# PROPARGYLATION OF NITROALKANES VIA THE COPPER-CATALYZED CROSS COUPLING

by

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## ABSTRACT

Chapter 1 begins with a brief introduction of the importance of nitroalkanes in organic synthesis. Nitroalkanes can easily be converted into different functional groups, such as carbonyls, oximes, amines, or corresponding alkanes. The nitronate anions can participate in a variety of reactions, including Henry reaction, Michael reaction, nitro-Mannich reaction, Tsuji-Trost allylation or Buchwald arylation, etc. Despite their exceptional ability to generate new C—C bonds, a simple reaction between nitroalkanes and alkyl halides had proved challenging due to an undesired *O*-alkylation. Our group has successfully used transition metal catalysis to perform *C*-alkylation of nitroalkanes.

Chapter 2 describes the discovery of the synthesis of homopropargylic nitroalkanes (*β*-nitroalkynes) from propargylic halides via a copper catalysis and its synthetic application. First, conventional methods and their limitations to synthesize *β*-nitroalkynes are reviewed. Then, optimization of reaction conditions is described: by using CuBr as catalyst and *N,N*-diisopropylethane-1,2-diamine as ligand, *β*-nitroalkynes are generated in high yield and the formation of *β*-nitroallenes is suppressed. Finally, we investigated on the substrate scope and concluded that this protocol tolerated a wide scope of functional groups.

# Chapter 1

# INTRODUCTION AND BACKGROUND

## 1.1 Organic Chemistry and Methodology in Organic Synthesis

Organic chemistry is the study of the structures, properties, and reactions of compounds that contain carbon and other elements, including nitrogen, silicon, phosphorous, oxygen, sulfur, halogens, and hydrogen.[1] These organic compounds can be classified into three different categories:

(a) natural compounds: produced by living organisms, such as saccharides, vitamins, amino acids, etc.,[2]

(b) synthetic compounds: synthesized in the laboratory by chemical reactions, such as polymers, pharmaceuticals, etc.,[3] and

(c) biotechnology-engineered compounds: produced by living organisms whose genetic material has been artificially altered to allow production of desired non-naturally occurring compounds.[4]

Importantly, organic compounds are widely used in pharmaceuticals, food, cosmetics, petrochemicals, agrochemicals, etc.[1,5] Therefore, among the crucial chemicals bonds, such as C–C, C–H, C–O, and C–X bonds, generating new C–C bonds has been one of the most attractive goals in the organic synthesis. Developing general protocols (referred to as methodology development) to build new C–C bonds that are compatible with other functional groups and provide high yield is of great interest to researchers both in academia and industry.[6]

Nitrogen-containing compounds, such as nitroalkanes, can serve as crucial synthetic precursors to pharmaceutical agents. Nitroalkanes also serve as useful intermediates for the synthesis of other complex molecules because of their transformative ability.[7] Depending on the reaction conditions, they can be converted to aldehydes or ketones via the Nef reaction. Additionally, nitroalkanes can be either partially reduced to oximes and alkyl-substituted hydroxylamines or fully reduced to amines. The C–N bond of nitroalkanes can also be homolytically cleaved to form new C–H bond in a denitration reaction. The use of nitroalkanes as useful synthetic intermediates in the aforementioned reactions has been extensively studied and reviewed.[7]

### 1.2 Nitroalkanes as Useful Synthetic Intermediates

#### 1.2.1 The Nef Reaction

A carbonyl group, including aldehydes, ketones, carboxylic acids and carboxylic acid derivatives, is one of the most important functional groups in organic synthesis. Hence, the ability to convert primary and secondary nitroalkanes into carbonyls is valuable and can be accomplished by the Nef reaction. In 1893, M. Konovalov observed the formation of acetophenone (**1.1b**) and 1-phenylnitroethane (**1.1c**) by adding the potassium salt of 1-phenylnitroethane (**1.1a**) to the dilute acid (AcOH, $H_2SO_4$) (Figure 1.1).[8] In 1894, J. U. Nef carefully studied the acidic hydrolysis of the sodium salt of nitroethane (**1.1d**) to afford acetaldehyde (**1.1e**) and nitrous oxide (**1.1f**) (Figure 1.1).[8] He developed and generalized this transformation independently of Konovalov's works. However, the harsh acidic conditions limited the functional group tolerance; when the pH >1, the by-products including oxime and hydroxynitroso

compounds were formed. To control the reaction outcome and functional group tolerance, great efforts have been made towards the modification of the reaction.

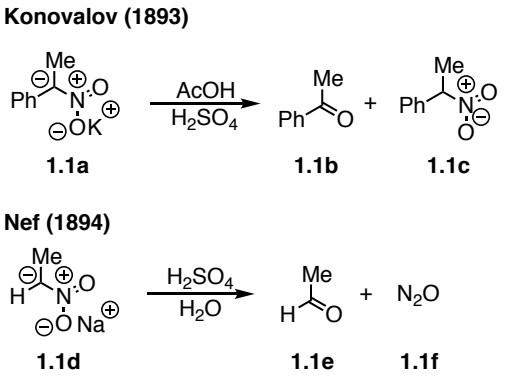



**Figure 1.1 Konovalov and Nef's Experiments**

First, the use of oxidizing agent allows the conversion of primary nitroalkanes to aldehydes or carboxylic acid, while secondary nitroalkanes are converted to ketones (Figure 1.2). Mechanistically, this process begins by the addition of an oxidant, such as Oxone, to the alpha carbon of a nitronate anion, followed by an intramolecular cyclization to generate an oxaziridine-type intermediate. Due to the three-membered ring strain, the C–N bond is cleaved to release the desired carbonyl compound and nitrite salt as by-product. Some examples of oxidants are potassium permanganate ($KMnO_4$), Oxone®, tetrapropylammonium perruthenate/ *N*-methylmorpholine *N*-oxide (TPAP/ NMO), Cu $(OAc)_2$/ $O_2$, or trimethylsilyl chloride (TMSCl)/ 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by *m*-chloroperoxybenzoic acid (*m*-CPBA).[9]

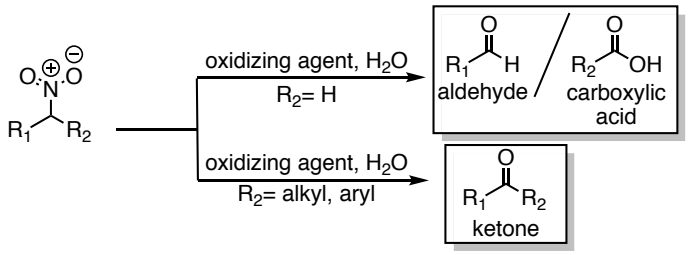



**Figure 1.2 Oxidative Methods for Nef Reactions**

As an example of the use of the oxidative Nef reaction in complex molecule synthesis, in 2001, Trost and coworkers carried out the Nef reaction to prepare a key intermediate (**1.3a**) in the asymmetric synthesis of a potent glycosidase inhibitor (–)- cyclophellitol (**1.3c**).[10] The (–)-cyclophellitol serves as an inactivator of *β*-glucosidase and an inhibitor of HIV and cancer metastasis.[10] Trost used dimethyldioxirane (DMDO) as an oxidizing agent under basic condition to convert nitrosulfone intermediate (**1.3a**) to the corresponding carboxylic acid (**1.3b**) in high yield (Figure 1.3).

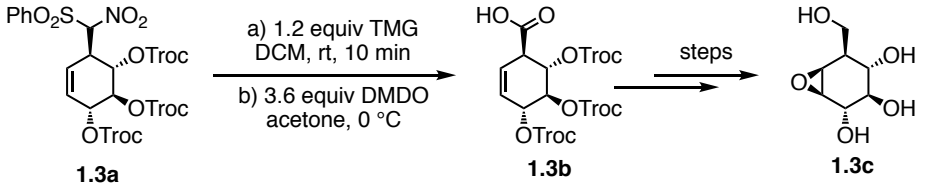



**Figure 1.3 Trost's Synthesis of (–)- Cyclophellitol using Oxidative Nef Reaction**

In contrast to these oxidative methods, reductive methods allowing direct transformation of nitroalkanes to aldehydes, ketones, or oximes have also been developed. The most commonly used reductive procedure, the McMurry method, uses $TiCl_3$ to reduce nitronate salts to an intermediate oxime.[11] The

oxime is then reduced to the imino derivative which, upon workup, forms the corresponding carbonyl compound (Figure 1.4).

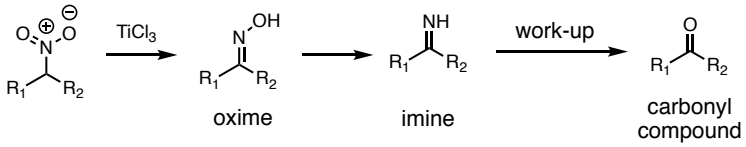



**Figure 1.4 Reductive Methods for Nef Reactions**

As an illustration of the reductive Nef reaction in the synthesis of complex molecules, in 2001, Lange reported a patent to synthesize a series of inhibitors of glycine transporter 1 (GlyT1) (**1.5c**). These inhibitors show a high potential in the treatment of neurological/ neuropsychiatric disorders, including depression, dementia, etc., or neurodegenerative diseases, such as Alzheimer's Huntington's, and Parkinson's.[12] The intermediate ketone (**1.5b**), which is a key building block to synthesize GlyT1 inhibitors, can be prepared by the reductive Nef reaction. First, 3-nitropiperdine (**1.5a**) is generated by an initial nitro-Mannich reaction, then a lactamization, followed by a reduction of piperidin-2-one. Then, this 3-nitropiperdine (**1.5a**) undergoes a reductive Nef reaction via McMurry procedure ($TiCl_3$•$NH_4OAc$) to form ketone (**1.5b**) (Figure 1.5).[12]

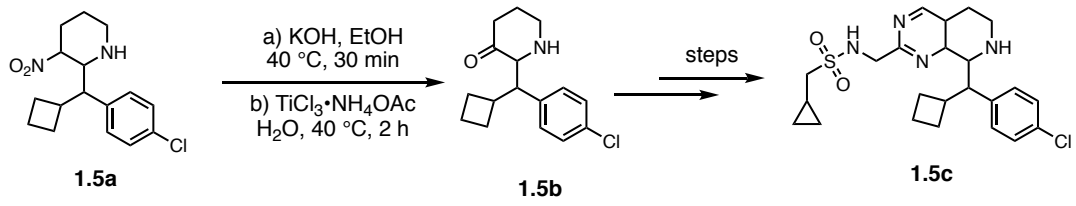



**Figure 1.5 Lange's Synthesis of the Inhibitors for GlyT1 using Reductive Nef Reaction**

### 1.2.2 Partial Reduction

The fully reduced products of nitroalkanes are amines, whereas the partial reduction products are alkyl-substituted hydroxylamines and oximes. These semi-reduced compounds can be isolated and used as useful synthetic intermediates. When using four equivalents of $SmI_2$ as a reductant and methanol as a proton source, nitroalkanes (**1.6a**) can be partially reduced to hydroxylamines (**1.6b**) in 60-90% yield. On the other hand, when six equivalents of $SmI_2$, nitroalkanes are fully reduced to amines (**1.6c**) in 50-80% yield (Figure 1.6).[13]

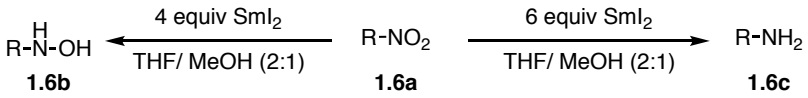



**Figure 1.6 Nitroalkanes Reduction by $SmI_2$**

Nylon 6, which is one of the most widely used of all commercially nylons, is a great example of the use of oximes in industrial applications. Oximes (**1.7a**) are the precursor to caprolactam (**1.7b**), a feedstock to produce Nylon 6 (**1.7c**), as shown in Figure 1.7.[14] First, the oxime (**1.7a**) is prepared from deoxygenation of nitroalkanes using hexamethyldisilane ($Me_3SiSiMe_3$).[15] Then, with a treatment of catalytic sulfuric acid, the oxime is cyclized forming caprolactam via Beckmann rearrangement.[16] The caprolactam is further heated to undergo a ring-opening and polymerization at 533 K under a stream of nitrogen, generating the final product–Nylon 6.

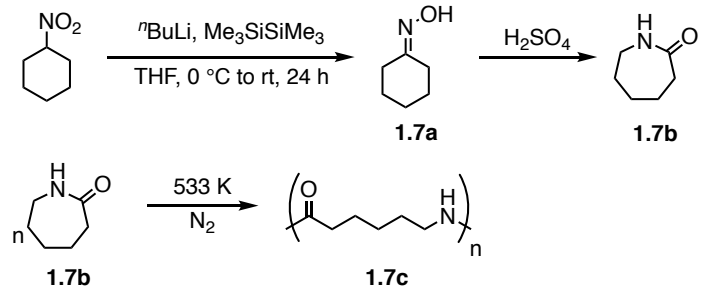



**Figure 1.7 Synthesis of Oximes and Theirs Application**

### 1.2.3 Full Reduction

Nitroalkanes can be fully reduced to amines, one of the most crucial feedstocks in the pharmaceutical industry (Figure 1.8).[17] There are a great number of protocols developed to reduce nitroalkanes to amines. The most commonly used protocols are the catalytic hydrogenation, such as palladium on carbon (Pd/C)[18] or Raney nickel[19] under hydrogen pressure. Hydrogen gas can also be replaced by ammonium formate.[20] Other common protocols are $Ni_2B/N_2H_4{\bullet}H_2O$, Zn/ AcOH, $LiAlH_4$, and electrochemical reduction.[21]

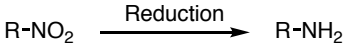



**Figure 1.8 The Reduction of Nitroalkanes to Amines**

The mechanism for the reduction using metal and $H^+$ was proposed as a sequence of single electron transfer (SET) and protonation reactions (Figure 1.9).[22] Initially, the nitro group (**1.9a**) is reduced to the nitroso group (**1.9b**). This nitroso group is then reduced to the *N*-substituted-hydroxylamine (**1.9c**), followed by the loss of water and the generation of amine (**1.9d**).

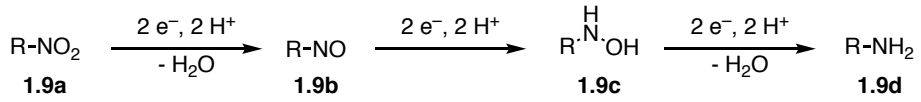



**Figure 1.9 Proposed Mechanism for the Reduction of Nitroalkanes to Amines**

In addition to the catalytic hydrogenation, the use of zinc and acid as proton source is also commonly used. The Watson group frequently employed this method to reduce the nitro compound to amine for the downstream functionalization. In 2019, they reported a method to synthesize enantioenriched *β*-nitroamides (**1.10a**) using a nickel catalyst (Figure 1.10). Then, after the trifluoromethylation (**1.10b**), the nitro group was stereoretentively reduced to the amine (**1.10c**) in 81% yield and 100% es by the treatment of zinc in hydrochloric acid.[23]

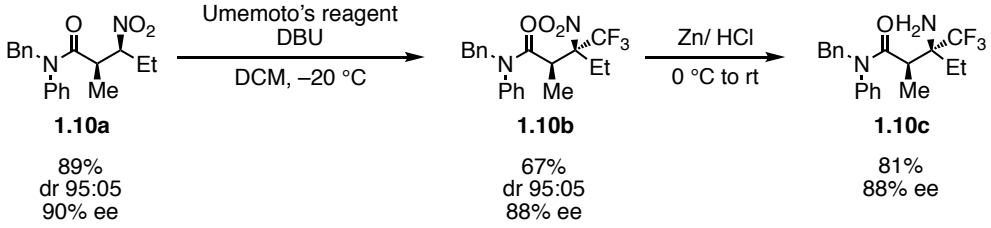
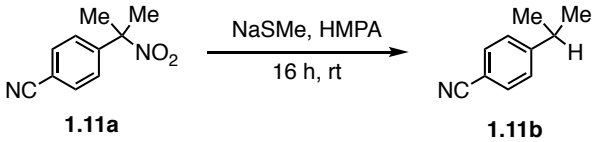



**Figure 1.10 Stereoretentive Reduction of Nitroalkanes to Amines**

### 1.2.4 Denitration

Denitration of nitroalkanes—replacement of the nitro group by a hydrogen atom—has been widely used in the synthesis of complex natural products. Denitration can occur via either radical or ionic pathway.

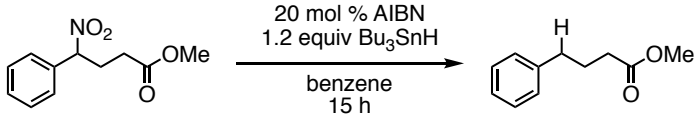
In 1979, Kornblum was the first to carry out the radical denitration of nitroalkanes (**1.11a**) to afford the corresponding alkanes (**1.11b**). With the treatment of methylmercaptan sodium, a tertiary nitro group was replaced by a hydrogen via a radical chain mechanism (Figure 1.11). However, this method was limited to tertiary nitroalkanes, secondary ones were less reactive, whereas primary ones showed no reactivity.[24]




**1.11a** **1.11b**

**Figure 1.11 Kornblum's Denitration of Tertiary Nitroalkanes**

Then, Ono and coworkers sought a solution to allow efficient denitration of secondary nitroalkanes. In 1981, they denitrated secondary nitroalkanes (**1.12a**) with radical initiator 2,2-azobisisobutyronitrile (AIBN) and $Bu_3SnH$ by cleaving the C–N bond to obtain the corresponding aliphatic chain (**1.12b**) in good yield 64% (Figure 1.12). However, primary nitroalkanes were inert to Ono's procedure.[25]

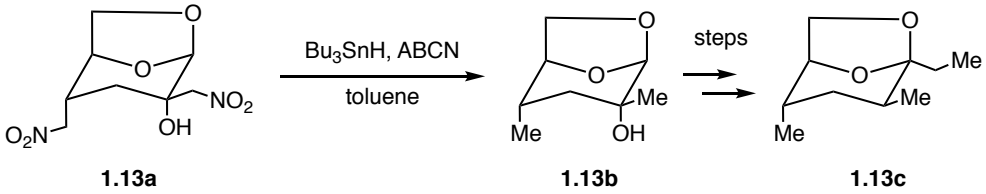



**1.12a** **1.12b**

**Figure 1.12 Ono's Denitration of Secondary Nitroalkanes**

The denitration of primary nitroalkanes remained challenging until 1995, Witczak came up with a solution to remove a nitro group in the *β*-nitro alcohol intermediate (**1.13a**) (Figure 1.13). This tertiary alcohol (**1.13b**) is a key building

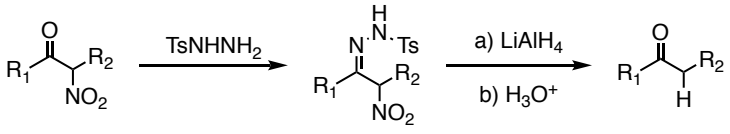
block for the stereoselective synthesis of (–)-δ-Multistriatin (**1.13c**) In order to obtain this alcohol intermediate, the primary nitroalkane (**1.13a**) is denitrated by the treatment of $Bu_3SnH$ in the presence of a radical initiator aza(biscyclohexenyl)nitrile (ABCN), affording new C–H bond (**1.13b**) in 70%.[26]




**1.13a** **1.13b** **1.13c**

**Figure 1.13 Witczak's Denitration of Primary Nitroalkanes**

Although the denitration is usually carried out via a radical pathway, it can also occur via an ionic process. Rosini and coworkers have successfully denitrated *α*-nitroketones (**1.14a**) to the corresponding ketones (**1.14c**) (Figure 1.14). They reduce the corresponding nitro-tosylhydrazone with $LiAlH_4$, in which a 1,4-elimination of $HNO_2$ takes place. Then, with an acidic work-up, they obtain the final des-nitro products (**1.14c**). Even though this method is limited to *α*-nitroketones, it avoids the use of toxic reagents such as HMPA or organotin compounds.[27]




**1.14a** **1.14b** **1.14c**

**Figure 1.14 Rosini's Denitration of *α*-Nitroketones**

### 1.3 Nitroalkanes as a Versatile Functional Group

The versatility of nitroalkanes in organic synthesis is mainly due to their facile transformation into a different range of functional groups. Deprotonated nitroalkanes (nitronate anions) serve as the precursors in the organic synthesis, participate in a variety of diverse reactions to build new C–C bonds. Examples of these reactions are the Henry reaction, the nitro-Mannich reaction, and the nitro-Michael reaction. In addition, they also participate in the palladium catalyzed cross-coupling reactions, including allylation and arylation of nitroalkanes.

#### 1.3.1 Henry Reactions (Nitro-Aldol Reactions)

Nitronate anions react with electrophilic aldehydes and ketones to generate *β*-nitroalcohols. This is known as the nitro-aldol reaction, or the Henry reaction. The reaction was first discovered by Louis Henry in 1895 when he reacted nitroalkanes with aldehydes or ketones under basic condition and obtained *β*-nitroalcohols (Figure 1.15).[28] *β*-nitro alcohols have a great ability to transform into different synthetic intermediates. These formed alcohols may undergo elimination of water to generate nitroalkenes,[29] which can further act as a dienophile in the Diels-Alder reaction or as a Michael acceptor. *β*-nitroalcohols can also be converted into *β*-nitrocarbonyls via oxidation,[30] *β*-aminoalcohols via reduction,[31] and secondary alcohol via denitration.[32]

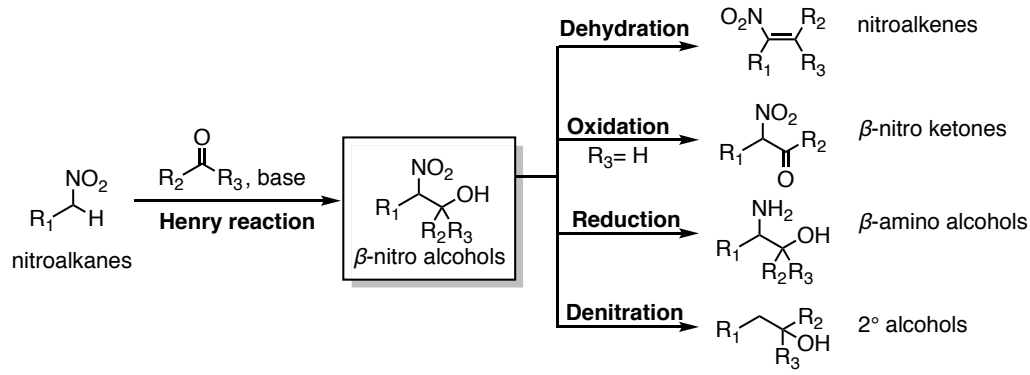



**Figure 1.15 The Henry Reaction and Its Applications**

The Henry reaction is reversible and the nitro-substituted carbon stereocenter is easily epimerized, hence, this reaction often provides a mixture of stereoisomers.[28] The Henry reaction was largely unselective until 1995 when Shibasaki reported the first diastereoselective and enantioselective nitro-aldol reactions from the prochiral starting materials (aldehydes and nitroalkanes) and the lithium-BINOL hetero-bimetallic complexes (**1.16a**) as asymmetric catalysts (Figure 1.16). With the treatment of the catalyst (**1.16a**), aldehyde and nitroethane are reacted to generate *β*-nitroalcohol (**1.16b**) with the predominant formation of the syn adduct.[33]

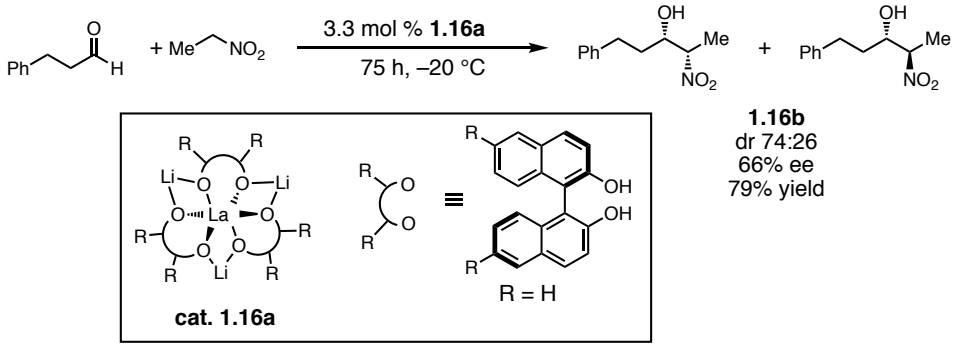



**Figure 1.16 Shibasaki's First Asymmetric Henry Reaction**

As a demonstration of the synthetic application of the Henry reaction, the reaction has been used to prepare crucial intermediates in their synthetic routes. For example, E. J. Corey and coworkers reported a concise synthetic route for the construction of Aspidophytine (**1.17b**), which is known as an anticockroach/insecticidal substance.[34] They started this synthetic route with the Henry reaction: nitroveratraldehyde (**1.17a**) reacted with nitromethane to afford the nitrostyrene intermediate in 86% yield (Figure 1.17).

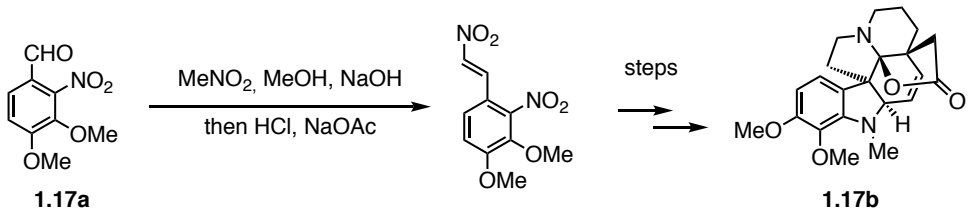



**Figure 1.17 Corey's Synthesis of Aspidophytine**

### 1.3.2 The Nitro-Mannich Reaction

When imines are used as electrophiles instead of carbonyls to react with nitroalkanes in the presence of the base, the nitro-Mannich reaction (or aza-

Henry reaction) takes place to generate *β*-nitroamines. In 1896, one year after discovering the Henry reaction, Louis Henry reported the nitro-Mannich reaction from methanolamine and nitromethane.[35] Synthetically versatile *β*-nitroamines provide a great access to other important organic building blocks, including *α*-aminocarbonyls via the Nef reaction, 1,2-diamines via reduction of the nitro group, and monoamines via denitration (Figure 1.18).[36]

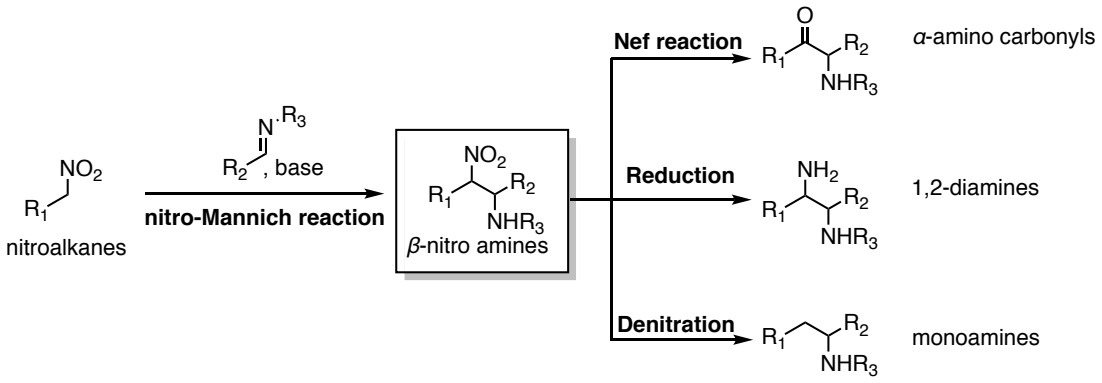
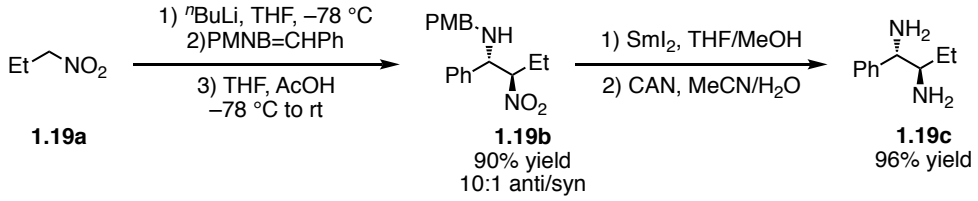



**Figure 1.18 The Nitro-Mannich Reaction and Its Applications**

In 1998, Anderson reported the first acyclic diastereoselective nitro-Mannich reaction as well as a convenient method to synthesize 1,2-diamines.[37] $^{n}$BuLi is used as a base to deprotonate nitroalkanes (**1.19a**), generating lithium nitronates. These nitronate salts then react with protected imines and acetic acid to afford the desired nitro-Mannich products (**1.19b**) with high anti diastereoselectivity. The pKa' is 9 for nitronate salt and 35 for the aza anion, hence, this reaction is thermodynamically disfavored. Therefore, adding acetic acid is essential to drive the reaction forward. Due to the instability of the *β*-nitroamines, the nitro group is first reduced to the amine group by $SmI_2$, then the protecting group *p*-methoxybenzyl (PMB) is removed by using ceric

ammonium nitrate (CAN) to generate the bis-primary amines (**1.19c**) (Figure 1.19).




**1.19a** **1.19b** 90% yield 10:1 anti/syn **1.19c** 96% yield

**Figure 1.19 Anderson's First Diastereoselective Nitro-Mannich Reactions**

In application, Johnston and coworkers developed a general method to synthesize *α*-unsubstituted *β*-amino acids enantioselectively (Figure 1.20). Nitro-Mannich reaction between the *α*-nitroester (**1.20b**) and the *N*-Boc protected imine (**1.20a**) in toluene with a chiral catalyst (**1.20e**) afforded *β*-nitroesters (**1.20c**).[38] This nitro group activates and controls the stereochemistry in the nitro-Mannich, which is later removed via the radical denitration to afford *β*-amino acid without the erosion of enantiomeric excess. This *β*-amino acid (**1.20c**) is a key constituent for the construction of (+)-chaenorhine (**1.20d**), a member of the polyamine family of alkaloids, was isolated and characterized in the laboratories of Schmidt and Hesse.[38]

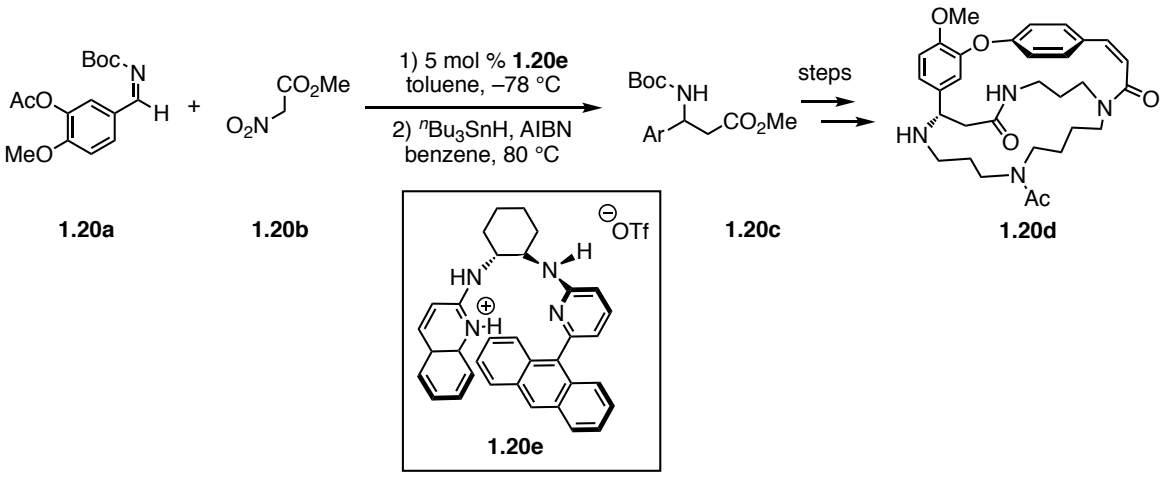



**Figure 1.20 Johnston's Total Synthesis of (+)-Chaenorhine**

### 1.3.3 The Nitro-Michael Reaction

Besides acting as an excellent nucleophile in the Henry reaction or nitro-Mannich reaction, nitroalkanes also serve as a good Michael donor and react with *α, β*-unsaturated electrophiles to generate *γ*-nitrosubstituted compounds under basic conditions.[7,39] This is known as nitro-Michael addition. These nitro-Michael products allow a facile transformation to a variety of structural motifs for organic syntheses, such as carbonyls via the Nef reaction,[40] amines via the reduction,[41] and new aliphatic C–H bond via denitration.[42] The *γ*-nitrosubstituted compounds also act as Michael donors and further participate in a 1,4-addition, generating more complex nitro-bearing-compounds (Figure 1.21).[43]

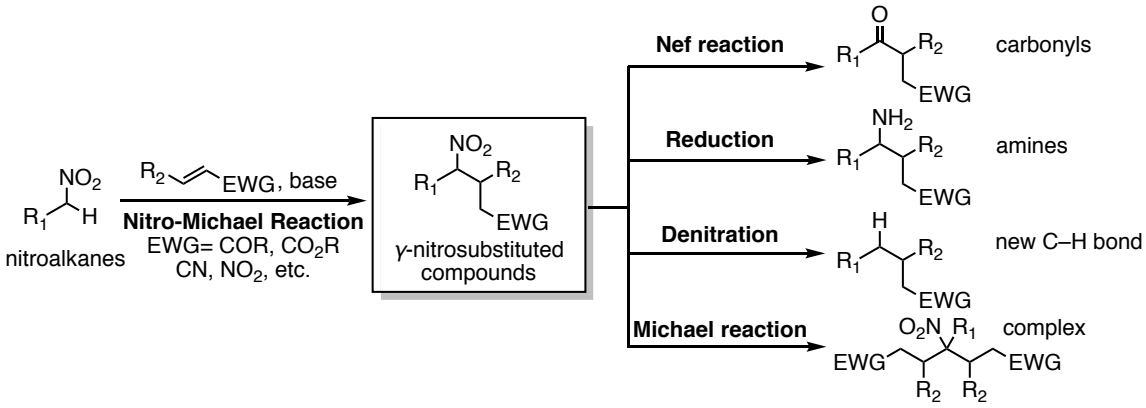
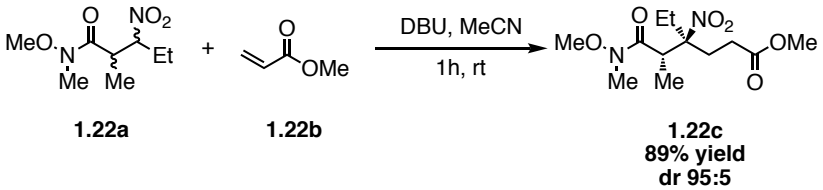



**Figure 1.21 The Nitro-Michael Reaction and Its Applications**

As an example, in 2015, the Watson group efficiently demonstrated the highly diastereoselective Michael reactions of *β*-nitrocarbonyls (**1.22a**) as Michael donors and methyl acrylates (**1.22b**) to afford tetrasubstituted nitrogen bearing stereocenters (**1.22c**) (Figure 1.22) in high yield and excellent diastereoselectivity.[44]




**1.22a** **1.22b** **1.22c**
**89% yield**
**dr 95:5**

**Figure 1.22 Watson's Highly Diastereoselective Nitro-Michael Reaction**

The diastereoselectivity was also explained in Figure 1.23. Since the deprotonation of *β*-nitrocarbonyls is fast and reversible (monitored by $^1$H NMR and DBU), there is a tautomerization between a *β*-nitrocarbonyl (**1.23a**) and an intermediate (**1.23b**). The proton coordinates to both the oxygen of the nitronate anion and the oxygen of the carbonyl, generating this cyclic intermediate (**1.23b**).

Then, the electrophile attacks the cyclic tautomer on the opposite side of the alpha substituents as shown in (**1.23c**), resulting the product (**1.23d**).[44]

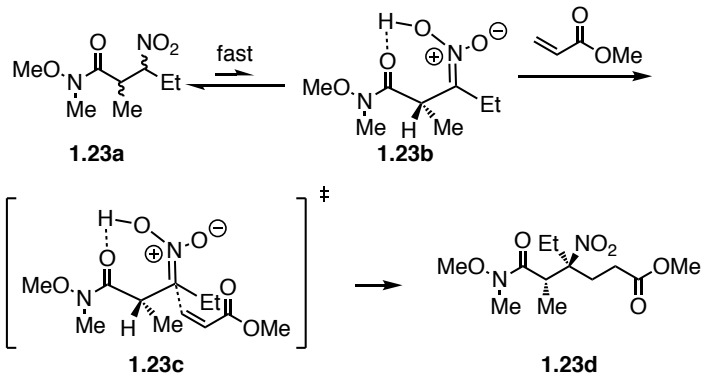



**Figure 1.23 Proposed Model for the Diastereoselectivity**

As an example of the nitro-Michael reaction in complex molecule synthesis, Hanessian reported a route to synthesize (+)-dihydromevinolin (**1.24f**), a potent hypocholesterolemic metabolite produced by Aspergillus terreus (Figure 1.24).[45] First, the compound (**1.24a**) undergoes a Henry reaction, followed by the elimination of mesylated product to afford the nitroolefin (**1.24b**). Then, the reduction of nitroolefin by sodium boron hydride ($NaBH_4$) and the desilylation/ acylation affords the intermediate (**1.24c**). This nitro intermediate serves as a Michael donor and undergoes 1,4-addition with a chiral cyclopentenone to generate this nitro adduct (**1.24d**) in 70%. With the treatment of tributyltin hydride and AIBN, the C–N bond is cleaved to generate the des-nitro derivative (**1.24e**) in 55% yield.[4]

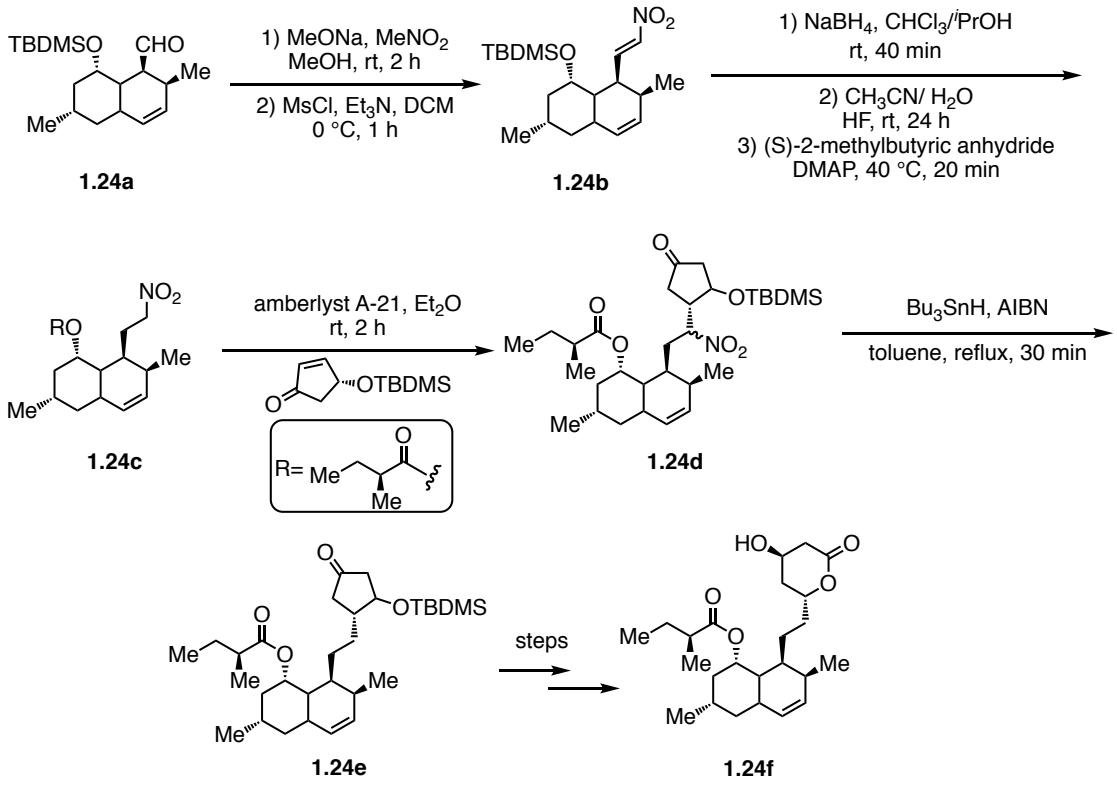



**Figure 1.24 Hanessian's Total Synthesis of (+)-Dihydromevinolin**

### 1.3.4 Allylation of Nitroalkanes

A cross-coupling reaction occurs when two different molecules react together to forge a new C–C (carbon-carbon) bond or C–X (carbon-heteroatom) bond with the aid of a transition metal catalyst.[46] In the case of the nitroalkane chemistry, the nitroalkanes serve as a nucleophile and alkyl halides serve as an electrophile. Among the transition metal that have been used in the cross coupling, such as palladium, iron, cobalt, copper, and nickel, palladium is frequently used due to the high functional group tolerance.[47]

The first palladium catalyzed cross-coupling reaction using nitroalkanes is the allylation. In 1982, Wade reported a method of allylation of nitroalkanes with allylic acetates (**1.25a**). Besides the homo-alkylated product (**1.25b**), there was a by-product (**1.25c**) formed due to the allylic rearrangement. The competitive attack at two sites of the *α*-allyl palladium intermediate accounted for this issue (Figure 1.25, top).[48]

At the same year, Aleksandrowicz also published a paper on the allylation of nitroalkanes. He employed allylic alcohols, allylic acetates and allylic phenyl ethers (**1.25d**) as the allylating agents to cross couple with aliphatic nitro compounds in Tsuji-Trost allylation to generate the desired product (**1.25e**). Nevertheless, this method suffered from the bis-allylation (**1.25f**) when an excess amount of allylic alcohol-EtOAc was used (Figure 1.25, bottom).[49]

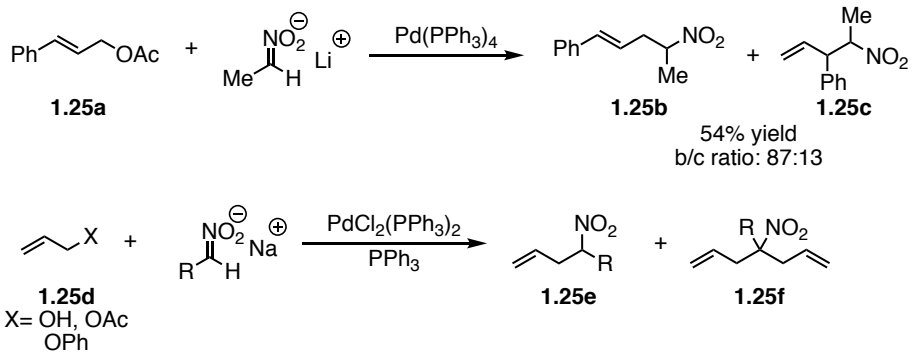



**Figure 1.25 Wade and Aleksandrowicz's Allylation of of Nitroalkanes**

In 2001, Trost successfully improved the stereoselectivity on Helmchen's[50] first asymmetric allylation of nitroalkanes (Figure 1.26).[51] By using a chiral 1,2-diamine ligand, cyclic allyl esters (**1.26a**) reacted with nitromethane to produce mono-alkylated products (**1.26b**) in high yields and excellent enantiomeric excess. This chemistry was further studied and the scope was expanded to complex nitroalkanes[52] as well as allyl epoxides,[53] etc.

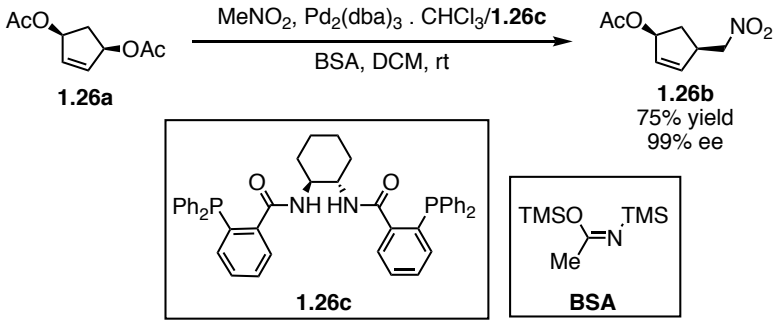



**Figure 1.26 Trost's Enantioselective Nitroalkane Allylation with Cyclic Allyl Esters**

In 2018, Wu reported the titanium-assisted palladium-catalyzed alkylation of nitroalkanes (**1.27a**) with allylic alcohols (**1.27b**) (Figure 1.27). In the report, Wu proposed that the titanium (IV) alkoxide and palladium complexes promote the formation of nitronate and π-allylpalladium intermediate (**1.27d**). To illustrate the synthetic application, they provided a route to synthesize (±)-adalinine (**1.27f**) in 60% yield from the *C*-arylated product (**1.27e**).[54] Adalinine is a piperidine alkaloid from the chemical defense that the European two-spotted ladybird Adalia bipunctata releases.[54]

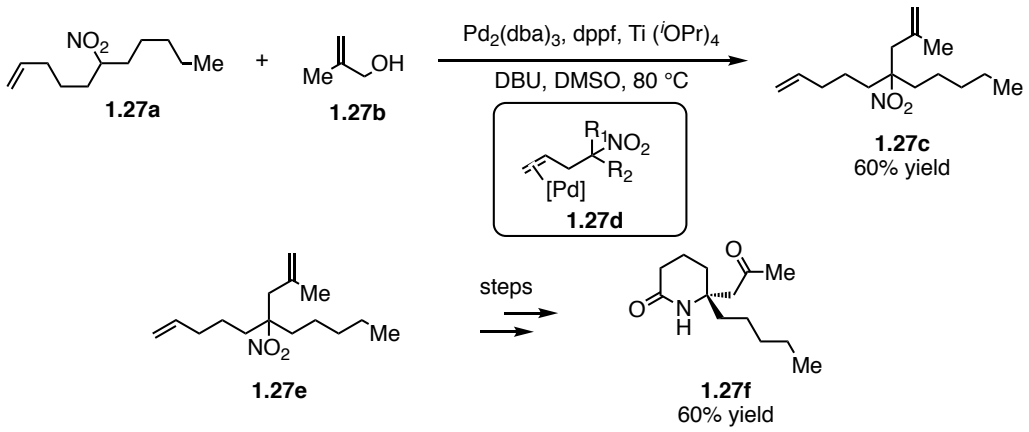



**Figure 1.27 Wu's Synthesis of (±)-Adalinine**

### 1.3.5 Arylation of Nitroalkanes

In the late 1990s, lots of attentions had been focused on the development of direct arylation of substrates via a transition metal catalyst.[55] In 1998, Muratake was the first one to report the intramolecular arylation of synthesized substrates bearing a nitro group (Figure 1.28).[56] Taking advantage of the acidic nature of the nitroalkanes, $Cs_2CO_3$ is used to deprotonate an *α*-proton to generate the cesium salt. This salt is then cyclized to an intramolecular aryl-palladium intermediate. As the results, the cyclization of primary nitroalkanes (**1.28a**) affords secondary nitroalkanes (**1.28b**) in good yields and *α*-tetralone (**1.28c**) in a modest yield (via the Nef reaction). On the other hand, the cyclization of secondary nitroalkanes (**1.28d**) generates tertiary nitro products (**1.28e**) in good yield. However, the elimination of $HNO_2$ resulted in styrene (**1.28f-g**). Overall, the nitro group serve as a terminating group in the intramolecular arylation to synthesize different functional groups, including ketones and alkenes.

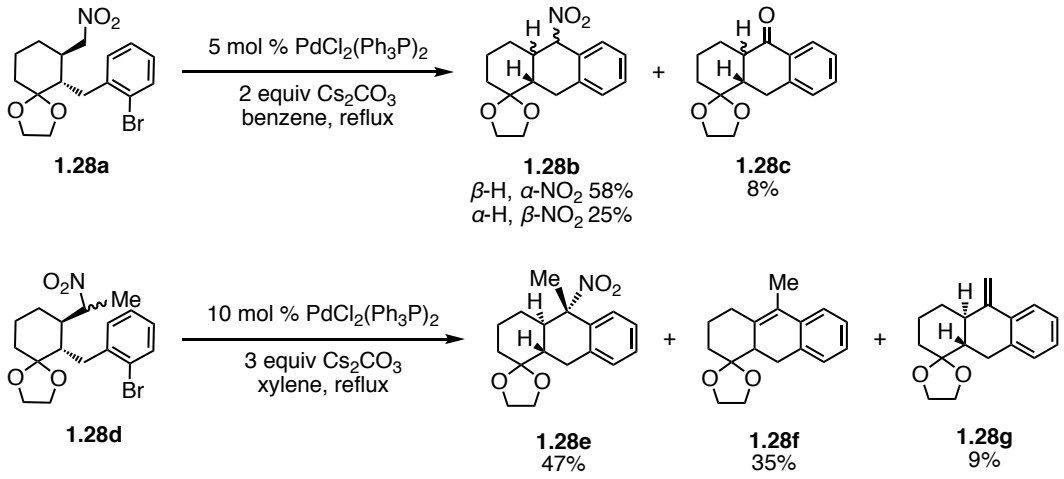



**Figure 1.28 Muratake's First Intramolecular Arylation of Nitroalkanes**

In 2000, Buchwald discovered an effective catalyst system—bulky and electron-rich phosphine ligand in combination with $Pd(OAc)_2$ (**1.29a**) and $K_3PO_4$—to perform *α*-arylation of diethyl malonate, 1,3-diketones, and nitroalkanes. In this paper, he reported the first intermolecular arylation of nitroalkanes with only two examples (**1.29b**).[57] Two years later, in 2002, Buchwald developed a general protocol for homoarylation of nitroalkanes. By changing the reaction parameters, including switching ($Pd(OAc)_2$ to $Pd_2(dba)_3$, $NaO^tBu$ to $Cs_2CO_3$, and dioxane to DME, he was able to cross couple the substituted aryl bromides (**1.29c**) and aryl chlorides with a variety of nitroalkanes to synthesize monoarylated nitroalkanes in good to excellent yields (**1.29d**) (Figure 1.29).[58]

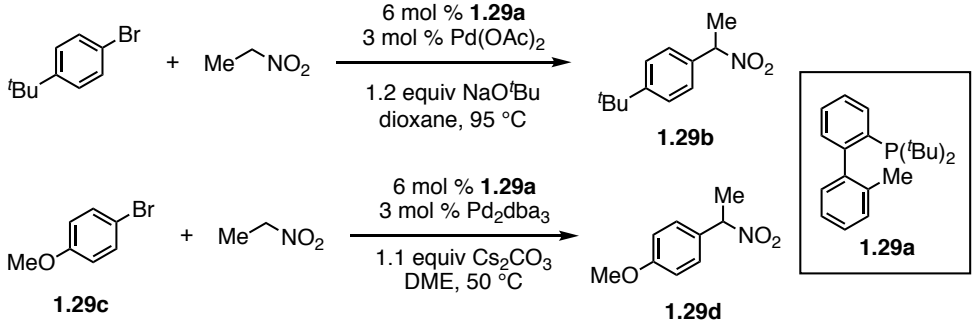



**Figure 1.29 Buchwald's First Intramolecular Arylation of Nitroalkanes**

Although Buchwald's protocol tolerates a wide range of functional groups, it provides a low yield when using nitromethanes and shows no reactivity for secondary nitroalkanes. In 2012, Kozlowski found a solution to the reactivity issues with nitromethane by slight modifications in reaction conditions (**1.30a**, Figure 1.30).[59] In 2015, Olofsson also reported a metal-free approach for the arylation of secondary nitroalkanes (**1.30b**, Figure 1.30).[60]

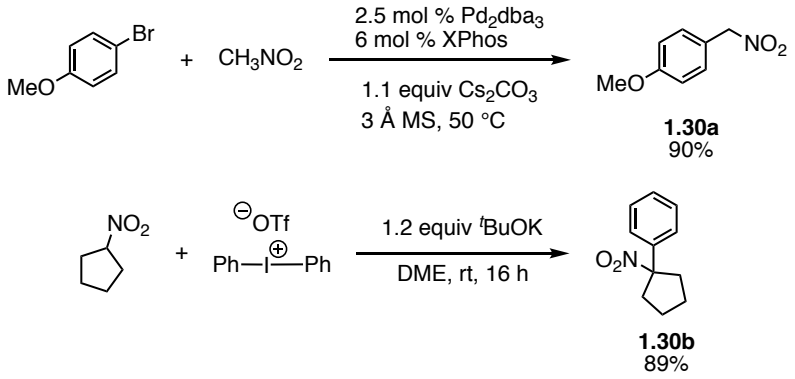



**Figure 1.30 Approaches to Arylation for Nitromethanes and Seconadary Nitroalkanes**

### 1.4 Previous Attempts of *C*-Alkylation of Nitroalkanes

Nitroalkanes can be transformed to carbonyls via Nef reaction (section **1.1.1**), alkyl-substituted hydroxylamines or oximes via partial reduction (section **1.1.2**), or amines via full reduction (section **1.1.3**). There are also a great number of reactions of nitroalkanes to generate new chemical bonds, such as the Henry reaction (section **1.2.1**), the nitro-Mannich reaction (section **1.2.2**), the nitro-Michael reaction (section **1.2.3**), palladium-catalyzed allylation (section **1.2.4**), and arylation (section **1.2.5**). Developing a general route to synthesize more complex nitroalkanes is attractive because nitroalkanes provide a facile access to a variety of functional groups, including heterocycles. Yet, the simple *C*-alkylation of nitroalkanes with alkyl halides proved challenging because of the undesired *O*-alkylation (Figure 1.31).[61]

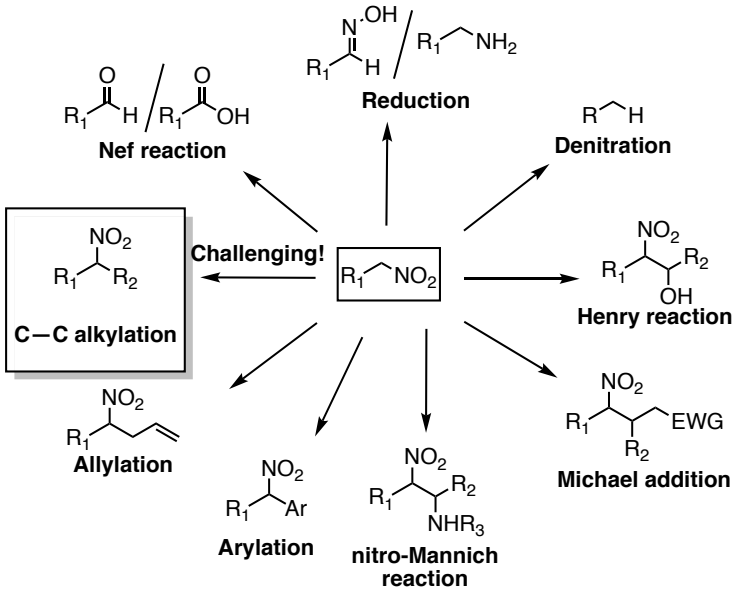



**Figure 1.31 Summary of Nitroalkanes' Transformations**

### 1.4.1 Hass and Bender's Early Study of *O*-Alkylation over *C*-Alkylation

Nitroalkanes serve as a convenient intermediate in organic synthesis, hence tremendous efforts have been devoted to develop the general synthetic route for *C*-alkylation of nitroalkanes.[5,7] In 1949, Hass and Bender attempted to generate *C*-alkylated products from nitronate salts and benzyl bromides (**1.32a**). However, they instead obtained benzaldehydes (**1.32b**) from hydrolysis of the *O*-alkylated intermediates; this is later known as the Hass-Bender oxidation or Hass-Bender carbonyl synthesis.[61] Mechanistically, the nitronate anion reacts with the benzyl bromide to generate a nitronic ester via the $S_N2$ reaction. This ester then undergoes the elimination to form benzyaldehyde and oxime as a by-product. Only trace amounts of the *C*-alkylated product were formed. However, there was one exception. The reaction of *p*- nitrobenzyl chloride (**1.32c**) gave only 1% of the *O*-alkylated byproduct and favored the *C*-alkylated product with 83% yield (**1.32d**) (Figure 1.32).

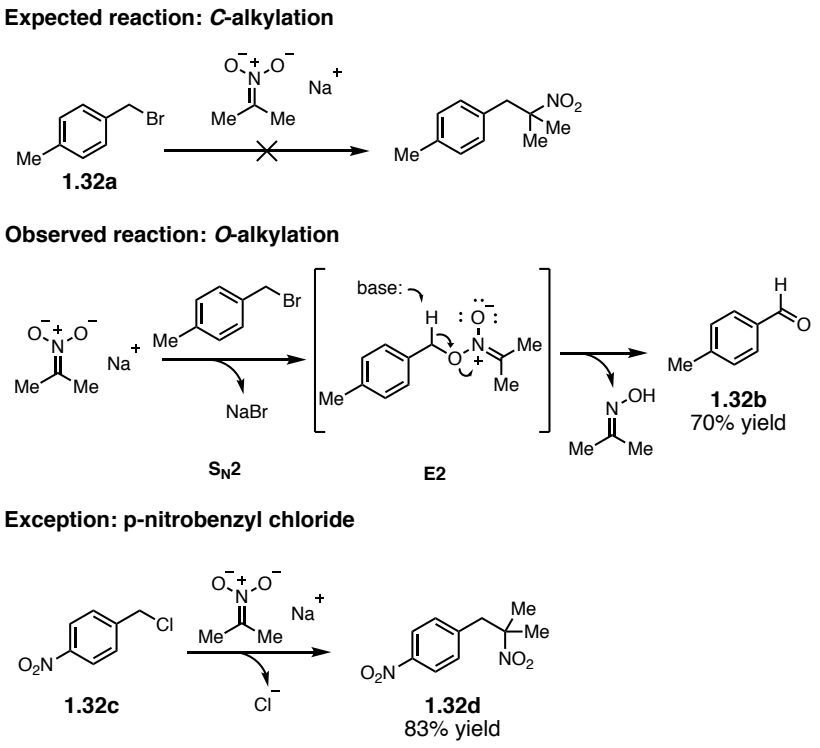



**Figure 1.32 Hass and Bender's Discovery of *O*-Alkylation**

### 1.4.2 Kornblum's Mechanistic Studies of *C*-Alkylation of Nitroalkanes

In 1975, Kornblum performed a series of mechanistic studies to explain this disparate reactivity.[62] He suggested that the observed reactivity was due to two factors: the leaving group ability of the alkyl halide and the electronic properties of the $-NO_2$ group. Having a better leaving groups (–Br, –I) favored the formation of *O*-alkylated product via $S_N2$ mechanism, while the poor leaving group (–Cl) yielded *C*-alkylated product via a proposed radical mechanism. The presence of a strong electron withdrawing nitro group in para position of the

benzyl halide provided an important additional delocalization for the radical and therefore supports radical anion formation.

To provide further support for his hypothesis on the radical nature of the *C*-alkylation of nitroalkanes, Kornblum exposed the reaction to a known radical inhibitor, *p*-dinitrobenzene (*p*-DNB), to suppress the reactivity. Adding 20 mol % of *p*-DNB enhanced the formation of *O*-alkylated product to 88%, whereas without *p*-DNB, 92% of *C*-alkylated product was formed. He then proposed a radical chain $S_{RN}1$ mechanism (Figure 1.33): the neutral benzyl radical (**1.33a**) underwent a radical-anion coupling with the nitronate anion (**1.33b**) to form the radical anion *β*-nitrobenzyl product (**1.33c**). It was then oxidized to afford the final product (**1.33d**), further propagating the chain reaction.[62]

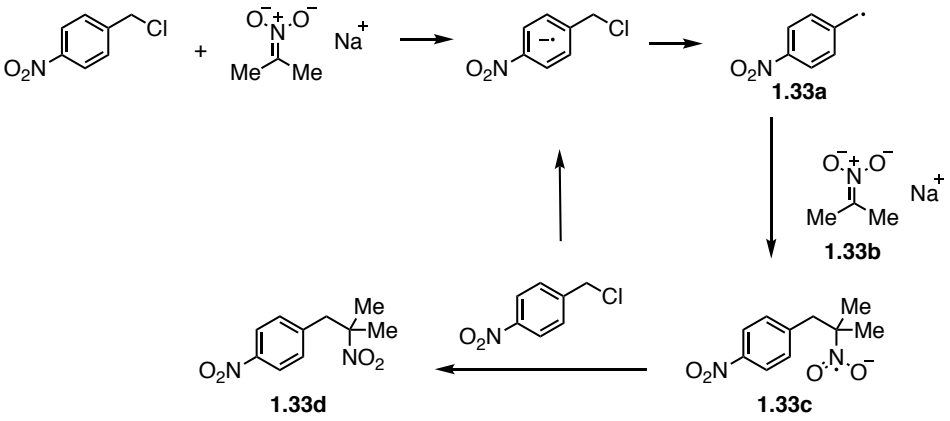



**Figure 1.33 Kornblum's Proposed Mechanism**

### 1.4.3 Seebach's *C*-Alkylation of *α, α*-Doubly Deprotonated Nitroalkanes

Many research groups had put significant efforts into investigating the *C*-alkylation of nitroalkanes. In 1976, Seebach and coworkers discovered that doubly deprotonating the nitroalkanes (**1.34a**) (by addition of two equivalents of $^{n}$BuLi) would enhance the *C*-nucleophilicity of the nitroalkanes, which could then promote an $S_N2$ reaction to occur.[63] In 1977, they improved reaction conditions to *C*-alkylate the dianionic nitronates with different aryl/alkyl halides. (Figure 1.34).[63] To prevent the competitive Nef reaction, they carried out the reaction with an arduous cooling and warming protocol. They found out that when adding the dianionic nitronates to the alkyl halides, they had to warm the reaction from –90 °C to –78 °C for 45 minutes, then from –78 °C to +15 °C for 14 h. Next, they added an excess amount of glacial acetic acid at –90 °, followed by an aqueous workup to generate the secondary nitroalkane product (**1.34b**) in 51% yield. However, if they warmed the reaction too quickly, the dianionic nitronates would decompose. Overall, the limited functional group tolerance due to the use of strong $^{n}$BuLi, the dependence on toxic solvent HMPA, and the requirement of tightly controlled cryogenic temperature restricted the reaction application.

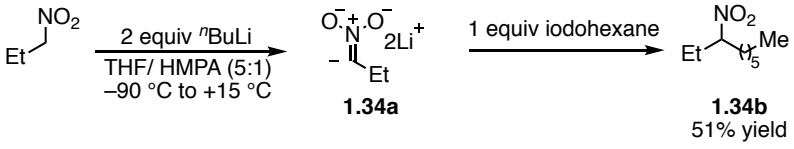



**Figure 1.34 Seebach's *C*-Alkylation of *α, α*-Doubly Deprotonated Nitroalkanes**

### 1.4.4 Russell's *C*-Alkylation of Nitroalkanes with Organomercy Halides

Russell and workers discovered a method of alkylating 2-nitropropane or nitrocyclohexane with secondary (**1.35a**) or tertiary alkyl mercury chlorides under photolytic conditions (Figure 1.35).[64] The reaction does not occur in the absence of light or with the addition of di-tert-butyl nitroxide. Hence, Russell proposed this chemistry would undergo a free radical chain nucleophilic substitution $S_{RN}1$ mechanism. Under the sunlamp, the alkyl mercury chloride (**1.35b**) is initiated to generate the alkyl radical (**1.35c**), Hg(0), and chloride anion. Then, this alkyl radical couples with the nitronate anion to afford the final *C*-alkylated product (**1.35d**). Nevertheless, the use of highly toxic alkylmercury as reagents and the limited functional group tolerance made this technique impractical.

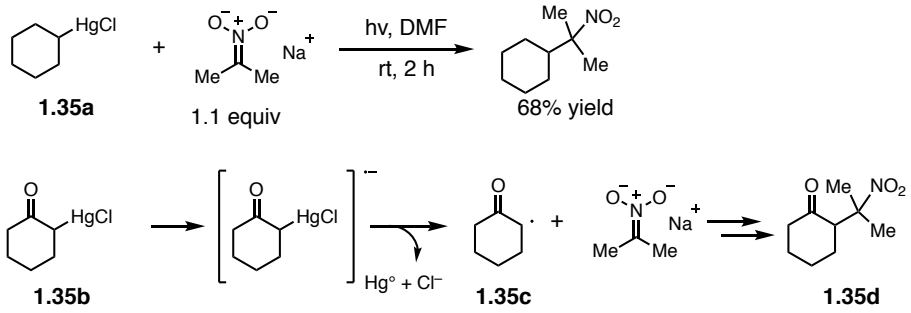



**Figure 1.35 Russell's *C*-Alkylation of Nitronate Anions with Organomercury Halides**

### 1.4.5 Branchaud's *C*-Alkylation of Nitronate Anions with Alkyl Cobaloximes

Branchaud and coworkers performed a cross coupling of alkyl cobaloximes (**1.36a**) and nitromethane or 1-nitropropane anions via a non-chain radical reaction under photolytic condition (Figure 1.36).[65] Mechanistically, the visible light homolytically cleaves the alkyl cobalt complex (**1.36b**) into an alkyl radical (**1.36c**) and a cobalt (II) radical (**1.36d**). This alkyl radical undergoes a radical-anion coupling to generate a nitro radical anion intermediate (**1.36e**). Via an electron transfer, this intermediate (**1.36e**) is oxidized to generate the final product (**1.36f**). Since Co(II) radical does not act as a chain terminating radical scavenger, this reaction proceeds via a non-chain pathway. Even though this method provides *C*-alkylated products in good yield, it also faces some synthetic drawbacks: the use of stoichiometric alkyl cobaloximes and the limited functional group tolerance.

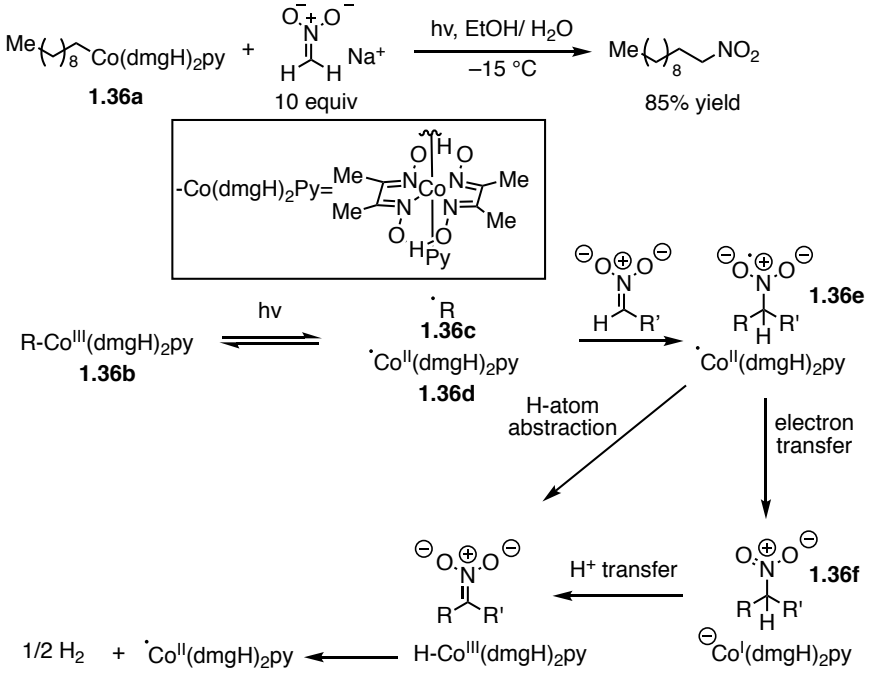



**Figure 1.36 Branchaud's *C*-Alkylation of Nitronate Anions with Alkyl Cobaloximes**

### 1.4.6. Katrizky's *C*-Alkylation of Nitronate Anions with Quinolinium Cations

In the 1900s, among the reported methods of *C*-alkylation of nitroalkanes, Katrizky's method proved to be the most effective because it avoided the use of toxic reagents.[66] The only disadvantage of his method is its poor atom economy: the generated stoichiometric by-product pyridines are not recoverable. Katrizky employed *N*-alkyl quinolinium (**1.37a**) or pyridinium salts (**1.37b**) as radical precursors and ran the reaction under mild conditions to afford alkylated products in good to excellent yield (Figure 1.37). He showed that this chemistry worked well with primary and secondary nitroalkanes, but he did not investigate on the functional group tolerance.

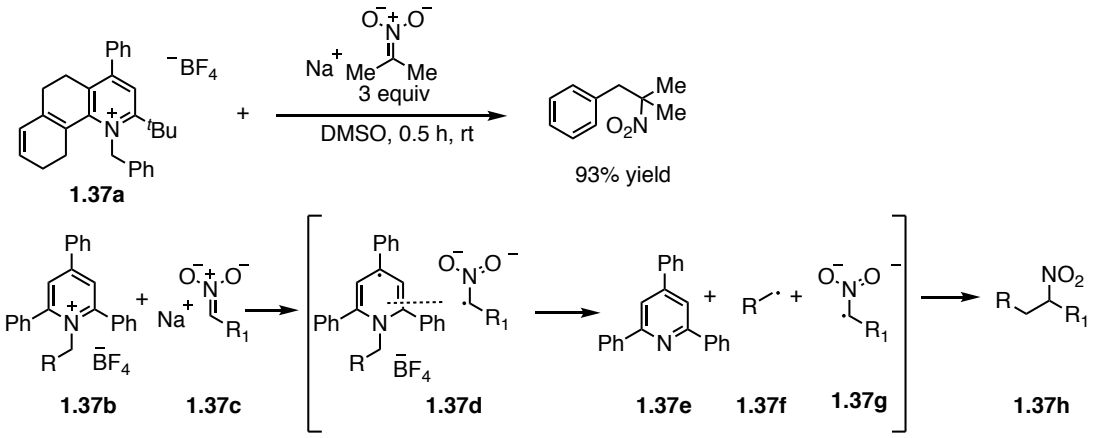



**Figure 1.37 Katrizky's *C*-Alkylation of Nitronate Anions with Pyridinium and Quinolinium Cations**

Different from Kornblum's proposed radical chain mechanism[62], Katrizky described his mechanism as a "non-chain radicaloid" (Figure 1.37).[66] The charge-transfer complex (**1.37d**) [from pyridinium salt (**1.37b**) and nitronate anion (**1.37c**)] decomposes to generate an alkyl radical (**1.37f**), an *α*-nitro

radical (**1.37g**), and triphenylpyridine (**1.37e**) as by-product. Then, the remaining alkyl radical and *α*-nitro radical combine to afford the *C*-alkylated product (**1.37h**). Surprisingly, the addition of radical scavenger (*p*-dinitrobenzene) does not inhibit the reaction.

## 1.5 Watson's Efforts Towards *C*-alkylation of Nitroalkanes via Transition Metal Catalysis

The previously mentioned methods proposed that a nitronate anion undergoes coupling with a radical precursor to generate a new C–C bond. With this mechanistic paradigm in mind, Watson hypothesized that by using a transition metal catalyst, a nucleophilic nitronate anion could undergo a radical-anion coupling with an alkyl halide to achieve a higher selectivity for *C*-alkylation over *O*-alkylation. This chemistry would effectively avoid the use of highly toxic and stoichiometric alkyl mercury and alkyl cobalt, could be run under mild reaction conditions, and tolerated a broad range of functional groups.

### 1.5.1 The Use of Electrophiles Bearing a Radical Stabilizing Groups (RSG)

In 2009, the Watson group discovered a copper catalyzed system for the benzylation of nitroalkanes to synthesize a variety of complex homobenzylic nitroalkanes (Figure 1.38).[67] These reactions took place at mild temperature (60 °C), used a cheap pre-catalyst CuBr and an easily-prepared 1,3-diketimine ligand, employed a variety of benzyl bromides and nitroalkanes to afford good yields of *C*-alkylated products. This copper catalyzed protocol allows great

access to a variety of homobenzylic nitroalkane compounds that can be further converted into phenethylamine derivatives, which are the medicinal agents used in the treatment of depression and obesity.[68]

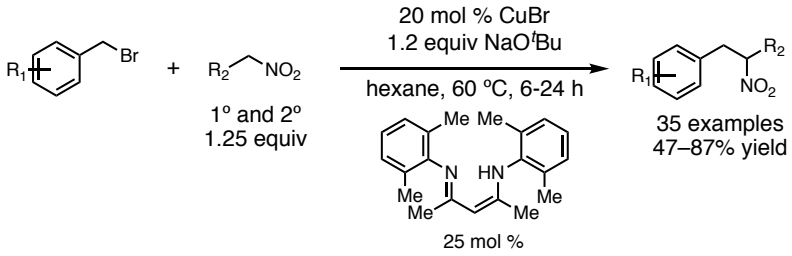



**Figure 1.38 Benzylation of Nitroalkanes**

The requirement for this nitroalkane chemistry is the use of electrophiles bearing adjacent radical stabilizing groups (RSG). The Watson group envisioned *α*-bromocarbonyls[69] as another electrophile bearing adjacent RSG since the radical is stabilized by the electron withdrawing carbonyl group. Under the same copper catalytic system, *β*-nitrocarbonyl[69] compounds are effectively synthesized (Figure 1.39). In application, *β*-amino acid[69], a useful synthetic precursor to make *β*-lactams,[70] could be prepared from *β*-nitrocarbonyls[69] by reduction (Figure 1.39).

Then, the Watson group envisioned *α*-bromonitriles[71] as a promising electrophile because the electron withdrawing nature of the cyano group can stabilize the adjacent radical. Similar to the aforementioned reactions, *β*-cyanonitroalkanes are synthesized with the aid of copper catalyst and 1,3-diketimine ligand. To illustrate the valuable application of this method, 5-aminoisoxazoles can be prepared from *β*-cyanonitroalkanes by the semi-reduction and subsequent cyclization (Figure 1.39).[71] 5-aminoisoxazoles are of

interest in medicinal chemistry, and they have been targeted by other research groups.[72]

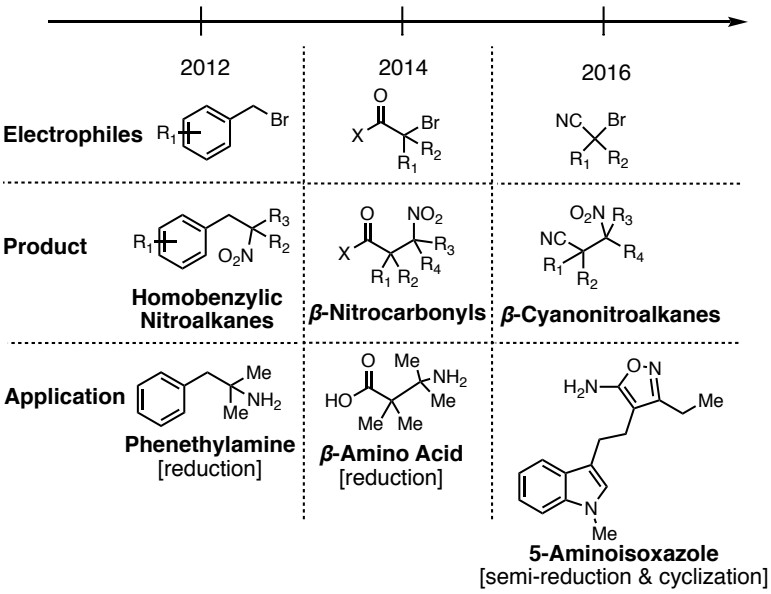



**Figure 1.39 The Diversity of Electrophiles**

A thermal redox mechanism was proposed: an electron rich Cu(I)(nacnac) complex (**1.40a**) abstracted a bromide from the alkyl bromide (**1.40c**) to form RSG-alkyl radical (**1.40b**) and Cu(II)-halide-nacnac complex (**1.40d**). Then, this RSG-alkyl radical underwent a rapid radical-anion coupling with nitroanate anion to form the reduced nitroalkane (**1.40e**). Lastly, the reduced nitroalkane got oxidized to afford the final product (**1.40f**) and regenerated the Cu(I)- nacnac catalyst (**1.40a**) (Figure 1.40).[67]

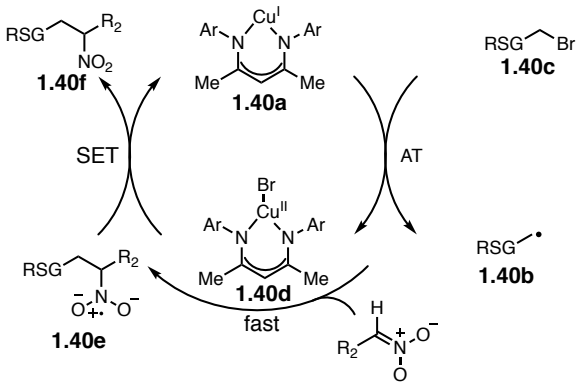
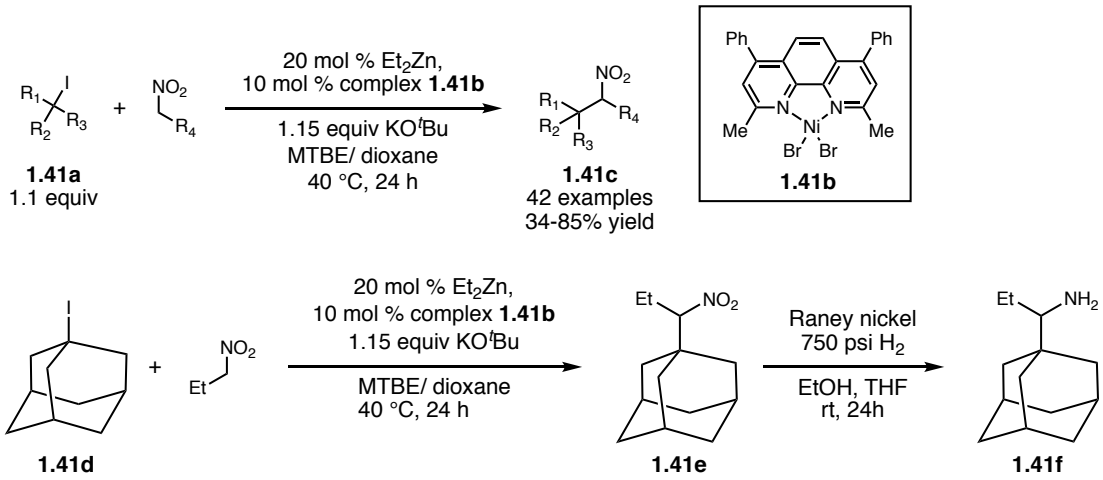



**Figure 1.40 Proposed Mechanism for *C*-Alkylation of Nitroalkanes with Electrophiles Bearing Radical Stabilizing Groups**

### 1.5.2 The Use of Unactivated Alkyl Iodides as Electrophiles

The Watson group discovered an innovative nickel catalyst system that promotes *C*-alkylation of nitroalkanes with the non-stabilized alkyl halides as electrophiles. From early studies on the benzylation of nitroalkanes, it was noted that the nickel catalyst did provide a trace amount of homobenzylic nitroalkanes even though it is less reactive compared to the copper catalyst. In 2017, a general catalytic method that effectively alkylates nitroalkanes with unactivated alkyl iodides (**1.41a**) (Figure 1.41) was published.[73] By employing a nickel(II) and bathocuproine single component complex (**1.41b**) as catalyst and diethyl zinc as reductant, this chemistry tolerates primary, secondary, and tertiary alkyl iodides and allows a great access to complex primary nitroalkanes (**1.41c**). However, it gave low yield in the case of secondary nitroalkanes and suffered from over-alkylation for nitromethane. In application, the anti-viral drug adapromine (**1.41f**) is effectively prepared in two steps from commercially available material—1-iodoadamantane (**1.41d**) and 1-nitropropane. The

reduction of the secondary nitroalkane (**1.41e**) affords the primary amine (**1.41f**) by Raney nickel reduction in quantitative yield.




**1.41 *C*-Alkylation of Nitroalkanes with Unactivated Alkyl Iodides**

### 1.5.3 Asymmetric *C*-Alkylation of Nitroalkanes

Not only was selective *C*-alkylation achieved over *O*-alkylation for a wide range of nitroalkanes, an asymmetric method to build enantioenriched nitro-containing compounds was also discovered. Moreover, the reduction of these enantioenriched nitroalkanes will provide a straightforward and convenient access to a variety of medicinally relevant amines, which are currently in a high demand for the pharmaceutical industry.[3,17]

In 2019, the Watson group was excited to report the first asymmetric alkylation of nitroalkanes with *α*-bromoamides (**1.42a**) as electrophiles. By using a chiral ligand and $NiCl_2$ complex (**1.42c**) as catalyst, and $Et_2Zn$ as reductant, *β*-nitroamides (**1.42b**) were obtained in excellent yield with high enantioselectivity and good diastereoselectivity. Under mild reaction conditions,

this method provides a useful route to prepare the highly substituted *β*-nitroamides and has a high tolerance of functional groups (Figure 1.42).[23]

A $Ni^{I}/Ni^{III}$ catalytic cycle was proposed (Figure 1.42). First, Ni(II) precatalyst is reduced to Ni(0) complex by $Et_2Zn$. Ni(0) is combined with an excess Ni(II) to generate Ni(I) complex (**1.42d**). An insoluble (or sparingly soluble) nitronate anion reacts with Ni(I) complex (**1.42d**) to form a soluble Ni(I) nitronate (**1.42e**). The alkyl bromide enters the cycle and reacts with the electron rich Ni(I) nitronate (**1.42e**) to generate a Ni(III) alkyl nitronate complex (**1.42f**) via oxidative addition. Last, the final product *β*-nitroamide (**1.42g**) is formed and Ni(I) complex (**1.42d**) is re-generated via reductive elimination.[23]

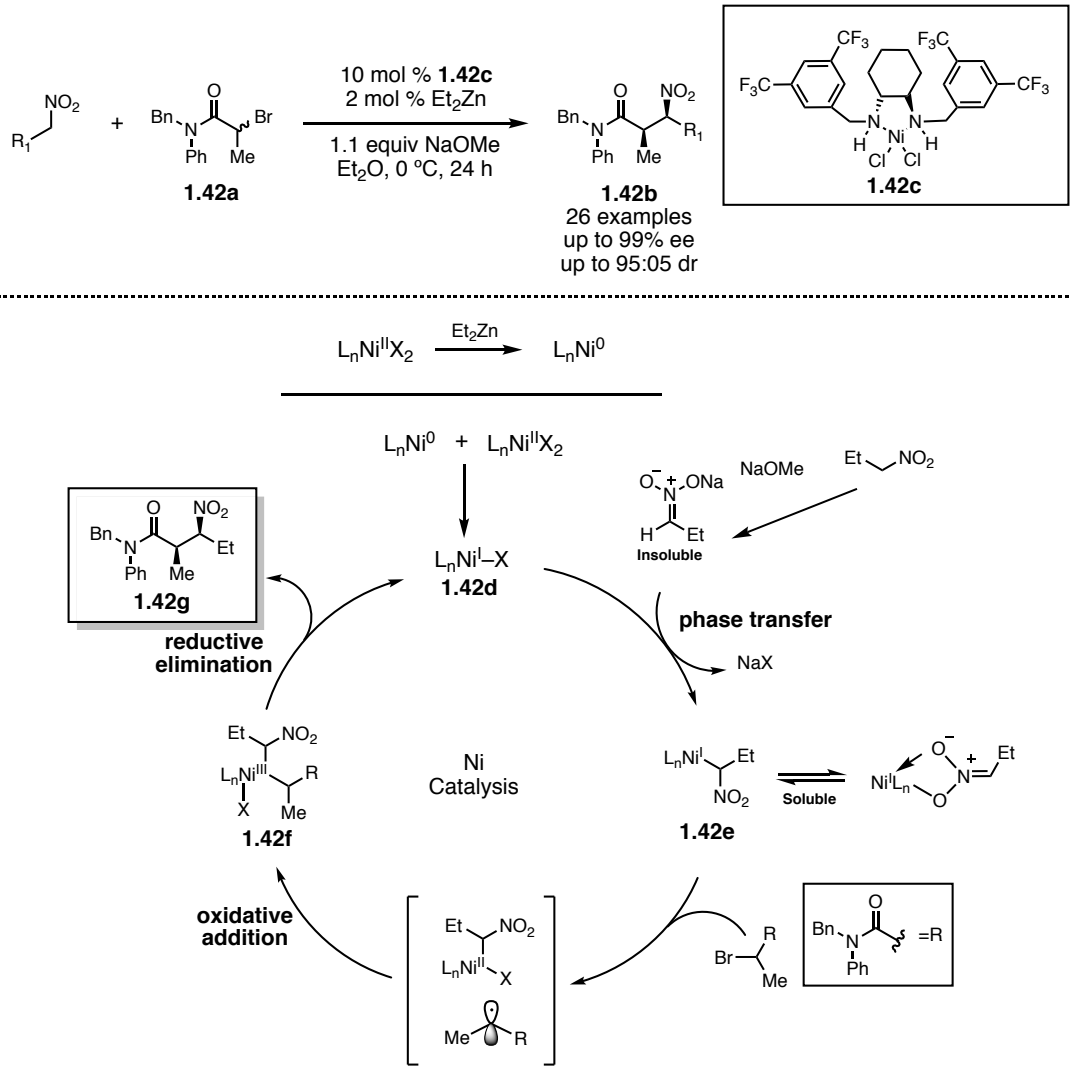



**Figure 1.42 Synthesis of Enantioenriched *β*-Nitroamides and Possible Mechanism**

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# Chapter 2

# TRANSITION METAL CATALYZED PROPARGYLATION OF NITROALKANES VIA CROSS COUPLING REACTIONS

## 2.1 Background of the Propargylation Chemistry

Propargylation has a high tolerance of functional groups and can be carried out at mild reaction conditions to forge new C–C (carbon-carbon) and C–X (carbon-heteroatom) bonds. With a breakthrough discovery of the use of transition metal catalyst, many research groups have taken advantage of its inherent properties (flexible ability to change the oxidation state) to perform propargylation.[1]

Transition metal-catalyzed propargylation reactions are mainly divided into two categories. The first one involves the propargylation of carbonyl compounds or imines (**2.1a**) with propargylic halides[2] (**2.1b**) and organometallic reagents,[3] including propargyl (**2.1c**) or allenyl (**2.1d**) metal species. The second one involves the direct propargylation of propargylic alcohols and their derivatives (**2.1e**) with nucleophiles (**2.1f**).[4] Ding and Hou wrote a comprehensive review on "*Catalytic Asymmetric Propargylation*".[1] I will mainly focus on the use of propargylic halides as electrophile in the propargylation chemistry.

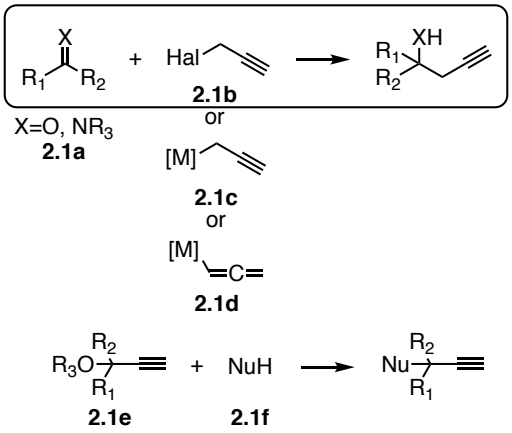



**Figure 2.1 Two Categories of Propargylation Chemistry**

In 2008, Fu and his coworker Smith reported the first Negishi cross-coupling reaction with the aid of a nickel catalyst (Figure 2.2).[2] They reacted secondary propargylic bromides and chlorides (**2.2a**) with secondary organozinc compounds (**2.2b**) to furnish new propargylated alkyl chains (**2.2c**). This nickel-based catalyst system with the use of terpyridine ligand features mild reaction conditions, provides products in high yields, and tolerates several functional groups, including ether, ester, alkene, and chlorides.

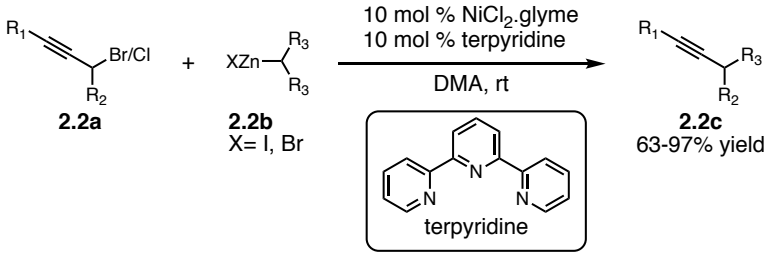



**Figure 2.2 Fu's Negishi Cross Coupling Reaction of Secondary Organozinc and Propargylic Halides**

## 2.2 Syntheses of Homopropargylic Nitroalkanes (*β*-Nitroalkynes)

Inspired by the previous reports in the Watson group on nitroalkane synthesis, I wanted to explore the diversity of electrophiles bearing adjacent radical stabilizing groups (RSG). I envisioned alkynes as a potential RSG for the selective *C*-alkylation of nitroalkanes. The unpaired electron in radicals adjacent to triple bonds are delocalized; in other words, radicals are effectively stabilized by conjugation.[5] Therefore, the homopropargylic nitroalkane is the next substrate class that I wanted to explore. (Figure 2.3)

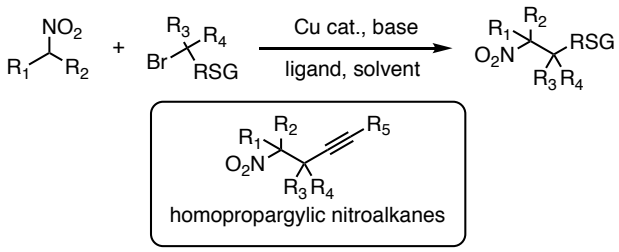



**Figure 2.3: Copper Catalyzed Cross-Coupling Reaction of Nitroalkanes**

Over the last decade, the Watson group has successfully performed *C*-alkylation of nitroalkanes selectively over *O*-alkylation to synthesize a variety of functionalized nitro compounds.[8] We recognized that homopropargylic nitroalkanes are useful intermediates in the synthesis of pyrroles and other small nitrogen-heterocycles and that a method to propargylate nitroalkanes would allow for their rapid synthesis. The discovery of such a method was the goal of this research effort.

## 2.3 Previous Attempts Toward Homopropargylic Nitroalkanes (*β*-Nitro Alkynes)

### 2.3.1 Conventional Routes to *β*-nitroalkynes

Traditionally, *β*-nitroalkynes can be prepared from a conventional $S_N2$ reaction of primary homopropargylic halides and sodium nitrite (Figure 2.4).[7] However, due to the steric hindrance, the formation of *β*-nitroalkynes remained challenging for secondary and tertiary homopropargylic halides. This method only targeted simple primary nitroalkanes and required the synthetic preparation of homopropargylic halides.

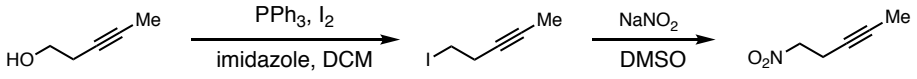



**Figure 2.4. Conventional Approach to *β*-Nitroalkynes**

### 2.3.2 Tomioka's Asymmetric Conjugate Addition of Arylalkynes to Nitroolefins

On the other hand, nitroalkenes could be employed as electrophiles to undergo 1,4-addition. For example, Tomioka reported an efficient method to synthesize *β*-nitroalkynes (**2.5c**) asymmetrically with high enantiomeric excess from acetylene (**2.5b**) and nitroolefins (**2.5a**).[9] The diastereoselectivity is controlled by the work-up: with saturated ammonium chloride quenching, the reaction favors the trans product; whereas with acetic acid quenching, the reaction favors the cis product. The enantioselectivity was predicted according to Noyori and Oguni' model (**2.5d**) in the enantioselective addition of diorganozincs to aldehydes catalyzed by *β*-amino alcohol. The dinuclear zinc

complex coordinates to the oxygen of the nitro group and the terminal end of the alkynes. Then, the alkynyl group undergoes conjugate addition at the double bond. However, this method is limited to simple nitrooelfins, such as 1-nitrocyclohexene or 1-nitrohexene, etc. and terminal aromatic alkynes (Figure 2.5).

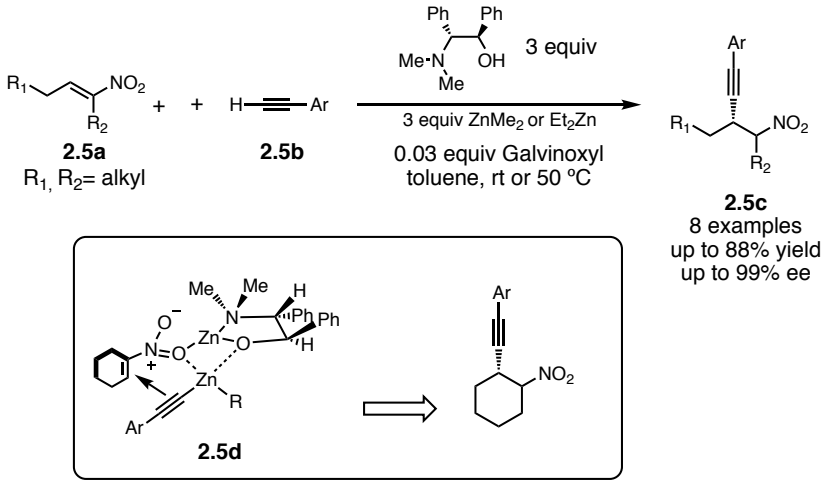



**Figure 2.5. Tomioka's Synthesis of Enantioenriched *β*-Nitroalkynes**

### 2.3.3 Alexakis' Asymmetric Conjugate Addition of Organometallic Reagents to Nitroenynes

Likewise, Alexakis developed a technique to prepare *β*-nitroalkynes enantioselectively under a copper catalyst system from nitroenynes and organometallic reagents.[10] By employing trialkylaluminum, the regioselectivity of *β*-nitroalkynes over *β*-nitroallenes and high enantiomeric excess are achieved. The use of larger nucleophiles is detrimental to the enantioselectivity: for example, there is a complete loss of asymmetric induction when using

triisobutylaluminum. Thus, this work is limited to simple nitroenynes and only generates new propargylic methyl-bearing stereocenters (Figure 2.6).

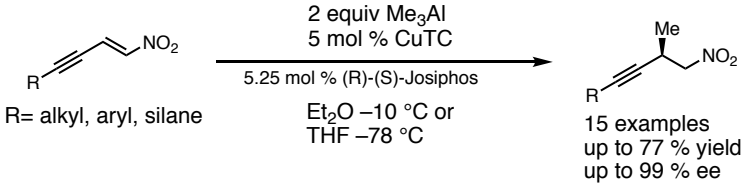



**Figure 2.6. Alexakis' Synthesis of Enantioenriched *β*-Nitroalkynes**

## 2.4 Proposed Method for the Synthesis of Homopropargylic Nitroalkanes

Tomioka and Alexakis formed substituted homopropargylic nitroalkanes both using conjugate-addition-type approaches (see Figure 2.5 and 2.6). In contrast, our proposed method could install new C–C bonds on the nitro-bearing carbon. If secondary propargylic halides are able to participate in this reaction, *α, β*-substituted homopropargylic nitroalkanes would be formed. This section outlines the process of optimization of the reaction conditions and investigation of the substrate scope.

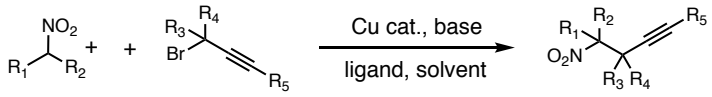



**Figure 2.7: Copper Catalyzed Propargylation of Nitroalkanes**

### 2.4.1 Significance of Homopropargylic Nitroalkanes

As a demonstration of the synthetic utility of homopropargylic nitroalkanes, trisubstituted pyrroles could be generated through downstream functionalization. Pyrroles play a crucial role in medicinal chemistry and organic

synthesis. They are commonly used as synthetic intermediates in the synthesis of pharmaceuticals, agrochemicals, dyes, perfumes, and more complex macrocycles. Many pyrrole-bearing natural products, such as porphyrins of heme and bile pigments, have significant biological characteristics.[6]

In 2011, Dixon reported a method to synthesize 2,5-disubstituted pyrroles using gold catalysis in a one pot reaction (Figure 2.8). Protected imine (**2.8a**) and homopropargylic nitroalkane (**2.8b**) underwent a nitro-Mannich/hydroamination to afford the targeted disubstituted pyrrole (**2.8c**) in good yield.[7] We envision that the more substituted *β*-nitroalkyne products from our proposed method could be further transformed into tri-substituted pyrroles (**2.8d**) using this method.

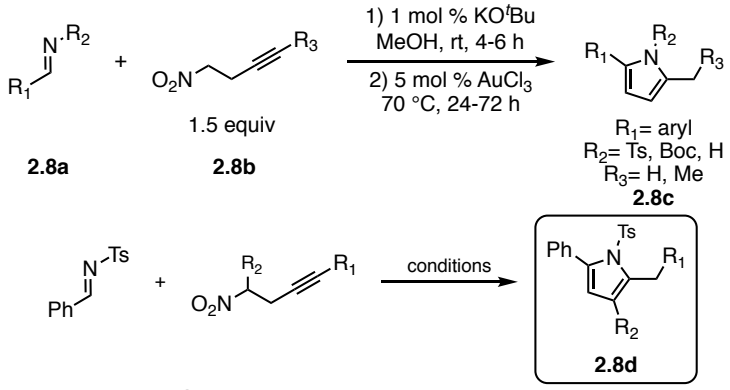



**Figure 2.8. Synthesis of Pyrroles**

### 2.5 Preliminary Results

A former colleague, Dr. Kirk Shimkin, first started to investigate the proposed reaction with 20 mol % CuBr and 25 mol % 1,3-diketimine ligand (**2.9b**) as catalyst since this was optimal reaction conditions for the previous reported

reactions. He observed the formation of $\beta$-nitroalkyne product (**2.9a**) in a modest 30% yield. He then switched to a different class of ligands, cyclohexyl diamine ligands (**2.9c**), and obtained an improved yield of 65% with limited optimization (Figure 2.9).

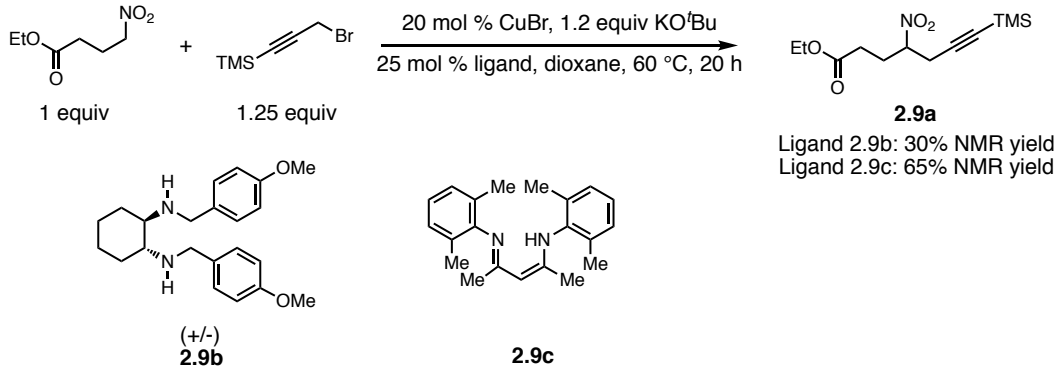



**Figure 2.9 Dr. Shimkin's Preliminary Result**

Then Raphael Kim investigated the effect of a variety of ligands, along with different parameters to improve upon the reactivity. He successfully increased the yield to 70-75% with Ligand **L1** (Figure 2.10). I then joined the project with Kim and we focused on optimizing the reaction conditions. Although chiral ligands were investigated, only minimal enantiomeric excess was observed.

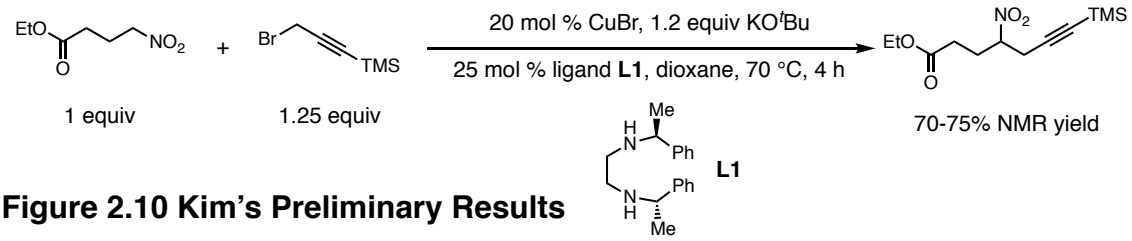
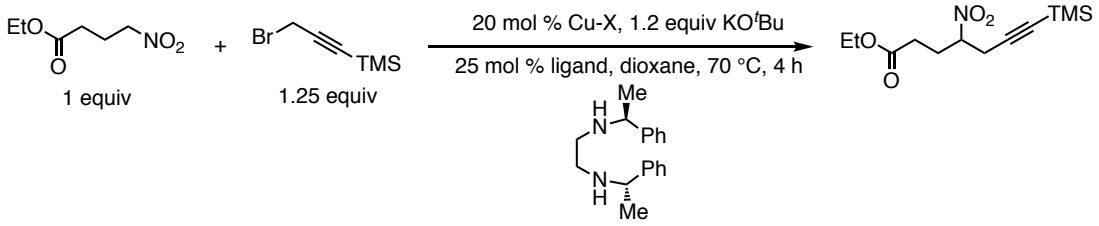



**Figure 2.10 Kim's Preliminary Results**

### 2.6 Optimization of Reaction Conditions for 3-Bromopropynyl-trimethylsilane

According to the proposed mechanism from the benzylation of nitroalkane chemistry, the copper and amine ligand complex would abstract the bromide anion from the propargylic bromide to form the propargylic radical.[8] Therefore, I first studied the effect of different copper sources on the reactivity. Table 1 shows that CuCl and CuBr gave similar yields, whereas CuI reduced the yield to 60%. There was no aldehyde formed in any cases, indicating that *C*-alkylation was favored over *O*-alkylation. We decided to use CuBr as the catalyst since it performed well in the reaction.

**Table 1. Effects of Different Copper Sources**




| Entry | Copper Source | Yield (%) |
|---|---|---|
| 1 | CuCl | 75 |
| 2 | CuBr | 75 |
| 3 | CuI | 60 |

%yield was determined via $^1$H NMR against internal standard TMB

I then screened different solvent concentrations. The more concentrated the reaction became, the lower the yield was (entry 5-6, Table 2). Inefficient stirring of the slurry mixture was likely the cause of this lowered reactivity. Conversely, making the reaction more dilute also did not improve the yield significantly (entry 1-2, Table 2). The concentration of 0.2 M using dioxane as solvent was selected for further optimization.

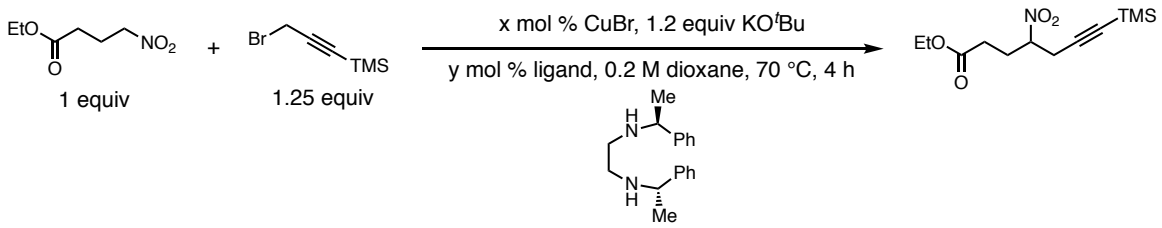
**Table 2. Effects of Solvent Concentrations**

| Entry | Solvent Concentration (M) | Yield (%) |
|---|---|---|
| 1 | 0.08 | 75 |
| 2 | 0.13 | 78 |
| 3 | 0.17 | 77 |
| 4 | 0.20 | 76 |
| 5 | 0.25 | 71 |
| 6 | 0.33 | 68 |

%yield was determined via $^{1}$H NMR against internal standard TMB

Next, I investigated the catalyst loading by maintaining the ratio between CuBr and ligand 1 to 1.25 and changing the amount (Table 3). I observed a decrease in yield to 23% when I only added 5 mol % CuBr. However, using 10 mol % CuBr resulted in a reproducible yield of 72%. At the same time, increasing the catalyst loading to 20 mol % CuBr did not improve the reactivity. I was able to obtain reproducible results for catalyst loading: 10 mol % CuBr and 12.5 mol % ligand.

**Table 3. Catalyst Loading Screening**




| Entry | Cu (mol %) | Ligand (mol %) | Yield (%) |
|---|---|---|---|
| 1 | 20 | 25 | 72 |
| 2 | 15 | 18.75 | 69 |
| 3 | 10 | 12.5 | 72 |
| 3 | 5 | 6.25 | 23 |

%yield was determined via $^1$H NMR
against internal standard TMB

After testing different reaction parameters and still obtaining sub-optimal results, I synthesized some new ligands to perform additional ligand screening. The ligands were prepared either by reductive amination or alkylation (Figure 2.11). Ligands **L5** and **L7** were synthesized via reductive amination by Kim and myself, respectively. We started with two equivalents of aldehyde and ethylene diamine to generate the Schiff-base adduct, which was then reduced to amine using $NaBH_4$. I prepared ligand **L1** while Kim synthesized ligand **L2** via alkylation from 1,2-dibromoethane and a chiral amine.

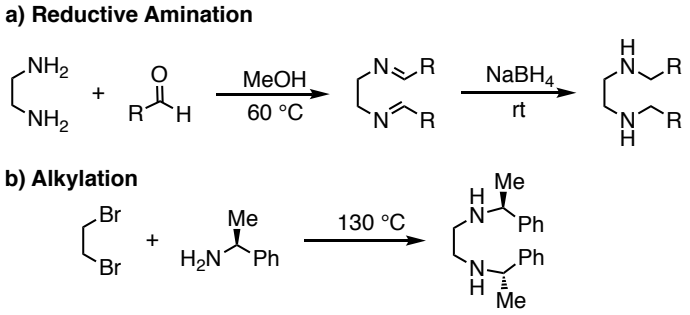



**Figure 2.11. Synthesis of Ligands**

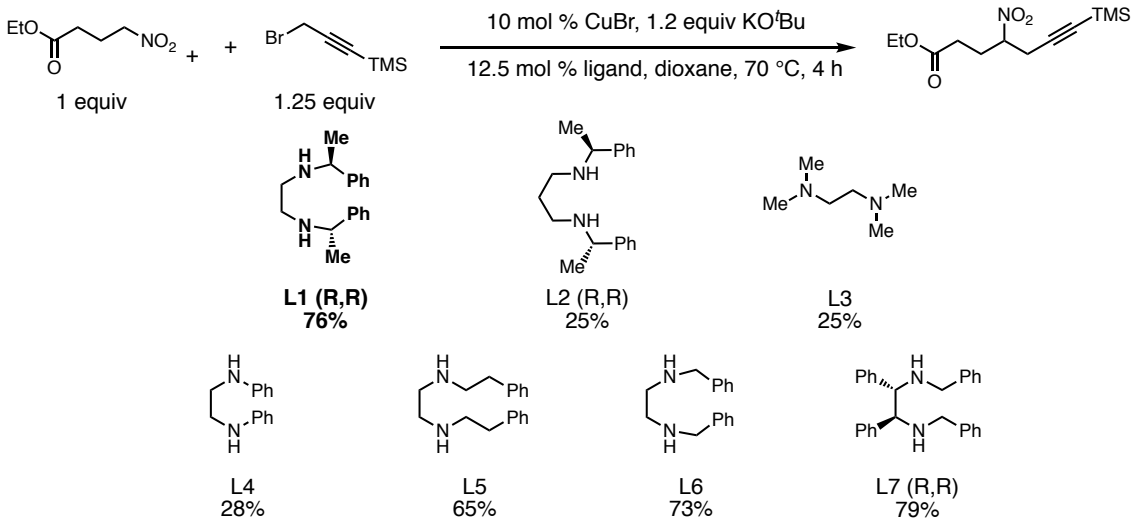
I started with ligand **L1** and wanted to study the effects of the steric and electronic properties on the ligand **L2** (Figure 2.12). Lengthening the linker chain on the diamine backbone (**L2**) negatively affected the yield of the propargylation reaction (25%). This indicates that tight binding of the ligand to the copper center is likely important in the reaction.

The Watson group's previous reports on nitroalkanes suggested the importance of the protic N–H bond, as the electron rich Cu(I)-amido species were formed by deprotonation of ligand.[8] This was also observed in our system as tetramethylethylene-diamine **L3** was ineffective in improving the reactivity.

Knowing that the ethylene backbone and N–H bonds were essential, I wanted to see if the aniline version (phenyl groups directly on the nitrogen) would affect the yield (Figure 2.12). The aniline derivative ligand **L4** was detrimental to the reactivity. This is likely a result of the weaker sigma-donor ability of the aniline group, compared to the dialkyl amine (**L1**).

Lengthening the alkyl chains also slightly decreased the yield to 65% (**L5**). I also tested ligand **L6** and obtained a good yield 73%. Then, I added the bulky phenyl groups on the diamine backbone and the yield slightly went up to 79%.

Among this set of ligands, ligand **L1**, **L6**, and **L7** provided the best reactivity. However, as **L1** and **L7** require several steps to prepared, and no enantioselectivity was observed in the reaction using these complex chiral ligands. Therefore, the commercially available ligand **L6** offer the best combination of practicality and efficiency, and was selected for further study.




*% yield was determined via $^1$H NMR against internal standard TMB*

**Figure 2.12. Ligand Screening**

### 2.7 Optimization of Reaction Conditions for 1-Bromobutyne

To see if the current conditions are general for other propargylic bromide electrophiles, I switched the substrate from 3-bromopropynyl-trimethylsilane to 1-bromobutyne. Interestingly, I observed the formation of an initially unexpected product, *β*-nitroallene (**B**, Figure 2.13). Kim characterized the structure by NMR experiments, including $^{1}$H-NMR, $^{13}$C-NMR, HSQC, HMBC, and COSY.

I did not observe the formation of allene from 3-bromopropynyl-trimethylsilane likely because the trimethylsilyl group is too bulky to allow the formation of allene. I hypothesized that the mechanism for the formation of allene could be either a radical or 2-electron pathway.

From the Watson group's previous reports,[8] mechanistically they believe that the alkyl radical is generated, then rapidly undergoes cross-coupling with nitronate anion (Figure 2.13a).[8]

On the other hand, for a two-electron argument, the small methyl group allows the attack of a nucleophilic nitronate anion, therefore allowing the reaction to follow an $S_N2$' mechanism to afford *β*-nitroallene (Figre 2.13b).

Last, analogous to the propargyl Claisen rearrangement, another potential mechanistic pathway would proceed by *O*-alkylation, followed by [3,3] sigmatropic rearrangement to afford the competitive allene by-product (Figure 2.13c).

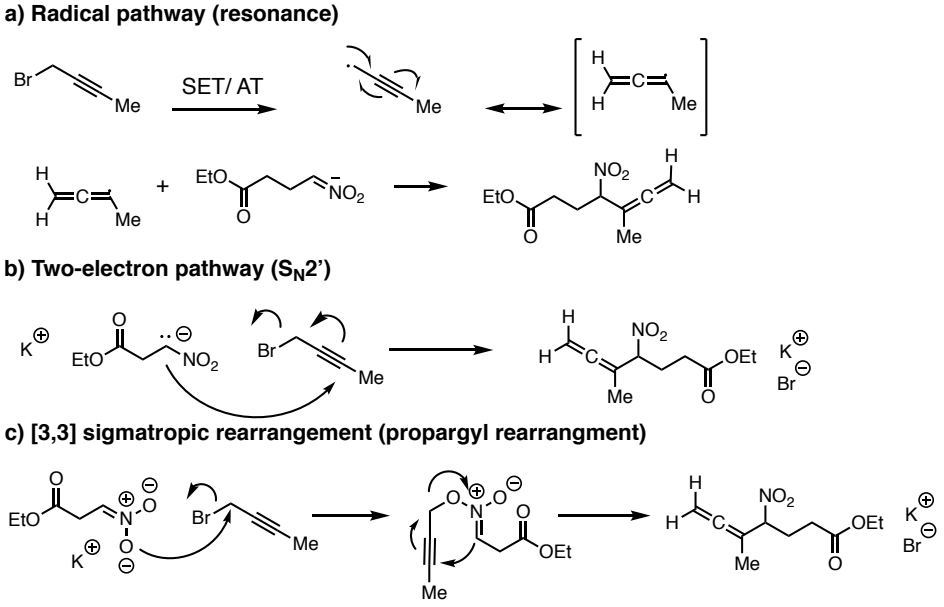
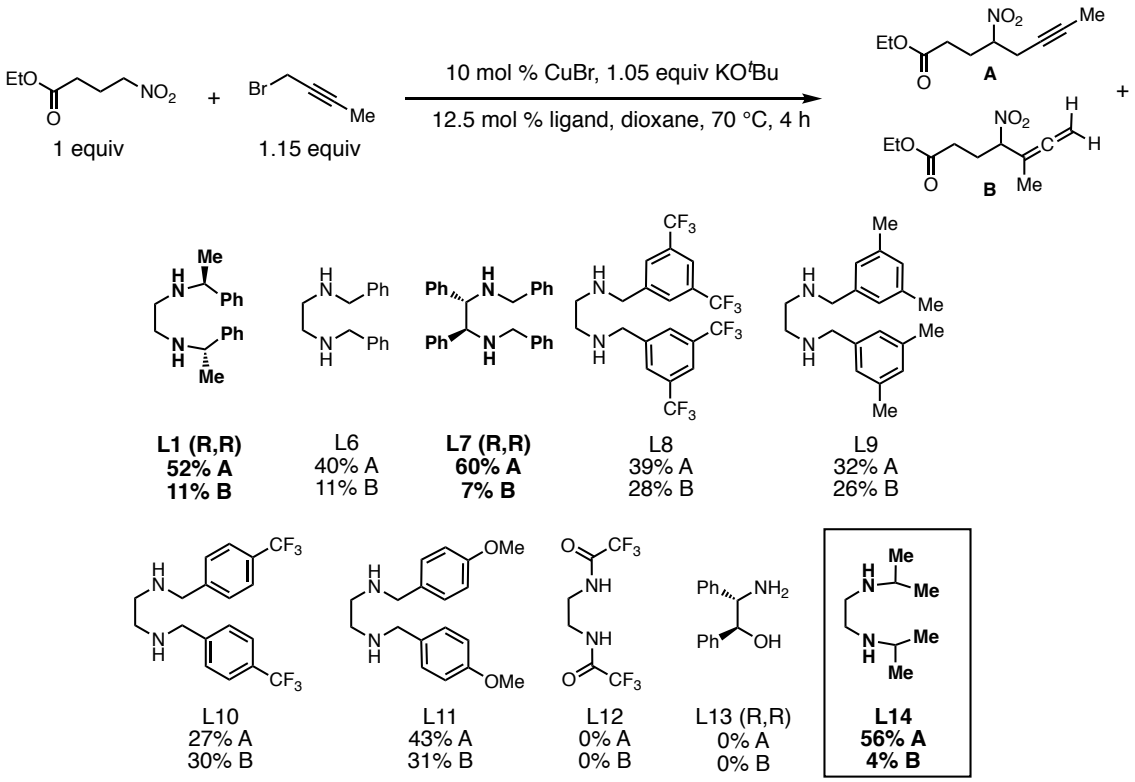



**Figure 2.13 Proposed Mechanism of the Allene's Formation**

Our next goal was to increase the yield of homopropargylic nitroalkanes and suppress the formation of this allene by-product with the methyl-substituted starting material. We first re-investigated the effect of ligands on the reactivity (Figure 2.14). Ligands that were previously optimal for 3-bromopropynyl-trimethylsilane such as **L1** and **L7** provided high yields (50-60%), whereas **L6** provided a less unfruitful result (40%).




*% yield was determined via $^1$H NMR against internal standard TMB (A/B%)*

**Figure 2.14 Ligand Screenings**

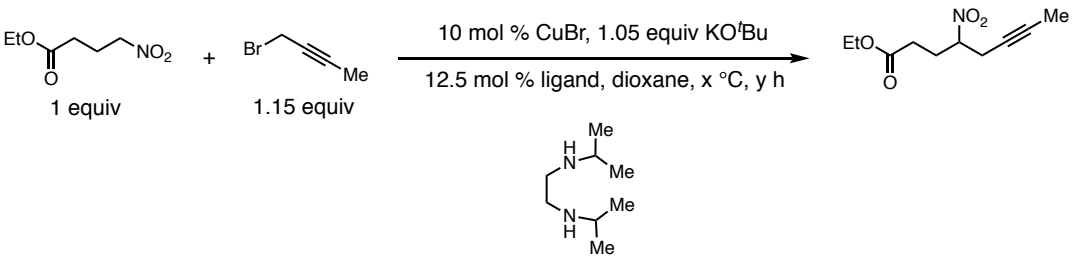
To further investigate the ligand effects in this more complex reaction setting, I then added substituents in either ortho- or para- position on the phenyl rings to examine the electronic and steric effects of the aromatic groups (Figure 2.14). Both electron withdrawing group (–$CF_3$) (**L8**, **L10**) and electron donating group (–Me **L9** or –OMe **L11**) in the 3,5 meta and para position reduced the yield of *β*-nitroalkyne from 50% to 30-40%, but enhanced the formation of allene isomer from 11% to 30%. When I removed all the substituents off the phenyl rings (**L6**), the yield for *β*- nitroallene was 11%. From those results, I concluded that adding the substituents slightly promoted the formation of allene.

Other classes of ligands were also examined at this point. Ligands bearing electron withdrawing trifluoroacetamide groups (**L12**) resulted in no product. Likewise, an electron rich, chiral ligand **L13**—featuring a complete different scaffold—inspired by Yamashita's paper was also tested and did not produce the desired product in this system (Figure 2.14).[9]

At the same time, Kim was looking at ligands with alkyl branches rather than benzylic groups on the nitrogen and he found that the isopropyl group worked the best in this case. Gratifyingly, a commercially available ligand (**L14**) demonstrated an impactful improvement: 56% of a desired product with only 4% of the allene byproduct (Figure 2.14). Evidently, the increased steric bulk of this branched ligand suppress the pathway leading the allenyl product.

After finding an optimal ligand, I ran a series of reactions and found out that the reaction could be run at ambient temperature, and at 70 °C the reaction was quite fast, reaching completion in 15 minutes. I obtained a consistent yield at room temperature with a 4-hour reaction time, showing that this chemistry was robust (Table 4).

**Table 4. Reaction Temperature and Time Screening**




| Entry | Tempt (°C) | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | 70 | 0.25 | 49 |
| 2 | 70 | 4 | 56 |
| 3 | 25 | 0.25 | 40 |
| 4 | 25 | 1 | 45 |
| 5 | 25 | 4 | 56 |

%yield was determined via $^1$H NMR
against internal standard TMB

Next, I investigated different bases (Table 5). Both trimethylsilanolate (entry 1-2) and carbonate (entry 3-4) bases failed to improve the reactivity. However, the *tert*-butoxide bases did give better reactivity. Among different *tert*-butoxide bases, KO$^t$Bu had the best performance (52%), in contrast to a low yield of NaO$^t$Bu (4%) or no conversion to product with LiO$^t$Bu (0%). This was due to the poor solubility of lithium and sodium salt; whereas the slightly soluble potassium salt allowed for a small concentration of nitronate anion in the heterogeneous solution which can perform radical-anion coupling, generating products.

Among –O$^t$Bu, –OEt, and –OMe anions, –O$^t$Bu worked the best because it is bulkier and less nucleophilic compared to the other two anions. KO$^t$Bu is also a stronger base. Next, KHMDS is a strong, non-nucleophilic base that could deprotonate the N–H bond, hence, provided a 45% yield. In contrast, the bulkier and weaker DBU base did not work. For practicality, KO$^t$Bu was selected for further use (Table 5).

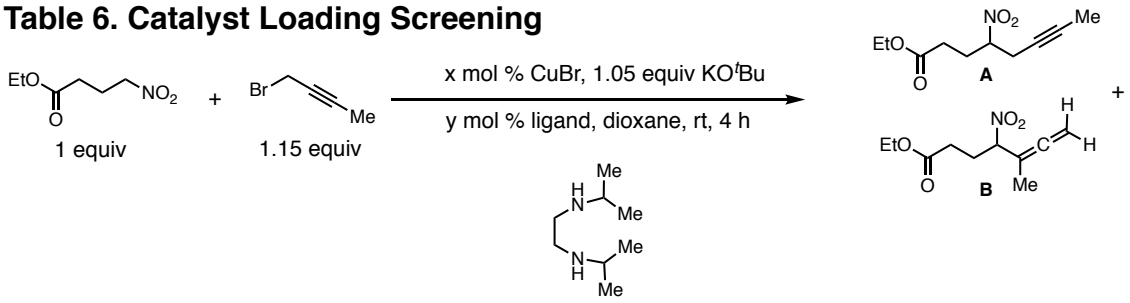
**Table 5. Bases Screening**

| Entry | Bases | Yield (%) |
|---|---|---|
| 1 | NaOTMS | 0 |
| 2 | KOTMS | 16 |
| 3 | $Cs_2CO_3$ | 9 |
| 4 | $K_2CO_3$ | 10 |
| 5 | LiO$^t$Bu | 0 |
| 6 | NaO$^t$Bu | 4 |
| 7 | KO$^t$Bu | 52 |
| 8 | KOMe | 35 |
| 9 | NaOEt | 6 |
| 10 | KHMDS | 45 |
| 11 | DBU | 0 |

%yield was determined via $^1$H NMR against internal standard TMB

I hypothesized that the ligands were getting alkylated and deactivated by propargylic bromide, hence, an excess of the ligand was required (Table 6). Among all the ratios between ligand and CuBr, the result of 1:3 (entry 4) or 1:4 (entry 5) ratio of CuBr and ligand provided minimal formation of allene isomer. However, the yields were low. Then, Kim repeated the reaction with the same ratio but increased the amount of CuBr to 10 mol %, he obtained 53% of *β*-nitroalkynes and suppressed the formation of *β*-nitroallenes to 1% (entry 9).

**Table 6. Catalyst Loading Screening**

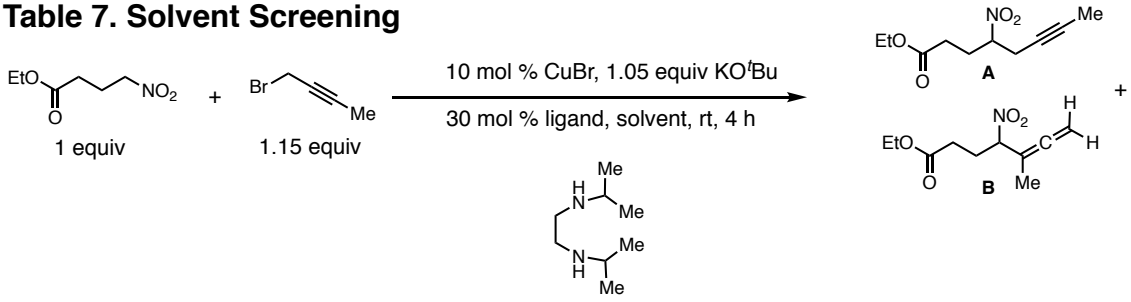



| Entry | CuBr (mol %) | Ligand (mol %) | A (% yield) | B (% yield) |
|---|---|---|---|---|
| 1 | 5 | 6.25 | 50 | 9 |
| 2 | 5 | 7.5 | 26 | 3 |
| 3 | 5 | 10 | 35 | 2 |
| 4 | 5 | 15 | 37 | 2 |
| 5 | 5 | 20 | 52 | 5 |
| 6 | 10 | 12.5 | 51 | 5 |
| 7 | 10 | 15 | 55 | 7 |
| 8 | 10 | 20 | 50 | 4 |
| 9 | 10 | 30 | 53 | 1 |
| 10 | 10 | 40 | 52 | 0 |

%yield was determined via $^1$H NMR
against internal standard TMB

Lastly, I screened a variety of solvents (Table 7). Nonpolar solvents like toluene, hexanes, or dioxane gave the best reactivity, which was consistent with our previous report. Increasing the polarity of the solvent (EtOAc) also increased the solvation of the nucleophile. Dipole-dipole interaction between solvent and nucleophile would take place, hence, deterred the reactivity. However, DMF and DMSO did not provide any reactivity in this propargylation reaction.

**Table 7. Solvent Screening**



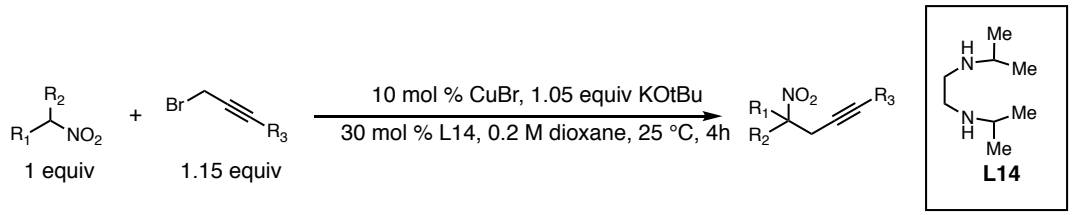

| Entry | Solvent | A (% yield) | B (% yield) |
|---|---|---|---|
| 1 | Toluene | 47 | 0 |
| 2 | Hexanes | 30 | 0 |
| 3 | Dioxane | 53 | 1 |
| 4 | EtOAc | 0 | 1 |
| 5 | DMF | 0 | 0 |
| 6 | DMSO | 0 | 0 |

%yield was determined via $^1$H NMR
against internal standard TMB

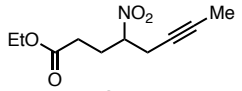
### 2.8 Scope of Homopropargylic Nitroalkanes

With the optimal condition developed, Kim and I then focused on investigating the substrate scope. As shown in Figure 2.15, this copper catalyzed propargylation of nitroalkanes tolerates a wide range of functional groups. Primary nitroalkanes react with primary propargylic bromides to form the homopropargylic nitroalkanes in good yield (**S1-S4**). In addition, secondary nitroalkanes provide good to excellent yield (**S5-S8**) since the double-alkylation is not possible. A good range of biologically relevant heterocycles, such as thiophene (**S5**) and 1,3-benzodioxole (**S5,S6**) also perform well. However, the reaction with secondary propargylic bromides requires a longer reaction time and/or higher concentration of catalyst loading CuBr to afford a good yield (50%). Furthermore, a broad scope of other functional group are well tolerated. These include esters (**S1**), nitriles (**S2, S3**), substituted benzene rings (**S4, S7, S8**), ketones (**S8**), protected amine (**S9**), and silyl protecting group (**S2, S6, S9**). Alkyl chlorides (**S10**) were also unaffected, allowing for further transformation.

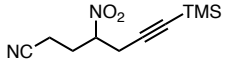
One limitation is that the terminal alkynes (**S11, S12**) did not work in this system. The copper acetylide (analogous to Sonogashira cross coupling[11]), might be forming *in situ*, hence, preventing the copper from binding to the ligand to initiate the desired reaction (Figure 2.15).



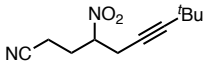

**Primary nitroalkanes and primary propargylic bromides**



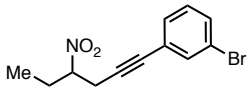
**S1**
**48%**



**S2**
**40%**[b]

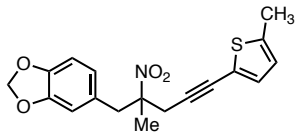


**S3**
**17%**

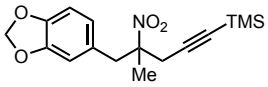


**S4**
**74%**[a]

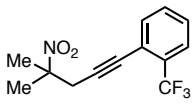
**Secondary nitroalkanes and primary propargylic bromides**



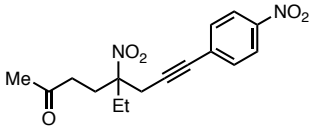
**S5**
**58%**



**S6**
**87%**

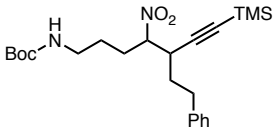


**S7**
**87%**

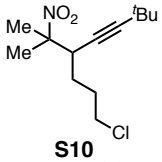


**S8**
**78%**

**Primary/ secondary nitroalkanes and secondary propargylic bromides**

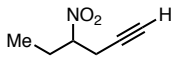


**S9**
**50%**[b]
**dr 49:51**

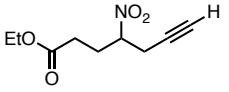


**S10**
**49%**[a,c]

**One exception: terminal alkynes**



**S11**
**0%**



**S12**
**0%**

[a] Synthesized and isolated by Kim, [b] 20 mol % CuBr, 20 h, [c] 20 h

## Figure 2.15 Scope of Propargylation of Nitroalkanes

## 2.9 Conclusion

In conclusion, we have developed a protocol to perform propargylation of nitroalkanes using a commercially available *N,N*-diisopropylethane-1,2-diamine ligand and CuBr catalyst. In contrast to the previous reports on the synthesis of nitroalkanes, 1,3-diketimine ligand was not well-performed in this chemistry. Through a major change in ligand structure, this new catalyst system allows great access to more complex homopropargylic nitroalkanes (*β*-nitroalkynes). This method also tolerates a wide range of functional groups as well as biologically relevant heterocycles. In addition, an interesting by-product *β*-nitroallene is discovered.

One of the significant future goals of this chemistry is the demonstration of the synthetic application of *β*-nitroalkynes. For examples, secondary *β*-nitroalkynes could be transformed into 2,3,5-trisubstituted pyrroles by the nitro-Mannich reaction, followed by a hydroamination via gold catalyst (Figure 2.16a).[3] Tertiary *β*-nitroalkynes, on the other hand, can be converted to 2,3-dihydro-pyrroles by a reduction of nitro group to amine, then an amine protection, followed by a cyclization (Figure 2.16b).

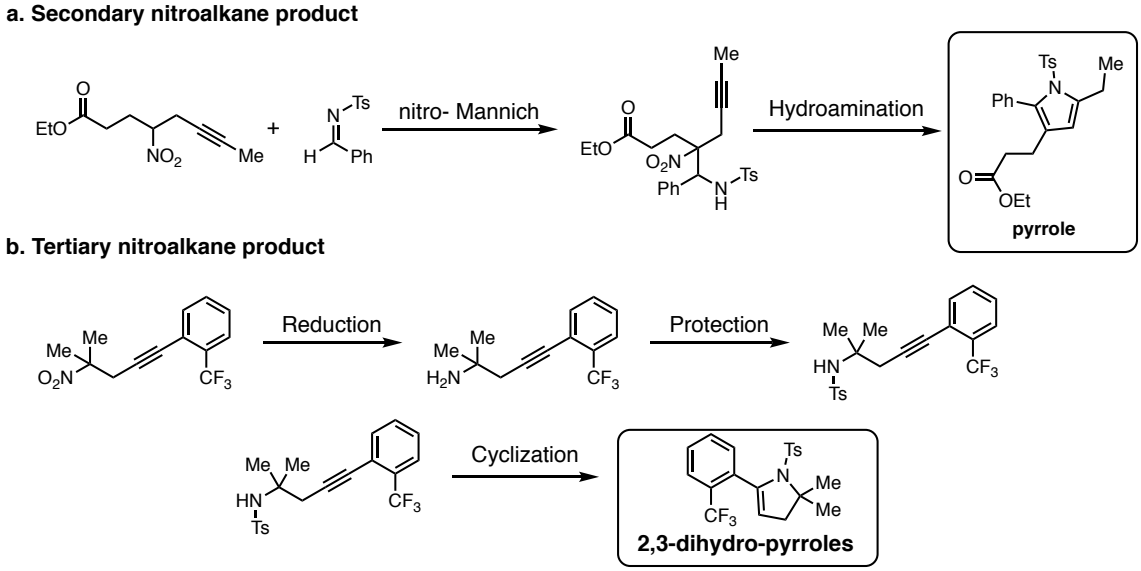



**Figure 2.16 Future Direction–Proposed Downstream Functionalization**

## 2.10 Experimental section

### 2.10.1 General Experimental Details

Dioxane, dichloromethane, tetrahydrofuran, diethyl ether, toluene, hexanes, ethyl acetate, dimethyl formamide, and dimethyl sulfoxide were dried on alumina according to a published procedure.[12] Copper bromide, copper iodide, copper (I) chloride, sodium trimethylsilanolate, potassium trimethylsilanolate, cesium carbonate, potassium carbonate, lithium tert-butoxide, potassium tert-butoxide, potassium methoxide, and sodium ethoxide were purchased commercially; the bulk was stored in a $N_2$ filled glovebox. Potassium bis(trimethylsilyl)amide, 1,8-diazabicyclo[5.4.0]undec-7-ene, tetramethylethylenediamine (TMEDA), 1,2-diphenylethane-1,2-diamine, 1,2-dibenzylethane-1,2-diamine, and 1,2-diisopropylethane-1,2-diamine were purchased commercially; the reagents were degassed by bubbling nitrogen in for 30 min, and stored in a $N_2$ filled glovebox. Copper bromide, potassium tert-butoxide, and 1,2-diisopropylethane-1,2-diamine were removed from the glovebox and stored in a desiccator under air for up to two weeks prior to use. Anhydrous glassware was either dried in a gravity oven at 150 °C overnight or flame-dried under vacuum, and then cooled to room temperature under vacuum before use. (*R*,*R*)-*N,N′*-dibenzyl-1,2-diphenylethane-1,2-diamine,[13] *N,N′*-bis(trifluoroacetyl)ethylenediamine,[14] 4,4-dimethylpent-2-yn-1-ol,[15] 1-bromo-4,4-dimethylpent-2-yne,[16] 3-(4-nitrophenyl)prop-2-yn-1-ol,[17] 1-(3-bromoprop-1-yn-1-yl)-4-nitrobenzene,[18] (*E*)-5-(2-nitroprop-1-en-1-yl)benzo[*d*][1,3]dioxole,[19] ethyl 4-nitrobutanoate,[22] *tert*-butyl (4-hydroxybutyl)carbamate,[23] tert-butyl (4-iodobutyl)carbamate,[24] 6-nitrohex-1-ene,[25] (*E*)-5-(2-

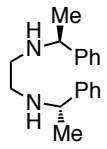
nitrovinyl)benzo[*d*][1,3]dioxole,[26] 5-(2-nitroethyl)benzo[*d*][1,3]dioxole,[27] 4-chlorobutanal,[28] 1-chloro-7,7-dimethyloct-5-yn-4-ol,[29] 5-bromo-8-chloro-2,2-dimethyloct-3-yne[29] were synthesized according to published procedures. All other reagents and chemicals were purchased from commercial suppliers at reagent grade or higher purity (typically >95%) and used as received. The reaction optimization was set up in the glovebox ($N_2$ atmosphere) on a 250 µm scale in 1-dram vials. The vials were sealed with caps, taken outside the glovebox and stirred in an oil bath at a designated time and temperature. All NMR chemical yields were determined using 1,3,5-trimethoxybenzene as an internal standard. All other reactions were set up outside the glovebox using standard Schlenk technique. Reactions were heated with stirring in temperature-controlled oil baths. “Double manifold” refers to a standard Schlenk-line gas manifold equipped with $N_2$ and vacuum (ca. 0.1 mm Hg).

**2.10.2 Instrumentation and Chromatography:**

400 MHz $^{1}$H, 101 MHz $^{13}$C, and 376 MHz $^{19}$F NMR spectra were obtained on a 400 MHz FT-NMR spectrometer equipped with a Bruker CryoPlatform. 600 MHz $^{1}$H, 151 MHz $^{13}$C, 565 MHz $^{19}$F, and 119 MHz $^{29}$Si spectra were obtained on a 600 MHz FT-NMR spectrometer equipped with a Bruker SMART probe. All samples were analyzed in the indicated deutero-solvent and were recorded at ambient temperatures. Chemical shifts are reported in ppm. $^{1}$H NMR spectra were calibrated using the residual protio-signal in deutero-solvents as a standard. $^{13}$C NMR spectra were calibrated using the deutero-solvent as a standard.[30] IR spectra were recorded on a Nicolet Magma-IR 560 FT-IR spectrometer as thin films on KBr plates. High resolution MS data was obtained

on a Thermo Scientific, Q-Exactive model Orbitrap instrument using electrospray ionization (ESI) or on a Waters GCT Premier spectrometer using chemical ionization (CI) or liquid injection field desorption ionization (LIFDI). Column chromatography was performed with 40-63 μm silica gel with the eluent reported in parentheses. Analytical thin-layer chromatography (TLC) was performed on precoated glass plates and visualized by UV or by staining with potassium permanganate ($KMnO_4$).

### 2.10.3 Synthesis of Ligands




**L1**
Chemical Formula: $C_{18}H_{24}N_2$
Exact Mass: 268.19
Molecular Weight: 268.40

**(L1)** Ligand **L1** was synthesized by the previously published procedure.[31] 250 mL oven-dried round bottom flask equipped with a stirbar and rubber septum was cooled under a stream of nitrogen. The septum was removed from the flask, (+)-(*R*)-*α*-phenylethylamine (10 mL, 80 mmol) was added under air, the septum was replaced, and the flask was sparged with nitrogen for ca. 5 min. Then, 1,2-dibromoethane (1.73 mL, 20 mmol) was added via syringe and the reaction was stirred at 130 °C for 30 min. Then the flask was cooled at rt, the mixture was quenched with NaOH solution (30 mL, 50 %, aqueous). The resulting biphasic mixture was stirred for 5 min, before being poured into a separatory funnel and rinsed with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by simple distillation to remove excess amine (60-80 °C, 300 mmHg)

and Kugelrohr distillation (170 °C, 100 mmHg) to afford a light yellow oil. The distilled product was purified by flash silica gel column chromatography (95:5 to 90:10 DCM: MeOH) to afford **L1** (3.7 g, 69%) as colorless oil.

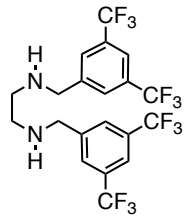
**$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 10H), 3.68 (q, *J* = 6.6 Hz, 2H), 2.55 (dt, *J* = 10.4, 7.6 Hz, 4H), 1.36 (d, *J* = 6.6 Hz, 6H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 146.0, 128.5, 126.9, 126.7, 58.3, 47.5, 24.5.

**FTIR** (thin film, $cm^{-1}$): 3060, 2961, 2826, 1492, 1450, 760, 700.

**HRMS** (ESI) m/z, calcd for $[C_{18}H_{25}N_2]^+$: 269.2012; found: 269.2020

**L1** is a known compound but was not completely characterized in the literature.[31] Hence, fully characterization was reported.



**L8**
Chemical Formula: $C_{20}H_{16}F_{12}N_2$
Exact Mass: 512.11
Molecular Weight: 512.34

(**L8**) Ligand **L8** was synthesized by the modification of a previously published procedure.[32] Ethane-1,2-diamine (1.20 g, 20 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (9.68 g, 40 mmol) were added in ethanol (160 mL) in a 500 mL round bottom flask that was equipped with a stirbar. The reaction mixture was stirred and refluxed at 80 °C for 16 h. Upon the formation of di-Schiff base (monitored by TLC), the reaction was cooled down to rt and the solvent was removed by rotary evaporation to afford white crystals (9.5 g, 94%). The solid product was used without further purification. Next, the imine (7.62 g, 15 mmol) and $NaBH_4$ (1.25 g, 33 mmol) was added in DCM (45 mL) in

a 250 mL round bottom flask. The mixture was stirred for 30 hours at rt. Upon completion of reduction (monitored by TLC), saturated $NaHCO_3$ (30 mL) was added to quench the reaction. The resulting biphasic mixture was stirred for 5 min, before being poured into a separatory funnel and rinsed with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (95:5 to 20:80 hexanes: EtOAc) to afford ligand **L8** as white crystals (6.14 g, 80%).

**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 7.81 (s, 4H), 7.77 (s, 2H), 3.92 (s, 4H), 2.78 (s, 4H).

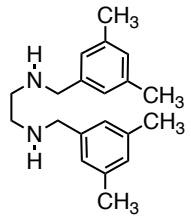
**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 143.3, 131.8 (q, $J$ = 33.3 Hz), 128.2 (d, $J$ = 4.1 Hz), 123.6 (q, $J$= 271.8 Hz), 121.2 – 121.1 (m), 53.12, 49.1.

**$^{19}$F NMR** (565 MHz, $CDCl_3$) $\delta$ –62.87, –62.91.

**FTIR** (thin film, $cm^{-1}$): 3238, 2822, 1381, 1300, 1123, 902, 707.

**HRMS** (ESI) m/z, calcd for $[C_{20}H_{17}N_2F_{12}]^+$: 513.1195; found: 513.1225

**Melting point**: 98–100 °C (DCM).



**L9**
Chemical Formula: $C_{20}H_{28}N_2$
Exact Mass: 296.22
Molecular Weight: 296.46

(**L9**) Ligand **L9** was synthesized by the modification of a previously published procedure.[32] Ethane-1,2-diamine (0.66 g, 11 mmol) and 3,5-dimethylbenzaldehyde (2.94 g, 22 mmol) were added in ethanol (88 mL) in a 250 mL round bottom flask that was equipped with a stirbar. The reaction mixture was

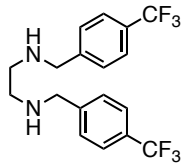
stirred and refluxed at 80 °C for 16 h. Upon the formation of di-Schiff base (monitored by TLC), the reaction was cooled down to rt and the solvent was removed by rotary evaporation to afford white crystals (2.92 g, 90%). The solid product was used without further purification. Next, the imine (2.92 g, 9 mmol) and $NaBH_4$ (0.832 g, 22 mmol) was added in DCM (60 mL) in a 250 mL round bottom flask. The mixture was stirred for 30 hours at rt. Upon completion of reduction (monitored by TLC), saturated $NaHCO_3$ (30 mL) was added to quench the reaction. The resulting biphasic mixture was stirred for 5 min, before being poured into a separatory funnel and rinsed with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (95:5 to 20:80 hexanes: EtOAc) to afford ligand **L9** as clear oil (2.14 g, 80%).

**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 6.93 (s, 4H), 6.88 (s, 2H), 3.70 (s, 4H), 2.77 (s, 4H), 2.30 (s, 12H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 140.5, 138.0, 128.6, 126.1, 54.0, 49.0, 21.4.

**FTIR** (thin film, $cm^{-1}$): 3011, 2916, 1606, 1460, 844, 692.

**HRMS** (ESI) m/z, calcd for $[C_{20}H_{29}N_2]^+$: 297.2325; found: 297.2335.



**L10**
Chemical Formula: $C_{18}H_{18}F_6N_2$
Exact Mass: 376.13
Molecular Weight: 376.35

(**L10**) Ligand (L10) was synthesized by modification of a previously published procedure.[32] Ethane-1,2-diamine (0.6 g, 10 mmol) and 4-(trifluoromethyl) benzaldehyde (3.48 g, 20 mmol) were added in ethanol (80 mL) in a 250 mL round bottome flask. The reaction mixture was stirred and refluxed at 80 °C for 16 h. Upon the formation of di-Schiff base (monitored by TLC), the reaction was cooled down at rt and concentrated *in vacuo* to afford white crystals (3.0 g, 81%). The solid product was used without further purification. Next, the imine (2.98 g, 8 mmol) and $NaBH_4$ (0.67 g, 17.6 mmol) was added in DCM (48 mL) in a 250 mL round bottom flask. The mixture was stirred for 30 hours at rt. Upon completion of reduction (monitored by TLC), saturated $NaHCO_3$ (30 mL) was added to quench the reaction. The resulting biphasic mixture was stirred for 5 min, before being poured into a separatory funnel and rinsed with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (95:5 to 20:80 hexanes: EtOAc) to afford ligand (**L10**) as clear oil (2.41 g, 80%).

**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 7.57 (d, $J$ = 7.9 Hz, 4H), 7.43 (d, $J$ = 7.9 Hz, 4H), 3.84 (s, 4H), 2.76 (s, 4H).

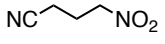
**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 144.8, 129.4 (q, $J$ = 32.4 Hz), 128.4, 125.4 (q, $J$ = 3.9 Hz), 124.4 (q, J = 273.3 Hz), 53.5, 49.0.

**$^{19}$F NMR (565 MHz, $CDCl_3$)** $\delta$ –62.42.

**FTIR** (thin film, $cm^{-1}$): 3298, 3105, 1702, 1564, 1182, 899, 712.

**HRMS** (ESI) m/z, calcd for $[C_{18}H_{19}N_2F_6]^+$: 377.1447; found: 377.1451

### 2.10.4 Synthesis of Nitroalkanes Starting Materials



**N2**
Chemical Formula: $C_4H_6N_2O_2$
Exact Mass: 114.04
Molecular Weight: 114.10

(**N2**) 4-nitrobutanenitrile was prepared according to the literature procedure.[33] Using a 250 mL round bottom flask equipped with a stirbar, DBU (3.0 mL, 20 mmol) was added dropwise by a syringe into a solution of nitromethane (54 mL, 500 mmol) in DCM (50 mL) at –25 °C. After stirring the reaction at –25 °C for 20 min, a solution of acrylonitrile (6.6 mL, 100 mmol) in DCM (10 mL) was added dropwise by a syringe at –25 °C. Then, the reaction was allowed to cool down at 0 °C and was run overnight. Upon completion of the conjugate addition (monitored by TLC), a solution of $NaHSO_4.H_2O$ (10 g in 30 mL $H_2O$) was added to quench the reaction. The resulting biphasic mixture was stirred for 5 min, before being poured into a separatory funnel and rinsed with DCM (10 mL). The aqueous layer was extracted with DCM (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (75:25 to 70:30 hexanes: $Et_2O$) to afford 4-nitrobutanenitrile (**N2**) as clear oil (2.88 g, 25%).

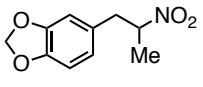
**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 4.60 – 4.49 (m, 2H), 2.58 (t, $J$ = 7.0 Hz, 2H), 2.37 (p, $J$ = 6.8 Hz, 2H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 117.1, 73.0, 23.2, 14.9.

**FTIR** (thin film, $cm^{-1}$): 2956, 2251, 1557, 1386, 1363, 617.

**HRMS** (ESI) m/z, calcd for $[C_4H_7N_2O_2]^+$: 115.0502; found: 115.0505

**N2** is a known compound but was not completely characterized in the literature.[33] Hence, fully characterization was reported.




**N5**
Chemical Formula: $C_{10}H_{11}NO_4$
Exact Mass: 209.07
Molecular Weight: 209.20

(**N5**) 5-(2-nitropropyl)benzo[*d*][1,3]dioxole was prepared according to the literature procedure.[27] Using a 1000 mL round bottom flask equipped with a stirbar, a yellow solid nitro styrene (*E*)-5-(2-nitroprop-1-en-1-yl)benzo[*d*][1,3]dioxole (5.2 g, 25 mmol) was dissolved in a solution of isopropanol (75 mL, 0.33 M) and chloroform (400 mL, 0.063 M) at rt. After 15 min of stirring, silica gel (75 g, 40–63 μm, Baker) was added to the solution, followed by the addition of $NaBH_4$ in 4 portions over a period of 30 min at rt. Upon completion of the reduction of nitro styrene (monitored by TLC, yellow mixture turned to cloudy white mixture), a solution of HCl (30 mL, 1 M, aqueous) was added to quench the reaction. The resulting biphasic mixture was stirred for 5 min, before being poured into a separatory funnel and rinsed with DCM (10 mL). The aqueous layer was extracted with DCM (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (90:10 to 80:20 hexanes: EtOAc) to afford 5-(2-nitropropyl)benzo[*d*][1,3]dioxole (**N5**) as clear oil (4.5 g, 86%).

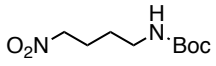
**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 6.73 (d, $J$ = 7.9 Hz, 1H), 6.65 – 6.58 (m, 2H), 5.93 (s, 2H), 4.72 (h, $J$ = 6.8 Hz, 1H), 3.22 (dd, $J$ = 14.1, 7.6 Hz, 1H), 2.92 (dd, $J$ = 14.1, 6.6 Hz, 1H), 1.53 (d, $J$ = 6.6 Hz, 3H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 148.1, 147.0, 129.2, 122.3, 109.3, 108.6, 101.2, 84.7, 41.0, 18.7.

**FTIR** (thin film, $cm^{-1}$): 2898, 1549, 1490, 1444, 1250, 1039, 929.

**HRMS** (ESI) m/z, calcd for $[C_{10}H_{12}NO_4]^+$: 210.0761; found: 210.0891.

**N5** is a known compound but was not completely characterized in the literature.[27] Hence, fully characterization was reported.



**N9**
Chemical Formula: $C_9H_{18}N_2O_4$
Exact Mass: 218.13
Molecular Weight: 218.25

(**N9**) *tert*-butyl (4-nitrobutyl)carbamate was prepared according to the literature procedure.[34] Using a 250 mL round bottom flask equipped with a stirbar, a clear oil *tert*-butyl (4-iodobutyl)carbamate (3.09 g, 10.3 mmol) was dissolved in DMF (21 mL, 0.5 M) at rt. After ca. 5 min of stirring, $NaNO_2$ (2.85 g, 41.2 mmol) was added in the solution under air. Upon completion of the substitution (monitored by TLC), DI water (30 mL) was added to quench the reaction. The resulting biphasic mixture was stirred for 5 min, before being poured into a separatory funnel and rinsed with $Et_2O$ (10 mL). The aqueous layer was extracted with $Et_2O$ (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography (90:10 to 85:15 hexanes: EtOAc) to afford *tert*-butyl (4-nitrobutyl)carbamate (**N9**) as clear oil (0.68 g, 30%).

**$^1$H NMR** (600 MHz, $CDCl_3$) δ 4.67 (s, 1H), 4.39 (t, *J* = 7.0 Hz, 2H), 3.14 (q, *J* = 6.8 Hz, 2H), 2.01 (p, *J* = 7.1 Hz, 2H), 1.55 (p, *J* = 7.0 Hz, 2H), 1.41 (s, 9H).

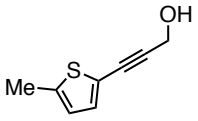
**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 156.1, 79.5, 75.2, 39.6, 28.5, 27.1, 24.6.

**FTIR** (thin film, $cm^{-1}$): 3352, 2978, 1698, 1554, 1367, 1172.

**HRMS** (ESI) m/z, calcd for $[C_9H_{19}N_2O_4]^+$: 219.1339; found: 219.1335.

**N9** is a known compound but was not completely characterized in the literature.[34] Hence, fully characterization was reported.

### 2.10.5 Synthesis of Homopropargylic Bromides




**O5**
Chemical Formula: $C_8H_8OS$
Exact Mass: 152.02
Molecular Weight: 152.21

(**O5**) Using a 250 mL round bottom flask equipped with a stirbar, tetrakis(triphenylphosphine)-palladium(0) (230 mg, 0.2 mmol) and copper(I) iodide (76 mg, 0.4 mmol) were added in water (100 mL, 0.2 M), followed by the addition of propargyl alcohol (1.77 mL, 30 mmol). Pyrrolidine (2.46 mL, 30 mmol) was added dropwise by a syringe to generate the copper acetylide intermediate. Then, 2-bromo-5-methylthiophene was added to the mixture (3.54 g, 20 mmol) and the reaction was stirred at 70 °C overnight. Upon completion of the cross-coupling reaction (monitored by TLC), saturated $NH_4Cl$ (30 mL) was added to quench the reaction. The resulting biphasic mixture was stirred for 5 min, before being poured into a separatory funnel and rinsed with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (30 mL x 3), the combined organic layers were washed with brine (15

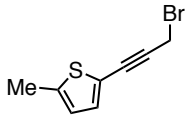
mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel column chromatography (100:0 to 90:10 Hexanes: EtOAc) to afford **O5** 3-(5-methylthiophen-2-yl)prop-2-yn-1-ol (2.74 g, 90 %) as brown oil.

**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 7.02 (d, $J$ = 3.5 Hz, 1H), 6.62 (d, $J$ = 3.2 Hz, 1H), 4.49 (d, $J$ = 6.0 Hz, 2H), 2.46 (s, 3H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 142.5, 132.8, 125.4, 90.5, 79.7, 52.0, 15.5.

**FTIR** (thin film, $cm^{-1}$): 3325, 2919, 1439, 1194, 1117, 799.

**HRMS** (ESI) m/z, calcd for $[C_8H_9SO]^+$: 153.0369; found: 153.0370.




**B5**
Chemical Formula: $C_8H_7BrS$
Exact Mass: 213.94
Molecular Weight: 215.11

**(B5)** A 250 mL oven-dried round bottom flask equipped with a stirbar and rubber septum was cooled under a stream of nitrogen. The septum was removed from the flask, 3-(5-methylthiophen-2-yl)prop-2-yn-1-ol (2.6 g, 17 mmol) was added under air, the septum was replaced, and the flask was sparged with nitrogen for ca. 5 min. DCM (47 mL, 0.36 M) was added via syringe and the reaction was stirred at 0 °C for 5 min. Then, $PBr_3$ (1.0 mL, 10.4 mmol) was added dropwise via a syringe at 0 °C. Upon completion of the bromination (monitored by TLC), saturated $NaHCO_3$ (30 mL) was added to quench the reaction. The resulting biphasic mixture was stirred for 10 min, before being poured into a separatory funnel and rinsed with DCM (10 mL). The aqueous layer was extracted with DCM (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous

$MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel column chromatography (100% hexanes) to afford **B5** 2-(3-bromoprop-1-yn-1-yl)-5-methylthiophene (2.53 g, 70 %) as dark yellow oil.

**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 7.04 (d, $J$ = 3.6 Hz, 1H), 6.63 (d, $J$ = 3.4 Hz, 1H), 4.18 (s, 2H), 2.46 (s, 3H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 143.2, 133.5, 125.2, 119.7, 87.5, 80.8, 15.8, 15.6.

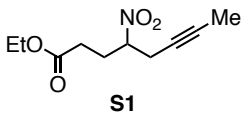
**FTIR** (thin film, $cm^{-1}$): 3072, 2919, 2216, 1205, 1161, 799.

**HRMS** (ESI) m/z, calcd for $[C_8H_8SBr]^+$: 214.9525; found: 214.9531.

### 2.10.6 Synthesis of Homopropargylic Nitroalkanes

**General protocol**: An oven dried 25 mL Schlenk flask equipped with magnetic stir bar and rubber septum was attached to a double manifold and cooled under vacuum. The flask was backfilled with $N_2$, the septum was removed, and CuBr (10 mol %) and KO$^t$Bu (1.05 equiv) were added. The septum was replaced, the flask was attached to a double manifold, evacuated and backfilled with nitrogen five times. Anhydrous dioxane (0.2 M with respect to nitroalkane) and ligand (**L15**) *N,N*-diisopropylethane-1,2-diamine (30 mol %) were added to the flask via syringe. After 10 min of stirring at rt, a nitroalkane (1 equiv) was added to the flask via syringe and stirred at rt for another 20 min. Then, propargylic bromide (1.15 equiv) was added via syringe. If propargylic bromide was a solid, it was added as a solution in dioxane via syringe. The resulting suspension was stirred for 4 h at rt. The flask was opened to air and

the reaction mixture was diluted with saturated $NH_4Cl$ (20 mL). The resulting biphasic mixture was stirred for 10 min, before being poured into a separatory funnel and rinsed with $Et_2O$ (10 mL). The aqueous layer was extracted with $Et_2O$ (30 mL x 3), the combined organic layers were washed with brine (15 mL) and dried over anhydrous $MgSO_4$, filtered through a glass frit, and concentrated *in vacuo*. The crude product was purified by flash silica gel column chromatography.




**S1**
Chemical Formula: $C_{10}H_{15}NO_4$
Exact Mass: 213.10
Molecular Weight: 213.23

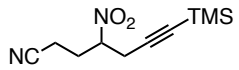
(**S1**) According to general protocol, ethyl 4-nitrobutanoate (322 mg, 2 mmol), 1-bromo-2-butyne (306 mg, 2.3 mmol), CuBr (28.7 mg, 0.2 mmol), ligand (**L14**) (86.4 mg, 0.6 mmol), KO*t*Bu (235.6 mg, 2.1 mmol), and anhydrous dioxane (10 mL) were combined under $N_2$ and stirred at rt for 4 h. After workup, the crude product was purified via silica gel flask column chromatography (100: 0 to 85: 15 hexanes: $Et_2O$) to afford homopropargylic nitroalkane **S1** (204.5 mg, 48%) as clear oil.

**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 4.63 (tt, $J$ = 7.5, 5.9 Hz, 1H), 4.15 (q, $J$ = 7.2 Hz, 2H), 2.81 (ddq, $J$ = 16.9, 7.5, 2.6 Hz, 1H), 2.69 (ddq, $J$ = 16.9, 7.1, 2.5 Hz 1H), 2.44 – 2.34 (m, 2H), 2.29 – 2.21 (m, 2H), 1.76 (t, $J$ = 2.5 Hz, 3H), 1.26 (t, $J$ = 7.1 Hz, 3H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 171.8, 85.7, 80.0, 71.9, 60.9, 30.1, 27.7, 24.1, 14.2, 3.6.

**FTIR** (thin film, $cm^{-1}$): 2983, 2924, 1734, 1554, 1371, 1189.

**HRMS** (ESI) m/z, calcd for $[C_{10}H_{16}O_4N]^+$: 214.1074; found: 214.10755.




**S2**
Chemical Formula: $C_{10}H_{16}N_2O_2Si$
Exact Mass: 224.10
Molecular Weight: 224.34

According to general protocol, 4-nitrobutanenitrile (114 mg, 1 mmol), (3-bromoprop-1-yn-1-yl)trimethylsilane (220 mg, 1.15 mmol), CuBr (28.8 mg, 0.2 mmol), ligand (**L14**) (43.2 mg, 0.3 mmol), KO*t*Bu (117.8 mg, 1.05 mmol), and anhydrous dioxane (5 mL) were combined under $N_2$ and stirred at rt for 24 h. After workup, the crude product was purified via silica gel flask column chromatography (100: 0 to 90: 10 hexanes: EtOAc) to afford homopropargylic nitroalkane **S2** (89.6 mg, 40 %) as yellow oil.

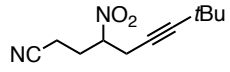
**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 4.68 (dtd, $J$ = 9.7, 6.5, 3.8 Hz, 1H), 2.95 (dd, $J$ = 17.2, 6.0 Hz, 1H), 2.87 (dd, $J$ = 17.2, 7.2 Hz, 1H), 2.60 – 2.39 (m, 3H), 2.34 – 2.27 (m, 1H), 0.16 (s, 9H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 117.7, 97.8, 90.8, 83.8, 28.2, 24.9, 14.4, 0.0.

**$^{29}$Si NMR** (119 MHz, $CDCl_3$) $\delta$ –17.42.

**FTIR** (thin film, $cm^{-1}$): 2961, 2250, 2183, 1557, 1251, 845.

**HRMS** (ESI) m/z, calcd for $[C_{10}H_{17}N_2O_2Si]^+$: 225.1054; found 225.1049.




**S3**
Chemical Formula: $C_{11}H_{16}N_2O_2$
Exact Mass: 208.12
Molecular Weight: 208.26

According to general protocol, 4-nitrobutanenitrile (228 mg, 2 mmol), 1-bromo-4,4-dimethylpent-2-yne (403 mg, 2.3 mmol), CuBr (28.7 mg, 0.2 mmol), ligand (**L14**) (86.4 mg, 0.6 mmol), KO*t*Bu (235.6 mg, 2.1 mmol), and anhydrous dioxane (10 mL) were combined under $N_2$ and stirred at rt for 4 h. After workup, the crude product was purified via silica gel flask column

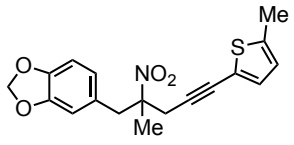
chromatography (100: 0 to 90: 10 hexanes: EtOAc) to afford homopropargylic nitroalkane **S3** (70.8 mg, 17%) as yellow oil.

**$^1$H NMR** (600 MHz, $CDCl_3$) δ 4.65 (dtt, *J* = 9.9, 6.6, 3.8 Hz, 1H), 2.86 (dd, *J* = 16.9, 6.1 Hz, 1H), 2.80 (dd, *J* = 16.9, 6.9 Hz, 1H), 2.55 (ddd, *J* = 15.9, 7.3, 5.0 Hz, 1H), 2.51 – 2.39 (m, 2H), 2.31 – 2.24 (m, 1H), 1.19 (s, 9H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 117.8, 94.4, 84.4, 70.5, 31.0, 29.9, 28.1, 24.0, 14.5.

**FTIR** (thin film, $cm^{-1}$): 3689, 2972, 2246, 2164, 1550, 799.

**HRMS** (ESI) m/z, calcd for $[C_{11}H_{16}N_2O_2]^+$: 209.1245; found: 209.1283.




**S5**
Chemical Formula: $C_{18}H_{17}NO_4S$
Exact Mass: 343.09
Molecular Weight: 343.40

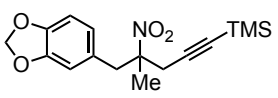
According to general protocol, 5-(2-nitropropyl)benzo[*d*][1,3]dioxole (209 mg, 1 mmol), 2-(3-bromoprop-1-yn-1-yl)-5-methylthiophene **B5** (247 mg, 1.15 mmol), CuBr (14.4 mg, 0.1 mmol), ligand (**L14**) (43.2 mg, 0.3 mmol), KO*t*Bu (117.8 mg, 1.05 mmol), and anhydrous dioxane (5 mL) were combined under $N_2$ and stirred at rt for 4 h. After workup, the crude product was purified via silica gel flask column chromatography (100: 0 to 80: 20 hexanes: EtOAc) to afford homopropargylic nitroalkane **S5** (198.9 mg, 58%) as brown oil.

**$^1$H NMR** (600 MHz, $CDCl_3$) δ 6.99 (d, *J* = 3.6 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.66 – 6.60 (m, 3H), 5.94 (s, 2H), 3.24 (q, *J* = 14.2 Hz, 2H), 3.03 (q, *J* = 17.0 Hz, 2H), 2.46 (s, 3H), 1.70 (s, 3H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 148.0, 147.3, 142.0, 132.42, 127.9, 125.3, 123.5, 120.3, 110.3, 108.6, 101.3, 90.8, 86.8, 78.4, 44.1, 29.5, 23.5, 15.5.

**FTIR** (thin film, $cm^{-1}$): 2921, 1609, 1542, 1489, 1444, 1250, 1039, 802.

**HRMS** (ESI) m/z, calcd for $[C_{18}H_{18}O_4NS]^+$: 344.0957; found: 344.0955.




**S6**
Chemical Formula: $C_{16}H_{21}NO_4Si$
Exact Mass: 319.12
Molecular Weight: 319.43

According to general protocol, 5-(2-nitropropyl)benzo[*d*][1,3]dioxole (209 mg, 1 mmol), (3-bromo-1-propynyl)-trimethylsilane (219 mg, 1.15 mmol), CuBr (14.4 mg, 0.1 mmol), ligand (**L14**) (43.2 mg, 0.3 mmol), KO$^t$Bu (117.8 mg, 1.05 mmol), and anhydrous dioxane (5 mL) were combined under $N_2$ and stirred at rt for 4 h. After workup, the crude product was purified via silica gel flask column chromatography (100: 0 to 95: 5 hexanes: EtOAc) to afford homopropargylic nitroalkane **S6** (277 mg, 87%) as white solid.

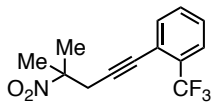
**$^1$H NMR** (600 MHz, $CDCl_3$) δ 6.73 (d, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 1.7 Hz, 1H), 6.60 (d, *J* = 1.8 Hz, 1H), 5.94 (s, 2H), 3.25 – 3.16 (m, 2H), 2.87 – 2.76 (m, 2H), 1.65 (s, 3H), 0.18 (s, 9H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 147.9, 147.3, 127.9, 123.4, 110.3, 108.5, 101.2, 100.6, 90.6, 89.9, 43.9, 29.5, 23.4, 0.0.

**FTIR** (thin film, $cm^{-1}$): 2960, 1898, 2180, 1544, 1490, 1445, 1251, 1039, 845, 761.

**HRMS** (ESI) m/z, calcd for $[C_{16}H_{22}NO_4Si]^+$: 320.1313; found: 320.1318.

**Melting point**: 69–70 ºC.



**S7**
Chemical Formula: $C_{13}H_{12}F_3NO_2$
Exact Mass: 271.08
Molecular Weight: 271.24

According to general protocol, 2-nitropropane (89 mg, 1.0 mmol), 1-(3-bromoprop-1-yn-1-yl)-2-(trifluoromethyl)benzene (302 mg, 1.15 mmol), CuBr (14.4 mg, 0.1 mmol), ligand (**L14**) (43.2 mg, 0.3 mmol), KO*t*Bu (117.8 mg, 1.05 mmol), and anhydrous dioxane (5 mL) were combined under $N_2$ and stirred at rt for 4 h. After workup, the crude product was purified via silica gel flask column chromatography (100: 0 to 95: 5 hexanes: EtOAc) to afford homopropargylic nitroalkane **S7** (235.8 mg, 87%) as yellow oil.

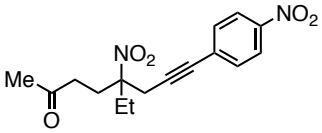
**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 7.64 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 3.12 (s, 2H), 1.75 (s, 6H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 134.2, 131.6, 131.4, 128.1, 125.8 (q, *J* = 6.0 Hz), 123.5 (q, *J* = 273 Hz), 121.0 (q, *J* = 1.5 Hz), 89.3, 86.9, 80.1, 31.7, 25.5.

**$^{19}$F NMR** (565 MHz, CDCl3) $\delta$ –62.36.

**FTIR** (thin film, $cm^{-1}$): 2994, 1544, 1318, 1172, 1133, 1112, 1063, 1034, 767.

**HRMS** (ESI) m/z, calcd for $[C_{13}H_{13}O_2NF_3]^+$: 272.0820; found: 272.0898.



**S8**
Chemical Formula: $C_{16}H_{18}N_2O_5$
Exact Mass: 318.12
Molecular Weight: 318.33

According to general protocol, 5-nitroheptan-2-one (159 mg, 1.0 mmol), 1-(3-bromoprop-1-yn-1-yl)-4-nitrobenzene (276 mg, 1.15 mmol), CuBr (14.4 mg, 0.1 mmol), ligand (**L14**) (43.2 mg, 0.3 mmol), KO*t*Bu (117.8 mg, 1.05 mmol), and anhydrous dioxane (5 mL) were combined under $N_2$ and

stirred at rt for 4 h. After workup, the crude product was purified via silica gel flask column chromatography (100: 0 to 95: 5 hexanes: EtOAc) to afford homopropargylic nitroalkane **S8** (248.1 mg, 78%) as white solid.

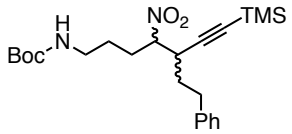
**$^1$H NMR** (600 MHz, $CDCl_3$) $\delta$ 8.21 – 8.13 (m, 2H), 7.57 – 7.49 (m, 2H), 3.24 – 3.03 (m, 2H), 2.60 – 2.33 (m, 4H), 2.18 (s, 3H), 2.10 (q, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta$ 205.8, 147.2, 132.5, 129.4, 123.6, 92.6, 88.4, 82.3, 37.7, 30.1, 30.0, 29.9, 25.8, 8.2.

**FTIR** (thin film, $cm^{-1}$): 3418, 3108, 2934, 2228, 1715, 1537, 1513, 1345, 854.

**HRMS** (ESI) m/z, calcd for $[C_{16}H_{17}N_2O_5]^+$: 317.1143; found: 317.1128.

**Melting point**: 98–100 ºC.




**S9**
Chemical Formula: $C_{23}H_{36}N_2O_4Si$
Exact Mass: 432.24
Molecular Weight: 432.64

According to general protocol, *tert*-butyl (4-nitrobutyl)carbamate (218 mg, 1.0 mmol), (3-bromo-5-phenylpent-1-yn-1-yl)trimethylsilane (339 mg, 1.15 mmol), CuBr (28.8 mg, 0.2 mmol), ligand (**L14**) (43.2 mg, 0.3 mmol), KO$^t$Bu (117.8 mg, 1.05 mmol), and anhydrous dioxane (5 mL) were combined under $N_2$ and stirred at rt for 20 h. After workup, the crude product was purified via silica gel flask column chromatography (100: 0 to 90: 10 hexanes: EtOAc) to afford homopropargylic nitroalkane **S9** (216.2 mg, 50% combined) as yellow oil. NMR analysis revealed a 49:51 mixture of syn and anti-isomers.

**S9 A: $^{1}$H NMR** (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 4.53 – 4.48 (m, 1H), 4.43 (td, *J* = 10.1, 3.0 Hz, 1H), 3.15 (dp, *J* = 20.3, 6.8 Hz, 2H), 2.99 – 2.88 (m, 2H), 2.70 (dt, *J* = 13.7, 8.4 Hz, 1H), 2.12 (dddd, *J* = 14.1, 9.7, 6.2, 3.0 Hz, 1H), 2.01 (dtd, *J* = 14.9, 10.4, 5.0 Hz, 1H), 1.75 – 1.70 (m, 2H), 1.58 – 1.51 (m, 2H), 1.43 (s, 9H), 0.20 (s, 9H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 155.9, 140.7, 128.5, 128.4, 126.2, 102.7, 91.2, 90.5, 77.4, 39.7, 36.8, 33.3, 32.8, 29.5, 28.4, 26.4, 0.0.

**$^{29}$Si NMR** (119 MHz, $CDCl_3$) δ –17.76.

**FTIR** (thin film, $cm^{-1}$): 3356, 3028, 2961, 2931, 2174, 1705, 1553, 1251, 1172, 845.

**HRMS** (ESI) m/z, calcd for $[C_{23}H_{35}N_2O_4Si]^-$: 431.2372; found: 431.2357.

**S9 B: $^{1}$H NMR** (600 MHz, $CDCl_3$) δ 7.29 7.29 (t, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 4.50 (q, *J* = 8.3, 6.5 Hz, 2H), 3.14 (td, *J* = 14.3, 7.0 Hz, 2H), 2.95 – 2.83 (m, 2H), 2.72 (dt, *J* = 13.7, 8.3 Hz, 1H), 2.06 (dtd, *J* = 14.8, 10.0, 5.6 Hz, 1H), 1.86 – 1.71 (m, 3H), 1.51 – 1.45 (m, 2H), 1.42 (s, 9H), 0.19 (s, 9H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 156.1, 140.9, 128.7, 128.6, 126.4, 102.8, 90.8, 90.2, 76.7, 39.8, 36.5, 33.3, 32.7, 28.6, 28.1, 26.9, 0.1.

**$^{29}$Si NMR** (119 MHz, $CDCl_3$) δ –17.71.

**FTIR** (thin film, $cm^{-1}$): 3354, 3021, 2961, 2931, 2174, 1710, 1554, 1251, 1173, 846.

**HRMS** (ESI) m/z, calcd for $[C_{23}H_{35}N_2O_4Si]^-$: 431.2372; found: 431.2357.

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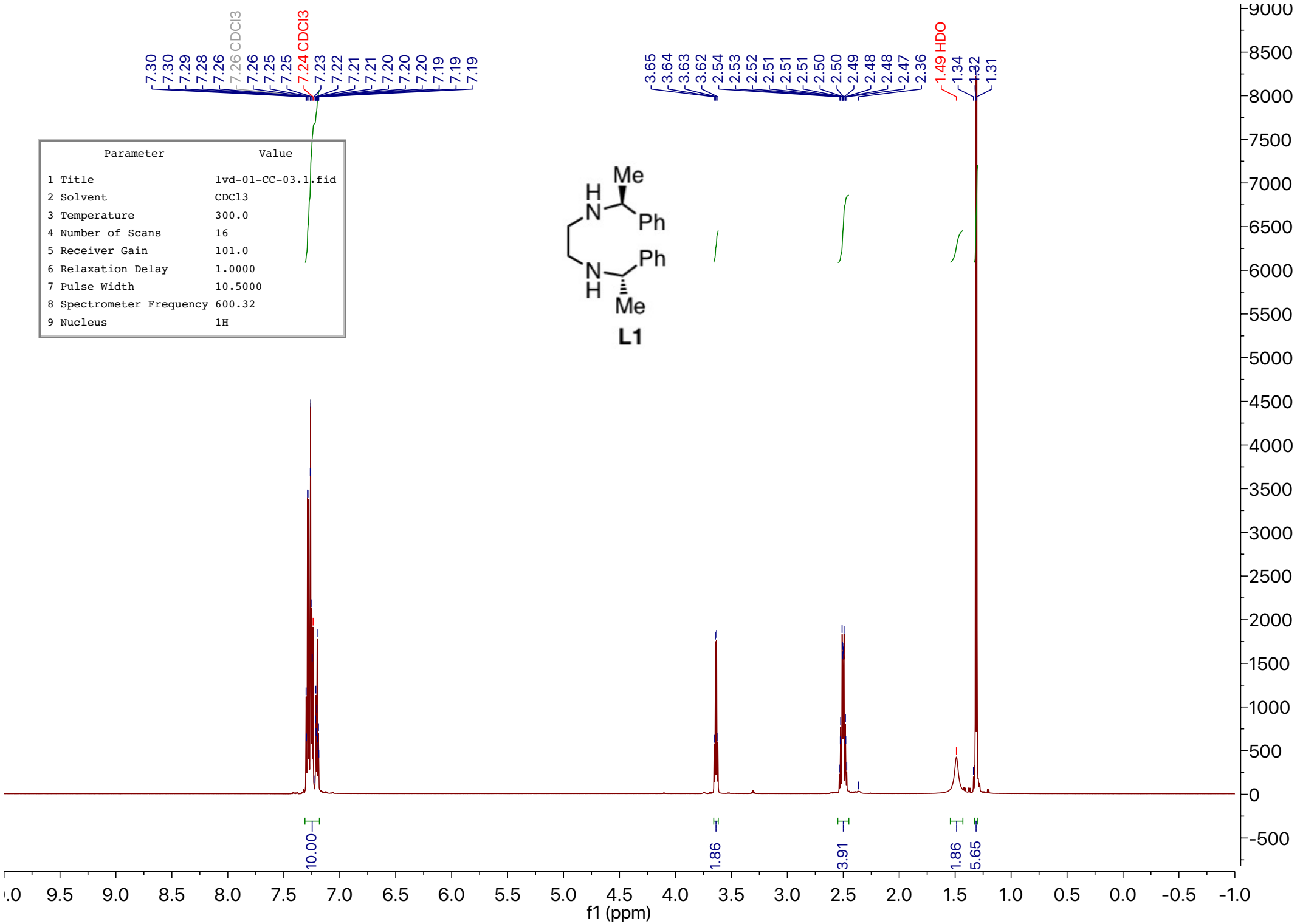
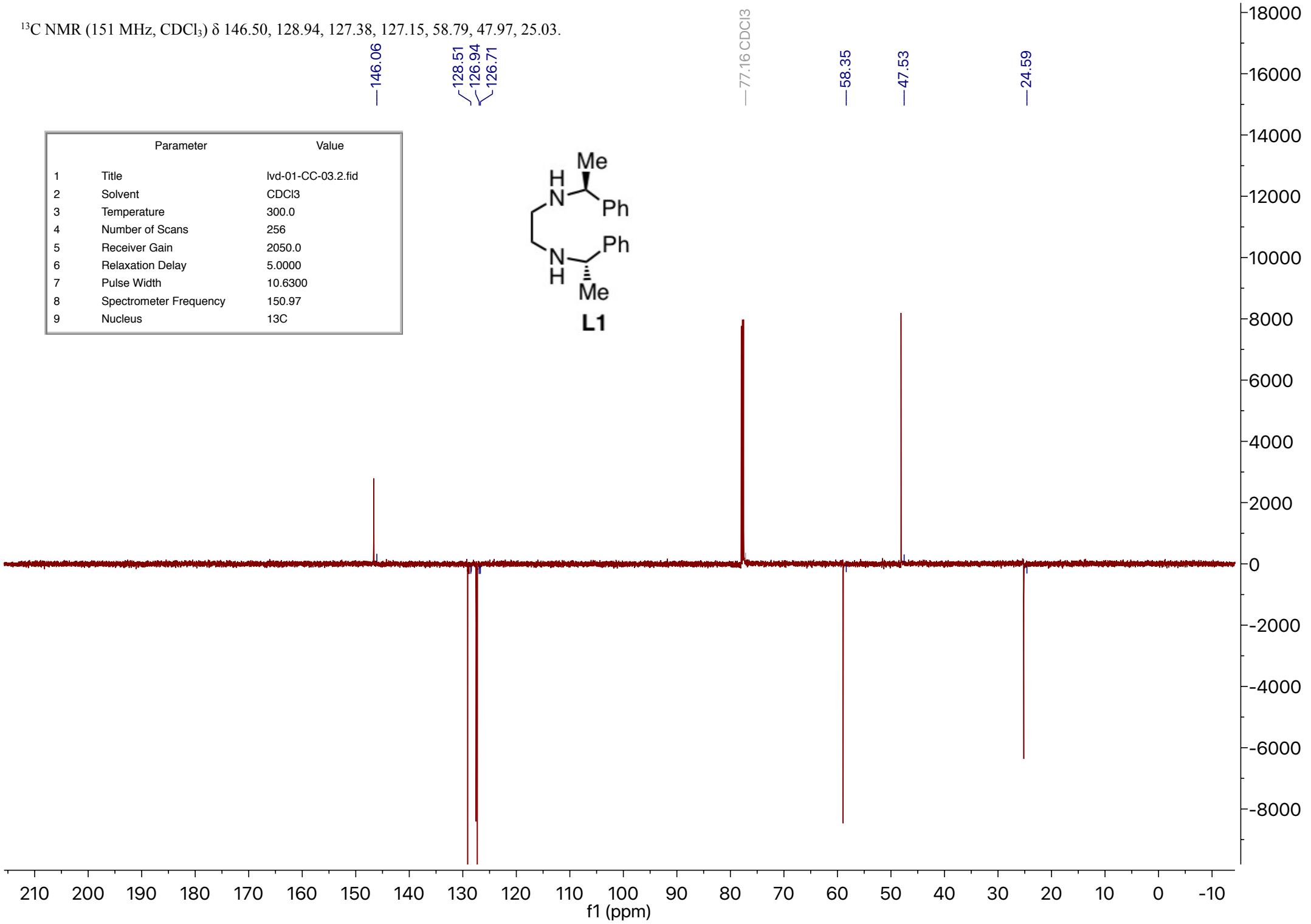
# Appendix A

# SPECTRAL DATA FOR CHAPTER 2


7.30 7.30 7.29 7.28 7.26 7.26 CDCl3 7.26 7.25 7.25 7.24 CDCl3 7.23 7.22 7.21 7.21 7.20 7.20 7.20 7.19 7.19 7.19
3.65 3.64 3.63 3.62 2.54 2.53 2.52 2.51 2.51 2.51 2.50 2.50 2.49 2.48 2.48 2.47 2.36 1.49 HDO 1.34 1.32 1.31
Parameter Value
1 Title lvd-01-CC-03.1.fid
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 16
5 Receiver Gain 101.0
6 Relaxation Delay 1.0000
7 Pulse Width 10.5000
8 Spectrometer Frequency 600.32
9 Nucleus 1H
Me
H
N
Ph
Ph
N
H
Me
L1
10.00
1.86
3.91
1.86
5.65
f1 (ppm)

$^{13}C$ NMR (151 MHz, $CDCl_3$) δ 146.50, 128.94, 127.38, 127.15, 58.79, 47.97, 25.03.

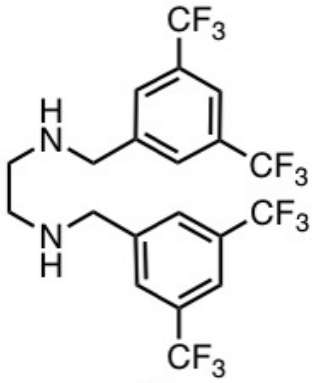



| | Parameter | Value |
|---|---|---|
| 1 | Title | lvd-01-CC-03.2.fid |
| 2 | Solvent | CDCl3 |
| 3 | Temperature | 300.0 |
| 4 | Number of Scans | 256 |
| 5 | Receiver Gain | 2050.0 |
| 6 | Relaxation Delay | 5.0000 |
| 7 | Pulse Width | 10.6300 |
| 8 | Spectrometer Frequency | 150.97 |
| 9 | Nucleus | 13C |




**L1**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-CC-04.1.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 181.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.5000 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |




**L8**

| Parameter | Value |
|---|---|
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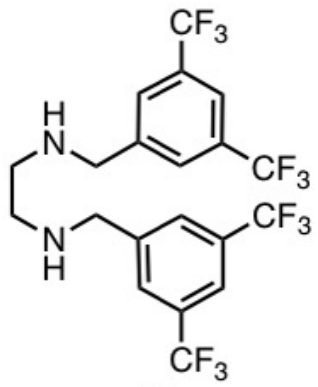
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 2048 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |




**L8**

| Parameter | Value |
|---|---|
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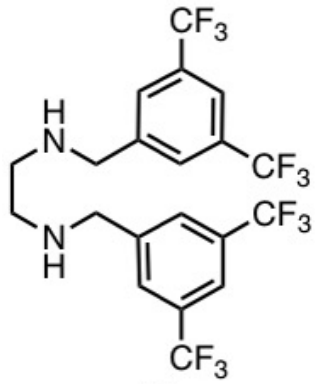
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 322.0 |
| 6 Relaxation Delay | 3.0000 |
| 7 Pulse Width | 11.4000 |
| 8 Spectrometer Frequency | 564.81 |
| 9 Nucleus | 19F |

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| Parameter | Value |
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| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 144.0 |
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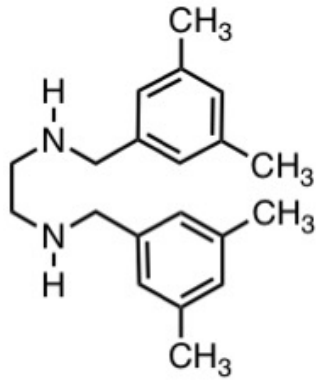
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |




**L9**

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|---|---|
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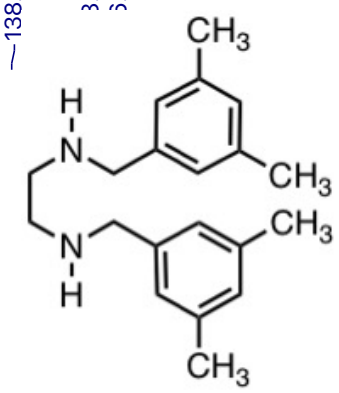
| 4 Number of Scans | 256 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |




**L9**

| Parameter | Value |
|---|---|
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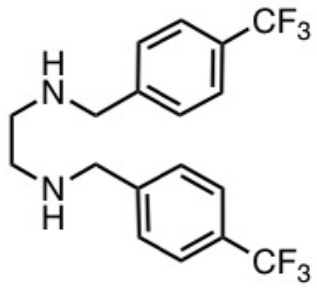
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 114.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.5000 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |




**L10**

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|---|---|
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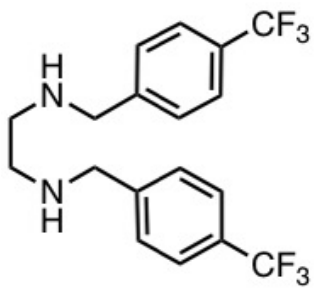
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 16.0000 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |




**L10**

144.79
129.71
129.49
129.28
129.06
128.36
127.11
125.46
125.44
125.41
125.38
125.30
123.50
121.70
77.16 CDCl3
53.52
48.96

f1 (ppm)

| Parameter | Value |
|---|---|
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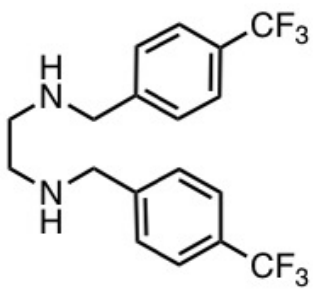
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 256.0 |
| 6 Relaxation Delay | 3.0000 |
| 7 Pulse Width | 11.4000 |
| 8 Spectrometer Frequency | 564.81 |
| 9 Nucleus | 19F |




**L10**

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| 4 Number of Scans | 16 |
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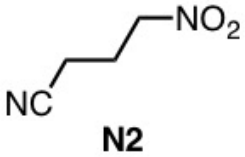
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.5000 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |




**N2**

| Parameter | Value |
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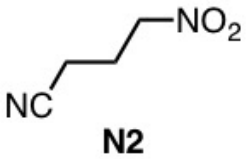
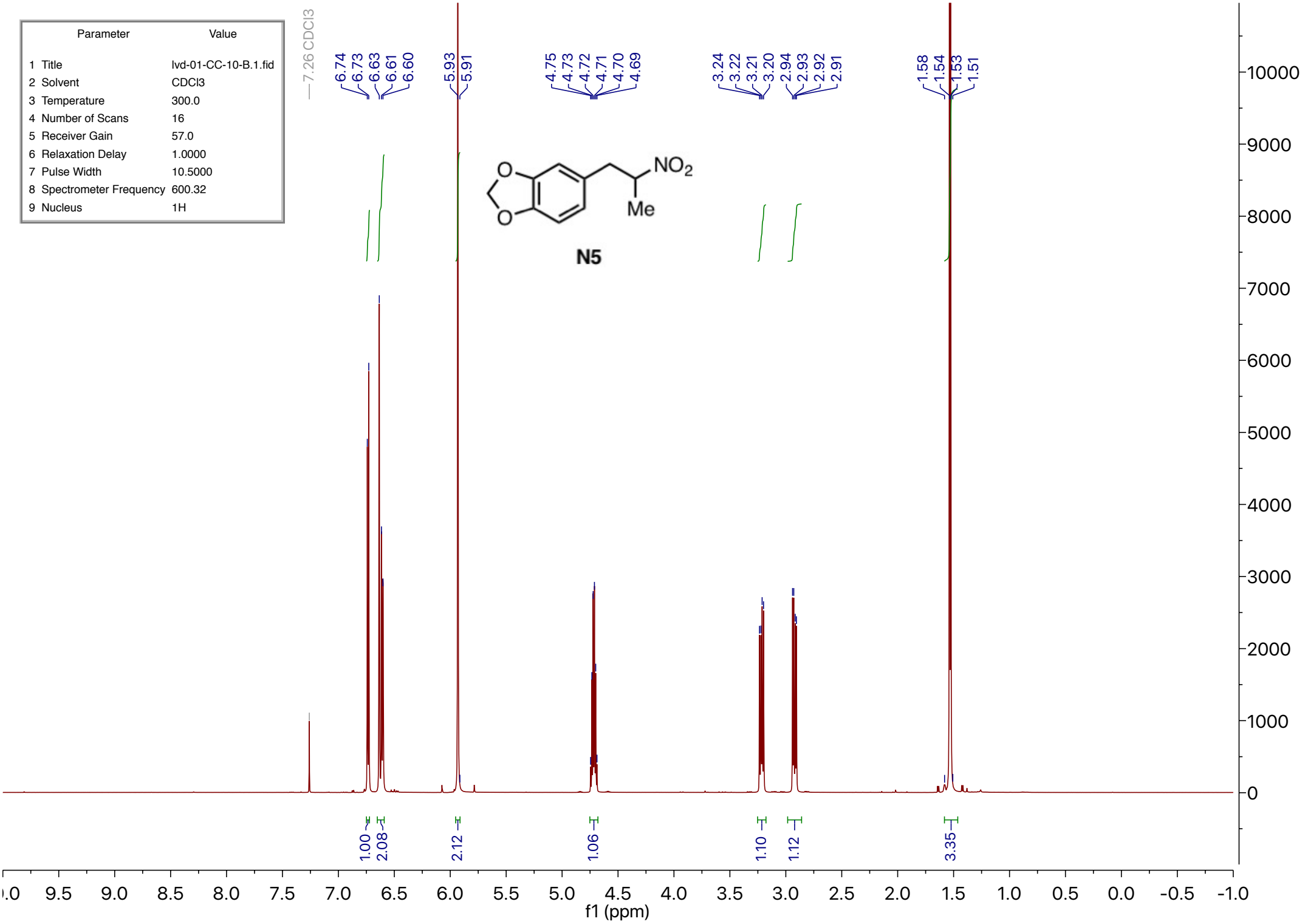
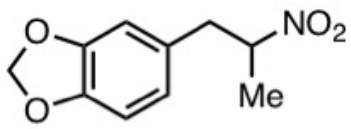
| 3 Temperature | 300.0 |
| 4 Number of Scans | 256 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |




**N2**

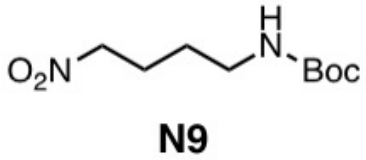

Parameter Value
1 Title lvd-01-CC-10-B.1.fid
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 16
5 Receiver Gain 57.0
6 Relaxation Delay 1.0000
7 Pulse Width 10.5000
8 Spectrometer Frequency 600.32
9 Nucleus 1H
7.26 CDCl3
6.74 6.73 6.63 6.61 6.60
5.93 5.91
4.75 4.73 4.72 4.71 4.70 4.69
3.24 3.22 3.21 3.20 2.94 2.93 2.92 2.91
1.58 1.54 1.53 1.51
O
O
O
NO2
Me
N5
1.00 2.08 2.12 1.06 1.10 1.12 3.35
10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-CC-10-B.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 256 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |



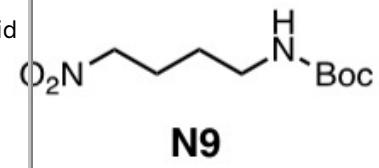

**N5**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-268-SI.1.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 28.5 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.6100 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |



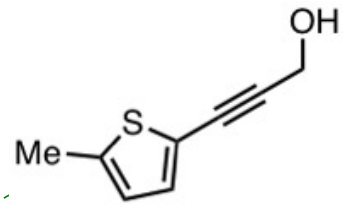

**N9**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-268-01.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 1024 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |



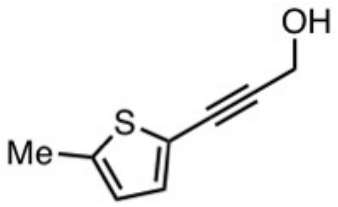

**N9**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-182-hivac.1.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 298.5 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 161.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.5000 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |



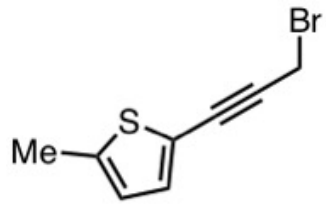

**O5**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-182-hivac.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.5 |
| 4 Number of Scans | 256 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |



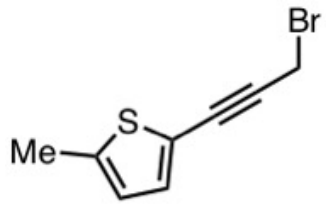

**O5**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-296-B5.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 128.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.6100 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |



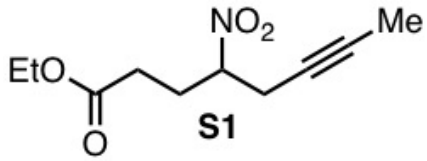

**B5**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-296-SI.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 1024 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |



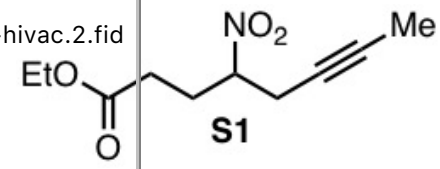

**B5**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-171-purified-2-hivac.1.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 298.2 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 4.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 15.0000 |
| 8 Spectrometer Frequency | 400.13 |
| 9 Nucleus | 1H |

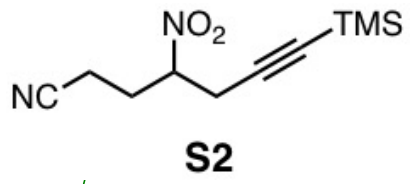



S1

| Parameter | Value |
|---|---|
| 1 Title | lve-01-171-purified-2-hivac.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 298.2 |
| 4 Number of Scans | 256 |
| 5 Receiver Gain | 512.0 |
| 6 Relaxation Delay | 3.0000 |
| 7 Pulse Width | 10.7000 |
| 8 Spectrometer Frequency | 100.62 |
| 9 Nucleus | 13C |

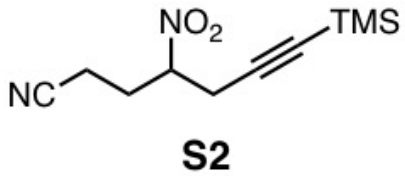


| Parameter | Value |
|---|---|
| 1 Title | evd-01-218-S1.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 128.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.6100 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |




**S2**

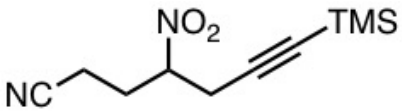
| Parameter | Value |
|---|---|
| 1 Title | lvd-01-218-SI.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 1024 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |




**S2**

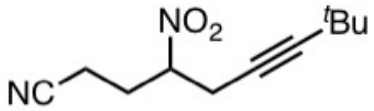
| Parameter | Value |
|---|---|
| 1 Title | lvd-01-218-SI.3.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 128 |
| 5 Receiver Gain | 1030.0 |
| 6 Relaxation Delay | 12.5000 |
| 7 Pulse Width | 13.5000 |
| 8 Spectrometer Frequency | 119.26 |
| 9 Nucleus | 29Si |

-17.42



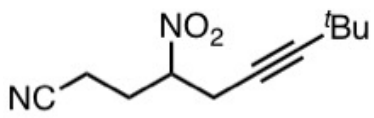

**S2**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-227-hivac.1.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 144.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.5000 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |



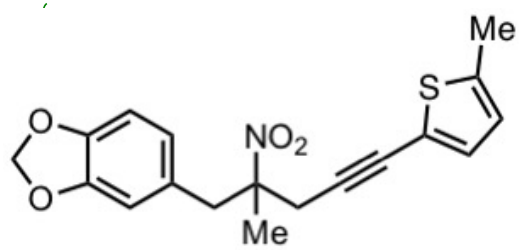

**S3**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-227-hivac.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 1024 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |



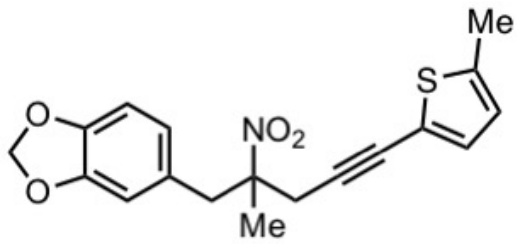

**S3**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-CC-17-B.1.1d |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 161.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.5000 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |



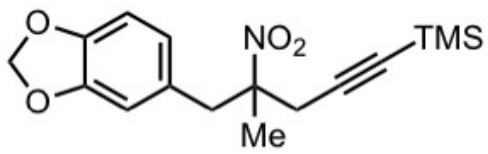

**S5**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-CC-17-A.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 256 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |



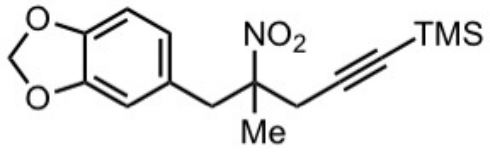

**S5**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-178-hivac.1.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 297.3 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 181.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 10.5000 |
| 8 Spectrometer Frequency | 600.32 |
| 9 Nucleus | 1H |



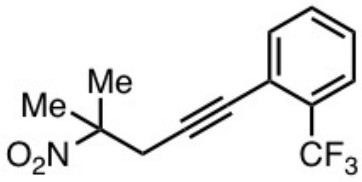

**S6**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-CC-09-B.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 256 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 10.6300 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |

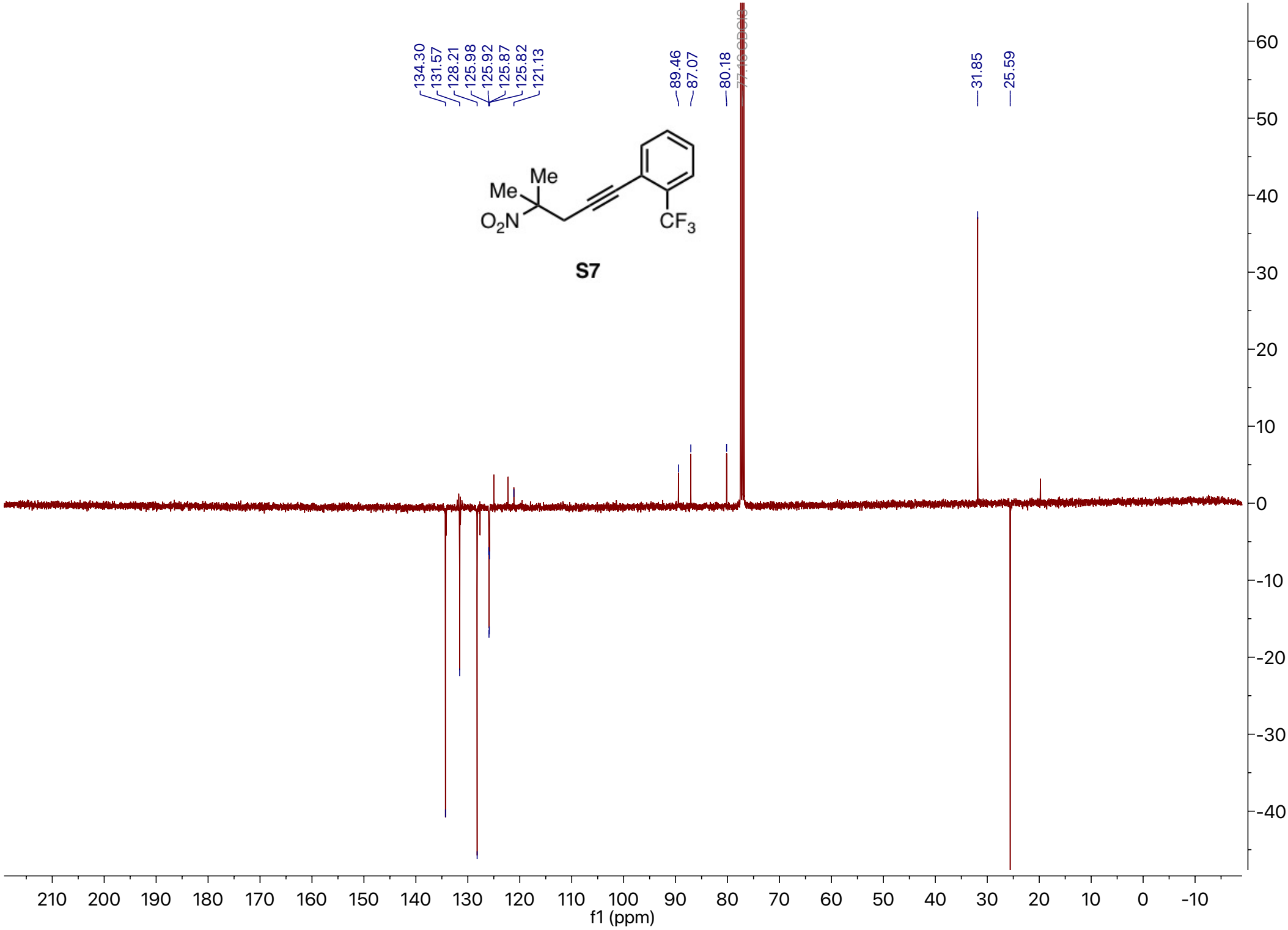



**S6**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-288-column-A.3.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 298.2 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 9.0 |
| 6 Relaxation Delay | 1.0000 |
| 7 Pulse Width | 15.0000 |
| 8 Spectrometer Frequency | 400.13 |
| 9 Nucleus | 1H |

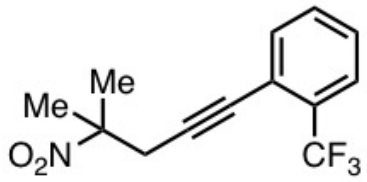



**S7**

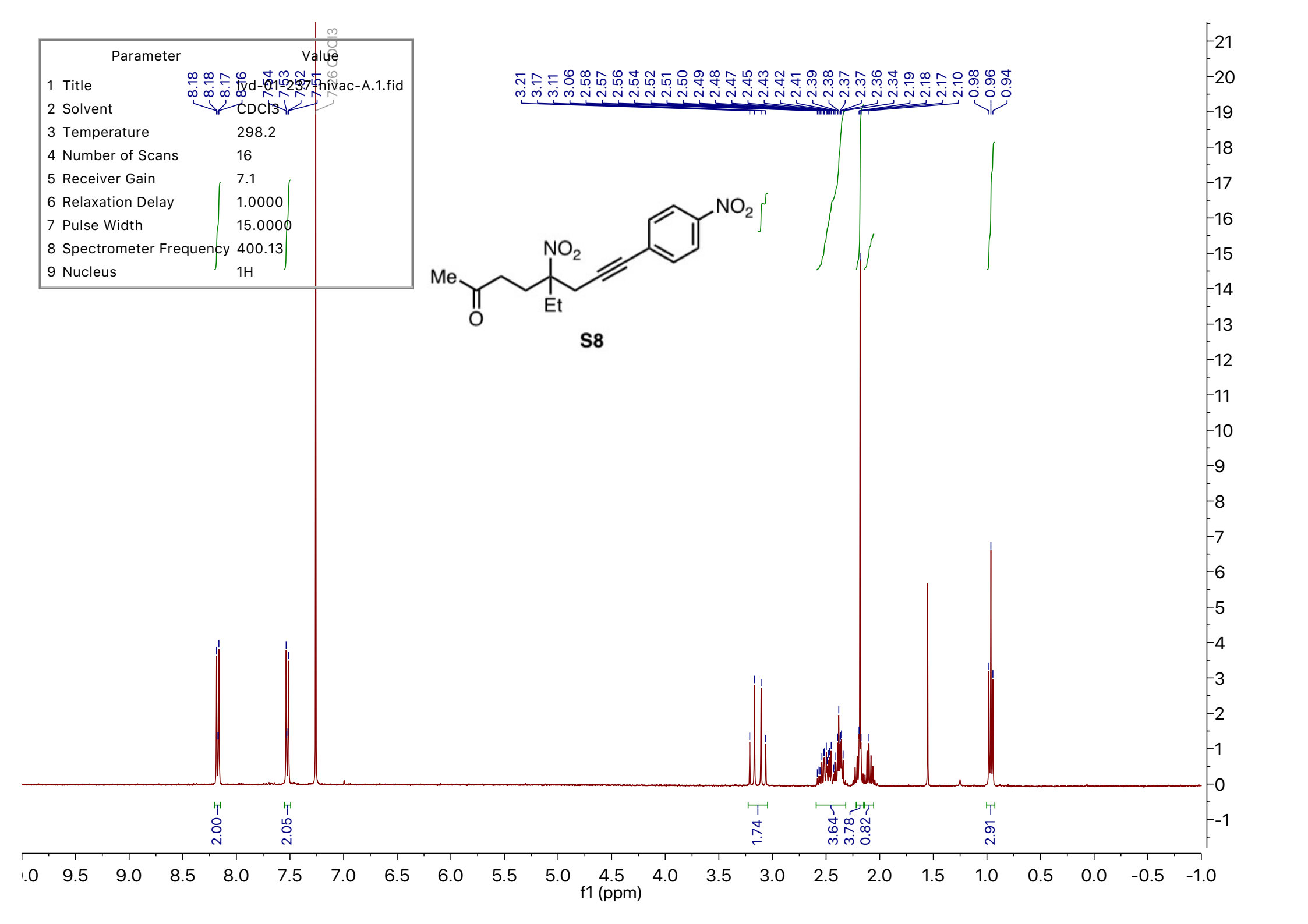

134.30
131.57
128.21
125.98
125.92
125.87
125.82
121.13
89.46
87.07
80.18
77.48 CDCl3
31.85
25.59
Me
Me
O2N
CF3
S7
60
50
40
30
20
10
0
-10
-20
-30
-40
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

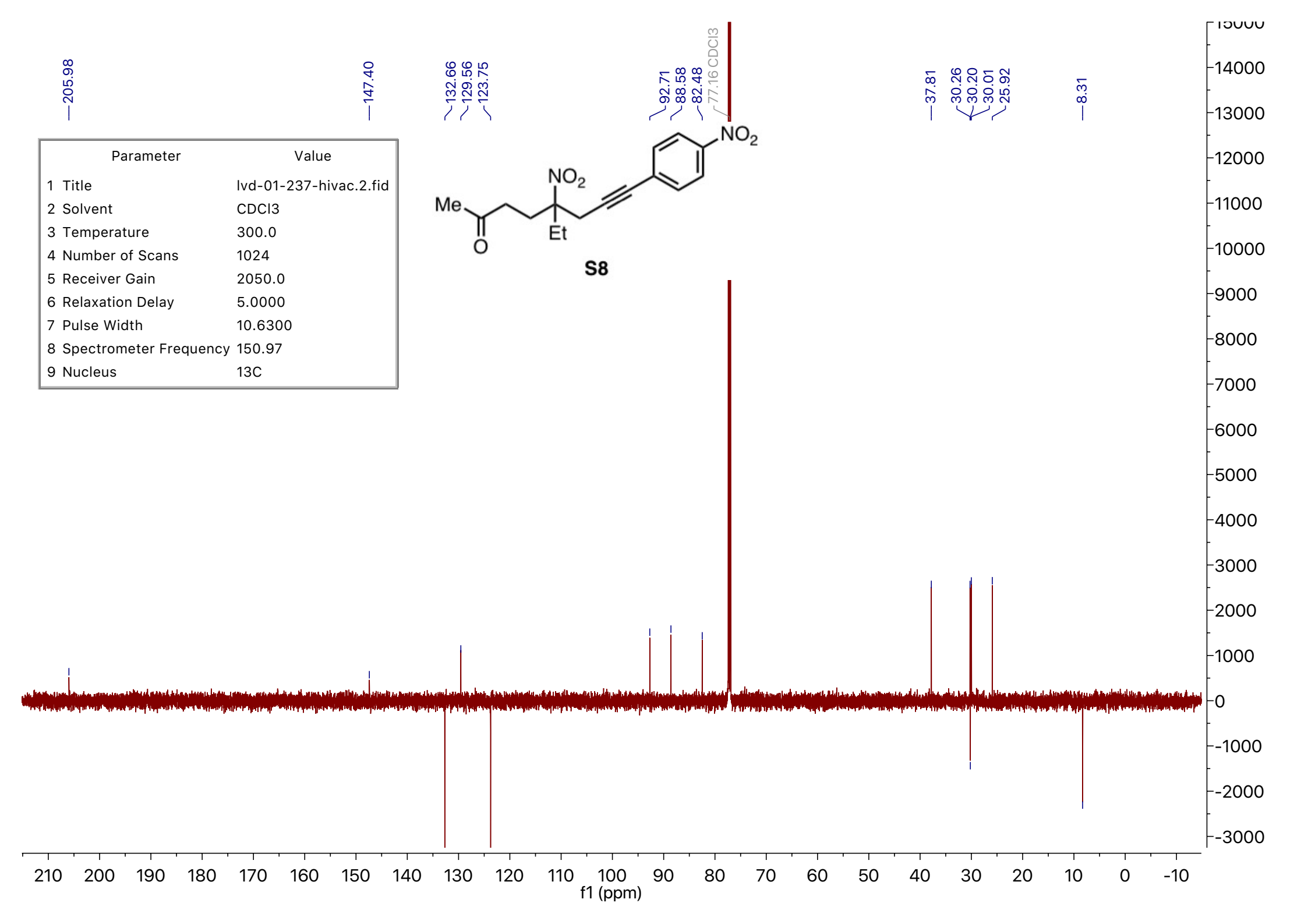
| Parameter | Value |
|---|---|
| 1 Title | lvd-01-288-F.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 298.1 |
| 4 Number of Scans | 16 |
| 5 Receiver Gain | 1625.5 |
| 6 Relaxation Delay | 2.0000 |
| 7 Pulse Width | 15.0300 |
| 8 Spectrometer Frequency | 376.46 |
| 9 Nucleus | 19F |

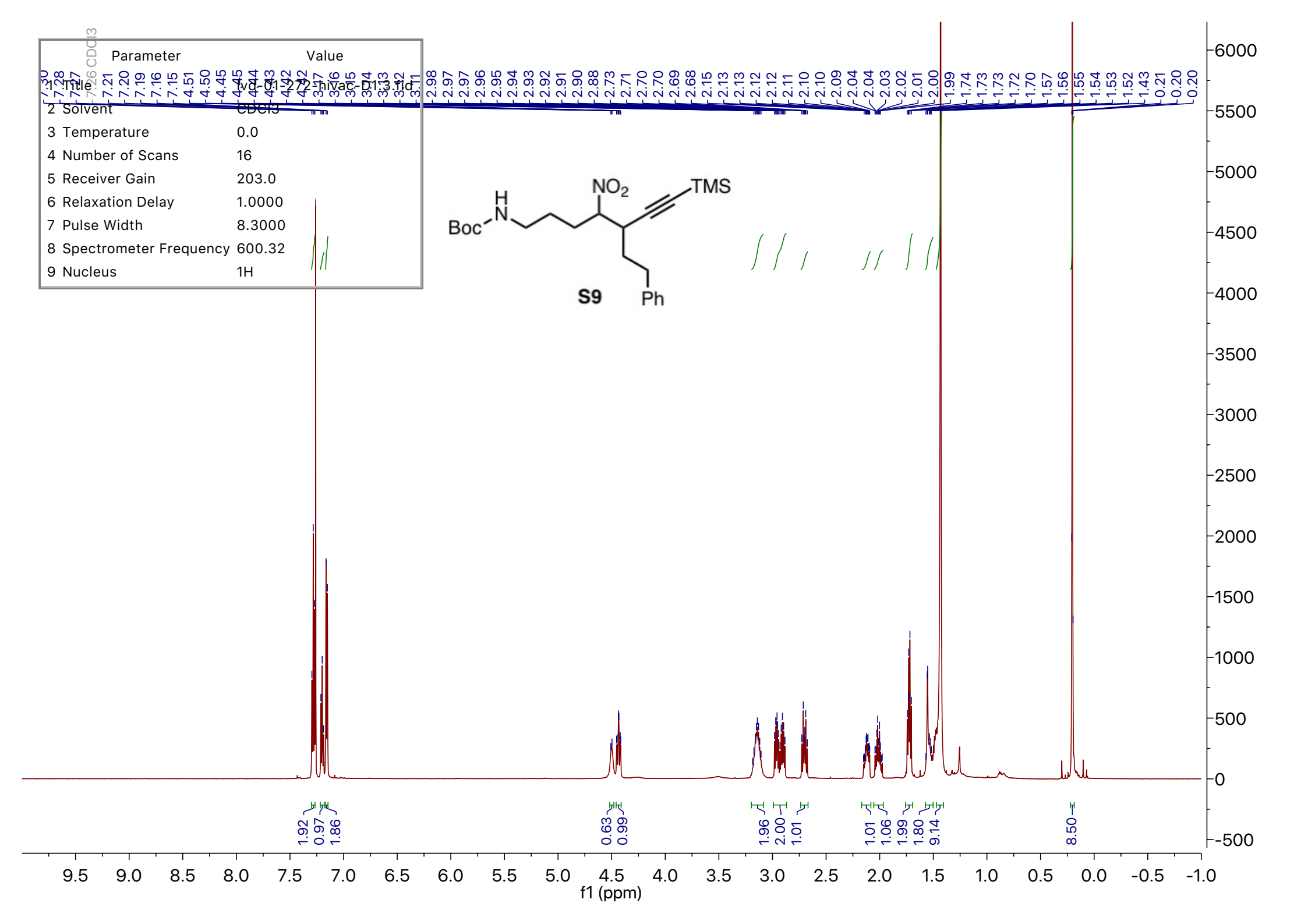
-62.36

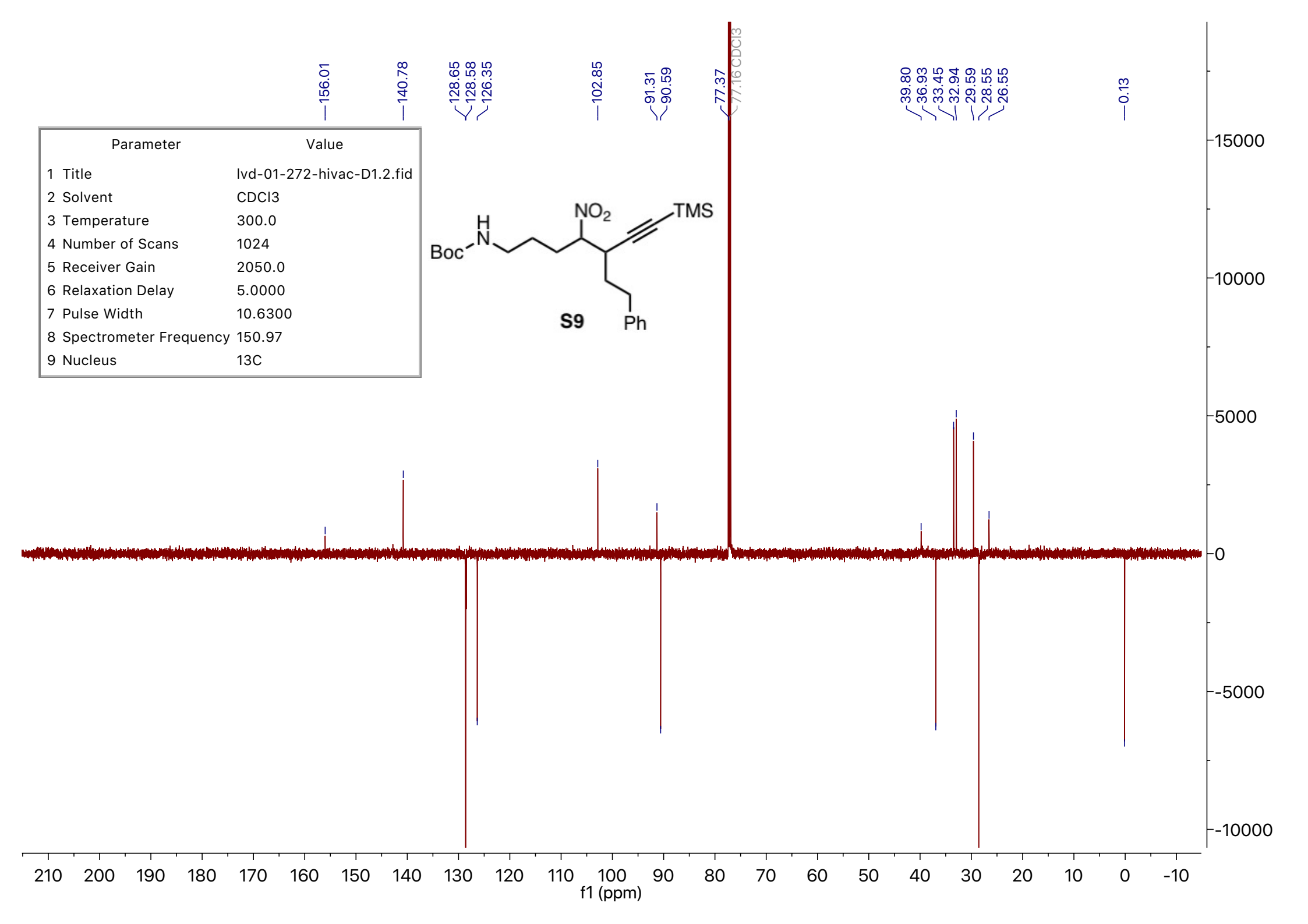



**S7**

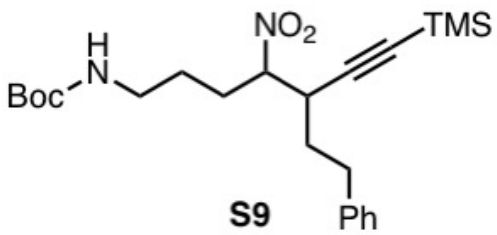

Parameter Value
1 Title lyd-01-237-hivac-A.1.fid
2 Solvent CDCl3
3 Temperature 298.2
4 Number of Scans 16
5 Receiver Gain 7.1
6 Relaxation Delay 1.0000
7 Pulse Width 15.0000
8 Spectrometer Frequency 400.13
9 Nucleus 1H
8.18 8.18 8.17 8.16 7.54 7.53 7.52 7.51 7.26 CDCl3
3.21 3.17 3.11 3.06 2.58 2.57 2.56 2.54 2.52 2.51 2.50 2.49 2.48 2.47 2.45 2.43 2.42 2.41 2.39 2.38 2.37 2.37 2.36 2.34 2.19 2.18 2.17 2.10 0.98 0.96 0.94
NO2
NO2
Me
Et
O
S8
2.00 2.05 1.74 3.64 3.78 0.82 2.91
f1 (ppm)


205.98
147.40
132.66
129.56
123.75
92.71
88.58
82.48
77.16 CDCl3
37.81
30.26
30.20
30.01
25.92
8.31
Parameter Value
1 Title lvd-01-237-hivac.2.fid
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 1024
5 Receiver Gain 2050.0
6 Relaxation Delay 5.0000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Nucleus 13C
NO2
NO2
Me
Et
O
S8
f1 (ppm)


Parameter Value
1 Title lvd-01-272-hivac-D1.3.fid
2 Solvent CDCl3
3 Temperature 0.0
4 Number of Scans 16
5 Receiver Gain 203.0
6 Relaxation Delay 1.0000
7 Pulse Width 8.3000
8 Spectrometer Frequency 600.32
9 Nucleus 1H
Boc
H
N
NO2
TMS
Ph
S9
1.92
0.97
1.86
0.63
0.99
1.96
2.00
1.01
1.01
1.06
1.99
1.80
9.14
8.50
f1 (ppm)


156.01
140.78
128.65
128.58
126.35
102.85
91.31
90.59
77.37
77.16 CDCl3
39.80
36.93
33.45
32.94
29.59
28.55
26.55
0.13
Parameter Value
1 Title lvd-01-272-hivac-D1.2.fid
2 Solvent CDCl3
3 Temperature 300.0
4 Number of Scans 1024
5 Receiver Gain 2050.0
6 Relaxation Delay 5.0000
7 Pulse Width 10.6300
8 Spectrometer Frequency 150.97
9 Nucleus 13C
Boc
H
N
NO2
TMS
Ph
S9
15000
10000
5000
0
-5000
-10000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-265-D1-SI.3.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 128 |
| 5 Receiver Gain | 1030.0 |
| 6 Relaxation Delay | 12.5000 |
| 7 Pulse Width | 13.5000 |
| 8 Spectrometer Frequency | 119.26 |
| 9 Nucleus | 29Si |




S9

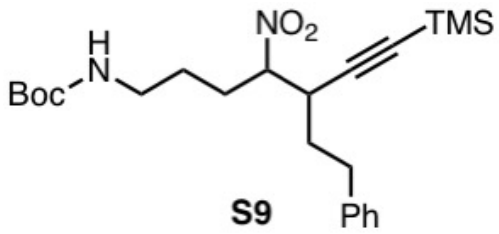
-17.76

1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200 -300 -400

80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180

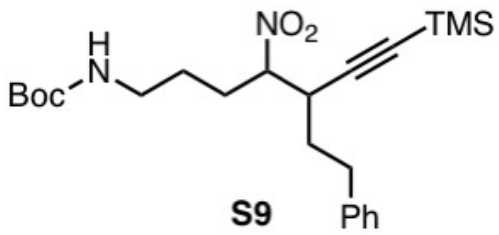
f1 (ppm)

| | Parameter | Value |
|---|---|---|
| 1 | Title | lvd-01-272-hivac-D2.3.fid |
| 2 | Solvent | CDCl3 |
| 3 | Temperature | 0.0 |
| 4 | Number of Scans | 16 |
| 5 | Receiver Gain | 144.0 |
| 6 | Relaxation Delay | 1.0000 |
| 7 | Pulse Width | 8.3000 |
| 8 | Spectrometer Frequency | 600.32 |
| 9 | Nucleus | 1H |



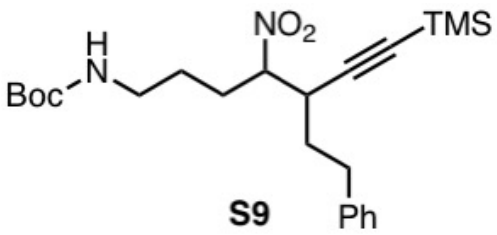

S9

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-272-hivac-D2.4.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 0.0 |
| 4 Number of Scans | 1024 |
| 5 Receiver Gain | 2050.0 |
| 6 Relaxation Delay | 5.0000 |
| 7 Pulse Width | 16.0000 |
| 8 Spectrometer Frequency | 150.97 |
| 9 Nucleus | 13C |




**S9**

| Parameter | Value |
|---|---|
| 1 Title | lvd-01-265-D2-SI.2.fid |
| 2 Solvent | CDCl3 |
| 3 Temperature | 300.0 |
| 4 Number of Scans | 128 |
| 5 Receiver Gain | 1030.0 |
| 6 Relaxation Delay | 12.5000 |
| 7 Pulse Width | 13.5000 |
| 8 Spectrometer Frequency | 119.26 |
| 9 Nucleus | 29Si |




S9