Studies on Selected Organocatalytic Mannich, Vinylogous Aldol and Conjugate Addition Reactions and the Stereoselective Synthesis of Selected Aspulvinones

by

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A thesis submitted to the School of Graduate Studies in partial fulfillment
of the requirements for the degree of Doctor of Philosophy

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To my family and friends

Abstract

The functionalized *γ*-butenolide (2-(5*H*) furanone) motif is found in various natural products and hence the synthesis of butenolides is of considerable interest. The organocatalytic direct Mannich reaction of *γ*-crotonolactone with cyclic imines or *in-situ* generated iminium ions, to provide the functionalized butenolides is not reported. Several new bifunctional thiourea catalysts incorporating a chiral phosphoramide functionality, were prepared and examined in these reactions. These furanones are potential precursors for the synthesis of functionalized quinolizidines such as the homopumiliotoxins and indolizidines such as the pumiliotoxins. Details of these studies are described in Chapter 1.

The organocatalytic Michael addition of cyclic ketones and aldehydes to *α*-nitrostyrenes, generated *in-situ* from the corresponding nitroacetates, was investigated. The use of pyrrolidine-based amine catalysts in the presence of a protonic acid was found to be optimal and provided enantiomerically enriched γ-nitro ketones or γ-nitro aldehydes in good yield. The utility of γ-nitro aldehydes in the synthesis of pyrrolidines was also established. Details of these studies are described in Chapter 2.

The aspulvinones, 3-aryl-5-arylidene tetronic acids, are a major group of fungal metabolites which have attracted considerable interest due to their biological activity. A modular synthesis of aspulvinones B, D and the recently isolated aspulvinone Q was developed. The methodology features a stereoselective aldol condensation of diazotetronic acid with aldehydes to provide the 5-arylidene diazotetronates. A catalytic, intermolecular C-H insertion reaction of 5-arylidene diazotetronates with arenes provides the aspulvinones. Variation of the aldehyde and the arene components furnishes synthetic analogues of the aspulvinones. These results are presented in Chapter 3.

The first organocatalytic asymmetric direct vinylogous aldol reaction of isatin with α-angelicalactone for the construction of 3-substituted-3-hydroxyindoles by using various phosphoramide-thiourea catalysts was developed. Details of these studies are described in Chapter 4.

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List of abbreviations

Ac	Acetyl
AD	asymmetric dihydroxylation
AIBN	Azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
APPI	atmospheric pressure photoionization
aq.	Aqueous
BINOL	1,1′-dinaphthalene-2,2′-diol
BnBr	benzyl bromide
Boc	*tert*-butoxycarbonyl
br	Broad
BzCl	benzoyl chloride
CAN	ceric ammonium nitrate
cat.	Catalytic
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethylene
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine

DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
eq.	equivalent (s)
ESI	electrospray ionization
esp	*α*,*α*,*α*',*α*'-tetramethyl-1,3-benzenedipropanoate
EtOAc	ethyl acetate
EVK	ethyl vinyl ketone
EWG	electron withdrawing group
g	gram (s)
h	hour (s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i-Bu	isobutyl
IR	Infrared
J	coupling constant

L	Ligand
LAH	lithium aluminum hydride
LCPA	lithium *N*-cyclohexyl-*N*-isopropylamide
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide
LICA	lithium isopropyl cyclohexylamide
LiDBB	lithium di-*tert*-butylbiphenylide
LiHMDS	lithium bis(trimethylsilyl)amide
M	Molar
M^+	molecular ion
Me	Methyl
mg	milligram(s)
MIDA	*N*-methylimidodiacetic acid
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance

PCC	pyridinium chlorochromate
Ph	Phenyl
ppm	parts per million
PTSA/*p*-TsOH	*para*-toluenesulfonic acid
R_f	retention factor
rt	room temperature
TBDMS/TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
TMS	Tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
UV	Ultraviolet

Chapter 1

Synthesis and Evaluation of Phosphoramide-Thiourea Organocatalysts in Direct Vinylogous Mannich Reaction of γ-Crotonolactone with Cyclic Imines

1.1 Introduction:

The Mannich reaction and the related Mukaiyama Mannich reaction are among the most powerful carbon-carbon bond forming tools in synthetic organic chemistry. An extension of the Mannich reaction, namely, the vinylogous Mannich reaction is of considerable interest and has gained significant attention in strategies developed for the synthesis of several alkaloids.[1] In contrast to the Mannich reaction, its vinylogous variant typically involves the reaction of nucleophilic dienolate derivatives with imines or iminium ions. For example, the addition of acyclic dienol ether **D** to cyclic or acyclic imines **A** to generate δ-aminocarbonyl compounds **E** (Figure 1.1) is an example of a vinylogous Mannich reaction that is related to the addition of an enol ether nucleophile to an iminium ion (**B** to **A** Figure 1.1). The dienol derivatives may also be cyclic, as exemplified by the addition of alkoxy furan **F** to cyclic or acyclic imines **A** to generate aminoalkyl-substituted γ-butenolide **G**, an active sub-unit that is found in a number of alkaloids.[1] Cyclization of **E** or of **G** leads to a functionalised quinolizidine (n = 1) or indolizidine (n = 2) skeleton **H** which is a characteristic motif found in a variety of alkaloids (Figure 1.1).[1] It may be noted that the conversion of **G** to **H** involves the rearrangement of a lactone to a lactam.

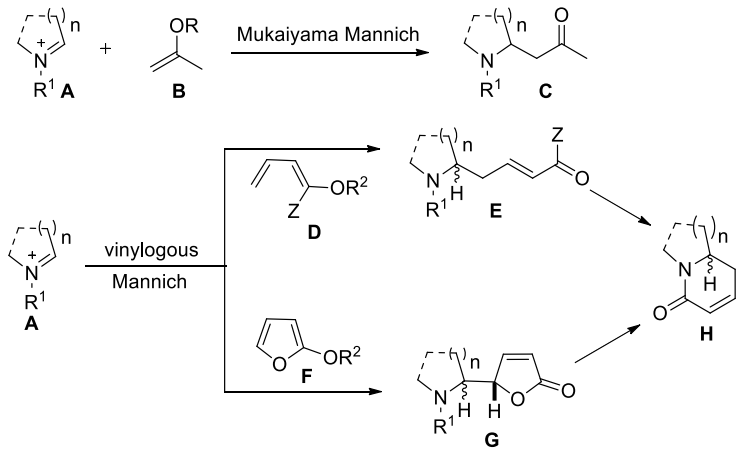


Figure 1.1 Mukaiyama Mannich vs. vinylogous Mannich reactions

1.2 Objectives:

We were interested in the development of a direct organocatalytic vinylogous Mannich reaction of γ-crotonolactone **1** and its analogs (Figure 1.2). The advantage of this approach was that it avoids the synthesis of dienol intermediates (Figure 1.1) which were often difficult to purify and have a limited shelf life. If successful, the organocatalytic procedure would generate a dienolate **2** *in situ* which would then react with an imine **3** (Figure 1.2). Only a few reports of such direct vinylogous Mannich reactions are available[1] and the reaction continues to be a synthetic challenge. Our specific objective was the development of an organocatalytic vinylogous Mannich reaction of γ-butenolides **2** and cyclic iminium ions **3** that are obtained *in situ* from suitably functionalized piperidine and pyrrolidine derivatives.

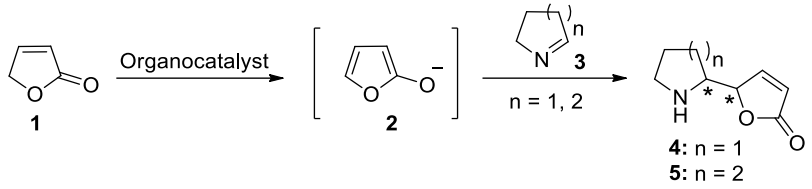


Figure 1.2 Direct vinylogous Mannich reaction of γ-crotonolactone with cyclic imines

A second objective was the conversion of the Mannich products **4** and **5** obtained from γ-crotonolactone **1** and a piperidine or pyrrolidine-based iminium ion **3** to provide the indolizidine or quinolizidine ring systems **6** and **8**, respectively.

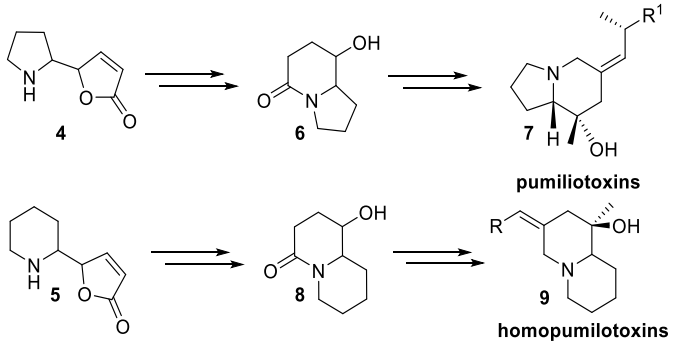


Figure 1.3 Conversion of Mannich products in some useful alkaloids

While the indolizidine **6** is potentially a key intermediate to the several pumiliotoxins alkaloids **7**, the quinolizidine **8** has been employed as a key synthetic intermediate to several homopumiliotoxin alkaloids **9** (Figure 1.3).[2]

The pumiliotoxin alkaloids are isolated in trace amounts from the skin of amphibians and more than 800 different alkaloids, consisting of more than 20 structural groups, have been identified.[2] Among them the pumiliotoxins **7**, featuring an indolizidine ring system, have been known since 1967[3] and were isolated from a population of a small neotropical Panamanian dendrobatid frog, the brightly colored (orange or red) *Dendrobates pumilo*[2,4] (Figure 1.4). In 1987, homopumiliotoxin 223G (**9a**), another bicyclic alkaloid in which the indolizidine moiety of the pumiliotoxin is replaced with a quinolizidine ring, was isolated in trace amounts from the Panamanian frog *Dendrobates pumilo*[2,5] and appeared to be unique to this family of amphibians. However, recent examination of skin extracts from nondendrobatid amphibians revealed that homopumiliotoxin 223G (**9a**) also occurs in the New World genus of bufonid toads *Melanophryniscus*[6] and the Madagascan genus of mantelline frogs *Mantella*.[7]

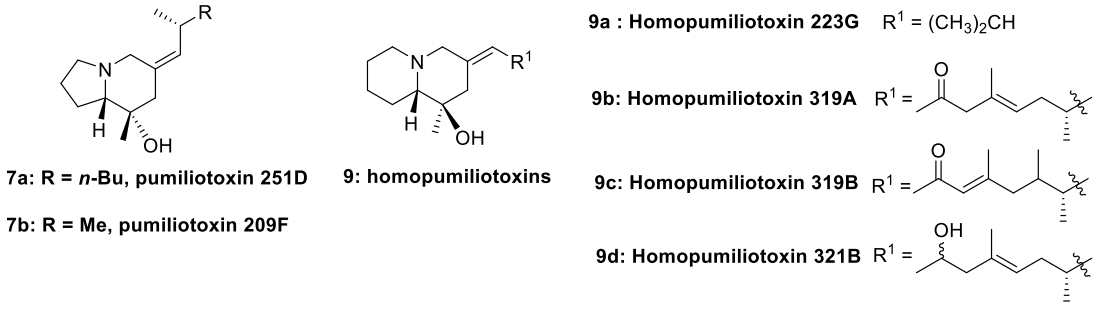


Figure 1.4 Structure of some poison frog alkaloids.

The former genus contains new members of the homopumiliotoxin class alkaloids and were characterized as homopumiliotoxins 319A, 319B, 321B[7] (Figure 1.4). The relative configuration of these homopumiliotoxin alkaloids has been tentatively established (except for the configuration

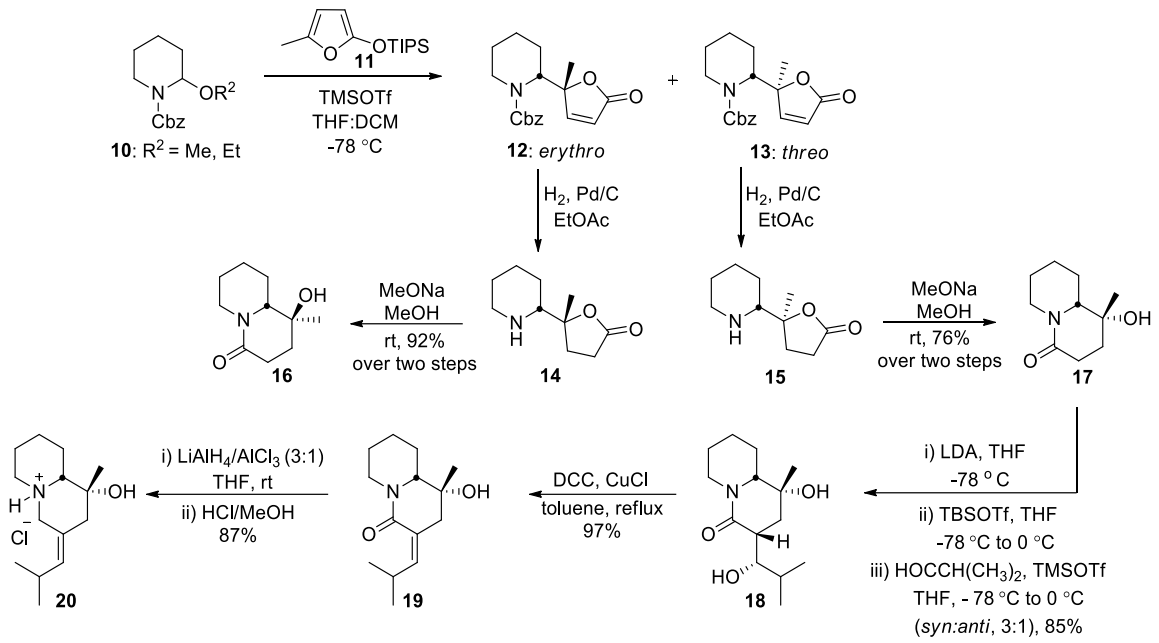
of the hydroxy group in the side chain in homopumiliotoxin 321B). These alkaloids have received much attention due to their biological activities such as myotonic and cardiotonic activity.[8] It is found that these alkaloids are ingested by the frogs in their diet consisting of small arthropods,[9] and then accumulate in the skin of the frog. The alkaloids are stored in granular skin glands and serve as a passive defense against predators and/or microorganisms.[10] Several synthetic approaches to the pumiliotoxins have been reported.[11] However, unlike pumiliotoxins, very few syntheses of (±)-homopumiliotoxin,[12] and more importantly of (+)- or (-)-homopumiliotoxin 223G, are reported.[13] The structural diversity and remarkable biological activities exhibited by these alkaloids, and their scarcity have made them interesting synthetic targets.

Since the objective of the present study was to develop methodology that would greatly simplify the synthesis of pumiliotoxins and homopumilitoxins, a brief survey of the known syntheses of a selection of these alkaloids is provided in the following section.

1.3 Known syntheses of homopumiliotoxin Alkaloids

1.3.1 Total synthesis of (±)-homopumiliotoxin 223G by Pilli

In 2001, Pilli and co-workers[12a] achieved the total synthesis of (±)-homopumiliotoxin 223G in six steps and 14% overall yield (Scheme 1.01). The addition of 5-methyl-2-triisopropylsilyloxyfuran **11** to the iminium ion generated *in situ* from a 2-alkoxypiperidine **10** provided the addition products **12** and **13**. Hydrogenation of the double bond followed by a cyclization reaction provided bicyclic lactams **16** and **17** as key intermediates. Mukaiyama aldol reaction of **17** and isobutyraldehyde catalyzed by TMSOTf afforded a 3:1 mixture of diastereomers of **18**. Stereospecific syn elimination of the major diastereomer using DCC and CuCl[14] gave **19**. Reduction of the amide in **19**, with AlH_3 (generated *in situ* with $LiAlH_4/AlCl_3$), provided (±)-homopumiliotoxin 223G which was converted into the hydrochloride salt **20** in 87% yield.

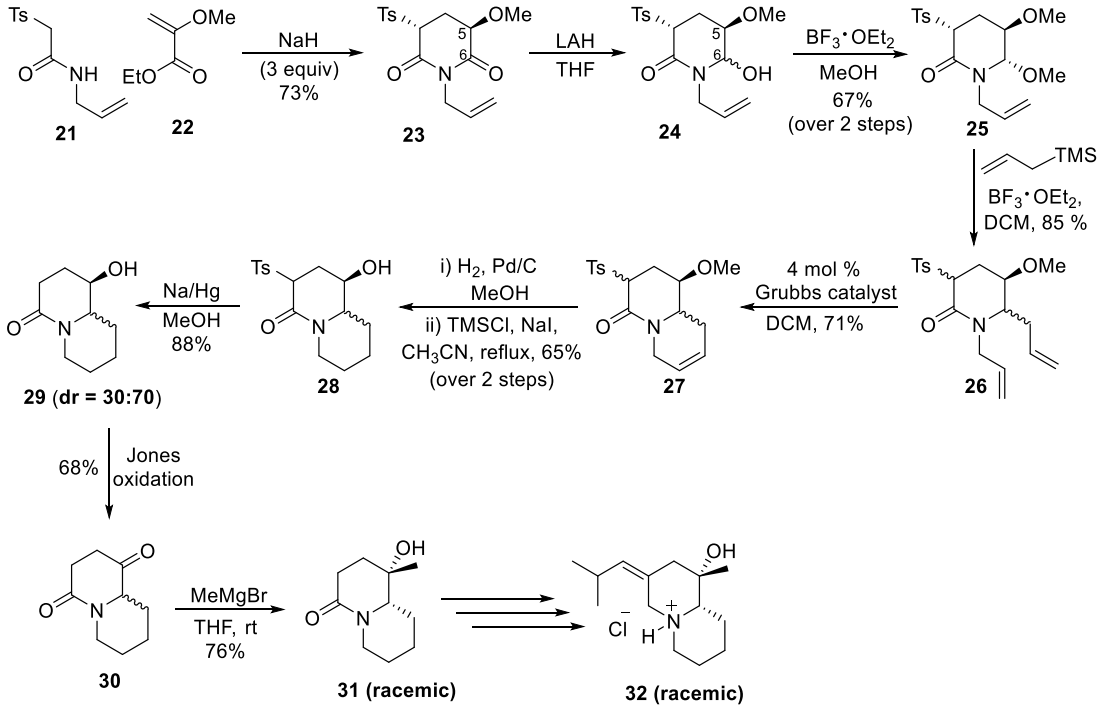


Scheme 1.01

1.3.2 Formal synthesis of (±)-homopumiliotoxin 223G by Chang

In 2004, Chang and co-workers[12b] reported a formal synthesis of (±)-homopumiliotoxin 223G in eleven steps and 9% overall yield (Scheme 1.02). They started their synthesis by a stepwise [3+3] reaction of α-sulfonyl acetamide **21** and ester **22** to provide the functionalized imide **23**. Regioselective reduction of the imide with $LiAlH_4$ afforded hydroxy lactam **24** which was converted to **25** by reaction with methanol in the presence of $BF_3{\cdot}Et_2O$. Allylation of **25** in presence of $BF_3{\cdot}Et_2O$ provided **26** as a mixture of three diastereomers (33:33:34 by ^1H NMR) due to the unexpected epimerization of the C-3 stereocenter under the reaction conditions. These diastereomers were not individually isolated and the mixture was subjected to a ring closing metathesis reaction with the Grubbs (I) catalyst at room temperature to provide a mixture of quinolizidines **27**. Hydrogenation of **27** followed by demethylation with NaI and TMSCl afforded **28**. Detosylation with Na/Hg provided hydroxy lactam **29** as a mixture of two isomers (30:70 by ^1H NMR). Oxidation of the secondary alcohol in **29** with Jones reagent provided ketone **30**.

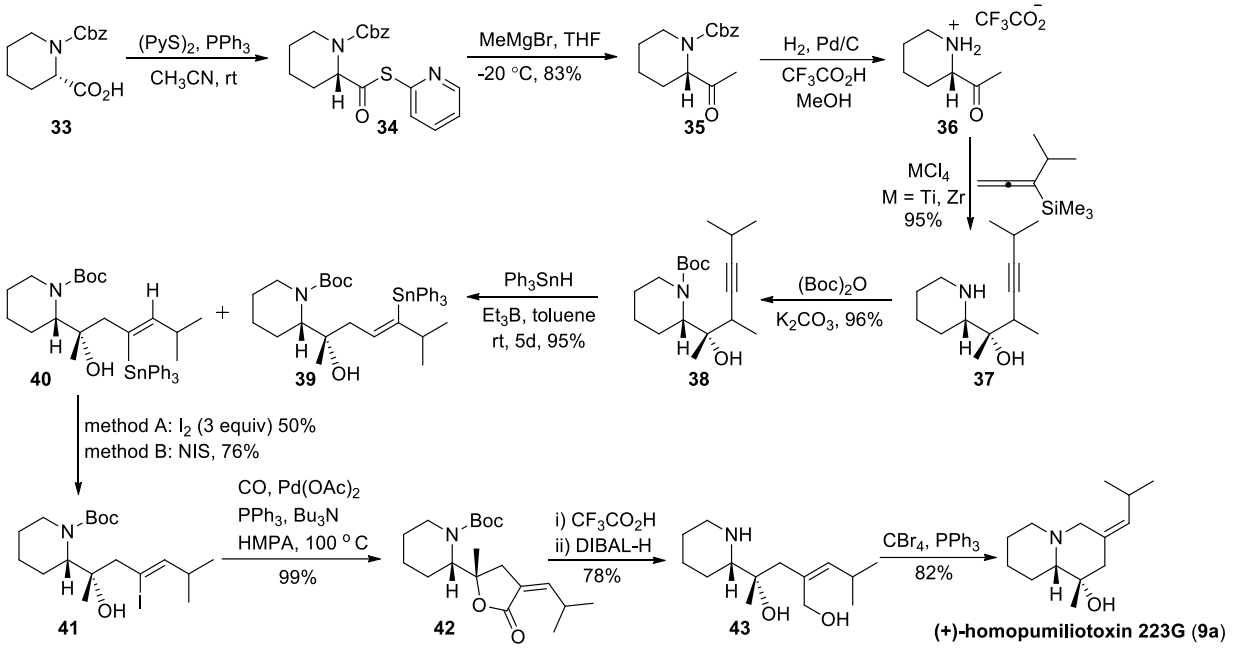
Subsequent stereoselective addition of methyl magnesium bromide to **30** afforded **31** as the only product. The conversion of **31** into (±)-homopumiliotoxin 223G in four steps was previously reported.[12a]



Scheme 1.02

1.3.3 Total synthesis of (+)-homopumiliotoxin 223G by Kibayashi

In 1998, the first total synthesis of (+)-homopumiliotoxin 223G, in eleven steps and 27% overall yield from *N*-Cbz-L-pipecolic acid **33**, was reported by Kibayashi.[13b] There are two key steps in this synthesis which involve 1) Lewis acid induced chelation controlled propargylation of **36** using silylallene for the direct construction of propargylic alcohol **37** with complete diastereoselectivity, and 2) palladium-catalyzed carbonylation of vinyl iodide **41** (CO, Bu_3N, $Pd(OAc)_2$ and Ph_3P) to provide lactone **42** with the required (Z)-alkylidene side chain.

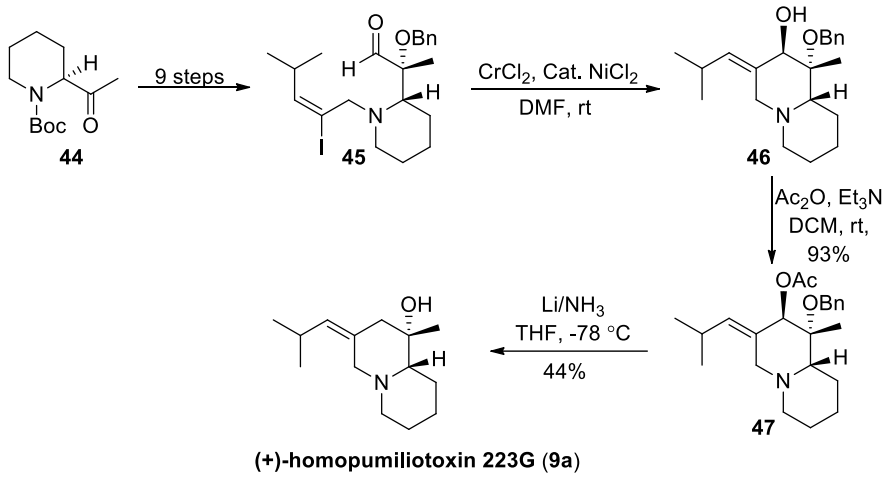


Scheme 1.03

Removal of the Boc group with trifluoroacetic acid followed by DIBAL-H reduction provided diol **43**. Conversion of **43** to the allylic bromide (CBr_4, Ph_3P)[15] induced ring closure, involving the secondary amine, to provide (+)-homopumiliotoxin 223G in 82% yield.

1.3.4 Total synthesis of (+)-homopumiliotoxin 223G by Kibayashi

In 2000, Kibayashi and co-workers[13a] accomplished the total synthesis of (+)-homopumiliotoxin 223G (**9a**) in twelve steps and 3% overall yield. Their synthesis begins with the *N*-(iodoalkenyl) aldehyde **45** which was prepared using (*S*)-*N*-Boc-2-acetyl-piperidine **44** according to the literature procedure in 9 steps.[16] Aldehyde **45** was then subjected to intramolecular chromium mediated cyclization to give the *trans*-quinolizidine intermediate **46** which was acetylated to give **47**. Reduction of **47** with lithium in liquid ammonia resulted in deacetoxylation and debenzylation to provide (+)-homopumiliotoxin 223G (**9a**).

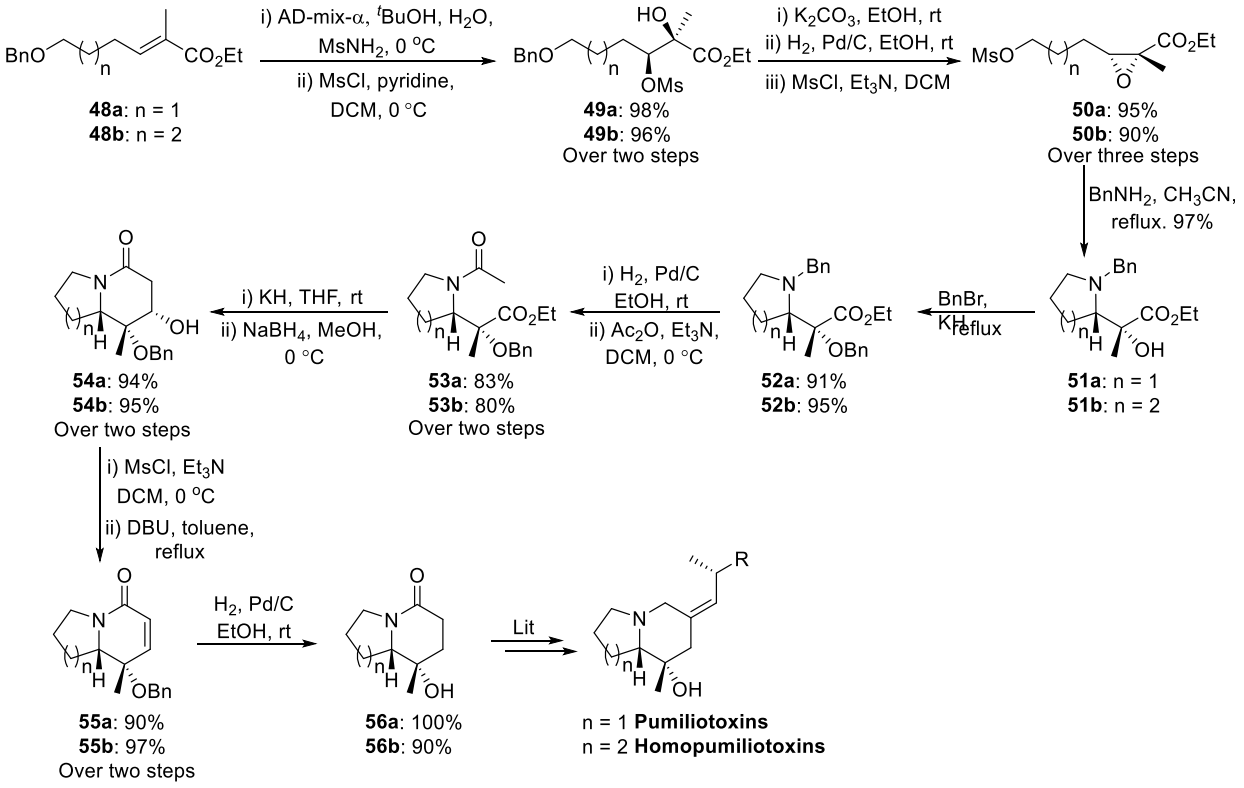


Scheme 1.04

1.3.5 Formal enantioselective synthesis of pumiliotoxin alkaloids by Lin

In 2003, Lin and Co-workers[13e] achieved the enantioselective formal synthesis of the pumiliotoxins in seventeen steps in overall 18% yield featuring a novel one-pot substitution ring-opening sequence and an efficient Claisen type condensation. They started their synthesis from trisubstituted olefin **48** which was readily prepared from 1,4-butanediol.[17] Sharpless asymmetric dihydroxylation of **48** with (AD-mix-α) followed by selective mesylation of the sterically unhindered hydroxyl group in the product diol afforded **49**. Treatment of **49** with K_2CO_3 afforded the epoxide with an inversion of configuration at the secondary stereocenter. Removal of the benzyl group by hydrogenation followed by mesylation afforded **50**. Displacement of the mesylate with benzylamine followed by regioselective intramolecular opening of the epoxide provided pyrrolidine or piperidine derivatives **51** in good yield. A series of protection/deprotection reactions furnished the acetamides **53**. The construction of the indolizidine/quinolizidine core was achieved by an intramolecular Claisen-type cyclization of **53**. Subsequent reduction of the Claisen product afforded bicyclic hydroxy lactams **54** without any change in enantiomeric excess with respect to that of **49**. Conversion of **54** to the enones **55** followed by a one-pot reduction of the alkene and

debenzylation gave the bicyclic lactams **56** which have been employed as the key intermediates in several syntheses of pumiliotoxins and homopumiliotoxins.

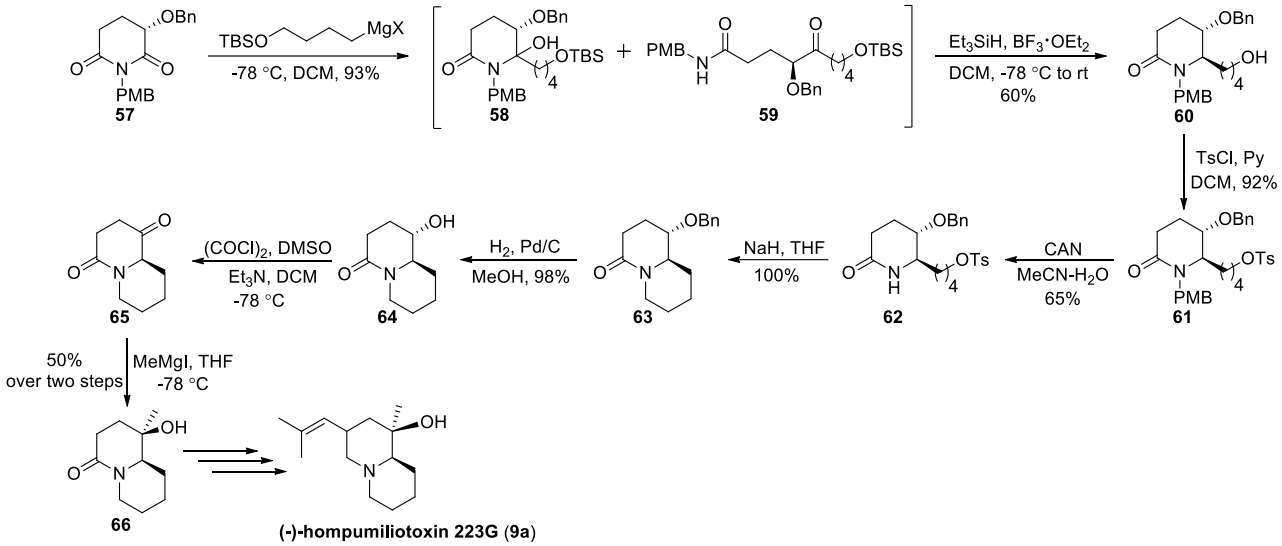


Scheme 1.05

1.3.6 Formal asymmetric synthesis of (-)-homopumiliotoxin 223G by Huang

In 2006, Huang and co-workers[13c] reported their formal asymmetric synthesis of (-)-homopumiliotoxin 223G in eight steps and 18% overall yield. This synthesis involves the flexible introduction of a functionalized C_4 side chain to (*S*)-3-benzyloxyglutarimide **57** (Scheme 1.06), easily prepared from 1,4-butanediol. The addition of Grignard reagent to **57** afforded a separable diastereomeric mixture of **58** and ring-opened δ-keto amide **59** in a combined yield of 93%. These two isomers are interconvertible through an *N*-acyliminium ion intermediate[18] and were used in the subsequent step without purification. Treatment of the mixture **58** and **59** with Et_3SiH/ $BF_3{\cdot}Et_2O$ provided the desilylated product **60** in 60% yield. Tosylation of **60** followed by

N-deprotection using ceric ammonium nitrate provided **62**. Intramolecular nucleophilic displacement of the tosyl group and removal of the benzyl group by catalytic hydrogenation afforded the key intermediate **64**. Utilization of a tandem Swern oxidation-Grignard reaction strategy afforded **66** as a single diastereomer with 90% ee. The conversion of **66** into (-)-homopumiliotoxin 223G is reported in the literature.[12a]

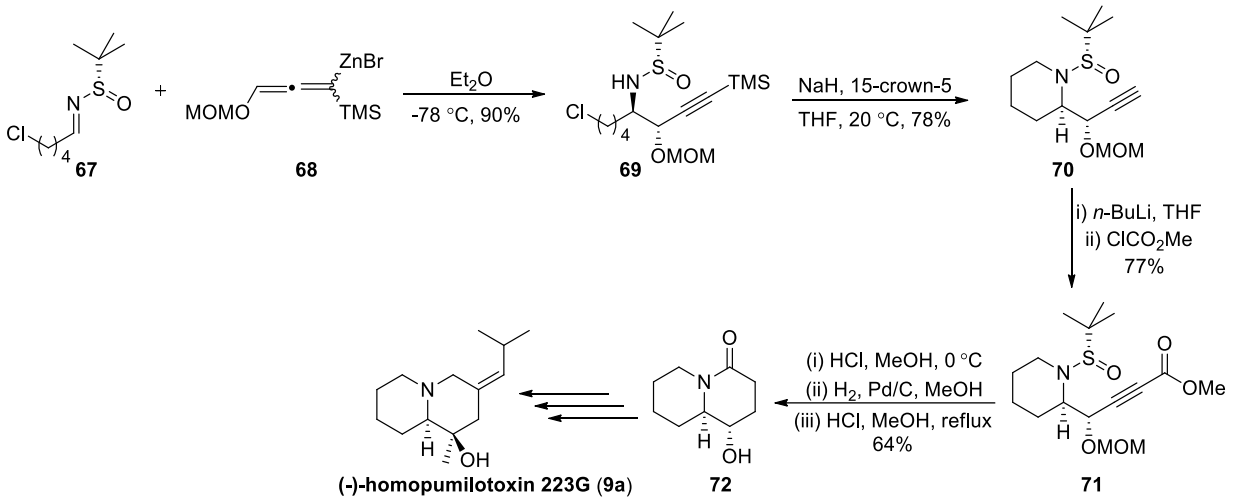


Scheme 1.06

1.3.7 Formal asymmetric synthesis of (-)-homopumiliotoxin 223G by Chemla

In 2007, Chemla and co-workers[13b] achieved the asymmetric synthesis of a key homopumiliotoxin intermediate, (-)-1-hydroxyquinolizidinone, in seven steps and in 25% overall yield from readily available 5-chloropentanal. Their synthesis started with (*S*s)-sulfinimine **67** derived from 5-chloropentanal and (*S*s)-*N*-*tert*-butanesulfinamide.[19] Reaction of **67** with the *in situ* generated racemic allenylzinc reagent **68**[20] afforded a mixture of two inseparable major and minor isomers of **69** in 90% yield (dr = 24:1, Scheme 1.07). Intramolecular displacement of chloride and desilylation of the terminal alkyne were achieved in a single step to provide **70** as a single isomer after purification. Acylation of the acetylene with methyl chloroformate led to intermediate **71**. Treatment of **71** with methanolic HCl resulted in the removal of the *tert*-butanesulfinyl auxiliary

on the nitrogen. Hydrogenation of the triple bond and subsequent cyclization afforded the corresponding bicyclic lactam which was deprotected (MOM removal) with methanolic HCl to give (-)-1-hydroxyquinolizidinone **72** which is a key intermediate in the synthesis of (-)-homopumiliotoxin 223G.[13]

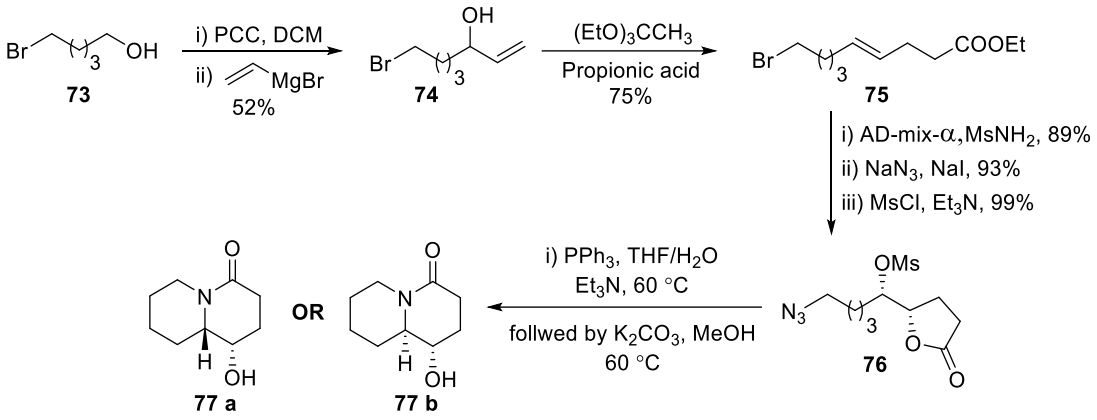


Scheme 1.07

1.3.8 Formal asymmetric synthesis of (-) and (+)-homopumiliotoxin 223G by Kim

In 2010, Kim and co-workers[21] developed an efficient and stereoselective route to the key intermediate 1-hydroxyquinolizidinone for the synthesis of homopumiliotoxin 223G in six steps and 25% overall yield (Scheme 1.08). Their synthesis started with commercially available alcohol **73** which was oxidized by PCC to the corresponding aldehyde. Subsequent addition of vinyl magnesium bromide provided allylic alcohol **74**. Claisen rearrangement of **74** with triethylorthoacetate afforded the (*E*)-alkene **75**, which upon dihydroxylation generated a hydroxy lactone. Subsequent heating of this lactone with sodium azide followed by mesylation afforded **76**. Exclusive formation of **77a** was observed when a more nucleophilic solvent (MeOH) was used. However, the other diastereomer **77b** was observed when a less nucleophilic solvent (MeCN) was

used. Lactams **77a** and **77b** are useful for the synthesis of (+) and (-) homopumiliotoxin 223G, respectively.[13]



Scheme 1.08

1.4 Studies on an organocatalytic vinylogous Mannich approach to key pumiliotoxin alkaloid intermediates:

As described above, there are several known syntheses of pumiliotoxin alkaloids. Kibayashi[13a, b] and Lin[13e] achieved their synthesis of pumiliotoxin alkaloids in eleven and fourteen steps, respectively. Huang[13c] and Chang[12b] achieved the formal synthesis of pumiliotoxin alkaloids in eight and eleven steps, but the synthesis of the starting material **21**, **22** and **57** was ignored in both the claims. Pilli and co-workers[12a] achieved the total synthesis of (±) homopumiliotoxin 223G in just six steps, which is considered to be the shortest total synthesis of pumiliotoxin alkaloids. All of these methods are primarily limited by the multiple steps needed for the synthesis of key bicyclic lactam intermediates.

As outlined in the objectives of this study, we decided to examine the organocatalytic direct vinylogous Mannich (ODVM) reaction of a cyclic imine, or an iminium ion that is generated *in situ* from its stable precursor, and γ-crotonolactone **1** (Figure 1.5) as the key step in our approach to bicyclic lactams leading to the pumiliotoxins. Notably, there are no reports on the vinylogous

Mannich reaction of imines or *in situ* generated iminium ions and crotonolactone **1**. If successful, our strategy would give access to the key lactam intermediate **H** in just five steps (Figure 1.5).

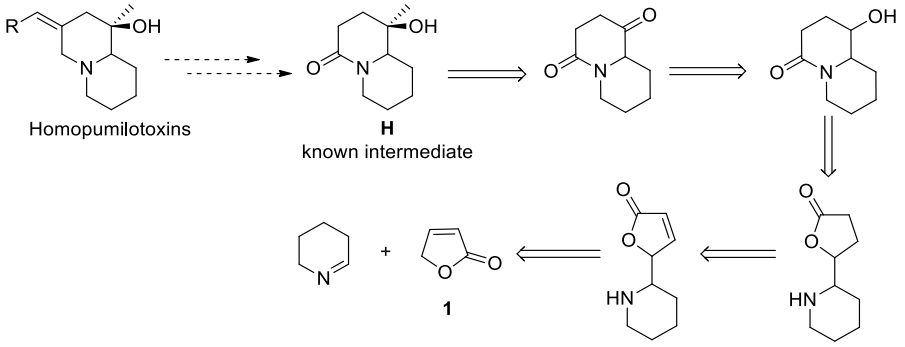


Figure 1.5 Retrosynthetic analysis

We chose to examine the possibility of using bifunctional organocatalysts for the proposed Mannich reaction. These catalysts contain a hydrogen bond donor functionality in the form of a thiourea, and also a Lewis basic tertiary amine functionality. It was anticipated that the hydrogen bond donor would either assist in generating an imine or it would activate a preformed imine electrophile, whereas the Lewis base would assist in the deprotonation of the butyrolactone to generate a nucleophilic furanoate (Figure 1.6).

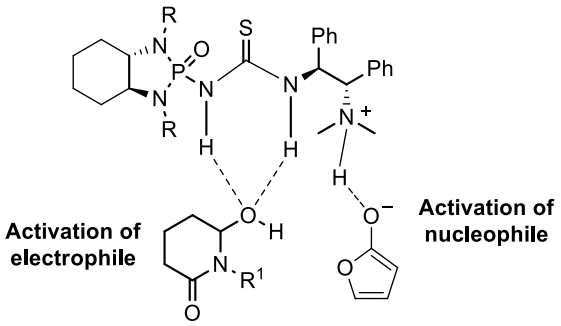


Figure 1.6 Activation of electrophile and nucleophile with phosphoramide-thiourea catalyst

1.5 Results and Discussion

Organocatalysis has been shown to be a useful and important technique to induce stereoselectivity in a wide variety of chemical transformations.[22] We have designed a new class of

phosphoramide-thiourea organocatalysts based on the Takemoto catalyst (catalyst **II,** Figure 1.8) as shown in Figure 1.7.

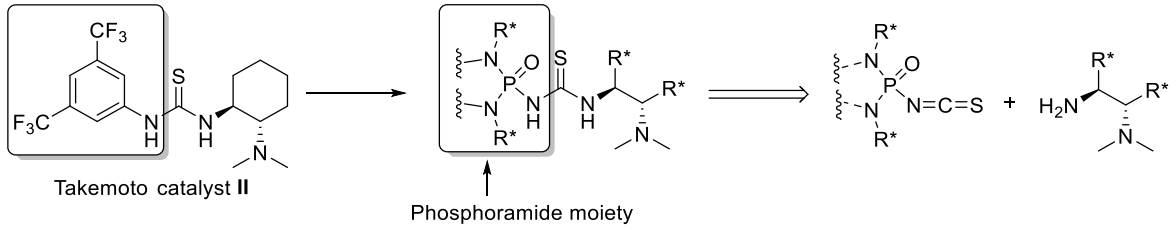


Figure 1.7. Design of a new class of phosphoramide-thiourea catalyst

Compared to the Takemoto catalyst **II**, our catalysts contain a chiral 1,2-diamine based amidophosphoryl moiety (for example compounds **VI-VIII**, Figure 1.8) instead of the 1,3-bis(trifluoromethyl)phenyl moiety. These catalysts have sites that can potentially activate electrophiles through hydrogen bonding[23] and also a basic site to activate the nucleophile.

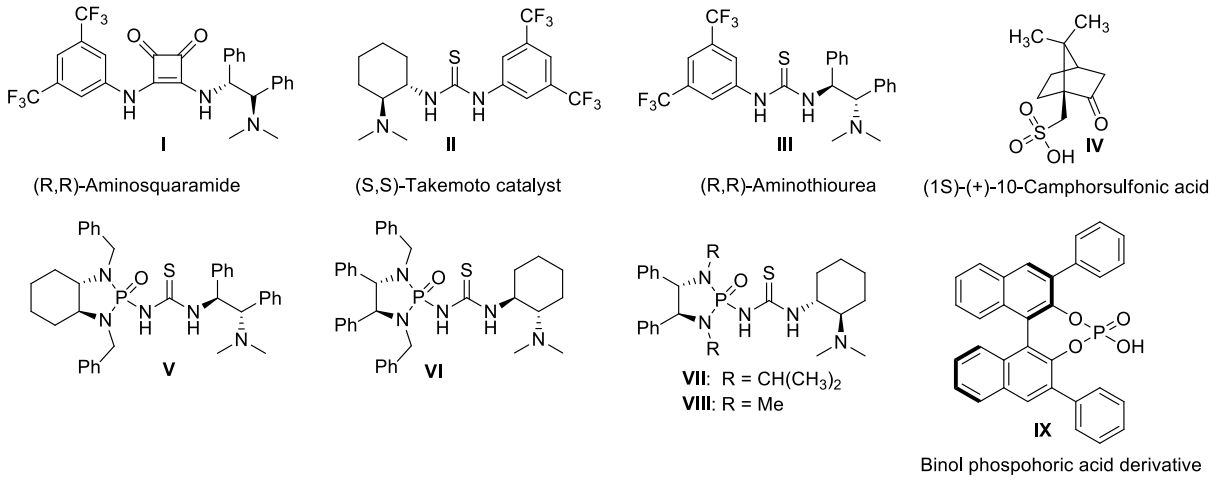
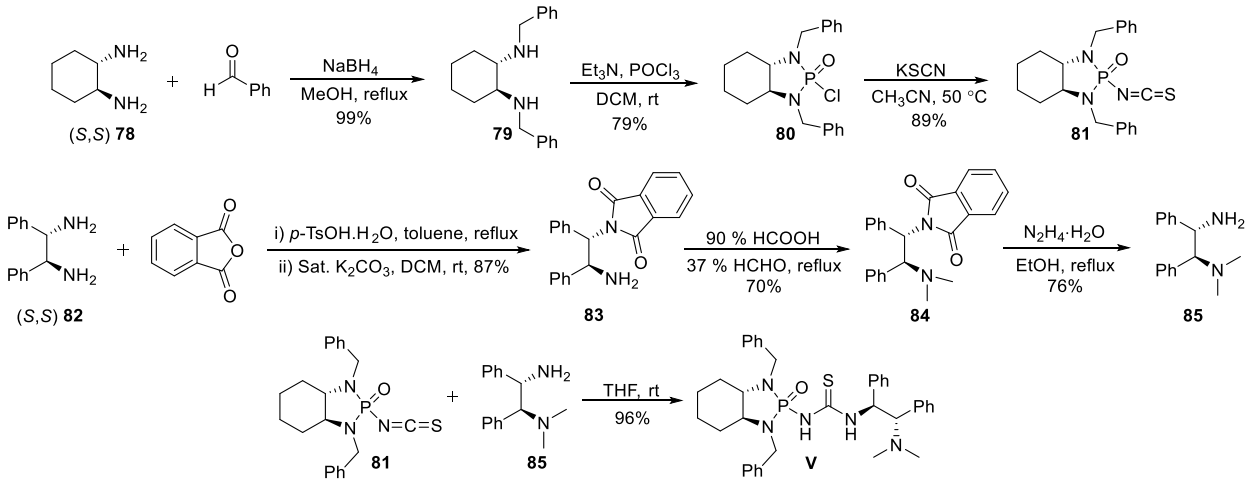


Figure 1.8 Organocatalysts used for the direct vinylogous Mannich reaction

In short, simultaneous activation of the electrophile and nucleophile can be potentially achieved with these bifunctional catalysts. In addition to the phosphoramide-thiourea catalysts, we also planned to study the effect of other bifunctional catalysts as well as chiral acids in the direct vinylogous Mannich reaction (Figure.1.8). The synthesis of several novel phosphoramide-thiourea catalysts is described below.

Our studies began with the preparation of building blocks required for the synthesis of the phosphoramide catalyst (**V**) from commercially available (1*S*,2*S*)-cyclohexane-1,2-diamine **78**. Reductive amination[24] of benzaldehyde with **78** afforded (1*S*,2*S*)-*N*,*N*'-dibenzylcyclohexane-1,2-diamine **79**, which on condensation with phosphorous oxychloride furnished diaminophosphoryl chloride **80**. Treatment of **80** with potassium isothiocyanate[25] afforded intermediate **81**. Simultaneously, (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diphenylethane-1,2-diamine **85** was prepared according to the procedure reported in the literature.[26]

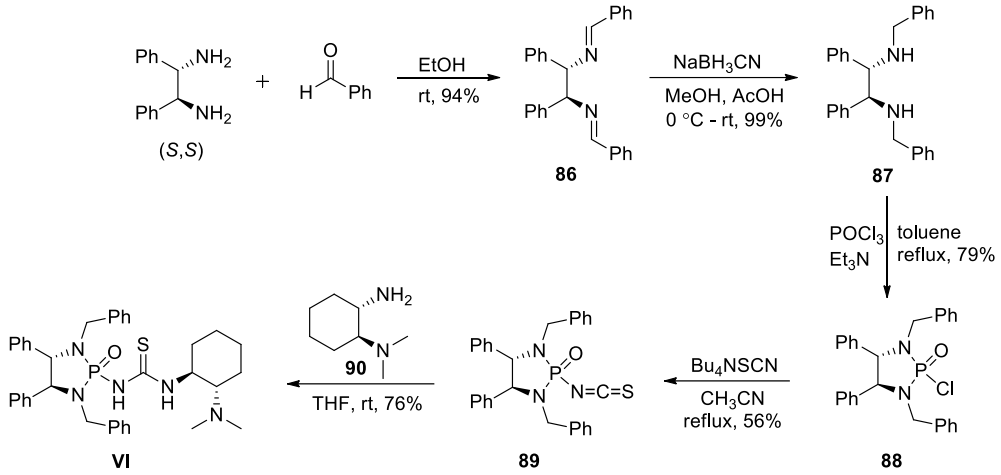


Scheme 1.09

The protection of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine **82** with phthalic anhydride produced the mono-phthalimido derivative **83**. Dimethylation of **83** followed by removal of the imide functionality with hydrazine hydrate afforded **85**. The coupling of intermediates **81** and **85** afforded catalyst **V** as a white solid in 96% yield (Scheme 1.09).

We have also synthesized several "switched" phosphoramide catalysts where the stilbene diamine moiety is on the phosphorous side and the cyclohexane diamine group is on the other side of the catalysts with respect to catalyst **V**. The building blocks required for the preparation of

switched phosphoramide catalysts were obtained by following different routes depending on the substituents on the nitrogen.

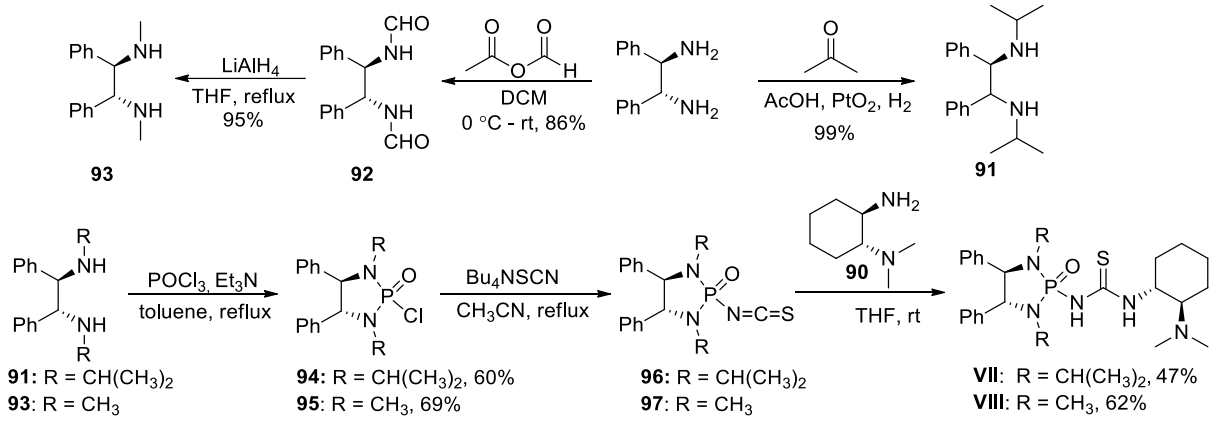


Scheme 1.10

The synthesis of the catalyst **VI** started with (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine which on reaction with benzaldehyde followed by reduction with sodium cyanoborohydride afforded **87**[27a]. Treatment of **87** with phosphorous oxychloride followed by reaction with tetrabutylammonium thiocyanate afforded intermediate **89**. The coupling of intermediate **89** and (1*S*,2*S*)-*N*,*N*-dimethylcyclohexane-1,2-diamine **90**[27b] afforded catalyst **VI** as a white solid in 76% yield (Scheme 1.10).

The synthesis of the catalysts **VII** and **VIII** started with the preparation of the intermediates **91** and **93** which were made easily from commercially available (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine. Reductive amination of acetone with stilbene diamine using Adam's catalyst in the presence of acetic acid and hydrogen afforded **91.**[28a] Alternatively, formylation of stilbene diamine with formic acetic anhydride followed by reduction of the bis-amide with lithium aluminium hydride afforded **93.**[28b] Once we had these intermediates in hand, the rest of the steps to achieve the syntheses of the catalysts **VII** and **VIII** were identical to the synthesis of catalyst **VI**. The

condensation of disubstituted diamines **91** and **93** with phosphorous oxychloride afforded diaminophosphoryl chlorides[29] **94** and **95**, respectively. The isothiocyanates **96** and **97** obtained by the reaction of the corresponding phosphoryl chlorides with Bu_4NSCN and were used without purification in the next step. The coupling of **96** and **97** with **90** afforded the phosphoramide catalysts **VII** and **VIII** as a white solids in 47% (94% based on recovered starting material **96**) and 62% respectively (Scheme 1.11).



Scheme 1.11

Analysis of the ^{1}H NMR spectra of the phosphoramide-based catalysts revealed an interesting feature of their conformations in solution. We had anticipated that the *N*-H^a proton (Figure 1.9), which is flanked by the thiocarbonyl and the phosphoryl group would resonate more downfield than the *N*-H^b proton. However, we observed that the *N*-H^b proton was more downfield shifted than *N*-H^a proton. It should be mentioned that, in catalyst **VI-VIII**, *N*-H^a and *N*-H^b can be readily distinguished by their chemical shift; whereas in catalyst **V** H^b appears as a broad singlet and the peak for H^a merges with aromatic protons (see Table 1.1).

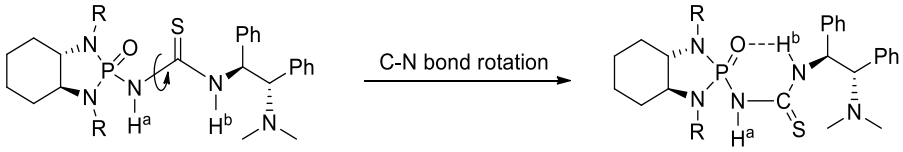
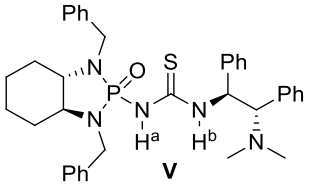
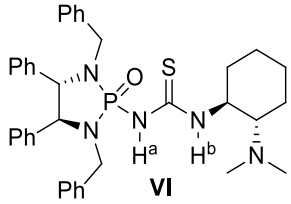
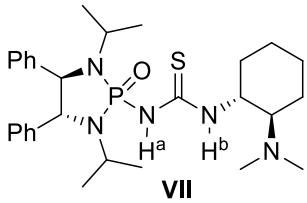
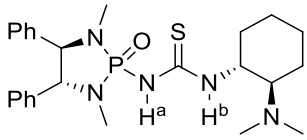


Figure 1.9 Intramolecular H-bonding in phosphoramide catalysts

A plausible reason for this observation is a preference for the thiourea conformation in which *N*-H^b is internally hydrogen bonded to the P=O oxygen. It is well known that hydrogen bonding induces a downfield shift in the hydrogen-bonded hydrogen atom.[30a]

Table 1.1 NMR characteristics of the thiourea protons (H^a and H^b) in phosphoramide catalysts.

Catalysts	H^a	H^b
 **V**	merges with Ar*H*	10.40 (br s, 1H),
 **VI**	6.99 (d, J = 9.8 Hz)	9.91 (d, $^3J_{H\text{-}H}$ = 7.9 Hz)
 **VII**	6.35 (d, J = 8.6 Hz)	9.90 (d, $^3J_{H\text{-}H}$ = 7.5 Hz)
 **VIII**	6.59 (br s, 1H)	9.63 (d, $^3J_{H\text{-}H}$ = 7.7 Hz)

The *N*-H^b proton appears in the range of 9.90-10.41 ppm, whereas the *N*-H^a appears in the range of 6.35-6.99 ppm (see the experimental section) in the ^{1}H NMR spectrum of the catalysts as shown in Table 1.1. This observation was also confirmed by heteronuclear ^{1}H-^{13}C correlation spectroscopy (HSQC).

These observations suggest that our phosphoramide-containing catalysts may not function as double-hydrogen bonding catalysts although they contain a thiourea functional group which is

a well-established double-hydrogen bond donor functionality.[30b] Instead, they may function as catalysts that engage in single hydrogen bond activation of suitable H-bond donor functional groups (Figure 1.10). It may be noted that the thiocarbonyl group is known to function as a hydrogen-bond acceptor.[30c]

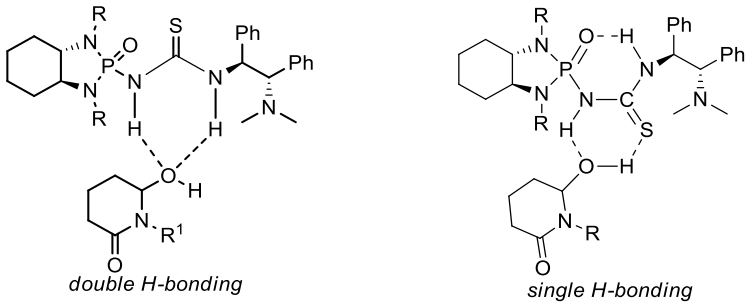


Figure 1.10 Hydrogen bonding of iminium ion precursor with phosphoramide-thiourea catalyst

With the catalysts **V-VIII** in hand, we initiated our investigation of an organocatalytic vinylogous Mannich reaction of a piperidine-derived imine or *in-situ* generated iminium ion with crotonolactone **1**, the key step in our planned synthesis of homopumiliotoxin alkaloids.

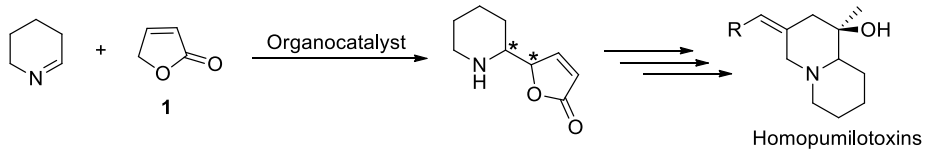
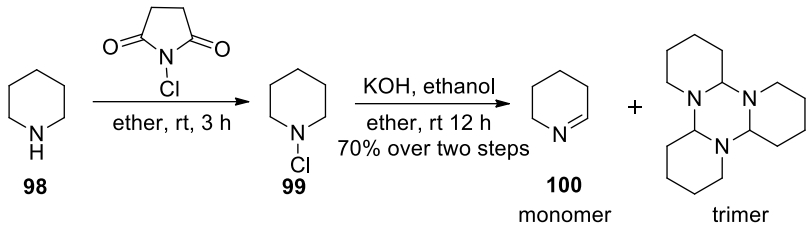


Figure 1.11: Organocatalytic vinylogous Mannich reaction as a key step of the synthesis

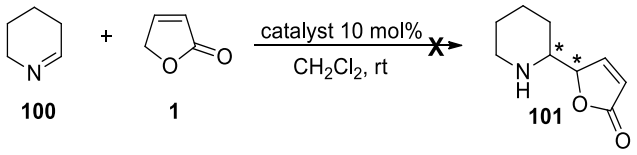
The requisite imine was readily obtained from piperidine by adaptation of the reported procedure.[31] *N*-Chlorination of piperidine **98** with *N*-chlorosuccinimide afforded *N*-chloropiperidine **99.** Treatment of **99** with ethanolic KOH gave a mixture of monomeric (minor) and trimeric (major) forms (^{1}H NMR) of **100**[31] (Scheme 1.12). The trimeric form is a convenient source of Δ^1-piperideine **100** which is generated by dissociation in solution. This material was used as such without purification.

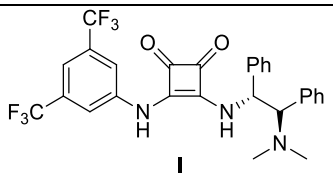
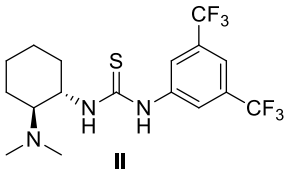
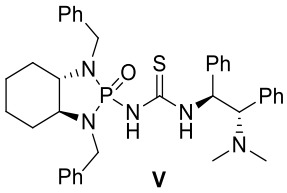


Scheme 1.12

We initially examined the reaction of imine **100** and crotonolactone **1** with stilbene diamine derived aminosquaramide catalyst **I** (entry 1, Table 1.2,). This reaction led to a complex mixture of products which did not contain any of the required product **101**. The use of Takemoto catalyst **II** and phosphoramide catalyst **V** (entries 2 and 3, Table 1.2) was not beneficial, and the required product was not obtained in either case.

Table 1.2 Vinylogous Mannich reaction of imine **100** with crotonolactone **1**

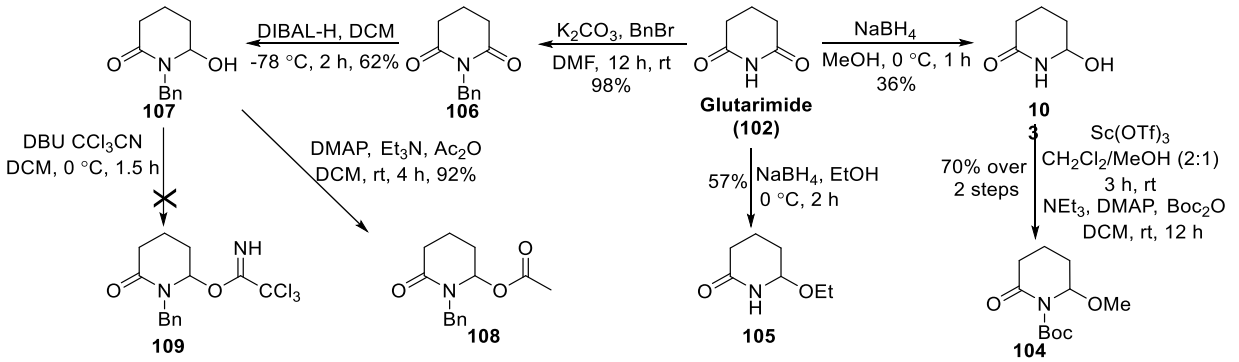


Entry[a]	Catalyst	Time	Result
1	 I	24 h	No required product
2	 II	24 h	No required product
3	 V	24 h	No required product

[a] 2 equiv of crotonolactone.

Given the failure of the vinylogous Mannich reaction of the imine **100** with crotonolactone **1**, we chose to prepare some other substrates that could generate an iminium ion *in-situ* under the reaction conditions. Selected iminium ion precursors were synthesized from commercially available glutarimide and valerolactam according to the literature procedures.[32-35] The yields of all these precursors were good, and they were bench-stable compounds.

The reduction of glutarimide **102** with sodium borohydride in MeOH afforded 6-hydoxypiperidin-2-one **103**.[32] Conversion of the hydroxyl group in **103** into a methoxy group followed by protection with *di*-tert-butyl dicarbonate (Boc anhydride, Boc_2O) afforded **104**. Reduction of **102** with sodium borohydride in EtOH provided 6-ethoxypiperidin-2-one **105**.[33] *N*-benzylation of glutarimide with benzyl bromide followed by reduction with DIBAL-H afforded 1-benzyl-6-hydroxypiperidin-2-one **107**.[34] The acetylation of **107** with acetic anhydride gave 1-benzyl-6-oxopiperidin-2-yl acetate **108**.[35] However, the reaction of **107** with trichloroacetonitrile in the presence of DBU was unsuccessful, and the required product was not obtained (Scheme 1.13). Compounds **103**, **104**, **105**, **107** and **108** are known to generate the corresponding iminium ions when treated with a Lewis acid or a protic acid.[32-35]

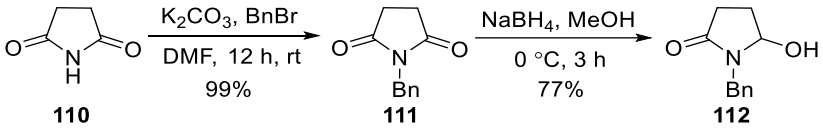


Scheme 1.13

Since the phosphoramides **V-VIII** have a hydrogen-bond donor functionality, we anticipated that they would also facilitate the formation of iminium ions by H-bonding with the

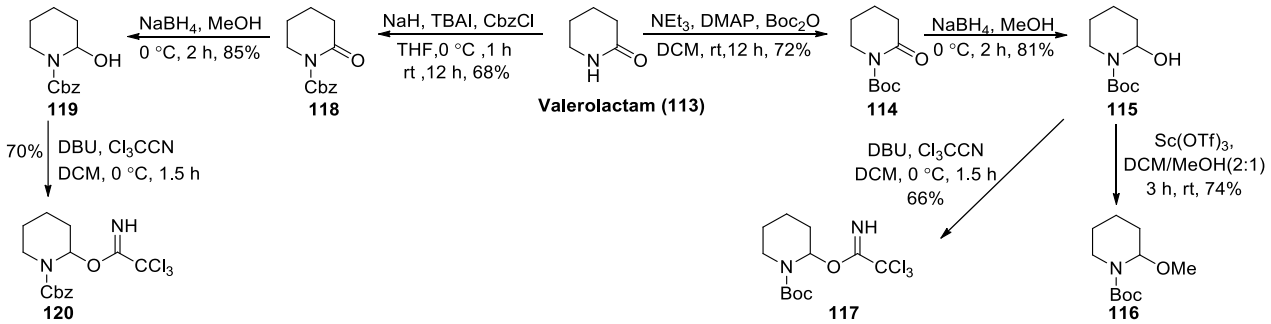
hemiaminal oxygen in compounds **103**, **104**, **105** and **107**, and with the acetate carbonyl oxygen in compound **108**.

A pyrrolidone-based iminium ion precursor was also synthesized from succinimide. Thus, *N*-benzylation of succinimide **110** followed by reduction with sodium borohydride afforded **112**.[36] (Scheme 1.14)



Scheme 1.14

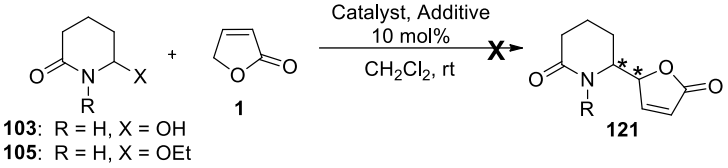
The valerolactam (**113**)-based iminium ion precursors were prepared by *N*-acylation of the valerolactam **113** with *di*-tert-butyl dicarbonate (Boc_2O) or benzyl chloroformate, followed by reduction with sodium borohydride which afforded **115**[37] and **119**[38] respectively. The reaction of **115** and **119** with trichloroacetonitrile in the presence of a stoichiometric amount of DBU afforded the hitherto unreported trichlroacetimidates **117** and **120**, respectively. The conversion of the hydroxyl group in **115** into its methoxy derivative afforded **116** in good yield (Scheme 1.15). Compounds **115**, **116**, **117**, **119** and **120** were anticipated to provide the corresponding iminium ions in the presence of H-bond donor containing organocatalysts.

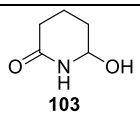
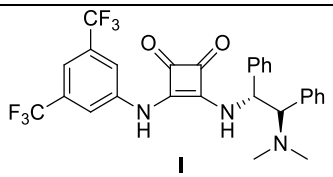
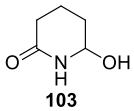
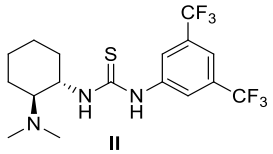
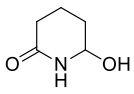
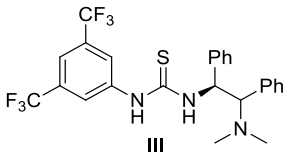
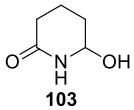
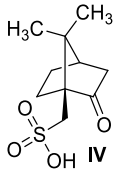
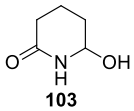
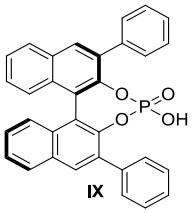
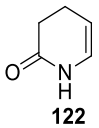


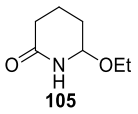
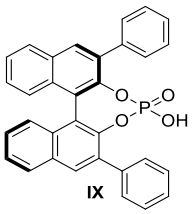
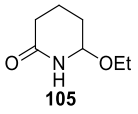
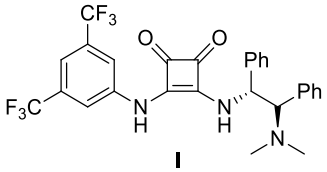
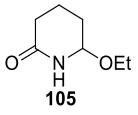
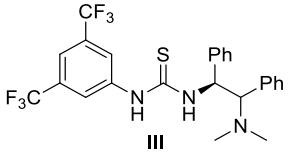
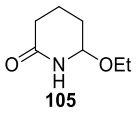
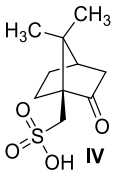
Scheme 1.15

Our studies of the organocatalytic vinylogous Mannich reaction began with the reaction of iminium ion precursor **103** with crotonolactone **1** in the presence of the aminosquaramide catalyst **I**. Initially, CH_2Cl_2 was chosen as a solvent to check the feasibility of the key step (entry 1, Table 1.3). However, this reaction provided a complex mixture which did not contain any of the required product (^{1}H NMR spectrum of the crude product).

Table 1.3 Vinylogous Mannich reaction of glutarimide derivatives and crotonolactone **1**



Entry[a]	Precursor	Catalyst	Additive	Time	Result
1	 **103**	 **I**	-	24 h	No required product
2	 **103**	 **II**	$Sc(OTf)_3$	24 h	No required product
3	 **103**	 **III**	-	24 h	No required product
4	 **103**	 **IV**	-	24 h	No required product
5	 **103**	 **IX**	-	24 h	 **122** 25%[b]

6	 **105**	 **IX**	-	24 h	No required product
7	 **105**	 **I**	-	24 h	No required product
8	 **105**	 **III**	-	24 h	No required product
9	 **105**	 **IV**	-	24 h	No required product

[a] 2 equiv. of crotonolactone. [b] Isolated by flash column chromatography.

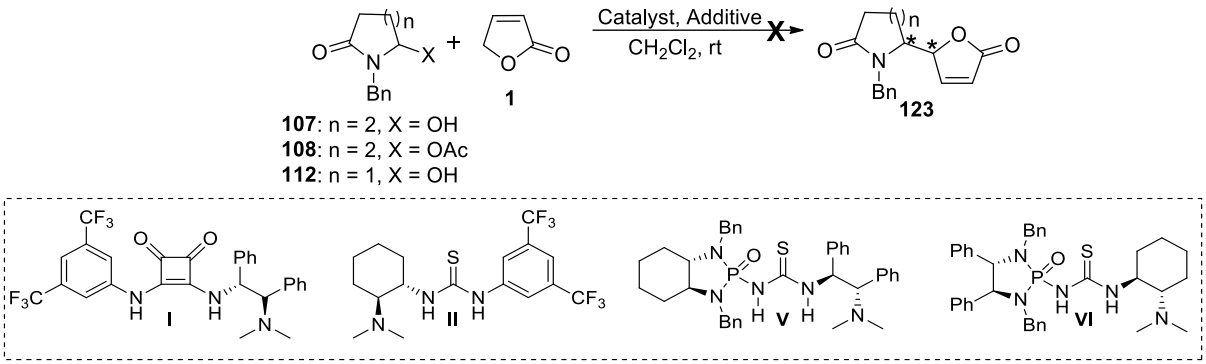
Other bifunctional catalysts and chiral acids (as co-catalysts) for the vinylogous Mannich reaction were examined next. In the presence of Takemoto catalyst **II** and stilbene derived thiourea catalyst **III**, the vinylogous Mannich reaction of **103** with crotonolactone **1** was not fruitful and failed to provide the required product **121**. The starting material **103** was recovered from the reaction mixture (entries 2 and 3, Table 1.3). Adding $Sc(OTf)_3$, as a Lewis acid that would promote the generation of an iminium ion from **103** or **105**, (entry 2, Table 1.3) did not alter the course of the reaction and the required product was not detected. It was confirmed from ^1H NMR of the crude and the starting material **103** or **105** was recovered from the reaction mixture. The effect of $Sc(OTf)_3$ was examined only when it was observed that there was no reaction (TLC) in the presence of the organocatalyst alone.

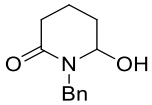
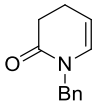
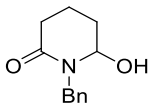
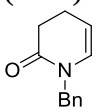
The use of (1*S*)-10-camphorsulfonic acid in the vinylogous Mannich reaction of **103** with crotonolactone **1** provided a complex mixture which did not contain any of the required product (entry 4 Table 1.3). A by-product enamide **122** was isolated in 25% yield when the binol

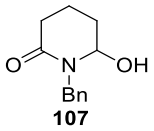
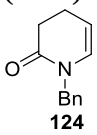
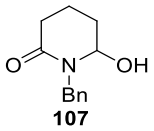
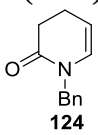
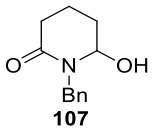
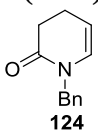
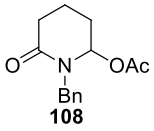
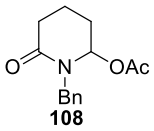
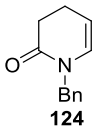
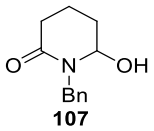
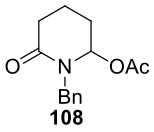
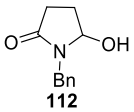
phosphoric acid derivative **IX** was used as a chiral acid catalyst. Spectroscopic data for **122** was in agreement with the reported data in the literature.[38c] The ethoxy lactam **105** also failed to give the required product with the use of the bifunctional catalysts **I** and **III** (entries 7 and 8, Table 1.3). The use of chiral acids **IV** and **IX** (entries 6 and 9, Table 1.3) did not have a substantial effect on the vinylogous Mannich reaction of **105** with crotonolactone **1** and these reactions also failed to provide the product required for the synthesis of homopumiliotoxin alkaloids. Only unreacted starting materials were observed in the crude reaction mixtures (^{1}H NMR) in both the cases.

We then studied the reaction of various *N*-benzylated glutarimide and succinimide iminium ion precursors. The reaction of **107** with crotonolactone **1** was examined using bifunctional catalysts **I** and **II** and afforded *N*-benzyl enamide **124** as the only by-product in both the cases (entries 1 and 2, Table 1.4), respectively.

Table 1.4 Vinylogous Mannich reaction of *N*-benzylated iminium ion precursors and crotonolactone **1**



Entry	Precursor	Catalyst	Additive	Base	Time	Result
1	 **107**	**I**	-	-	12 h	 **124** (95%)[a]
2	 **107**	**II**	-	-	12 h	 **124**

3	 **107**	**V**	$Sc(OTf)_3$	-	48 h	(90%)[a]  **124**
4	 **107**	**VI**	$Sc(OTf)_3$	-	48 h	(90%)[a]  **124**
5	 **107**	-	$Sc(OTf)_3$	-	12 h	(90%)[a]  **124**
6	 **108**	**I**	-	-	12 h	(95%)[a] No required product
7	 **108**	**II**	-	-	12 h	 **124**
8	 **107**	**II**	$Sc(OTf)_3$	TEA, DBU	48 h	43% SM recovered[b]
9	 **108**	**II**	$Sc(OTf)_3$	TEA, DBU	48 h	SM recovered[b]
10	 **112**	**I**	$Sc(OTf)_3$	-	12 h	No required product
11	 **112**	**II**	$Sc(OTf)_3$	-	12 h	No required product

[a]Yield of crude product, [b]Carried out at 0 °C.

The vinylogous Mannich reaction of **107** with crotonolactone **1** in the presence of the phosphoramide catalyst **V** or **VI** and $Sc(OTf)_3$ afforded only the *N*-benzyl enamide **124** (Table 1.4, entries 3 and 4) and none of the required product. The formation of the *N*-benzyl enamide **124** was not detected in the absence of $Sc(OTf)_3$ in these reactions. Notably, the *N*-benzyl enamide **124** was

also observed in the reaction of **107** with crotonolactone **1** in the presence of $Sc(OTf)_3$ without the addition of catalyst **V** or **VI** (entry 5, Table 1.4). These observations suggests that the formation of **124** observed in the reactions involving catalyst **V** or **VI** and $Sc(OTf)_3$ (entries 3 and 4, Table 1.4) is due to $Sc(OTf)_3$ and that the organocatalysts **V** and **VI** are not involved in this dehydration. In the presence of catalyst **I**, the reaction of **108** with crotonolactone **1** provided a mixture of products with no traces of the required product (entry 6, Table 1.3). However, a reaction with Takemoto catalyst **II** afforded *N*-benzyl enamide **124** as a by-product in 43% yield but failed to provide the required product.

As described above, formation of the by-product **124** could not be avoided in several of the reactions examined. Nonetheless, the formation of **124** indicated that the required iminium ion was formed under the examined conditions, but it failed to react with the nucleophile present in the reaction mixture. Instead, the iminium ion formed in the reaction mixture loses a proton to generate the *N*-benzyl enamide **124** (Figure 1.12). This process is presumably faster than addition of the crotonolactone-derived enolate at ambient temperature.

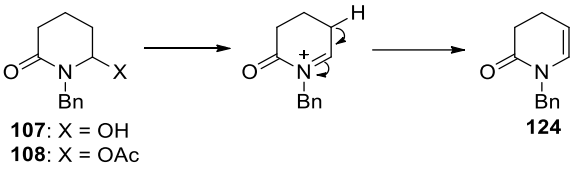


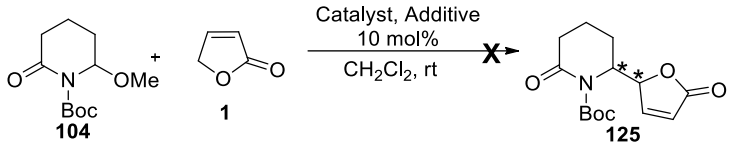
Figure 1.12 Formation of *N*-benzyl enamide **119**

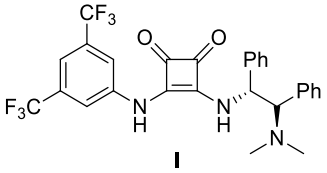
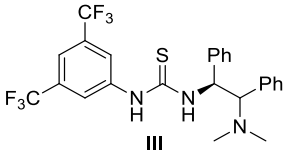
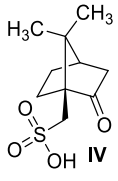
Assuming that ambient temperature promotes elimination from the iminium ion, a few reactions with catalyst **II** were conducted at lower temperature (0 ^oC). Unfortunately, although this prevented the formation of **124**, the required Mannich product product **123** was not observed (entries 8 and 9, Table 1.4). The possibility of the lack of enolization of the crotonolactone was also considered and the effect of added bases such as triethyl amine and DBU was also examined. Unfortunately, and unexpectedly, this change had no effect and the starting materials were

recovered from the reaction mixture (entries 8 and 9, Table 1.3). Because of the formation of moderate amount of undesired by-product **124**, the succinimide-derived iminium ion precursor **112** was also investigated in the presence of catalysts **I** and **II** to examine the influence of the ring size on the course of the reaction. Unfortunately, there was no reaction at all, and the desired product was not obtained (entries 10 and 11, Table 1.3). Unreacted starting material was recovered from the reaction mixture in both cases.

We also investigated the vinylogous Mannich reaction of *N*-Boc protected iminium ion precursor **104** with crotonolactone **1** (Table 1.5). In the presence of bifunctional catalysts, **I**, **III**, or camphorsulfonic acid **IV**, the reaction of **104** with crotonolactone **1** failed to give the desired product (entries 1, 2 and 3, Table 1.5).

Table 1.5 Vinylogous Mannich reaction of *N*-Boc protected iminium ion precursor with crotonolactone **1**



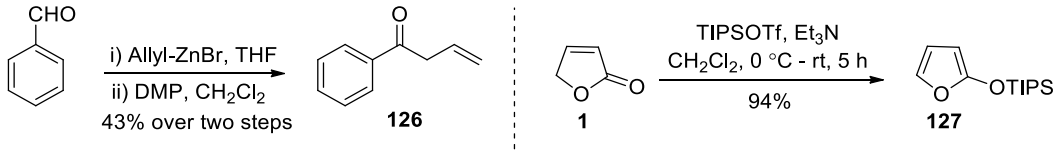
Entry[a]	Catalyst	Additive	Time	Result
1	 **I**	-	72 h	No required product
2	 **III**	-	72 h	No required product
3	 **IV**	-	72 h	No required product
4	-	$InCl_3$	48 h	

				No required product
5	-	$Sc(OTf)_3$	48 h	No required product

[a] 2 equiv. of crotonolactone

In addition, the use of Lewis acids such as $InCl_3$ and $Sc(OTf)_3$ in the vinylogous Mannich reaction of **104** with crotonolactone **1** was not fruitful (entries 4 and 5, Table 1.5) and the starting material **104** was recovered from the reaction mixture in both cases. These results suggest that the iminium ion precursor **104** does not provide the iminium ion under the examined conditions.

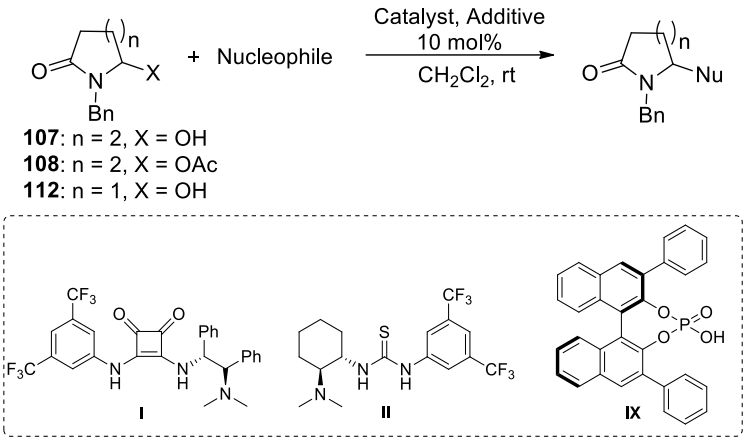
Given the failure of reactions involving crotonolactone, a few other carbon nucleophiles were tested for their reactivity in the desired vinylogous Mannich reaction. We noted that β,γ-unsaturated allylic ketone **126** was used as a nucleophile in several catalytic asymmetric reactions such as vinylogous aldol, Mannich reactions and Michael addition reactions.[39] In addition, (furan-2-yloxy)triisopropylsilane[40] **127** and dimethoxy benzene **128** were also tested as nucleophiles. These nucleophiles were synthesized by the adaptation of known methods reported in the literature. The allyl phenyl ketone **126** was prepared by the treatment of benzaldehyde with allyl zinc bromide followed by oxidation with the Dess martin periodinane reagent (DMP).[41] *O*-protection of crotonolactone with *i*Pr_3SiOTf provided 94% of (furan-2-yloxy)triisopropylsilane **127** (Scheme 1.16).

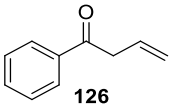
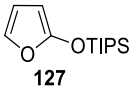
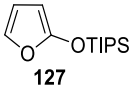
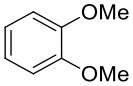
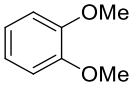
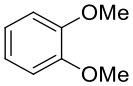
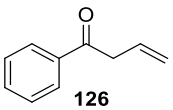


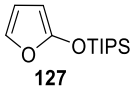
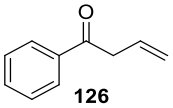
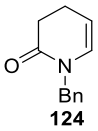
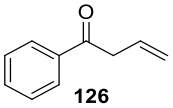
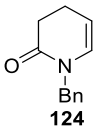
Scheme 1.16

We then explored the reaction of these more reactive nucleophiles in the presence of bifunctional catalysts and chiral acid with iminium ion precursors derived from glutarimide and succinimide (Table 1.6).

Table 1.6 Reactions of Iminium Ion Precursor with Various Nucleophiles



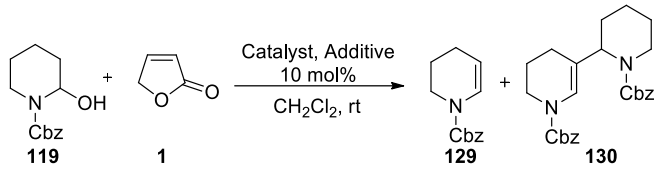
Entry	Precursor	Nucleophile	Catalyst	Additive	Time	Result
1	**107**	 **126**	**I**	$Sc(OTf)_3$	24 h	No required product
2	**107**	 **127**	**I**	-	24 h	No required product
3	**107**	 **127**	**IX**	-	24 h	No required product
4	**107**	 **128**	**I**	$Sc(OTf)_3$	24 h	No required product
5	**107**	 **128**	**II**	$Sc(OTf)_3$	24 h	No required product
6	**107**	 **128**	**IX**	$Sc(OTf)_3$	24 h	No required product
7	**112**	 **126**	**II**	$Sc(OTf)_3$	24 h	No required product
8	**112**		**II**	$Sc(OTf)_3$	24 h	

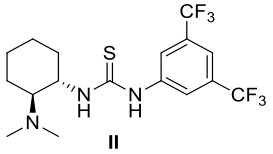
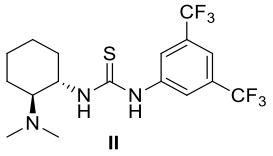
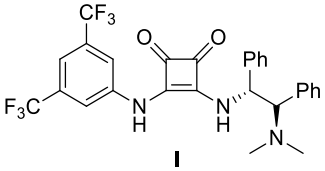
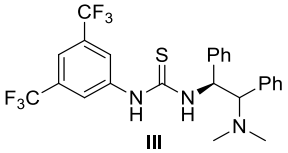
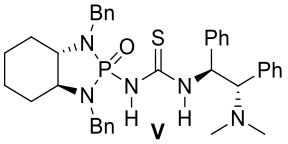
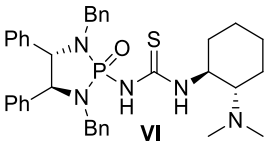
		 **127**				No required product
9	**108**	 **126**	**I**	-	48 h	 **124** 3%
10	**108**	 **126**	**II**	-	48 h	 **124** 7%

The reaction of allyl phenyl ketone **126** with the iminium ion precursor **107** in the presence of the Takemoto catalyst and $Sc(OTf)_3$ did not provide the required product (Table 1.6, entry 1). The reaction of **107** with the siloxyfuran **127** in the presence of aminosqaramide catalyst **I** and chiral acid **IX** failed to produce the required product (entries 2 and 3, Table 1.6). The use of dimethoxy benzene **128** as the nucleophile in the presence of bifunctional catalyst **I**, **II** and chiral acid **IX** with the iminium ion precursor **107** did not provide the required product. Surprisingly, no by-product (enamide) was observed after the introduction of $Sc(OTf)_3$ (entries 4, 5 and 6, Table 1.6). Unreacted starting material **107** was isolated from all of the above reactions. The reaction of **112** with allyl phenyl ketone **126** and siloxyfuran **127**, in the presence of Takemoto catalyst and $Sc(OTf)_3$ respectively (entries 7 and 8, Table 1.6), was also unsuccessful. Nevertheless, in the presence of bifunctional catalysts **I** and **II**, the reaction of the iminium ion precursor **108** with allyl phenyl ketone **126** resulted in a complex mixture of products that did not contain any of the required product. In both the cases, the by-product *N*-benzyl enamide **124** was isolated in 3% and 7% from the reaction mixture, respectively.

We next examined the valerolactam-derived iminium ion precursors with the nucleophiles previously used in the vinylogous Mannich reaction as shown in Table 1.7.

Table 1.7 Attempted reactions of benzyl 2-hydroxypiperidine-1-carboxylate **119** with crotonolactone **1**



Entry	Catalyst	Additive	Time	Yield (%) 129	Yield (%) 130
1	 II	$Sc(OTf)_3$	10 mins	36	19
2[a]	 II	$Sc(OTf)_3$	30 mins	31	20
3	-	$Sc(OTf)_3$	6 h	>95[b]	-
4	 I	$Sc(OTf)_3$	6 h	20	10
5	 III	$Sc(OTf)_3$	1h	7	-
6	 V	$Sc(OTf)_3$	48 h	-	90%[b]
7	 VI	$Sc(OTf)_3$	48 h	-	90%[b]

[a]-20 °C - 1h, 0 °C - 1h, rt - 30 mins, [b]yield of crude product.

Our investigations began with the reaction of the iminium ion precursor **119** with crotonolactone **1** in the presence of Takemoto catalyst **II** and $Sc(OTf)_3$. It was noted that the

starting material in the reaction mixture did not change before $Sc(OTf)_3$ was added to the reaction mixture. Notably, formation of the enecarbamate **129** (1:1 mixture of rotamers by ^1H NMR) and the dimeric product **130** (1:1 mixture of rotamers by ^1H NMR) was observed only after the addition of $Sc(OTf)_3$ in 36% and 19% respectively (entry 1, Table 1.7). Since these by-products were obtained at room temperature, the same reaction was therefore repeated at lower temperature in order avoid the side reactions. Unfortunately, no reaction was observed at lower temperature and formation of **129** (31%) and **130** (20%) was observed only after stirring the reaction mixture at ambient temperature for 30 min (entry 2, Table 1.7). The only product observed in the presence of $Sc(OTf)_3$, catalysts **III**, **V** and **VI** (entries 3 and 5-7 Table 1.7) was enecarbamate **129** (no dimeric product **130**). The use of aminosquaramide catalyst **I** produced enecarbamate **129** and dimeric product **130** in 20% and 10% respectively and failed to provide the required product.

The plausible mechanism for the formation of the dimeric product is shown in Figure 1.13 and it involves the nucleophilic addition of the enecarbamate **129** to its precursor iminium ion.

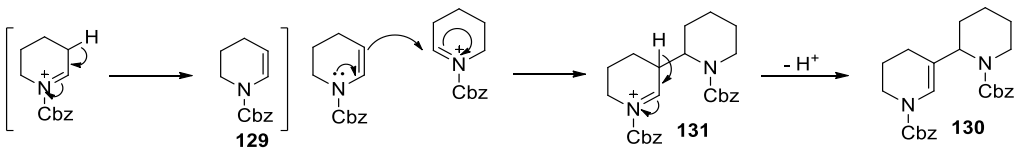
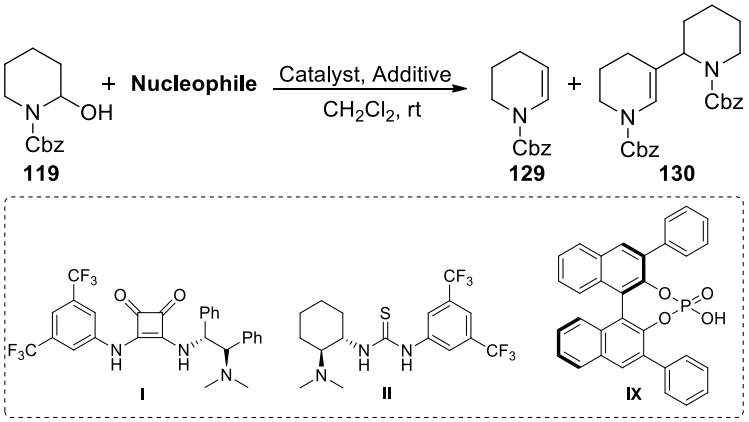
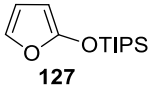
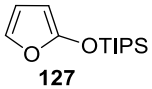
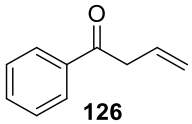
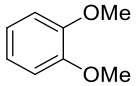
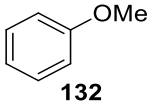


Figure 1.13 Formation of enecarbamate **129** and its side reaction

We also investigated the reaction of the iminium ion precursor **119** with other nucleophiles such as allyl phenyl ketone **126**, (furan-2-yloxy)triisopropylsilane **127**, commercially available dimethoxy benzene **128** and methoxy benzene **132** in the presence of various bifunctional catalysts (Table 1.8). The synthesis of **126** and **127** has been described in Scheme 1.16.

Table 1.8 Attempted reactions of the iminium ion precursor **119** with various nucleophiles



Entry	Nucleophile	Catalyst	Additive	Time	Yield (%) 129	Yield (%) 130
1	 127	**I**	-	12 h	-	-
2	 127	**IX**	-	12 h	17	-
3	 126	**I**	-	2 h	>95[a]	
4	 128	**II**	$Sc(OTf)_3$	6 h	-	10
5	 132	**II**	$Sc(OTf)_3$	12 h	31	21

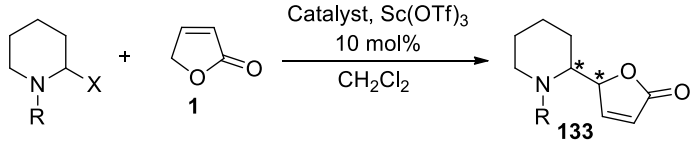
[a]yield of crude product.

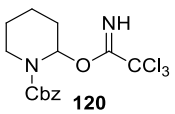
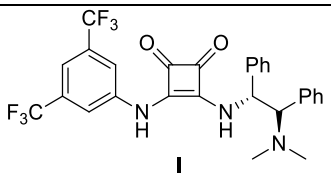
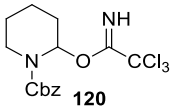
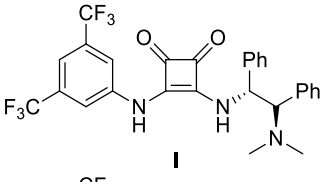
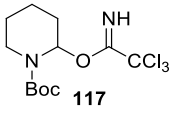
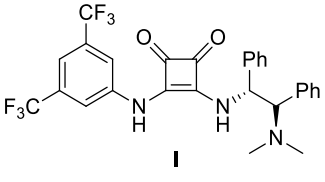
In the presence of aminosquaramide catalyst **I**, the reaction of the iminium ion precursor **119** with siloxyfuran **127** did not provide the required product and the starting material **119** was recovered from the reaction mixture (entry 1, Table 1.8). The use of chiral binol phosphoric acid **IX**, however, afforded a complex mixture which did not contain any of the required product but the enecarbamate **129** was isolated in 17% from this mixture (entry 2, Table 1.8). The reaction with allyl phenyl ketone **126** in the presence of aminosquaramide catalyst **I** only provided the enecarbamate **129**. The use of Takemoto catalyst along with $Sc(OTf)_3$ in the vinylogous Mannich

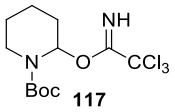
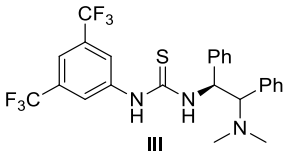
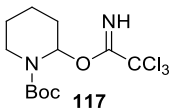
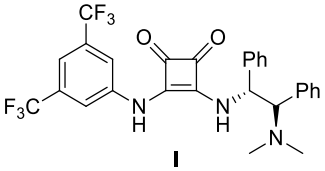
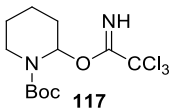
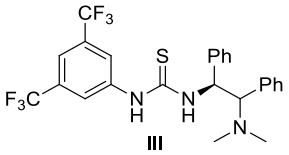
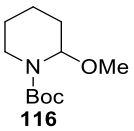
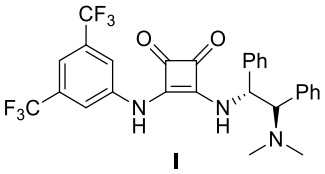
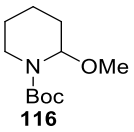
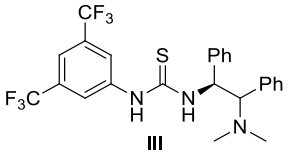
reaction of **119** with dimethoxy benzene **128** together afforded a complex mixture of products. The dimeric product **130** was isolated in 10% yield from this mixture (entry 4, Table 1.8). The use of anisole (**132**) provided only enecarbamate **129** and dimeric product **130** in 31% and 21% yields respectively (entry 5, Table 1.8).

We also investigated reactions of the iminium ion precursors derived from valerolactam (**116**, **117** and **120**) with crotonolactone **1** in the presence of various bifunctional catalyst as shown in Table 1.9. In the presence of aminosquaramide catalyst **I** and $Sc(OTf)_3$ at ambient temperature, the reaction of **120** with crotonolactone **1** resulted in a complex mixture that did not contain any of the required product. At lower temperature, unreacted starting material was recovered from the reaction mixture (entries 1 and 2, Table 1.9).

Table 1.9 Attempted reactions of valerolactam derivatives with crotonolactone **72**



Entry	Precursor	Catalyst	Temp	Time	Result
1	 **120**	 **I**	rt	48 h	No required product
2	 **120**	 **I**	-78 ^{o}C - rt	5 h	No required product
3	 **117**	 **I**	rt	48 h	No required product

4	 **117**	 **III**	rt	48 h	No required product
5	 **117**	 **I**	reflux	4 h	No required product
6	 **117**	 **III**	reflux	4 h	No required product
7	 **116**	 **I**	rt	24 h	No required product
8	 **116**	 **III**	rt	24 h	No required product

[a] 2 equiv. of crotonolactone

In the presence of bifunctional catalysts **I** and **III** and $Sc(OTf)_3$ at ambient temperature, the reaction of the iminium ion precursor **117** with crotonolactone **1** did not give the required product. There was also no change in the reaction mixture at reflux and, in all cases, unreacted starting material was recovered from the reaction mixture (entries 3-6, Table 1.9). The iminium ion precursor **116** did not react with crotonolactone **1** and was recovered from the reaction mixture (entries 7 and 8, Table 1.9).

As seen above, some of the iminium ion precursors were able to generate the iminium ion which provided the enecarbamate by loss of a proton. However, there is no Mannich reaction involving nucleophilic addition of the carbon nucleophile (crotonolactone) used in the reaction. There are two possibilities that may explain this observation: 1) the crotonolactone enolate is not formed under the reaction conditions, and 2) the enolate is formed, but it does not react with the

iminium ion. Of these possibilities, the first was considered unlikely since we had previously shown that vinylogous aldol reactions of crotonolactone with aromatic[42a] and aliphatic[42b] aldehydes can be achieved with aminothiourea catalysts (Figure 1.14).

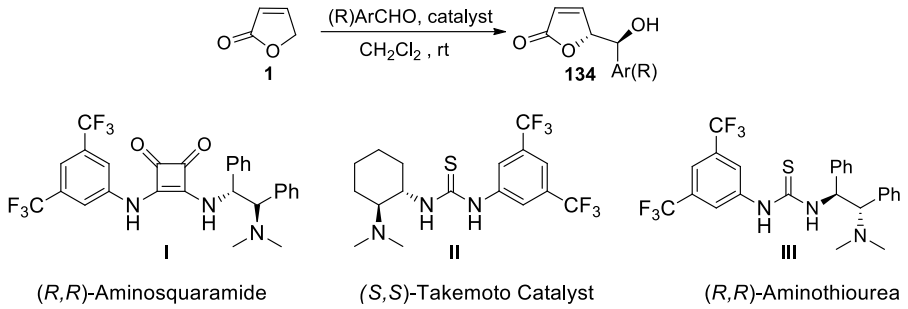
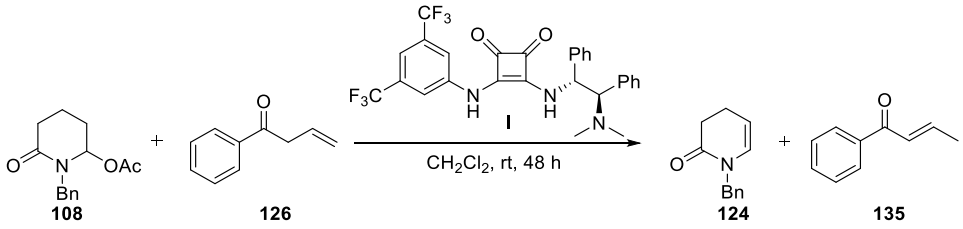


Figure 1.14 Vinylogous Aldol reaction of various aliphatic and aromatic aldehydes

In order to examine the possibility of the lack of deprotonation of the nucleophile, the vinylogous Mannich reaction of **108** and the ketone **126** was examined in the presence of the aminosquaramide catalyst **I**. Interestingly, although the desired Mannich product was not obtained, the enecarbamate **124** and the isomerized ketone **135** were obtained in trace amounts from the reaction mixture (Scheme 1.17).



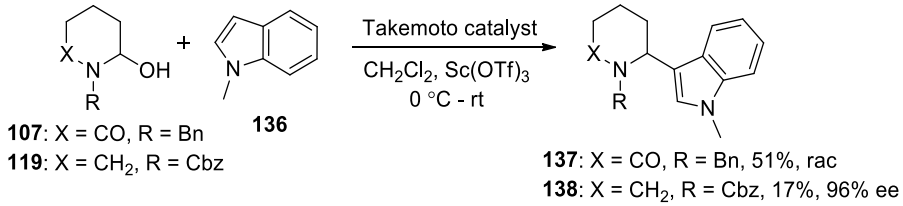
Scheme 1.17

These observations confirmed the formation of an iminium ion from **108** and of an enolate from **126**. The reasons for the lack of reaction between these two species are not known at this time.

1.6 Studies on the Mannich reactions of indoles:

Since the above studies had provided some evidence of the formation of reactive iminium ions from cyclic precursors, the possibility of their reactions with indoles was examined. The main reason for these investigations was the well-known nucleophilicity of electron rich or electron-neutral indoles. In addition, these reactions would provide direct access to functionalized indole frameworks with established biological activity,[43] and could also provide potential precursors to more complex alkaloid natural products.[44]

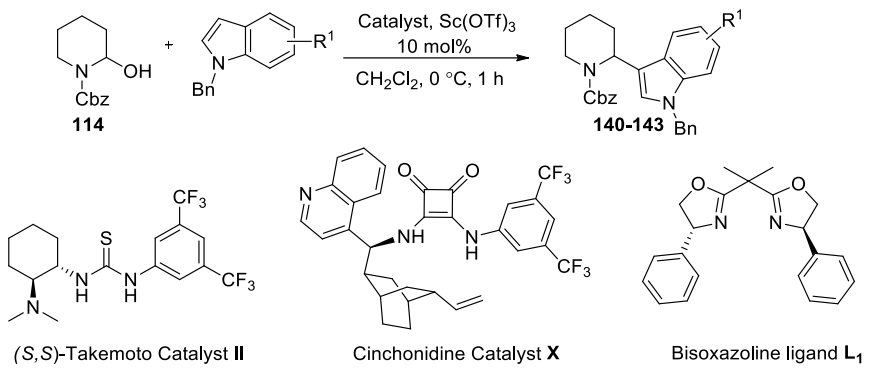
In preliminary studies, *N*-methyl indole **136** was examined as the nucleophile with the best iminium ion precursors in the presence of a bifunctional catalyst and a Lewis acid (Scheme 1.18).



Scheme 1.18

As anticipated, the reaction of the iminium ion precursor **107** with *N*-methyl indole **136** in the presence of the Takemoto catalyst **II** and $Sc(OTf)_3$ furnished the required product **137** in 51% yield, but with no enantiomeric excess (racemic product). In comparison, the reaction of **119** with *N*-methyl indole **136** provided **138** with high enantiomeric excess (96% ee) but in low yield (17%, Scheme 1.18). Spurred by the success with *N*-methyl indole, we examined *N*-benzyl indole **139** as a nucleophile with the iminium ion precursor **119**. Satisfyingly, the required product **140** was obtained in good yield (77%) and with excellent enantioselectivity (96% ee, entry 1, Table 1.10).

Table 1.10 Mannich reactions of *N*-benzyl indoles



Entry	R^1	Catalyst	Product	Yield (%)	ee (%)[a]
1	H	**II**	**140**	77	96
2	5-Br	**II**	**141**	70	15
3	5-MeO	**II**	**142**	57	0.5
4	6-F	**II**	**143**	52	1.0
5	6-F	**X**	**143**	40	0.6
6	6-F	**L_1**	**143**	48	1.4

[a] Determined by chiral HPLC

This promising result encouraged us to try the reaction with a selection of electron rich and electron deficient indoles. Unfortunately, although the required Mannich products were obtained in reasonable yields (entries 2-6, Table 1.10), they were all racemic. An explanation for these unusual results is not available at this time.

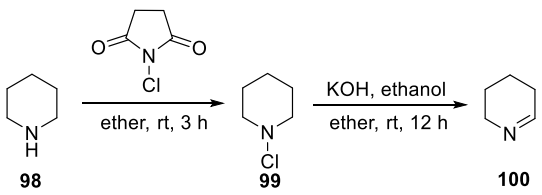
1.7 Conclusion:

In conclusion, we have synthesized a selection of novel phosphoramide-aminothiourea catalysts and examined them in selected vinylogous Mannich reactions. Piperidine based iminium ion precursors along with crotonolactone and phenyl allyl ketone as the nucleophilic component were examined in the presence of the phosphoramide-thiourea catalysts as well as other

bifunctional catalysts such as aminothioureas and aminosquaramides. The vast majority of the reactions that were examined either did not provide the required product or provided unwanted by-products arising from side reactions of the iminium ions generated *in situ*. Although evidence was obtained for enolate formation from allyl phenyl ketone, this enolate did not react with the iminium ion that was also generated in the same reaction. The precise reasons for the failure of the vinylogous Mannich reaction are not known at this time. Finally, the Mannich reaction of indoles and *in situ* generated iminium ions was also achieved. Although some of these reactions proceeded with high enantioselectivity, small changes in the substitution of the indole nucleus at sites remote to the reaction site had a drastic effect on the enantioselection and racemic products were obtained. The use of phosphoramide-thiourea catalysts in the addition of indole nucleophiles to *N*-Cbz-2-hydroxy piperidine **114** will be further investigated in the Pansare group.

1.8 Experimental Section

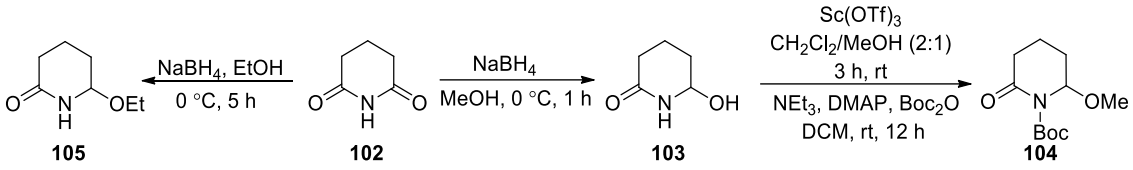
2,3,4,5-Tetrahydropyridine (**100**):[31]



To a solution of N-chlorosuccinimide (3.78 g, 27.9 mmol) in diethyl ether (75 mL) was added a solution of distilled piperidine (2.48 mL, 25.2 mmol) in ether (50 mL) over 30 min at room temperature. The reaction mixture was stirred for 3 h at ambient temperature after which it was filtered through a pad of celite and the residue was washed with ether (1 x 25 mL). The combined filtrates were washed with water (3 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated without heating to give *N*-chloropiperidine **99**.

An ethereal solution of the above *N*-chloropiperidine was added dropwise to ethanolic KOH (prepared by heating 2.1 equiv of solid KOH in ethanol (15.0 mL) to 85 °C) at room temperature and the reaction was left to stir overnight. The white precipitate of KCl formed was then separated by filtration through a pad of Celite. The filtrate was concentrated to remove ethanol and the residue was diluted with ethyl acetate. The resulting solution was washed with water (3 x 20 mL) to provide the piperidine **100** (1.45 g, 70% yield over two steps).

Synthesis of glutarimide derivatives:



***tert*-Butyl 2-methoxy-6-oxopiperidine-1-carboxylate (104):**

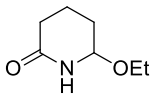
A glutarimide **102** (226 mg, 1.99 mmol) was dissolved in MeOH (5 mL) at 0 °C and sodium borohydride (189 mg, 4.97 mmol) as added portionwise. After the end of the addition, the reaction mixture was stirred at 0 °C for 2 h. The excess of sodium borohydride was destroyed in 15-20 mins at the temperature of the reaction by adding an aqueous solution of sodium bicarbonate. Reaction mixture evaporated to dryness and purified by flash column chromatography on silica gel using 5% MeOH/CH_2Cl_2 afforded 6-hydroxypiperidin-2-one **103** (83 mg, 36%). *Rf* = 0.28 (MeOH/CH_2Cl_2 95:5)

To the solution of 6-hydroxypiperidin-2-one (55 mg, 0.470 mmol) in CH_2Cl_2 (2 mL) and MeOH (1 mL), scandium triflate (2.3 mg, 0.004 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated to dryness and was used as such in the next step without any purification.

To a solution 6-methoxypiperidin-2-one (365 mg, 2.82 mmol) in CH_2Cl_2 (8 mL) were added DMAP (344 mg, 2.82 mmol), NEt_3 (0.40 mL, 2.82 mmol), Boc_2O (1.23 g, 5.65 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvent was then evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel using 20% EtOAc/hexanes afforded *tert*-butyl 2-methoxy-6-oxopiperidine-1-carboxylate **104** (452 mg, 70%). *Rf* = 0.28 (EtOAc/hexanes, 1:4).

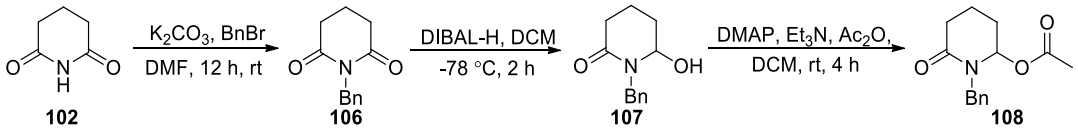
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47-5.42 (m, 1H, NC*H*), 3.37 (s, 3H, OCH_3), 2.70-2.58 (m, 1H, CH_2), 2.50-2.37 (m, 1H, CH_2), 2.16-2.00 (m, 2H, CH_2), 1.89-1.67 (m, 2H, CH_2), 1.54 (s, 9H, C(CH_3)$_3$).

6-Ethoxypiperidin-2-one (105):[33]



A glutarimide (500 mg, 1.76 mmol) was dissolved in EtOH (9 mL) at 0 °C and sodium borohydride (244 mg, 6.45 mmol) as added portion wise. After the end of the addition, the reaction mixture was stirred at 0 °C for 2 h. The excess of sodium borohydride was destroyed in 15-20 mins at the temperature of the reaction by adding 2N HCl solution till pH = 3. Reaction mixture was then neutralized with 1% KOH in ethanol. The reaction mixture was evaporated to dryness. Extraction of residue with $CHCl_3$ and evaporation of extract afforded 6-methoxypiperidin-2-one **105** (358 mg, 57%).

1-Benzyl-6-oxopiperidin-2-yl acetate (108):[35]



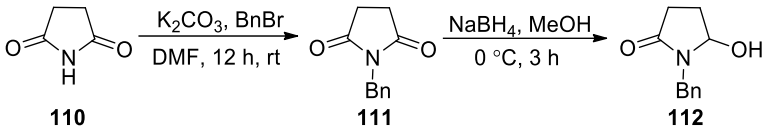
To a solution of glutarimide (0.50 g, 4.42 mmol) in DMF (8 mL) was added potassium carbonate (1.80 g, 13.26 mmol) at room temperature. After stirring it for 30 mins at room temperature, benzyl bromide (1.00 mL, 8.84 mmol) was added dropwise and the reaction mixture was stirred for 12 h at ambient temperature. Ice cold water (15 mL) and EtOAc (20 mL) were then added. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic layers were washed with cold water (2 x 15 mL), then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 30% EtOAc/hexanes affording 1-benzylpiperidine-2,6-dione **106** (888 mg, 98%) as a white solid.

DIBAL-H (2.84 mmol, 1M solution in toluene) was added dropwise at -78 °C to a stirred solution of 1-benzylpiperidine-2,6-dione **106** (290 mg, 1.42 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at -78 °C for 1h. Water (1.4 mL), NaOH (2 N, 0.4 mL) were cautiously added and the reaction mixture was poured into a saturated solution of Rochelle's salt (10 mL). The mixture was then extracted with CH_2Cl_2 (10mL). The combined extracts were then washed with brine (5 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure to yield a crude residue, which was purified by flash chromatography on silica gel (EtOAc/hexanes mixtures) affording 1-benzyl-6-hydroxypiperidin-2-one **107** (181 mg, 62%).

To a solution of 1-benzyl-6-hydroxypiperidin-2-one **107** (500 mg, 2.43 mmol) in CH_2Cl_2, DMAP (30 mg, 0.24 mmol), NEt_3 (0.40 mL, 3.14 mmol) were added, followed by dropwise addition of acetic anhydride (0.50 mL, 4.86 mmol). The reaction mixture was stirred for 1 h at room temperature. Water was added to the reaction mixture (5 mL) and the resulting solution was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were concentrated, and the

residue was purified by flash column chromatography on silica gel using (70% EtOAc/hexanes) affording 1-benzyl-6-oxopiperidin-2-yl acetate **108** (549 mg, 92%).

1-Benzyl-5-hydroxypyrrolidin-2-one (112):[36]

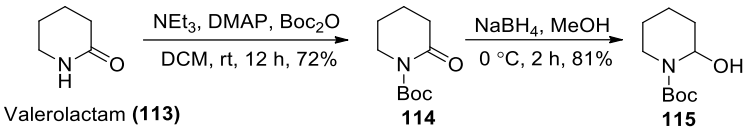


110 **111** **112**

To a solution of succinimide (0.50 g, 5.04 mmol) in DMF (8 mL) was added potassium carbonate (2.86 g, 15.1 mmol) at room temperature. After stirring it for 30 mins at room temperature, benzyl bromide (1.20 mL, 10.1 mmol) was added dropwise and the reaction mixture was stirred for 12 h at ambient temperature. Ice cold water (15 mL) and EtOAc (20 mL) were then added. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic layers were washed with cold water (2 x 15 mL), then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 50% EtOAc/hexanes affording 1-benzylpiperidine-2,6-dione **111** (931 mg, 99%) as a white solid.

Succinimide (200 mg, 1.05 mmol) was dissolved in MeOH (5 mL) at 0 ℃ and sodium borohydride (198 mg, 5.25 mmol) as added portion wise. After the end of the addition, the reaction mixture was stirred at 0 °C for 3 h. afforded 6-methoxypiperidin-2-one **102** (132 mg, 66%). Upon complete conversion of the imide, methanol was removed under reduced pressure and the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (5 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate concentrated under reduced pressure to yield 1-benzyl-5-hydroxypyrrolidin-2-one **112** (154 mg, 77%).

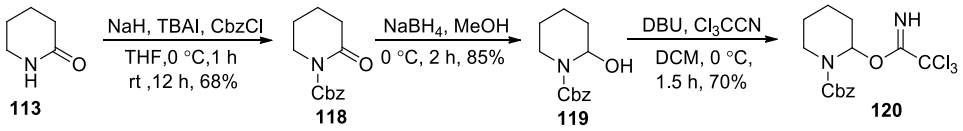
***tert*-Butyl 2-hydroxypiperidine-1-carboxylate (115):**[37]



To a solution of *δ*-valerolactam **113** (1.00 g, 10.0 mmol) in CH_2Cl_2 (20 mL) were added DMAP (1.23 g, 10.0 mmol), NEt_3 (1.40 mL, 10.0 mmol), Boc_2O (4.40 g, 20.1 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvent was then evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel using 40% EtOAc/hexanes affording tert-butyl 2-oxopyrrolidine-1-carboxylate **114** (1.45 g, 72%) as a white amorphous powder. *Rf* = 0.34 (EtOAc/hexanes, 2:3).

Protected lactam **114** (1.00 g, 5.01 mmol) was dissolved in methanol (20 mL) at 0 °C and sodium borohydride (379 mg, 10.03 mmol) was added portion wise. After the end of the addition, the reaction mixture was stirred at 0 °C for 2 h and poured onto ice-water (15 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL). The organic layers were washed with brine (10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give *tert*-butyl 2-hydroxypiperidine-1-carboxylate **115** (818 mg, 81%) which was used without purification.

Benzyl 2-(2,2,2-trichloro-1-iminoethoxy)piperidine-1-carboxylate (120):



δ-Valerolactam **113** (500 mg, 5.04 mmol) was dissolved in THF (10 mL). The reaction mixture was cooled to -78 °C and n-BuLi (2.5 M in hexane, 2 mL, 5.04 mmol) was added dropwise to the resulting suspension. After 30 min at -78 °C, a solution of benzylchloroformate (0.7 mL, 5.04 mmol) in THF (5 mL) was added dropwise. After 4 h at -78 °C, the reaction mixture was

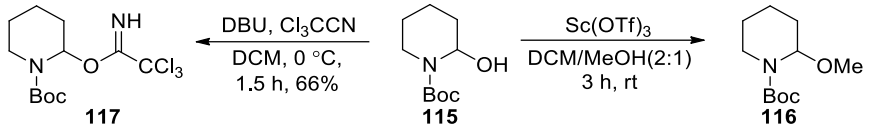
quenched with sat. NH_4Cl (10 mL) and warmed to room temperature. The reaction mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the Cbz protected lactam **118** (794 mg, 68%). *Rf* = 0.34 (EtOAc/hexanes, 3:2)

Protected lactam **118** (750 mg, 3.21 mmol) was dissolved in methanol (7 mL) at 0 °C and sodium borohydride (243 mg, 6.43 mmol) was added portionwise. After the end of the addition, the reaction mixture was stirred at 0 °C for 2 h and poured onto ice-water (15 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL). The organic layers were washed with brine (10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give benzyl 2-hydroxypiperidine-1-carboxylate **119** (639 mg, 85%) which was used without purification.

To the solution of benzyl 2-hydroxypiperidine-1-carboxylate **119** (400 mg, 1.70 mmol) and DBU (0.50 mL, 3.40 mmol) in CH_2Cl_2 (3 mL) at 0 °C, trichloroacetonitrile (0.3 mL, 3.40 mmol) was added dropwise. The reaction mixture was allowed to stir for 1.5 h. The reaction mixture was concentrated to dryness on rota vapour and purified by flash column chromatography on silica gel to give benzyl 2-(2,2,2-trichloro-1-iminoethoxy)piperidine-1-carboxylate **120** (450 mg, 70%) as colourless liquid. *Rf* = 0.31 (EtOAc/hexanes, 1:4).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.27 (m, 5H, Ar*H*), 7.11 (br s, 1H, N*H*), 6.15-6.05 (m, 1H, NC*H*), 5.18 (s, 2H, CH_2Ph), 4.08 (d, 1H, *J* = 13.5 Hz, NCH_2), 3.06-2.90 (m, 1H, NCH_2), 2.02-1.90 (m, 1H, CH_2), 1.86-1.65 (m, 3H, CH_2), 1.64-1.46 (m, 2H, CH_2).

Synthesis of valerolactam derivatives:



***tert*-Butyl 2-methoxypiperidine-1-carboxylate (116):**

To a solution of *tert*-butyl 2-hydroxypiperidine-1-carboxylate **115** (250 mg, 1.25 mmol) in CH_2Cl_2/MeOH (2:1) (4ml), was added scandium triflate (6.00 g, 0.01 mmol). The reaction mixture was stirred at room temperature for 3 h. Reaction mixture was concentrated to dryness and the residue was quenched with saturated solution of sodium bicarbonate (5 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were concentrated, and residue was purified by flash column chromatography on silica gel to give *tert*-butyl 2-methoxypiperidine-1-carboxylate **116** (160 mg, 74%). *Rf* = 0.2 (EtOAc/hexanes, 3:7).

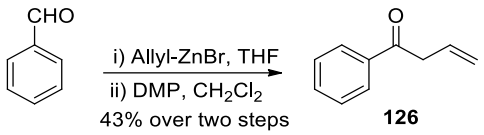
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48-5.17 (m, 1H NC*H*), 4.03-3.73 (m, 1H, NCH_2), 3.23 (s, 3H, OCH_3), 3.02-2.80 (m, 1H, NCH_2), 1.91-1.79 (m, 1H, NCHCH_2), 1.78-1.65 (m, 1H, NCHCH_2), 1.63-1.51 (m, 2H CH_2), 1.47 (br s, 11H, CH_2 and C(CH_3)$_3$).

***tert*-Butyl 2-(2,2,2-trichloro-1-iminoethoxy)piperidine-1-carboxylate (117):**

To the solution of *tert*-butyl 2-hydroxypiperidine-1-carboxylate **115** (450 mg, 2.25 mmol) and DBU (0.70 ml, 4.51 mmol) in CH_2Cl_2 (5 mL) at 0 °C, trichloroacetonitrile (0.45 mL, 4.51 mmol) was added dropwise. The reaction mixture was allowed to stir for 1.5 h. The reaction mixture was concentrated to dryness on rota vapour and purified by flash column chromatography on silica gel to give *tert*-butyl 2-(2,2,2-trichloro-1-iminoethoxy)piperidine-1-carboxylate **117** (517 mg, 66%) as a white solid. *Rf* = 0.32 (EtOAc/hexanes, 1:4).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (br s, 1H, N*H*), 6.06-5.97 (m, 1H, NC*H*), 4.02 (d, 1H, *J* = 13.5 Hz, NCH_2), 2.87 (ddd, 1H, *J* = 13.5, 12.1, 3.0 Hz, NCH_2), 1.99-1.87 (m, 1H, CH_2), 1.85-1.67 (m, 3H, CH_2), 1.63-1.50 (m, 2H, CH_2), 1.48 (s, 9H, C(CH_3)$_3$).

1-Phenylbut-3-en-1-one (126):[41]



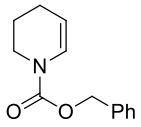
Allyl bromide (0.81 ml, 9.42 mmol) in THF (2 ml) was added dropwise to a stirred suspension of commercial zinc dust (615 mg, 9.42 mmol) in THF (5 mL) at room temperature and the mixture was stirred for half an hour after which the benzaldehyde (1.00 g, 9.42 mmol) in THF (5ml) and NH_4OAc (2.17 g, 28.2 mmol) were added. The reaction mixture was quenched by saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined extract was dried over $MgSO_4$ and evaporated to give crude product which was purified by flash column chromatography on silica gel, afforded 1-phenylbut-3-en-1-ol (831 mg, 60%) as a clear colourless liquid. *Rf* = 0.3 (EtOAc/hexanes, 1:9).

To a solution of DMP (3.66 g, 8.63 mmol) in CH_2Cl_2 (4 mL) at room temperature was added a solution of allyl alcohol (800 mg, 5.39 mmol) in CH_2Cl_2 (4 mL). After 4 hours of stirring, the mixture was diluted with ether (20 mL) and washed with 1/1 10% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution, followed by brine solution (5 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, afforded 1-phenylbut-3-en-1-one **126** (570 mg, 72%) as a colourless oil. *Rf* = 0.2 (EtOAc/hexanes, 5:95).

General procedure for the direct vinylogous Mannich reaction:

To the catalyst (0.1 mmol, in a standard 3 mL vial) was added the imine or iminium ion precursor (1 mmol) followed by respective nucleophile (2 mmol) in dichloromethane (1mL). The reaction mixture was stirred at ambient temperature for the specified period and was monitored by TLC. After completion, the reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes) to provide the corresponding products.

Benzyl 3,4-dihydropyridine-1(2*H*)-carboxylate (129):

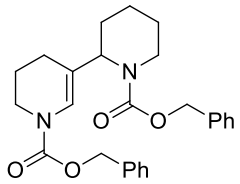


The reaction of 2-hydroxypiperidine-1-carboxylate **114** (100 mg, 0.42 mmol), γ-crotonolactone (2-(5*H*)-furanone, 60 µL, 0.85 mmol), Takemoto catalyst **II** (18 mg, 0.04 mmol) and $Sc(OTf)_3$ (21 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) at ambient temperature for 30 mins, according to the general procedure provided, after purification by flash column chromatography on silica gel (EtOAc/hexanes 2:8), 46 mg (35%) of **129** as a colorless solid. R*f* = 0.23 (EtOAc/hexanes 2:8).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.28 (m, 5H, Ar*H*), 6.79 (d, 1H, *J* = 8.4 Hz, NC*H*), 5.18 (s, 2H, *CH*$_2$Ph), 4.90-4.81 (m, 1H, CH_2C*H*), 3.69-3.55 (m, 2H, N*CH*$_2$), 2.09-1.98 (m, 2H, *CH*$_2$), 1.90-1.73 (m, 2H, CH_2).

^{1}H NMR (300 MHz, $CDCl_3$): minor rotamers δ 7.43-7.28 (m, 5H, Ar*H*), 6.88 (d, 1H, *J* = 8.4 Hz, NC*H*), 5.18 (s, 2H, *CH*$_2$Ph), 5.02-4.92 (m, 1H, CH_2C*H*), 3.69-3.55 (m, 2H, N*CH*$_2$), 2.09-1.98 (m, 2H, *CH*$_2$), 1.90-1.73 (m, 2H, CH_2).

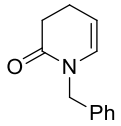
Benzyl 5-(1-((benzyloxy)carbonyl)piperidin-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate (130):



^{1}H NMR (300 MHz, $CDCl_3$): Major rotamer δ 7.43-7.26 (m, 10H, Ar*H*), 6.85 (s, 1H, NC*H*=C), 5.18 (br s, 4H, CH_2Ph), 4.82 (br s, 1H, NC*H*CH_2), 4.04 (d, 1H, *J* = 13.0 Hz, NCH_2), 3.66-3.48 (m, 2H, NCH_2), 2.78 (t, 1H, *J* = 13.0 Hz, NCH_2), 2.10-1.73 (m, 5H, C*H*2), 1.71-1.34 (m, 5H, CH_2).

^{1}H NMR (300 MHz, $CDCl_3$): Minor rotamer δ 7.43-7.26 (m, 10H, Ar*H*), 6.71 (s, 1H, NC*H*=C), 5.17-5.05 (m, 4H, CH_2Ph), 4.82 (br s, 1H, NC*H*CH_2), 4.04 (d, 1H, *J* = 13.0 Hz, NCH_2), 3.66-3.48 (m, 2H, NCH_2), 2.78 (t, 1H, *J* = 13.0 Hz, NCH_2), 2.10-1.73 (m, 5H, C*H*2), 1.71-1.34 (m, 5H, CH_2).

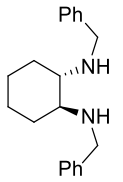
1-Benzyl-3,4-dihydropyridin-2(1*H*)-one (124):



The reaction of 1-benzyl-6-hydroxypiperidin-2-one **107** (50 mg, 0.20 mmol), γ-crotonolactone (2-(5H)-furanone, 29 μL, 0.40 mmol) and Takemoto catalyst **II** (10 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) at ambient temperature for 30 mins, according to the general procedure provided, after purification by flash column chromatography on silica gel (EtOAc/hexanes 2:3), 46 mg (35%) of **124** as a colorless solid. R*f* = 0.23 (EtOAc/hexanes 2:3).

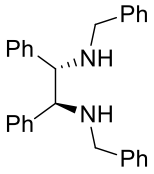
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.27 (m, 3H, Ar*H*), 7.25-7.20 (m, 2H, Ar*H*), 6.02 (dt, 1H, *J* = 7.7, 1.6 Hz, NC*H*), (dt, 1H, *J* = 7.7, 4.4 Hz, NCHC*H*), 4.69 (s, 2H, CH_2Ph), 2.59 (t, 2H, *J* = 8.0 Hz, CH_2), 2.28-2.40 (m, 2H, CH_2).

(1*S*,2S)-*N*,*N*-Dibenzylcyclohexane-1,2-diamine (79):



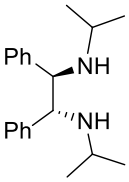
Prepared from (1*S*,2*S*)-1,2-cyclohexanediamine and benzaldehyde according to the literature procedure.[24] Spectroscopic data for **79** was in agreement with the reported data.[24]

(1*S*,2*S*)-*N*,*N*'-Dibenzyl-1,2-diphenylethane-1,2-diamine (87):



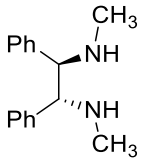
Prepared from (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine and benzaldehyde according to the literature procedure.[27a] Spectroscopic data for **87** was in agreement with the reported data.[27a]

(1*R*,2*R*)-*N*,*N*'-Diisopropyl-1,2-diphenylethane-1,2-diamine (91):



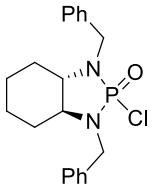
To the mixture of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (500 mg, 2.35 mmol) in acetone (5mL) were added PtO2 (53 mg 0.2 mmol) and acetic acid (26 µL, 0.4 mmol). The hydrogenation reaction proceeded at room temperature under a pressure of H_2 balloon for 48 h. After completion, the crude product was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to yield (695 mg, 99%) of **91** as a white solid. Spectroscopic data for **91** was in agreement with the reported data.[28a]

(1*R*,2*R*)-*N*,*N*'-Dimethyl-1,2-diphenylethane-1,2-diamine (93):



Prepared from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine and acetic formic anhydride according to the literature procedure.[28b] Spectroscopic data for **93** was in agreement with the reported data.[28b]

(3aS,7aS)-1,3-Dibenzyl-2-chlorooctahydro-1H-benzo[d][1,3,2]diazaphosphole 2-oxide (80):



To a solution of the diamine **79** (2.30 g, 7.81 mmol) in CH_2Cl_2 was added $POCl_3$ (1.04 ml, 10.9 mmol). Triethylamine (2.7 ml, 18.7 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 24 h. After completion, reaction mixture was passed through a thick pad of silica gel and washed with CH_2Cl_2 until all the product was obtained. Evaporation of the solvent under vacuum to give white thick solid which was then dissolved in CH_2Cl_2 and water. The solution was poured in 250 mL separatory funnel and organic layer was extracted and concentrated to give 2.30 g (79%) of **80** as pure white solid.

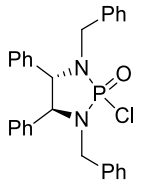
Mp: 206.4 - 207.1 ^oC; IR (neat): 3029, 2937, 2907, 2851, 1494, 1452, 1439, 1362, 1342, 1316, 1297, 1277, 1230, 1209, 1179, 1148, 1110, 1067, 1051, 1025, 966, 926, 901, 881, 861, 841, 773, 741, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50-7.20 (m, 10H, Ar*H*), 4.59 - 4.37 (m, 2H, CH_2Ph), 4.21 (dd, J = 15.7, 10.7 Hz, CH_2Ph), 3.74 (dd, J = 15.7, 7.7 Hz, CH_2Ph), 3.03 - 2.84 (m, 2H, CH_2C*H*N), 1.81-1.54 (m, 4H, CH_2), 1.27-0.90 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1 (d, $^3J_{CP}$ = 9.7 Hz, ArC_{ipso}), 137.5 (d, $^3J_{CP}$ = 3.6 Hz, ArC_{ipso}), 128.5 (2 x Ar*C*), 128.4 (2 x

Ar*C*), 127.9 (2 x Ar*C*), 127.8 (2 x Ar*C*), 127.42 (Ar*C*), 127.40 (Ar*C*), 63.4 (d, $^{2}J_{CP}$ = 10.4 Hz, CH_2CHN), 63.2 (d, $^{2}J_{CP}$ = 10.5 Hz, CH_2CHN), 47.5 (d, $^{2}J_{CP}$ = 2.7 Hz, CH_2Ph), 46.6 (d, $^{2}J_{CP}$ = 4.5 Hz, CH_2Ph), 29.2 (d, $^{3}J_{CP}$ = 10.0 Hz, CH_2), 29.0 (d, $^{3}J_{CP}$ = 5.1 Hz, CH_2), 24.2 (d, $^{4}J_{CP}$ = 1.1 Hz, CH_2), 23.8 (d, $^{4}J_{CP}$ = 1.8 Hz, CH_2); HRMS (ESI, pos.): *m*/*z* 374.1303 (374.1315 calc. for $C_{20}H_{24}ClN_2OP$ $(M)^+$), 375.1378 (375.1393 calc. for $C_{20}H_{25}ClN_2OP$ $(M+H)^+$), 397.1191 (397.1212 calc. for $C_{20}H_{24}ClN_2NaOP$ $(M+Na)^+$).

General procedure for the synthesis of diaminophosphoryl chlorides 88, 94, and 95:

To a solution of the diamine in toluene was added triethyl amine. The solution was cooled to 0 °C and $POCl_3$ was added dropwise. The mixture was then warmed to room temperature, heated to reflux for 4 h and then cooled to room temperature. The white precipitate that was formed was removed by filtration, and the filter cake was washed toluene (10 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 9:1) to provide the phosphoryl chlorides.

(4*S*,5*S*)-1,3-Dibenzyl-2-chloro-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (88):

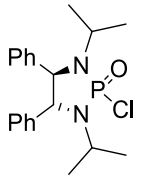


The reaction of **87** (1.71 g, 4.35 mmol), NEt_3 (1.30 mL, 8.71 mmol) and $POCl_3$ (0.42 mL, 4.35 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 1.62 mg (79%) of **88** as a white solid; R_f = 0.20 (hexanes/EtOAc, 9:1).

IR (neat): 3061, 3031, 2924, 2906, 2866, 1494, 1452, 1273, 1255, 1212, 1108, 1028, 765, 734, 698, 517, 493 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.12 (m, 16H, Ar*H*), 7.06-6.96 (m, 4H,

Ar*H*), 4.58 (dd, 1H, *J* = 14.8, 10.5, PhC*H*), 4.16 (t, 1H, *J* = 14.7, PhCH_2), 4.10-3.94 (m, 3H, PhCH_2) 3.65 (dd, 1H, *J* = 14.8, 10.9, PhC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7 (d, $^3J_{CP}$ = 3.5, ArC_{ipso}), 137.3 (d, $^3J_{CP}$ = 8.9, ArC_{ipso}), 135.37 (d, $^3J_{CP}$ = 3.6, ArC_{ipso}), 135.32 (d, $^3J_{CP}$ = 2.9, ArC_{ipso}), 129.4 (2 x Ar*C*), 129.1 (2 x Ar*C*), 128.9 (2 x Ar*C*), 128.8 (2 x Ar*C*), 128.69 (Ar*C*), 128.64 (Ar*C*), 128.60 (2 x Ar*C*), 128.3 (2 x Ar*C*), 128.1 (2 x Ar*C*), 127.94 (2 x Ar*C*), 127.89 (Ar*C*), 127.7 (Ar*C*), 68.2 (d, $^2J_{CP}$ = 13.6, Ph*C*H_2), 66.7 (d, $^2J_{CP}$ = 12.8, Ph*C*H_2), 47.6 (d, *J* = 4.6, Ph*C*H), 45.7 (d, *J* = 6.0, Ph*C*H); HRMS (ESI, pos.): *m/z* 472.1471 (472.1471 calc. for $C_{28}H_{26}ClN_2OP$, M^+) and 473.1543 (473.1550 calc. for $C_{28}H_{27}ClN_2OP$, $(M+H)^+$).

(4*R*,5*R*)-2-Chloro-1,3-diisopropyl-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (94):

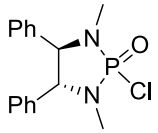


The reaction of **91** (495 mg, 1.66 mmol), NEt_3 (0.50 ml, 3.34 mmol) and $POCl_3$ (0.15 mL, 1.67 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 357 mg (60%) of **94** as a colorless gum; R_f = 0.21 (hexanes/EtOAc, 9:1).

IR (neat): 3033, 2980, 2929, 2883, 1492, 1456, 1391, 1369, 1263, 1160, 1131, 1086, 1021, 789, 730, 699, 626, 565, 518 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 - 7.30 (m, 6H, Ar*H*), 7-25-7.22 (m, 2H, Ar*H*), 7.21-7.17 (m, 2H, Ar*H*), 4.29 (t, 1H, *J* = 6.7 Hz, PhC*H*), 4.18 (dd, *J* = 6.7, 3.0 Hz, PhC*H*), 3.48 - 3.26 (m, 2H, C*H*$(CH_3)_2$), 1.44 (d, 3H, *J* = 6.9 Hz, CH_3), 1.38 (d, 3H, *J* = 6.9 Hz, CH_3), 1.13 (d, 3H, *J* = 6.6 Hz, CH_3), 1.02 (d, 3H, *J* = 6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.2 (d, $^3J_{CP}$ = 4.4 Hz, ArC_{ipso}), 139.3 (d, $^3J_{CP}$ = 2.7 Hz, ArC_{ipso}), 128.9 (2 x Ar*C*), 128.8 (2 x Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 127.6 (2 x Ar*C*), 127.3 (2 x Ar*C*), 67.6 (d, $^2J_{CP}$ = 13.5 Hz, Ph*C*H),

65.9 (d, $^{2}J_{CP}$ = 14.6 Hz, PhCH), 47.5 (d, $^{2}J_{CP}$ = 4.8 Hz, CH$(CH_3)_2$), 46.7 (d, $^{2}J_{CP}$ = 4.2 Hz, CH$(CH_3)_2$), 21.2 (d, $^{3}J_{CP}$ = 1.2 Hz, CH_3), 20.6 (d, $^{3}J_{CP}$ = 2.3 Hz, CH_3), 20.2 (d, $^{3}J_{CP}$ = 3.3 Hz, CH_3), 20.1 (d, $^{3}J_{CP}$ = 2.3 Hz, CH_3); HRMS (ESI, pos.): *m/z* 376.1477 (376.1471 calc. for $C_{20}H_{26}ClN_2OP$ $(M)^+$), 377.1550 (377.1550 calc. for $C_{20}H_{27}ClN_2OP$ $(M+H)^+$).

(4*R*,5*R*)-2-Chloro-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (95):



The reaction of **92** (1.00 g, 4.16 mmol), NEt_3 (1.20 mL, 8.32 mmol) and $POCl_3$ (0.400 mL, 4.16 mmol) according to the general procedure, provided after purification by flash column chromatography 1.11 g (82%) of **95** as a colorless oil; R_f = 0.23 (hexanes/EtOAc, 9:1).

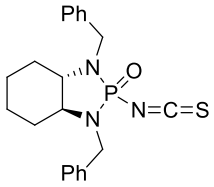
IR (neat): 3004, 2936, 2866, 2826, 1452, 1273, 1209, 1152, 1109, 741, 697, 513, 491 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 6H, Ar*H*), 7.17-7.11 (m, 2H, Ar*H*), 7.10-7.04 (m, 2H, Ar*H*), 4.15 (dd, 1H, *J* = 8.6, 4.3, PhC*H*), 3.85 (d, 1H, *J* = 8.6, PhC*H*), 2.60 (d, 3H, *J* = 10.5, CH_3), 2.46 (d, 3H, *J* = 14.4, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.8 (d, $^{3}J_{CP}$ = 5.5, ArC_{ipso}), 135.8 (d, $^{3}J_{CP}$ = 12.8, ArC_{ipso}), 128.75 (2 x Ar*C*), 128.73 (Ar*C*), 128.69 (2 x Ar*C*), 128.5 (Ar*C*), 127.8 (2 x Ar*C*), 127.6 (2 x Ar*C*), 70.8 (d, $^{2}J_{CP}$ = 12.1, PhCH), 70.2 (d, $^{2}J_{CP}$ = 12.0, PhCH), 29.9 (d, $^{2}J_{CP}$ = 2.6, CH_3), 29.0 (d, $^{2}J_{CP}$ = 5.3, CH_3); HRMS (APPI, pos.): *m/z* 320.0854 (320.0845 calc. for $C_{16}H_{18}ClN_2OP$, $(M)^+$) and 321.0928 (321.0924 calc. for $C_{16}H_{19}ClN_2OP$, $(M+H)^+$).

General procedure for the synthesis of isothiocyante intermediates 81, 89, 96 and 97:

To a solution of diaminophosphoryl chloride in dry CH_3CN was added tetrabutylammonium thiocyanate or potassium thiocyanate. The solution was heated to reflux for indicated time and then cooled to room temperature and concentrated under reduced pressure. The

residue was purified by flash column chromatography on silica gel to provide corresponding isothiocyanate.

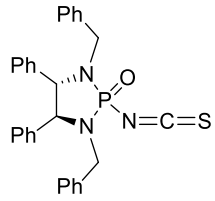
(3a*S*,7a*S*)-1,3-Dibenzyl-2-isothiocyanatooctahydro-1*H*-benzo[*d*][1,3,2]diazaphosphole 2-oxide (81):



To a solution of diaminophosphoryl chloride **80** (300 mg, 0.80 mmol) in dry CH_3CN was added potassium thiocyanate (156 mg, 1.60 mmol), the solution was heated to reflux for 30 h and then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to provide 282 mg (89%) of isothiocyanate **81** as white solid; R_f = 0.22 (hexanes/EtOAc, 8:2).

Mp: 146.2-147.2 ^oC; IR (neat): 3060, 3029, 2935, 2848, 2038, 1984, 1601, 1494, 1451, 1437, 1324, 1296, 1230, 1208, 1177, 1147, 1111, 1067, 1050, 1027, 1001, 963, 924, 879, 862, 811, 736, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.22 (m, 10H, Ar*H*), 4.49-4.41 (m, 1H, PhCH_2), 4.40-4.33 (m, 1H, PhCH_2), 4.13 (dd, J = 15.7, 11.2 Hz, PhCH_2), 3.89 (dd, J = 15.7, 7.9 Hz, PhCH_2), 2.99-2.84 (m, 2H, CH_2CHN), 1.85-1.62 (m, 4H, CH_2), 1.22-0.95 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.3 (*C*=S), 137.8 (d, $^3J_{CP}$ = 7.2 ArC_{ipso}), 137.4 (d, $^3J_{CP}$ = 3.3 ArC_{ipso}), 128.6 (2 x Ar*C*), 128.5 (2 x Ar*C*), 128.0 (2 x Ar*C*), 127.8 (2 x Ar*C*), 127.5 (Ar*C*), 63.9 (d, $^2J_{CP}$ = 10.8 Hz, CH_2CHN), 63.2 (d, $^2J_{CP}$ = 11.2 Hz, CH_2CHN), 46.83 (d, $^2J_{CP}$ = 2.5 Hz, CH_2Ph), 46.79 (d, $^2J_{CP}$ = 3.6 Hz, CH_2Ph), 29.2 (d, $^3J_{CP}$ = 8.8 Hz, CH_2), 29.5 (d, $^3J_{CP}$ = 11.4 Hz, 1 CH_2), 24.1 (d, $^4J_{CP}$ = 1.4 Hz, CH_2), 23.9 (d, $^4J_{CP}$ = 1.8 Hz, CH_2); HRMS (APPI, pos.): *m*/*z* 397.1393 (397.1378 calc. for $C_{21}H_{24}N_3OPS$ $(M)^+$) and 398.1465 (398.1456 calc. for $C_{21}H_{24}N_3OPS$ $(M+H)^+$).

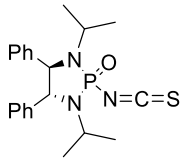
(4*S*,5*S*)-1,3-Dibenzyl-2-isothiocyanato-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (89):



To a solution of diaminophosphoryl chloride **33** (300 mg, 0.634 mmol) in dry CH_3CN was added tetrabutylammonium thiocyanate (571 mg, 1.90 mmol), the solution was heated to reflux for 24 h and then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 8:2) to provide 210 mg (67%) of isothiocyanate **34** as colorless oil; R_f = 0.2 (hexanes/EtOAc, 8:2).

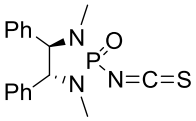
IR (neat): 3063, 3030, 2918, 2036, 1986, 1494, 1455, 1361, 1257, 1208, 1173, 1139, 1097, 1067, 759, 740, 480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.17 (m, 14H, Ar*H*), 7.16-7.08 (m, 2H, Ar*H*), 7.08-6.96 (m, 4H, Ar*H*), 4.47 (dd, 1H, *J* = 14.7, 10.8, PhC*H*$_2$), 4.30 (dd, 1H, *J* = 14.9, 11.4, PhC*H*$_2$), 4.08 (t, 1H, *J* = 5.7, PhC*H*), 3.95 (dd, 1H, *J* = 7.7, 5.7, PhC*H*), 3.84 (dd, 1H, *J* = 14.9, 12.2, PhC*H*), 3.68 (dd, 1H, *J* = 14.7, 11.0, PhC*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1 (d, $^2J_{CP}$ = 9.2, *C*=S), 137.9 (d, $^3J_{CP}$ = 3.9, Ar*C*$_{ipso}$), 137.3 (d, $^3J_{CP}$ = 6.6, Ar*C*$_{ipso}$), 135.1 (d, $^3J_{CP}$ = 2.4, Ar*C*$_{ipso}$), 134.9 (d, $^3J_{CP}$ = 2.8, Ar*C*$_{ipso}$), 128.91 (3 x Ar*C*), 128.89 (3 x Ar*C*), 128.76 (2 x Ar*C*), 128.50 (Ar*C*), 128.46 (3 x Ar*C*), 128.41 (2 x Ar*C*), 127.7 (2 x Ar*C*), 127.48 (2 x Ar*C*), 127.43 (2 x Ar*C*), 67.1 (d, $^2J_{CP}$ = 14.6, Ph*C*H), 66.5 (d, $^2J_{CP}$ = 14.0, Ph*C*H), 46.6 (d, $^2J_{CP}$ = 4.8, Ph*C*H$_2$), 45.9 (d, $^2J_{CP}$ = 5.7, Ph*C*H$_2$); HRMS (APPI, pos.): *m/z* 495.1557 (495.1534 calc. for $C_{29}H_{26}N_3OPS$ $(M)^+$) and 496.1629 (496.1612 calc. for $C_{29}H_{27}N_3OPS$ $(M+H)^+$).

(4*R*,5*R*)-1,3-Diisopropyl-2-isothiocyanato-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (96):



To a solution of diaminophosphoryl chloride **94** (280 mg, 0.74 mmol) in dry CH_3CN was added tetrabutylammonium thiocyanate (893 mg, 2.97 mmol), the solution was heated to reflux for 24 h and then cooled to room temperature and concentrated under reduced pressure. The residue was used in the next step without purification.

(4*R*,5*R*)-2-Isothiocyanato-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (97):

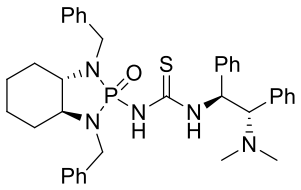


To a solution of diaminophosphoryl chloride **95** (800 mg, 2.49 mmol) in dry CH_3CN was added tetrabutylammonium thiocyanate (3.00 mg, 9.97 mmol), the solution was heated to reflux for 24 h and then cooled to room temperature and concentrated under reduced pressure. The residue was used in the next step without purification.

General procedure for the synthesis of catalysts V-VIII:

To the solution of corresponding isothiocyante in THF (3 ml), *N*,*N*-dimethyl diamine was added at ambient temperature. The mixture was stirred for 3 h, the solvent was removed, and the residue was purified by flash column chromatography on silica gel to provide requisite catalyst in good yield.

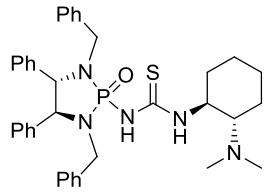
1-((3a*S*,7a*S*)-1,3-Dibenzyl-2-oxidohexahydro-1*H*-benzo[*d*][1,3,2]diazaphosphol-2(3*H*)-yl)-3-((1*S*,2*S*)-2-(dimethylamino)-1,2-diphenylethyl)thiourea (V):



The reaction of **81** (400 mg, 1.00 mmol) in THF (3 ml) was added *N*,*N*-dimethyl stilbene diamine (242 mg**,** 1.00 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 610 mg (96%) of **V** as a white solid; R_f = 0.24 (hexanes/EtOAc, 7:3).

M.P. - 108.6-109.2 ^{o}C; IR (neat): 3060, 3028, 2935, 2860, 2828, 2782, 1552, 1491, 1450, 1334, 1203, 1170, 1107, 1067, 1046, 966, 852, 805, 736, 696, 608, 546 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.41 (br s, 1H, PhCHN*H*), 7.50-7.44 (m, 2H, Ar*H*), 7.40-7.28 (m, 6H, Ar*H*), 7.26-6.85 (m, 13H, Ar*H* & P(O)N*H*), 5.88 (dd, 1H, *J* = 10.9, 7.8 Hz, PhC*H*), 4.69 (t, 1H, *J* = 14.7 Hz, PhCH_2), 4.24-4.01 (m, 2H, PhCH_2), 3.98-3.84 (m , 2H, 1 x PhCH_2 & PhC*H*N$(CH_3)_2$), 2.96-2.78 (m, 2H, CH_2C*H*N), 1.95 (s, 6H, (C$H_3)_2$), 1.75-1.51 (m, 4H, CH_2), 1.22-0.84 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.7 (d, $^{2}J_{CP}$ = 3.8 Hz, *C*=S), 139.8 (ArC_{ipso}) 139.3 (d, $^{3}J_{CP}$ = 6.8, ArC_{ipso}), 136.8 (d, $^{3}J_{CP}$ = 2.2, ArC_{ipso}), 132.9 (ArC_{ipso}), 129.7 (2 x Ar*C*), 128.43 (2 x Ar*C*), 128.38 (2 x Ar*C*), 128.2 (2 x Ar*C*), 128.0 (2 x Ar*C*), 127.8 (2 x Ar*C*), 127.6 (2 x Ar*C*), 127.5 (2 x Ar*C*), 127.24 (Ar*C*), 127.23 (Ar*C*), 127.1 (Ar*C*), 126.8 (Ar*C*), 73.6 (Ph*C*HN$(CH_3)_2$), 64.0 (d, $^{2}J_{CP}$ = 10.0 Hz, CH_2*C*HN), 61.6 (d, $^{2}J_{CP}$ = 11.0 Hz, CH_2*C*HN) 59.8 (Ph*C*H), 46.3 (d, $^{2}J_{CP}$ = 3.9 Hz, Ph*C*H_2), 45.8 (d, $^{2}J_{CP}$ = 3.4 Hz, Ph*C*H_2), 40.9 (*C*$H_3)_2$, 29.3 (d, $^{3}J_{CP}$ = 9.9 Hz, *C*H_2), 28.3 (d, $^{3}J_{CP}$ = 9.7 Hz, *C*H_2), 24.1 (*C*H_2), 23.9 (*C*H_2); HRMS (APPI, pos.): *m*/*z* 637.3019 (637.3004 calc. for $C_{37}H_{44}N_5OPS$ $(M)^+$) and 638.3089 (638.3082 calc. for $C_{37}H_{45}N_5OPS$ $(M+H)^+$).

1-((4*S*,5*S*)-1,3-Dibenzyl-2-oxido-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl)-3-((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)thiourea (VI):

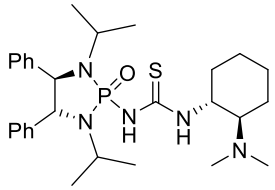


The reaction of **89** (680 mg, 1.37 mmol) in THF (7 ml) was added *N*,*N*-dimethyl diaminocyclohexane (195 mg**,** 1.79 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 710 mg (81%) of **VI** as a white solid; R_f = 0.22 (DCM/MeOH, 97:3).

Mp: 101.7-102.4 ^{o}C; IR (neat): 3062, 3030, 2927, 2857, 2825, 2777, 1556, 1494, 1454, 1338, 1289, 1203, 1170, 1133, 1063, 1028, 910, 861, 836, 757, 741, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): Major rotamer δ 9.97 (d, 1H, *J* = 7.5 Hz, C*H*NH), 7.33-7.29 (m, 2H, Ar*H*), 7.28-7.16 (m, 12H, Ar*H*), 7.14-7.09 (m, 1H, Ar*H*), 7.08-7.01 (m, 3H, Ar*H*), 6.97-6.90 (m, 1H, Ar*H*), 6.87-6.83 (m, 1H, Ar*H*), 6.33 (d, 1H, *J* = 8.8 Hz, P(O)N*H*), 4.45 (dd, 2H, *J* = 15.5, 9.7 Hz,CH_2Ph), 4.33-4.26 (m, 1H, C*H*NH), 4.05 (dd, 1H, *J* = 8.9, 5.4 Hz, PhC*H*), 3.93 (t, 1H, *J* = 5.4 Hz, PhC*H*), 3.76 (dd, 1H, *J* = 14.8, 8.5 Hz, CH_2Ph), 3.60 (dd 1H, *J* = 14.8, 13.0 Hz, CH_2Ph), 2.56-2.47 (m, 1H, C*H*N$(CH_3)_2$), 2.44 (d, 1H, *J* = 12.4 Hz, CH_2), 2.21 (s, 6H, N(CH_3)$_2$), 1.88-1.75 (m, 2H, CH_2), 1.75-1.61 (m, 1H, CH_2), 1.39-1.27 (m, 1H, CH_2), 1.26-1.14 (m, 3H, CH_2); ^{1}H NMR (300 MHz, $CDCl_3$): Minor rotamer δ 9.84 (d, 1H, *J* = 8.2 Hz, C*H*NH), 7.33-7.29 (m, 2H, Ar*H*), 7.28-7.16 (m, 12H, Ar*H*), 7.14-7.09 (m, 1H, Ar*H*), 7.08-7.01 (m, 3H, Ar*H*), 6.97-6.90 (m, 1H, Ar*H*), 6.87-6.83 (m, 1H, Ar*H*), 6.33 (d, 1H, *J* = 8.8 Hz, P(O)N*H*), 4.41 (dd, 1H, *J* = 14.9, 10.4 Hz,CH_2Ph), 4.26-4.15 (m, 1H, C*H*NH), 4.23 (dd, 1H, *J* = 14.9, 10.4 Hz,CH_2Ph), 4.01 (t, 1H, *J* = 6.0 Hz, PhC*H*), 3.89 (dd, 1H, *J* = 6.0, 4.1 Hz, PhC*H*), 3.78 (dd, 1H, *J* = 14.6, 11.0 Hz, CH_2Ph), 3.55 (t, 1H, *J* = 14.6

Hz, C*H*$_2$Ph), 2.56-2.47 (m, 1H, C*H*N(CH$_3$)$_2$), 2.38 (d, 1H, *J* = 12.1 Hz, CH$_2$), 2.14 (s, 6H, N(C*H*$_3$)$_2$), 1.88-1.75 (m, 2H, C*H*$_2$), 1.75-1.61 (m, 1H, C*H*$_2$), 1.39-1.27 (m, 1H, C*H*$_2$), 1.26-1.14 (m, 3H, C*H*$_2$); ^{13}C NMR (75 MHz, CDCl$_3$): Major rotamer δ 181.2 (d, $^2J_{CP}$ = 3.7 Hz, *C*=S), 138.4 (d, $^3J_{CP}$ = 4.7 Hz, Ar*C*$_{ipso}$), 138.2 (d, $^3J_{CP}$ = 3.7 Hz, Ar*C*$_{ipso}$), 137.8 (d, $^3J_{CP}$ = 6.0 Hz, Ar*C*$_{ipso}$), 137.7 (d, $^3J_{CP}$ = 5.1 Hz, Ar*C*$_{ipso}$), 129.5 (Ar*C*), 129.22 (Ar*C*), 129.17 (Ar*C*), 129.1 (2 x Ar*C*), 129.0 (Ar*C*), 128.8 (2 x Ar*C*), 128.71 (Ar*C*), 128.67 (Ar*C*), 128.6 (Ar*C*), 128.54 (Ar*C*), 128.49 (Ar*C*), 128.0 (Ar*C*), 127.92 (Ar*C*), 127.85 (Ar*C*), 127.7 (Ar*C*), 127.64 (Ar*C*), 127.58 (Ar*C*), 127.3 (Ar*C*), 67.7 (d, $^2J_{CP}$ = 13.5 Hz, Ph*C*H), 67.2 (*C*HN(CH$_3$)$_2$), 66.2 (d, $^2J_{CP}$ = 13.5 Hz, Ph*C*H), 57.0 (*C*HNH), 46.5 (d, $^2J_{CP}$ = 5.6 Hz, *C*H$_2$Ph), 46.0 (d, $^2J_{CP}$ = 4.9 Hz, *C*H$_2$Ph), 40.7 (N(*C*H$_3$)$_2$), 32.2 (*C*H$_2$), 25.2 (*C*H$_2$), 25.0 (*C*H$_2$), 22.9 (*C*H$_2$); ^{13}C NMR (75 MHz, CDCl$_3$): Minor rotamer δ 181.2 (d, $^2J_{CP}$ = 3.7 Hz, *C*=S), 135.9 (d, $^3J_{CP}$ = 1.6 Hz, Ar*C*$_{ipso}$), 135.8 (d, $^3J_{CP}$ = 2.9 Hz, Ar*C*$_{ipso}$), 135.5 (d, $^3J_{CP}$ = 3.5 Hz, Ar*C*$_{ipso}$), 135.4 (d, $^3J_{CP}$ = 1.1 Hz, Ar*C*$_{ipso}$), 129.5 (Ar*C*), 129.22 (Ar*C*), 129.17 (Ar*C*), 129.1 (2 x Ar*C*), 129.0 (Ar*C*), 128.8 (2 x Ar*C*), 128.71 (Ar*C*), 128.67 (Ar*C*), 128.6 (Ar*C*), 128.54 (Ar*C*), 128.47 (Ar*C*), 128.0 (Ar*C*), 127.92 (Ar*C*), 127.85 (Ar*C*), 127.7 (Ar*C*), 127.64 (Ar*C*), 127.58 (Ar*C*), 127.3 (Ar*C*), 66.8 (*C*HN(CH$_3$)$_2$), 66.7 (d, $^2J_{CP}$ = 11.8 Hz, Ph*C*H), 66.6 (d, $^2J_{CP}$ = 13.6 Hz, Ph*C*H), 57.0 (*C*HNH), 45.8 (d, $^2J_{CP}$ = 5.7 Hz, *C*H$_2$Ph), 45.6 (d, $^2J_{CP}$ = 6.0 Hz, *C*H$_2$Ph), 40.7 (N(*C*H$_3$)$_2$), 32.1 (*C*H$_2$), 25.2 (*C*H$_2$), 24.8 (*C*H$_2$), 22.2 (*C*H$_2$); HRMS (ESI, pos.): *m*/*z* 637.2991 (637.3004 calc. for C$_{37}$H$_{44}$N$_5$OPS (M^+) and and 638.3077 (638.3082 calc. for C$_{37}$H$_{45}$N$_5$OPS $(M+H)^+$).

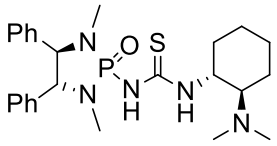
1-((4*R*,5*R*)-1,3-Diisopropyl-2-oxido-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl)-3-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)thiourea (VII):



The reaction of **96** (269 mg, 0.67 mmol) in THF (3 ml) was added *N*,*N*-dimethyl diaminocyclohexane (96 mg**,** 0.67 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 171 mg (47%, brsm 94%) of **VII** as a white solid; R_f = 0.22 (DCM/MeOH, 95:5).

Mp: 180.1-181.7 °C: IR (neat): 3030, 2967, 2929, 2858, 2824, 2776, 1556, 1493, 1454, 1387, 1347, 1267, 1163, 1132, 1099, 1038, 1024, 1006, 874, 849, 787, 722, 697, 633, 561, 519 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.90 (d, 1H, *J* = 7.5 Hz, N*H*CH), 7.37-7.29 (m, 6H, Ar*H*), 7.27-7.22 (m, 2H, Ar*H*), 7.11-7.05 (m, 2H, Ar*H*), 6.35 (d, 1H, *J* = 8.6 Hz, P(O)N*H*), 4.28-4.20 (m, 1H, NHC*H*), 4.24 (dd, 1H, *J* = 6.5, 2.5 Hz, PhC*H*) 4.15 (dd, 1H, *J* = 6.5, 4.5 Hz, PhC*H*), 3.26-3.01 (m, 2H, C*H*$(CH_3)_2$), 2.56-2.40 (m, 2H, 1 x CH_2 & C*H*N(C$H_3)_2$), 2.27 (s, 6H, N(C$H_3)_2$), 1.90-1.64 (m, 3H, CH_2), 1.36 (t, 6H, *J* = 6.7 Hz, CH(C$H_3)_2$), 1.32-1.17 (m 4H, CH_2), 1.12 (d, 3H, *J* = 6.5 Hz, CH(C$H_3)_2$), 1.03 (d, 3H, *J* = 6.6 Hz, CH(C$H_3)_2$; ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0 (d, $^2J_{CP}$ = 3.5 Hz, *C*=S), 139.3 (t, $^3J_{CP}$ = 6.4 Hz, 2 x ArC_{ipso}), 128.9 (2 x Ar*C*), 128.8 (2 x Ar*C*), 128.4 (2 x Ar*C*), 127.5 (2 x Ar*C*), 127.0 (2 x Ar*C*), 67.3 (d, $^2J_{CP}$ = 13.4 Hz, Ph*C*H), 67.1 (d, $^2J_{CP}$ = 13.4 Hz, Ph*C*H), 66.4 (*C*HNH), 56.7 (*C*HN$(CH_3)_2$), 46.9 (d, $^2J_{CP}$ = 3.9 Hz, *C*H$(CH_3)_2$), 46.2 (d, $^2J_{CP}$ = 4.7 Hz, *C*H$(CH_3)_2$), 40.4 (N(*C*$H_3)_2$), 32.1 (*C*H_2), 25.0 (*C*H_2), 24.7 (*C*H_2), 22.4 (*C*H_2), 20.5 (4 x *C*H_3); HRMS (APPI, pos.): *m*/*z* 541.3019 (541.3004 calc. for $C_{29}H_{44}N_5OPS$ $(M)^+$) and 542.3090 (542.3080 calc. for $C_{29}H_{45}N_5OPS$ $(M+H)^+$).

1-((4*R*,5*R*)-1,3-Dimethyl-2-oxido-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl)-3-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)thiourea (VIII):



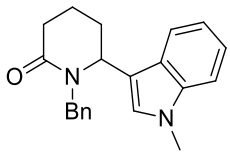
The reaction of **97** (613 mg, 1.79 mmol) in THF (3 ml) was added *N*,*N*-dimethyl diaminocyclohexane (254 mg**,** 1.79 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 540 mg (62%) of **VIII** as a white solid; R_f = 0.22 (DCM/MeOH, 95:5).

Mp: 129.3-130.6 ºC; IR (neat): 3030, 2928, 2857, 2823, 2778, 1553, 1492, 1454, 1341, 1307, 1246, 1152, 1038, 1017, 992, 863, 746, 698, 518 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.63 (d, 1H, *J* = 7.7 Hz,CHN*H*), 7.35-7.27 (m, 6H, Ar*H*), 7.17-7.07 (m, 2H, Ar*H*), 7.05-6.98 (m, 2H, Ar*H*), 6.59 (br s, 1H, P(O)N*H*) 4.28-4.13 (m, 1H, C*H*NH), 4.05 (d, 1H, *J* = 8.6 Hz, PhC*H*), 3.90 (d, 1H, *J* = 8.6 Hz, PhC*H*), 2.61-2.53 (m, 1H, C*H*N$(CH_3)_2$), 2.50 (d, 1H, *J* = 6.6 Hz, NCH_3), 2.52-2.43 (m, 1H, CH_2), 2.47 (d, 1H, *J* = 7.2 Hz, NCH_3), 2.29 (s, 6H, N(CH_3)$_2$), 1.91-1.69 (m, 3H, CH_2), 1.40-1.22 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.4 (d, $^{2}J_{CP}$ = 3.3 Hz, *C*=S), 136.6 (d, $^{3}J_{CP}$ = 9.0, ArC_{ipso}), 136.5 (d, $^{3}J_{CP}$ = 9.2 ArC_{ipso}), 128.74 (2 x Ar*C*), 128.66 (2 x Ar*C*), 128.61 (Ar*C*), 128.58 (Ar*C*), 127.9 (2 x Ar*C*), 127.6 (2 x Ar*C*), 71.2 (d, $^{2}J_{CP}$ = 11.9 Hz, Ph*C*H), 70.1 (d, $^{2}J_{CP}$ = 11.4 Hz, Ph*C*H), 66.6 (*C*HN$(CH_3)_2$), 56.7 (*C*HNH), 40.4 (N(*C*H_3)$_2$), 31.9 (*C*H_2), 29.6 (d, $^{2}J_{CP}$ = 3.4 Hz, *C*H_3), 28.5 (d, $^{2}J_{CP}$ = 4.1 Hz, *C*H_3), 25.0 (*C*H_2), 24.7 (*C*H_2), 22.5 (*C*H_2); HRMS (ESI, pos.): *m*/*z* 485.2365 (485.2378 calc. for $C_{25}H_{36}N_5OPS$ ($(M)^+$) and 486.2436 (486.2456 calc. for $C_{25}H_{37}N_5OPS$ $(M+H)^+$).

General procedure for the intermolecular addition of indoles:

To a solution of iminium ion precursor (1 equiv) and the indole (2 equiv) in CH_2Cl_2 (1 mL) were added a catalyst (10 mol%) and $Sc(OTf)_3$ (10 mol%) at 0 °C in a sample vial. After stirring the reaction mixture for indicated time, the reaction mixture was concentrated and, the residue was purified by flash chromatography on silica gel to provide the required product.

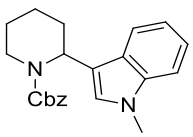
1-Benzyl-6-(1-methyl-1*H*-indol-3-yl)piperidin-2-one (137):



The reaction of 1-benzyl-6-hydroxypiperidin-2-one **107** (50 mg, 0.2 mmol), *N*-methyl indole **136** (61 µL, 0.4 mmol), Takemoto catalyst **II** (10 mg, 0.02 mmol) and $Sc(OTf)_3$ (12 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at ambient temperature for 30 h, according to the general procedure provided, after purification by flash column chromatography on silica gel (EtOAc/hexanes 2:3), 39 mg (51%) of **137** as a colorless solid. R*f* = 0.23 (EtOAc/hexanes 2:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 1H, *J* = 8.0, Ar*H*), 7.37-7.21 (m, 5H, Ar*H*), 7.17 (dd, 2H, *J* = 7.6 , 1.5 Ar*H*), 7.11 (ddd, 1H, *J* = 8.0, 6.9, 1.1 Hz, Ar*H*), 6.86 (s, 1H, CH_3NCH), 5.59 (d, 1H, *J* = 14.8, CH_2Ph), 4.85 (t, 1H, *J* = 4.6 Hz, NC*H*CH_2), 3.78 (s, 3H, CH_3), 3.67 (d, 1H, *J* = 14.8, CH_2Ph), 2.71-2.49 (m, 2H, CH_2), 2.13-1.95 (m, 2H, CH_2), 1.94-1.76 (m, 1H, CH_2), 1.74-1.61 (m, 1H, CH_2).

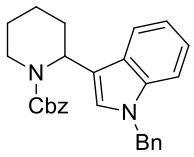
Benzyl 2-(1-methyl-1*H*-indol-3-yl)piperidine-1-carboxylate (138):



The reaction of 2-hydroxypiperidine-1-carboxylate **119** (50 mg, 0.2 mmol), *N*-methyl indole **136** (53 µL, 0.4 mmol), Takemoto catalyst **II** (9 mg, 0.02 mmol) and $Sc(OTf)_3$ (10 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at ambient temperature for 1h, according to the general procedure provided, after purification by flash column chromatography on silica gel (EtOAc/hexanes 2:3), 13 mg (17%) of **138** as a colorless solid. R*f* = 0.24 (EtOAc/hexanes 1:9).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, 1H, *J* = 8.0, Ar*H*), 7.40-7.26 (m, 6H, Ar*H*), 7.21 (ddd, 1H, *J* = 8.0, 6.8, 1.2 Hz, Ar*H*), 7.02 (ddd, 1H, *J* = 8.0, 6.8, 1.2 Hz, Ar*H*), 6.92 (d, 1H, *J* = 1.2 Hz, CH_3NCH), 5.83 (d, 1H, *J* = 5.2 Hz, NC*H*CH_2), 5.23 (s, 2H, CH_2Ph), 4.06 (d, 1H, *J* = 13.4 Hz, NCH_2), 3.75 (s, 3H, CH_3), 2.90 (ddd, 1H, *J* = 13.4, 12.2, 3.7, Hz, NCH_2), 2.25 (d, 1H, *J* = 12.2, NCH_2CH_2), 2.30-1.88 (m, 1H, CH_2), 1.86-1.65 (m, 2H, CH_2), 1.64-1.46 (m, 3H, CH_2).

Benzyl 2-(1-benzyl-1*H*-indol-3-yl)piperidine-1-carboxylate (140):

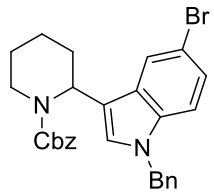


The reaction of 2-hydroxypiperidine-1-carboxylate **119** (50 mg, 0.2 mmol), *N*-benzyl indole (88 mg, 0.4 mmol), Takemoto catalyst **II** (9 mg, 0.02 mmol) or cinchonidine catalyst **X** (9 mg, 0.02 mmol) or bisoxazoline ligand $\mathbf{L_1}$ (7 mg, 0.02 mmol) and $Sc(OTf)_3$ (10 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at 0 ^oC for 20 mins, according to the general procedure provided, after purification by flash column chromatography on silica gel (EtOAc/hexanes 2:3), 72 mg (77%) of **140** as a colorless solid. R*f* = 0.24 (EtOAc/hexanes 1:4).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, 1H, *J* = 8.0 Hz, Ar*H*), 7.40-7.25 (m, 8H. Ar*H*), 7.25-7.20 (m, 1H, Ar*H*), 7.15 (ddd, 1H, *J* = 8.0, 6.9, 1.1 Hz, Ar*H*), 7.11-7.06 (m, 2H, Ar*H*), 7.05-6.98 (m, 2H, Ar*H* and N-C*H*), 5.86 (d, 1H, *J* = 4.7 Hz, NC*H*CH2), 5.29 (s, 2H, OCH_2Ph), 5.23 (s, 2H,

C*H*$_2$Ph), 4.06 (d, 1H, *J* = 14.2 Hz, NC*H*$_2$), 2.88 (ddd, 1H, *J* = 14.2, 12.3, 3.6 Hz, NC*H*$_2$), 2.25 (d, 1H, *J* = 12.3 Hz, C*H*$_2$), 2.03-188 (m, 1H, C*H*$_2$), 1.87-1.64 (m, 2H, C*H*$_2$),1.62-1.46 (m, 2H, C*H*$_2$).

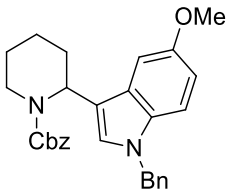
Benzyl 2-(1-benzyl-5-bromo-1*H*-indol-3-yl)piperidine-1-carboxylate (141):



The reaction of 2-hydroxypiperidine-1-carboxylate **119** (50 mg, 0.2 mmol), 1-benzyl-5-bromo-1*H*-indole (121 mg, 0.42 mmol), Takemoto catalyst **II** (9 mg, 0.02 mmol) and Sc(OTf)$_3$ (10 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at 0 ^oC for 30 mins, according to the general procedure provided, after purification by flash column chromatography on silica gel (EtOAc/hexanes 1:9), 78 mg (70%) of **141** as a colorless solid. R*f* = 0.22 (EtOAc/hexanes 1:9).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 1H, *J* = 1.8 Hz, Ar*H*), 7.40-7.27 (m, 8H, Ar*H*), 7.23 (dd, 1H, *J* = 8.7, 1.8 Hz, Ar*H*), 7.08 (d, 1H, *J* = 8.7 Hz, Ar*H*), 7.05-7.02 (m, 2H, Ar*H*), 7.01 (d, 1H, *J* = 1.0 Hz, NC*H*) 5.79 (d, 1H, *J* = 5.9 Hz, NC*H*CH_2), 5.33-5.16 (m, 4H, C*H*$_2$Ph & OC*H*$_2$Ph), 4.07 (d, 1H, *J* = 12.5, NC*H*$_2$), 2.85 (ddd, 1H, *J* = 13.6, 12.5, 4.6 Hz, NC*H*$_2$), 2.26-2.16 (m, 1H, NCH_2CH_2), 2.03-1.89 (m, 1H, C*H*$_2$), 1.78-1.66 (m, 2H, C*H*$_2$), 1.63-1.57 (m, 2H, C*H*$_2$).

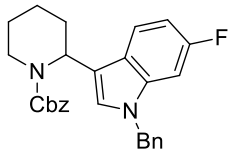
Benzyl 2-(1-benzyl-5-methoxy-1*H*-indol-3-yl)piperidine-1-carboxylate (142):



The reaction of 2-hydroxypiperidine-1-carboxylate **119** (50 mg, 0.2 mmol), 5-methoxy-1H-indole (101 mg, 0.42 mmol), Takemoto catalyst **II** (9 mg, 0.02 mmol) and Sc(OTf)$_3$ (10 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at 0 ^oC for 1 h, according to the general procedure provided, after

purification by flash column chromatography on silica gel (EtOAc/hexanes 4:1), 55 mg (57%) of **142** as a colorless solid. R*f* = 0.23 (EtOAc/hexanes 4:1).

Benzyl 2-(1-benzyl-5-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylate (143):



The reaction of 2-hydroxypiperidine-1-carboxylate **119** (50 mg, 0.2 mmol), 1-benzyl-6-fluoro-1*H*-indole (96 mg, 0.42 mmol), Takemoto catalyst **II** (9 mg, 0.02 mmol) and $Sc(OTf)_3$ (10 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at 0 ^oC for 30 mins, according to the general procedure provided, after purification by flash column chromatography on silica gel (EtOAc/hexanes 4:1), 49 mg (52%) of **143** as a colorless solid. R*f* = 0.23 (EtOAc/hexanes 4:1).

^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (dd, 1H, *J* = 8.8, 5.4 Hz, Ar*H*), 7.40-7.27 (m, 8H, Ar*H*), 7.10-7.04 (m, 2H, Ar*H*), 6.99 (d, 1H, *J* = 1.1 Hz, NC*H*), 6.87 (dd, 1H, *J* = 9.8, 2.3 Hz, Ar*H*), 6.75 (ddd, 1H, *J* = 9.8, 8.8, 2.3 Hz, Ar*H*), 5.82 (d, 1H, *J* = 4.9 Hz, NC*H*CH_2), 5.23 (s, 2H, OC*H*2Ph), 5.22 (s, 2H, CH_2Ph), 4.05 (d, 1H, *J* = 3.4 Hz, NCH_2), 2.83 (ddd, 1H, *J* = 13.3, 12.5, 3.4, NCH_2), 2.21 (d, 1H, *J* = 12.5, NCH_2CH_2), 2.05-1.88 (m, 1H, CH_2), 1.86-1.68 (m, 2H, CH_2), 1.64-1.44 (m, 2H, CH_2).

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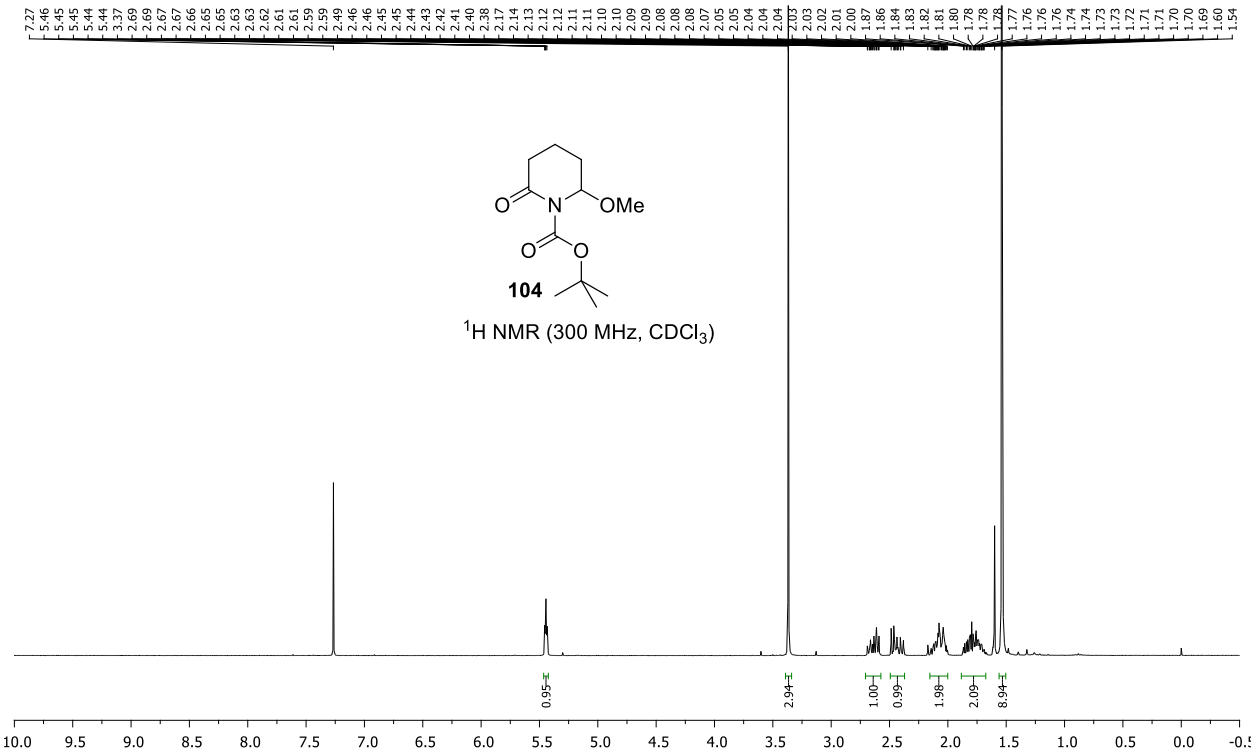

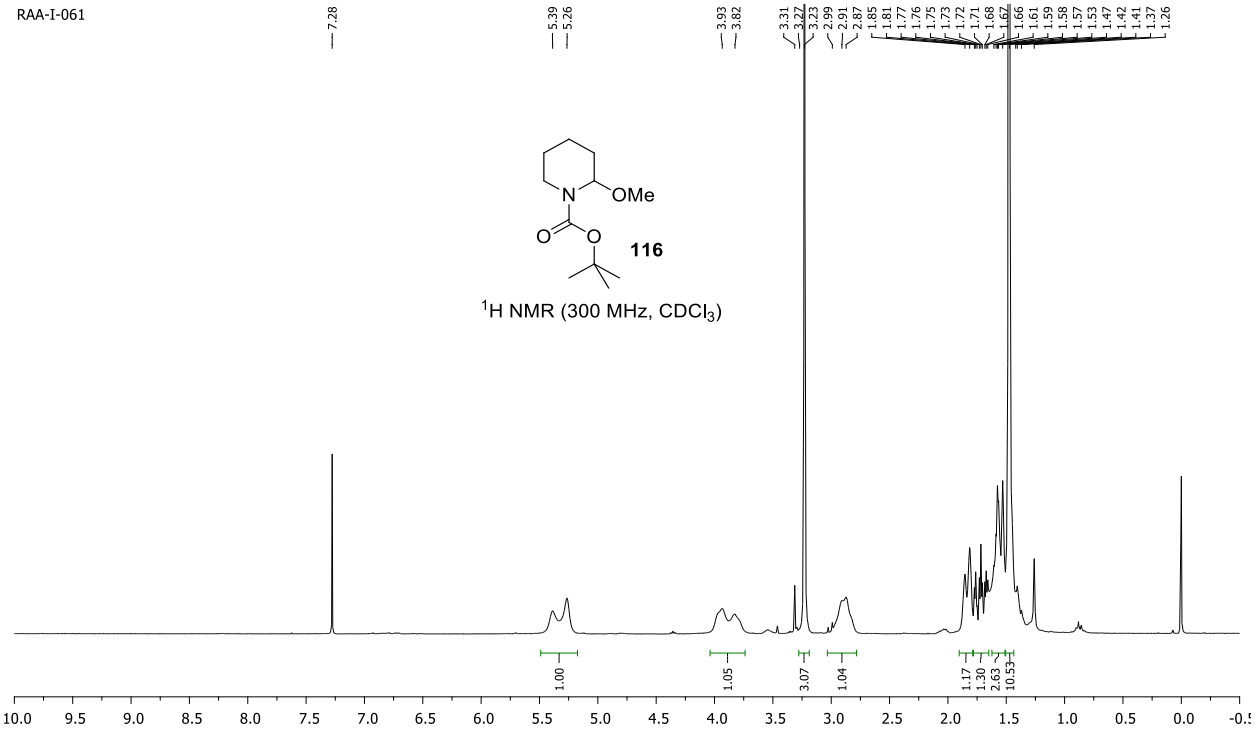

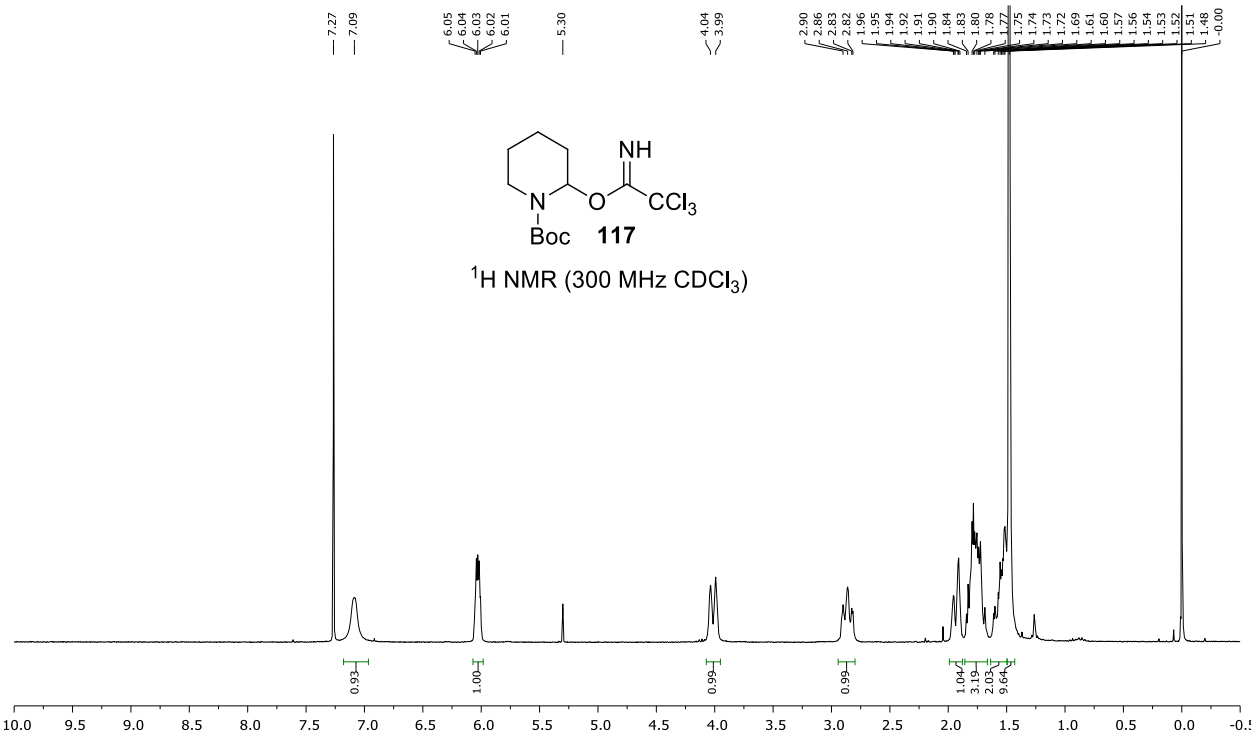
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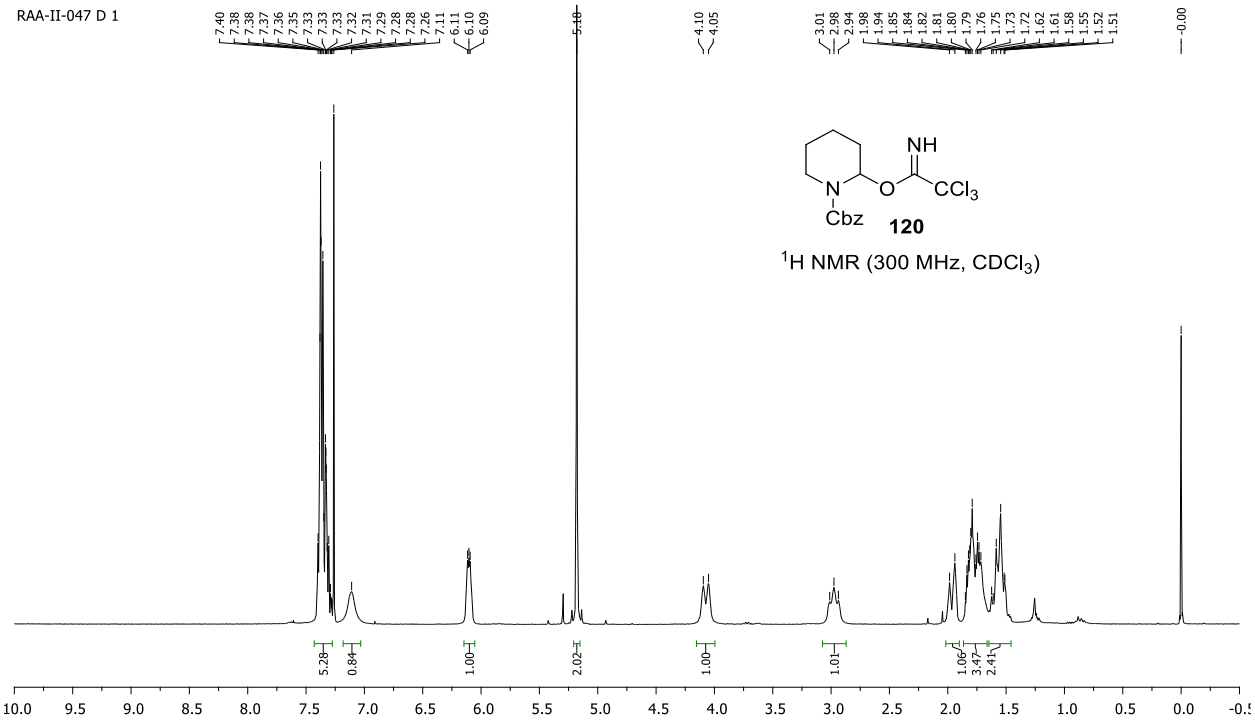
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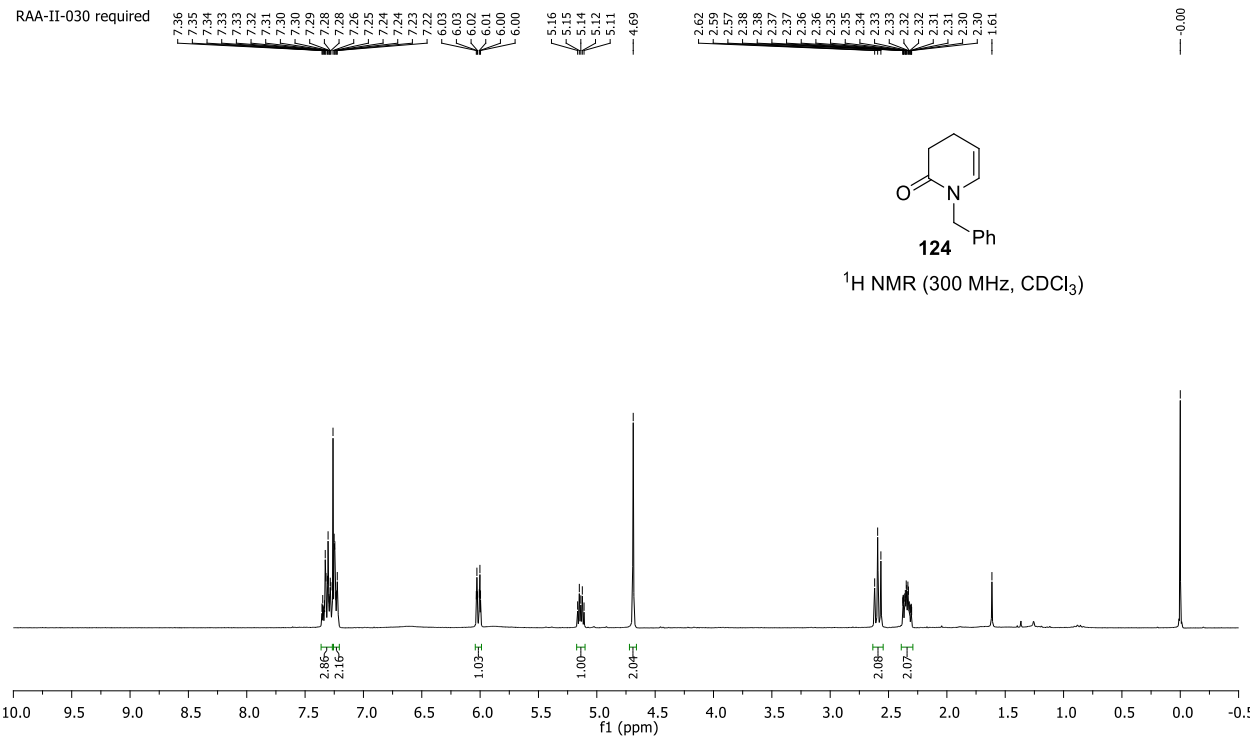
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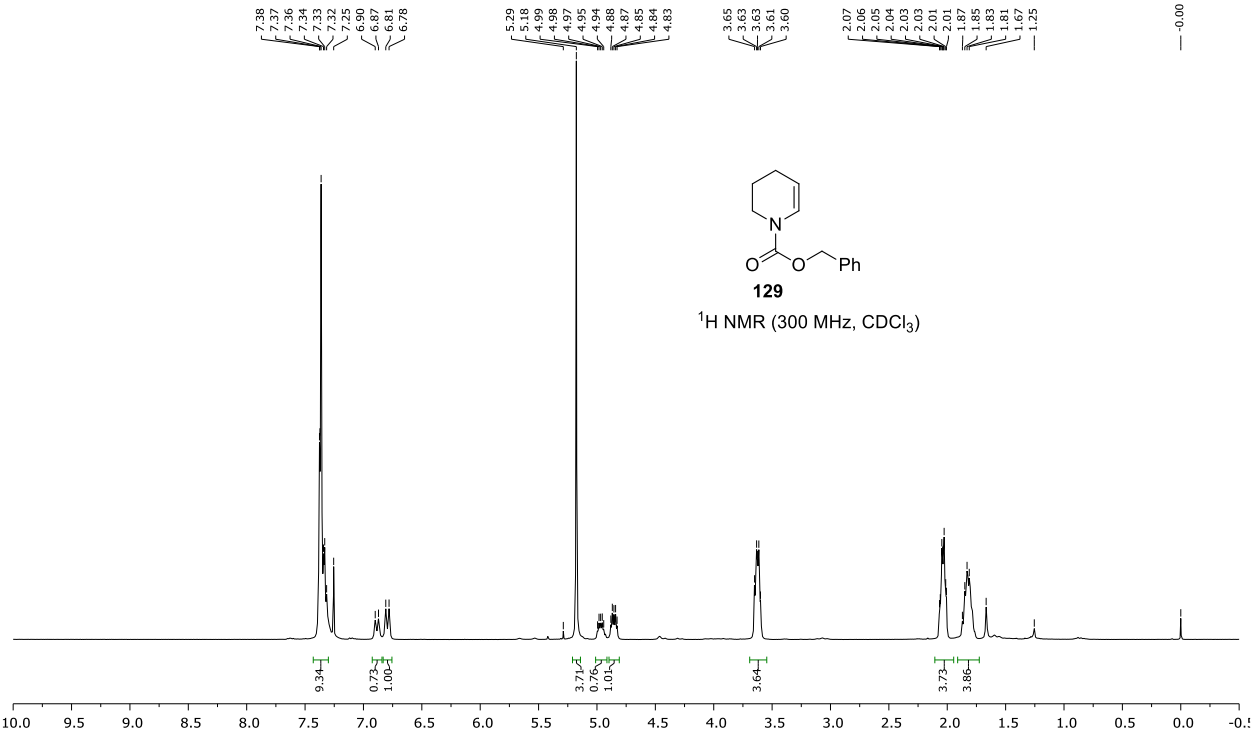
5.16 5.15 5.14 5.12 5.11 4.69
2.62 2.59 2.57 2.38 2.38 2.37 2.37 2.36 2.36 2.35 2.35 2.34 2.33 2.33 2.32 2.32 2.31 2.31 2.30 2.30 1.61
-0.00
O
N
Ph
124
1H NMR (300 MHz, CDCl3)
2.86 2.16 1.03 1.00 2.04 2.08 2.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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3.65 3.63 3.63 3.61 3.60
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N
O
O
Ph
129
1H NMR (300 MHz, CDCl3)
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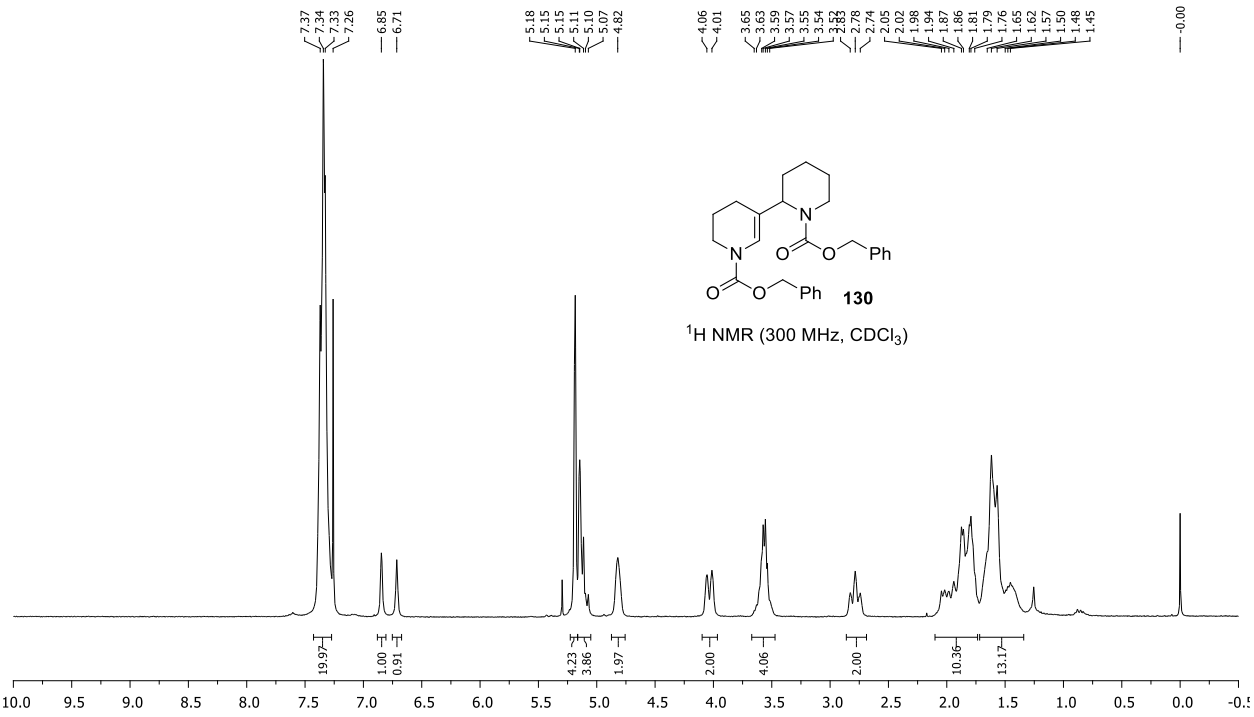
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1.79
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19.97
1.00
0.91
4.23
3.86
1.97
2.00
4.06
2.00
10.36
13.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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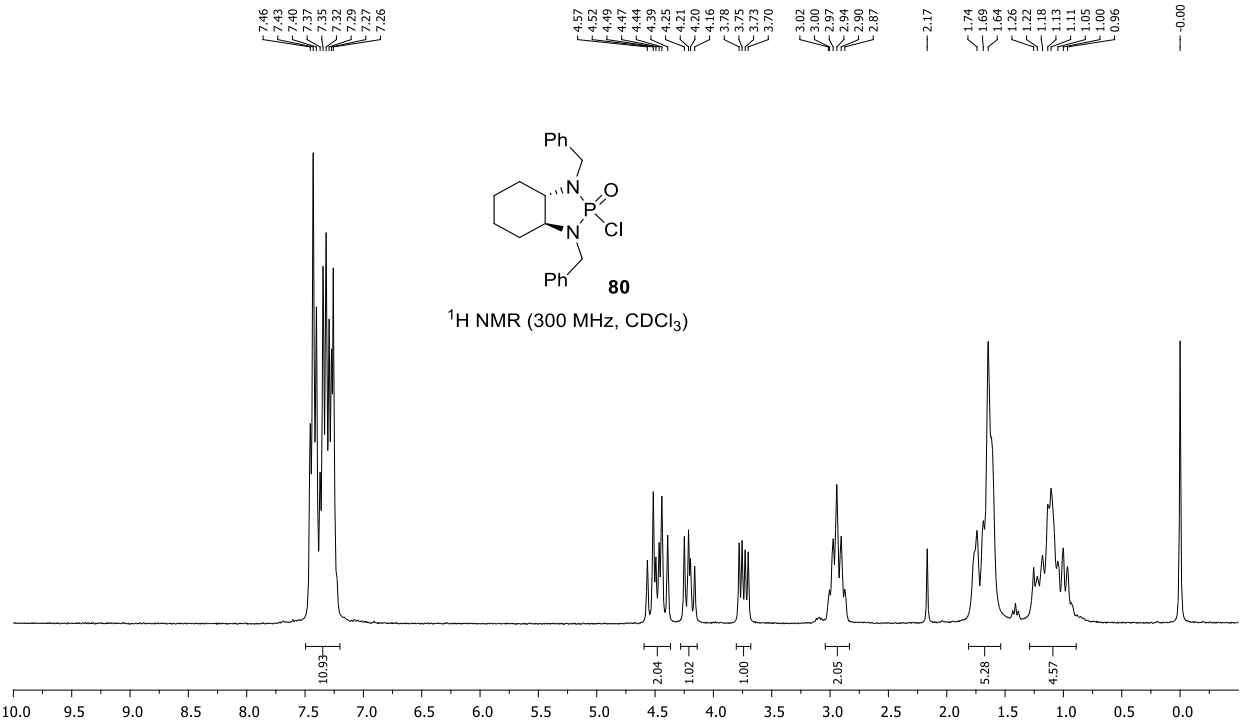
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3.00
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2.94
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2.05
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4.57
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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Cl
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Ph
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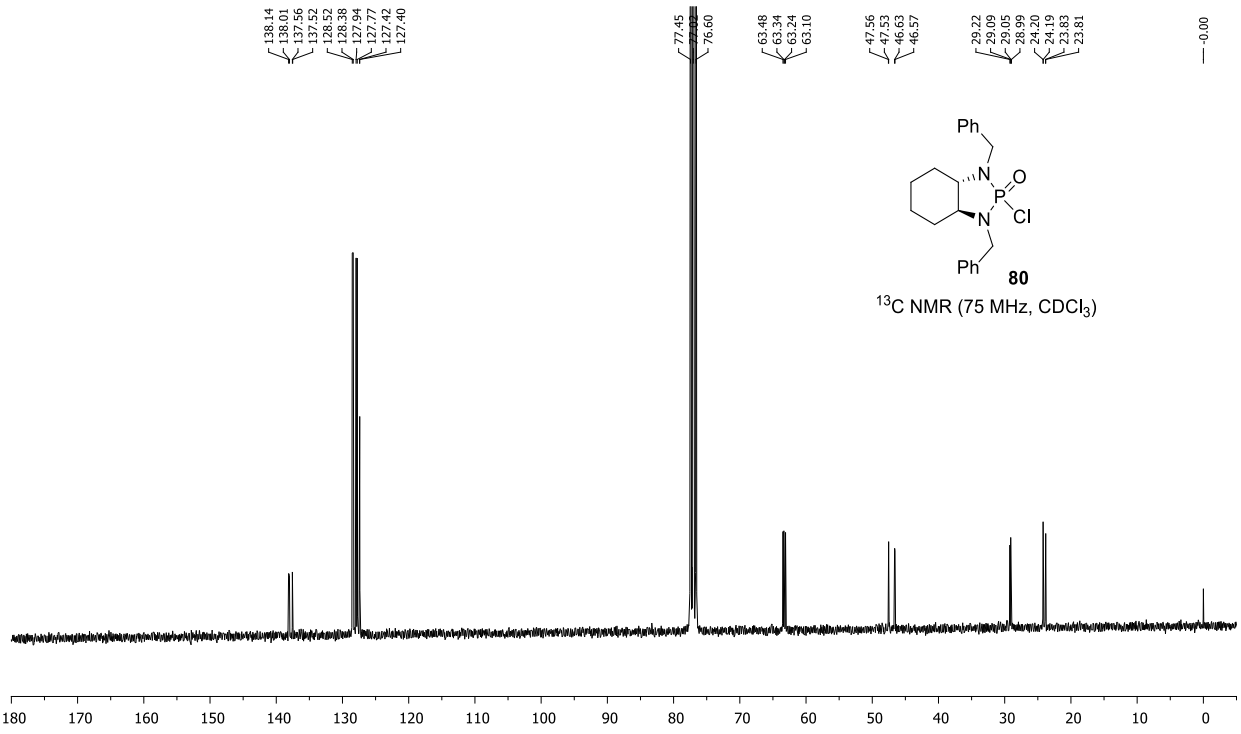
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24.19
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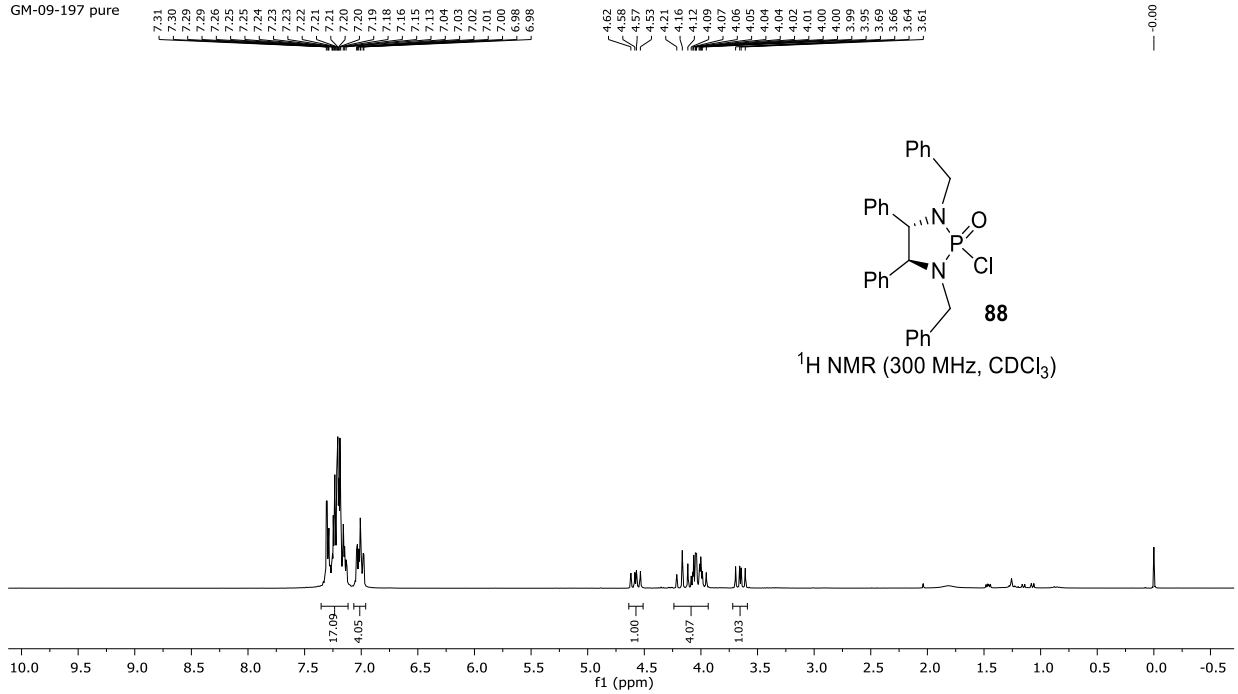
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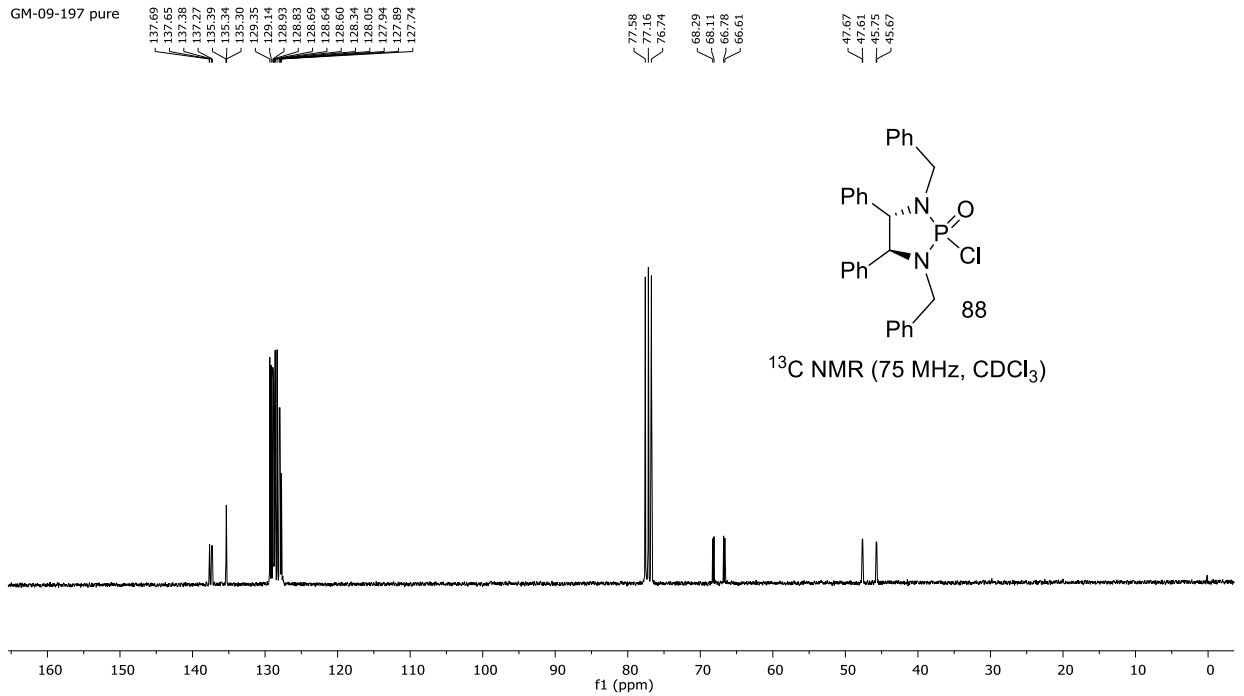
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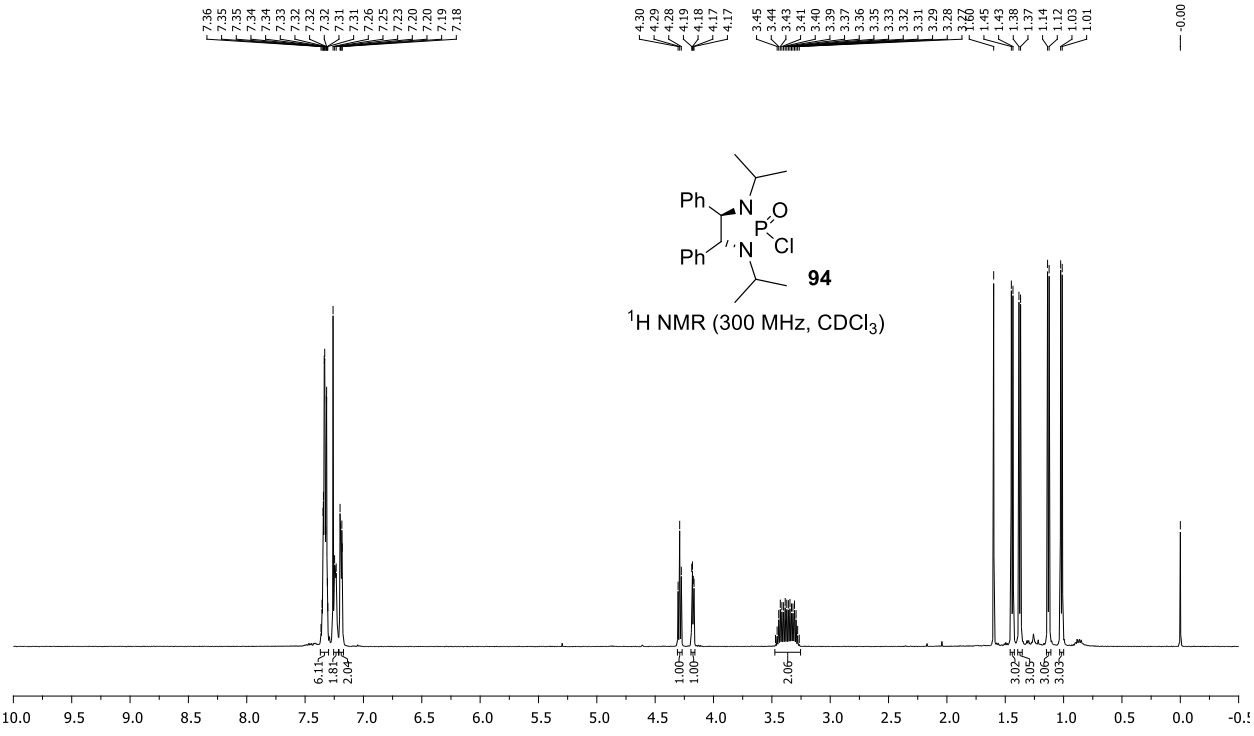
f1 (ppm)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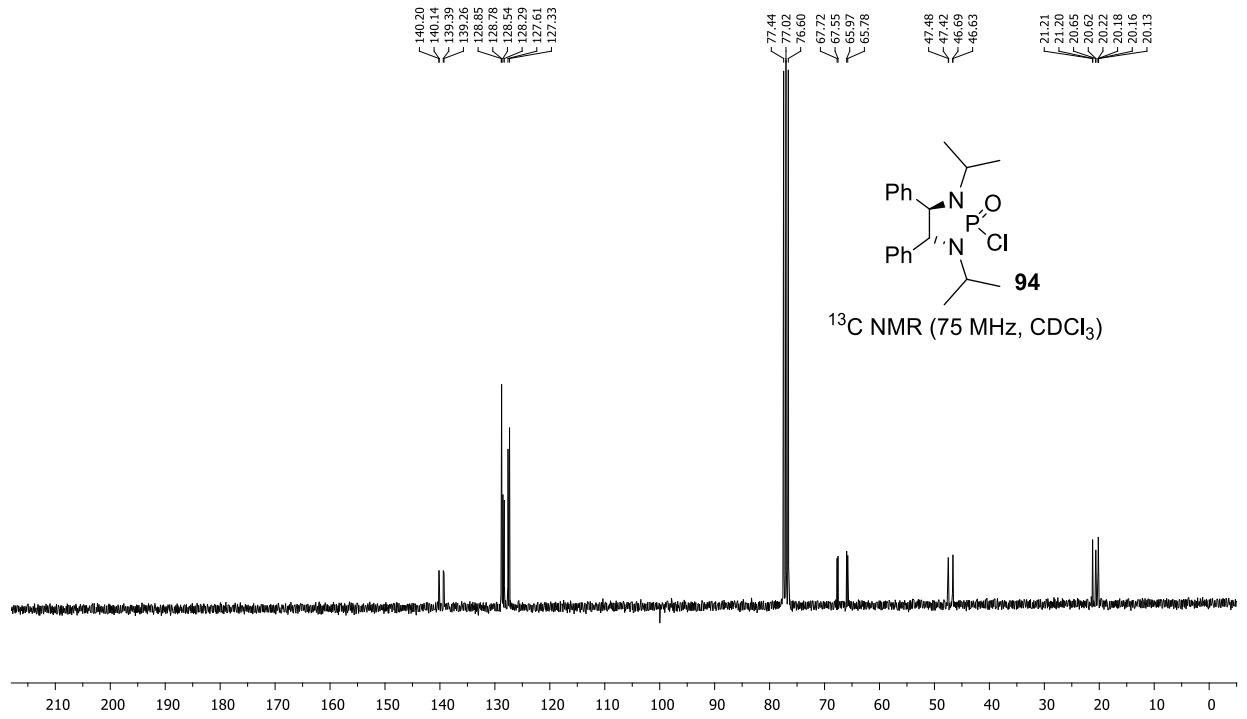
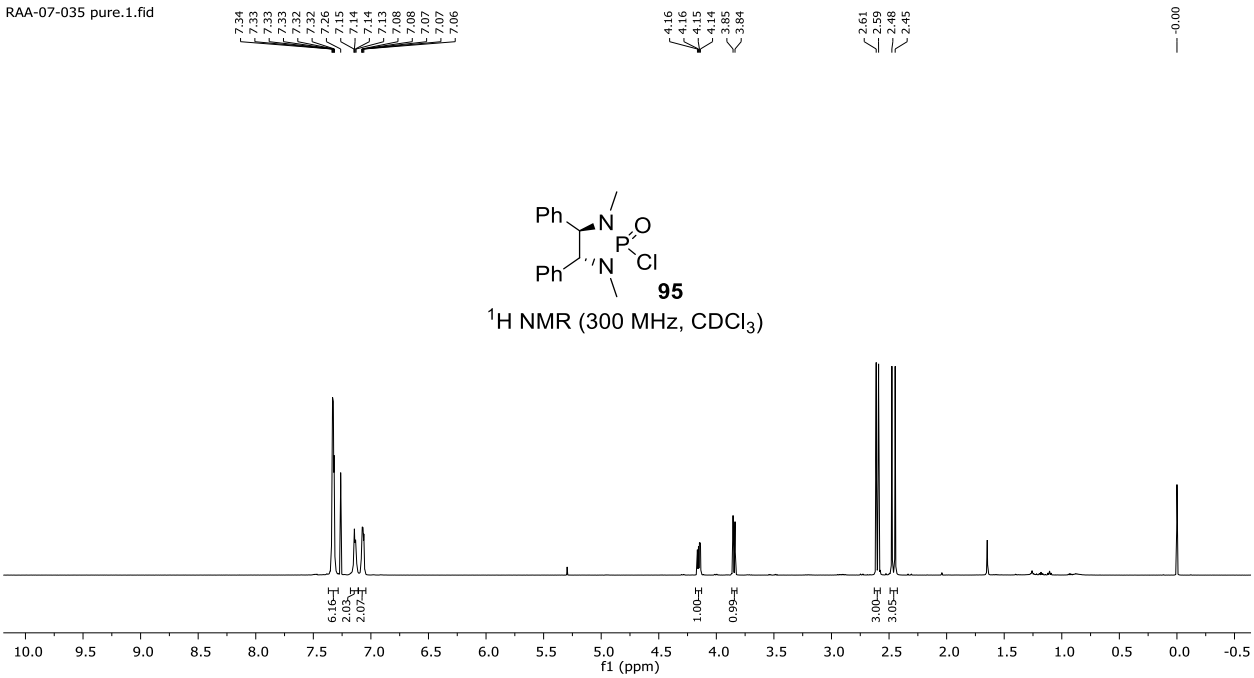
N
O
P
Cl
Ph
N
94
^{1}H NMR (300 MHz, CDCl$_3$)
6.11
1.81
2.04
1.00
1.00
2.06
3.02
3.05
3.06
3.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



^{13}C NMR (75 MHz, $CDCl_3$)



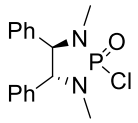
^{1}H NMR (300 MHz, $CDCl_3$)

GM-10-33 pure

136.80
136.73
135.90
135.73
128.75
128.73
128.69
128.53
127.75
127.58

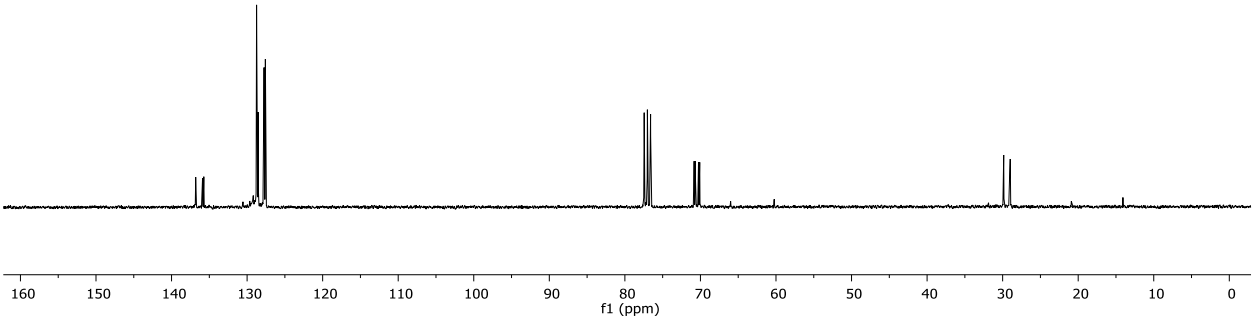
77.44
77.02
76.60
70.83
70.67
70.25
70.09

29.89
29.86
29.06
28.99



95

^{13}C NMR (75 MHz, $CDCl_3$)

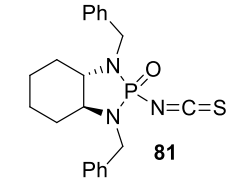


7.44
7.43
7.41
7.38
7.35
7.33
7.32
7.30
7.28
7.27
7.26
7.25
7.23

4.48
4.44
4.43
4.39
4.38
4.34
4.17
4.14
4.12
4.08
3.93
3.91
3.88
3.85
2.97
2.96
2.94
2.93
2.91
2.90
2.87
2.86

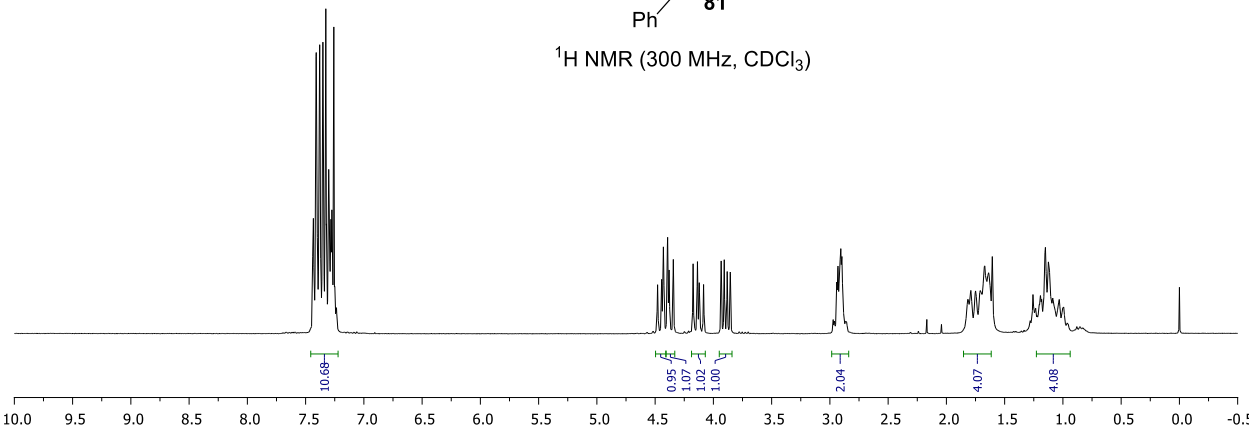
1.82
1.79
1.75
1.71
1.67
1.64
1.61

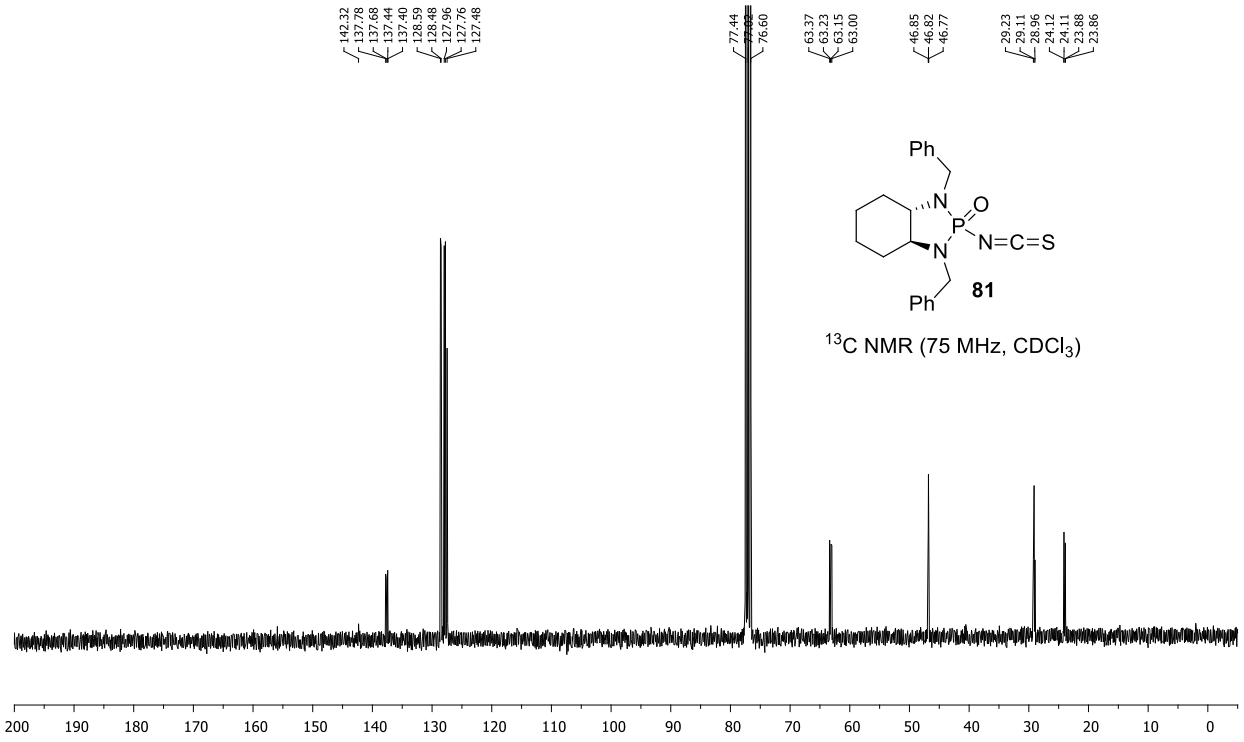
1.26
1.19
1.18
1.15
1.12
1.12
1.09
1.03
1.00
0.98
0.00



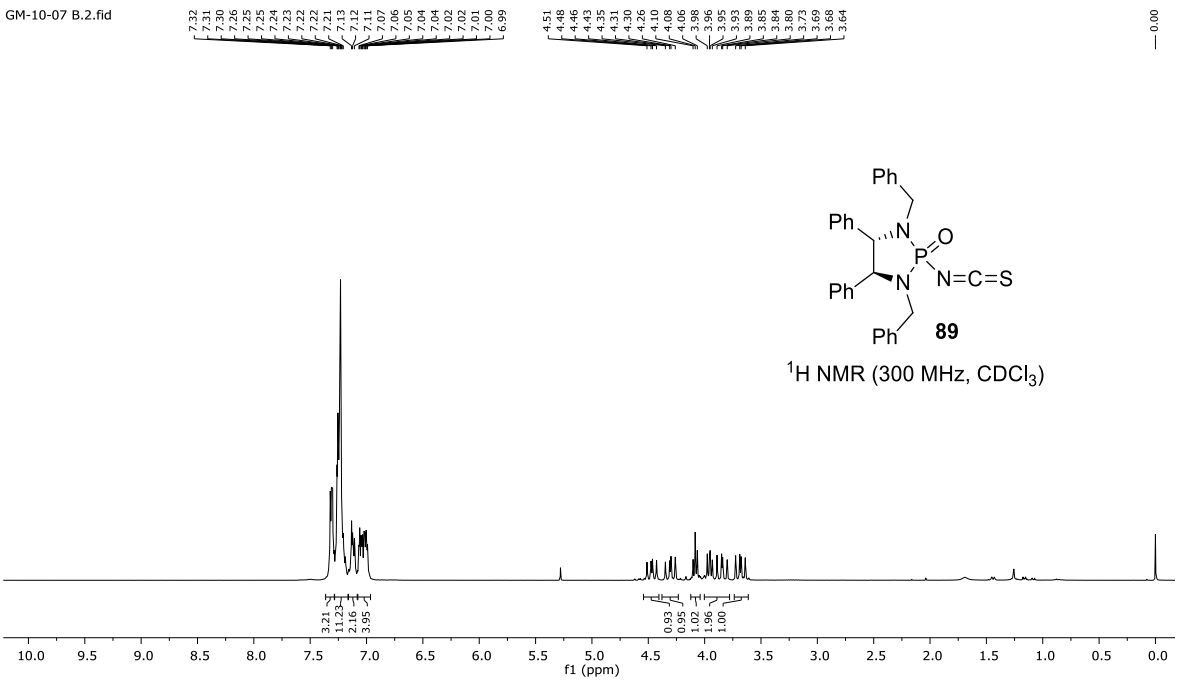
81

^{1}H NMR (300 MHz, $CDCl_3$)

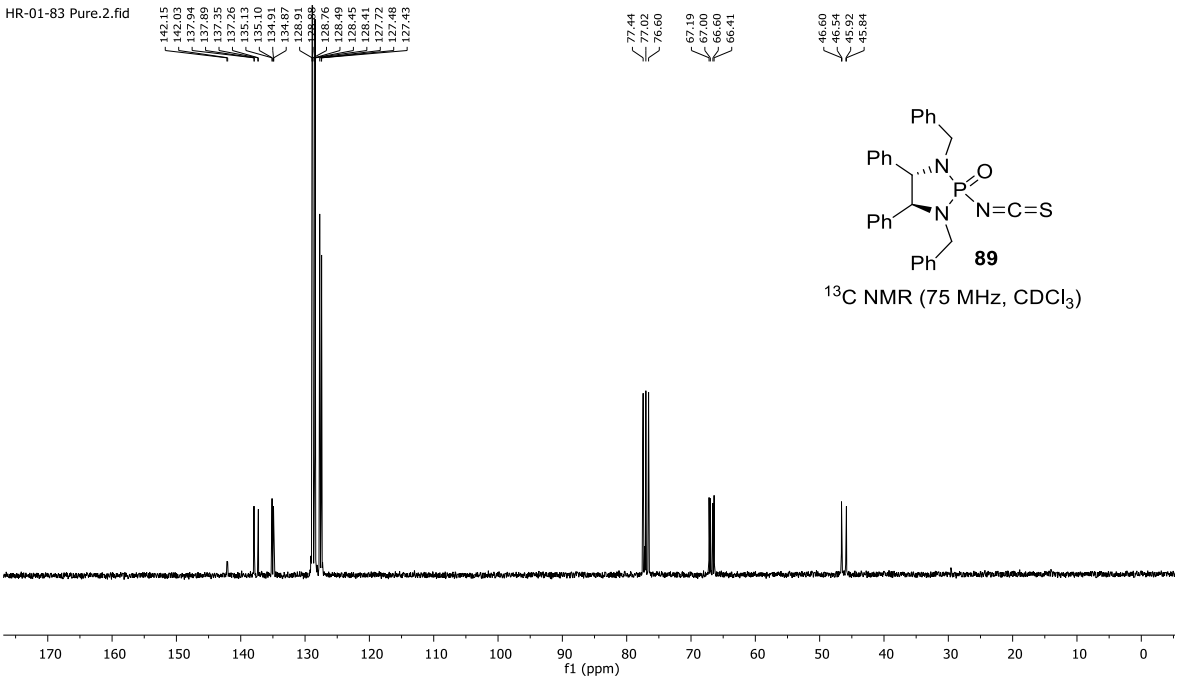


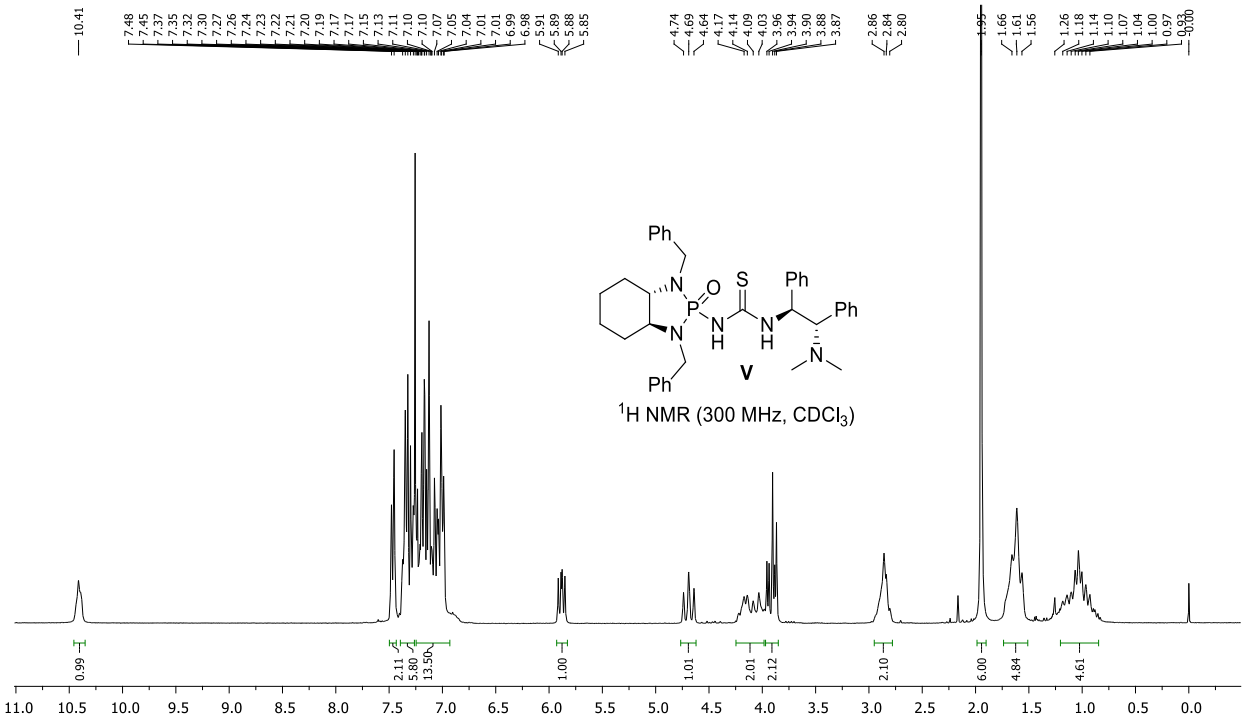


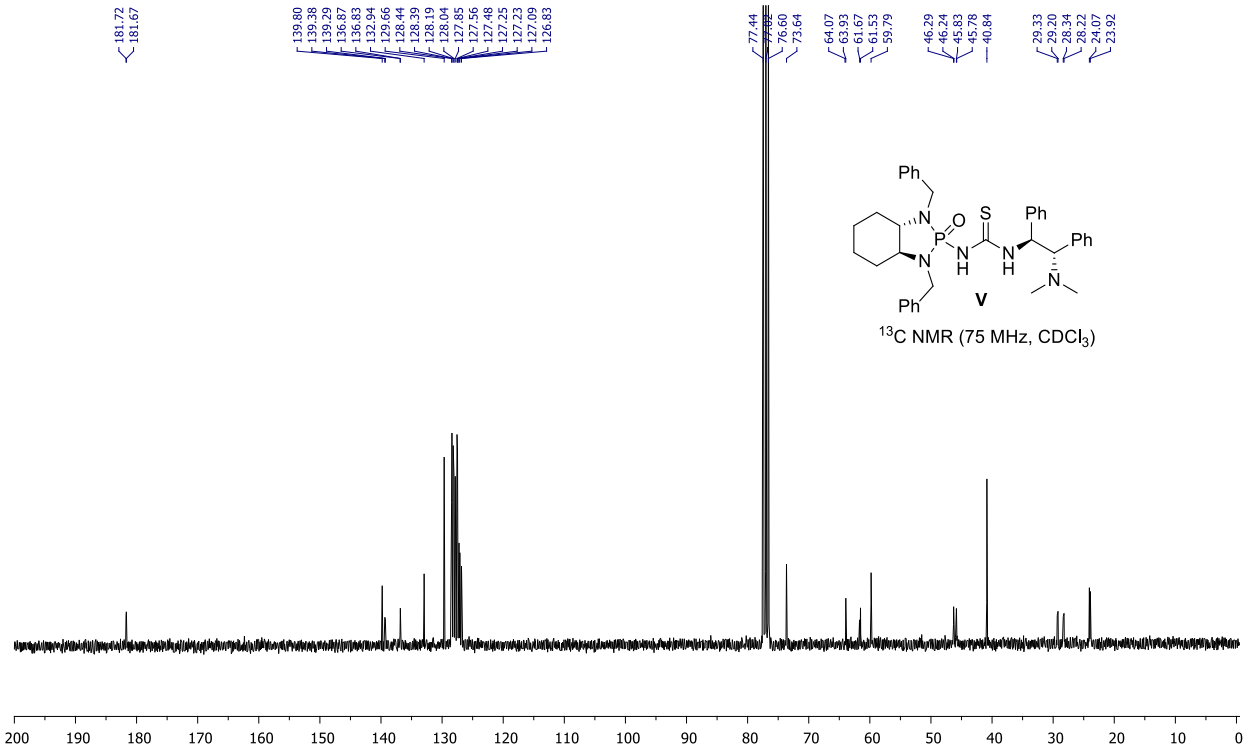
^{13}C NMR (75 MHz, $CDCl_3$)



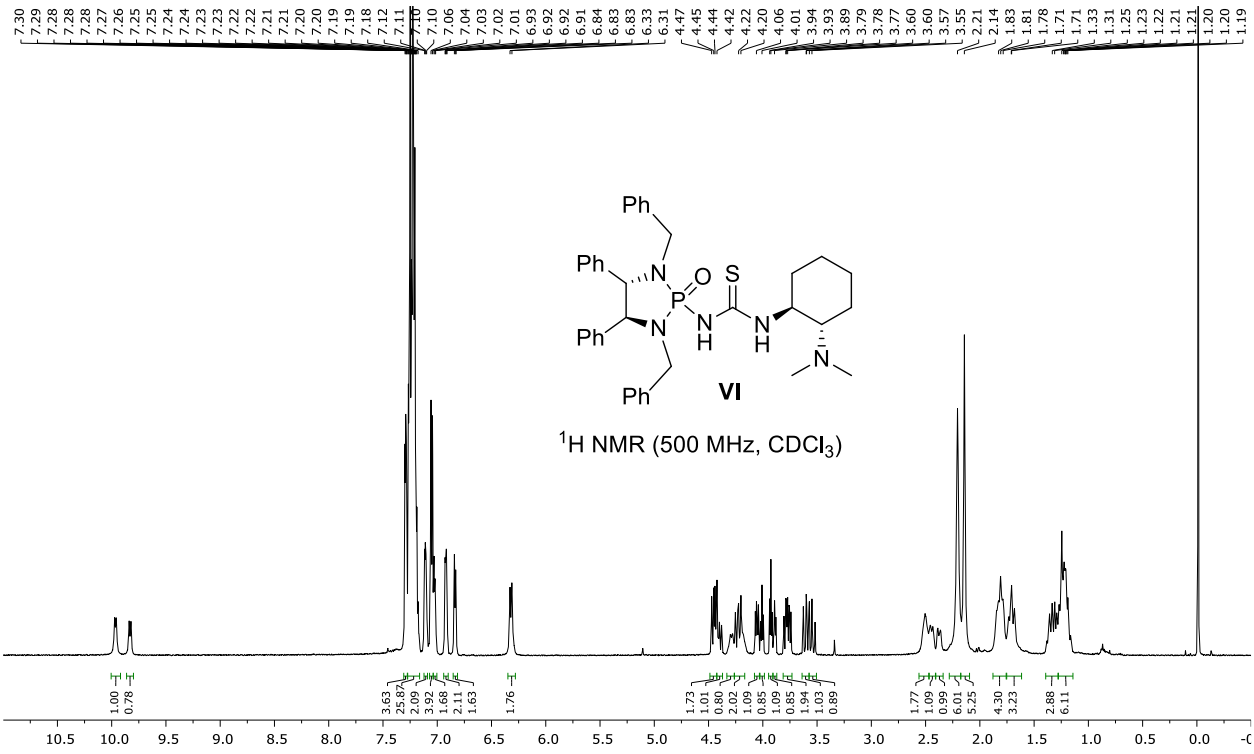
^{1}H NMR (300 MHz, $CDCl_3$)


HR-01-83 Pure.2.fid
142.15
142.03
137.94
137.89
137.35
137.26
135.13
135.10
134.91
134.87
128.91
128.88
128.76
128.49
128.45
128.41
127.72
127.48
127.43
77.44
77.02
76.60
67.19
67.00
66.60
66.41
46.60
46.54
45.92
45.84
Ph
Ph
N
P
O
N=C=S
Ph
N
Ph
89
13C NMR (75 MHz, CDCl3)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

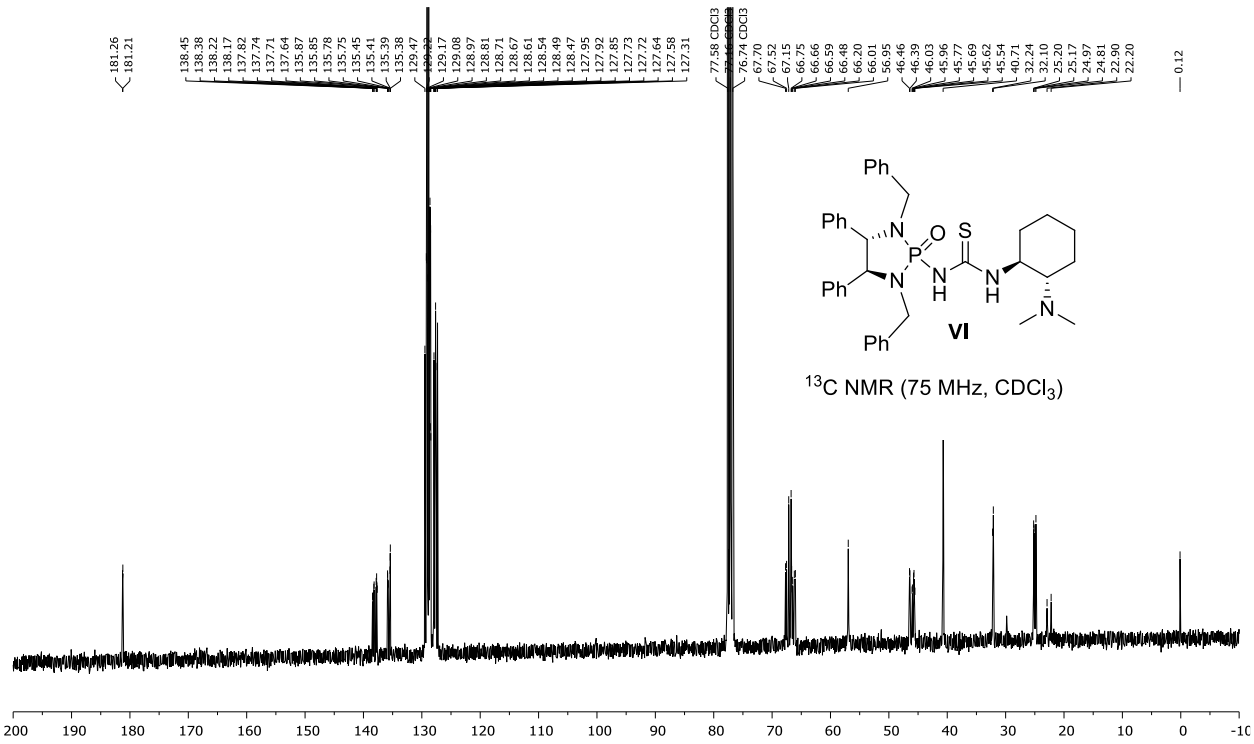

10.41
7.48
7.45
7.37
7.35
7.32
7.30
7.27
7.26
7.24
7.23
7.22
7.21
7.20
7.19
7.17
7.17
7.15
7.13
7.11
7.10
7.10
7.07
7.05
7.04
7.01
7.01
6.99
6.98
5.91
5.89
5.88
5.85
4.74
4.69
4.64
4.17
4.14
4.09
4.03
3.96
3.94
3.90
3.88
3.87
2.86
2.84
2.80
1.95
1.66
1.61
1.56
1.26
1.18
1.14
1.10
1.07
1.04
1.00
0.97
0.93
0.00
Ph
N
P
O
S
Ph
Ph
N
H
N
H
N
N
Ph
V
1H NMR (300 MHz, CDCl3)
0.99
2.11
5.80
13.50
1.00
1.01
2.01
2.12
2.10
6.00
4.84
4.61
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

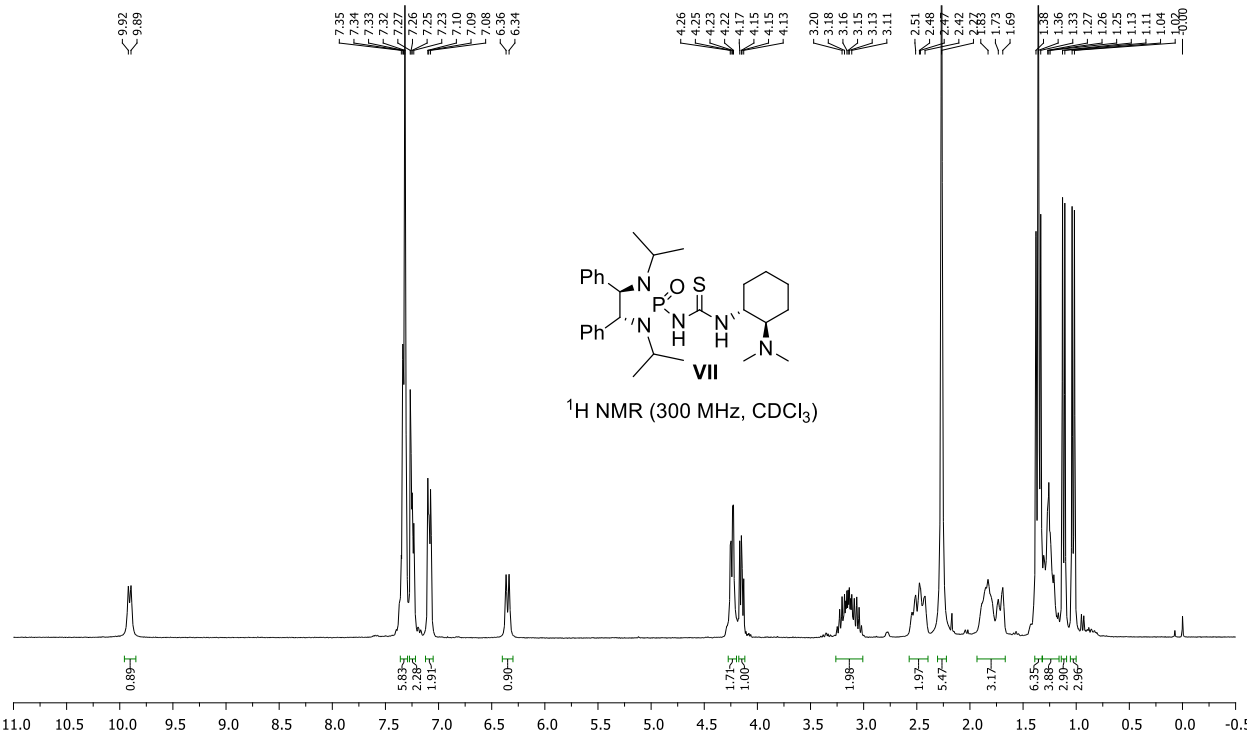


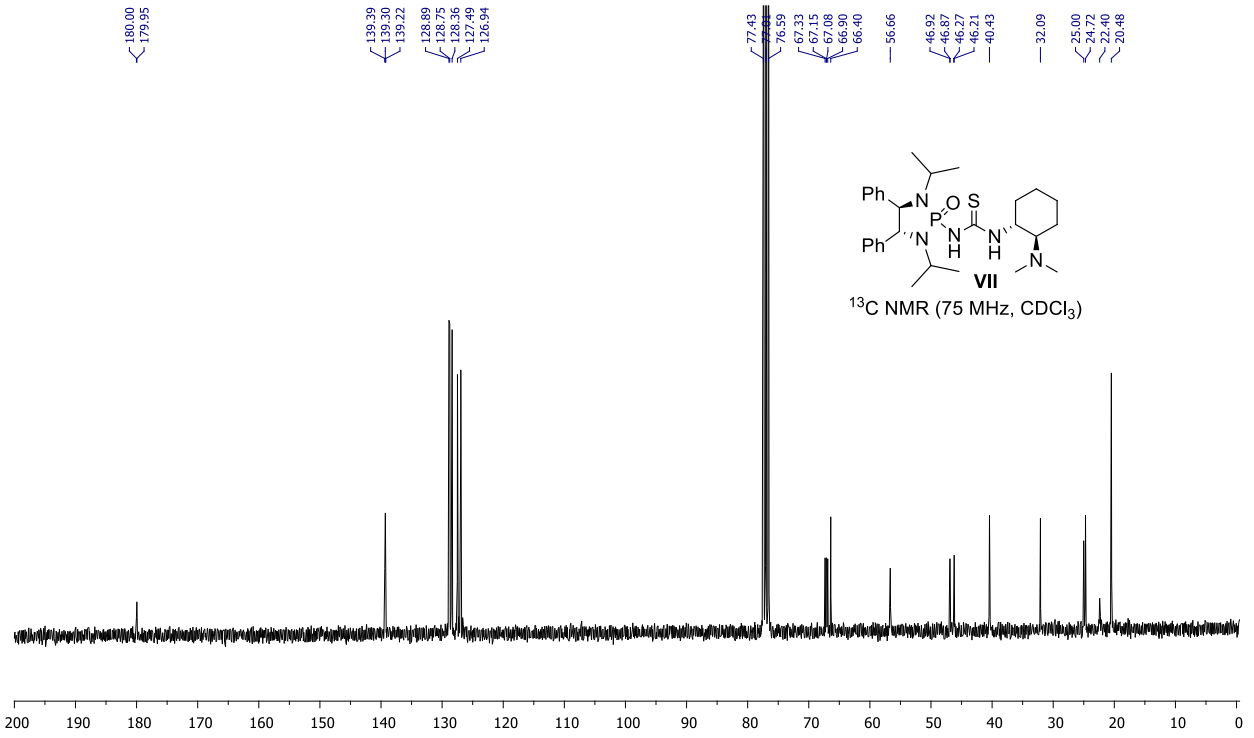
^{13}C NMR (75 MHz, $CDCl_3$)

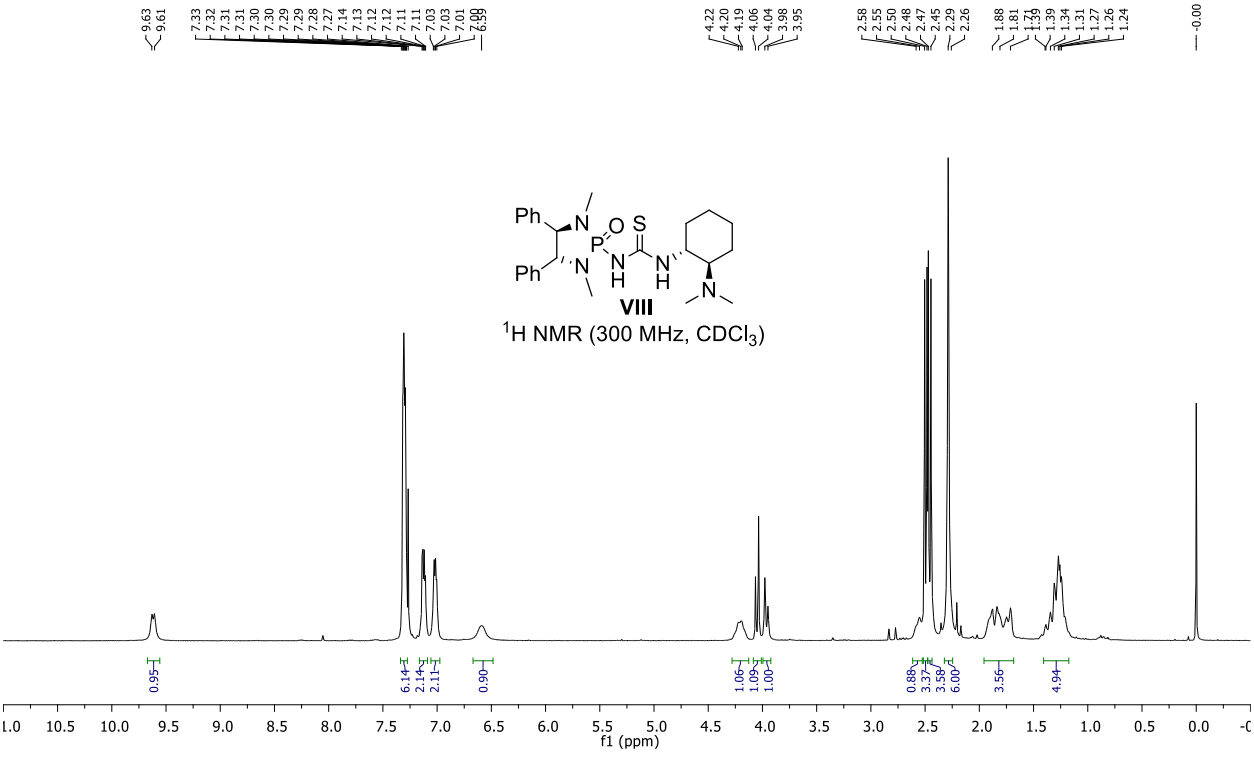


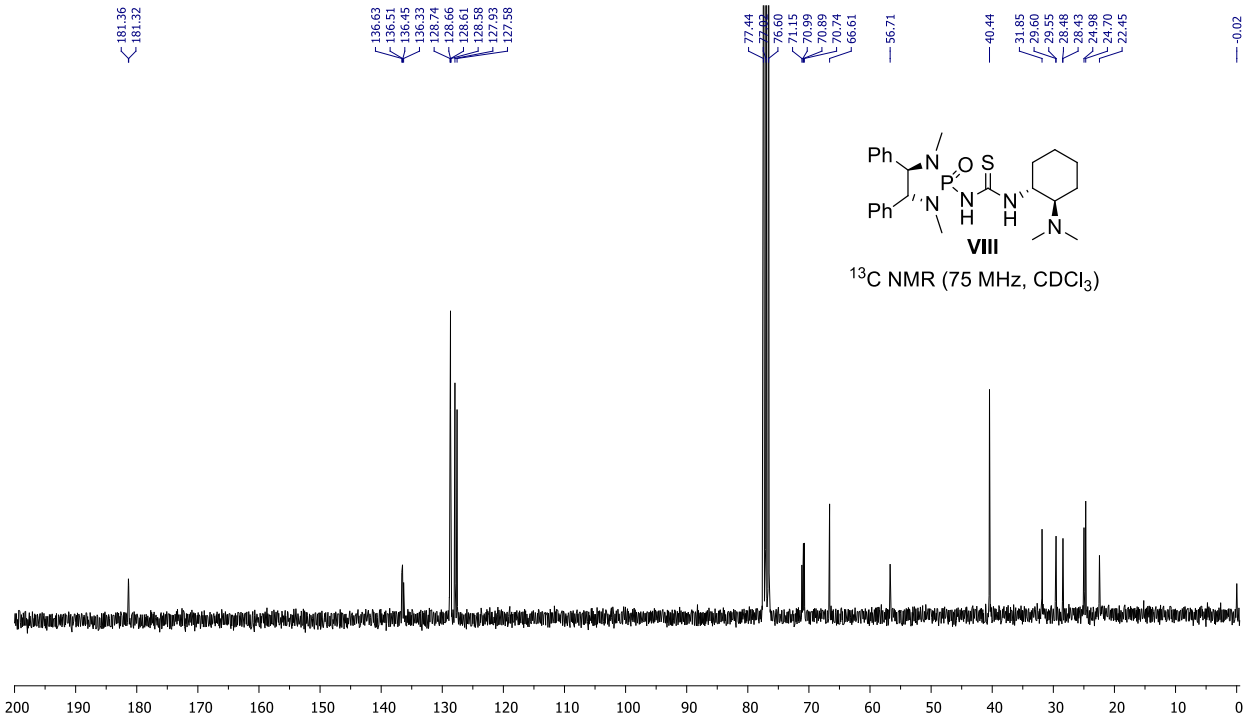
^{1}H NMR (500 MHz, $CDCl_3$)

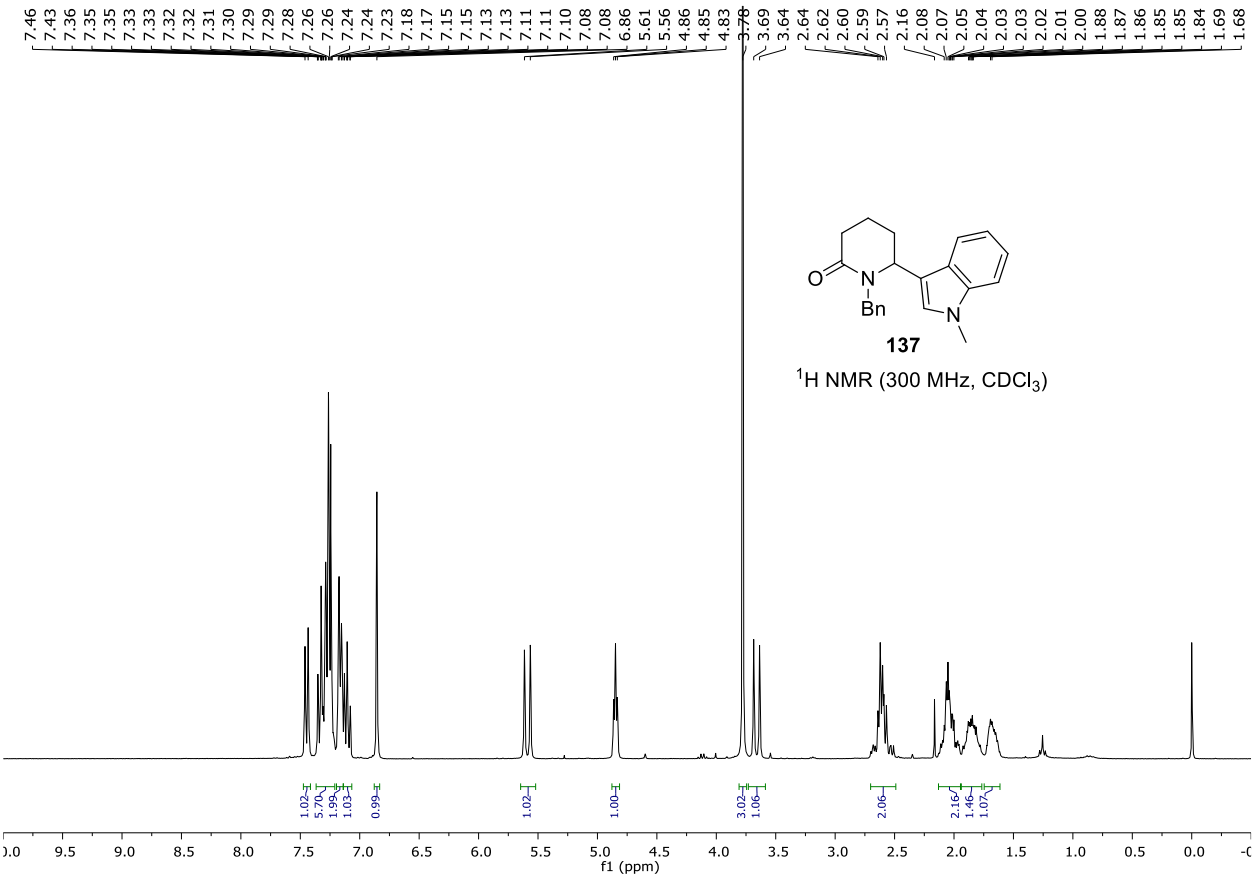

181.26
181.21
138.45
138.38
138.22
138.17
137.82
137.74
137.71
137.64
135.87
135.85
135.78
135.75
135.45
135.41
135.39
135.38
129.47
129.17
129.08
128.97
128.81
128.71
128.67
128.61
128.54
128.49
128.47
127.95
127.92
127.85
127.73
127.72
127.64
127.58
127.31
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
67.70
67.52
67.15
66.75
66.66
66.59
66.48
66.20
66.01
56.95
46.46
46.39
46.03
45.96
45.77
45.69
45.62
45.54
40.71
32.24
32.10
25.20
25.17
24.97
24.81
22.90
22.20
0.12
Ph
N
O
S
P
N
H
N
H
N
Ph
Ph
N
Ph
VI
13C NMR (75 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

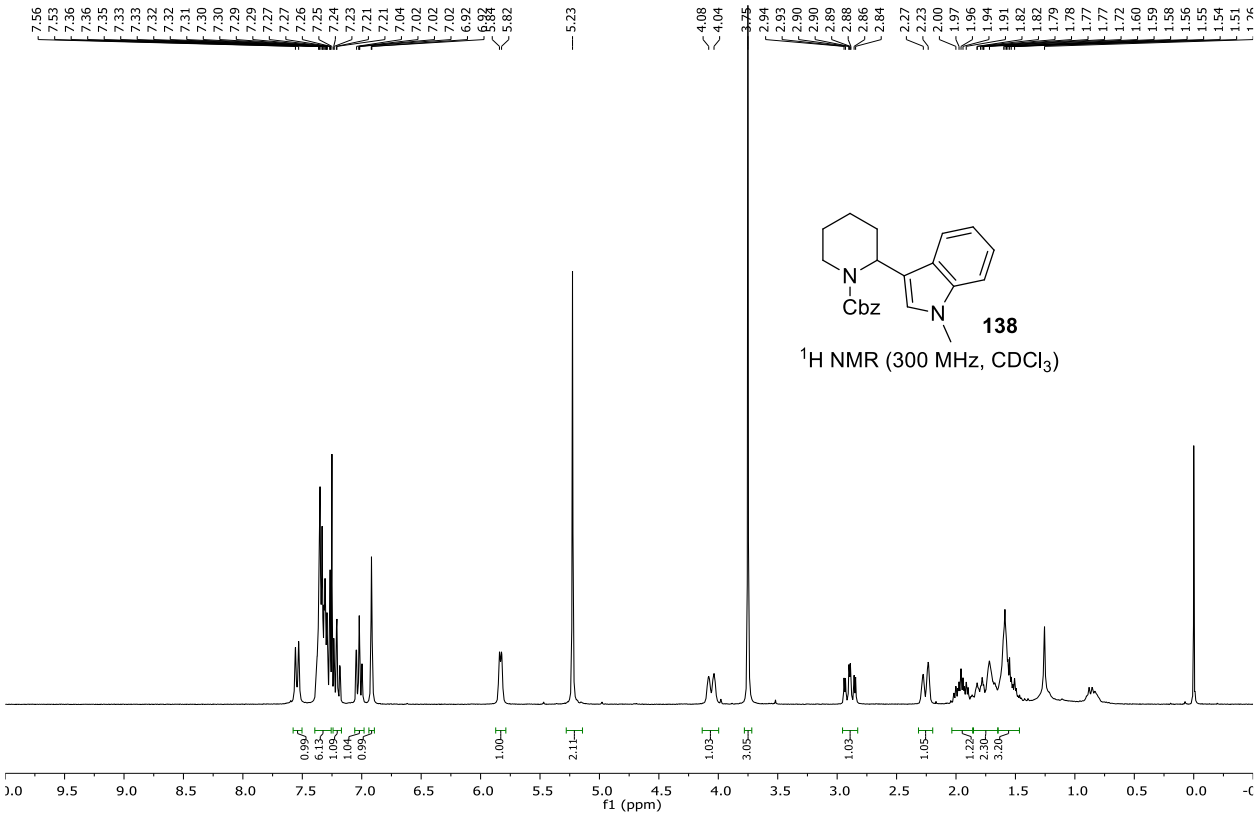

9.92
9.89
7.35
7.34
7.33
7.32
7.27
7.26
7.25
7.23
7.10
7.09
7.08
6.36
6.34
4.26
4.25
4.23
4.22
4.17
4.15
4.15
4.13
3.20
3.18
3.16
3.15
3.13
3.11
2.51
2.48
2.42
1.83
1.73
1.69
1.38
1.36
1.33
1.27
1.26
1.25
1.13
1.11
1.04
1.02
-0.00
0.89
5.83
2.28
1.91
0.90
1.71
1.00
1.98
1.97
5.47
3.17
6.35
3.88
2.90
2.96
Ph
N
O
S
P
N
H
N
H
N
Ph
N
VII
1H NMR (300 MHz, CDCl3)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


180.00
179.95
139.39
139.30
139.22
128.89
128.75
128.36
127.49
126.94
77.43
77.01
76.59
67.33
67.15
67.08
66.90
66.40
56.66
46.92
46.87
46.27
46.21
40.43
32.09
25.00
24.72
22.40
20.48
Ph
N
O
S
P
N
H
N
H
N
Ph
N
VII
13C NMR (75 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

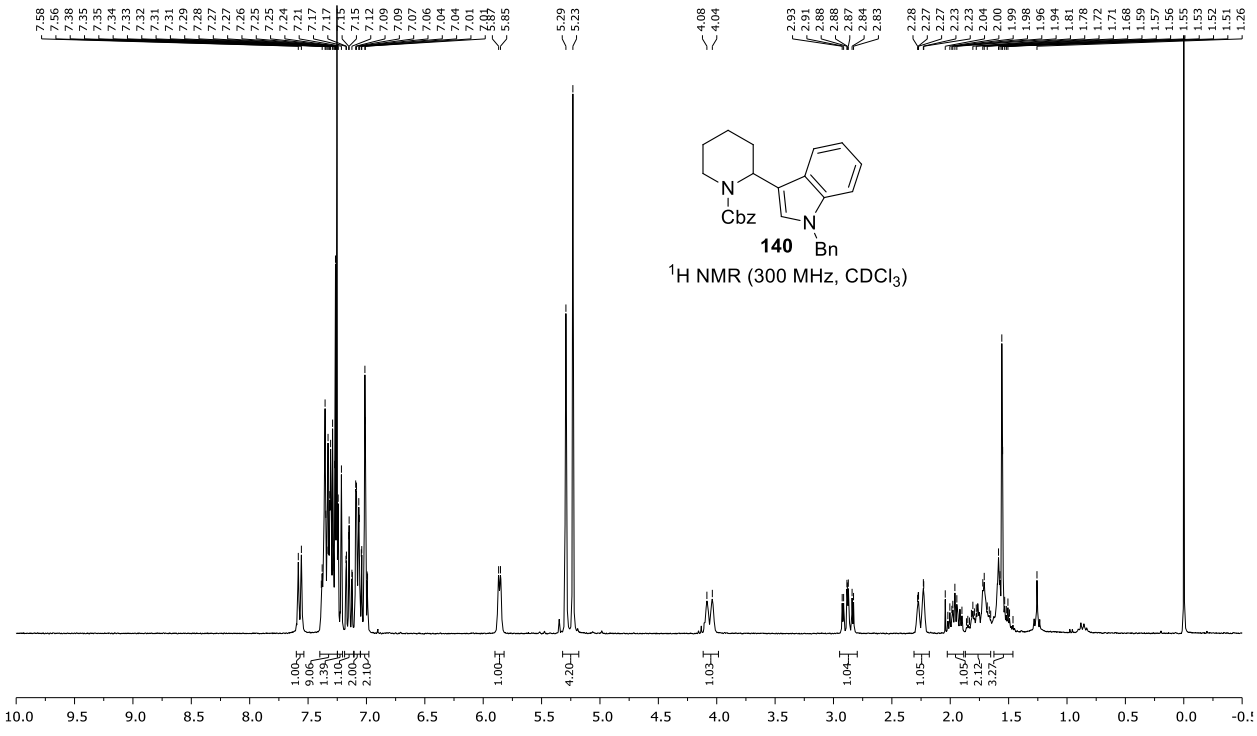

9.63
9.61
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.14
7.13
7.12
7.12
7.11
7.11
7.03
7.03
7.01
7.00
6.99
4.22
4.20
4.19
4.06
4.04
3.98
3.95
2.58
2.55
2.50
2.48
2.47
2.45
2.29
2.26
1.88
1.81
1.71
1.39
1.39
1.34
1.31
1.27
1.26
1.24
-0.00
Ph
N
O
S
P
N
H
N
H
N
Ph
N
VIII
1H NMR (300 MHz, CDCl3)
0.95
6.14
2.14
2.11
0.90
1.06
1.09
1.00
0.88
3.37
3.58
6.00
3.56
4.94
f1 (ppm)


181.36
181.32
136.63
136.51
136.45
136.33
128.74
128.66
128.61
128.58
127.93
127.58
77.44
76.60
71.15
70.99
70.89
70.74
66.61
56.71
40.44
31.85
29.60
29.55
28.48
28.43
24.98
24.70
22.45
-0.02
Ph
N
O
S
P
N
H
N
H
Ph
N
N
VIII
13C NMR (75 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

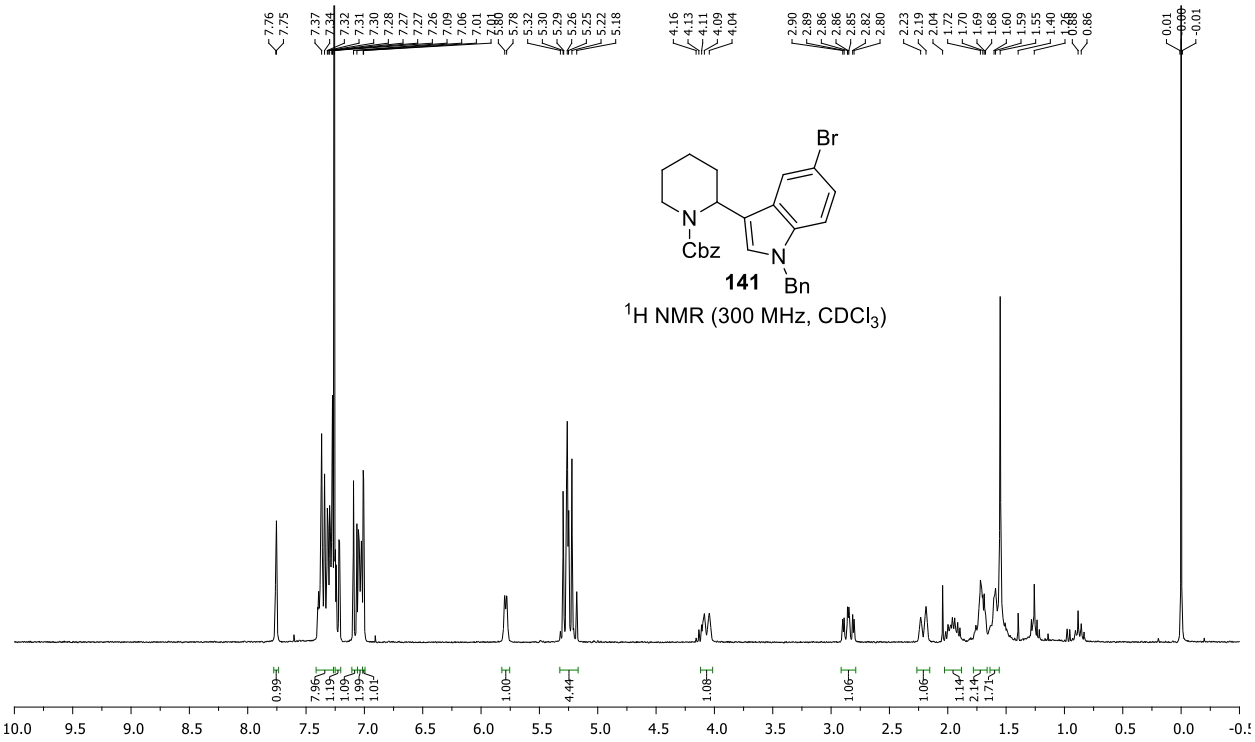

7.46
7.43
7.36
7.35
7.35
7.33
7.33
7.32
7.32
7.31
7.30
7.29
7.29
7.28
7.26
7.26
7.24
7.24
7.23
7.18
7.17
7.15
7.15
7.13
7.13
7.11
7.11
7.10
7.08
7.08
6.86
5.61
5.56
4.86
4.85
4.83
3.78
3.69
3.64
2.64
2.62
2.60
2.59
2.57
2.16
2.08
2.07
2.05
2.04
2.03
2.03
2.02
2.01
2.00
1.88
1.87
1.86
1.85
1.85
1.84
1.69
1.68
O
N
Bn
N
137
1H NMR (300 MHz, CDCl3)
1.02
5.70
1.99
1.03
0.99
1.02
1.00
3.02
1.06
2.06
2.16
1.46
1.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

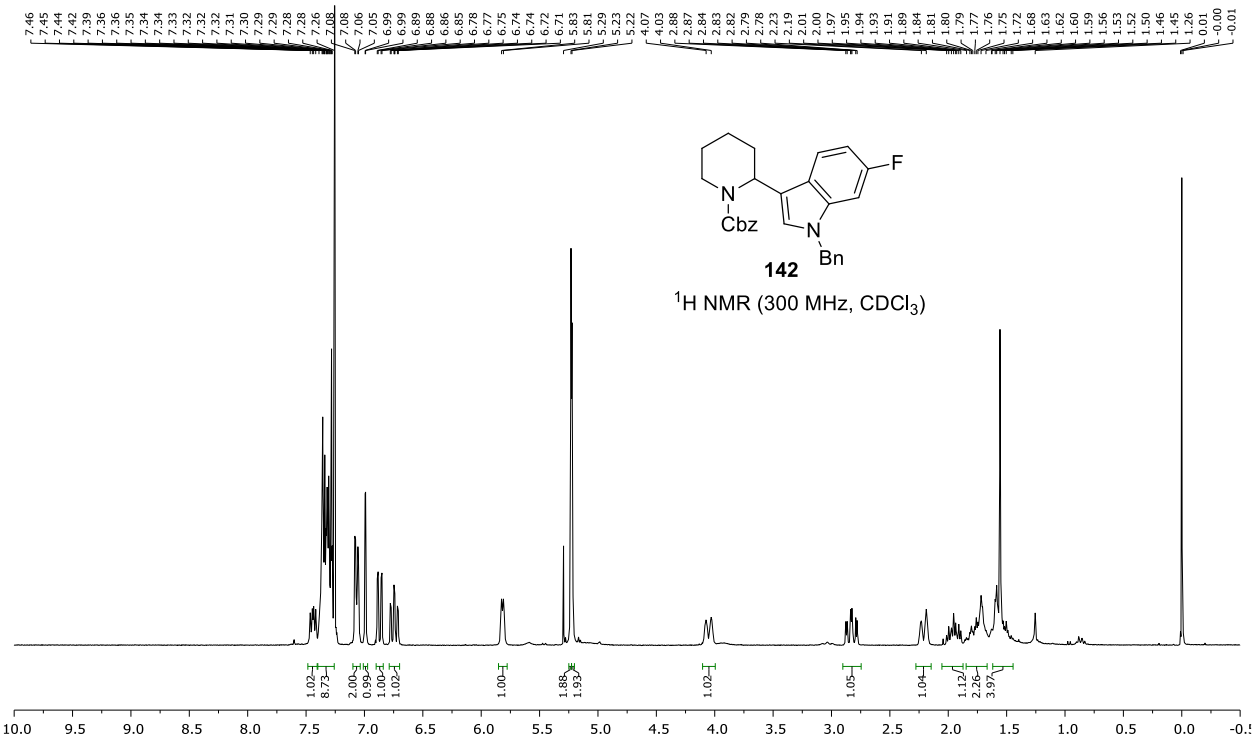


^{1}H NMR (300 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)


Br
N
Cbz
N
Bn
141
^{1}H NMR (300 MHz, $CDCl_3$)


F
N
Cbz
N
Bn
142
^{1}H NMR (300 MHz, $CDCl_3$)

1.11 Selected HPLC traces:

Memorial University

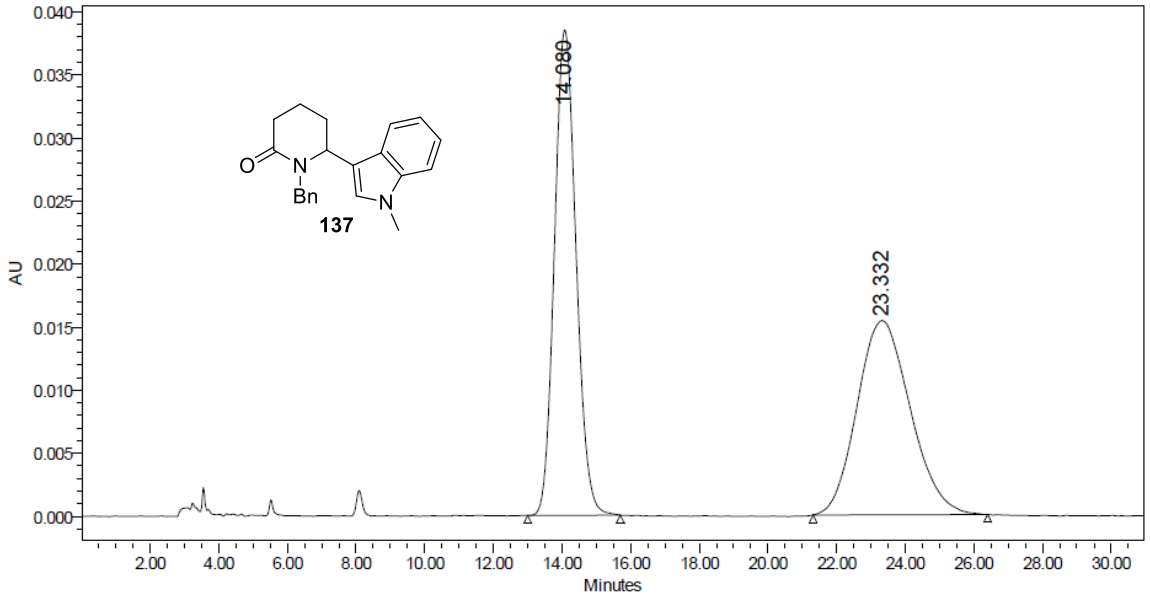
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-II-078 B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	17/06/2016 4:26:16 PM NDT
Vial:	1	Acq. Method:	AS_H 70%HEX 30%IPA
Injection #:	1	Date Processed:	17/06/2016 4:58:04 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.080	1680726	50.32	38476	71.41
2	23.332	1659192	49.68	15401	28.59

Report Method: Individual Control Report

Page: 1 of 1

Printed: 31/01/2020

3:38:13 PM Canada/Newfoundland

Memorial University

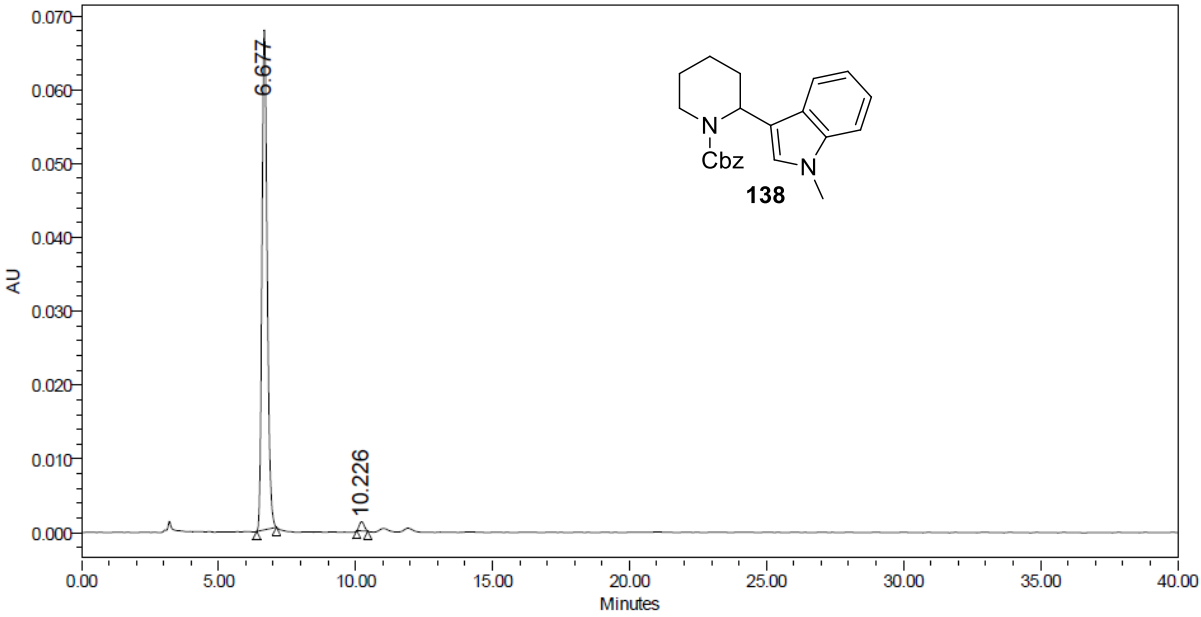
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-II-076A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	17/06/2016 11:25:25 AM NDT
Vial:	1	Acq. Method:	AS_H 80%HEX 20%IPA
Injection #:	1	Date Processed:	17/06/2016 12:06:01 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



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1	6.677	908108	98.33	67822	98.20
2	10.226	15382	1.67	1243	1.80

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	15/03/2017 6:05:25 PM NDT
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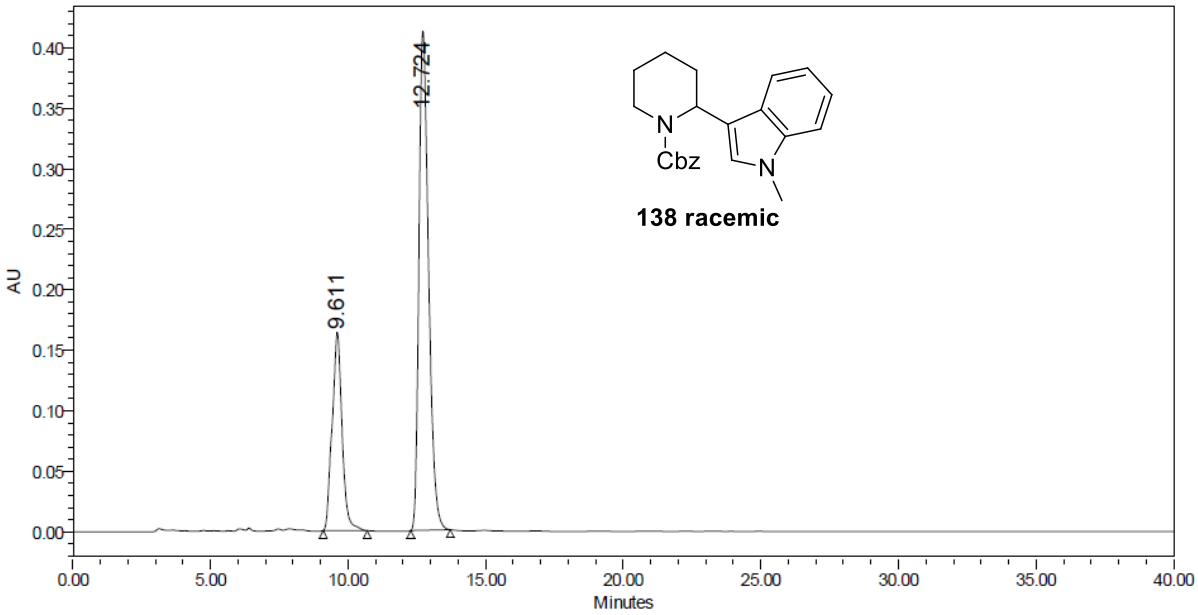

138 racemic

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	9.611	4111568	29.03	163605	28.38
2	12.724	10053225	70.97	412889	71.62

Memorial University

Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	13/03/2017 2:28:24 PM NDT
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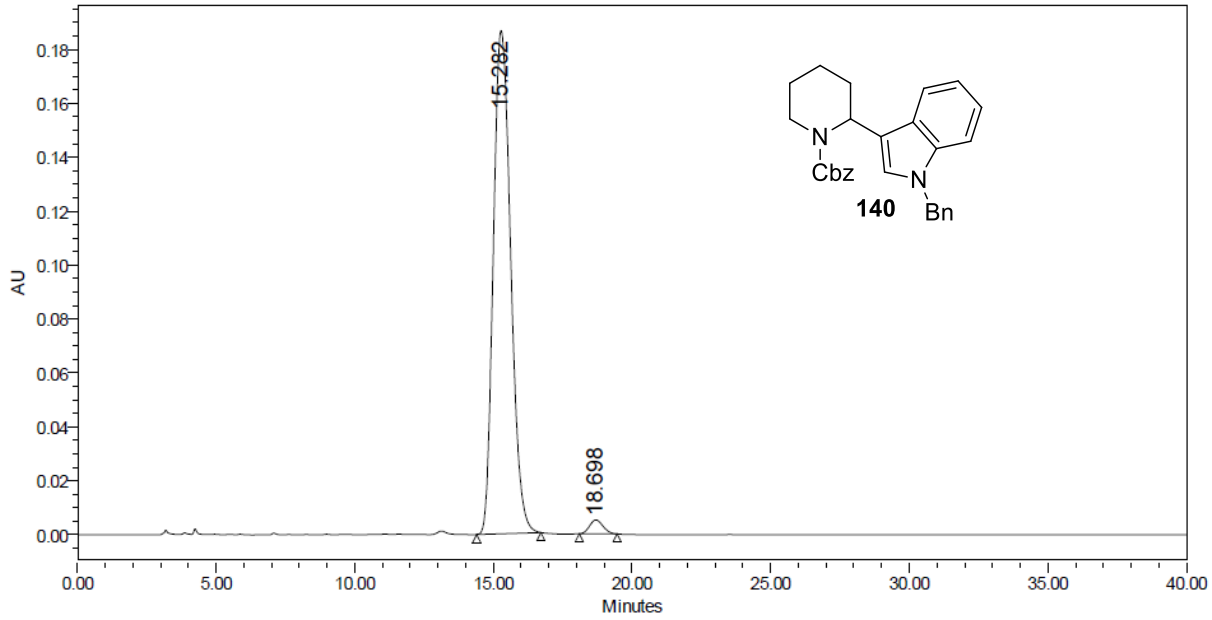

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.282	8100951	97.90	186697	97.31
2	18.698	174149	2.10	5163	2.69

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	15/03/2017 5:03:28 PM NDT
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Injection #:	1	Date Processed:	15/03/2017 5:43:17 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
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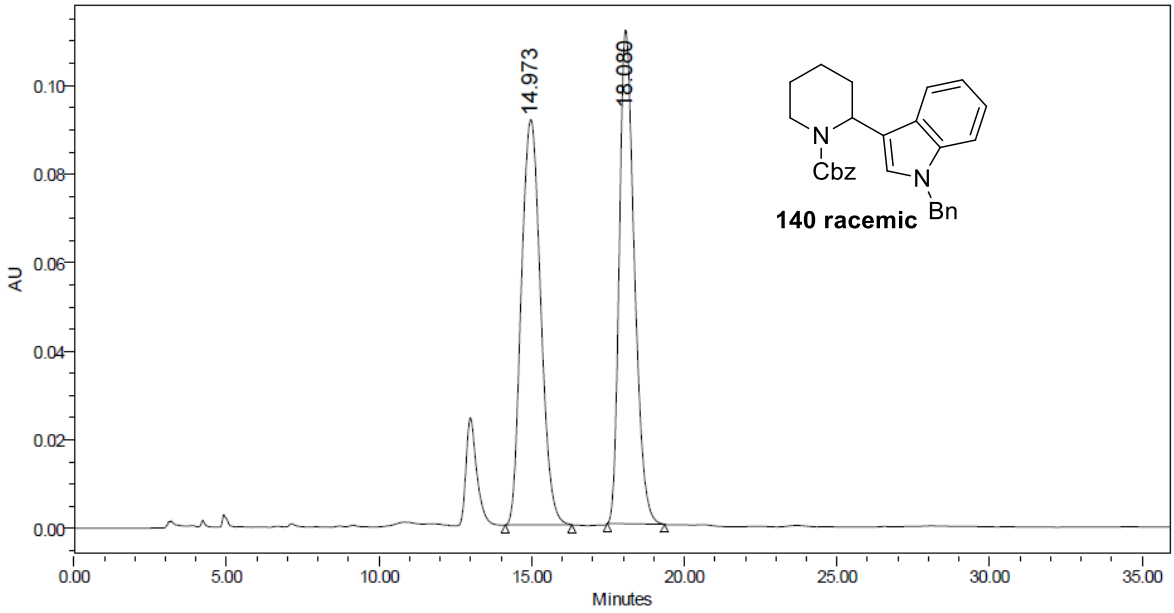

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.973	4033195	51.34	91559	45.09
2	18.080	3821950	48.66	111517	54.91

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	29/04/2017 3:55:10 PM NDT
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Injection #:	1	Date Processed:	31/01/2020 3:43:23 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
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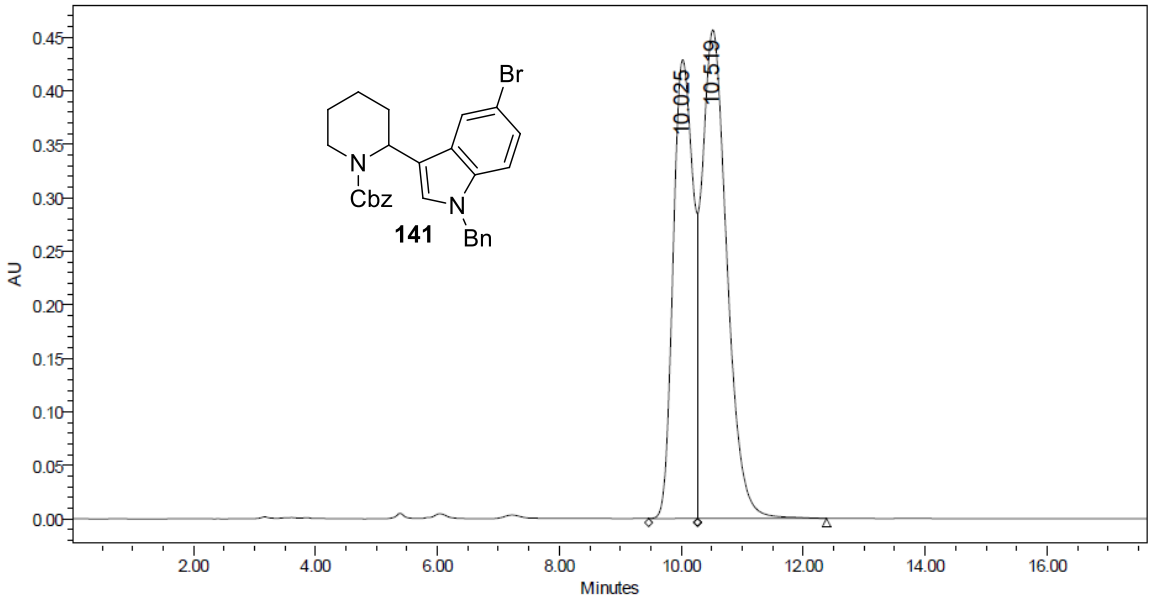


	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	10.025	9766787	42.65	428836	48.43
2	10.519	13133632	57.35	456571	51.57

Memorial University

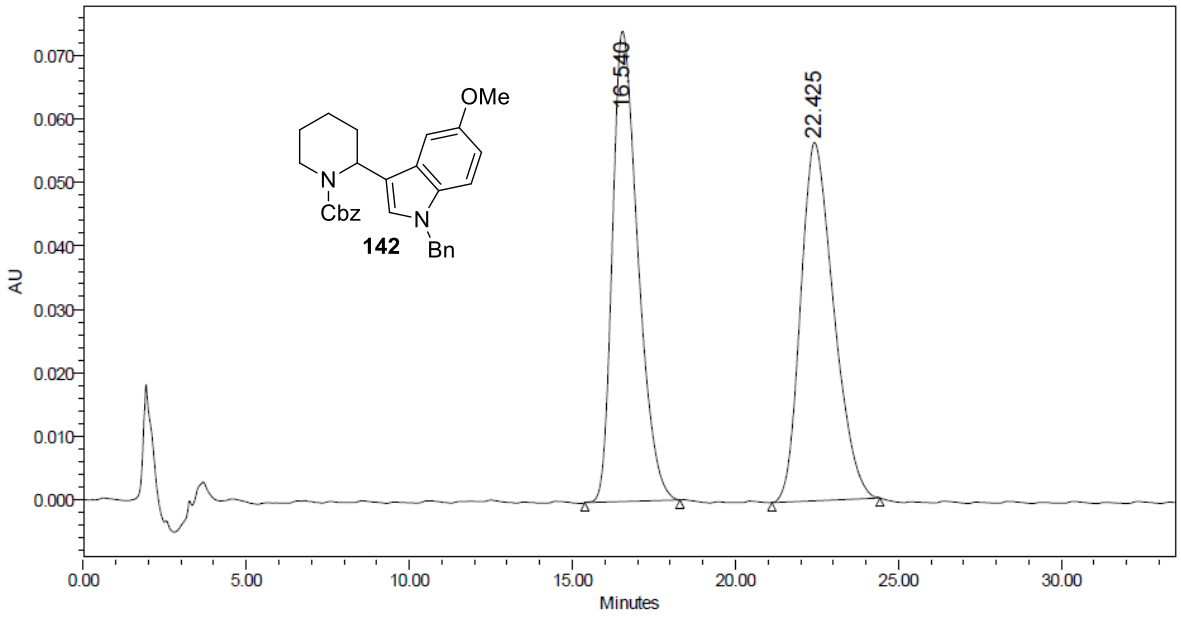
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-IV-121 A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	12/06/2017 3:44:27 PM NDT
Vial:	1	Acq. Method:	OD_H 90% hex 10% IPA
Injection #:	2	Date Processed:	12/06/2017 4:18:16 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.540	4025549	50.25	74165	56.76
2	22.425	3985246	49.75	56492	43.24

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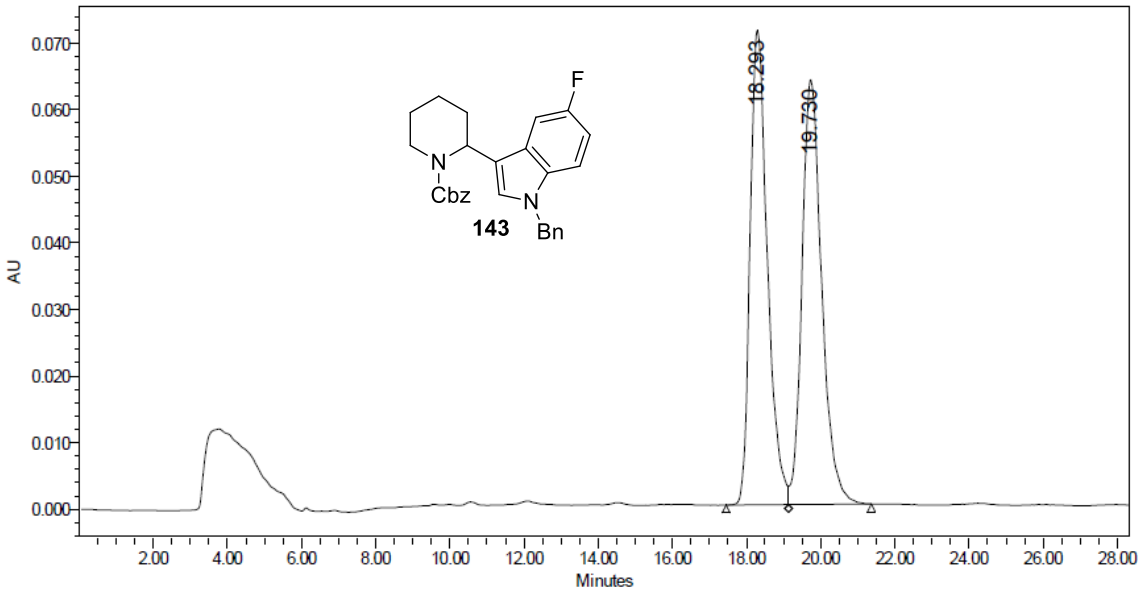
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-IV-113	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	06/06/2017 5:39:51 PM NDT
Vial:	1	Acq. Method:	AS_H 95% HEX 5% IPA
Injection #:	1	Date Processed:	11/02/2020 11:59:21 AM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.293	2308966	49.52	71295	52.79
2	19.730	2353600	50.48	63760	47.21

Memorial University

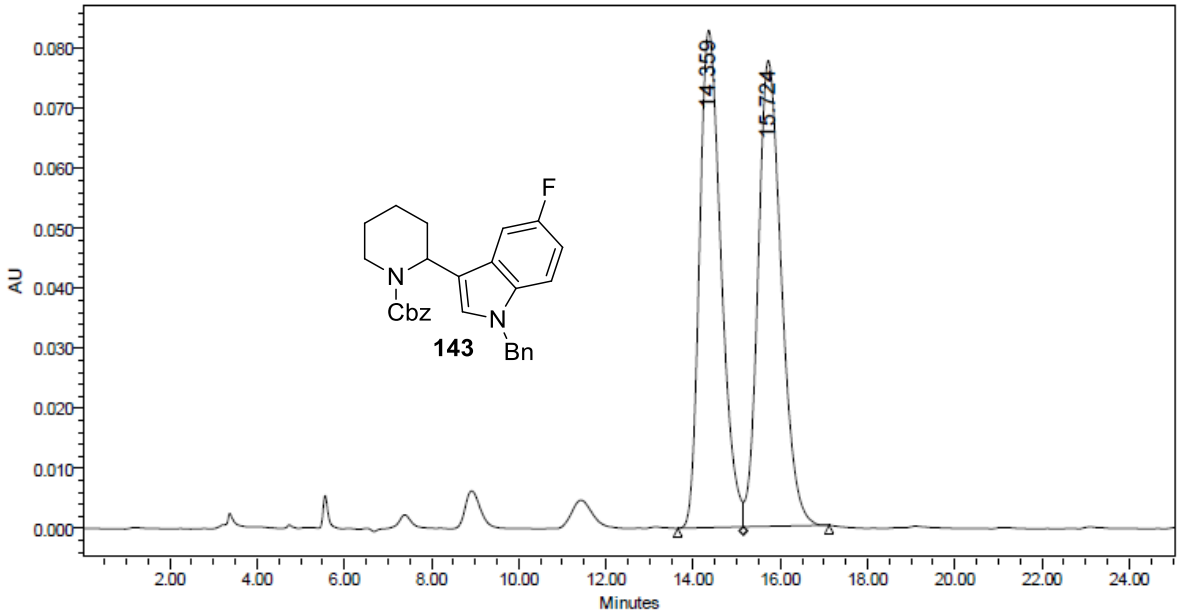
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-IV-115B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	08/06/2017 1:59:09 PM NDT
Vial:	1	Acq. Method:	AS_H 95% HEX 5% IPA
Injection #:	1	Date Processed:	11/02/2020 11:54:39 AM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.359	2852183	49.67	82974	51.64
2	15.724	2890513	50.33	77705	48.36

Memorial University

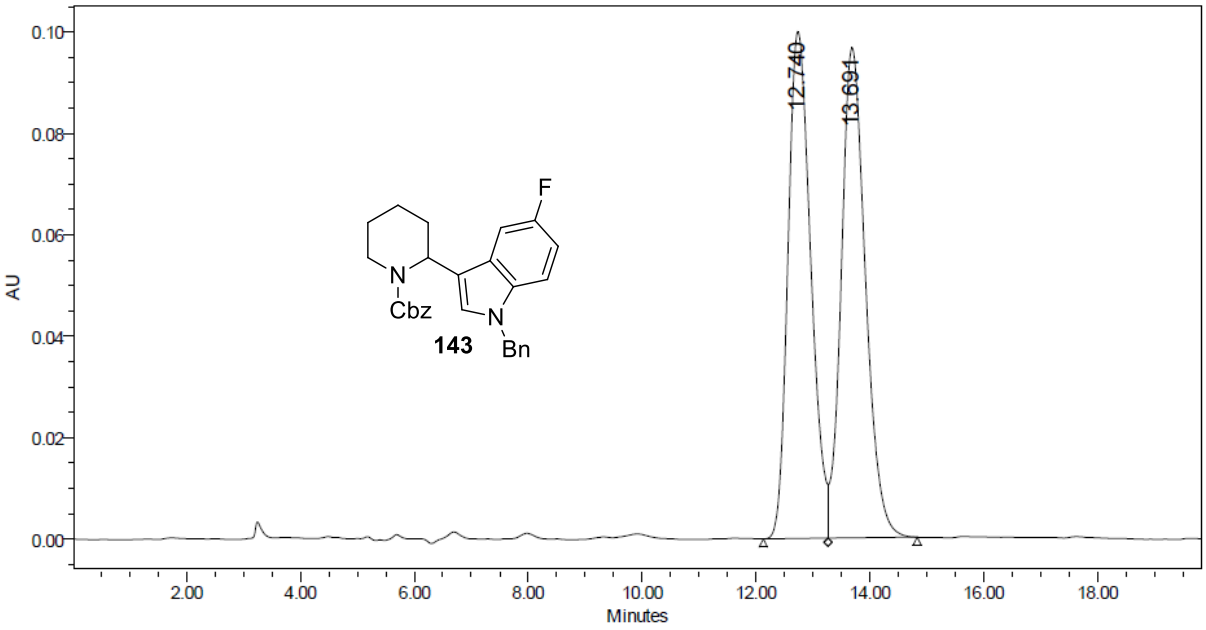
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-IV-131A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	19/06/2017 11:23:33 AM NDT
Vial:	1	Acq. Method:	AS_H 95% HEX 5% IPA
Injection #:	1	Date Processed:	19/06/2017 11:57:42 AM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.740	2778662	49.31	100066	50.84
2	13.691	2856784	50.69	96753	49.16

Chapter 2

Studies on the Organocatalytic Enantioselective Michael Addition of Cyclic Ketones and α, α-Disubstituted Aldehydes to α-Nitrostyrenes

The work described in this chapter has been published in Current Organocatalysis.

Annadate, R. A.; N. V. G., Moorthy; Pansare, S. V. *Curr. Organocatalysis*, **2018**, *5*, 66-73.

2.1 Introduction

Organocatalytic, asymmetric carbon-carbon and carbon-heteroatom bond forming reactions have been extensively investigated in recent years[1-5] and the organocatalyzed Michael addition reaction has attracted significant attention.[6-18] Within this category, the enamine mediated Michael addition reaction of ketones and aldehydes with nitroalkenes is particularly interesting since it generates two contiguous stereocenters in a single step. The synthetic utility of a variety of Michael acceptors has been documented, among which β-nitrostyrenes ((2-nitrovinyl) arenes) have been extensively investigated.[19] However, the isomeric α-nitrostyrenes ((1- nitrovinyl) arenes) have received very little attention, and there are only a few studies with α-nitroalkenes ((1-nitrovinyl)- alkenes) as Michael acceptors reported[20-22] in the literature.

In a broader context, the use of β-nitroalkenes as Michael acceptors in the stereoselective Michael addition reaction of various aldehyde or ketone nucleophiles is subject to 1,2-asymmetric induction (generation of α, β or β, γ stereocenters) whereas the stereoselective Michael addition of an aldehyde or a ketone nucleophile to an α-nitrostyrene is subject to 1,3 asymmetric induction (generation of α, γ stereocenters, Figure. 2.1).

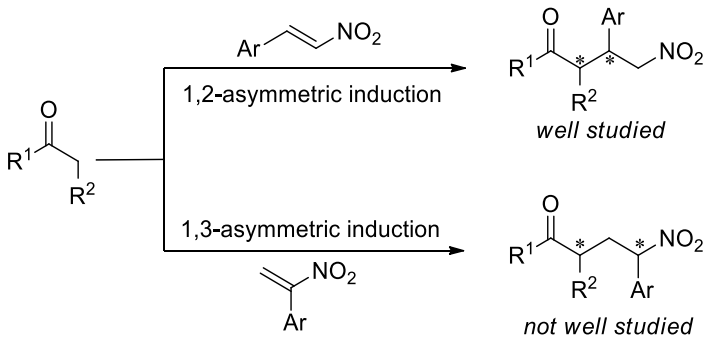


Figure 2.1. Organocatalytic 1,2 and 1,3-asymmetric induction in nitrostyrene Michael addition reactions.

In contrast to catalytic 1,2 asymmetric induction (generation of α, β or β, γ stereocenters), catalytic versions of 1,3-asymmetric induction processes are less established (Figure 2.1), and all of the recent efforts are directed towards the construction of γ-quaternary stereocenters.[23-31]

This chapter describes the enamine-mediated enantioselective organocatalytic Michael addition reaction of cyclic ketones and α,α- disubstituted aldehydes to α-nitrostyrenes, involving the enantioselective protonation of a nitronate as the crucial step.

2.2 Objective:

The conjugate addition of carbonyl compounds to nitroalkenes provides synthetically useful γ-nitroketones that have numerous applications in the synthesis of complex synthetic targets.[32] This reaction has been exhaustively investigated with β-nitrostyrenes as the Michael acceptors but the use of α-nitrostyrenes, for establishing non-adjacent stereocenters in the product, is not well studied (Figure 2.1). The aim of this study was to investigate the organocatalytic asymmetric, enamine mediated, Michael addition reaction of cyclic ketones and α,α-disubstituted aldehydes to *in-situ* generated α-nitrostyrenes and to optimize the diastereoselectivity and the enantioselectivity of the reaction. (Figure 2.2)

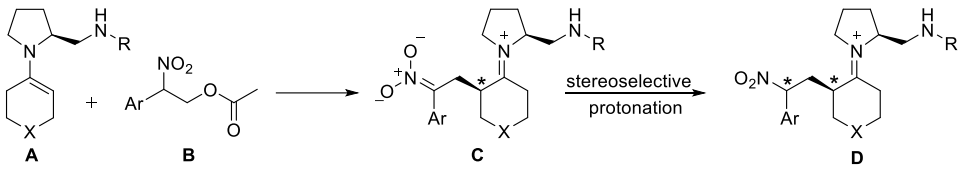


Figure 2.2 Enamine mediated Michael addition reaction of carbon nucleophiles and α-nitrostyrenes

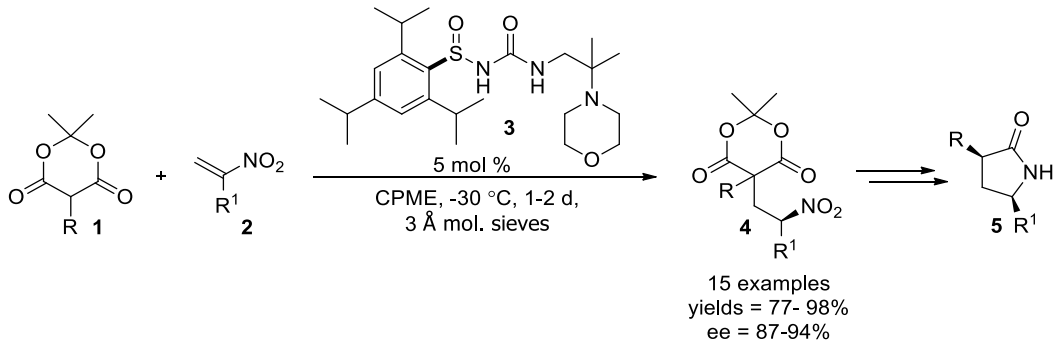
The nitro group in the Michael adduct is particularly versatile as it may be transformed into various functionalities. The conversion of a nitroalkane into a carbonyl compound by Nef reaction

or into a hydroxylamine or an amine by reduction are widely used transformations in organic synthesis. In addition, nitro compounds are also good precursors for various nitrogen-containing organic compounds such as nitriles, oximes, and imines. One such potential use of γ-nitroketone adducts derived from the addition of aliphatic aldehydes to α- nitrostyrenes is their conversion into chiral functionalized pyrrolidines.[33]

2.3 Literature Survey

The Michael addition reaction of cyclic ketones and aldehydes has been exhaustively investigated with β-nitrostyrenes as the Michael acceptors but the use of α-nitrostyrenes, for establishing nonadjacent stereocenters in the product, was not well established when we started our investigations. As noted previously, there are only a few studies on the organocatalytic Michael addition to α-nitroalkenes. In addition, all of these studies were done with α-alkyl-α-nitroalkenes and the α-aryl analogues were not examined. The following is a brief summary of previous studies on the organocatalytic Michael addition of carbon nucleophiles to α-alkyl-α-nitroalkenes these.

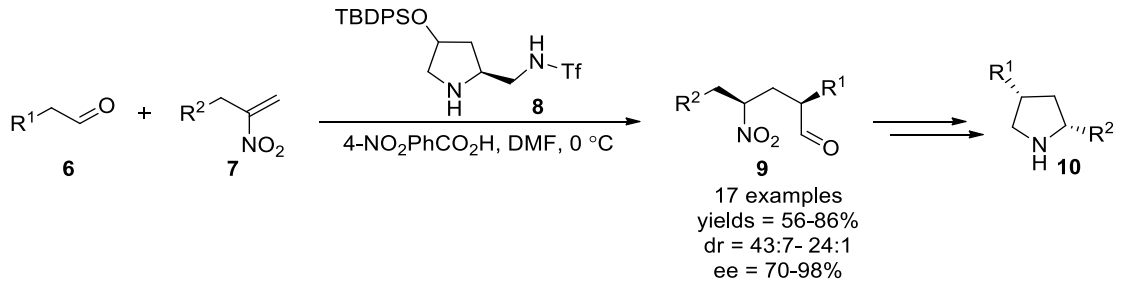
In 2012, Ellman and co-workers[20] reported the enantio- and diastereoselective addition of α-substituted Meldrum's acid **1** to α-substituted nitroalkenes **2** followed by kinetic protonation of the nitronate addition product to provide **4** in good yields (77-98%) and high enantioselectivity (87-94%, Scheme 2.1).



Scheme 2.1

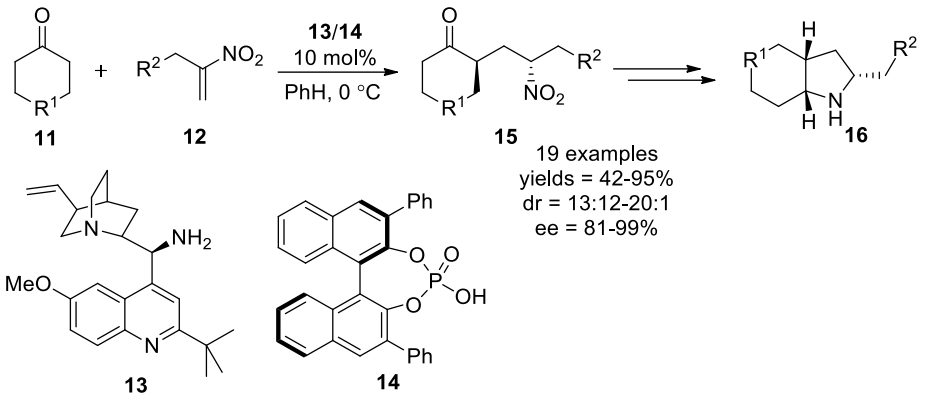
The catalyst of choice was the *N*-sulfinyl urea **3** which has chirality at sulfur. The addition products **4** were readily converted to pharmaceutically relevant 3,5-disubstituted pyrrolidinones **5** in high yield.

In 2013, Peng and co-workers[21] reported the first organocatalytic asymmetric Michael addition of aldehydes **6** with a series of α-substituted nitroolefins **7** by using the (*S*)-proline derived catalyst **8** (Scheme 2.2). The γ-nitro aldehydes **9** were formed with good yields and good diastereo- and enantioselectivity. Reduction of the nitro group followed by intramolecular reductive amination successfully afforded various optically active 2,4-disubstituted pyrrolidines **10**.



Scheme 2.2

In 2015, Peng and co-workers[22] also reported the use of a binary catalytic system involving the combination of a quinine-based chiral primary amine **13** with a 3,3'-diphenyl BINOL-derived phosphoric acid **14** in the asymmetric Michael addition of a series of cyclic ketones **11** to nitroalkenes **12** (Scheme 2.3). The resulting Michael addition adducts **15** were transformed into chiral octahydroindoles **16** which are potentially biologically active.



Scheme 2.3

2.4 Results and Discussion

Our investigations began with the Michael addition reactions of various ketones with *in situ* generated α-nitrostyrenes. We noted that α-nitrostyrenes such as **18** are reported to be unstable and they can undergo polymerization[34] and or isomerization[35] to the more stable β-nitrostyrenes. These undesired processes are generally not an issue with β-nitrostyrenes. We therefore chose to generate α-nitrostyrenes **18** *in situ* from stable precursors (the corresponding nitroacetates **17**, Figure 2.3) rather than attempting to isolate them (Figure. 2.3).

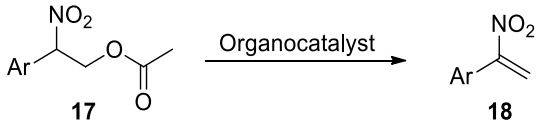
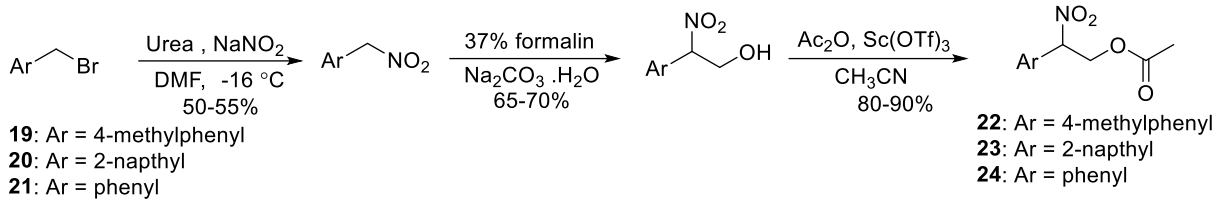


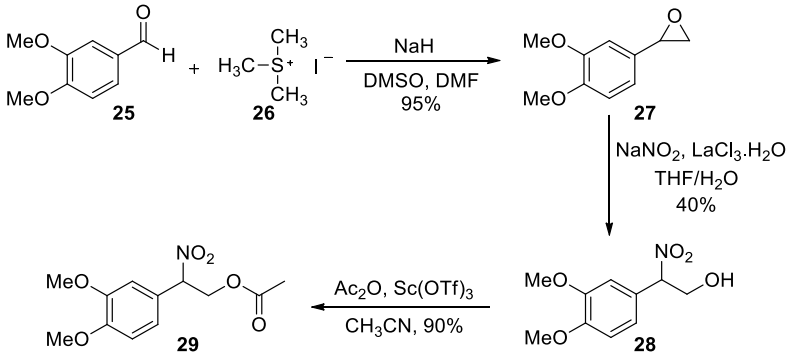
Figure 2.3 α-nitrostyrene generated *in situ* from the corresponding nitroacetate **17**

The nitroacetates used in this study were synthesized from commercially available aryl bromides using reported procedures. Substitution reactions of the aryl bromides **19-21** with $NaNO_2$ provided the corresponding nitro compounds[36] which underwent a nitroaldol reaction in the presence of Na_2CO_3 and 37% formalin solution[37] to afford the nitro alcohols in 65-70% yield. The nitro alcohols were subjected to acetylation with acetic anhydride in the presence of scandium triflate to afford the nitroacetates **22-24** in 80-90% yield (Scheme 2.4).



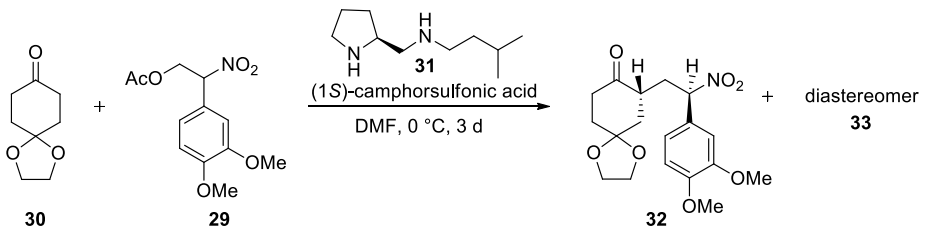
Scheme 2.4

The synthesis of nitroacetate **29** was achieved by an alternative method. The reaction of commercially available veratraldehyde (**25**) with the sulfur ylide derived from trimethylsulphonium iodide (**26**) following the Corey-Chaykovsky protocol provided the epoxide **27**. Regioselective ring opening of the epoxide with $NaNO_2$ provided the nitro alcohol **28**. Acetylation of **28** in the presence of scandium triflate afforded nitroacetate **29** in 90% yield.



Scheme 2.5

In previous studies conducted in the Pansare group,[38] the Michael addition of the cyclic ketone **30** to the α-nitrostyrene generated *in-situ* from nitroacetate **29** was selected as the model reaction for determining the optimum reaction conditions. After conducting a brief solvent survey,[38] catalyst and co-catalyst screening, it was determined that the best result was obtained with the diamine catalyst[38] **31** and (1*S*)-camphorsulfonic acid in DMF at ambient temperature. The γ-nitroketone adduct **32** obtained was used in the synthesis of quinolizidine based alkaloids such as (+)-lasubine II and (−)-subcosine II, in the Pansare group.[38] The absolute configuration of **32** was assigned by X-ray crystallographic analysis.[38]



Scheme 2.6

Based upon the conditions developed previously in our group for the Michael addition reaction of ketone **30**, the utility of diamine catalyst **31** was examined for the Michael addition reaction of a variety of cyclic (6-membered) ketones **30**, **34-36** with for α-nitrostyrene precursors **22** and **23** (Figure. 2.4).

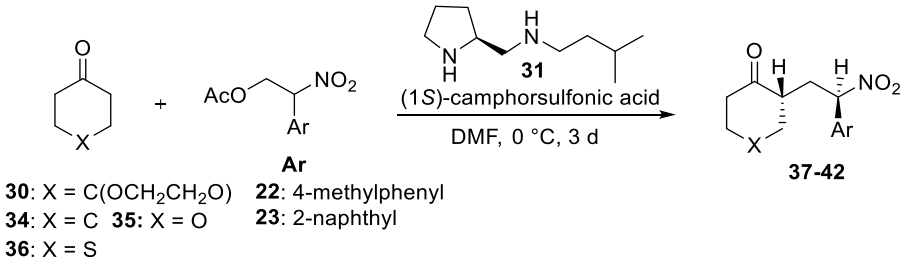
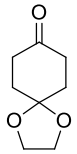
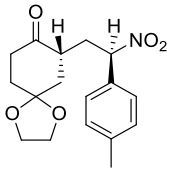
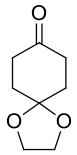
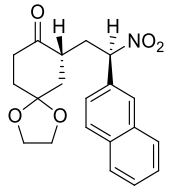
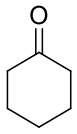
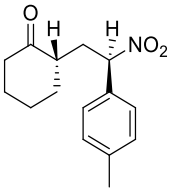
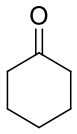
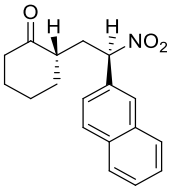
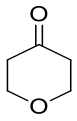
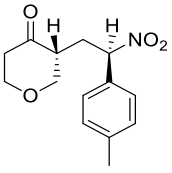
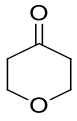
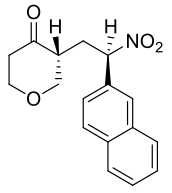
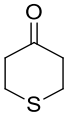
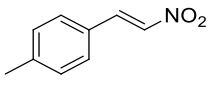
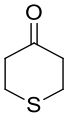
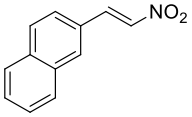


Figure 2.4 Organocatalyzed reaction of ketones **30**, **34-36** and 2-nitro-2-arylethyl acetates **22** and **23**

These reactions proceeded efficiently with moderate diastereoselectivity (1:1 to 1.9:1) but the major diastereomers **37-42** were easily isolated by flash column chromatography and were obtained in moderate to good enantiomeric excess (59-89%) as shown in Table 2.1.

Table 2.1 Results of organocatalytic Michael addition of a variety of cyclic ketones to *in-situ* generated α-nitrostyrenes

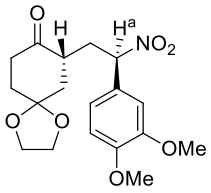
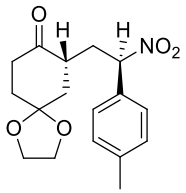
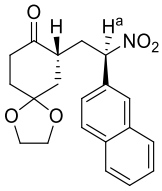
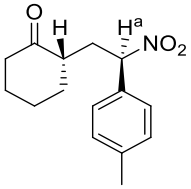
Entry *a*	Cyclic ketones	Nitroacetate precursor	Product	Yield [b] (%)	dr [c]	ee [d] (%)
1	 **30**	**22**	 **37**	46	1.9:1	89
2	 **30**	**23**	 **38**	43	1:1	86
3	 **34**	**22**	 **39**	26	1.3:1	69
4	 **34**	**23**	 **40**	34	1.3:1	76
5	 **35**	**22**	 **41**	43	1:1	69
6	 **35**	**23**	 **42**	28	1.3:1	59
7	 **36**	**22**	 **43**	90[e]	-	-

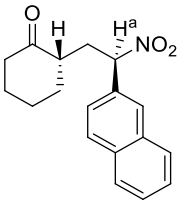
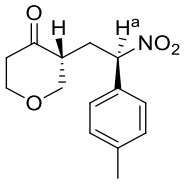
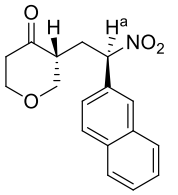
8	 **36**	**23**	 **44**	90[e]	-	-

[a] All reactions were done in DMF for 72 h at 0 °C with 5 equiv of ketone. [b] Isolated yields.
[c] Determined by ^{1}H NMR of crude product. [d] Chiral HPLC analysis. [e] Yield of crude product.

The stereochemistry of the major γ-nitroketone product is assigned by the observed trend in chemical shift, multiplicity and the coupling constants of the distinctive benzylic proton H[a] in **37-42** by comparison to that for **32** as shown in Table 2.2.

Table 2.2 Chemical shift, multiplicity and the coupling constants of the benzylic proton H[a] in the γ-nitroketone product.

Entry	Product	δ H[a] (ppm)	Multiplicity	Coupling constants
1	 **32**	5.63	dd	(*J* = 10.3, 4.4 Hz)
2	 **37**	5.66	dd	(*J* = 10.2, 4.4 Hz)
3	 **38**	5.85	dd	(*J* = 10.2, 4.1 Hz)
4	 **39**	5.65	dd	(*J* = 10.0, 4.5 Hz)

5	 **40**	5.87	dd	(*J* = 10.1, 4.5 Hz)
6	 **41**	5.66	dd	(*J* = 10.1, 4.7 Hz)
7	 **42**	5.87	dd	(*J* = 10.1, 4.6 Hz)

The highest levels of diastereoselectivity and enantiomeric excess are obtained with the ketone **30** which suggests that the spirocyclic ring system is beneficial for stereoselectivity (entries 1 and 2, Table 2.1). The Michael addition reaction of cyclic ketone **36** with different precursors of α-nitrostyrenes was unsuccessful and significant amounts of the isomerized nitroalkenes **43** and **44** were obtained in these reactions. This rearrangement was not observed in any of the other reactions described in Table 2.1. Overall, the organocatalytic Michael addition of cyclic, six-membered ketones with *in situ* generated α-nitrostyrenes gave the required products with good yield, moderate diastereoselectivity and enantioselectivity. A mechanism that explains the formation of **32** and **33** is proposed in Figure. 2.5.

It is plausible that the Michael addition of the enamine, derived from **30** and the catalyst **31**, to the α-nitrostyrene derived from **29** proceeds *via* the hydrogen-bonded [39] intermediate **E** (Figure 2.5) in which the nitroalkene is delivered to the *re*-face of the enamine (Figure 2.5, Path **I**). This step establishes the α-stereocenter in the ketone as *R*, and it probably generates the 1,2-

oxazine *N*-oxide intermediate **F**. Similar intermediates have been characterized[40,41] in stoichiometric reactions of achiral enamines with α-nitrostyrenes. Subsequent opening of the oxazine produces the nitronate **G**, which is protonated stereoselectively to generate **H** which has the *R* benzylic stereocenter in **32**. The reason for the high stereoselectivity of the protonation of **G**, which leads to the formation of *R*,*R*-**32**, is not known at present.

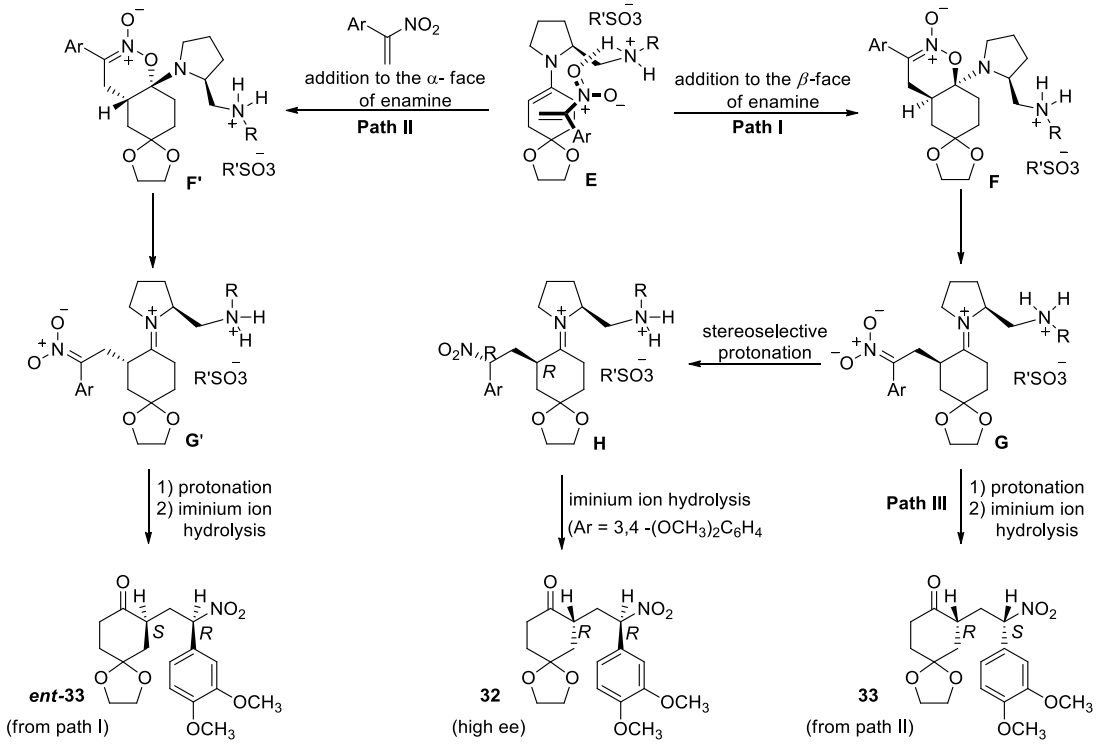


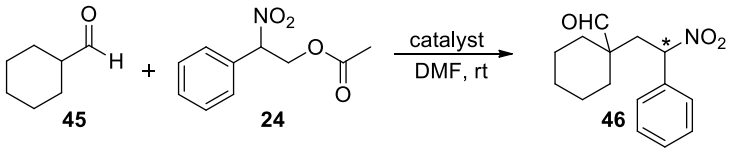
Figure 2.5 Formation of the γ-nitro ketone **32** and **33** from **30** using the catalyst **31**

However, since one of the stereocenters is established prior to the protonation step, the observed influence of the chirality of the acid additive on the stereoselectivity of protonation is reasonable. The low diastereoselectivity of the Michael addition may be due to two reasons: 1) the inherently high reactivity of the α-nitrostyrene enables a competing non-hydrogen-bonded addition to the *si*-face of the enamine to generate intermediate **F'** (Figure. 2.5, Path **II**) which, *via* **G'**, would provide ***ent*-33** with *S* stereochemistry at the ring stereocenter, and 2) the unselective protonation of intermediate **G** (Figure. 2.5, Path **III**) provides a small amount of **33** with *S* stereochemistry at the

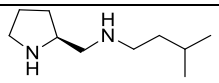
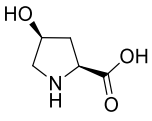
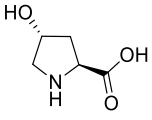
benzylic stereocenter. Although the factors that control the formation of **33** and ***ent*-33** are not known at this time, the low enantiomeric excess of **33** suggests that both Path **II** and Path **III** (Figure. 2.5) are operative. It should also be noted that previous studies in the Pansare group[38] had determined that the initial Michael addition step is not reversible under the reaction conditions.

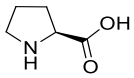
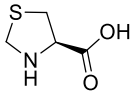
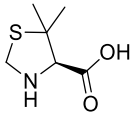
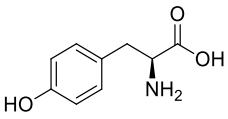
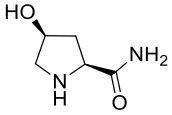
Having established the feasibility of the Michael addition of cyclic ketones to *in situ* generated α-nitrostyrenes, we investigated the Michael addition reaction of symmetrical α,α-disubstituted aldehydes to *in situ* generated α-nitrostyrenes. Symmetrical α,α-Disubstituted aldehydes were used as the nucleophilic component in order to avoid the formation of diastereomeric Michael addition products. It was noticed that the diamine **31**, which is the best catalyst for the reactions with ketones, was not useful for the Michael additions of cyclohexane carboxaldehyde **45** to α-nitrostyrene obtained *in situ* from **24** (entry 1, Table 2.3). Consequently, a survey of chiral amines was conducted for this reaction as shown in Table 2.3.

Table 2.3 Catalyst screening for the organocatalytic Michael addition of aldehydes to *in situ* generated α-nitrostyrenes



45 24 46

Entry	Catalyst	Time	Yield (%)	ee (%)
1	 **31**	3d	-	-
2	 **47**	2d	45	60
3	 **48**	3d	32	50

4	 **49**	16 h	43	70
5	 **50**	8d	-	-
6	 **51**	21 h	33	racemic
7	 **52**	8d	25	84
8	 **53**	8d	-	-

[a] Isolated yield. [b] Chiral HPLC analysis.

Studies with the some of these amines were more fruitful and gave better results. The use of *cis* 4-hydroxy-proline **47** and *trans* 4-hydroxy-proline **48** as catalysts gave Michael adduct with moderate yield and low enantioselectivity (entries 2 and 3, Table 2.3). However, in the case of (*S*)-4-thiazolidinecarboxylic acid **50** and proline amide **53**, the desired product was not observed (entries 5 and 8, Table 2.3). The use of (*S*)-tyrosine as the catalyst **52** gave the desired product in low yield (25%), but in good enantiomeric excess (84% ee). The use of (*S*)-proline **49** as the catalyst gave us promising results with 43% yield and 70% ee as shown in Table 2.3.

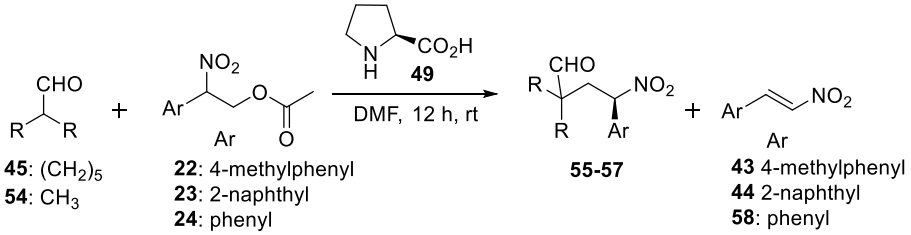
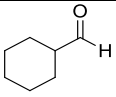
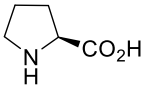
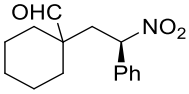
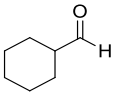
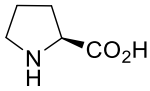
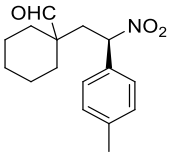
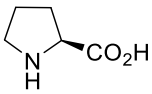
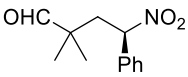
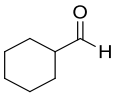
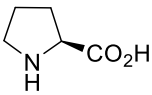
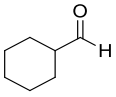
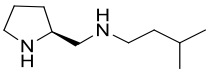
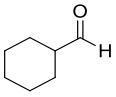
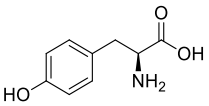


Figure 2.6 Organocatalyzed reaction of symmetrical α,α-disubstituted aldehydes with different precursors of α-nitrostyrene

After conducting catalyst screening, *S*-proline was found to be the most suitable catalyst for these reactions. We then investigated the reaction of selected aliphatic aldehydes with different nitroacetates as shown in Table 2.4.

Table 2.4 Results of organocatalytic Michael addition of α,α-disubstituted aldehydes to *in-situ* generated α-nitrostyrenes

Entry	Aliphatic aldehydes	Nitroacetate precursor	Catalyst	Product	Yield (%)	ee (%)	Nitroalkene (%)
1	 **45**	**24**	 **49**	 **55**	43	76	**58** (38)
2	 **45**	**22**	 **49**	 **56**	14	52	**43** (83)
3	 **54**	**24**	 **49**	 **57**	32	45	**58** (25)
4	 **45**	**23**	 **49**	not obtained	-	-	**44** (90)
5	 **45**	**23**	 **31**	not obtained	-	-	**44** (85)
6	 **45**	**23**	 **52**	not obtained	-	-	**44** (37)

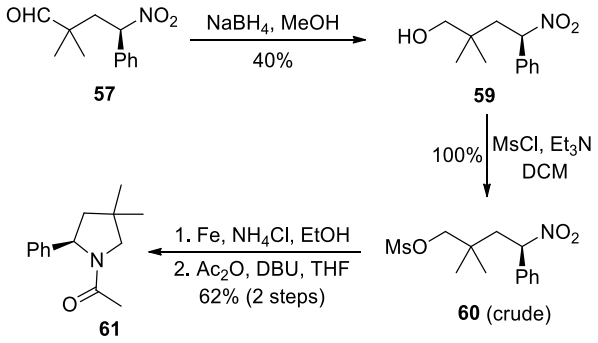
[a] Isolated yields. [b] Chiral HPLC analysis. [c] Isolated yields of rearranged β-nitrostyrenes.

The yields of all these reactions are moderate and formation of the isomerised β-nitrostyrenes could not be prevented in these reactions. The ^{1}H NMR of these nitroalkenes **55-57** agreed with those reported in the literature.[42] At this stage, the stereochemistry of the major

enantiomer of the γ-aryl γ-nitroaldehyde Michael adduct was assigned by analogy to the products obtained from the cyclic ketones.

Surprisingly, the Michael addition reaction of cyclohexane carboxaldehyde **45** and naphthalene nitroacetate **23** under the optimised conditions was unsuccessful and we obtained the rearranged β-nitrostyrene **44** in quantitative yield. The use of other catalysts such as the diamine catalyst **31** and *S*-tyrosine **52** was not fruitful, and we obtained the isomerised nitroalkene **44** in both cases. Since other reactions of **45** provide the desired product (entries 1 and 2, Table 2.4), these observations suggest that the α-nitrostyrene derived from the nitroacetate **23** is unreactive towards the enamine derived form **45** and hence it undergoes isomerization to provide **44** under the reaction conditions.

The synthetic utility of the γ-nitro aldehydes was established by the conversion of **57** into a functionalized pyrrolidine[33] (Scheme 2.7).



Scheme 2.7

Reduction of **57** with sodium borohydride to the nitroalcohol **59** followed by mesylation with methane sulfonyl chloride provided the nitro mesylate **60**. Crude **60** was converted into the *N*-acetyl pyrrolidine **61** by reductive cyclization with iron followed by *N*-acetylation. The *R* configuration of **61** confirmed the stereochemical assignment for the nitroaldehyde **57** and, by analogy, the configurations of **55** and **56**.

The results indicate that the Michael addition reaction of aliphatic aldehydes to α-nitrostyrenes has some limitations. The rearrangement of α-nitrostyrenes to β-nitrostyrenes is a competing side-reaction and the enantioselectivity of the Michael addition is not very high.

2.5 Conclusion

In conclusion, the organocatalytic enantioselective Michael addition of α,α-disubstituted aldehydes and cyclic ketones to α-nitrostyrenes to provide enantiomerically enriched γ-aryl-γ-nitro ketones and γ-aryl-γ-nitro aldehydes were developed. These Michael adducts have considerable potential as intermediates in the synthesis of pyrrolidines and 4-arylindolizidine alkaloids[38] and their analogues. The stereoselectivity of the Michael addition reactions is moderate, presumably due to the inherent reactivity of the α-nitrostyrene. In view of the high electrophilicity of α-nitrostyrenes, it is notable that the organocatalysts employed in this study are not deactivated by *N*-alkylation with the nitrostyrene.

2.6 Experimental section

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. CH_2Cl_2 was distilled from CaH_2. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 1100 series LC/MSD (Trap) or an Agilent 6200 LC/MSD (TOF) chromatographic system. HPLC analyses were performed on a Waters chromatographic system using the Breeze software. The nitroalcohol precursors of nitroacetates **22-24**[37] were prepared by adaptation of the literature procedures.

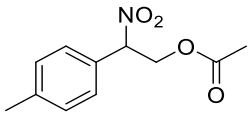
General procedure for the synthesis of 2-aryl-2-nitroethanols from aryl nitromethanes (19-21):

To a solution of the aryl nitromethane in THF was added Na_2CO_3 monohydrate followed by aqueous formaldehyde (37% w/v) and the mixture was stirred at ambient temperature for 12 h. The THF was removed under reduced pressure and ethyl acetate was added to the residue. The resulting mixture was washed with water and the solution obtained was dried over sodium sulphate and concentrated under reduced pressure to provide the crude product which was purified by flash chromatography on silica gel.

General procedure for the synthesis of 2-aryl-2-nitroethyl acetates (22-24):

To a solution of the nitro alcohol in acetonitrile was added Ac_2O followed by $Sc(OTf)_3$ and the reaction mixture was stirred for 15 min at -10 ℃ and then at ambient temperature for 2 h. The reaction mixture was cooled to 0 ℃, water was added, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated to provide the crude 2-aryl-2-nitroethyl acetates.

2-Nitro-2-(4-methylphenyl)ethyl acetate (22):

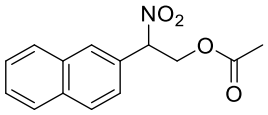


Reaction of 1-methyl-4-(nitromethyl)benzene (0.54 g, 3.60 mmol), Na_2CO_3 monohydrate (0.48 g, 3.92 mmol) and aqueous formaldehyde (37% w/v, 0.28 mL, 3.57 mmol) in THF (5 mL) according to the general procedure provided, after purification of the crude product by flash chromatography on silica gel (hexanes/EtOAc, 8:2) provided 0.51 g (79%) of 2-nitro-2-(4-methylphenyl)ethanol.

Reaction of the nitro alcohol (0.51 g, 2.84 mmol), Ac_2O (0.50 mL, 5.68 mmol), and $Sc(OTf)_3$ (11 mg, 0.022 mmol) in acetonitrile (5 mL) according to the general procedure provided 0.60 g (94%) of **22** as a white solid.

Mp: 45-47 ^oC; IR (neat): 3012, 2953, 2921, 1734, 1553, 1513, 1365, 1251, 1183, 1049, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 2H, J = 8.2 Hz, Ar*H*), 7.22 (d, 2H, J = 8.0 Hz, Ar*H*), 5.68 (dd, 1H, J = 10.7, 3.4 Hz, C*H*NO_2), 4.94 (dd, 1H, J = 12.3, 10.7 Hz, C*H*$_2$OCOCH$_3$), 4.48 (dd, 1H, J = 12.3, 3.4 Hz, C*H*$_2$OCOCH$_3$), 2.37 (s, 3H, ArC*H*$_3$), 2.09 (s, 3H, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (*C*=O), 140.9 (Ar*C*$_{ipso}$), 130.0 (2 × Ar*C*), 127.8 (Ar*C*$_{ipso}$), 127.6 (2 × Ar*C*), 88.7 (*C*HNO_2), 63.9 (*C*H$_2$OCOCH$_3$), 21.3 (*C*OCH$_3$ or Ar*C*H$_3$), 20.6 (Ar*C*H$_3$ or *C*OCH$_3$); HRMS (ESI, pos.): *m*/*z* 223.0861 (223.0844 calc. for $C_{11}H_{13}NO_4$ (M^+)) and 246.0749 (246.0742 calc. for $C_{11}H_{13}NNaO_4$ $(M+Na)^+$).

2-(Naphthalen-2-yl)-2-nitroethyl acetate (23):

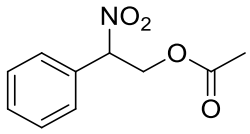


Reaction of 2-(nitromethyl)naphthalene (0.54 g, 2.91 mmol), Na_2CO_3 monohydrate (0.39 g, 3.20 mmol) and aqueous formaldehyde (37% w/v, 0.20 mL, 2.91 mmol) in THF (5 mL) according to the general procedure provided, after purification of the crude product by flash chromatography on silica gel (hexanes/EtOAc, 8:2), 0.40 g (63%) of the nitroalcohol as a white solid.

Reaction of the nitro alcohol (0.40 g, 1.84 mmol), Ac_2O (0.26 mL, 2.76 mmol) and $Sc(OTf)_3$ (9.00 mg, 0.018 mmol) in acetonitrile (5 mL) according to the general procedure provided 0.38 g (85%) of **23** as a pale yellow solid.

Mp: 90-92 ^{o}C; IR (neat): 2953, 1735, 1552, 1507, 1368, 1333, 1244, 1165, 1054, 1012, 960 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96-7.83 (m, 4H, Ar*H*), 7.60-7.50 (m, 3H, Ar*H*), 5.89 (dd, 1H, *J* = 10.6, 3.4 Hz, C*H*NO_2), 5.07 (dd, 1H, *J* = 12.3, 10.6 Hz, C*H*$_2$OCOCH_3), 4.60 (dd, 1H, *J* = 12.3, 3.4 Hz, C*H*$_2$OCOCH_3), 2.12 (s, 3H, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (*C*=O), 134.0 (Ar*C*$_{ipso}$), 133.0 (Ar*C*$_{ipso}$), 129.4 (Ar*C*), 128.3 (Ar*C*), 127.9 (Ar*C*), 127.9 (Ar*C*$_{ipso}$), 127.8 (Ar*C*), 127.6 (Ar*C*), 127.1 (Ar*C*), 124.0 (Ar*C*), 89.0 (*C*HNO_2), 63.9 (*C*H$_2$OC(O)CH_3), 20.7 (CO*C*H$_3$); HRMS (ESI, pos.): *m*/*z* 259.0849 (259.0844 calc. for $C_{14}H_{13}NO_4$ (M^+)) and 282.0742 (282.0742 calc. for $C_{14}H_{13}NNaO_4$ $(M+Na)^+$).

2-Nitro-2-phenylethyl acetate (24):



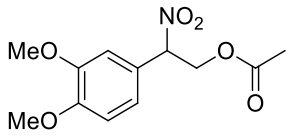
Reaction of (nitromethyl)benzene (0.90 g, 6.60 mmol), Na_2CO_3 monohydrate (0.89 g, 7.20 mmol) and aqueous formaldehyde (37% w/v, 0.20 mL, 6.60 mmol) in THF (7 mL) according to the general procedure provided, after purification of the crude product by flash chromatography on silica gel (hexanes/EtOAc, 8:2), 0.45 g (45%) of the nitroalcohol as a white solid.

Reaction of the above nitroalcohol (0.50 g, 3.00 mmol), Ac_2O (0.42 mL, 4.50 mmol) and $Sc(OTf)_3$ (15.0 mg, 0.030 mmol) in acetonitrile (5 mL) according to the general procedure provided 0.56 g (90%) of **24** as a dark orange liquid.

IR (neat): 1744, 1553, 1366, 1304, 1218, 1043 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.48 (m, 5H, Ar*H*), 5.73 (dd, 1H, *J* = 10.6, 3.4 Hz, C*H*NO_2), 4.95 (dd, 1H, *J* = 12.3, 10.6 Hz, C*H*$_2$OCOCH_3), 4.50 (dd, 1H, *J* = 12.3, 3.4 Hz, C*H*$_2$OCOCH_3), 2.08 (s, 3H, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1 (*C*=O), 130.6 (Ar*C*$_{ipso}$), 130.6 (Ar*C*), 129.3 (2 x Ar*C*), 127.6 (2 x Ar*C*),

88.8 (*C*HNO$_2$), 63.8 (*C*H$_2$OC(O)CH$_3$), 20.6 (CO*C*H$_3$); HRMS (ESI, pos.): *m*/*z* 209.0692 (209.0688 calc. for $C_{10}H_{11}NO_4$ (M^+)) and 232.0579 (232.0586 calc. for ($C_{10}H_{11}NNaO_4$ (M+Na)$^+$).

2-(3,4-Dimethoxyphenyl)-2-nitroethyl acetate (29):



A mixture of 2-(3,4-dimethoxyphenyl)oxirane **27** (4.00 g, 22.2 mmol), $NaNO_2$ (11.9 g, 173 mmol) and $LaCl_3 \cdot 7H_2O$ (10.9 g, 44.4 mmol) in THF: H_2O (1:1, 160 mL) was vigorously stirred at ambient temperature for 12 h. The mixture was then extracted with ether (4 × 25 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1:1) to provide 1.50 g (30%) of 2-(3,4-dimethoxyphenyl)-2-nitroethanol **28** as a yellow foam.

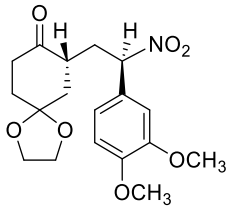
Reaction of the above nitroalcohol **28** (1.84 g, 8.1 mmol), Ac_2O (1.14 mL, 12.1 mmol) and $Sc(OTf)_3$ (40 mg, 0.08 mmol) in aectonitrile (40 mL) according to the general procedure provided 1.70 g (81%) of **29** as a yellow solid.

IR (neat): 1742, 1550, 1516, 1448, 1427, 1394, 1366, 1224, 1146, 1022 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.3, 2.0 Hz, Ar*H*), 6.95 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.88 (d, 1H, *J* = 8.3 Hz, Ar*H*), 5.67 (dd, 1H, *J* = 10.7, 3.4 Hz, C*H*NO$_2$), 4.95 (dd, 1H, *J* = 12.3, 10.7 Hz, C*H*$_2$OCOCH$_3$), 4.48 (dd, 1H, *J* = 12.3, 3.4 Hz, C*H*$_2$OCOCH$_3$), 3.90 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 2.09 (s, 3H, OCOC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*=O), 150.8 (Ar*C*$_{ipso}$), 149.5 (Ar*C*$_{ipso}$), 122.9 (Ar*C*$_{ipso}$), 120.7 (Ar*C*), 111.3 (Ar*C*), 110.2 (Ar*C*), 88.6 (*C*HNO$_2$), 63.9 (*C*H$_2$OC(O)CH$_3$), 56.1 (CO*C*H$_3$); HRMS (ESI, pos.): *m*/*z* 270.1015 (270.0978 calc. for ($C_{12}H_{16}NO_6$ (M+H)$^+$) and 292.0794 (292.0797 calc. for ($C_{12}H_{15}NNaO_6$ (M+Na)$^+$).

General procedure for the Michael addition of ketones to α-nitrostyrenes

To a solution of the ketone, catalyst **31**, and (1*S*)-camphorsulfonic acid in DMF was added the nitroacetate and the resulting solution was stirred at 0 °C for 72 h except when noted otherwise. Ethyl acetate (5 mL) was added and the solution was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel.

(*R*)7-((*R*)-2-(3,4-Dimethoxyphenyl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (32):

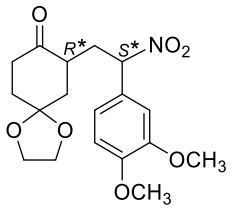


Reaction of ketone **30** (5.80 g, 37.2 mmol) and nitroacetate **29** (2.00 g, 7.40 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine (**31**) (252 mg, 1.49 mmol), and (1*S*)-camphorsulfonic acid (345 mg, 1.49 mmol) in DMF (23 mL) at 0 °C for 72 h according to the general procedure provided, after purification by flash column chromatography on silica gel, 1.38 g (51%) **30** with as a white solid with 92% ee and 0.81 g (30%) of **32** as a colourless gum. Data for **32** was in agreement with that reported in the literature.[37]

R_f = 0.25 (hexanes/EtOAc, 7:3); IR (neat): 2959, 2873, 1708, 1546, 1510, 1264, 1231, 1150, 1137, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.30, 2.1 Hz, Ar*H*), 6.96 (d, 1H, *J* = 2.1 Hz, Ar*H*), 6.86 (d, 1H, *J* = 8.3 Hz, Ar*H*), 5.63 (dd, 1H, *J* = 10.3, 4.4 Hz, C*H*NO_2), 4.03-4.01 (m, 4H, OCH_2CH_2O), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 2.75-2.63 (m, 2H, COC*H*, CH_2CHNO_2), 2.35-2.49 (m, 2H, CH_2CH_2CO, CH_2CHNO_2), 2.30 (dd, 1H, *J* = 10.3, 4.1 Hz, CH_2CH_2CO), 2.13-1.99 (m, 2H, COCH_2, COCHCH_2), 1.97 (dd, 1H, *J* = 13.6, 4.9 Hz, COCH_2) 1.78 (t, 1H, *J* = 13.3 Hz, COCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.4 (*C*O), 150.2 (ArC_{ipso}), 149.2 (ArC_{ipso}), 127.2 (ArC_{ipso}), 120.3 (Ar*C*), 111.1 (ArC_{ipso}), 110.2 (Ar*C*), 106.8 (O*C*O), 89.6

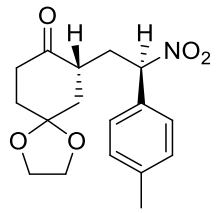
(*C*HNO$_2$), 64.9 (O*C*H$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 56.0 (O*C*H$_3$), 55.9 (O*C*H$_3$), 43.3 (CO*C*H), 41.4 (*C*H$_2$CHC(O)O), 38.3 (*C*H$_2$CHNO$_2$), 34.8 (*C*H$_2$CO), 34.0 (*C*H$_2$CH$_2$C(O)O); MS (ESI, neg.): 364.1 (M-H)$^-$; HRMS (ESI, neg.): *m/z* 365.1469 (365.1475 calc. for $C_{18}H_{23}NO_7(M^-)$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 60/40, flow rate 1 mL min^{-1}, λ= 247 nm): t_{major} = 10. 20 min., t_{minor} = 12.98 min., 92% ee.

(*R)7-((*S**)-2-(3,4-Dimethoxyphenyl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (33):**



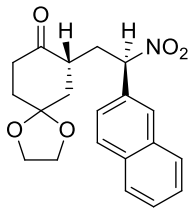
IR (neat): 2960, 2891, 2839, 1712, 1547, 1515, 1261, 1240, 1142, 1122, 1023, 762, 730 cm^{-1}; 1H NMR (500 MHz, CDCl3): δ 6.97 (dd, 1H, *J* = 8.3, 2.1 Hz, Ar*H*), 6.92 (d, 1H, *J* = 2.1 Hz, Ar*H*), 6.86 (d, 1H, *J* = 8.3 Hz, Ar*H*), 5.66 (t, 1H, *J* = 7.8 Hz, C*H*NO$_2$), 4.00 (s, 4H, O(C*H*$_2$)$_2$O), 3.91 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 2.86 (dt, 1H, *J* = 14.8, 7.6 Hz, C*H*$_2$CHNO$_2$), 2.62-2.48 (m , 2H, C*H*$_2$), 2.40-2.34 (m, 1H, C*H*$_2$), 2.11-2.06 (m, 1H, C*H*$_2$), 2.05-1.96 (m, 2H, C*H*$_2$), 1.95 (td, 1H, *J* = 13.6, 5.0 Hz, C*H*$_2$), 1.78 (t, 1H, *J* = 13.2 Hz, C*H*$_2$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 210.2 (*C*O), 150.5 (Ar*C*$_{ipso}$), 149.5 (Ar*C*$_{ipso}$), 126.7 (Ar*C*$_{ipso}$), 120.9 (Ar*C*), 111.3 (O-*C*-O or Ar*C*), 110.6 (O-*C*-O or Ar*C*), 106.9 (Ar*C*), 88.2 (*C*NO$_2$), 64.9 (O*C*H$_2$), 64.7 (O*C*H$_2$), 56.2 (O*C*H$_3$), 56.1 (O*C*H$_3$), 43.1 (*C*H$_2$), 40.9 (*C*H$_2$), 38.2 (*C*H$_2$), 34.7 (CH$_2$*C*HCH$_2$), 33.5 (*C*H$_2$); HRMS (ESI, pos.): *m*/*z* 365.1477 (365.1475 calc. for $C_{18}H_{23}NO_7$ (M^+)); 388.1377 (388.1372 calc. for $C_{18}H_{23}NNaO_7$ $(M+Na)^+$).

(*R*)-7-((*R*)-2-Nitro-2-(4-methylphenyl)ethyl)-1,4-dioxaspiro[4.5]decan-8-one (37):



Reaction of ketone **30** (174 mg, 1.11 mmol) and nitroacetate **22** (50.0 mg, 0.20 mmol) in the presence of catalyst **31** (8.00 mg, 0.044 mmol) and (1*S*)-camphorsulfonic acid (10.0 mg, 0.044 mmol) in DMF (0.6 mL) for 72 h at 0 ºC provided, after purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 33 mg (46%) of **37** as a white solid. Mp: 90-93 ºC; IR (neat): 2899, 1712, 1544, 1444, 1352, 1281, 1111, 1051, 990, 934 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 2H, J = 8.1 Hz, Ar*H*), 7.19 (d, 2H, J = 7.9 Hz, Ar*H*), 5.65 (dd, 1H, J = 10.2, 4.4 Hz, C*H*NO_2), 4.05-3.98 (m, 4H, OCH_2CH_2O), 2.74-2.61 (m, 2H, CH_2CHNO_2), 2.47-2.24 (m, 3H, COCH_2, COC*H*), 2.36 (s, 3H, ArCH_3), 2.15-1.89 (m, 3H, CH_2CH_2, CHCH_2 (ring)), 1.77 (t, 1H, J = 13.0 Hz, CHCH_2 (ring)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.4 (*C*=O), 139.9 (ArC_{ipso}), 131.9 (ArC_{ipso}), 129.7 (2 x Ar*C*), 127.3 (2 x Ar*C*), 106.8 (O*C*O), 89.6 (*C*HNO_2), 64.93 (O*C*H_2CH_2O), 64.69 (OCH_2*C*H_2O), 43.3 (*C*HC=O), 41.4 (*C*H_2C-O), 38.3 (*C*H_2C-O), 34.8 (*C*H_2CHNO_2), 34.0 (*C*H_2C=O), 21.3 (Ar*C*H_3); HRMS (APPI, pos.): *m*/*z* 319.1429 (319.1420 calc. for $C_{17}H_{21}NO_5$ $(M)^+$) and 320.1503 (320.1498 calc. for $C_{17}H_{22}NO_5$ $(M+H)^+$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 70/30, flow rate 1 mL min^{-1}, λ = 254 nm): t_{major} = 7.46 min., t_{minor} = 8.37 min., 89% ee.

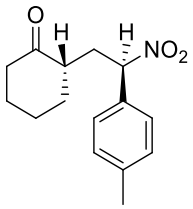
(*R*)-7-((*R*)-2-(Naphthalen-2-yl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (38):



Reaction of ketone **30** (151 mg, 0.96 mmol) and nitroacetate **23** (50.0 mg, 0.19 mmol) in the presence of catalyst **31** (6.00 mg, 0.038 mmol), and (1*S*)-camphorsulfonic acid (9.00 mg, 0.038 mmol) in DMF (0.6 mL) for 72 h at 0 ℃ for provided, after purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 29 mg (43%) of **38** as a white solid.

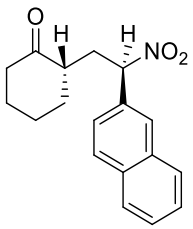
Mp: 118-120 ^{o}C; IR (neat): 2949, 1716, 1554, 1368, 1307, 1122, 1060, 1025, 983, 923 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (br s, 1H, Ar*H*), 7.90 - 7.81 (m, 3H, Ar*H*), 7.59-7.49 (m, 3H, Ar*H*), 5.85 (dd, 1H, *J* = 10.2 Hz, 4.1 Hz, C*H*NO_2), 4.04-3.99 (m, 4H, OC*H*$_2$C*H*$_2$O), 2.82-2.62 (m, 2H, C*H*$_2$CHNO_2), 2.59-2.35 (m, 3H, COC*H*$_2$,COC*H*), 2.19-1.89 (m, 3H, CH_2C*H*$_2$, CHC*H*$_2$ (ring)), 1.80 (t, 1H, *J* = 13.2 Hz, CHC*H*$_2$ (ring)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.5 (*C*=O), 133.7 (Ar*C*$_{ipso}$), 133.0 (Ar*C*$_{ipso}$), 132.1 (Ar*C*$_{ipso}$), 129.1 (Ar*C*), 128.3 (Ar*C*), 127.8 (Ar*C*), 127.4 (Ar*C*), 127.1 (Ar*C*), 126.8 (Ar*C*), 124.1 (Ar*C*), 106.9 (O*C*O), 90.0 (*C*HNO_2), 64.95 (O*C*H$_2$CH$_2$O), 64.70 (OCH$_2$*C*H$_2$O), 43.4 (*C*HC=O), 41.4 (*C*H$_2$C-O), 38.3 (*C*H$_2$C-O), 34.8 (*C*H$_2$CHNO_2), 34.2 (*C*H$_2$C=O); HRMS (APPI, pos.): *m*/*z* 355.1416 (355.1420 calc. for $C_{20}H_{21}NO_5$ (M^+)) and 356.1491 (356.1498 calc. for $C_{20}H_{22}NO_5$ $(M+H)^+$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ = 254 nm): t_{major} = 15.81 min., t_{minor} = 23.10 min., 82% ee.

(*S*)-2-((*R*)-2-Nitro-2-(4-methylphenyl)ethyl)cyclohexanone (39):



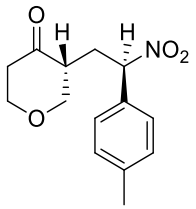
Reaction of ketone **34** (0.10 mL, 1.11 mmol) and nitroacetate **22** (50.0 mg, 0.20 mmol) in the presence of catalyst **31** (8.00 mg, 0.044 mmol) and (1*S*)-camphorsulfonic acid (9.00 mg, 0.044 mmol) in DMF (0.6 mL) for 72 h at 0 °C provided, after purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 14 mg (26%) of **39** as a white solid. Mp: 96-97 ºC; IR (neat): 2925, 1706, 1541, 1420, 1361, 1292, 1134 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.19 (d, 2H, *J* = 8.0 Hz, Ar*H*), 5.65 (dd, 1H, *J* = 10.0, 4.5 Hz, C*H*NO_2), 2.50-2.37 (m, 2H, C*H*$_2$CO), 2.36 (s, 3H, ArC*H*$_3$), 2.35-2.23 (m, 3H, COC*H*CH_2, COCHC*H*$_2$), 2.22-2.05 (m, 2H C*H*$_2$), 1.93-1.81 (m, 1H, C*H*), 1.76-1.58 (m, 2H, C*H*$_2$), 1.51-1.35 (m, 1H, C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.7 (*C*=O), 139.8 (Ar*C*$_{ipso}$), 132.0 (Ar*C*$_{ipso}$), 129.7 (2 x Ar*C*), 127.4 (2 x Ar*C*), 89.8 (*C*HNO_2), 47.4 (*C*HCH_2), 42.3 (*C*H_2CO), 34.95 (*C*H_2CHNO_2), 34.38 (*C*H_2), 28.1 (*C*H_2), 25.2 (CH_2), 21.2 (Ar*C*H_3); HRMS (APPI, pos.): *m*/*z* 261.1369 (261.1365 calc. for $C_{15}H_{19}NO_3$ (M^+)) and 262.1444 (262.1443 calc. for $C_{15}H_{20}NO_3$ $(M+H)^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 7.35 min., t_{major} = 8.49 min., 69% ee.

(*S*)-2-((*R*)-2-(Naphthalen-2-yl)-2-nitroethyl)cyclohexan-1-one (40):



Reaction of ketone **34** (91.0 μL, 0.96 mmol) and nitroacetate **23** (50.0 mg, 0.19 mmol) in the presence of catalyst **31** (7.00 mg, 0.038 mmol) and (1*S*)-camphorsulfonic acid (9.00 mg, 0.038 mmol) in DMF (0.6 mL) for 72 h at 0 ℃ provided, after purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 20 mg (35%) of **40** as a white solid. Mp: 123-125 ºC; IR (neat): 2922, 1706, 1542, 1443, 1348, 1290, 1128, 907 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (br d, 1H J = 2.0 Hz, Ar*H*), 7.90-7.81 (m, 3H, Ar*H*), 7.60-7.49 (m, 3H, Ar*H*), 5.87 (dd, 1H, J = 10.1, 4.5 Hz, C*H*NO_2), 2.61-2.27 (m, 5H, C*H*$_2$CO, C*H*$_2$CHNO_2, C*H*(CO)), 2.26-2.06 (m, 2H, C*H*$_2$), 1.95-1.85 (m, 1H, C*H*), 1.77-1.59 (m, 2H, C*H*$_2$), 1.54-1.38 (m, 1H, C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.7 (*C*=O), 133.7 (Ar*C*$_{ipso}$), 133.0 (Ar*C*$_{ipso}$), 132.2 (Ar*C*$_{ipso}$), 129.0 (Ar*C*), 128.3 (Ar*C*), 127.7 (Ar*C*), 127.5 (Ar*C*), 127.1 (Ar*C*), 126.8 (Ar*C*), 124.2 (Ar*C*), 90.1(*C*HNO_2), 47.4 (*C*HCH$_2$), 42.3 (*C*H$_2$CO), 34.98 (*C*H$_2$CHNO_2), 34.58 (*C*H$_2$), 28.1 (*C*H$_2$), 25.3 (*C*H$_2$); HRMS (APPI, pos.): *m*/*z* 297.1368 (297.1365 calc. for $C_{18}H_{19}NO_3$ $(M)^+$) and 298.1444 (298.1443 calc. for $C_{18}H_{20}NO_3$ $(M+H)^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 12.35 min., t_{major} = 15.45 min., 76% ee.

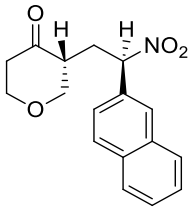
(*R*)-3-((*R*)-2-Nitro-2-(4-methylphenyl)ethyl)tetrahydro-4H-pyran-4-one (41):



Reaction of ketone **35** (0.1 mL, 1.1 mmol) and nitroacetate **22** (50.0 mg, 0.20 mmol) in the presence of catalyst **31** (8.00 mg, 0.044 mmol) and (1*S*)-camphorsulfonic acid (10.0 mg, 0.044 mmol) in DMF (0.6 mL) for 72 h at 0 ℃ provided, after purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 8:2), 26 mg (44%) of **41** as a colourless gum.

IR (neat): 2956, 2922, 2853, 1712, 1547, 1364, 1225, 1207, 1150, 1101, 970 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.20 (d, 2H, *J* = 8.1 Hz, Ar*H*), 5.65 (dd, 1H *J* = 10.1, 4.7 Hz, C*H*NO_2), 4.33-4.18 (m, 2H, OCH_2), 3.66 (td, 1H, *J* = 11.5, 2.9 Hz, OCH_2), 3.36 (t, 1H, *J* = 10.8 Hz, OCH_2), 2.73-2.52 (m, 2H, COCH_2), 2.46-2.37 (m, 2H, COCHCH_2), 2.36 (s, 3H, ArCH_3), 2.30-2.16 (m, 1H, COC*H*CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.9 (*C*=O), 140.1(ArC_{ipso}), 131.6 (ArC_{ipso}), 129.9 (2 x Ar*C*), 127.4 (2 x Ar*C*), 89.2 (*C*HNO_2), 72.7 (O*C*H_2CH), 68.9 (O*C*$H_2C H_2$), 48.2 (OCH_2*C*H), 42.9 (CO*C*H_2), 29.8 (COCH*C*H_2), 21.2 (Ar*C*H_3); HRMS (APPI, pos.): *m*/*z* 263.1151 (263.1158 calc. for $C_{14}H_{17}NO_4$ $(M)^+$) and 264.1235 (264.1236 calc. for $C_{14}H_{18}NO_4$ $(M+H)^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 13.73 min., t_{major} = 30.59 min., 69% ee.

(*R*)-3-((*R*)-2-(Naphthalen-2-yl)-2-nitroethyl)tetrahydro-4H-pyran-4-one (42):



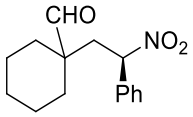
Reaction of ketone **35** (97.0 μL, 0.96 mmol) and nitroacetate **23** (50.0 mg, 0.19 mmol) in the presence of catalyst **31** (7.00 mg, 0.038 mmol) and (1*S*)-camphorsulfonic acid (9.00 mg, 0.038 mmol) in DMF (0.6 mL) for 72 h at 0 ºC provided, after purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 8:2), 16 mg (28%) of **42** as a white solid. Mp: 124-126 ºC; IR (neat): 2921, 1709, 1545, 1365, 1206, 1148, 1101, 970 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (br d, 1H, *J* = 2.0 Hz, Ar*H*), 7.91 - 7.82 (m, 3H, Ar*H*), 7.58- 7.50 (m, 3H, Ar*H*), 5.87 (dd, 1H, *J* = 10.1 Hz, 4.6 Hz, C*H*NO_2), 4.33-4.23 (m, 2H, OCH_2), 3.67 (td, 1H, *J* = 11.7, 3.2 Hz, OCH_2), 3.39 (t, 1H, *J* =10.9 Hz, OCH_2), 2.76-2.59 (m, 2H, COCH_2), 2.57-2.30 (m, 3H, COC*H*CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.0 (*C*=O), 133.8 (ArC_{ipso}), 133.0 (ArC_{ipso}),

131.7 (ArC_{ipso}), 129.2 (Ar*C*), 128.3 (Ar*C*), 127.8 (Ar*C*), 127.6 (Ar*C*), 127.2 (Ar*C*), 126.9 (Ar*C*), 123.9 (Ar*C*), 89.6 (*C*HNO_2), 72.6 (O*C*H_2CH), 68.8 (O*C*H_2CH_2), 48.2 (OCH_2*C*H), 42.8 (CO*C*H_2), 29.9 (COCH*C*H_2); HRMS (APPI, pos.): *m*/*z* 299.1159 (299.1158 calc. for $C_{17}H_{17}NO_4$ (M^+)) and 300.1233 (300.1236 calc. for $C_{17}H_{18}NO_4$ $(M+H)^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 22.54 min., t_{major} = 25.15 min., 59% ee.

General procedure for the Michael addition of aldehydes to α-nitrostyrenes

To a solution of the aldehyde and (*S*)-proline in DMF was added the nitroacetate and the resulting solution was stirred at ambient temperature for 12 h. After completion of the reaction (TLC), ethyl acetate (5 mL) was added and the resulting solution was washed with water (5 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel.

(*R*)-1-(2-nitro-2-phenylethyl)cyclohexanecarbaldehyde (55):

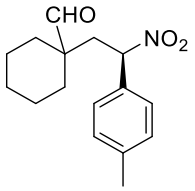


Reaction of **45** (0.14 mL, 1.2 mmol) and **24** (50 mg, 0.24 mmol) in the presence of (*S*)-proline **49** (5.40 mg, 0.047 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (95:5 hexanes/ethyl acetate), 27 mg (43%) of **55** as a white gum.

IR (neat): 2932, 2856, 1721, 1552, 1453, 1363 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.32 (s, 1H, C*H*O), 7.47-7.36 (m, 5H, Ar*H*), 5.48 (dd, 1H, *J* = 8.0, 5.0, C*H*NO_2), 2.89 (dd, 1H, *J* = 15.3, 8.0, CH_2CHNO_2), 2.21 (dd, 1H, *J* = 15.3, 5.0, CH_2CHNO_2), 1.96-1.84 (m, 2H, CH_2), 1.57-1.51 (m, 2H, CH_2), 1.38-1.26 (m, 6H, CH_2); ^{13}C NMR(75 MHz, $CDCl_3$): δ 204.7 (*C*HO), 135.3 (ArC_{ipso}), 130.0 (Ar*C*), 129.2 (2 x Ar*C*), 127.6 (2 x Ar*C*), 87.3 (*C*HNO_2), 49.0 (*C*-CHO), 39.8 (*C*H_2CHNO_2),

31.4 (*C*H_2), 30.3 (*C*H_2), 25.3 (*C*H_2), 22.09 (*C*H_2), 21.99 (*C*H_2); HRMS (APPI, pos.): *m/z* 262.1357 (262.1365 calc. for $C_{15}H_{19}NO_3[M]^+$), 262.1434 (262.1443 calc. for $C_{15}H_{20}NO_3[M+H]^+$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 98/2, flow rate 1 mL min−1, λ = 254 nm): t_{major} = 28.97 min., t_{minor} = 27.70 min., 76% ee.

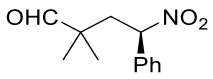
(*R*)-1-(2-Nitro-2-(4-methylphenyl)ethyl)cyclohexanecarbaldehyde (56):



Reaction of **45** (0.13 mL, 1.11 mmol) and **22** (50.0 mg, 0.22 mmol) in the presence of (*S*)-proline **49** (5.00 mg, 0.044 mmol) in DMF (0.6 mL) according to the general procedure gave, after purification of the crude product by flash column chromatography on silica gel (98:2 hexanes/ethyl acetate), 9 mg (14%) of **56** as a colourless gum.

IR (neat): 2947, 1716, 1553, 1367, 1307, 1121, 1060, 1025, 924 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.30 (s, 1H, C*H*O), 7.34-7.29 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.21-7.15 (d, 2H, *J* = 8.1 Hz, Ar*H*), 5.44 (dd, 1H, *J* = 7.7, 5.3 Hz, C*H*NO_2), 2.80 (dd, 1H, *J* = 15.2, 7.7 Hz, CH_2CHNO_2), 2.35 (s, 3H, ArCH_3), 2.22 (dd, 1H, *J* = 15.2, 5.3 Hz, CH_2CHNO_2), 1.97-1.81 (m, 2H, CH_2), 1.65-1.47 (m, 4H, CH_2), 1.42-1.18 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7 (*C*HO), 140.2 (ArC_{ipso}), 132.3 (ArC_{ipso}), 129.8 (2 x Ar*C*), 127.5 (2 x Ar*C*), 87.1 (*C*HNO_2), 49.0 (CH(O)-*C*-CH_2), 39.8 (*C*H_2CHNO_2), 31.5 (*C*H_2), 30.3 (*C*H_2), 25.3 (*C*H_2), 22.1 (*C*H_2), 22.0 (*C*H_2), 21.3 (Ar*C*H_3); HRMS (APPI, pos.): *m*/*z* 275.1532 (275.1521 calc. for $C_{16}H_{21}NO_3$ (M^+)) and 276.1606 (276.1600 calc. for $C_{17}H_{22}NO_3$ $(M+H)^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL min^{-1}, λ = 254 nm): t_{minor} = 6.21 min., t_{major} = 6.78 min., 52% ee.

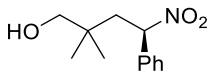
(*R*)-2,2-Dimethyl-4-nitro-4-phenylbutanal (57):



Reaction of isobuteraldehyde **54** (0.20 mL, 2.30 mmol) and **24** (100 mg, 0.47 mmol) in the presence of (*S*)-proline **49** (11.0 mg, 0.095 mmol) in DMF (1.2 mL) provided, after purification of the crude product by flash column chromatography on silica gel, 34 mg (32%) of **57** as a colourless gum.

IR (neat): 2968, 1724, 1549, 1472, 1456, 1364, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.33 (s, 1H, C*H*O), 7.49-7.43 (m, 2H, Ar*H*), 7.42-7.38 (m, 3H, Ar*H*), 5.53 (dd, 1H, *J* = 8.3, 4.8 Hz, C*H*NO_2), 2.84 (dd, 1H, *J* = 15.2, 8.3 Hz, C*H*$_2$CHNO_2), 2.32 (dd, 1H, *J* = 15.2, 4.8 Hz, C*H*$_2$CHNO_2), 1.13 (s, 3H, C*H*$_3$), 1.10 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.4 (*C*HO), 135.2 (Ar*C*$_{ipso}$), 130.0 (Ar*C*$_{ipso}$), 129.2 (2 x ArC), 127.5 (2 x ArC), 88.0 (*C*HNO_2), 45.3 (CH(O)-*C*-$(CH_3)_2$), 40.3 (CH_2), 22.2 (CH_3), 20.7 (CH_3); HRMS (APPI, neg.): *m*/*z* 221.1041 (221.1052 calc. for $C_{12}H_{15}NO_3$ $(M)^-$) and 220.0969 (220.0974 calc. for $C_{12}H_{14}NO_3$ $(M-H)^-$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ = 254 nm): t_{major} = 9.20 min., t_{minor} = 10.06 min., 45% ee.

(*R*)-2,2-Dimethyl-4-nitro-4-phenylbutan-1-ol (59):

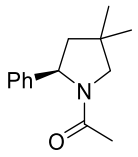


To a solution of 2,2-dimethyl-4-nitro-4-phenylbutanal **57** (52 mg, 0.2 mmol) in MeOH (2 mL) at 0 ^{o}C was added sodium borohydride (13 mg, 0.3 mmol). The mixture was stirred at 0 ^{o}C for 2 h. Aqueous HCl (1 N, 2 mL) was added and the mixture was concentrated under reduced pressure to remove MeOH. The residue was suspended in water (2 mL), the mixture was extracted with ethyl acetate (2 x 2 mL) and the combined organic layers were dried and concentrated. The

residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 85:15) to provide 21 mg (40%) of **59** as a colourless gum.

IR (neat): 3400 (br), 2959, 2926, 2874, 1547, 1473, 1455, 1363, 1041 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.45 (m, 2H, Ar*H*), 7.41-7.35 (m, 3H, Ar*H*), 5.69 (dd, 1H, *J* = 8.6, 4.3 Hz, C*H*NO_2), 3.32 (s, 2H, C*H*$_2$OH), 2.73 (dd, 1H, *J* = 15.1, 8.6 Hz, C*H*$_2$CHNO_2), 2.04 (dd, 1H, *J* = 15.1, 4.3 Hz, C*H*$_2$CHNO_2), 1.61 (bs, 1H, O*H*), 0.91 (s, 3H, C(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): *d* 136.3 (ArC_{ipso}), 129.7 (Ar*C*), 129.1 (2 x ArC), 127.6 (2 x ArC), 88.6 (*C*HNO_2), 71.3 (*C*H$_2$OH), 42.3 (*C*H$_2$CHNO_2), 35.4 (*C*(CH$_3$)$_2$) , 23.9 (*C*H$_3$), 29.9 (*C*H$_3$); HRMS (APPI, pos.): *m*/*z* 223.1206 (223.1208 calc. for $C_{12}H_{17}NO_3$ $(M)^+$).

(*R*)-1-(4,4-dimethyl-2-phenylpyrrolidin-1-yl)ethan-1-one (61):



To a solution of 2,2-dimethyl-4-nitro-4-phenylbutan-1-ol **59** (44 mg, 0.1 mmol) in dichloromethane (1.2 mL) was added triethylamine (71 μL, 0.5 mmol) followed by methane sulfonyl chloride (20 μL, 0.2 mmol) at -78 ^{o}C and the mixture was stirred at -78 ^{o}C for 1 h. Cold water (2 mL) was added, the mixture was stirred for a few minutes and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to provide the crude mesylate **60** as a colourless gum. This was used in the next step without purification.

A mixture of Fe powder (66 mg, 1.1 mmol), aq. NH_4Cl (21 mg, 0.3 mmol in 1 mL water) and the above nitro mesylate **60** (59 mg, 0.1 mmol) in ethanol (4 mL) was heated at 80 ^{o}C for 3 h. The mixture was then cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated, and the residue was dissolved in dichloromethane (1 mL). The resulting solution was

washed with aq. NaOH (5%, 2 x 2 mL), dried and concentrated to provide 26 mg (76%) of 4,4-dimethyl-2-phenylpyrrolidine as a colourless gum which gradually decomposed at -5 ^{o}C (fridge). The freshly prepared pyrrolidine was therefore used immediately in the next step without purification.

To a solution of 4,4-dimethyl-2-phenylpyrrolidine (26 mg, 0.1 mmol) in THF (3 mL) were added acetic anhydride (18 μL, 0.1 mmol) and DBU (27 μL, 0.1 mmol). The mixture was stirred at ambient temperature for 1 h and the solvent was removed under reduced pressure. Aqueous HCl (0.1 M, 2 mL) was added and the mixture was extracted with dichloromethane (2 x 2 mL). The combined extracts were dried (Na_2SO_4) and concentrated to provide 26 mg (81%) of **61** as a colourless gum.

IR (neat): 2956, 2868, 1640, 1408, 1352, 1284, 1226, 1176, 1128, 1030, 969, 920 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): Major rotamer: δ 7.38-7.27 (m, 2H, Ar*H*), 7.26-7.15 (m, 3H, Ar*H*), 4.84 (dd, 1H, *J* = 8.9, 7.4 Hz, NC*H*), 3.93 (dd, 1H, *J* = 11.4, 4.9 Hz, NCH_2), 3.24 (d, 1H, *J* = 11.4 Hz, NCH_2), 2.29-2.20 (m, 1H, CHCH_2), 1.78-1.65 (m, 1H, CHCH_2), 1.73 (s, 3H, NCOCH_3), 1.12 (s, 6H, C(CH_3)$_2$); minor rotamer: δ 7.38 -7.27 (m, 2H, Ar*H*), 7.28-7.15 (m, 3H, Ar*H*), 5.06 (t, 1H, *J* = 8.4 Hz, NC*H*)), 3.48-3.39 (m, 2H, NCH_2), 2.20-2.15 (m, 1H, CHCH_2), 2.09 (s, 3H, NCOCH_3), 1.78-1.65 (m, 1H, CHCH_2), 1.09 (s, 6H, C(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): Major rotamer: δ171.0 (N-*C*O), 144.2 (ArC_{ipso}), 129.2 (2 × Ar*C*), 125.5 (3 × Ar*C*), 62.6 (N*C*H), 59.9 (N*C*H_2), 52.2 (CH*C*H_2), 37.1 (*C*(CH_3)$_2$), 26.2 (*C*H_3), 26.1 (*C*H_3), 22.5 (NCO*C*H_3); minor rotamer : δ 169.3 (N-*C*O), 143.9 (ArC_{ipso}), 128.6 (2 × Ar*C*), 127.4 (2 × Ar*C*), 126.7 (Ar*C*), 62.0 (N*C*H_2), 60.8 (N*C*H), 49.6 (CH*C*H_2), 38.6 (*C*(CH_3)$_2$), 26.4 (*C*H_3), 26.1 (*C*H_3), 23.2 (NCO*C*H_3); HRMS (APPI, pos.): *m*/*z* 217.1473 (217.1467 calc. for $C_{14}H_{19}NO$ $(M)^+$), 218.1546 (218.1545 calc. for $C_{14}H_{20}NO$ $(M+H)^+$).

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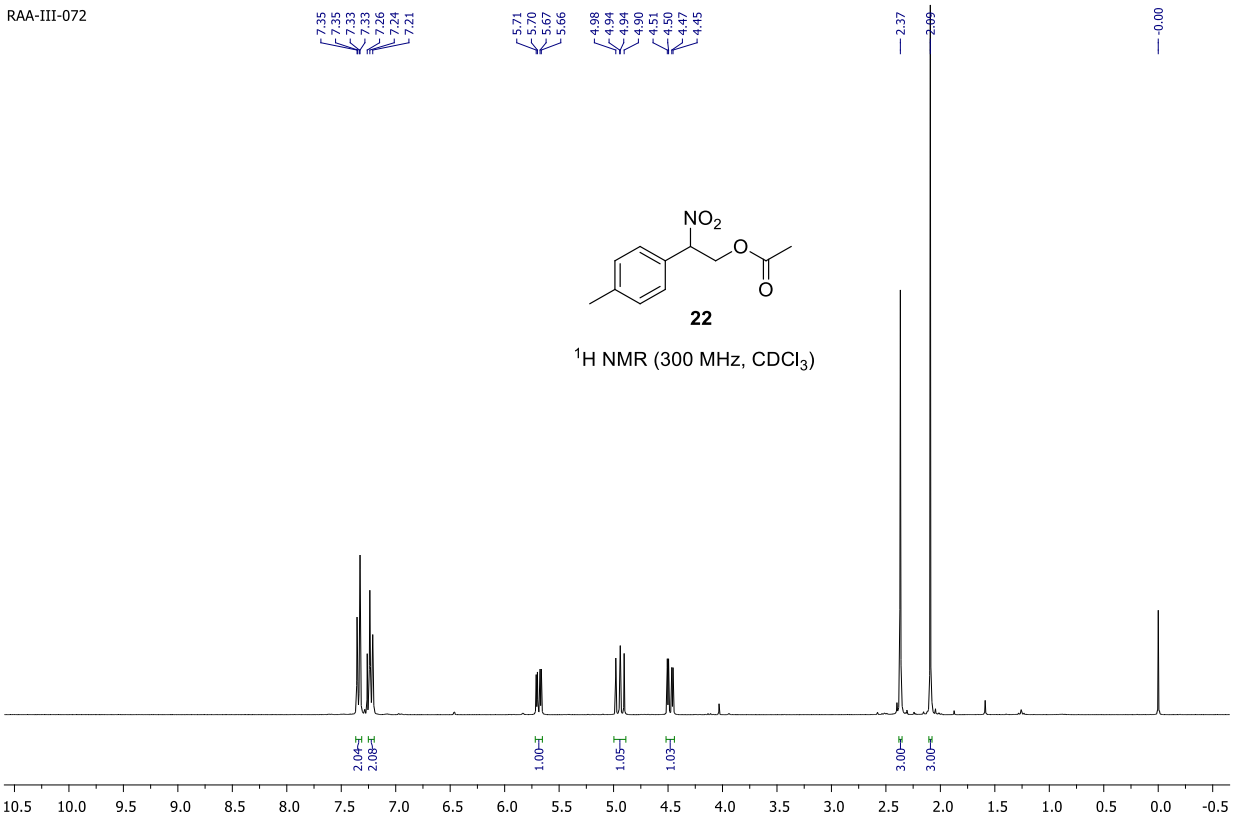
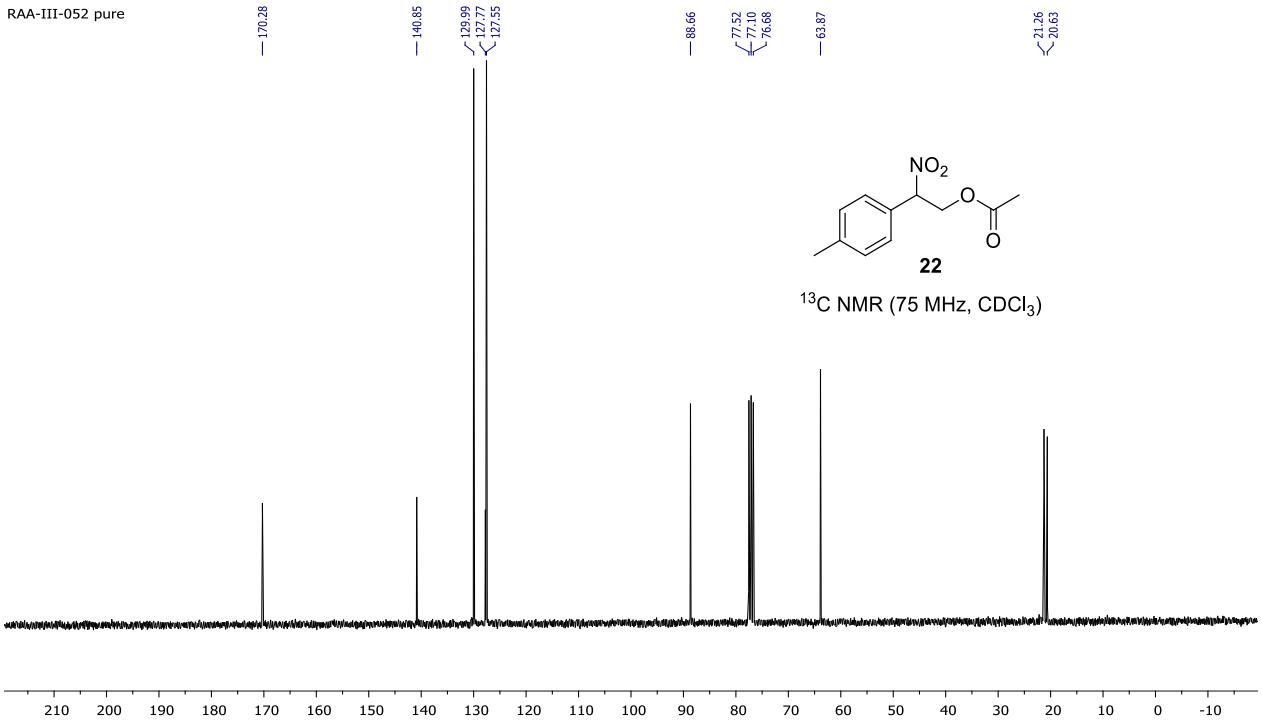
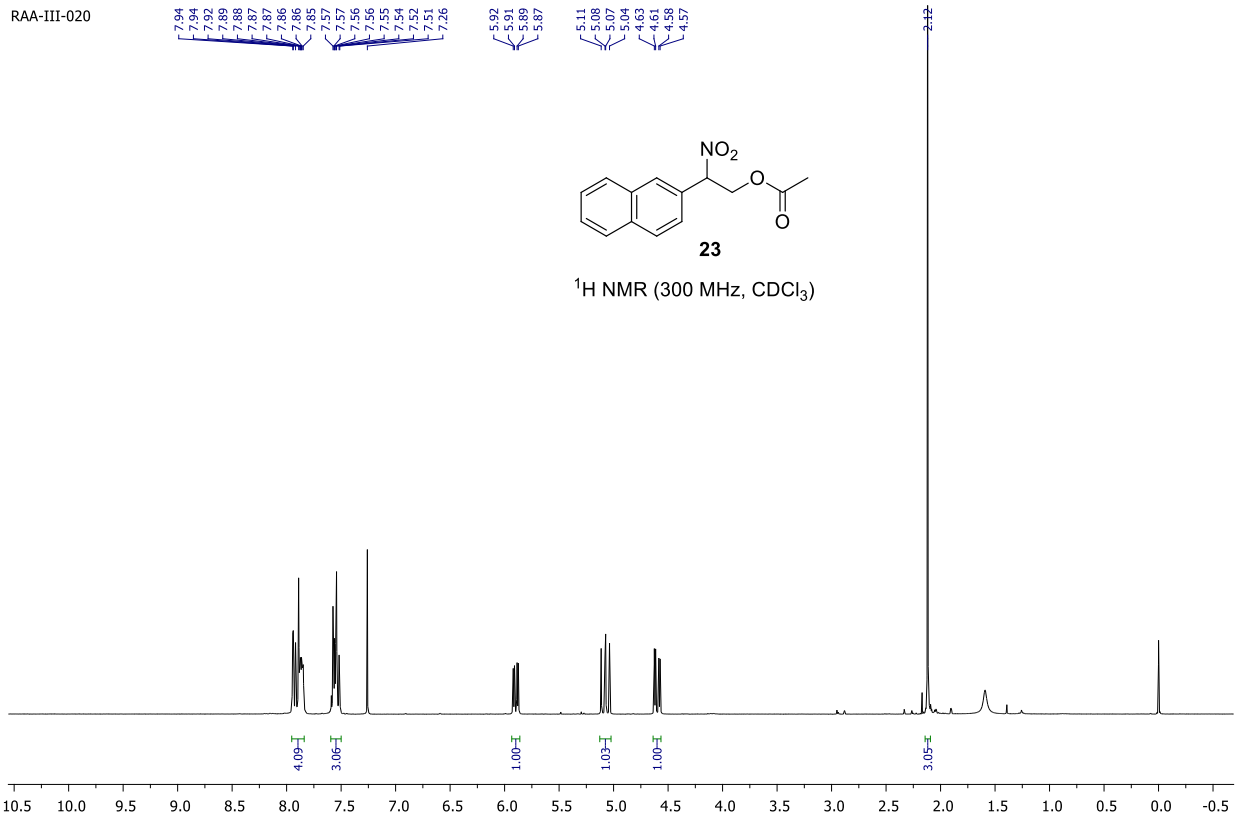
2.8 Selected ^{1}H and ^{13}C NMR spectral data:

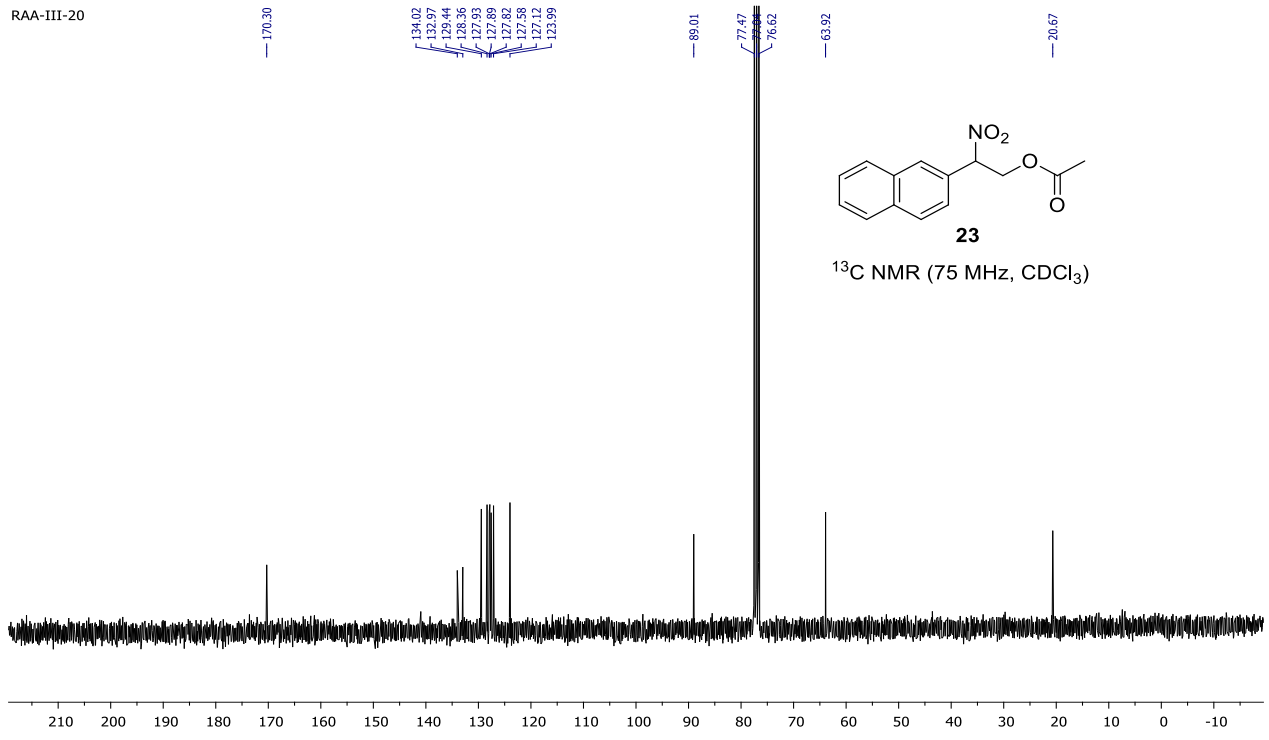






23

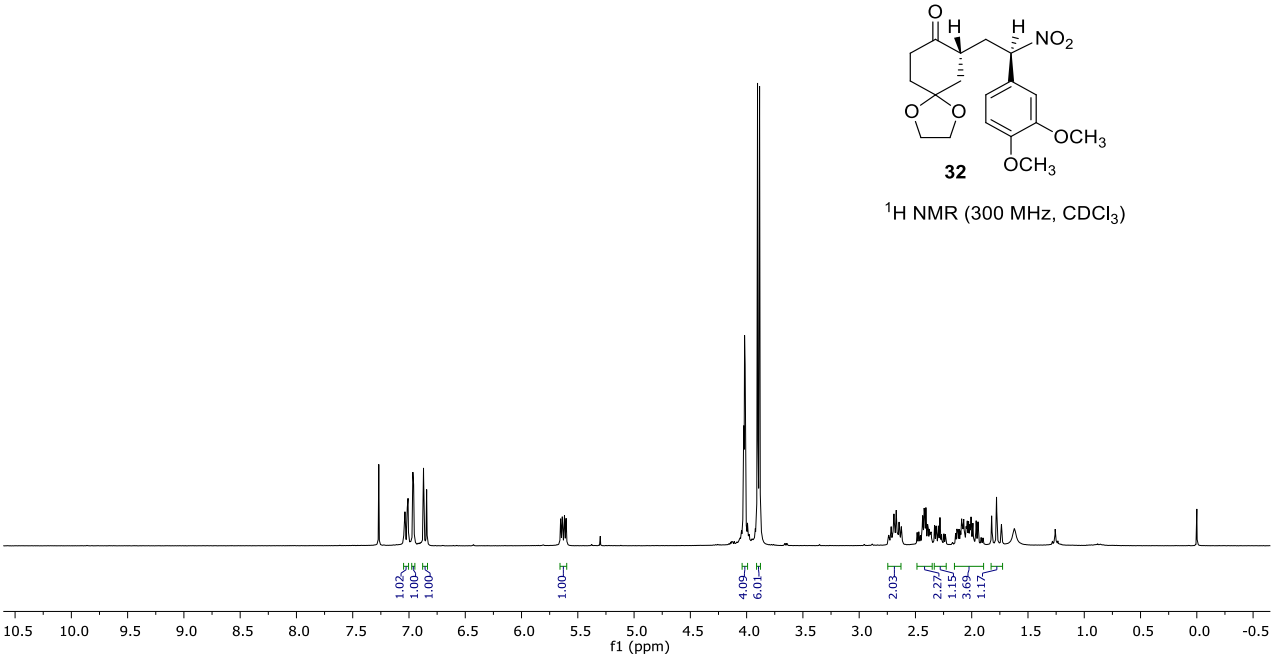
^{1}H NMR (300 MHz, $CDCl_3$)



23

^{13}C NMR (75 MHz, $CDCl_3$)

NVG-09-35A MA TOP.1.fid



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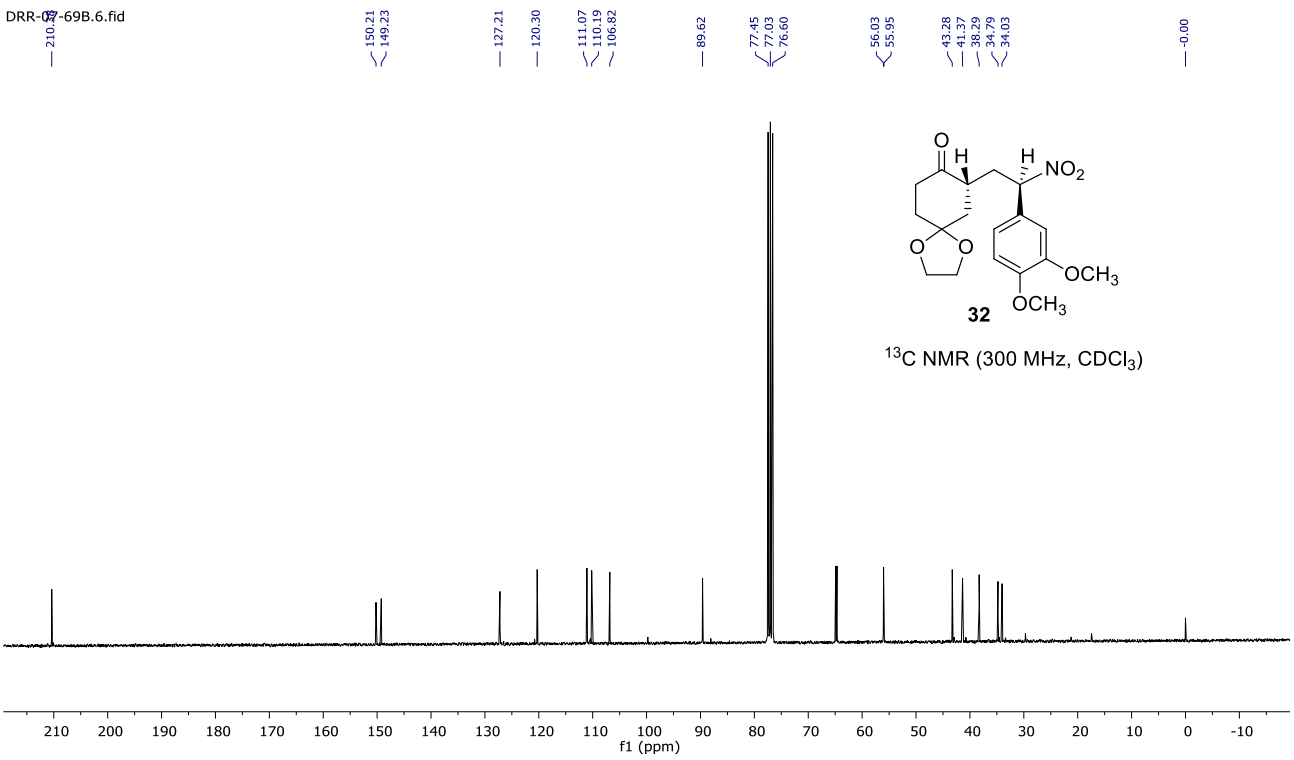
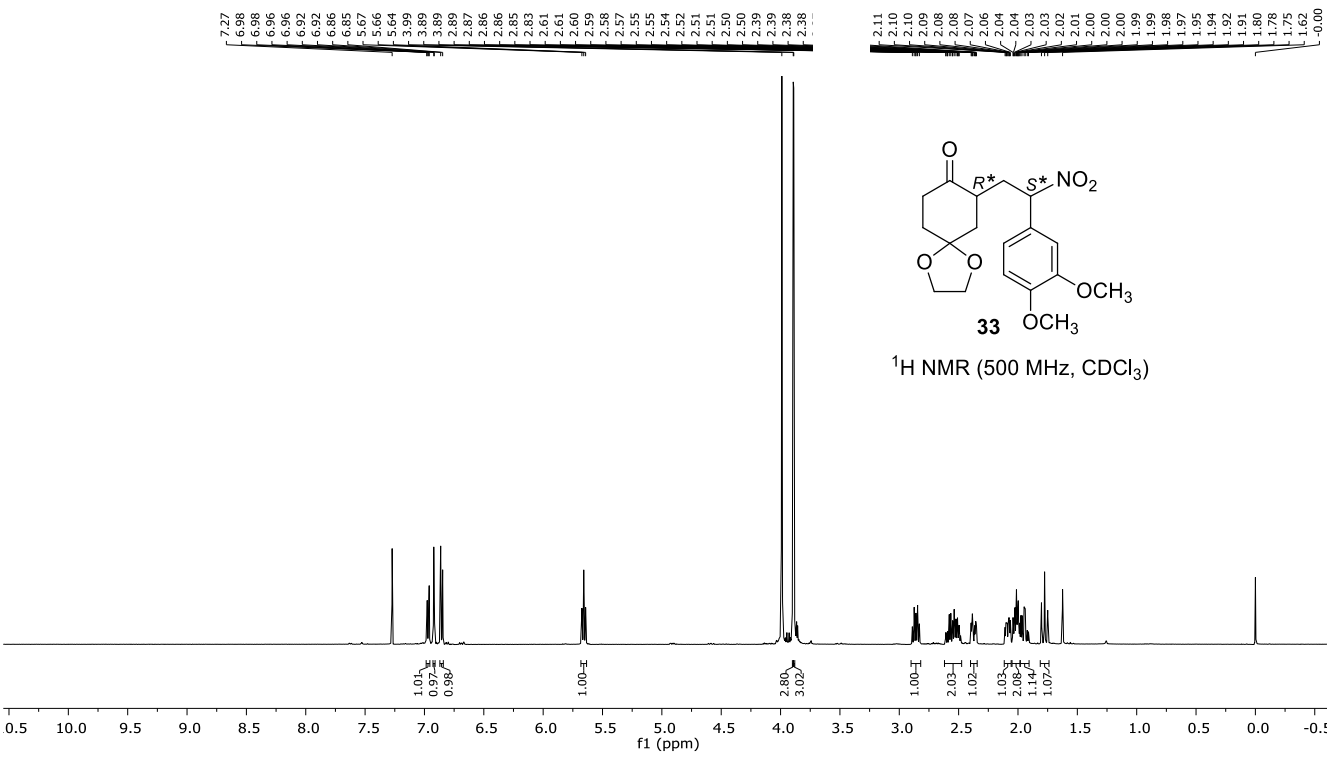
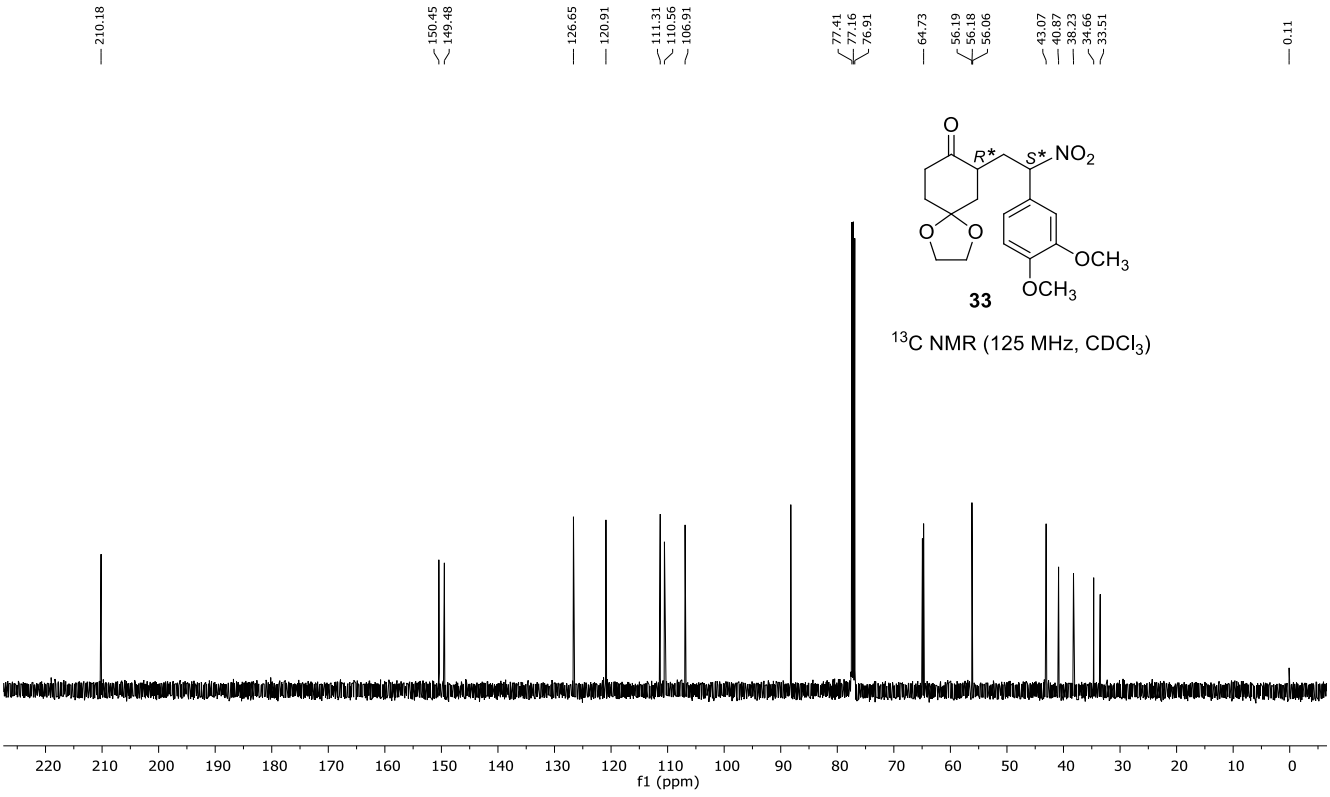




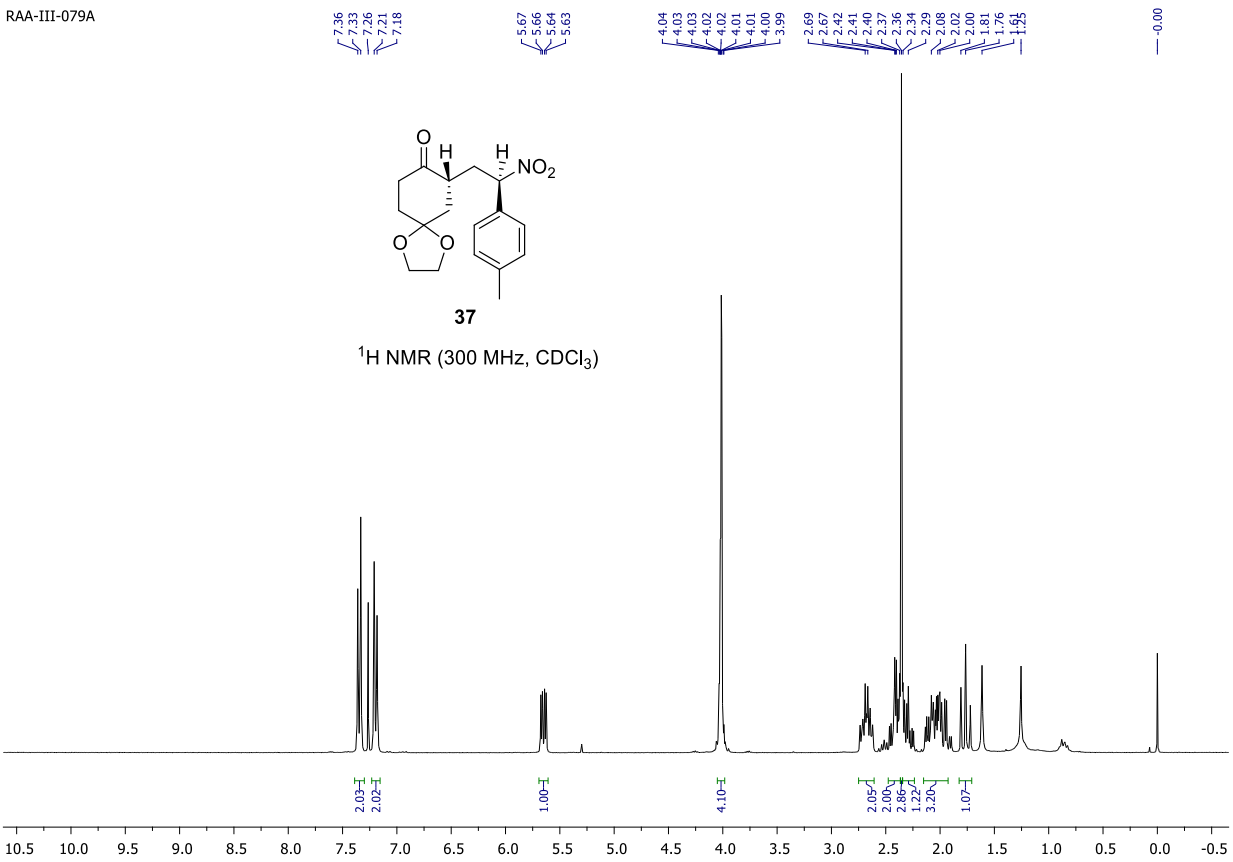
33

^{1}H NMR (500 MHz, $CDCl_3$)



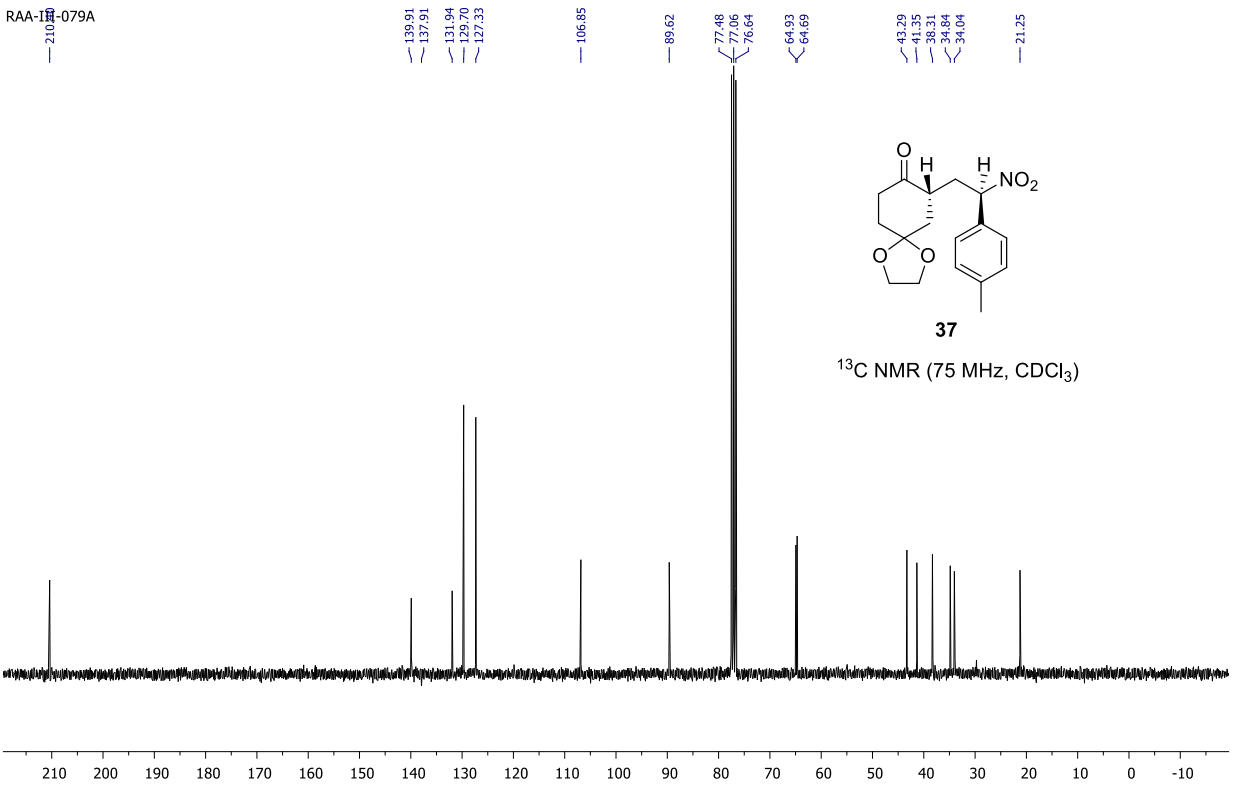
33

^{13}C NMR (125 MHz, $CDCl_3$)



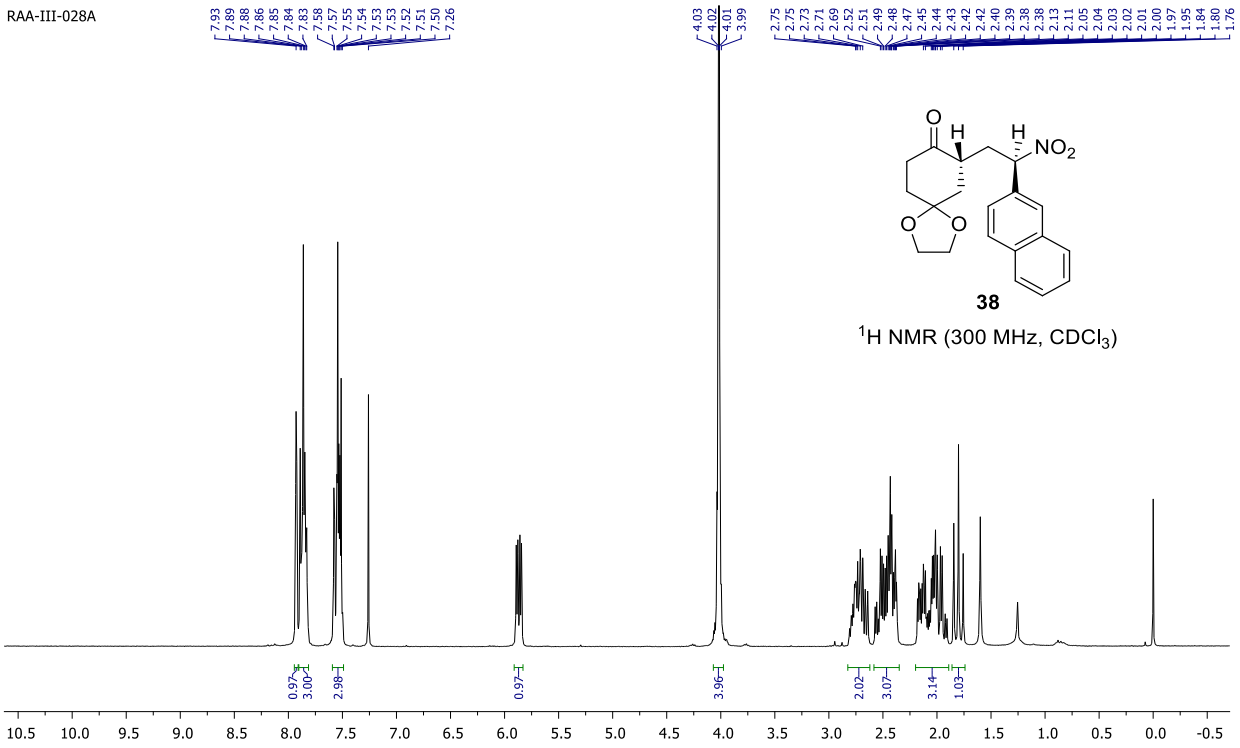
37

^{1}H NMR (300 MHz, $CDCl_3$)



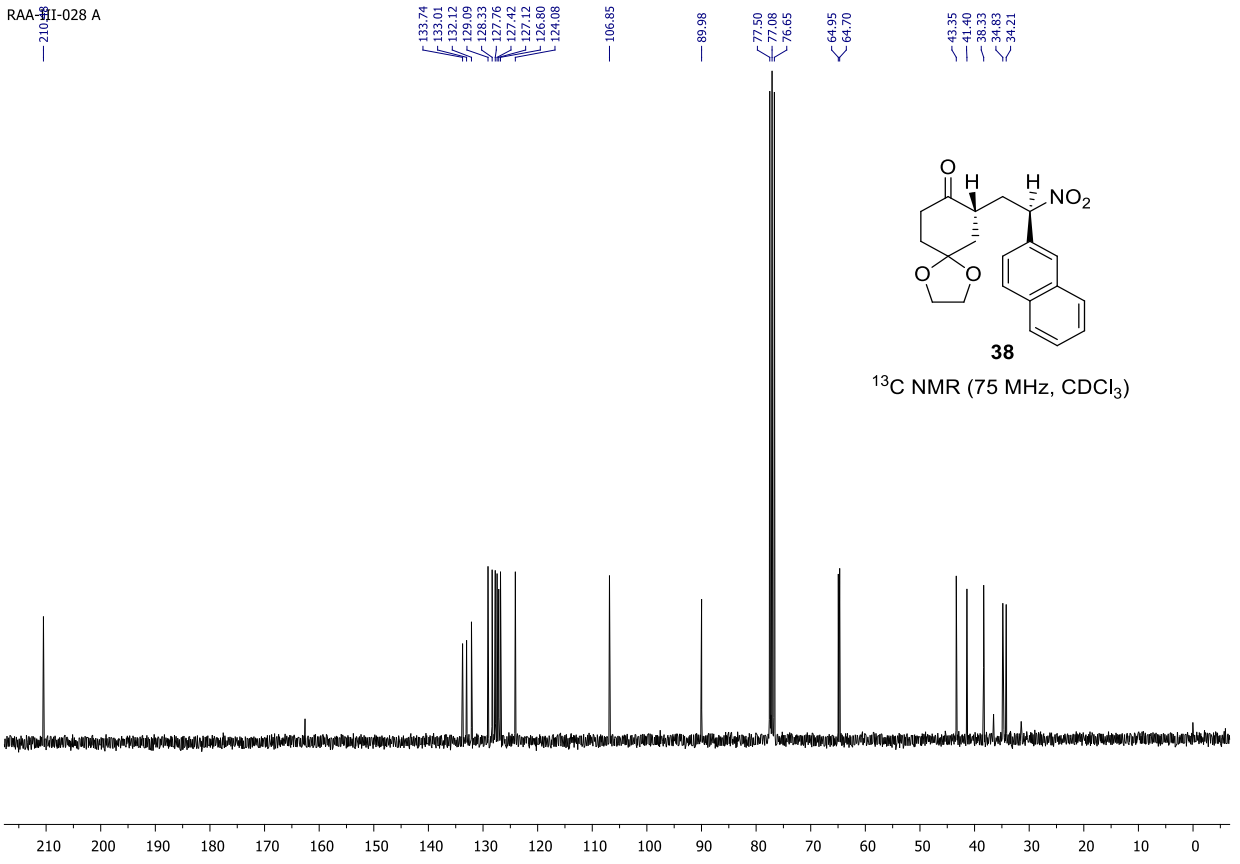
37

^{13}C NMR (75 MHz, $CDCl_3$)



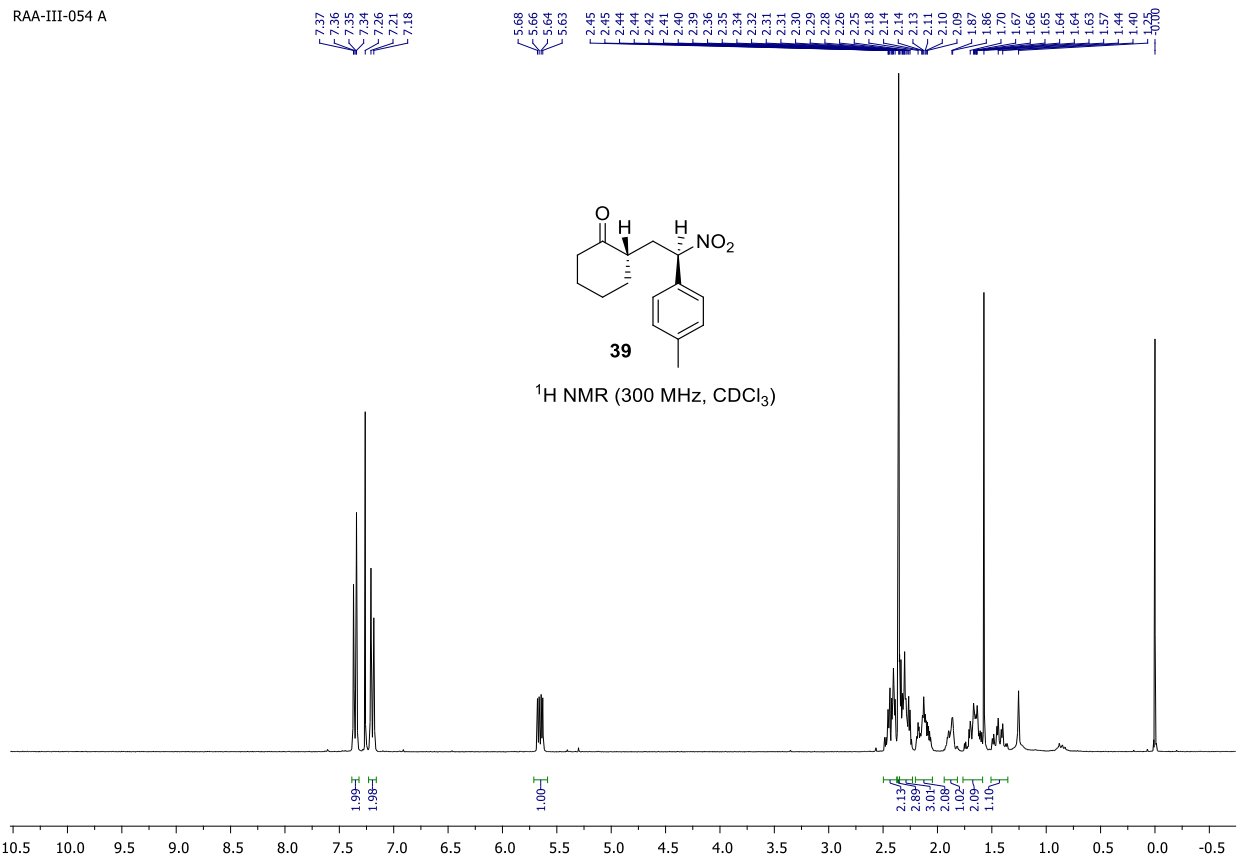
38

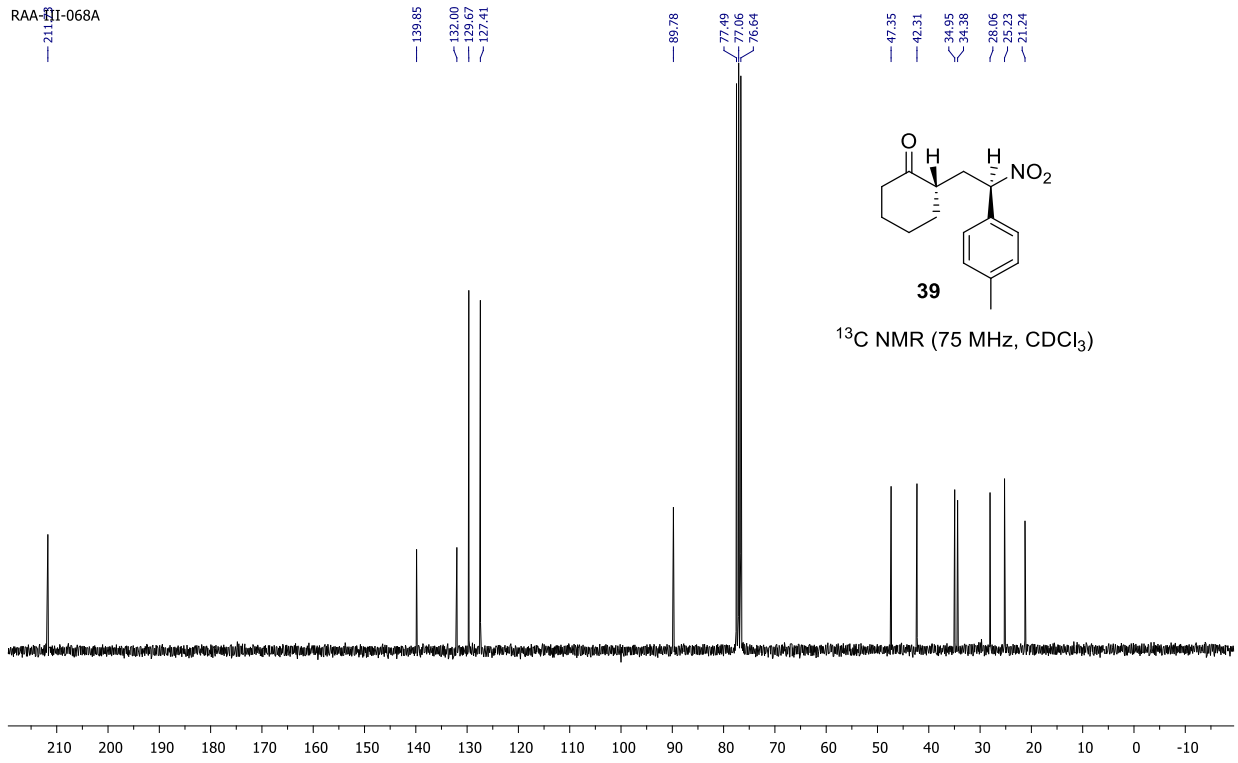
^{1}H NMR (300 MHz, $CDCl_3$)



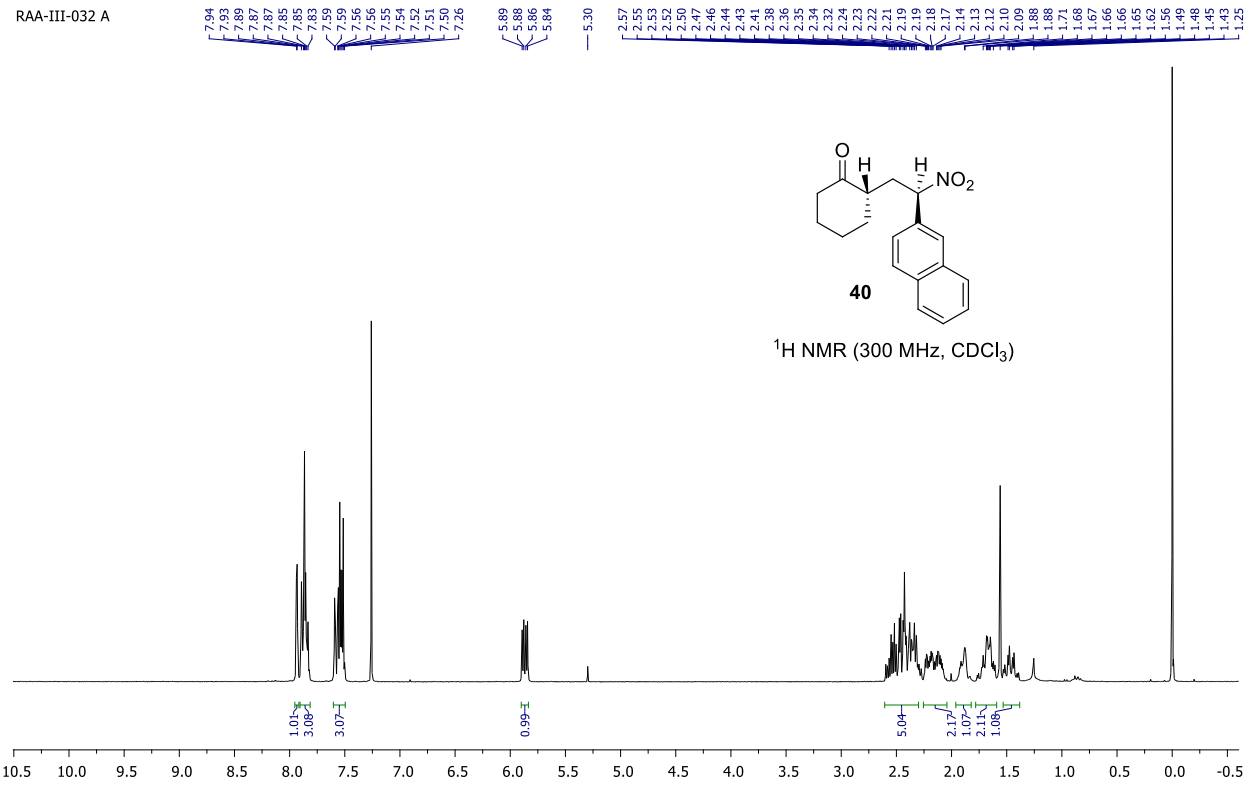
38

^{13}C NMR (75 MHz, $CDCl_3$)


RAA-III-054 A
7.37
7.36
7.35
7.34
7.26
7.21
7.18
5.68
5.66
5.64
5.63
2.45
2.44
2.42
2.41
2.40
2.39
2.36
2.35
2.34
2.32
2.31
2.30
2.29
2.28
2.26
2.25
2.18
2.14
2.13
2.11
2.10
2.09
1.87
1.86
1.70
1.67
1.66
1.65
1.64
1.64
1.63
1.57
1.44
1.40
1.25
0.00
O
H
H
NO2
39
1H NMR (300 MHz, CDCl3)
1.99
1.98
1.00
2.13
2.89
3.01
2.08
1.02
2.09
1.10
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


RAA-III-068A
211.43
139.85
132.00
129.67
127.41
89.78
77.49
77.06
76.64
47.35
42.31
34.95
34.38
28.06
25.23
21.24
O
H
H
NO2
39
13C NMR (75 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

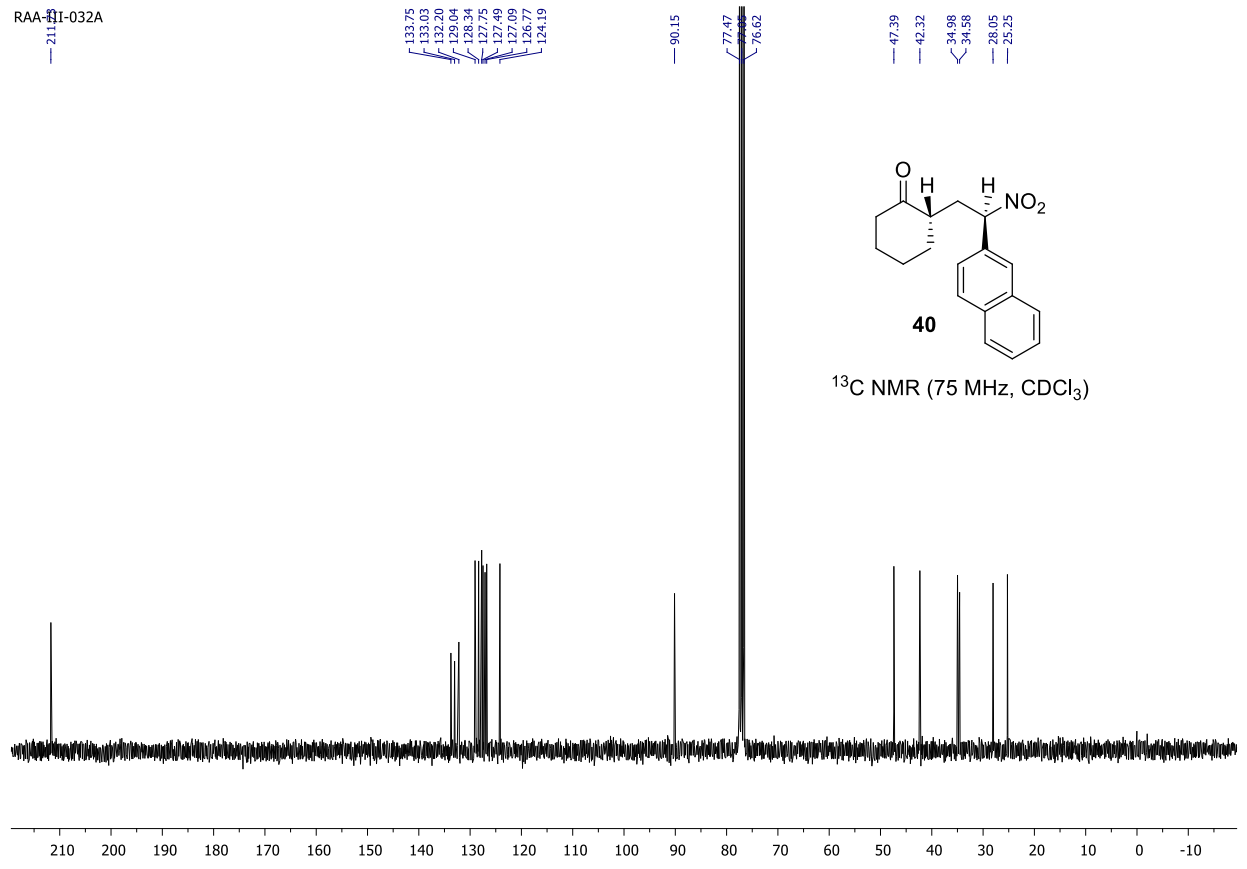
RAA-III-032 A



40

^{1}H NMR (300 MHz, $CDCl_3$)

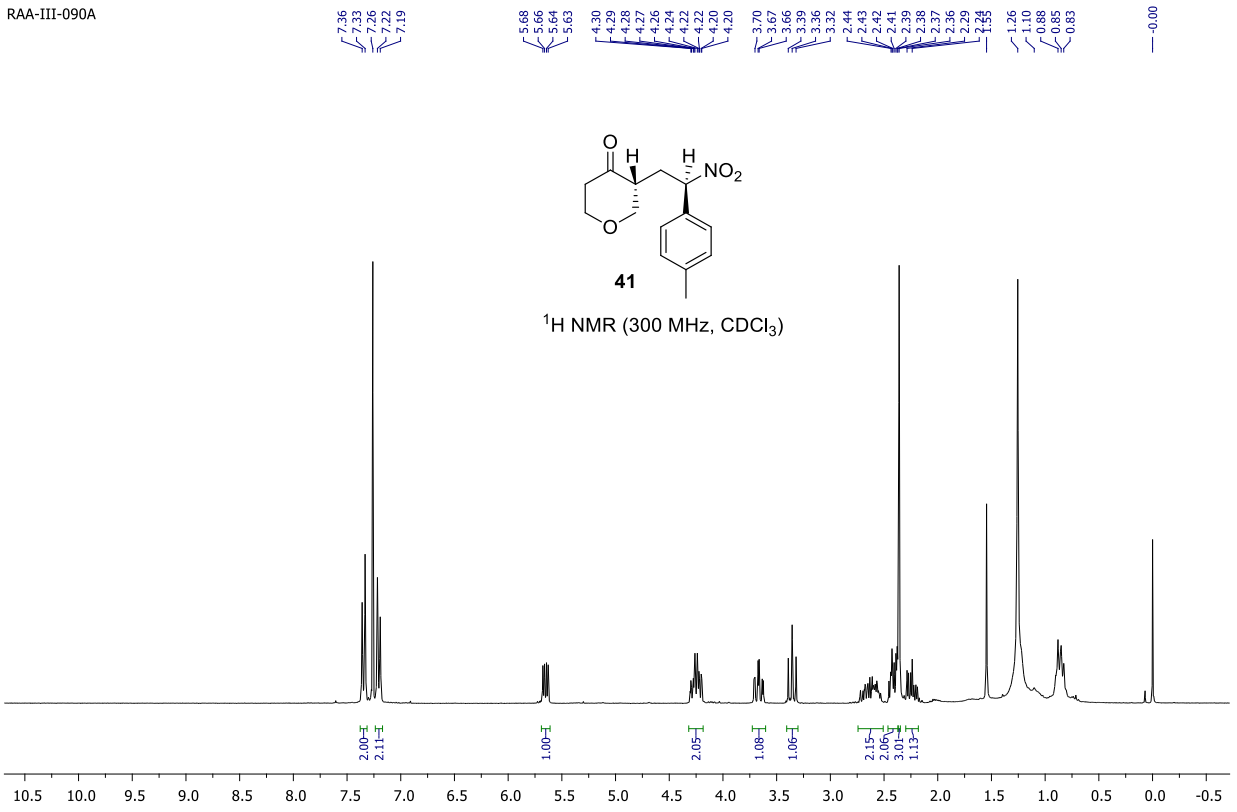
RAA-III-032A



40

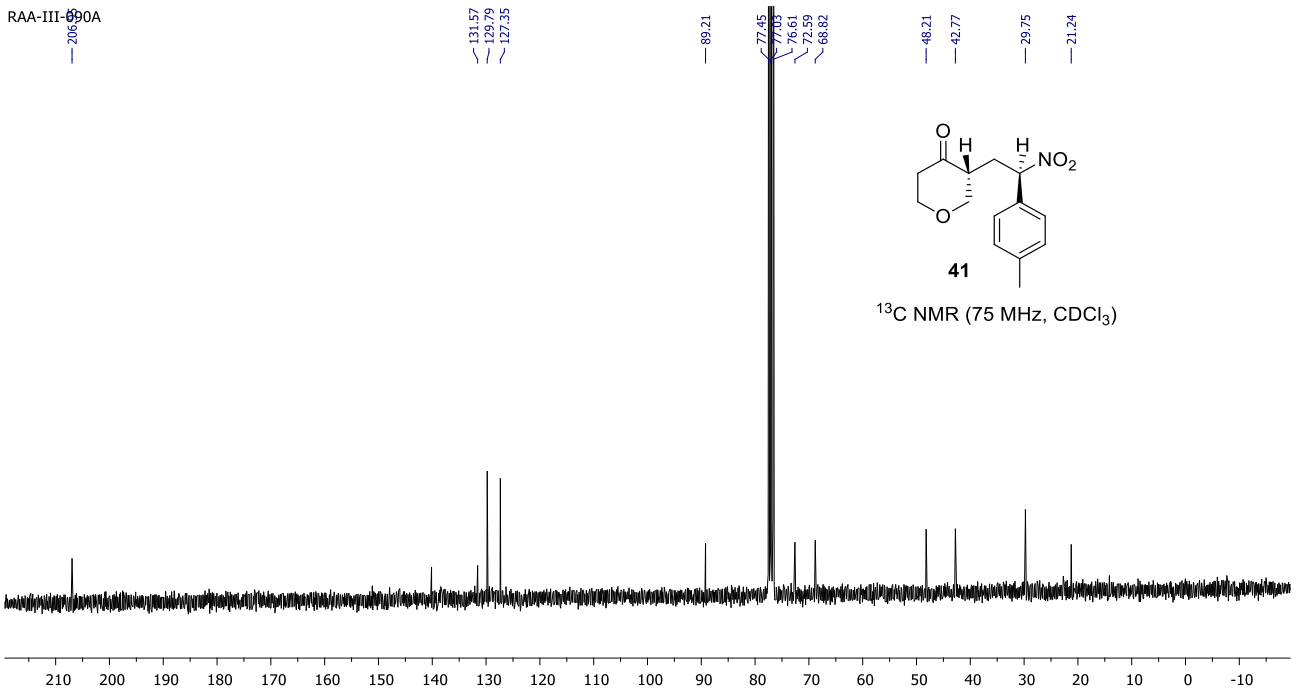
^{13}C NMR (75 MHz, $CDCl_3$)

RAA-III-090A

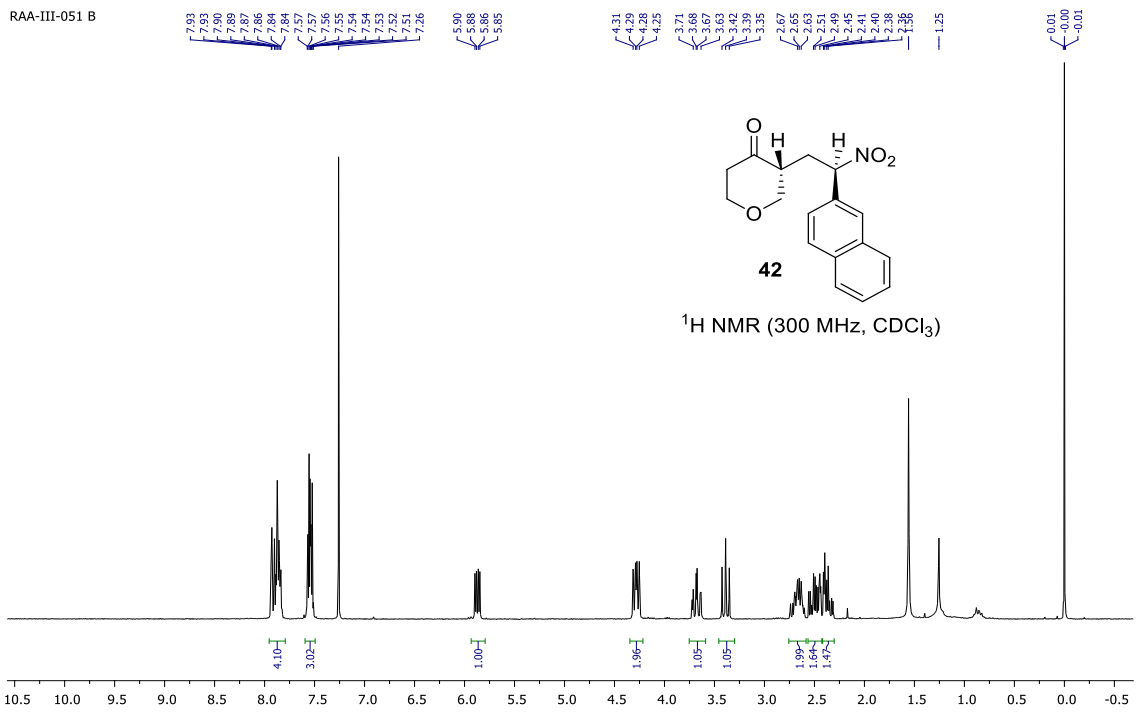


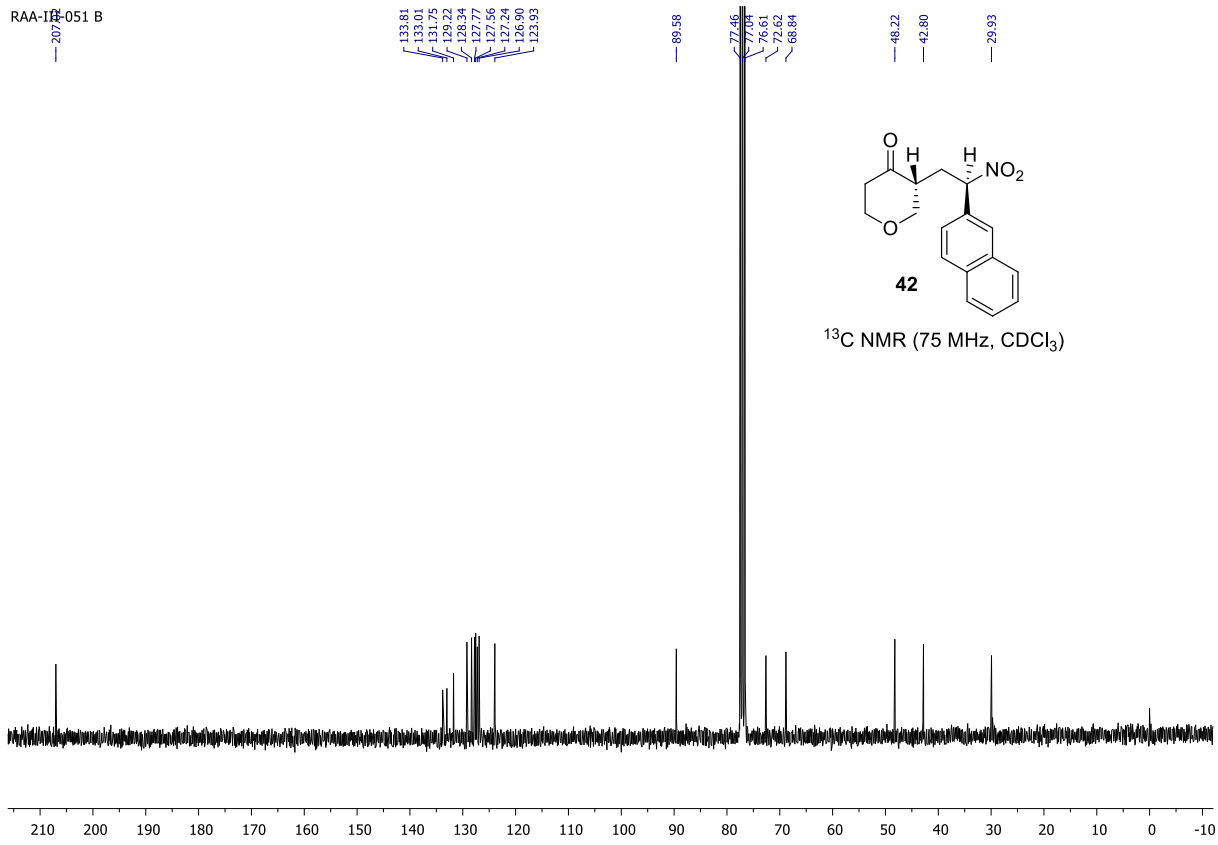
^{1}H NMR (300 MHz, $CDCl_3$)

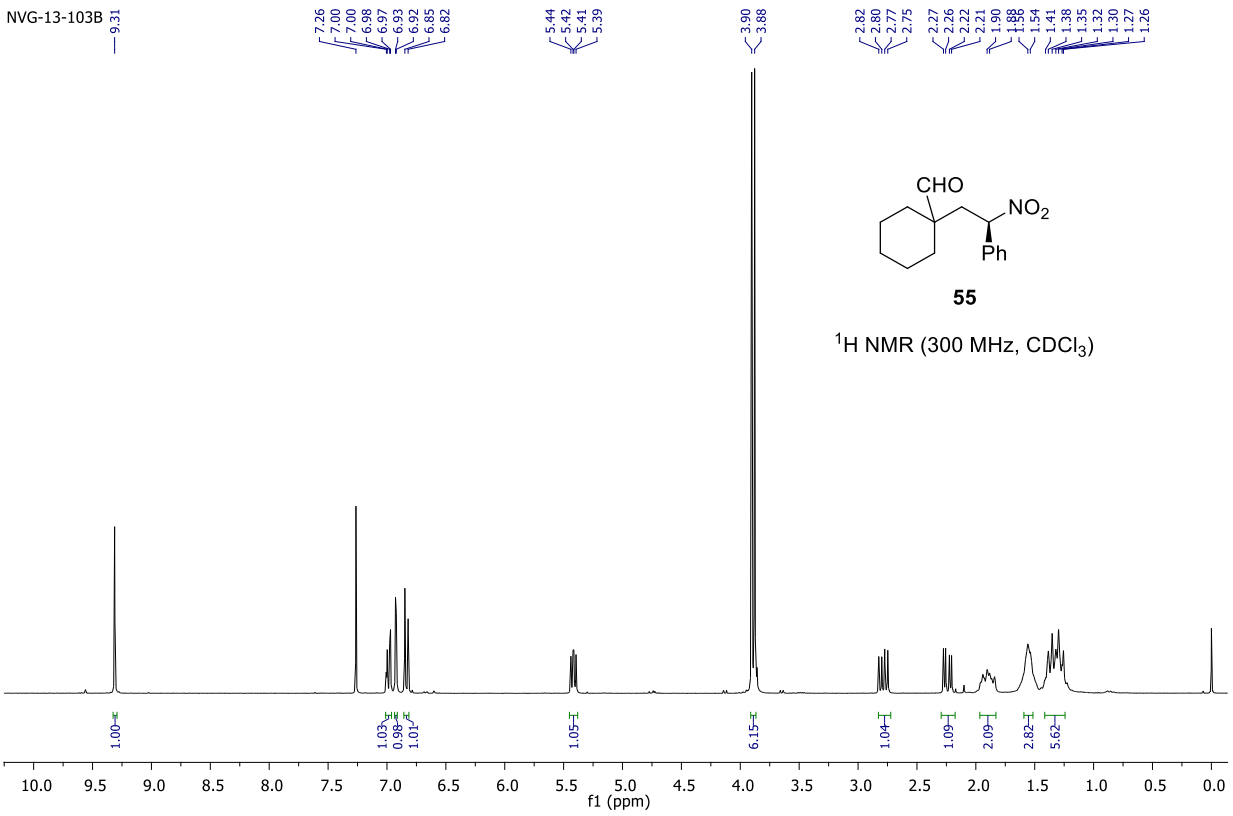
RAA-III-090A



^{13}C NMR (75 MHz, $CDCl_3$)

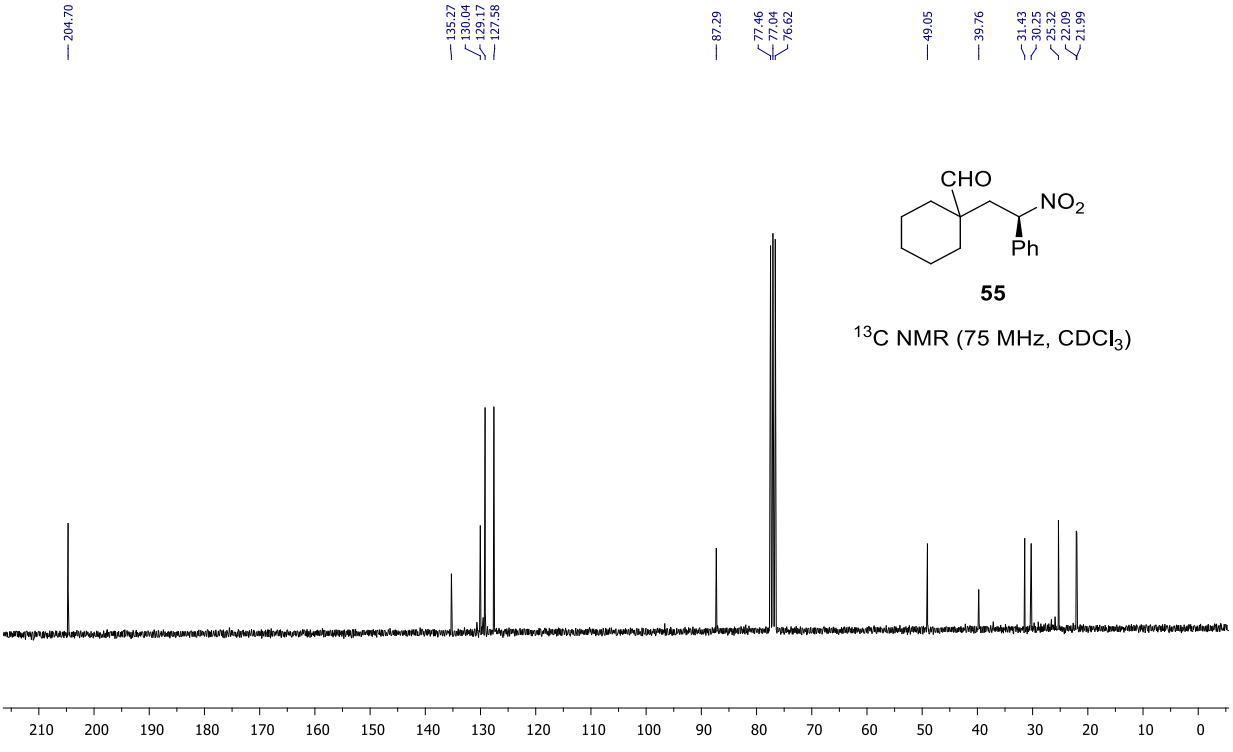

RAA-III-051 B
7.93
7.93
7.90
7.89
7.87
7.86
7.84
7.84
7.57
7.57
7.56
7.55
7.54
7.54
7.53
7.52
7.51
7.26
5.90
5.88
5.86
5.85
4.31
4.29
4.28
4.25
3.71
3.68
3.67
3.63
3.42
3.39
3.35
2.67
2.65
2.63
2.51
2.49
2.45
2.41
2.40
2.38
1.25
0.01
0.00
-0.01
O
H
H
NO2
O
42
1H NMR (300 MHz, CDCl3)
4.10
3.02
1.00
1.96
1.05
1.05
1.99
1.64
1.47
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


RAA-III-051 B
207.15
133.81
133.01
131.75
129.22
128.34
127.77
127.56
127.24
126.90
123.93
89.58
77.46
77.04
76.61
72.62
68.84
48.22
42.80
29.93
O
H
H
NO2
O
42
13C NMR (75 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



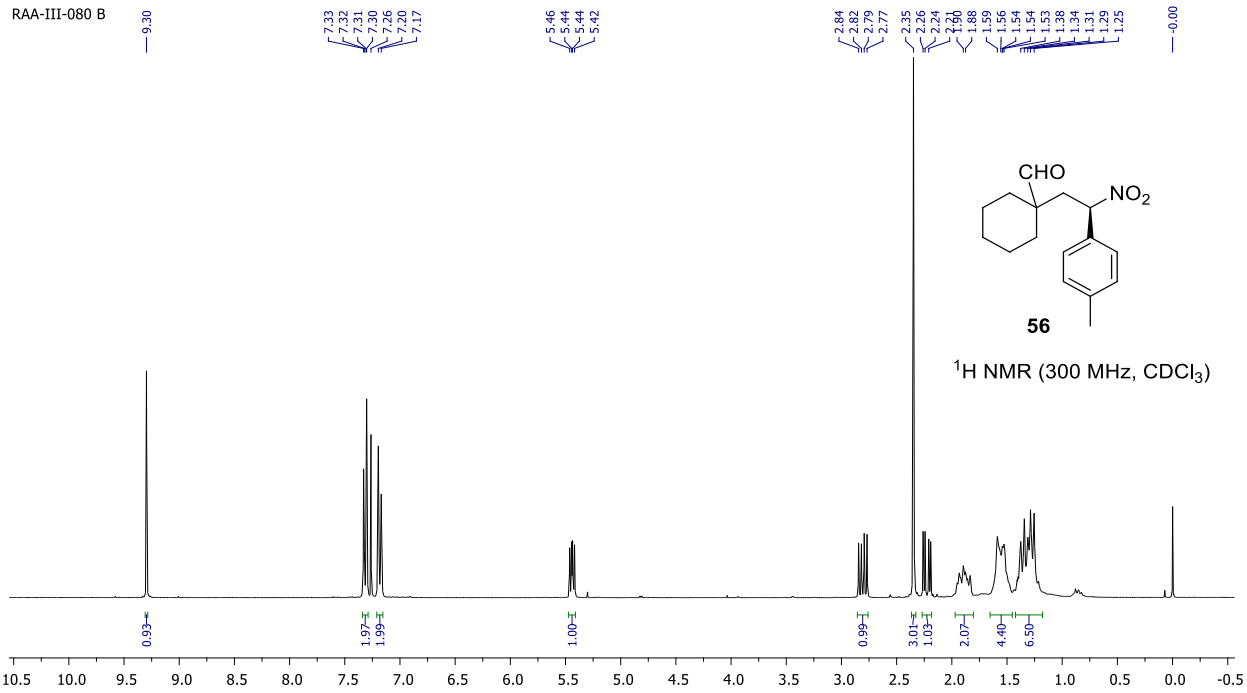
55

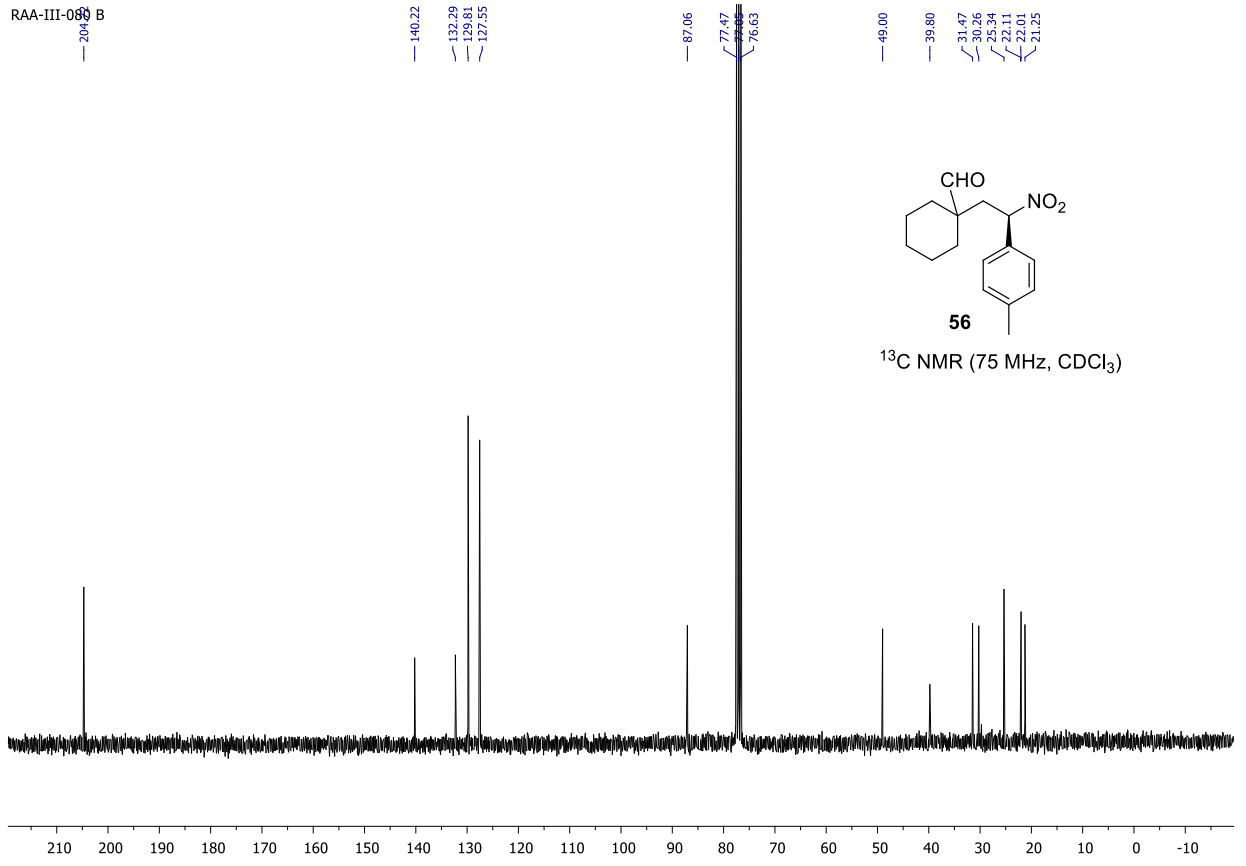
^{1}H NMR (300 MHz, $CDCl_3$)

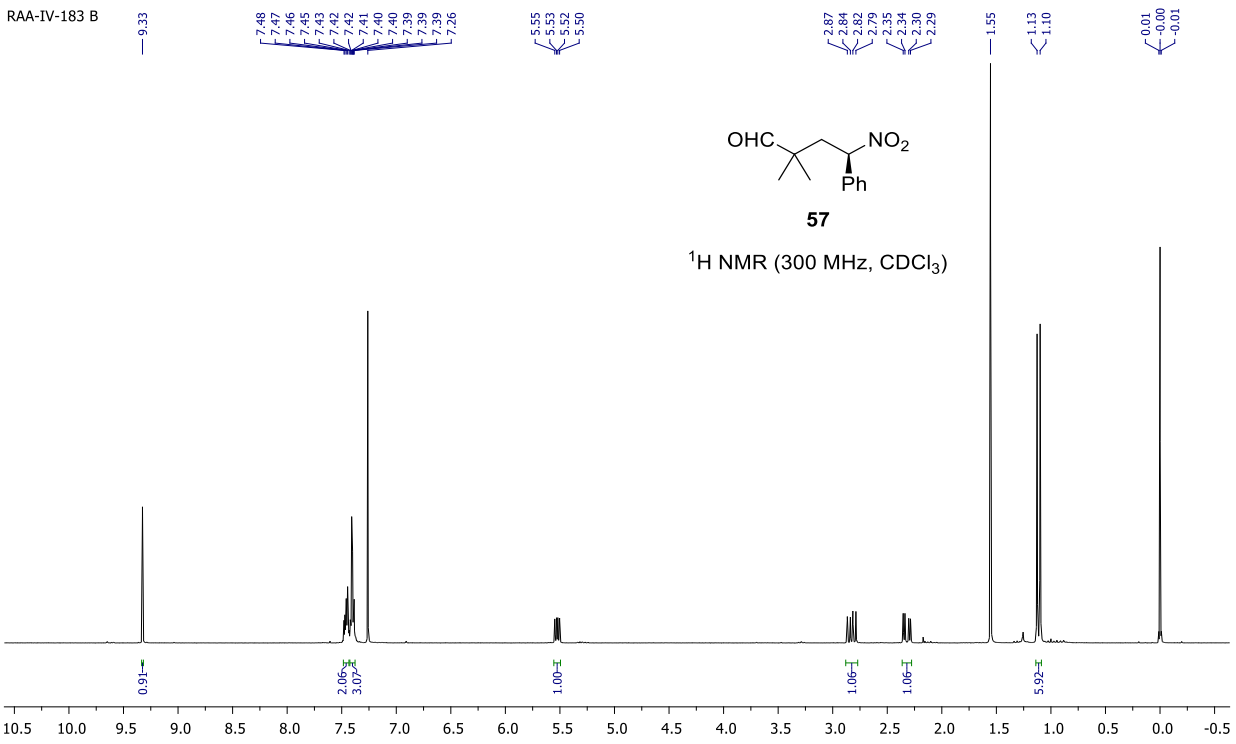


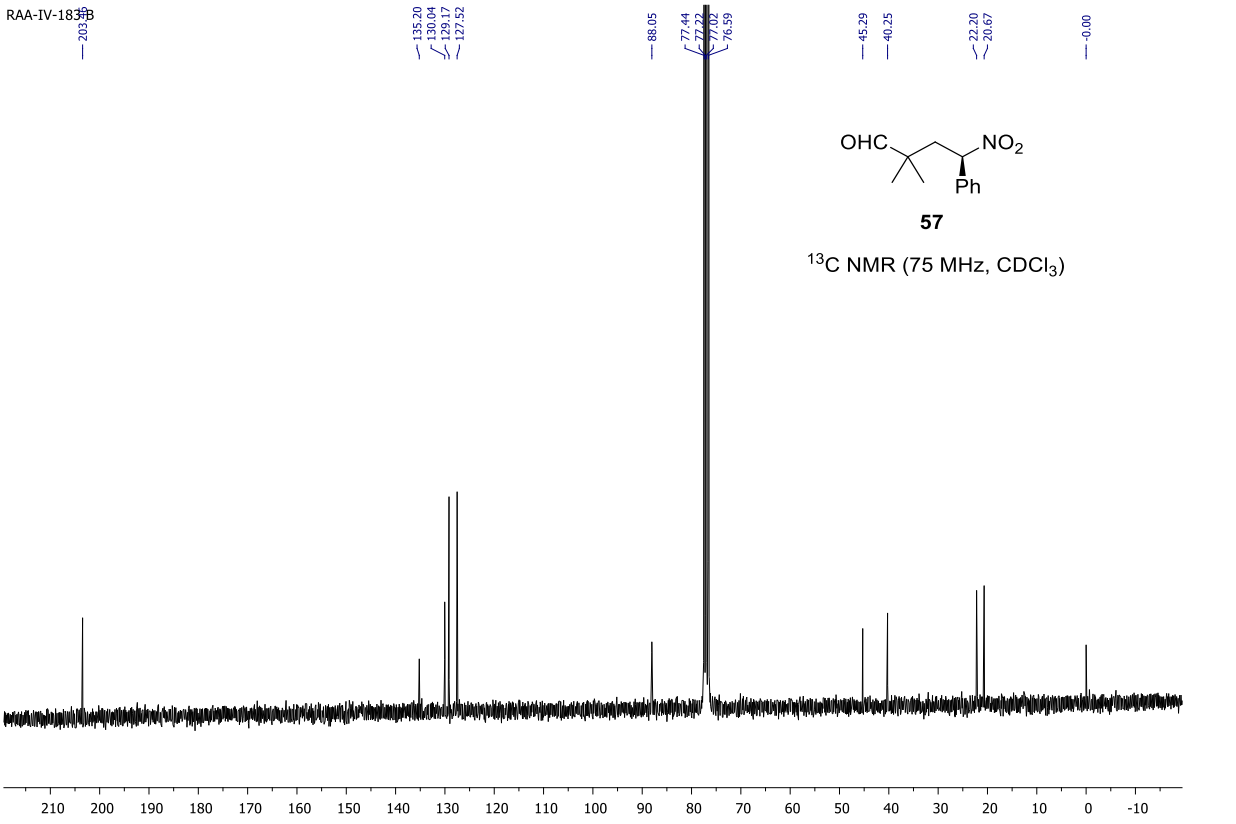
55

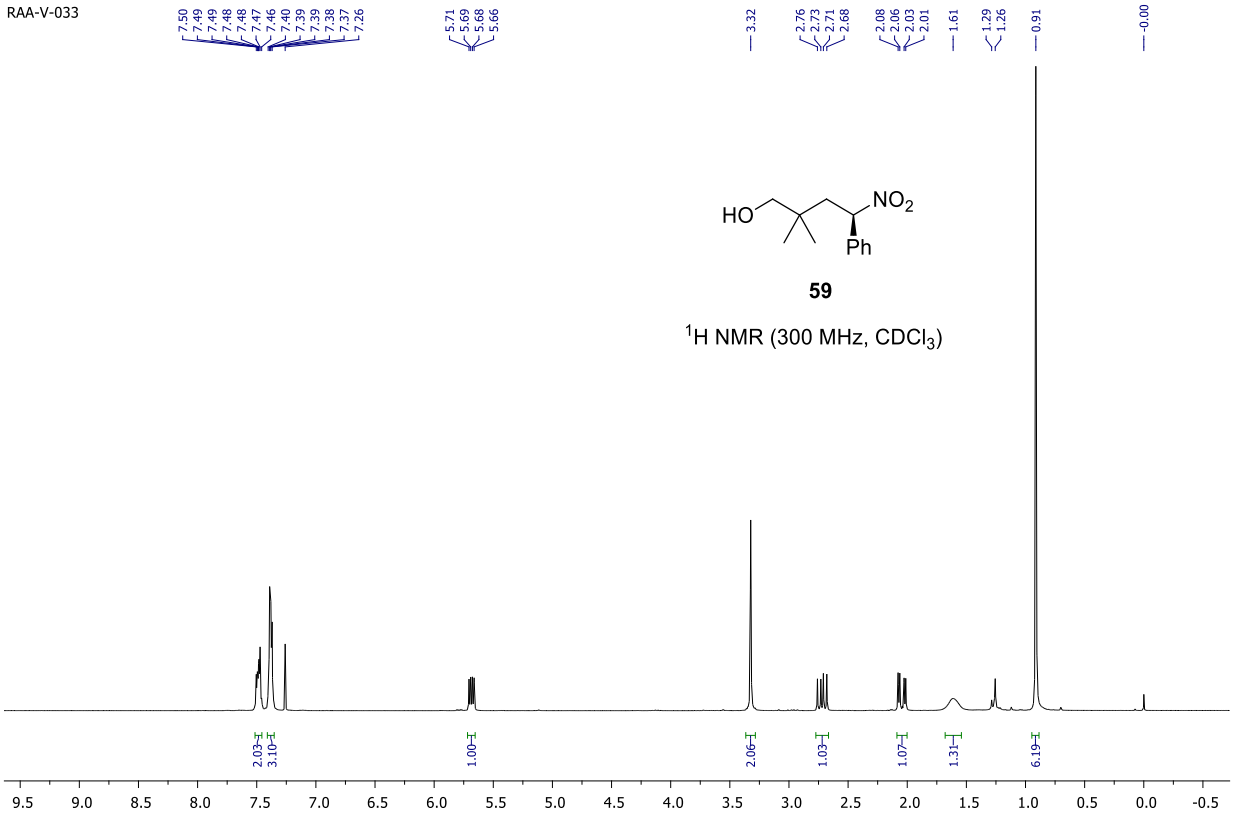
^{13}C NMR (75 MHz, $CDCl_3$)

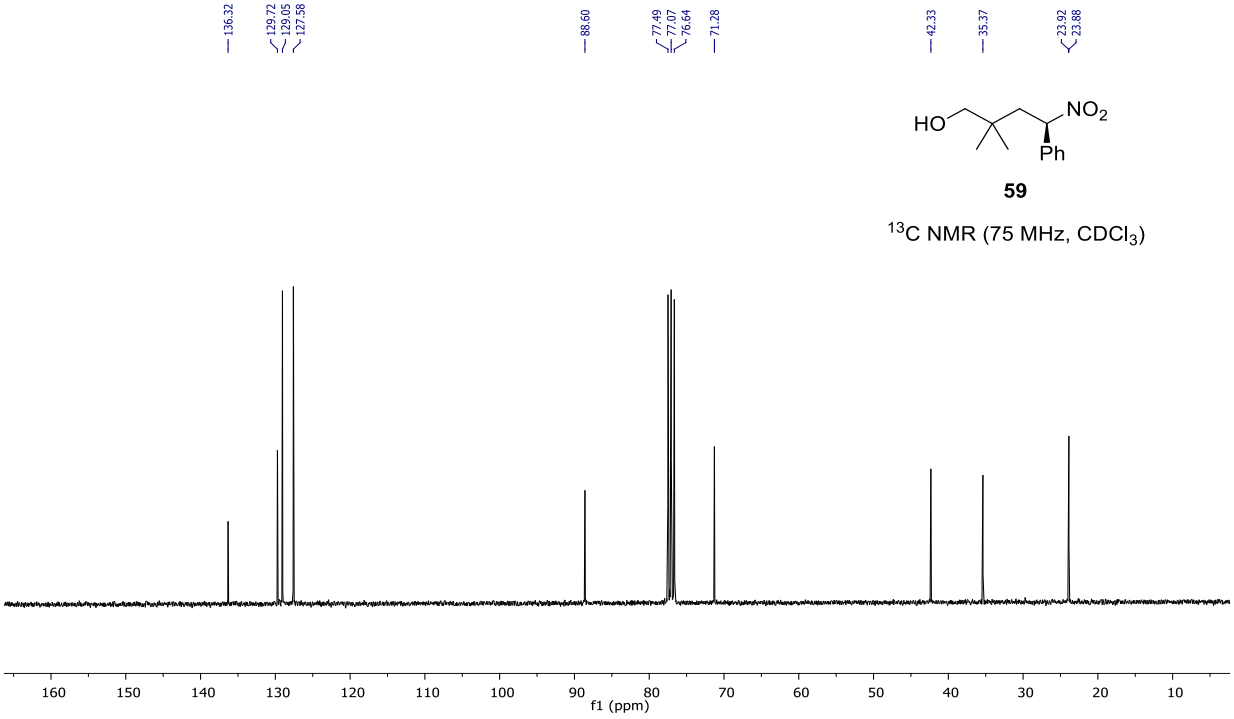

RAA-III-080 B
9.30
7.33
7.32
7.31
7.30
7.26
7.20
7.17
5.46
5.44
5.44
5.42
2.84
2.82
2.79
2.77
2.35
2.26
2.24
2.21
1.90
1.88
1.59
1.56
1.54
1.54
1.53
1.38
1.34
1.31
1.29
1.25
0.00
CHO
NO2
56
1H NMR (300 MHz, CDCl3)
0.93
1.97
1.99
1.00
0.99
3.01
1.03
2.07
4.40
6.50
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

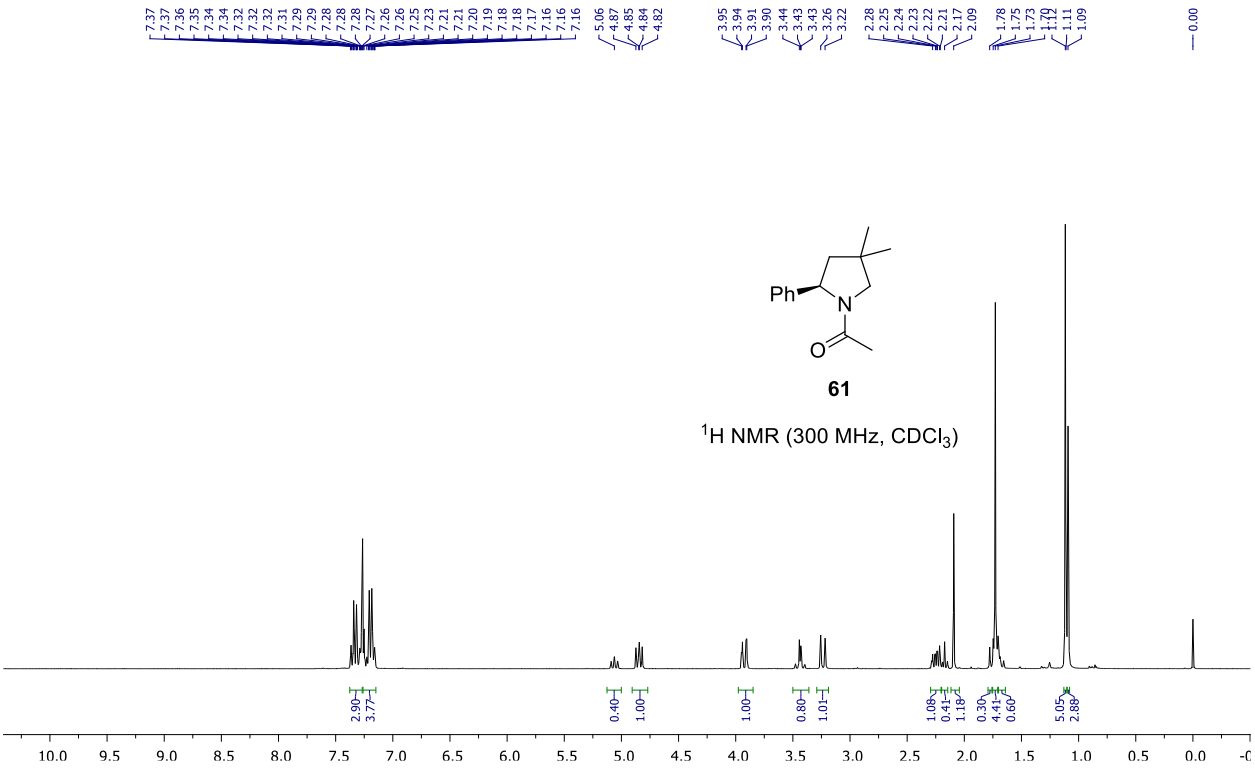

RAA-III-080 B
204.71
140.22
132.29
129.81
127.55
87.06
77.47
77.26
76.63
49.00
39.80
31.47
30.26
25.34
22.11
22.01
21.25
CHO
NO2
56
13C NMR (75 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

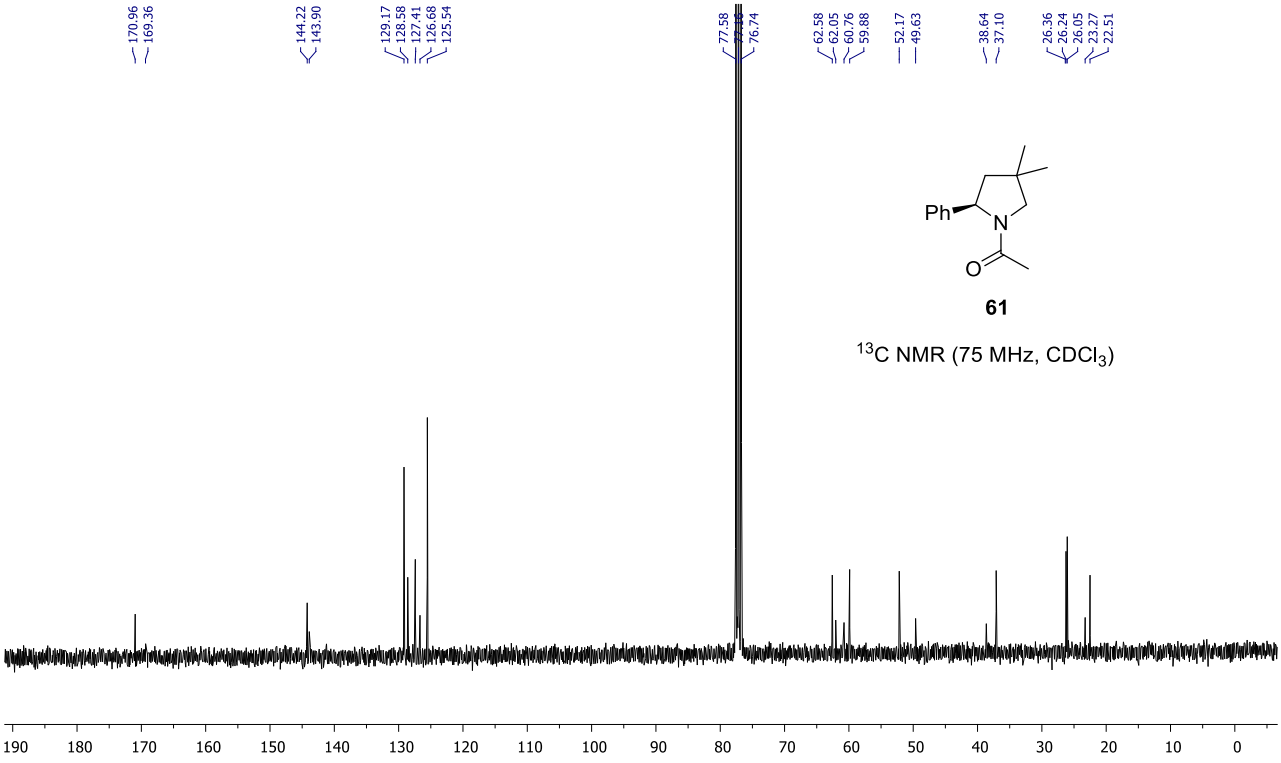

RAA-IV-183 B
OHC
NO2
Ph
57
1H NMR (300 MHz, CDCl3)


RAA-IV-183 B
OHC
NO2
Ph
57
13C NMR (75 MHz, CDCl3)


RAA-V-033
7.50
7.49
7.49
7.48
7.48
7.47
7.46
7.40
7.39
7.39
7.38
7.37
7.26
5.71
5.69
5.68
5.66
3.32
2.76
2.73
2.71
2.68
2.08
2.06
2.03
2.01
1.61
1.29
1.26
0.91
-0.00
HO
NO2
Ph
59
1H NMR (300 MHz, CDCl3)
2.03
3.10
1.00
2.06
1.03
1.07
1.31
6.19
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


136.32
129.72
129.05
127.58
88.60
77.49
77.07
76.64
71.28
42.33
35.37
23.92
23.88
HO
NO2
Ph
59
13C NMR (75 MHz, CDCl3)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Ph
N
O
61
1H NMR (300 MHz, CDCl3)


Ph
N
O
61
13C NMR (75 MHz, CDCl3)

2.9 Selected HPLC traces:

Memorial University

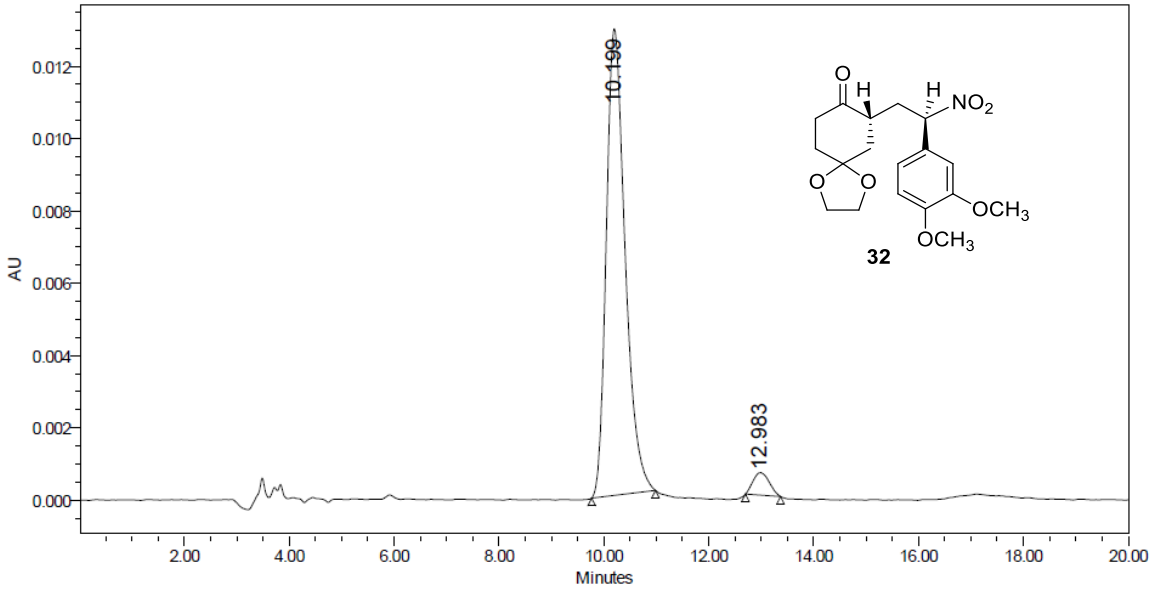
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-08-44A MICHAEL TOP	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	17/08/2015 7:50:16 PM NDT
Vial:	1	Acq. Method:	ASH 60%HEX 40%IPA
Injection #:	1	Date Processed:	17/08/2015 8:16:27 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	20.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



32

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	10.199	322486	96.00	12907	95.41
2	12.983	13435	4.00	622	4.59

Report Method: Individual Control Report

Page: 1 of 1

Printed: 19/08/2015

5:35:25 PM Canada/Newfoundland

Memorial University

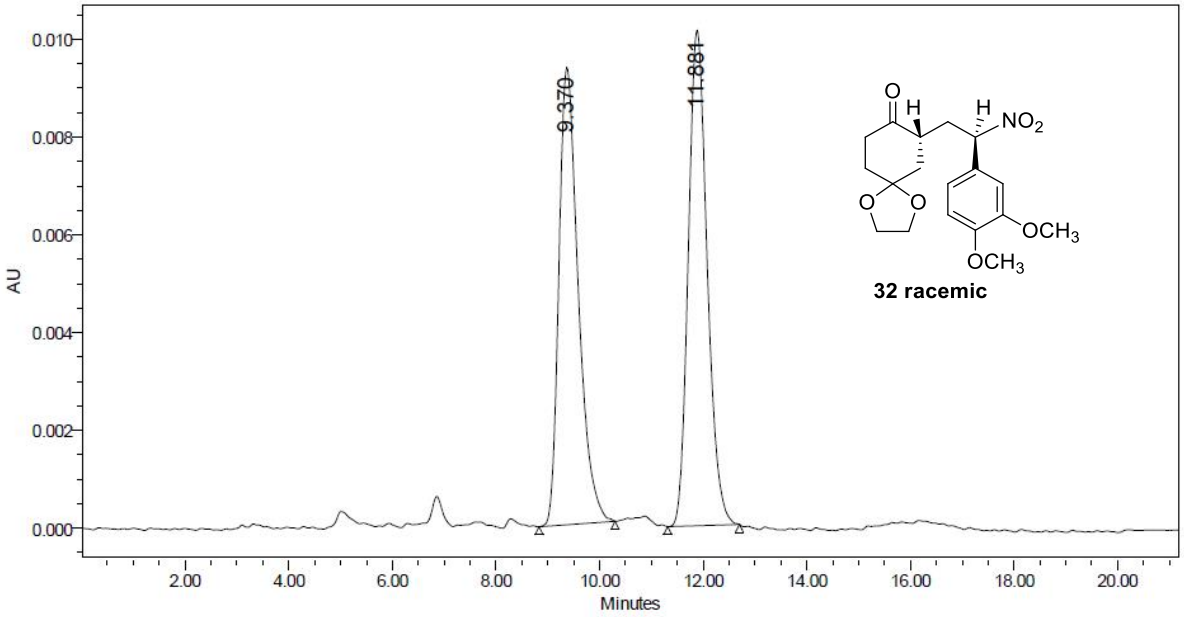
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-12-36A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	29/09/2016 10:14:54 AM NDT
Vial:	89	Acq. Method:	ASH 60%HEX 40%IPA
Injection #:	1	Date Processed:	03/12/2017 2:41:04 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



32 racemic

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	9.370	243187	48.70	9351	47.99
2	11.881	256179	51.30	10136	52.01

Report Method: Individual Control Report

Page: 1 of 1

Printed: 03/12/2017

2:41:55 PM Canada/Newfoundland

Memorial University

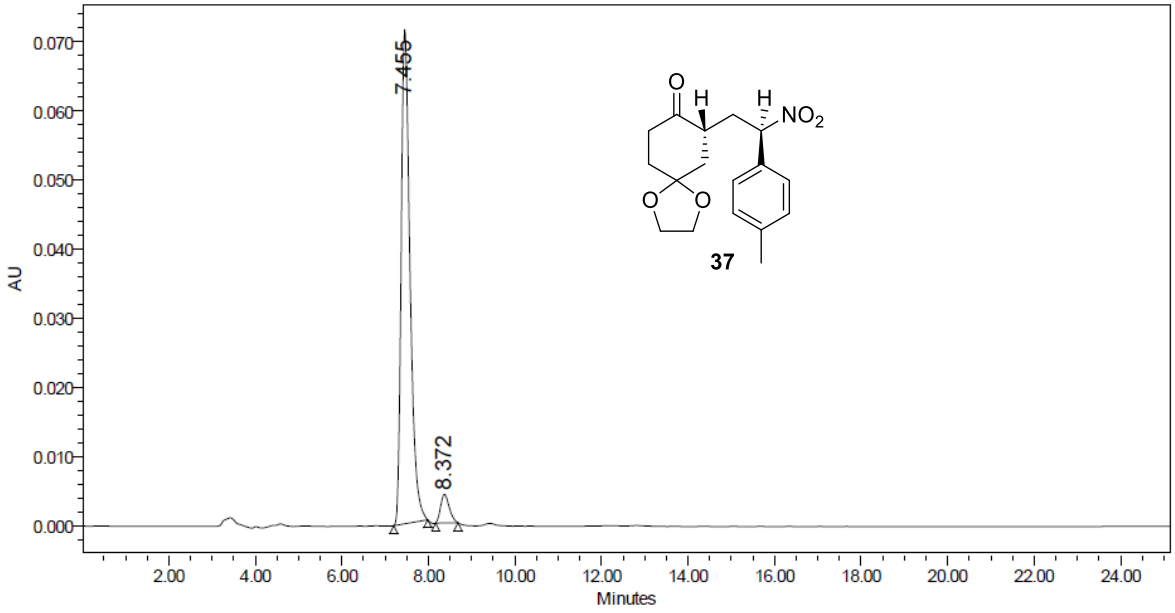
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-III-079A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/01/2017 4:23:35 PM NST
Vial:	1	Acq. Method:	AS_H 70%HEX 30%IPA
Injection #:	2	Date Processed:	11/01/2017 4:47:12 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



37

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.455	1012734	94.62	71530	94.52
2	8.372	57553	5.38	4147	5.48

Report Method: Individual Control Report

Page: 1 of 1

Printed: 11/01/2017 4:49:27 PM Canada/Newfoundland

Memorial University

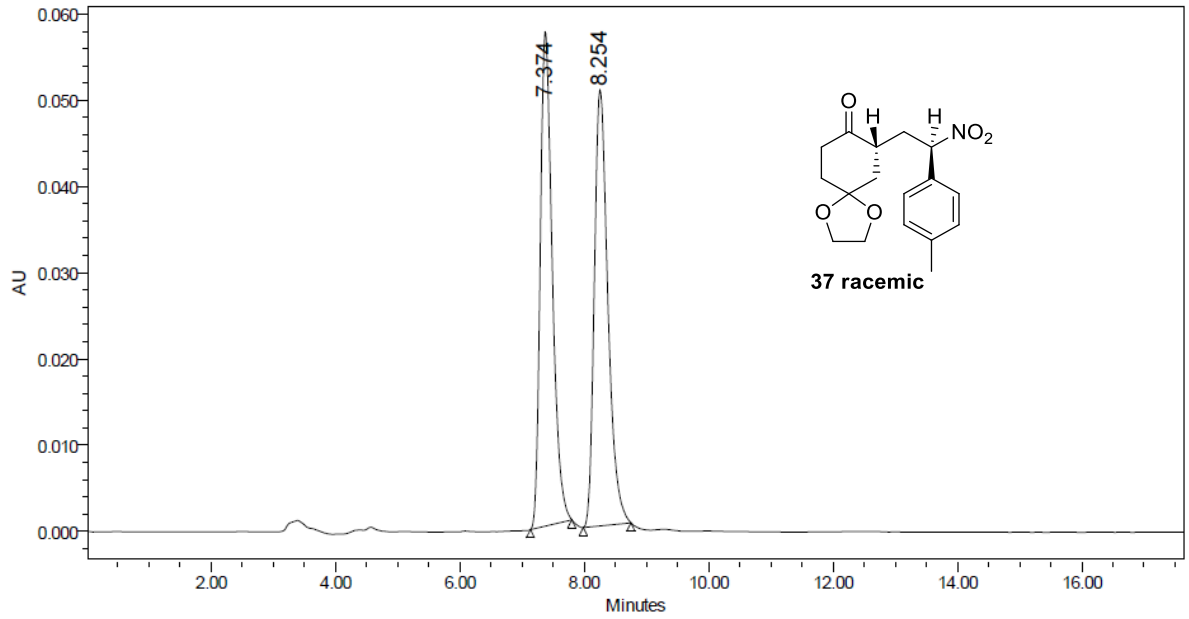
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-III-082A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/01/2017 4:55:34 PM NST
Vial:	1	Acq. Method:	AS_H 70%HEX 30%IPA
Injection #:	3	Date Processed:	11/01/2017 5:12:46 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.374	769570	50.14	57533	53.18
2	8.254	765127	49.86	50655	46.82

Memorial University

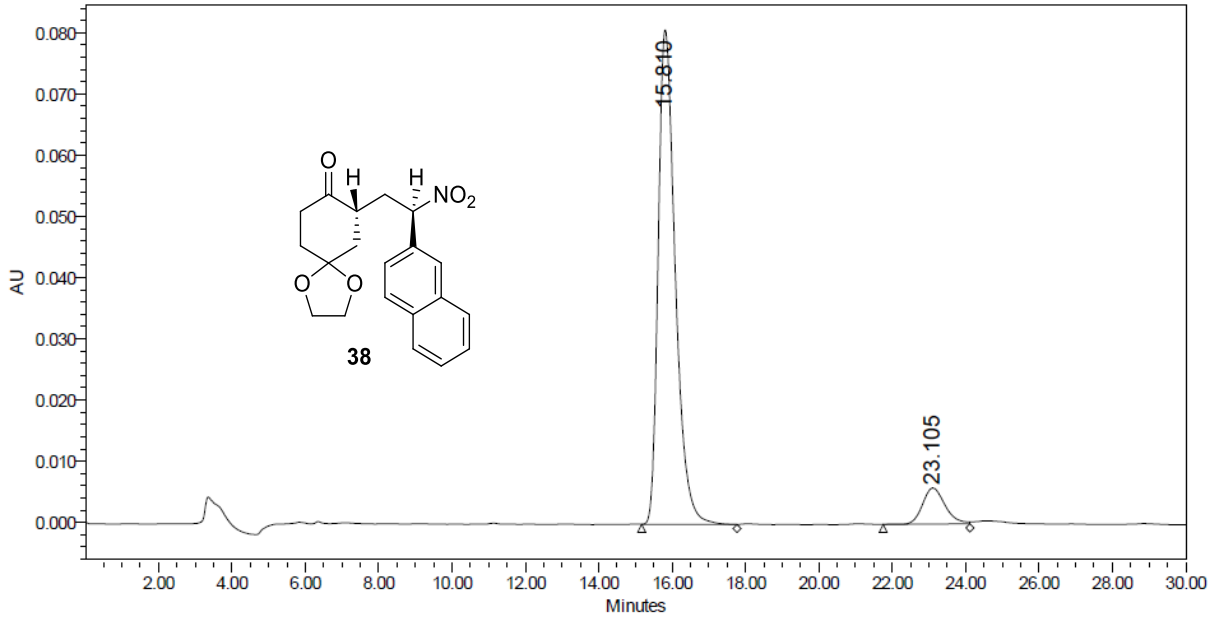
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-III-028A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/01/2017 2:26:27 PM NST
Vial:	1	Acq. Method:	AS_H 90% HEX 10% IPA
Injection #:	4	Date Processed:	02/12/2017 1:08:11 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.810	2607552	91.21	80776	93.21
2	23.105	251320	8.79	5881	6.79

Memorial University

Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-III-086A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/01/2017 12:47:56 PM NST
Vial:	1	Acq. Method:	AS_H 90% HEX 10% IPA
Injection #:	3	Date Processed:	11/01/2017 2:09:18 PM NST
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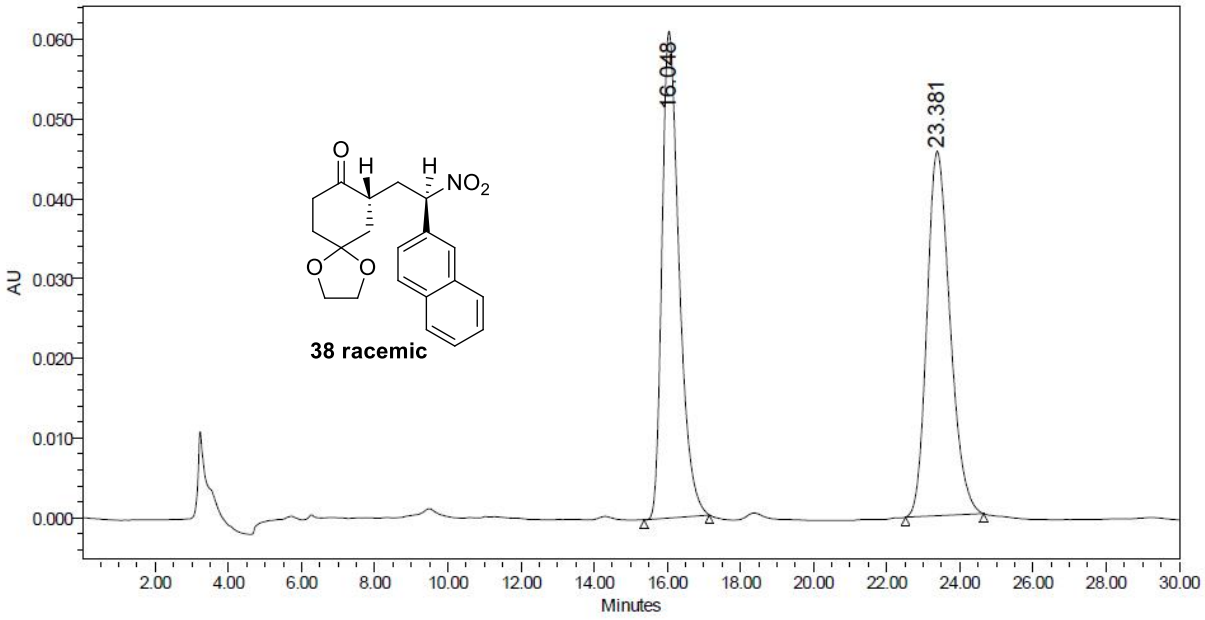

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2	23.381	2005592	50.23	45681	42.80

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Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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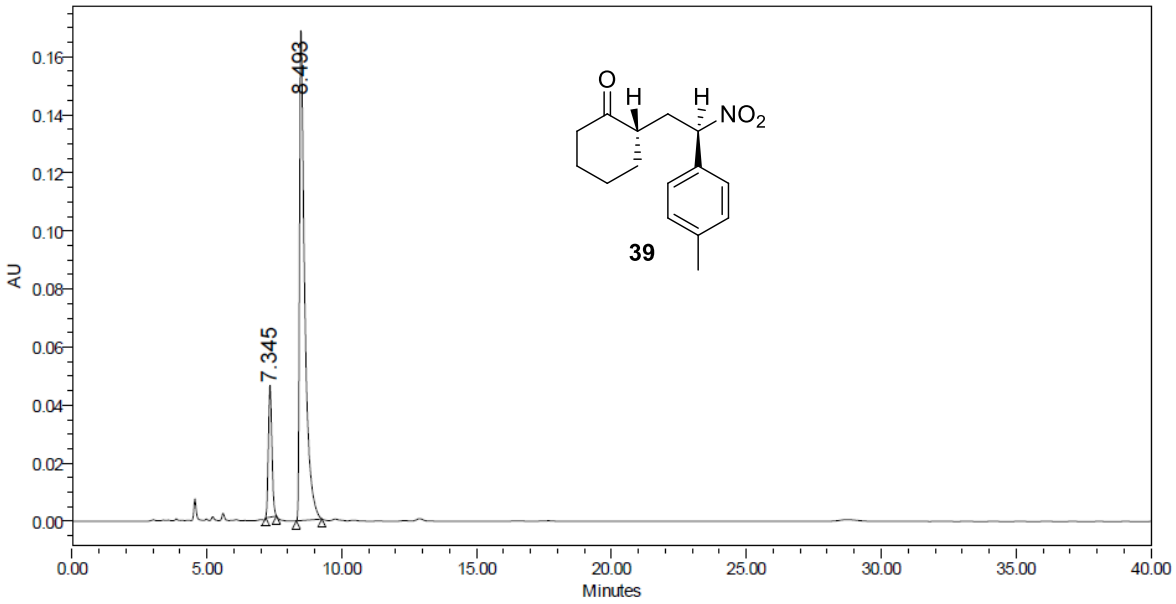

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Report Method: Individual Control Report

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Printed: 30/09/2016 1:04:46 PM Canada/Newfoundland

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	28/10/2016 4:25:22 PM NDT
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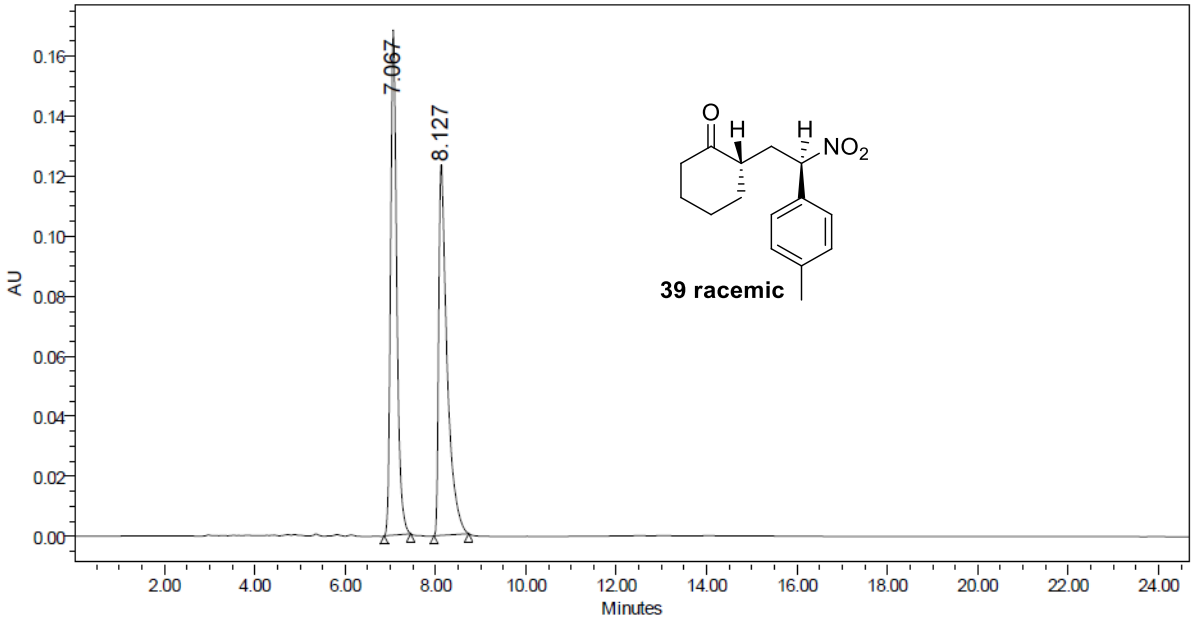

39 racemic

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.067	1605632	50.05	168055	57.35
2	8.127	1602171	49.95	124963	42.65

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	12/01/2017 11:22:08 AM NST
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Injection #:	2	Date Processed:	12/01/2017 11:47:08 AM NST
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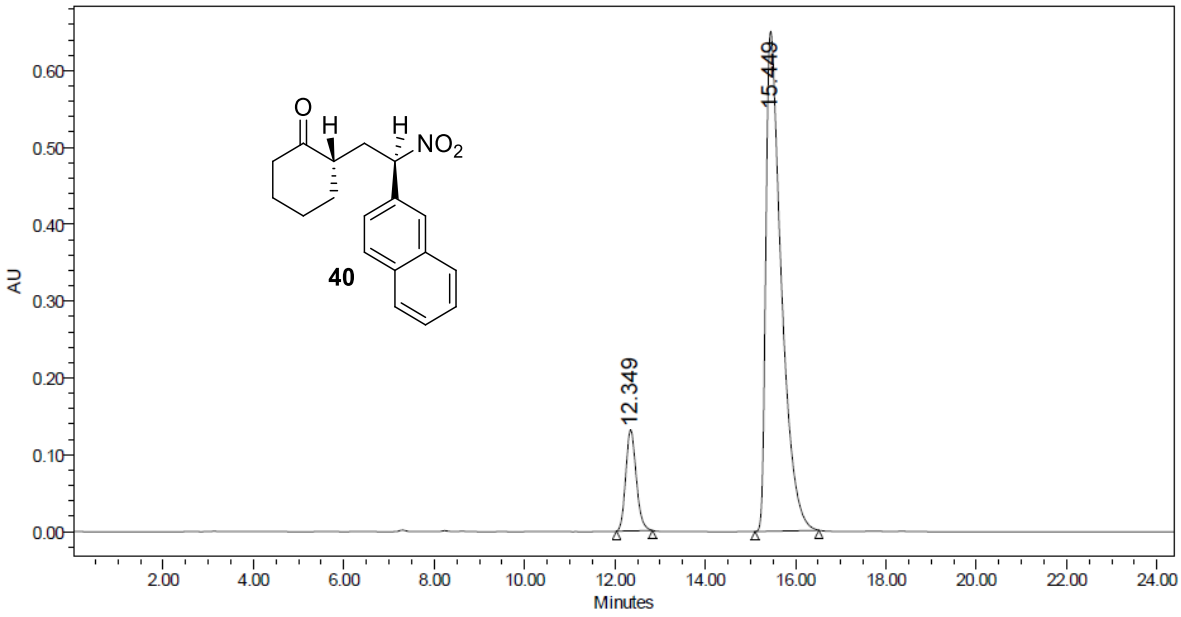
Column Type:		Sample Set Name	



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2	15.449	15452535	87.89	651014	83.20

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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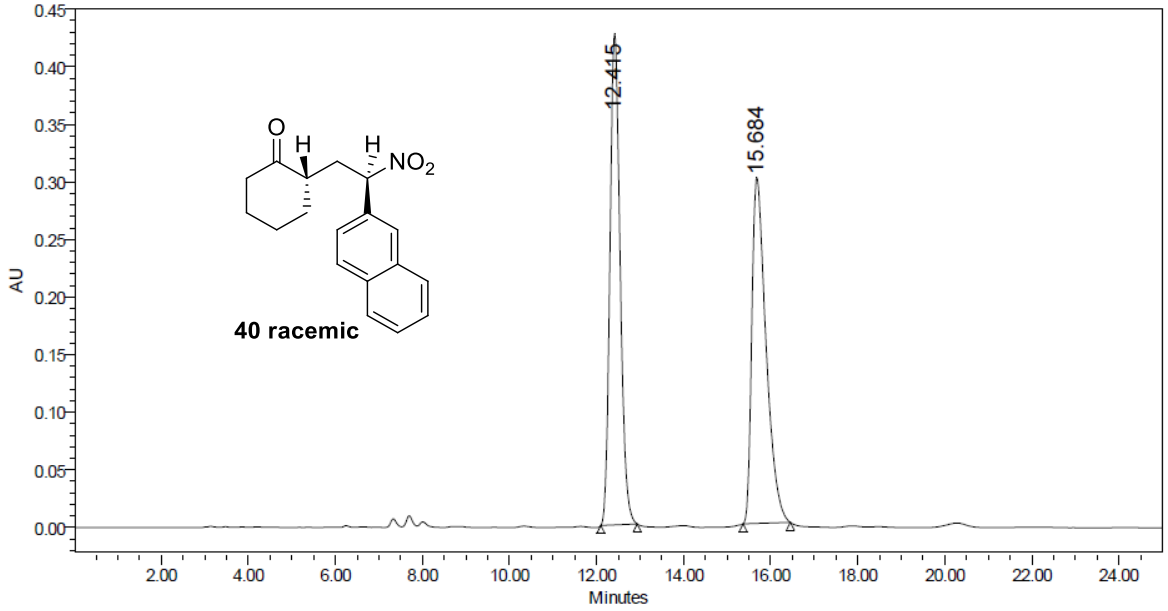

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2	15.684	6810455	49.61	300229	41.30

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	07/11/2016 11:33:08 AM NST
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Injection #:	1	Date Processed:	07/11/2016 4:06:18 PM NST
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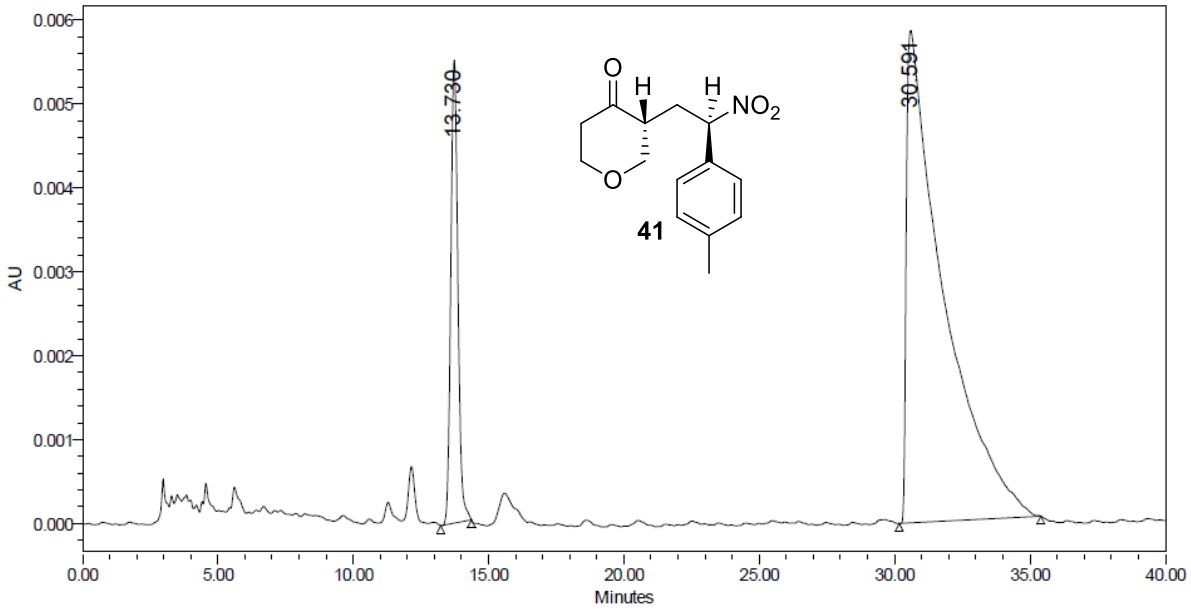

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1	13.730	100747	15.34	5522	48.48
2	30.591	556206	84.66	5868	51.52

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	04/11/2016 2:55:15 PM NDT
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Injection #:	1	Date Processed:	04/11/2016 4:08:09 PM NDT
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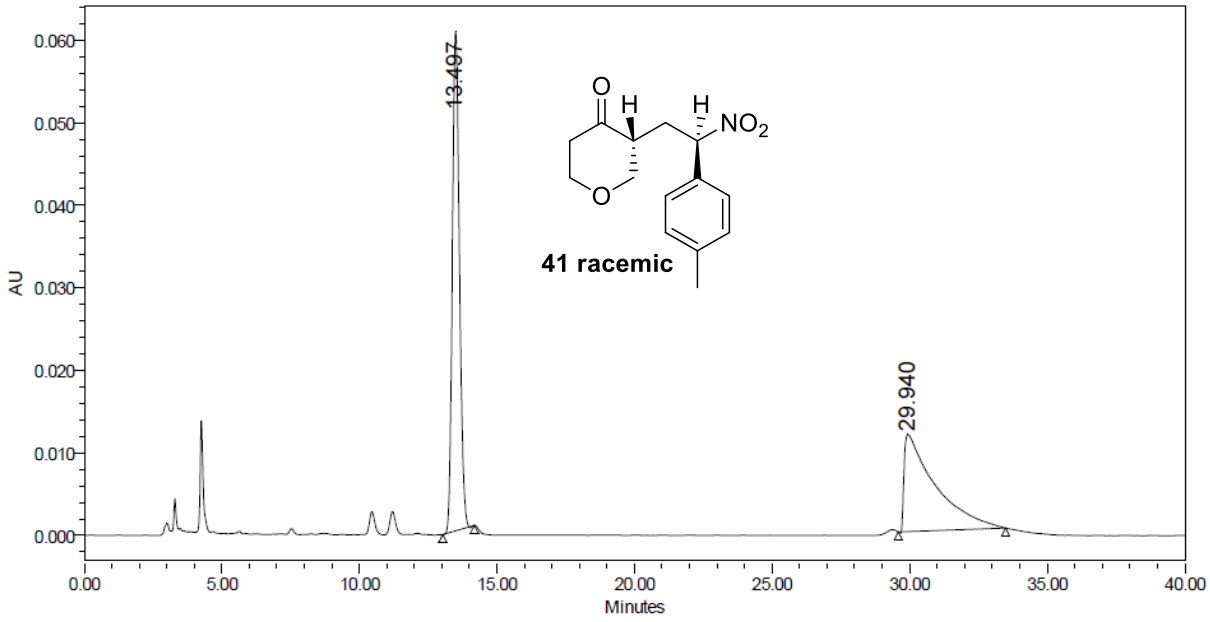

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1	13.497	1081041	53.91	60562	83.72
2	29.940	924310	46.09	11780	16.28

Memorial University

Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	31/08/2016 10:40:02 AM NDT
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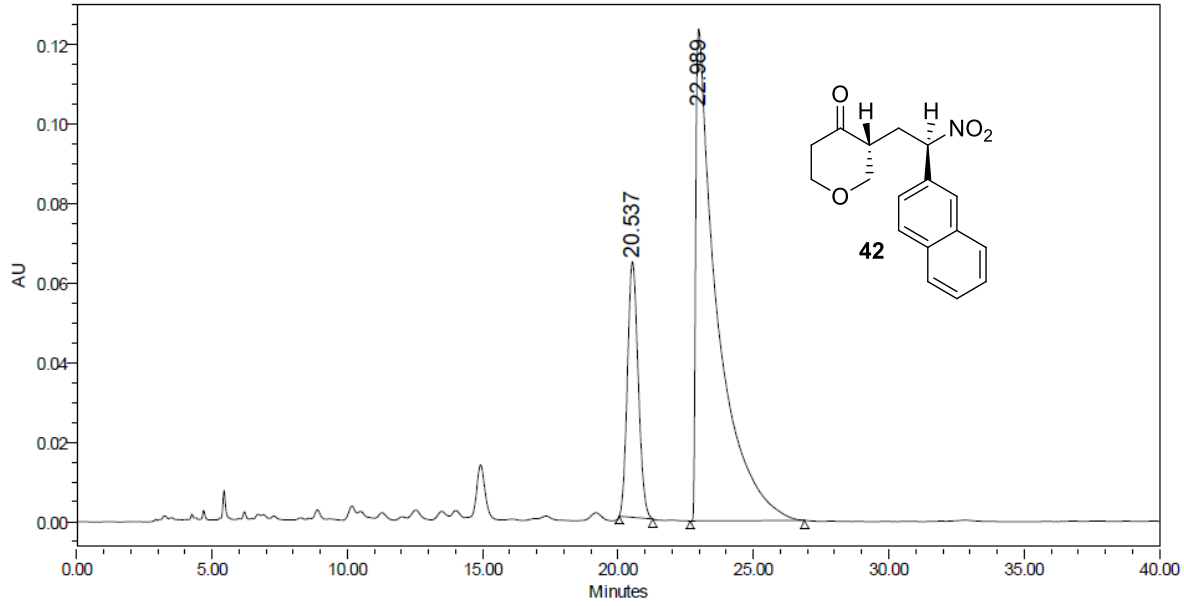

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1	20.537	1777448	20.73	64328	34.19
2	22.989	6795615	79.27	123798	65.81

Report Method: Individual Control Report

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Printed: 31/08/2016

11:21:56 AM Canada/Newfoundland

Memorial University

Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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Injection #:	2	Date Processed:	12/01/2017 3:44:47 PM NST
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Run Time:	40.00 Minutes	Channel Desc.:	
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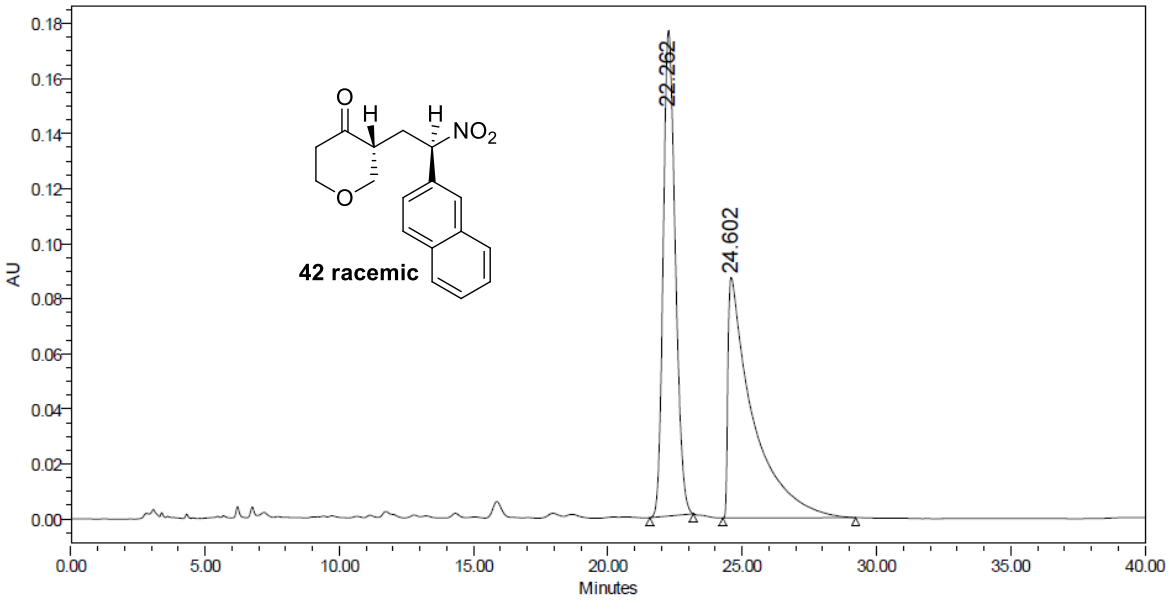

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1	22.262	5522811	49.70	176521	66.91
2	24.602	5589397	50.30	87315	33.09

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Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Injection #:	1	Date Processed:	11/03/2016 11:58:43 AM NST
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Run Time:	40.00 Minutes	Channel Desc.:	
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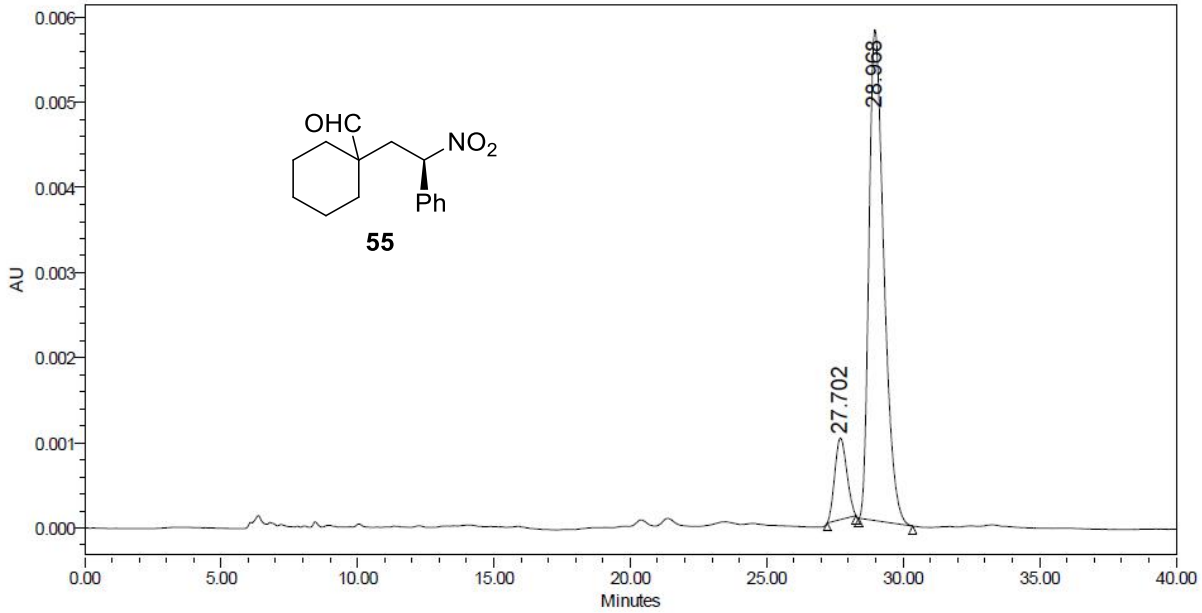

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1	27.702	29228	11.80	959	14.26
2	28.968	218567	88.20	5767	85.74

Memorial University

Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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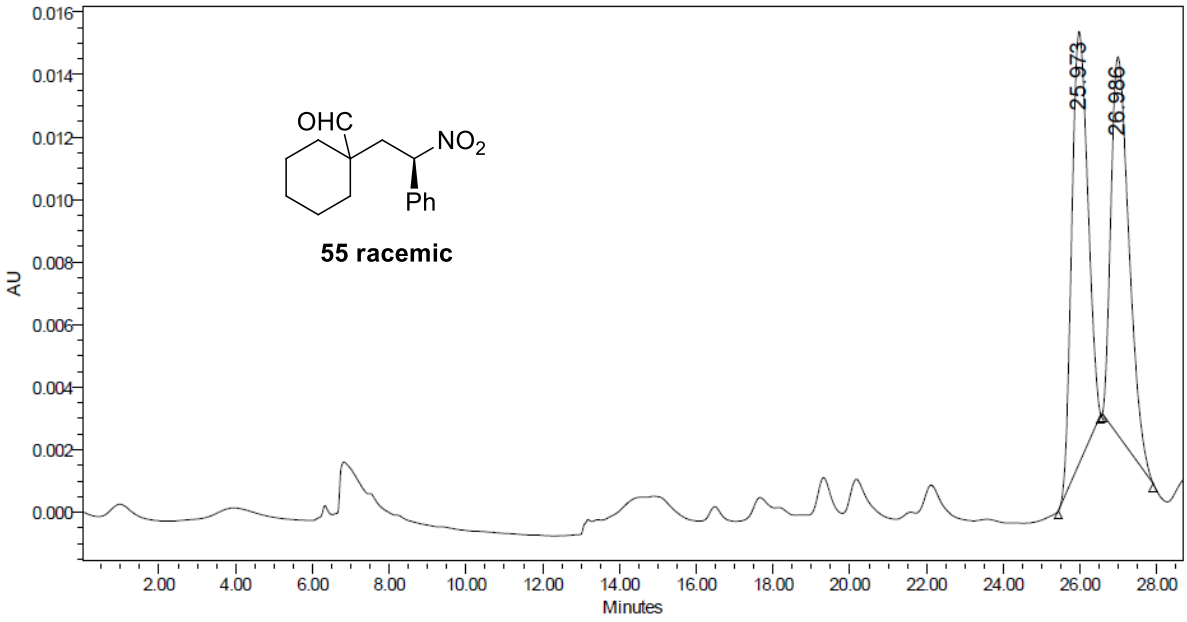

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	25.973	400664	50.32	13826	53.35
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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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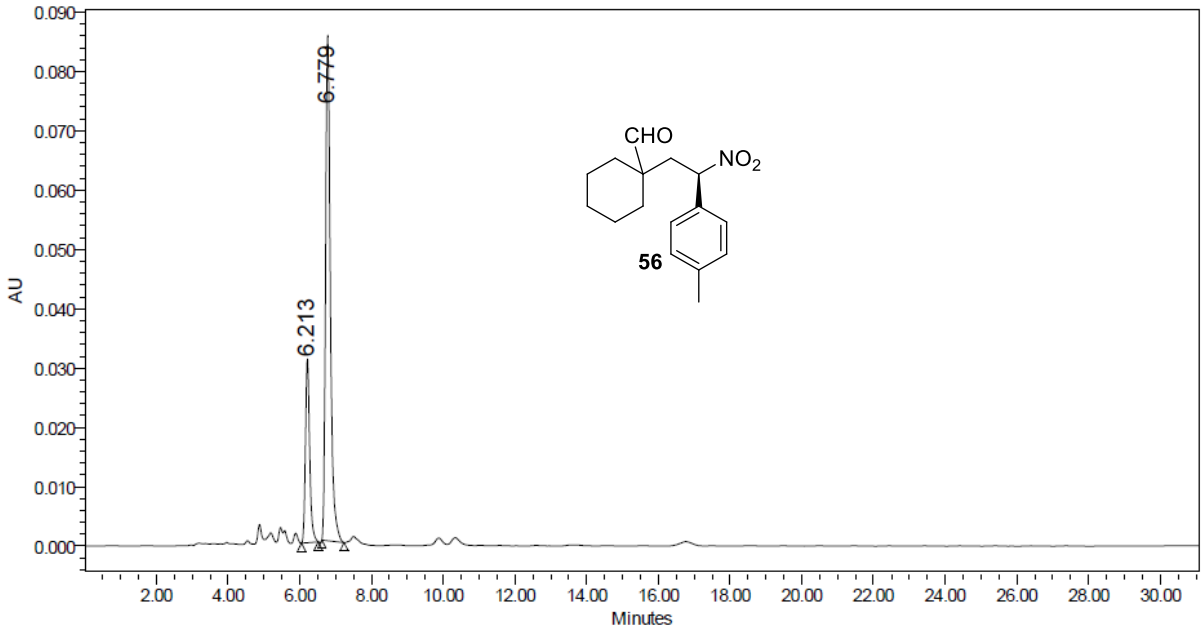
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	6.213	253260	24.12	30986	26.63
2	6.779	796945	75.88	85368	73.37

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Page: 1 of 1

Printed: 29/09/2016 3:07:24 PM Canada/Newfoundland

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Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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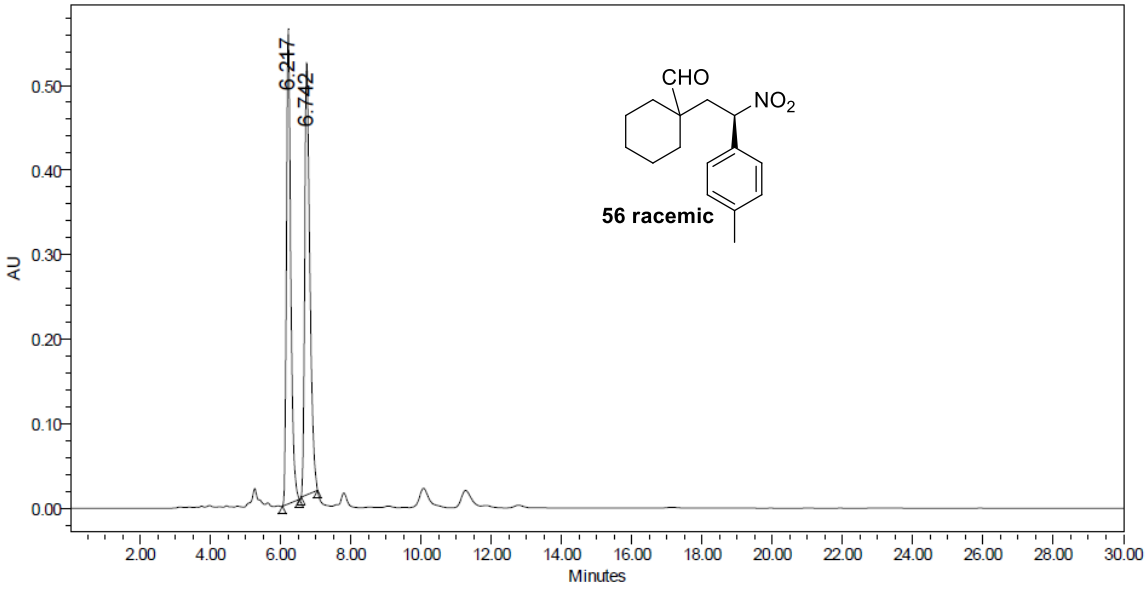

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	6.217	4825956	48.09	560604	52.09
2	6.742	5208594	51.91	515716	47.91

Memorial University

Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Injection #:	1	Date Processed:	24/02/2018 6:12:52 PM NST
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Run Time:	40.00 Minutes	Channel Desc.:	
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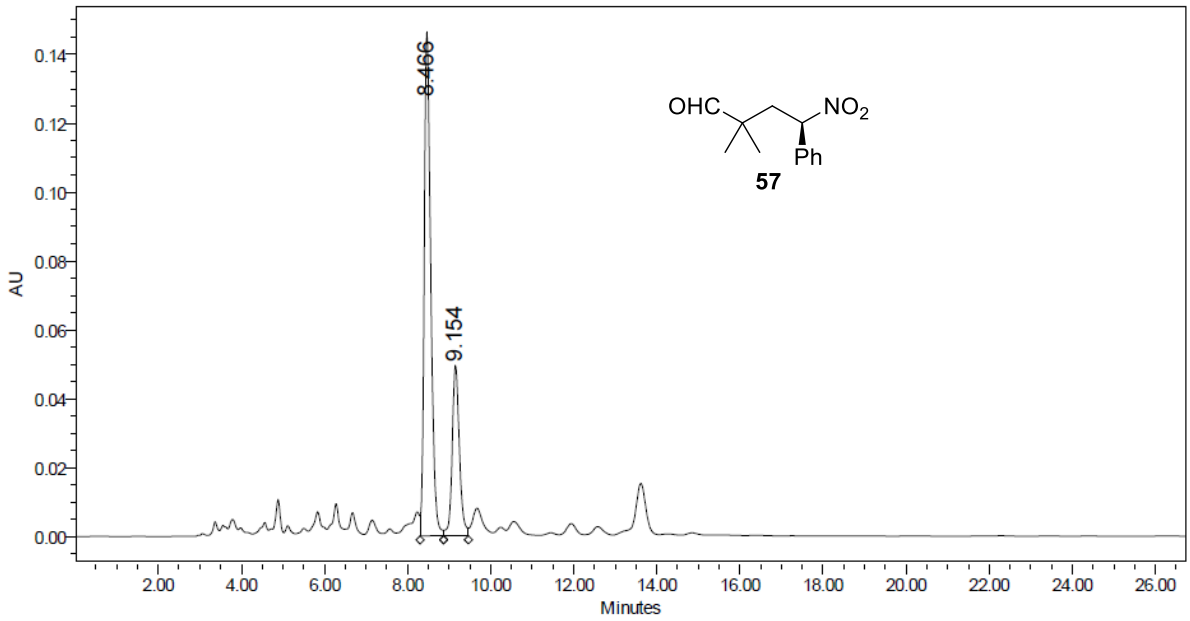

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.466	1591685	72.71	146285	74.71
2	9.154	597263	27.29	49524	25.29

Memorial University

Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-V-17B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	28/08/2017 1:11:04 PM NDT
Vial:	1	Acq. Method:	AD_H 90%HEX 10%IPA
Injection #:	1	Date Processed:	28/08/2017 1:34:54 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
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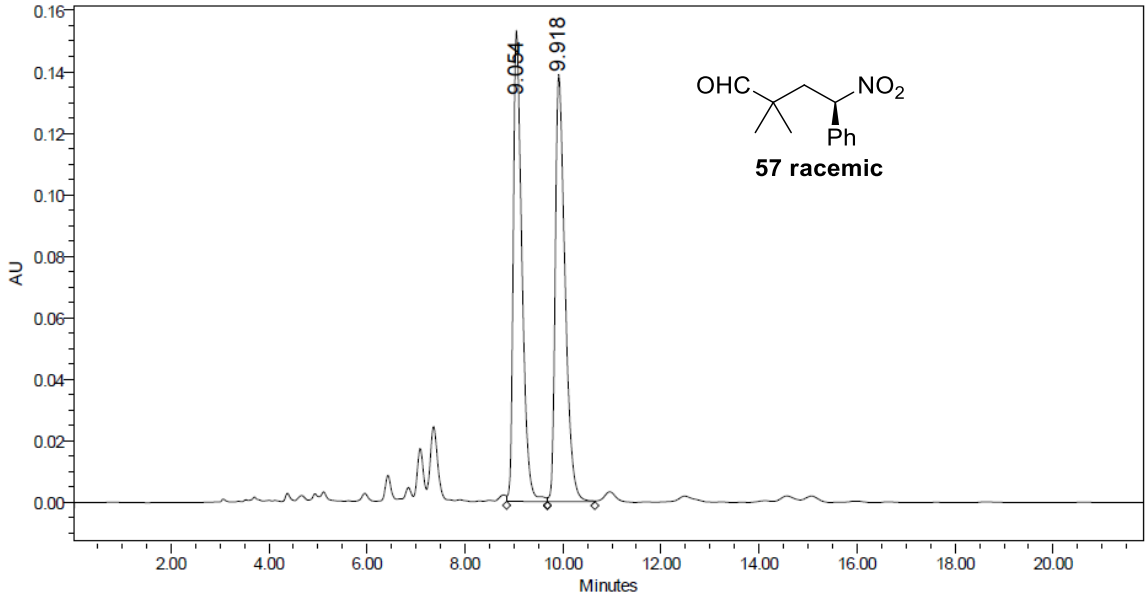


	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	9.054	1872787	49.36	153302	52.48
2	9.918	1921664	50.64	138824	47.52

Report Method: Individual Control Report

Page: 1 of 1

Printed: 28/08/2017 1:35:25 PM Canada/Newfoundland

Chapter 3

Functionalization of Diazotetronic Acid and Application in a Stereoselective Modular Synthesis of Aspulvinones B, D and Q

The work described in this chapter has been published in Organic and Biomolecular Chemistry: Manchoju, A.; Annadate, R.A.; Desquien, L.; Pansare, S.V. *Org. Biomol. Chem.* **2018**, *16*, 6224-6238.

3.1 Introduction

The tetronic acid (4-hydroxy-5*H*-furan-2-one) motif is a characteristic structural unit in many fungal metabolites.[1,2] Among these, the pulvinones[3] (hydroxylated versions of 3-aryl-4-hydroxy-5-arylidene furan-2(5*H*)-ones) constitute a major group of naturally-occurring tetronic acids, which were first isolated as yellow pigments from the mushroom Larch Bolete (*Suillus grevillei*) in 1973 by Edwards and Gill.[4] Two years later, Seto and co-workers isolated a significant number of yellow colored metabolites from the cultures of *Aspergillus terreus*[5] which includes several novel prenylated derivatives of pulvinones. These were named as aspulvinones since their structures were determined[6,7] to be very similar to the pulvinones isolated earlier. A more recent addition (2016) to the aspulvinone family was aspulvinone Q which was isolated from the cultures of *Aspergillus flavipes* PJ03-11.[8] Prominent examples of naturally occurring aspulvinones are shown in Figure 3.1.

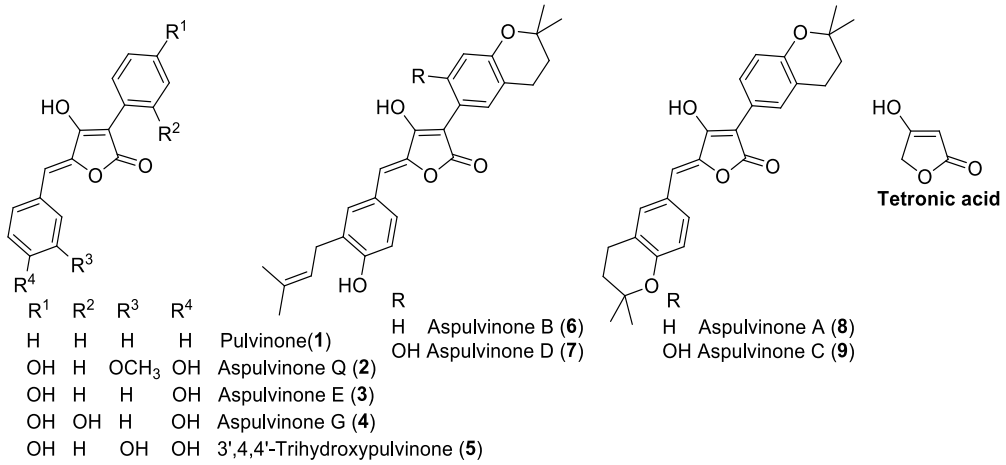


Figure 3.1 Naturally occurring Aspulvinones

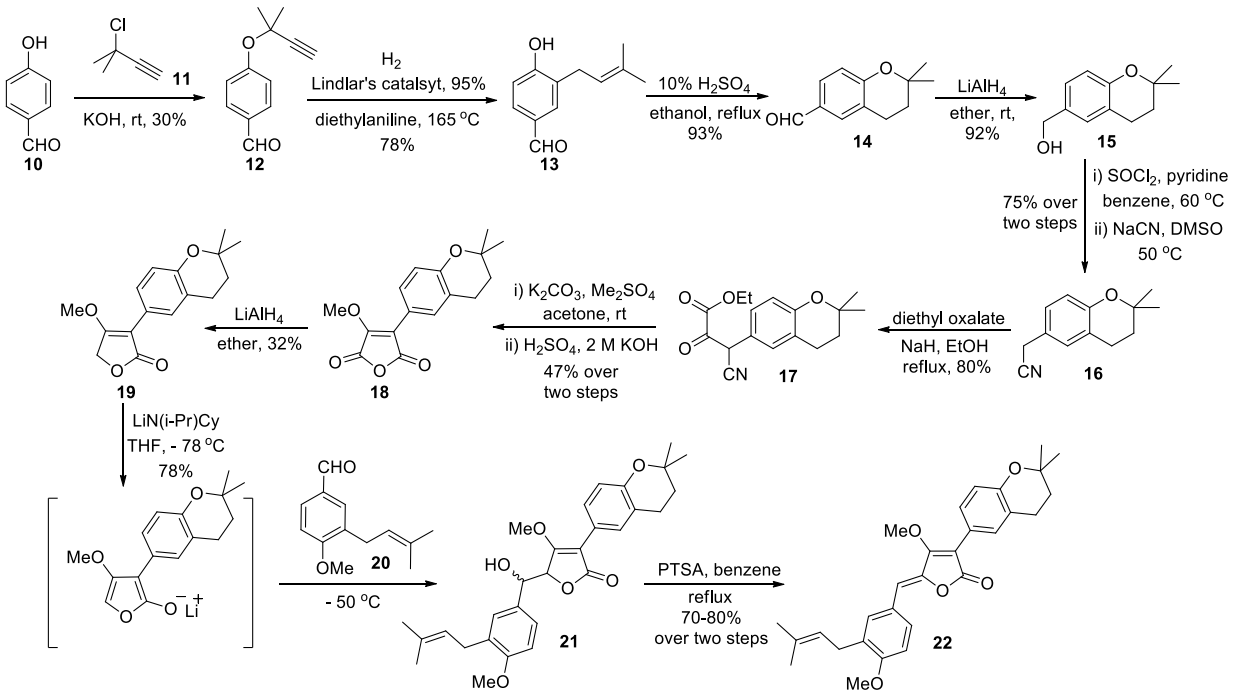
Natural or synthetic pulvinones display a wide range of biological activities such as anticoagulant,[9] antibacterial,[10] peptidoglycan biosynthesis inhibitory,[11] anti-inflammatory,[12] antidiabetic,[13] anti-epileptic,[14] and antifungal[15] activities. Members of the aspulvinone family have

shown antiviral,[16] α-glucosidase inhibitory[17] and firefly luciferase inhibitory[18] activity. The wide spectrum of biological activity exhibited by pulvinones has contributed to extensive interest in their synthesis and the following section provides known synthetic routes to natural as well as non-natural pulvinones.

3.2 Known Synthetic Routes to Pulvinones

3.2.1 The Pattenden synthesis of pulvinones

Pattenden and co-workers[7] reported a synthesis of pulvinones in 1979 in fourteen steps in 1% overall yield. They started their synthesis from commercially available 4-hydroxybenxaldehyde **10** (Scheme 3.01). Reaction of the potassium salt of **10** with **11** afforded dimethylprop-2-ynyl ether **12**. Partial hydrogenation of the alkyne in **12** followed by a Claisen rearrangement of the resulting allyl ether afforded **13**.

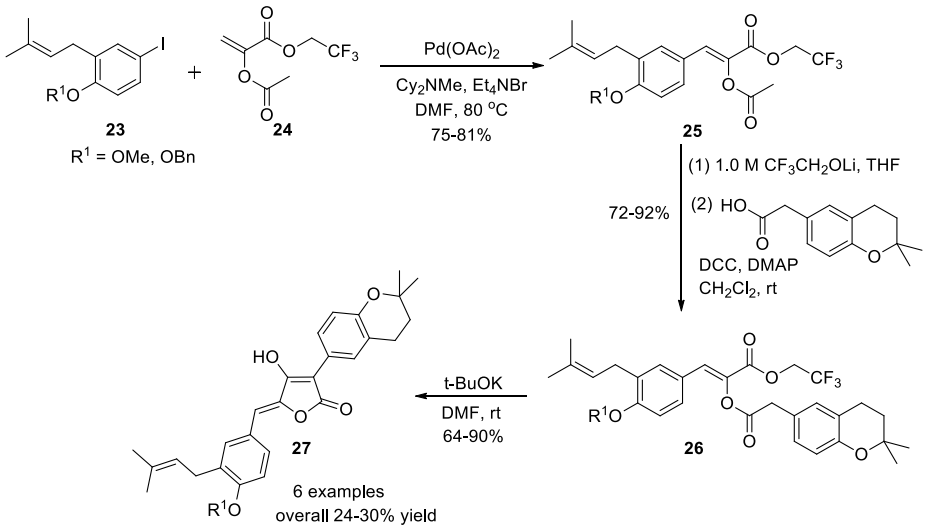


Scheme 3.01

Acid catalyzed cyclization of **13** afforded the chroman **14**. This was reduced with $LiAlH_4$ to provide the alcohol **15** which provided the nitrile **16** via the corresponding chloride. Condensation of the carbanion obtained from **16** and diethyl oxalate afforded pyruvate **17**. Methylation of **17** followed by acid hydrolysis and cyclization afforded anhydride derivative **18**. Regioselective reduction of the anhydride with lithium aluminum hydride afforded **19**. Metallation of **19** with lithium *N*-cyclohexyl-*N*-isopropylamide (LCPA) followed by addition of the enolate to the aldehyde **20** furnished the aldol product **21**. Acid catalyzed dehydration of **21** provided the pulvinone **22** as a single diastereomer.

3.2.2 The Bruckner synthesis of pulvinones

In 2007, Brückner and co-workers[19] reported the syntheses of pulvinones which includes Heck alkenylations of iodoarenes, transesterification and Dieckmann cyclization reactions as the key steps (Scheme 3.02).



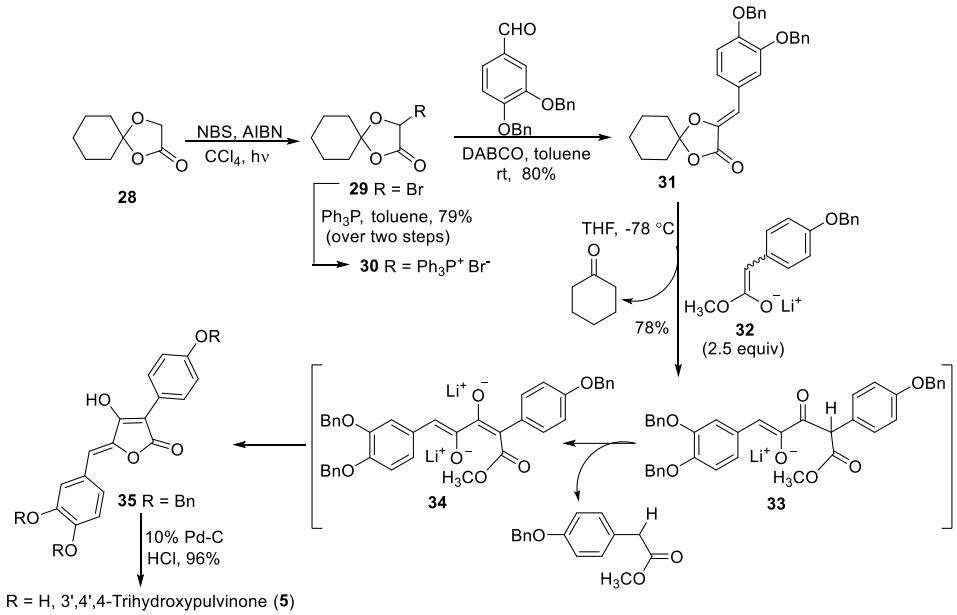
Scheme 3.02

Stereoselective Heck coupling of iodoarenes **23** with trifluoroethyl 2-acetoxyacrylates **24** provided the corresponding trifluoroethyl (*Z*)-2-acetoxycinnamates **25**. These were converted into trifluoroethyl (*Z*)-2-(arylacetoxy) cinnamates **26** by deacetylation and esterification of the enol

form with a selected aryl acetic acid. Dieckmann cyclization of **26** in the presence of potassium *tert*-butoxide (*t*-BuOK) provided pulvinones **27** as single diastereomers. A total of six naturally occurring pulvinones were synthesized, and the overall yields ranged from 24-30%.

3.2.3 The Ramage synthesis of 3',4',4-trihydroxypulvinone (5):

In 1984, Ramage and co-workers[20] developed a method to synthesize 3',4',4-trihydroxypulvinone (**35**, Scheme 3.03). Bromination of the glycolic acid-derived dioxolanone **28** with *N*-bromosuccinimide provided **29**, which was immediately treated with triphenylphosphine in toluene to provide the phosphonium salt **30**. Condensation of the phosphorane obtained from **30**, in the presence of DABCO, and 3,4-dibenzyloxybenzaldehyde provided **31**. Claisen condensation of **31** and the lithium enolate **32** provided the tetronic acid derivative **35** as a single diastereomer which was then debenzylated (Pd-C and HCl) to provide 3',4',4-trihydroxypulvinone (**5**).

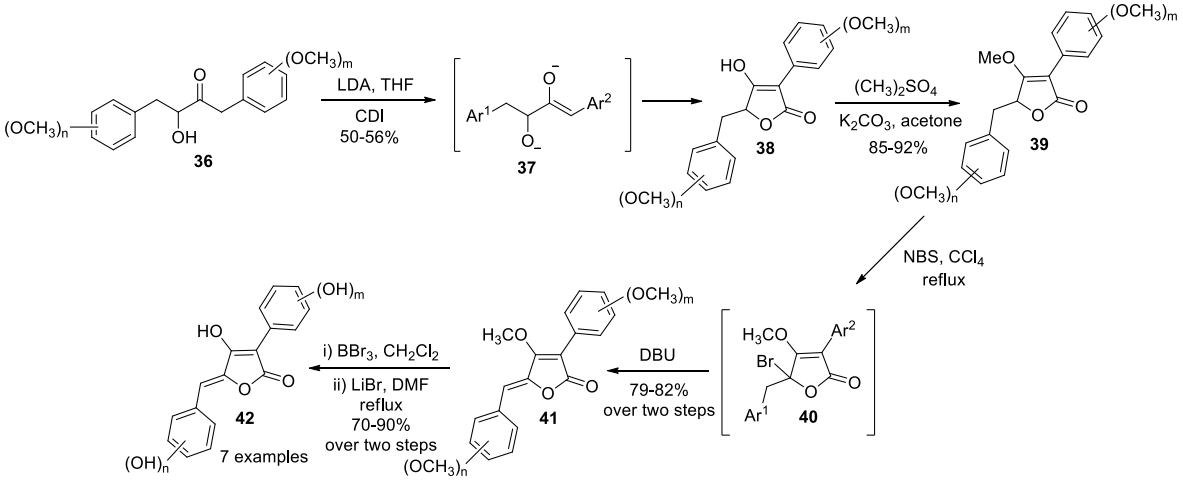


Scheme 3.03

The use of 2.5 equivalents of ester enolate **32** was necessary in the condensation reaction. The first equivalent of **32** opens the dioxolanone ring, resulting in the formation of lithium enolate **33** and the second equivalent forms the lithium bis(enolate) **34** which cyclizes to provide **35**.

3.2.4 The Gill synthesis of pulvinones

In 1990, Gill and coworkers[21] reported a synthesis of pulvinones in six steps in 23% overall yield from unsymmetrical acyloins (**36**, Scheme 3.04). Treatment of **36** with LDA generated the alcoholate-enolate dianions **37** which upon acylation with carbonyldiimidazole (CDI) and subsequent cyclization provided the dihydropulvinones **38**. Methylation of **38** with dimethyl sulfate provided **39** which was brominated with NBS to give **40** which was not isolated. Direct *in-situ* dehydrobromination of **40** with DBU afforded the *O*-methyl pulvinones **41** as single diastereomers. Treatment of **41** with BBr_3 followed by treatment with LiBr in DMF under reflux condition afforded the corresponding pulvinones **42**.

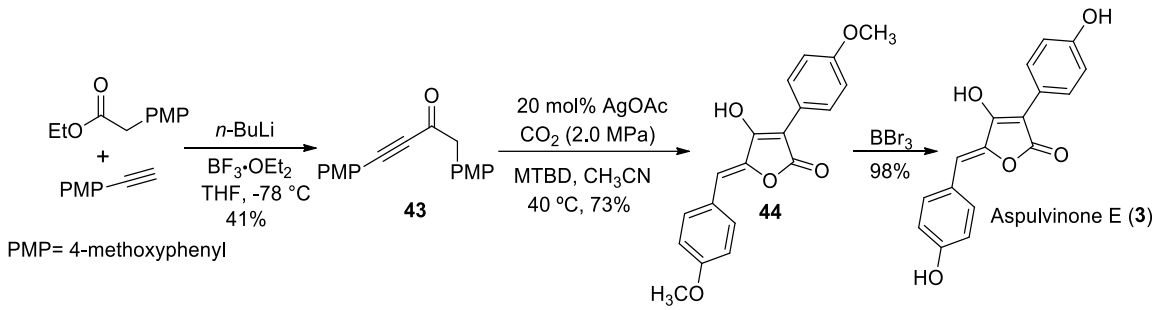


Scheme 3.04

3.2.5 The Yamada synthesis of aspulvinone E (3):

Yamada and co-workers[22] recently developed a synthesis of Aspulvinone E in three steps in 29% overall yield, employing silver-catalyzed reactions of conjugated ynones with CO_2. Thus,

the acylation of (4-methoxyphenyl)acetylene with ethyl (4-methoxyphenyl)acetate in the presence of *n*-BuLi and $BF_3.OEt_2$ provided ynone **43**. Silver-catalyzed reaction of **43** with carbon dioxide provided 5-arylidene tetronic acid **44** which was then demethylated with BBr_3 to give aspulvinone E (**3**) (Scheme 3.05).



Scheme 3.05

3.3 Objective

As discussed above, previous syntheses of 3-aryl-5-arylidene tetronic acid motifs rely on starting materials that have the functionality present in the target tetronic acid. Pattenden and co-workers started their synthesis from 3-aryl tetronic acid which was a key functionality present in the target, while the Brückner synthesis relied on the cyclization of a functionalized precursor to provide the tetronic acid motif. Also, although the Yamada synthesis claims to be the shortest route to aspulvinone E, the steps required to synthesize the phenyl acetates and the functionalized acetylene starting materials are ignored in this claim. Notably, all of these the approaches are limited by the requirement of starting materials that contain the substituted arene or arenes in the target pulvinones. Therefore, we chose to develop a synthesis of pulvinones that would overcome these limitations.

Previous studies in the Pansare group had established that C5-functionalized diazotetronates react with various arenes in the presence of a rhodium catalyst to provide the corresponding 3-aryl tetronates as a product of net insertion of the diazotetronate into the arene

C-H bond.[23] We reasoned that a similar strategy could be applied for the synthesis of natural and unnatural pulvinones. The key features of our synthetic strategy for pulvinone synthesis are: 1) introduction of the C5 alkylidene/arylidene functionality by a stereoselective aldol condensation of diazotetronate **45** with various aliphatic and aromatic aldehydes and 2) installation of the C3 aryl substituent in a single step by a C-H insertion reaction involving the diazo functionality to provide the pulvinone motif **47** (Figure 3.2).

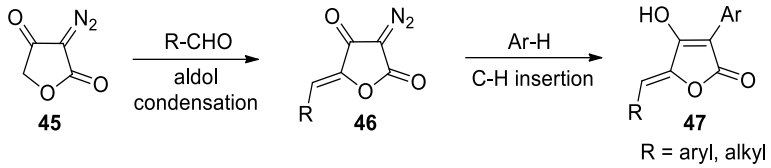


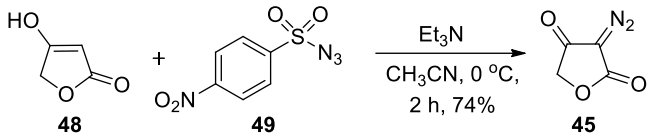
Figure 3.2 Synthetic approaches to pulvinones and two-step strategy

During the initial stages of our studies on pulvinone synthesis, we had noted that the syntheses of aspulvinone D (**7**, Figure 3.1) and aspulvinone Q (**2**) were not reported and that the sole reported synthesis of aspulvinone B (**6**) had provided the target as an inseparable mixture with unidentified by-products. Hence, aspulvinones B, D and Q were selected as the synthetic targets of this study. Aspulvinones A, C, E, G and 3',4',4-trihydroxypulvinone were also synthesized in parallel studies conducted by Dr. A. Manchoju in the Pansare group.[24]

3.4 Results and Discussion

One of the key steps in our proposed methodology is the stereoselective aldol condensation of diazotetronate **45** to provide **46** which are potentially the immediate precursors of the required pulvinones. Diazotetronate **45** is easily prepared from commercially available tetronic acid in one step,[25] and the aldol condensation reaction of **45** was therefore the subject of our initial investigations. *p*-Tolualdehyde was selected as the representative aldehyde for these studies and its aldol condensation reaction with **45** was investigated under a variety of conditions. It should be mentioned that the formation of an aldol product (instead of an aldol condensation product) was

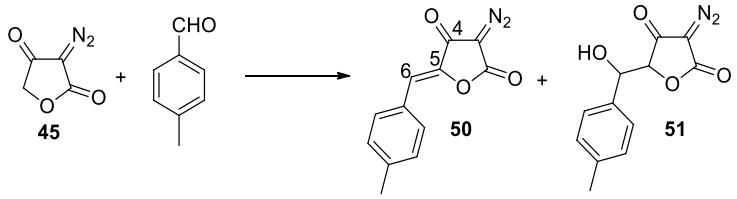
considered to be a distinct possibility and, if so, dehydration to the aldol product to the required arylidene derivative would be necessary. Since previous studies[26] on related compounds had shown that this two-step process often leads to an isomeric mixture of *E* and *Z* arylidene tetronates, our objective was to develop a direct, stereoselective aldol condensation reaction of **45**. The diazotetronic acid **45** was prepared by modification of the reported procedure (Scheme 3.06).



Scheme 3.06

Initially, an aldol condensation of **45** and *p*-tolualdehyde was attempted with the titanium enolate of **45** (using the $TiCl_4$-Et_3N reagent[27] Table 3.1, entry 1). To our delight, this directly provided the aldol condensation product **50** as a single diastereomer, but in low yield (41%). Replacing $TiCl_4$ with $BF_3.OEt_2$ (Table 3.1 entry 2) provided only the aldol addition product **51** as a mixture of diastereomers (dr = 1:1).

Table 3.1 Optimization of the aldol condensation of **45** with *p*-tolualdehyde.



Entry	Reagents and conditions	50[a]	51[a]
1.	$TiCl_4$, -78 °C, 20 min; Et_3N, -78 °C, 40 min to 0 °C, 1.5 h	41	-
2.	$BF_3.OEt_2$, -78 °C, 20 min; Et_3N, -78 °C, 40 min; 0 °C, 1 h; rt, 1 h	-	38
3.	$TiCl_4$, -78 °C, 20 min; pyridine, -78 °C, 30 min; 0 °C, 2 h; rt, 41 h	82	-
4.	$TiCl_4$, -78 °C, 20 min; *N*-methylimidazole, -78 °C, 30 min; 0 °C, 1 h 20 min; rt, 18 h	77	-
5.	$TiCl_4$, -78 °C, 20 min; 2,4,6-collidine, -78 °C, 30 min; 0 °C, 30 min	82	-

[a]isolated yields

Changing the base from triethylamine to heteroaromatic bases such as pyridine, *N*-methylimidazole and 2,4,6-collidine prevented the formation of aldol addition product **51** and improved the yield of the aldol condensation product **50**. With pyridine and *N*-methylimidazole (Table 3.1, entries 3 and 4), alkene **50** was obtained in good yields (82% and 77% respectively), but the reaction was sluggish. Finally, the use of 2,4,6-collidine as the base not only provided **50** in good yield (82%, Table 3.1, entry 5), but the reaction was significantly faster (80 min) than those with *N*-methylimidazole (~20 h) or pyridine (~43 h) as the base. With these optimal conditions in hand, the scope of the reaction was tested with the variety of aldehydes to provide alkylidene diazotetronates **50**-**57** (Figure 3.3).

We were pleased to find that the aldol condensation reaction of **45** with electron-rich and electron-deficient aromatic aldehydes, as well as aliphatic aldehydes, provided 5-arylidene-3-diazofuran-2,4(3*H*,5*H*)-diones **50-57** as single diastereomers in excellent to moderate yields (Figure 3.3). Notably, the arylidene diazotetronates **53**, **56** and **57** are potentially the immediate precursors of aspulvinones Q, B and D. In case of aliphatic aldehydes, the reaction of **45** with hydrocinnamaldehyde did not provide any of the required product, and the reaction with pivalaldehyde was less efficient providing **54** in modest yield (40%).

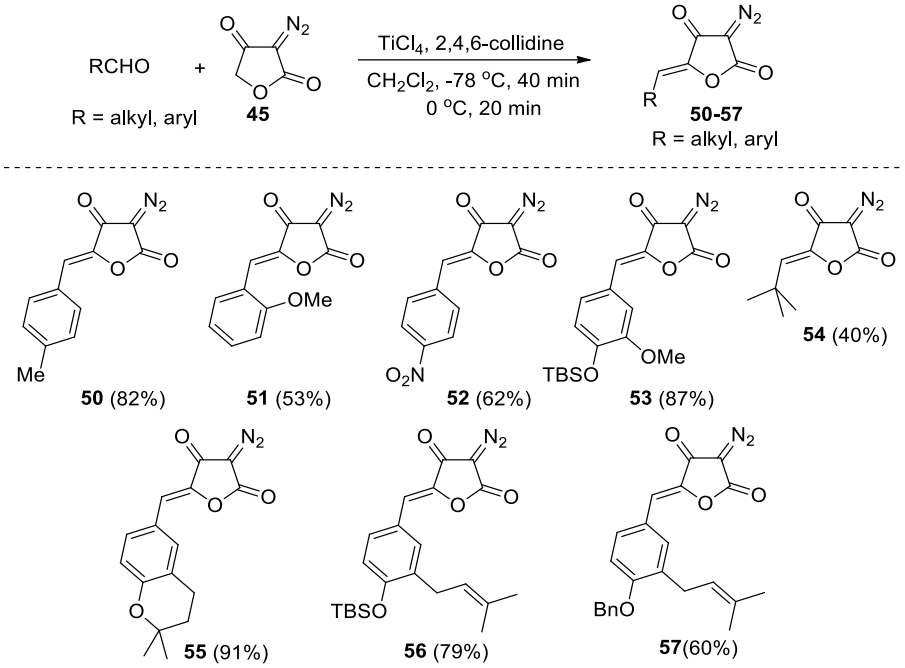
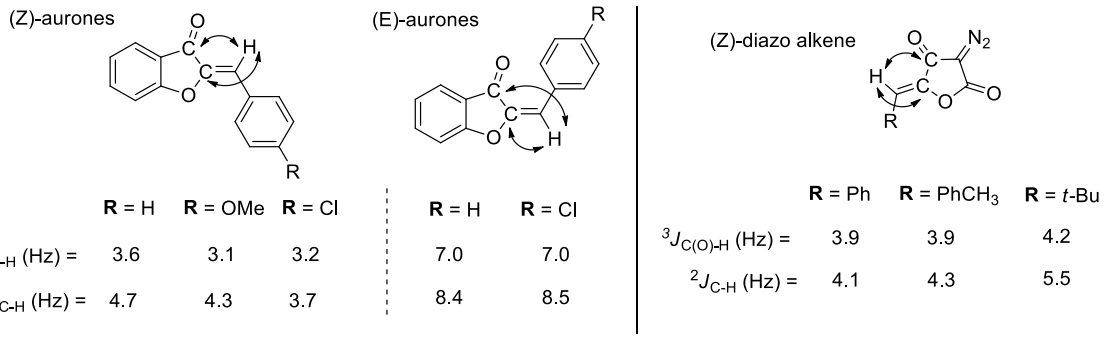


Figure 3.3 Aldol condensation products of **45** with selected aldehydes

At this stage, we assigned the stereochemistry of the double bond present in the diazo alkene **50** as *Z* based on selected ^{13}C-^{1}H coupling constant. The $^{3}J_{C(4)\text{-}H(6)}$ (three bond ^{13}C-^{1}H coupling constant) for the exocyclic methine and the ketone carbonyl carbon in **50** is 3.9 Hz and $^{2}J_{C(5)\text{-}H(6)}$ (two bonds ^{13}C-^{1}H coupling constant) in **50** is 4.3 Hz (Figure 3.4). These values are in good agreement with those reported[28] for several *Z*-aurones ($^{3}J_{C\text{-}H}$ = 3.1-3.6 Hz; $^{2}J_{C\text{-}H}$ = 3.7-4.7 Hz) that are structurally related to **50**. Notably, the reported $^{3}J_{C\text{-}H}$ and $^{2}J_{C\text{-}H}$ values for *E*-aurones are

higher (7.0-8.5 Hz). The stereochemical assignment was eventually confirmed by the conversion several diazo alkenes to naturally occurring pulvinones, thus providing unambiguous evidence for the alkene geometry in **50**-**57**.



	R = H	**R** = OMe	**R** = Cl	**R** = H	**R** = Cl
$^{3}J_{C(O)-H}$ (Hz) =	3.6	3.1	3.2	7.0	7.0
$^{2}J_{C-H}$ (Hz) =	4.7	4.3	3.7	8.4	8.5

	R = Ph	**R** = $PhCH_3$	**R** = *t*-Bu
$^{3}J_{C(O)-H}$ (Hz) =	3.9	3.9	4.2
$^{2}J_{C-H}$ (Hz) =	4.1	4.3	5.5

Figure 3.4 Determination of the stereochemistry of the aldol condensation products

Having established a general synthesis of 5-arylidene-3-diazofuran-2,4(3*H*,5*H*)-diones, our next target was the introduction of an aryl substituent at C3 to construct the C3-aryl-C5-arylidene/alkylidene tetronic acid (pulvinone) motif. This would help us to confirm the *Z*-geometry of the diazo alkene by the synthesis of known pulvinones. Previous studies in the Pansare group for the synthesis of aspulvinones A and C had identified $Rh_2(esp)_2$ (Du Bois catalyst) as the catalyst of choice for the C-H insertion reaction using $PhCF_3$ as a solvent.[29] Hence, these conditions were also used in the studies described here.

3.4.1 Retrosynthetic analysis for Aspulvinones

A retrosynthetic analysis for the synthesis of aspulvinones B and D is outlined in Figure 3.5. We reasoned that these natural products could be obtained from net C-H insertion reaction of diazo tetronates **58** and chromans **59**. The diazo tetronates **58** could be obtained by the aldol condensation reaction of diazotetronate **45** and corresponding aldehydes **60**.

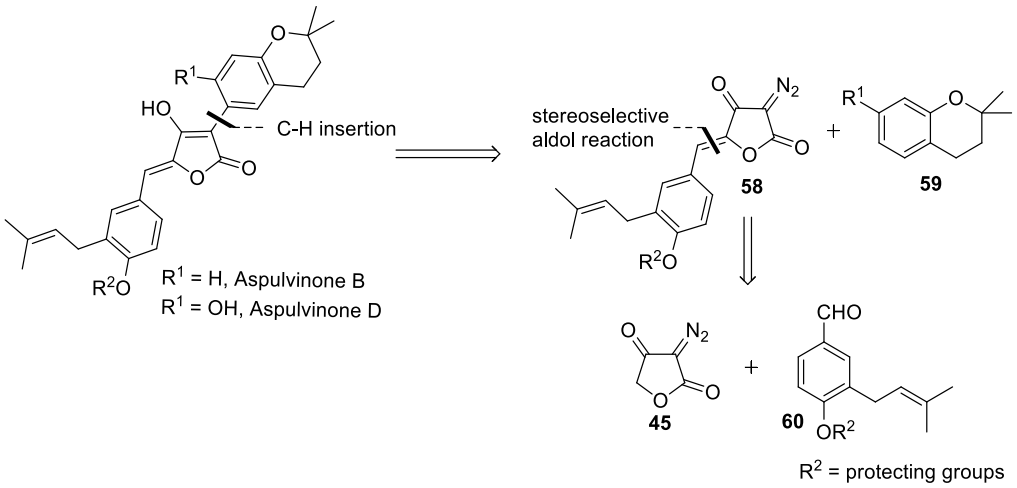
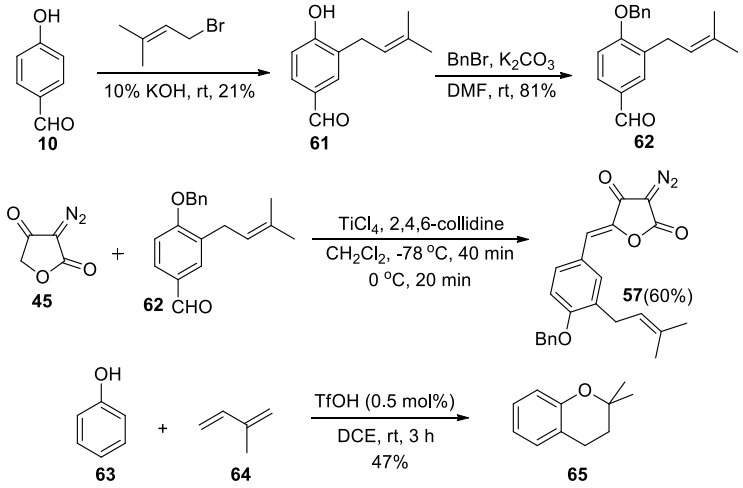


Figure 3.5 Retrosynthetic route for synthesis of aspulvinones B and D

3.4.2 Synthesis of naturally occurring pulvinones

Our initial attempt at the synthesis of aspluvinone B started with the preparation of aldehyde **62** in which the phenol was protected as a benzyl group (Scheme 3.07). The synthesis of **62** began with prenylation of 4-hydroxy benzaldehyde (**10**) with prenyl bromide in the presence of 10% KOH to provide **61** which was subsequently benzylated to provide **62**.[30]

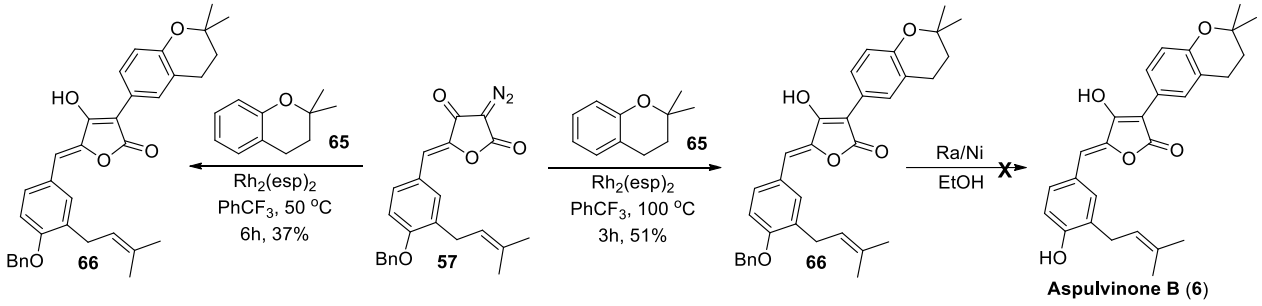


Scheme 3.07

The 5-arylidene diazo tetronate **57** was obtained by the aldol condensation of **62** and diazotetronate **45** (Scheme 3.07) using our optimized aldol condensation procedure (Table 3.1 and Figure 3.3).

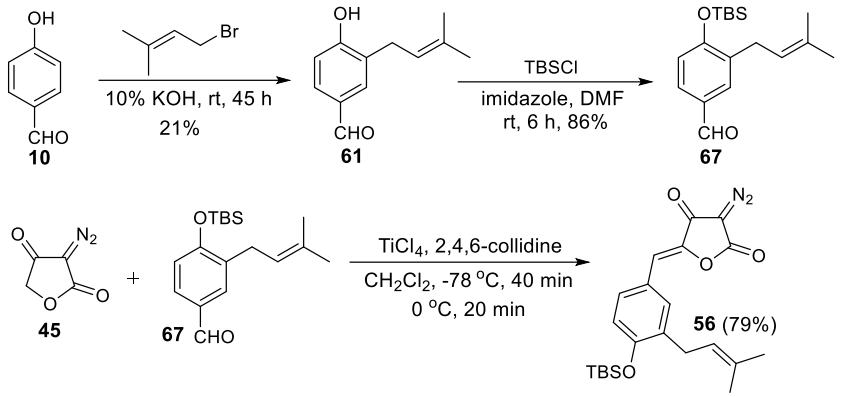
The synthesis of the 2,2-dimethylchromane **65**, a nucleophilic partner for the net C-H insertion reaction was achieved by the acid catalysed reaction of phenol **63** with isoprene **64** (Scheme 3.07).

Initially, a C-H insertion reaction of the diazotetronic acid derivative **57** with four equivalents of chromane **65** in the presence of the Du Bois catalyst ($Rh_2(esp)_2$) was conducted in $PhCF_3$ at 50 ^oC. This provided the required product **66** (Scheme 3.08), but in low yield (37%). Increasing the reaction temperature to 100 ^oC was beneficial and a higher yield of **66** (51%) was obtained. With **66** in hand, its conversion to aspulvinone B (**6**) was examined. Unfortunately, the attempted debenzylation of **66** Raney Nickel in the absence of an atmosphere of H_2[31] led to a complex mixture of products which did not contain any aspulvinone B (Scheme 3.08). This observation was surprising, since previous studies[31] in the Pansare group had successfully used this procedure for the selective hydrogenolysis of a benzyl ether in the presence of a tetrasubstituted alkene.



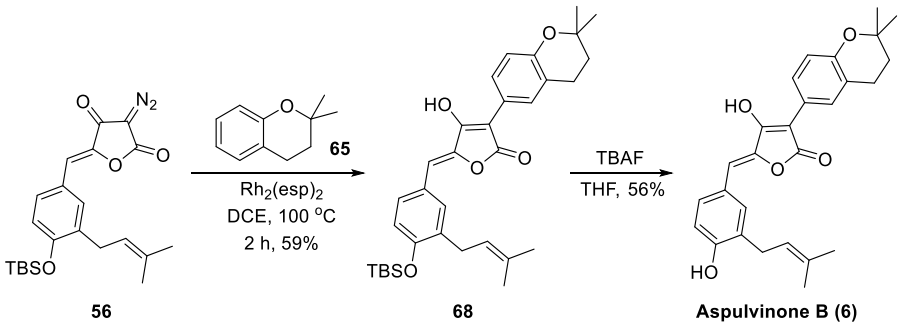
Scheme 3.08

Given the failure of the debenzylation reaction, an alternative protecting group for the phenolic functionality in **61** became necessary. The TBS protected aldehyde **67** was selected as an alternative to **62** and it was prepared by adaptation of the procedure reported in the literature[32] (Scheme 3.09).



Scheme 3.09

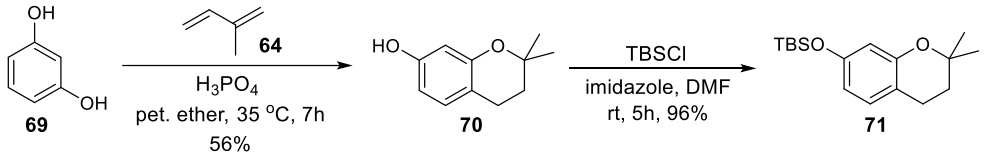
Initially the reaction of the 5-arylidene diazo tetronate **56** with the chromane **65** was examined by using the Du Bois catalyst and $PhCF_3$ as the solvent, but the yield of the C-H insertion product was extremely low (15%). After some experimentation, it was observed that changing the solvent from $PhCF_3$ to 1,2-dichloroethane was crucial. With this modification, the C-H insertion reaction of **56** with chromane **65** provided **68** in 59% yield. Subsequent removal of the TBS protecting group in **68** with TBAF provided aspulvinone B (**6**, 56%, Scheme 3.10). The spectroscopic data (^1H and ^{13}C) of **6** are in agreement with those reported in the literature.[19] The formation of aspulvinone B supports our initial assumption that the aldol condensation reaction of diazotetronate **45** and aldehyde **67** provides *Z*-**56** stereoselectively.



Scheme 3.10

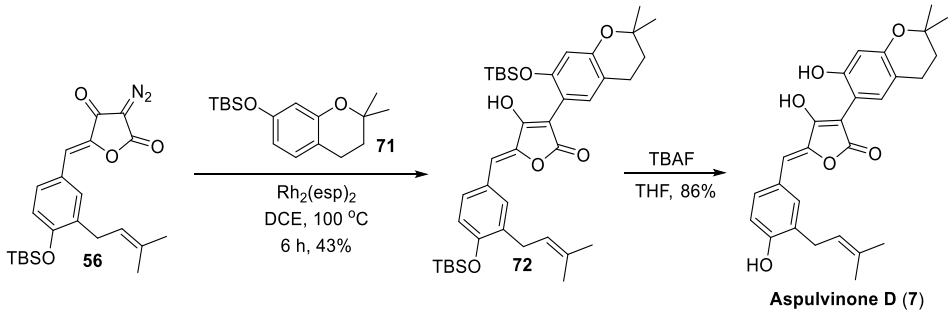
Next, the synthesis of aspulvinones D (**7**) and Q (**2**) was investigated using the strategy described for the synthesis of aspulvinone B. Due to the successful desilylation reaction described

above, we chose to synthesize the TBS protected chroman derivative **71** for the C-H insertion reaction to be employed in the synthesis of aspulvinone D. The synthesis of TBS ether **71** was achieved by an acid catalysed reaction of resorcinol **69** with isoprene **64** to provide the corresponding hydroxychroman **70** and subsequent protection of the phenol functionality with TBSCl (Scheme 3.11).



Scheme 3.11

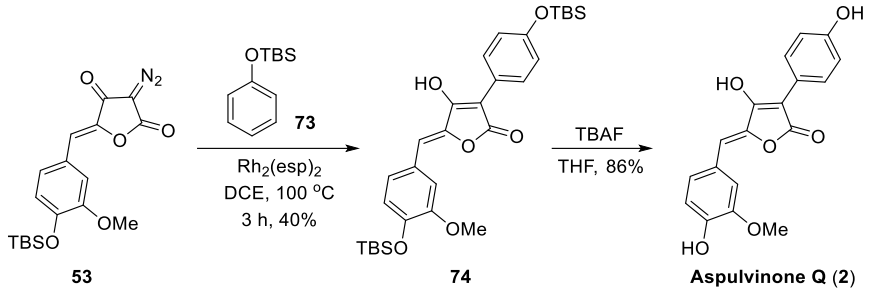
The Rh (II)-catalyzed C-H insertion reaction of **56** with *tert*-butyl-((2,2-dimethylchroman-7-yl)oxy)-dimethylsilane **71** provided **72** in 43% yield. Desilylation of **72** provided aspulvinone D (**7**, 86%, Scheme 3.12).



Scheme 3.12

Our next objective was the synthesis of aspulvinone Q. To this effect, the C-H insertion reaction of **56** with tert-butyldimethyl(phenoxy)silane **73** in the presence of $Rh_2(esp)_2$ provided **74** in 40% yield. Interestingly, the regioisomeric product which is observed with anisole as the reacting partner (C-H insertion *ortho* to the OMe group), was not observed in this reaction. It is reasonable to assume that this selectivity is due to steric reasons (the OTBS group is sterically

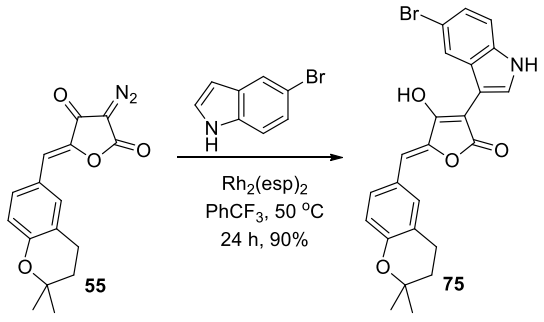
more demanding than the OMe group). Removal of the TBS protecting group in **72** with TBAF provided aspulvinone Q (**2**) in good yield (86%, Scheme 3.13).



Scheme 3.13

3.4.3 Synthesis of an unnatural pulvinone

Over the years, interest in the biological activity of pulvinones and aspulvinones has resulted in intense investigation of the synthesis of structural variants of the natural isolates.[33,34] In a study aimed at preparing a focused library of tetronic acid-indole hybrid structures, the C-H insertion reaction of **55** with 5-bromoindole was examined under the optimized reaction conditions ($Rh_2(esp)_2$, $PhCF_3$, 50 °C, Scheme 3.14). Gratifyingly, the expected product **75** was obtained in excellent yield (90%). Studies of other diazotetronates and indoles are being investigated in the Pansare group.



Scheme 3.14

3.5 Conclusion

In conclusion, we have developed a versatile methodology for the synthesis of naturally occurring as well as unnatural pulvinones and their derivatives. The syntheses of aspulvinones B, D and Q were achieved in three steps from the diazoteronate **45**. The methodology provides direct access to a wide range of stereoisomerically pure (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones in a single step and 5-arylidene-4-hydroxy-3-aryl-5-furan-2(5*H*)-ones in just two steps from diazotetronic acid. This strategy has potential for application in a rapid synthesis of focused libraries of aspulvinone-like natural product analogues.

3.6 Experimental section

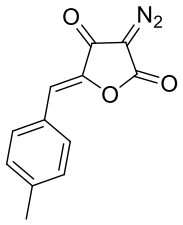
Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purification. All reactions were carried out under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring. Commercially available α,α,α-trifluorotoluene was used as received. CH_2Cl_2 and DCE were distilled from CaH_2. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 6200 LC/MSD (TOF) chromatographic system.

General procedure for the aldol condensation of diazotetronate 45 and aldehydes:

To a solution of **45** (1.0 equiv) and aldehyde (1.0 equiv) in CH_2Cl_2 was added $TiCl_4$ (3.0 equiv) at -78 °C. The solution was stirred for 20 min, 2,4,6-collidine (3.0 equiv) was added and the mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min. Saturated aqueous NH_4Cl (~ 3 mL) was added followed by cold water (~ 2 mL). The resulting mixture was extracted with

CH_2Cl_2 (3 x 6 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to provide the arylidene or alkylidene diazotetronates **50-57**.

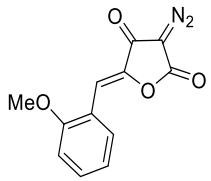
(*Z*)-3-Diazo-5(4-methylbenzylidene)furan-2,4(3*H*,5*H*)-dione (50):



The reaction of **45** (126 mg, 1.00 mmol), 4-methylbenzaldehyde (118 µL, 1.00 mmol), $TiCl_4$ (0.32 mL, 3.0 mmol) and 2,4,6-collidine (0.40 mL, 3.0 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 188 mg (82%) of **50** as a white solid.

R_f = 0.32 (hexanes/EtOAc, 8.5:1.5); mp: 147-150 °C; IR (neat): 2157, 1758, 1689, 1634, 1602, 1362, 1339, 1313, 1251, 1078, 1048, 962, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.23 (d, 2H, *J* = 8.1 Hz, Ar*H*), 6.68 (s, 1H, ArC*H*=C), 2.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (*C*=O), 160.5 (O*C*=O), 141.6 (O-*C*=CHAr or ArC_{ipso}), 141.3 (O-*C*=CHAr or ArC_{ipso}), 131.6 (2 × Ar*C*), 129.9 (2 × Ar*C*), 128.3 (ArC_{ipso}), 112.2 (Ar*C*H=C), 21.8 (*C*H_3); HRMS (APPI, pos.): *m/z* 228.0537 (228.0535 calc. for $C_{12}H_8N_2O_3$, $(M)^+$).

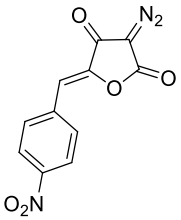
(*Z*)-3-Diazo-5-(2-ethoxybenzylidene)furan-2,4(3*H*,5*H*)-dione (51):



The reaction of **45** (75 mg, 0.6 mmol), 2-methoxybenzaldehyde (81 mg, 0.6 mmol), $TiCl_4$ (0.2 mL, 1.8 mmol) and 2,4,6-collidine (0.2 mL, 1.8 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 77 mg (53%) of **51** as a yellow solid.

R_f = 0.23 (hexanes/EtOAc, 9:1); IR (neat): 3080, 2923, 2840, 2152, 1775, 1699, 1648, 1592, 1483, 1462, 1359, 1305, 1283, 1254, 1233, 1193, 1138, 1070, 1045, 1018, 955 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (dd, 2H, *J* = 7.6, 1.7, ArH), 7.37 (ddd, 1H *J* = 8.3, 7.6, 1.7 Hz), 7.28 (s, 1H, ArC*H*), 7.01 (br t, 1H, *J* = 7.6, Ar*H*), 6.91 (br d, 1H, J = 8.3, Ar*H*), 3.88 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.5 (O-*C*=O), 158.7 (ArC_{ipso}), 141.8 (ArC_{ipso}), 132.1 (O-*C*=CHAr), 131.7 (Ar*H*), 121.0 (Ar*H*), 119.9 (Ar*C*H), 110.8 (Ar*H*), 106.2 (Ar*H*), 55.6 (OCH_3); HRMS (APPI, pos.): m/z 244.0847 (244.0484 calc. for $C_{12}H_8N_2O_4$ (M^+)), 245.0560 (245.0562 calc. for $C_{12}H_9N_2O_4$ $(M+H)^+$).

(*Z*)-3-Diazo-5-(4-nitrobenzylidene)furan-2,4(3*H*,5*H*)-dione (52):

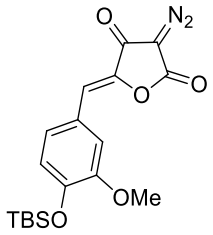


The reaction of **45** (75 mg, 0.59 mmol), 4-nitrobenzaldehyde (90 mg, 0.59 mmol), $TiCl_4$ (0.20 mL, 1.78 mmol) and 2,4,6-collidine (0.2 mL, 1.78 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1), 95 mg (62%) of **52** as a light brown solid.

R_f = 0.20 (hexanes/EtOAc, 4:1); IR (neat): 2922, 2850, 2162, 1767, 1706, 1643, 1504, 1362, 1338, 1296, 1240, 1070, 962, 911, 857, 828, 750 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.34 (d, 2H, *J* = 8.9, Ar*H*), 8.09 (d, 2H, *J* = 8.9, Ar*H*), 6.92 (s, 1H, ArC*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ

174.4 (*C*=O), 160.1 (O-*C*=O), 147.2 (ArC_{ipso}), 144.5 (ArC_{ipso}), 137.8 (O-*C*=CHAr), 131.7 (2 x Ar*H*), 124.0 (2 x Ar*H*), 106.5 (Ar*C*H); HRMS (APPI, pos.): m/z 259.0224 (259.0229 calc. for $C_{11}H_5N_3O_5$ (M^+)), 260.0296 (260.0307 calc. for $C_{11}H_6N_3O_6$ $(M+H)^+$).

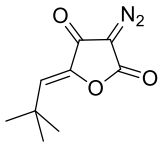
(*Z*)-5-(4-(*tert*-Butyldimethylsilyloxy)-3-methoxybenzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (53):



The reaction of **45** (100 mg, 0.79 mmol), 4-(*tert*-butyldimethylsilyloxy)-3-methoxybenzaldehyde (211 mg, 0.790 mmol), $TiCl_4$ (0.25 mL, 2.38 mmol) and 2,4,6-collidine (0.3 mL, 2.38 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9.2:0.8), 257 mg (87%) of **53** as a yellow solid.

R_f = 0.30 (hexanes/EtOAc, 9.2:0.8); IR (neat): 2957, 2931, 2856, 2147, 1786, 1708, 1649, 1591, 1508, 1463, 1419, 1364, 1344, 1310, 1276, 1248, 1169, 1132, 1072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 1H, *J* = 2.1 Hz, Ar*H*), 7.24 (dd, 1H, *J* = 8.3, 2.1 Hz, Ar*H*), 6.88 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.65 (s, 1H, ArC*H*), 3.86 (s, 3H, OCH_3), 1.00 (s, 9H, C(CH_3)$_3$), 0.18 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.5 (O-*C*=O), 151.4 (ArC_{ipso}), 148.0 (ArC_{ipso}), 140.7 (ArC_{ipso}), 126.1 (Ar*C*), 124.9 (O-*C*=CHAr), 121.4 (Ar*H*), 114.5 (Ar*C*H), 112.6 (Ar*C*), 55.7 (O*C*H_3), 25.8 (C(*C*H_3)$_3$), 18.7 (*C*(CH$_3$)$_3$), -4.4 (Si(*C*H_3)$_2$); HRMS (ESI, pos.): *m*/*z* 374.1295 (374.1298 calc. for $C_{18}H_{22}N_2O_5Si$ $(M)^+$), 397.1187 (397.1196 calc. for $C_{18}H_{22}N_2NaO_5Si$ $(M+Na)^+$).

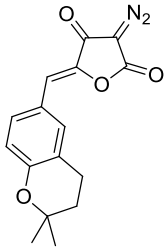
(*Z*)-3-Diazo-5-(2,2-dimethylpropylidene)furan-2,4(3*H*,5*H*)-dione (54):



The reaction of **45** (75 mg, 0.59 mmol), pivalaldehyde (64 μL, 0.59 mmol), $TiCl_4$ (0.2 mL, 1.78 mmol) and 2,4,6-collidine (0.23 mL, 1.78 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9.5:0.5), 49 mg (43%) of **54** as a colourless gum.

R_f = 0.19 (hexanes/EtOAc, 9.5:0.5); IR (neat): 2963, 2907, 2870, 2148, 1780, 1712, 1622, 1356, 1241, 1083, 988 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (s, 1H, $((CH_3)_3C)$-C*H*), 1.23 (s, 9H, $(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, (*C*=O), 160.3 (O-*C*=O), 142.3 (O-*C*=CH($C(CH_3)_3$)), 124.8 (Ar*C*H), 33.0 ($C(CH_3)_3$), 29.7 ($CH_3)_3$; HRMS (APPI, pos.): *m*/*z* 194.0699 (194.0691 calc. for $C_9H_{10}N_2O_3$ $(M)^+$), 195.0769 (195.0770 calc. for $C_9H_{11}N_2O_3$ $(M+H)^+$).

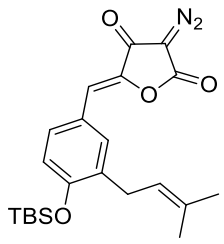
(*Z*)-3-Diazo-5-((2,2-dimethylchroman-6-yl)methylene)furan-2,4(3*H*,5*H*)-dione (55):



The reaction of **45** (200 mg, 1.59 mmol), 2,2-dimethylchroman-6-carbaldehyde (302 mg, 1.59 mmol), $TiCl_4$ (0.52 mL, 4.8 mmol) and 2,4,6-collidine (0.63 mL, 4.8 mmol) in CH_2Cl_2 (9 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 to 7:3), 430 mg (91%) of **55** as a yellow-orange solid.

R_f = 0.46 (hexanes/EtOAc, 7:3); mp: 156-161 °C; IR (neat): 2979, 2926, 2163, 1774, 1702, 1641, 1598, 1570, 1490, 1364, 1308, 1269, 1116, 1074, 1054, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (br s, 1H, Ar*H*), 7.50 (dd, 1H, *J* = 8.3, 2.1 Hz, Ar*H*), 6.81 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.64 (s, 1H, ArC*H*=C), 2.81 (t, 2H, *J* = 6.7 Hz, ArC$H_2$$CH_2$), 1.83 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.36 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*=O), 160.6 (O*C*=O), 156.6 (ArC_{ipso}), 140.1 (O-*C*=CHAr), 133.3 (Ar*C*), 131.4 (Ar*C*), 122.6 (ArC_{ipso}), 121.7 (ArC_{ipso}), 118.1 (Ar*C*), 112.7 (Ar*C*H=C), 75.5 (Ar-O-*C*$(CH_3)_2$), 32.5 (Ar*C*$H_2$$CH_2$), 26.9 (2 × *C*$H_3$), 22.4 (Ar$CH_2$*C*$H_2$); HRMS (ESI, pos.): *m/z* 298.0939 (298.0954 calc. for $C_{16}H_{14}N_2O_4$, $(M)^+$), 299.1012 (299.1032 calc. for $C_{16}H_{15}N_2O_4$, $(M+H)^+$) and 321.0827 (321.0851 calc. for $C_{16}H_{14}N_2NaO_4$, $(M+Na)^+$).

(*Z*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (56):

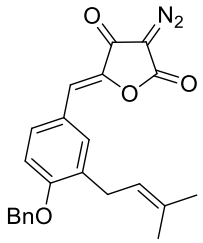


The reaction of **45** (350 mg, 2.78 mmol), 4-((tert-butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde (846 mg, 2.78 mmol), $TiCl_4$ (0.90 mL, 8.3 mmol) and 2,4,6-collidine (1.10 mL, 8.33 mmol) in CH_2Cl_2 (12 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 19:1), 902 mg (79%) of **56** as a yellow solid.

R_f = 0.63 (hexanes/EtOAc, 7:3); mp: 118-121 °C; IR (neat): 2961, 2929, 2858, 2137, 1782, 1708, 1648, 1598, 1497, 1364, 1276, 1076, 931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, 1H, *J* = 8.4, 2.3 Hz, Ar*H*), 7.49 (d, 1H, *J* = 2.3 Hz, Ar*H*), 6.82 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.66 (s, 1H, ArC*H*=C), 5.24-5.33 (m, 1H, $(CH_3)_2$C=C*H*), 3.30 (d, 2H, *J* = 7.1 Hz, C=CHCH_2), 1.77 (br d, 3H,

J = 1.0 Hz, C*H*$_3$), 1.71 (br s, 3H, C*H*$_3$), 1.02 (s, 9H, 3 × C*H*$_3$), 0.27 (s, 6H, 2 × C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.4 (O*C*=O), 156.0 (ArC_{ipso}), 140.4 (O-*C*=CHAr), 133.61 (Ar*C*), 133.57 (ArC_{ipso} or $(CH_3)_2C$=CH), 133.1 (ArC_{ipso} or $(CH_3)_2C$=CH), 130.6 (Ar*C* or $(CH_3)_2$C=*C*H), 123.9 (ArC_{ipso} or $(CH_3)_2C$=CH), 121.7 (Ar*C* or Ar*C*H=C), 118.9 (Ar*C* or Ar*C*H=C), 112.6 (Ar*C* or Ar*C*H=C), 28.4 (*C*H$_2$), 25.7 (4 × *C*H$_3$), 18.3 (Si-*C*$(CH_3)_3$), 17.9 (*C*H$_3$), -4.1 (2 × Si*C*H$_3$); HRMS (APPI, pos.): *m/z* 412.1827 (412.1818 calc. for $C_{22}H_{28}N_2O_4Si$, $(M)^+$) and 413.1859 (413.1897 calc. for $C_{22}H_{29}N_2O_4Si$, $(M+H)^+$).

(*Z*)-5-(4-(Benzyloxy)-3-(3-methylbut-2-enyl)benzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (57):



The reaction of **45** (100 mg, 0.79 mmol), 4-(benzyloxy)-3-(3-methylbut-2-enyl)benzaldehyde (222 mg, 0.79 mmol), $TiCl_4$ (0.25 mL, 2.38 mmol) and 2,4,6-collidine (0.3 mL, 2.38 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 180 mg (60%) of **57** as a yellow solid.

R_f = 0.25 (hexanes/EtOAc, 9:1); IR (neat): 2962, 2913, 2854, 2142, 1773, 1701, 1644, 1596, 1497, 1463, 1453, 1419, 1359, 1283, 1079, 981 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, 1H, *J* = 8.6, 2.3 Hz, Ar*H*), 7.55 (d, 1H, *J* = 2.3 Hz, Ar*H*), 7.46-7.30 (m, 5H, ArH), 6.95 (d, 1H, *J* = 8.6 Hz, Ar*H*), 6.66 (s, 1H, ArC*H*), 5.34-5.26 (m, 1H, CH_2CH=$C(CH_3)_2$), 5.15 (s, 2H, C*H*$_2$Ph), 3.40 (d, *J* = 7.4 Hz, C*H*$_2$CH=$C(CH_3)_2$), 1.76 (d, 3H, *J* = 0.9 Hz, (C*H*$_3$)), 1.67 (s, 3H, C*H*$_3$). ^{13}C NMR (75

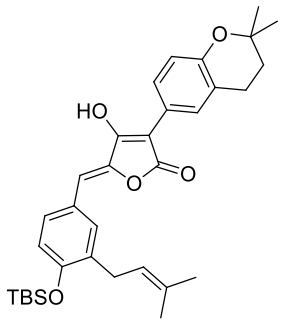
MHz, $CDCl_3$): δ 174.8 (*C*=O), 160.6 (O-*C*=O), 158.5 (ArC_{ipso}), 140.5 (ArC_{ipso}), 136.7, (ArC_{ipso} or $(CH_3)_2C$=C), 133.6 (O-*C*=CHAr), 133.2 (Ar*H*), 131.4 (ArC_{ipso} or $(CH_3)_2C$=C), 131.2 (Ar*H*), 128.7 (2 x Ar*C*), 128.1 (Ar*C*), 127.3 (2 x Ar*C*), 123.7 (ArC_{ipso}), 121.8 ($(CH_3)_2$C=*C*), 112.6 (Ar*C*), 112.0 (Ar-*C*H), 70.0 (Ar*C*H_2), 28.7 (*C*H_2), 25.9 (*C*H_3), 18.0 (*C*H_3); HRMS (APPI, pos.): *m*/*z* 388.1441 (388.1423 calc. for $C_{23}H_{20}N_2O_4$ $(M)^+$), 389.1514 (389.1501 calc. for $C_{23}H_{21}N_2O_4$ $(M+H)^+$).

General procedures for the insertion reactions of (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones and arenes:

To a suspension of (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-dione (1 equiv) in α,α,α-trifluorotoluene or DCE was added the aromatic compound (4 equiv) followed by the Rh(II) catalyst (1 mol%) at room temperature and the reaction mixture was placed in an oil bath that was pre-heated to 50 °C or to 100 °C. The mixture was heated until complete consumption of the diazo compound (TLC), then cooled to room temperature and concentrated. The residue was purified by flash chromatography on silica gel.

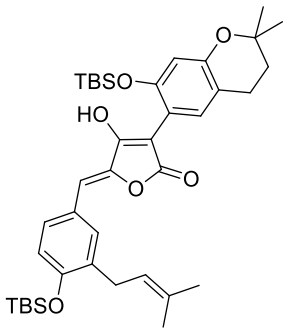
(*Z*)-5-(4-(*tert*-Butyldimethylsilyloxy)-3-(3-methylbut-2-enyl)benzylidene)-3-(2,2-dimethylchroman-6-yl)-4-hydroxyfuran-2(5*H*)-one (68):

The reaction of (*Z*)-5-(4-(*tert*-butyldimethylsilyloxy)-3-(3-methylbut-2-enyl)benzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (**56**) (50 mg, 0.12 mmol), 2,2-dimethylchromane (**65**, 78 mg, 0.48 mmol) $Rh_2(esp)_2$ (0.9 mg, 0.001 mmol) in DCE at reflux for 2 h according to the general procedure provided, after purification of by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 39 mg (59%) of **68** as a yellow solid.



R_f = 0.19 (hexanes/EtOAc, 9:1); IR (neat): 2929, 2856, 1711, 1599, 1495, 1258, 1223, 1156, 1117, 991, 935, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (dd, 1H, *J* = 8.4, 2.1 Hz, Ar*H*), 7.46 (d, 1H, *J* = 2.0 Hz, Ar*H*) 7.39 (br s, 1H, Ar*H*), 7.34 (br dd, 1H, *J* = 8.4, 1.8 Hz, Ar*H*), 6.84 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.79 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.71-6.54 (bs, 1H, O*H*), 6.26 (s, 1H, ArC*H*), 5.34-5.25 (m, 1H, $(CH_3)_2C=CH$), 3.32 (d, 2H, *J* = 7.0 Hz, $CH_2CH=(CH_3)_2$), 2.80 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.80 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.76 (s, 3H, $CH=C(CH_3)_2$), 1.71 (s, 3H, $CH=C(CH_3)_2$), 1.33 (s, 6H, $O-C(CH_3)_2$), 1.02 (s, 9H, $C(CH_3)_3$), 0.26 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (*C*=O or *C*=*C*OH), 160.6 (*C*=O or C=*C*OH), 154.8 (ArC_{ipso}), 154.3 (ArC_{ipso}), 140.1 (O-*C*=CHAr), 133.1 (ArC_{ipso} or $(CH_3)_2C$=C), 132.9 (ArC_{ipso} or $(CH_3)_2C$=C), 132.7 (Ar*C*), 129.6 (Ar*C*), 129.2 (ArC_{ipso}), 126.9 (Ar*C*), 125.8 (Ar*C*), 122.4 (ArC_{ipso}), 122.0 (ArC_{ipso}), 119.9 ($(CH_3)_2C=CH$), 119.0 (Ar*C*), 118.1 (Ar*C*), 108.7 (Ar-*C*H), 103.1 (*C*=COH), 74.9 ($O-C(CH_3)_2$), 32.8 (CH_2), 28.7 (CH_2), 27.0 (($O-C(CH_3)_2$), 25.9 (($Si-C(CH_3)_3$) and 1 × $C=C(CH_3)_2$), 22.6 (CH_3), 18.5 (($Si-C(CH_3)_3$), 18.0 (1 × $C=C(CH_3)_2$), -4.0 ($Si(CH_3)_2$); HRMS (ESI, pos.): *m*/*z* 546.2799 (546.2802 calc. for $C_{33}H_{42}O_5Si$ $(M)^+$) and 547.2872 (547.2880 calc. for $C_{33}H_{43}O_5Si$ $(M+H)^+$) and 569.2690 (569.2699 calc. for $C_{33}H_{42}NaO_5Si$ $(M+Na)^+$).

(*Z*)-3-(7-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylchroman-6-yl)-5-(4-(*tert*-butyldimethylsilyloxy)-3-(3-methylbut-2-enyl)benzylidene)-4-hydroxyfuran-2(5*H*)-one (72):

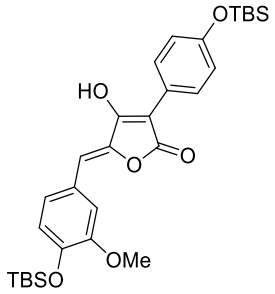


The reaction of (*Z*)-5-(4-(*tert*-butyldimethylsilyloxy)-3-(3-methylbut-2-enyl)benzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (**56**, 47 mg, 0.11 mmol), *tert*-butyl(2,2-dimethylchroman-7-yloxy)dimethylsilane (**71**, 133 mg, 0.450 mmol), $Rh_2(esp)_2$ (0.8 mg, 0.001 mmol) in DCE at reflux for 6 h according to the general procedure provided, after purification of by flash column chromatography on silica gel (hexanes/EtOAc, 9.7:0.3), 29 mg (38%, 43% based on recovered SM) of **72** as a yellow solid.

R_f = 0.18 (hexanes/EtOAc, 9.7:0.3); IR (neat): 2955, 2929, 2857, 1753, 1611, 1600, 1495, 1471, 1325, 1276, 1254, 1119, 1091, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.73 (s, 1H, OH), 7.68 (dd, *J* = 8.5, 2.4 Hz, Ar*H*), 7.60 (br s, 1H, Ar*H*), 7.49 (d, 1H, *J* = 2.4 Hz, Ar*H*), 6.83 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.39 (s, 1H, Ar*H*), 6.27 (s, 1H, ArC*H*), 5.36-5.28 (m, 1H, $(CH_3)_2C=CH$), 3.33 (d, 2H, *J* = 7.2 Hz, $CH_2CH=(CH_3)_2$), 2.78 (t, 2H, *J* = 6.8 Hz, $ArCH_2CH_2$), 1.80 (t, 2H, *J* = 6.8 Hz, $ArCH_2CH_2$), 1.77 (s, 3H, $CH=C(CH_3)_2$), 1.73 (s, 3H, $CH=C(CH_3)_2$), 1.33 (s, 6H, $C(CH_3)_2$) 1.02 (s, 9H, $C(CH_3)_3$), 0.96 (s, 9H, $C(CH_3)_3$), 0.26 (s, 6H, $Si(CH_3)_2$), 0.20 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (*C*=O or *C*=*C*OH), 161.6 (*C*=O or *C*=*C*OH), 154.9 (ArC_{ipso}), 154.5 (ArC_{ipso}), 150.4 (ArC_{ipso}), 140.4 (O-*C*=CHAr), 133.1 (ArC_{ipso} or $(CH_3)_2C$=C) , 132.8 (ArC_{ipso} or $(CH_3)_2C$=C), 132.5 (Ar*C*), 130.4 (Ar*C*), 129.5 (Ar*C*), 126.2 (ArC_{ipso}), 122.4 ($(CH_3)_2C=C$), 119.0 (Ar*C*), 116.7 (ArC_{ipso}), 113.3 (ArC_{ipso}), 109.2 (Ar-*C*H) , 107.8 (Ar*C*) , 100.3 (*C*=COH), 75.1 ($C(CH_3)_2$), 32.9 (CH_2), 28.7 (CH_2), 27.0 ((O-$C(CH_3)_2$), 25.9 (2 × (Si-$C(CH_3)_3$), 1 × C=$C(CH_3)_2$),

22.0 (*C*H_2). 18.53 (Si-*C*(CH_3)$_2$), 18.48 (Si-*C*(CH_3)$_2$), 18.1 (1× C=C(*C*H_3)$_2$), -3.9 (Si(*C*H_3)$_2$), -4.2 (Si(*C*H_3)$_2$); HRMS (APPI, pos.): *m*/*z* 676.3616 (676.3615 calc. for $C_{39}H_{56}O_6Si_2$ $(M)^+$) and 677.3686 (677.3694 calc. for $C_{39}H_{57}O_6Si_2$ $(M+H)^+$).

(*Z*)-5-(4-(*tert*-Butyldimethylsilyloxy)-3-methoxybenzylidene)-3-(4-(*tert* butyldimethylsilyloxy)phenyl)-4-hydroxyfuran-2(5*H*)-one (74):

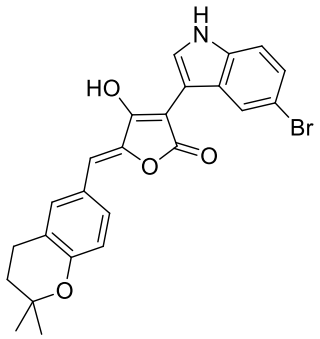


The reaction of (*Z*)-5-(4-(*tert*-butyldimethylsilyloxy)-3-methoxybenzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (**53**, 150 mg, 0.40 mmol), *tert*-butyldimethyl(phenoxy)silane (**73**, 334 mg, 1.60 mmol), $Rh_2(esp)_2$ (3 mg, 0.004 mmol) in DCE at reflux for 3 h according to the general procedure provided, after purification of by flash column chromatography on silica gel (hexanes/EtOAc, 9.2:0.8), 29 mg (40%) of **74** as a yellow solid.

R_f = 0.19 (hexanes/EtOAc, 9.2:0.8); IR (neat): 3012, 2950, 2927, 2884, 2855, 1693, 1658, 1627, 1597, 1510, 1468, 1426, 1399, 1360, 1292, 1264, 1248, 1149, 1130, 967, 911 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.88-7.82 (m, 2H, Ar*H*), 7.34 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.25 (dd, 1H, *J* = 8.4, 2.0 Hz, Ar*H*), 6.95-6.89 (m, 3H, Ar*H*), 6.63 (s, 1H, ArC*H*), 3.82 (s, 3H, OCH_3), 0.97 (s, 9H, Si-C(CH_3)$_3$), 0.96 (s, 9H, Si-C(CH_3)$_3$), 0.21 (s, 6H, Si(CH_3)$_2$), 0.16 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.0 (*C*=O or *C*=*C*OH), 162.6 (*C*=O or *C*=*C*OH), 154.1 (ArC_{ipso}), 150.6 (ArC_{ipso}), 145.3 (O-*C*=CHAr), 141.0 (ArC_{ipso}), 128.5 (2 × Ar*C*), 126.8 (ArC_{ipso}), 123.7 (Ar*C*), 123.2 (ArC_{ipso}), 120.9 (Ar*C*), 119.7 (2 × Ar*C*), 113.7 (Ar*C*), 107.4 (Ar-*C*H), 99.6 (*C*=COH), 55.4 (O*C*H_3), 25.6 (C(*C*H_3)$_3$), 25.5 (C(*C*H_3)$_3$), 18.2 (*C*(CH_3)$_3$), 18.0 (*C*(CH_3)$_3$), -4.5 (Si(*C*H_3)$_2$), -4.7

(Si(*C*H_3)$_2$); HRMS (ESI, pos.): *m*/*z* 554.2508 (554.2520 calc. for $C_{30}H_{42}O_6Si_2$ $(M)^+$), 555.2581 (555.2598 calc. for $C_{30}H_{43}O_6Si_2$ $(M+H)^+$), 577.2400 (577.2418 calc. for $C_{30}H_{42}NaO_6Si_2$ $(M+Na)^+$).

(*Z*)-3-(5-Bromo-1*H*-indol-3-yl)-5-((2,2-dimethylchroman-6-yl)methylene)-4-hydroxyfuran-2(5*H*)-one (75):



The reaction of (*Z*)-3-diazo-5-((2,2-dimethylchroman-6-yl)methylene)furan-2,4(3*H*,5*H*)-dione (**55**, 50 mg, 0.16 mmol), 5-bromoindole (131 mg, 0.67 mmol), $Rh_2(esp)_2$ (1.2 mg, 0.001 mmol) in $PhCF_3$ at 50 ^oC for 24 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 1:1), 70 mg (90 %,) of **75** as a green solid.

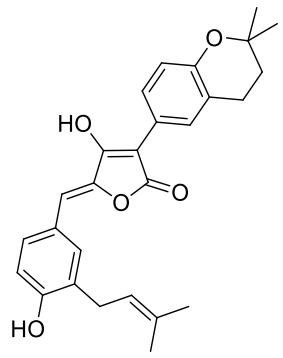
R_f = 0.2 (hexanes/EtOAc, 3:2); IR (neat): 3427, 2972, 2926, 1711, 1605, 1574, 1531, 1496, 1453, 1295, 1264, 1254, 1153, 1116 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 11.57 (s, 1H, O*H*), 8.22 (s, 1H, Ar*H*), 7.78 (s, 1H, Ar*H*), 7.50-7.42 (m, 2H, Ar*H*), 7.39 (d, 1H, *J* = 8.5 Hz, Ar*H*), 7.24 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.80 (s, 1H, *J* = 8.5 Hz, Ar*H*), 6.47 (s, 1H, ArC*H*), 2.79 (br t, 2H, *J* = 6.8 Hz, CH_2), 1.80 (br t, 2H, *J* = 6.8 Hz, CH_2), 1.30 (s, 6H, (CH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6 (*C*=O or *C*=*C*OH), 161.5 (*C*=O or *C*=*C*OH), 154.2 (ArC_{ipso}), 141.5 (O-*C*=CHAr), 134.7 (ArC_{ipso}), 131.4 (Ar*C*), 129.4 (Ar*C*), 127.2 (ArC_{ipso}), 126.5 (Ar*C*), 124.7 (ArC_{ipso}), 124.0 (Ar*C*), 123.8 (Ar*C*), 121.4 (ArC_{ipso}), 117.4 (Ar*C*), 113.6 (Ar*C*), 111.4 (ArC_{ipso}), 106.2 (Ar*C*H), 104.2

(*C*=COH), 96.7 (ArC_{ipso}), 74.9 (O-*C*$(CH_3)_2$), 32.0 (*C*H_2), 26.6 (*C*$H_3)_2$, 21.8 (*C*H_2); HRMS (ESI, pos.): *m*/*z* 465.0589 (465.0576 calc. for $C_{24}H_{20}Br^{79}NO_4$ $(M)^+$), 466.0662 (467.0654 calc. for $C_{24}H_{21}Br^{79}NO_4$ $(M+H)^+$), 468.0646 (469.0633 calc. for $C_{24}H_{21}Br^{81}NO_4$ $(M+H)^+$), 488.0482 (488.0473 calc. for $C_{24}H_{20}{}^{79}BrNNaO_4$ $(M+Na)^+$), 490.0465 (491.0452 calc. for $C_{24}H_{20}{}^{81}BrNNaO_4$ $(M+Na)^+$).

General procedure for the deprotection of TBS ethers 68, 72, 74:

To a solution of the TBS protected substrate in THF was added TBAF (1M in THF) at 0 ^oC. The mixture was warmed to room temperature and stirred until consumption of the starting material (TLC). The solvent was removed under educed pressure, the residue suspended in water and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulphate and concentrated. The residue was purified by flash chromatography on silica gel.

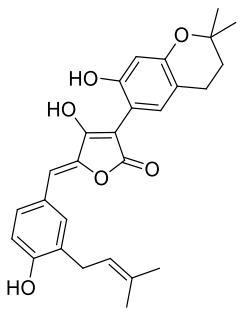
(*Z*)-3-(2,2-Dimethylchroman-6-yl)-4-hydroxy-5-(4-hydroxy-3-(3-methylbut-2-enyl)benzylidene)furan-2(5*H*)-one (Aspulvinone B (6)):[19]



The reaction of **68** (50 mg, 0.091 mmol) and TBAF (0.18 ml, 0.18 mmol) in THF (2 mL) according to the general procedure for 1 h. provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7.5:2.5, 1% AcOH), 22 mg (56%) of **6** as a yellow solid.

R_f = 0.23 (hexanes/EtOAc, 7.5:2.5, 1% vol AcOH); mp: 146-149 °C; IR (neat): 3310 (br), 2973, 2927, 1704, 1598, 1496, 1434, 1261, 1221, 1156, 1116, 989 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.87 (s, 1H, O*H*), 7.70-7.63 (m, 2H, Ar*H*), 7.47-7.41 (m, 2H, Ar*H*), 6.87 (d, 1H, *J* = 8.2, Ar*H*), 6.75 (d, 1H, *J* = 8.5, Ar*H*), 6.54 (s, 1H, ArC*H*) 5.29 (br t, 1H, *J* = 7.4 Hz, CH_2CH=$(CH_3)_2$), 3.24 (d, 2H, *J* = 7.4 Hz, CH_2CH=$(CH_3)_2$), 2.76 (br t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.78 (br t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$) 1.72 (s, 3H, CH=$(CH_3)_2$), 1.70 (s, 3H, CH=$(CH_3)_2$), 1.29 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.3 (*C*=O or *C*=*C*OH), 162.6 (*C*=O or C=*C*OH), 156.0 (ArC_{ipso}), 152.6 (ArC_{ipso}), 140.1 (O-*C*=CHAr), 131.9 (ArC_{ipso} or $(CH_3)_2C$=C), 131.6 (Ar*C*), 129.3 (Ar*C*), 128.2 (Ar*C*), 128.0 (ArC_{ipso} or $(CH_3)_2C$=C), 126.2 (Ar*C*), 123.9 (ArC_{ipso}), 122.4 ($(CH_3)_2C$=*C*), 121.6 (ArC_{ipso}), 120.5 (ArC_{ipso}), 116.5 (Ar*C*), 115.4 (Ar*C*), 107.5 (Ar*C*H), 99.1 (*C*=COH), 74.3 (O-*C*$(CH_3)_2$), 32.2 (*C*H_2), 27.8 (*C*H_2), 26.6 ((O-C(*C*$H_3)_2$), 25.5 (C=C(*CH*$_3)_2$), 22.0 (*C*H_2), 17.7 (C=C(*CH*$_3)_2$); HRMS (APPI, pos.): *m*/*z* 432.1929 (432.1937 calc. for $C_{27}H_{28}O_5$ $(M)^+$), 433.2001 (433.2015 calc. for $C_{27}H_{29}O_5$ $(M+H)^+$).

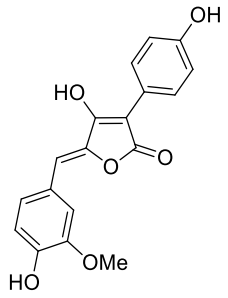
(*Z*)-4-Hydroxy-3-(7-hydroxy-2,2-dimethylchroman-6-yl)-5-(4-hydroxy-3-(3-methylbut-2-enyl)benzylidene)furan-2(5*H*)-one (Aspulvinone D (7)):[6,35]



The reaction of **72** (165 mg, 0.243 mmol) and TBAF (0.70 ml, 0.73 mmol) in THF (3 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.0:2.0, 1% AcOH), 90 mg (83%) of **7** as a yellow solid.

R_f = 0.20 (hexanes/EtOAc, 8.0:2.0, 1% vol AcOH); MP: 199-201 ^oC (decomposed); IR (neat): 3300 (br), 2973, 2925, 1696, 1662, 1589, 1505, 1425, 1344, 1276, 1229, 1157, 1090, 990 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.81 (bs, 1H, O*H*), 7.47 (br d, 1H, *J* = 1.9 Hz, Ar*H*), 7.45 (br dd, 1H, *J* = 8.3, 1.9 Hz, Ar*H*), 7.10 (s, 1H, Ar*H*), 6.86 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.27 (s, 1H, Ar*H* or ArC*H*), 6.24 (s, 1H, ArC*H* or Ar*H*), 5.29 (br t, 1H, *J* = 6.7 Hz, CH_2CH=$(CH_3)_2$), 3.24 (d, 2H, *J* = 6.7 Hz, CH_2CH=$(CH_3)_2$), 2.64 (br t, 2H, *J* = 6.5 Hz, $ArCH_2CH_2$), 1.73 (t, 2H, *J* = 6.5 Hz, $ArCH_2CH_2$), 1.72 (s, 3H, CH=C(CH_3)$_2$), 1.70 (s, 3H, CH=C(CH_3)$_2$), 1.27 (s, 6H, *C*(CH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6 (*C*=O or *C*=*C*OH), 163.3 (*C*=O or *C*=*C*OH), 155.8 (ArC_{ipso}), 154.1 (2 × ArC_{ipso}), 140.6 (O-*C*=CHAr), 131.8 (ArC_{ipso} or $(CH_3)_2C$=C), 131.6 (Ar*C*), 130.7 (Ar*C*), 129.2 (Ar*C*), 128.0 (ArC_{ipso} or $(CH_3)_2C$=C), 124.0 (ArC_{ipso}), 122.5 ($(CH_3)_2C$=*C*), 115.3 (Ar*C*), 111.6 (ArC_{ipso}), 108.7 (ArC_{ipso}), 106.1 (Ar-*C*H), 103.4 (Ar*C*), 98.0 (*C*=COH), 74.1 (O-*C*(CH_3)$_2$), 32.4 (*C*H_2), 27.9 (*C*H_2), 26.6 (C(*C*H_3)$_2$), 25.5 (C=C(*CH*$_3$)$_2$), 21.2 (*C*H_2), 17.7 (C=C(*CH*$_3$)$_2$); HRMS (ESI, pos.): *m*/*z* 448.1890 (448.1886 calc. for $C_{27}H_{28}O_6$ $(M)^+$), 449.1963 (449.1964 calc. for $C_{27}H_{29}O_6$ $(M+H)^+$), 471.1778 (471.1784 calc. for $C_{27}H_{28}NaO_6$ $(M+Na)^+$).

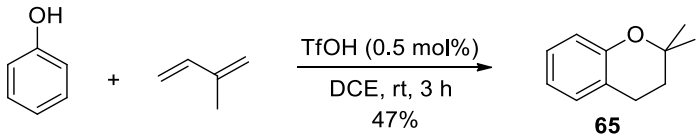
(*Z*)-4-Hydroxy-5-(4-hydroxy-3-methoxybenzylidene)-3-(4-hydroxyphenyl)furan-2(5*H*)-one (Aspulvinone Q (2)):[36]



The reaction of **74** (75 mg, 0.135 mmol) and TBAF (0.40 ml, 0.40 mmol) in THF (2 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:2 1% AcOH), 38 mg (86%) of **2** as a yellow solid.

*R*f = 0.23 (hexanes/EtOAc, 3:2, 1% vol AcOH); mp: 223-225 ºC; IR (neat): 3300 (br), 3129, 2931, 1692, 1624, 1592, 1512, 1432, 1406, 1277, 1234, 1148, 1130, 1095 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.49 (bs, 2H, O*H*), 7.80 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.30 (s, 1H, Ar*H*), 7.18 (dd, 1H, *J* = 8.1, 2.0 Hz,), 6.86 (d, 1H, *J* = 8.1 Hz, Ar*H*), 6.80 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.53 (br s, 1H, ArC*H*), 3.80 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6 (*C*=O or *C*=*C*OH), 163.6 (*C*=O or *C*=*C*OH), 156.1 (Ar*C*ipso), 147.7 (Ar*C*ipso), 147.6 (Ar*C*ipso), 141.0 (O-*C*=CHAr), 128.1 (2 × Ar*C*), 124.6 (Ar*C*ipso), 124.0 (Ar*C*), 121.5 (Ar*C*ipso), 115.9 (Ar*C*), 115.0 (2 × Ar*C*), 113.7 (Ar*C*), 106.7 (Ar-*C*H), 98.5 (*C*=COH), 55.6 (O*C*H_3); HRMS (APPI, pos.): *m*/*z* 326.0781 (326.0790 calc. for $C_{18}H_{14}O_6$ $(M)^+$), 327.0853 (327.0869 calc. for $C_{18}H_{15}O_6$ $(M+H)^+$).

2,2-Dimethylchromane (65):[37]

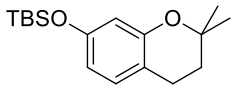


To a solution of phenol (1.00 g, 10.6 mmol) in dichloroethane (25 mL) was added isoprene (1.60 mL, 15.9 mmol) followed by triflic acid (5.0 µL, 5.3×10^{-2} mmol) at room temperature and the mixture was stirred for 3 h. The mixture was then concentrated, and the residue was directly purified by flash column chromatography on silica gel (hexanes) to provide 647 mg (38%) of **65** as a colorless liquid.

R_f = 0.21 (hexanes/EtOAc, 9.5:0.5); IR (neat): 2974, 2927, 1582, 1489, 1452, 1368, 1305, 1254, 1219, 1155, 1121, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12-7.01 (m, 2H, Ar*H*), 6.82 (dd, 1H, *J* = 7.3, 1.2 Hz, Ar*H*), 6.77 (br d, 1H, *J* = 8.4 Hz, Ar*H*), 2.77 (t, 2H, *J* = 6.7 Hz, ArC$H_2$$CH_2$), 1.80 (t, 2H, *J* = 6.7 Hz, Ar$CH_2$$CH_2$), 1.33 (s, 6H, 2 × C$H_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0

(ArC_{ipso}), 129.4 (Ar*C*), 127.2 (Ar*C*), 120.9 (ArC_{ipso}), 119.6 (Ar*C*), 117.2 (Ar*C*), 74.1 (Ar-O-*C*$(CH_3)_2$), 32.8 (Ar*C*H_2CH_2), 26.9 (2 × *C*H_3), 22.5 (ArCH_2*C*H_2).

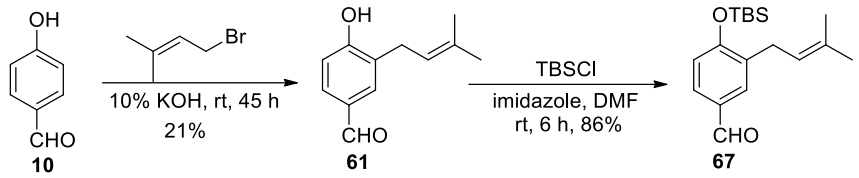
***tert*-Butyl(2,2-dimethylchroman-7-yloxy)dimethylsilane (71):**



To a solution of 2,2-dimethylchroman-7-ol[36] (650 mg, 3.65 mmol) in DMF (8 mL) was added imidazole (348 mg, 5.11 mmol) followed by TBSCl (715 mg, 4.74 mmol) at room temperature and the mixture was stirred for 2 h. Cold water (8 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (1 × 10 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide 850 mg (80%) of **71** as a colorless liquid.

Rf = 0.6 (hexanes/EtOAc, 9:1); IR (neat): 2974, 2929, 2895, 2857, 1617, 1576, 1501, 1472, 1344, 1307, 1281, 1253, 1168, 1149, 1120, 1106, 999, 836, 777 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.33 (dd, 1H, *J* = 8.2, 2.4 Hz, Ar*H*), 6.29 (d, 1H, *J* = 2.4 Hz, Ar*H*), 2.69 (t, 2H, *J* = 6.8 Hz, ArC*H*$_2$CH$_2$), 1.77 (t, 2H, *J* = 6.8 Hz, ArCH$_2$C*H*$_2$) 1.31 (s, 6H, 2 × C*H*$_3$), 0.97 (s, 9H, C(C*H*$_3$)$_3$), 0.18 (s, 6H, Si(C*H*$_3$)$_2$)). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2 (Ar*C*ipso), 155.0 (Ar*C*ipso), 130.0 (Ar*C*), 114.2 (Ar*C*ipso), 112.4 (Ar*C*), 108.9 (Ar*C*), 74.5 (Ar-O-*C*$(CH_3)_2$), 33.4 (Ar*C*H_2CH_2), 27.3 (2 × *C*H_3), 26.1 (C(*C*H_3)$_3$), 22.3 (Si-*C*$(CH_3)_3$), 18.6 (ArCH_2*C*H_2), -4.0 (Si(*C*H_3)$_2$). HRMS (APPI, pos.): *m*/*z* 292.1865 (292.1858 calc. for $C_{17}H_{28}O_2Si$ $(M)^+$) and 293.1944 (239.1937 calc. for $C_{17}H_{29}O_2Si$ $(M+H)^+$).

4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde (67):[32]



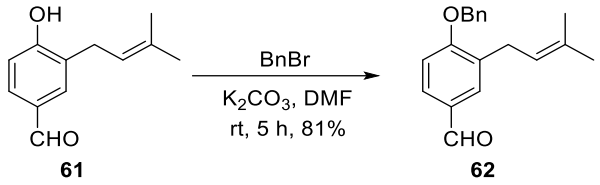
To a solution of 4-hydroxybenzaldehyde (**10**, 3.20 g, 26.5 mmol) in 10% aqueous potassium hydroxide (15 mL) was added prenyl bromide (5.50 mL, 47.6 mmol) dropwise over 10 min at room temperature and the mixture was stirred for 45 h. The reaction mixture was then cooled to 0 °C and acidified to pH~3 with 2 N HCl. The resulting suspension was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 9:1) to provide, 1.04 g (21%) of 4-hydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde as a pale-yellow liquid **61**.

To a solution of 4-hydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde (**61**, 500 mg, 2.63 mmol) in DMF (10 mL) was added imidazole (250 mg, 3.67 mmol) followed by TBSCl (515 mg, 3.42 mmol) at room temperature and the mixture was stirred for 7 h. Cold water (8 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water (1 × 10 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 98:2) to provide 641 mg (80%) of **67** as a colorless liquid.

R_f = 0.33 (hexanes/EtOAc, 9.5:0.5); IR (neat): 2956, 2930, 2858, 1693, 1598, 1493, 1256, 1110, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H, CO), 7.67 (d, 1H, *J* = 2.1 Hz, Ar*H*), 7.62 (dd, 1H, *J* = 8.2, 2.1 Hz, Ar*H*), 6.88 (d, 1H, *J* = 8.2 Hz, Ar*H*), 5.36-5.27 (m, 1H, C=C*H*), 3.34 (d, 1H, *J* = 7.5 Hz, CH_2CH=C), 1.77 (br d, 3H, *J* = 0.9 Hz, CH_3), 1.70 (s, 3H, CH_3), 1.03 (s,

9H,C(CH_3)$_3$), 0.29 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2 (*C*HO), 159.3 (ArC_{ipso}), 133.6 (ArC_{ipso} or C=*C*(CH$_3$)$_2$), 133.3 (ArC_{ipso} or C=*C*(CH$_3$)$_2$), 131.4 (Ar*C*), 130.2 (ArC_{ipso} or C=*C*(CH$_3$)$_2$), 129.6 (Ar*C*), 121.5 (Ar*C* or H*C*=C(CH$_3$)$_2$), 118.4 (Ar*C* and H*C*=C(CH$_3$)$_2$, or 2 × Ar*C*), 28.4 (*C*H$_2$), 25.8 (*C*H$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 17.9 (*C*H$_3$), -4.1 (Si(*C*H$_3$)$_2$).

4-(Benzyloxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde (62):



To a solution of 4-hydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde (**61**) (85 mg, 0.45 mmol) in DMF (1 mL) was added K_2CO_3 (74 mg, 0.54 mmol) followed by benzyl bromide (64 µL, 0.54 mmol) at room temperature and the mixture was stirred for 5 h. Cold water (2 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 4 mL). The combined organic layers were washed with water (1 × 4 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 95:5) to provide 101 mg (81%) of **62** as colorless liquid.

R_f = 0.32 (hexanes/EtOAc, 9:1); IR (neat): 2968, 2913, 2730, 1684, 1597, 1496, 1453, 1435, 1250, 1112, 1005 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H, C*H*O), 7.70 (s, 1H, Ar*H*), 7.69 (dd (partial overlap with s at 7.70), 1H, *J* = 8.2, 2.2 Hz, Ar*H*), 7.45-7.38 (m, 4H, Ar*H*), 7.37-7.32 (m, 1H, Ar*H*) 6.99 (d, 1H, *J* = 8.2 Hz, Ar*H*), 5.34-5.29 (m 1H, C=C*H*), 5.18 (s, 2H, PhCH_2), 3.41 (d, 1H, *J* = 7.3 Hz, CH_2CH=), 1.75 (br s, 3H, CH_3), 1.65 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3 (*C*HO), 161.6 (ArC_{ipso}), 136.4 (ArC_{ipso}), 133.6 (ArC_{ipso}), 131.5 (ArC_{ipso} or C=*C*(CH$_3$)$_2$), 130.65 (Ar*C*), 130.63 (Ar*C*), 129.9 (ArC_{ipso} or C=*C*(CH$_3$)$_2$), 128.8 (2 × Ar*C*), 128.2 (Ar*C*), 127.3 (2 × Ar*C*), 121.5 (H*C*=C(CH$_3$)$_2$), 111.3 (Ar*C*), 70.3 (Ph*C*H$_2$), 28.7 (H$_2$*C*H*C*=C), 25.9 (*C*H$_3$), 17.9

(*C*H_3); HRMS (ESI, pos.): *m/z* 280.1467 (280.1463 calc. for $C_{19}H_{20}O_2$, $(M)^+$), 281.1535 (281.1542 calc. for $C_{19}H_{21}O_2$, $(M+H)^+$) and 303.1356 (303.1361 calc. for $C_{19}H_{20}NaO_2$, $(M+Na)^+$).

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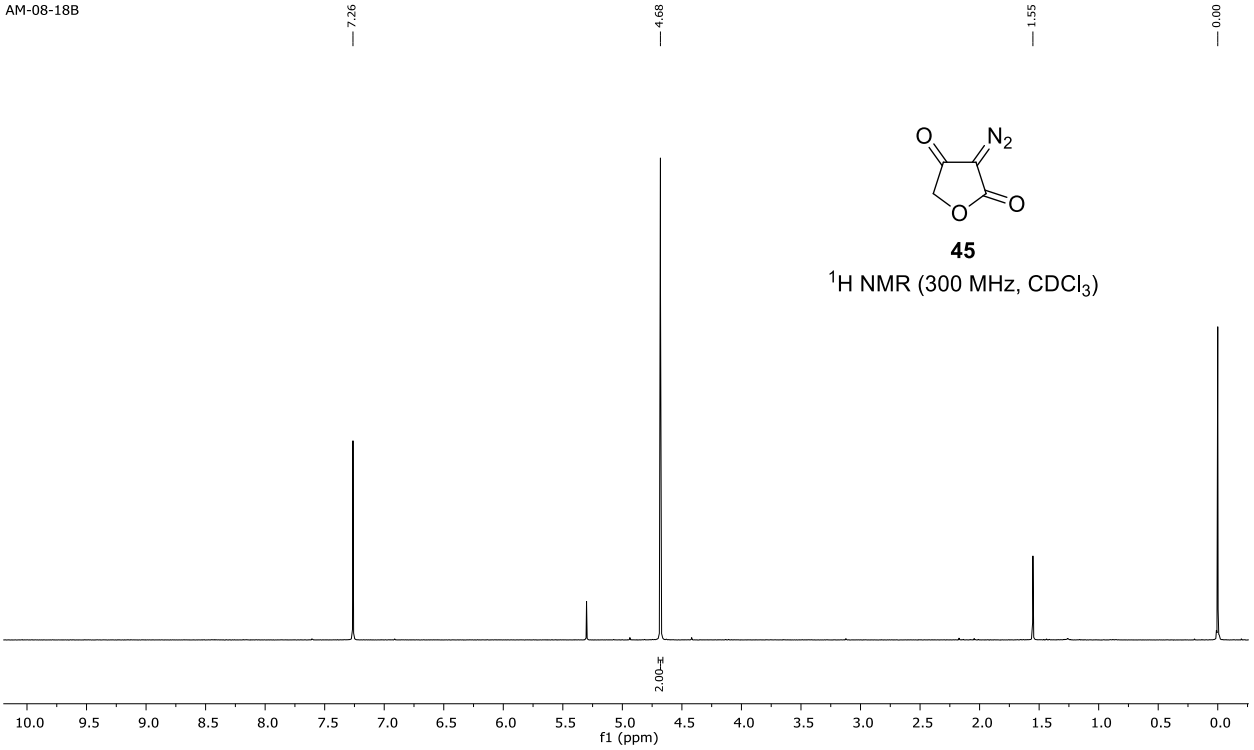
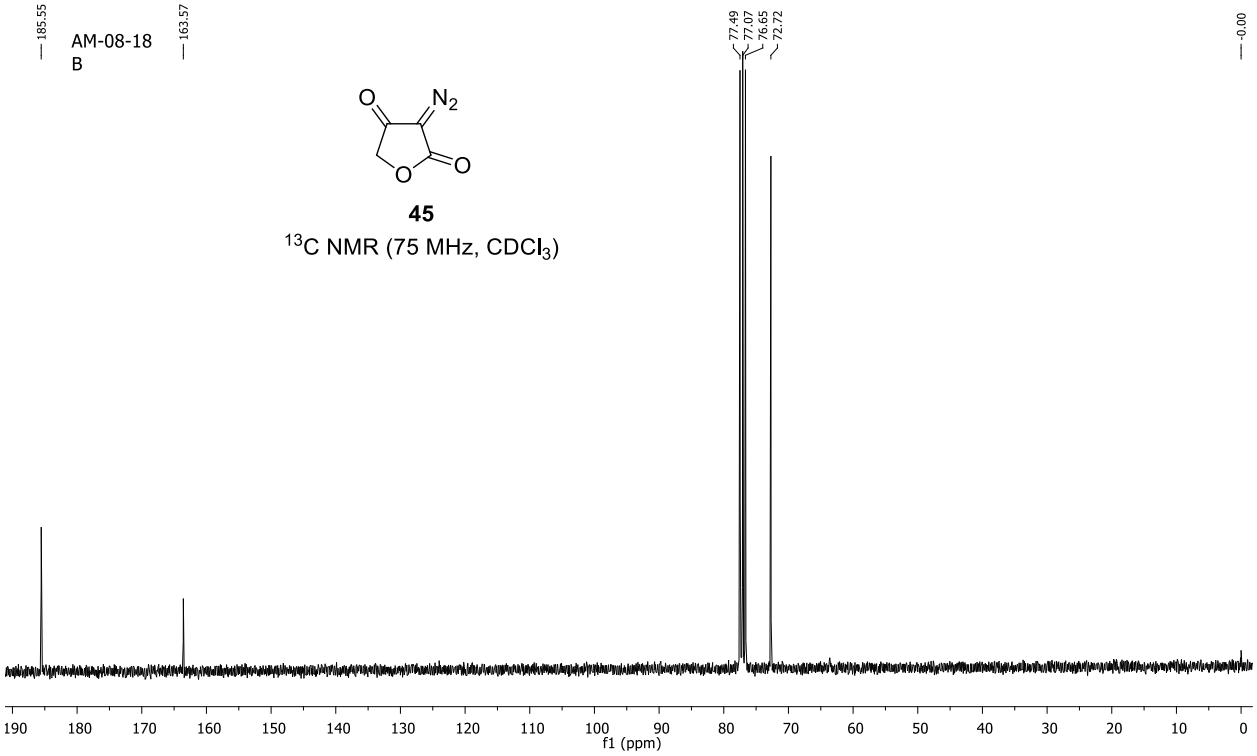
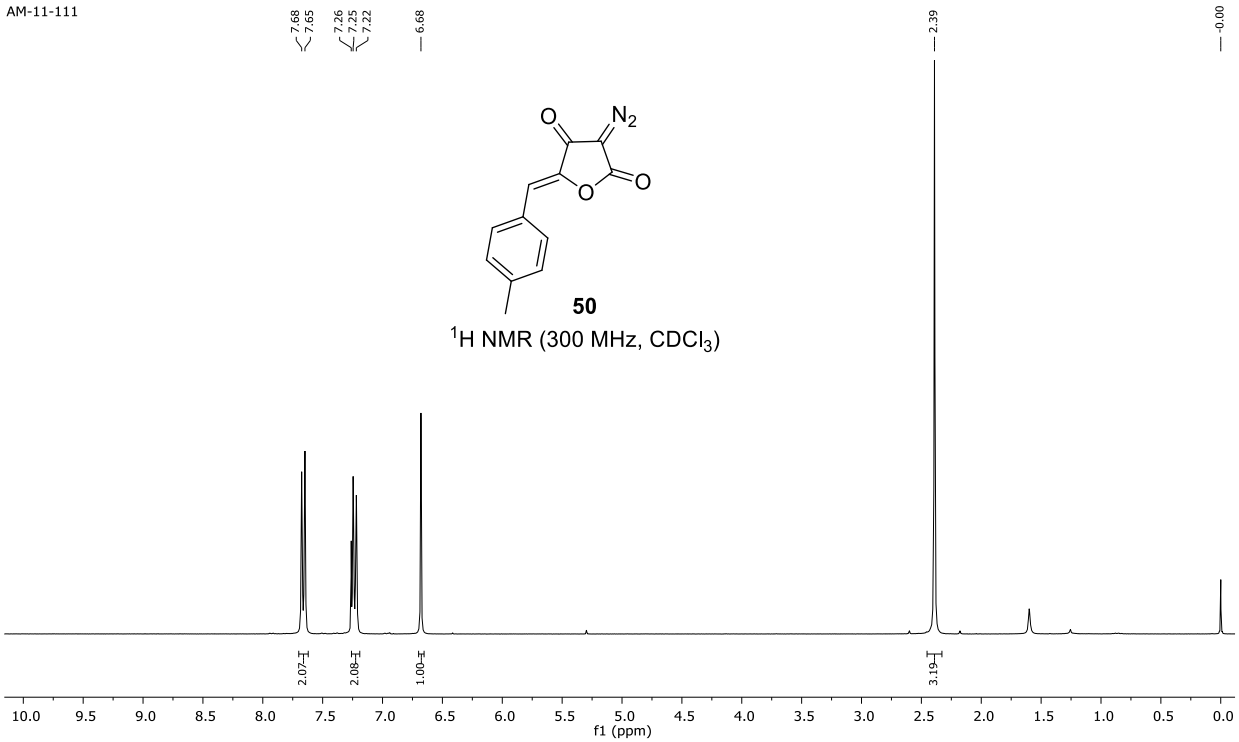
3.8 Selected ^{1}H and ^{13}C NMR spectral data:

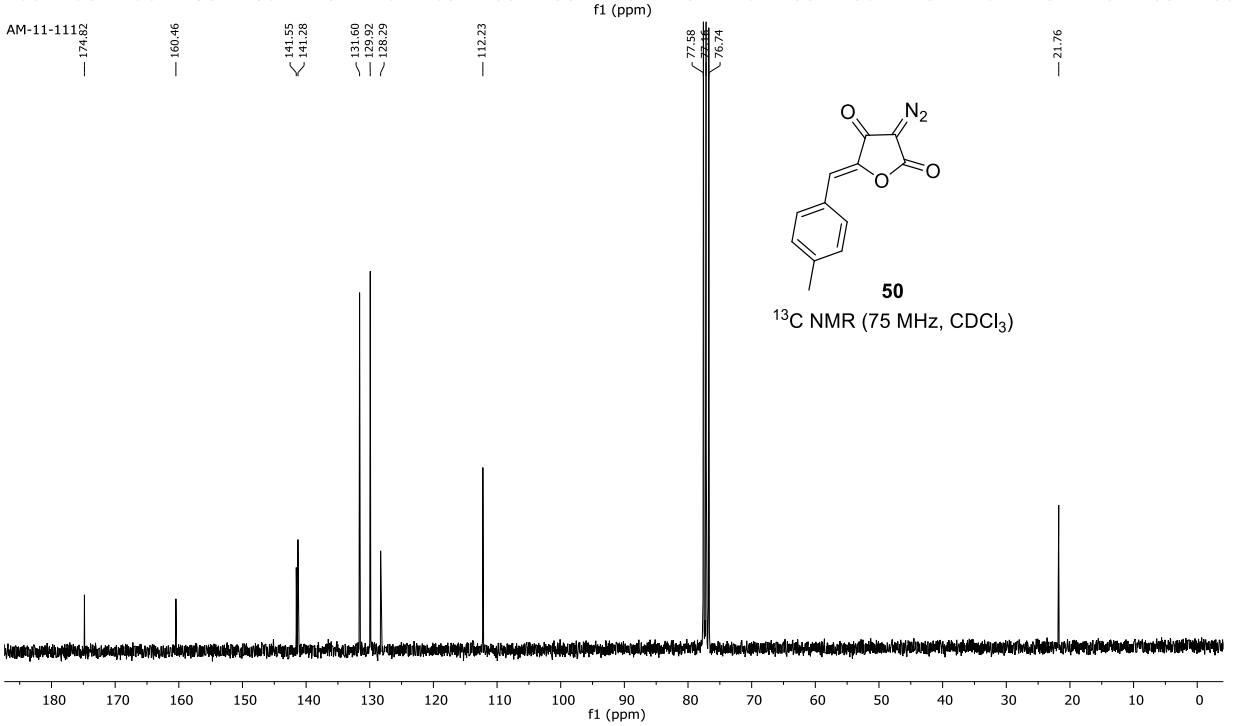






50

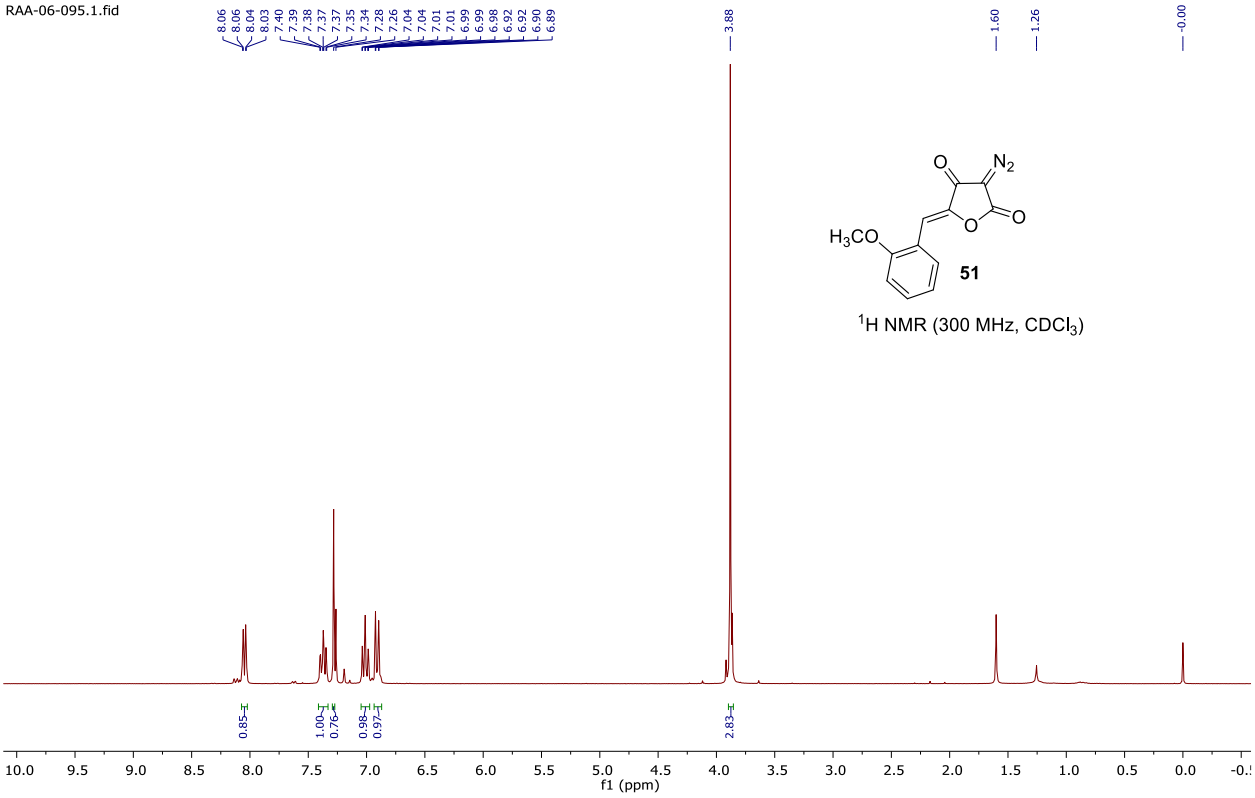
^{1}H NMR (300 MHz, $CDCl_3$)



50

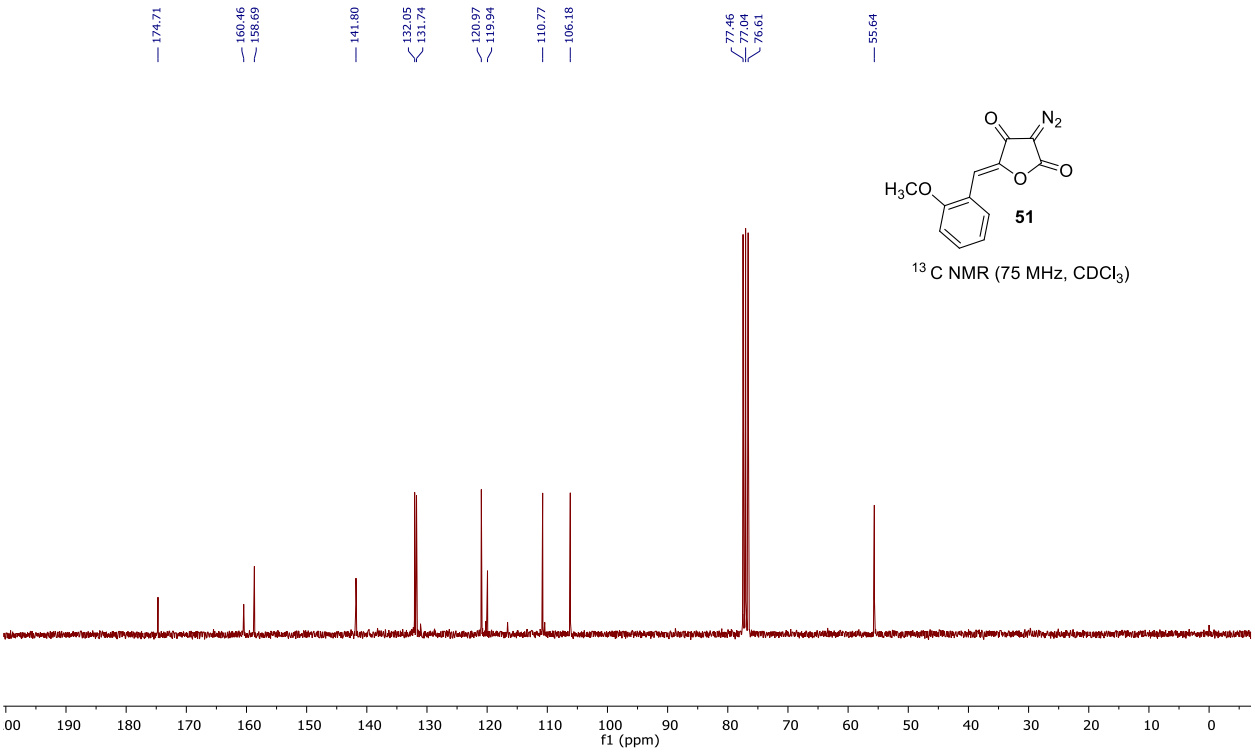
^{13}C NMR (75 MHz, $CDCl_3$)

RAA-06-095.1.fid



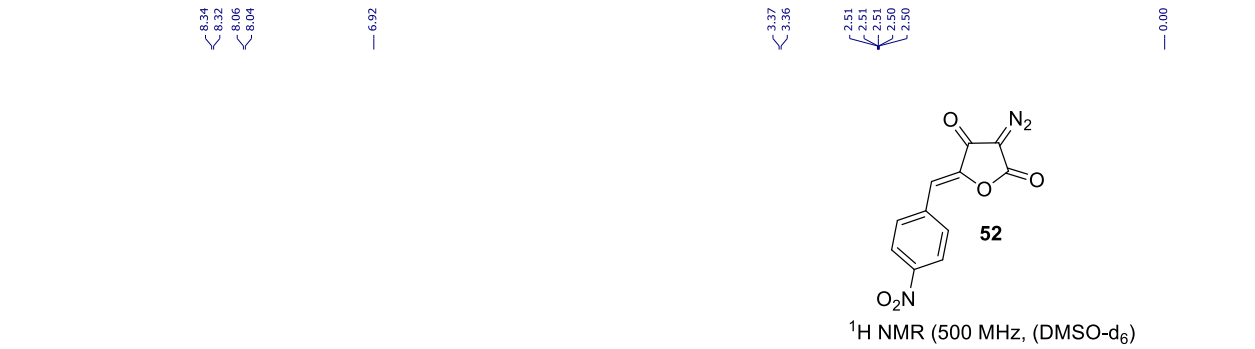
51

^{1}H NMR (300 MHz, $CDCl_3$)



51

^{13}C NMR (75 MHz, $CDCl_3$)



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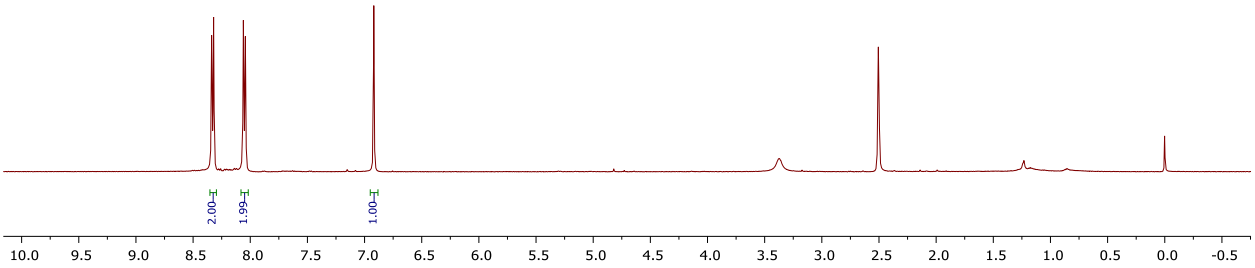

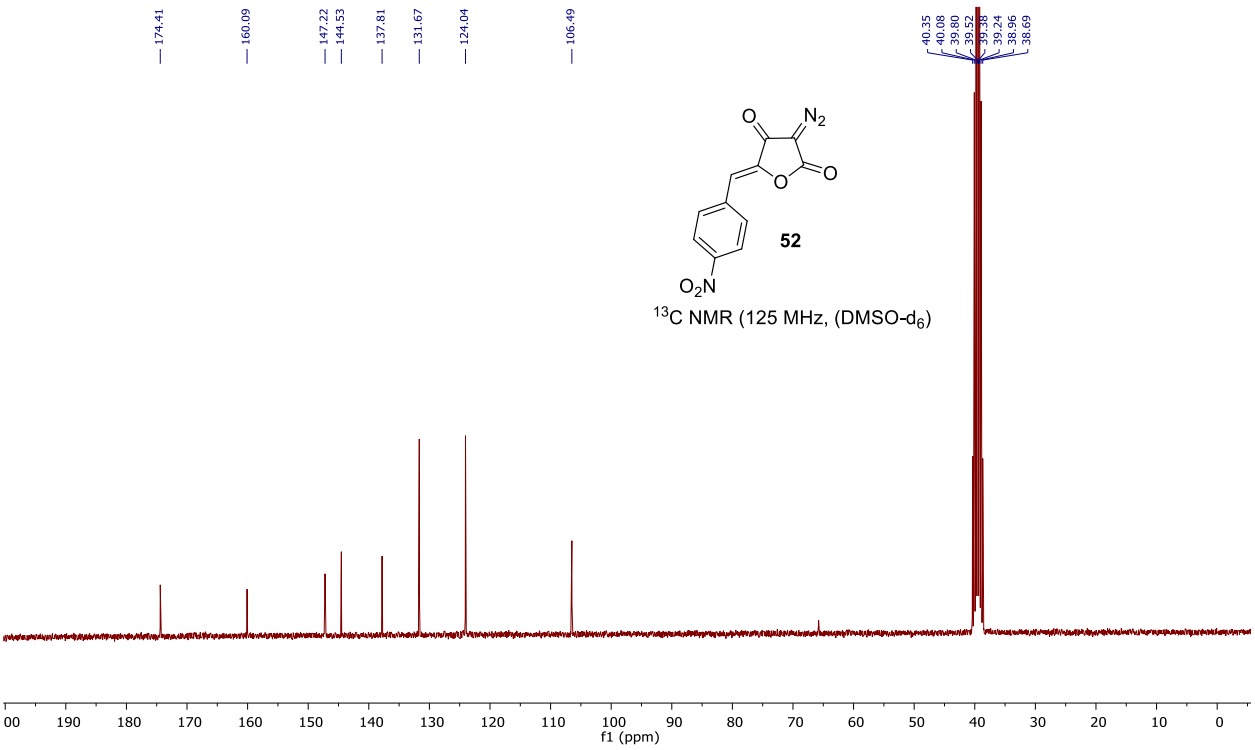

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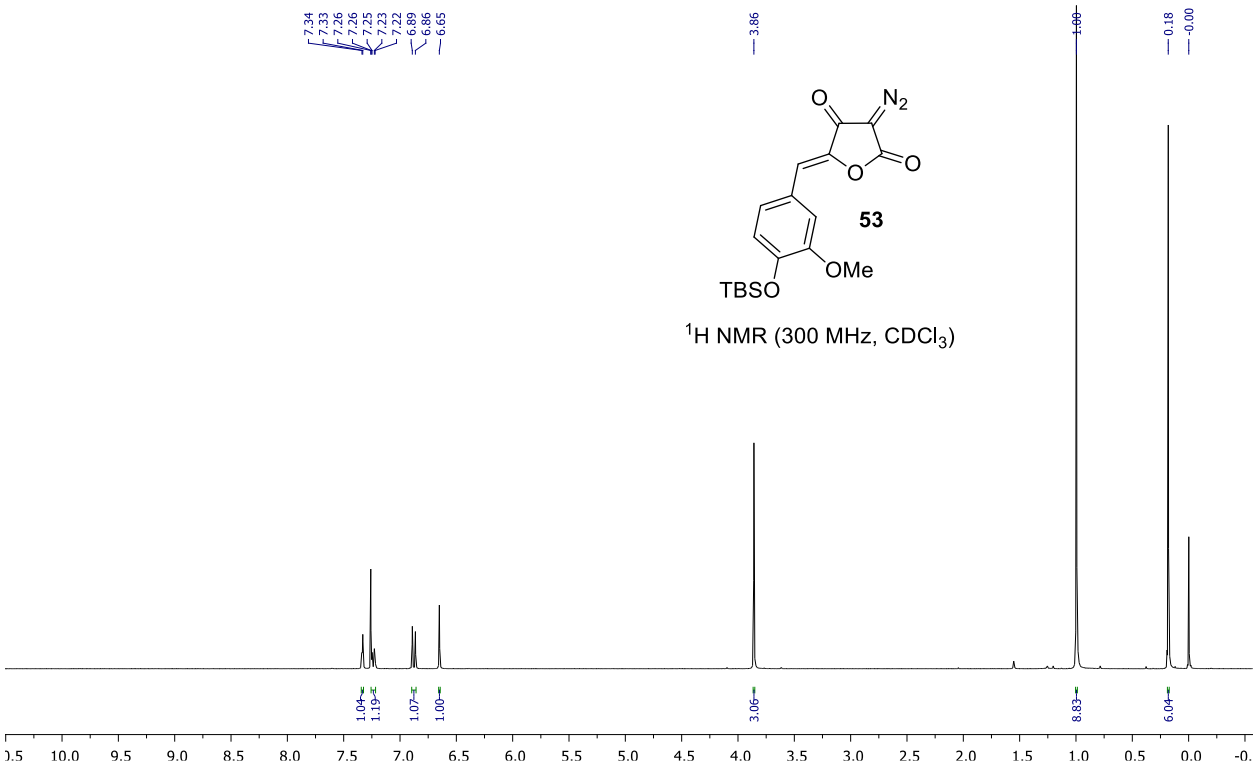

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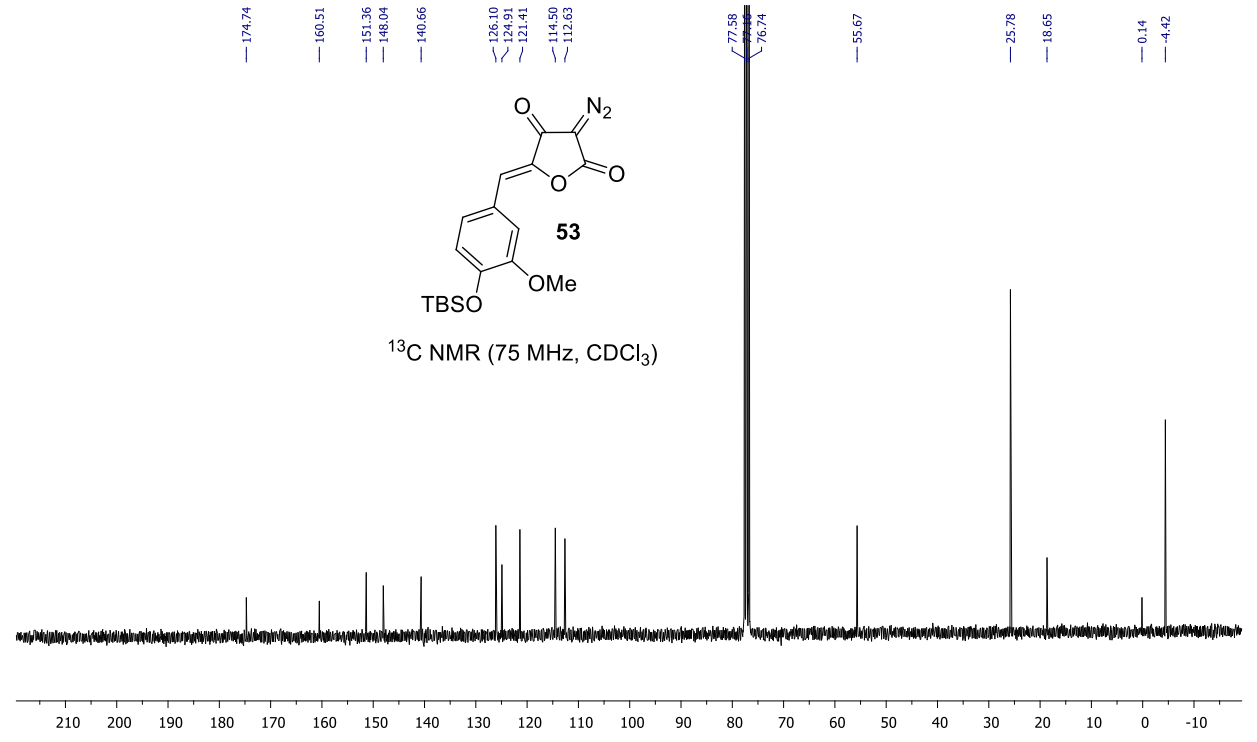

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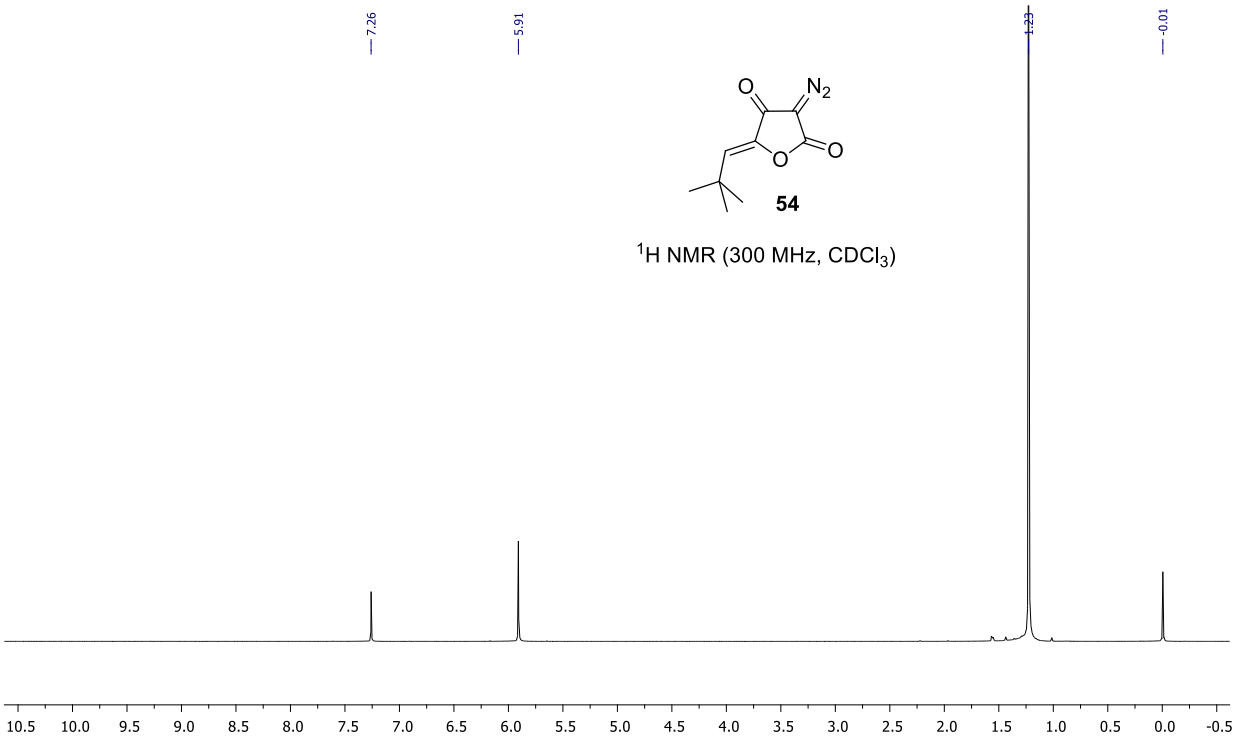
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1.23
-0.01
O
N2
O
O
54
1H NMR (300 MHz, CDCl3)
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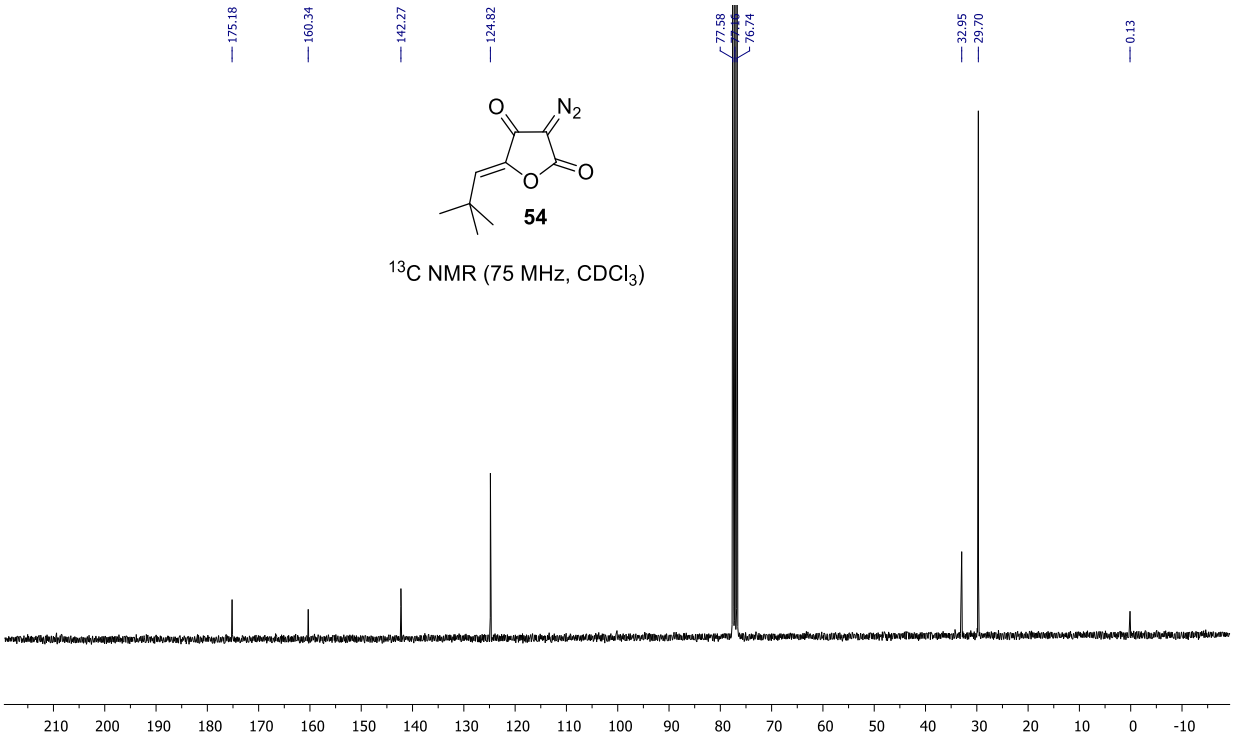
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124.82
77.58
77.16
76.74
32.95
29.70
0.13
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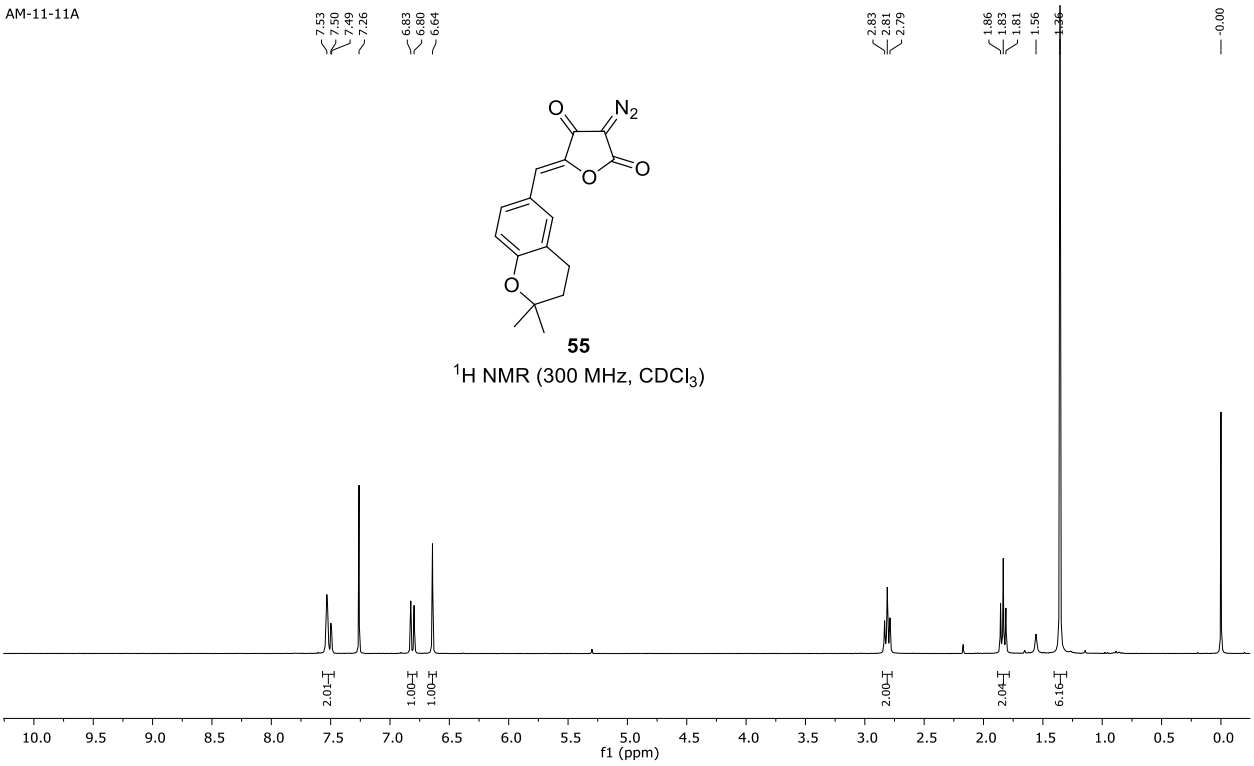
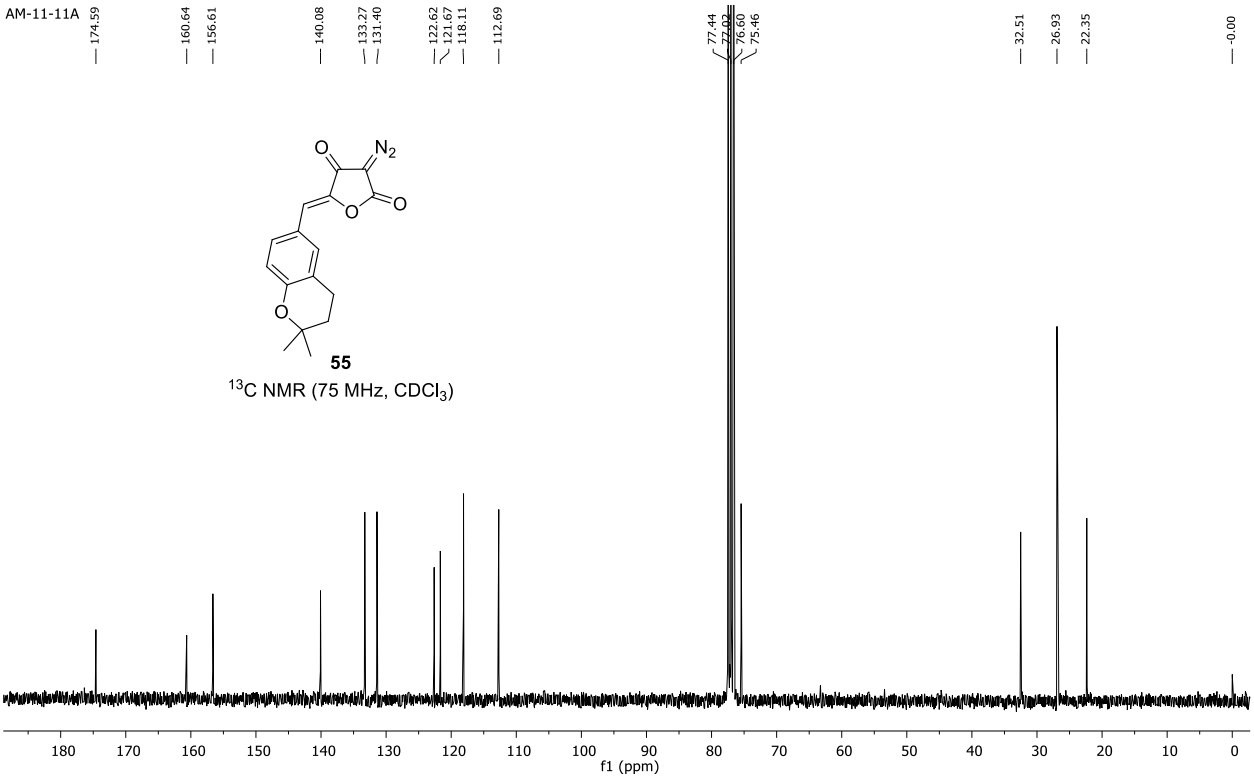
N2
O
O
54
13C NMR (75 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10



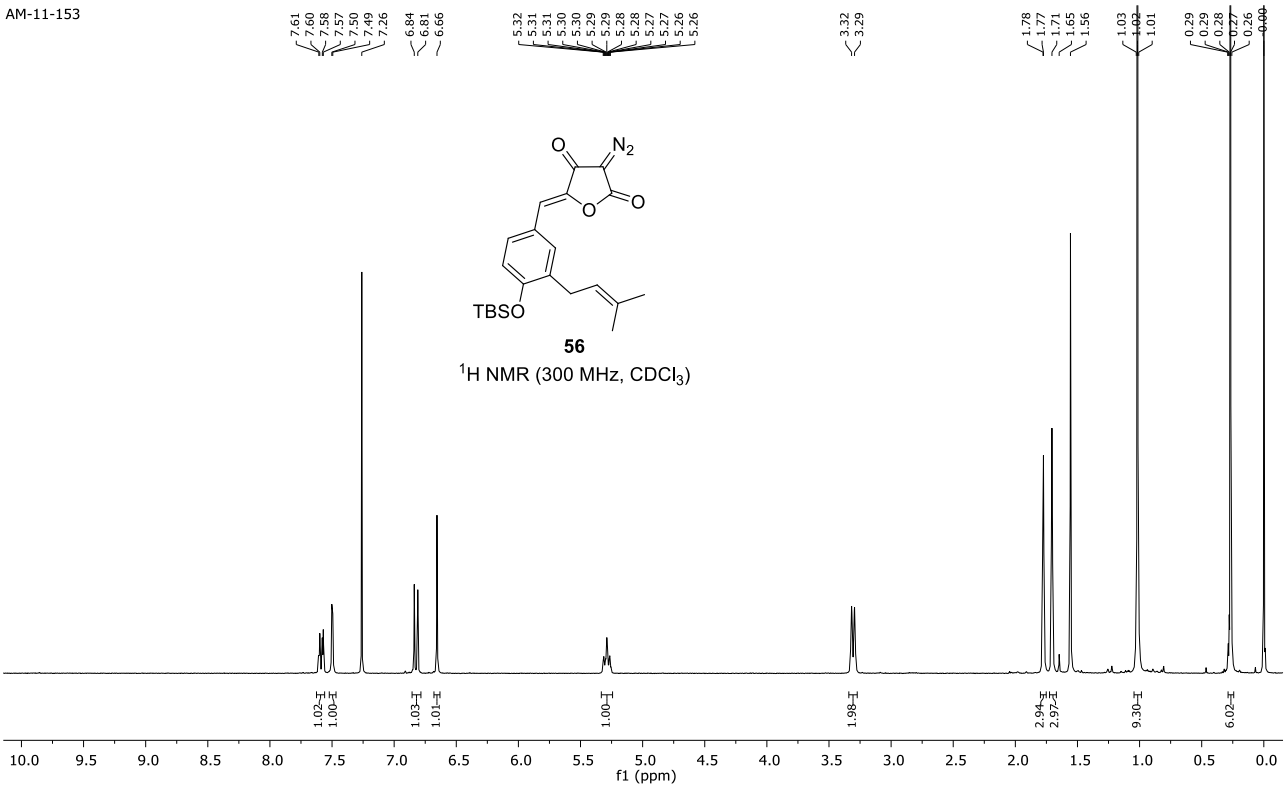
55

^{1}H NMR (300 MHz, $CDCl_3$)



55

^{13}C NMR (75 MHz, $CDCl_3$)



56

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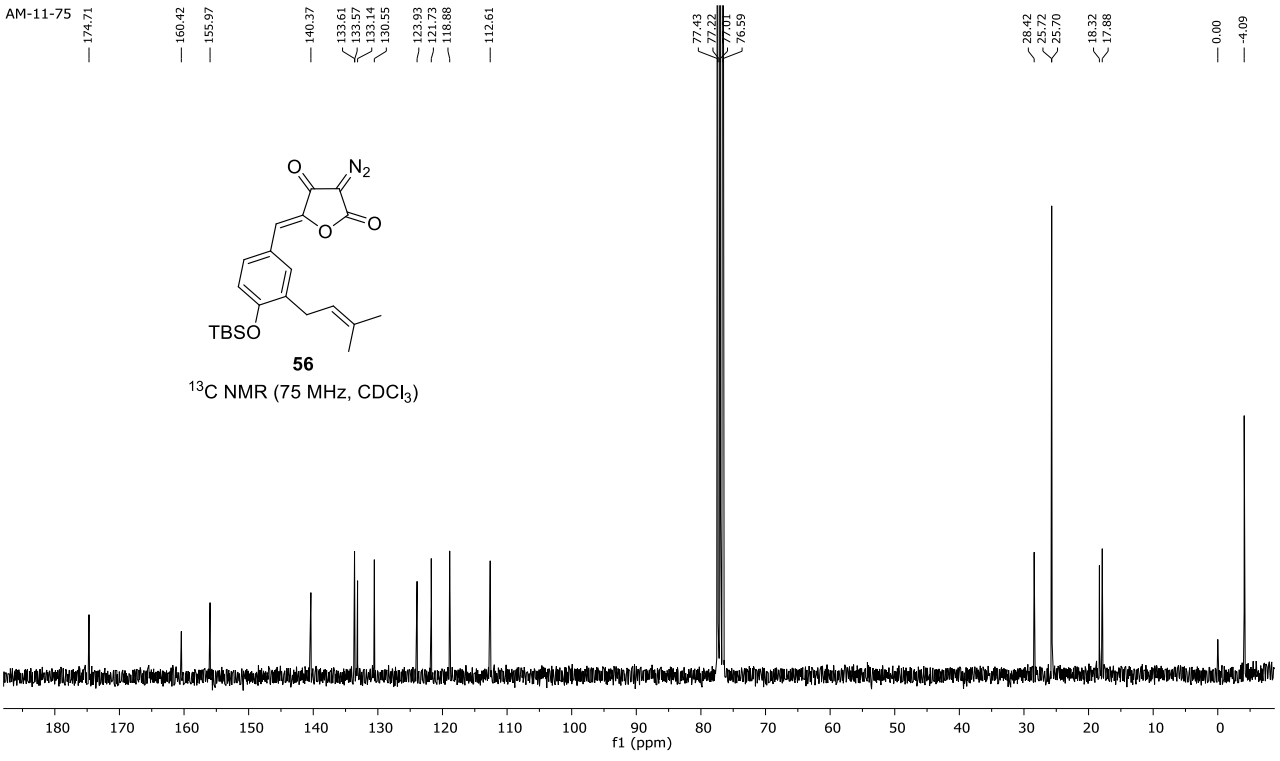
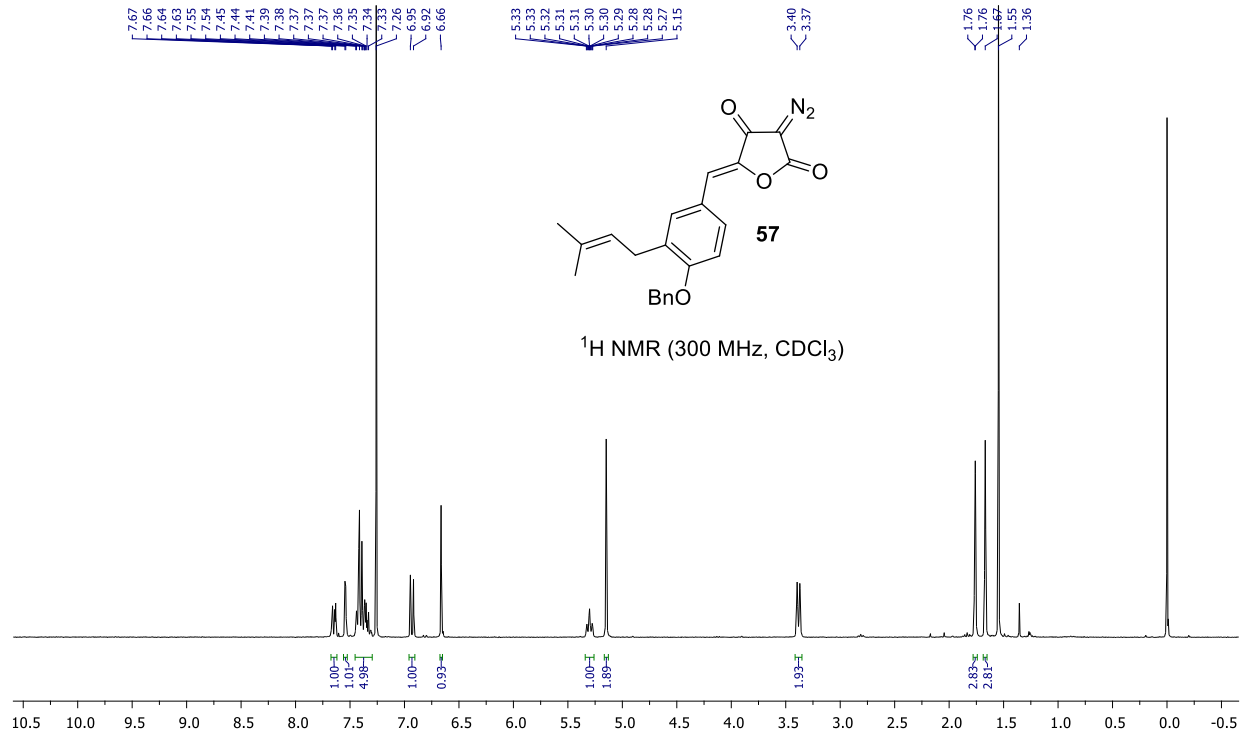
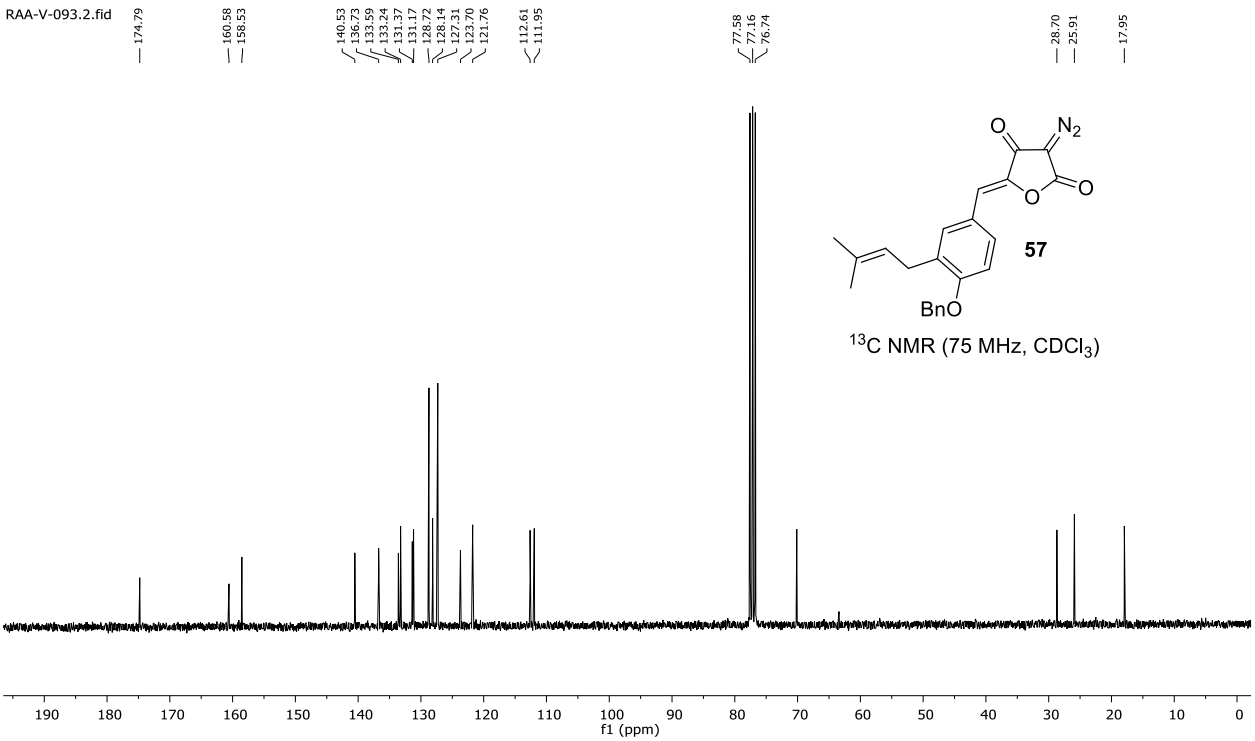
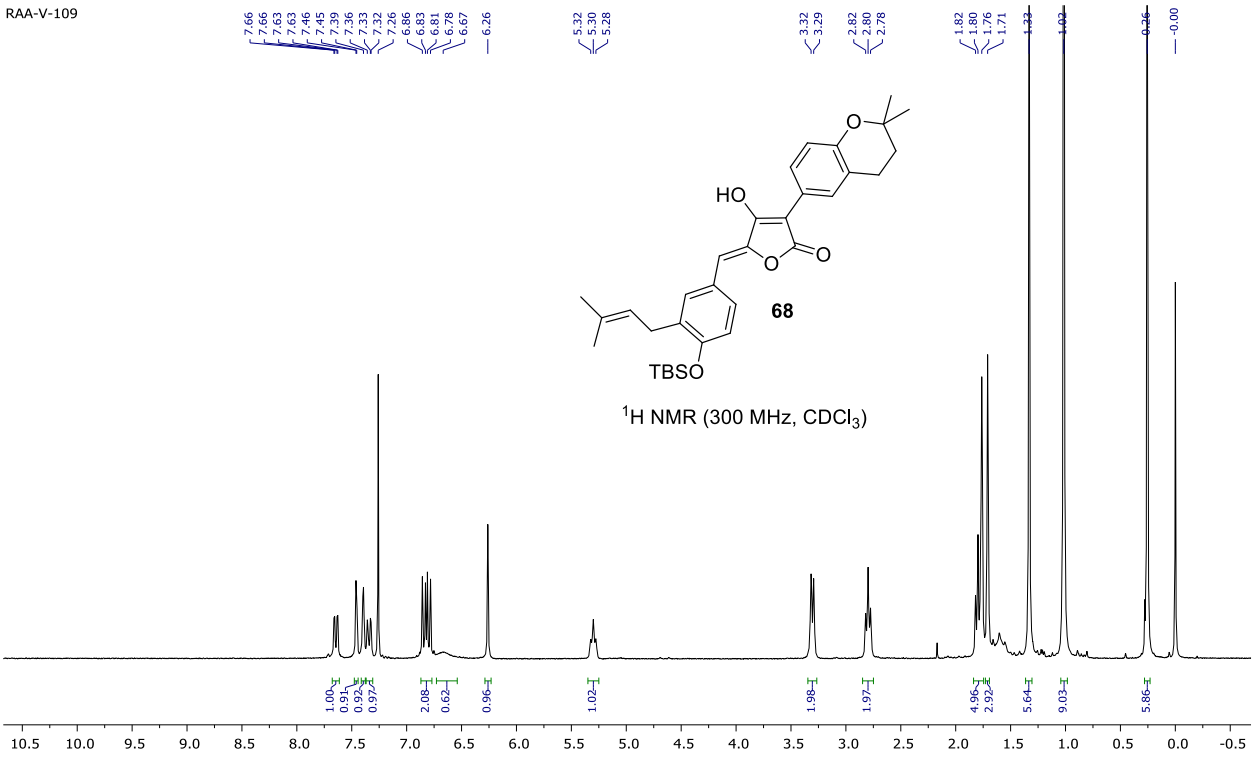


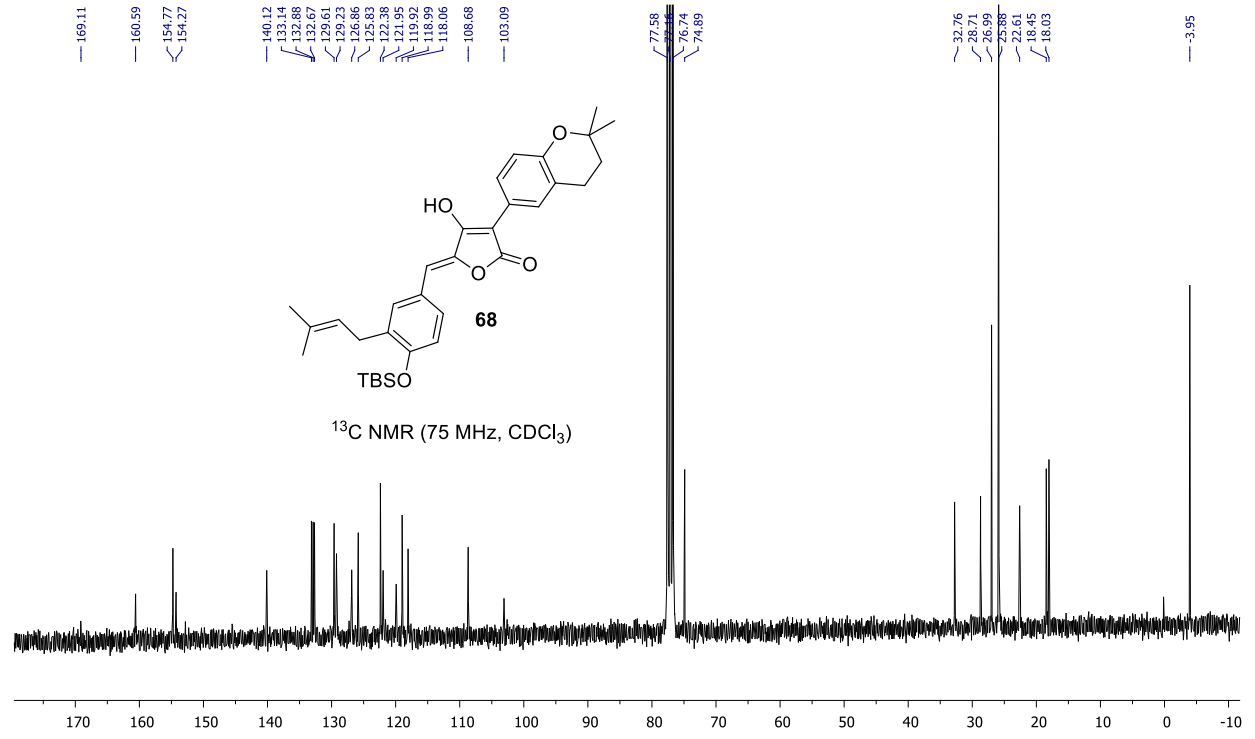
56

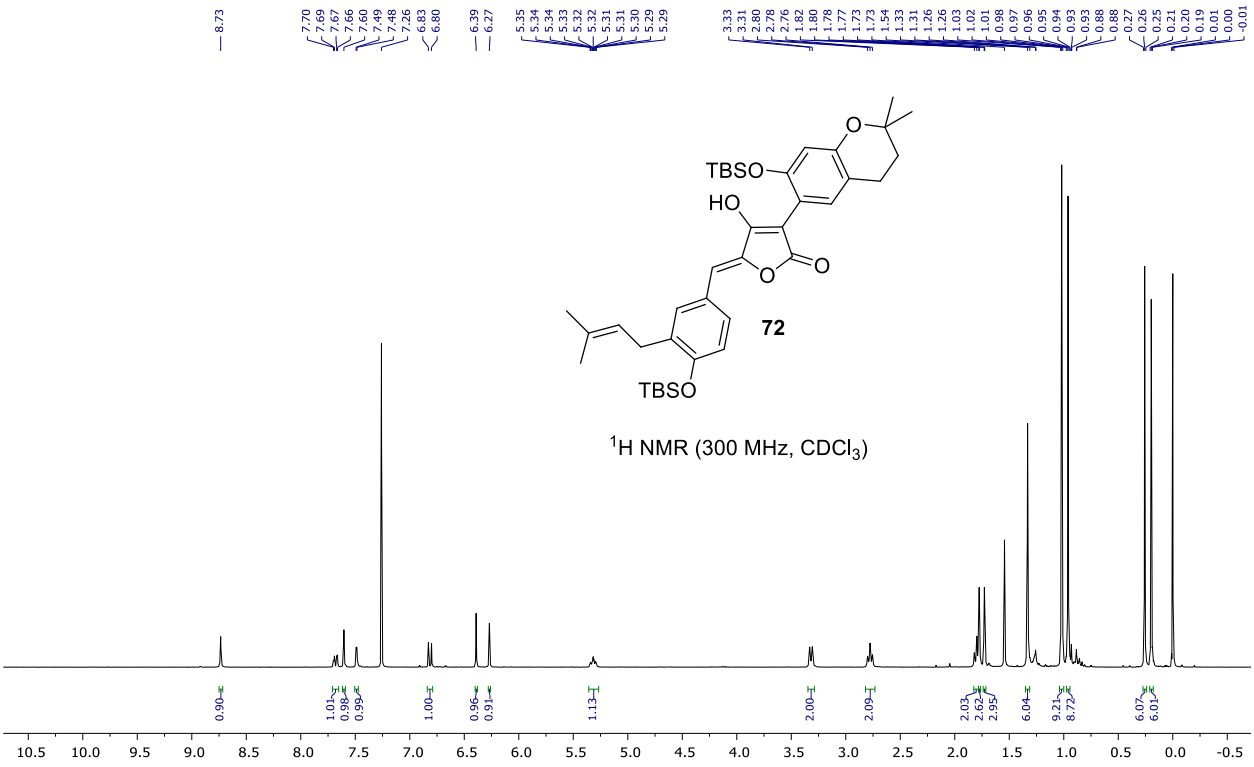
^{13}C NMR (75 MHz, $CDCl_3$)


7.67
7.66
7.64
7.63
7.55
7.54
7.45
7.44
7.41
7.39
7.38
7.37
7.37
7.37
7.36
7.35
7.34
7.33
7.26
6.95
6.92
6.66
5.33
5.33
5.32
5.31
5.31
5.30
5.30
5.29
5.28
5.28
5.27
5.15
3.40
3.37
1.76
1.76
1.67
1.55
1.36
O
N2
O
O
57
BnO
1H NMR (300 MHz, CDCl3)
1.00
1.01
4.98
1.00
0.93
1.00
1.89
1.93
2.83
2.81
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

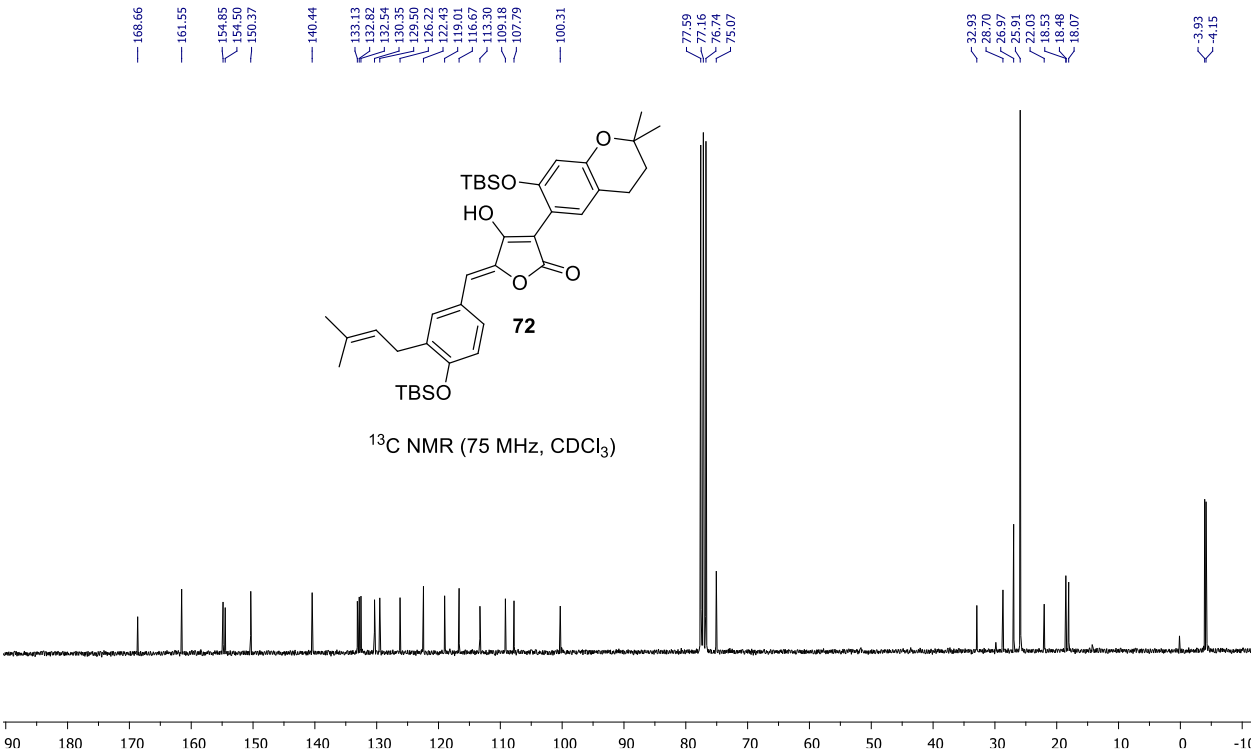

RAA-V-093.2.fid
174.79
160.58
158.53
140.53
136.73
133.59
133.24
131.37
131.17
128.72
128.14
127.31
123.70
121.76
112.61
111.95
77.58
77.16
76.74
28.70
25.91
17.95
O
N2
O
O
57
BnO
13C NMR (75 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


RAA-V-109
HO
O
O
O
68
TBSO
^{1}H NMR (300 MHz, $CDCl_3$)

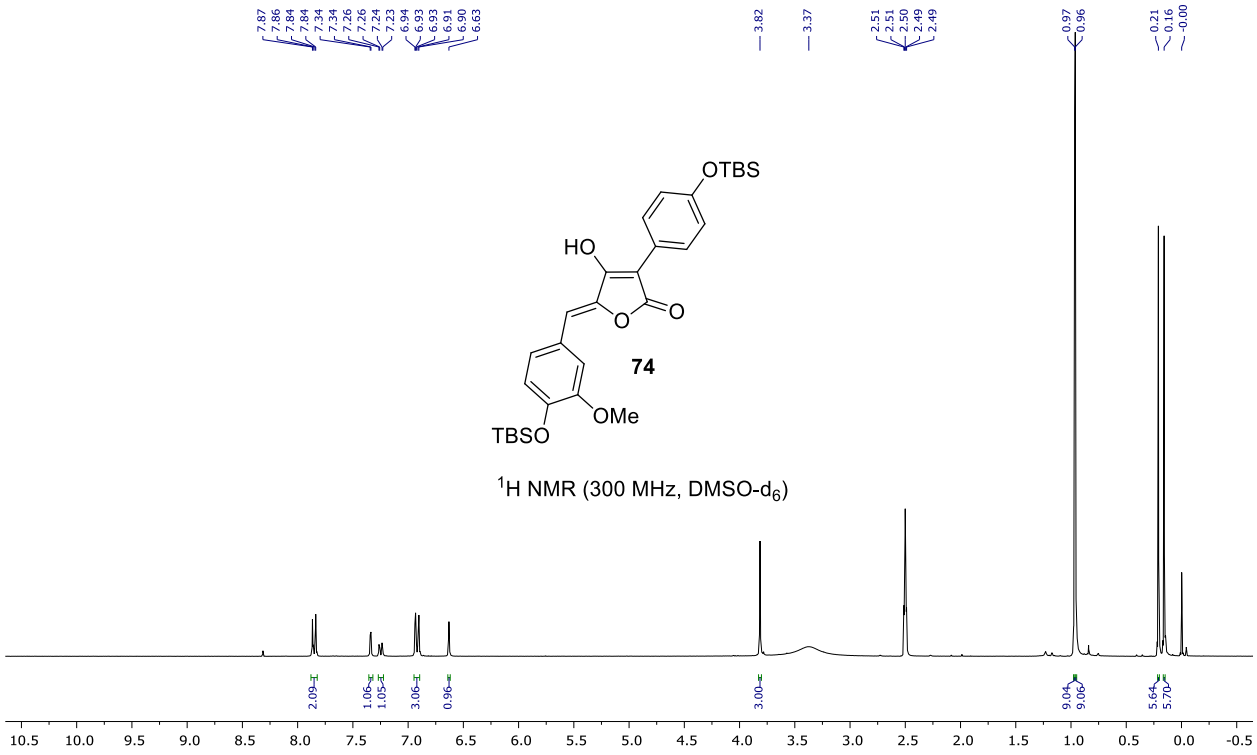

HO
O
O
O
68
TBSO
^{13}C NMR (75 MHz, $CDCl_3$)

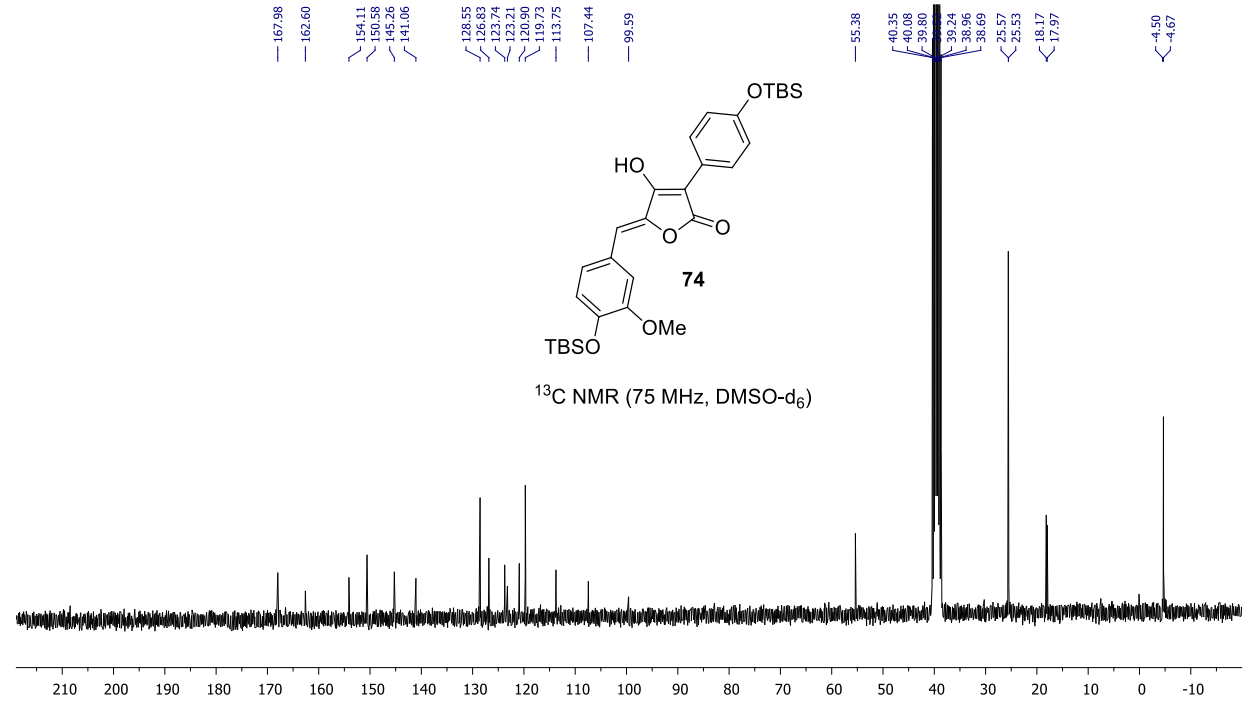


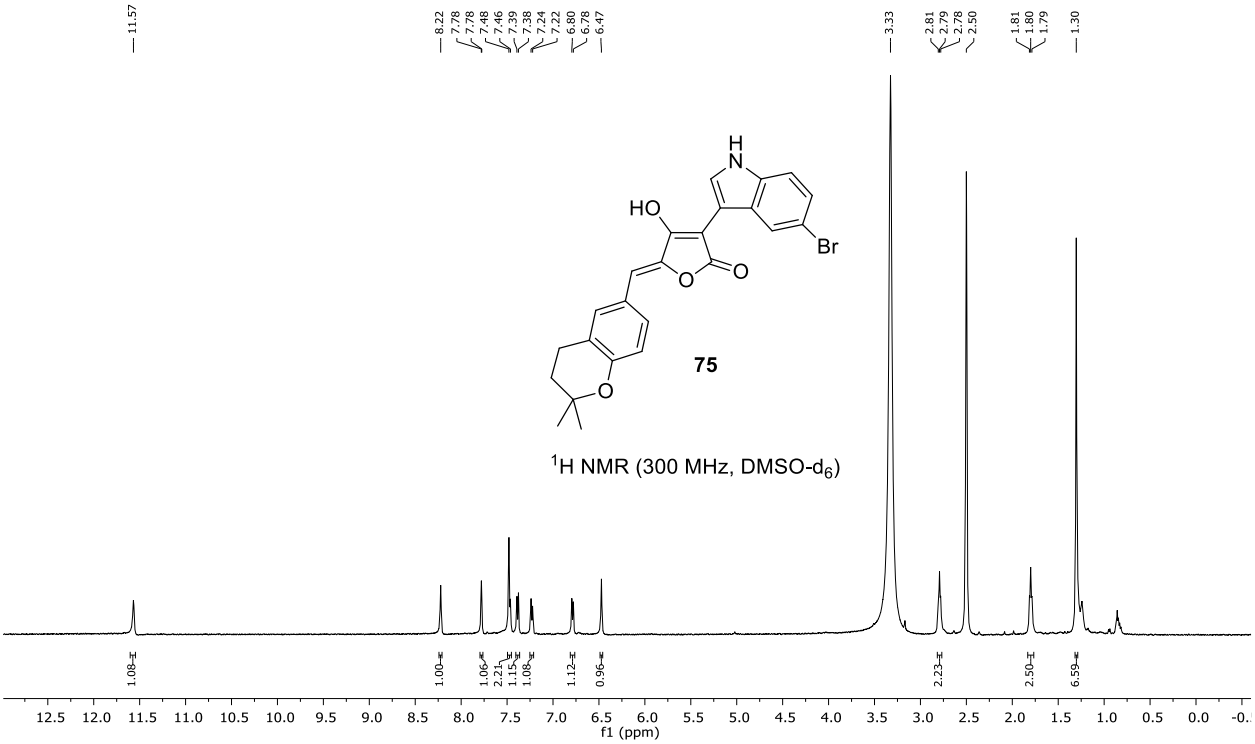
^{1}H NMR (300 MHz, $CDCl_3$)

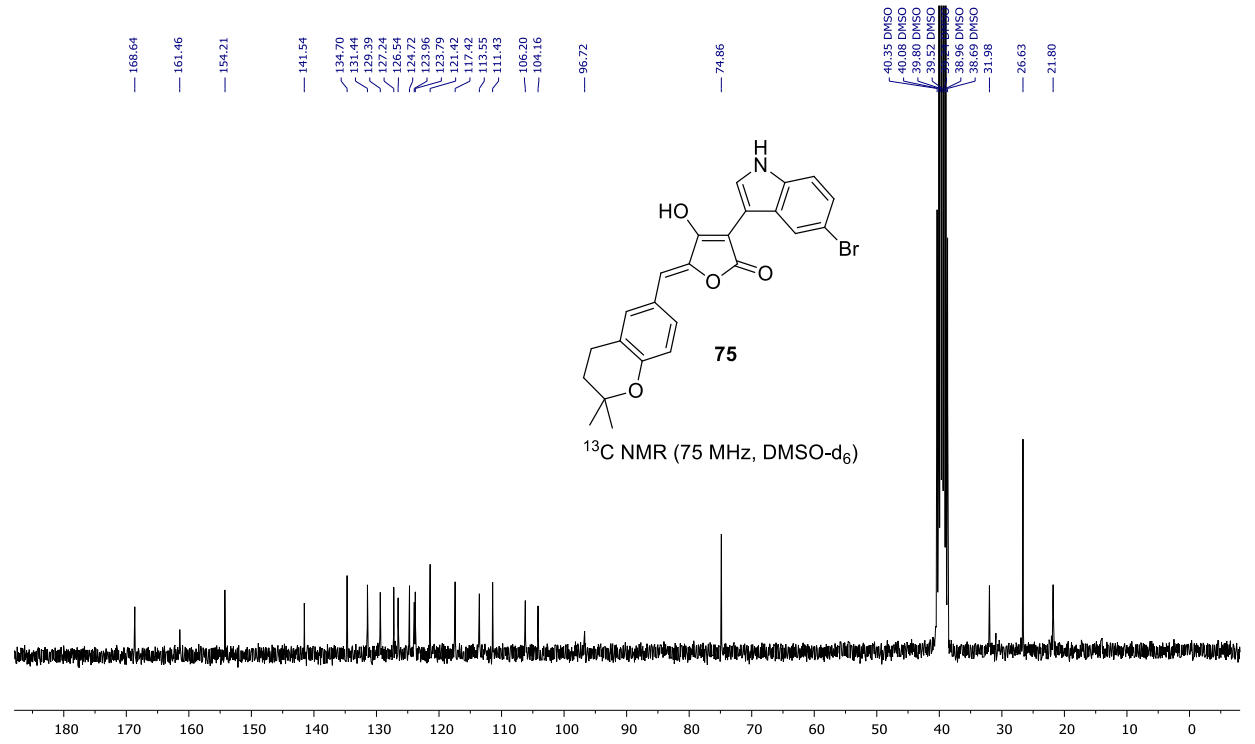


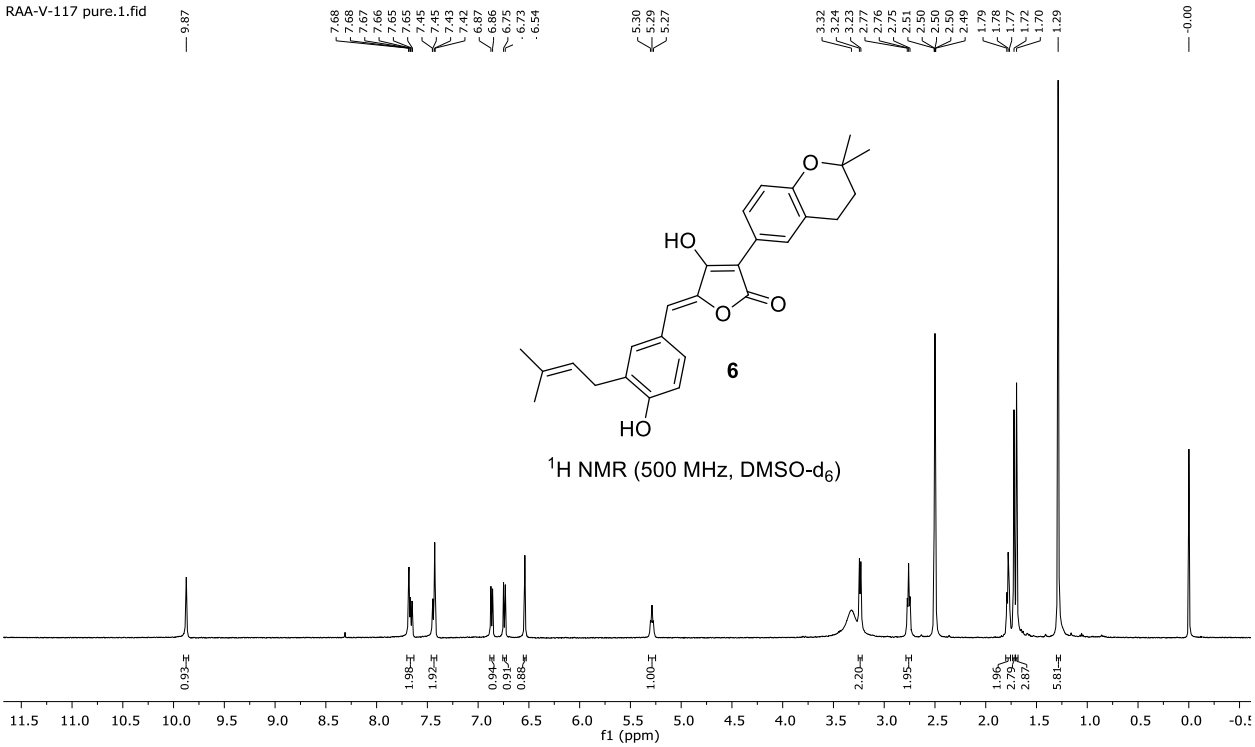
^{13}C NMR (75 MHz, $CDCl_3$)

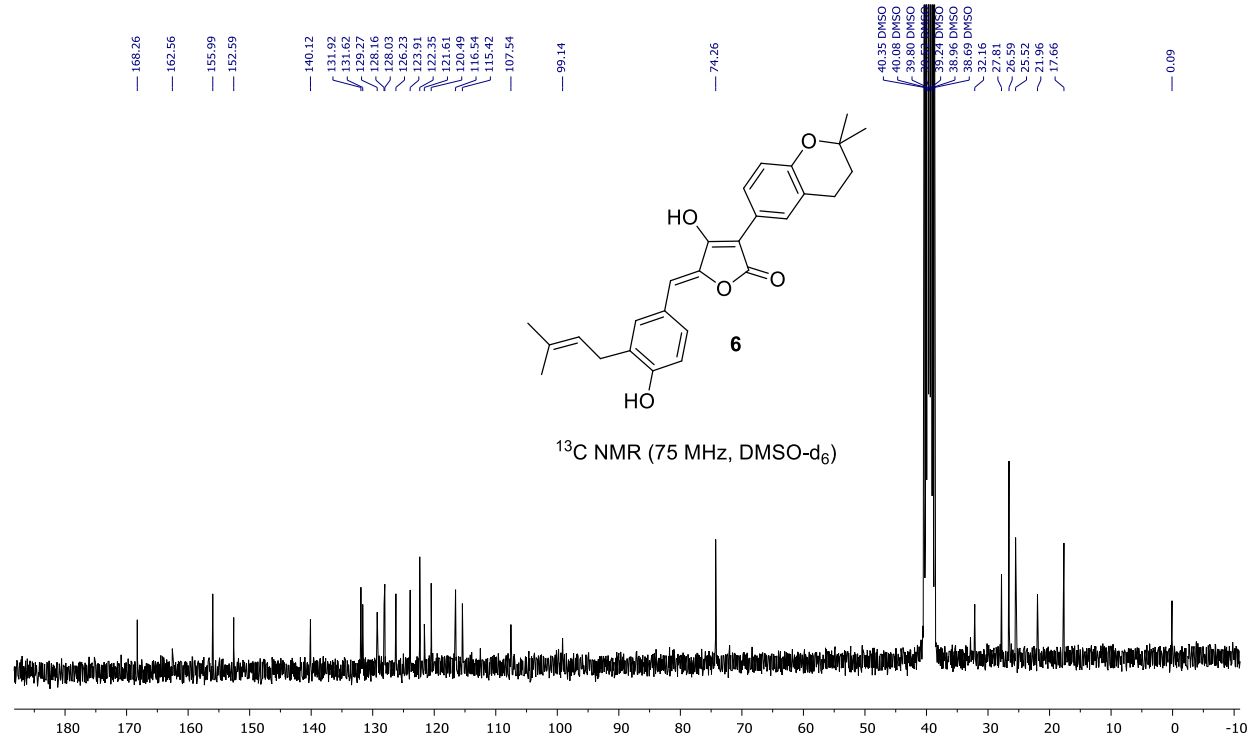

OTBS
HO
O
O
74
OMe
TBSO
1H NMR (300 MHz, DMSO-d6)


OTBS
HO
O
O
74
OMe
TBSO
13C NMR (75 MHz, DMSO-d6)

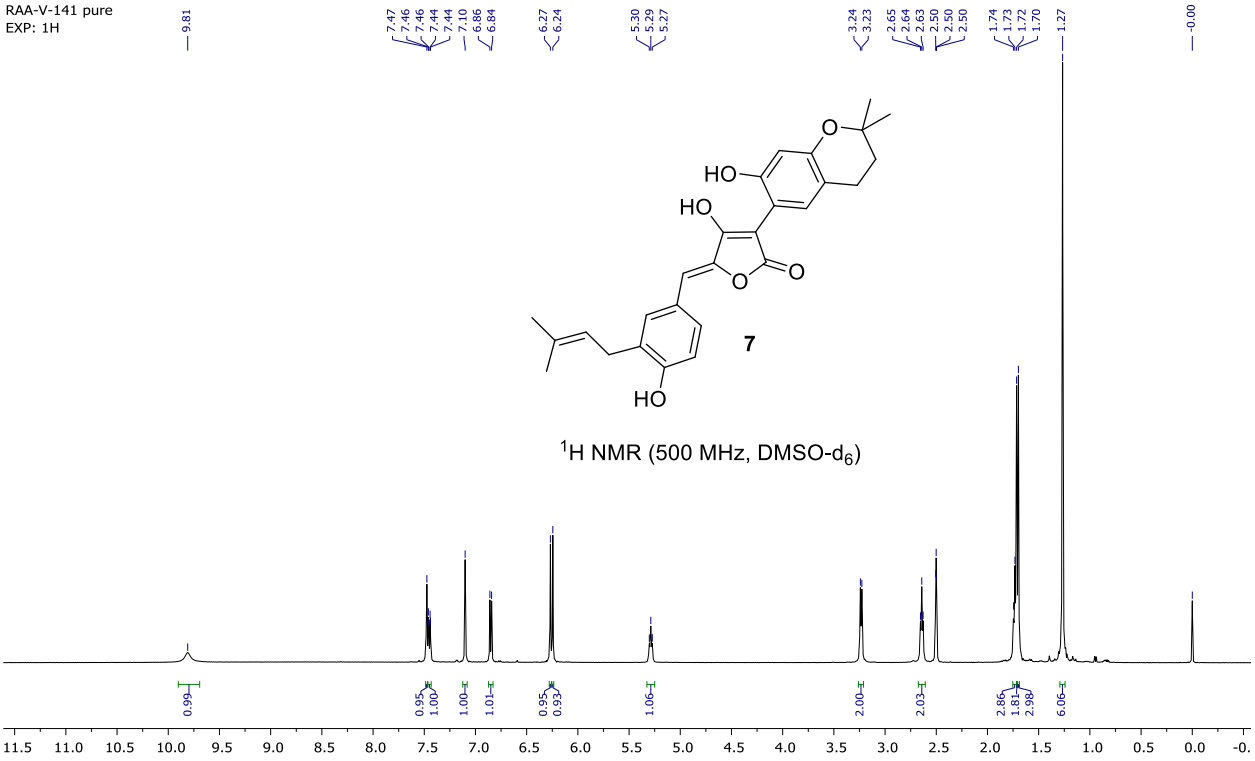

11.57
8.22
7.78
7.78
7.48
7.46
7.39
7.38
7.24
7.22
6.80
6.78
6.47
3.33
2.81
2.79
2.78
2.50
1.81
1.80
1.79
1.30
HO
Br
O
O
O
H
N
75
1H NMR (300 MHz, DMSO-d6)
1.08
1.00
1.06
2.21
1.15
1.08
1.12
0.96
2.23
2.50
6.59
f1 (ppm)


168.64
161.46
154.21
141.54
134.70
131.44
129.39
127.24
126.54
124.72
123.96
123.79
121.42
117.42
113.55
111.43
106.20
104.16
96.72
74.86
40.35 DMSO
40.08 DMSO
39.80 DMSO
39.52 DMSO
38.96 DMSO
38.69 DMSO
31.98
26.63
21.80
HO
Br
O
O
O
H
N
75
13C NMR (75 MHz, DMSO-d6)

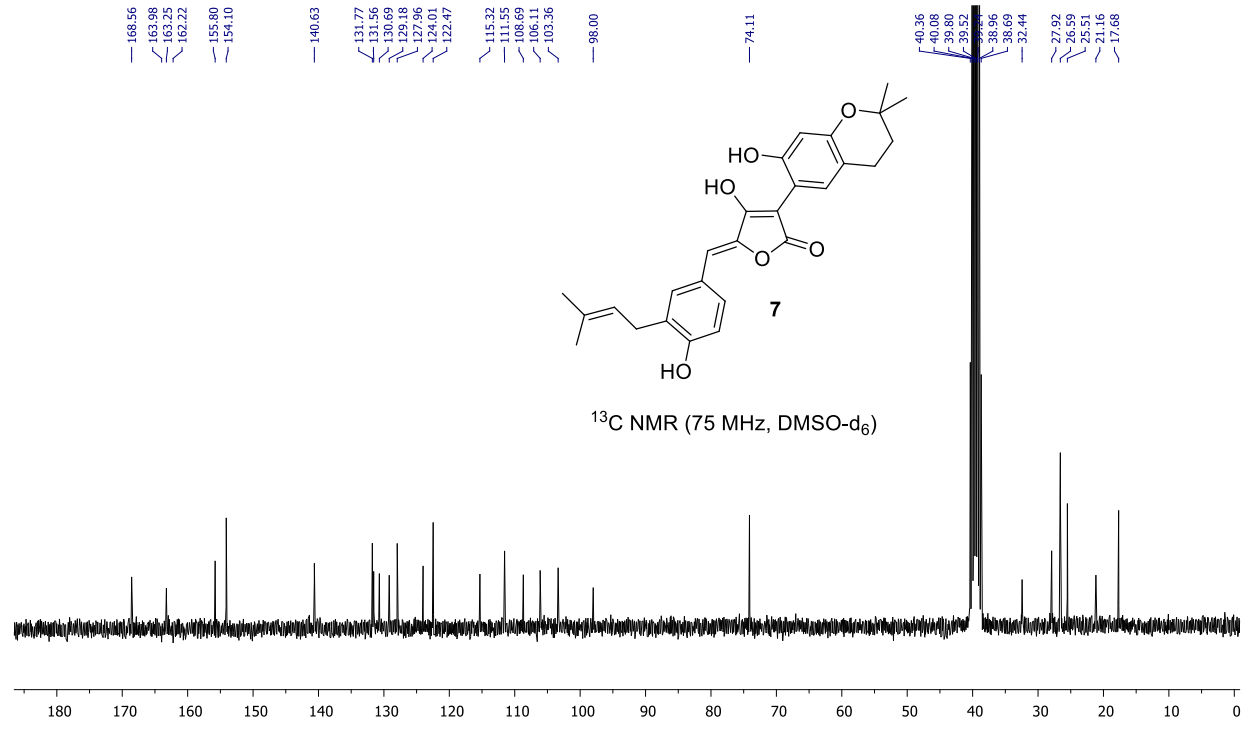

RAA-V-117 pure.1.fid
9.87
7.68
7.68
7.67
7.66
7.65
7.65
7.45
7.45
7.43
7.42
6.87
6.86
6.75
6.73
6.54
5.30
5.29
5.27
3.32
3.24
3.23
2.77
2.76
2.75
2.51
2.50
2.50
2.50
2.49
1.79
1.78
1.77
1.72
1.70
1.29
-0.00
HO
O
O
O
HO
6
1H NMR (500 MHz, DMSO-d6)
0.93
1.98
1.92
0.94
0.91
0.88
1.00
2.20
1.95
1.96
2.79
2.87
5.81
f1 (ppm)


168.26
162.56
155.99
152.59
140.12
131.92
131.62
129.27
128.16
128.03
126.23
123.91
122.35
121.61
120.49
116.54
115.42
107.54
99.14
74.26
40.35 DMSO
40.08 DMSO
39.80 DMSO
39.24 DMSO
38.96 DMSO
38.69 DMSO
32.16
27.81
26.59
25.52
21.96
17.66
0.09
HO
O
O
O
HO
6
13C NMR (75 MHz, DMSO-d6)

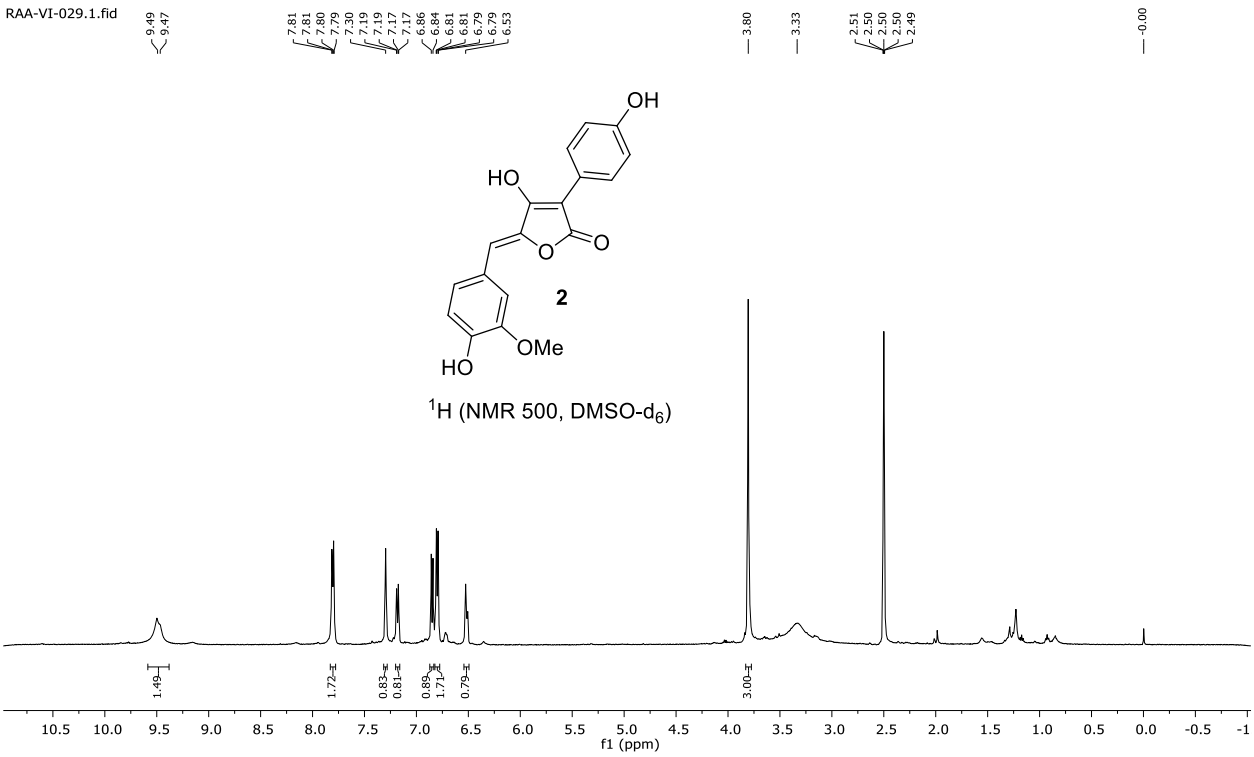
RAA-V-141 pure
EXP: 1H

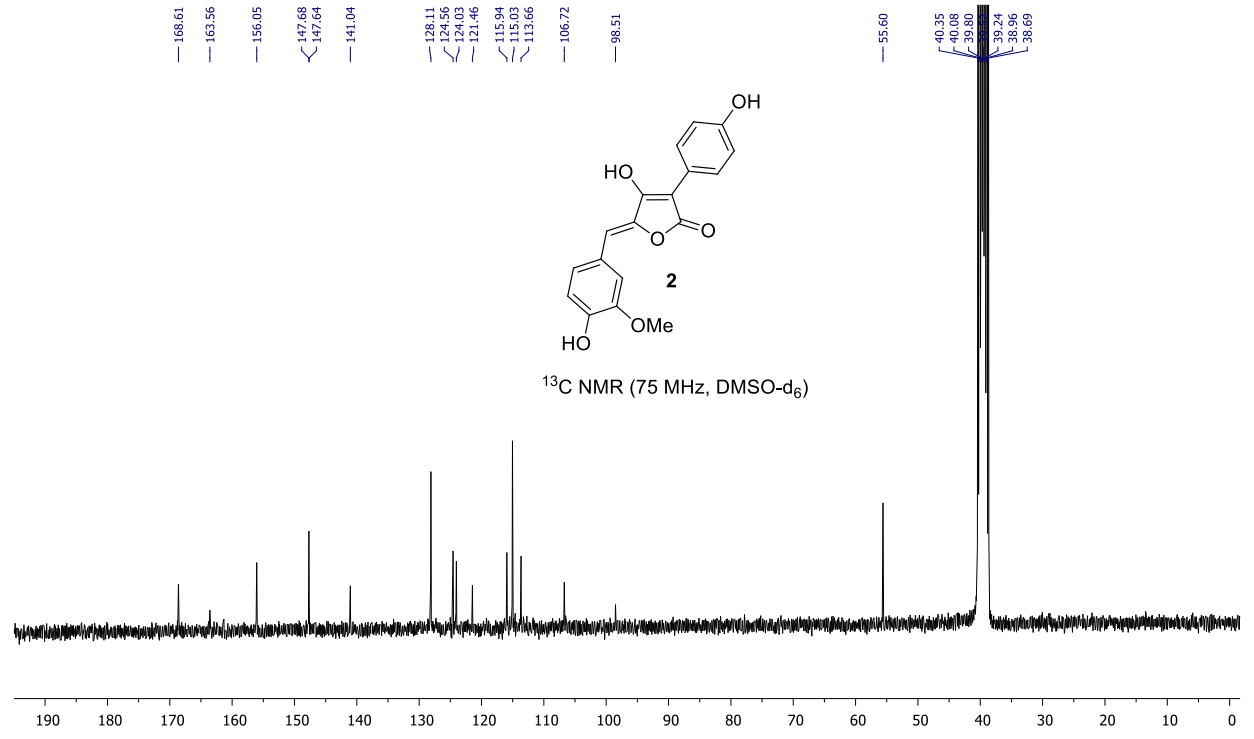


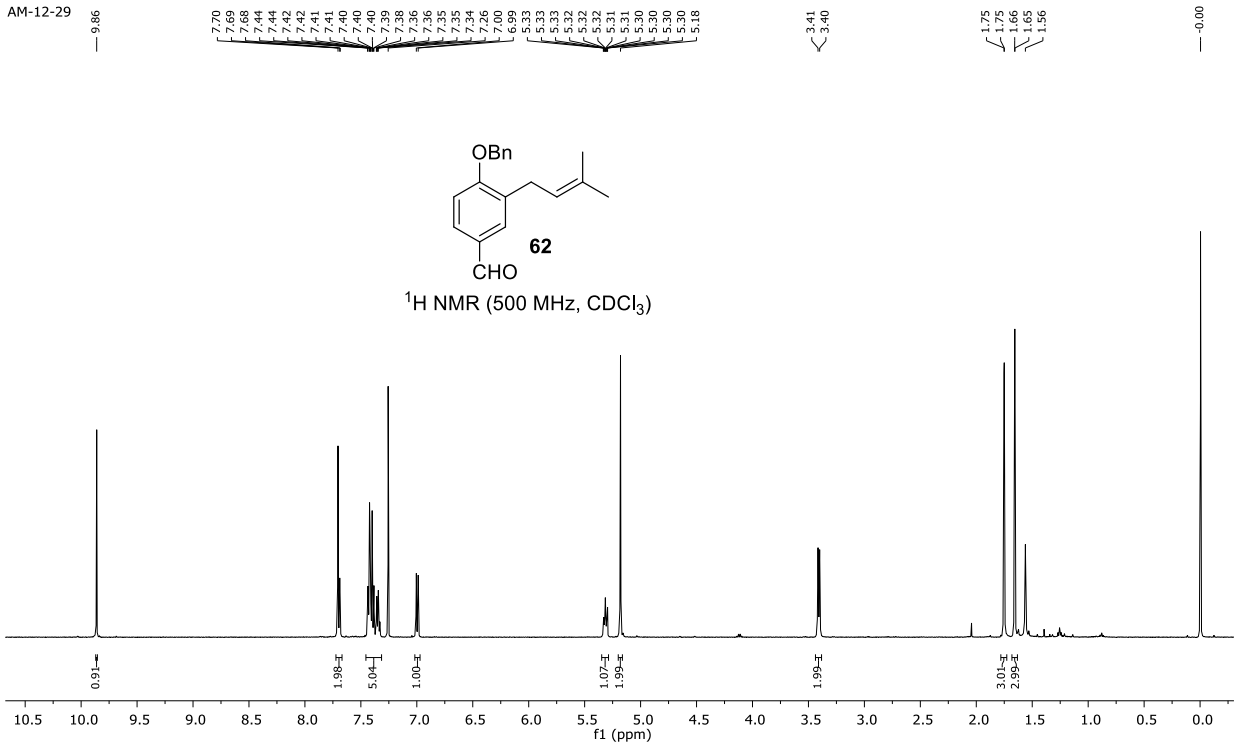
^{1}H NMR (500 MHz, DMSO-d_6)

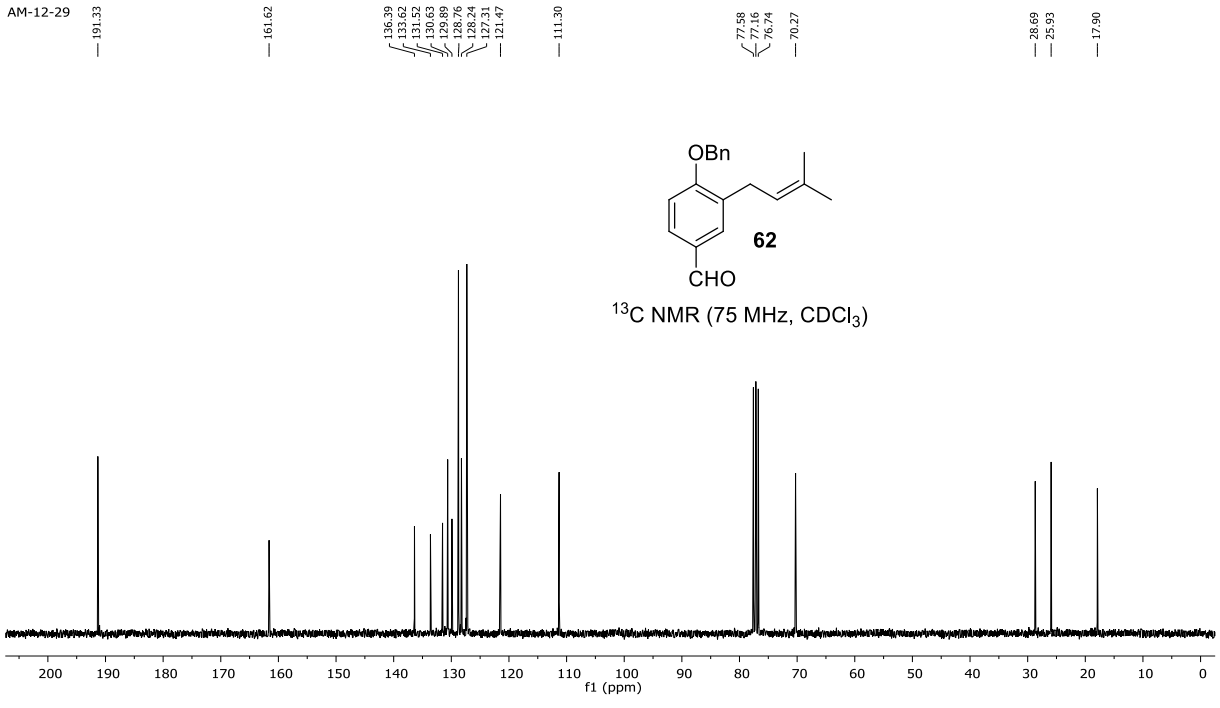


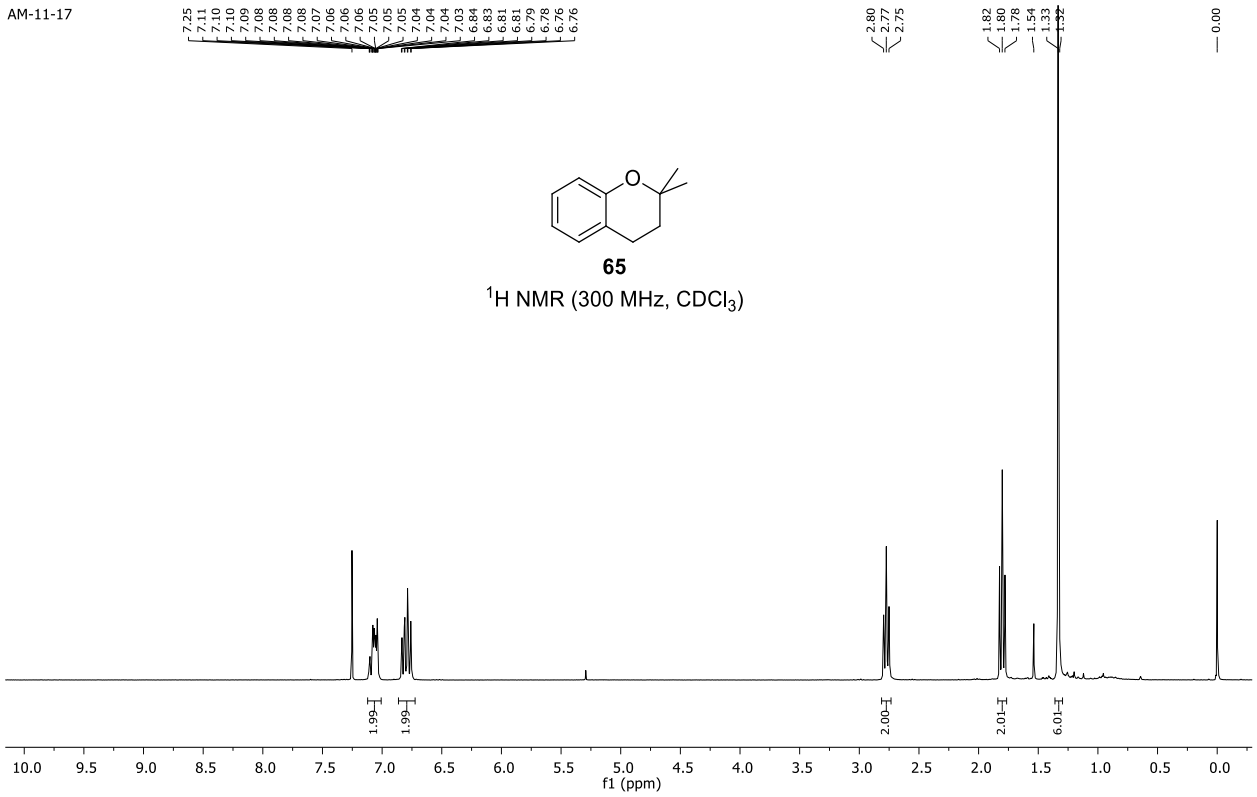
^{13}C NMR (75 MHz, DMSO-d_6)

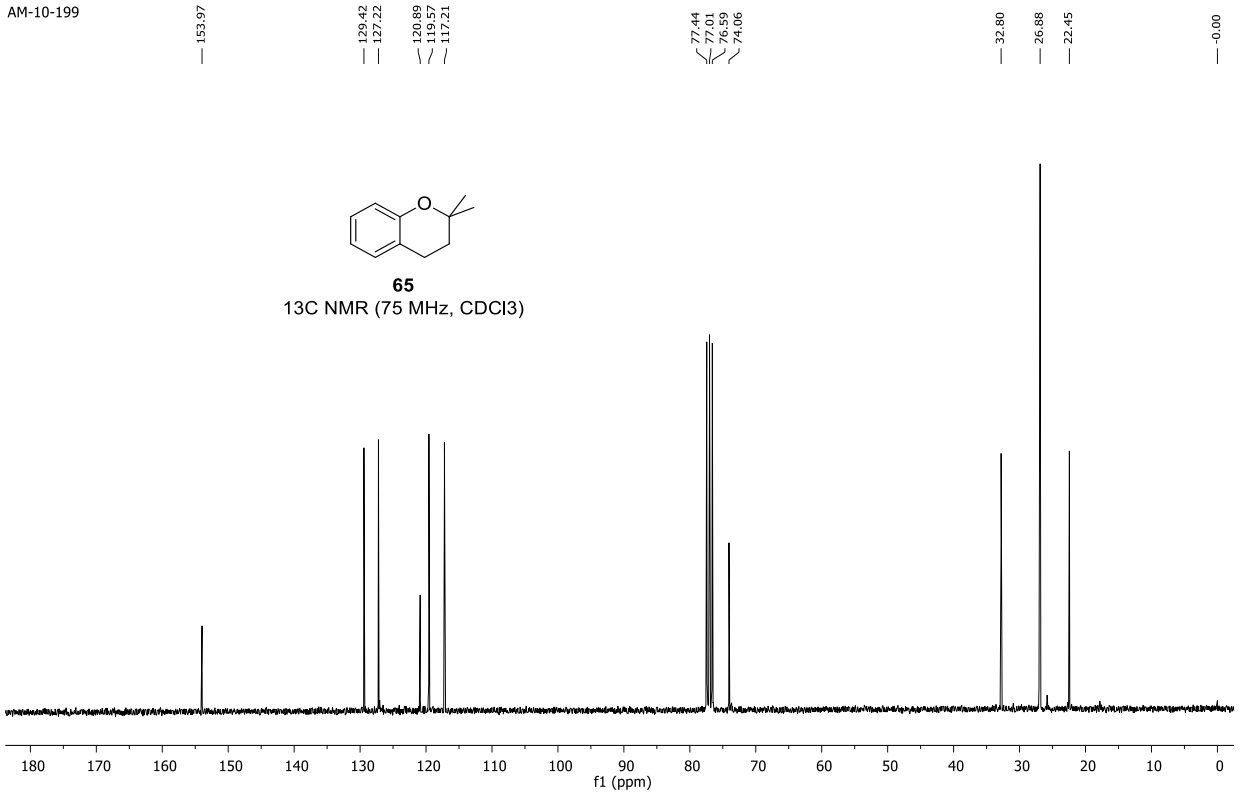

RAA-VI-029.1.fid
9.49
9.47
7.81
7.81
7.80
7.79
7.30
7.19
7.19
7.17
7.17
6.86
6.84
6.81
6.81
6.79
6.79
6.53
3.80
3.33
2.51
2.50
2.50
2.50
2.49
-0.00
OH
HO
O
O
2
OMe
HO
1H (NMR 500, DMSO-d6)
1.49
1.72
0.83
0.81
0.89
1.71
0.79
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

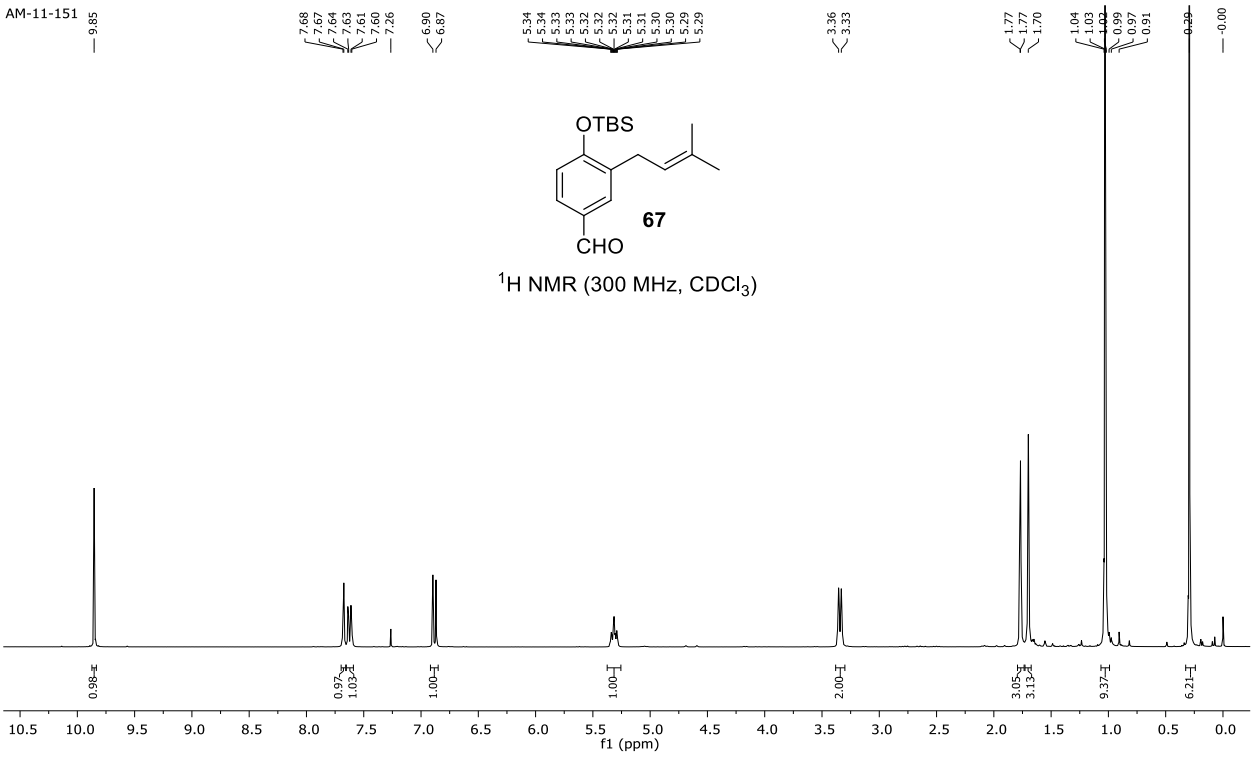

168.61
163.56
156.05
147.68
147.64
141.04
128.11
124.56
124.03
121.46
115.94
115.03
113.66
106.72
98.51
55.60
40.35
40.08
39.80
39.24
38.96
38.69
OH
HO
O
O
2
OMe
HO
13C NMR (75 MHz, DMSO-d6)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

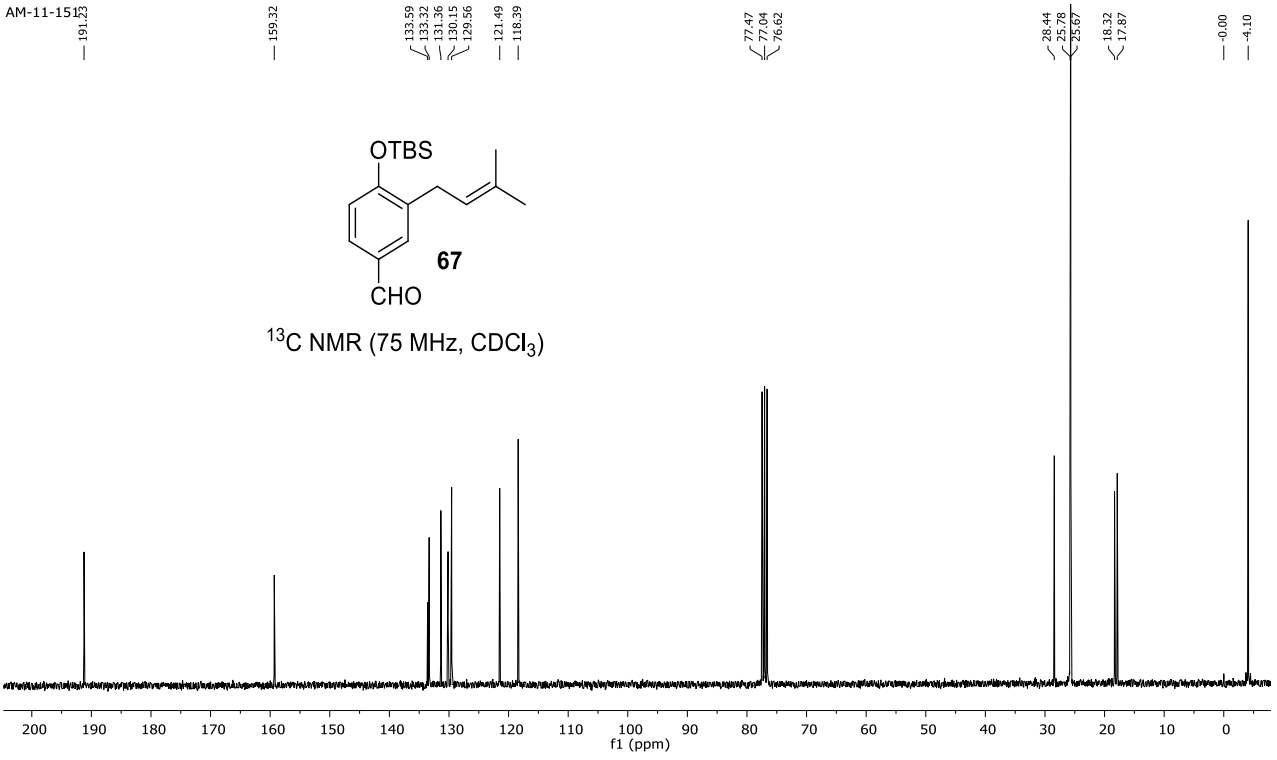

AM-12-29
9.86
7.70
7.69
7.68
7.44
7.42
7.42
7.41
7.41
7.40
7.40
7.40
7.39
7.38
7.36
7.36
7.35
7.35
7.34
7.26
7.00
6.99
5.33
5.33
5.32
5.32
5.32
5.31
5.31
5.30
5.30
5.30
5.30
5.18
3.41
3.40
1.75
1.75
1.66
1.65
1.56
0.00
OBn
62
CHO
1H NMR (500 MHz, CDCl3)
0.91
1.98
5.04
1.00
1.07
1.99
1.99
3.01
2.99
f1 (ppm)

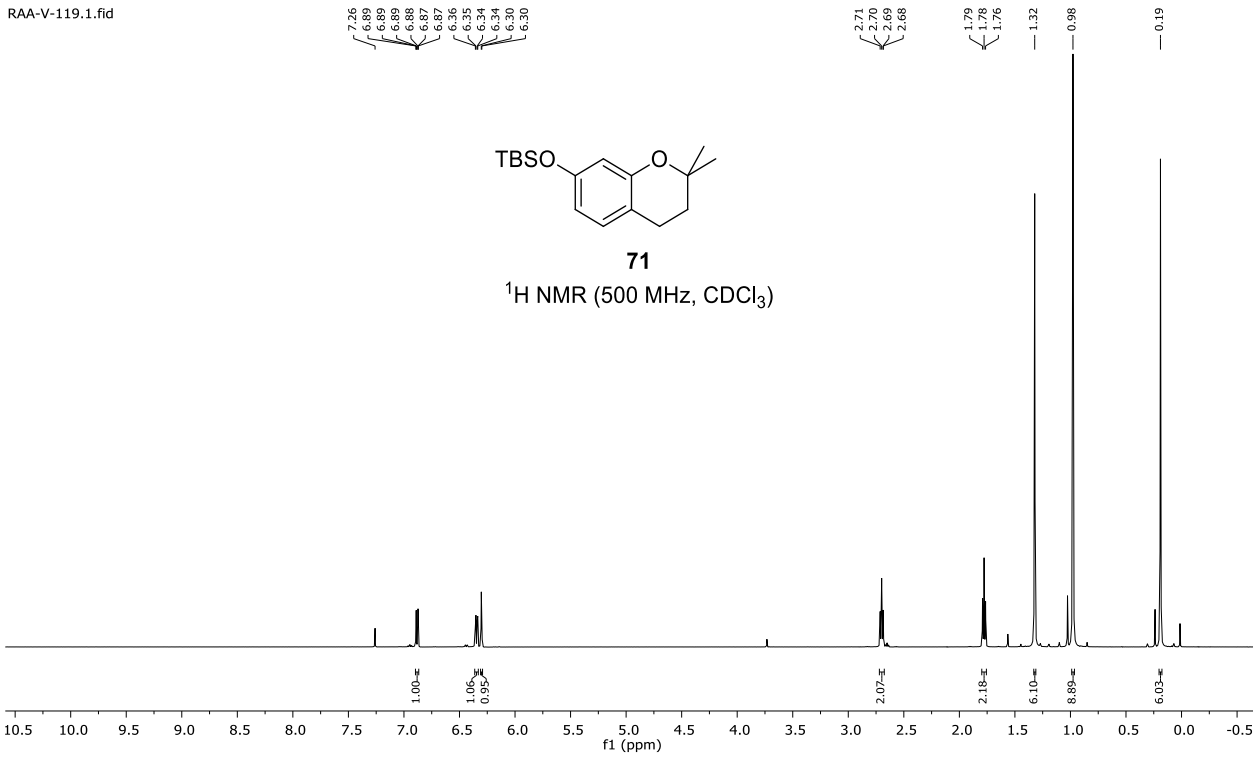

AM-12-29
191.33
161.62
136.39
133.62
131.52
130.63
129.89
128.76
128.24
127.31
121.47
111.30
77.58
77.16
76.74
70.27
28.69
25.93
17.90
OBn
62
CHO
13C NMR (75 MHz, CDCl3)
f1 (ppm)


AM-11-17
7.25
7.11
7.10
7.10
7.09
7.08
7.08
7.08
7.08
7.07
7.06
7.06
7.06
7.05
7.05
7.05
7.04
7.04
7.04
7.03
6.84
6.83
6.81
6.81
6.79
6.78
6.76
6.76
2.80
2.77
2.75
1.82
1.80
1.78
1.54
1.33
1.32
0.00
O
65
1H NMR (300 MHz, CDCl3)
1.99
1.99
2.00
2.01
6.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


AM-10-199
153.97
129.42
127.22
120.89
119.57
117.21
77.44
77.01
76.59
74.06
32.80
26.88
22.45
-0.00
O
65
13C NMR (75 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

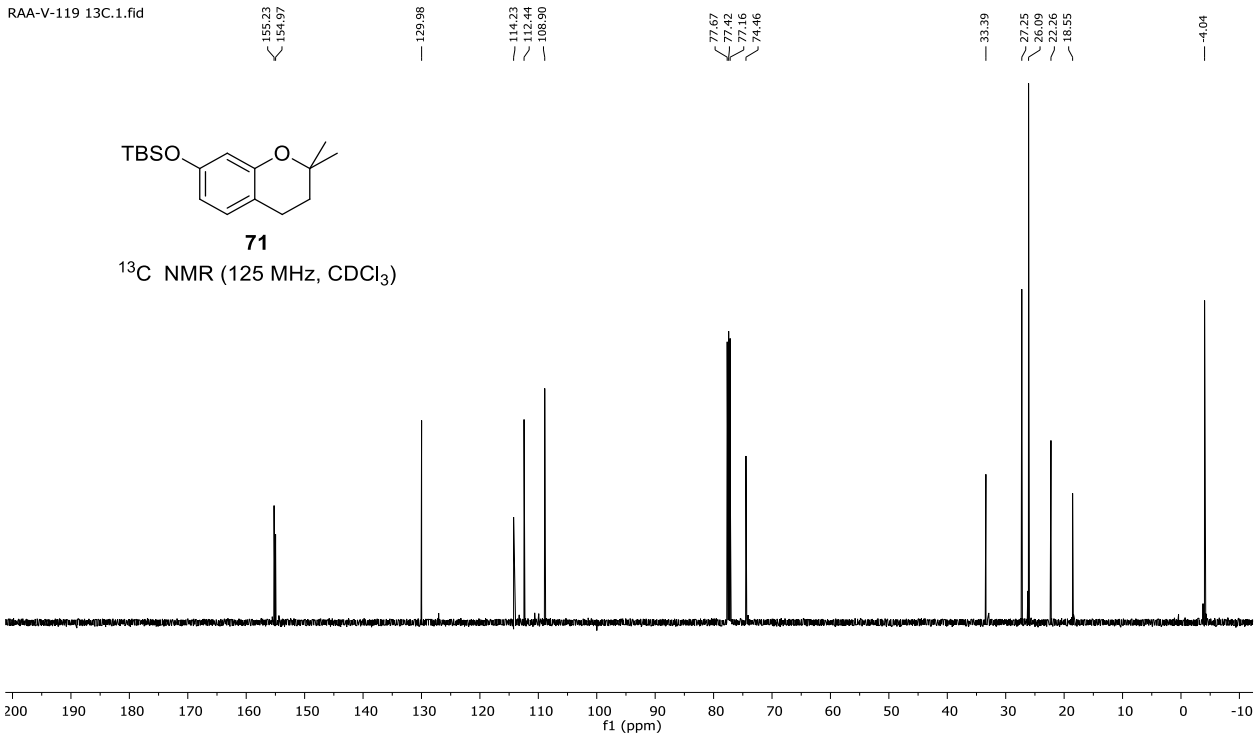

AM-11-151
OTBS
67
CHO
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)


AM-11-151
OTBS
67
CHO
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)



71

^{1}H NMR (500 MHz, $CDCl_3$)



71

^{13}C NMR (125 MHz, $CDCl_3$)

Chapter 4

Organocatalytic Direct Vinylogous Aldol Reaction of Isatins with α-Angelicalactone

4.1 Introduction

The aldol reaction (Fig. 4.1) is one of the most powerful C-C bond forming reactions in synthetic organic chemistry. An extension of the aldol reaction, the vinylogous aldol reaction, has also been intensively investigated.[1] Within the domain of vinylogous aldol reactions, the vinylogous Mukaiyama aldol (VMA) reaction employing silyloxy dienes has also been extensively investigated.[2] In terms of atomic economy, the organocatalytic direct vinylogous aldol (ODVA) reaction, which uses unmodified aldehydes and ketones as nucleophiles, is the most attractive version. However, this strategy may be limited by the problems of regioselectivity associated with the dienolate nucleophiles.

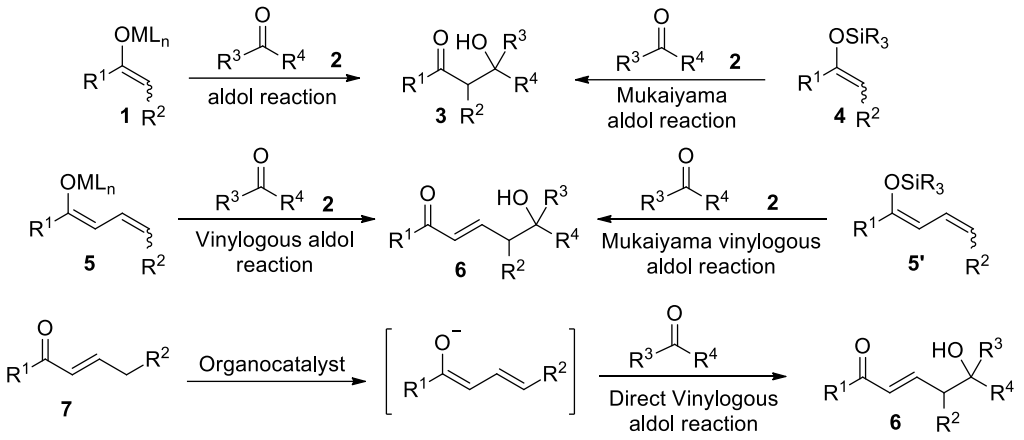


Figure 4.1 Various types of aldol reactions

In recent years, the synthesis of 3-alkyl-3-hydroxy-2-oxindoles has received considerable attention because of their biological importance and the occurrence of these motifs in several bioactive indole derivatives[3,4] (Figure 4.2).

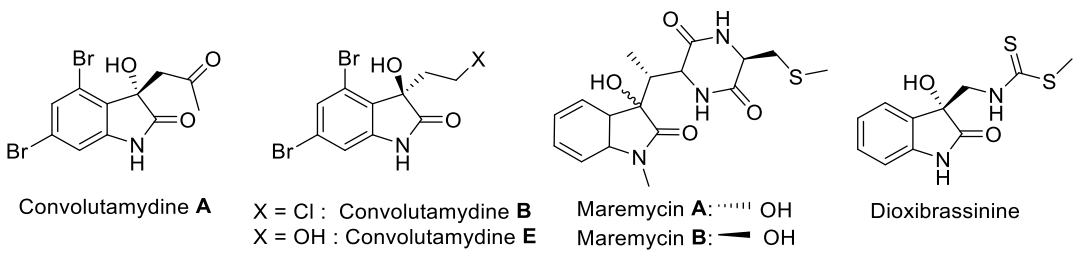


Figure 4.2 Biologically active 3-alkyl-3-hydroxy-2-oxindoles

In addition, 3-alkyl-3-hydroxy-2-oxindoles are potential precursors of spirocyclic indole derivatives (Figure 4.3) which are known pharmacophores with useful biological activities.[5,6]

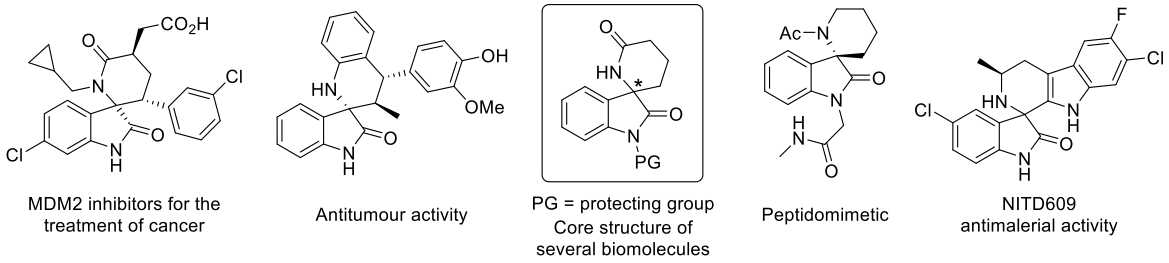


Figure 4.3 Some examples of bioactive spirocyclic alkaloids

The spirocyclic indole motif is found in numerous naturally occurring alkaloids and pharmaceutically active compounds and has been demonstrated to have a wide range of biological activities such as antitumor,[7] antibacterial,[8] analgesic[9] or antitubercular[10] activities (Figure 4.3).

Given their utility as precursors of indole-based alkaloid motifs, the synthesis of functionalized 3-hydroxy-2-oxindoles has attracted significant attention. In this context, the stereoselective addition of carbon nucleophiles, particularly γ-butyrolactone-derived enolates, to isatins has been thoroughly examined and, in recent years, the use of metal catalysts and organocatalysts (metal-free organic catalysts) for the VMA reaction of isatin derivatives has also been demonstrated (Figure 4.4).[11] Notably, the generation of two adjacent stereogenic centers in this reaction poses a stereochemical challenge.[12]

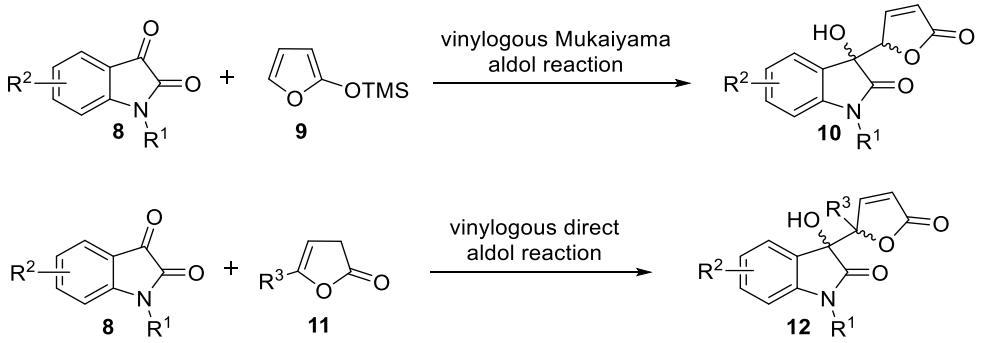


Figure 4.4 Vinylogous Mukaiyama aldol and vinylogous direct aldol reaction of isatins with γ-butyrolactone nucleophiles

4.2 Objectives:

Our objective was the development of an organocatalytic direct vinylogous aldol reaction of α-angelicalactone **13** to isatins for the construction of 3-substituted 3-hydroxyindoles **14** (Figure 4.5). The previously synthesized phosphoramide-aminothiourea catalysts (Chapter 1) as well as some new analogues of these catalysts were examined in these studies.

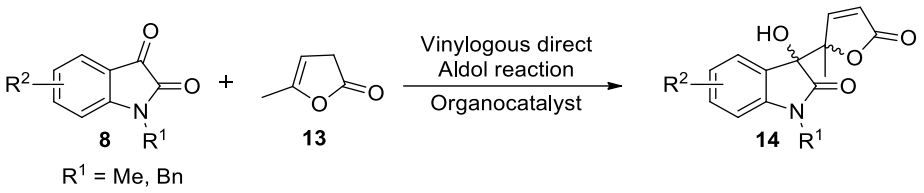


Figure 4.5 Vinylogous direct aldol reaction of isatin with α-angelicalactone

We also envisioned the synthesis of spirocyclic indoles such as **16** (Figure 4.6) from the aldol products **14** via the intermediacy of the amino compounds **15**. We anticipated that intramolecular ring opening of the lactone by the amine in **15** would provide **16**. This approach could potentially lead to a method for the synthesis of bioactive indoles such as those shown in Figure 4.3. It may be noted that the conversion of 3-alkyl-3-hydroxy-2-oxindoles such as **14** to the corresponding 3-alkyl-3-amino-2-oxindoles **15** is well known,[13] but a diastereoselective version of this reaction is not reported.

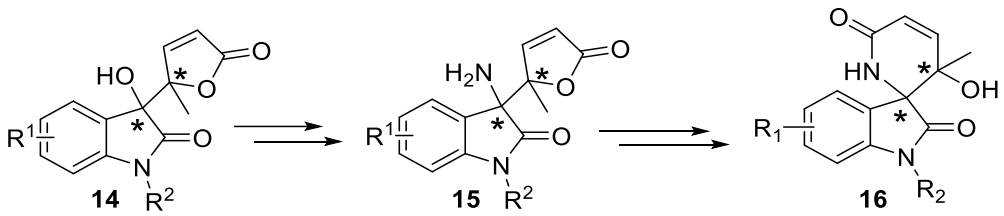


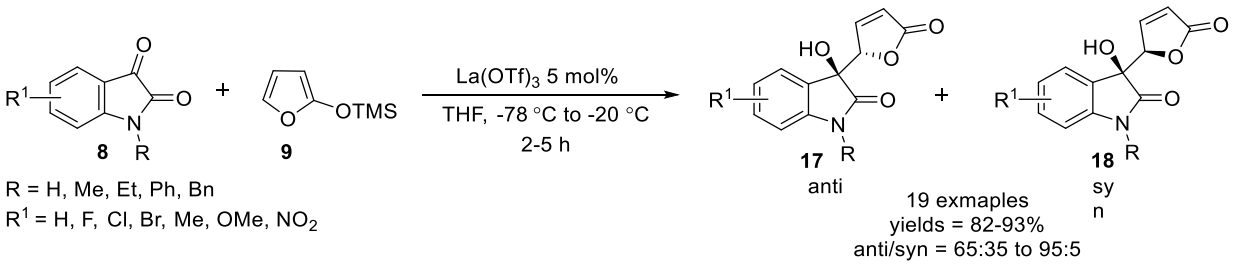
Figure 4.6 Conversion of aldol adducts into spirocyclic core compounds

Since the objective of the present study was to develop a vinylogous aldol reaction of α-angelicalactone and isatins, the following section provides a brief summary of the reported vinylogous aldol reactions of isatins.

4.3 Previous reports on the aldol reactions of isatins and butenolide derivatives

4.3.1 Diastereoselective vinylogous Mukaiyama aldol reaction by Meshram:

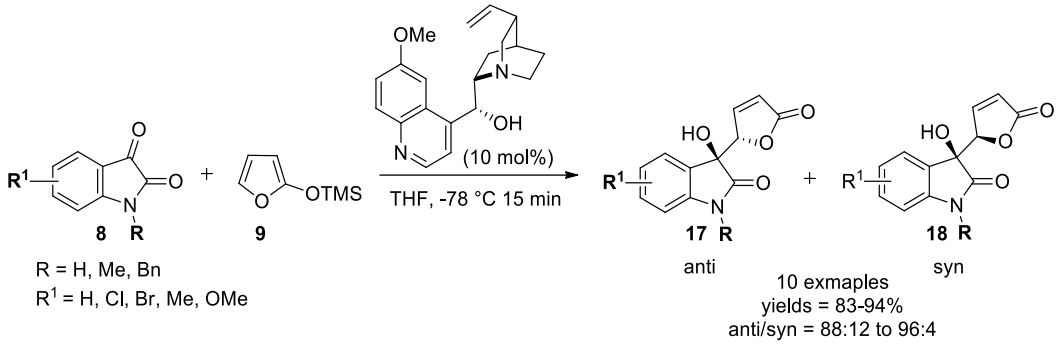
In 2011, Meshram and co-workers[11a] developed an efficient method to synthesize 3-substituted 3-hydroxyindole which involves the Mukaiyama aldol reaction of 2-(trimethylsilyloxy) furan **9** with various *N*-alkyl isatins **8** catalysed by Lewis acid. These reactions proceeded rapidly and provided an inseparable mixture of diastereomeric VMA products **17** and **18** in high yields (82-93%) and with good diastereoselectivity (anti/syn up to 95:5).



Scheme 4.01

4.3.2 Diastereoselective vinylogous Mukaiyama aldol reaction by Kong:

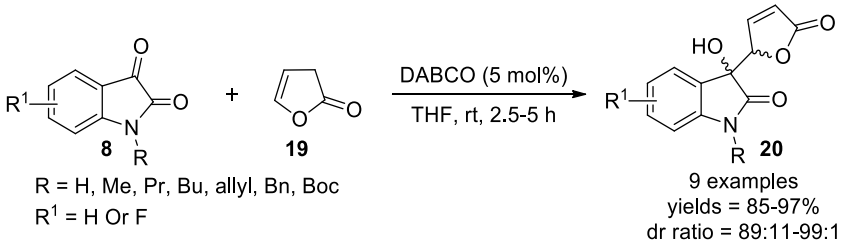
In 2014, Kong and co-workers[11b] achieved the diastereoselective formation of δ-hydroxyalkyl butenolide oxindoles **17** and **18** via a vinylogous Mukaiyama aldol reaction of various *N*-alkyl isatins **8** with 2-(trimethylsilyloxy) furan **9** by using quinine as the catalyst. The reaction worked well and afforded an inseparable mixture of VMA products in good yields (83-94%) with high diastereoselectivities (anti/syn ratio up to 96:4).



Scheme 4.02

4.3.3 A direct vinylogous Aldol reaction by Meshram and co-workers:

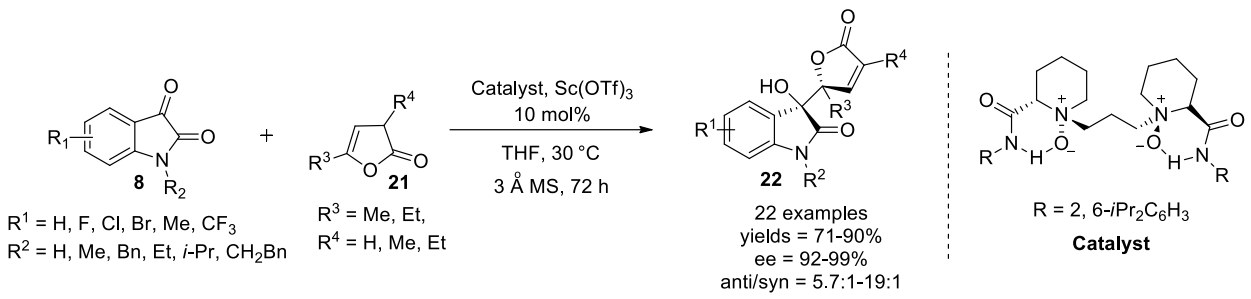
In 2017, Meshram and co-workers[14] developed the first direct vinylogous aldol reaction of furan-2(3*H*)-one **19** with isatins **8** by using DABCO as an organocatalyst at room temperature. The synthetic protocol is atom-economical and provides easy access to a variety of oxindole derivatives **20** in high yield (86-97%) and with excellent diastereoselectivity (dr ratio up to 99:1). The stereochemistry of the major diastereomer (anti or syn) was not defined in this study.



Scheme 4.03

4.3.4 Catalytic asymmetric direct vinylogous Aldol reaction by Feng and co-workers

Recently, Feng and co-workers[15] developed a highly diastereo- and enantioselective direct vinylogous aldol reaction of *β, γ*-unsaturated butenolides **21** with isatins **8** by using an efficient L-PrPr$_2$-Sc(OTf)$_3$ complex as the catalyst. A range of chiral *δ*-hydroxy *γ,γ*-disubstituted butenolide carbonyl derivatives with adjacent stereocenters were obtained in high yields (71-90%) and with good diastereoselectivity (anti/syn = 5.7:1-19:1) and enantioselectivity.



Scheme 4.04

As discussed above, there are only a few reported examples of vinylogous aldol reactions with isatins and most of these methods have some limitations. For example, the use of 2-(trimethylsilyloxy) furan **2** in Mukaiyama aldol rection[11] is not convenient since it has to be prepared separately and it gradually decomposes upon storage. Although this issue is avoided in the synthesis by Meshram which uses the direct vinylogous aldol reaction, an enantioselective version of this reaction is more desirable. The Feng[15] protocol is enantioselective, but it involves metal-based catalysts. Notably, there are no reports on the enantioselective organocatalytic direct vinylogous aldol reaction of α-angelicalactone **13** with isatins.

4.4 Results and discussions:

In initial studies, the phosphoramide-aminothiourea catalysts (Figure 4.7, **I** and **II**, described in Chapter 1 of this thesis) were examined in the organocatalytic direct vinylogous aldol reaction of α-angelicalactone **13** with isatins.

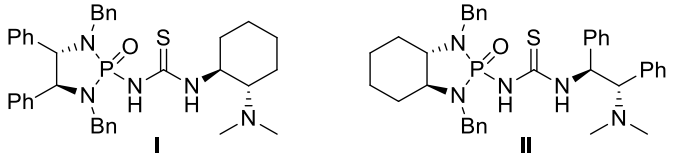
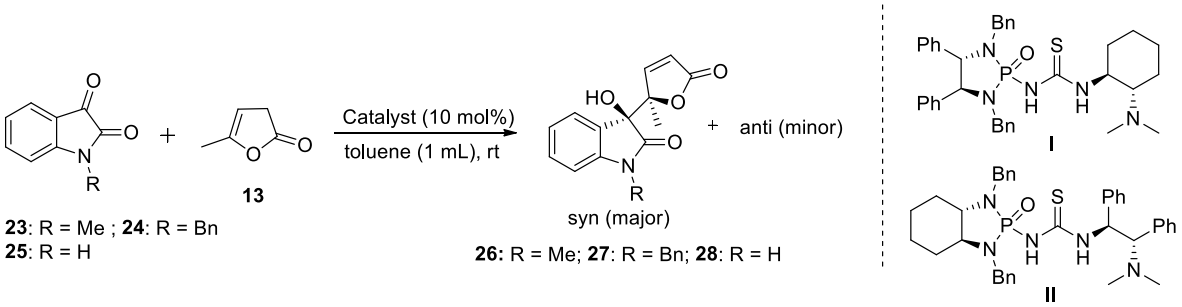


Figure 4.7 Chiral phosphoramide-aminothiourea catalysts examined for the vinylogous aldol reaction

The vinylogous aldol reaction of α-angelicalactone **13** with *N*-methylisatin **23** was selected as the model reaction for optimisation studies. Firstly, phosphoramide catalyst **I** (10 mol%) was examined in toluene at room temperature (Table 4.1). Although **I** did promote the reaction, the required products **26** were obtained as an inseparable mixture of diastereomers in only 17% yield. In addition, the diastereoselectivity and the enantioselectivity of the reaction was moderate (Table 4.1, entry 1). An increase in diastereoselectivity and enantioselectivity was observed when catalyst **II** was employed (entry 2 Table 4.1).

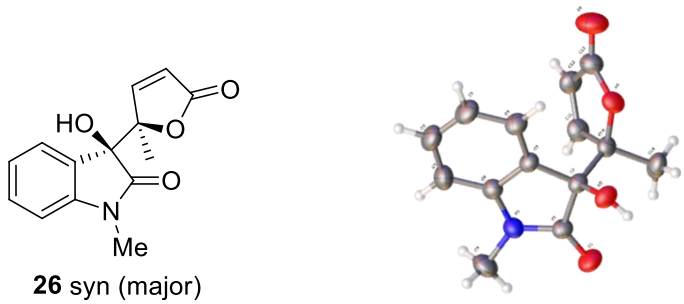
Table 4.1 Asymmetric Vinylogous Aldol Reaction of α-Angelica lactone **13** and Isatin



Entry[a]	Isatin	Catalyst	Time	syn/anti[b]	Yield (%)	Product	syn ee (%)[c]
1	**23**	**I**	12 h	3.7:1	17	**26**	14
2	**23**	**II**	7 h	5.9:1	17	**26**	57
3	**24**	**II**	7 h	4.8:1	21	**27**	35
4	**25**	**II**	12 h	3.8:1	13	**28**	-
5	**23**	**II**	26 h	6.6:1	15[d]	**26**	50
6	**23**	**II**	24 h	4.3:1	7[e]	**26**	45
7	**23**	**II**	6h	12.5:1	16[f]	**26**	50

[a] 1.5 equiv. of α-angelicalactone. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] reaction at 0 ^{o}C. [e] 4 Å MS. [f] 3 equiv. of butenolide

The reaction of *N*-benzyl isatin **24** with α-angelicalactone **13** in the presence of catalyst **II** afforded a diastereomeric mixture of the required products **27** in 21% yield and 35% ee (entry 3, Table 4.1). The reaction of isatin **25**, lacking the *N*-alkyl group, was also investigated but the diastereoselectivity as well as the yield was not good and hence the enantioselectivity of the reaction was not determined (entry 4, Table 4.1). These initial results suggested that catalyst **II** performs better than catalyst **I**. Further optimization studies were therefore conducted with **II**. The reaction of *N*-methyl isatin **23** with α-angelicalactone **13** was conducted at 0 ^{o}C but failed to improve the yield as well as the enantioselectivity of the reaction, although a small increment in the diastereoselectivity was observed (compare entries 2 and 5, Table 4.1). The use of molecular sieves was detrimental to the reaction and **26** was obtained in only 7% yield (entry 6, Table 4.1). A significant increase in the diastereoselectivity (syn/anti 12.5:1) was observed when the amount of α-angelicalactone **15** was increased to a 3-fold excess with respect to isatin (entry 7, Table 4.1). Low to moderate enantioselectivities were obtained with both the catalysts and the highest enantioselectivity was observed with catalyst **II**. These results are summarized in Table 4.1. The absolute configuration of the major diastereomer **26** was determined to be (3*S*,2'*R*) by X-ray crystallographic analysis. The absolute configuration of the minor diastereomer was not determined in this study.

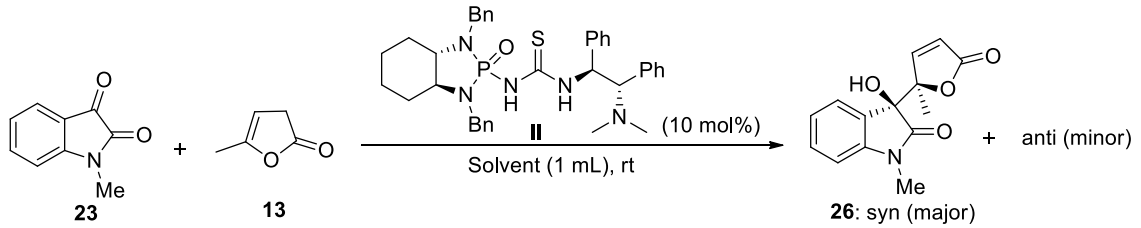


26 syn (major)

Figure 4.8. X-ray crystal structure of major (syn) diastereomer **26**

From the above results, it was observed that the best result was obtained with catalyst **II**. Based on these results, a solvent survey was conducted for the vinylogous aldol reaction of **13** with isatin **23** (Table 4.2). The reaction proceeded smoothly in most of the solvents examined, and the expected aldol products were obtained as an inseparable mixture of diastereomers with **26** as the major product.

Table 4.2 Solvent Survey for Organocatalytic Direct Vinylogous Aldol Reaction of *N*-methyl Isatin **23** and α-Angelicalactone **13**



Entry[a]	Solvent	Time	syn/anti[b]	Yield (%)	Product	syn ee (%)[c]
1	DMF	9 h	1.5:1	21	**26**	23
2	DMSO	9 h	1.1:1	32	**26**	16
3	CF_3CH_2OH	3 h	1.4:1	12	**26**	4
4	THF	9 h	16:1	10	**26**	52
5	CF_3Ph	6 h	10:1	17	**26**	60
6	DME	8 h	5:1	13	**26**	67
7	$CHCl_3$	7 h	6.6:1	11	**26**	43
8	DCM	8h	5:1	18	**26**	47
9	DCE	8 h	5:1	17	**26**	47
10	CH_3CN	6 h	2.4:1	15	**26**	43
11	EtOAc	6 h	6.3:1	17	**26**	46

12	H_2O	12 h	1:1	-	**26**	-
13	Et_2O	19 h	20:1	25	**26**	77
14	MTBE	48 h	20:1	15	**26**	56

[a] 1.5 equiv. of α-angelicalactone. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.

Overall, catalyst **II** provided moderate to good enantioselectivities for the major product **26**, except in DMF, DMSO and trifluoroethanol (entries 1-3, Table 4.2). Trifluorotoluene, THF and DME emerged as promising solvents, in terms of enantioselectivity, but the low diastereoselectivity in DME precluded further studies in this solvent (entries 4-6, Table 4.2). Nonetheless, the yield of **26** in THF (10%), trifluorotoluene (17%) and in DME (13%) was low. Moderate enantioselectivities and low yields for **26** were also observed in chlorinated solvents (entries 7-9, Table 4.2). In comparison, much better results were obtained in ethereal solvents like MTBE and diethyl ether (entries 13 and 14, Table 4.2). Since the results with diethyl ether were better than those with DME with respect to both yield (25%) and enantioselectivity (77%), it was the solvent of choice for further investigations.

Based on the results in Table **4.1** and **4.2**, the phosphoramide catalyst **II** bearing a chiral cyclohexane diamine-derived phosphoramide functionality and a stilbene diamine-derived basic functionality on the thiocarbonyl moiety was the most promising. In order to improve the enantioselectivity and yield of the vinylogous aldol reaction, we turned our focus to the synthesis of analogues of **II** in which the *N*-alkyl group in the cyclohexanediamine portion was 2-naphthylmethyl (**IV**) or neopentyl (**III**). In order to examine the effect of changing the tertiary amine functionality, catalysts incorporating a piperidinyl (**V**) and a pyrrolidinyl (**VI**) moiety were also prepared. These newly synthesized catalysts are shown in Figure 4.9.

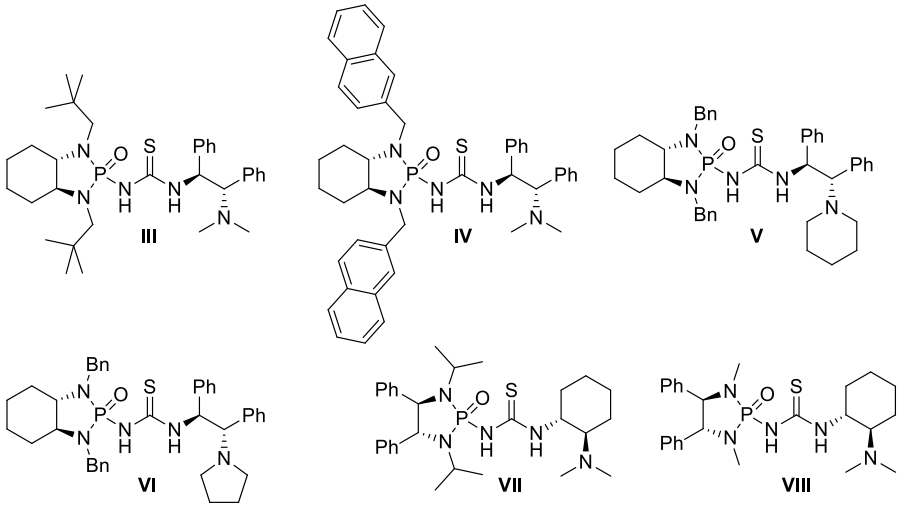
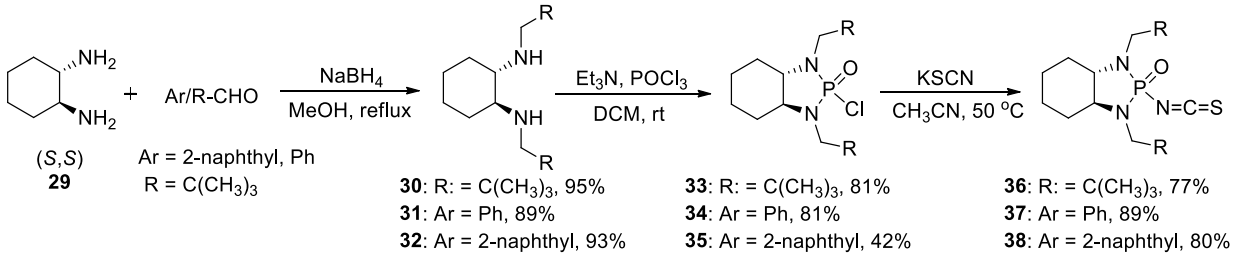


Figure 4.9 Phosphoramide-thiourea organocatalysts used for direct vinylogous aldol reaction

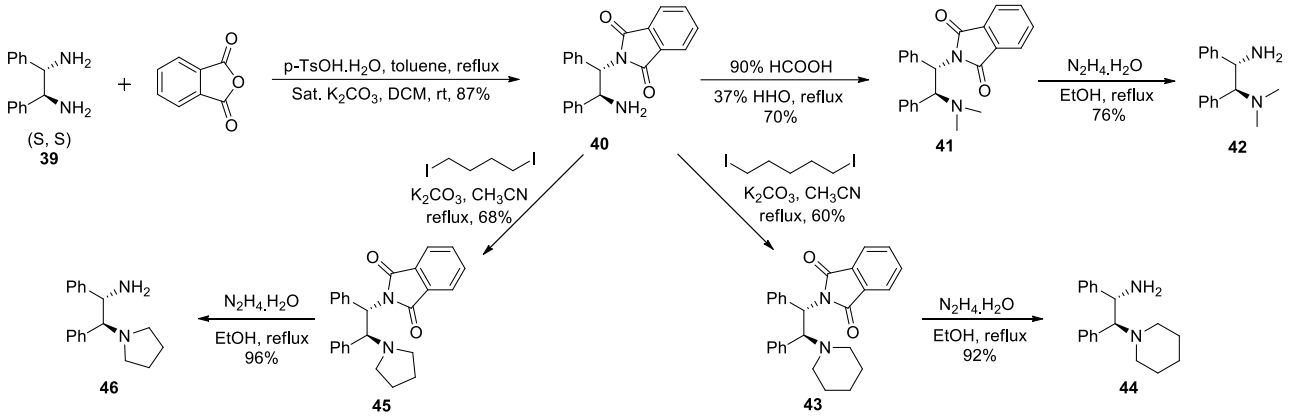
The synthesis of the phosphoramide-thiourea catalysts **(III-VI)** began with the preparation of the requisite starting materials. Reductive amination[16] of the respective aromatic or aliphatic aldehyde with **29** afforded (1*S*,2*S*)-*N*,*N*'-diaryl/dialkyl cyclohexane-1,2-diamines **30-32** which on condensation with phosphorous oxychloride furnished bisamidophosphoryl compounds **33-35**. Treatment of **33-35** with potassium isothiocyanate[17] afforded the key intermediates **36-38** (Scheme 4.05).



Scheme 4.05

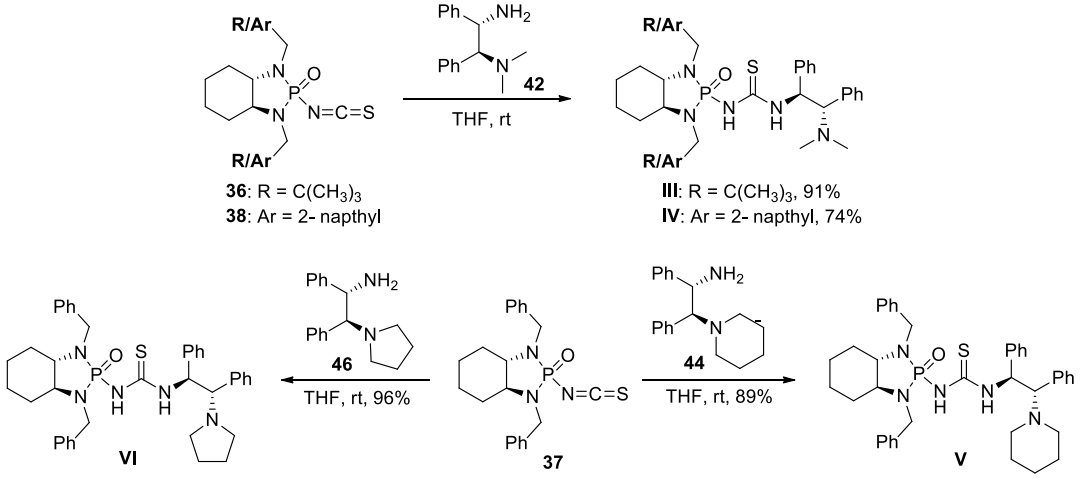
Simultaneously, (1*S*,2*S*)-*N*,*N*-dimethyl-1,2-diphenylethane-1,2-diamine **42**[18] was prepared according to the procedure described in Chapter 1 of this thesis (see page 16). The intermediates (1*S*,2*S*)-1,2-diphenyl-2-(piperidin-1-yl)ethanamine **44** and (1*S*,2*S*)-1,2-diphenyl-2-(piperidin-1-yl)ethanamine **46** were prepared according to the literature procedure.[19] The protection of (1*S*,2*S*)-

1,2-diphenylethane-1,2-diamine **39** with phthalic anhydride produced the mono-phthalimido derivative **40**. Dimethylation of **40** followed by removal of the imide functionality with hydrazine hydrate afforded **42.** Alternatively, **43** (60%) and **45** (68%) were obtained by the reaction of **40** with 1,5-diiodopentane and 1,4-diiodopentane respectively in the presence of potassium carbonate in refluxing acetonitrile (Scheme 4.06).



Scheme 4.06

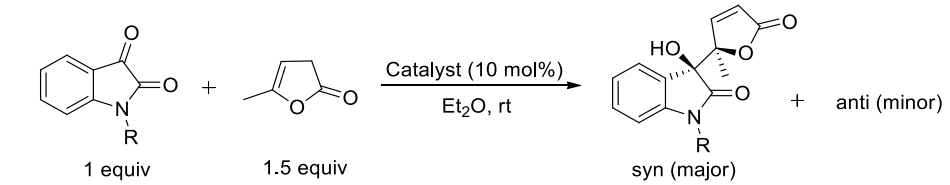
Removal of the imide functionality in **43** and **45** with hydrazine hydrate afforded diamine **44** (92%) and the diamine **46** (96%), respectively. The coupling of the intermediates **42**, **44**, and **46** with the respective isothiocyanate **(36-38)** afforded catalysts **III-VI** in excellent yields (Scheme 4.07)

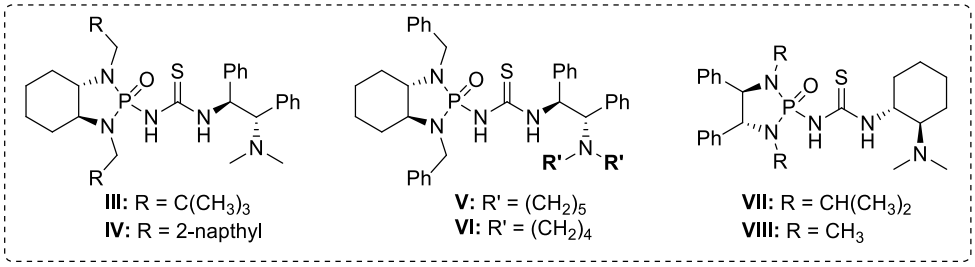


Scheme 4.07

With the catalysts **III-VI** in hand, studies aimed at identifying the optimal catalyst, were conducted in diethyl ether. The results obtained from this catalyst survey are summarized in Table 4.3.

Table 4.3 Catalysts Screening for Asymmetric Vinylogous Aldol Reaction





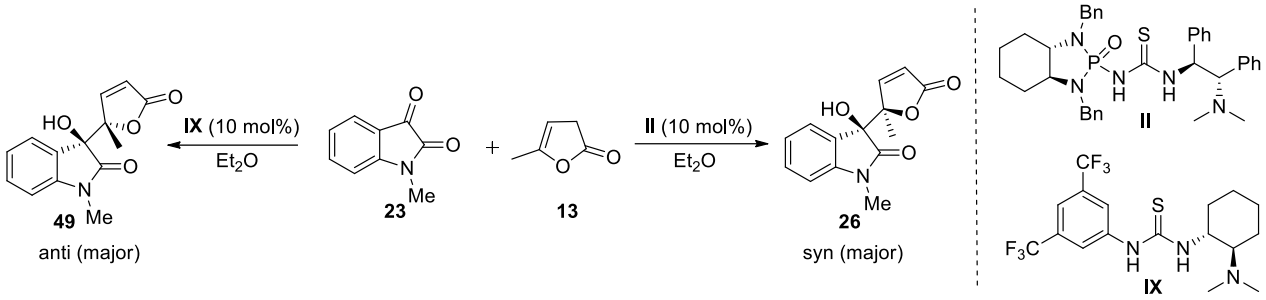
Entry	Isatin	Catalyst	Time	syn/anti[a]	Yield (%)	Product	syn ee (%)[b]
1	**23**	**III**	48 h	Single diastereomer	25	**26**	43
2	**23**	**IV**	48 h	20:1	20[c]	**26**	72
3	**23**	**V**	48 h	8.3:1	20[c]	**26**	65
4	**23**	**VI**	48 h	20:1	19	**26**	73
5	**23**	**VII**	16 h	5:1	20	**26**	44
6	**23**	**VIII**	16 h	3.2:1	17	**26**	6
7	**45**	**II**	48 h	2.4:1	21	**47**	nd
8	**46**	**II**	12 h	-	13	**48**	nd

[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC. [c] 20 mol % Catalyst. [nd] not determined.

Exclusive formation of major diastereomer **26** was observed when catalyst **III** was employed in the direct vinylogous aldol reaction, but **26** was obtained in only 25% yield and with 43% enantiomeric excess. Interestingly, the use of catalyst **IV** (*N*-2-naphthylmethyl) afforded the required product with higher enantiomeric excess (72%), but the yield remained low (20%). (entries 1 and 2, Table 4.3). Incorporation of a piperidine (catalyst **V**) or a pyrrolidine (catalyst **VI**) as a basic unit did not improve the yield or the enantioselectivity of the reaction (entries 3 and 4, Table 4.3). The use of *N*-Boc isatin (**45**) or *N*-Cbz isatin (**46**) was not beneficial. The enantioselectivity of both the reactions was not determined due to the low diastereomeric ratio of the products **47** and **48**, respectively (entries 7 and 8, Table 4.3). The use of previously synthesized "switched" phosphoramide catalysts such as **VII** and **VIII**, in which the phosphoramide portion was derived from stilbenediamine, was not helpful and the level of stereoselection (average dr = 4:1) was lower than that obtained with phosphoramide catalysts (entries 5 and 6, Table 4.3).

A direct comparison of catalyst **II** to the well-known, commercially available, aminothiourea catalyst **IX** (the Takemoto catalyst) in the direct vinylogous aldol reaction of *N*-methyl isatin **23** and α-angelicalactone **13** was also carried out. As mentioned before, the phosphoramide catalyst **II** afforded the required aldol products with excellent diastereoselectivity and moderate enantioselectivity of the major diastereomer **26** at ambient temperature in diethyl ether as a solvent (entry 1, Table 4.2). This observation prompted us to conduct the reaction at lower temperature. Unfortunately, cooling the reaction mixture was not beneficial (entry 2, Table 4.4). In comparison, the same reaction in the presence of Takemoto catalyst **IX** afforded a mixture of products with opposite diastereoselectivity compared to the diastereoselectivity observed with catalyst **II**.

Table 4.4 Comparison of the Takemoto catalyst (**IX**) and the Aminophosphoramide catalyst (**II**)



Entry[a]	Temp	Catalyst	Time	syn/anti[b]	Yield (%)	Product	ee (%)[c]
1	rt	**II**	19 h	20:1	25	**26**	77
2	0 °C	**II**	3 d	5:1	12	**26**	67
3	rt	**IX**	30 min	1:2.6	23	**49**	3
4	0 °C	**IX**	30 h	1:8.3	23	**49**	4

[a] 1.5 equiv. of *a*-angelicalactone. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.

It was also observed that the use of Takemoto catalyst **IX** was not beneficial either at ambient temperature or at 0 °C, and the enantiomeric excess of **26** was negligible (entries 3 and 4, Table 4.4). These results suggest that, for the described reaction, catalyst **II** is much superior than the Takemoto catalyst (**IX**).

A plausible transition state assembly that explains the observed stereochemical outcome of the reaction is shown in Figure 4.10. It is reasonable to assume hydrogen bonding of the phosphoryl N-H functionality in **II** with *N*-methyl isatin **23**, and an ionic interaction of the deprotonated α-angelica lactone and the resultant ammonium functionality in **II** (Figure 4.10). In the arrangement shown, the *re* face of the ketone in the isatin is shielded by the *N*-benzyl group in the catalyst. Reaction of the *si* face of α-angelicalactone and the *si* face of the ketone leads to 3*S*,2'*R*-**26** as the major product.

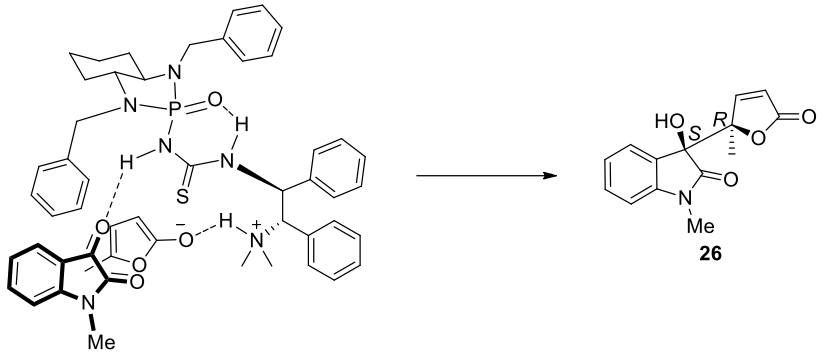


Figure 4.10 Proposed transition state assembly for the formation of **26**

4.6 Conclusion:

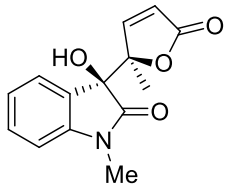
In summary, we have successfully developed an organocatalytic direct vinylogous aldol reaction of natural α-angelica lactone **13** with isatins by employing a novel series of phosphoramide-aminothiourea catalysts and a plausible transition state has been proposed to explain the origin of the asymmetric induction. Results of the direct vinylogous aldol reaction are promising and future efforts will focus on improving the yield and the enantioselectivity of the reaction. These studies are ongoing in the Pansare group.

4.6 Experimental Section:

General procedure for the vinylogous aldol reaction of α-angelicalactone 13 with *N*-methyl isatin 23:

To the solution of catalyst (10 mol%) in a diethyl ether (1 mL), were added α-angelicalactone (1 mmol) and N-alkyl isatin (1.5 mmol) at room temperature and the mixture was stirred at ambient temperature for specific period. After completion, reaction mixture was concentrated and purified by flash column chromatography on silica gel (EtOAc/Hexanes) to provide the inseparable mixture of aldol addition products.

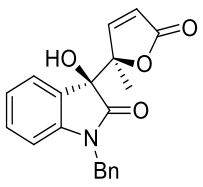
(*S*)-3-Hydroxy-1-methyl-3-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (26):



The reaction of *N*-methyl isatin **23** (40 mg, 0.2 mmol), α-angelicalactone **13** (33 µL, 0.3 mmol) in the presence of phosphoramide catalyst **II** (16 mg, 0.02 mmol) in Et_2O (1mL) for 19 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:2), 30 mg (25%) of **26** as a light yellow solid.

IR (neat): 3407, 3364, 3077, 2923, 2853, 1754, 1706, 1609, 1495, 1467, 1364, 1295, 1254, 1204, 1164, 1116, 1088, 1047, 951, 906, 866, 824, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (ddd, 1H, *J* = 7.6, 1.4, 0.6 Hz, Ar*H*), 7.39-7.31 (m, 2H, Ar*H* and C*H*=CHCO), 7.09 (td, 1H, *J* = 7.6, 0.9 Hz, Ar*H*), 6.83 (d, 1H, *J* = 7.8 Hz, Ar*H*), 5.94 (d, 1H, *J* = 5.7 Hz, CH=C*H*CO), 3.19 (s, 3H, NCH_3), 1.71 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6 (O-,*C*=O), 171.9 (N-*C*O), 156.3 (*C*=C-CO), 143.6 (Ar*C ipso*), 130.8 (Ar*C*), 126.5 (Ar*C ipso*),125.7 (Ar*C*), 123.6 (Ar*C*), 122.9 (Ar*C*), 108.9 (C=*C*-CO), 90.4 (*C*-OH), 79.0 (CH_3*C*O), 26.6 (N*C*H_3), 18.3 (*C*H_3). HRMS (APPI, pos.): *m*/*z* 259.0847 (259.0844 calc. for $C_{14}H_{13}NO_4$ $(M)^+$) and 260.0920 (260.0923 calc. for $C_{14}H_{14}NO_4$ $(M+H)^+$). HPLC: Chiralpak IA (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ= 247 nm): t_{major} = 19.46 min., t_{minor} = 22.42 min., 77% ee.

(*S*)-1-Benzyl-3-hydroxy-3-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (27):



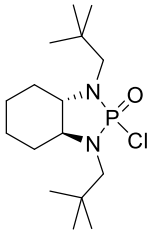
The reaction of *N*-benzyl isatin **24** (40 mg, 0.2 mmol), α-angelicalactone **13** (29 µL, 0.3 mmol) in the presence of phosphoramide catalyst **II** (14 mg, 0.02 mmol) in Et_2O (1mL) for 22 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8:2), 20 mg (21%) of **27** as a light yellow solid.

IR (neat): 3414, 3074, 2985, 2925, 2855, 1756, 1696, 1608, 1489, 1466, 1449, 1373, 1351, 1222, 1120, 1078, 1052, 1025, 959, 911, 866, 824, 755, 737, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (ddd, 1H, *J* = 7.5, 1.3, 0.6 Hz, Ar*H*), 7.38-7.27 (m, 6H, Ar*H* and C*H*=CHCO), 7.26-7.22(m, 1H, Ar*H*), 7.06 (td, 1H, *J* = 7.5, 1.0 Hz, Ar*H*), 6.76 (d, 1H, *J* = 7.8 Hz, Ar*H*), 5.95 (d, 1H, *J* = 5.8 Hz, C*H*CO), 5.03 (d, 1H, *J* = 15.6 Hz, CH_2Ph), 4.72 (d, 1H, *J* = 15.6 Hz, CH_2Ph), (3.07 (s, 1H, O*H*), 1.74 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (O-*C*=O), 171.6 (N-*C*O), 156.1 (*C*=C-CO), 142.8 (Ar*C ipso*), 135.0 (Ar*C ipso*), 130.6 (Ar*C*), 129.0 (2 x Ar*C*), 128.0 (Ar*C*), 127.3 (2 x Ar*C*), 126.4 (Ar*C ipso*), 125.7 (Ar*C*), 123.4 (Ar*C*), 122.7 (Ar*C*), 109.8 (C=*C*-CO), 90.2 (*C*-OH), 78.8 (CH_3*C*O), 44.2 (*C*H_2Ph), 18.3 (*C*H_3). HRMS (APPI, pos.): *m*/*z* 335.1156 (335.1158 calc. for $C_{20}H_{17}NO_4$ $(M)^+$) and 336.1229 (336.1236 calc. for $C_{20}H_{18}NO_4$ $(M+H)^+$).

General procedure for the synthesis of phosphoryl chlorides 33 and 35:

To a solution of the diamine in methylene dichloride, was added phosphorous oxychloride. Triethylamine was added dropwise to the reaction mixture at 0 ^oC and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated, and the residue was purified by flash column chromatography on silica gel to the provide phosphoryl chloride.

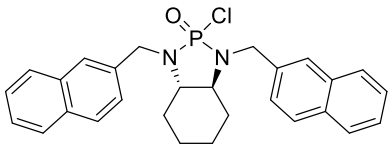
(3a*S*,7a*S*)-2-Chloro-1,3-dineopentyloctahydro-1*H*-benzo[*d*][1,3,2]diazaphosphole 2-oxide (33):



The reaction of **30** (1.95 mg, 7.66 mmol), $POCl_3$ (1.02 ml, 10.7 mmol) and TEA (2.7 ml, 18.4 mmol) in dichloromethane (20 ml), according to the general procedure provided, after purification by flash column chromatography on silica gel, 2.07 gm (81%) of **33** as a colorless gum; R_f = 0.21 (hexanes/EtOAc, 9:1).

IR (neat): 2950, 2866, 1475, 1400, 1365, 1327, 1270, 1168, 1124, 1102, 1073, 1020, 843, 800, 749, 665, 614, 542, 520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.13 (dd, 1H, J = 13.9, 12.8 Hz, C*H*$_2$C(CH$_3$)$_3$), 2.88-2.73 (m, 2H, C*H*$_2$C(CH$_3$)$_3$ and CH$_2$C*H*N), 2.62-2.50 (m, 1H, CH$_2$C*H*N), 2.28 (dd, 1H, J = 20.2, 14.6 Hz, CH$_2$C(CH$_3$)$_3$), 2.21 (dd, 1H, J = 15.3, 14.6, Hz, CH$_2$C(CH$_3$)$_3$), 1.93-1.80 (m, 2H, C*H*$_2$), 1.76-1.62 (m, 2H, C*H*$_2$), 1.25-1.05 (m, 4H, C*H*$_2$), 0.83 (s, 9H, C(C*H*$_3$)$_3$), 0.81 (s, 9H, C(C*H*$_3$)$_3$; ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.5 (d, $^2J_{CP}$ = 9.6 Hz, CH$_2$*C*HN), 62.7 ($^2J_{CP}$ = 11.5 Hz, CH$_2$*C*HN), 56.5 (d, $^2J_{CP}$ = 2.2 Hz, *C*H$_2$C(CH$_3$)$_3$), 55.0 (*C*H$_2$C(CH$_3$)$_3$), 32.2 (d, $^3J_{CP}$ = 0.4 Hz, *C*(CH$_3$)$_3$), 31.2 (d, $^3J_{CP}$ = 3.4 Hz, *C*(CH$_3$)$_3$), 29.9 (d, $^3J_{CP}$ = 7.8 Hz, *C*H$_2$), 29.8 (d, $^3J_{CP}$ = 14.0 Hz, *C*H$_2$), 27.97 (C(*C*H$_3$))$_3$, 27.90 (C(*C*H$_3$))$_3$ 24.2 (d, $^4J_{CP}$ = 0.6 Hz, *C*H$_2$), 23.9 (d, $^4J_{CP}$ = 1.8 Hz, *C*H$_2$); HRMS (APPI, pos.): *m*/*z* 334.1928 (334.1941 calc. for $C_{16}H_{32}ClN_2OP$ $(M)^+$), 335.2000 (335.2019 calc. for $C_{16}H_{33}ClN_2OP$ $(M+H)^+$).

(3a*S*,7a*S*)-2-Chloro-1,3-bis(naphthalen-2-ylmethyl)octahydro-1*H*-benzo[*d*][1,3,2]diazaphosphole 2-oxide (35):



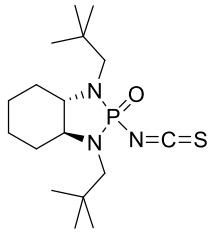
The reaction of **32** (1.00 g, 2.53 mmol), Et_3N (0.80 ml, 5.82 mmol) and $POCl_3$ (0.34 mL, 3.54 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 500 mg (42%) of **35** as a colorless gum; R_f = 0.23 (hexanes/EtOAc, 8:2).

Mp: 192.1-193.3 ºC; IR (neat): 3055, 2923, 2855, 1600, 1508, 1431, 1349, 1293, 1258, 1220, 1189, 1139, 1108, 1078, 1054, 957, 919, 899, 850, 812, 785, 767, 745, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90-7.78 (m, 8H, Ar*H*), 7.66 (dd, 1H, *J* = 8.5, 1.3 Hz, Ar*H*), 7.58 (dd, 1H, *J* = 8.4, 0.9 Hz, Ar*H*), 7.52-7.41 (m, 4H, Ar*H*), 4.71 (t, 1H, *J* = 15.0 Hz, NCH_2), 4.64 (t, 1H, *J* = 15.0 Hz, NCH_2), 4.39 (dd, 1H, *J* = 15.8, 10.4 Hz, NCH_2), 3.91 (dd, 1H, *J* = 15.8, 6.9 Hz, NCH_2), 3.10-2.92 (m, 2H, C*H*N), 1.84-1.74 (m, 1H, CH_2), 1.72-1.63 (m, 1H, CH_2), 1.62-1.49 (m, 2H, CH_2), 1.22-0.82 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7 (d, $^3J_{CP}$ = 10.2 Hz, ArC_{ipso}), 135.2 (d, $^3J_{CP}$ = 3.8 Hz, ArC_{ipso}), 133.3 (ArC_{ipso}) 133.2 (ArC_{ipso}), 132.9 (2 x ArC_{ipso}), 128.4 (Ar*C*), 128.2 (Ar*C*), 127.83 (Ar*C*), 127.78 (Ar*C*), 127.7 (2 x Ar*C*), 126.6 (Ar*C*), 126.3 (Ar*C*), 126.17 (Ar*C*), 126.15 (Ar*C*), 126.1 (Ar*C*), 126.0 (Ar*C*), 125.9 (Ar*C*), 125.8 (Ar*C*), 64.6 (d, $^2J_{CP}$ = 10.4 Hz, CH_2CHN), 63.3 (d, $^2J_{CP}$ = 18.5 Hz, CH_2CHN), 47.9 (d, $^2J_{CP}$ = 2.7 Hz, -NCH_2), 46.9 (d, $^2J_{CP}$ = 4.5 Hz, -NCH_2), 29.3 (d, $^3J_{CP}$ = 12.5 Hz, *C*H_2), 29.1 (d, $^3J_{CP}$ = 7.6 Hz, *C*H_2), 24.1 (d, $^4J_{CP}$ = 0.8 Hz, *C*H_2), 23.8 (d, $^4J_{CP}$ = 1.7 Hz, *C*H_2); HRMS (APPI, pos.): *m*/*z* 474.1647 (474.1628 calc. for $C_{28}H_{28}ClN_2OP$ $(M)^+$), 475.1718 (475.1706 calc. for $C_{28}H_{29}ClN_2OP$ $(M+H)^+$).

General procedure for the synthesis of isothiocyante intermediates 36 and 38:

To a solution of diaminophosphoryl chloride in dry CH_3CN was added tetrabutylammonium thiocyanate or potassium thiocyanate. The solution was heated to reflux for indicated time and then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to provide corresponding isothiocyanate.

(3a*S*,7a*S*)-2-Isothiocyanato-1,3-dineopentyloctahydro-1*H*-benzo[*d*][1,3,2]diazaphosphole 2-oxide (36):

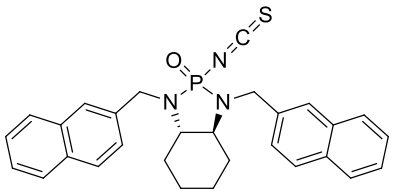


To a solution of phosphoryl chloride **33** (300 mg, 0.89 mmol) in dry CH_3CN was added potassium thiocyanate (174 mg, 1.79 mmol), the solution was heated to reflux for 3 h and then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to provide 245 mg (77%) of isothiocyanate **36** as white solid; R_f = 0.22 (hexanes/EtOAc, 9:1).

IR (neat): 2942, 2863, 2023, 1476, 1445, 1363, 1328, 1274, 1167, 1125, 1100, 1071, 1016, 935, 842, 802, 765, 745, 617, 566, 502 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 3.32 (t, 1H, J = 14.1 Hz, CH_2C$(CH_3)_3$), 2.86 (dd, 1H, J = 18.2, 14.1 Hz, CH_2C$(CH_3)_3$), 2.85-2.76 (m, 1H, CH_2CHN), 2.75-2.65 (m, 1H, CH_2CHN), 2.45 (dd, 1H, J = 16.2, 14.5 Hz, CH_2C$(CH_3)_3$), 2.34 (dd, 1H, J = 19.3, 14.5 Hz, CH_2C$(CH_3)_3$), 2.05 - 1.95 (m, 2H, CH_2), 1.90-1.78 (m, 2H, CH_2), 1.36-1.22 (m, 4H, CH_2), 0.96 (s, 9H, C(C$H_3)_3$), 0.95(s, 9H, C(C$H_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4 (*C*=S), 65.8 (d, $^2J_{CP}$ = 10.2 Hz, CH_2CHN), 63.1 (d, $^2J_{CP}$ = 11.3 Hz, CH_2CHN), 57.3 (d, $^2J_{CP}$ = 1.8 Hz,

*C*H$_2$C(CH$_3$)$_3$), 55.4 (*C*H$_2$C(CH$_3$)$_3$), 32.3 (d, $^3J_{CP}$ = 0.6 Hz, *C*(CH$_3$)$_3$), 31.7 (d, $^3J_{CP}$ = 2.5 Hz, *C*(CH$_3$)$_3$), 30.8 (d $^3J_{CP}$ = 9.3 Hz, *C*H2), 30.2 ($^3J_{CP}$ = 12.8 Hz, *C*H$_2$), 28.2 (C(*C*H$_3$)$_3$), 28.1 (C(*C*H$_3$)$_3$), 24.4 (d, $^4J_{CP}$ = 1.1 Hz, *C*H$_2$), 24.3 (d, $^4J_{CP}$ = 1.8 Hz, *C*H$_2$); HRMS (APPI, pos.): *m*/*z* 357.2015 (357.2004 calc. for $C_{17}H_{32}N_3OPS$ $(M)^+$) and 358.2087 (358.2082 calc. for $C_{17}H_{33}N_3OPS$ $(M+H)^+$).

(3a*S*,7a*S*)-2-Isothiocyanato-1,3-bis(naphthalen-2-ylmethyl)octahydro-1*H* benzo[*d*][1,3,2]diazaphosphole 2-oxide (38):



To a solution of phosphoryl chloride **35** (300 mg, 0.63 mmol) in dry CH_3CN was added potassium thiocyanate (123 mg, 1.26 mmol), the solution was heated to reflux for 30 h and then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to provide 257 mg (80%) of isothiocyanate **38** as white solid; R_f = 0.23 (hexanes/EtOAc, 8:2).

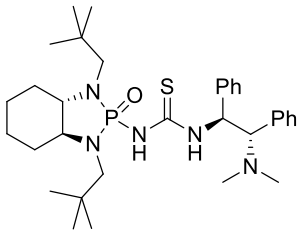
Mp: 148.2-149.0 ºC; IR (neat): 3059, 2937, 2863, 2020, 1970, 1600, 1509, 1437, 1297, 1249, 1224, 1196, 1146, 1109, 1078, 1017, 964, 920, 899, 877, 854, 815, 776, 763, 747, 722 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90-7.78 (m, 8H, Ar*H*), 7.64-7.53 (m, 2H, Ar*H*), 7.52-7.40 (m, 4H, Ar*H*), 4.61 (td, 2H, *J* = 15.9, 4.0 Hz, NC*H*$_2$), 4.29 (dd, 1H, *J* = 15.7, 10.8 Hz, NC*H*$_2$), 4.06 (dd, 1H, *J* = 15.7, 8.4 Hz, NC*H*$_2$), 3.06-2.90 (m, 2H, CH$_2$C*H*N), 1.88-1.78 (m, 1H, C*H*$_2$), 1.76-1.68 (m, 1H, C*H*$_2$), 1.64-1.51 (m, 2H, C*H*$_2$), 1.22-0.83 (m, 4H, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4 (d, $^2J_{CP}$ = 7.0 Hz, *C*=S), 135.4 (d, $^3J_{CP}$ = 7.7 Hz, Ar*C*$_{ipso}$), 135.1 (d, $^3J_{CP}$ = 3.5 Hz, Ar*C*$_{ipso}$) 133.34 (Ar*C*$_{ipso}$), 133.27 (Ar*C*$_{ipso}$), 132.9 (2 x Ar*C*$_{ipso}$), 128.5 (Ar*C*), 128.3 (Ar*C*), 127.84 (Ar*C*), 127.81 (Ar*C*), 127.7 (2 x Ar*C*), 126.6 (Ar*C*), 126.3 (Ar*C*), 126.2 (2 x Ar*C*), 126.0 (Ar*C*), 125.9 (3 x Ar*C*),

63.5 (d, $^{2}J_{CP}$ = 9.1 Hz, CH_2CHN), 63.3 (d, $^{2}J_{CP}$ = 9.4 Hz, CH_2CHN), 47.2 (d, $^{2}J_{CP}$ = 1.9 Hz, NCH_2), 47.1 (d, $^{2}J_{CP}$ = 3.2 Hz, NCH_2), 29.3 (d, $^{3}J_{CP}$ = 9.4 Hz, CH_2), 29.2 (d, $^{3}J_{CP}$ = 12.0 Hz, CH_2), 24.0 (d, $^{4}J_{CP}$ = 0.7 Hz, CH_2), 23.8 (d, $^{4}J_{CP}$ = 1.5 Hz, CH_2); HRMS (APPI, pos.): *m*/*z* 497.1703 (497.1691 calc. for $C_{29}H_{28}N_3OPS$ $(M)^+$) and 498.1775 (498.1769 calc. for $C_{29}H_{29}N_3OPS$ $(M+H)^+$).

General procedure for the synthesis of catalysts III-VI:

To the solution of corresponding isothiocyante in THF (3 ml), *N*,*N*-dimethyl diamine was added at ambient temperature. The mixture was stirred for 3 h, the solvent was removed, and the residue was purified by flash column chromatography on silica gel to provide requisite catalyst in good yield.

1-((1*S*,2*S*)-2-(Dimethylamino)-1,2-diphenylethyl)-3-((3a*S*,7a*S*)-1,3-dineopentyl-2-oxidohexahydro-1*H*-benzo[*d*][1,3,2]diazaphosphol-2(3*H*)-yl)thiourea (III):

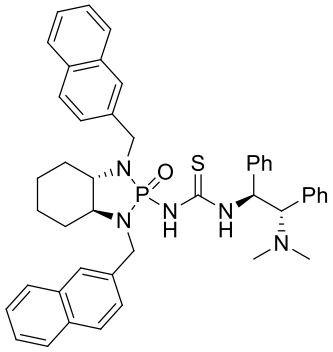


The reaction of **36** (200 mg, 0.55 mmol) in THF (3 ml) was added N,N-dimethyl stilbene diamine (134 mg**,** 0.55 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 304 mg (90%) of **III** as a white solid; R_f = 0.22 (hexanes/EtOAc, 7:3).

IR (neat): 3066, 3031, 2939, 2861, 2829, 2781, 1540, 1498, 1478, 1365, 1338, 1200, 1129, 1102, 1075, 1060, 1020, 847, 798, 757, 746, 707, 631, 613, 527 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.4 (d, 1H, *J* = 7.2 Hz, PhCHN*H*), 7.24-7.09 (m, 5H, Ar*H*), 7.08-6.96 (m, 5H, Ar*H*), 6.38 (d, 1H, *J* = 9.0 Hz, P(O)N*H*), 5.80 (dd, 1H, *J* = 11.1, 7.2 Hz, PhC*H*NH), 3.88 (d, 1H, *J* = 11.1 Hz, PhC*H*N$(CH_3)_2$), 3.19 (t, 1H, *J* = 14.9 Hz, C*H*$_2$C$(CH_3)_3$), 2.95 (t, 1H, *J* = 15.1 Hz, C*H*$_2$C$(CH_3)_3$),

2.83-2.75 (m, 1H, CH_2CHN), 2.69-2.59 (m, 1H, CH_2CHN), 2.46 (t, 1H, J = 15.1 Hz, $CH_2C(CH_3)_3$), 2.33 (t, 1H, J = 14.9 Hz, $CH_2C(CH_3)_3$), 2.17 (s, 6H, $N(CH_3)_2$), 2.01-1.89 (m, 2H, CH_2), 1.86-1.74 (m, 2H, CH_2), 1.35-1.19 (m, 4H, CH_2), 0.99 (s, 9H, $C(CH_3)_3$), 0.78 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8 (d, $^2J_{CP}$ = 5.6 Hz, *C*=S), 140.3 (ArC_{ipso}), 133.3 (ArC_{ipso}), 129.7 (2 x Ar*C*), 128.3 (2 x Ar*C*), 127.6 (2 x Ar*C*), 127.5 (2 x Ar*C*), 127.3 (Ar*C*), 126.6 (Ar*C*), 73.6 (Ph*C*HN$(CH_3)_2$), 64.9 (d, $^2J_{CP}$ = 10.1 Hz, CH_2CHN), 64.4 (d, $^2J_{CP}$ = 11.0 Hz, $CH_2CHN)_3$, 60.1 (Ph*C*H), 56.4 ($CH_2C(CH_3)_3$, 55.7 ($CH_2C(CH_3)_3$, 40.9 ($N(CH_3)_2$), 32.1 (d, $^3J_{CP}$ = 0.9 Hz, $C(CH_3)_3$), 31.7 (d, $^3J_{CP}$ = 1.8 Hz, $C(CH_3)_3$), 30.7 (d, $^3J_{CP}$ = 11.1 Hz, CH_2), 30.6 (d, $^3J_{CP}$ = 9.7 Hz, CH_2), 28.3 ($CH_3)_3$, 28.1 ($CH_3)_3$, 24.5 (CH_2), 24.3 (CH_2); HRMS (APPI, pos.): 597.3653 (597.3630 calc. for $C_{33}H_{52}N_5OPS$ $(M)^+$) and 598.3724 (598.3708 calc. for $C_{33}H_{53}N_5OPS$ $(M+H)^+$).

1-((3a*S*,7a*S*)-1,3-Bis(naphthalen-2-ylmethyl)-2-oxidohexahydro-1*H* benzo[*d*][1,3,2]diazaphosphol-2(3*H*)-yl)-3-((1*S*,2*S*)-2-(dimethylamino)-1,2 diphenylethyl)thiourea (IV):

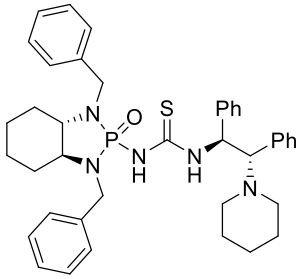


The reaction of **38** (225 mg, 0.45 mmol) in THF (3 ml) was added N,N-dimethyl stilbene diamine (109 mg**,** 0.45 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 220 mg (74%) of **IV** as a white solid; R_f = 0.23 (hexanes/EtOAc, 7:3).

M.P. – 229.2 - 230.5 ^{o}C; IR (neat): 3056, 2925, 2856, 2783, 1555, 1492, 1452, 1364, 1339, 1307, 1184, 1169, 1144, 1106, 1075, 1052, 967, 900, 851, 814, 744, 697, 632, 546, 472 cm $^{-1}$; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 10.5 (d, 1H, *J* = 7.6 Hz, PhCHN*H*), 7.92-7.80 (m, 4H, Ar*H*), 7.79-7.63 (m, 5H, Ar*H*), 7.58 (d, 1H, *J* = 8.6 Hz, Ar*H*), 7.52-7.37 (m, 4H, Ar*H*), 7.31 (d, 1H, *J* = 8.6 Hz, Ar*H*), 7.20 (d, 2H, *J* = 7.1 Hz, Ar*H*), 7.16-7.08 (m, 3H, Ar*H*), 7.06-6.94 (m, 5H, Ar*H* & P(O)N*H*), 5.91 (dd, 1H, *J* = 10.8, 7.6 Hz, PhC*H*NH), 4.89 (t, 1H, *J* = 14.5 Hz, CH_2-napthyl), 4.36-4.20 (m, 2H, CH_2-napthyl), 4.19-4.10 (m, 1H, CH_2-napthyl), 3.92 (d, 1H, *J* = 10.8 Hz, PhC*H*N$(CH_3)_3$), 3.04-2.83 (m, 2H, CH_2C*H*N), 1.94 (s, 6H, N(CH_3)$_2$), 1.72-1.62 (m, 2H, CH_2), 1.58-1.45 (m, 2H, CH_2), 1.13-0.93 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8 (d, $^2J_{CP}$ = 3.9 Hz, *C*=S), 139.7 (ArC_{ipso}), 136.9 (d, $^3J_{CP}$ = 7.0 Hz, ArC_{ipso}), 134.7 (d, $^3J_{CP}$ = 3.0 Hz, ArC_{ipso}), 133.4 (ArC_{ipso}), 133.2 (ArC_{ipso}), 132.9 (ArC_{ipso}), 132.84 (ArC_{ipso}), 132.77 (ArC_{ipso}), 129.7 (2 x Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 128.2 (2 x Ar*C*), 127.9 (3 x Ar*C*), 127.8 (Ar*C*), 127.71 (Ar*C*), 127.66 (Ar*C*), 127.5 (2 x Ar*C*), 127.3 (Ar*C*), 126.9 (Ar*C*), 126.6 (Ar*C*), 126.2 (Ar*C*), 126.08 (Ar*C*), 126.07 (Ar*C*), 126.05 (Ar*C*), 126.0 (Ar*C*), 125.8 (Ar*C*), 125.7 (Ar*C*), 73.6 (Ph*C*HN$(CH_3)_2$), 64.0 (d, $^2J_{CP}$ = 10.1 Hz, CH_2*C*HN), 62.0 (d, $^2J_{CP}$ = 10.9 Hz, CH_2*C*HN), 59.9 (Ph*C*HNH), 46.6 (d, $^2J_{CP}$ = 4.0 Hz, *C*H_2Ph), 46.2 (d, $^2J_{CP}$ = 3.6 Hz, *C*H_2Ph), 41.0 (N(*C*H_3)$_2$), 29.4 (d, $^3J_{CP}$ = 10.4 Hz, *C*H_2), 28.6 (d, $^3J_{CP}$ = 9.2 Hz, *C*H_2), 24.1 (*C*H_2), 23.9 (*C*H_2); HRMS (APPI, pos.): 737.3324 (737.3317 calc. for $C_{45}H_{48}N_5OPS$ $(M)^+$) and 738.3395 (738.3395 calc. for $C_{45}H_{49}N_5OPS$ $(M+H)^+$).

1-((3a*S*,7a*S*)-1,3-Dibenzyl-2-oxidohexahydro-1*H*-benzo[*d*][1,3,2]diazaphosphol-2(3H)-yl)-3-((1*S*,2*S*)-1,2-diphenyl-2-(piperidin-1-yl)ethyl)thiourea (V):

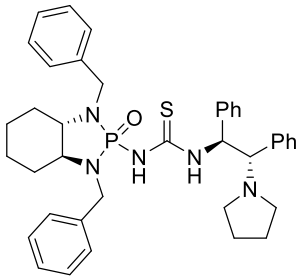


The reaction of **37** (208 mg, 0.52 mmol) in THF (3 ml) was added (1S,2S)-N,N-dimethyl-1,2-diphenyl-2-(piperidin-1-yl)ethanamine (146 mg**,** 0.52 mmol) according to the general

procedure provided, after purification by flash column chromatography on silica gel, 314 mg (89%) of **V** as a white solid; R_f = 0.22 (hexanes/EtOAc, 7:3).

IR (neat): 3061, 3029, 2931, 2853, 2804, 1550, 1492, 1450, 1331, 1205, 1174, 1152, 1106, 1068, 1047,990, 966, 856, 805, 735, 696, 607, 547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.5 (d, 1H, *J* = 6.9 Hz, PhCHN*H*), 7.46 (d, 2H, *J* = 7.3 Hz, Ar*H*), 7.42-7.35 (m, 1H, Ar*H*), 7.34-7.22 (m, 5H, Ar*H*), 7.21-7.07 (m, 8H, Ar*H*), 7.06-9.93 (m, 5H, Ar*H* & P(O)N*H*), 5.83 (dd, 1H, *J* = 10.9, 6.9 Hz, PhC*H*NH), 4.70 (dd, 1H, *J* =15.8, 13.6 Hz, CH_2Ph), 4.04 (d, 2H, *J* = 12.4 Hz, CH_2Ph), 3.90 (dd, 1H, J = 16.9, 6.8 Hz, CH_2Ph) 3.88 (d, 1H, *J* = 10.9 Hz, PhC*H*N), 2.99-2.82 (m, 2H, CH_2*C*HN), 2.46-2.32 (m, 2H, CH_2), 2.24-2.14 (m, 2H, CH_2), 1.65-1.53 (m, 4H, CH_2), 1.35-1.10 (m, 5H, CH_2), 1.08-0.83 (m, 5H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.6 (d, $^2J_{CP}$ = 4.4 Hz, *C*=S), 140.4 (ArC_{ipso}), 139.2 (d, $^3J_{CP}$ = 6.7 Hz, ArC_{ipso}), 137.2 (d, $^3J_{CP}$ = 3.1 Hz, ArC_{ipso}), 134.0 (ArC_{ipso}), 129.6 (2 x Ar*C*), 128.4 (2 x Ar*C*), 128.3 (2 x Ar*C*), 128.1 (2 x Ar*C*), 127.9 (2 x Ar*C*), 127.7 (2 x Ar*C*), 127.4 (2 x Ar*C*), 127.3 (2 x Ar*C*), 127.12 (Ar*C*), 127.08 (2 x Ar*C*), 126.6 (Ar*C*), 74.9 (Ph*C*HN), 64.4 (d, $^2J_{CP}$ = 10.2 Hz, CH_2*C*HN), 61.9 (d, $^2J_{CP}$ = 10.9 Hz, CH_2*C*HN), 59.5 (Ph*C*HNH), 50.3 (2 x N*C*H_2), 46.9 (d, $^2J_{CP}$ = 4.2 Hz, *C*H_2Ph), 46.0 (d, $^2J_{CP}$ = 3.4 Hz, *C*H_2Ph), 29.5 (d, $^3J_{CP}$ = 9.9 Hz, *C*H_2), 28.5 (d, $^3J_{CP}$ = 9.3 Hz, *C*H_2), 26.1 (2 x *C*H_2), 24.3 (*C*H_2), 24.1 (*C*H_2), 24.0 (*C*H_2); HRMS (APPI, pos.): *m*/*z* 677.3320 (677.3317 calc. for $C_{40}H_{48}N_5OPS$ $(M)^+$) and 678.3390 (678.3395 calc. for $C_{40}H_{48}N_5OPS$ $(M+H)^+$).

1-((3a*S*,7a*S*)-1,3-Dibenzyl-2-oxidohexahydro-1*H*-benzo[*d*][1,3,2]diazaphosphol-2(3*H*)-yl)-3-((1*S*,2*S*)-1,2-diphenyl-2-(pyrrolidin-1-yl)ethyl)thiourea (VI):



The reaction of **37** (245 mg, 0.61 mmol) in THF (3 ml) was added (1S,2S)-N,N-dimethyl-1,2-diphenyl-2-(pyrrolidin-1-yl)ethanamine (164 mg**,** 0.61 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 401 mg (96%) of **VI** as a white solid; R_f = 0.23 (hexanes/EtOAc, 7:3).

IR (neat): 3130, 3031, 2940, 2862, 2827, 2782, 2038, 1552, 1495, 1478, 1452, 1362, 1339, 1186, 1167, 1126, 1101, 1073, 1059, 1019, 846, 798, 760, 745, 696, 633, 616, 550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.4 (d, 1H, *J* = 7.7 Hz, PhCHN*H*), 7.48 (d, 2H, *J* = 7.3 Hz, Ar*H*), 7.40-7.25 (m, 6H, Ar*H*), 7.22-7.07 (m, 8H, Ar*H*), 7.06-6.93 (m, 5H, Ar*H*, P(O)N*H*), 5.91 (t, 1H, *J* = 7.7 Hz, PhC*H*NH), 4.54 (dd, 1H, *J* = 15.8, 13.6 Hz, CH_2Ph), 4.04 (dd, 2H, *J* = 11.3, 5.8 Hz, CH_2Ph), 3.98 (d, 1H, 7.7 Hz, PhC*H*N), 3.92 (dd, 1H, *J* = 15.8, 6.7 Hz, CH_2Ph), 3.00-2.79 (m, 2H, CH_2*C*HN), 2.56-2.42 (m, 4H, CH_2), 1.75-1.53 (m, 4H, CH_2), 1.48-1.37 (m, 4H, CH_2) 1.20-0.93 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9 (d, $^2J_{CP}$ = 4.2 Hz, *C*=S), 139.3 (ArC_{ipso}), 139.0 (d, $^3J_{CP}$ = 6.3 Hz, ArC_{ipso}), 136.8 (d, $^3J_{CP}$ = 2.7 Hz, ArC_{ipso}), 136.3 (ArC_{ipso}), 129.5 (2 x Ar*C*), 128.5 (2 x Ar*C*), 128.4 (2 x Ar*C*), 128.1 (2 x Ar*C*), 128.0 (2 x Ar*C*), 127.7 (2 x Ar*C*), 127.6 (2 x Ar*C*), 127.4 (2 x Ar*C*), 127.27 (Ar*C*), 127.26 (Ar*C*), 127.1 (Ar*C*), 126.7 (Ar*C*), 71.9 (Ph*C*HN), 64.1 (d, $^2J_{CP}$ = 10.2 Hz, CH_2*C*HN), 61.9 (d, $^2J_{CP}$ = 10.8 Hz, CH_2*C*HN), 61.5 (Ph*C*HNH), 50.4 (*C*H_2), 46.7 (d, $^3J_{CP}$ = 4.1 Hz, *C*H_2), 46.1 (d, $^3J_{CP}$ = 3.5 Hz, *C*H_2), 29.4 (d, $^3J_{CP}$ = 9.7 Hz, *C*H_2), 28.4 (d, $^3J_{CP}$ = 9.4 Hz,

CH_2), 24.1 (CH_2), 23.9 (CH_2), 23.0 (2 x CH_2); HRMS (APPI, pos.): *m*/*z* 663.3150 (633.3161 calc. for $C_{39}H_{46}N_5OPS$ $(M)^+$) and 664.3239 (664.3220 calc. for $C_{39}H_{47}N_5OPS$ $(M+H)^+$).

4.7 X-Ray crystallographic data for 26

Experimental details

Single-crystal X-ray diffraction data was collected at 291(2) K on a XtaLAB Synergy-S, Dualflex, HyPix-6000HE diffractometer using Cu-K radiation (λ = 1.5406 Å). Crystal was mounted on nylon CryoLoops with Paraton-N. The data collection and reduction were processed within *CrysAlisPro* (Rigaku OD, 2019). A Gaussian absorption correction was applied to the collected reflections. Using Olex^2 [1], the structure was solved with the ShelXT [2] structure solution program using Intrinsic Phasing and refined with the ShelXL [3] refinement package using Least Squares minimisation. All non-hydrogen atoms were refined anisotropically. The hydroxyl hydrogen atom was located in difference Fourier maps and refined by using the HTAB command. The organic hydrogen atoms were generated geometrically.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst*. 42, 339-341.
2. Sheldrick, G.M. (2015). *Acta Cryst*. A71, 3-8.
3. Sheldrick, G.M. (2015). *Acta Cryst*. C71, 3-8.

Table 1. Crystal data and structure refinement

Empirical formula	$C_{14}H_{13}NO_4$
Formula weight	259.25
Temperature/K	291(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.08200(9)
b/Å	5.49247(5)
c/Å	12.75023(12)
β/°	99.3659(9)
Volume/Å^3	627.536(11)
Z	2
ρ_{calc}g/cm^3	1.372
μ/mm^{-1}	0.847
F(000)	272.0
Crystal size/mm^3	0.449 × 0.135 × 0.09
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.026 to 154.592
Index ranges	-11 ≤ *h* ≤ 11, -6 ≤ *k* ≤ 6, -16 ≤ *l* ≤ 16
Reflections collected	20947
Independent reflections	2635 [R_{int} = 0.0563, R_{sigma} = 0.0244]
Data/restraints/parameters	2635/1/178
Goodness-of-fit on F^2	1.081
Final R indexes [I>=2σ (I)]	R_1 = 0.0449, wR_2 = 0.1283
Final R indexes [all data]	R_1 = 0.0490, wR_2 = 0.1367
Largest diff. peak/hole / e Å^{-3}	0.33/-0.20

Flack parameter	0.04(6)

Table 2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$). U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O1	-34(2)	6027(4)	744.5(15)	49.6(5)
O2	1512.0(19)	1405(3)	1366.9(14)	37.3(4)
O3	4590.5(18)	2903(3)	1600.0(14)	38.5(4)
O4	6910(2)	3088(6)	2519(2)	67.3(7)
N1	632(2)	6631(4)	2537.2(16)	36.6(5)
C1	749(2)	5612(4)	1591.8(18)	33.6(5)
C2	2021(2)	3693(4)	1773.6(16)	30.6(5)
C3	2397(2)	3652(4)	2971.2(17)	31.5(5)
C4	3355(3)	2217(5)	3665.2(19)	40.1(6)
C5	3515(3)	2688(7)	4755(2)	49.9(6)
C6	2738(3)	4578(7)	5131(2)	50.7(7)
C7	1741(3)	6011(6)	4445(2)	46.1(6)
C8	1586(2)	5492(4)	3370.7(18)	34.0(5)
C9	-488(3)	8402(6)	2699(3)	49.2(7)
C10	3375(2)	4582(4)	1259.6(17)	31.4(5)
C11	3983(3)	6983(4)	1681(2)	37.8(5)
C12	5370(3)	6720(5)	2169(2)	42.0(6)
C13	5780(3)	4132(6)	2153(2)	42.6(5)
C14	3059(3)	4586(7)	52.9(19)	48.6(7)

Table 3. Selected Bond Distances (Å)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.214(3)	C3	C4	1.382(3)
O2	C2	1.408(3)	C3	C8	1.395(3)
O3	C10	1.449(3)	C4	C5	1.398(3)
O3	C13	1.368(3)	C5	C6	1.384(5)
O4	C13	1.202(3)	C6	C7	1.396(4)
N1	C1	1.349(3)	C7	C8	1.383(3)
N1	C8	1.404(3)	C10	C11	1.496(3)
N1	C9	1.446(3)	C10	C14	1.518(3)
C1	C2	1.553(3)	C11	C12	1.319(4)
C2	C3	1.510(3)	C12	C13	1.470(4)
C2	C10	1.563(3)			

Table 4. Selected Bond Angles

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C13	O3	C10	109.85(19)	C6	C5	C4	120.5(3)
C1	N1	C8	111.3(2)	C5	C6	C7	121.4(2)
C1	N1	C9	124.5(2)	C8	C7	C6	117.1(3)
C8	N1	C9	123.6(2)	C3	C8	N1	110.1(2)
O1	C1	N1	126.7(2)	C7	C8	N1	127.5(2)
O1	C1	C2	125.0(2)	C7	C8	C3	122.4(2)
N1	C1	C2	108.26(19)	O3	C10	C2	106.78(17)
O2	C2	C1	111.06(17)	O3	C10	C11	103.57(17)
O2	C2	C3	111.46(18)	O3	C10	C14	108.3(2)
O2	C2	C10	110.96(18)	C11	C10	C2	113.23(18)
C1	C2	C10	110.01(17)	C11	C10	C14	111.2(2)
C3	C2	C1	101.64(17)	C14	C10	C2	113.18(19)
C3	C2	C10	111.37(17)	C12	C11	C10	109.9(2)
C4	C3	C2	132.2(2)	C11	C12	C13	108.9(2)
C4	C3	C8	119.6(2)	O3	C13	C12	107.7(2)
C8	C3	C2	108.19(19)	O4	C13	O3	121.2(3)
C3	C4	C5	118.9(2)	O4	C13	C12	131.1(3)

Table 5. Hydrogen Bonds

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O2	H2	O1[1]	0.93(5)	1.91(5)	2.814(3)	164(5)

[1]-X,-1/2+Y,-Z

Table 6. Selected Torsion Angles

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O1	C1	C2	O2	-51.5(3)	C3	C4	C5	C6	-0.7(4)
O1	C1	C2	C3	-170.2(3)	C4	C3	C8	N1	-176.9(2)
O1	C1	C2	C10	71.7(3)	C4	C3	C8	C7	2.5(4)
O2	C2	C3	C4	56.1(3)	C4	C5	C6	C7	2.2(5)
O2	C2	C3	C8	-124.9(2)	C5	C6	C7	C8	-1.3(5)
O2	C2	C10	O3	-65.4(2)	C6	C7	C8	N1	178.3(2)
O2	C2	C10	C11	-178.72(18)	C6	C7	C8	C3	-1.0(4)
O2	C2	C10	C14	53.6(3)	C8	N1	C1	O1	172.0(3)
O3	C10	C11	C12	1.6(3)	C8	N1	C1	C2	-5.2(3)
N1	C1	C2	O2	125.8(2)	C8	C3	C4	C5	-1.6(4)
N1	C1	C2	C3	7.1(2)	C9	N1	C1	O1	1.0(4)
N1	C1	C2	C10	-111.0(2)	C9	N1	C1	C2	-176.3(2)
C1	N1	C8	C3	0.9(3)	C9	N1	C8	C3	172.0(2)
C1	N1	C8	C7	-178.4(3)	C9	N1	C8	C7	-7.3(4)
C1	C2	C3	C4	174.5(2)	C10	O3	C13	O4	179.4(2)
C1	C2	C3	C8	-6.5(2)	C10	O3	C13	C12	-1.2(3)
C1	C2	C10	O3	171.31(17)	C10	C2	C3	C4	-68.4(3)
C1	C2	C10	C11	58.0(2)	C10	C2	C3	C8	110.6(2)
C1	C2	C10	C14	-69.7(3)	C10	C11	C12	C13	-2.3(3)
C2	C3	C4	C5	177.3(2)	C11	C12	C13	O3	2.2(3)

C2	C3	C8	N1	4.0(2)	C11	C12	C13	O4	-178.4(3)
C2	C3	C8	C7	-176.7(2)	C13	O3	C10	C2	-119.92(19)
C2	C10	C11	C12	116.8(2)	C13	O3	C10	C11	-0.2(2)
C3	C2	C10	O3	59.4(2)	C13	O3	C10	C14	117.9(2)
C3	C2	C10	C11	-53.9(2)	C14	C10	C11	C12	-114.4(2)
C3	C2	C10	C14	178.4(2)					

4.8 References:

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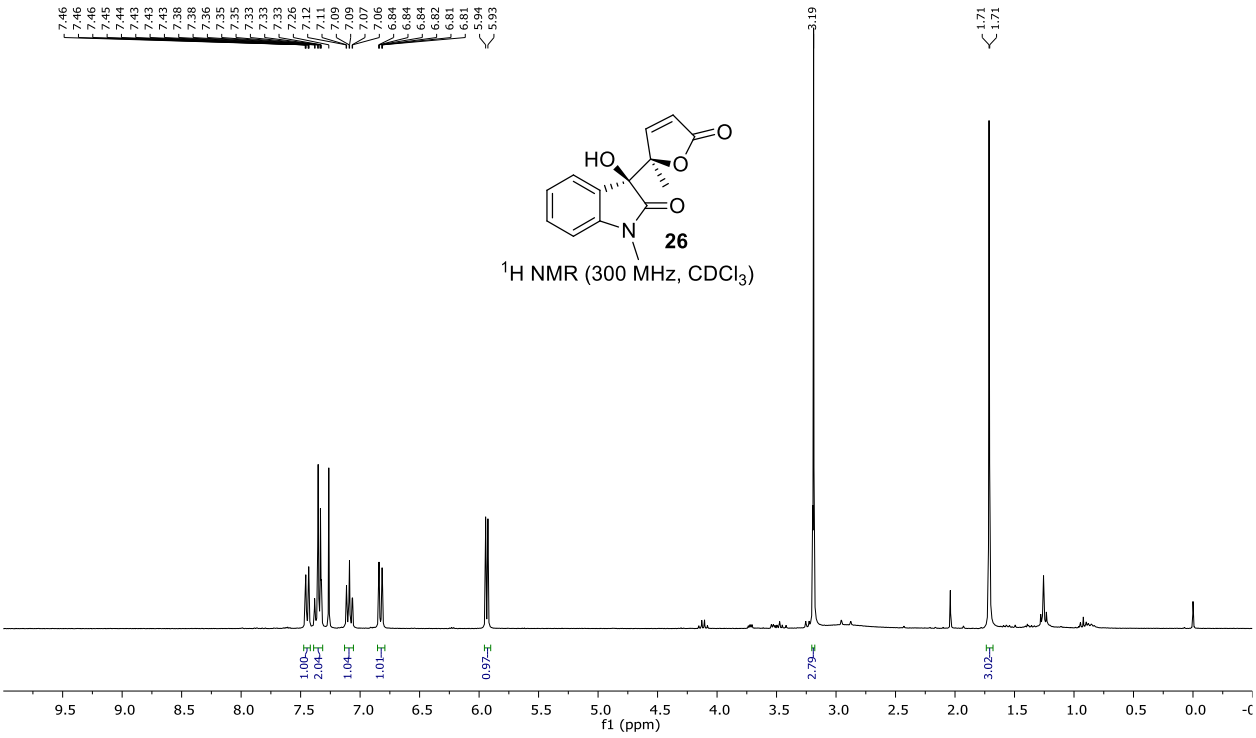
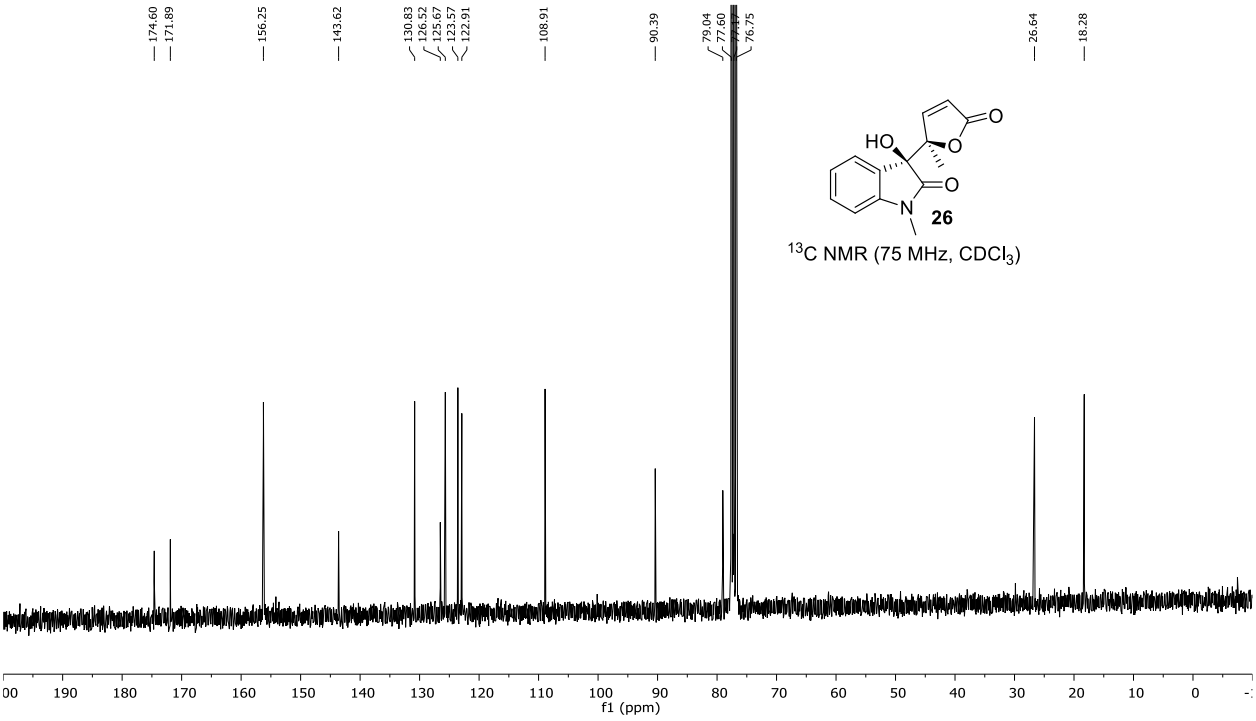
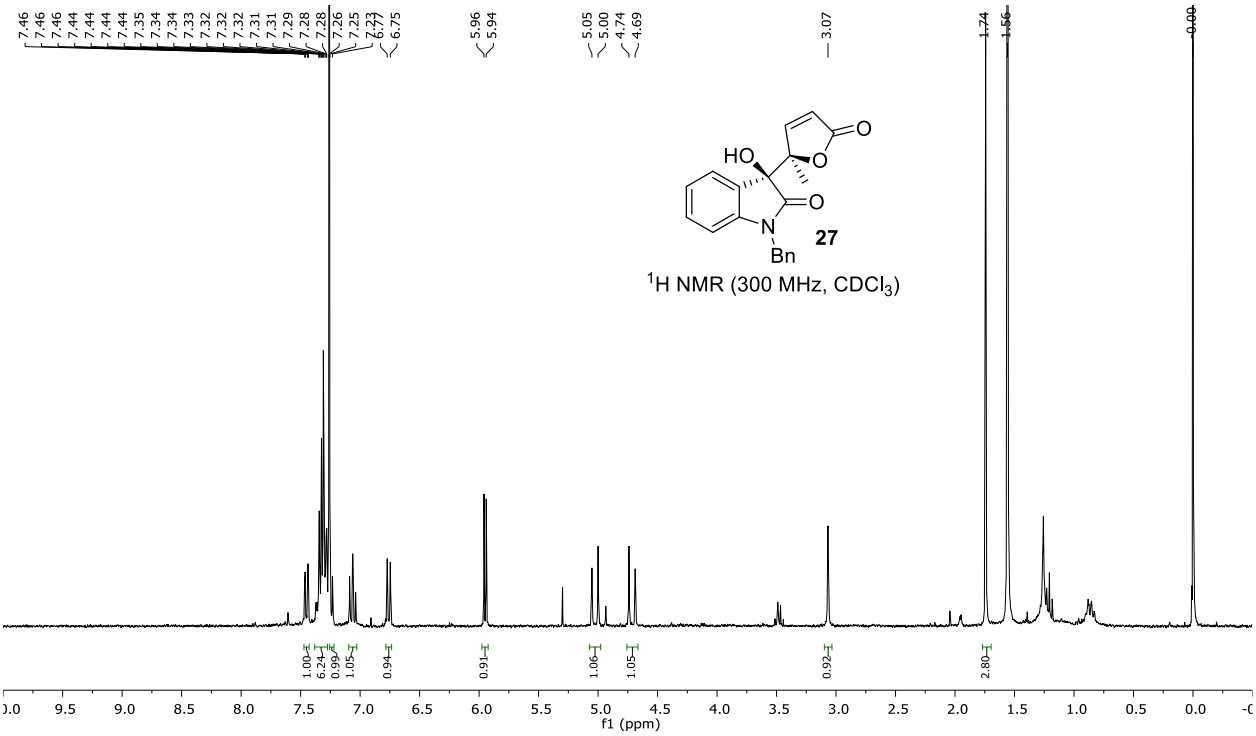
4.10 **Selected ^{1}H NMR, ^{13}C NMR Spectra:**







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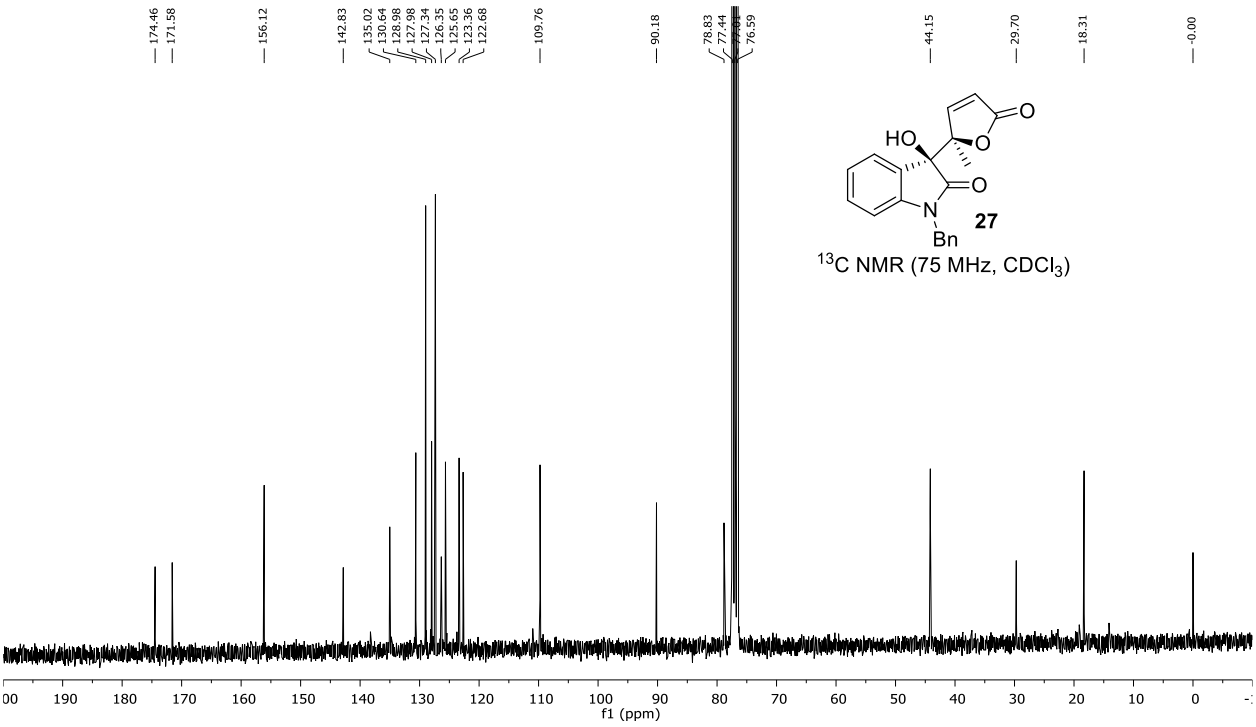

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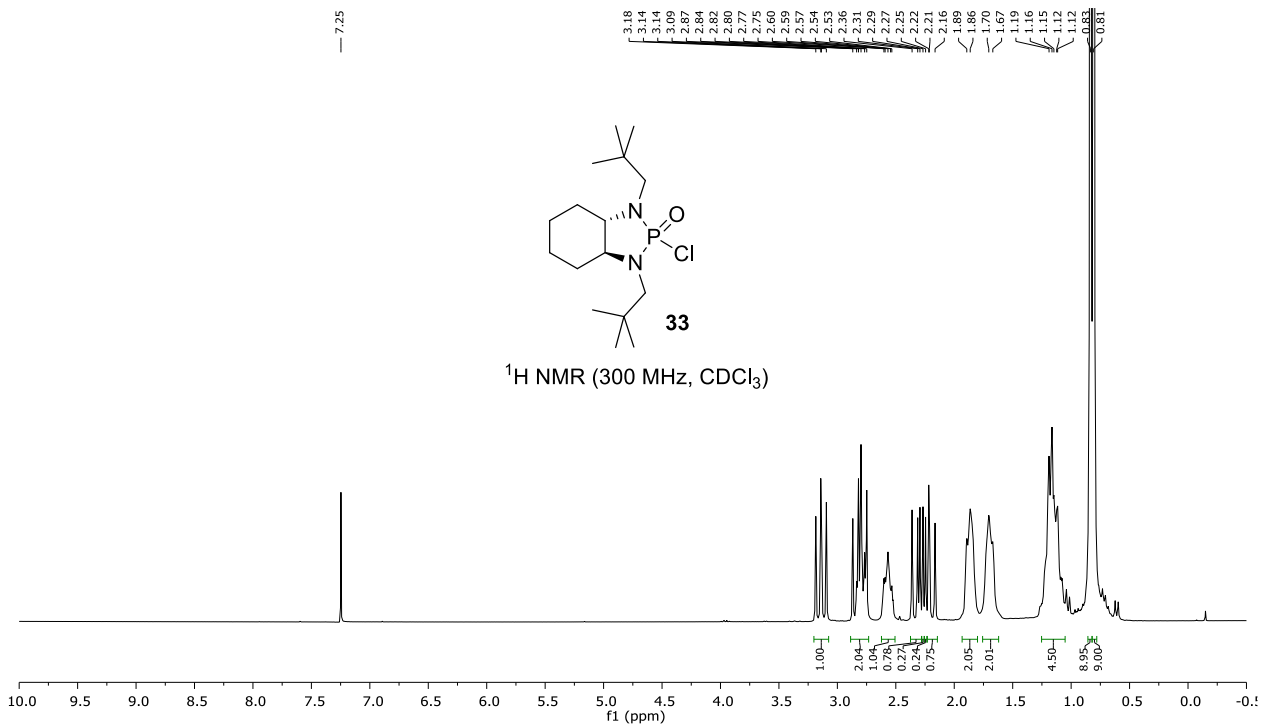

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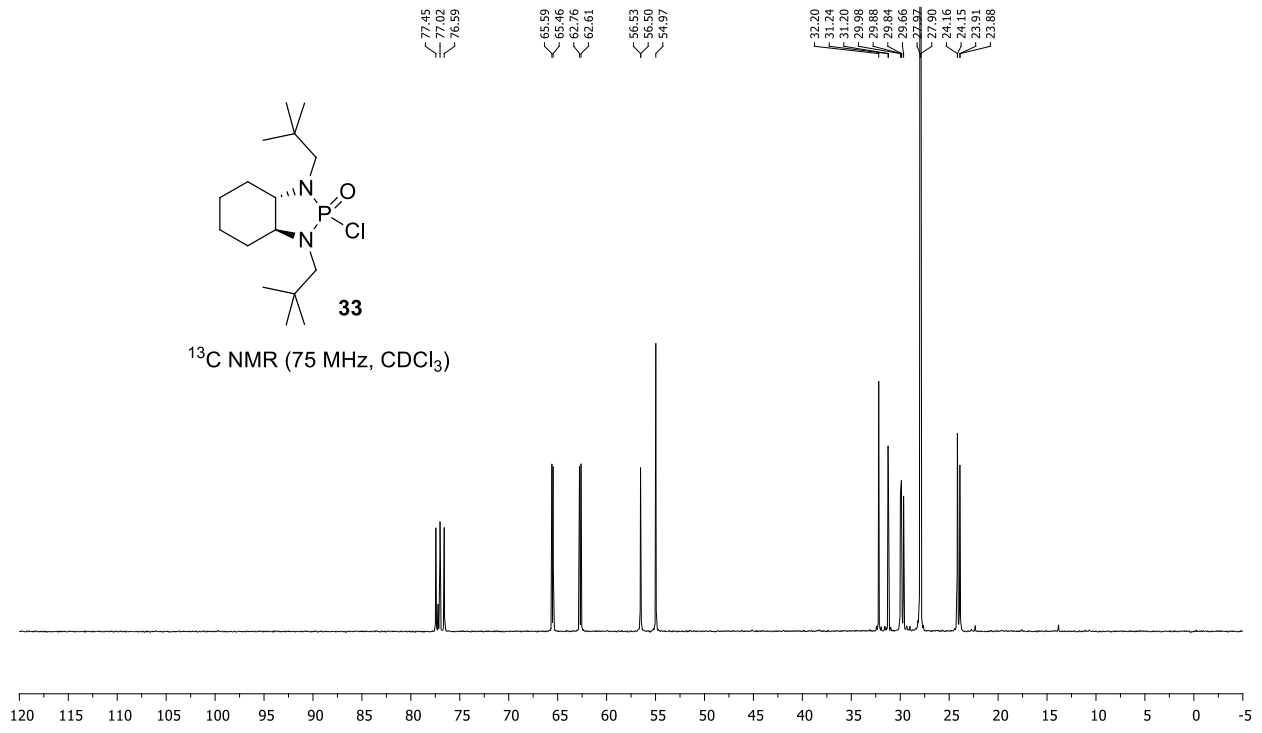

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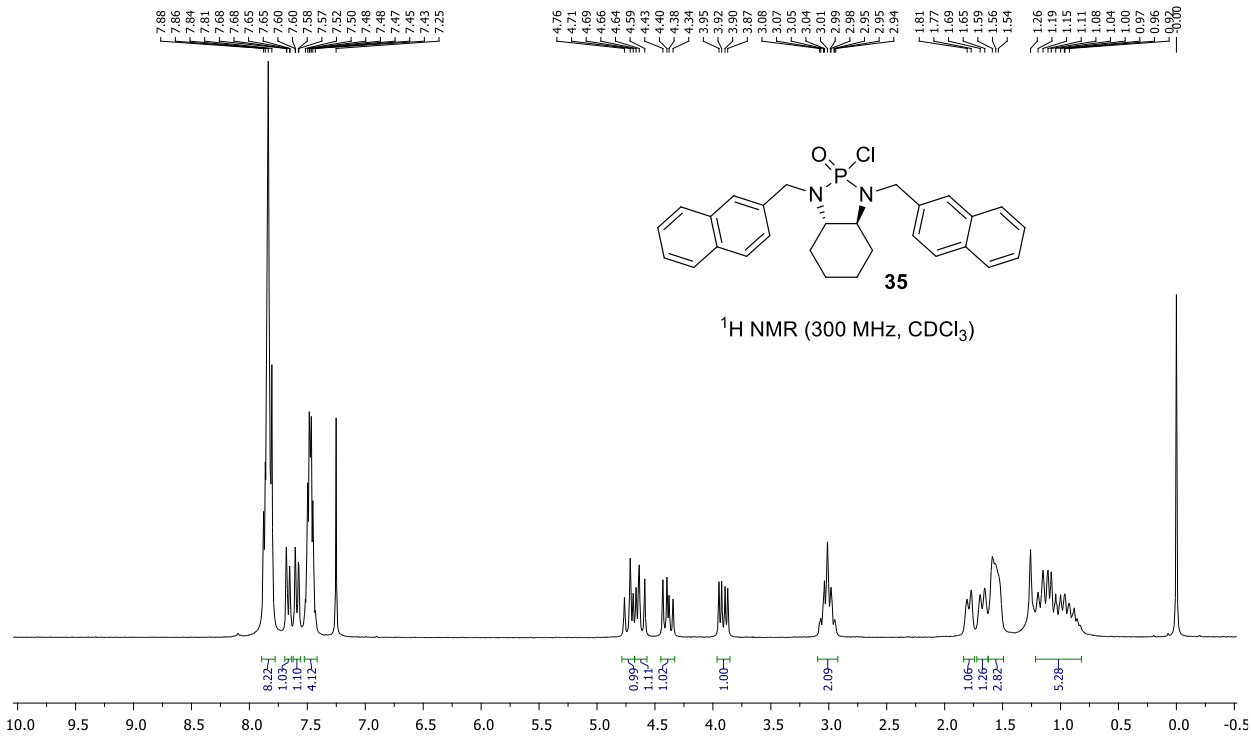
^{13}C NMR (75 MHz, $CDCl_3$)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Cl
P
N
N
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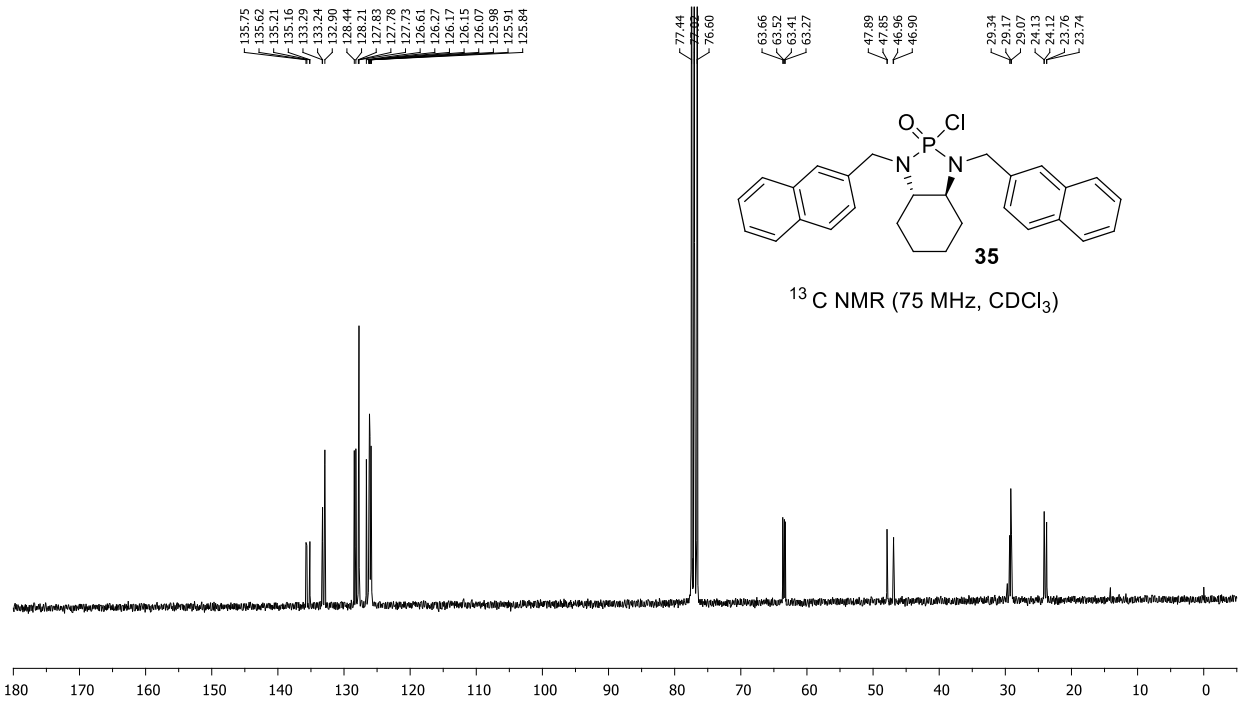
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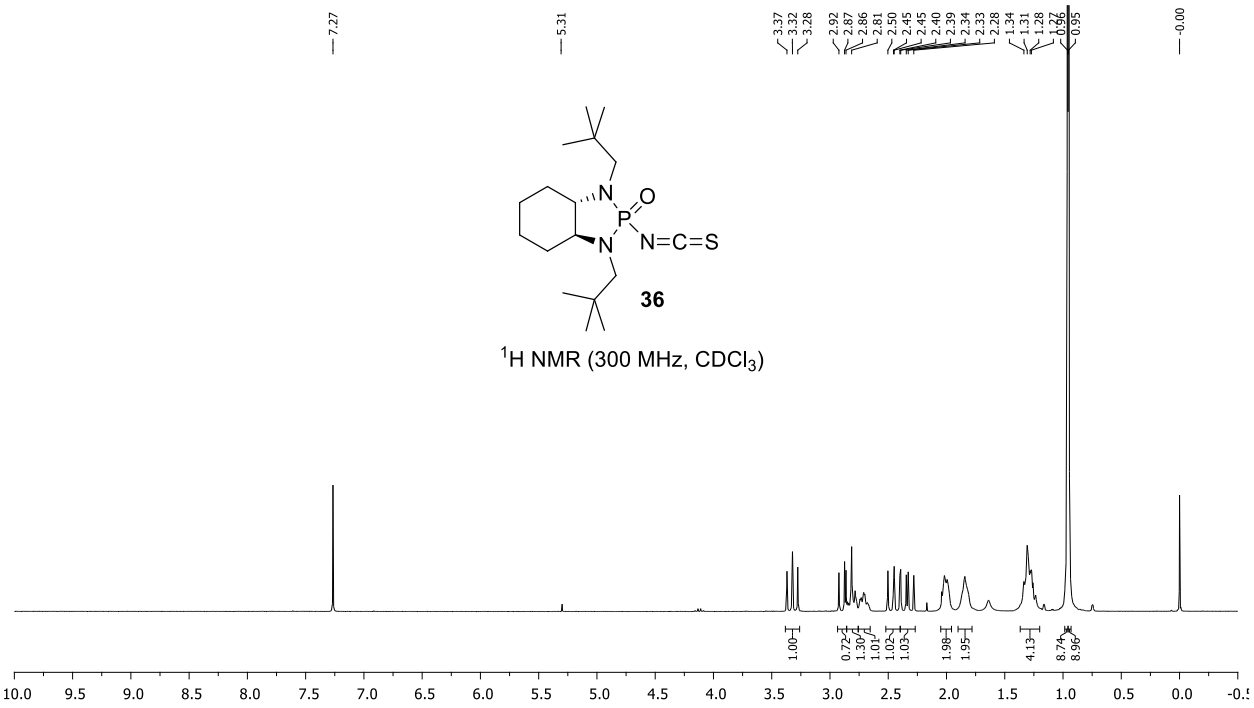

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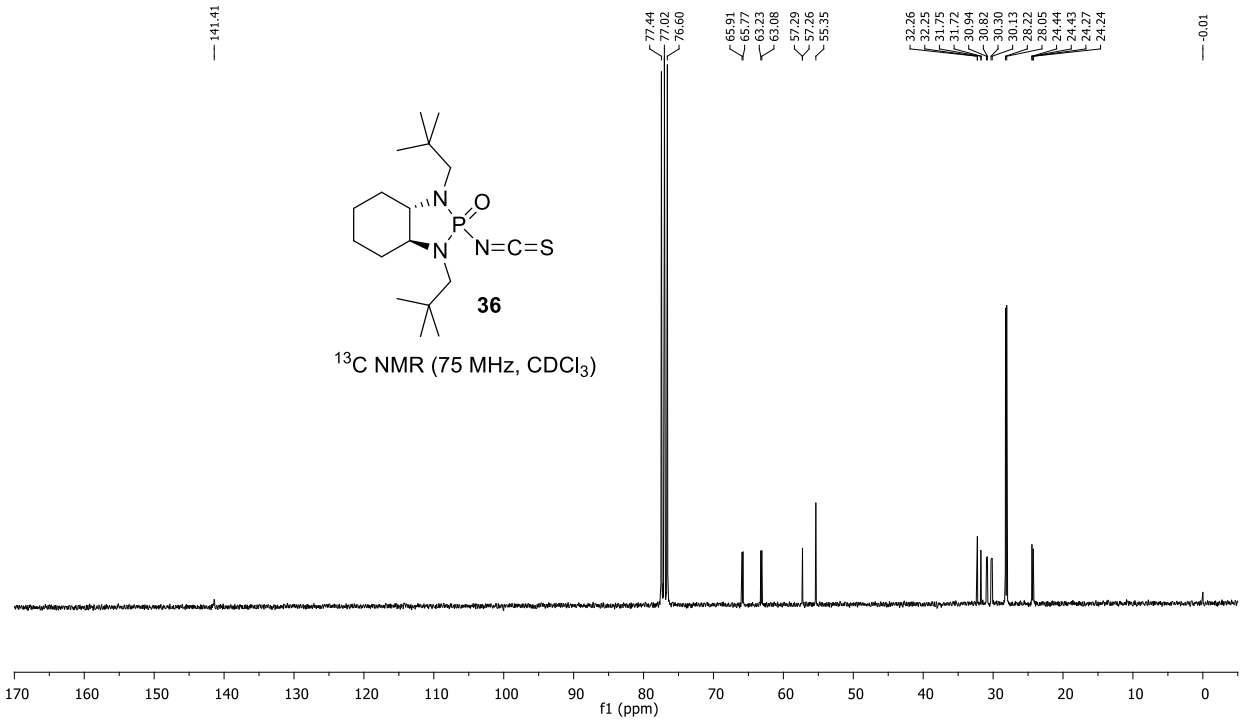

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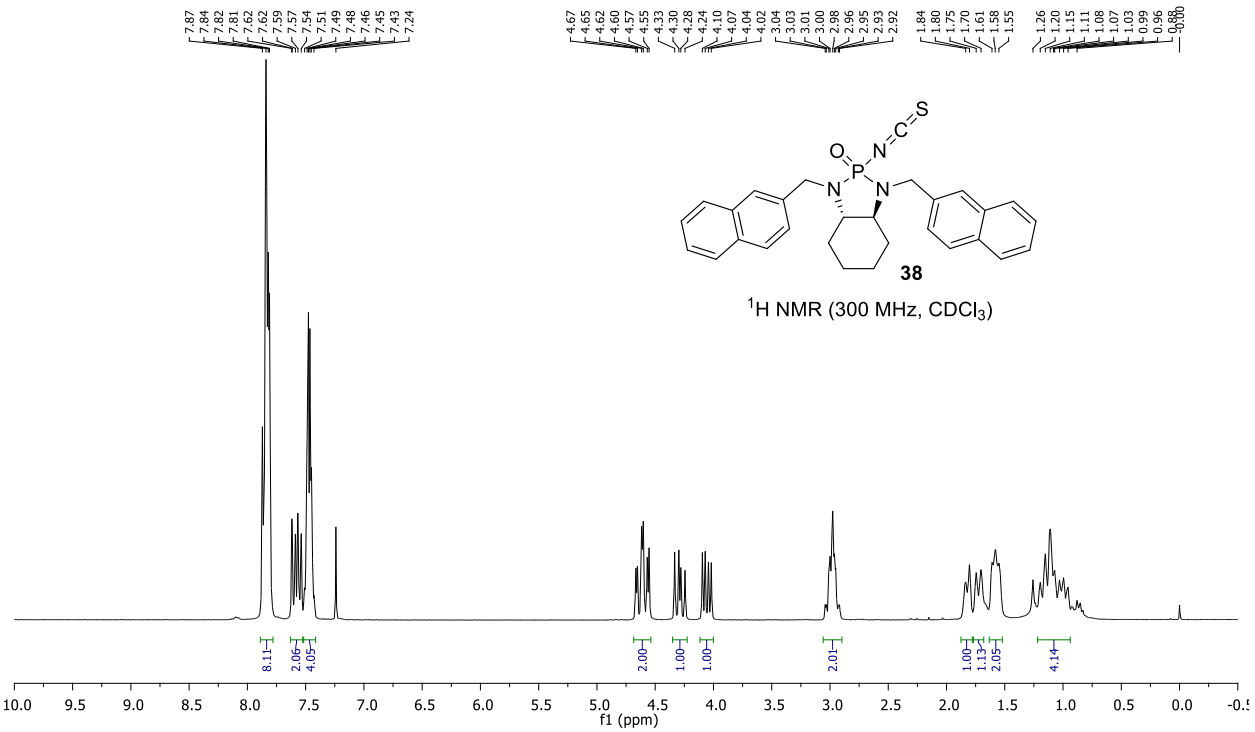
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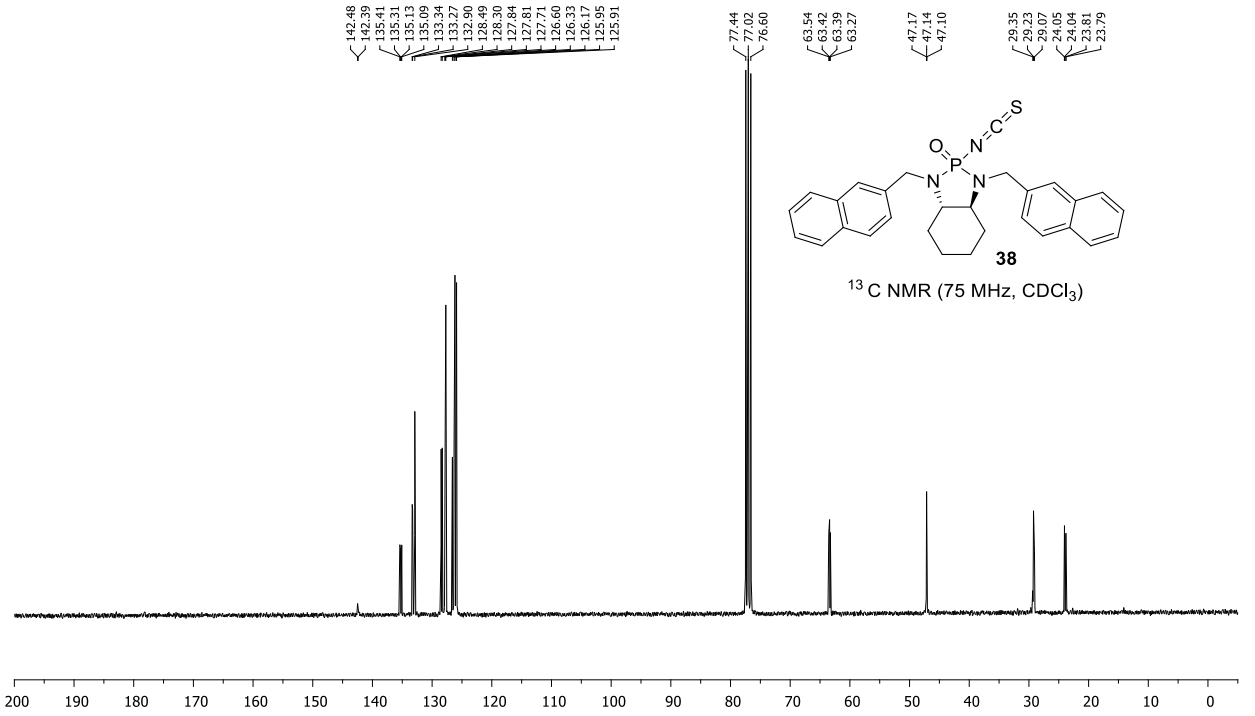
f1 (ppm)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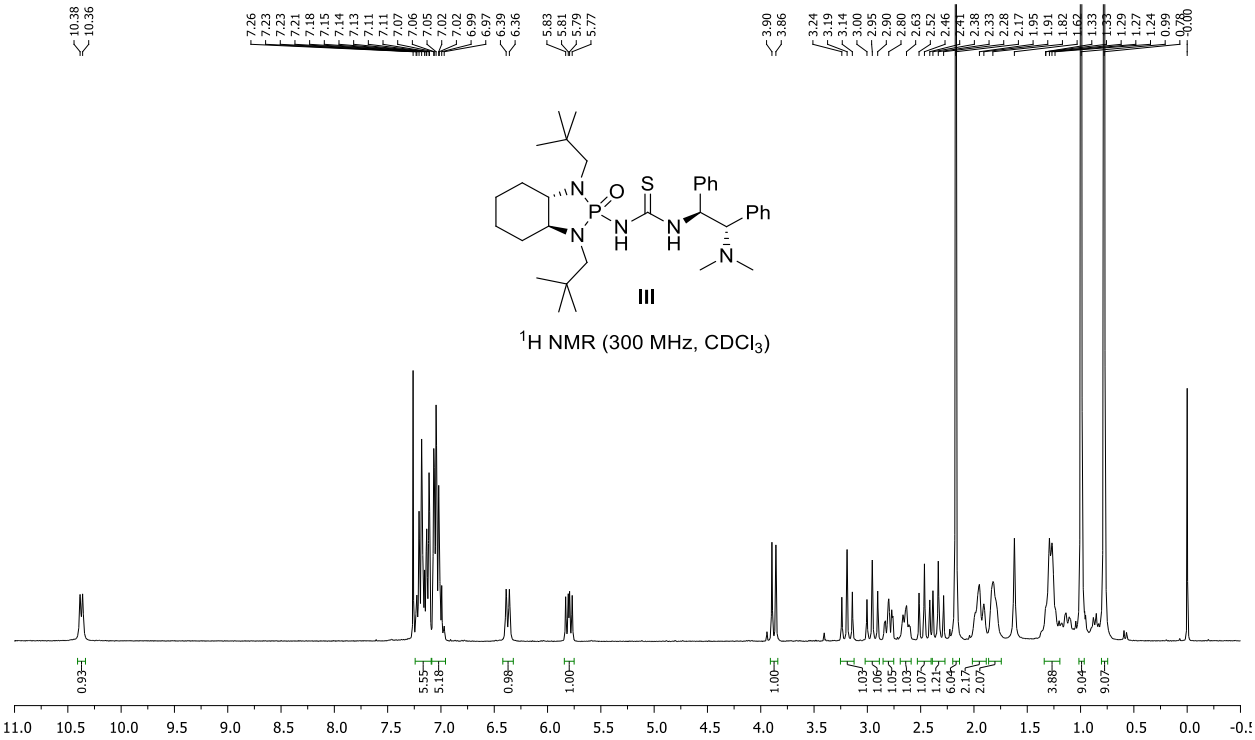
13 C NMR (75 MHz, CDCl3)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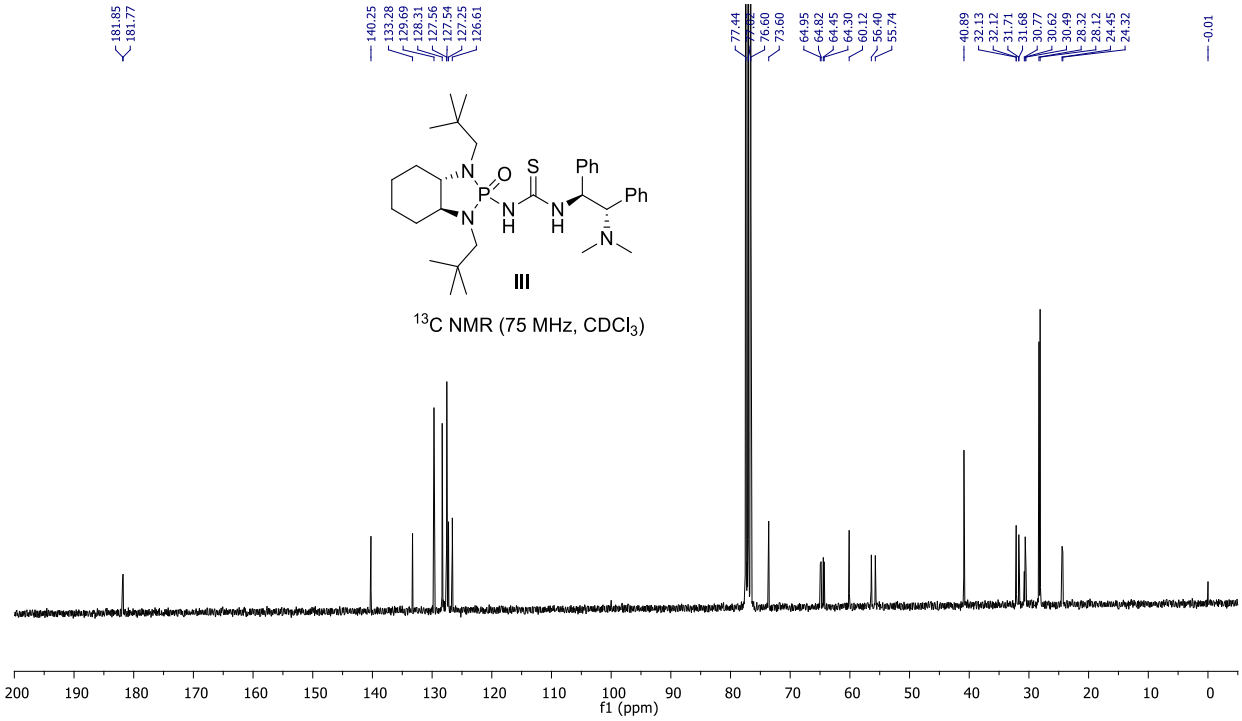
III
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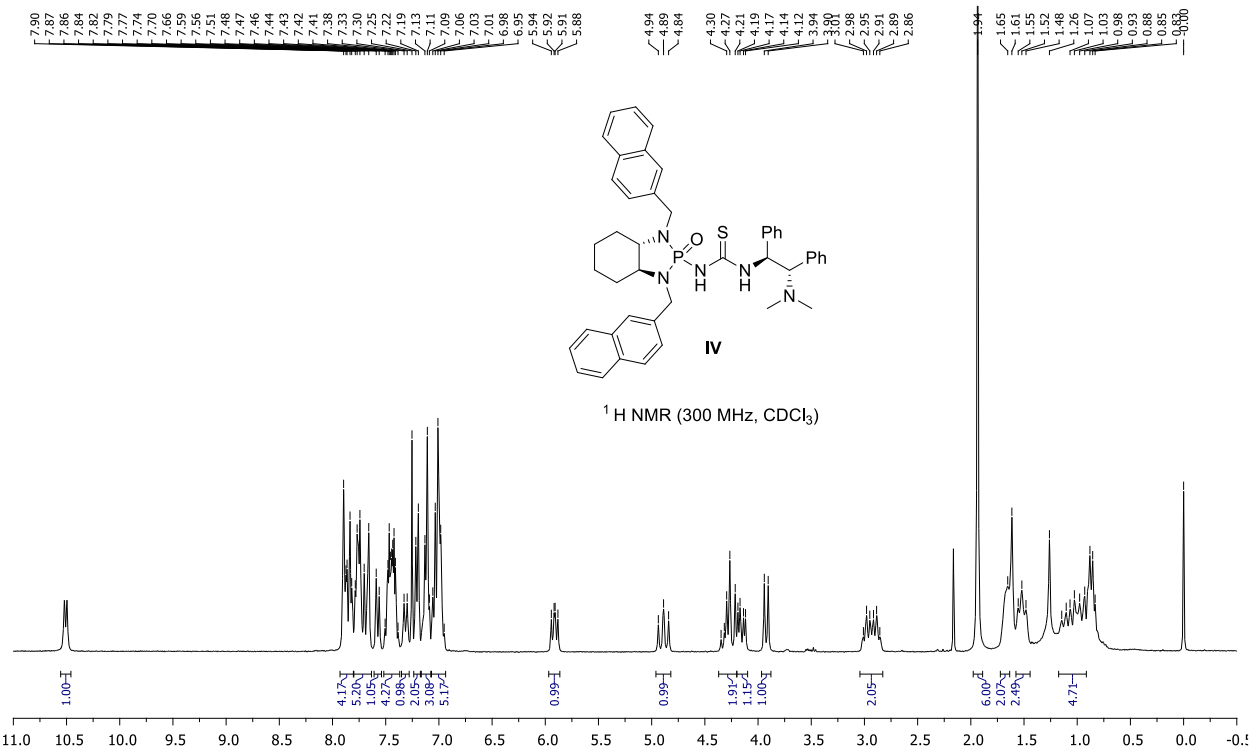
f1 (ppm)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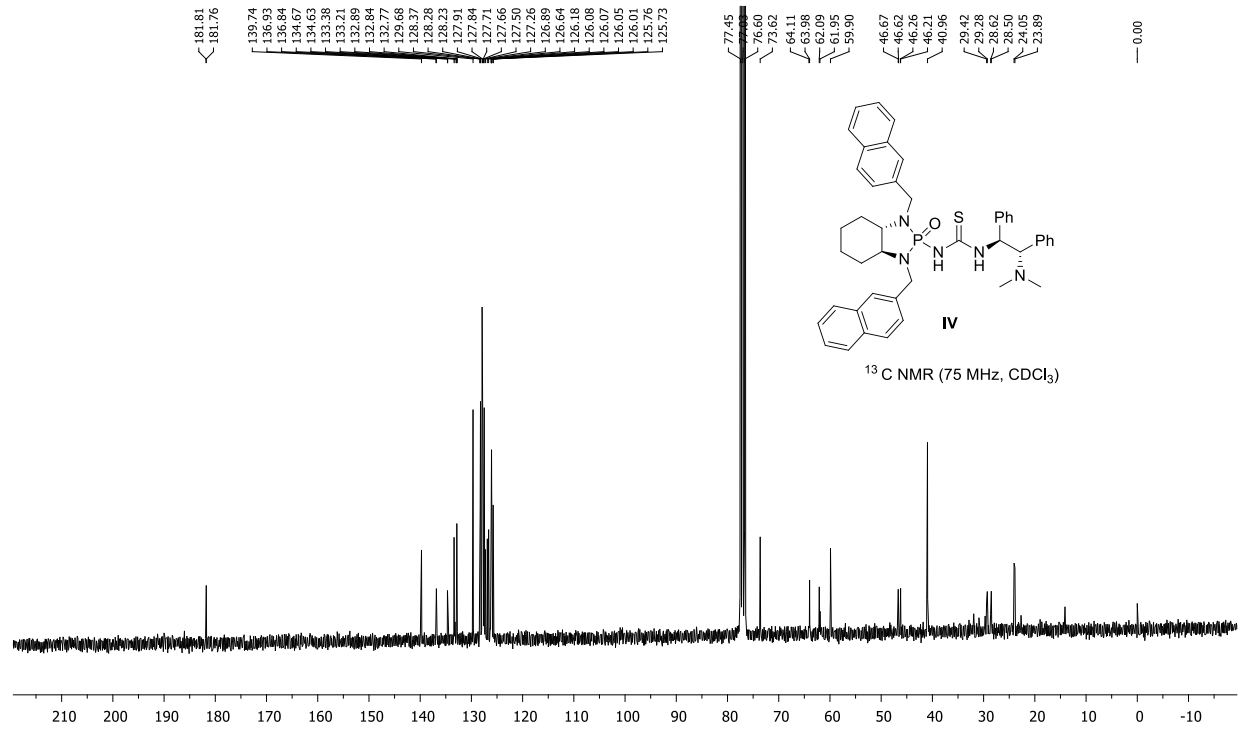
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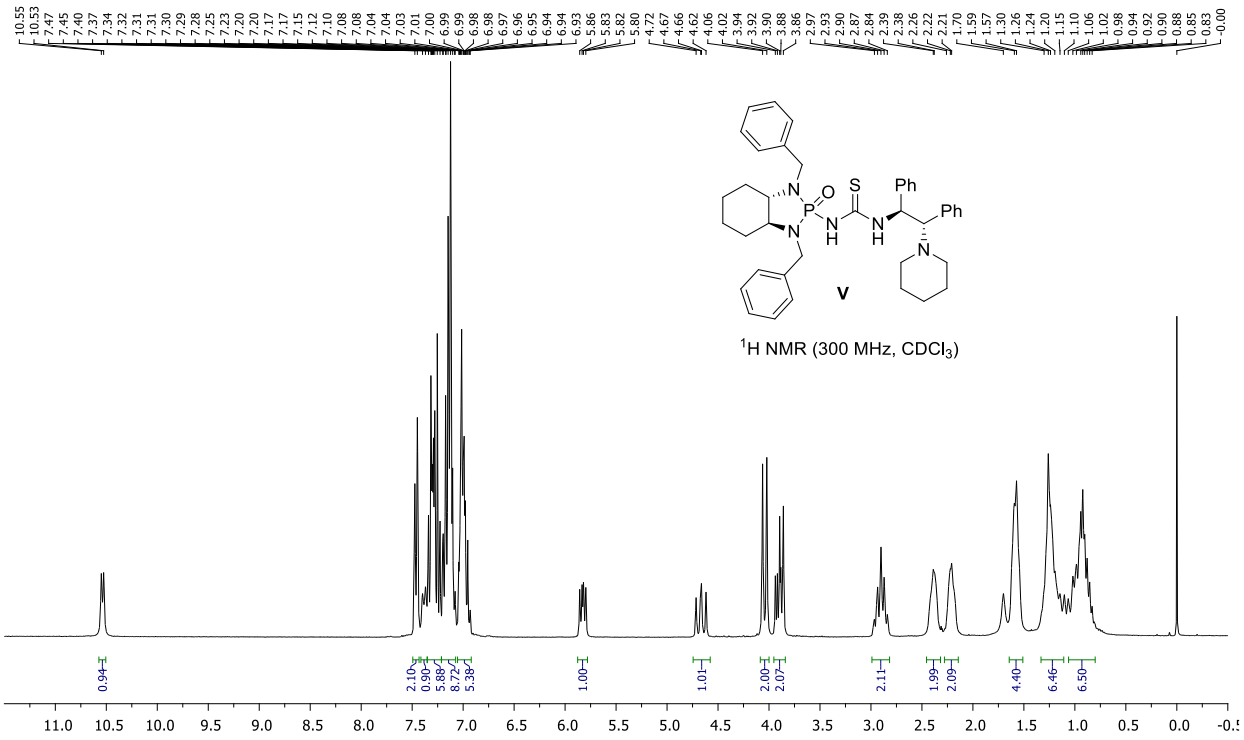
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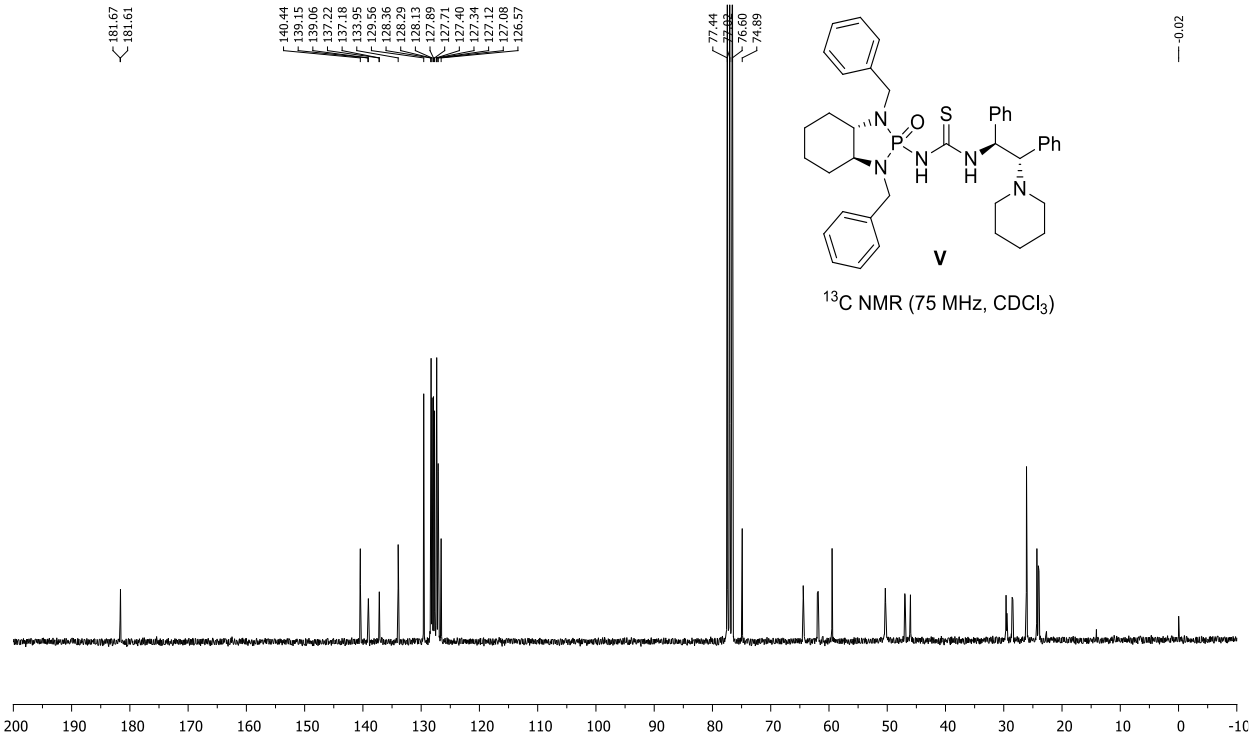
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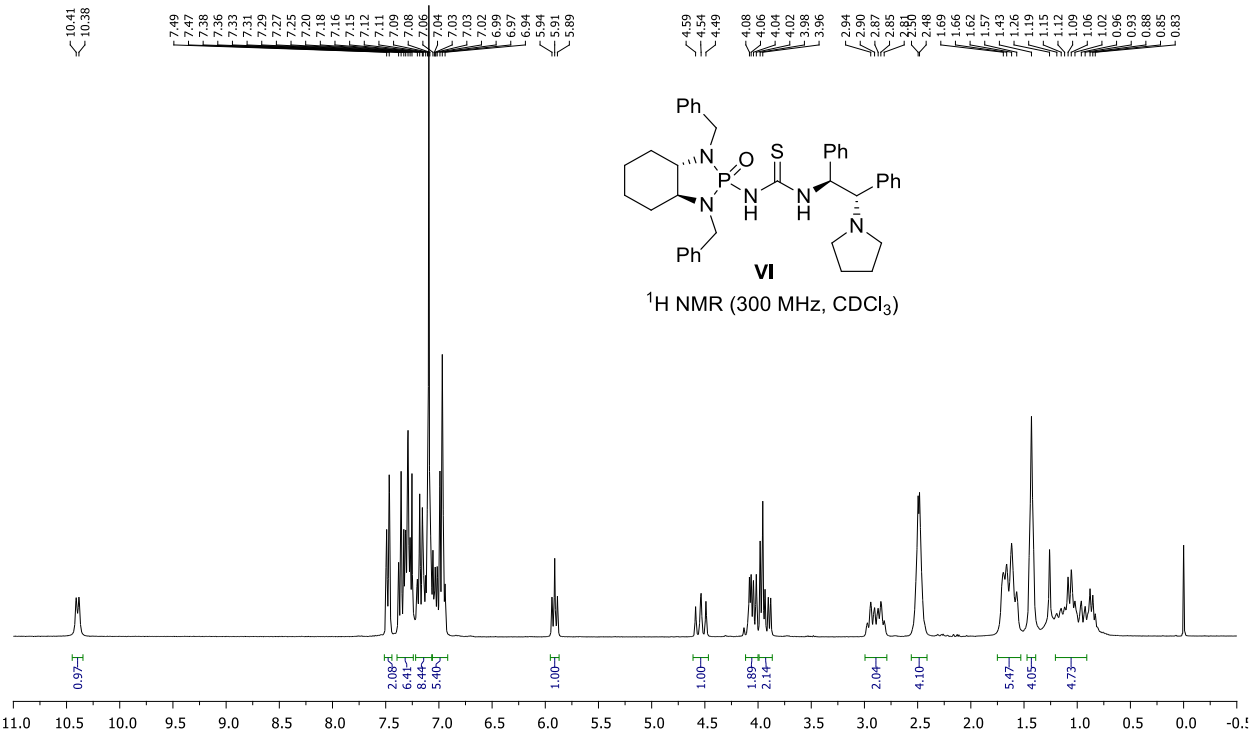

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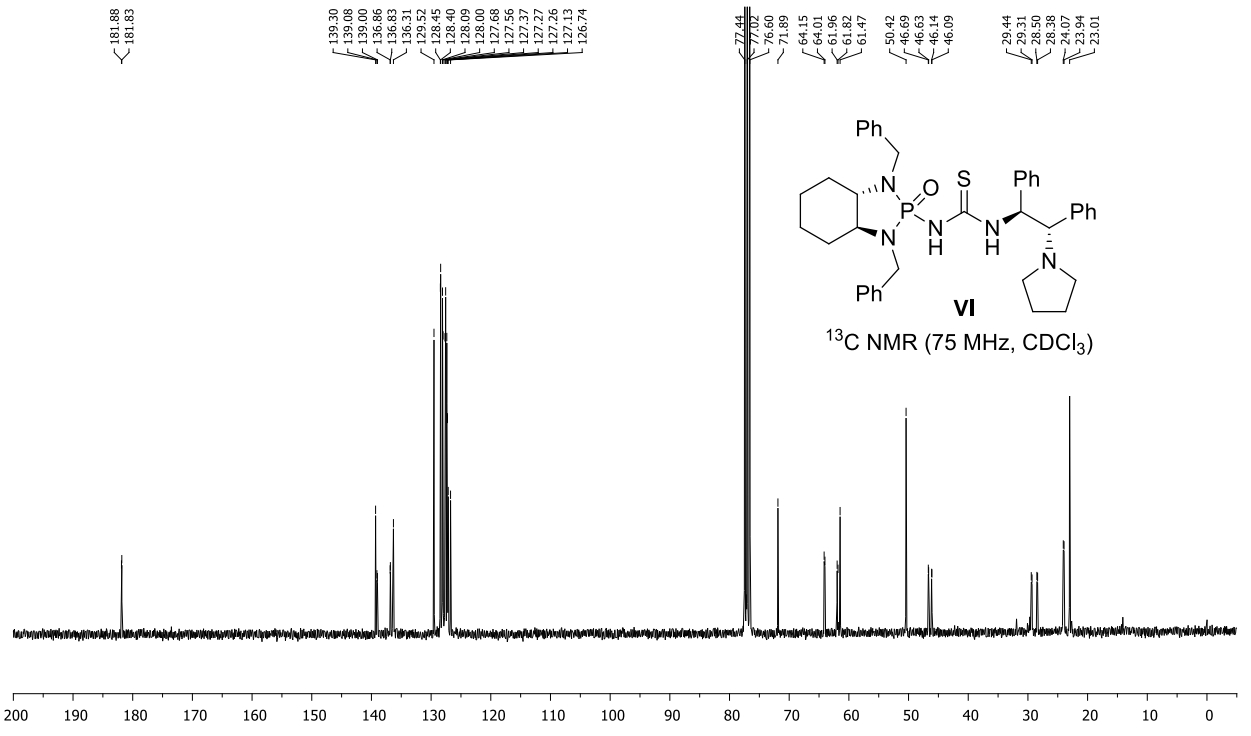


^{13}C NMR (75 MHz, $CDCl_3$)

4.10 Selected HPLC traces:

Memorial University

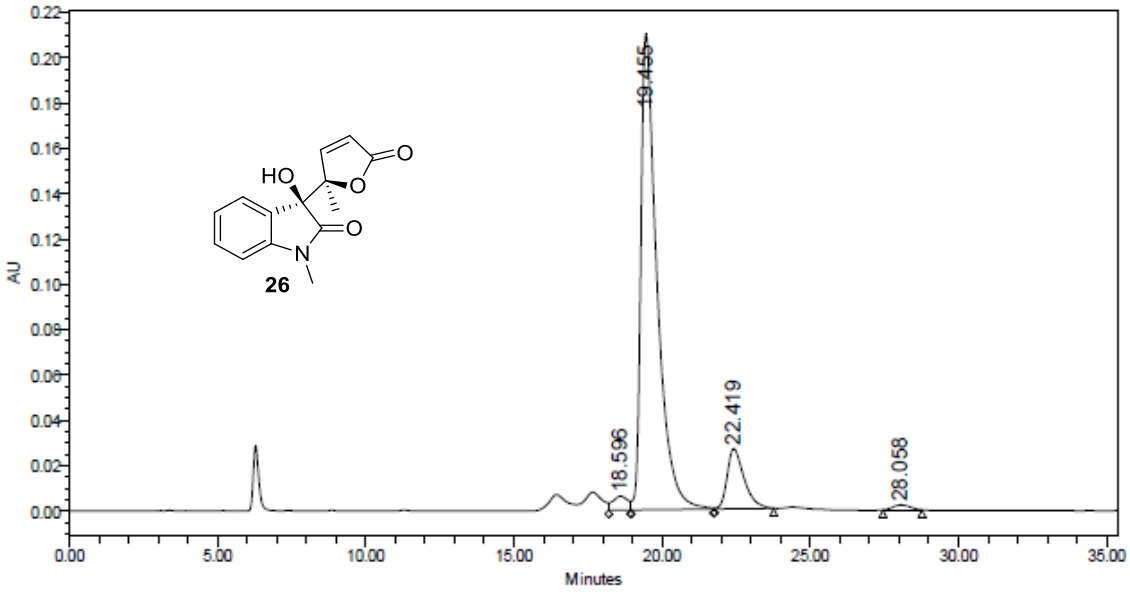
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-08-33 req	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	29/05/2019 1:28:35 PM NDT
Vial:	1	Acq. Method:	IA 90%HEX 10%IPA
Injection #:	1	Date Processed:	29/05/2019 2:01:42 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	50.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	18.596	215412	2.32	6109	2.50
2	19.455	7938734	85.40	209753	85.76
3	22.419	1054253	11.34	26493	10.83
4	28.058	87471	0.94	2222	0.91

Report Method: Individual Control Report

Page: 1 of 1

Printed: 29/05/2019

2:04:23 PM Canada/Newfoundland

Memorial University

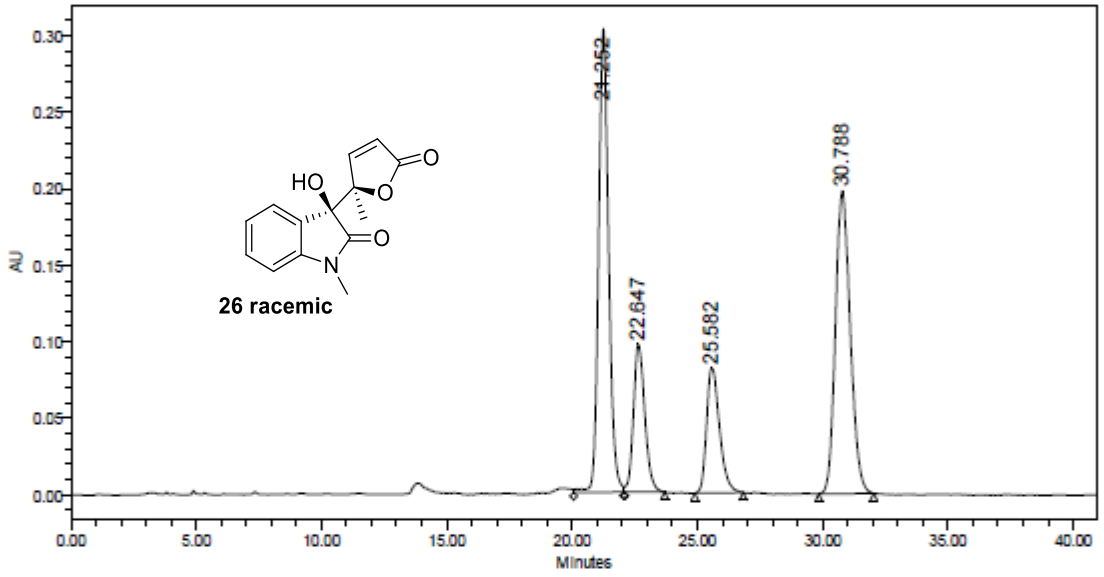
Project Name Ritesh

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	RAA-08-145 B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	05/09/2019 3:54:41 PM NDT
Vial:	1	Acq. Method:	IA 90%HEX 10%IPA
Injection #:	1	Date Processed:	03/03/2020 5:16:13 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	50.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
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2	22.647	3034934	13.46	96563	14.23
3	25.582	2930804	13.00	81409	12.00
4	30.788	8144021	36.11	197823	29.15

Report Method: Individual Control Report

Page: 1 of 1

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Chapter 5

Conclusions

5.1 Summary of the thesis

Novel phosphoramide-aminothiourea catalysts were synthesized and examined in selected vinylogous Mannich reactions. Reactions of piperidine based iminium ion precursors with various nucleophiles were examined in the presence of the phosphoramide-thiourea catalysts as well as other bifunctional catalysts such as aminothioureas and aminosquaramides (Chapter 1). Many of the reactions that were examined either did not provide the required product or provided unwanted byproducts arising from side reactions of the iminium ions generated *in situ*. The precise reasons for the failure of the vinylogous Mannich reaction are not known at this time.

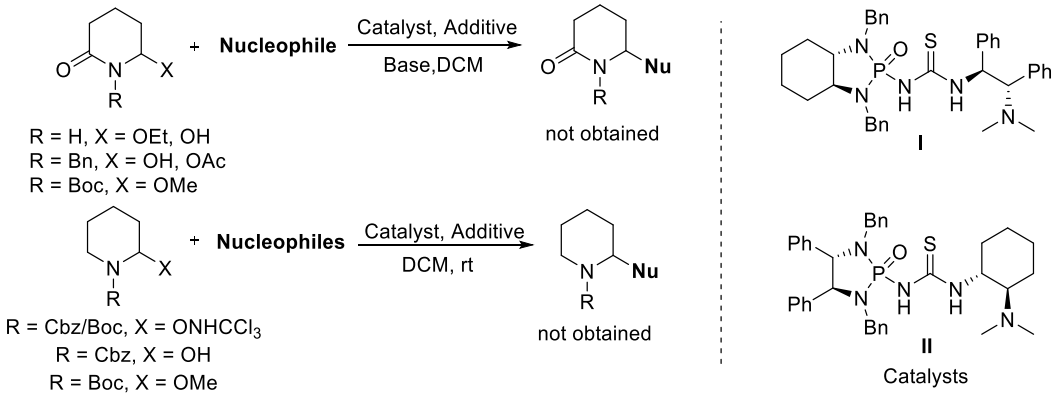


Figure 5.1 Attempted reactions of piperidine based iminium ion precursors with different nucleophiles

The Mannich reaction of indoles and *in-situ* generated iminium ions was also examined. Although some of these reactions proceeded with high enantioselectivity, small changes in the substitution of the indole nucleus at sites remote to the reaction site had a drastic, and detrimental effect on the enantioselection. Details of these studies are described in Chapter 1 of the thesis.

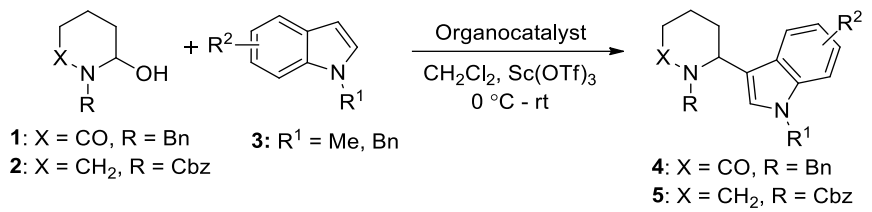


Figure 5.2 Mannich reactions of *N*-alkyl indoles and piperidine based iminium ion precursors

The enamine mediated Michael addition of cyclic ketones **6-8** and α,α-disubstituted aldehydes **(19** and **20)** to *in situ* generated α -nitrostyrenes (**9**, **10** and **21**) proceeds with moderate to good levels of 1,3-asymmetric induction. In case of cyclic ketones, a (*S*)-proline derived diamine **11** was found to be the optimal catalyst and in case of cyclic aldehydes (*S*)-proline **22** gave the best result. The optimized conditions were employed in the study of the scope of the reaction with a variety of cyclic ketones and aldehydes with various precursor of α -nitrostyrenes and provides access to enantiomerically enriched γ-aryl-γ-nitro ketones **(12-18)** and γ-aryl- γ-nitro aldehydes **(22-26)**. The Michael adducts were obtained with moderate diastereoselectivities (1:1 to 1.9:1) and moderate to good enantioselectivities (59-89%). Details of these studies are described in Chapter 2 of the thesis.

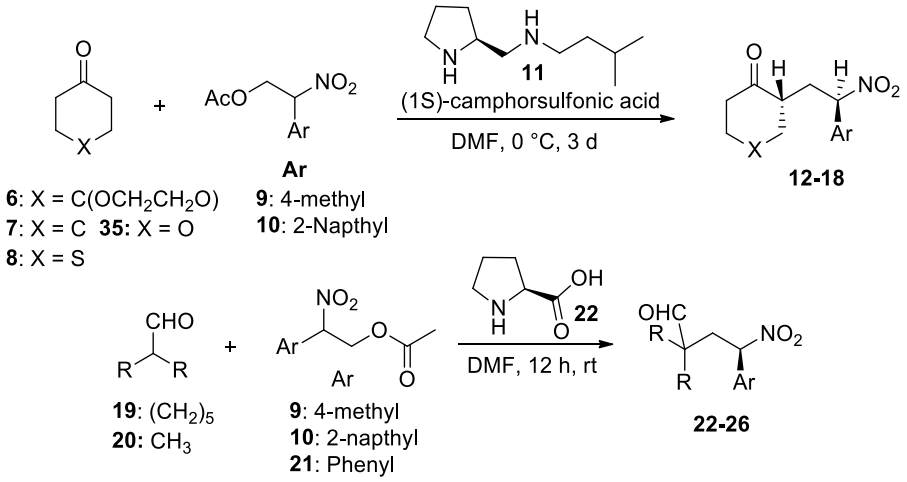


Figure 5.3 Organocatalyzed reaction of cyclic ketones and aldehydes with 2-nitro-2-arylethyl acetates

A two-step synthesis of 3-aryl-5-arylidene tetronates **29** was developed from diazotetronic acid **27** as the starting material. This synthetic approach follows highly stereoselective aldol condensation of **27** with a variety of aliphatic or aromatic aldehydes under optimized conditions ($TiCl_4$, 2,4,6-collidine) to provide (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones **28** in excellent yields (8 examples, Scheme 5.1) as single diastereomers. The aryl substituents at C-3, required in the targeted pulvinones, were installed by employing undirected, intermolecular C-H insertion reactions.

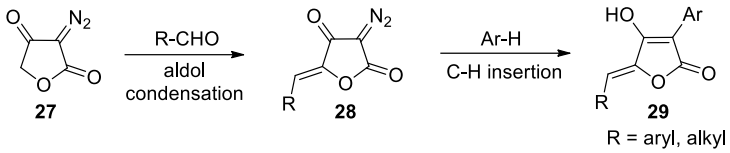
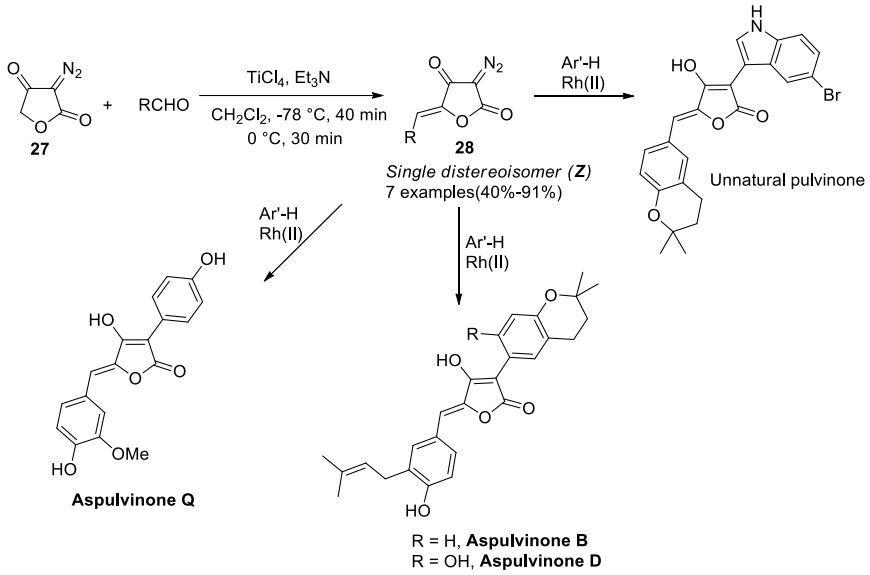


Figure 5.4 A two-step strategy for 3-aryl-5-arylidene tetronates

The utility of the methodology was demonstrated by application in the synthesis of naturally occurring aspulvinones (**B**, **D**, and **Q** Scheme 5.1) as well as non-natural pulvinones.



Scheme 5.1

This strategy provides the shortest route to functionalized tetronates and has potential for the rapid synthesis of focused libraries of aspulvinone-like natural product analogues (Scheme 5.1). Details of this study are described in Chapter 3.

An organocatalytic direct vinylogous aldol reaction of α-angelica lactone **32** with isatins was developed by employing a novel series of phosphoramide-aminothiourea catalysts. A range of chiral 3-substituted 3-hydroxyindoles with congested, vicinal tetrasubstituted stereocenters were obtained in up to 25% yield, 20:1 d.r. and 77% ee.

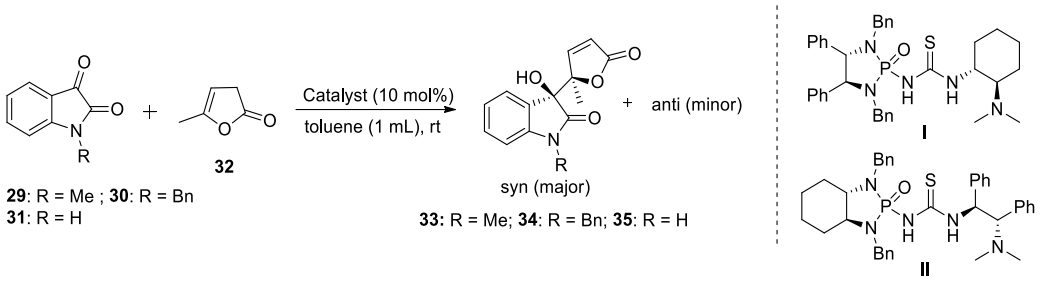


Figure 5.5 Organocatalytic Direct Vinylogous Aldol Reaction of isatin and α-angelicalactone **32**

Details of this study are described in Chapter 4.

5.2 Future work

The use of phosphoramide-thiourea catalysts (**I** and **II**) in the addition of indole nucleophiles to *N*-Cbz-2-hydroxy piperidine **36** is a possibility.

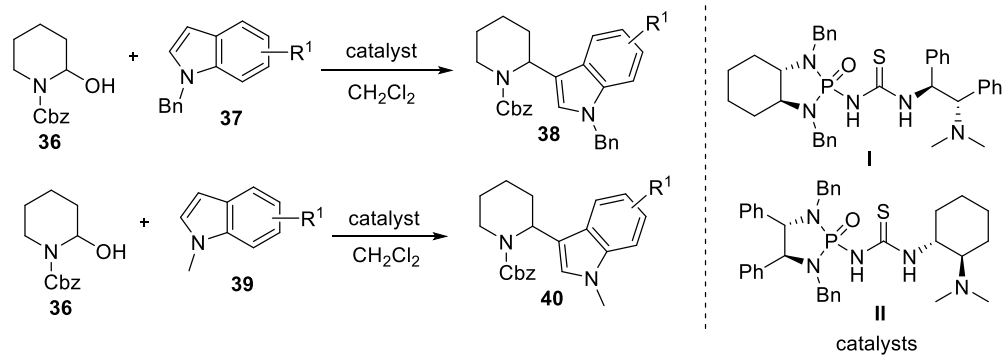


Figure 5.6 Reaction of iminium ion precursors with *N*-alkyl indoles

A direct vinylogous aldol reaction of *N*-alkyl isatins with α-angelicalactone was developed for the construction of 3-substituted 3-hydroxyindoles intermediates. These intermediates have received considerable attention because of their biological importance and the occurrence of these motifs in several bioactive indole derivatives[1,2] (Chapter 4). Results of the direct vinylogous aldol reaction are promising and future efforts will focus on improving the yield and the enantioselectivity of the reaction. These studies are ongoing in the Pansare group.

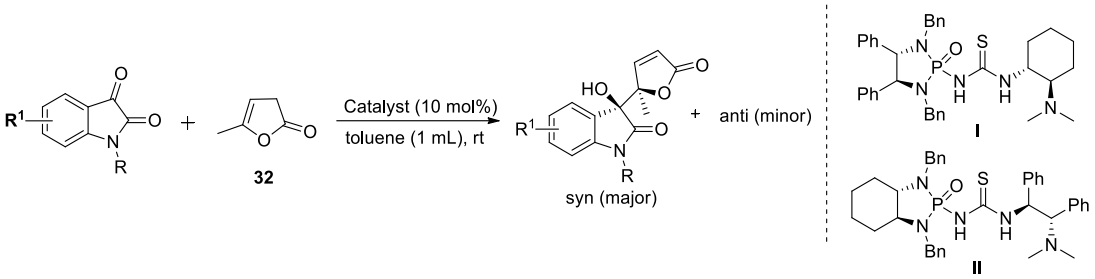


Figure 5.7 Asymmetric Vinylogous Aldol Reaction of α-Angelica lactone **32** and Isatin

The conversion of aldol product into spirocyclic indole such as **43** via the intermediacy of the amino compounds **42**. The spirocyclic indole motif is found in numerous naturally occurring alkaloids and pharmaceutically active compounds (Chapter 4).

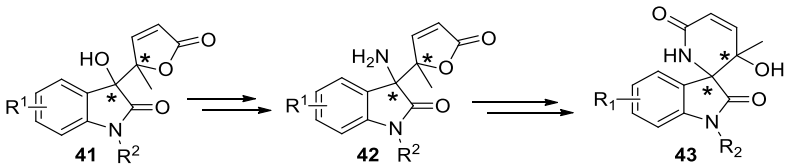


Figure 5.8 Conversion of Aldol adducts into spirocyclic core compounds

It may be noted that the conversion of 3-alkyl-3-hydroxy-2-oxindoles such as **41** to the corresponding 3-alkyl-3-amino-2-oxindoles **42** is well known,[3] but a diastereoselective version of this reaction is not reported.

5.3 References:

1. (a) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett*. **2006**, *8*, 507. (b) Alcaide, B.; Almendros, P.; Rodriguez- Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346.
2. (a) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677. (b) Chen, G.; Wang, Y.; He, H.; Gao, S.; Yang, X.; Hao, X. *Heterocycles* **2006**, *68*, 2327. (c) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. *J. Org. Lett.* **2006**, *8*, 2715.
3. Piemontesi, C.; Wang, Q.; Zhu. *J. Org. Biomol. Chem*. **2013**, *11*, 1533.