

# Adapting polymerisation techniques for small molecule synthesis

*A thesis submitted in fulfillment of the requirement for the admission to the degree of*

Doctor of philosophy



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"The structure known, but not yet accessible by synthesis, is to the chemist what the unclimbed mountain, the uncharted sea, the untilled field, the unreached planet, are to others."

**R.B. Woodward**



## ***Declaration***

Except where specific acknowledgements of others are made, the work described in this thesis was carried out by the Author between February 2017 and January 2023 at the Australian national university, under the supervision of **Professor Michelle L. Coote** and **Professor Michael S. Sherburn**. The material presented has not been submitted for any other degree.

Alfred Kam Ki Fung

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**To everyone that supported me over these years, I would have quit without your support.**

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## ***Abbreviations***

|      |                                        |              |                                       |
|------|----------------------------------------|--------------|---------------------------------------|
| %    | Percentage yield                       | Hz           | Hertz                                 |
| °C   | Degree(s) Celsius                      | <i>i</i> -Pr | Isopropyl                             |
| A\$  | Australian dollar                      | <i>J</i>     | Coupling constant                     |
| Ac   | Acetyl                                 | K            | Degrees(s) Kelvin                     |
| Aq   | Aqueous                                | kbar         | Kilobar                               |
| Ar   | Aryl                                   | LDA          | Lithium diisopropylamide              |
| ATRP | Atom transfer radical polymerisation   | M            | molar                                 |
| Bn   | Benzyl                                 | Me           | Methyl                                |
| δ    | Chemical shift                         | Min          | Minutes                               |
| d    | doublet                                | mol. equiv   | Molar equivalent                      |
| DBU  | 1,8-diazabicyclo[5,4,0]undec-7-ene     | m.p.         | Melting point                         |
| DFT  | Density functional theory              | MS           | Mass spectroscopy                     |
| DMF  | Dimethylformamide                      | MW           | Molecular weight                      |
| DMP  | Dess-Martin periodinane                | NMP          | Nitroxide mediated polymerisation     |
| EI   | Electron Impact                        | NMR          | Nuclear magnetic resonance            |
| ESI  | Electrospray ionisation                | ph           | Phenyl                                |
| Et   | Ethyl                                  | ppm          | Parts per million                     |
| eV   | Electronvolt(S)                        | RAFT         | Reversible addition fragment transfer |
| EWG  | Electron withdrawing group             | q            | Quartet                               |
| FG   | Functional group                       | sat.         | Saturated                             |
| g    | Gram(s)                                | t            | triplet                               |
| h    | Hour(s)                                | Ts           | Para-toluenesulfonyl                  |
| HPLC | High Performance liquid chromatography | w/w          | Mass percentage                       |

## ***Abstract***

Atom transfer radical polymerisation (ATRP) is an industrially important methodology for controlled radical polymerisation. Copper-catalysed ATRP is one of the two original methodologies discovered in 1995; It remains the most developed variant, with advancements enabling air tolerance and ppm-level catalyst loadings. These advancements beg the question, can these advancements be adapted for small molecule synthesis? In this thesis, we bridge the gap between atom transfer radical polymerisation and small molecule synthesis; by strategically applying ATRP mediators and methodology to cross-coupling chemistry. Then we attempted to develop a new generation of ATRP mediators, thereby improving the scope of both ATRP and our developed methods involving ATRP mediators.

Our journey to bridge the gap between ATRP and small molecule methodology begins with the development of a copper-catalysed C-N bond cross-coupling, using a cheap and accessible ATRP mediator, which proved effective using a stoichiometric amount of a broad range of coupling partners, under mild reaction conditions. A novel mechanism elucidated via computational calculations highlighting the difference between our ATRP-inspired approach and conventional two-electron cross-coupling approaches.

The introduction of air tolerance was a breakthrough in ATRP methodology, greatly improving the industrial appeal of the once oxygen-sensitive process. In small molecule synthesis, the introduction of air tolerance into oxygen sensitive reactions is a paradigm that is not normally found for oxygen-sensitive cross-coupling reactions. Inspired by the use of supplementary reducing agents in ATRP methodologies, we successfully introduced air tolerance via the addition of a supplementary reducing agent (ascorbic acid derivatives) into the Cadiot-Chodkiewicz and Sonogashira cross couplings via sodium ascorbate and ascorbic acid.

Finally, we sought to improve the scope of ATRP via the development of a model synthesis towards new generation of capped ATRP ligands previously computationally evaluated to be far more active than the current generation of ATRP mediators. Together, these developments links together the fields of ATRP and small molecule synthesis, and lay the foundations expanding the scope of both ATRP and our C-N cross coupling.

## Publications and Presentations

The following list details the publications and presentations during the candidature for the degree of Doctor of Philosophy.

### Publications

1. **A. K. K. Fung**; L. Yu, M. S. Sherburn, M. L. Coote, ATRP-inspired room temperature (sp<sup>3</sup>)C–N coupling, *J. Org. Chem.*, **2021**, *86*, 9723–9732. <https://doi.org/10.1021/acs.joc.1c01029>
2. N. Uddin, J. Langley, C. Zhang, **A. K. K. Fung**, H. Lu, X. Yin, J. Liu, Z. Wan, , H. T. Nguyen.; Y. Li, N. Cox, A. T. S. Wee, Q. Bao, S. Xi, D. Golberg, M. L. Coote, Z. Yin, Zero-emission multivalorization of light alcohols with self-separable pure H<sub>2</sub> fuel, *Appl. Catal. B*, **2021**, *292*, 120212–120222. <https://doi.org/10.1016/j.apcatb.2021.120212>
3. R. J. Goodwin, M. T. Blyth, **A. K. K. Fung**, L. M. Smith, P. L. Norcott, S. Tanovic, M. L. Coote, N.G.White, Simple acyclic molecules containing a single charge-assisted O–H group can recognize anions in acetonitrile:water mixtures, *Org. Bio. Chem.*, **2021**, *19*, 2794-2803. <https://dx.doi.org/10.1039/d1ob00282a>
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5. Y. B. Vogel, C. W. Evans, M. Belotti, L. Xu, I.C. Russell, L. Yu, **A. K. K. Fung**, N. S. Hill, N. Darwish, V. R. Gonçalves, M. L. Coote, K. S. Iyer, S. Ciampi, The corona of a surface bubble promotes electrochemical reactions, *Nat. Comm.*, **2020**, *11*, 6323–6331, <https://doi.org/10.1038/s41467-020-20186-0>
6. N. S. Hill, B.B. Noble, F. J. M. Rogers, **A. K. K. Fung**, M. L. Coote, Computational tools for nitroxide design, in nitroxides: synthesis, properties and applications, Ouari, O.; Giggles, D., Eds. *Royal Society of Chemistry*; **2020** ISBN-10: 1788017528, ISBN-13: 978-1788017527.
7. V. Doan, B. B. Noble, **A. K. K. Fung**, M. L. Coote, Rational Design of Highly Activating Ligands for Cu-based Atom Transfer Radical Polymerization, *J. Org. Chem.*, **2019**, *84*, 15624-15632. <https://doi.org/10.1021/acs.joc.9b02915>

### Presentations

1. **A. K.K. Fung**, L. J. Yu, M. S. Sherburn, M. L. Coote (contributed talk), “*Adapting polymerisation techniques for small molecule synthesis*”, RACI NSW Organic Group 41st Annual One-Day Symposium, University of Sydney, Sydney, Australia. (Winner of best student presentation) (2021)

2. **A. K.K. Fung**, V. Doan, B. B., Noble, M. L, Coote (poster), *“Exploring the frontiers of atom transfer radical polymerisation catalysts”*, Excellence in graduate polymer research symposium. (Winner of Best presentation award) (2020)
3. **A. K.K. Fung**, M. L, Coote (poster), *“Evaluation of triazine for persistent radical polymerisations”*, 24th RACI Organic Chemistry Conference “Organic 18”, University of Western Australia, Perth, Australia. (2018)
4. **A. K.K. Fung**, M. L, Coote (poster), *“Synthesis of SOMO- HOMO inverted nitroxide”*, RACI Centenary Congress, Melbourne, Australia. (2017)

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## ***Chapter one :***

### *introduction*

## Introduction

Synthesis of compounds with desirable properties that are impractical or impossible to obtain from natural sources has created the modern world. While the medicinal uses for these compounds occupy the public spotlight, the impact of synthetic chemistry extends far beyond medicine. The synthesis of fertilizers and pesticides allows farmers to improve the yields of their land without relying on traditional farming practices; supporting the recent explosion in the world's population.<sup>1</sup> Additionally, synthetic compounds replace natural products which are difficult and ecologically irresponsible to produce, for example, the synthesis of Mauvine from aniline replaced the classical Tyrian purple dyes. The commercial success of the mauvine spurred the development of the methodology to produce synthetic dyes from coal tar derivatives, initiating the dye industry's transition to produce these cost-effective synthetic alternatives.<sup>2</sup> Finally, the development of plastics replaced traditional building materials, such as silk, cotton, wood, and metal. A plethora of polymers can be easily synthesized with a myriad of physical properties. In addition to their malleability, low cost, low weight, and durability, polymers can be rapidly formed into consumer goods via processing techniques such as injection molding,<sup>3</sup> which is far faster, requires less training, and is more amenable to mass production in comparison to traditional manufacturing techniques. Together these examples illustrate the role of synthetic chemistry in our modern society.

Organic and polymer chemistry both aim to answer the central question; what is the most efficient way to produce our desired product? Thus, significant efforts on both sides have been devoted to developing and improving methodologies<sup>4</sup> that give us superior control over the molecules we are working with. In this thesis, we wish to demonstrate the benefits of merging ideas from these disparate fields into each other.

Advancements in organic synthesis have allowed us to interact and control carbon-based molecules from which we can create unique architectures. The toolbox of a synthetic organic chemist is replete with many named reactions<sup>5</sup> which can be employed in various sequences to construct any structure desired, given enough time and resources<sup>6</sup>; however, the development of organic chemistry is far from complete. Despite a plethora of named reactions, only a very specific subset has garnered much industrial appeal,<sup>7</sup> demonstrating the need for methodological developments to improve the scope, efficiency, and environmental impact.<sup>8</sup>

Organic chemistry needs to step from the age of possibility into an age of accessibility. One of the most formative lessons I've learned during my studies in organic chemistry is the idea of an ideal synthesis. At its core, the ideal synthesis exhibits maximal efficiency, scalability, and robustness, allowing us to synthesize complex molecules in a single synthetic operation; in a cheap and environmentally responsible fashion, using a minimal amount of catalyst, with little to no workup necessary.<sup>9</sup> However, no ideal synthesis has yet been reported. The path to a perfect synthesis of any molecule is very long, and the incremental improvements to the methodology slowly lead us forward toward the ideal. A sentiment that is echoed by the progressive improvements made in the development of ATRP

The utility of plastics resulted in a multi-billion-dollar industry, where millions of tons of polymers are produced worldwide each year. Where current research targets new methods to control the specific physical characteristics of the material produced.<sup>10</sup> Free radical polymerization is an industrially critical process, responsible for producing roughly half the polymers created.<sup>11</sup> Free radical polymerization appeals to the industry with its mild reaction conditions, short reaction time, robustness, and functional group tolerance.<sup>12</sup> Free radical polymerizations occur starting with the decomposition of an initiator **1.1** into the initiating radical **1.2** (**Fig. 1.1**). The initiating radical **1.2** adds to a monomer unit **1.3** creating the propagating chain **1.4** which can add to additional units of monomer **1.3** to grow the polymer chain **1.5**; the propagating radical **1.5** is terminated by reaction with another propagating radical **1.6** via either a combination or a disproportionation pathway to form products **1.7-1.11**. Despite its dominance, free radical polymerization suffers from an inherent lack of control over tacticity, dispersity, and chain end functionality.<sup>13</sup> While tacticity can be influenced via a variety of methods,<sup>14,15,16,17,18</sup> dispersity, and chain end composition are manipulated using controlled radical polymerizations.<sup>19</sup>



and has inherited its air sensitivity. Over the years, the careful development of mechanistic variants has introduced many beneficial features, such as the development of stable precatalysts,<sup>26</sup> dropping catalytic loadings,<sup>26</sup> and oxygen tolerance,<sup>27</sup> all of which greatly improve ATRP's industrial appeal. The diligent improvements on the classical ATRP methodology was supported by a rigorous understanding of the underlying mechanism and kinetics of the ATRP equilibria and potential side reactions. (see **chapter two**)

However, despite the advancement of ATRP methodology and its clear connection to small molecule organic chemistry, little research into the application of valuable innovations within the field of ATRP in small molecule synthesis has been conducted. Consequently, this thesis makes this conceptual leap, connecting the fields of controlled radical polymerization with small molecule organic chemistry through the development of new reaction methodology and ligand architectures.

### **Aims of this thesis**

In this thesis, we review the mechanism and limitations of ATRP, along with the development of mechanistic variants which improved the accessibility and industrial appeal of ATRP. We then showcase the applicability of ATRP mediators in small molecule synthesis, by developing a mechanistically unique ( $sp^3$ ) C–N cross-coupling using an ATRP mediator. We then wish to adapt advancement from the mechanistic variants to introduce air tolerance into traditionally air-sensitive copper-catalyzed reactions. Finally, we aim to expand the scope of ATRP, through the synthesis of a previously computationally evaluated family of ligands.

### **Thesis outline**

In this work we adapt the mediator and mechanistic variants of ATRP for the synthesis of small molecules. We present this work as a thesis by Compilation comprising of three papers, in addition to an account of current work on a fourth project.

**Chapter two**, reviews the advancements in mechanism and methodology of ATRP in the article "Atom transfer Radical Polymerisation: A Mechanistic Perspective. We explore the (1) mechanism and side reactions behind ATRP (2) mechanistic variants and their impact upon ATRP (3) ligand structure/ activity trends. (4) functional group effects upon alkyl halide

stability towards homolysis. We specifically wanted to understand in detail the mechanism of ATRP since this would prove invaluable for the modification of these methodologies for small molecule synthesis. These opportunities were further investigated in chapters three four and five.

**Chapter three (Fig. 1.2)** showcases the tactical application of an ATRP mediator in catalysing a small molecule reaction. Radical chemistry is experiencing a renaissance in popularity driven by advancements in photochemical and electrochemical methods. We intended to highlight the effectiveness of employing an ATRP mediator system in organic synthesis, through the development of a copper-mediated  $sp^3$  C–N cross-coupling methodology. We successfully activated a variety of alkyl halides using a cheap and abundant ATRP mediator system, using only a stoichiometric amount of coupling partners. Furthermore, we computationally confirmed our mechanism proceeds via sequential single electron transfer.

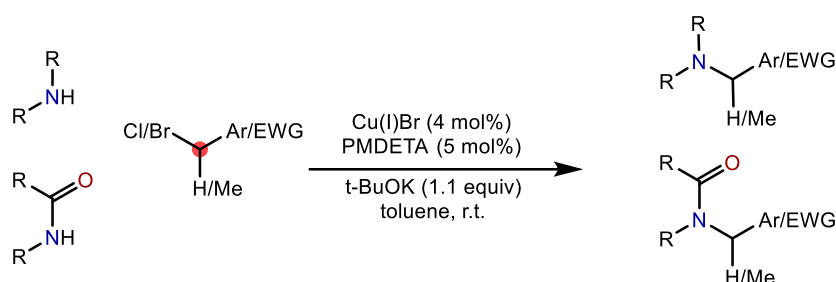


**Fig 1.2:** C–N bond coupling explored in **chapter three**.

**Chapter four (Fig. 1.3)** highlights an alternative use of activator regeneration by electron transfer (ARGET) techniques in small molecule synthesis, where we showcase our air-tolerant Cadiot Chodkiewicz and Sonogashira cross-coupling using sodium ascorbate or ascorbic acid. Both ARGET ATRP by Fokin–Sharpless azide/alkyne (3+2) click reactions has demonstrated the effectiveness of ascorbic acid and sodium ascorbate for the introduction of air tolerance into metal catalysed reactions. We aimed to introduce air tolerance to both the Cadiot Chodkiewicz and Sonogashira cross-coupling reactions via the addition of ascorbic acid or sodium ascorbate. This allowed us to eliminate the Glaser homocoupling from both reactions.

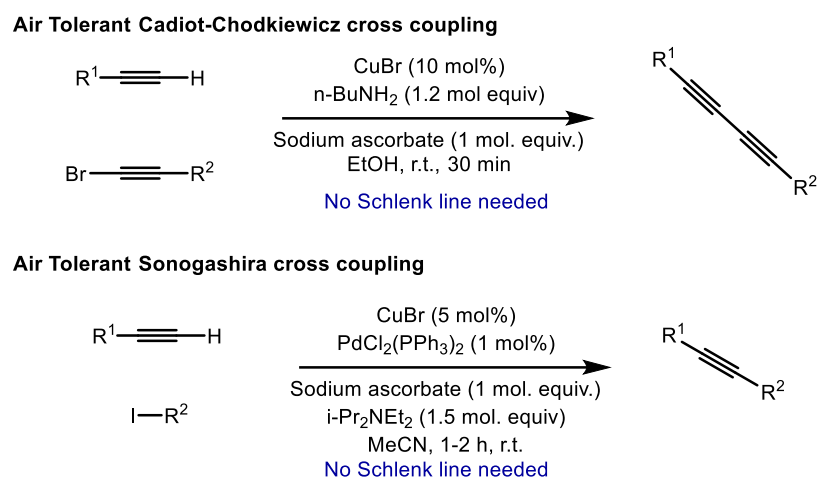
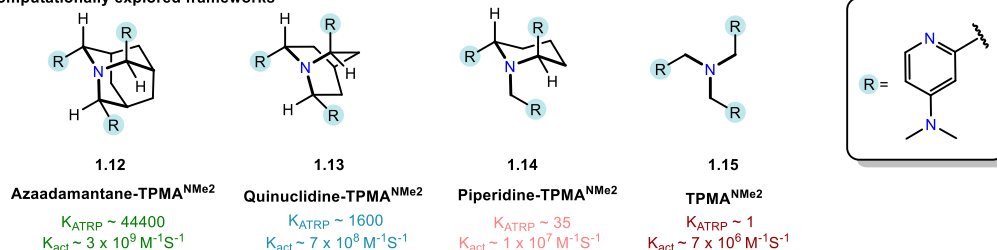


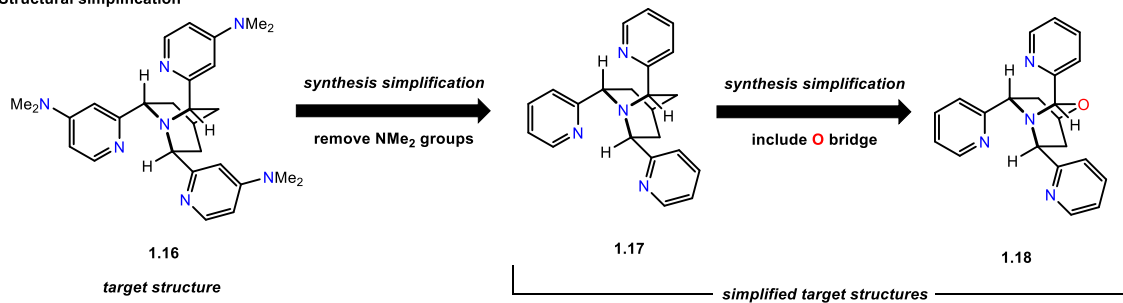
**Fig 1.3:** Air tolerant couplings explored in **chapter four**.

**Chapter five**, (**Fig. 1.4**) details our journey to expand the monomer scope of ATRP via the development the synthesis of a family of computationally predicted ligands **1.12–1.15**. To the best of our knowledge, no synthetic attempts towards these ligand frameworks have been reported. Of the previously computed ligands, the Quinuclidine-TPMA<sup>NMe2</sup> **1.13** represents the best compromise between synthesizability and ligand activity. Our model synthesis targets a pair of structurally simplified ligands **1.17**, **1.18**. We have pursued various synthetic pathways toward our desired ligand backbone, with significant progress made toward the completion of the ligand. The current synthesis allows for a decagram scale push towards a key piperidone intermediate **1.21**. Currently, the model synthesis has accessed an advanced intermediate **1.23** was synthesised where all C–C bond within the molecular framework has been completed.

Previously computationally explored frameworks



Structural simplification



Current progress

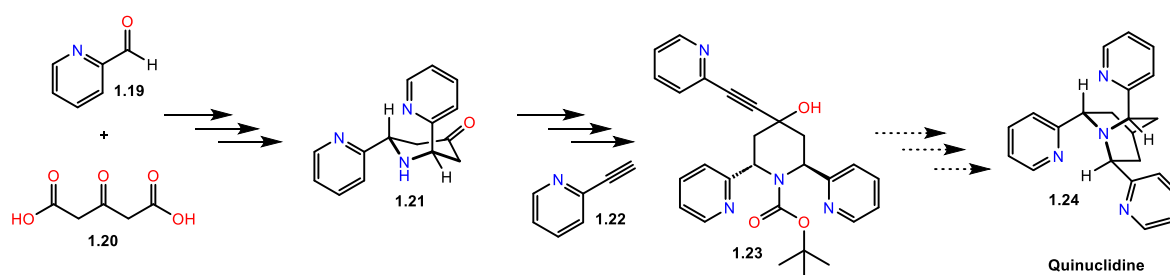


**Fig 1.4:** Model synthesis of the quinuclidine ligand **1.13**.

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## ***Chapter two:***

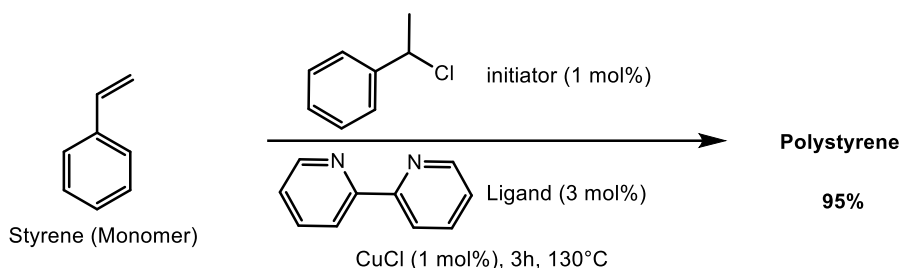
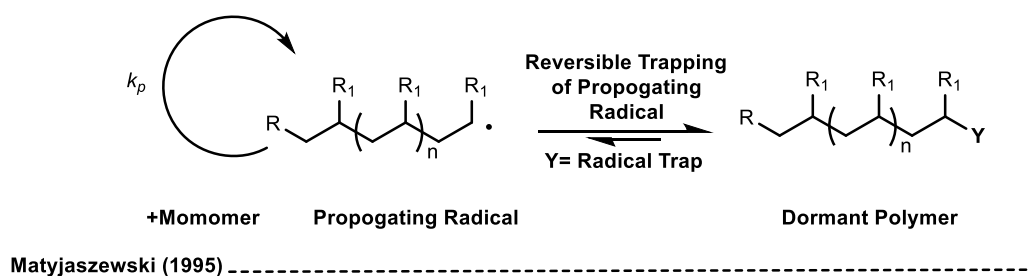
### ***A Mechanistic Perspective on Atom Transfer Radical Polymerization***

## ***Introduction.***

Free radical polymerisation's significance is demonstrated industrially where it is responsible for the production of roughly half of the polymers made.<sup>1</sup> Free radical polymerization appeals to industry with its mild reaction conditions, short reaction time, moisture, and functional group tolerance. Despite its appeal, free radical polymerization fails to control the tacticity, dispersity, and chain end composition of the polymer produced, control over these properties is critical to controlling the physical properties of the polymer.

Controlled radical polymerization techniques were designed to address the limitations of free radical polymerization's control over dispersity and chain end composition. Dispersity refers to the homogeneity of the mass of the polymer chains within a sample. Polymers produced via free radical polymerization tend to have high dispersities ( $D > 1.3$ ) due to undesired termination events that occur during the polymerization. Controlled radical polymerization reversibly traps the propagating radical,<sup>2</sup> reducing the relative number of termination events relative to the total number of growing and dormant polymer chains, thus allowing superior control over the dispersity. Separate approaches to controlled radical polymerization differ on the reagents (radical trap) and the mechanism by which the radical is reversibly released. Of the current controlled radical polymerizations techniques arguably the most important are Nitroxide-mediated polymerization,<sup>3</sup> reversible addition-fragmentation chain transfer,<sup>4</sup> and atom transfer radical polymerization<sup>5</sup>.

### Controlled Radical Polymerization



### Sawamoto (1995)

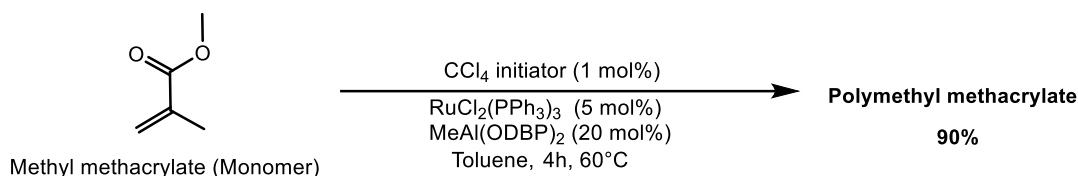


**Fig 2.1:** Controlled radical polymerisation and the variations of atom transfer radical polymerisation.

In 1995 Mitsuo Sawamoto<sup>6</sup> and Krzysztof Matyjaszewski<sup>7</sup> (**Fig 2.1**) independently developed methods for ATRP, both methods successfully controlled the tacticity of the polymer produced. Despite the differences in their choice of reagents, both publications proposed that their process occurs via a radical mechanism, where the propagating radical is reversibly trapped as a dormant alkyl halide.

In this chapter, we focus on the copper-mediated variant of atom transfer radical polymerization, starting with the mechanism and limitation of the classic variant of atom transfer radical polymerization. we then examine the various mechanistic variations which were made to improve the industrial appeal of the process. We proceed to study the scope of ATRP concerning the copper ligand mediator complex and the relative stabilities of alkyl halides. Finally, we discuss side reactions to the ATRP process and potential applications in synthesis. We hope to take inspiration from the processes explored within this chapter and

adapt these methodologies to small molecule synthesis where we can improve upon the efficiency of small molecule reactions.

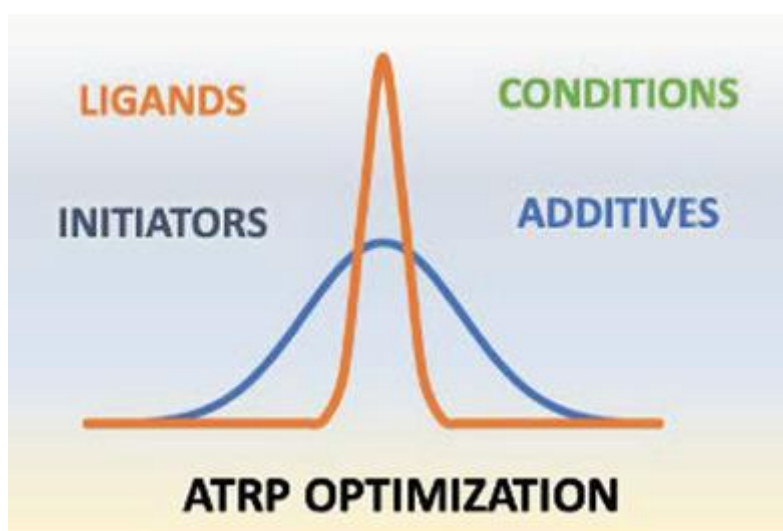
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## ***Publication 1: A mechanistic perspective on atom transfer radical polymerization***

Alfred Fung, Michelle Coote

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This manuscript was published in the Journal “polymer international” on 24<sup>th</sup> Sep, 2020. The article is reprinted with permission from authors. The authors were invited to contribute this review as part of the excellence in graduate polymer research symposia. Alfred K.K. Fung collaborated with Professor Michelle L. Coote in the initial drafting. Professor Michelle L. Coote edited the manuscript.

# A mechanistic perspective on atom transfer radical polymerization

Alfred KK Fung and Michelle L Coote\* 

## Abstract

Since its invention 25 years ago, atom transfer radical polymerization has become one of the most dominant methods in controlled radical polymerization. This rise in importance is due in large part to increases in scope, reduced catalyst loading and improved oxygen tolerance. These developments have been in turn underpinned by an improved understanding of the mechanism, kinetics and structure–reactivity trends. This mini-review outlines these mechanistic developments with a particular emphasis on the relationship between structure and activity in both the catalyst and alkyl halide substrate, and their implications for future catalyst design.

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Supporting information may be found in the online version of this article.

**Keywords:** atom transfer radical polymerization; structure–reactivity analysis; ATRP catalyst design; cross-coupling

## INTRODUCTION

The use of polymers has had an immutable impact upon our daily lives, with millions of tons produced worldwide per annum. One of the critical processes in the production of polymers is free radical polymerization.<sup>1</sup> However, free radical polymerization suffers from an inherent lack of control over dispersity and tacticity. Controlled radical polymerization techniques have been developed in order to address this problem.<sup>2</sup> Controlled radical polymerization relies upon the reversible storage of the active radical so as to reduce the number of termination events relative to the total number of polymer chains. This not only provides superior control over the molecular weight and dispersity, but also controls the chain end composition, thus allowing for the construction of specialized chain architectures such as grafts, stars, blocks and so forth.<sup>3</sup> There are a number of different types of controlled radical polymerization process, differing primarily in the nature of the dormant form and the reaction(s) converting it to the active form. Of these, arguably the most important are nitroxide mediated polymerization,<sup>4</sup> reversible addition fragmentation chain transfer polymerization<sup>5</sup> and atom transfer radical polymerization (ATRP).<sup>6,7</sup> For each of these techniques, there have been numerous reviews of their chemistry and applications. Here, we do not duplicate these but rather focus specifically on structure–reactivity analyses of ATRP and their lessons for catalyst design.

ATRP was separately discovered by Sawamoto and colleagues<sup>6</sup> and Wang and Matyjaszewski in 1995.<sup>7</sup> In its original form, it harnessed and improved upon the chemistry of atom transfer radical addition, which uses copper catalysts to generate carbon-centred radicals ( $R^\bullet$ ) from alkyl halide ( $R-X$ ) bonds. (The Cu catalyst is not strictly a catalyst but rather an activator, although it is functionally distinct from both traditional free radical initiators or the alkyl halides that are referred to as initiators in the ATRP process. For clarity, we therefore retain the term catalyst throughout this

review.) Scheme 1 shows the basic ATRP control equilibrium. Active radicals are generated from dormant alkyl halides via an inner sphere electron transfer reaction, mediated through a metal ligand complex. The equilibrium constant  $K_{ATRP}$  is the ratio between the activation and deactivation of the mediator complex and is a key factor governing the concentration of transient radicals in solution, and hence the rate of polymerization and the extent of molecular weight control.  $K_{ATRP}$  depends on the nature of the ATRP catalyst and the strength of the  $R-X$  bond and corresponding stability of  $R^\bullet$ , which in turn depends on which monomer is being polymerized. While copper-based ATRP is the most popular, ATRP can be executed using other metals such as Ti, Mo, Re, Fe, Ru, Os, Rh, Co, Ni and Pd,<sup>8</sup> and indeed Sawamoto's seminal work<sup>6</sup> itself made use of ruthenium catalysts. Nonetheless, copper remains the most prominent and is the focus of the present review.

## MECHANISM

Given the fundamental stability of the carbon–halogen ( $R-X$ ) bond, homolytic cleavage requires the assistance of a mediator. The use of copper to generate a carbon centred radical ( $R^\bullet$ ) is a topic well explored in synthetic organic chemistry through processes such as atom transfer radical addition,<sup>9</sup> Ullmann cross-coupling<sup>10</sup> and photoredox catalysis.<sup>11</sup> Metal mediated activation of alkyl and aryl halides to create radicals in solution could proceed in principle via four possible mechanistic pathways: oxidative

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Michelle L Coote completed a PhD in polymer chemistry at the University of New South Wales in 2000. Following postdoctoral work at the University of Durham, UK, she joined the Australian National University in 2001, where she is now an ARC Laureate Fellow, an Associate Editor of *Journal of the American Chemical Society* and an elected fellow of the Australian Academy of Science. Her group uses theory and experiment to design new synthetic methods, with an emphasis on non-traditional methods of bond activation using electricity and light.



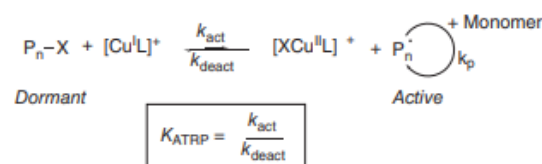
experiment have shown that the inner sphere mechanism is preferred.<sup>12–14</sup> This can be understood in terms of the very high energetic cost of electron transfer from  $[L_nCu^I]$  to the alkyl halide, which is partially compensated by the halide affinity of the  $Cu^{II}$  product. Hence a concerted ISET reaction, which avoids the high energy intermediate  $[L_nCu^I]^+$ , is typically 30 kcal mol<sup>−1</sup> more favourable than the stepwise process.<sup>14,15</sup> Although oxidative addition is also concerted, it is less favourable than ISET due to steric crowding around the  $[L_nCu^I]$ . This has also been shown to be true of Ullmann cross-coupling,<sup>16</sup> although it should be noted that in some cross-coupling applications, where for example monodentate phosphines are used as ligands,<sup>17</sup> oxidative addition is much more favourable due to the lower oxidation potential of the catalyst and reduced steric crowding.

### Mechanistic variants of ATRP

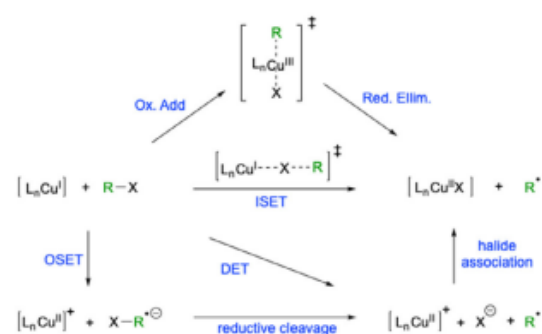
In addition to standard ATRP, there are a number of variants that have been designed to reduce catalyst loading, improve oxygen tolerance and generally improve the industrial attractiveness of the process and broaden its scope. In reverse ATRP<sup>18</sup> the catalyst is added in its oxidized ( $Cu^{II}$ ) state and a conventional free radical initiator is employed instead of alkyl halides (Scheme 3). Propagating radicals are generated and these react with the  $Cu^{II}$  catalyst to form alkyl halides and the reduced  $Cu^I$  catalyst, following which the process proceeds in the same manner as standard ATRP. The advantage of reverse ATRP is that the  $Cu^{II}$  catalyst is much less sensitive to air and easier to handle, thus making the process more suitable for highly active catalysts, applicable to mini-emulsions and more amenable to industry.<sup>19,20</sup> The disadvantage, however, is that the non-halide end of the dormant chain bears the initiator fragment, rather than a designer functional group, which limits chain topology and functionality. To address this, simultaneous reduction and normal initiation (SR&NI) was subsequently developed (Scheme 3).<sup>21</sup> This is similar to reverse ATRP except that both a conventional initiator and alkyl halides are used. The decomposition of the initiator generates a small population of the active  $Cu^I$  catalyst from the oxidized  $Cu^{II}$  catalyst, while the majority of the polymer chains are initiated from alkyl halide in the normal manner and can thus be easily functionalized. While SR&NI is an improvement on reverse ATRP, a small fraction of chain ends still bear initiator fragments. This problem was overcome by replacing the conventional radical initiator with a non-radical reducing agent such as ascorbic acid. In this process, known as AGET (activators generated by electron transfer), the  $Cu^{II}$  is converted to the active  $Cu^I$  form *in situ* by the reducing agent, while all propagating chains are initiated from the alkyl halide in the normal manner.<sup>22</sup> The reducing agent can also mop up any dissolved oxygen, making it suitable for a wide range of media including mini-emulsions.<sup>23</sup>

The above processes focus on altering the initial stages of the ATRP so as to generate the  $Cu^I$  catalyst *in situ* from the more stable  $Cu^{II}$ . However, it was soon realized that these alternative approaches to generating the  $Cu^I$  from  $Cu^{II}$  could also be applied throughout the entire process (Scheme 3). This supplemental regeneration provides a means of regenerating the active form of the catalyst that would otherwise remain inert due to the loss of propagating radicals through bimolecular termination. This allows the process to occur with parts per million catalyst concentrations, which is not only a cost saving but also enables catalyst removal to be avoided in many applications. The use of lower catalyst concentrations also eliminates or minimizes side reactions involving the catalyst. In ARGET (activators regenerated by

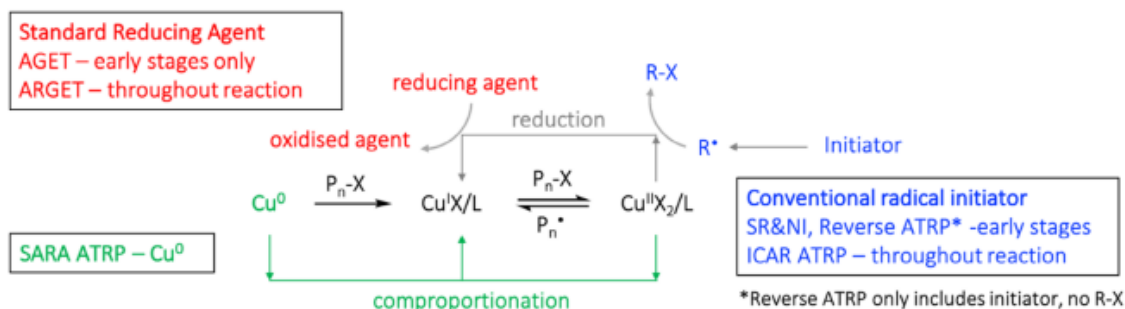
insertion, inner sphere electron transfer (ISET), stepwise outer sphere electron transfer and dissociative electron transfer (Scheme 2). The relative favourability of the alternative processes is influenced by the ligands, the nature of the activation process (e.g. thermal *versus* photochemical *versus* electrochemical) and the structure of the R–X substrate. For ATRP, theory and



**Scheme 1.** Control equilibrium in ATRP.



**Scheme 2.** Possible R–X activation mechanisms: oxidation addition (Ox. Add) followed by reductive elimination (Red. Elim.); inner sphere electron transfer (ISET); stepwise outer sphere electron transfer (OSET) followed by reductive cleavage and then halide association; dissociative electron transfer (DET) followed by halide association.



**Scheme 3.** Variants of ATRP.

electron transfer), like AGET, a non-radical forming reducing agent is used so as to ensure high chain end fidelity.<sup>24</sup> In ICAR (initiators for continuous activator regeneration), like SR&NI, a conventional radical initiator is used.<sup>25</sup> This sacrifices some of the chain end fidelity but leads to much faster reactions, with kinetics resembling conventional radical polymerization.<sup>26</sup> The mechanistic cross-over from AGET to ARGET, and from SR&NI to ICAR, is governed by the concentrations of supplemental activators, their reaction rates and in some cases whether or not they are slowly added throughout the process.<sup>27</sup>

Zero-valent metals such as metallic Cu, Fe, Mg and Zn have been shown to rapidly increase the rate of ATRP.<sup>28–30</sup> Two different mechanistic interpretations of their role have been put forward. Matyjaszewski *et al.*<sup>28,29,31–33</sup> have argued that the metal acts as a supplemental reducing agent by reacting with the Cu<sup>II</sup> in a comproportionation reaction to form the active Cu<sup>I</sup> catalyst (Scheme 3). However, unlike the reducing agents used in ARGET, the metals can also directly activate alkyl halide initiators, albeit at a slower rate than Cu<sup>I</sup>. Thus, the process is known as SARA (supplemental activator reducing agent). In the alternative mechanistic interpretation, known as SET-LRP (single electron transfer living radical polymerization), Percec *et al.*<sup>30</sup> argue that disproportionation rather than comproportionation is dominant, and so there is little or no Cu<sup>I</sup> present and it is the Cu<sup>0</sup> that acts as the main activator via an outer sphere electron transfer process, with Cu<sup>II</sup> the main deactivator.<sup>30</sup> There has been considerable debate as to the relative validity of the alternative mechanisms;<sup>34,35</sup> however, kinetic measurements of the disproportion rate of Cu<sup>I</sup> support the SARA mechanism, even in polar solvents.<sup>33</sup>

Other methods of supplemental regeneration, using electrochemistry,<sup>36</sup> photochemistry<sup>37</sup> and sonochemistry,<sup>38</sup> have also been explored. These offer various advantages over traditional methods, particularly with respect to temporal (and in the case of light also spatial) control. Their enhanced ability to control the regeneration of Cu<sup>I</sup> from Cu<sup>II</sup> with an external stimulus allows the polymerizations to be essentially oxygen tolerant. For reviews of these see references 36, 39 and 40.

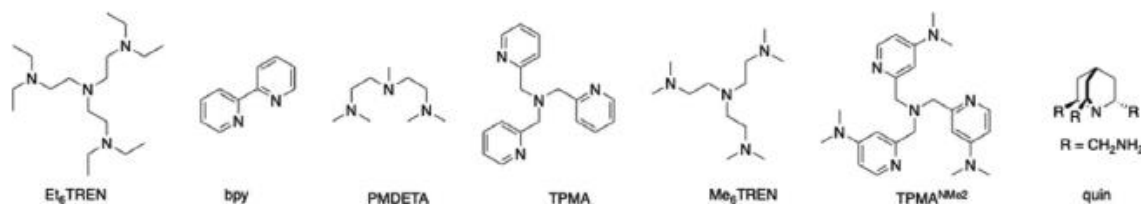
### Effect of the ligand

A common feature of ATRP copper-based mediators is their nitrogen ligands.<sup>8</sup> Copper(I) complexes generally form tetrahedral or square planar complexes, and hence a cationic species coordinates a tetradentate or two bidentate ligands, while neutral complexes coordinate tridentate ligands. Copper(II) species form trigonal bipyramidal structures with tetradentate and bidentate ligands; with tridentate ligands, a square pyramidal structure is

formed in which the incoming group occupies the axial position.<sup>41</sup> The original ATRP mediator system tested by Wang and Matyjaszewski<sup>7</sup> was CuX/bpy (2,2'-bipyridine; see Scheme 4 for the ligand structures). This was able to control the dispersity of styrene effectively, but not monomers with less stable propagating radicals such as vinyl acetate. Moreover, the reaction is relatively slow and requires elevated temperatures.<sup>42,43</sup> Structurally related ligands such as phenanthroline derivatives were also investigated, both for thermal activation<sup>44,45</sup> and photo-activation.<sup>46,47</sup> Subsequent investigations of linear and branched amines led to the discovery of a range of cheap and highly efficient catalysts such as *N,N,N',N'*-pentamethyldiethylenetriamine (PMDETA),<sup>48</sup> tris(2-pyridylmethyl)amine (TPMA)<sup>49</sup> and tris[2-(dimethylamino)ethyl]amine (Me<sub>6</sub>TREN).<sup>50</sup> While not substantially expanding monomer scope, these ligands allowed the temperature to be decreased from 100 °C to room temperature.<sup>50</sup> TPMA and Me<sub>6</sub>TREN are regarded as the best catalysts of that era as they balance high reactivity, ease of synthesis and relatively fast reaction rates under mild conditions. More recently a series of new ligands based upon the TPMA backbone, such as TPMA<sup>NMe2</sup>, have been developed with activities unparalleled by any from the previous generation of ATRP catalysts.<sup>51,52</sup> Computational studies suggest that this activity could be further improved by capping of the amine ligand (e.g. using quin, ((2*R*,6*R*,7*R*)-quinuclidine-2,6,7-triyl) trimethanamine) so as to destabilize the Cu<sup>I</sup> and lower its oxidation potential.<sup>15</sup>

To date, tetradentate amine ligands have been undeniably the best option for copper-based ATRP mediators.<sup>53</sup> Phosphorus ligands have been explored experimentally<sup>8,54–57</sup> and theoretically<sup>15</sup> without success, due to speciation issues. However, it should be noted that phosphines improve the favourability of electron transfer compared with amines, albeit at the cost of both halophilicity and ligand affinity of the Cu<sup>II</sup> catalyst.<sup>15</sup> Phosphines, however, can be used with metals with high inherent halophilicity such as osmium and ruthenium in order to facilitate efficient catalysis.<sup>54</sup> Interestingly, recent work has shown that phosphorus ligands are suitable for copper-based photoredox catalysts with ISET capability in small molecule reactions like cross-coupling.<sup>11</sup>

Figure 1 shows experimental *k*<sub>act</sub> values for CH<sub>3</sub>CH<sub>2</sub>(COOCH<sub>3</sub>)Br with CuBr in MeCN at 22 °C and a wide range of ligands.<sup>51,52,58</sup> These values range over 10 orders of magnitude for available ligands,<sup>51,52,58</sup> with another 3 orders of magnitude improvement in activity possible if the computationally designed ligands are considered as well.<sup>15</sup> A number of experimental and computational structure–reactivity studies have been published and the structure–reactivity trends are reasonably well understood. The



**Scheme 4.** Ligands used in ATRP catalysts.

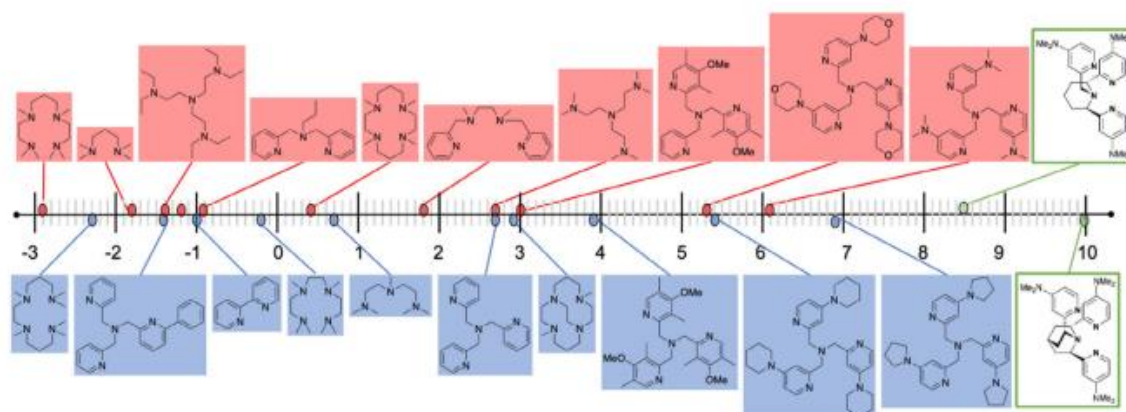


**Figure 1.** Selected experimental activation rate constants  $k_{act}$  ( $L \cdot mol^{-1} \cdot s^{-1}$ ) for ATRP with various N-based ligands with the initiator  $CH_3CH_2(COOCH_3)Br$  in the presence of  $Cu^I Br$  in MeCN at 22 °C. Experimental data taken from references <sup>51, 52, 58</sup>. The species in green boxes are computationally predicted values for new ligands taken from reference 15; other more active ligands are also predicted in this paper but these are the ones with synthetic precedent.

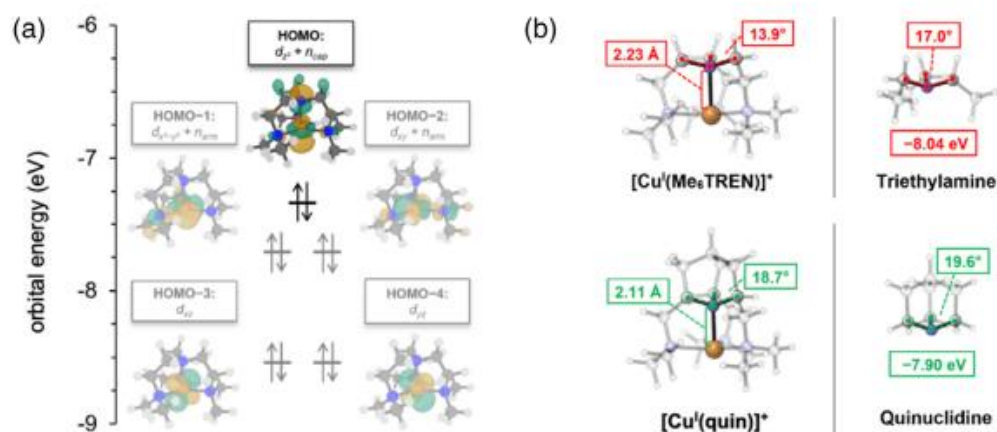


**Figure 2.** (a) The highest occupied orbitals in  $[Cu^I(Me_6TREN)]^+$ . (b) Geometries and POAV ( $\pi$ -Orbital Axis Vector) N-pyramidalization angles for the  $[Cu^I(Me_6TREN)]^+$  and  $[Cu^I(quin)]^+$  complexes as well as the corresponding core structures (triethylamine and quinuclidine). Reproduced from reference 15 with permission. Copyright (2019) American Chemical Society.

catalytic activity depends in large part on the ability of the ligand to stabilize  $Cu^{II}$  versus  $Cu^I$ , and indeed excellent semilogarithmic correlations between the reduction potential of the  $Cu^{II}$  complex and  $K_{ATRP}$  have been observed.<sup>58–60</sup> To a first approximation, the stability of the  $Cu^{II}$  versus  $Cu^I$  oxidation state depends on the electron donation capacity of the ligand, with the activity of ligands decreasing in the following order: alkyl amine  $\approx$  pyridine  $>$  alkyl imine  $>$  aryl imine  $>$  aryl amine.<sup>58–60</sup> Some of the most active

ligands, such as  $TPMA^{NMe_2}$ , are then further substituted with electron donating amine or methoxy substituents.<sup>51,52</sup>

However, within these broad trends, there is still considerable variation with chemical structure that is best understood by examining the molecular orbitals of the  $Cu^I$  complex (Fig. 2). By Koopman's theorem, the favourability of electron transfer in ATRP depends on the energy of the highest occupied molecular orbital (HOMO) in the  $[LCu^I]^+$  catalyst: the higher the energy, the more

easily an electron is removed. Figure 2(a) shows, as a typical example, the highest five occupied orbitals in  $[\text{Cu}^{\text{I}}(\text{Me}_6\text{TREN})]^+$ .<sup>15</sup> In the HOMO, there is a node between the axial nitrogen and the Cu, and hence any reduction of the distance between N and Cu leads to increased repulsion between them, resulting in turn in a destabilized HOMO and a more easily oxidized  $\text{Cu}^{\text{I}}$  catalyst.<sup>15</sup> Conversely, an elongation of the axial bond stabilizes the HOMO and hence raises the oxidation potential of the complex. As a result, steric factors can play a significant role in activating or deactivating the complex toward electron transfer. An extreme example is provided in Fig. 2(b) which compares the geometries of  $[\text{Cu}^{\text{I}}(\text{Me}_6\text{TREN})]^+$  with  $[\text{Cu}^{\text{I}}(\text{quin})]^+$ , the latter a computationally designed complex with a predicted increase in  $k_{\text{act}}$  of 2.5 orders of magnitude relative to  $[\text{Cu}^{\text{I}}(\text{Me}_6\text{TREN})]^+$  despite the same basic substitution pattern.<sup>15</sup> The cage structure that caps the quin ligand sterically pushes the axial nitrogen toward the Cu resulting in a decrease in the axial bond strength and a concurrent destabilization of the HOMO and decrease in oxidation potential.

While the ability of the ligand to stabilize  $\text{Cu}^{\text{II}}$  versus  $\text{Cu}^{\text{I}}$  is the main factor governing activity, other factors also play a role. In particular, the backbone flexibility of the ligand is critical to its ability to accommodate the geometry change from the tetrahedral or square planar  $\text{Cu}^{\text{I}}$  structure to trigonal bipyramidal  $\text{Cu}^{\text{II}}$  structure.<sup>11</sup> Moreover, the degree of steric hindrance the ligand presents to the incoming X–R species during the reaction also dramatically affects activity, as seen in the comparison of  $\text{Et}_6\text{TREN}$  and  $\text{Me}_6\text{TREN}$ .<sup>61</sup> The increased steric bulk in the latter results in a decrease of  $k_{\text{act}}$  by roughly 4 orders of magnitude because the bulkier side chains bury the reaction centre. In addition to steric effects, the halophilicity of the  $\text{Cu}^{\text{II}}$  catalyst is also critical and, while the largest factor governing this is the nature of the halogen (*vide infra*), the ligands on the catalyst also play a role. For a given halogen, the halophilicity of the catalyst depends primarily on how electronegative the  $\text{Cu}^{\text{II}}$  catalyst is, with studies showing a good correlation between natural charge on the  $\text{Cu}^{\text{II}}$  and halophilicity.<sup>15</sup> At some level, therefore, efforts to lower the oxidation potential of  $\text{Cu}^{\text{I}}$  through electron donation are countered by detrimental effects on the halophilicity of the resulting  $\text{Cu}^{\text{II}}$ . Nonetheless, within the nitrogen-based ligands at least, the former effect

dominates and stabilizing  $\text{Cu}^{\text{II}}$  versus  $\text{Cu}^{\text{I}}$  results in improvement in catalyst activity.

### Effect of the alkyl halide

The activity of alkyl halides (i.e. initiators and dormant propagating species) in ATRP depends on both the strength of the alkyl halide bond and the halogenophilicity of the ATRP catalyst. The bond strengths have been widely studied for unimeric radical species. A particularly large compilation of R–Cl strengths, studied quantum chemically at a consistently high level of theory, can be found in references 62 and 63 and are collected together in Table S1. Figure 3(a) shows the relationship between these bond strengths and their corresponding R–H bond strengths, calculated at the same level of theory in the same study. While there is some correlation between the two, it is quite poor ( $R^2 = 0.65$ ). Whereas the R–H bond strength is dominated by the stability of the R $^{\cdot}$  radical product, the R–Cl bond has a contribution from the ability of R to stabilize the polar covalent bond through  $\text{R–Cl} \leftrightarrow \text{R}^+ \text{Cl}^-$  resonance. As a result, whereas both electron donors and acceptors stabilize R $^{\cdot}$  and hence weaken R–H bond dissociation free energies (BDFEs), only acceptors weaken R–Cl. This is seen clearly in Fig. 4(a) where some of the strongest R–Cl bonds also have some of the weakest R–H bonds. These bonds feature radical stabilizing lone donor groups such as  $\text{NH}_2$  and OH that stabilize R–Cl, despite the high stability of R $^{\cdot}$ . The reason that this is of relevance to ATRP is that the inclusion of additional electron donating  $\text{CH}_3$  groups around the radical centre can sometimes counterintuitively reduce the activity of the alkyl halide, despite the fact that the extra methyl groups stabilize R $^{\cdot}$  and are sterically detrimental to the bond strength. This is illustrated in Fig. 4(b) which shows the bond strengths for series of primary, secondary and tertiary R groups. In all cases, the R–H bond strength decreases with increasing methyl substitution, whereas in most cases R–Cl bond strength actually increases. The rare exceptions to this are when the primary substituent is an effective electron acceptor. In these cases, captodative stabilization of R $^{\cdot}$  with increasing methylation helps to counter effects on R–Cl bond strengths. In practical terms, this means that 2-phenylpropyl halides are less effective initiators for styrene polymerization than

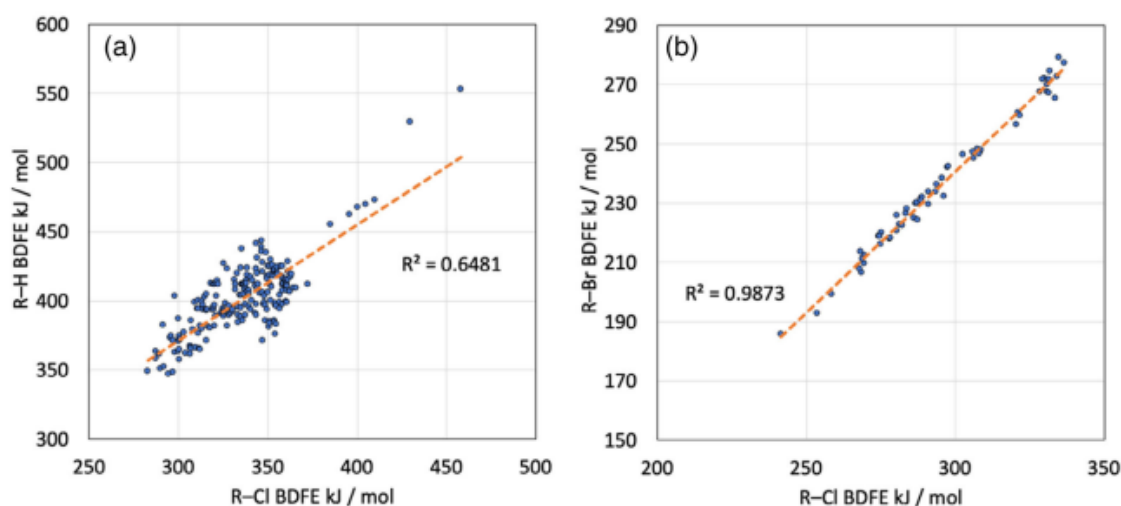


**Figure 3.** (a) Correlation between gas phase R–H and R–Cl bond dissociation Gibbs free energies from references 62 and 63. (b) Correlation between acetoneitrile R–Br and R–Cl bond dissociation Gibbs free energies from reference 64. All data<sup>64</sup> for both (a) and (b) are collected in Tables S1 and S2.

1-phenylethyl halides, while those based on electron withdrawing acrylates, acrylamides and nitriles show reactivity trends that are less sensitive to methyl substitution than might be expected based on the corresponding  $R^\cdot$  stability trends.

Comparing next alkyl halides and bromides, Fig. 3(b) shows that their bonds correlated well with one another over a broad representative test set of substituents ( $R^2 = 0.99$ ).<sup>64</sup> This is because both sets of bonds are polar and so are affected by donating and withdrawing groups in a similar manner. Hence the same structure–reactivity analysis outlined above for alkyl chlorides is equally applicable to the alkyl bromides. While the trends are the same, the bond strengths themselves are considerably different in magnitude with a typical alkyl bromide bond being  $60 \text{ kJ mol}^{-1}$  weaker than the corresponding halide due to poor orbital overlap.<sup>64</sup> This normally leads to the expectation that bromides are considerably more reactive than chlorides in radical processes.

However, in ATRP activity also depends on the halogenophilicity of the ATRP catalyst, and chlorides have greater affinity for the  $\text{Cu}^{\text{I}}$  species due to their greater electronegativity.<sup>58</sup> As a result, differences between  $K_{\text{ATRP}}$  for corresponding halides and bromides are less than an order of magnitude. This is illustrated in Fig. 5 for a set of representative experimental data, taken from reference 58.

### Side reactions

The coordination of organic radicals to the metal centre is well known and is the basis for the formation of organometallics such as the Grignard reagent.<sup>66</sup> In polymer chemistry, the ability to coordinate radicals to a metal centre in order to generate a dormant organometallic intermediate is the basis of organometallic mediated radical polymerization (OMRP). In principle, the ATRP process occurs in equilibrium with OMRP (Scheme 5). Trapping

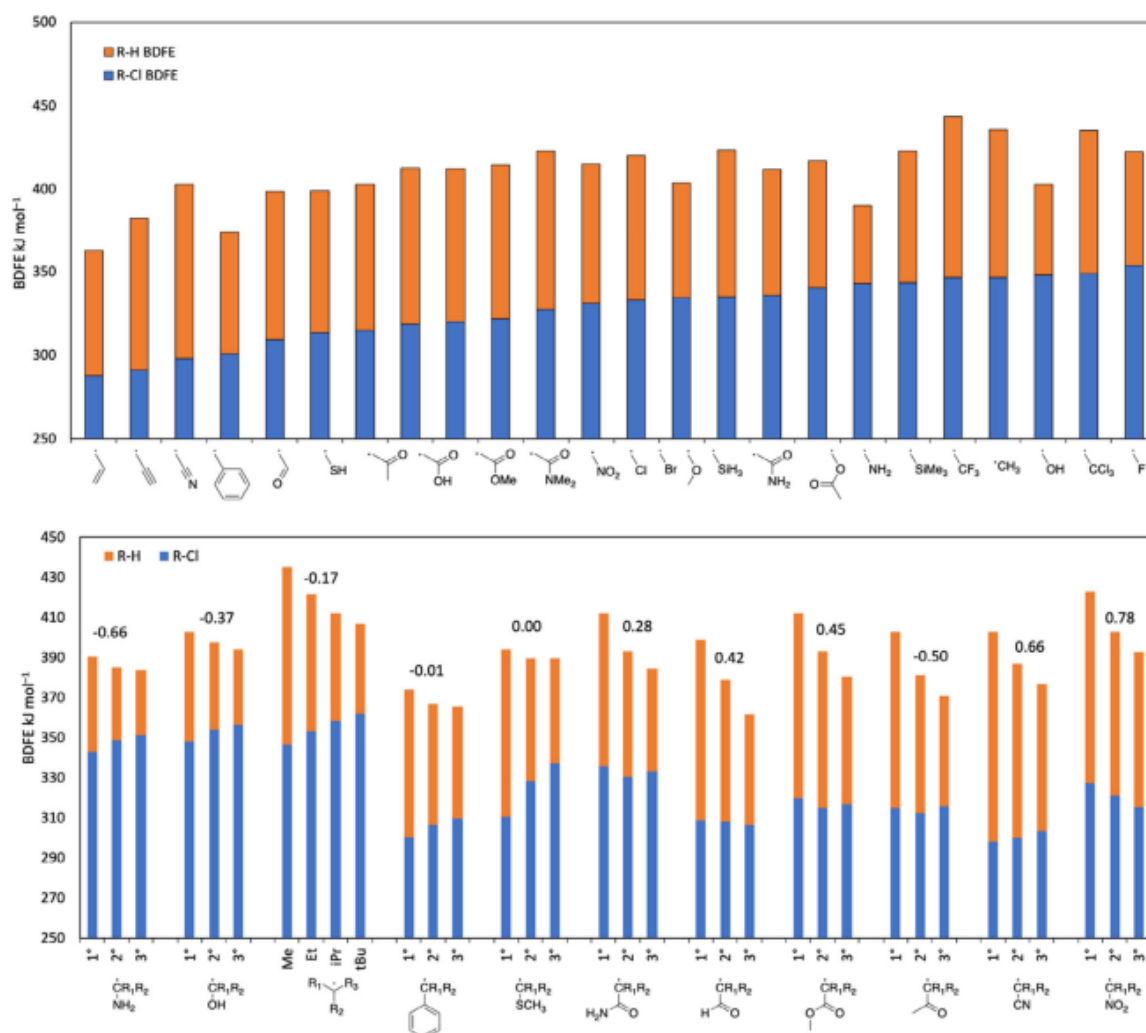


**Figure 4.** Selected gas phase R–H and R–Cl bond dissociation Gibbs free energies (BDFEs) ( $298 \text{ K}$ ,  $\text{kJ mol}^{-1}$ ) from references 62 and 63. The total column height is the R–H BDFE and the blue portion is the R–Cl BDFE, which is lower in all cases. (a) A series of primary R groups,  $\text{CH}_2\text{X}$  as a function of X; (b) the effect of increasing methyl substitution on  $\text{CR}_1\text{R}_2\text{X}$  ( $1^\circ \text{ R}_1 = \text{R}_2 = \text{H}$ ;  $2^\circ \text{ R}_1 = \text{H}$  and  $\text{R}_2 = \text{CH}_3$ ;  $3^\circ \text{ R}_1 = \text{R}_2 = \text{CH}_3$ ). The numbers at the top of the columns in (b) are the Hammett parameters taken from reference 65. All data for both (a) and (b) are collected in Table S1.

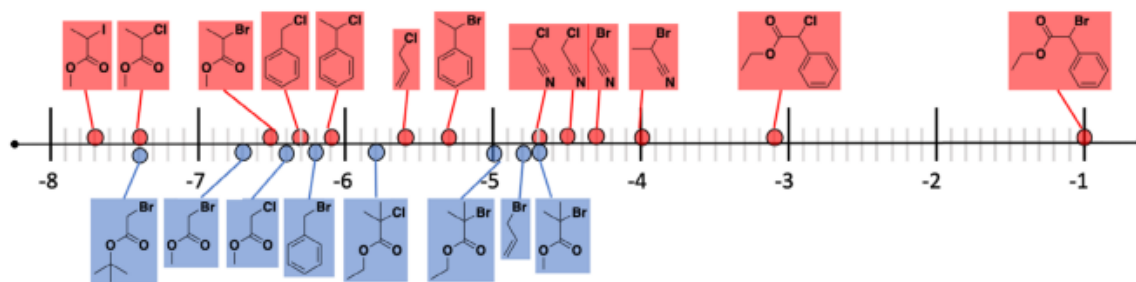
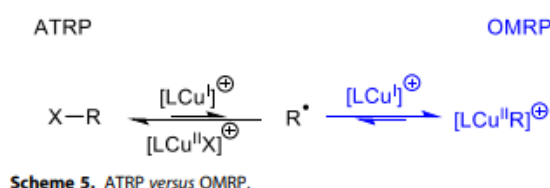


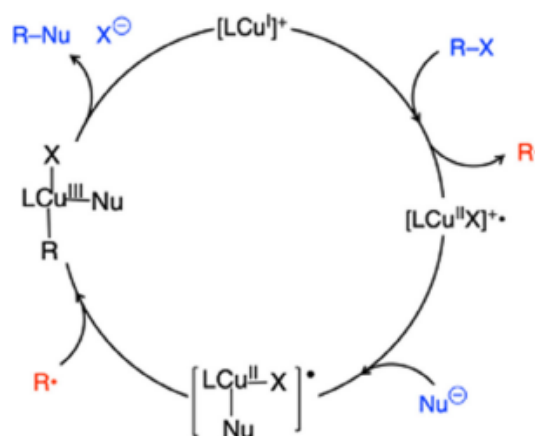
**Figure 5.** Selected experimental ATRP equilibrium constants for various initiators with  $\text{CuX/TPMA}$  ( $\text{X} \equiv \text{Br, Cl}$ ) in acetonitrile at 22 °C. Data taken from reference 58. The ATRP equilibrium constant depends on the halogenophilicity of the catalyst as well as the strength of the breaking bond, which is why the R-Br species perform a lot better than expected based on their relative bond strengths.



of  $\text{R}^\bullet$  serves to reduce the reaction rate but not the degree of control. Thus, in practice, OMRP is a slower process than ATRP, especially when using the new generation of ATRP catalysts.<sup>67</sup> However, the trapping of radicals as organometallic compounds could be an important feature which reduces the risk of a runaway radical polymerization in electrochemically mediated ATRP (eATRP)<sup>68</sup> and mechanically controlled ATRP (mechanoATRP)<sup>69</sup> where a high concentration of  $\text{LCu}^{\text{I}}$  and  $\text{R}^\bullet$  can build up at the surface–solution interface.

The effects of solvents upon the favourability of redox processes have been well studied.<sup>70,71</sup> In general, polar solvents stabilize highly charged species better than non-polar solvents. Hence, the relative stability of  $\text{Cu}^{\text{II}}$  versus  $\text{Cu}^{\text{I}}$  increases with solvent polarity, and this is accompanied by an increase in  $k_{\text{act}}$ , a decrease in  $k_{\text{deact}}$  and hence an overall increase in  $K_{\text{ATRP}}$ .<sup>72–74</sup> Nonetheless, it should be noted that the overall increase in  $K_{\text{ATRP}}$  is small in comparison with the choice of monomer/initiator.<sup>74</sup> Fortunately, coordinating solvents fail to compete effectively against the binding strength of conventional ATRP ligands. The halide concentration also affects ATRP. Whilst the ATRP reaction mixture contains many species, the dominant  $\text{Cu}^{\text{I}}$  complex in ATRP is  $[\text{LCu}^{\text{I}}]^+$ .<sup>75</sup> In contrast, the deactivator complex requires the halide bound species in order to facilitate the deactivation of the propagating radical. Thus, a high halide concentration in solution is critical to favouring the deactivation of the propagating radical and improving the control over dispersity.

Finally, acidic monomers such as acrylic acid and methacrylic acid have been a known problem for ATRP for several reasons, including the protonation of the ligands at low pH leading to deactivation of the mediator complex,<sup>76,77</sup> displacement of the halide anion from the deactivator complex<sup>77</sup> and coordination of the carboxylate anion onto the mediator centres.<sup>76</sup> However, the problem of monomers bearing acidic functional groups was overcome in 2016 by Fantin *et al.*<sup>78</sup> through the use of low pH in order to protonate the carboxylate and a chloro initiator to



**Scheme 6.** ATRP-inspired cross-coupling cycle.

suppress background substitution cyclization of the chain end into the related lactone.

## CONCLUSION AND OUTLOOK

ATRP was originally developed from atom transfer radical addition (ATRA). However, the last 25 years has seen massive improvements in ATRP catalyst activity due in large part to our improved understanding of structure–reactivity trends. Moreover, this has been accompanied by process developments such as AGET, ARGET, ICAR and SARA that allow for oxygen tolerance and parts per million catalyst concentrations. These developments in carbon–halogen bond activation now offer new opportunities in small molecule synthesis. For example, in ATRA, the use of ATRP catalysts has led to reduced catalytic loading and lower temperatures in order to execute these transformations.<sup>9</sup> Another application of ATRP catalysts is in cross-coupling where the reactivity of a  $\text{Cu}^{\text{III}}$  intermediate in reductive elimination has recently been exploited in order to facilitate the room temperature coupling of alkyl halides to amides and heteroaromatic amines in high yields.<sup>79</sup> In this work, the catalyst activates the alkyl halide bonds in the normal manner and then  $\text{Cu}^{\text{II}}$  species coordinates both the nucleophile and radical, forming a short-lived  $\text{Cu}^{\text{III}}$  intermediate that rapidly undergoes reductive elimination (Scheme 6). Interestingly, this type of process has been observed as a minor side

reaction in ATRP, where end-group analysis of poly(methyl methacrylate) revealed the formation of a lactone.<sup>78</sup> Further exploration of this chemistry in couplings to other substrates, such as alkynes, is currently under way. As increasingly active catalysts are developed, the scope of these small molecule reactions, as well ATRP itself, will be further improved.

## ACKNOWLEDGEMENTS

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## SUPPORTING INFORMATION AVAILABLE

An extensive compilation of R–H, R–Cl and R–Br bond dissociation Gibbs free energies, as taken from references 62–64 and used in the construction of Figs 3 and 4.

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## ***Chapter Three:***

### ***ATRP Inspired Synthetic Methodology***

## Introduction

The development of effective chemical transformations is a fundamental cornerstone to the ideal synthesis described by Wender.<sup>1</sup> Pd(0)-mediated cross-couplings represent one of the greatest advancements in synthetic methodology. Researchers involved in its development were awarded the Nobel prize in 2010. The method permits the formation of bonds between aryl halides and various coupling partners, such as organometallic reagents, terminal alkynes, amines, and alcohols, to form C–C, C–N, and C–O bonds.<sup>2,3,4</sup> The prevalence of this methodology is underpinned by the easily accessible coupling partners and its ease of execution. Palladium-based cross-couplings follow a catalytic cycle starting from the Pd(0) catalyst **3.1** (Fig 3.1), which oxidatively inserts into the aryl or alkenyl pseudohalide/halide **3.2**, followed by the transfer of an organic group from an organometallic reactant **3.4** to the Pd(II) intermediate **3.3**. This transmetalated product **3.6** then undergoes reductive elimination to regenerate the Pd(0) catalyst **3.1** and to produce the desired cross-coupled product **3.7**.

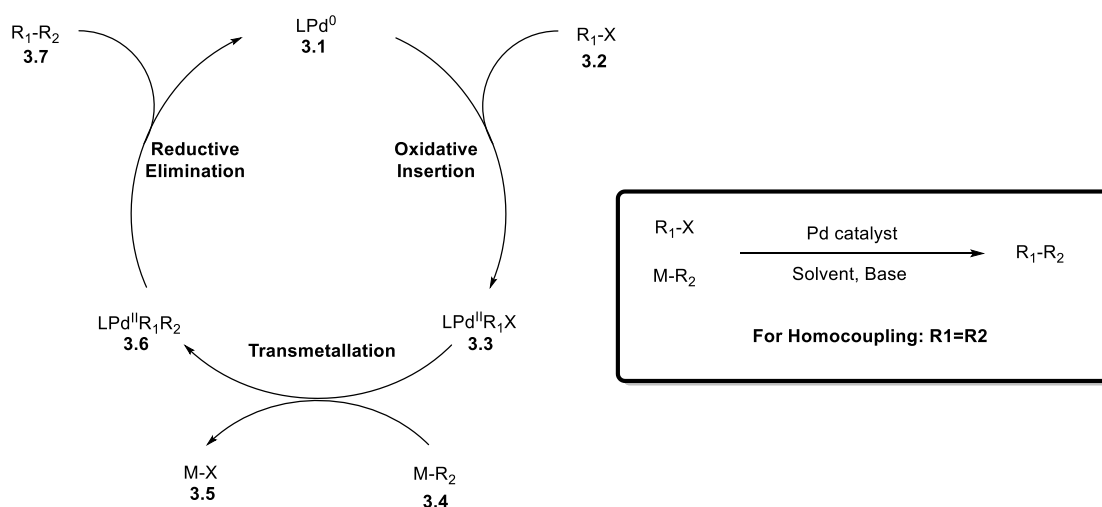


**Fig 3.1:** Generalized scheme for cross-couplings involving a Pd(0)-Pd(II) catalytic cycle.

Despite its utility, there remain several drawbacks of Pd(0)-catalyzed cross couplings including air sensitivity, the environmental and economic cost of palladium, and the deployment of alkyl halides, which undergo competing  $\beta$ -elimination.<sup>5</sup> In this chapter, we report the use of cheap, earth-abundant copper-based catalysts for cross-coupling between an alkyl halide and a heteroaromatic amine nucleophile.

Nitrogen-containing functional groups are ubiquitous in natural products, pharmaceutical agents, and functional materials.<sup>6,7</sup> A classical reaction that forms an (sp<sup>2</sup>) C–

C–N bond is the Ullmann-Goldberg cross-coupling, a copper-catalysed process. However, Ullmann-Goldberg cross-coupling requires aggressive heating to overcome the high kinetic barrier associated with the formation of the key aryl copper (III) intermediate, which decomposes thermally unstable organic structures.<sup>8</sup> Ullmann cross-coupling was superseded by the Buchwald Hartwig cross-coupling.<sup>9</sup> The Buchwald-Hartwig coupling efficiently forms ( $sp^2$ ) C–N bonds through a Pd(0)/Pd(II) catalytic cycle, resulting in significantly milder conditions and complementary electrophile reactivity, greatly extending the scope of ( $sp^2$ ) C–N couplings catalysed by transition metals. To reduce the environmental impact of chemical processes needing rare earth metals, alternatives must be developed using earth-abundant metals to create environmentally responsible reactions. Thus, the use of earth-abundant metals such as copper is currently being revisited in the development of new cross-coupling protocols. Recent developments in metalla-photoredox chemistry have resulted in alternative pathways to the key organo aryl/alkyl copper(III) intermediate, which allows C–N bonds to be formed through the stepwise single electron oxidation of copper (I) salt to the copper(III) salt via a copper (II) intermediate.

Two general strategies using metalla-photoredox catalysis exist, exemplified by the works of Fu<sup>10</sup> and MacMillan<sup>10</sup> (**Fig 3.2**). In Fu's system, the copper photocatalyst **3.8** absorbs a photon forming an excited state complex **3.9** which undergoes a single electron transfer with an alkyl halide **3.10** to generate an alkyl radical **3.11** and a copper (II) complex **3.12**. The copper (II) complex **3.12** undergoes a coupling reaction with the alkyl radical **3.11** to give the desired product **13** and copper (I) salt **3.14**, which reforms the photocatalyst **3.8** via a ligand exchange with the nucleophile **3.15**.

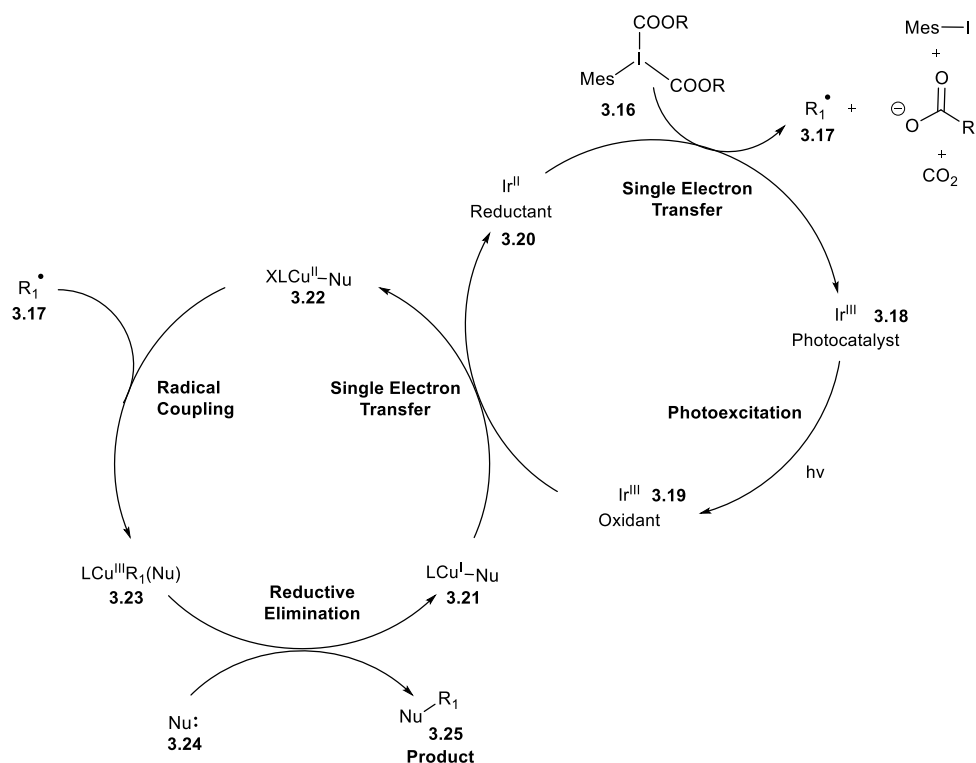
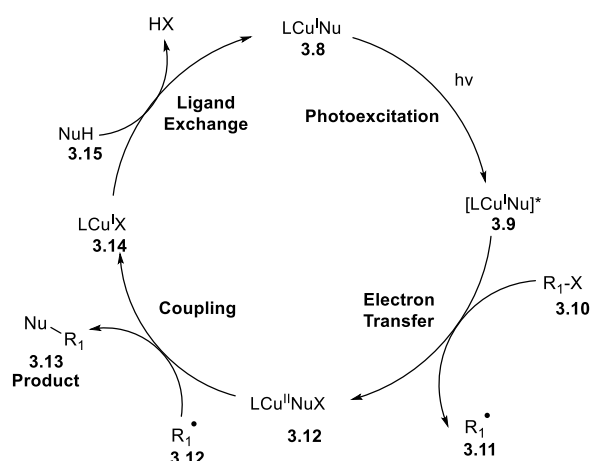


**Fig 3.2:** Examples for the strategies for the photoredox C-N couplings, (top) copper-centered photocatalyst,<sup>10</sup> (bottom) secondary photocatalyst driving the copper catalytic cycle.<sup>11</sup>

MacMillian's method begins with the oxidation of an iridium (II) pre-catalyst **3.20** using a hypervalent iodine reagent **3.16** to produce an alkyl radical **3.17** and the active Ir (III) photocatalyst **3.18**. The photocatalyst **3.18** absorbs a photon to generate the excited Ir(III) complex **3.19** which undergoes a single electron transfer with the copper (I) precatalyst **3.21** to form a copper (II) complex **3.22**. The radical **3.17** then couples onto the copper (II) complex **3.22** to form the key organometallic Cu(III) intermediate **3.23**, which undergoes reductive

elimination and ligand association to form the desired product **3.25** and the copper precatalyst **3.21**. Metalla-photoredox catalysis expanded the scope of copper catalysed C-N couplings to include ( $sp^3$ ) C-N coupling across a plethora of alkyl substituents under ambient conditions. However, photoexcitation degrades photosensitive substrates, so in this work, we aim to address this issue by developing a non-irradiative ( $sp^3$ ) C-N coupling.

Nucleophilic substitution is the classical methodology to form  $sp^3$  C-N bonds but it is prone to poly-alkylation and competing elimination. Thus, alternative methods to synthesize C-N bonds were developed addressing these shortcomings, including reductive amination, olefin hydroamination to transition metal catalysed cross-coupling.<sup>12</sup> Previous thermal copper catalysed ( $sp^3$ ) C-N couplings proceed via a two-electron copper (I)/copper (III) based catalytic cycles, has a limited substrate scope, require expensive chiral ligands, and superstoichiometric amounts of coupling partners (**Fig 3.3**).<sup>12</sup>

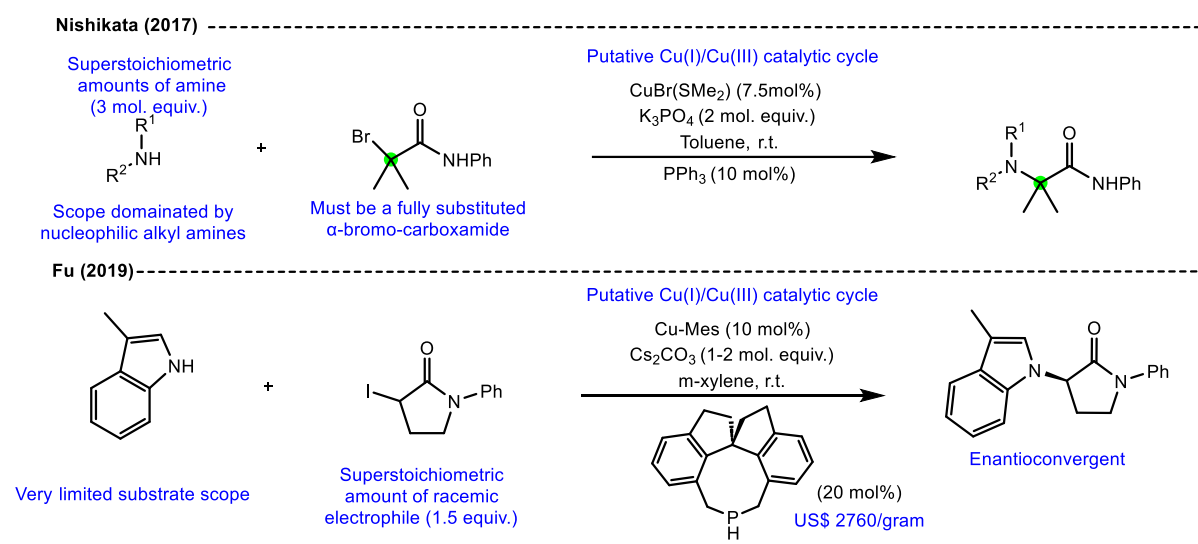


**Fig 3.3:** Previous thermal copper catalysed ( $sp^3$ ) C-N couplings

In this chapter, we develop a mechanistically unique C-N cross-coupling (**Fig 3.4**). We overcame the kinetic stability of the alkyl halide bond using an ATRP mediator **3.26** instead of a photocatalyst to facilitate the mesolytic cleavage of an alkyl halide **3.27** via inner sphere electron transfer to give an alkyl radical **3.28** and the corresponding copper (II) salt **3.29**. The amine/amide **3.30** associates with the metal centre to give the amino copper (II) intermediate **3.31**, which reacts with the alkyl radical **3.28** in a radical coupling to produce the key organometallic copper (III) **3.32**. The organometallic copper (III) intermediate undergoes reductive elimination to give the desired product **3.33** and regenerates the catalyst **3.26**.

Thermal, Stepwise Electron Transfer.

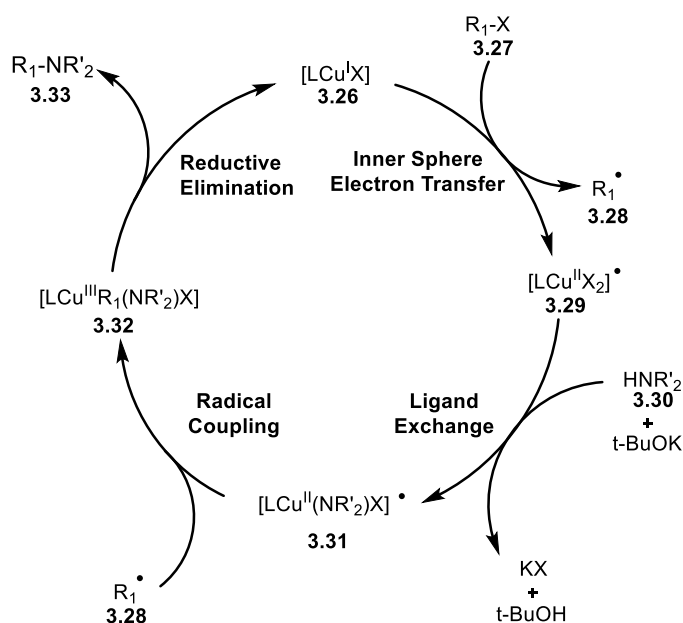


**Fig 3.4:** ATRP inspired (sp<sup>3</sup>)C-N cross-coupling.

Atom transfer radical polymerization, as reviewed in chapter 2, is a form of controlled radical polymerization independently developed by Mitsuo Sawamoto<sup>13</sup> and Krzysztof Matyjaszewski in 1995.<sup>14</sup> Originally, ATRP was inspired by atom transfer radical addition, which uses a copper catalyst to aid the mesolytic cleavage of an alkyl halide bond via single electron transfer.  $K_{\text{ATRP}}$  is a key factor governing the concentration of propagating radicals.  $K_{\text{ATRP}}$  depends on the strength of the R–X bond, the stability of the corresponding R<sup>•</sup> and the ATRP mediator deployed.<sup>15</sup> ATRP can be performed with a variety of metal and organic systems.<sup>16</sup> While copper remains the most developed, over the years a wide range of ligands have been developed and evaluated for ATRP. In this work, we use N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA) and copper(I) bromide as the pre-catalysts. We believe the low cost and accessibility of PMDETA suits an efficient generalizable methodology. Several superior ligands have been evaluated for ATRP and can be deployed for recalcitrant substrates identified in this study.

We aim to extend the current scope of thermal (sp<sup>3</sup>) C–N coupling reaction by developing an alternative methodology that is cheap, accessible, and adaptable.<sup>12</sup> We hope to overcome the limitations in current methodologies, such as requiring a super-stoichiometric amount of coupling partners and a limited scope of reactivity.<sup>12</sup> We endeavour to demonstrate the effectiveness of our catalytic system by coupling weakly nucleophilic

nitrogen-bearing functional groups such as amides, and a range of bulky heterocyclic amines using a stoichiometric amount of reagents.

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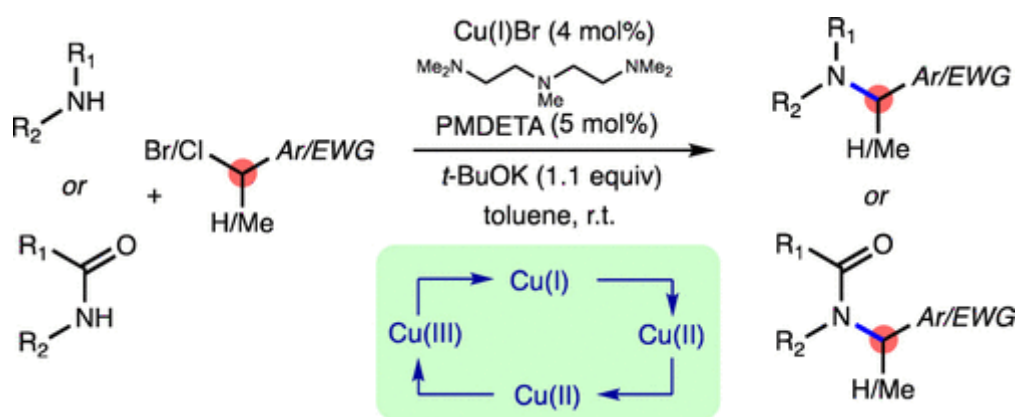
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# Publication 2: Atom Transfer Radical Polymerization-Inspired Room Temperature ( $sp^3$ )C–N Coupling

Alfred. K. K. Fung, Li-Juan Yu, Michael S. Sherburn, and Michelle L. Coote

*J. Org. Chem.* **2021**, 86, 9723–9732. <https://doi.org/10.1021/acs.joc.1c01029>



This manuscript was published in the Journal “Journal of Organic Chemistry” on 28 June, 2021. Reprinted with permission from (authors). Alfred. K. K. Fung completed all synthetic work present. Project was conceived designed and evolved in collaboration between Alfred. K. K. Fung, Prof. M. L. Coote and Prof. M. S. Sherburn. Dr Li-Juan Yu performed the DFT calculations under the direction of Prof. M.L. Coote who performed the mechanistic analysis. Alfred K.K. Fung collaborated with Professor Michelle L. Coote and Professor Michael S. Sherburn in the initial drafting. Professors Michelle L. Coote and Michael S. Sherburn edited the manuscript.

Atom Transfer Radical Polymerization-Inspired Room Temperature (sp<sup>3</sup>)C–N Coupling

Alfred. K. K. Fung, Li-Juan Yu, Michael S. Sherburn,\* and Michelle L. Coote\*

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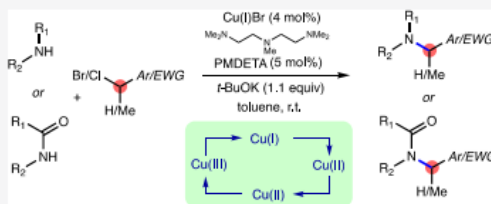
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**ABSTRACT:** A simple nonphotochemical procedure is reported for Cu(I)-catalyzed C–N coupling of aliphatic halides with amines and amides. The process is loosely based on the Goldberg reaction but takes place readily at room temperature. It uses Cu(I)Br, a commonly used and inexpensive atom transfer radical polymerization precatalyst, along with the cheap ligand *N,N,N',N'',N'''*-pentamethyldiethylenetriamine, to activate the R–X bond of the substrate via inner-sphere electron transfer. The procedure brings about productive C–N bond formation between a range of alkyl halide substrates with heterocyclic aromatic amines and amides. The mechanism of the coupling step, which was elucidated through application of computational methods, proceeds via a unique Cu(I) → Cu(II) → Cu(III) → Cu(I) catalytic cycle, involving (a) inner-sphere electron transfer from Cu(I) to the alkyl halide to generate the alkyl radical; (b) successive coordination of the N-nucleophile and the radical to Cu(II); and finally reductive elimination. In the absence of a nucleophile, debrominative homocoupling of the alkyl halide occurs. Control experiments rule out S<sub>N</sub>-type mechanisms for C–N bond formation.



## INTRODUCTION

There exists a plethora of cross-coupling methods for the formation of C–N bonds.<sup>1</sup> Buchwald–Hartwig amination revolutionized the formation of (sp<sup>3</sup>)C–N bonds by the introduction of a Pd(0)/Pd(II) catalytic cycle for cross-coupling. The process greatly extended the scope of Cu(I)-catalyzed Ullmann-type (sp<sup>2</sup>)C–N bond formation through the introduction of significantly milder reaction conditions and complementary electrophile reactivity. Nonetheless, as demonstrated by recent photoredox-based approaches,<sup>2,3</sup> there is a pressing need for better methods for (sp<sup>3</sup>)C–N bond formation and for the replacement of rare metals with earth-abundant ones.<sup>4</sup>

The simplest way to make an (sp<sup>3</sup>)C–N bond is by direct (i.e., uncatalyzed) nucleophilic substitution. The main problem with a classical S<sub>N</sub>2 approach (Scheme 1) is the tendency for competing amine polyalkylation and alkyl halide elimination. Important advances have been recently described by the Nishikata<sup>5</sup> and Fu<sup>6</sup> laboratories through the invention of Cu(I)/Cu(III)-based catalytic cycles.

These approaches, which bring about C–N bond formation under mild and photochemistry-free conditions, permit the generation of products that are not feasible through direct S<sub>N</sub>2-based processes.

Herein, we describe a new Cu(I)-catalyzed method for (sp<sup>3</sup>)C–N bond formation that is mechanistically distinct from both Ullmann-type processes and the Nishikata/Fu Cu(I)–Cu(III) catalytic cycle. Our method is effective over a broader range of substrates and, importantly, is effective with 1:1 precursor stoichiometry. Akin to photoredox catalysis

methods, our approach involves carbon-centered radical intermediates. Our method uses ambient reaction conditions and inexpensive and readily available catalysts and reagents (Scheme 1). Our method is also photochemistry-free, hence applicable to light-sensitive substrates and products.

Our approach takes advantage of the highly active catalysts developed for carbon-centered radical generation from alkyl halides in atom transfer radical polymerization (ATRP).<sup>7,8</sup> In ATRP, a Cu(I) catalyst reversibly generates a low concentration of carbon-centered radicals from “dormant” alkyl halides in order to control radical polymerization (Scheme 2). Originally based on atom transfer radical addition (ATRA) methodologies,<sup>9</sup> successive generations of Cu(I) catalysts have led to an improvement in activity of more than seven orders of magnitude simply by varying the ligand (Figure 1).<sup>10–12</sup> As a result, currently available catalysts can trigger the reversible cleavage of relatively strong (sp<sup>3</sup>)C–X bonds at room temperature at low catalytic loading.<sup>13</sup> Until now, these catalysts have been used to generate radicals exclusively for ATRP and ATRA processes. Herein, we demonstrate for the first time that their enhanced reactivity can be harnessed for (sp<sup>3</sup>)C–N coupling processes to achieve outcomes akin to

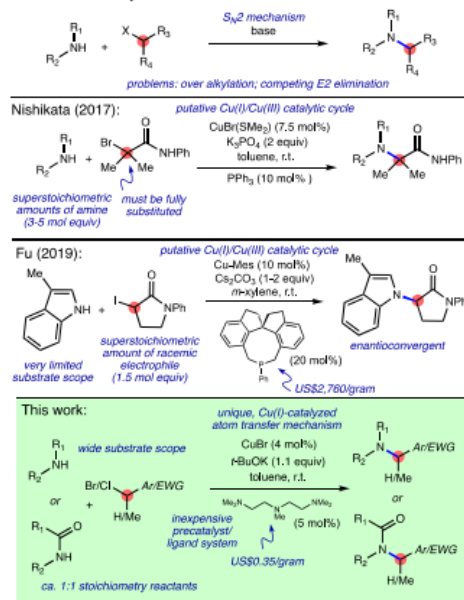
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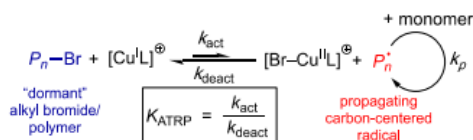


### Scheme 1. Classical $S_N$ Approach, State-of-the-Art Methods,<sup>5,6</sup> and Current Work on Nonphotochemical Cu(I)-Catalyzed ( $sp^3$ )C–N Cross-Coupling

classical amine alkylation:



### Scheme 2. Generalized Mechanism of ATRP



those from photoredox-based methods but without irradiation and under mild conditions.

As proof of concept for our process, we use copper(I) bromide and  $N,N,N',N'',N'''$ -pentamethyldiethylenetriamine (PMDETA) as a cheap and readily available precatalyst and

ligand. While PMDETA is not the most active ligand available,<sup>10</sup> it is attractive as it is low in cost and easy to obtain. As will be shown, the *in situ*-generated [(PMDETA)-Cu(I)Br] catalyst is sufficiently reactive to outcompete uncatalyzed processes such as  $S_N2$  processes and base-mediated eliminations, even in the presence of *t*-BuOK.

## RESULTS AND DISCUSSION

**Reaction Development.** The conversion of benzotriazole 1 and benzyl bromide 2 into 1-benzyl benzotriazole 3 proceeds at ambient temperature in toluene using low loadings of the precatalyst Cu(I)Br and the ligand PMDETA in the presence of a stoichiometric amount of *t*-BuOK (Table 1, entry 1). This

**Table 1. Reaction Development: Isolated Yields of C–N Cross-Coupling Product 3 from the Reaction of Benzotriazole 1 and Benzyl Bromide 2 as a Function of Reactant, Precatalyst (Cu(I)Br), and Ligand (PMDETA) Molar Ratios and Solvent**

| entry | molar ratios used |        | 1   | 2   | solvent                         | yield 3 (%) |
|-------|-------------------|--------|-----|-----|---------------------------------|-------------|
|       | Cu(I)Br           | PMDETA |     |     |                                 |             |
| 1     | 0.05              | 0.1    | 1.0 | 1.0 | PhMe                            | 86          |
| 2     | 0                 | 0      | 1.0 | 1.0 | PhMe                            | 0           |
| 3     | 0.01              | 0.02   | 1.0 | 1.0 | PhMe                            | 63          |
| 4     | 0.20              | 0.29   | 1.0 | 1.0 | PhMe                            | 89          |
| 5     | 0.50              | 0.58   | 1.0 | 1.0 | PhMe                            | 33          |
| 6     | 0.20              | 0.29   | 1.6 | 1.0 | PhMe                            | 93          |
| 7     | 0.20              | 0.29   | 1.0 | 1.8 | PhMe                            | 89          |
| 8     | 0.20              | 0.29   | 1.0 | 1.0 | CH <sub>2</sub> Cl <sub>2</sub> | 87          |
| 9     | 0                 | 0      | 1.0 | 1.0 | CH <sub>2</sub> Cl <sub>2</sub> | 0           |
| 10    | 0.20              | 0.29   | 1.0 | 1.0 | Et <sub>2</sub> O               | 89          |
| 11    | 0                 | 0      | 1.0 | 1.0 | Et <sub>2</sub> O               | 0           |
| 12    | 0.20              | 0.29   | 1.0 | 1.0 | DMSO                            | 88          |
| 13    | 0                 | 0      | 1.0 | 1.0 | DMSO                            | 61          |
| 14    | 0.20              | 0.29   | 1.0 | 1.0 | MeCN                            | 92          |
| 15    | 0                 | 0      | 1.0 | 1.0 | MeCN                            | 71          |

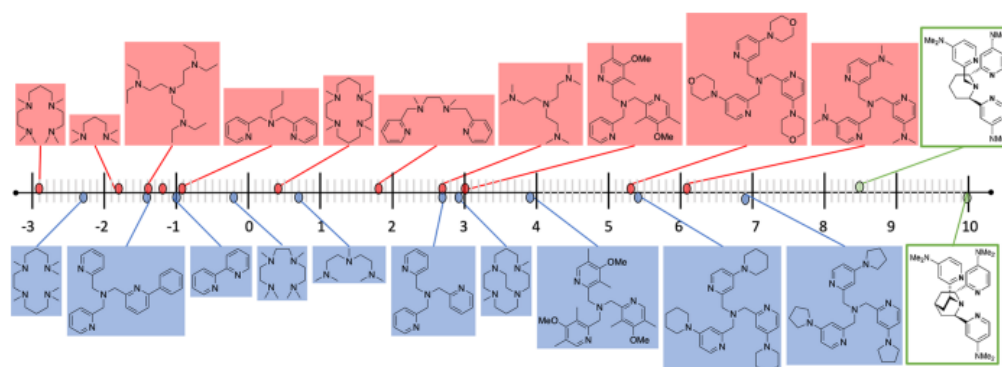


**Figure 1.** Selected experimental activation rate constants  $\log(k_{\text{act}}/(M^{-1} s^{-1}))$  for ATRP involving various N-based ligands with the initiator  $CH_3CH_2(COOCH_3)Br$  in the presence of Cu<sup>I</sup>Br in MeCN at 22 °C. Computational values are shown for the ligands in green boxes. Reproduced with permission from ref 15.

precatalyst/ligand combination was chosen since it has been previously optimized for ATRP processes.<sup>14</sup> The conversion of  $1 + 2 \rightarrow 3$  has been previously carried out under  $S_N2$  conditions using a large excess of concentrated aqueous NaOH in MeCN.<sup>16</sup> This published reaction presumably involves the *in situ* conversion of the acidic ( $pK_a = 8.2$ )<sup>17</sup> benzotriazole (1) into its more nucleophilic, conjugate base. A repeat of our entry 1 reaction but omitting the Cu(I)Br precatalyst and PMDETA (entry 2) gave no detectable conversion of  $1 + 2 \rightarrow 3$ , thereby dismissing the uncatalyzed  $S_N2$  mechanism for entry 1. It seems reasonable to assume that the nonpolar toluene solvent inhibits the *t*-BuOK-induced formation and  $S_N2$  reaction of the conjugate base of 1.

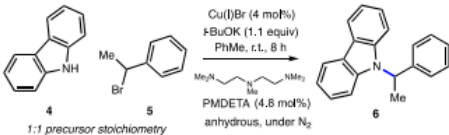
Precatalyst/ligand loadings from low to moderate levels (entries 3 and 4) do not have an adverse effect on the process, although very high loadings (entry 5) result in lower yields of C–N coupled product, accompanied by the formation of significant amounts of 1,2-diphenylethane.

The reaction is also tolerant of changes in precursor stoichiometry, with high yields, irrespective of whether 1 or 2 is the limiting reactant (entries 6 and 7). These observations identify a significant advantage over recently published Cu(I)-catalyzed C–N couplings (Scheme 1), which need super-stoichiometric amounts of either the amine<sup>5</sup> or alkyl halide<sup>6</sup> reactant.

Since the ATRP activity of the  $[(\text{PMDETA})\text{Cu}(\text{I})\text{Br}]$  complex increases with solvent polarity,<sup>18</sup> we recognized that a switch to more polar solvent systems may be advantageous. Our C–N coupling reaction is effective over a range of solvents (entries 8–15). There is no competing  $S_N2$  process in dichloromethane and diethyl ether (entries 8–11) but the uncatalyzed process also occurs in the most polar solvents DMSO and MeCN (entries 12–15).

**Experimental Mechanistic Studies.** In order to further probe the requirements for successful C–N coupling, the reaction between carbazole 4 and 1-bromoethylbenzene 5 was examined under a range of conditions (Table 2). Interestingly, the conversion  $4 + 5 \rightarrow 6$  has not previously been described,

**Table 2. Control Experiments: Yields of C–N Cross-Coupling Product 6 for Reactions of Carbazole 4 and 1-Bromoethyl Benzene 5 with Variations from the Standard Conditions<sup>a</sup>**



| entry | conditions                                                             | yield 6 (%) |
|-------|------------------------------------------------------------------------|-------------|
| 1     | as specified in the equation                                           | 81          |
| 2     | no Cu(I)Br                                                             | 0           |
| 3     | no PMDETA                                                              | 0           |
| 4     | no <i>t</i> -BuOK                                                      | 18          |
| 5     | Et <sub>3</sub> N in place of <i>t</i> -BuOK                           | 75          |
| 6     | Et <sub>3</sub> N in place of <i>t</i> -BuOK, no Cu(I)Br               | 0           |
| 7     | Cs <sub>2</sub> CO <sub>3</sub> in place of <i>t</i> -BuOK             | 78          |
| 8     | Cs <sub>2</sub> CO <sub>3</sub> in place of <i>t</i> -BuOK, no Cu(I)Br | 0           |
| 9     | no ambient light                                                       | 65          |
| 10    | open flask, vigorous stirring                                          | 0           |
| 11    | Cu(I)Br (50 mol %), PMDETA (58 mol %)                                  | 27          |

although the molecule has been recently prepared by Fe(III)- and Cu(I)-catalyzed hydroamination of styrene with carbazole<sup>19,20</sup> and base-mediated coupling of acetophenone tosylhydrazone with carbazole.<sup>21</sup>

The reaction proceeds smoothly under standard conditions (Table 2, entry 1) but, once again, no product is observed in the absence of Cu(I)Br (entry 2). Consistent with previous observations of its significant rate enhancement in ATRP chemistry, the PMDETA ligand is also necessary for C–N coupling (entry 3).

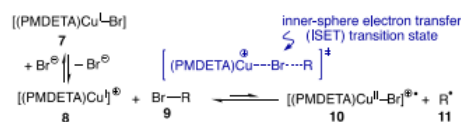
The absence of *t*-BuOK (entry 4) results in a low but still notable yield of product 6, which signals the possibility of the tertiary amine groups of the PMDETA ligand serving as a base. In ATRP, this causes a decrease in binding of PMDETA to the metal center, thereby deactivating the catalytically active species.<sup>22</sup> The use of either Et<sub>3</sub>N or Cs<sub>2</sub>CO<sub>3</sub> in place of *t*-BuOK (entries 5 and 7) gave similar yields of product 6. No product is observed in the absence of Cu(I)Br with each of these alternative bases (entries 6 and 8). We generally favor the use of *t*-BuOK as a base since it gives optimal yields across a broader range of substrates.

As entry 9 shows, the reaction does not require photo-activation, perhaps unsurprisingly, given the proposed structure of the catalytic species. The reaction has inherited some level of oxygen sensitivity from ATRP,<sup>23</sup> resulting in the need to thoroughly degas solvents before execution (entry 10).

Entry 11 shows, once again (cf. Table 1, entry 5), that high precatalyst/ligand loadings lead to homocoupling as a competing process. With bromide 5, 2,3-diphenylbutane was isolated. These unoptimized reactions show the potential of ATRP catalysts in (sp<sup>3</sup>)C–(sp<sup>3</sup>)C bond formation, consistent with earlier experiments on polystyryl alkyl halides.<sup>24</sup> Potentially, high precatalyst/ligand loadings result in increased amounts of benzylic free radicals, which would undergo direct radical–radical coupling to form these bibenzyl compounds.

**Computational Mechanistic Studies.** To ascertain the most likely mechanism for our C–N cross-coupling process, density functional theory calculations were performed using, as a case study, the reaction between carbazole 4 (as the amine or its conjugate base) and 1-bromoethyl benzene 5. Full details of the theoretical study are provided in the [Supporting Information](#). The mechanism of carbon–halogen bond activation for this catalyst and substrate has been studied previously within the context of ATRP.<sup>25,26</sup> Under ATRP reaction conditions, complexation of the tridentate, electron-rich PMDETA ligand to Cu(I)Br to form neutral complex 7, results in dissociation of the bromide ion to form the catalytically active cationic species 8 (Scheme 3). Activation of the carbon–bromine bond then proceeds via a reversible inner-sphere electron transfer (ISET) with the alkyl halide 9, which results in a concerted reductive cleavage of the C–Br bond to form carbon-centered radical R• 11 and Cu(II) complex 10.

**Scheme 3. Mechanism of Carbon–Halogen Bond Activation in ATRP**



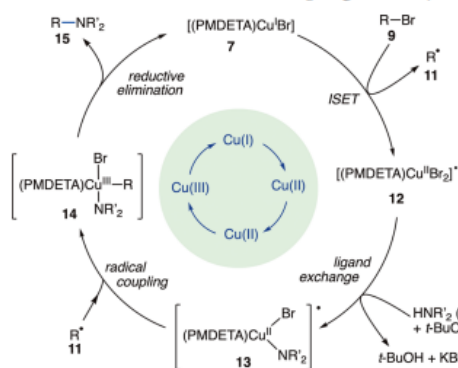
In the present work, our conditions differ from ATRP in two crucial aspects: (a) deprotonated nucleophile is present and (b) a nonpolar solvent, toluene, is used in place of acetonitrile. Under these conditions, dissociation of the  $[(\text{PMDETA})\text{Cu}^{\text{I}}\text{Br}]$  catalyst **7** is strongly thermodynamically disfavored, although reversible ligand exchange with the deprotonated amine nucleophile to form  $[(\text{PMDETA})\text{Cu}^{\text{I}}(\text{NR}'_2)]$  **16** is possible (Scheme S1, Supporting Information). Both of these species are capable of undergoing ISET reactions with the substrate to form a neutral  $\text{Cu}^{\text{II}}$  species,  $[(\text{PMDETA})\text{Cu}^{\text{II}}\text{Br}(\text{NR}'_2)]^{\bullet}$  **13** or  $[(\text{PMDETA})\text{Cu}^{\text{II}}\text{Br}_2]^{\bullet}$  **12**, respectively (Scheme S2, Supporting Information). Our calculated equilibrium constant for the exchange reaction favors  $[(\text{PMDETA})\text{Cu}^{\text{I}}(\text{NR}'_2)]$  **16** over  $[(\text{PMDETA})\text{Cu}^{\text{I}}\text{Br}]$  **7** by a factor of 1078, but the latter species undergoes the subsequent ISET process with a rate coefficient that is 7788 times higher and thus is the dominant pathway overall by a factor of 7. However, carbazole **4** is quite sterically hindered, and thus one would expect the ISET reactions of  $[(\text{PMDETA})\text{Cu}^{\text{I}}(\text{NR}'_2)]$  **16** to become more competitive for less hindered nucleophiles. In any case, any  $[(\text{PMDETA})\text{Cu}^{\text{II}}\text{Br}_2]^{\bullet}$  **12** formed readily undergoes ligand exchange with  $\text{NR}'_2$  to form  $[(\text{PMDETA})\text{Cu}^{\text{II}}\text{Br}(\text{NR}'_2)]^{\bullet}$  **13**.

As in standard ATRP, the corresponding outer-sphere processes have Marcus theory barriers more than 100 kJ mol<sup>-1</sup> higher than the ISET pathways and can thus be discounted (Scheme S2, Supporting Information). Due to steric crowding, viable oxidative addition transition states could not be located for these tetradentate  $\text{Cu}^{\text{I}}$  species, and we note that these pathways have been likewise ruled out for related Ullman-type cross-coupling by Houk, Buchwald, and co-workers.<sup>27</sup>

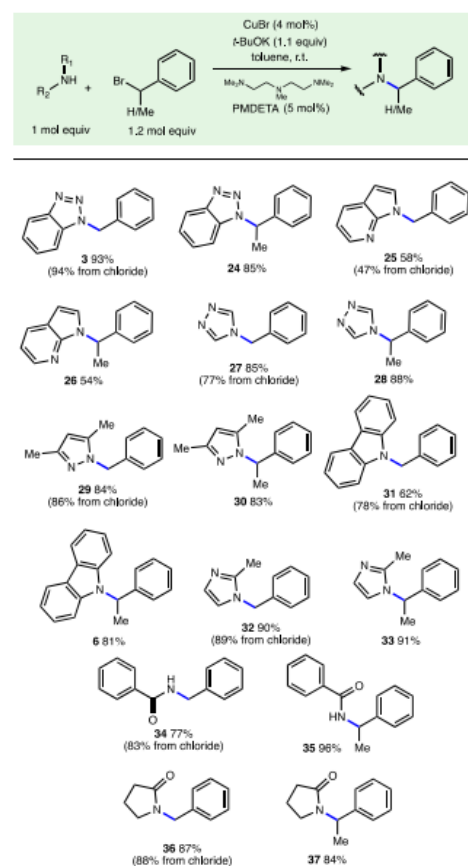
Once  $[(\text{PMDETA})\text{Cu}^{\text{II}}\text{Br}(\text{NR}'_2)]^{\bullet}$  **13** forms, it then undergoes barrierless radical coupling with  $\text{R}^{\bullet}$  **11** to form a triplet species that is effectively a weak  $\pi$ -complex of  $\text{R}^{\bullet}$  with  $[(\text{PMDETA})\text{Cu}^{\text{II}}\text{Br}(\text{NR}'_2)]^{\bullet}$  (see Figure S3, Supporting Information). This undergoes an intersystem crossing through the modest barrier of 60 kJ mol<sup>-1</sup> to form an open-shell singlet  $[(\text{PMDETA})\text{Cu}^{\text{III}}\text{Br}(\text{NR}'_2)]$  **14**, in which the R-group is formally coordinated. This is then kinetically trapped by an almost barrierless reductive elimination to form the cross-coupled product,  $\text{R}-\text{NR}'_2$  **15**, and to regenerate the catalyst,  $[(\text{PMDETA})\text{Cu}^{\text{I}}\text{Br}]$  **7**. The overall mechanism thus involves a fascinating  $\text{Cu}(\text{I}) \rightarrow \text{Cu}(\text{II}) \rightarrow \text{Cu}(\text{III}) \rightarrow \text{Cu}(\text{I})$  catalytic cycle (Scheme 4).

**Scope.** To explore the scope of the C–N coupling process, we first investigated variations in the nitrogen-based component while restricting the alkyl halide to primary and secondary benzyl halides (Table 3). Control experiments revealed that piperidine, *t*-butyl amine, and aniline reacted through uncatalyzed  $\text{S}_{\text{N}}2$  processes; hence, only less reactive N-based coupling partners were deployed. Thus, in addition to benzotriazole **1** (Table 1) and carbazole **4** (Table 2), 7-azaindole **18**, 1,2,4-triazole **19**, 3,5-dimethylpyrazole **20**, 2-methylimidazole **21**, benzamide **22**, and 2-pyrrolidone **23** underwent benzylation and 1-methylbenzylation under mild  $\text{Cu}(\text{I})\text{Br}/\text{PMDETA}$ -catalyzed conditions with reactant molar ratios close to 1:1. Control experiments showed that no reaction occurred in the absence of the precatalyst and ligand.

As shown in Table 3, for a given amine, benzyl chloride **38** and 1-chloroethylbenzene **39** furnished similar yields of C–N coupled products to the corresponding bromide. As has been demonstrated in ATRP studies, the chlorophilicity of the

Scheme 4. Most Favored Cross-Coupling Pathway<sup>a</sup>

<sup>a</sup>The corresponding Gibbs free energies are provided in the SI. An alternative process in which  $\text{Br}/\text{NR}'_2$  ligand exchange occurs prior to the ISET reaction, rather than after, is likely to contribute, particularly for less hindered nucleophiles and is shown in Figure S5 of the Supporting Information.

Table 3.  $[(\text{PMDETA})\text{Cu}^{\text{I}}\text{Br}]$ -Catalyzed Benzylation and 1-Methylbenzylation of Heterocyclic Amines and Amides

$\text{Cu}(\text{I})$  catalyst compensates to a large extent for the stronger  $\text{R}-\text{Cl}$  versus  $\text{R}-\text{Br}$  bond, resulting in similar reactivity and, in

this study, similar yields.<sup>26</sup>  $S_N2$  processes are sensitive to substitution at the electrophilic carbon. The results depicted in Table 3 reveal a contrast to this reactivity: for a particular amine/amide, primary and secondary benzyl halides react with a similar ease to furnish benzylated products in similar yields.

To unequivocally demonstrate that these C–N bond formations are the result of Cu(I)-catalyzed processes, the progress of reactions performed in toluene- $d_8$  was followed by  $^1\text{H}$  NMR spectroscopy. As can be seen by inspection of Figure 2, when 2-pyrrolidone 23, benzyl bromide 2, and a

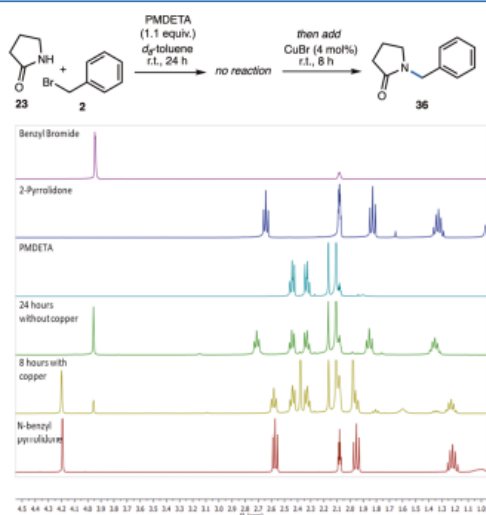


**Figure 2.** 400 MHz  $^1\text{H}$  NMR stacked plots of the reaction between 2-pyrrolidone 23, benzyl bromide 2, PMDETA, and Cu(I)Br at ambient temperature in toluene- $d_8$ : (a) reaction mixture after 24 h reaction time in the absence of Cu(I)Br; (b) after addition of Cu(I)Br and a further 8 h reaction time.

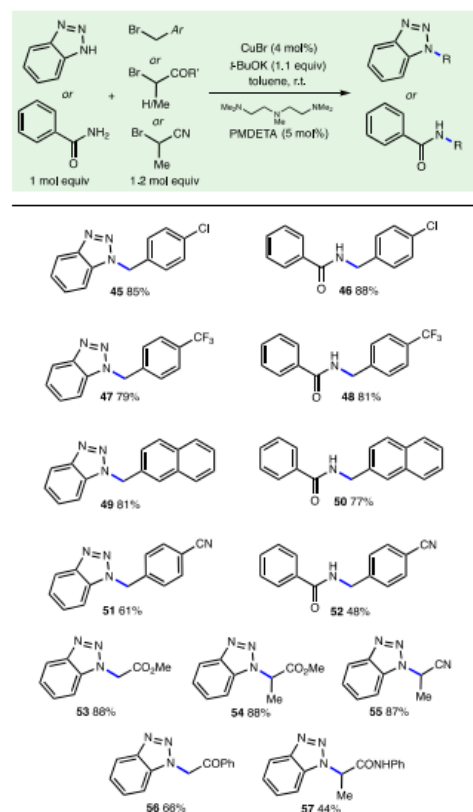
stoichiometric quantity PMDETA (to serve as both a soluble base and ligand) are mixed at ambient temperature in toluene- $d_8$ , no detectable reaction occurs over a period of 24 h. Upon addition of Cu(I)Br to this sample, smooth conversion to N-benzylpyrrolidone 36 is witnessed over an 8 h period.

Variation in the alkyl bromide component is also tolerated by the reaction (Table 4). Benzotriazole 1 and benzamide 40 react smoothly with substituted benzyl bromides 41–44 under the mild reaction conditions to form C–N coupled products 45–52. Benzotriazole 1 also reacts productively with methyl 2-bromoacetate 58, methyl 2-bromopropanoate 59, 2-bromopropanenitrile 60, 2-bromo-1-phenylethan-1-one 61, and 2-bromo-N-phenylpropanamide 62 to form coupled products 53–57. These latter bromides do not undergo productive C–N couplings with the less reactive benzamide 40 under the standard conditions.

The use of ATRP-based activation methods offers new modes of reactivity and selectivity in cross-coupling reactions. Thus, Scheme 5 demonstrates an interesting example of ligand-controlled selectivity in the C–N coupling of benzotriazole 1 with two closely related alkyl bromides 58 and 60.

These reactions were monitored by  $^1\text{H}$  NMR spectroscopy (stack plots are provided in the SI). When the reactants were mixed under the usual conditions but with the omission of Cu(I)Br, no reaction took place over 24 h. After addition of

**Table 4.** [(PMDETA)Cu<sup>I</sup>Br]-Catalyzed Alkylations of Benzotriazole 1 and Benzamide 40 with Various Alkyl Bromides



**Scheme 5.** Ligand-Controlled Selectivity in C–N Couplings



Cu(I)Br and a further 8 h reaction time, smooth conversion to C–N coupled products was seen. With PMDETA as a ligand, a mixture of the two possible products 53 and 55 was obtained. Using the less activating (Figure 1) BIPY ligand, however, only the more substituted bromide 60 couples, generating 55 as the sole product. We ascribe this outcome to a selective ISET reaction (Scheme 5) between the weaker [(BIPY)Cu(I)Br] ATRP catalyst and the more easily reduced bromide. Attempts to investigate the selectivity of the corresponding  $S_N2$  reaction by heating a reaction mixture of the same precursors in the absence of Cu(I)Br and PMDETA were thwarted by the generation of a complex product mixture.

## SUMMARY AND CONCLUSIONS

In summary, an operationally simple, room temperature, photochemistry-free, Cu(I)-catalyzed C–N coupling reaction has been developed. The process, which uses an inexpensive

(ATRP) precatalyst and ligand, proceeds via a novel Cu(I)  $\rightarrow$  Cu(II)  $\rightarrow$  Cu(III)  $\rightarrow$  Cu(I) catalytic cycle.

In line with other recently reported Cu(I)-catalyzed methods (Scheme 1), the reaction is currently limited to activated C–Cl and C–Br bonds (i.e., those carrying an aryl-, acyl-, or cyano-substituent). This reactivity profile is consistent with previous studies of R–X activation in the context of ATRP.<sup>26</sup> To date, for Cu catalysts, only photoredox processes have succeeded for non-activated bonds at room temperature. However, considerably more active ligands for ATRP catalysts are in development (Figure 1).<sup>11</sup> Thus further improvements toward non-activated bonds could be envisaged.

Despite the limitations summarized above, the substrate scope of this method is broader than the nonphotochemical processes recently reported by Nishikata<sup>5</sup> and Fu,<sup>6</sup> which are limited to 2-halo-amides (Scheme 1). Moreover, since ATRP catalyst activity can be tuned over seven orders of magnitude simply by changing the ligand, this technique has the potential to selectively activate specific C–X bonds within a substrate. These studies and ligand-controlled enantioselective C–N couplings are currently under investigation.

## EXPERIMENTAL SECTION

**General Information.** The starting materials were purchased from commercial suppliers and were used as received. Toluene was dried according to the procedure outlined by Grubbs and co-workers.<sup>28</sup> Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F254 plates and visualized by exposure to UV light (254 nm) and by staining with potassium permanganate:potassium carbonate:5% sodium hydroxide aqueous solution:water (3 g:20 g:5 mL:300 mL) followed by heating. Flash chromatographic separations were carried out with silica gel 60 (40–63  $\mu$ m) as the stationary phase using the laboratory-grade solvents indicated. Proton (<sup>1</sup>H) and proton-decoupled carbon (<sup>13</sup>C) and APT <sup>13</sup>C NMR spectra were recorded at room temperature in CDCl<sub>3</sub> on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. <sup>1</sup>H NMR data are recorded as follows: chemical shift ( $\delta$ ) [multiplicity, coupling constant(s)  $J$  (Hz), relative integral] where multiplicity is defined as follows: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; or combinations thereof. The signal due to residual CHCl<sub>3</sub> appearing at  $\delta_{\text{H}} = 7.26$  ppm and the central resonance of the CDCl<sub>3</sub> 1:1:1 triplet appearing at  $\delta_{\text{C}} = 77.16$  ppm were used to reference <sup>1</sup>H and <sup>13</sup>C NMR spectra, respectively. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic sector machine.

**General Experimental Procedure.** To a flask containing copper(I) bromide (3.0 mg, 0.021 mmol), potassium *tert*-butoxide (62 mg, 0.55 mmol), and amine or amide (0.50 mmol) under dry N<sub>2</sub> were added toluene (1.2 mL) and then PMDETA (0.050 mL, 0.024 mmol). The alkyl halide (0.60 mmol) was added dropwise over 90 min, and the reaction mixture was stirred for 8 h at ambient temperature. After dilution with EtOAc (30 mL), the solution was washed with water (10 mL  $\times$  3), then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography using the solvent system indicated.

**1-Benzyl-1H-benzo[1,2,3]triazole 3.** Relative amounts of the precatalyst, ligand, and amine shown in Table 1 (entry 6) were used. Column chromatography was performed with EtOAc:*n*-hexane (1:9). Synthesis from benzyl chloride: colorless needles (0.098 g, 94%). Synthesis from benzyl bromide: white powder (0.097 g, 93%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.99 (d,  $J = 8.2$  Hz, 1H), 7.61–6.95 (m, 8H), 5.76 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 146.5, 134.9, 133.0, 129.1, 128.6, 127.7, 127.5, 124.0, 120.2,

109.9, 52.4. MS (ESI, +ve)  $m/z$  232.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  210.1023 [M + H]<sup>+</sup> (calcd for C<sub>13</sub>H<sub>12</sub>N<sub>3</sub>, 210.1031). Data are consistent with those reported in the literature.<sup>29</sup>

**Larger-Scale (10 mmol) Preparation of 1-Benzyl-1H-benzo[1,2,3]triazole 3.** To a flask containing copper(I) bromide (71 mg, 0.50 mmol), potassium *tert*-butoxide (1.23 g, 11 mmol), and benzotriazole (1.20 g, 10 mmol) under dry N<sub>2</sub> were added toluene (12 mL) and then PMDETA (0.15 mL, 0.75 mmol). Benzyl chloride (1.15 mL, 10 mmol) was then added dropwise and the reaction mixture was stirred for 8 h at ambient temperature. Methanol (100 mL) and silica gel (125 mL) were added before evaporation under reduced pressure. The residue was loaded onto a silica gel column eluting with ethyl acetate:*n*-hexane (1:4) to give 1-benzyl-1H-benzo[1,2,3]triazole 3 as a white powder (1.71 g, 82%).

**1-(1-Phenylethyl)-1H-benzo-1,2,3-triazole 24.** Column chromatography was performed with EtOAc:*n*-hexane (1:9) to give the product as colorless needles (0.095 g, 85%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.25 (dd,  $J = 4.7, 1.6$  Hz, 1H), 7.82 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.30–7.14 (m, 5H), 6.98 (dd,  $J = 7.8, 4.7$  Hz, 1H), 6.39 (d,  $J = 3.6$  Hz, 1H), 6.26 (q,  $J = 7.2$  Hz, 1H), 1.82 (d,  $J = 7.1$  Hz, 3H). <sup>13</sup>C APT NMR  $\delta$ /ppm 147.5, 142.9, 142.4, 128.7, 127.6, 126.6, 125.3, 120.8, 116.0, 100.1, 52.0, 21.0. MS (ESI, +ve)  $m/z$  224.1 [(M + H)<sup>+</sup>, 100%]. HRMS  $m/z$  224.1180 [M + H]<sup>+</sup> (calcd for C<sub>14</sub>H<sub>14</sub>N<sub>3</sub>, 224.1188). Data are consistent with those reported in the literature.<sup>30</sup>

**1-Benzyl-1H-pyrrolo[2,3-*b*]pyridine 25.** Column chromatography was performed with EtOAc:*n*-hexane (1:9). Synthesis from benzyl chloride: pale yellow oil (0.049 g, 47%). Synthesis from benzyl bromide: pale yellow oil (0.060 g, 58%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.03 (d,  $J = 7.5$  Hz, 1H), 7.91–7.78 (m, 1H), 7.48 (d,  $J = 6.3$  Hz, 1H), 7.34–7.24 (m, 5H), 6.77 (m, 1H), 6.64 (m, 1H), 5.84 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 147.8, 143.1, 137.9, 128.9, 128.8, 128.0, 127.7, 127.6, 120.6, 116.0, 100.2, 47.9. MS (ESI, +ve)  $m/z$  231 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  209.1077 [M + H]<sup>+</sup> (calcd for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>, 209.1079). Data are consistent with those reported in the literature.<sup>31</sup>

**1-(1-Phenylethyl)-1H-pyrrolo[2,3-*b*]pyridine 26.** Column chromatography was performed with EtOAc:*n*-hexane (1:9) to give the product as a pale yellow powder (0.060 g, 54%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.24 (dd,  $J = 4.7, 1.6$  Hz, 1H), 7.80 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.32–7.06 (m, 5H), 6.96 (dd,  $J = 7.8, 4.7$  Hz, 1H), 6.38 (d,  $J = 3.6$  Hz, 1H), 6.24 (d,  $J = 7.2$  Hz, 1H), 1.84–1.76 (m, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 147.5, 142.8, 142.4, 129.0, 128.7, 127.6, 126.6, 125.3, 120.8, 116.0, 100.1, 52.1, 21.0. MS (ESI, +ve)  $m/z$  223.1 [(M + H)<sup>+</sup>, 100%]. HRMS  $m/z$  245.1059 [M + Na]<sup>+</sup> (calcd for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>Na, 245.1055). Data are consistent with those reported in the literature.<sup>32</sup>

**4-Benzyl-4H-1,2,4-triazole 27.** Column chromatography was performed with EtOAc:*n*-hexane (1:4). Synthesis from benzyl chloride: white solid (0.061 g, 77%). Synthesis from benzyl bromide: white solid (0.068 g, 85%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.99 (s, 1H), 7.90 (s, 1H), 7.48–7.08 (m, 5H), 5.27 (s, 2H). <sup>13</sup>C APT NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 152.2, 134.5, 129.1, 128.7, 128.0, 53.6. MS (ESI, +ve)  $m/z$  160.1 [(M + H)<sup>+</sup>, 100%]. HRMS  $m/z$  160.0864 [M + H]<sup>+</sup> (calcd for C<sub>9</sub>H<sub>10</sub>N<sub>3</sub>, 160.0874). Data are consistent with those reported in the literature.<sup>31,33</sup>

**4-(1-Phenylethyl)-4H-1,2,4-triazole 28.** Column chromatography was performed with EtOAc:*n*-hexane (3:7) to give the product as a white solid (0.076 g, 88%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.03–7.81 (m, 2H), 7.38–7.06 (m, 5H), 5.47 (q,  $J = 6.8$  Hz, 1H), 1.85 (d,  $J = 7.0$  Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 151.9, 140.0, 129.0, 128.5, 126.5, 59.7, 21.3. MS (ESI, +ve)  $m/z$  196.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  196.0852 [M + Na]<sup>+</sup> (calcd for C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>Na, 196.0851). Data are consistent with those reported in the literature.<sup>34</sup>

**1-Benzyl-3,5-dimethyl-1H-pyrazole 29.** Column chromatography was performed with EtOAc:*n*-hexane (1:9). Synthesis from benzyl chloride: white powder (0.080 g, 86%). Synthesis from benzyl bromide: white powder (0.078 g, 84%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.32–7.13 (m, 3H), 6.98 (d,  $J = 7.3$  Hz, 2H), 5.77 (s, 1H), 5.13 (s, 2H), 2.16 (s, 3H), 2.05 (s, 3H). <sup>13</sup>C APT NMR (100 MHz,

CDCl<sub>3</sub>)  $\delta$ /ppm 147.6, 139.30, 137.4, 128.7, 127.4, 126.6, 105.7, 52.6, 13.5, 11.1. MS (ESI, +ve)  $m/z$  187.1 [(M + H)<sup>+</sup>, 100%]. HRMS  $m/z$  187.1224 [(M + H)<sup>+</sup> (calcd for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>, 187.1235)]. Data are consistent with those reported in the literature.<sup>35</sup>

**3,5-Dimethyl-1-(1-phenylethyl)-1H-pyrazole 30.** Column chromatography was performed with EtOAc:n-hexane (1:4) to give the product as a white solid (0.083 g, 83%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.24–7.09 (m, 3H), 7.04–6.99 (m, 2H), 5.74 (s, 1H), 5.26 (q,  $J$  = 7.1 Hz, 1H), 2.20 (s, 3H), 2.00 (s, 3H), 1.82 (d,  $J$  = 7.0 Hz, 3H). <sup>13</sup>C APT NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 147.1, 143.1, 139.1, 128.9, 127.7, 127.1, 125.7, 116.4, 55.0, 22.3, 13.4. MS (ESI, +ve)  $m/z$  223.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  201.1383 [(M + H)<sup>+</sup> (calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>, 201.1391)]. Data are consistent with those reported in the literature.<sup>36</sup>

**9-Benzylcarbazole 31.** Column chromatography was performed with EtOAc:n-hexane (1:9). Synthesis from benzyl chloride: colorless plates (0.100 g, 78%). Synthesis from benzyl bromide: white solid (0.080 g, 62%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.02 (d,  $J$  = 7.6 Hz, 2H), 7.45–6.89 (m, 11H), 5.35 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 140.7, 137.3, 128.8, 127.5, 126.5, 125.9, 123.1, 120.5, 119.3, 109.0, 46.6. MS (ESI, +ve)  $m/z$  258.1 [(M + H)<sup>+</sup>, 100%]. HRMS  $m/z$  258.1287 [(M + H)<sup>+</sup> (calcd for C<sub>19</sub>H<sub>16</sub>N, 258.1283)]. Data are consistent with those reported in the literature.<sup>37</sup>

**9-(1-Phenylethyl)-9H-carbazole 6.** Column chromatography was performed with EtOAc:n-hexane (1:9) to give the product as colorless plates (0.091 g, 67%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.01 (d,  $J$  = 7.7 Hz, 2H), 7.36–6.96 (m, 11H), 5.95 (q,  $J$  = 7.1 Hz, 1H), 1.87 (d,  $J$  = 7.1 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 140.8, 139.9, 128.7, 127.4, 126.6, 125.5, 123.5, 120.4, 119.0, 110.2, 52.4, 17.5. MS (ESI, +ve)  $m/z$  272.1 [(M + H)<sup>+</sup>, 100%]. HRMS  $m/z$  272.1430 [(M + H)<sup>+</sup> (calcd for C<sub>20</sub>H<sub>18</sub>N, 272.1439)]. Data are consistent with those reported in the literature.<sup>20</sup>

**1-Benzyl-2-methyl-1H-imidazole 32.** Column chromatography was performed with EtOAc:n-hexane (3:7). Synthesis from benzyl chloride: appearance (0.076 g, 89%). Synthesis from benzyl bromide: appearance (0.078 g, 90%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.27–6.70 (m, 7H), 4.96 (s, 2H), 2.24 (s, 3H). <sup>13</sup>C APT NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 136.5, 128.9, 127.9, 127.4, 126.6, 49.8, 13.1. MS (ESI, +ve)  $m/z$  195.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  173.1071 [(M + H)<sup>+</sup> (calcd for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>, 173.1078)]. Data are consistent with those reported in the literature.<sup>38</sup>

**2-Methyl-1-(1-phenylethyl)-1H-imidazole 33.** Column chromatography was performed with EtOAc:n-hexane (1:4) to give the product as a colorless oil (0.085 g, 91%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.31–7.14 (m, 3H), 6.94 (m, 4H), 5.21 (q,  $J$  = 6.7 Hz, 1H), 2.20 (q,  $J$  = 3.3 Hz, 3H), 1.73 (d,  $J$  = 5.8 Hz, 3H). <sup>13</sup>C APT NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 144.9, 141.8, 129.0, 127.8, 127.2, 125.8, 116.5, 55.1, 22.4, 13.5. MS (ESI, +ve)  $m/z$  209.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  187.1227 [(M + H)<sup>+</sup> (calcd for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>, 187.1235)]. Data are consistent with those reported in the literature.<sup>39</sup>

**N-Benzylbenzamide 34.** Column chromatography was performed with EtOAc:n-hexane (2:3). Synthesis from benzyl chloride: white solid (0.088 g, 83%). Synthesis from benzyl bromide: white solid (0.081 g, 77%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.91–7.49 (m, 2H), 7.49–7.10 (m, 8H), 6.66 (s, 1H), 4.51 (d,  $J$  = 5.9 Hz, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 167.6, 138.4, 134.5, 131.6, 128.8, 128.6, 128.0, 127.6, 127.1, 44.2. MS (ESI, +ve)  $m/z$  234.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  212.1093 [(M + H)<sup>+</sup> (calcd for C<sub>14</sub>H<sub>14</sub>NO, 212.1075)]. Data are consistent with those reported in the literature.<sup>40</sup>

**N-(1-Phenylethyl)benzamide 35.** Column chromatography was performed with EtOAc:n-hexane (1:4) to give the product as a white solid (0.108 g, 96%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.73–7.65 (m, 2H), 7.46–7.07 (m, 8H), 6.40 (d,  $J$  = 7.5 Hz, 1H), 5.25 (p,  $J$  = 7.1 Hz, 1H), 1.51 (d,  $J$  = 6.9 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 166.6, 143.2, 134.6, 131.5, 128.8, 128.6, 127.5, 127.0, 126.3, 49.2, 21.8. MS (ESI, +ve)  $m/z$  248.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  248.1051 [(M + Na)<sup>+</sup> (calcd for C<sub>15</sub>H<sub>15</sub>NNaO, 248.1051)]. Data are consistent with those reported in the literature.<sup>41</sup>

**1-Benzylpyrrolidin-2-one 36.** Column chromatography was performed with EtOAc. Synthesis from benzyl chloride: colorless oil (0.077 g, 88%). Synthesis from benzyl bromide: colorless oil (0.076 g, 87%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.35–7.09 (m, 5H), 4.38 (s, 2H), 3.18 (t,  $J$  = 7.1 Hz, 2H), 2.36 (t,  $J$  = 8.1 Hz, 2H), 2.03–1.81 (m, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 175.0, 136.7, 128.7, 128.2, 127.6, 46.7, 46.7, 31.0, 17.8, 17.7. MS (ESI, +ve)  $m/z$  198.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  198.0909 [(M + Na)<sup>+</sup> (calcd for C<sub>11</sub>H<sub>13</sub>NNaO, 198.0895)]. Data are consistent with those reported in the literature.<sup>41</sup>

**1-(1-Phenylethyl)pyrrolidin-2-one 37.** Column chromatography was performed with EtOAc:n-hexane (3:7) to give the product as colorless plates (0.079 g, 84%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.22 (m, 5H), 5.41 (q,  $J$  = 7.1 Hz, 1H), 3.36–3.17 (m, 1H), 2.90 (m, 1H), 2.50–2.26 (m, 2H), 1.84 (m, 2H), 1.44 (d,  $J$  = 7.1 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 174.4, 140.3, 128.5, 127.4, 127.0, 48.9, 42.3, 31.4, 17.9, 16.2. MS (ESI, +ve)  $m/z$  212.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  212.1045 [(M + Na)<sup>+</sup> (calcd for C<sub>12</sub>H<sub>15</sub>NNaO, 212.1051)]. Data are consistent with those reported in the literature.<sup>41</sup>

**1-(4-Chlorobenzyl)-1H-benzo[d][1,2,3]triazole 45.** Column chromatography was performed with EtOAc:n-hexane (3:7) to give the product as colorless needles (0.104 g, 85%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.00 (d,  $J$  = 8.3 Hz, 1H), 7.50–7.21 (m, 5H), 7.13 (d,  $J$  = 8.4 Hz, 2H), 5.74 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 146.5, 134.7, 133.4, 132.8, 129.4, 129.1, 127.8, 124.2, 120.4, 109.6, 51.7. MS (ESI, +ve)  $m/z$  266.0 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  266.0465 [(M + Na)<sup>+</sup> (calcd for C<sub>13</sub>H<sub>10</sub><sup>35</sup>ClN<sub>3</sub>Na, 266.0461)]. Data are consistent with those reported in the literature.<sup>42</sup>

**N-(4-Chlorobenzyl)benzamide 46.** Column chromatography was performed with EtOAc:n-hexane (3:7) to give the product as a white solid (0.108 g, 88%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.69 (dd,  $J$  = 7.1, 1.7 Hz, 2H), 7.41 (td,  $J$  = 7.3, 1.7 Hz, 1H), 7.31 (td,  $J$  = 7.5, 1.7 Hz, 2H), 7.17 (tdd,  $J$  = 8.5, 6.3, 3.0 Hz, 4H), 6.71 (s, 1H), 4.55–4.37 (m, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 166.5, 135.8, 133.1, 132.2, 130.6, 128.1, 127.7, 127.6, 126.0, 42.3. MS (ESI, +ve)  $m/z$  268.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  268.0536 [(M + Na)<sup>+</sup> (calcd for C<sub>14</sub>H<sub>12</sub><sup>35</sup>ClN<sub>3</sub>Na, 268.0505)]. Data are consistent with those reported in the literature.<sup>43</sup>

**1-(4-(Trifluoromethyl)benzyl)-1H-benzo[d][1,2,3]triazole 47.** Column chromatography was performed with EtOAc:n-hexane (2:8) to give the product as a white solid (0.110 g, 79%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.00 (d,  $J$  = 8.1 Hz, 1H), 7.50 (d,  $J$  = 8.1 Hz, 2H), 7.41–7.24 (m, 5H), 5.82 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 146.5, 138.9 (d, <sup>2</sup> $J_{C-F}$  = 1.8 Hz), 132.9, 130.9 (q, <sup>1</sup> $J_{C-F}$  = 32.7 Hz), 127.9, 127.9, 126.2 (q, <sup>2</sup> $J$  = 3.7 Hz), 124.3, 123.9 (q, <sup>3</sup> $J$  = 27.2 Hz), 120.4, 109.5, 51.6. MS (ESI, +ve)  $m/z$  300.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  278.0911 [(M + H)<sup>+</sup> (calcd for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>F<sub>3</sub>, 278.0905)]. Data are consistent with those reported in the literature.<sup>44</sup>

**N-(4-(Trifluoromethyl)benzyl)benzamide 48.** Column chromatography was performed with EtOAc:n-hexane (2:8) to give the product as colorless needles (0.113 g, 81%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.74–7.69 (m, 2H), 7.50 (d,  $J$  = 8.0 Hz, 2H), 7.46–7.40 (m, 1H), 7.35 (d,  $J$  = 8.1 Hz, 4H), 6.67 (t,  $J$  = 5.9 Hz, 1H), 4.59 (d,  $J$  = 6.0 Hz, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 167.6, 142.4, 134.0, 131.8, 129.8 (q, <sup>1</sup> $J_{C-F}$  = 32.3 Hz), 128.7, 127.9, 127.7, 125.7 (q, <sup>2</sup> $J_{C-F}$  = 3.8 Hz), 122.7, 43.5. MS (ESI, +ve)  $m/z$  302.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  302.0772 [(M + Na)<sup>+</sup> (calcd for C<sub>15</sub>H<sub>12</sub>F<sub>3</sub>NNa, 302.0769)]. Data are consistent with those reported in the literature.<sup>45</sup>

**1-(Naphthalen-2-ylmethyl)-1H-benzo[d][1,2,3]triazole 49.** Column chromatography was performed with EtOAc:n-hexane (2:8) to give the product as a white solid (0.105 g, 81%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 8.08 (d,  $J$  = 7.8 Hz, 1H), 7.87–7.72 (m, 4H), 7.53–7.46 (m, 2H), 7.36 (m, 4H), 6.00 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 146.4, 133.2, 133.1, 132.9, 132.2, 129.1, 127.9, 127.8, 127.5, 126.7, 126.7, 126.5, 125.0, 124.0, 120.1, 109.8, 52.5. MS (ESI, +ve)  $m/z$  282.1 [(M + Na)<sup>+</sup>, 100%]. HRMS  $m/z$  282.1022 [(M + Na)<sup>+</sup> (calcd for C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>Na, 282.1007)].

**N-(Naphthalen-2-ylmethyl)benzamide 50.** Column chromatography was performed with EtOAc:n-hexane (2:8) to give the product

as a pale yellow solid (0.101 g, 77%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 7.91–7.74 (m, 6H), 7.62–7.34 (m, 6H), 6.63 (s, 1H), 4.79 (d,  $J$  = 5.7 Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 167.4, 135.7, 134.4, 133.4, 132.8, 131.6, 128.6, 127.8, 127.7, 127.0, 126.5, 126.3, 126.0, 126.0, 44.3. MS (ESI, +ve)  $m/z$  284.1 [(M + Na) $^+$ , 100%]. HRMS  $m/z$  284.1063 [M + Na] $^+$  (calcd for  $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$ , 284.1051). Data are consistent with those reported in the literature.<sup>46</sup>

**4-((1H-Benzo[d][1,2,3]triazol-1-yl)methyl)benzonitrile 51.** Column chromatography was performed with EtOAc:n-hexane (3:7) to give the product as colorless needles (0.072 g, 61%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 8.04 (dd,  $J$  = 8.3, 1.1 Hz, 1H), 7.57 (d,  $J$  = 8.3 Hz, 2H), 7.44–7.37 (m, 2H), 7.33–7.25 (m, 3H), 5.84 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 146.5, 140.1, 133.0, 132.9, 128.2, 128.2, 124.5, 120.6, 118.3, 112.8, 109.3, 51.6. MS (ESI, +ve)  $m/z$  257.1 [(M + Na) $^+$ , 100%]. HRMS  $m/z$  257.0811 [M + Na] $^+$  (calcd for  $\text{C}_{14}\text{H}_{10}\text{N}_4$ , 257.0803). Data are consistent with those reported in the literature.<sup>44</sup>

**N-(4-Cyanobenzyl)benzamide 52.** Preparative thin-layer chromatography was performed with EtOAc:n-hexane (3:7) to give the product as colorless plates (0.057 g, 48%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 7.80 (d,  $J$  = 7.3 Hz, 2H), 7.62 (d,  $J$  = 8.1 Hz, 2H), 7.53 (d,  $J$  = 7.3 Hz, 1H), 7.45 (dd,  $J$  = 7.5, 5.2 Hz, 4H), 6.62 (m, 1H), 4.71 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 167.7, 144.0, 133.9, 132.7, 132.1, 128.9, 128.4, 127.1, 118.8, 111.5, 43.7. MS (ESI, +ve)  $m/z$  259.1 [(M + Na) $^+$ , 100%]. HRMS  $m/z$  259.0861 [M + Na] $^+$  (calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}$ , 259.0847). Data are consistent with those reported in the literature.<sup>47</sup>

**2-(1H-Benzo-1,2,3-triazol-1-yl)propanenitrile 53.** Column chromatography was performed with EtOAc:n-hexane (4:6) to give the product as a yellow oil (0.076 g, 88%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 8.05 (d,  $J$  = 8.4 Hz, 1H), 7.67–7.63 (m, 1H), 7.53 (ddd,  $J$  = 8.3, 7.0, 1.0 Hz, 1H), 7.39 (ddd,  $J$  = 8.1, 7.0, 1.0 Hz, 1H), 5.94 (q,  $J$  = 7.3 Hz, 1H), 2.04 (d,  $J$  = 7.3 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 146.5, 131.4, 128.6, 124.9, 120.7, 115.9, 109.2, 45.1, 19.6. MS (ESI, +ve)  $m/z$  195.1 [(M + Na) $^+$ , 100%]. HRMS  $m/z$  195.0650 [M + Na] $^+$  (calcd for  $\text{C}_9\text{H}_8\text{N}_4$ , 195.0646).

**Methyl 2-(1H-benzo-1,2,3-triazol-1-yl)acetate 54.** Column chromatography was performed with EtOAc:n-hexane (4:6) to give the product as a white solid (0.084 g, 88%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 7.81 (dd,  $J$  = 6.6, 3.1 Hz, 2H), 7.34 (dd,  $J$  = 6.6, 3.1 Hz, 2H), 5.47 (s, 2H), 3.73 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 166.6, 144.9, 126.9, 118.3, 57.00, 53.1. MS (ESI, +ve)  $m/z$  214.0 [(M + Na) $^+$ , 100%]. HRMS  $m/z$  214.0589 [M + Na] $^+$  (calcd for  $\text{C}_9\text{H}_8\text{N}_3\text{NaO}_2$ , 214.0592). Data are consistent with those reported in the literature.<sup>48</sup>

**Methyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)propanoate 55.** Column chromatography was performed with EtOAc:n-hexane (4:6) to give the product as a white solid (0.089 g, 87%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 8.01 (d,  $J$  = 8.3 Hz, 1H), 7.49–7.38 (m, 2H), 7.31 (ddd,  $J$  = 8.1, 6.3, 1.6 Hz, 1H), 5.64 (q,  $J$  = 7.4 Hz, 1H), 3.66 (s, 3H), 1.96 (d,  $J$  = 7.6 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 169.7, 146.3, 132.5, 127.6, 124.1, 120.3, 109.9, 57.1, 53.0, 16.7. MS (ESI, +ve)  $m/z$  228.1 [(M + Na) $^+$ , 100%]. HRMS  $m/z$  228.0744 [M + Na] $^+$  (calcd for  $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2\text{Na}$ , 228.0749).

**2-(1H-Benzo[d][1,2,3]triazol-1-yl)-N-phenylethan-1-one 56.** Column chromatography was performed with EtOAc:n-hexane (2:8) to give the product as a white solid (0.094 g, 66%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 8.01 (d,  $J$  = 8.0 Hz, 2H), 7.90 (d,  $J$  = 7.7 Hz, 2H), 7.66 (t,  $J$  = 7.4 Hz, 1H), 7.53 (t,  $J$  = 7.3 Hz, 2H), 7.41 (d,  $J$  = 7.7 Hz, 2H), 6.20 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 190.4, 145.1, 134.5, 134.4, 129.2, 128.8, 128.6, 128.3, 126.9, 126.9, 118.4, 62.0. MS (ESI, +ve)  $m/z$  238.1 [(M + H) $^+$ , 100%]. HRMS  $m/z$  260.0788 [M + Na] $^+$  (calcd for  $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}$ , 260.0800). Data are consistent with those reported in the literature.<sup>49</sup>

**2-(1H-Benzo[d][1,2,3]triazol-1-yl)-N-phenylpropanamide 57.** Column chromatography was performed with EtOAc:n-hexane (2:8) to give the product as a white solid (0.062 g, 44%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 8.43 (s, 1H), 7.93 (dd,  $J$  = 6.6, 3.0 Hz, 2H), 7.52–7.41 (m, 4H), 7.29 (t,  $J$  = 7.8 Hz, 2H), 7.11 (t,  $J$  = 7.4 Hz, 1H), 5.76 (t,  $J$  = 7.3 Hz, 1H), 2.11 (d,  $J$  = 7.3 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$

NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm 166.1, 144.7, 137.0, 129.2, 127.5, 125.1, 120.3, 118.4, 66.6, 18.9. MS (ESI, +ve)  $m/z$  267.1 [(M + H) $^+$ , 100%]. HRMS  $m/z$  267.1251 [M + H] $^+$  (calcd for  $\text{C}_{10}\text{H}_{15}\text{N}_4\text{O}$ , 267.1246).

**Computational Methods.** All geometry optimizations, frequency calculations, and single-point energy calculations were performed using the Gaussian 16 software package.<sup>50</sup> The level of theory used in the current study is based on that previously benchmarked for the initial ISET reaction,<sup>25</sup> the only change being the use of solution-phase optimized geometries in the present work in place of gas-phase optimized geometries. Geometries were optimized in solution with the  $\omega$ -B97XD functional and a mixed basis set of SDD<sup>51</sup> for Cu and Rassolov corrected 6-31G(d)<sup>52</sup> for other atoms (denoted as Basis-set-1). Single-point energies were calculated using the  $\omega$ -B97XD functional with the Def2TZVP basis set<sup>53</sup> in toluene using the CPCM solvation model<sup>54</sup> for higher-level electronic energy correction. Reported Gibbs free energies in solution at 298 K were calculated using the direct method<sup>55,56</sup> based on solution-phase optimized geometries, including zero-point correction, thermal corrections, and entropy calculated at  $\omega$ -B97XD/Basis-set-1 and electronic energy calculated at  $\omega$ -B97XD/Def2TZVP. The activation free energy for the outer-sphere single electron transfer reaction was calculated using the Marcus theory<sup>57,58</sup> (see the Supporting Information for more details). Detailed results and discussion, including reaction energetics, total energies of all species, and optimized geometries are provided in Section S2 of the Supporting Information.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.1c01029>.

General experimental details,  $^1\text{H}$ ,  $^{13}\text{C}\{^1\text{H}\}$ , and  $^{13}\text{C}$  APT NMR spectra, and computational details including Gaussian archive files for gas-phase geometries (PDF)

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### Notes

The authors declare no competing financial interest.

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## ***Chapter four:***

### ***ARGET-ATRP Inspired Synthetic Methodology***

## introduction

Despite its role to sustain life, the exposure of a reaction to oxygen is a problem often encountered within the experimental laboratory. As a result, methods and equipment have been developed to exclude oxygen from chemical reactions. Oxygen sensitivity detracts from the appeal and robustness of a reaction due to the need to maintain an inert atmosphere.<sup>1</sup> While the use of techniques (freeze-pump-thaw degassing) and equipment (Schlenk lines and gloveboxes) exclude oxygen from the reaction, these methods are time-consuming and costly. An alternative approach to solving the problem of oxygen sensitivity *that is specific to species that reversibly oxidise* involves the *in-situ* use of a supplementary reducing agent. The use of supplementary reducing agents is an underdeveloped synthetic paradigm, that allows for simpler and more robust reaction conditions with lower catalytic loadings.

Oxygen tolerance would simplify the way that low valent transition metal-mediated cross-coupling reactions are executed. Cross-coupling reactions can be performed using a variety of metals, with Pd(0) catalysts being the most common. These catalysts are intolerant to oxygen. As a result, there is a need to employ an inert atmosphere for such reactions, in addition to time-consuming freeze-pump-thaw-degas protocols.

Previous work by Fokin and Sharpless,<sup>2</sup> (**Fig 4.1**) introduced air tolerance into the copper (I) catalysed 3+2 cycloaddition of azides **4.1** onto terminal acetylenes **4.2** (click reaction) via the introduction of sodium ascorbate. Copper catalysed reactions involving a terminal acetylene **4.2** is prone suffer from the competing Glaser coupling when exposed to oxygen. In the absence of sodium ascorbate the click reaction produces side products such as diacetylenes **4.4**, bis-triazoles **4.5** and 5-hydroxy-triazoles **4.6**. Instead of excluding oxygen, sodium ascorbate was added to reduce any oxidized Cu(II) catalyst. The use of sodium ascorbate not only introduces air tolerance, it further allows the use of a copper (II) precatalyst, which is less costly and often purer than their copper (I) counterparts.<sup>3</sup>

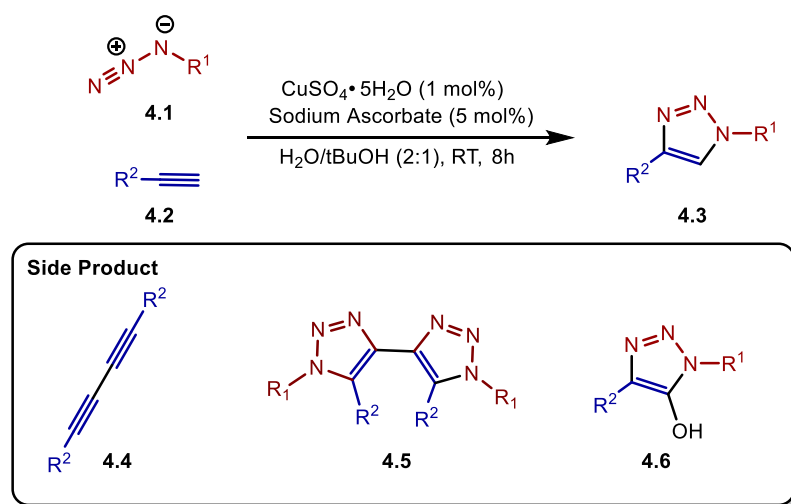


**Fig 4.1:** Conditions used by Folkin and Sharpless for their air tolerant 3+2 cycloaddition

A similar problem of oxygen sensitivity was encountered in atom transfer radical polymerization (ATRP). As reviewed in chapter two, ATRP, uses a copper mediator to aid the mesolytic cleavage of an alkyl halide bond via inner sphere electron transfer. ATRP can be performed with a variety of metal and organic systems,<sup>3</sup> even so, copper the focus of this chapter, remains the most prominent and developed. The seminal conditions used for ATRP developed by Wang and Matyjaszewski required high mediator loadings.<sup>4</sup> This is necessary, since a portion of the copper(I) activator is irreversibly trapped as the copper (II) deactivator from unavoidable radical terminations and the presence of adventitious oxygen during the reaction. The high mediator loadings led to side reactions involving organometallic intermediates,<sup>5</sup> and the need to remove or recycle the transition metal complexes from the product. To execute ATRP at low mediator loadings, strategies were developed to reduce the irreversibly trapped copper (II) deactivator back into the copper (I) activator.

A number of reducing agent were evaluated for the regeneration of the copper(I) activator. Furthermore, electrochemical,<sup>6</sup> and photoredox<sup>7</sup> methods have been used to regenerate the activator for ATRP. Regeneration of the copper (I) activator lowered mediator loadings into the ppm regime, and introduced air tolerance into the methodology. Inspired by this approach, in this chapter, we aim to explore the use of ascorbic acid as an additive in copper-catalysed cross couplings.

Copper-mediated cross-couplings such as Ullman coupling require aggressive reaction conditions, due to the high kinetic barrier to the generation of the high valent Cu(III) arene complexes. These processes have been superseded by Pd(0)-mediated cross-

couplings, due to the milder reaction conditions and broader substrate scope. However, the reductive elimination step of copper-mediated cross-coupling reactions are occasionally more favourable than even palladium and nickel.<sup>8</sup> Intriguingly, the formation of sp-sp C-C bonds remain the domain of copper-catalysed transformations, such as the Glaser, Eglinton, and Cadiot-Chodkiewicz reactions (**Fig 4.2**). Both Glaser and Eglinton reactions are air tolerant but are mainly limited to homocouplings ( $R_3=R_4$ ), otherwise a large excess of one reagent is sacrificed to achieve reasonable yields.

The Cadiot-Chodkiewicz reaction is the cross-coupling reaction between an alkyne **4.7** and a 1-haloalkyne **4.12** using a copper (I) catalyst, selectively forming sp-sp bonds without using of a large excess of one coupling partner. The presence of air leads to the deactivation of the active copper (I) catalyst and the Glaser reaction, leading to homocoupled side products. Although hydroxylamine HCl is occasionally used as a supplementary reducing agent for the Cadiot-Chodkiewicz reaction it is generally paired with an inert atmosphere such as nitrogen or argon for optimal results. Thus, we aim eliminate the need for an inert atmosphere, by the addition of sodium ascorbate into the Cadiot-Chodkiewicz reaction to protect the reaction against oxygen.

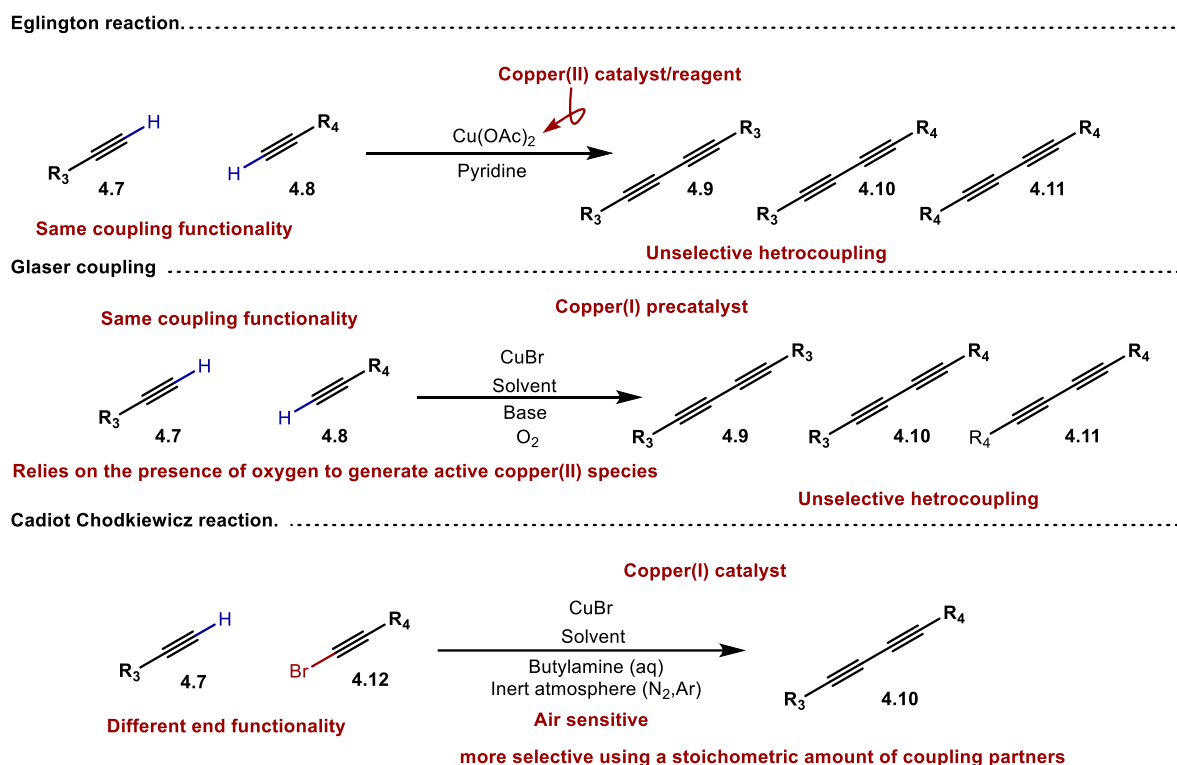


**Fig 4.2:** Comparison between the Eglinton reaction, Glaser coupling and Cadiot-Chodkiewicz reaction

To generalize this synthetic paradigm to cross-coupling chemistry, we endeavour to show its applicability in Sonogashira cross-couplings. The Sonogashira cross-coupling is a Pd (0) catalysed cross-coupling of an aryl halide onto a terminal alkyne. Although the palladium catalyst is responsible for driving the main catalytic cycle, a copper co-catalyst is added to aid the trans-metalation of the terminal acetylene onto the palladium centre.<sup>9</sup>

Unfortunately, the Glaser coupling is a significant problem for Sonogashira cross-coupling,<sup>10</sup> consuming the terminal acetylene. Thus, an excess of acetylene is needed to completely consume the aryl halide. Furthermore, oxygen can oxidize the palladium catalyst, stopping the reaction prematurely. The addition of ascorbic acid as a supplementary reducing agent would reduce any oxidized copper (II) salts back into the active copper (I) co-catalyst, protecting the reaction from adventitious oxygen (**Fig 4.3**).

#### Ascorbic acid Sonogashira

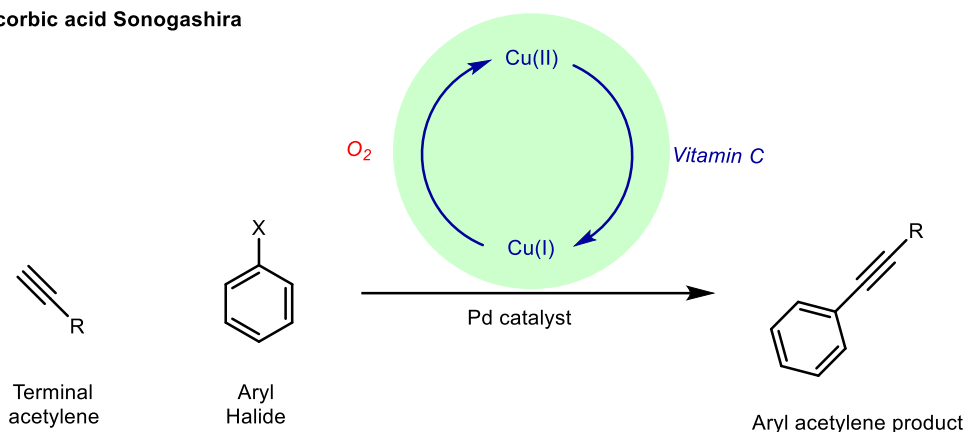


**Fig 4.3:** Air tolerant Sonogashira cross-coupling.

In summary, in this chapter, we demonstrate the effectiveness of the use of a supplementary reducing agent as a paradigm for introducing oxygen tolerance into both the Cadiot-Chodkiewicz reaction and Sonogashira cross-coupling.

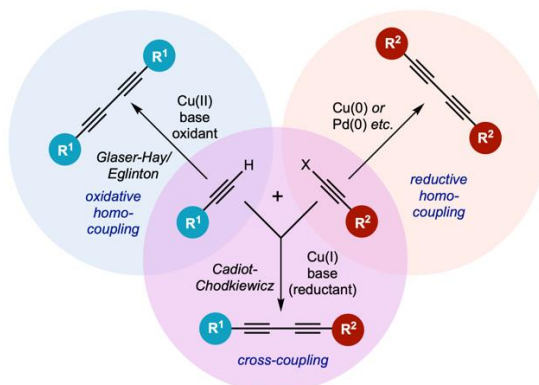
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## ***Publication 3: Air Tolerant Cross-Couplings For C-C Bond Formation***

Alfred K.K. Fung, Madison J. Sowden, Michelle L. Coote, Michael S. Sherburn

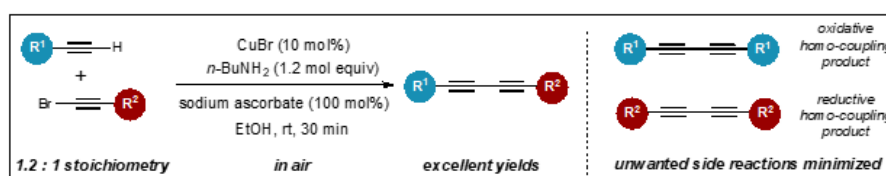


Article submitted to Org. Lett.

This manuscript was submitted the Journal "Organic Letters". Reprinted with permission from authors. Alfred. K. K. Fung completed all experimental work present. Project was conceived, designed, and evolved in collaboration between Alfred. K. K. Fung and the other authors. The Manuscript was drafted and edited in collaboration between Prof. Michelle L. Coote and Prof. Michael S. Sherburn

# Air-Tolerant Cross-Couplings For C–C Bond Formation

Alfred K. K. Fung, Madison J. Sowden, Michelle L. Coote, and Michael S. Sherburn\*



**ABSTRACT:** Cadiot-Chodkiewicz cross-couplings generate an unsymmetric buta-1,3-diyne by way of a Cu(I)-catalyzed coupling between a terminal alkyne and a 1-haloalkyne. Despite their widespread use, Cadiot-Chodkiewicz reactions are plagued by the generation of symmetric buta-1,3-diyne side products, formed through competing: (a) formal reductive homo-coupling of the 1-haloalkyne, and (b) oxidative (Glaser-Hay/Eglinton) homo-coupling of the terminal alkyne. To overcome this issue, a large excess of one of the two reacting alkynes is commonly deployed, and difficult separations of cross- and homo-coupled products are often encountered. Here, we demonstrate that the use of ascorbate as reductant leads to a suppression of these unwanted side reactions, hence permitting excellent yields with a roughly stoichiometric ratio of reactants. The procedure also avoids an inert gas atmosphere and uses a sustainable solvent. A similar approach is effective for cross-couplings involving a Pd(0)/Pd(II) catalytic cycle, with air-tolerant Sonogashira couplings also established.

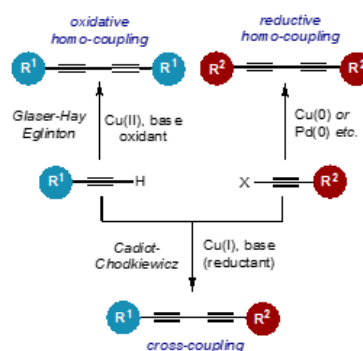
The union of two terminal alkynes to generate a buta-1,3-diyne functionality is a textbook transformation. Such *sp*–*sp* couplings are amongst the most widely used C–C bond forming reactions, with applications ranging from materials chemistry<sup>1</sup> to natural product synthesis.<sup>2</sup> The two mainstay reactions, namely Glaser-Hay/Eglinton couplings<sup>3,4</sup> and Cadiot-Chodkiewicz couplings,<sup>5,6</sup> are especially significant due to their use of an inexpensive and abundant metal, Cu.

Glaser-Hay couplings<sup>7,8</sup> (Figure 1) unite two terminal alkynes directly, by way of an oxidative process that is generally mediated by a Cu(I) precatalyst, a stoichiometric amount of base, and oxygen (air) as oxidant. Recent findings<sup>9</sup> appear to favor a mechanism proposed by Bohlmann,<sup>10</sup> involving the cooperation and shuttling between Cu(I) and Cu(II) states in a dinuclear Cu intermediate. The Eglinton variant<sup>11</sup> uses Cu(OAc)<sub>2</sub> in pyridine. Glaser-Hay/Eglinton reactions are generally limited to terminal alkyne homo-couplings, although notable variants permitting hetero-couplings with close to stoichiometric quantities of two different terminal alkynes have recently been reported.<sup>12,13,14</sup> While important advances, these approaches are not general solutions to the preparation of unsymmetric buta-1,3-diynes.

Cadiot-Chodkiewicz cross-couplings<sup>15,16,17</sup> (Figure 1) bring about the selective union of two different alkynes, after one of them has been converted into a 1-haloalkyne derivative. The reaction is widely used for the synthesis of unsymmetric buta-1,3-diynes. It employs a Cu(I) [Cu(II)] source as [pre]catalyst, a stoichiometric amount of (usually amine) base, an environment of N<sub>2</sub> or Ar and/or hydroxylamine hydrochloride as reductant. The mechanism of the Cadiot-Chodkiewicz reaction has been proposed to involve a Cu(I)/Cu(III) catalytic cycle involving the formation of a mixed Cu(III) diacetylide halide then reductive

elimination to form the cross-coupled product and regeneration of Cu(I).<sup>16</sup> An inert atmosphere is needed to avoid oxidation of the air sensitive Cu(I) catalyst into Cu(II), thereby compromising cross-coupling and permitting homo-coupling pathways.

**Figure 1:** Buta-1,3-diyne synthesis through *sp*–*sp* couplings between terminal alkynes and haloalkynes.



The problematic nature of the Cadiot-Chodkiewicz cross-coupling is well established.<sup>18</sup> As depicted in Figure 1, the two reactants can homo-couple to give symmetric buta-1,3-diynes, thereby decreasing the yield of the cross-coupled product and prompting an arduous separation to isolate the desired product in pure form. To overcome this issue, the Negishi group invented a 5 step alternative synthetic pathway to avoid a Cadiot-Chodkiewicz cross-coupling.<sup>19</sup>

The unwanted, oxidative homo-coupled terminal alkyne presumably originates from the aforementioned Glaser-

Hay/Eglinton coupling, brought about by a Cu(II) species formed through an adventitious oxidant (e.g., air). The origin of the other common byproduct, namely the reductively homo-coupled 1-haloalkyne, is less well understood but potentially involves a complementary Cu(0)→Cu(II) mediated process. Preparative syntheses of symmetric buta-1,3-diyne from 1-haloalkynes have been reported using various methods including [Pd(PPh<sub>3</sub>)<sub>4</sub>] or Cu powder.<sup>20,21,22,23,24</sup>

The original Cadiot-Chodkiewicz method deploys NH<sub>2</sub>OH·HCl as a Cu(II)→Cu(I) reductant, along with a recommendation to perform the reaction under either Ar or N<sub>2</sub>. In this process, NH<sub>2</sub>OH·HCl is converted into a mixture of NO and O<sub>2</sub>. Aside from the potential hazards involving NO exposure,<sup>25</sup> O<sub>2</sub> serves as an effective Cu(I)→Cu(II) oxidant, hence directly undermining its intended role. Borrowing from both Fokin-Sharpless azide/alkyne “click” technology<sup>26</sup> and Matyjaszewski ARGET-ATRP methodology,<sup>27</sup> we reasoned that ascorbic acid might perform much better as a Cu(II)→Cu(I) reductant, hence preventing the unwanted homo-couplings depicted in **Figure 1** and potentially allowing the Cadiot-Chodkiewicz reaction to be performed in air. To our knowledge, there are no reports of the use of ascorbic acid in Cadiot-Chodkiewicz couplings.<sup>28</sup> Furthermore, we could not find precedent for an application of vitamin C as a reductant in cross-coupling reactions more generally.

The first entry of Table 1 shows optimized conditions for high yielding Cadiot-Chodkiewicz cross-coupling using close to stoichiometric amounts of reactants, propargyl alcohol TBS ether **1** and bromoethynylbenzene **2**. The cross-coupling is performed in air. It also uses a sustainable and relatively innocuous solvent (EtOH) and oxidant (sodium ascorbate). Reactants **1** and **2** were chosen since they are recalcitrant partners in Cadiot-Chodkiewicz cross-couplings, with each undergoing facile homo-coupling.<sup>29</sup> Nonetheless, under optimized conditions (entry 1), **1** and **2** give the cross-coupled product in excellent yield, with only minimal amounts of the two symmetric homo-coupled byproducts.

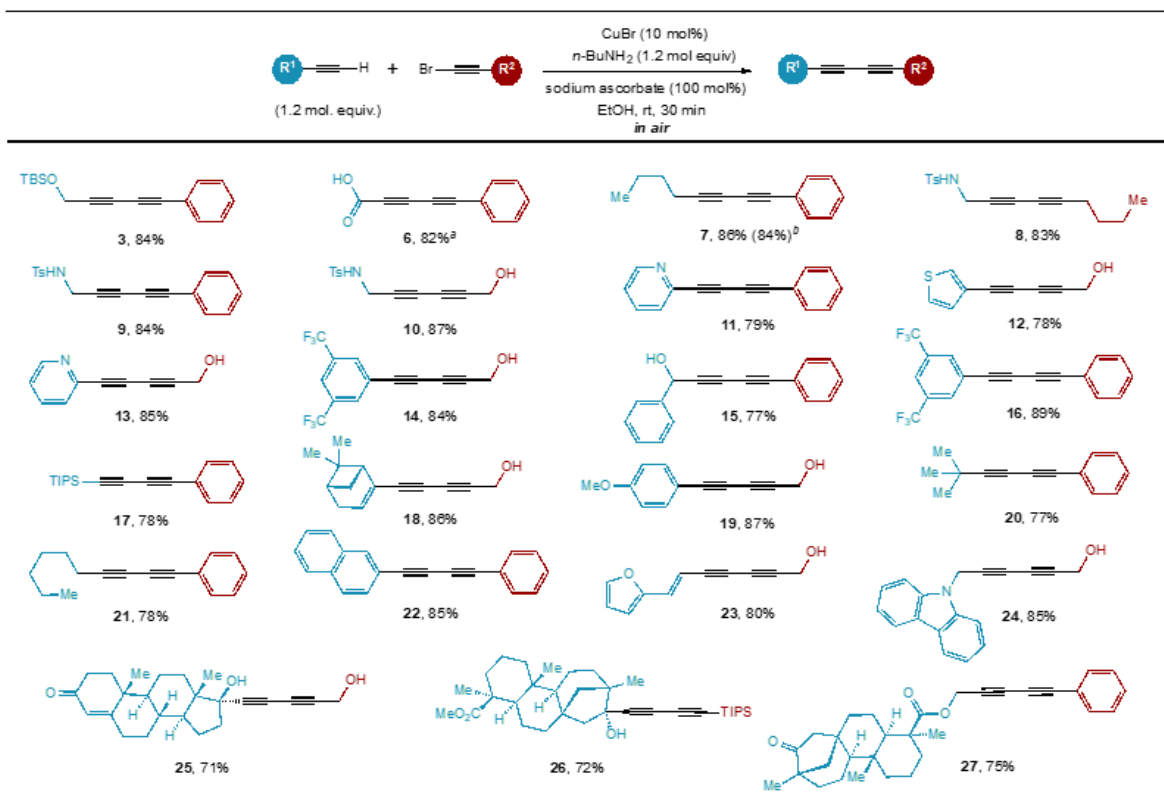
The datasets in Table 1 are presented relative to optimized conditions (i.e., entry 1). Entries 2–4 demonstrate that the 1.2:1 stoichiometry of the process is optimal. Entries 5–8 vary the base and show that the primary amine *n*-BuNH<sub>2</sub> is preferred, although pyrrolidine<sup>30</sup> also functions well. Entries 9 and 10 show that without a reductant to constantly regenerate the Cu(I) catalyst, the reaction is both slower and less selective for the cross-coupled product. Entries 11 and 12 establish that a sub-stoichiometric amount of sodium ascorbate and a stoichiometric amount of ascorbic acid are less efficient for Cu(II)→Cu(I) reduction. Entries 13–14 show that 10 mol% of CuBr is optimal, and entries 15–16 show that CuCl and CuBr<sub>2</sub> are also effective but slightly less so than CuBr. Entry 17 supports the premise that sodium ascorbate is superior to hydroxylamine hydrochloride as reductant, and entries 18–20 show that the original literature protocols<sup>15,16</sup> are inferior.

**Table 1.** Dependence of reaction conditions on outcome of Cu(I)-catalyzed cross-couplings.

| Entry           | Conditions                                                                                                                                        | Yield <sup>a,c</sup><br>3:4:5<br>(%) |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| 1               | As specified in the equation                                                                                                                      | 82, 3, 9                             |
| 2               | 1.3 mol. equiv. of <b>1</b>                                                                                                                       | 77, 2, 5                             |
| 3               | 1.1 mol. equiv. of <b>1</b>                                                                                                                       | 59, 0, 17                            |
| 4               | 1.0 mol. equiv. of <b>1</b>                                                                                                                       | 50, 0, 15                            |
| 5               | Et <sub>3</sub> N in place of <i>n</i> -BuNH <sub>2</sub>                                                                                         | 1, 0, 0                              |
| 6               | ( <i>i</i> -Pr) <sub>3</sub> NH in place of <i>n</i> -BuNH <sub>2</sub>                                                                           | 0, 0, 0                              |
| 7               | PMDETA <sup>e</sup> in place of <i>n</i> -BuNH <sub>2</sub>                                                                                       | 0, 4, 0                              |
| 8               | pyrrolidine in place of <i>n</i> -BuNH <sub>2</sub>                                                                                               | 64, 1, 15                            |
| 9               | Sodium ascorbate omitted                                                                                                                          | 33, 21, 9                            |
| 10              | As entry 9 but 3 h reaction time                                                                                                                  | 41, 13, 28                           |
| 11              | 50 mol% sodium ascorbate                                                                                                                          | 42, 2, 11                            |
| 12              | Ascorbic acid in place of sodium ascorbate                                                                                                        | 43, 0, 19                            |
| 13              | CuBr (5 mol%) used                                                                                                                                | 43, 0, 19                            |
| 14              | CuBr (15 mol%) used                                                                                                                               | 76, 2, 14                            |
| 15              | CuCl in place of CuBr                                                                                                                             | 62, 2, 14                            |
| 16              | CuBr <sub>2</sub> in place of CuBr                                                                                                                | 58, 0, 13                            |
| 17              | NH <sub>2</sub> OH·HCl in place of sodium ascorbate                                                                                               | 44, 11, 12                           |
| 18              | CuCl (10 mol%), <i>n</i> -BuNH <sub>2</sub> (1.2 mol equiv), NH <sub>2</sub> OH·HCl (120 mol%), CH <sub>2</sub> Cl <sub>2</sub> -H <sub>2</sub> O | 63, 1, 16                            |
| 19 <sup>d</sup> | CuCl (10 mol%), <i>n</i> -BuNH <sub>2</sub> (1.2 mol equiv), NH <sub>2</sub> OH·HCl (120 mol%), H <sub>2</sub> O                                  | 10, 1, 2                             |
| 20 <sup>d</sup> | CuCl (30 mol%), <i>n</i> -BuNH <sub>2</sub> (1.2 mol equiv), NH <sub>2</sub> OH·HCl (120 mol%), H <sub>2</sub> O                                  | 29, 5, 8                             |

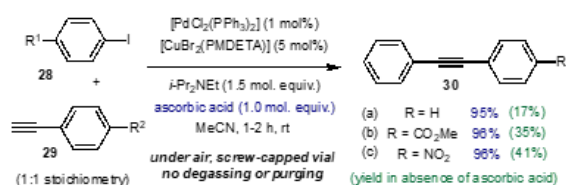
<sup>a</sup> Values based upon analysis of crude product mixture by <sup>1</sup>H NMR spectroscopy by integration against an internal standard. Spectra are provided in the SI. <sup>b</sup> Amount of each unreacted alkyne **1** and **2** remaining. <sup>c</sup> Percentage of products **3**, **4** and **5** formed. <sup>d</sup> Large amounts of insoluble solids formed. <sup>e</sup> PMDETA = *N,N,N',N',N''*-pentamethyldiethylenetriamine.

Table 2 displays the scope of the improved process. Twenty-three examples of successful couplings with molecules of varying size and complexity are shown. Substrates with a wide variety of steric and electronic demands are cleanly cross-coupled, and products of various polarities, from hydrocarbons to those containing the most polar functional groups, are readily isolated in excellent yields. Five unsymmetric buta-1,3-diyne in Table 2 (**20–24**) were specifically chosen since they have been reported to deliver Cadiot-Chodkiewicz cross-coupling products in low yields (18–41%). Significantly improved yields of 77–85% were obtained through a procedure that is fast and simple to perform.

**Table 2.** The scope of the optimized Cadiot-Chodkiewicz protocol.

<sup>a</sup> 2 mol. equiv. *n*-BuNH<sub>2</sub> used. <sup>b</sup> Yield obtained from reversing the terminal alkyne/bromoalkyne precursors.

Having demonstrated the ability of ascorbate to serve, in effect, as a protector of an air sensitive Cu(I) catalyst, we wondered if the method could extend to an air sensitive Pd(0) catalyst. The successful realization of this approach is depicted in Scheme 1. Thus, Sonogashira cross couplings<sup>31</sup> between iodo-benzene **28** and terminal alkynes **29** give high yields of tolans **30** from reactions performed in air and in screw-capped vials. Ascorbic acid is mandatory for high yielding reactions, since low yields are obtained from reactions performed without it.

**Scheme 1.** Pd(0)-catalyzed Sonogashira cross-couplings in air. (PMDTA = *N,N,N',N',N''*-pentamethyldiethylenetriamine.)

The reactions shown in Scheme 1 were successful on scales of 0.5 mmol to 5 mmol. Furthermore, yields remained high with only 0.2 mol% of [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] and 1.0 mol% of [CuBr<sub>2</sub>(PMDTA)].

Sonogashira couplings generally use a Pd(0) catalyst and Cu(I) co-catalyst. Here, we deploy a Pd(II) and Cu(II) precatalysts. In principle, the terminal alkyne, tertiary amine and

ascorbate could separately reduce the Pd(II)/Cu(II) precatalyst into the catalytically active Pd(0)/Cu(I) species.<sup>32</sup> In practice, ascorbic acid is needed for optimal results.

Screw-capped vials were needed for high yields in these Sonogashira couplings, with reactions performed in flasks open to the air giving incomplete conversions. Evidently, when open to the air, the aerobic oxidation of Pd(0)→Pd(II) cannot be fully countered by the ascorbate reduction of Pd(II)→Pd(0).<sup>33</sup>

In summary, a significantly improved protocol for Cadiot-Chodkiewicz cross-couplings has been developed. The procedure borrows the use of ascorbic acid for in situ reduction of Cu(II)→Cu(I) from both azide/alkyne “click” and ARGET-ATRP methods in order to maximize both selectivity and operational simplicity in cross-couplings. The method allows the reaction to be performed in air, leads to short reaction times, and deploys a sustainable solvent and reductant. Roughly stoichiometric amounts of reactants are tolerated and the procedure exhibits broad substrate scope. A similar method has also been developed for high yielding Sonogashira cross-couplings, offering the prospect of other Pd(0)-catalyzed processes. The convenience offered by this protocol compares favorably with other recently reported optimizations,<sup>34-36</sup> and augurs well for its widespread use.

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, characterization data, NMR spectra. (PDF)

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#### Author Contributions

The manuscript was written through contributions of all authors.

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#### Notes

The authors declare no competing financial interest.

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## ***Chapter five:***

### ***Towards The Synthesis Of Better ATRP Ligands***

## Introduction

The dawn of the polymer industry experienced exponential growth as polymers are recognised as a superior alternative to traditional building materials.<sup>1,2</sup> Polymers have served as the building block of modern society because of their low cost, high malleability, durability, and ability to be synthesized with specific physical characteristics suited for their prospective role.<sup>3</sup> From the commercial success of early polymers such as Bakelite, nylon, and polyethylene, the polymer industry has exploded into a multi-billion-dollar industry that is growing as our society evolves.

Free radical polymerization is responsible for roughly half the polymers produced via industrial processes. Free radical polymerization appeals to industry with its mild reaction conditions, short reaction time, moisture, and functional group tolerance.<sup>4</sup> In free radical polymerizations, first the initiator **5.1** decomposes into the initiating radical **5.2** via either heat or light (**Fig. 5.1**). The initiating radical **5.2** adds to a monomer unit **5.3** creating the propagating chain **5.4**. The propagating chain **5.4** continues to add into more monomer **5.3** to grow the polymer chain **5.5**; the propagating chain **5.5** is terminated by another propagating chain **5.6** via either a combination or a disproportionation pathway to form products **5.7-5.11**.

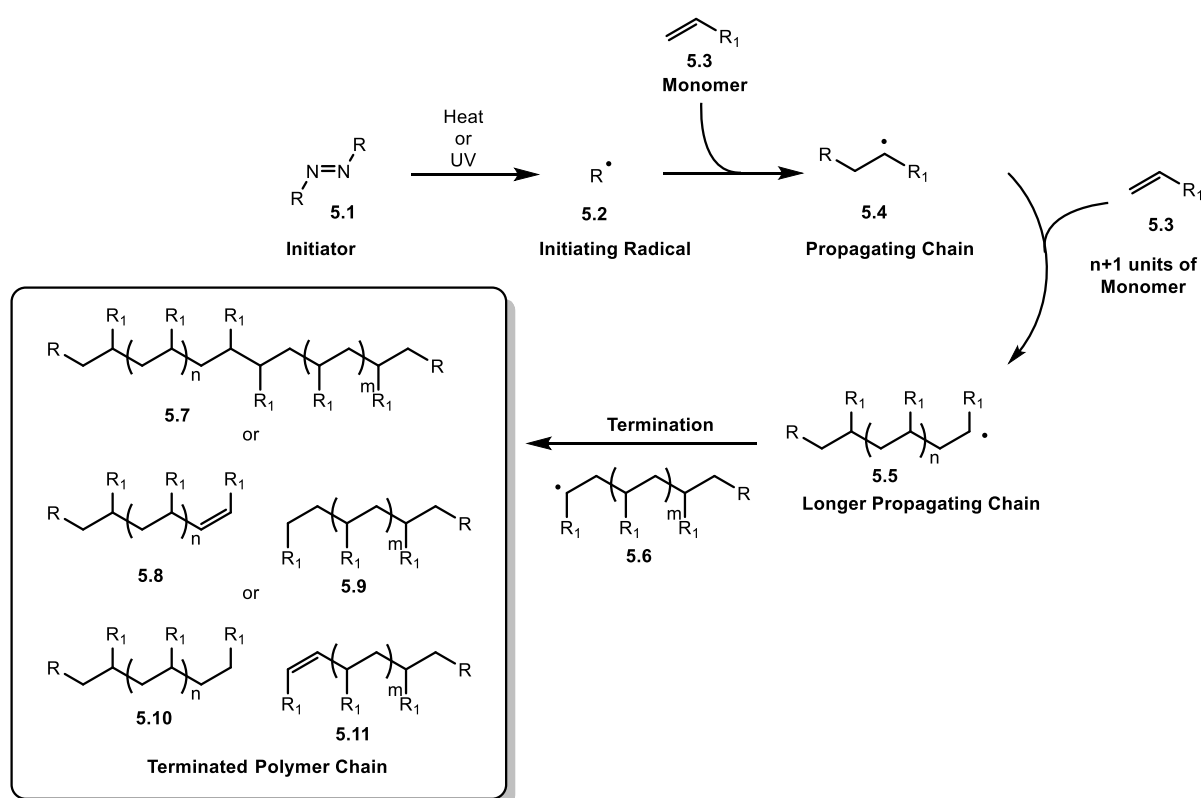


**Fig 5.1:** Free radical polymerization, producing a variety of products.

Polymerization reactions produce mixtures of compounds that are not easy to separate. The wider the range of polymer structures produced, the wider the range of properties. Modern materials such as “smart” polymers require a narrow structural variation with specific physical characteristics.<sup>5</sup> Although effective at the production of vast quantities of polymers, free radical polymerization lacks control over the tacticity, dispersity, and chain end composition.<sup>6</sup> Controlled radical polymerization techniques (nitroxide mediated polymerization, reversible addition fragment transfer, atom transfer radical polymerization) were developed to address these issues.<sup>6</sup> Controlled radical polymerization reversibly traps the propagating radical. This reduces the number of termination events relative to the length of polymer chains, thus allowing superior control over the dispersity of the polymer sample. The reversible trapping of the propagating chains necessitates a trapping moiety, which also becomes the polymer chain end, allowing us better control over chain end composition. Controlled radical polymerization methodologies such as nitroxide-mediated polymerization (NMP),<sup>7</sup> reversible addition fragment transfer (RAFT),<sup>8</sup> and atom transfer radical addition (ATRP)<sup>9</sup> were developed to address the shortcomings of free radical polymerization, in dispersity and chain end control. In this chapter, we will focus on expanding the scope of ATRP via the development of synthetic approaches towards better ligands.

ATRP was independently discovered in 1995 by Mitsuo Sawamoto<sup>10</sup> and Krzysztof Matyjaszewski;<sup>9</sup> we will focus on the variant developed by Wang and Matyjaszewski in this chapter. In ATRP, the propagating radical is trapped as an alkyl halide (**Fig. 5.2**). Given the relative stability of the carbon halogen bond, a mediator is necessary to facilitate its reversible dissociation of the alkyl halide **5.14** into the propagating radical **5.12**. The copper mediator facilitates the homolytic cleavage of the alkyl halide **5.14** via an inner sphere electron transfer mechanism. The equilibrium can be described by the overall rate constant  $K_{\text{ATRP}}$ , which is dictated by the stability of the alkyl halide bond and the relative stability of the  $\text{LCu(I)}^+$  **5.15** and  $\text{LCu(II)}^+$  **5.13** mediator complexes; these factors must be balanced for the reaction to proceed smoothly, where deviations will result in an uncontrolled polymerization or no reaction. Thus, the mediator complex must be matched to the monomer-initiator pair for a selective reaction.<sup>11</sup>

### Atom Transfer Radical Polymerization

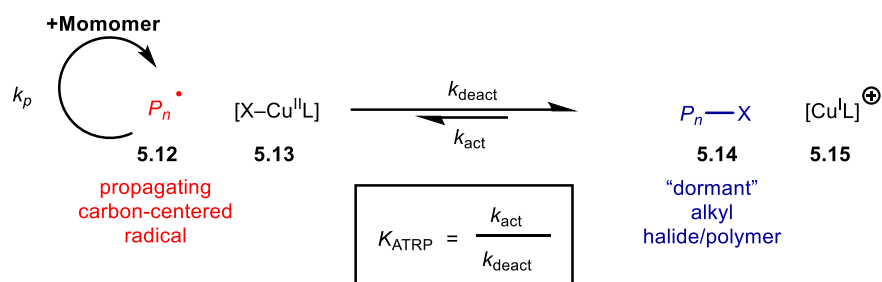


**Fig 5.2:** Atom transfer radical polymerization.

The original version of ATRP uses a low-activity mediator complex, between a copper (I) halide and bipyridine (bpy). Unfortunately, for a given alkyl halide, polymerizations using low-activity mediator complexes often need to be sped up using elevated temperatures or pressure. Alternatively, the recalcitrant alkyl halide can be paired with more active mediator complexes, allowing the reaction to take place under milder conditions. Current ligands are capable of efficiently and reversibly trapping stabilised radicals produced from monomers such as styrene, butyl acrylate, and methyl methacrylate under ambient conditions, however, existing mediators are unable to activate certain industrially critical monomers such as ethylene. More active mediator complexes must be developed to facilitate the ATRP of these monomers.<sup>12</sup> Previous computational work<sup>10</sup> shows that strained cyclic structures can influence the catalytic activity of ATRP ligands (**Fig. 5.3**).

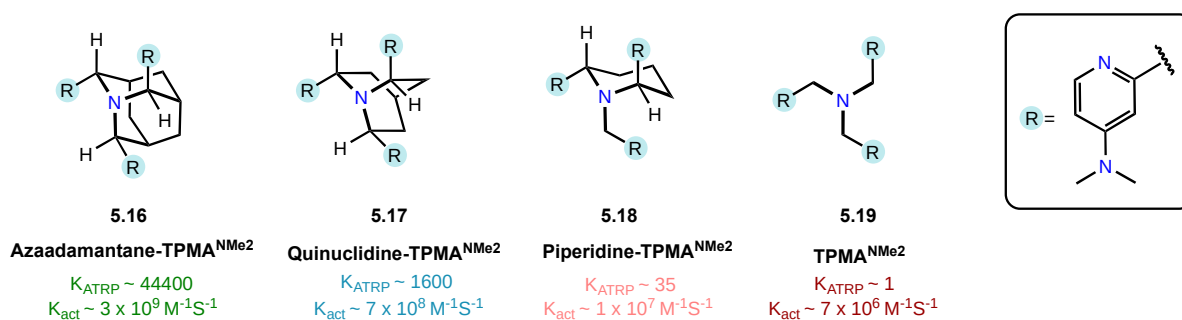


**Fig 5.3:** Approximate kinetic and thermodynamic performances of three rigid analogues of TPMA<sup>NMe2</sup>

This method is effective because the highest occupied molecular orbital (HOMO) of the mediator complex has a node along the axial Cu–N bond. As a result, a decrease in the Cu–N bond length results in the destabilization of the mediator complex's HOMO, which as per Koopman's theorem, making the mediator complex more easily oxidised. In this computational study, it was suggested that the Cu–N distance can be decreased via the

incorporation of the axial nitrogen into a cyclic structure, as in compounds **5.16-5.18**. Various end caps were incorporated onto the then best ligand TPMA<sup>NMe<sub>2</sub></sup> **5.19**, the best ligand evaluated being azaadamantane-TPMA<sup>NMe<sub>2</sub></sup> **5.16**, with a predicted  $K_{\text{ATRP}}$  roughly 44400 times that of **5.19**. This predicted improvement upon the current generation of ligands demonstrates the potential of this approach.

Thus, we decided to embark on the total synthesis of rigidified ATRP ligands. The four major structural motifs targeted (**Fig. 5.4**) are the piperidine **5.18**, quinuclidine **5.17**, oxygen-bridged quinuclidine **5.20**, and azaadamantane **5.16** ligands.<sup>12,13</sup> There is a compromise between ease of synthesis and mediator activity when choosing a ligand to prepare. We decided to target the quinuclidine **5.21** and oxygen-bridged quinuclidine **5.20** ligands initially, as they represent a reasonable middle ground between synthetic difficulty and ligand activity, where structural analogues exist in patent literature.<sup>14</sup> The oxygen bridged quinuclidine was thought to be the easier synthetic target to access synthetically, as the caged hemiaminal ether **5.22** should be accessible via conditions explored by Hardegger and Ott.<sup>15</sup>

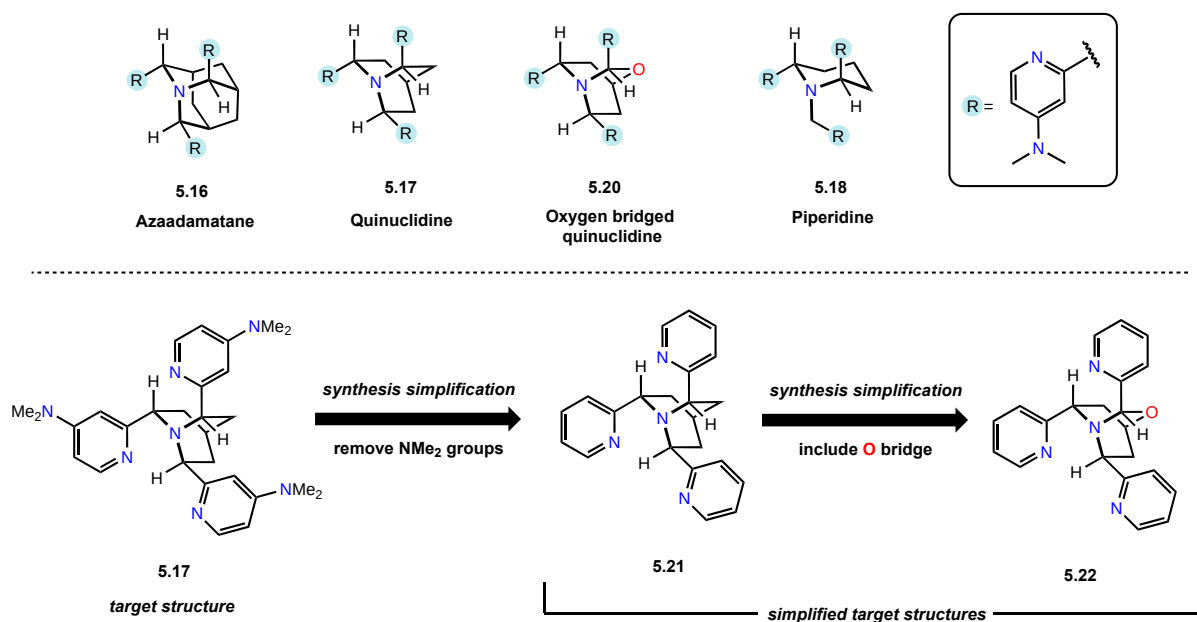


**Fig 5.4:** Explored structural motifs for the next generation of ATRP ligands, our synthetic target, and structurally simplified targets for ease of synthesis.

We removed the *para*-dimethylamino groups from the desired target molecule **5.17**, hence generating the simplified “model” structure **5.21**. Removal of these groups would simplify the synthesis in 2 ways: (a) it would decrease the likelihood of unwanted reactions

(DMAP is an excellent nucleophilic catalyst and Lewis base); (b) it would ease isolation and purification, since *para*-dimethylamino pyridine groups are of high polarity. The removal of the *para*-dimethylamino groups will significantly reduce the activity of the mediator complex, hence ligand **5.21** will be much less active than ligand **5.17** in ATRP studies.<sup>12</sup> Nonetheless, to develop a synthesis of the *tripyridyl*quinuclidine ligand framework, it is prudent to remove them in the first instance. Once a method for preparing ligand **5.21** is in hand, the more challenging ligand **5.17** will then be tackled. Additionally, the simplified target ligand will experimentally confirm the effects of capping the ligands against the parent unsubstituted *tris*(2-pyridylmethyl)amine (TPMA) ligand **5.19**. The replacement of a single methylene carbon by oxygen **5.21** → **5.22** was expected to further simplify the chemical synthesis.

Multiple stereoisomers **5.21–5.26** exist for the quinuclidine and O-bridged quinuclidine ligand architectures. Computational evaluation of the *para*-substituted frameworks was reported by Stewart *et. al.* which shows all possible stereoisomers geometries **5.21–5.25** to be viable candidates for ATRP ligands, where **5.26** was the thermodynamically less stable epimer of **5.22**. stereochemical control in this synthesis was not considered to be an important issue.

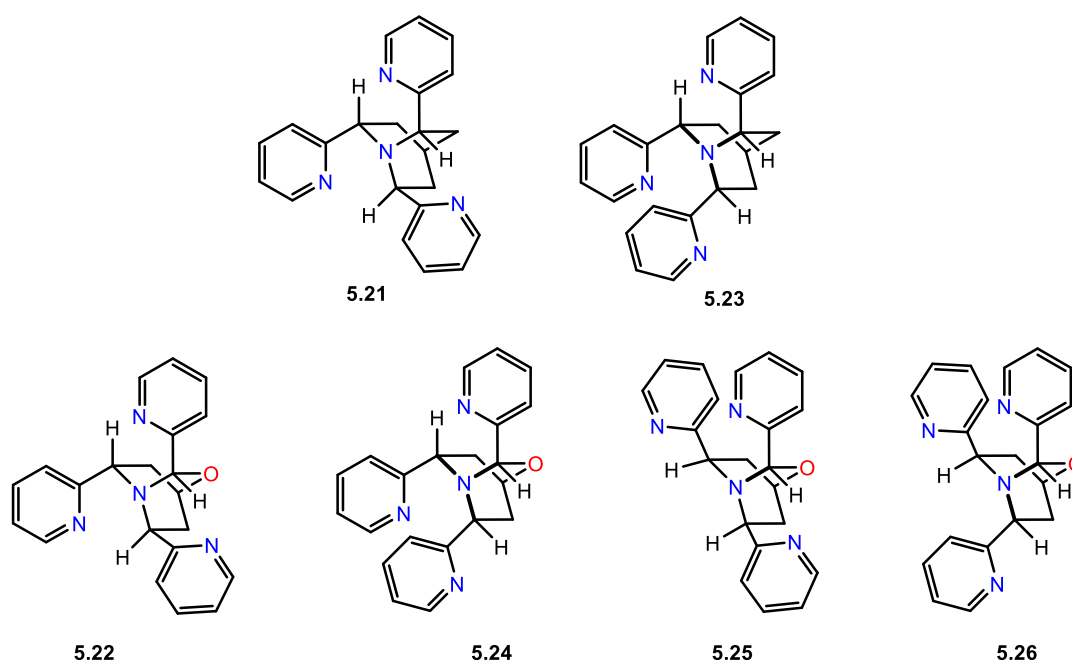


**Fig 5.5:** Possible diastereomeric forms of the simplified target ligands.

The initial aim of this work was to complete the total synthesis of any of the possible stereoisomers of the quinuclidine ligands **5.21–5.25** from 2-formylpyridine **5.27** and 1,3

acetonedicarboxylic acid **5.28** (Fig 5.6). In principle, condensing these two reactants can give rise to both the *cis* and *trans* piperidones **5.29**, **5.31**. Then the *trans* piperidone intermediate **5.29** can be converted into bridged ring system **5.21** through a sequence involving (a) aldol condensation with 2-acetyl pyridine **5.30** (b) reduction of the C=C double bond, and (c) a transannular reductive amination to close the bridge. Alternatively, hydride reduction of the ketone of then amination with 2-formylpyridine **5.27**, produces the oxa bridged target **5.22**. The same synthetic sequences could be applied to the *cis* piperidone **5.31**, to synthesise the quinuclidine **5.23** and oxygen bridge quinuclidines **5.24** and **5.25**.

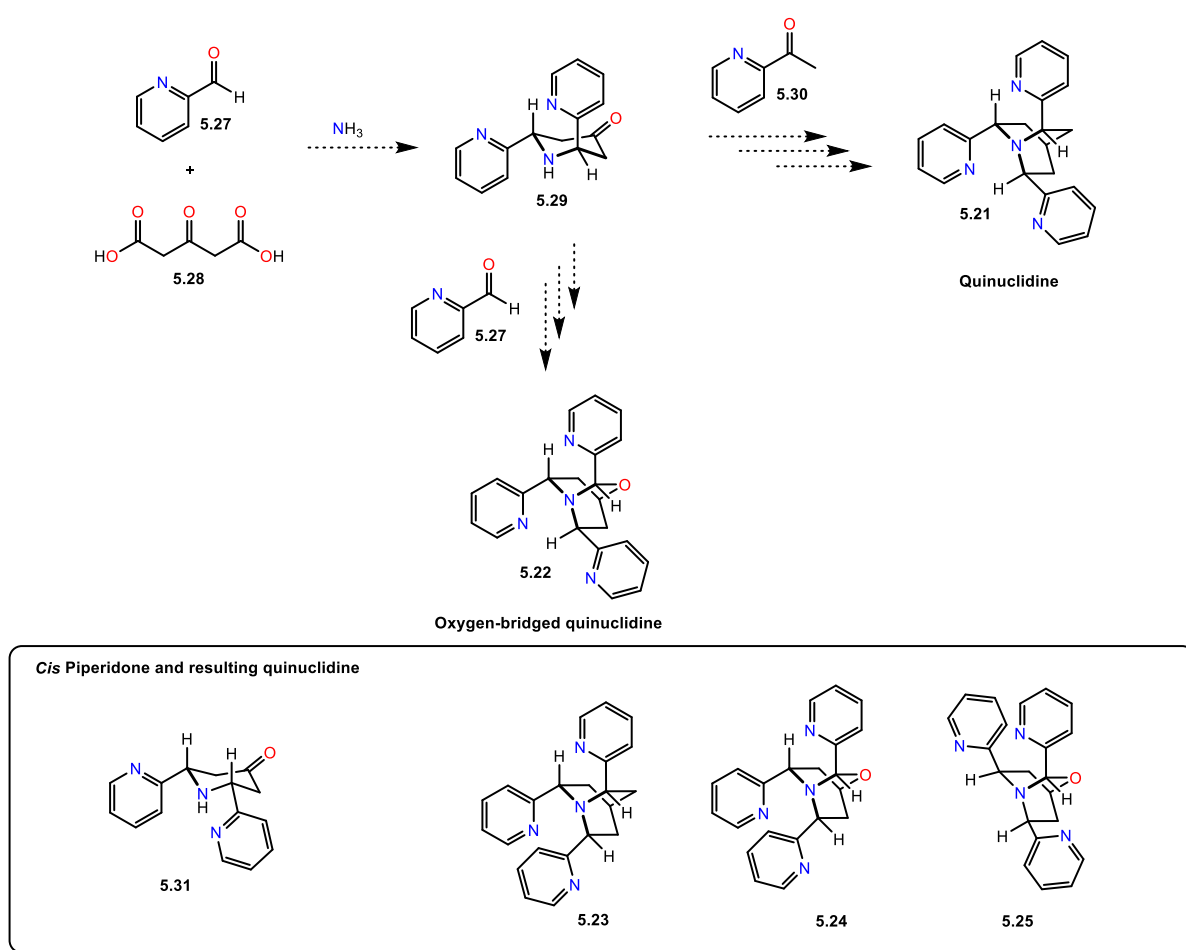


**Fig 5.6:** Synthetic plan for preparation of structurally simplified quinuclidine ligands **5.21**–**5.25**.

The methodology developed for the quinuclidine/oxygen-bridged quinuclidine ligands **5.21**–**5.25** could be adapted in two ways for the synthesis of the dimethylamino-substituted quinuclidine ligand **5.17** (Fig 5.7). In the first approach, the 2-formyl-4-dimethylamino pyridine **5.31** directly replaces 2-formylpyridine **5.27** at the start of the

synthesis. Alternatively, chlorinated precursors **5.35** is used to construct the trichlorinated bridged systems **5.37** and **5.39**, which would then be subjected to late-stage threefold substitution through nucleophilic aromatic substitution or Buchwald-Hartwig reaction.<sup>16</sup>

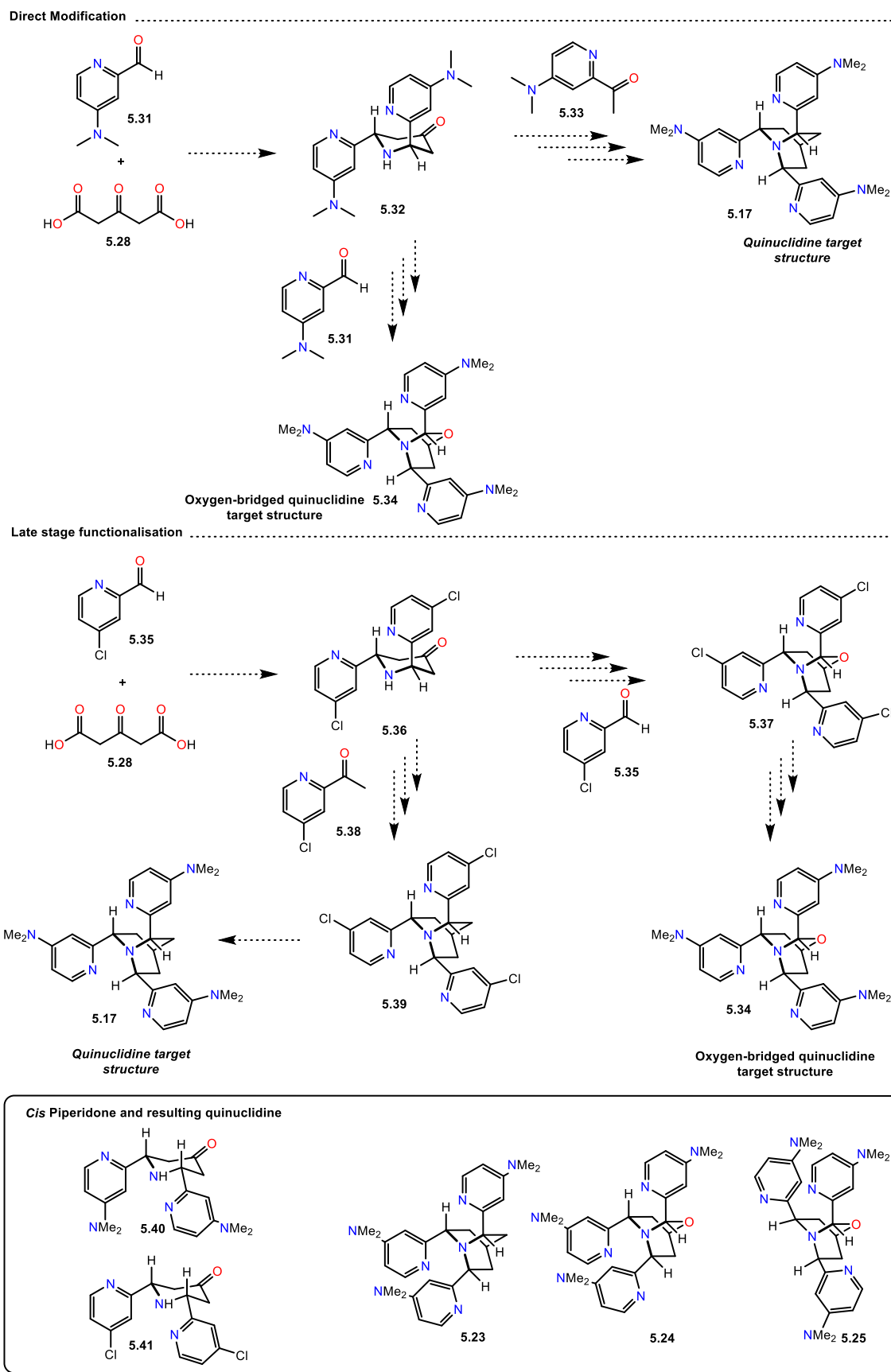


**Fig 5.7:** Proposed synthesis of dimethyl amino ligand via direct modification of the starting material or the late stage modification of a chloro-derivative.

The late-stage threefold substitution pathway uses the three chloro substituents as functional handles for incorporating the three amino groups. The use of the chloro precursor avoids potential side reactions that result from carrying the polar and basic dimethylamino group through the synthesis. However, this approach requires the use of an expensive starting material 4-chloro-2-pyridinecarbaldehyde **5.31** (A\$ 103.46 for 250 mg), making it unsuitable for an initial/model attempt. Thus, initial work focused on 2-formylpyridine as starting material.

### Initial Approach

Previous syntheses of substituted quinuclidines proceed via piperidine intermediates followed by subsequent closure of the final bridge.<sup>17,18</sup> A patented synthesis developed by Chen *et. al.* (**Fig 5.8**)<sup>19</sup> synthesised a *cis*-2,6-di-substituted piperidones **5.43** via a double Mannich reaction using 2-formyl-3methyl-pyridine **5.42**, ammonium acetate, and acetone-1,3-dicarboxylic acid **5.28**. This approach was repeated by Loftus *et. al.*,<sup>20</sup> for the synthesis of the piperidine derivative **5.45**. Only the *cis*-piperidone was reported in both studies. Unfortunately, the characterisation data provided by Chen *et. al.* is insufficient to confirm the relative stereochemistry of the piperidone **5.43**. Furthermore, the low isolated yield (60%) of the double Mannich reaction does not preclude the chance that the *trans*-isomer was formed during the reaction and lost during purification. The publication by Loftus begins with the synthesised piperidine precursor, which they cite as being synthesised following the methodology of Chen *et. al.* but the procedure and yield are not reported. The stereochemistry of the piperidine **5.46** produced was confirmed via X-ray crystallography.

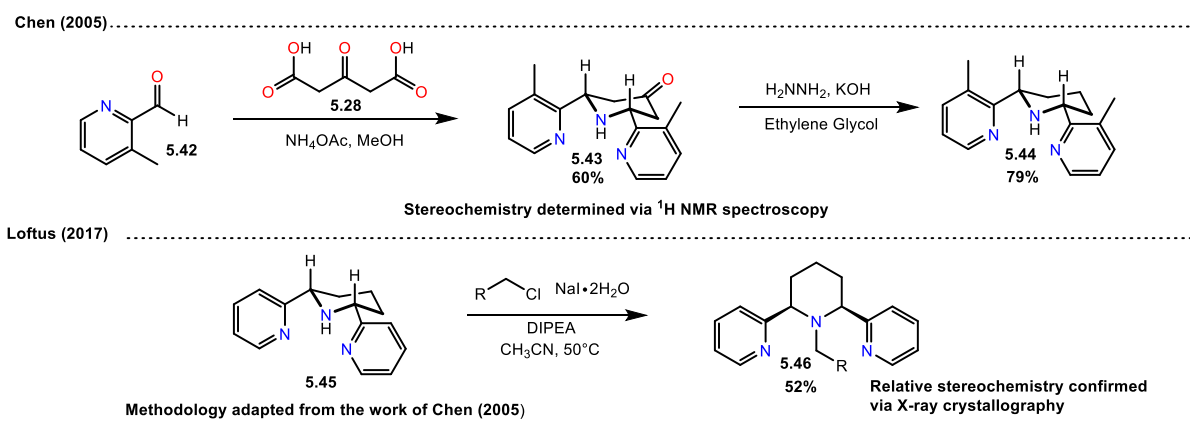


**Fig 5.8:** Previous work by Chen *et. al.* (2005)<sup>19</sup> and Loftus *et. al.*(2017).<sup>20</sup>

2,6-Piperidones are generally thermodynamically favoured products from (reversible) double Mannich reactions, since the two substituents are in less sterically demanding equatorial orientations.<sup>21</sup> To access the *trans*-piperidones **5.29** alternative means are needed to influence the diastereoselectivity of the process (**Fig 5.9**). A kinetically controlled double aza-Michael reaction might be feasible. The *cis*-piperidone is an achiral, *meso* compound. The *trans*-diastereomer is chiral. Controlled formation of one of these enantiomers might be possible using chiral Lewis acids<sup>22,23</sup> **5.50**, **5.51** or organocatalytic<sup>24,25</sup> **5.48**, **5.49** processes.

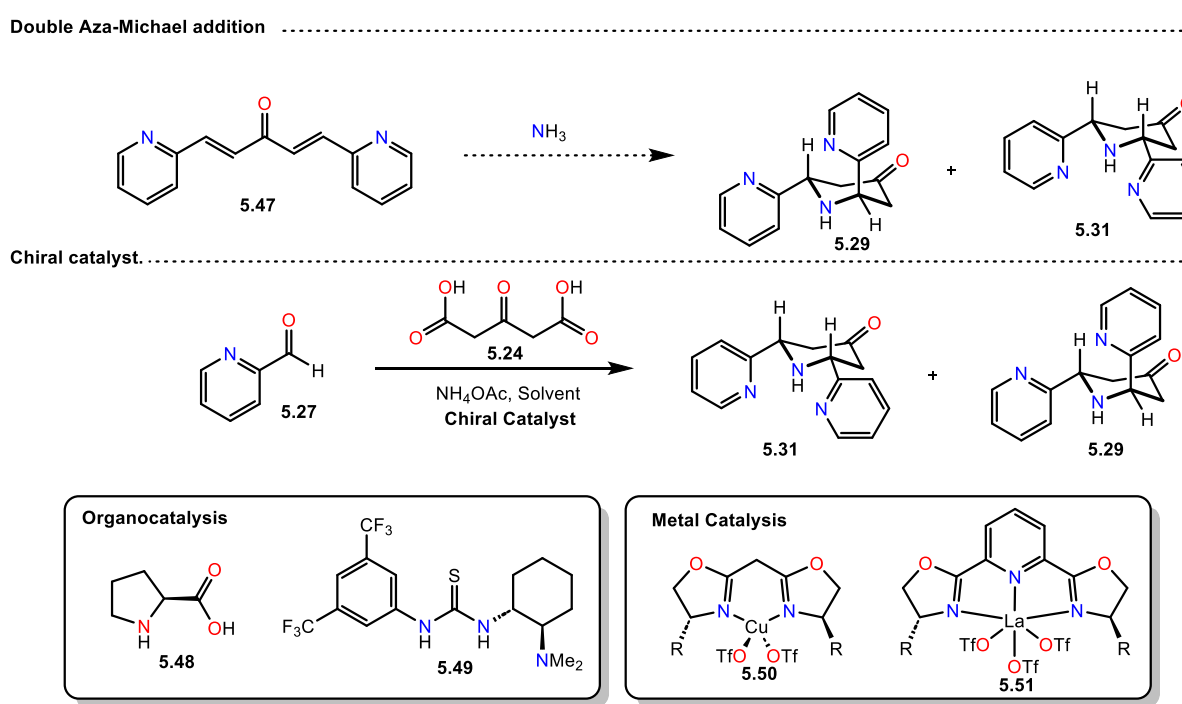


**Fig 5.9:** Alternate approaches for the synthesis of the *trans*-piperidone **5.29**.

We envisaged that a subsequent crossed aldol condensation of 2-acetylpyridine **5.30** with piperidone **5.31** would establish the necessary carbon-carbon bonds for the all-carbon quinuclidine framework **5.52** (**Fig 5.10**). The final bridging ring would be then closed through 1,4-reduction of the enone **5.52** to give **5.53** followed by transannular reductive amination to give the desired target ligand (**5.53** → **5.23**). The oxygen-bridged quinuclidine **5.24**, **5.25** could be synthesized from the common piperidone intermediate **5.31** through a borohydride reduction of the ketone to piperin-4-ols (**5.31** → **5.54**), (**5.31** → **5.55**) followed by amination condensation to produce the oxygen bridged quinuclidines (**5.54** + **5.27** → **5.24**), (**5.55** + **5.27** → **5.25**).

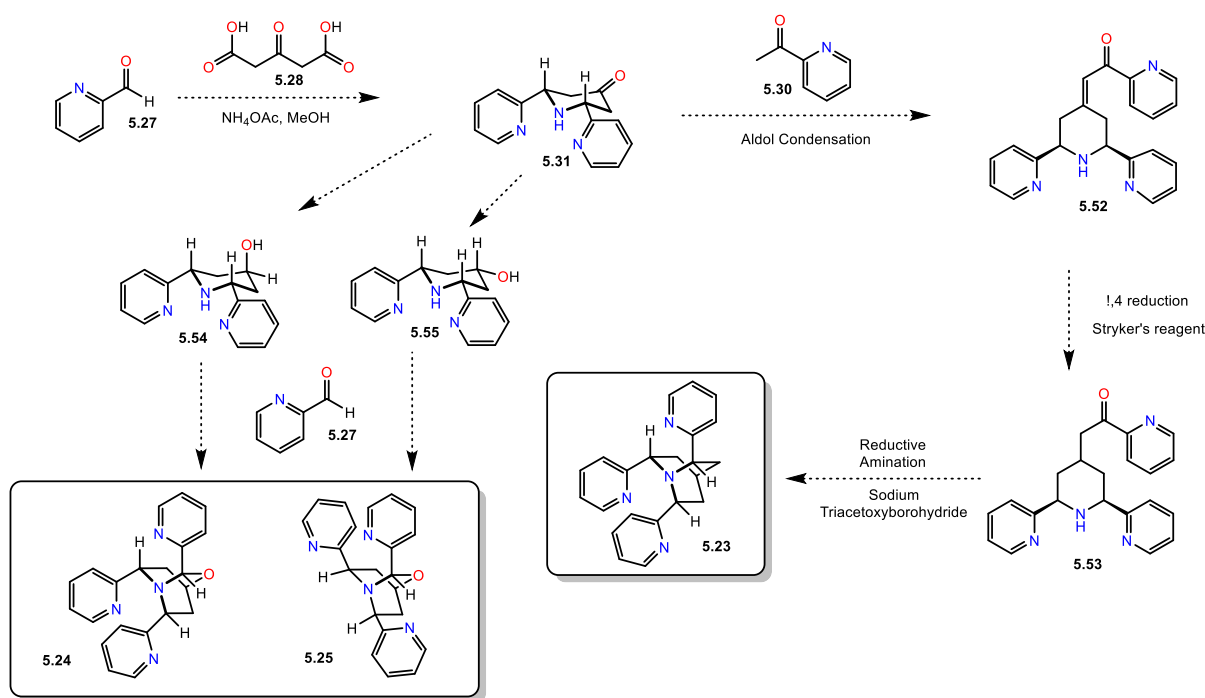


**Fig 5.10:** Our planned synthetic sequence to the quinuclidine ligand.

Attempts to perform the double Mannich reaction ( $5.27 + 5.28 \rightarrow 5.31$ ) under the conditions reported by Chen *et. al.*<sup>19</sup> did not yield an appreciable amount of the desired product. Instead, 3-(pyridin-2-yl)imidazo[1,5-a]pyridine **5.56** was isolated in high yield (78%). This result is consistent with work by Singh *et. al.*,<sup>26</sup> who achieved similar results using ammonium acetate and 2-formylpyridine **5.27**, albeit in the absence of acetone-1,3-dicarboxylic acid **5.28** and using a different solvent (**Fig 5.11**). Our conditions allow for similar yields as the work by Singh,<sup>26</sup> at a lower temperature and shorter reaction time.

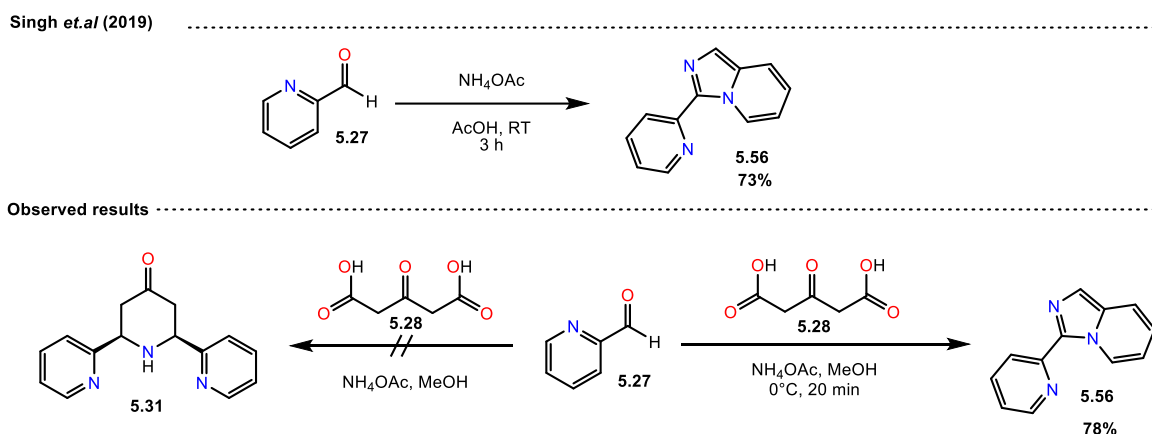


**Fig 5.11:** Previous synthesis of 3-(pyridin-2-yl)imidazo[1,5-a]pyridine **5.56** by Singh *et.al.*<sup>26</sup> and our serendipitous synthesis of the same compound.

We propose a mechanism toward the synthesis of 3-(pyridin-2-yl)imidazo[1,5-a]pyridine **5.56** from two equivalents of 2-formyl pyridine **5.27** and ammonium acetate in **Fig 5.12**. Protonation of 2-formyl pyridine (**5.27**→**5.57**) would allow it to condense with ammonia to form the imine (**5.57**→**5.58**→**5.59**→**5.60**→**5.61**). The imine **5.61** then adds to the protonated aldehyde **5.57** to form an hemiaminal **5.62**. The hemiaminal ether undergoes a proton transfer resulting in the elimination of water (**5.63**→**5.64**) to generate an aza-allenium intermediate **5.64**. The molecule then undergoes an intramolecular addition forming a pyridinium intermediate **5.65**, which is deprotonated to form the desired product **5.56**.

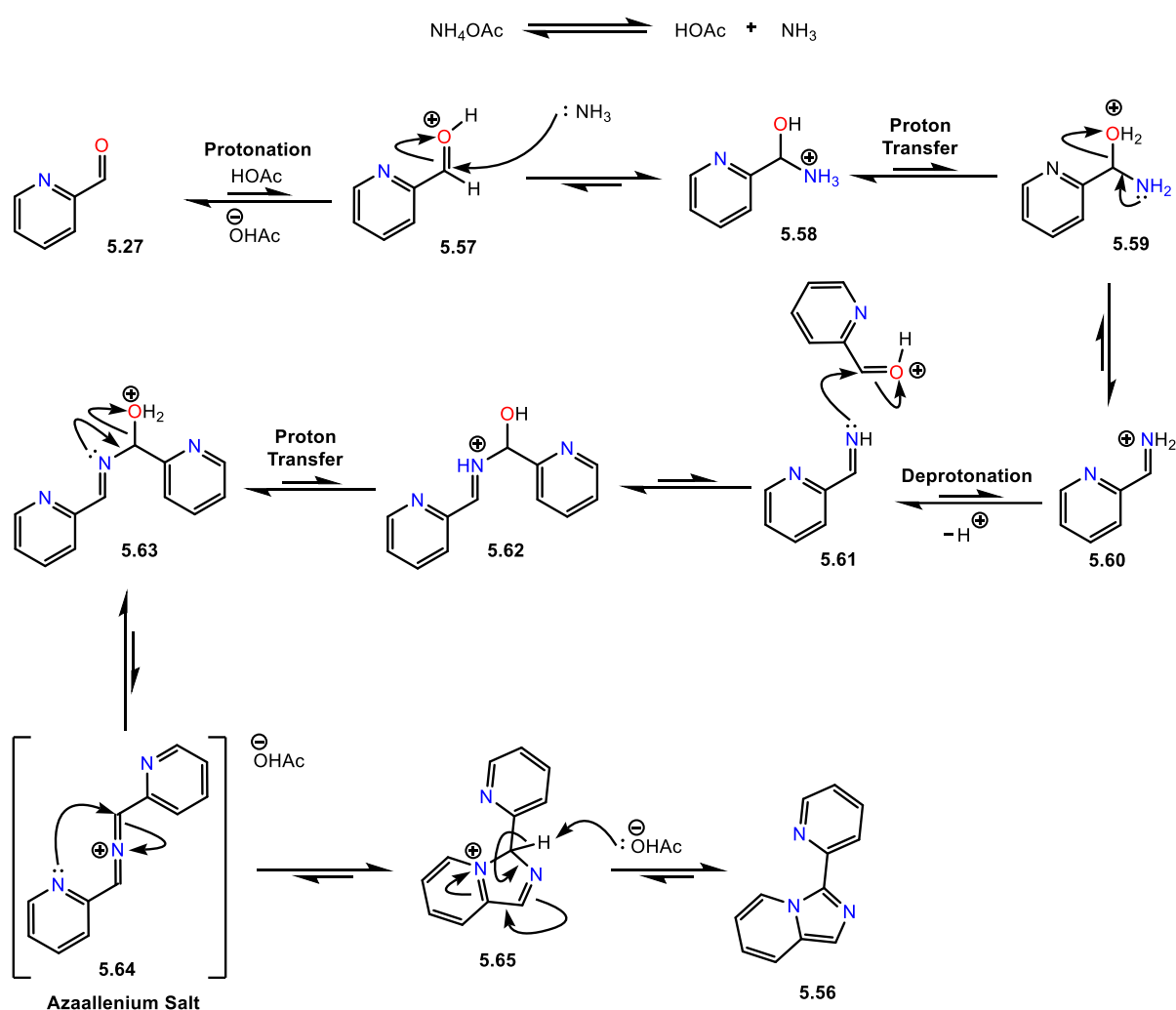


**Fig 5.12:** Proposed mechanism for the formation of 3-(pyridin-2-yl)imidazo[1,5-a]pyridine **5.56**.

The formation of 3-(pyridin-2-yl)imidazo[1,5-a]pyridine **5.56** demonstrates that a different synthetic procedure from that reported by Chen is needed to prepare *cis*-piperidone **5.31**

(and/or its *trans*-isomer **5.29**). As shown in **fig 5.13**, we decided upon a double aldol condensation to establish the carbon backbone **5.47**, followed with a double aza-Michael reaction to produce the piperidone **5.31**, **5.29**. We reasoned that establishing the carbon backbone (**5.27**→**5.47**) before the introduction of the amine eliminate the competing side reaction forming 3-(pyridin-2-yl)imidazo[1,5-a]pyridine **5.56**.

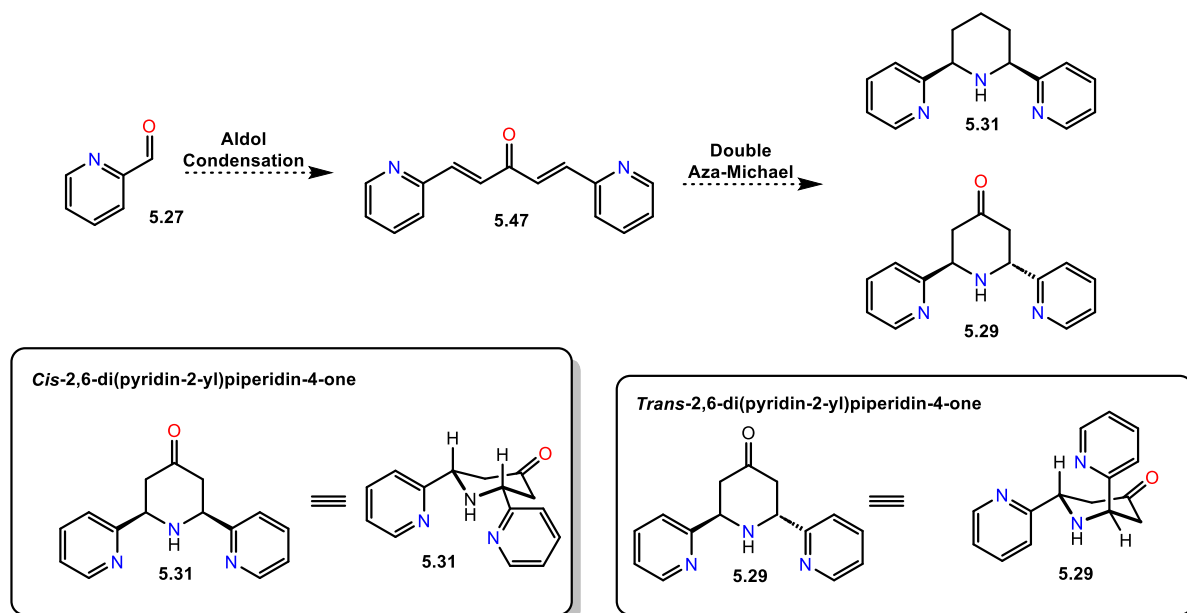
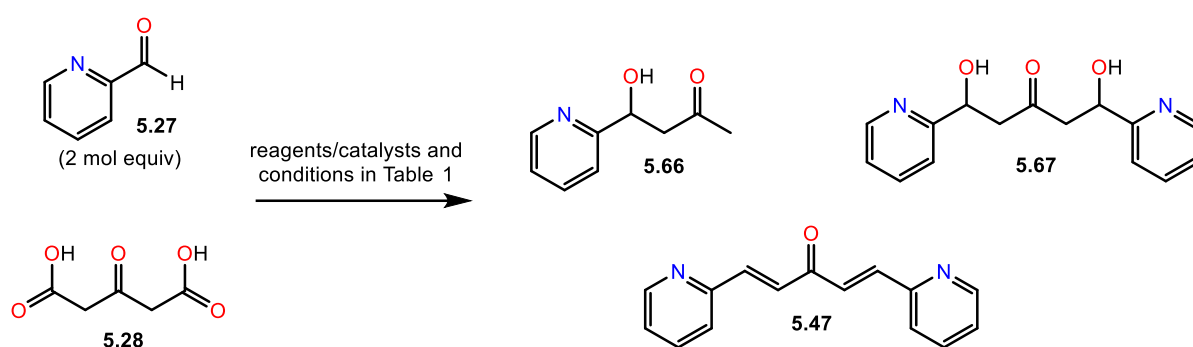


**Fig 5.13:** A revised synthetic pathway towards *cis* and *trans* 2,6-di(pyridin-2-yl)piperidin-4-one **5.31**, **5.29**.

Various conditions for the synthesis of (1*E*,4*E*)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one **5.47** were explored (Table 5.1). Although, double aldol condensation product **5.47** was desired, aldol addition products **5.66** and **5.67** were formed in higher quantities, so a 2 step approach involving double aldol addition then double dehydration was developed are possible. Entries 1-4 using various acid catalysts gave no products. No CO<sub>2</sub> evolution was observed in these runs, which suggests issues with the decarboxylation of 1,3-acetonedicarboxylic acid **5.24** under acidic conditions. Previous work by Wiig,<sup>27</sup> are consistent with these findings. Basic conditions (entries 7 and 8) give mainly aldol products **5.66** and **5.67**, with optimal results for the double aldol addition product **5.67** using NEt<sub>3</sub> in an aprotic solvent CH<sub>2</sub>Cl<sub>2</sub>. Replacing 1,3-acetonedicarboxylic acid **5.28** with acetone gave inferior results under acidic and basic conditions (entries 5 and 6)



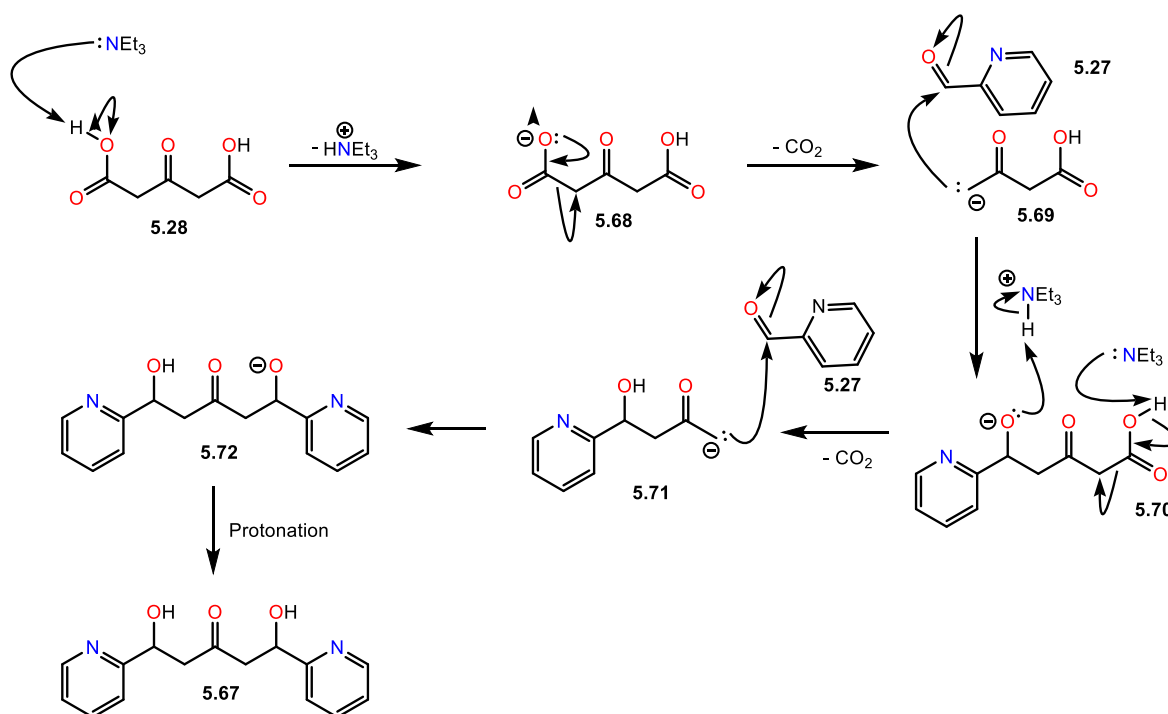
| Entry | Reagents and conditions <sup>a</sup>                                                                                                   | Yield <sup>b</sup> <b>5.27</b> : |
|-------|----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
|       |                                                                                                                                        | <b>5.66</b> : <b>5.67</b> :      |
|       |                                                                                                                                        | <b>5.47</b> (%)                  |
| 1     | AcOH (5 mol%), MeOH, rt, 3 h                                                                                                           | 186:0:0:0                        |
| 2     | AcOH (5 mol%), MeOH, reflux, 3 h                                                                                                       | 180:0:0:0                        |
| 3     | TsOH (5 mol%), MeOH, reflux, 3 h                                                                                                       | 175:0:0:0                        |
| 4     | 10-CSA (5 mol%), MeOH, reflux, 3 h                                                                                                     | 177:0:0:0                        |
| 5     | Acetone, <sup>c</sup> AcOH (5 mol%), MeOH, reflux, 2 h                                                                                 | 36:0:0:0                         |
| 6     | Acetone, <sup>c</sup> K <sub>2</sub> CO <sub>3</sub> (1.0 mol. equiv.), EtOH-PhMe-H <sub>2</sub> O (10:4:1), reflux, 12 h <sup>d</sup> | 6:24:12:21                       |
| 7     | NaOH (2.0 mol. equiv.), MeOH, rt, 3 h                                                                                                  | 88:68:0:0 <sup>e</sup>           |
| 8     | Et <sub>3</sub> N (2.0 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , rt, 3 h                                                         | 0:8:73:0 <sup>e</sup>            |

**Table 5.1:** Developing conditions for the aldol addition/condensation of 2-formylpyridine **5.27** with 1,3-acetonedicarboxylic acid **5.28**. <sup>a</sup>Procedure: To a mixture of 2-formylpyridine **5.27** and the listed reagents is added 1,3 acetonedicarboxylic acid. The reaction is stirred for the reported time at the reported temperature. <sup>b</sup>Isolated percentage yields of products **5.66**, **5.67** and **5.47** and recovered aldehyde **5.27** obtained after flash chromatographic separation. Yields based upon **5.28** as limiting reactant. <sup>c</sup>Acetone (1.0 mol. equiv.) used in place of **5.28** <sup>d</sup>Literature conditions by Samaan *et. al.*<sup>28</sup> <sup>e</sup>Vigorous gas evolution observed upon addition of **5.28**.

The 1,3-acetonedicarboxylic acid **5.28** serves as an active chemical equivalent to acetone allowing us to generate the enolate under mild conditions (**Fig 5.14**). The reaction begins with the deprotonation of 1,3-acetonedicarboxylic acid (**5.28**→**5.68**) which leads to its irreversible decarboxylation into the enolate **5.69** which adds to 2-formyl pyridine **5.27** to generate the alkoxide **5.70**. The alkoxide **5.70** undergoes a proton transfer, triggering a

second decarboxylation to generate the enolate **5.71** which adds into another unit of 2 formylpyridine to generate the alkoxide **5.72** which traps a proton to generate the product **5.67**. The intermediates **5.69** and **5.71** can trap a proton forming the undesirable side product **5.64**.

Mechanism for the formation of diol **5.67** .....



Formation of side product .....

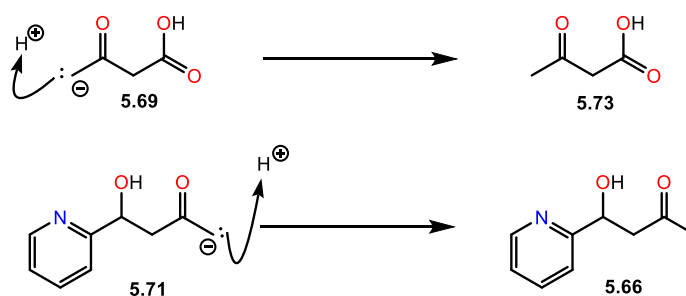
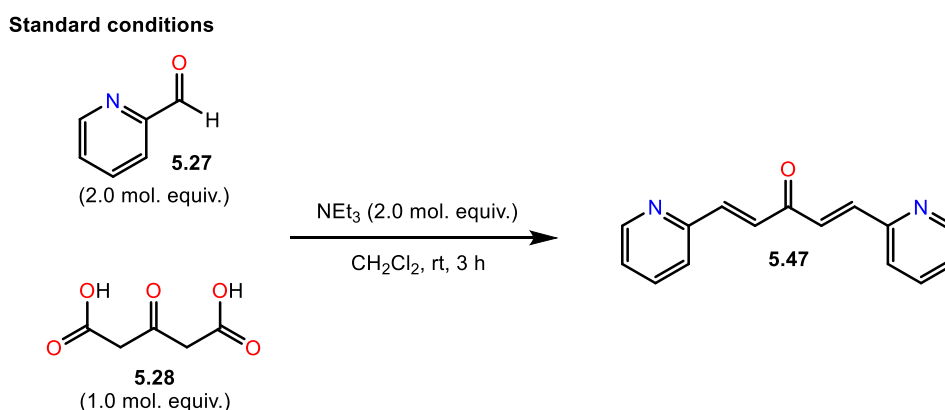


**Fig 5.14:** Mechanism of formation of double aldol addition product **5.67**.

The isolation of the proton-trapped mono-adduct **5.66** demonstrates the incompatibility of 1,3 acetone-dicarboxylic acid **5.28** with protic solvents. The high concentration of labile protons present in a protic solvent is irreversibly trapping the enolate resulting in the generation of monoadducts **5.66**. Thus, we surmised that 1,3-acetone-dicarboxylic acid **5.28** should be deployed along with an aprotic solvent and a mild base for optimal effect. We decided that further experimentation upon the methylene chloride,

triethylamine system is necessary to optimize the reaction before upscaling. Current literature yields for the synthesis of 1,5-dihydroxy-1,5-di(pyridin-2-yl)pentan-3-one **5.57** are low. (42% highest yield found on sci-finder)<sup>29</sup> Thus, an improved synthesis was developed, as shown in **Table 5.2**.



| Entry | Deviations from initial conditions <sup>a</sup>                                              | Yield <sup>b</sup> <b>5.66</b> (%) |
|-------|----------------------------------------------------------------------------------------------|------------------------------------|
| 1     | Initial conditions                                                                           | 73                                 |
| 2     | MgSO <sub>4</sub> added as desiccant                                                         | 75                                 |
| 3     | Molecular sieves 3Å as desiccant                                                             | 76                                 |
| 4     | 2.2 mol. equiv. of <b>5.27</b>                                                               | 69                                 |
| 5     | 1.1 mol. equiv. of <b>5.28</b>                                                               | 65                                 |
| 6     | Dropwise addition of <b>5.27</b> over 1 h                                                    | 6                                  |
| 7     | Portionwise addition of <b>5.28</b> over 1 h <sup>c</sup>                                    | 85                                 |
| 8     | Portionwise addition of <b>5.28</b> over 1 h <sup>c</sup> , NEt <sub>3</sub> (3 mol. equiv.) | 88                                 |

**Table 5.2:** Optimization of the double aldol reaction. <sup>a</sup> Procedure: To a solution of 2-formylpyridine **5.27** in methylene chloride under an N<sub>2</sub> atmosphere, was added NEt<sub>3</sub> (and desiccant for entries 2 and 3), followed by 1,3-acetone dicarboxylic acid **5.28**. The reaction was stirred for 3 hours at room temperature. <sup>b</sup> Isolated percentage yields of product **5.66**. Yields based upon **5.28** as limiting reactant. <sup>c</sup> Sample split into 8 portions for portion-wise addition.

Several methods were attempted to improve upon our initial conditions (**Table 5.2**), including the inclusion of desiccants, altering the reagent concentrations, and slow addition of reagents. The use of desiccants and using an excess of 2-formylpyridine **5.27** resulted in a similar yield as the initial conditions. Using an excess of 1,3-acetonedicarboxylic acid **5.28** and dropwise addition of 2-formylpyridine **5.27** resulted in a reduction of reaction yield. The

portionwise addition of the 1,3-acetonedicarboxylic acid **5.28** allowed us to improve the overall yield of the process. This is attributed to the lower transient concentration of 1,3-acetonedicarboxylic acid **5.28** and therefore the enolates **5.69** and **5.71**, which in turn can be protonated by the 1,3-acetonedicarboxylic acid **5.28** present. Thus, portionwise addition allows us to lower the transient concentration of the carboxylic acid **5.28** favouring the production of the desired product.

It is also noted that changes in supplier and batch number of the 1,3-acetonedicarboxylic acid **5.28** result in fluctuations in the overall yields obtained. Since impure samples of 1,3-acetonedicarboxylic acid **5.28** is prone to decomposition when stored at elevated temperature, older batches of 1,3-acetonedicarboxylic acid **5.28** gave a reduced yield. It was found that the reproducibility can be increased by freshly synthesized samples of 1,3-acetonedicarboxylic acid **5.28** by the decarboxylation of citric acid. Using the optimised conditions, we executed the double aldol addition reaction using freshly prepared 1,3-acetonedicarboxylic acid **5.28** on 80 gram scale (**Fig 5.15**).

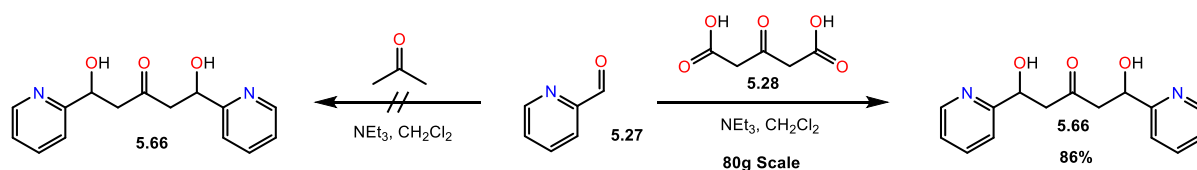
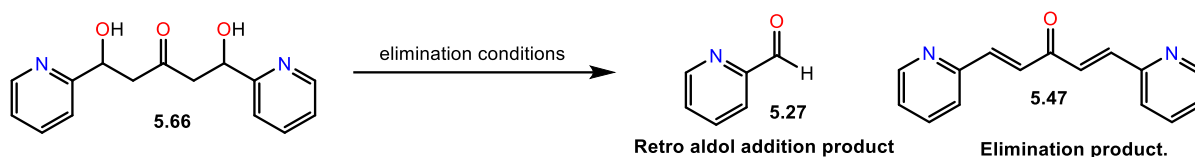


**Fig 5.15:** Generation of 1,3-acetonedicarboxylic acid and 1,5-dihydroxy-1,5-di(pyridin-2-yl)pentan-3-one **5.66**.

The purification conditions translate well onto large-scale chromatography techniques such as dry column vacuum chromatography (DCVC).<sup>30</sup> Given the success of the initial aldol addition, we proceeded to generate the Michael acceptor **5.47** via a 2-fold elimination (**Table 5.3**).



| Entry | Reagents and conditions <sup>a</sup>                                                                              | Yield 5.66 : 5.27:<br>5.47 (%) <sup>b</sup> |
|-------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| 1     | NEt <sub>3</sub> (5 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , rt, 20 h                                      | 96 : 0 : 0                                  |
| 2     | NEt <sub>3</sub> (5 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , reflux, 20 h                                  | 95: 0 : 0                                   |
| 3     | 10-CSA (5 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , rt, 8 h                                                 | 97: 0 : 0                                   |
| 4     | 36% HCl <sub>aq</sub> (5 mol. equiv.), MeOH, reflux                                                               | 0: 194 : 0                                  |
| 5     | NaOH (5 mol. equiv.), MeOH rt, 3 h                                                                                | 61 : 66 : 0                                 |
| 6     | NaOH (5 mol. equiv.), MeOH, reflux, 3 h                                                                           | 0 : 177 : 0                                 |
| 7     | DBU (5 mol. equiv.), MeOH, rt, 3 h                                                                                | 43: 87 : 0                                  |
| 8     | SOCl <sub>2</sub> (2.2 mol. equiv.), NEt <sub>3</sub> (20 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , rt, 1 h | 0 : 0 : 0 <sup>c</sup>                      |
| 9     | POCl <sub>3</sub> (2.2 mol. equiv.), NEt <sub>3</sub> (20 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , rt, 1 h | 0 : 0 : 0 <sup>c</sup>                      |
| 10    | AcCl (2.2 mol. equiv.), NEt <sub>3</sub> , (20 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , rt, 3 h            | 0 : 0 : 65                                  |
| 11    | TsCl (2.2 mol. equiv.), NEt <sub>3</sub> , (20 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , rt, 3 h            | 0 : 0 : 63                                  |

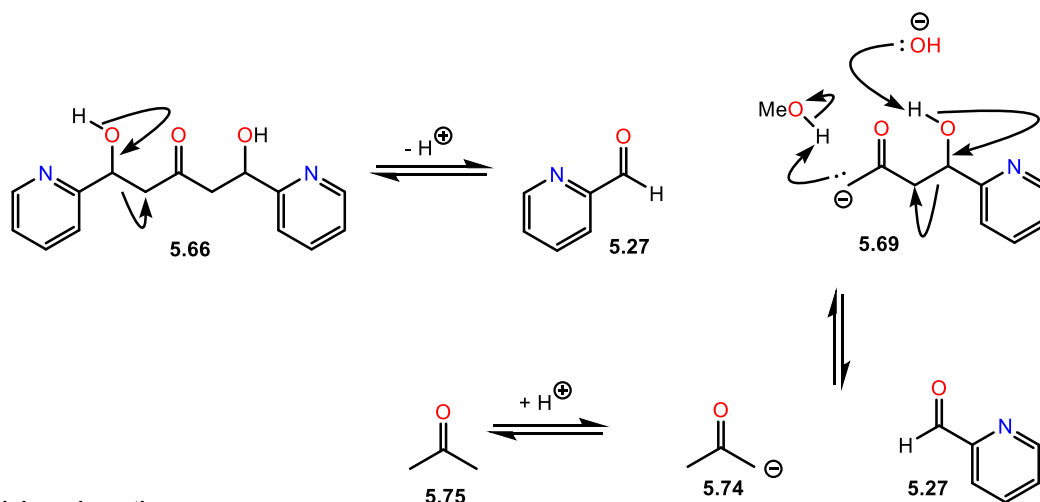
**Table 5.3:** Reaction screening for the double dehydration of 1,5-dihydroxy-1,5-di(pyridin-2-yl) pentan-3-one **5.66**. <sup>a</sup> Procedure: To a solution of 1,5-dihydroxy-1,5-di(pyridin-2-yl) pentan-3-one **5.66** dissolved in (solvent in conditions) under a N<sub>2</sub> atmosphere. Reagents (listed above) were added and the reaction is stirred for the time listed. <sup>b</sup> Isolated percentage yields of products **5.47**, recovered aldehyde **5.27** recovered starting material **5.66** obtained after flash chromatographic separation. Yields based upon **5.66** as limiting reactant. <sup>c</sup> decomposed starting material.

We initially attempted to develop compatible reaction conditions (**table 5.3**), for elimination that would allow a one-pot aldol addition–elimination reaction sequence. The elimination the diol **5.66** failed in methylene chloride under both acidic and basic conditions. Thus, we switched the reaction to methanol hoping the protic polar solvent would accelerate the elimination reaction via hydrogen bonding. Sadly, these conditions resulted in the retro–aldol reaction instead. We thought generating a better-leaving group will improve the likelihood of elimination. Initially, we tried to use either thionyl chloride or phosphoryl chloride to generate the chloro derivative in situ before elimination. However,

both proved too aggressive and the starting material **5.66** decomposed. Milder reagents such as tosyl and acetyl chloride allowed us to successfully produce our product **5.47** in modest yield. Both reagents result in comparable yields for the generation of the desired product **5.47** (entries 10, 11). We decided acetyl chloride is the superior reagent for generation of the leaving group, due to its low cost and superior atom economy compared to the tosyl derivative. However, further optimisation of the reaction conditions is necessary to improve overall yield.

The facile retro-aldol reaction seen in the elimination reaction mirrors the problems encountered during optimisation of the aldol addition. The aldol addition product **5.66** can eliminate in two separate directions (**Fig 5.16**), either as a retro-aldol regenerating 2-formylpyridine **5.27** and the corresponding enolate **5.69** or generating the aldol condensation product **5.76**, which undergoes a second elimination to produce our desired product **5.47**.

### Retro-aldol reaction



### Aldol condensation

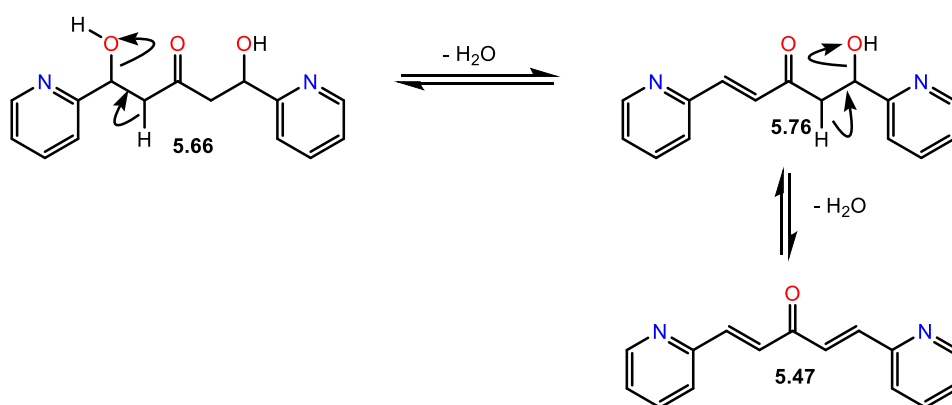
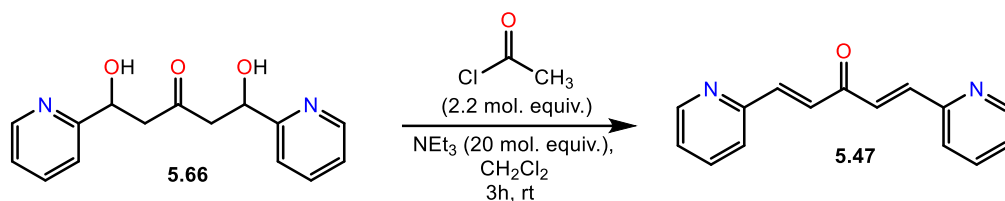


**Fig 5.16:** Competing retro-aldol reaction and dehydration.

Both reactions are favoured in dilute solution where the unimolecular reaction is allowed to dominate over the bimolecular reverse reaction. Thus, the creation of a superior leaving group out of the alcohol is the prudent option to direct the elimination of 1,5-dihydroxy-1,5-di(pyridin-2-yl)pentan-3-one **5.66** to give our desired product **5.47**. Next, we aimed to improve the yield of the elimination process (**Table 5.4**).



| Entry | Deviations from initial conditions <sup>a</sup>        | Yield 5.47 (%) <sup>b</sup> |
|-------|--------------------------------------------------------|-----------------------------|
| 1     | Initial conditions                                     | 65                          |
| 2     | 1 h reaction time                                      | 42                          |
| 3     | 15 h reaction time                                     | 82                          |
| 4     | Dropwise addition of acetyl chloride (2.2 mol. equiv.) | 67                          |
| 5     | acetyl chloride (3.0 mol. equiv.)                      | 83                          |
| 6     | acetyl chloride (3.0 mol. equiv.), 15 h                | 96                          |
| 7     | acetyl chloride (3.0 mol. equiv.), reflux, 3 h         | 94                          |

**Table 5.4:** Optimization of the dehydration.<sup>a</sup> Procedure: To a solution of **5.66** in methylene chloride under an N<sub>2</sub> atmosphere, was added NEt<sub>3</sub>, followed by acetyl chloride. <sup>b</sup>Isolated percentage yields of product **5.47**. Yields based upon **5.66** as limiting reactant.

Initially, we extended the reaction time to find that the elimination reaction using a slight excess of acetyl chloride slowed down after the first 3 hours, which we ascribed to the presence of acetic anhydride in our acetyl chloride. Acetic anhydride is a weaker acetylation reagent generated from the hydrolysis of acetyl chloride. This will result in the slowing of the overall reaction rate. Thus, to compensate for the slowing rate of conversion an excess of acetyl chloride was added to push the reaction forward. The reaction was then tested for its scalability to 50 grams, which was smoothly converted into the desired product at high yields. It is noted that both the optimized double aldol additions and elimination use the same solvent and base. Thus, we attempted to combine the reactions for a more efficient synthesis of (1*E*,4*E*)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one **5.47** (Fig 5.17).

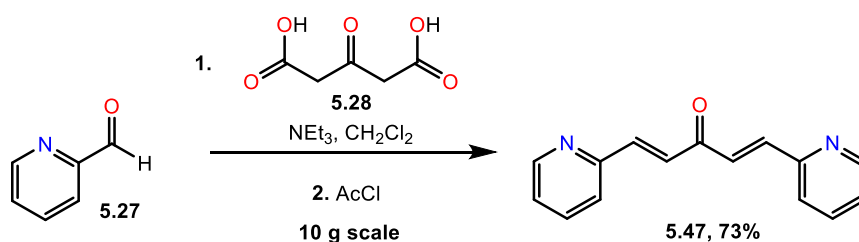


**Fig 5.17:** One pot two step reaction for (1*E*,4*E*)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one **5.47**.

We successfully executed the two reactions in one pot. Sadly, the overall yield of the combined process is lower than that of its constituent steps. This could be due to interference from increased amounts of triethylamine or its protonated salts in the reaction flask. Furthermore, the combined reactions proved to be more difficult to purify. Thus, we opted to separate the individual steps and isolate the intermediate 1,5-dihydroxy-1,5-di(pyridin-2-yl)pentan-3-one **5.55**. We then shifted our focus onto forming the piper-4-one (Fig 5.18).

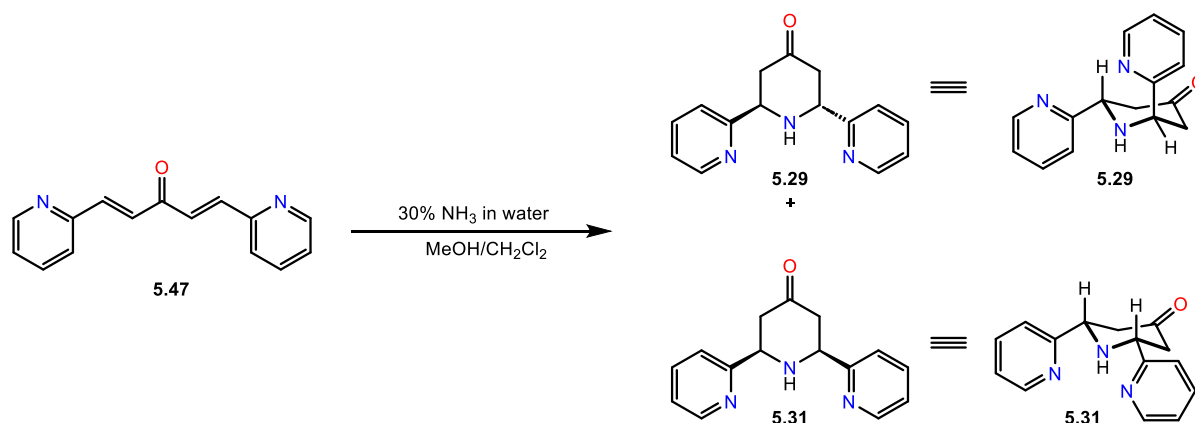


**Fig 5.18:** Double aza Michael addition of ammonia to (1*E*,4*E*)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one **5.47**.

We adapted the conditions examined by Magann *et. al.* for the synthesis of lythranidine (Fig 5.19).<sup>31</sup> Both the *cis* and *trans* products **5.31**, **5.29** can be converted into interesting ligands for ATRP. However, a robust methodology needs to be developed for the separation of the two diastereomers. Since using a protected amine would necessitate subsequent reactions for deprotection, which will add steps to the overall length of the synthesis, we decided to start with aqueous ammonia as our initial amine source.

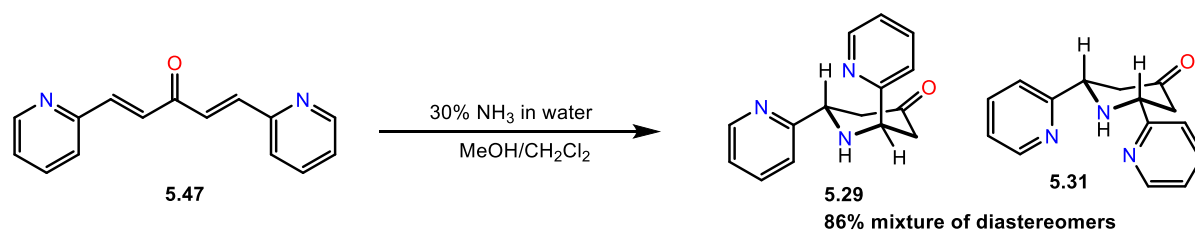
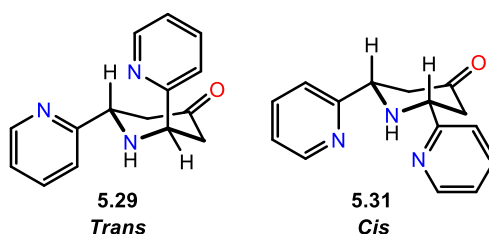


**Fig 5.19:** Double aza Michael addition of ammonia with (1*E*,4*E*)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one **5.47**.

Our attempt was successful using 30% ammonia in water as the amine source. Contrary to the methodology of Chen and Loftus, a mixture *cis* and *trans* 2,6-di(pyridin-2-

yl)piperidin-4-one **5.31**, **5.29** was synthesized from (1*E*,4*E*)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one **5.47** via the double aza-Michael transform in high yields (86%). A mixture of diastereomeric piperidones was isolated, with a *cis*: *trans* ratio of 1:2 identified via <sup>1</sup>H NMR spectroscopy. The presence of both diastereomers of the piperidone sets the stage for us to access all of the ligand architectures (**Fig 5.6**)(**5.21-5.25**) DFT calculations show the quinuclidine ligand synthesized from *cis* 2,6-di(pyridin-2-yl)piperidin-4-one **5.31** should be more active due to a more exposed active site.<sup>13</sup> The *trans* isomer **5.29** remains synthetically interesting since these ligands are not restricted to the synthesis of polymers. Applying a chiral catalyst to a small molecule transformation such as the previously mentioned (**Chapter 3**) C-N cross-coupling chemistry would allow the development of an enantioselective variant of the chemistry.



| Entry     | Conditions                                                                  | % isolated ( <b>5.29</b> : mixture:<br><b>5.31</b> ) |
|-----------|-----------------------------------------------------------------------------|------------------------------------------------------|
| <b>1</b>  | Reverse phase, (TFA(1%), MeCN H <sub>2</sub> O(10%))                        | 0:98:0                                               |
| <b>2</b>  | Reverse phase, (MeCN)                                                       | 0:98:0                                               |
| <b>3</b>  | SiO <sub>2</sub> , (EtOAc, MeOH) (9:1)                                      | 0:87:0                                               |
| <b>4</b>  | Al <sub>2</sub> O <sub>3</sub> , (EtOAc, MeOH) (9:1)                        | 0:96:0                                               |
| <b>5</b>  | Al <sub>2</sub> O <sub>3</sub> , (EtOAc, NEt <sub>3</sub> ) (9:1)           | 0:95:0                                               |
| <b>6</b>  | Al <sub>2</sub> O <sub>3</sub> , (EtOAc)                                    | 0:98:0                                               |
| <b>7</b>  | SiO <sub>2</sub> , (EtOAc, NEt <sub>3</sub> (2%))                           | 8:84:3                                               |
| <b>8</b>  | SiO <sub>2</sub> washed with NEt <sub>3</sub> , (EtOAc)                     | 10:82:5                                              |
| <b>9</b>  | buffered SiO <sub>2</sub> Merck (pH = 7.0), (EtOAc)                         | 42:35:22                                             |
| <b>10</b> | SiO <sub>2</sub> Merck (pH = 7.0), (EtOAc)                                  | 59:5:32                                              |
| <b>11</b> | buffered SiO <sub>2</sub> Chemsupply (pH = 6.8 after buffering),<br>(EtOAc) | 41:36:21                                             |
| <b>12</b> | SiO <sub>2</sub> Chemsupply (pH = 4.3), (EtOAc)                             | 0:65:0 <sup>a</sup>                                  |

**Table 5.5:** Separation attempts with **5.29** and **5.31** under different chromatography conditions. <sup>a</sup>. Total recovered after flushing with 20% MeOH in EtOAc.

Unfortunately, reverse-phase chromatography failed to separate the diastereomers. (Table 5.5) We then tried several stationary phases used for chromatography. Buffered silica and silica eluted with ethyl acetate provide the best conditions for isolation. It is also noted that changing brands of silica affected the resulting separation, a problem that is solved by buffering. It is suspected the acidity of the silica leads to the protonation of the *cis* and *trans*-2,6-di (pyridin-2-yl)piperidin-4-one **5.31**, **5.29**, resulting in its high affinity to the silica surface.

After we successfully isolated both the *cis* and *trans*-2,6-di (pyridin-2-yl)piperidin-4-one **5.31**, **5.29**, synthesizing the hemiaminal ether **5.22** was our first synthetic target. We envisioned a 5 step pathway towards its synthesis (Fig 5.20).

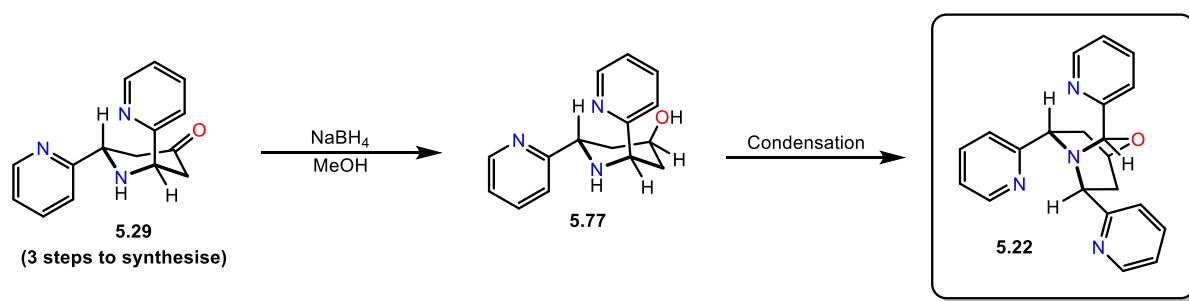


**Fig 5.20:** Synthetic approach to the synthesis of the hemiaminal ether product **5.22**.

Thus, the *trans* piperidone **5.29** would be reduced to form *trans* 2,6-di(pyridin-2-yl)piperidin-4-ol **5.77**, followed by the condensation with 2-formylpyridine **5.27** to form the desired hemiaminal ether product **5.22**. We chose to reduce the *trans*-piperidone **5.29** to minimise the complexity of the product mixture from the reduction, since the *cis*-piperidone **5.31** reduction can give two products (Fig 5.21).

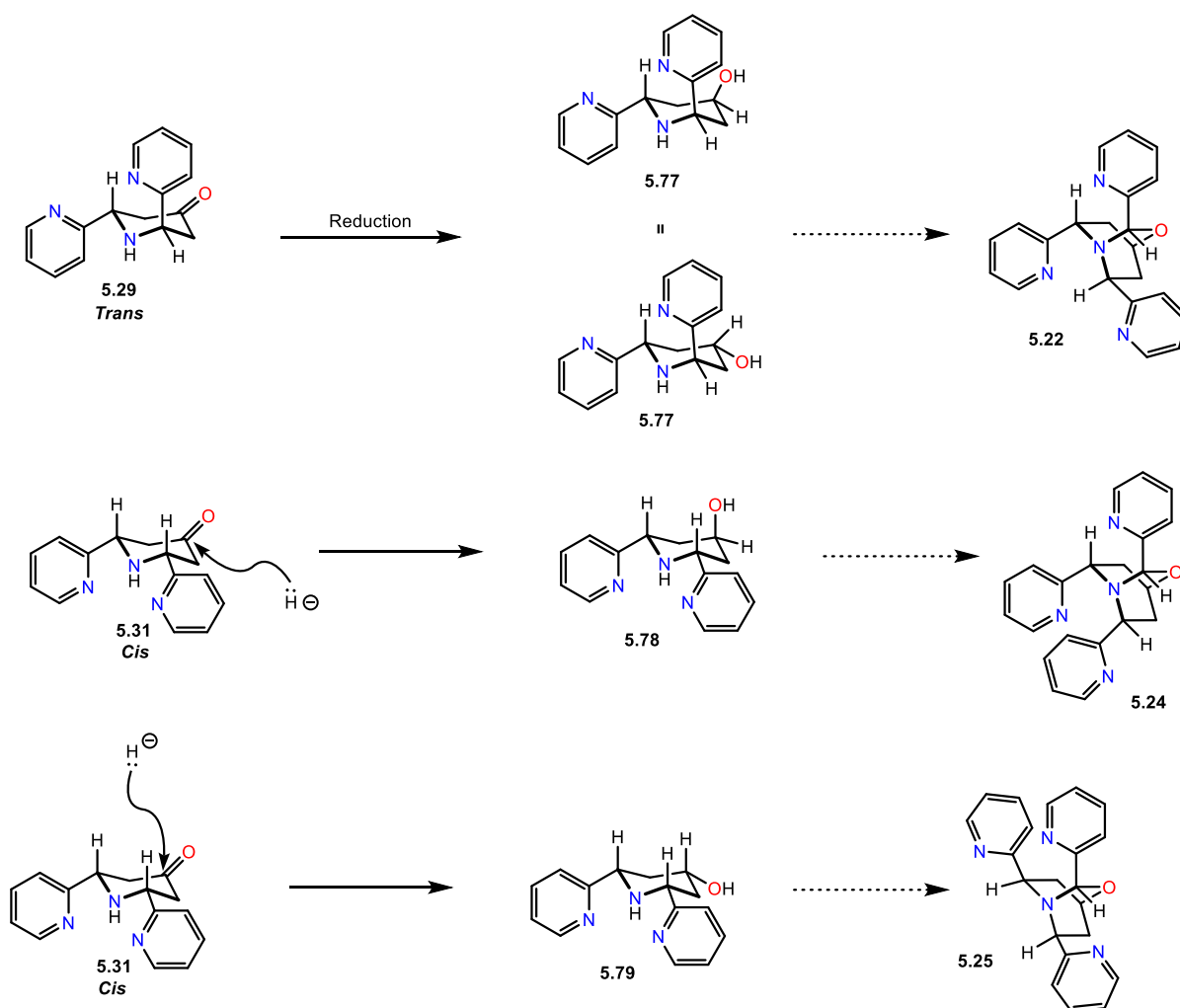
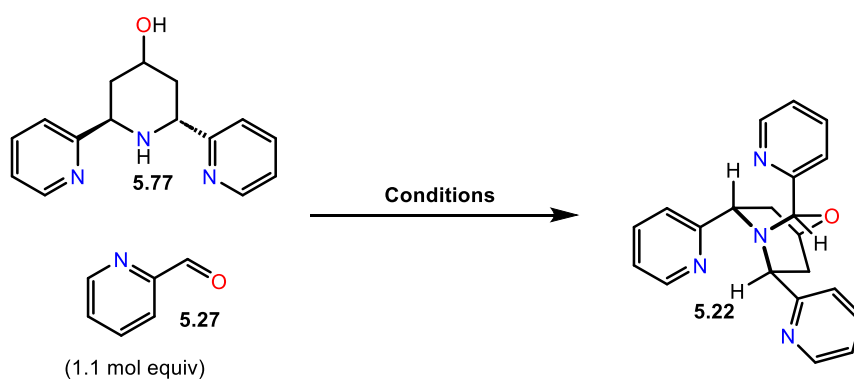


**Fig 5.21:** Potential isomers from reduction of both *cis* and *trans* 2,6-di(pyridin-2-yl)piperidin-4-one **5.31**, **5.29**.

The *cis* piperidone **5.31**, creates a pair of diastereomeric products **5.78** and **5.79** upon reduction where the alcohol formed can be either in the same face or the opposite face as the two pyridyl groups. Each of these diastereomeric outcomes results in an alternative diastereomer of the product ligand (**5.31**  $\rightarrow$  **5.78**  $\rightarrow$  **5.24**), (**5.31**  $\rightarrow$  **5.79**  $\rightarrow$  **5.25**). The diastereoselectivity of the reduction will be dictated by the steric bulk of the two pyridyl group favouring the formation of **5.79**. While the *trans* piperidone **5.29** produces the same product **5.78** regardless of which face of the ketone the hydride adds onto. The ketone reduction was executed using sodium borohydride. This reaction was rapid and efficient, and no isomerization was detected. Thus, we moved on to testing the subsequent hemiaminal ether condensation (Table 5.6).



| Reagents and conditions <sup>a</sup>                                                   | Yield 5.22 (%) <sup>b</sup> |
|----------------------------------------------------------------------------------------|-----------------------------|
| H <sub>2</sub> SO <sub>4</sub> (5 mol. equiv.), MeOH, 5 h                              | 0 <sup>c</sup>              |
| 10-CSA (5 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> , rt, 14 h                     | 0                           |
| 10-CSA (5 mol. equiv.), MgSO <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> , rt, 14 h | 0                           |
| 10-CSA (5 mol. equiv.), Toluene, Dean-Stark apparatus, reflux, 5 h                     | 0 <sup>c</sup>              |
| Ti(OEt) <sub>4</sub> , rt, 18 h                                                        | 0 <sup>d</sup>              |
| Ti(OEt) <sub>4</sub> , reflux, 5 h                                                     | 0 <sup>d</sup>              |

**Table 5.6:** Conditions for amination dehydration. <sup>a</sup> Procedure: To a solution of 2,6 dipyridyl-piperidin-4-ol **5.66** in (solvent listed) under an N<sub>2</sub> atmosphere, was added the reagent listed, followed by 2-formyl pyridine. <sup>b</sup> Isolated percentage yields of products **5.22** obtained after flash chromatographic separation. Yields based upon **5.66** as limiting reactant. <sup>c</sup> decomposition observed, unable to isolate decomposition product <sup>d</sup> decomposition observed, terpyridine **5.84** isolated from mixture.

The condensation between our piperidin-4-ol **5.77** and 2-formyl pyridine **5.27** (Table 5.6) was unsuccessful across a range of conditions. Decomposition of the starting material **5.77** was observed when refluxed in toluene with CSA or stirred in methanol with sulfuric acid. Unfortunately, attempts to isolate decomposition products proved fruitless. Stirring in CH<sub>2</sub>Cl<sub>2</sub> with 10-CSA with and without a desiccant (MgSO<sub>4</sub>) resulted in the recovery of the starting material **5.77**. We decided to attempt to force the reaction using a self-drying, oxophilic Lewis acid, titanium ethoxide. The *trans*-2,6-di(pyridin-2-yl)piperidin-4-ol **5.77** was completely consumed but terpyridine **5.84**, was isolated, instead of the desired bridged product **5.22**. The conversion of piperidin-4-ol **5.77** into terpyridine **5.84** likely occurs starting with the dehydration of the alcohol (Fig 5.22).

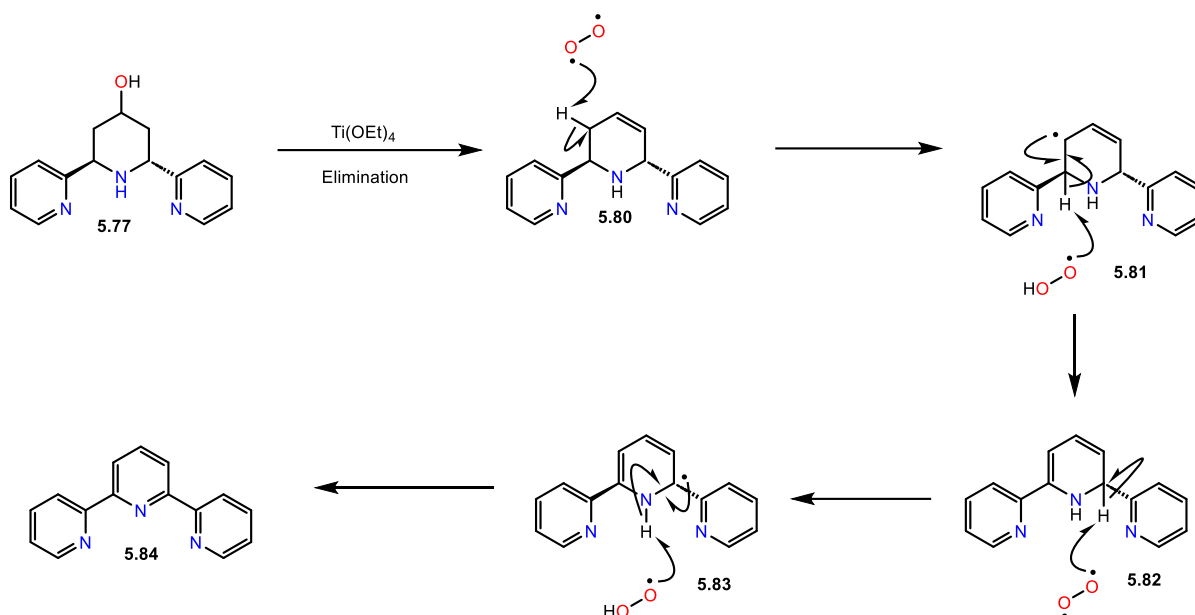


**Fig 5.22:** Plausible mechanism for the generation of terpyridine **5.84**.

The tetrahydro-terpyridine **5.80** could possibly be autoxidised (**5.80**  $\rightarrow$  **5.81**  $\rightarrow$  **5.82**  $\rightarrow$  **5.83**  $\rightarrow$  **5.84**) during the workup into terpyridine **5.84**. At this point, with time being short, we shifted our focus toward the synthesis of the quinuclidine backbone halting further synthetic efforts towards for the hemiaminal ether **5.22**. Using the previously synthesized *trans* piperidone **5.29**, we attempted to synthesize the quinuclidine ligand **5.21** using either an aldol addition or elimination to establish the carbon framework (**Fig 5.22**).

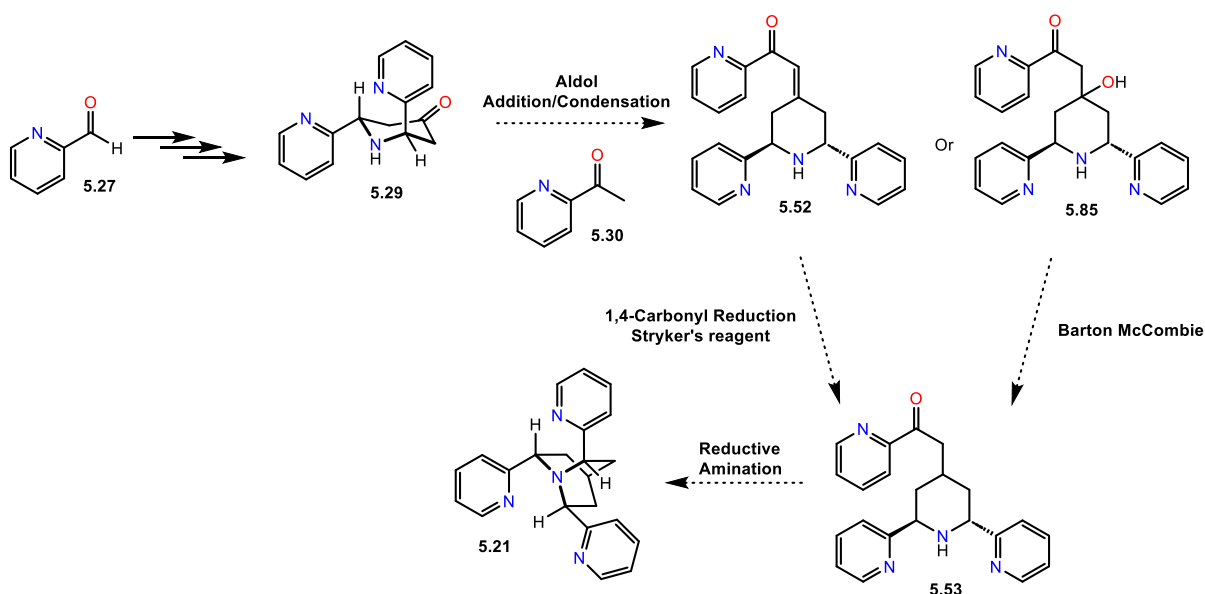
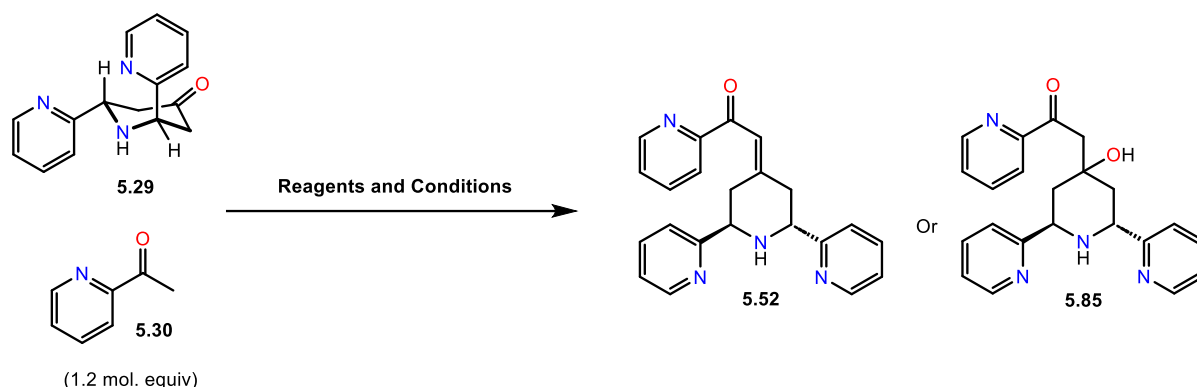


**Fig 5.23:** proposed synthetic pathway to the quinuclidine ligand target **5.21**, through *trans* 2,6-di(pyridin-2-yl)piperidin-4-one **5.29** using an aldol reaction as the final key C-C forming step.

Several strategies were devised towards the quinuclidine ligand. Our first plan was to complete the installation of the carbon backbone via either an aldol addition or condensation (**Fig 5.23**) depending on the most successful result while screening. Both addition **5.85** and condensation **5.52** products can be converted into *trans* 2,6-di(pyridin-2-yl)piperidin-4-yl)-1-(pyridin-2-yl)ethan-1-one **5.53** which can be cyclized to form our desired quinuclidine **5.21** via reductive amination



| Entry | Reagents and conditions <sup>a</sup>                                   | <b>5.29</b> : <b>5.52</b> : <b>5.85</b> % isolated <sup>b</sup> |
|-------|------------------------------------------------------------------------|-----------------------------------------------------------------|
| 1     | 36% HCl <sub>(aq)</sub> (10 mol. equiv.), MeOH, rt, 6 h                | 86:0:0                                                          |
| 2     | BF <sub>3</sub> etherate (2.5 mol. equiv.), Et <sub>2</sub> O, rt, 6 h | 83:0:0                                                          |
| 3     | NaOH (1.5 mol. equiv.), MeOH, rt, 6 h                                  | 88:0:0                                                          |
| 4     | NaOH (1.5 mol. equiv.), MeOH, reflux, 6 h                              | 58:0:0                                                          |
| 5     | LDA (1.1 mol. equiv.), THF, -78°C, 5 h                                 | 42:0:0                                                          |
| 6     | LiTMP (1.1 mol. equiv.), THF, -78°C, 5 h                               | 35:0:0                                                          |

**Table 5.7:** Aldol reaction between 2-acetylpyridine **5.30** and *trans* 2,6-di(pyridin-2-yl)piperidin-4-one **5.29**.<sup>a</sup> Procedure: To a solution of 2-acetylpyridine **5.30** in solvent under an N<sub>2</sub> atmosphere (**For entries 5,6:** chill in an acetone, dry ice bath.), was added reagents (listed in table) followed by the 2,6 dipiperidone **5.25** (**For entries 5,6:** reaction allowed to stir for 10 min prior to addition of piperidone.). <sup>b</sup> Isolated percentage yields of products **5.52** and **5.85** and recovered piperidone **5.27** obtained after flash chromatographic separation. Yields based upon **5.27** as limiting reactant.

No reaction was observed under general brønsted acid, Lewis acid, and base catalysis (**Table 5.7**). Consumption of starting materials was observed upon heating in the presence of sodium hydroxide, but we were unable to isolate either of our desired products **5.85**, **5.52**. We hypothesized this is due to the unselective deprotonation of alpha protons associated with both 2-acetylpyridine **5.30**, and *trans*-piperidone **5.29**. Thus, we decided to

use a stronger base to irreversibly deprotonate the 2-acetyl-pyridine **5.30** to generate the desired enolate before adding it to the *trans*-piperidone **5.30**. Unfortunately, a mixture of both acetylpyridine **5.30** and the *trans*-piperidone **5.29** was consumed and no product was isolated from the complex mixture. Given the problems encountered, we envisaged an alternative route to synthesize the enone **5.52** via the Wittig reaction (**Fig 5.24**).

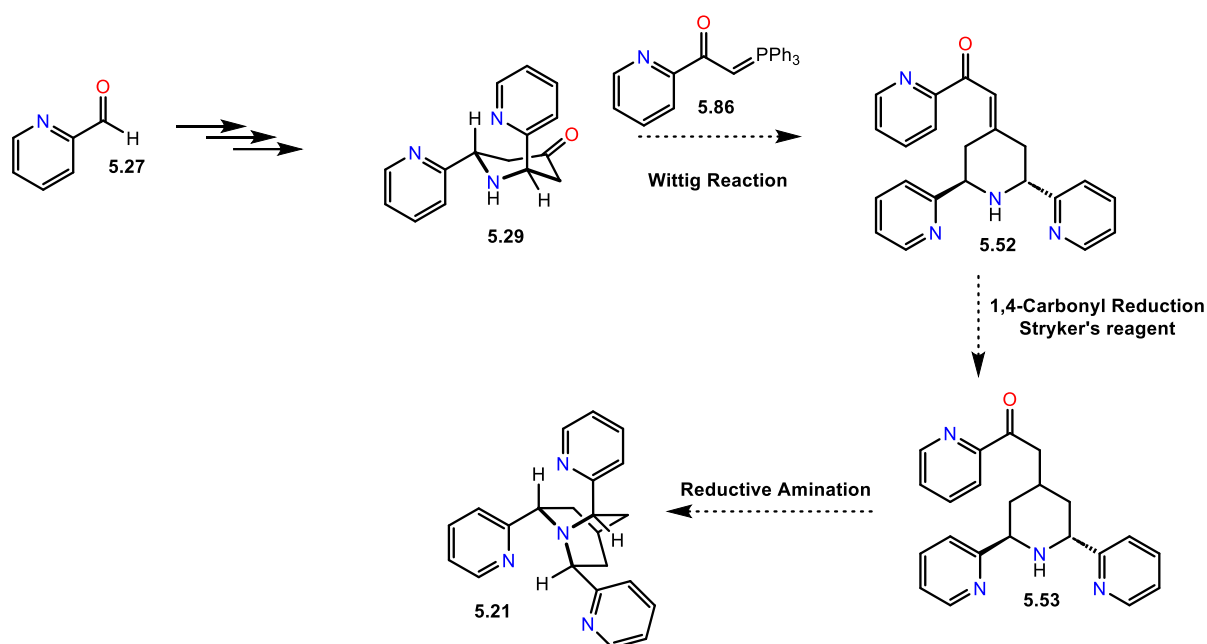
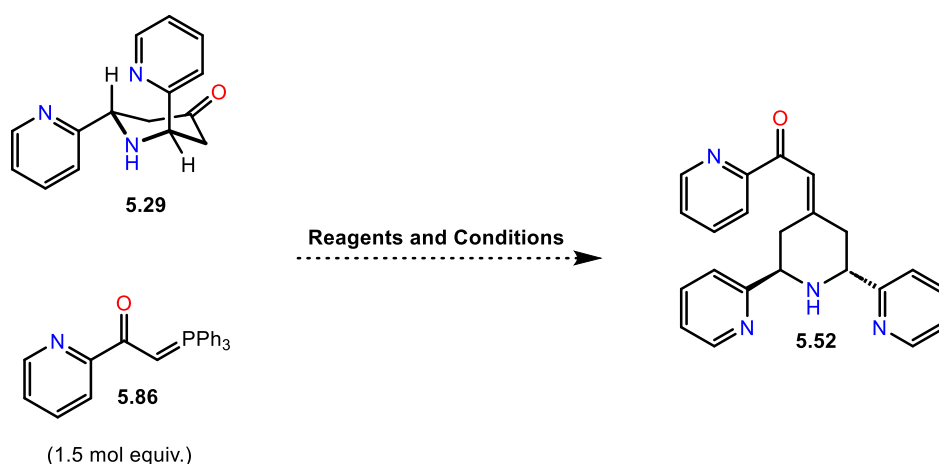


**Fig 5.24:** Revisiting the total synthesis using a Wittig key step.

Thus, our piperidone **5.29** would be anticipated to give  $\alpha,\beta$ -unsaturated ketone **5.52** on reaction with the phosphonium ylide.<sup>32</sup> The quinuclidine ring system might then be accessed using a conjugate enone reduction to produce the ketone **5.53** which would be cyclised via reductive amination into the desired ligand **5.21**.



| Entry | Reagents and conditions <sup>a</sup>                                 | 5.29 : 5.52 Yield (%) <sup>b</sup> |
|-------|----------------------------------------------------------------------|------------------------------------|
| 1     | Acetonitrile, rt, 24 h                                               | 95: 0                              |
| 2     | Acetonitrile, reflux, 24 h                                           | 96: 0                              |
| 3     | Chlorobenzene, reflux, 24 h                                          | 94: 0                              |
| 4     | Dichlorobenzene, reflux, 24 h                                        | 98: 0                              |
| 5     | CH <sub>2</sub> Cl <sub>2</sub> , High pressure 10 Kbar, rt, 3 days  | 97: 0                              |
| 6     | CH <sub>2</sub> Cl <sub>2</sub> , High-pressure 19 kbar, rt, 21 days | 98: 0                              |

**Table 5.8:** Conditions attempted for the Wittig reaction <sup>a</sup>Procedure: To a solution of starting material **5.25** in solvent (**For entries 1-4:** under an N<sub>2</sub> atmosphere), was added the ylid, (**For entries 1-4:** The reaction was stirred for the specified time and temperature)(For entries 5-6: reaction placed into an ultra-high pressure reactor, and left for the specified amount of time). <sup>b</sup>Isolated percentage yields of products **5.52** and recovered piperidone **5.29** obtained after flash chromatographic separation. Yields based upon **5.29** as limiting reactant.

Increasingly aggressive conditions were attempted for the Wittig reaction but *trans* piperid-4-one **5.29** was reisolated from all attempts in essentially at quantitative yields (**Table 5.8**). Clearly, despite our aggressive conditions we are unable to overcome the kinetic barrier of the Wittig reaction. Thus, we decided to alter our strategy towards the quinuclidine **5.21** once again. A previous synthesis developed by E. J. Corey<sup>17</sup> of a chiral C3 symmetric quinuclidine employs a Meyer–Schuster rearrangement as a key step. Given the previous success, we planned to emulate this tactic (**Fig 5.25**).

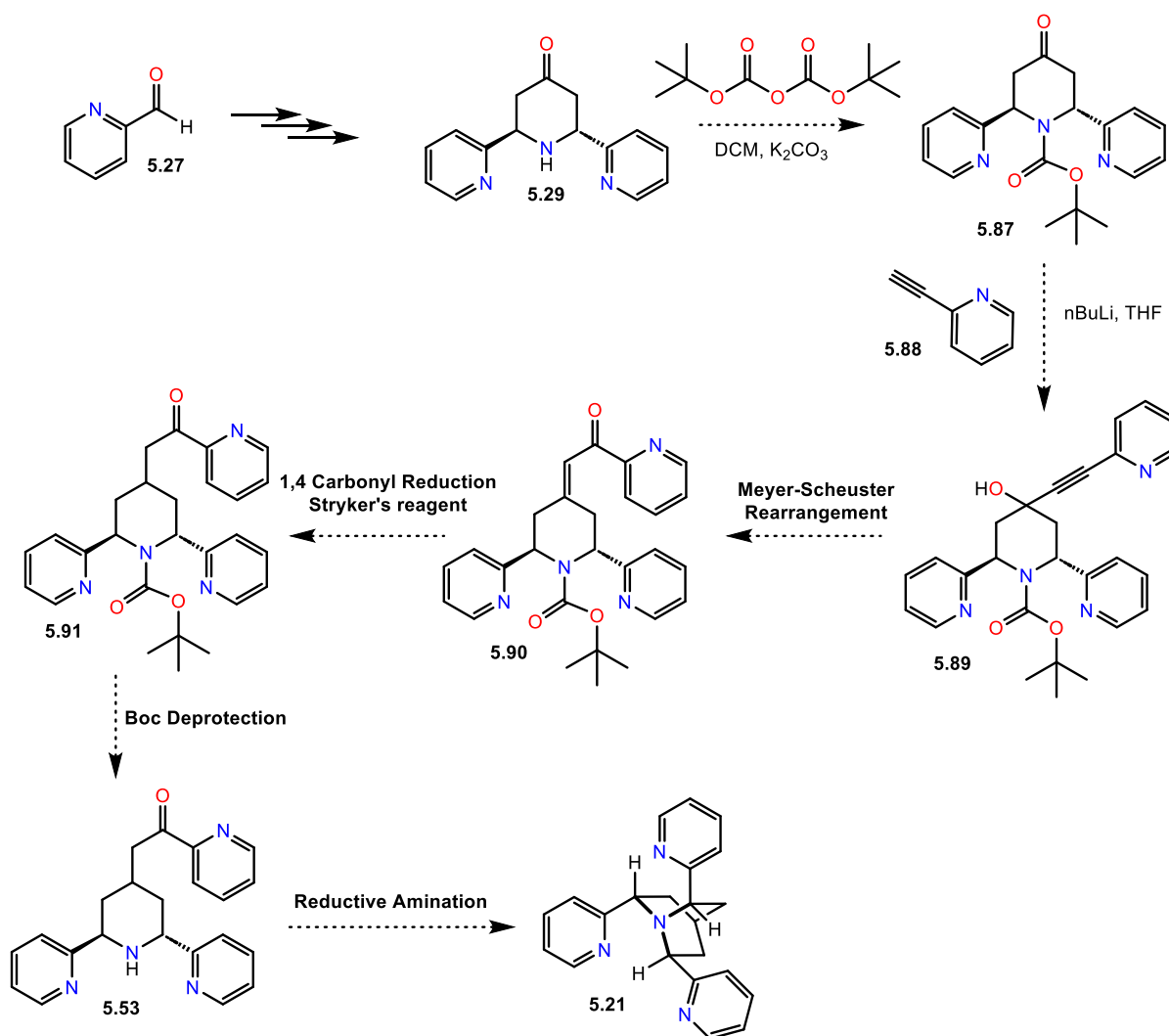


**Fig 5.25:** A revised synthetic plan for **5.21**, taking inspiration from the work of Corey *et. al.*<sup>17</sup>

The secondary amine group of *trans* 2,6-di(pyridin-2-yl)piperidin-4-one **5.21** would first be protected using a Boc group making **5.87**. Next, we would form propargyl-alcohol **5.89** via the addition of 2-ethynyl-pyridine **5.88**, which is then subject to a Meyer-Schuster rearrangement to create the protected enone **5.90**. We then would close the quinuclidine ring using a 1-4-reduction followed by a Boc deprotection to access 2,6-di(pyridin-2-yl)piperidin-4-yl)-1-(pyridin-2-yl)ethan-1-one **5.53**, and reductive amination sequence would finally to access the quinuclidine ligand **5.21**. The inclusion of the Boc protecting group (**Fig 5.26**) allowed us to remove the mildly acidic N-H proton of the piperidone and block the main binding pocket of the ligand. This prevents the piperidone from interfering with metal-catalysed reactions, and participating in undesirable deprotonation by organolithium bases.

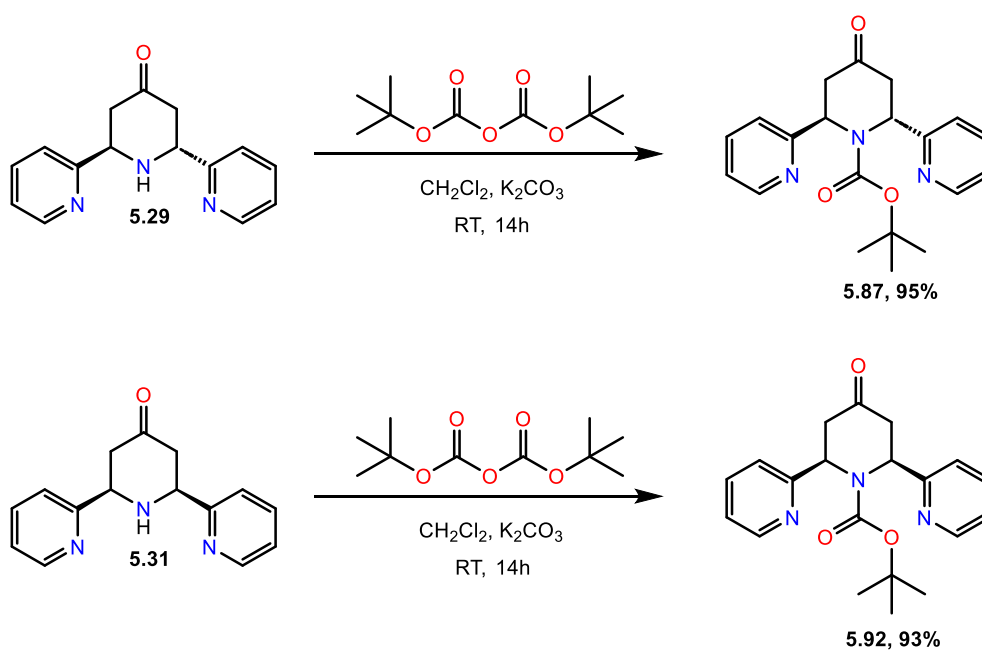
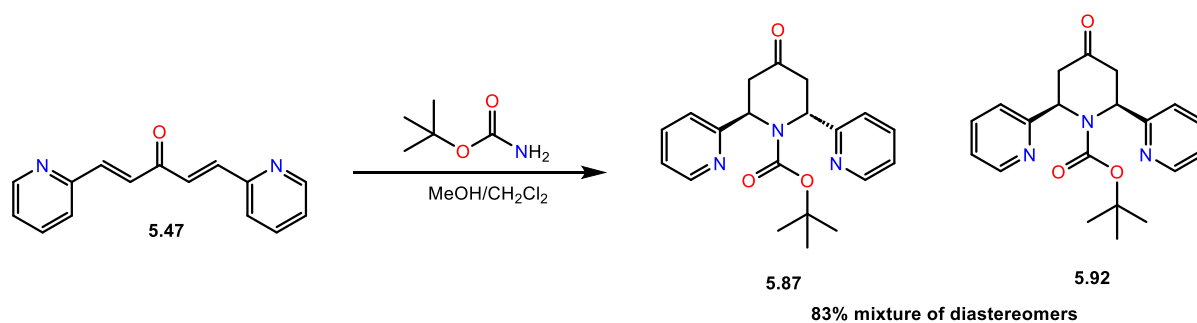


**Fig 5.26:** Boc protection of *cis* and *trans* 2,6-di(pyridin-2-yl)piperidin-4-one **5.29**, **5.31**.

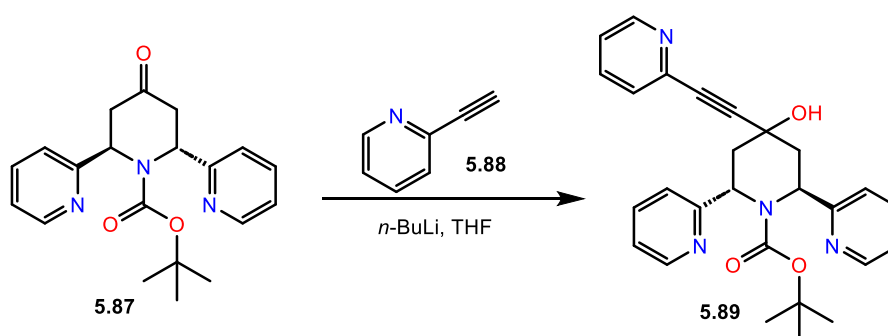
Thus, we hoped its presence would allow the subsequent reactions to proceed successfully. Both Boc protected piperidones **5.87**, **5.92** was successfully synthesized under very mild conditions (**Fig 5.26**). We also attempted an alternative route towards the protected piperidones **5.87**, **5.92** directly from the parent double Michael acceptor **5.47** (**Table 5.9**).



| Entry | Conditions                                                                                    | isolated <b>5.87</b> : mixture: <b>5.92</b><br>(%) |
|-------|-----------------------------------------------------------------------------------------------|----------------------------------------------------|
| 1     | SiO <sub>2</sub> Merck (pH = 7.0), (1:1 <i>n</i> -hexane:EtOAc)                               | 0:99:0                                             |
| 2     | buffered SiO <sub>2</sub> Merck (pH = 7.0), (1:1 <i>n</i> -hexane:EtOAc)                      | 0:98:0                                             |
| 3     | SiO <sub>2</sub> Merck (pH = 7.0), (3:2 <i>n</i> -hexane:EtOAc)                               | 0:99:0                                             |
| 4     | SiO <sub>2</sub> Merck (pH = 7.0), (7:3 <i>n</i> -hexane:EtOAc)                               | 0:85:0                                             |
| 5     | SiO <sub>2</sub> Merck (pH = 7.0), (65:35 <i>n</i> -hexane:EtOAc)                             | 0:97:0                                             |
| 6     | SiO <sub>2</sub> Merck (pH = 7.0), (Et <sub>2</sub> O),                                       | 0:99:0                                             |
| 7     | SiO <sub>2</sub> Merck (pH = 7.0), (1:9 <i>n</i> -hexane:Et <sub>2</sub> O)                   | 0:98:0                                             |
| 8     | SiO <sub>2</sub> Merck (pH = 7.0), (2:8 <i>n</i> -hexane:Et <sub>2</sub> O)                   | 0:95:0                                             |
| 9     | SiO <sub>2</sub> Merck (pH = 7.0), (2:8 <i>n</i> -hexane:CH <sub>2</sub> Cl <sub>2</sub> )    | 0:94:0                                             |
| 10    | SiO <sub>2</sub> Merck (pH = 7.0), (15:85 <i>n</i> -hexane: CH <sub>2</sub> Cl <sub>2</sub> ) | 0:95:0                                             |

**Table 5.9:** Attempt to isolate **5.87** and **5.92** via flash chromatography.

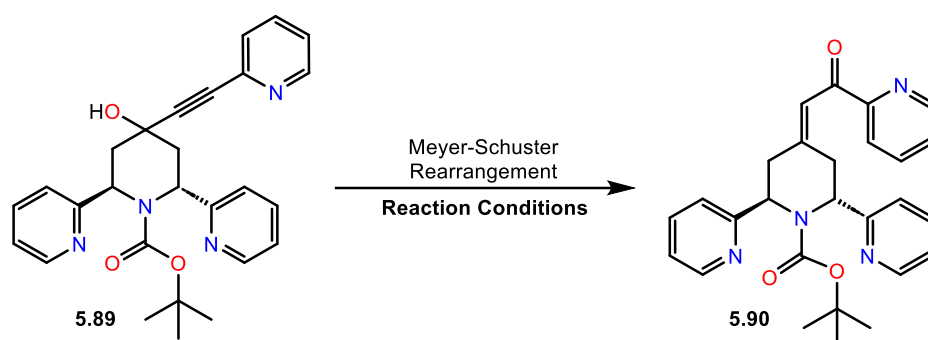
Following the methodology for our parent piperidone we synthesised a mixture of the *cis* and *trans* diastereomers of Boc-protected piperidones **5.87**, **5.92**. Unfortunately we are unsuccessful in our attempts to chromatographically separate the *cis* and *trans* isomers. We proceeded with our synthesis of the carbon framework using the diastereomerically pure samples obtained from the original route, and separate Boc protection (**Fig 5.26**). The next step of the synthesis involved the nucleophilic addition to the Boc protected piperidone (**Table 5.10**)



| Entry | Reagents and conditions <sup>a</sup>                                  | Yield <b>5.89</b> (%) <sup>b</sup> |
|-------|-----------------------------------------------------------------------|------------------------------------|
| 1     | <b>5.78</b> (1.5 mol. equiv.), <i>n</i> -BuLi (1.2eq), -78, 3 h       | 15                                 |
| 2     | <b>5.78</b> (1.5 mol. equiv.), <i>n</i> -BuLi (1.2eq), -78, 6 h       | 27                                 |
| 3     | <b>5.78</b> (1.5 mol. equiv.), <i>n</i> -BuLi (1.2eq), -78 -> 0, 3 h  | 45                                 |
| 4     | <b>5.78</b> (1.5 mol. equiv.), <i>n</i> -BuLi (1.2eq), -78 -> 0, 6 h  | 51                                 |
| 5     | <b>5.78</b> (1.5 mol. equiv.), <i>n</i> -BuLi (1.2eq), -78 -> rt, 3 h | 54                                 |
| 6     | <b>5.78</b> (1.5 mol. equiv.), <i>n</i> -BuLi (1.2eq), -78 -> rt, 6 h | 52                                 |
| 7     | <b>5.78</b> (2.0 mol. equiv.), <i>n</i> -BuLi (1.7 eq), -78 -> 0, 6 h | 65                                 |
| 8     | <b>5.78</b> (2.5 mol. equiv.), <i>n</i> -BuLi (2.2eq), -78 -> 0, 6 h  | 69                                 |
| 9     | <b>5.78</b> (3.0 mol. equiv.), <i>n</i> -BuLi (2.5 eq), -78 -> 0, 6 h | 66                                 |

**Table 5.10:** Conditions for nucleophilic addition. <sup>a</sup> Procedure: A solution of 2-ethynylpyridine in dissolved in tetrahydrofuran was placed under a N<sub>2</sub> atmosphere in an acetone–dry ice bath. *n*-BuLi was introduced dropwise. <sup>b</sup>Isolated percentage yields of products **5.89** obtained after flash chromatographic separation. Yields based upon **5.87** as limiting reactant.

Initially, the addition reaction was attempted at low temperatures (-78°C) (**Table 5.10**). Unfortunately, yields under these conditions were poor, which we attributed to the sluggish deprotonation rates at low temperatures, resulting in incomplete deprotonation of the acetylene **5.88**. Thus, we warmed the reaction up to 0 °C after the addition of *n*-BuLi. This resulted in a large increase in the yield of the reaction. Further improvements were made to the reaction through using a larger excess of the lithiated 2-ethynylpyridine. With a successful addition achieved we moved on to testing potential conditions for the Meyer-Schuster rearrangement (**table 5.11**).

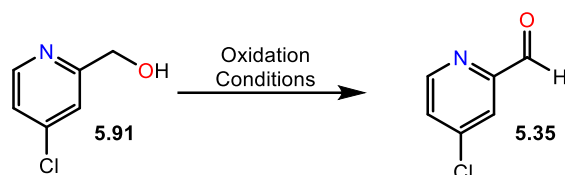


| Entry | Reagents and conditions <sup>a</sup>                                                                      | Yield 5.90 (%) <sup>b</sup> |
|-------|-----------------------------------------------------------------------------------------------------------|-----------------------------|
| 1     | HCl (10 mol. equiv.), MeOH, reflux, 15 h,                                                                 | 0 <sup>c</sup>              |
| 2     | TFA (10 mol. equiv.), MeOH, reflux, 15 h                                                                  | 0 <sup>d</sup>              |
| 3     | 10 CSA (10 mol. equiv.), THF, reflux, 15 h                                                                | 0 <sup>d</sup>              |
| 4     | H <sub>2</sub> SO <sub>4</sub> (10 mol. equiv.), <i>i</i> -PrOH, 85 °C, 15 h                              | 0 <sup>c</sup>              |
| 5     | TsOH (10 mol. equiv.), 15 h, THF, reflux                                                                  | 0 <sup>d</sup>              |
| 6     | VO(acac) <sub>2</sub> (5%) toluene, rt, 24 h                                                              | 0                           |
| 7     | VO(acac) <sub>2</sub> (5%), AuCl(PPh <sub>3</sub> ) (5%), AgOTf (5%), toluene, rt, 24 h                   | 0                           |
| 8     | MoO <sub>2</sub> (acac) <sub>2</sub> (5%), AuCl(PPh <sub>3</sub> ) (5%), AgOTf (5%), toluene, rt, 24 h    | 0                           |
| 9     | MoO <sub>2</sub> (acac) <sub>2</sub> (50%), AuCl(PPh <sub>3</sub> ) (50%), AgOTf (50%), toluene, rt, 24 h | 0                           |

**Table 5.11:** Meyer-Schuster rearrangement. <sup>a</sup> Procedure: To a solution of **5.89** in solvent listed, was added the catalysts/reagents. The reaction is allowed to stir for the listed time and temperature. <sup>b</sup> Isolated percentage yields of products **5.90**, obtained after flash chromatographic separation. Yields based upon **5.90** as limiting reactant. <sup>c</sup> alternative product isolated. <sup>c</sup> starting material consumed. <sup>d</sup> deprotection of Boc group.

Many different conditions for the Meyer-Schuster rearrangement were explored (**Table 5.11**). Traditional Brønsted acid-mediated conditions led to the decomposition or deprotection of the starting material. While Lewis acid-mediated conditions also proved fruitless, it is suspected the pyridyl group on the ligand are binding to the catalyst and preventing its proper function despite the presence of the Boc protecting group. Concurrent with efforts in the unsubstituted pyridine series described so far, we also worked through the sequence using 4-chloropyridyl group.

Since 4-chloro-2-pyridinecarbaldehyde **5.31** is prohibitively expensive (A\$ 103. 46 for 250 mg) we prepared this precursor by oxidation of the less expensive (4-Chloro-pyridin-2-yl)-methanol **5.83** (**Table 5.12**).



| Entry | Reagents and conditions <sup>a</sup>                                                                                                  | Yield <b>5.35</b><br>(%) <sup>b</sup> |
|-------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| 1     | (COCl) <sub>2</sub> (1.2 mol. equiv.), DMSO (1.5 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub>                                        | 0                                     |
| 2     | Dess-Martin periodinane (1.0 mol. equiv.), K <sub>2</sub> CO <sub>3</sub> (2 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> (50ml)     | 53                                    |
| 3     | MnO <sub>2</sub> , CHCl <sub>3</sub> (reflux)                                                                                         | 0                                     |
| 4     | SeO <sub>2</sub> , 1,4-Dioxane (reflux)                                                                                               | 0                                     |
| 5     | Cu(MeCN) <sub>4</sub> (5 mol%), bpy (5 mol%), TEMPO (5 mol%), NMI (10%) MeCN                                                          | 12                                    |
| 6     | Dess-Martin periodinane (1.0 mol. equiv.), K <sub>2</sub> CO <sub>3</sub> (2 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> (10 ml)    | 33                                    |
| 7     | Dess-Martin periodinane (1.5 mol. equiv.), K <sub>2</sub> CO <sub>3</sub> (2 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> (50ml)     | 57                                    |
| 8     | Dess-Martin periodinane (3.0 mol. equiv.), K <sub>2</sub> CO <sub>3</sub> (2 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub> (50ml)     | 63                                    |
| 9     | Dess-Martin periodinane (1.0 mol. equiv.), K <sub>2</sub> CO <sub>3</sub> (2 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub><br>(100ml) | 65                                    |
| 10    | Dess-Martin periodinane (1.0 mol. equiv.), K <sub>2</sub> CO <sub>3</sub> (2 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub><br>(250ml) | 77                                    |
| 11    | Dess-Martin periodinane (1.0 mol. equiv.), K <sub>2</sub> CO <sub>3</sub> (2 mol. equiv.), CH <sub>2</sub> Cl <sub>2</sub><br>(500ml) | 85                                    |

**Table 5.12:** Conditions for oxidation. <sup>a</sup>Procedure: To a solution of **5.91** dissolved in the solvent under an N<sub>2</sub> atmosphere, was added the reagents listed. The reaction is allowed to proceed under the conditions listed. <sup>b</sup> Isolated percentage yields of products **5.35**, obtained after flash chromatographic separation. Yields based upon **5.91** as limiting reactant.

The comparatively affordable alcohol **5.91** (A\$110.00 +shipping for 25 g) was subject to several different oxidation conditions (Swern oxidation<sup>33</sup>, Dess-Martin oxidation<sup>34</sup> and Stahl oxidation<sup>35</sup>) (**table 5.12**). Swern and Stahl oxidations proved inadequate for the synthesis of 4-chloro-2 formyl pyridine **5.35**. We attributed this to the low temperatures required for the Swern oxidation, and the proximity of the nearby pyridine to the reacting alcohol interfering with the copper-catalyzed Stahl oxidation. Alternative metal mediated oxidations, using MnO<sub>2</sub> and SeO<sub>2</sub> also failed to produce product also failed to create the desired product. The failures of the Stahl and different metal catalysed approaches

dissuaded us from attempting other metal-mediated oxidations such as the Ley-Griffith oxidation. Although, operationally simple the Dess-Martin oxidation of (4-chloro-pyridin-2-yl)-methanol **5.91** requires very high dilutions to provide a reasonable yield. This poses difficulties in upscaling the reaction due to the volumes of solvent required for the transformation. Furthermore, the synthesized aldehyde is prone to decomposition under standard laboratory conditions, increasing the difficulty of this synthesis. We pressed onwards with the synthesis despite not being able to push through a large amount of starting material through this oxidation (**Fig 5.27**).

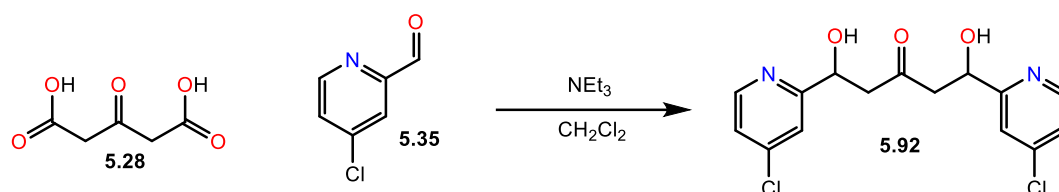


**Fig 5.27:** Double addition of 1,3-acetonedicarboxylic acid **5.28** into 4-chloropicolinaldehyde **5.35**

Initial attempts at double aldol addition involving this aldehyde produced a side product that was difficult to separate from the desired product **5.84**. A lack of time precluded further experimental work.

### Summary Conclusion and Future work

We have successfully installed all of the carbon and nitrogen atoms into an advanced intermediate towards a new generation of ATRP ligands. We successfully elucidated the formation of 3-(pyridin-2-yl)imidazo[1,5-a]pyridine **5.56** in a new process that is more efficient than previously reported. This discovery lead us to plot an alternative synthesis for the desired intermediate 2,6-di(pyridin-2-yl)piperidin-4-one **5.31/5.29**, wherein we reverse the sequence of addition of the reagents. We successfully managed to synthesize *cis* and *trans* 2,6-di(pyridin-2-yl)piperidin-4-ones **5.31** and **5.29** in a scalable three-step sequence where we successfully isolated large amounts of both *cis* and *trans* isomers via flash column chromatography. Following our synthesis of *cis* and *trans* 2,6-di(pyridin-2-yl)piperidin-4-one **5.35** and **5.25**, we attempted several methods to complete the synthesis of the target ligands. We successfully created the carbon backbone, via the carbonyl addition of 2 ethynyl pyridine **5.88** into tert-butyl 4-oxo-2,6-di(pyridin-2-yl)piperidine-1-carboxylate **5.87**. Whilst the synthesis of our desired ligand remains incomplete, we have successfully prepared an advanced intermediate to the prospective synthesis of our desired quinuclidine **5.21**.

Significant progress has been made toward the synthesis of quinuclidine ligands, but there remain several avenues of investigation. Our initial attempt for the aldol addition of 2 acetyl-pyridine **5.30** onto 2,6-di(pyridin-2-yl)piperidin-4-one **5.29** yielded a complex mixture of products despite using a strong non-nucleophilic base such as lithium diisopropylamide (**table 5.6**). Firstly, the Boc protected piperidone **5.87** could improve the overall viability of the aldol reaction (**Fig 5.28**) by removing the acidic proton on the piperidone **5.29**. Furthermore, a large increase in yield was observed when switching from an acetone-dry ice bath to an ice bath during the deprotonation of 2 ethynyl pyridine **5.88**. We hope that similar success can be achieved for the deprotonation of 2 acetylpyridine **5.30**, allowing us to construct tert-butyl-4-(2-oxo-2-(pyridin-2-yl)ethyl)-2,6-di(pyridin-2-yl)piperidine-1-carboxylate **5.93**. The Reformatski reaction is an alternative that starts with the direct metalation of a 2-bromo-1-(pyridin-2-yl)ethan-1-one **5.94**, forming an organometallic intermediate allowing for an efficient addition into tert-butyl-4-oxo-2,6-di(pyridin-2-yl)piperidine-1-carboxylate **5.93**.

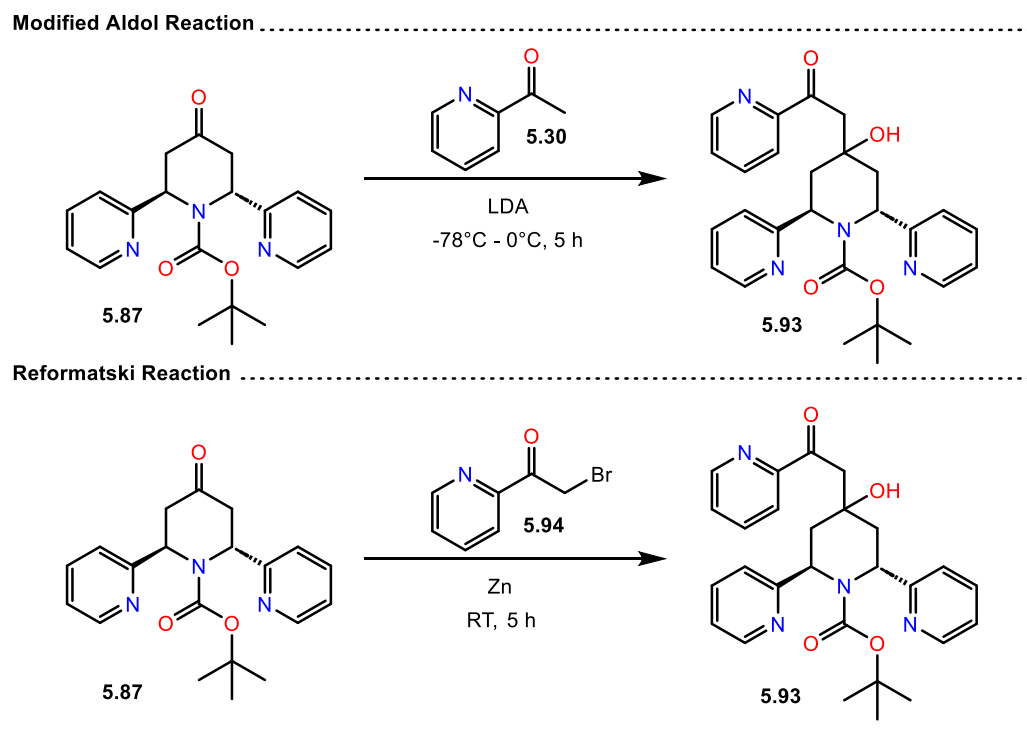


**Fig 5.28:** Alternative approaches to the aldol addition reaction.

A different pathway to synthesize the quinuclidine ligand is to design alternative conditions for a Meyer-Schuster rearrangement (**Fig 5.29**). Traditionally the Meyer-Schuster

rearrangement relies on the use of either a Brønsted or Lewis acid to drive the dehydration (rearrangement) of propargylic alcohol **5.89**. Changing the conditions of the Meyer-Schuster rearrangement from acidic to basic because of the abundance of basic sites on the propargyl alcohol **5.89** can help avoid inherent chemical incompatibilities with the current conditions. Under basic conditions, the propargyl alcohol **5.89** can be modified into a more labile functional group **5.94** which is eliminated into an allene cationic intermediate **5.95**. The allene cation **5.95** can be then trapped by an incoming water molecule forming the intermediate **5.96**, which is deprotonated to form the hydroxy-allene **5.97**. The hydroxy-allene **5.97** then undergoes a keto enol tautomerisation to form the enone **5.90**

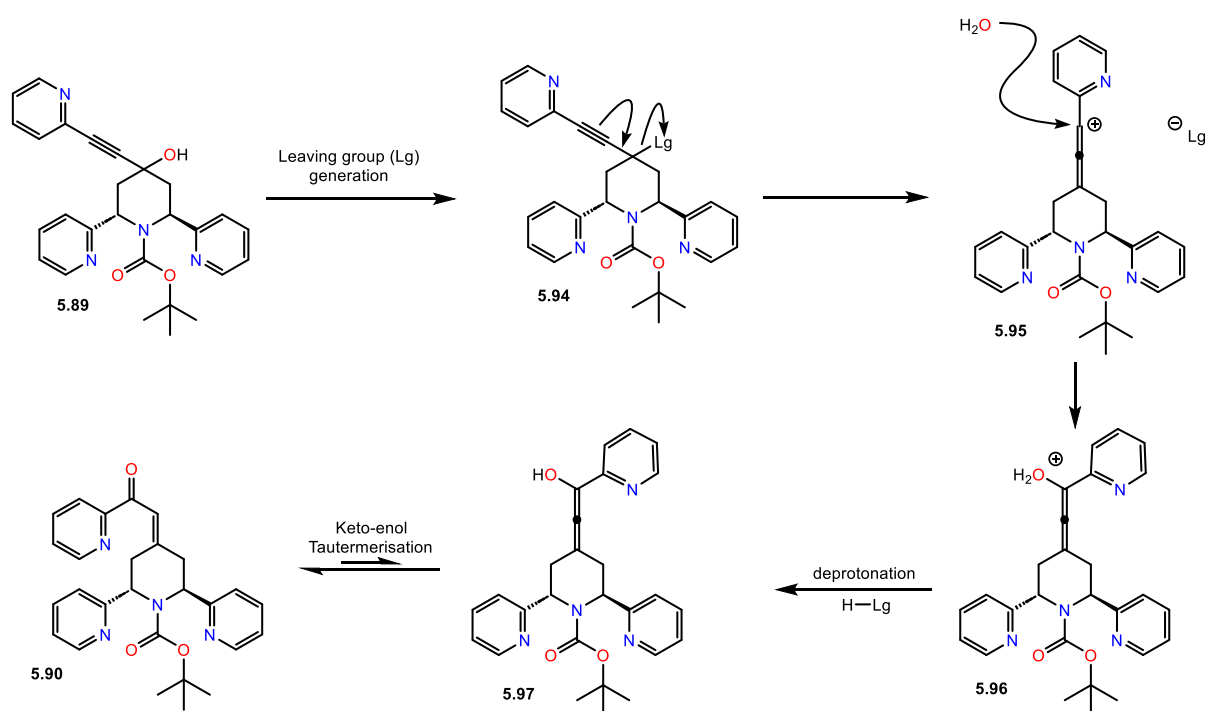


**Fig 5.29:** Alternative approaches to the Meyer-Schuster reaction.

Alternatively, we can target some of the other computationally designed ligand structures instead (**Fig 5.3**). The quinuclidine ligand was initially evaluated as an excellent compromise between ligand activity and expected ease of synthesis, given the literature precedent.<sup>20,19</sup> However, given the problems with this synthesis, we can instead structurally simplify the adamantane-capped ligand **5.16**. (**Fig 5.3**) This is predicted to be roughly 28 times more active than the quinuclidine ligand **5.17** but lacked literature precedent. Applying a similar simplification as the hemiaminal ether we can identify the aza-adamantane structure as a Bispidine derivative **5.91**. As the asymmetric synthesis of substituted bispidines is well known. This could be a potential synthetic target, unlike our

hemiaminal ether motif **5.22**, Bredt's rule would prevent the aromatization of the central ring, making the ligand an interesting synthetic target.

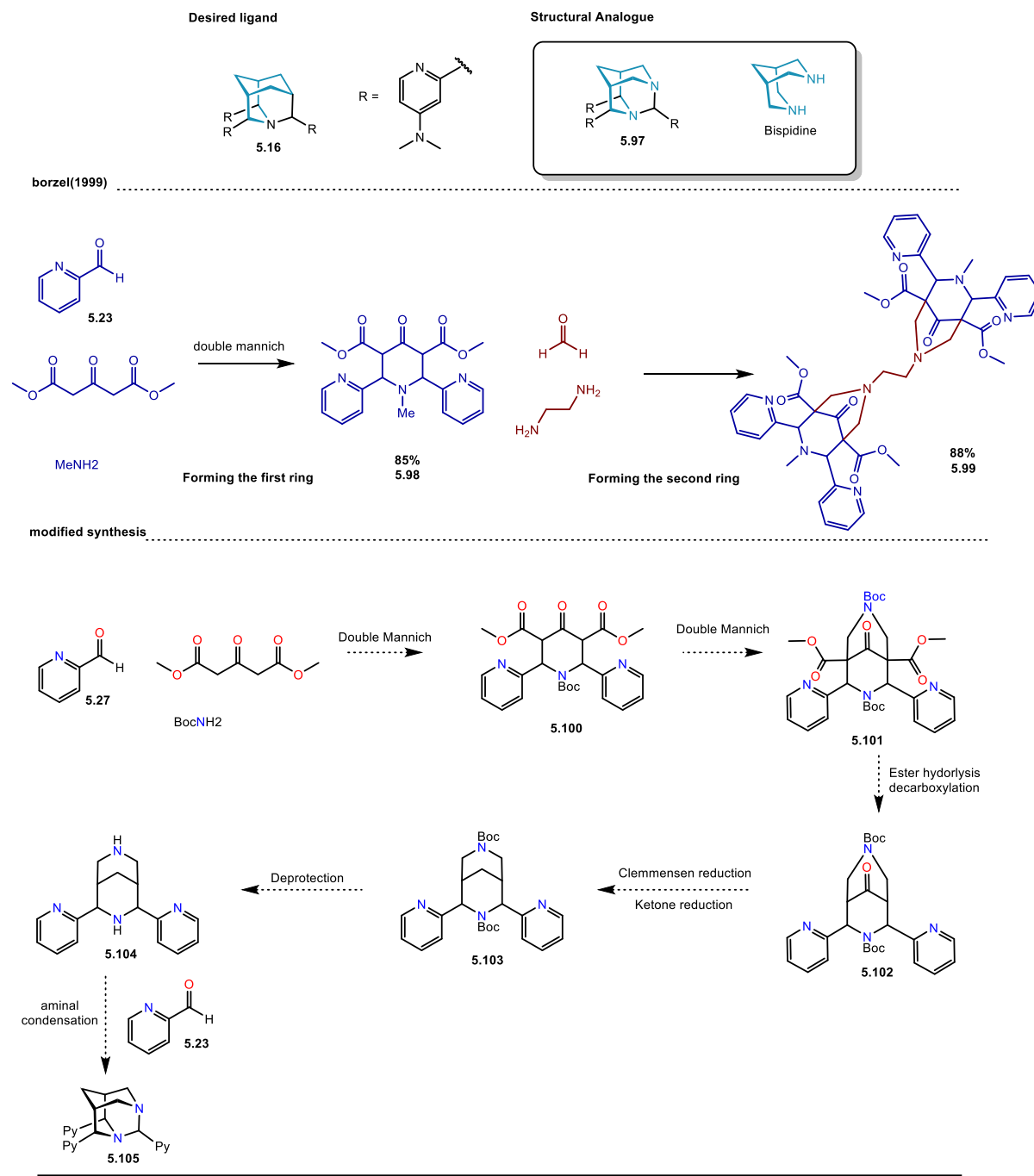


**Fig 5.30:** Alternative ligand design based on a bispidine framework.<sup>36</sup>

Borzel *et. al.*,<sup>36</sup> (**Fig 5.30**) successfully synthesized substituted bispidine ligands where the A and B rings bear different substituents. This is achieved via two independent double Mannich reactions the first establishing a dipyridyl piperidone **5.98**, where the unsubstituted B ring is attached again via a double Mannich reaction, forming the bispidine

framework **5.99**. We believe the work by Brozel and co-workers can be effectively adapted for the synthesis of a structurally simplified aza-adamantane ligand for ATRP.

The synthesis of the bispidine ligand starts with the aldehyde **5.27**. An initial double Mannich reactions folds the substituted piperidone **5.100**, a second double Mannich reaction establishes a heavily substituted asymmetric bispidine **5.101**. The bispidines are then defunctionalized first with the demethylation and decarboxylation of the bispidine **5.101** into **5.102**. The intermediate bispidine **5.102** is then reduced to remove the ketone to create **5.103** which is subsequently deprotected to give our desired bispidine **5.104**. From the bispidine **5.104** the desired ligand is accessed via an amination condensation. Using a substituted amine for the initial double Mannich reaction avoids the possibility of generating the aza-allenium intermediate. However, increasing the number of stereocenters in the intermediate poses a problem to the isolation of all the diastereomers present. The ketone can be leveraged to epimerize the product under mild conditions. The lessons learned in the isolation of the quinuclidine diastereomers suggest that screening conditions using buffered silica would be the most prudent method to isolate the isomers.

Although more modest in its improvements when compared to the quinuclidine and azaadamantane ligands, theoretically the cyclohexyl ligands **5.18** can be synthesized in two steps from an intermediate piperidone **5.32** (Fig 5.31).

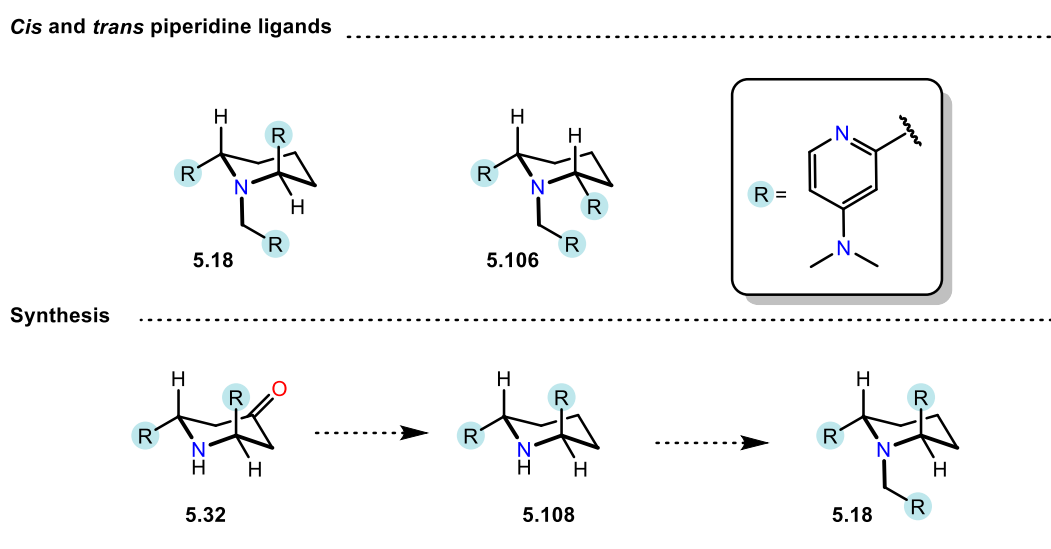


**Fig 5.31:** Cyclohexyl-capped ligand, an alternative ligand design.

The patent by Chen *et. al.*<sup>19</sup> mentioned earlier suggests the use of a Wolff Kischner reduction (**5.32**→ **5.108**) followed by a direct substitution using the 2-bromomethyl pyridine (**5.108**→ **5.18**). The dimethyl amino substituted cyclohexyl TPMA derivative **5.18** is predicted to be 35 times more active than the dimethylamino TPMA ligand **5.19**, while the quinuclidine **5.17** and azaadamantane ligands **5.16** are calculated to be 1600 and 44400 times more active respectively. Although, inferior to the quinuclidine **5.17** and azaadamantane **5.16** ligands the synthetic pathway toward these ligands is considerably simpler and can prove to be an excellent ligand for ATRP.

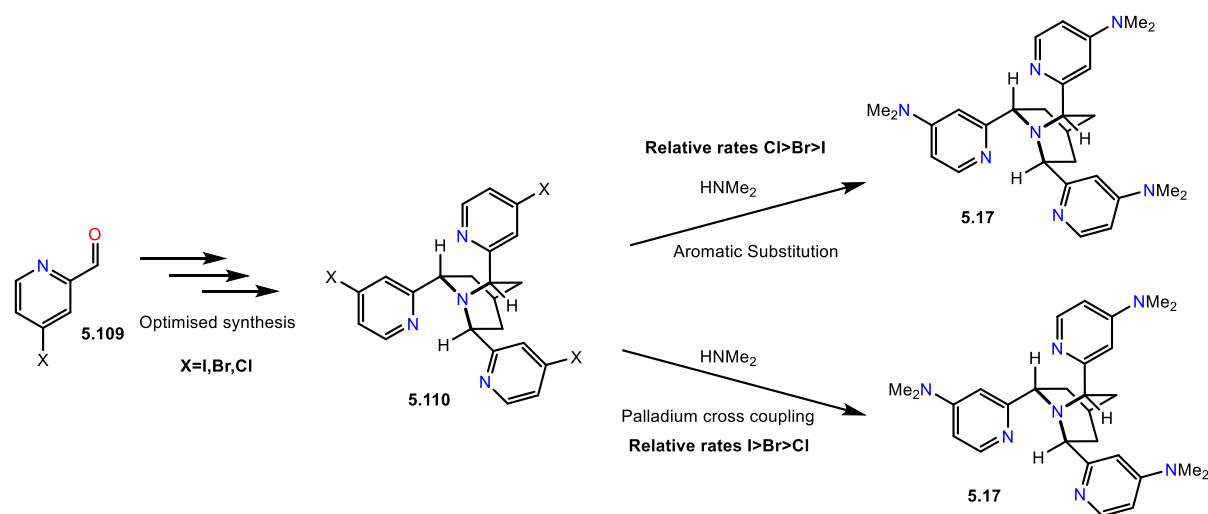


**Fig 5.32:** Synthetic plans for the substituted quinuclidine ligand.

Finally, the total synthesis of 4-halo quinuclidine **5.110** derivatives from the respective 2-formyl-4-halo pyridine **5.109** needs to be established and the methodology optimized (**Fig 5.32**). The choice of halogen would favour separate late-stage strategies, while palladium cross couplings favour heavier halogens,<sup>37</sup> the inverse trend can be observed for the nucleophilic aromatic substitution of the aryl halide.<sup>38</sup> Therefore, we should select the halogen which cooperates best with our synthetic sequence and adjust our late-stage modification strategies accordingly to access the desired dialkyl amino pyridine.

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## ***Chapter Six:***

### ***Conclusions and Future Work***

In this thesis, we have successfully demonstrated the compatibility and utility of ATRP methodology to the advancement of synthetic methodology, through a series of exploratory projects. First, we reviewed the mechanism, scope, and limitation of atom transfer radical polymerization. In our review, we cover the fundamental mechanistic details which inspired the subsequent chapters of work, covering the development of an ATRP-inspired C–N cross-coupling methodology and the introduction of air tolerance into the Cadiot-Chodkiewicz and Sonogashira cross-couplings. Following the success of these methodological developments, we have made significant progress towards the model synthesis of a new generation of ATRP ligands which had previously been calculated<sup>1</sup> to be over 3000 times more active than the current best ligands. These projects have allowed us to glimpse the myriad of possibilities achievable from these exploratory works.

**Chapter three** highlights our development of a mechanistically unique ( $sp^3$ ) C–N cross-coupling inspired by the mechanism for ATRP (**Fig 1**). Our protocol allows the coupling of amines/amides with a range of alkyl bromides/chlorides containing different functional groups. Enabled by the adoption of a cheap and easily accessible ATRP catalyst system, good yields were obtained using a stoichiometric amount of coupling partners at room temperature. This work highlights the cost-effectiveness of employing an ATRP-inspired catalyst system in organic synthesis. The ATRP mediator undergoes stepwise single electron oxidation at the copper centre in a process reminiscent of modern photoredox-catalysis based couplings. Our process differs in that it proceeds without irradiation, thereby showing an alternative thermally induced pathway to overcoming the high kinetic barrier to access key organocopper(III) intermediates.

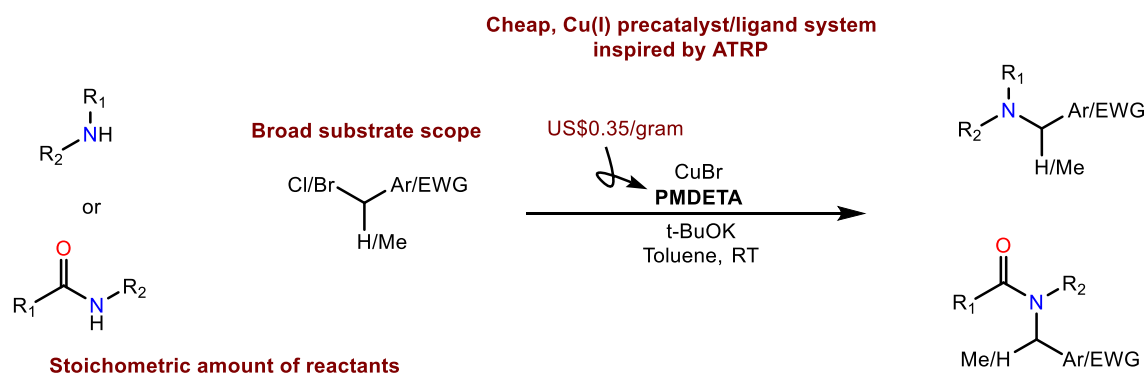
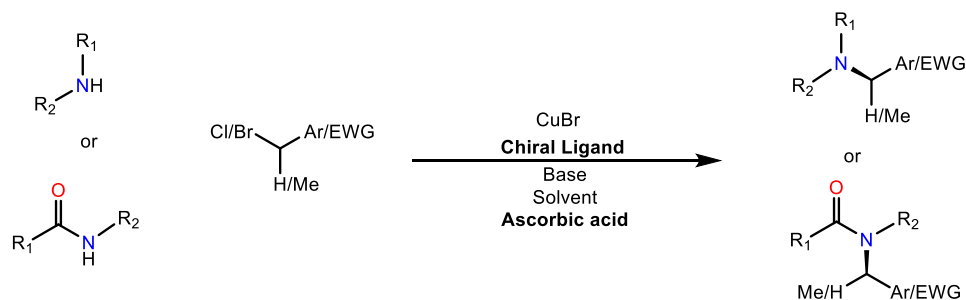


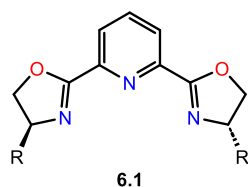
**Fig 1:** ATRP-inspired C–N cross-coupling highlighted in Chapter three

Several options exist moving forwards with our ATRP-inspired C–N cross-coupling. Firstly, a superior ligand can be investigated to extend the scope of the reaction (see **Chapter 5** for studies towards this end). Our current metal ligand precatalyst system (CuBr, PMDETA) was chosen for this work because of its low cost and availability. Although our current precatalyst system has proven to be effective, far more active mediators exist for ATRP.<sup>2</sup> The use of a superior ligand could extend the scope of the C–N coupling to include a broader range of alkyl halides. Alternatively, developing an enantioselective variant of the chemistry would further enhance its utility. The use of a chiral ligand would allow us to potentially influence the enantioselectivity of the reaction, in cases where a stereocentre is generated (**Fig 2**). The py-box type pincer ligands **6.1** are commercially available and, hence would be attractive as an initial candidate, with a wide range of side chains available to influence the enantioselectivity. Furthermore, the axial pyridyl group can be functionalized with an electron-donating group (**6.2**, **6.3**) to increase the activity of the overall catalyst complex. An alternative candidate ligand would be the *trans*-2,6-di(pyridin-2-yl)piperidin-4-one **6.4** synthesized in chapter five, although resolution of the ligand is necessary, since the compound was prepared as a racemic mixture. Additionally, the arms of the 2,6-di(pyridin-2-yl)piperidin-4-one **6.4** can be easily switched for bulkier and electron-rich motifs to increase both the selectivity and activity of the catalyst complex. Finally, borrowing from the work in Chapter 4, ascorbate salts could be added to introduce a degree of air tolerance and lower the catalyst loading of the reaction. Together, the introduction of more active ligands, air tolerance and enantioselectivity will expand the scope and accessibility of our C–N bond cross-coupling.

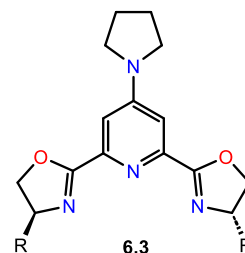
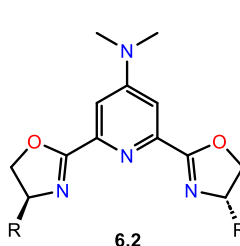
Enantioselective, air tolerant, C-N cross coupling



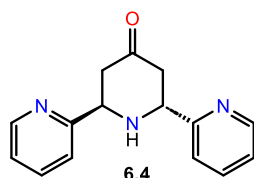
Py-box ligands



Synthesisable ligands



Synthesised in chapter 5



Synthesisable targets

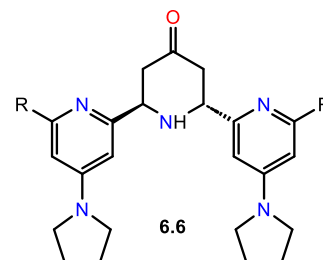
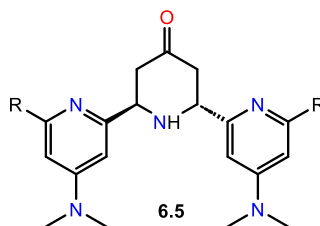


**Fig 2:** Proposed enantioselective C–N couplings and possible chiral ligands.

Synthesisable In **Chapter four**, the use of a supplementary reducing agent to address oxygen sensitivity of catalysts was investigated. This important yet underdeveloped synthetic paradigm involves the in-situ regeneration of air-sensitive catalysts. We developed a significantly improved methodology for both the Cadiot-Chodkiewicz and Sonogashira cross couplings (**Fig 3**), which can be executed in air while avoiding the production of Glaser homocoupling products. This demonstrates the generalizability of using ascorbic acid/sodium ascorbate as a supplementary reducing agent to reduce undesirable copper (II) salts back into the catalytic copper (I) salt, an approach previously employed for both azide-alkyne “click” reaction<sup>3</sup> and ARGET-ATRP.<sup>4</sup>

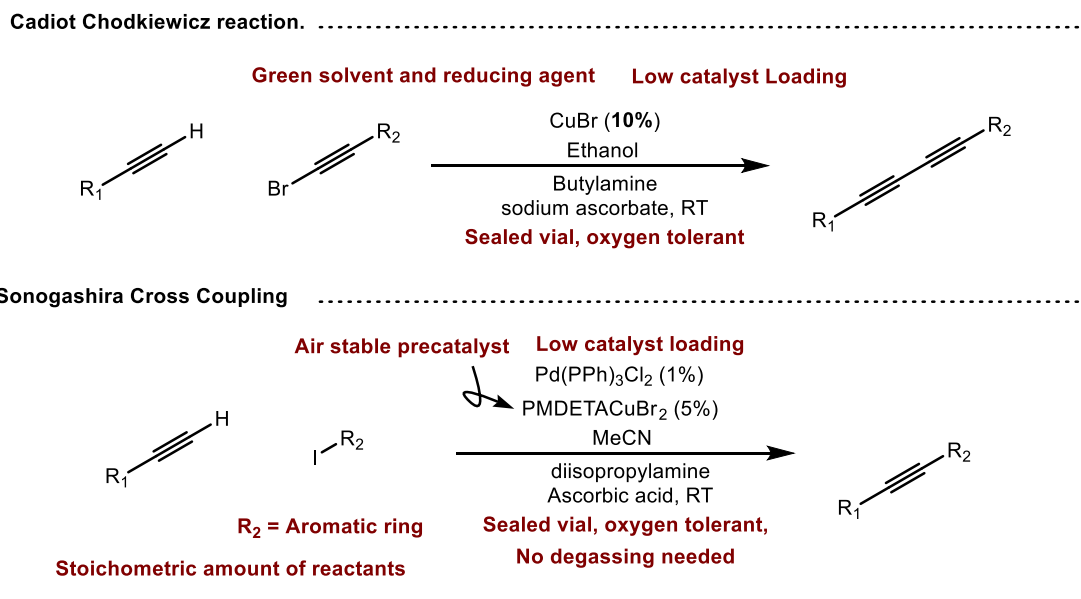


**Fig 3:** Air tolerant Cadiot-Chodkiewicz reaction and Sonogashira cross-coupling highlighted in **Chapter Four**

The air-tolerant Cadiot-Chodkiewicz and Sonogashira cross-coupling reactions in Chapter four highlight the effectiveness of both ascorbic acid **6.7** and sodium ascorbate **6.8** to introduce air tolerance to cross-coupling reactions. The next step in this research should expand this approach to encompass other Pd(0)-catalysed cross-couplings. It has been previously demonstrated that palladium(II) acetate in solution with triphenylphosphine can be reduced with ascorbic acid **6.7** to produce *tetrakis*(triphenylphosphine)palladium(0).<sup>5</sup> This demonstrates the ability of ascorbic acid to reduce oxidised palladium species, at least under elevated temperatures. Another interesting avenue of research is to find alternative sustainable reducing agents to ascorbic acid which are more soluble in low polarity solvents such as THF and toluene. The high polarity of ascorbic acid and sodium ascorbate renders them only sparingly soluble in common organic solvents. Ascorbic acid derivatives **6.9 – 6.11** (**Fig 4**) can be synthesized readily, and have similar redox properties to ascorbic acid/sodium ascorbate, yet are more soluble in organic solvents. Alkylammonium salts such as (tetra-*n*-butyl ammonium) ascorbate **6.9** is more soluble in organic solvents than sodium ascorbate. Likewise, conversion of the sidechain 1,2-diol into the corresponding ketal, as in compounds **6.10**, **6.11** should improve solubility in organic solvents. Improving solvent compatibility of this technique will be invaluable to the development of air tolerant palladium cross couplings.

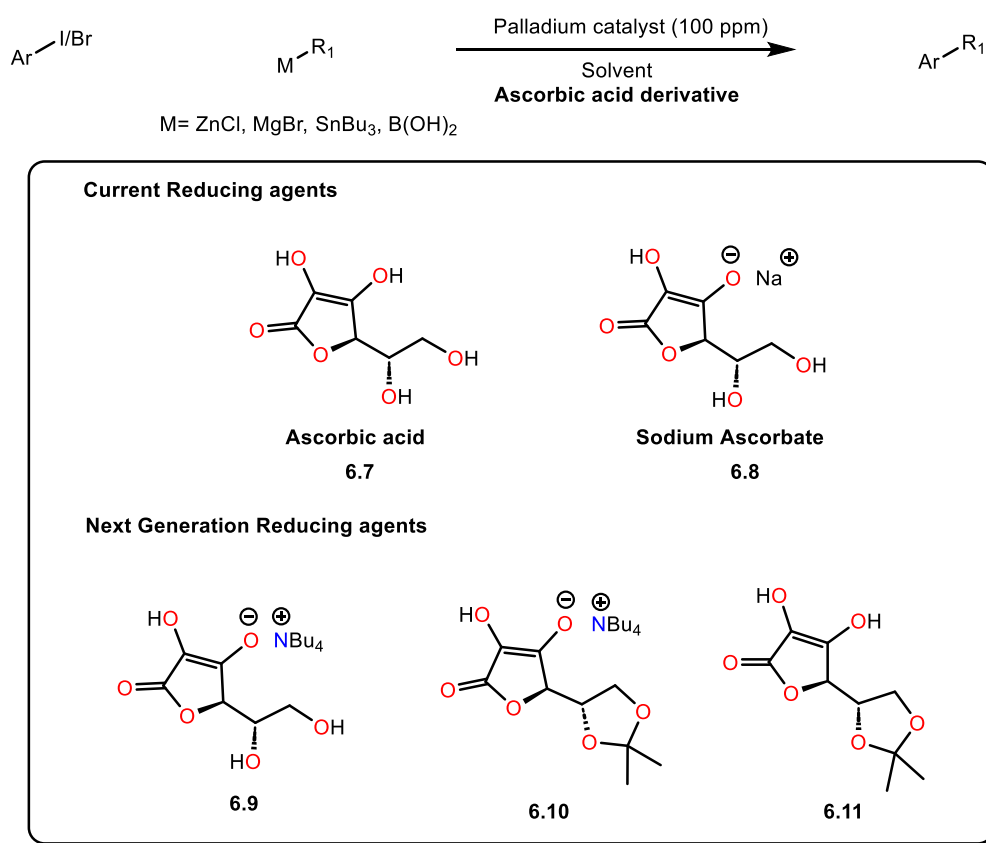


**Fig 4:** Plan for the generalized air tolerant cross couplings, the future generation of more organic solvent soluble ascorbic acid-based reducing agents.

In **chapter five**, we detail our various attempts towards the synthesis of a previously designed and computationally evaluated quinuclidine-based ligand **6.13** (**Fig 5**). No synthetic attempts have been reported towards these ligand frameworks, although a triphenyl derivative **6.12** was previously synthesised by Corey and co-workers.<sup>6</sup> Work by Chen et al.<sup>7</sup> suggests a rapid route to the key *cis/trans*-2,6-di(pyridin-2-yl)piperidine-4-one intermediate (**6.16**, **6.17**). Unfortunately, we were not able to reproduce their results. We successfully synthesized and isolated **6.16** and **6.17** on a large scale chromatographically, using an alternative three-step synthesis. Several attempts to complete the carbon framework were made, with Boc protection followed by the addition of an alkyne **6.18** into a protected piperidone, finishing the carbon framework.

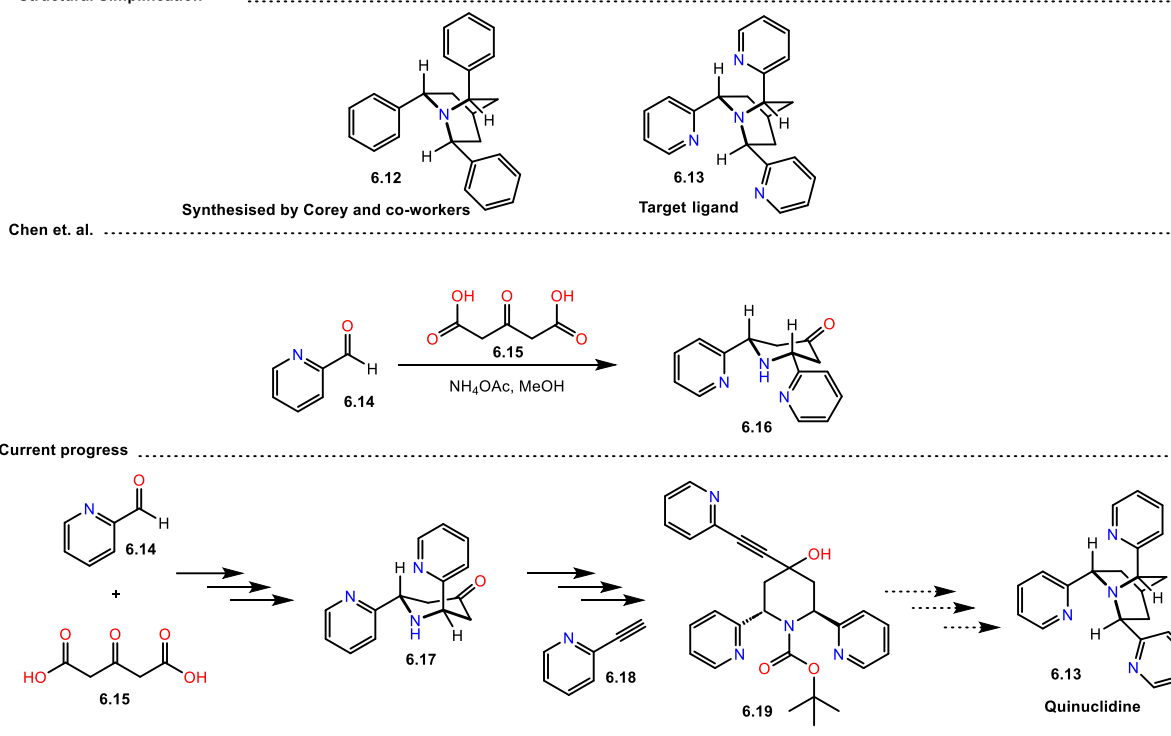
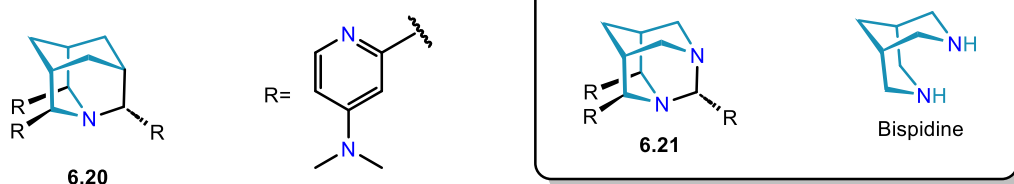


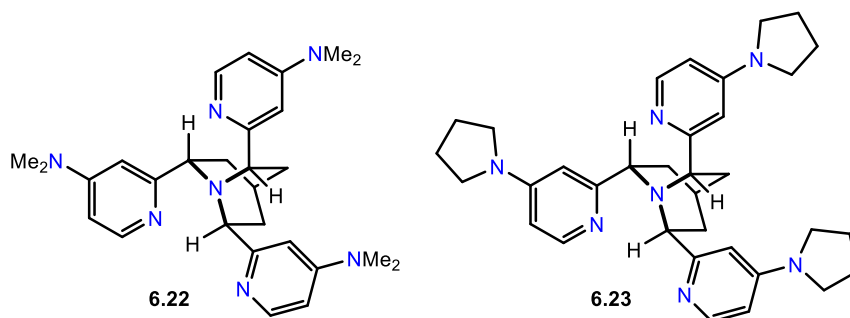
**Fig 5:** Serendipitous discoveries and the current state of the synthesis of the model quinuclidine ligand highlighted in Chapter five.

In the future, the synthesis of the quinuclidine ligand complex from chapter five needs to be finished, then it needs to be adapted for the dimethyl amino **6.22** and pyrrolidine **6.23** substituted ligands (**Fig 6**). Furthermore, the development of bispidine-based ligands **6.21** as a potentially structurally simplified synthetic ligand target is interesting since the azaadamantane ligands **6.20** are evaluated to be 28 times more activating than even the quinuclidine ligands targeted in this work. Finally, although piperidine-based ligands **6.25**, **6.26** are previously computed<sup>1</sup> to be less active than both the azaadamantane and quinuclidine ligands, it remains superior to currently synthesized mediator complexes. The already prepared *trans*-2,6-di(pyridin-2-yl)piperidin-4-one **6.17** in principle can serve as an advanced intermediate in the synthesis of the model piperidine ligand **6.24**.

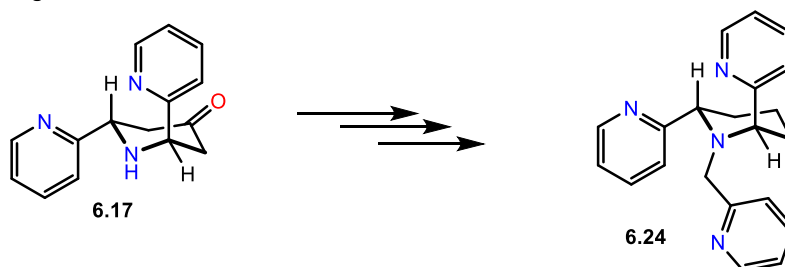
#### Azaadamantane ligand and derivatives



#### Desired Compound



#### Piperidine ligands



#### Substituted Piperidine ligands

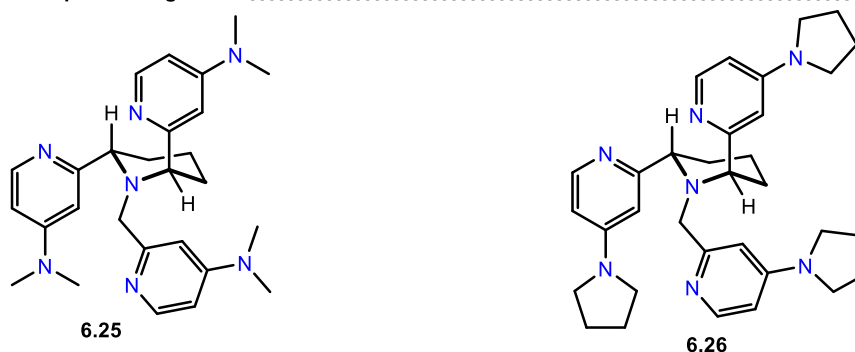


**Fig 6:** Alternative ligand structural targets that can be targeted in future work.

#### Concluding statement

Finally, we have explored the possibility of adapting the methodologies developed to further atom transfer radical polymerization, where we found a myriad of possibilities where there are crossovers between the worlds of small molecule synthesis and material chemistry. There are clear avenues forward with each of the projects detailed within this thesis, from developing enantioselective C–N formations without the need for stimuli such as irradiation

or electric currents to developing air-tolerant palladium cross-coupling reactions. We hope to have demonstrated the potential of these methodologies in the world of synthesis through this exploratory work.

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## ***Appendix Section 1 :***

### *Statements of contribution*

### Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with [https://policies.anu.edu.au/ppi/document/ANUP\\_003405](https://policies.anu.edu.au/ppi/document/ANUP_003405)

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: A mechanistic perspective on atom transfer radical polymerization

Authors: Alfred K.K. Fung, Michelle. L. Coote

Publication outlet: Polymer International

Current status of paper: Not Yet Submitted/Submitted/Under Revision/Accepted/Published

Contribution to paper: Alfred K.K. Fung collaborated with Professor Michelle L. Coote in the initial drafting. Professor Michelle L. Coote edited the manuscript.

Senior author or collaborating authors endorsement: \_\_\_\_\_

Kam Ki Alfred Fung  
Candidate – Print Name

  
Signature

04/05/2023  
Date

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Michelle Coote \_\_\_\_\_  \_\_\_\_\_ 13/5/23

Primary Supervisor – Print Name

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I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: Atom Transfer Radical Polymerization-Inspired Room Temperature (sp<sup>3</sup>)C–N Coupling

Authors: Alfred. K. K. Fung, Li-Juan Yu, Michael S. Sherburn, and Michelle L. Coote

Publication outlet: Journal of Organic Chemistry

Current status of paper: Not Yet Submitted/Submitted/Under Revision/Accepted/**Published**

Contribution to paper: Alfred. K. K. Fung completed all synthetic work present. Project was conceived designed and evolved in collaboration between Alfred. K. K. Fung, Prof. M. L. Coote and Prof. M. S. Sherburn. Dr Li-Juan Yu performed the DFT calculations under the direction of Prof. M.L. Coote who performed the mechanistic analysis. Alfred K.K. Fung collaborated with Professor Michelle L. Coote and Professor Michael S. Sherburn in the initial drafting. Professors Michelle L. Coote and Michael S. Sherburn edited the manuscript.

Senior author or collaborating authors endorsement:

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Candidate – Print Name

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Michelle Coote \_\_\_\_\_ *Michelle Coote* \_\_\_\_\_ 13/5/23

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Delegated Authority – Print Name \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

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I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: Optimized Cadiot–Chodkiewicz cross–couplings in air

Authors: Alfred. K. K. Fung, Madison J. Sowden, Michelle L. Coote, Michael S. Sherburn

Publication outlet: Organic Letters

Current status of paper: Not Yet Submitted/**Submitted**/Under Revision/Accepted/Published

Contribution to paper: Alfred. K. K. Fung completed all experimental work present. Project was conceived, designed, and evolved in collaboration between Alfred. K. K. Fung and the other authors. The Manuscript was drafted and edited in collaboration between Prof. Michelle L. Coote and Prof. Michael S. Sherburn.

Senior author or collaborating authors endorsement:

Kam Ki Alfred Fung  
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Signature

04/05/2023  
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Michelle Coote \_\_\_\_\_  \_\_\_\_\_ 13/5/23

Primary Supervisor – Print Name

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### Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with [https://policies.anu.edu.au/ppl/document/ANUP\\_003405](https://policies.anu.edu.au/ppl/document/ANUP_003405)

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Title: Toward the synthesis of better ATRP ligands

Authors: Alfred K. K. Fung, Michelle L Coote, Michael S. Sherburn

Publication outlet: To be determined

Current status of paper: **Not Yet Submitted**/Submitted/Under Revision/Accepted/Published

Contribution to paper: Alfred K. K. Fung completed all experimental work present, Project was conceived designed and evolved in collaboration between Alfred K. K. Fung, Prof. Michelle L. Coote and Prof. Michael S. Sherburn

Senior author or collaborating authors endorsement:

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04/05/2023  
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Signature

Date

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Date

## ***Appendix Section 2 :***

*Supporting information For Ch. 3.*

For the supporting information of the publication Atom transfer radical polymerisation -inspired room temperature ( $\text{sp}^3$ ) C–N coupling.

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.1c01029>.

### ***Appendix Section 3 :***

*Supporting information for Ch. 4*

Supporting Information for

## **Air Tolerant Cross-Couplings For C-C Bond Formation**

Alfred K. K. Fung, Madison J. Sowden,  
Michelle L. Coote, and Michael S. Sherburn\*

## Contents

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## General Methods

### NMR Spectroscopy

$^1\text{H}$  NMR spectra were recorded at 400 MHz using a Bruker AVANCE 400 spectrometer or at 600 MHz using a Bruker AVANCE 600 spectrometer in  $\text{CDCl}_3$ . Residual protio-solvent peaks were used as an internal reference for  $^1\text{H}$  NMR spectra ( $\text{CHCl}_3$   $\delta$  7.26 ppm). Coupling constants ( $J$ ) are quoted to the nearest 0.1 Hz. The assignment of proton signals was assisted by COSY, HSQC and HMBC experiments where necessary.  $^{13}\text{C}$  NMR spectra were recorded at 101 MHz using a Bruker AVANCE 400 spectrometer or at 175 MHz using a Bruker AVANCE 700 spectrometer in  $\text{CDCl}_3$ . Solvent peaks were used as an internal reference for  $^{13}\text{C}$  NMR spectra ( $\text{CDCl}_3$   $\delta$  77.0 ppm). Assignment of carbon signals was assisted by HSQC and HMBC experiments. The following abbreviations (or combinations thereof) are used to denote  $^1\text{H}$  NMR multiplicities: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet.

### Mass Spectrometry

Low-resolution EI mass spectra were recorded on an Agilent HP 6890 gas chromatograph/mass spectrometer with a 7683 series injector fitted with a Phenomenex Zebron ZB-1 column (15 m length x 0.25 mm internal diameter x 0.25  $\mu\text{m}$  film thickness) using EI+ ionization mode at 70 eV or a Finnigan Polaris Q ion trap mass spectrometer using electron impact (EI+) ionization mode at 40 or 70 eV. High-resolution EI mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. Low-resolution ESI mass spectra were recorded on a Micromass ZMD spectrometer using electrospray (ESI+) ionization mode. High resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) spectrometer using electrospray ionization (ESI+).

### Melting Points

Melting points were measured on a Stanford Research Systems Optimelt Automated Melting Point System and are uncorrected.

### Experimental Procedures, Reagents, and Glassware

Reactions were conducted in a 2 mL glass vial under a standard lab (air) atmosphere, at room temperature, unless specified otherwise. Anhydrous solvents were either obtained from commercial sources or dried according to the procedure outlined by Grubbs and co-workers.<sup>11</sup> Commercially available chemicals were used as purchased, or where specified, purified by standard techniques.<sup>2</sup>

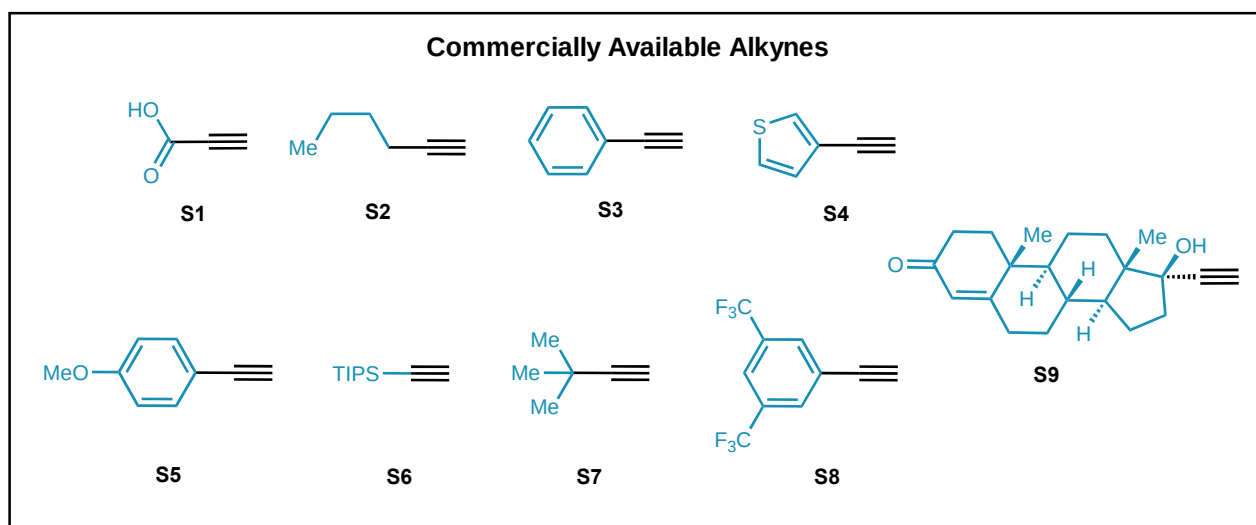
## Chromatography

Analytical thin-layer chromatography was conducted with aluminum-backed silica gel 60 F<sub>254</sub> (0.2 mm) plates supplied by Merck, and visualized using UV fluorescence ( $\lambda_{\text{max}} = 254$  nm), or developed using KMnO<sub>4</sub> or *p*-anisaldehyde stains, followed by heating. Flash chromatography employed Merck Kieselgel 60 silica gel (230–400 mesh). PS 40–60 °C refers to petroleum spirits, boiling point fraction 40–60 °C. PS 30–40 °C refers to petroleum spirits, boiling point fraction 30–40 °C.

## Optical Rotations

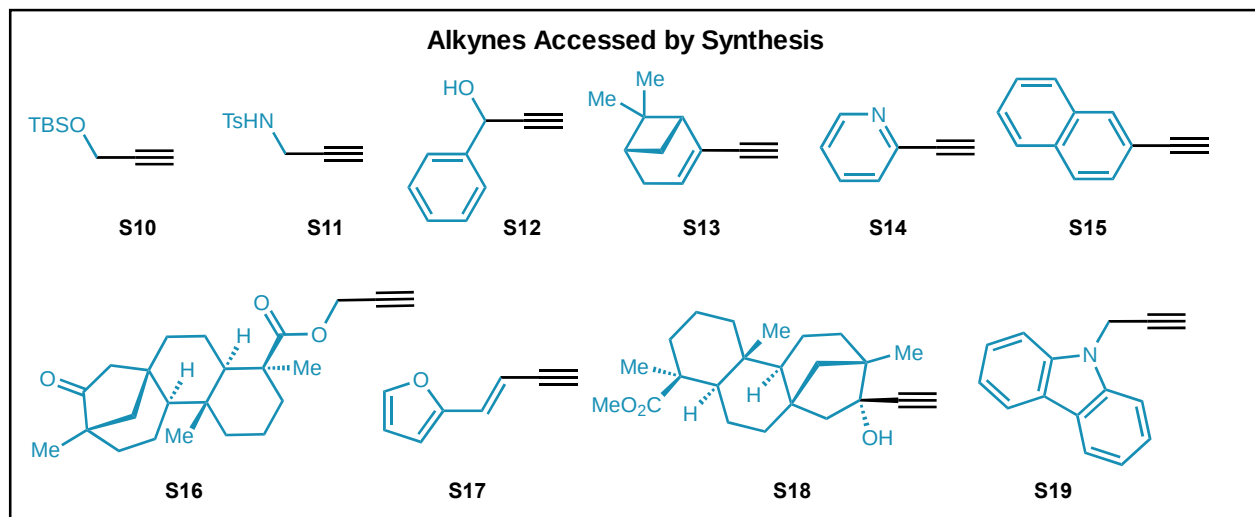
Optical rotations were measured on a Rudolph Research Analytical Autopol I Automatic Polarimeter using a sodium lamp (589 nm) as the light source over a path length of 10 cm.  $[\alpha]_{\text{D}}$  values are reported in units of  $\text{deg} \cdot \text{mL} \cdot \text{g}^{-1} \cdot \text{dm}^{-1}$  at room temperature (20 °C) at a concentration (*c*) in g/100 mL.

## Commercial Terminal Alkynes



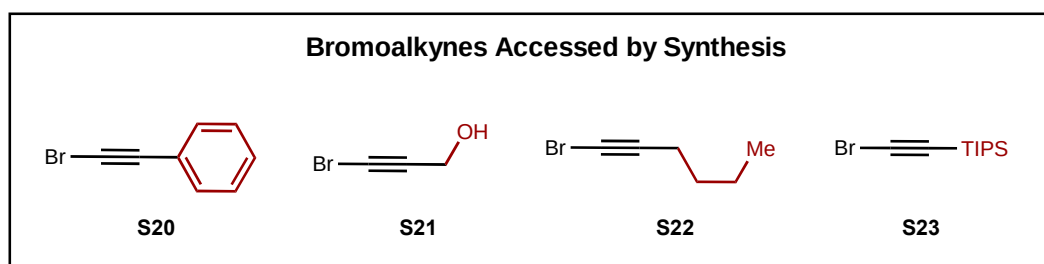
Alkynes S1-S9 were purchased from commercial sources and were used as received.

## Synthesis of Terminal Alkynes



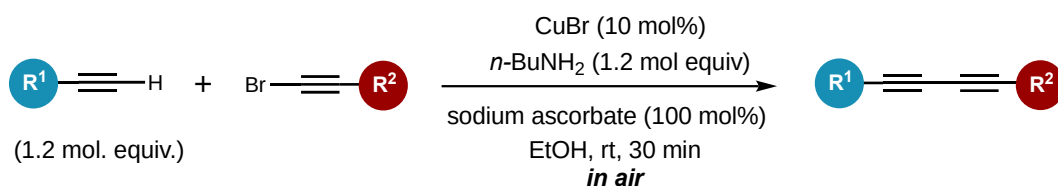
*tert*-Butyldimethyl(prop-2-yn-1-yloxy)silane (**S10**), 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**S11**), 1-phenylprop-2-yn-1-ol (**S12**), (1*R*,5*S*)-3-ethynyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (**S13**), 2-ethynylpyridine (**S14**), 2-ethynynaphthalene (**S15**), prop-2-yn-1-yl(4*S*,4*aR*,6*aR*,9*S*,11*aS*,11*bR*)-4,9,11*b*-trimethyl-8-oxotetradecahydro-6*a*,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (**S16**), (*E*)-2-(but-1-en-3-yn-1-yl)furan (**S17**), methyl (4*S*,4*aR*,6*aR*,8*R*,9*S*,11*aS*,11*bR*)-8-ethynyl-8-hydroxy-4,9,11*b*-trimethyltetradecahydro-6*a*,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (**S18**) and 9-(prop-2-yn-1-yl)-9*H*-carbazole (**S19**) were prepared according to literature procedures.<sup>3,4,5,6,7,8,9,10,11</sup>

## Synthesis of Bromoalkynes



(Bromoethynyl)benzene (**S20**), 3-bromoprop-2-yn-1-ol (**S21**), 1-bromohex-1-yne (**S22**) and (bromoethynyl)triisopropylsilane (**S23**) were prepared according to literature procedures.<sup>12,13,14,15</sup>

## Standard Procedure A: Cadiot-Chodkiewicz Cross-Couplings



To a stirred, cooled (ice bath) suspension of ethanol (0.5 mL), CuBr (3.6 mg, 0.025 mmol, 10 mol%) and sodium ascorbate (50 mg, 0.25 mmol, 1.0 mol. equiv) in a vial open to the air was added a solution of the terminal alkyne (0.30 mmol, 1.2 mol. equiv.) in ethanol (0.5 mL) followed by *n*-butylamine (52  $\mu$ L, 0.25 mmol, 1.0 mol. equiv.). A solution of 1-bromoalkyne (0.25 mmol) in ethanol (0.5 mL) was added, the reaction mixture was removed from the ice bath and allowed to stir at room temp for 30 minutes. Work up, isolation and purification were performed as described below.

### *tert*-Butyldimethyl((5-phenylpenta-2,4-diyn-1-yl)oxy)silane (3)



Prepared according to **Standard Procedure A** as a white powder (57 mg, 0.21 mmol, 84%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (100% PS 30-40  $^{\circ}$ C).

Characterization data corresponded to those reported in the literature.<sup>16</sup>

**R<sub>f</sub>** = 0.33 (PS 30-40)

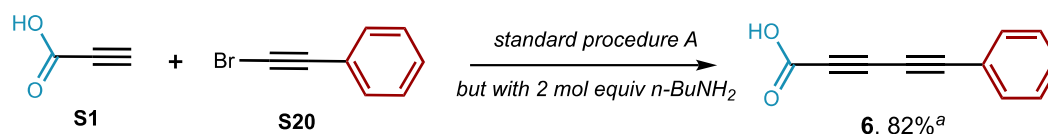
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.49 (d, *J* = 6.9 Hz, 2H), 7.34 (m, 3H), 4.46 (s, 2H), 2.17 (s, 1H), 0.92 (s, 9H), 0.15 (s, 6H) ppm

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 132.7, 129.3, 128.5, 121.8, 81.3, 78.1, 73.7, 69.6, 52.4, 25.9, 18.5, -5.0 ppm

**MS** (70 eV, EI): *m/z* (%): 270.1 ([M]<sup>+</sup>•, 100)

**HRMS** (EI): calcd for C<sub>17</sub>H<sub>22</sub>OSi: 270.1440; found: 270.1438.

### 5-Phenylpenta-2,4-diynoic acid (6)



Prepared according to **Standard Procedure A** but with 2 equiv of amine as a white solid (35 mg, 0.21 mmol, 82%).

**Work up:** the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (30 mL) and extracted with 1 M aqueous  $\text{NaOH}$  ( $3 \times 10$  mL). The combined aqueous phase was acidified with 2M aqueous  $\text{HCl}$  (60 mL) and the product was extracted into  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give the product.

**Purification:** no purification was required.

Characterization data corresponded to those reported in the literature.<sup>17</sup>

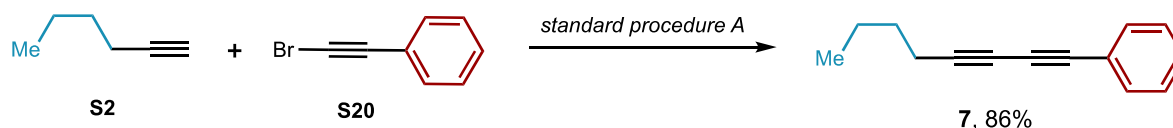
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.01 (s, 1H), 7.58 (d,  $J$  = 7.5 Hz, 2H), 7.46 (t,  $J$  = 7.4 Hz, 1H), 7.38 (t,  $J$  = 7.6 Hz, 2H) ppm

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 156.3, 133.3, 130.9, 128.8, 119.9, 85.1, 73.8, 72.0, 71.0 ppm

**MS** (70 eV, EI):  $m/z$  (%): 170.0 ( $[\text{M}]^{+\bullet}$ , 100), 126.0 ( $[\text{M}-\text{CO}_2]^{+\bullet}$ , 100)

**HRMS** (EI): calcd for  $\text{C}_{11}\text{H}_6\text{O}_2$ : 170.0368; found: 170.0368.

### Octa-1,3-diyn-1-ylbenzene (7)



Prepared according to **Standard Procedure A** as a colorless oil (39 mg, 0.22 mmol, 86%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (100% PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>16</sup>

$R_f$  = 0.62 (100% PS 30-40 °C).

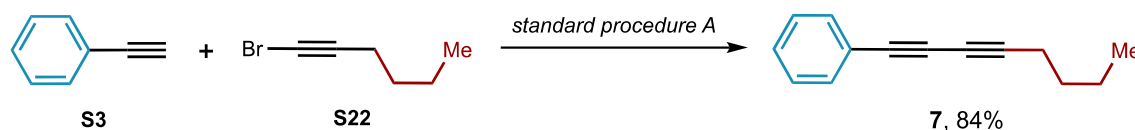
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.47 (d,  $J$  = 6.9 Hz, 2H), 7.36 – 7.27 (m, 3H), 2.37 (t,  $J$  = 7.0 Hz, 3H), 1.63 – 1.41 (m, 4H), 0.93 (t,  $J$  = 7.2 Hz, 3H) ppm.

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 132.6, 128.9, 128.5, 122.3, 85.0, 74.8, 74.5, 65.2, 30.4, 22.1, 19.4, 13.7 ppm.

**MS** (70 eV, EI):  $m/z$  (%): 182.1 ( $[M]^{+\bullet}$ , 100)

**HRMS** (EI): calcd for  $C_{14}H_{14}$ : 182.1096; found: 182.1099.

#### Alternative Synthesis of Octa-1,3-diyn-1-ylbenzene (7)



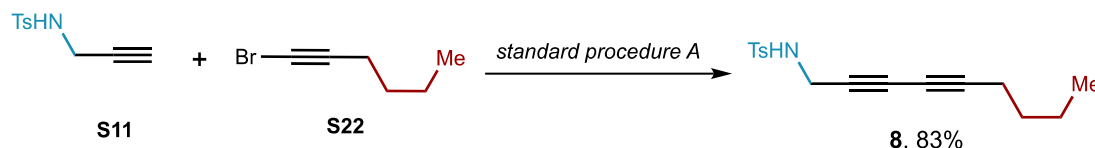
Prepared according to **Standard Procedure A** as a colorless oil (38 mg, 0.21 mmol, 84%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (100% PS 30-40 °C).

Characterization data corresponded to those reported above and in the literature.<sup>16</sup>

#### 4-Methyl-*N*-(nona-2,4-diyn-1-yl)benzenesulfonamide (8)



Prepared according to **Standard Procedure A** as a brown foam (60 mg, 0.21 mmol, 83%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (30% diethyl ether in PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>18</sup>

$R_f$  = 0.47 (30% diethyl ether in PS 30-40 °C)

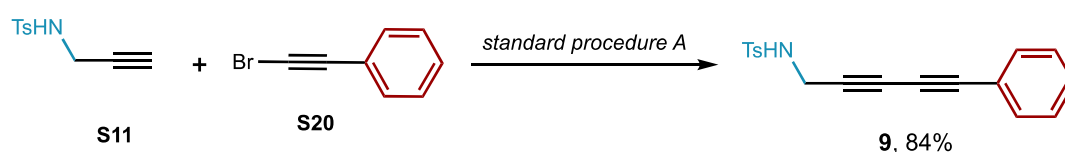
**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.76 (d,  $J$  = 8.3 Hz, 2H), 7.33 (d,  $J$  = 8.0 Hz, 2H), 4.48 (s, 1H), 3.89 (d,  $J$  = 6.1 Hz, 2H), 2.43 (s, 3H), 2.23 (t,  $J$  = 6.9 Hz, 2H), 1.53 – 1.32 (m, 4H), 0.90 (t,  $J$  = 7.2 Hz, 3H) ppm.

**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 144.0, 136.6, 129.8, 127.5, 81.2, 70.0, 69.6, 64.2, 33.8, 30.2, 22.0, 21.7, 18.9, 13.6 ppm.

**MS** (ESI):  $m/z$  (%): 312.1 ( $[M+Na]^{+\bullet}$ , 100)

**HRMS** (ESI): calcd for  $C_{16}H_{19}NO_2SNa$ : 312.1034; found: 312.1039.

#### 4-Methyl-*N*-(5-phenylpenta-2,4-diyn-1-yl)benzenesulfonamide (9)



Prepared according to **Standard Procedure A** as a pale yellow oil (65 mg, 0.21 mmol, 84%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (30% diethyl ether in PS 30-40 °C).

**R<sub>f</sub>** = 0.41 (30% diethyl ether in PS 30-40 °C)

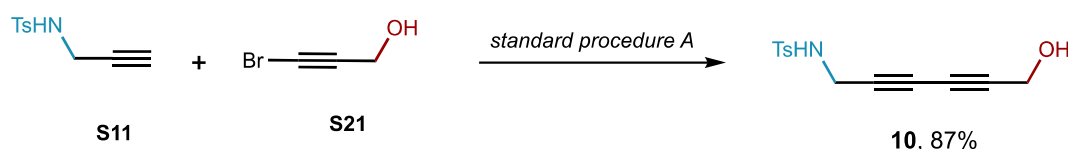
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.81 (d, *J* = 7.4 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.43 – 7.31 (m, 5H), 4.54 (s, 1H), 4.03 (s, 2H), 2.44 (s, 3H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 144.3, 136.6, 132.7, 130.0, 129.6, 128.6, 127.6, 121.3, 78.2, 76.6, 73.0, 69.7, 34.0, 21.8 ppm.

**MS** (ESI): *m/z* (%): 332.1 ([M+Na]<sup>+</sup>•, 100)

**HRMS** (ESI): calcd for C<sub>18</sub>H<sub>15</sub>NO<sub>2</sub>SNa: 332.0721; found: 332.0725.

### *N*-(6-Hydroxyhexa-2,4-diyn-1-yl)-4-methylbenzenesulfonamide (10)



Prepared according to **Standard Procedure A** as a pale yellow solid (57 mg, 0.22 mmol, 87%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (50% diethyl ether in PS 30-40 °C).

**Melting point:** >400 °C

**R<sub>f</sub>** = 0.30 (50% diethyl ether in PS 30-40 °C)

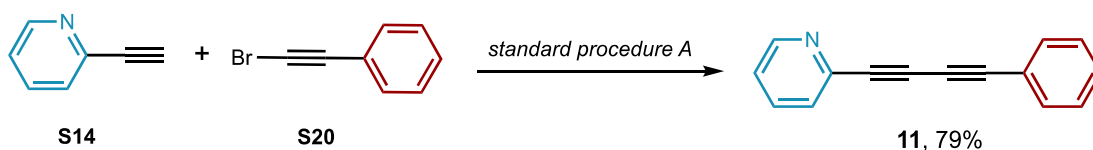
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.72 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.90 (t, *J* = 6.3 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.84 (d, *J* = 6.2 Hz, 2H), 3.25 (t, *J* = 6.3 Hz, 1H), 2.42 (s, 3H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CD<sub>3</sub>CN):  $\delta$  = 145.1, 138.0, 130.7, 128.1, 79.3, 75.2, 68.5, 68.4, 50.9, 33.9, 21.6 ppm.

**MS** (ESI): *m/z* (%): 286.1 ([M+Na]<sup>+</sup>•, 100)

**HRMS** (ESI): calcd for C<sub>13</sub>H<sub>13</sub>NO<sub>3</sub>SNa: 286.0514; found: 286.0513.

### 2-(Phenylbuta-1,3-diyn-1-yl)pyridine (11)



Prepared according to **Standard Procedure A** as a light brown solid (40 mg, 0.20 mmol, 79%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (10% diethyl ether in PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>19</sup>

**R<sub>f</sub>** = 0.43 (10% diethyl ether in PS 30-40 °C)

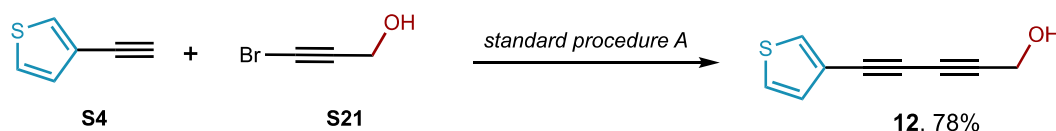
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.62 (d, *J* = 4.8 Hz, 1H), 7.73 – 7.64 (m, 1H), 7.57 – 7.50 (m, 3H), 7.44 – 7.31 (m, 3H), 7.30 – 7.25 (m, 1H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.3, 142.3, 136.2, 132.7, 129.6, 128.5, 128.1, 123.5, 121.3, 82.5, 80.1, 73.9, 73.5 ppm.

**MS** (70 eV, EI): *m/z* (%): 203.1 ([M]<sup>+</sup>•, 100).

**HRMS** (EI): calcd for C<sub>15</sub>H<sub>9</sub>N: 203.0735; found: 203.0737.

#### 5-(Thiophen-3-yl)penta-2,4-diyn-1-ol (12)



Prepared according to **Standard Procedure A** as a brown oil (32 mg, 0.20 mmol, 78%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (30% diethyl ether in PS 30-40 °C).

Characterization data corresponded to those reported in the literature. **Error! Bookmark not defined.**

**R<sub>f</sub>** = 0.53 (30% diethyl ether in PS 30-40 °C)

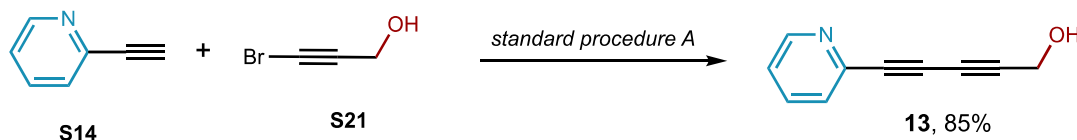
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.62 – 7.58 (m, 1H), 7.31 – 7.27 (m, 1H), 7.19 – 7.14 (m, 1H), 4.43 (d, *J* = 1.4 Hz, 2H), 1.82 (s, 1H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 131.8, 130.3, 125.8, 120.6, 80.4, 74.0, 73.0, 70.6, 51.8 ppm.

**MS** (70 eV, EI): *m/z* (%): 162.0 ([M]<sup>+</sup>•, 100)

**HRMS** (EI): calcd for C<sub>9</sub>H<sub>6</sub>OS: 162.0139; found: 162.0137.

#### 5-(Pyridin-2-yl)penta-2,4-diyn-1-ol (13)



Prepared according to **Standard Procedure A** as a yellow foam (33 mg, 0.21 mmol, 85%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (30% diethyl ether in PS 30-40 °C).

$R_f$  = 0.35 (30% diethyl ether in PS 30-40 °C)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.58 (d,  $J$  = 4.4 Hz, 1H), 7.68 (t,  $J$  = 7.8 Hz, 1H), 7.50 (d,  $J$  = 7.8 Hz, 1H), 7.32 – 7.27 (m, 1H), 4.44 (s, 2H) ppm.

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 150.1, 142.0, 136.6, 128.5, 123.9, 82.8, 76.5, 74.0, 69.5, 51.3 ppm.

**MS** (70 eV, EI):  $m/z$  (%): 157.1 ( $[\text{M}]^{+\bullet}$ , 100).

**HRMS** (EI): calcd for  $\text{C}_{10}\text{H}_7\text{NO}$ : 157.0528; found: 157.0526.

#### 5-(3,5-Bis(trifluoromethyl)phenyl)penta-2,4-diyne-1-ol (**14**)



Prepared according to **Standard Procedure A** as a white solid (turns red slowly in air) (61 mg, 0.21 mmol, 84 %).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (10% diethyl ether in PS 30-40 °C).

**Melting Point:** 225.9 – 230.2 (10% ether in PS 30-40)

$R_f$  = 0.47 (10% diethyl ether in PS 30-40 °C)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.91 (s, 2H), 7.85 (s, 1H), 4.45 (s, 2H) ppm.

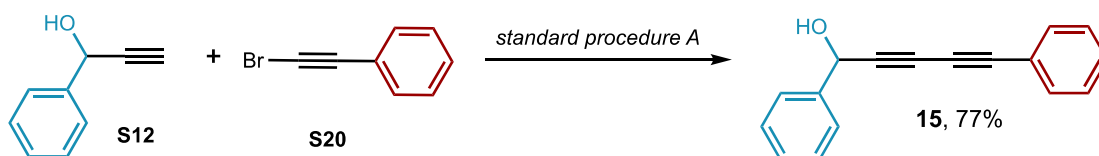
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 133.2 – 131.6 (q,  $J$  = 33.9 Hz), 132.7 – 132.4 (m), 124.1, 122.7 (q,  $J$  = 273.0 Hz), 123.0 – 122.6 (m), 82.7, 77.2, 76.6, 75.0, 69.7, 51.7 ppm.

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –63.2 ppm

**MS** (70 eV, EI):  $m/z$  (%): 292.0 ( $[\text{M}]^{+\bullet}$ , 100)

**HRMS** (EI): calcd for  $\text{C}_{13}\text{H}_6\text{F}_6\text{O}$ : 292.0323; found: 292.0325.

#### 1,5-Diphenylpenta-2,4-diyne-1-ol (**15**)



Prepared according to **Standard Procedure A** as a white foam (44 mg, 0.19 mmol, 77%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (10% diethyl ether in PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>20</sup>

$R_f$  = 0.26 (100% PS 30-40 °C)

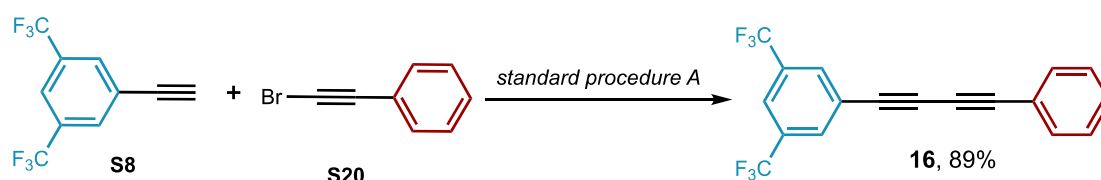
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.41 (d,  $J$  = 7.3 Hz, 2H), 7.35 (d,  $J$  = 6.8 Hz, 2H), 7.30 – 7.15 (m, 6H), 5.46 (d,  $J$  = 6.2 Hz, 1H), 2.08 (d,  $J$  = 6.3 Hz, 1H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 139.8, 132.7, 129.6, 128.9, 128.9, 128.6, 126.8, 121.5, 81.7, 79.6, 73.3, 71.5, 65.4 ppm.

**MS** (70 eV, EI):  $m/z$  (%): 232.1 ([M]<sup>+</sup>•, 100)

**HRMS** (EI): calcd for C<sub>17</sub>H<sub>12</sub>O: 232.0883; found: 232.0879.

### 1-(Phenylbuta-1,3-diyn-1-yl)-3,5-bis(trifluoromethyl)benzene (16)



Prepared according to **Standard Procedure A** as a pale yellow solid (75 mg, 0.22 mmol, 89%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (100% PS 30-40 °C).

**Melting Point:** 103.2 – 105.6 °C (PS 30-40°C)

$R_f$  = 0.54 (100% PS 30-40 °C)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.97 (s, 2H), 7.87 (s, 1H), 7.66 – 7.50 (m, 2H), 7.41 (m, 3H) ppm.

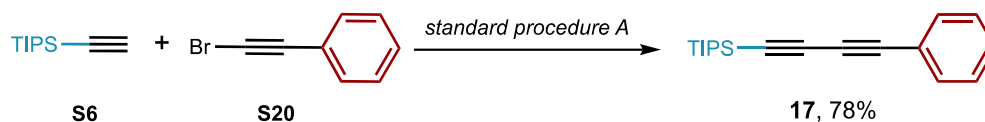
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 132.7, 132.3 – 132.1 (m), 132.2 (q,  $J$  = 33.8 Hz), 129.8, 128.6, 124.4, 122.8 (q,  $J$  = 273.6 Hz), 122.5 – 122.2 (m), 121.0, 83.7, 77.8, 77.4, 72.9 ppm.

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta$  = –63.2 ppm.

**MS** (70 eV, EI):  $m/z$  (%): 338.1 ([M]<sup>+</sup>•, 100)

**HRMS** (EI): calcd for C<sub>18</sub>H<sub>8</sub>F<sub>6</sub>: 338.0530; found: 338.0527.

### Triisopropyl(phenylbuta-1,3-diyn-1-yl)silane (17)



Prepared according to **Standard Procedure A** as a colorless oil (55 mg, 0.20 mmol, 78%)

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (100% PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>16</sup>

$R_f$  = 0.75 (100% PS 30-40 °C)

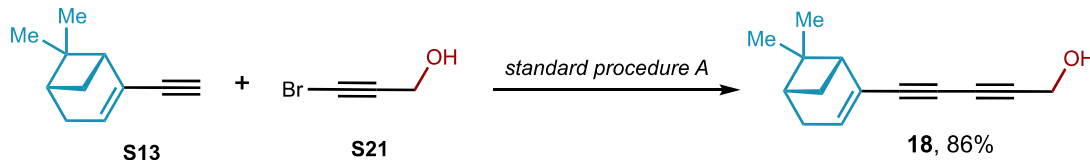
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.51 (d,  $J$  = 7.9, 2H), 7.43 – 7.29 (m, 3H), 1.39 – 0.92 (m, 21H) ppm.

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 132.8, 129.4, 128.5, 121.7, 89.6, 88.0, 75.7, 74.81 18.7, 11.5 ppm.

**MS** (70 eV, EI):  $m/z$  (%): 282.2 ( $[\text{M}]^{+\bullet}$ , 10)

**HRMS** (EI): calcd for  $\text{C}_{19}\text{H}_{26}\text{Si}$ : 282.1798; found: 282.1805.

### 5-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)penta-2,4-diyn-1-ol (18)



Prepared according to **Standard Procedure A** as a white solid (turns red slowly in air) (43 mg, 0.22 mmol, 86%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (20% diethyl ether in PS 30-40 °C).

**Melting point:** 213.4 - 218.9°C (20% diethyl ether in PS 30-40°C)

$R_f$  = 0.32 (20% diethyl ether in PS 30-40 °C)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.18 (s, 1H), 4.38 (s, 2H), 2.61 – 2.20 (m, 4H), 2.11 (s, 1H), 1.29 (s, 3H), 1.26 – 1.20 (m, 2H), 0.87 (s, 3H) ppm

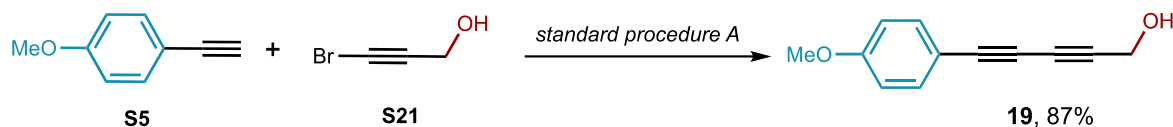
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 135.9, 128.8, 80.8, 79.4, 73.2, 70.9, 51.9, 46.7, 40.2, 38.1, 32.5, 31.5, 26.1, 21.2 ppm

**MS** (70 eV, EI):  $m/z$  (%): 200.1 ( $[\text{M}]^{+\bullet}$ , 100)

**HRMS** (EI): calcd for  $\text{C}_{14}\text{H}_{16}\text{O}$ : 200.1196; found: 200.1201.

$$[\alpha]_D^{23} = -27^\circ \text{ (c = 0.50, dichloromethane)}$$

### 5-(4-Methoxyphenyl)penta-2,4-diyn-1-ol (19)



Prepared according to **Standard Procedure A** as a white foam (41 mg, 0.22 mmol, 87%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (20% diethyl ether in PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>21</sup>

$R_f$  = 0.31 (20% diethyl ether in PS 30-40 °C)

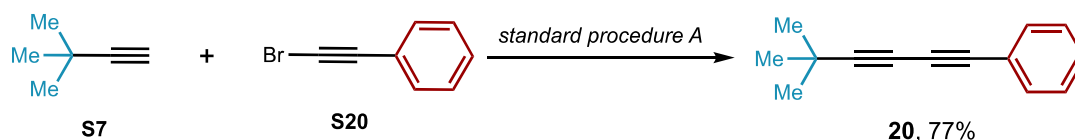
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.44 (d,  $J$  = 8.5 Hz, 2H), 6.84 (d,  $J$  = 8.6 Hz, 2H), 4.42 (d,  $J$  = 5.2 Hz, 2H), 3.82 (s, 3H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 160.6, 134.4, 114.3, 113.4, 80.0, 79.0, 72.1, 70.9, 55.5, 51.9 ppm.

**MS** (70 eV, EI):  $m/z$  (%): 186.1 ([M]<sup>+</sup>•, 100)

**HRMS** (EI): calcd for C<sub>12</sub>H<sub>12</sub>O<sub>2</sub>: 186.0675; found: 186.0680.

### 5,5-Dimethylhexa-1,3-diyn-1-ylbenzene (20)



Prepared according to **Standard Procedure A** as a white foam (35 mg, 0.19 mmol, 77%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (100% PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>Error! Bookmark not defined.</sup>

$R_f$  = 0.55 (100% PS 30-40 °C)

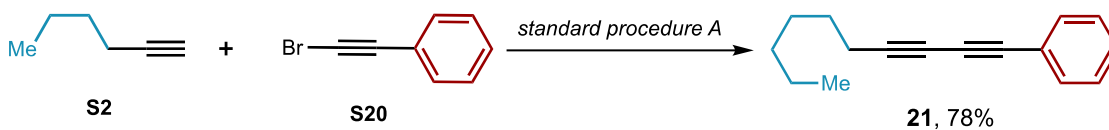
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.46 (d,  $J$  = 7.9 Hz, 2H), 7.36 – 7.27 (m, 3H), 1.29 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 132.6, 128.9, 128.5, 122.3, 92.4, 76.1, 74.3, 63.9, 30.7, 28.5 ppm.

**MS** (70 eV, EI):  $m/z$  (%): 182.1 ([M]<sup>+</sup>•, 100).

**HRMS** (EI): calcd for C<sub>14</sub>H<sub>14</sub>: 182.1096; found: 182.1097.

### Deca-1,3-diyn-1-ylbenzene (21)



Prepared according to **Standard Procedure A** as a colorless oil (41 mg, 0.20 mmol, 78%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (100% PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>22</sup>

**R<sub>f</sub>** = 0.62 (100% PS 30-40 °C)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.54 – 7.43 (m, 2H), 7.40 – 7.27 (m, 3H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.63 – 1.50 (m, 2H), 1.42 (t, *J* = 7.5 Hz, 2H), 1.30 – 1.17 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 132.6, 128.9, 128.5, 122.3, 85.1, 74.8, 74.6, 65.2, 31.5, 28.7, 28.4, 22.7, 19.8, 14.2 ppm.

**MS** (70 eV, EI): *m/z* (%): 210.1 ([M]<sup>+</sup>, 100).

**HRMS** (EI): calcd for C<sub>16</sub>H<sub>18</sub>: 210.1409; found: 210.1406.

### 2-(Phenylbuta-1,3-diyn-1-yl)naphthalene (22)



Prepared according to **Standard Procedure A** as a white solid (54 mg, 0.21 mmol, 85%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (100% PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>Error! Bookmark not defined.</sup>

**R<sub>f</sub>** = 0.43 (100% PS 30-40 °C)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.08 (s, 1H), 7.85 – 7.78 (m, 3H), 7.58 – 7.49 (m, 5H), 7.41 – 7.32 (m, 3H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 133.3, 133.2, 133.0, 132.7, 129.4, 128.6, 128.6, 128.3, 128.0, 128.0, 127.4, 126.9, 122.0, 119.2, 82.2, 81.9, 74.4, 74.2 ppm.

**MS** (70 eV, EI): *m/z* (%): 252.1 ([M]<sup>+</sup>, 100).

**HRMS** (EI): calcd for C<sub>20</sub>H<sub>12</sub>O<sub>2</sub>: 252.0939; found: 252.0941.

**((E)-7-(Furan-2-yl)hepta-6-en-2,4-diyn-1-ol (23)**



Prepared according to **Standard Procedure A** as a brown oil (34 mg, 0.20 mmol, 80%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (30% diethyl ether in PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>23</sup>

**R<sub>f</sub>** = 0.52 (30% diethyl ether in PS 30-40 °C)

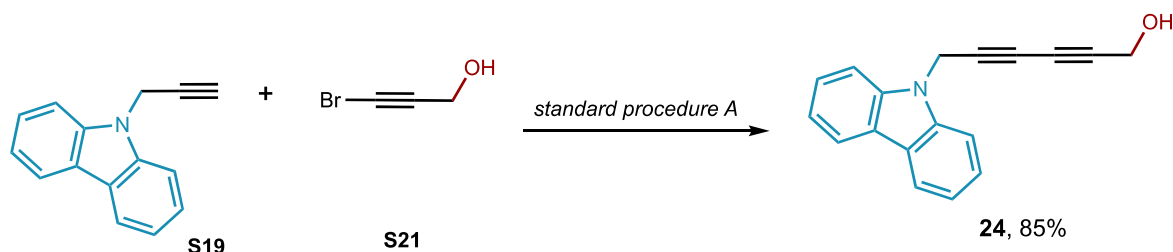
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.40 (s, 1H), 6.83 (d, *J* = 16.0 Hz, 1H), 6.47 – 6.36 (m, 2H), 6.07 (d, *J* = 16.0 Hz, 1H), 4.41 (s, 2H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 151.8, 143.9, 131.7, 112.3, 111.6, 104.4, 81.5, 78.5, 76.2, 71.0, 51.9 ppm.

**MS** (70 eV, EI): *m/z* (%): 172.1 ([M]<sup>+</sup>•, 100).

**HRMS** (EI): calcd for C<sub>11</sub>H<sub>8</sub>O<sub>2</sub>: 172.0524; found: 172.0525.

**9-(5-Phenylpenta-2,4-diyn-1-yl)-9H-carbazole (24)**



Prepared according to **Standard Procedure A** as a white solid (rapidly turns red under ambient light) (52 mg, 0.21 mmol, 85%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (10% diethyl ether in PS 30-40 °C).

Characterization data corresponded to those reported in the literature.<sup>24</sup>

**R<sub>f</sub>** = 0.51 (10% diethyl ether in PS 30-40 °C)

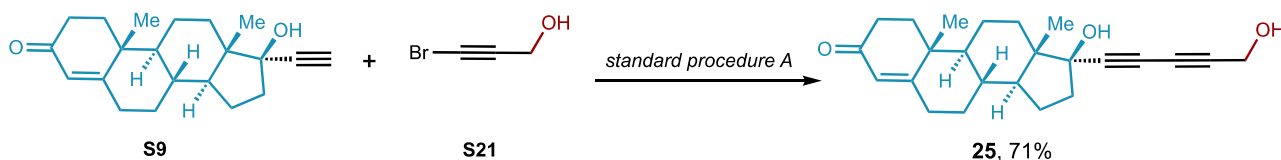
**<sup>1</sup>H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  = 8.03 (s, 2H), 7.43 – 7.29 (m, 4H), 7.19 (ddd, *J* = 8.0, 6.5, 1.6 Hz, 2H), 5.06 (s, 2H), 4.15 (s, 2H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  = 139.8, 126.0, 123.3, 120.4, 119.7, 108.7, 77.2, 74.0, 69.0, 67.6, 51.1, 33.0 ppm.

**MS** (ESI):  $m/z$  (%): 282.1 ( $[M+Na]^+$ , 100)

**HRMS** (ESI): calcd for  $C_{18}H_{13}NONa$ : 282.0895; found: 282.0897.

**(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-Hydroxy-17-(5-hydroxypenta-1,3-diyn-1-yl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (25)**



Prepared according to **Standard Procedure A** as a white solid (65 mg, 0.18 mmol, 71%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (30% diethyl ether in PS 30-40 °C).

**Melting Point:** 192.2 – 195.3 °C (10% ether in PS 30-40 °C)

$R_f$  = 0.24 (30% diethyl ether in PS 30-40 °C)

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 5.76 (s, 1H), 4.37 (s, 2H), 2.59 (s, 1H), 2.51 – 2.26 (m, 5H), 2.12 – 1.36 (m, 10H), 1.27 (s, 3H), 1.22 (m, 3H), 1.13 – 0.97 (m, 2H), 0.92 (s, 3H) ppm.

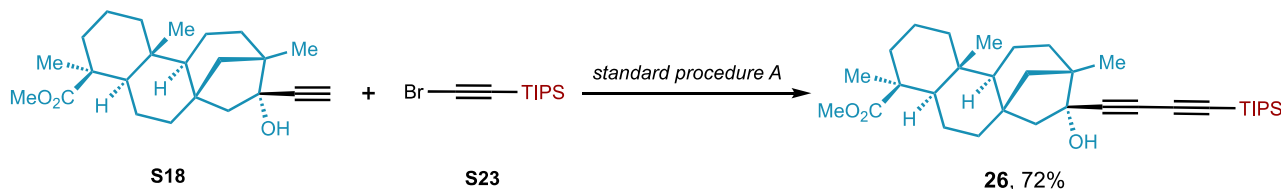
**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  = 199.4, 171.0, 123.7, 87.1, 79.5, 74.0, 69.6, 53.2, 51.3, 49.7, 46.5, 38.7, 38.5, 36.1, 35.5, 33.8, 32.6, 32.3, 31.3, 29.5, 22.9, 20.6, 17.3, 12.5 ppm.

**MS** (ESI):  $m/z$  (%): 366.2 ( $[M+Na]^+$ , 100)

**HRMS** (ESI): calcd for  $C_{24}H_{30}O_3Na$ : 389.2093; found: 389.2094.

$[\alpha]_D^{23} = -56^\circ$  (c = 0.50, dichloromethane)

**Methyl (4*S*,4*aR*,6*aR*,8*R*,9*S*,11*aS*,11*bR*)-8-hydroxy-4,9,11*b*-trimethyl-8-((triisopropylsilyl)buta-1,3-diyn-1-yl)tetradecahydro-6*a*,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (26)**



Prepared according to **Standard Procedure A** as a white solid (97 mg, 0.18 mmol, 72%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (30% diethyl ether in PS 30-40 °C).

**Melting point:** 382.3–387.4 °C (30% diethyl ether in PS 30-40°C)

**R<sub>f</sub>** = 0.43 (30% diethyl ether in PS 30-40 °C)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 3.61 (s, 3H), 2.28 (dd, *J* = 14.5, 2.7 Hz, 1H), 2.14 (s, 1H), 2.08 (d, *J* = 14.5 Hz, 1H), 1.87 (s, 1H), 1.79 (ddd, *J* = 13.7, 7.1, 3.2 Hz, 3H), 1.74 – 1.64 (m, 2H), 1.64 – 1.49 (m, 5H), 1.43 – 1.22 (m, 3H), 1.16 (s, 3H), 1.09 (s, 21H), 1.05 – 0.97 (m, 6H), 0.91 – 0.81 (m, 1H), 0.68 (s, 3H) ppm

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 178.2, 89.3, 85.0, 81.4, 79.8, 70.5, 57.1, 55.7, 55.3, 51.4, 51.3, 46.4, 43.9, 41.9, 41.6, 40.0, 38.2, 38.1, 35.4, 29.0, 22.9, 21.8, 20.6, 19.1, 18.7, 13.2, 11.4 ppm only 27 (should be 34) C environments

**MS** (ESI): *m/z* (%): 561.4 ([*M*+Na]<sup>+</sup>, 100)

**HRMS** (ESI): calcd for C<sub>34</sub>H<sub>54</sub>O<sub>3</sub>SiNa: 561.3740; found: 561.3743.

**[α]<sub>D</sub><sup>23</sup>** = –58° (*c* = 0.50, dichloromethane)

**5-Phenylpenta-2,4-diyn-1-yl (4*S*,4*aR*,6*aR*,9*S*,11*aS*,11*bR*)-4,9,11*b*-trimethyl-8-oxotetradecahydro-6*a*,9-methanocyclohepta[*a*]naphthalene-4-carboxylate (27)**



Prepared according to **Standard Procedure A** as a white solid (86 mg, 0.19 mmol, 75%).

**Work up:** the reaction mixture was concentrated under reduced pressure.

**Purification:** column chromatography (20% diethyl ether in PS 30-40 °C).

**Melting point:** >400°C (20% diethyl ether PS 30-40°C)

**R<sub>f</sub>** = 0.31 (20% diethyl ether in PS 30-40 °C)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 7.53 – 7.39 (m, 2H), 7.32 – 7.22 (m, 3H), 4.73 (s, 2H), 2.60 (dd, *J* = 18.7, 3.7 Hz, 1H), 2.14 (d, *J* = 13.5 Hz, 1H), 1.90 – 1.46 (m, 9H), 1.44 – 1.28 (m, 4H), 1.24 – 1.06 (m, 6H), 0.97 – 0.82 (s, 5H), 0.68 (s, 3H).

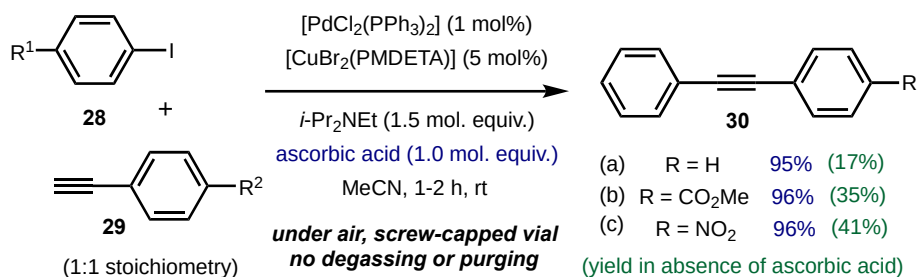
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ = 222.6, 176.5, 132.9, 129.6, 128.6, 121.4, 78.8, 76.4, 73.2, 71.2, 57.3, 54.9, 54.4, 52.3, 48.9, 48.6, 44.2, 41.6, 39.9, 39.6, 38.2, 38.1, 37.5, 28.9, 21.9, 20.5, 20.0, 19.1, 13.6 ppm

**MS** (ESI): *m/z* (%): 479.3 ([*M*+Na]<sup>+</sup>, 100)

**HRMS** (ESI): calcd for C<sub>31</sub>H<sub>36</sub>O<sub>3</sub>Na: 479.2562; found: 479.2564.

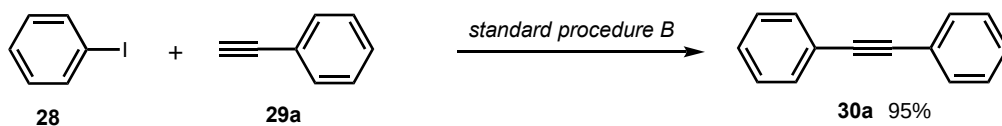
**[α]<sub>D</sub><sup>23</sup>** = –80° (*c* = 0.50, dichloromethane)

## Standard Procedure B: Sonogashira Cross-Couplings



A solution of [CuBr<sub>2</sub>(PMDETA)] (10 mg, 0.025 mmol, 5 mol%), [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (2.5 mg, 0.005 mmol, 1 mol%) and ascorbic acid (50 mg, 0.25 mmol, 1.0 mol equiv) in acetonitrile (2.0 mL) was stirred at ambient temperature for 5 minutes in a closed vial. Arylacetylene **29a-b** (0.5 mmol, 1.0 mol equiv), iodoarene **28a-b** (0.5 mmol, 1.0 mol equiv), and diisopropylamine (106  $\mu\text{L}$ , 0.75 mmol, 1.5 mol equiv) were then added to the vial. The vial was then closed and the reaction allowed to stir at ambient temperature for 1 hour. The reaction mixture was then diluted with diethyl ether (15 mL) and washed with aqueous 1M HCl (3  $\times$  10 mL). The organic extract was then dried over NaSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification was performed as described below.

### 1,2-Diphenylethyne (30a)



Prepared according to **Standard Procedure B** as a white solid (85 mg, 0.48 mmol, 95%).

**Purification:** column chromatography (100% *n*-hexanes).

Characterization data corresponded to those reported in the literature.<sup>25</sup>

**Melting point:** 60.4 - 64.5°C (hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.51 – 7.42 (m, 4H), 7.31 – 7.20 (m, 6H) ppm

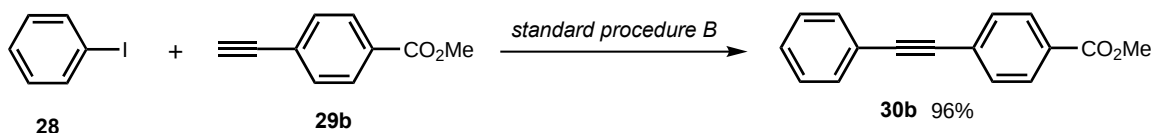
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 131.8, 128.5, 128.4, 123.4, 89.5 ppm

**MS** (70 eV, EI): *m/z* (%): 178.1 ([M]<sup>+</sup>, 100)

**HRMS** (EI): calcd for C<sub>14</sub>H<sub>10</sub>: 178.0878; found: 178.0875.

This experiment was repeated *with the ascorbic acid omitted* to give the same product as a white solid (15 mg, 0.090 mmol, 17%).

### Methyl 4-(phenylethynyl)benzoate (30b)



Prepared according to **Standard Procedure B** as a white solid (113 mg, 0.48 mmol, 96%).

**Purification:** column chromatography (10% diethyl ether in PS 40-60 °C).

Characterization data corresponded to those reported in the literature.<sup>26</sup>

**Melting point:** 118.7 - 122.3°C (10% diethyl ether in hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.02 (d,  $J$  = 8.3 Hz, 2H), 7.59 (d,  $J$  = 8.3 Hz, 2H), 7.57 – 7.53 (m, 2H), 7.38 – 7.35 (m, 3H), 3.93 (s, 3H) ppm

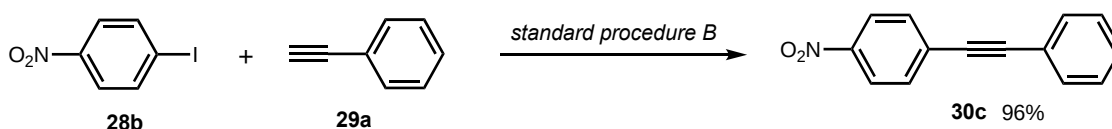
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.7, 131.9, 131.6, 129.7, 129.6, 128.9, 128.6, 128.1, 122.8, 92.5, 88.8, 52.4 ppm

**MS** (70 eV, EI):  $m/z$  (%): 236.1 ([M]<sup>+</sup>•, 100)

**HRMS** (EI): calcd for C<sub>16</sub>H<sub>12</sub>O<sub>2</sub>: 236.0837; found: 236.0838.

This experiment was repeated *with the ascorbic acid omitted* to give the same product as a white solid (41 mg, 0.18 mmol, 35%).

### 1-Nitro-4-(phenylethynyl)benzene (30c)



Prepared according to **Standard Procedure B** as a white solid (107 mg, 0.48 mmol, 96%).

**Purification:** column chromatography (10% diethyl ether in PS 40-60 °C).

Characterization data corresponded to those reported in the literature.<sup>27</sup>

**Melting point:** 123.5 - 127.1°C (10% diethyl ether in hexanes)

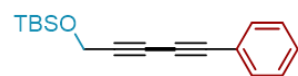
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.21 – 8.09 (m, 2H), 7.63 – 7.57 (m, 2H), 7.48 (dd,  $J$  = 6.5, 3.0 Hz, 2H), 7.31 (dd,  $J$  = 5.2, 1.9 Hz, 3H) ppm

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 147.1, 132.4, 132.0, 130.4, 129.4, 128.7, 123.8, 122.2, 94.8, 87.7 ppm

**MS** (70 eV, EI):  $m/z$  (%): 223.1 ([M]<sup>+</sup>•, 100)

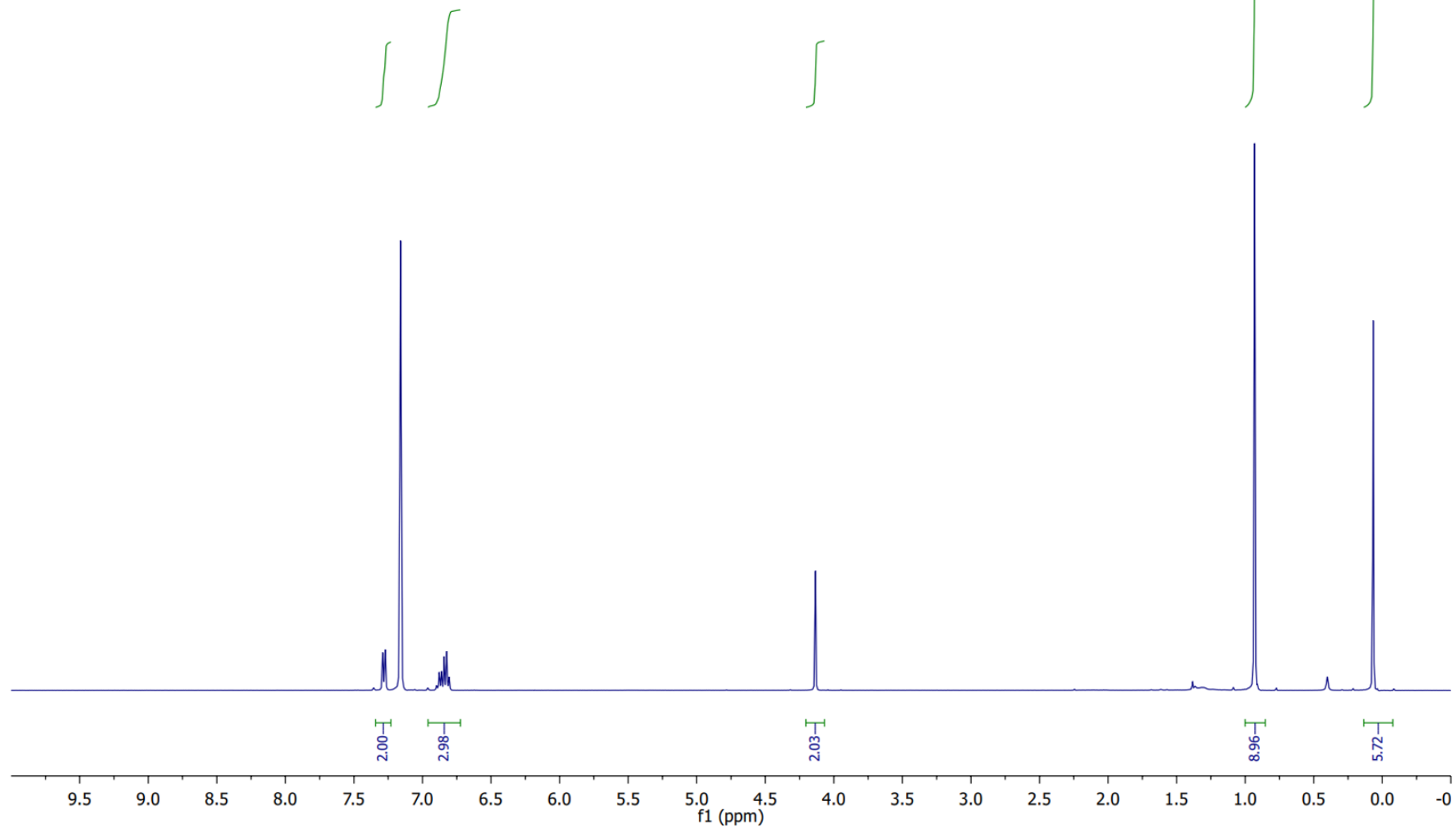
**HRMS** (EI): calcd for C<sub>14</sub>H<sub>9</sub>NO<sub>2</sub>: 223.0633; found: 223.0635.

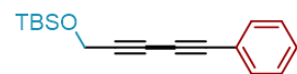
This experiment was repeated *with the ascorbic acid omitted* to give the same product as a white solid (46 mg, 0.21 mmol, 41%).



(3)

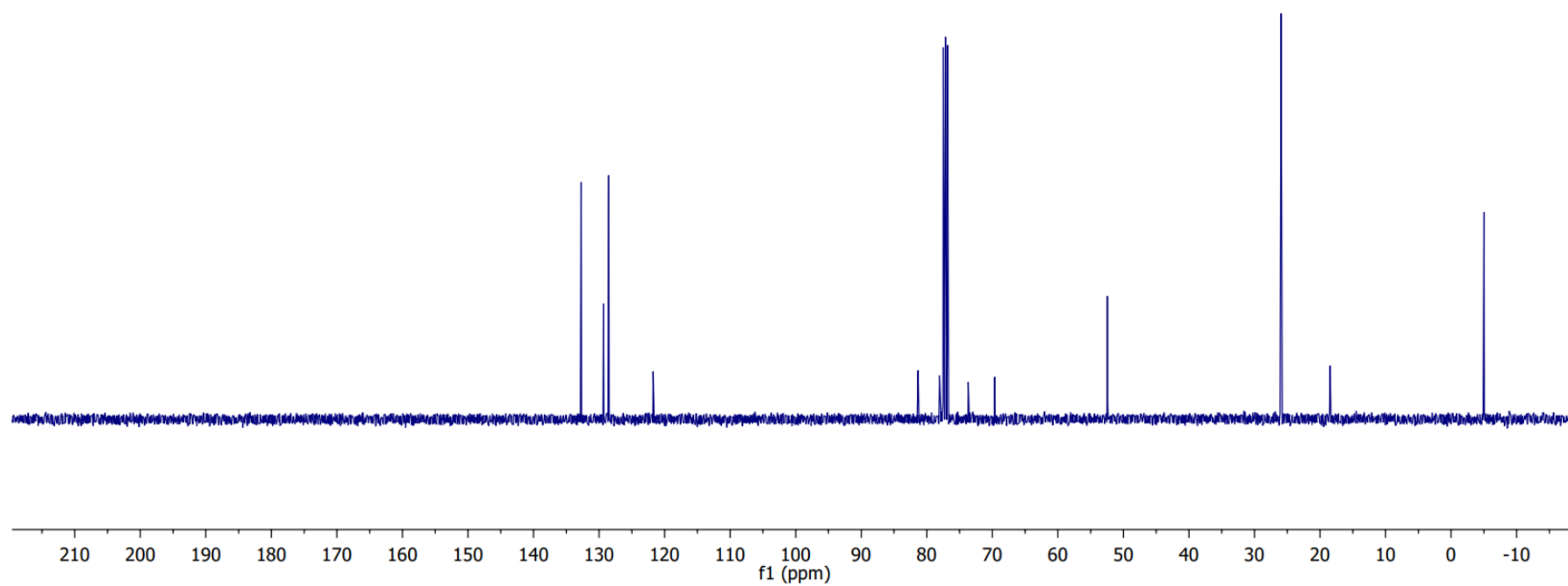
$^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ )

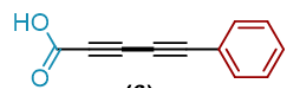




(3)

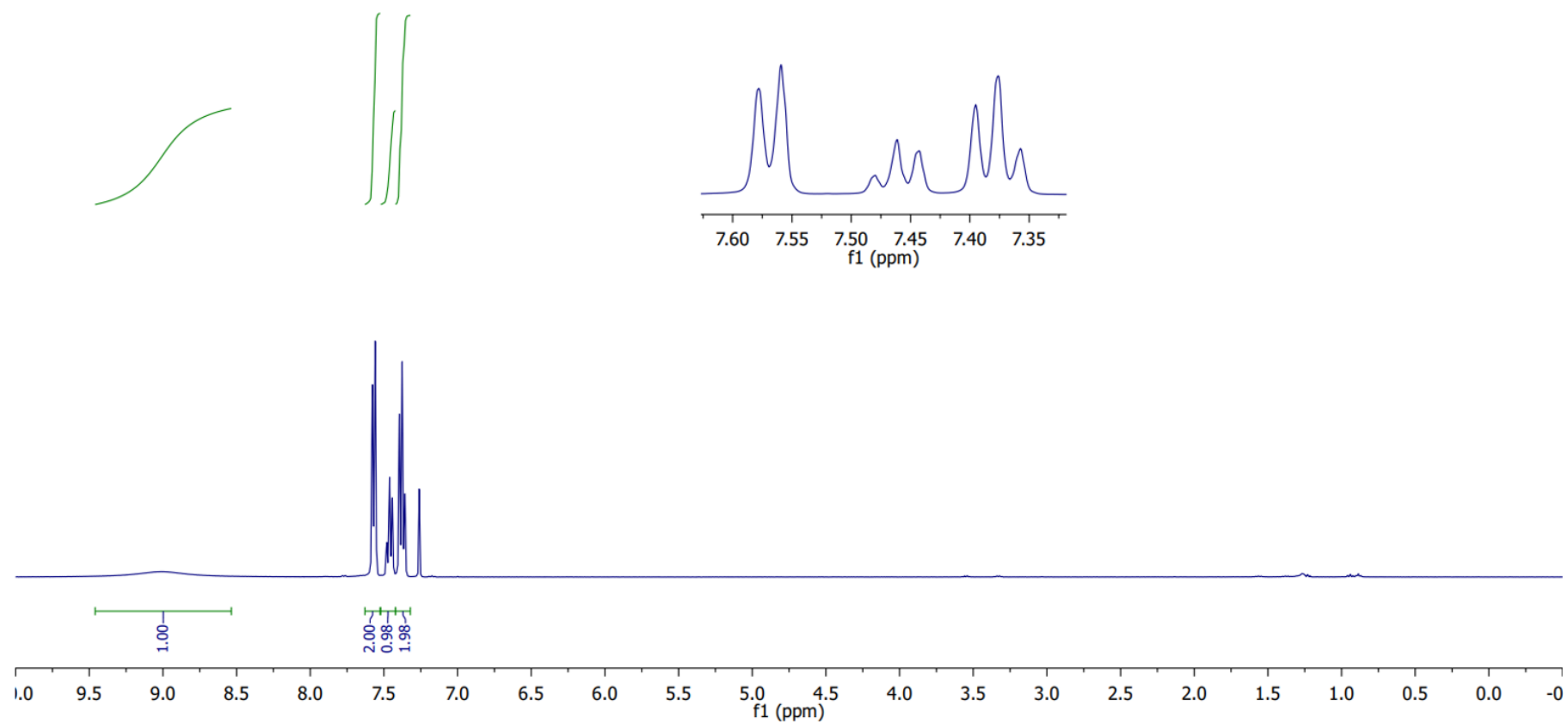
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

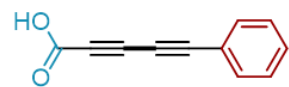




(6)

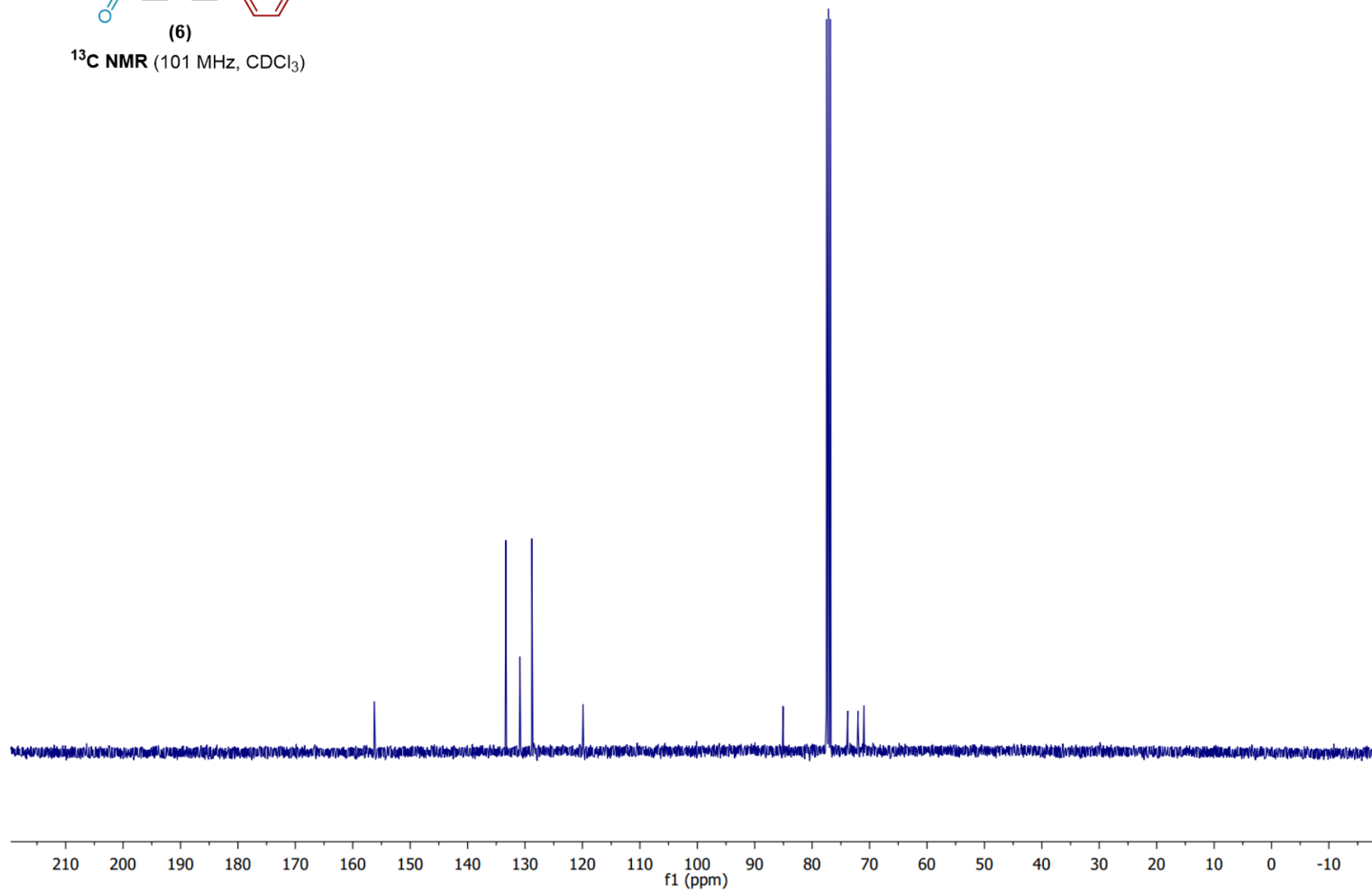
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

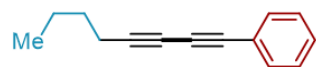




(6)

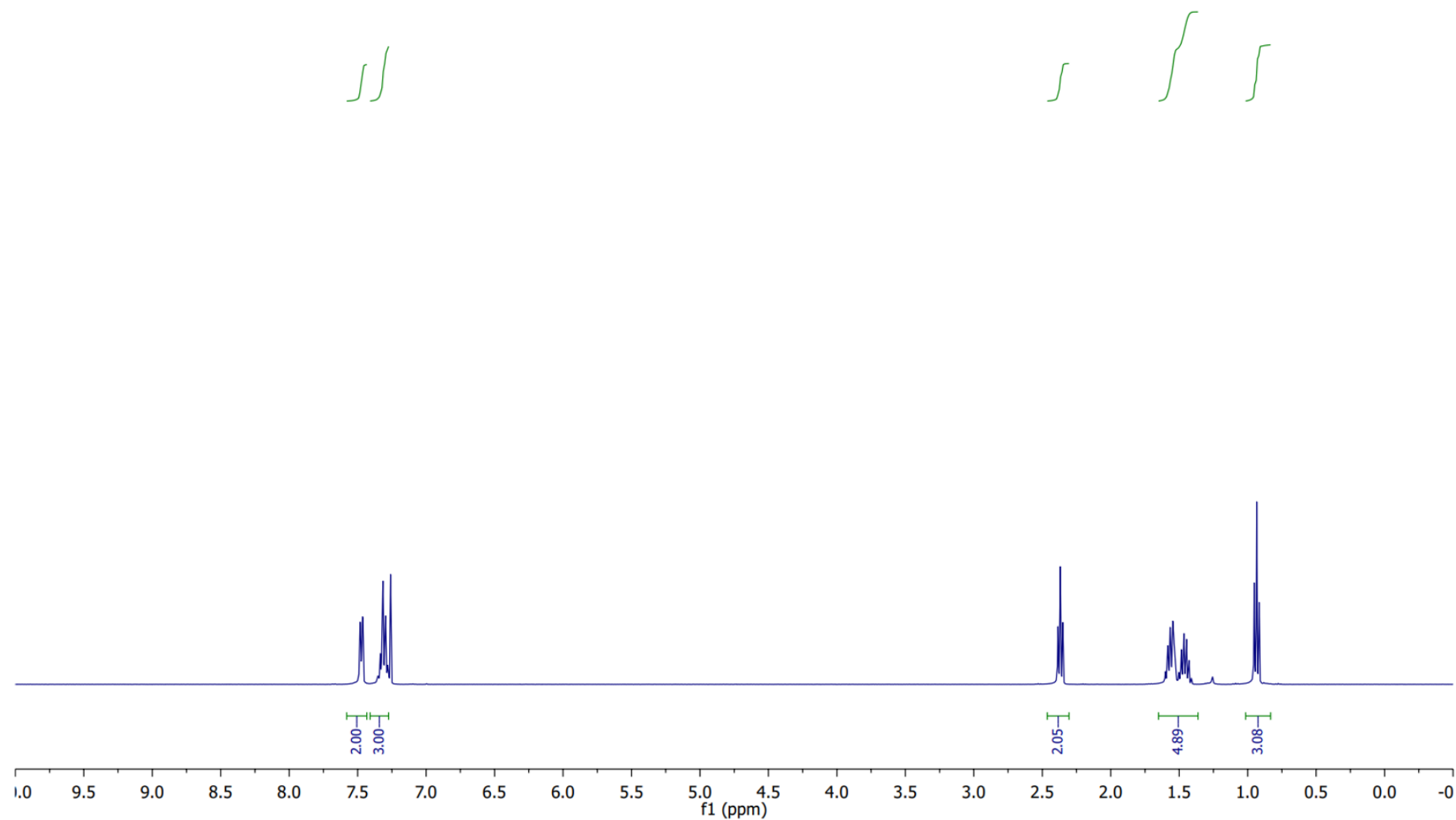
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

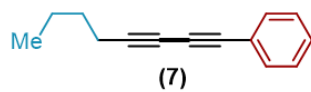




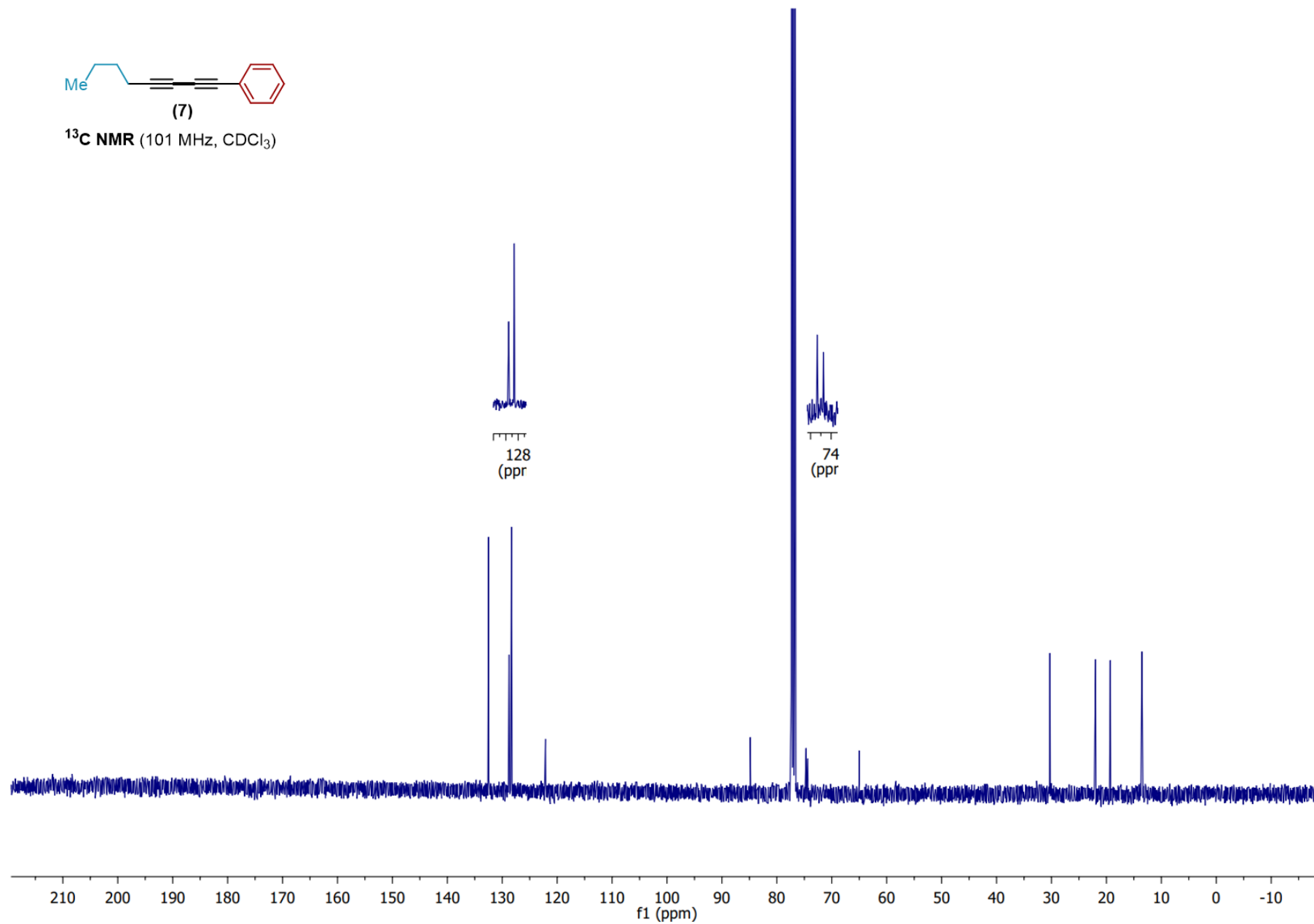
(7)

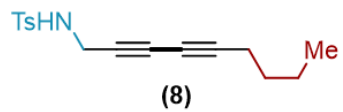
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



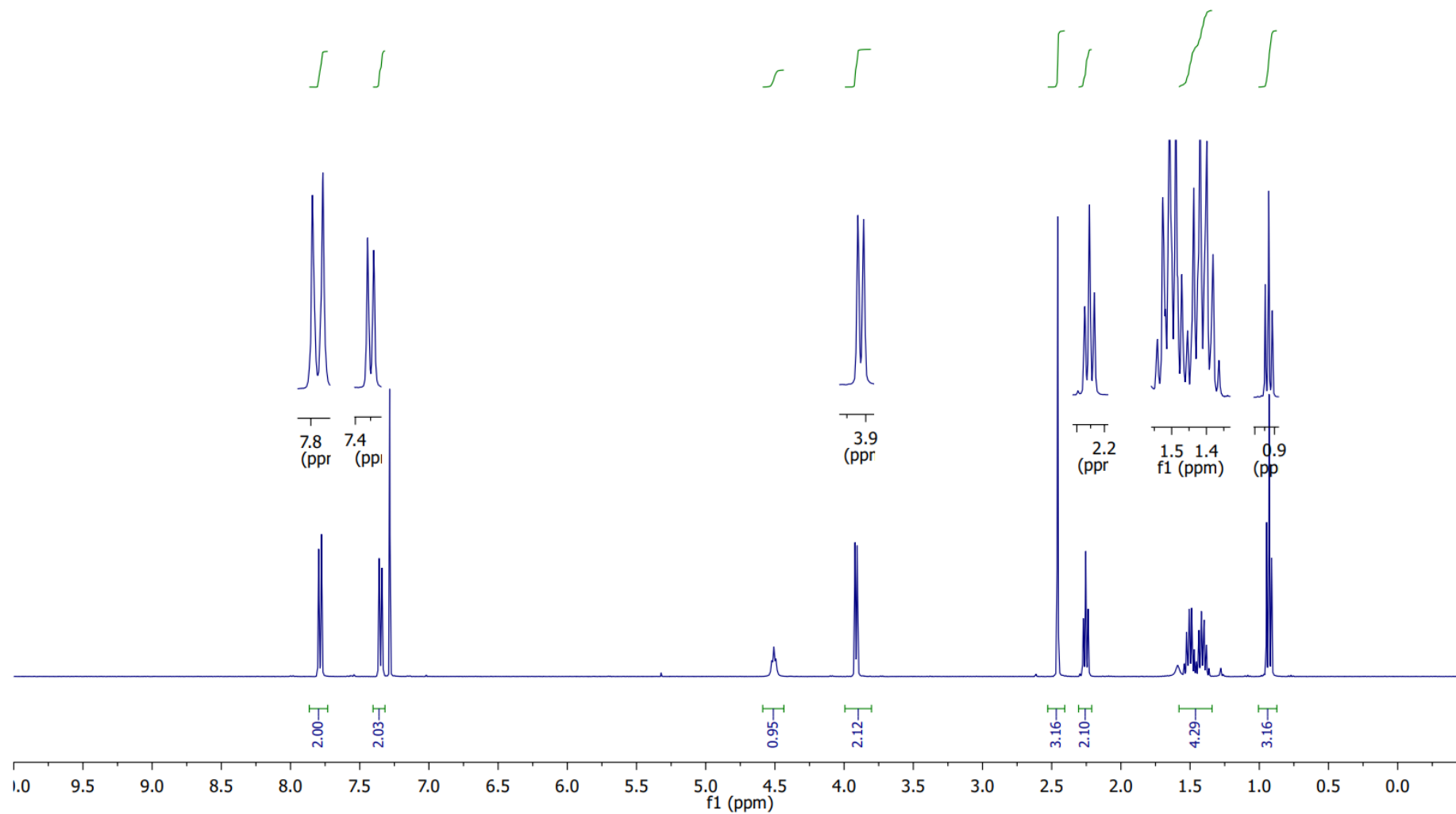


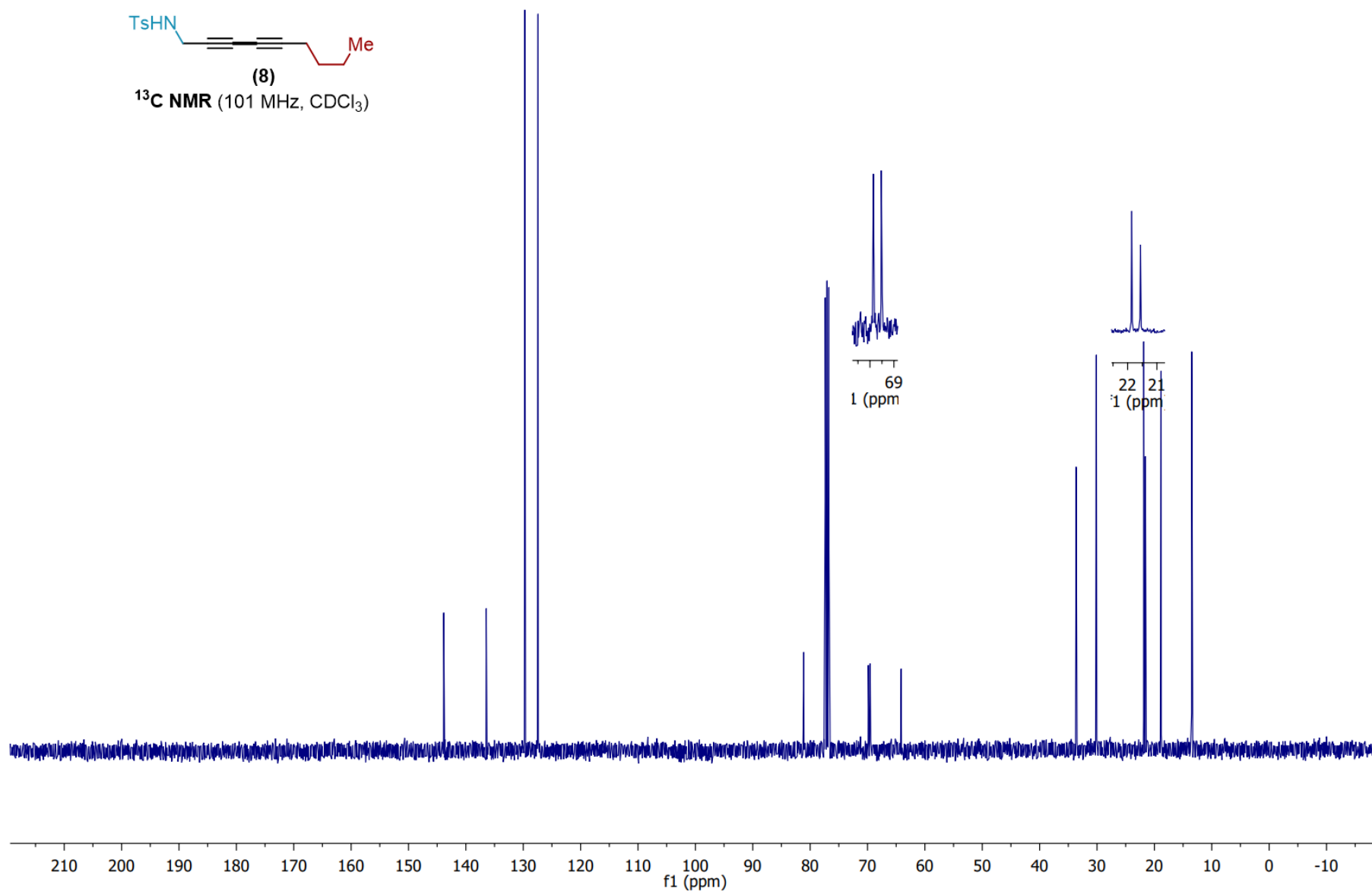
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

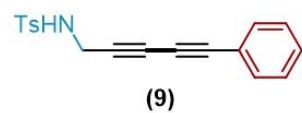




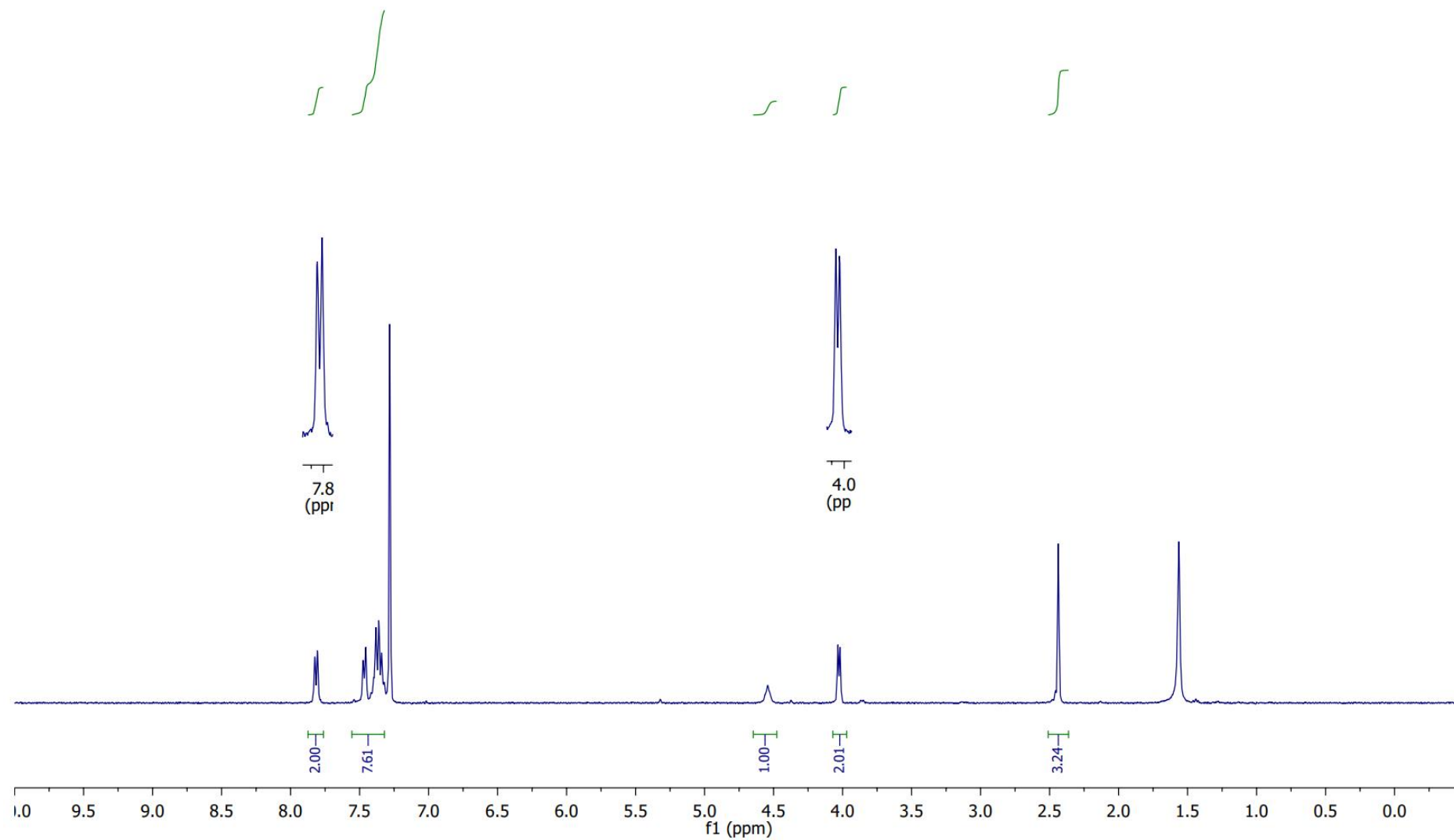
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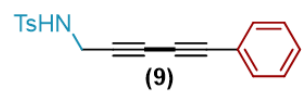




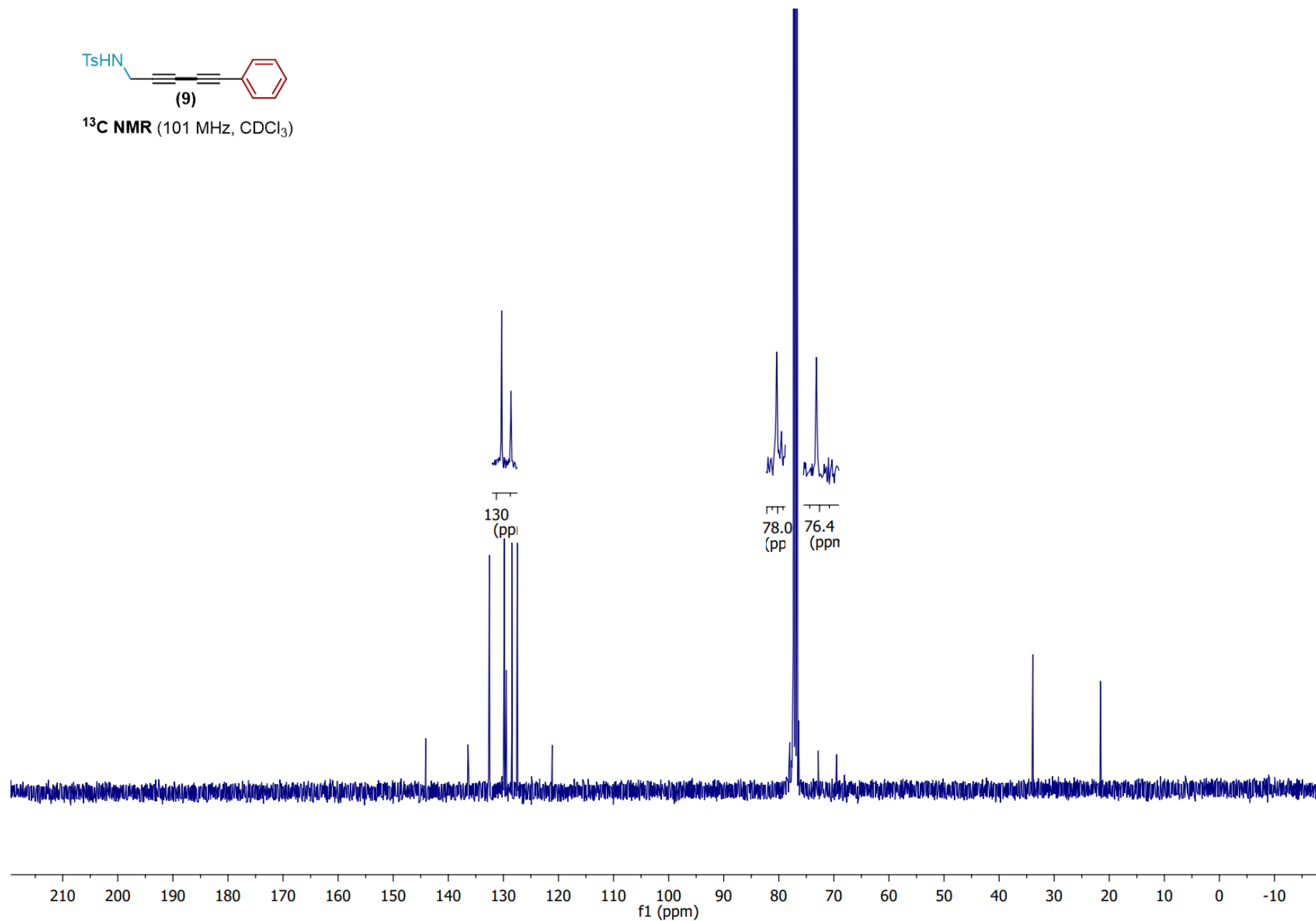


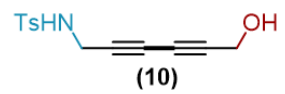
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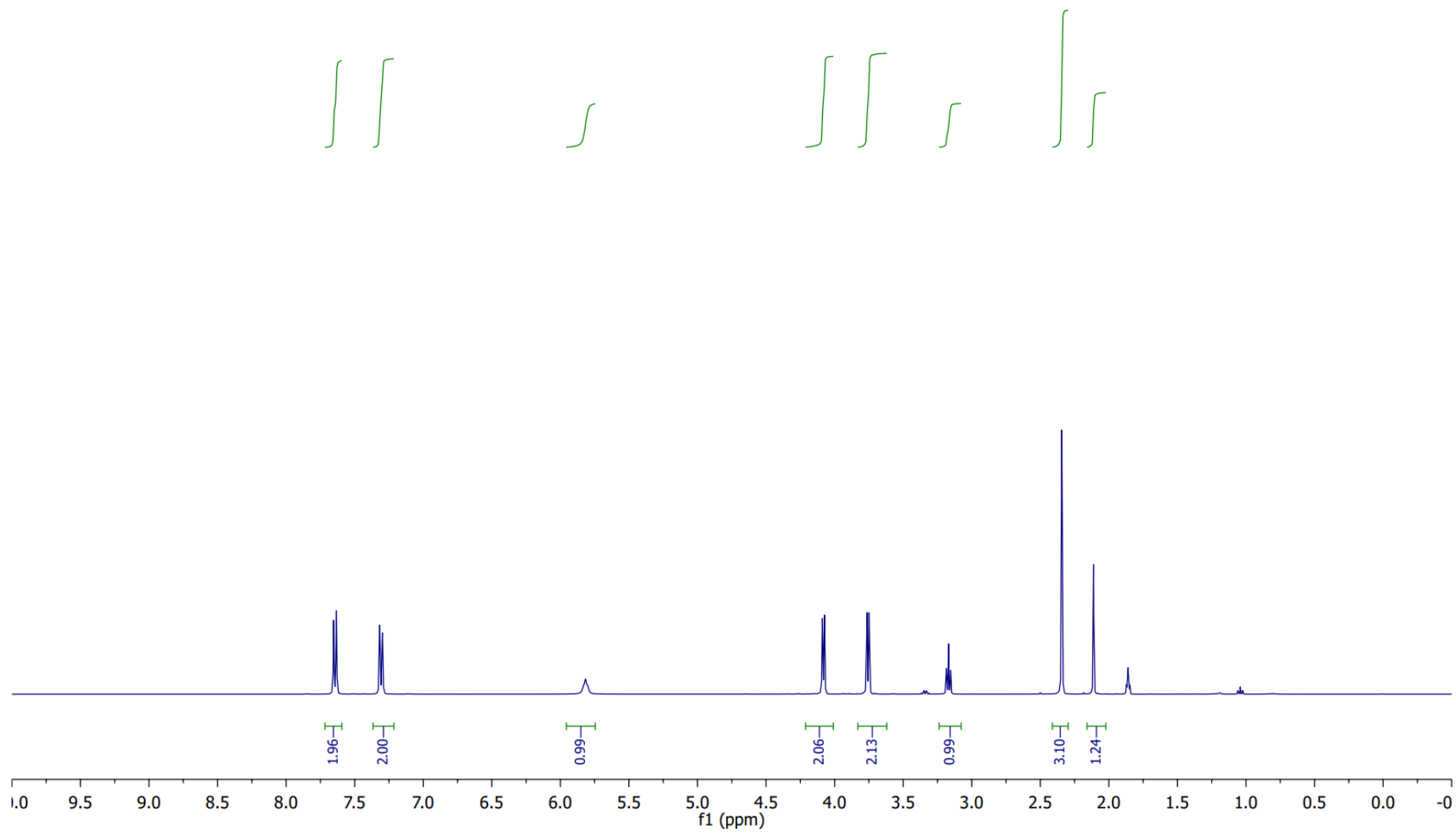


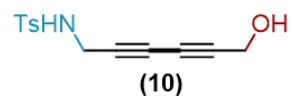
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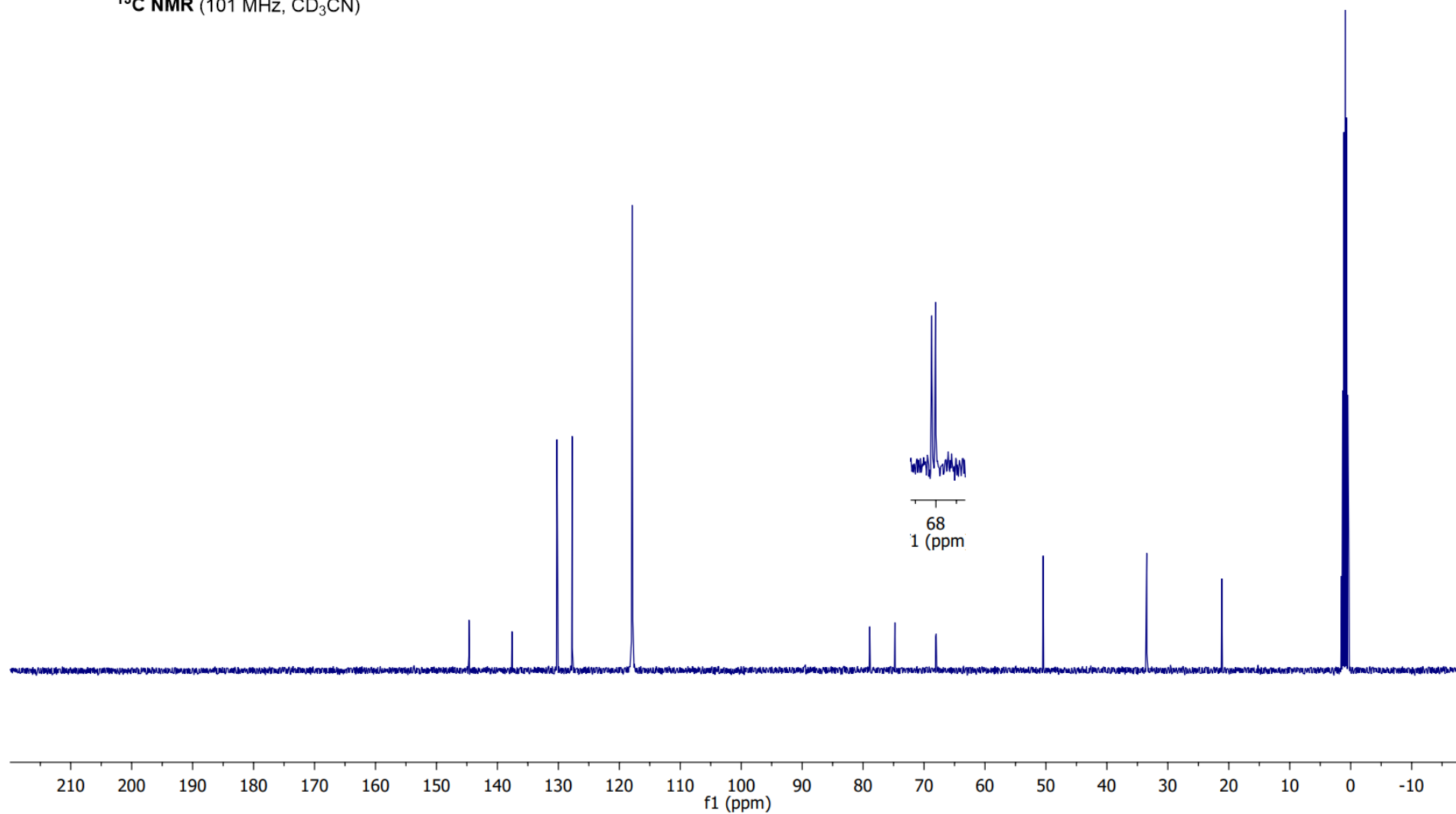


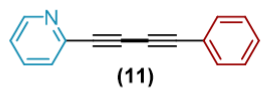
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN)



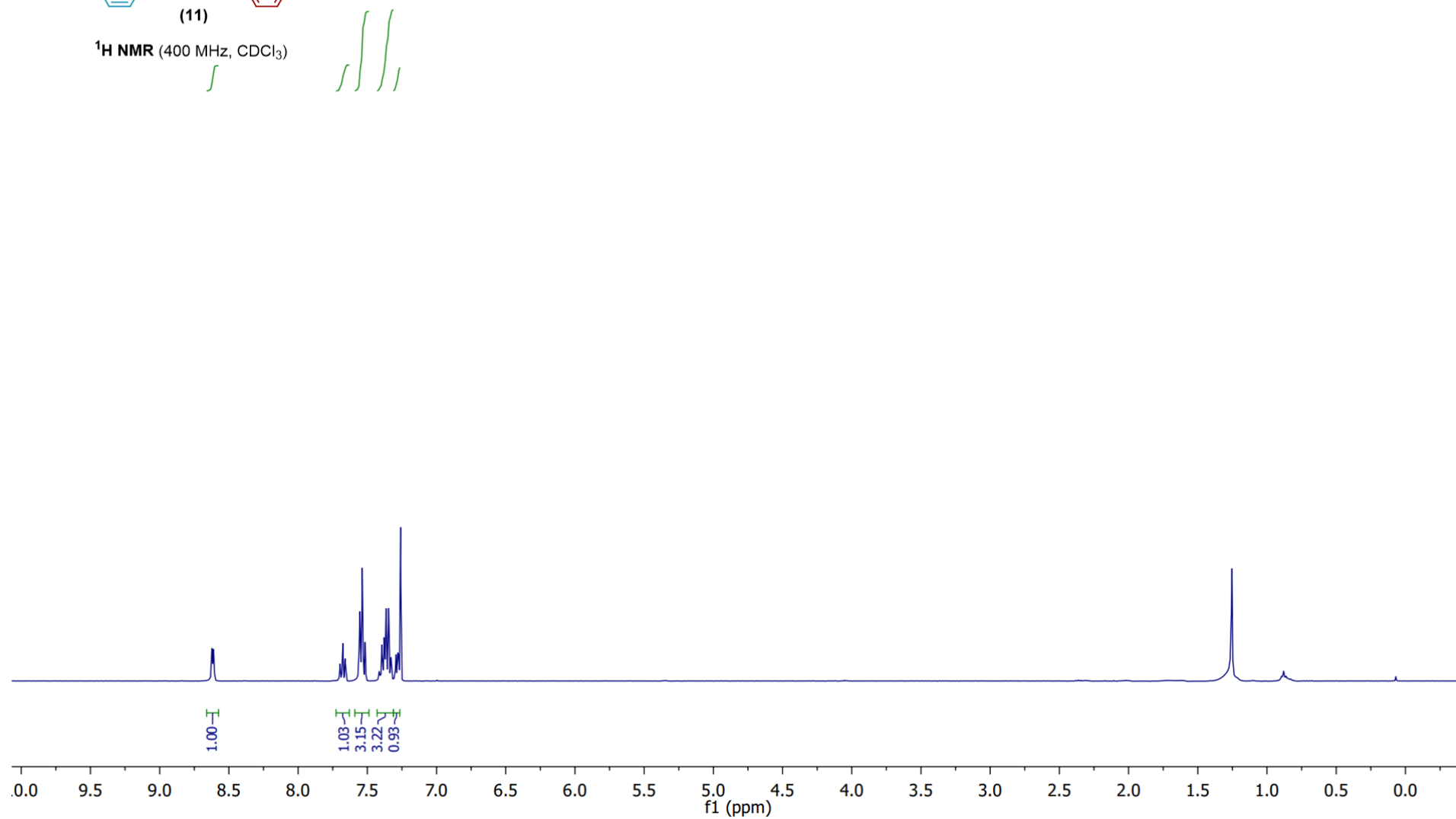


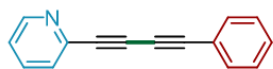
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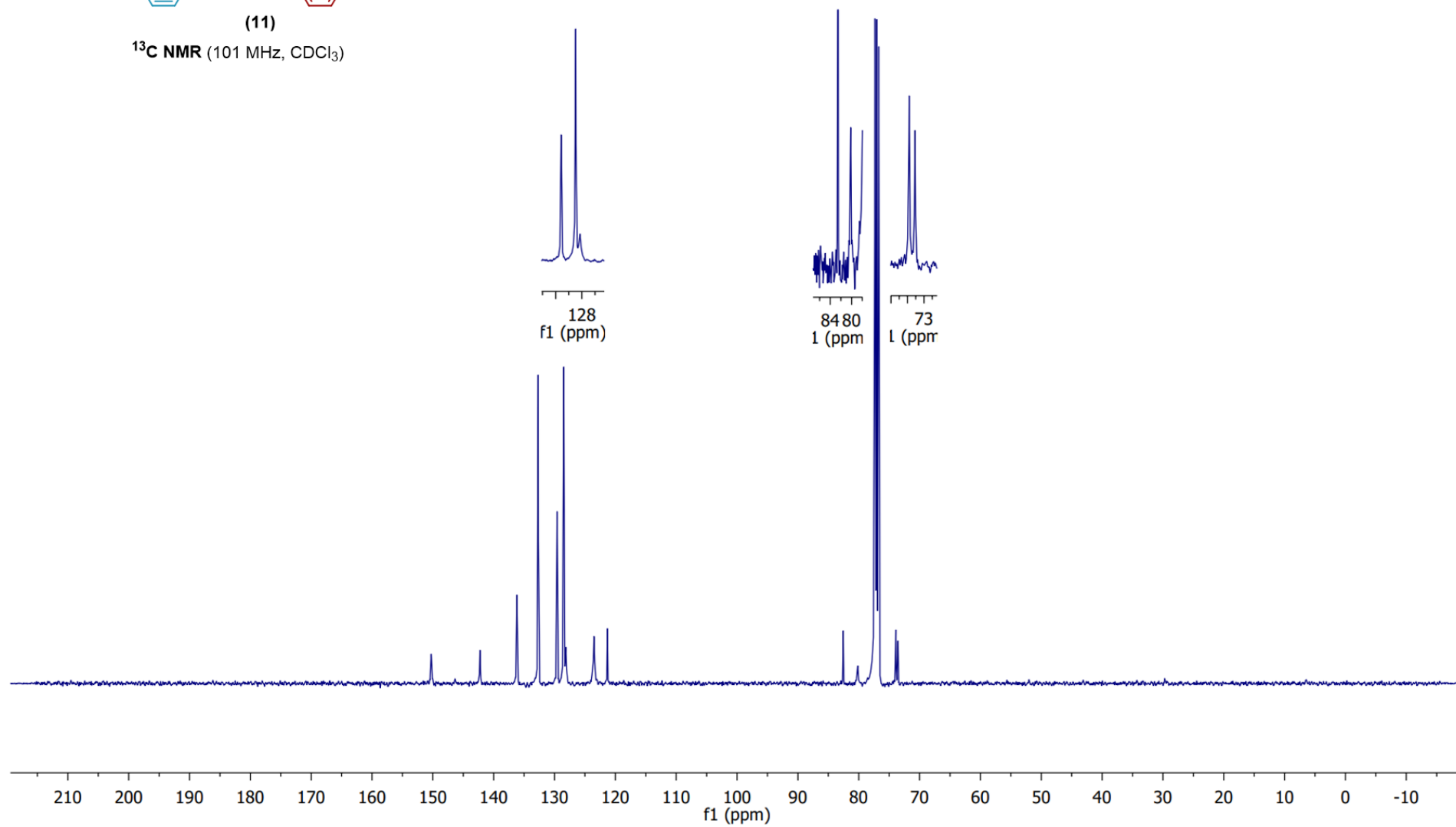
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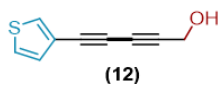




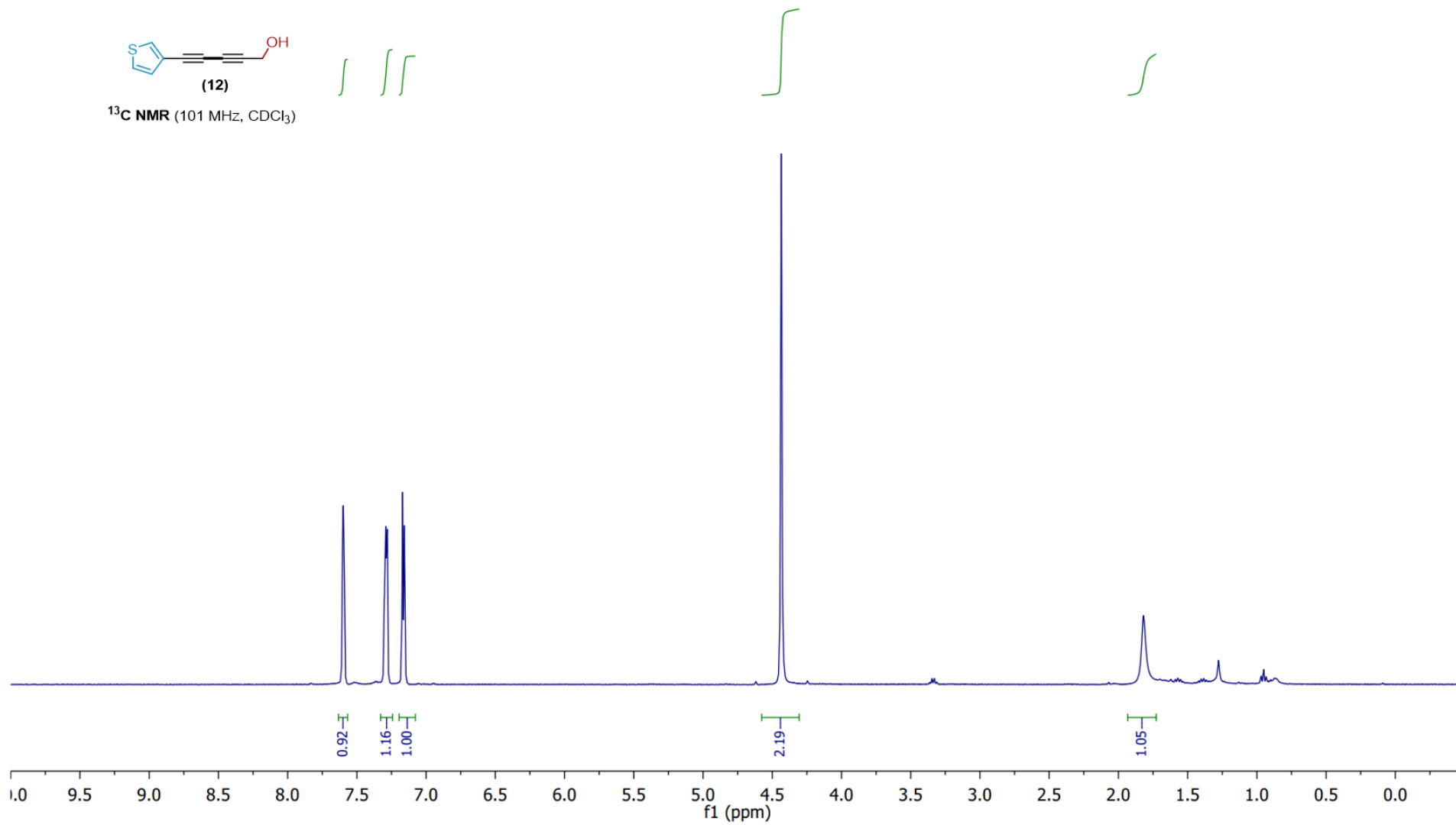
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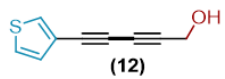
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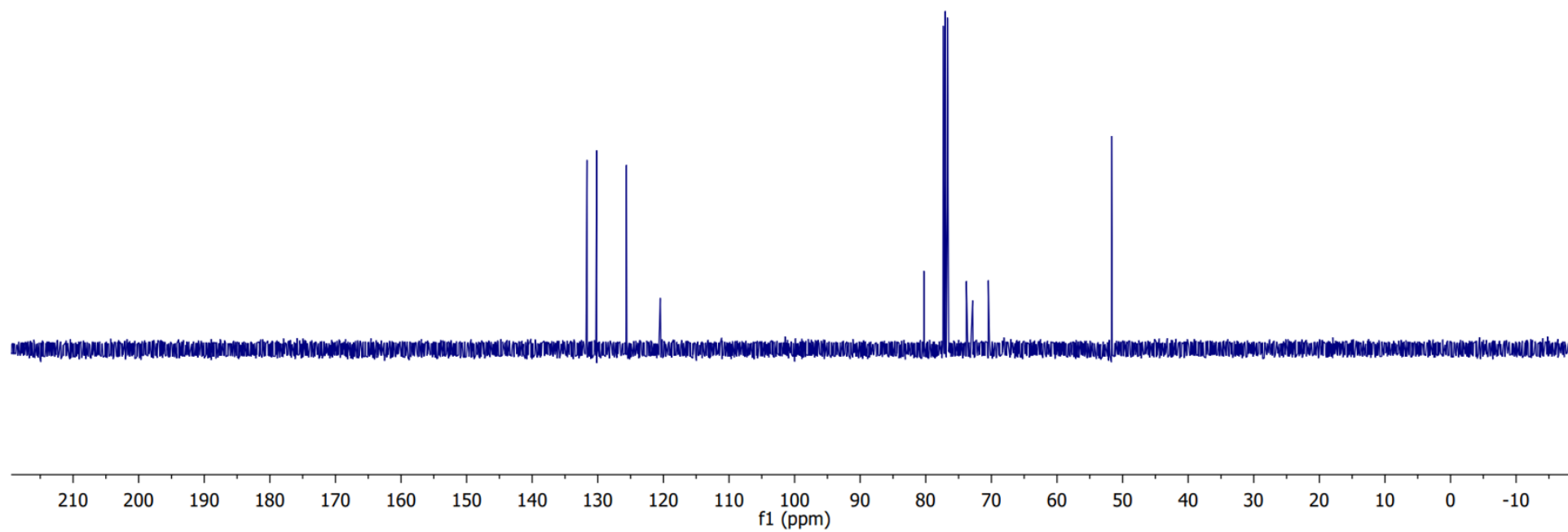


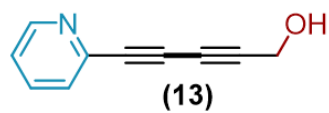
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



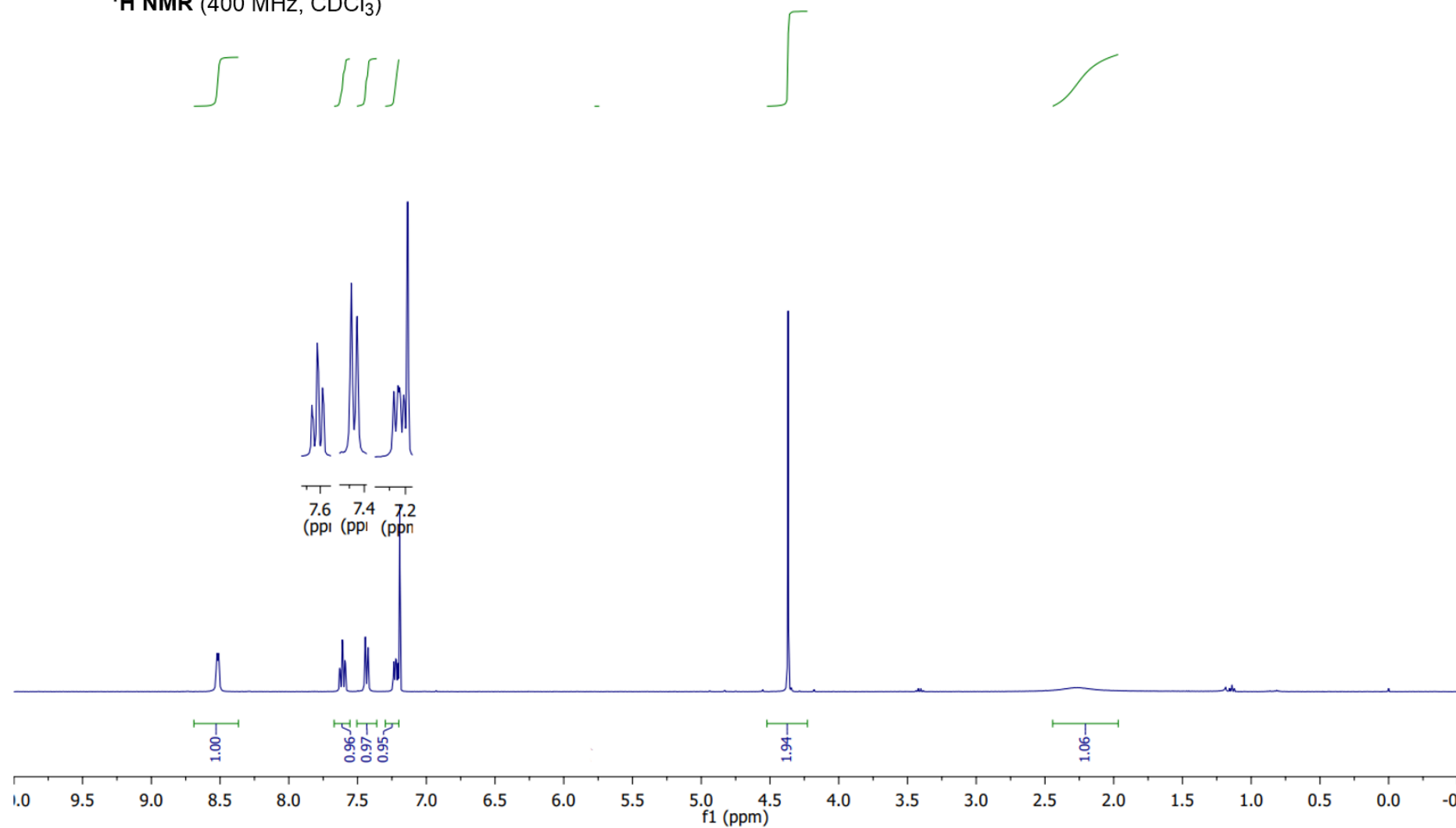


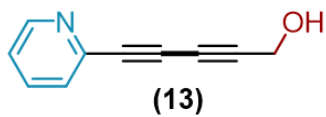
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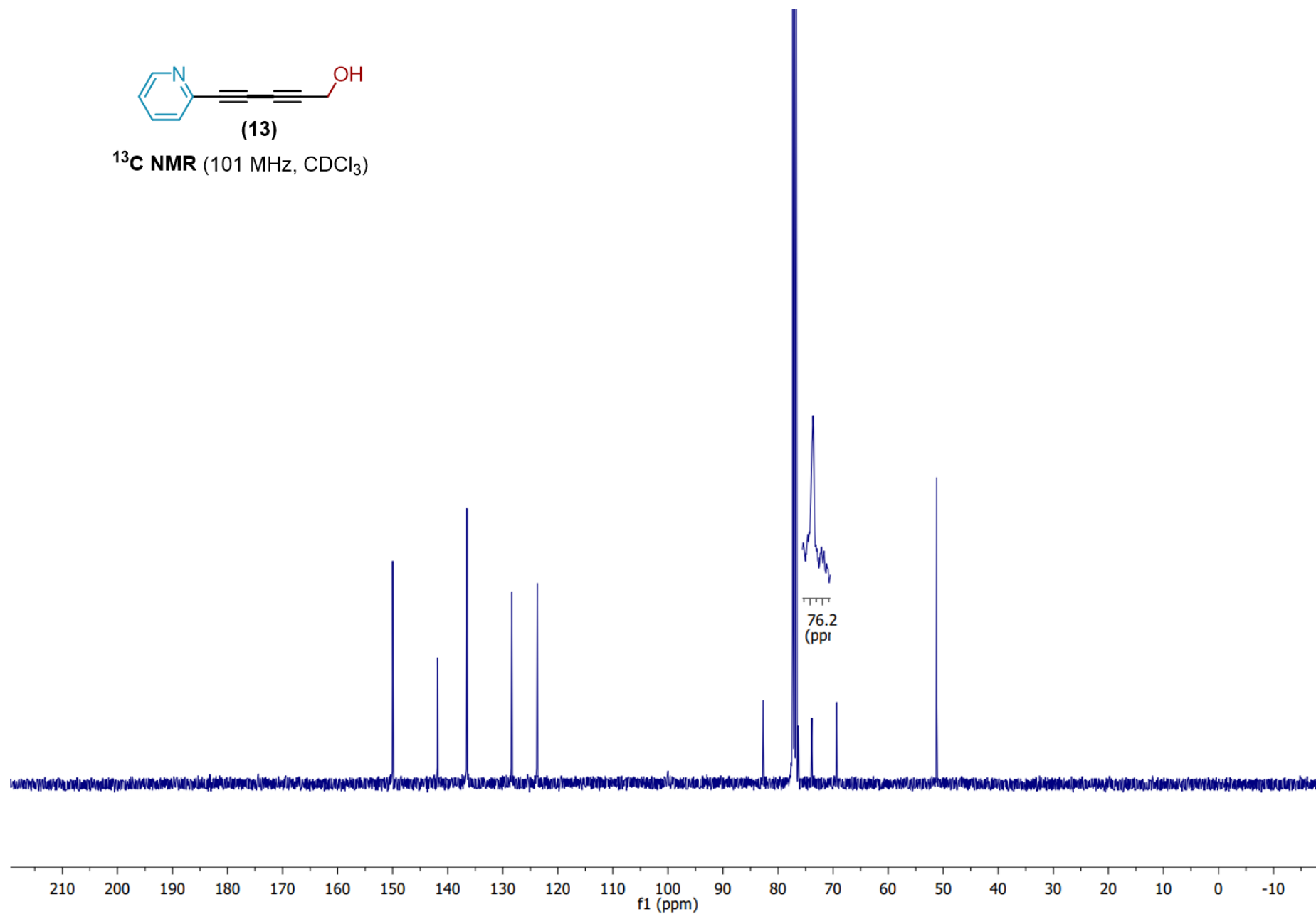


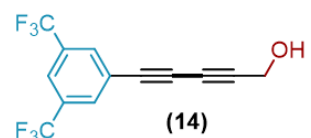
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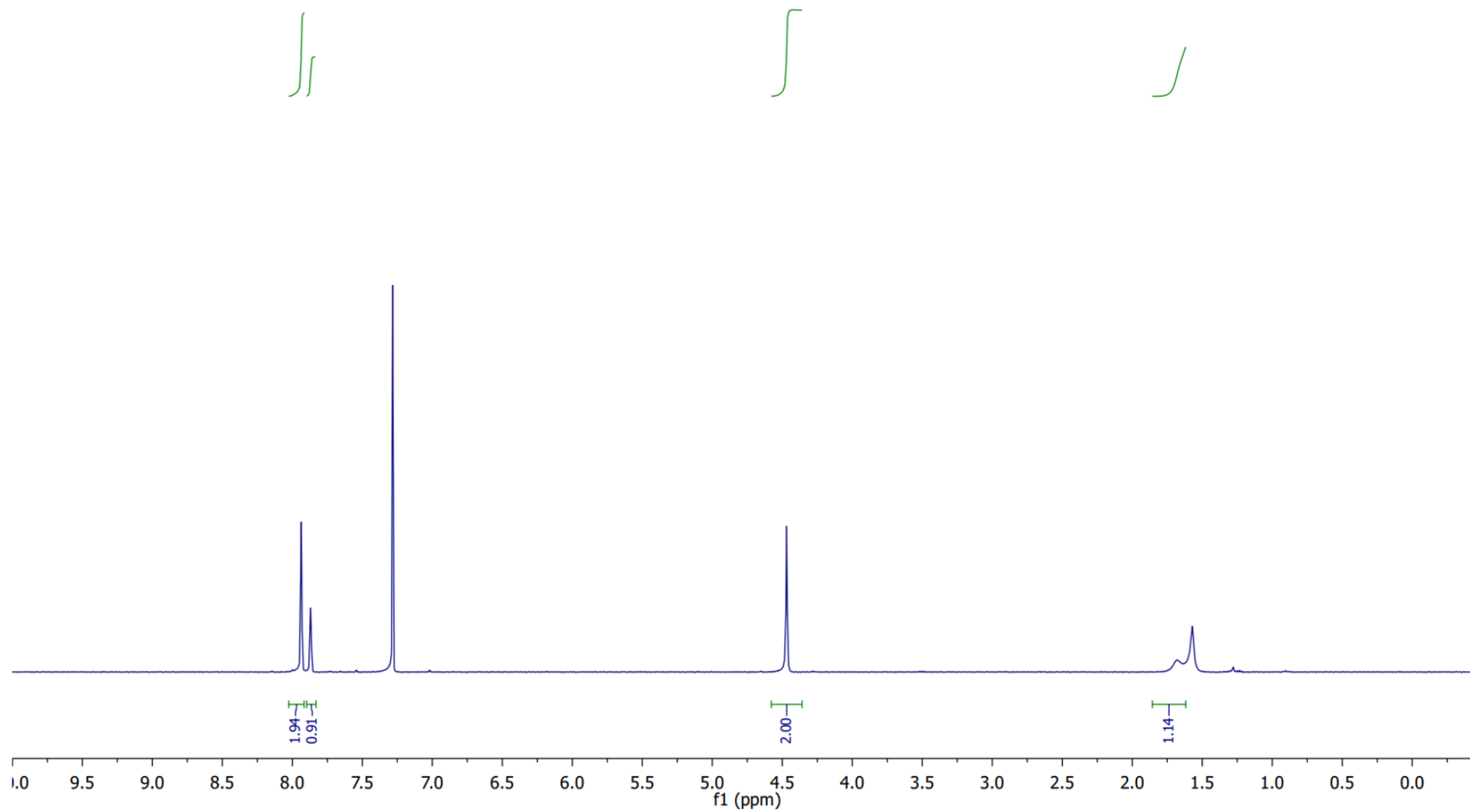


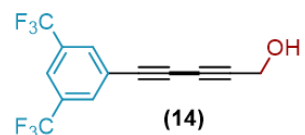
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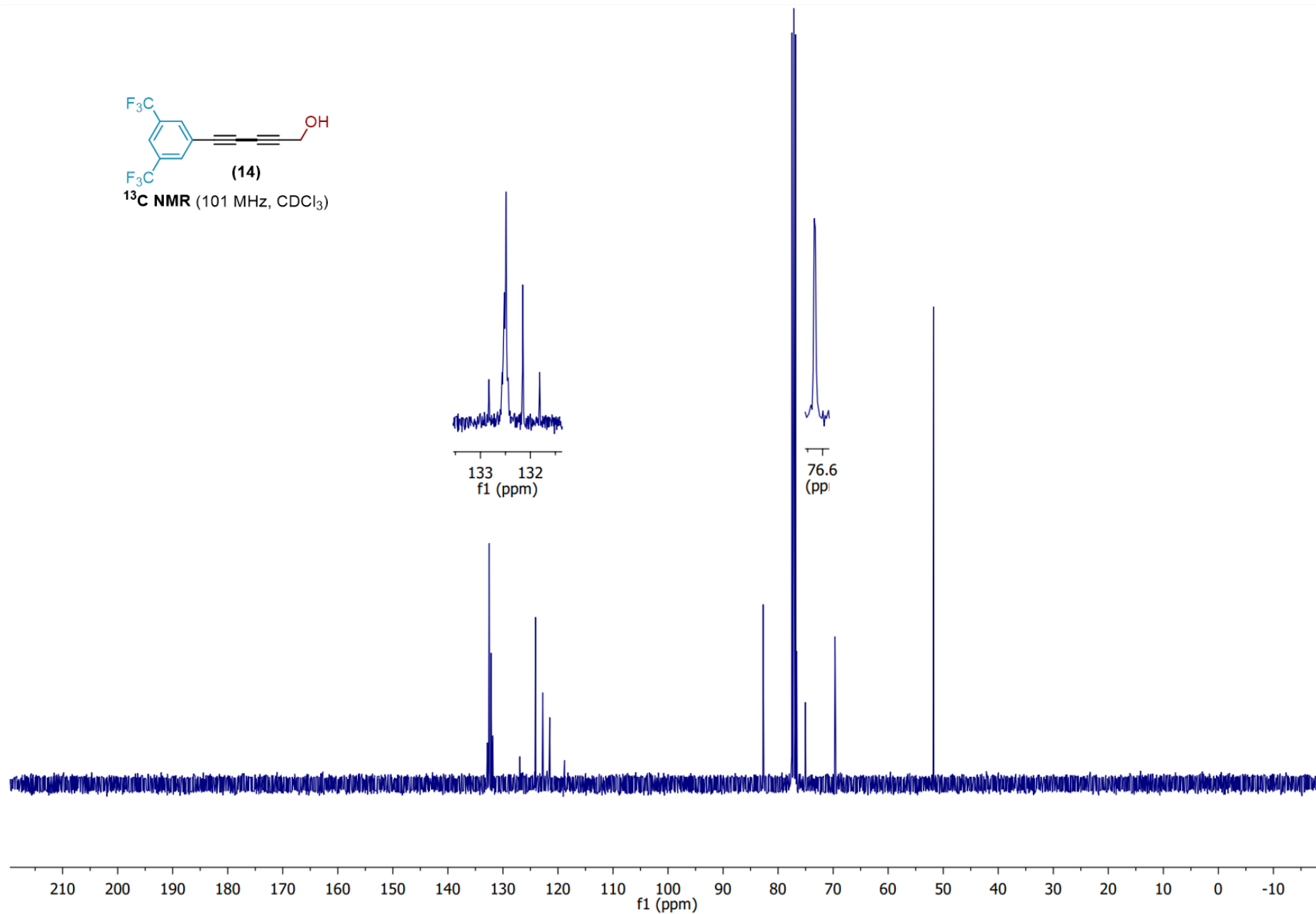


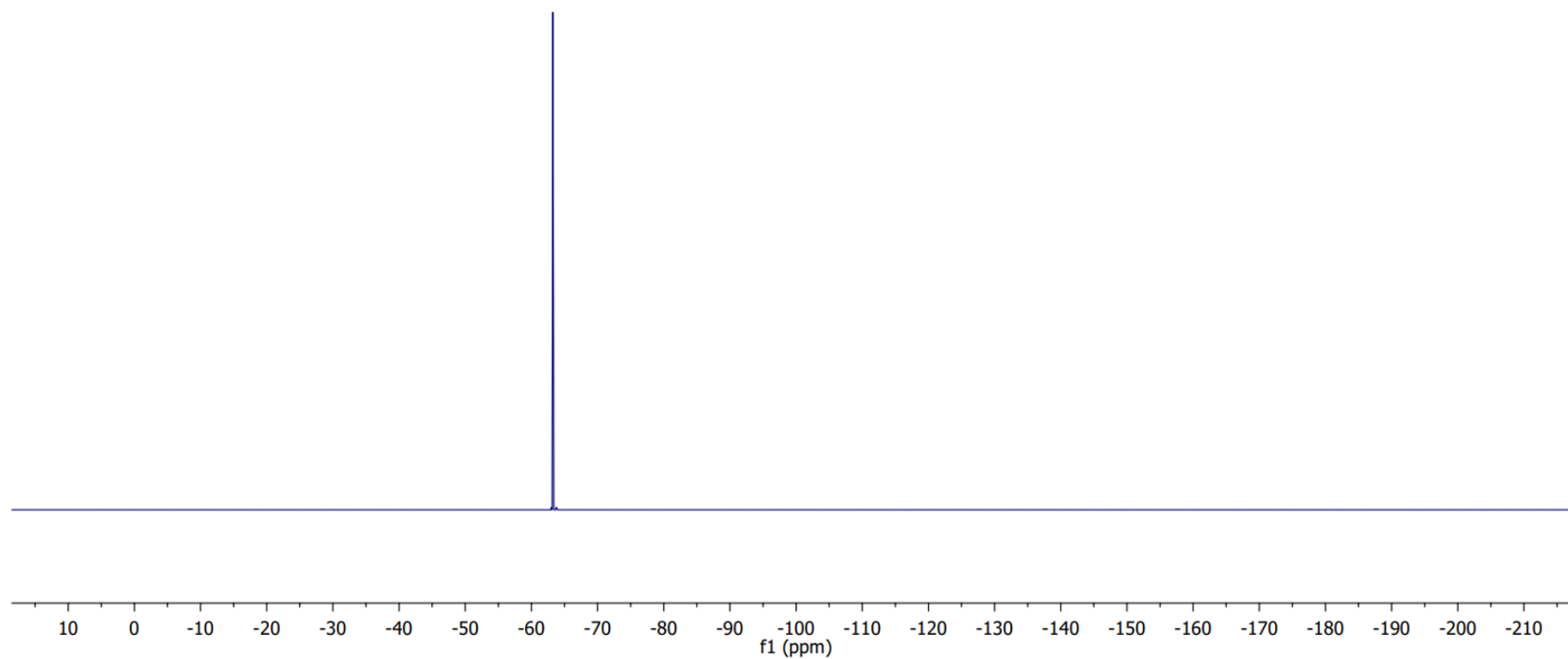
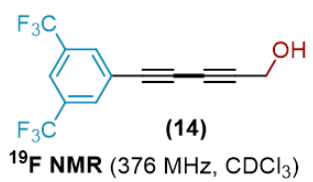
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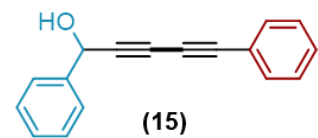




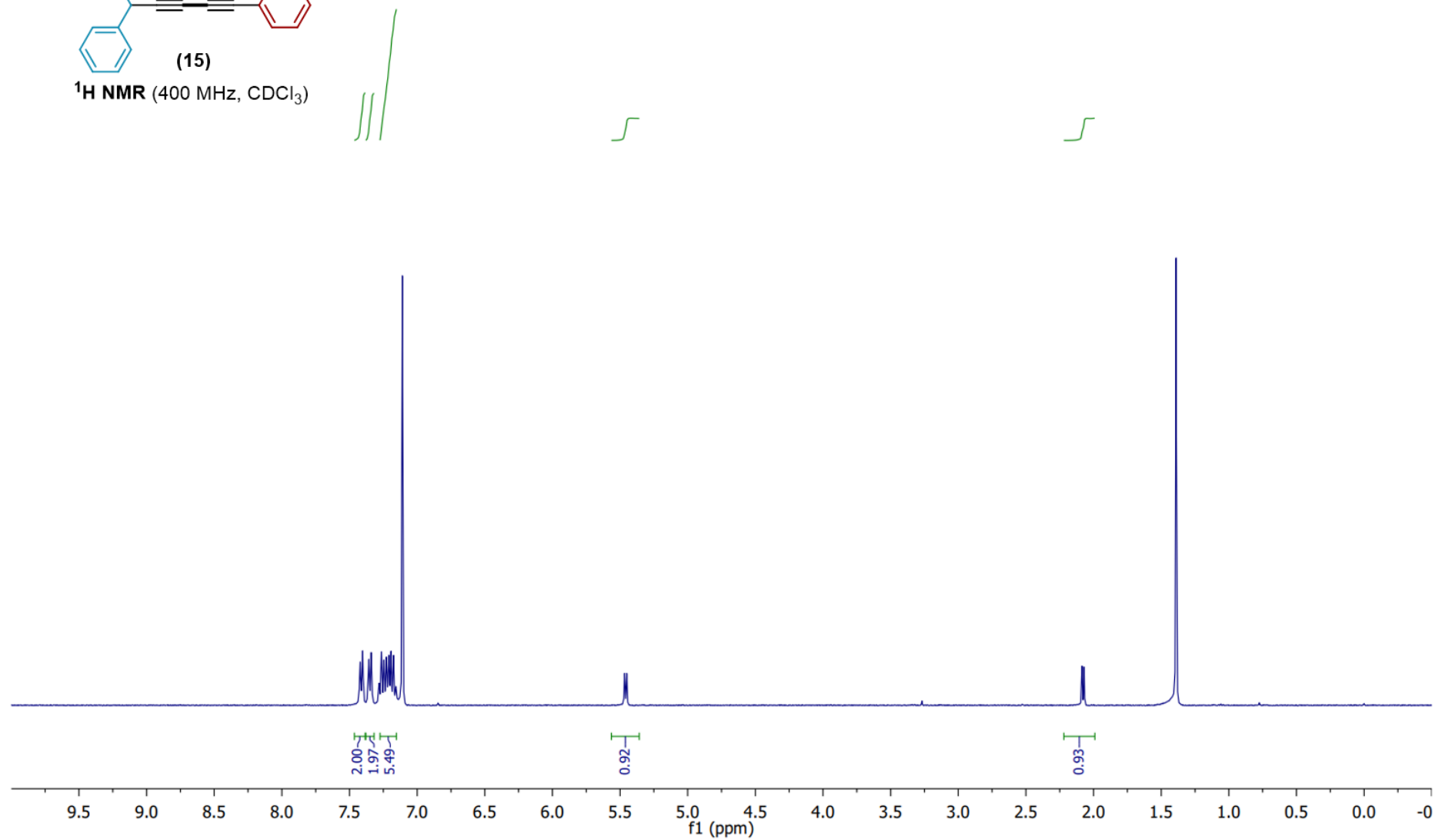
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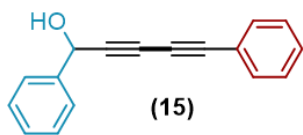




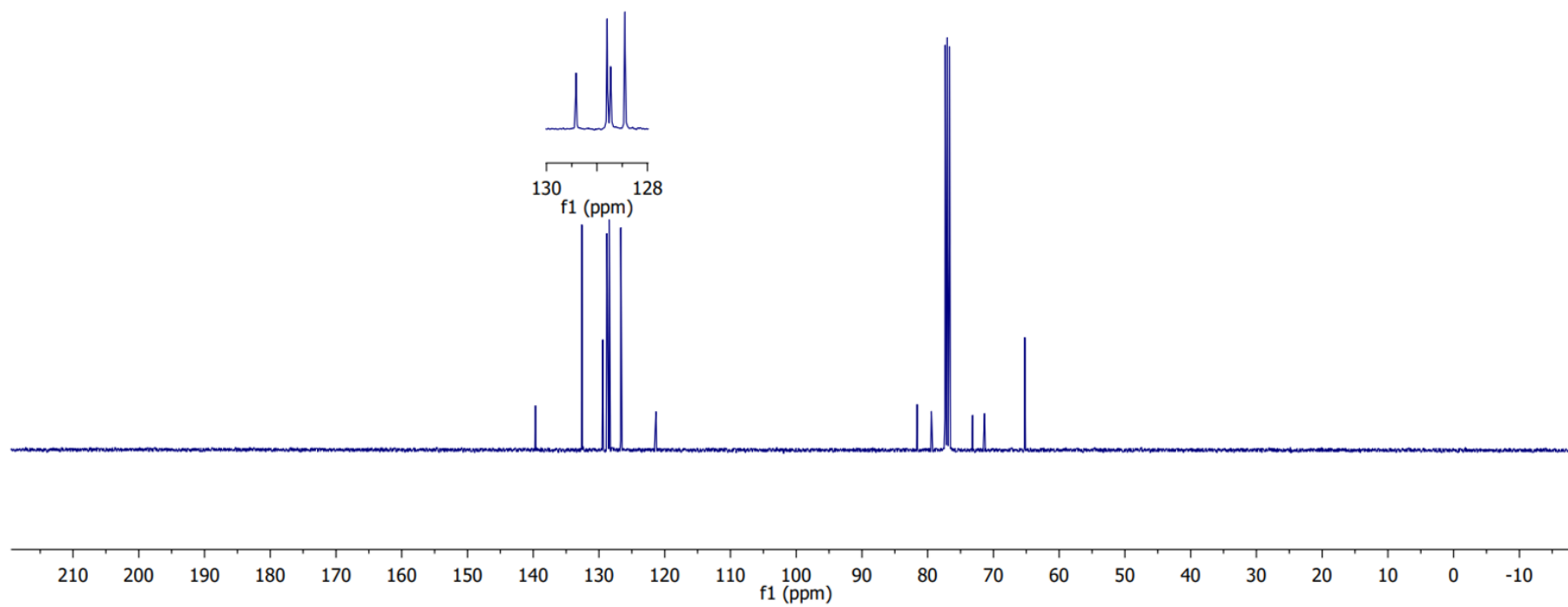


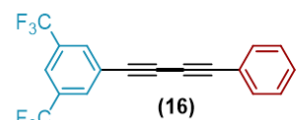
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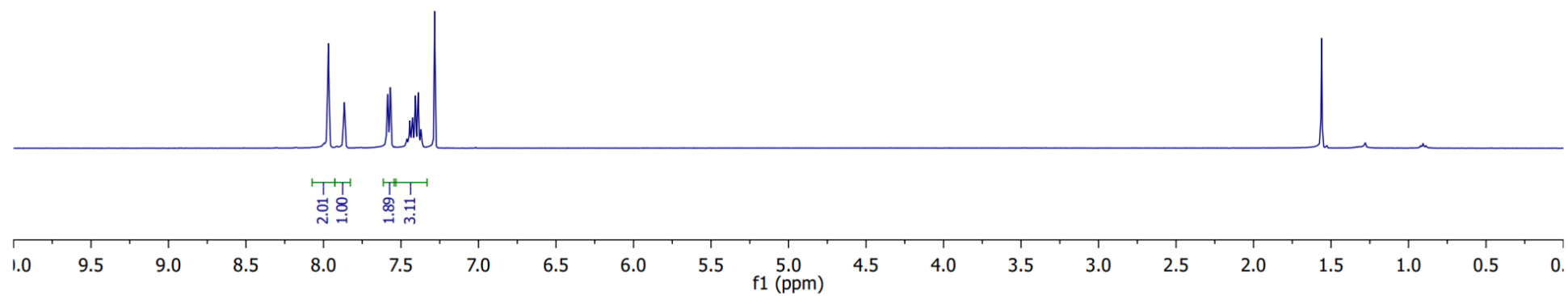
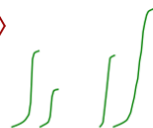


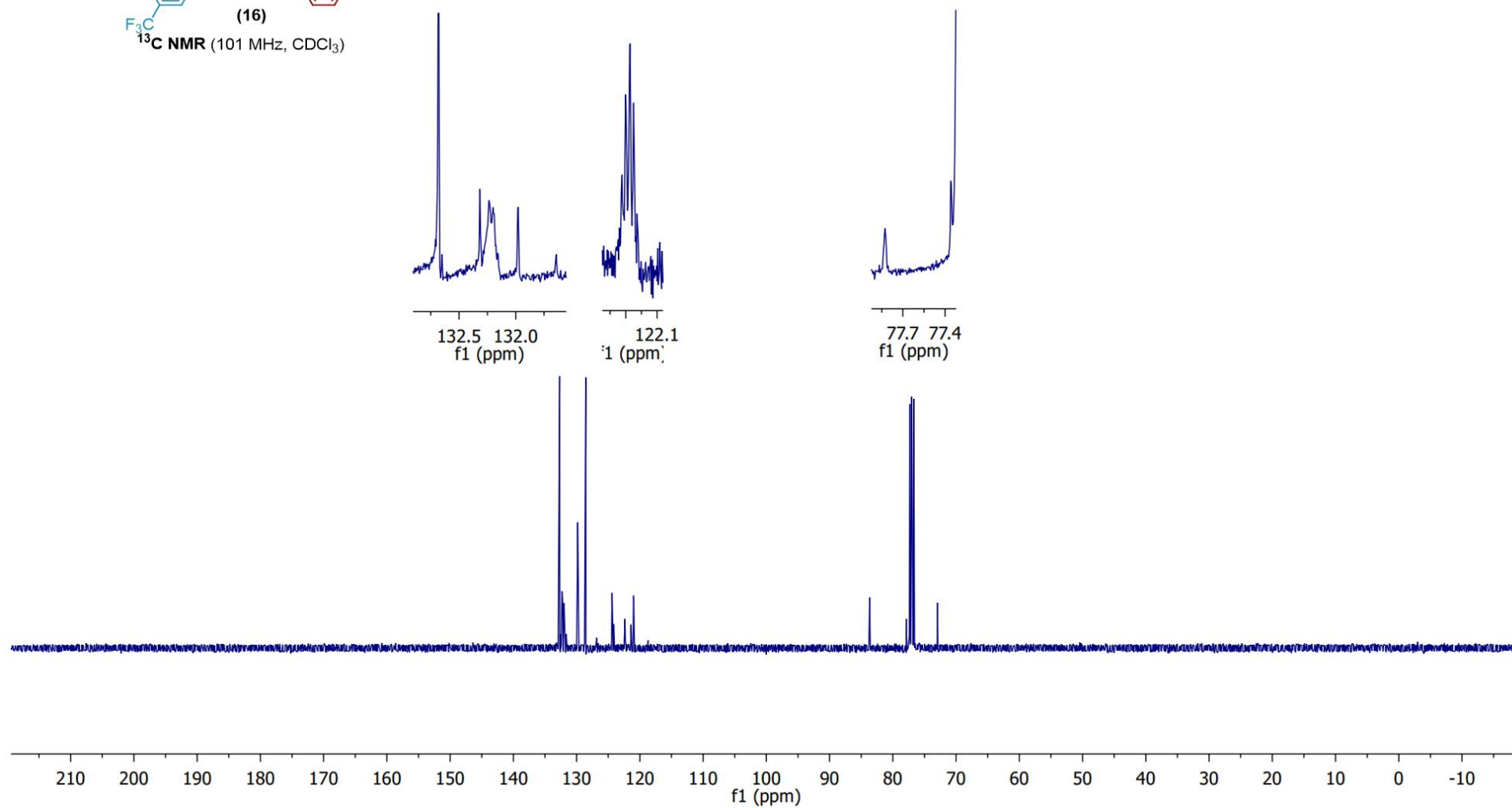
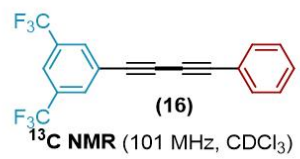
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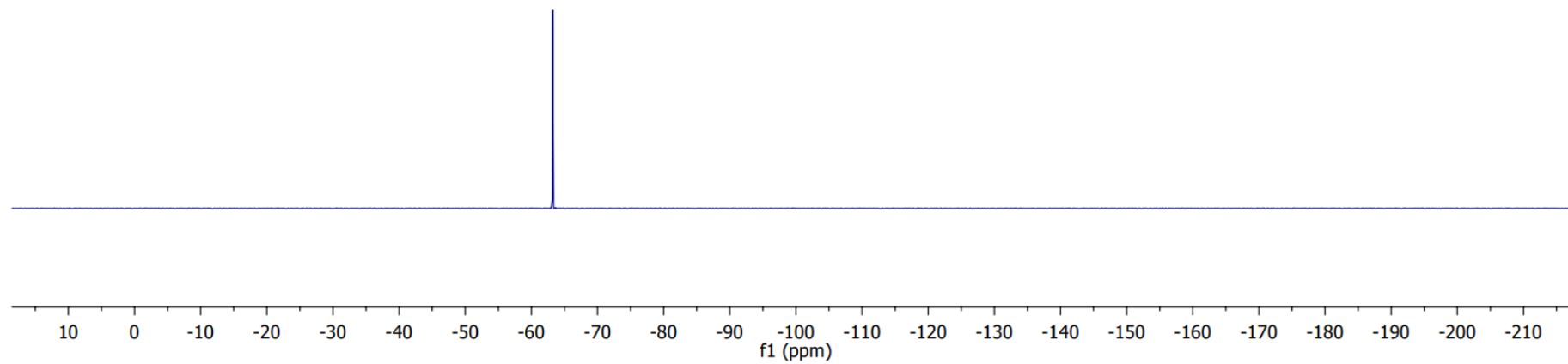
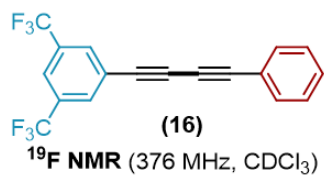


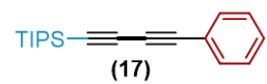


<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



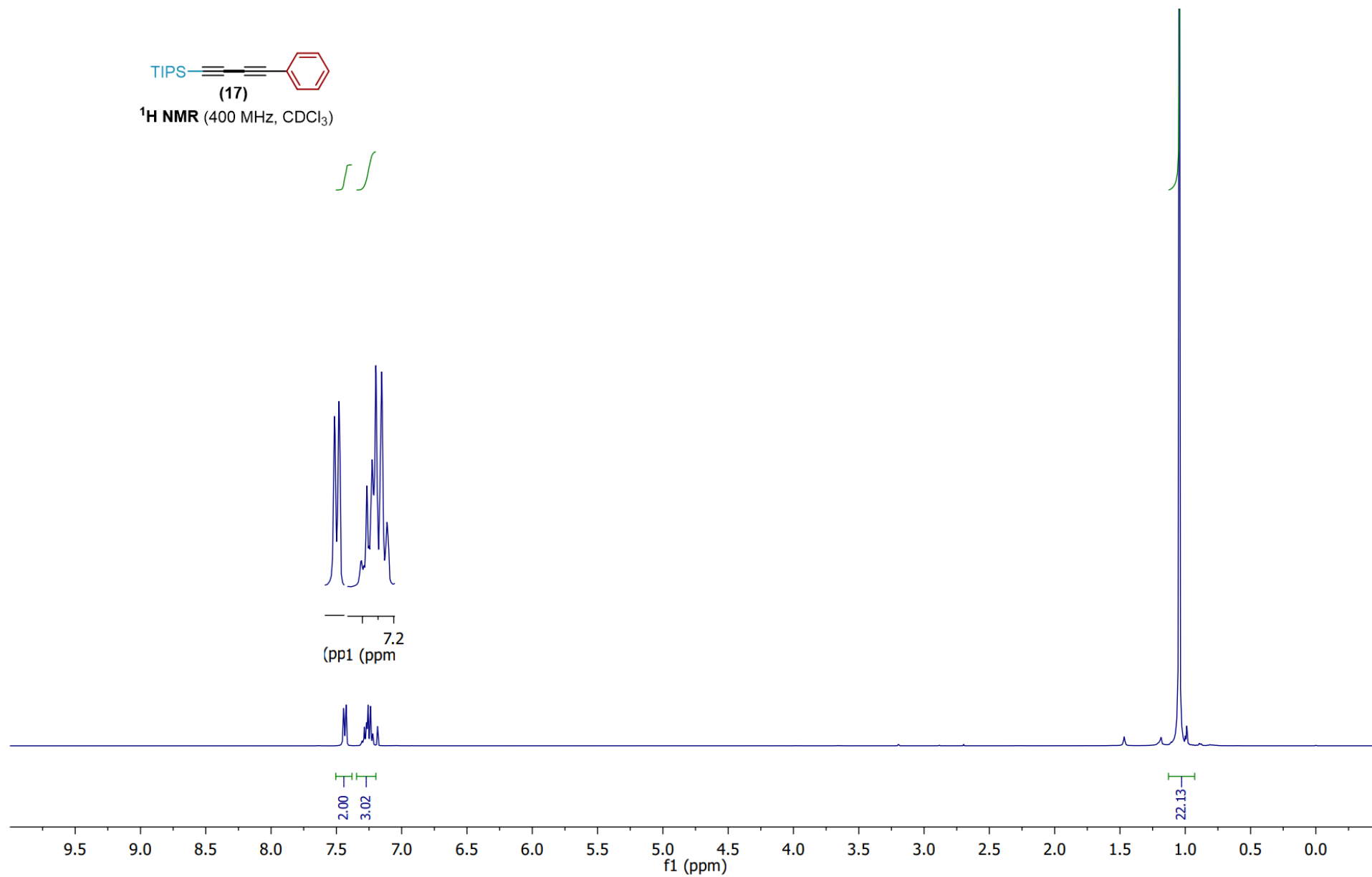


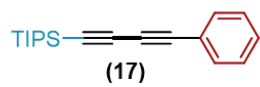




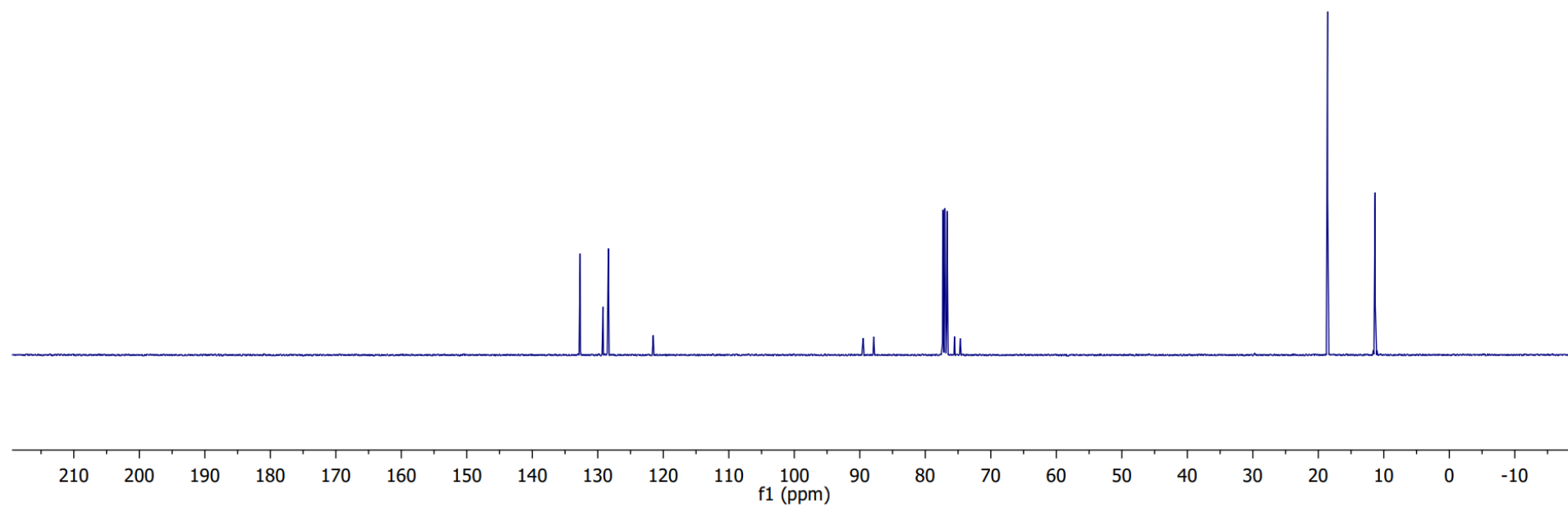
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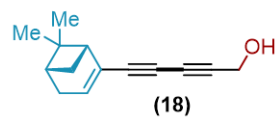
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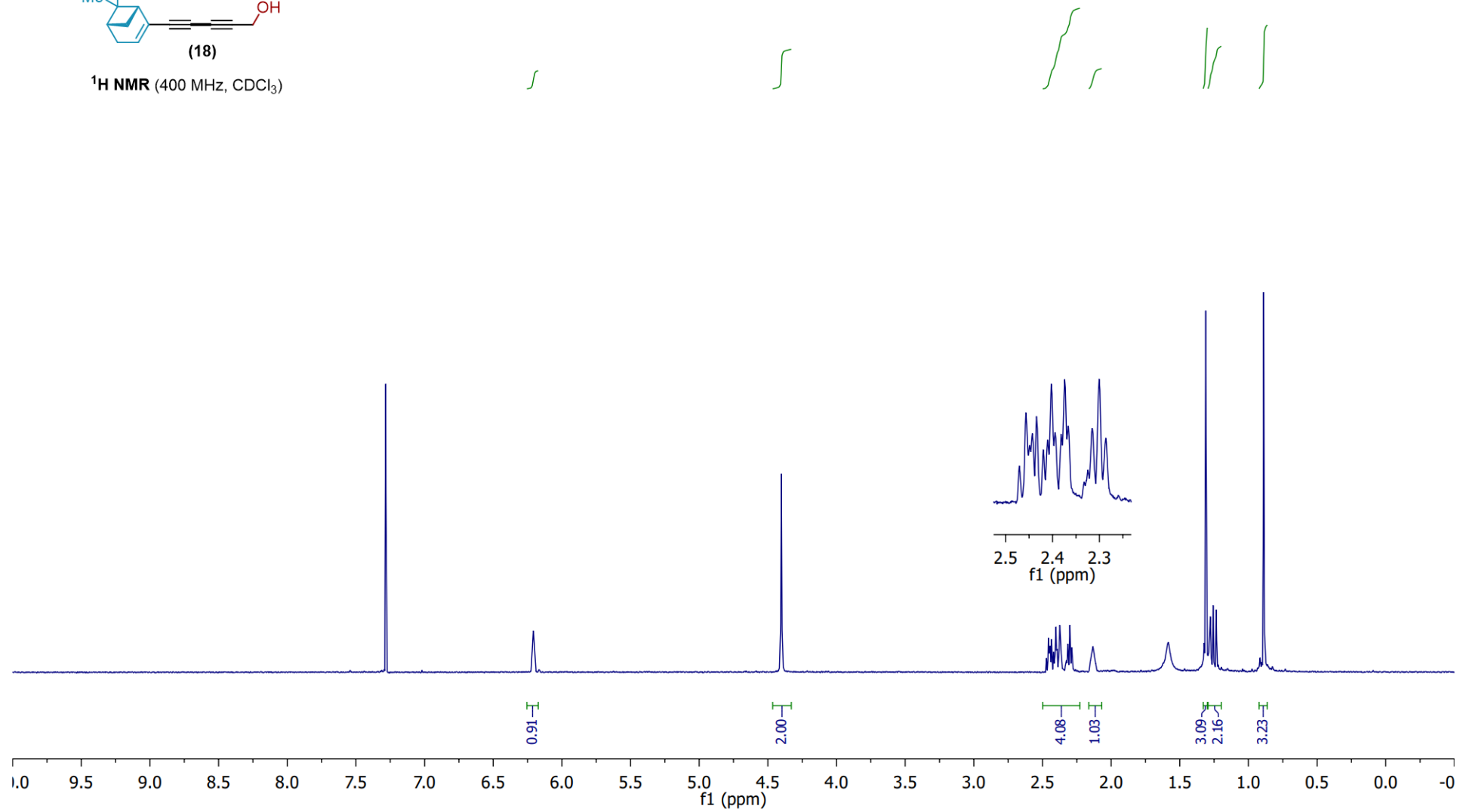


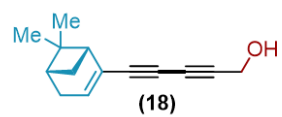
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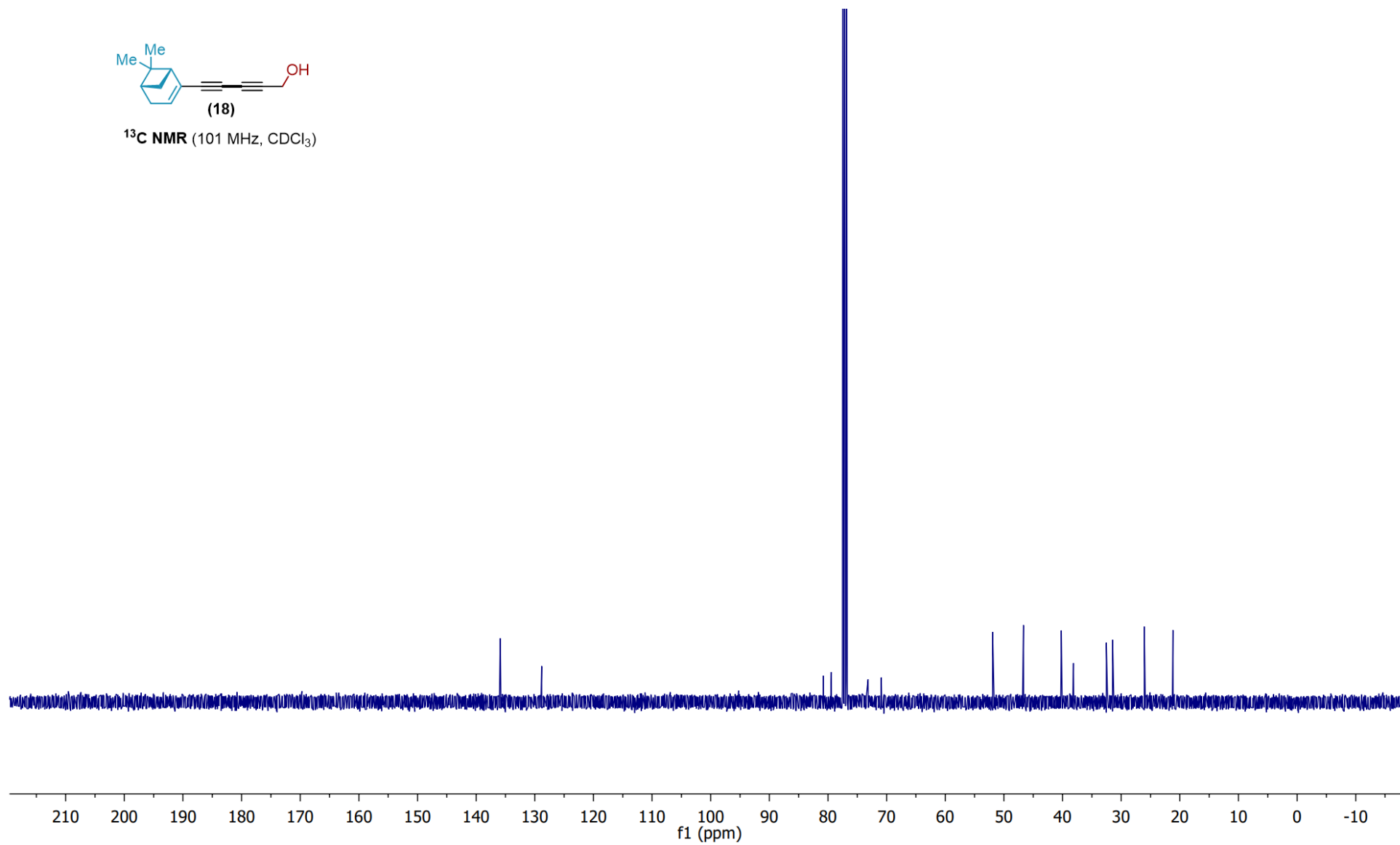


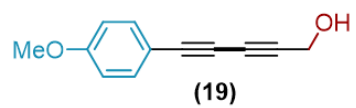
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



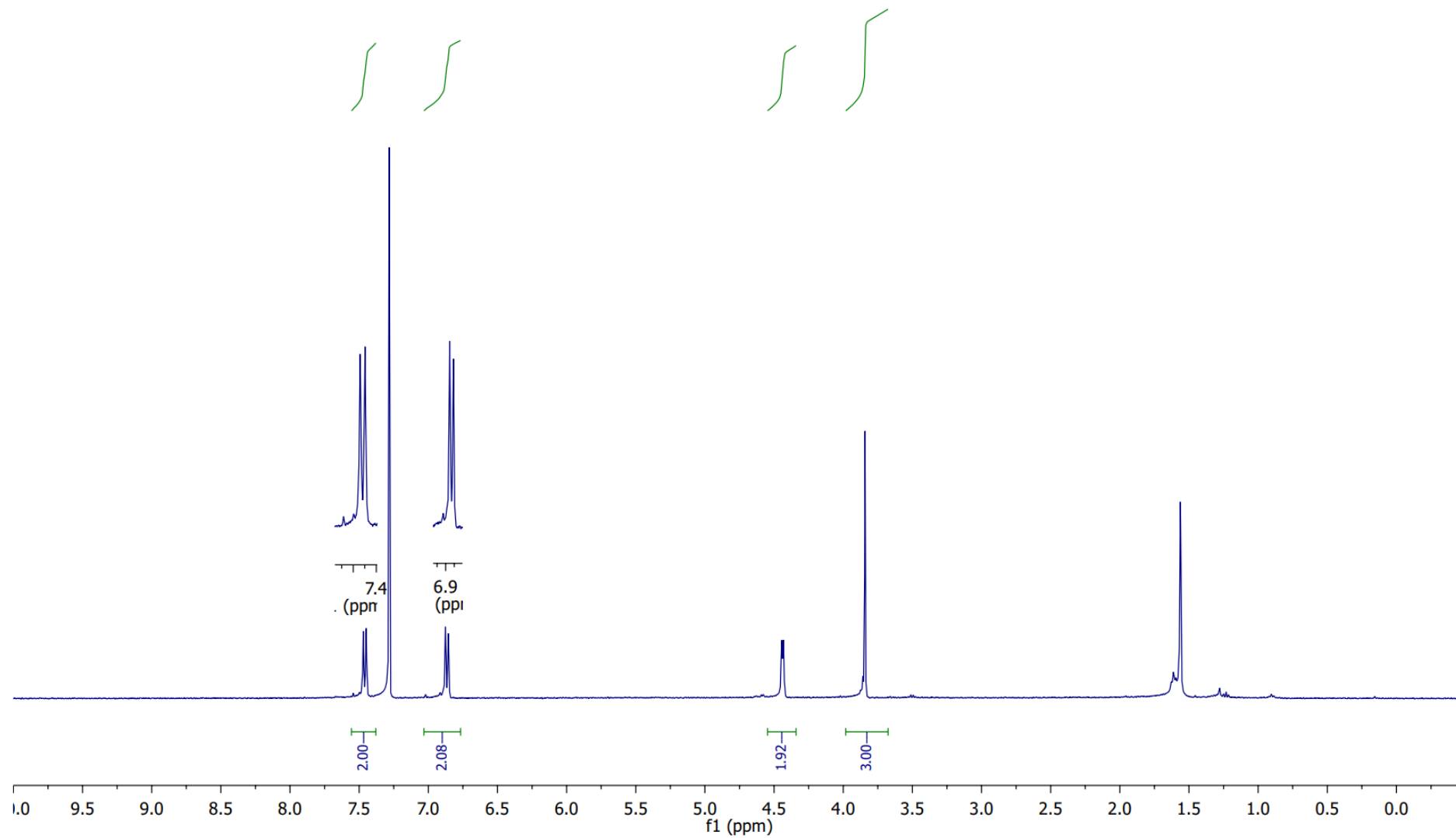


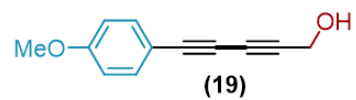
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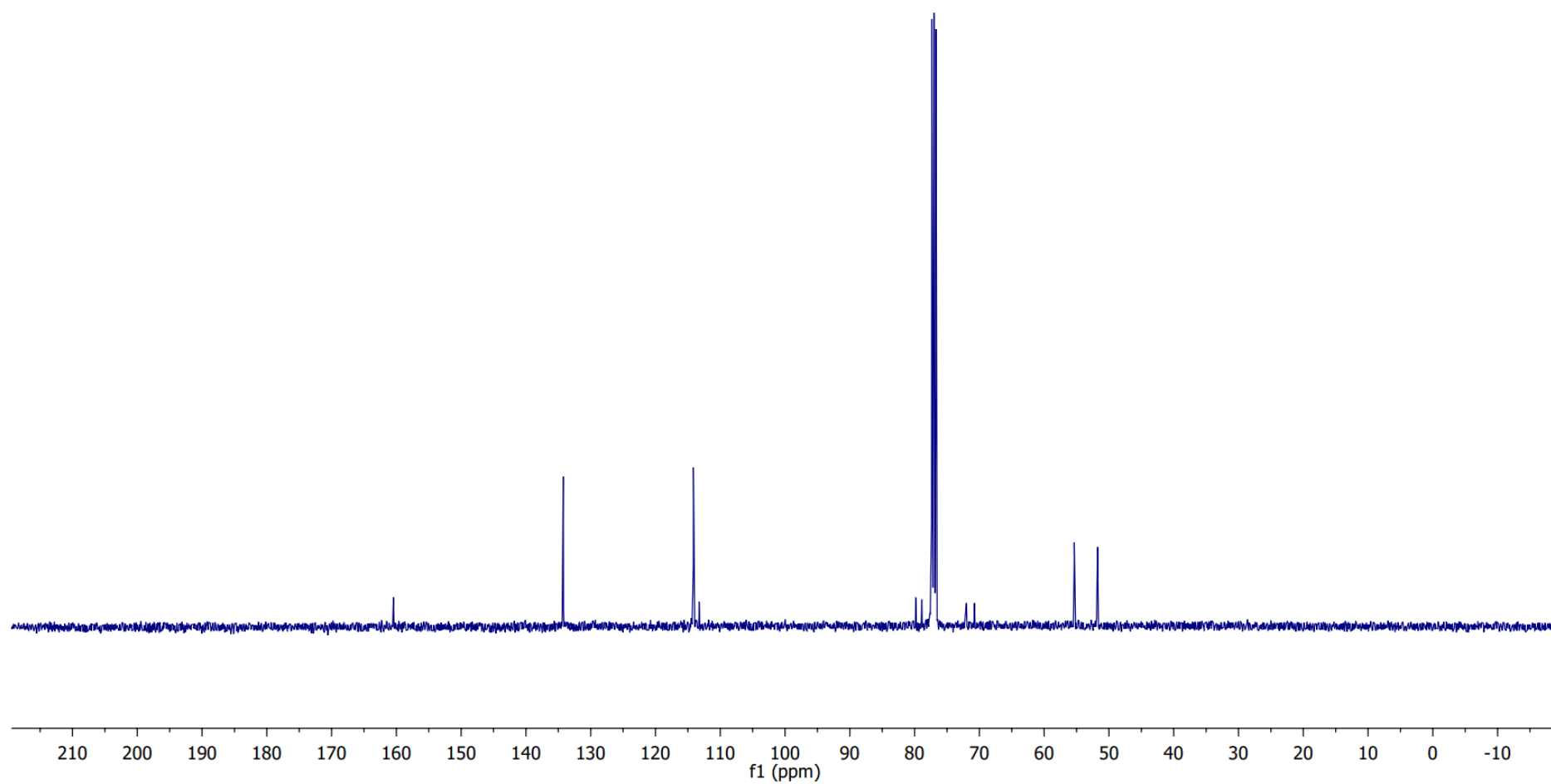


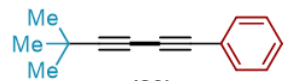
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)





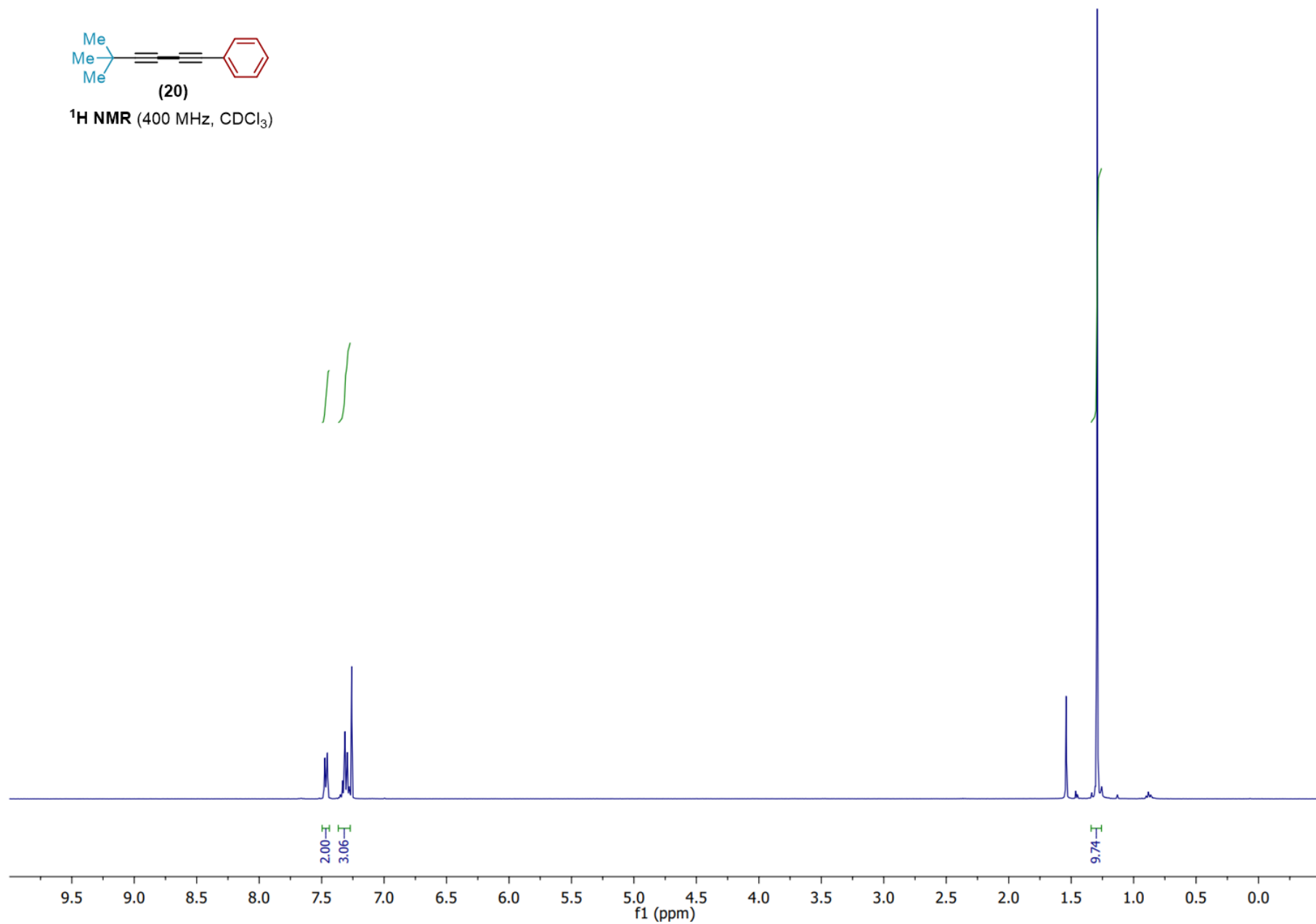
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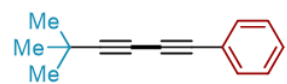




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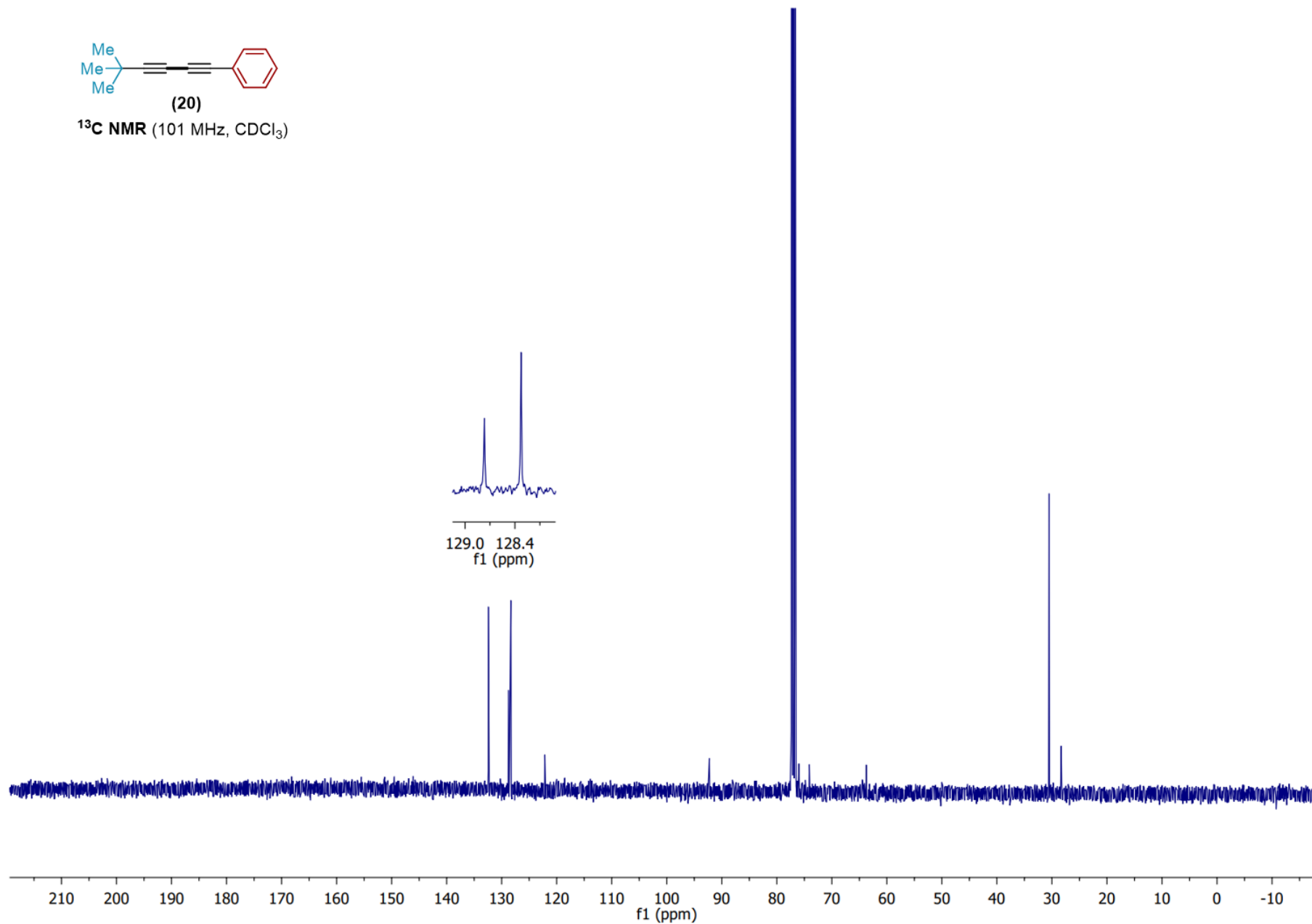
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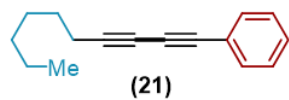




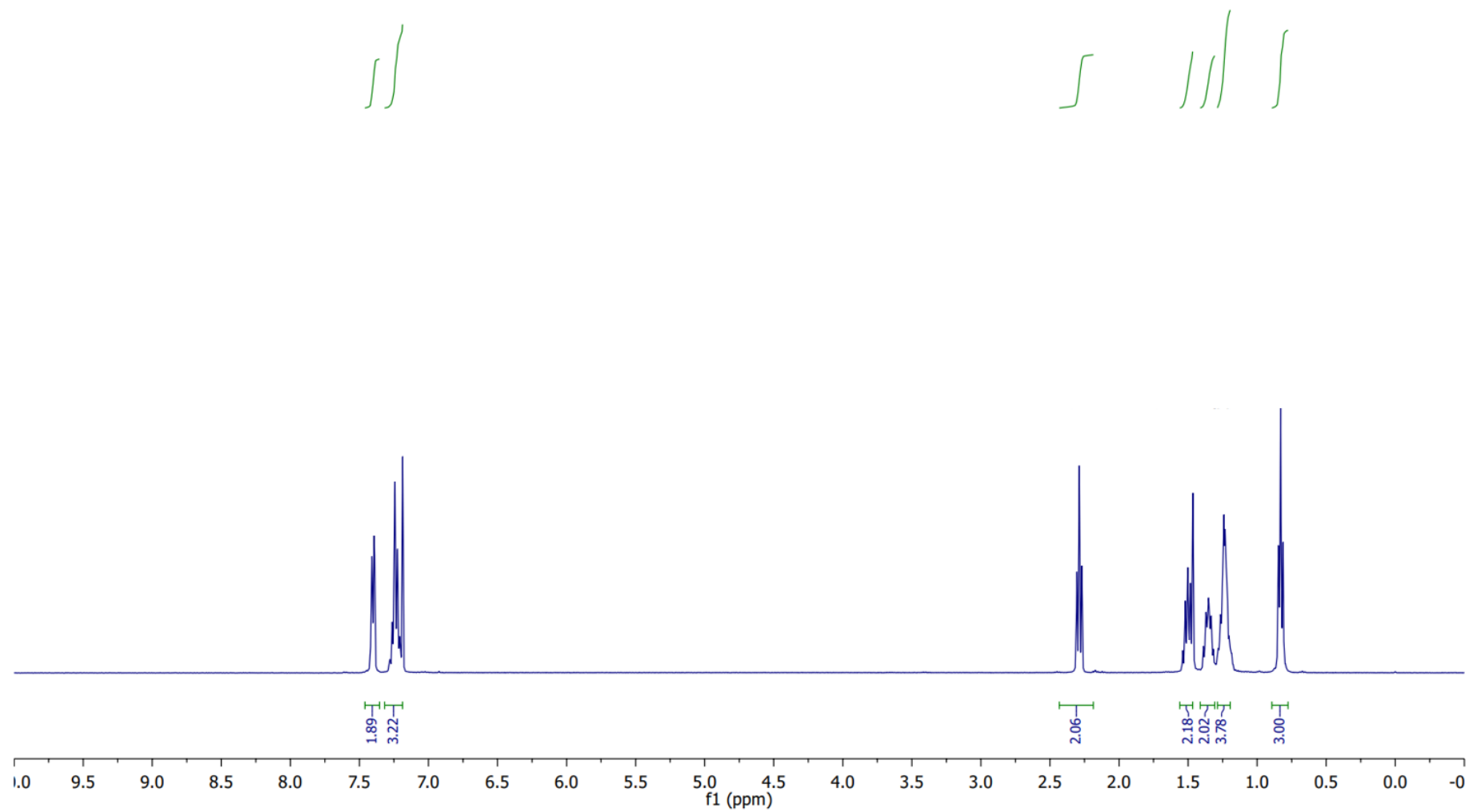
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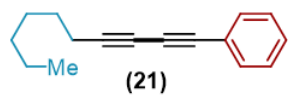
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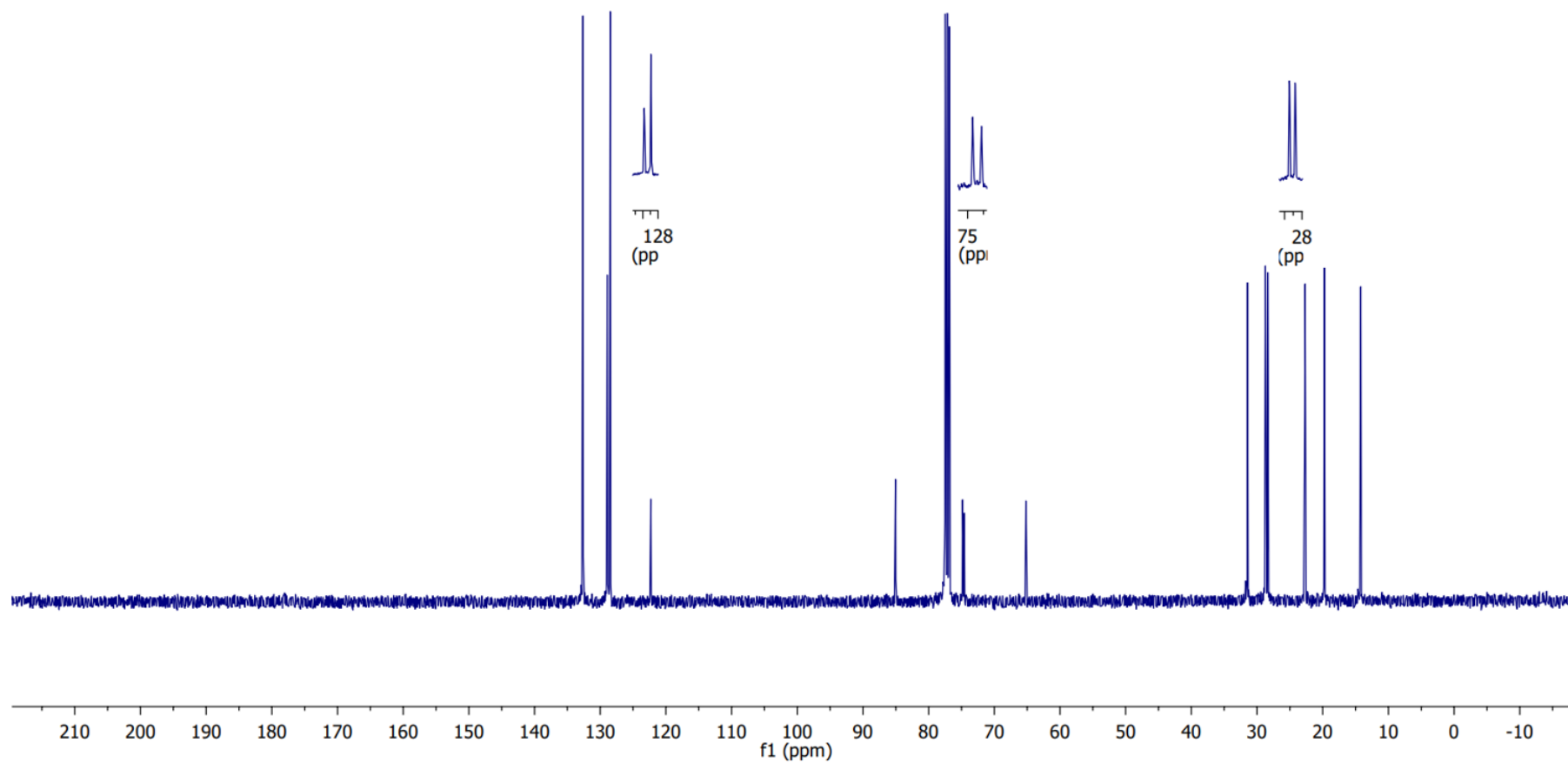


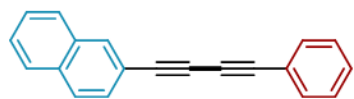
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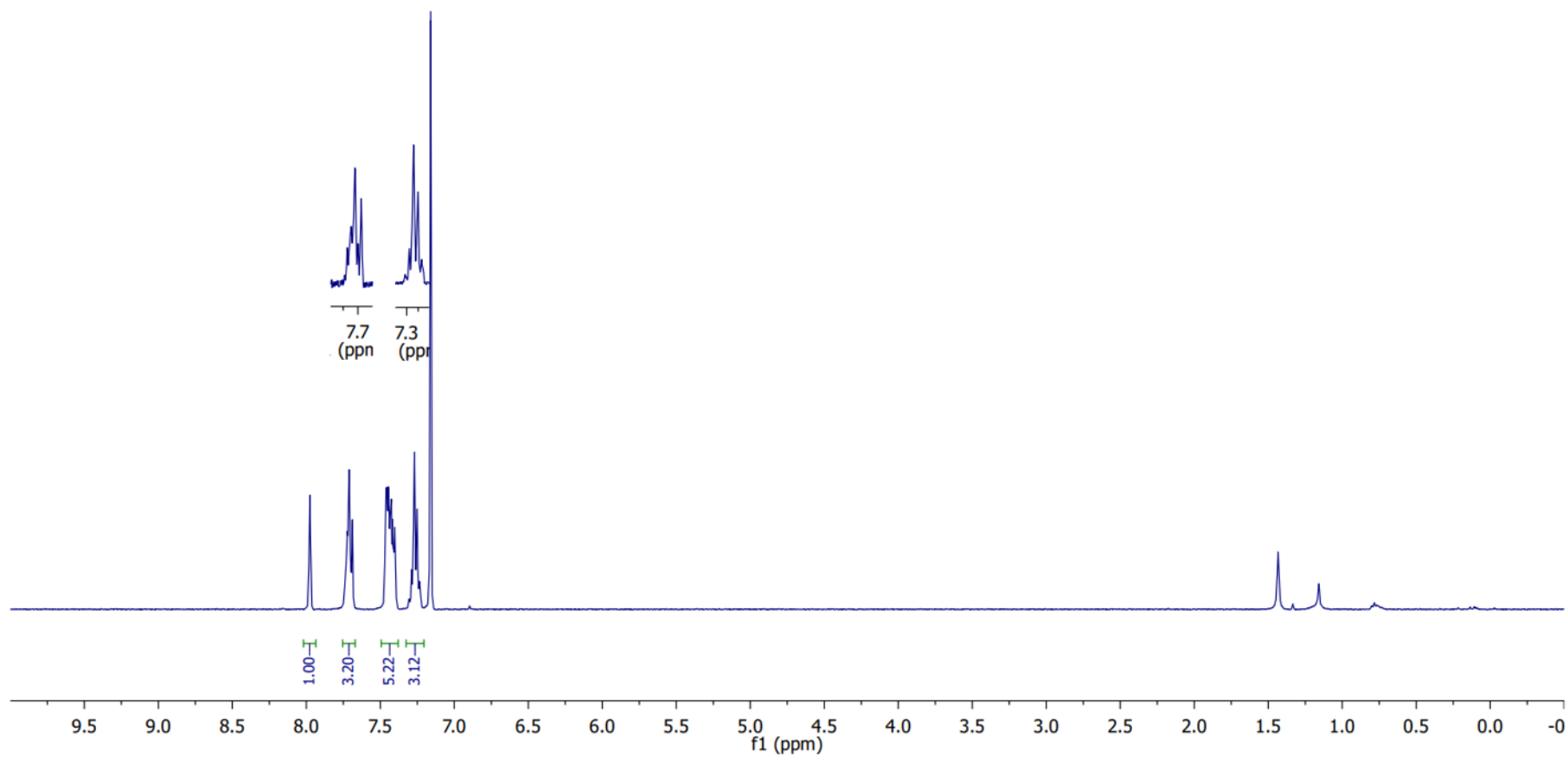
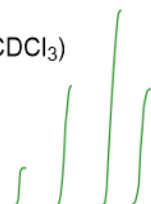
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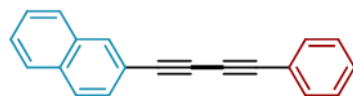




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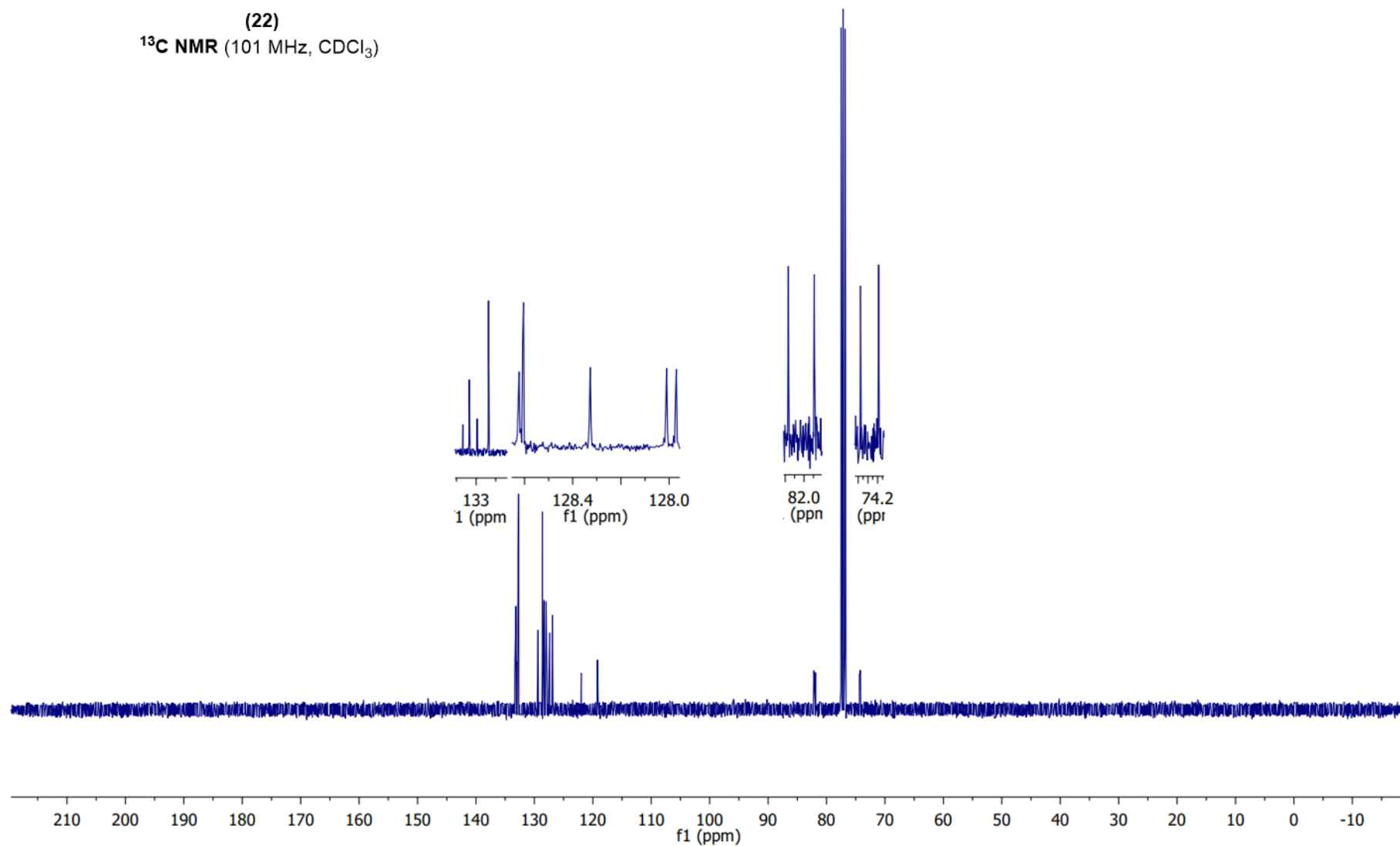
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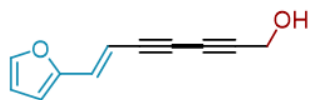




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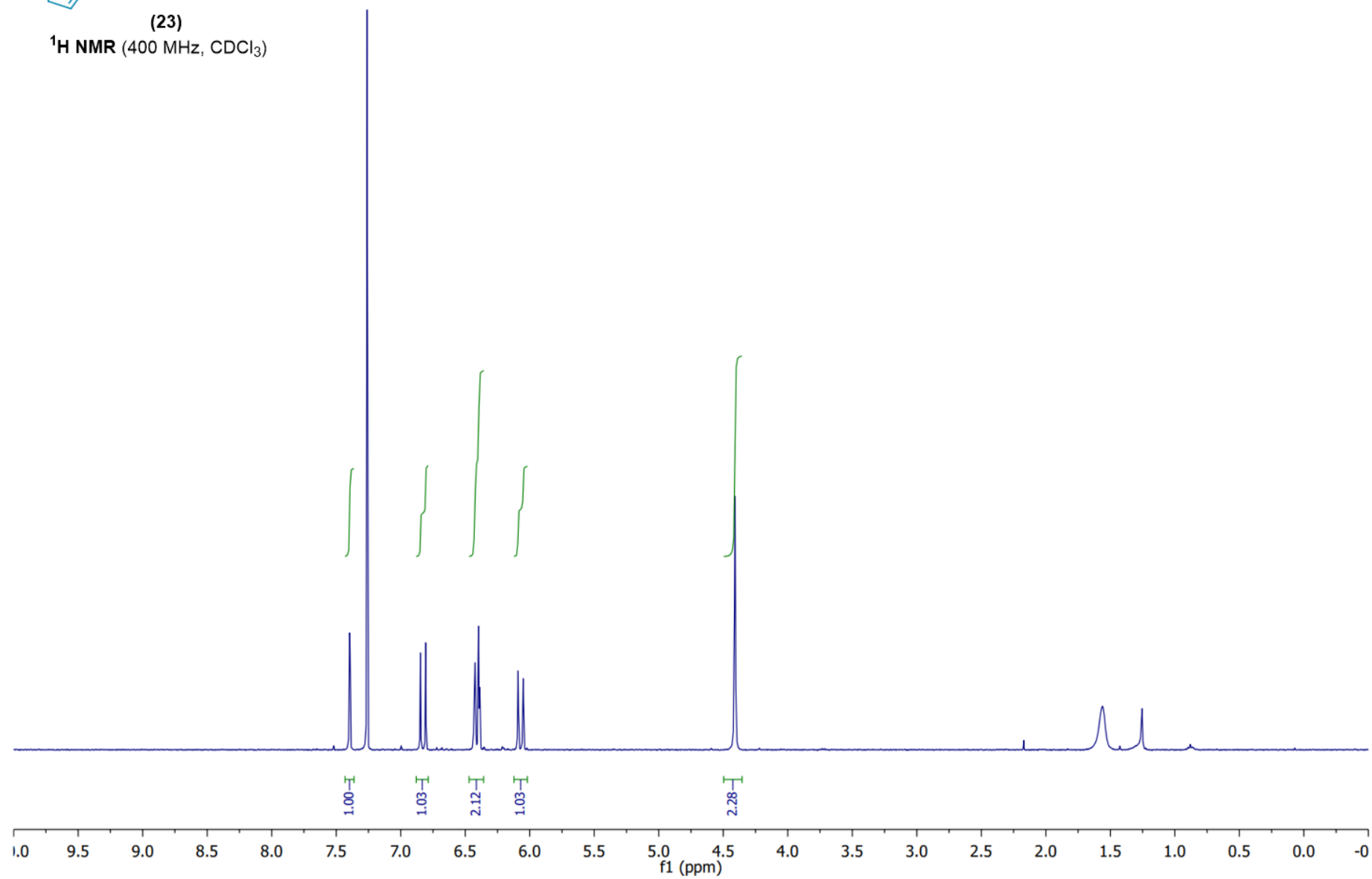
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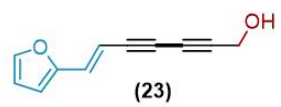




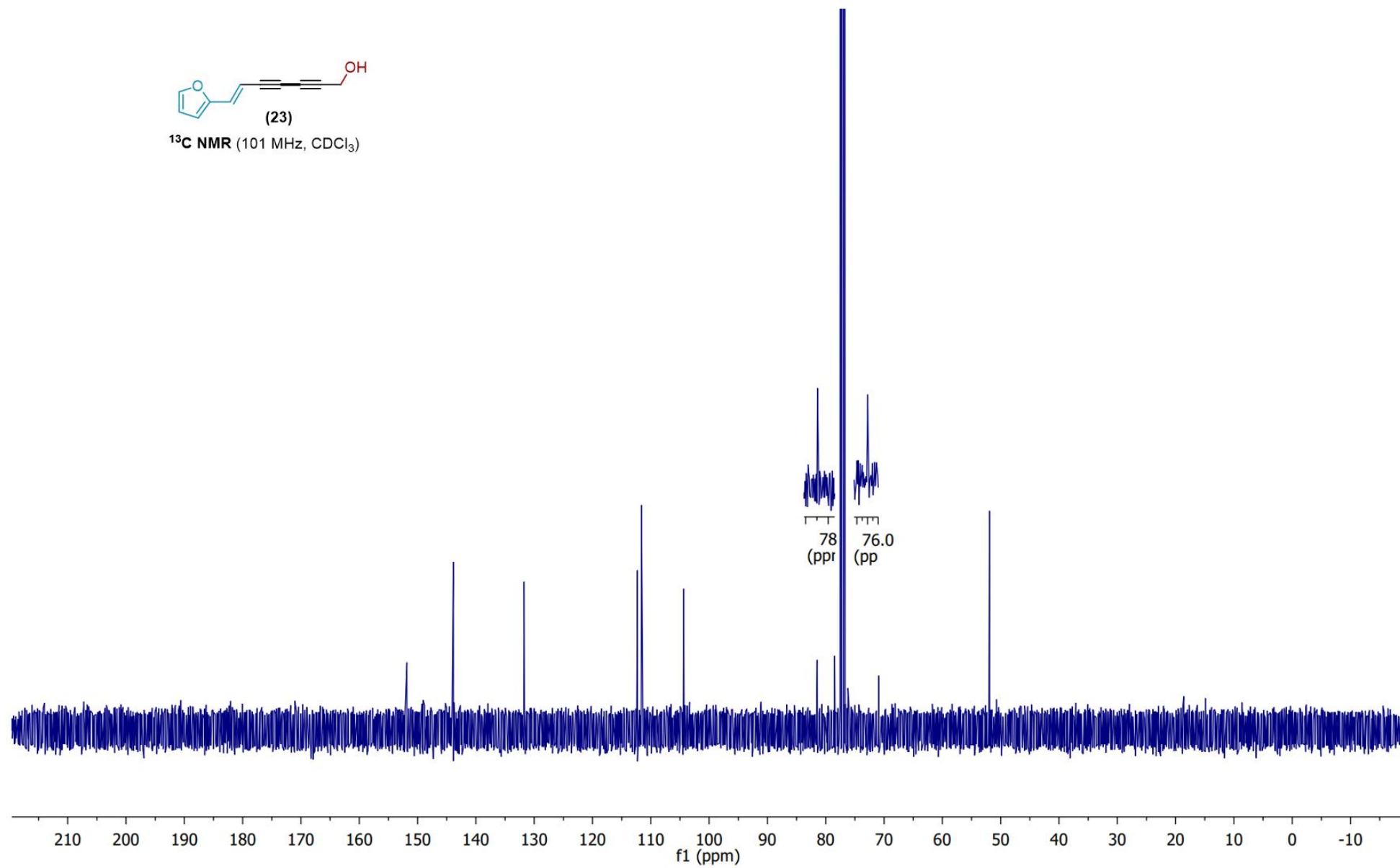
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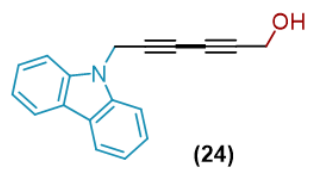
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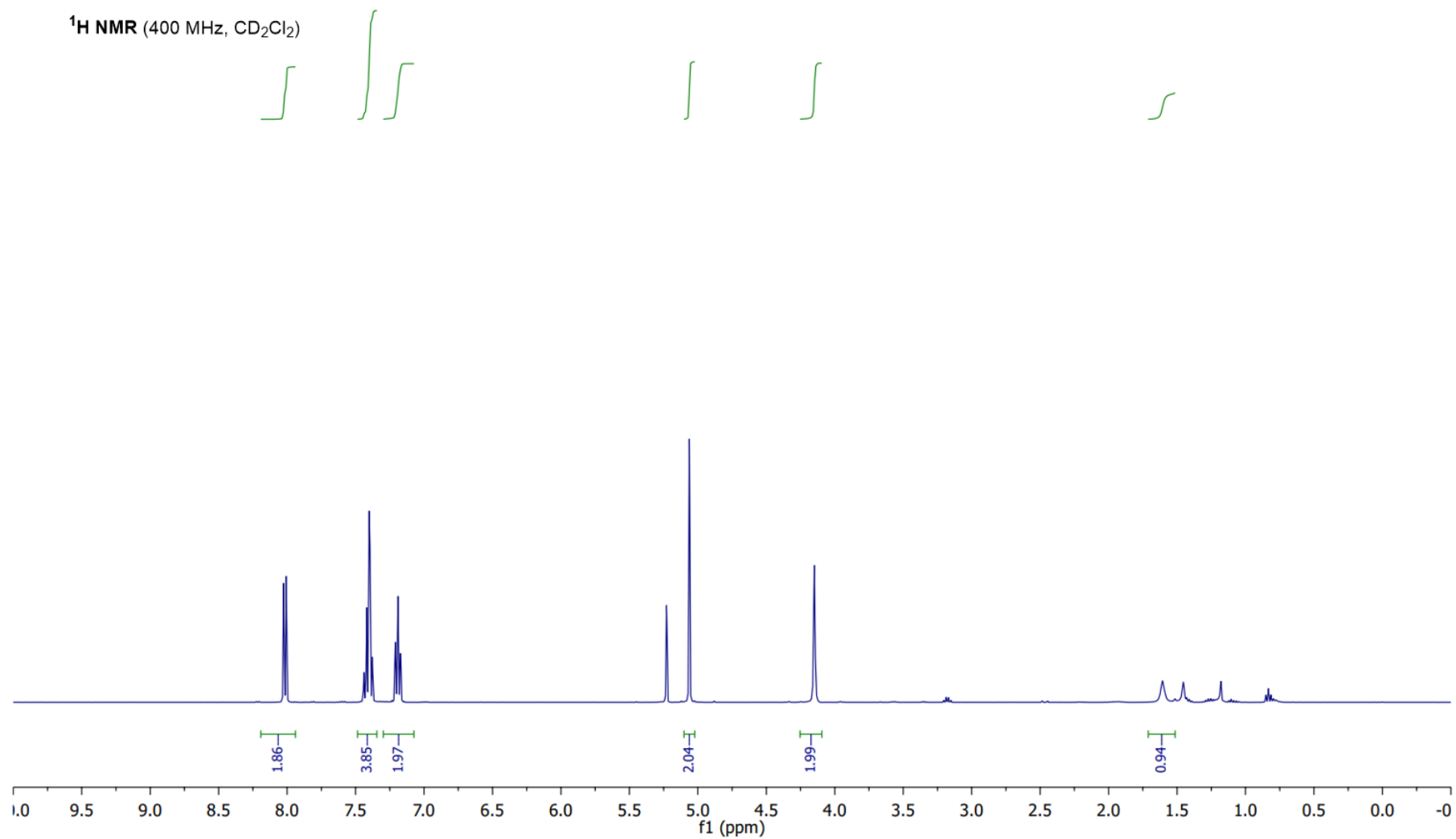


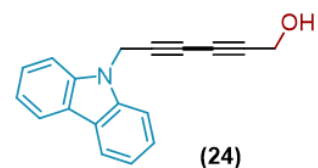
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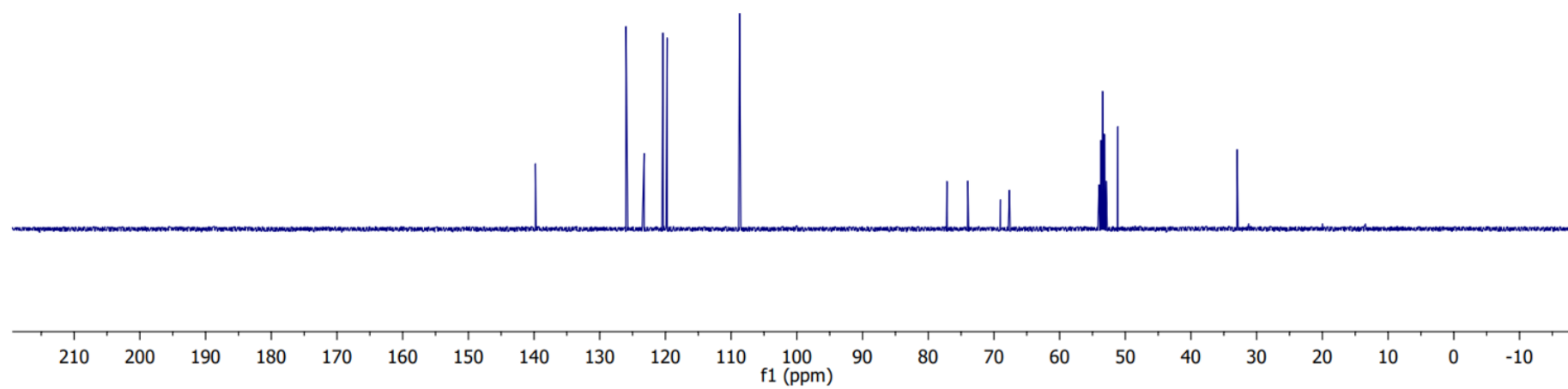


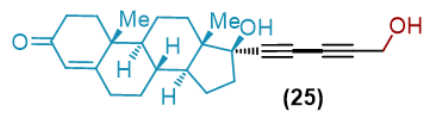
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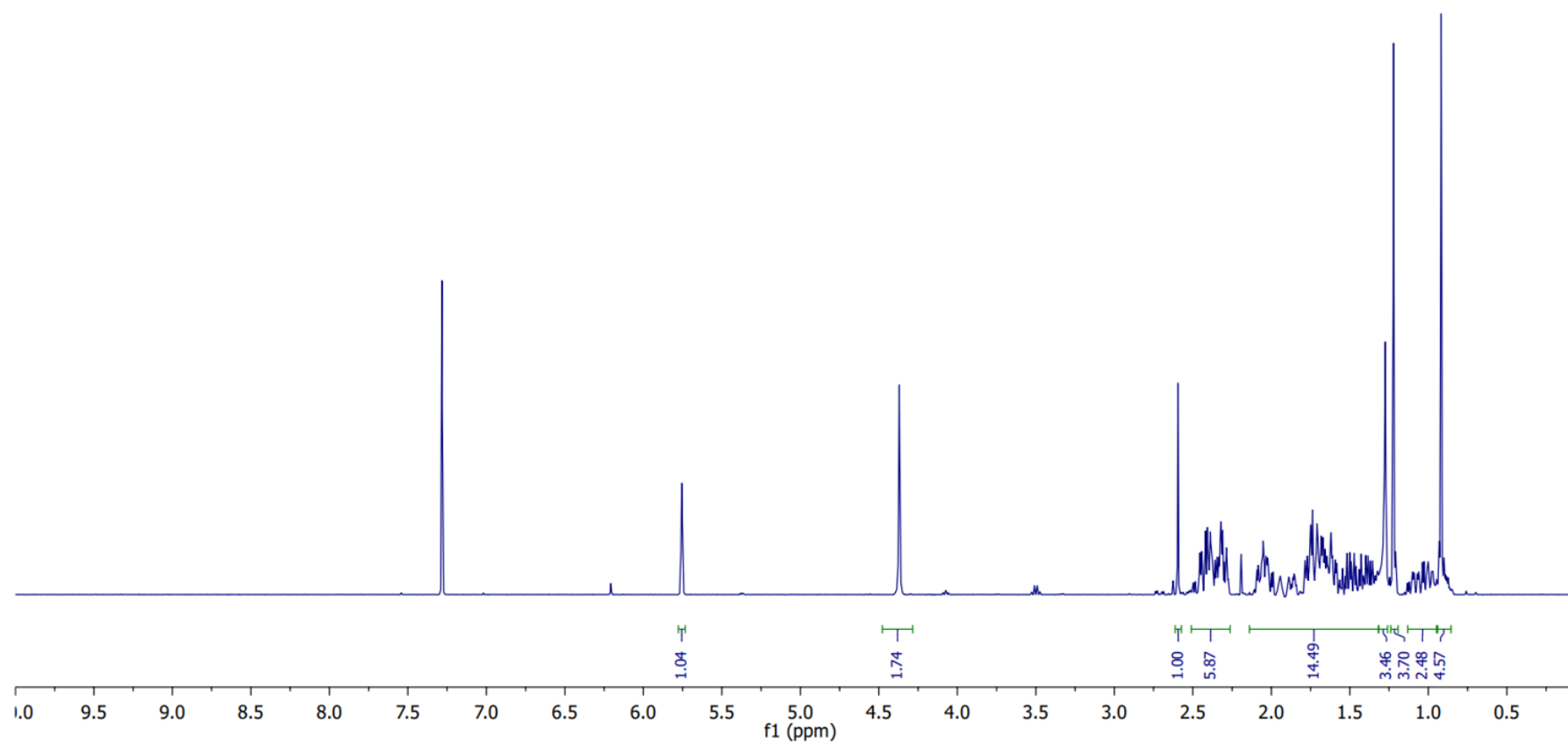


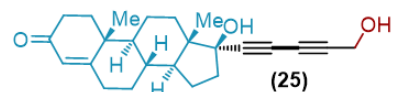
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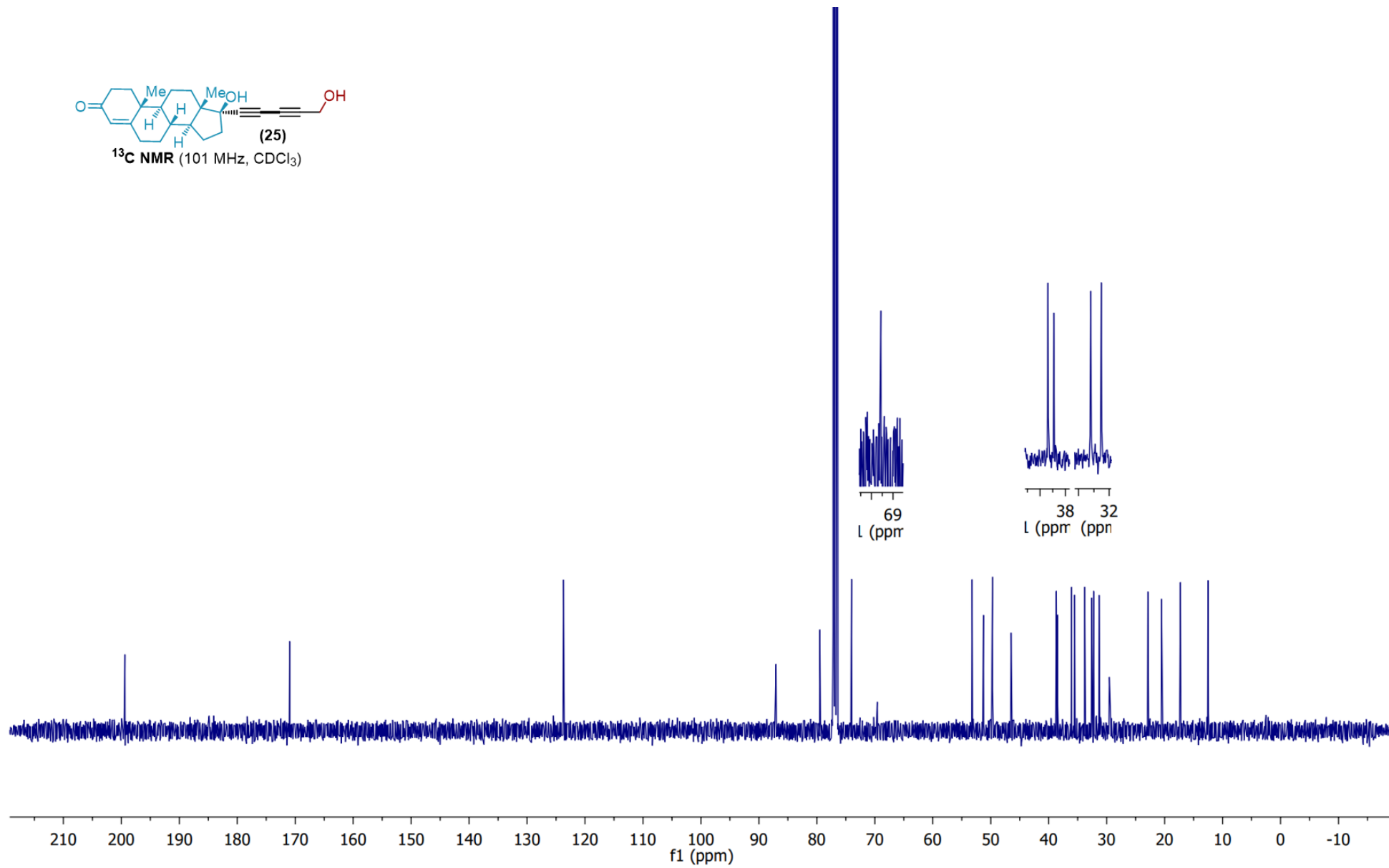


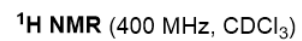
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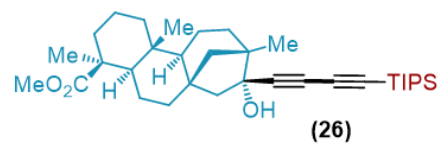




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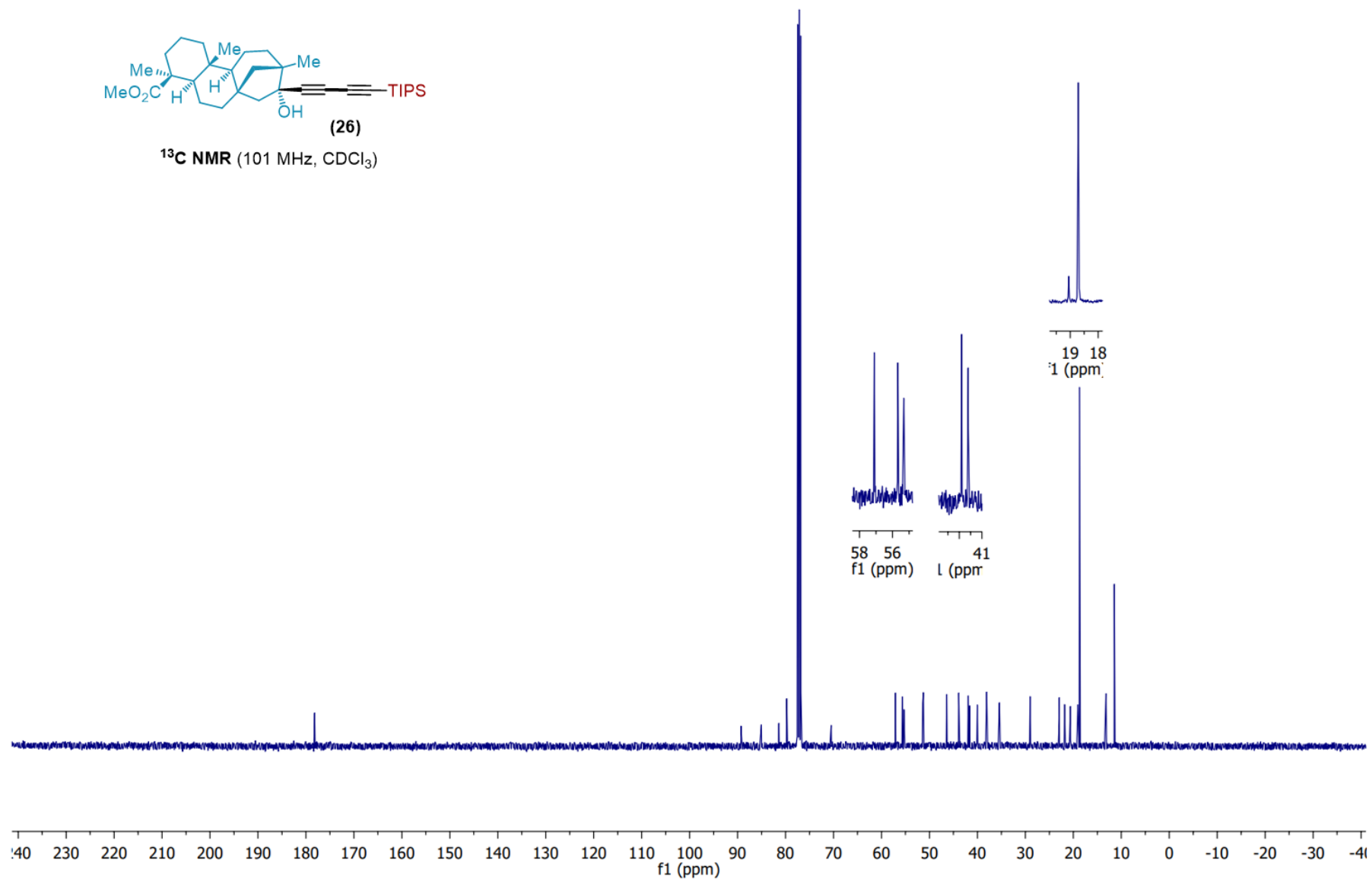


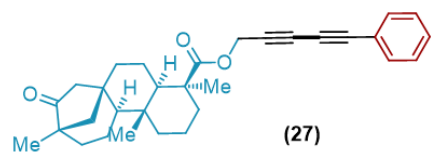




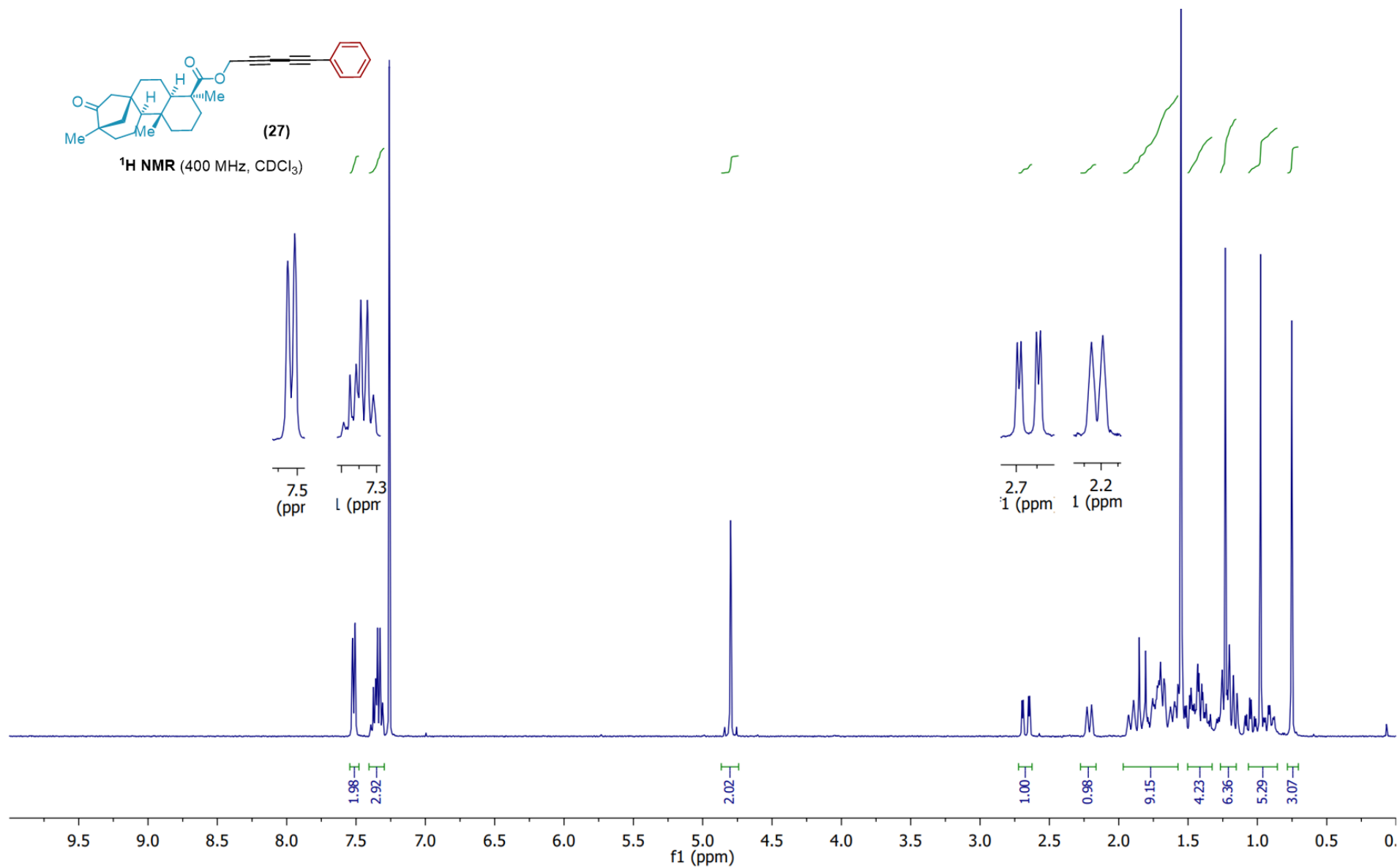
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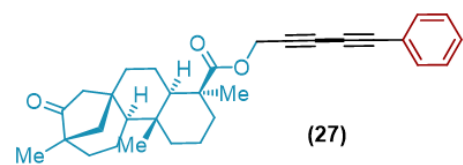
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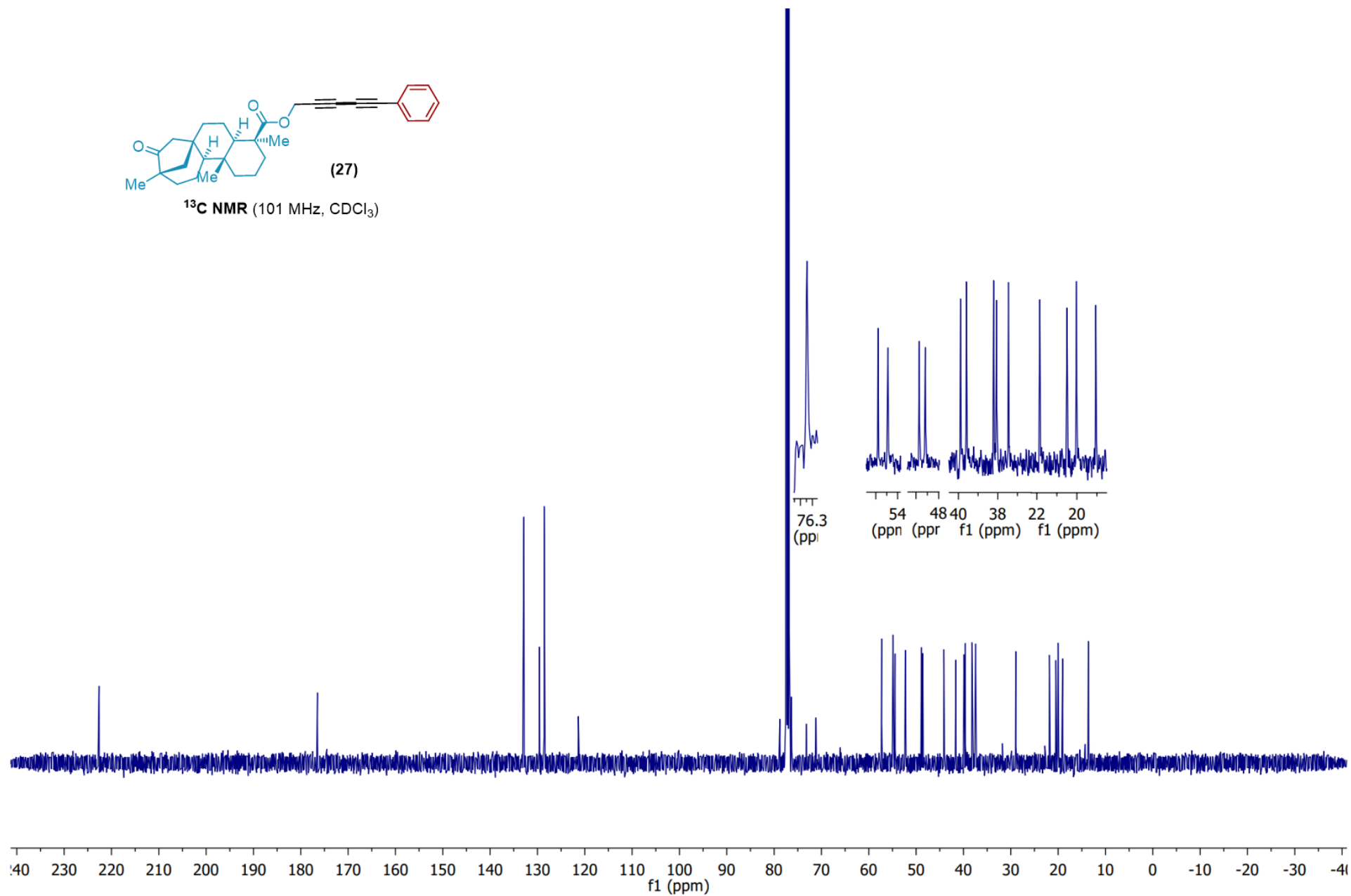
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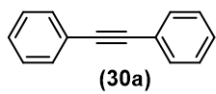




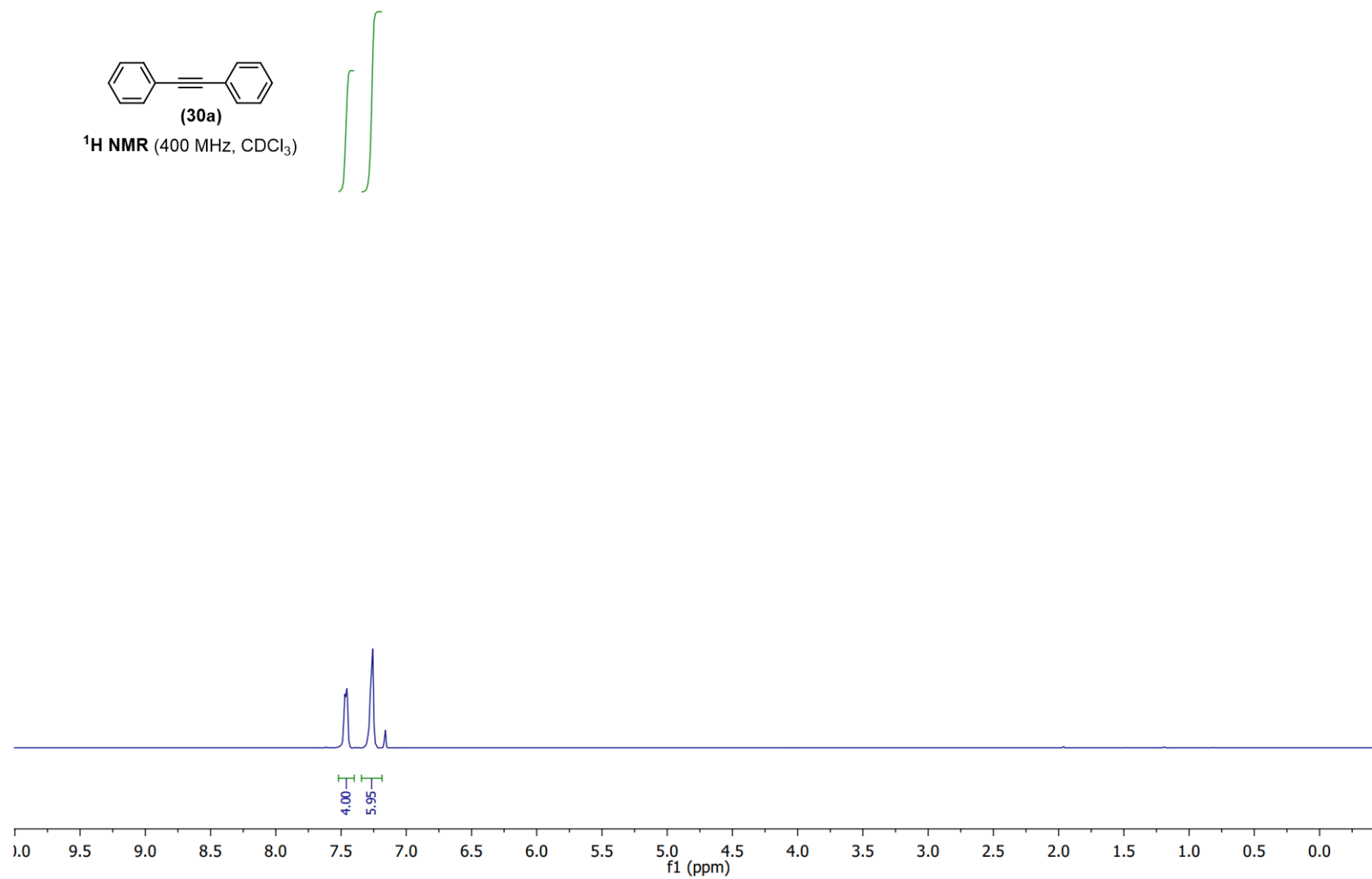
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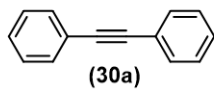
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



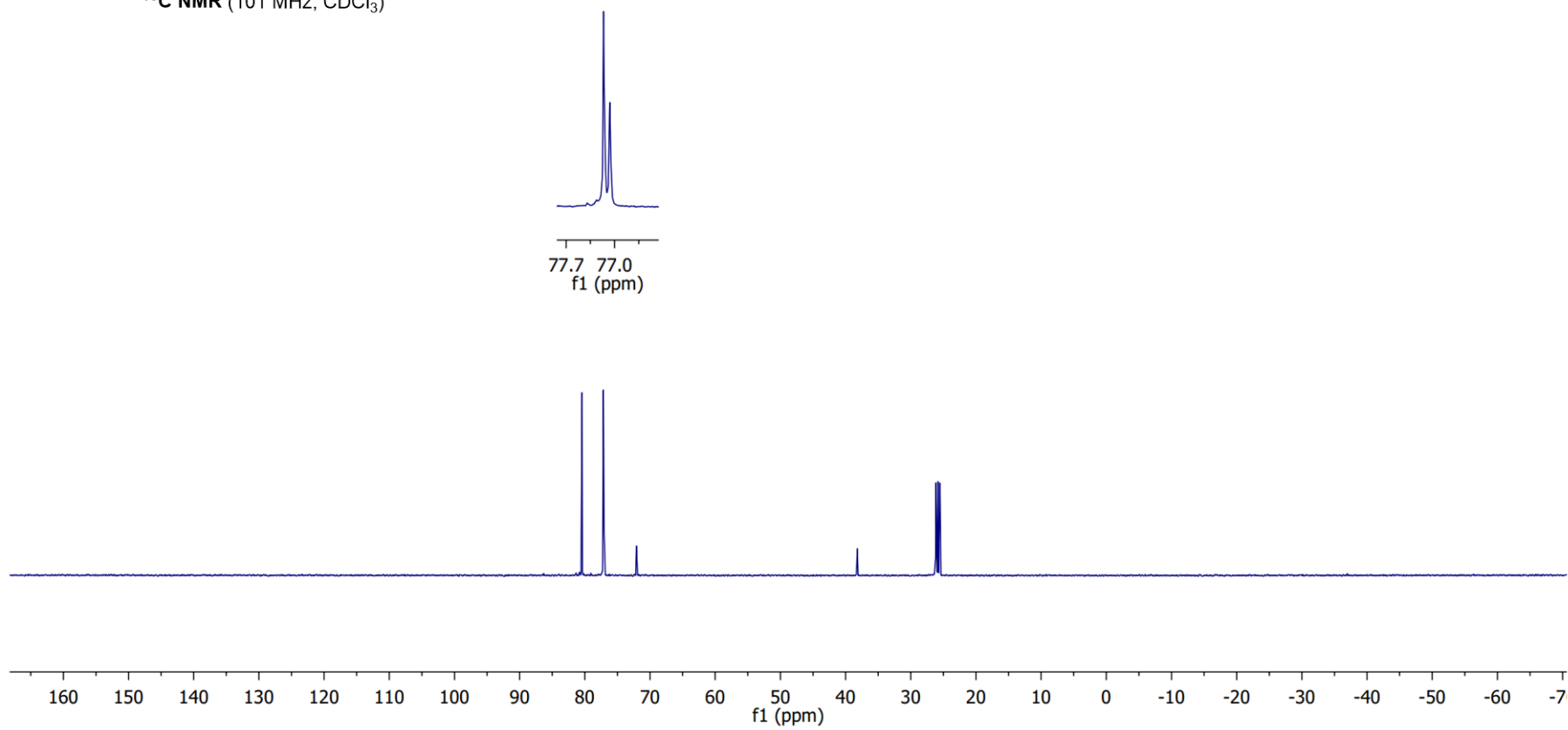


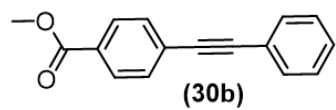
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



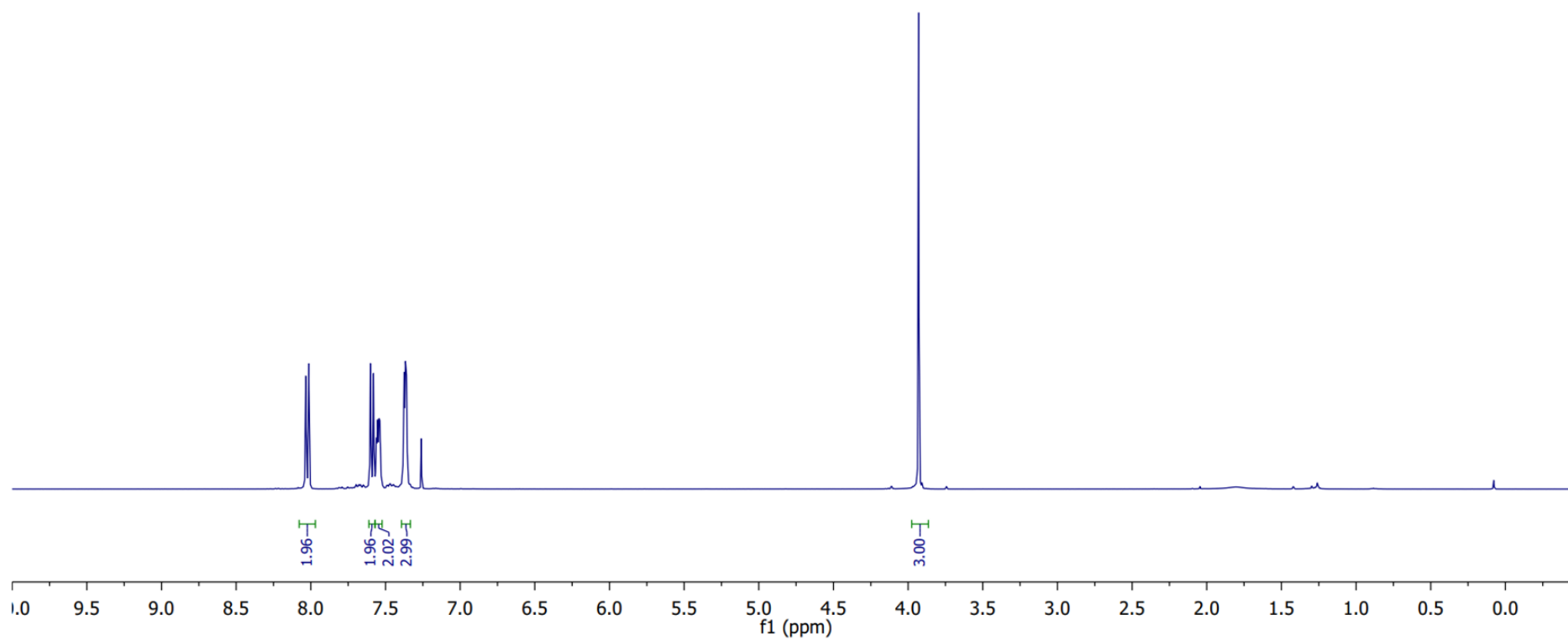


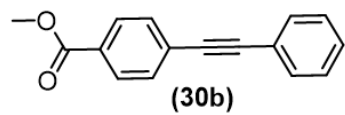
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



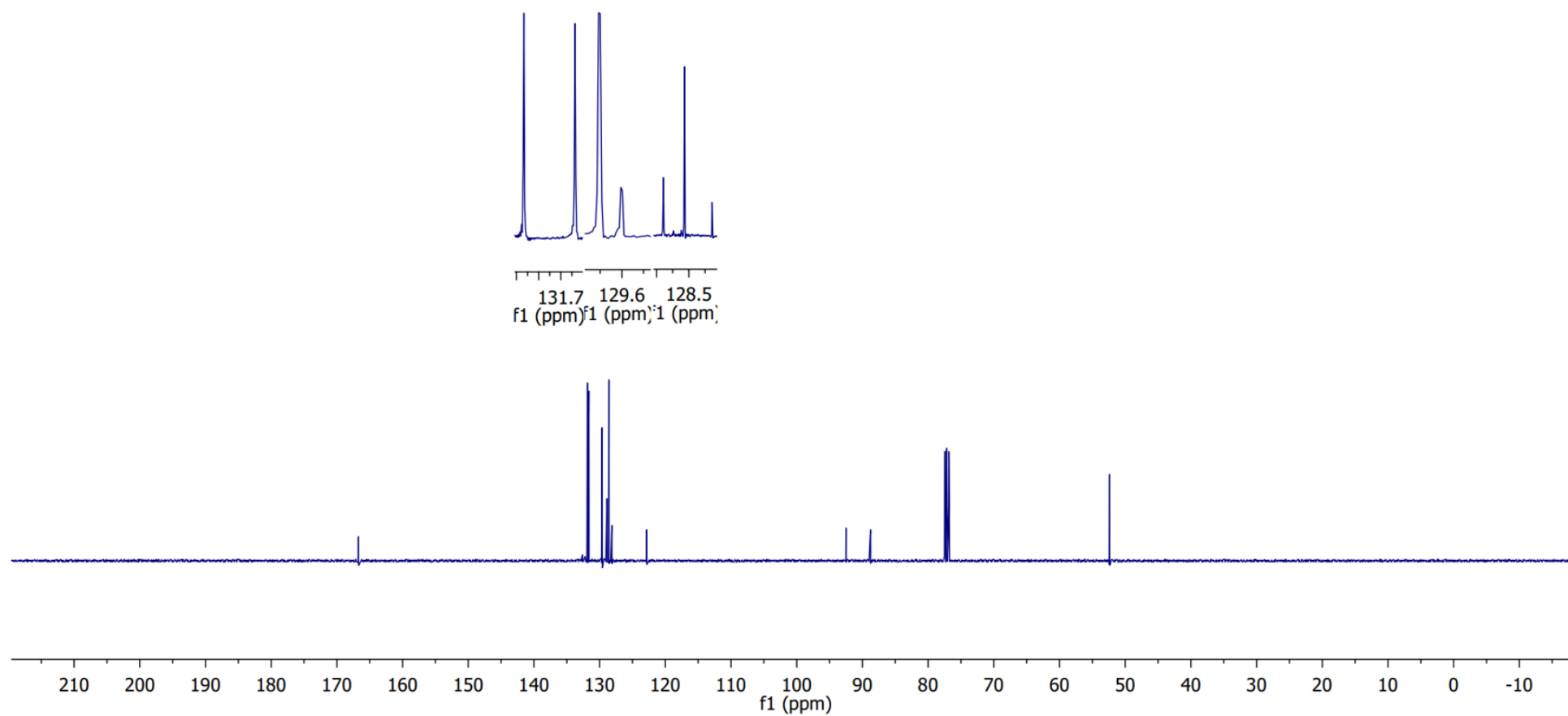


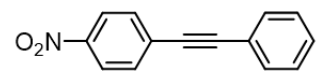
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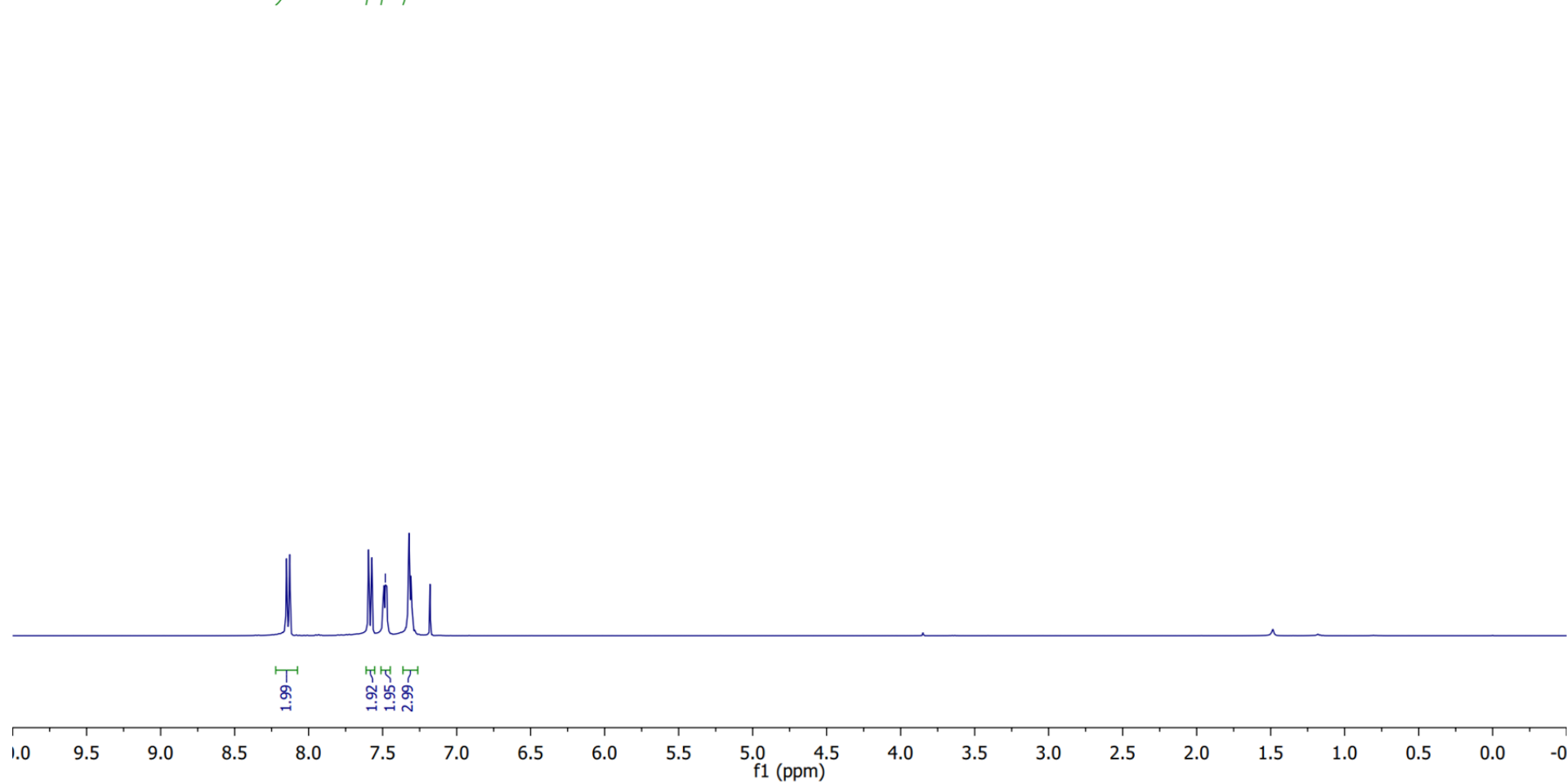
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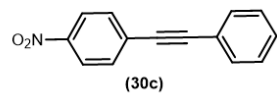




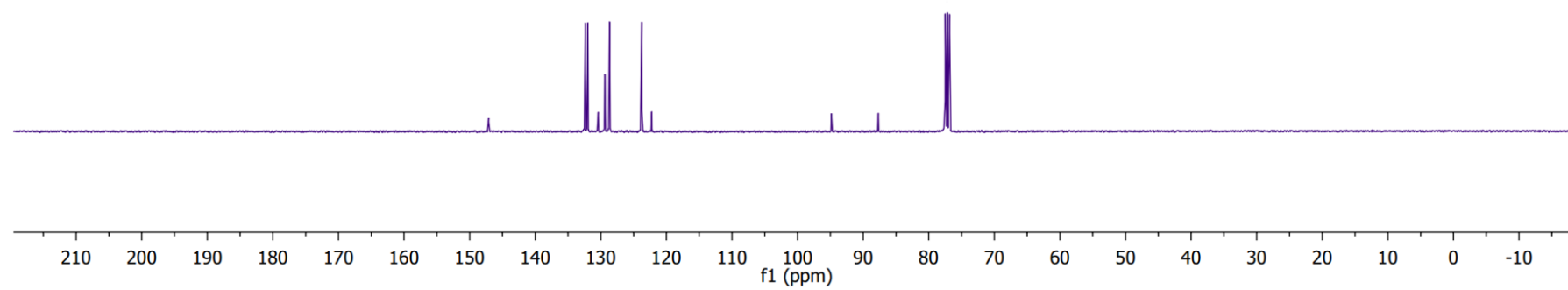
(30c)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )





$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



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## ***Appendix Section 4 :***

*Supporting information for Ch. 5*

**Supporting Information for**

**Towards The Synthesis Of Better ATRP Ligands**

## Contents

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## NMR Spectroscopy

$^1\text{H}$  NMR spectra were recorded at 400 MHz using a Bruker AVANCE 400 spectrometer or at 600 MHz using a Bruker AVANCE 600 spectrometer in  $\text{CDCl}_3$ . Residual protio-solvent peaks were used as an internal reference for  $^1\text{H}$  NMR spectra ( $\text{CHCl}_3$   $\delta$  7.26 ppm). Coupling constants ( $J$ ) are quoted to the nearest 0.1 Hz. The assignment of proton signals was assisted by COSY, HSQC and HMBC experiments where necessary.  $^{13}\text{C}$  NMR spectra were recorded at 101 MHz using a Bruker AVANCE 400 spectrometer or at 175 MHz using a Bruker AVANCE 700 spectrometer in  $\text{CDCl}_3$ . Solvent peaks were used as an internal reference for  $^{13}\text{C}$  NMR spectra ( $\text{CDCl}_3$   $\delta$  77.2 ppm). Assignment of carbon signals was assisted by HSQC and HMBC experiments. The following abbreviations (or combinations thereof) are used to denote  $^1\text{H}$  NMR multiplicities: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet.

## Mass Spectrometry

Low-resolution EI mass spectra were recorded on an Agilent HP 6890 gas chromatograph/mass spectrometer with a 7683 series injector fitted with a Phenomenex Zebron ZB-1 column (15 m length x 0.25 mm internal diameter x 0.25  $\mu\text{m}$  film thickness) using EI<sup>+</sup> ionization mode at 70 eV or a Finnigan Polaris Q ion trap mass spectrometer using electron impact (EI<sup>+</sup>) ionization mode at 40 or 70 eV. High-resolution EI mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. Low-resolution ESI mass spectra were recorded on a Micromass ZMD spectrometer using electrospray (ESI<sup>+</sup>) ionization mode. High resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) spectrometer using electrospray ionization (ESI<sup>+</sup>).

## Experimental Procedures, Reagents, and Glassware

Reactions were conducted under a standard lab (air) atmosphere, at room temperature, unless specified otherwise. Anhydrous solvents were either obtained from commercial sources or dried according to the procedure outlined by Grubbs and co-workers.<sup>1</sup> Commercially available chemicals were used as purchased, or where specified, purified by standard techniques.<sup>2</sup> Solutions of *n*-BuLi were titrated against salicylaldehyde phenylhydrazone according to the procedure of Love and Jones.<sup>3</sup>

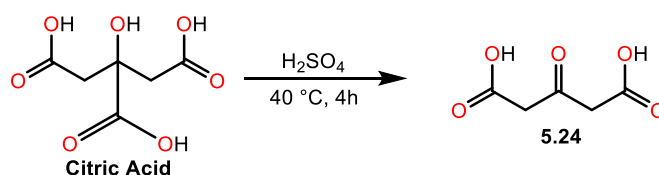
## Chromatography

Analytical thin-layer chromatography was conducted with aluminum-backed silica gel 60 F<sub>254</sub> (0.2 mm) plates supplied by Merck, and visualized using UV fluorescence ( $\lambda_{\text{max}} = 254 \text{ nm}$ ), or developed using phosphomolybdic acid (PMA) stain, followed by heating. Flash chromatography employed Merck Kieselgel 60 silica gel (230–400 mesh). PS 40–60 °C refers to petroleum spirits, boiling point fraction 40–60 °C. PS 30–40 °C refers to petroleum spirits, boiling point fraction 30–40 °C.

## Buffered silica

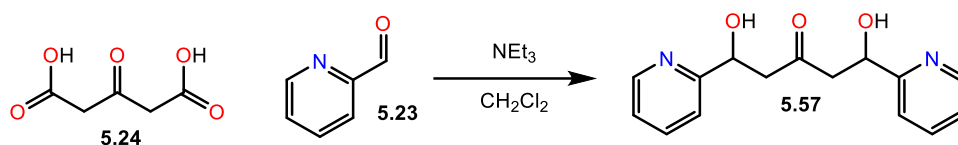
The preparation of buffered silica was adapted from a literature procedure.<sup>4</sup> Silica (500 g) was added to a 1M aqueous solution of K<sub>2</sub>HPO<sub>4</sub> (500 mL). The resulting slurry was sonicated for 20 minutes with gentle swirling. The pH of the slurry was checked. (The pH should be 7. If not, additional K<sub>2</sub>HPO<sub>4</sub> should be added to neutralize the solution.) The slurry was then filtered and the resulting solid was dried via rotary evaporation (5 mbar pressure, 60 °C bath temperature) until a free-flowing powder was obtained.

## 3-Oxopentanedioic acid (5.24)



This procedure was adapted from a published method.<sup>5</sup> Citric acid (7 × 10 g) was added portionwise into concentrated sulfuric acid (150 mL) with stirring at 40 °C (**Caution: effervescence, rapid evolution of gas**) and the reaction mixture was stirred at 40 °C for 4 h. External cooling was applied until the internal temperature reached –5 °C then ice (240 g) was added slowly. The resulting suspension was collected by filtration, dissolved in ethyl acetate (500 mL) and washed with water (5 × 200 mL). The organic phase was dried over sodium sulfate then concentrated under reduced pressure until a white/pale yellow solid formed. This solid was suspended in ice-cold diethyl ether (250 mL), collected by filtration and the solid was rinsed with ice-cold ether (3 × 50 mL) to give the product **5.24** as a white powder (44.2 g, 83% yield), which was used without further purification.

### 1,5-Dihydroxy-1,5-di(pyridin-2-yl)pentan-3-one (5.52)



An alternative approach to the reported synthesis<sup>6</sup> was developed. To a solution of 2-formylpyridine **5.23** (80.0 mL, 841 mmol, 2 mol. equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (750 mL) was added triethylamine (176 mL, 1.26 mol, 1.5 mol. equiv.). 3-Oxopentanedioic acid **5.24** (61.4 g, 420 mmol) (**Caution: effervescence, rapid evolution of gas**) was then added in 3 batches and the resulting mixture was stirred for 3 h. The reaction mixture was then washed with aqueous saturated sodium metabisulfite solution (3 × 20 mL), the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated under reduced pressure to yield a brown solid. Purification via vacuum chromatography (400 g SiO<sub>2</sub>) eluting with ethyl acetate yielded the desired product **5.57** as a white solid (98.8 g, 363 mmol, 86%).

**Mp**= 124.5 – 128.8 °C (EtOAc)

**R<sub>f</sub>**= 0.33 (EtOAc)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 8.52 (d, *J* = 4.9 Hz, 2H), 7.77 – 7.69 (m, 2H), 7.46 (t, *J* = 8.2 Hz, 2H), 7.21 (dd, *J* = 7.4, 5.1 Hz, 2H), 5.24 (m, 2H), 3.19 – 2.88 (m, 4H) ppm.

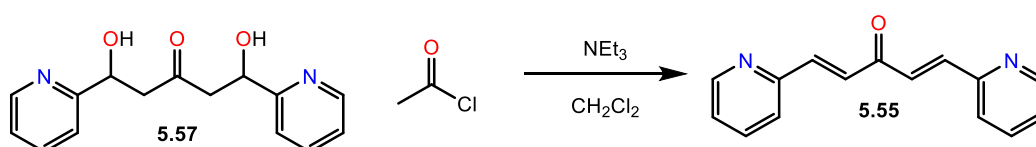
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 209.6, 161.5, 148.3, 137.0, 122.4, 120.5, 69.8, 50.9 ppm.

**MS** (ESI): *m/z* (%): 273.1 ([M+H]<sup>+</sup>, 100)

**HRMS** (ESI): calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub>: 273.1239; found: 273.1237.

Melting point data and low resolution mass spectrometry corresponded with published data.<sup>6</sup> No NMR and HRMS data is present in literature to the best of our knowledge.

### (1*E*,4*E*)-1,5-Di(pyridin-2-yl)penta-1,4-dien-3-one



An alternative approach to published methods<sup>7,8,9</sup> was developed. To a stirred solution of 1,5-dihydroxy-1,5-di(pyridin-2-yl)pentan-3-one **5.57** (50 g, 0.184 mol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 L) under N<sub>2</sub> was added triethylamine (500 mL, 3.67 mol, 20 mol. equiv.). Acetyl chloride (39 mL, 0.551 mol, 3 mol. equiv.) was added dropwise. After 18 h, the reaction mixture was filtered and the filtrate was washed with water (5 × 250 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> then concentrated via rotary evaporation to produce a brown residue. Purification via gradient vacuum chromatography (250 g, SiO<sub>2</sub>) eluting with (4:1 Et<sub>2</sub>O in *n*-hexane → Et<sub>2</sub>O) yielded the target compound as a yellow foam **5.55** (41 g, 170 mmol, 95%).

**Mp**= 117.2 – 121.3 °C (1:1 *n*-Hexane in EtOAc)

**R<sub>f</sub>**= 0.41 (Et<sub>2</sub>O)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 8.72 – 8.66 (m, 2H), 7.81 – 7.69 (m, 4H), 7.62 (dd, *J* = 15.7, 1.3 Hz, 2H), 7.49 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.29 (m, 2H) ppm.

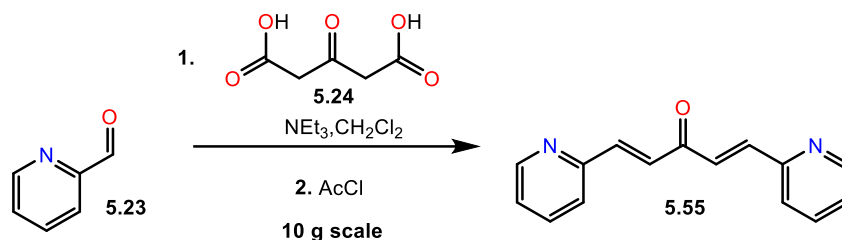
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 189.7, 153.3, 150.3, 142.2, 137.1, 129.0, 125.1, 124.6 ppm.

**MS** (ESI): *m/z* (%): 259.1 ([M+Na]<sup>+</sup>, 100)

**HRMS** (ESI): calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>ONa: 259.0847; found: 259.0849.

All characterization data corresponded with published information.<sup>9</sup>

### (1*E*,4*E*)-1,5-Di(pyridin-2-yl)penta-1,4-dien-3-one – *one flask synthesis*

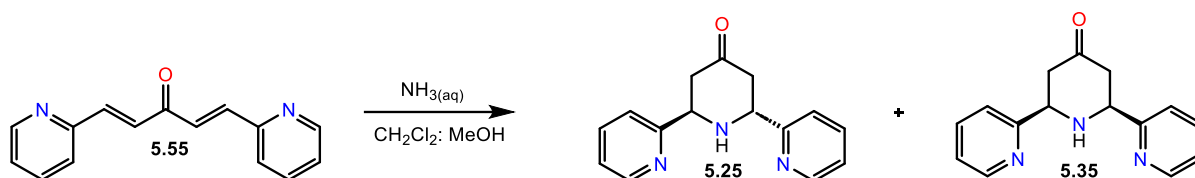


To a stirred solution of 2-formylpyridine **5.23** (9.0 mL, 95 mmol 2 mol. equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (75 mL) under N<sub>2</sub> was added triethylamine (19.8 mL, 142 mmol, 3.0 mol. equiv.). 3-Oxopentanedioic acid **5.24** (6.9 g, 47 mmol) (**Caution: effervescence, rapid evolution of gas**)

was then added in 3 batches and the reaction was stirred for 3 hours. Triethylamine (35 mL, 0.25 mol, 5.3 mol. equiv.) was added, followed by acetyl chloride (10 mL, 140 mmol, 3.0 mol. equiv.). After 15 hours the reaction was filtered and the filtrate was washed with a saturated solution of sodium metabisulfite (3 × 50 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> then concentrated via rotary evaporation to produce a brown residue. Purification via gradient flash chromatography (120 g, SiO<sub>2</sub>) eluting with (4:1 Et<sub>2</sub>O in n-hexane → Et<sub>2</sub>O) yielded the desired product **5.55** as a pale-yellow solid (8.0 g, 34 mmol, 73%).

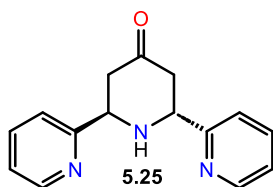
Characterization data matched that obtained from the stepwise synthesis (see above).

### Cis/trans 2,6-di (pyridine-2-yl)piperidin-4-one



The procedure was adapted from the work of Magann et. al.<sup>10</sup> To a stirred solution of (1E,4E)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one **5.55** (8.5 g, 36 mmol) in CH<sub>2</sub>Cl<sub>2</sub>: MeOH (1:1) (600 mL), under N<sub>2</sub> was added 30% aqueous ammonia (36 mL, 570 mmol, 16 mol. equiv.). After 16 hours, brine (150 mL) was added then the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 250 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> then concentrated via rotary evaporation to produce a brown residue. Purification via flash column chromatography (300 g, SiO<sub>2</sub>) using EtOAc gave *cis*-2,6-di(pyridin-2-yl)piperidin-4-one **5.35** (2.1 g, 8.2 mmol, 23%) as a yellow foam and *trans*-2,6-di(pyridin-2-yl)piperidin-4-one **5.25** (4.7 g, 18 mmol, 51%) as a brown foam.

### Trans-2,6-di (pyridin-2-yl)piperidin-4-one



R<sub>f</sub> = 0.08 (EtOAc)

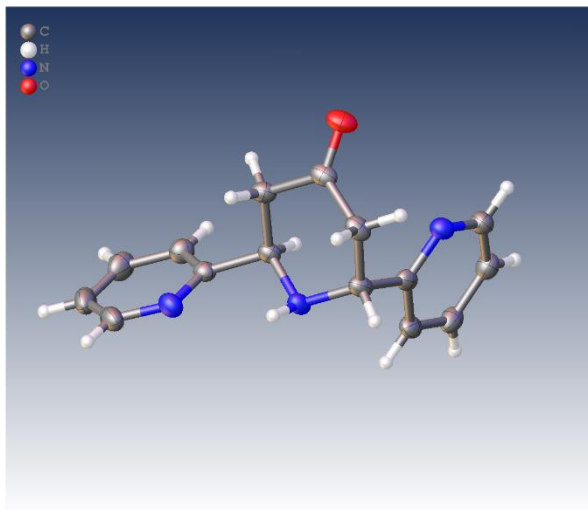
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.68 – 8.55 (m, 2H), 7.68 (tt,  $J$  = 7.8, 1.4 Hz, 2H), 7.33 (d,  $J$  = 7.8 Hz, 2H), 7.24 – 7.19 (m, 2H), 4.56 (t,  $J$  = 5.9 Hz, 2H), 2.97 – 2.80 (m, 4H) ppm.

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 208.1, 160.9, 149.4, 136.8, 122.4, 121.6, 56.9, 46.0 ppm.

**MS** (ESI):  $m/z$  (%): 276.1 ( $[\text{M}+\text{Na}]^+$ , 100)

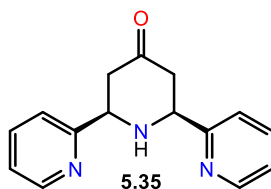
**HRMS** (ESI): calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}\text{Na}$ : 276.1113; found: 276.1116.

#### X Ray Crystallographic Data.



$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$ ,  $M_r$  = 253.30, monoclinic,  $C2/c$  (No. 15),  $a$  = 16.9177(4) Å,  $b$  = 5.5227(2) Å,  $c$  = 28.3944(9) Å,  $\beta$  = 105.319(3)°,  $\alpha = \gamma = 90^\circ$ ,  $V$  = 2558.67(14) Å<sup>3</sup>,  $T$  = 149.99(10) K,  $Z$  = 8,  $Z'$  = 1,  $m(\text{Cu K}\alpha)$  = 0.682, 6873 reflections measured, 2248 unique ( $R_{\text{int}}$  = 0.0234) which were used in all calculations. The final  $wR_2$  was 0.0877 (all data) and  $R_1$  was 0.0356 ( $I \geq 2\sigma(I)$ ).

#### *Cis*-2,6-di (pyridin-2-yl)piperidin-4-one



$R_f$  = 0.12 (EtOAc)

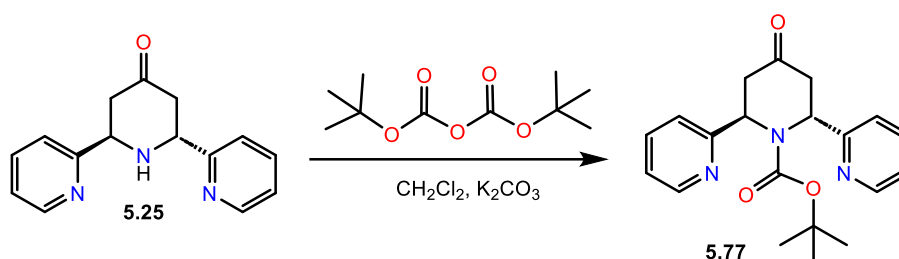
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.61 (d,  $J$  = 4.9 Hz, 2H), 7.70 (td,  $J$  = 7.7, 1.7 Hz, 2H), 7.36 (d,  $J$  = 7.8 Hz, 2H), 7.25 – 7.20 (m, 2H), 4.37 (d,  $J$  = 11.2 Hz, 2H), 2.96 – 2.66 (m, 4H), ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 208.8, 160.0, 149.7, 137.0, 122.9, 121.5, 61.7, 48.6 ppm.

**MS** (ESI):  $m/z$  (%): 276.1 ([M+Na]<sup>+</sup>, 100)

**HRMS** (ESI): calcd for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>ONa: 276.1113; found: 276.1114.

***Trans-tert-butyl-4-oxo-2,6-di(pyridin-2-yl)piperidine-1-carboxylate***



The procedure was adapted from the work of Abadie et.al.<sup>11</sup> To a stirred solution of *cis*-2,6-di-(pyridin-2-yl)piperidin-4-one **5.35** (200 mg, 0.79 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under N<sub>2</sub> was added K<sub>2</sub>CO<sub>3</sub> (550 mg, 4.0 mmol, 5 mol. equiv.) followed by di-*tert*-butyl-dicarbonate (260 mg, 1.2 mmol, 1.5 mol. equiv.). After 14 hours, the reaction mixture was filtered. The filtrate was concentrated under rotary evaporation yielding a yellow residue. Purification via flash chromatography (8 g, SiO<sub>2</sub>) eluting with diethyl ether yielded the desired product **5.82** as a pale yellow solid (260 mg, 0.73 mmol, 93%).

**Mp**= 183.6 – 187.2 °C (40% Et<sub>2</sub>O in hexanes)

**R<sub>f</sub>** = 0.46 (Et<sub>2</sub>O)

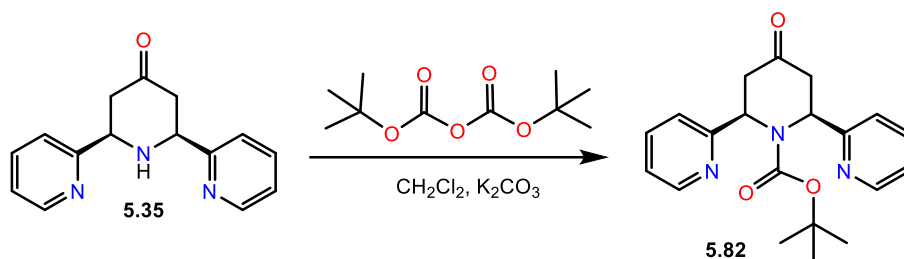
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.50 – 8.41 (m, 2H), 7.61 (dd,  $J$  = 7.7, 1.8 Hz, 2H), 7.33 (m, 2H), 7.10 (d,  $J$  = 7.5 Hz, 2H), 5.59 (m, 2H), 3.26 (m, 2H), 3.11 – 2.70 (m, 2H), 1.21 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  207.0, 161.9, 155.4, 149.2, 136.6, 122.1, 120.6, 80.7, 55.3, 43.4, 28.1 ppm.

**MS** (ESI):  $m/z$  (%): 376.2 ([M+Na]<sup>+</sup>, 100)

**HRMS** (ESI): calcd for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>ONa: 376.1637; found: 376.1641.

***Cis-tert-butyl-4-oxo-2,6-di(pyridin-2-yl)piperidine-1-carboxylate***



Following the synthesis of the cis 2,6-di (pyridin-2-yl)piperidin-4-one **5.25** above, trans-2,6-di (pyridin-2-yl)piperidin-4-one **5.77** was prepared as a brown foam (270 mg, 0.75 mmol, 95%).

$R_f$  = 0.46 (Et<sub>2</sub>O)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.34 (m, 2H), 7.53 (m, 2H), 7.30 (s, 2H), 7.04 (d,  $J$  = 7.4, 2H), 5.54 (s, 2H), 3.23 – 2.99 (m, 2H), 2.67 (m, 2H), 1.17 (s, 9H) ppm.

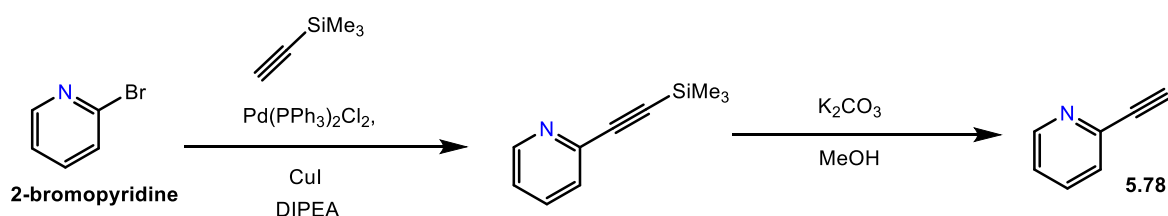
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 207.1, 161.6, 155.9, 148.5, 136.6, 122.0, 121.4, 81.0, 56.9, 43.2, 28.0 ppm.

$R_f$  = 0.12 (EtOAc)

MS (ESI):  $m/z$  (%): 376.2 ([M+Na]<sup>+</sup>, 100)

HRMS (ESI): calcd for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>ONa: 376.1637; found: 376.1639.

## 2-Ethynylpyridine



The procedure was adapted from the work of Ha et al.<sup>12</sup> A flask charged with Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (740 mg, 1 mmol, 2.0 mol%) and CuI (200 mg, 1 mmol, 2.0 mol%) was evacuated and refilled with nitrogen thrice. A degassed solution of 2-bromopyridine (5.0 mL, 8.3 g, 52 mmol) and diisopropylamine (85 mL) were added, followed by trimethylsilylacetylene (8.2 mL, 5.2 g, 58 mmol, 1.1 mol equiv) (**Caution: exothermic**). After 3 h, Et<sub>2</sub>O (50 mL) was added and the reaction was filtered. The filtrate was concentrated via rotary evaporation to yield a brown residue. The residue was added to MeOH (100 mL) followed by K<sub>2</sub>CO<sub>3</sub> (15 g, 110 mmol, 2.1 eq). After 3 hours, the reaction mixture was concentrated via rotary evaporation to yield a

brown residue. 1 M HCl (50 mL) was added to the residue and the aqueous solution was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 mL). 1M NaOH (75 mL) was added to basify the aqueous phase, which was then extracted using CH<sub>2</sub>Cl<sub>2</sub> (5 × 20 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated using rotary evaporation. Purification via flash column chromatography (50 g, SiO<sub>2</sub>) (1:1) Et<sub>2</sub>O: *n*-hexanes yielded the target material **5.78** as a dark oil (4.7 g, 46 mmol, 87%).

$R_f$  = 0.52 (1:1 Et<sub>2</sub>O : *n*-hexanes)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.55 – 8.52 (m, 1H), 7.61 (td,  $J$  = 7.8, 1.8 Hz, 1H), 7.43 (dd,  $J$  = 7.8, 1.1 Hz, 1H), 7.22 (ddd,  $J$  = 7.8, 4.9, 1.2 Hz, 1H), 3.13 (s, 1H) ppm.

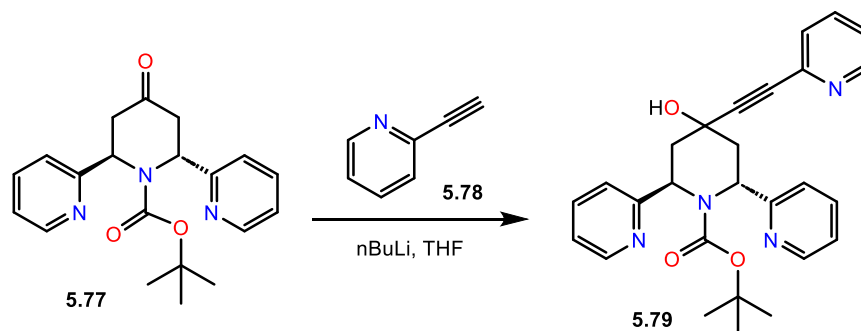
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.1, 142.4, 136.2, 127.5, 123.5, 82.78, 77.2 ppm.

MS (ESI):  $m/z$  (%): 104.1 ([M+H]<sup>+</sup>, 100)

HRMS (ESI): calcd for C<sub>7</sub>H<sub>6</sub>N: 104.0500; found: 104.0502.

Characterization data corresponded with literature values.<sup>12</sup>

***Trans-tert-butyl 4-hydroxy-2,6-di(pyridin-2-yl)-4-(pyridin-2-ylethynyl)piperidine-1-carboxylate***



A solution of 2-ethynylpyridine **5.77** (182 mg, 2.5 mmol 3.0 mol. equiv.) in dry tetrahydrofuran (20 mL) was subjected to three freeze pump thaw degas cycles. The resulting solution was chilled in a –78 °C cooling bath (dry ice/acetone). *n*-BuLi (1.2 M in hexane, 1.3 mL, 1.6 mmol, 2.2 mol eq) was added dropwise. The reaction mixture was stirred at 0 °C (ice bath) for 30 minutes. *trans-tert*-Butyl-4-oxo-2,6-di(pyridin-2-yl)-piperidine-1-carboxylate **5.79** (250 mg, 0.70 mmol) was added. After 3 hours, 1M aqueous ammonium chloride (20 mL) was added followed by 1M aqueous NaOH (30 mL). The

resulting mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated via rotary evaporation. Purification via gradient flash column chromatography (6 g, SiO<sub>2</sub>, 50% EtOAc in hexanes to EtOAc) yielded the target product **5.78** as a yellow foam (223 mg, 0.49 mmol, 69%).

**R<sub>f</sub>** = 0.52 (EtOAc)

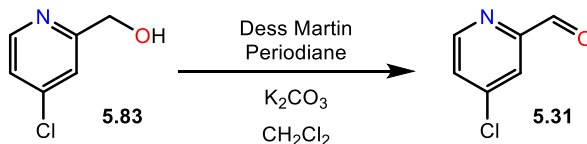
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.49 – 8.33 (m, 3H), 7.79 – 7.60 (m, 2H), 7.49 (tt, *J* = 7.7, 2.1 Hz, 2H), 7.20 – 7.04 (m, 4H), 6.95 (dd, *J* = 7.4, 4.9 Hz, 1H), 5.72 (s, 1H), 4.91 (dd, *J* = 8.2, 4.3 Hz, 1H), 2.75 (d, *J* = 5.5 Hz, 2H), 2.57 (m, 2H), 1.02 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  162.1, 161.3, 155.9, 149.8, 148.8, 147.6, 143.2, 137.8, 136.1, 135.9, 127.3, 124.5, 122.8, 122.7, 121.5, 120.8, 93.3, 81.8, 80.5, 64.3, 57.1, 55.4, 43.9, 39.2, 28.0 ppm.

**MS** (ESI): *m/z* (%): 479.2 ([M+Na]<sup>+</sup>, 100)

**HRMS** (ESI): calcd for C<sub>27</sub>H<sub>28</sub>N<sub>3</sub>ONa: 479.2059; found: 479.2062.

#### 4-Chloropicolinaldehyde



The procedure was adapted from the work of Thongsornkleeb et.al.<sup>13</sup> To a stirred solution of (4-chloropyridin-2-yl)methanol **5.83** (4.0 g, 28 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 L), under N<sub>2</sub> was added K<sub>2</sub>CO<sub>3</sub> (7.7 g, 56 mmol, 2 mol. eq.) followed by Dess-Martin periodinane (11.8 g, 28 mmol). After 15 h, the reaction mixture was concentrated under reduced pressure. The residue was suspended in Et<sub>2</sub>O (250 mL), filtered and the solid was rinsed with Et<sub>2</sub>O (2 × 50 mL). The filtrate was concentrated via rotary evaporation to give a yellow residue. The residue was purified by vacuum chromatography (15 g, SiO<sub>2</sub>, 40% Et<sub>2</sub>O in hexanes) producing the target compound **5.31** as a yellow solid (3.04 g, 21 mmol, 77%) that turned brown slowly when left under standard laboratory conditions.

**Mp** = 37.7 – 41.3 °C (40% Et<sub>2</sub>O in Hexanes)

**R<sub>f</sub>** = 0.67 (40% Et<sub>2</sub>O in hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 10.08 (d, *J* = 1.1 Hz, 1H), 8.80 – 8.63 (m, 1H), 8.03 – 7.89 (m, 1H), 7.64 – 7.46 (m, 1H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CD<sub>3</sub>CN) δ 194.2, 153.4, 150.9, 137.9, 128.7, 121.9 ppm.

**MS** (ESI): *m/z* (%): 142.0 ((<sup>35</sup>Cl) [M+H]<sup>+</sup>, 100), 144.0 ((<sup>37</sup>Cl)[M+H]<sup>+</sup>, 33),

**HRMS** (ESI): calcd for C<sub>6</sub>H<sub>5</sub>NOCl: (<sup>35</sup>Cl) 142.0060, (<sup>37</sup>Cl) 144.0030; found: 142.0063((<sup>35</sup>Cl) [M+H]<sup>+</sup>, 100), 144.0032 ((<sup>37</sup>Cl) [M+H]<sup>+</sup>, 33)

Characterization corresponded with literature values.<sup>14</sup>

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effect of a thienyl moiety on the reactivity of Pd0( $\eta^2$ -thn-dba)(PPh<sub>3</sub>)<sub>2</sub>/Pd0(PPh<sub>3</sub>)<sub>2</sub> (n = 1 or 2) and Pd0( $\eta^2$ -th<sub>2</sub>-dba)(dppe)/Pd0(dppe) in oxidative addition reactions with iodobenzene, *Organometallics*, **2009**, *28*, 824-829. [https://doi.org/ 10.1021/om800975w](https://doi.org/10.1021/om800975w)

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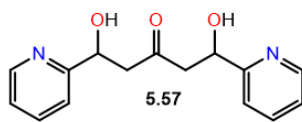
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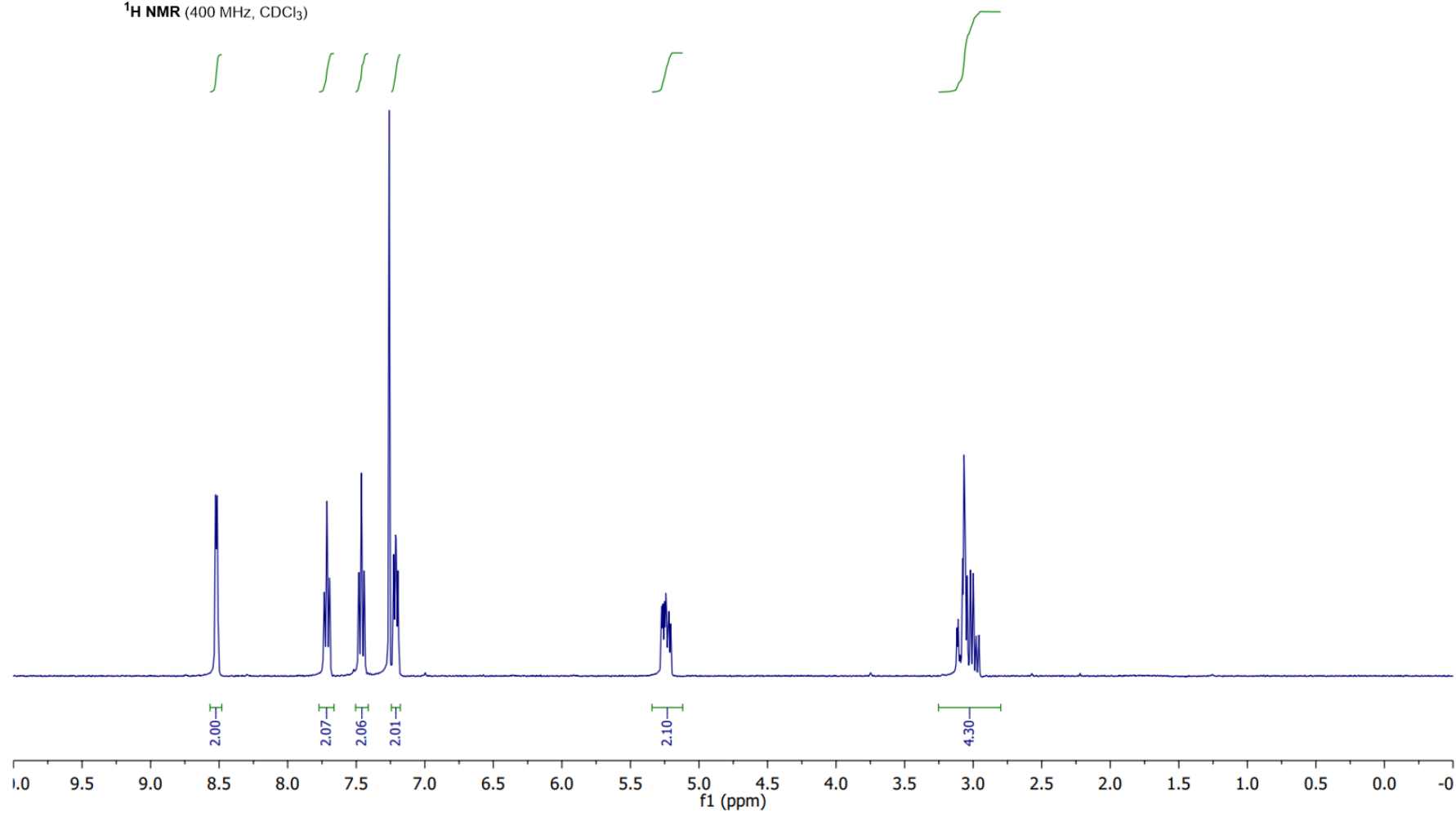
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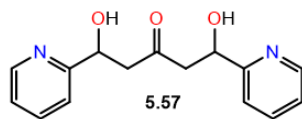
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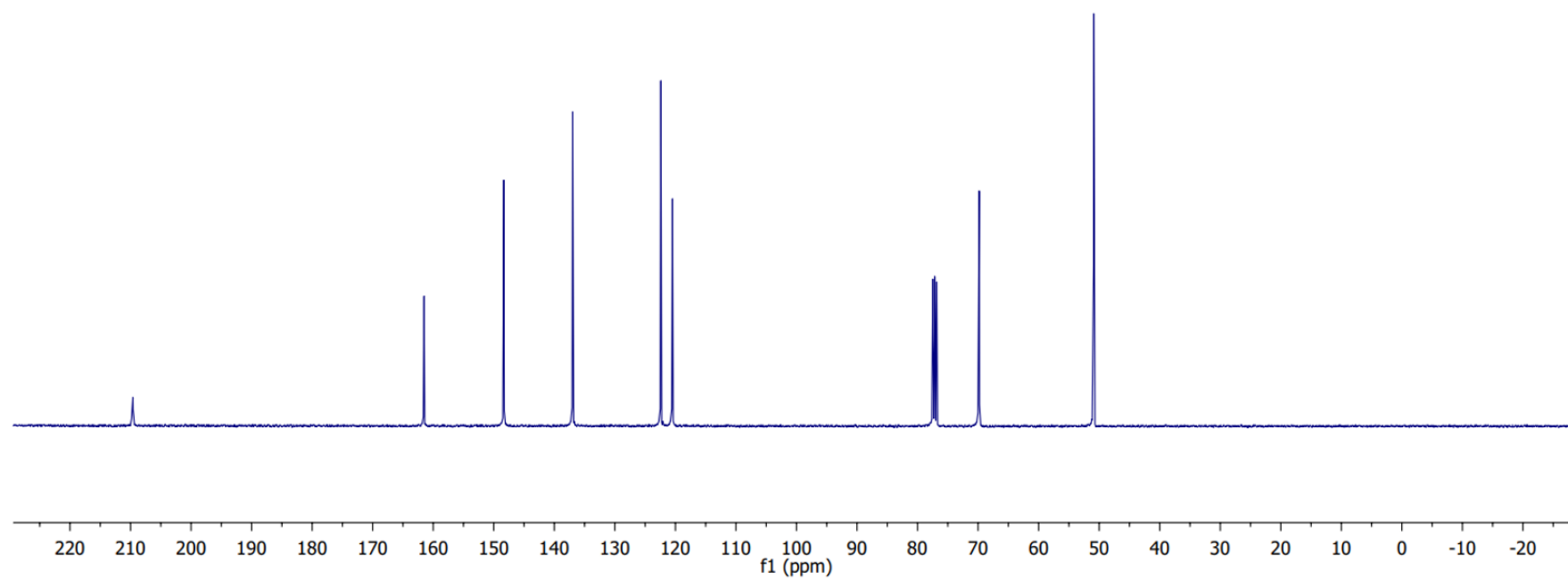


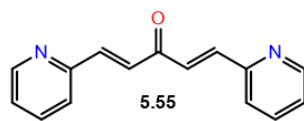
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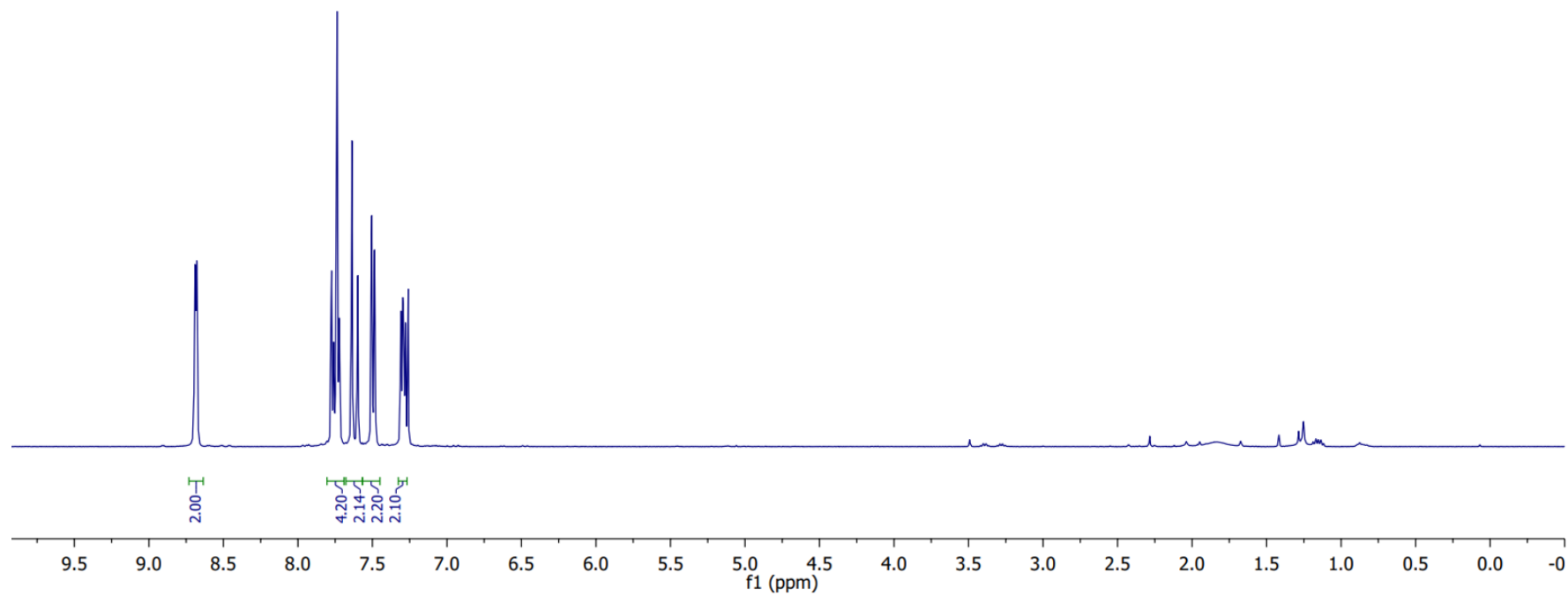


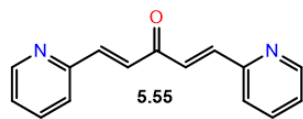
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



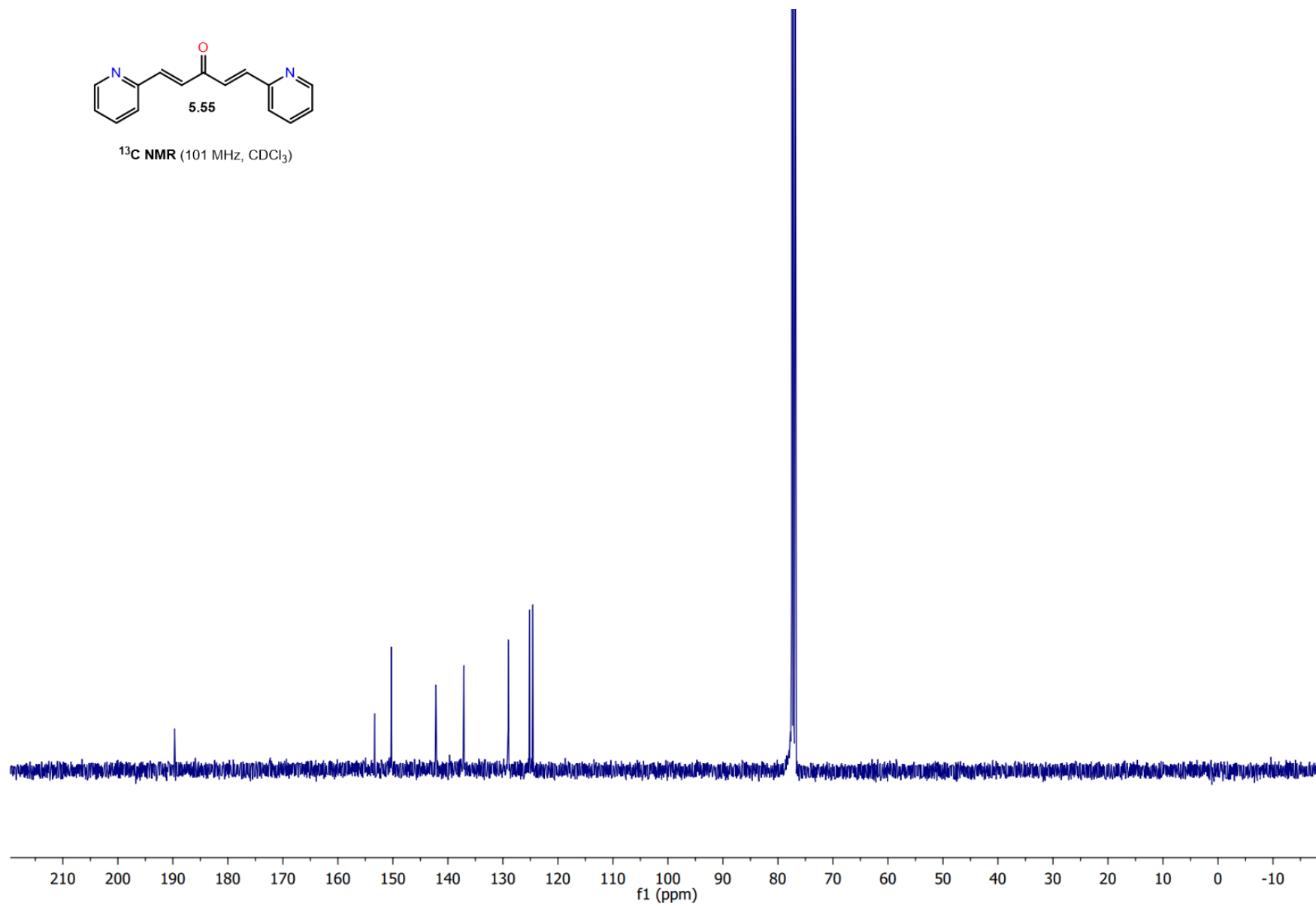


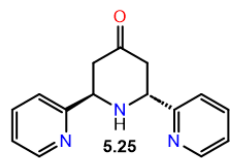
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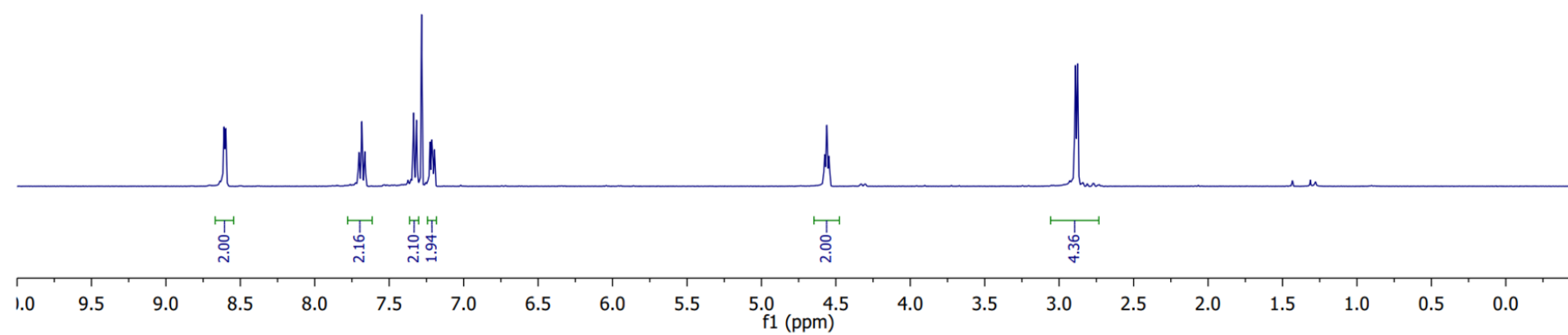


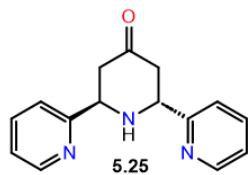
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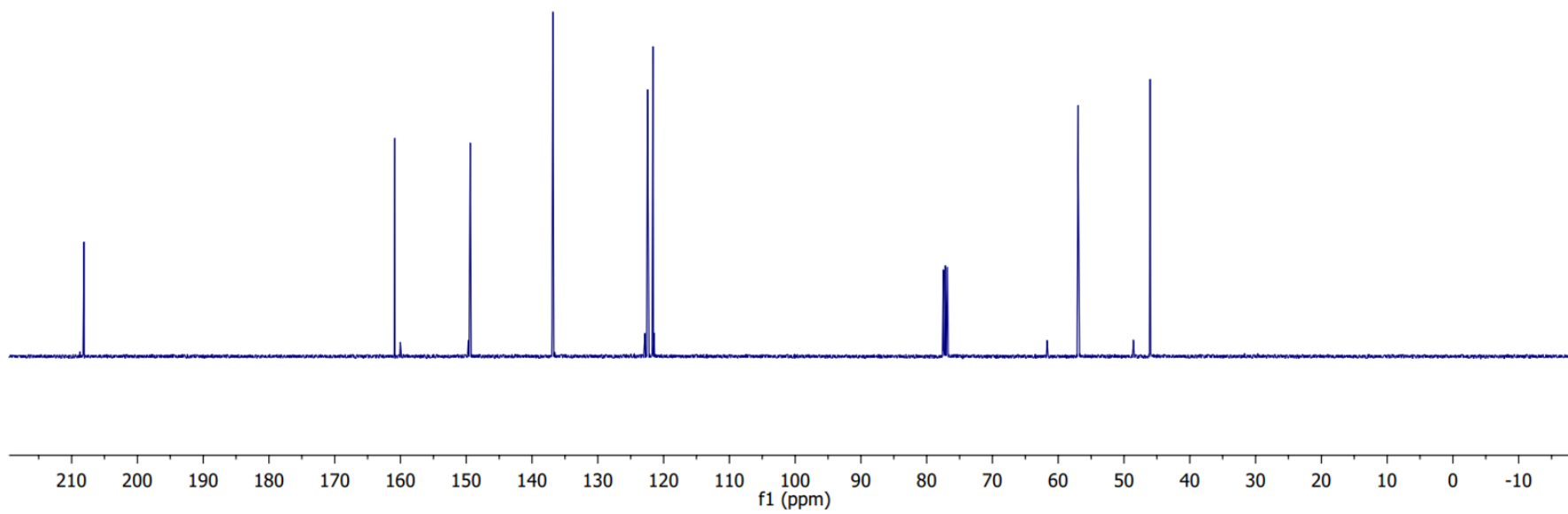


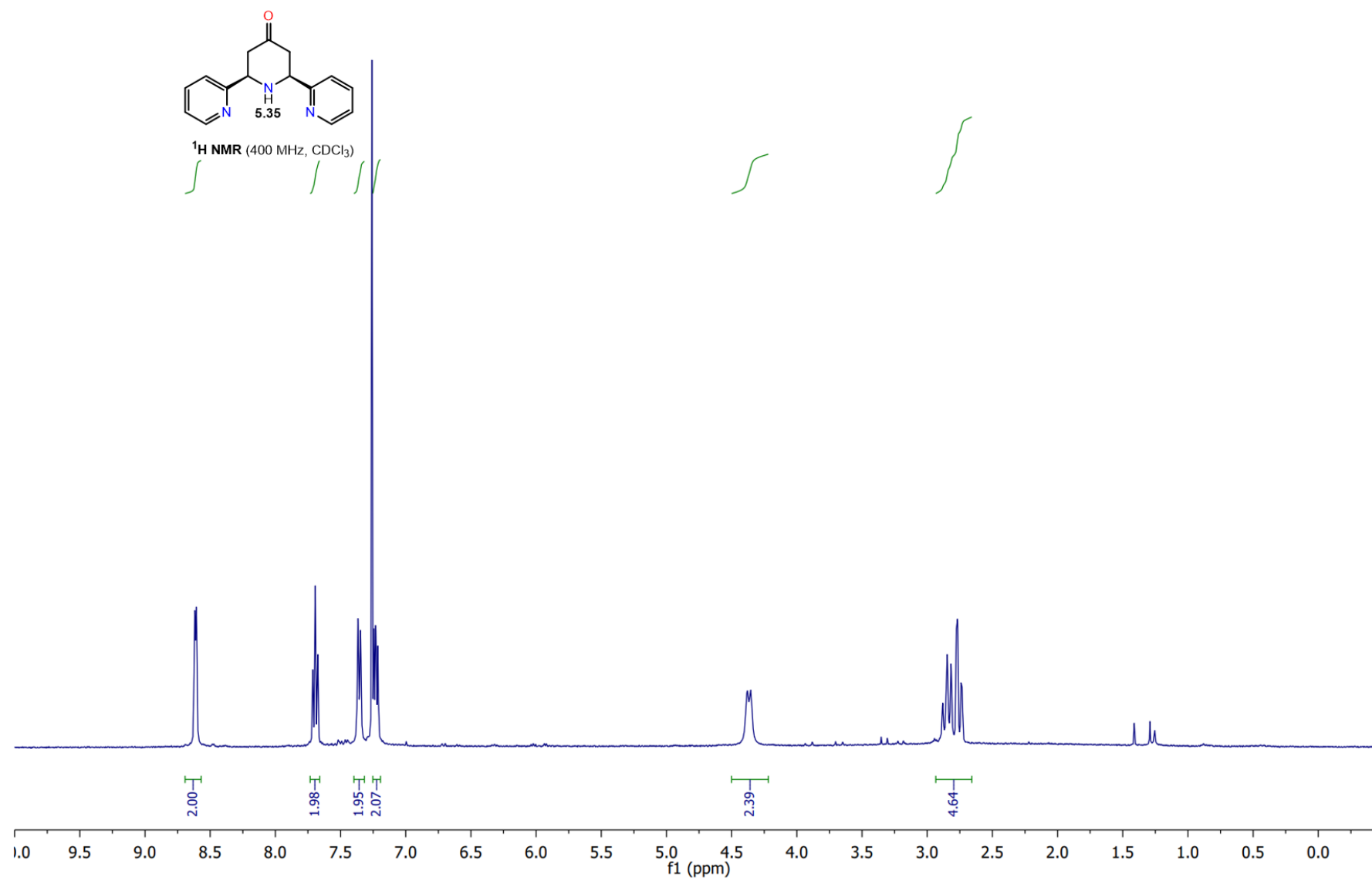
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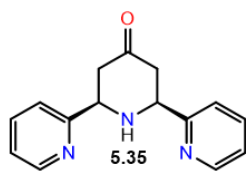




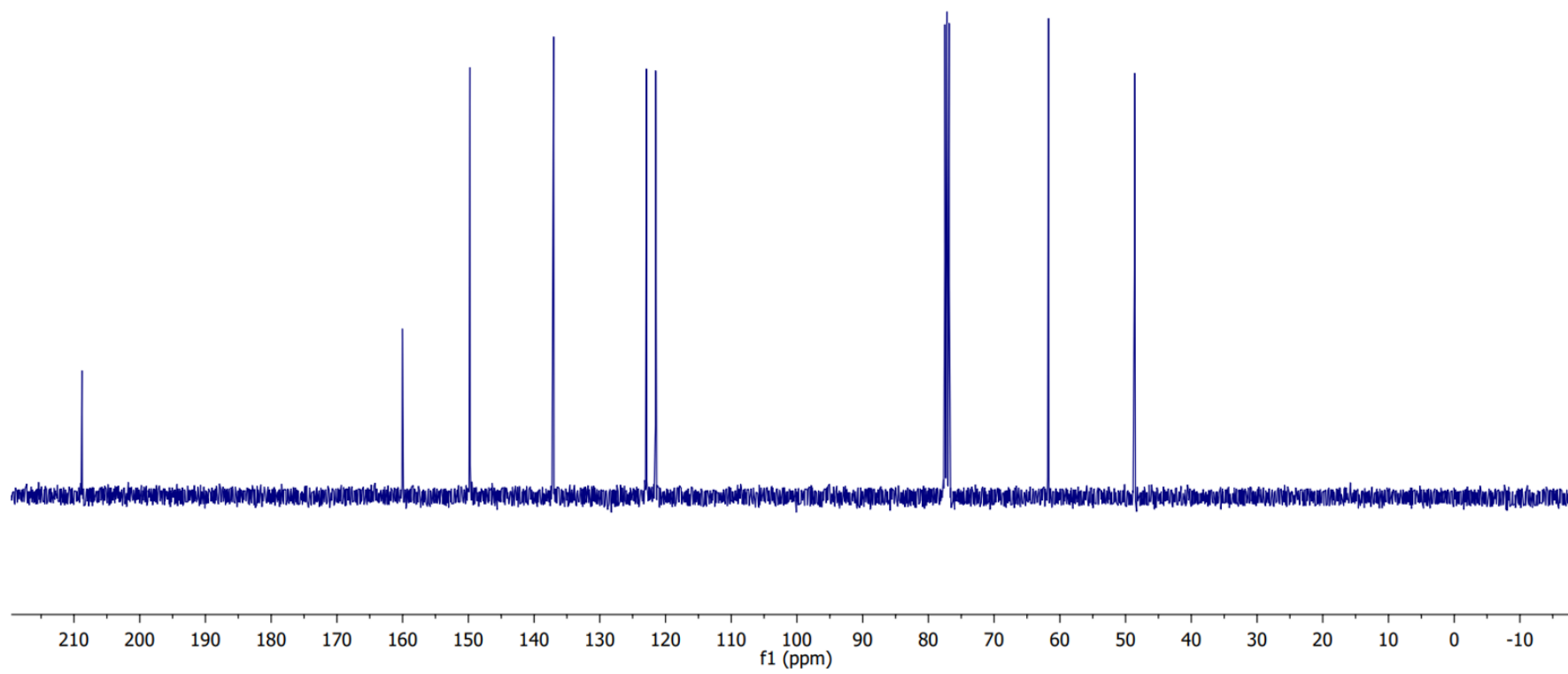
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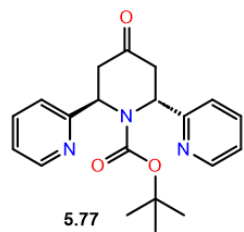




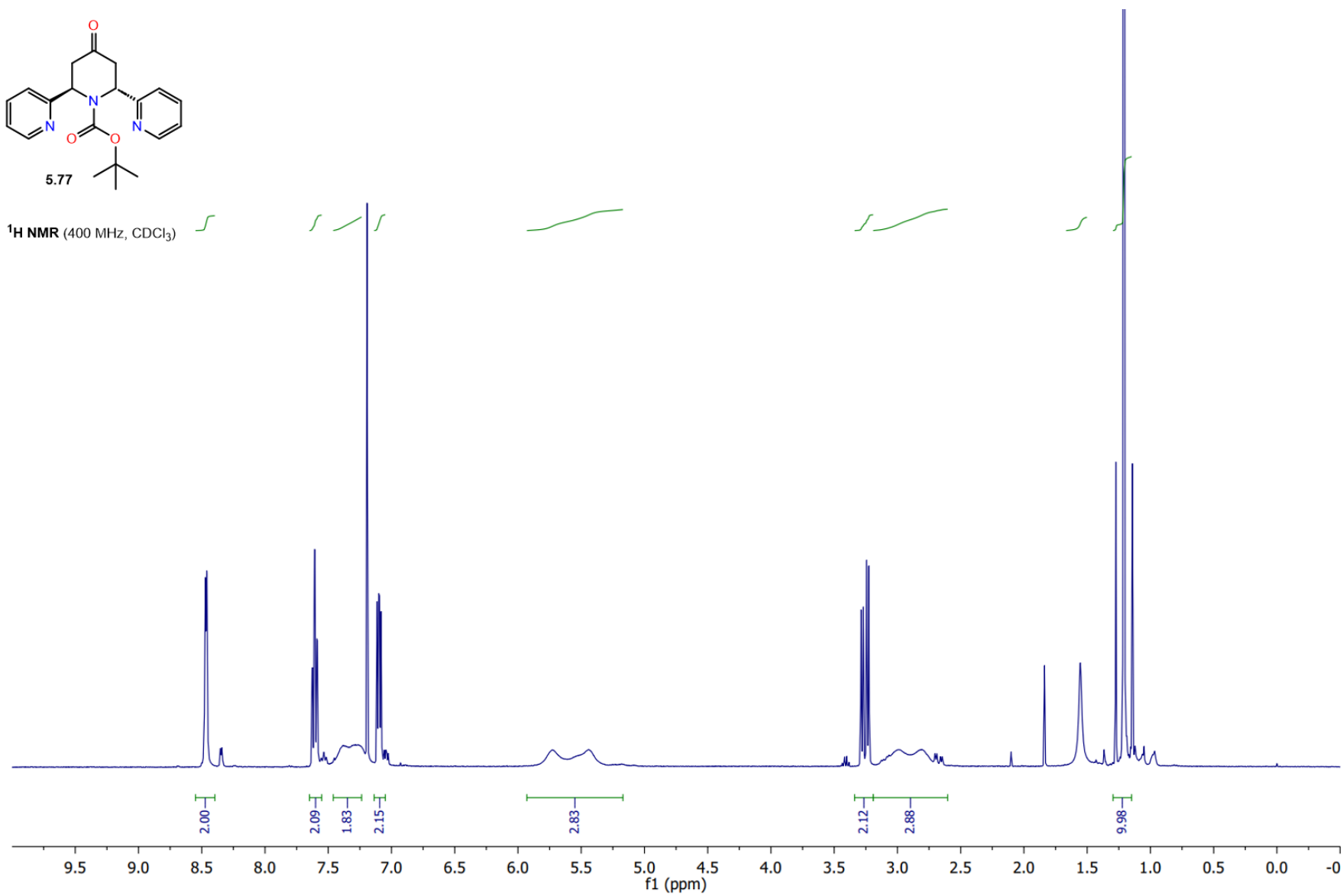


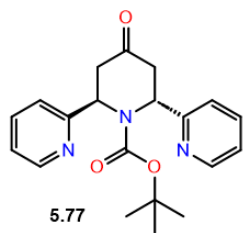
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



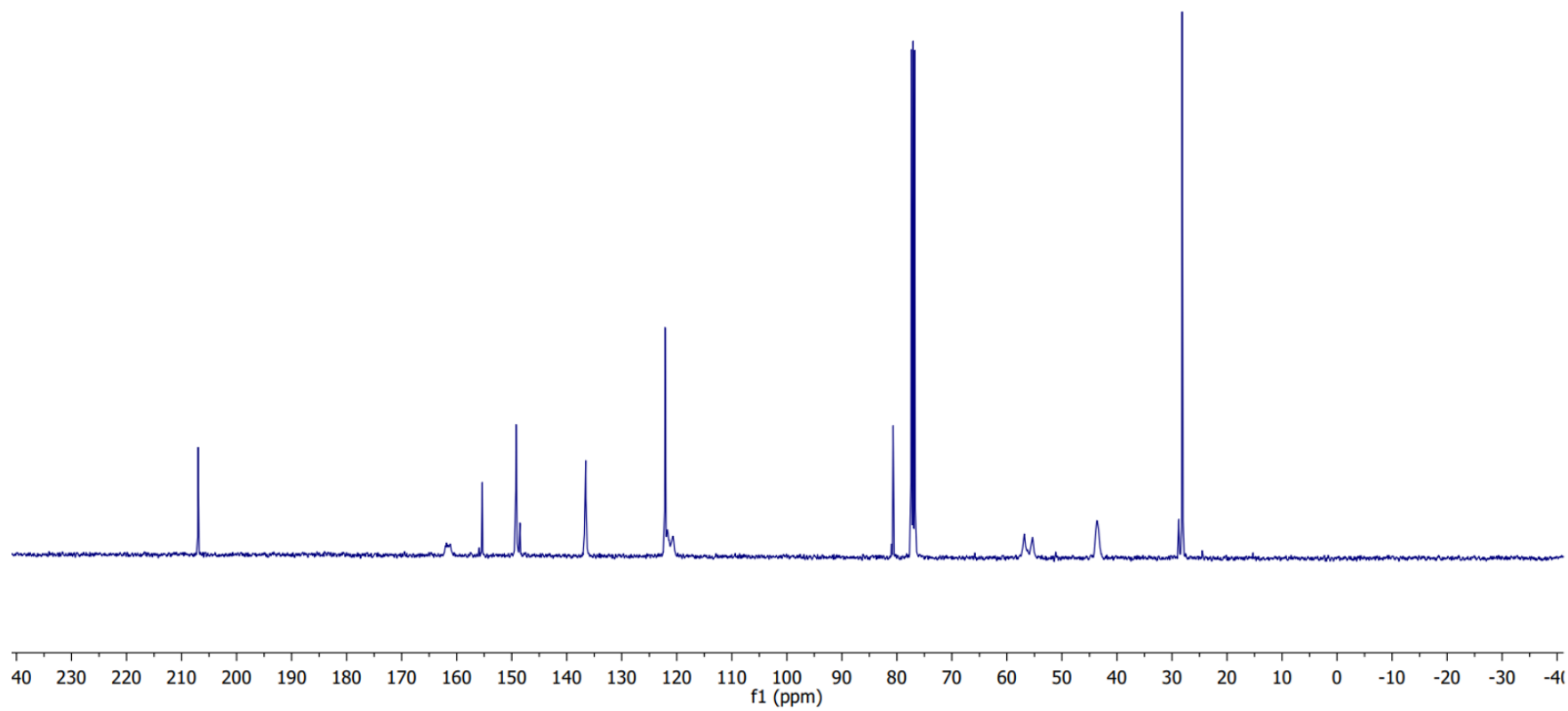


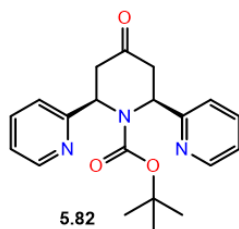
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



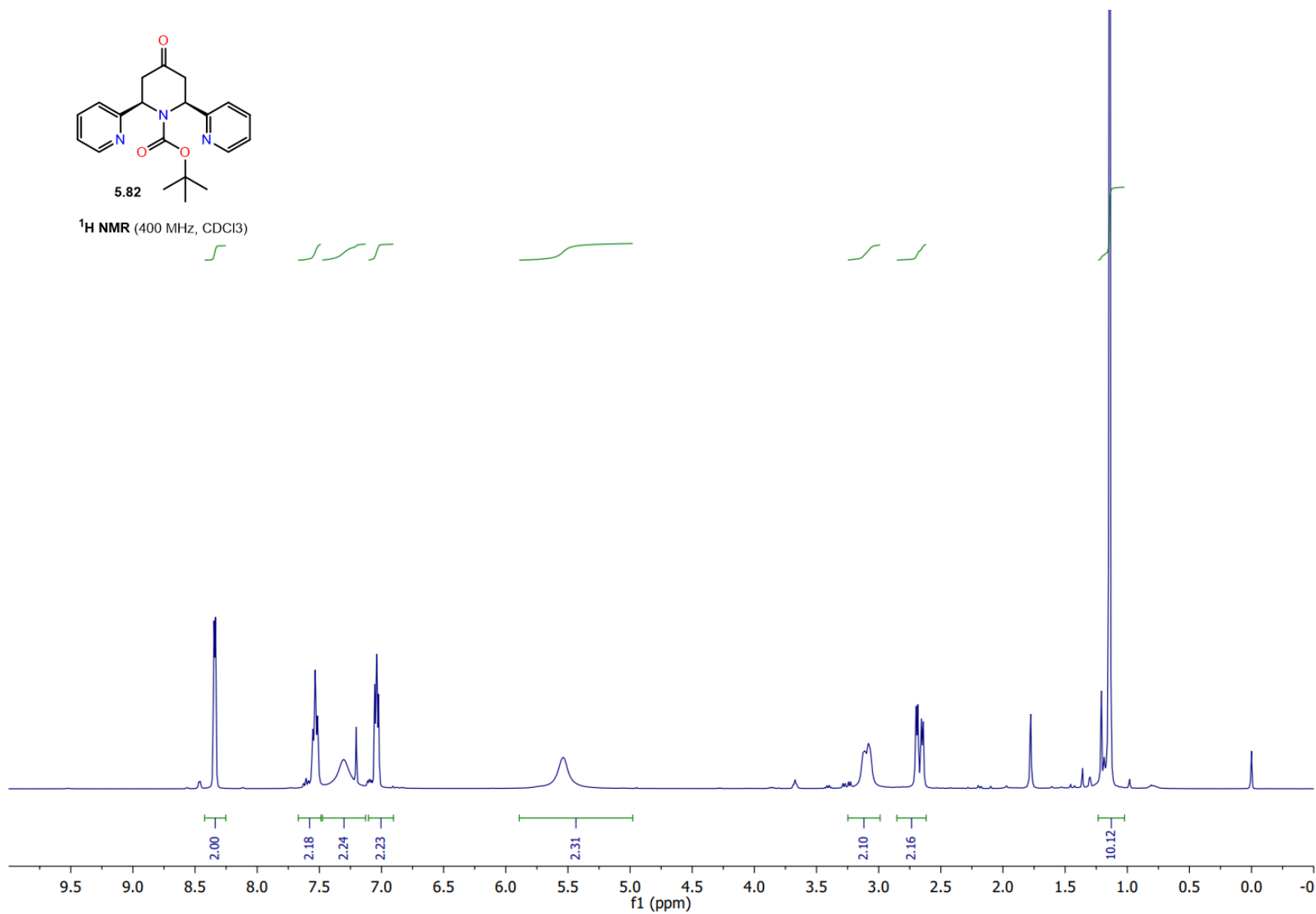


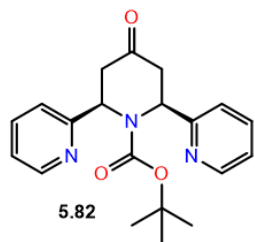
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



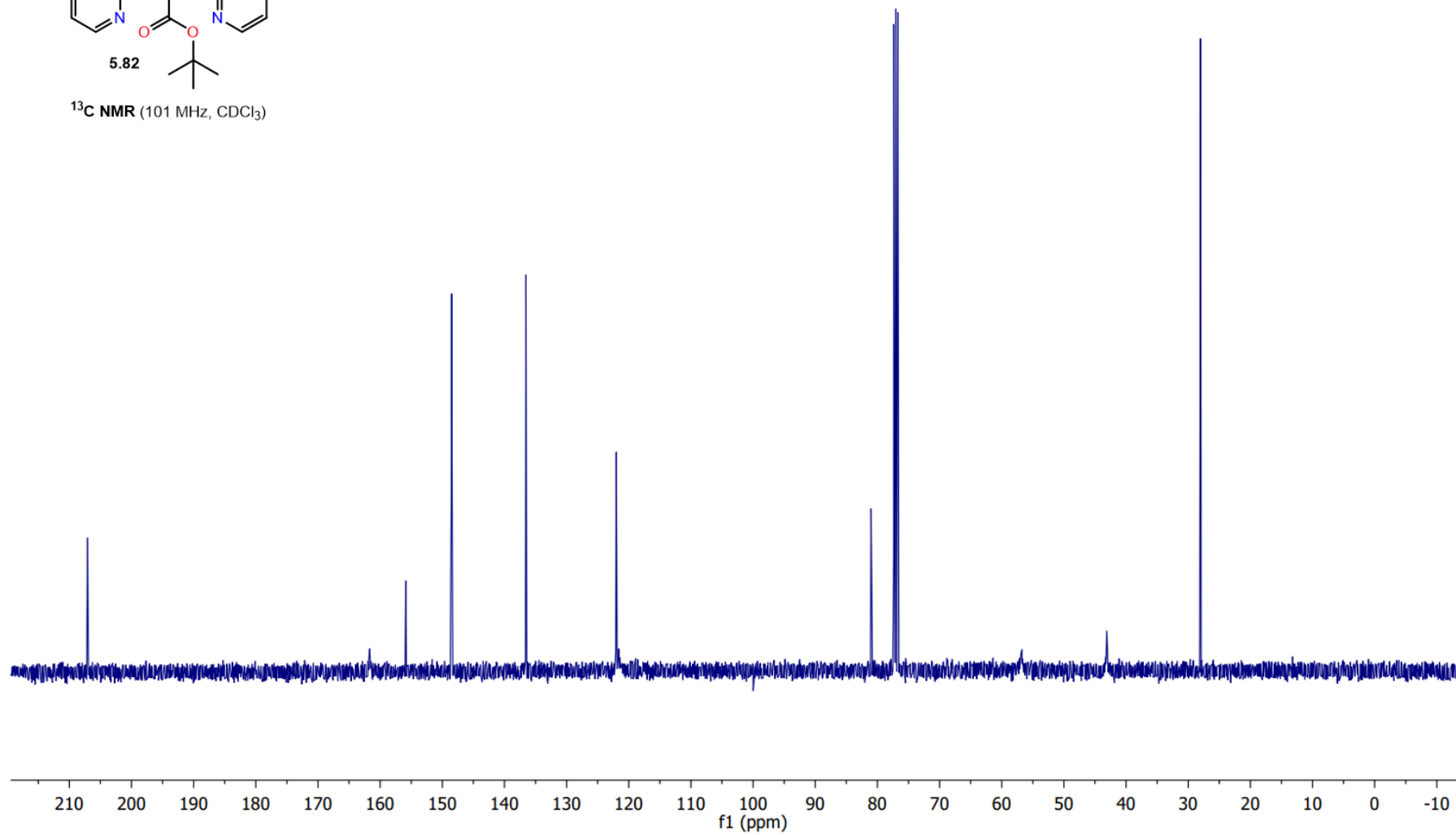


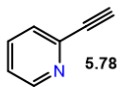
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)





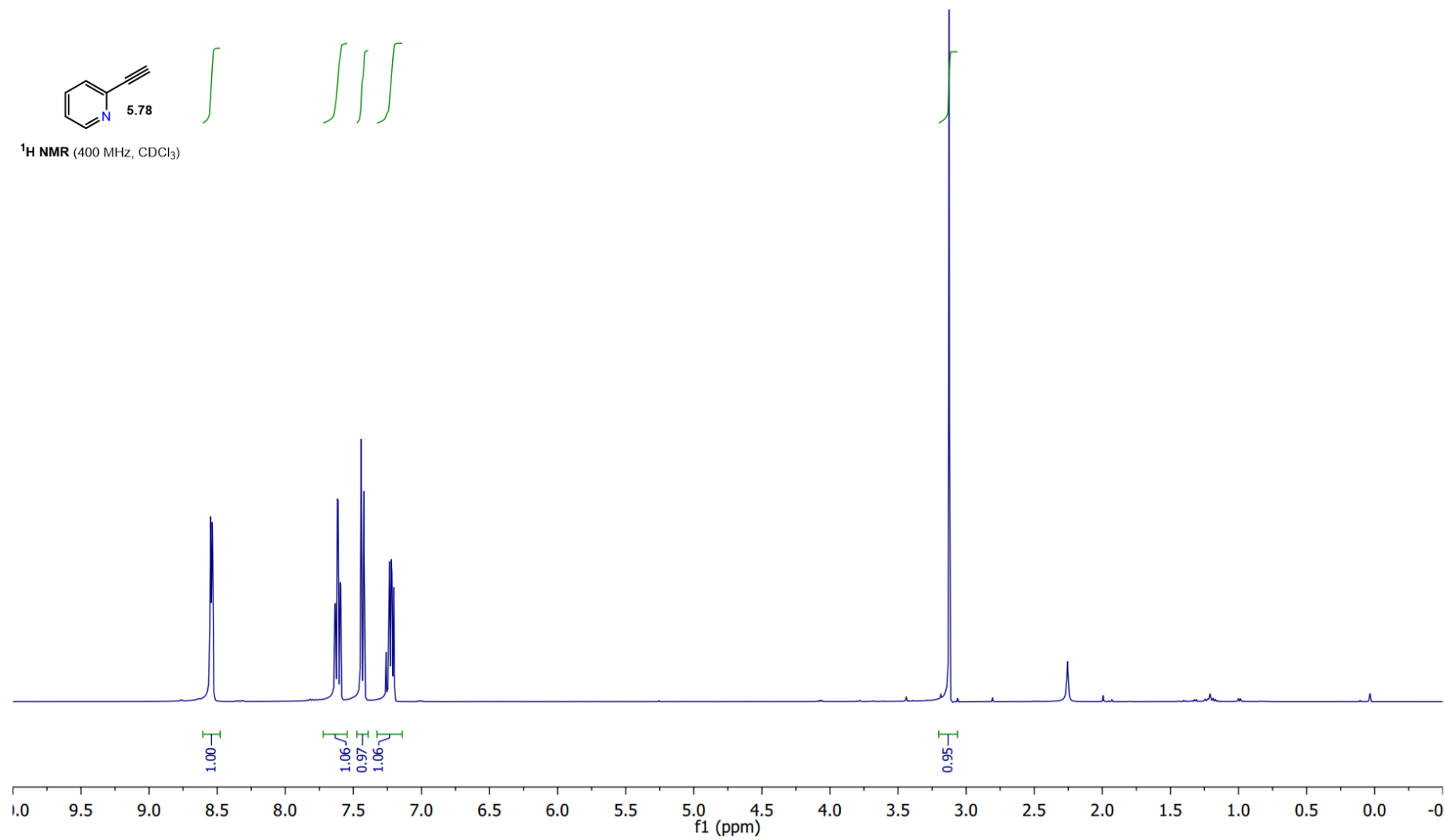
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

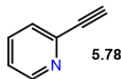




5.78

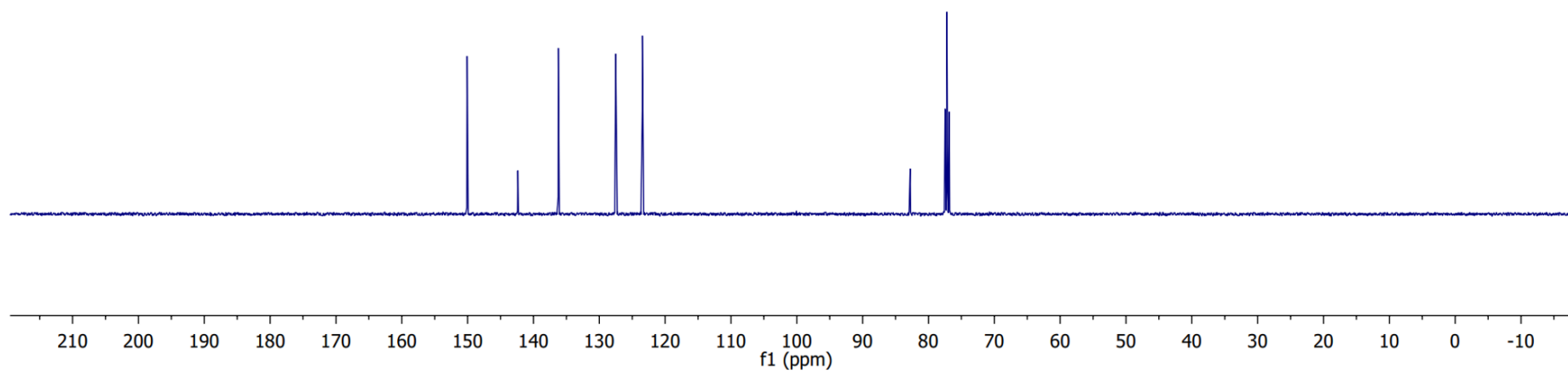
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

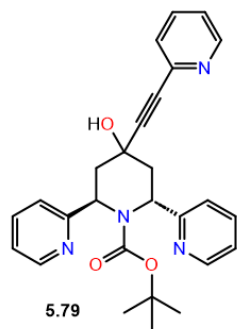




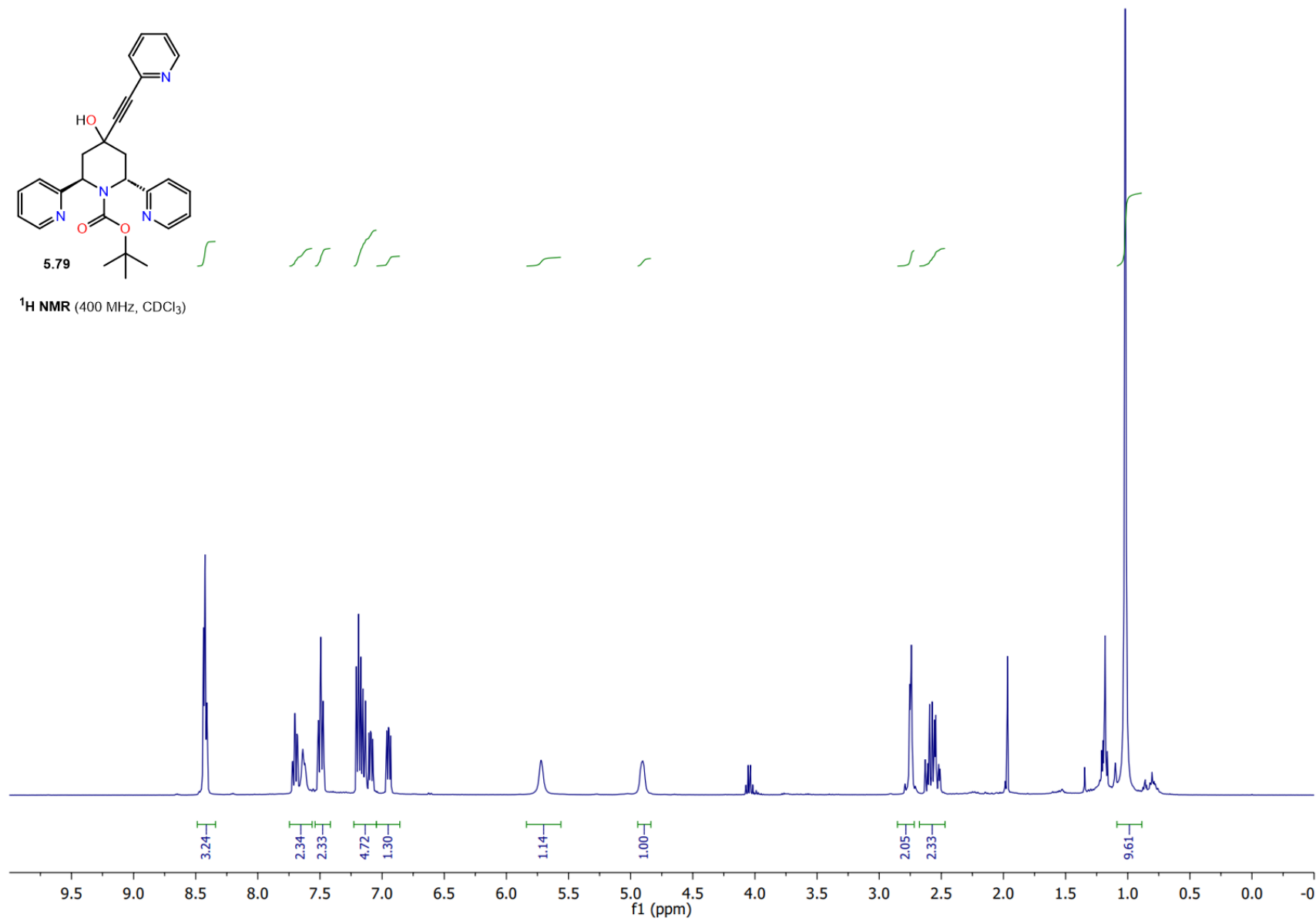
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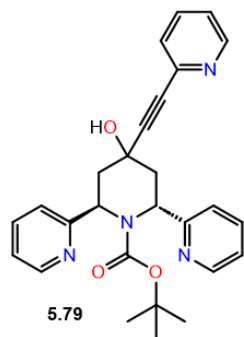
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



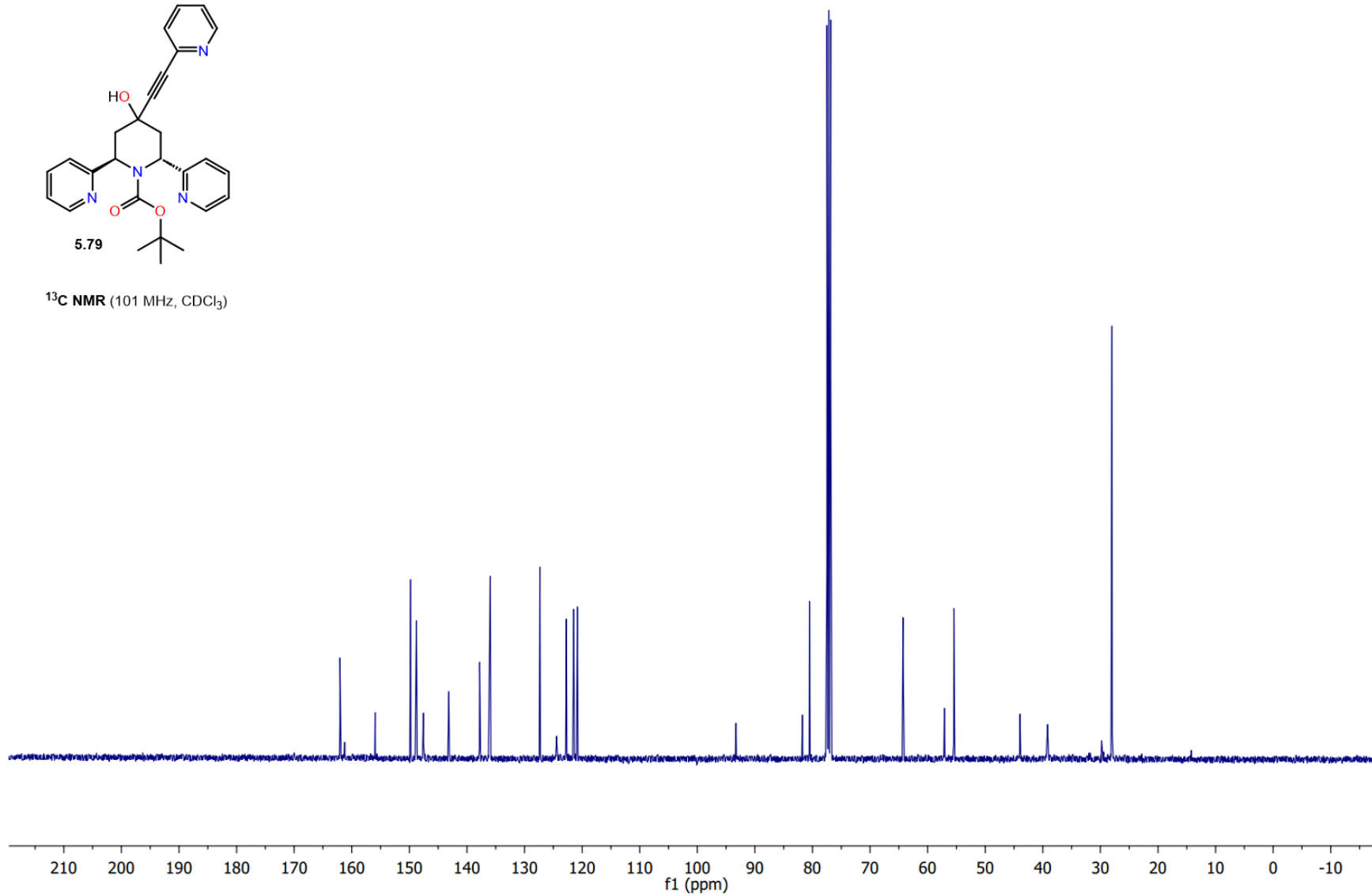


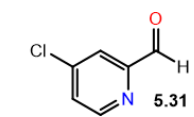
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



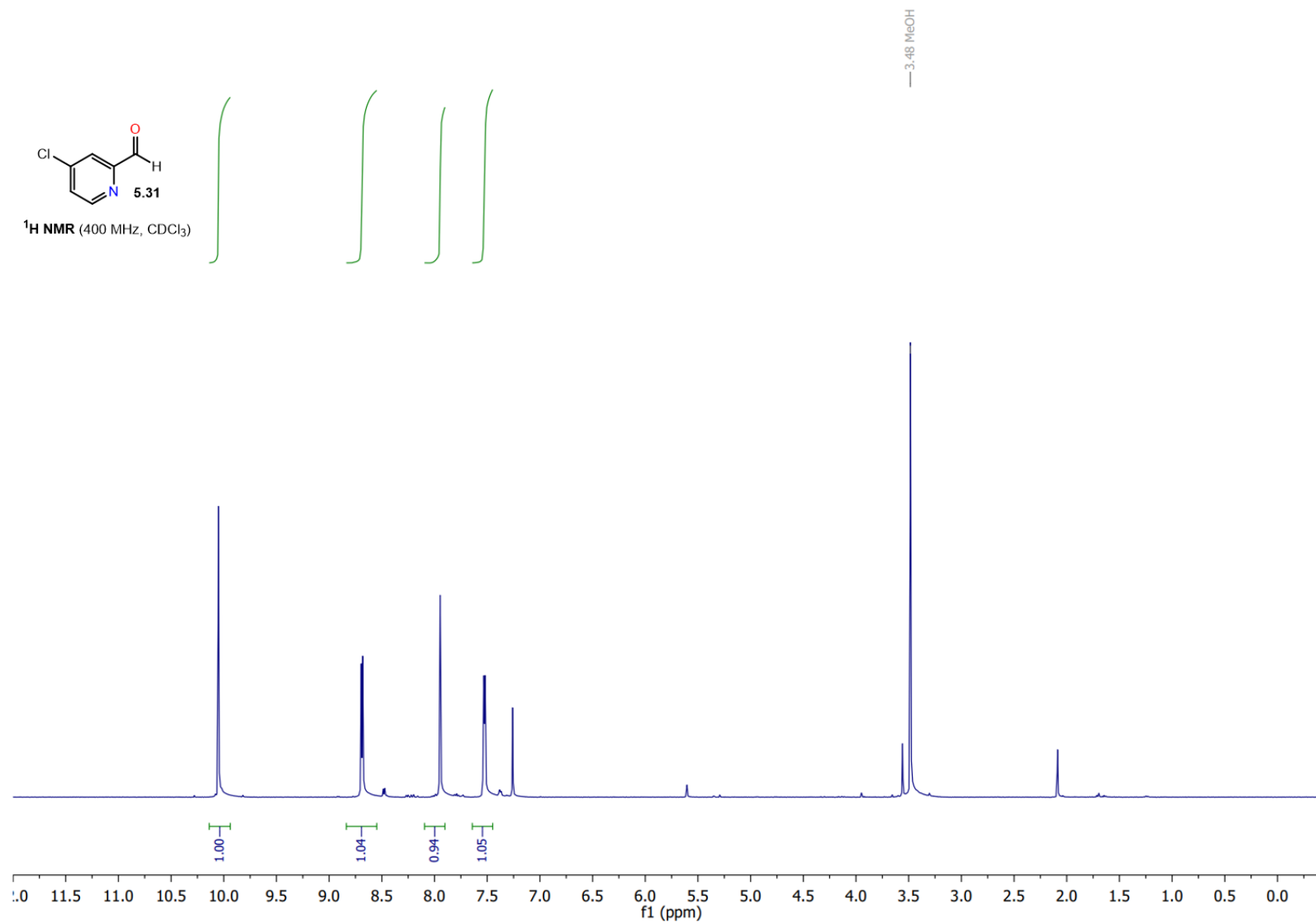


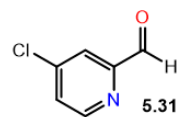
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )





<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)





<sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>CN)

