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Microwave-Promoted Iminyl Radical Fragmentations: A Practical and Efficient Method of Functionalization

Mary Megan Jackman

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Master of Science

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Department of Chemistry and Biochemistry

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ABSTRACT

Microwave-Promoted Iminyl Radical Fragmentations: A Practical and Efficient Method of Functionalization

Mary Megan Jackman
Department of Chemistry and Biochemistry, BYU
Master of Science

We report a novel fragmentation and functionalization method using a cyclic iminyl radical. Formation of this radical occurs by microwave heating under mild conditions and short reaction times. The reaction avoids the use of explosive or toxic radical initiators and propagating agents. This reaction is versatile, with the ability to install two functional groups that are ultimately derived from a ketone in the substrate precursor. A variety of radical traps capable of forming both carbon-carbon bonds and carbon-heteroatom bonds have been tested, and the products are obtained in good yields. We demonstrate the power of this reaction by functionalizing complex natural products.

Keywords: methodology, iminyl radical, fragmentation, microwave irradiation

ACKNOWLEDGEMENTS

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I am indebted to Sia Im and Seth Bohman for their relentless work on the project. Their accomplishments and persistence inspired me to continue working.

I would like to thank my late father, Dennis Blackburn, for instilling in me a confidence to pursue an education in science—and his indignation that anyone would assume I couldn't. I would like to thank my mother, Debi Blackburn, for her unique combination of charity and strength.

Most of all, I would like to thank my wonderful husband, Trent, for his unwavering support. His pride in me, although oftentimes undeserved, helped me push through difficult times. His willingness to be the primary caretaker of our son, his countless days on campus to facilitate feedings, and his enthusiasm to help me finish can never be repaid. It is to him and our son Dennis that I dedicate this thesis.

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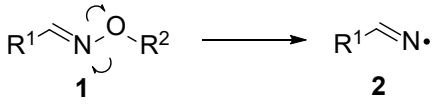
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CHAPTER 1. INTRODUCTION

1.1 Development of oxime derivatives as iminyl radical precursors

Iminyl radical chemistry is an appealing strategy to form carbon–nitrogen bonds present in many pharmaceuticals and bioactive natural products. Although this chemistry has been traditionally limited in applicability due to explosive and toxic radical generators and propagators, recent advances have decreased the need for unfavorable hazards.[1] Due to key advances in reaction conditions, processes using iminyl radicals have been gaining momentum as viable synthetic strategies.[2]

The elimination of explosive and toxic radical initiators and propagators has resulted from Walton's pioneering work with oxime derivatives.[3] Walton's work has provided operable precursors to generate iminyl radicals via microwave, UV, or visible light irradiation.[2] As shown in Scheme 1-1, the incorporation of a weak N–O bond in **1** provides a site for homolytic cleavage, resulting in an iminyl radical **2**. Iminyl radicals undergo slower reductions and faster cyclizations than analogous aminyl radicals, providing a potent reactive intermediate for the formation of cyclization products.[4]



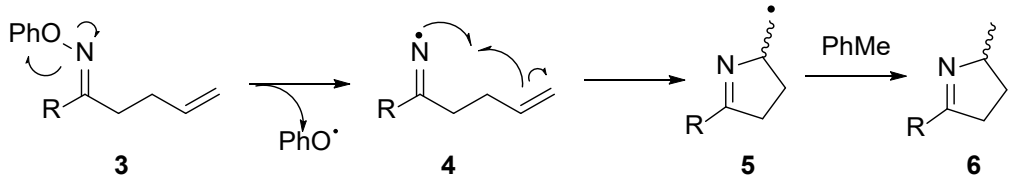
1 **2**

Scheme 1-1. Formation of iminyl radical *via* an oxime derivative

1.2 Iminyl radical cyclization reactions

Many groups, including those of Walton,[4] Bower,[5] Leonori,[6] Yu,[7] and us[8] have used oxime derivatives to form iminyl radicals that transform straight-chain precursors into cyclization products. Oxime ethers, oxime esters, acyloximes, dioxime oxalates, and oxime carbonates have all been shown as viable starting materials for iminyl radical generation *via* microwave irradiation, UV irradiation, or visible light irradiation.[2] Depending on precursor design, many privileged pharmaceutical scaffolds have been synthesized in good to excellent yields, including dihydropyrroles, pyrroles, 2-acylpyrroles, dihydroquinazolines, quinazolines, phenanthridines, isoquinolines, quinolines, and highly substituted pyridines.[2]

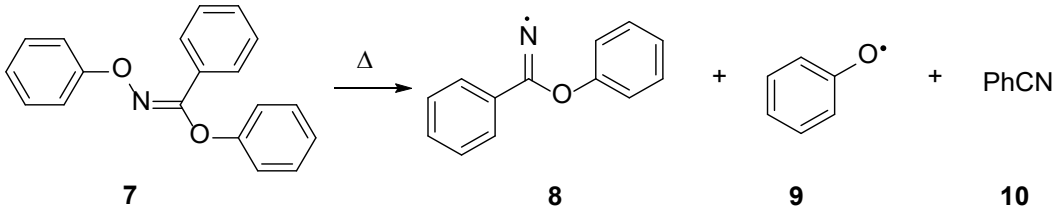
Strategic design of the starting materials has placed reactive moieties (π bonds, aromatic systems) in favorable positions to facilitate 5-*endo*, 5-*exo*, 6-*endo*, or 6-*exo* cyclization products.[2] Scheme 1-2 shows an example of the proposed mechanism for a 5-*exo* cyclization reported by Walton.[3b] Microwave irradiation cleaves the weak N–O bond, and results in a phenoxy radical byproduct (that presumably abstracts a hydrogen atom from the solvent to form phenol, or forms dimerization byproducts) and iminyl radical intermediate **4**. The iminyl radical intermediate undergoes an intramolecular addition to the π bond in a 5-*exo* cyclization, resulting in primary carbon radical **5**. The carbon radical abstracts a hydrogen atom from toluene, resulting in compound **6**, which was isolated by Walton.



Scheme 1-2. Example of 5-exo iminyl radical cyclization (Walton)

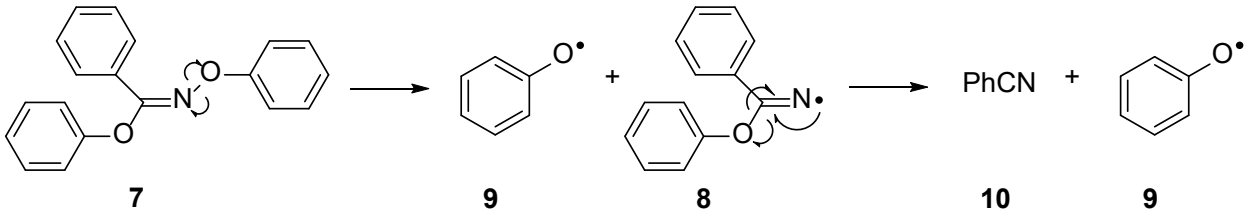
1.3 Incidents of nitrile formation in literature

In some cases, even with an optimized radical acceptor, cyclization products did not occur. Interestingly, nitrile formation was occasionally observed. Ingold reported nitrile formation in the reaction highlighted in Scheme 1-3.[9] Starting material **7** produced varying yields of **8, 9,** and **10** after thermal decomposition.



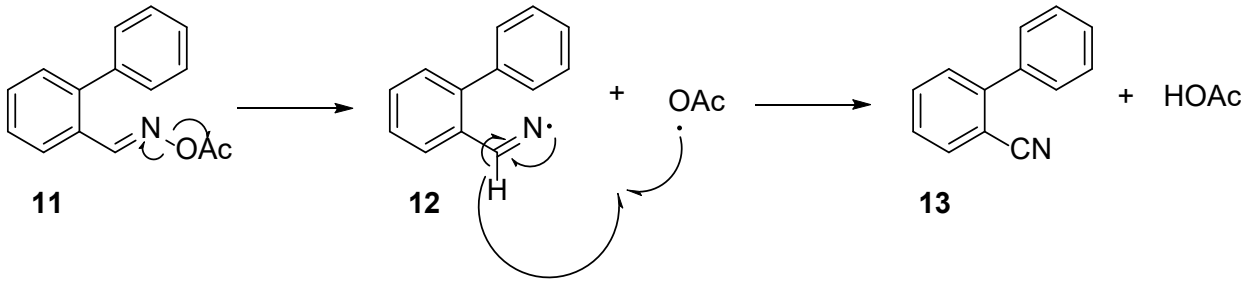
Scheme 1-3. Formation of nitrile from iminyl radical (Ingold)

One possible mechanism of formation of nitrile **10** is shown in Scheme 1-4. The N–O bond of **7** is cleaved *via* heat, resulting in the resonance stabilized byproduct of **9** and iminyl radical **8**. Instead of cyclization, the observed products indicate that further fragmentation of **8** occurs. Nitrile formation could occur by the formation of an additional π bond, utilizing the iminyl radical and the homolytic cleavage of the neighboring C–O bond. This would result in observed product **10**, and formation of an additional equivalent of byproduct **9**.



Scheme 1-4. Mechanism of nitrile formation *via* fragmentation

Rodriguez,[10] Walton,[11] and Yu[12] also report nitrile products that could be the result of H-abstraction *via* a radical mechanism. A plausible mechanism for H-abstraction and nitrile formation is proposed in Scheme 1-5, using Rodriguez's work as a template.

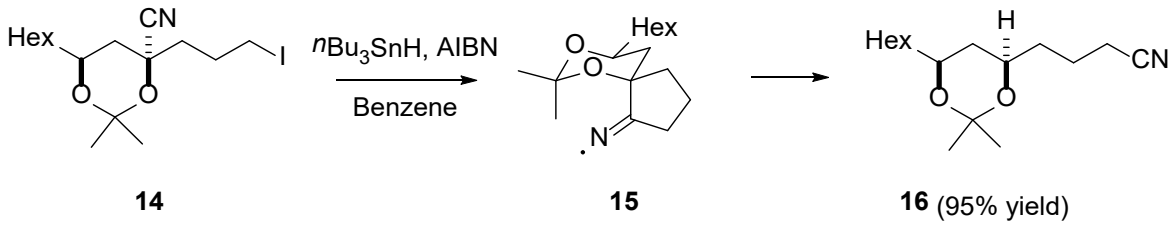


Scheme 1-5. Mechanism of H-abstraction and nitrile formation (Rodriguez)

In the previously cited works, the nitrile product was an unwanted byproduct, and optimization attempted to minimize nitrile synthesis. The work presented in this thesis seeks to exploit this nitrile formation *via* fragmentation. Nitriles are historically versatile functional groups,[13] and deliberate formation of the nitrile can lead to further functionalization of the starting material. The pattern of fragmentation can also beneficially rearrange bonds that are traditionally difficult to manipulate.

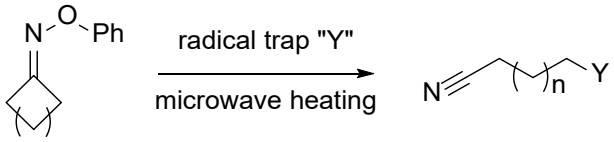
1.4 Deliberate nitrile formation and fragmentation

This work explores the fragmentation of cyclic oxime ether precursors into straight chain products, as shown in Scheme 1-6. The fragmentation of the starting material forms a carbon radical in addition to the generation of the nitrile functional group. Previous work has shown nitrile formation and carbon radical formation *via* fragmentation, but the reactions were completed in the presence of hydrogen atom donors. [14] The resulting carbon radical was subsequently reduced, and further functionality was lost. As shown in Scheme 1-6, Rychnovsky demonstrated good yields of nitrile migration *via* radical intermediate **15**. Subsequent hydrogen atom abstraction of nBu$_3$SnH provided reduced compound **16** with an effective transformation, but no further functionality added to the compound.



Scheme 1-6. Nitrile formation and subsequent compound reduction (Swenson)

This work aims to gain further functionality by avoiding the use of hydrogen donors and carefully selecting radical traps to interact with the nascent carbon radical. This results in the ability to form C–C, C–O, C–I, or C–N bonds in the same pot as nitrile generation.



Scheme 1-7. Reaction exploration of this thesis

The reaction advantageously avoids the use of toxic and explosive radical initiators and propagators, reduces reaction times by using microwave heating, enables potent experimental design with tailor–made carbon–heteroatom or carbon–carbon bonds, and installs two new functional groups in place of one.

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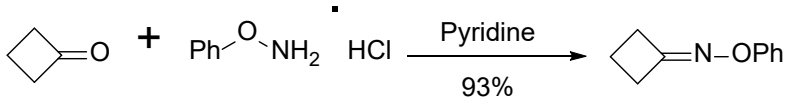
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CHAPTER 2. IMINYL RADICAL FRAGMENTATION OPTIMIZATION

2.1 Initial Reaction Results

Previous projects in the lab had focused on cyclization of iminyl radicals. We noted that byproducts of some published cyclizations often included nitriles. This sparked interest in purposely synthesizing nitriles *via* iminyl radical fragmentations.

Using previous protocols employed in our lab, we synthesized compound **18**, the hydrochloride salt of phenoxyamine.[1] We then coupled the phenoxyamine salt **18** with target ketones to form desired oxime ether substrates.[2] An example of the formation of an oxime ether from cyclobutanone is shown in Scheme 2-1.

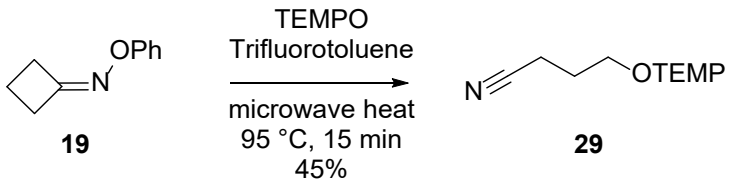


17 **18** **19**

Scheme 2-1. Oxime ether formation

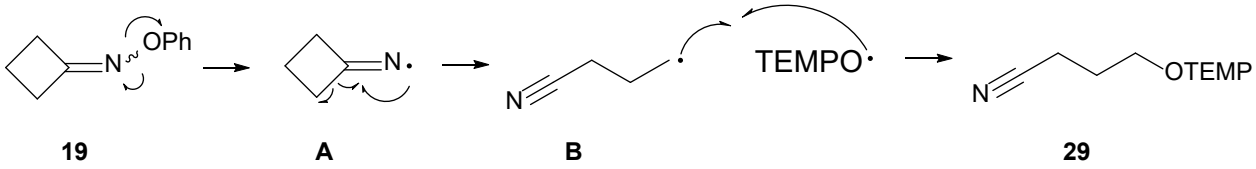
After generating the oxime ether starting material, we attempted the fragmentation of **19**, as shown in Scheme 2-2. Based on our previous work, trifluorotoluene was chosen in place of toluene as the solvent in order to eliminate the presence of a hydrogen atom donor. TEMPO was employed as a stable radical that could trap transient radical intermediate because of its historic success as a radical trap.[3] Other ongoing experiments in our lab indicated that a concentration of

0.03 M would be beneficial to eliminate competition from intermolecular H-atom abstraction. Lowering the concentration further had no significant effect on the yield. The experiment displayed in Scheme 2-2 was conducted by Dr. Steven Castle.



Scheme 2-2. Initial attempt at fragmentation

Although yields were moderate, we were encouraged by the feasibility of this reaction. We propose a radical mechanism, as shown in Scheme 2-3. The microwave heat cleaves the N–O bond of **19** to form an iminyl radical. Subsequently, the C–C bond between the α–carbon and the iminyl carbon in intermediate **A** homolytically cleaves to form the nitrile and carbon radical present in intermediate **B**, in a fashion analogous to Norrish Type 1 photochemistry.[4] TEMPO then traps the carbon radical to form product **29**.



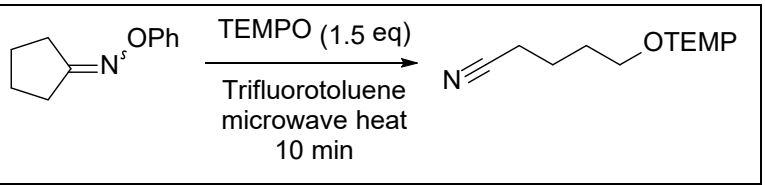
Scheme 2-3. Proposed mechanism for iminyl radical fragmentation

2.2 Perceived Reaction Floor

After initial success in the fragmentation reaction, we proceeded to determine the optimal reaction temperature. Table 2-1 shows varying success dependent on reaction temperature. Percent yield dramatically decreases when temperatures below 80 °C are used, as seen when comparing entries 3 and 4. This is the perceived reaction temperature floor, with the hypothesis that not enough energy enters the system when the temperature is below 80 °C to achieve the activation

energy needed for homolytic cleavage. It is unclear whether increasing reaction times at temperatures below 80 °C would increase yield. Future work may be done to assess the temperature floor in other solvents.

Table 2-1. Reaction temperature optimization



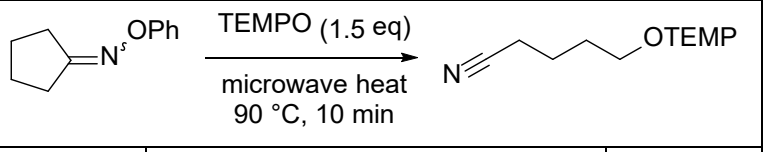
Entry	Temperature	Yield
1	90 °	57
2	85 °	71
3	**80 °**	**74**
4	**75 °**	**25**
5	70°	20

2.3 Solvent Optimization

Further optimization of the reaction involved the solvent. Table 2-2 shows different solvents employed and the resulting yields.

Of particular interest was the trend that increasing solvent polarity corresponded with increasing percent yield. We hypothesize that solvent polarity increases yield in two ways: 1) it conducts the microwave irradiation better, ensuring proper heating of the solution, and 2) it stabilizes the iminyl radical transition state which results in preference of the radical pathway over possible byproduct pathways. Acetonitrile was selected as the preferred solvent for future reactions. Entries 3-6 were performed by Sia Im.

Table 2-2. Solvent optimization



Entry	Solvent	Yield
1	Trifluorotoluene	57
2	Dichloroethane	28
3	*t*-butylbenzene, emimPF_6	30
4	MeOH	87
5	**CH_3CN**	**94**
6	Trifluoroethanol	80

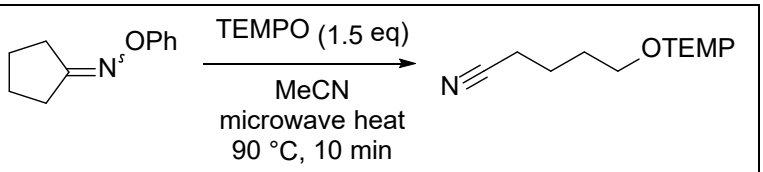
2.4 Synthesis of various oxime ethers for fragmentation in the presence of TEMPO

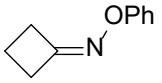
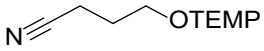
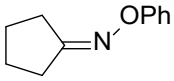
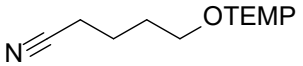
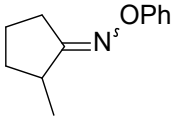
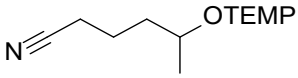
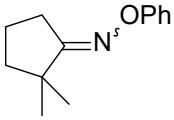
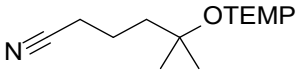
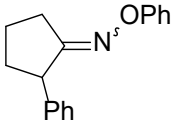
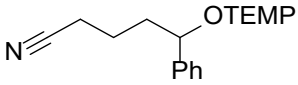
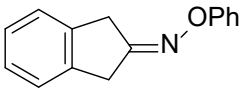
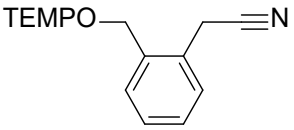
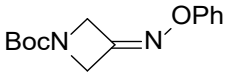
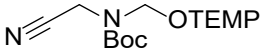
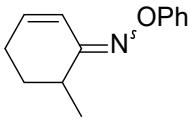
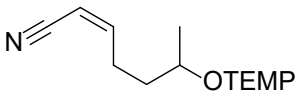
In addition to optimizing the fragmentation, we began to explore the reaction scope. The first alteration we attempted was changing the scaffold for the oxime ether substrates used as starting material. The oxime ether substrates employed are shown in Table 2-3.

All oxime ethers were synthesized from commercially available ketones, with the exception of the ketone precursors for **23** and **26.** These ketones were synthesized according to protocols reported in the literature (**23**[5] and **26**[6]), and subsequently used to form their corresponding oxime ethers.

The fragmentation worked best with 4- and 5-membered rings, resulting in good to excellent yields. We attempted to expand the scope to 6-membered rings with limited success. We attempted to encourage fragmentation by increasing ring strain by incorporating two additional sp^2 carbons through a double bond in **26** to increase ring strain, but only moderate success was observed.

Table 2-3. Percent yield for fragmentation of various oxime ethers



Oxime Ether	Product	Yield
 **19**	 **29**	85
 **20**	 **30**	94
 **21**	 **31**	68
 **22**	 **32**	91
 **23**	 **33**	92
 **24**	 **34**	75
 **25**	 **35**	45
 **26**	 **36**	27

The low yield for the fragmentation of compound **26** indicates that ring size has a substantial effect on the yield. Further work on the project could look to optimize the reaction for 6-membered rings.

Compound **20** was fragmented by Sia Im. Compound **25** was fragmented by Amanda Garrity. Compounds **19, 22,** and **23** were fragmented by Seth Bohman.

Initial work with the fragmentation of cyclic oxime ethers indicated possible success for methodology development. Optimization of the temperature and solvent delivered excellent yields when utilizing TEMPO as a radical trap. This optimization enabled us to fragment various cyclic oxime ethers with good to excellent yields.

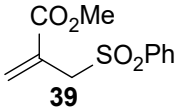
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2. Portella-Cubillo, F.; Scott, J. S.; Walton, J. C. *Chem. Commun.* **2007**, 4041.
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CHAPTER 3. UTILIZING ALTERNATIVE RADICAL TRAPS FOR FRAGMENTATION

3.1 Radical Traps for C–C Bond Formation

Due to our successful fragmentation reactions involving TEMPO, we decided to explore other possible radical traps. In order to form a C–C bond, we determined that methyl 2-((phenylsulfonyl)methyl)acrylate (**39**, Figure 3-1) would be a good candidate for a radical trap.[1]



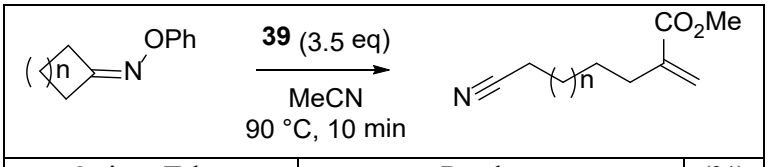
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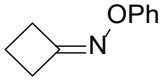
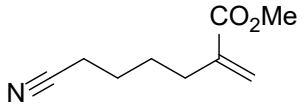
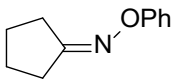
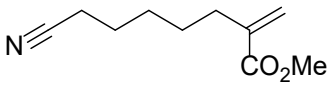
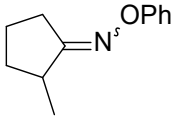
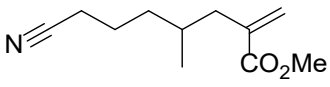
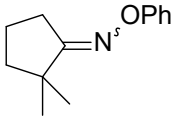
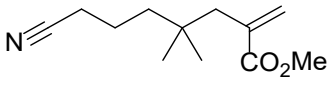
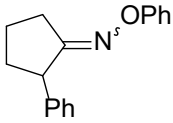
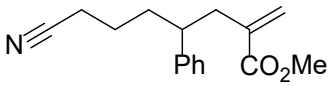
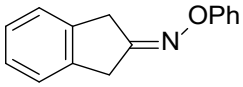
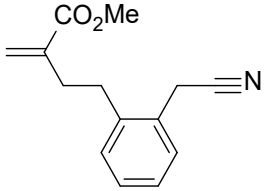
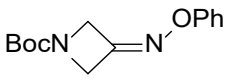
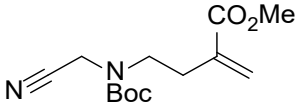
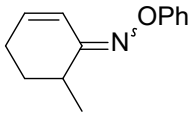
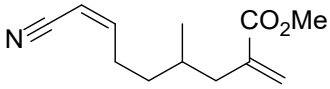
Figure 3-1. Methyl 2-((phenylsulfonyl)methyl)acrylate

Acrylate **39** was synthesized according to previously reported protocols[1] by Dr. Steven Castle. After successful isolation of acrylate **39**, it was tested in fragmentations with a variety of oxime ethers. The results are shown in Table 3-1.

Optimization studies by Seth Bohman included testing various temperatures, solvents, reaction times, and equivalents of acrylate **39**. No significant change of yield was observed for variation of reaction times; the range of times tested fell between 10 and 30 minutes. Temperature also had little effect on yields unless the reaction was run below 80 °C, in which the yield dropped dramatically. Solvent had the biggest impact on yield with acetonitrile being the most effective. The yield fell when either 1 or 6 equivalents of acrylate **39** was used. The best yields were

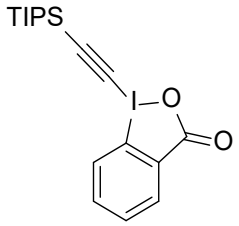
Table 3-1. Yields obtained from use of acrylate 39



Oxime Ether	Product	(%)
 **19**	 **40**	73
 **20**	 **41**	85
 **21**	 **42**	84
 **22**	 **43**	68
 **23**	 **44**	59
 **24**	 **45**	58
 **25**	 **46**	80
 **26**	 **47**	13

obtained by using 3.5 equivalents of acrylate **39**. The optimization and experiments in Table 3-1 were performed by Seth Bohman.

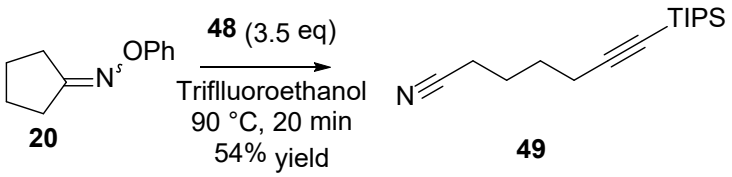
Another candidate we evaluated for a radical trap that would form C–C bonds is IBX-derivative **48**, shown in Figure 3-2.



48

Figure 3-2. Hypervalent iodide reagent used as a carbon radical trap

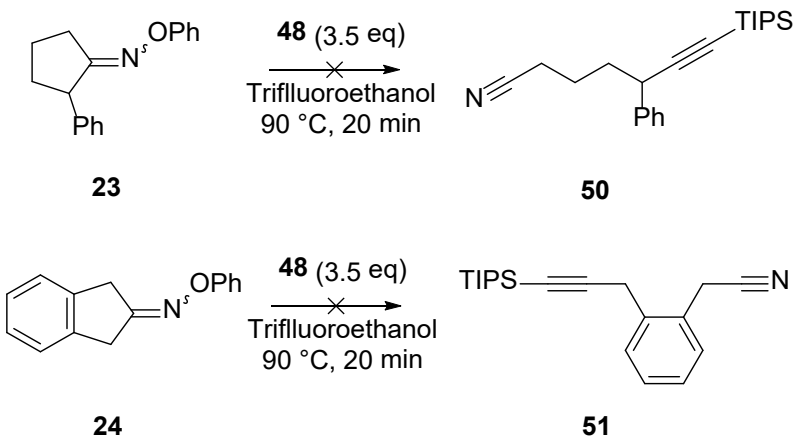
Hypervalent iodide reagent **48** was synthesized according to protocols reported in the literature.[2] Interestingly, reagent **48** was not soluble in acetonitrile, so methanol and trifluoroethanol were tested as reaction solvents. Trifluoroethanol gave the best yields, as reported in Scheme 3-1.



20 **49**

Scheme 3-1. Fragmentation with radical trap 48

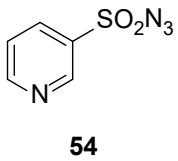
Reagent **48** did not afford product when we tried to trap benzylic carbon radicals, as shown in Scheme 3-2. Both benzo-fused and linear chain benzylic carbon radicals failed to give any significant amount of product.



Scheme 3-2. Unsuccessful trapping of benzylic radicals by radical trap 48

3.2 Azide radical trap

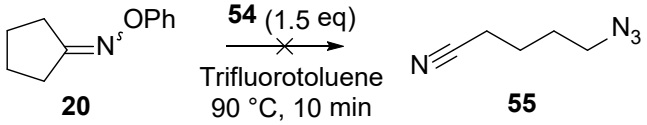
In addition to C–C bond formation, we were interested in forming C–N bonds *via* iminyl radical fragmentations. We first targeted azide radical trap **54**, as shown in Figure 3-3. Radical trap **54** was synthesized according to protocols found in the literature.[3]



54

Figure 3-3. Pyridinyl benzyl azide radical trap

After synthesis of radical trap **54**, we attempted fragmentation with oxime ether **20**, as shown in Scheme 3-3. No significant yield was obtained.

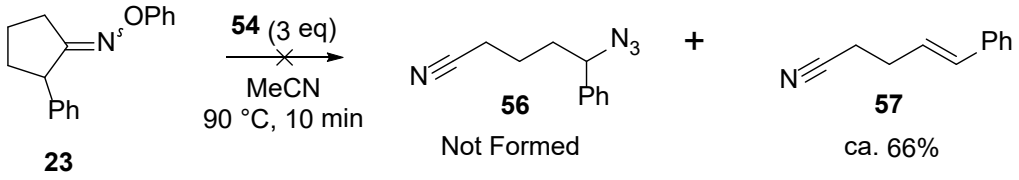


20 **55**

Scheme 3-3. Unsuccessful fragmentation with radical trap 54

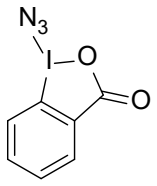
We first suspected there was difficulty in isolating product **55** due to potential challenges in detection (resulting from both low molecular weight and lack of UV activity or staining properties). In response to this, we designed and synthesized oxime ether **23**, which

advantageously increased the molecular weight and added a UV active moiety. When fragmenting oxime ether **23** with radical trap **54**, we still did not observe product **56**. Upon further analysis of the products, we did find strong evidence for product **57**. We hypothesize that the carbon radical was trapped by the azide functional group, but a combination of heat and the basic pyridine present in radical trap **54** caused an elimination of the azide functional group and formed a conjugated π bond. These results are summarized in Scheme 3-4. The spectral data for **57** matched spectra reported in the literature.This reaction was also attempted using 2-iodopropane as a radical trap, and compound **57** was also identified in the crude ^{1}H NMR.



Scheme 3-4. Formation of elimination product from fragmentation

Although product **57** was not our intended compound, we were encouraged because the formation of product **57** implied initial formation of product **56**. Based on our moderate success with hypervalent iodide radical trap **48**, we synthesized[2] analogue **58** (Figure 3-4) in attempt to use a different nitrogen radical trap without introducing the pyridinal moiety of **54** to the reaction.

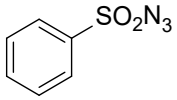


58

Figure 3-4. IBX derivative azide radical trap

Fragmentation with radical trap **58** by Seth Bohman again afforded the elimination product **57** in 48% yield, with trace amounts of product **56**. Unsure of the reactivity of byproducts from

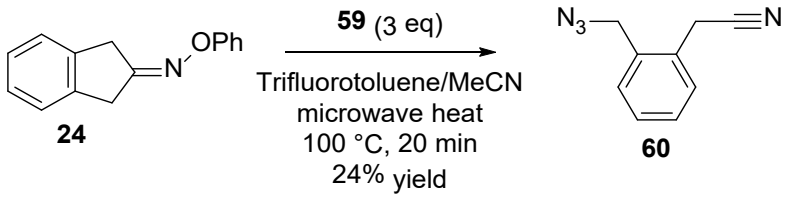
radical trap **58** (and their effect on product **56**), we decided to attempt one more azide radical trap. We synthesized benzyl sulfonyl azide radical trap **59** shown in Figure 3-5.[4]



59

Figure 3-5. Benzyl sulfonyl azide radical trap

We decided to synthesize oxime ether **24**, which provided the same advantages of a higher molecular weight and UV activity as oxime ether **23**, but prevented the formation of an elimination product. The results of fragmentation of oxime ether **24** with radical trap **59** are shown in Scheme 3-5.

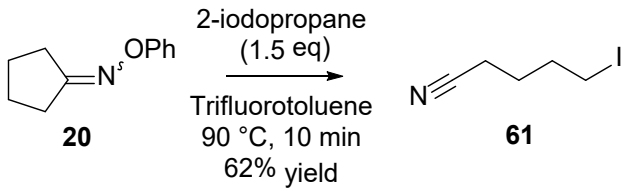


Scheme 3-5. Fragmentation with azide radical trap 59

The reaction resulted in a low yield, but a C–N bond was formed. A complex mixture was observed in the crude ^{1}H NMR. Oxime ether **24** was not soluble in acetonitrile, so sufficient trifluorotoluene was added to solvate oxime ether **24**. We also attempted fragmentation of oxime ether **24** with radical traps **58** and **54** without success. We are encouraged by the results we obtained in the formation of C–N bonds, and could consider further optimization as an option for future projects.

3.3 Radical Traps for C–X Bond Formation

In addition to C–O, C–C, and C–N bond formation, we also explored the possibility of C–X bond formation. We employed 2-iodopropane as a radical trap, as shown in Scheme 3-6.



Scheme 3-6. Fragmentation with 2-iodopropane as radical trap

Trifluorotoluene and acetonitrile were both tried as solvents, but observed yield was better in trifluorotoluene. One possible explanation for lower yields may be that 2-iodopropane is not as soluble in acetonitrile as it is in trifluorotoluene. Studies of the change in yield between trifluorotoluene and acetonitrile are underway now.

3.4 References

1. Rouquet, G.; Robert, F.; Méreau, R.; Castet, F.; Landais, Y. *Chem. Eur. J.* **2011**, *17*, 13904.

2. Wang, C.-Y.; Song, R.-J.; Xie, Y.-X., Li; J.-H. *Synthesis* **2016**, *48*, 223.

3. Panchaud, P.; Renaud, P. *Adv. Synth. Catal.* **2004**, *346*, 925.

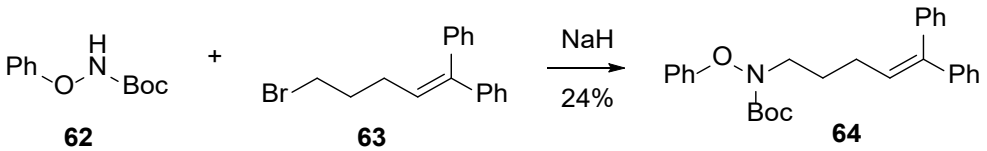
4. Jafarpour, M.; Rezaeifard, A.; Golshani, T. *Phosphorus Sulfur Silicon Relat. Elem.* **2011**, *186*, 140.

CHAPTER 4. OTHER ATTEMPTED NITROGEN–CENTERED RADICAL TRANSFORMATIONS

4.1 Aminyl radical 5-*exo* cyclization

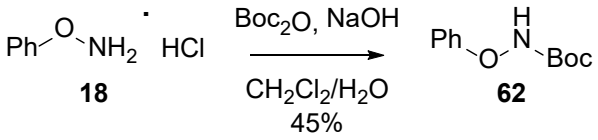
Previous success in our lab with iminyl radical transformations (both fragmentations and cyclizations) incited curiosity about the feasibility of aminyl radical generation and transformation. We decided to pursue cyclization first, which entailed design of an aryloxyamine radical precursor and an alkene in the same molecule, poised for 5-*exo* cyclization. Another challenge included the formation of the C–N single bond present in the aryloxyamine. Previous efforts had been made in the lab to reduce oxime ethers to aryloxyamines, but harsh conditions cleaved the N–O bond instead of the C–N π bond.

An alternate synthetic route was designed to couple the Boc-protected phenoxyamine **62** with bromoalkene **63** *via* substitution chemistry.[1] Cyclization precursor **64** was synthesized according to Scheme 4-1.



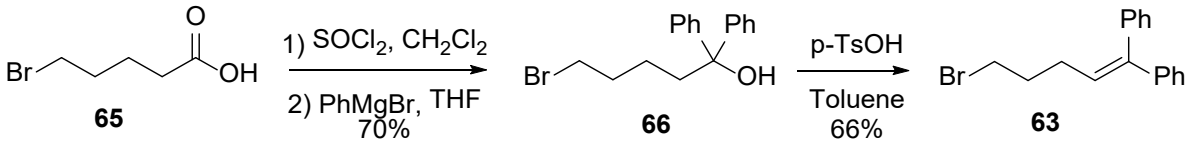
Scheme 4-1. Coupling to produce designed cyclization precursor

The synthesis of Boc-protected phenoxyamine **62** started from previously synthesized phenoxyamine **18**. The Boc protection of compound **18** followed protocols found in the literature,[2] and is outlined in Scheme 4-2. We decided to protect phenoxyamine **18** in efforts to increase the acidity of the N–H bond, enabling deprotonation and generation of a strong nucleophile for the subsequent substitution reaction. We also hoped to remove the Boc protecting group in the same pot as the microwave fragmentation, thereby minimizing the extra synthetic steps that protecting groups can introduce to a synthesis.



Scheme 4-2. Boc protection of phenoxyamine 16

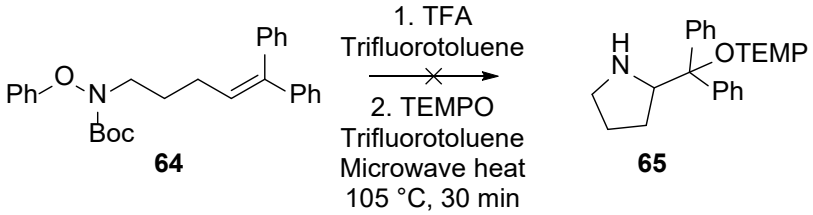
The generation of bromoalkene **63** followed the strategy outlined in Scheme 4-3. Bromovaleric acid **65** was first converted to the corresponding acid chloride, and then diarylated to form compound **66**, according to previously reported protocols.[3] Elimination of the hydroxyl group in compound **66** resulted in bromoalkene **63**.[3]



Scheme 4-3. Formation of bromoalkene 63

After the synthesis and coupling of compounds **62** and **63**, we produced cyclization precursor **64**. Initial attempts to cyclize involved trying to first deprotect compound **64** and observe the free amine prior to cyclization. Compound **64** was subjected to deprotection conditions and after 26 hours an additional TLC spot formed. We were unable to detect the deprotected alkoxyamine *via* MS, and were wary of purification protocols that might lead to decomposition.

Hoping that the new TLC spot was the deprotected amine, we subjected the mixture to microwave irradiation as shown in Scheme 4-4.



Scheme 4-4. Attempted microwave aminyl radical cyclization

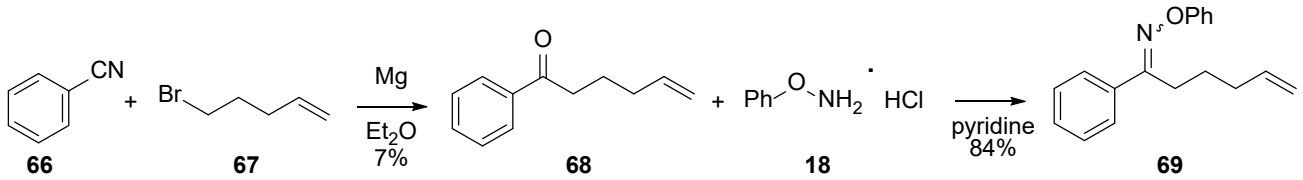
A mixture of products was formed, with seven distinct TLC spots. After attempted purification, no pyrrolidine was isolated from the mixture.

We next proceeded to attempt the deprotection and cyclization in the same reaction vessel. Based on literature reports that microwave heat can accelerate Boc deprotection,[4] we subjected compound **64** to Boc deprotection conditions and cyclization conditions simultaneously under microwave irradiation. MS revealed total consumption of starting material **64**, but twelve distinct TLC spots were formed, and further purification did not isolate pyrrolidine **65**.

Further work could be done to encourage the success of aminyl radical cyclization. One option would be to troubleshoot the Boc deprotection, and demonstration *via* ^{1}H NMR the isolation of the deprotected amine prior to microwave fragmentation. This would eliminate the deprotection step as a possible source of error. A variation on this strategy could be to attempt the Boc deprotection after successful cyclization. Another option would be to try the cyclization in acetonitrile, and see if the solvent would select for the radical cyclization. An additional attempt could also be made to find alternative coupling conditions for phenoxyamine **16** and precursor **63**, eliminating the need for protection altogether.

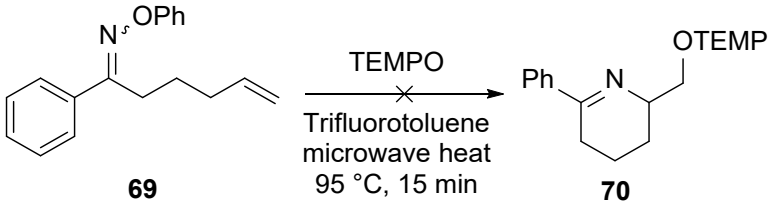
4.2 Iminyl radical 6-*exo* cyclization

Another project focused on nitrogen–centered radicals is 6-*exo* iminyl cyclization. There has been reported success with 5-*exo* iminyl cyclization, and there have been examples of 6-membered cyclization delivering products with concomitant aromatization.[5] We sought to promote 6-*exo* iminyl cyclization without the driving force of aromatic products and instead form tetrahydropyridines. Our synthetic route to the cyclization substrates is shown in Scheme 4-5.



Scheme 4-5. Formation of iminyl radical 6-*exo* cyclization precursor

Formation of compound **68** followed protocols found in the literature.[6] Coupling of the phenoxyamine salt to ketone **68** is outlined in Chapter 2. After the synthesis of precursor **69**, we attempted microwave cyclization as shown in Scheme 4-6.



Scheme 4-6. Attempted 6-*exo* cyclization of an iminyl radical

After attempted cyclization, the crude ^{1}H NMR indicated consumption of the starting material, but did not show anticipated product peaks in any significant quantity. TLC analysis revealed nine distinct UV active spots. Purification did not yield any significant results.

Further work could be done to encourage 6-*exo* cyclization. Precursor design could equip phenyl or electron-withdrawing groups on the alkene to stabilize the formation of the carbon

radical, thereby driving the reaction towards cyclization. The reaction could also be attempted in acetonitrile. Variations could be tested for time and temperature of microwave irradiation.

Although two attempted nitrogen-centered radical cyclizations did not succeed, there are reasonable efforts that could be made to encourage favorable reaction results for both aminyl 5-*endo* cyclization and iminyl 6-*endo* cyclization. The consumption of the starting material in both cases indicates that some type of transformation of the starting material is indeed occurring. The ideas listed in this chapter are simple alterations that could encourage further success with these projects.

4.3 References

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2. Ali, M. A.; Yao, X.; Sun, H.; Lu, H. *Org. Lett.* **2015**, *17*, 1513.
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CHAPTER 5. APPLICATIONS, FUTURE WORK, AND CONCLUSIONS

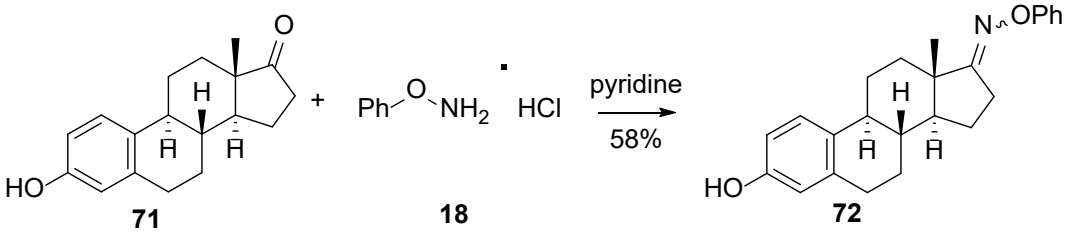
5.1 Application of iminyl radical fragmentation to the ring distortion strategy

The applications of iminyl radical chemistry we are focusing on relate to the successful iminyl radical fragmentation reactions. One exciting prospect is the application of iminyl radical fragmentation to the ring distortion strategy proposed by Hergenrother.[1] This strategy employs derivatization of complex natural products through transformations to the carbon ring structure scaffold that take on average three chemical steps. This enables facile production of diverse and complex compounds that can be used in screening collections. Hergenrother demonstrated the potency of the ring distortion strategy with the transformation of gibberellic acid, adrenosterone, and quinine to create numerous analogues with reduced effort. The distortion of adrenosterone is most applicable to the iminyl radical fragmentation, with five of the nine derivatizations involving the fragmentation of a five membered cyclic ketone.

We see the ability to apply our developed iminyl radical fragmentation methodology to the same strategy, with the added advantage of using milder conditions. Instead of harsh oxidizing agents or strong acids used by Hergonrother, we would employ the use of microwave irradiation and added radical traps. A great degree of variation can be achieved simply by choosing a different radical trap, with the opportunity to further permutate created compounds through the subsequent

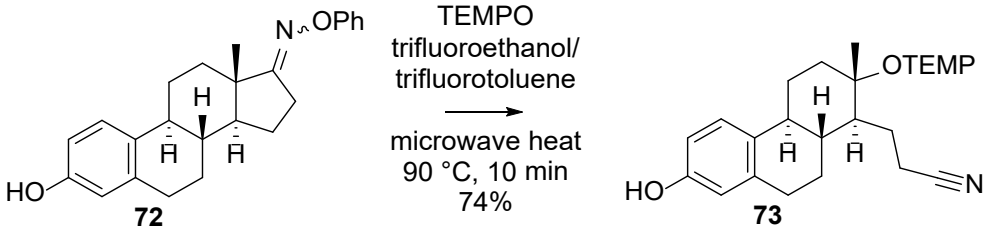
transformation of the nitrile. Having these two points of easy alteration allows for exponential growth of transformations with each new reaction applied to the compound.

We decided to apply the ring distortion strategy to estrone, an economic and commercially available starting material. Concordia Lo conducted the estrone ring distortion experiments. We first synthesized the oxime ether, as shown in Scheme 5-1. Coupling estrone **71** with phenoxyamine salt **16** gave oxime ether **72**.



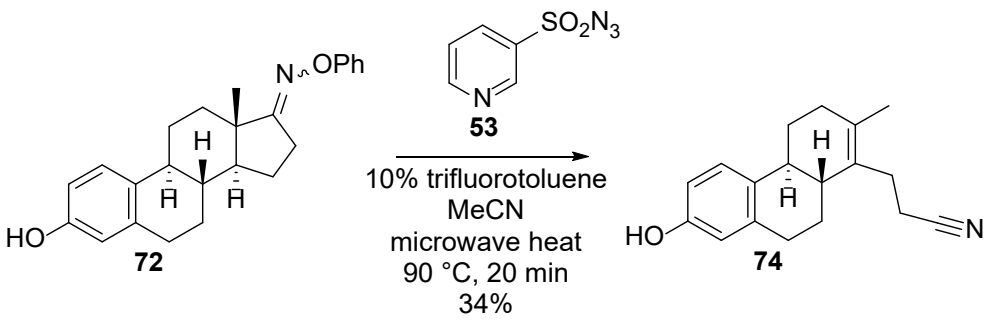
Scheme 5-1. Formation of estrone oxime ether

After successful formation of oxime ether **72**, we proceeded to fragment it according to our previously optimized conditions. The first radical trap used was TEMPO, as shown in Scheme 5-2. Oxime ether **72** was fragmented with good yields in a 3:1 ratio of trifluoroethanol and trifluorotoluene.



Scheme 5-2. Fragmentation of estrone oxime ether 72 with TEMPO

Another estrone derivative was synthesized with the use of azide radical trap **54**. The final product contains a π bond, presumably formed from elimination of the azide functional group that would trap the nascent carbon radical during the fragmentation reaction. The results of this reaction are summarized in Scheme 5-3.



Scheme 5-3. Formation of estrone derivative 74 *via* elimination of trapped azide

Although this reaction has a less than ideal yield, we are currently working on optimizing the formation of compound **74**. Scheme 5-3 represents the first attempt of using radical trap **53**, and optimized purification conditions could feasibly give a higher yield.

In addition to the optimization of the formation of compound **74**, there are efforts underway to fragment estrone oxime ether **72** with acrylate radical trap (insert number), $CBrCl_3$, and CCl_4. We also attempted trapping with 2-iodopropane, but hypothesize that the reaction did not work because estrone oxime ether **72** fragments to produce a tertiary carbon radical. Trapping with 2-iodopropane forms a secondary carbon radical, which would be less thermodynamically stable than the tertiary carbon radical, and would not encourage reaction procession.

5.2 Stereochemistry

Future work in the iminyl radical fragmentation project could involve investigation of the stereoselectivity of the reaction. With the formation of a carbon radical and the addition of a radical trap, there is potential in the reaction for the formation of a new stereocenter. Many radical reactions proceed with high stereoselectivity,[2] and further work is necessary to determine stereoselectivity of the iminyl radical fragmentation. One simple experiment to determine if any stereoselectivity even exists would be the fragmentation a starting material with a stereocenter removed from the site of fragmentation. If the resulting product is a mixture of diastereomers, this

would indicate that the reaction is not stereoselective. If the resulting product is a single diastereomer, this would indicate the reaction is stereoselective.

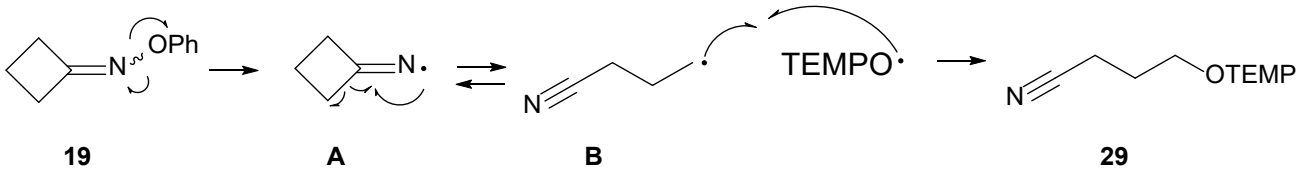
If the reaction is stereoselective, this could have major potency for introduction of stereocenters into straight chain products. Although generating a stereocenter on straight chain compounds is difficult, significant work has been accomplished in the generation of stereocenters through enolate, aldol, and conjugate addition chemistry on cyclic compounds.[3] In the case that the radical trapping is stereoselective, iminyl radical fragmentation could be a design strategy to produce a straight chain stereocenter. The fragmentation would also need to be regioselective in order for this to be a feasible application. In the case of asymmetric alpha carbons (which are probable through aldol and enolate chemistry), we have previously observed regioselectivity. However, we have observed regioselectivity that is selective for cleaving the more hindered side, which has the potential to destroy the stereocenter. This remains a barrier that would need to be tested and addressed if installation of stereocenters was pursued. If the alpha carbons have the same number of substituents (which is probable through conjugate addition chemistry), then further studies would have to be done to observe regioselectivity of the fragmentation.

5.3 Six Membered Ring Fragmentation

Another area of future work includes the fragmentation of six membered rings. As noted in Chapter 2, yields drop dramatically when fragmenting six membered rings *via* iminyl radical fragmentation. We would like to optimize this reaction in order to be able to apply it to a large number of natural products that contain six membered cyclic ketones.

We suspect the transformation between intermediates A and B is reversible, as outlined in Scheme 5-4. In the case of four and five membered rings, we hypothesize that the straight chain intermediate is more stable due to the ring strain present in the cyclic intermediate, which drives

the reaction to completion. While fragmenting six membered rings, cyclic ketone was observed in the crude reaction mixture, indicating a possibility of imine formation and subsequent hydrolysis during workup to create the ketone. This could be explained if the cyclic intermediate was more stable than the straight chain intermediate, which would remove the driving force from the reaction.



Scheme 5-4. Possible reversible step during iminyl radical fragmentation

In order to make conditions more favorable for six membered ring fragmentation, we could try other methods of incorporating ring strain into the starting materials. We could also attempt fragmentation in acetonitrile, which has proved more effective than trifluorotoluene for many fragmentation reactions.

5.4 Conclusion

In summary, we have optimized an efficient method to functionalize cyclic oxime ethers derived from simple ketone precursors. We install two functional groups in the place of one. The method proceeds *via* an iminyl radical generated by microwave irradiation. Depending on the choice of radical trap, a variety of bond types can be installed. C–O bonds and C–C bonds can be formed in excellent yields, while C–I and C–N bonds can be formed in poor to moderate yields. Besides the functional group installed through the radical trap, a nitrile is also formed. Additional work can be done to fragment six membered rings and determine stereoselectivity of the reaction. Work is underway on a practical application to ring distortion strategy. Iminyl radical fragmentation displays potency as a viable and strategic method in organic synthesis.

5.5 References

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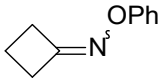
3. (a) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106,* 446. (b) Ooi. T.; Doda, K.; Maruoka, K. *Org. Lett.* **2001**, *3*, 1273. (c) Yamamoto, Y. *Stereoselective Synthesis,* 4th edn, *Vol. E21b*, Georg Thieme Verlag, Stuttgart, pp. 2041-2067.

CHAPTER 6: EXPERIMENTAL AND SPECTROSCOPIC DATA

6.1 General Methods

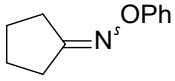
All dry solvents were dried by passage through a dry solvent system employing activated alumina cylinders. Flash chromatography was carried out using 230 mesh silica gel. ^{1}H NMR spectra were obtained on a Varian 500 MHz spectrometer, with chloroform (7.27 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (doublet of doublets), dt (doublet of triplets), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were obtained on Varian 125 MHz, with chloroform (77.23 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI mass spectrometry.

6.2 Experimental Details

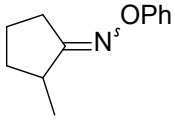


Cyclobutanone O-phenyl oxime (19). An oven dried reaction vessel with stir bar was charged with cyclobutanone (27.6 mg, 0.310 mmol, 1 equiv), pyridine (1.25 ml), and phenoxyammonium chloride (49.7 mg, 0.341 mmol, 1.1 equiv). The vessel was sealed under argon atmosphere, and stirred at room temperature overnight. Flash chromatography (1-3% EtOAc in hexanes gradient elution) afforded **19** (35 mg, 0.217 mmol, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz)

δ7.33-7.26 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 3.12 (t, *J* = 8.5 Hz, 2H), 3.07 (t, *J* = 7.9 Hz, 2H), 2.14-2.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 159.6, 129.2, 129.2, 121.7, 114.3, 114.3, 31.6, 31.5, 14.6; IR (film) ν_{max} 2964,1685, 1560, 964; HRMS (ESI) *m/z* 162.0917 (MH^+, $C_{10}H_{11}NOH^+$ requires 162.0913).

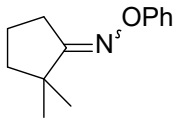


Cyclopentanone O-phenyl oxime (20). In a procedure similar to the formation of **19**, cyclopentanone (33.7 mg, 0.401 mmol, 1 equiv) and phenoxyammonium chloride (64.2 mg, 0.440 mmol, 1.1 equiv) afforded **20** (68.5 mg, 0.357 mmol, 89%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.34-7.26 (m, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 2.65 (t, *J* = 6.8 Hz, 2H), 2.53 (t, *J* = 6.7 Hz, 2H), 1.88-1.79 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 159.7, 129.2, 129.2, 121.7, 114.6, 114.5, 31.1, 28.4, 25.2, 24.7; IR (film) ν_{max} 3039, 2964, 2873, 1659, 1594, 958; HRMS (ESI) *m/z* 176.1069 (MH^+, $C_{11}H_{13}NOH^+$ requires 5176.1070).

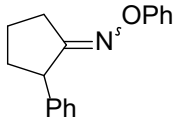


2-Methylcyclopentan-1-one O-phenyl oxime (21). In a procedure similar to the formation of **19**, 2-methylcyclopentanone (32.0 mg, 0.33 mmol, 1 equiv) and phenoxyammonium chloride (47.5 mg, 0.363 mmol, 1.1 equiv) afforded **21** (51.2 mg, 0.274 mmol, 83%) that was a mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz, major diastereomer) δ 7.31 (t, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.00 (t, *J* = 7.3 Hz, 1H), 2.76-2.67 (m, 2H), 2.66-2.56 (m, 1H), 2.11-2.02 (m, 1H), 1.94-1.87 (m, 1H), 1.73-1.67 (m, 1H), 1.45-1.36 (m, 1H), 1.29 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 172.5, 159.8, 159.7, 129.2, 121.5, 114.5, 34.4, 28.3, 22.6, 17.2,

17.1; IR (film) ν_{max} 3039, 2962, 2872, 1659, 1596, 936; HRMS (ESI) *m/z* 190.1239 (MH^+, $C_{12}H_{15}NOH^+$ requires 190.1226).

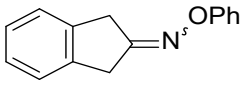


2,2-Dimethylcyclopentan-1-one O-phenyl oxime (22). In a procedure similar to the formation of **19**, 2,2-dimethylcyclopentanone (31.2 mg, 0.293 mmol, 1 equiv) and phenoxyammonium chloride (52.7 mg, 0.362 mmol, 1.1 equiv) afforded **22** (44.9 mg, 0.231 mmol, 79%) as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32-7.27 (m, 2H), 7.20-7.13 (m, 2H), 7.01-6.95 (m, 1H), 2.71 and 2.57 (2t, J = 7.5 and 7.3 Hz, 2H), 1.86-1.78 (m, 2H), 1.74-1.66 (m, 2H), 1.42 and 1.26 (2s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz, only major stereoisomer reported) δ 174.7, 159.8, 129.2 (2C), 121.5 (2C), 114.4, 42.7, 41.0, 27.9, 26.6, 20.9 (2C); IR (film) ν_{max} 3284, 2960, 1694.2, 1651, 1591, 1489, 927; HRMS (ESI) *m/z* 204.1385 (MH^+, $C_{13}H_{17}NOH^+$ requires 204.1383).

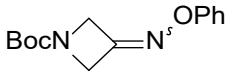


2-Phenylcyclopentan-1-one O-phenyl oxime (23). In a procedure similar to the formation of **19**, 2-phenylcyclopentanone (395.5 mg, 2.51 mmol, 1 equiv) and phenoxyammonium chloride (409.1 mg, 2.76 mmol, 1.1 equiv) afforded **23** (574.5 mg, 2.32 mmol, 93%) as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.17 (m, 8H), 7.11-7.07 (m, 1 H), 6.98-6.91 (m, 1H), 4.26 and 3.93 (2t, J = 7.7 and 8.1 Hz, 1H), 2.99-2.91 and 2.79-2.70 (2m, 2H), 2.41-2.35 and 2.35-2.28 (2m, 1H), 2.05-1.94 and 1.86-1.78 (2m, 1H), 1.96-1.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 159.7, 141.4, 129.1, 128.4, 128.0, 127.3, 121.7, 114.5, 35.0, 32.0,

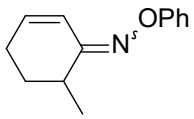
29.0, 22.8; IR (film) ν_{max} 2961, 1596, 1489, 1231, 965.3; HRMS (ESI) *m/z* 252.1378 (MH^+, $C_{17}H_{17}NOH^+$ requires 252.1383).



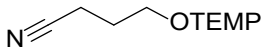
1,3-Dihydro-2H-inden-2-one O-phenyl oxime (24). In a procedure similar to the formation of **19**, 2- 1,3-dihydro-*2H*-inden-2-one (149.9 mg, 1.13 mmol, 1 equiv) and phenoxyammonium chloride (177.2 mg, 1.25 mmol, 1.1 equiv) afforded **24** (197.0 mg, 0.878 mmol, 78%) as a light brown solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.31 (m, 4H), 7.30-7.25 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 4.05 (s, 2H), 3.97 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7, 159.5 (2C), 138.8 (2C), 129.3, 127.3, 127.2, 125.1, 124.8, 122.1 (2C), 114.6, 36.6, 35.3; IR (film) ν_{max} 2933, 1588, 1479, 969; HRMS (ESI) *m/z* 224.1071 (MH^+, $C_{15}H_{13}NOH^+$ requires 224.1070).



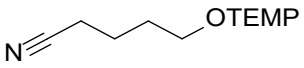
Tert-butyl 3-(phenoxyimino)azetidine-1-carboxylate (25). In a procedure similar to the formation of **19**, tert-butyl 3-oxoazetidine-1-carboxylate (69.4 mg, 0.375 mmol, 1 equiv) and phenoxyammonium chloride (68.4 mg, 0.412 mmol, 1.1 equiv) afforded **25** (62.5 mg, 0.240 mmol, 64%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.30 (m, 2H), 7.15-7.12 (m, 2H), 7.04 (t, *J* = 7.04, 1H), 4.79 (t, *J* = 3.1 Hz, 2H), 4.75 (t, *J* = 3.1 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 156.1, 151.9, 129.4 (2C), 122.6, 114.3 (2C), 80.8 (2C), 28.3 (3C); IR (film) ν_{max} 3504, 2977, 1699, 1592, 1489, 1456, 946; HRMS (ESI) *m/z* 263.1387 (MH^+, $C_{14}H_{18}N_2O_2H^+$ requires 263.1390).



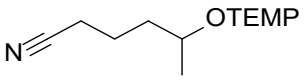
6-Methylcyclohex-2-en-1-one O-phenyl oxime (26). In a procedure similar to the formation of **19**, 6-methylcyclohex-2-en-1-one (77.2 mg, 0.70 mmol, 1 equiv) and phenoxyammonium chloride (130.0 mg, 0.875 mmol, 1 equiv) afforded **26** (96.0 mg, 0.476 mmol, 68%) as a mixture of 3:1 diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.29 (m, 2H), 7.24-7.20 (m, 2H), 7.04-6.98 (m, 1H), 6.92 and 6.22-6.18(dt, *J* = 5.1, and m, 1H), 6.41 and 6.35-6.31 (dt, *J* = 5.2, and m, 1H), 3.65-3.57 and 2.74-2.66 (m, m, 1H), 2.40-2.26 and 2.22-2.15 (m, m, 3H), 1.99-1.92 and 1.92-1.85 (m, m, 1H), 1.74-1.68 and 1.68-1.66 (m, m, 1H), 1.29 and 1.21 (d, *J* = 6.8 Hz and d, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, only reporting data for major diastereomer) δ 162.5, 159.1, 140.3, 137.2, 129.2, 122.9, 121.7, 117.1, 114.6, 33.0, 29.9, 24.5, 17.4; IR (film) ν_{max} 3036, 2964, 2931, 1628, 1591, 1489, 955; HRMS (ESI) *m/z* 202.1221 (MH^+, $C_{13}H_{15}NOH^+$ requires 202.1226).



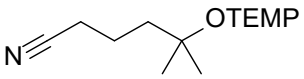
4-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)butanenitrile (29). An oven dried reaction vessel was charged with compound **19** (16.0 mg, 0.099 mmol, 1 equiv), TEMPO (33.0 mg, 0.20 mmol, 2 equiv), and trifluorotoluene (3.3 ml) and sealed under an argon atmosphere. The vessel was subjected to microwave irradiation (300 W) at 90 °C for 10 min. The mixture was then cooled to room temperature and concentrated *in vacuo*. Flash chromatography (3-15% EtOAc in hexanes gradient elution) afforded **29** (8.4 mg, 0.084 mmol, 85%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.89 (t, *J*=5.89 Hz, 2H), 2.50 (t, *J*=7.23 Hz, 2H), 1.90 (quin, *J*=6.57 Hz, 2H), 1.48-1.44 (m, 4H), 1.18-1.13 (s, 6H), 1.13-1.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 119.7, 73.6, 59.8, 39.6 (4C), 33.1 (2C), 25.1, 20.1, 17.1, 14.5; IR (film) ν_{max} 2930, 2230, 1615, 1573; HRMS (ESI) *m/z* 204.1393 (MH^+, $C_{13}H_{24}N_2OH^+$ requires 204.1383).



5-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)pentanenitrile (30). In a procedure similar to the formation of **29**, compound **20** (6.2 mg, 0.032 mmol, 1 equiv), TEMPO (8.7 mg, 0.049 mmol, 1.5 equiv), and acetonitrile (1.1 mL) afforded **30** (7.2 mg, 0.030 mmol, 94%).: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.78 (t, *J* = 5.9 Hz, 2H), 2.42 (t, *J* = 7.1 Hz, 2H), 2.18 (s, 2H), 1.84-1.76 (m, 2H), 1.73-1.65 (m, 2H), 1.47-1.42 (m, 4H), 1.15 (s, 6H), 1.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 119.8, 75.6, 59.7, 39.6 (4C), 33.1, 30.1, 27.9, 23.0, 20.1, 17.4, 17.1; IR (film) ν_{max} 2933, 2246, 1724, 1454; HRMS (ESI) *m/z* 239.2122 (MH^+, $C_{14}H_{26}N_2OH^+$ requires 239.2118).

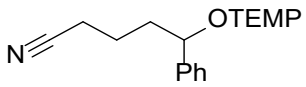


5-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexanenitrile (31). In a procedure similar to the formation of **29**, compound **21** (22.8 mg, 0.12 mmol, 1 equiv), TEMPO (28.2 mg, 0.18 mmol, 1.5 equiv), and acetonitrile (5 mL) afforded **31** (20.3 mg, 0.080 mmol, 67%) as a 20:1 mixture of regioisomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.95 (sextet, *J* = 5.81 Hz, 1H), 2.40 (t, *J* = 7.09 Hz, 2H), 1.84-1.68 (m, 2H), 1.63-1.55 (m, 2H), 1.49-1.43 (m, 4H), 1.36-1.30 (m, 2H) 1.19 (d, *J* = 6.43 Hz, 3H), 1.14 (s, 3H), 1.11 (s, 6H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 119.9, 40.3, 40.2, 39.6, 35.8 (2C), 34.4, 21.9, 20.5, 19.7 (2C), 17.6 (2C), 17.3 (2C); IR (film) ν_{max} 3414, 2933, 2246, 1606, 1595; HRMS (ESI) *m/z* 253.2287 (MH^+, $C_{15}H_{28}N_2OH^+$ requires 253.2274).

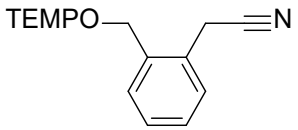


5-Methyl-5-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexanenitrile (32). In a procedure similar to the formation of **29**, compound **22** (14.9 mg, 0.073 mmol, 1 equiv), TEMPO (22.9 mg, 0.147 mmol, 2 equiv), and acetonitrile (2.5 mL) afforded **32** (5.9 mg, 0.059 mmol, 81%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.39 (t, *J* = 7.2 Hz, 2H), 1.95-1.81 (m, 2H), 1.81-1.67 (m, 2H), 1.54-1.43

(m, 4H), 1.31 (s, 6H), 1.30-1.27 (m, 2H) 1.14 (s, 6H), 1.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 119.9, 78.0, 59.2, 42.8 (2C), 40.8 (2C), 34.8 (2C), 27.0 (2C) 20.7 (2C), 20.4, 17.8, 17.1; IR (film) ν_{max} 2972, 2931, 2246, 1468; HRMS (ESI) *m/z* 267.2434 (MH^+, $C_{16}H_{30}N_2OH^+$ requires 267.2431).

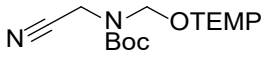


5-Phenyl-5-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pentanenitrile (33). In a procedure similar to the formation of **29**, compound **23** (8.9 mg, 0.035 mmol, 1 equiv), TEMPO (11.1 mg, 0.708 mmol, 2 equiv), and acetonitrile (1.2 mL) afforded **33** (10.3 mg, 0.033 mmol, 92%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35-7.31 (m, 2H), 7.29-7.26 (m, 3H) 4.68-4.63 (m, 1H), 2.24 (t, *J* = 7.24, 2H) 2.21-2.15 (m, 1H), 2.03-1.94 (m, 1H), 1.53-1.48 (m, 2H), 1.48-1.39 (m, 4H), 1.39-1.32 (m 2H), 1.31 (s, 3H), 1.18 (s, 3H), 1.01 (s, 3H), 0.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.7, 128.1 (2C), 127.5 (2C), 127.4, 119.6, 86.3, 40.4 (4C), 34.9, 34.0 (2C), 21.3 (2C), 17.2 (2C), 17.1; IR (film) ν_{max} 2932, 2247, 1494, 1455; HRMS (ESI) *m/z* 315.2431 (MH^+, $C_{20}H_{30}N_2OH^+$ requires 315.2431).

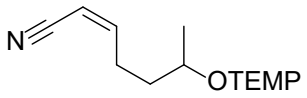


2-(2-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)phenyl)acetonitrile (34). In a procedure similar to the formation of **29**, compound **24** (16.3 mg, 0.073 mmol, 1 equiv), TEMPO (28.5 mg, 0.146 mmol, 2 equiv), and acetonitrile (2.4 mL) and CH_2Cl_2 (0.6 mL) afforded **34** (15.6 mg, 0.054 mmol, 75%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51-7.47 (m, 1H), 7.44-7.40 (m, 1H), 7.39-7.33 (m, 2H), 4.88 (s, 2H) 3.88 (s, 2H), 1.55-1.49 (m, 4H), 1.42-1.35 (m, 2H), 1.25 (s, 6 H), 1.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.2, 129.5, 128.7, 128.6, 128.4, 128.2, 117.8, 110.0, 60.0, 39.7

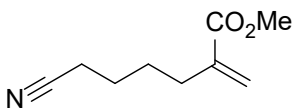
(2C) 33.2 (2C). 21.5 (2C), 20.3 (2C), 17.1; IR (film) ν_{max} 2931, 2250, 1454, 1374; HRMS (ESI) *m/z* 287.2111 (MH^+, $C_{13}H_{17}NOH^+$ requires 287.2118).



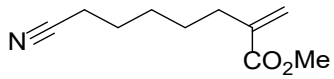
Tert-butyl (cyanomethyl)(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)carbamate (35). In a procedure similar to the formation of **29**, compound **25** (17.6 mg, 0.067 mmol, 1 equiv), TEMPO (20.3 mg, 0.134 mmol, 2 equiv), and acetonitrile (2.4 mL) afforded **35** (9.5 mg, 0.030 mmol, 45%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.97-4.93 (m, 2H), 4.30 and 4.18 (2s, 2H), 1.55-1.49 (m, 9H), 1.37-1.31 (m, 2H) 1.49-1.45 (m, 4H), 1.19 (s, 6H), 1.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.9, 116.1, 82.4 and 82.0, 81.5, 60.0 (2C), 39.7 (3C), 35.7, 34.8, 33.1, 29.7, 28.2, 20.0 (2C), 17.0; IR (film) ν_{max} 2977, 2933, 2247, 1716, 1473; HRMS: not recorded yet.



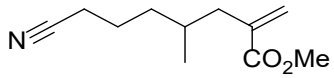
(*Z*)-6-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)hept-2-enenitrile (36). In a procedure similar to the formation of **29**, compound **26** (27.2 mg, 0.135 mmol, 1 equiv), TEMPO (43.7 mg, 0.270 mmol, 2 equiv), and acetonitrile (4.5 mL) afforded **36** (9.6 mg, 0.036 mmol, 27%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.68-6.61 (m, 1H), 5.41 (d, *J* = 10.4 Hz, 1H), 4.09-4.02 (m, 1H), 2.67-2.60 (m, 2H), 1.95-1.85 (m, 2H), 1.74-1.66 (m, 4H), 1.47-1.40 (m, 2H), 1.32 (d, *J* = 5.7 Hz, 3H), 1.22 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.7, 116.2, ,99.5, 77.4, 40.4 (2C), 34.9, 34.6, 28.6 (2C), 20.7, 19.8, 17.5 (4C); IR (film) ν_{max} 2973, 2933, 2219, 1621, 1466; HRMS (ESI) *m/z* 265.2284 (MH^+, $C_{16}H_{28}NO_2H^+$ requires 265.2274).



Methyl 6-cyano-2-methylenehexanoate (40). An oven dried reaction vessel was charged with compound **19** (5.5 mg, 0.034 mmol, 1 equiv), radical trap **39** (28.7 mg, 0.120 mmol, 3.5 equiv), and acetonitrile (1.1 ml) and sealed under an argon atmosphere. The vessel was subjected to microwave irradiation (300 W) at 90 °C for 10 min. The mixture was then cooled to room temperature and concentrated *in vacuo*. Flash chromatography (3-15% EtOAc in hexanes gradient elution) afforded **40** (4.0 mg, 0.024 mmol, 73%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.19 (s, 1H), 5.58, (d, J = 1.26 Hz, 1H), 3.77 (s, 3H), 2.38 (t, J = 6.8 Hz, 2H), 2.36, (t, J = 6.8 Hz, 2H), 1.74-1.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 139.6, 125.5, 119.6, 51.9, 31.1, 27.5, 24.9, 17.0; IR (film) ν_{max} 2952, 2247, 1720, 1631, 1439; HRMS (ESI) *m/z* 168.1017 (MH^+, $C_9H_{13}NO_2H^+$ requires 168.1019).

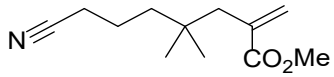


Methyl 7-cyano-2-methyleneheptanoate (41). In a procedure similar to the formation of **37**, compound **20** (10.3 mg, 0.059 mmol, 1 equiv), radical trap **39** (51.6 mg, 0.206 mmol, 3.5 equiv), and acetonitrile (2 mL) afforded **41** (9.1 mg, 0.050 mmol, 85%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.17 (s, 1H), 5.56 (d, J = 1.3 Hz, 1H), 3.77 (s, 3H), 2.36 (t, J = 7.2 Hz, 2H), 2.33 (t, J = 7.4 Hz, 2H), 1.70 (quin, J = 7.1 Hz, 2H), 1.56-1.47 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 140.1, 125.1, 119.7, 51.8, 31.6, 28.2, 27.6, 25.1, 17.1; IR (film) ν_{max} 2949, 2864, 2245, 1720, 1631, 1439; HRMS (ESI) *m/z* 182.1178 (MH^+, $C_{10}H_{15}NO_2H^+$ requires 182.1176).

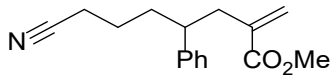


Methyl 7-cyano-4-methyl-2-methyleneheptanoate (42). In a procedure similar to the formation of **37**, compound **21** (10.2 mg, 0.054 mmol, 1 equiv), radical trap **39** (46.6 mg, 0.189 mmol, 3.5 equiv), and acetonitrile (1.8 mL) afforded **42** (8.8 mg, 0.045 mmol, 84%): ^{1}H NMR ($CDCl_3$, 500

MHz) δ 6.20 (d, *J* = 1.5 Hz, 1H), 5.54 (d, *J* = 1.2 Hz, 1H), 3.76 (s, 3H), 2.38-2.37 (m, 1H), 2.37-2.33 (m, 2H) 2.11-2.03 (m, 1H), 1.82-1.62 (m, 2H), 1.52-1.44 (m, 1H), 1.35-1.24 (m, 2H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 138.9, 126.5, 119.7, 51.9, 39.5, 35.6, 31.2, 23.0, 19.1, 17.3; IR (film) ν_{max} 2955, 2245, 1720, 1630, 1440; HRMS (ESI) *m/z* 196.1337 (MH^+, $C_{11}H_{17}NO_2H^+$ requires 196.1332).

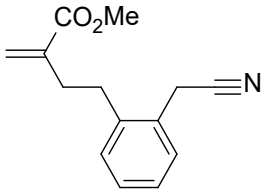


Methyl 7-cyano-4,4-dimethyl-2-methyleneheptanoate (43). In a procedure similar to the formation of **37**, compound **22** (14.8 mg, 0.073 mmol, 1 equiv), radical trap **39** (61.4 mg, 0.255 mmol, 3.5 equiv), and acetonitrile (2.4 mL) afforded **43** (2.9 mg, 0.014 mmol, 19%)**.**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.22 (d, *J* = 1.7 Hz, 1H), 5.50 (s, 1H), 3.76 (s, 3H), 2.34-2.30 (m, 4H), 1.72-1.64 (m, 2H), 1.36-1.30 (m, 2H), 0.86 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 138.0, 127.8, 119.7, 52.0, 42.5, 41.0, 33.8, 26.3 (2C), 20.5, 17.9; IR (film) ν_{max} 2957, 2873, 2245, 1722, 1626, 1439; HRMS (ESI) *m/z* 210.1498 (MH^+, $C_{12}H_{19}NO_2H^+$ requires 210.1489).

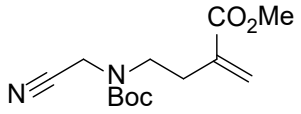


Methyl 7-cyano-2-methylene-4-phenylheptanoate (44). In a procedure similar to the formation of **37**, compound **23** (9.9 mg, 0.039 mmol, 1 equiv), radical trap **39** (36.5 mg, 0.137 mmol, 3.5 equiv), and acetonitrile (1.3 mL) afforded **44** (5.9 mg, 0.023 mmol, 59%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32-7.24 (m, 2H), 7.24-7.17 (m, 1H), 7.14-7.09 (m, 2H), 6.05 (d, *J* = 1.3Hz, 1H), 5.31 (d, *J* = 1.1 Hz, 1H), 3.73 (s, 3H), 2.87-2.79 (m, 1H), 2.72-2.65 (m, 1H), 2.58-2.50 (m, 1H), 2.27 (t, *J* = 7.0 Hz, 2H), 1.90-1.80 (m, 1H), 1.79-1.68 (m, 1H), 1.61-1.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 143.4, 138.1, 128.6, 128.5, 127.7, 127.1 (2C), 119.5, 110.0, 51.8, 44.3, 39.7,

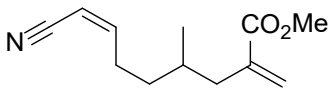
34.7, 23.4, 17.1; IR (film) ν_{max} 2950, 2245, 1717, 1630, 1453; HRMS (ESI) *m/z* 258.1499 (MH^+, $C_{16}H_{19}NO_2H^+$ requires 258.1489).



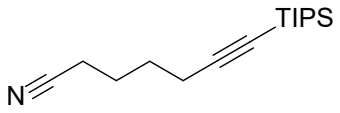
Methyl 4-(2-(cyanomethyl)phenyl)-2-methylenebutanoate (45). In a procedure similar to the formation of **37**, compound **24** (11.2 mg, 0.050 mmol, 1 equiv), radical trap **39** (42.0 mg, 0.175 mmol, 3.5 equiv), and acetonitrile (1.7 mL) afforded **45** (6.7 mg, 0.029 mmol, 58%)**.**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, *J* = 7.5 Hz, 1H), 7.32-7.22 (m, 3H), 6.21 (d, *J* = 1.1 Hz, 1H), 5.62 (d, *J* = 12 Hz, 1H), 3.80 (d, *J* = 6.9 Hz, 5H), 2.83-2.77 (m, 2H), 2.60-2.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 139.3 (2C), 129.9, 129.1, 128.5, 128.2, 127.1, 126.2, 118.0, 52.0, 33.5, 32.4, 21.2; IR (film) ν_{max} 2953, 2248, 1717, 1631, 1492, 1441; HRMS (ESI) *m/z* 230.1176 (MH^+, $C_{14}H_{15}NO_2H^+$ requires 230.1176).



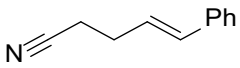
Methyl 4-((tert-butoxycarbonyl)(cyanomethyl)amino)-2-methylenebutanoate (46). In a procedure similar to the formation of **25**, compound **20** (11.6 mg, 0.044 mmol, 1 equiv), radical trap **39** (36.2 mg, 0.150 mmol, 3.4 equiv), and acetonitrile (1.48 mL) afforded **46** (9.5 mg, 0.035 mmol, 80%) as a mixture of rotamers: ^{1}H NMR ($CDCl_3$, 500 MHz not recorded yet; ^{13}C NMR ($CDCl_3$, 125 MHz) δ not recorded yet; IR not recorded yet; HRMS not recorded yet.



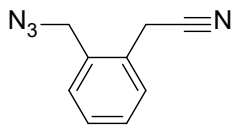
Methyl (*Z*)-8-cyano-4-methyl-2-methyleneoct-7-enoate (47). In a procedure similar to the formation of **37**, compound **47** (mg, mmol, equiv), radical trap **39** (mg, mmol, equiv), and acetonitrile (mL) afforded **26** (mg, mmol, %): ^{1}H NMR ($CDCl_3$, 500 MHz) δ not recorded yet; ^{13}C NMR ($CDCl_3$, 125 MHz) δ not recorded yet; IR not recorded yet; HRMS not recorded yet.



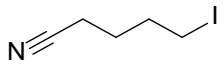
7-(Triisopropylsilyl)hept-6-ynenitrile (48). An oven dried reaction vessel was charged with compound **19** (11.8 mg, 0.0673 mmol, 1 equiv), radical trap **48** (100.1 mg, 0.2356 mmol, 3.5 equiv), and trifluoroethanol (2.25 ml) and sealed under an argon atmosphere. The vessel was subjected to microwave irradiation (300 W) at 90 °C for 20 min. The mixture was then cooled to room temperature and concentrated *in vacuo*. Flash chromatography (3-15% EtOAc in hexanes gradient elution) afforded **48** (9.5 mg, 0.036 mmol, 54%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.41 (t, *J* = 7.3, 2H), 2.34 (t, *J* = 6.8, 2H), 1.84 (quin, *J* = 7.9, 2H), 1.70 (quin, *J* = 7.5, 2H), 1.07 (d, *J* = 4.8, 18H), 1.05-1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 129.7, 119.4, 107.2, 81.5, 77.5, 27.4, 24.3, 19.0, 18.6 (6C), 16.7, 11.2; IR not recorded yet; HRMS not recorded yet.



(E)-5-Phenylpent-4-enenitrile (57). An oven dried reaction vessel was charged with compound **23** (13.4 mg, 0.053 mmol, 1 equiv), radical trap **54** (54.5 mg, 0.187 mmol, 3.5 equiv), and acetonitrile (1.8 ml) and methanol (0.9 ml) and sealed under an argon atmosphere. The vessel was subjected to microwave irradiation (300 W) at 90 °C for 10 min. The mixture was then cooled to room temperature and concentrated *in vacuo*. Flash chromatography (3-15% EtOAc in hexanes gradient elution) afforded **57** (4 mg, 0.025 mmol, 48%) as a yellow oil. Spectra are identical to reported literature values.

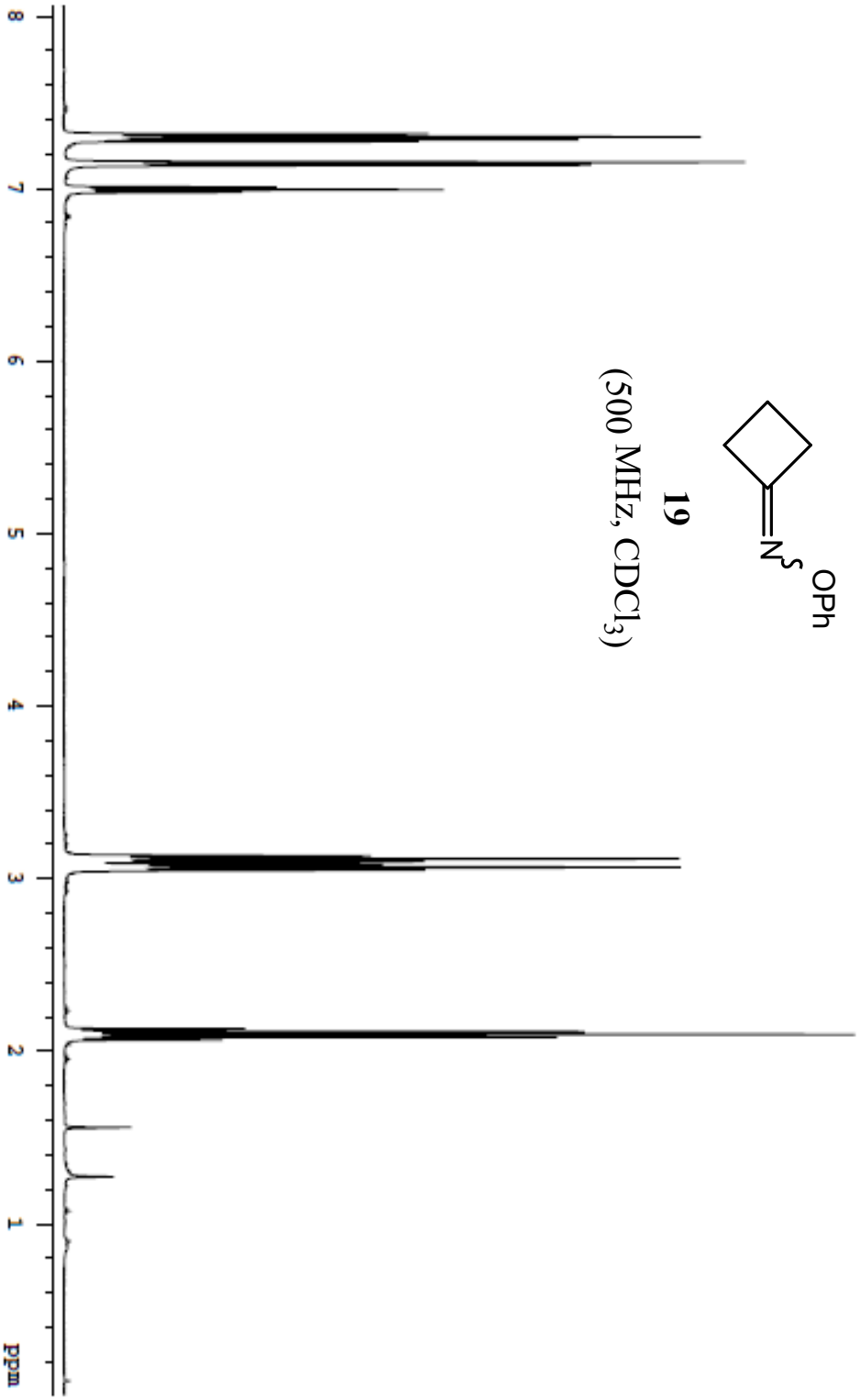


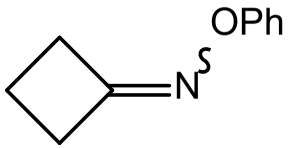
2-(2-(azidomethyl)phenyl)acetonitrile (60). An oven dried reaction vessel was charged with compound **24** (15.1 mg, 0.067 mmol, 1 equiv), radical trap **59** (35.6 mg, 0.202 mmol, 3 equiv), and trifluorotoluene (1.75 ml) and acetonitrile (0.50 ml) and sealed under an argon atmosphere. The vessel was subjected to microwave irradiation (300 W) at 100 °C for 20 min. The mixture was then cooled to room temperature and concentrated *in vacuo*. Flash chromatography (3-15% EtOAc in hexanes gradient elution) afforded **29** (2.9 mg, 0.017 mmol, 25%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ not recorded yet; ^{13}C NMR ($CDCl_3$, 125 MHz) δ not recorded yet; IR not recorded yet; HRMS not recorded yet.



5-iodopentanenitrile (61). An oven dried reaction vessel was charged with compound **19** (mg, mmol, equiv), 2-iodopropane (mg, mmol, equiv), and acetonitrile (ml) and sealed under an argon atmosphere. The vessel was subjected to microwave irradiation (300 W) at 90 °C for 10 min. The mixture was then cooled to room temperature and concentrated *in vacuo*. Flash chromatography (3-15% EtOAc in hexanes gradient elution) afforded **61** (mg, mmol, %) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ not recorded yet; ^{13}C NMR ($CDCl_3$, 125 MHz) δ not recorded yet; IR not recorded yet; HRMS not recorded yet.

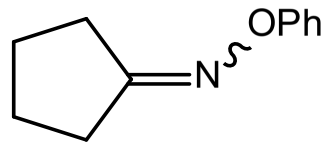
6.3 Selected NMR Spectra





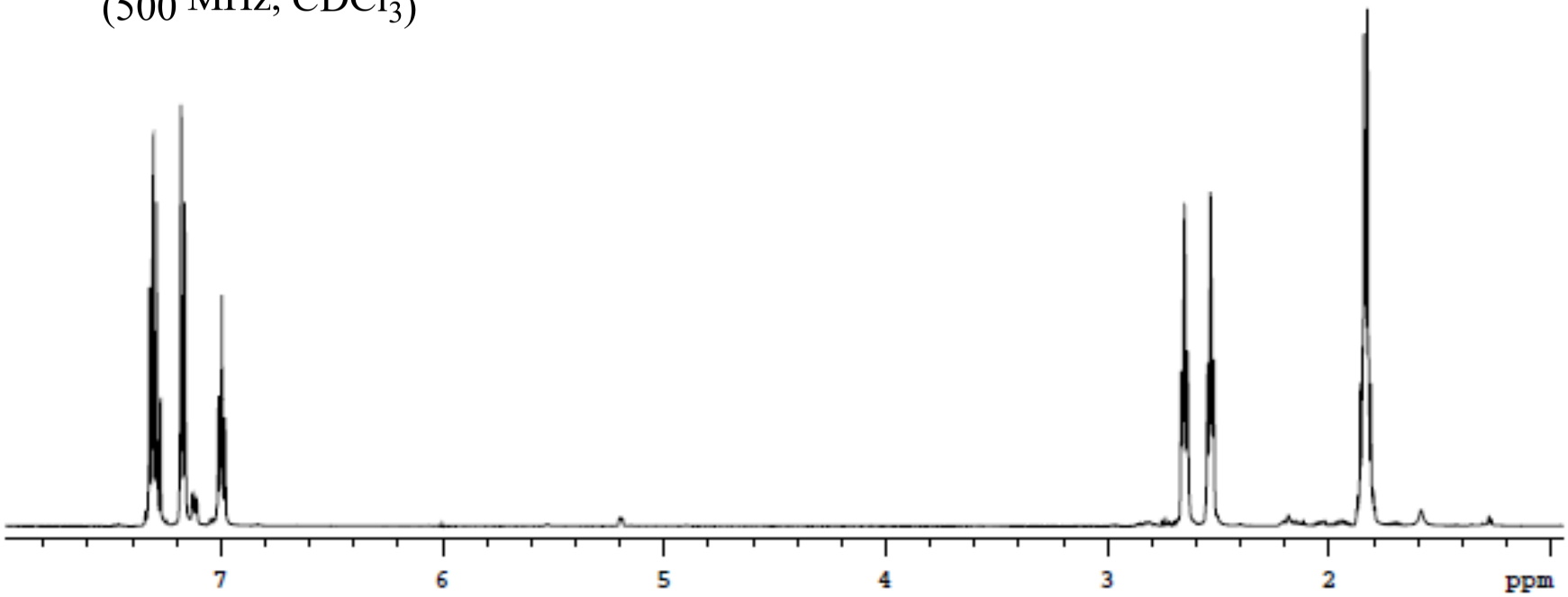
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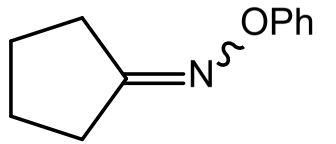
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20

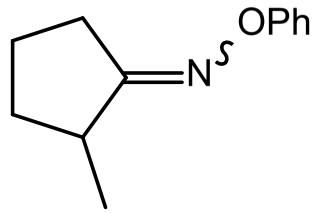
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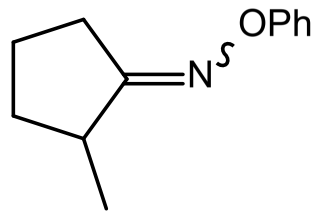
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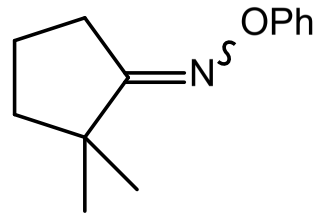
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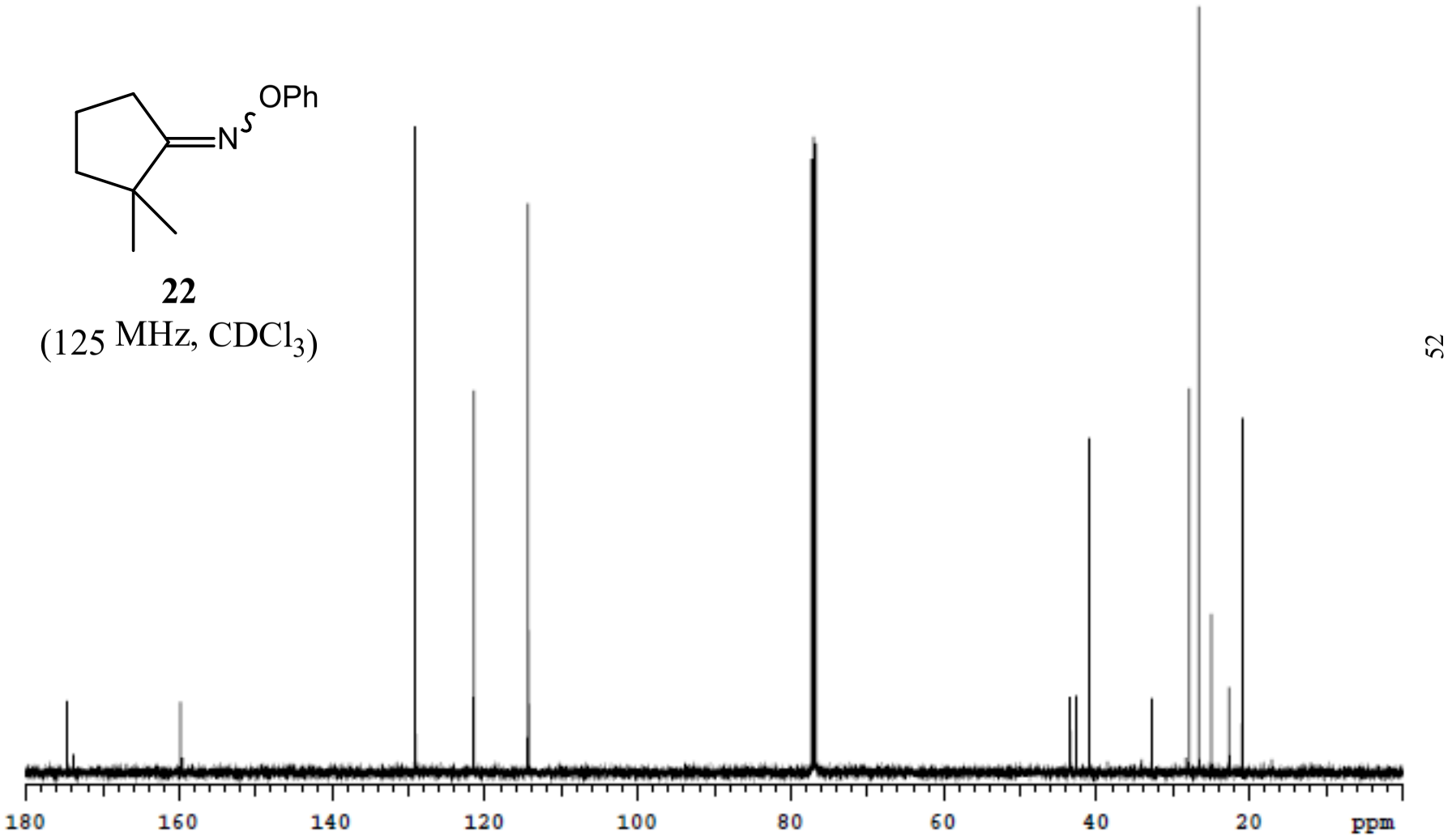
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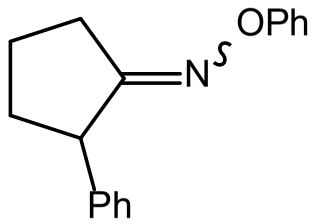
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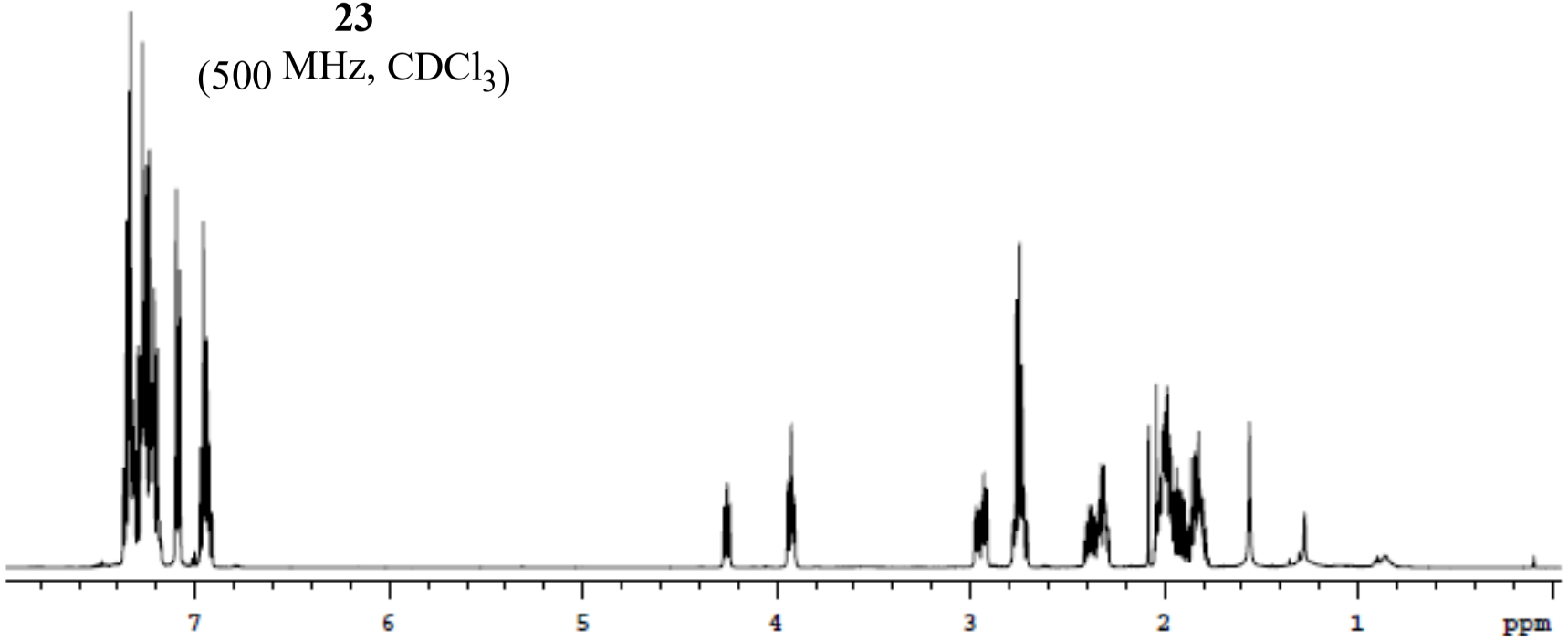
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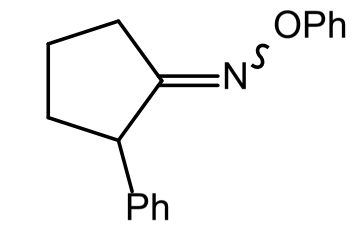
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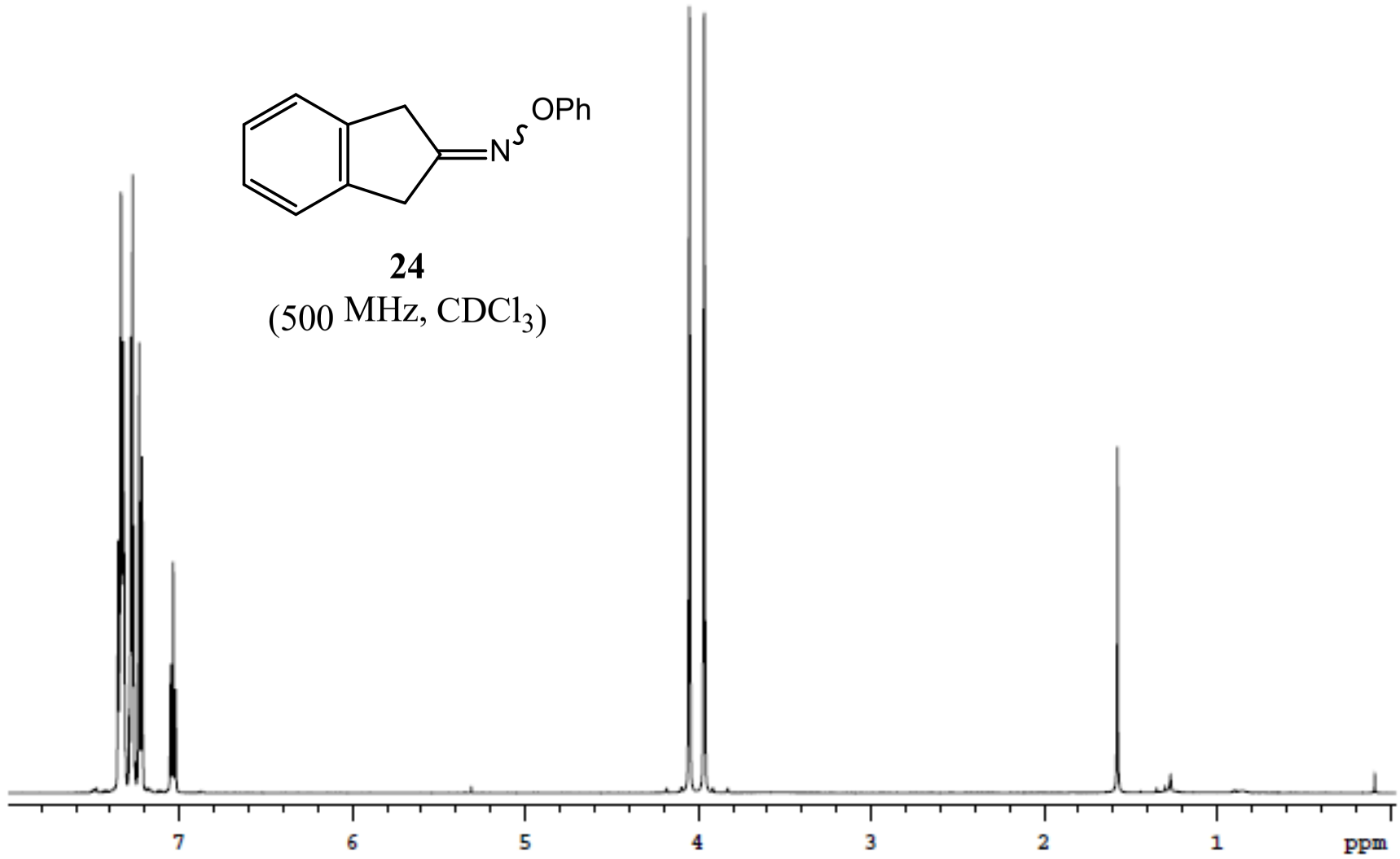
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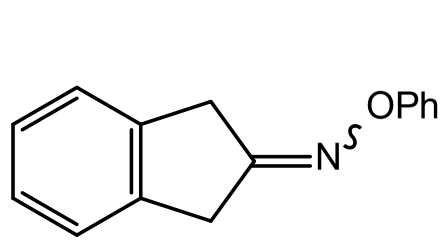
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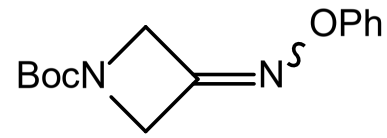
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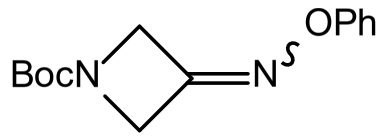
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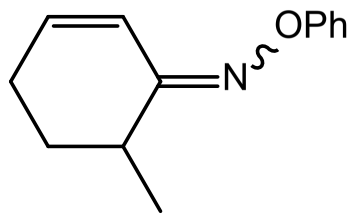
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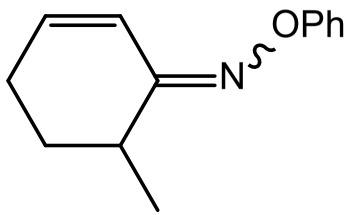
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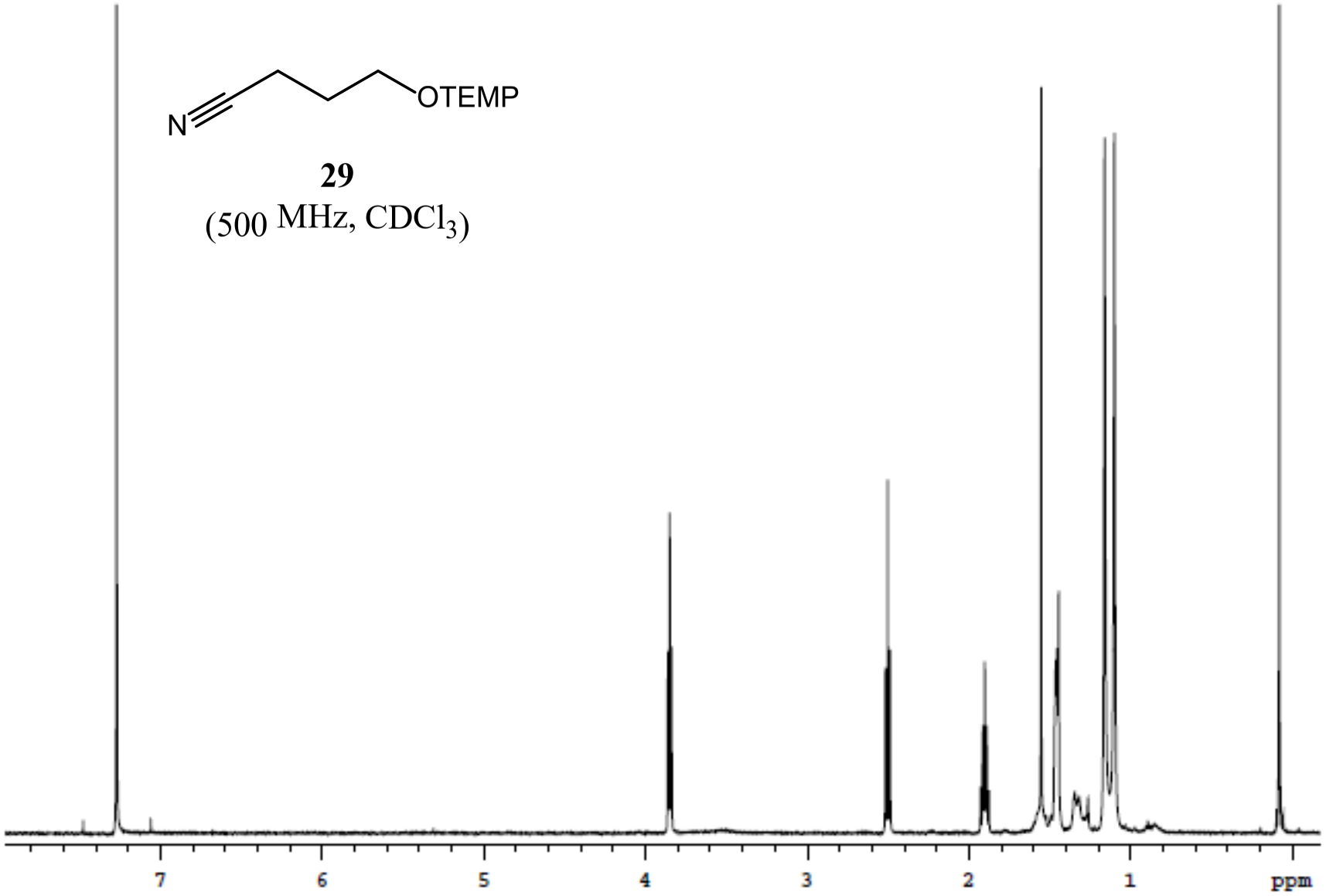
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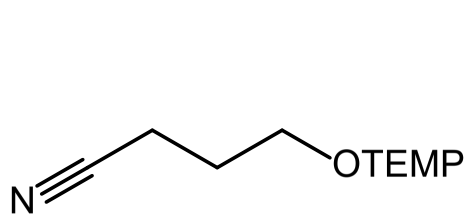
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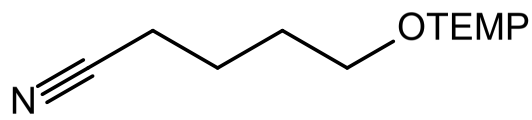
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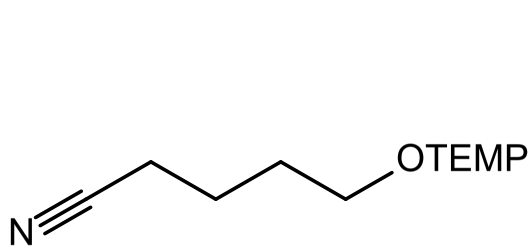
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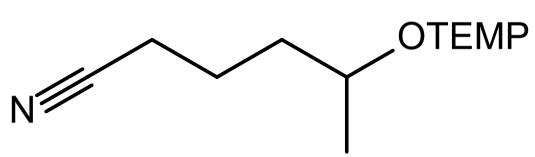
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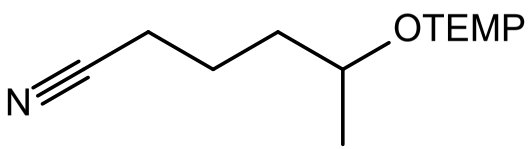
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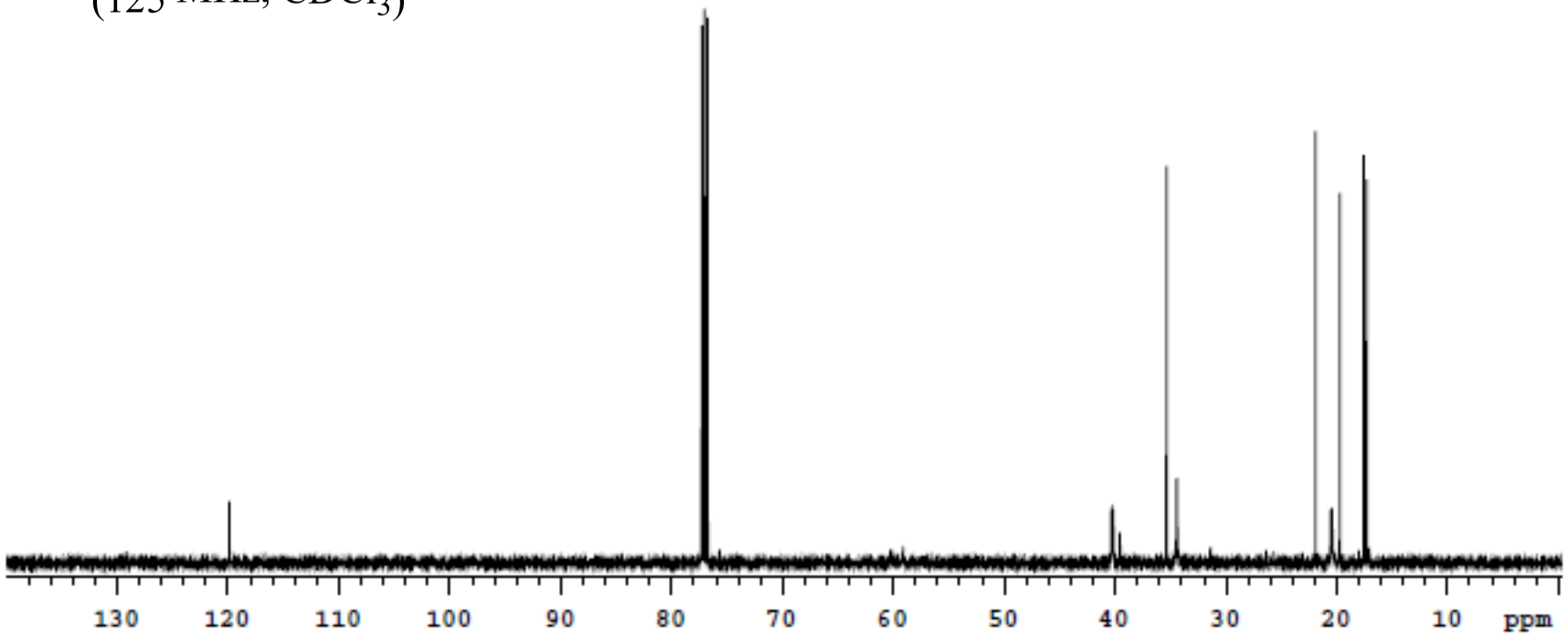
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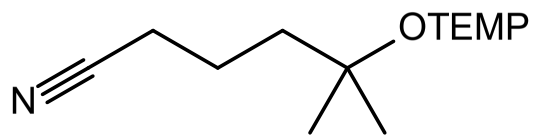
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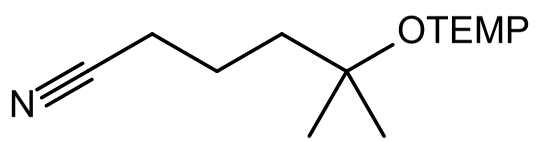
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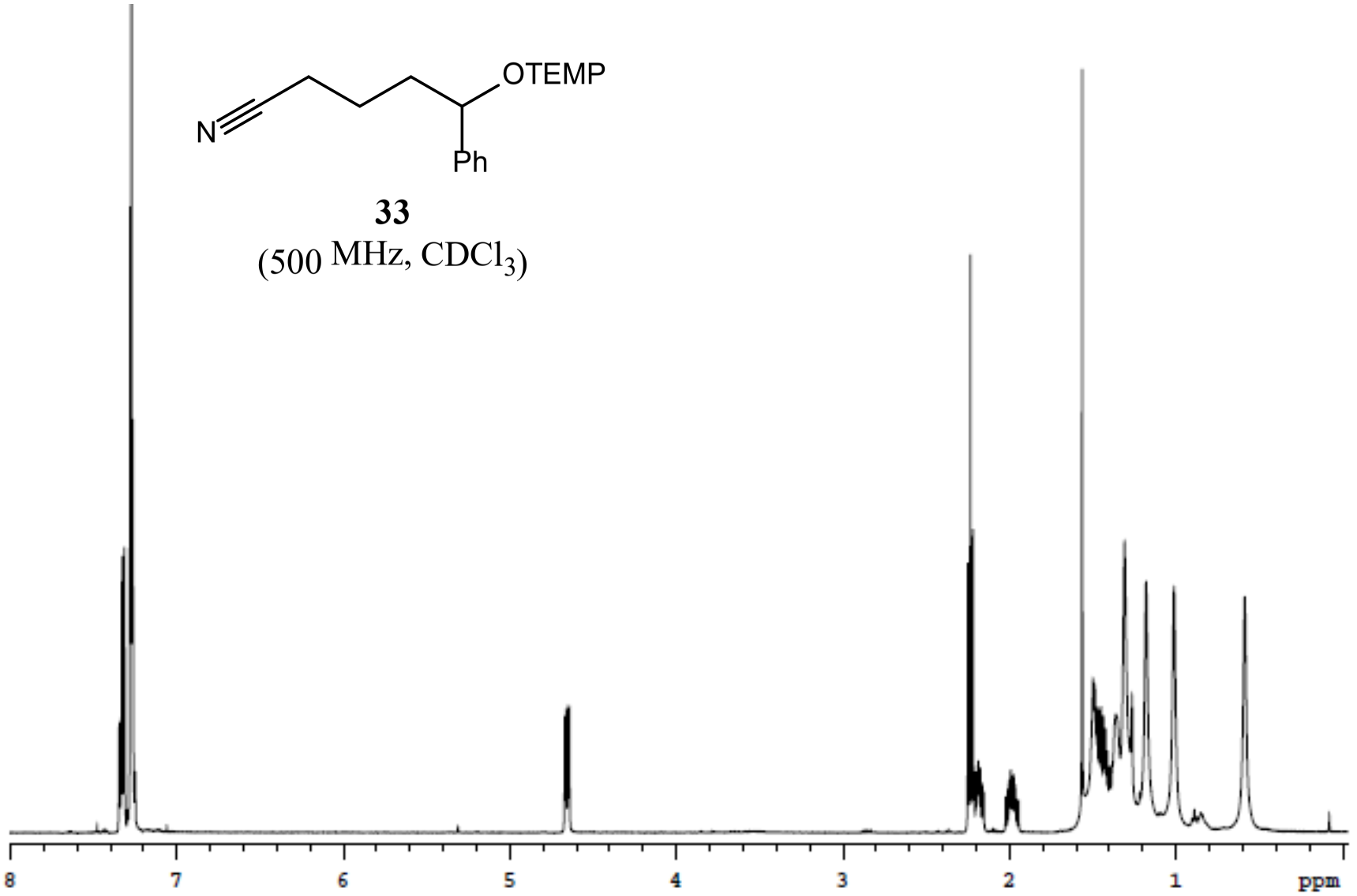
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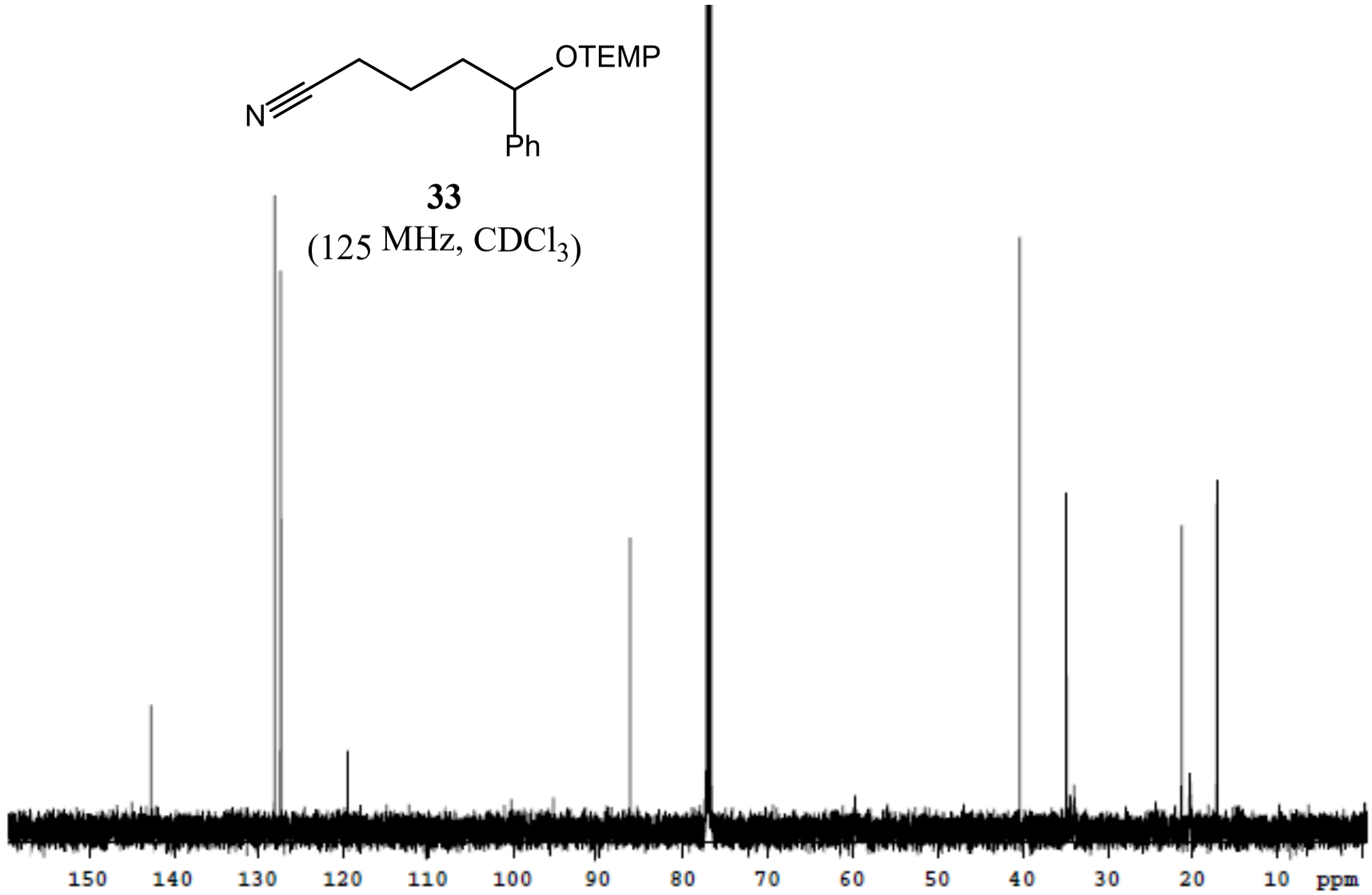
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(125 MHz, $CDCl_3$)



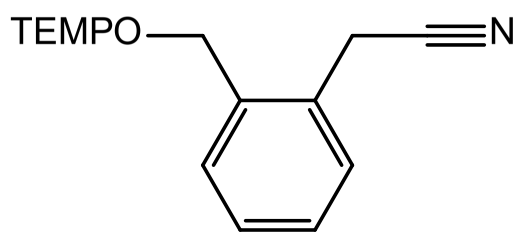
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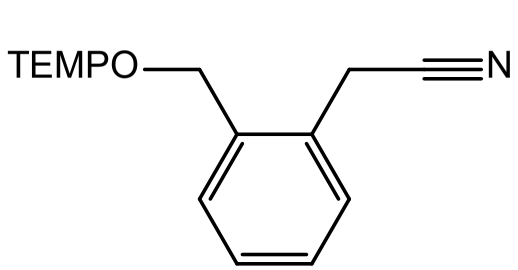
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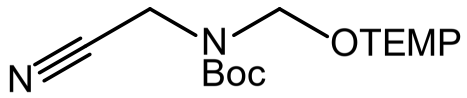
34

(500 MHz, $CDCl_3$)



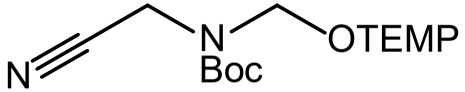
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(125 MHz, $CDCl_3$)



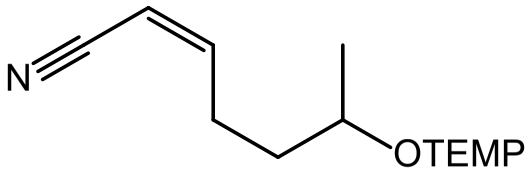
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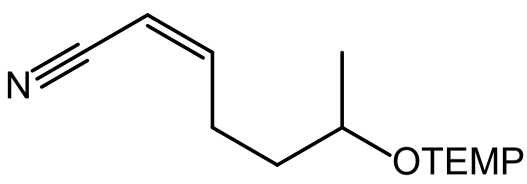
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(125 MHz, $CDCl_3$)



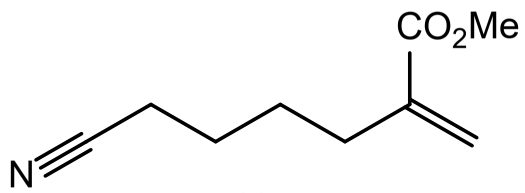
36

(500 MHz, $CDCl_3$)



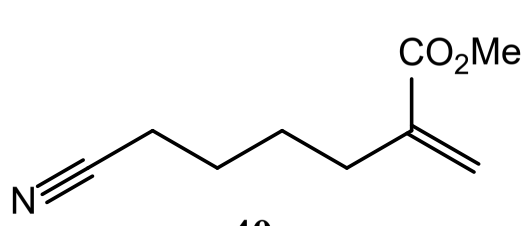
36

(125 MHz, $CDCl_3$)



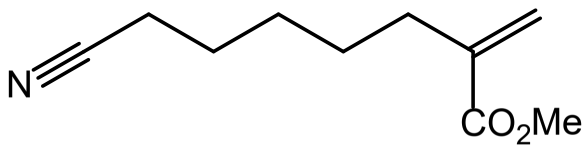
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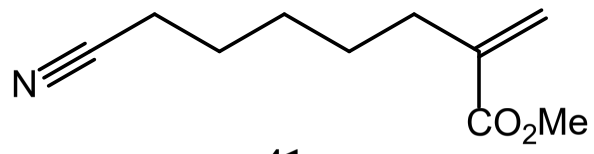
40

(500 MHz, $CDCl_3$)



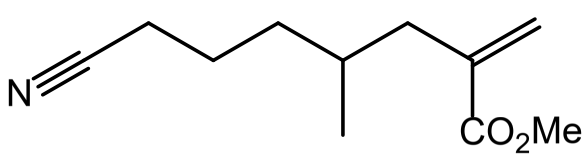
41

(500 MHz, $CDCl_3$)



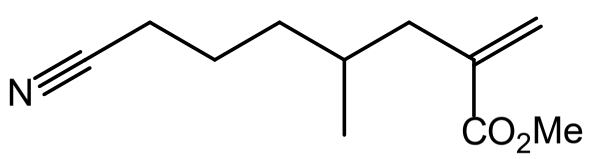
41

(500 MHz, $CDCl_3$)



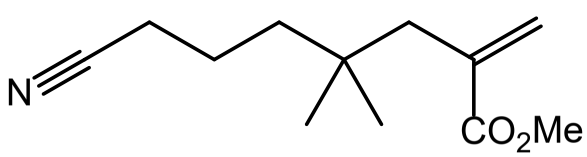
42

(500 MHz, $CDCl_3$)



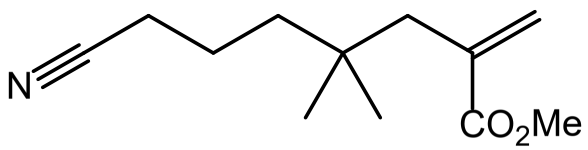
42

(500 MHz, $CDCl_3$)



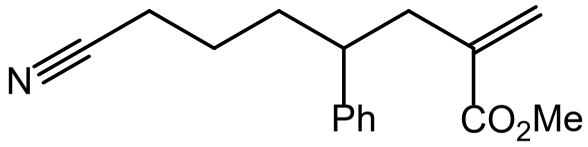
43

(500 MHz, $CDCl_3$)



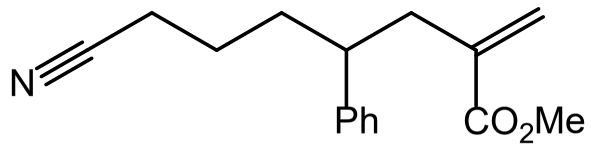
43

(125 MHz, $CDCl_3$)



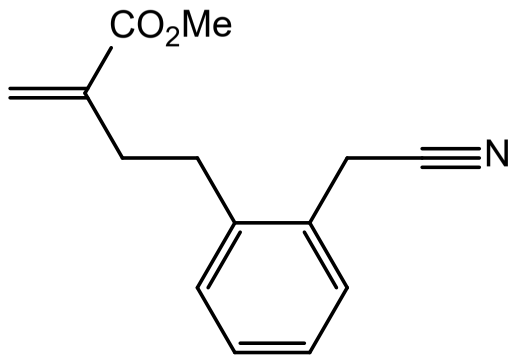
44

(500 MHz, $CDCl_3$)



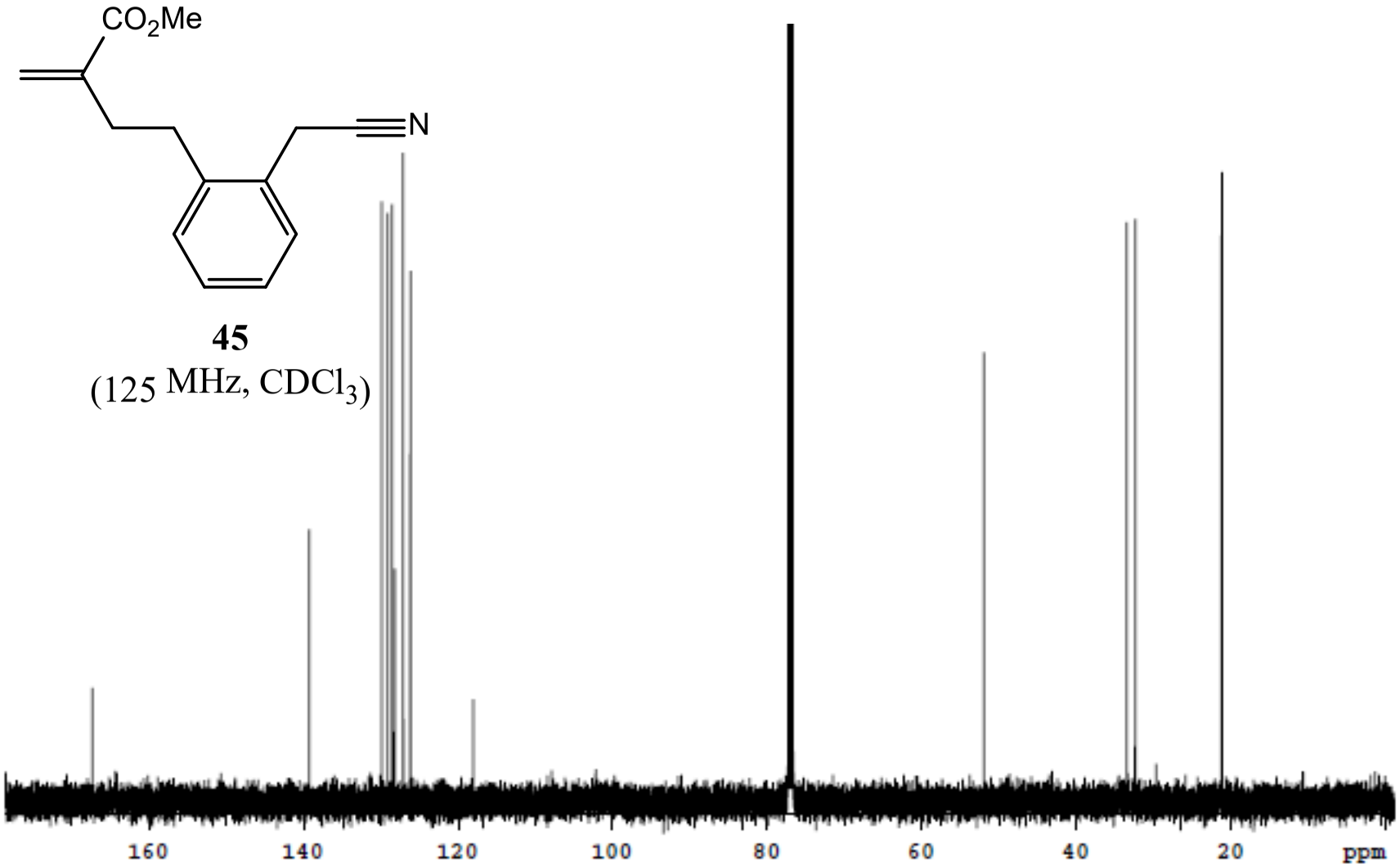
44

(125 MHz, $CDCl_3$)



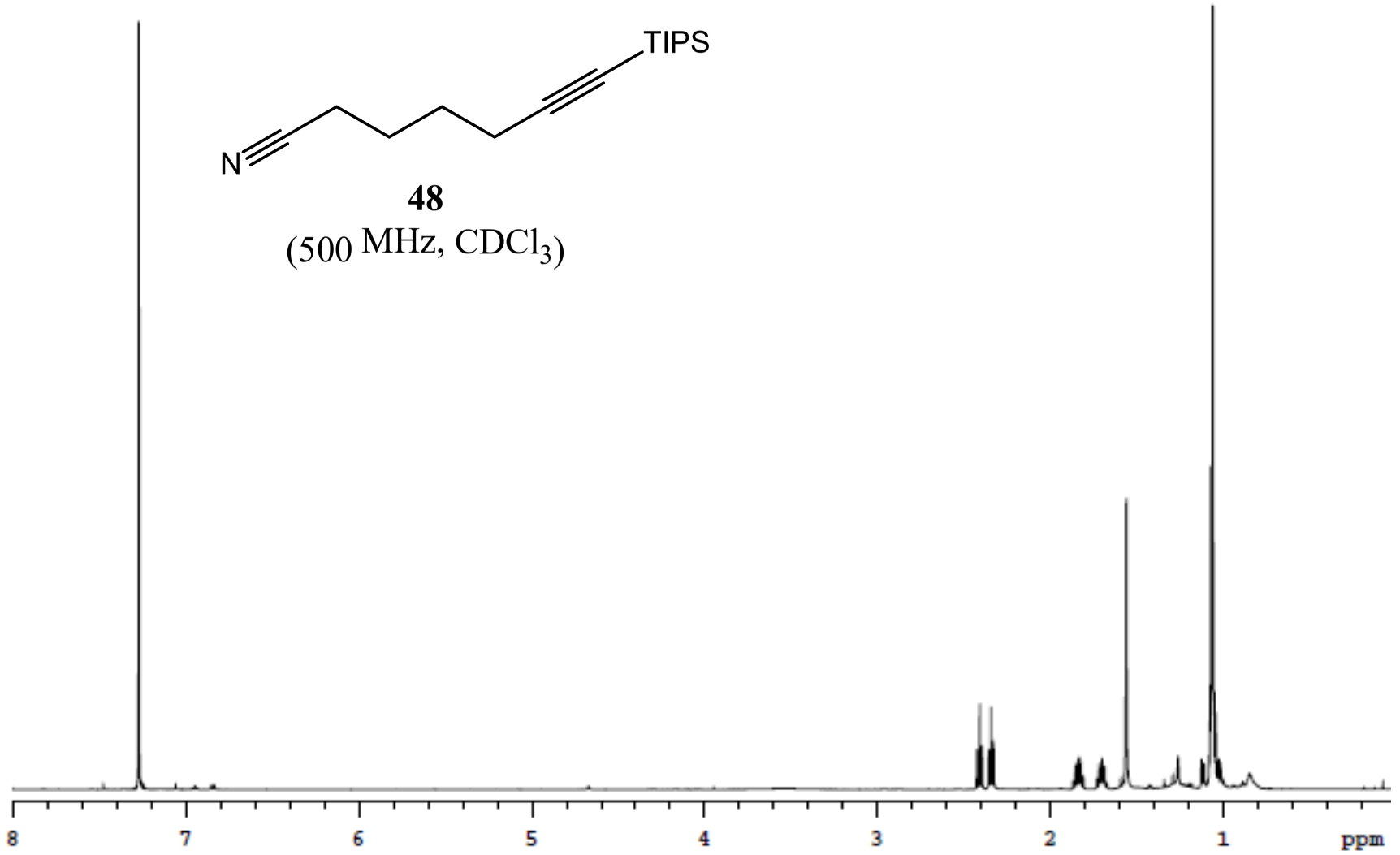
45

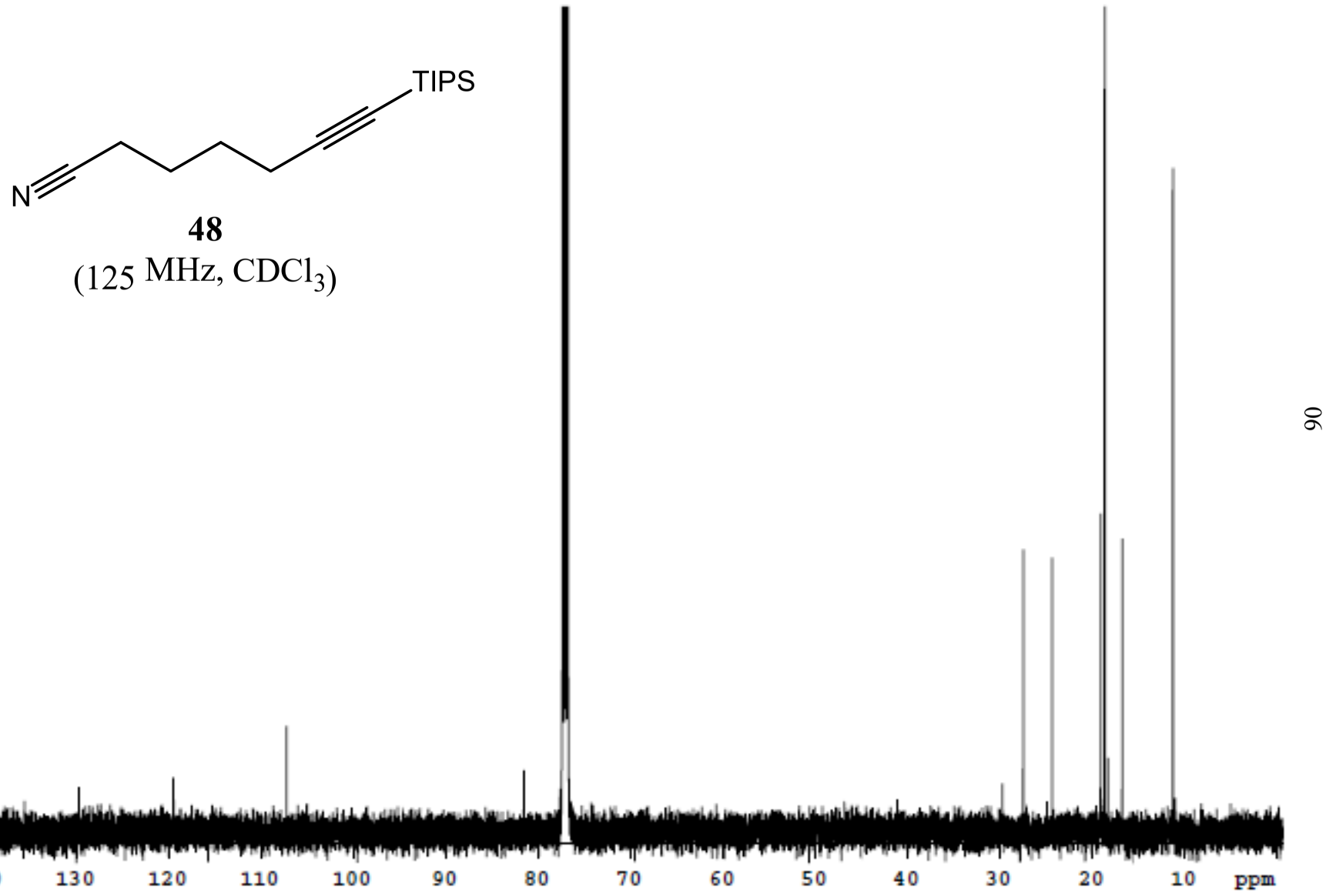
(500 MHz, $CDCl_3$)



45

(125 MHz, $CDCl_3$)


TIPS
N
48
(500 MHz, CDCl3)
8
7
6
5
4
3
2
1
ppm


TIPS
N
48
(125 MHz, CDCl3)
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm