DISSERTATION

ENANTIOSELECTIVE β-FUNCTIONALIZATION OF ENALS VIA N-HETEROCYCLIC CARBENE CATALYSIS

Submitted by

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ABSTRACT

ENANTIOSELECTIVE β-FUNCTIONALIZATION OF ENALS VIA N-HETEROCYCLIC CARBENE CATALYSIS

A series of δ-nitroesters were synthesized through the N-heterocyclic carbene catalyzed coupling of enals and nitroalkenes. The asymmetric coupling of these substrates via the homoenolate pathway afford δ-nitroesters in good yield, diastereoselectivity, and enantioselectivity. This methodology allows for the rapid synthesis of δ-lactams. Using this approach, we synthesized the pharmaceutically relevant piperidines paroxetine and femoxetine.

A novel single-electron oxidation pathway for the N-heterocyclic carbene generated Breslow intermediate has been developed. Nitroarenes have been shown to transfer an oxygen from the nitro group to the β-position of an enal in an asymmetric fashion to generate β-hydroxy esters. This reaction affords desired β-hydroxy ester products in good yield and enantioselectivity and tolerates a wide range of enal substrates.

A dimerization of aromatic enals to form 3,4-disubstituted cyclopentanones has been investigated. Using a single-electron oxidant, aromatic enals couple to form cyclopenanone products in good yield, good enantioselectivity, and excellent diastereoselectivity. A cross coupling has also been developed to afford non-symmetrical cyclopentanone products.

ACKNOWLEDGEMENTS

First, and foremost, I would like to thank my advisor, Professor Tomislav Rovis for his supervision and guidance over the past five years. I cannot imagine a better environment for me to have conducted my graduate work. Tom has motivated me to become a better scientist than I had ever thought possible through his unwavering belief in my own ability to solve any problem facing me. I also thank Tom for the many times we discussed things outside the realm of chemistry, I will always appreciate the valuable advice he has given me. Thank you Tom for being both a mentor and a friend.

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I would like to thank my high school chemistry teacher Joe Anastasia for sparking my interest in chemistry. Prior to his class, I was convinced chemistry was something I would never understand. I also thank Professor James Babler who initiated my interest in organic chemistry and

gave me an opportunity to become a researcher. He was my first mentor, and I will always cherish his friendship.

Finally, I thank my family. When I decided to come home for graduate school I never imagined how wonderful it would be to have a chance to spend this time together. I have been spoiled by your love and support; I will always be thankful for this time we shared together.

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Chapter 1

Background on N-Heterocyclic Carbene Catalyzed Reactions

1.1 Introduction

N-heterocyclic carbene (NHC) catalysis represents an important aspect of modern organic chemistry.[1] NHC catalysis is an intriguing field of study as it allows for polarity inversion in aldehydes, rendering the typically electrophilic acyl carbon nucleophilic. In nature, this type of reactivity is operative in transketolase enzymes in the presence of coenzyme thiamine **1** (vitamin B_1).[2] In 1951, Mizuhara et al. discovered that the catalytically active species of the coenzyme thiamine is a nucleophilic carbene.[3] The biochemistry of thiamine-dependent enzymes has been studied in extensive detail which has resulted in the development of a broad range of synthetic tools.[4]

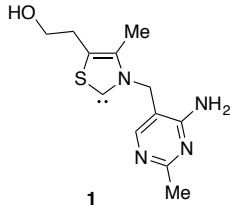

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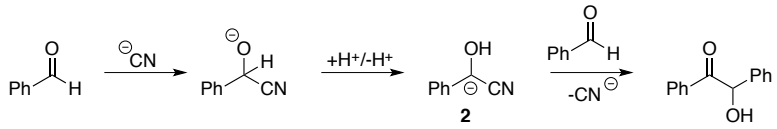
Figure 1.1.1

In the realm of organic chemistry NHC reactivity is embodied by acyl anion reactivity, exemplified by the benzoin condensation and Stetter reaction. The NHC-catalyzed benzoin condensation has been the focus of intense investigation. The cyanide catalyzed coupling of benzaldehyde to form benzoin was discovered in 1832 by Wöhler and Liebig.[5] In 1903 Lapworth

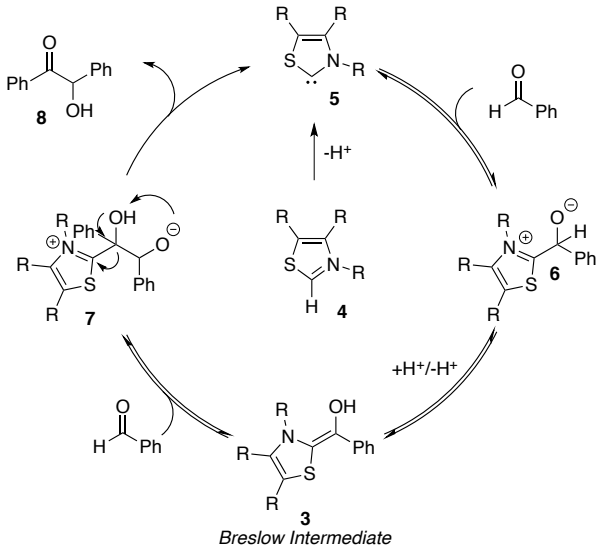
postulated a mechanism for this reaction wherein an intermediate carbanion **2** is formed by cyanide anion addition to benzaldehyde followed by deprotonation (Scheme 1.1.1).[6] This carbanion **2** exemplifies the "umolung" concept of polarity inversion.

Scheme 1.1.1



Ukai discovered in 1943 that thiazolium salts are also capable of catalyzing the benzoin condensation.[7] Building upon this work, in 1958 Breslow first hypothesized that the key intermediate in carbene catalyzed reactions is eneaminol **3** which has since been dubbed the *Breslow intermediate*.[8] Breslow hypothesized that base deprotonates thiazolium **4** to generate a free carbene **5**. This carbene then adds 1,2 to an aldehyde to produce tetrahedral intermediate **6**. This tetrahedral intermediate undergoes a proton transfer to generate eneaminol **3** or the Breslow intermediate. The Breslow intermediate then attacks a second equivalent of aldehyde to form species **7**, which then undergoes a proton transfer and collapses to form benzoin **8** and liberate cabene catalyst **5** (Scheme 1.1.2).

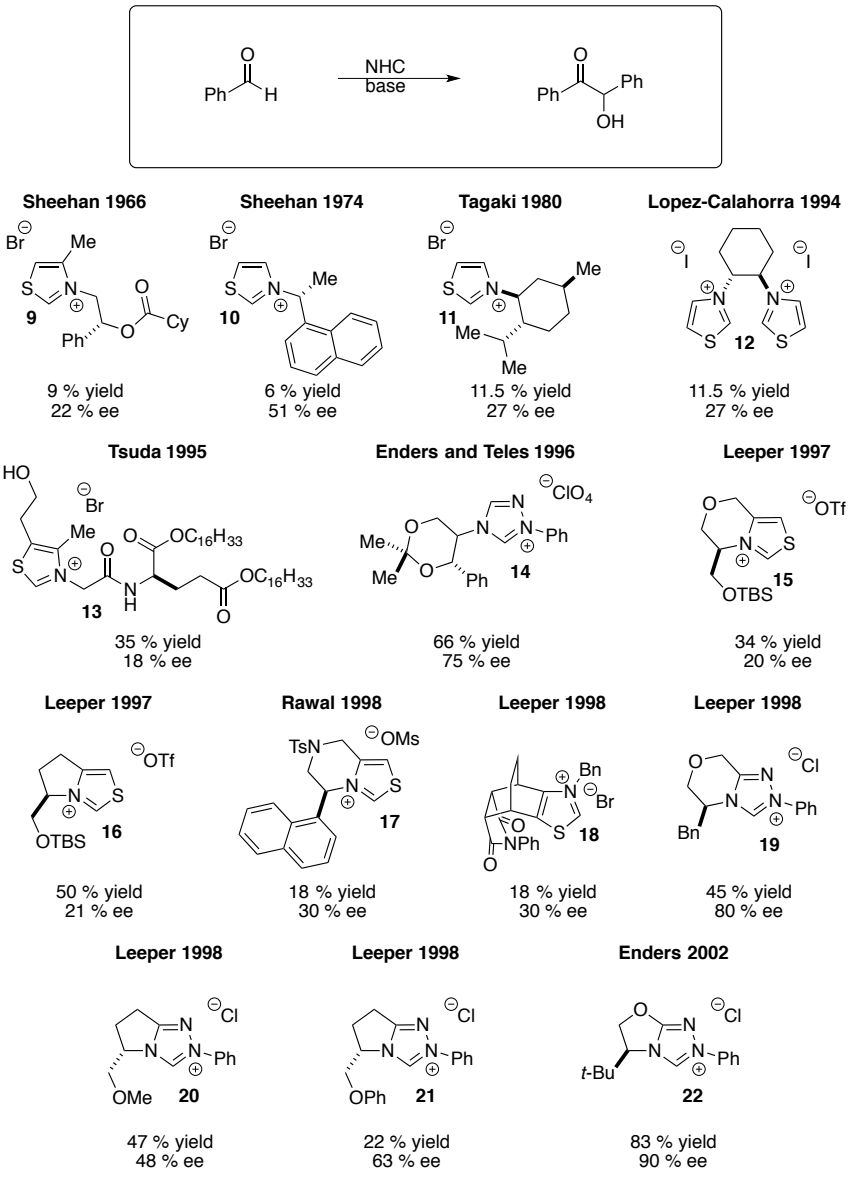
Scheme 1.1.2



1.2 Development of the Asymmetric Benzoin Reaction

After Ukai discovered thiazolium salts are capable of catalyzing the benzoin reaction, a number of groups became interested in developing an asymmetric variant. The first such example was reported by Sheehan and Hunneman in 1966.[9] By empoloying chiral thiazolium salt **9**, they observed product in a meager but encouraging 22% ee. In the following 30 years, a number of groups attempted to improve the selectivity of the reaction but with only limited success.[10] The first major advancement came in 1996 when Enders and Teles showed triazolydine catalyst **14** is capable of delivering product in 75% ee and 66% yield.[11] By synthesizing and evaluating a variety of bicyclic triazolium salt pre-catalysts, Leeper was able to increase the enantioselectivity further, while maintaining reasonable reactivity.[12] Finally, in 2002 Enders reported chiral triazolium salt **22**, which is capable of producing benzoin product in 83 % yield and an impressive 90% ee (Scheme 1.2.1).[13]

Scheme 1.2.1

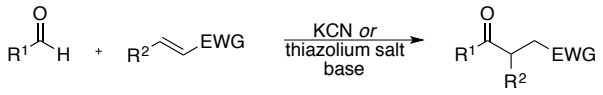


1.3 Development of the Asymmetric Stetter Reaction

In 1973 Stetter reported cyanide or thiazolidine carbenes are capable of coupling aldehydes and Michael acceptors to form 1,4-dicarbonyl compounds, expanding the scope of umpolung reactivity (Scheme 1.3.1).[14] Stetter demonstrated a variety of Michael acceptors are competent

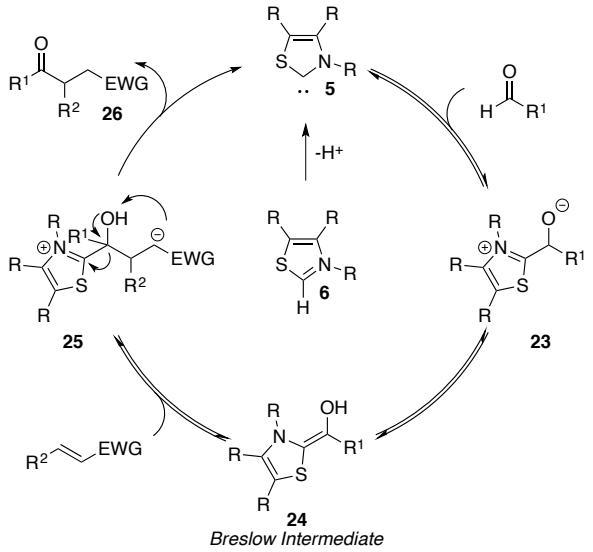
coupling partners in this reaction including: α,β-unsaturated esters, α,β-unsaturated ketones, and α,β- unsaturated nitriles.[15]

Scheme 1.3.1



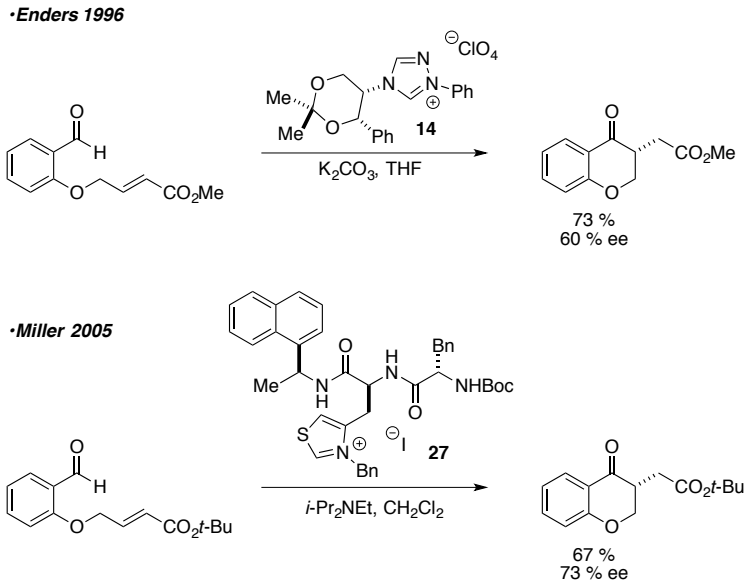
Mechanistically, this transformation is very similar to that of the benzoin condensation. First, the carbene adds 1,2 to the aldehyde to form tetrahedral intermediate **23**. This tetrahedral intermediate undergoes a proton transfer to from Breslow intermediate **24**. The Breslow intermediate then attacks the Michael acceptor in a 1,4-fashion to produce **25**, which undergoes a proton transfer allowing the carbonyl to collapse, delivering product **26** and liberating catalyst (Scheme 1.3.2).

Scheme 1.3.2



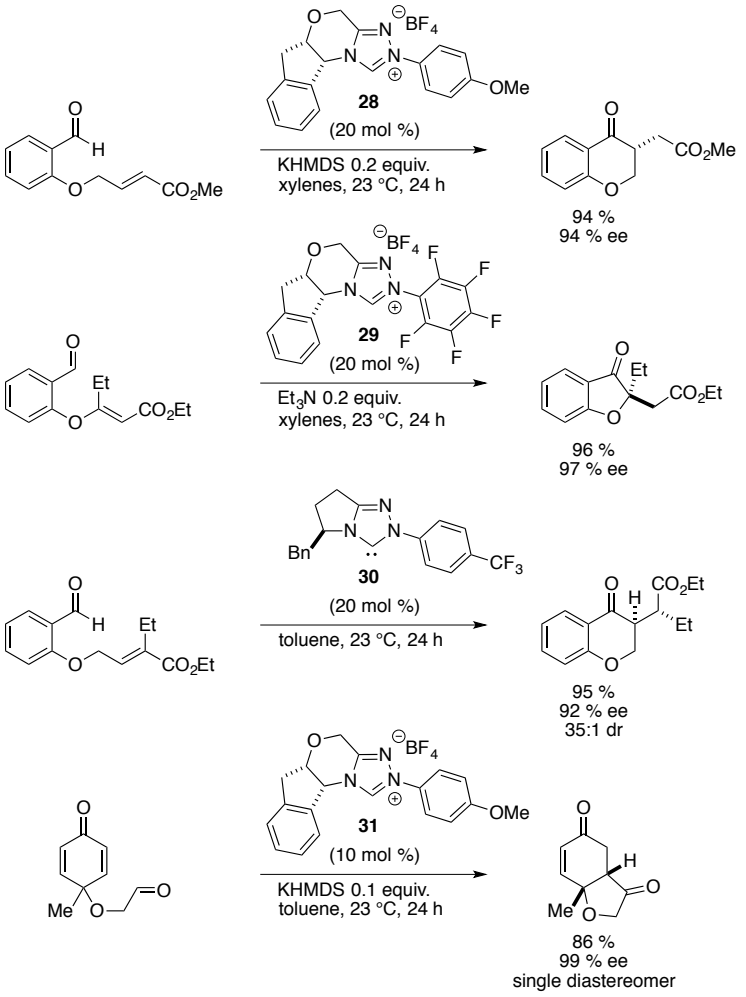
Since the initial reports from Stetter, a number of asymmetric variants of this reaction have been developed. The first asymmetric example was disclosed by Enders in 1996 using chiral triazolium precatalyst **24**.[16] This report showed product forming in high yields, but modest enantioselectivity. Miller and co-workers also reported an asymmetric intramolecular Stetter reaction and were able to achieve 67% yield and 73% ee using NHC **27** (Scheme 1.3.3).[17]

Scheme 1.3.3



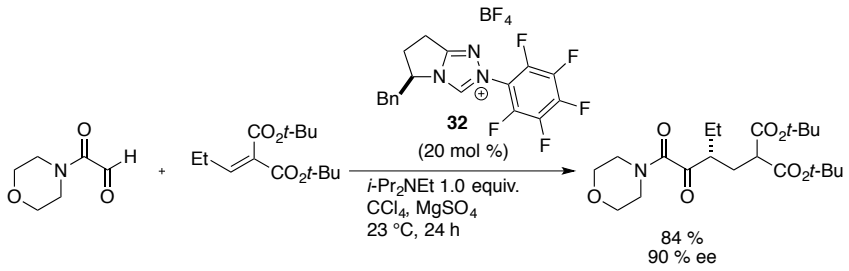
However, our group was the first to report a highly efficient asymmetric intramolecular Stetter reaction. Our first report was disclosed in 2002 where it was shown chiral NHC **28** provides product in high yields and excellent enantioselectivity.[18] We have since disclosed a number of efficient catalysts for a variety of intramolecular Stetter reactions (Scheme 1.3.4).[19]

Scheme 1.3.4



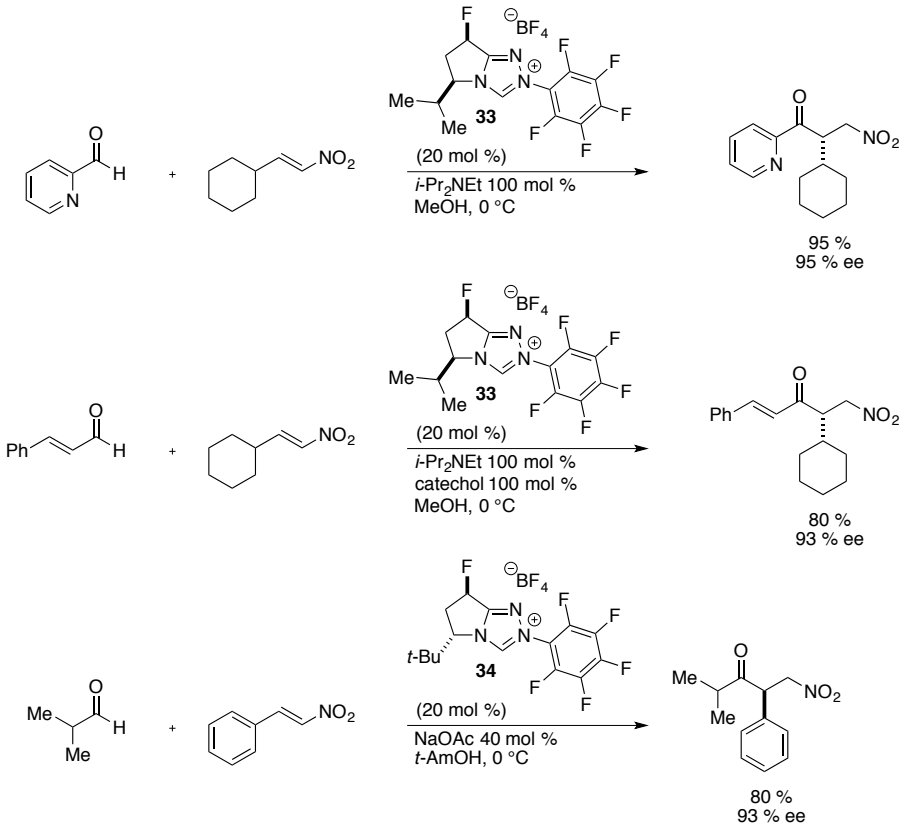
The Rovis group has also developed a number of efficient intermolecular Stetter reactions. The coupling of glyoxamindes and alkylidinemalonates was reported in 2008 and represents the first example of a highly enantioselective intermolecular Stetter reaction (Scheme 1.3.5).[20]

Scheme 1.3.5



Nitroalkenes have also been shown by us to be productive coupling partners for the intermolecular Stetter reaction. Aryl aldehydes, enals, and aliphatic aldehydes have all been shown to participate in the intermolecular Stetter reaction with nitroalkenes in high yields and excellent enantioselectivity. Key to the success of these reaction methodologies was the identification of catalysts **33** and **34**, which proved essential to achieve high enantioselectivities (Scheme 1.3.6)[21]

Scheme 1.3.6



1.4 Umplong Reactivity of Enals

Enals represent an interesting class of substrates for NHC catalysis. Typically, enals are electrophillic at the acyl and β-carbons. However, when reacted with cyanide or a NHC catalyst, enals undergo an a^1 to d^1 and an a^3 to d^3 umpolong rendering both the acyl and β-carbon nucleophilic (Figure 1.4.1).

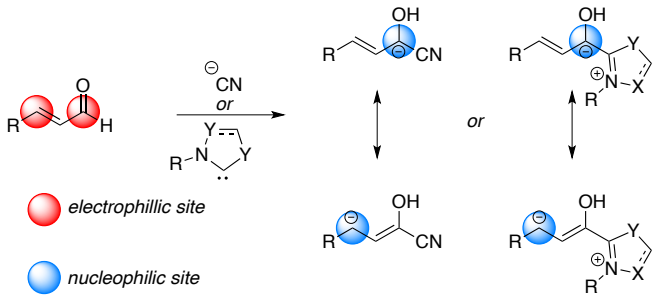
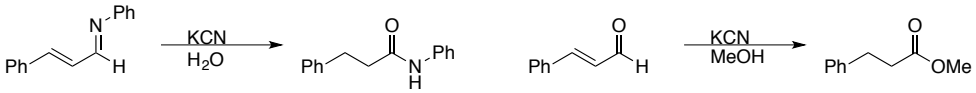


Figure 1.4.1

1.5 Cyanide Catalyzed Enal Umplong Reactions

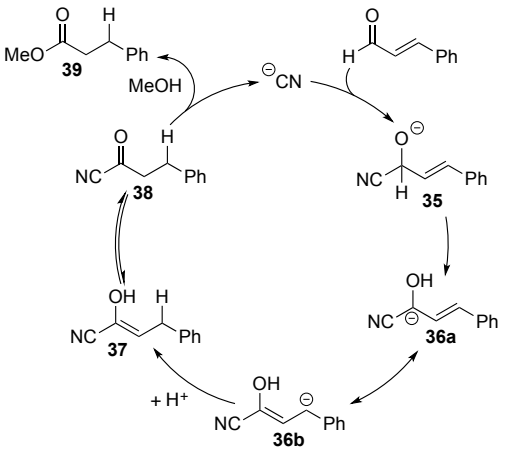
The umpolong reactivity of enals via cyanide catalysis was first reported in 1964 by Walia et al.[22] These researchers showed that α,β-unsaturated aldimines are converted to the corresponding saturated amide in the presence of a catalytic amount of cyanide in water. Subsequently, enals were shown to afford the corresponding saturated methyl ester when reacted with a catalytic amount of cyanide in methanol (Scheme 1.5.1).[23]

Scheme 1.5.1



The cyanide catalyzed synthesis of saturated esters from enals proceeds via attack of the acyl carbon from cyanide to generate tetrahedral intermediate **35**. This tetrahedral intermediate undergoes a proton transfer to form carbanion **36a**, which is in resonance with **36b**. Intermediate **36b** may be protonated by solvent to produce enol **37** which tautomerizes to acyl cyanide **38**. The acyl cyanide is then attacked by methanol to form product **38** and liberate cyanide, closing the catalytic cycle (Scheme 1.5.2).

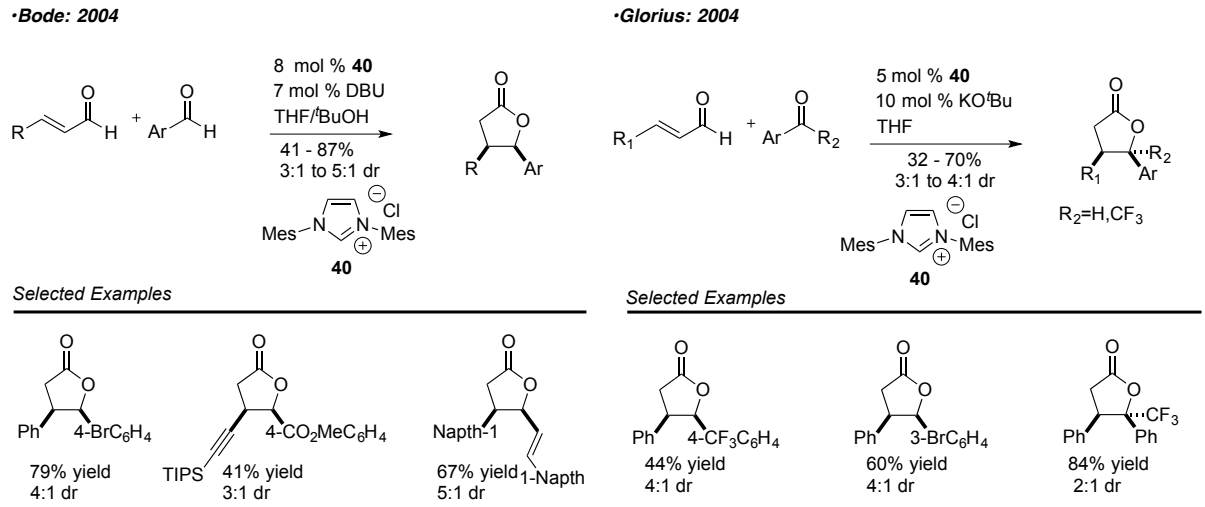
Scheme 1.5.2



1.6 Oxygen Heterocycle Synthesis via the NHC-Homoenolate Pathway

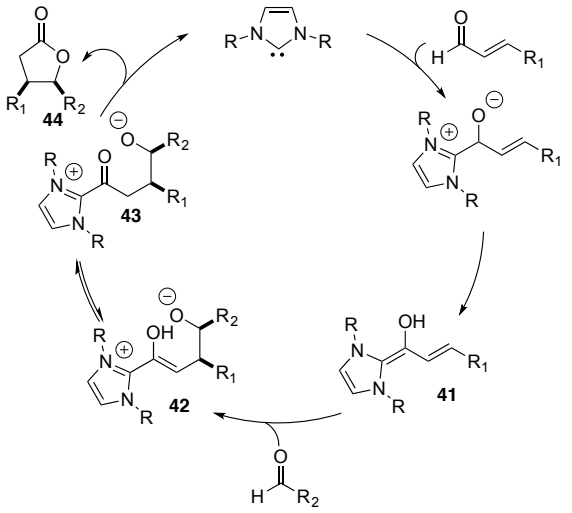
This type of reactivity lay dormant for nearly 30 years until 2004 when Glorius and Bode independently and concurrently reported the NHC-catalyzed coupling of enals and aldehydes via the homoenolate to synthesize γ-lactones.[24] These reports represent the first example of a NHC-catalyzed reaction which proceeds through the homoenolate pathway. A variety of aryl enals were shown to couple with aryl aldehydes to form *syn* γ-lactones in good yield and moderate diastereoselectivity (Scheme 1.6.1).

Scheme 1.6.1



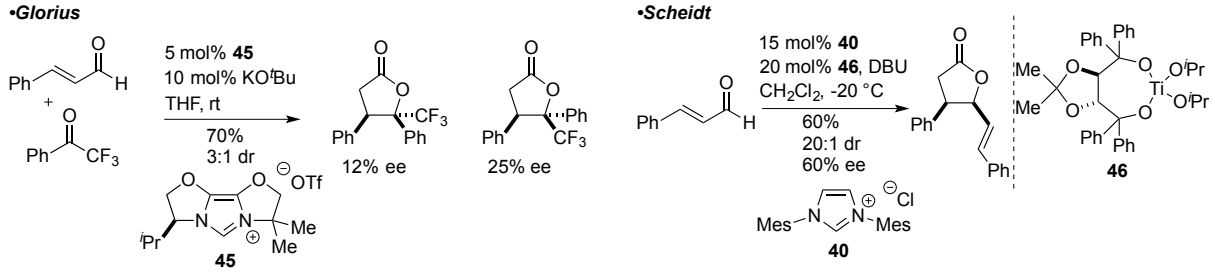
This reaction is understood to proceed via formation of Breslow intermediate **41**, which attacks an aldehyde via the β-carbon to produce **42**. Intermediate **42** undergoes tautomerization to acyl azolium **43**, which is in turn attacked in an intramolecular fashion by the tethered alkoxide to liberate catalyst and form product **44** (Scheme 1.6.2).

Scheme 1.6.2



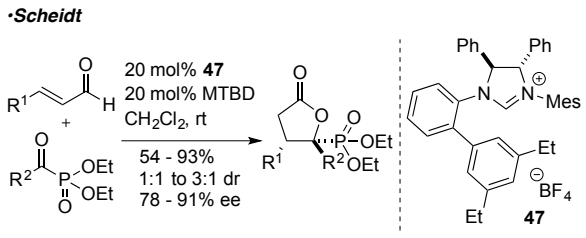
This coupling of enals and aldehydes to synthesize γ-lactones has been rendered asymmetric via the implementation of achiral NHC catalyst **45**, and the cooperative use of achiral NHC **40** in the presence of chiral Lewis acid additive **46**.[24a,25] Although these examples provide enriched product, a general NHC-catalyzed method to synthesize highly enantiomerically enriched γ-lactones from enals and aldehydes is yet to be realized (Scheme 1.6.3).

Scheme. 1.6.3



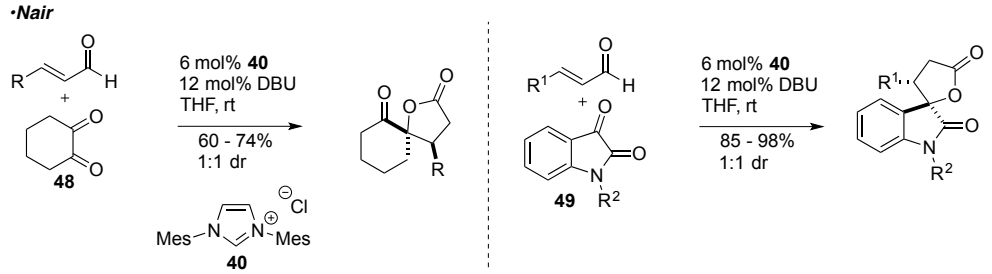
A similar reaction was reported by Scheidt an co-workers in 2014 wherein ynals were coupled with acyl phosphonates to synthesize γ-lactones in high enantioselectivity via a chiral NHC catalyst **47** designed in collaboration with the Cheong group using the aid of computational modeling.[26] This work represents some of the highest enantioselectivities realized to date in the coupling of the homoenolate with an aldehyde to generate γ-lactones (Scheme 1.6.4).

Scheme 1.6.4



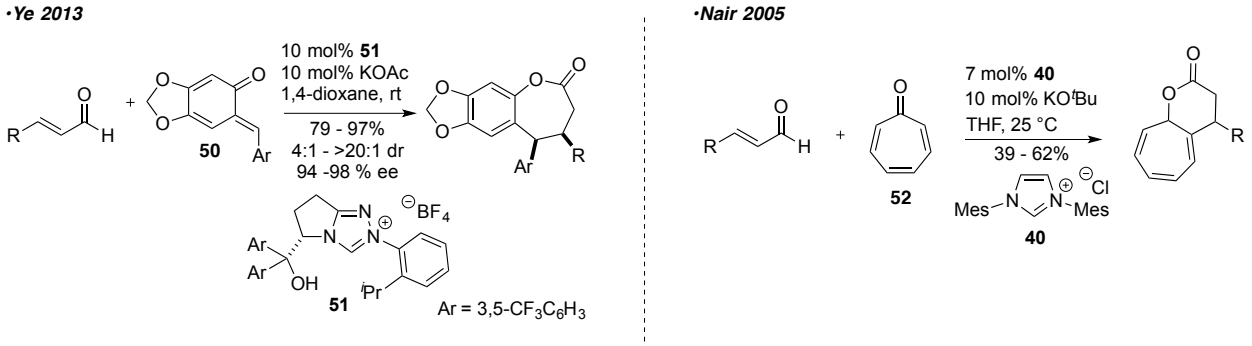
This approach has also been utilized to synthesize spirocyclic lactones by coupling enals with cyclohexane-1,2-dione **48** and isatin derivatives **49.**[27] The synthesis of spirocyclic γ-lactones via NHC-catalysis has seen a considerable amount of attention and this class of reaction has been expanded accordingly (Scheme 1.6.5).[28]

Scheme 1.6.5



Larger oxygen heterocycles have also been synthesized via the NHC-generated homoenolate equivalent. In 2013, Ye and co-workers demonstrated the coupling of enals with dioxolane-fused *o*-quinone methides **50** bearing aryl substituents off the *exo*-olefin to generate seven-membered lactones.[29] Nair et al. also discovered an NHC-catalyzed annulation of enals and tropone **52** to generate fused six-membered lactones (Scheme 1.6.6).[30]

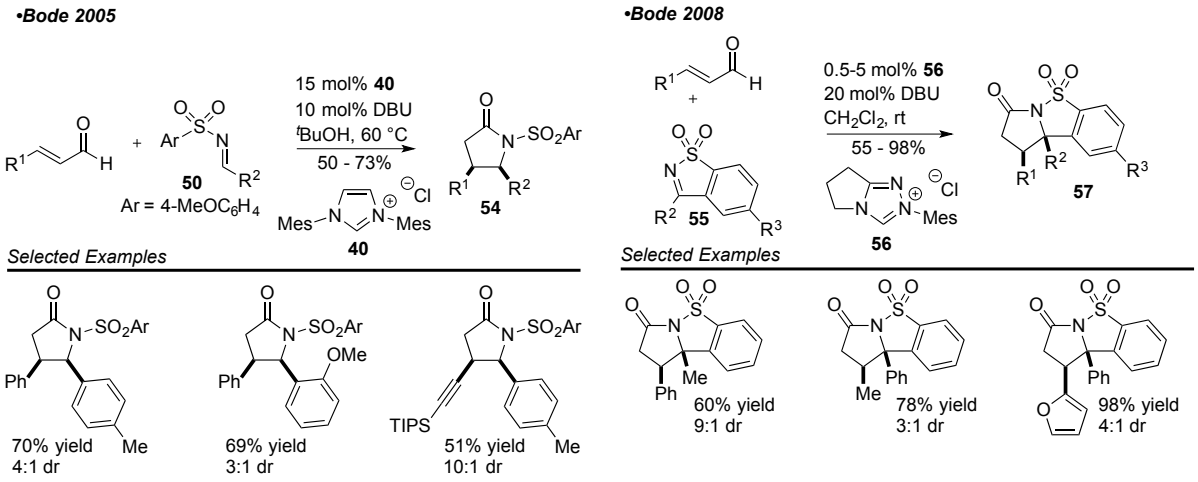
Scheme 1.6.6



1.7 Nitrogen Heterocycle Synthesis via the NHC-Homoenolate Pathway

In addition to the efforts put towards oxygen heterocycle synthesis, a number of useful NHC-catalyzed methodologies for the synthesis of nitrogen heterocycles have also been developed. The first example was reported in 2005 from He and Bode.[31] They demonstrated the coupling of enals and *N*-sulfonylimines **53** to generate *syn* 4,5-disubstituted γ-lactams **54** in good yield and moderate diastereoselectivity. This reaction is understood to proceed via the same mechanism as the addition of enals to aldehydes to form γ-lactones, the only difference being that the nitrogen of the imine attacks the acyl azolium to liberate catalyst and form the heterocycle. This initial report was limited to imines bearing 4-methoxyphenylsulfonamide as the *N*-substituent. Later work by Bode overcame some of the limitations of this initial report by using cyclic sulfonylketamines **55** to synthesize fused γ-lactams **57** (Scheme 1.7.1).[32]

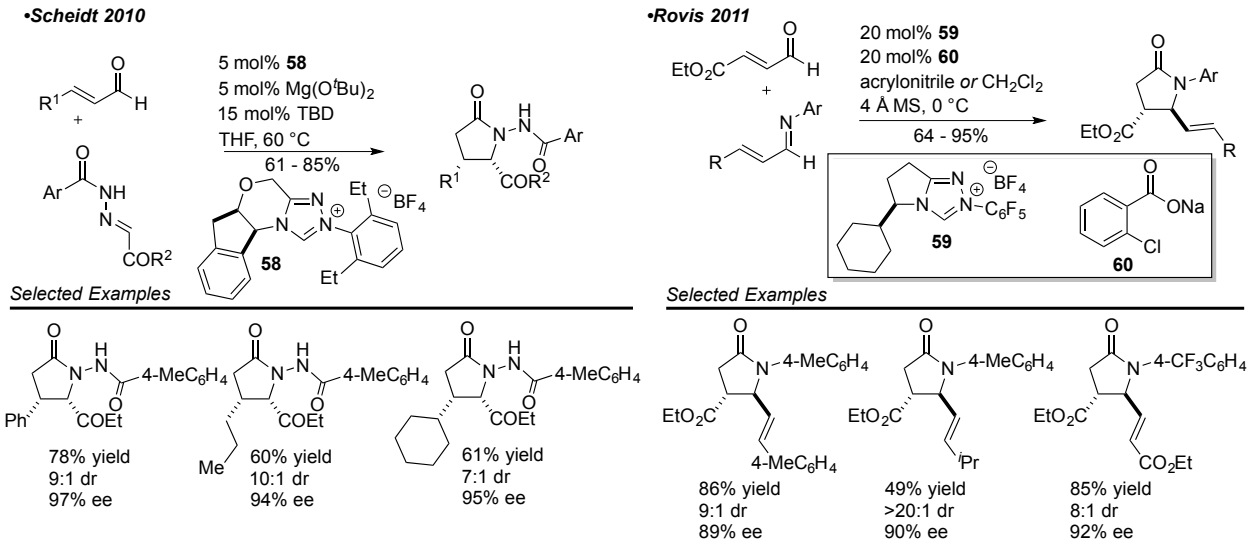
Scheme 1.7.1



Subsequently, the groups of Scheidt and Rovis both reported asymmetric variants of this transformation. Schiedt and Chan reported *N*-acyl hydrazones are competent coupling partners of the NHC-generated homoenolate equivalent in a cooperative NHC/Lewis acid mediated transformation.[33] In this reaction it is proposed that Mg(O*t*-Bu)$_2$ coordinates to the acyl oxygen and the nitrogen of the hydrazone, activating the acyl hydrazone towards nucleophilic addition. The authors demonstrated that both aliphatic and aryl enals participate in the reaction, providing product in good yields, diastereoselectivity, and enantioselectivity. Rovis and co-workers developed a cooperative Brønsted acid/NHC catalytic system to synthesize γ-lactams from enals and azadienes.[34] In this report, it is proposed that a small amount of weak base **60** deprotonates chiral azolium salt **59** to generate the free carbene which reacts with the enal to form the extended Breslow intermediate. The conjugate acid of **60** then protonates the azadiene, making it more electrophilic. Evidence for this mode of activation was provided when an achiral NHC was used in conjunction with a chiral carboxylate base and asymmetric induction was observed in the lactam product. Interestingly, this methodology provides *trans* γ-lactams, in contrast to the products

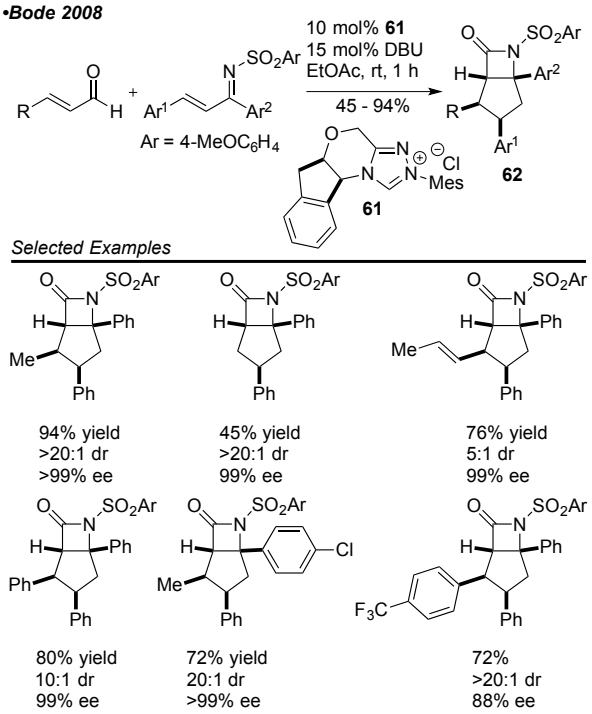
observed by Bode and Scheidt in their syntheses of γ-lactams (Scheme 1.7.2).

Scheme 1.7.2



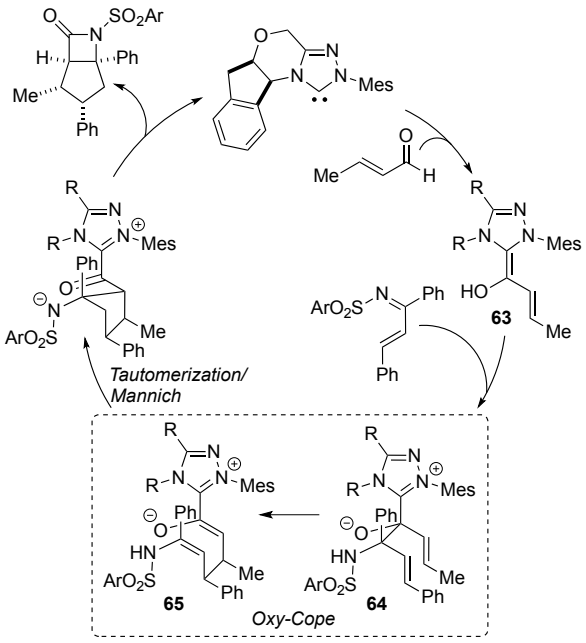
In addition to γ-lactams, a number of other nitrogen containing heterocycles have also been synthesized via the homoenolate pathway. Bode reported a synthesis of fused β-lactams **62** by coupling enals with α,β-unsaturated *N*-sulfonyl ketimines.[35] This is a notable transformation as it favors β-lactam formation despite competing enal dimerization and hetero-Diels-Alder pathways (Scheme 1.7.3).[36]

Scheme 1.7.3



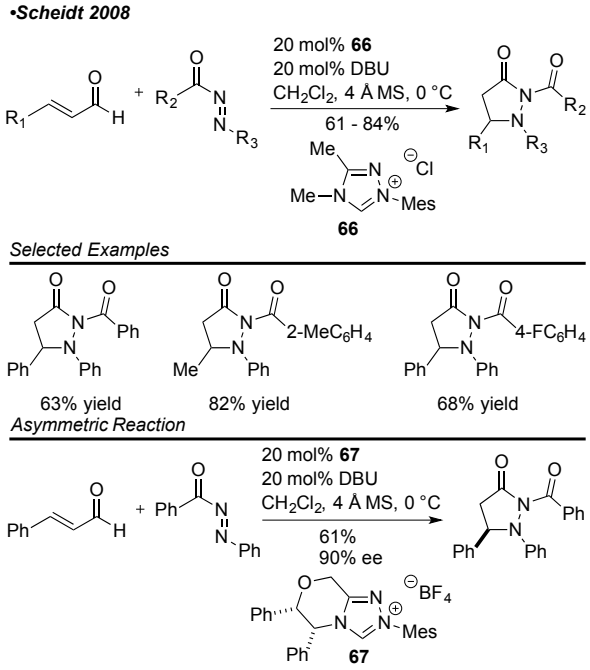
Bode proposed that this reaction proceeds via a cross aza-benzoin reaction followed by an oxy-Cope rearrangement cascade. It is postulated that the Breslow intermediate **63** first adds to the ketamine via the acyl anion pathway to produce **64** followed by an oxy-Cope rearrangement to furnish enolate **65**. This enolate then adds to the imine via a Mannich reaction and the nitrogen anion cyclizes on the acyl azolium liberating catalyst and producing the β-lactam product. However, it is possible that the homoenolate adds 1,4 to the ketamine, directly furnishing **65** under a more traditional homoenolate-type reaction mechanism (Scheme 1.7.4).

Scheme 1.7.4



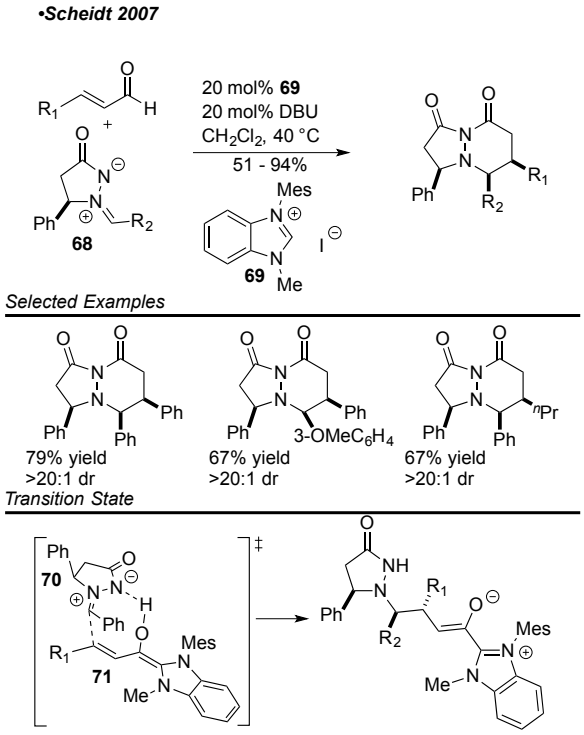
Diazenes have also been shown to be competent coupling partners in NHC-catalyzed homoenolate annulations. Chan and Scheidt showed that electron-rich aryl diazenes may react with electron-deficient and electron-rich aryl enals in the presence of a NHC catalyst to furnish pyrazolidinone products in good yield.[37] In this report, there is one example shown with a chiral NHC catalyst and the desired product is formed in 61% yield and 90% ee (Scheme 1.7.5).

Scheme 1.7.5



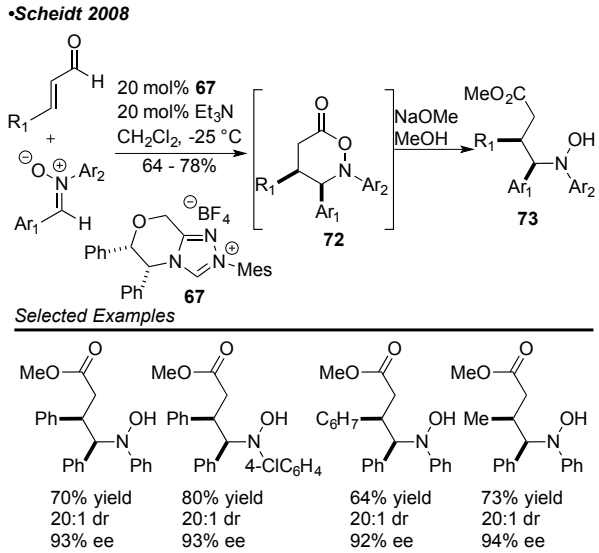
In a related transformation, Scheidt and Chan showed that azomethine ylides **68** may react with the NHC-generated homoenolate in a formal [3+3] to furnish pyridazinones.[38] Electron-rich, aliphatic, and dienyl enals participate in the reaction. Both electron-rich and electron-poor susbstituents are tolerated on the imine moiety; however, enolizable and 2-substituted aryl imines do not participate. The reaction proceeds with high yields and excellent diastereoselectivity. The high diastereoselectivity is attributed to a hydrogen bond between the Breslow intermediate **71** and azomethine ylide **70**, preoganizing the transition state for a *syn*-addition (Scheme 1.7.6).

Scheme 1.7.6



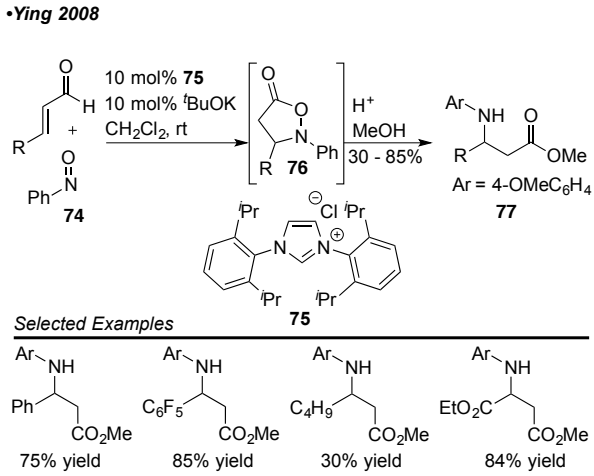
Nitrones have also been reacted under the homoenolate manifold. Scheidt demonstrated that aryl nitrones may couple with aryl and aliphatic aldehydes via a formal [3+3] annulation to generate heterocyclic lactones.[39] The NHC-generated homoenolate attacks the nitrone and then tautomerizaes to the acyl azolium. Intramolecular interception of the acyl azolium liberates carbene and generates heterocyclic lactone **72**. This lactone is then opened in a second step to produce the linear ester product **73** (Scheme 1.7.7).

Scheme 1.7.7



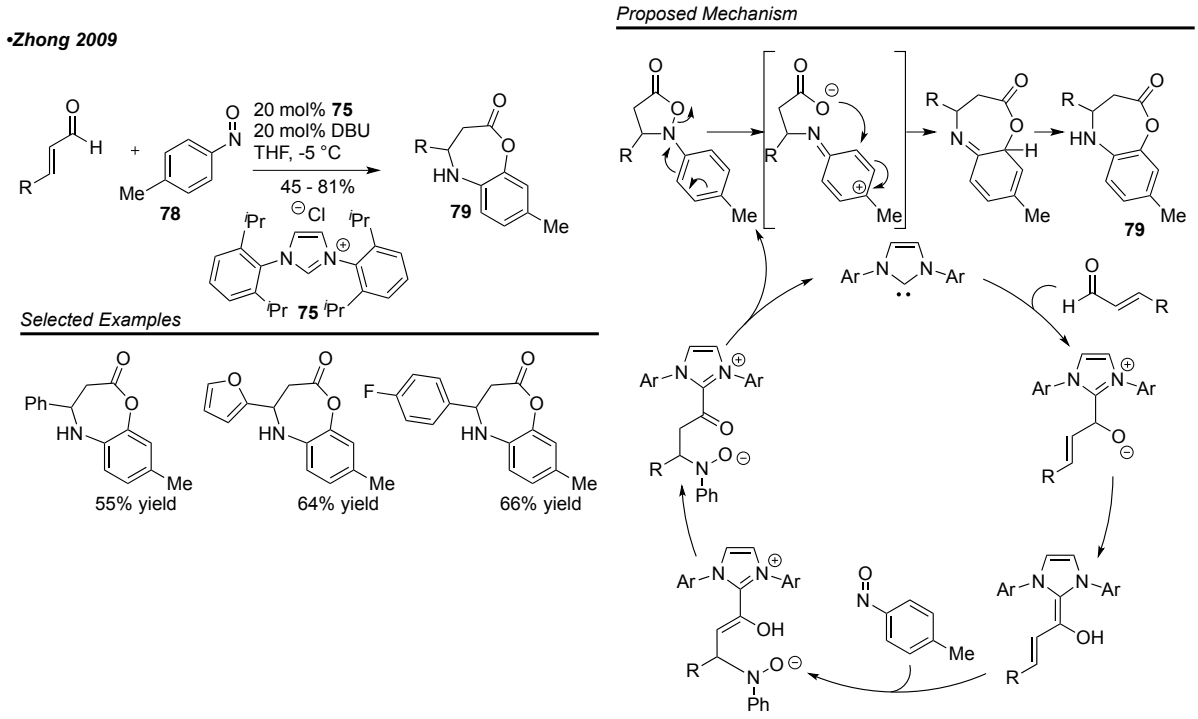
Finally, the nitroso group has been utilized as a coupling handle for the synthesis of nitrogen containing heterocycles via NHC catalysis. In 2008 this type of reactivity was first demonstrated when enals were coupled with nitrosobenzene **74** to furnish isoxazolidinone products **76**.[40] The reaction is understood to proceed via attack on the nitrogen of the nitroso from the homoenolate position, followed by cyclization of the pendant alkoxide onto the acyl azolium. These isoxazolidinone products **76** were further elaborated to the β-amino ester **77** upon treatment with acid and methanol (Scheme 1.7.8).

Scheme 1.7.8



In an interesting extension of this chemistry, nitroso compounds were demonstrated to couple with the homoenolate equivalent via a formal [4+3] annulation.[41] Mechanisticaly, this is thought to first proceed via the [3+2] isoxazolidinone formation above, but then undergoes a 1,2-Bamberger-type rearrangement to furnish the seven membered lactone **79**. Electron-rich and electron-poor aromatic and heteroaromatic enals are tolerated in the reaction; however, the nitroso component is limited to 1-methyl-4-nitrosobenzene **78** Scheme 1.7.9).

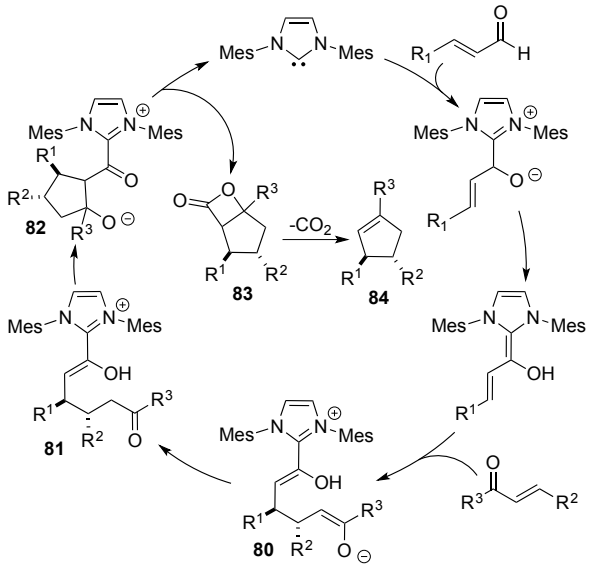
Scheme 1.7.9



1.8 Carbocycle Synthesis via the NHC-Homoenolate Pathway

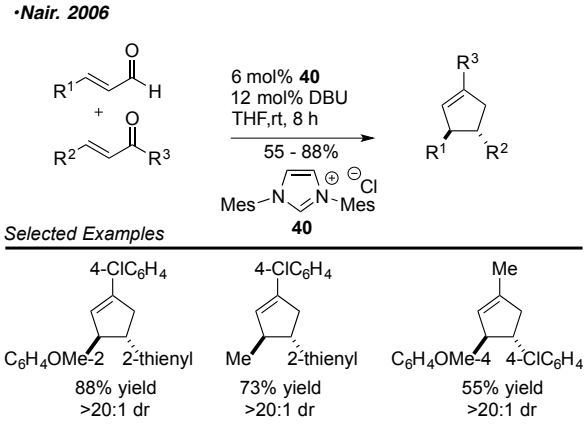
Carbocyclic compounds have also been synthesized via a variety of NHC-catalyzed methodologies. The first example was reported by Nair and co-workers in 2006. It was found that enals couple with chalcones to furnish 1,3,4-trisubstituted cyclopentenes.[42] The accepted mechanism for this transformation begins with formation of the extended Breslow intermediate followed by a 1,4 addition of the homoenolate to the chalcone furnishing intermediate **80**. Tautomerization of **80** leads to ketone **81**, which then undergoes an aldol reaction with the enol-azolium to provide alkoxide **82**. Cyclization of the alkoxide onto the acylazolium liberates the active catalyst and furnishes β-lactone **83**, which decarboxylates to provide the observed cylopentene product **84** (Scheme 1.8.1).

Scheme 1.8.1



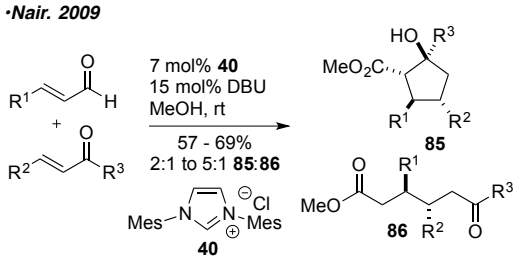
A variety of both chalcones and enals participate in this reaction and yields are generally good. Diastereoselectivity is excellent, with the *trans* substituted product being formed in >20:1 dr in all cases. Aliphatic substation is tolerated on both the chalcone and the enal coupling partners (Scheme 1.8.2).

Scheme 1.8.2



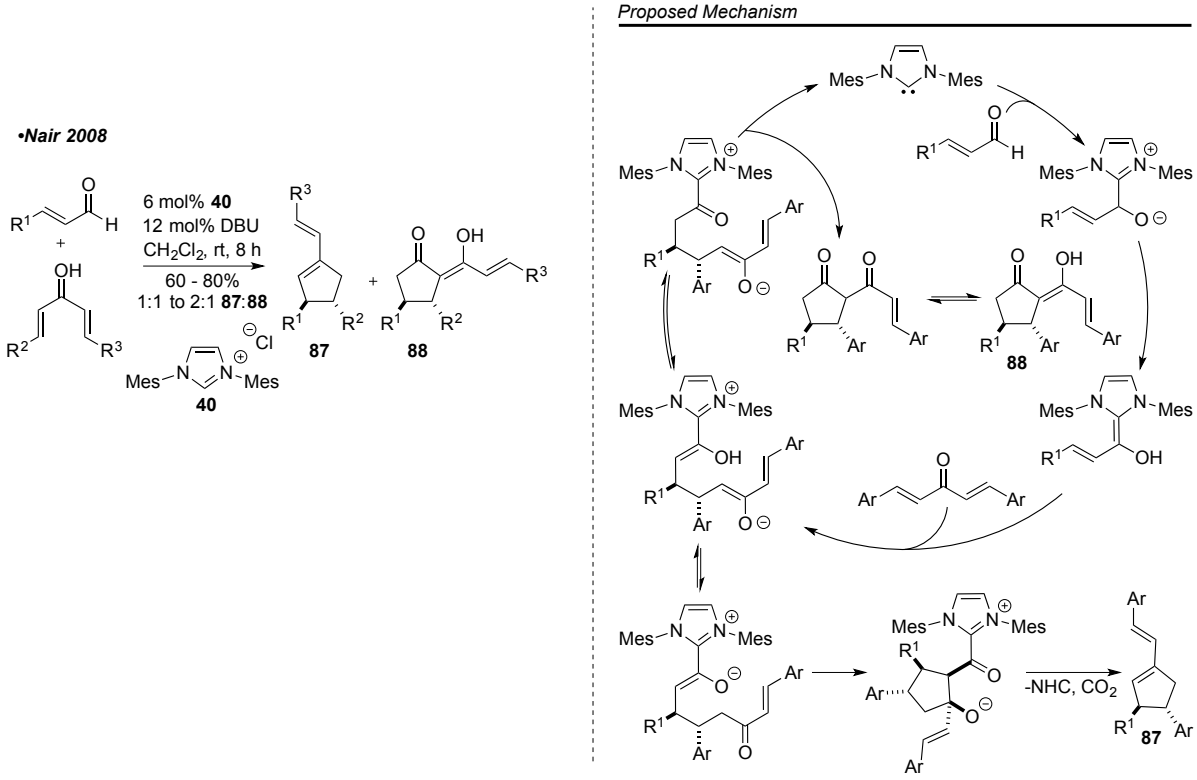
In an extension of this work Nair et al. also showed that the acylazolium may be intercepted by an exogenous alcohol to generate either cyclic ester **85** or straight chain ester **86**.[43] The yields of this reaction range from 57 to 69%, with products forming as a single diastereomer, and in a product ratio of 2:1. In this case, the scope of the transformation is limited to aryl enals and bis-aryl enones (Scheme 1.8.3).

Scheme 1.8.3



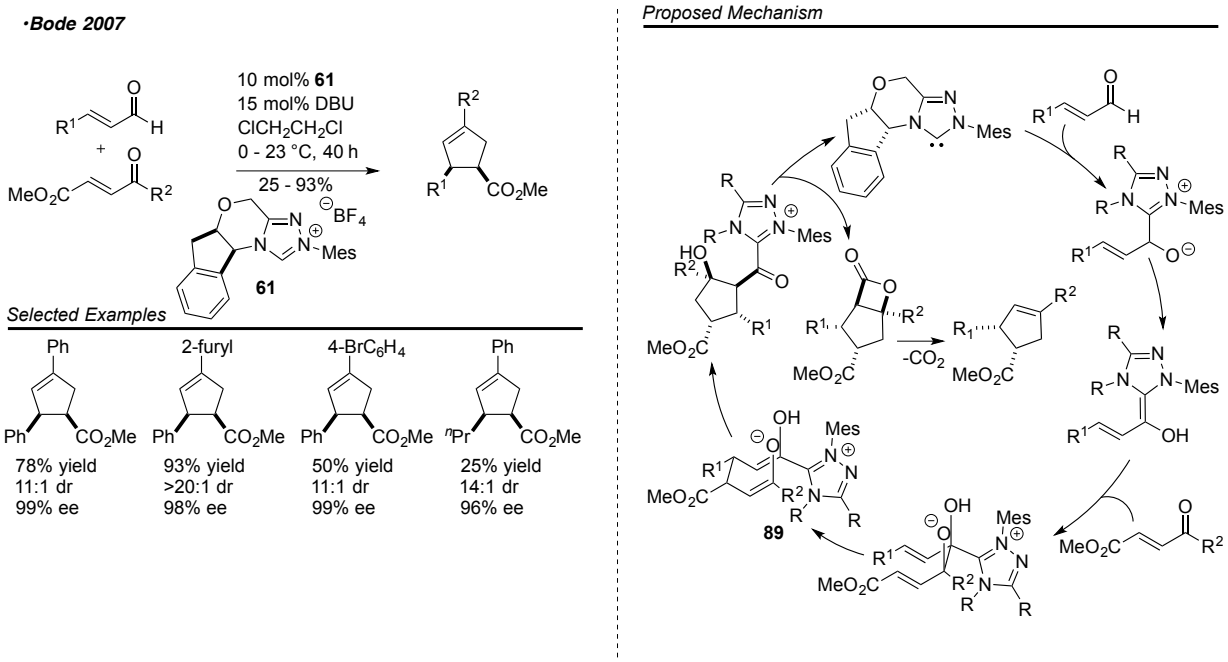
The reaction of dialkylidine ketones with enals has also been shown, forming cyclopentanone **87** and cyclopentene products **88**.[44] The origin of product selectivity is believed to arise from C-acylation of the acylazolium leading to the cyclopentanone product (Scheme 1.8.4), while the cyclopentene product results from an intramolecular aldol / decarboxylation pathway (*vide supra*). The product selectivity appears to be substrate controlled, but generally gives a distribution of up to 2:1, favoring the cyclopentene product (Scheme 1.8.4). This reaction represents a rare example of carbon attacking the acyl azolium.

Scheme 1.8.4



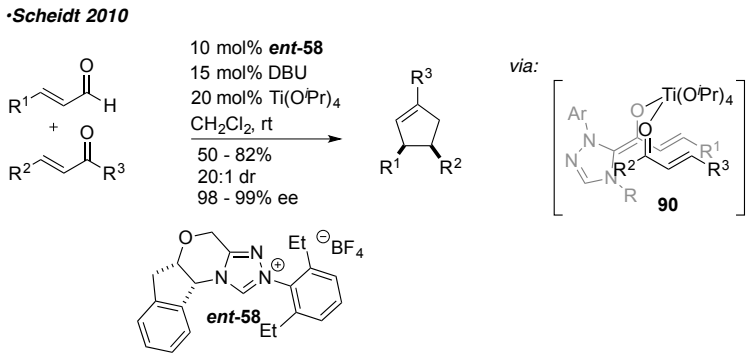
Shortly after Nair's group reported the first NHC-catalyzed cyclopentene forming reaction, Bode and co-workers reported an enantioselective variant of the reaction, coupling enals to 4-oxoenoates.[45] This report from Bode is notable as it provides the *cis*-cyclopentene product, in contrast to Nair's report which exclusively generates the *trans*-diastereomer. Bode and co-workers propose that their cyclopentene forming reaction proceeds via a cross-benzoin reaction between the enal and 4-oxoenoate followed by an NHC-promoted oxy-Cope rearrangement to funish **89** (Scheme 1.8.5). However, it is also possible that the reaction proceeds via the homoenolate, as proposed by Nair.

Scheme 1.8.5



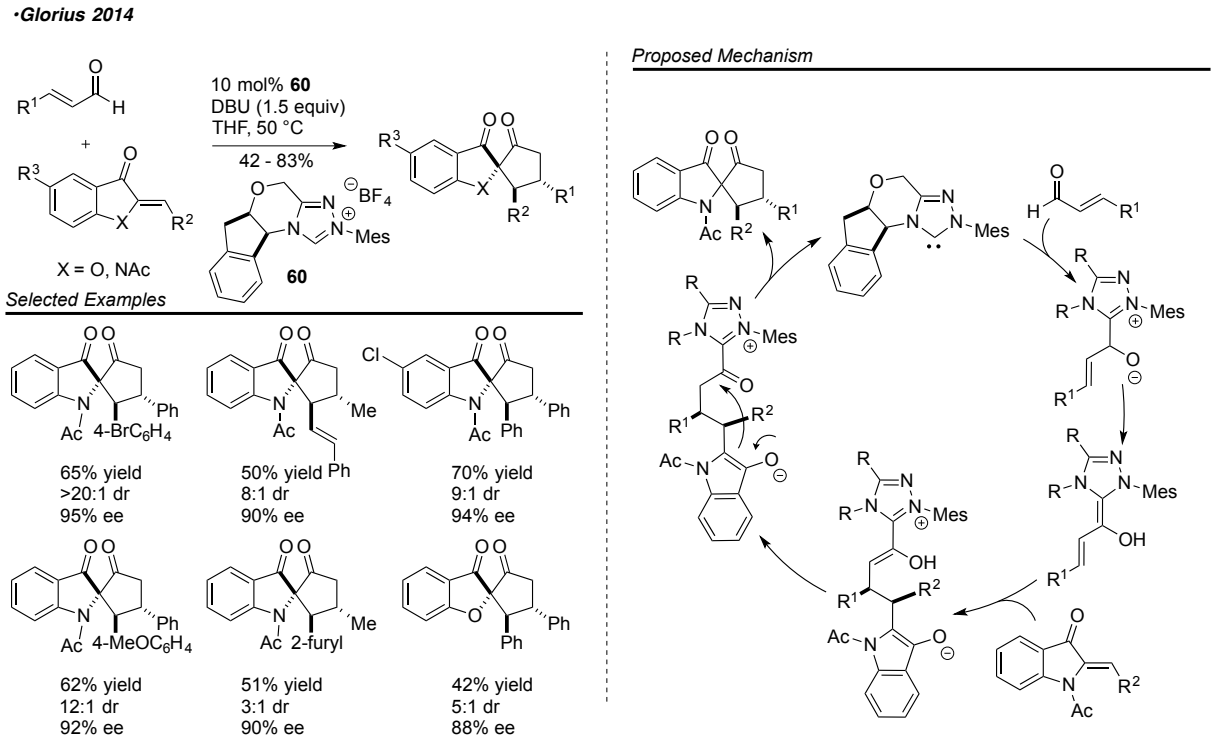
Scheidt and co-workers also reported an asymmetric variant of this reaction wherein the addition of a Lewis acid co-catalyst allows for the coupling of the same enals and chalcones that Nair achieved in his earlier report.[46] Interestingly, this methodology also produces the *cis*-diastereomer that was observed by Bode et al. However, the opposite enantiomer of product is observed even though Scheidt employed the opposite antipode of carbene catalyst. The authors argue that the Lewis acid coordinate to the extended Breslow intermediate and the chalcone to pre-organize the s-*cis* transition state **90** (Scheme 1.8.6).

Scheme 1.8.6



Finally, Glorius and co-workers demonstrated an asymmetric coupling of enals and aurenones via a [3+2] annulation.[47] This reaction is believed to proceed via 1,4 addition of the NHC-generated homoenolate equivalent to the Michael acceptor. The resultant enol azolium tautomerizes to the acyl azolium which is in turn attacked via the pendant enolate. This protocol tolerates aryl and aliphatic enals as well as aurones bearing a variety of substitution. This reaction represents a rare example of carbon turnover of the acyl azolium (Scheme 1.8.7).

Scheme 1.8.7



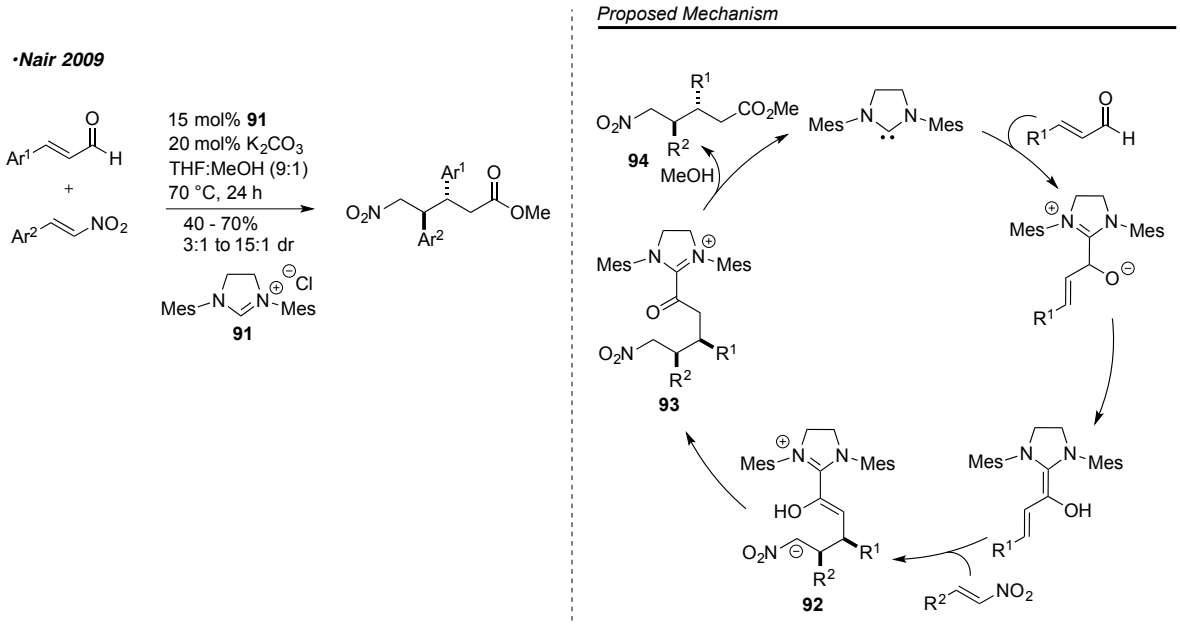
1.9 β-Functionalization of Enals to Generate Acyclic Esters

The utility of the NHC-generated homoenolate pathway is not limited to annulative processes. The first examples of such a transformation were reported in 2005 by Scheidt and Bode. These initial reports demonstrated that the extended Breslow intermediate may undergo protonation at the β-position to generate saturated esters.[48,49] In these reports, aliphatic and aryl enals were both shown to participate in the reaction, providing products in high yields.

Nair and co-workers demonstrated the coupling of enals and nitroalkenes to generate δ-nitroesters in 2009. Aryl enals were shown to couple with nitrostyrene devivatives in good yield and moderate diastereoselectivity for the *anti*-diastereomer. [50] Mechanistically, the reaction is believed to proceed via 1,4-addition of the extended Breslow intermediate to the nitroalkene. The resultant

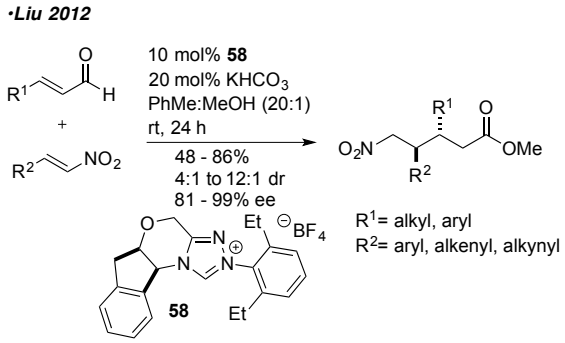
nitronate **92** is protonated and the enol azolium tautomerizes to form acylazolium **93**. The acylazolium is then intercepted by methanol to furnish product **94** and liberate catalyst (Scheme 1.9.1).

Scheme 1.9.1



In 2012 the Liu group reported an asymmetric variant of this reaction using chiral catalyst **58**.[51] This protocol allowed for the coupling of both aryl and aliphatic enals with aryl, dienyl, and yne-enyl nitroalkenes. Products were isolated in good yields, high enantioselectivity, and good diastereoselectivity for the *anti*-diastereomer (Scheme 1.9.2). We reported an asymmetric coupling of enals and nitroalkenes to synthesize *syn*-nitroesters in 2013.[52] For a detailed account of our efforts towards the asymmetric coupling of enals and nitroalkenes, see Chapter 2.

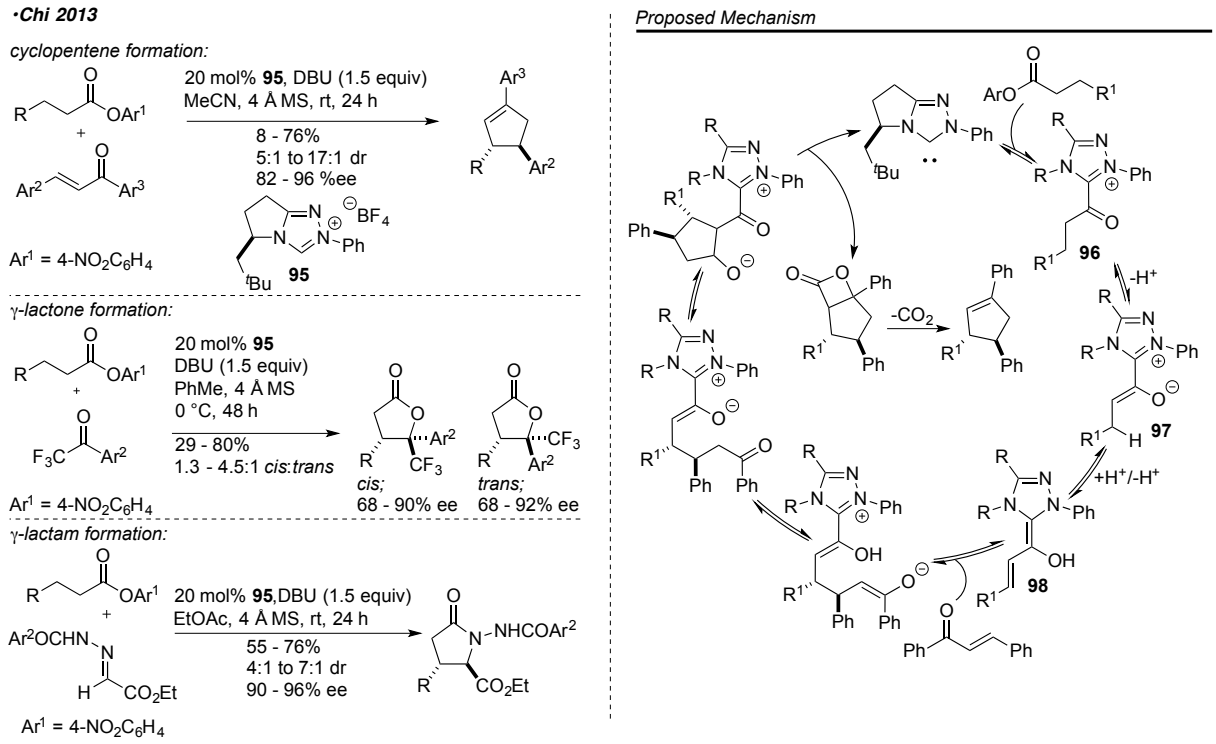
Scheme 1.9.2



1.10 Alternate Access to the Homoenolate Pathway

In 2009, Bode reported that α-hydroxy enones are efficient bench-stable surrogates of enals for NHC-catalyzed homoenolate additions to various electrophiles.[53] A limitation is that the increased steric demand of these substrates inhibits their use with bulky chiral catalysts. In 2013, Chi and co-workers demonstrated that saturated esters are potential homoenolate precursors.[54] This reactivity is notable because it functionalizes a traditionally non-reactive β-carbon of a *saturated* ester. The reaction is proposed to proceed by initial addition of the carbene to the electron deficient aryl ester generating acylazolium **96**, which then tautomerizes to enolate azolium **97**. This intermediate can then undergo a proton transfer from the β-carbon to the enolate oxygen furnishing extended Breslow intermediate **98** (Scheme 1.10.1). Using this methodology, cyclopentene products form in 8-76% yield, 5:1 to 17:1 dr, and 82-96% ee. Aliphatic and aryl esters are tolerated as the homoenolate precursor and bis-aryl enones are used for the Michael acceptor. γ-Lactones may be synthesized using this methodology by coupling CF_3/aryl ketones with hydrocinnamates to furnish products in 29-80% yield, 68-92% ee, and 1.3:1 to 4.5:1 dr. This method was also used to synthesize nitrogen heterocycles. γ-Lactams are formed in 55-76% yield, 90-96% ee, and 4:1 to 7:1 dr (Scheme 1.10.1).

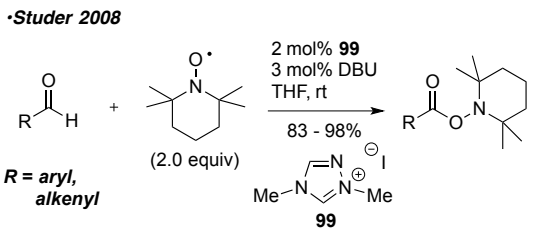
Scheme 1.10.1



1.11 Single-Electron Pathways in NHC-Catalysis

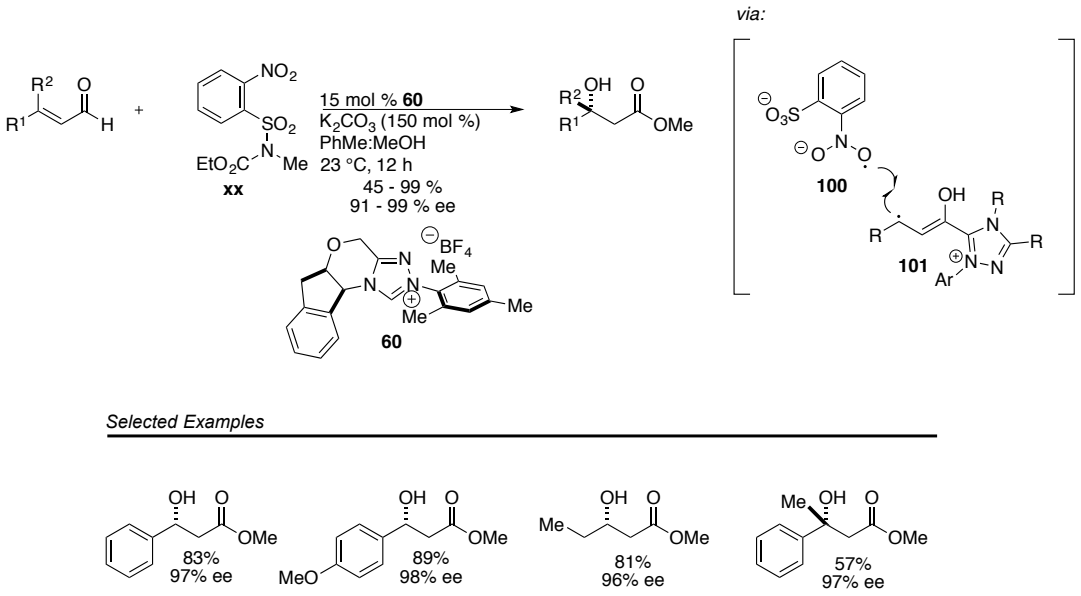
Studer reported the first example of the Breslow intermediate undergoing a single-electron oxidation in 2008 within the context of the TEMPO oxidation of aldehydes to esters.[55] In this reaction, the Breslow intermediate undergoes two single-electron oxidations for a net two-electron oxidation of the Breslow intermediate to the acyl azolium (Scheme 1.11.1).

Scheme 1.11.1



The first example of a NHC-catalyzed pathway involving a radical bond forming reaction was reported by us in 2014.[56] For a detailed account of this reaction see Chapter 3. In 2015 Chi and co-workers reported a NHC-catalyzed β-hydroxylation of enals that is understood to proceed via a radical mechanism. [57] It is postulated that an electron-deficient nitroarene abstracts a single-electron from the Breslow intermediate and then recombines through an oxygen centered radical of the nitroarene **100** at the β-position of the radical cation derived from the Breslow intermediate **101** (Scheme 1.11.2).

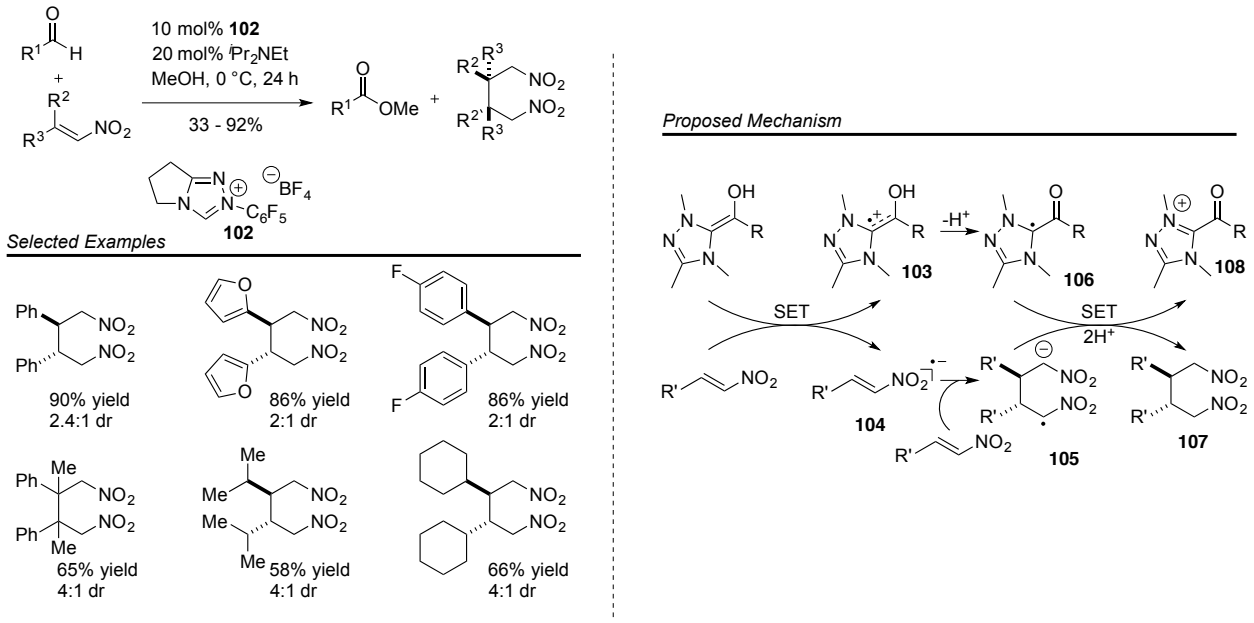
Scheme 1.11.2



In 2014 Chi and co-workers reported a strategy for the dimerization of nitroalkenes wherein it is proposed that the Breslow intermediate acts a single electron reductant of the nitroalkene.[58] It is postulated that first the Breslow intermediate donates a single electron to the nitroalkene to generate radical cation **103** and radical anion **104**. The radical anion then attacks a second equivalent of nitroalkene to furnish radical anion intermediate **105**. At this point, the radical Breslow intermediate loses a proton to become neutral radical **106**. Radical anion **105** abstracts a

second single electron from neutral Breslow radical and accepts two protons to furnish product **107** and to generate acylazolium **108**. The acyl azolium is then intercepted by methanol to regenerate catalyst and liberate ester product (Scheme 1.11.3). This mechanistic proposal is supported by EPR analysis of the nitroalkene centered radical anion. Electron-rich and electron-poor aryl and aliphatic nitroalkenes undergo the dimerization with yields ranging from 33-92% and dr ranging from 2:1 to 9:1. β,β-disubstituted nitroalkenes also participate in this reaction. Aryl aldehydes are required as the electron donor in this reaction (Scheme 1.11.3).

Scheme 1.11.3



1.12 Conclusion

In summary, this chapter serves as an introduction to the historical context of NHC-catalyzed reactions. Specifically, it is meant to demonstrate the wide range of methodologies that have been developed to functionalize enals at the β-position under the NHC-generated homoenolate equivalent manifold, as well as outline the contibutions of the Rovis group to NHC

catalysis. This history sets the stage for further exploration of the NHC-generated homoenolate equivalent for the β-functionalization of enals.

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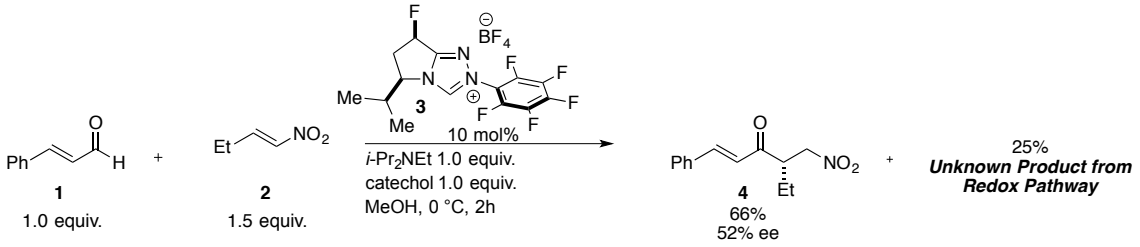
Chapter 2

Asymmetric Addition of Enals to Nitroalkenes to Generate δ-Nitroesters via the N-Heterocyclic Carbene Generated Homoenolate Equivalent

2.1 Introduction

During my former colleague Dan DiRocco's investigation into the NHC-catalyzed Stetter reaction between enals and nitroalkenes an unknown side product was observed when cinnamaldehyde **1** was reacted with (*E*)-1-nitrobut-1-ene **2**.[1] The expected Stetter product **4** was formed in 66% yield and 52% ee with the remainder of the mass balance being the unknown ester product (Scheme 2.1.1).

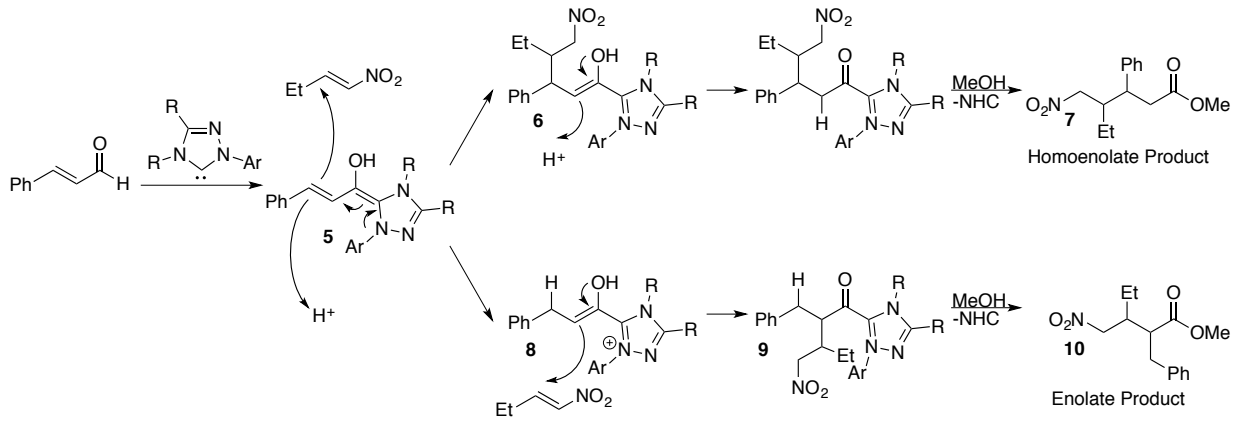
Scheme 2.1.1



It was initially hypothesized that this may either be the product of a NHC-generated homoenolate addition to the nitroalkene or a NHC-generated enolate addition to the nitroalkene (Scheme 2.1.2). The homoenolate derived product would arise from the extended Breslow intermediate **5** first attacking the nitroalkene to form the C-C bond at the β-position to form enol azolium **6**, which after tautomerization to and addition of methanol forms product **7**. Conversely,

an enolate derived product would form via the extended Breslow intermediate **7** being protonated at the β-position to form enol azolium **8**, which then attacks the nitroalkene to form acyl azolium **9**. Acyl azolium **9** then undergoes attack by methanol to from product **10** (Scheme 2.1.2).

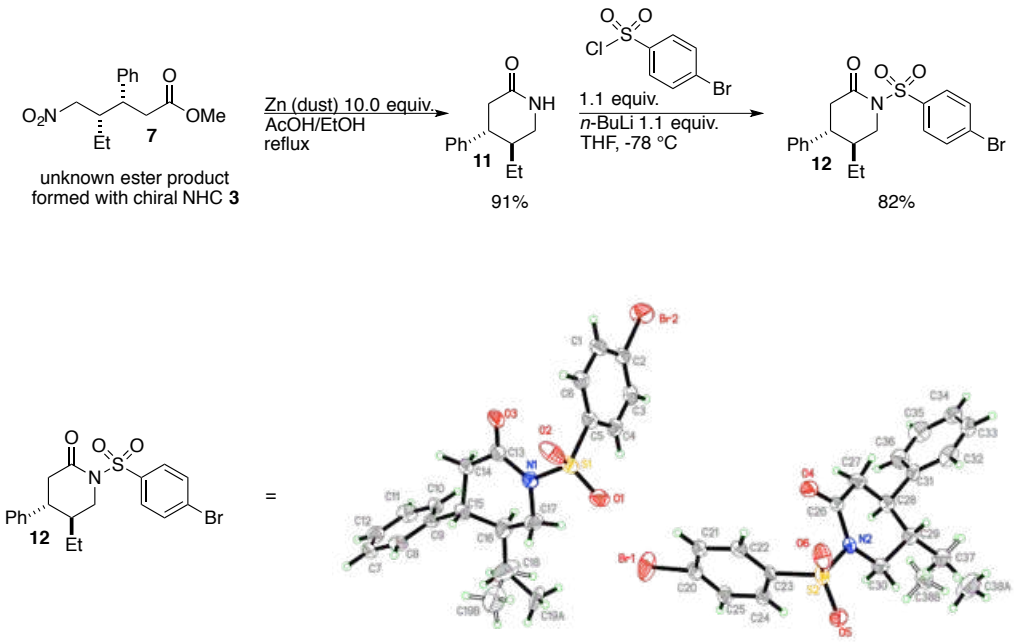
Scheme 2.1.2



Due to complexities associated with diastereotopic protons from the two stereocenters, ^{1}H-NMR was ambiguous in product determination. Furthermore, the ^{13}C-NMR was also unclear in determining unequivocally which product was being formed. To resolve these complexities, we opted to derivitize the product to form a product suitable for x-ray crystallographic analysis. This also gave us an avenue to determine absolute and relative stereochemistry. It was determined that the unknown ester product was the product of the homoenolate pathway **7**. Our derivitization began by subjecting the unknown ester product **7** formed using chiral catalyst **3** to reducing conditions with zinc dust in acetic acid and ethanol to form the corresponding lactam **11**. This reduction/cyclization proceeded in 91% yield. The lactam **11** was then treated with *n*-butyl lithium and 4- bromobenzenesulfonyl chloride in THF and the desired brosylated lactam **12** was afforded in 82% yield. Lactam **12** formed a crystalline solid which was analyzed by x-ray crystallography. X-ray crystallography revealed δ-lactam **12** contains *trans* stereochemistry, which arises from a

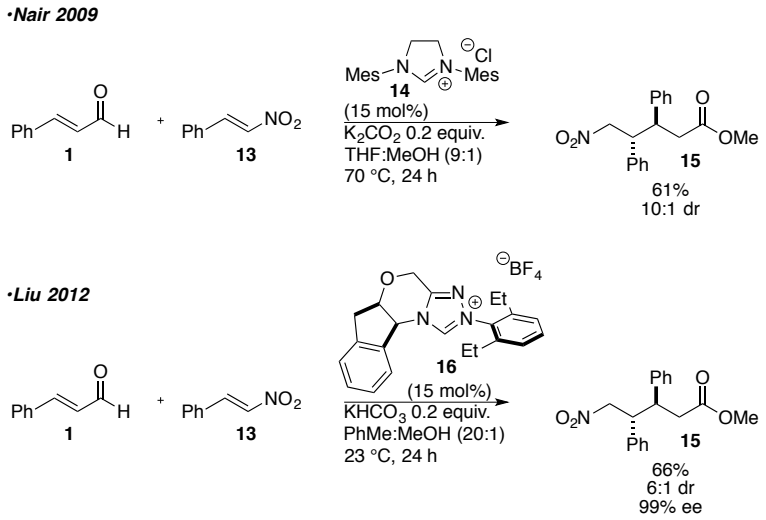
syn nitroester product **7** (Scheme 2.1.3).

Scheme 2.1.3



Previously, Nair and co-workers had developed a racemic NHC catalyzed coupling of enals and nitroalkenes to form δ-nitroesters.[2] In this report, aromatic enals and nitrostyrene derivatives were shown to be coupled in good yields and good diastereoselectivity for the *anti* diastereomer (scheme 2.1.4). It was found that the SI-Mes NHC catalyst **14** and potassium carbonate as base in a mixture of methanol and THF provided optimal results for the homoenolate reaction. During the course of our work in this area, Liu and co-workers reported an asymmetric variant of the reaction utilizing amino indanol derived catalyst **16** to couple aryl and alkyl enals with nitrostyrene derivatives in good yields, excellent enantioselectivity, and good *anti* diastereoselectivity (scheme 2.1.4).[3] It is noteworthy that the nitroester formed in our investigation is the *syn* diastereomer, and that the examples from Nair and Liu both provide access to the *anti* diastereomer.

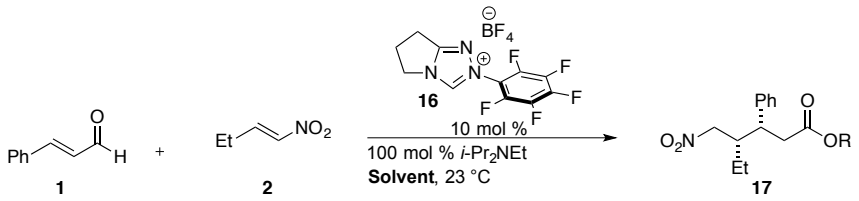
Scheme 2.1.4



2.2 Development of the Racemic Reaction

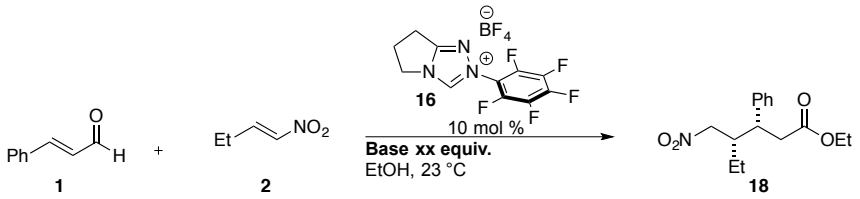
Once we had unequivocally determined the structure of the product formed in the reaction, we turned our attention to developing a reaction which gave exclusively the homoenolate product of the Stetter. We focused on the coupling of cinammaldehyde **1** with (*E*)-1-nitrobut-1-ene **2**. Conducting the reaction at 23 °C instead of 0 °C, as per the Stetter reaction conditions, gave a slight increase in yield providing desired nitroester **17** in 30% yield with the remainder of the mass balance being Stetter product **4**. An initial screen of solvents revealed ethanol to be the optimal solvent for the reaction. When the reaction is conducted in solvent mixtures, the desired reaction pathway was suppressed and hydrocinnamaldehyde, the result of β-protonation of the homoenolate intermediate, became the major product (Scheme 2.2.1).[4]

Scheme 2.2.1



Entry	Solvent	Yield (%)	d.r.
1	MeOH	30	17:1
2	EtOH	33	17:1
3	*i*PrOH	15	17:1
4	*n*PrOH	25	17:1
5	*n*BuOH	23	17:1
6	THF:EtOH (20:1)	< 5	-
7	DCM:EtOH (20:1)	< 5	-
8	PhMe:EtOH (20:1)	< 5	-
9	Et_2O:EtOH (20:1)	< 5	-

At this point we turned our attention to the effect of the base on the reaction. To probe this variable, we utilized high-throughput experimentation (HTE) to rapidly screen a multitude of bases and base equivalency. The results of this experiment showed NaOAc as the optimal base and that when using NaOAc there is not a significant dependence on base equivalency. Upon scale up of the reaction using 1.0 equivalents of NaOAc the nitroester product **18** was formed in 38% yield (Figure 2.2.1).



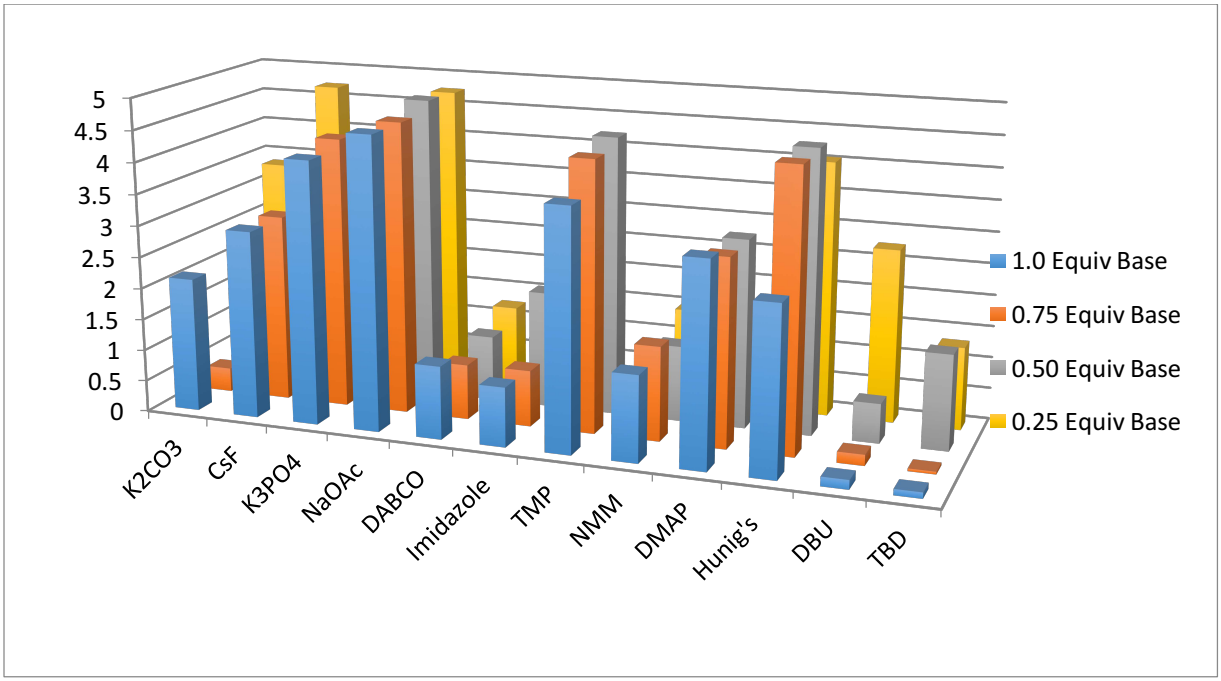
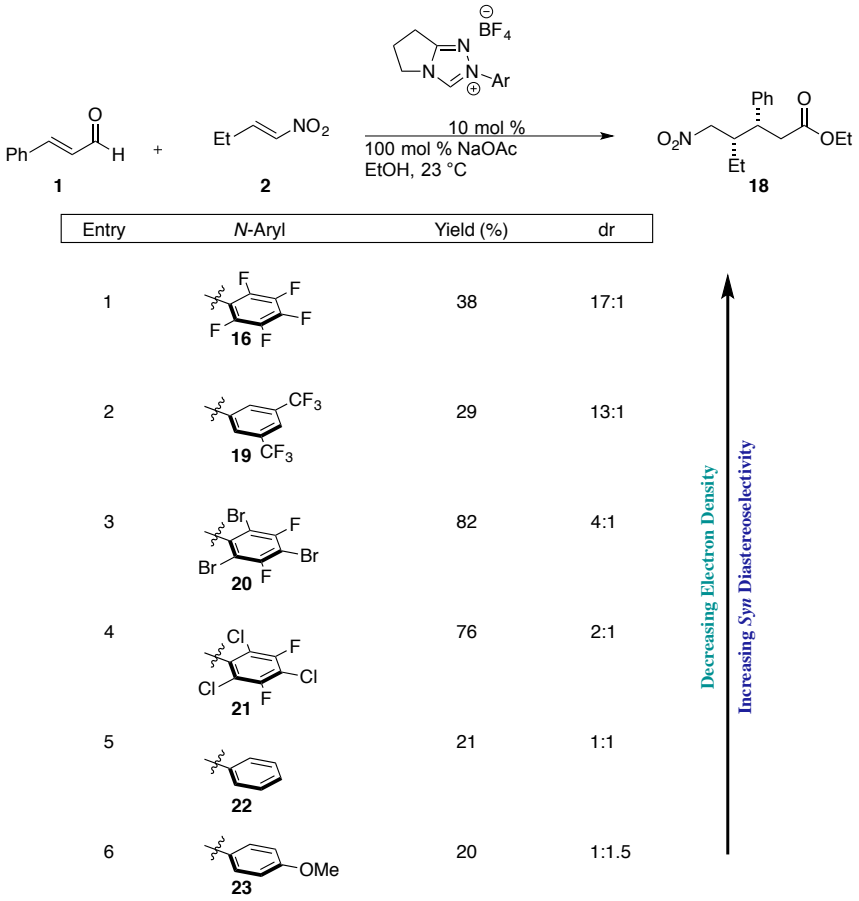


Figure 2.2.1

Next, we chose to explore variations of the NHC catalyst used in the reaction. A strong correlation between diastereoselectivity of the product and the electronics of the *N*-aryl substituent on the NHC catalyst was observed. As the electronics of the *N*-aryl substituent change from strongly electron withdrawing to less electron withdrawing, the diastereoselectivity goes from almost exclusively *syn* to a mixture of *syn/anti*. In fact, using the highly electron donating 4-methoxy phenyl **23** as the *N*-aryl substituent actually inverts the diastereoselectivity to slightly favor the *anti* diastereomer (the major diastereomer in the reports from Nair and Liu). In these reactions, the majority of the mass balance was the Stetter product (Table 2.2.1). To shut down the Stetter pathway we hypothesized that a catalyst bearing an *N*-aryl group with bulky substituents in

the ortho,ortho' positions would prevent the acyl carbon of the extended Breslow intermediate from attacking the nitroalkene (Figure 2.2.2). To probe this hypothesis, the tribromodifluoro aryl catalyst **20** and the trichlorodifluoro catalyst **21** were synthesized and subjected to the reaction. By employing these catalysts, the Stetter pathway was suppressed considerably and the nitroester product was formed in good yields (82% yield, 4:1 dr with catalyst **20**, 76% yield, 2:1 dr with catalyst **21**). However, diastereoselectivity did suffer as a result of the aryl group being less electron deficient (Table 2.2.1). With these conditions in hand we felt that we had developed a good understanding of the racemic variant of the reaction and turned our efforts towards developing an asymmetric methodology.

Table 2.2.1



Entry	*N*-Aryl	Yield (%)	dr
1	**16**	38	17:1
2	**19**	29	13:1
3	**20**	82	4:1
4	**21**	76	2:1
5	**22**	21	1:1
6	**23**	20	1:1.5

Decreasing Electron Density

Increasing *Syn* Diastereoselectivity

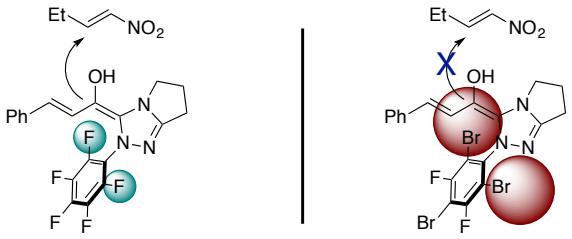
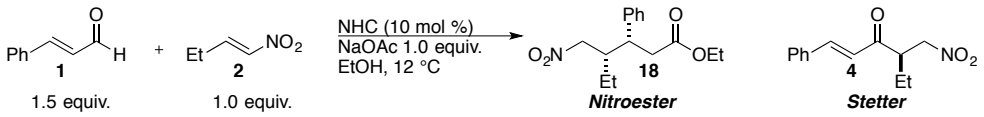


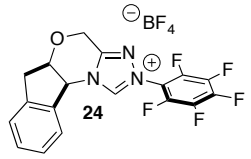
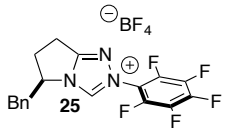
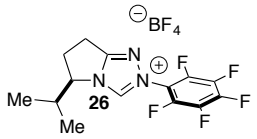
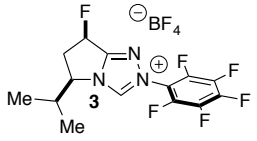
Figure 2.2.2

2.3 Development of the Asymmetric Reaction

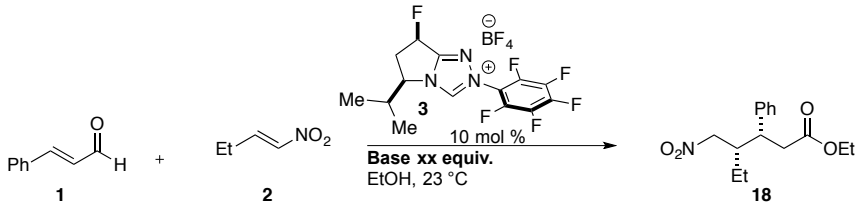
We began our investigation of the asymmetric coupling of enals and nitroalkenes to form nitroesters by screening a variety of chiral *N*-pentafluorophenyl catalysts in ethanol with NaOAc as the base. In our initial screen we found that backbone-fluorinated NHC **3**[5] provides product in the highest enantioselectivities, although it is unselective for the formation of the Stetter product **4** and the desired nitroester **18** (Table 2.3.1).

Table 2.3.1



Entry	NHC	nitroester:Stetter	Nitroester Yield (%)	ee (%)	dr
1		2:1	25	40	17:1
2		2.5:1	62	66	17:1
3		1:1	43	70	17:1
4		1:1	42	83	17:1

We then chose to attempt to optimize the reaction with catalyst **3** using HTE. A variety of bases and base equivalents were explored. Unfortunately, we were unable to optimize past our previous high-water mark of 42% yield and 83% ee (Figure 2.3.1).



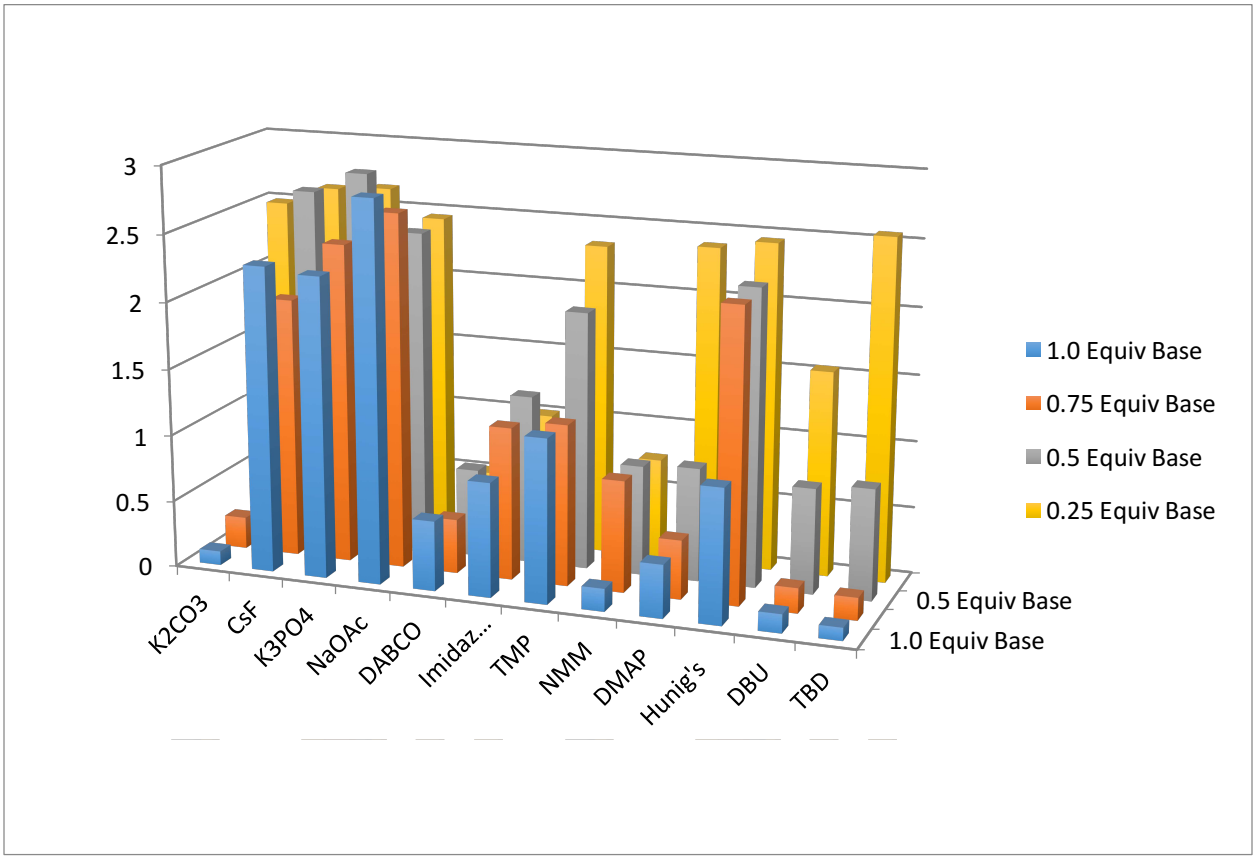
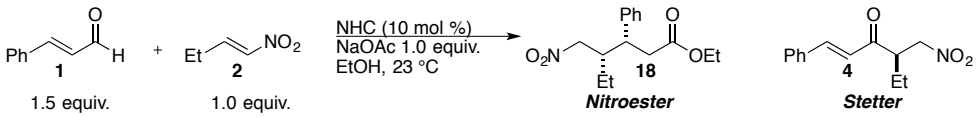
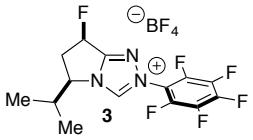
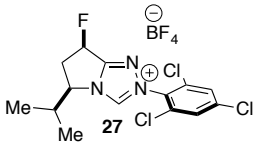
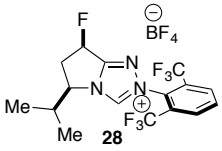


Figure 2.3.1

Unable to optimize the asymmetric reaction with catalyst **3** beyond 42% yield, we turned our attention to catalyst development. We initially postulated that bulking up the ortho,ortho' positions of the *N*-aryl, similar to our solution for the racemic reaction, may provide higher yields for the desired product. To test our hypothesis, we synthesized catalysts **27** and **28** and subjected them to the reaction conditions. These catalysts provided good selectivity for the nitroester over the Stetter pathway, however, the enantioselectivity suffered considerably (Table 2.3.2).

Table 2.3.2

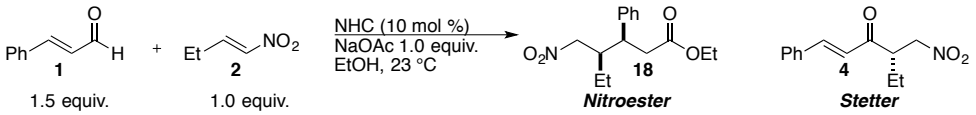


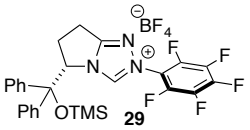
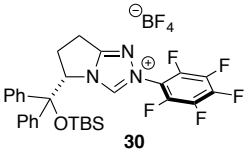
Entry	NHC	nitroester:stetter	Nitroester Yield (%)	ee (%)	dr
1		1:1	42	83	17:1
2		5:1	70	22	2:1
3		6:1	60	30	15:1

After finding that increasing the steric bulk of the *N*-aryl substituent provides good product selectivity but erodes the enantioselectivity, we turned our attention towards changing the chiral substituent on the aliphatic backbone of the NHC catalyst. We imagined that a sufficiently bulky chiral group may provide a similar effect of the bulky *N*-aryl to favor the homoenolate over the acyl anion pathway. We were pleased to find that NHC catalyst **29**[6] bearing a bis-phenyl TMS-protected tertiary alcohol as the source of chiral information provided the desired product in excellent enantioselectivity, diastereoselectivity, and product selectivity with the Stetter product being formed in only trace amounts.[7] However, the product was formed in a meager 16% yield with the remainder of the mass balance being unreacted enal starting material. We then synthesized and evaluated catalyst **30** bearing a TBS protecting group in place of the TMS group. Once again, the product was formed in excellent selectivities, and encouragingly the Stetter product was

observed in only trace amounts. However, the desired product was formed in low yield, 8% (Table 2.3.3).

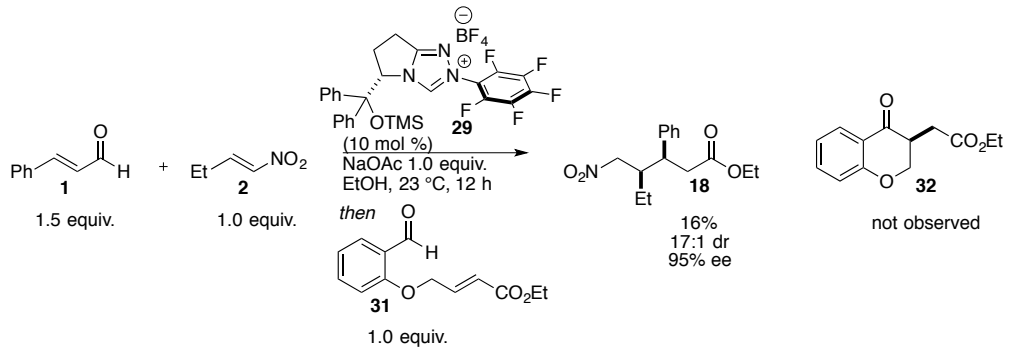
Table 2.3.3



Entry	NHC	nitroester:stetter	Nitroester Yield (%)	ee (%)	dr
1		>20:1	16	95	17:1
2		>20:1	8	97	17:1

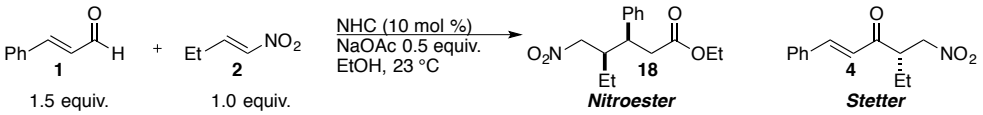
We believe that the cause of low conversion in these reactions is due to decomposition of the NHC catalyst. We subjected chromanone substrate **31** to the reaction mixture after 12 hours and observed no formation of product **32**. If NHC **29** were still active, chromanone product **32** should have formed. In a control experiment wherein catalyst **29** was reacted with chromanone substrate **31** in the presence of NaOAc and ethanol, the desired chromanone product **32** was formed in 73% yield (Scheme 2.3.1).

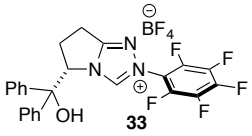
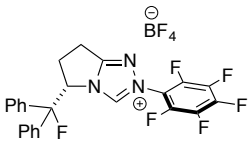
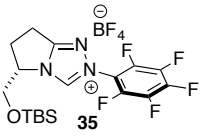
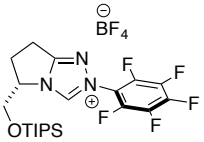
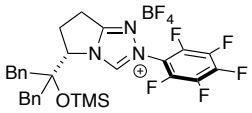
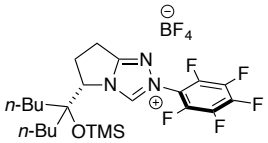
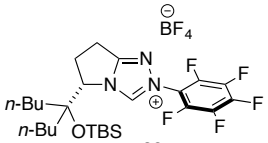
Scheme 2.3.1



With this in mind, we began to explore different variations of catalyst **29** in an attempt to find a more stable catalyst platform. We found that catalyst **33,** bearing an unprotected hydroxyl group, provided only trace amounts of product. Replacing the hydroxyl group with a fluorine atom yielded similar results. We found catalysts **35** and **36** featuring protected primary hydroxyl groups restored reactivity, however, enantioselectivity was only 60% and 70% ee respectively. In an effort to improve enantioselectivity while maintaining high conversion we synthesized o-silyl tertiaryalcohol NHC catalyts **37**, **38**, and **39**. We were delighted to find that the bis-butyl trimethylsilyl protected catalyst **38** provided desired product in 70% yield, 17:1 dr, and 93% ee. With this catalyst, the Stetter product **4** is observed in only trace amounts and the remainder of the mass balance is hydrocinnamaldehyde, the product of β-protonation of the homoenolate position (Table 2.3.4).

Table 2.3.4



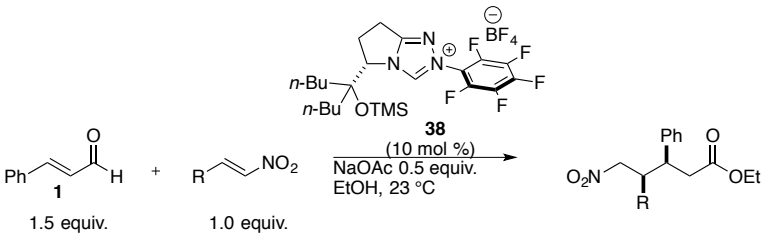
Entry	NHC	nitroester:stetter	Nitroester Yield (%)	ee(%)	dr
1	 **33**	-	<5	-	-
2	 **34**	-	<5	-	-
3	 **35**	>20:1	83	70	17:1
4	 **36**	>20:1	62	60	17:1
5	 **37**	>20:1	37	84	17:1
6	 **38**	>20:1	70	93	17:1
7	 **39**	>20:1	45	88	17:1

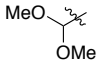
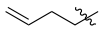
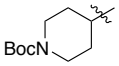
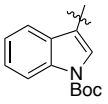
NHC salts 33,34,35, and 36 were subjected to the reaction conditions unpurified

2.4 Reaction Scope

Upon identifying catalyst **38** we began to explore the substrate scope of the reaction. An assortment of aryl and aliphatic nitroalkenes were reacted with cinnamaldehyde and we were pleased to find that yields, diastereoselectivities, and enantioselectivities were generally good. We found that nitrostyrene derivatives (entries 11-15 table 2.4.1) provide product in higher yields than their aliphatic counterparts, however diastereoselectivity and enantioselectivity are slightly lower.

Table 2.4.1

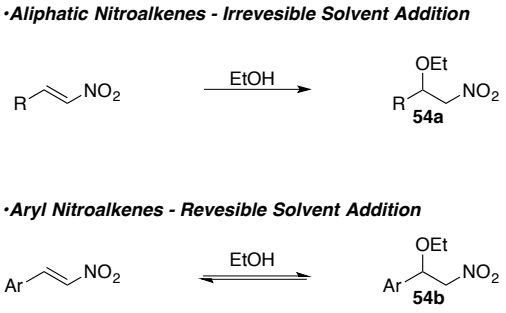


Entry	R	Product	Yield (%)	ee (%)	dr
1	Et	**18**	70	93	17:1
2	Me	**40**	60	85	17:1
3	*i*-Pr	**41**	57	94	20:1
4	*n*-Bu	**42**	72	91	20:1
5	*i*-Bu	**43**	67	91	20:1
6	Cy	**44**	59	96	20:1
7		**45**	49	79	8:1
8		**46**	72	89	12:1
9		**47**	66	88	18:1
10		**48**	65	94	19:1
11	Ph	**49**	95	87	6:1
12	2-furyl	**50**	90	81	3:1
13		**51**	86	87	8:1
14		**52**	73	86	5:1
15	4-chlorophenyl	**53**	75	86	4:1

Of note are entries 7 and 8 (table 2.4.1) which contain potential handles for further manipulation in the form of an acetal and terminal alkene respectively. NBoc protected nitrogen is tolerated in the reaction (entry 10 Table 2.4.1). Heteroaromatic nitroalkenes (entries 13 and 14 Table 2.4.1) participate in the reaction as well.

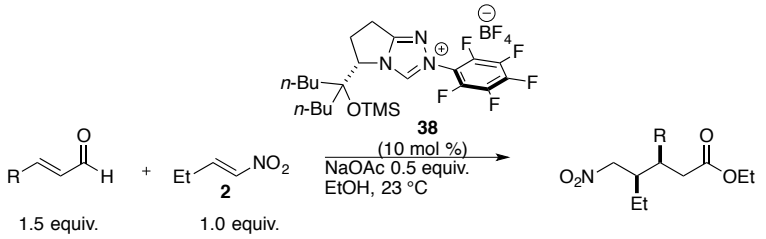
It is postulated that aliphatic nitroalkenes suffer lower yields in this transformation due to a 1,4-addition of the solvent. In our studies, we isolated a small amount of side product **54a** from the reaction mixture in all cases where an aliphatic nitroalkene was used. We did not observe any of this side product when nitrostyrene derivatives were used. Nitrostyrene derivatives are able to undergo the reverse reaction to regenerate the reactive nitrostyrene, whereas aliphatic nitroalkenes are less likely to undergo this reverse reaction.

Scheme 2.4.1



We then explored the reaction scope with respect to the enal coupling partner. Electron-rich and electron-deficient aryl enals participate in the reaction to generate product in moderate to good yields and with good selectivities (Table 2.4.2).

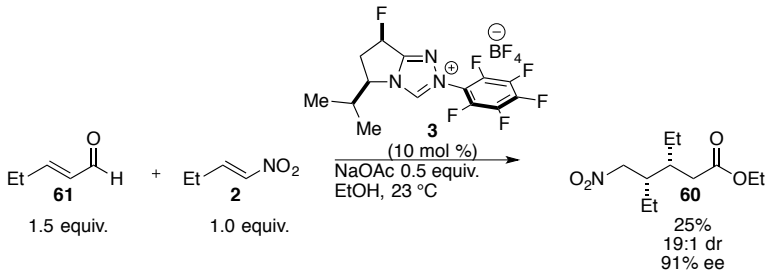
Table 2.4.2



Entry	R	Product	Yield (%)	ee (%)	dr
1	4-chlorophenyl	**55**	73	82	20:1
2	4-nitrophenyl	**56**	48	90	10:1
3	4-methoxyphenyl	**57**	35	86	5:1
4	2-furyl	**58**	79	91	19:1
5	2-methoxyphenyl	**59**	46	82	9:1
6	Et	**60**	<5 %	-	-

Unfortunately, subjecting *E*-2-pentenal **61** (entry 6 table 2.4.2) to the reaction conditions afforded product in only trace amounts with the Stetter product being the major product. We found that by using catalyst **3** in place of catalyst **38**, *E*-2-pental participates in the reaction to afford desired product in 25% yield (19:1 dr, 91% ee).

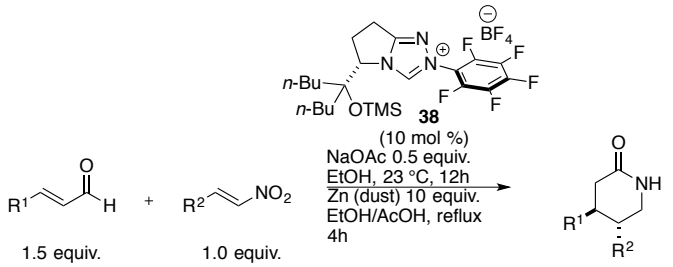
Scheme 2.4.2

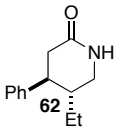
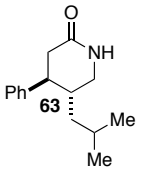
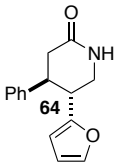
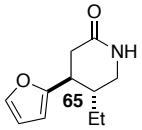
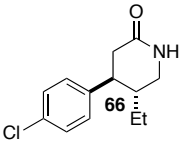


Due to the orthogonality of the two ends of the nitroester products we were motivated to explore the manipulation of the nitroester product to deliver valuable synthons. We found we could generate the corresponding δ-lactams in good yield via a one-pot two-step process.[8] Addition

of zinc dust and acetic acid to the crude reaction mixture after 12 hours, followed by heating for an additional 4 hours, provides an operationally simple protocol for the one-pot synthesis of δ-lactams.[9] In this reaction sequence the lactam product is formed in yields corresponding to those in the synthesis of the nitroester and the enantioselectivity and diastereoselectivity do not suffer (Table 2.4.3).

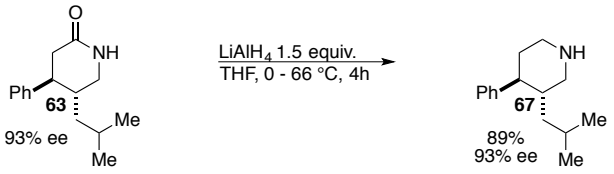
Table 2.4.3



Entry	Product	Yield (%)	ee (%)	dr
1		63	93	17:1
2		65	90	19:1
3		82	82	3:1
4		60	91	19:1
5		70	82	20:1

The δ-lactam product may be further converted to the piperidine via a $LiAlH_4$ reduction in excellent yield (Scheme 2.4.3).[10]

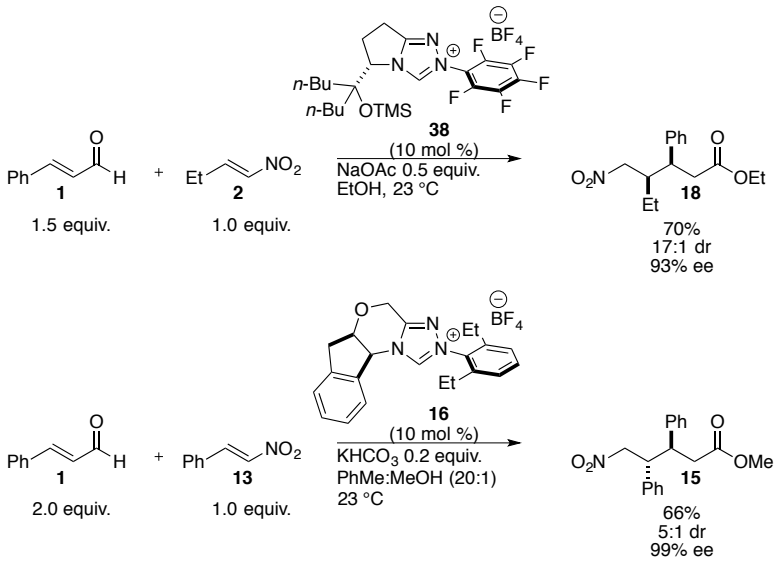
Scheme 2.4.3



2.5 Stereochemical Model

We believe that the trend associated with diastereoselectivity of the nitroester product and the electronics of the *N*-aryl moiety of the NHC catalyst are due to a change in the Breslow intermediate geometry. In our studies we focused on utilizing the electron-deficient pentafluorophenyl aryl group on our catalyst to provide high diastereoselectivity for the *syn* nitroester. In both Nair and Liu's work, electron-rich NHC catalysts are utilized and high selectivity for the *anti* diastereomer are observed. Furthermore, in Liu's asymmetric variant of the reaction, pseudo-enantiomeric catalyst provide product which correlates to the nitroalkene approaching the enal from the same enantiotopic face (Scheme 2.5.1).

Scheme 2.5.1



The inversion of diastereoselectivity between our reaction and that observed in Liu's reaction is intriguing. Complicating matters is that the same stereochemistry is observed at the β-position in the product in spite of the fact that the pseudo-enantiomeric catalysts are used. This suggests that the electrophile approaches from the opposite prochiral face of the enal, most likely because of an inversion of Breslow intermediate geometry. The reasons for this are not clear at this time, but may have much to do with the nature of the *N*-aryl substituent. We present an analysis of the diastereomeric transition state structures that may be involved in settling these issues of selectivity (Figure 2.5.1). We believe that the electron-deficient nature of the pentafluoro phenyl aryl group leads to the oxygen of the Breslow intermediate being *cis* to the aryl ring. In the case of more electron-rich aryl groups, the Breslow intermediate forms the isomer where the oxygen is *trans* to the aryl ring. Furthermore, we believe that the use of electron-deficient aryl rings on the catalyst promotes a closed transition state. In the case of electron-rich aromatic ring on the catalyst, the reaction proceeds through a more traditional open transition state.

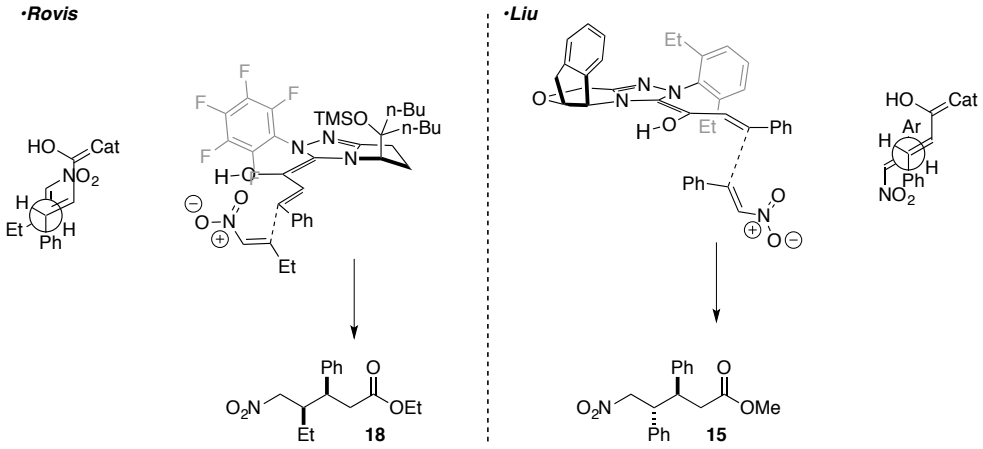


Figure 2.5.1

2.6 Synthesis of Paroxetine and Femoxetine

After we completed the development of the nitroester and lactam methodologies we turned our attention towards the synthesis of the biologically relevant piperidines paroxetine (*Paxil*) **68** and femoxetine **69** (Figure 2.6.1). Paroxetine is a selective serotonin reuptake inhibitor (SSRI) developed in the 1970's and introduced to market in 1992 as a treatment for anxiety, depression, and panic disorder.[11] A related SSRI femoxetine, was discovered concurrently with paroxetine but was not pursued. We thought that our protocol for the rapid synthesis of δ-lactams would allow for concise syntheses of these two molecules.

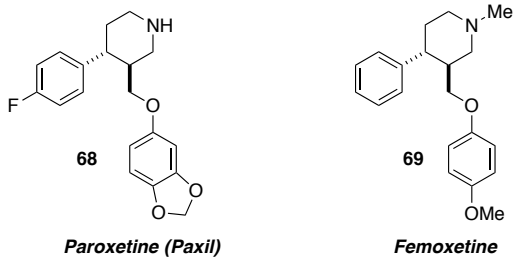


Figure 2.6.1

Since initially being reported, many different syntheses of paroxetine have been published relying upon the establishment of a single enantiomer of *N*-protected *trans*-4-(4-fluorophenyl)-3-piperidinemethanol **72**, followed by alkylation with sesemol and deprotection (Figure 2.6.2). Approaches to set the stereochemistry often depend the chiral pool,[12] resolutions,[13] chiral auxiliaries,[14] chiral bases,[15] and asymmetric catalysis.[16] These methods have been clearly proven effective and are represented in the literature accordingly. However, a highly convergent synthesis in which all the carbons of paroxetine are introduced in a single stereocontrolled step is previously unreported.

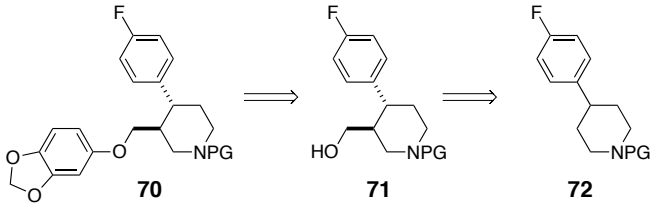


Figure 2.6.2

We envisioned that paroxetine could be synthesized by coupling 4-fluorocinnamaldehyde **73** with nitroalkene **74** to generate lactam **75** which would then be reduced to furnish the final piperidine product **68** (Figure 2.6.3).

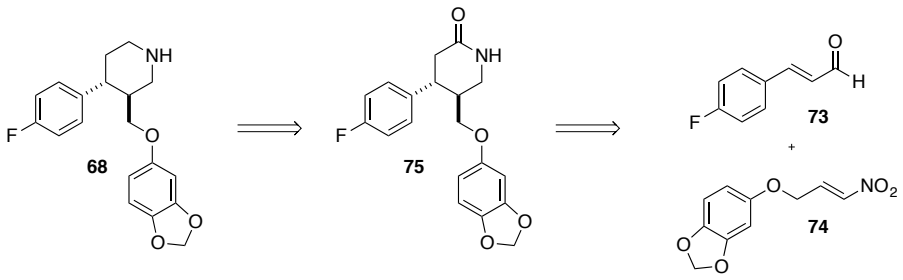
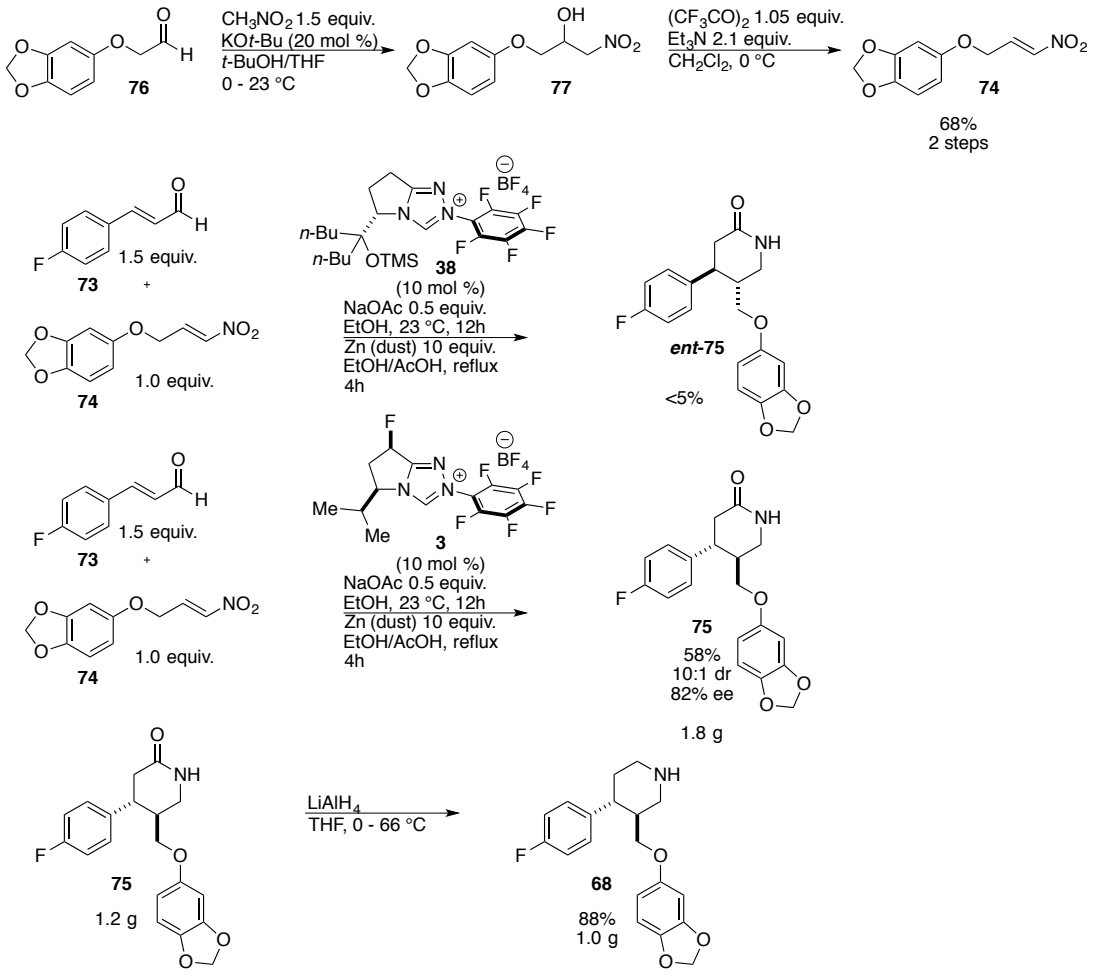


Figure 2.6.3

Our syntheses began by coupling known aldehyde **76** with nitromethane via a Henry reaction to generate β-hydroxy nitroalkane **77**. This was then converted to the desired nitroalkene by treating crude nitroalkane **77** with trifluoroacetic anhydride and triethylamine in dichloromethane at 0 °C to form nitroalkene **74** in 68% yield over two steps. We then attempted to couple 4-fluorocinnamaldehyde **73** and nitroalkene **74** to form the desired lactam using catalyst **38** and our previously developed conditions. Unfortunately, this reaction provided only trace amounts of the desired product. Ultimately, this problem was circumvented by using catalyst **3** and the desired lactam product was isolated in 58% yield with 10:1 dr and 82% ee. This coupling reaction was conducted on 1.8 g scale. We then reduced lactam **75** with $LiAlH_4$ to furnish

paroxetine in 88% yield. This synthesis is four steps from commercially available starting materials and provides the product in an overall yield of 35% (Scheme 2.6.1). Compared to the previously reported syntheses of this molecule, our approach represents the most concise synthesis to date.

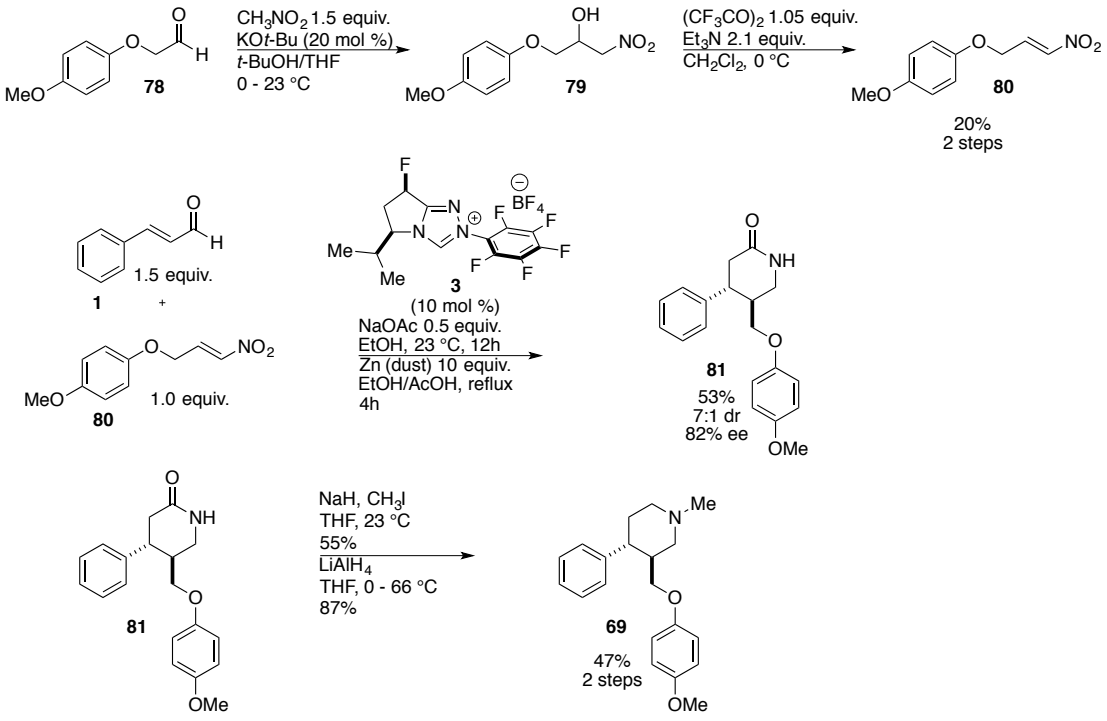
Scheme 2.6.1



We implemented our synthesis of femoxetine via a similar route. First, we synthesized the requisite nitroalkene **80** via the Henry reaction of aldehyde **78** with nitromethane, followed by an elimination reaction (20% yield over two steps). We then coupled nitroalkene **80** with cinnamaldehyde **1** with our one-pot lactam protocol to furnish **81**. Lactam **81** was methylated on

nitrogen with sodium hydride and methyl iodide in 55% yield and then reduced with $LiAlH_4$ in 87% yield to furnish femoxetine **69** in five total steps and an overall yield of 5% (Scheme 2.6.2). The synthesis of paroxetine and femoxetine was carried out with the assistance of Kerem Ozboya and Darrin Flanigan

Scheme 2.6.2



2.7 Conclusion

In conclusion, we have developed a methodology for the synthesis of enantioenriched δ-nitroesters via the coupling of enals and nitroalkenes with a novel NHC catalyst. Key to this methodology was the identification of catalyst **38**, which is highly selective for the homoenolate over the acyl anion (Stetter) pathway. This methodology tolerates a range of aliphatic and aryl nitroalkenes, but is limited to aryl enals. This work represents the first example of a *syn*-selective NHC catalyzed coupling of enals and nitroalkenes to furnish δ-nitroesters. A one-pot two-step

sequence was also developed for the rapid synthesis of stereodefined 3,4 substituted *trans* δ-lactams. We then used this methodology to execute the synthesis of the pharmaceutically relevant molecules (-) paroxetine and (-) femoxetine.

2.8 References

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Chapter 3

Asymmetric β-hydroxylation of Enals via Oxygen Transfer from Electron-Deficient Nitro-Arenes

3.1 Introduction

N-Heterocyclic carbene (NHC) catalysis has been an area of intense research focus for the past two decades.[1] The advent of NHC catalysis embodied acyl anion reactivity exemplified by the benzoin and Stetter reactions.[2] The presence of a nearby leaving group or a reducible functionality opened the door for NHC-based redox catalysis.[3] The use of enals in NHC catalysis is particularly illustrative (figure 3.1.1): they have been demonstrated to undergo the asymmetric Stetter reaction (figure 3.1.1 eq 1),[4] β-protonation/esterification via the redox pathway (figure 3.1.1 eq 2),[5] or trapping with exogenous aldehyde,[6] imine,[7] or nitroalkene from the homoenolate position (figure 3.1.1 eq 3).[8] Enals have also been demonstrated to undergo direct oxidation to form α,β-unsaturated esters (figure 3.1.1 eq 4).[9] All of these previously described NHC-catalyzed reaction presumably operate via a two-electron manifold.[10] We hypothesized that it may possible to access a single-electron pathway through the judicious choice of a single-electron oxidant (figure 3.1.1 eq 5) which would enable a new class of reactivity.

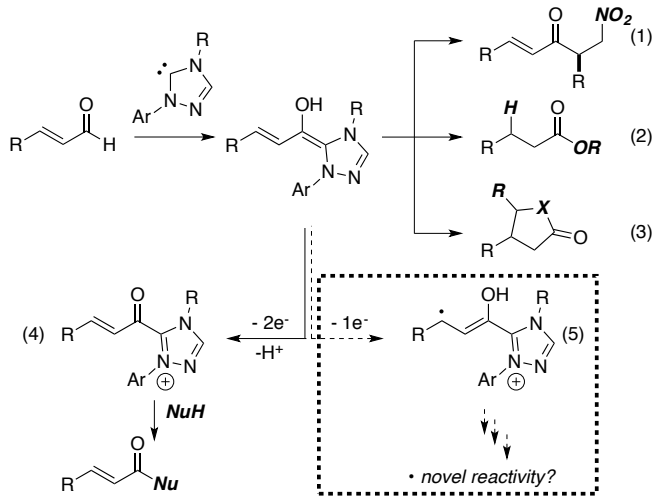
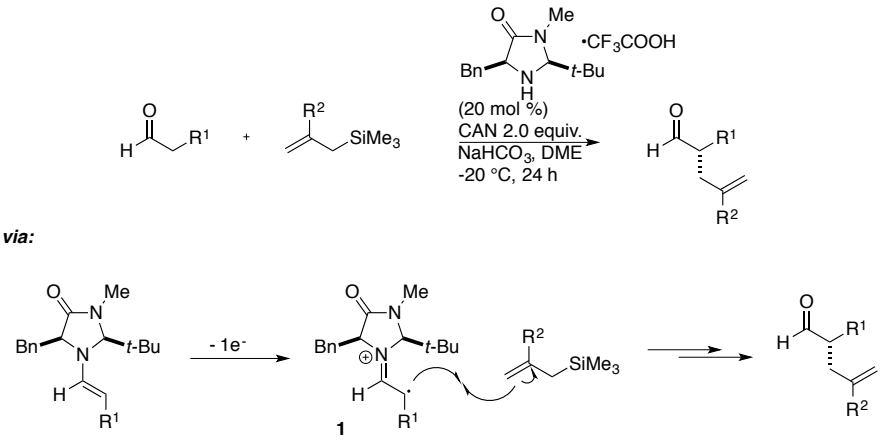


Figure 3.1.1

A similar approach of single-electron oxidation has been applied to secondary amine catalysis and has proved to be a transformative tool to the field of organocatalysis. In 2007 MacMillan and co-workers reported the ceric ammonium nitrate promoted single-electron oxidation of catalytically generated enamines to form radical cation **1**. The initial report reported oxidation of the enamine followed by trapping of the resultant radical with allyl silanes to ultimately produce asymmetric α-functionalized aldehydes (Scheme 31.1).[11] This type of reactivity has been dubbed singly occupied molecular ortibal catalysis (SOMO-catalysis). This approach has been utilized in a large variety of novel transformations.[12] It has also been coupled with photo-redox catalysis to provide a dual catalytic manifold for the generation of radical species to be coupled with SOMO-philes.[13]

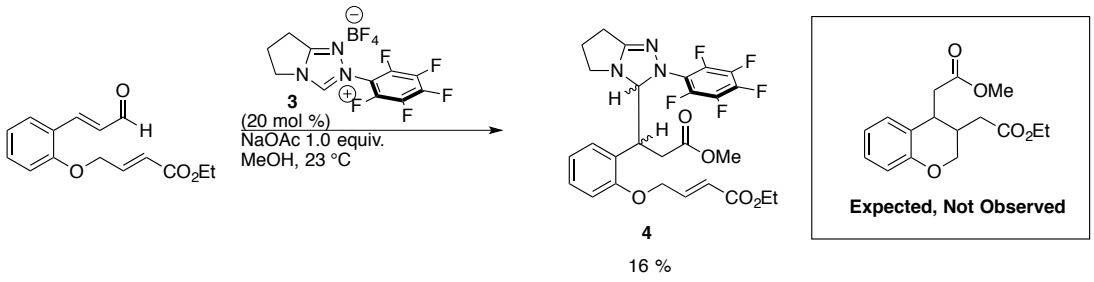
Scheme 3.1.1



3.2 Reaction Discovery

During the course of our investigation into NHC catalyzed β-functionalization of enals we noted that the triazolium salt pre-catalyst **3** is capable of undergoing attack from the β-position of enals to generate product **4** (Scheme 3.2.1).

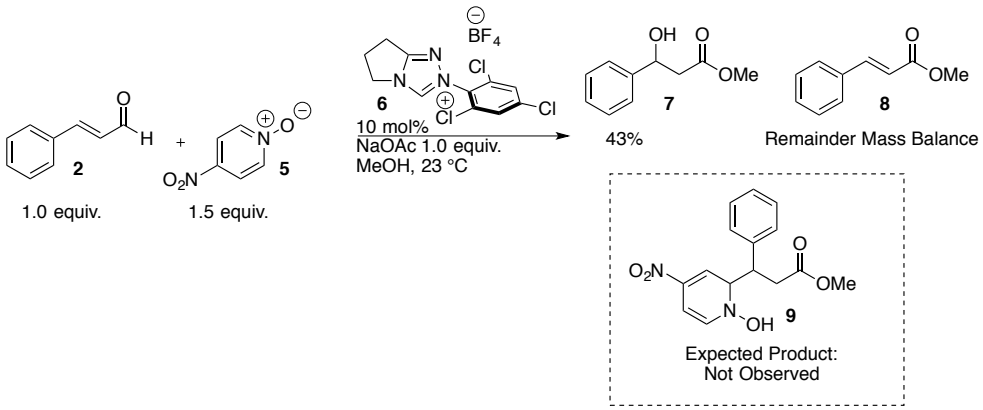
Scheme 3.2.1



Intrigued by this reactivity we were inspired to evaluate aromatic imminium salts as electrophiles for the NHC generated homoenolate. In an attempt to form product **9**, we reacted cinnamaldehyde **2** with 4-nitropyridine *N*-oxide **5** with achiral NHC catalyst **6** in the presence of

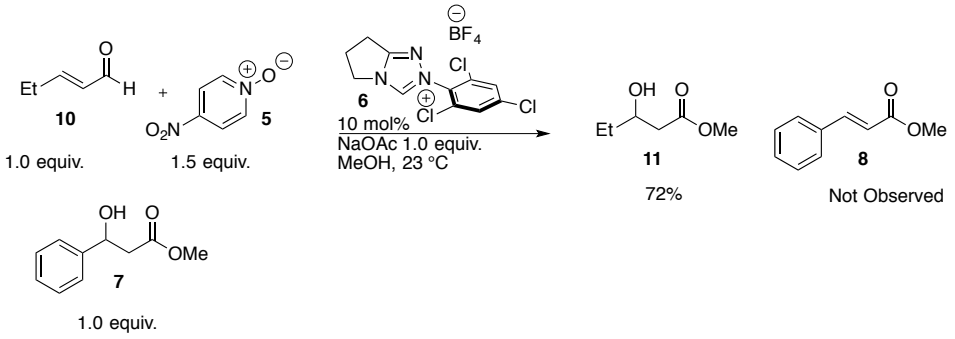
NaOAc in methanol. We did not observe desired product **9**, but instead isolated β-hydroxy ester **7** in 45% yield. The remainder of the mass balance was isolated as methyl cinnamate **8**, the product of a 2-electron oxidation of the Breslow intermediate (Scheme 3.2.2). Intrigued by this unexpected and unprecedented product we were motivated to explore this reaction further.

Scheme 3.2.2



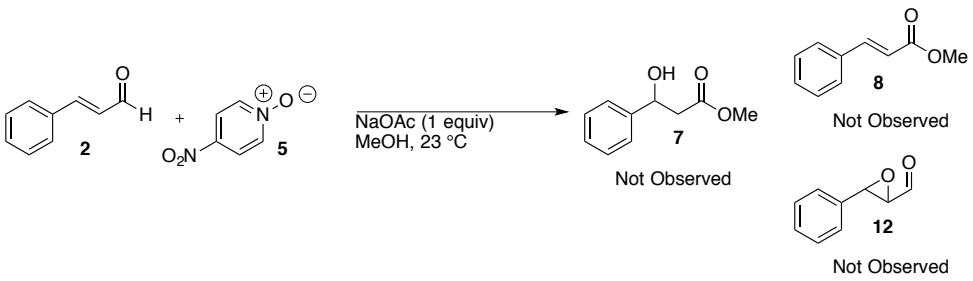
Upon identifying the products formed in the reaction we became interested if the methyl cinnamate was being formed via an elimination of the β-hydroxyl group or if it was arising from a different mechanistic pathway. An experiment wherein β-hydroxy ester **7** was present from the beginning of the reaction of *E*-2-pentenal **10** with 4-nitropyridine *N*-oxide **5** in methanol with catalyst **6** and NaOAc was conducted to probe this hypothesis. From this reaction we did not isolate any detectable amounts of methylcinnamate **8**, suggesting that the enoate product does not arise from a simple elimination of the alcohol (Scheme 3.2.3).

Scheme 3.2.3



In 2004 Bode and Chow demonstrated α-epoxy enals are converted to the corresponding β-hydroxy ester in the presence of a NHC catalyst and alcohol solvent.[14] We wondered if the enal was undergoing an epoxidation from the *N*-oxide which then reacts via the same manifold as Bode's reaction. A control experiment was conducted in the absence of the NHC catalyst and we found the enal did not undergo any reaction with 4-nitropyridine *N*-oxide **5** (Scheme 3.2.4). This also demonstrated both the need for the NHC catalyst in our reaction and that the reaction is proceeding via a different mechanism than that reported by Bode.

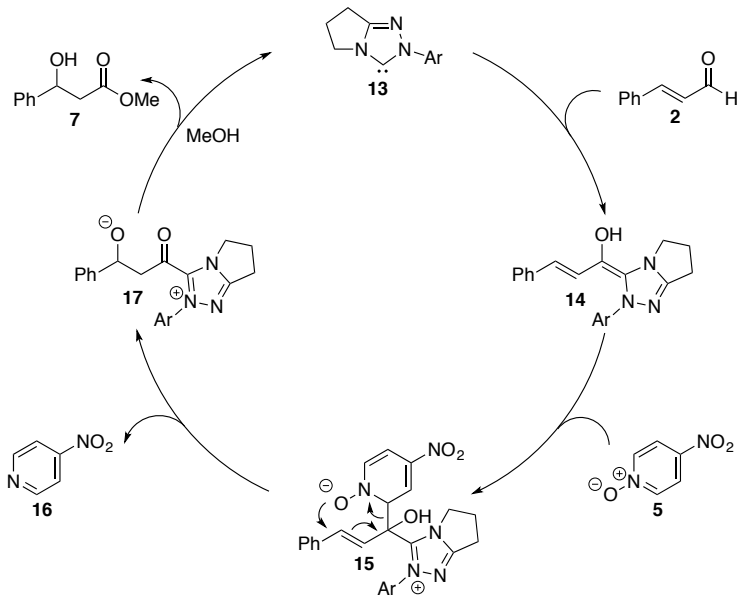
Scheme 3.2.4



At this point we postulated that the oxygen being transferred to the β-position of the enal was occurring from the *N*-oxide moiety of oxidant **5**. Two mechanistic pathways were proposed.

The first postulated mechanism involves formation of the Breslow intermediate **14** followed by attack of the *N*-oxide from the acyl anion to form intermediate **15**. Intermediate **15** then transfers the oxygen to the β-position of the enal via a group transfer-type mechanism to generate β-alkoxy acyl azolium **17** and 4-nitropyridine **16**. Acyl azolium **17** is turned over by methanol to furnish β-hydroxy ester **7** (scheme 3.2.5).

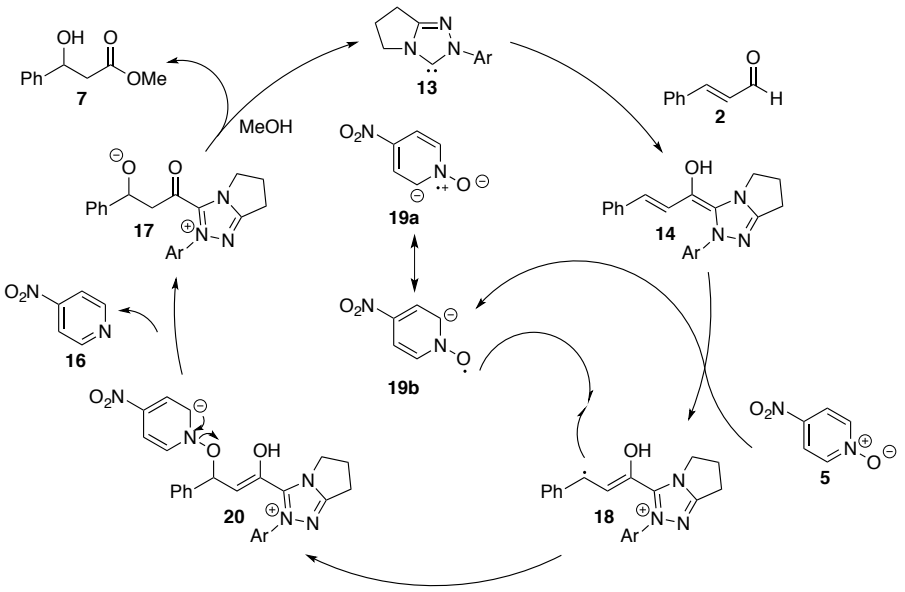
Scheme 3.2.5



Alternatively, we postulated that the transformation may proceed via a single-electron transfer from Breslow intermediate **14** to 4-nitropyridine *N*-oxide **5** to generate the Breslow intermediate derived radical cation **18** and the 4-nitropyridine *N*-oxide derived radical anion **17**. The Breslow intermediate radical cation **18** could then combine at the β-position with the oxygen atom of the *N*-oxide derived radical anion **19** to furnish intermediate **20** This intermediate may then collapse to generate 4-nitropyridine **16** and β-alkoxy acyl azolium **17**. Acyl azolium **17** is

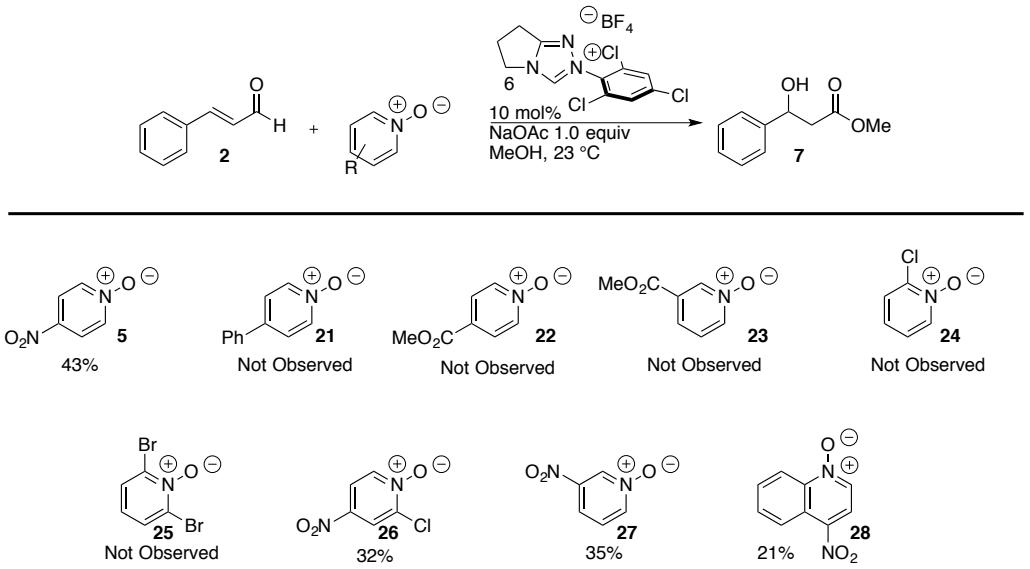
then turned over by methanol to furnish β-hydroxy ester **7** and close the catalytic cycle (scheme 3.2.6).

Scheme 3.2.6



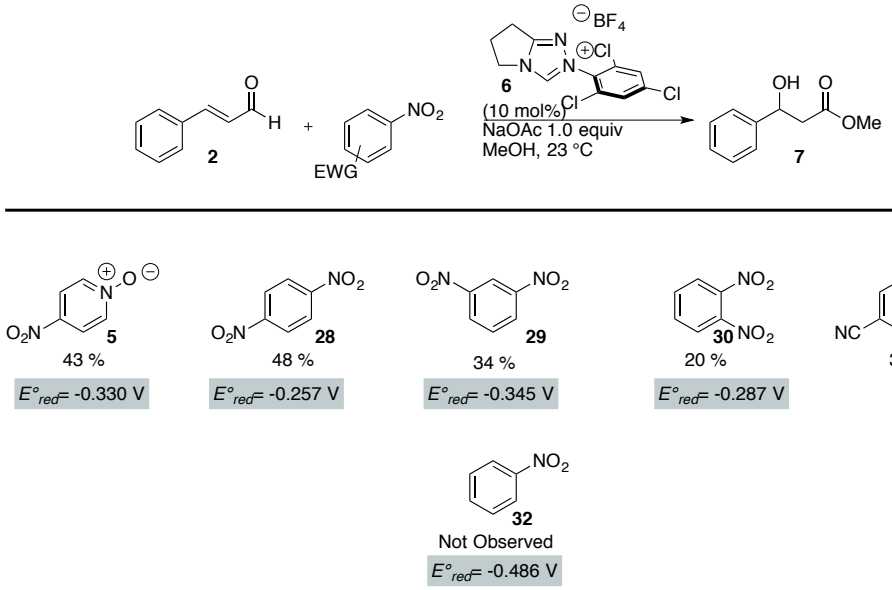
With these preliminary mechanistic proposals in mind, we began to explore optimization of the reaction. First, a variety of pyridine *N*-oxides were investigated. We were discouraged to find that the majority of *N*-oxides that were subjected to the reaction gave no desired product. Upon closer inspection of the *N*-oxides that did deliver product, it was noted that only *N*-oxides bearing a nitro group are capable of converting the enal to the desired β-hydroxy ester product **7** (Table 3.2.1).

Table 3.2.1



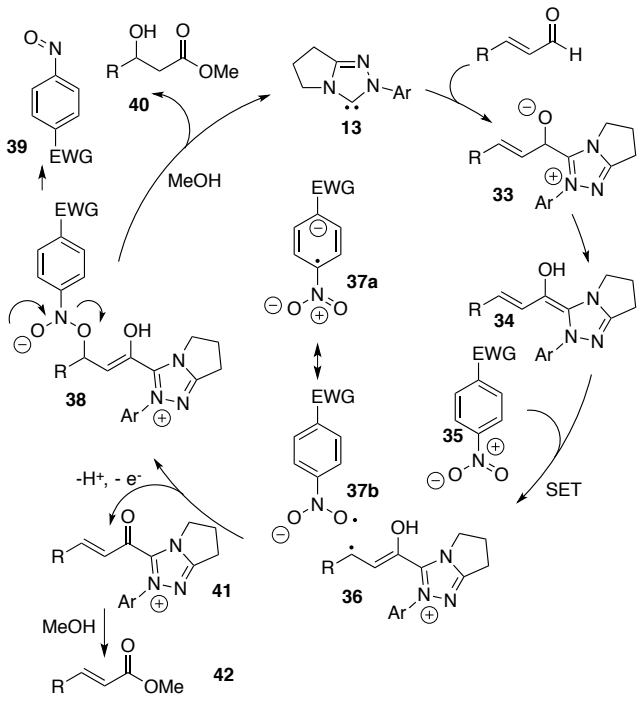
Upon the realization that only nitro containing *N*-oxides provide desired product we evaluated a number of nitrobenzene derivatives as the oxidant in the reaction. This study showed that the *N*-oxide moiety is not necessary for the reaction and that it is the nitro group that is responsible for the observed reactivity. In our group's previous study of the aza-Breslow intermediate, it was found that the aza-Breslow intermediate derived from cinnamaldehyde **2** exhibited a reduction potential of -0.49 V vs SCE.[15] We postulate that this is the reason that nitrobenzene **32**, which has a reduction potential of -0.48 V is not a strong enough oxidant to effect the oxidation of the Breslow intermediate. Indeed, when we employ nitrobenzene **32** in the reaction, only hydrocinnamaldehyde, the product of β-protonation is observed (Table 3.2.2).

Table 3.2.2



Once it was determined that the nitro moiety rather than the *N*-oxide was responsible for the oxygenation, we proposed the following mechanism. First, the carbene and the enal react to form Breslow intermediate **33**. The Breslow intermediate then transfers a single electron to the electron deficient nitroarene to generate Breslow intermediate derived radical cation **34** and nitroarene derived radical anion **37**. The radical anion **37a** may then access a resonance structure wherein the radical resides on an oxygen of the nitro group. Radical cation **34** and radical anion **37a** combine to form a new C-O bond at the β-position of the enal to generate intermediate **38**. Intermediate **38** then collapses to form nitrosoarene **37** and β-alkoxy acyl azolium. The acyl azolium then reacts with methanol to form β-hydroxy ester **40** and liberate catalyst to close the catalytic cycle. The enoate products that we observe as a side product in the reaction may form from radical Breslow intermediate **36** undergoing deprotonation followed by a second single electron abstraction to form α,β-unsaturated acyl azolium **41** which then reacts with methanol to produce enoate **42** (Scheme 3.2.7).

Scheme 3.2.7

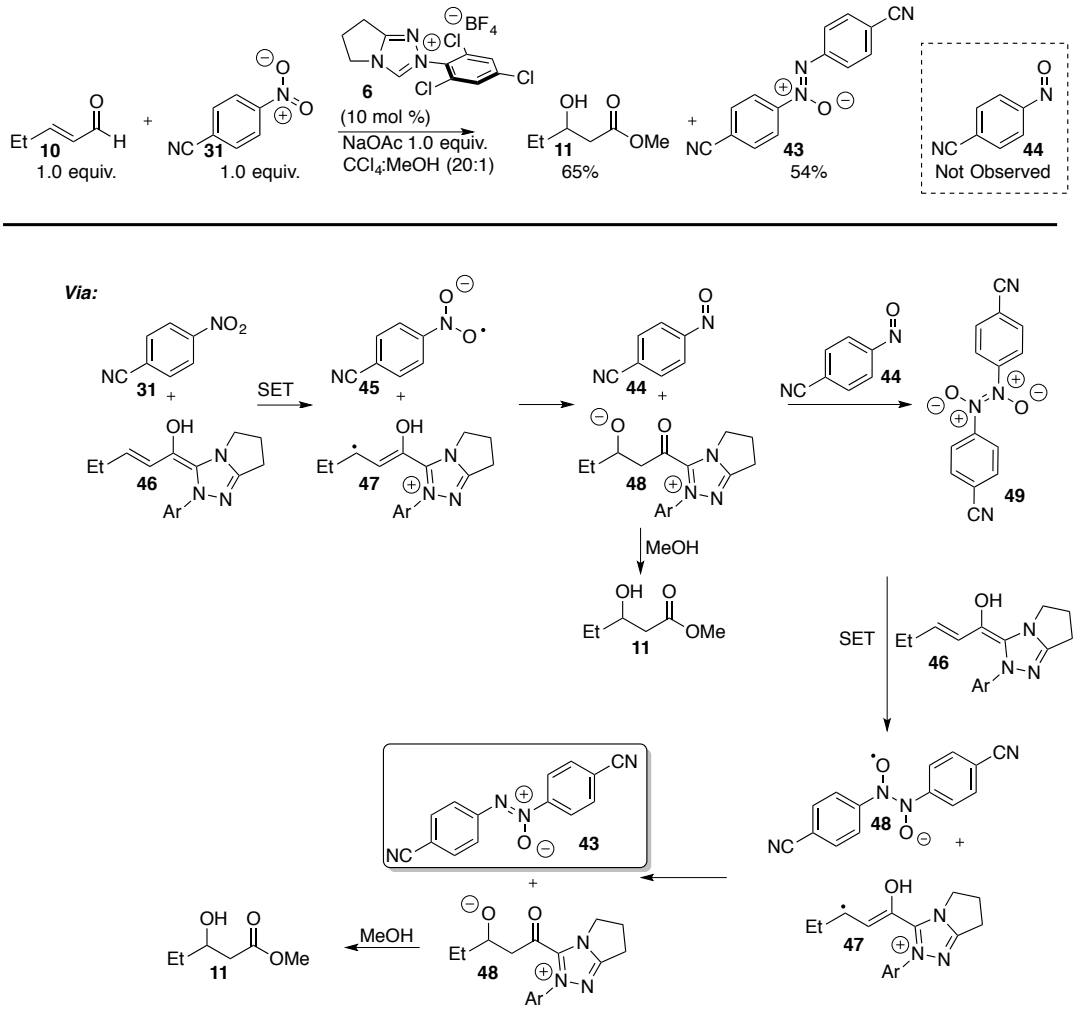


3.3 Mechanistic Studies

In an effort to validate our proposed mechanism we attempted to isolate the nitroso product from the reaction mixture. Our initial attempts to isolate the corresponding nitroso from 4-nitropyridine *N*-oxide **5** proved fruitless. We then attempted to isolate nitroso **44** from 4-cyanonitrobenzene **31**. In this experiment, we were unable to isolate nitroso **44**, but instead isolated diazene *N*-oxide **43**. It is known that nitroso compounds spontaneously dimerize in solution to form diazene dioxides.[16] We postulate that diazene dioxide **48** formed after two catalytic cycles can then abstract a single electron from a second equivalent of Breslow intermediate **46** to produce Breslow intermediate radical cation **47** and diazene dioxide centered radical anion **48**. These radicals then recombine through oxygen and the β-carbon of radical Breslow intermediate to deliver a second molecule of β-hydroxy ester product **11** and the isolated diazene *N*-oxide **43**

(Scheme 3.3.1). The revalation that diazene *N*-oxide is the ultimate fate of the nitroarene reagent is intriguing as it shows that less than 1.0 equivalents of oxidant are required to effect full conversion of the enal to the β-hydroxy ester product.

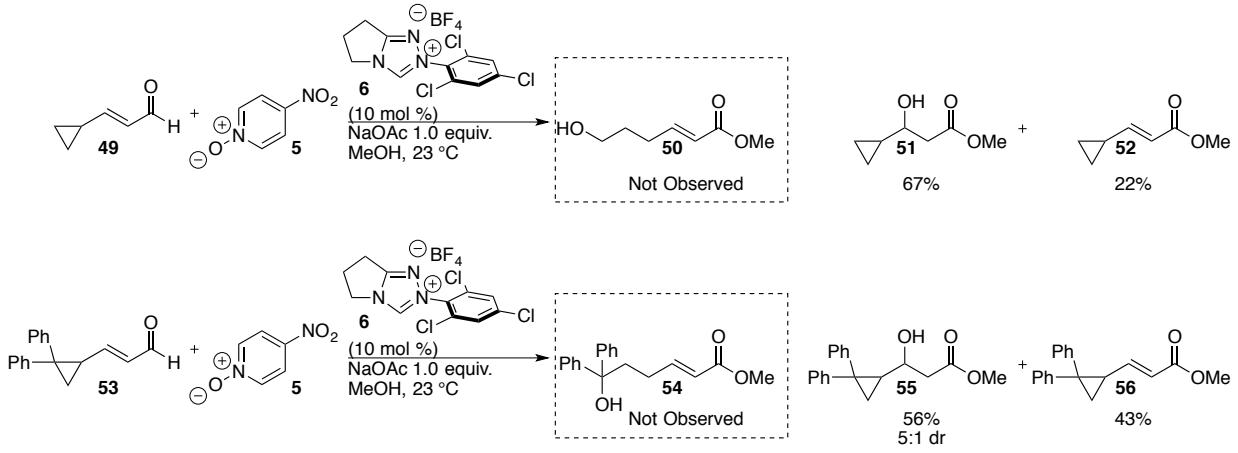
Scheme 3.3.1



A classic probe of radical mechanisms is cyclopropane radical clocks. α-cyclopropyl carbinyl radical are known to open to the more stable homoallyl radical,with a ring opening rate constant of $8.6(10^7\ s^{-1})$.[17] In an effort to support our proposed radical mechanism we synthesized cyclopropyl substituted enal **49**. Unfortunately, when we subjected this substrate to the reaction

conditions, no ring-opened products were observed and we isolated β-hydroxy ester **51** in 67% yield with the remainder of the mass balance being α,β-unsaturated ester **52**. In an effort to enhance the stability of the ring opened radical, we synthesized bisphenyl cyclopropyl enal **53**. Upon subjection of this enal to the reaction conditions, we once again observed no ring opened products and isolated β-hydroxy ester **55** in 56% yield (5:1 dr, major diastereomer not determined) with the remainder of the mass balance being α,β-unsaturated ester **56** (Scheme 3.3.2).

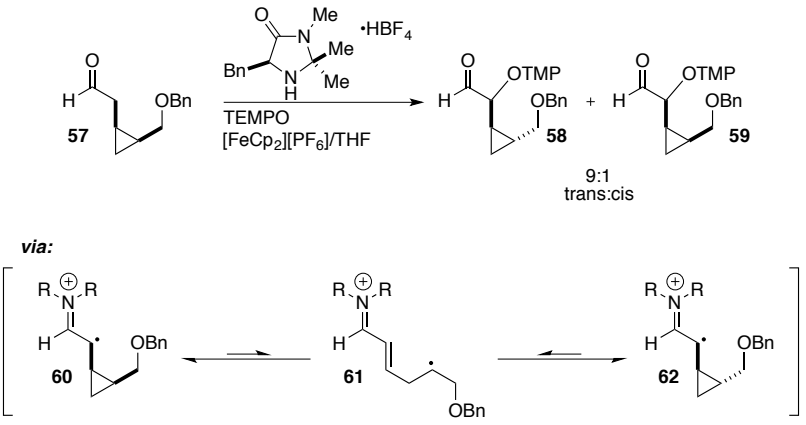
Scheme 3.3.2



We were initially concerned that our cyclopropyl substrates did not open under the reaction conditions and questioned if these results indicated that the reaction was not proceeding via radical intermediates. We became aware of a report from MacMillan and co-workers wherein they were attempting to validate radical intermediates in the $FeCl_3$-catalyzed α-oxyamination of aldehydes.[18] In their studies, they found that the phenyl-substituted cyclopropane did not open under the reaction conditions, but instead isomerized from the *cis* cyclopropane to the more thermodynamically stable *trans* cyclopropane. In this reaction it is proposed that the radical stabilization provided by the imminium outweighs energetic stabilization of the cyclopropane

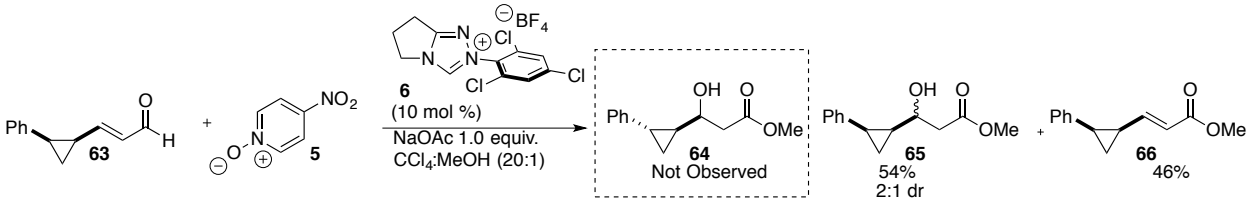
opening. However, there is an equilibrium between the open and closed form of the cyclopropane that allows for the *cis* to *trans* isomerization (Scheme 3.3.3).

Scheme 3.3.3



Cis cyclopropyl enal **63** was synthesized as a probe to explore if this type of isomerization may validate our proposed radical mechanism. Unfortunately, subjecting enal **63** to our reaction conditions gives no detectable amounts of *trans* cyclopropyl β-hydroxy ester **64** (Scheme 3.3.4).

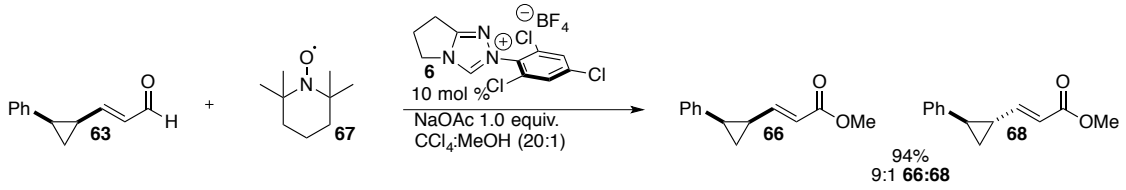
Scheme 3.3.4



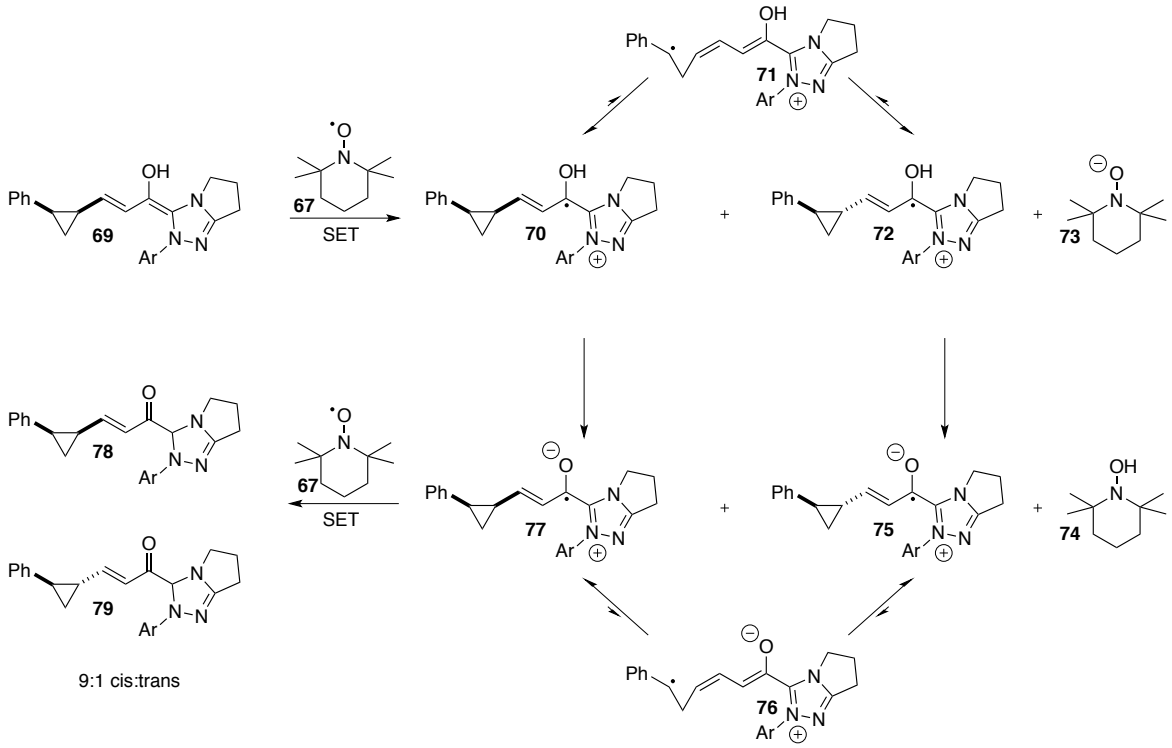
To further explore the validity of this experiment, we subjected *cis* cyclopropyl enal **63** to TEMPO **67** in the presence of NHC **6**. The use of TEMPO as an oxidant in NHC catalysis was first reported by Stüder and co-workers and is understood to proceed via two single-electron oxidations of the Breslow intermediate.[19] In this experiment, we only observed a slight isomerization to the *trans* enoate product **68** (Scheme 3.3.5). This is notable, as in this reaction,

two equivalents of TEMPO are required to effect the two-electron oxidation of the Breslow intermediate **69** to the α,β-unsatured acyl azolium **78**/**79** and therefore there are two discreet radical intermediates that have a chance to undergo *cis* to *trans* isomerization (Scheme 3.3.6). In the β-hydroxylation reaction that we discovered, there is only one radical intermediate that may undergo isomerization before being intercepted by the nitroarene centered radical. With this result in hand, we postulated that the absence of cyclopropane opening in our reaction is not necessarily proof of the absence of radical intermediates in our proposed mechanism.

Scheme 3.3.5

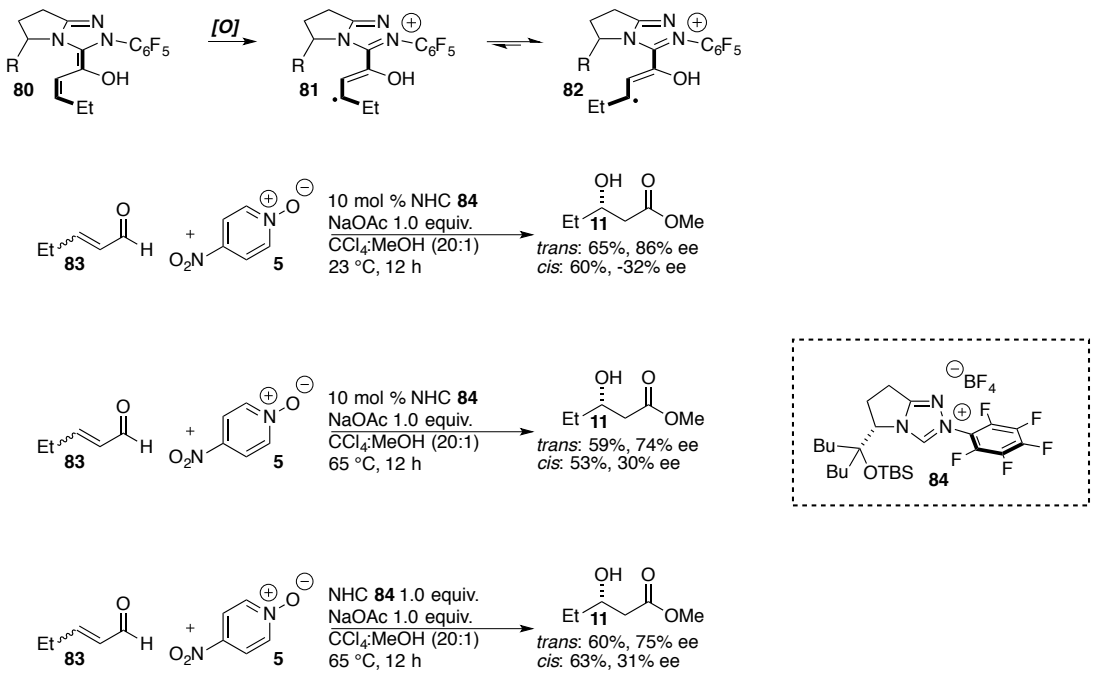


Scheme 3.3.6



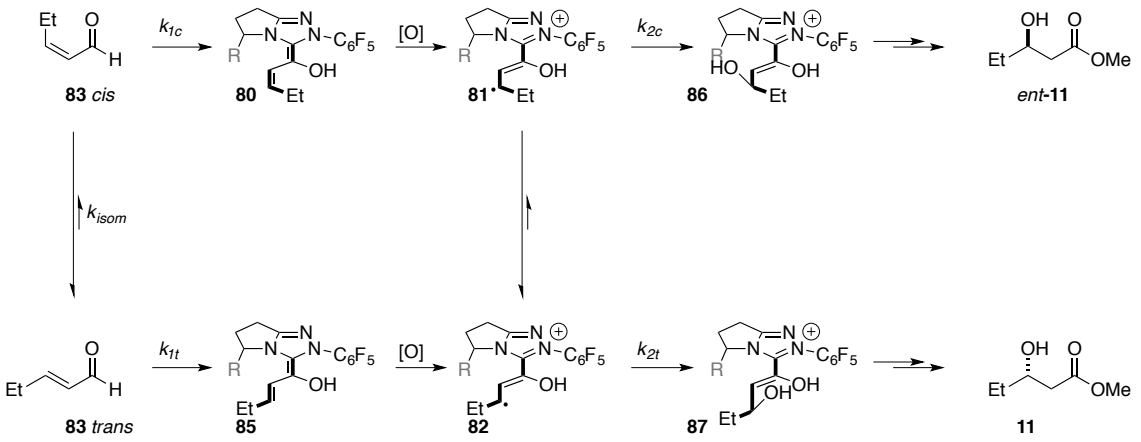
We then investigated the stereochemical course of the reaction when using *cis*- and *trans*-enals. If the reaction proceeds via a radical mechanism and the radical recombination is slower than bond rotation, the *cis*- and *trans*-enals should provide the same major enantiomer via interconversion of presumed intermediates **81** and **82** (Scheme 3.3.7). At ambient temperature, *cis*- and *trans*-olefin isomers gave opposite major enantiomers. However, at 65 °C we observed enantiomeric convergence, supporting the notion that the reaction proceeds via a discrete radical intermediate.[20,21]

Scheme 3.3.7



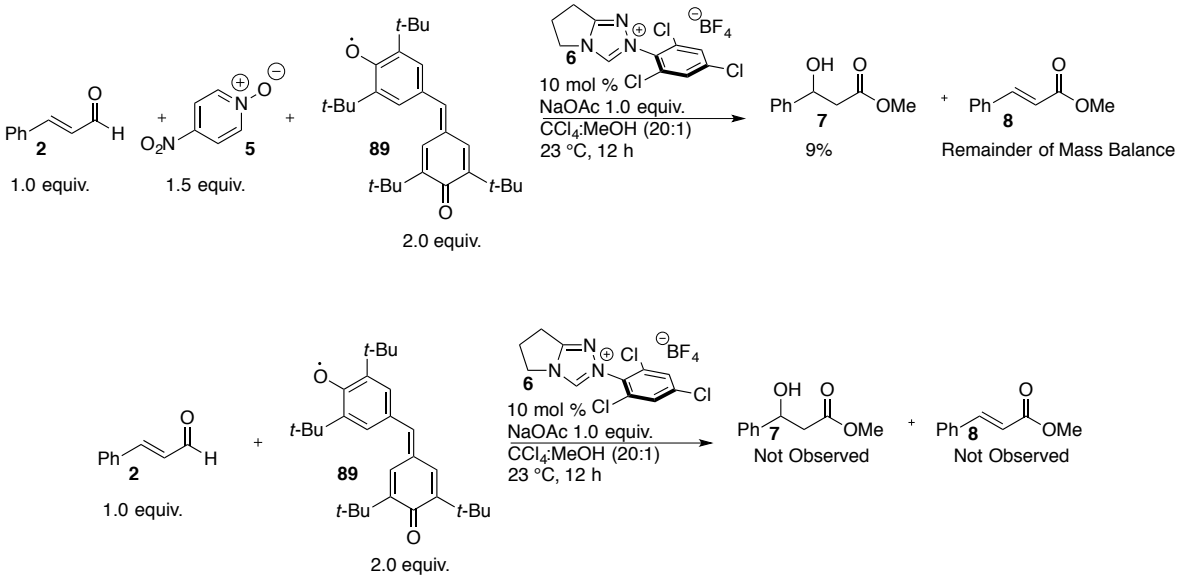
We further found that a reaction conducted with stoichiometric catalyst results in similar yields and identical enantioselectivities to the reaction conducted with 10 mol% catalyst. These results suggest that there is enantioconvergence at elevated temperatures, most likely due to the interception of a common intermediate, radical cation **82**. There is some background cis/trans isomerization of the enal under the reaction conditions even at ambient temperatures (at a rate of k_{epim}, illustrated graphically below). Formation of the Breslow intermediate from the aldehyde proceeds at a rate of k_{1c} and k_{1t} and is presumably first order in catalyst for both steps. The fact that identical selectivities are observed with both catalytic and stoichiometric NHC means the rates of enal isomerization (k_{epim}) is irrelevant to the stereochemical outcome of the reaction. That is, if the interconversion of **81** and **82** was not occurring, acceleration of k_{1c}•[catalyst] against k_{1t}•[catalyst] would lead to different selectivities assuming a constant k_{epim} (Scheme 3.3.8).

Scheme 3.3.8



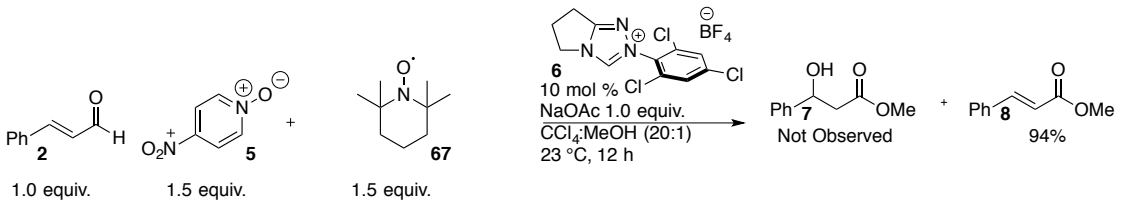
As a further probe of our proposed radical mechanism, we conducted the reaction in the presence of the known radical inhibitor, galvinoxyl radical **89**.[22] In this experiment, the desired β-hydroxy ester product **7** was isolated in substantially reduced yield, 9%. The remainder of the mass balance in this experiment was methyl cinnamate **8**. A control experiment revealed that galvinoxyl **89** is not a competent oxidant in the absence of the 4-nitro-pyridine *N*-oxide **5** (Scheme 3.3.9).

Scheme 3.3.9



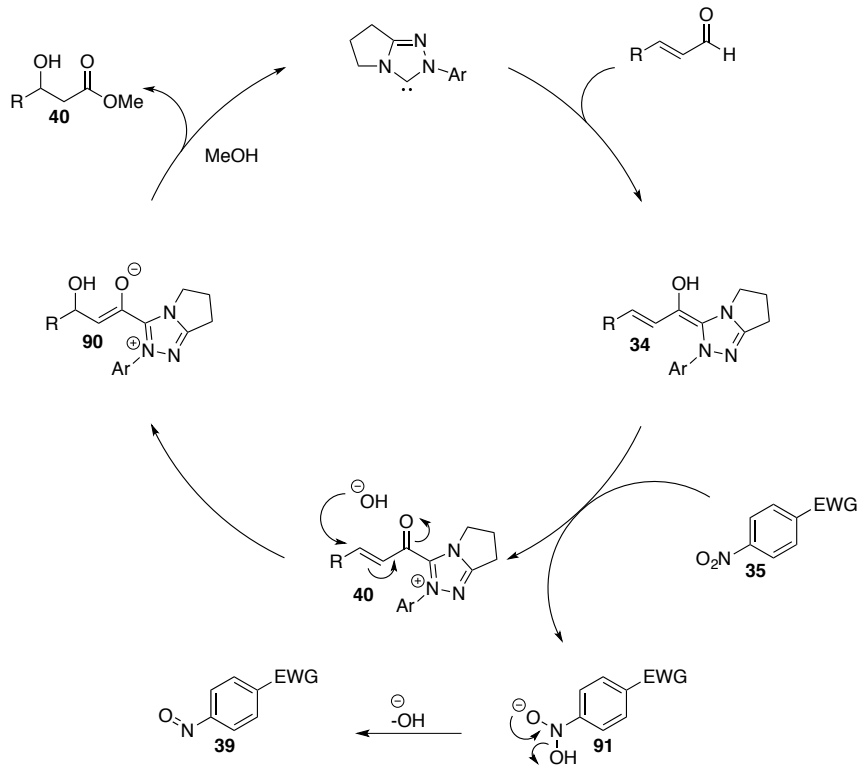
As a final mechanistic probe we added TEMPO to our standard reaction conditions. In this experiment, only methyl cinnamate **8** was observed and no desired β-hydroxy ester **7** was isolated from the reaction mixture (Scheme 3.3.10).

Scheme 3.3.10



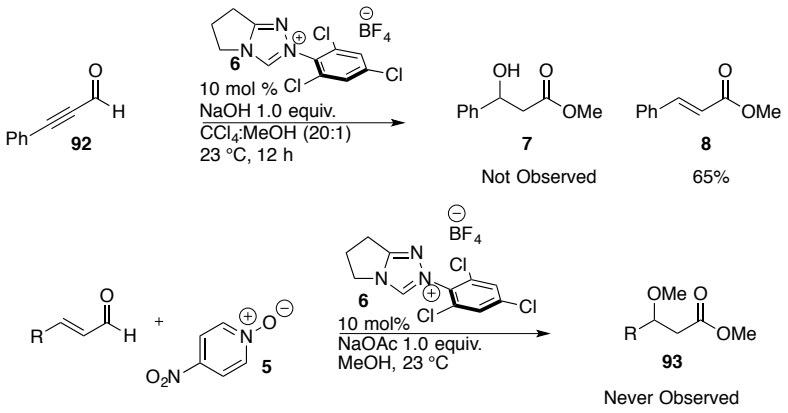
Another mechanistic proposal that we entertained was that the Breslow intermediate **34** undergoes a two-electron oxidation to the α,β-unsaturated acyl azolium **40** as the 4-nitropyridine *N*-oxide is reduced to intermediate **91**. Intermediate **91** may then liberate hydroxide and form nitroso **39**. The hydroxide anion may then attack α,β-unsaturated acyl azolium **40** to form enolate azolium **90**, which in turn could react with methanol to regenerate catalyst and produce β-hydroxy ester **40** (Scheme 3.3.11).

Scheme 3.3.11



To probe this hypothesis we reacted 3-phenylpropiolaldehyde **92** (ynals are direct precursors for the α,β-unsatured acyl azolium)[23] with catalyst **6** and NaOH in methanol. We did not oberve any of the desired β-hydroxy ester product and isolated methyl cinnamate **8** in 65% yield. Furthermore, we do not think that this mechanism is operative in our studies because we never isolate any of the β-methoxy ester **93**, the product of solvent addition to the α,β-unsaturated acyl azolium (Scheme 3.3.12).

Scheme 3.3.12



Finally, we considered the possibility that the homoenolate effects a nucleophilic attack on the oxygen of the nitro group. The nitro group as an electrophilic source of oxygen is rare in the literature, reacting only with very strong nucleophiles such as the Grignard reagent in the Bartoli indole synthesis.[24] Furthermore, there is strong evidence that this reaction proceeds via single-electron transfer.[25]

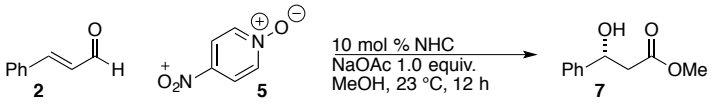
With all of this information taken into account, we believe this reaction proceeds via single-electron transfer from the Breslow intermediate to the electron-deficient nitroarene followed by radical recombination through the β-carbon of the Breslow intermediate and the oxygen of the nitro group (as shown in scheme 3.2.7). A similar reaction was reported by Chi et al. shortly after we completed our studies of this reaction and a similar mechanistic conclusion was reached in their work.[26]

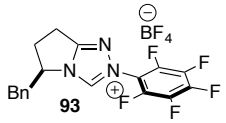
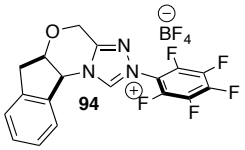
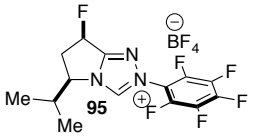
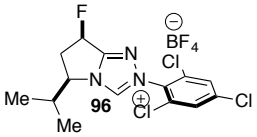
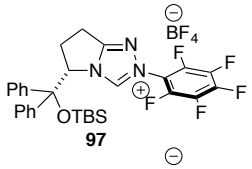
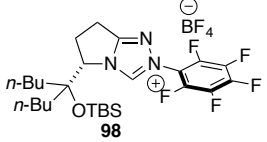
3.4 Reaction Optimization

We began our reaction optimization by screening a variety of chiral NHC catalysts in methanol with NaOAc as base. Initially, we were discouraged to see only moderate levels of

enantioselectivity. We found that tertiary silyl protected alcohol containing catalysts **97** and **98** provided the highest enantioselectivities. We chose to pursue catalyst **98** in our further optimizations as it gave higher yields than **97**, even though it provided product in lower enantioselectivity (Table 3.4.1). We chose to do this as we had noticed reactivity issues with catalyst **97** in the coupling of enals and nitroalkenes that we had developed previously (see chapter 2 section 2.3).

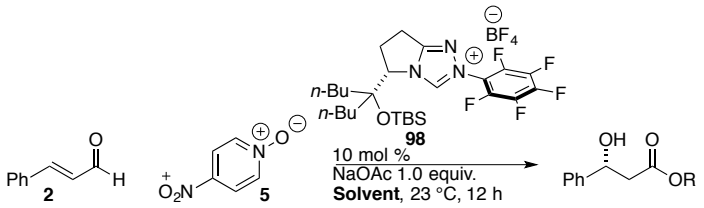
Table 3.4.1



Entry	NHC	Yield (%)	ee (%)
1	 **93**	39	-25
2	 **94**	22	0
3	 **95**	36	- 7
4	 **96**	42	- 8
5	 **97**	15	66
6	 **98**	31	51

We then explored the effect of solvent on the asymmetric reaction and were pleased to find a strong correlation between the solvent polarity and the ee of the product. We found that simply moving from methanol to *n*-butanol the ee increased from 51 to 85% with a comcomitant improvement in yield. We then explored solvent mixtures with methanol. Again, we saw an increase in enantioselectivity as the overall solvent polarity decreased. Our optimal result came with a 20:1 mixture of carbon tetrachloride to methanol, providing product in 92% ee and 45% yield (entry 9 table 3.4.2).

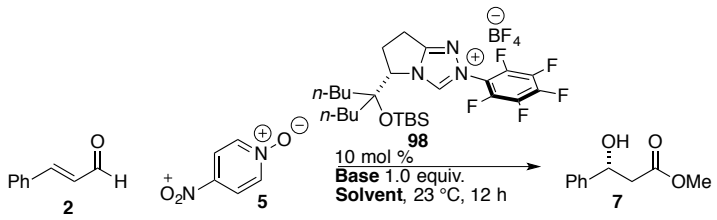
Table 3.4.2



Entry	Solvent	Yield (%)	ee (%)
1	MeOH	31	51
2	EtOH	33	73
3	*n*-PrOH	45	83
4	*n*-BuOH	39	85
5	DCM:MeOH (20:1)	36	79
6	Et_2O:MeOH (20:1)	19	89
7	MePh:MeOH (20:1)	30	87
8	CF_3Ph:MeOH (20:1)	44	88
9	CCl_4:MeOH (20:1)	45	92

After identifying catalyst **98** we turned our attention to high-throughput experimentation techniques (HTE) to rapidly assay a variety of solvents against bases in an effort to improve the yield of the reaction. Unfortunately, we were unable to identify conditions that provided product

in higher yield than NaOAc in CCl_4:MeOH (20:1) (Figure 3.4.1).



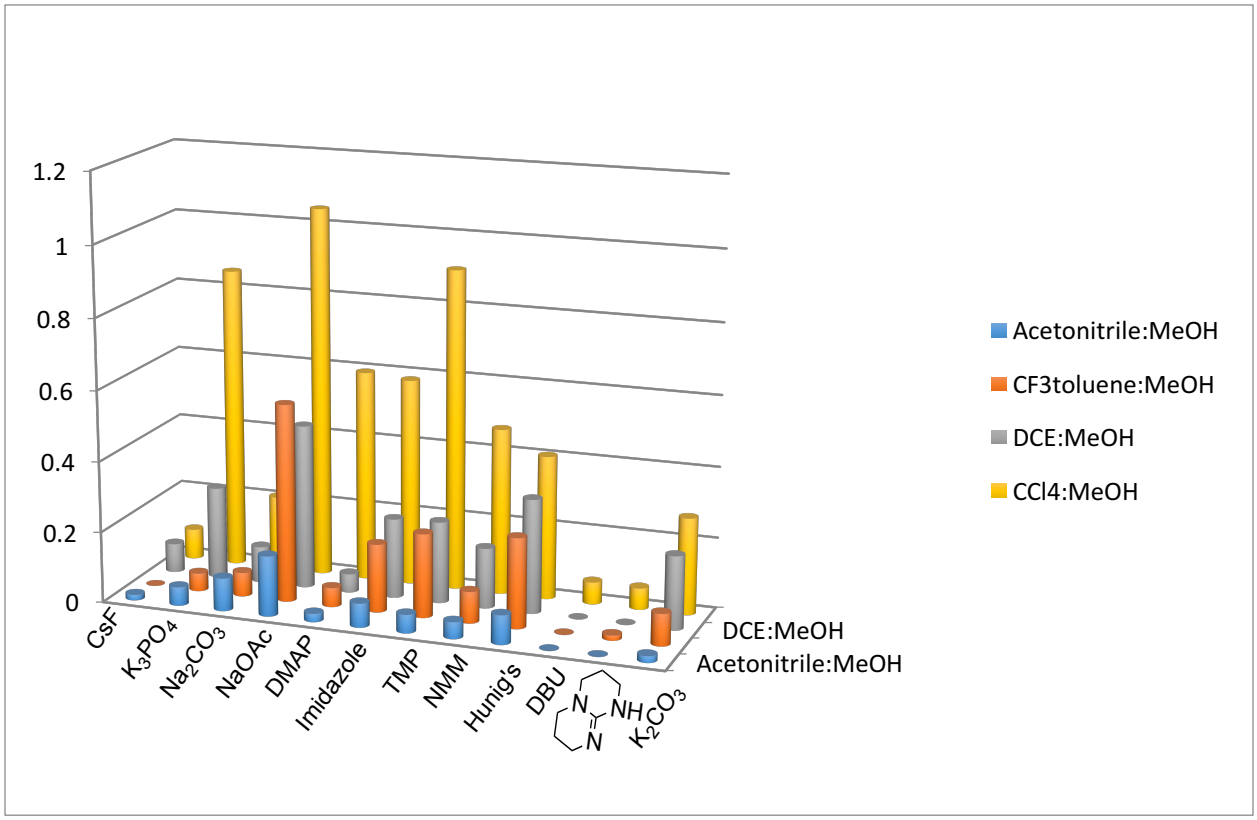
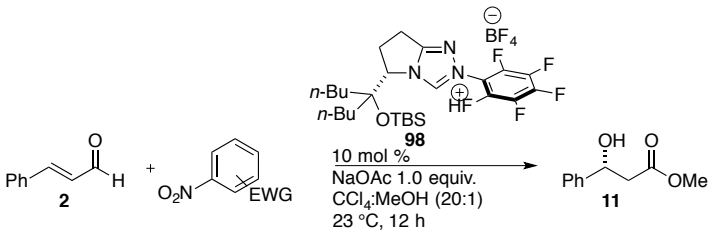
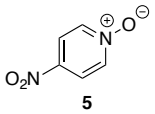
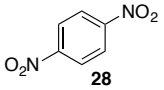
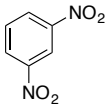
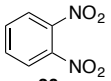


Figure 3.4.1

We then explored using different oxidants coupled with NHC **98** in the reaction. Again, we were unable to identify conditions to provide product in yield higher than 45%. Interestingly, large variations in enantioselectivity are observed as different oxidants are employed. 1,4-substituted nitroarenes provide product in the highest enantioselectivities and 1,2-substituted nitroarene **30** provides product in only 12% ee (Table 3.4.3).

Table 3.4.3

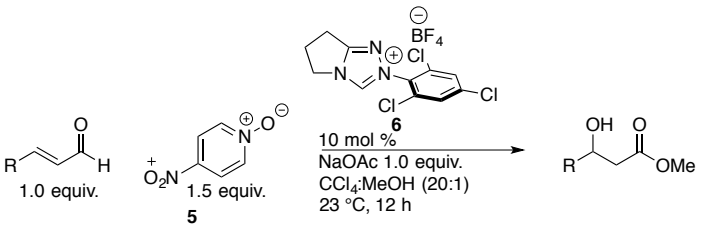


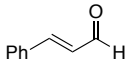
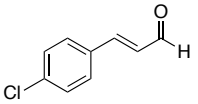
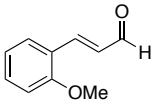
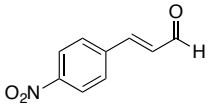
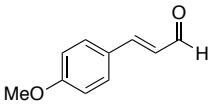
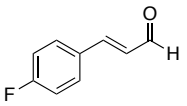
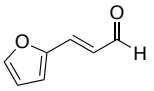
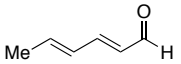
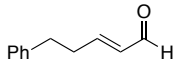
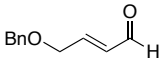
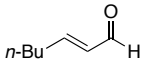
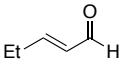
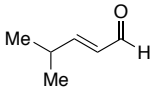
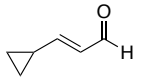
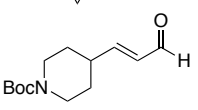
Entry	Oxidant	Yield (%)	ee (%)
1	 **5**	45	92
2	 **28**	34	84
3	 **29**	32	76
4	 **30**	12	16

3.5 Substrate Scope of the Racemic Reaction

Unable to optimize the product yield beyond 45% with cinnamaldehyde **2**, we began to explore the substrate scope. First, we investigated the reaction with 10 mol% of achiral NHC **6** in the presence of 1.5 equivalents of oxidant **5**, 1.0 equivalents of NaOAc in a 20:1 mixture of CCl_4:MeOH. We were pleased to find a variety of aliphatic enals participate in the reaction and provide product in good yields (typicall >50%). Notably, entry 10 in table 3.5.1, which bears a potential leaving group in the γ-position and entry 15 table 3.5.1 containing a protected amine are competent substrates. Electron-rich and electron-deficient aryl enals participate in the reaction, although yield is lower than with their aliphatic counterparts (Table 3.5.1).

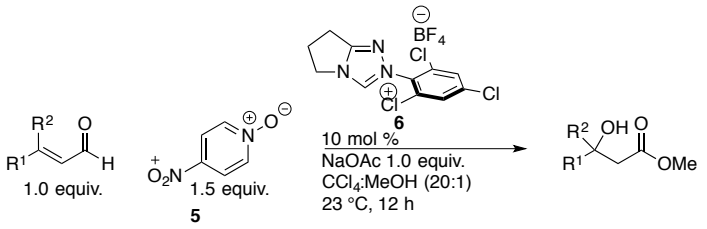
Table 3.5.1

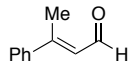
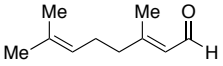
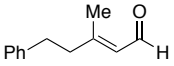


Entry	Aldehyde	Product	Yield (%)
1		**7**	50
2		**99**	56
3		**100**	43
4		**101**	30
5		**102**	38
6		**103**	45
7		**104**	43
8		**105**	43
9		**106**	65
10		**107**	71
11		**108**	71
12		**109**	65
13		**110**	69
14		**111**	67
15		**112**	73

We also explored β,β-disubsituted enals and were pleased to find they react in reasonable yields to furnish tertiary alcohols (Table 3.5.2).

Table 3.5.2

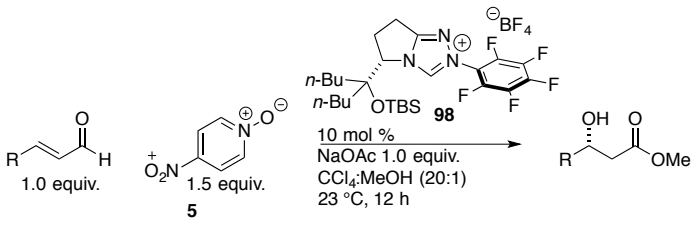


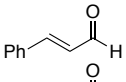
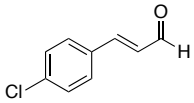
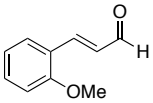
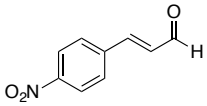
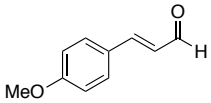
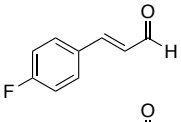
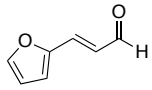
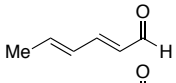
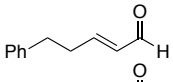
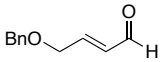
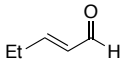
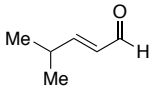
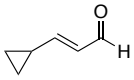
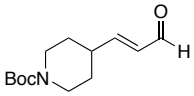
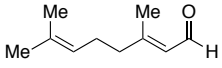
Entry	Aldehyde	Product	Yield (%)
1		**113**	48
2		**114**	37
3		**115**	51

3.6 Substrate Scope of the Asymmetric Reaction

We then turned our attention towards the substrate scope in the asymmetric reaction. We conducted this scope using chiral NHC **98** with NaOAc as base in a 20:1 mixture of CCl_4:MeOH. Again, we were pleased to see the reaction is remarkably broad, tolerating electron-rich and electron-deficient aryl enals, aliphatic enals, and β,β-disubstituted enals. Yields are generally highest when aliphatic enals are used. In most cases the remainder of the mass balance in these reaction is the α,β-unsaturated methyl ester. The reaction of 4-nitrocinnamaldehyde (entry 4 table 3.6.1) provided product **101** in 20% yield, presumably as a result of rapid β-protonation that outcompetes oxidation. In all other cases, no β-protonation was observed. Notably, a β,β-disubstituted enal (entry 15, table 3.6.1) is a competent substrate for the reaction, although it is generated in moderate yield and decreased enantioselectivity (40% yield, 63% ee).

Table 3.6.1



Entry	Aldehyde	Product	Yield (%)	ee (%)
1		**7**	45	92
2		**99**	57	90
3		**100**	44	80
4		**101**	20	80
5		**102**	41	91
6		**103**	46	91
7		**104**	56	84
8		**105**	46	85
9		**106**	58	80
10		**107**	71	81
11		**109**	44	80
12		**110**	71	86
13		**111**	61	80
14		**112**	74	84
15		**115**	40	63

3.7 Conculsion

In conclusion, we have developed the first example of a reaction wherein the Breslow intermediate is oxidized to a radical cation that then combines with another radical to generate a new bond. Key to the development of this reaction was the identification of electron deficient nitroarenes which are capable of both acting as oxidant for the Breslow intermediate and as the source of the radical coupling partner. An asymmetric variant has been developed using chiral NHC **98**, which provides β-hydroxy ester products in good yields and enantioselectivities. Mechanistically, we have strong evidence that the source of the oxygen atom is the nitro group of the nitroarene. We have found stereochemical convergence between *cis* and *trans* enals to provide the same major enantiomer of product. This strongly implicates radical character of the Breslow intermediate to allow for such a bond rotation. This reaction discovery represents entry into a new class of NHC-catalyzed reactions which break the two-electron pathway paradigm which has previously dominated the field of NHC catalysis.

3.8 References

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Chapter 4

Asymmetric Cyclopentanone Synthesis from Enals via Single-Electron Oxidation of the Breslow Intermediate

4.1 Introduction

N-heterocyclic carbene (NHC) catalyzed annulation reactions have received a tremendous amount of attention since Glorius and Bode first reported the NHC generated homoenolate independently and concurrently in 2004. In these initial reports, it was disclosed that enals are capable of coupling with aldehydes to generate γ-lactones in good yields and good *syn* selectivities (figure 4.1 eq 1).[1] In 2005, Bode extended this reactivity to include imines as the coupling partner to synthesize γ-lactams (figure 4.1 eq 2).[2] Nair extended the area of homoenolate annulation chemistry in 2006 by coupling enals and chalcones to furnish cyclopentenes (figure 4.1 eq 3).[3] The majority of the reports in the homoenolate literature have focused on these types of annulations.[4]

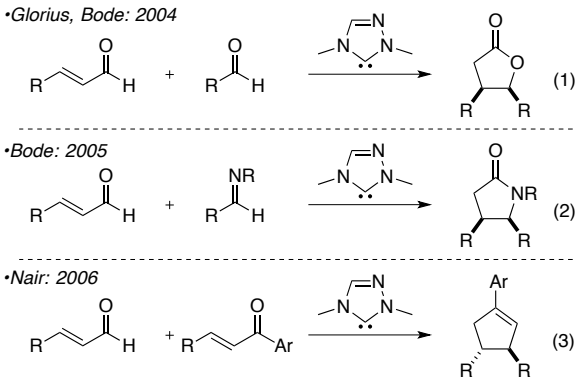
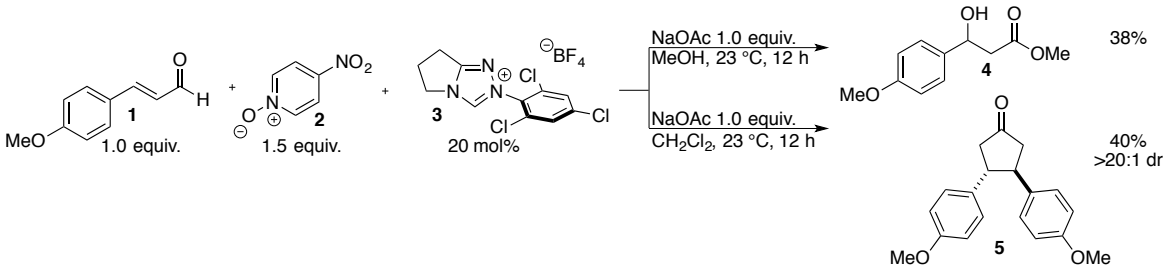


Figure 4.1

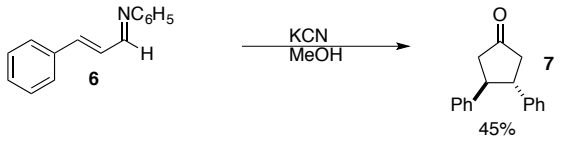
During our investigation into the NHC-catalyzed single-electron oxidation of enals to generate β-hydroxy esters **4**, we found that conducting the reaction in pure dichloromethane affords an unexpected cyclopentanone dimer product **5**. Interestingly, in our optimization of the β-hydroxylation of enals, we never observe cyclopentanone **5** in the reaction medium when a nucleophilic solvent or co-solvent is present (Scheme 4.1.1). For cyclopentanone **5** to form, the reaction must be conducted in the complete absence of alcohol nucleophiles.

Scheme 4.1.1



This is not the first time this product has been synthesized via an umpolong catalytic method. In 1982, Sing and Mandal reported a cyanide catalyzed annulation of cinnamaniline in methanol that affords *trans*-3,4-diphenylcyclopentan-1-one **7** in 45% yield (Scheme 4.1.2).[5]

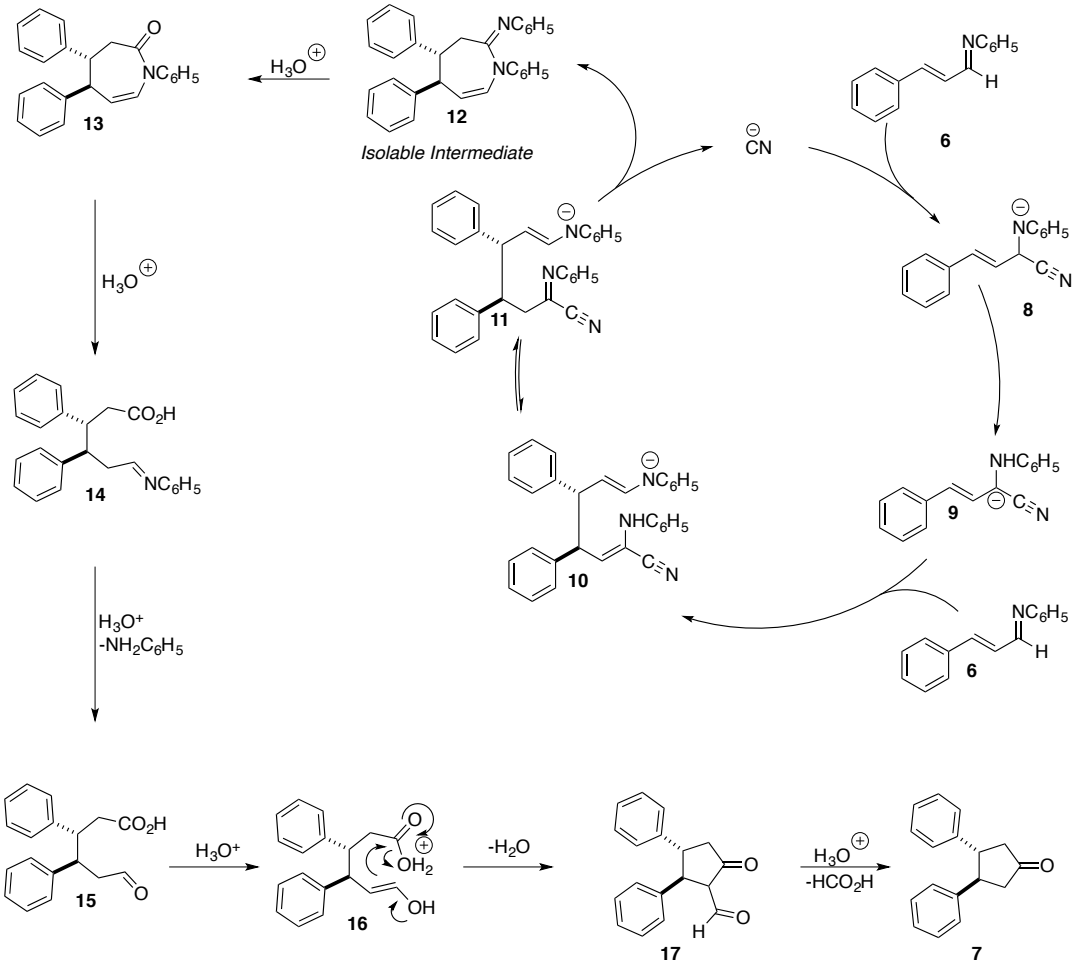
Scheme 4.1.2



Singh and Mandal propose that cinnamaniline **6** is attacked by cyanide to form intermediate **8**, which undergoes proton transfer to form acyl anion-type intermediate **9**. Acyl anion-type intermediate **9** than attacks a second equivalent of cinnamaniline **6** to form the C-C bond at the β-position and generate intermediate **10**. Intermediate **10** tautomerizes to **11**, which then undergoes

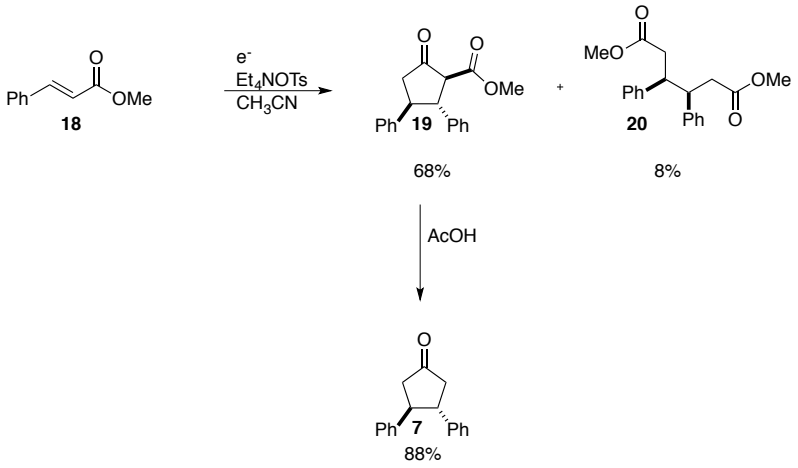
intramolecular cyclization to liberate cyanide and form imine **12** closing the catalytic cycle. This imine is hydrolyzed to produce amide **13**. Amide **13** then opens with acid and the imine is hydrolyzed to generate aldehyde **15**. Aldehyde **15** tautomerizes to the enol which then cyclizes to form β-keto aldehyde **17**. Acid then attacks β-keto aldehyde **17** to liberate formic acid via a retro Claisen reaction and generate cyclopentanone **7**. Singh and Mandal isolated intermediate **12**, which upon treatment with acid form cyclopentanone **7** in support of this proposed mechanism (Scheme 4.1.3).

Scheme 4.1.3



Furthermore, cyclopentanone **7** has previously been synthesized via electrochemical reduction of methyl cinnamate **18** to produce β-keto ester **19**, which is then hydrolyzed and decarboxylated to form cyclopentanone **7**.[6] In this chemistry, the *trans* cyclopentanone product is the only isomer formed. A *meso* bis-ester **20** is formed as a side product in this reaction, presumably because the bulk of the phenyls in the 3- and 4-positions do not allow for cyclization to the β-keto ester (Scheme 4.1.4).

Scheme 4.1.4

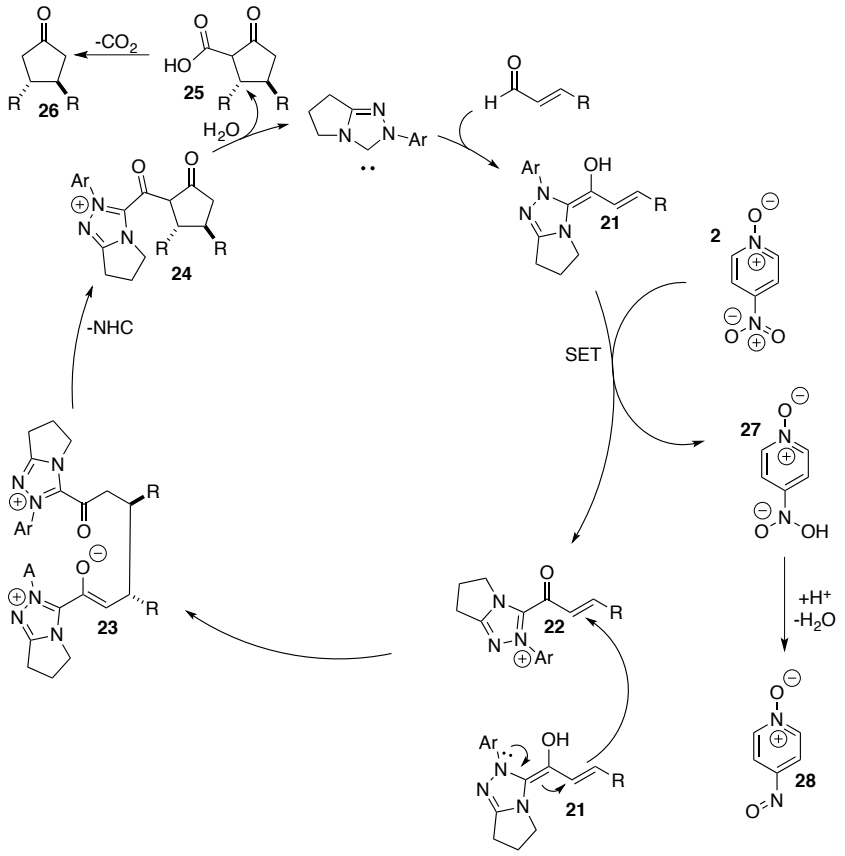


4.2 Mechanistic Investigations

The NHC-catalyzed oxidative formation of cyclopentanone **5** was an unexpected and unprecedented result. We were intrigued by this reactivity and began a mechanistic investigation. Initially, we hypothezied that nitroarene **2** may effect a two-electron oxidation of Breslow intermediate **21** to α,β-unsaturated acyl azolium **22**. Acyl azolium **22** would then act as a 1,4-acceptor for a native, non-oxidized, Breslow intermediate **21** to form the C-C bond between the two β-positions of the enals to form intermediate **23**. Intermediate **23** could then cyclize to liberate one equivalent of catalyst to form β-keto acyl azolium **24**. This acyl azolium could then be attacked

by water to form β-keto acid **25** which could undergo decaboxylation to furnish cyclopentaone **26** (Scheme 4.2.1).

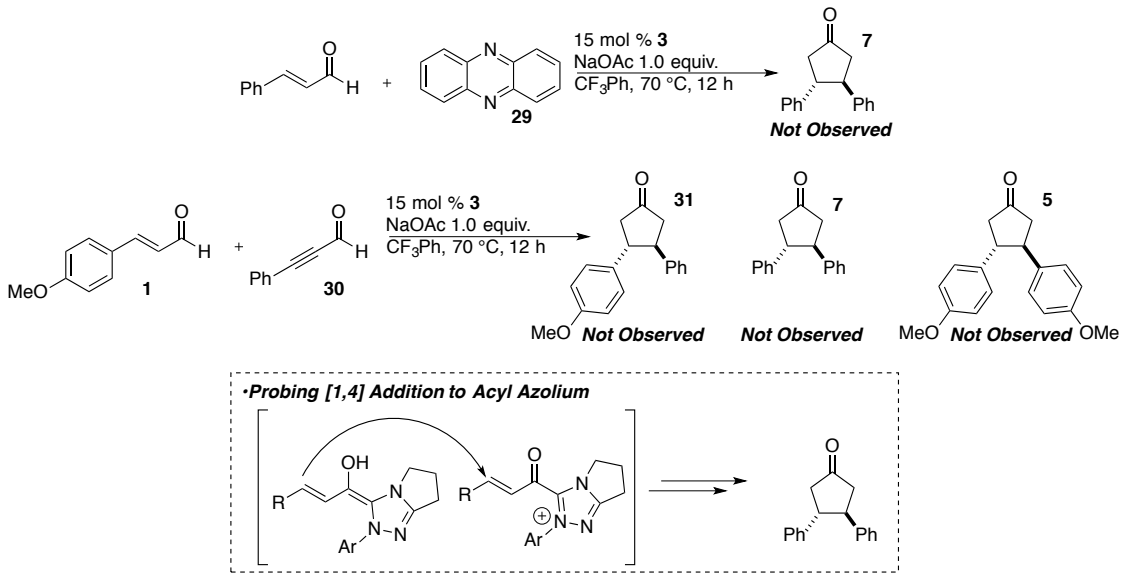
Scheme 4.2.1



To test this hypothesis we utilized phenazine **29** (a known two-electron oxidant for the Breslow intermediate)[7] to the reaction conditions. In this experiment, we did not observe any cyclopentanone formation. Furthermore, we subjected ynal **30** (a known precursor to the α,β- acyl azolium)[8] to the reaction conditions with 4-methoxycinnamaldehyde **1** as the precursor for the Breslow intermediate in the absence of any oxidant. Again, this reaction produced no detectable amounts of any cyclopentanone product (we did not observe cross product **31**, dimer **5**, or dimer **7**). These results led us to rule out the proposed mechanism wherein one Breslow intermediate

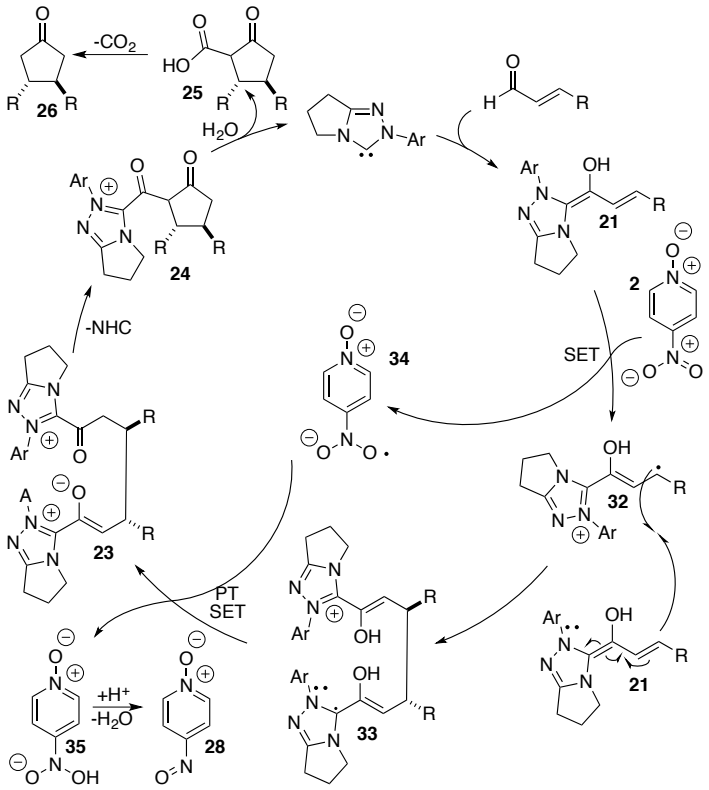
undergoes a two-electron oxidation followed by attack of a second, native Breslow intermediate (Scheme 4.2.2).

Scheme 4.2.2



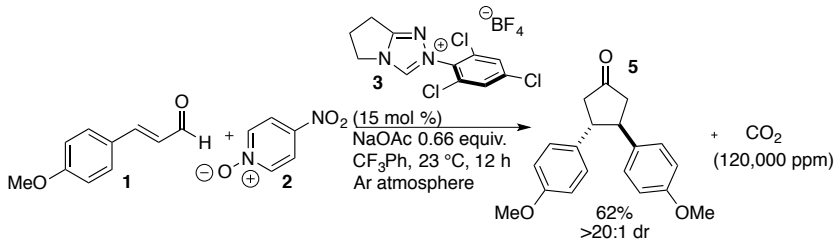
The other mechanistic proposal we envisioned is as follows: one Breslow intermediate **21** undergoes a single electron transfer to the electron-deficient nitroarene to form Breslow intermediate derived radical cation **32** and nitroarene derived radical anion **34**. The radical Breslow intermediate **32** is then attacked at the β-position by a second, native Breslow intermediate **21** to form radical species **33**. This newly generated radical then transfers a second electron to the nitroarene derived radical anion to form bis-azolium **23** and arene **35**. The arene species **35** may then lose water to form nitroso **28**. Bis-azolium **23** may then undergo an intramolecular Claisen reaction to form β-keto azolium **24** and liberate one equivalent of catalyst. β-keto azolium **24** is then intercepted with water to liberate the second equivalent of catalyst and β-keto acid **25** is generated, which then undergoes decarboxylation to form cyclopentanone **26**.

Scheme 4.2.3



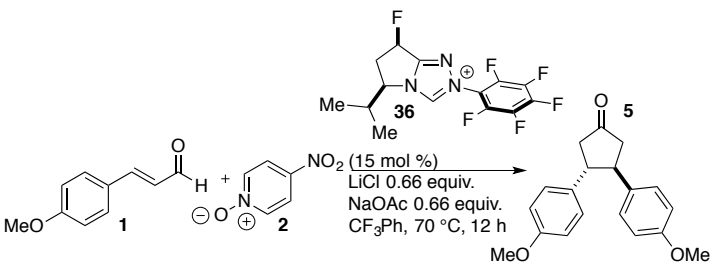
We hypothesize that the excised carbon in this transformation is lost as CO_2 in a decarboxylation event. In an effort to validate this hypothesis we conducted an experiment in a sealed vial with a septum cap under and argon atmosphere (reaction was set up in an argon atmosphere glove box). We then analyzed the headspace of the reaction vessel for CO_2 and found the headspace contained 120,000 ppm CO_2. This is approximately 300 times the concentration of atmospheric CO_2 (we thank Daniel Reuss for his assistance in this analysis). This result, in our opinion, validates the intermediacy of **25** in the reaction (Scheme 4.2.4).

Scheme 4.2.4



We believe that our second proposed mechanism is operative in this reaction. The reaction uses the same single-electron oxidant as the radical hydroxylation reaction we had previously developed (see chapter 3), two-electron oxidants do not provide desired product, acyl azolium precursor **30** does not provide product, and an oxidant is necessary as the excised carbon is lost as CO_2.

In an attempt to implicate two equivalents of catalyst in the reaction mechanism we performed a non-linear effect experiment using chiral NHC **36** and *ent*-NHC **36**.[9] Unfortunately, we did not observe the expected non-linear effect (Figure 4.2.1). A possible explanation for this is that two stereocenters are set during the bond-forming event. Thus, when opposite antipodes of catalyst are involved in the bond-forming event, a different diastereomeric transition state may be encountered, potentially leading to enrichment of the meso adduct at the expense of ee increase or decrease. The meso intermediate may then lead to other products. In Kise's electrochemical reductive coupling of cinnamates, he observes that the meso adduct does not close to the cyclopentanone.[6] In our investigation into non-linear effects, we always saw >20:1 dr of the *trans* product.



%ee catalyst	%ee product	%ee expected
0	0	0
20	12	17
40	30	35
60	50	52
80	64	69
100	87	87

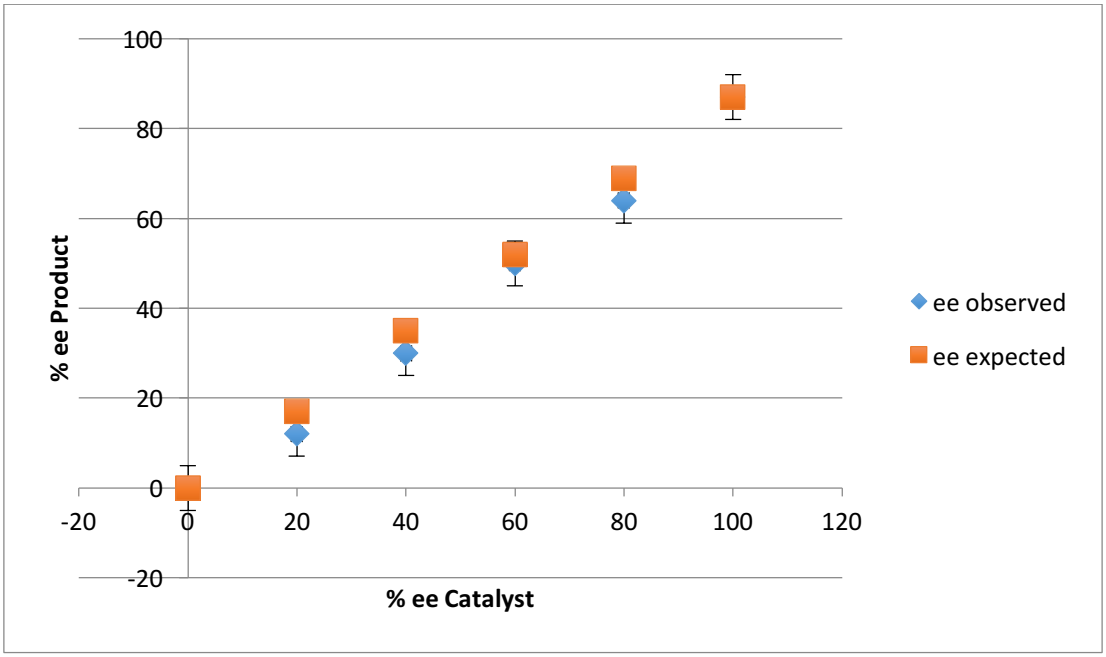
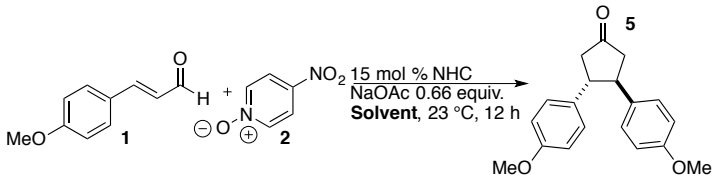


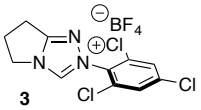
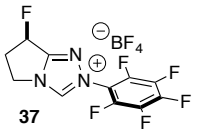
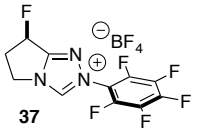
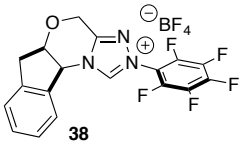
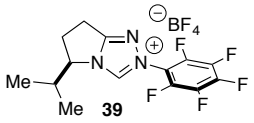
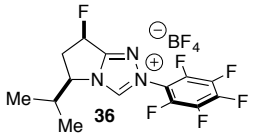
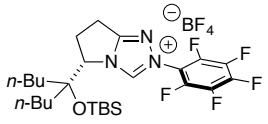
Figure 4.2.13

4.3 Reaction Optimization

We began our investigation into the dimerization of 4-methoxycinnamaldehyde to form cyclopentanone **5** by exploring a variety of chiral NHC catalysts in dichloromethane at 23 °C with NaOAc as base. We were discouraged to find that only backbone-fluorinated catalyst **37** provided any product (25% yield, 12% ee). By switching the solvent to toluene we were pleased to see an increase in enantioselectivity to 66% ee and 28% yield (Table 4.3.1).

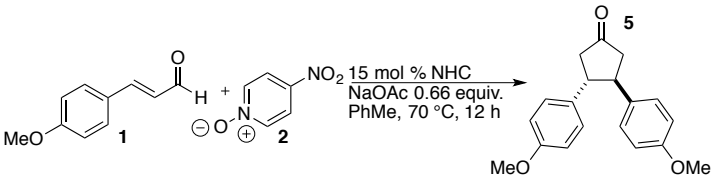
Table 4.3.1

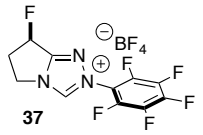
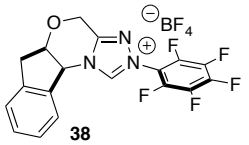
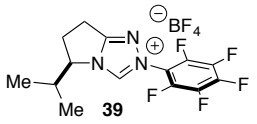
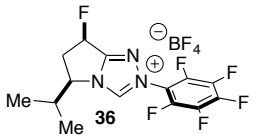
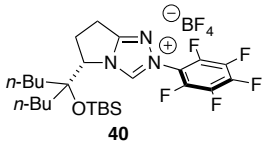


Entry	NHC	Solvent	Yield (%)	ee(%)
1	 **3**	CH_2Cl_2	49	-
2	 **37**	CH_2Cl_2	25	12
3	 **37**	PhMe	28	60
4	 **38**	CH_2Cl_2	<5	-
5	 **39**	CH_2Cl_2	<5	-
6	 **36**	CH_2Cl_2	<5	-
7	 **40**	CH_2Cl_2	<5	-

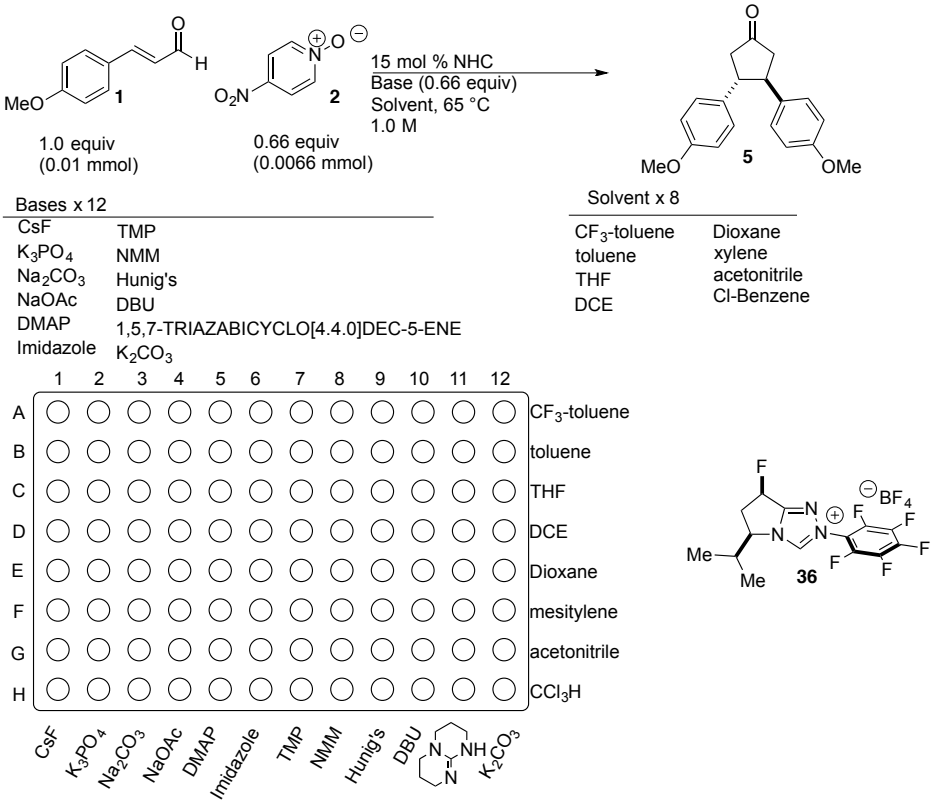
We then evaluated the reaction with chiral NHC catalysts at 70 °C in toluene and found that reactivity was restored with chiral catalysts. Ultimately, we found catalyst **36** provides product in the highest enantioselectivity (84% ee, 51% yield) (Table 4.3.2).[10]

Table 4.3.2



Entry	NHC	Yield (%)	ee (%)
2	 **37**	46	50
4	 **38**	30	50
5	 **39**	44	76
6	 **36**	51	84
7	 **40**	44	-76

We turned our attention to high-throughput experimentation (HTE) in an effort to improve the yield of the reaction. We screened eight different solvents across twelve different bases and ultimately found NaOAc as base in trifluorotoluene proved optimal. Upon bench-top scale-up of this reaction, we isolated cyclopentanone **5** in 64% yield and 84% ee (Figure 4.3.1).


MeO
1
1.0 equiv
(0.01 mmol)
O2N
2
0.66 equiv
(0.0066 mmol)
15 mol % NHC
Base (0.66 equiv)
Solvent, 65 °C
1.0 M
MeO
5
OMe
Bases x 12
CsF
K3PO4
Na2CO3
NaOAc
DMAP
Imidazole
TMP
NMM
Hunig's
DBU
1,5,7-TRIAZABICYCLO[4.4.0]DEC-5-ENE
K2CO3
Solvent x 8
CF3-toluene
toluene
THF
DCE
Dioxane
xylene
acetonitrile
Cl-Benzene
1 2 3 4 5 6 7 8 9 10 11 12
A CF3-toluene
B toluene
C THF
D DCE
E Dioxane
F mesitylene
G acetonitrile
H CCl3H
CsF K3PO4 Na2CO3 NaOAc DMAP Imidazole TMP NMM Hunig's DBU TBD K2CO3
BF4
Me
Me
36

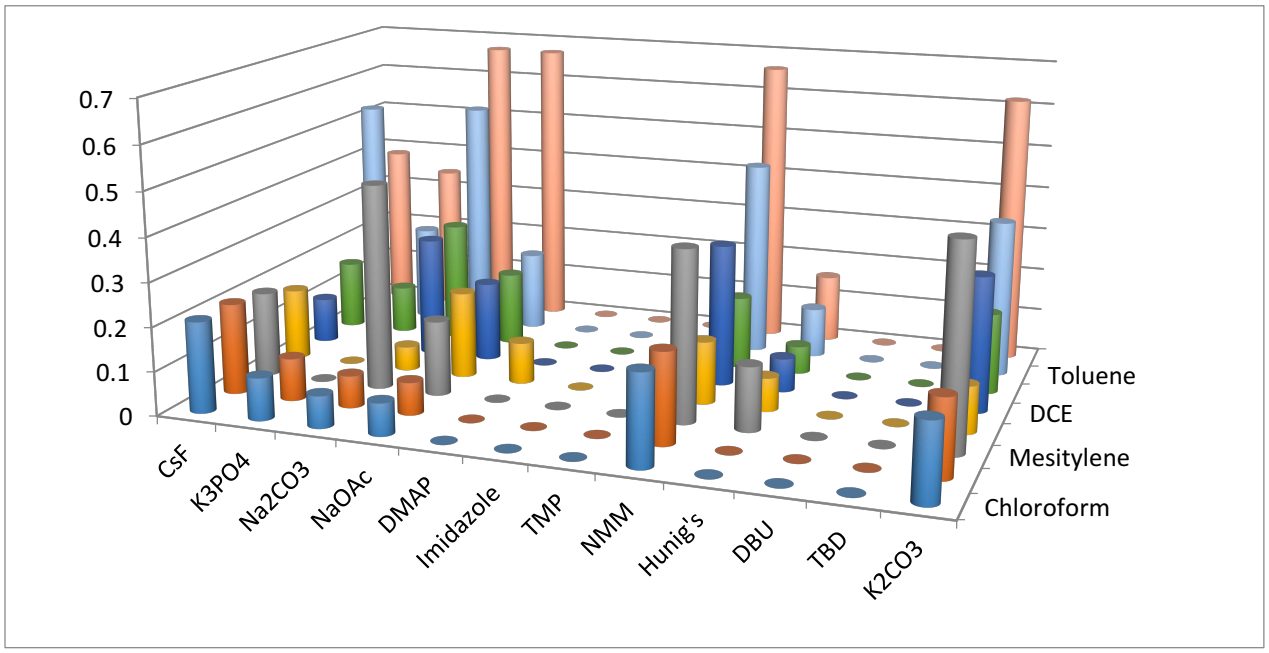
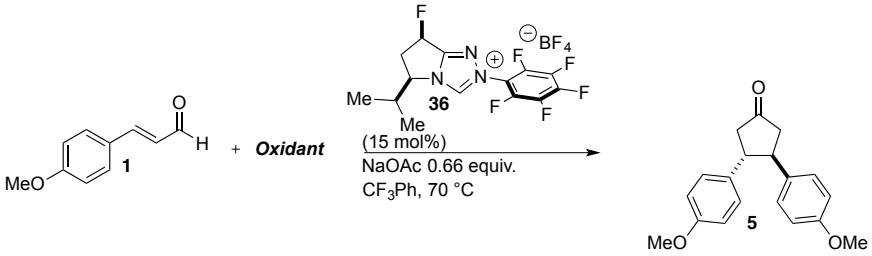
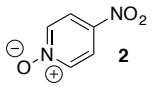
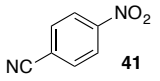
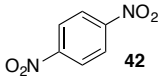
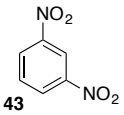
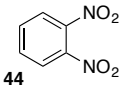
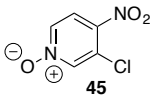

0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
CsF
K3PO4
Na2CO3
NaOAc
DMAP
Imidazole
TMP
NMM
Hunig's
DBU
TBD
K2CO3
Toluene
DCE
Mesitylene
Chloroform

Figure 4.3.1

After conducting this solvent screen, we explored the effect of different nitroarene oxidants on the reaction. We found a variety of different nitroarenes provide product. 4-nitropyridine *N*-oxide **2** provides product in the highest yield. Enantioselecivity is not dependent upon oxidant (Table 4.3.3).

Table 4.3.3



Entry	Oxidant	Yield (%)	dr	ee (%)
1	 **2**	64	>20:1	84
2	 **41**	15	>20:1	-
3	 **42**	14	>20:1	-
4	 **43**	44	>20:1	85
5	 **44**	59	>20:1	85
6	 **45**	13	>20:1	-

Upon identifying 4-nitropyridine *N*-oxide as the optimal oxidant, we were curious to explore the effect of Lewis acid additives on the reaction. We hypothesized that the addition of a Lewis acid may increase the enantioselectivity or the yield of the reaction via coordination to the oxygen of the enal. We screened five Lewis acids against four nitroarenes and were surprised to find that in all but one case (LiCl with 4-nitropyridine *N*-oxide) the Lewis acid additive actually inhibited the reaction. However, the combination of LiCl with 4-nitropyridine *N*-oxide provided an increase in the reaction efficiency from 64 to 79% yield with enantioselectivity remaining the same (84% ee) (Figure 4.3.2).

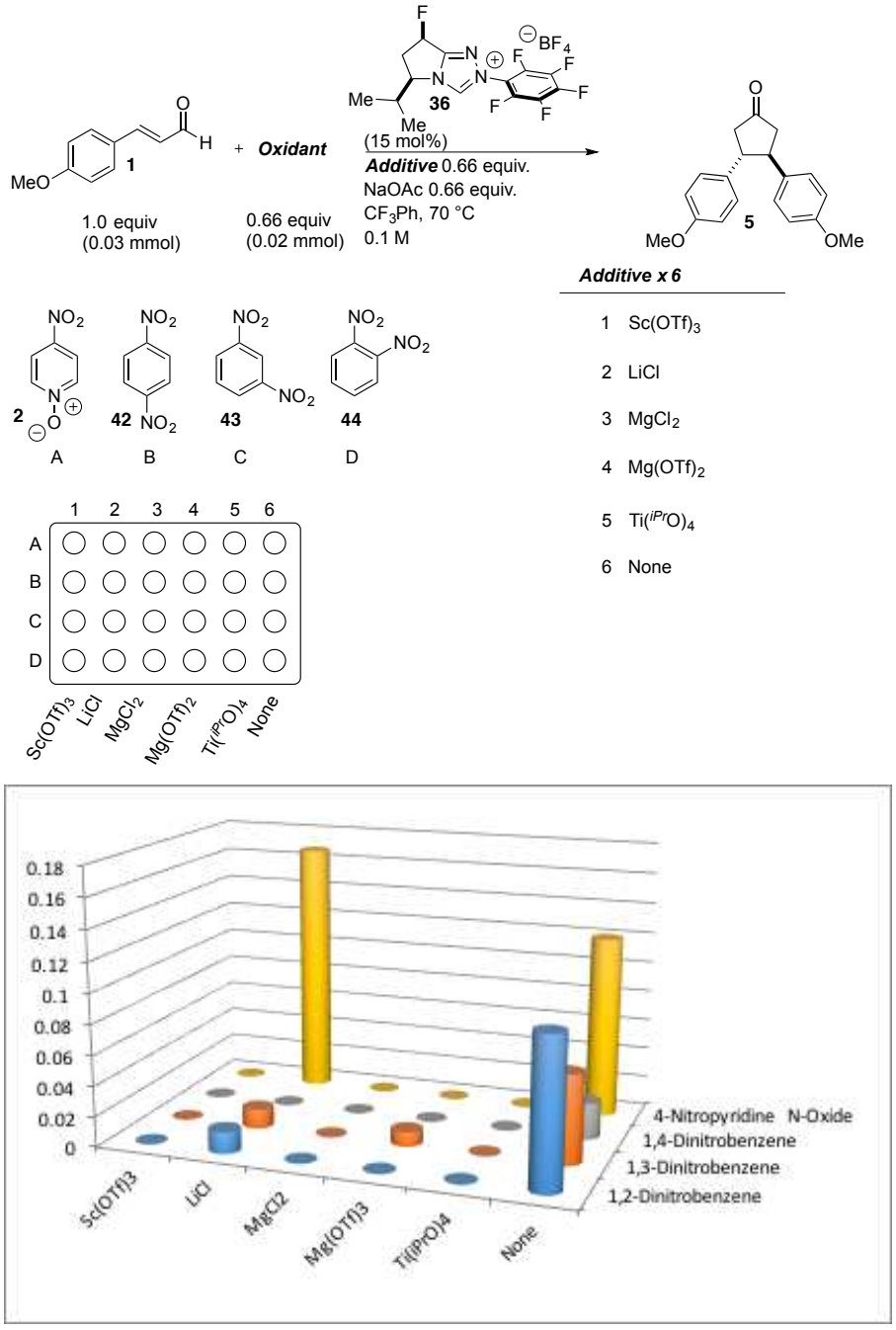
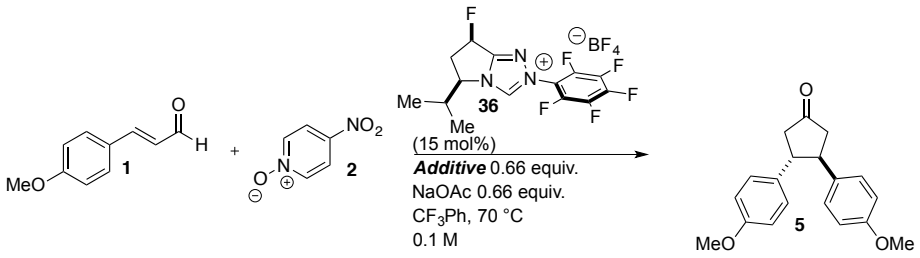


Figure 4.3.2

We then subjected a variety of other lithium containing Lewis acids to the reaction. A similar improvement in yield was observed with most of the lithium salts, however, LiCl proved to be the most efficient additive to the reaction (Table 4.3.4). The role of lithium in this reaction is

not fully understood, however, we postulate that it coordinates to the oxygen of the enal and either improves the rate of addition of the carbene, or it helps to activate the radical Breslow cation for attack from the native Breslow intermediate.[11]

Table 4.3.4



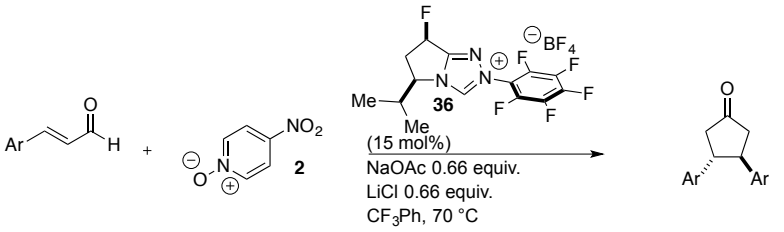
Entry	Additive	Yield (%)	ee (%)
1	-	64	84
2	LiBr	56	84
3	LiI	68	82
4	LiF	70	84
5	Li_2CO_3	47	84
6	$LiClO_4$	57	83
7	$LiBF_4$	76	84
8	LiCl	79	84
9	NaCl	55	84

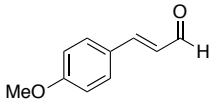
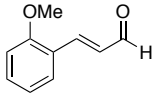
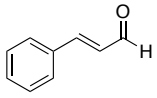
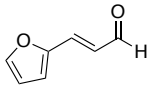
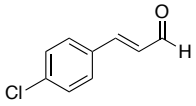
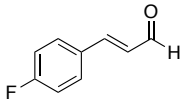
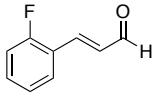
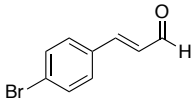
4.4 Cyclopentanone Dimerization Substrate Scope

With optimized conditions identified, we explored the scope of the dimerization. Electron-rich and electron-deficient aryl enals are tolerated in the reaction. Electron-rich substrates proved to provide higher yields than their electron-poor counterparts. The heteroaromatic 2-furylcinnamaldehyde works in the reaction as well. Unfortunately, aliphatic enals do not participate. To our delight, 4-bromocinnamaldeyde provides product in reasonable yield and contains a potential handle for cross coupling reactions. In all cases, the cyclo-pentanone products

are formed as a single diastereomer (Table 4.4.1). The remainder of the mass balance in these reactions is the α,β-unsaturated acid, the result of a two-electron oxidation of the Breslow intermediate to form the acyl azolium, followed by attack by adventitious water.

Table 4.4.1



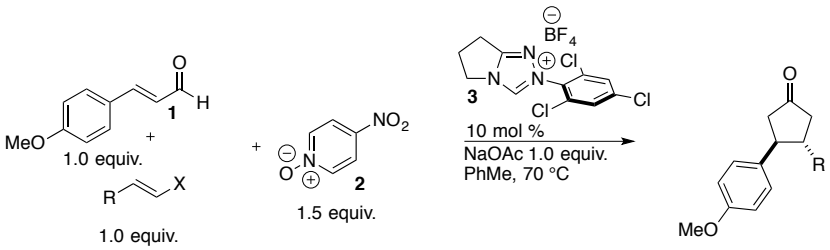
Entry	Enal	Product	Yield (%)	dr	ee (%)
1		**5**	79	>20:1	84
2		**46**	71	>20:1	91
3		**47**	74	>20:1	84
4		**48**	66	>20:1	65
5		**49**	63	>20:1	84
6		**50**	65	>20:1	85
7		**51**	65	>20:1	85
8		**52**	60	>20:1	84

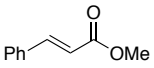
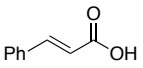
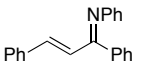
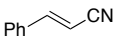
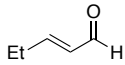
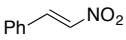
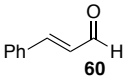
4.5 Development of a Cross-Annulation

Motivated to expand the utility of this transformation, we explored the possibility of effecting a cross-reaction. We attempted to cross enal **1** with α,β- unsaturated esters, α,β-

unsaturated acids, α,β-unstaruated imines, α,β-unsaturated nitriles, aliphatic enals, and nitroalkenes. All of these attempts at a cross-reaction were met with failure. The only way we were able to effect a cross-annulation was by employing two different enals in the reaction (table 4.5.1 entry 7). In the reaction between two different enals, the desired cross product was formed in 25% yield with the remainder mass balance being the dimer formed from enal **1** and the dimer formed from enal **60**.

Table 4.5.1

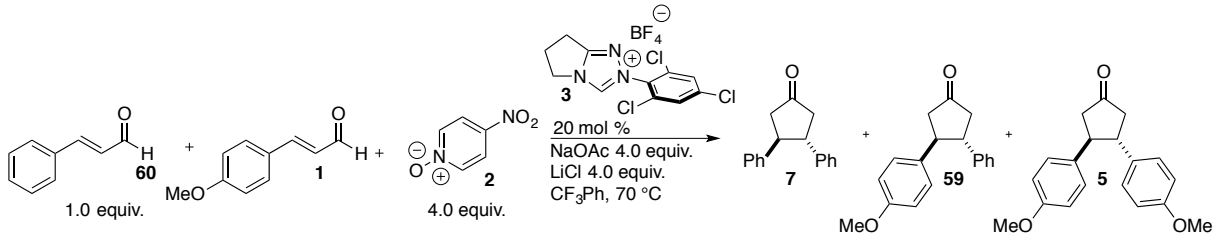


Entry	Michael Acceptor	Product	Yield (%)
1		**53**	not observed
2		**54**	not observed
3		**55**	not observed
4		**56**	not observed
5		**57**	not observed
6		**58**	not observed
7	 **60**	**59**	25

We were able to optimize the formation of cross-product **59** by varying the equivalency of the enal coupling partners. We found that using an excess of the more reactive (more electron-rich) enal, that cross product **59** may be formed in good yield. We found the optimal reaction conditions are employing four equivalents of the electron-rich enal, four equivalents of oxidant,

four equivalents of LiCl, and four equivalents of NaOAc in CF_3Ph at 70 °C (table 4.5.2, entry 4). When four equivalents of the excess enal are employed, only trace amounts of the cyclopentanone dimer of the limiting enal is observed in the reaction mixture (Table 4.5.2).

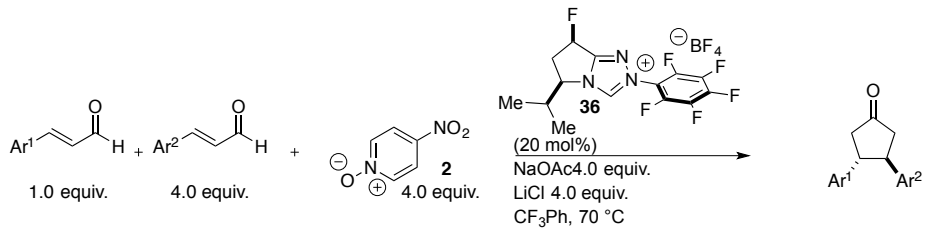
Table 4.5.2

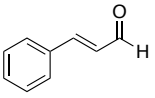
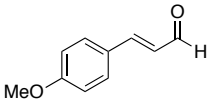
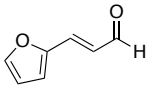
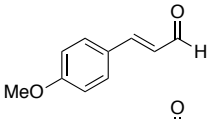
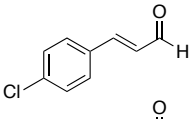
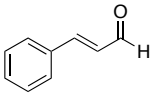
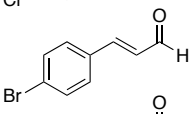
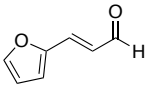
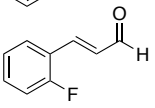
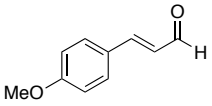


Entry	Equiv. **1**	Yield **59** (%)	ratio **7:59:5**
1	1.0	28	1:1:1.3
2	2.0	35	1:4.6:4.9
3	3.0	55	1:6.2:10.8
4	4.0	67	-:1:3.5

After identifying these conditions, we explored the asymmetric cross-annulation reaction using chiral catalyst **36**. Yields in this reaction were generally good, diastereoselectivity remained excellent, and enantioselectivity ranged from 75-86% ee. Electron-rich and electron-deficient aryl enals may be coupled via this methodology. In all examples, only trace amounts of the dimer arising from the limiting enal is observed (Table 4.5.3).

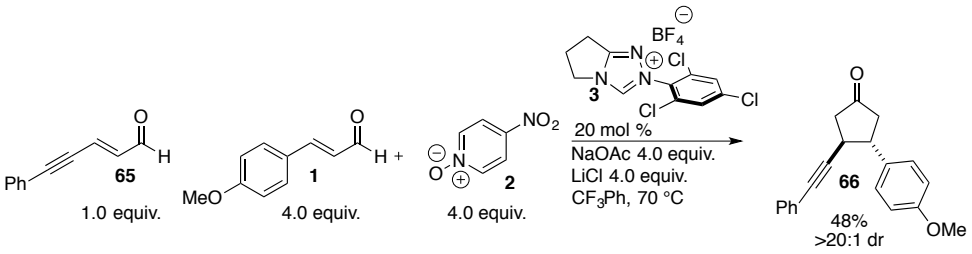
Table 4.5.3



Entry	Enal (limiting	Enal (excess)	Product	Yield (%)	dr	ee (%)
1			**59**	65	>20:1	85
2			**61**	59	>20:1	80
3			**62**	60	>20:1	86
4			**63**	56	>20:1	75
5			**64**	60	>20:1	82

In an attempt to further the scope of the reaction beyond the coupling of aryl enals, we subjected yne-enal **65** to the reaction conditions with achiral catalyst **3**. Cross-product **66** was formed in 48% yield and as a single diastereomer (Scheme 4.5.1). Unfortunately, attempts to render this reaction asymmetric failed. However, this does represent a potentially interesting direction to pursue as it allows access to an aliphatic surrogate. Furthermore, the issues associated with chiral catalysts may potentially be overcome with further development of the reaction conditions.

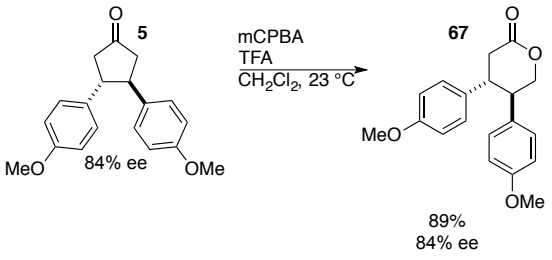
Scheme 4.5.1

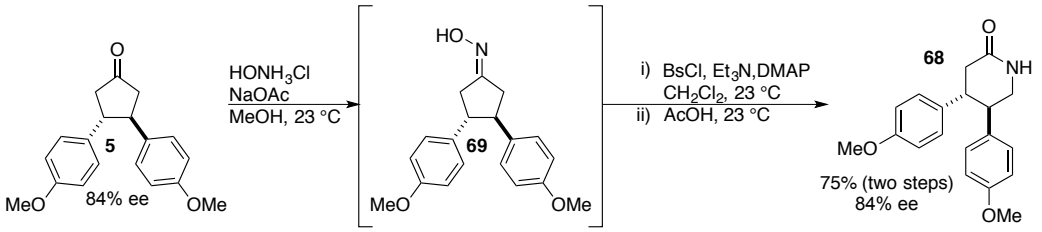


4.6 Product Derivatization

To demonstrate the synthetic utility of the cyclopentanone products, we derivatized cyclopentanone **5** to the corresponding lactone **67** and lactam **68**. Lactone **67** was synthesized by subjection of cyclopentanone **5** to *m*CPBA (*meta*-chloroperoxybenzoic acid) and trifluoroacetic acid in dichloromethane. The corresponding lactone product **67** was formed in 89% yield with no loss of enantioselectivity. The lactam product was formed by first subjecting cyclopentanone **5** to hydroxymethylamine•HCl with NaOAc in methanol. The resultant oxime **69** was then treated with 4-bromobenzenesulfonyl chloride, triethylamine, and a catalytic amount of DMAP (dimethyl amino pyridine) in dichloromethane. The solvent was removed *in vacuo* and acetic acid was added. The resultant lactone **68** was isolated in 75% over two-steps with complete stereofidelity (Scheme 4.7.1).

Scheme 4.7.1





4.8 Conclusion

A novel asymmetric NHC-catalyzed annulation of enals to generate *trans*-3,4-disubstituted cyclopentanones has been developed. This methodology allows for the dimerization of enals to generate C-2 symmetric cyclopentanones. 4-nitropyridine *N*-oxide was found to be the optimal oxidant for this transformation, although a variety of nitroarenes have been shown to promote this transformation. Key to this reaction development was the identification of LiCl as a Lewis acid additive to improve the efficiency of the transformation. A cross-annulation between two-different aryl enals has also been realized. The cross reaction relies on excess of one of the coupling partners to achieve high selectivity for the cross product. Mechanistically, we believe the product forms via the coupling of a native Breslow intermediate with a Breslow intermediate derived radical cation.

4.8 References

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[10] DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc*. **2009**, *131*, 10872.

Appendix 1. Chapter 2 Experimental

Asymmetric Addition of Enals to Nitroalkenes to Generate δ-Nitroesters via the N-Heterocyclic Carbene Generated Homoenolate Equivalent

Materials and Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dichloromethane was degassed with argon and passed through two col- umns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Methanol was purchased from Fisher Scientific and dried with activated 3Å molecular sieves. N,N-Diisopropylethylamine was purchased from Aldrich and distilled from Calcium hydride prior to use. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light or KMnO4 stain followed by heating.

^{1}H NMR spectra were recorded on Varian 300 or 400 MHz spectrometers at ambient temperature. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm) or acetone-D_6 (2.03 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ^{13}C NMR were recorded on Varian 300 or 400 MHz spectrometers (at 75 or 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.36 ppm) or acetone-D_6 (205.87, 30.6 ppm).

Aldehydes were either purchased from Aldrich or prepared via literature procedures. Nitroalkenes were prepared according to the general procedure as described within.

General Procedure for the Synthesis of Nitro-Esters

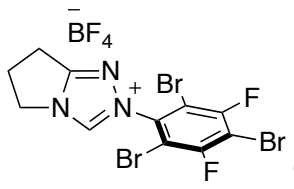
To a screw cap vial charged with a stirbar was added triazolium salt **38** (15 mg, 0.025 mmol) and NaOAc (10 mg, .125 mmol). This vial was then fitted with a rubber septum and evacuated and refilled with argon three times. 0.75 ml EtOH was then added via syringe. To this solution was then added (*E*)-1-nitrobut-1-ene **2** (26 µL, 0.25 mmol, 1 equiv) followed by *trans*-cinnamaldehyde **1** (49 µL, 0.375 mmol, 1.5 equiv). The septum was then quickly removed and replaced with a screw cap. This was then allowed to stir at ambient temperature for 12 hours. After 12 hours the reaction was concentrated via rotary evaporation and then purified by silica gel chromatography (8:2 hexanes:ether) to yield 49 mg (70 %) (3*S*,4*R*)-ethyl 4-(nitromethyl)-3-phenylhexanoatein **18** as a colorless oil.

General Procedure for One-Pot Synthesis of δ-Lactams

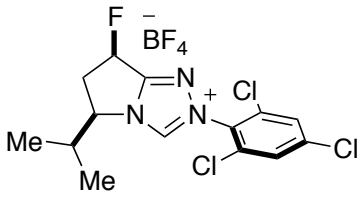
To a screw cap vial charged with a stirbar was added triazolium salt **38** (15 mg, 0.025 mmol) and NaOAc (10 mg, .125 mmol). This vial was then fitted with a rubber septum and evacuated and refilled with argon three times. 0.75 mL EtOH was then added via syringe. To this solution was then added (*E*)-1-nitrobut-1-ene **2** (26 µL, 0.25 mmol, 1 equiv) followed by *trans*-cinnamaldehyde **1** (49 µL, 0.375 mmol, 1.5 equiv). The septum was then quickly removed and replaced with a screw cap. This was then allowed to stir at ambient temperature for 12 hours. After 12 hours the screw cap was removed and Zinc dust (165 mg, 2.5 mmol) was added followed by 0.75 mL AcOH. The screw cap was replaced and the reaction was then heated to reflux in an oil bath. After four hours the vial was removed from the oil bath and allowed to cool. Upon cooling, the reaction was filtered through celite and rinsed with 10 ml EtOAc. The filtrate was then diluted with an additional

10 ml EtOAc and quenched with 20 mL saturated $NaHCO_3$. The organic layer was then separated, washed with brine (1 x 20mL), dried (Na_2SO_4), and concentrated *in vacuo.* The crude residue was then subjected to column chromatography (1:1 hexanes:EtOAc) to yield 32 mg (63 %) (4*S*,5*R*)-5-ethyl-4-phenylpiperidin-2-one **63** as a white solid.

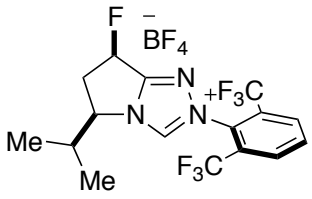
Characterization Data:



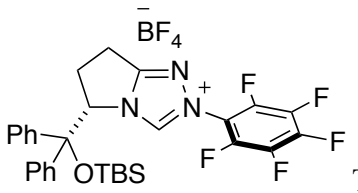
Triazolium (**20**): To a flame-dried flask with magnetic stir bar was added pyrrolidin-2-one (0.46 mL, 6.0 mmol, 1.0 equiv). The flask was then evacuated and back-filled with argon. Dichloromethane (30 mL) and trimethyloxonium tetrafluoroborate (883 mg, 6.0 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 6 hours). (2,4,6-tribromo-3,5-difluorophenyl)hydrazine (2.228 g, 6.0 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 18 hours at which point dichloromethane was removed *in vacuo.* Chlorobenzene (30.0 mL) and trimethylorthoformate (4 mL) was then added and the solution was heated in a 130 °C oil bath for 12 h. After cooling to room temperature, the reaction was filtered and the resultant solid was washed with ether and dried under vacuum for 12 h to give triazolium salt **20** (1.8 g, 55%) as an off-white solid. **^{1}H-NMR** (400 MHz; aceton-d_6): δ 10.30 (s, 1H), m4.83 (t, *J* = 7.4 Hz, 2H), 3.46 (t, *J* = 7.8 Hz, 2H), 3.02 (dt, *J* = 15.2, 7.6 Hz, 2H); **^{13}C NMR** (101 MHz; acetone): δ 164.9, 157.7 (m), 155.3 (m), 143.1, 106.8 (m), 48.8, 26.7, 21.7 **IR** (ATR, neat) 1420, 1054, 733 cm-1; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 455.8, found 455.8



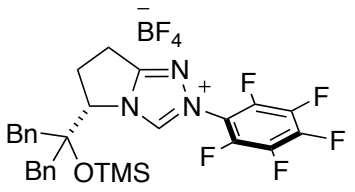
Triazolium Salt (**27**) To a flame-dried flask with magnetic stir bar was added (3*R*,5*R*)-3-fluoro-5-isopropylpyrrolidin-2-one[1] (290.3 mg, 2.0 mmol, 1.0 equiv). The flask was then evacuated and back-filled with argon. Dichloromethane (15 mL) and trimethyloxonium tetrafluoroborate (296 mg, 2.0 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 6 hours). (2,4,6-trichlorophenyl)hydrazine (422.9 mg, 2.0 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 18 hours at which point dichloromethane was removed *in vacuo.* Trimethylorthoformate (20 mL) was then added and the solution was heated in a 110 °C oil bath for 1 h. After cooling to room temperature, the reaction concentrated *in vacuo* and 20 mL chlorobenzene was added and the solution was refluxed for 10 minutes. Upon cooling in an ice bath the product precipitated out and was filtered to yield triazolium salt (**27**) (366 mg, 42 %) as an off-white solid. $[\alpha]_D^{21}$ = 11.8 (c = 0.010 g/ml, acetone); **^{1}H-NMR** (400 MHz; aceton-d_6): δ 10.60 (s, 1H), 7.97 (s, 2H), 6.55 (ddd, *J* = 54.7, 7.6, 2.1 Hz, 1H), 5.26-5.20 (m, 1H), 3.72-3.57 (m, 1H), 3.00-2.88 (m, 1H), 2.58 (dq, *J* = 12.8, 6.5 Hz, 1H), 1.10 (dd, *J* = 30.7, 6.8 Hz, 6H). **^{13}C-NMR** (101 MHz; acetone): δ 160.3, 160.1, 143.9, 139.3, 134.1, 130.2, 129.5, 84.4, 82.6, 66.6, 37.1, 36.8, 31.5, 17.3, 16.2 **IR** (ATR, neat) 2960, 1571, 1054, 1034, 825 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 348.0, found 348.0l



Triazolium Salt (**28**): To a flame-dried flask with magnetic stir bar was added (3*R*,5*R*)-3-fluoro-5-isopropylpyrrolidin-2-one[1] (290.3 mg, 2.0 mmol, 1.0 equiv). The flask was then evacuated and back-filled with argon. Dichloromethane (15 mL) and trimethyloxonium tetrafluoroborate (296 mg, 2.0 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 6 hours). (2,6-bis(trifluoromethyl)phenyl)hydrazine (488.3 mg, 2.0 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 18 hours at which point dichloromethane was removed *in vacuo.* Trimethylorthoformate (20 mL) was then added and the solution was heated in a 110 °C oil bath for 1 h. After cooling to room temperature, the reaction concentrated *in vacuo* and purified by column chromatography to yield triazolium salt (**28**) (234 mg, 25 %) as an off-white solid R_f = 0.41 (19:1 CH_2Cl_2:MeOH) $[\alpha]_D^{21}$ = 20.6 (c = 0.010 g/ml, acetone); **^{1}H-NMR** (400 MHz; aceton-d_6): δ 10.73 (s, 1H), 8.48 (d, *J* = 8.0 Hz, 2H), 8.37-8.32 (m, 1H), 6.60 (ddd, *J* = 54.7, 7.7, 1.9 Hz, 1H), 5.34 (dq, *J* = 8.5, 4.2 Hz, 1H), 3.69 (dddd, *J* = 27.5, 16.0, 8.6, 7.5 Hz, 1H), 2.96 (dddd, *J* = 28.3, 15.8, 3.3, 2.0 Hz, 1H), 2.65-2.57 (m, 1H), 1.07 (dd, *J* = 33.0, 6.9 Hz, 6H). **^{13}C-NMR** (101 MHz; acetone): δ 160.0, 159.7, 144.51, 144.49, 144.46, 134.95, 134.92, 132.34, 132.30, 132.25, 132.21, 132.18, 132.13, 132.09, 132.04, 129.3, 129.06, 129.01, 128.7, 126.0, 123.5, 123.2, 120.8, 120.5, 84.4, 82.6, 66.9, 36.8, 36.6, 31.5, 17.1, 15.6; **IR** (ATR, neat) 2972, 2925, 1513, 1295, 1140, 1052, 1035, 836, 676 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 382.1, found 382.1

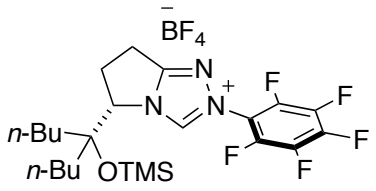


Triazolium Salt (**30**):To a flame-dried flask with magnetic stir bar was added (*S*)-5-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidin-2-one[2] (2.28 mg, 6.0 mmol, 1.0 equiv) **S2**. The flask was then evacuated and back-filled with argon. Dichloromethane (30 mL) and trimethyloxonium tetrafluoroborate (883 mg, 6.0 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 5 hours). Pentafluorophenyl hydrazine (1.18 g, 6.0 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 18 hours at which point dichloromethane was removed *in vacuo.* The resulting yellow oil was then dissolved in acetonitrile (30 mL) and trimethylorthoformate (4 mL). This solution was refluxed in an oil bath for 24 hours. After 24 hours the solvent was removed *in vacuo* and the desired product was recrystallized in EtOAc to yield triazolium salt (**30**) (1.3 g, 33 %) as a white solid. $[\alpha]_D^{21}$ = -112.8 (c = 0.010 g/ml, acetone); **^{1}H-NMR** (400 MHz; aceton-d_6): δ 9.98 (s, 1H), 7.62 (t, *J* = 3.4 Hz, 2H), 7.51-7.43 (m, 6H), 7.36 (d, *J* = 6.7 Hz, 2H), 6.36 (dd, *J* = 9.2, 2.3 Hz, 1H), 3.43-3.32 (m, 1H), 3.12-3.03 (m, 2H), 1.99-1.89 (m, 1H), 0.94 (s, 9H), -0.23 (s, 3H), -0.31 (s, 3H). **^{13}C-NMR** (101 MHz; acetone): δ 165.0, 143.7, 139.91, 139.86, 129.4, 129.06, 128.93, 128.56, 128.45, 82.5, 25.6, 20.6, 18.4, -4.0; **IR** (ATR, neat) 2955, 2931, 1529, 1070 cm-1; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 572.2, found 572.2



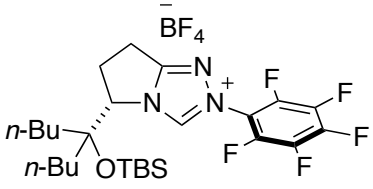
Triazolium Salt (**37):** (*S*)-5-(2-hydroxy-1,3-diphenylpropan-2-yl)pyrrolidin-2-one (**S1**) (1.18 g, 4 mmol, 1 equiv) was dissolved in CH_2Cl_2 (50 mL) and cooled

to 0 °C in an ice bath. Trimethylsilyl trifluoromethanesulfonate (1.67 mL, 9.32 mmol, 2.33 equiv) and 2,6-lutidine (1.39 mL, 12 mmol, 3 equiv) were added dropwise to the cooled solution. The solution was allowed to stir at 0 °C for 1.5 hours and then allowed to warm to room temperature and stir for 12 hours. After 12 hours the reaction was cooled to 0 °C and quenched with 50 mL saturated ammonium chloride and extracted 3 x 50 mL EtOAc, dried over sodium sulfate, and concentrated *in vacuo* to quantitatively yield (*S*)-5-(1,3-diphenyl-2-((trimethylsilyl)oxy)propan-2-yl)pyrrolidin-2-one as a colorless oil. To a flame-dried flask with magnetic stir bar was added crude (*S*)-5-(1,3-diphenyl-2-((trimethylsilyl)oxy)propan-2-yl)pyrrolidin-2-one (1.1 g, 3.0 mmol, 1.0 equiv). The flask was then evacuated and back-filled with argon. Dichloromethane (15 mL) and trimethyloxonium tetrafluoroborate (443 mg, 3.0 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 6 hours). Pentafluorophenyl hydrazine (594 mg, 3.0 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 12 hours at which point dichloromethane was removed *in vacuo*. The resulting yellow oil was then dissolved in acetonitrile (15 mL) and trimethylorthoformate (2 mL). This solution was refluxed in an oil bath for 24 hours. After 24 hours the solvent was removed *in vacuo* and the desired product purified by column chromatography to yield triazolium salt (**6i**) (1.3 g, 67 %) as an off-solid. R_f = 0.45 (19:1 CH_2Cl_2:MeOH) $[\alpha]_D^{21}$ = -29.7 (c = 0.010 g/ml, acetone); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 9.39 (s, 1H), 7.40-7.24 (m, 8H), 7.15-7.10 (m, 2H), 5.26 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.33-2.86 (m, 8H), 0.37 (s, 9H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 162.0, 143.4, 134.7, 134.4, 130.69, 130.64, 130.58, 130.3, 130.1, 129.10, 128.94, 128.63, 128.44, 128.30, 127.9, 127.3, 80.2, 69.0, 48.5, 40.6, 28.8, 21.8, 2.51, 2.42 **IR** (ATR, neat) 2955, 1685, 1600, 1526, 1066, 1002, 840, 702 cm-1; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 558.2, found 558.2



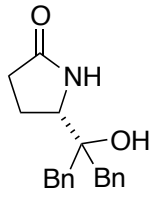
Triazolium Salt (**38**): (*S*)-5-(5-hydroxynonan-5-yl)pyrrolidin-2-one (**S2**) (1.136 g, 5 mmol, 1 equiv) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C in an ice bath. Trimethylsilyl trifluoromethanesulfonate (2.12 mL, 11.7 mmol, 2.33 equiv) and 2,6-lutidine (1.7 mL, 12 mmol, 3 equiv) were added dropwise to the cooled solution. The solution was allowed to stir at 0 °C for 1.5 hours and then allowed to warm to room temperature and stir for 12 hours. After 12 hours the reaction was cooled to 0 °C and quenched with 50 mL saturated ammonium chloride and extracted 3 x 50 mL EtOAc, dried over sodium sulfate, and concentrated *in vacuo* to quantitatively yield (*S*)-5-(5-((trimethylsilyl)oxy)nonan-5-yl)pyrrolidin-2-one as a colorless oil. To a flame-dried flask with magnetic stir bar was added crude (*S*)-5-(5-((trimethylsilyl)oxy)nonan-5-yl)pyrrolidin-2-one (1.46 g, 4.87 mmol, 1.0 equiv). The flask was then evacuated and back-filled with argon. Dichloromethane (25 mL) and trimethyloxonium tetrafluoroborate (720 mg, 4.87 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 6 hours). Pentafluorophenyl hydrazine (965 mg, 4.87 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 12 hours at which point dichloromethane was removed *in vacuo.* The resulting yellow oil was then dissolved in acetonitrile (25 mL) and trimethylorthoformate (6 mL). This solution was refluxed in an oil bath for 24 hours. After 24 hours the solvent was removed *in vacuo* and the desired product purified by column chromatography to yield triazolium salt (**38**) (1.1 g, 39 %) as a red amorphous solid. R_f = 0.43 (19:1 CH_2Cl_2:MeOH) $[\alpha]_D^{21}$ = 16.4 (c = 0.010 g/ml, acetone); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 9.83 (s, 1H), 5.01 (dd, *J* = 8.6, 2.9 Hz, 1H), 3.30-3.00 (m, 3H),

2.68 (d, *J* = 3.6 Hz, 1H), 1.63-1.04 (m, 12H), 0.90 (dt, *J* = 14.9, 7.3 Hz, 6H), 0.10--0.01 (m, 9H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 164.0, 143.4, 79.4, 68.9, 37.0, 36.4, 28.4, 25.7, 25.5, 23.2, 22.8, 21.9, 13.81, 13.75 **IR** (ATR, neat) 2958, 2873, 1525, 1065, 1001, 841 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 490.2, found 490.2



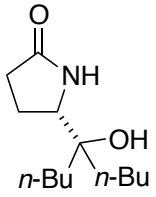
Trizolium Salt (**39**): (*S*)-5-(5-hydroxynonan-5-yl)pyrrolidin-2-one (**S2**) (1.5 g, 6.5 mmol, 1 equiv) was dissolved in CH_2Cl_2 (80 mL) and cooled to 0 °C in an ice bath. Trifluoromethanesulfonic acid tert-butyldimethylsilyl ester (3.4 mL, 15 mmol, 2.33 equiv) and 2,6-lutidine (3.2 mL, 20 mmol, 3 equiv) were added dropwise to the cooled solution. The solution was allowed to stir at 0 °C for 1.5 hours and then allowed to warm to room temperature and stir for 12 hours. After 12 hours the reaction was cooled to 0 °C and quenched with 80 mL saturated ammonium chloride and extracted 3 x 80 mL EtOAc, dried over sodium sulfate, and concentrated *in vacuo* to quantitatively yield (*S*)-5-(5-((*tert*-butyldimethylsilyl)oxy)nonan-5-yl)pyrrolidin-2-one as a colorless oil. To a flame-dried flask with magnetic stir bar was added crude (*S*)-5-(5(*S*)-5-(5-((*tert*-butyldimethylsilyl)oxy)nonan-5-yl)pyrrolidin-2-one (2.23 g, 6.5 mmol, 1.0 equiv). The flask was then evacuated and back-filled with argon. Dichloromethane (25 mL) and trimethyloxonium tetrafluoroborate (961 mg, 6.5 mmol, 1.0 equiv) were then added via powder funnel. The heterogeneous mixture was stirred at room temperature until the reaction was homogeneous (about 6 hours). Pentafluorophenyl hydrazine (1.28 mg, 6.5 mmol, 1.0 equiv) was added in one portion and the mixture was stirred for 12 hours at which point dichloromethane was removed *in vacuo.* The resulting yellow oil was then dissolved in acetonitrile (25 mL) and trimethylorthoformate (8 mL). This solution was refluxed in an oil bath for 24 hours. After 24

hours the solvent was removed *in vacuo* and the desired product was recrystallized from EtOAc to yield triazolium (**39**) (675 mg, 16 %) as a white solid. $[\alpha]_D^{21}$ = -47.6 (c = 0.010 g/ml, acetone); **^{1}H-NMR** (400 MHz; aceton-d_6): δ 10.46 (s, 1H), 5.26 (dd, *J* = 8.4, 5.8 Hz, 1H), 3.20-3.02 (m, 2H), 2.80 (d, *J* = 13.5 Hz, 2H), 1.94-1.76 (m, 4H), 1.52-1.34 (m, 8H), 0.95-0.89 (m, 6H), 0.79 (s, 9H), 0.22 (s, 3H), 0.09 (s, 3H). **^{13}C-NMR** (101 MHz; acetone): δ 165.1, 143.8, 79.2, 69.8, 37.1, 36.1, 25.93, 25.75, 25.3, 22.9, 22.6, 21.6, 18.1, 13.34, 13.22, -2.47, -2.60; **IR** (ATR, neat) 2957, 2931, 2860, 1600, 1543, 1069, 1003, 836, 775 cm-1; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 532.3, found 532.3

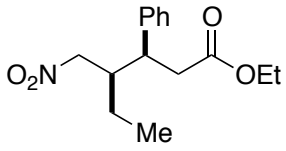


(*S*)-5-(2-hydroxy-1,3-diphenylpropan-2-yl)pyrrolidin-2-one (**S1**): To a flame dried dry 250 ml 3-neck round bottom flask containing a magnetic stirbar and fitted with a reflux condenser was added 1.9 g Magnesium turnings (80 mmols) followed by 15 mL dry THF. To this was added dropwise a solution of 9.5 mL benzyl bromide (80 mmols) in 55 mL dry THF with the use of an addition funnel at a rate sufficient to maintain reflux. After completion of the benzyl bromide addition the reaction was refluxed for 30 minutes. After 30 minutes the heat source was removed and the reaction was cooled to 0 °C in an ice bath. To this mixture was added a solution of 2.8 grams (20 mmols) (*S*)-methyl 5-oxopyrrolidine-2-carboxylate in 80 mL dry THF dropwise over 30 minutes. Upon completion of addition the reaction was allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 °C in an ice bath and quenched with 80 mL saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted 3 x 50 mL EtOAc. The organic layers were combined and washed 1 x 100 mL brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The resulting white solid was then

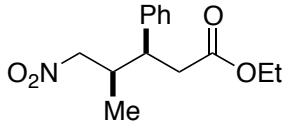
triturated with hexanes to yield 2.5 grams (42 %) of the (*S*)-5-(2-hydroxy-1,3-diphenylpropan-2-yl)pyrrolidin-2-one as a white solid. $[\alpha]_D^{21}$ = 52.4 (c = 0.010 g/ml, CH_2Cl_2); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.34-7.21 (m, 8H), 7.15-7.12 (m, 2H), 6.26 (s, 1H), 3.62 (dd, *J* = 8.2, 6.1 Hz, 1H), 2.97 (d, *J* = 13.6 Hz, 1H), 2.75 (d, *J* = 1.3 Hz, 2H), 2.67 (d, *J* = 13.6 Hz, 1H), 2.43-2.28 (m, 2H), 2.21-2.12 (m, 1H), 2.11-2.01 (m, 1H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 178.2, 135.99, 135.80, 130.8, 130.3, 128.53, 128.49, 126.91, 126.88, 75.4, 59.7, 42.3, 40.3, 30.2, 21.7. **IR** (ATR, neat) 3384, 3298, 1686, 700 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 296.2, found 296.1



(*S*)-5-(5-hydroxynonan-5-yl)pyrrolidin-2-one (**S2**): To a solution of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (2.8g, 20 mmol) in THF (60 ml) cooled to 0 °C was added 42.5 ml *n*-Butyl Lithium in hexanes (1.6 M, 68 mmol) dropwise. The solution was allowed to warm to room temperature slowly and stirred for 4 hours at room temp. After four hours the reaction was quenched with 60 ml saturated sodium bicarbonate. The THF was then removed via rotary evaporation and the solution was extracted 3x 50 ml EtOAc and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield a white solid that was triturated with hexanes to yield the product as a white solid (1.15 g, 25 %). $[\alpha]_D^{21}$ = -13.3 (c = 0.010 g/ml, CH_2Cl_2); **^{1}H-NMR** (400 MHz; CDCl3): δ 6.68 (s, 1H), 3.67-3.64 (m, 1H), 2.38-2.22 (m, 2H), 2.05-1.98 (m, 2H), 1.47-1.41 (m, 3H), 1.32-1.16 (m, 9H), 0.90-0.87 (m, 6H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 74.8, 60.7, 36.2, 33.5, 25.6, 25.2, 23.32, 23.23, 21.2, 14.0. **IR** (ATR, neat) 3247, 2954, 2933, 2871, 1691, 1458, 1277 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 228.2, found 228.2

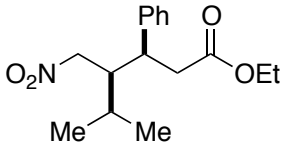


(3*S*,4*R*)-ethyl 4-(nitromethyl)-3-phenylhexanoate (**18**): Colorless Oil. R_f= 0.28 (8:2 Hexanes:Ether); 70 % yield, 17:1 d.r., 93 % ee;$[\alpha]_D^{21}$ = -4.9 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 21.1 min, minor: 22.6 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.32-7.28 (m, 2H), 7.24 (d, *J* = 6.4 Hz, 1H), 7.17-7.15 (m, 2H), 4.31 (dd, *J* = 6.7, 2.1 Hz, 2H), 4.02-3.96 (m, 2H), 3.30 (q, *J* = 7.3 Hz, 1H), 2.72-2.70 (m, 2H), 2.45 (ddd, *J* = 8.5, 6.5, 4.5 Hz, 1H), 1.55-1.48 (m, 1H), 1.30-1.034 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.5, 139.8, 128.5, 128.3, 127.2, 76.8, 60.6, 43.7, 42.4, 37.4, 21.2, 14.0, 11.0. **IR** (ATR, neat) 2966, 2929, 2878, 1730, 1549, 1379, 1217, 702 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 280.2, found 280.1

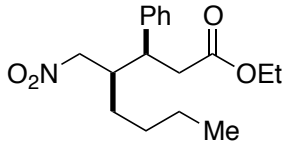


(3*S*,4*R*)-ethyl 4-methyl-5-nitro-3-phenylpentanoate (**40**): R_f = 0.21 (8:2 Hexanes:Ether); $[\alpha]_D^{21}$ = -0.17 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 31.6 min, minor: 28.5 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.32-7.24 (m, 4H), 7.13 (d, *J* = 7.6 Hz, 3H), 4.36 (dd, *J* = 12.1, 6.1 Hz, 1H), 4.08-3.95 (m, 3H), 3.23 (q, *J* = 6.7 Hz, 1H), 2.73 (d, *J* = 7.7 Hz, 2H), 2.80-2.57 (d, *J* = 7.7 Hz, 4H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.4, 139.1, 128.51,

128.41, 127.3, 79.9, 60.6, 43.8, 37.9, 36.7, 14.0, 13.8. **IR** (ATR, neat) 2979, 2924, 1731, 1550, 1378, 1173, 1031, 702 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 266.1, found 266.1

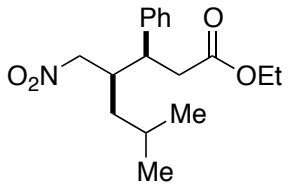


(3*S*,4*R*)-ethyl 5-methyl-4-(nitromethyl)-3-phenylhexanoate (**41**): Colorless Oil. R_f= 0.29 (8:2 Hexanes:Ether); 57 % yield, 20:1 d.r., 94 % ee; $[\alpha]_D^{21}$ = -29.5 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 18.9 min, minor: 16.1 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.29 (t, *J* = 7.3 Hz, 2H), 7.23-7.18 (m, 2H), 4.43-4.33 (m, 2H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.25 (td, *J* = 9.7, 5.1 Hz, 1H), 2.69-2.58 (m, 2H), 2.56-2.50 (m, 1H), 1.66 (dtd, *J* = 13.8, 6.9, 3.5 Hz, 1H), 1.02 (t, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.68 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.7, 141.2, 128.6, 127.8, 127.1, 75.1, 60.5, 47.5, 43.8, 38.4, 27.5, 21.4, 16.4, 13.9. **IR** (ATR, neat) 2959, 2926, 2856, 1732, 1552, 1378, 1163, 1032 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 294.2, found 294.1

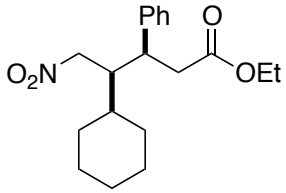


(3*S*,4*R*)-ethyl 4-(nitromethyl)-3-phenyloctanoate (**42**): Colorless Oil. R_f= 0.26 (8:2 Hexanes:Ether); 72 % yield, 20:1 d.r., 93 % ee; $[\alpha]_D^{21}$ = -2.3 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 15.1 min, minor: 16.2 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.32-7.28 (m, 2H), 7.25-7.22 (m, 1H), 7.17-7.15

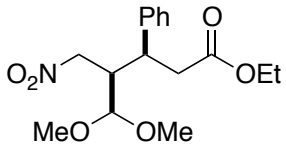
(m, 2H), 4.28 (d, J = 6.8 Hz, 2H), 3.99 (qd, J = 7.1, 0.8 Hz, 2H), 3.31 (td, J = 7.7, 5.8 Hz, 1H), 2.71 (d, J = 7.8 Hz, 2H), 2.51 (dqd, J = 8.6, 6.3, 4.3 Hz, 1H), 1.48-1.41 (m, 1H), 1.30-1.23 (m, 4H), 1.08 (t, J = 7.1 Hz, 3H), 1.03 (dt, J = 9.3, 4.7 Hz, 1H), 0.83 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.5, 139.7, 128.50, 128.33, 127.2, 77.2, 60.6, 42.5, 42.0, 37.2, 28.7, 27.8, 22.5, 13.97, 13.81. **IR** (ATR, neat) 2958, 2931, 2871, 1731, 1550, 1379, 1163, 1032, 702 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 308.2, found 308.1



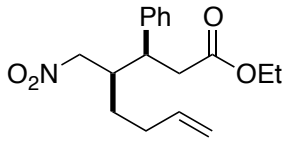
(3*S*,4*R*)-ethyl 6-methyl-4-(nitromethyl)-3-phenylheptanoate (**43**): Colorless Oil. R_f= 0.24 (8:2 Hexanes:Ether); 67 % yield, 20:1 d.r., 91 % ee; $[\alpha]_D^{21}$ = 0.71 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 12.3 min, minor: 15.0 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.30 (tt, J = 7.3, 1.6 Hz, 2H), 7.25-7.21 (m, 1H), 7.17-7.15 (m, 2H), 4.24-4.22 (dq, 2H), 4.03-3.98 (m, 2H), 3.34 (td, J = 7.8, 4.9 Hz, 1H), 2.72-2.70 (m, 2H), 2.59 (dddd, J = 9.2, 6.8, 4.5, 2.1 Hz, 1H), 1.59-1.50 (m, 1H), 1.26 (ddd, J = 14.0, 9.3, 4.6 Hz, 1H), 1.10 (d, J = 14.3 Hz, 3H), 0.95 (ddd, J = 14.3, 9.4, 5.0 Hz, 1H), 0.88 (dd, J = 6.5, 2.2 Hz, 6H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.4, 139.4, 128.50, 128.45, 127.2, 77.3, 60.6, 42.4, 39.8, 37.1, 36.7, 25.2, 23.2, 21.7, 14.0. **IR** (ATR, neat) 2958, 2930, 2871, 1732, 1551, 1380, 1170, 738, 703 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 308.2, found 308.2



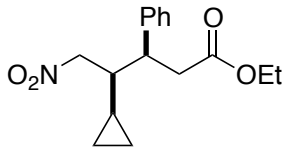
(3*S*,4*R*)-ethyl 4-cyclohexyl-5-nitro-3-phenylpentanoate (**44**): Colorless Oil. R_f = 0.27 (8:2 Hexanes:Ether); 59 % yield, 20:1 d.r. 96 % ee; $[\alpha]_D^{21}$ = -8.9 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 16.6 min, minor: 14.1 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.29 (ddd, *J* = 8.0, 6.4, 1.3 Hz, 2H), 7.24-7.17 (m, 3H), 4.38 (qd, *J* = 13.8, 5.7 Hz, 2H), 3.96-3.91 (m, 2H), 3.36-3.30 (m, 1H), 2.68-2.57 (m, 2H), 2.51-2.45 (m, 1H), 1.69-0.86 (m, 11H), 1.08-0.99 (m, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.7, 141.2, 128.6, 127.8, 127.1, 75.7, 60.5, 47.4, 42.7, 38.0, 37.8, 31.8, 27.7, 26.4, 26.17, 26.16, 13.9. **IR** (ATR, neat) 2925, 2853, 1732, 1551, 1374, 1032 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 334.2, found 334.2



(3*S*,4*R*)-ethyl 5,5-dimethoxy-4-(nitromethyl)-3-phenylpentanoate (**45**): Colorless Oil. R_f= 0.1 (8:2 Hexanes:Ether); 49 % yield, 8:1 d.r., 79 % ee; $[\alpha]_D^{21}$ = -22.1 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 98:2 hexanes/*iso*-propanol, 1.0 mL/min. Major: 50.6 min, minor: 55.9 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.33-7.19 (m, 5H), 4.69 (dd, *J* = 14.1, 5.0 Hz, 1H), 4.31 (dd, *J* = 14.1, 6.3 Hz, 1H), 3.98-3.91 (m, 2H), 3.81 (d, *J* = 4.0 Hz, 1H), 3.35-3.33 (m, 1H), 3.23 (d, *J* = 6.0 Hz, 6H), 2.96-2.91 (m, 1H), 2.71 (qd, *J* = 14.1, 7.8 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.4, 144.1, 128.7, 128.0, 127.3, 73.7, 60.5, 55.7, 55.2, 45.0, 41.6, 38.1, 25.3, 13.9 **IR** (ATR, neat) 2923, 1733, 1557, 1065 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 362.2, found 362.2.

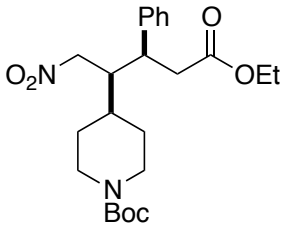


(3*S*,4*R*)-ethyl 4-(nitromethyl)-3-phenyloct-7-enoate (**46**): Colorless Oil. R_f = 0.24 (8:2 Hexanes:Ether) 72 % yield, 12:1 d.r., 89 % ee; $[\alpha]_D^{21}$ = -3.4 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 16.8 min, minor: 23.6 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.30 (td, *J* = 7.2, 1.4 Hz, 2H), 7.25-7.23 (m, 1H), 7.17-7.15 (m, 2H), 5.67 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.02-4.96 (m, 2H), 4.31-4.29 (m, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.33 (td, *J* = 7.7, 5.8 Hz, 1H), 2.71 (d, *J* = 7.7 Hz, 2H), 2.57-2.52 (m, 1H), 2.12-1.99 (m, 2H), 1.56 (dddd, *J* = 12.0, 8.4, 6.2, 3.8 Hz, 1H), 1.15 (dd, *J* = 14.2, 5.5 Hz, 1H), 1.13-1.07 (m, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.4, 139.6, 137.0, 128.6, 128.3, 127.3, 115.9, 76.9, 60.6, 42.4, 41.3, 37.1, 30.7, 27.4, 14.0.**IR** (ATR, neat) 2978, 2927, 1732, 1551, 1379, 1162, 916 cm^{-1}; LRMS (ESI + APCI) *m/z* [M+H] calcd 306.2, found 306.1

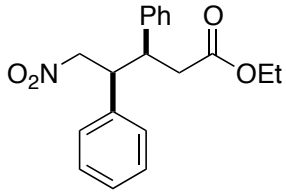


(3*S*,4*R*)-ethyl 4-cyclopropyl-5-nitro-3-phenylpentanoate (**47**): Colorless Oil. R_f= 0.23 (8:2 Hexanes:Ether); 68 % yield, 18:1 d.r., 88 % ee;$[\alpha]_D^{21}$ = -37.5 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 16.4 min, minor: 19.2 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.33-7.29 (m, 2H), 7.26-7.20 (m, 3H), 4.31 (dd, *J* = 12.1, 7.9 Hz, 1H), 4.24 (dd, *J* = 12.0, 6.7 Hz, 1H), 4.06-3.98 (m, 2H), 3.39 (td, *J* = 8.0, 3.8 Hz, 1H), 2.89 (d, *J* = 8.0 Hz, 2H), 1.85-1.78 (m, 1H), 1.11 (d, *J* = 14.3 Hz, 3H), 0.67 (tdd, *J* = 8.2, 5.7, 4.0 Hz, 1H), 0.52-0.35 (m, 3H), 0.13-0.08 (m, 1H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ

171.6, 138.9, 128.7, 128.4, 127.3, 78.9, 60.5, 46.9, 43.6, 37.5, 14.0, 10.1, 5.3, 2.6.**IR** (ATR, neat) 2960, 2925, 1731, 1552, 1378, 1175, 1028, 740 cm^{-1}; LRMS (ESI + APCI) *m/z* [M+H] calcd 292.2, found 292.2

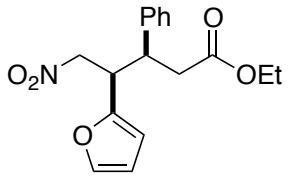


tert-butyl 4-((2*R*,3*S*)-5-ethoxy-1-nitro-5-oxo-3-phenylpentan-2-yl)piperidine-1-carboxylate (**48**): Colorless Oil. R_f= 0.26 (6:4 Hexanes:Ether); 65 % yield, 19:1 d.r., 94 % ee;$[\alpha]_D^{21}$ = 9.11 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 85:15 hexanes/*iso*-propanol, 1.0 mL/min. Major: 31.4 min, minor: 41.3 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.32-7.29 (m, 2H), 7.22-7.22 (m, 1H), 7.20-7.17 (m, 2H), 4.37 (d, *J* = 5.7 Hz, 2H), 4.04 (m, 2H), 3.95 (qd, *J* = 7.1, 0.9 Hz, 2H), 3.36-3.30 (m, 1H), 2.65-2.63 (m, 2H), 2.55-2.51 (m, 2H), 2.39-2.31 (m, 1H), 1.56-1.31 (m, 5H), 1.39 (s, 9H), 1.04 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.5, 154.5, 140.7, 128.8, 127.7, 127.3, 79.5, 75.3, 60.6, 46.6, 36.6, 28.4, 13.9. **IR** (ATR, neat) 2976, 2927, 2854, 1732, 1688, 1553, 1425, 1366, 1169, 766 cm^{-1}; LRMS (ESI + APCI) *m/z* [M+H] calcd 435.2, found 435.2



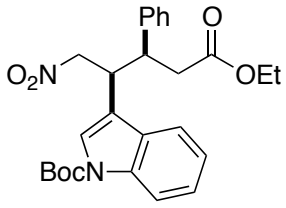
(3*S*,4*S*)-ethyl 5-nitro-3,4-diphenylpentanoate (**49**): White Solid. R_f= 0.26 (8:2 Hexanes:Ether); 95 % yield, 6:1 d.r., 87 % ee; $[\alpha]_D^{21}$ = -26.8 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralcel OD-H column, 98:2 hexanes/*iso*-propanol, 1.0 mL/min. Major: 43.0

min, minor: 54.6 min. **^{1}H-NMR** (400 MHz; CDCl3): δ 7.38-7.28 (m, 1H), 7.24-7.17 (m, 5H), 6.84-6.79 (m, 4H), 4.65 (ddd, *J* = 56.8, 12.8, 7.8 Hz, 2H), 4.04 (qt, *J* = 7.1, 3.5 Hz, 2H), 3.88 (ddd, *J* = 8.6, 7.0, 5.7 Hz, 1H), 3.55 (td, *J* = 7.7, 5.6 Hz, 1H), 2.75-2.57 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.4, 138.4, 135.7, 128.90, 128.82, 128.22, 128.11, 127.8, 127.4, 77.9, 60.7, 47.8, 44.0, 37.9, 14.0.**IR** (ATR, neat) 2958, 2924, 2854, 1728, 1551, 1377, 1156, 1029 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 328.2, found 328.1

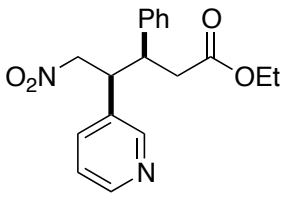


(3*S*,4*R*)-ethyl 4-(furan-2-yl)-5-nitro-3-phenylpentanoate (**50**): Colorless Oil. R_f= 0.31 (8:2 Hexanes:Ether); 90 % yield, 3:1 d.r., 81 % ee; $[\alpha]_D^{21}$ = -1.9 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 23.3 min, minor: 31.6 min. **^{1}H-NMR**, isolated as a 2:1mixture of diastereomers (400 MHz; $CDCl_3$): δ 7.40-7.20 (m, 5H), 6.86 (dd, *J* = 6.7, 2.8 Hz, 1H), 6.31-6.24 (m, 1H), 5.97 (d, *J* = 3.3 Hz, 1H), 4.57-4.47 (m, 2H), 4.18 (dd, *J* = 12.7, 4.2 Hz, 0.33H, minor diastereomer), 4.05 (qt, *J* = 7.2, 3.6 Hz, 2.33H), 3.90-3.80 (m, 1H), 3.53 (td, *J* = 7.7, 4.8 Hz, 0.66H, major diastereomer), 3.46 (td, *J* = 10.4, 5.0 Hz, 0.33H, minor diastereomer), 2.85-2.66 (m, 1.32H, major diastereomer), 2.50 (qd, *J* = 17.1, 7.4 Hz, 0.66H, minor diastereomer), 1.13 (t, *J* = 7.1 Hz, 2H, major diastereomer), 1.01 (t, *J* = 7.1 Hz, 1H, minor diastereomer); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.3, 171.1, 150.4, 150.0, 142.8, 142.2, 139.9, 138.4, 129.1, 127.81, 127.72, 127.5, 110.38, 110.36, 109.5, 108.7, 77.1,

75.8, 60.7, 60.4, 43.7, 43.37, 43.34, 41.6, 39.5, 37.8, 14.03, 13.91.**IR** (ATR, neat) 2981, 2923, 1729, 1553, 1376, 1162, 702 cm^{-1}; LRMS (ESI + APCI) *m/z* [M+H] calcd 318.1, found 318.1

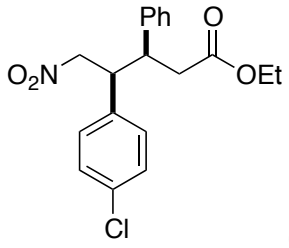


tert-butyl 3-((2*S*,3*S*)-5-ethoxy-1-nitro-5-oxo-3-phenylpentan-2-yl)-1*H*-indole-1-carboxylate (**51**): Colorless Oil. R_f = 0.61 (6:4 Hexanes:Ether) 86 % yield, 8:1 d.r., 87 % ee; $[\alpha]_D^{21}$ = 12.7 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 96:4 hexanes/*iso*-propanol, 1.0 mL/min. Major: 30.73 min, minor: 31.44 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 8.09 (ddd, *J* = 8.4, 1.6, 0.6 Hz, 1H), 7.41-7.19 (m, 6H), 7.01 (dd, *J* = 6.5, 3.0 Hz, 2H), 6.89-6.88 (m, 1H), 4.71 (dd, *J* = 12.9, 7.2 Hz, 1H), 4.52 (dd, *J* = 12.9, 8.4 Hz, 1H), 4.30-4.25 (m, 1H), 4.07-3.97 (m, 2H), 3.72 (td, *J* = 7.7, 4.8 Hz, 1H), 2.77-2.59 (m, 2H), 1.61 (s, 9H), 1.10 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.5, 138.7, 129.9, 128.7, 128.3, 127.6, 124.7, 124.5, 122.7, 118.9, 115.28, 115.15, 84.0, 60.6, 43.1, 39.1, 37.2, 28.1, 14.0**IR** (ATR, neat) 2924, 2853, 1731, 1553, 1452, 1153 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 466.5, found 466.4

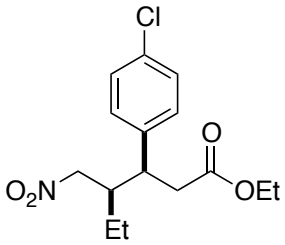


(3*S*,4*S*)-ethyl 5-nitro-3-phenyl-4-(pyridin-3-yl)pentanoate (**52**): Colorless Oil. R_f = 0.12 (6:4 Hexanes:Ether) 73 % yield, 5:1 d.r., 86 % ee; $[\alpha]_D^{21}$ = -24.9 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiracel OD-H column, 80:20hexanes/*iso*-propanol, 1.0 mL/min.

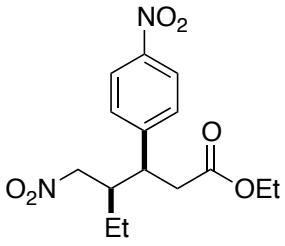
Major: 27.5 min, minor: 20.7 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 8.47 (s, 1H), 8.17 (s, 1H), 7.24-7.07 (m, 5H), 6.81 (td, *J* = 3.9, 1.6 Hz, 2H), 4.79 (dd, *J* = 13.0, 6.6 Hz, 1H), 4.59 (dd, *J* = 13.0, 9.1 Hz, 1H), 4.11-4.03 (m, 2H), 3.95-3.89 (m, 1H), 3.59-3.53 (m, 1H), 2.67 (qd, *J* = 18.0, 7.6 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.1, 149.9, 148.9, 137.8, 136.4, 128.57, 128.50, 127.8, 123.1, 77.5, 60.9, 45.6, 43.9, 37.9, 14.0. **IR** (ATR, neat) 2980, 2924, 1729, 1553, 1378, 1160, 1026 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 329.2, found 329.1



(3*S*,4*S*)-ethyl 4-(4-chlorophenyl)-5-nitro-3-phenylpentanoate (**53**): White Solid. R_f = 0.62 (6:4 Hexanes:Ether) 75 % yield, 4:1 d.r., 86 % ee; $[\alpha]_D^{21}$ = -49.2 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 90:10 hexanes/*iso*-propanol, 1.0 mL/min. Major: 12.7 min, minor: 20.8 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.24-7.16 (m, 4H), 6.84-6.81 (m, 2H), 6.76-6.74 (m, 2H), 4.71 (dd, *J* = 12.9, 6.6 Hz, 1H), 4.53 (dd, *J* = 12.8, 9.1 Hz, 1H), 4.05 (qd, *J* = 7.1, 2.1 Hz, 2H), 3.86 (dt, *J* = 9.0, 6.2 Hz, 1H), 3.54-3.49 (m, 1H), 2.72-2.57 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.3, 138.2, 134.2, 133.7, 130.2, 128.7, 128.45, 128.28, 127.5, 77.8, 60.8, 47.3, 44.0, 37.9, 14.0.**IR** (ATR, neat) 2981, 2924, 1728, 1552, 1493, 1377, 1014, 828 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 362.1, found 362.2

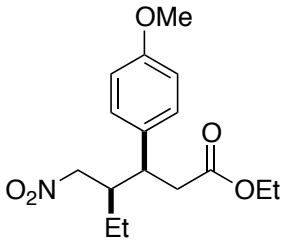


(3*S*,4*R*)-ethyl 3-(4-chlorophenyl)-4-(nitromethyl)hexanoate (**55**): Colorless Oil. R_f = 0.58 (6:4 Hexanes:Ether) 73 % yield, 20:1 d.r., 82 % ee; $[\alpha]_D^{21}$ = -2.3 (c = 0.010 g/ml, CH_2Cl_2); Could not separate via HPLC, ee inferred from lactam **6e**. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.30 (qd, *J* = 14.1, 6.6 Hz, 2H), 3.99 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.27 (dt, *J* = 8.9, 6.4 Hz, 1H), 2.68 (dd, *J* = 7.7, 3.9 Hz, 2H), 2.42 (tdd, *J* = 8.7, 4.4, 1.9 Hz, 1H), 1.49 (ddd, *J* = 14.3, 7.4, 4.3 Hz, 1H), 1.12-1.00 (m, 1H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.2, 138.4, 133.0, 129.6, 128.7, 76.6, 60.7, 43.6, 42.0, 37.4, 21.2, 14.0, 11.0. **IR** (ATR, neat) 2966, 2925, 1731, 1549, 1162, 830 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 314.1, found 314.1

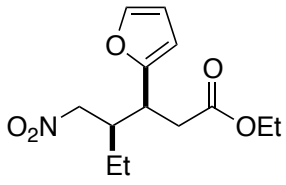


(3*S*,4*R*)-ethyl 4-(nitromethyl)-3-(4-nitrophenyl)hexanoate (**56**): Yellow Solid. R_f = 0.48 (6:4 Hexanes:Ether) 48 % yield, 10:1 d.r., 90 % ee; $[\alpha]_D^{21}$ = -9.5 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 90:10 hexanes/*iso*-propanol, 1.0 mL/min. Major: 32.9 min, minor: 36.5 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 4.42-4.27 (m, 2H), 3.99 (qd, *J* = 7.1, 2.8 Hz, 2H), 3.41 (dt, *J* = 9.0, 6.5 Hz, 1H), 2.75 (dd, *J* = 7.6, 3.7 Hz, 2H), 2.53-2.45 (m, 1H), 1.48 (ddd, *J* = 14.3, 7.4, 4.3 Hz, 1H), 1.10

(t, J = 7.1 Hz, 3H), 1.10-0.98 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 170.7, 147.8, 129.2, 123.8, 98.7, 76.2, 60.9, 43.5, 42.5, 37.2, 21.5, 14.0, 10.9. **IR** (ATR, neat) 2973, 2937, 1731, 1552, 1521, 1347 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 325.1, found 325.1

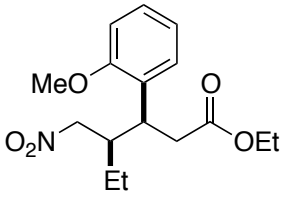


(3*S*,4*R*)-ethyl 3-(4-methoxyphenyl)-4-(nitromethyl)hexanoate (**57**) White Solid. R_f= 0.27 (7:3 Hexanes:Ether); 35 % yield, 5:1 d.r., 88 % ee; $[\alpha]_D^{21}$ = -3.9 (c = 0.010 g/ml, CH_2Cl_2); **HPLC Analysis** – Chiralpak IC column, 98:2 hexanes/*iso*-propanol, 1.0 mL/min. Major: 43.6 min, minor: 48.8 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.08 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 4.30-4.28 (m, 2H), 4.00 (q, J = 7.1 Hz, 2H), 3.77 (d, J = 0.9 Hz, 3H), 3.28-3.22 (m, 1H), 2.68-2.66 (m, 2H), 2.43-2.38 (m, 1H), 1.30-1.21 (m, 2H), 1.10 (td, J = 7.1, 1.0 Hz, 3H), 1.16-1.02 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.5, 131.6, 129.3, 114.1, 113.9, 76.9, 60.5, 55.2, 43.8, 41.7, 37.6, 21.0, 14.0, 11.1.**IR** (ATR, neat) 2959, 2924, 2854, 1732, 1551, 1513, 1250, 1035 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 310.2, found 310.2

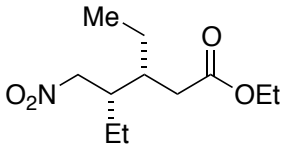


(3*S*,4*R*)-ethyl 3-(furan-2-yl)-4-(nitromethyl)hexanoate (**58**): Colorless Oil. R_f= 0.22 (8:2 Hexanes:Ether); 83 % yield, 19:1 d.r., 91 % ee ;$[\alpha]_D^{21}$ = 11.3 (c = 0.010 g/ml,

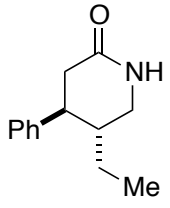
CH_2Cl_2); Could not separate via HPLC, ee inferred from lactam **6c**. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.32 (ddd, *J* = 4.0, 2.0, 0.8 Hz, 1H), 6.27 (td, *J* = 3.7, 1.8 Hz, 1H), 6.11-6.09 (m, 1H), 4.34 (qd, *J* = 12.7, 6.9 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.47 (td, *J* = 6.0, 3.1 Hz, 1H), 2.74-2.58 (m, 2H), 2.51-2.46 (m, 1H), 1.54 (ddd, *J* = 14.4, 7.5, 5.2 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.20-1.07 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.2, 153.5, 141.9, 110.1, 107.3, 77.4, 60.8, 42.4, 36.2, 35.2, 21.2, 14.1, 11.6.**IR** (ATR, neat) 2966, 2928, 1731, 1550, 1374, 1162, 1011, 808 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 270.1, found 270.1



(3*S*,4*R*)-ethyl 3-(2-methoxyphenyl)-4-(nitromethyl) (**59**): White Solid. R_f=0.29 (8:2 Hexanes:Ether); % yield, 9:1 d.r., 82 % ee; $[\alpha]_D^{21}$ = -15.7 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 97:3 hexanes/*iso*-propanol, 1.0 mL/min. Major: 24.1 min, minor: 30.8 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.22-7.18 (m, 1H), 7.06 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.90-6.84 (m, 2H), 4.29 (qd, *J* = 13.8, 6.7 Hz, 2H), 3.99 (qd, *J* = 7.1, 2.6 Hz, 2H), 3.79 (s, 3H), 3.81-3.76 (m, 1H), 2.76-2.65 (m, 2H), 2.63-2.55 (m, 1H), 1.53-1.41 (m, 1H), 1.16-1.04 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.9, 157.2, 128.53, 128.36, 128.1, 120.3, 110.7, 76.9, 60.4, 55.2, 41.9, 36.1, 35.9, 21.6, 14.0, 10.9.**IR** (ATR, neat) 2964, 2925, 1731, 1550, 1492, 1242, 1028, 756m cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 310.2, found 310.2

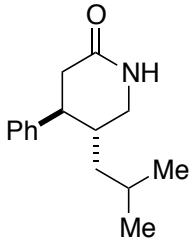


(3*R*,4*S*)-ethyl 3-ethyl-4-(nitromethyl)hexanoate (**60**): Synthesized by a modified procedure: To a screw cap vial charged with a stirbar was added triazolium salt **6d** (10.5 mg, 0.025 mmol) and NaOAc (10 mg, .125 mmol). This vial was then fitted with a rubber septum and evacuated and refilled with argon three times. 0.75 ml EtOH was then added via syringe. To this solution was then added (*E*)-1-nitrobut-1-ene (26 μL, 0.25 mmol, 1 equiv) followed by *trans*-2-pentenal (31.5 mg, 1.5 equiv). The septum was then quickly removed and replaced with a screw cap. This was then allowed to stir at 50 °C for 12 hours. After 12 hours the reaction was concentrated via rotary evaporation and then purified by silica gel chromatography (8:2 hexanes:ether) to yield 15 mg (25 %) (3*R*,4*S*)-ethyl 3-ethyl-4-(nitromethyl)hexanoate as a colorless oil. R_f= 0.21 in (8:2 Hexanes:Ether); 25 % yield, 20:1 d.r., 91 % ee; $[\alpha]_D^{21}$ = -3.3 (c = 0.010 g/ml, CH_2Cl_2); **GC Analysis** – Varian BDM column, 130 °C, 1mL/min. Major: 39.237 min, minor: 39.836 min. **^{1}H-NMR** (400 MHz; CDCl3): δ 4.35 (dd, *J* = 12.0, 6.2 Hz, 1H), 4.24 (dd, *J* = 12.0, 7.7 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.30-2.26 (m, 1H), 2.28-2.14 (m, 2H), 2.03-1.97 (m, 1H), 1.46-1.41 (m, 1H), 1.37-1.27 (m, 3H), 1.27-1.23 (m, 3H), 0.96-0.92 (m, 6H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 172.7, 77.2, 60.6, 41.3, 37.3, 35.5, 23.8, 21.6, 14.1, 11.8, 11.6. **IR** (ATR, neat) 2963, 2927, 2877, 1733, 1553, 1463, 1377, 1181, 1034 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 232.2, found 232.0

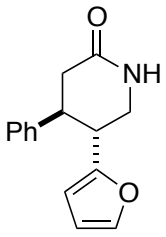


(4*S*,5*R*)-5-ethyl-4-phenylpiperidin-2-one (**62**): White Solid. R_f = 0.18 (100 %

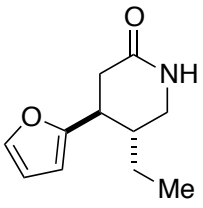
EtOAc)63 % yield, 17:1 d.r., 93 % ee; $[\alpha]_D^{21}$ = 30.0 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 80:20 hexanes/*iso*-propanol, 1.0 mL/min. Major: 37.9 min, minor: 40.3 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.31 (qd, *J* = 5.6, 2.2 Hz, 2H), 7.25-7.20 (m, 1H), 7.15-7.12 (m, *J* = 8.1 Hz, 2H), 6.62 (s, 1H), 3.47 (ddd, *J* = 12.1, 5.0, 3.8 Hz, 1H), 3.04 (t, *J* = 11.1 Hz, 1H), 2.76 (td, *J* = 10.8, 5.5 Hz, 1H), 2.62 (dd, *J* = 17.8, 5.5 Hz, 1H), 2.49 (dd, *J* = 17.8, 11.1 Hz, 1H), 1.96-1.87 (m, 1H), 1.29 (dtd, *J* = 14.3, 7.3, 3.7 Hz, 1H), 1.02 (ddt, *J* = 14.2, 9.3, 7.2 Hz, 1H), 0.77 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 172.2, 142.7, 128.8, 127.4, 126.8, 46.2, 44.5, 39.9, 39.0, 24.0, 11.0. **IR** (ATR, neat) 2960, 2930, 1678, 1495, 701 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 232.2, found 232.1



(4*S*,5*R*)-5-isobutyl-4-phenylpiperidin-2-one (**63**): White Solid. R_f = 0.34 (19:1 EtOAc:MeOH) 65 % yield, 19:1 d.r., 93 % ee; $[\alpha]_D^{21}$ = 55.1 (c = 0.010 g/ml, CH_2Cl_2); HPLC analysis – Chiralpak IC column, 80:20 hexanes/*iso*-propanol, 1.0 mL/min. Major: 31.6 min, minor: 33.8 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.26-7.22 (m, 1H), 7.14-7.12 (m, 2H), 6.01 (s, 1H), 3.46 (ddd, *J* = 12.1, 4.8, 3.8 Hz, 1H), 3.03-2.97 (m, 1H), 2.74 (td, *J* = 10.5, 5.5 Hz, 1H), 2.67-2.62 (m, 1H), 2.51 (dd, *J* = 17.8, 10.8 Hz, 1H), 2.10-2.01 (m, 1H), 1.50-1.40 (m, 1H), 1.01-0.98 (m, 2H), 0.77 (dd, *J* = 6.5, 3.2 Hz, 6H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 172.1, 142.8, 128.8, 127.3, 126.8, 46.7, 45.1, 40.6, 38.9, 36.1, 25.0, 23.7, 21.1 .**IR** (ATR, neat) 3210, 2955, 2924, 1669, 1495, 1348, 758 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 310.2, found 310.2

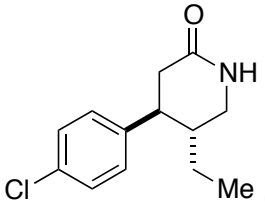


(4*S*,5*R*)-5-(furan-2-yl)-4-phenylpiperidin-2-one (**64**): White Solid. R_f = 0.42 (19:1 EtOAc:MeOH) 82 % yield, 3:1 d.r., 82 % ee; $[\alpha]_D^{21}$ = 50.6 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 85:15 hexanes/*iso*-propanol, 1.0 mL/min. Major: 42.5 min, minor: 46.1 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.31-7.11 (m, 6H), 6.22 (s, 1H), 6.12 (s, 1H), 5.87 (s, 1H), 3.60-3.51 (m, 2H), 3.45-3.32 (m, 2H), 2.82-2.60 (m, 2H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.4, 153.1, 141.8, 141.4, 128.6, 127.01, 126.90, 110.0, 106.9, 45.2, 42.9, 39.6, 38.0**IR** (ATR, neat) 3206, 2923, 2854, 1669, 1495, 1011, 760 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 242.1, found 242.1

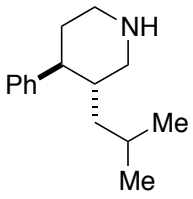


(4*S*,5*R*)-5-ethyl-4-(furan-2-yl)piperidin-2-one (**65**): White Solid. R_f = 0.44 (19:1 EtOAc:MeOH) 60 % yield, 19:1 d.r., 91 % ee $[\alpha]_D^{21}$ = 3.0 (c = 0.010 g/ml, CH_2Cl_2); **GC Analysis** – Varian BDM column, 170 °C, 1mL/min. Major: 16.453 min, minor: 16.594 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.33 (d, *J* = 1.6 Hz, 1H), 6.30 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.06 (dd, *J* = 9.3, 5.8 Hz, 1H), 3.41-3.37 (m, 1H), 3.06-2.93 (m, 2H), 2.63 (dt, *J* = 7.0, 3.6 Hz, 2H), 2.03-1.94 (m, 1H), 1.43-1.34 (m, 1H), 1.28-1.18 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.3,

155.5, 141.5, 110.1, 105.9, 45.5, 44.3, 38.7, 37.5, 24.0, 11.1 **IR** (ATR, neat) 3102, 2962, 2924, 1667, 1495, 1014 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd194.1, found 194.1

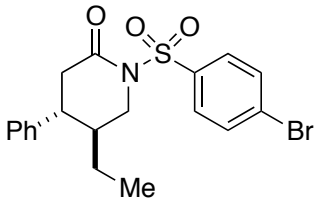


(4*S*,5*R*)-4-(4-chlorophenyl)-5-ethylpiperidin-2-one (**66**): White Solid. R_f = 0.31 (19:1 EtOAc:MeOH) 70 % yield, 20:1 d.r., 82 % ee; $[\alpha]_D^{21}$ = 28.3(c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis** – Chiralpak IC column, 85:15 hexanes/*iso*-propanol, 1.0 mL/min. Major: 50.9 min, minor: 54.3 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.30-7.28 (m, 2H), 7.09-7.07 (m, 2H), 6.15 (s, 1H), 3.50-3.44 (m, 1H), 3.05 (t, *J* = 11.1 Hz, 1H), 2.79-2.72 (m, 1H), 2.61 (dd, *J* = 17.8, 5.5 Hz, 1H), 2.45 (dd, *J* = 17.8, 11.2 Hz, 1H), 1.93-1.84 (m, 1H), 1.35-1.24 (m, 1H), 1.09-1.00 (m, 1H), 0.78 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 171.8, 141.1, 132.6, 129.0, 128.7, 46.1, 43.9, 39.8, 38.8, 23.9, 11.0. **IR** (ATR, neat) 3212, 2960, 2928, 2874, 1668, 1491, 1089, 837, 818 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 238.1, found 238.1



(3*R*,4*S*)-3-isobutyl-4-phenylpiperidine (**67**): To a flame dried10 ml round bottom containing a stir bar, 46 mg **6b** (0.2 mmol, 1 equiv.) was dissolved in 6 ml dry THF and cooled to 0 °C in an ice bath. Then 11.3 mg Lithium aluminum hydride (0.3 mmol, 1.5 equiv.) was added in two portions over 5 minutes. This was stoppered with septum and placed under argon and allowed

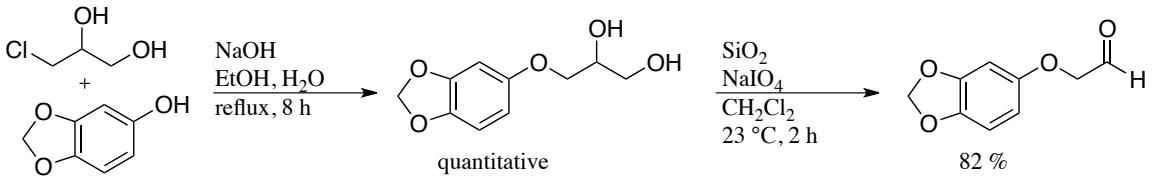
to stir for 1 hour. After 1 hour the ice bath was removed and the flask was fitted with a condenser and the reaction was refluxed for 4 hours. After 4 hours the heat source was removed and the flask was cooled to 0 °C in an ice bath and quenched with 2 ml 1 M HCl. This solution was then transferred to a separatory funnel and diluted with 15 ml brine and extracted 3x 15 ml DCM. The organic layer was dried over sodium sulfate and the solvent was removed via rotary evaporation to yield 38 mg (89 %) (3*R*,4*S*)-3-isobutyl-4-phenylpiperidine as a colorless oil. Rf = 0.12 (19:1 EtOAc:MeOH) 89 % yield, >20:1 d.r., 93 % ee; $[\alpha]_D^{21}$ = 35.5 (c = 0.010 g/ml, CH_2Cl_2); **HPLC Analysis** - Chiralpak IC column, 60:40 hexanes/*iso*-propanol, 1.0 mL/min. Major: 35.38 min, minor: 33.76 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 9.76-9.63 (m, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.23-7.18 (m, 3H), 3.65-3.56 (m, 2H), 2.96-2.88 (m, 1H), 2.59-2.56 (m, 1H), 2.40-2.23 (m, 3H), 1.95 (d, *J* = 14.2 Hz, 1H), 1.47-1.38 (m, 1H), 0.93 (ddd, *J* = 14.4, 9.9, 4.2 Hz, 2H), 0.72 (d, *J* = 13.6 Hz, 6H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 142.4, 128.7, 127.6, 127.0, 48.7, 47.8, 44.4, 40.5, 36.0, 31.0, 24.7, 23.7, 21.1 **IR** (ATR, neat) 3352, 2955, 2925, 2869, 2721, 2492, 1454, 1066, 758, 702 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 218.2, found 218.2



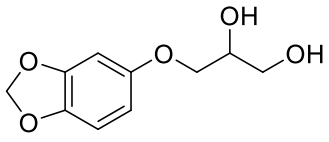
(4*R*,5*S*)-1-((4-bromophenyl)sulfonyl)-5-ethyl-4-phenylpiperidin-2-one (**12**): To a flame dried 25 mL round bottom flask containing a stirbar was added 107 mg (4*S*,5*R*)-5-ethyl-4-phenylpiperidin-2-one (**7a**) (synthesized via catalyst **5b**) (0.52 mmol, 1 equiv.) and 10 mL THF and cooled to -78 °C. To this was then added dropwise 0.357 mL *n*-Butyl lithium (1.6 M, hexanes) (0.572 mmol, 1.1 equiv). After stirring at -78 °C for 10 minutes a solution (146 mg

4-bromobenzenesulfonyl chloride (0.572 mmol, 1.1 equiv.) in 5 mL THF) was added dropwise to the reaction. This was stirred at -78 °C for 1 hour and then allowed to warm to room temperature and stir overnight. After 12 hours the reaction was cooled to 0 °C and quenched with 8 mL saturated NH_4Cl. The reaction was extracted 3 x 10 mL CH_2Cl_2, dried with anhydrous Na_2SO_4 and then concentrated *in vacuo*. The resulting crude oil was then purified by column chromatography to yield 180 mg (4*R*,5*S*)-1-((4-bromophenyl)sulfonyl)-5-ethyl-4-phenylpiperidin-2-one (82 %) as a crystalline white solid. Rf = 0.51 (1:1 hexanes:ether) $[\alpha]_D^{21}$ = -11.8 (c = 0.010 g/ml, CH_2Cl_2); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.93-7.90 (m, 2H), 7.69-7.65 (m, 2H), 7.31-7.27 (m, 2H), 7.22 (dt, *J* = 7.2, 1.9 Hz, 1H), 7.06-7.04 (m, 2H), 4.22 (dd, *J* = 12.5, 4.7 Hz, 1H), 3.48 (dd, *J* = 12.5, 9.4 Hz, 1H), 2.75 (dt, *J* = 10.1, 5.0 Hz, 1H), 2.71-2.65 (m, 1H), 2.56 (dd, *J* = 17.4, 10.5 Hz, 1H), 2.05-1.96 (m, 1H), 1.40 (dtd, *J* = 14.4, 7.3, 4.1 Hz, 1H), 1.21-1.14 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ 169.9, 141.7, 137.7, 132.0, 130.3, 129.12, 128.95, 127.21, 127.09, 49.8, 44.0, 41.5, 41.1, 24.3, 11.1; **IR** (ATR, neat) 1960, 2923, 1692, 1170 cm^{-1}; **LRMS** (ESI + APCI) *m/z* [M+H] calcd 422.0, found 422.1

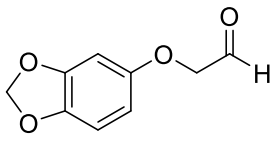
Synthesis of Aldehyde 74



Aldehyde **74** is commercially available from Aurora Building Blocks. Catalogue number: A00.552.03. However, we chose to synthesize it via the above route.

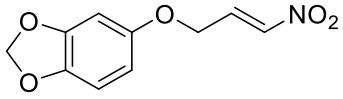


3-(benzo[d][1,3]dioxol-5-yloxy)propane-1,2-diol **(S3)**: Prepared according to a literature procedure.[cxii] A 100 mL round bottom flask was charged with sesamol (6.906 g, 50.0 mmol) and dissolved in 30 mL EtOH. To this solution was added a solution of NaOH (2.50 g, 62.5 mmol, 1.2 eq.) in 10 mL H_2O and the mixture was heated to reflux for 10 min. After this time, a solution of 3-chloro-1,2-propane diol (5.0 mL, 6.6 g, 60.0 mmol, 1.25 eq.) in 5 mL EtOH was added and the resulting mixture was allowed to reflux overnight (~8 hr) until TLC indicated complete reaction. After this time, solution was allowed to cool to rt and volatiles were removed *in vacuo*. The resulting residue was diluted with EtOAc (50 mL) and H_2O (50 mL), and the layers separated. The aqueous layer was extracted with EtOAc (6 x25 mL) and the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give a pale orange off-white solid (10.9 g) which was used in the next step without further purification. Rf= 0.12 in (3:2 Hexanes:EtOAc); quant., **1H-NMR** (400 MHz; $(CD_3)_2CO$): δ 6.71 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 2.8 Hz, 1H), 6.37 (dd, J = 8.4, 2.8 Hz, 1H), 5.91 (s, 2H), 4.11 – 3.87 (m, 4H), 3.72 – 3.59 (m, 3H) **13C NMR** (101 MHz; $(CD_3)_2CO$): δ 154.7, 148.3, 141.6, 107.7, 105.7, 101.1, 97.8, 70.5, 70.4, 63.2; **LRMS** (ESI) *m/z* calcd 212.1, found 212.0; **IR** (neat) 3320, 2933, 2894, 1487, 1194, 1038, 928 cm^{-1}



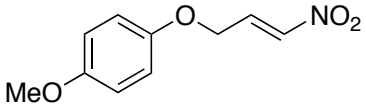
2-(benzo[d][1,3]dioxol-5-yloxy)acetaldehyde **(76)**: Prepared according to a literature procedure.[cxii] To a vigorously stirred solution of silica gel (50 g) in 350 mL CH_2Cl_2 was added a solution of 6.952 g $NaIO_4$ (32.5 mmol) in 50 mL H_2O, followed by a solution of 5.305 g

3-(benzo[d][1,3]dioxol-5-yloxy)propane-1,2-diol (25.0 mmol) in 50 mL CH_2Cl_2. The resulting mixture was allowed to stir at rt open to the air for 2 hr until TLC completed complete reaction. After this time, the reaction mixture was filtered over a bed of silica gel and the silica gel was rinsed with ~1 L of CH_2Cl_2. The Solvent was then removed *in vacuo* to give 3.63 g (20.5 mmol) 2-(benzo[d][1,3]dioxol-5-yloxy)acetaldehyde as an analytically pure white solid. Rf= 0.42 in (3:2 Hexanes:EtOAc); 82 % yield, **1H-NMR** (400 MHz; $(CD_3)_2CO$): δ 9.75 (s, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.94 (s, 2H), 4.67 (s, 2H) **13C NMR** (101 MHz; $(CD_3)_2CO$): δ 198.4, 153.6, 148.5, 142.3, 107.8, 105.9, 101.3, 97.9, 73.5.; **LRMS** (ESI) *m/z* calcd 180.0, found 180.0; **IR** (neat) 2900, 2832, 1738, 1503, 1488, 1187, 1037 cm^{-1}



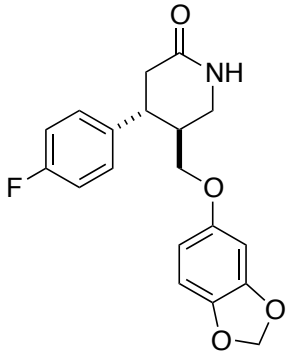
(E)-5-((3-nitroallyl)oxy)benzo[d][1,3]dioxole **(74):** To an oven-dried round bottom flask was added 3.42 g 2-(benzo[d][1,3]dioxol-5-yloxy)acetaldehyde (19.0 mmol), 1.5 mL nitromethane (28.0 mmol), and 1:1 THF/*t*-BuOH (25 mL). This solution was then cooled to 0 °C and 426 mg potassium tert-butoxide (3.8 mmol) was added in one portion. The reaction was allowed to stir at 0 °C for 15 min then warmed to room temperature and stirred for another 2 h until TLC indicated complete reaction. After completion, saturated aqueous NH_4Cl solution (50 mL) was added to quench the reaction and then the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. After drying the crude residue under vacuum (4 mm) for 0.5 h, CH_2Cl_2 (50 mL) was added and the solution was cooled to 0 °C. Trifluoroacetic anhydride (3.0 mL, 10.9 mmol) was then added followed by the slow dropwise addition of 5.6 mL Et_3N (40 mmol). After stirring for ~15 min at 0

°C the reaction was diluted with H_2O (30 mL) and CH_2Cl_2 (50 mL) and the layers separated. The organic layer was then washed with sat. aq. NH_4Cl (2 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give brown-yellow solid, which was then purified by column chromatography (3:1 hexanes:ethyl acetate) to give 2.893 g (13.0 mmol) of (E)-5-((3-nitroallyl)oxy)benzo[d][1,3]dioxole as a bright yellow solid. Rf= 0.4 in (3:1 Hexanes:EtOAc); 68 % yield, **1H-NMR** (400 MHz; $(CD_3)_2CO$): δ 7.47 (dt, *J* = 13.6, 3.6 Hz, 1H), 7.39 (dt, *J* = 13.6, 2.0 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.95 (s, 2H), 4.11 (dd, *J* = 3.6, 2.0 Hz, 2H), **13C NMR** (101 MHz; $(CD_3)_2CO$): δ 153.3, 148.5, 142.4, 139.7, 137.9, 107.8, 106.0, 101.4, 101.4, 98.0, 64.6; **LRMS** (ESI) *m/z* calcd 223.1, found 223.0; **IR** (neat) 3439, 3124, 1635, 1435, 933, 733 cm^{-1}



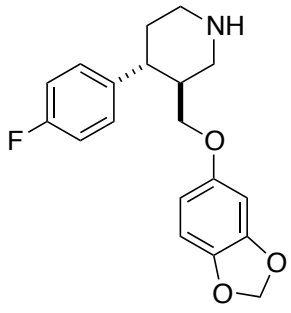
(*E*)-1-methoxy-4-((3-nitroallyl)oxy)benzene **(80):** In a dry round bottom flask, 1.69 g (10.17 mmol) of 2-(4-methoxyphenoxy)acetaldehyde (prepared according to reference 1) was dissolved in 40 mL of a 1:1 solution of THF/tBuOH. 0.82 ml (15.25 mmol, 1.5 equiv.) of Nitromethane was added, and the reaction was cooled to 0 °C in an ice water bath. Potassium t-Butoxide (228 mg, 2.03 mmol, 0.2 equiv) was added and the reaction was stirred at room temperature overnight. The reaction was quenched with a saturated NH4Cl solution and extracted with EtOAc (3 x 20 ml). The organic layers were combined and washed with a brine solution. The organic layer was then dried over $MgSO_4$, filtered, and concentrated. The crude oil was then dissolved in CH_2Cl_2 (30 ml) and cooled to 0 °C. Trifluoroacetic anhydride (1.41ml, 10.17 mmol, 1 equiv) was added to the reaction, followed by slow addition of Et_3N (2.83 ml, 20.39 mmol, 2 equiv). The reaction was stirred at 0 °C for 2 hours, then quenched with water. The

organic layer was washed with saturated NH_4Cl. The organic extract was dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by silica gel column chromatography, eluting with 0 to 20% EtOAc/Hexanes. Isolated 424 mg (20% yield) of an orange solid. **1H-NMR** (400 MHz; $CDCl_3$): δ 7.39-7.28 (m, 2H), 6.85 (s, 4H), 4.73 (dd, J = 3.3, 1.9 Hz, 2H), 3.77 (s, 3H). **13-C NMR** (101 MHz; $CDCl_3$): δ 154.7, 151.5, 140.2, 136.9, 115.7, 114.8, 64.5, 55.7; LR**MS**: m/z [M-1] calcd 209.1, found 208.1; **IR**: 3123, 3052, 2907, 2836, 1788, 1659, 1526, 1505, 1440, 1359, 1226, 1033, 936, 824, 732 cm^{-1}



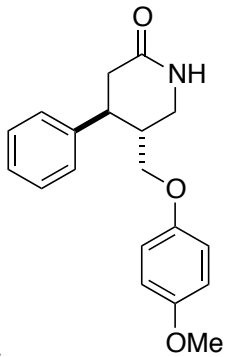
(4*R*,5*S*)-5-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-2-one **(75)**: To a 100 mL flame dried round bottom flask containing a magnetic stirbar was added nitroalkene **74** (2.01 g, 9 mmol, 1.0 equiv), NHC **3** (377 mg, 0.9 mmol, 10 mol%), sodium acetate (370 mg, 4.5 mmol, 0.5 equiv), 4-fluorocinnamaldehyde (2.03 g, 13.5 mmol, 1.5 equiv), followed by 30 mL ethanol. The flask was then fitted with a rubber septum and stirred under an atmosphere of argon for 12 hours at 23 °C. After 12 hours, the septum was removed and zinc dust (5.85 g, 90 mmol, 10 equiv) was added followed by 30 ml of acetic acid. The flask was then fitted with a reflux condenser and heating mantle. The reaction was then refluxed for four hours. After four hours, the heat source was removed and the reaction was allowed to cool. Upon cooling, the reaction was filtered through celite and rinsed with 30 mL EtOAc. The filtrate was then diluted with an additional 20 mL EtOAc and quenched with 60 mL saturated $NaHCO_3$. The organic layer was then separated, washed with brine (1 x 60 mL), dried

(Na_2SO_4), and concentrated *in vacuo*. The crude residue was then purified by column chromatography (5 % MeOH in CH_2Cl_2) to yield 1.8 g (4*R*,5*S*)-5-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-2-one, 58 %, 10:1 dr, and 82 % ee as an off-white solid. **Rf**: 0.51 (10:1:0.1 Dicholoromethane:Methanol:NH_4OH); **HPLC Analysis**: Chiralpak IA column, 80:20 hexanes/*iso*-propanol, 1.0 mL/min. Major: 12.27 min, minor 16.74 min; **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.16 (dt, *J* = 6.8, 3.5 Hz, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.11 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.90 (bs, 1H), 5.88 (s, 2H), 3.69-3.59 (m, 2H), 3.52 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.46-3.40 (m, 1H), 3.08 (td, *J* = 11.2, 5.6 Hz, 1H), 2.71-2.51 (m, 2H), 2.44-2.35 (m, 1H).; **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 171.5, 161.8 (d, J=245.5 Hz, C), 153.8, 148.2, 141.9, 137.1 (d, J=3.2 Hz, C), 128.6 (d, J=7.9 Hz, CH), 115.9, 107.9 (d, J=21.3 Hz, CH), 105.5, 101.2, 97.9, 68.3, 44.5, 40.2, 39.3, 38.7.; **IR**: (ATR neat) 3214, 2923, 1664, 1507, 1485, 1362, 1226, 1184, 1135, 1101, 1034, 927, 842, 759 cm^{-1}; **LRMS**: (ESI + APCI) *m/z* [M+H] calcd 344.1, found 344.1; **Optical Rotation**: $[\alpha]_D^{21}$ = - 72.2



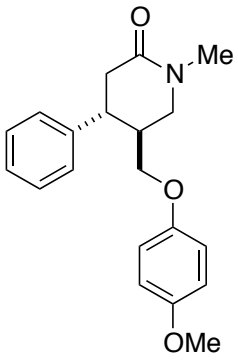
(-)-Paroxetine (68): To a flame dried 250 mL round bottom flask containing a stirbar was added 1.22 g lactam **75** (3.55 mmol, 1.0 equiv) and 120 mL dry THF. This flask was fitted with a rubber septum connected to an argon line and cooled to 0 °C in an ice bath. At 0 °C, 228 mg $LiAlH_4$ (6 mmol, 1.5 equiv) was added portionwise over the course of five

minutes. The reaction was allowed to stir at 0 °C for 1 hour and then the ice bath was removed and the flask was fitted with a reflux condenser and the reaction was refluxed for four hours. After four hours the heat source was removed and the flask was cooled to 0 °C in an ice bath and carefully quenched with 100 mL saturated Rochelle's salt and stirred until complete separation was observed, approximately 1 hour. The solution was then transferred to a separatory funnel and extracted 3 x 70 mL CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was removed via rotary evaporation. The crude oil was purified by column chromatography (100 % EtOAc to 10:1:01 CH_2Cl_2:MeOH:NH_4OH) to yield 1.0 g paroxetine as a colorless oil. **Rf**: 0.34 (10:1:0.1 Dicholoromethane:Methanol:NH_4OH); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.17 (dd, *J* = 8.6, 5.3 Hz, 2H), 6.96 (t, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.10 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.86 (bs, 2H), 5.52 (s, 1H), 3.58-3.54 (m, 2H), 3.46-3.39 (m, 2H), 2.94-2.84 (m, 2H), 2.73 (td, *J* = 11.8, 3.8 Hz, 1H), 2.35 (dddd, *J* = 13.8, 10.7, 6.6, 3.7 Hz, 1H), 2.05 (qd, *J* = 13.0, 3.9 Hz, 1H), 1.90 (dd, *J* = 13.7, 3.0 Hz, 1H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 161.8 (J=245.9 Hz, C), 153.7, 148.2, 142.0, 137.1 (J=3.1 Hz, C), 128.9 (J=7.8 Hz, CH), 115.8 (J=21.3 Hz, CH), 107.8, 105.5, 101.2, 97.9, 67.4, 46.7, 44.4, 41.6, 39.3, 29.9; **IR**: (ATR neat) 3394, 2925, 1609, 1510, 1482, 1464, 1226, 1187, 1136, 1097, 1038, 930, 831 cm^{-1}; **LRMS**: (ESI + APCI) *m/z* [M+H] calcd 330.2, found 330.2



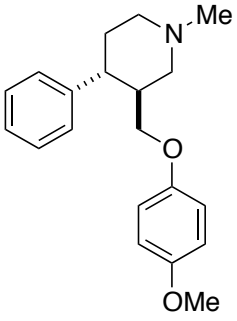
(4*S*,5*R*)-5-((4-methoxyphenoxy)methyl)-4-phenylpiperidin-2-one **(81)**: To a screw cap vial containing a magnetic stirbar was added 42 mg nitroalkene **80** (0.2 mmol, 1.0 equiv), 40 mg cinnamaldehyde (0.3 mmol, 1.5 equiv), 8 mg NHC **3**

(0.02 mmol, 10 mol%), 8 mg NaOAc (0.1 mmol, 50 mol%), and 0.6 mL ethanol. The vial was flushed with argon and the screwcap replaced and stirred at 23 °C for 12 hours. After 12 hours, the screw cap was removed and 130 mg zinc dust (2.0 mmol, 10 equiv) was added, followed by 0.6 mL AcOH. The screw cap was replaced and the reaction was refluxed for four hours. After four hours, the heat source was removed and the reaction was allowed to cool. Upon cooling, the reaction was filtered through celite and rinsed with 10 mL EtOAc. The filtrate was then diluted with an additional 5 mL EtOAc and quenched with 20 mL saturated $NaHCO_3$. The organic layer was then separated, washed with brine (1 x 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was then purified by column chromatography (5 % MeOH in CH_2Cl_2) to yield 33 mg (4*S*,5*R*)-5-((4-methoxyphenoxy)methyl)-4-phenylpiperidin-2-one 53 %, 7:1 dr, and 82 % ee as an off-white solid. **Rf**: 0.34 (95:5 Dicholromethane:Methanol); **HPLC**: Chiralpak IA column, 85:15 hexanes/*iso*-propanol, 1.0 mL/min. Major: 21.84 min, minor: 23.68 min; **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.32 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 3.6 Hz, 1H), 7.20-7.18 (m, 2H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.65 (d, *J* = 9.1 Hz, 2H), 6.56 (bs, 1H), 3.72 (s, 3H), 3.71-3.63 (m, 2H), 3.54 (dd, *J* = 9.3, 7.7 Hz, 1H), 3.42 (dd, *J* = 21.5, 11.0 Hz, 1H), 3.06 (td, *J* = 11.0, 5.7 Hz, 1H), 2.63 (qd, *J* = 19.4, 8.5 Hz, 2H), 2.48-2.39 (m, 1H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 171.9, 154.0, 152.5, 141.5, 129.0, 127.23, 127.17, 115.3, 114.6, 68.3, 55.7, 44.7, 41.0, 39.1, 38.6; **IR**: (ATR neat) 3250, 2931, 1675, 1508, 1242, 1035, 832, 705 cm^{-1}; **MS**: (ESI + APCI) *m/z* [M+H] calcd 312.2, found 312.1; **Optical Rotation**: $[\alpha]_D^{21}$ = - 26.4



(4*R*,5*S*)-5-((4-methoxyphenoxy)methyl)-1-methyl-4-phenylpiperidin-2-one

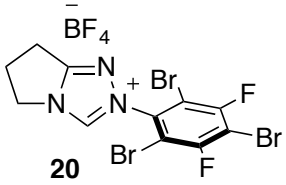
(S4): (4*R*,5*S*)-5-((4-methoxyphenoxy)methyl)-4-phenylpiperidin-2-one (34 mg, 0.11mmol) was dissolved in dry THF (2 ml) in a round bottom flask and cooled to 0 °C. NaH (6 mg, 0.16 mmol, 1.5 equiv., 60% dispersion in mineral oil) was added to the reaction, followed by 10 μL of MeI (0.16 mmol, 1.5 equiv). The reaction was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The organic fractions were collected, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by column chromatography, eluting with 0 to 10%MeOH/DCM. Isolated 20 mg of a pale orange oil (55% yield). **1H-NMR** (400 MHz; $CDCl_3$): δ 7.30 (d, *J* = 7.6 Hz, 3H), 7.25 (s, 2H), 7.19-7.17 (m, 2H), 6.75 (d, *J* = 9.1 Hz, 3H), 6.68-6.65 (m, 2H), 3.72 (s, 3H), 3.72-3.67 (m, 4H), 3.60-3.52 (m, 3H), 3.44 (dd, *J* = 12.3, 10.4 Hz, 1H), 3.05-3.03 (m, 1H), 3.02 (s, 3H), 2.66 (dd, *J* = 27.0, 8.6 Hz, 2H). **13-C NMR** (101 MHz; $CDCl_3$): δ 169.2, 154.0, 152.5, 141.3, 128.9, 127.19, 127.13, 115.3, 114.6, 55.7, 52.5, 41.4, 39.7, 39.4, 34.5; **MS**: m/z=326.21 (M+); **IR**: 3060, 3028, 2923, 1643, 1506, 1465, 1420, 1355, 1229, 1144, 1035, 825, 745, 702; $[\mathbf{a}]_D^{23} = -17°$



Femoxetine (69): 16 mg (0.05 mmol) of (4*R*,5*S*)-5-((4-methoxyphenoxy)methyl)-1-methyl-4-phenylpiperidin-2-one was dissolved in THF (2 ml) and 4 mg of $LiAlH_4$ (0.1 mmol, 2 equiv) was added carefully. The reaction was stirred at room temperature overnight. The reaction was cooled to 0 °C and $Na_2SO_4x10H_2O$ was added carefully (approx. 200 mg). The slurry was stirred for 2 hours at room temperature. The mixture was filtered through a plug of celite, washing with EtOAc. The filtrate was concentrated and then purified by silica gel column chromatography, eluting with 0.5%NH_4OH/10%MeOH/DCM. Isolated 13mg as a pale yellow oil (87% yield). ^1H NMR, ^{13}C NMR and mass match previously reported synthesis[cxiii].

General Procedure for the Synthesis of Nitroalkenes

To a dry round bottom flask was added cyclopentane carboxaldehyde (1.02 g, 10.4 mmol), nitromethane (840 μL, 15.6 mmol), and 1:1 THF/*t*-BuOH (10 mL). This solution was cooled to 0 °C and potassium tert-butoxide (0.233 g, 2.08 mmol) added in one portion. The reaction was then stirred at 0 °C for 1 h then warmed to room temperature and stirred for 12 h. After completion, saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction and then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. After drying the crude residue under vacuum (4 mm) for 1 h, CH_2Cl_2 (20 mL) was added followed by cooling to 0 °C. Trifluoroacetic anhydride (1.52 mL, 10.9 mmol) was added followed by the slow dropwise addition of Et3N (3.04 mL, 21.8 mmol). After stirring for 1 h at 0 °C the reaction was allowed to warm to room temperature and stirred an additional 2 h. The reaction was diluted with CH_2Cl_2 (20 mL) followed by the addition of water (20 mL). The organic layer was separated and washed with saturated aqueous NH_4Cl solution (3 x 20 mL), dried (Na_2SO4) and concentrated *in vacuo* to give a yellow oil that was purified by column chromatography (20:1 hexanes:ether) yielding 0.779 g (53%) of (*E*)-(2- nitrovinyl)cyclopentane as a pale yellow oil.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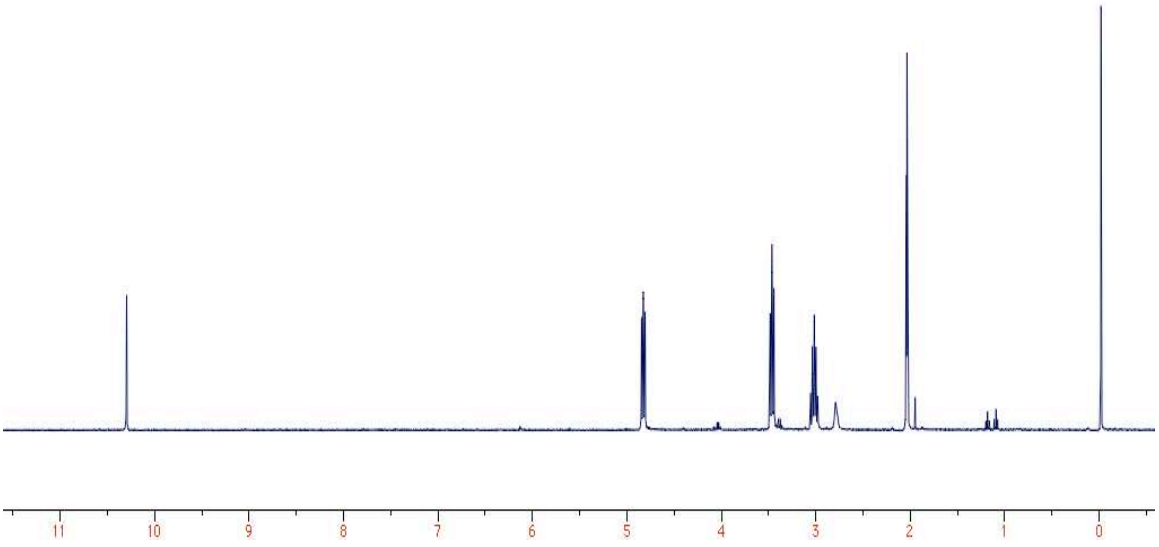
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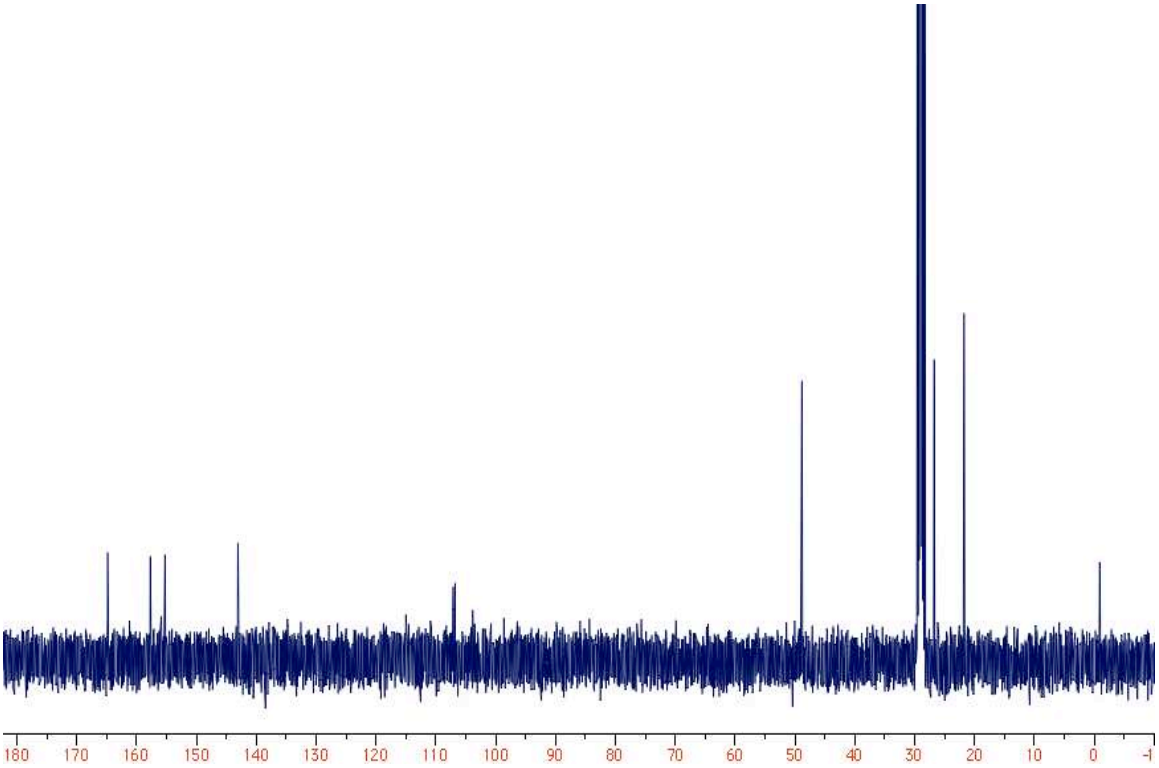
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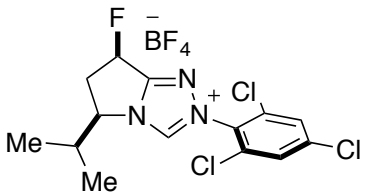
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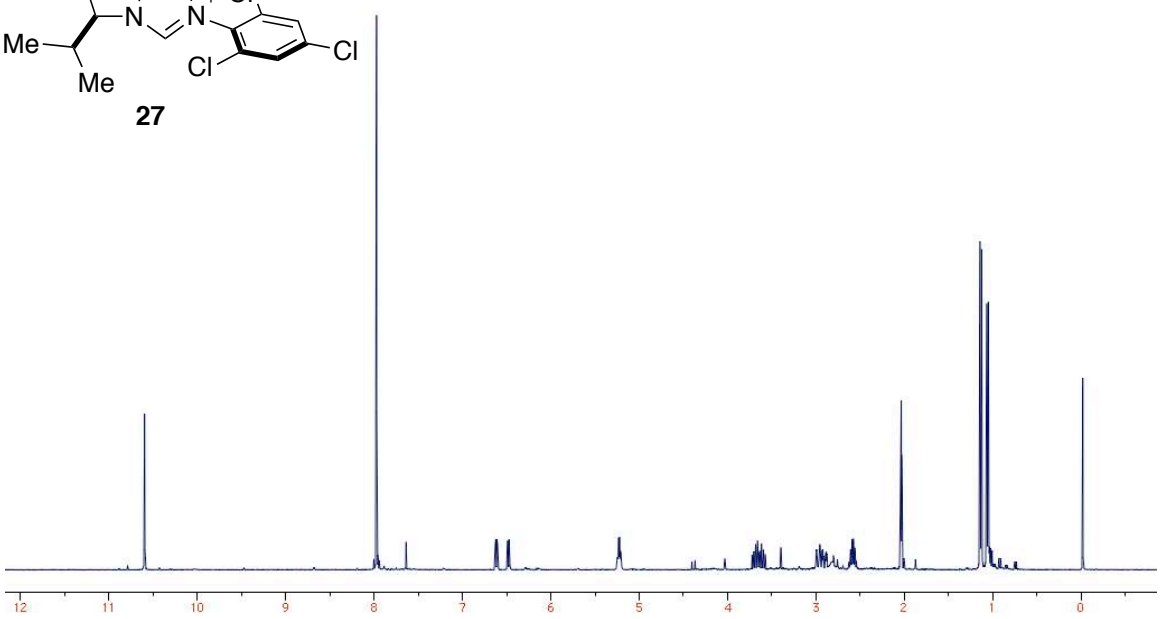
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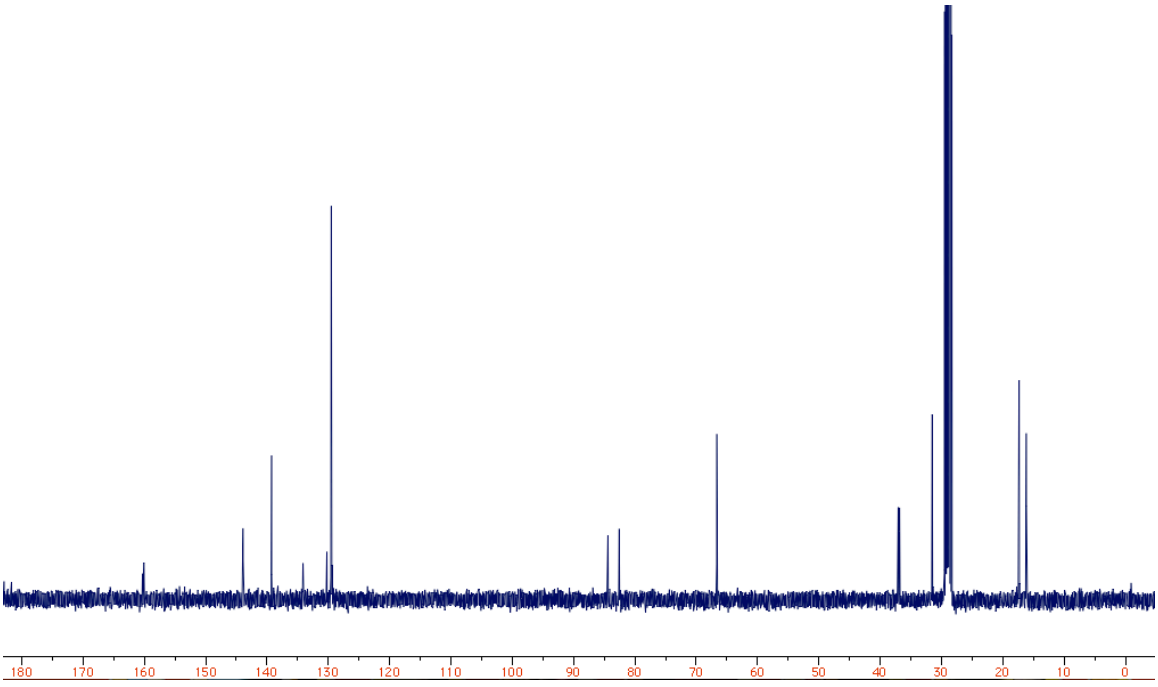
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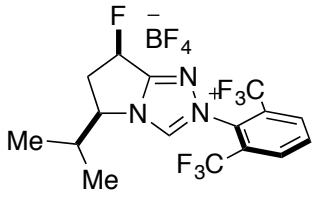
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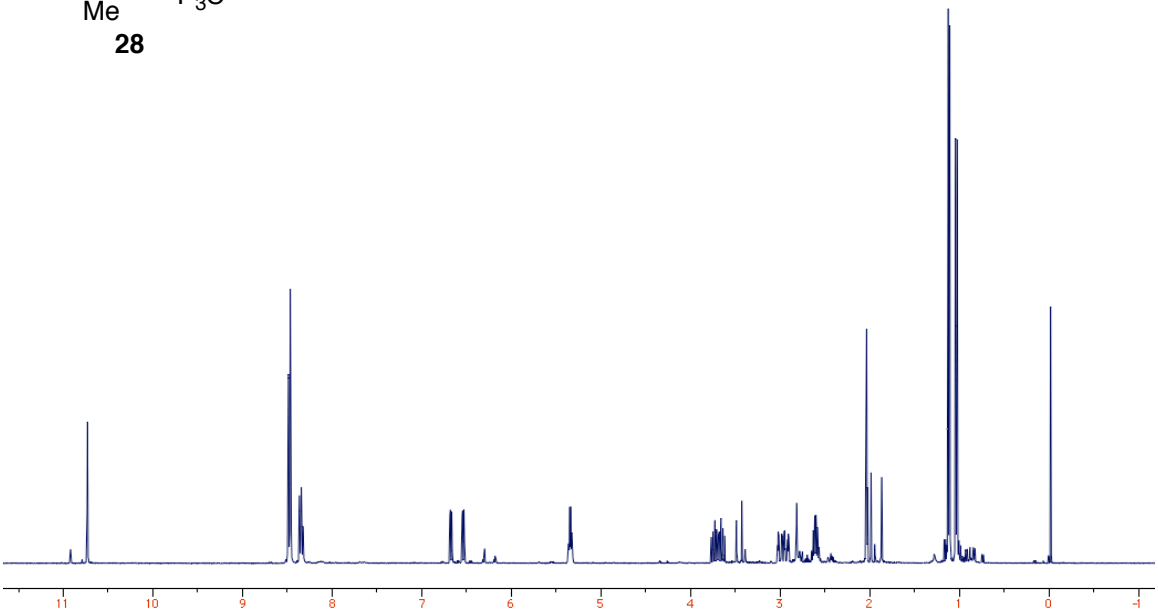
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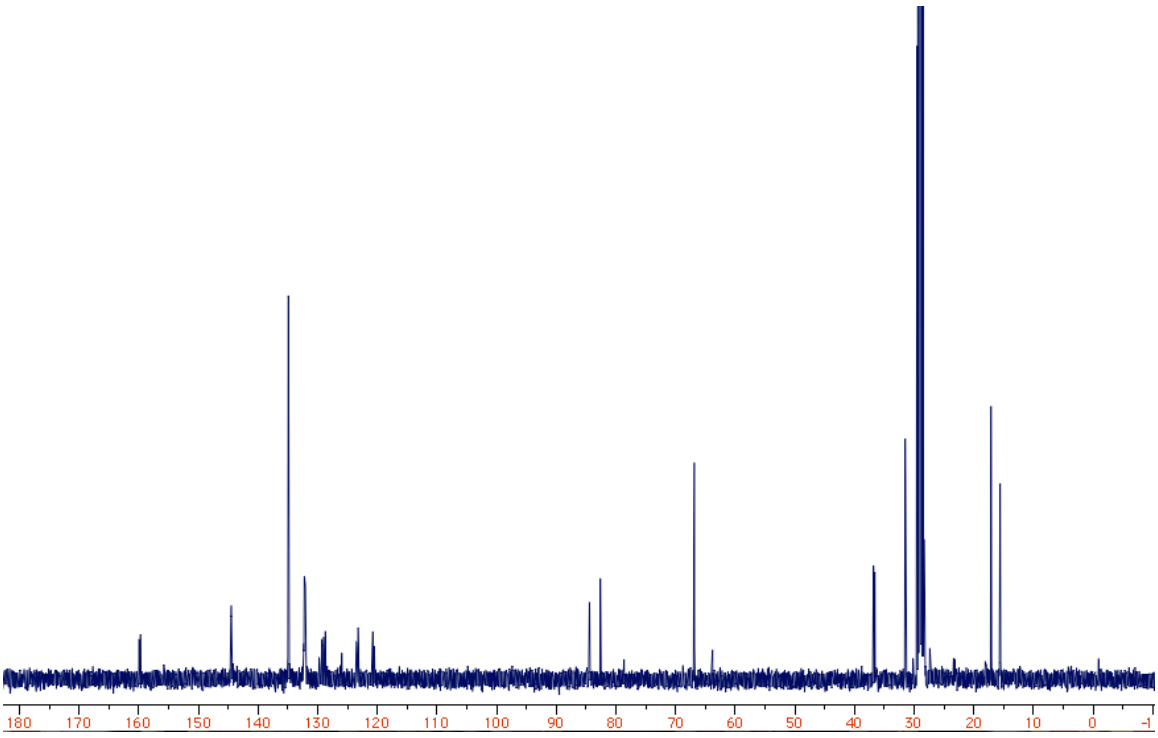
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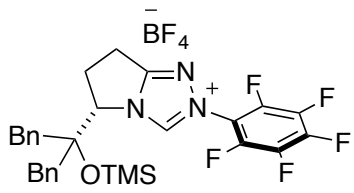

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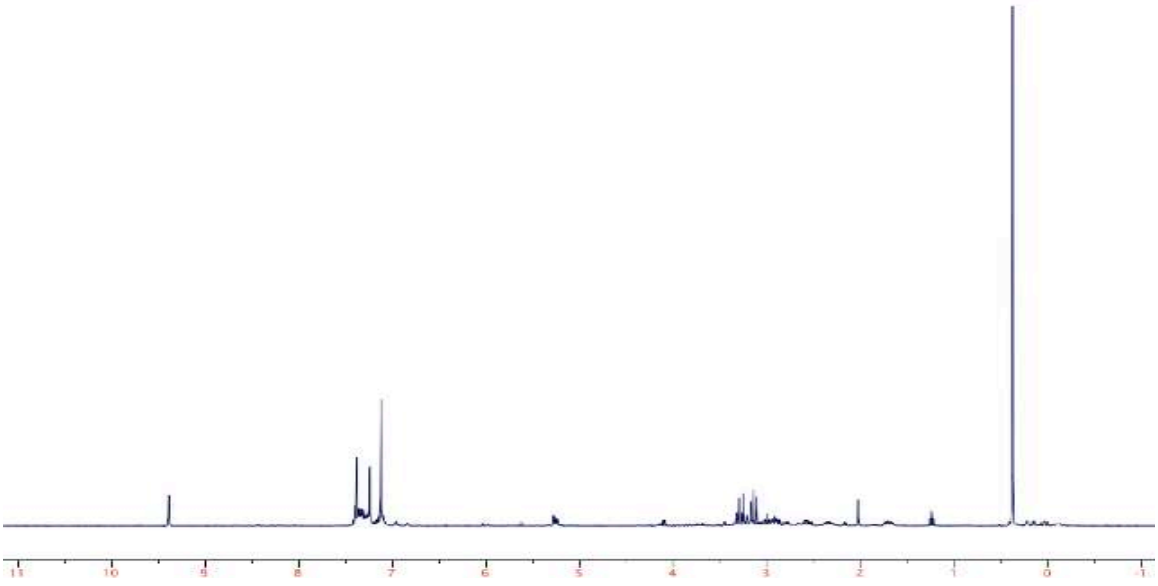

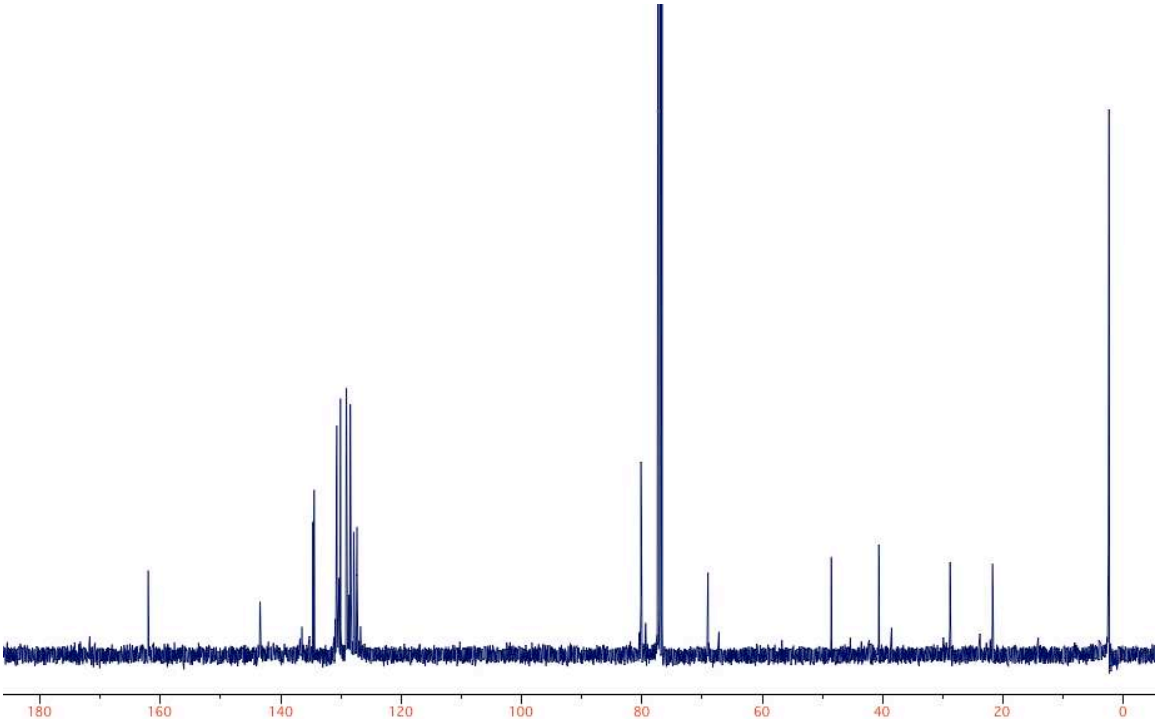

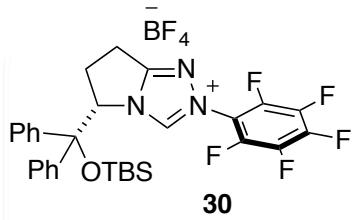
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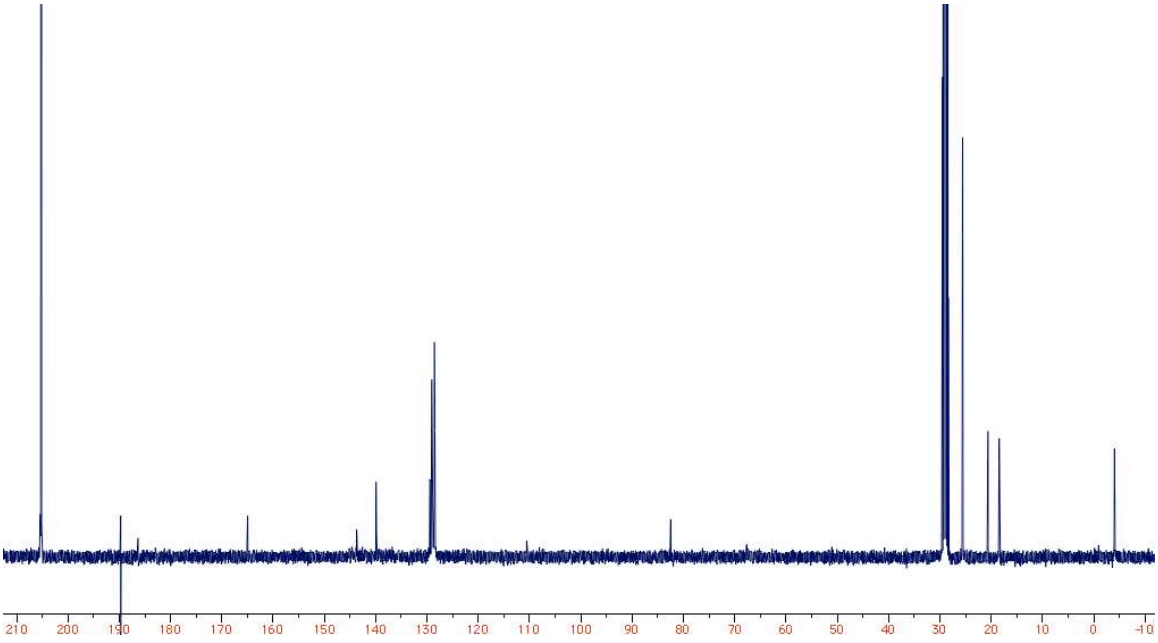
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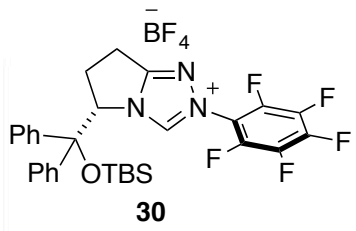
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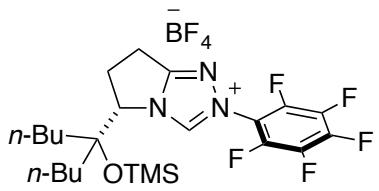
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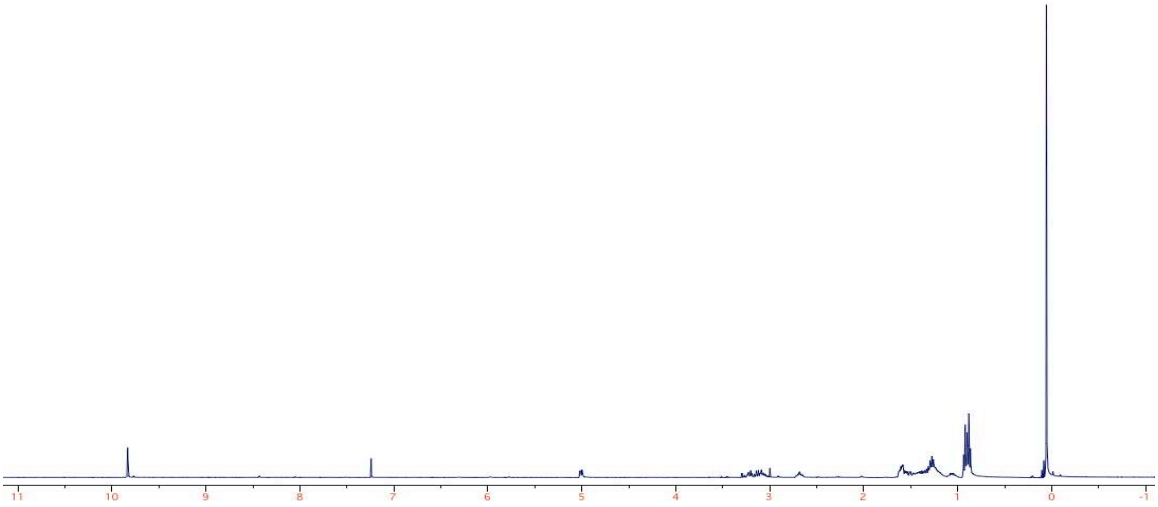
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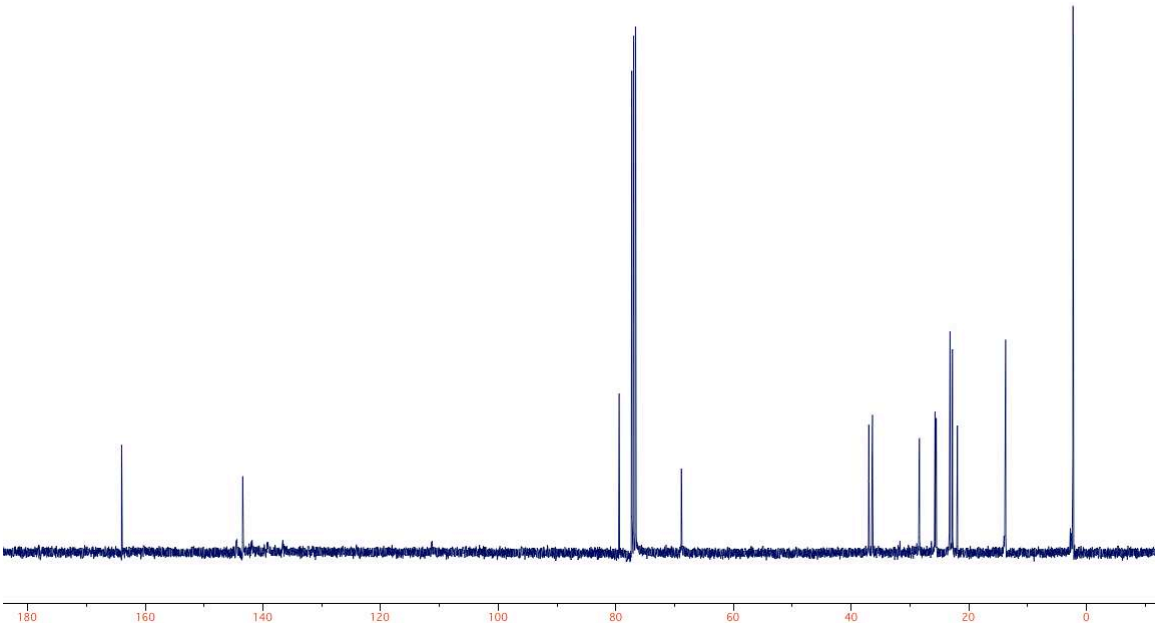
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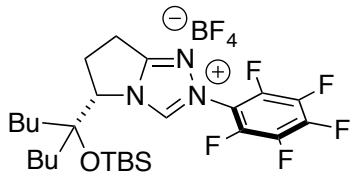
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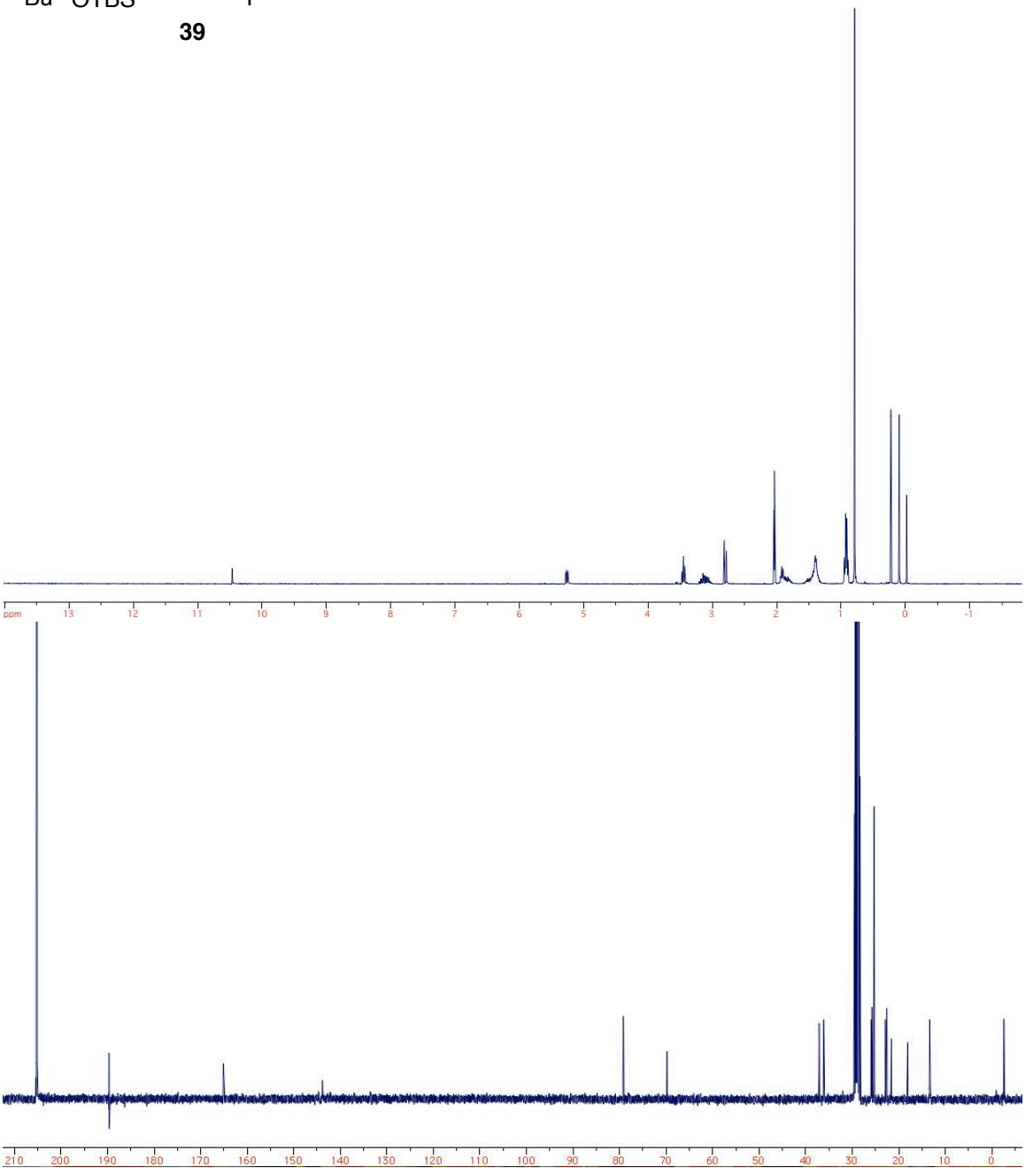
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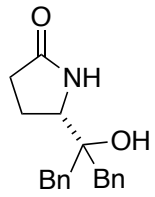
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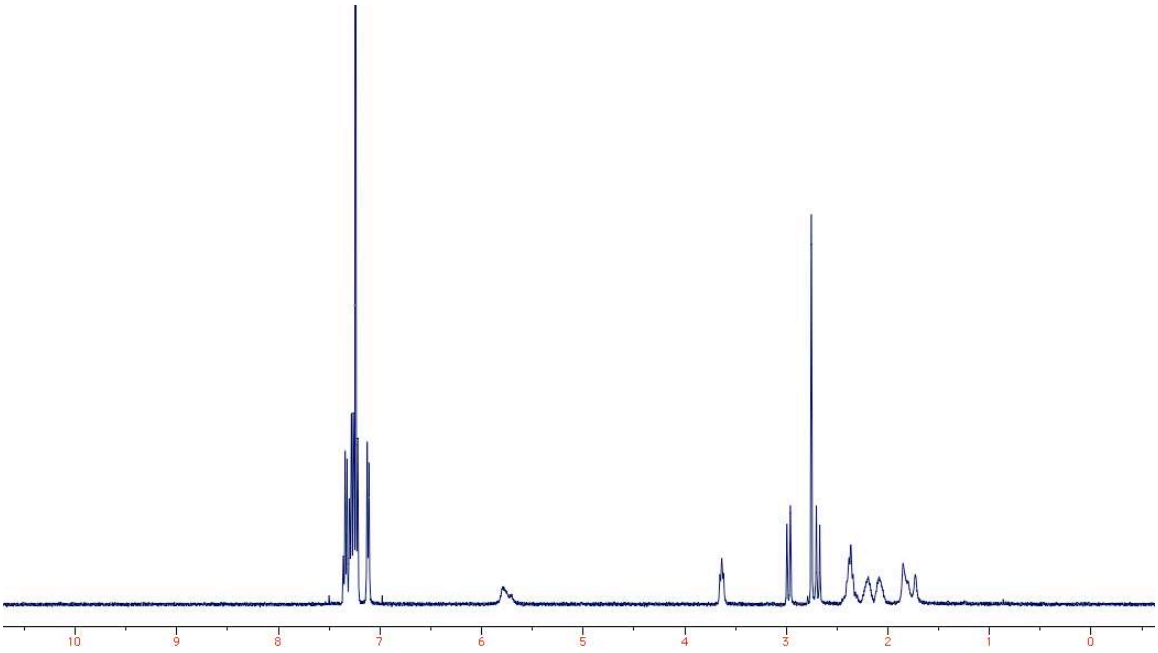
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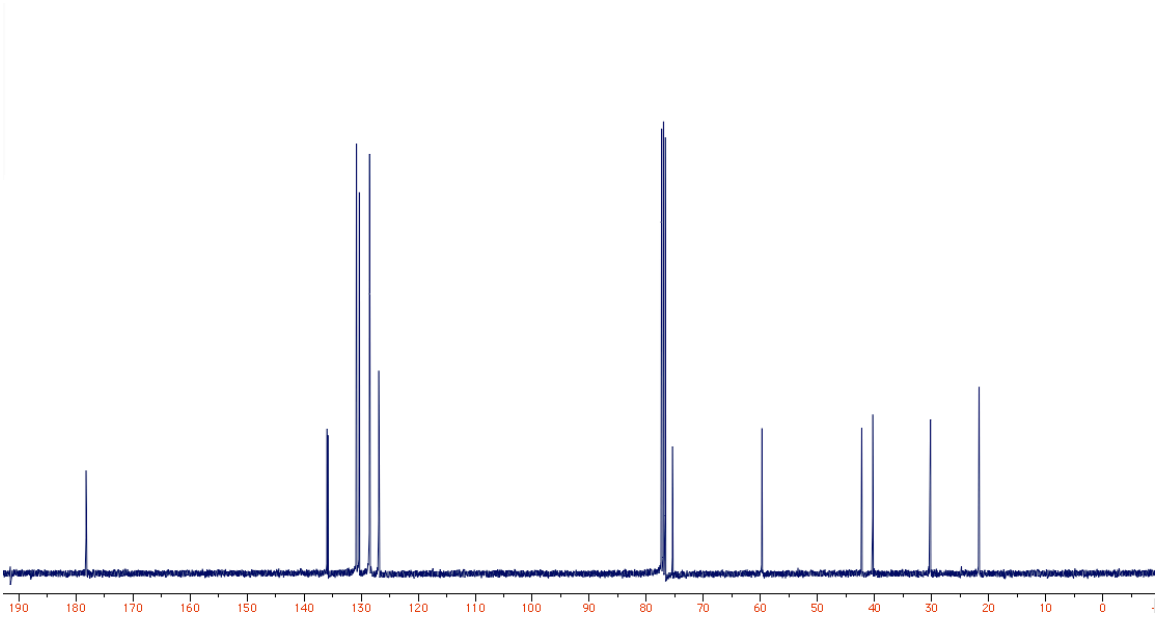
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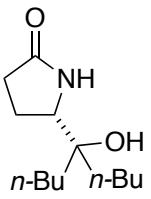
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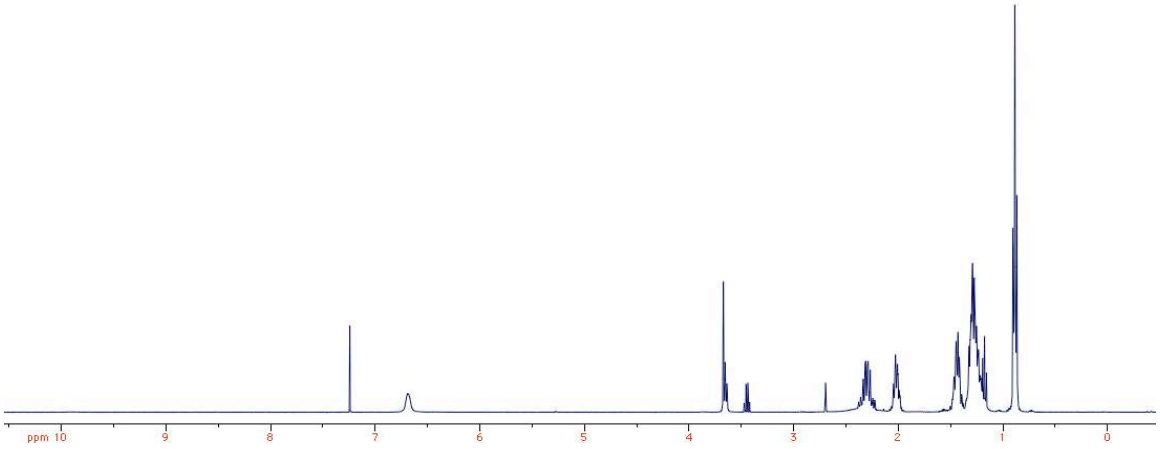
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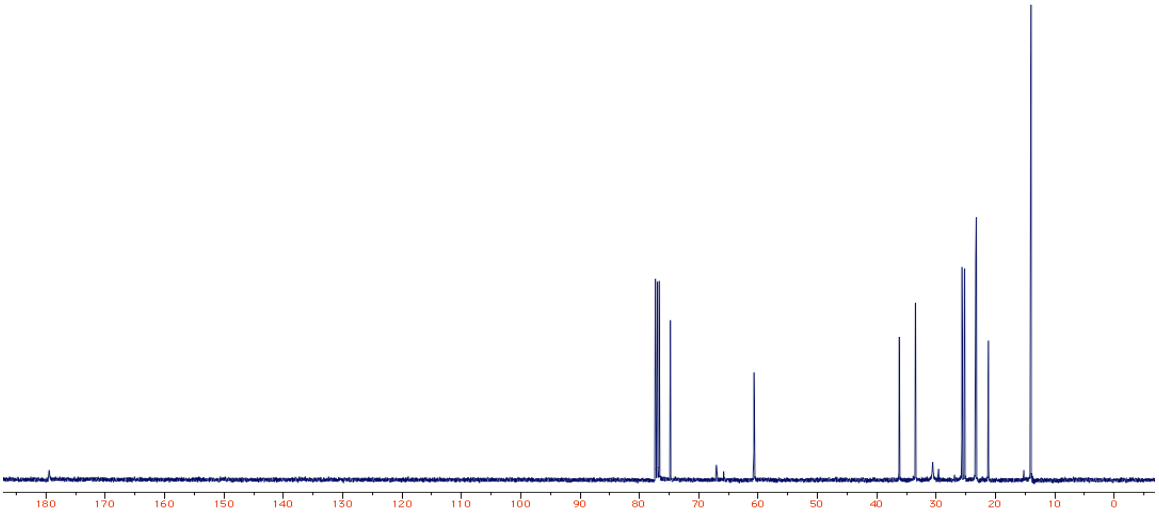
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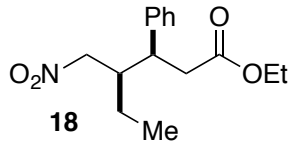
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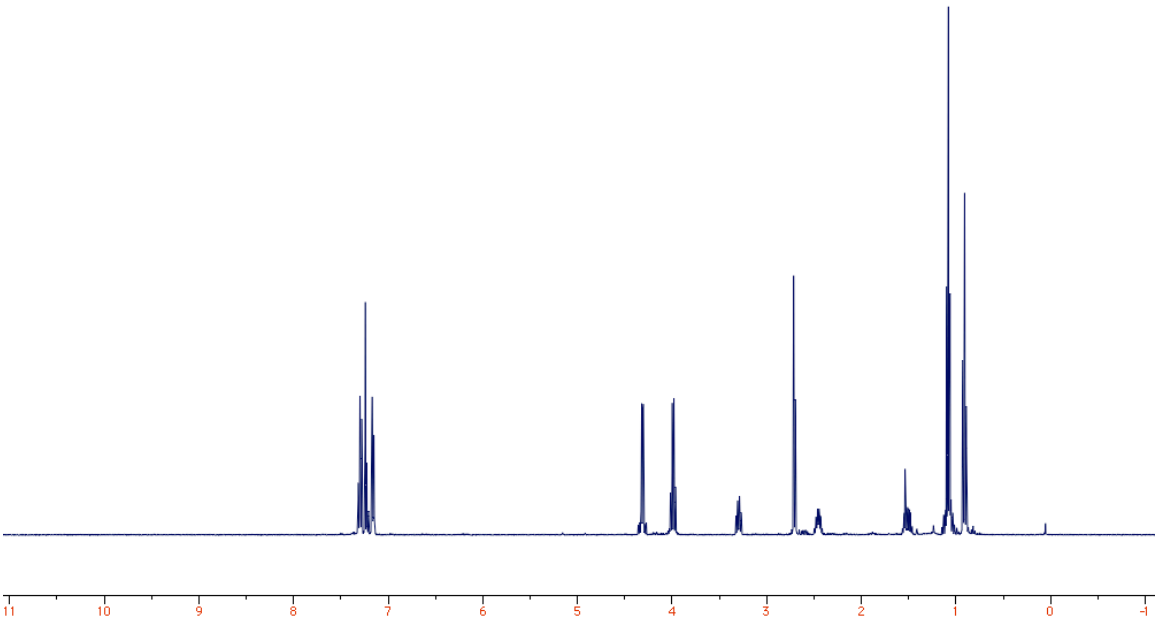
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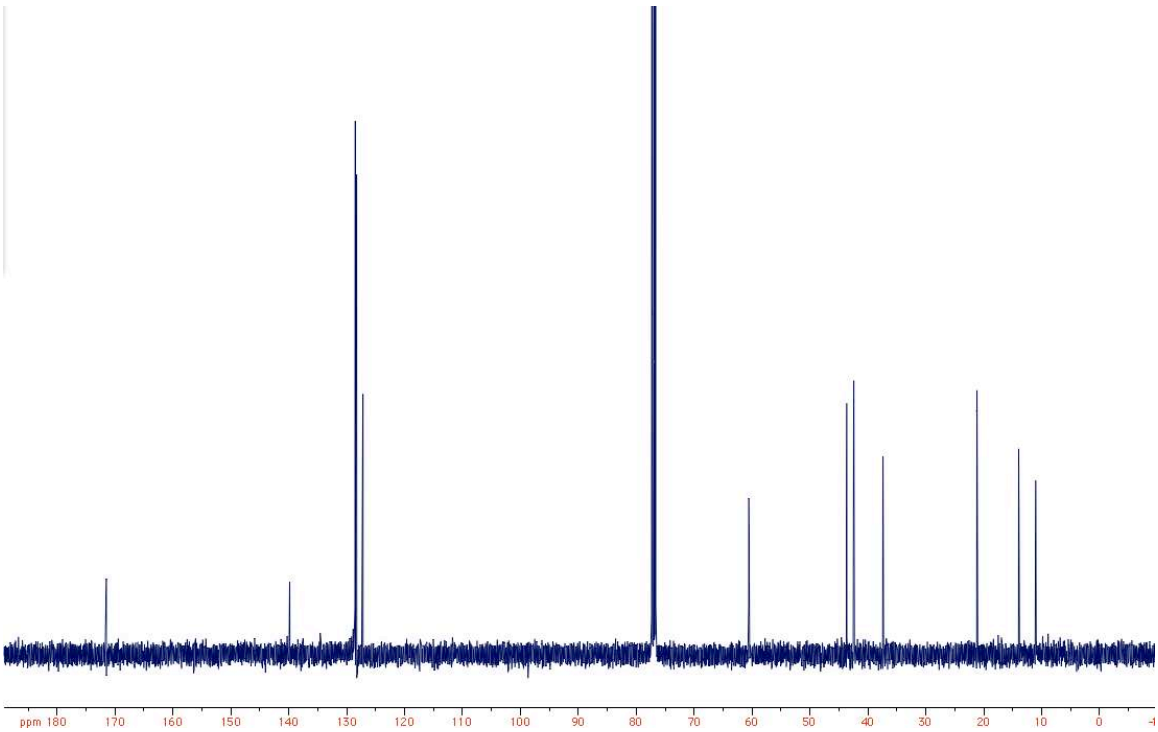
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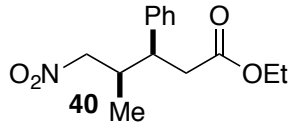
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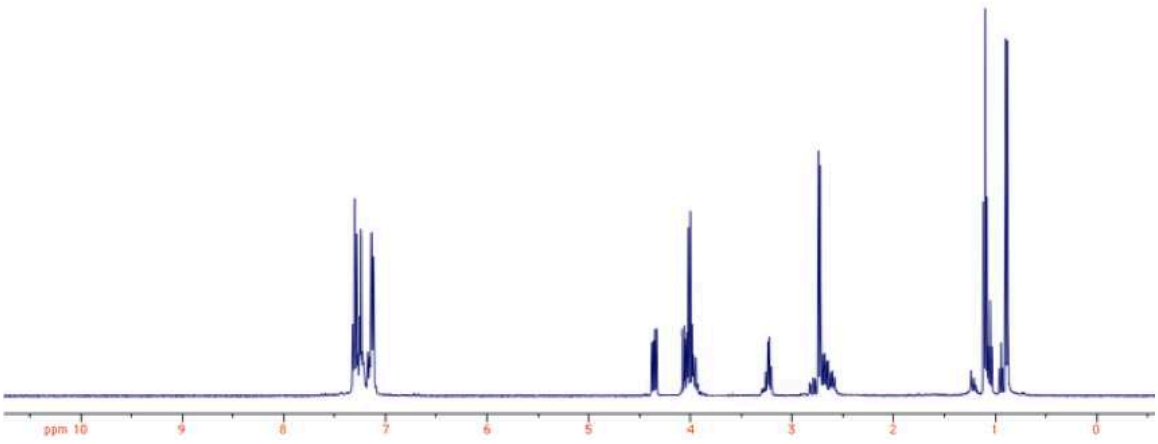
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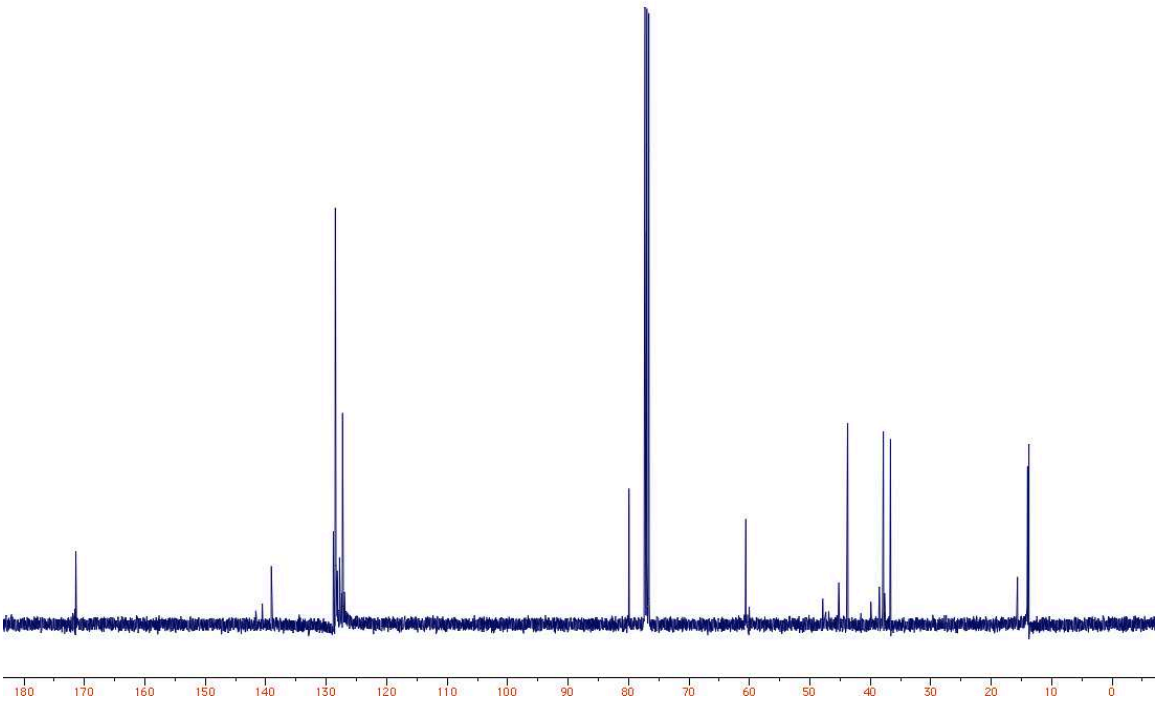
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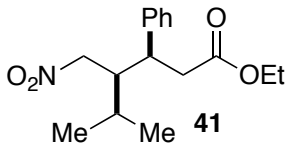
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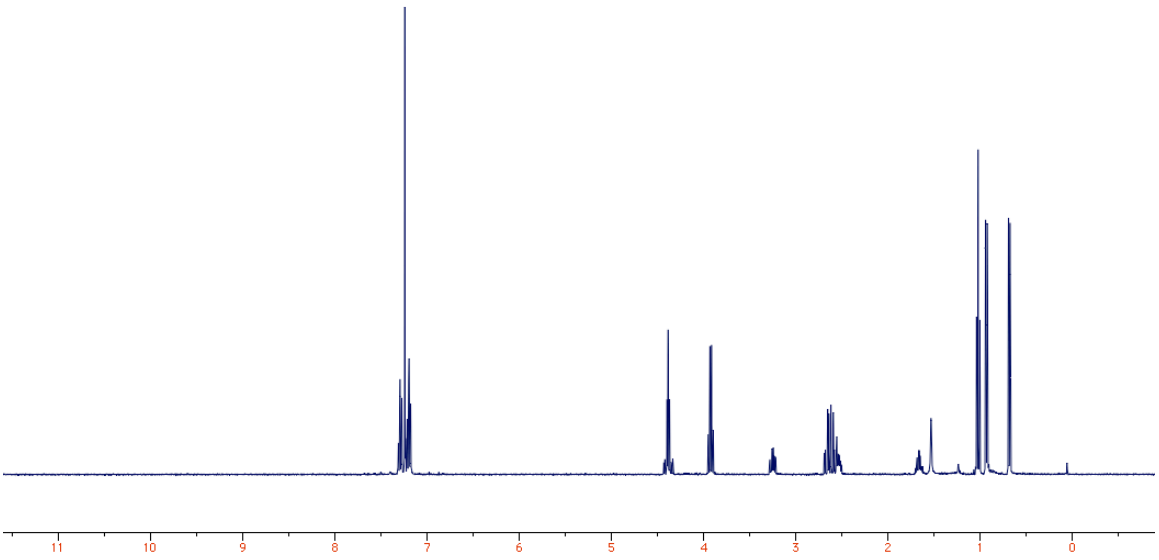
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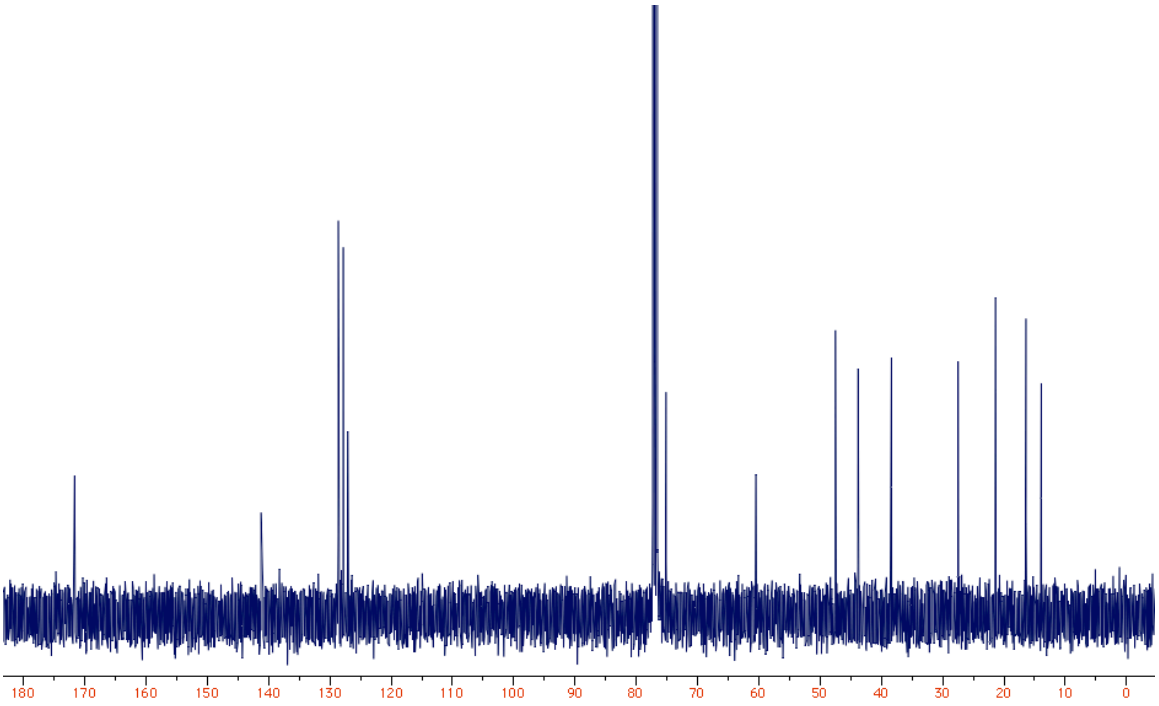
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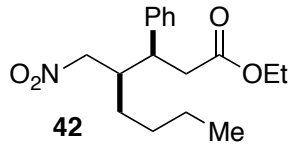
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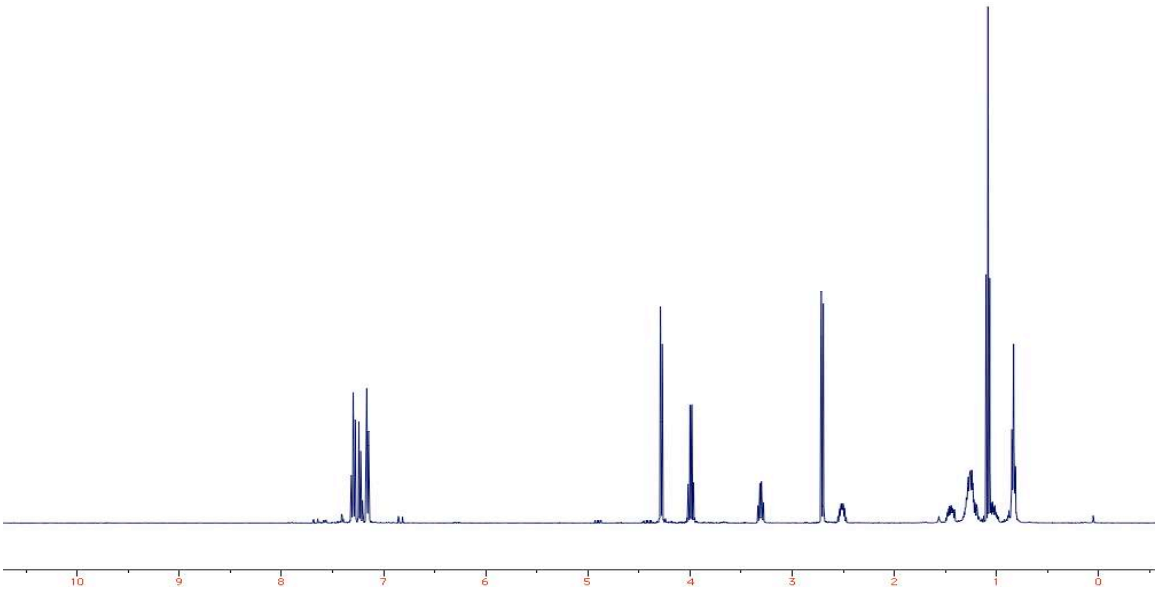
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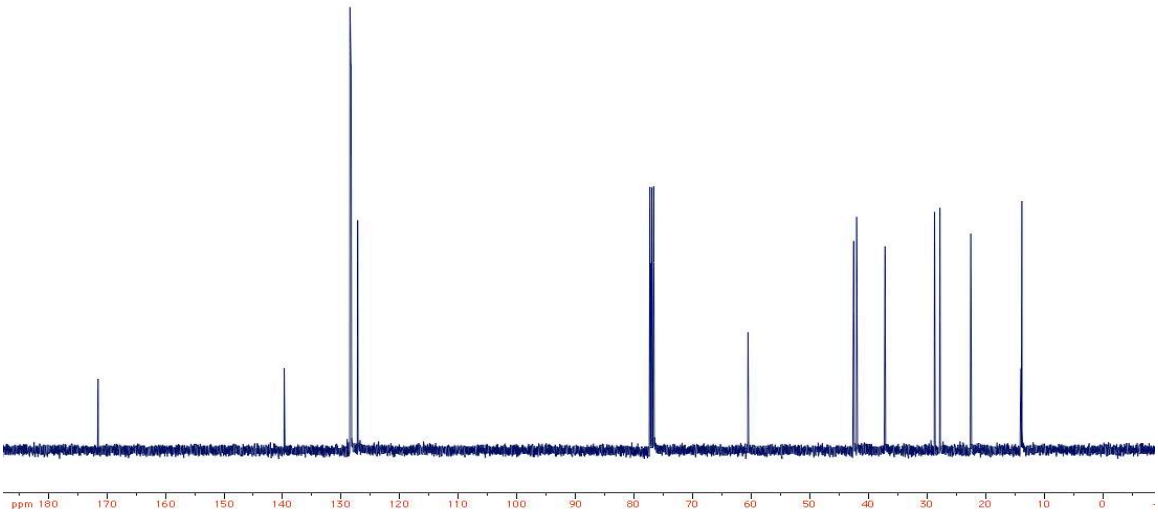
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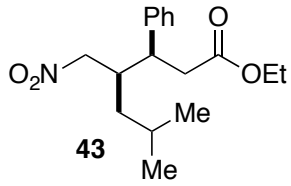
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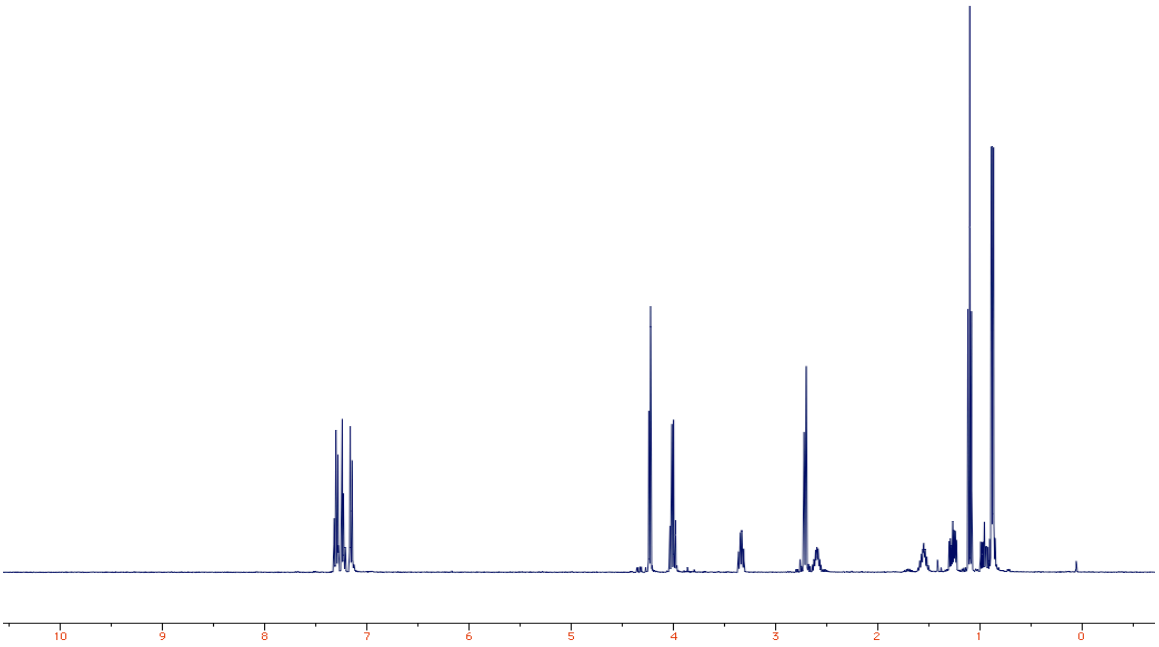
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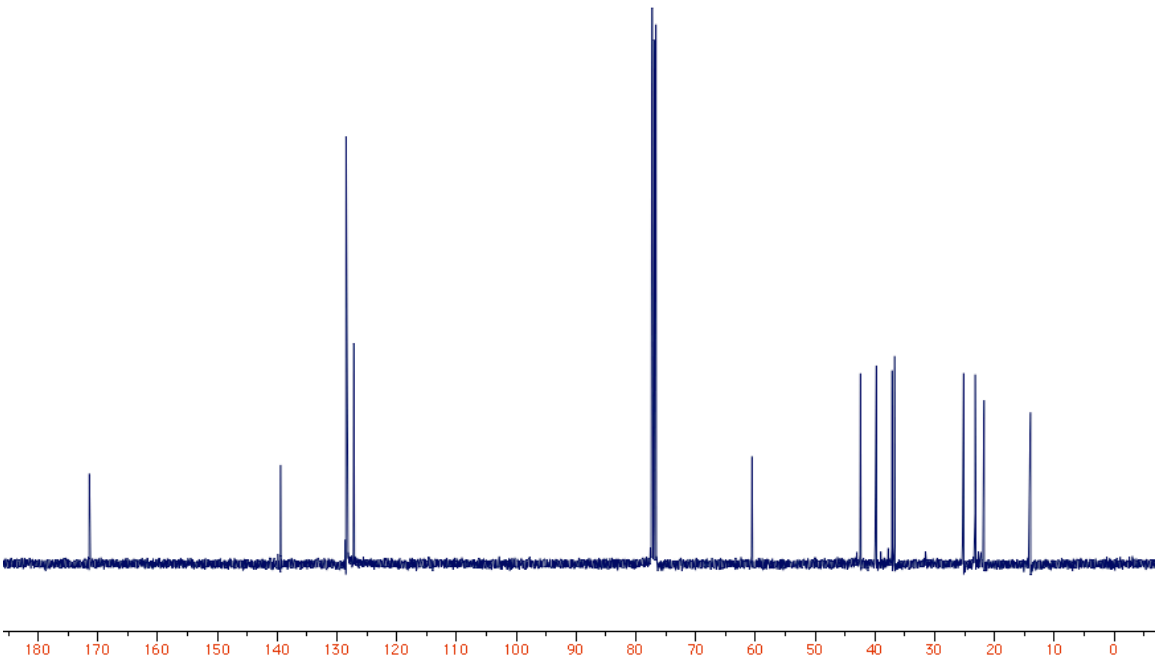
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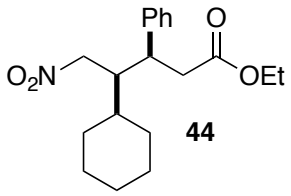
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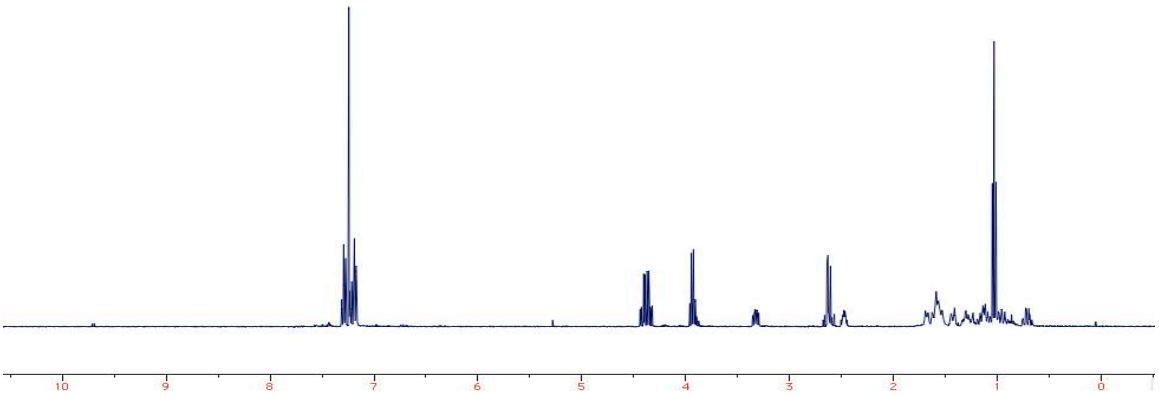
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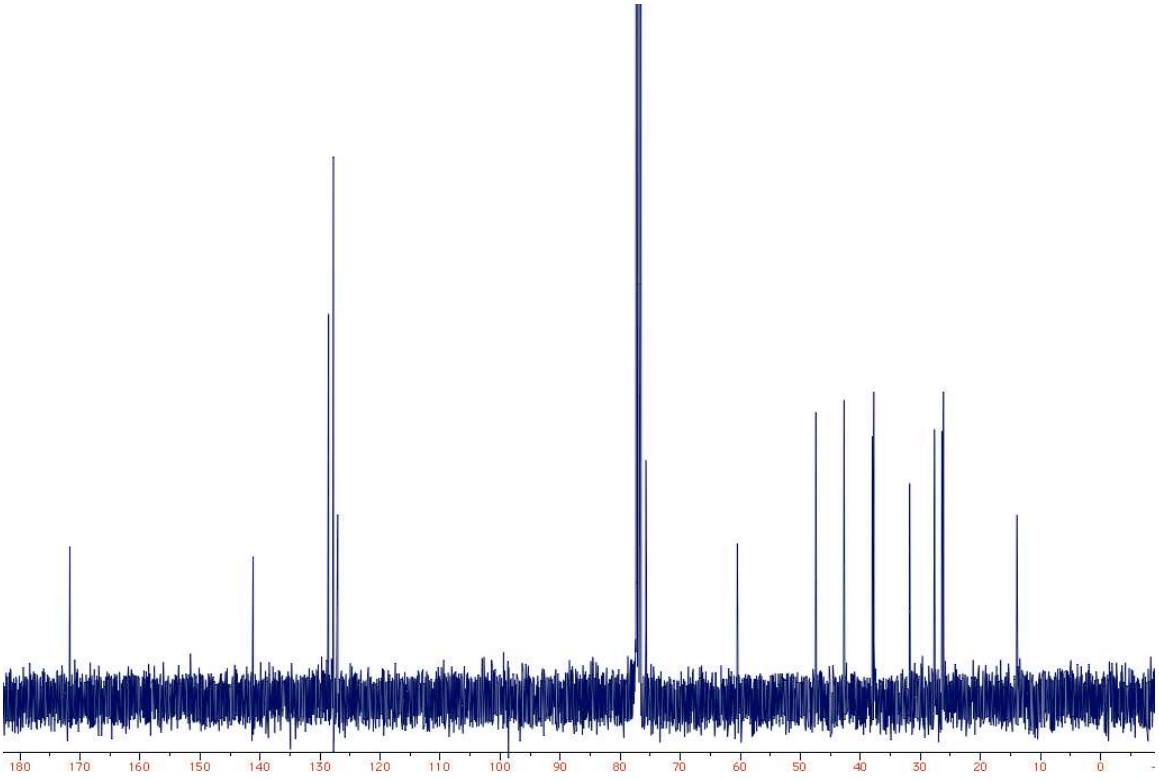
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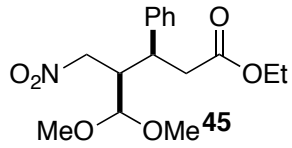
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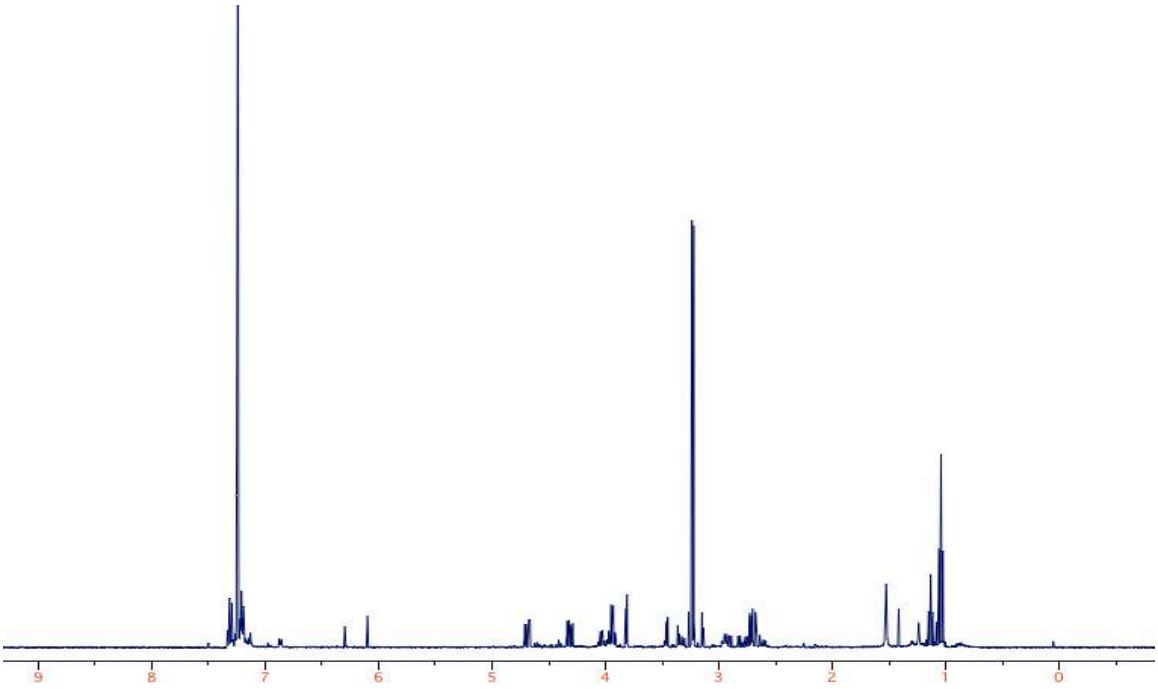
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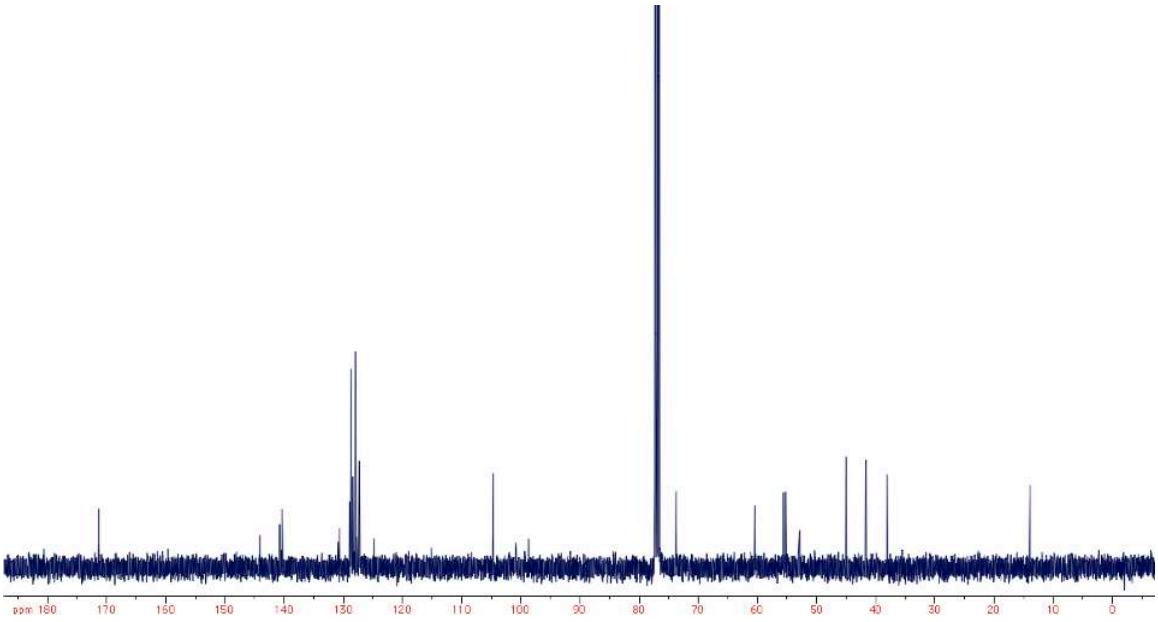
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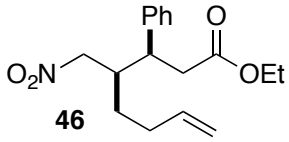
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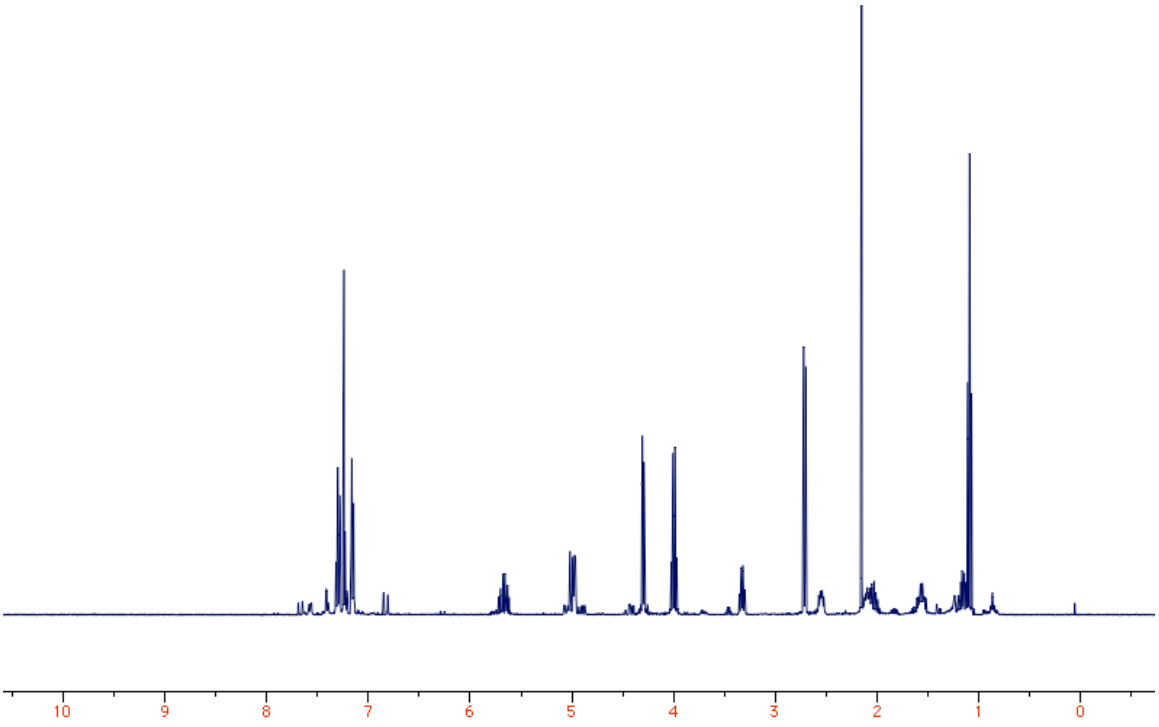
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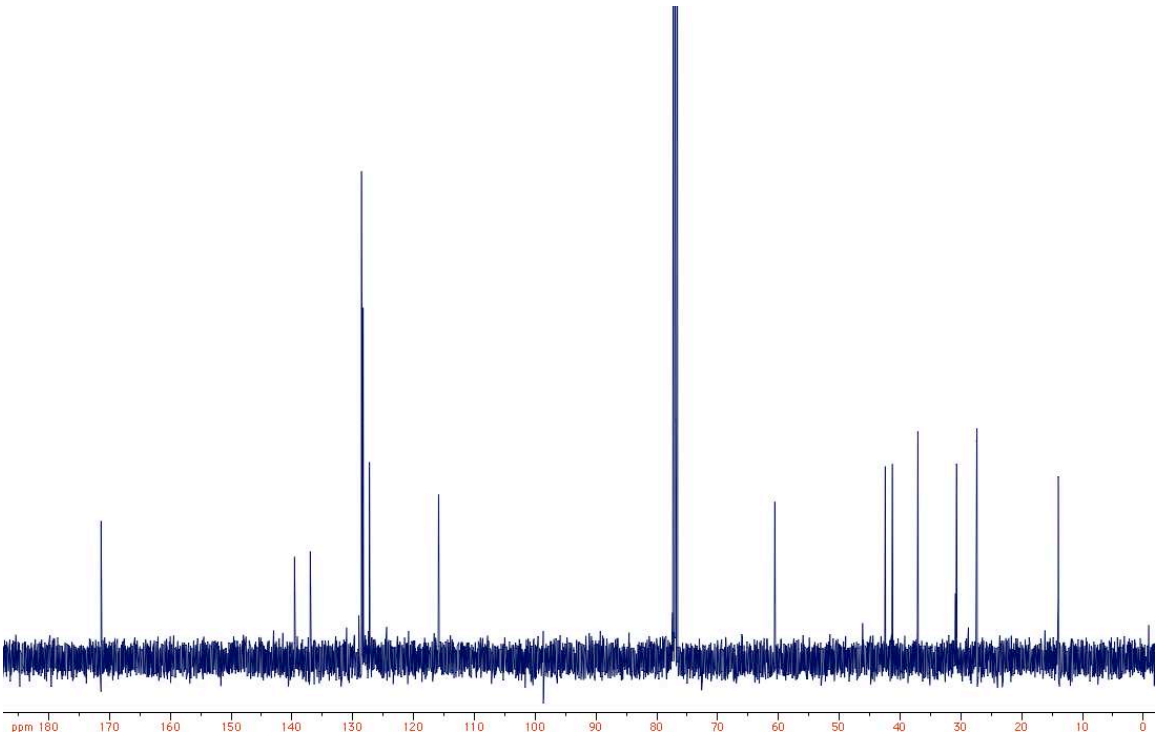
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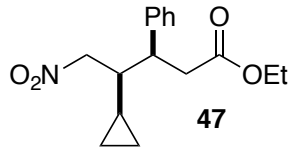
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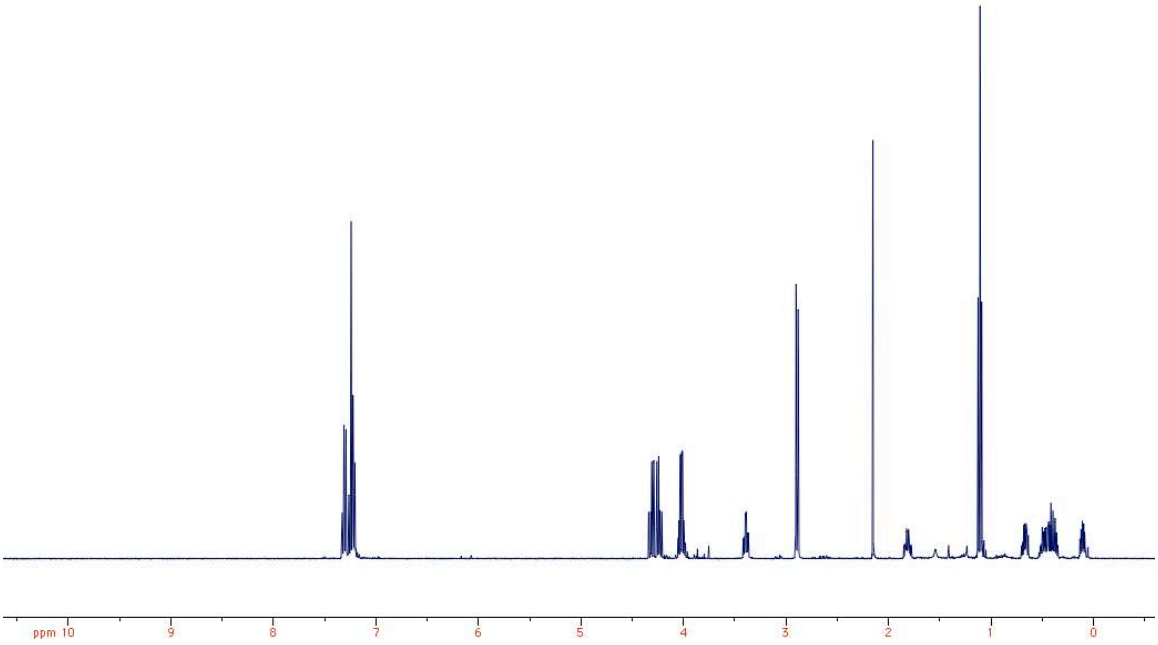
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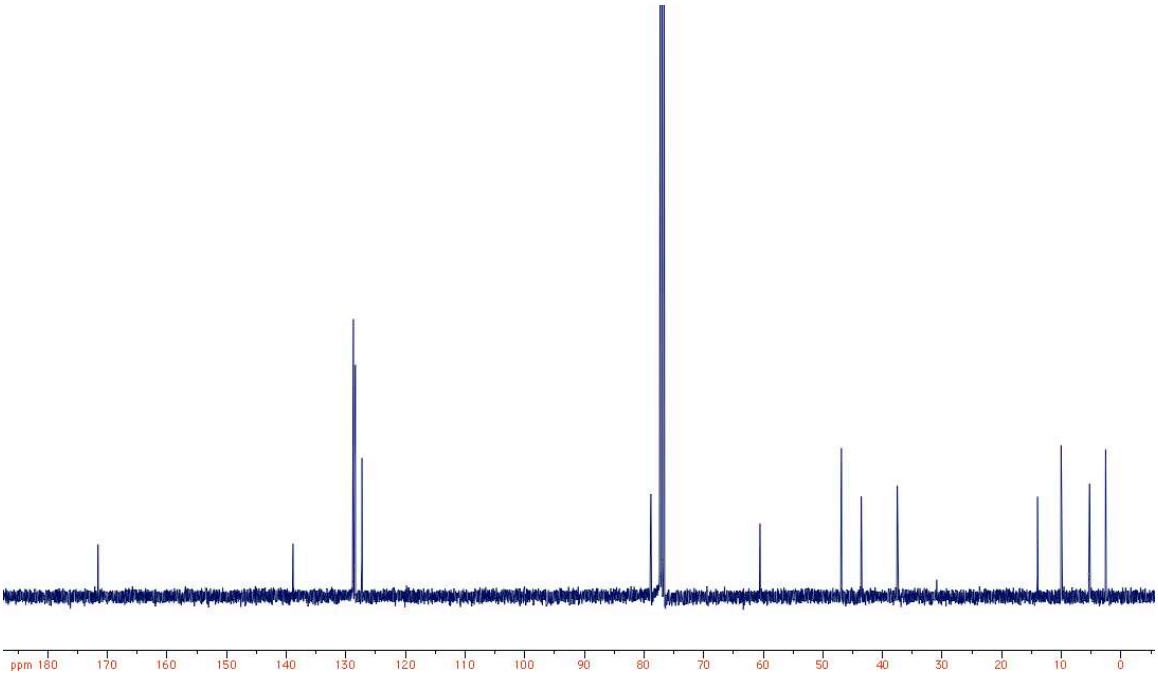
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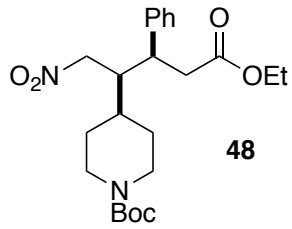
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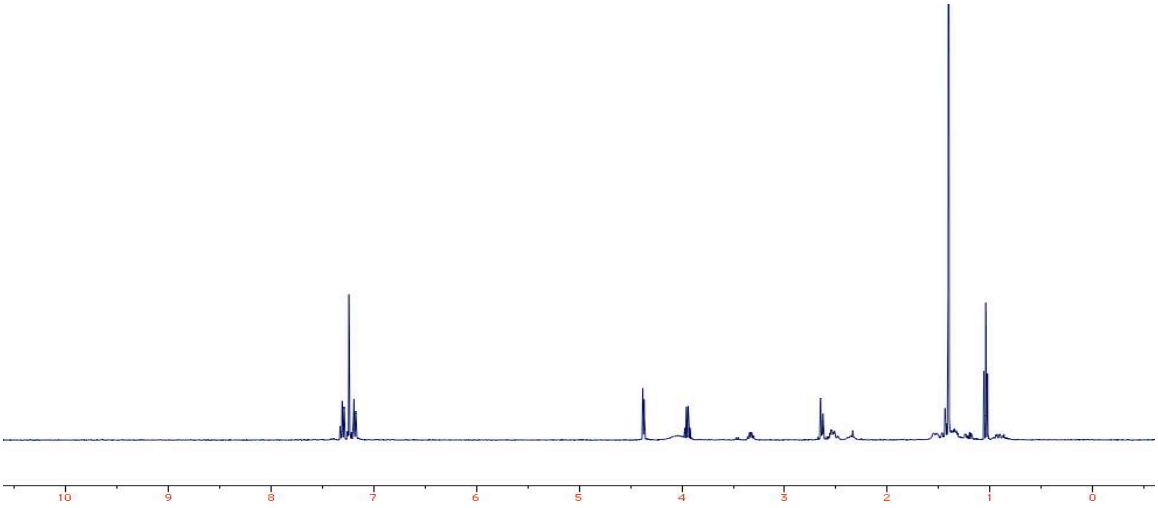
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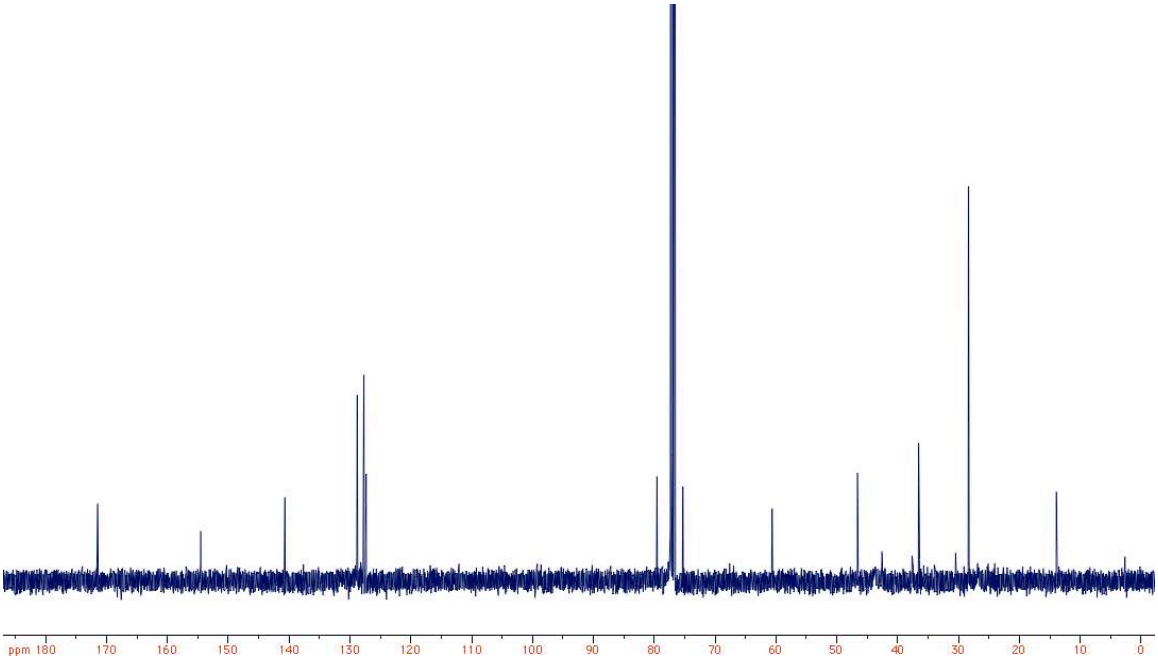
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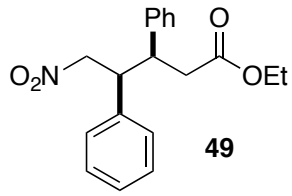
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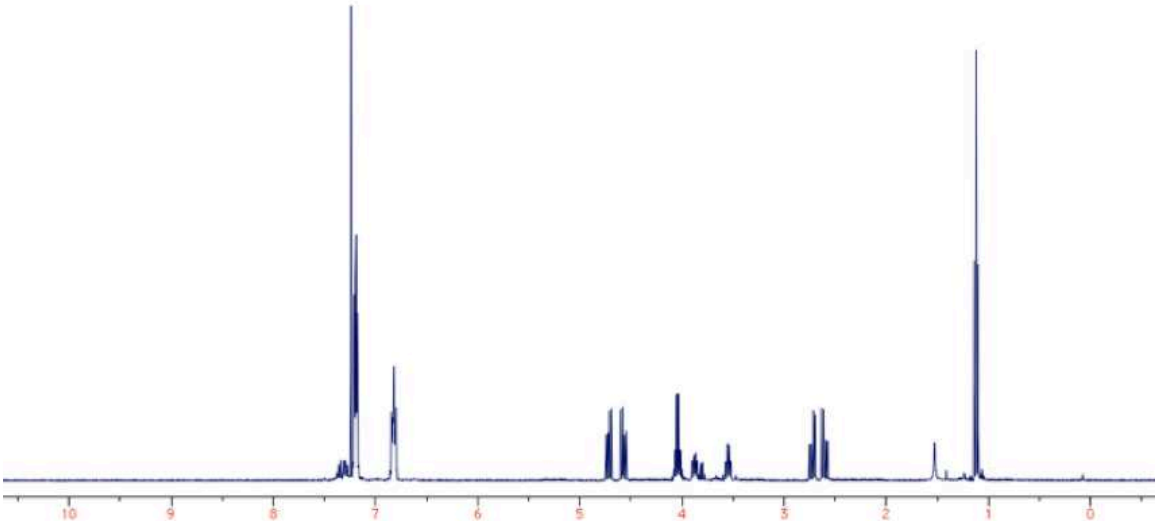
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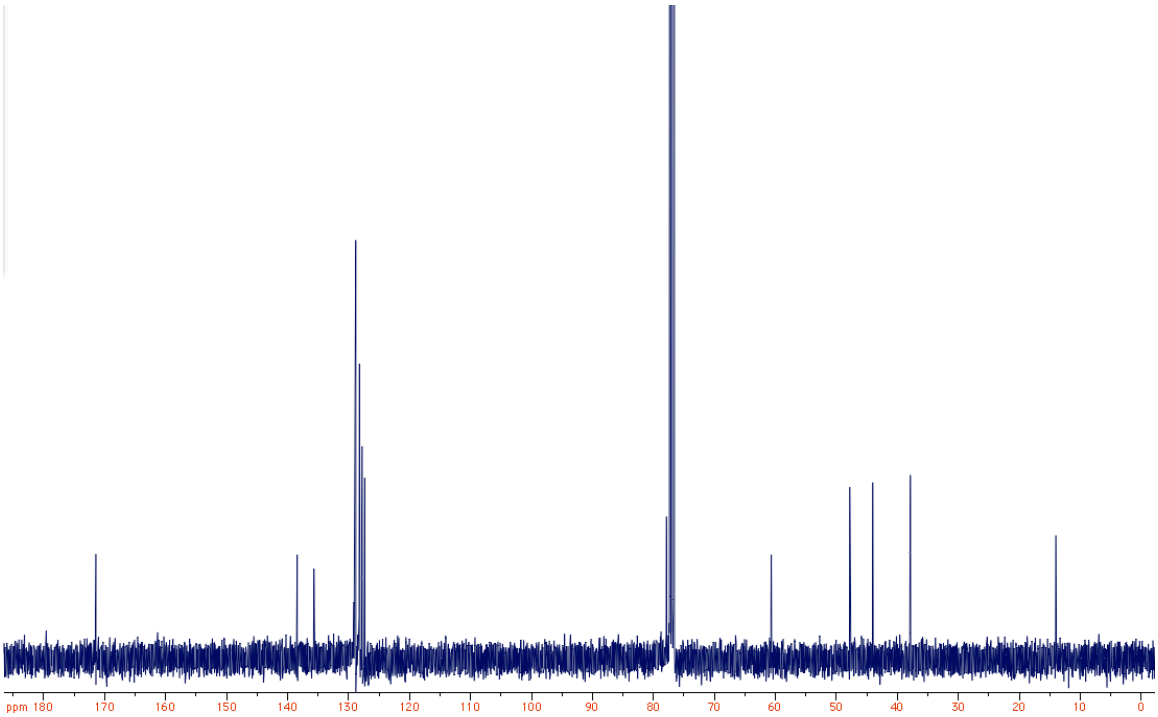
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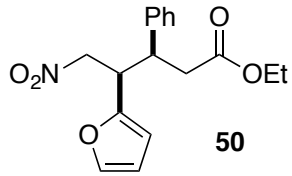
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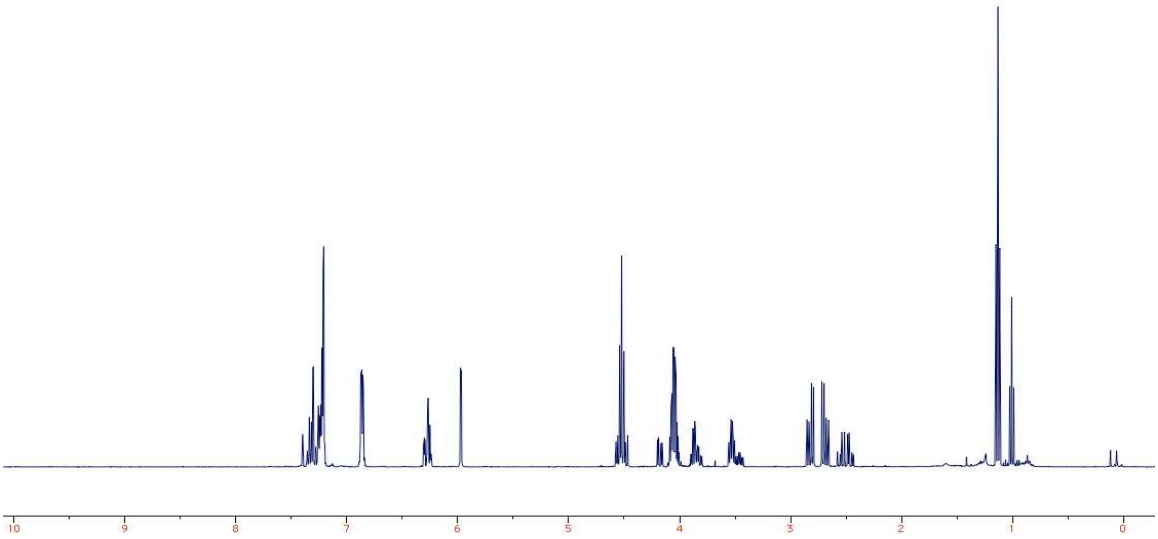
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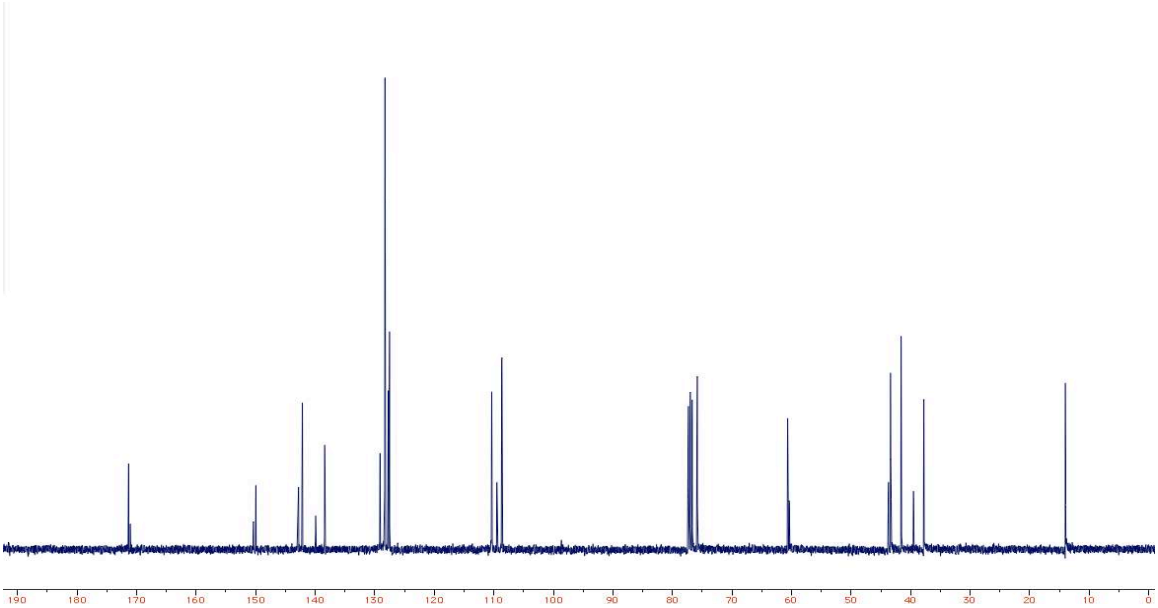
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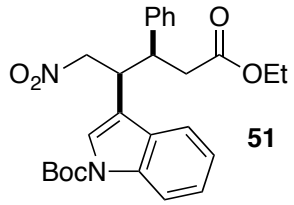

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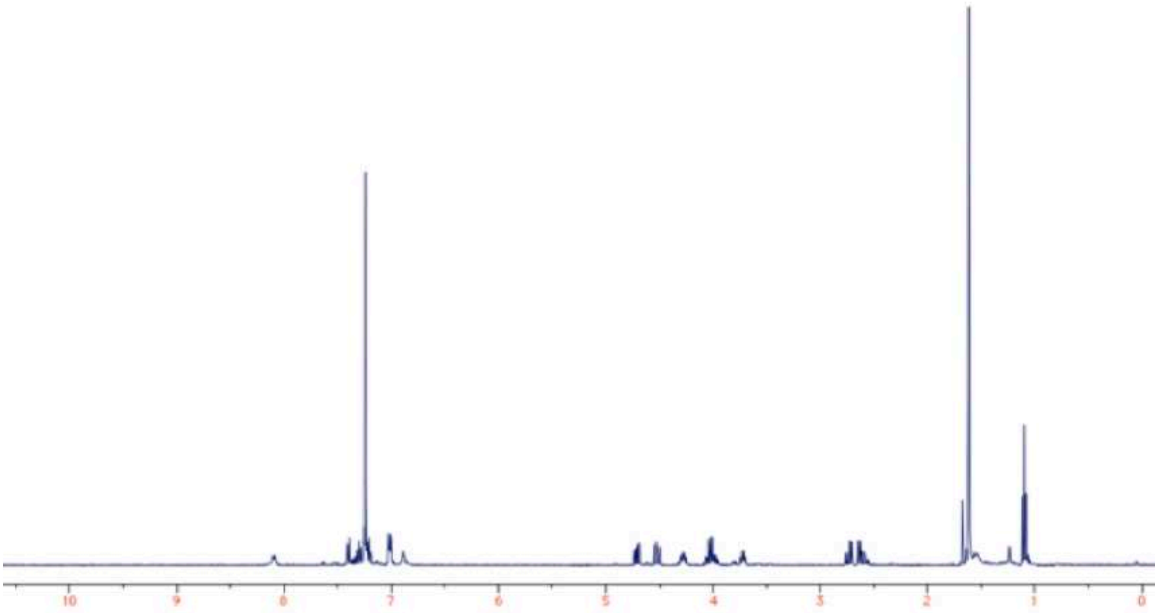

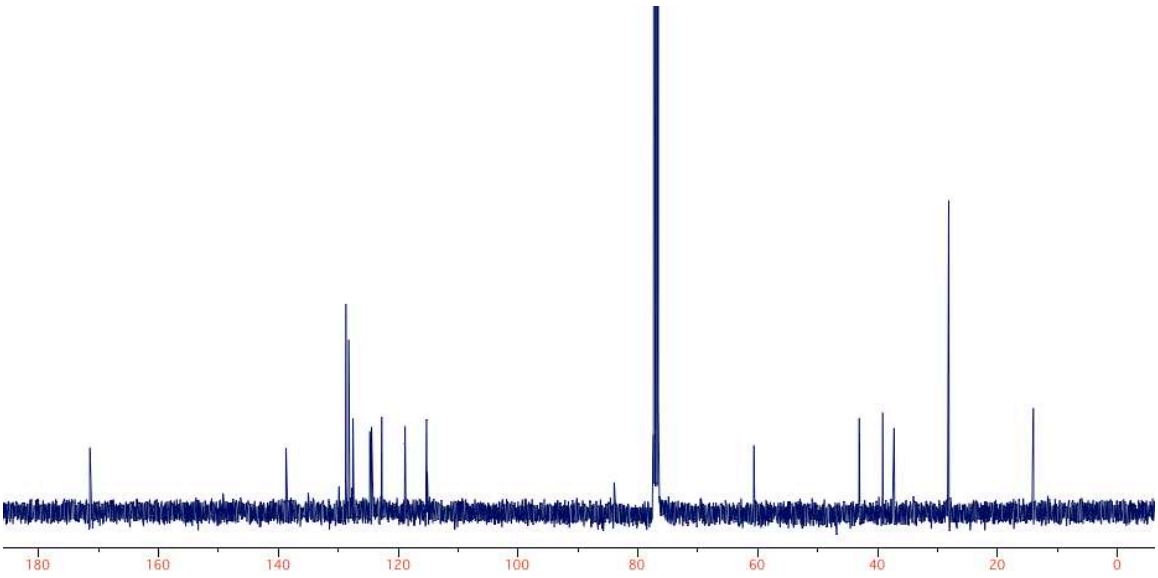

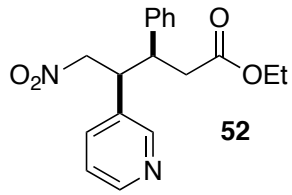
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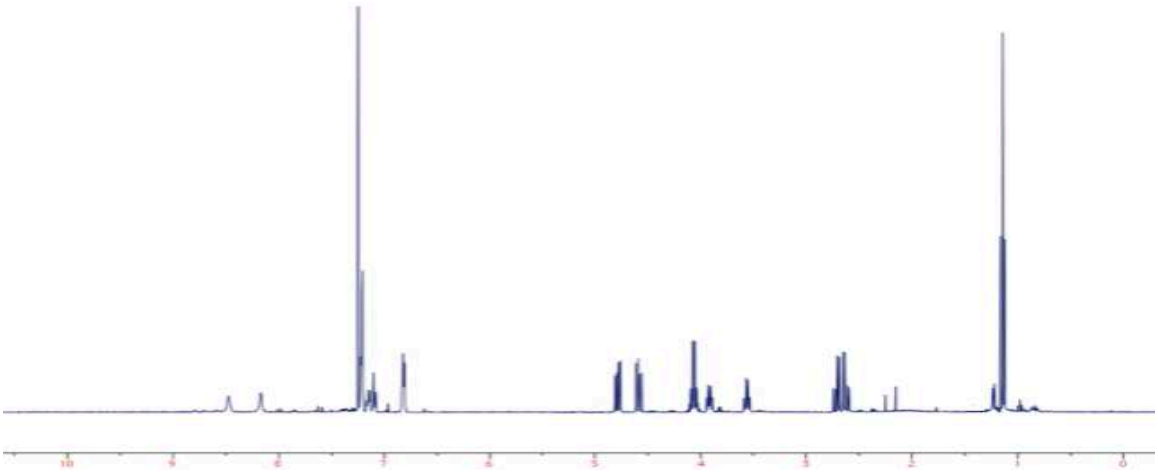

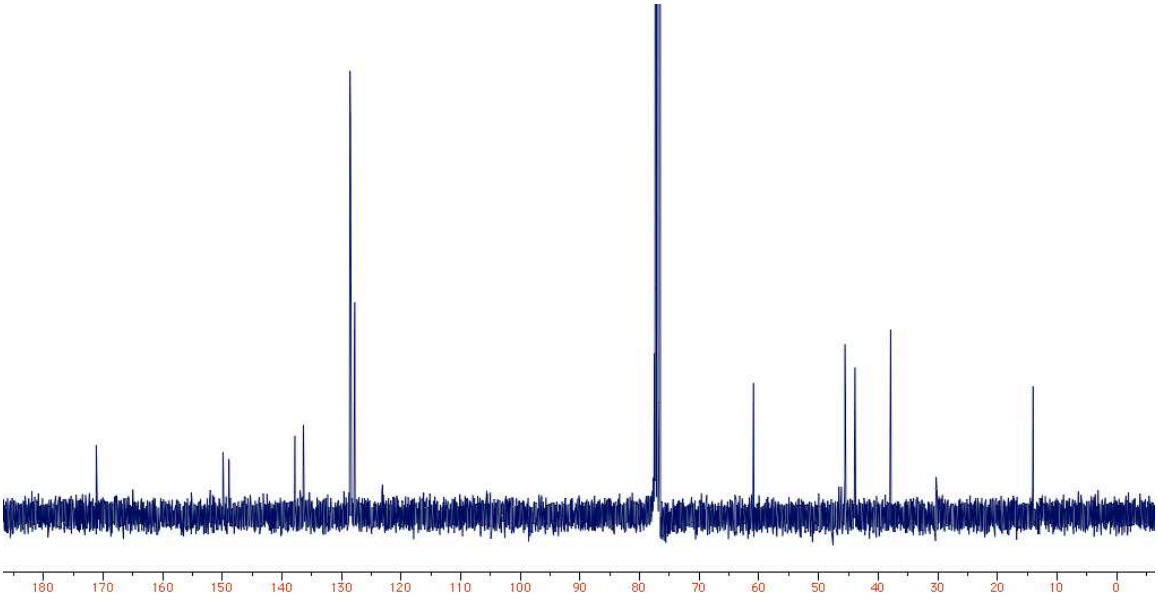
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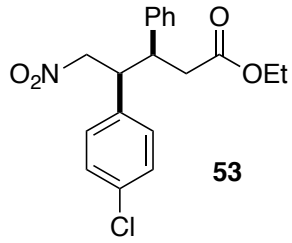
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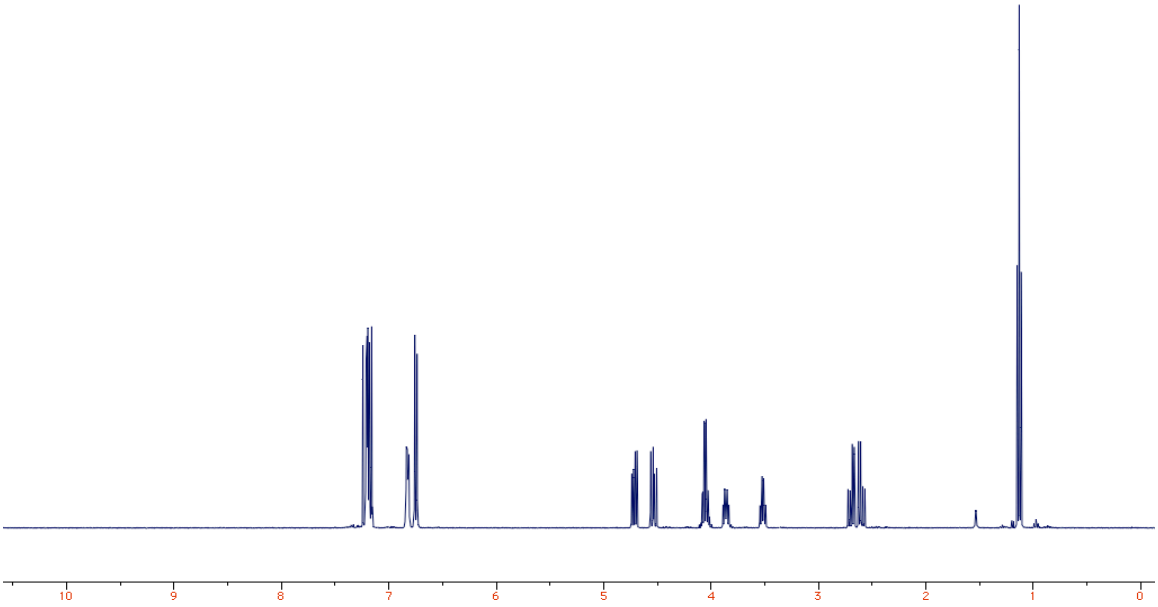
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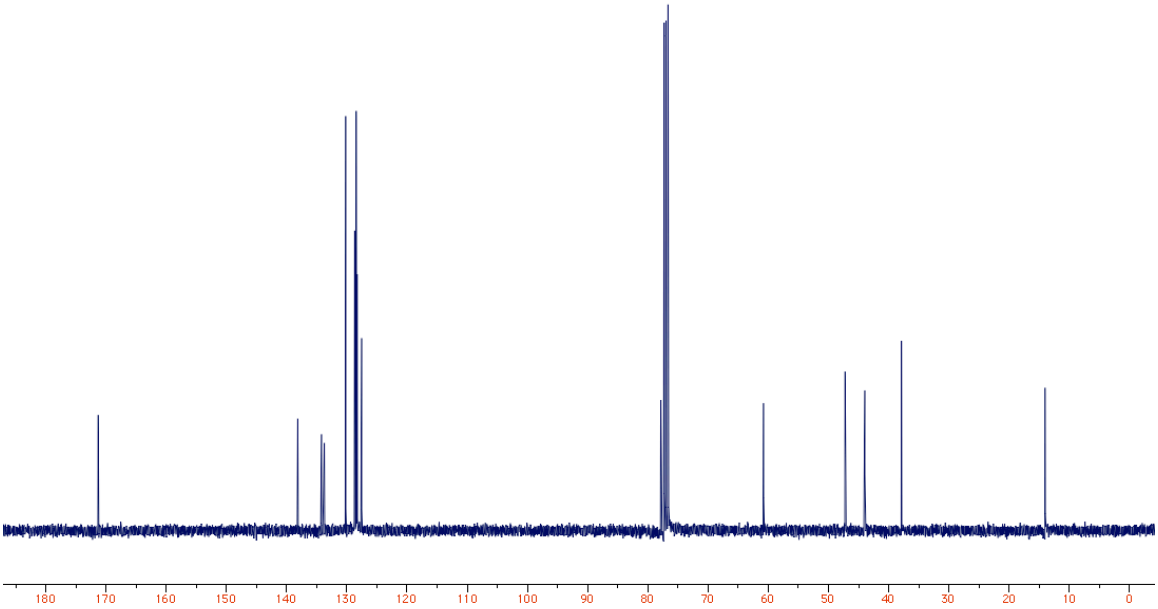
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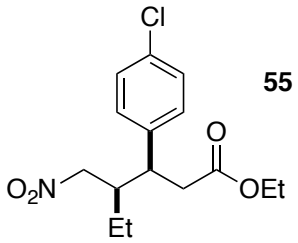
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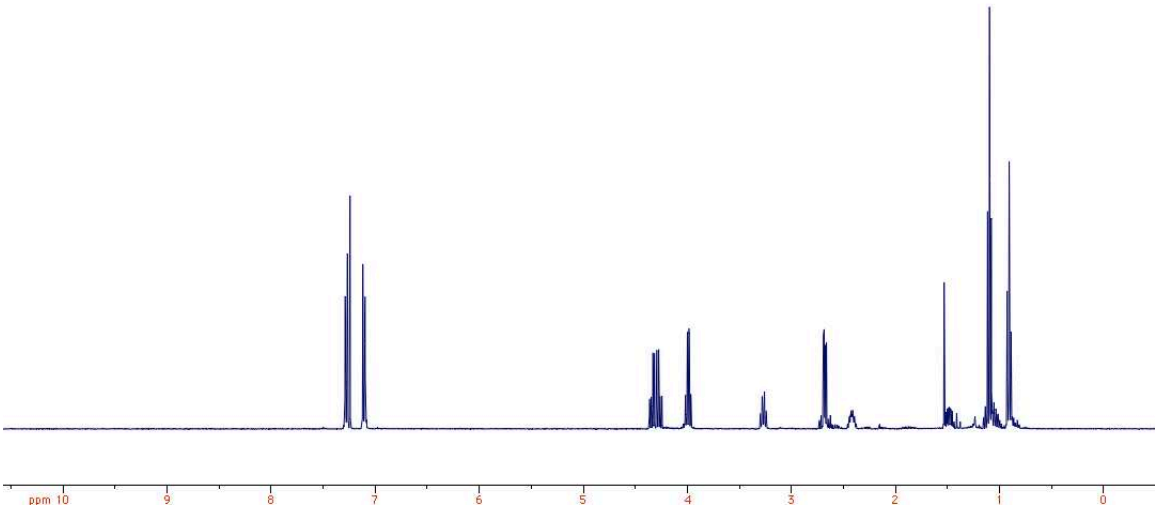
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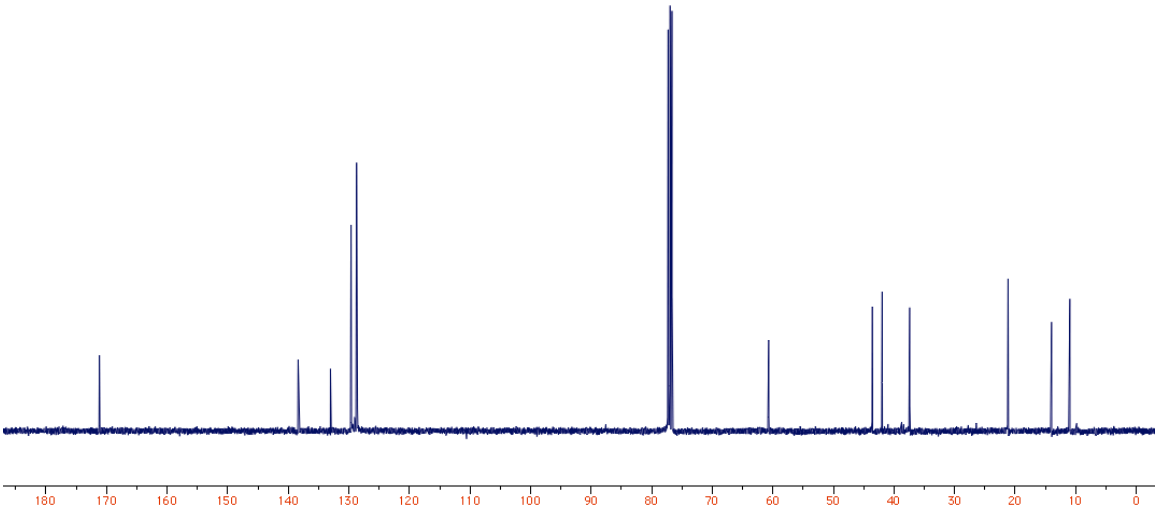
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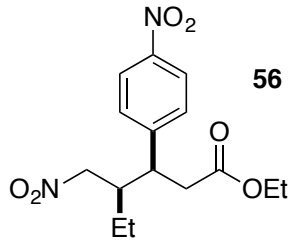
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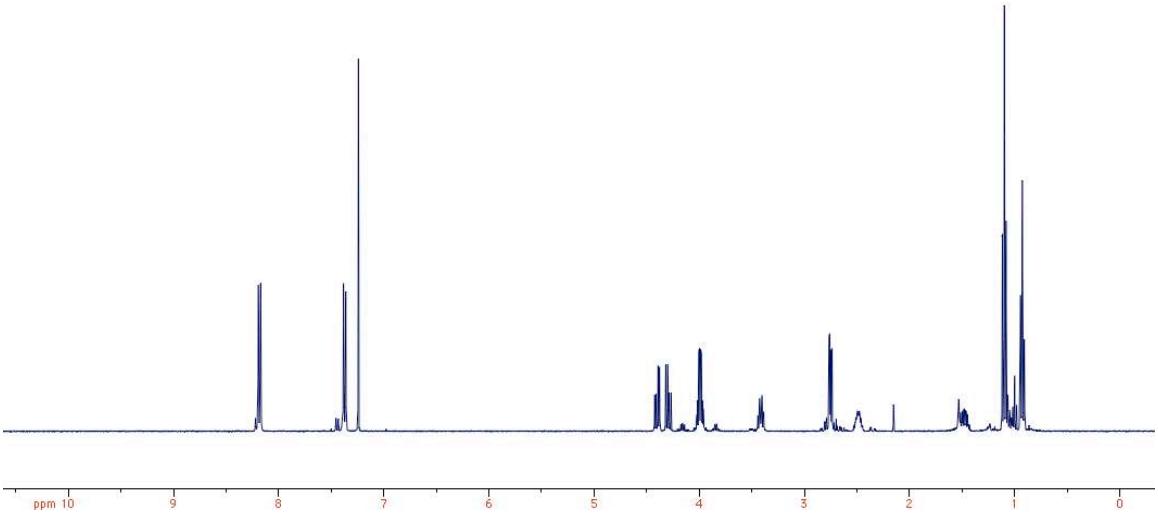
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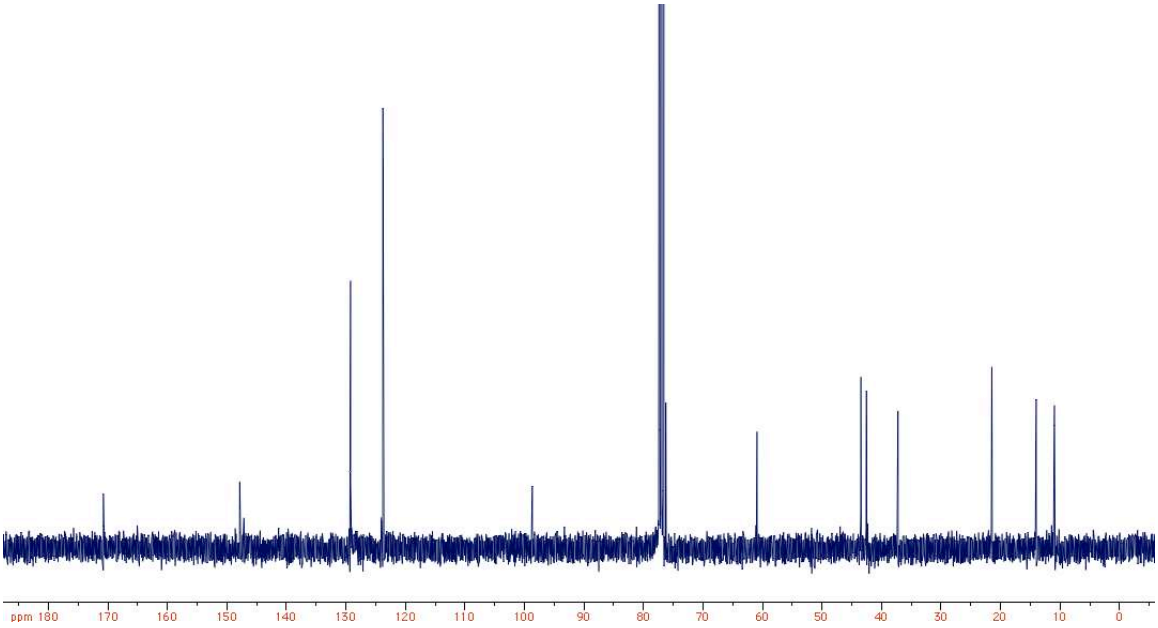
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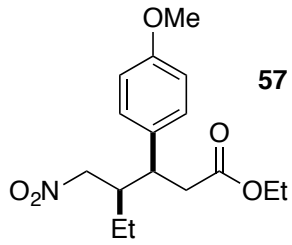

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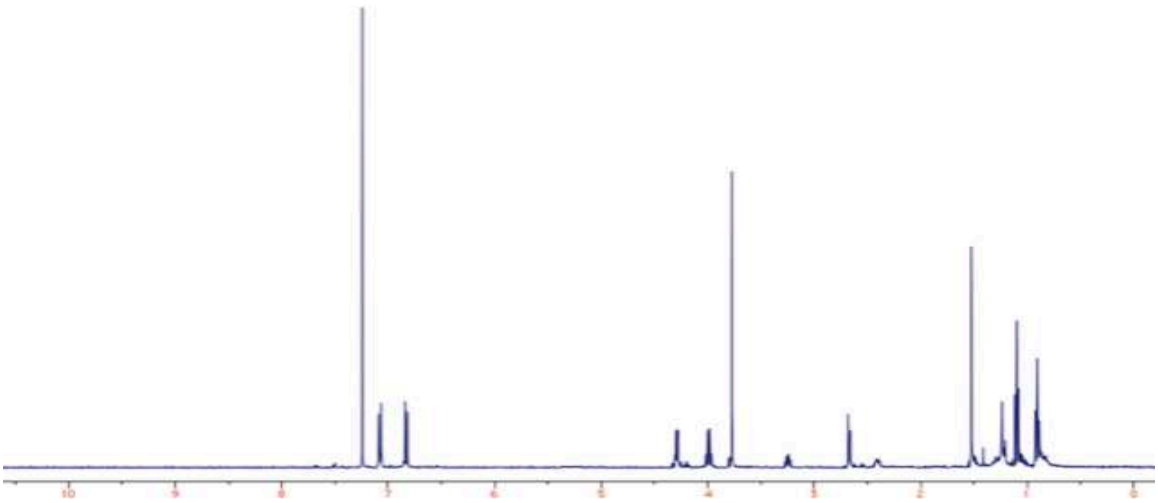

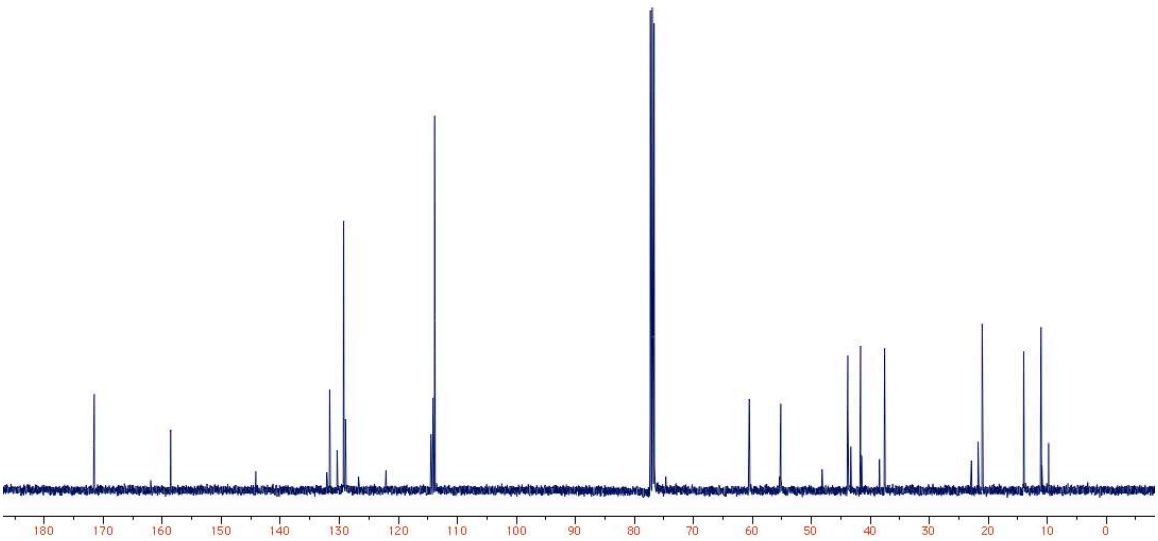

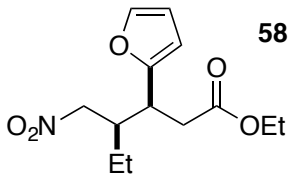
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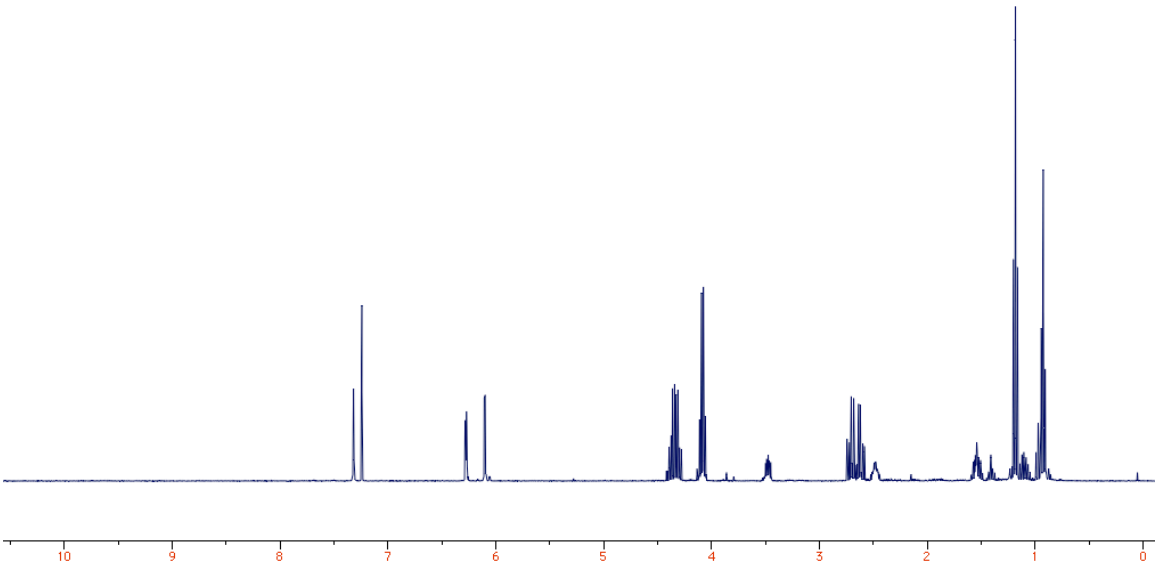
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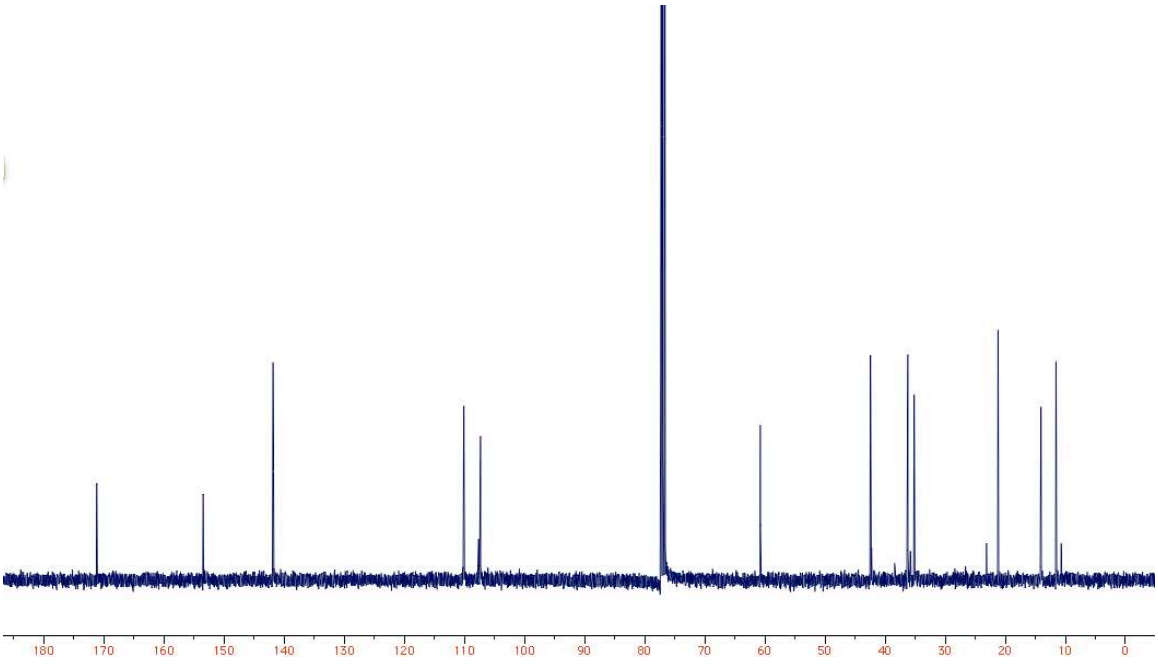
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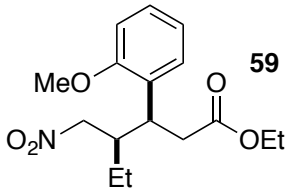
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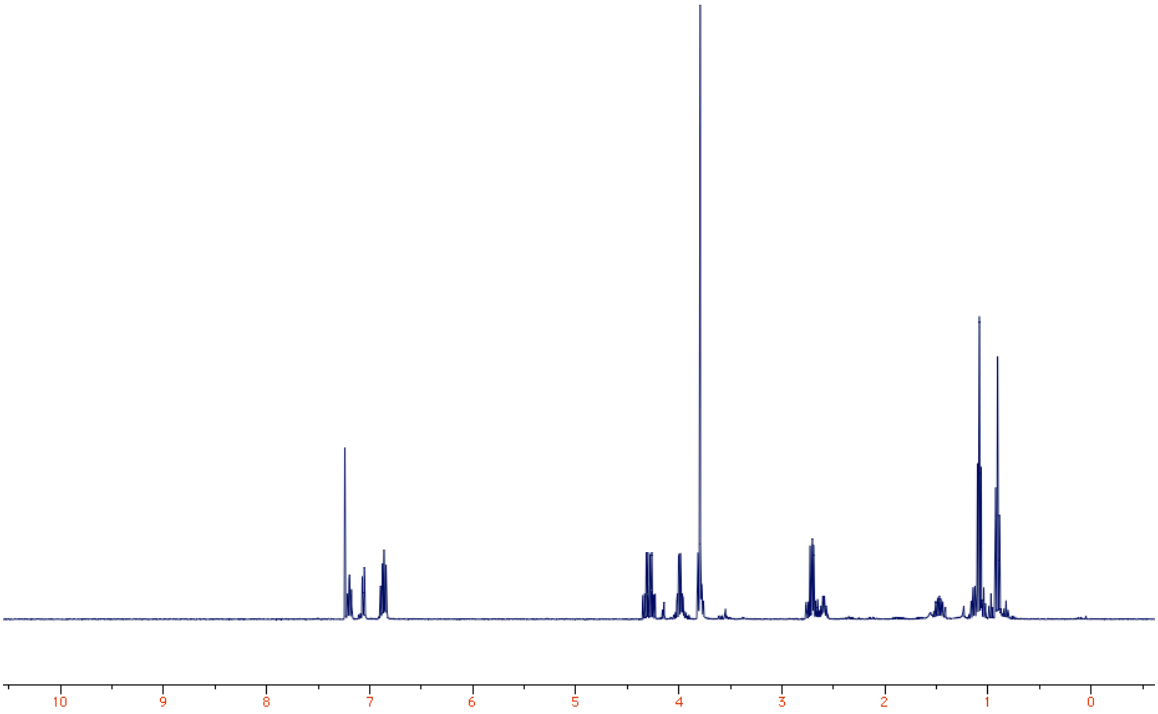
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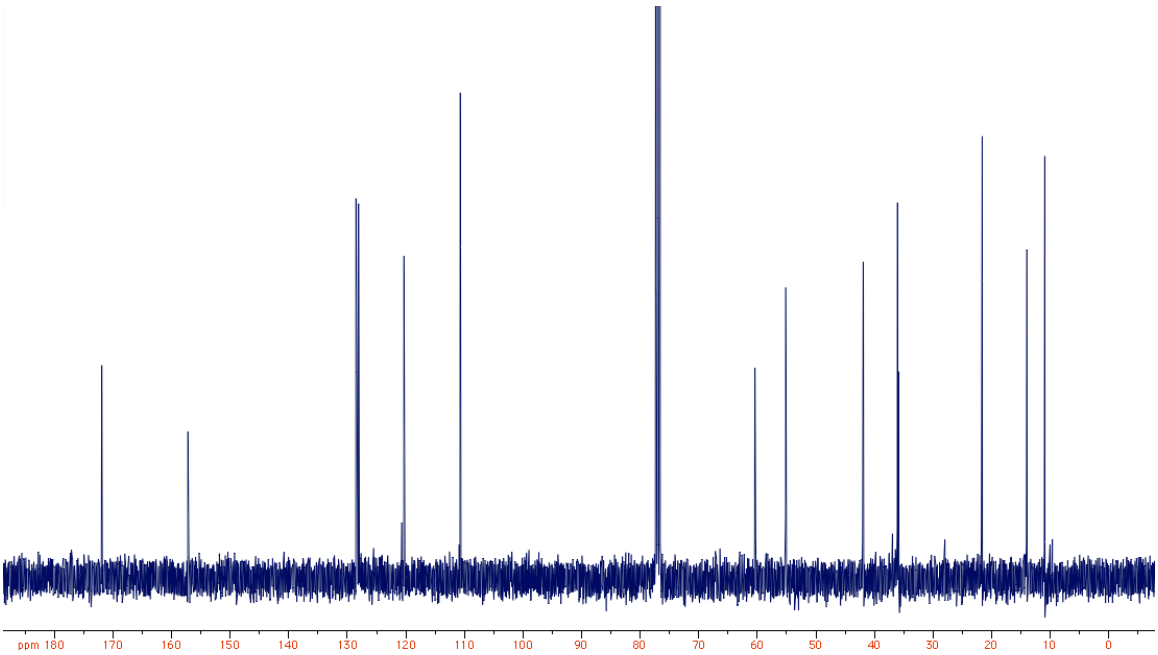
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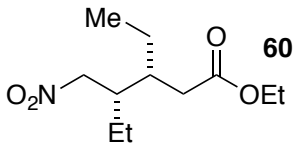
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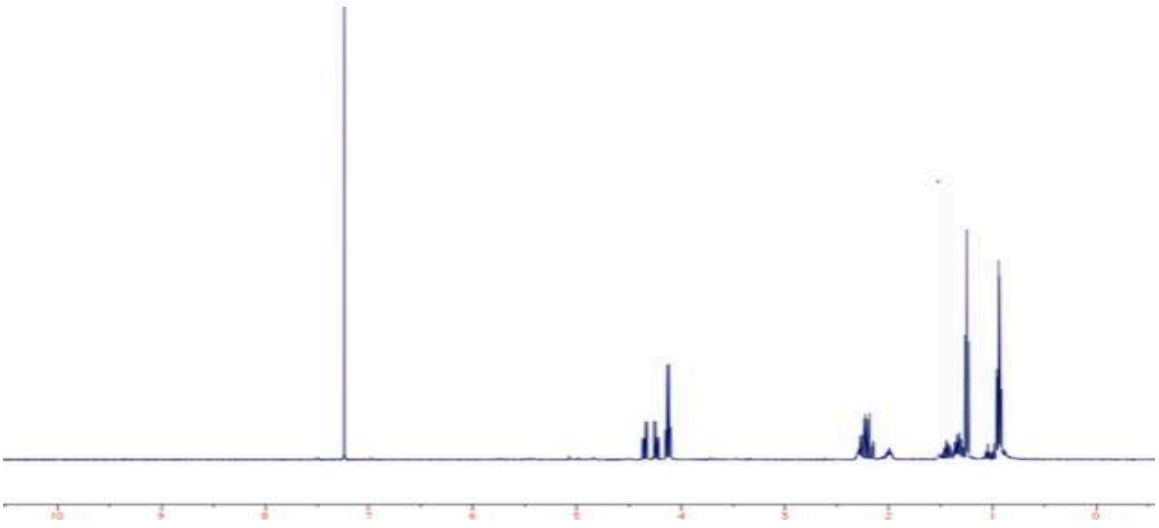

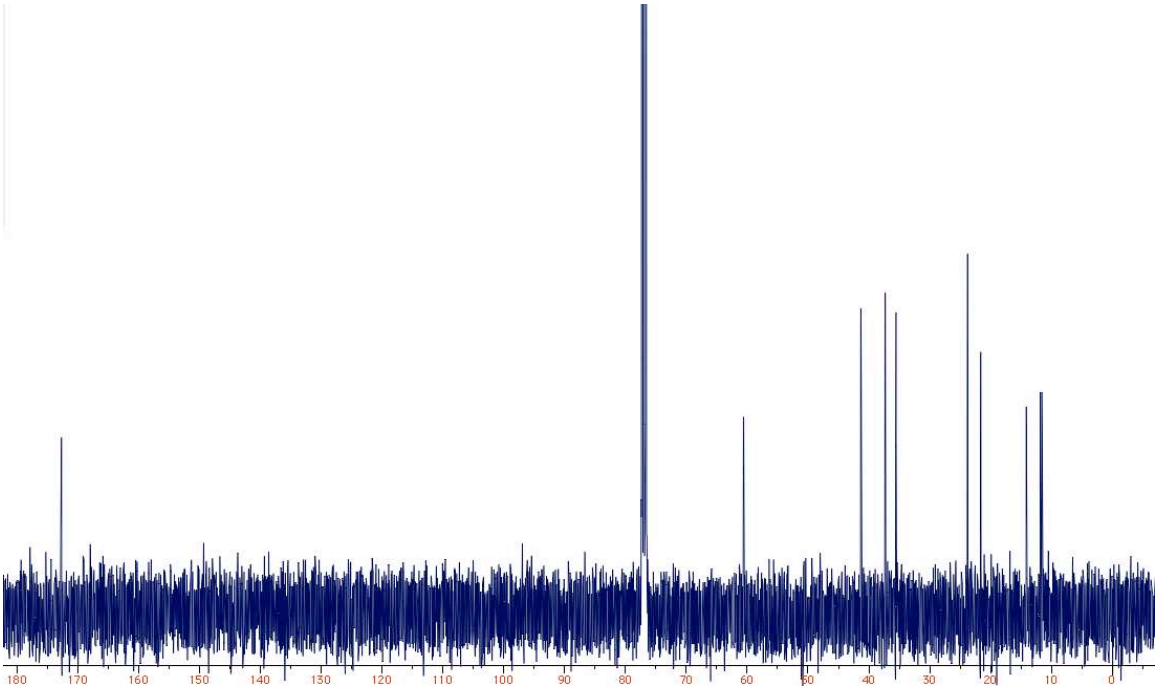
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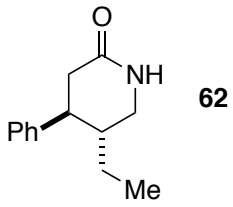
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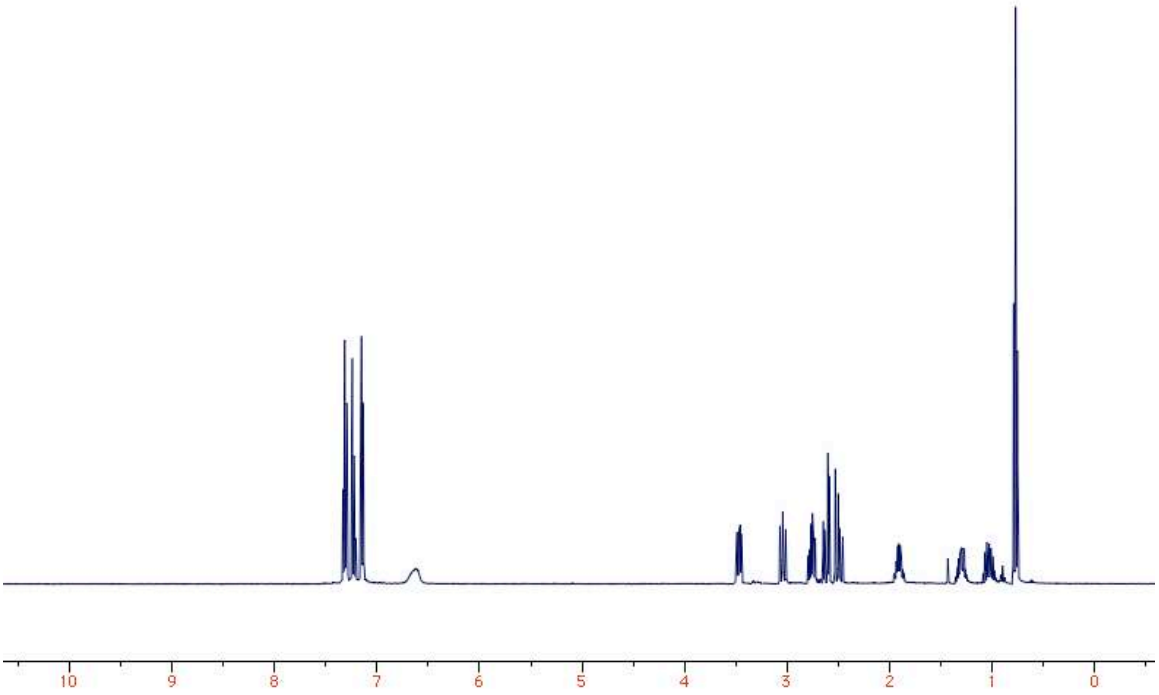
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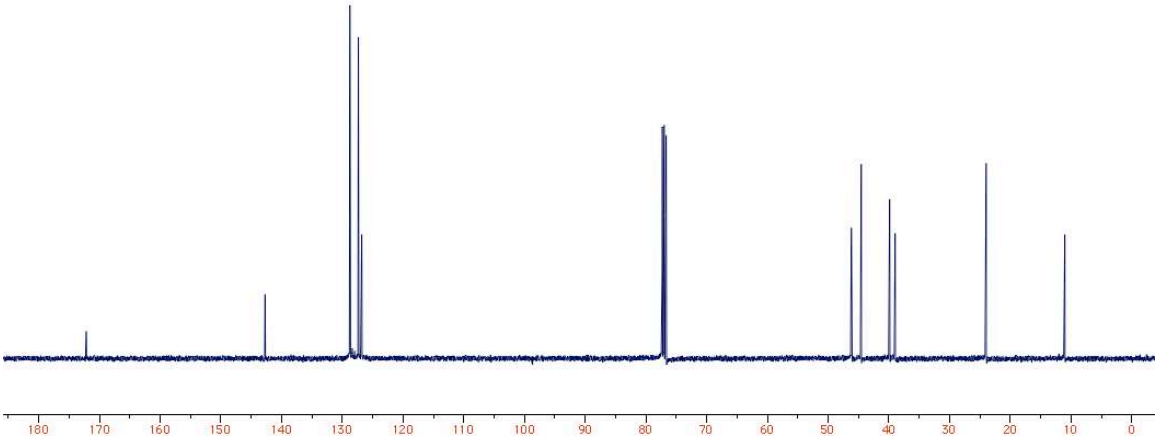
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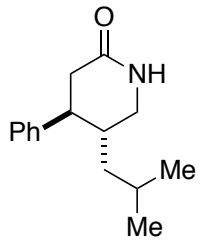
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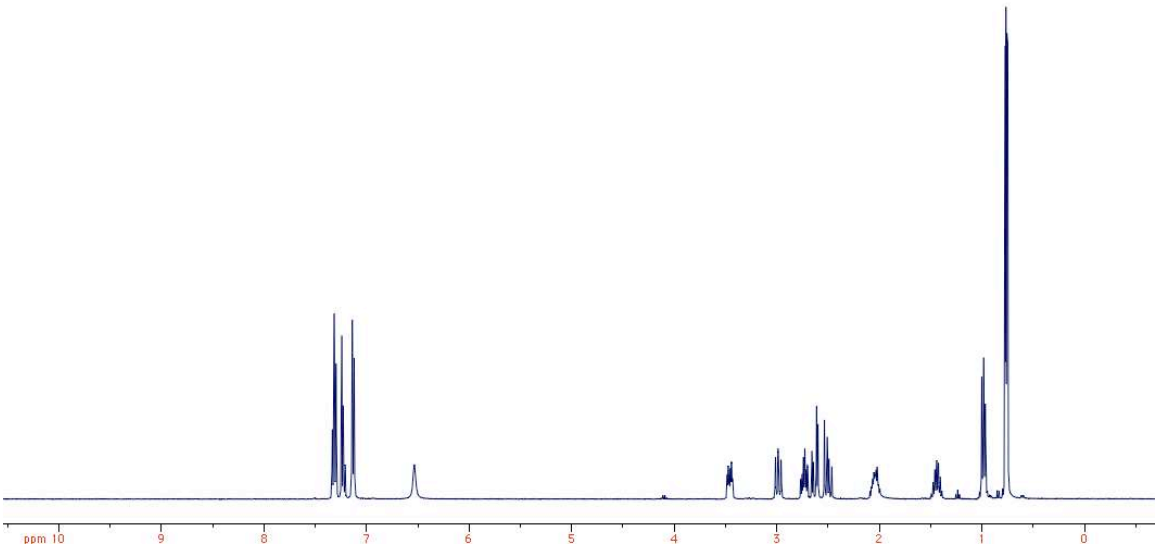
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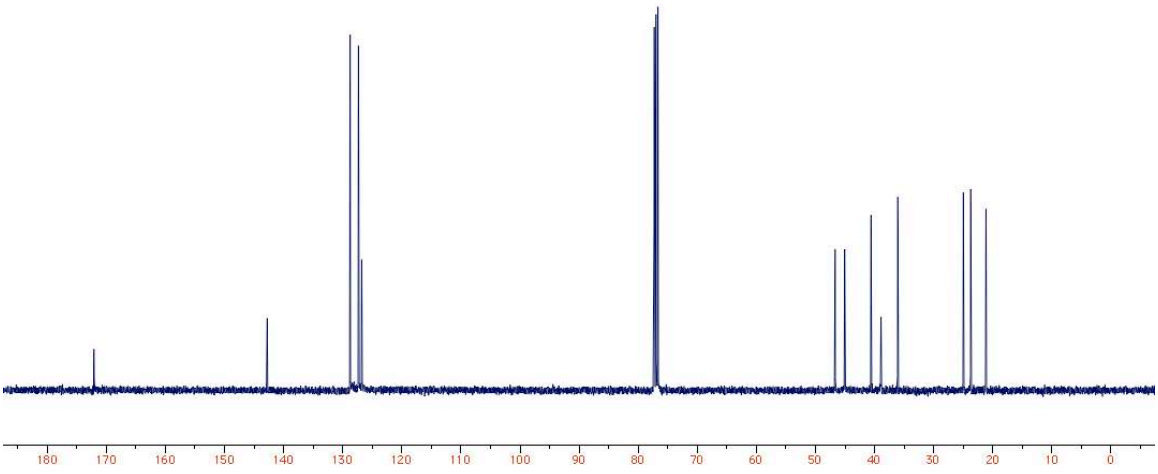
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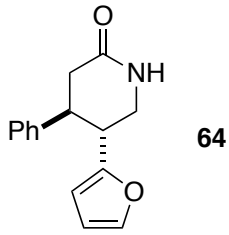
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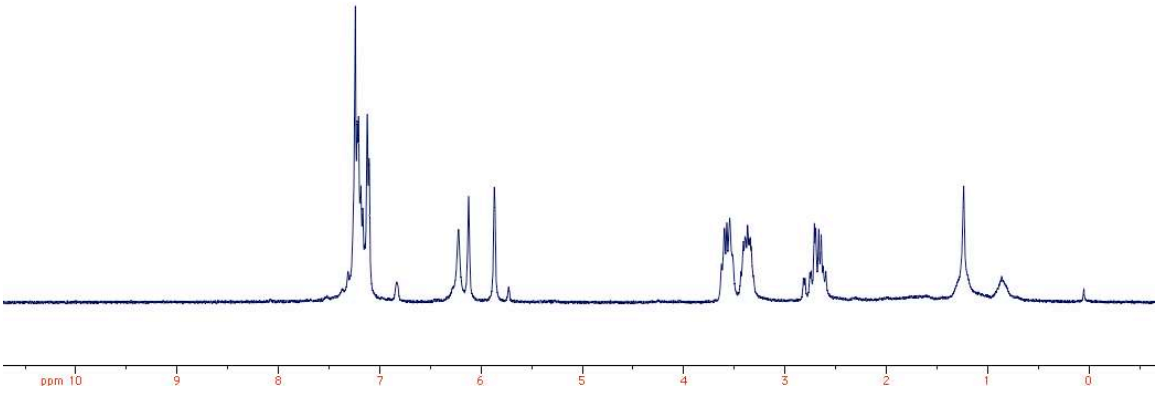
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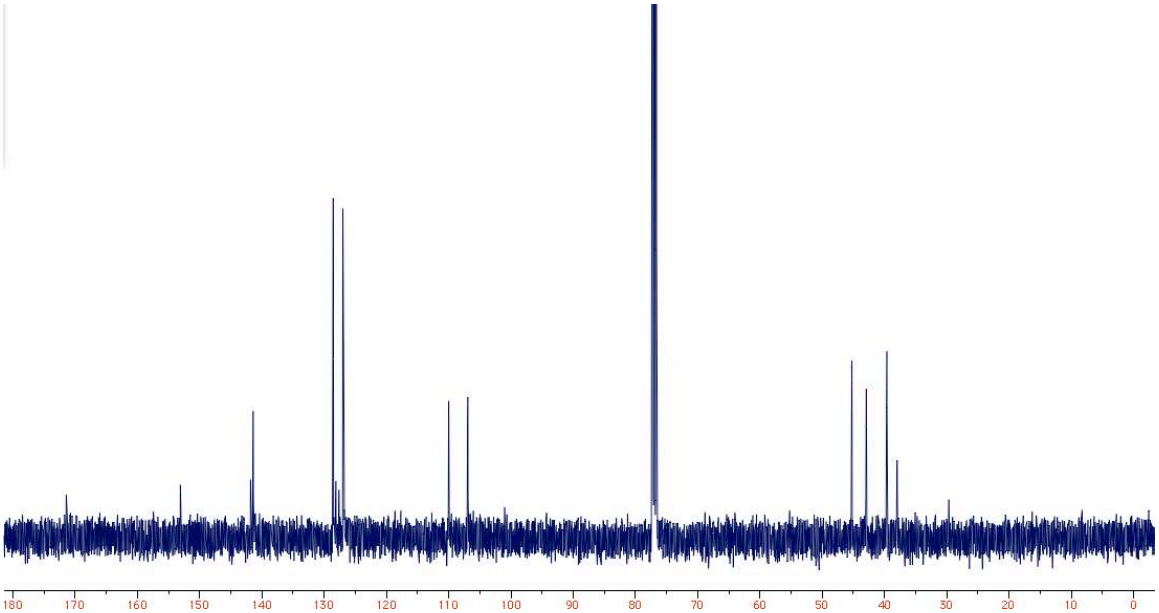
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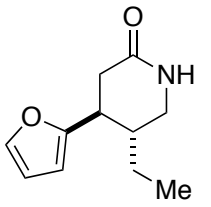

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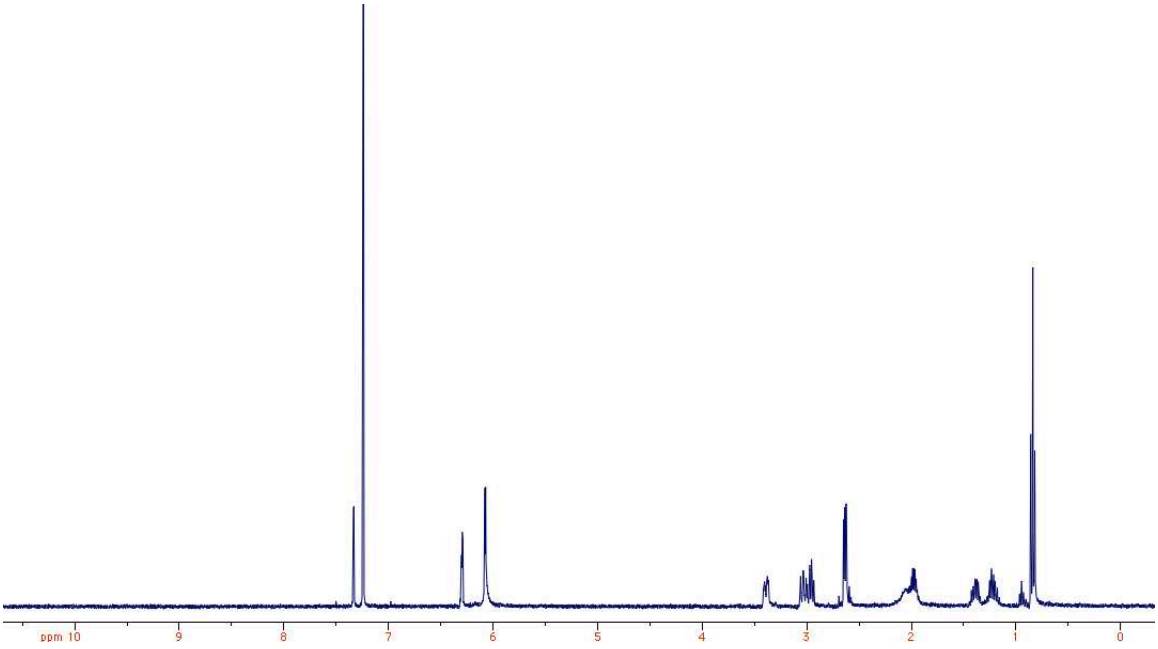

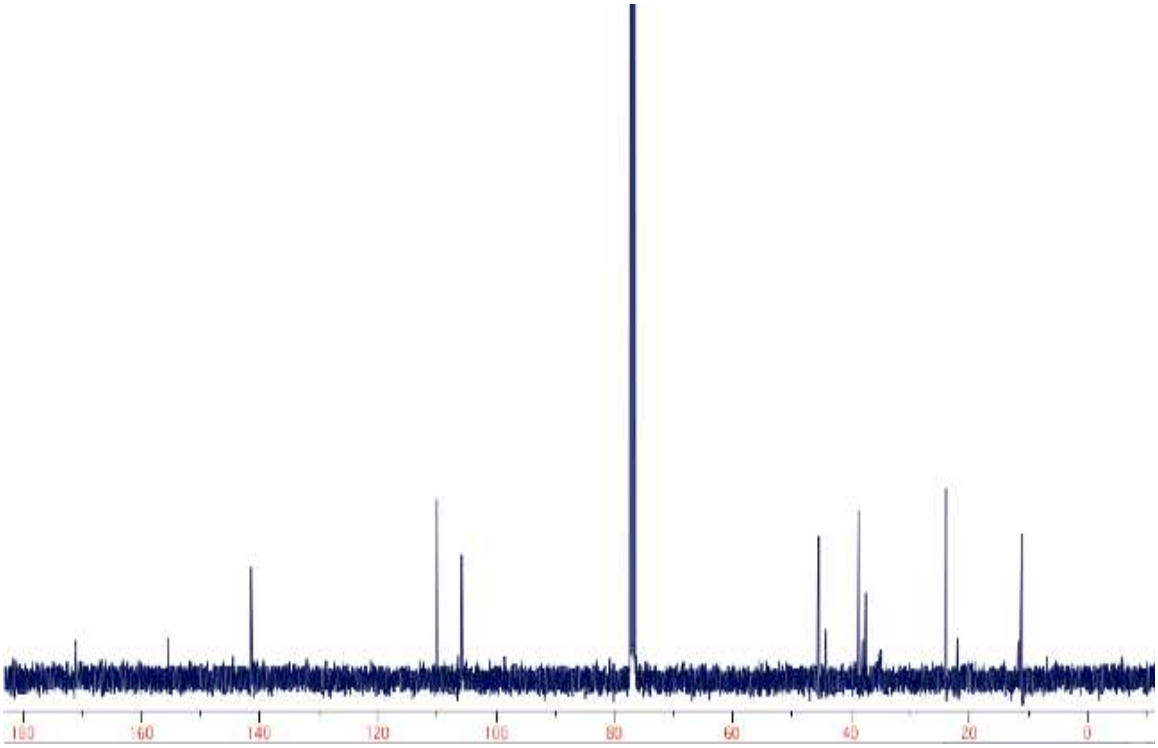

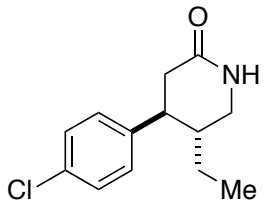
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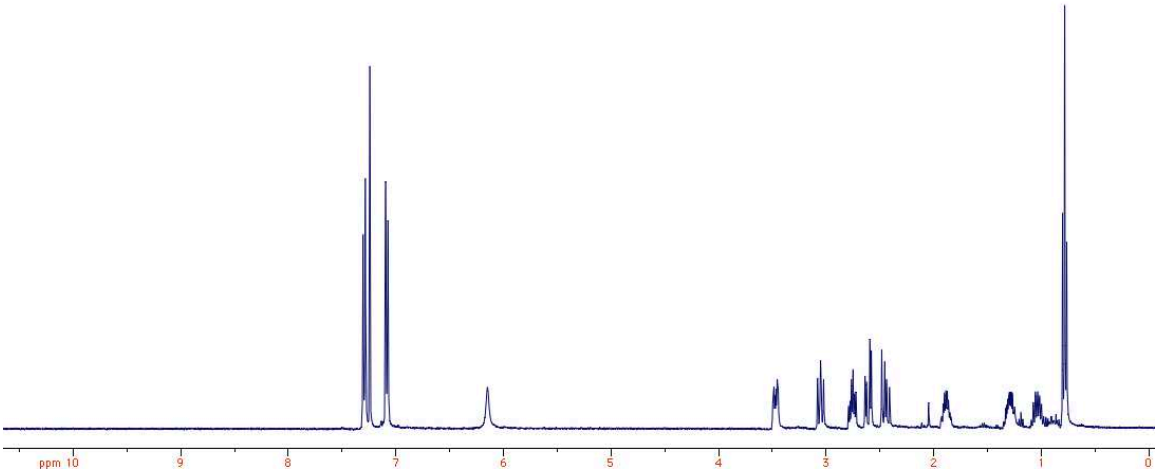
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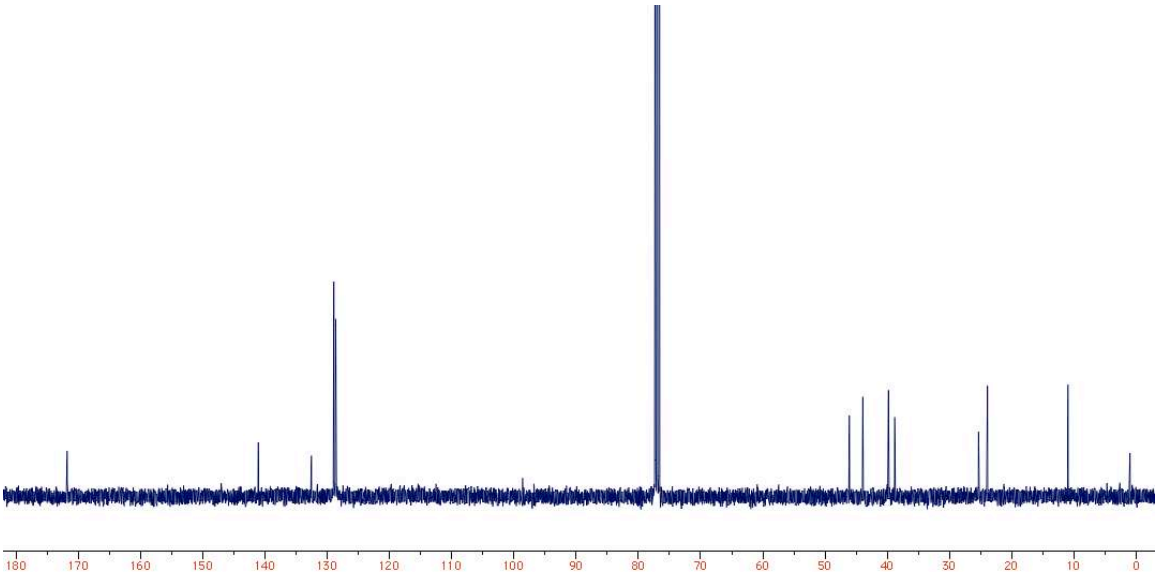
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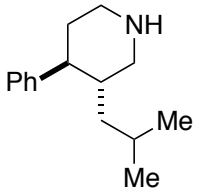
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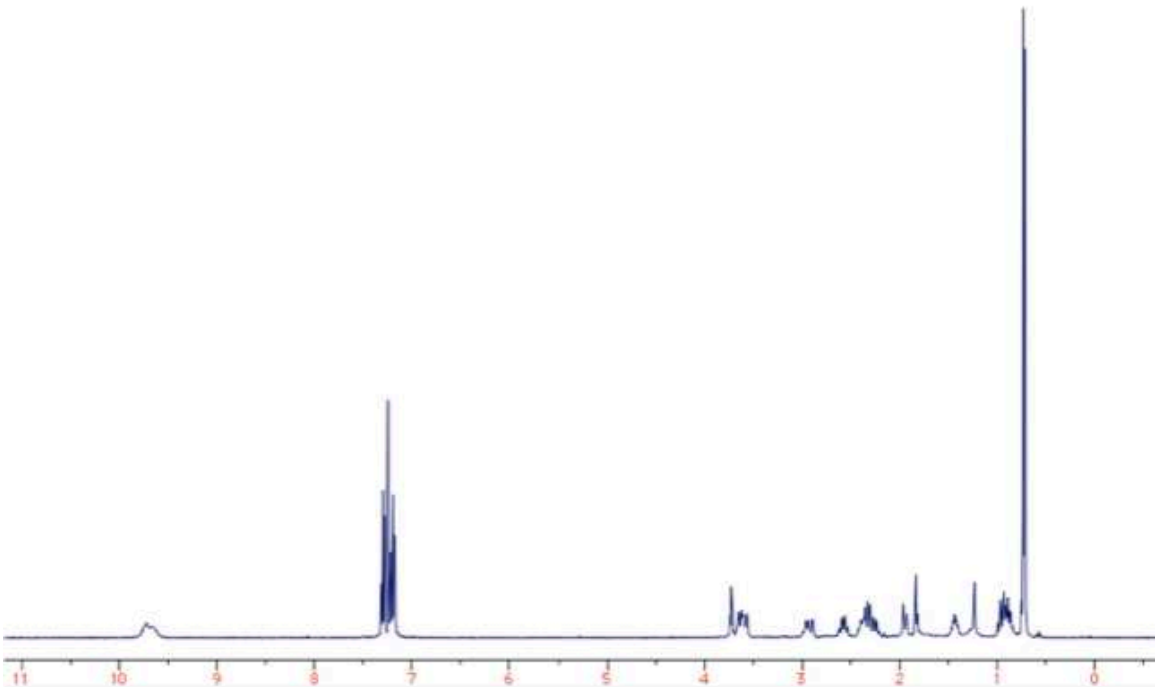
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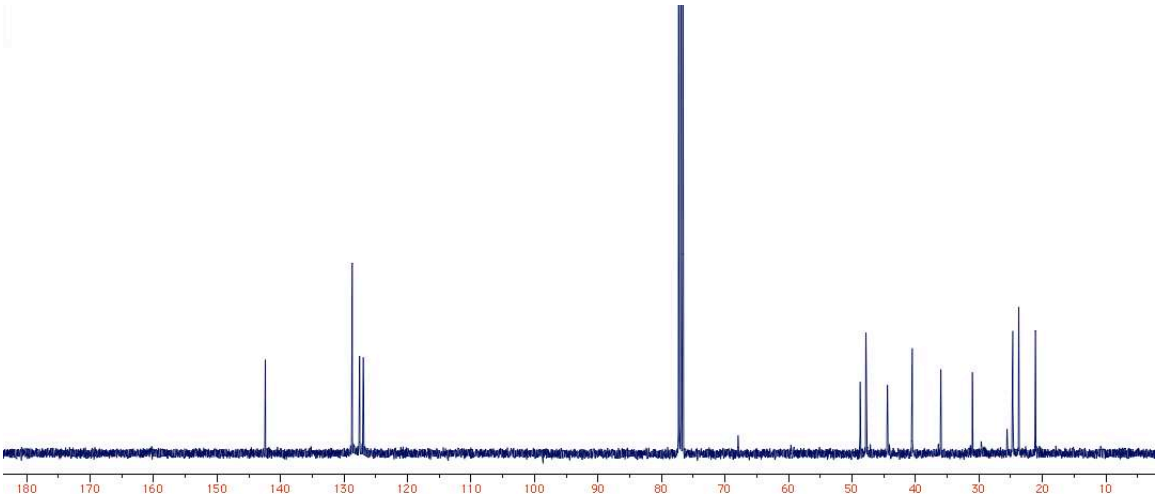
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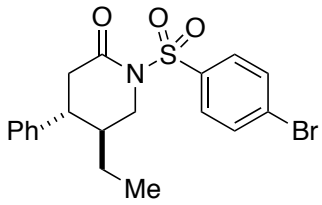
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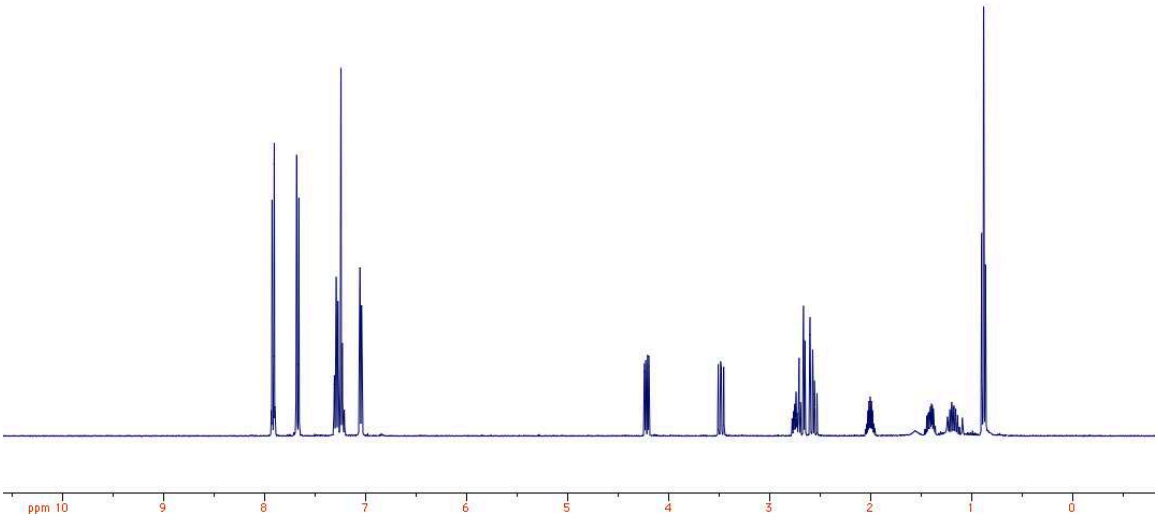
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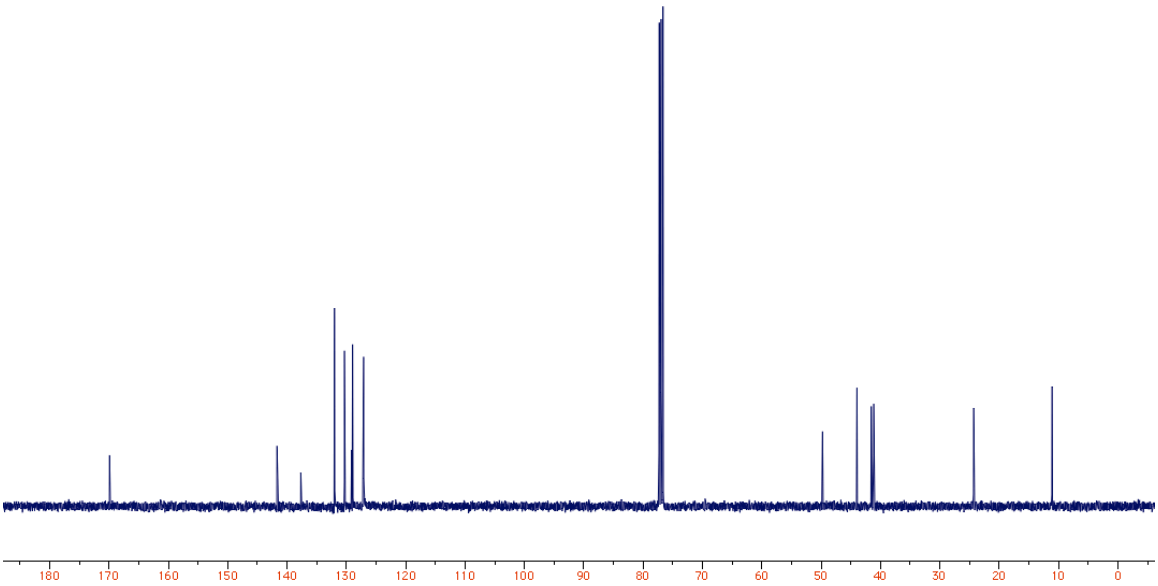
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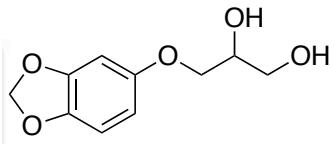
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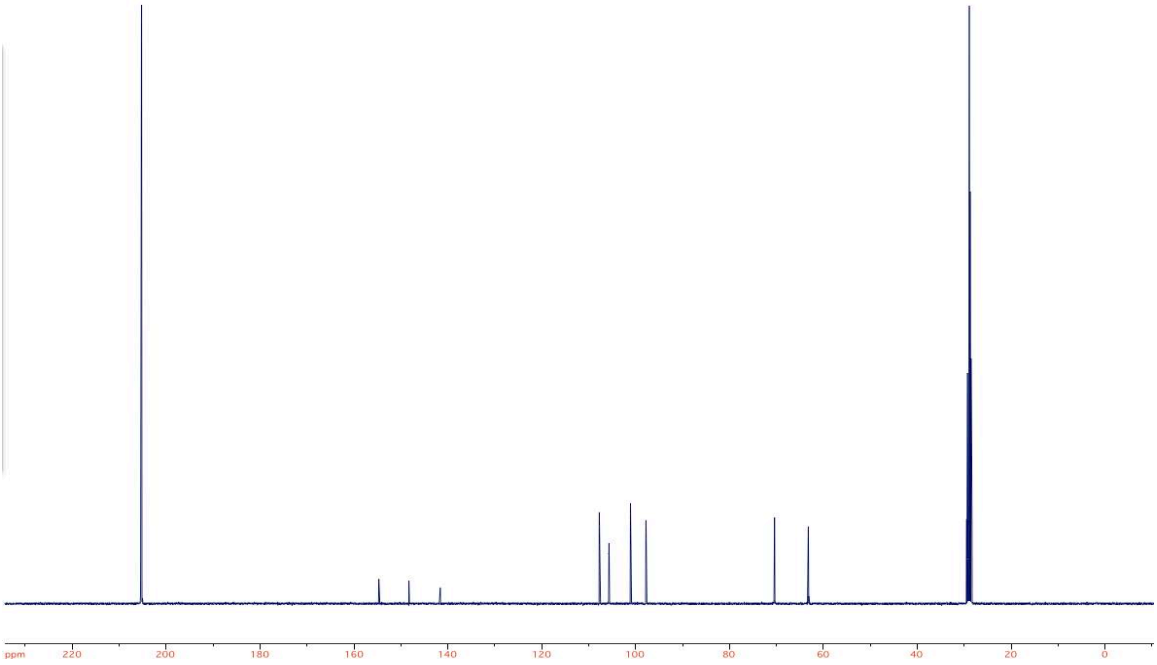
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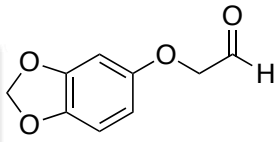

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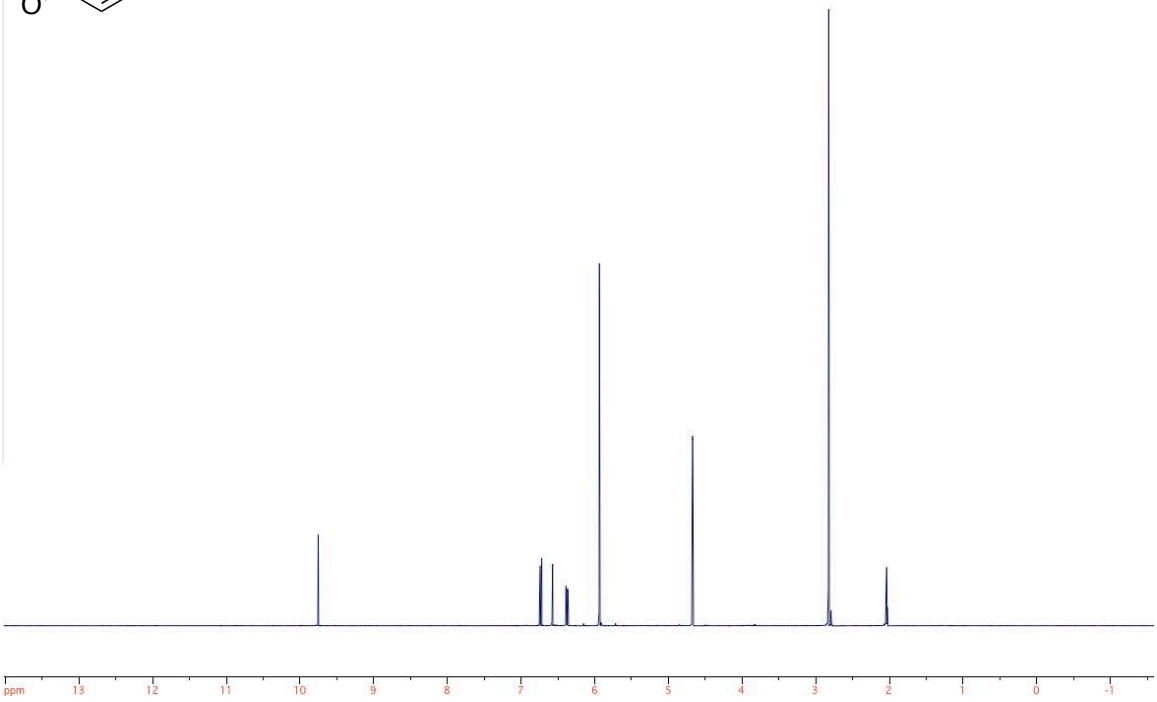
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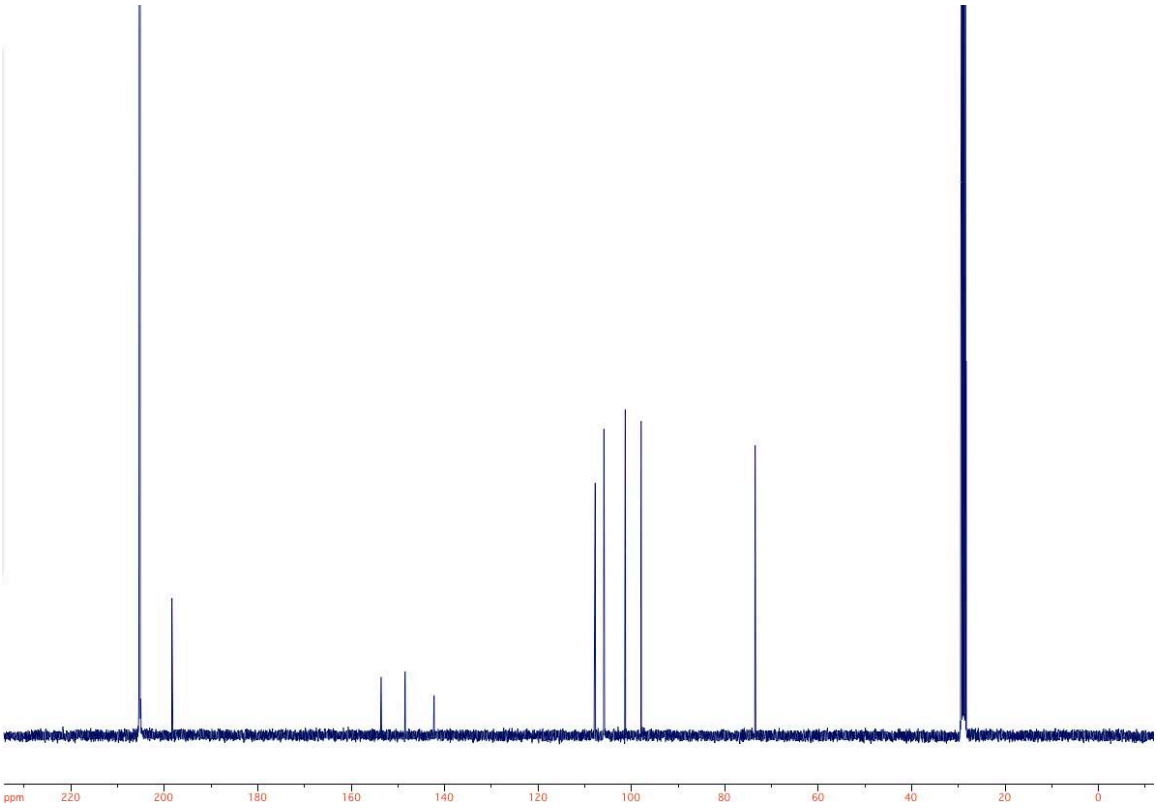
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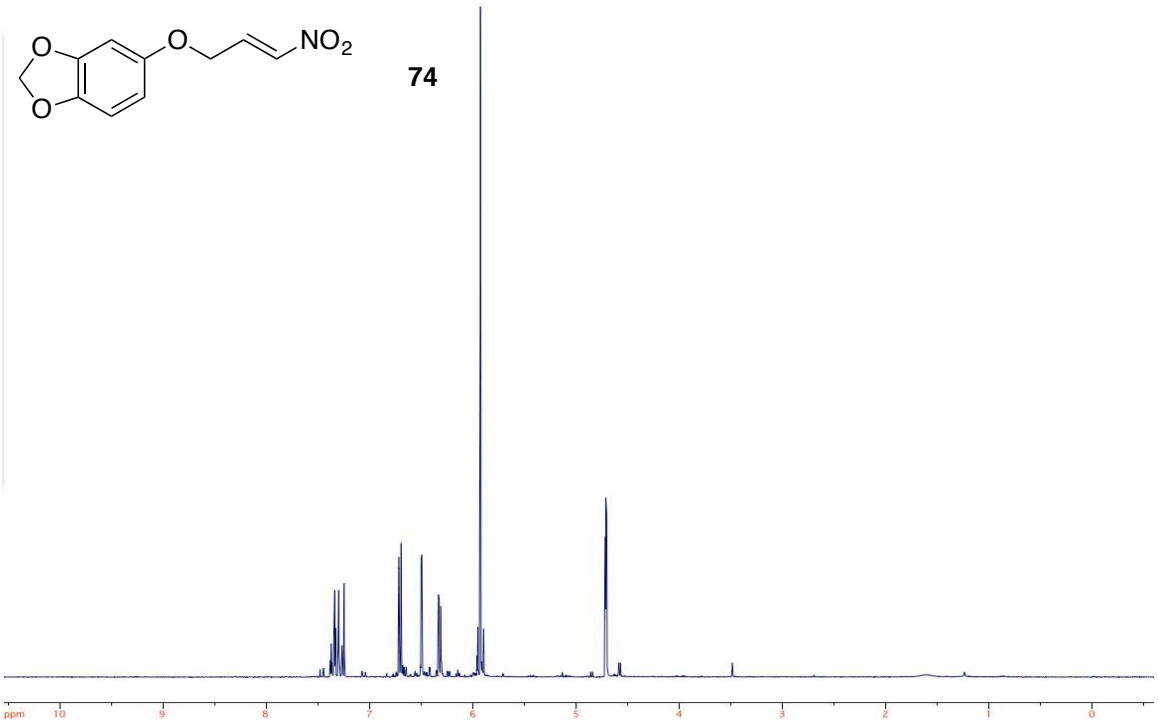
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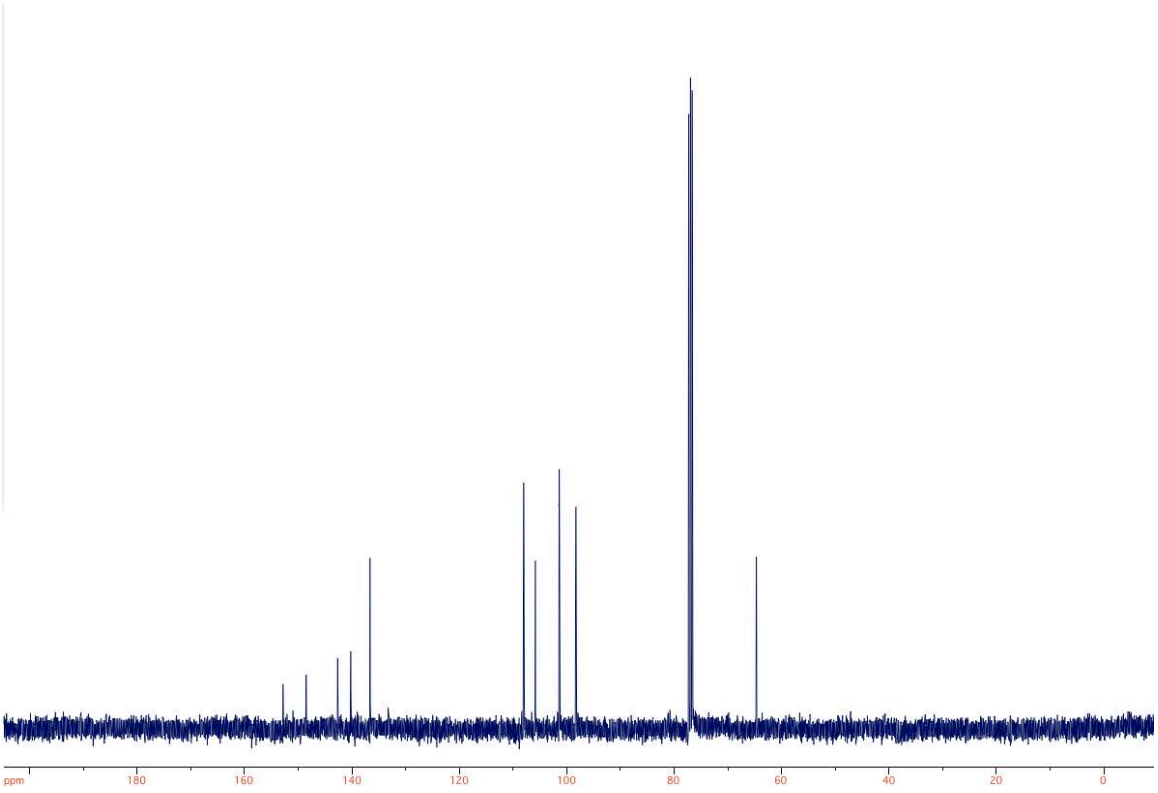
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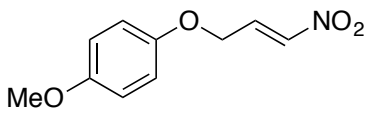
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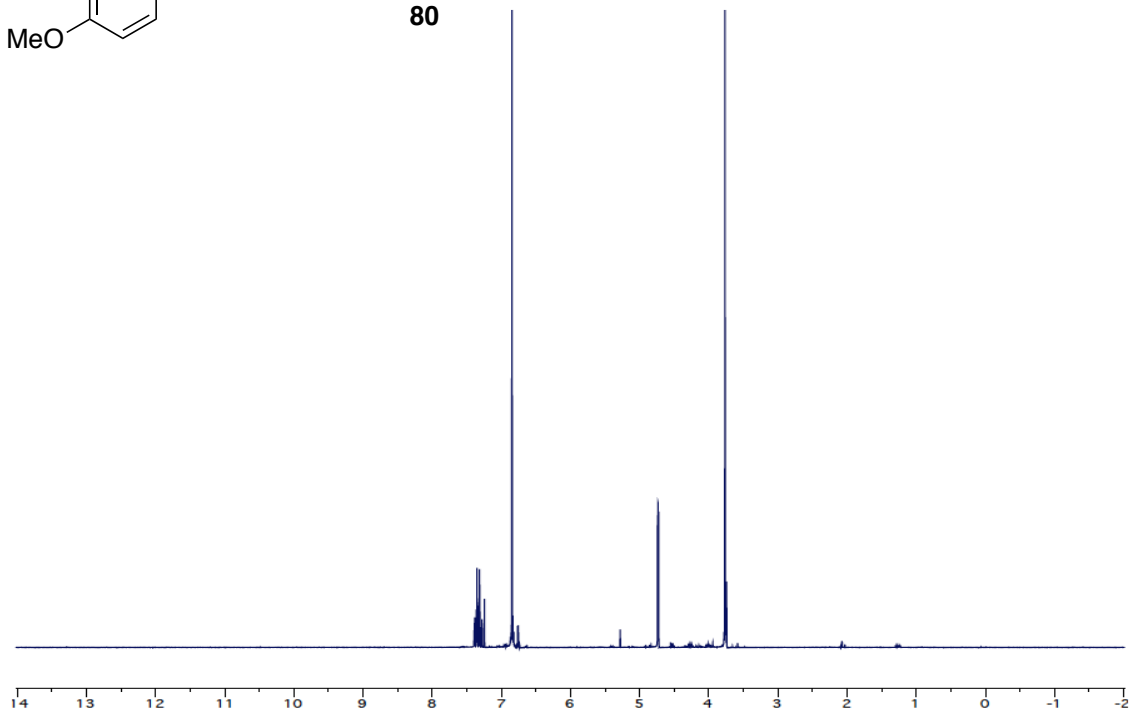
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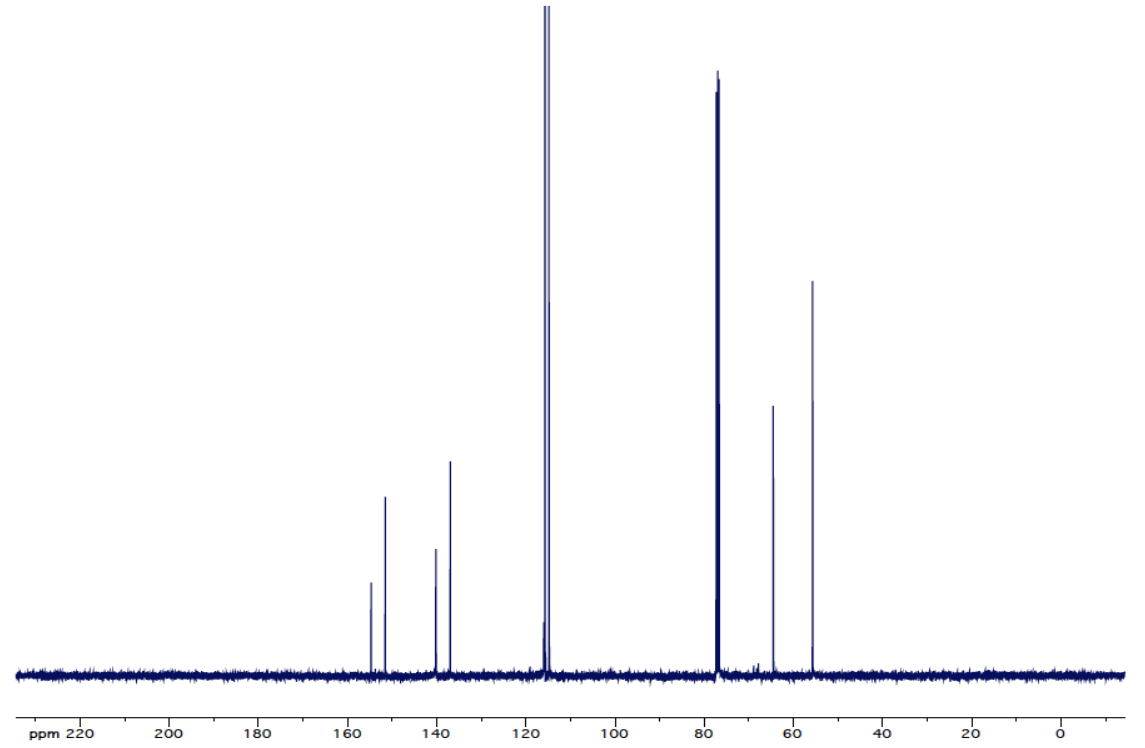
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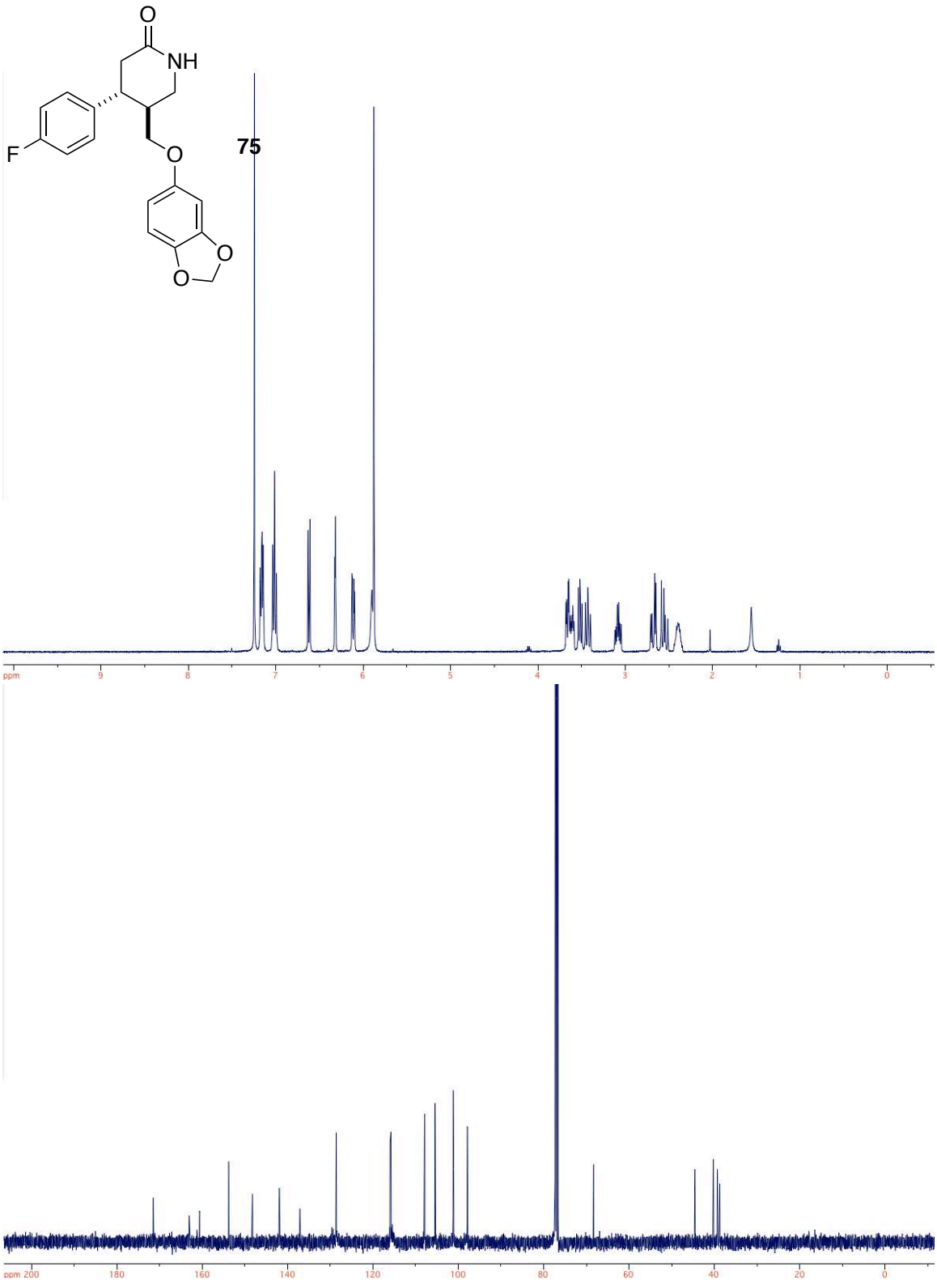
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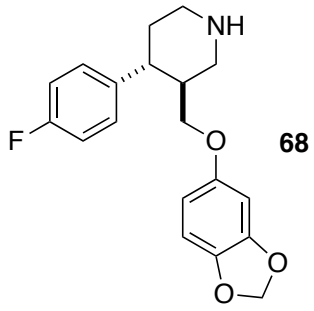

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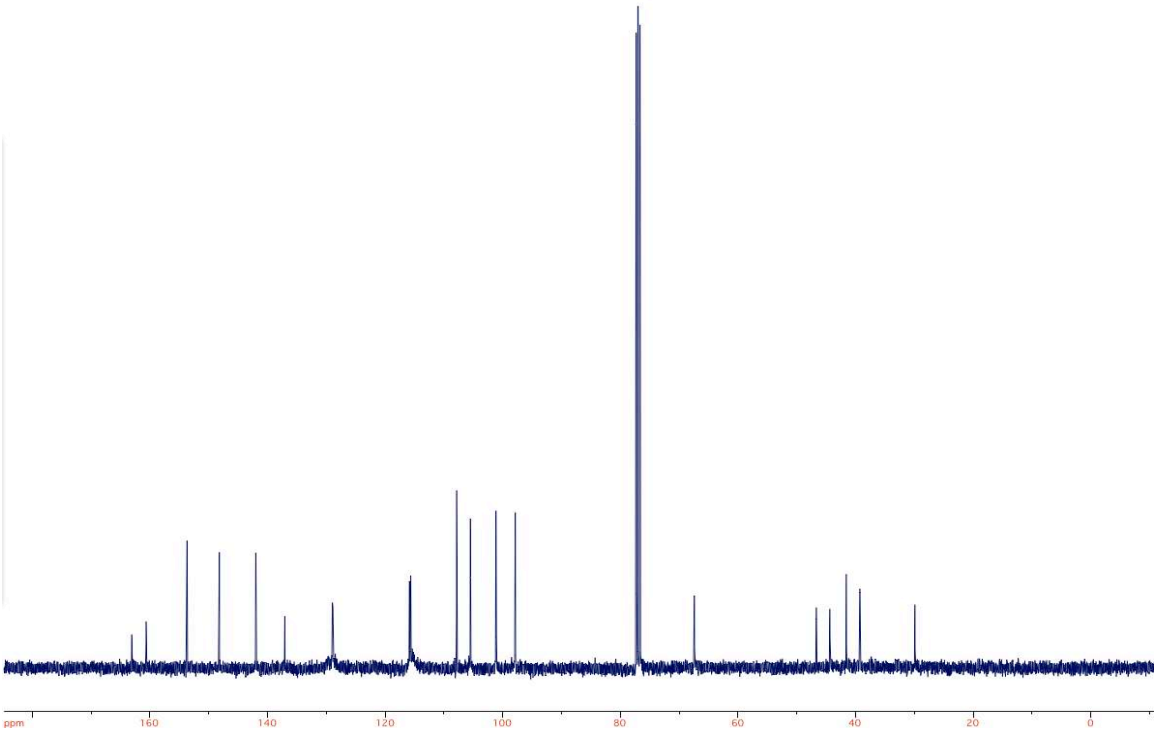

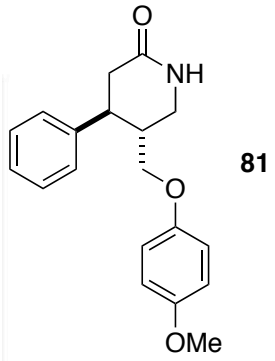

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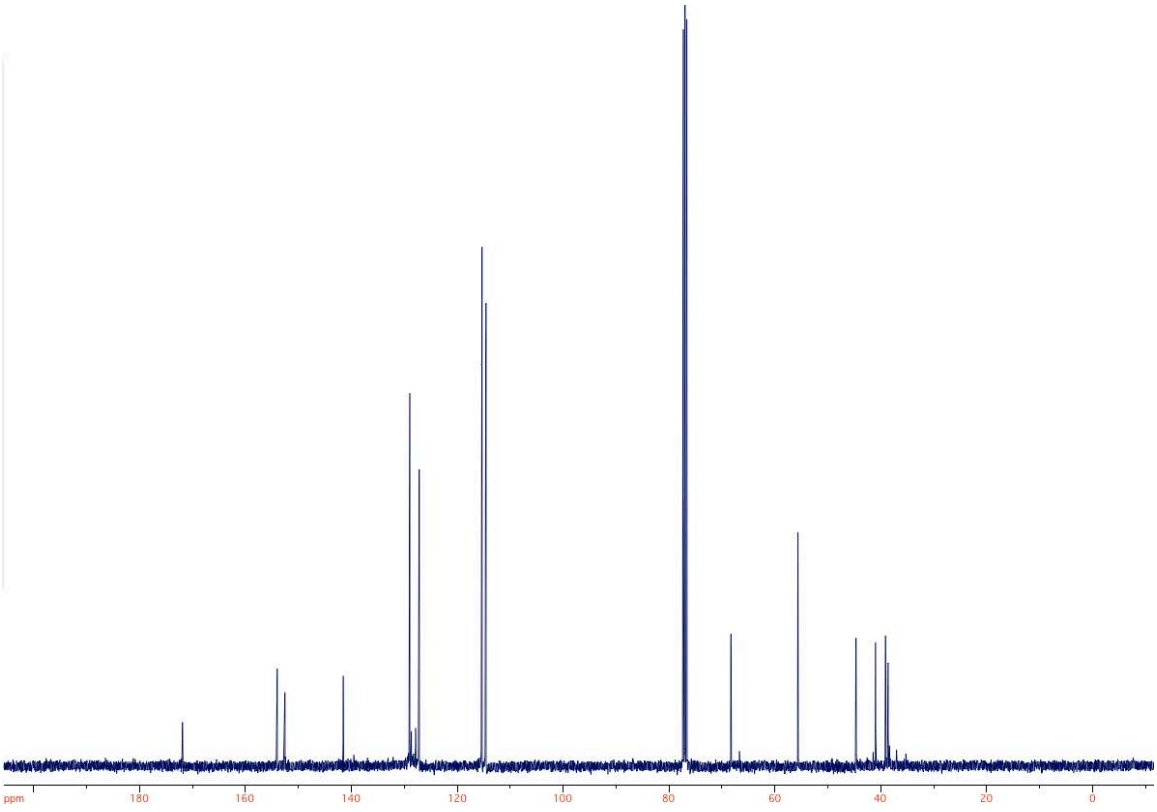

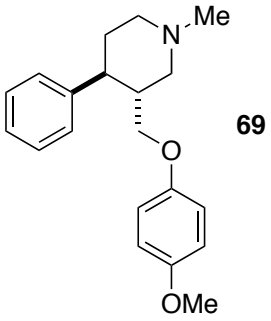
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OMe

69

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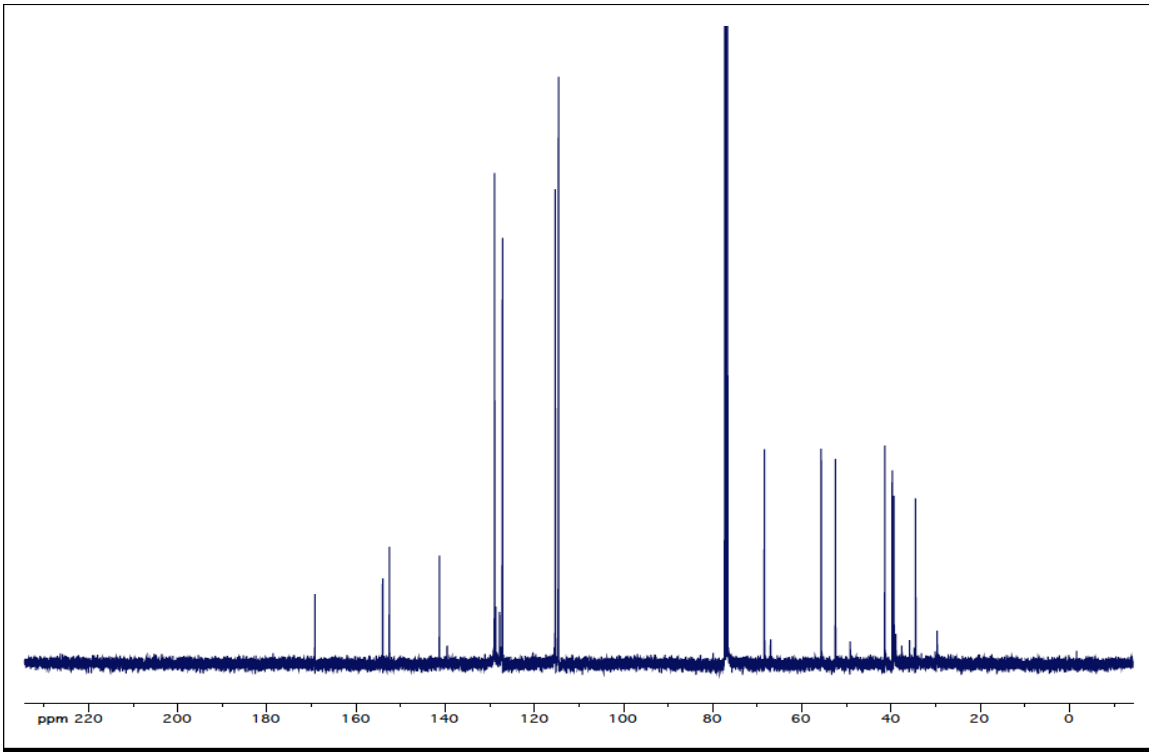
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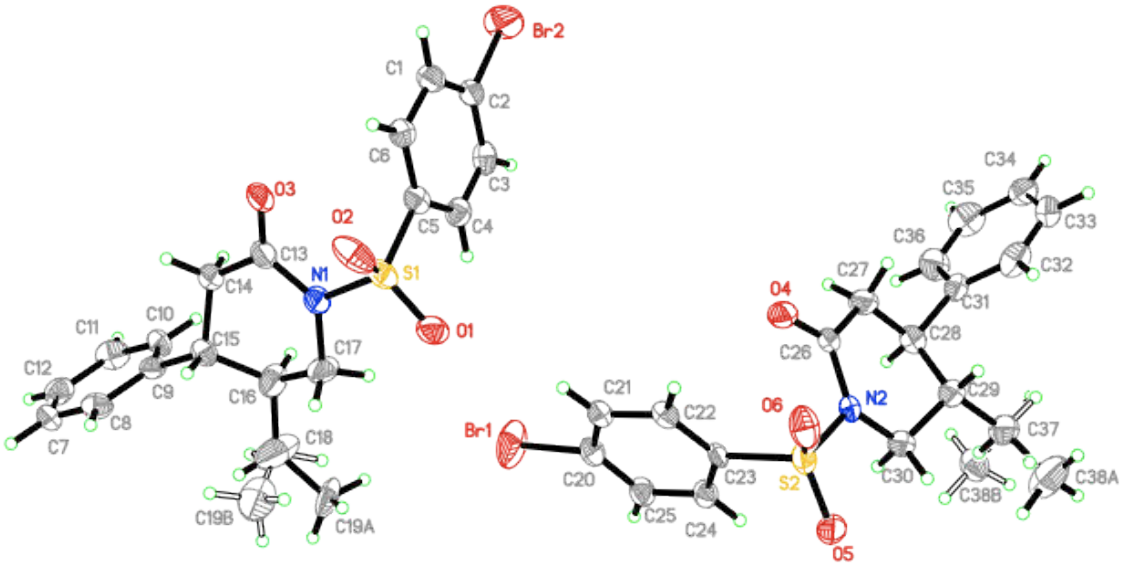

Table A.1.1 Crystal data and structure refinement for Rovis161. **12**

Identification code	rovis161	
Empirical formula	C_{19} H_{20} Br N O_3 S	
Formula weight	422.33	
Temperature	120 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P* 2_1	
Unit cell dimensions	*a* = 5.8036(5) Å	α = 90°.
	b = 21.9511(18) Å	β = 95.263(5)°.
	c = 14.3746(12) Å	γ = 90°.
Volume	1823.5(3) $Å^3$	
Z	4	
Density (calculated)	1.538 Mg/m^3	

Absorption coefficient	2.387 mm^{-1}
F_{000}	864
Crystal size	0.37 x 0.11 x 0.10 mm^3
Theta range for data collection	1.70 to 26.39°.
Index ranges	$-7 \leq h \leq 7$, $-27 \leq k \leq 27$, $-17 \leq l \leq 17$
Reflections collected	32881
Independent reflections	7371 [R_{int} = 0.0412]
Completeness to theta = 26.39°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8015 and 0.4721
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7371 / 35 / 472
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0453, wR2 = 0.0880
R indices (all data)	R1 = 0.0659, wR2 = 0.0964
Absolute structure parameter	0.013(10)
Largest diff. peak and hole	0.927 and -1.456 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Rovis161. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)

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Br(1)	1838(1)	7724(1)	7695(1)	72(1)
Br(2)	2151(1)	5738(1)	2630(1)	61(1)
C(1)	5687(9)	6608(3)	3097(4)	32(1)
C(2)	3664(10)	6352(2)	3371(4)	31(1)
C(3)	2684(9)	6552(3)	4154(4)	32(1)
C(4)	3729(8)	7022(2)	4682(4)	30(1)
C(5)	5750(9)	7278(2)	4396(4)	26(1)
C(6)	6737(9)	7081(2)	3612(4)	28(1)
C(7)	1001(11)	11231(3)	3885(4)	38(1)
C(8)	2398(8)	10745(3)	4210(3)	33(1)
C(9)	1637(9)	10157(2)	4109(3)	26(1)
C(10)	-544(9)	10054(3)	3687(4)	34(1)
C(11)	-1920(9)	10536(3)	3358(4)	40(2)
C(12)	-1153(11)	11120(3)	3465(4)	41(2)
C(13)	5245(9)	8686(3)	3886(4)	32(1)
C(14)	3688(10)	9218(2)	3634(4)	34(1)
C(15)	3238(8)	9639(2)	4433(3)	31(1)
C(17)	4235(11)	8793(3)	5565(4)	43(2)
C(20)	3572(9)	7136(2)	8433(4)	31(1)
C(21)	5562(9)	6907(3)	8119(4)	30(1)
C(22)	6695(9)	6437(2)	8623(4)	28(1)

C(23)	5795(9)	6226(2)	9425(3)	23(1)
C(24)	3840(8)	6477(2)	9743(4)	28(1)
C(25)	2700(9)	6943(3)	9240(4)	32(1)
C(26)	5094(9)	4847(2)	8895(3)	30(1)
C(27)	3370(10)	4348(3)	8663(4)	39(1)
C(28)	2005(8)	4101(2)	9432(3)	35(1)
C(30)	4225(9)	4763(2)	10582(3)	32(1)
C(31)	1101(9)	3467(2)	9118(4)	32(1)
C(32)	2362(9)	2932(3)	9256(4)	38(1)
C(33)	1462(10)	2390(3)	8912(4)	40(1)
C(34)	-708(11)	2366(3)	8428(4)	44(2)
C(35)	-1948(10)	2902(3)	8298(4)	49(2)
C(36)	-1023(10)	3437(3)	8627(4)	43(1)
C(16)	2435(10)	9260(2)	5213(4)	47(2)
C(18)	1577(17)	9596(4)	6026(5)	85(3)
C(19A)	1410(30)	9419(6)	6948(9)	63(5)
C(19B)	2960(20)	9930(6)	6518(9)	65(3)
C(29)	3412(9)	4113(2)	10364(3)	36(1)
C(37)	2178(10)	3845(3)	11165(4)	43(1)
C(38A)	3430(20)	3780(7)	12034(8)	73(4)
C(38B)	29(17)	4166(4)	11370(8)	41(3)
N(1)	5379(7)	8492(2)	4801(3)	29(1)
N(2)	5506(7)	5021(2)	9829(3)	28(1)

O(1)	6672(6)	7760(2)	6045(2)	41(1)
O(2)	9311(6)	7972(2)	4846(3)	47(1)
O(3)	6287(7)	8431(2)	3302(3)	41(1)
O(4)	6143(7)	5100(2)	8309(3)	36(1)
O(5)	7009(6)	5750(2)	11052(2)	41(1)
O(6)	9431(6)	5533(2)	9774(3)	42(1)
S(1)	7023(2)	7873(1)	5087(1)	33(1)
S(2)	7204(2)	5630(1)	10083(1)	31(1)

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[cxii] N, Guimond.; M. J. MacDonald; V. Lemieux; A. M. Beauchemin. *J. Am. Chem. Soc.* **2012**, *134*, 16571-16577.

[cxiii] M. Amat, J. Bosch, J. Hidalgo, M. Cantó, M. Pérez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque *J. Org. Chem*. **2000**, *65*, 3074-3084.

Table 3. Bond lengths [Å] and angles [°] for Rovis161.

Br(1)-C(20)	1.900(5)	C(5)-C(6)	1.379(7)
Br(2)-C(2)	1.886(6)	C(5)-S(1)	1.762(6)
C(1)-C(6)	1.384(8)	C(7)-C(12)	1.360(9)
C(1)-C(2)	1.391(7)	C(7)-C(8)	1.394(8)
C(2)-C(3)	1.378(7)	C(8)-C(9)	1.367(8)
C(3)-C(4)	1.388(8)	C(9)-C(10)	1.372(8)
C(4)-C(5)	1.396(7)	C(9)-C(15)	1.515(6)
		C(10)-C(11)	1.383(8)
		C(11)-C(12)	1.362(9)
		C(13)-O(3)	1.215(6)
		C(13)-N(1)	1.377(7)

C(13)-C(14)	1.502(8)	C(33)-C(34)	1.382(9)
C(14)-C(15)	1.515(6)	C(34)-C(35)	1.383(9)
C(15)-C(16)	1.505(6)	C(35)-C(36)	1.359(9)
C(17)-N(1)	1.489(6)	C(16)-C(18)	1.506(8)
C(17)-C(16)	1.517(8)	C(18)-C(19B)	1.257(14)
C(20)-C(21)	1.374(7)	C(18)-C(19A)	1.394(13)
C(20)-C(25)	1.374(7)	C(29)-C(37)	1.530(7)
C(21)-C(22)	1.392(7)	C(37)-C(38A)	1.394(12)
C(22)-C(23)	1.387(7)	C(37)-C(38B)	1.485(11)
C(23)-C(24)	1.377(7)	N(1)-S(1)	1.690(4)
C(23)-S(2)	1.769(5)	N(2)-S(2)	1.681(4)
C(24)-C(25)	1.385(7)	O(1)-S(1)	1.432(4)
C(26)-O(4)	1.218(6)	O(2)-S(1)	1.419(4)
C(26)-N(2)	1.396(6)	O(5)-S(2)	1.433(3)
C(26)-C(27)	1.499(8)	O(6)-S(2)	1.421(4)
C(27)-C(28)	1.519(7)		
C(28)-C(29)	1.504(6)	C(6)-C(1)-C(2)	119.6(5)
C(28)-C(31)	1.540(7)	C(3)-C(2)-C(1)	121.7(5)
C(30)-N(2)	1.480(6)	C(3)-C(2)-Br(2)	118.9(4)
C(30)-C(29)	1.527(7)	C(1)-C(2)-Br(2)	119.3(4)
C(31)-C(36)	1.365(8)	C(2)-C(3)-C(4)	119.4(5)
C(31)-C(32)	1.387(7)	C(3)-C(4)-C(5)	118.3(5)
C(32)-C(33)	1.374(8)	C(6)-C(5)-C(4)	122.6(5)

C(6)-C(5)-S(1)	120.6(4)	C(23)-C(22)-C(21)	119.0(5)
C(4)-C(5)-S(1)	116.9(4)	C(24)-C(23)-C(22)	121.8(5)
C(5)-C(6)-C(1)	118.4(5)	C(24)-C(23)-S(2)	118.2(4)
C(12)-C(7)-C(8)	119.7(6)	C(22)-C(23)-S(2)	120.0(4)
C(9)-C(8)-C(7)	120.9(5)	C(23)-C(24)-C(25)	119.4(5)
C(8)-C(9)-C(10)	118.6(5)	C(20)-C(25)-C(24)	118.2(5)
C(8)-C(9)-C(15)	119.6(5)	O(4)-C(26)-N(2)	119.2(5)
C(10)-C(9)-C(15)	121.8(5)	O(4)-C(26)-C(27)	123.0(5)
C(9)-C(10)-C(11)	120.4(5)	N(2)-C(26)-C(27)	117.8(4)
C(12)-C(11)-C(10)	120.7(5)	C(26)-C(27)-C(28)	118.7(4)
C(7)-C(12)-C(11)	119.7(6)	C(29)-C(28)-C(27)	111.4(4)
O(3)-C(13)-N(1)	122.0(5)	C(29)-C(28)-C(31)	114.8(4)
O(3)-C(13)-C(14)	121.2(5)	C(27)-C(28)-C(31)	107.3(4)
N(1)-C(13)-C(14)	116.8(4)	N(2)-C(30)-C(29)	112.0(4)
C(13)-C(14)-C(15)	115.6(4)	C(36)-C(31)-C(32)	118.2(5)
C(16)-C(15)-C(14)	108.4(4)	C(36)-C(31)-C(28)	117.5(5)
C(16)-C(15)-C(9)	114.9(4)	C(32)-C(31)-C(28)	124.1(5)
C(14)-C(15)-C(9)	111.6(4)	C(33)-C(32)-C(31)	120.2(5)
N(1)-C(17)-C(16)	113.2(4)	C(32)-C(33)-C(34)	120.9(5)
C(21)-C(20)-C(25)	123.4(5)	C(33)-C(34)-C(35)	118.3(5)
C(21)-C(20)-Br(1)	118.9(4)	C(36)-C(35)-C(34)	120.3(6)
C(25)-C(20)-Br(1)	117.7(4)	C(35)-C(36)-C(31)	122.1(6)
C(20)-C(21)-C(22)	118.1(5)	C(15)-C(16)-C(18)	117.0(5)

C(15)-C(16)-C(17)	111.8(4)
C(18)-C(16)-C(17)	109.9(5)
C(19B)-C(18)-C(19A)	74.0(10)
C(19B)-C(18)-C(16)	118.8(10)
C(19A)-C(18)-C(16)	131.2(8)
C(28)-C(29)-C(30)	109.4(4)
C(28)-C(29)-C(37)	114.2(5)
C(30)-C(29)-C(37)	111.2(4)
C(38A)-C(37)-C(38B)	104.6(9)
C(38A)-C(37)-C(29)	118.1(7)
C(38B)-C(37)-C(29)	115.2(6)
C(13)-N(1)-C(17)	125.3(4)
C(13)-N(1)-S(1)	117.5(3)
C(17)-N(1)-S(1)	117.2(3)
C(26)-N(2)-C(30)	123.0(4)
C(26)-N(2)-S(2)	118.2(3)
C(30)-N(2)-S(2)	118.0(3)
O(2)-S(1)-O(1)	118.7(2)
O(2)-S(1)-N(1)	109.7(2)
O(1)-S(1)-N(1)	104.2(2)
O(2)-S(1)-C(5)	109.2(2)
O(1)-S(1)-C(5)	108.9(3)
N(1)-S(1)-C(5)	105.1(2)
O(6)-S(2)-O(5)	119.1(2)
O(6)-S(2)-N(2)	110.2(2)
O(5)-S(2)-N(2)	105.1(2)
O(6)-S(2)-C(23)	109.4(2)
O(5)-S(2)-C(23)	108.1(2)
N(2)-S(2)-C(23)	103.8(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for Rovis161. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	84(1)	65(1)	72(1)	37(1)	33(1)	50(1)
Br(2)	75(1)	55(1)	54(1)	-19(1)	10(1)	-37(1)
C(1)	33(3)	28(3)	35(3)	-3(2)	6(2)	1(2)
C(2)	41(3)	23(3)	28(3)	0(2)	-1(2)	1(2)
C(3)	23(3)	29(3)	43(3)	10(2)	3(2)	0(2)
C(4)	29(3)	31(3)	31(3)	5(2)	3(2)	5(2)
C(5)	22(3)	25(3)	31(3)	1(2)	-6(2)	8(2)
C(6)	25(3)	27(3)	31(3)	2(2)	1(2)	4(2)
C(7)	57(4)	23(3)	35(3)	-4(2)	11(3)	-8(2)
C(8)	28(3)	38(3)	32(2)	-7(2)	2(2)	-2(2)
C(9)	29(3)	26(3)	22(2)	-3(2)	3(2)	4(2)
C(10)	40(3)	26(3)	34(3)	-2(2)	1(2)	-12(2)
C(11)	25(3)	54(4)	40(3)	-7(3)	-3(2)	-7(3)
C(12)	55(4)	40(3)	28(3)	4(3)	3(3)	16(3)

C(13)	36(3)	23(3)	37(3)	-1(2)	12(2)	-1(2)
C(14)	47(3)	25(3)	32(3)	0(2)	12(2)	3(2)
C(15)	36(3)	23(2)	34(2)	-1(2)	4(2)	8(2)
C(17)	59(4)	42(3)	28(3)	0(3)	14(3)	20(3)
C(20)	35(3)	23(3)	36(3)	1(2)	3(2)	10(2)
C(21)	39(3)	21(3)	31(3)	-1(2)	6(2)	-2(2)
C(22)	27(3)	22(3)	34(3)	-3(2)	5(2)	1(2)
C(23)	29(3)	13(2)	26(3)	1(2)	-1(2)	0(2)
C(24)	29(3)	24(3)	31(3)	2(2)	7(2)	-5(2)
C(25)	34(3)	26(3)	37(3)	3(2)	9(2)	6(2)
C(26)	47(3)	18(3)	26(3)	1(2)	8(2)	6(2)
C(27)	58(4)	30(3)	29(3)	-5(2)	8(2)	-11(3)
C(28)	43(3)	28(2)	35(2)	1(2)	5(2)	4(2)
C(30)	41(3)	28(3)	27(3)	-2(2)	4(2)	-3(2)
C(31)	42(3)	29(3)	26(2)	5(2)	4(2)	-2(2)
C(32)	20(2)	56(4)	37(3)	8(2)	-6(2)	-4(2)
C(33)	51(4)	33(3)	37(3)	7(2)	2(3)	8(3)
C(34)	69(4)	31(3)	31(3)	-2(3)	4(3)	-24(3)
C(35)	35(3)	63(5)	48(4)	-4(3)	-6(3)	-16(3)
C(36)	36(3)	44(3)	47(3)	0(3)	-3(3)	9(3)
C(16)	63(4)	40(3)	42(3)	13(2)	22(3)	27(3)
C(18)	129(7)	93(6)	35(4)	7(3)	17(4)	70(5)
C(19A)	105(13)	46(8)	45(7)	30(6)	43(8)	48(8)

C(19B)	61(8)	68(8)	68(8)	15(6)	24(6)	24(5)
C(29)	49(3)	30(3)	28(2)	1(2)	5(2)	-3(2)
C(37)	62(4)	36(3)	34(3)	2(2)	12(3)	-14(3)
C(38A)	89(10)	82(9)	43(6)	14(6)	-13(6)	-44(8)
C(38B)	41(6)	33(5)	49(6)	4(5)	12(5)	-6(4)
N(1)	31(2)	25(2)	32(2)	1(2)	6(2)	8(2)
N(2)	42(3)	17(2)	26(2)	3(2)	2(2)	-2(2)
O(1)	55(2)	32(2)	32(2)	-5(2)	-8(2)	14(2)
O(2)	27(2)	36(2)	78(3)	-21(2)	-1(2)	-4(2)
O(3)	58(3)	21(2)	47(2)	-2(2)	24(2)	6(2)
O(4)	49(2)	31(2)	30(2)	-3(2)	15(2)	-3(2)
O(5)	59(2)	32(2)	29(2)	0(2)	-13(2)	-12(2)
O(6)	29(2)	34(2)	61(2)	11(2)	-2(2)	2(2)
S(1)	31(1)	25(1)	41(1)	-5(1)	-4(1)	7(1)
S(2)	34(1)	23(1)	35(1)	5(1)	-5(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Rovis161.

	x	y	z	U(eq)

H(1)	6329	6462	2571	38
H(3)	1335	6373	4327	38
H(4)	3099	7164	5214	36
H(6)	8078	7262	3435	33
H(7)	1541	11629	3955	45
H(8)	3868	10822	4501	40
H(10)	-1100	9657	3621	40
H(11)	-3383	10460	3061	48
H(12)	-2099	11442	3251	49
H(14A)	2214	9064	3358	41
H(14B)	4364	9456	3159	41
H(15)	4726	9820	4663	37
H(17A)	5405	8992	5985	51
H(17B)	3500	8484	5919	51
H(21)	6136	7062	7584	36
H(22)	8035	6267	8426	33
H(24)	3289	6335	10290	34
H(25)	1380	7120	9443	38
H(27A)	4189	4010	8411	47
H(27B)	2268	4496	8165	47

H(28)	662	4366	9474	42
H(30A)	2893	5018	10665	39
H(30B)	5217	4765	11163	39
H(32)	3822	2941	9583	46
H(33)	2323	2035	9006	48
H(34)	-1317	1998	8196	52
H(35)	-3421	2896	7983	59
H(36)	-1864	3794	8515	51
H(16)	1110	9025	4935	56
H(18A)	2494	9966	6076	102
H(18B)	23	9724	5803	102
H(18C)	286	9849	5784	102
H(18D)	970	9297	6435	102
H(19A)	762	9747	7283	95
H(19B)	2916	9321	7237	95
H(19C)	421	9068	6959	95
H(19D)	2183	10110	7010	97
H(19E)	3531	10245	6136	97
H(19F)	4239	9689	6784	97
H(29)	4797	3865	10305	43
H(37A)	846	4099	11249	52
H(37B)	1594	3446	10971	52
H(37C)	1796	3423	11019	52

H(37D)	3244	3847	11726	52
H(38A)	2455	3609	12470	109
H(38B)	3983	4171	12253	109
H(38C)	4727	3514	11976	109
H(38D)	-636	3965	11874	61
H(38E)	-1056	4162	10824	61
H(38F)	390	4580	11543	61

References:

(1) DiRocco, D. A.; Oberg, K, M.; Dalton D. M., Rovis, T, *J. Am. Chem. Soc*. **2009**, *131*, 10872 – 10874.

(2) Ostendorf, M.; Dijkink, J.; Rutjes, F.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, *1*, 115-124.

Appendix 2. Chapter 3 Experimental

Asymmetric β-hydroxylation of Enals via Oxygen Transfer from Electron-Deficient Nitro-Arenes

Materials and Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Carbon tetracholoride was purchased from Aldrich and stored over 3Å molecular sieves. Dichloromethane was degassed with argon and passed through two col- umns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Tetrahydrofuran was degassed with argon and passed through one column of neutral alumina. Methanol was purchased from Fisher Scientific and dried with activated 3Å molecular sieves. Sodium acetate was purchased from Aldrich. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light or KMnO4 stain followed by heating.

^{1}H NMR spectra were recorded on Varian 400 MHz spectrometers at ambient temperature. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm) or acetone-D_6 (2.03 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ^{13}C NMR were recorded on Varian 400 MHz spectrometers (at 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.36 ppm) or acetone-D_6 (205.87, 30.6 ppm). Mass spectra were recorded on an Agilent

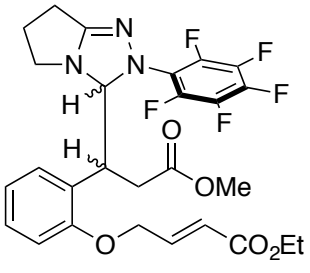
6130 Quadrupole LC/MS.

Aldehydes were either purchased from Aldrich or prepared via known literature procedures. Nitrobenzenes were purchased from Aldrich.

General Procedure for the β-Hydroxylation of Enals

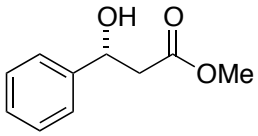
To an oven dried screw cap vial charged with a magnetic stirbar was added triazolium salt **5f** (25 mg, 0.04 mmol), NaOAc (33 mg, 0.4 mmol), 4-nitropyridine N-oxide (84 mg, 0.6 mmol) and 2.0 mL of a 20:1 Carbon tetrachloride:methanol mixture followed by *trans*-cinnamaldehyde (53 μL, 0.4 mmol). The cap was then screwed on and the reaction was allowed to stir at room temperature for 12 hours. After 12 hours the reaction was concentrated via rotary evaporation and then purifired by silica gel chromatography (6:4 hexanes:ether) to yield 32 mg (45 %) (*R*)-methyl 3-hydroxy-3-phenylpropanoate as a colorless oil.

Compound Characterization

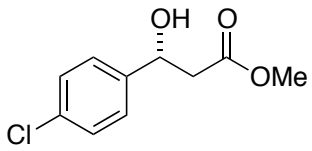


ethyl (*E*)-4-(2-(3-methoxy-3-oxo-1-(2-(perfluorophenyl)-2,5,6,7-tetrahydro-3*H*-pyrrolo[2,1-*c*][1,2,4]triazol-3-yl)propyl)phenoxy)but-2-enoate (**4**): Colorless oil. 15 %; R_f=0.23 (100% EtOAc); **^{1}H-NMR** (300 MHz; $CDCl_3$): δ 7.14-7.04 (m, 2H), 6.77-6.66 (m, 2H), 6.18 (dt, *J* = 15.8, 2.1 Hz, 1H), 5.51 (d, *J* = 3.2 Hz, 1H), 4.66 (dt, *J* = 4.1, 2.1 Hz, 2H), 4.27-

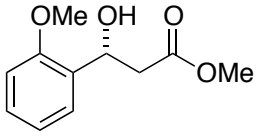
4.16 (m, 4H), 3.63 (s, 3H), 3.32-3.24 (m, 2H), 2.95-2.86 (m, 1H), 2.50-2.34 (m, 5H), 1.31 (t, *J* = 7.1 Hz, 3H). **LRMS** (ESI + APCI) *m/z* [M+H] calcd 567.1, found 567.1



(*R*)-methyl 3-hydroxy-3-phenylpropanoate (**7**): Colorless Oil. 45 % yield 92 % ee; R_f=0.29 (1:1 hexanes:ether); **HPLC analysis**: Chiralpak IB column, 90:10 hexanes/*iso*-propanol, 1.0 mL/min. Major: 6.5 min, minor: 7.3 min; **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.11 (dd, *J* = 9.0, 3.9 Hz, 1H), 3.69 (s, 3H), 3.35 (bs, 1H), 2.73 (td, *J* = 14.3, 7.8 Hz, 2H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 172.7, 142.6, 128.5, 127.8, 125.6, 70.3, 51.9, 43.2. Spectra matched that of the previously reported compound.[1]

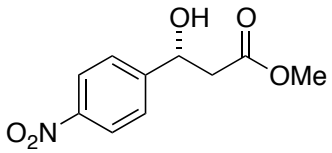


(*R*)-methyl 3-(4-chlorophenyl)-3-hydroxypropanoate (**99**): Colorless Oil. 57 % yield, 90 % ee. R_f=0.29 (1:1 hexanes:ether); **HPLC analysis**: Chiralcel OJ-H column, 99:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 35.6 min, minor: 38.9. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.33-7.28 (m, 4H), 5.10 (ddd, *J* = 8.0, 4.6, 3.5 Hz, 1H), 3.71 (s, 3H), 3.27 (d, *J* = 3.5 Hz, 1H), 2.71-2.69 (m, 2H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 172.6, 140.9, 133.5, 128.7, 127.0, 69.6, 51.9, 42.9. Spectra matched that of the previously reported compound.[2]

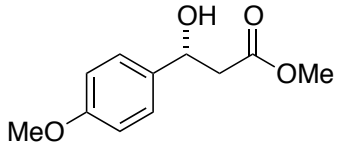


(*R*)-methyl 3-hydroxy-3-(2-methoxyphenyl)propanoate (**100**): Colorless Oil. 44 % yield, 80 % ee. R_f=0.27 (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 90:10

hexanes/*iso*-propanol, 1.0 mL/min. Major: 9.3 min, minor: 10.3 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.41 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.25 (td, *J* = 7.8, 1.9 Hz, 1H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.35 (dt, *J* = 9.0, 4.4 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.38 (d, *J* = 5.3 Hz, 1H), 2.85-2.67 (m, 2H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.0, 156.0, 130.4, 128.6, 126.5, 120.8, 110.3, 66.6, 55.2, 51.7, 41.5. Spectra matched that of the previously reported compound.[3]

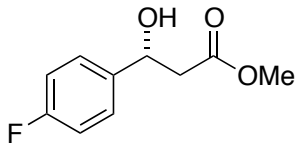


(*R*)-methyl 3-hydroxy-3-(4-nitrophenyl)propanoate (**101**): Pale Yellow Solid. 20 % yield, 80 % ee. R_f=0.23 (1:1 hexanes:ether); **HPLC analysis**: Chiralcel OJ-H column, 93:7 Hexanes:*iso*-propanol, 1.0mL/min. Major: 41.4 min, minor: 44.7.**^{1}H-NMR** (400 MHz; $CDCl_3$): δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 5.22 (dt, *J* = 8.2, 4.1 Hz, 1H), 3.73 (s, 3H), 3.54 (d, *J* = 3.7 Hz, 1H), 2.77-2.67 (m, 2H); **^{13}C-NMR** (101 MHz; CDCl3): δ 172.3, 149.5, 126.4, 123.8, 69.3, 52.1, 42.7. Spectra matched that of the previously reported compound.[4]

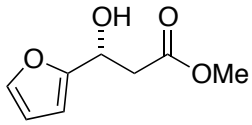


(*R*)-methyl 3-hydroxy-3-(4-methoxyphenyl)propanoate (**102**): 41 % yield, 92 % ee. R_f=0.25 (1:1 Hexanes:Ether); **HPLC analysis**: Chiralcel OB-H column, 80:20 hexanes/*iso*-propanol, 1.0 mL/min. Major: 10.6 min, minor: 14.5 min.**^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.06 (dd, *J* = 9.2, 3.7 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.07 (bs, 1H), 2.78-2.63 (m, 2H);**^{13}C-NMR** (101 MHz; $CDCl_3$): δ 172.7,

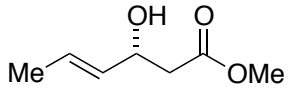
159.2, 134.7, 126.9, 113.9, 69.9, 55.2, 51.8, 43.1. Spectra matched that of the previously reported compound.[5]



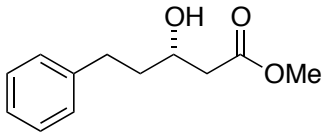
(*R*)-methyl 3-(4-fluorophenyl)-3-hydroxypropanoate (**103**): Colorless Oil. 46 % yield, 91 % ee. R_f=0.28 (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 99:1 hexanes/*iso*-propanol, 1.0mL/min. Major: 19.2 min, minor: 18.5. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.04-7.00 (m, 2H), 5.10 (dt, *J* = 8.3, 3.9 Hz, 1H), 3.71 (s, 3H), 3.27 (d, *J* = 3.9 Hz, 1H), 2.76-2.64 (m, 2H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 172.6, 162.3 (J=245.7 Hz, C), 138.2 (J=3.0 Hz, C), 127.3 (J=8.2 Hz, CH), 115.4 (J=21.4 Hz, CH), 69.6, 51.9, 43.1. Spectra matched that of the previously reported compound.[6]



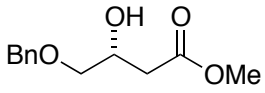
(*R*)-methyl 3-(furan-2-yl)-3-hydroxypropanoate (**104**): Colorless Oil. 56 % yield, 84 % ee. R_f=0.27 (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 90:10 hexanes/*iso*-propanol, 1.0 mL/min. Major: 9.6 min, minor: 5.6 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.28 (dt, *J* = 3.3, 0.8 Hz, 1H), 5.14 (dd, *J* = 8.5, 4.1 Hz, 1H), 3.73 (s, 3H), 3.09 (s, 1H), 2.88 (qd, *J* = 15.9, 6.3 Hz, 2H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 172.3, 154.6, 142.2, 110.2, 106.3, 64.2, 51.9, 39.6. Spectra matched that of the previously reported compound.[5]



(*R*,*E*)-methyl 3-hydroxyhex-4-enoate (**105**): Colorless Oil. 46 % yield, 85 % ee. R_f=0.32 (1:1 hexanes:ether); **GC analysis**: Varian BDM column, 70 °C 3.0 mL/min. Major: 35.6 min, minor: 39.7 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 5.77-5.68 (m, 1H), 5.49 (ddq, *J* = 15.3, 6.6, 1.6 Hz, 1H), 4.47 (q, *J* = 6.6 Hz, 1H), 3.69 (s, 3H), 2.53-2.51 (m, 2H), 1.68 (dt, *J* = 6.6, 0.8 Hz, 3H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 172.7, 131.7, 127.5, 68.9, 51.7, 41.3, 17.6. Spectra matched that of the previously reported compound.[7]

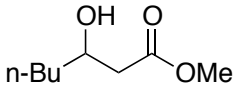


(*S*)-methyl 3-hydroxy-5-phenylpentanoate (**106**): Colorless Oil. 58 % yield, 80 % ee (*Note: reaction was ran in a 20:1 mixture of trifluorotoluene:methanol*). R_f=0.23 (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 80:20 hexanes/*iso*-propanol, 1.0 mL/min. Major: 7.1 min, minor: 7.9 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.31-7.17 (m, 4H), 4.02 (tt, *J* = 8.4, 4.1 Hz, 1H), 3.71 (s, 3H), 2.99 (s, 1H), 2.83 (ddd, *J* = 14.1, 9.3, 5.2 Hz, 1H), 2.70 (ddd, *J* = 13.8, 9.4, 7.0 Hz, 1H), 2.55-2.42 (m, 2H), 1.90-1.81 (m, 1H), 1.74 (dddd, *J* = 13.8, 9.6, 6.9, 4.2 Hz, 1H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.3, 141.7, 128.42, 128.40, 125.9, 67.2, 51.8, 41.1, 38.1, 31.7. Spectra matched that of the previously reported compound.[8]

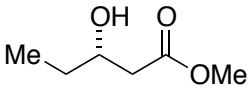


(*R*)-methyl 4-(benzyloxy)-3-hydroxybutanoate (**107**): Colorless Oil. 71 % yield, 81 % ee. R_f=0.31 (1:1 hexanes:ether); **HPLC analysis**: Chiralpak IB column, 90:10 hexanes:*iso*-propanol, 1.0 mL/min. Major: 9.4 min, minor: 8.5 min.;**^{1}H-NMR** (400 MHz; $CDCl_3$):

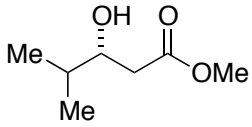
δ 7.37-7.28 (m, 5H), 4.56 (s, 2H), 4.27-4.21 (m, 1H), 3.69 (s, 3H), 3.50 (qd, *J* = 9.8, 5.2 Hz, 2H), 2.79 (bs, 1H), 2.56 (d, *J* = 6.3 Hz, 2H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 172.5, 137.8, 128.4, 127.78, 127.70, 73.4, 73.1, 67.2, 51.8, 38.0. Spectra matched that of the previously reported compound. Absolute configuration was compared to that of the known compound.[9] All other absolute configurations were assigned via correlation.



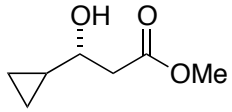
methyl 3-hydroxyheptanoate (**108**): Colorless Oil. R_f = 0.25 (1:1 hexanes:ether**)** **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 4.03-3.97 (m, 1H), 3.71 (s, 2H), 2.52 (dd, *J* = 16.5, 3.1 Hz, 1H), 2.65 (bs, 1H), 2.41 (dd, *J* = 16.4, 9.0 Hz, 1H), 1.54-1.19 (m, 7H), 0.90 (dd, *J* = 8.3, 5.5 Hz, 3H). 13-C NMR (101 MHz; cdcl3): δ 173.5, 68.0, 51.7, 41.1, 36.2, 27.6, 22.6, 14.0 Spectra matched that of previously reported compound.[10]



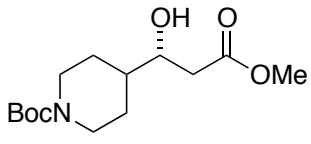
(*S*)-methyl 3-hydroxypentanoate (**109**): Colorless Oil. 65 % yield, 86 % ee; R_f=0.26 (1:1 hexanes:ether); **GC analysis**: Varian BDM column, 70 °C, 1.0 mL/min. Major: 28.6 min, minor: 31.9 min; **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 3.91 (ddd, *J* = 12.6, 9.0, 3.4 Hz, 1H), 3.71 (s, 3H), 3.10 (bs, 1H), 2.51-2.35 (m, 2H), 1.58-1.41 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.4, 69.3, 51.7, 40.6, 29.4, 9.8. Spectra matched that of the previously reported compound.[11]



(*R*)-methyl 3-hydroxy-4-methylpentanoate (**110**): Colorless Oil. 73 % yield, 88 % ee. R_f=0.28 (1:1 hexanes:ether); **GC analysis**: Varian BDM column, 80 °C, 1.5 mL/min. Major: 18.9 min, minor: 20.3 min; **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 3.78 (ddd, *J* = 9.3, 6.0, 3.1 Hz, 1H), 3.72 (s, 3H), 2.80 (bs, 1H), 2.54-2.38 (m, 2H), 1.71 (dq, *J* = 13.1, 6.6 Hz, 1H), 0.94 (dd, *J* = 11.3, 6.8 Hz, 6H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.9, 72.7, 51.7, 38.2, 33.1, 18.3, 17.7. Spectra matched that of the previously reported compound.[12]

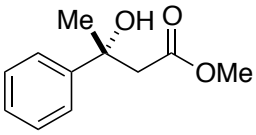


(*R*)-methyl 3-cyclopropyl-3-hydroxypropanoate (**111**): Colorless Oil. 61 % yield, 80 % ee. R_f=0.23 (1:1 hexanes:ether) **HPLC analysis**: Chiralpak IB column, 99:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 5.1 min, minor: 4.7 min (*Note: ee was obtained using the benzyl ether of compound **3e**)*; **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 3.71 (s, 3H), 3.32 (td, *J* = 8.4, 3.9 Hz, 1H), 2.71 (bs, 1H), 2.68-2.56 (m, 2H), 0.99-0.90 (m, 1H), 0.59-0.47 (m, 2H), 0.39 (dq, *J* = 9.3, 4.6 Hz, 1H), 0.22 (dq, *J* = 9.2, 4.6 Hz, 1H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.0, 72.7, 51.7, 41.2, 16.8, 3.1, 2.2. Spectra matched that of the previously reported compound.[13]

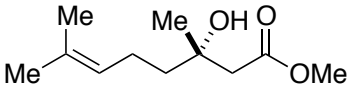


(*R*)-*tert*-butyl 4-(1-hydroxy-3-methoxy-3-oxopropyl)piperidine-1-carboxylate (**112**): Colorless Oil. 74 % yield, 84 % ee. R_f=0.40 (100 % ether); **HPLC analysis**: Chiralcel OC column, 90:10 hexanes:*iso*-propanol, 1.0 mL/min. Major: 34.2 min, minor: 39.7 min.

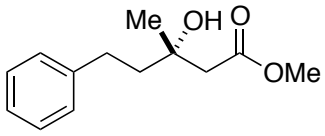
^{1}H-NMR (400 MHz; $CDCl_3$): δ 4.15-4.12 (m, 2H), 3.79 (ddd, *J* = 9.2, 6.4, 2.8 Hz, 1H), 3.71 (s, 3H), 2.98 (bs, 1H), 2.65 (t, *J* = 12.9 Hz, 2H), 2.53 (dd, *J* = 16.4, 2.8 Hz, 1H), 2.42 (dd, *J* = 16.4, 9.4 Hz, 1H), 1.83 (dt, *J* = 13.2, 2.5 Hz, 1H), 1.60-1.55 (m, 1H), 1.50 (m, *J* = 3.5 Hz, 1H), 1.44 (s, 9H), 1.28-1.16 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.6, 154.8, 79.4, 71.2, 41.4, 38.2, 28.4, 27.9 IR (ATR neat): 3458, 2976, 1775, 1693, 1433, 1162; **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 288.1, found 288.1 $[\alpha]_D^{21}$ = -7.6 (c = 0.010 g/ml, MeOH)



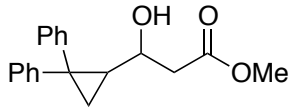
(*R*)-methyl 3-hydroxy-3-phenylbutanoate (**113**): Colorless Oil. 36 % yield, 28 % ee. R_f=0.26 (7:3 Hexanes:Ether); **HPLC analysis**: Chiralcel OJ-H column, 90:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 11.2 min. minor: 13.3 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.46-7.24 (m, 5H), 4.31 (s, 1H), 3.61 (s, 3H), 2.90 (dd, *J* = 75.0, 16.0 Hz, 2H), 1.55 (s, 3H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.1, 128.3, 125.3, 124.4, 72.7, 51.7, 46.2, 30.6. Spectra matched that of the previously reported compound.[14]



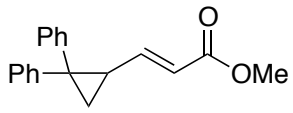
(*S*)-methyl 3-hydroxy-3,7-dimethyloct-6-enoate (**114**): Colorless Oil. 40 % yield, 63 % ee. R_f=0.41 (1:1 Hexanes:Ether); **HPLC analysis**: Chiralpak IB column, 99:1 hexanes:*iso*-propanol, 1.0 mL/min. Major: 5.6 min, minor: 6.0 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): 5.10-5.06 (m, 1H), 3.70 (s, 3H), 3.40 (bs, 1H), 2.48 (q, *J* = 15.9 Hz, 2H), 2.07-2.01 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.52 (td, *J* = 8.4, 4.2 Hz, 2H), 1.23 (s, 3H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.4, 131.8, 124.0, 70.9, 51.6, 44.7, 41.8, 26.6, 25.6, 22.6, 17.6. Spectra matched that of the previously reported compound.[14]



(*S*)-methyl 3-hydroxy-3-methyl-5-phenylpentanoate (**115**): Colorless Oil. 32 % yield, 46 % ee. R_f=0.33 (7:3 hexanes:ether); **HPLC analysis**: Chiralpak IB column, 99:1 hexanes/*iso*-propanol, 1.0 mL/min. Major: 11.8 min, minor: 12.6 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.30-7.16 (m, 5H), 3.72 (s, 3H), 3.54 (bs, 1H), 2.75-2.69 (m, 2H), 2.55 (q, *J* = 15.8 Hz, 2H), 1.86-1.80 (m, 2H), 1.32 (s, 3H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.4, 142.2, 128.40, 128.31, 125.8, 70.8, 51.7, 44.8, 43.8, 30.3, 26.7. Spectra matched that of the previously reported compound.[14]

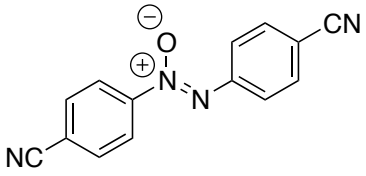


methyl 3-(2,2-diphenylcyclopropyl)-3-hydroxypropanoate (**55**): Colorless Oil. R_f = 0.30 (1:1 hexanes:ether) **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.49 (d, *J* = 7.2 Hz, 2H), 7.32-7.21 (m, 7H), 7.15-7.12 (m, 1H), 3.67 (s, 3H), 3.24 (ddd, *J* = 9.6, 7.7, 4.7 Hz, 1H), 2.79 (bs, 1H), 2.68-2.59 (m, 2H), 1.83 (td, *J* = 9.2, 6.4 Hz, 1H), 1.26 (dt, *J* = 8.5, 4.1 Hz, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 173.0, 146.1, 140.9, 130.3, 128.5, 128.25, 128.14, 126.8, 126.1, 69.2, 51.7, 40.9, 36.6, 31.3, 16.9 **IR** (ATR neat) 3415, 3026, 3001, 2952, 1732, 1604, 1497, 1437, 698; **LRMS** (ESI + APCI) *m/z* [M+H] calcd. .297.1, found 297.1

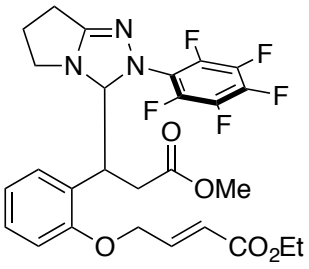


(*E*)-3-(2,2-diphenylcyclopropyl)acrylaldehyde (**56**): White Amorphous Solid R_f = 0.25 (8:2 hexanes:ether) **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 9.26 (d, *J* = 7.9 Hz, 1H), 7.36-7.18 (m, 10H), 6.30 (dd, *J* = 15.4, 7.9 Hz, 1H), 6.05 (dd, *J* = 15.4, 10.4 Hz, 1H), 2.54 (ddd, *J* =

10.3, 8.5, 5.5 Hz, 1H), 1.93 (dd, *J* = 8.5, 5.1 Hz, 1H), 1.83 (t, *J* = 5.3 Hz, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 193.0, 159.8, 144.9, 140.2, 131.7, 130.4, 128.7, 128.5, 127.4 127.3, 126.6, 30.6, 24.1 **IR**: 3056, 3025, 1681, 1629, 1494, 1446, 1177; **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 249.1, found 249.1



(*Z*)-1,2-bis(4-cyanophenyl)diazene oxide (**43**): Off White Amorphous Solid. R_f = 0.34 (1:1 hexanes:ether); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 8.46 (d, *J* = 8.7 Hz, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H). **^{13}C-NMR** (101 MHz; cdcl3): δ 133.1, 132.8, 126.0, 123.4; **IR** (ATR Neat): 3104, 2224, 1600, 1490, 1459, 1344, 1311, 1291, 842. **LRMS** (ESI + APCI) *m/z* [M+H] calcd 249.1, found 249.1 Spectra matched that of the previously reported compound.[15]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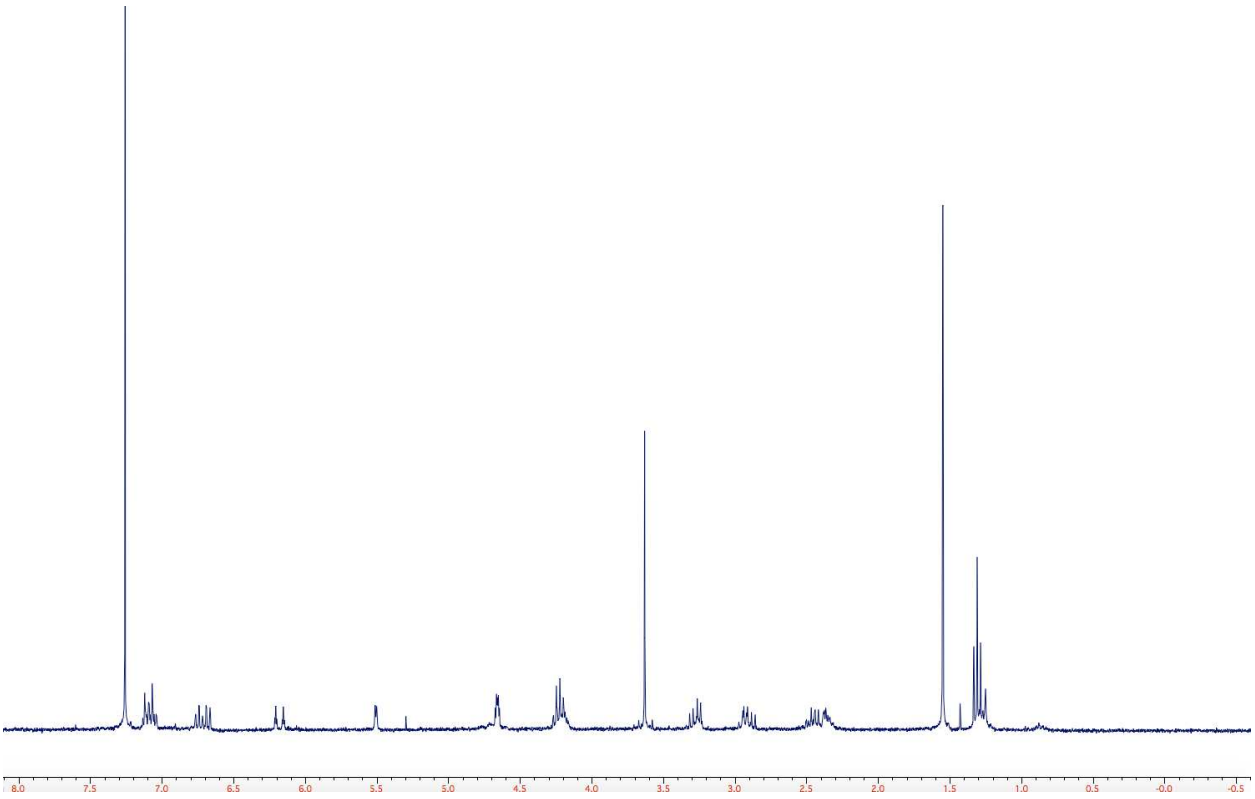
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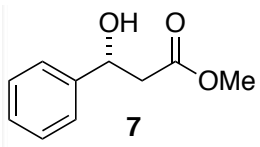
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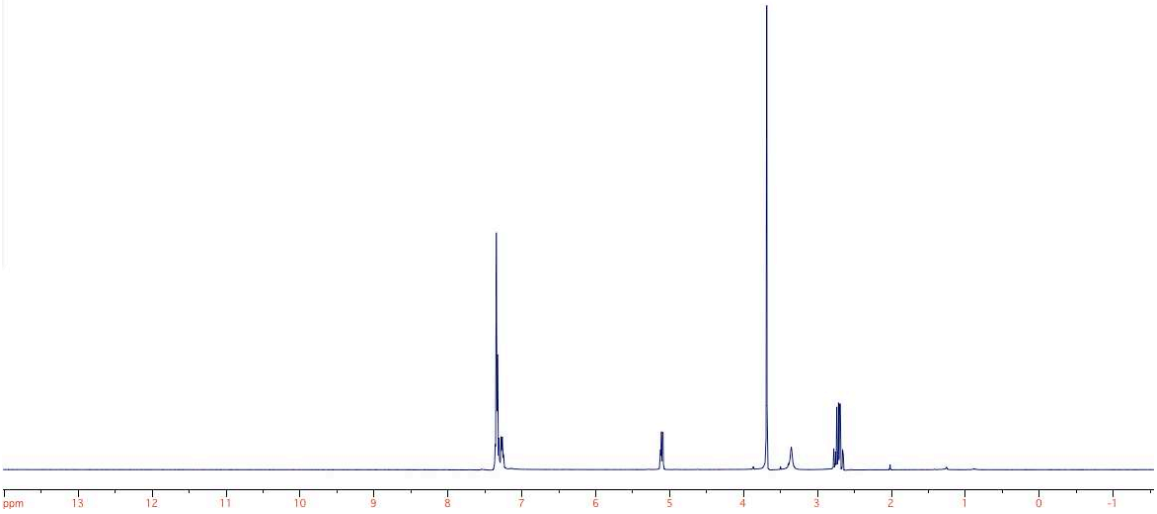
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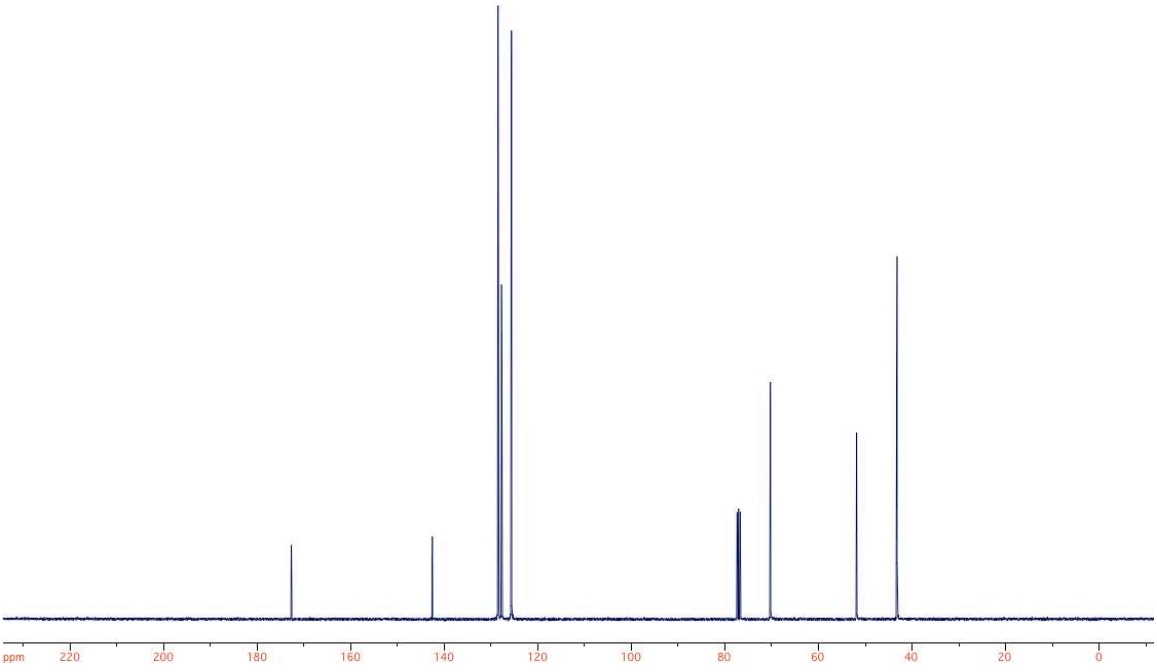
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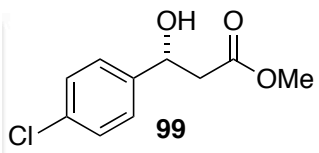
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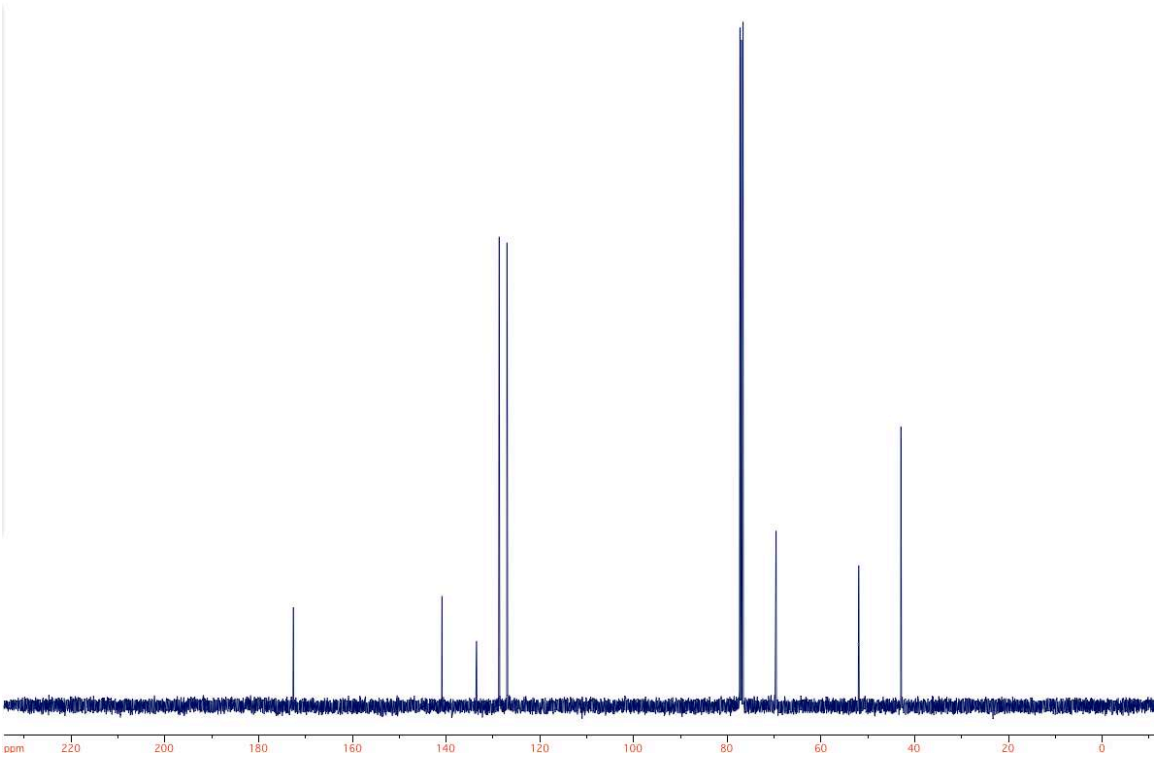
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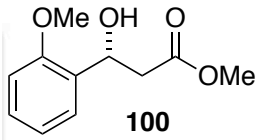
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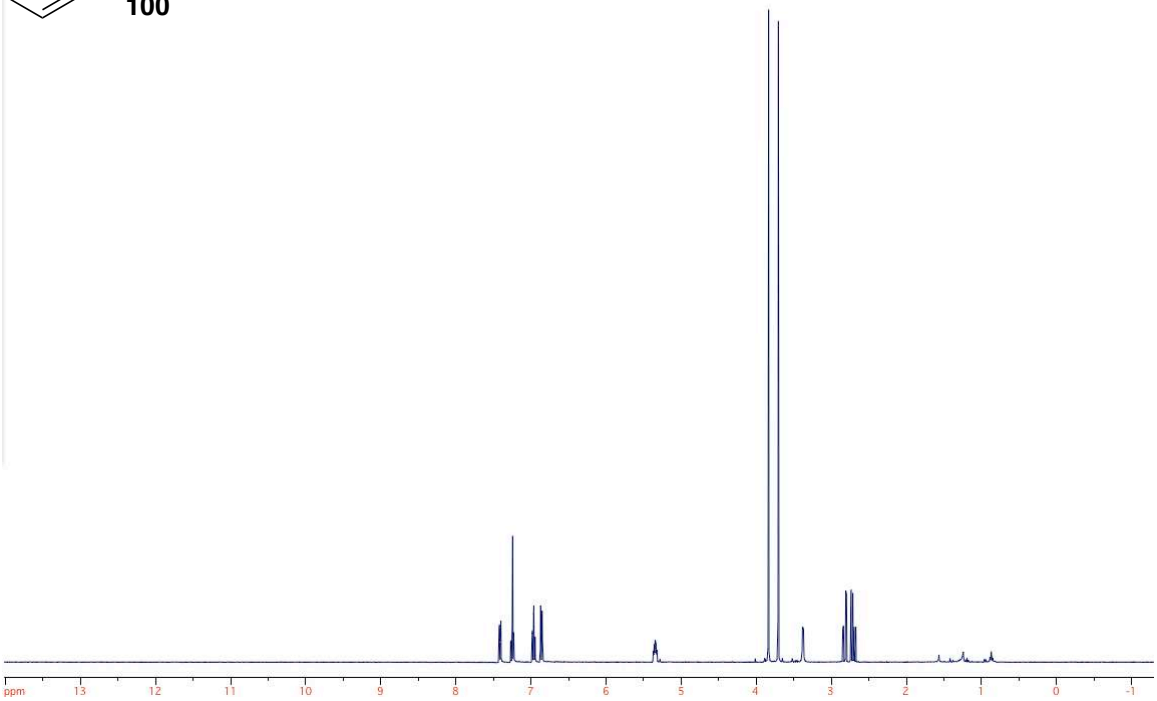
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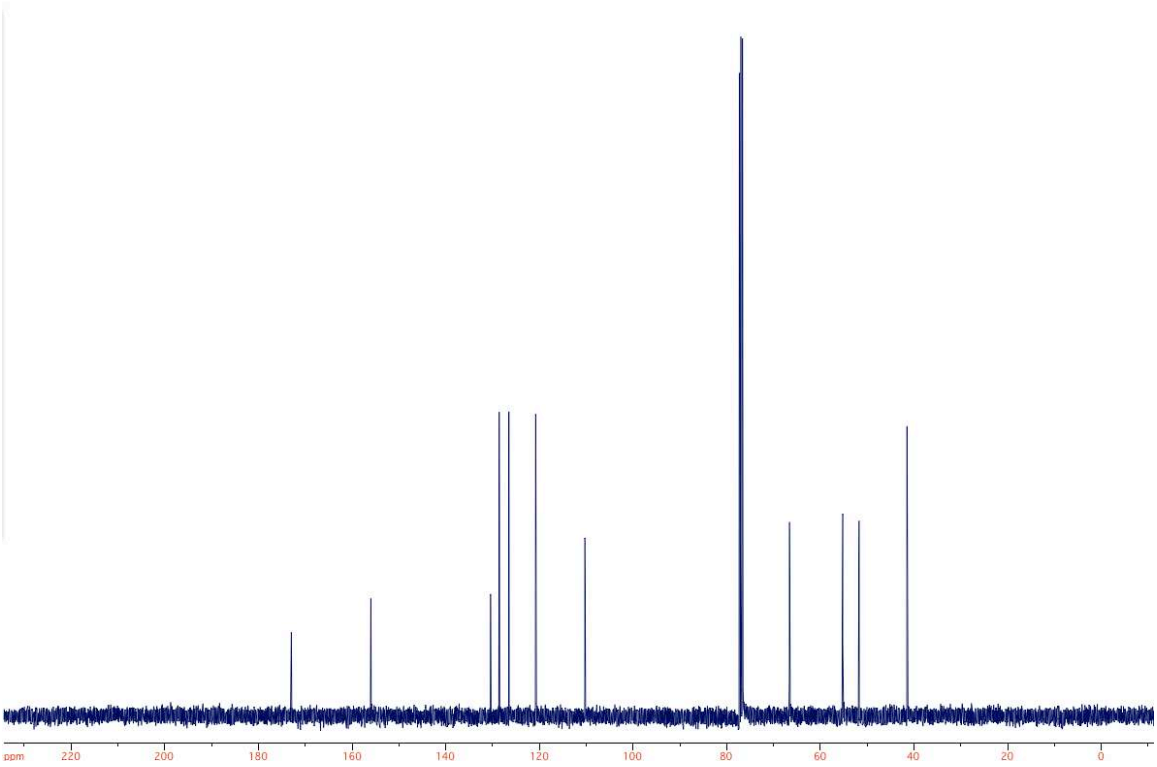
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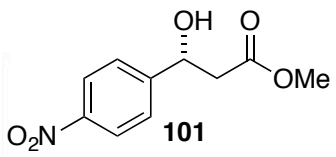
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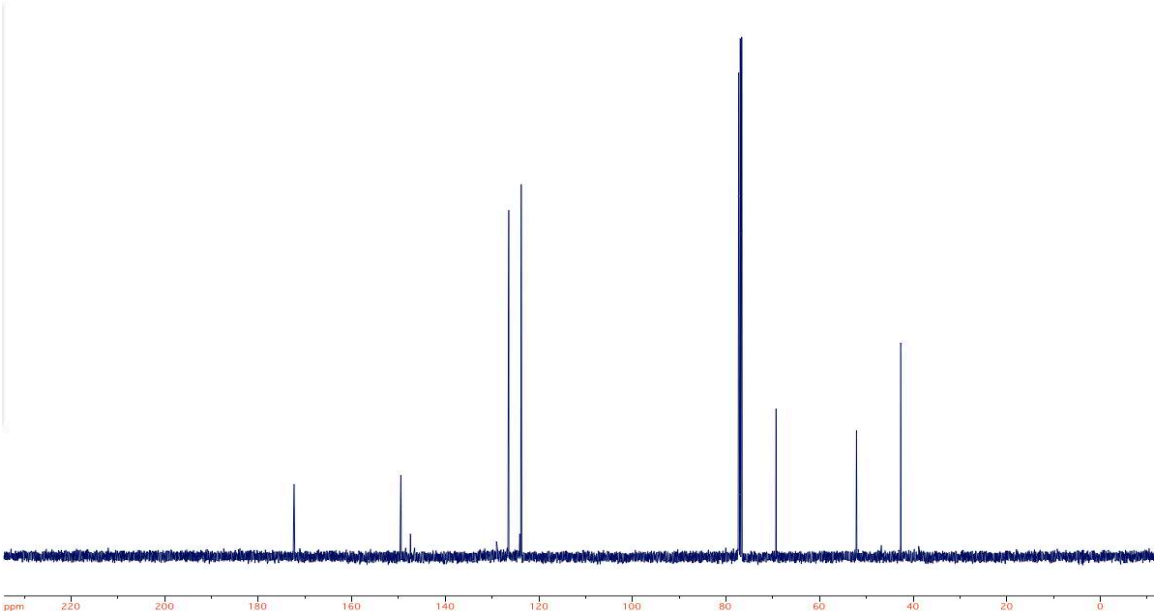
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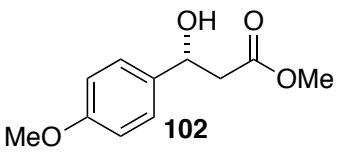
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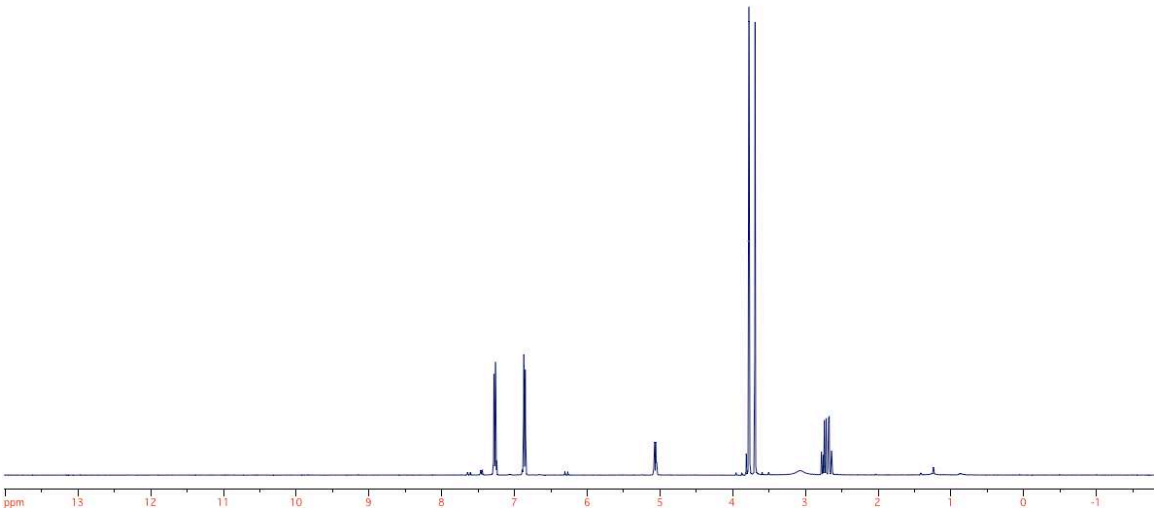
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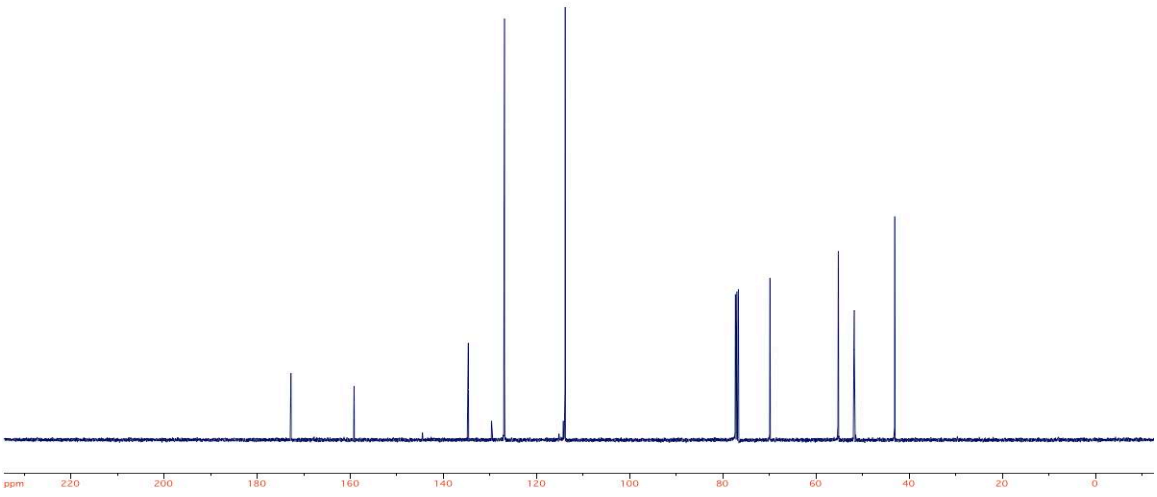
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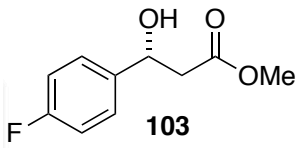
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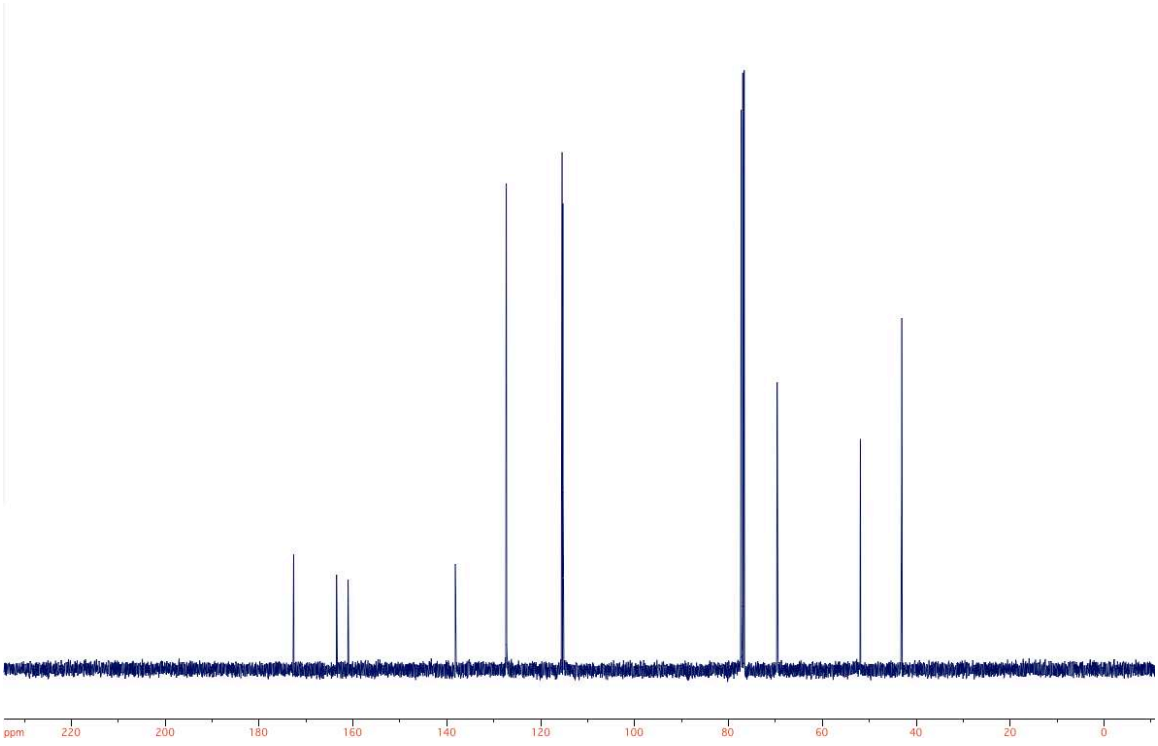
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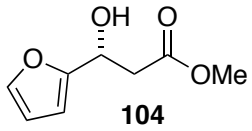
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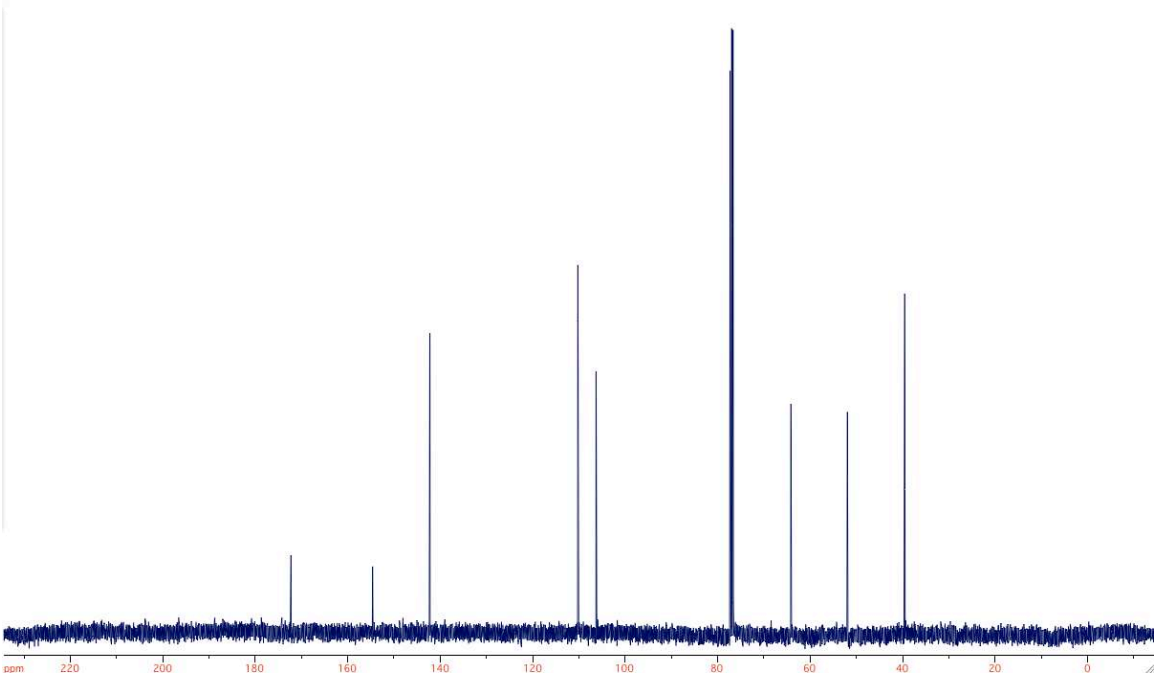
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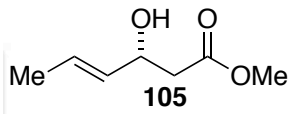
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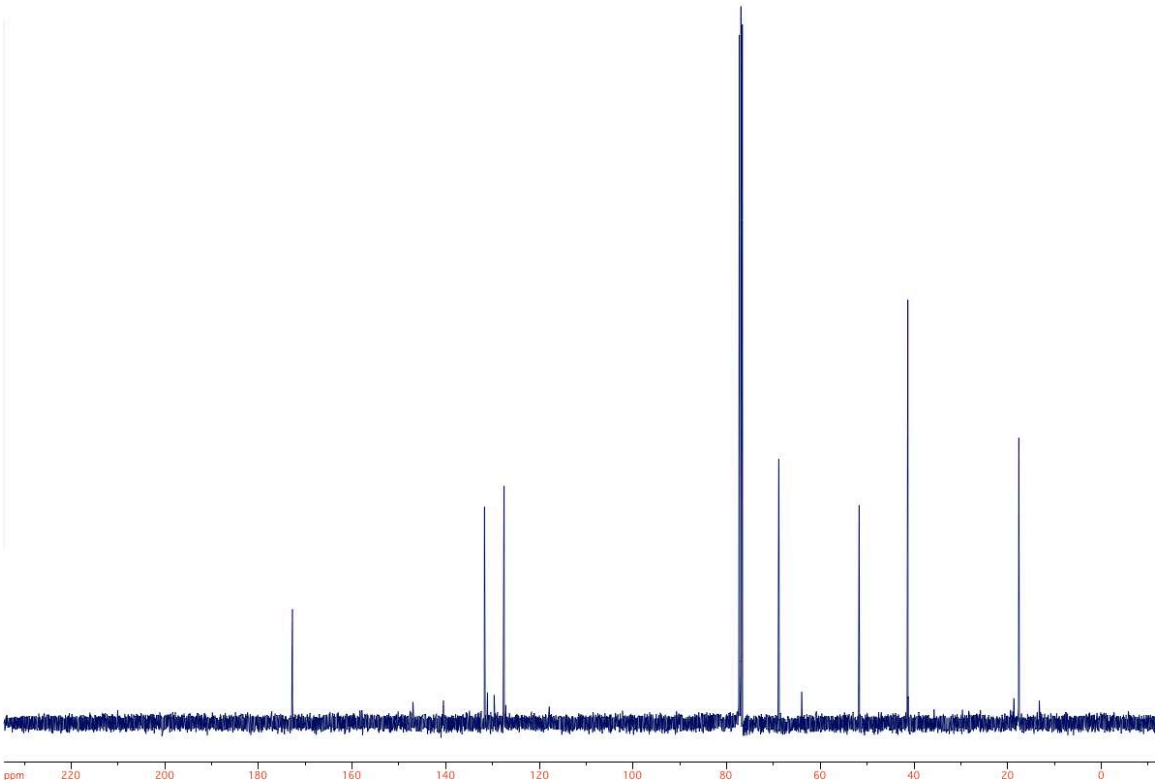
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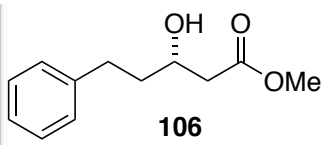
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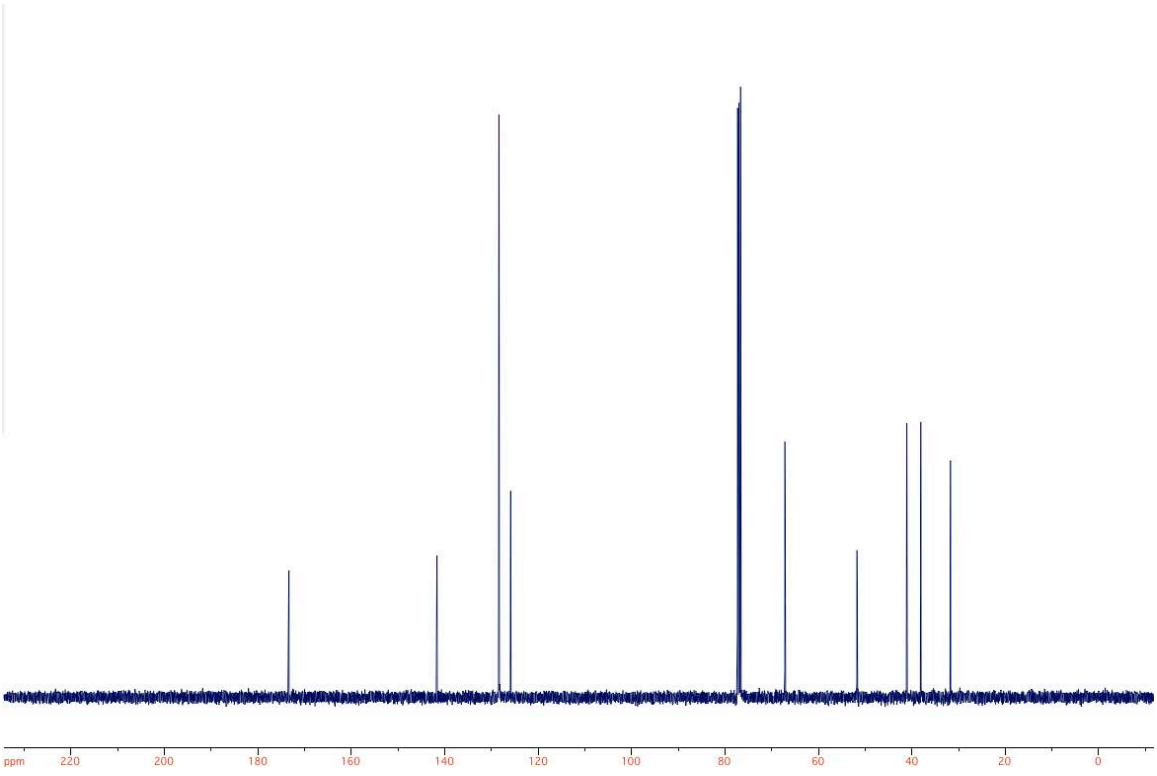
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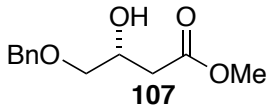
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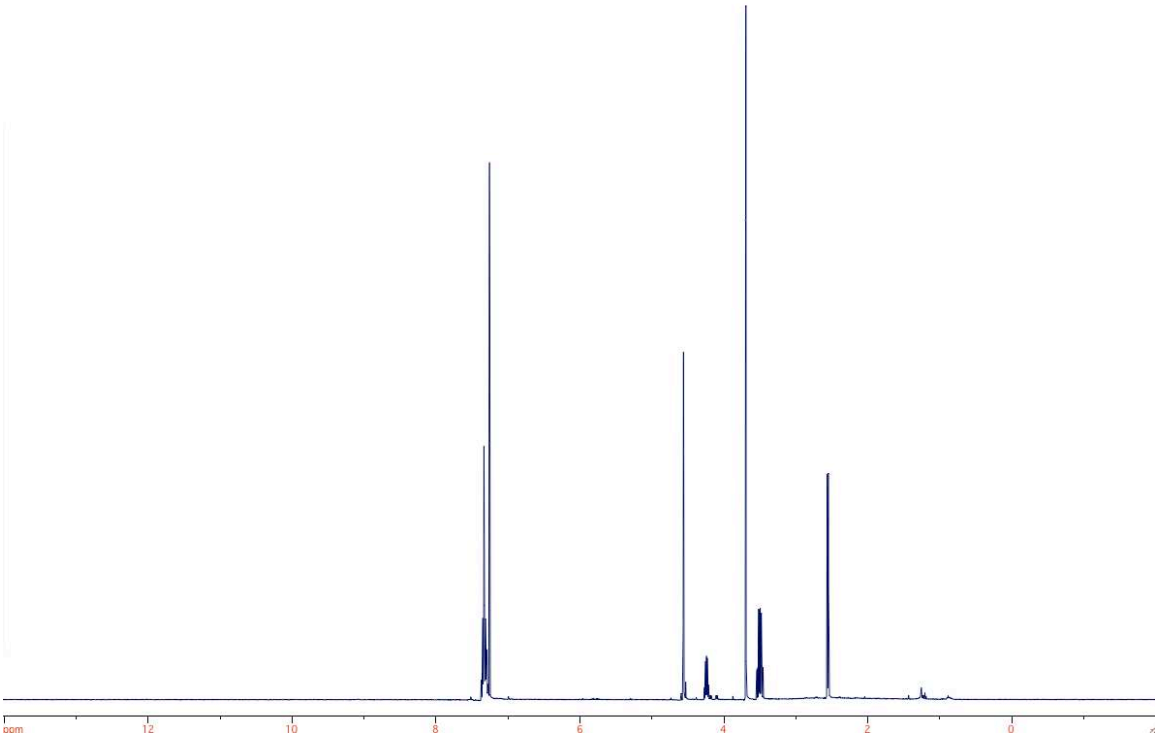
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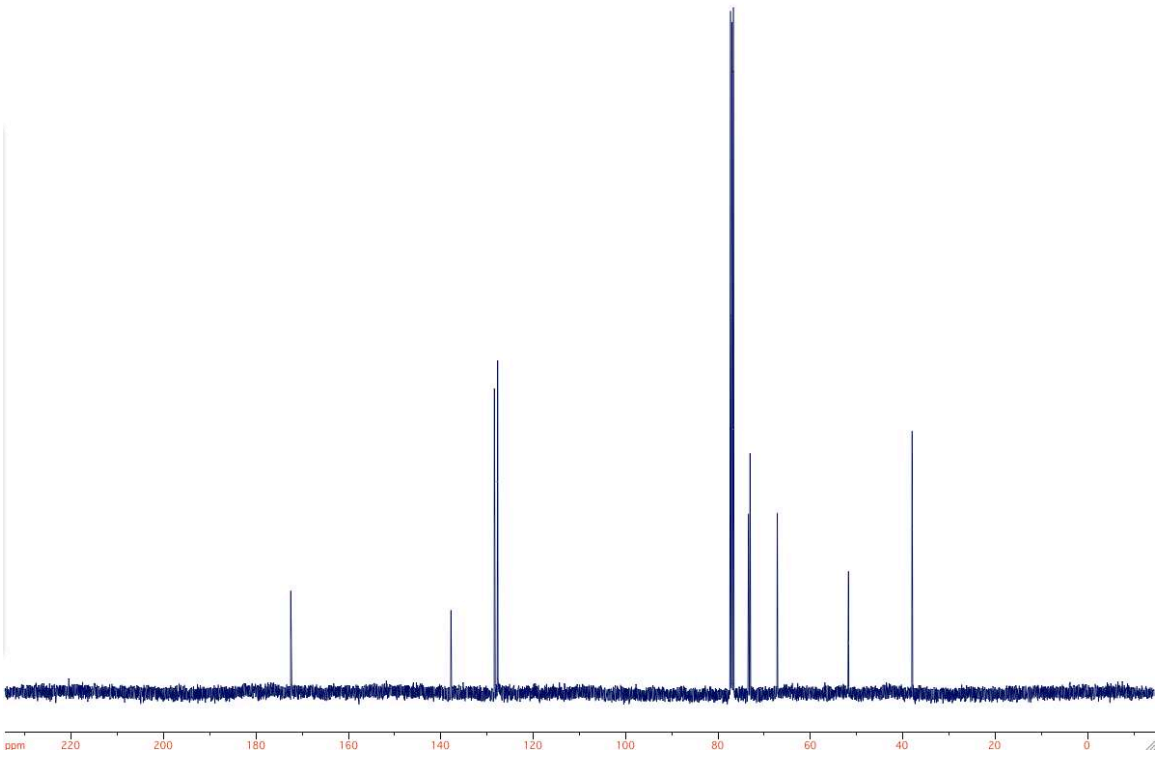
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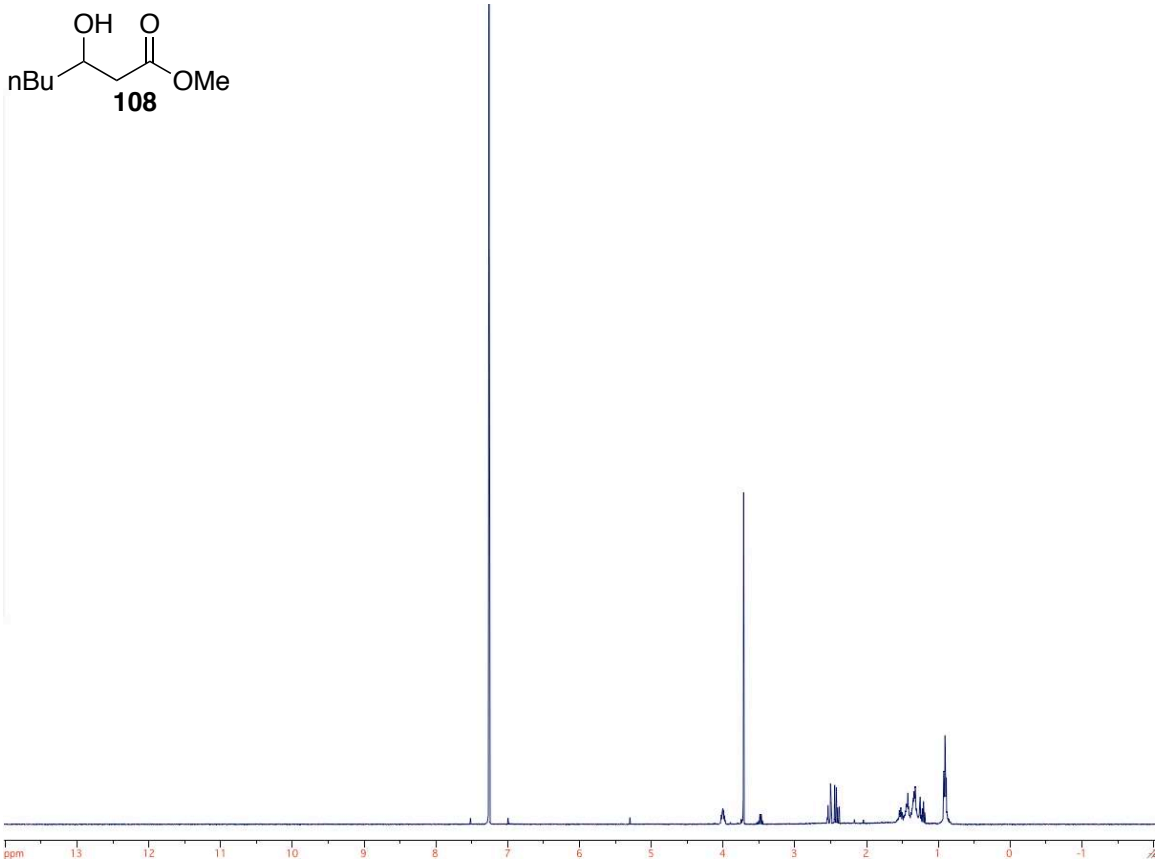
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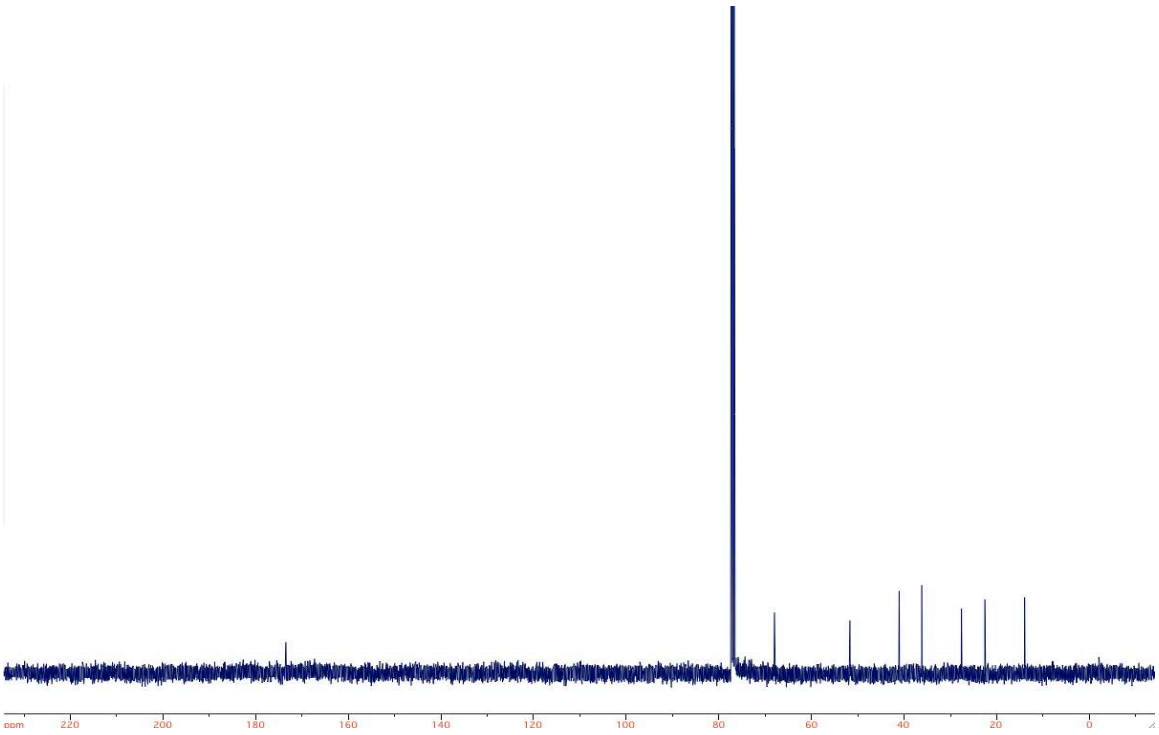
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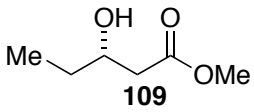
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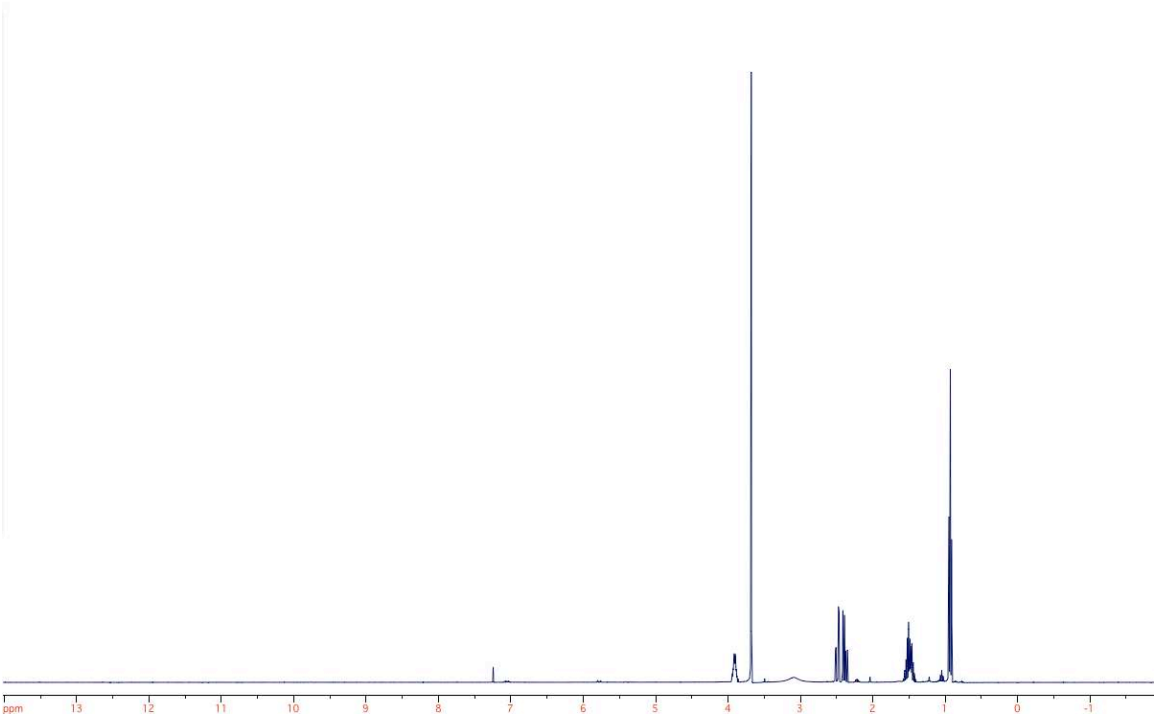
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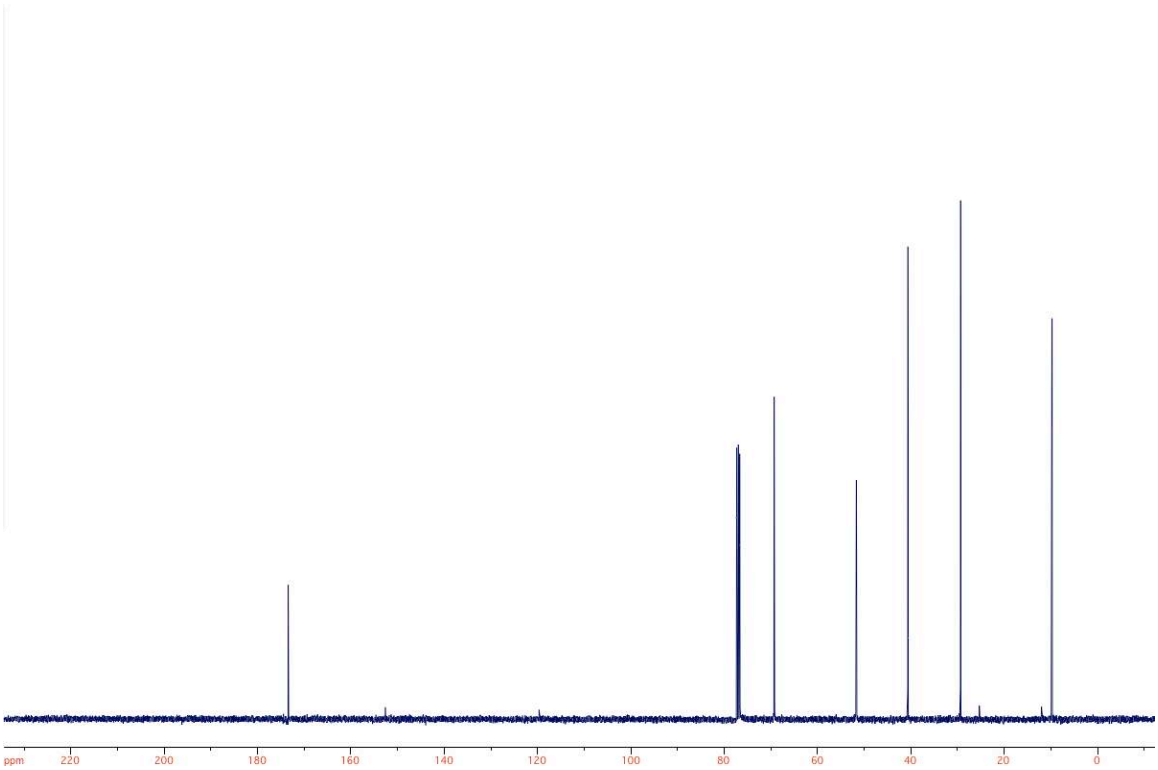
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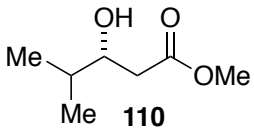
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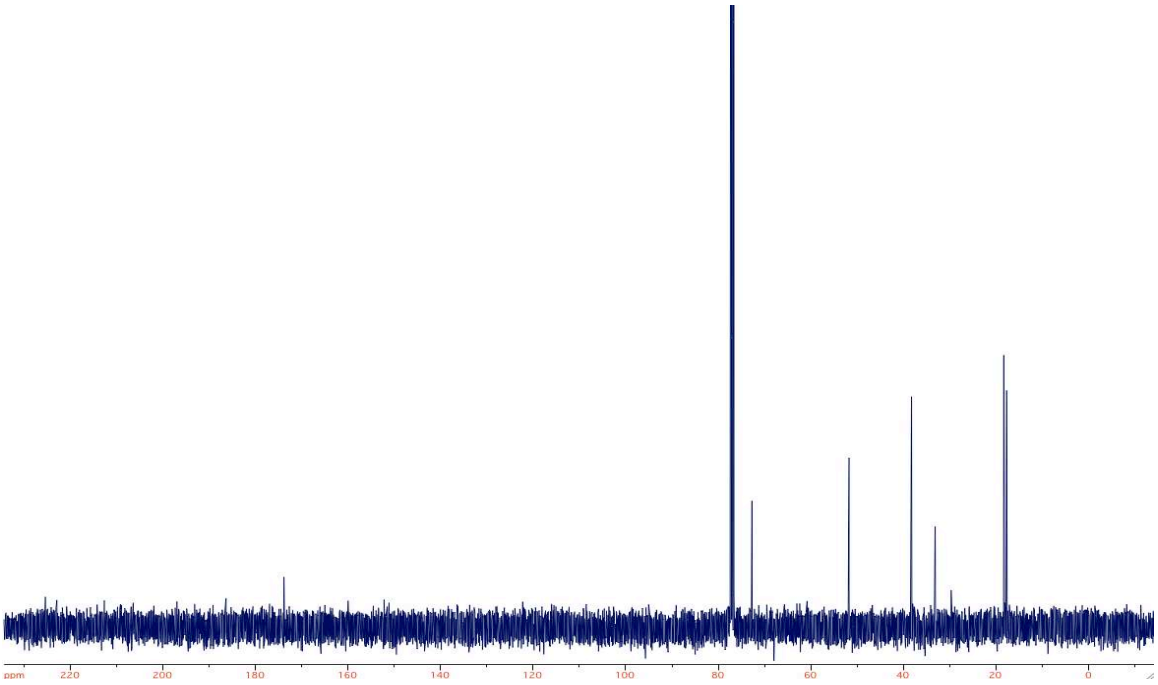
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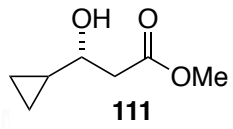
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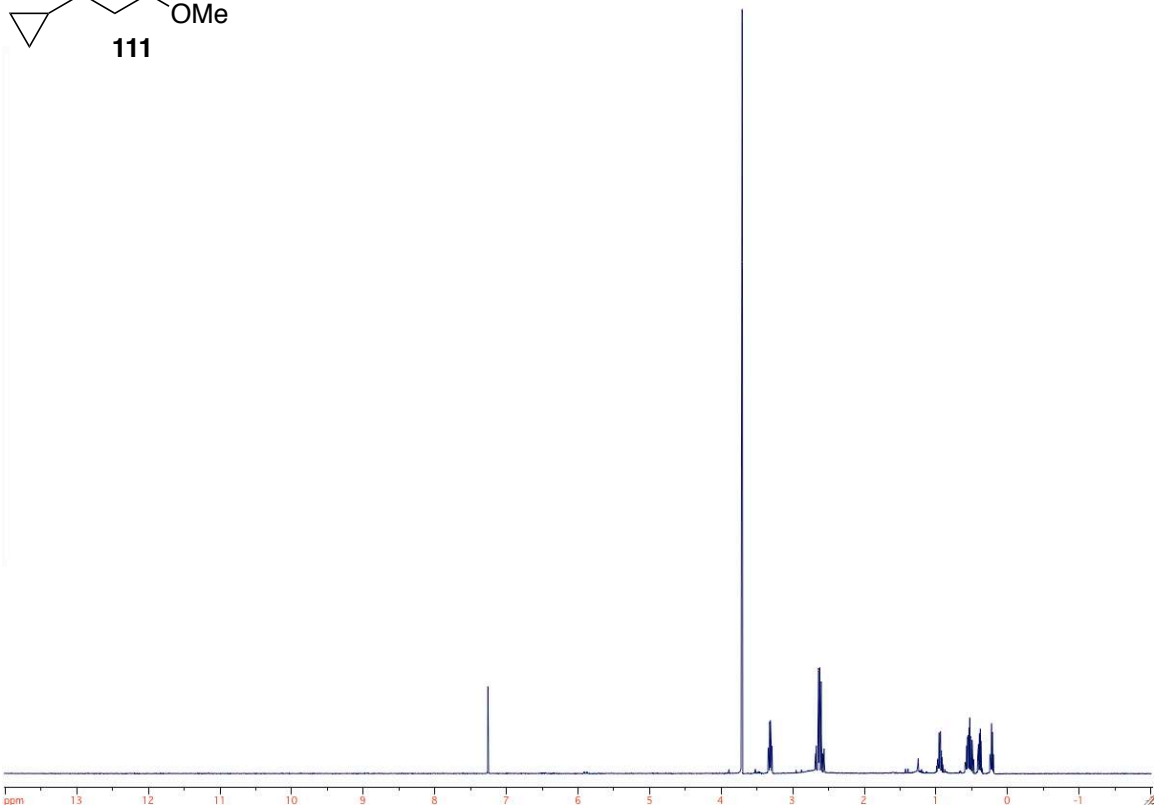
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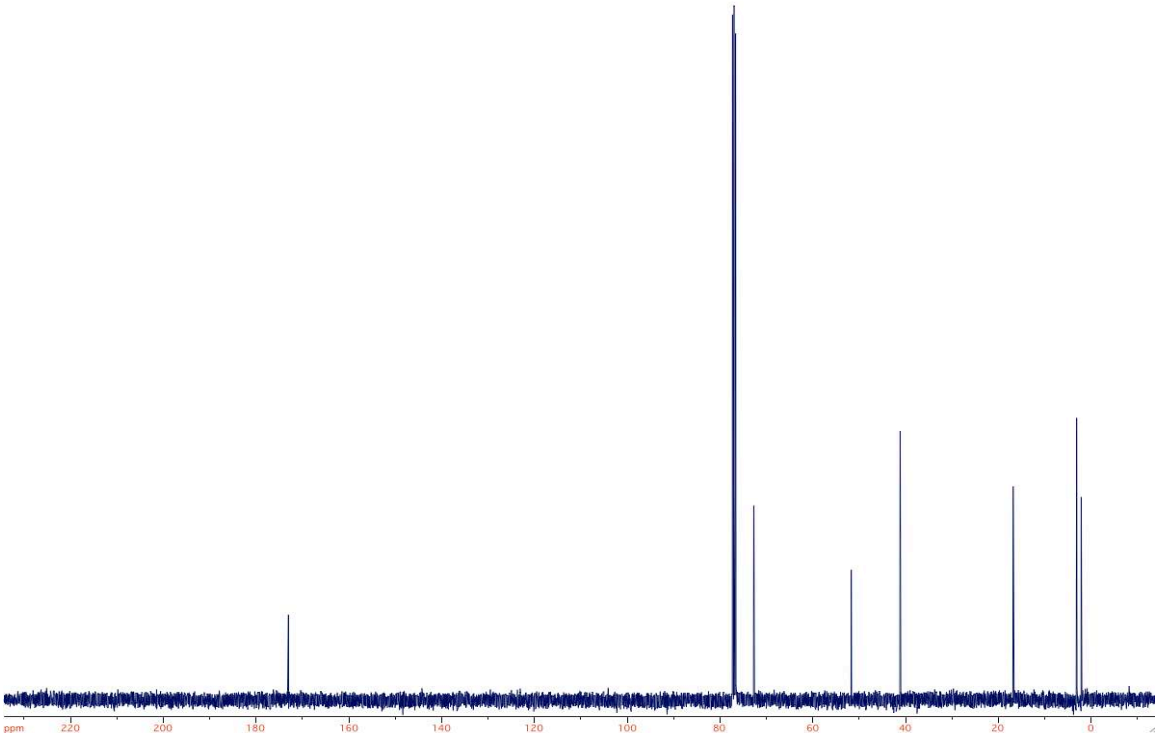
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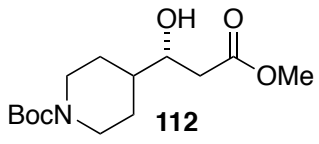
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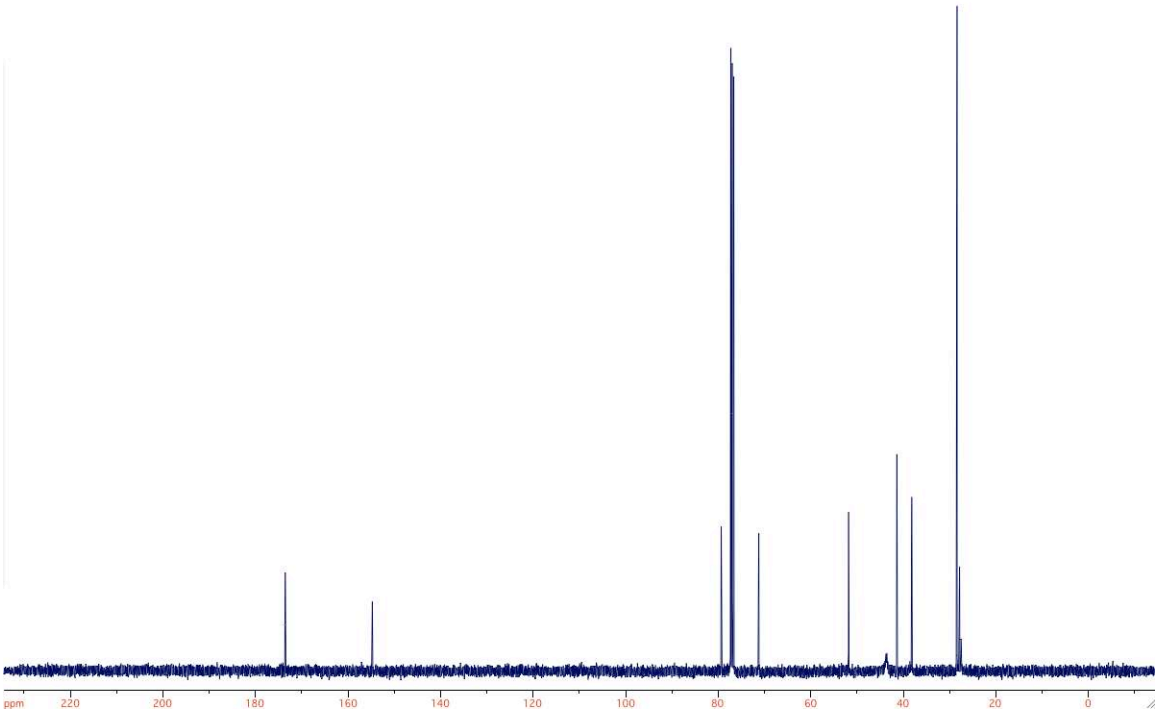
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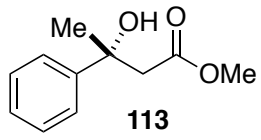
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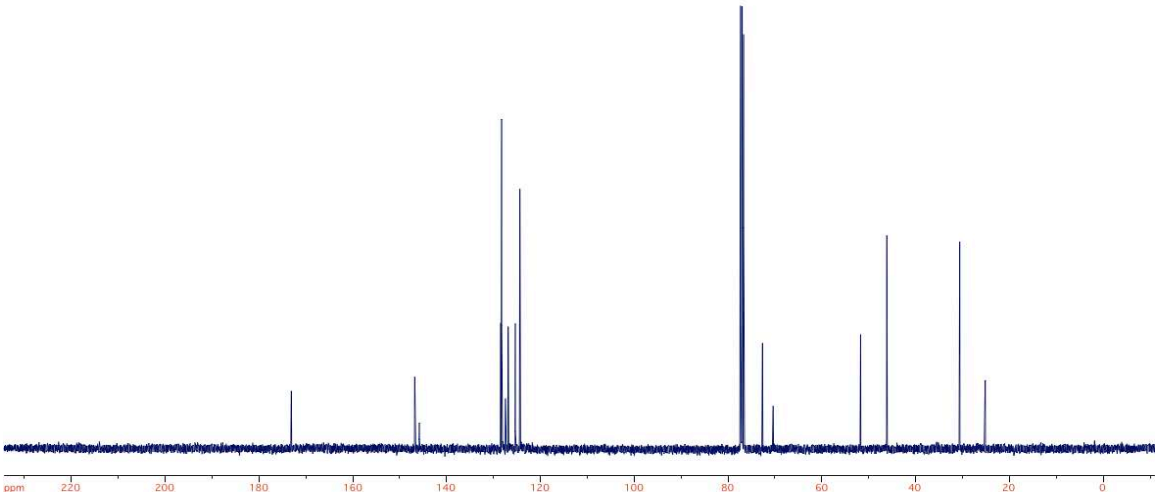
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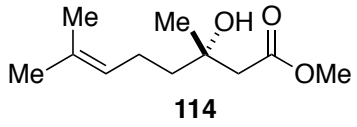

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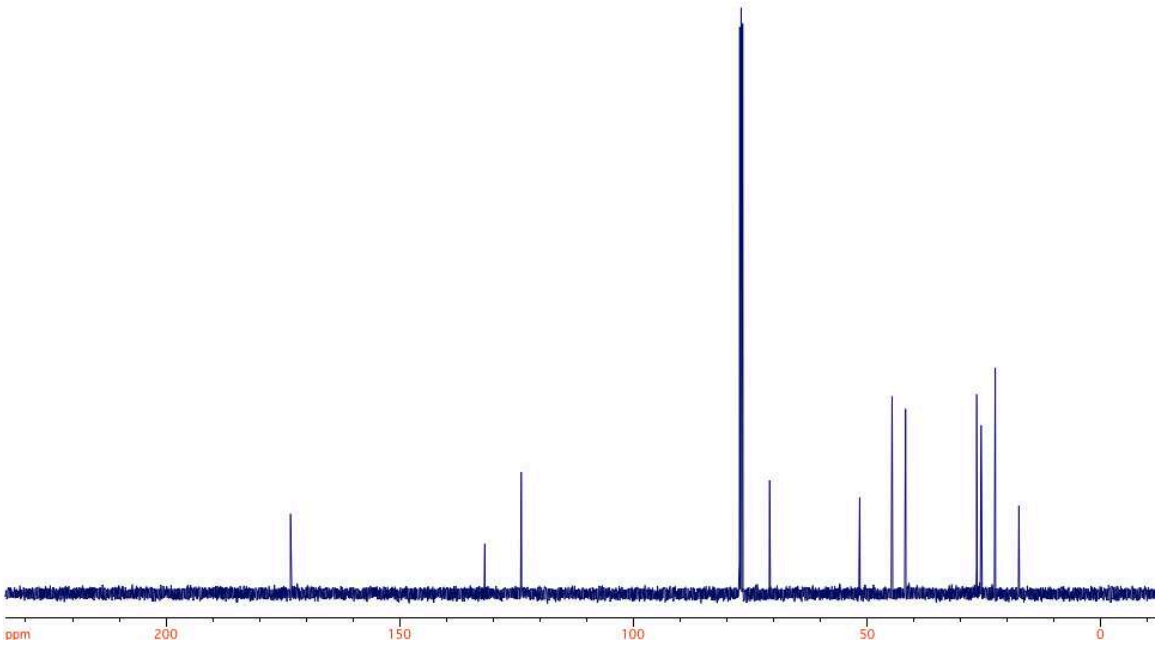

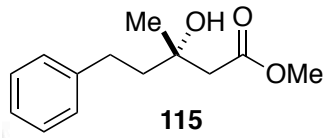
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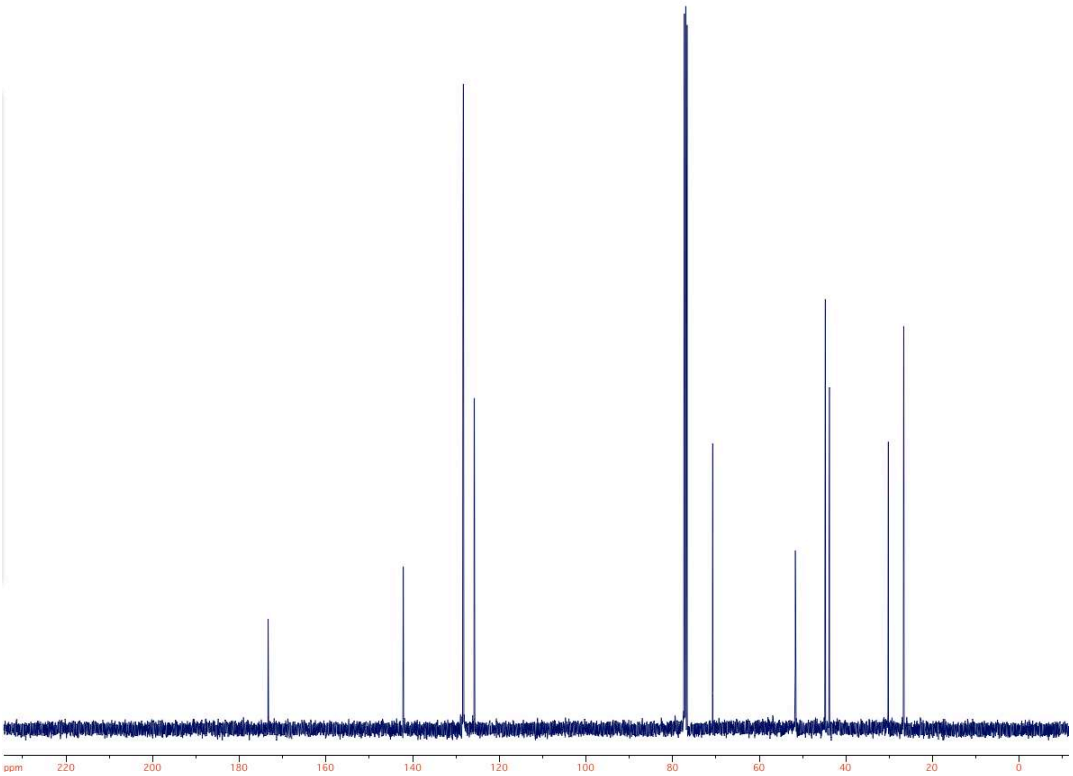
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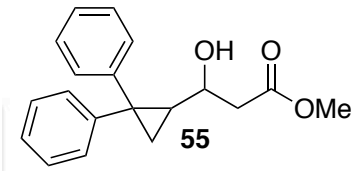
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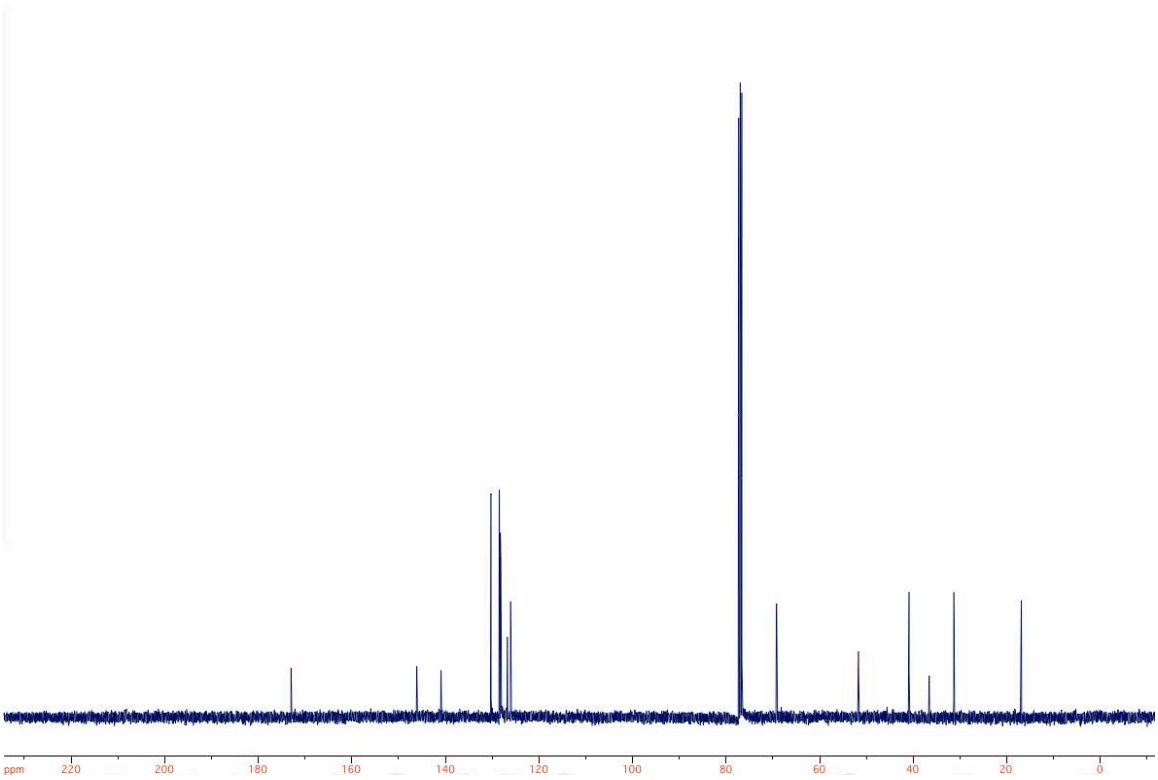
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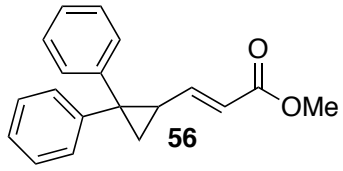
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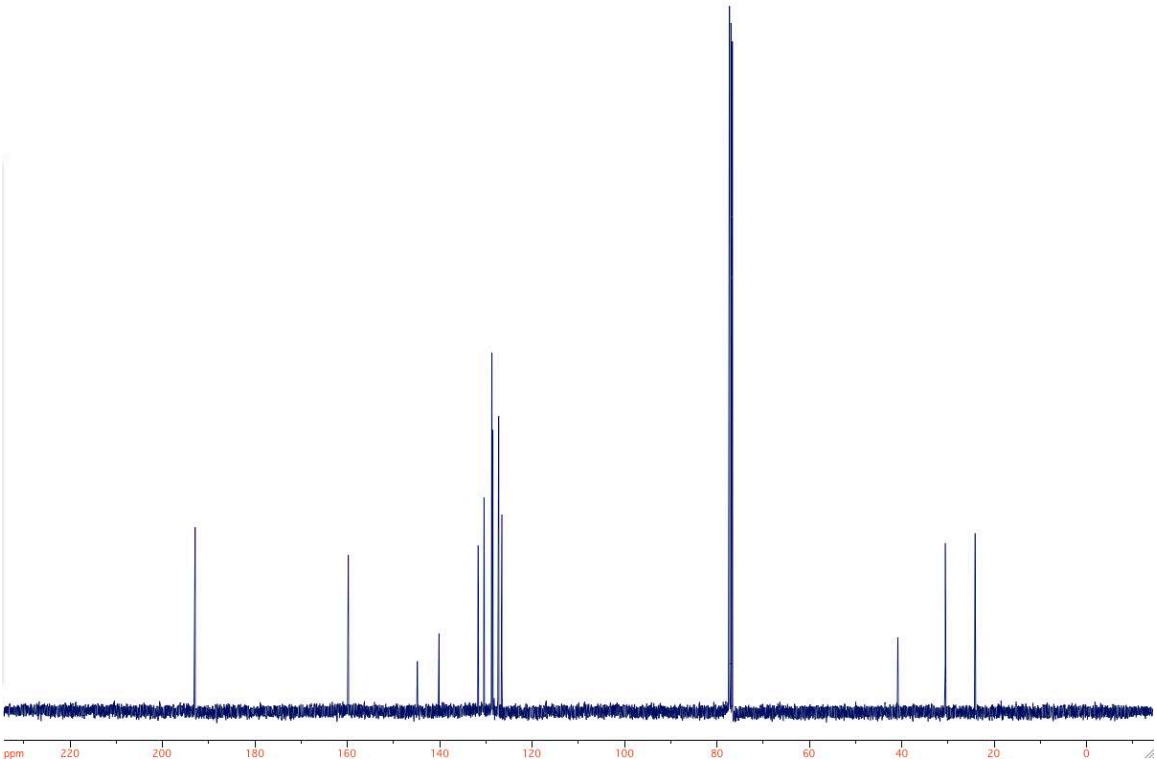
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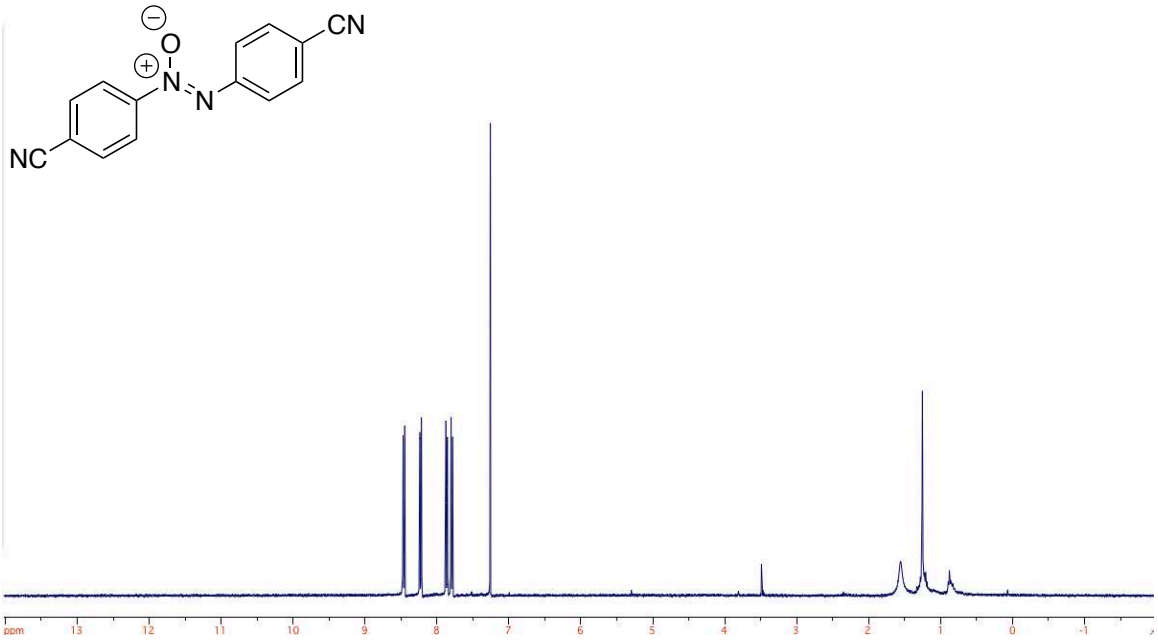
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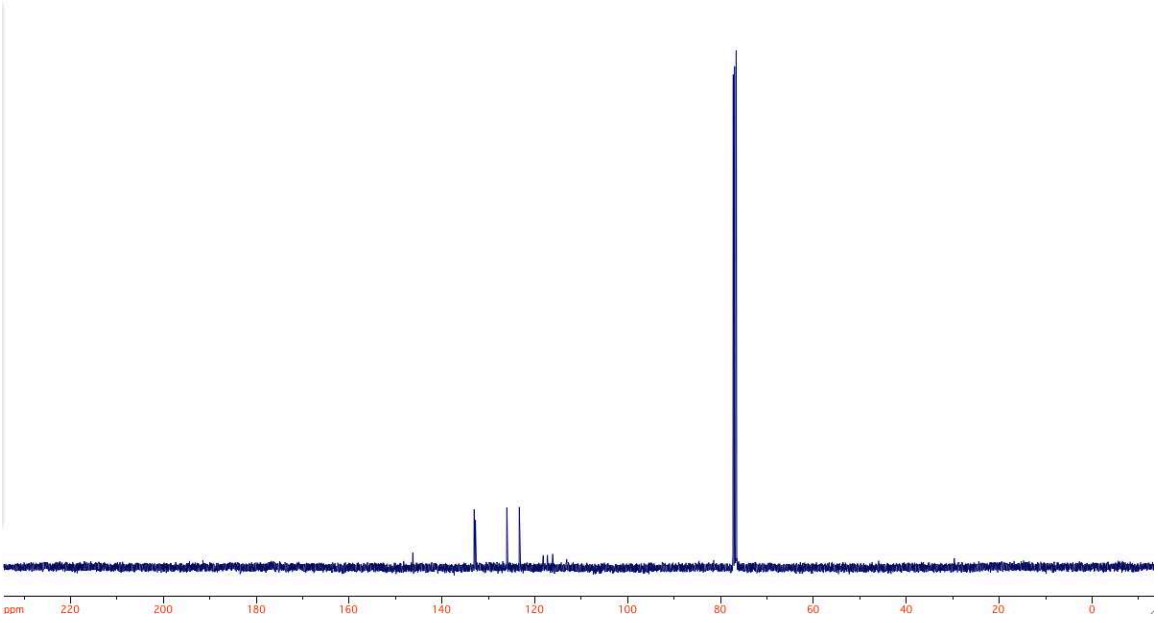
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References

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Appendix 3. Chapter 4 Experimenal

Asymmetric Cyclopentanone Synthesis from Enals via Single-Electron Oxidation of the Breslow Intermediate

Materials and Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Trifluorotoluene was purchased from Aldrich in a Sure-Seal container and stored in a glove box. Dichloromethane was degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Tetrahydrofuran was degassed with argon and passed through one column of neutral alumina. Sodium acetate was purchased from Aldrich. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light or KMnO4 stain followed by heating.

^{1}H NMR spectra were recorded on Varian 400 MHz spectrometers at ambient temperature. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm) or acetone-D_6 (2.03 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ^{13}C NMR were recorded on Varian 400 MHz spectrometers (at 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.36 ppm) or acetone-D_6 (205.87, 30.6 ppm). The ^{13}C NMR show an anomaly at 194.8 ppm (in $CDCl_3$) that is an artifact of the instrument. Mass spectra were recorded on an Agilent 6130 Quadrupole LC/MS. Aldehydes were either purchased from Aldrich or prepared via known

literature procedures. Nitroarenes were purchased from Aldrich.

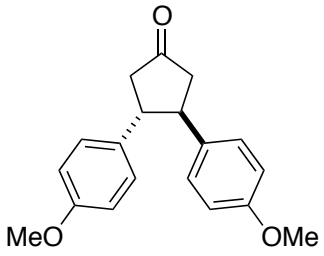
General Procedure for the Enal Dimerization to Form Cyclopentanones

To a flame dried screw cap vial charged with a stirbar was added triazolium salt **36** (17 mg, 0.04 mmol), 4-methoxycinnamaldehyde **60** (49 mg, 0.3 mmol), 4-nitropyridine N-oxide **2** (28 mg, 0.2 mmol), NaOAc (16 mg, 0.2 mmol), and LiCl (8 mg, 0.2 mmol). This vial was then pumped into a glove box containing an argon atmosphere. 1.0 mL of dry trifluorotoluene ($PhCF_3$) was then added and the cap tightly screwed on, removed from the glove box, and wrapped in parafilm tape. The reaction was then heated to 70 °C and stirred for 12 hours. After 12 hours the reaction was concentrated via rotary evaporation and then purified via silica gel chromatography (7:3 hexanes:ether) to yield 35 mg (79 %) (3*R*,4*R*)-3,4-bis(4-methoxyphenyl)cyclopentanone **5** as an off-white solid in 84 % ee and as a single diastereomer.

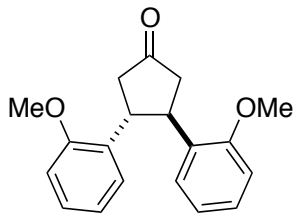
General Procedure for the Cross Annulation to Form Cyclopentanones

To a flame dried screw cap vial charged with a stirbar was added triazolium salt **36** (17 mg, 0.04 mmol), cinnamaldehyde **60** (26 mg, 0.2 mmol), 4-methoxycinnamaldehyde **1** (131 mg, 0.8 mmol), 4-nitropyridine N-oxide **2** (112 mg, 0.8 mmol), NaOAc (66 mg, 0.8 mmol), and LiCl (34 mg, 0.8 mmol). This vial was then pumped into a glove box containing an argon atmosphere. 3.0 mL of dry trifluorotoluene ($PhCF_3$) was then added and the cap tightly screwed on, removed from the glove box, and wrapped in parafilm tape. The reaction was then heated to 70 °C and stirred for 12 hours. After 12 hours the reaction was concentrated via rotary evaporation and then purified via silica gel chromatography (8:2 hexanes:ether) to yield 35 mg (65 %) (3*R*,4*R*)-3-(4-

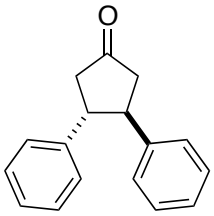
methoxyphenyl)-4-phenylcyclopentanone **59** as an off-white solid in 83 % ee and as a single diastereomer.



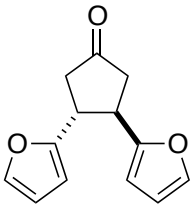
(3*R*,4*R*)-3,4-bis(4-methoxyphenyl)cyclopentanone (**5**): Off-White Amorphous Solid. 79 % yield, 84 % ee, >20:1 dr., Rf: 0.25 (1:1 hexanes:ether); $[\alpha]_D^{21}$ = -67.4 (c = 0.010 g/ml, CH_2Cl_2); **HPLC Analysis**: Chiralpak IB column 80:20 hexanes/*iso*propanol, 1.0 mL/min, Major: 10.6 min, minor: 10.2 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.04-7.01 (m, 4H), 6.80-6.76 (m, 4H), 3.76 (s, 6H), 3.42-3.33 (m, 2H), 2.85-2.79 (m, 2H), 2.56-2.49 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 216.1, 158.3, 132.9, 128.1, 113.9, 55.2, 49.6, 47.3. Spectra matched that of the previously reported compound.[129]



(3*R*,4*R*)-3,4-bis(2-methoxyphenyl)cyclopentanone (**46**): Off-White Amorphous Solid. 71 % yield, 91 % ee, >20:1 dr., Rf: 0.31 (1:1 hexanes:ether); $[\alpha]_D^{21}$ = -60.3 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 98:2 hexanes/*iso*propanol, 1.0 mL/min, Major: 12.8 min, minor: 13.8 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.16-7.12 (m, 4H), 6.85-6.81 (m, 4H), 4.04-3.97 (m, 2H), 3.78 (s, 5H), 2.93-2.86 (m, 2H), 2.48-2.40 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 218.0, 157.5, 130.2, 127.52, 127.46, 120.6, 110.5, 55.2, 46.1, 41.5. Spectra matched that of the previously reported compound.[129]

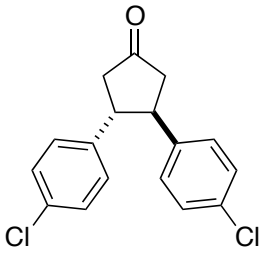


(3*R*,4*R*)-3,4-diphenylcyclopentanone (**47**): Off-White Amorphous Solid. 74 % yield, 84 % ee, >20:1 dr., Rf: 0.42 (8:2 hexanes:ether); $[\alpha]_D^{21}$ = -64.1 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Reverse phase Chiralpak IB column 95:5 H_2O/acetonitrile, 1.0 mL/min, Major: 21.2 min, minor: 20.8 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.34-7.01 (m, 10H), 3.54-3.45 (m, 2H), 2.90-2.84 (m, 2H), 2.67-2.51 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.8, 140.8, 128.5, 127.2, 126.8, 50.2, 47.2. Spectra matched that of the previously reported compound.[129]

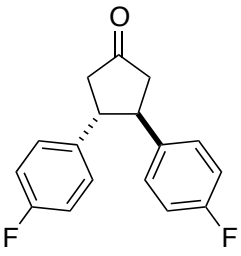


(3*R*,4*R*)-3,4-di(furan-2-yl)cyclopentanone (**48**): Pale Yellow Oil.

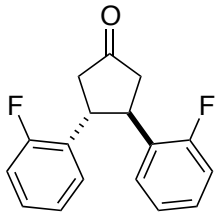
66 % yield, 65 % ee, >20:1 dr., Rf: 0.53 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -24.3 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 95:5 hexanes/*iso*propanol, 1.0 mL/min, Major: 7.6 min, minor: 7.0 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.34 (dd, *J* = 1.9, 0.8 Hz, 2H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 2H), 6.05 (d, *J* = 3.2 Hz, 2H), 3.72-3.64 (m, 2H), 2.80-2.73 (m, 2H), 2.62-2.54 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.0, 154.5, 141.7, 110.2, 105.9, 43.3, 40.8. Spectra matched that of the previously reported compound.[129]



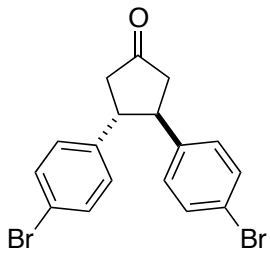
(3*R*,4*R*)-3,4-bis(4-chlorophenyl)cyclopentanone (**49**): Off-White Amorphous Solid. 63 % yield, 84 % ee, >20:1 dr., Rf: 0.13 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -77.2 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 80:20 hexanes/*iso*propanol, 1.0 mL/min, Major: 10.1 min, minor: 9.6 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.22 (d, *J* = 8.2 Hz, 4H), 7.02 (d, *J* = 8.3 Hz, 4H), 3.44-3.35 (m, 2H), 2.88-2.82 (m, 2H), 2.57-2.50 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.4, 138.8, 132.8, 128.8, 128.5, 49.8, 46.9. **IR** (ATR neat): 2910, 1745, 1492, 1412, 1192, 1142, 1091, 1013, 826. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 305.0, found 304.9



(3*R*,4*R*)-3,4-bis(4-fluorophenyl)cyclopentanone (**50**): Pale Yellow Oil. 65 % yield, 85 % ee, >20:1 dr., Rf: 0.20 (7:3 hex:ether); $[\alpha]_D^{21}$ = -41.4 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralcel OC column 97:3 30 hexanes/*iso*propanol, 1.0 mL/min, Major: 13.0 min, minor: 11.7 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.07-7.03 (m, 4H), 6.96-6.91 (m, 4H), 3.44-3.35 (m, 2H), 2.88-2.82 (m, 2H), 2.59-2.50 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.9, 161.89 (d, J_{CF} = 245.45 Hz), 136.11 (d, J_{CF} =3.48 Hz), 128.57 (d, J_{CF} = 7.74 Hz), 115.46 (d, J_{CF} = 21.33 Hz), 49.9, 47.1. Spectra matched that of the previously reported compound.[129]

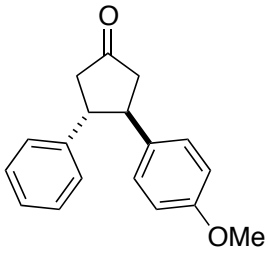


(3*R*,4*R*)-3,4-bis(2-fluorophenyl)cyclopentanone (**51**): Pale Yellow Oil. 54 % yield, 62 % ee, >20:1 dr., Rf: 0.44 (1:1 hexanes:ether); $[\alpha]_D^{21}$ = -72.6 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis:** Chiralpak IB column 97:3 hexanes/*iso*propanol, 1.0 mL/min, Major: 14.2 min, minor: 15.2 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.24-7.14 (m, 4H), 7.04 (td, *J* = 7.5, 1.3 Hz, 2H), 6.97 (ddd, *J* = 10.8, 8.2, 1.2 Hz, 2H), 3.98-3.89 (m, 2H), 2.93-2.86 (m, 2H), 2.60-2.52 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.1, 161.1 (d, J_{CF} = 245.51 Hz), 128.5 (d, J_{CF} = 8.52 Hz), 128.2 (d, J_{CF} = 4.71 Hz), 127.5 (d, J_{CF} = 13.58 Hz), 124.3 (d, J_{CF} = 3.71 Hz), 115.7 (d, J_{CF} = 22.35 Hz), 45.9, 41.6. **IR** (ATR neat): 3066, 2962, 1745, 1616, 1585, 1492, 1456, 1404, 1368, 1230, 1189, 1143, 756. **LRMS** (ESI + APCI) *m/z* [M+Na] calcd. 295.1, found 295.1

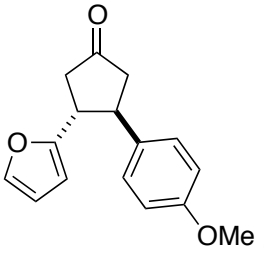


(3*R*,4*R*)-3,4-bis(4-bromophenyl)cyclopentanone (**52**): White Solid

60 % yield, 84 % ee, >20:1 dr., Rf: 0.21 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -78.9 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 90:10 hexanes/*iso*propanol, 1.0 mL/min, Major: 22.1 min, minor: 20.4 min. **^{1}** (400 MHz; $CDCl_3$): δ 7.37 (d, *J* = 8.5 Hz, 4H), 6.97 (d, *J* = 8.5 Hz, 4H), 3.42-3.34 (m, 2H), 2.88-2.81 (m, 2H), 2.58-2.47 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.4, 139.3, 131.8, 128.9, 120.8, 49.8, 46.9. **IR** (ATR neat): 2917, 1743, 1489, 1402, 1188, 1139, 1073, 1009, 822. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 395.0, found 394.9



(3*R*,4*R*)-3-(4-methoxyphenyl)-4-phenylcyclopentanone (**59**): Off-White Amorphous Solid. 65 % yield, 85 % ee, >20:1 dr., Rf: 0.53 (7:3 hexanes:ether): $[\alpha]_D^{21}$ = -62.3 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Reverse phase Chiralpak IB column 95:5 H_2O:acetonitrile, 1.0 mL/min, Major: 21.1 min, minor: 20.7 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.26-7.16 (m, 3H), 7.13-7.11 (m, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 3H), 3.48-3.39 (m, 2H), 2.89-2.81 (m, 2H), 2.61-2.50 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.9, 158.4, 140.9, 132.8, 128.5, 128.1, 127.2, 126.8, 113.9, 55.2, 50.4, 49.4, 47.31, 47.23. **IR** (ATR neat): 2959, 2936, 1742, 1603, 1513, 1249, 1178, 1129, 1034. **LRMS** (ESI + APCI) *m/z* [M+H] calcd.267.1, found 267.1

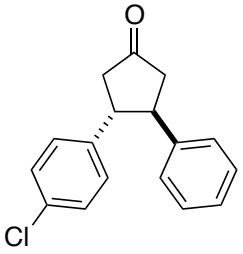


(3*R*,4*R*)-3-(furan-2-yl)-4-(4-methoxyphenyl)cyclopentanone (**61**):

Pale yellow oil. 59 % yield, 80 % ee, >20:1 dr., Rf: 0.15 (7:3 hexanes:ether);

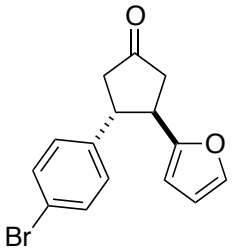
$[\alpha]_D^{21}$ = -76.4 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 99:5 hexanes/*iso*propanol, 1.0 mL/min, Major: 12.0 min, minor: 11.4 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.31 (t, *J* = 0.9 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.23 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.92 (d, *J* = 3.2 Hz, 1H), 3.78 (s, 3H), 3.58-3.45 (m, 2H), 2.83-2.76 (m, 2H), 2.66-2.59 (m, 1H), 2.53-2.46 (m, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.5, 158.5, 154.4, 141.4,

133.0, 128.0, 114.0, 110.1, 106.0, 55.2, 46.8, 46.5, 44.4, 43.6. **IR** (ATR neat): 2931, 2837, 1744, 1612, 1514, 1463, 1303, 1248, 1179, 1149, 1033, 830. **LRMS** (ESI + APCI) *m/z* [M+Na] calcd 279.1, found 279.0



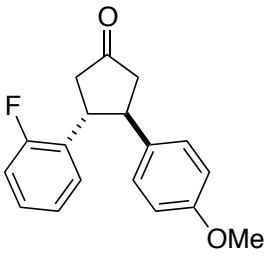
(3*R*,4*R*)-3-(4-chlorophenyl)-4-phenylcyclopentanone (**62**):

Pale Yellow Oil. 61 % yield, 86 % ee, >20:1 dr.; Rf: 0.28 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -41.2 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IA column 97:3 hexanes/*iso*propanol, 1.0 mL/min, Major: 13.0 min, minor: 11.6 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.25-7.15 (m, 7H), 7.09-7.07 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 3.48-3.36 (m, 2H), 2.88-2.80 (m, 2H), 2.60-2.47 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.2, 140.4, 139.2, 132.6, 128.69, 128.64, 128.52, 127.16, 127.05, 50.3, 49.7, 47.16, 47.01. **IR** (ATR neat): 3029, 2914, 1744, 1492, 1402, 1190, 1136, 1091, 1013, 765, 699. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 271.1, found 271.1

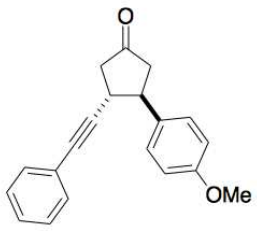


(3*R*,4*R*)-3-(4-bromophenyl)-4-(furan-2-yl)cyclopentanone (**63**): PalePink Amorpous Solid. 56 % yield, 75 % ee, >20:1 dr., Rf: 0.36 (1:1 hexanes:ether); $[\alpha]_D^{21}$ = -82.2 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 90:10 hexanes/*iso*propanol, 1.0 mL/min, Major: 10.7 min, minor: 10.2 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.31 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.92

(d, *J* = 3.2 Hz, 1H), 3.59-3.45 (m, 2H), 2.84-2.77 (m, 2H), 2.65 (ddd, *J* = 18.6, 10.8, 1.5 Hz, 1H), 2.49 (ddd, *J* = 18.6, 11.3, 1.6 Hz, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.6, 153.7, 141.7, 139.9, 131.7, 128.8, 120.8, 110.2, 106.3, 47.2, 46.1, 44.3, 43.4. **IR** (ATR neat): 2920, 2745, 1489, 1402, 1191, 1148, 1073, 1010, 823,737. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 305.0, found 305.0



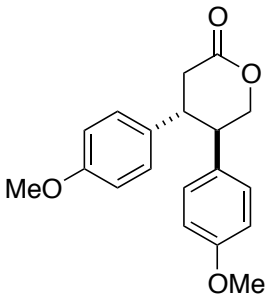
(3*R*,4*R*)-3-(2-fluorophenyl)-4-(4-methoxyphenyl)cyclopentanone (**64**): Off-White Amorphous Solid. 60 % yield, 82 % ee, >20:1 dr., Rf: 0.41 (7:3 hexanes:ether): $[\alpha]_D^{21}$ = -56.1 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralcel OB-H column 90:10 hexanes/*iso*propanol, 1.0 mL/min, Major: 32.5 min, minor: 46.7 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.17 (tdd, *J* = 10.1, 5.3, 2.5 Hz, 2H), 7.10-6.94 (m, 4H), 6.78 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 3H), 3.71 (dt, *J* = 11.3, 5.6 Hz, 1H), 3.60 (ddd, *J* = 16.7, 11.1, 5.4 Hz, 1H), 2.84 (dt, *J* = 18.1, 9.0 Hz, 2H), 2.60-2.48 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.7, 159.9, 158.4, 132.6, 130.3, 128.45, 128.41, 128.35, 128.26, 127.97, 127.82, 124.28, 124.24, 115.8, 115.5, 114.5, 113.9, 55.2, 47.37, 47.19, 45.90, 45.88, 43.7. **IR** (ATR neat): 2926, 1743, 1672, 1602, 1513, 1492, 1456, 1305, 1248, 1228, 1179, 1136, 1033, 829, 758. **LRMS** (ESI + APCI) *m/z* [M+Na] calcd. 307.1, found 307.1



trans-3-(4-methoxyphenyl)-4-(phenylethynyl)cyclopentan-1-one (**66**)

Prepared according to the standard procedure for the synthesis of unsymmetrical cyclopentanones

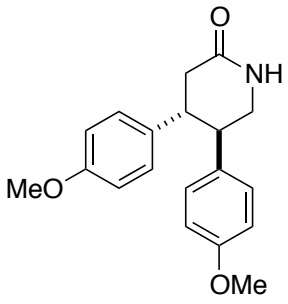
using catalyst **3**. 48 % yield, >20:1 dr., Rf = 0.27 (6:4 hexanes:ether), **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.36-7.26 (m, 7H), 6.91 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.50-3.42 (m, 1H), 3.19 (td, *J* = 10.5, 7.6 Hz, 1H), 2.89-2.74 (m, 2H), 2.57-2.43 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.8, 158.8, 132.4, 131.6, 128.20, 128.07, 128.01, 114.1, 89.6, 83.1, 55.3, 48.2, 45.6, 45.3, 36.5. **IR** (ATR neat): 2915, 1746, 1514, 1490, 1442, 1249, 1180, 1033, 757. **LRMS** (ESI + APCI) *m/z* [M+Na] calcd. 313.1, found 313.2



(4*R*,5*R*)-4,5-bis(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-one (**67**):

To a flame dried vial charged with a magnetic stirbar was added (3*R*,4*R*)-3,4-bis(4-methoxyphenyl)cyclopentanone **5** (47 mg, 0.16 mmol) and 1.0 mL dichloromethane and cooled to 0 °C in an ice water bath. Then mCPBA (102 mg, 0.416 mmol) and trifluoroacetic acid (12 μL, 0.16 mmol) were added and the vial was sealed with a cap. The reaction was then allowed to warm to room temperature over the course of an hour and then stirred for an additional hour at room temperature. Upon completion, the reaction was diluted with an additional 3 mL of dichloromethane and quenched with 3 mL saturated sodium bicarbonate. The organic layer was then separated in a separatory funnel and the sodium bicarbonate was extracted with an additional 3 mL dichloromethane. The organic layers were then combined and washed 2x with 6 mL brine, dried over sodium sulfate and concentrated via rotary evaporation. The crude residue was then purified via column chromatography (3:1 ether:hexanes) to yield 44 mg (89 %) (4*R*,5*R*)-4,5-bis(4-

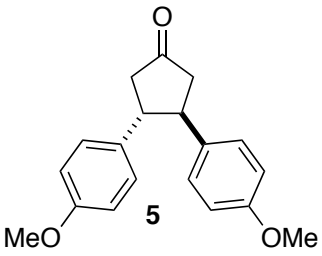
methoxyphenyl)tetrahydro-2*H*-pyran-2-one as a colorless oil in 84 % ee, and as a single diastereomer. Rf: 0.35 (3:1 ether:hexanes). $[\alpha]_D^{21}$ = -48.5 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 70:30 hexanes/*iso*propanol, 1.0 mL/min, Major: 18.0 min, minor: 16.9 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.03-6.97 (m, 4H), 6.77-6.74 (m, 4H), 4.46 (dd, *J* = 11.5, 5.0 Hz, 1H), 4.36 (dd, *J* = 11.5, 10.3 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.35 (td, *J* = 10.2, 6.4 Hz, 1H), 3.22 (td, *J* = 10.4, 5.0 Hz, 1H), 3.01 (dd, *J* = 17.7, 6.4 Hz, 1H), 2.74 (dd, *J* = 17.7, 9.8 Hz, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 170.9, 158.7, 158.4, 133.8, 130.0, 128.8, 128.1, 114.14, 114.10, 73.2, 55.2, 46.1, 43.4, 37.9. **IR** (ATR neat): 2956, 2933, 2909, 2836, 1734, 1611, 1513, 1464, 1248, 1179, 1032, 830. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 313.1, found 313.2



(4*R*,5*R*)-4,5-bis(4-methoxyphenyl)piperidin-2-one (**68**):

To a flame dried vial charged with a magnetic stir bar was added (3*R*,4*R*)-3,4-bis(4-methoxyphenyl)cyclopentanone **5** (65 mg, 0.22 mmol), hydroxylamine hydrochloride (23 mg, 0.33 mmol), NaOAc (36 mg, 0.44 mmol), and 5 mL MeOH. The cap was screwed on and the reaction was allowed to stir at room temperature for 6 hours at room temperature. After 6 hours, the mixture was concentrated via rotary evaporation and the crude residue was dissolved in 10 mL $CHCl_3$. The resulting solution was washed with H_2O and brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting crude oxime was used in the next step without further purification. The crude oxime from the previous step was then dissolved in 10 mL dichloromethane and added *p*-bromobenzenesulfonyl chloride (84 mg, 0.33 mmol), Et_3N (51 μL,

0.37 mmol), and a catalytic amound of DMAP. The reaction was stirred at room temperature for 1 hour then concentrated via rotary evaporation. The residue was then dissolved in 5 mL AcOH and stirred at room temperature for 1 hour. After 1 hour, the reaction was quenched with saturated, aqueous $NaHCO_3$. The mixture was extracted 2x with dichloromethane and the organic layers were combined and washed with brine. The solution was then dried with sodium sulfate and concentrated via rotary evaporation. The residue was purified via column chromatography (1:1 hexanes:EtOAc to 100 EtOAc) to yield 51 mg (75 %, over two-steps) (4*R*,5*R*)-4,5-bis(4-methoxyphenyl)piperidin-2-one as an off-white amorphous solid in 84 % ee and as a single diastereomer. Rf: 0.22 (100 % ethyl acetate); $[\alpha]_D^{21}$ = -92.8 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 90:10 hexanes/*iso*propanol, 1.0 mL/min, Major: 56.4 min, minor: 63.9 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.01-6.95 (m, 4H), 6.70 (d, *J* = 8.0 Hz, 4H), 6.57 (bs, 1H), 3.70 (s, 6H), 3.52-3.42 (m, 2H), 3.30-3.24 (m, 1H), 3.20-3.14 (m, 1H), 2.77-2.71 (m, 1H), 2.63-2.55 (m, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 158.2, 158.0, 134.2, 132.0, 128.8, 128.2, 113.85, 113.82, 55.1, 48.8, 45.2, 43.8, 39.96, 39.94. **IR** (ATR neat): 3217, 2953, 2932, 2909, 2835, 1663, 1611, 1512, 1246, 1178, 1033, 828. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 312.2, found 312.2[130]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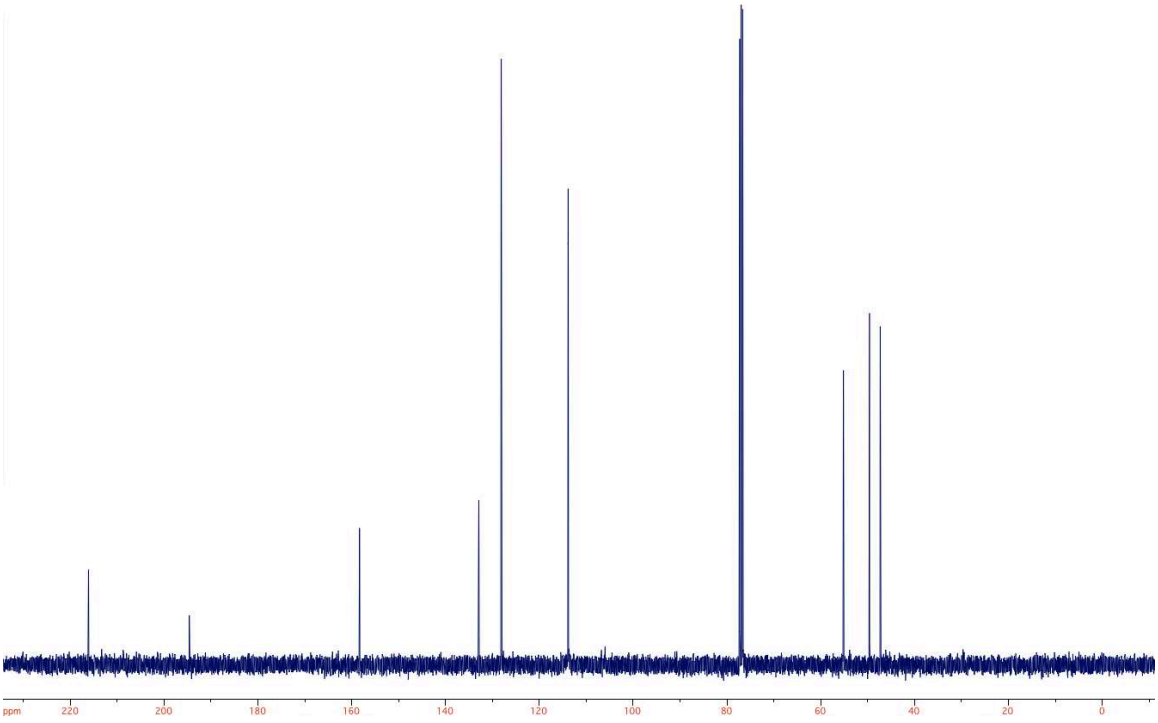
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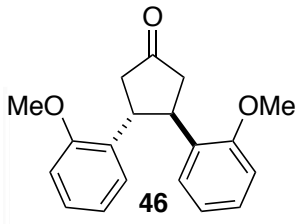
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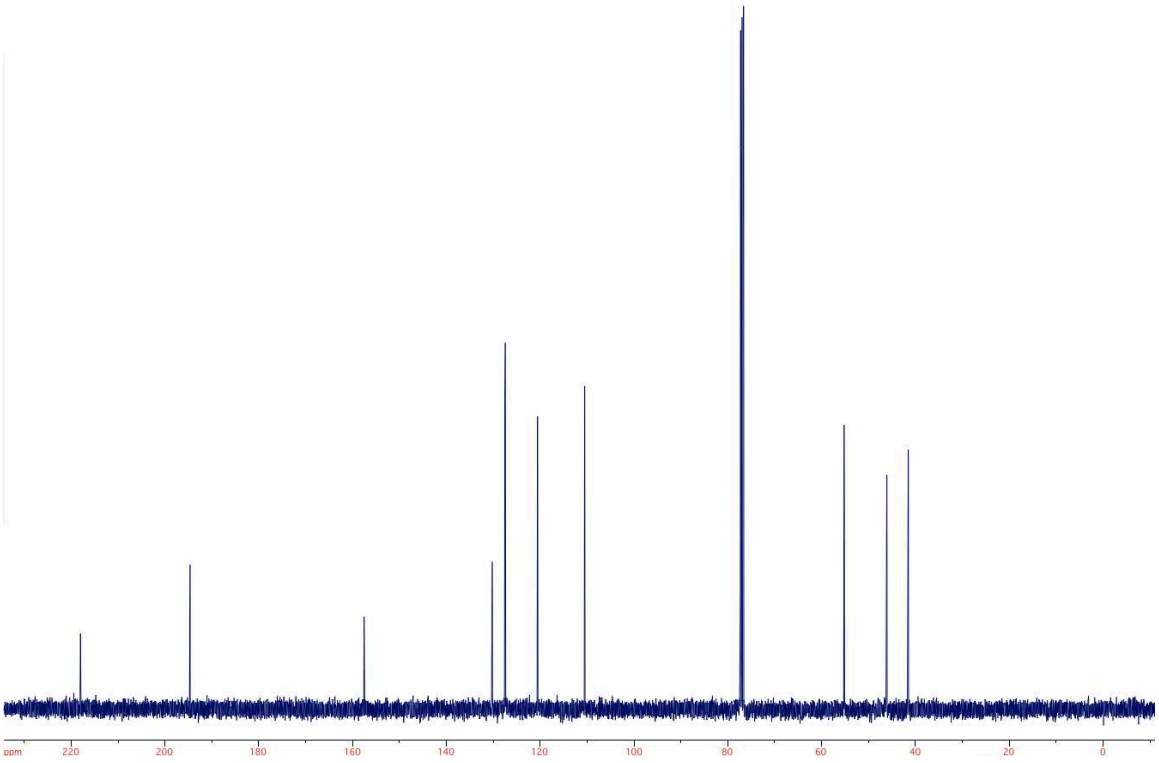
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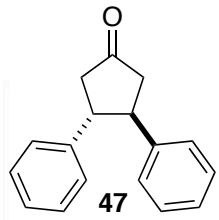

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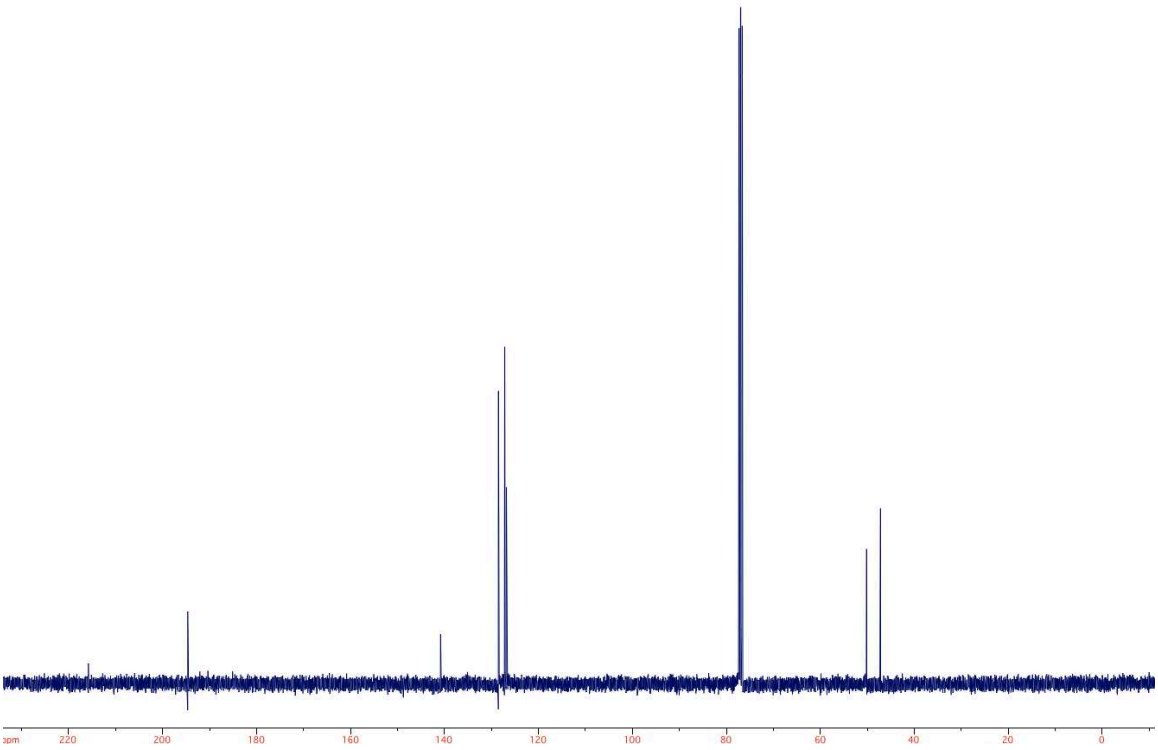

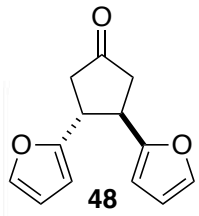
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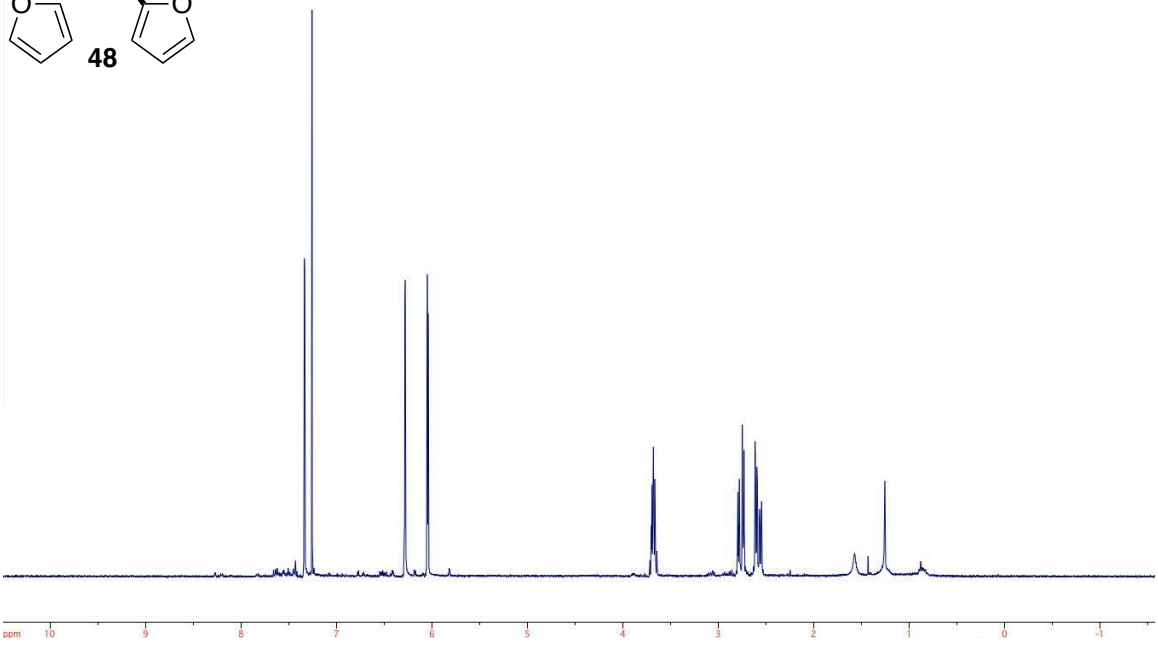
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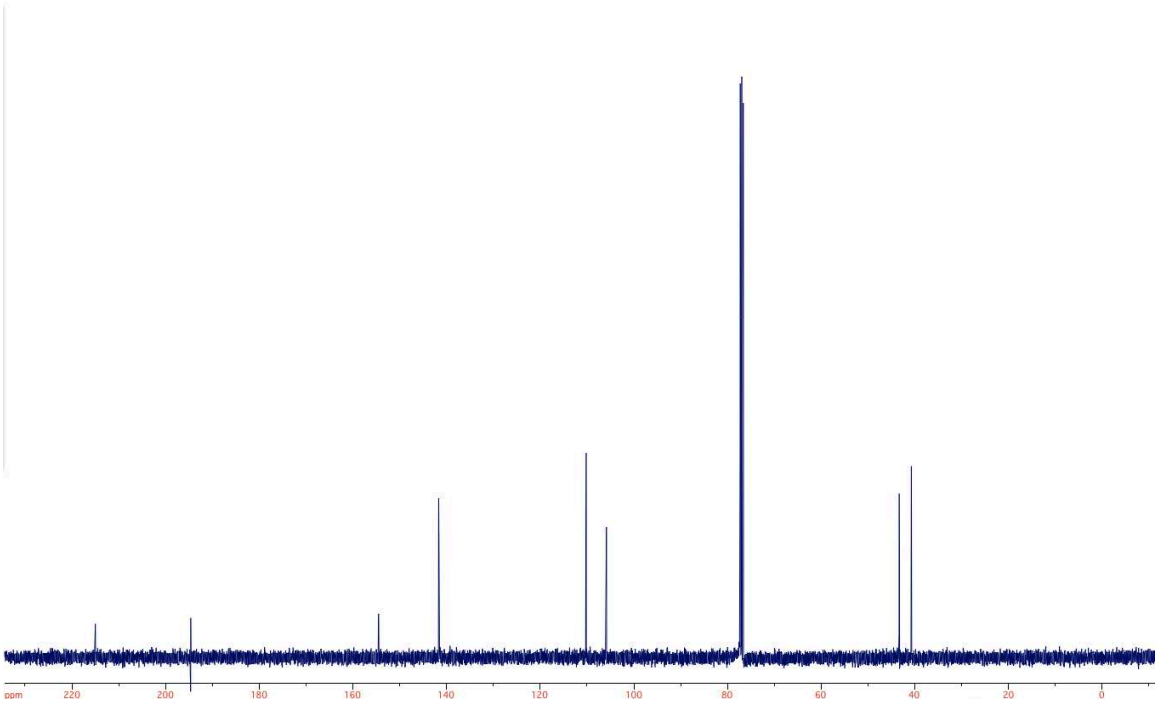
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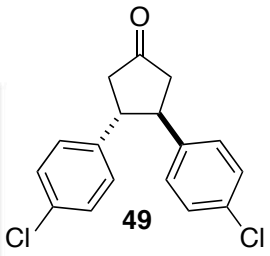
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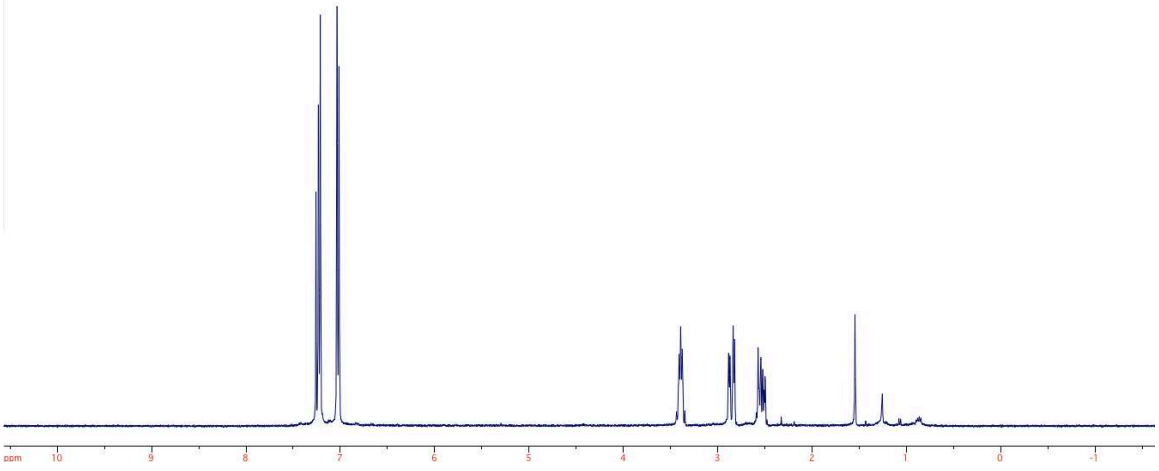
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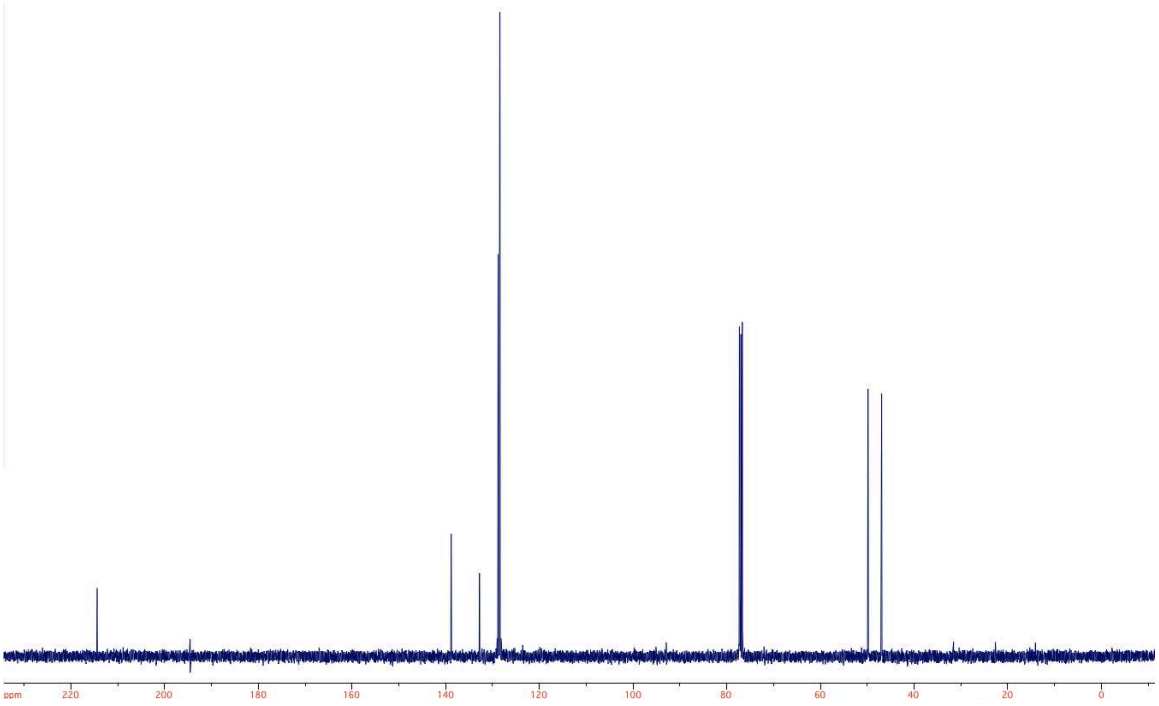
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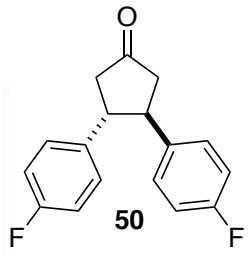
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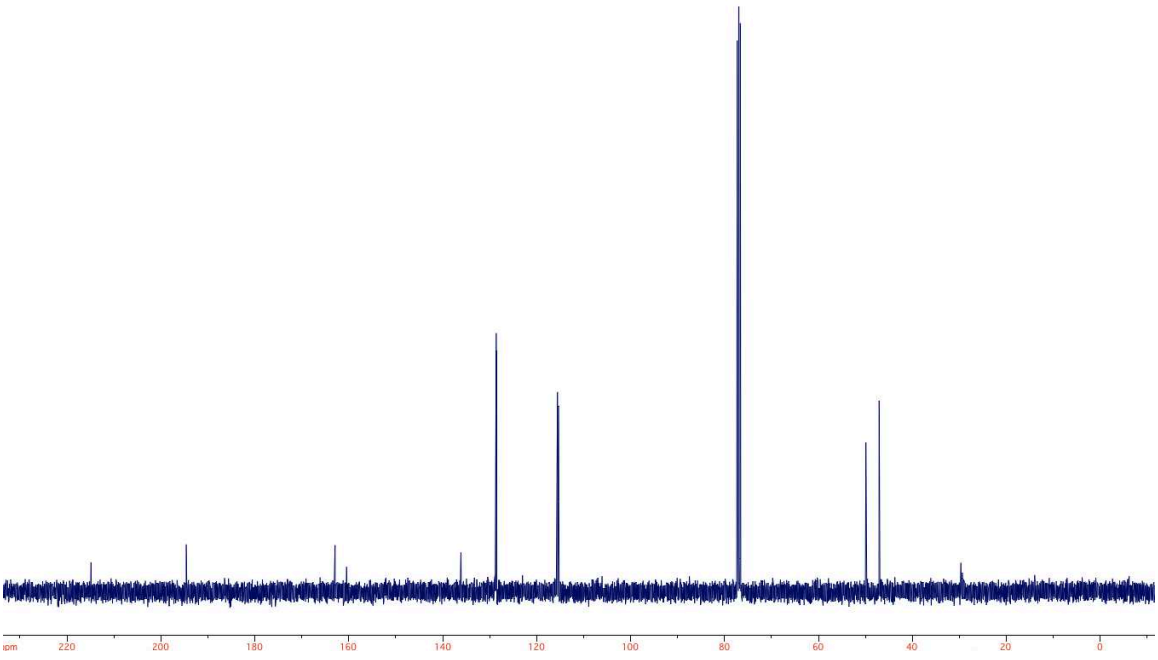
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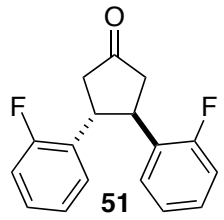
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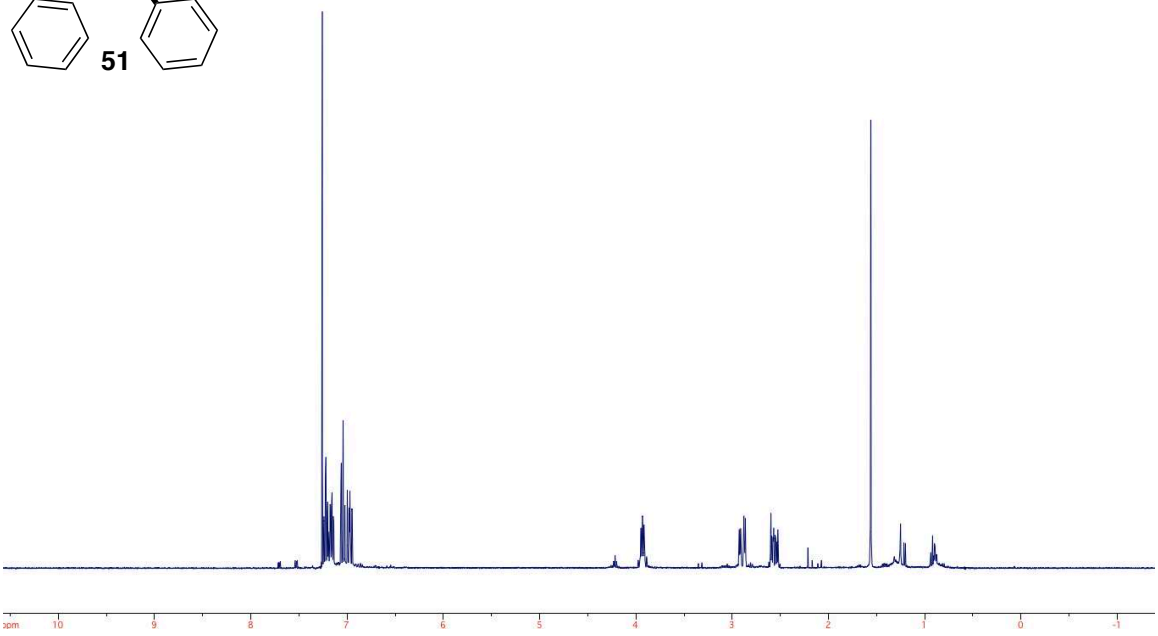
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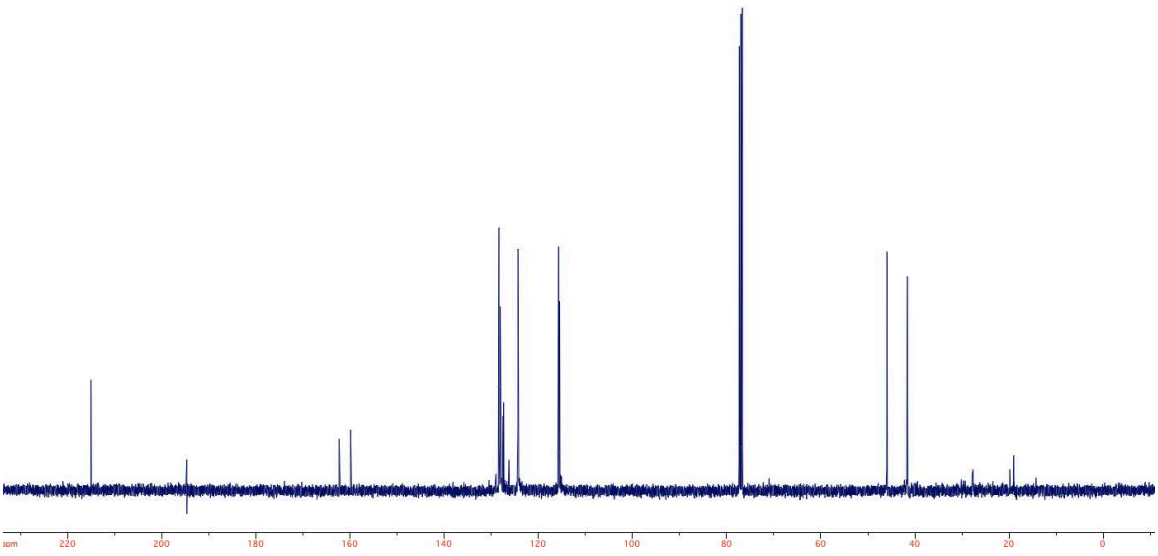
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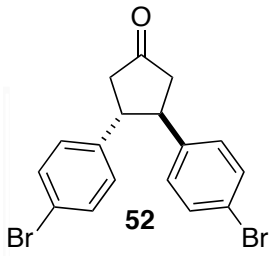
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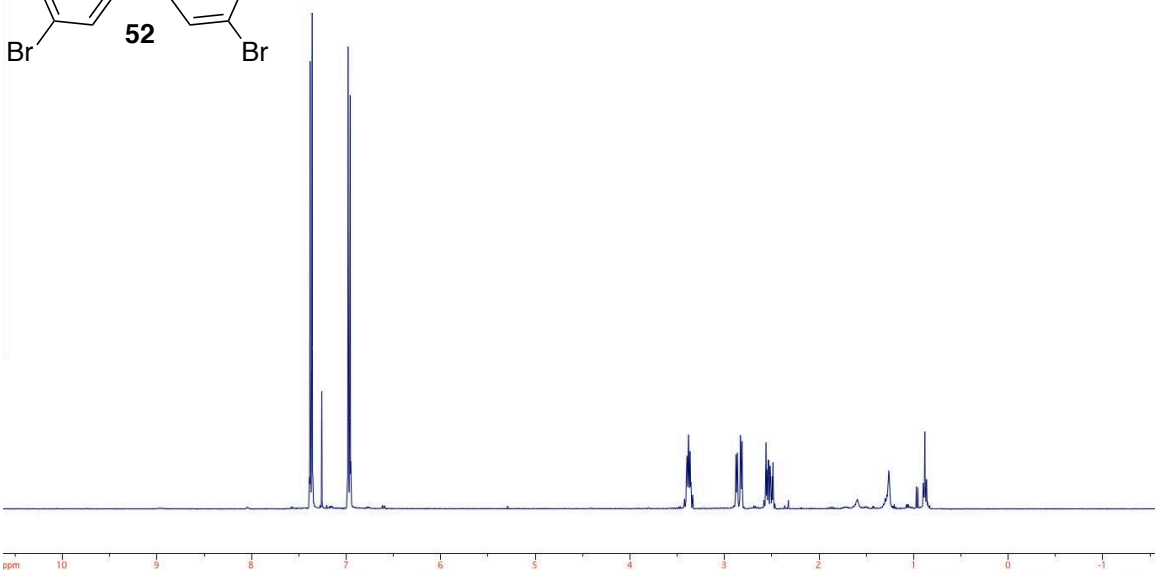
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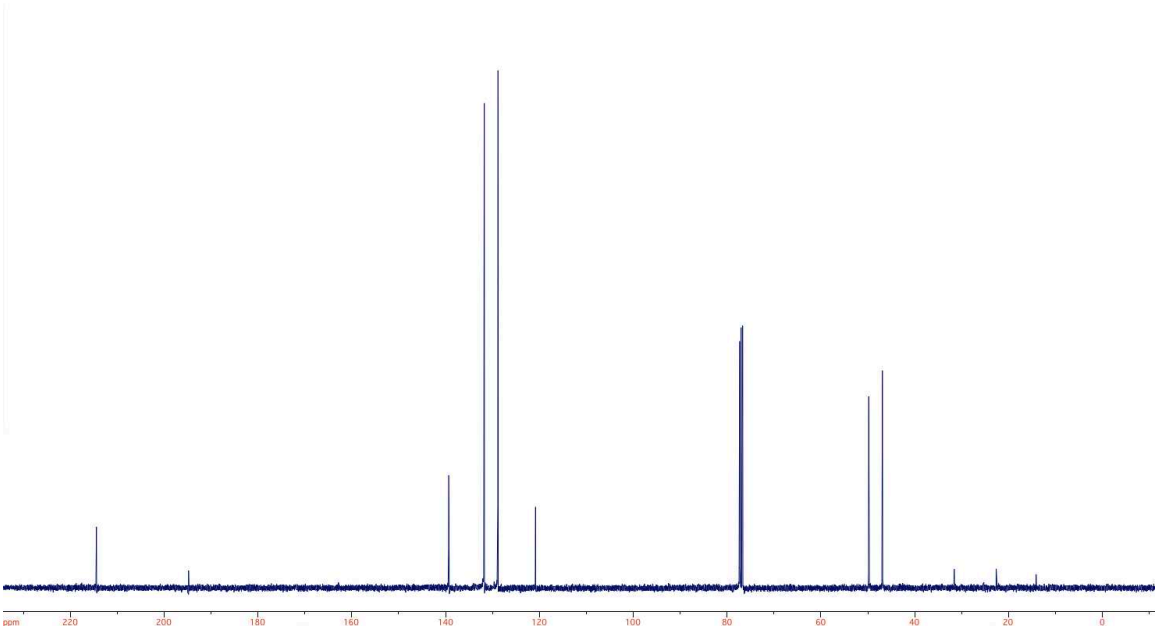
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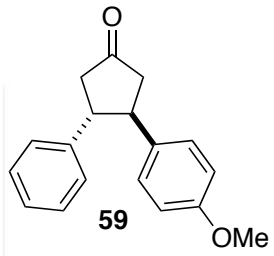
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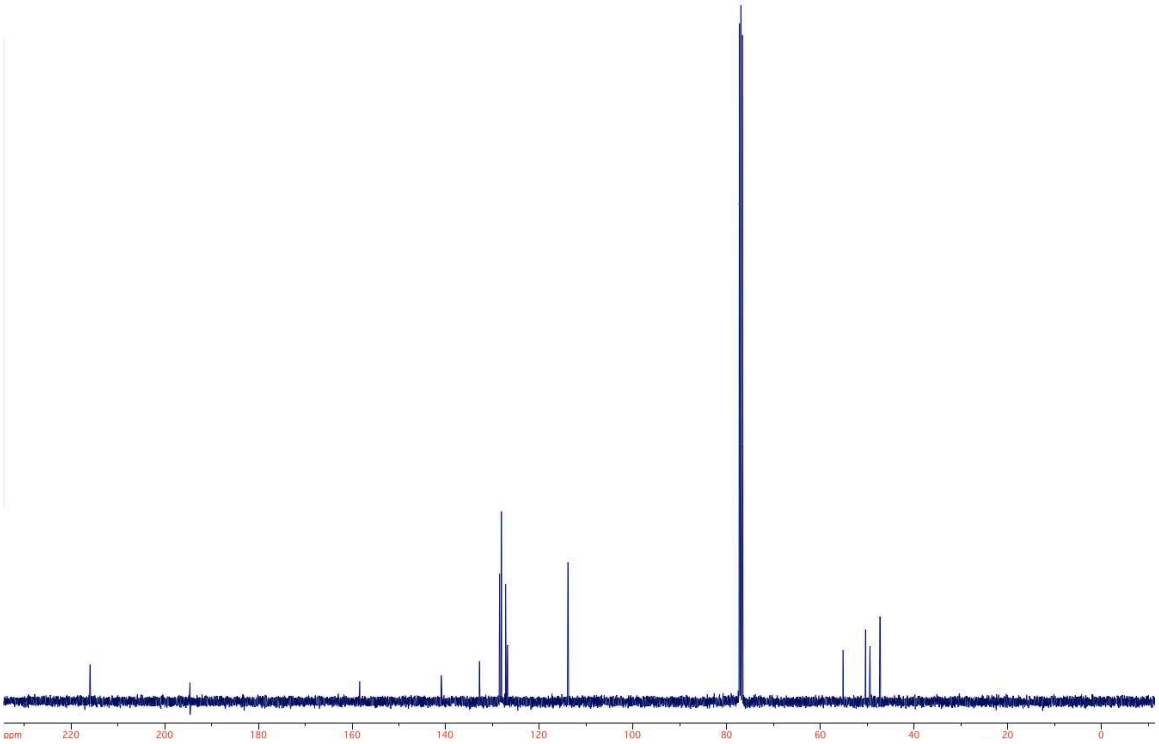
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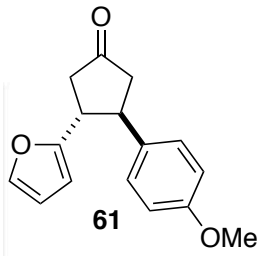
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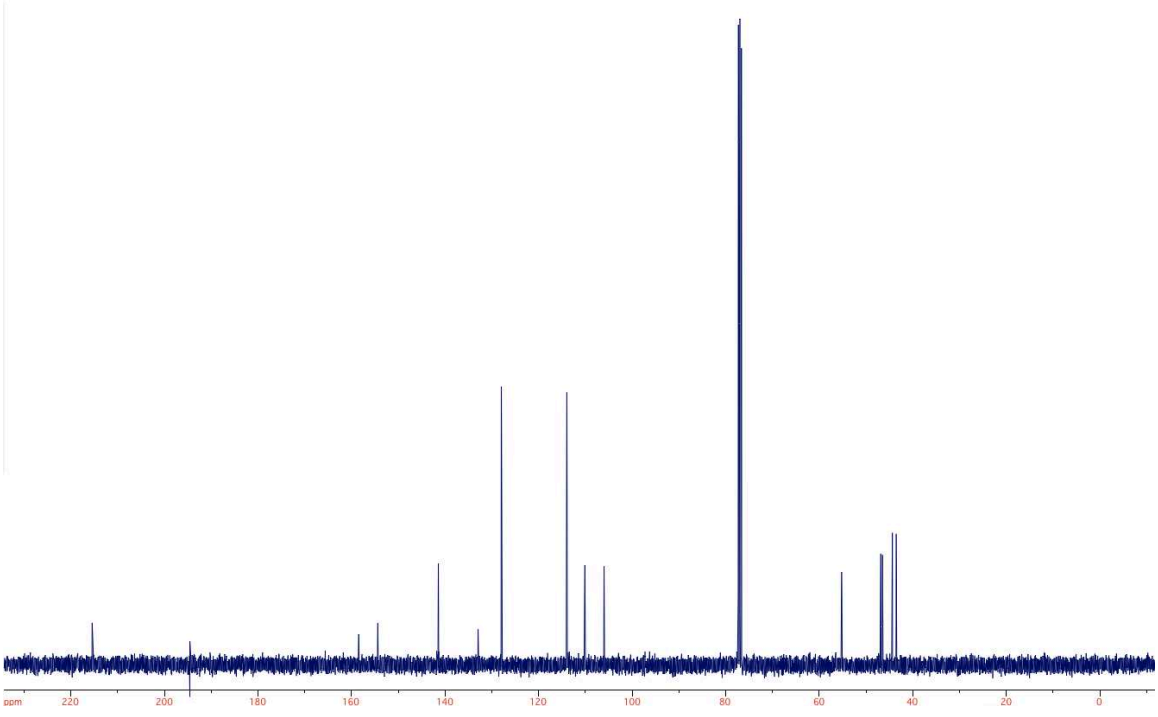
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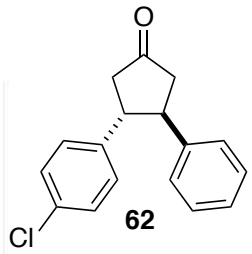
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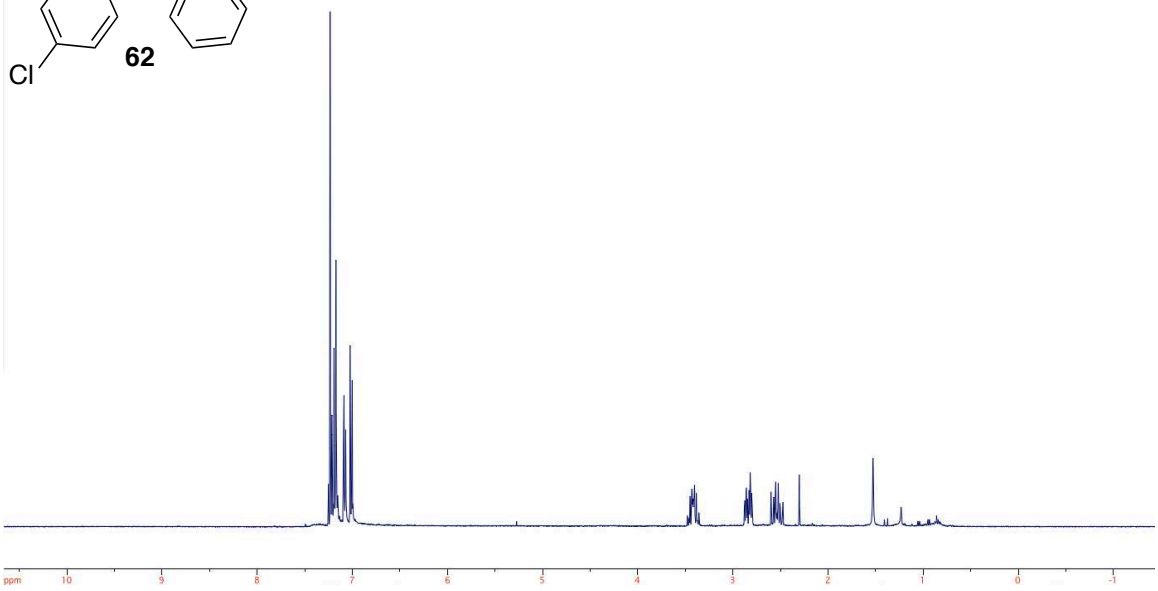
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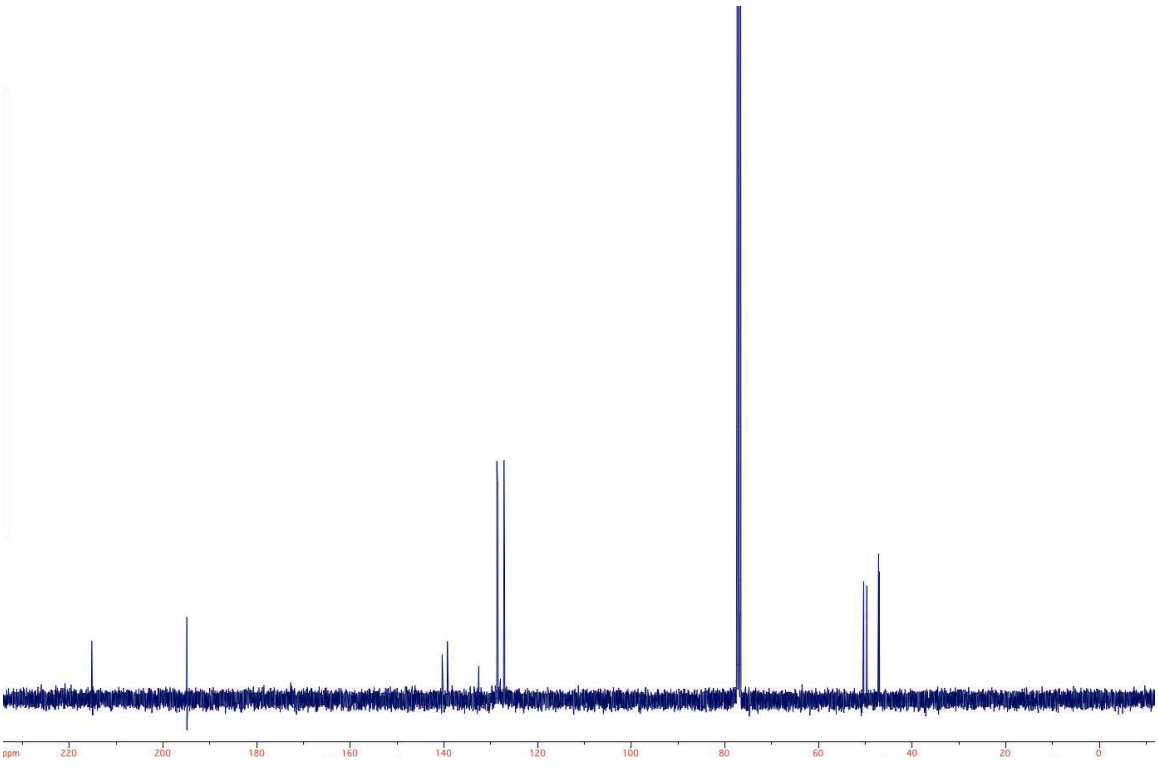
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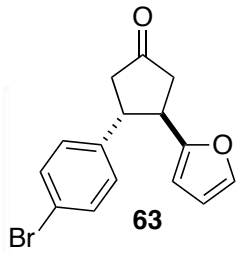
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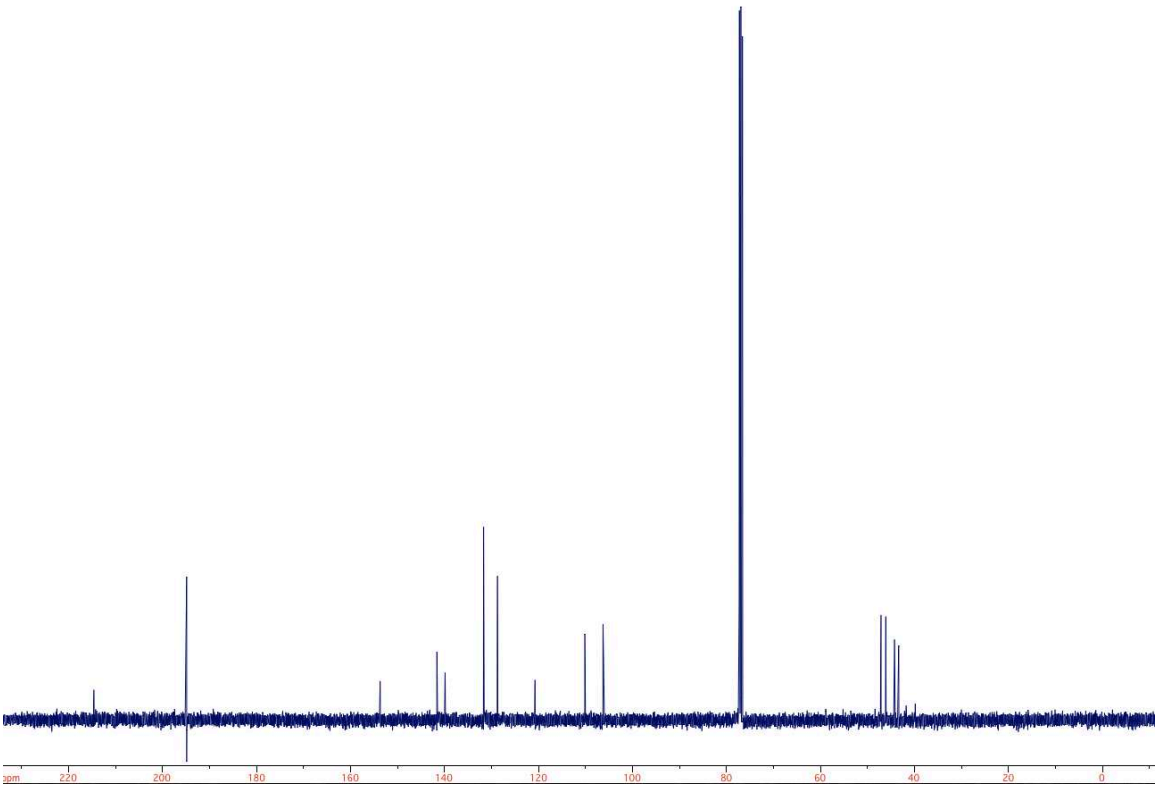
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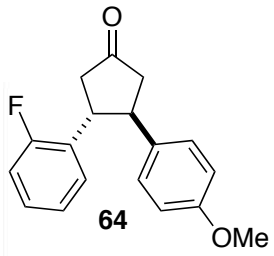
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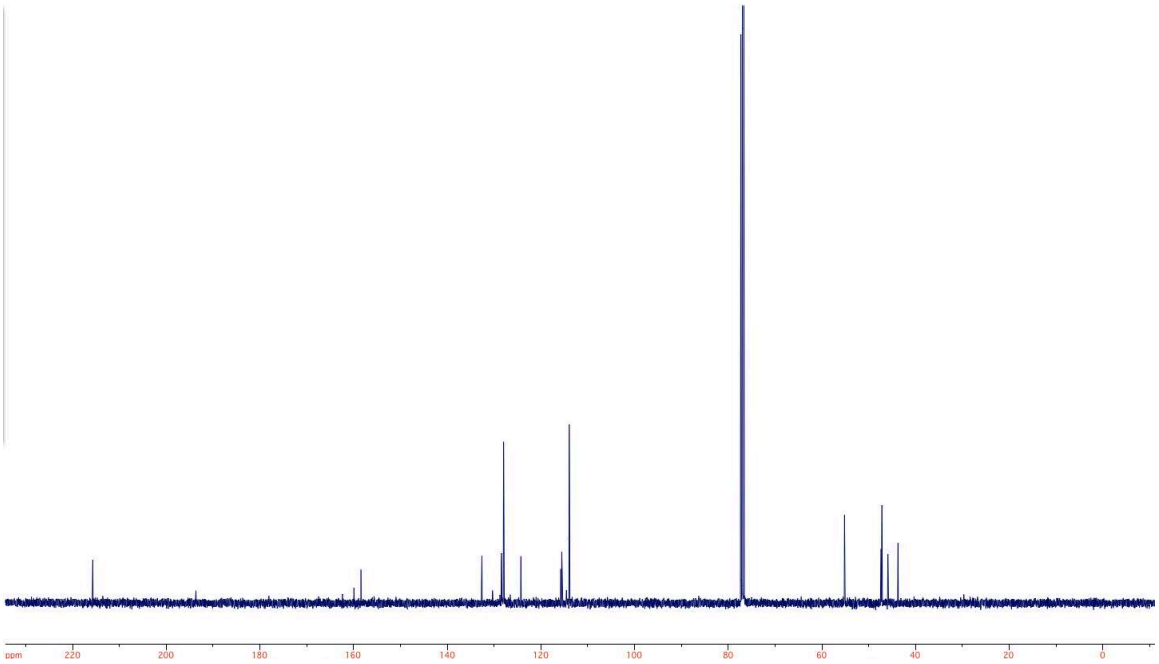
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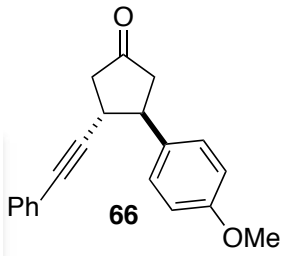

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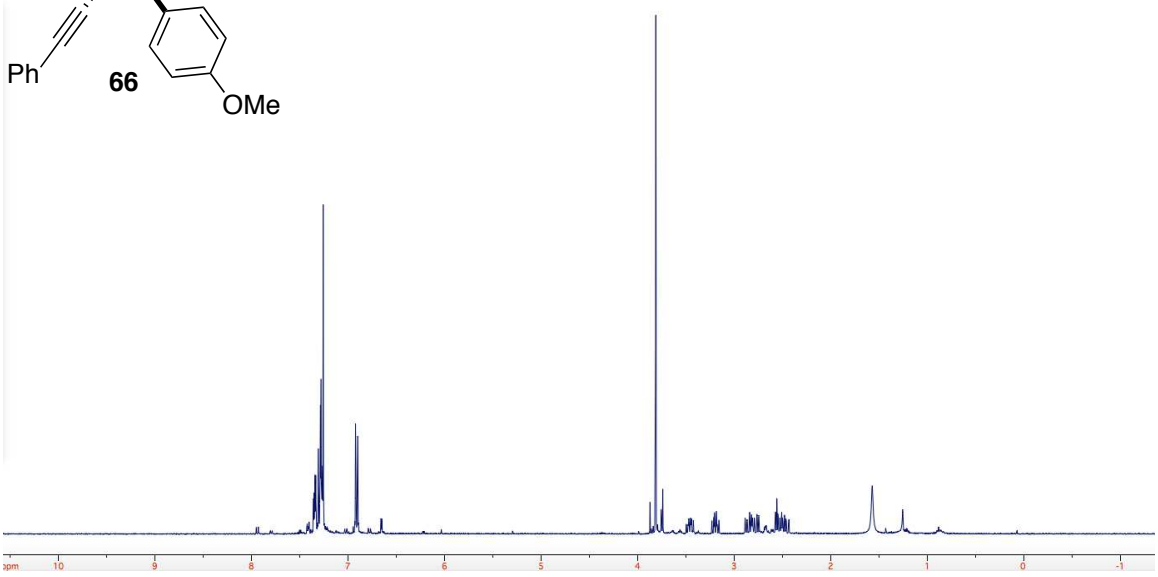

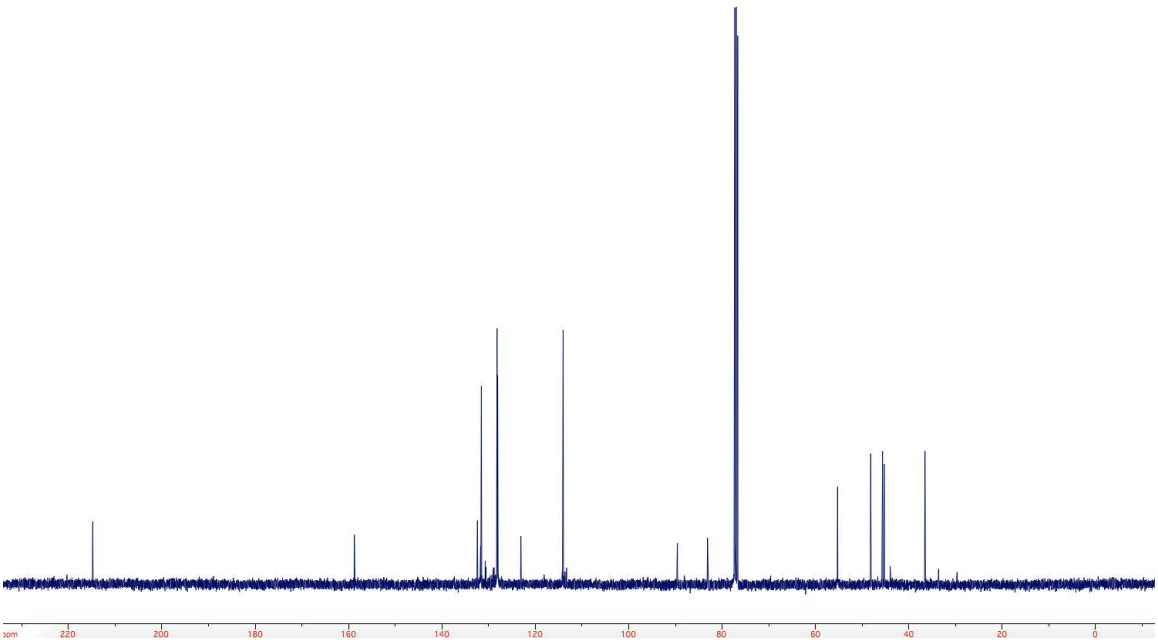

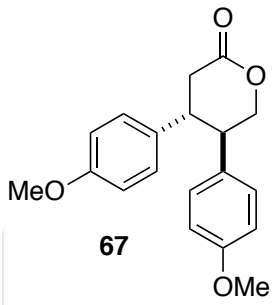
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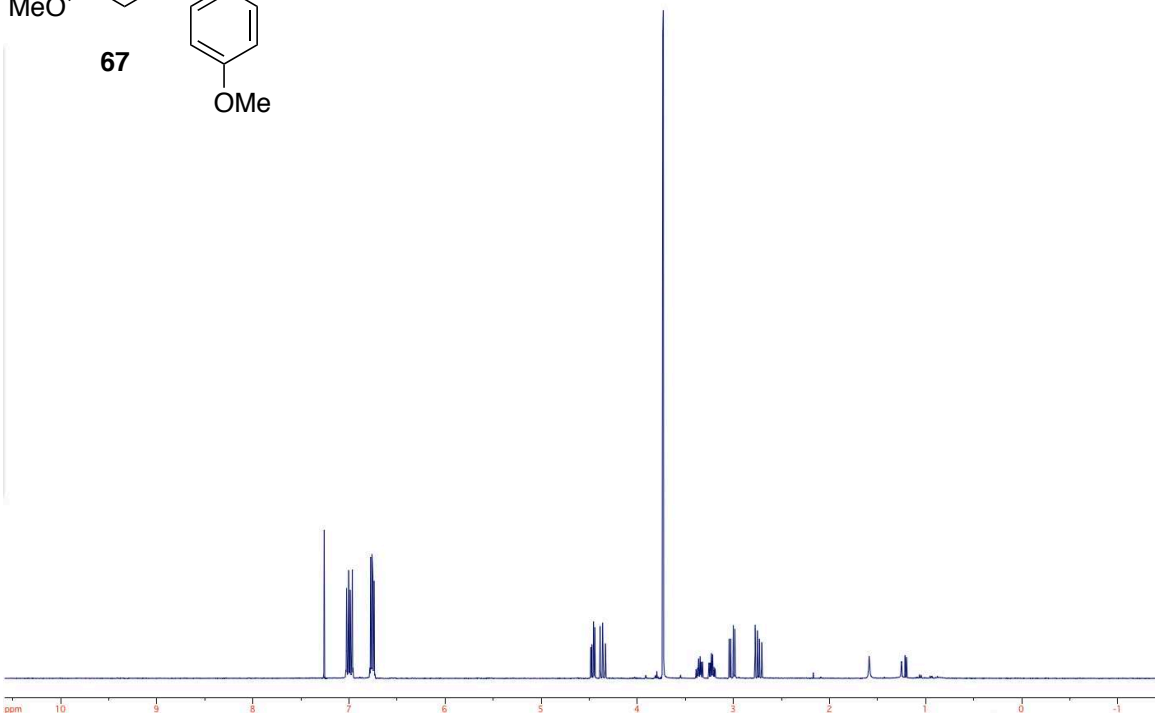
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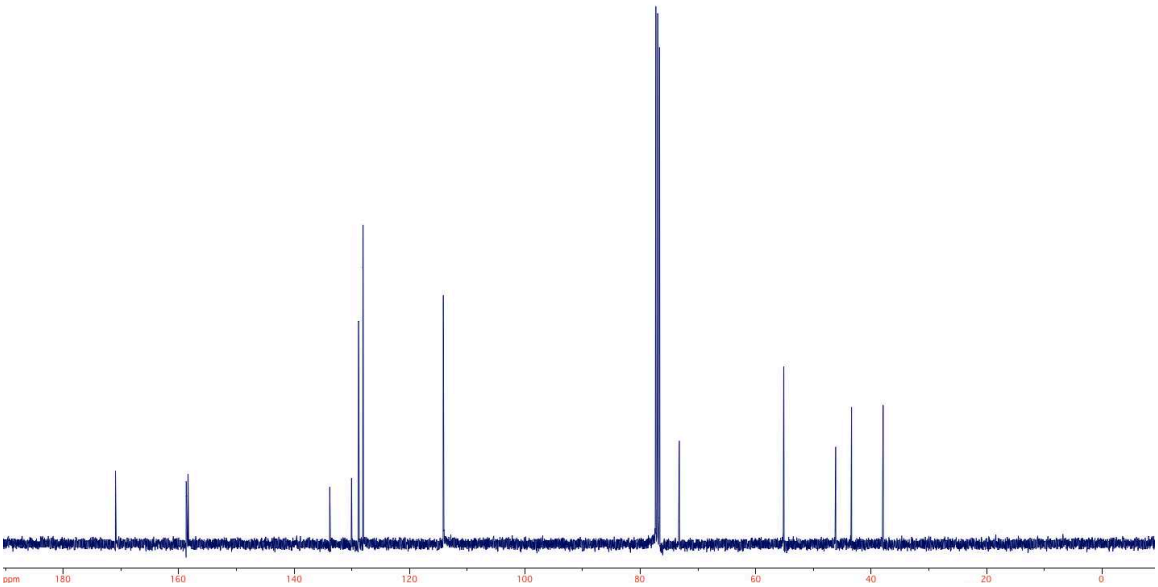
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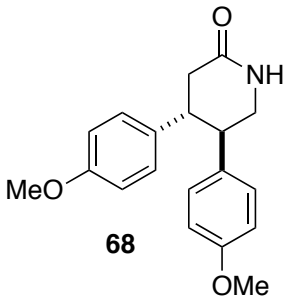
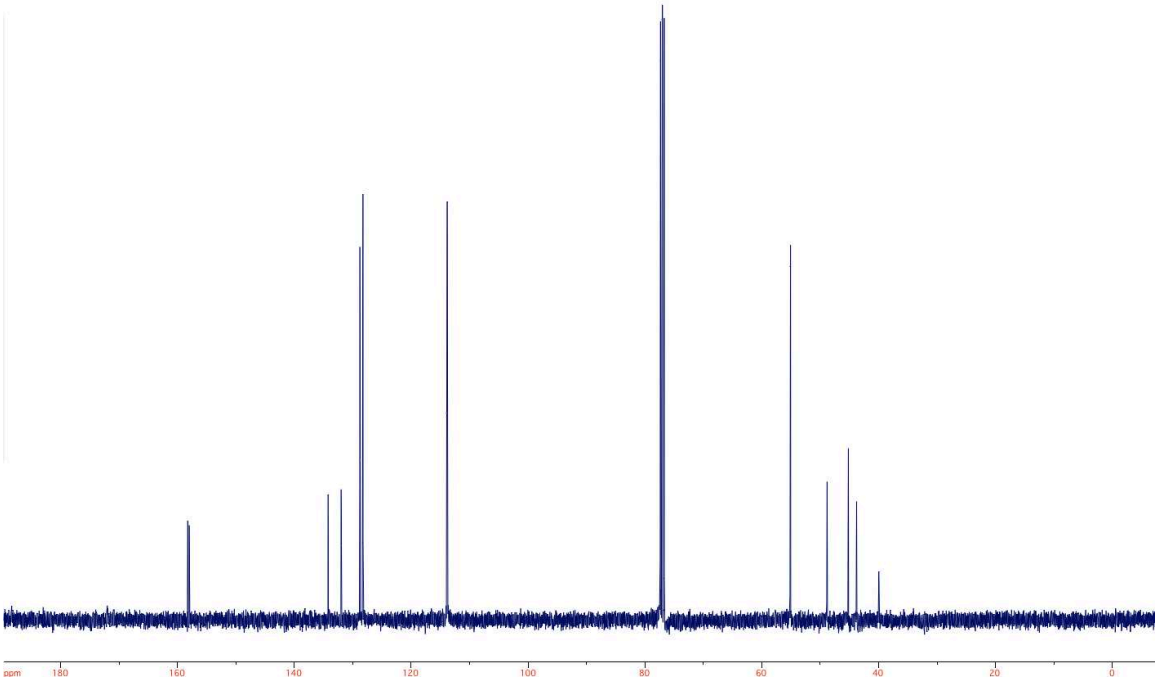


68



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[2] White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871.