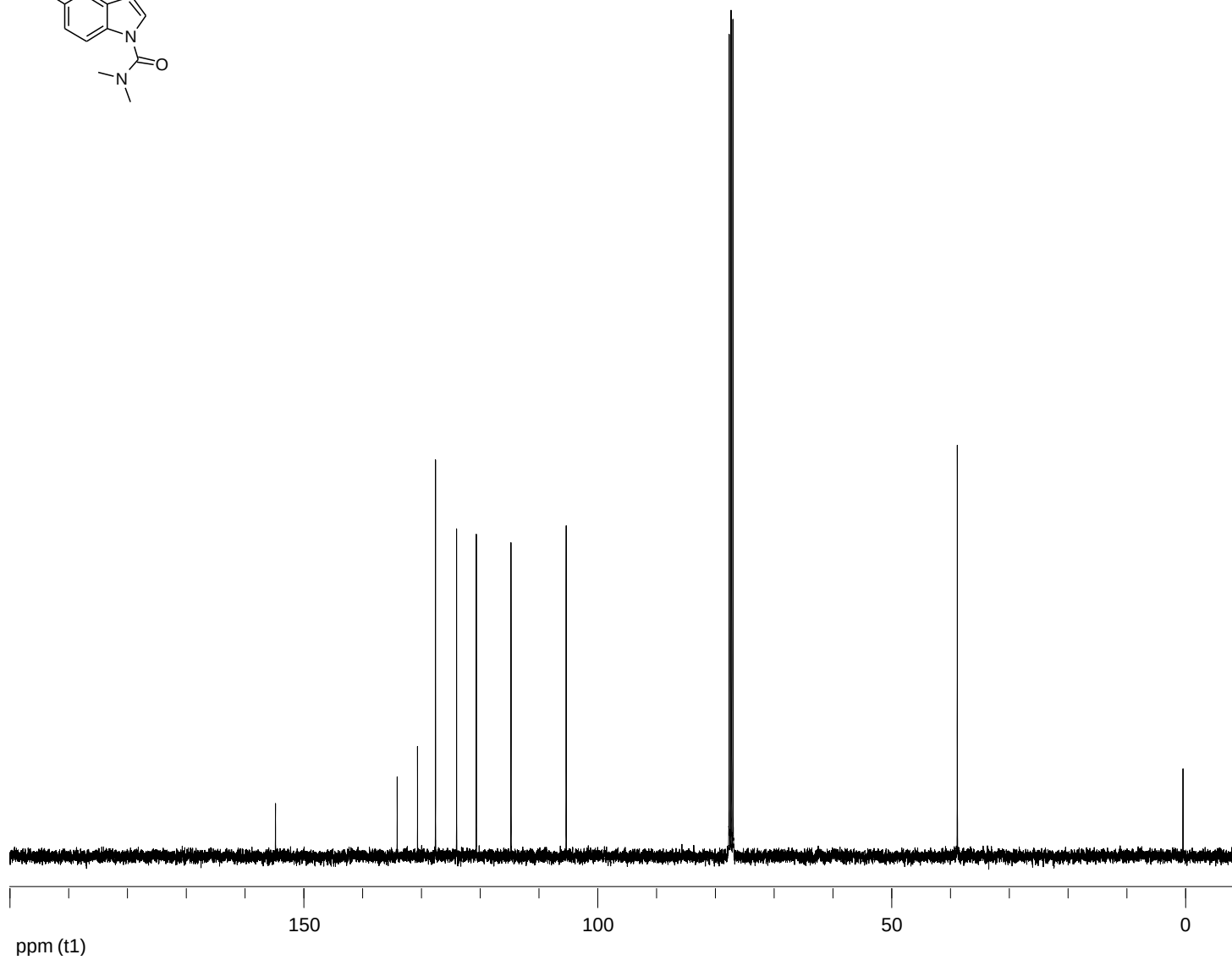
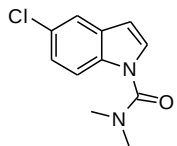


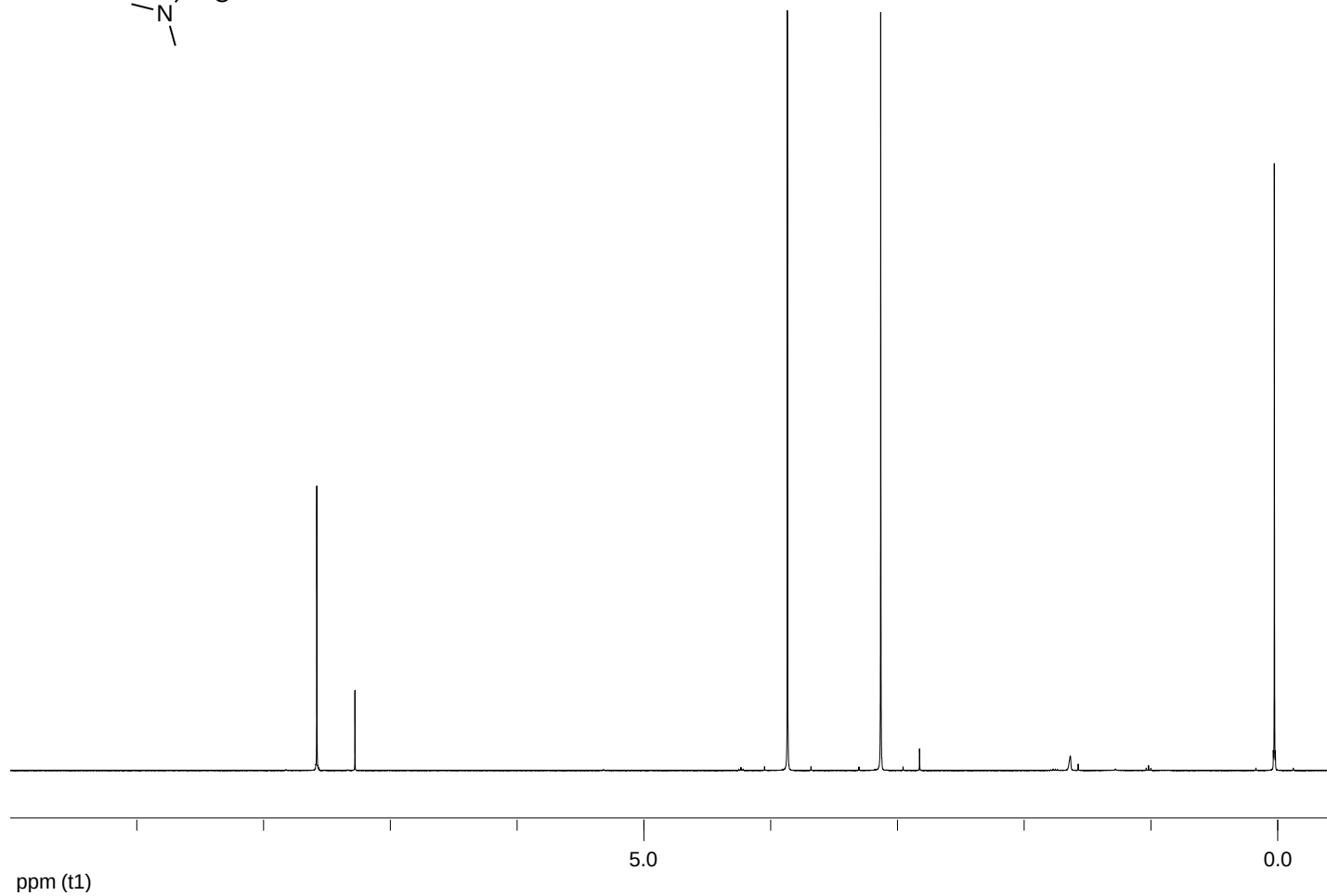
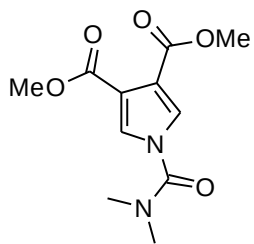


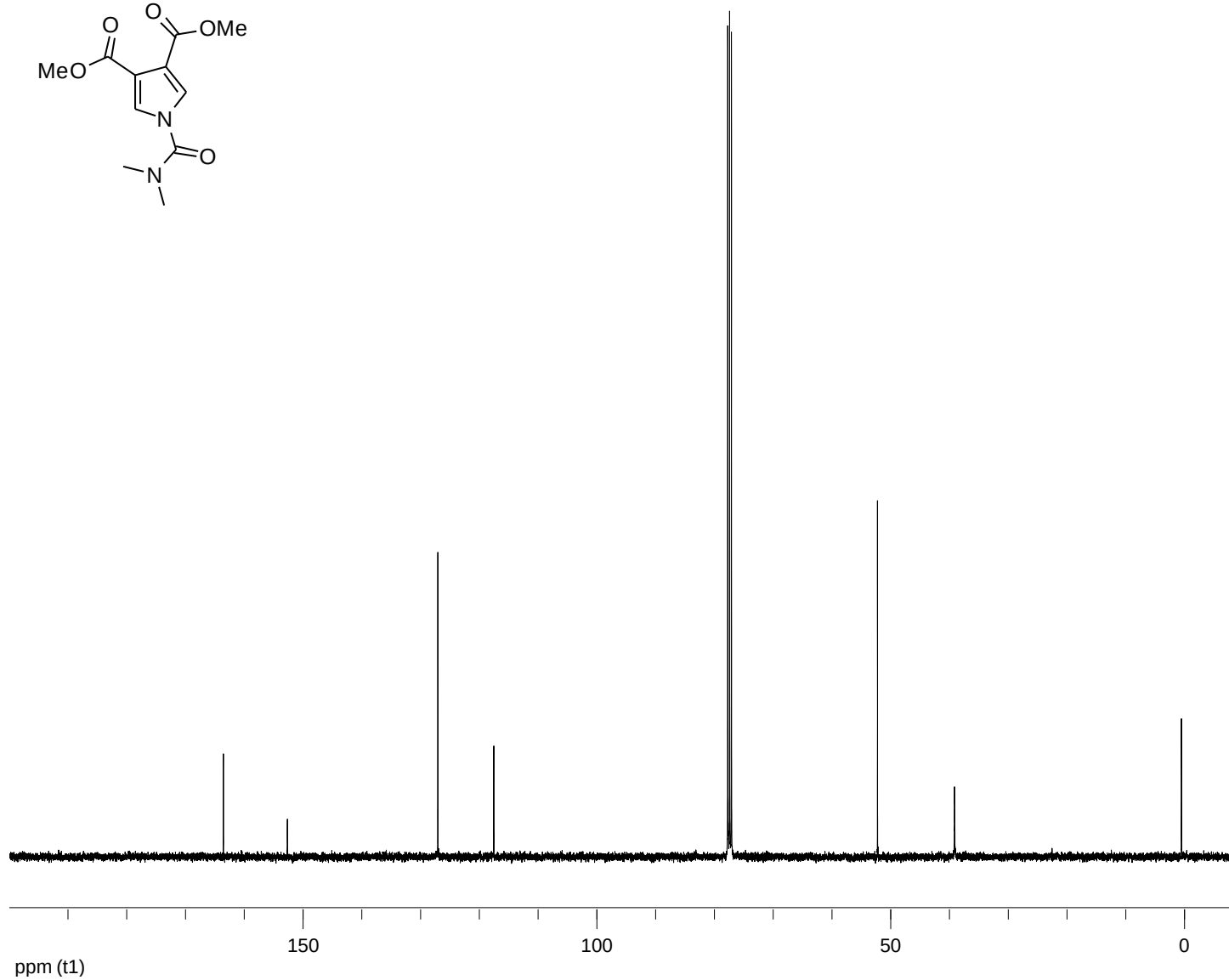
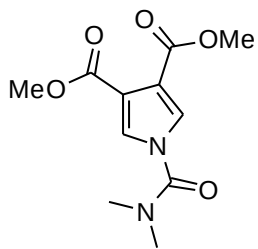


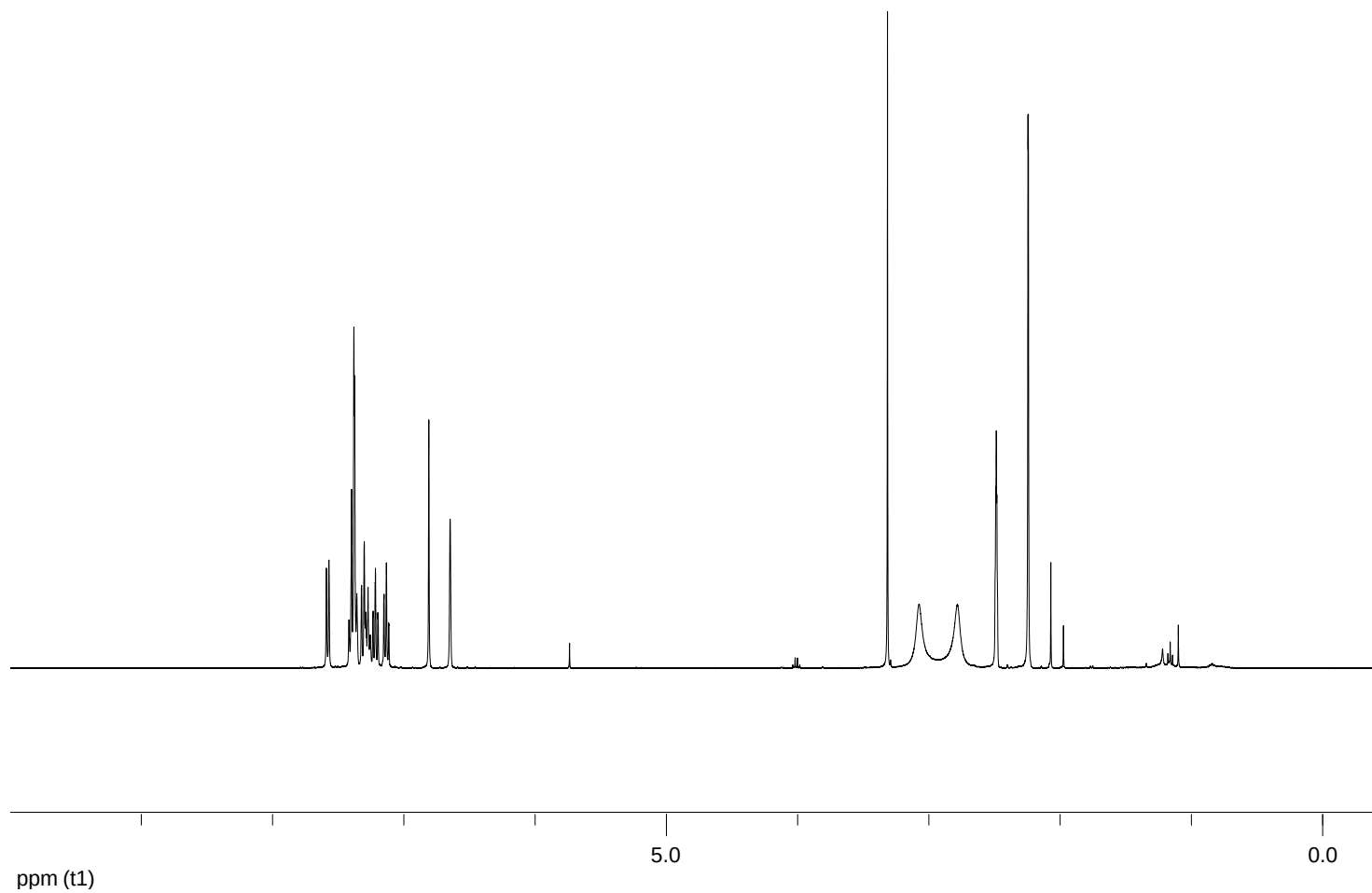
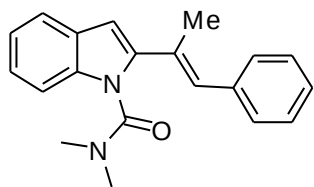


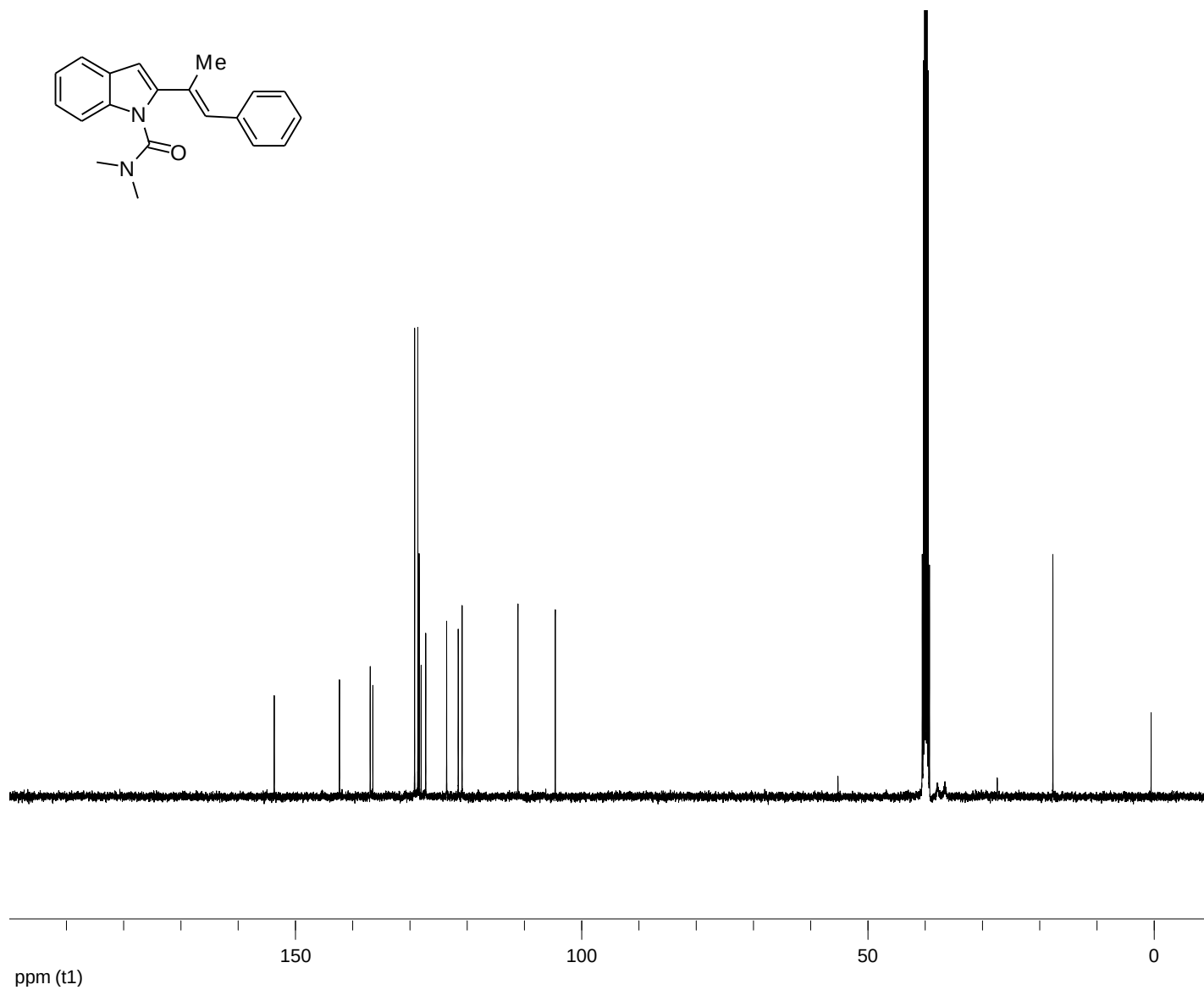
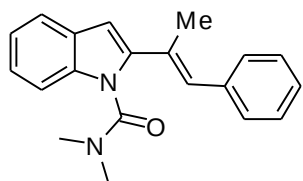


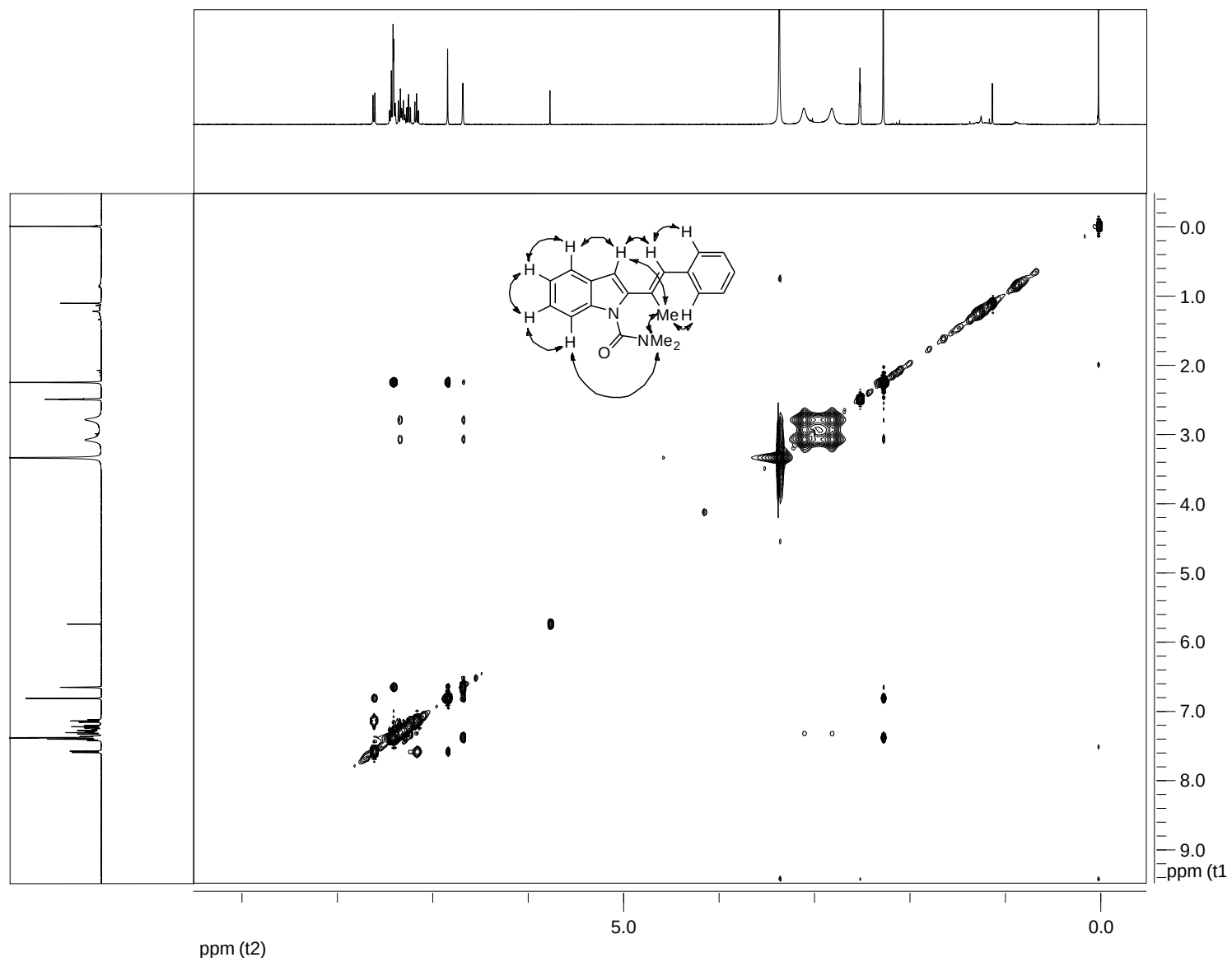


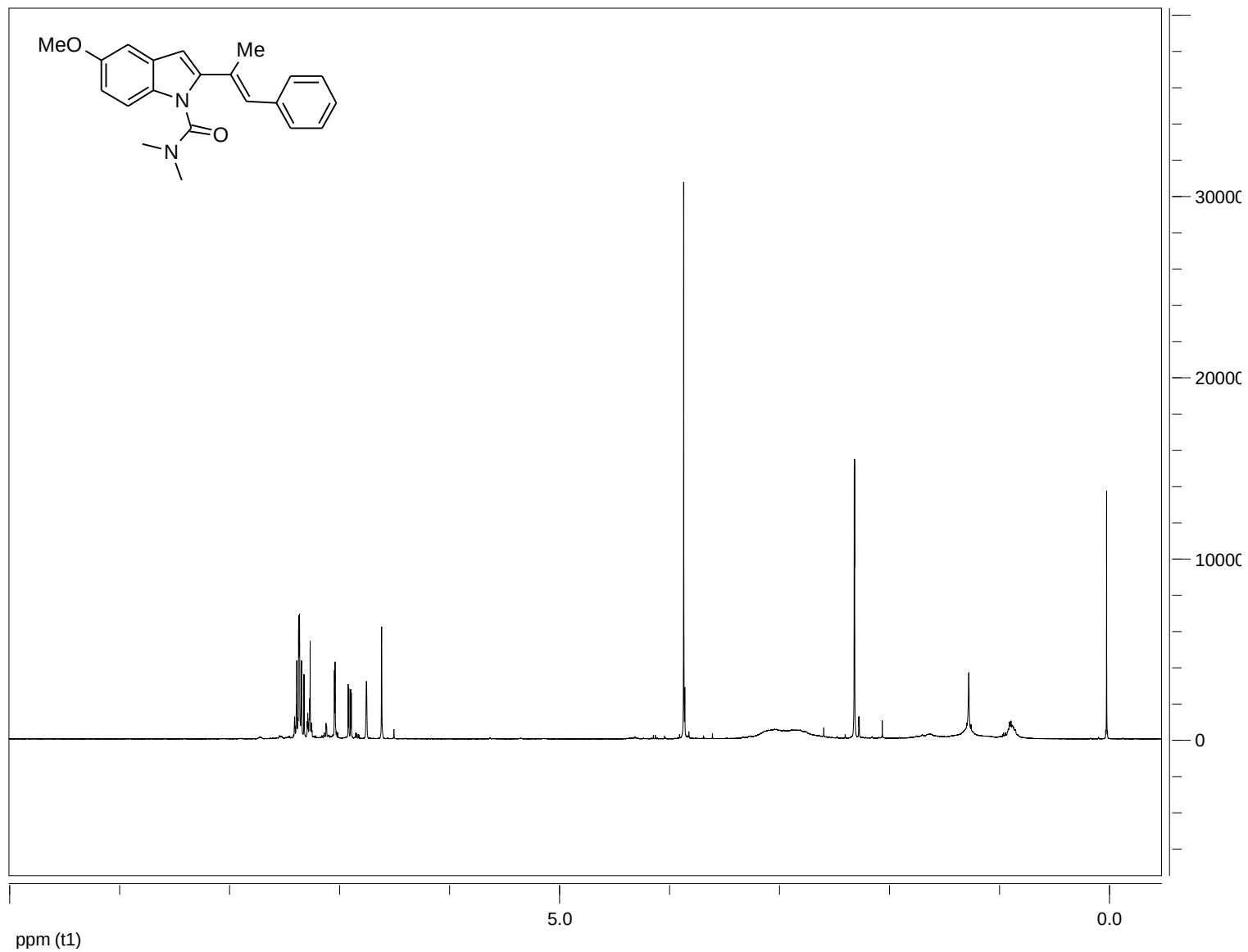


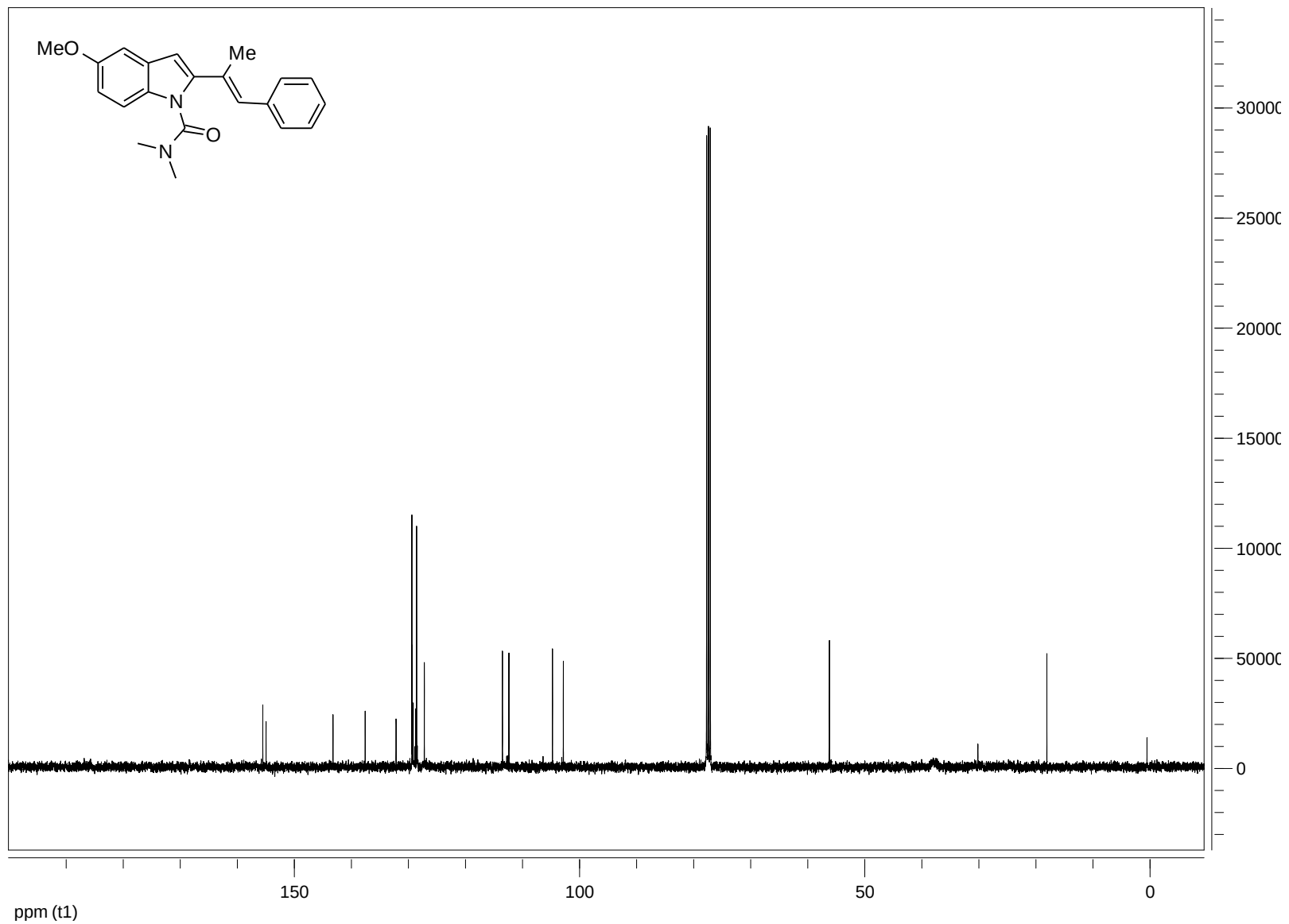


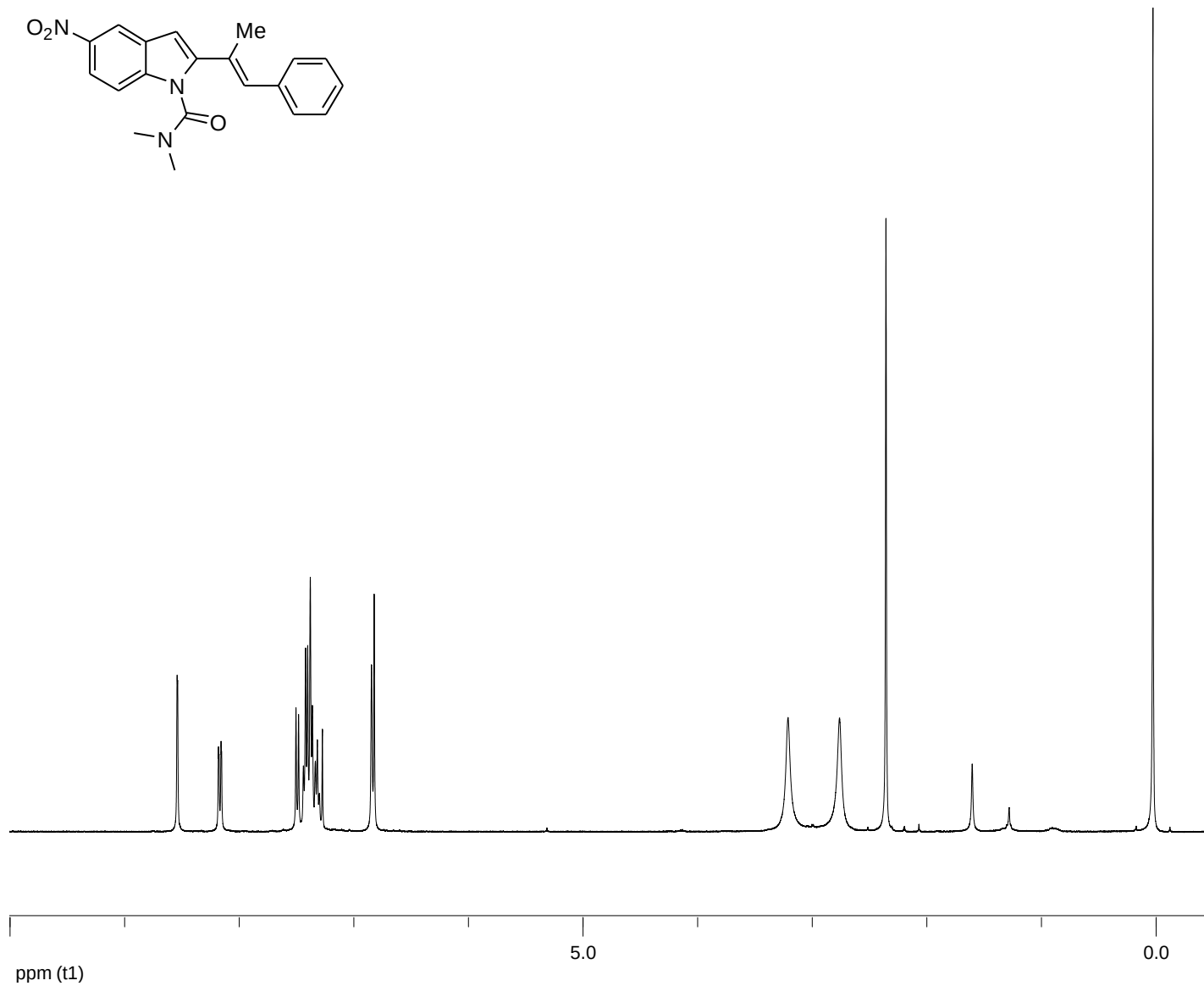
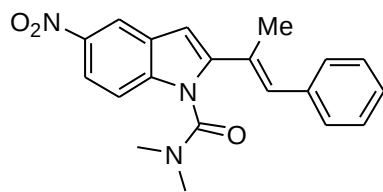


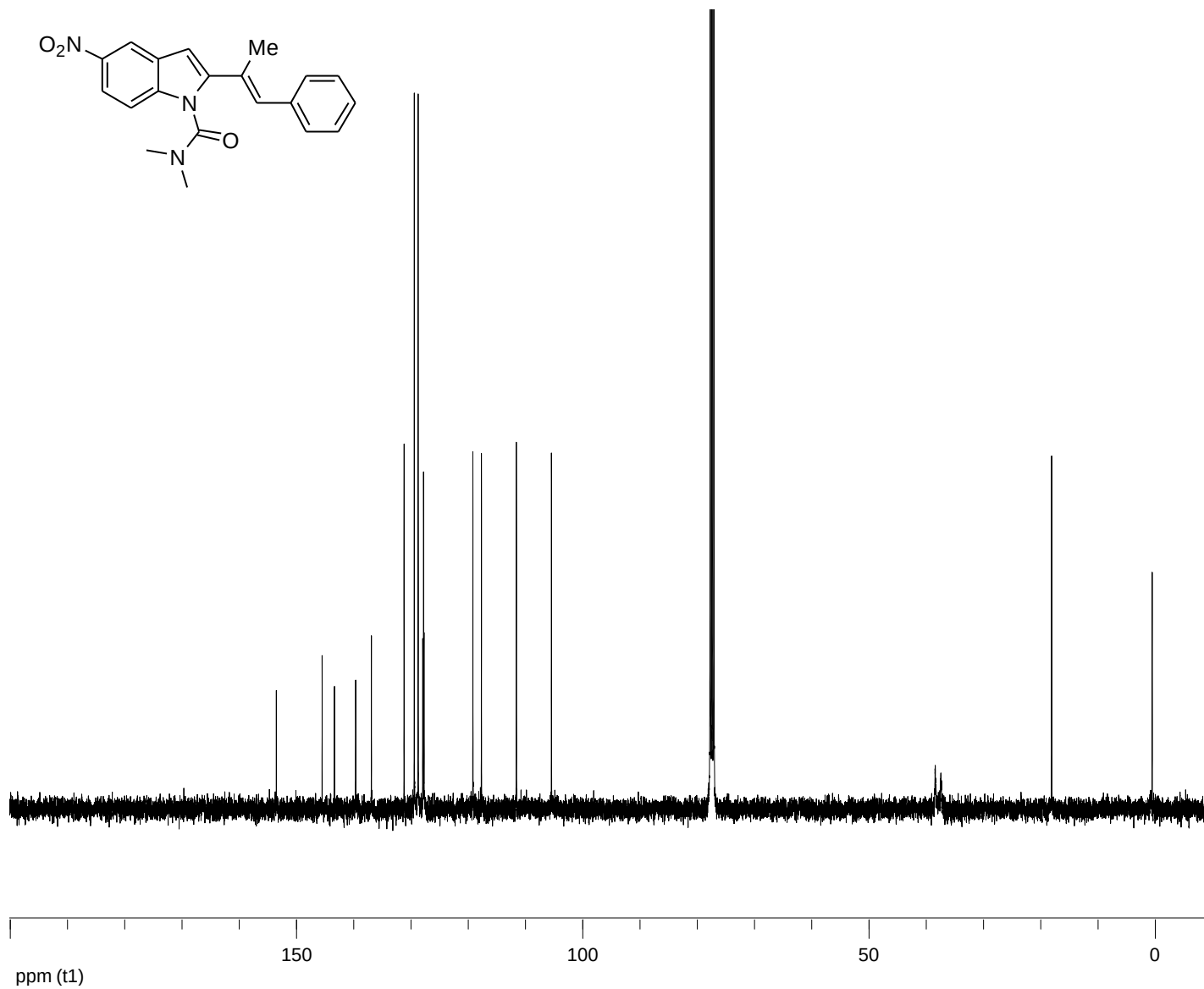
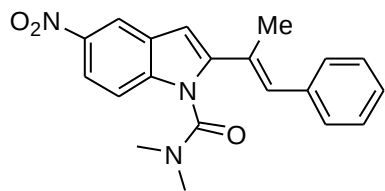


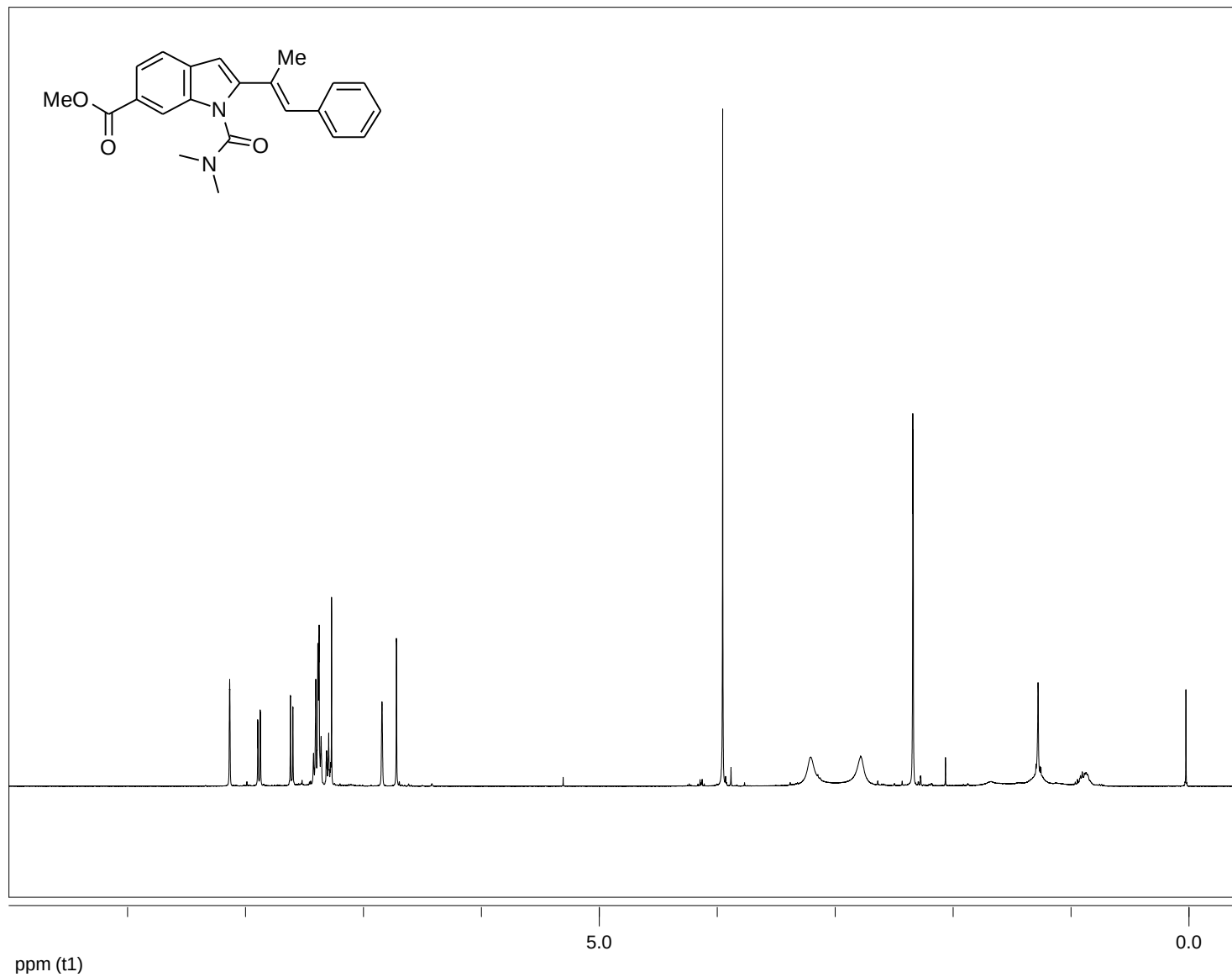


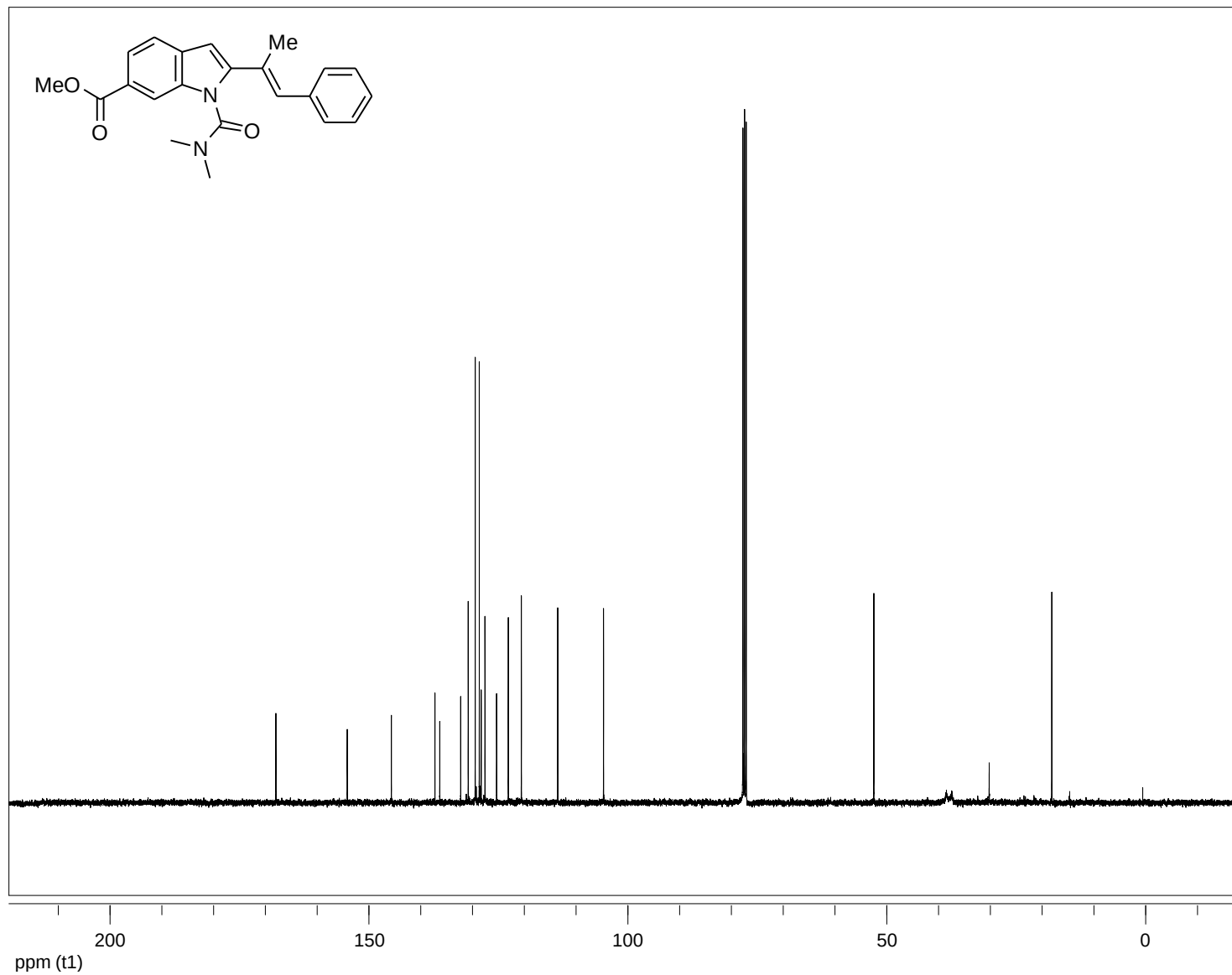


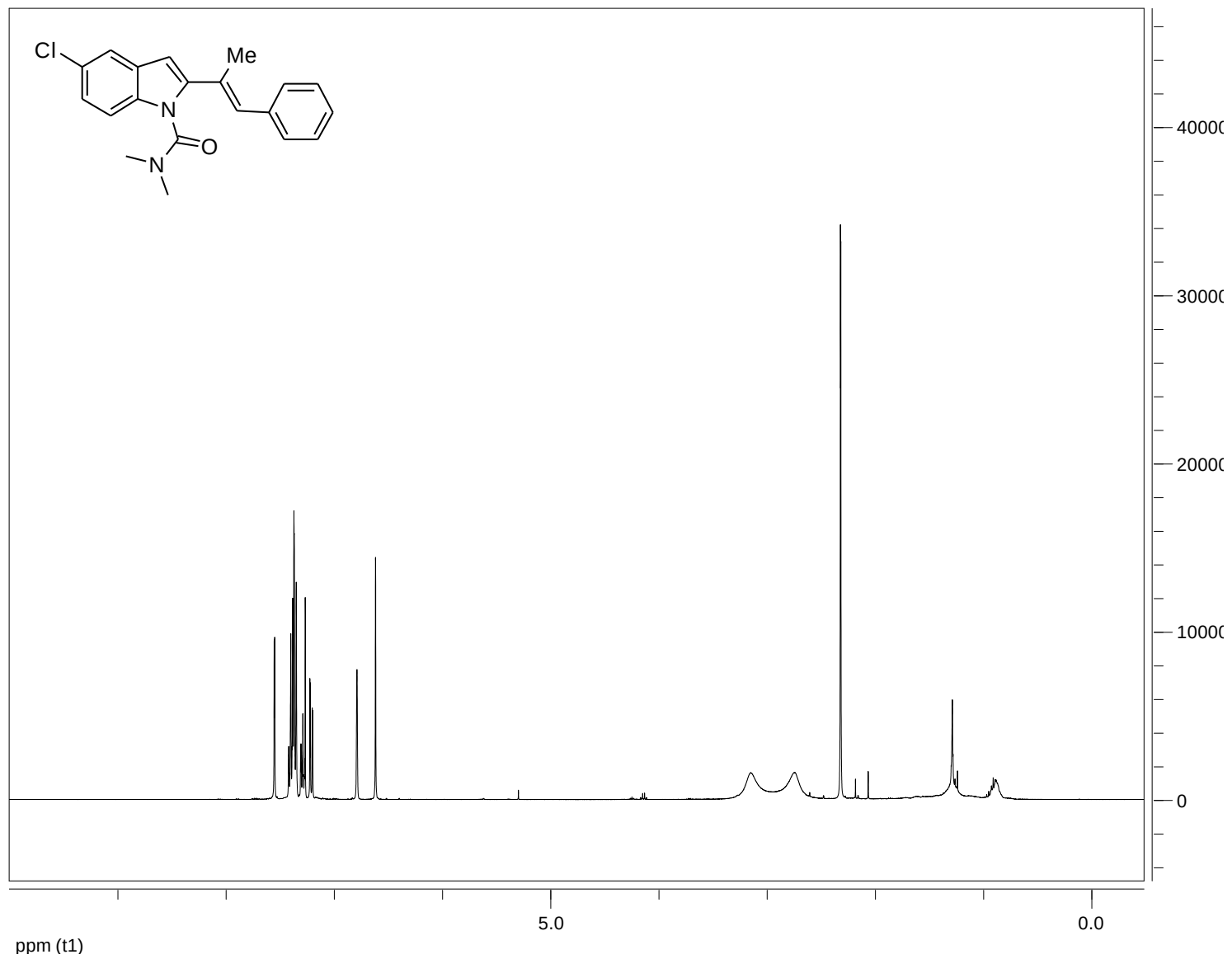


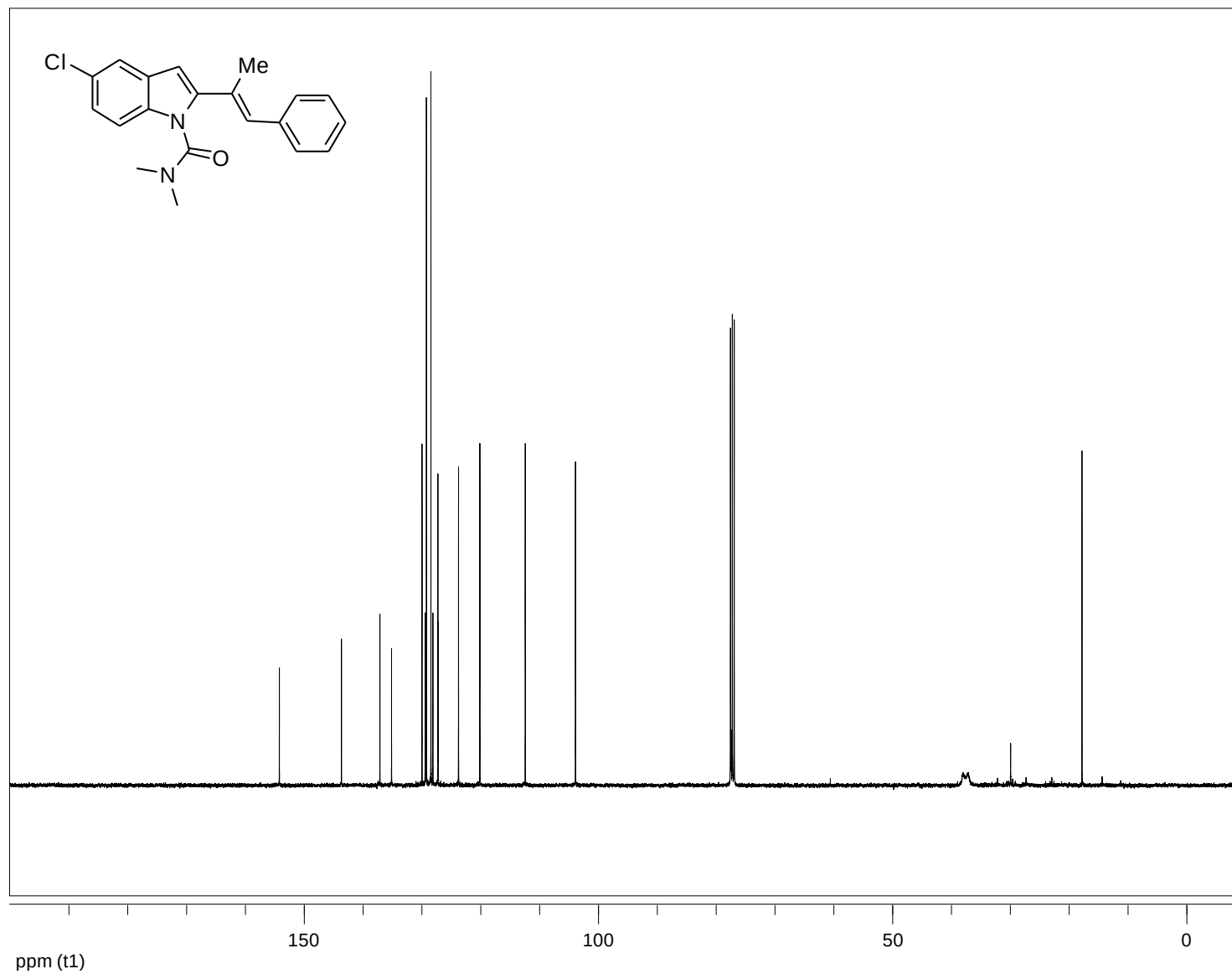


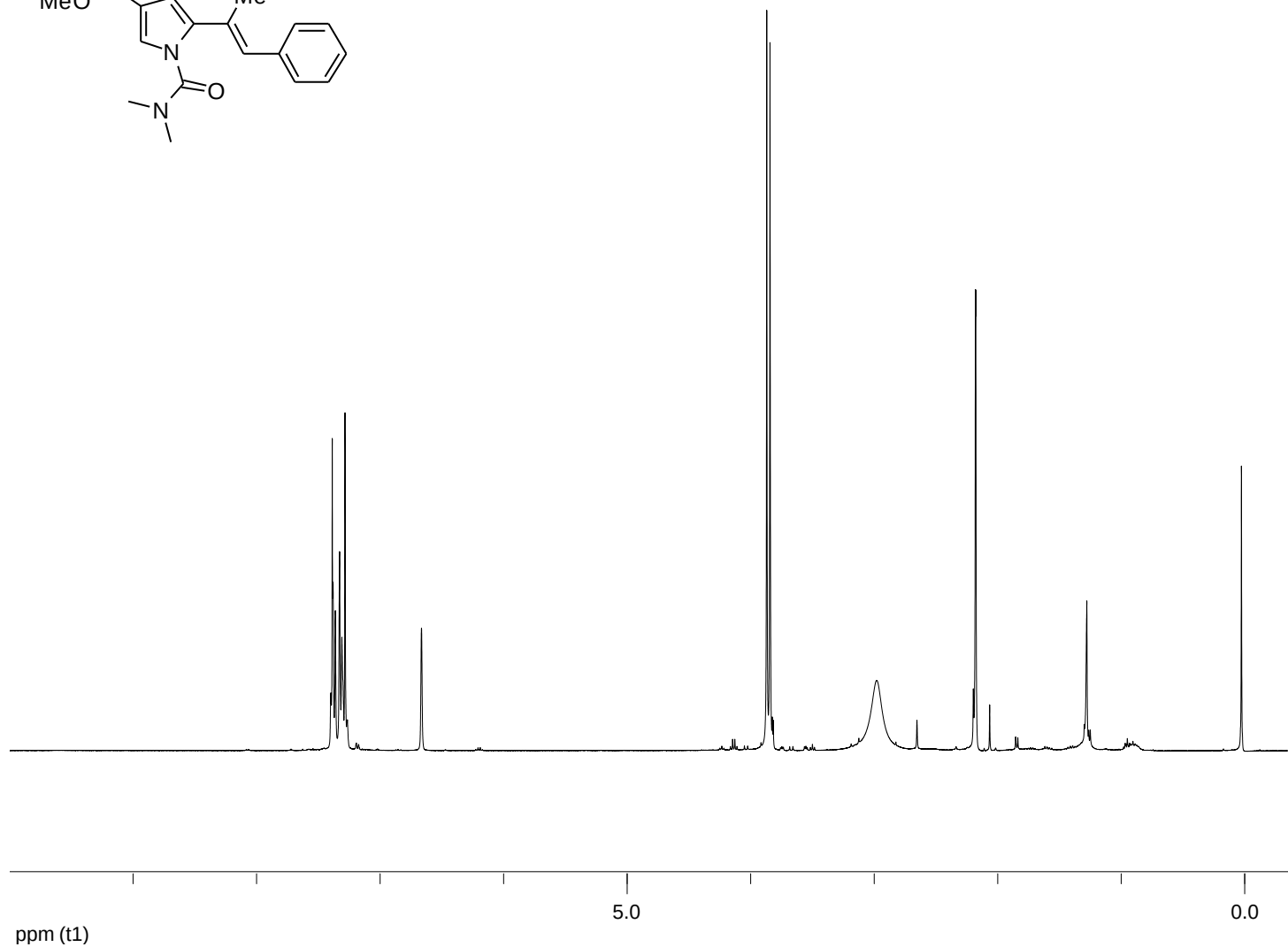
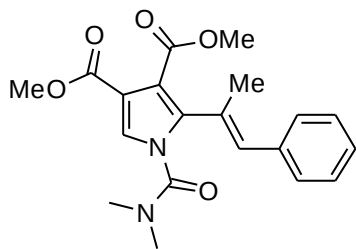


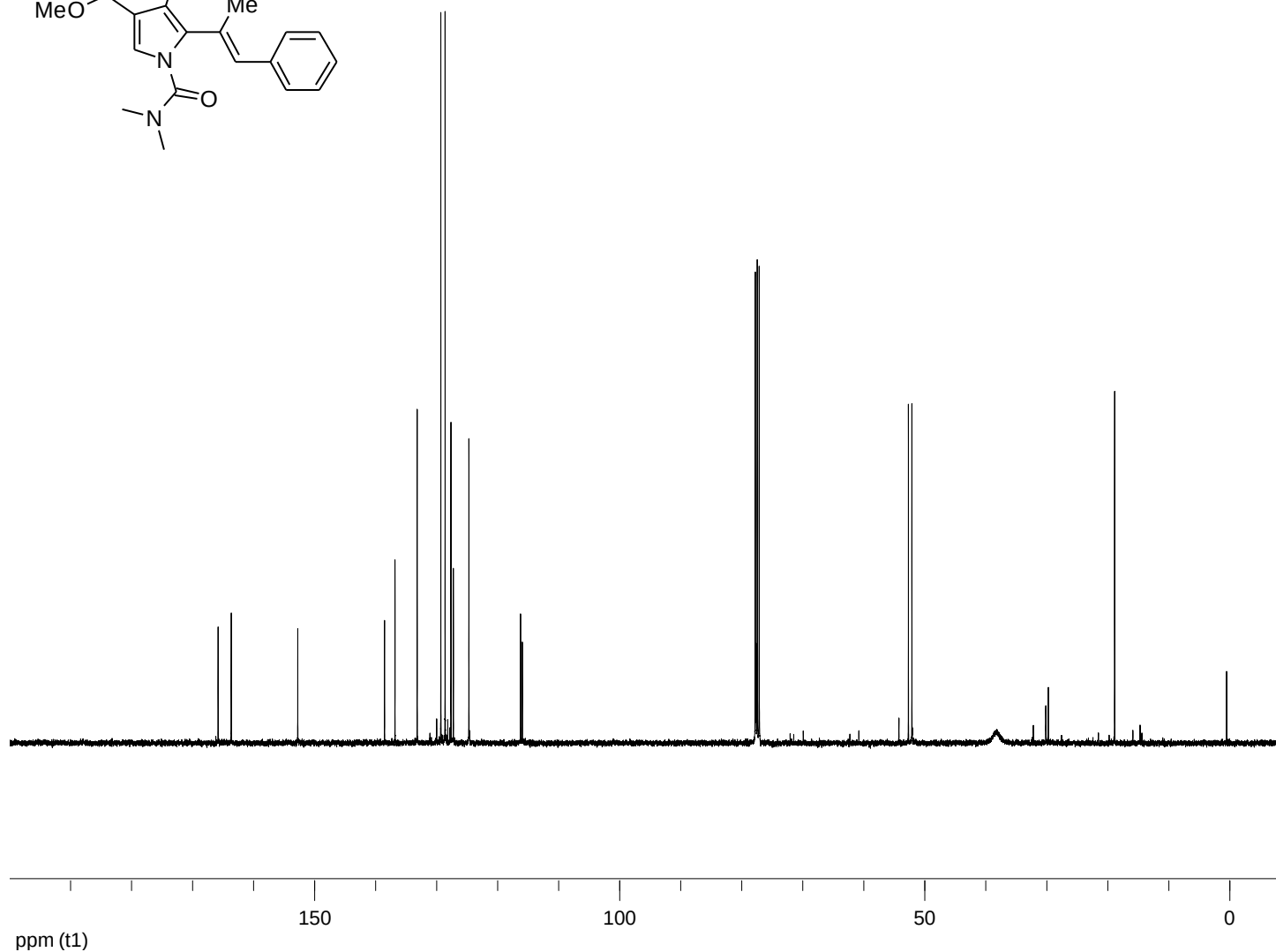
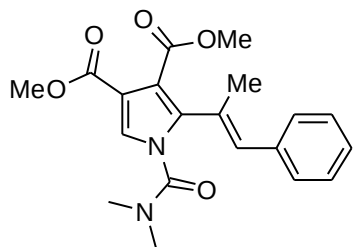


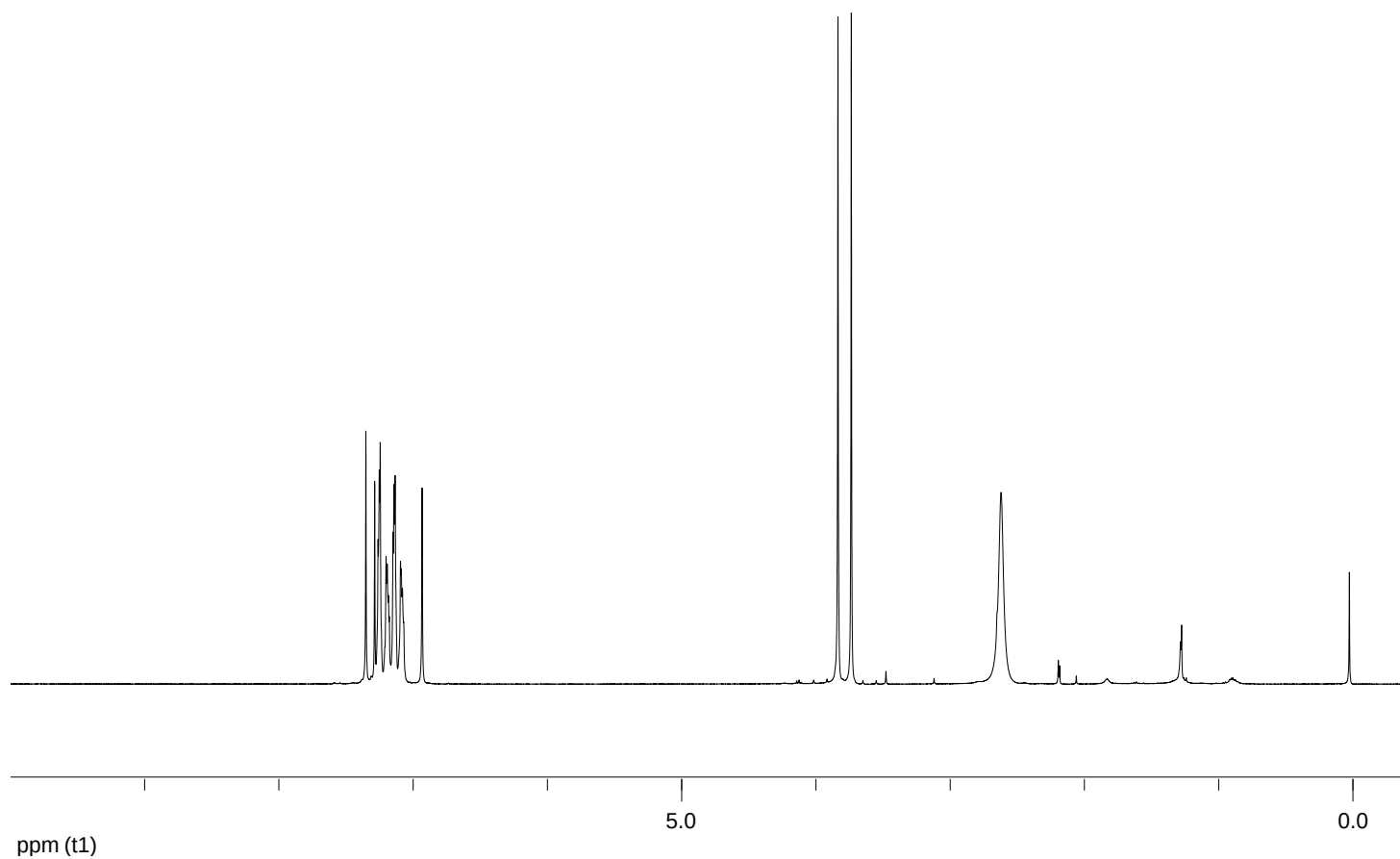
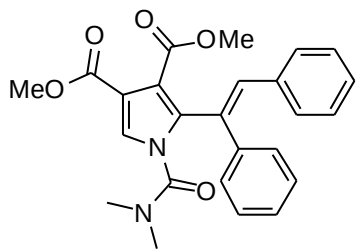


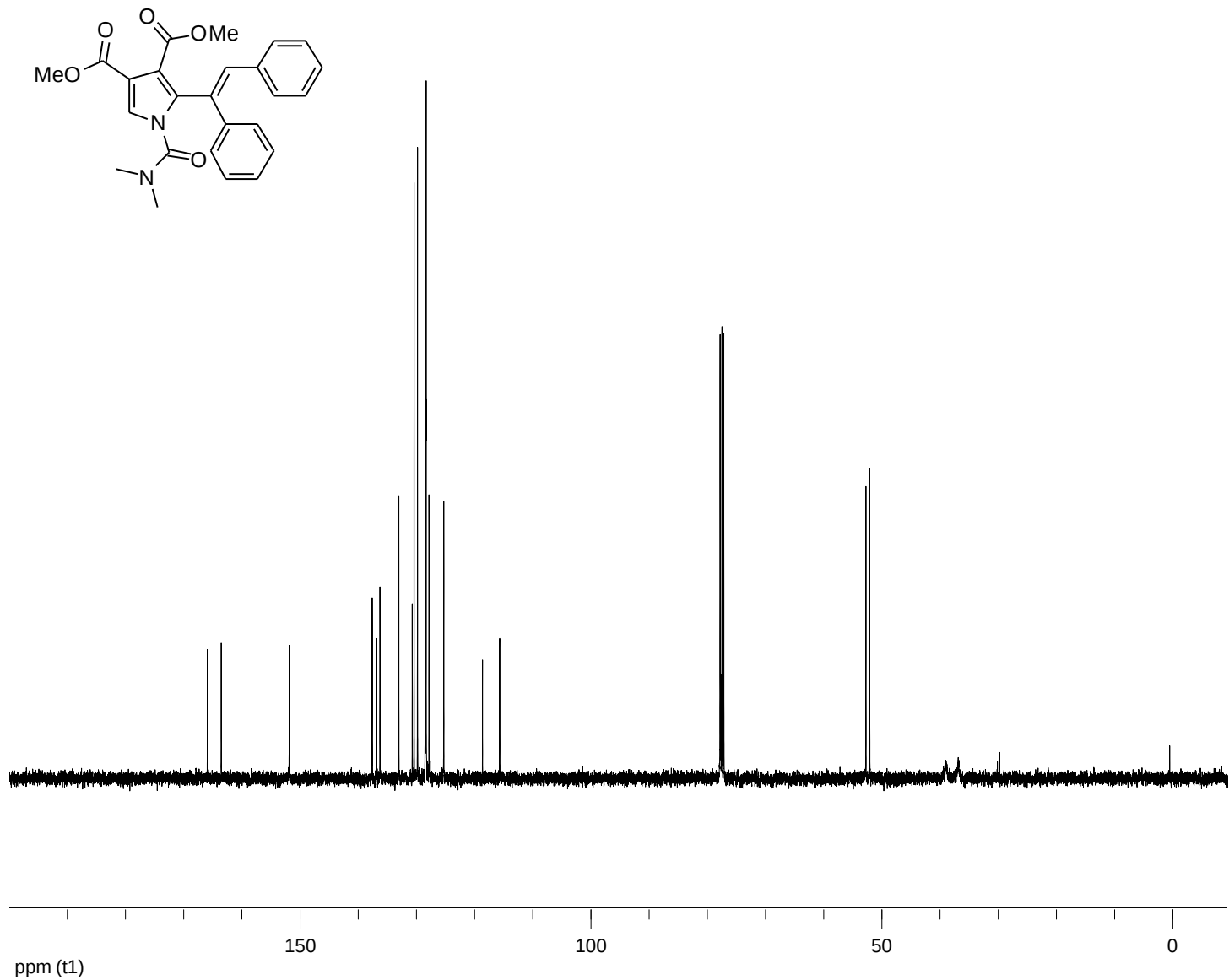


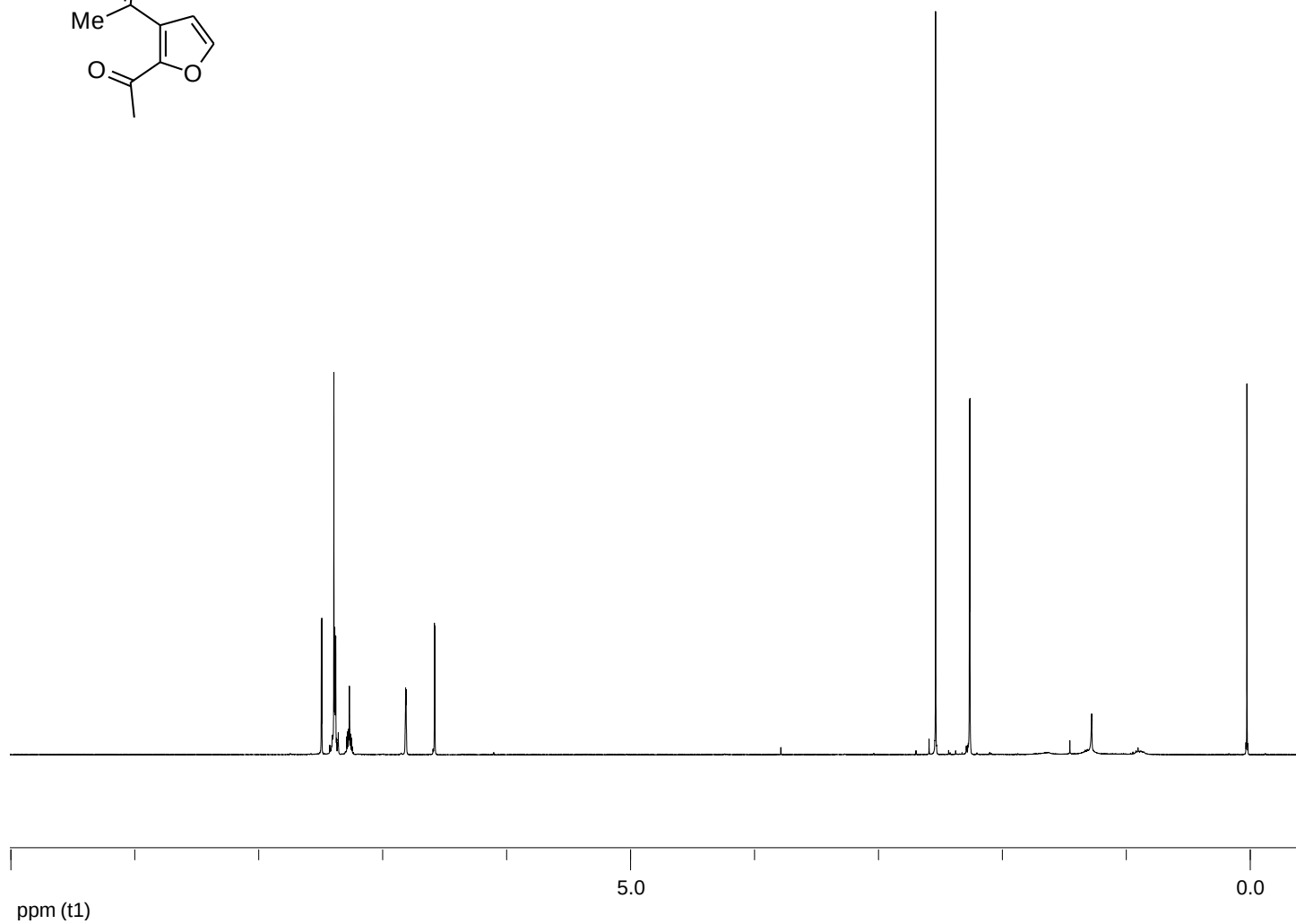
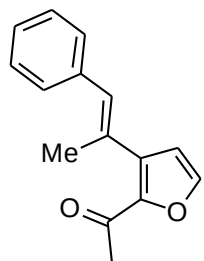


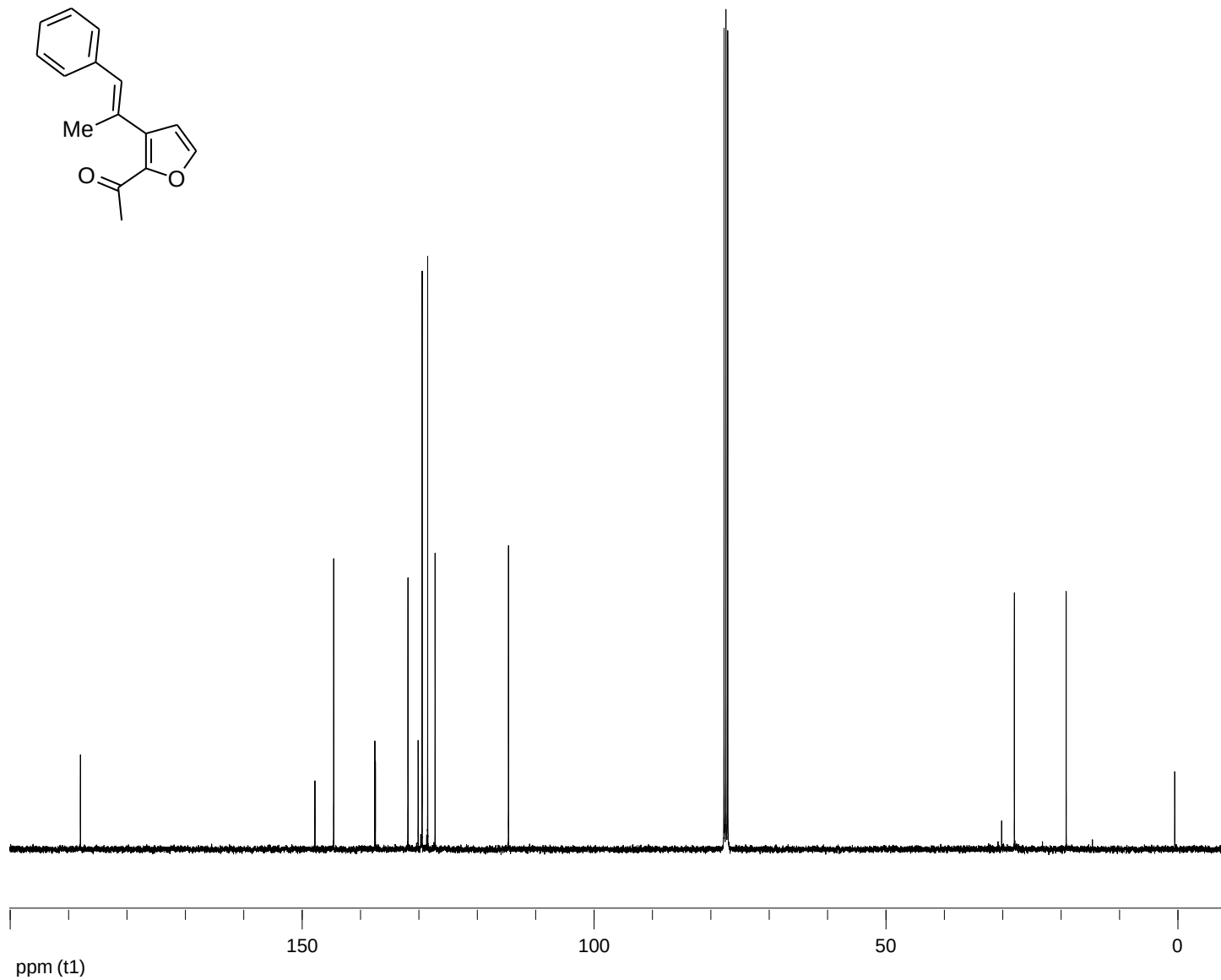
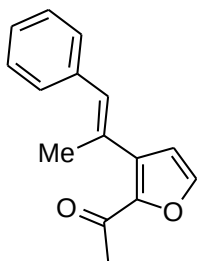


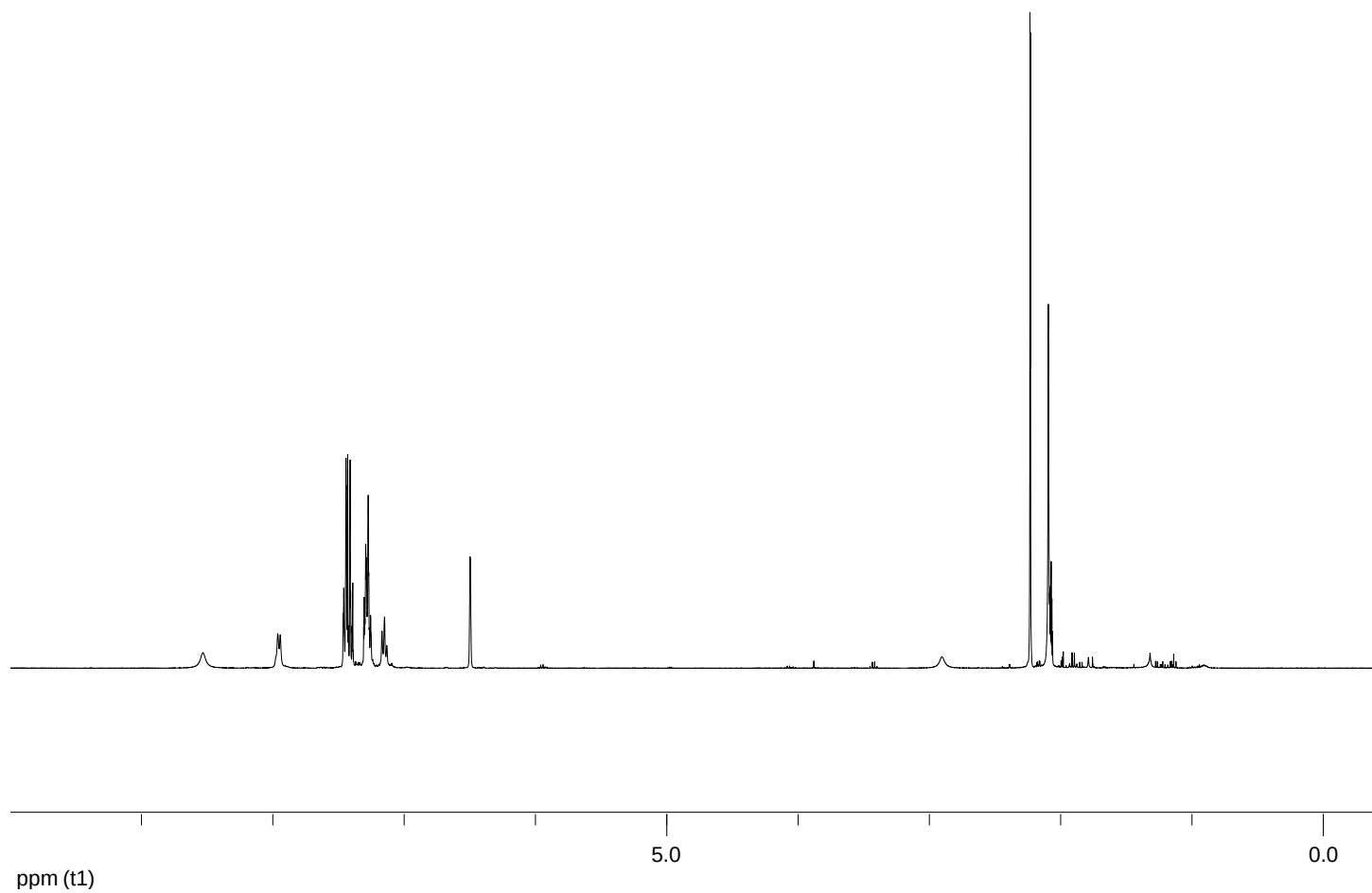
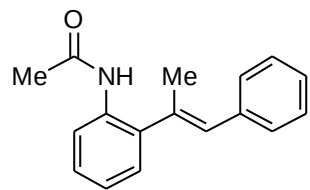


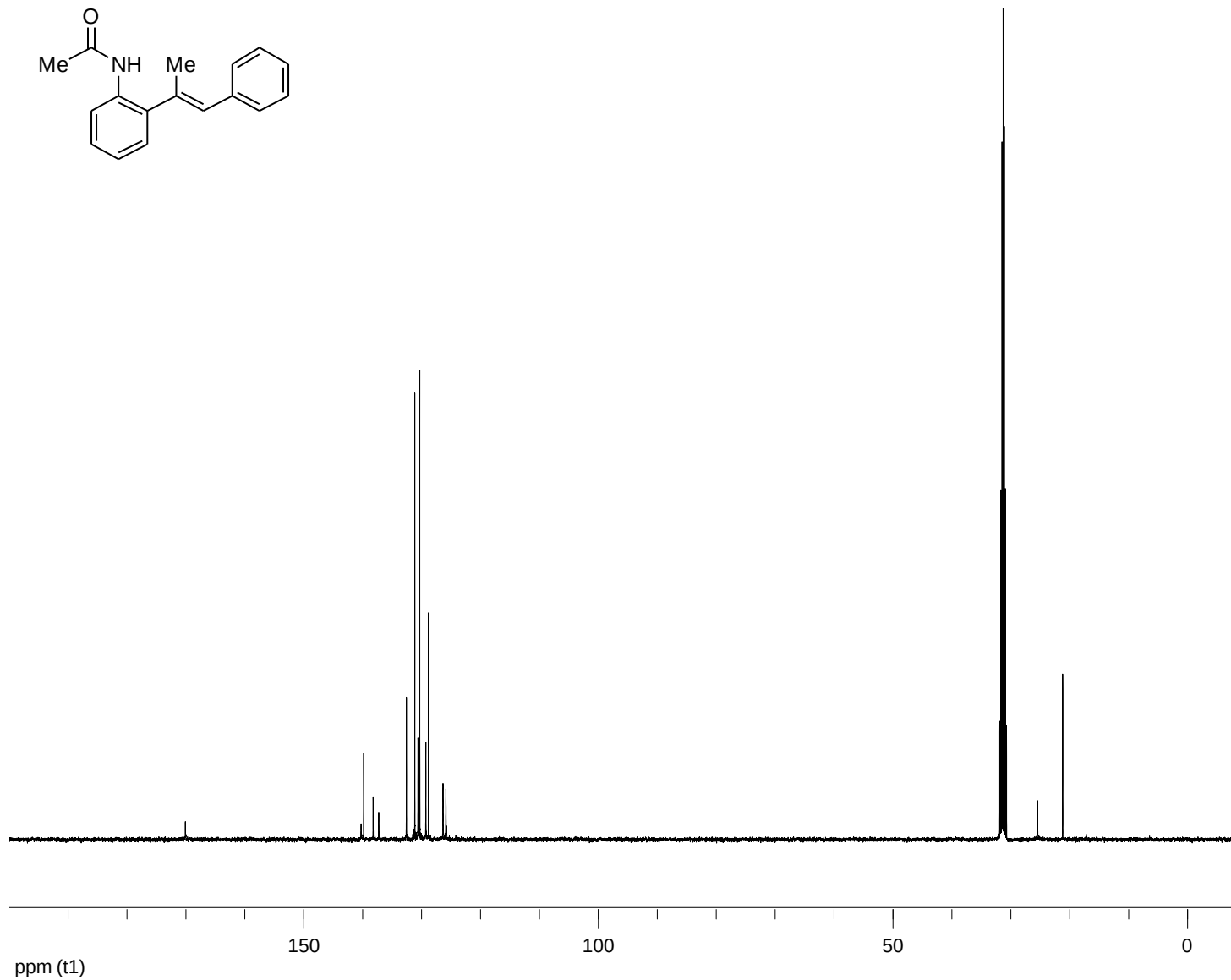
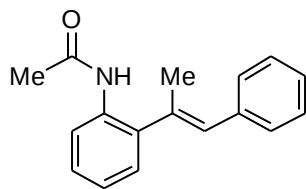


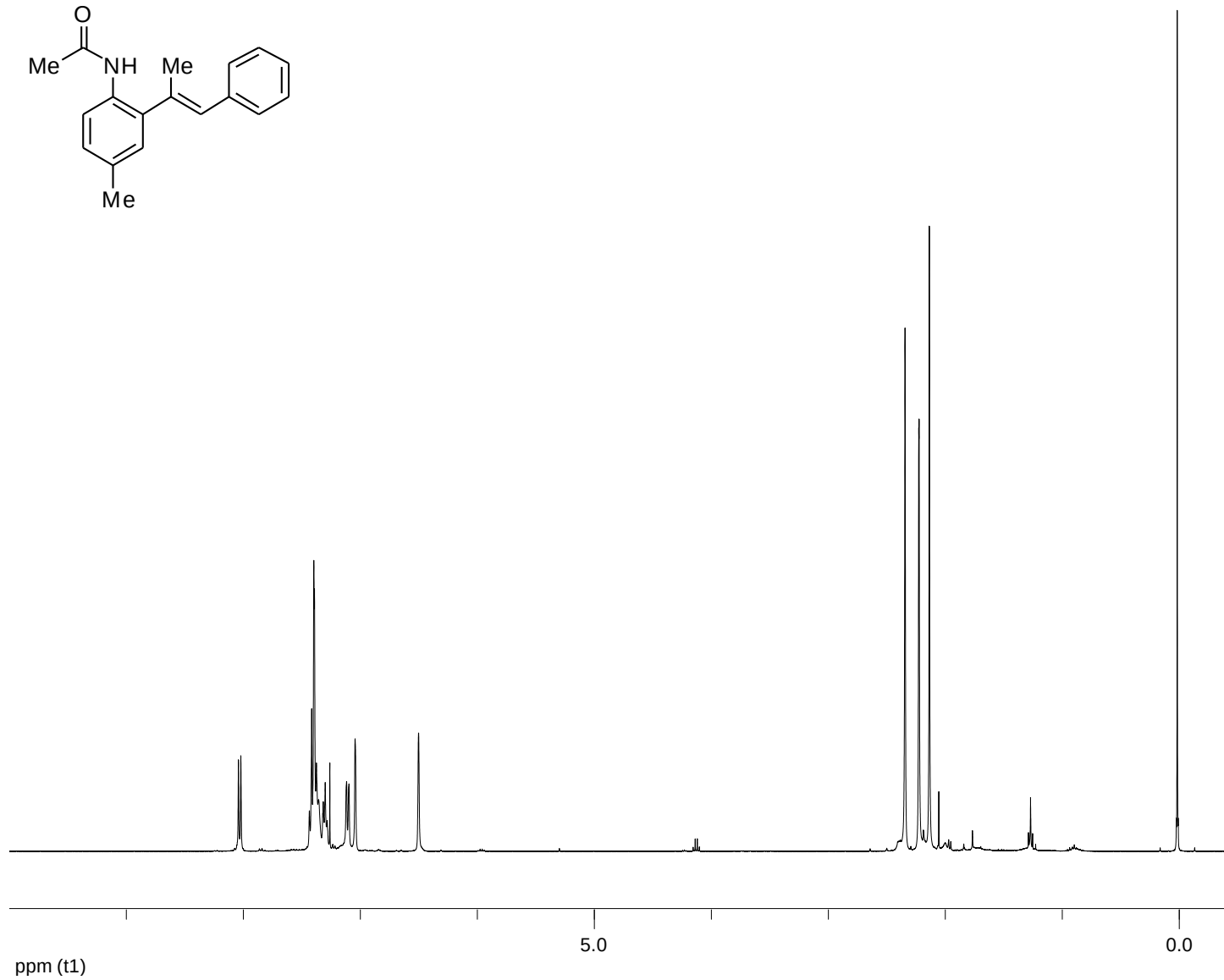
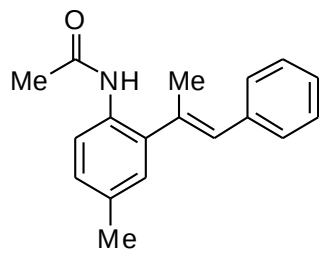


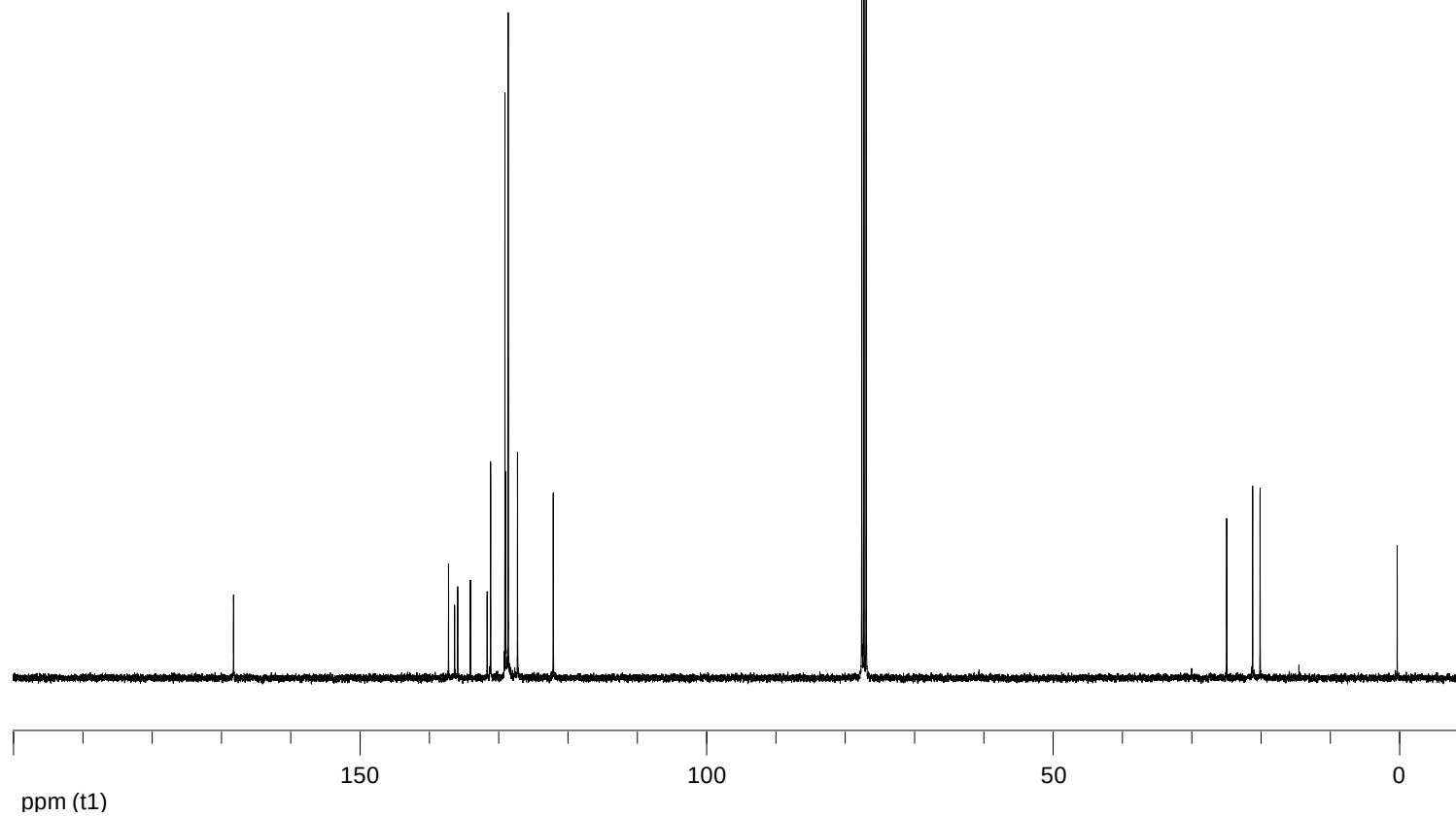
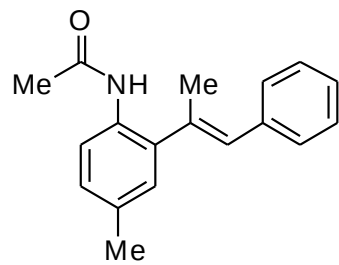


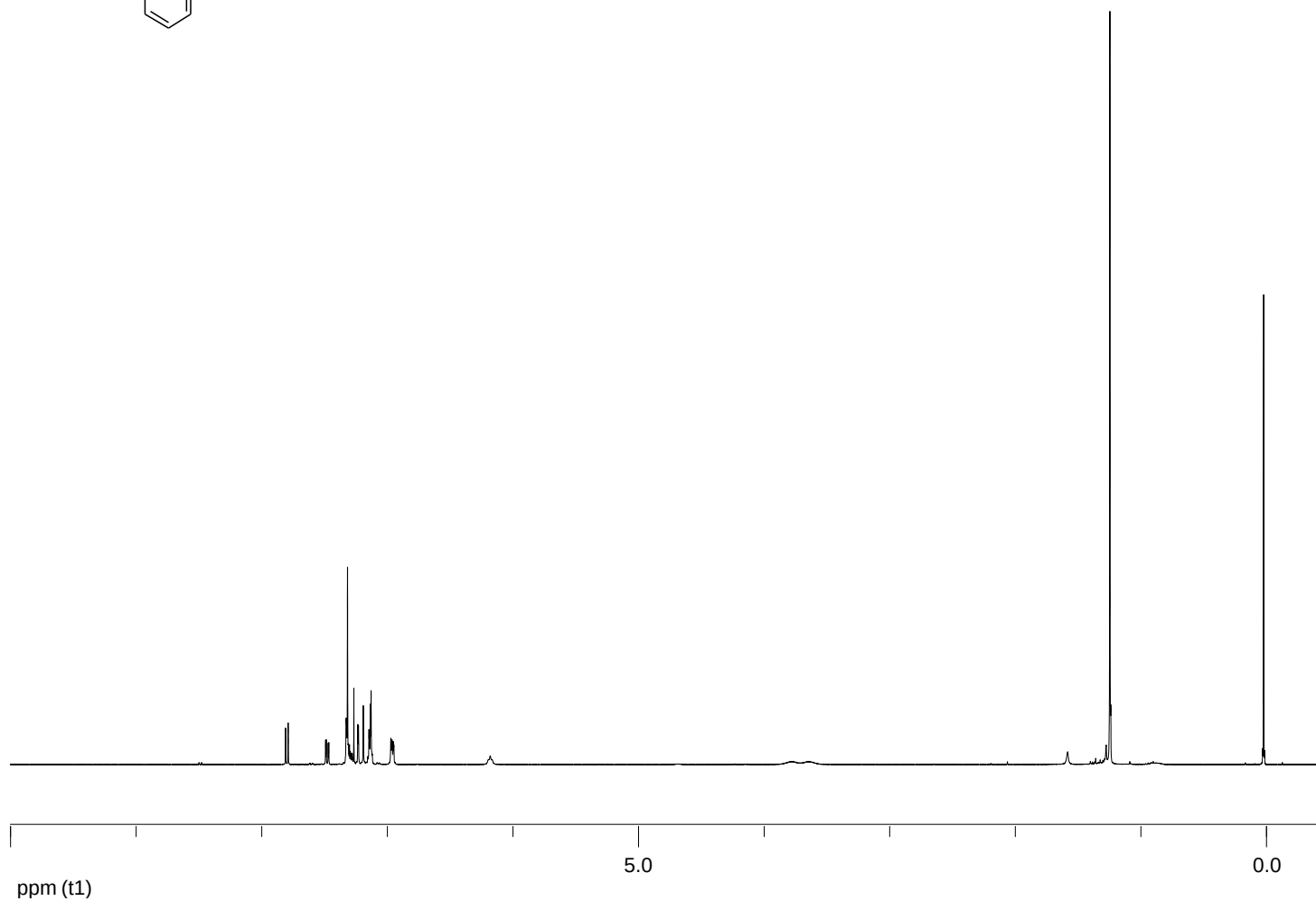
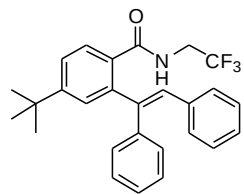


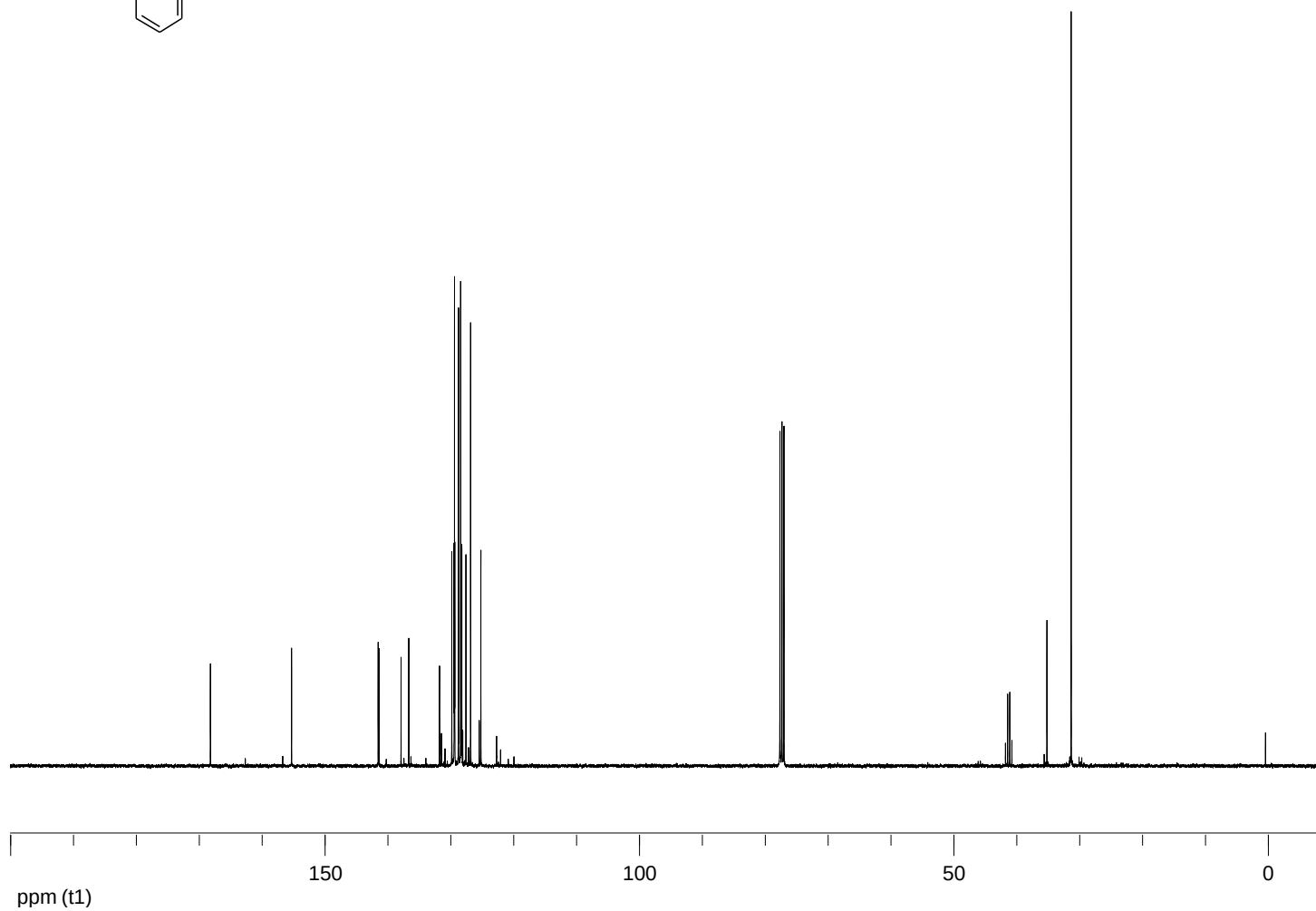
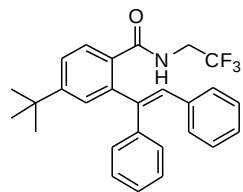


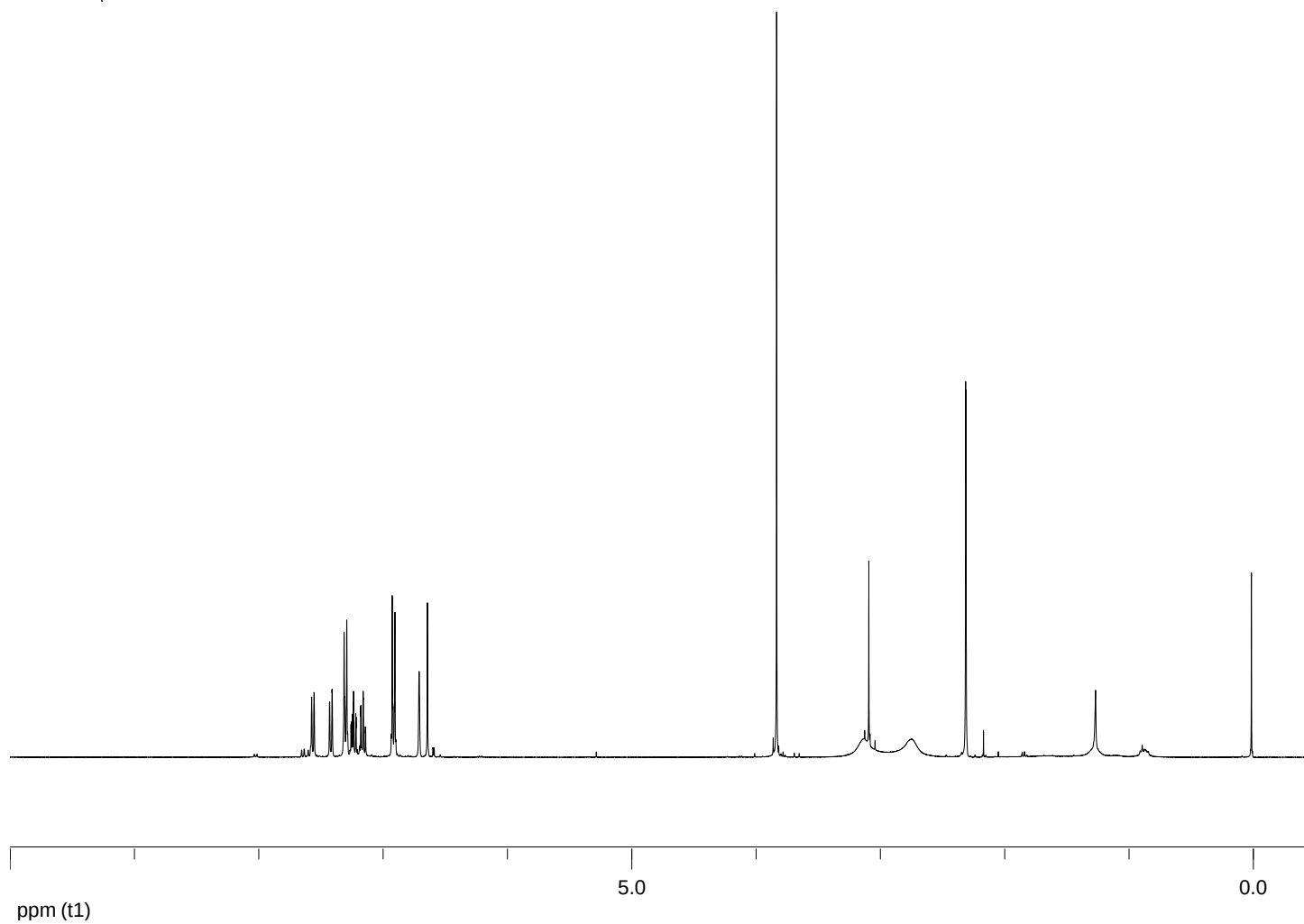
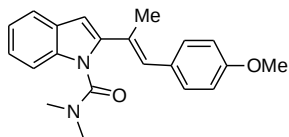


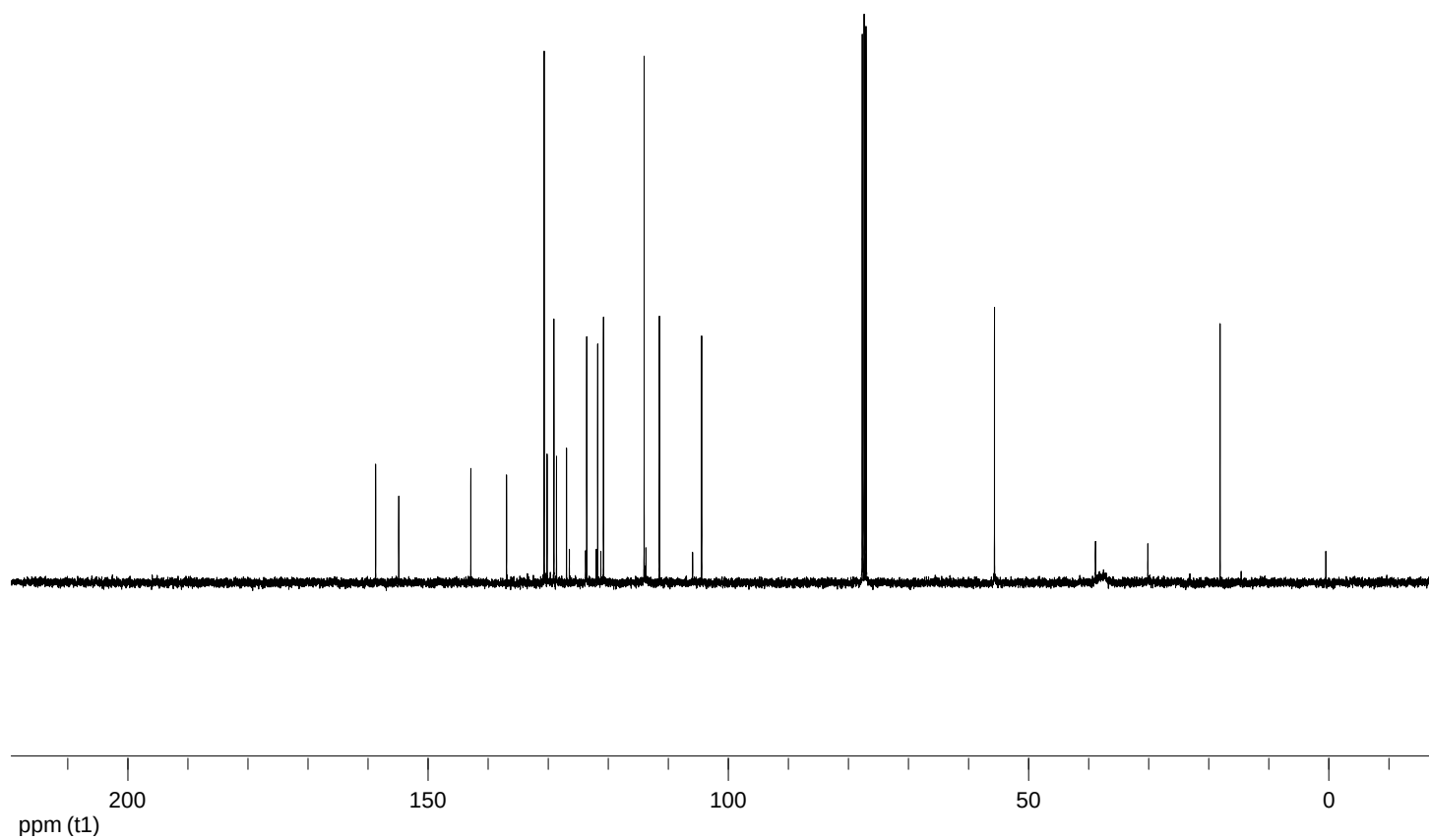
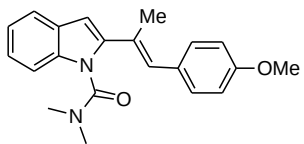


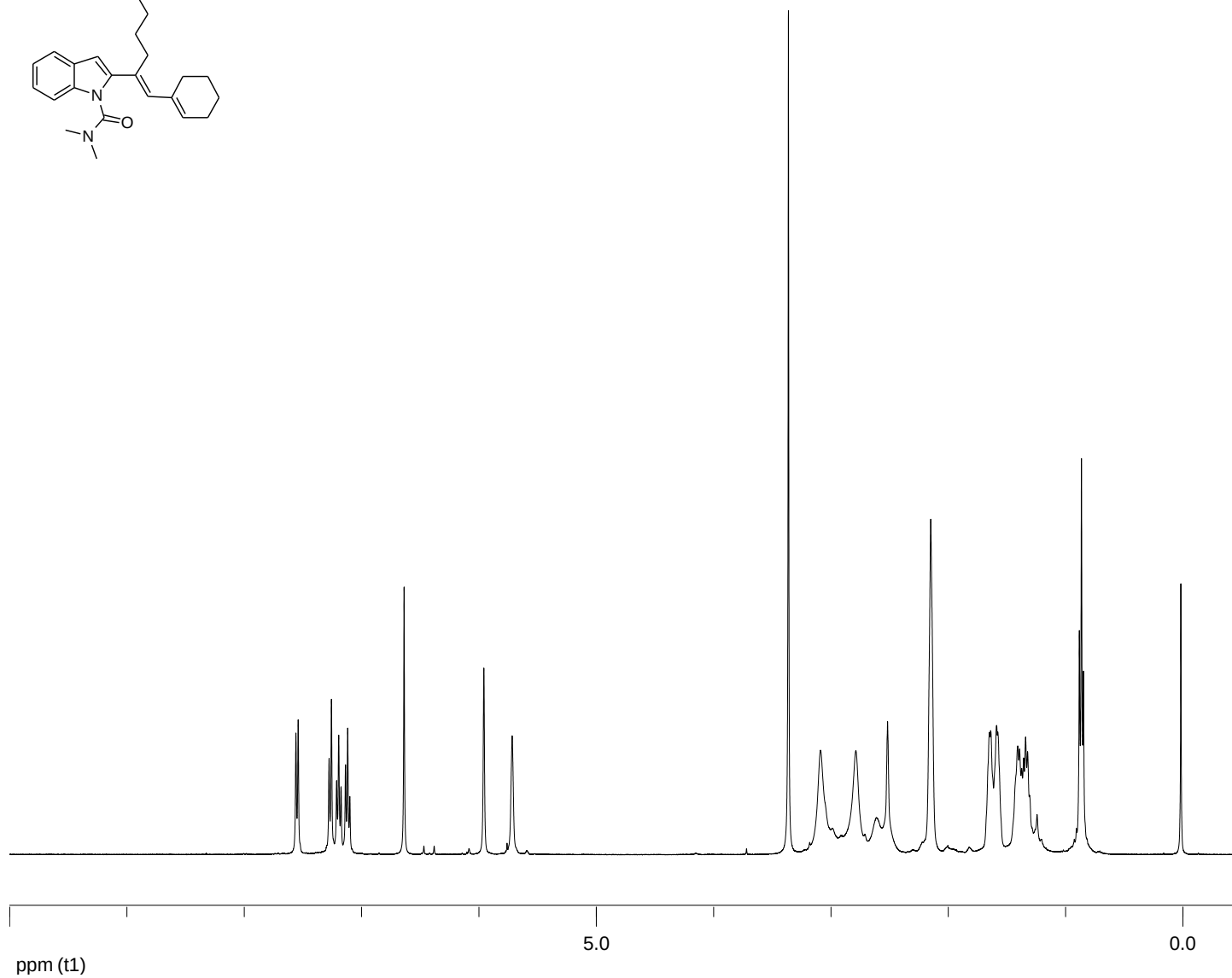
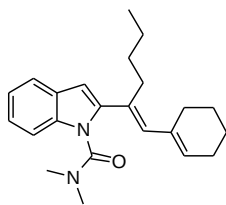


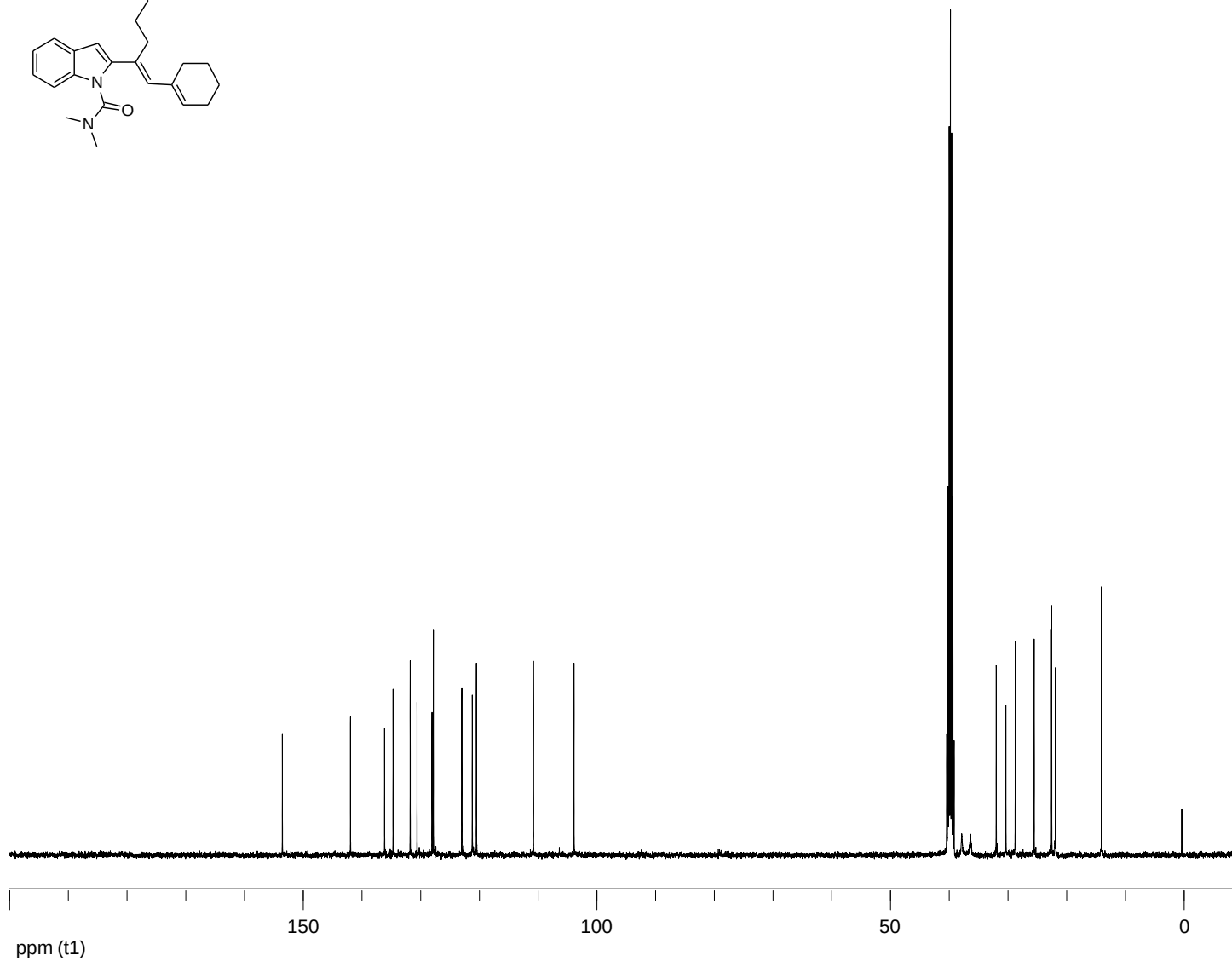
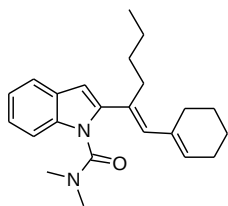


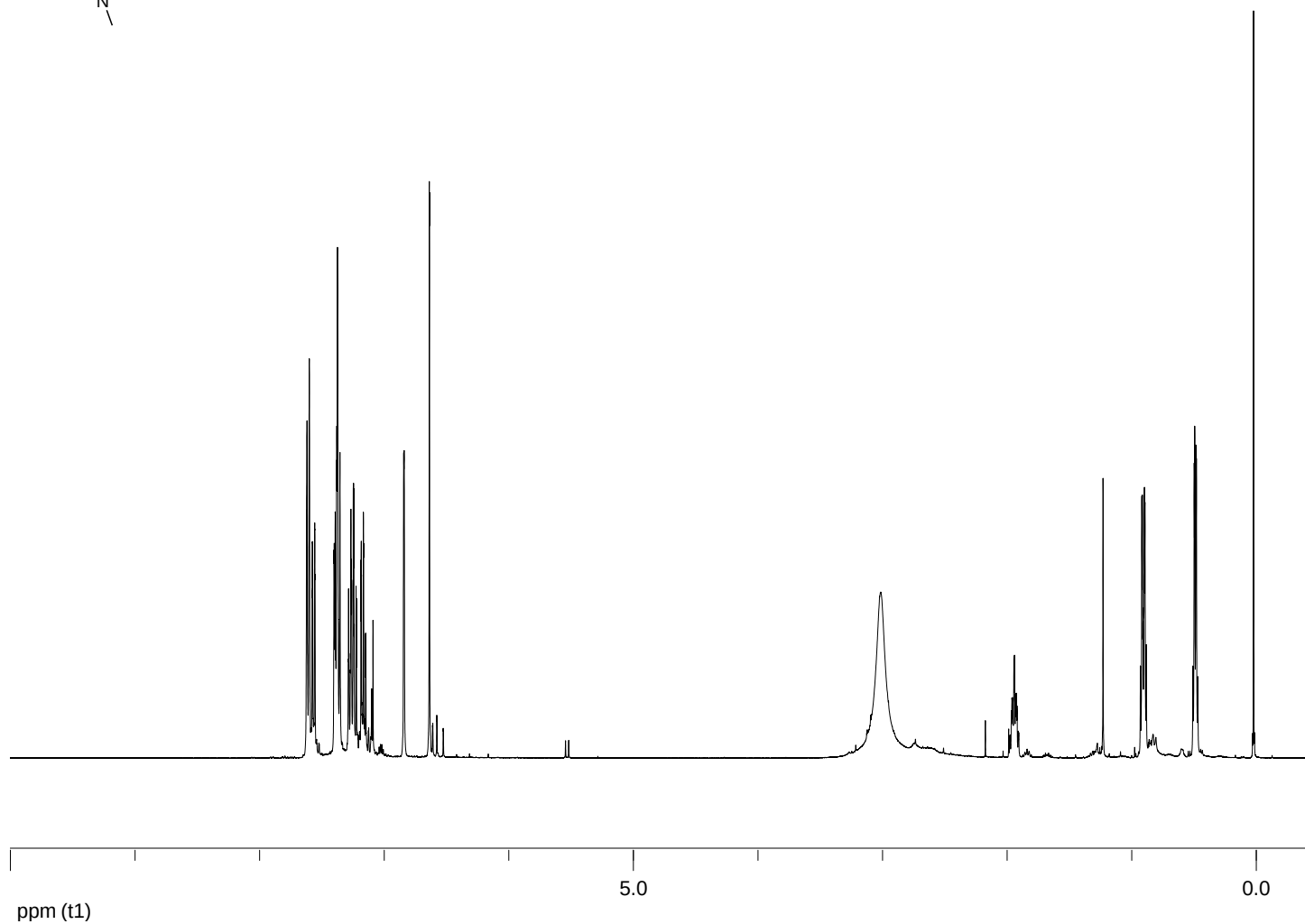
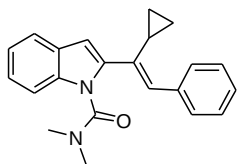


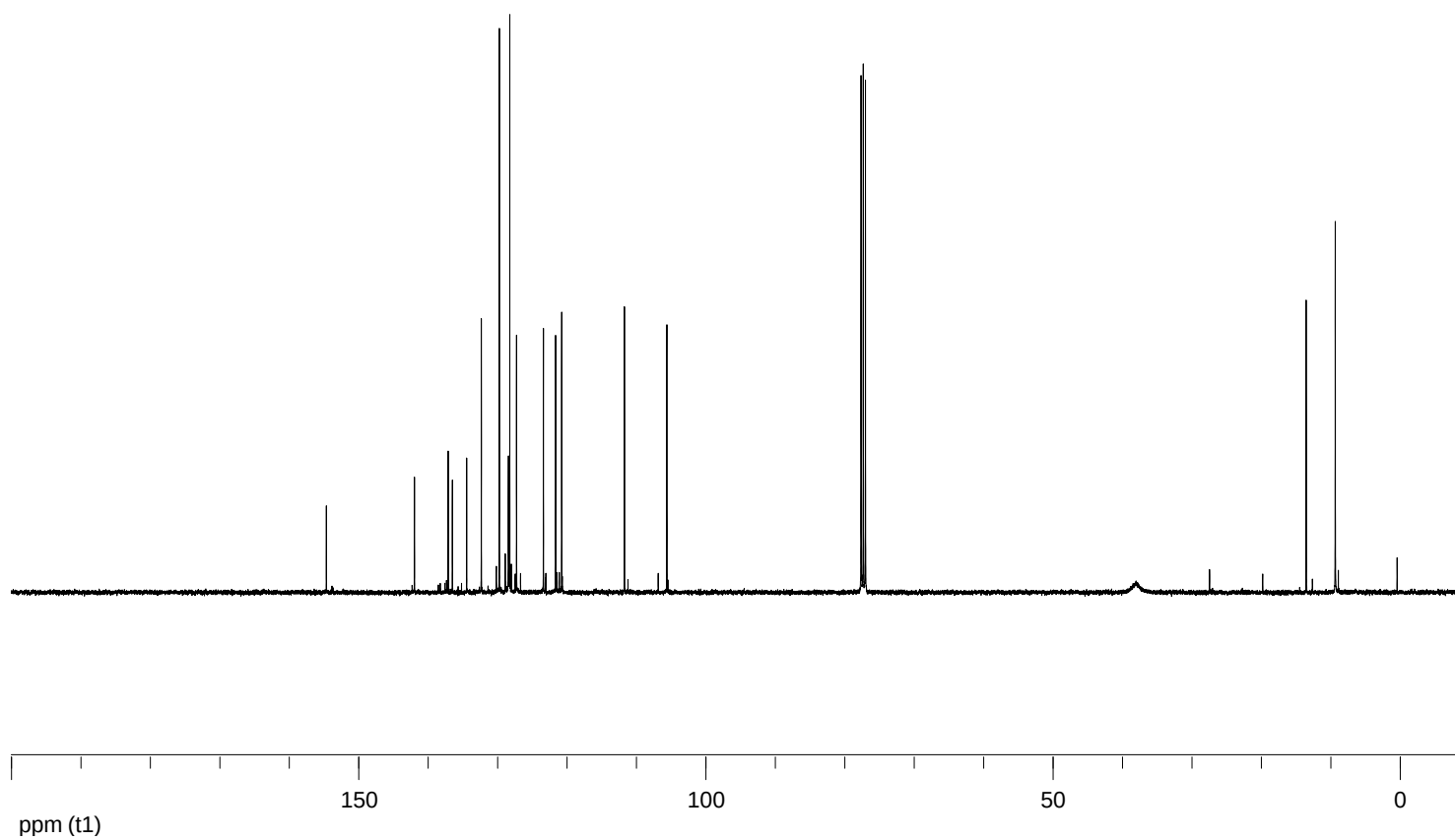
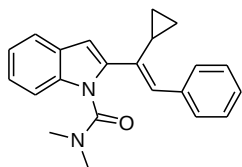


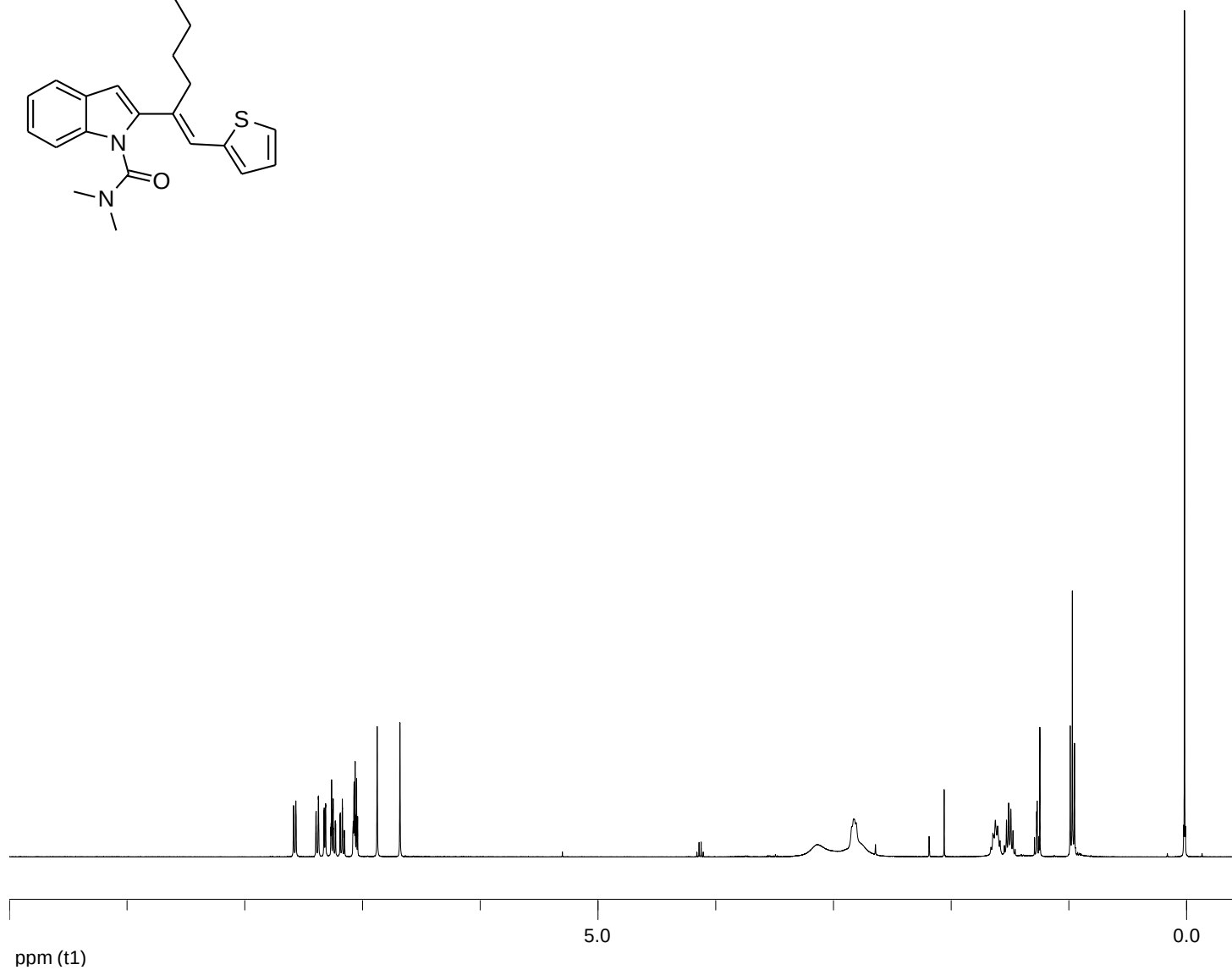
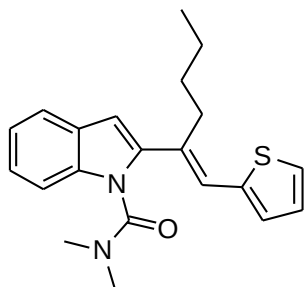


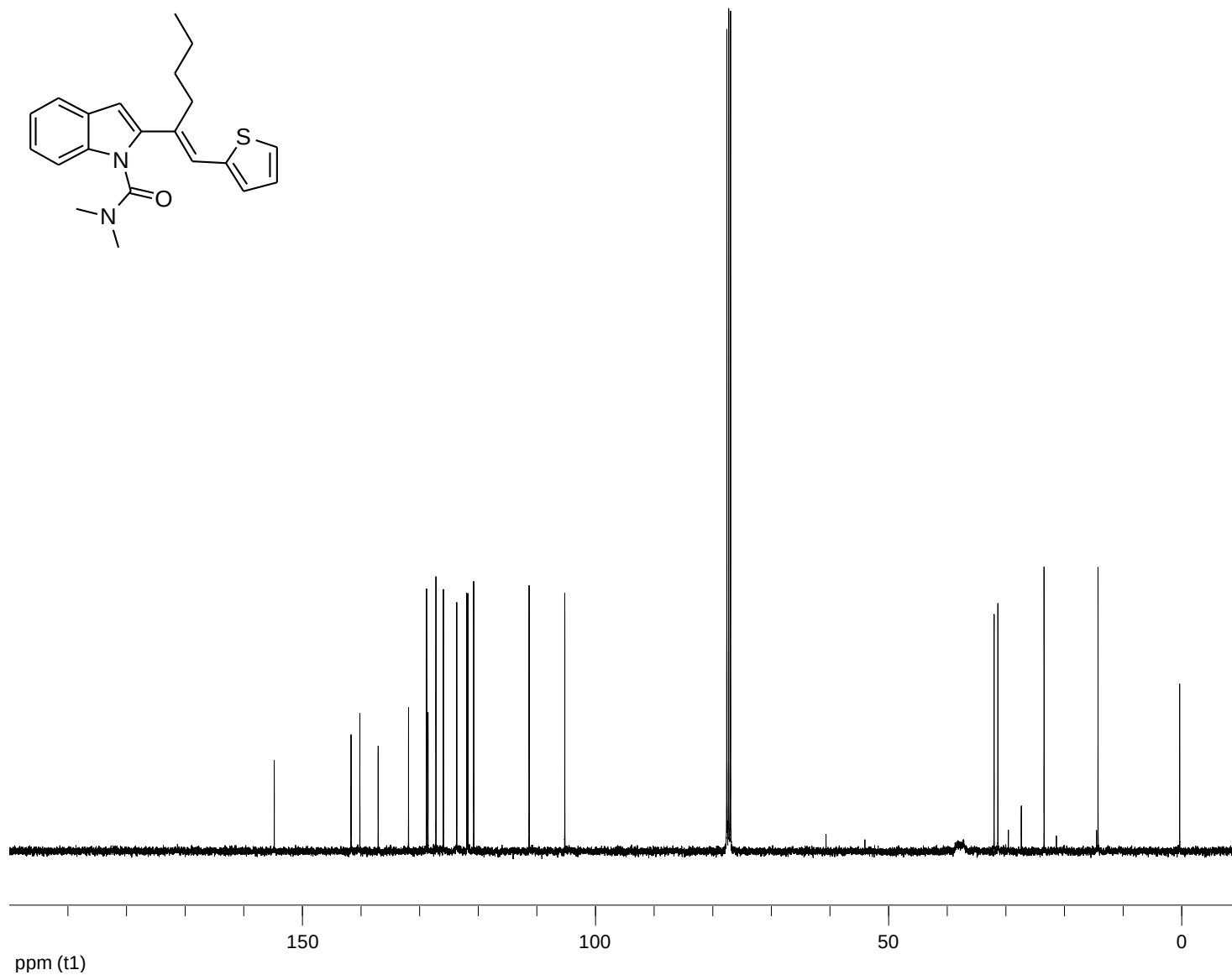
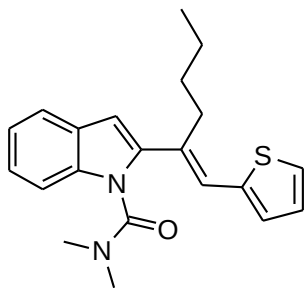


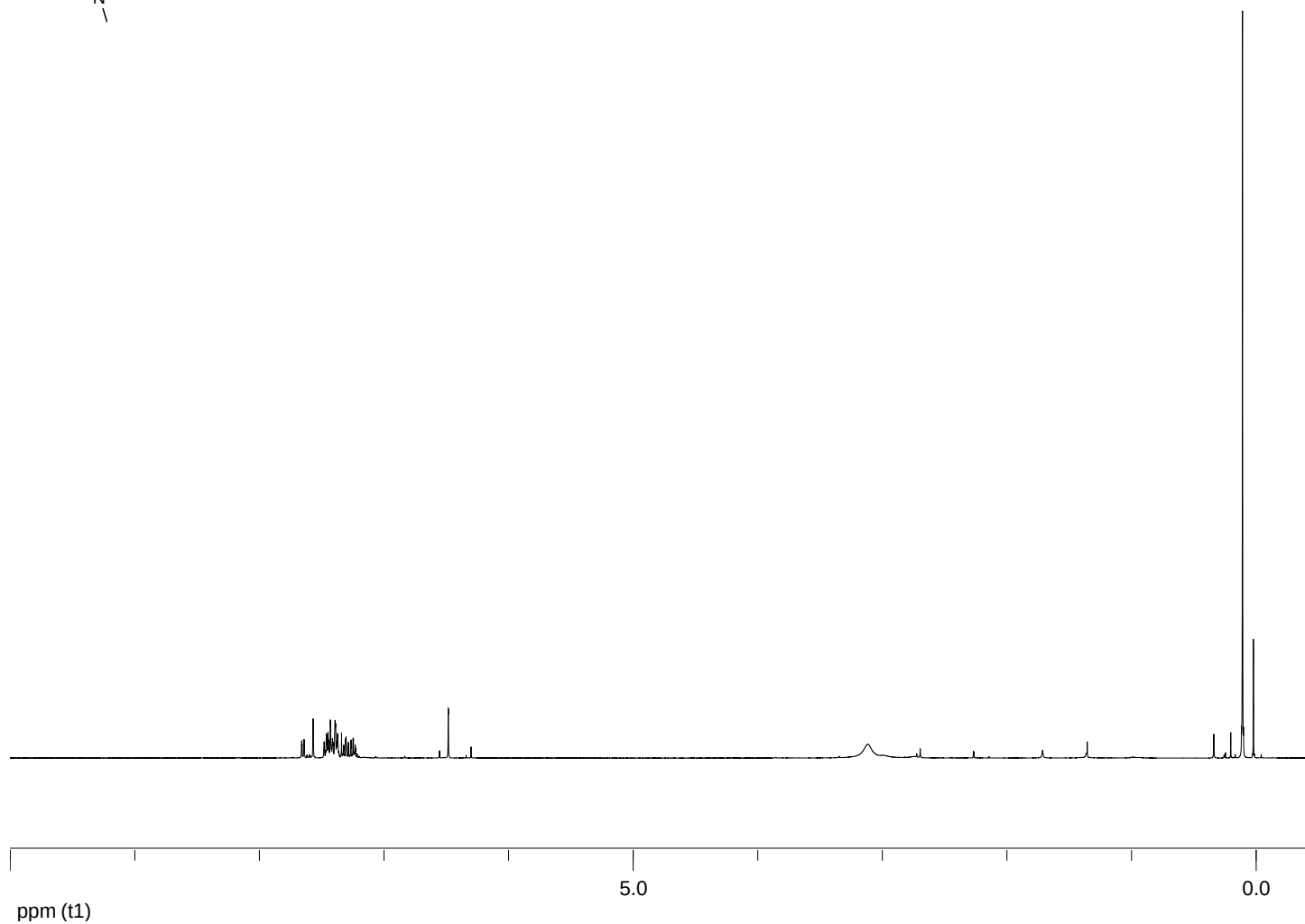
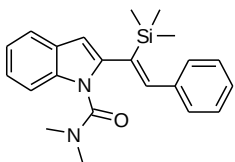


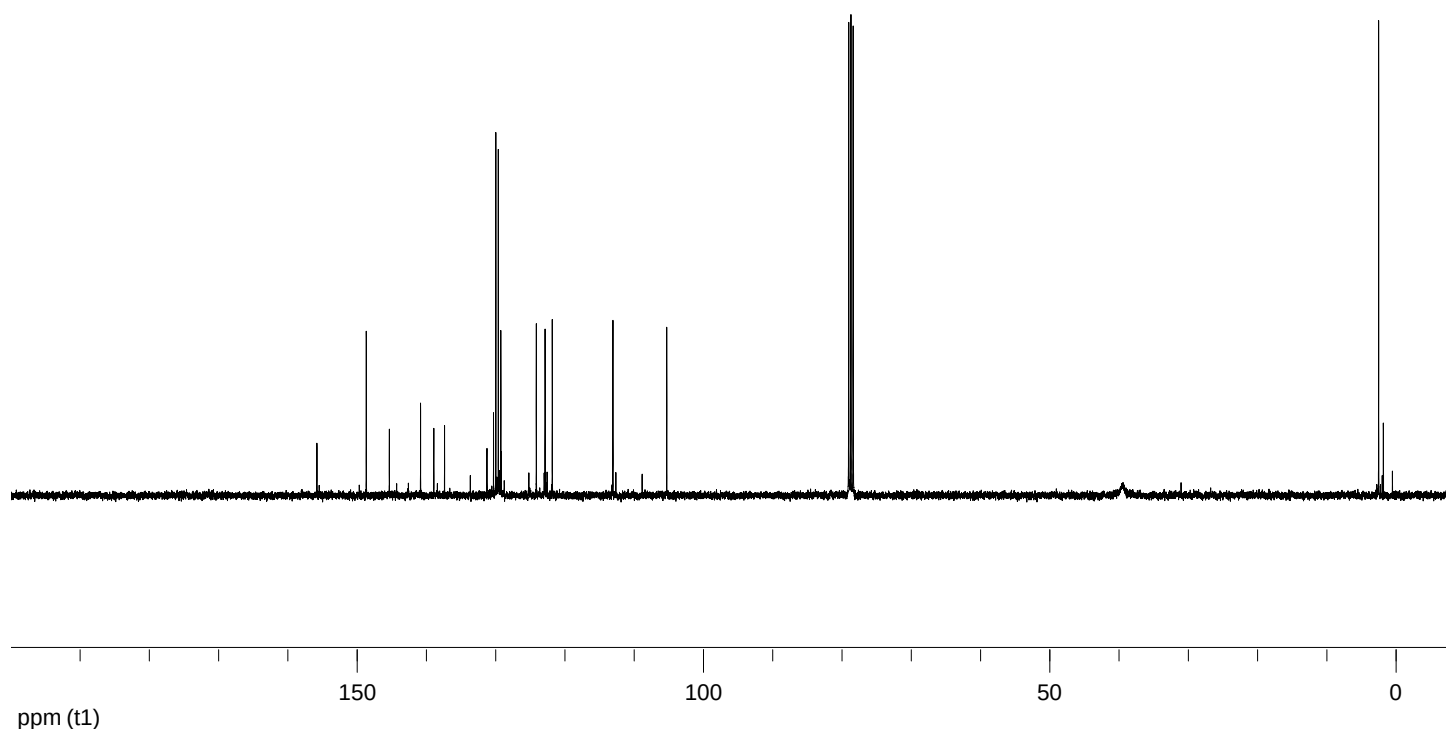
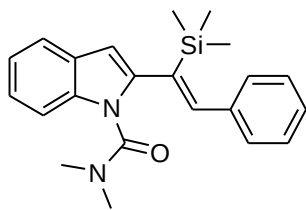


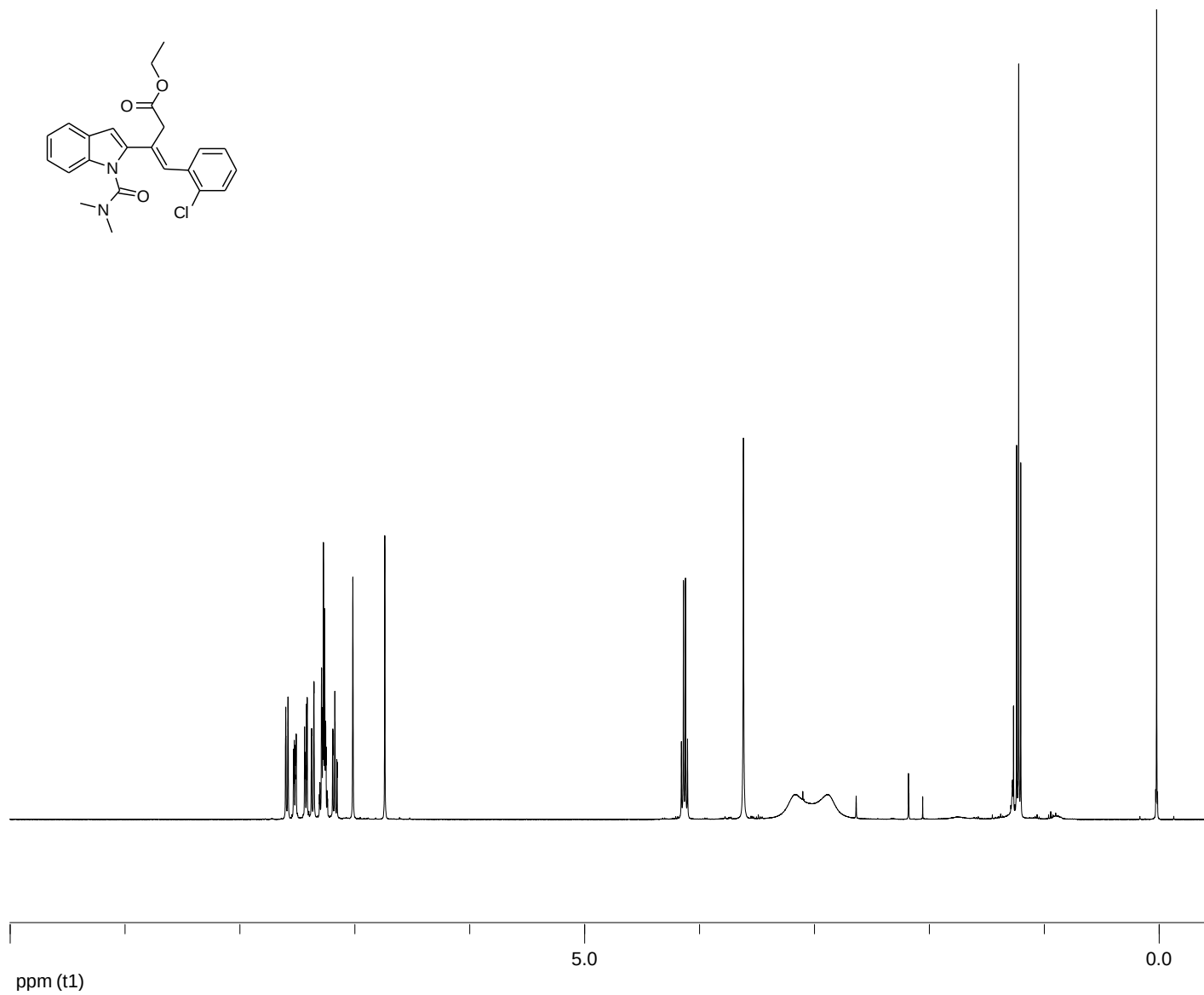
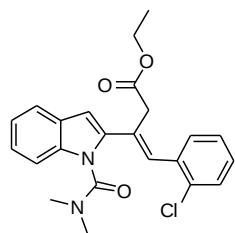


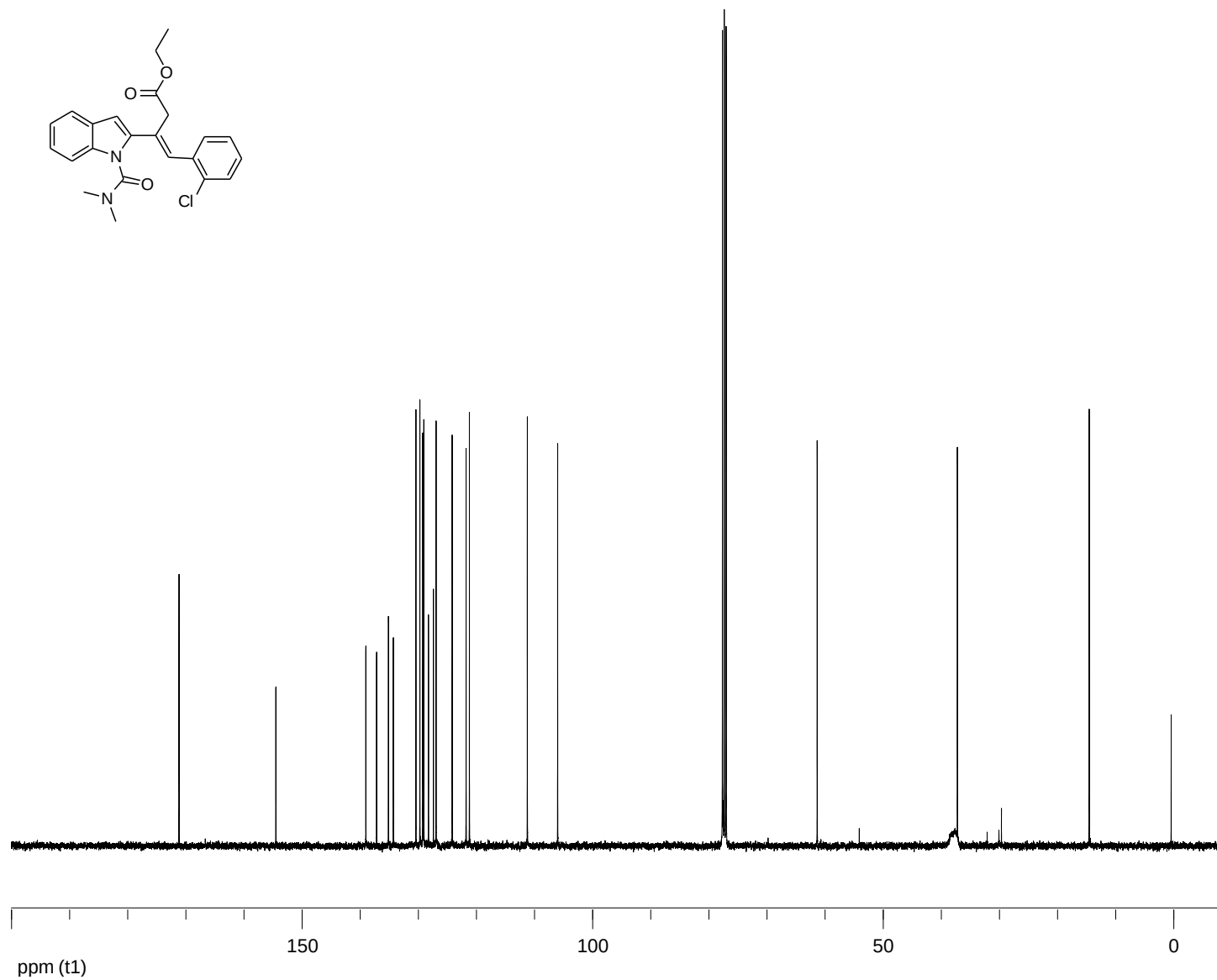
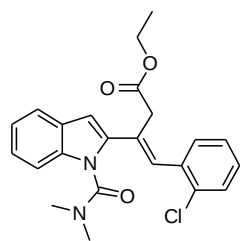


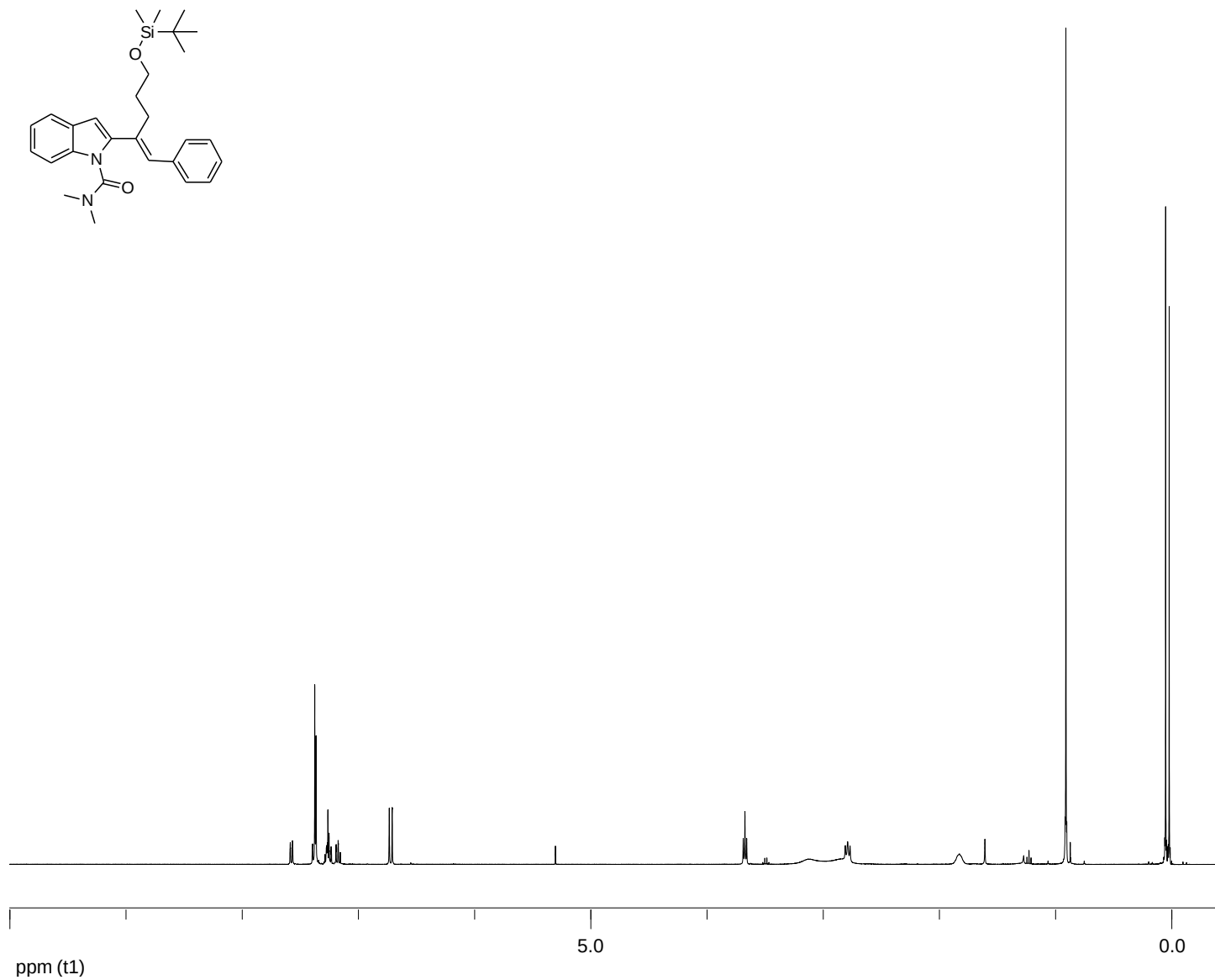


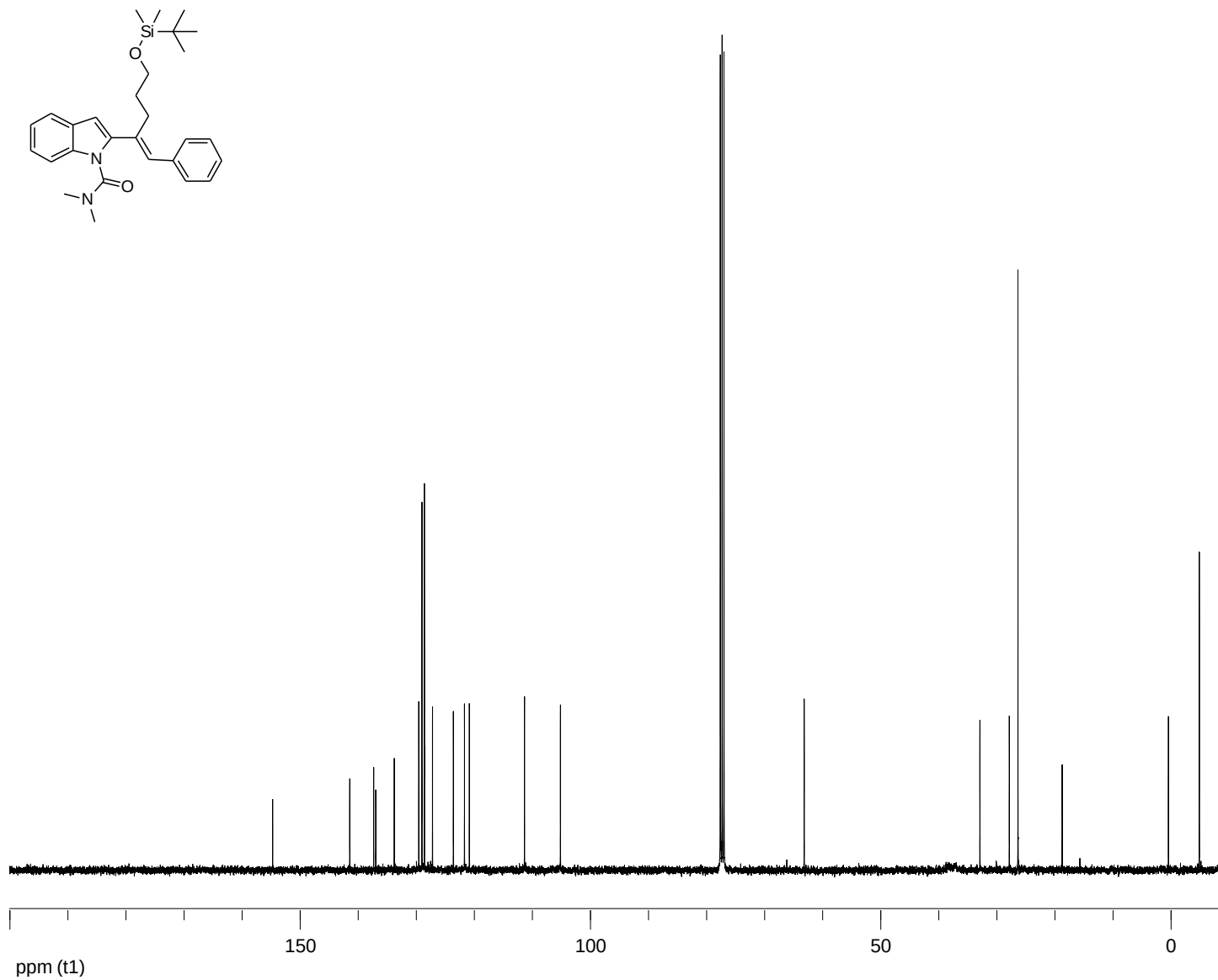


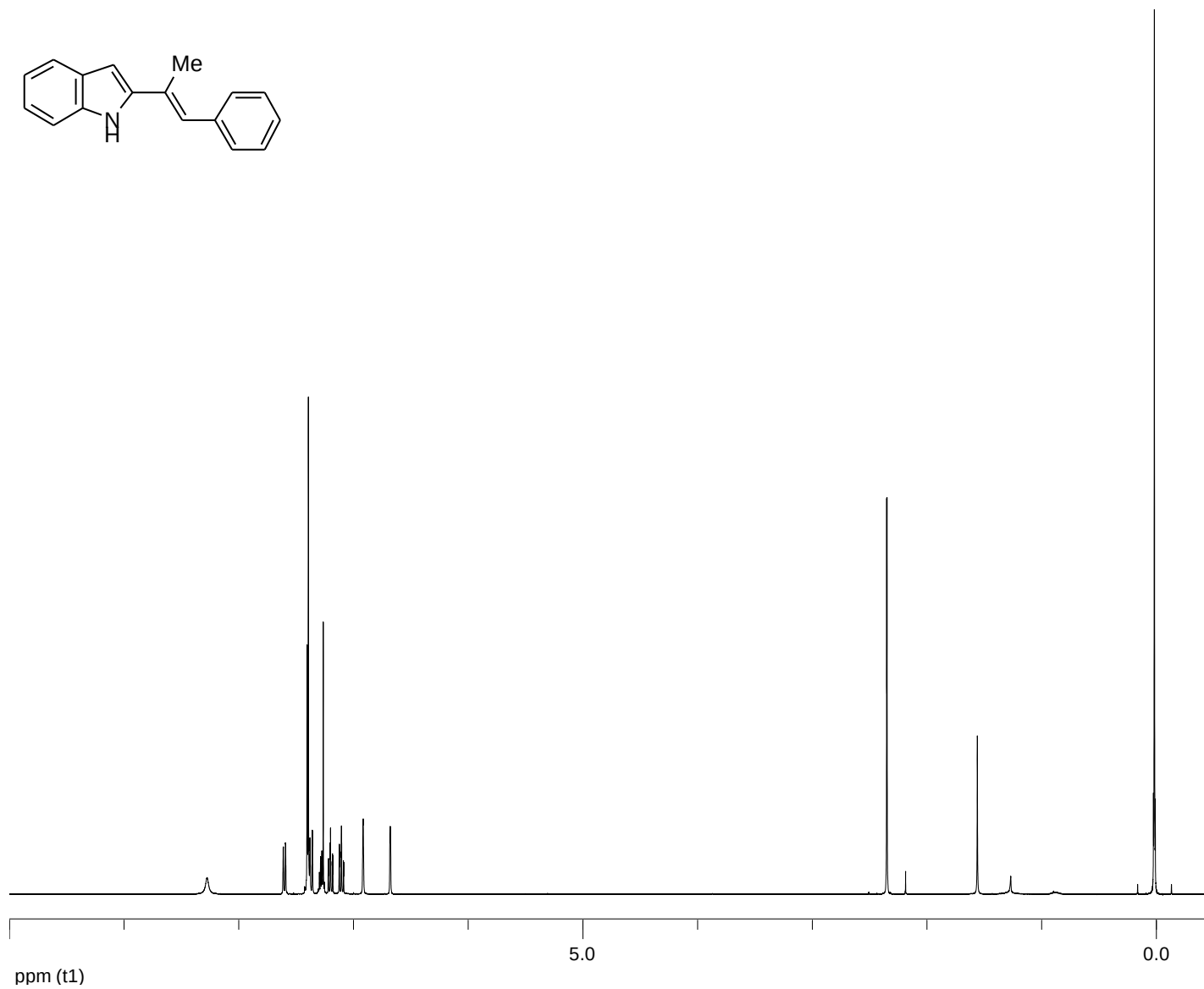
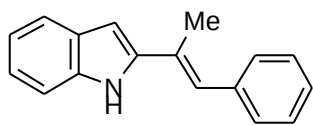


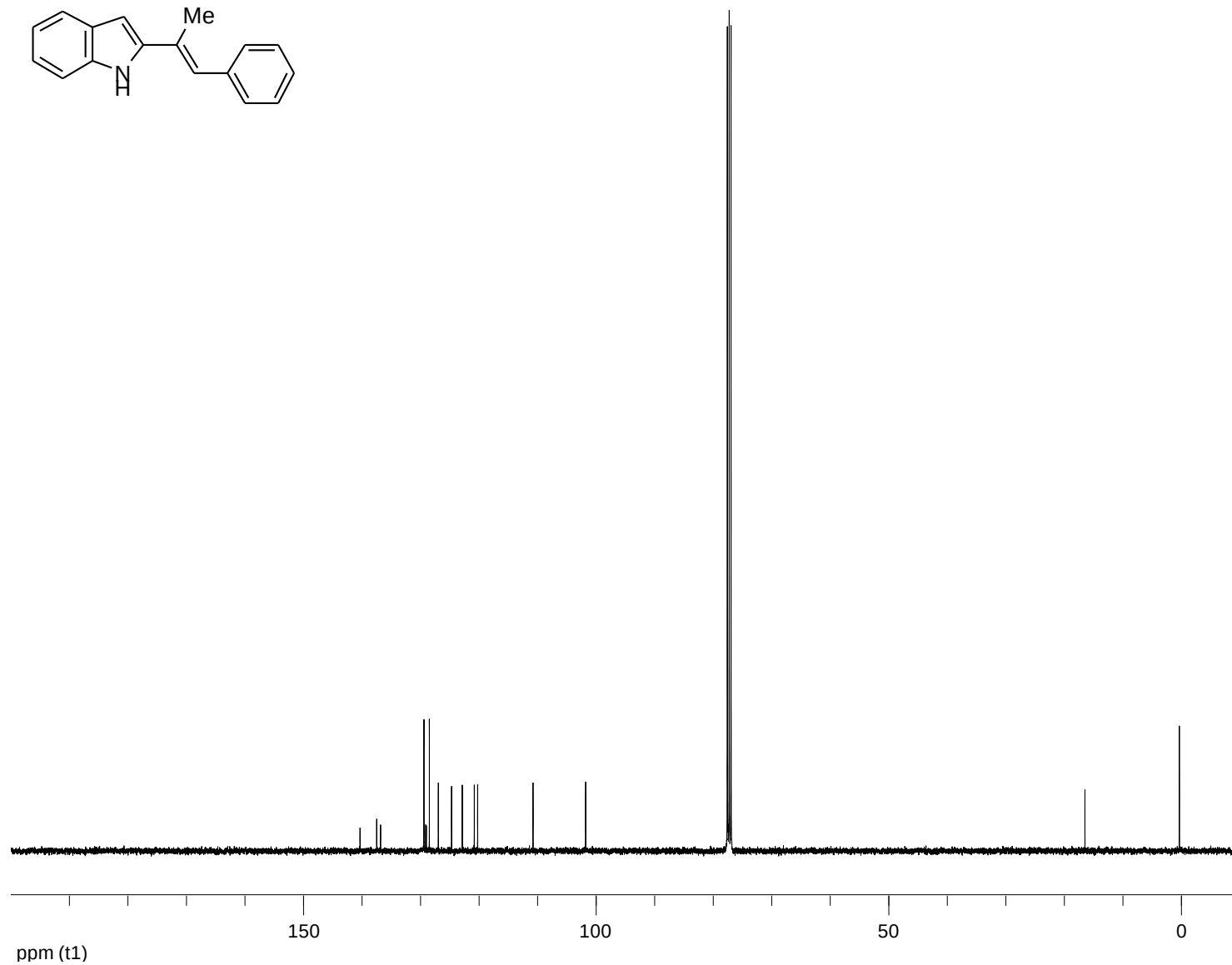
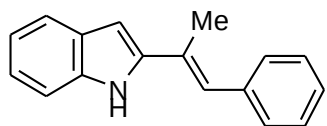


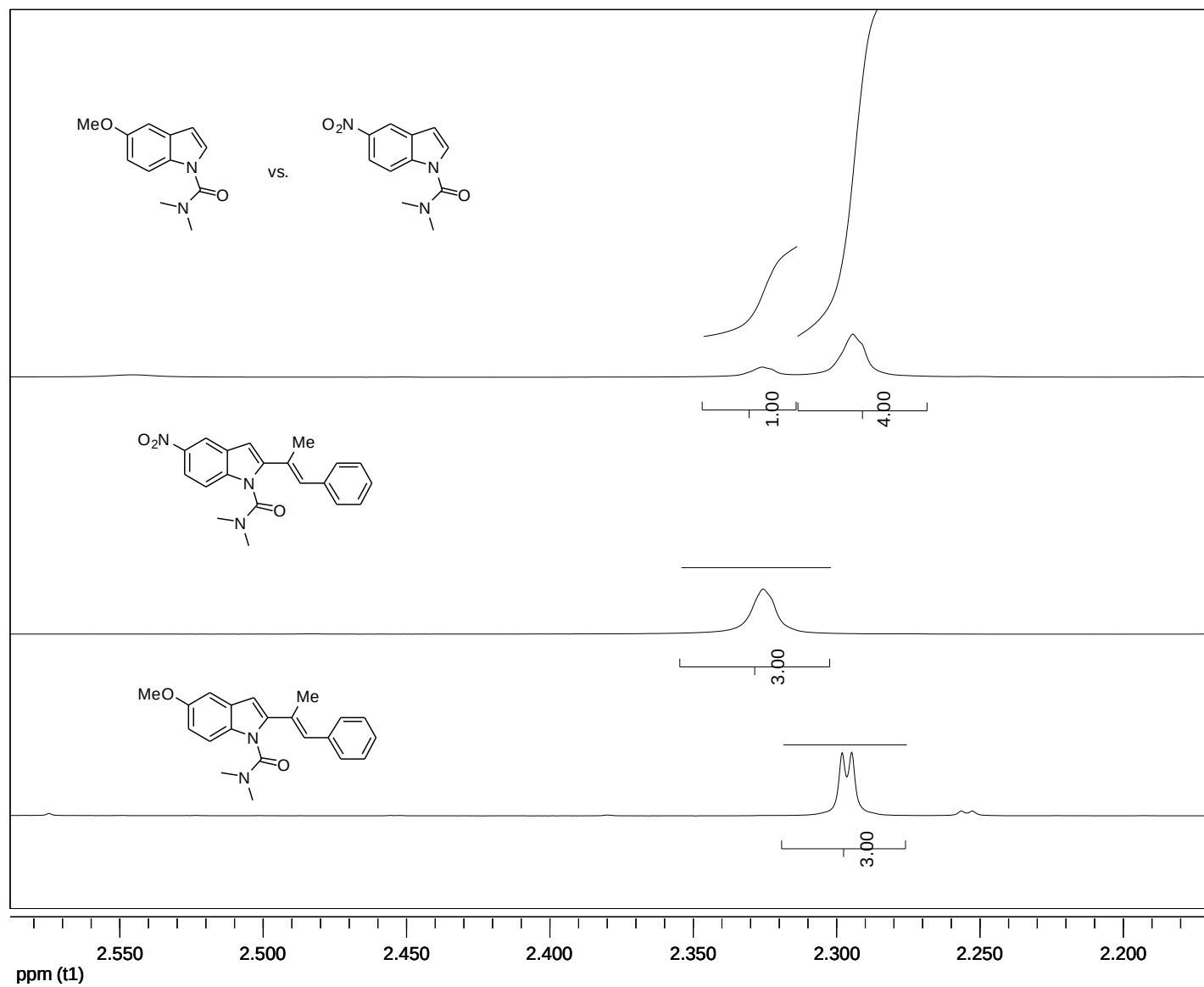




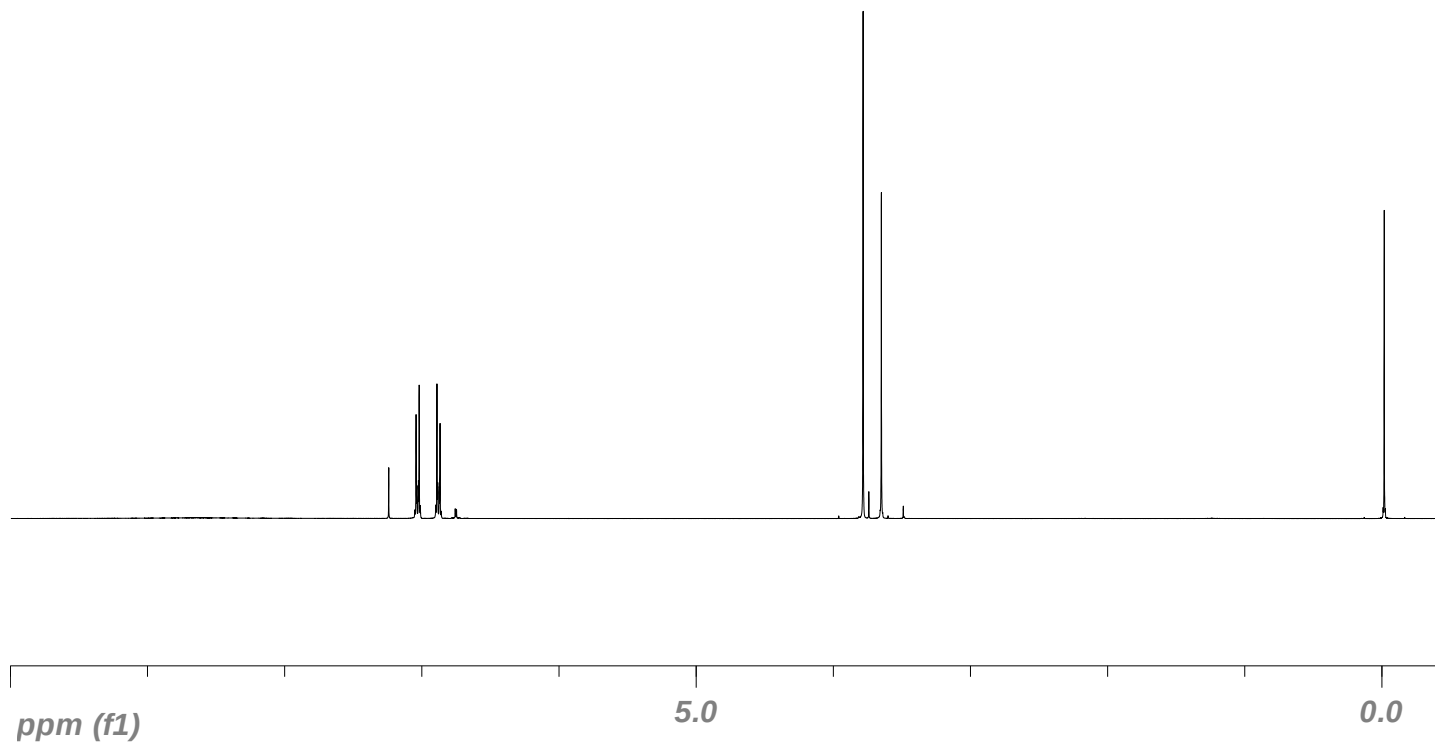
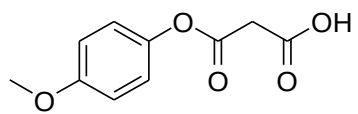


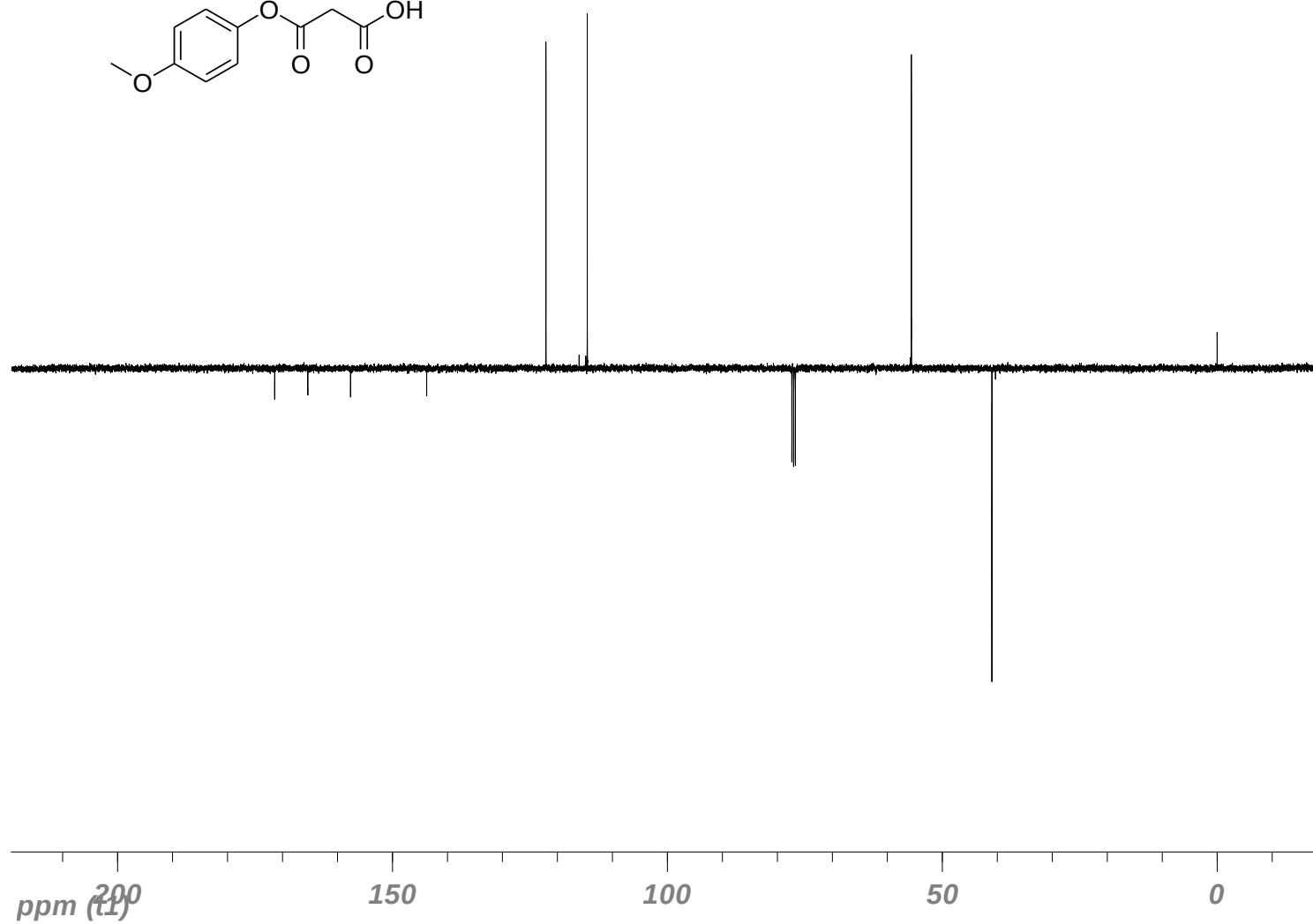
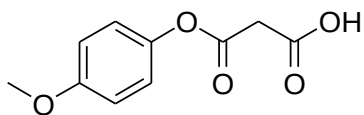


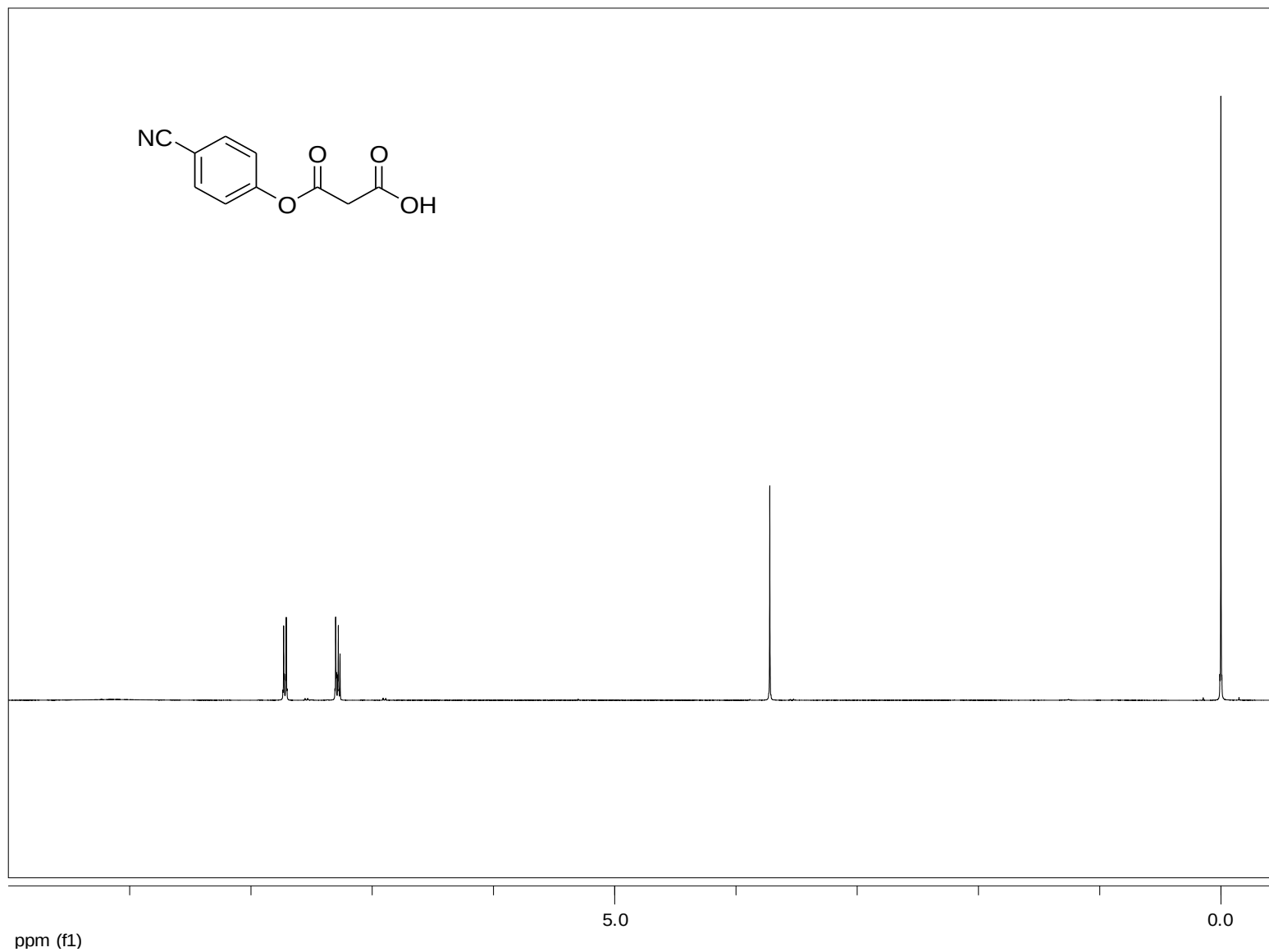
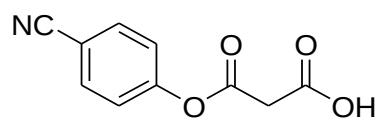


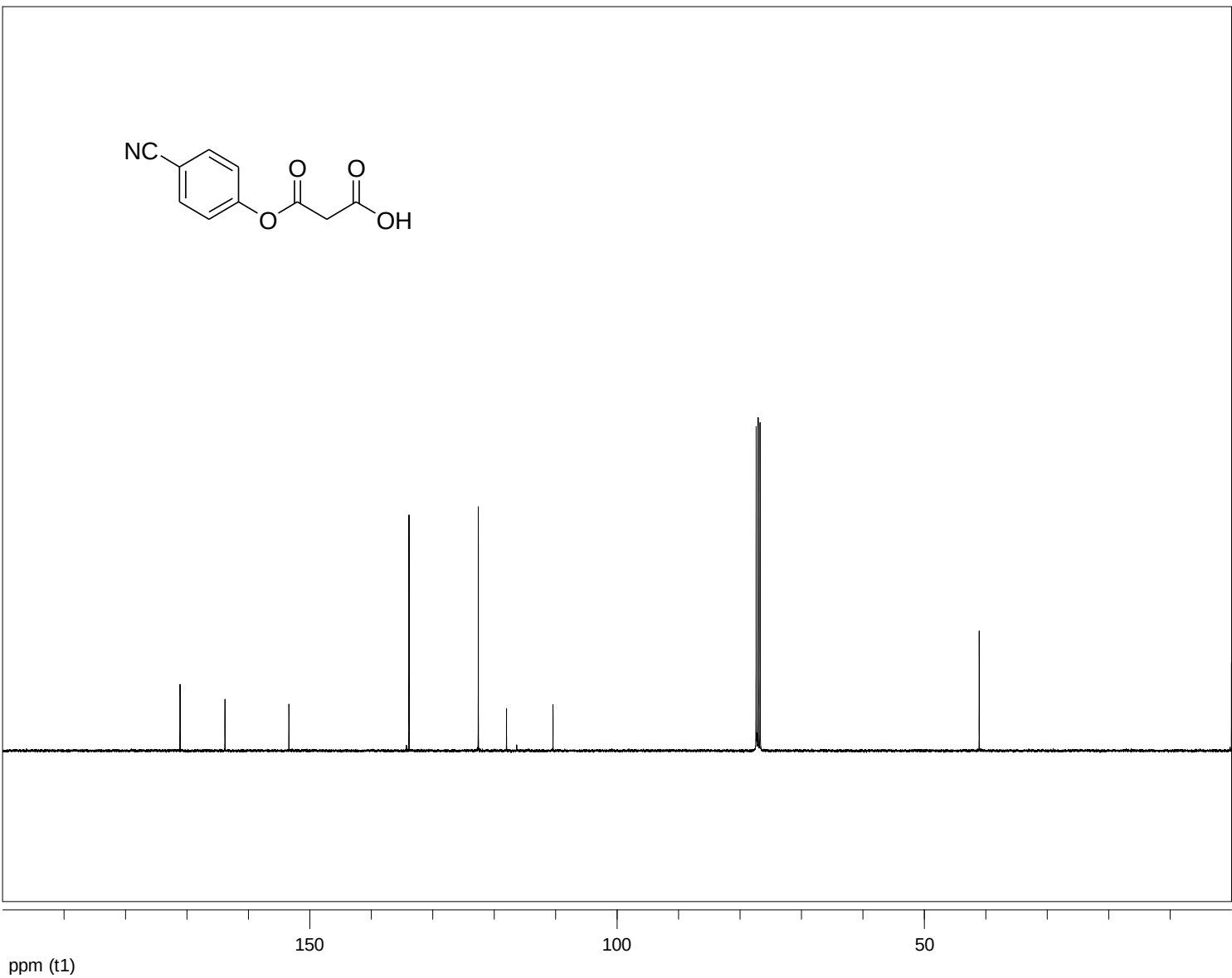


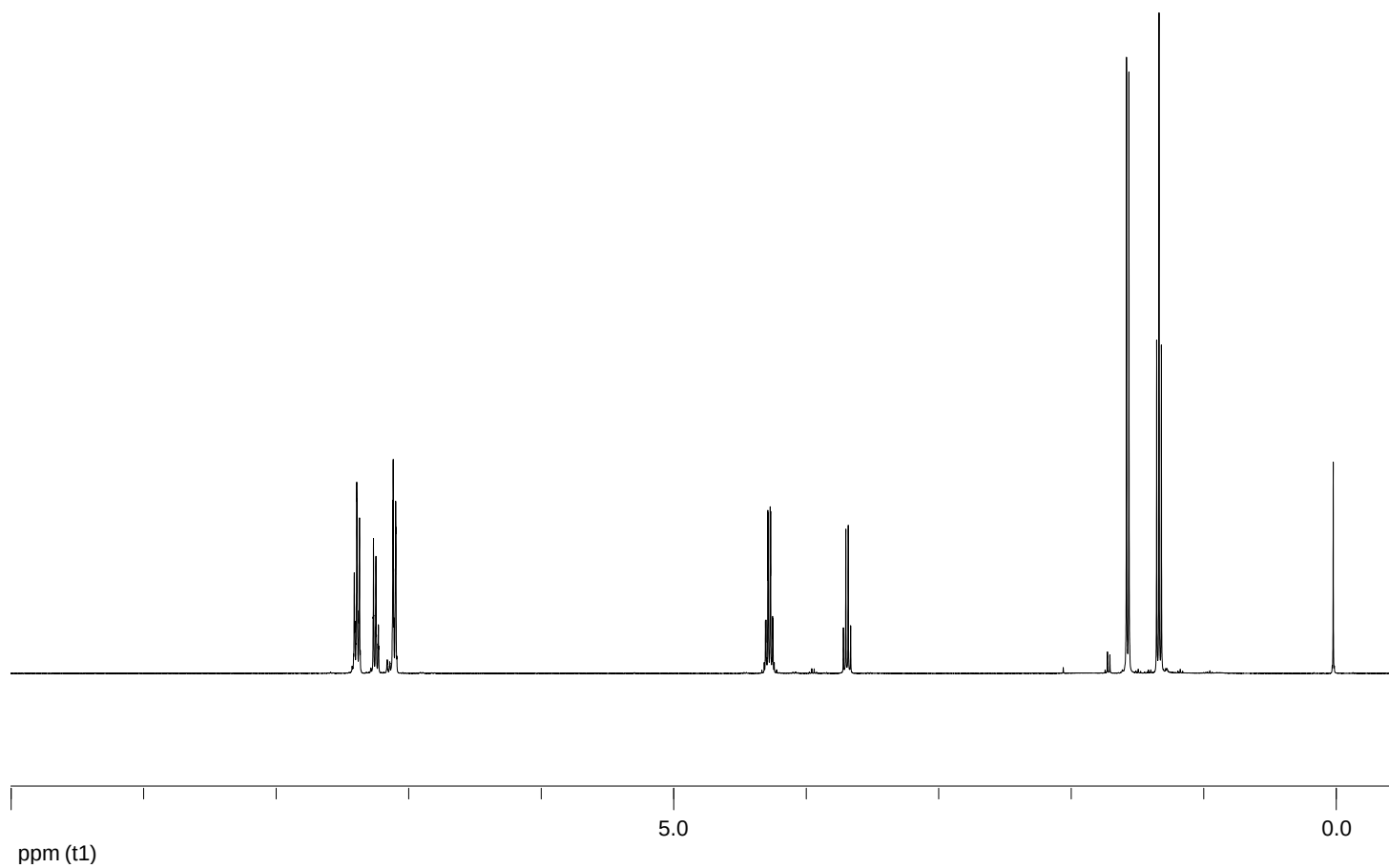
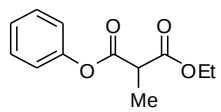
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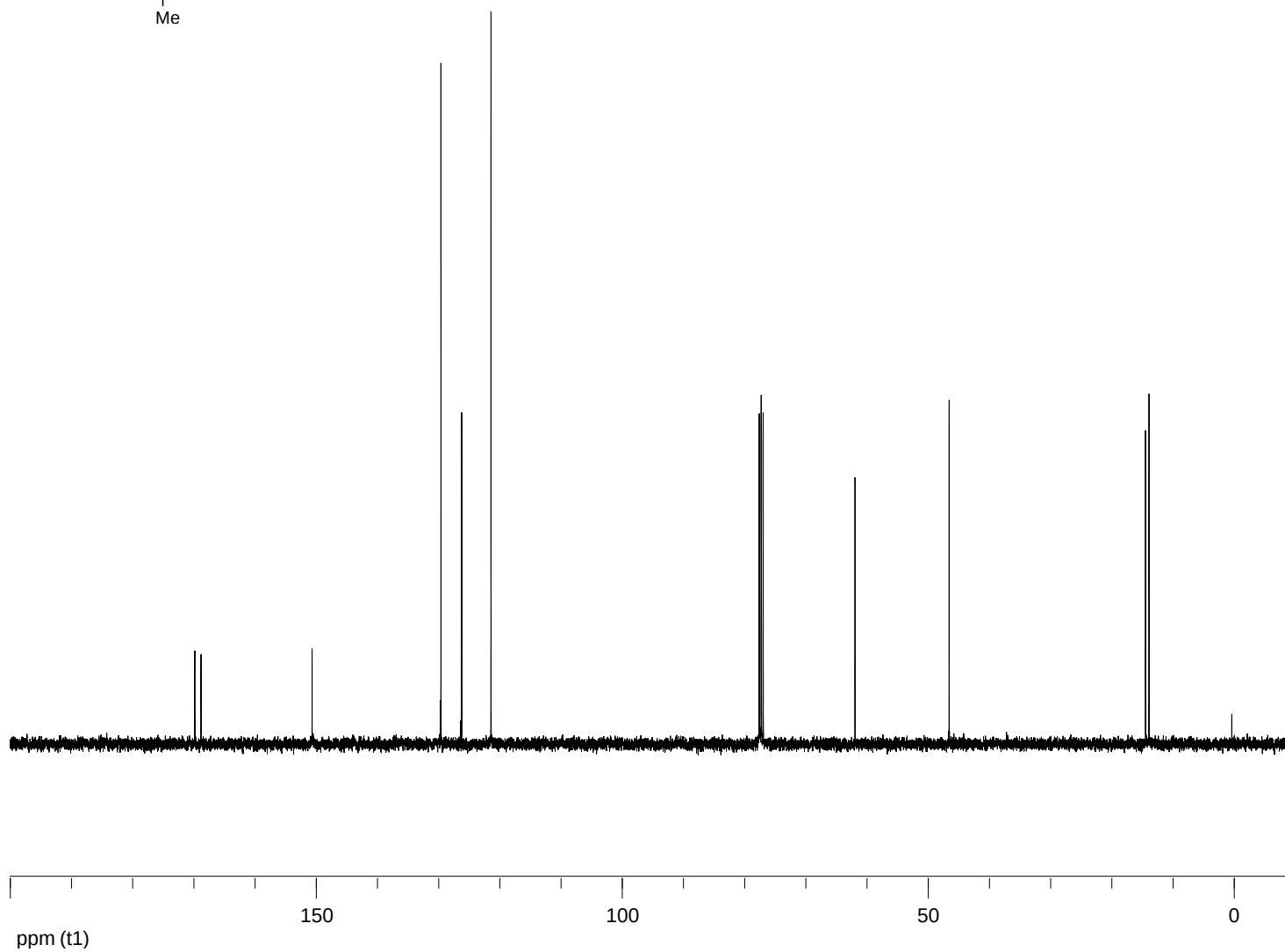
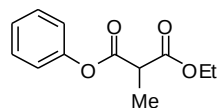


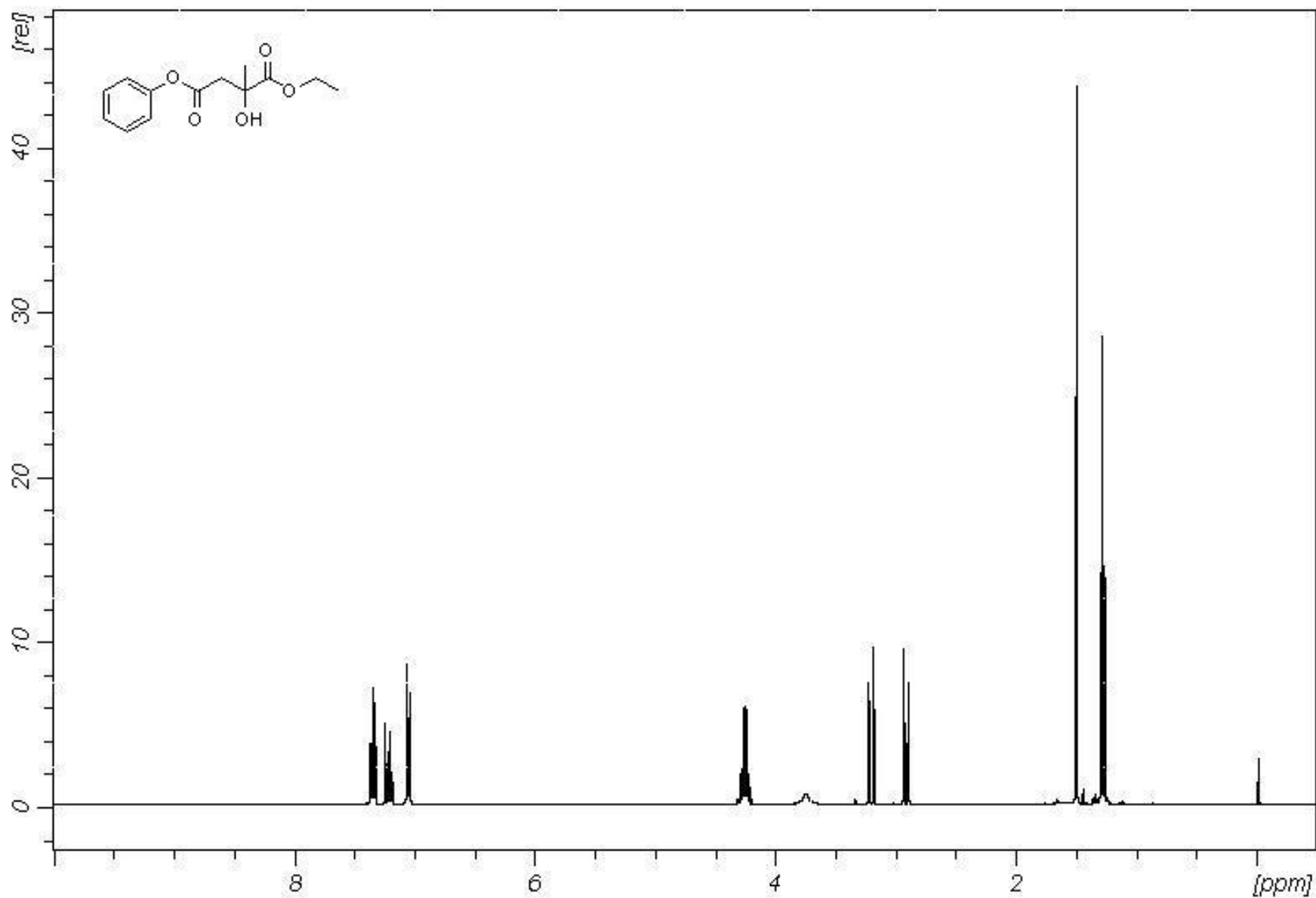


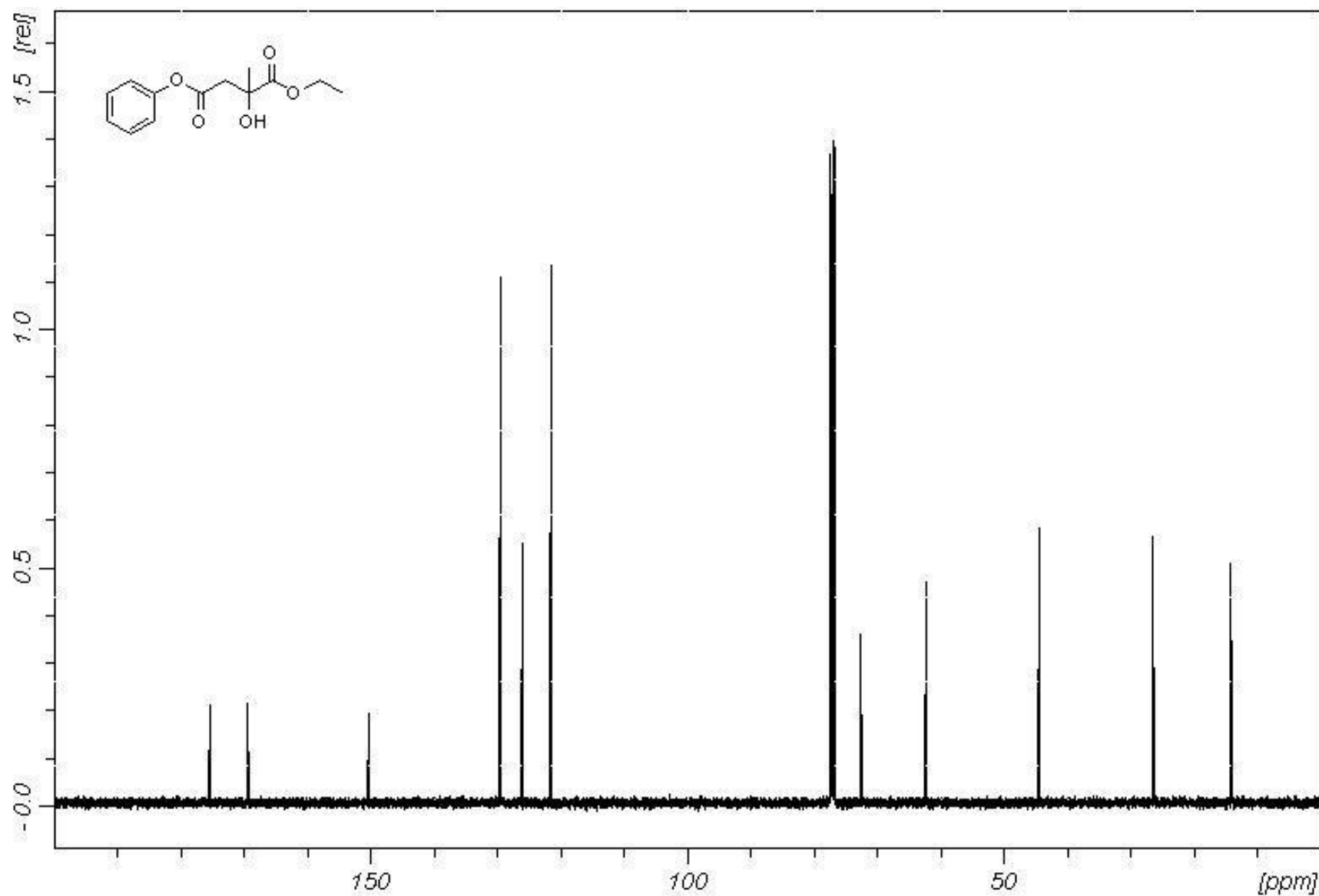


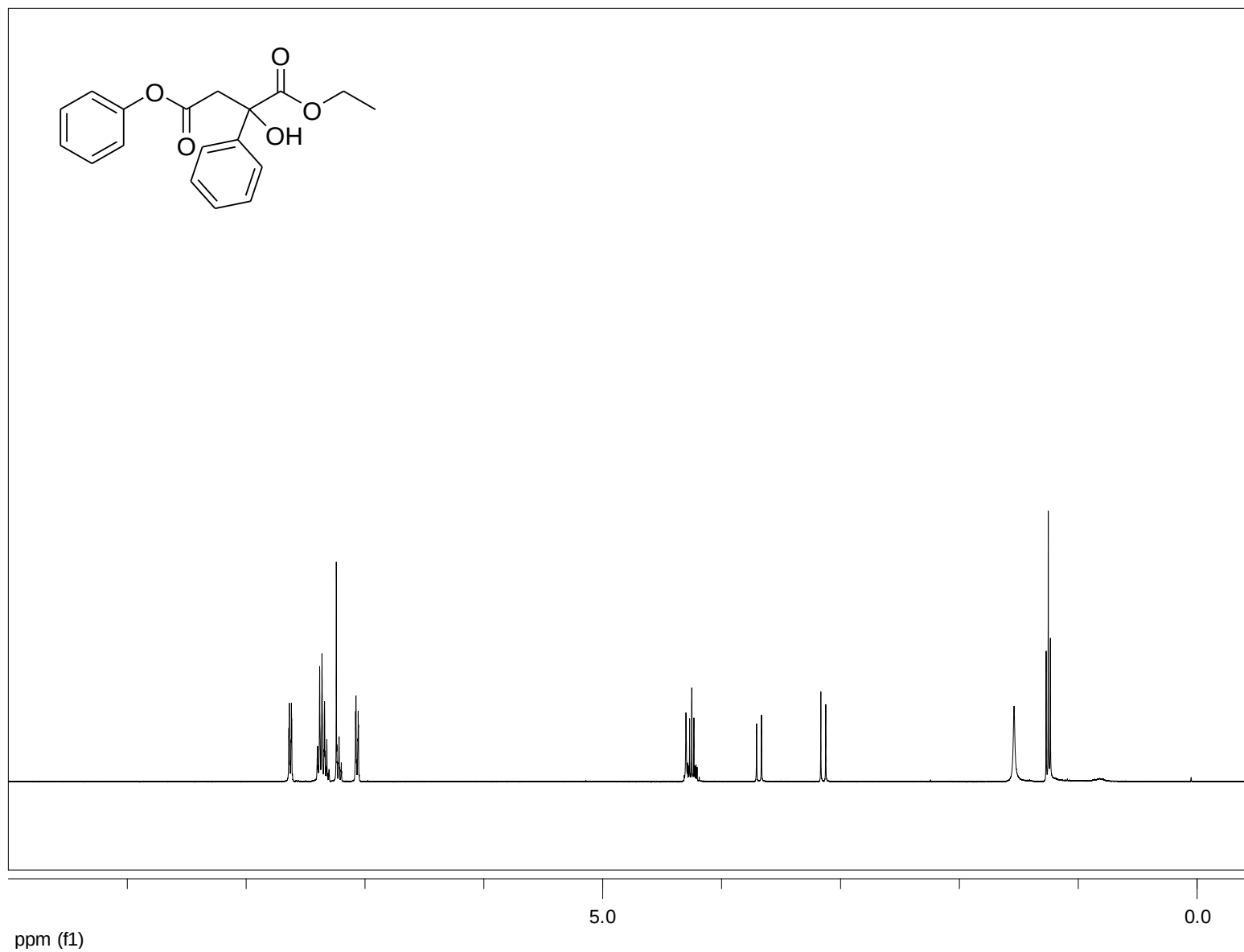
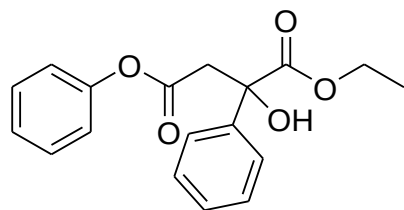


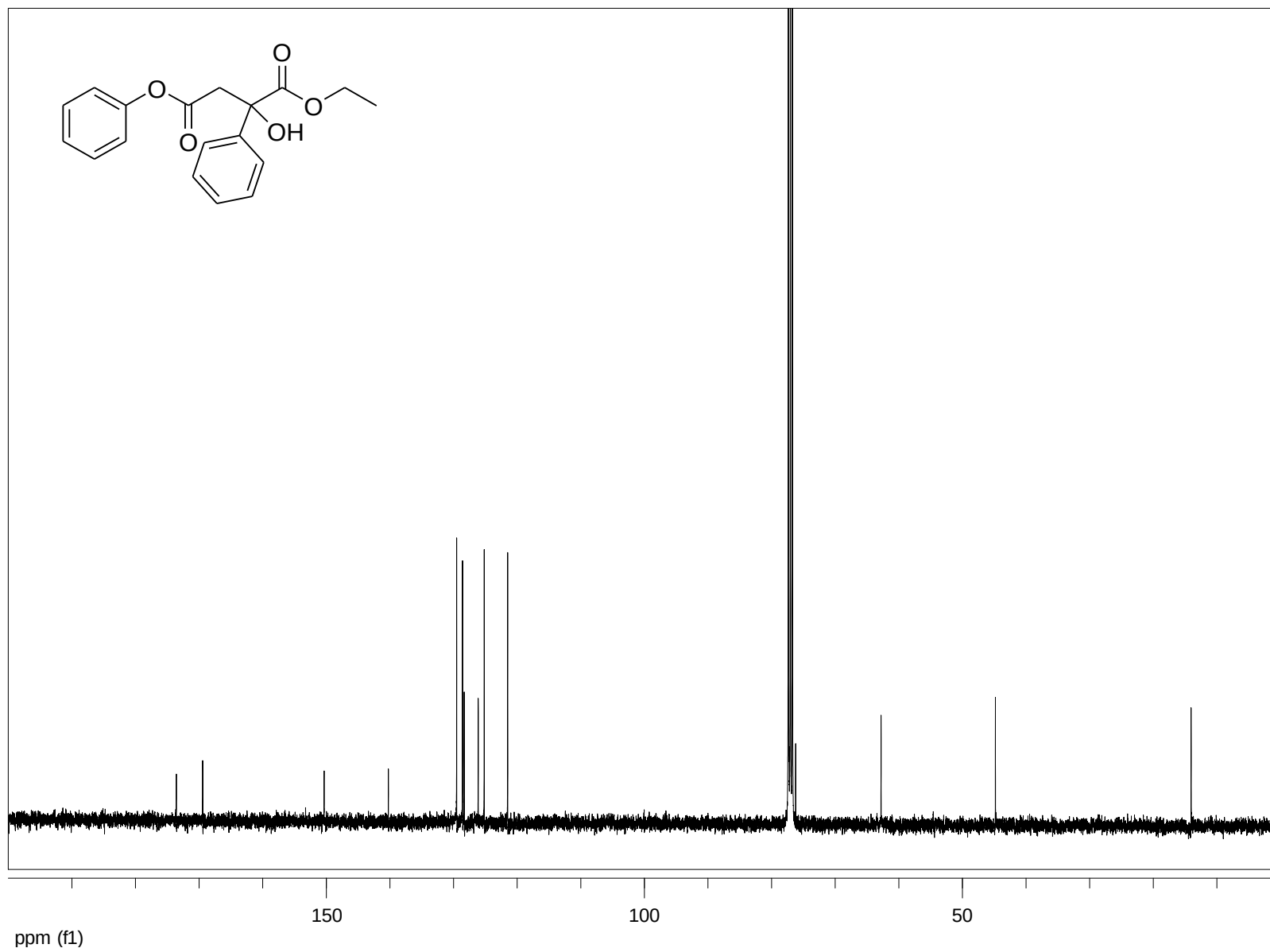
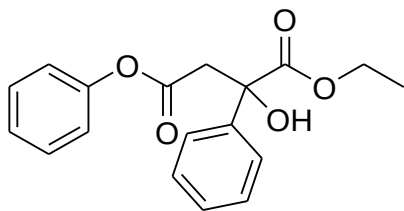


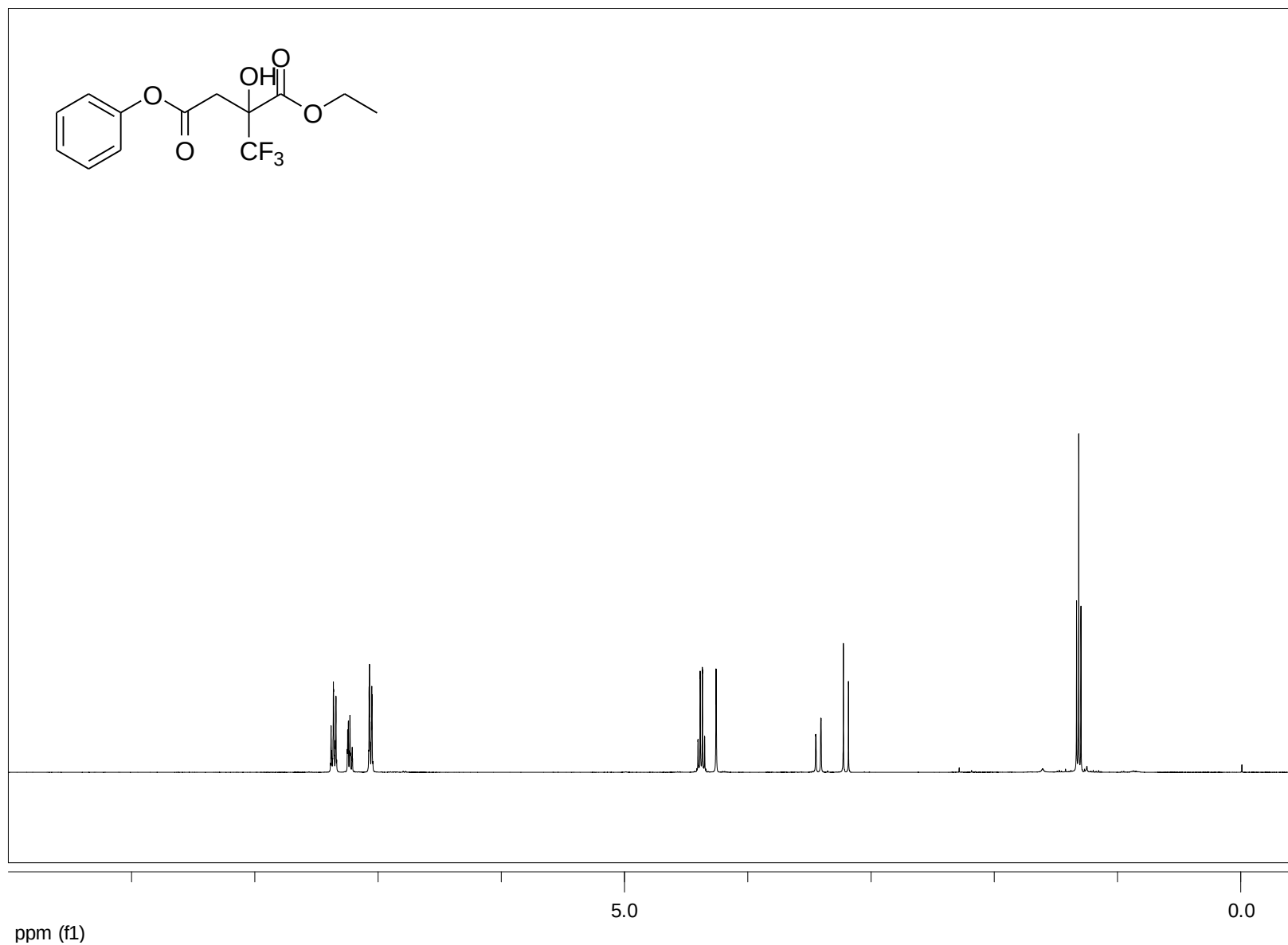
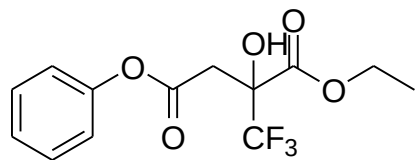


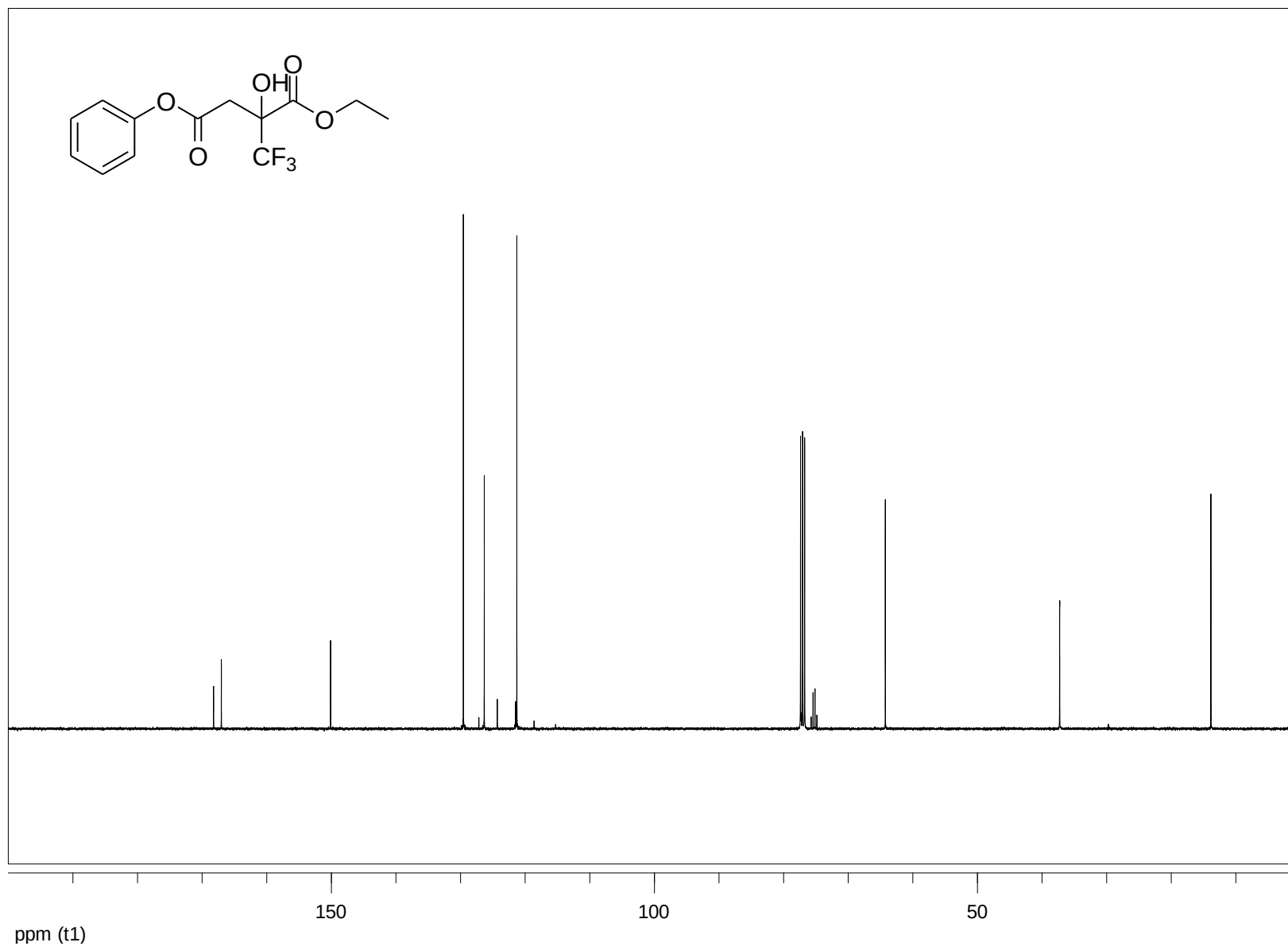
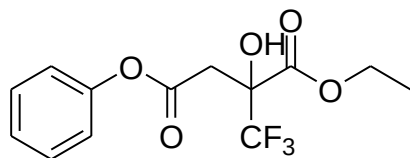


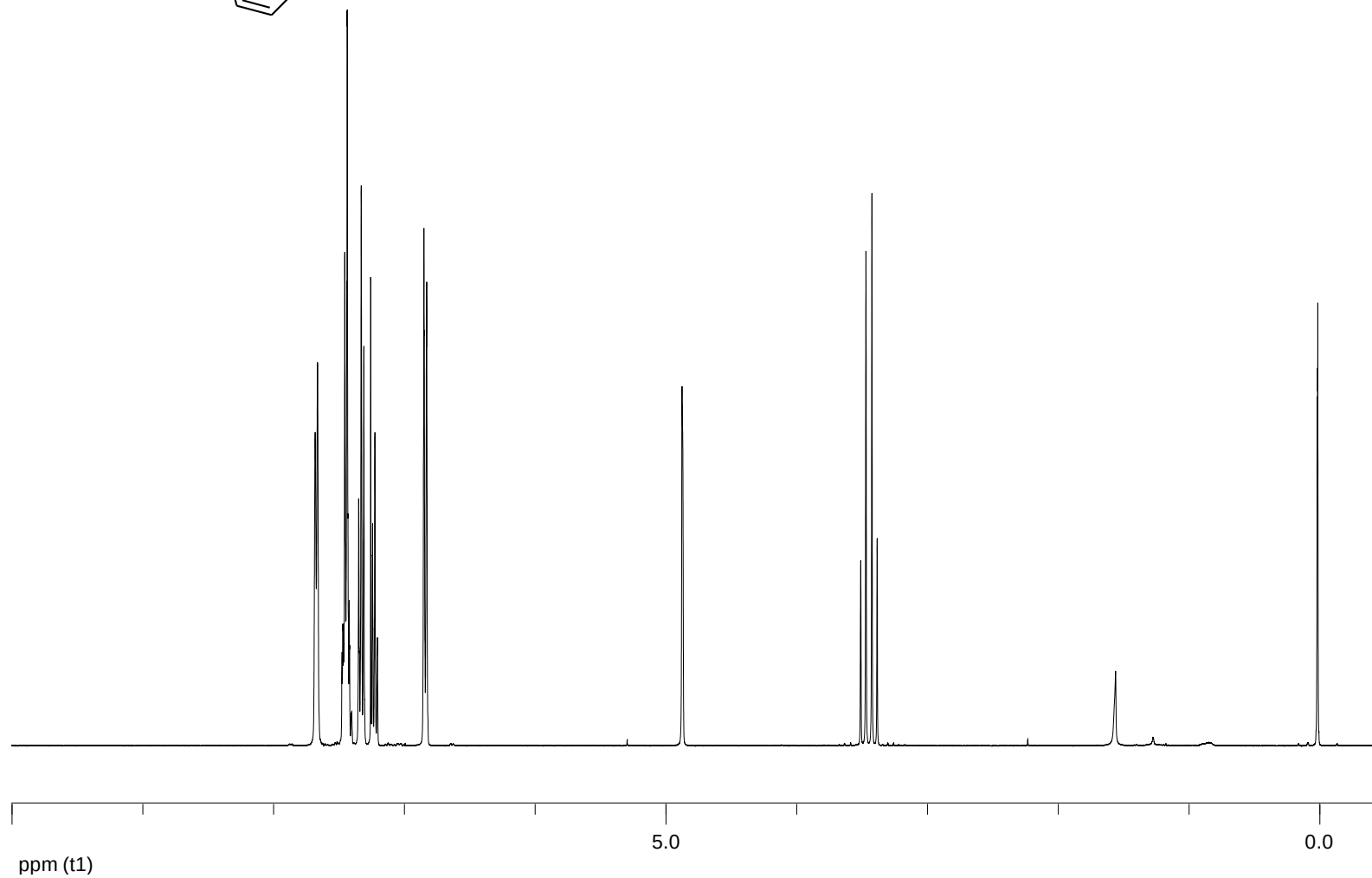
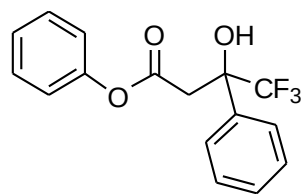


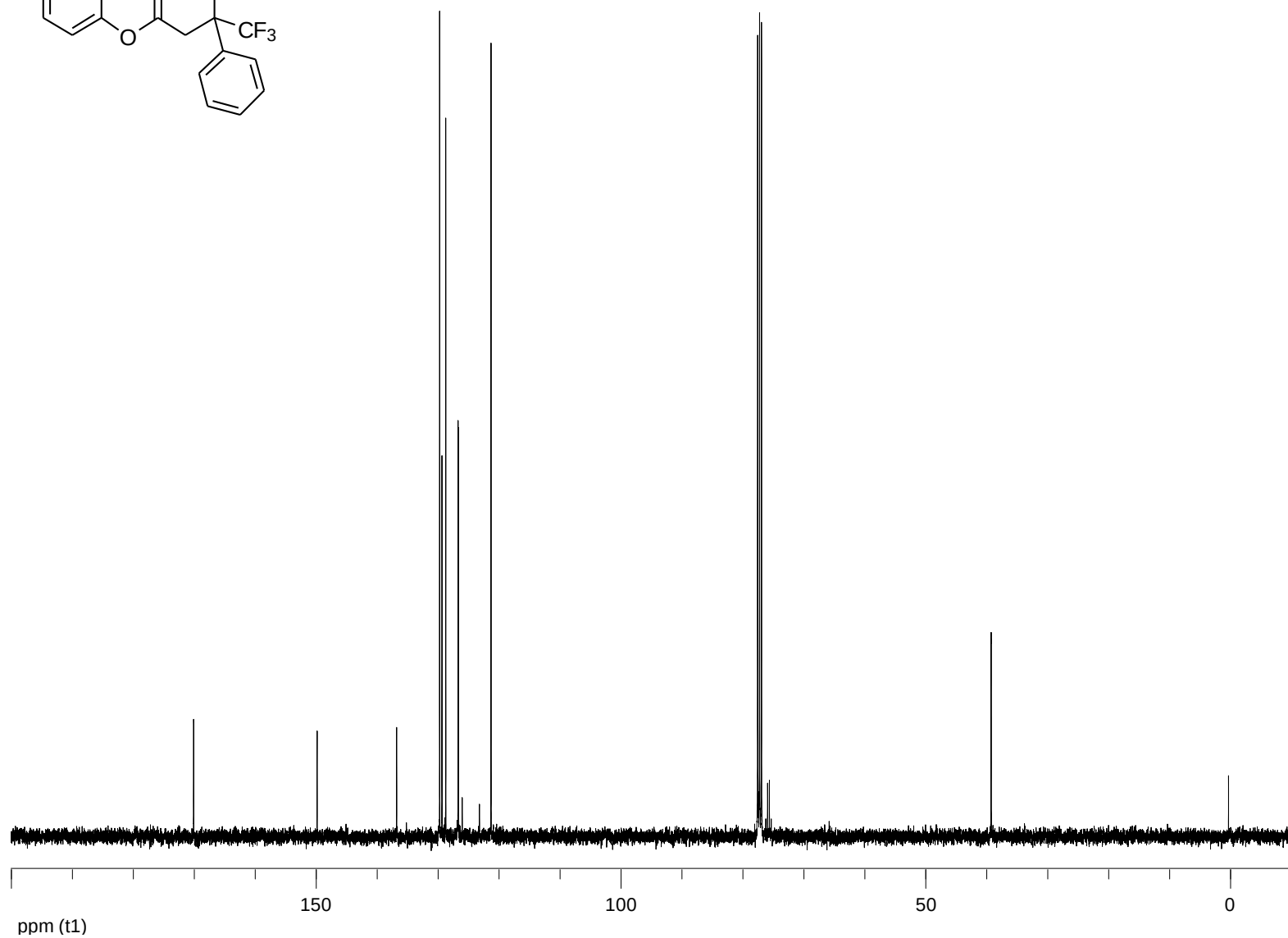
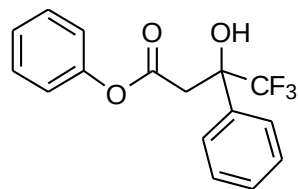


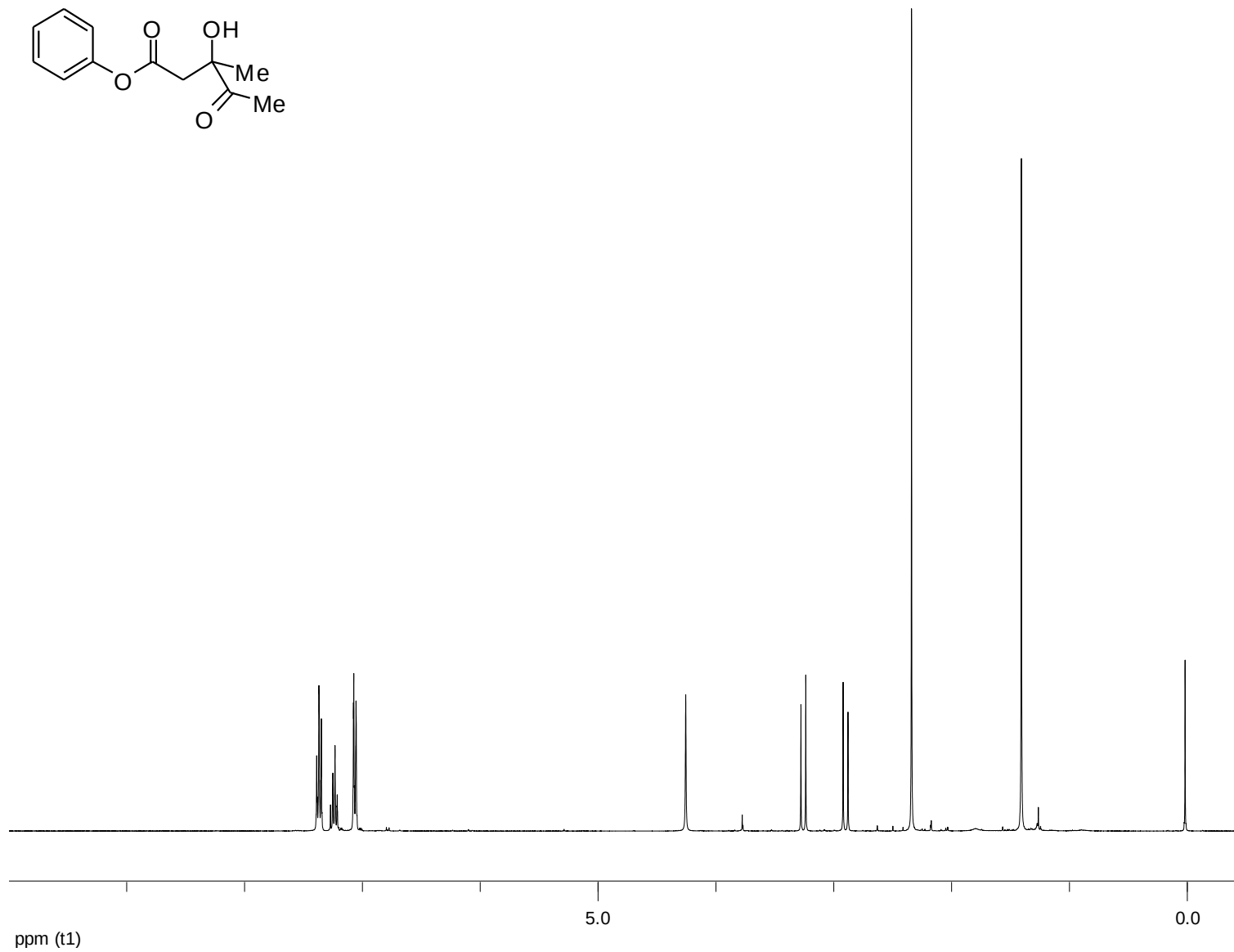
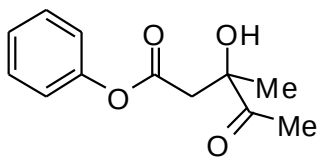


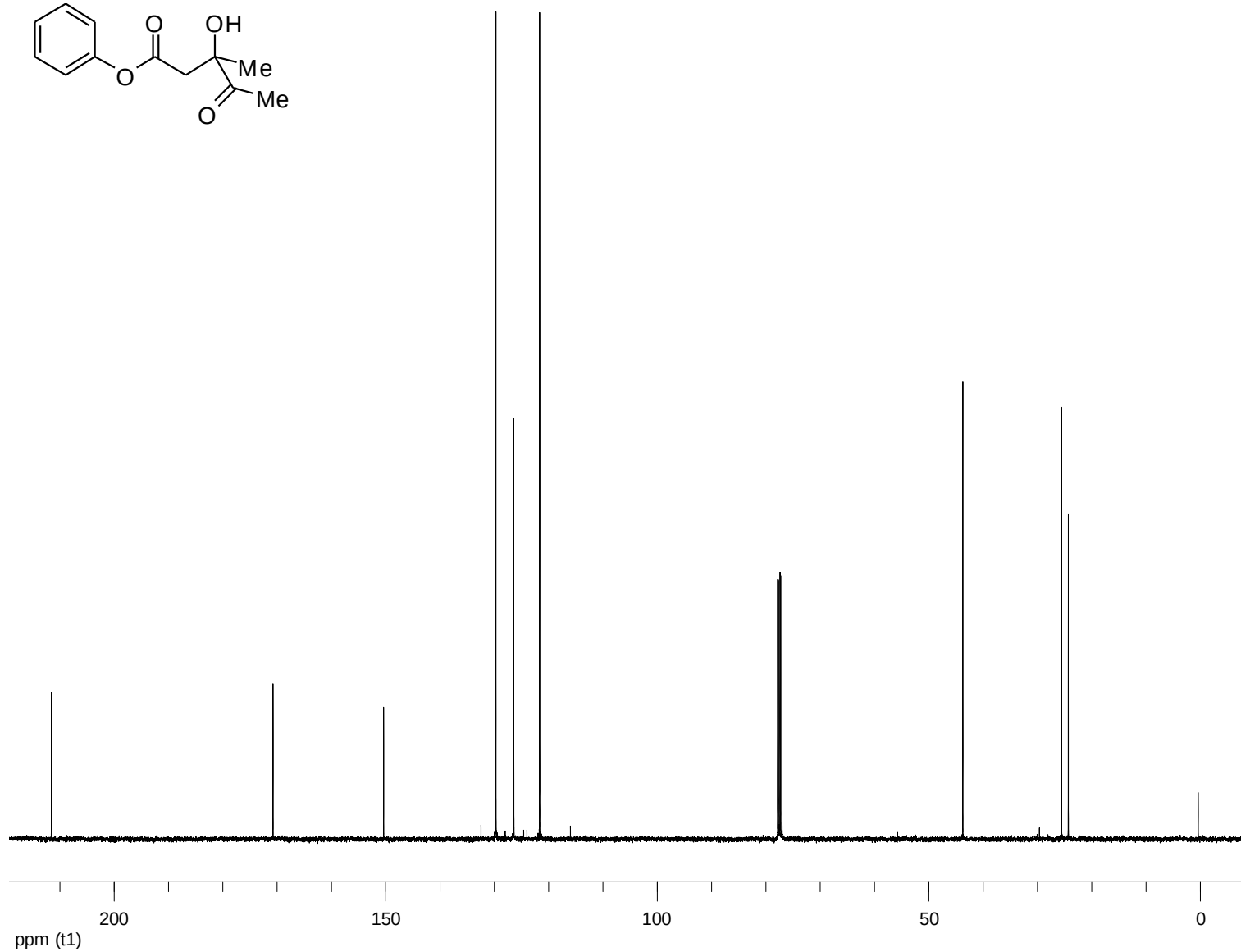
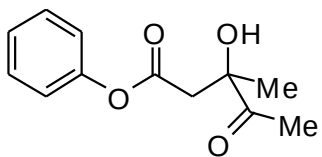


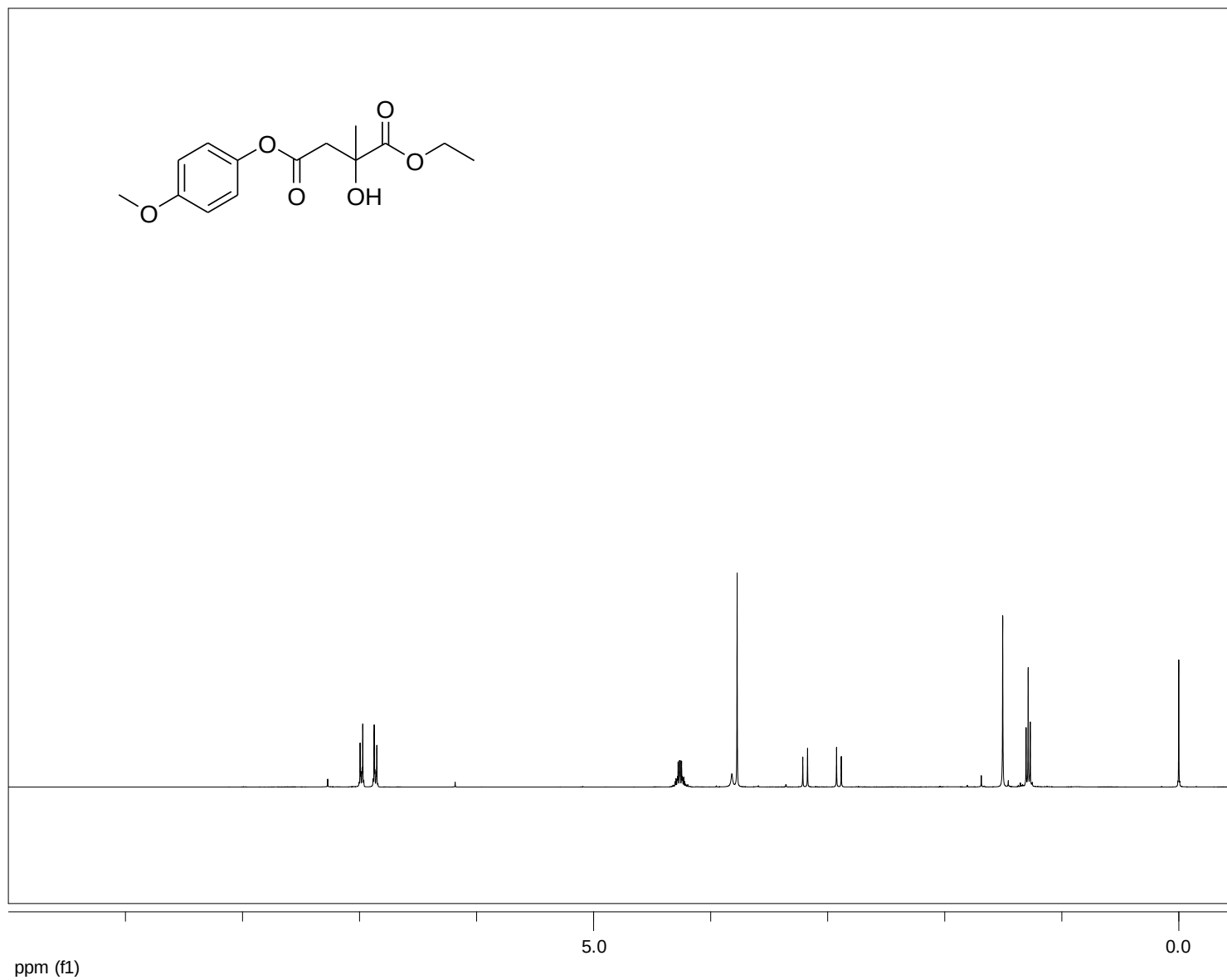
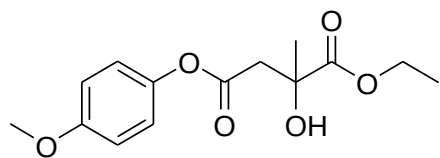


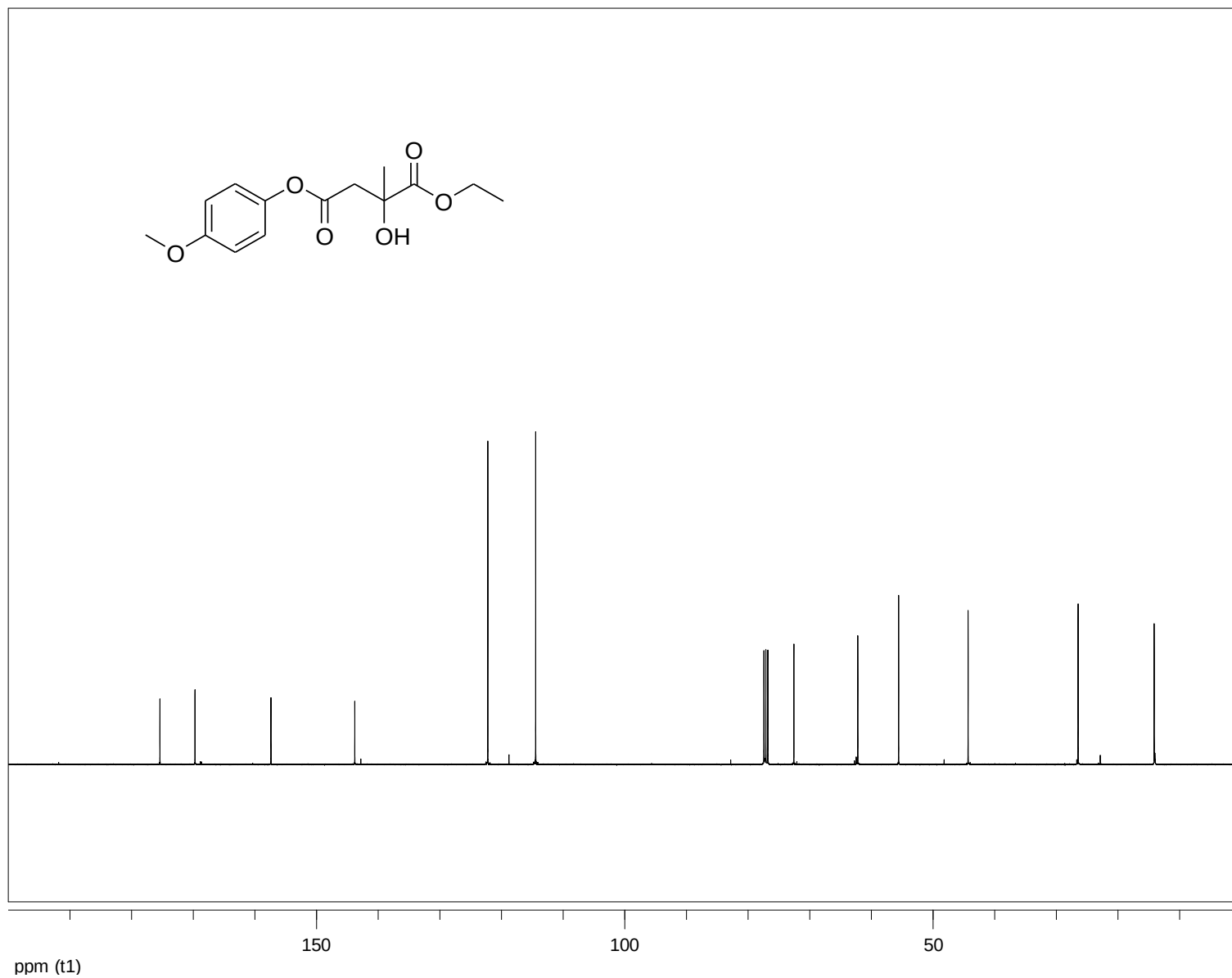
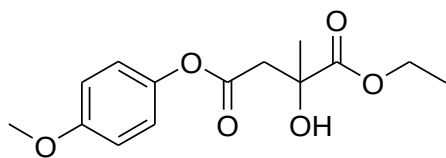


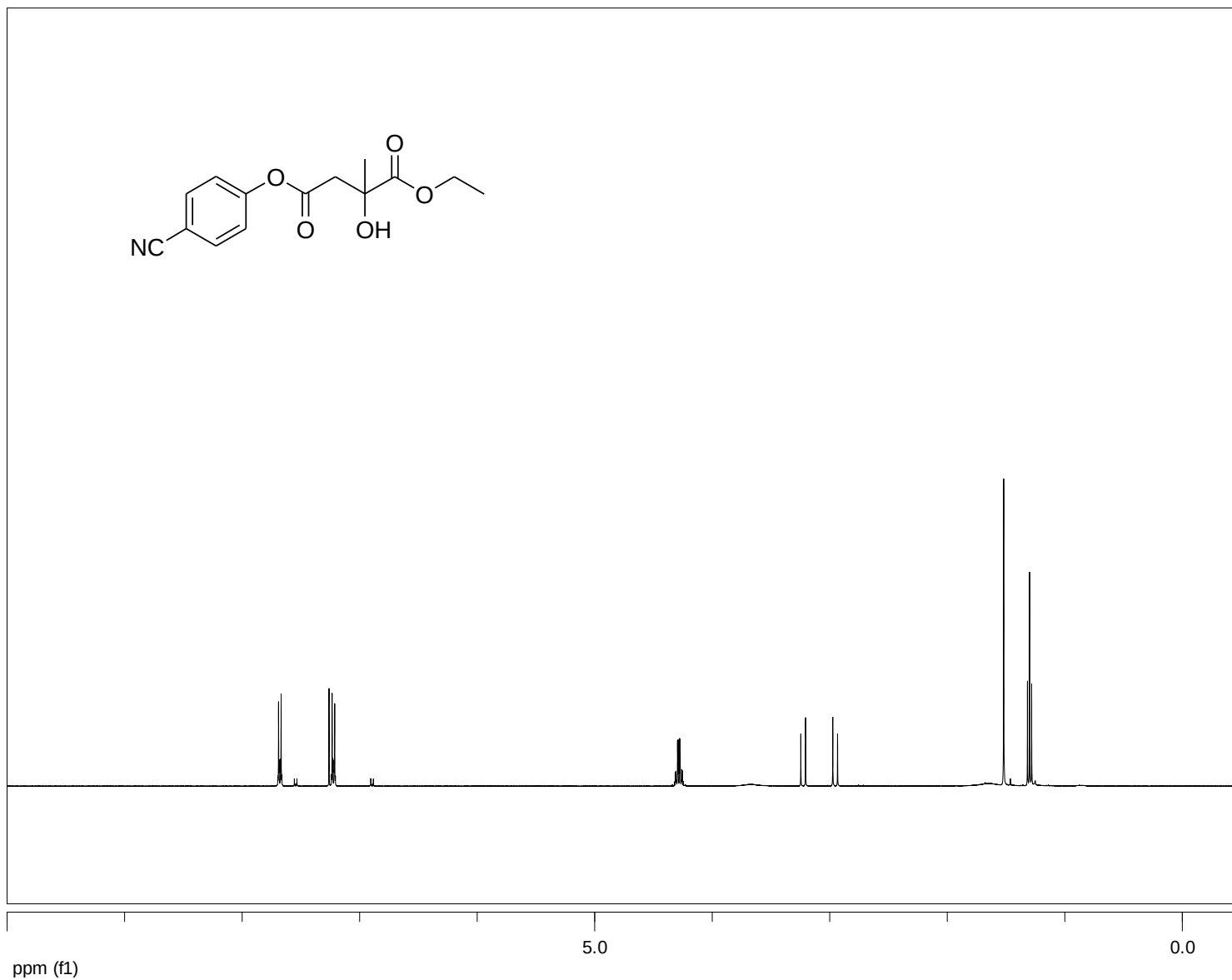
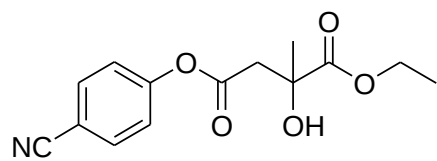


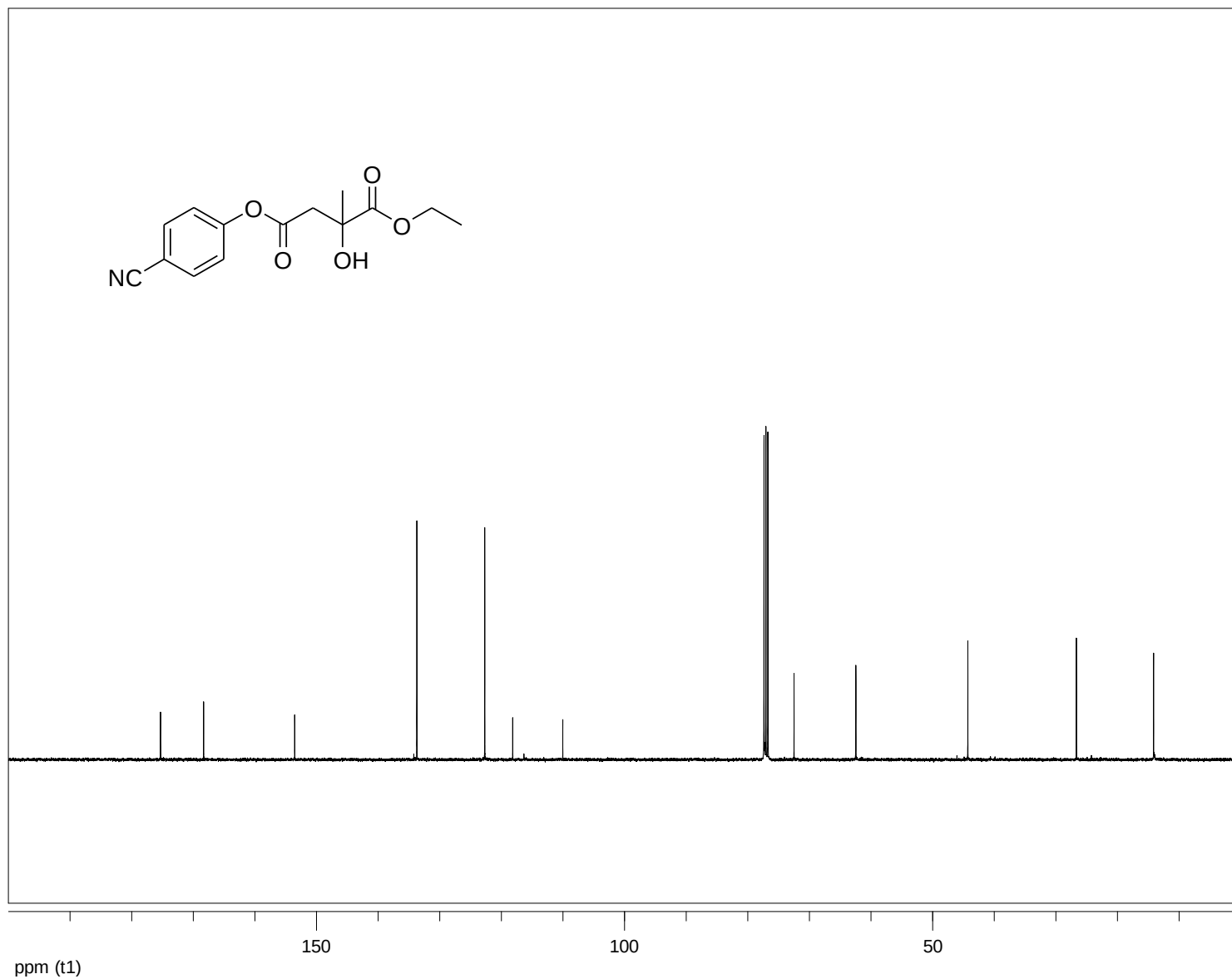
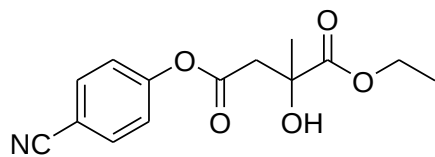


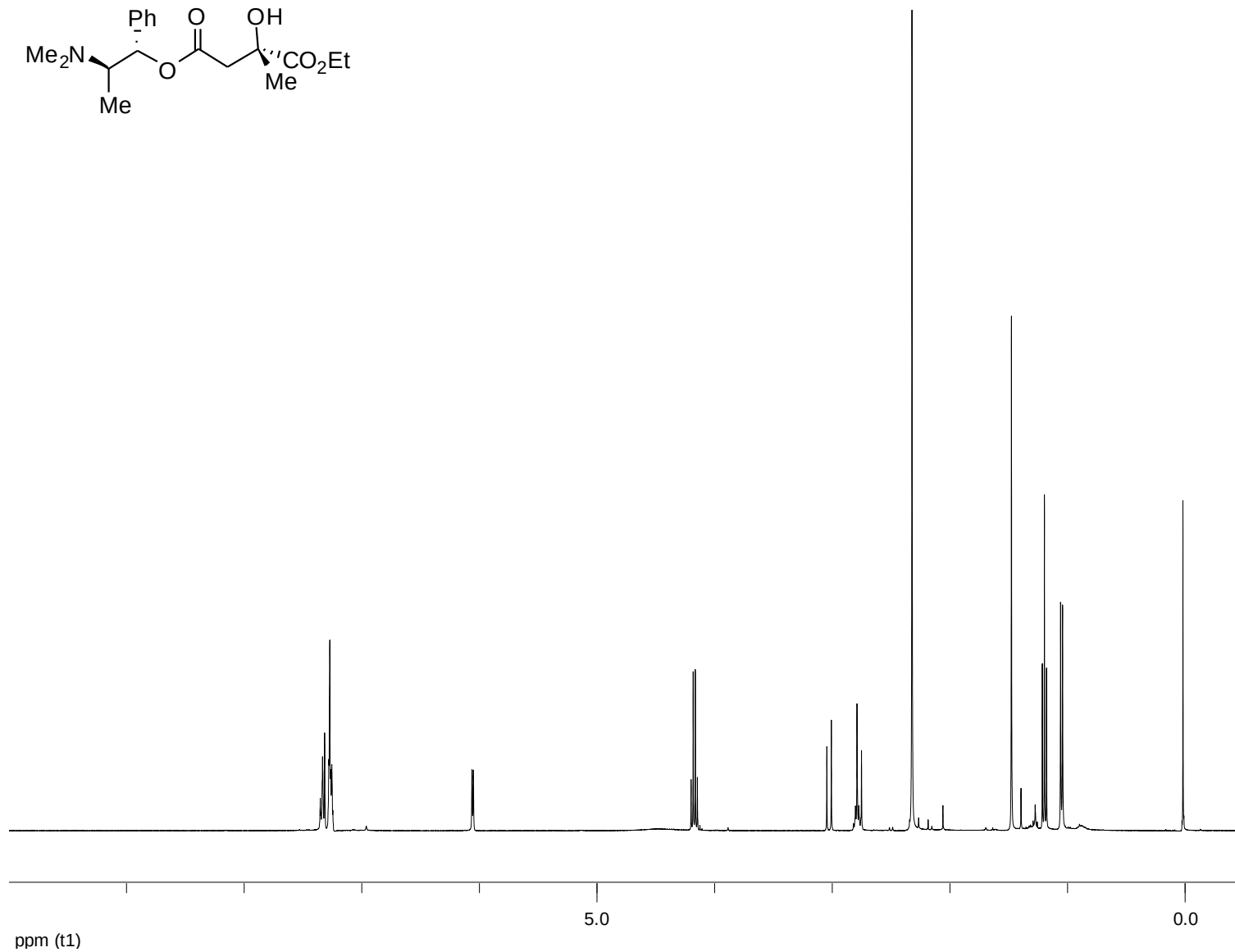
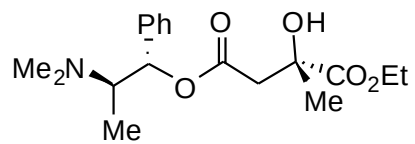


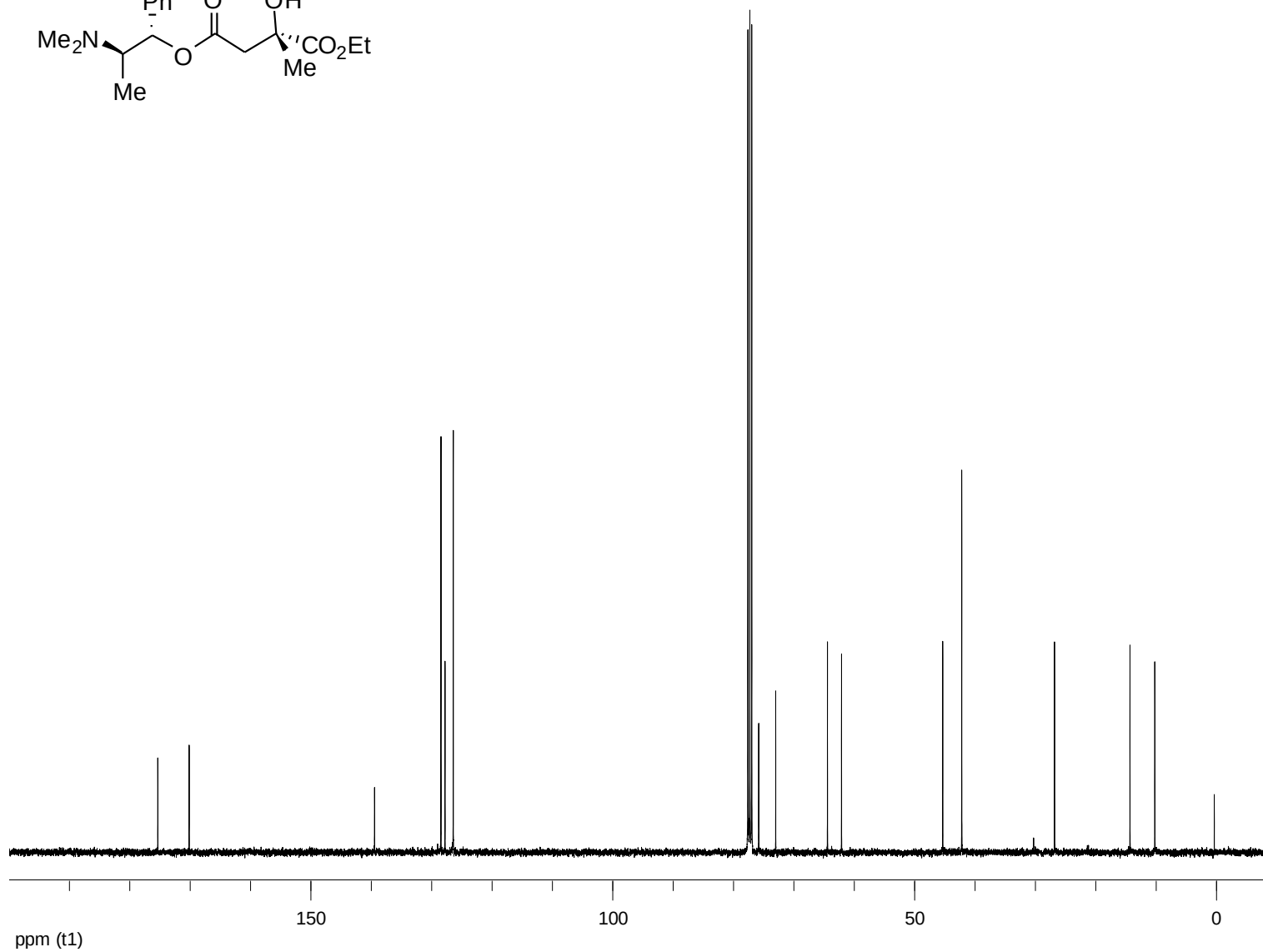
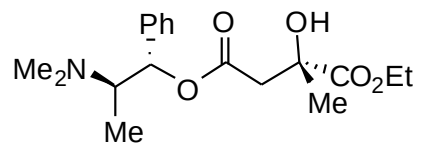


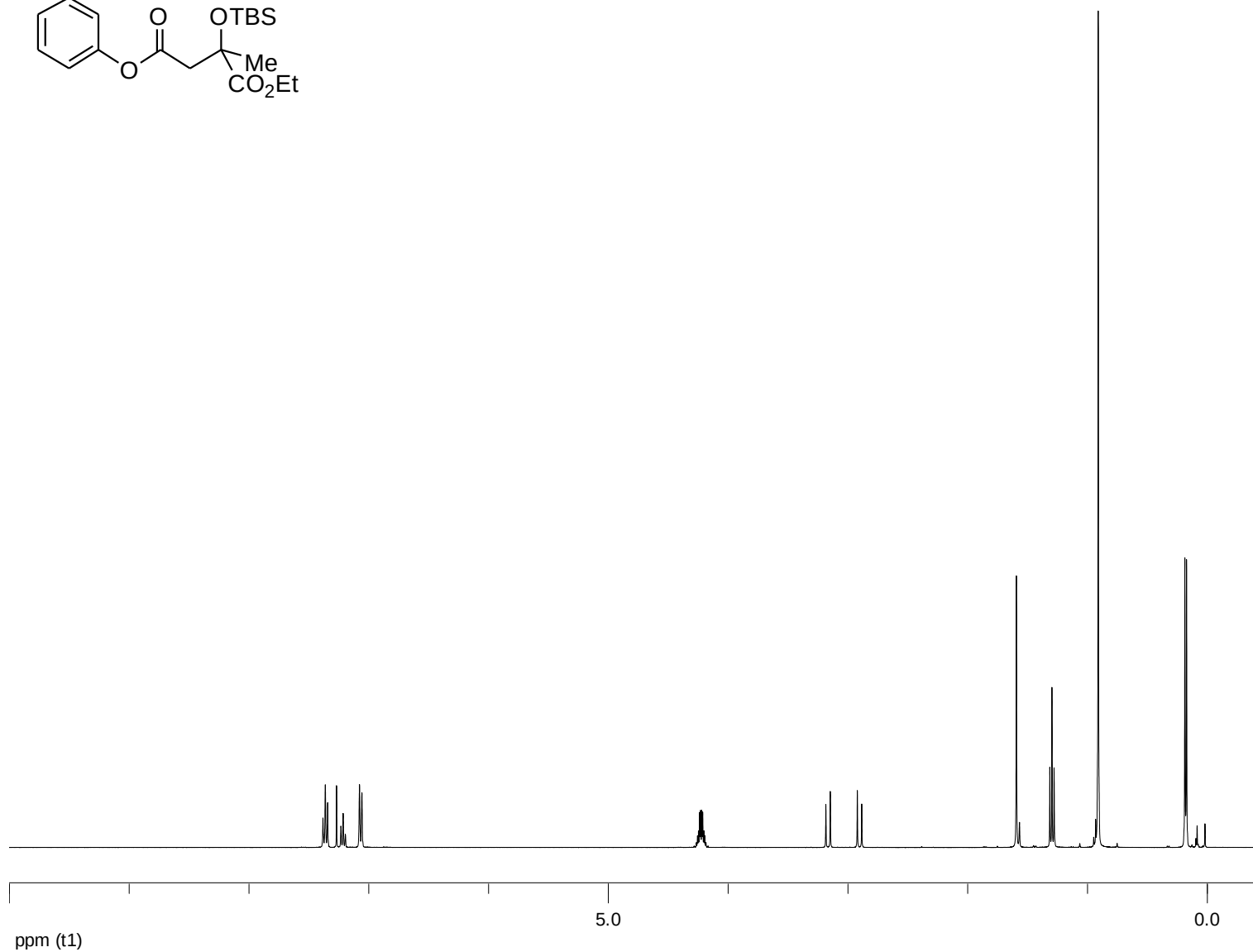
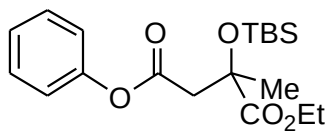


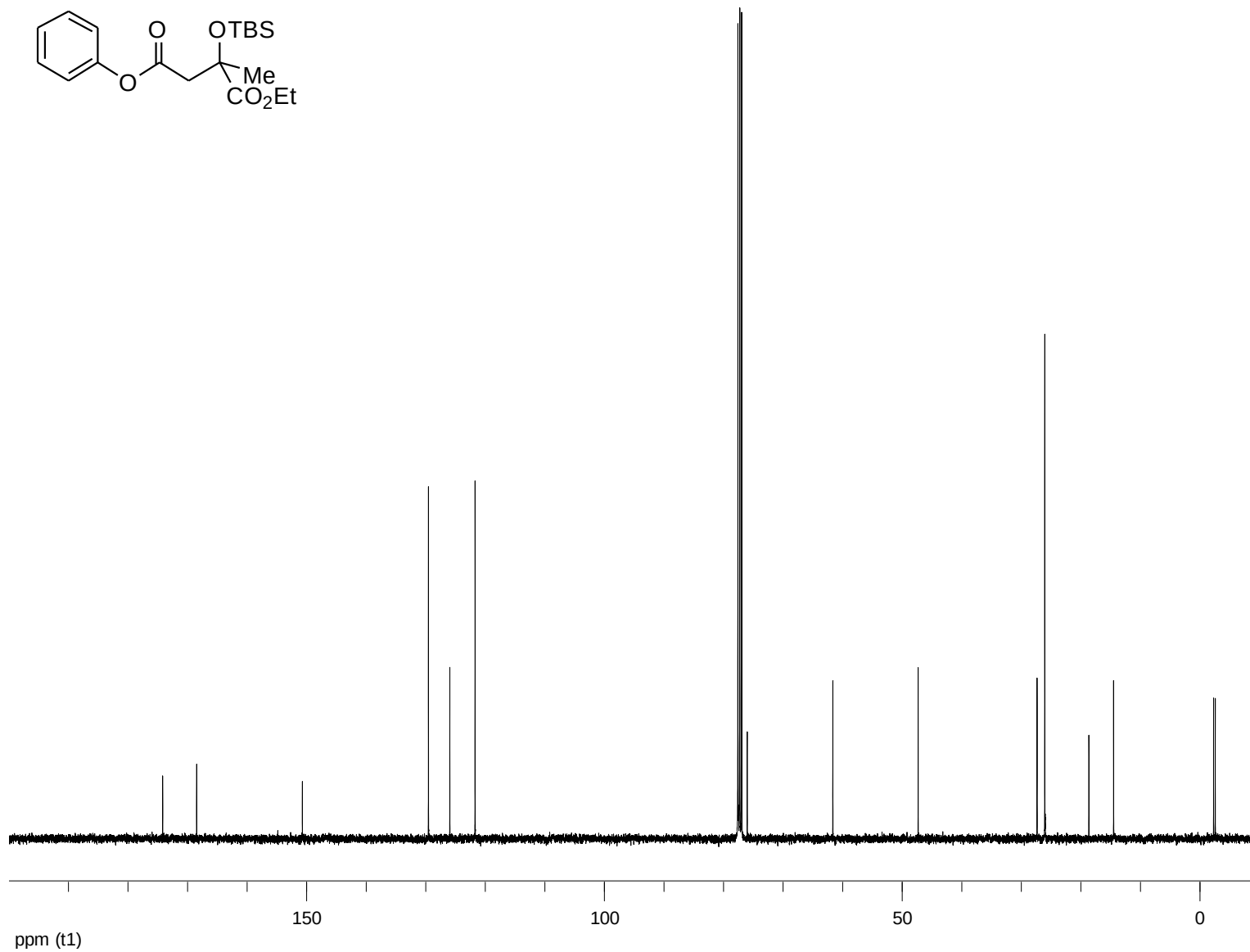
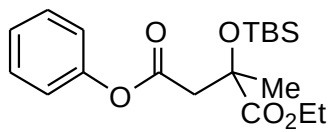












Chapter 7 – Spectral Data

