Boston College

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Department of Chemistry

# HALOGEN ATOM TRANSFER REACTIONS VIA METALLORADICAL CATALYSIS

A thesis

by

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## Abstract

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Halogen Atom Transfer Reactions via Metalloradical Catalysis

(Under the direction of Professor X. Peter Zhang)

Halogenated compounds are useful synthetic organic molecules. One valuable tool for synthesizing halogen containing molecules are atom transfer radical addition (ATRA) reactions which can difunctionalize olefins with a halogen moiety. Many transition complexes can catalyze these reactions but have drawbacks such as the need for harsh conditions and additives. Herein we describe the first ATRA reaction catalyzed by cobalt metalloradical catalysis (Co-MRC) which shows a broad substrate scope, moderate temperatures and uses no additives. This reaction showed excellent regioselectivity, when applicable, and low levels of enantioselectivity (up to 33% ee).

**Acknowledgments**

I would like to thank my advisor, Professor X. Peter Zhang, for guidance throughout my studies here and during this project. I would also like to thank my committee members, Professor Jeffery Byers and Professor Masayuki Wasa, for taking the time to review this work. I would like to thank the other members of the Zhang group. Specifically, my mentors in life and lab, Dr. Yong Wang and Xin Wen. I would also like to thank the many friends at Boston College who have helped me with this process, including Michael Crockett, Xavier Riart-Ferrer, Lucas Parvin and Dr. Filippo Romiti. Finally, my family for their constant love and support.

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**List of Abbreviations**

| | |
|---|---|
| AIBN | Azobisisobutyronitrile |
| Ar | Aromatic group |
| ATRA | Atom Transfer Radical Addition |
| ATRC | Atom Transfer Radical Cyclization |
| ATRP | Atom Transfer Radical Polymerization |
| Cod | 1,5-Cyclooctadiene |
| Cp | Cyclopentadienyl |
| DIOP | 2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| DMAP | 4-Dimethylaminopyridine |
| ee | enantiomeric excess |
| er | enantiomeric ratio |
| h | hour |
| L | Ligand |
| Me | Methyl |
| MRC | Metalloradical Catalysis |
| Mol | Mole |
| MWD | Molecular Weight Dispersity |
| Ni | Nickel |
| NMR | Nuclear magnetic resonance |
| Ph | Phenyl |
| PhH | Benzene |
| PhMe | Toluene |
| TBME | *tert*-butyl methyl ether |
| TMP | Thymidine-5'-Phosphate |

| | |
|---|---|
| TON | Turnover number |
| TPP | Tetraphenylporphyrin |

## I. Introduction

Halogenated compounds are well sought-after building blocks in synthetic organic chemistry.[1] Their utility for further transformations is vast, while the ubiquity in natural products is well known.[2] While there are many different methods to synthesize these types of products[3,4], radical atom transfer reactions (ATRA) are some of the most common and efficient.[5] ATRA reactions, also known as Kharasch reactions[5], have shown to be some of the most straightforward methods for installing halogen compounds and simultaneously difunctionalizing olefins.[6] This radical method is complementary in reactivity to many of the ionic halogenation reactions of olefins.

## II. Background

Morris Kharasch first developed the ATRA reaction in 1945[7] (Scheme 1) using the preactivated halogen compound, carbon tetrachloride, and a radical initiator to difunctionalize olefins, initially styrenes, as they showed high levels of activity and selectivity.

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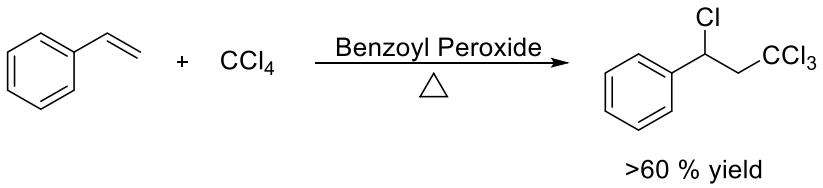
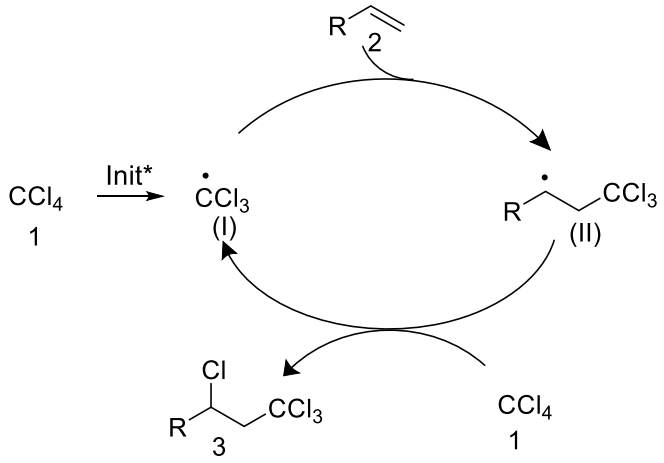
[1] Sigman, M. S., Jana, R., Pathak, T. P., *Chem. Rev.,* **2011**, *111*, 1417.
[2] G. W. Gribble, in, *Naturally Occurring Organohalogen Compounds – A Comprehensive Update* ed. G. W. Gribble, Springer Vienna, Vienna, **2010**, pp. 9–348; (b) B. G´al, C. Bucher and N. Z. Burns, Mar. *Drugs*, **2016**, *14*, 206.
[3] C. L. Hill, J. A. Smegal and T. J. Henly, *J. Org. Chem.,* **1983**, *48*, 3277–3281.
[4] A. E. Shilov and A. A. Shteinman*, Coord. Chem. Rev.*, **1977**, *24*, 97–143.
[5] Pintauer, T. *Eur. J. Inorg. Chem.* **2010**, 2449.
[6] Denmark, S.E. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938.
[7] Kharasch, M.S., Jensen, E.V., Urry, W.H., *Science*, **1945**, *102*, 128.

**Scheme 1:** First Atom Transfer Radical Addition Reaction by Morris Kharasch




Kharasch quoted "Strange as the reactions cited may appear, the explanation of their mechanisms is not too difficult." Throughout the years, this mechanism has become well understood and frequently utilized (Scheme 2).

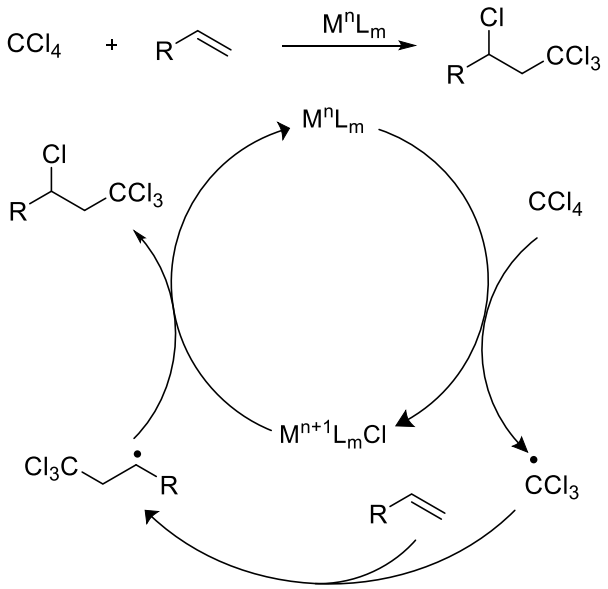
**Scheme 2**. Non-Metal Catalyzed Atom Transfer Radical Addition Reaction Mechanism




The initiator abstracts the halogen to form an alkyl radical (**I**), which adds to the olefin (**2**) to form the more stable radical (**II**). This benzylic radical can abstract a halogen atom back from the carbon tetrachloride (**1**) to form the monadduct product (**3**) and continue the radical chain cycle. Noteworthy is that the initiator (in this case benzoyl peroxide) only provides entry into the radical chain cycle. Because of the nature of radicals this reaction was limited at first by the various side products that could form and required a well-devised, polarity matched system to form the desired products. More specifically, non-metal

catalyzed systems showed the inability to control the chain transfer constant, which resulted in high yields of the polymer product. Because of this, there became interest in the analogous metal complex-catalyzed process.

**Scheme 3**: General Mechanism for Metal-Catalyzed Atom Transfer Radical Addition Reaction

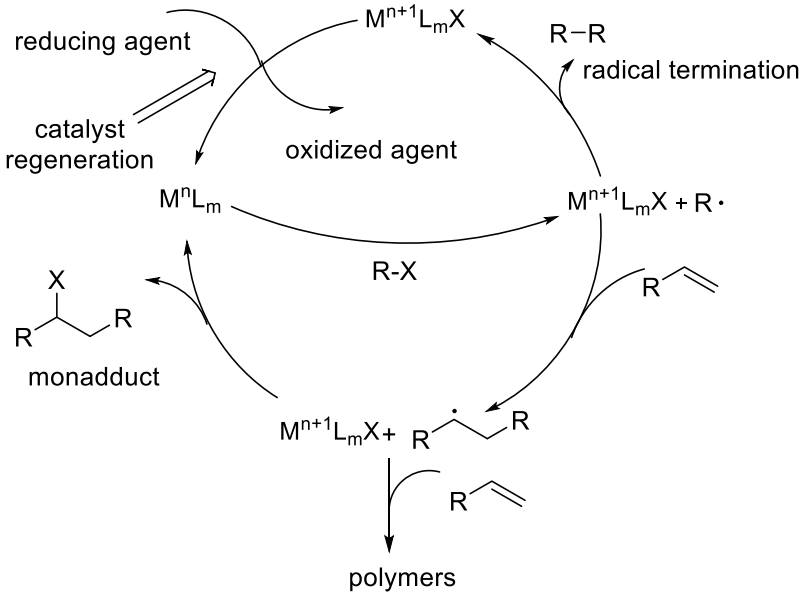



In this catalytic cycle (Scheme 3), the metal becomes oxidized by abstracting a halogen. The newly formed radical can undergo radical addition, followed by a reduction at the metal center and loss of halogen forming the difunctionalized product with a new carbon-halogen bond. This metal catalyzed system can control the concentration of free radicals and therefore minimize undesired side products as the metal is directly involved in each catalytic turnover.

The first catalytic system was discovered by Minisci[8,9] in which he ran a thermal polymerization of acrylonitrile in carbon tetrachloride and chloroform. Instead of forming the desired polymers in a classic atom transfer polymerization reaction (ATRP)[10], he saw significant yields of the monoadduct (the ATRA product), which he discovered was catalyzed by the iron chlorides in the corroded autoclave. Since this discovery, various metals have been developed to undergo ATRA reactions, but the most common of which were complexes of Cu, Ru, Fe and Ni.[11,12,13,14] These complexes have become successful for controlling product selectivity as well as catalyzing this reaction with a wide variety of halogenated starting materials (including alkyl and aryl halides[15,16], *N*-chloroamines[12], alkylsufonyl halides[17] and polyhalogenated molecules[14,18]). The key guidelines for these catalytic systems to increase selectivity for the monoadduct product are suppression of radical termination reactions, suppression of further activation by the monoadduct (specifically, a halogen abstraction from the newly formed product), and suppression of the polymerization reaction[19] (Scheme 4).

[8] M. De Malde, F. Minisci, U. Pallini, E. Volterra, A. Quilico, *Chem. Ind.* (*Milan, Italy)* **1956**, *38*, 386.
[9] F. Minisci, *Gazz. Chim. Ital.* **1961**¸ *91*, 386.
[10] Matyjeszewski, K., Xia, Jianhui, X. *Chem. Rev.*, **2001**, *101*, 2921.
[11] J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev.* **1994**, *94*, 519.
[12] R. A. Gossage, L. A. Van De Kuil, G. Van Koten, *Acc. Chem. Res*
[13] A.J. Clark, *Chem. Soc. Rev.* **2002**, *31*, 1.
[14] H. Nagashima, in *Ruthenium in Organic Synthesis* (Ed.: S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**, pp. 333
[15] Minisci, F. *Acc. Chem. Res.* **1975**, *8*, 165.
[16] Baban, J.A., Roberts, B.P., *J. Chem. Soc. Perkin Trans. 2* **1981**, *1*, 161.
[17] Asscher, M., Vofsi, D. *J. Chem. Soc.* **1961**, 2261.
[18] Truce, W.E., Wolf. G.C., *J. Org. Chem.* **1971**, *36*, 1727.
[19] Pintauer, T. *Eur. J. Inorg. Chem.* **2010**, 2449.

**Scheme 4**: Possible Side Reactions for Metal-Catalyzed Atom Transfer Radical Addition Reactions



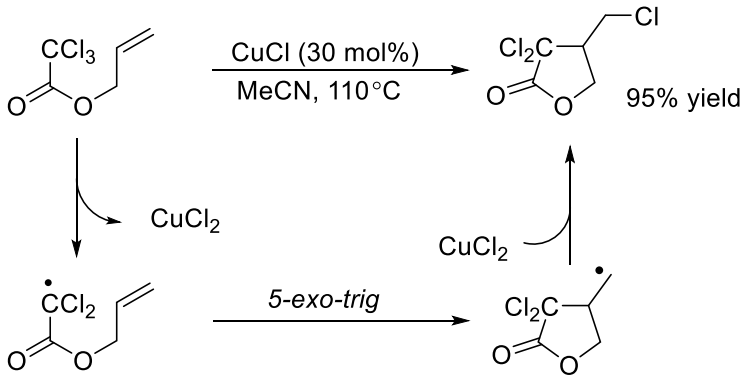

Therefore, the rate of activation by the catalyst should be much lower than that of the deactivation (reverse reaction) to keep the concentrations of free radicals low. The rate of deactivation of the metal (final step) also should be much larger than the rate of the polymer propagation. These challenges require unique catalysts complexes to yield selective ATRA reactions.

Copper-based complexes have shown to be one of the most robust metal catalysts for these reactions[20] and after the first discovery by Minisci, copper salts were used as cheap and effective catalysts. In 1965, Murai and Tsutsumi showed that dichloro- and trichloroacetonitriles could be readily activated to undergo these types of reactions,[21] but

[20] Clark, A.J. *Chem. Soc.* **2002**, *31*, 1.
[21] Murai, S., Tsutsumi, S. *J. Org. Chem.* **1966**, *31*, 3000.

require temperatures of 130 ºC. Similarly, one of the first catalytic systems for atom transfer radical cyclization (ATRC reactions) was done by Tsuji in 1983 (Scheme 5).[22]

**Scheme 5**: Copper-Catalyzed Atom Transfer Radical Cyclization Reaction




He was able to use simple copper chloride to undergo an atom transfer radical cyclization (ATRC) reaction with an activated halogenated starting material. The cyclization followed a 5-exo-trig pathway and was very limited in substrate scope. Copper-based systems have become one of the most used metals in these types of reaction because of its relative availability and the many unique ligand systems. However, in order to undergo these types of reactions, most catalytic systems require nitrogen ligand systems[13], which can limit substrate scope to non-coordinating substrates (such as pyridine-based substrates). This requirement for nitrogen-based ligand systems stemmed from many of the different drawbacks of these copper specific catalytic systems. These disadvantages include various side reactions, which can cause catalyst deactivation and undesired side products. The first possible side reaction being an outer sphere electron transfer by the carbon radical to the metal center (either the oxidized or reduced state), to form either a cation or anion, or this

[22] Tsuji, J. *Tet. Lett.* **1983**, *24*, 2395.

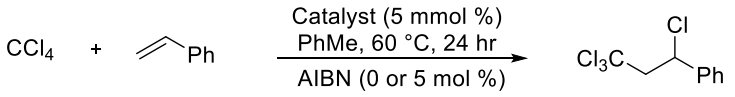
carbon radical adding to the metal center itself and forming an inactive alkyl ligated catalyst. Alkene coordination to the metal center could also lead to an inactive catalyst. As well, direct β-H abstraction could occur by the metal from the weakened carbon hydrogen bond adjacent to the radical. Ideally, the right catalytic system can minimize these effects.

Ruthenium-based systems have shown to be the most common in these catalytic reactions.[16] The reason for ruthenium's commonality is due to the relative ease of activation of these complexes, as well as the tunability of the wide variety of ligand systems developed for ruthenium systems. Noels and coworkers first demonstrated rutheniums capability in 2000 by studying a broad study on ruthenium complexes but found $RuCl(Cp^*)(PPh_3)_2$ to be the most active towards Kharasch-type reactions.[23] It was believed that a phosphine ligand must dissociate prior to the halogen activation. The dissociation was believed to be the key step, hence this specific catalyst design. Severin and coworkershas done extensive work into this ruthenium-catalyzed reaction.[24] It was found that although the activation of the halogenated substrate was relatively facile and the ruthenium catalysts showed high activity to various substrates, it suffered from low catalyst stability. The result is a need for high catalyst loadings with low turnover numbers (TONs). Specifically, because of the nature of this free radical process, unwanted side reactions could lead to a build-up of the oxidized and inactive [Ru(III)Cl] complex. Severin found that by introducing azobis(isobutyronitile) (AIBN) into the reaction, it greatly improved the turnover rate. They hypothesized that AIBN generates free radicals capable of abstracting the chlorine from the ruthenium. Severin demonstrated that AIBN was not

[23] Simal, F., Wlodarczak, L., Demonceau, A., Noels, A.F. *Tet. Lett.* **2000**, *41*, 6071.
[24] Severin, K. *Curr. Org. Chem.* **2006**, *10*, 217.

acting as the radical initiator for the Kharasch reaction by carrying out the reaction with AIBN in the absence of the ruthenium catalyst (Scheme 6) which led to 0% yield of the monoadduct product.[25]

**Scheme 6**: AIBN Phenomenon on Ruthenium-Catalyzed Atom Transfer Radical Addition Reactions




| Catalyst | AIBN | Yield (%) |
|---|---|---|
| $Cp^*Ru(PPh_3)_2Cl$ | — | 3 |
| $Cp^*Ru(PPh_3)_2Cl$ | + | 83 |
| $Cp^*Ru(PPh_3)_2Cl_2$ | + | 85 |
| — | + | 0 |

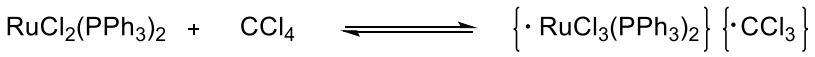
With the success of the ruthenium-based catalysts, many groups began to assess the scope of ruthenium catalytic systems. In 2007, Andersson[26] and coworkers used $[RuCl_2(PPh_3)_3]$ complexes to probe the regioselective of these ATRA reactions. Using only 1 mol % of catalyst in refluxing benzene, moderate to excellent regioselectivity in moderate to excellent yields were observed. Both phenyl and carbonyl moieties were used as directing groups to stabilize the forming radical. The reactions showed a preference for forming benzylic radicals over radicals adjacent to esters and alcohols. These ruthenium complexes could also catalyze the addition to aliphatic compounds.

Mechanistic investigations have been thoroughly described for these systems.[27] Matsumoto[28] and Kamigata[29] have described these $RuCl_2(PPh_3)_3$ complexes to proceed

[25] Quebbatte, L., Thommes, K., Severin, K. *J. Am. Chem. Soc.* **2006**, *128*, 7440.
[26] Anndersson, P.G., *Coll. Of Czech. Chem. Comm.* **2007**, *72*, 1005.
[27] Gossage, R.A., Van De Kuil, L.A., Van Koten, G. *Acc. Chem. Res.* **1998**, *31*, 423.
[28] Matsumoto, H., Motegi, T., Nakano, T., Nagai, Y. *J. Organomet. Chem.* **1979**, *174*, 157.
[29] Kameyama, M., Kamigata, N., Kobayashi, M. *J. Org. Chem.* **1987**, *52*, 3312.

through a "radical reaction in the coordination sphere".[28] This was used to explain the increased selectivity of the desired compounds, as they hypothesized that these radicals remained under the influence of the metal center ("caged"). Davis and coworkers described a coordinated radical pair intermediate (Scheme 7) that was used to explain selectivity.[30]

**Scheme 7**: Activation Equilibrium of Ruthenium Catalysts



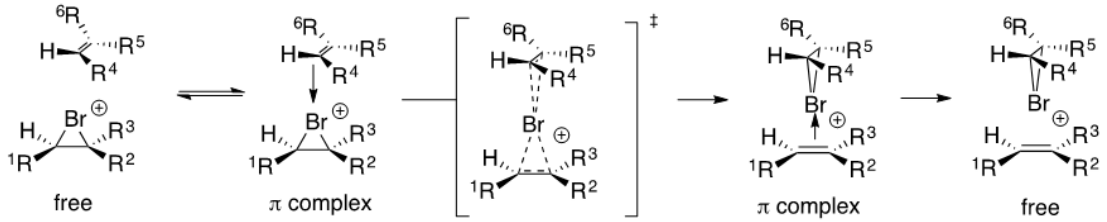

There was no evidence of a coordination event of the alkene to the metal center, so direct addition by the alkyl radical to the alkene. While this radical-radical interaction could help selectivity for the monoadduct product, this equilibrium is from a closed shell ruthenium metal catalyst to an open shell catalyst, which could make this a relatively slow activation step and could cause the equilibrium to lay to the right. If this equilibrium does lie to the left, however, this could aid in keeping the alkyl radical concentration low. While both copper and ruthenium are thought to go through this mechanism, there is still some debate if other metals, such as rhodium, undergo this same mechanism because this radical pair intermediate would not be generated, as most rhodium complexes would form a closed-shell intermediate.

Not only have achiral halogen containing compounds been an ongoing investigation in organic synthesis, formation of chiral halogen compounds has remained even more elusive. Both ionic and radical methods have had limited success thus far to generate chiral carbon-halogen bonds in a facile manor. This stems from the necessary

[30] (a) Bland, W.J., Davis, R., Durrant, J.L.A. *J. Organomet. Chem.* **1984**, *267*, C45. (b) Bland, W.J., Davis, R., Durrant, J.L.A. *J. Organomet. Chem.* **1985**, *280*, 397.

planar intermediates halogenation reactions go through, such as those of halonium delivery or halirenium opening, halide trapping by carbocations, and halogen trapping by carbon radicals. Many methods typical of generating carbon stereocenters for other heteroatoms are not applicable to halogens due to their unique structures. Ring-opening chiral halonium intermediates do not work as they would with, for example, epoxides because these intermediates can undergo inter-alkene halonium transfers which lead to a loss of optical activity (Scheme 8).

**Scheme 8**: Inter-Alkene Halonium Transfers Leading to Loss of Optical Activity




This observation was made by Denmark[31] and showed that by introducing an alkene to enantiopure halogenated compounds in the presence of base there was significant erosion of enantiospecificity. Recently, there has been some success using directed groups in these reactions[32], but this limits the substrate scope substantially. Another challenge associated with halogens is their non-basicity. Many other atoms can form new stereocenters through Lewis basic reactions, such as nitrene reactions[33], however halogens are unable to do so as there is no "halene" equivalent. Finally, halides are unable to carry leaving groups, so many substitution reactions are not accessible. This ability is commonly used with other

[31] Denmark, S.E. *J. Am. Chem. Soc.*, **2010**, *132*, 1232.
[32] Denmark, S.E. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938.
[33] Aube, J. *J. Am. Chem. Soc.*, **2005**, *127*, 15712.

heteroatoms, such as enantioselective Shi epoxidations[34], but this strategy cannot be applied to halogen reactions. This difficulty to synthesize enantiopure halogenated compounds and the synthetic utility of these compounds show the importance of these asymmetric reactions.

Asymmetric induction is conceivable through ATRA reactions. A chain transfer propagation event, where the initiator is not participating in the enantiodetermining step of halogen atom abstraction from the initial substrate, will always form a racemic compound. However, using metal complex-catalyzed pathways, the metal could potentially be involved in this final enantiodetermining step and could occur in an asymmetric fashion due to the chiral ligands.

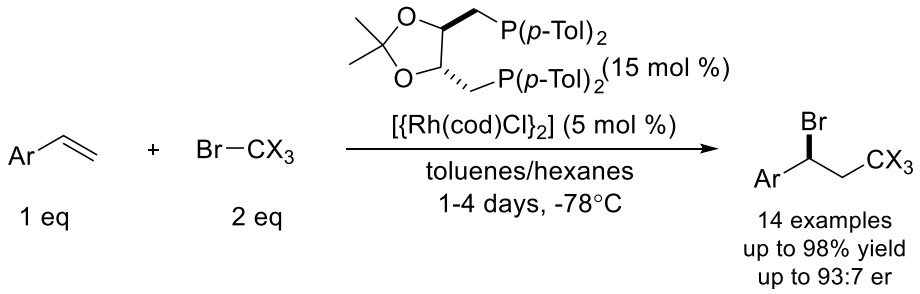
In 1987, Kamigata used $[Ru_2Cl_4(Diop)_3]$ complexes to catalyze the addition of $ArSO_2Cl$ to styrene and obtained up to 40% ee.[35] In 2007, Kamigaito and coworkers developed an enantioselective version of ruthenium-catalyzed reactions[36] based on the seminal report by Sonoda.[37] In this system, they also used a chiral diop ligand to induce enantioselectivity. Even with a very active precursor of bromocarbontrichloride, they were only able to obtain poor yields of up to 26% and could only reach up to 32% ee.

The most recent development of this catalytic system was done by Ready and Liu[38] in 2017 (Scheme 9). This work was particularly state of the art because it was able to

[34] Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
[35] Kamigata, N., Kobayashi, M., Kameyama, M., *J. Org. Chem.*, **1987**, *52*, 3312.
[36] Kamigaito, M. *Eur. J. Org. Chem.*, **2007**, 782.
[37] Sonoda, N. *Angew. Chem., Int Ed. Engl.*, **1981**, *20*, 475.
[38] Ready, J.M., Liu, P., *et al.*, *Angew. Chem. Int. Ed.*, **2017**, *56*, 8780.

produce these Kharasch products with high enantioselectivity. This was the first time that these types of reactions were carried out with high stereochemical fidelity.

**Scheme 9**: Rhodium-Catalyzed Asymmetric Atom Transfer Radical Addition Reaction[24]




In this work, the authors used a rhodium catalyst. To date, rhodium has shown to be the most active metal towards ATRA reactions. They showed a wide variety of styrenes but were limited to styrene derivatives. Two heteroaryl groups were tolerated, although in diminished yields. Moderate to excellent levels of enantioselectivity were achieved with these types of substrates. A few disadvantages included the requirement of a particularly activated substrate, Br-$CCl_3$, with an extremely weakened carbon halogen bond. The analogous chloride substrate, $CCl_4$ showed extremely lowered yields and required high catalyst loading. The authors hypothesized these lowered yields was due to the inactive [(Diop)$RhCl_2$] complexes that could be formed, which demonstrates the sensitivity of this reaction. Reactions required a temperature of -78 $^oC$ and up to 4 days reaction time. It also required slow addition of the olefin which is not as practical when applied on a large scale under air free conditions. Several further transformations were demonstrated that were able to retain high levels of enantioselectivity. Mechanistically, it was hypothesized that the halogen atom abstraction occurred directly by the rhodium center. Through experiments and DFT calculations, an olefin insertion mechanism was ruled out. Instead, the

termination event was expected to be by an outer-sphere halogen atom abstraction by the benzylic radical from the rhodium-chloride species.

To date, cobalt-based systems have yet to be used for ATRA reactions. One of the reasons for this scarcity is cobalt complexes have the ability and more importantly, the preference to catalyze atom transfer radical polymerization reactions.[39] In 1994, Wayland[40] and coworkers demonstrated that [Co(TMP)R] complexes could catalyze these polymerization reactions. ATRP reactions rely on the equilibrium between the capped metal-alkyl species and the free radical species to control both the number average molecular weight and allow for a narrow molecular weight dispersity (MWD) throughout. This cobalt catalyst is a $d^7$ species and therefore a metalloradical in nature and can easily couple with the propagating radical and keep the concentration of free radicals in solution low while inhibiting early termination events. This $Co^{III}$-alkyl species could undergo homolytic cleavage to reproduce the alkyl radical. This radical can then add to another equivalent of olefin to continue the polymer propagation. This ability for these Co(II)-metalloradicals to couple easily with alkyl radicals was one that prevented the success with these types of catalysts with ATRA reactions.

## III. Research Goal

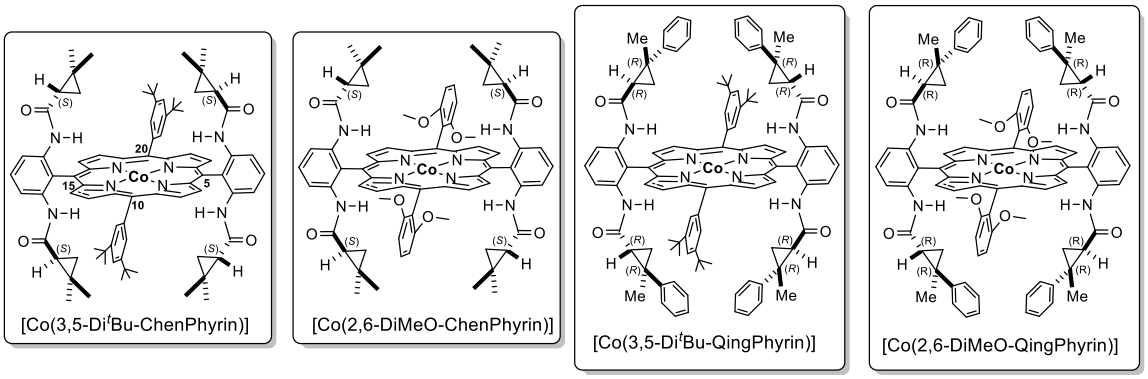
Cobalt(II)-metalloporphyrins have the potential to provide new kinds of reactivity to ATRA reactions due to their unique structures and the metal's electronic structure. Specifically, our group has developed a new branch of radical chemistry, metalloradical

[39] Matsumoto, M., Matsubara, K. *J. Polym. Sci. A* **2006**, *44*, 4222.
[40] Wayland, B., *J. Am. Chem. Soc.*, **1994**, *116*, 7943.

catalysis (MRC)[41], which could provide a new, well defined catalytic system for these types of reactions. At the heart of this catalytic system is the uniquely designed Co(II)-based porphyrin complexes. These $d^7$ catalysts are designed for the single electron to lie in the $d_z^2$ orbital, which lies perpendicular to the porphyrin plane, allowing for a reactive radical at the cobalt center. Typically, after reacting with a radical precursor, such as a diazo or azide reagent, these catalysts translocate the radical character onto the atom at the alpha-position. These subsequent organic radicals can be stabilized by a half π-bond, through the backbonding of a filled d-orbital with a half-filled p-orbital. This allows for the organic radical to be stabilized while still being reactive. These α-Co(III) radicals have shown to undergo many typical radical reactions, such as radical addition and hydrogen atom abstraction. The final step usually involves a substitution reaction at the cobalt center to close the catalytic cycle. Most important about the development of this catalyst system has been the design and variability of new types of $D^2$-symmetric chiral porphyrin ligand. Highlighted below are just a few of our many synthesized catalyzed, which demonstrate the ability to change the chiral amido-substituents at positions 5- and 15- as well as the non-stereogenic substituents, at positions 10- and 20- on the porphyrin complex (Scheme 10).

[41] Cui, X.; Xu, X.; Lu, H.-J.; Zhu, S.-F.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 3304–3307.

**Scheme 10**: Representative Examples of Chiral Cobalt Porphyrin Catalysts

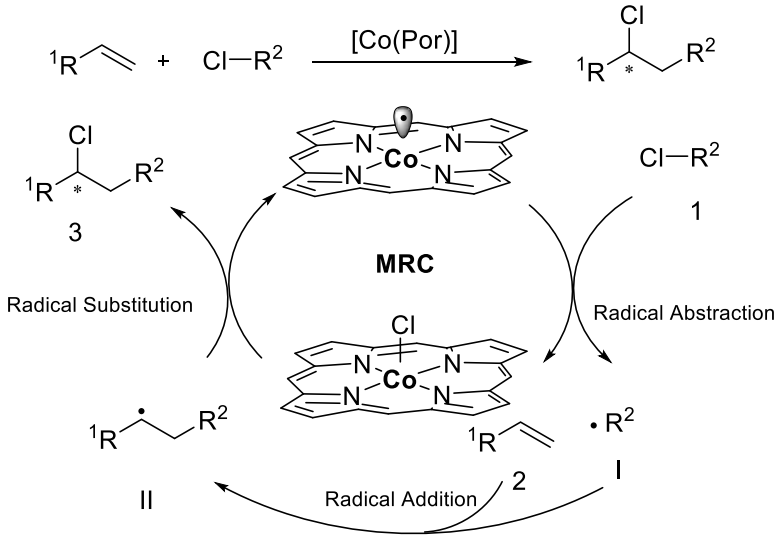



The various classes of ligands allow for the tunability of both sterics and electronics of the catalyst system.

While this catalytic system has been well developed for different reactions such as olefin cylopropanation[42], olefin aziridination[43], C-H alkylation[44] and C-H amination[45], all of which are limited to diazo and azide reagents or precursors of these reagents. The question became whether this catalyst had the capability of undergoing a Kharasch-type reaction, where the metalloradical catalysts directly abstracts a halogen (Scheme 11).

[42] Zhu, S.-F.; Xu, X.; Perman, J. A.; Zhang, X. P. *J. Am. Chem. Soc.* **2010**, *132*, 12796.
[43] Subbarayan, V.; Ruppel, J. V.; Zhu, S.-F.; Perman, J. A.; Zhang, X. P. *Chem. Commun.* **2009**, 4266.
[44] Wang, Y.; Wen, X.; Cui, X.; Zhang, X. P. *J. Am. Chem. Soc.* **2018**, *140*, 4792.
[45] Lu, H.-J.; Subbarayan, V.; Tao, J.; Zhang, X. P. *Organometallics* **2010**, *29*, 389.

**Scheme 11**: General Mechanism for Atom Transfer Radical Addition Reactions via Co(II)-MRC

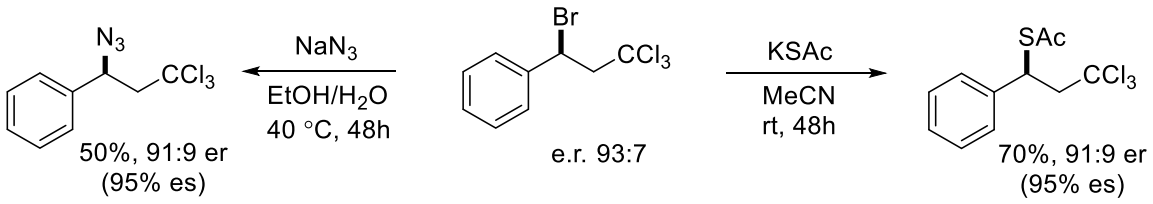



The cycle would follow that is similar to other metal complex-catalyzed Kharasch reactions, where the metal would abstract the halogen to form Co(III)-Cl complex and an free radical. This radical could undergo radical addition to an olefin (**2**) followed by radical atom abstraction back from the cobalt complex to form a new carbon-halogen bond and turnover the catalytic cycle.

So the question became can we use this well-defined catalytic system, Co(II)-MRC and apply it to ATRA reactions to show unique reactivity and most importantly, high selectivity? Could the amidoporphyrin ligands provide a cavity to diminish all side products of the free radical and control regioselectivity? And even more importantly, our group has shown the capability of these chiral porphyrins to induce high enantioselectivity[42-45]. Could we achieve this with a halogen abstraction and a free radical intermediate, unlike the previous systems our group has developed? Ideally the free radical would stay bound within the cavity-like catalyst and could ultimately control the

enantiodetermining final substitution step, forming a new enantioenriched carbon halogen bond. Moreover, could we achieve this without the need for additives and under mild reaction conditions? If we were able to achieve these, the applications to organic synthesis would be highly important, as these chiral halogen compounds could easily be further transformed into a wide variety of enantioenriched compounds in one step (Scheme 12).[46]

**Scheme 12:** Further Transformation of Benzyl Bromide Derivatives with High Enantiospecificity



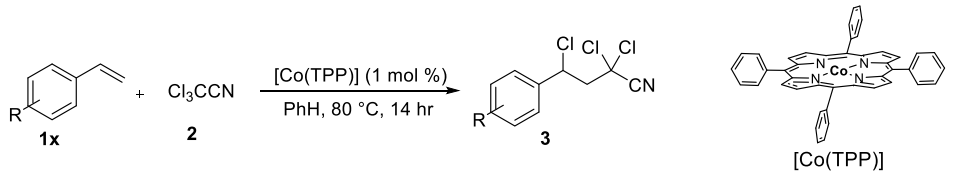

This method could provide a way to build up complex, chiral compounds effectively and efficiently. Current systems for enantioselective ATRA reactions are limited in the scope of substrates, both in in olefins and in halogen sources. Specifically rhodium- and ruthenium-based systems struggle with chlorine atom abstraction due to the formation of inactive $RuCl_2$ and $RhCl_2$ compounds, which significantly decrease turnover numbers (TONs). However, $Co^{II}$-MRC catalysts are incapable of forming these dihalogen compounds due to the unique coordination environment of the porphyrin ligands and the electronic structure of the cobalt center

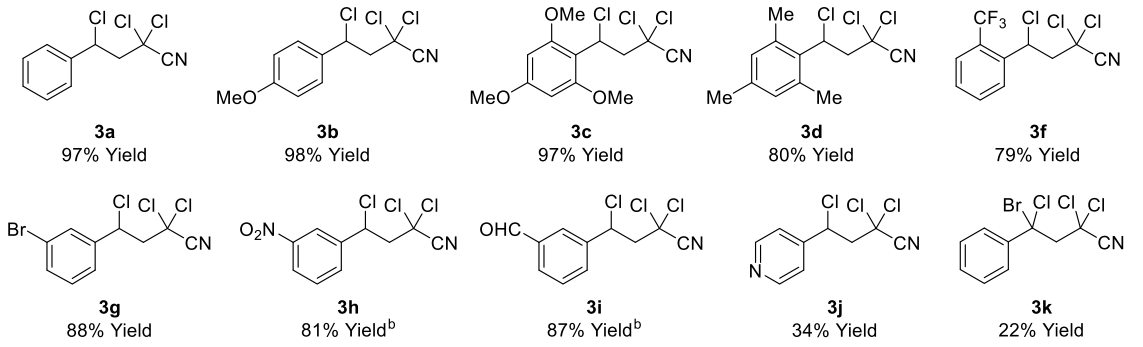
[46] Ready, J.M., Liu, P., *et al.*, *Angew. Chem. Int. Ed.*, **2017**, *56*, 8780.

## IV. Development of Non-Asymmetric ATRA Reactions via Co-MRC

To first probe this reaction, we sought to examine the reactivity of simple starting materials (Scheme 13). Using styrene and trichloroacetonitrile, we found that this reaction proceeded smoothly using only 1 mol % of commercially available [Co(TPP)] at 80 °C to form the difunctionalized polyhalogenated product in 97% yield.

**Scheme 13**: [Co(TPP)]-Catalyzed Atom Transfer Radical Addition of Styrene Derivatives and Trichloroacetonitrile




[a]Isolated yields. [b]Regioisomer observed.

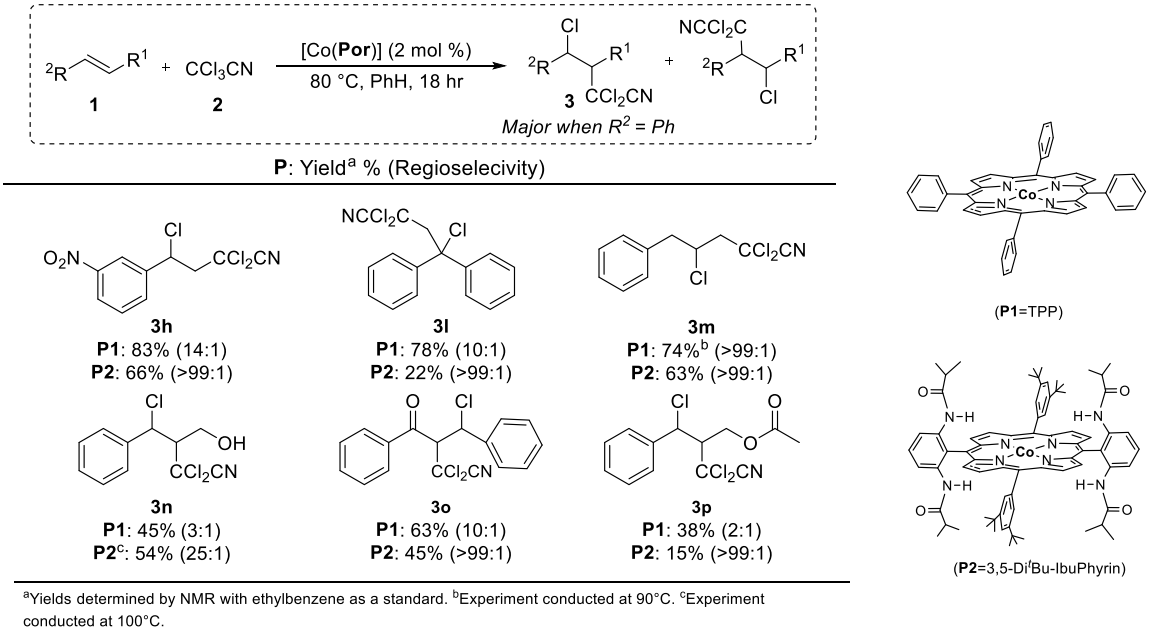
We investigated various styrene derivatives, including electron-rich styrenes such as para-methoxy (**3b**) and 2,4,6-trimethoxy styrene (**3c**) which both proceeded in almost quantitative yields. Bulkier styrenes, such as mesityl styrene showed good reactivity. Electron-withdrawing substituents were also tolerated, although in slightly diminished yields (**3f–3i**). Both halogenated and nitro-containing arenes were also well tolerated (**3g**–**3h**). Most importantly vinyl pyridines (**3j**) were tolerated by this system, although in

lowered yields of 34%. Most other catalytic systems showed difficulties with heteroaryl substrates due to their strong coordinating abilities.[10] Excitingly, forming a tertiary dihalogenated carbon center was also possible by using α-bromstyrene, albeit in low yields. Most importantly, these clean reactions showed very minimal side reactions, which was not the case with many other catalytic systems.

Interestingly, when investigating these styrene derivatives, we found that when using the most electron-withdrawing styrene, 3-nitrostyrene and 3-vinylbenzaldehyde, we obtained a mixture of regioisomers. We rationalized this was due to the polarity reversal at the olefin moiety which causes the relatively electrophilic radical to add to the benzylic carbon which now holds a partial negative charge. This effect does not completely outcompete the stabilization of forming a benzylic radical after radical addition to the terminal carbon of the olefins, which is what we see in most cases of addition to styrenes. We hypothesized that by using one of our amidoporphyrin catalysts we could better control this regioselectivity by using the more closed cavity-like environment. Gratifyingly, using our achiral catalyst, [Co(3,5-Di$^t$Bu-IbuPhyrin)], we could near perfectly control the regioselectivity of the addition to 3-nitrostyrene, forming the more thermodynamically stable radical at the benzylic position. To further investigate this phenomenon, we sought to investigate the regioselectivity of other olefins, more specifically internal olefins that benefit from stabilization of the radical after addition to either sides of the olefin as they will both be secondary radicals. Our first investigation was again with the commercial available Co(TPP) catalyst. Using both internal and less activated terminal olefins (Scheme 14) we were able to obtain regioselectivity ranging from moderate to poor. The internal

olefins saw an extremely diminished regioselectivity when using this relatively open chain catalyst, however yields remained good to moderate.

**Scheme 14**: [Co(Por)]-Catalyzed Regioselective Atom Transfer Radical Addition Reactions



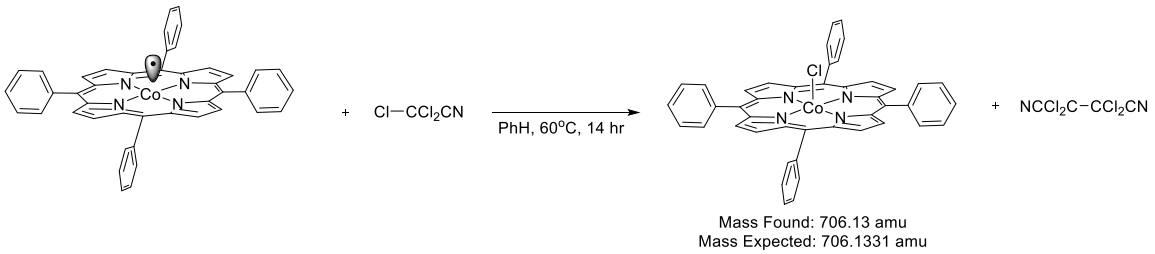

[a]Yields determined by NMR with ethylbenzene as a standard. [b]Experiment conducted at 90°C. [c]Experiment conducted at 100°C.

Using these same substrates with achiral catalyst [Co(**P2**)] there was a substantial change in regioselectivity. Using terminal olefins (**3h**−**3m**), regioselectivity improved to excellent, although yields decreased significantly from 83% to 66%, 78% to 22%, and 74% to 63%, respectively. Moving to internal olefins (**3n**-**3p**), where before regioselectivity was particularly poor, we saw an increase to excellent to near perfect regioselectivity. However, again yields were decreased from those with [Co(TPP)]. We tried unactivated substrates such as octene and cyclohexadiene, but only saw trace amounts of the desired products. Evidently, the effects of the conjugated phenyl ring are very important for the reactivity of this system. This phenomenon, with the improved selectivity with our amindoporphyrin

ligand systems shows the distinctiveness of this catalytic system for these types of reactions.

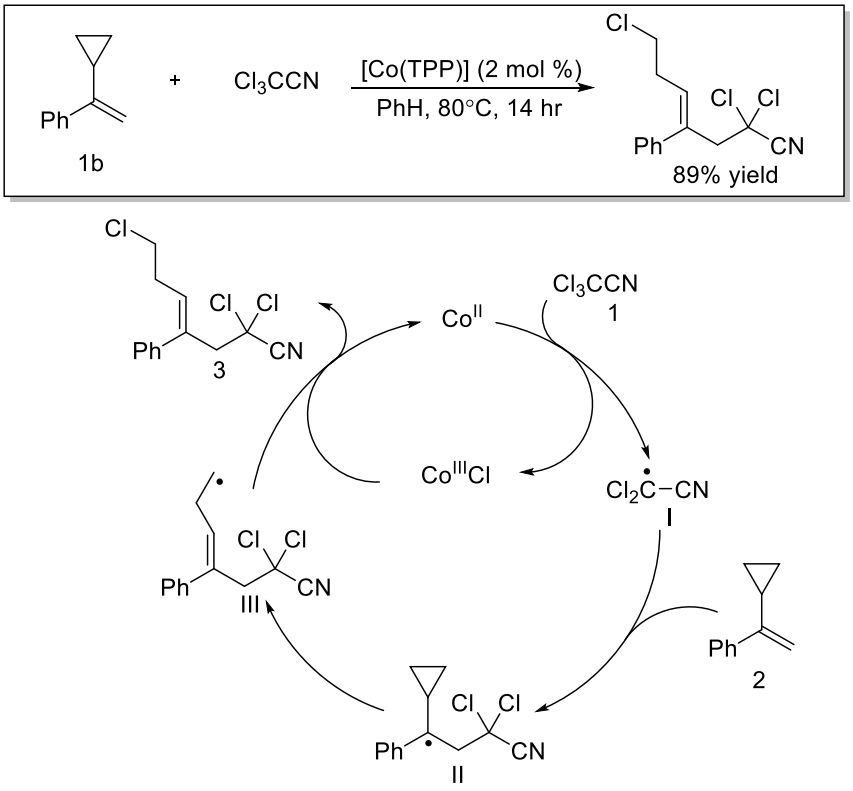
To probe the mechanism of this catalytic reaction, and provide evidence for this stepwise radical mechanism, on we sought to investigate two intermediates that were hypothesized. The first intermediate we sought was one that our group has not shown before, which is the [(Por)$Co^{III}$-Cl] intermediate after the initial halogen abstraction (Scheme 15). Excitingly, we were able to isolate and characterize [Co(TPP)Cl] intermediate by both high resolution mass spectroscopy and $^1H$ NMR spectroscopy.

**Scheme 15**: Formation of [Co(TPP)Cl]




Although the Co−Cl bond is significantly weak, we were still able to detect small amounts of the [Co(TPP)Cl] while the major peak was still the [Co(TPP)] fragment. By isolating and characterizing this catalytic intermediate it provides significant evidence to support our mechanism, specifically that the cobalt metalloradical can abstract a halogen atom through an inner-sphere type mechanism. The second intermediate we chose to probe was intermediate II (Scheme 8). We hypothesized that we could perform a radical clock experiment on this stable benzylic radical. Indeed, by using a vinylcyclopropane substrate (**1b**), we can isolate the ring-opened product in a high yield (Scheme 16).

**Scheme 16**: Radical Clock Experiment for Evidence of Stepwise Radical Mechanism




This reaction provided further evidence that this mechanism was a stepwise radical mechanism, plausibly going through a benzylic radical intermediate.

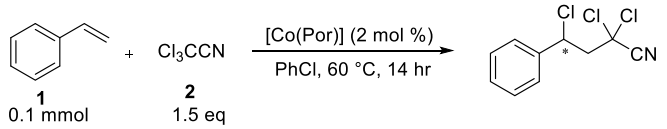
## V. Development of Asymmetric ATRA Reactions via Co-MRC

While these initial investigations showed the distinctiveness in reactivity of Co-MRC applied to ATRA reactions, we knew that there was more potential than this. As mentioned above, the exceptionality of these cobalt-based metalloporphryins is our groups' ability to build a wide library of chiral amidoporphyrins. Since our catalyst was reactive, we wondered if we could undergo these reactions in an asymmetric manner as well. We were hopeful that introducing dimethylamide units onto the catalyst structure, we could significantly improve the regioselectivity of the reaction. It is hypothesized that there is

some effect by the amide units. Could we install chiral amide units and induce facial selectivity during the final proposed halogen abstraction by the carbon radical from the Co-Cl? As well, could we ensure that no background reactions were occurring? This innate radical chain process, that does not involve the catalyst, would significantly diminish enantioenrichment of the product. If we could overcome these many challenges, Co-MRC presents a unique opportunity to be able to use one catalyst to be able to control a wide scope of substrates.

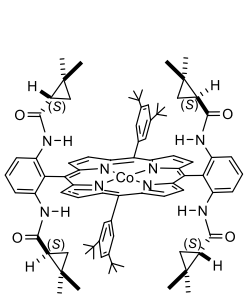
We began this investigation with our first-generation catalyst [Co(3,5-Di$^t$Bu-ChenPhyrin)]. To our delight, we obtained the product in 77% yield with 24% ee from simple starting materials. This was especially exciting for us as these starting materials contained minimal functionalization, which usually show less enantioselectivity due to less interaction with the catalyst. The catalyst also contained a relatively simplistic scaffold so could be easily expanded going forward. With these exciting results, we further sought to improve the enantioselectivity by tuning the ligand properties of these catalysts (Scheme 17). Next, we turned to the ability to tune the asymmetric arms of the ligand scaffold. As mentioned, our group has been able to synthesize a wide variety of chiral catalysts which can alter both the electronic and steric properties by using different chiral amide units.

**Scheme 17**: Catalyst Effect on Co(II)-Catalyzed Atom Transfer Radical Addition Reactions of Styrene with Trichloroacetonitrile

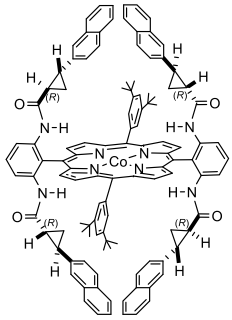



**1**
0.1 mmol

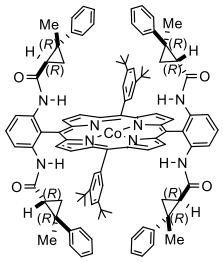
**2**
1.5 eq



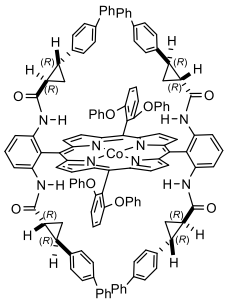
(**P2**=3,5-Di$^t$Bu-ChenPhyrin)
*entry 1*
77% yield, 24% ee



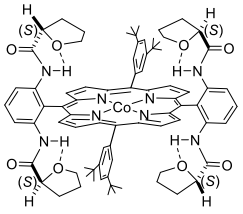
(**P3**=3,5-Di$^t$Bu-Xu(2'-Naph)Phyrin)
*entry 2*
61% yield, 5% ee



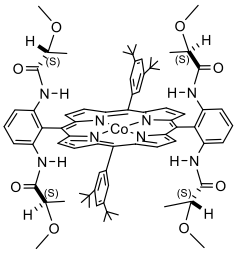
(**P4**=3,5-Di$^t$Bu-QingPhyrin)
*entry 3*
46% yield, 14% ee



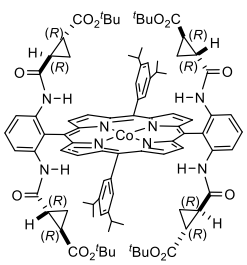
(**P5**=2,6-DiPhO-4-PhXuPhyrin)
*entry 4*[a]
79% yield, 14% ee



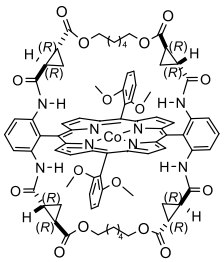
(**P6**=3,5-Di$^t$Bu-ZhuPhyrin)
*entry 5*
60% yield, 14% ee



(**P7**=3,5-Di$^t$*Bu*-RuppelPhyrin)
*entry 6*[a]
88% yield, 18% ee



(**P8**=3,5-Di$^i$Pr-TaoPhyrin)
*entry 7*[a]
87% yield, 16% ee



(**P9**=2,6-DiMeO-Hu($C_6$)Phyrin)
*entry 8*[a]
25% yield, 10% ee

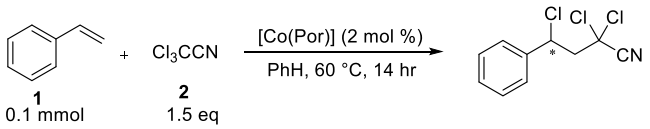
Isolated yields [a]PhH used as solvent

Thinking that aromatic-aromatic interactions between catalyst and styrene would increase selectivities of this reaction, we installed napthyl- and phenyl-substituted cyclopropanes on the chiral amide units (entries 2 and 3). Unfortunately, this had a very negative effect on both the yield and enantioselectivity. Recently, one of our group members developed an even more complex aromatic system, [Co(**P5**)], where not only are the chiral units are bisphenyl-substituted cyclopropanes, but there is a 2,6-diphenoxyphenyl group as the non-chiral substituent. This complex has been shown by x-

ray crystallography to have a unique π-stacking interaction between the chiral amide units and non-chiral substituents, forming a highly rigid catalyst structure. Unfortunately, this well-defined catalyst pocket did not have a positive effect on the enantioselectivity although unlike the other, bulkier napthyl- and phenyl-substituted catalysts, it improved the yield to 79%. Theoretically, this was due to the aromatic-aromatic interactions between substrate and catalyst. Seeing that bulkier, aromatic ligands decreased enantioselectivities, as compared to that of the dimethyl cyclopropane (ChenPhyrin), we synthesized other, less bulky catalysts (entries 5−7). These all showed high reactivity although enantioselectivities remained poor and showed no significant improvement. Thinking a closed catalyst pocket could decrease the background radical chain process by keeping the radical inside the catalyst pocket, a new type of basket-shaped porphyrins were used, [Co(**P9**)], entry 8. Unfortunately this showed a significant decrease inyields and enantioselectivities.

Observing that the ChenPhyrin derivatives (dimethylcyclopropylamide ligands) yielded some of the highest enantioselectivities, we investigated tuning the steric and electronic properties on the phenyl substituents, while keeping the chiral units constant (Scheme 18).

**Scheme 18**: Ligand Effect of ChenPhyrin Derivatives on Co(II)-Catalyzed for Atom Transfer Radical Addition Reactions of Styrene with Trichloroacetonitrile

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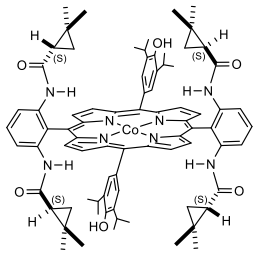
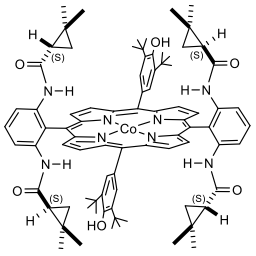
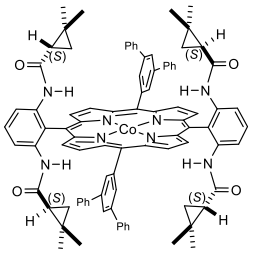
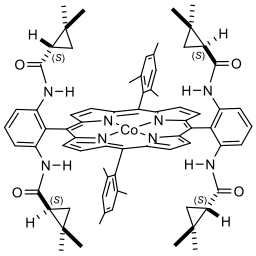
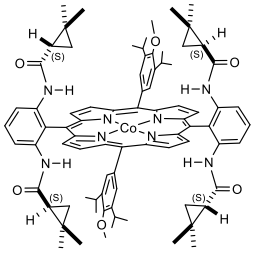
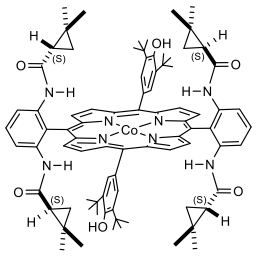
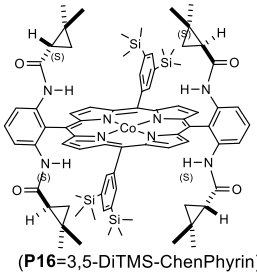
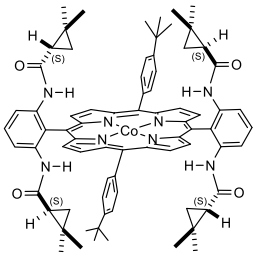
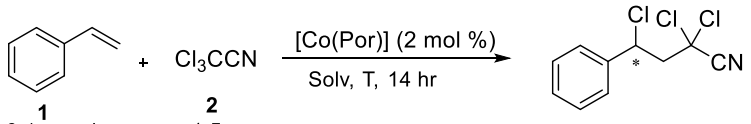
|  |  |  |  |
| (**P10**=3,5-Di$^{i}$Pr-4'-OH-ChenPhyrin) *entry 1* 73% yield, 26% ee | (**P11**=3,5-Di$^{t}$Bu-4'-OH-ChenPhyrin) *entry 2* 77% yield, 22% ee | (**P12**=3,5-DiPh-ChenPhyrin) *entry 3* 43% yield, 17% ee | (**P13=**Mesityl-ChenPhyrin) *entry 4* 60% yield, 14% ee |
|  |  |  |  |
| (**P14**=3,5-Di$^{i}$Pr-4'-OMe-ChenPhyrin) *entry 5* 64% yield, 24% ee | (**P15**=3,5-Di$^{t}$Bu-4'-OH-ChenPhyrin) *entry 6* 64% yield, 12% ee | (**P16**=3,5-DiTMS-ChenPhyrin) *entry 7* 61% yield, 18% ee | (**P17**=4-$^{t}$Bu-ChenPhyrin) *entry 8* 74% yield, 29% ee |

Isolated yields

We synthesized a number of phenyl derivatives to differ the non-asymmetric ligands, beginning from more sterically encumbered such as [Co(P11)] and [Co(**P12**)], which seemed to decrease both yield and selectivity (entries 2 and 3). Alternatively, decreasing the sterics using catalysts such as [Co(**P13**)] also seemed to decrease both yield and selectivity (entry 4). Only [Co(**P17**)] showed any increase of enantioselectivity to 29% (entry 8). These steric properties of the ligand did not seem to greatly affect the asymmetric induction of this reaction. However, all these catalyst derivatives showed the capability to affect the enantioselectivity, which encouraged us that there was a specific catalyst capable of yielding an enantiopure ATRA product.

As tuning of the catalyst did not yield a product with high enantiopurity, we also investigated the solvent and temperature effect on this reaction.

**Table 1**: Solvent Effect on Atom Transfer Radical Addition Reactions of Styrene with Trichloroacetonitrile via Co(II)-MRC

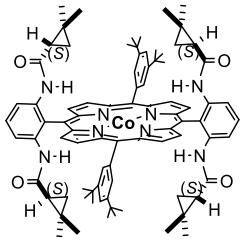



**1**
0.1 mmol

**2**
1.5 eq

| Entry | T (°C) | Solv | Yield (%) | ee(%) |
|---|---|---|---|---|
| 1 | 60 | PhCl | 77 | 24 |
| 2 | 80 | PhCl | 89 | 21 |
| 3 | 40 | THF | 10 | 32 |
| 4 | 60 | THF | 64[a] | 26 |
| 5 | 80 | Toluene | 35 | 8 |
| 6 | 60 | $C_6H_{12}$ | 19 | 33 |
| 7 | 60 | EtOH/$H_2O$ | NR | - |
| 8 | 60 | TBME | 2[a] | - |

[a] Yields determined via NMR.




[Co(3,5-Di$^t$Bu-ChenPhyrin)]

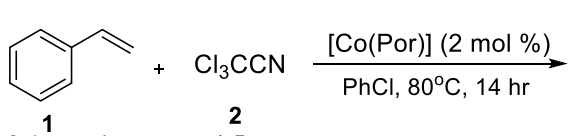
Increasing the temperature to 80 °C (entry 2) showed an increase in yield, showing comparable yields to the reactions done with the commercially available catalyst [Co(TPP)], however there was a slight drop in ee. Using a more polar and coordinating solvent, tetrahydrofuran (THF), there was a slight increase in enantioselectivity to 26%, although a decrease in yield. Coordinating solvents, unlike in other copper-based systems are tolerated in this system. Decreasing the temperature of this reaction to 40 °C (entry 3), showed an expected decrease in yield, but also an increase in enantioselectivity to 32%. This encouraging result could potentially be due to higher catalyst control stemming from

a slower reaction. However, it could also be due to suppression of the non-catalytic radical chain process. This result did give us hope however that with a more active catalyst or substrate, a high enantioselectivity could be possible. More polar solvents (entries 7 and 8) almost shut down the reaction. Alternatively, non-polar solvents including toluene (entry 5) and cyclohexane (entry 4) showed a significant decrease in yield at 60 ºC. Excitingly, cyclohexane showed an improvement of 33% ee at 60 ºC (entry 6), however in decreased yields.

In the past, using coordinating additives have had a positive effect on the enantioselectivity.[47,48] Coordination to the cobalt center that is perpendicular to the porphyrin plane along the $d_z^2$ axis can slightly bend the porphyrin ligand away from this coordination site and therefore towards the reactive cobalt radical center. This can positively affect the catalyst cavity by pushing the amide ligands towards the center and therefore tighten the catalytic pocket. We hypothesize this phenomenon leads to better interaction with the chiral amide units. Therefore, we also used various coordinating additives.

[47] Zhang, X.P., *J. Org. Chem.*, **2003**, *68*, 8179.
[48] Zhang, X.P., *J. Am. Chem. Soc.*, **2004**, *126*, 14718.

**Table 2**: Additive Effect on Atom Transfer Radical Addition Reactions of Styrene with Trichloroacetonitrile

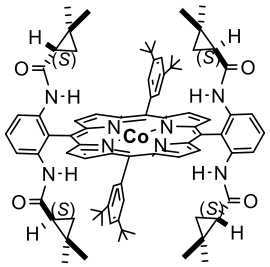



**1**
0.1 mmol

**2**
1.5 eq

| Entry | Additive | Yield (%) | ee(%) |
|---|---|---|---|
| 1 | DMAP (10 mol %) | NR | - |
| 2 | $Et_3N$ (10 mol %) | 12 | 18 |
| 3 | $PPh_3$ (10 mol %) | NR | - |

Yields determined via NMR.




[Co(3,5-Di$^t$Bu-ChenPhyrin)]

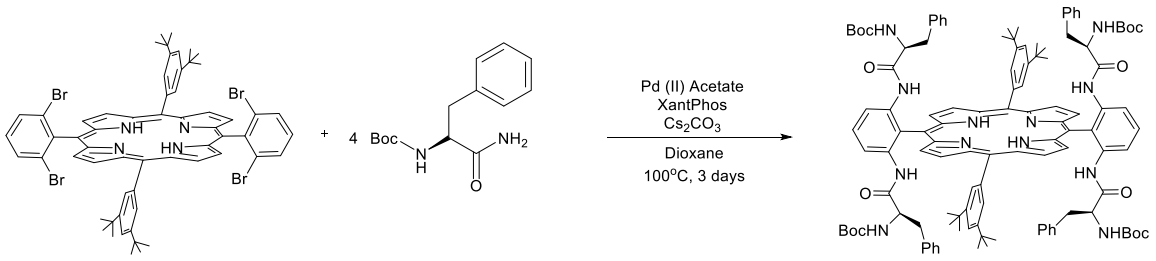
Although DMAP (entry 1) has been successful in previous MRC systems[49], it completely shut down the reaction, as did triphenylphosphine (entry 3). Triethylamine yielded product, however with significantly decreased yields and enantioselectivity.

The low enantioselectivity could either be attributed to poor catalyst control or an indicator that the free radical was involved in a non-catalytic radical chain process. There was clearly a positive effect of having the chiral center of the catalyst close to cobalt porphyrin system as well as having a sterically unhindered amide unit. This led to the rationale to design a new catalyst that contained a chiral center very close to the porphyrin center, could extend the ligand units significantly to encase the free radical better, and a catalyst system with high variability. Amino acids provide such a variability and provide a convenient chiral library we sought to exploit. Thinking that by simply coupling an amide-derived protected amino acid (Scheme 19) using Buchwald-Hartwig[50] conditions used

[49] Ruppel, J. V.; Gauthier, T. J.; Snyder, N. L.; Perman, J. A.; Zhang, X. P. *Org. Lett.* **2009**, *11*, 2273.
[50] Buchwald, S.L., Ruiz-Castillo, P. *Chem. Rev.* **2016**, *116*, 12564.

previously, we could synthesize this amino acid-derived porphyrin ligand. If possible, the chiral catalyst library could grow through the various amino acids and the potential to couple a second amino acid fragment to the first.

**Scheme 19**: Buchwald-Hartwig Amination of Boc-Amino Acid Derivatives with Bromo-Porphyrin Synthons



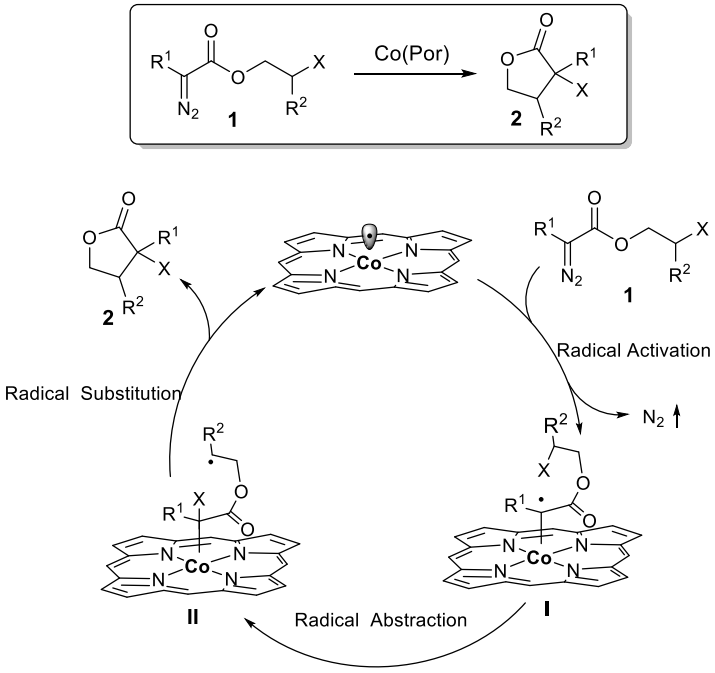

Standard coupling conditions by our group[51] were unsuccessful and varying the base, temperature and time did not yield the desired product. While this attempt did not prove successful, designing new types of chiral catalysts should ultimately be capable of yielding a highly asymmetric ATRA procuess with mild conditions, without the need for additives and with a broad substrate scope.

Our catalytic system could easily undergo this ATRA reaction and showed some promising enantioselectivity. However, there was the potential that the free radical process could not be suppressed. Inspired by previous work done recently in our group[52,53] with asymmetric intramolecular 1,5-hyrdogen atom abstraction (HAT) reactions, we theorized this could apply to halogen atom abstraction reactions and could potentially better control the enantioselectivity. By activating a diazo or diazo-precursor to form an α-$Co^{III}$-alkyl

[51] Wang, Y.; Zhang, X. P. "[Co(3,5-Di-*t*-Bu-ChenPhyrin)]" *e*-EROS, John Wiley & Sons, **2018**.
[52] Wang, Y.; Wen, X.; Cui, X.; Zhang, X.P. *J. Am. Chem. Soc.*, **2018**, *140*, 4792.
[53] Wen, X.; Wang, Y.; Zhang, X.P. *Chem. Sci.*, **2018**, *9*, 5082.

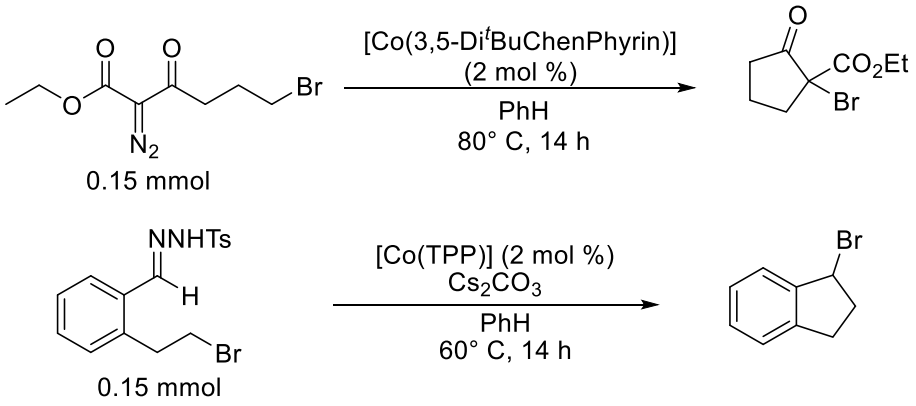
radical, this radical could potentially undergo 1,5-halogen atom abstraction to form a new γ-$Co^{III}$-alkyl radical (**intermediate II**). This radical could undergo radical substitution at the cobalt center, as previously demonstrated, to form the new carbon-halogen bond, while regenerating the metal catalyst (Scheme 20).

**Scheme 20**: General Mechanism for Cobalt Catalyzed Intramolecular 1,5- Halogen Atom Transfer




The main concern was, while 1,5-HAT reactions are well demonstrated in the literature, 1,5-halogen atom transfer reactions are scarce. Theoretically this is due to the limited available bonding orbitals. While hydrogens also has these limitations, halogens are larger and more electronegative as compared to that of hydrogen, which could cause the potential challenges. We synthesized different starting materials with both diazo moieties as well as diazo precursors, tosyl hydrazones, and representative examples are shown below (Scheme 21).

**Scheme 21**: Representative Examples of Cobalt Catalyzed Intramolecular 1,5-Halogen Atom Transfer




Unfortunately, no desired products were obtained in these reactions. We hypothesized that compared the hydrogen atom, the halogen is much larger. The α-cobalt center where the halogen abstraction is already very congested, which is why this larger halogen molecule may not abstract. As well, the longer bond angle may not be optimal for this type of reactions. However, we hypothesized that for the future, we could optimize these substrates for 1,5-HAT reactions which, although not a direct halogen atom abstraction, could still form a newly enantioenriched carbon center.

## VI. Conclusion

We have developed a highly regioselective ATRA reaction via Co-MRC using non-chiral porphryin ligands. Utilizing cobalt amindo-porphyrin complexes, we were able to show high regioselectivity for internal olefins as well as electron-deficient olefins. This methodology requires relatively low temperatures without the need for any additives. This reaction was also able to achieve a promising level of enantioselectivity of up to 33% ee. The right catalyst ligand system has the potential in the future to furnish this product highly

enantioselective with a broad substrate scope. Mechanistic evidence coincides with the theorized stepwise radical mechanism.

## VII. Experimental

### General Information:

$^1$H NMR spectra were recorded on a Varian INOVA 400 (400 MHz), 500 (500 MHz) or 600 (600 MHz) spectrometer. The chemical shifts are reported in ppm using the solvent resonance as the internal standard ($CDCl_3$; 7.26 ppm). Reported as the following: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets), and coupling constants to the nearest 0.5 Hz. High-resolution mass spectrometry was performed on (ESI and MALDI) was performed at the Mass Spectrometry Facility at Boston College. HPLC measurements were carried out on a Shimadzu HPLC system with Chiralcel AD-H, OD-H, IC and IA.

Unless otherwise noted, all ATRA reactions were performed under an atmosphere of dry $N_2$, in an oven-dried Schlenk glassware with standard vacuum techniques. Gas tight syringes were used to transfer liquid reagents and solvents in catalytic reactions. Anhydrous solvents, as well as other commercial reagents were purchased from the following companies: Sigma-Aldrich, Acros, Alfa Aesar, Strem, Oakwood Products Inc., TCI, Fisher, or Matrix Scientific and used as received unless otherwise stated. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 Å F254). Flash column chromatography was performed with ICN silica gel (60 Å, 230-400 mesh, 32-63 μm). Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle and visualization was performed using ultraviolet light (254 nm). HPLC measurements were carried out on a Shimadzu HPLC system with Chiralcel AD-H. The UV-Vis absorption spectra in the range 200 – 700 nm were measured with an Evolution 300 UV-VIS spectrophotometer using quartz cuvettes with 1.0 cm optical path length.

### *Preparation of [Co(Por)]-Catalyzed Atom Transfer Radical Addition Reactions*

An oven-dried Schlenk tube was equipped with a stirring bar and charged with [Cobalt(II) Tetraphenylporphyrin] (2 mol %). The Schlenk tube was evacuated and back filled with nitrogen 3 times. The Teflon screw cap was removed and replaced with a rubber septum, and 3-bromostyrene (0.1 mmol), trichloroacetonitrile (0.15 mmol, 1.5 eq) and benzene (0.5 mL) were added. The Schlenk tube was then purged with nitrogen for 30 s and the rubber septum was replaced with a Teflon screw cap. The mixture was stirred at 80°C. After 14 hr, the reaction mixture was cooled to room temperature, concentrated and purified by flash chromatography. Solvents were removed in vacuo to yield the desired compound.

***General Procedure for Preparation of [Co(Por)] Catalysts***

[$H_2$(Por)] were synthesized according to our previous reported procedure[54]. The 5,15-bis(2,6-dibromophenyl)-10,20-bis(X)-porphyrin (0.2 mmol), carboxamide (3.2 mmol), 4 Å molecular sieves, $Pd(OAc)_2$ (0.08 mmol), Xantphos (0.16 mmol), and $Cs_2CO_3$ (3.2 mmol) were placed in an oven-dried, resealable Schlenk tube. The tube was capped with a Teflon screwcap, evacuated, and backfilled with nitrogen for three times. After that, the screwcap was replaced with a rubber septum, and dioxane (10 mL) was added via gas-tight syringe. The tube was purged with nitrogen for 2 minutes, and then the septum was replaced with the Teflon screwcap. The tube was sealed and stirred at 100 ºC for 72 hrs. The resulting mixture was cooled to room temperature, diluted in ethyl acetate, filtrated through a silica pad and concentrated in vacuo. The pure compound was obtained as a purple solid after purification by flash column chromatography.

[Co(Por)] was synthesized according to our previous reported procedure[46]. Free base porphyrin [H2(Por)] and anhydrous $CoCl_2$ (8 equiv.) were placed in an oven-dried, resealable Schlenk tube. The tube was capped with a Teflon screwcap, evacuated, and backfilled with nitrogen. The screwcap was then replaced with a rubber septum, 2,6-lutidine (4 equiv.) and anhydrous THF were added via gas-tight syringe. The tube was purged with nitrogen for 2 minutes, and then the septum was replaced with the Teflon screwcap. The reaction was conducted at 80 ºC for 12 hrs. The resulting mixture was cooled to room temperature, diluted with ethyl acetate, and transferred to a separatory funnel. The reaction mixture was washed with water for 2 times and concentrated in vacuo. The target compound [Co(Por)] was isolated as a purple solid after purification by flash column chromatography.

**2,2,4-trichloro-4-phenylbutanenitrile.** The title compound **3a** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:20 ethyl acetate / hexanes) to afford a clear oil (97% yield). $R_f$ = 0.42 (ethyl acetate / hexanes = 1:20). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.60 (t, *J* = 1.7 Hz, 1H), 7.52 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.37 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 – 7.24 (m, 1H), 5.16 (t, *J* = 6.7 Hz, 1H), 3.34 (ddd, *J* = 15.1, 7.2, 1.2 Hz, 1H), 3.18 (ddd, *J* = 15.2, 6.3, 1.2 Hz, 1H). $^{13}$C NMR (126 MHz, $cdcl_3$) δ 140.79, 132.68, 130.67, 130.37, 125.92, 123.07, 114.34, 65.76, 56.36, 55.76, 29.69. HRMS (Dart+) ($[M+H]^+$) Calcd. For $C_{10}H_8Cl_3N^+$: 246.9722, Found: 246.9726.

**4-(3-bromophenyl)-2,2,4-trichlorobutanenitrile.** The title compound **3g** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:20 ethyl acetate / hexanes) to afford a yellow oil (88% yield). $R_f$ = 0.42 (ethyl acetate / hexanes = 1:20). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 5.16 (t, *J* = 6.7 Hz, 1H), 3.34 (dd, *J* = 15.2, 7.2 Hz, 1H), 3.18 (dd, *J* = 15.2, 6.2 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 140.79, 132.68,

[54] Chen, Y.; Fields, K. B.; Zhang, X. P. *J. Am. Chem. Soc*. **2004**, *126*, 14718.

130.67, 130.37, 125.92, 123.07, 114.34, 77.25, 77.00, 76.74, 65.76, 56.36, 55.76. IR (neat, $cm^{-1}$): 3061.34, 2927.03, 2850.14, 2251.48, 1593.59, 1429.66, 1214.52, 1073.72, 997.50, 828.19, 695.82. HPLC analysis: ADH (100% hexanes, 1.0 mL/min). $t_1$ = 21.48 min, $t_2$ = 29.34 min. HRMS (Dart+) ($[M+H]^+$) Calcd. For $C_{10}H_7BrCl_3N^+$: 324.8827, Found: 324.8831.

**2,2,4-trichloro-4-(4-methoxyphenyl)butanenitrile.** The title compound **3b** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:10 ethyl acetate / hexanes) to afford a clear oil (98% yield). Rf = 0.35 (ethyl acetate / hexanes = 1:10). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.34 (m, 2H), 7.01 – 6.88 (m, 2H), 5.21 (td, *J* = 6.8, 1.1 Hz, 1H), 3.83 (d, *J* = 1.3 Hz, 3H), 3.36 (ddd, *J* = 15.0, 6.7, 1.2 Hz, 1H), 3.23 (ddd, *J* = 15.0, 7.0, 1.2 Hz, 1H).

**2,2,4-trichloro-4 -(2,4,6-trimethoxyphenyl)butanenitrile.** The title compound **3c** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:10 ethyl acetate / hexanes) to afford a clear oil (97% yield). $R_f$ = 0.29 (ethyl acetate / hexanes = 1:10). $^1$H NMR (500 MHz, Chloroform-*d*) δ 6.63 (s, 2H), 5.12 (td, *J* = 6.7, 3.1 Hz, 1H), 4.11 (qd, *J* = 7.2, 2.9 Hz, 1H), 3.94 – 3.86 (m, 14H), 3.85 (s, 3H), 3.39 – 3.28 (m, 1H), 3.17 (dtd, *J* = 14.0, 4.7, 4.2, 2.0 Hz, 1H).

**2,2,4-trichloro-4-mesitylbutanenitrile.** The title compound **3d** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:20 ethyl acetate / hexanes) to afford a yellow oil (80% yield). $R_f$ = (ethyl acetate / hexanes = 1:20). $^1$H NMR (500 MHz, Chloroform-*d*) δ 6.95 – 6.88 (m, 2H), 5.75 (ddd, *J* = 6.7, 5.0, 1.0 Hz, 1H), 3.59 (ddd, *J* = 15.3, 6.8, 1.1 Hz, 1H), 3.35 (ddd, *J* = 15.4, 4.9, 1.1 Hz, 1H), 2.58 (s, 3H), 2.48 (s, 3H), 2.30 (s, 3H).

**2,2,4-trichloro-4-(2-(trifluoromethyl)phenyl)butanenitrile.** The title compound **3f** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:20 ethyl acetate / hexanes) to afford a yellow oil (79% yield). $R_f$ = 0.42 (ethyl acetate / hexanes = 1:20). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.55 – 7.46 (m, 1H), 5.71 (dd, *J* = 8.6, 4.5 Hz, 1H), 3.35 (ddd, *J* = 15.4, 8.5, 0.9 Hz, 1H), 3.17 (ddd, *J* = 15.3, 4.5, 0.9 Hz, 1H).

**2,2,4-trichloro-4-(3-nitrophenyl)butanenitrile.** The title compound **3h** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:20 ethyl acetate / hexanes) to afford a yellow oil (81% yield) as a mixture of inseparable regioisomers. $R_f$ = 2.1 (ethyl acetate / hexanes = 1:20). $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.33 (t, *J* = 2.0 Hz, 1H), 8.24 (ddd, *J* = 8.3, 2.2, 1.0 Hz, 1H), 7.79 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 5.31 (t, *J* = 6.8 Hz, 1H), 3.40 (dd, *J* = 15.2, 6.8 Hz, 1H), 3.25 (dd, *J* = 15.2, 6.7 Hz, 1H).

**2,2,4-trichloro-4-(3-formylphenyl)butanenitrile.** The title compound **3i** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:20 ethyl acetate / hexanes) to afford a yellow oil (87% yield) as a mixture of inseparable regioisomers. $R_f$ = (ethyl acetate / hexanes = 1:20). $^1$H NMR (400 MHz, Chloroform-*d*) δ 10.00 (s, 1H), 7.94 (d, *J* = 1.8 Hz, 1H), 7.87 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.74 – 7.67 (m, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 5.27 (t, *J* = 6.8 Hz, 1H), 5.04 (dd, *J* = 8.5, 6.0 Hz, 0H), 4.00 (dd, *J* = 11.4, 6.0 Hz, 0H), 3.91 (dd, *J* = 11.3, 8.5 Hz, 0H), 3.37 (dd, *J* = 15.1, 6.9 Hz, 1H), 3.21 (dd, *J* = 15.2, 6.6 Hz, 1H).

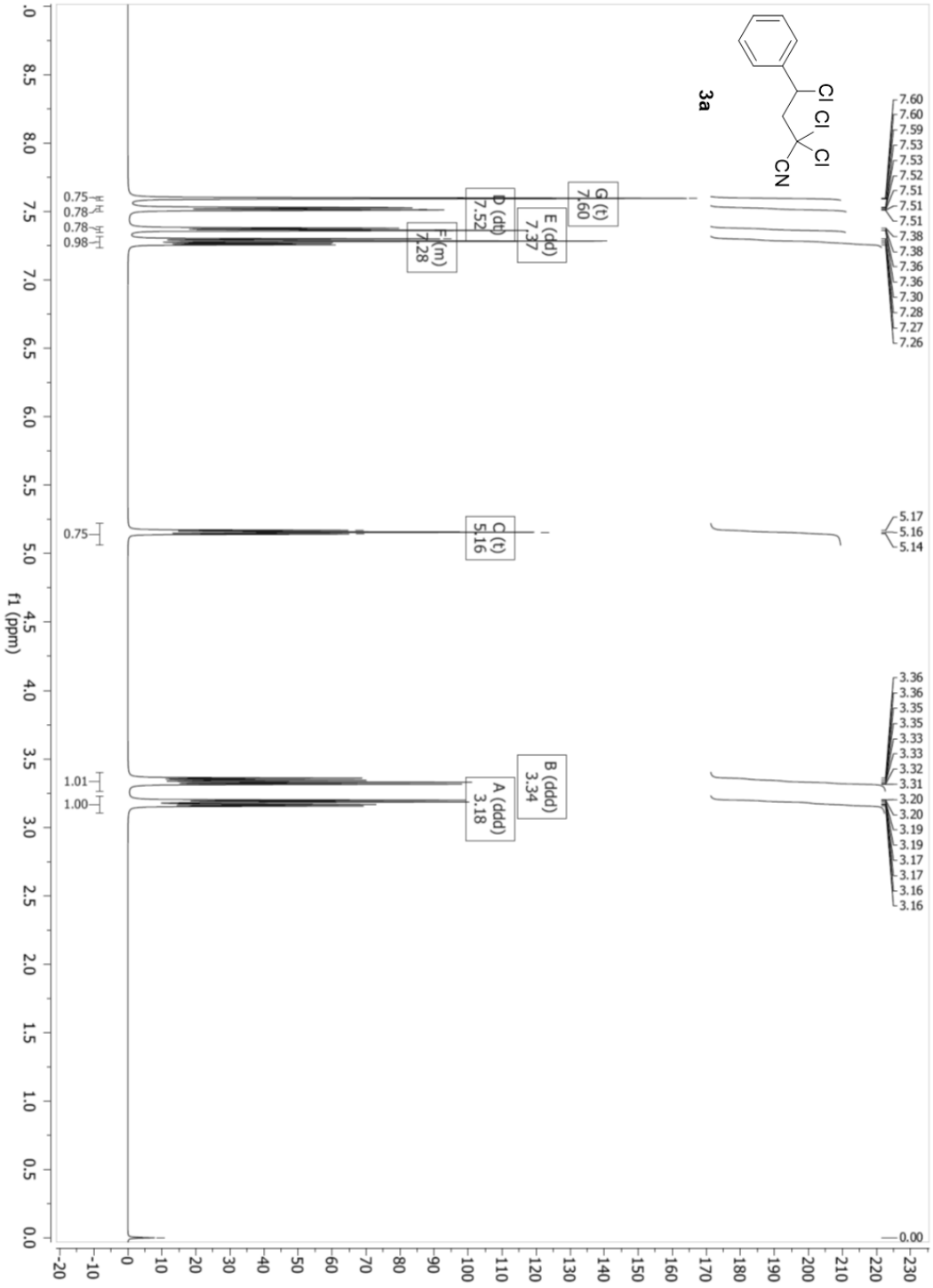
**2,2,4-trichloro-4-(pyridin-4-yl)butanenitrile.** The title compound **3j** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:10 ethyl acetate / hexanes) to afford a clear oil (34% yield). $R_f$ = 0.27 (ethyl acetate / hexanes = 1:10). $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.73 – 8.62 (m, 2H), 7.44 – 7.28 (m, 2H), 5.15 (dd, *J* = 7.4, 5.7 Hz, 1H), 3.32 (ddd, *J* = 15.3, 7.4, 1.4 Hz, 1H), 3.14 (ddd, *J* = 15.2, 5.7, 1.5 Hz, 1H).

**4-bromo-2,2,4-trichloro-4-phenylbutanenitrile.** The title compound **3k** was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:20 ethyl acetate / hexanes) to afford a yellow oil (22% yield). $R_f$ = 0.42 (ethyl acetate / hexanes = 1:20). $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.15 (m, 5H), 4.65 (s, 0H), 4.09 (s, 0H), 3.86 (s, 3H).

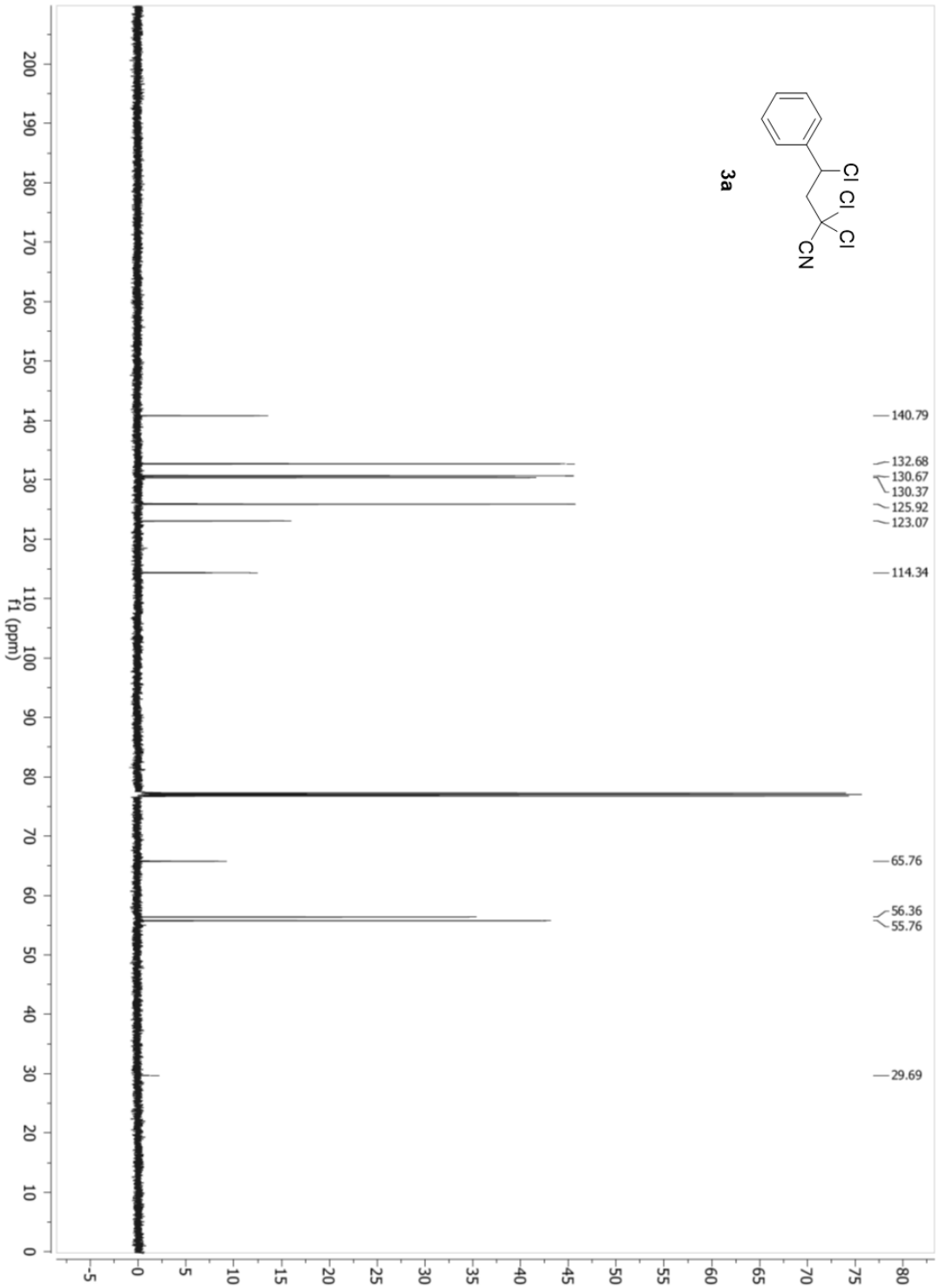
**5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine cobalt(II)-chloride.** The title compound was prepared using the representative procedure, however, 0.05 mmol of [Co(TPP)] were used and 10 equiv. of trichloroacetonitrile. HRMS (MALDI) ($[M+H]^+$) Calcd. For $C_{44}H_{28}ClCoN_4^+$: 706.1331, Found: 706.13.

**(Z)-2,2,7-trichloro-4-phenylhept-4-enenitrile.** The title compound was prepared using the representative procedure. The crude reaction mixture was purified on silica gel (1:20 ethyl acetate / hexanes) to afford a light yellow oil (89% yield). $R_f$ = 0.39 (ethyl acetate / hexanes = 1:20). $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.30 (m, 4H), 6.00 (t, *J* = 7.4 Hz, 1H), 3.77 (s, 2H), 3.66 (t, *J* = 6.6 Hz, 2H), 2.82 (q, *J* = 6.8 Hz, 2H).

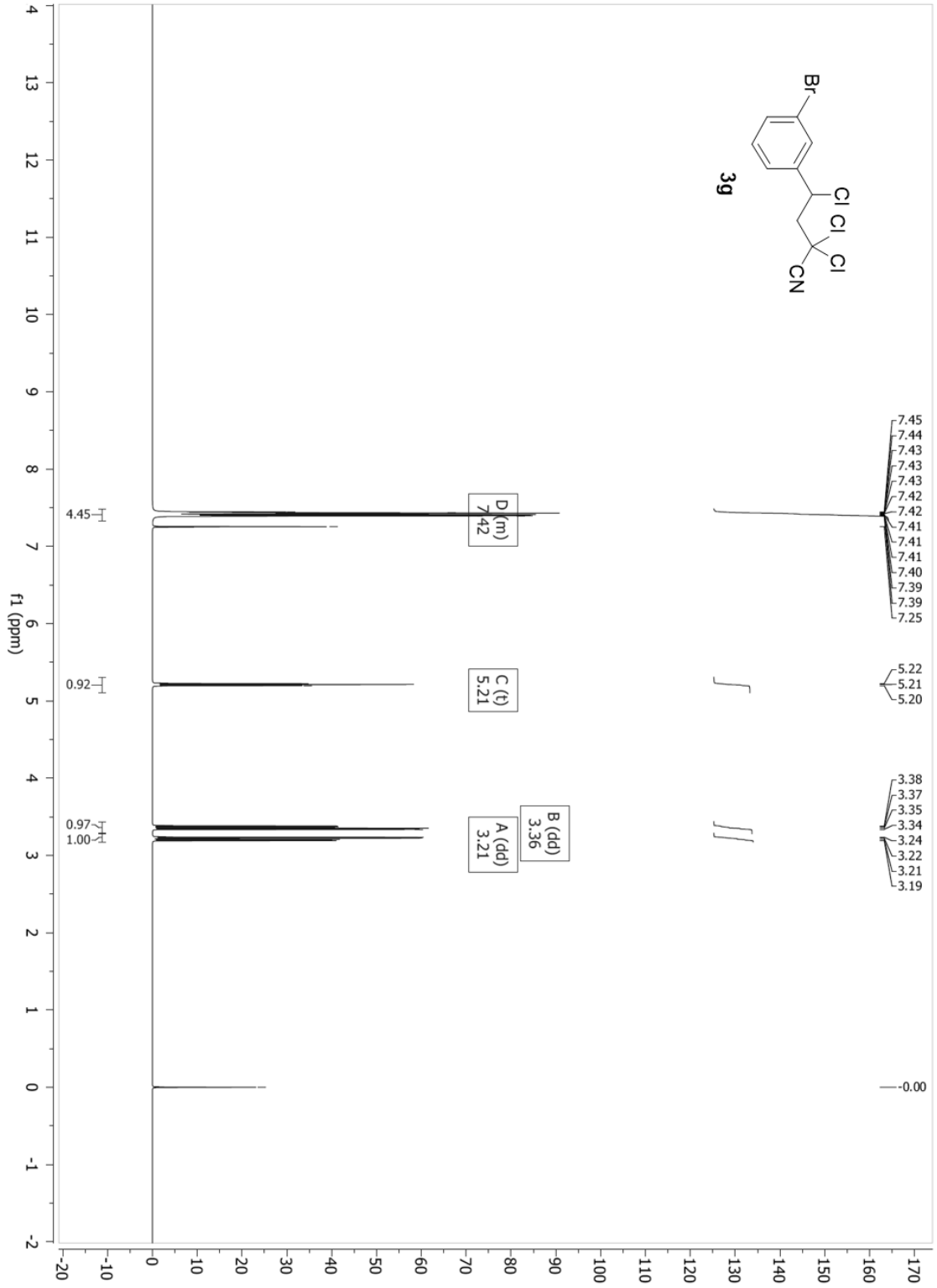
$^{1}$H NMR (500 MHz, Chloroform-*d*)



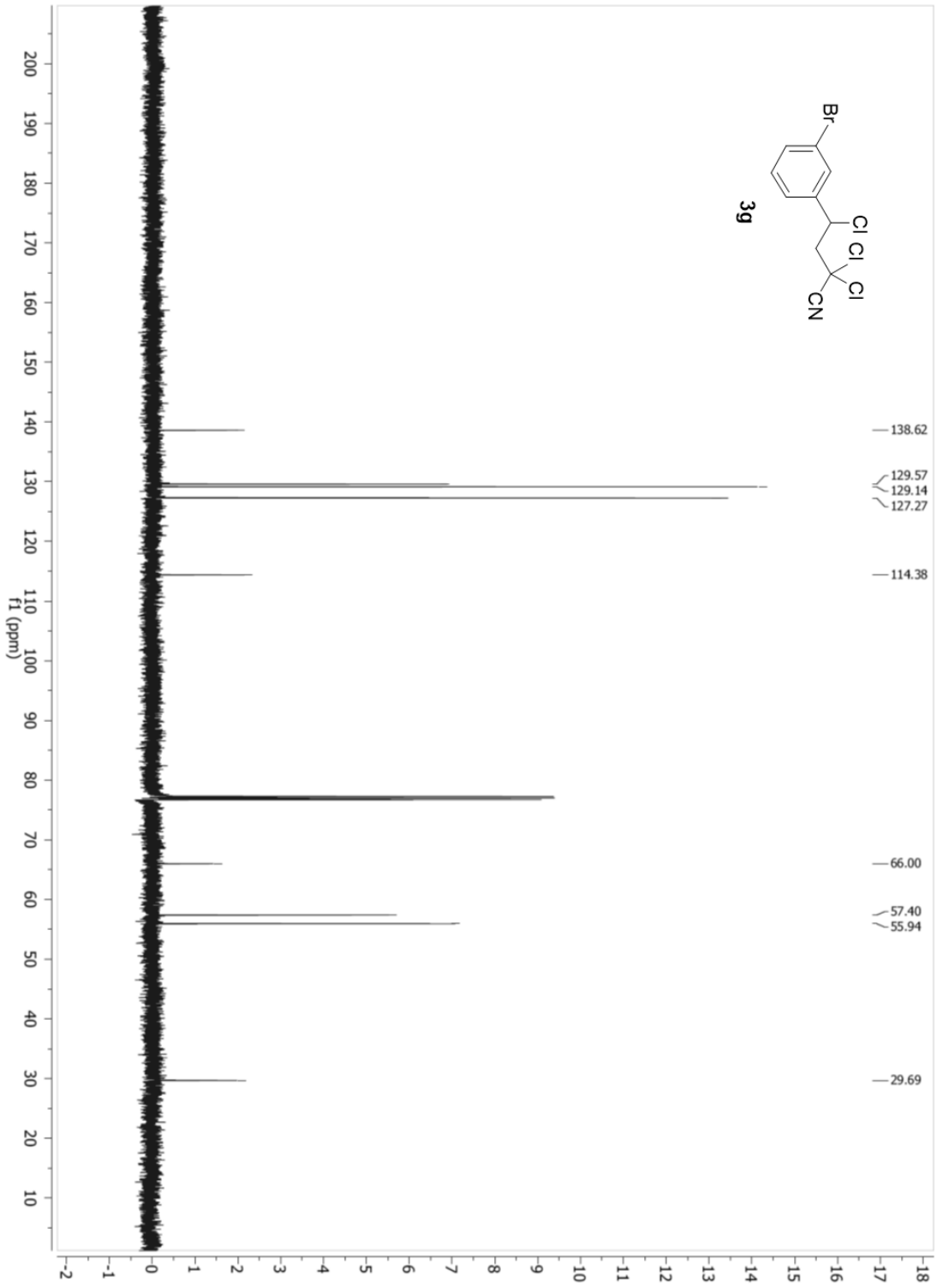
$^{13}C$ NMR (126 MHz, $cdcl_3$)



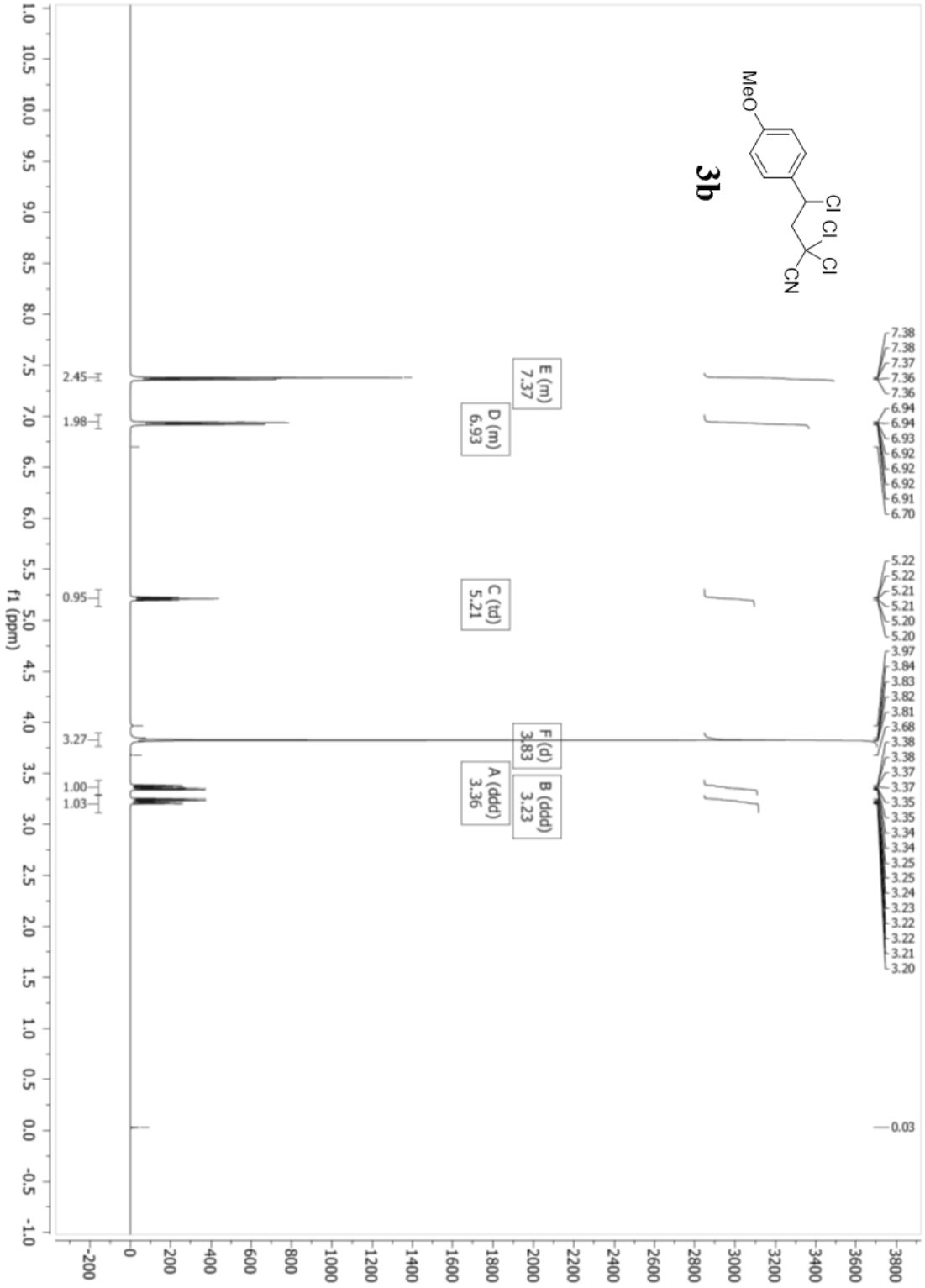
$^{1}$H NMR (500 MHz, Chloroform-*d*)



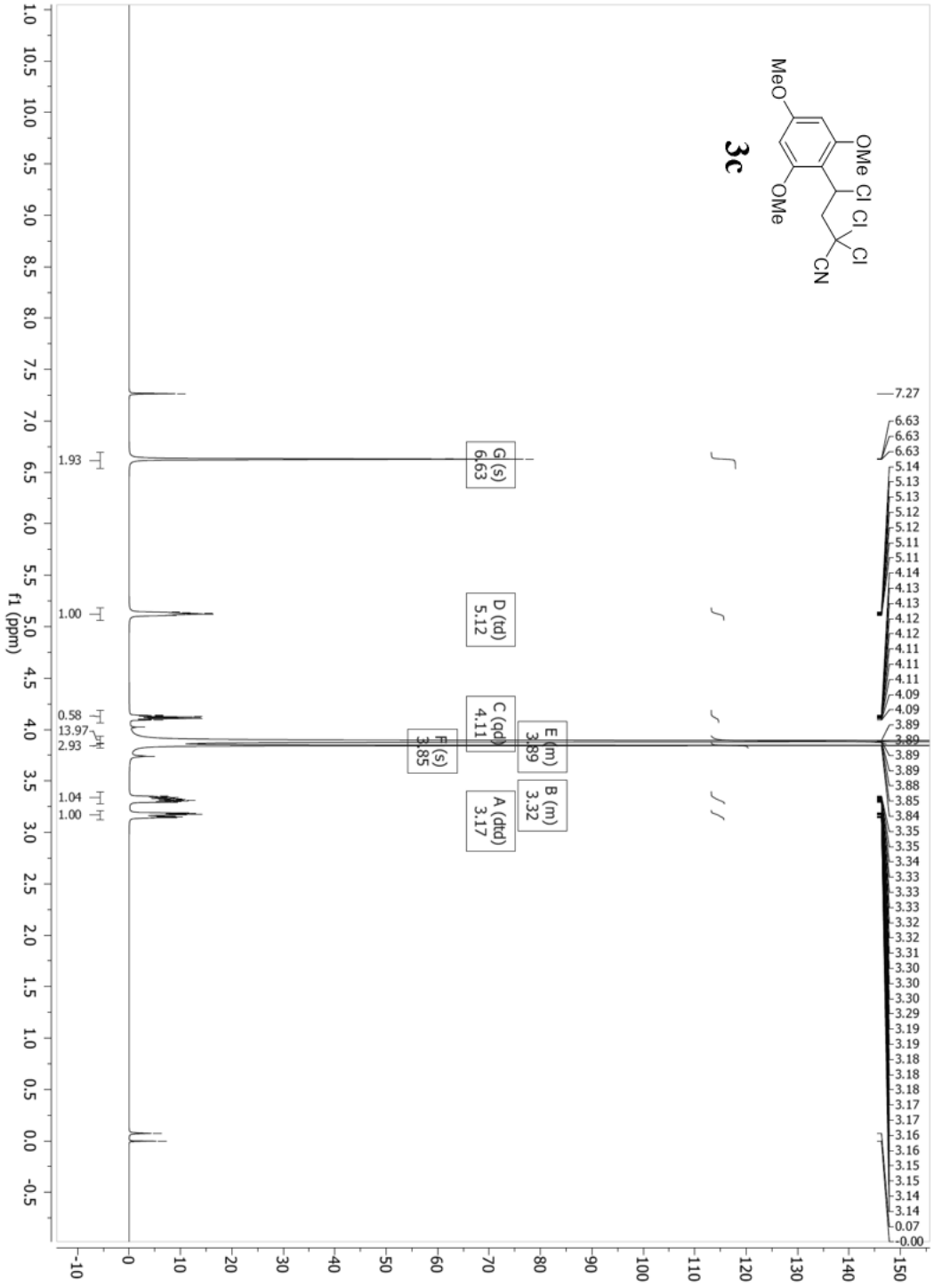
$^{13}C$ NMR (126 MHz, cdcl$_3$)



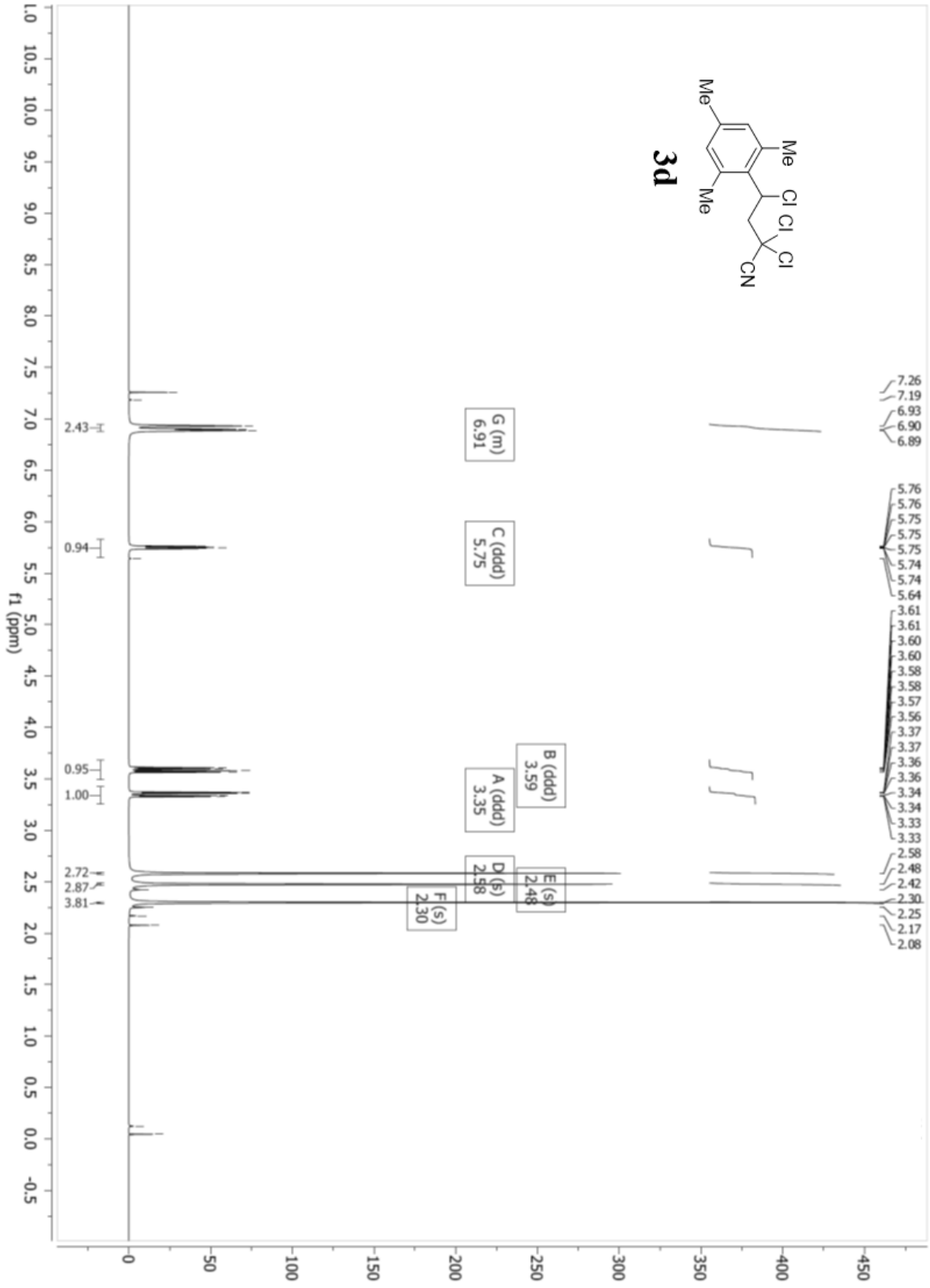
$^{1}$H NMR (500 MHz, Chloroform-*d*)

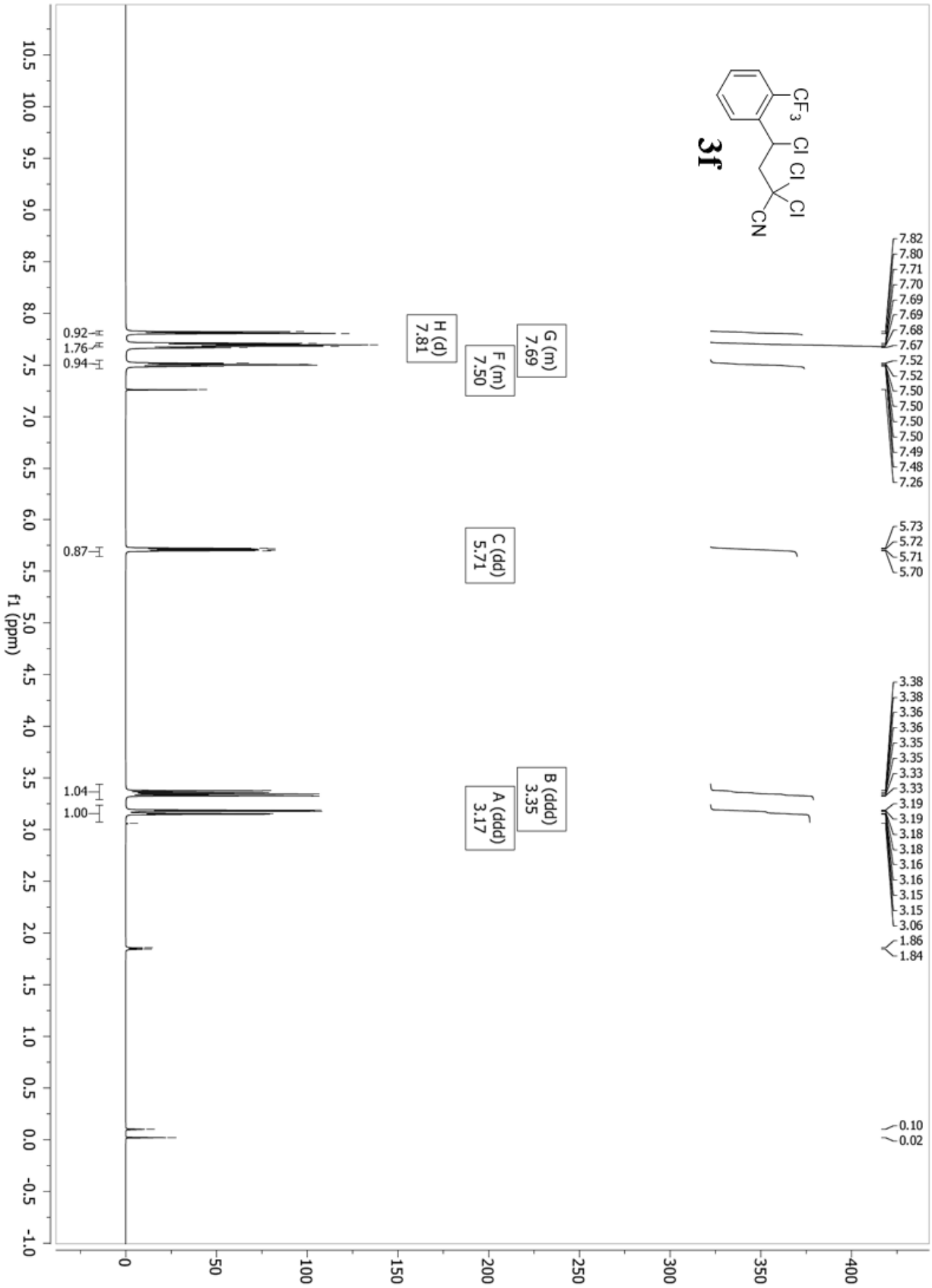


$^{1}$H NMR (500 MHz, Chloroform-*d*)



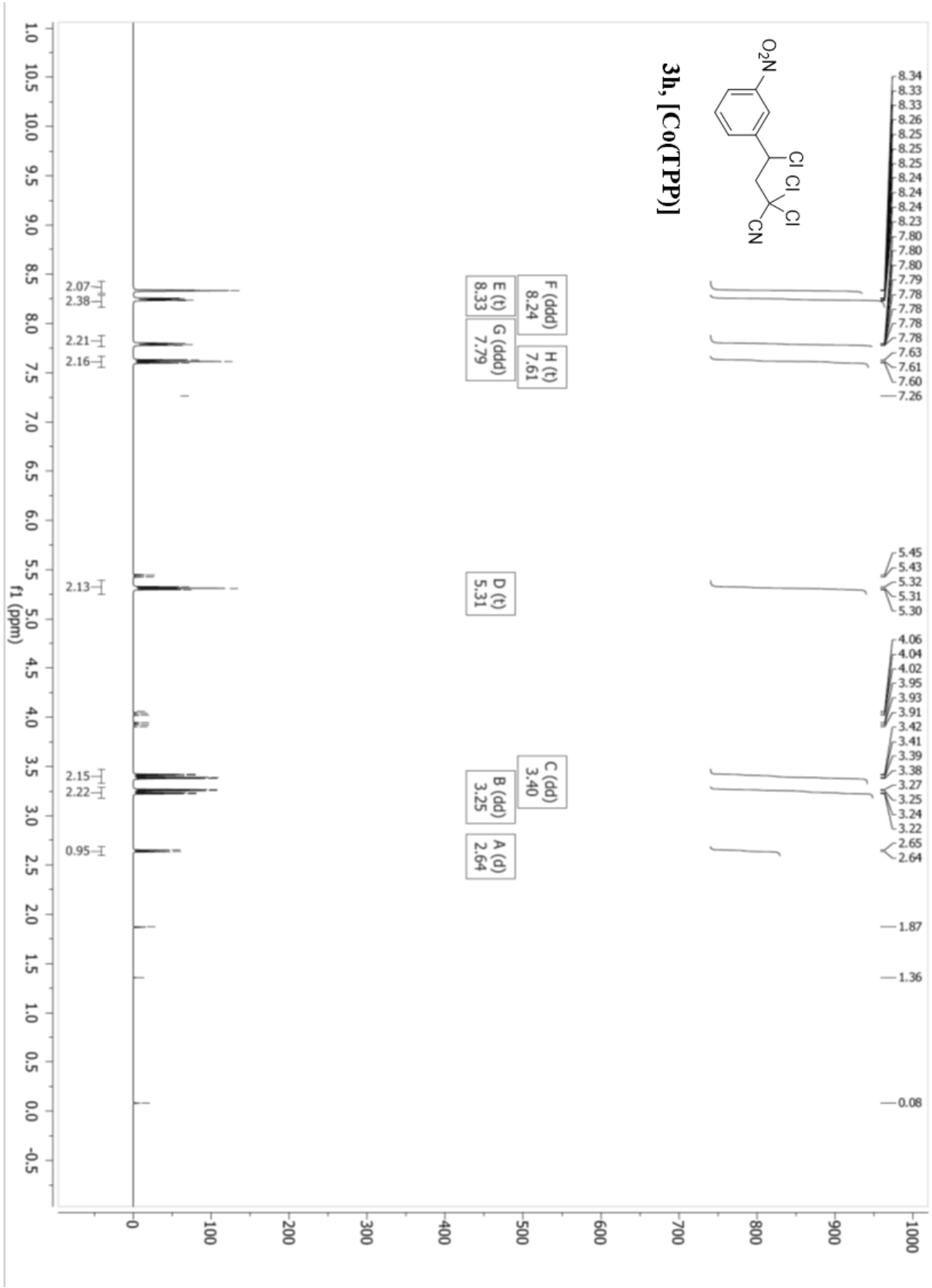
$^{1}$H NMR (500 MHz, Chloroform-*d*)

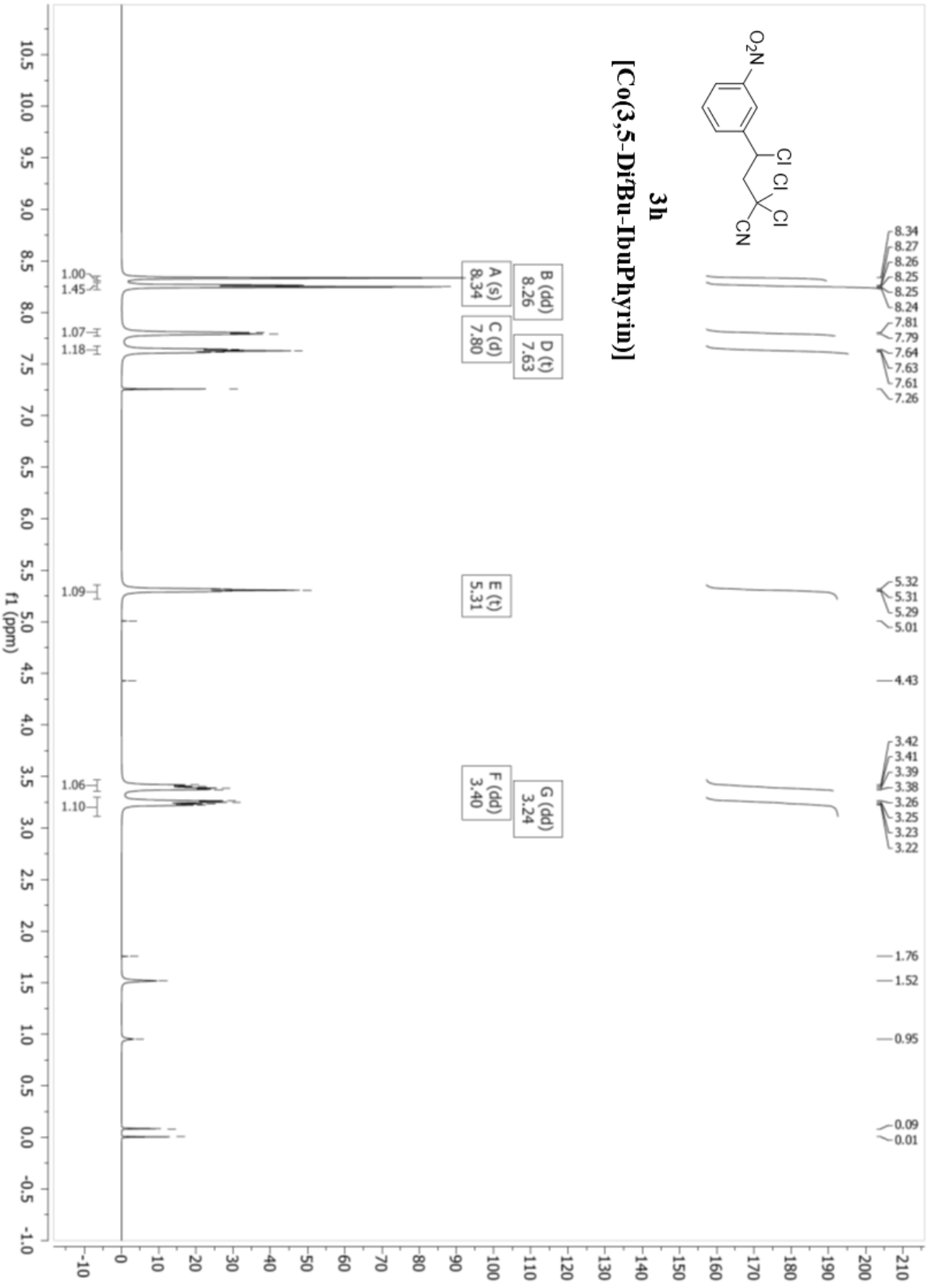




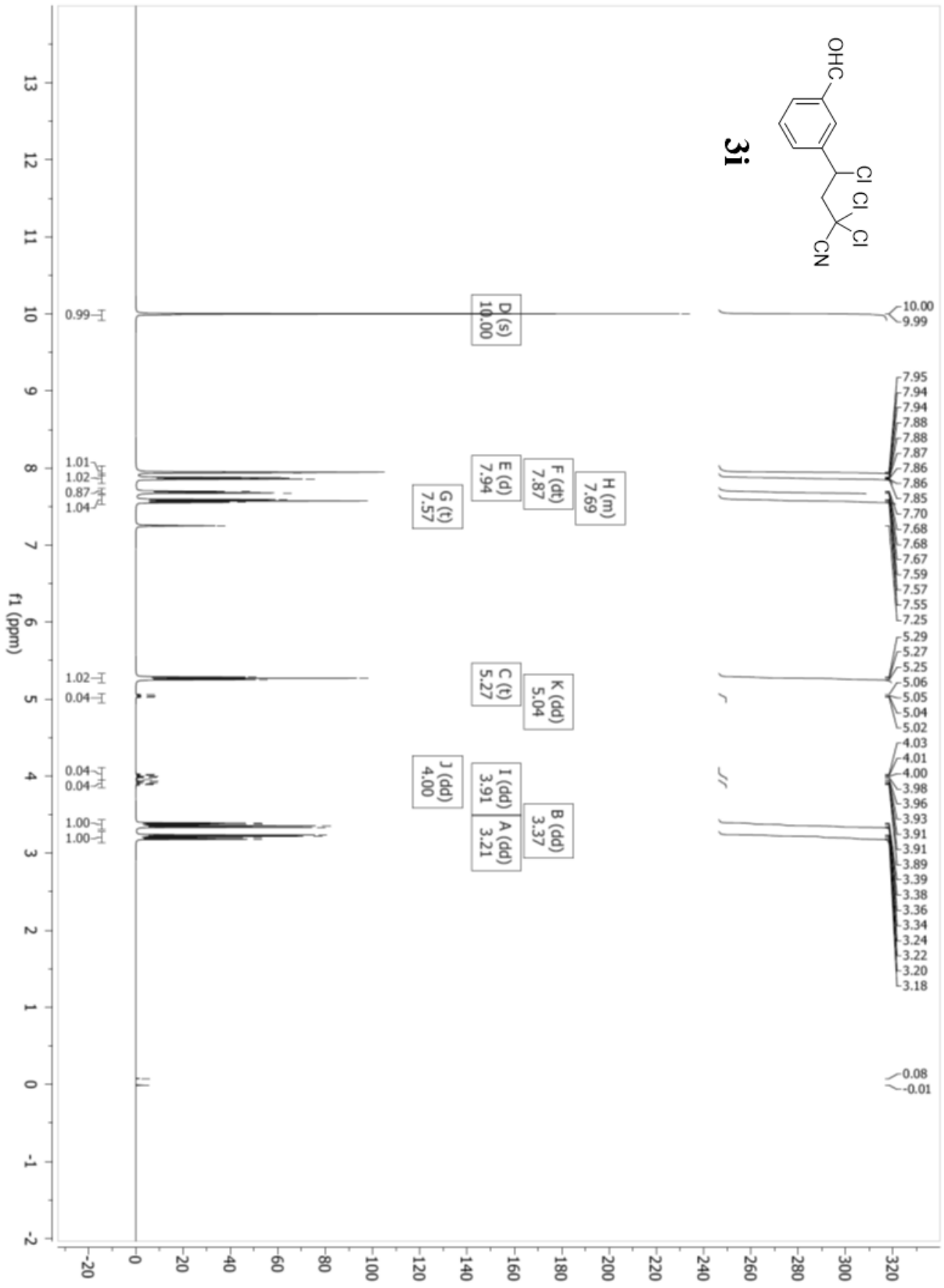

$^{1}$H NMR (500 MHz, Chloroform-*d*)

$^{1}$H NMR (500 MHz, Chloroform-*d*)

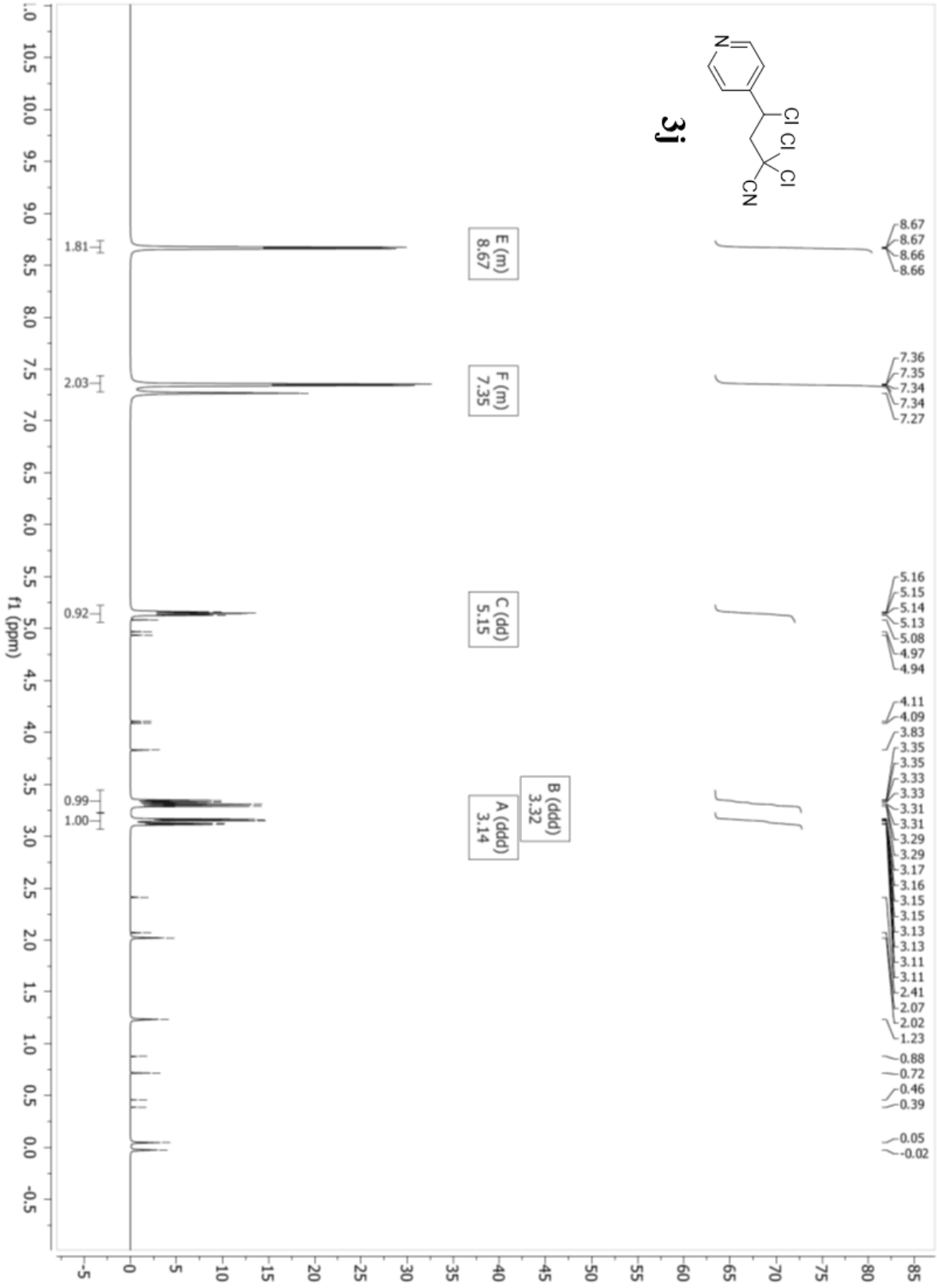




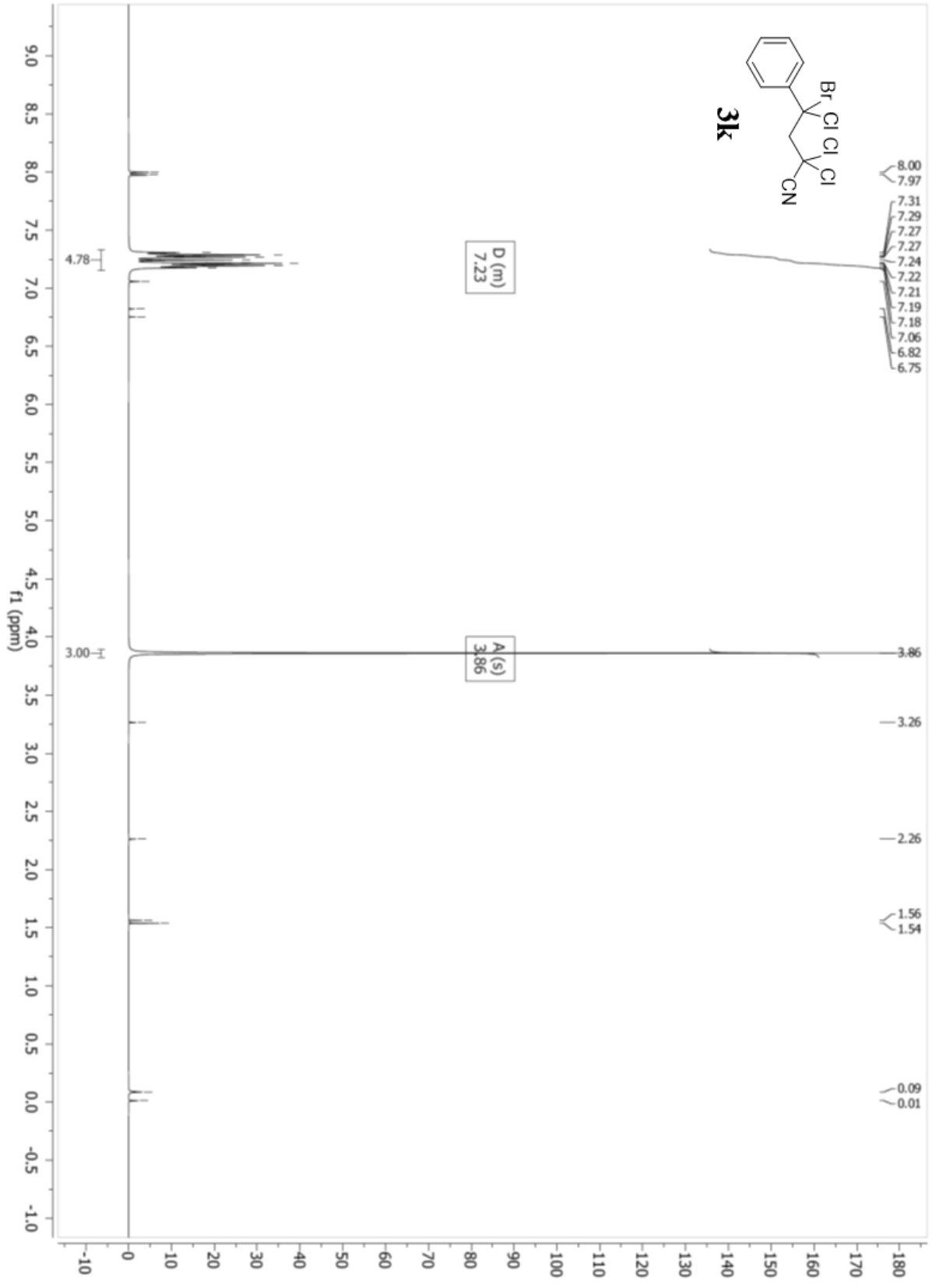

$^{1}$H NMR (500 MHz, Chloroform-*d*)



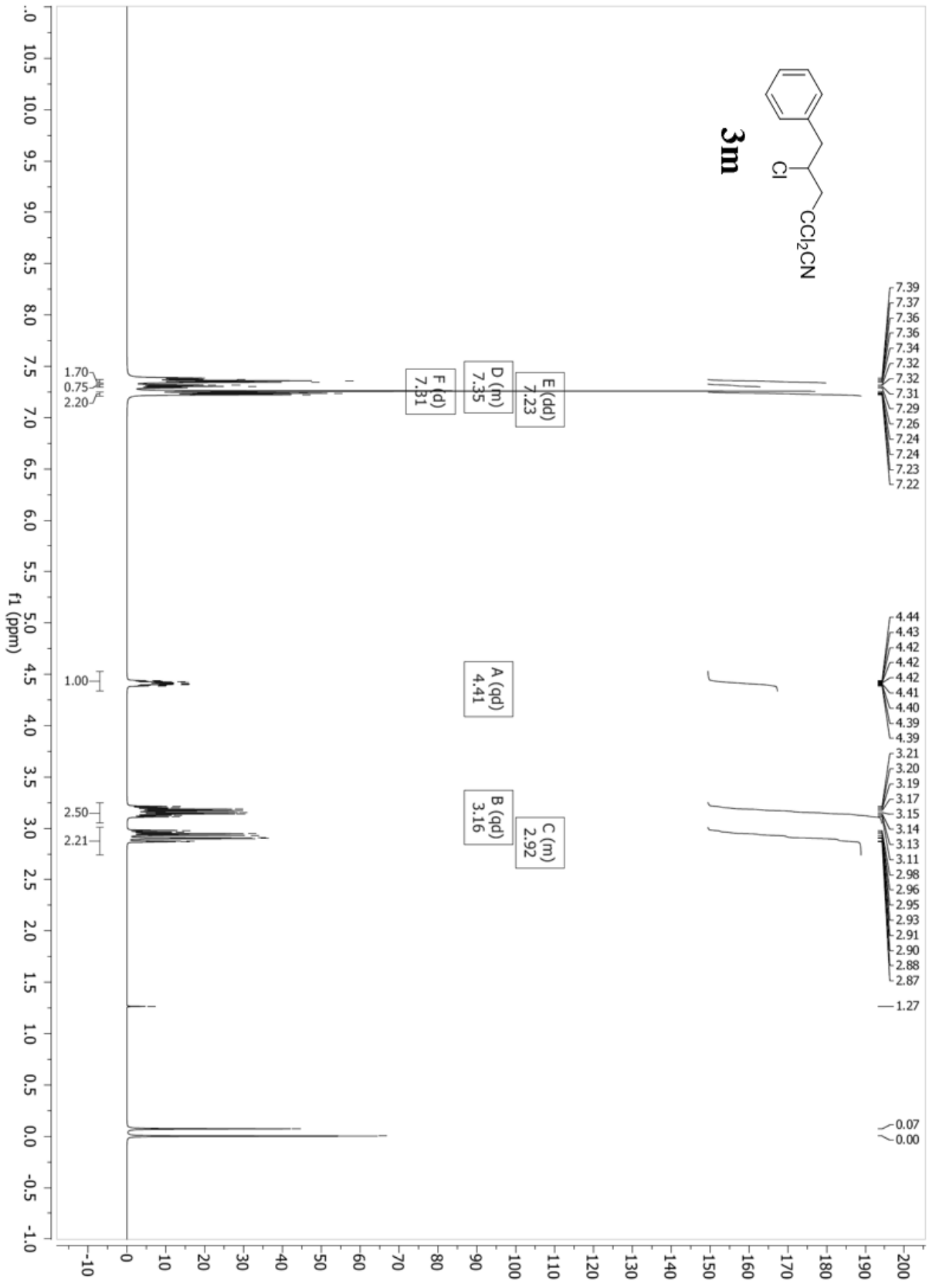

$^{1}$H NMR (500 MHz, Chloroform-*d*)




$^{1}$H NMR (500 MHz, Chloroform-*d*)

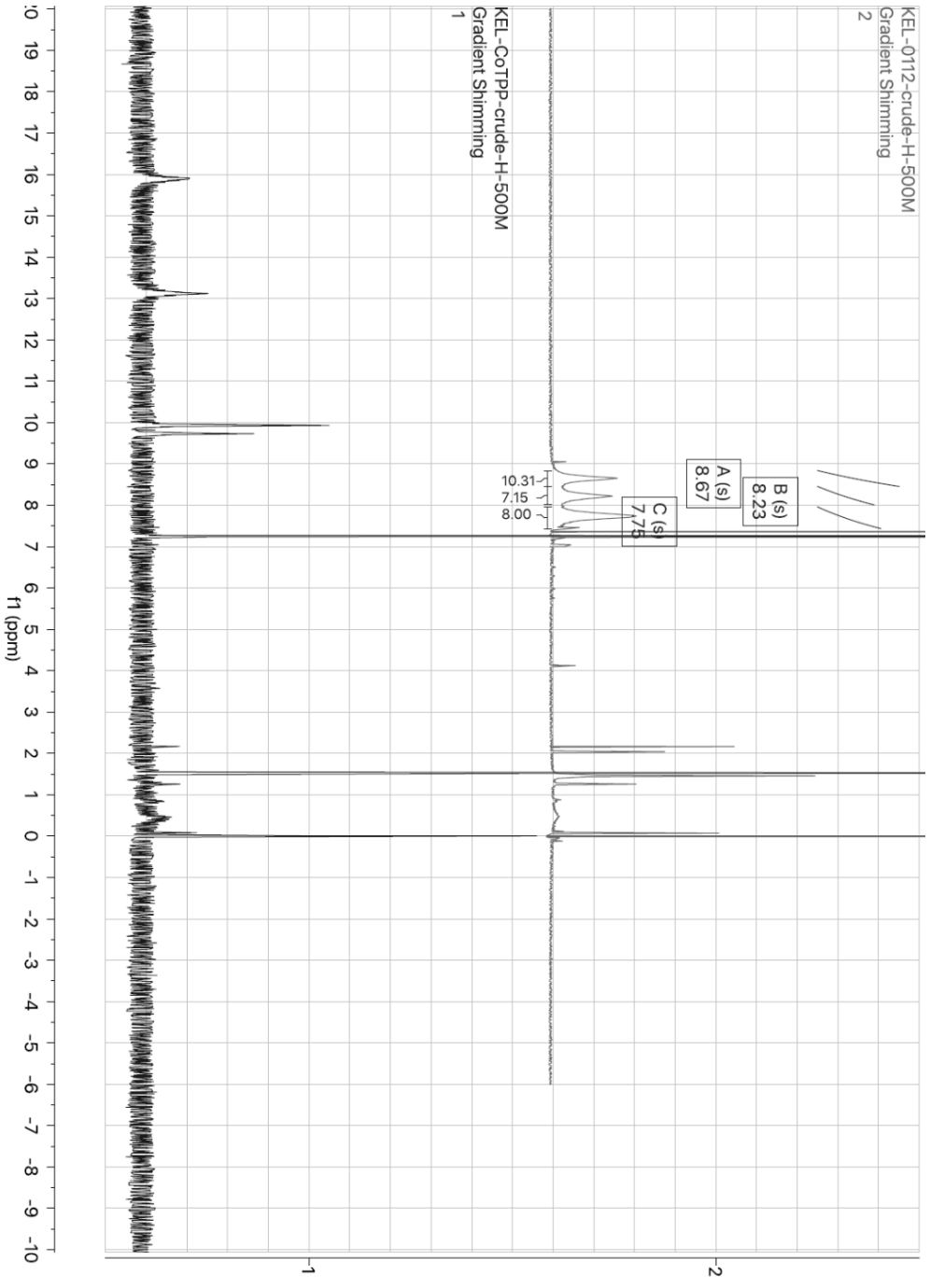



$^{1}$H NMR (500 MHz, Chloroform-*d*)

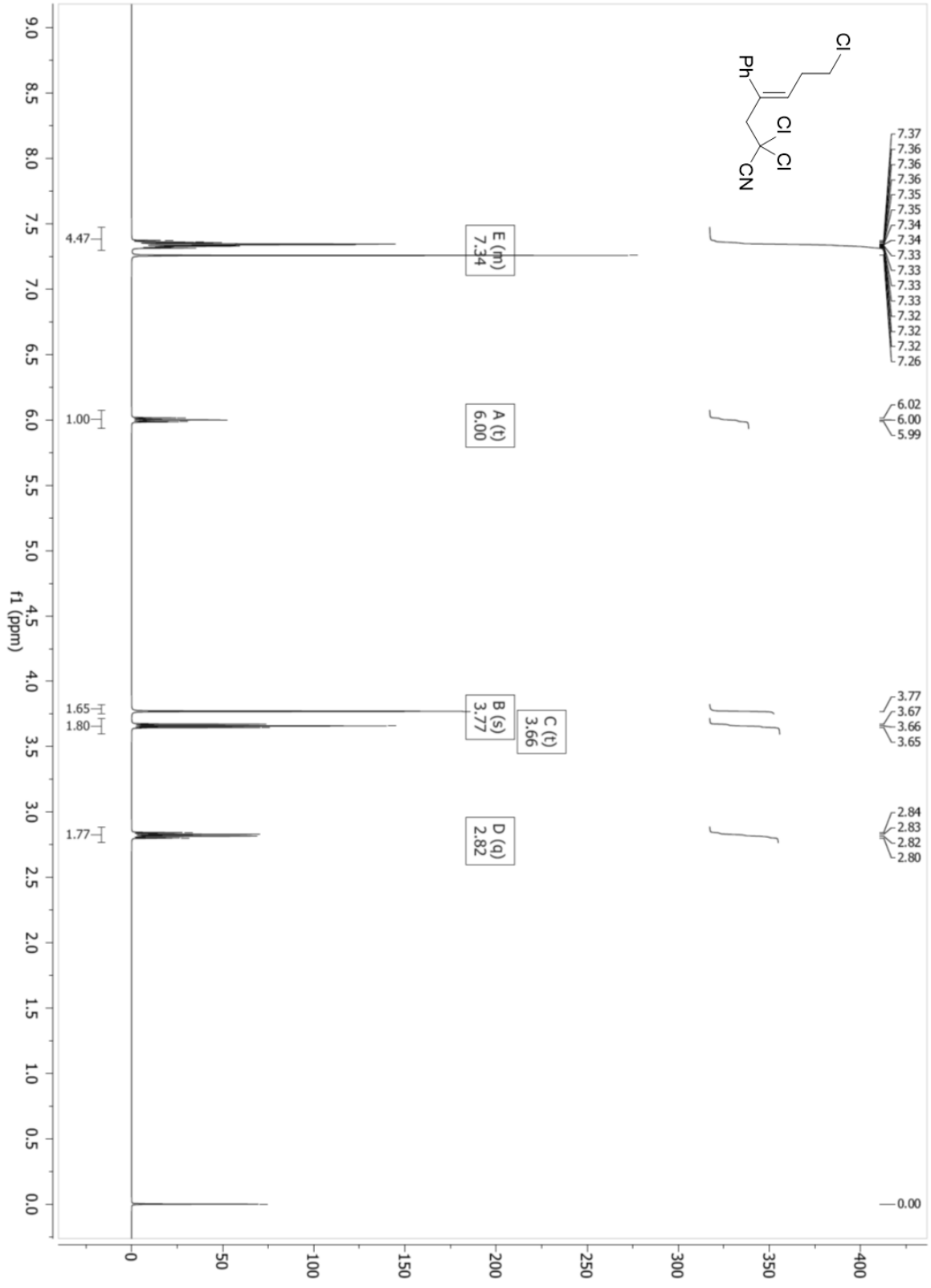



$^{1}$H NMR (500 MHz, Chloroform-*d*)

[Co(TPP)] vs [Co(TPP)Cl]




Reported Literature: 1H NMR (CDCl , δ, ppm): 7.70, 8.19, 8.70
Chen, P., *Inorg. Chem.*, **2004**, *44*, 2588.


Cl
Ph
Cl
Cl
CN
7.37
7.36
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.33
7.33
7.32
7.32
7.32
7.26
6.02
6.00
5.99
3.77
3.67
3.66
3.65
2.84
2.83
2.82
2.80
0.00
E (m) 7.34
A (t) 6.00
B (s) 3.77
C (t) 3.66
D (q) 2.82
4.47
1.00
1.65
1.80
1.77
f1 (ppm)