UNIVERSITY OF CALIFORNIA,
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Synthesis of Epidithiodioxopiperazine Analogues and the Development of a Copper-Catalyzed Stereodivergent 1,3-Dipolar Cycloaddition Reaction

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Chemistry

by

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Thesis Committee:
Professor Larry Overman, Chair
Professor Elizabeth Jarvo
Professor Sergey Pronin

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Dedication

for my grandfather

Eugene Behun

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Abstract of the Thesis

Synthesis of Epidithiodioxopiperazine Analogues and the
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By

Mary C. Walton

Master of Science in Chemistry

University of California, Irvine, 2015

Professor Larry E. Overman, Chair

In Chapter 1, epipolythiodioxopiperazine (ETP) natural products and a short synthesis of novel ETP analogues are introduced. Analogue synthesis and structure-activity relationship studies of their anticancer activity are described.

In Chapter 2, studies toward the development of a catalytic, diastereoselective, and enantioselective 1,3-dipolar cycloaddition (1,3-DC) reaction to improve upon the synthesis of ETP analogues are described. Over 75 different ligands were tested for their effectiveness in accomplishing this goal. A trend between catalyst electronic structure and the reaction diastereoselectivity was discovered where the use of an electron-deficient phosphite ligand resulted in a highly endo adduct-selective reaction. Alternatively, when a bulky electron-rich phosphine was used, the diastereoselectivity reversed to favor the exo cycloadduct.

In Chapter 3, the generality of the diastereodivergent 1,3-DC reactions are explored by investigating aryl imine starting materials with different electronic properties as well as different dipolarophiles. Computational studies performed by our collaborators at UCLA are also described. It was shown that methacrylonitrile is the ideal dipolarophile to exhibit the dramatic changes in diastereoselectivity depending on the ligand used in the catalytic 1,3-DC reaction.

Chapter 1: Synthesis and Biological Testing of Novel Epidithiodioxopiperazine Derivatives

1.1 Introduction

Epipolythiodioxopiperazine (ETP) natural products are a class of alkaloids with intriguing structural features and diverse biological activities.[1] Their general structure is described by a 2,5-dioxopiperazine core[2] with a bridging polysulfide unit, where in natural sources, the number of sulfur atoms can range between two and four (**1.1**, Figure 1.1). ETPs are amino acid-derived[3] secondary metabolites that are isolated from filamentous fungi.[4] While the role of ETP secondary metabolites is presently not well understood, the variety of ETP bioactivities as well as their isolation from a phylogenetically diverse range of fungi[5] suggests their importance in the defense and survival of the organisms that produce them. Recent studies have described a broad range of bioactivities attributed to ETPs, and their potent anticancer activity is of particular interest.[1] The complex and diverse array of structural features of ETPs, as well as the underexplored reports of structure-activity relationship studies,[6] have intrigued organic chemists to direct synthetic efforts toward this unique class of alkaloids.

1.1.1 ETP Natural Products' Mechanisms of Toxicity

Weindling reported the first isolated ETP natural product, gliotoxin (**1.2**, Figure 1.1), in 1932.[7] Since its discovery, gliotoxin has remained one of the most studied ETP alkaloids in terms of its structure,[8] synthesis,[9,10] and biological activity.[11] Similarly, ETPs chaetocin A[12] (**1.3**) and chaetomin[13] (**1.4**) have been used to elucidate the mechanisms of ETP toxicity, which have been attributed to the labile bridging disulfide moiety of these natural products.[14,15] Three common mechanisms of toxicity have been described: (1) Generation of reactive oxygen species

via redox cycling,[16] (2) formation of mixed thiol species by thiol-disulfide exchange with essential thiol groups on proteins,[17] and (3) chelation and extrusion of metal cofactors from proteins (Figure 1.2).[18]

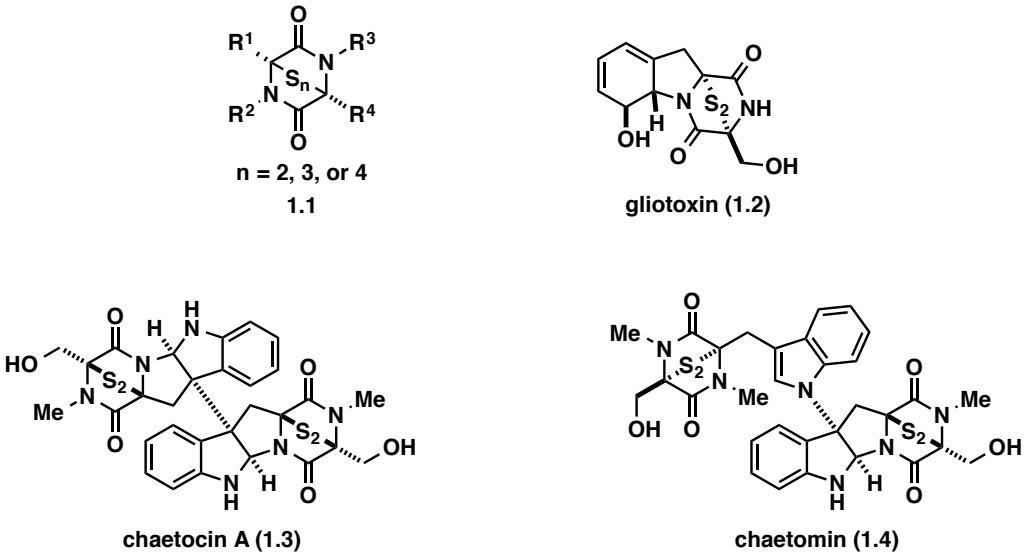


Figure 1.1. Generic Structure of ETP Alkaloids and Three Well Studied ETP Natural Products

The internal disulfide bridge of an ETP can be reduced in vivo to the corresponding dithiol species. This reduction is thought to occur by glutathione,[19] a ubiquitous intracellular tripeptide that has antioxidant properties because of its ability to undergo redox cycling between a reduced form (GSH) and a dimeric oxidized form (GSSG) (Figure 1.2A).[20] The resulting reduced ETP is aerobically unstable and undergoes facile single-electron oxidation by molecular oxygen.[21] This process results in reformation of the parent ETP disulfide bridge, but also generates superoxide anion radicals. Further processing of superoxide anion radicals results in the formation of highly reactive hydrogen peroxide or hydroxyl radicals, which cause oxidative cellular damage.[22] Studies have shown that rapid oxidative cell death occurs in cells treated with ETP and a large excess of GSSG, which is thought to promote formation of reduced ETP,

thereby supporting this proposed mechanism of ETP toxicity.[23] The redox properties of ETP analogues therefore suggest a possible mechanism of cellular damage and death.

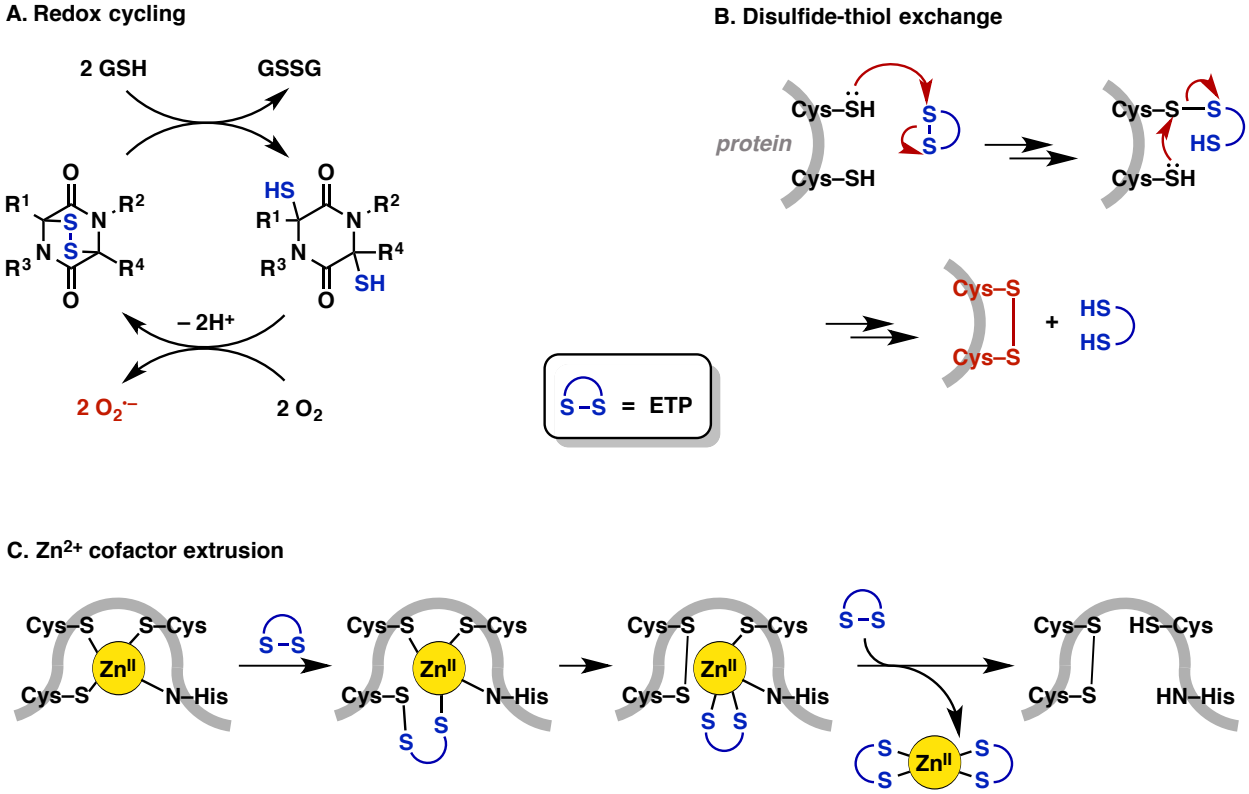


Figure 1.2. Mechanisms of ETP Toxicity

Additionally, the episulfide moiety of ETP analogues is subject to nucleophilic attack by thiol groups on proteins (Figure 1.2B). Such attack results in the formation of mixed polysulfide species, which may be directly toxic, or, in the presence of a second nearby thiol residue, can result in extrusion of reduced ETP while forming an internal polysulfide bridge within the protein. Both of these mechanisms result in detrimental changes to the protein's tertiary structure, which may result in loss of activity. Radiolabeling studies have demonstrated that gliotoxin forms protein adducts with bovine serum albumin,[14c] creatine kinase,[24] viral RNA polymerase $3D^{pol}$,[25] alcohol dehydrogenase,[11a] farnesyl transferase,[26] and transcription factor

NF-κB.[27] Together with loss of function data, these studies demonstrate that gliotoxin inactivates certain proteins by the formation of mixed thiol adducts.

The sulfur atoms of ETP natural products have also been shown to chelate Zn^{2+} ions in the CH1 domain of p300 protein (Figure 1.2C).[28,29] Schofield and coworkers studied this interaction specifically by treating CH1 with increasing equivalents of gliotoxin.[29] It was observed that the Zn^{2+} cofactor was completely extruded from the protein when treated with a large excess of gliotoxin (20 equiv). Partial zinc ejection was observed by treating CH1 with structurally simplified synthetic ETPs, demonstrating that the observed effect is attributed to the simple ETP disulfide core **1.1**. Toxic effects of ETPs were relieved when zinc supplementation was enforced.[29] This observation is consistent with reports of reversing toxic effects in grazing animals affected by sporidesmin[30] poisoning.[31] While this third potential mechanism of ETP toxicity is comparatively less explored, the interaction of sulfur with metal cofactors may help explain the selective toxicity profiles of ETPs.

1.1.2 Anticancer Activity of ETP Natural Products

While the toxicity of natural ETPs gliotoxin, chaetomin, and chaetocin A is broad, recent studies have elucidated specific anticancer activity of ETP alkaloids. ETPs have been shown to be important inhibitors of two distinct pathways: Hypoxic cell signaling and epigenetic modifications dictated by histone methylation. In hypoxic cellular microenvironments, such as those in solid tumors, levels of the protein hypoxia-inducible factor 1-α (HIF-1α) accumulate. HIF-1α is translocated into the nucleus and binds to hypoxia response elements, along with proteins ARNT, CREB, p300, and cJUN. This assembly enables the transcription of genes that lead to the production of proteins that are essential for cell survival in a hypoxic environment.[32] As mentioned in the previous section, gliotoxin has been shown to extrude Zn^{2+} ions from the

CH1 domain of protein p300, resulting in HIF-1α/p300 binding inhibition.[29] Disruption of HIF-1α/p300 binding exhibited by ETPs has demonstrated antiproliferative effects in in vivo studies.[6a,33] Therefore, the development of HIF inhibitors is an attractive target for anticancer therapy.[34]

Chaetocin A has been the subject of many studies as a result of its documented inhibition of the SUV39 family of histone methyl transferases.[35,36] Histone methyl transferases are important enzymes involved in epigenetic regulation of chromatin organization and gene expression, making them attractive targets for anticancer therapy.[37] For example, G9a,[38] a histone lysine methyl transferase (HKMT), has been shown to be inhibited by a variety of natural and synthetic ETPs in vitro.[6c,39] Additionally, chaetocin A has been demonstrated to form covalent adducts with HKMT G9a in vitro.[40] A hypothesis for the selective HKMT inhibition of ETPs is proposed to be due to their ability to coordinate to Zn^{2+} ions; Zn^{2+} ions have been reported to be present in HKMTs SU(VAR)3–9 and G9a, but not SET7/9, thus positively correlating with the ETP HKMT toxicity profile.[1b] Studies directly linking ETP anti-HKMT activity to anticancer activity are, however, yet to be disclosed.

1.2 Synthesis and Biological Testing of Novel ETP Analogues

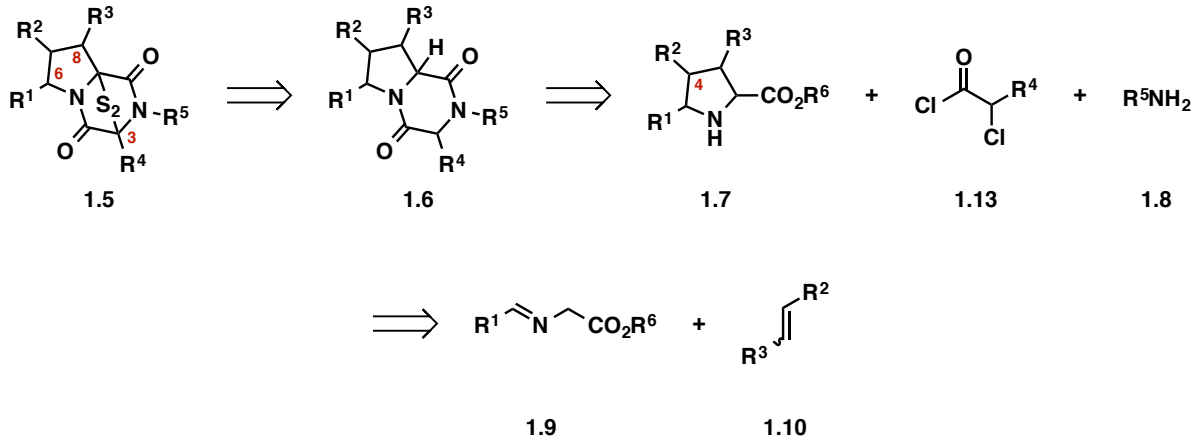
The Overman group became interested in the synthesis of ETP natural products to not only address the challenges associated with their structural complexity[41] but also because of their promising anticancer activity.[6e,42] As described previously, natural ETP alkaloids exhibit potent anticancer activity, but their therapeutic applications are limited as a result of their broader toxicity.[34b] We hypothesized that more selective anticancer activity could be accomplished by truncating the ETP scaffold to focus on the activity-bearing polysulfide bridge. Consequently,

a short and modular synthesis of unnatural ETP analogues was developed, and collaboration was established with the City of Hope National Medical Center in order to explore SAR trends.

1.2.1 Overview of the Synthetic Route

Because of the conservation of a fused pyrrolidine-dioxopiperazine core in ETP natural products with potent anticancer activity (Figure 1.1), our goal was to develop structurally simplified synthetic ETP analogues that contain this motif (**1.5**, Scheme 1.1). Retrosynthetic analysis of this structure led us to investigate late-stage installation of the labile polysulfide bridge. The dioxopiperazine core **1.6** was proposed to be easily accessed by acylation of a C2-ester-substituted pyrrolidine **1.7**, with ring closure being accomplished through reaction with a primary amine **1.8**. Substituted pyrrolidines are routinely synthesized by 1,3-dipolar cycloaddition reactions between imines **1.9** and electron-deficient olefins **1.10**.

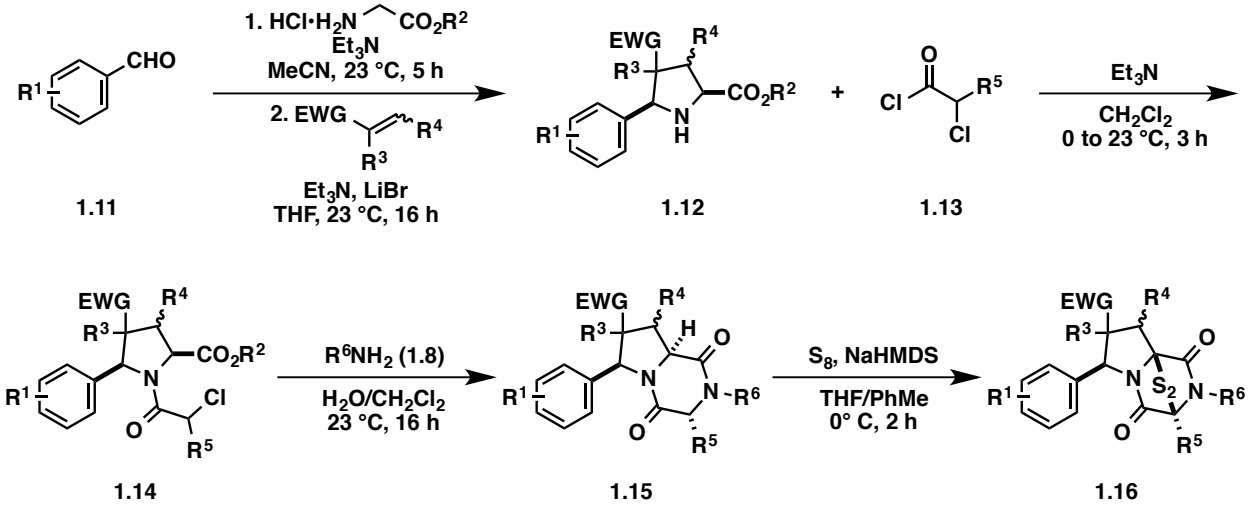
Scheme 1.1. Retrosynthetic Analysis for Novel ETP Analogues



A two-step process to access substituted pyrrolidines was developed by first preparing imines from condensation between aromatic aldehydes **1.11** and glycine ester salts in acetonitrile (Scheme 1.2). Subsequent 1,3-dipolar cycloaddition with electron-deficient olefins was promoted by the addition of superstoichiometric LiBr and Et_3N in THF,[43] affording pyrrolidine products **1.12** harboring C4 substitution. The dioxopiperazine core was synthesized by acylation of the

secondary amine with 2-chloroacetyl chlorides **1.13** to generate reactive α-chloroamides **1.14**, which underwent facile cyclization with primary amines **1.8** to afford dioxopiperazines **1.15**. Successful installation of the sulfide bridge to access epidithiodioxopiperazines **1.16** was accomplished utilizing conditions described by Nicolaou and coworkers.[44] Using this route, over 70 unique ETP derivatives have been synthesized and their anticancer activity has been tested.

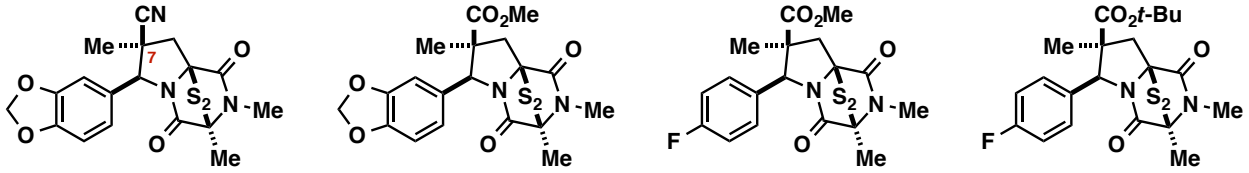
Scheme 1.2. Five-Step Sequence to Access Highly Substituted ETP Analogues



1.2.2 SAR Trends

The development of a short and modular synthesis of novel ETP analogues led to us to quickly prepare a number of diverse products that were subsequently screened for anticancer activity against two common cancer cell lines, PC3 human prostate DU145 and human melanoma A2058.[42] Early in our SAR studies, we identified ETP **1.17** as a particularly potent analogue against the tested cancer cell lines (Figure 1.3). The importance of nitrile substitution at the C7 position was illustrated by comparing the biological data of ETP analogues **1.17** and **1.18**, where methyl ester-substituted congener **1.18** exhibited no observable cell growth inhibition at the tested concentrations. Additional acrylate-derived ETPs **1.19** and **1.20** were inactive against DU145 and A2058 cancer cell lines. Synthetic efforts were then directed toward accessing

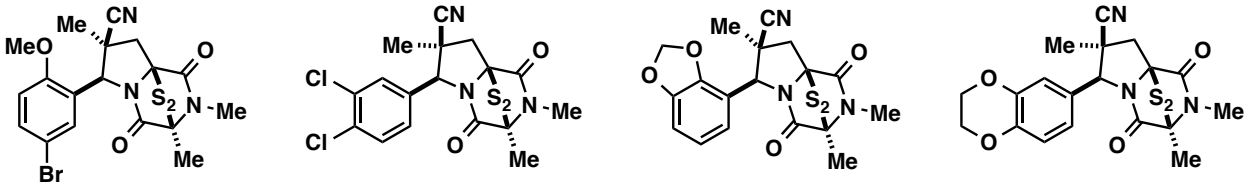
C7-nitrile-substituted ETPs derived from the pyrrolidine products of a 1,3-dipolar cycloaddition between imines **1.9** and methacrylonitrile.



IC_{50} Values	IC_{50} Values	IC_{50} Values	IC_{50} Values
DU145: 100 nM A2058: 60 nM	DU145: >5000 nM A2058: >5000 nM	DU145: >5000 nM A2058: >5000 nM	DU145: >5000 nM A2058: >5000 nM

Figure 1.3. Influence of C7 Substitution on Anticancer Activity

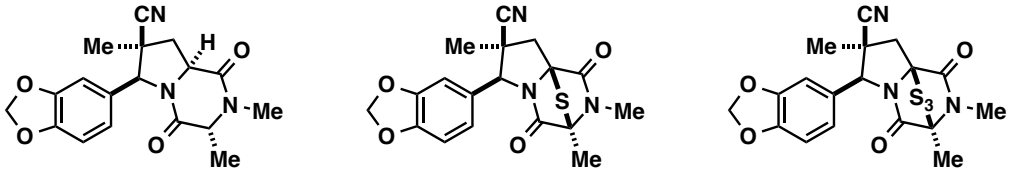
After demonstrating the importance of the C7 nitrile functionality for the biological activity of ETP analogues, a number of such derivatives were synthesized. The effect of aromatic substitution on ETP anticancer activity was explored by using various aromatic aldehydes **1.11** (Scheme 1.2). 5-Bromo-2-methoxyphenyl ETP **1.21** exhibited IC_{50} values of 3700 nM and 2000 nM against DU145 and A2058 cell lines, respectively (Figure 1.4). 3,4-Dichlorophenyl ETP **1.22** displayed 5- and 15-fold decreases in potency against DU145 and A2058 cell lines compared to **1.17**, respectively, suggesting that oxygen substitution is important to the observed potency of analogue **1.17**. 2,3-Methylenedioxyphenyl ETP **1.23** is not as potent as 3,4-methylenedioxyphenyl analogue **1.17**, indicating that oxygen functionality at positions C3 and C4 on the aromatic ring are necessary to access ETPs of high potency. The importance of the methylene bridge of **1.17** was demonstrated by synthesizing derivative **1.24**, which possesses an ethylene bridge; **1.17** was twice as potent as **1.24** against both of the tested cell lines. As a result, future ETP analogue syntheses focused on the use of piperonal as the parent aldehyde (Scheme 1.2).



1.21	1.22	1.23	1.24
IC_{50} Values	IC_{50} Values	IC_{50} Values	IC_{50} Values
DU145: 3700 nM A2058: 2000 nM	DU145: 500 nM A2058: 880 nM	DU145: 520 nM A2058: 400 nM	DU145: 200 nM A2058: 120 nM

Figure 1.4. Effects of Aromatic Substitution Patterns on ETP Anticancer Activity

The effect of the number of sulfur atoms in the polysulfide bridge on ETP cytotoxicity was investigated (Figure 1.5). The anticancer activity of dioxopiperazine **1.25** and monosulfide **1.26** were tested against the prostate cancer and melanoma cell lines and it was observed that both compounds lacked activity. Trisulfide **1.27**, which was isolated as a byproduct in the sulfenylation reaction to access disulfide **1.17**,[45,46] exhibited IC_{50} values of 460 nM and 240 nM against DU145 and A2058 cell lines, respectively. As a result, future synthetic efforts were focused on accessing the more potent ETP disulfide products.

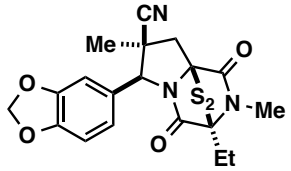


1.25	1.26	1.27
IC_{50} Values	IC_{50} Values	IC_{50} Values
DU145: >5000 nM A2058: >5000 nM	DU145: >5000 nM A2058: >5000 nM	DU145: 460 nM A2058: 240 nM

Figure 1.5. Anticancer Activity of ETP Derivatives with Different Polysulfide Bridge Lengths

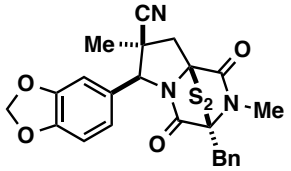
Utilizing different 2-chloroacetyl chlorides **1.13**, ETPs **1.28** and **1.29** were synthesized with ethyl and benzyl substitution at position C3, respectively (Scheme 1.2). Comparing the IC_{50} values of analogues **1.28** and **1.29** to those of lead compound **1.17**, it was determined that

incorporation of larger alkyl groups at position C3 resulted in decreased potency against both of the tested cell lines (Figure 1.6). Additionally, various primary amines **1.8** were employed to synthesize ETPs **1.30**–**1.33** (Scheme 1.2). Products derived from ethylamine (**1.30**) and cyclopropylamine (**1.31**) exhibited slightly higher IC_{50} values than derivative **1.17**. *N*-Allyl and *N*-butyl ETPs **1.32** and **1.33** were even less potent than analogue **1.17** (Figure 1.7). The corresponding anticancer activities of these analogues demonstrate that smaller alkyl groups are tolerated at the N2 position, but substitution with larger allyl and *n*-butyl groups results in significantly increased IC_{50} values. While ETP **1.17** remains the most potent analogue tested to date, new analogues are still being synthesized in order to discover new ETP derivatives with potent anticancer activity.



1.28

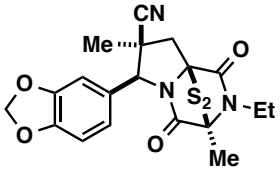
IC_{50} Values
DU145: 140 nM
A2058: 160 nM



1.29

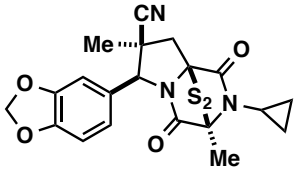
IC_{50} Values
DU145: 310 nM
A2058: 350 nM

Figure 1.6. Effect of C3 Substitution on ETP Analogue Anticancer Activity



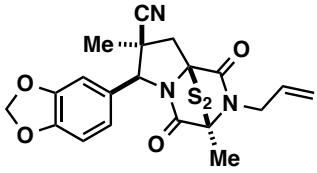
1.30

IC_{50} Values
DU145: 240 nM
A2058: 100 nM



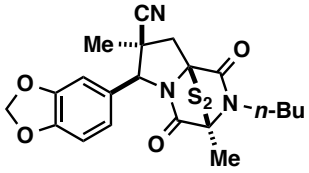
1.31

IC_{50} Values
DU145: 260 nM
A2058: 70 nM



1.32

IC_{50} Values
DU145: 520 nM
A2058: 200 nM



1.33

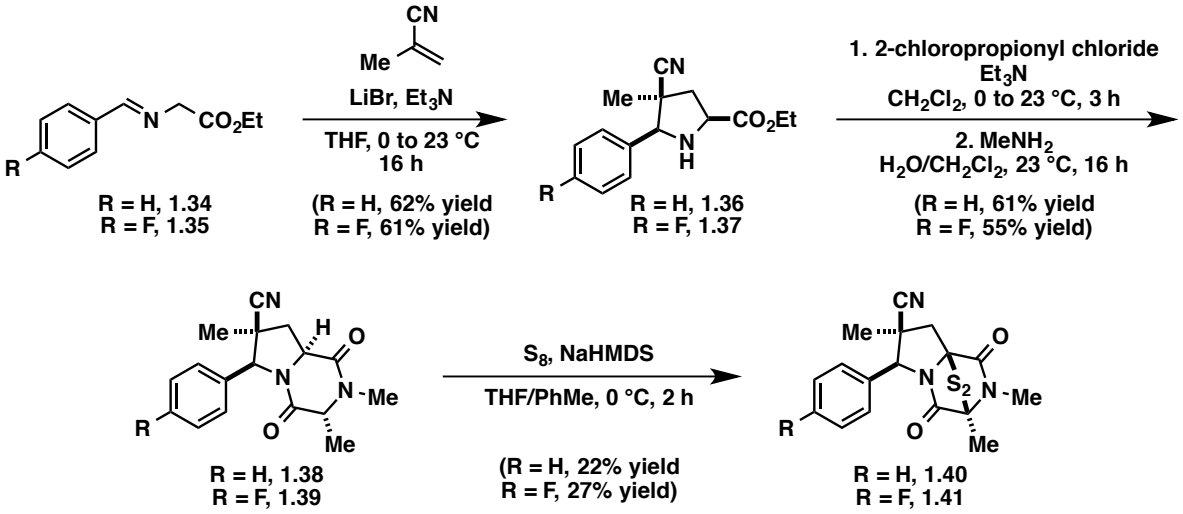
IC_{50} Values
DU145: 1200 nM
A2058: 820 nM

Figure 1.7. Alkyl Group Substitutions at the N2 Position

1.2.3 Substrate Synthesis

Using the route outlined in Scheme 1.2, three new nitrile-containing ETP analogues were synthesized for subsequent evaluation at City of Hope. The 1,3-dipolar cycloaddition between benzaldehyde-derived imine **1.34** and methacrylonitrile afforded pyrrolidine product **1.36** in 62% yield and a 3.3:1 endo:exo adduct ratio (Scheme 1.3). Endo pyrrolidine adduct **1.36** was carried forward in the synthesis:[47] Acylation with 2-chloropropionyl chloride and cyclization using aqueous methylamine afforded dioxopiperazine **1.38** in 61% yield over two steps, after trituration from MeOH. Disulfenylation of **1.38** with S_8 and NaHMDS afforded ETP **1.40** in 22% yield after tedious purification.[48] Similarly, ETP **1.41** was prepared in 9% overall yield from 4-fluorobenzaldehyde.

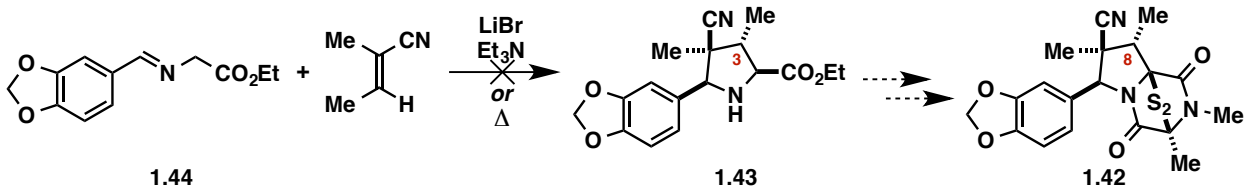
Scheme 1.3. Synthesis of ETPs 1.40 and 1.41



To broaden our SAR studies, the synthesis of C8-methyl-substituted ETP analogue **1.42** was pursued (Scheme 1.4). Previous experiments were attempted to directly access C3-methyl pyrrolidine **1.43** by 1,3-dipolar cycloaddition between imine **1.44** and 2-methyl-2-butenenitrile using the LiBr and Et_3N (Scheme 1.2); however, this resulted in recovery of starting material.[49]

A thermal 1,3-dipolar cycloaddition was then pursued, but was met without success.[50] This required a revision to the original synthetic plan in order to access desired ETP **1.42**.

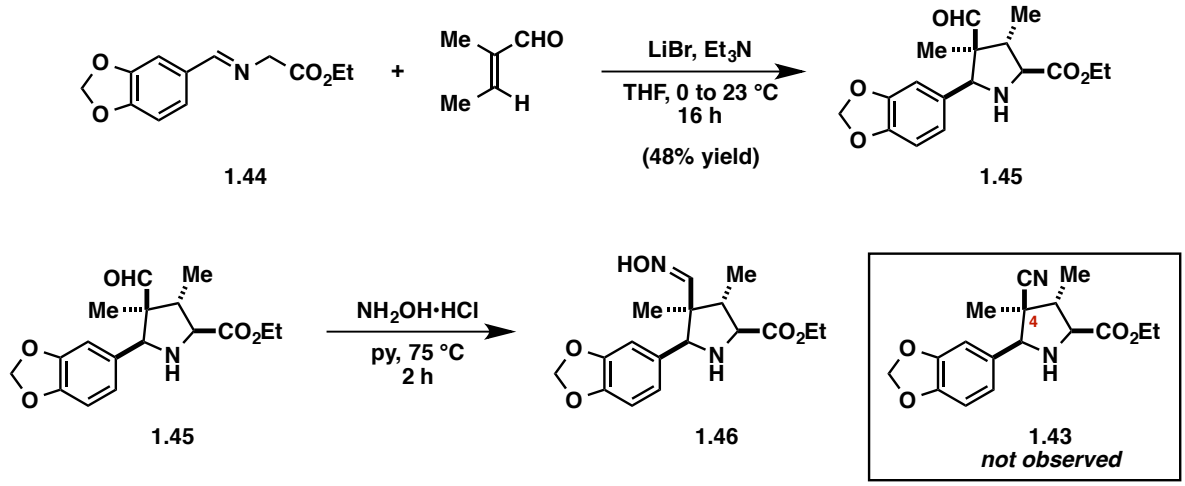
Scheme 1.4. Unsuccessful Strategies to Access Pyrrolidine 1.43



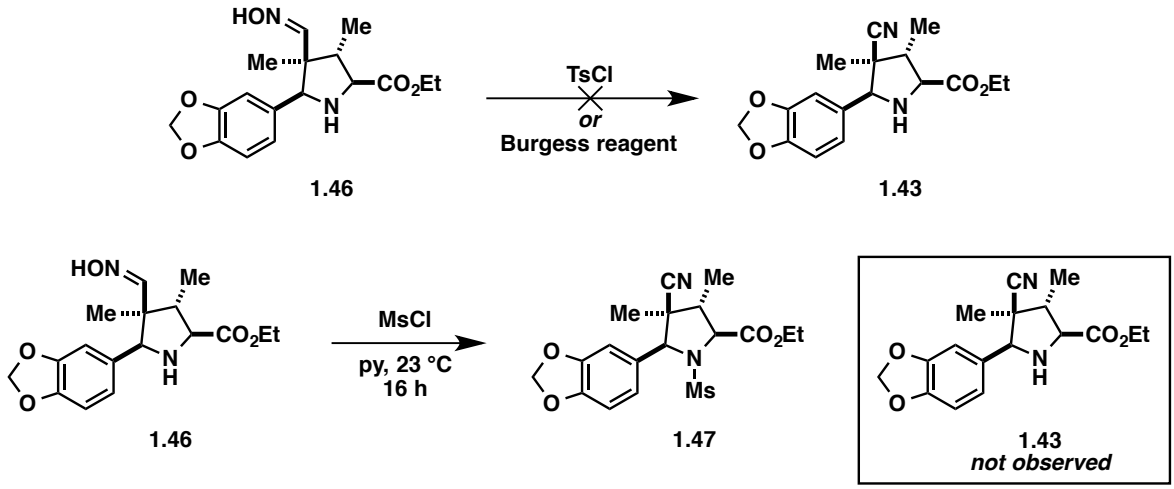
1.44 **1.43** **1.42**

A 1,3-dipolar cycloaddition was successfully achieved between imine **1.44** and *trans*-2-methyl-2-butenal, affording endo cycloadduct **1.45** in 48% yield and a 4:1 dr. While treatment of pyrrolidine **1.45** with hydroxylamine hydrochloride in DMSO did not directly access desired product **1.43**,[51] oxime **1.46** was synthesized by this method (Scheme 1.5). Next, dehydration conditions were investigated in order to access the desired nitrile functionality at the C4 position of the pyrrolidine ring. Dehydration was initially attempted using tosyl chloride (TsCl);[52] however, these conditions resulted in a complex mixture of unidentifiable products (Scheme 1.6). Similarly unproductive dehydration attempts were made using the Burgess reagent.[53] The use of mesyl chloride (MsCl) as a dehydrating agent promoted the desired transformation of the oxime to nitrile functionality,[54] but resulted in undesired mesylation of the secondary amine, affording *N*-Ms pyrrolidine **1.47**. Dehydration was ultimately accomplished by treating oxime **1.46** with an excess of 2-chloropropionyl chloride to afford α-chloroamide **1.48** with the desired nitrile functionality at C4 (Scheme 1.7). With the desired C4-methyl-substituted pyrrolidine core in hand, unpurified α-chloroamide **1.48** was treated with aqueous methylamine to afford dioxopiperazine **1.49** as a 2:1 mixture of epimers at C3. This mixture was carried forward in the disulfenylation reaction, affording ETP **1.42** in 3% yield over four steps.

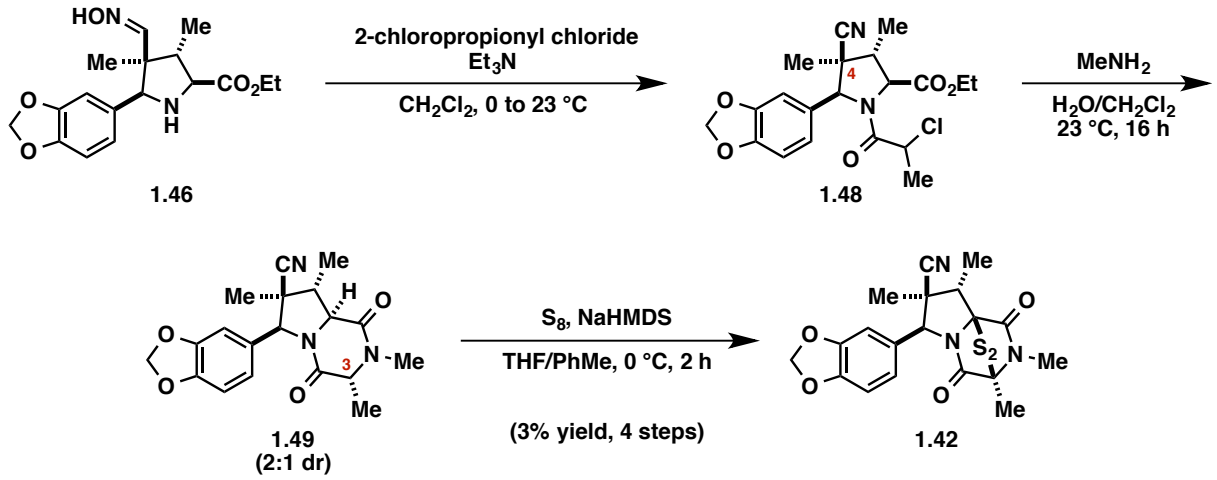
Scheme 1.5. Synthesis of Oxime 1.46



Scheme 1.6. Attempts to Access Pyrrolidine 1.43 by Dehydration of Oxime 1.46



Scheme 1.7. Completion of ETP 1.42



1.2.4 Determination of ETP Anticancer Activity

Growth inhibition assays were performed at the City of Hope National Medical Center by our collaborators Dr. Sangkil Nam and Dr. David Horne. Thus, the anticancer activities of over 70 ETP analogues **1.5** against PC3 human prostate DU145 and human melanoma A2058 cancer cell lines have been determined. The IC_{50} values of novel analogues **1.40**, **1.41**, and **1.42** were compared to those of lead compound **1.17** (Figure 1.8). Analogues **1.40** and **1.41** exhibited lower potency than ETP **1.17**, which supports our previous observations that 3,4-dioxy substitution on the aromatic ring is important in accessing high potency anticancer agents.[42] Finally, the installation of a methyl group at the C8 position resulted in dramatic increases in IC_{50} values for ETP **1.42** against the two cell lines. While analogues **1.40**, **1.41**, and **1.42** supplied us with important SAR data, ETP **1.17** still harnesses the most potent anticancer activity observed to date.

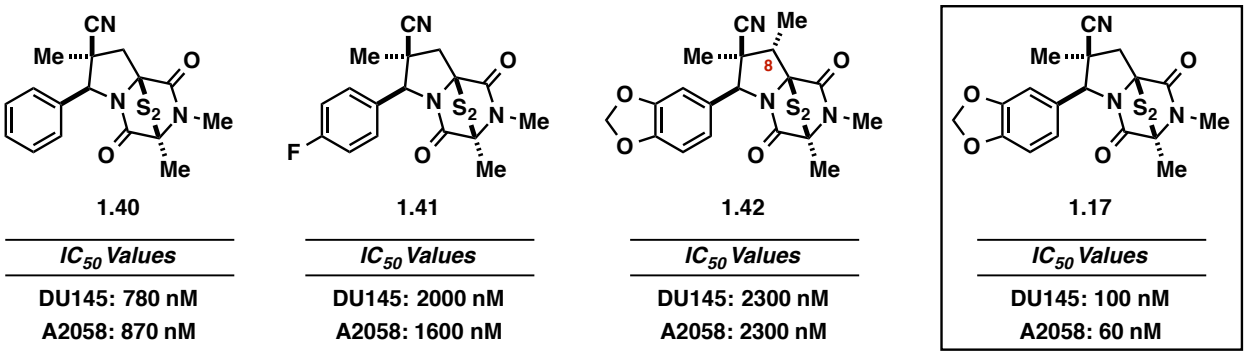


Figure 1.8. IC_{50} Values of ETP Analogues 1.40, 1.41, 1.42, and 1.17

1.3 Conclusion

Synthetic endeavors toward ETP natural products have been revived in recent years as a result of more detailed studies of their potent anticancer activity being described.[1] As the cytotoxic activity of ETPs has been elucidated to arise from the labile polysulfide bridge,[14,15] the Overman group pursued a study on accessing unnatural ETP analogues with increased potency with regard to anticancer activity while reducing broad toxicity.[42]

Using the short and robust ETP analogue synthesis developed by our group, three new ETP products were accessed. Congeners **1.40** and **1.41** were synthesized without incident, while C8-methyl ETP **1.42** demanded the use of an aldehyde in the 1,3-dipolar cycloaddition step. Consequently, the development of appropriate dehydration conditions was required to access the desired nitrile functionality at the C4 position of the resulting pyrrolidine core. The IC_{50} values of ETPs **1.40**, **1.41**, and **1.42** were determined at City of Hope to establish SAR trends in efforts to develop ETP analogues with potent anticancer activity.

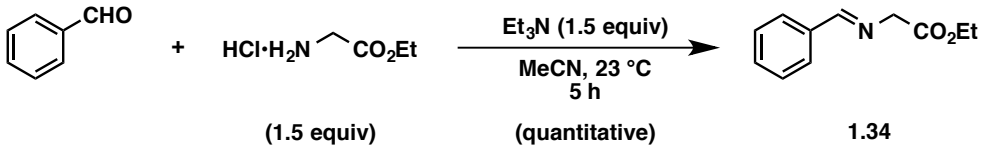
1.4 Appendix A: Experimental Procedures

1.4.1 Materials and Methods

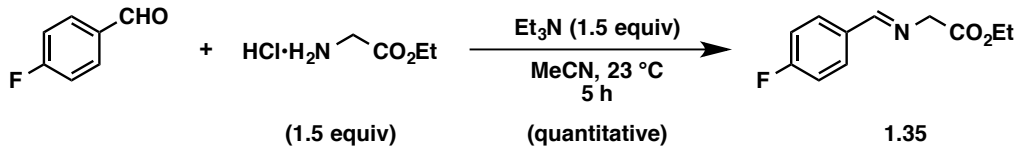
Unless stated otherwise, reactions were conducted in flame- or oven-dried glassware under a positive pressure of nitrogen (N_2) or argon (Ar) using anhydrous solvents (dried by passing through activated alumina columns under a positive pressure of Ar). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were conducted on EMD silica gel 60 F_{254} glass-backed plates (250 μm and 500 μm, respectively) and visualized by exposure to UV light (254 nm), or by Dragendorff–Munier or potassium permanganate staining. Flash chromatography was performed using forced flow of the indicated solvent system on EMD Geduran® silica gel 60 (particle size 0.040–0.063 mm). NMR spectra were recorded at 298 K on Bruker FT-NMR spectrometers at the indicated frequencies. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual deuterated solvent signals ($CDCl_3$). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant [*J*, reported in Hertz (Hz)], and integration. Splitting patters are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), apparent (app), and broad (br). Carbon multiplicity was determined by a combination of DEPTQ and HMQC experiments. Chemical shifts (δ) for ^{19}F NMR spectra are reported in parts per million (ppm) and referenced to the corresponding calibrated ^{1}H NMR spectrum. Infrared (IR) spectra were recorded on a Varian 640-IR spectrometer as thin films in CH_2Cl_2 on KBr plates and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the

UC Irvine Mass Spectrometry Facility with a Micromass LCT spectrometer. Melting points (mp) were determined on a melting point apparatus (Thomas Hoover, Uni-Melt) and are uncorrected. Abbreviations used can be found on the Internet at: http://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf.

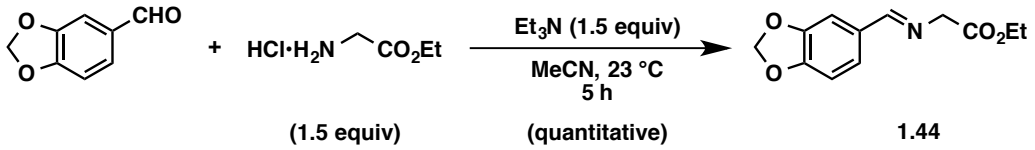
1.4.2 Synthesis of Imines



Ethyl (*E*)-2-(benzylideneamino)acetate (1.34). A 50 mL round-bottom flask was charged with a magnetic stir bar and glycine ethyl ester hydrochloride (525 mg, 3.75 mmol, 1.50 equiv). MeCN (4.2 mL, 0.6 M) and benzaldehyde (250 μL, 2.5 mmol, 1.0 equiv) were then added, followed by Et_3N (520 μL, 3.75 mmol, 1.50 equiv). The resulting heterogeneous mixture was vigorously stirred at 23 °C for 5 h. Concentration of the reaction mixture under reduced pressure afforded an amorphous colorless solid, which was transferred to a separatory funnel using CH_2Cl_2 (15 mL) and H_2O (30 mL). The layers of the resulting biphasic mixture were partitioned and the organic layer was extracted with H_2O (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford imine **1.34** (480 mg, quantitative yield) as a clear oil. Imine **1.34** was carried further in subsequent reactions without further purification.[55] ^1H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.79–7.77 (m, 2H), 7.47–7.40 (m, 3H), 4.40 (s, 2H), 4.24 (q, J = 7.2, 2H), 1.31 (t, J = 7.2, 3H).

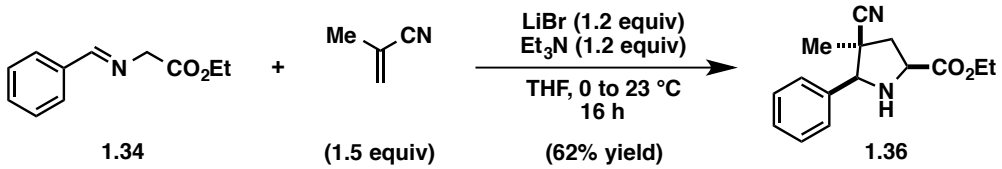


Ethyl (*E*)-2-((4-fluorobenzylidene)amino)acetate (1.35). According to the procedure described for the synthesis of imine **1.34**, imine **1.35** was prepared from 4-fluorobenzaldehyde (270 μL, 2.5 mmol, 1.0 equiv) and received as a light yellow oil (520 mg, quantitative yield). Imine **1.35** was carried further in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.78 (app dd, J = 8.6, 5.9, 2H), 7.11 (app t, J = 8.6, 2H), 4.39 (s, 2H), 4.24 (q, J = 7.2, 2H), 1.31 (t, J = 7.2, 3H).



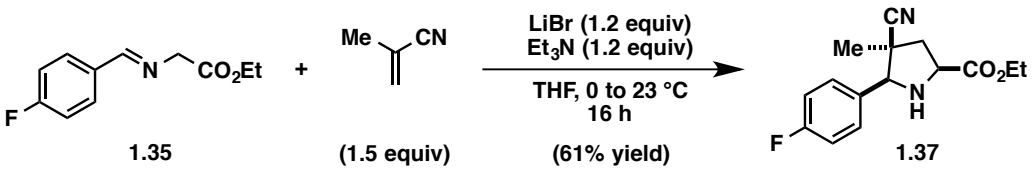
Ethyl (*E*)-2-((benzo[*d*][1,3]dioxol-5-ylmethylene)amino)acetate (1.44). According to the procedure described for the synthesis of imine **1.34**, imine **1.44** was prepared from piperonal (375 mg, 2.50 mmol, 1.00 equiv) and obtained as a light yellow oil[56] (588 mg, quantitative yield). Imine **1.44** was carried further in subsequent reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.41 (s, 1H), 7.15 (d, J = 7.9, 1H), 6.83 (d, J = 7.9, 1H), 6.01 (s, 2H), 4.35 (s, 2H), 4.23 (q, J = 6.8, 2H), 1.30 (t, J = 6.8, 3H).

1.4.3 Synthesis of Pyrrolidines

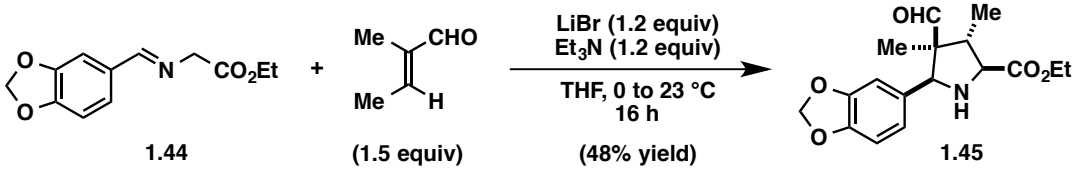


Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-4-methyl-5-phenylpyrrolidine-2-carboxylate (1.36). A 100 mL round-bottom flask was charged with a magnetic stir bar, imine **1.34** (2.9 g, 15 mmol,

1.0 equiv), LiBr (1.6 g, 18 mmol, 1.2 equiv), THF (25 mL, 0.6 M), and Et_3N (2.5 mL, 18 mmol, 1.2 equiv). The mixture was cooled to 0 °C in an ice-water bath. After 5 min, methacrylonitrile (1.90 mL, 22.5 mmol, 1.50 equiv) was added dropwise. The resulting heterogeneous yellow mixture slowly warmed to 23 °C and was maintained at this temperature for 16 h. The volatile components were removed under reduced pressure and the resulting oil was transferred to a separatory funnel with CH_2Cl_2 (25 mL) and H_2O (40 mL). The layers of the resulting biphasic mixture were partitioned and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the resulting residue indicated a 3.3:1 mixture of endo:exo cycloadducts. The residue was purified by flash chromatography (1:1 hexanes:EtOAc) to yield pyrrolidine endo adduct **1.36** (2.4 g, 62% yield) as a clear oil. R_f 0.32 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (app d, J = 7.1, 2H), 7.41–7.34 (m, 3H), 4.34–4.24 (m, 2H), 3.98 (dd, J = 9.6, 4.2, 1H), 3.93 (s, 1H), 2.90 (br s, 1H), 2.82 (dd, J = 13.6, 4.2, 1H), 2.29 (dd, J = 13.6, 9.6, 1H), 1.42 (s, 3H), 1.34 (t, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0 (C), 136.5 (C), 128.9 (CH), 128.6 (2CH), 127.6 (2CH), 121.9 (C), 72.4 (CH), 61.7 (CH_2), 57.3 (CH), 44.1 (C), 42.4 (CH_2), 22.0 (CH_3), 14.2 (CH_3); IR (thin film): 3348, 2980, 2234, 1734, 1454 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{18}N_2O_2Na$, 281.1266; found, 281.1263. Characterization data are consistent with those previously reported.[42]



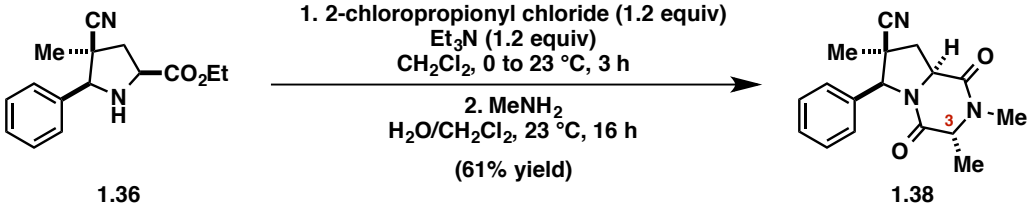
Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-5-(4-fluorophenyl)-4-methylpyrrolidine-2-carboxylate (1.37). According to the procedure described for the synthesis of pyrrolidine **1.36**, endo cycloadduct **1.37** was prepared from imine **1.35** (3.1 g, 15 mmol, 1.0 equiv) and methacrylonitrile (1.90 mL, 22.5mmol, 1.50 equiv) and isolated as a clear oil (2.5 g, 61% yield). R_f 0.29 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (app dd, J = 8.7, 5.4, 2H), 7.09 (app t, J = 8.7, 2H), 4.34–4.24 (m, 2H), 3.99 (dd, J = 9.6, 4.2, 1H), 3.95 (s, 1H), 2.83 (dd, J = 13.7, 4.2, 1H), 2.82 (br s, 1H), 2.29 (dd, J = 13.7, 9.6, 1H), 1.41 (s, 3H), 1.34 (t, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9 (C), 163.2 (d, $J_{C–F}$ = 245.8, C), 132.4 (C), 129.4 (d, $J_{C–F}$ = 8.3, 2CH), 121.8 (C), 115.7 (d, $J_{C–F}$ = 21.5, 2CH), 71.7 (CH), 61.9 (CH_2), 57.3 (CH), 44.0 (C), 42.2 (CH_2), 22.0 (CH_3), 14.3 (CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ –112.7; IR (thin film): 3348, 2982, 2235, 1736, 1605, 1510 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{17}FN_2O_2Na$, 299.1172; found, 299.1177. Characterization data are consistent with those previously reported.[42]



Ethyl *rac*-(2*S*,3*S*,4*S*,5*S*)-5-(benzo[*d*][1,3]dioxol-5-yl)-4-formyl-3,4-dimethylpyrrolidine-2-carboxylate (1.45). According to the procedure described for the synthesis of pyrrolidine **1.36**, endo cycloadduct **1.45** was prepared from imine **1.44** (3.5 g, 15 mmol, 1.0 equiv) and *trans*-2-methyl-2-butenal (2.20 mL, 22.5 mmol, 1.50 equiv) and isolated as an orange oil (2.3 g, 48% yield). R_f 0.16 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.06 (s, 1H), 6.91 (s, 1H), 6.83 (d, J = 7.9, 1H), 6.75 (d, J = 7.9, 1H), 5.94 (s, 2H), 4.34–4.24 (m, 2H), 4.09

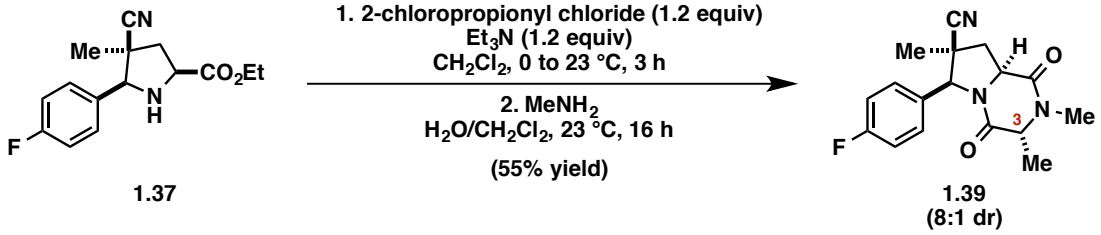
(s, 1H), 3.57 (d, *J* = 8.8, 1H), 2.73 (dq, *J* = 8.8, 7.1, 1H), 2.59 (br s, 1H), 1.35 (t, *J* = 7.1, 3H), 1.16 (s, 3H), 1.06 (d, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.0, 173.5, 148.2, 147.5, 132.4, 120.5, 108.4, 107.7, 101.3, 71.9, 66.3, 61.4, 58.8, 40.8, 15.6, 14.4, 13.5; IR (thin film): 3344, 2976, 2902, 2726, 1721, 1504, 1488 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{17}H_{21}NO_5Na$, 342.1317; found, 342.1306.

1.4.4 Synthesis of Dioxopiperazines



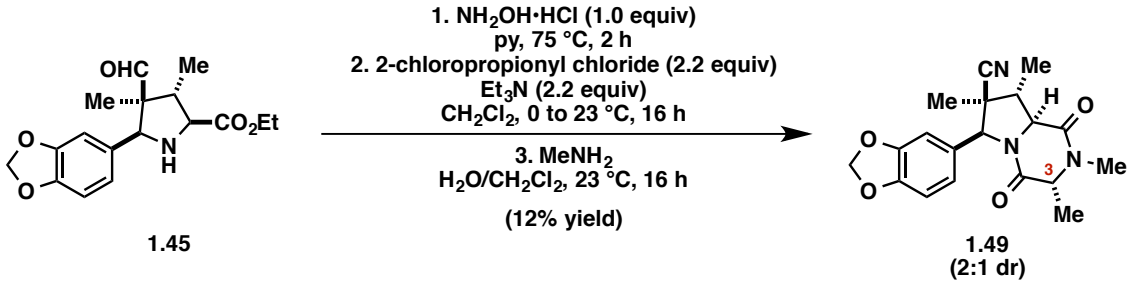
***Rac*-(3*R*,6*S*,7*S*,8a*S*)-2,3,7-trimethyl-1,4-dioxo-6-phenyloctahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile (1.38).** A 100 mL round-bottom flask was charged with pyrrolidine **1.36** (2.4 g, 9.3 mmol, 1.0 equiv), a magnetic stir bar, and CH_2Cl_2 (20 mL, 0.5 M). The solution was cooled to 0 ºC in an ice-water bath. Et_3N was added (1.60 mL, 11.2 mmol, 1.20 equiv), followed by dropwise addition of 2-chloropropionyl chloride (1.10 mL, 11.2 mmol, 1.20 equiv). The reaction was maintained at 0 ºC for 5 min, then at 23 ºC for 3 h. The reaction was quenched with H_2O (25 mL). The resulting phases were partitioned in a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). Combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting yellow foam was dissolved in CH_2Cl_2 (20 mL) and a solution of $MeNH_2$ (20 mL, 40% in H_2O) was added. The biphasic mixture was vigorously stirred at 23 ºC for 16 h. The phases were partitioned in a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). Combined extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^{1}H NMR analysis of the unpurified material indicated a 10:1 mixture of C3-methyl epimers. The pale

yellow foam was dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL) was added. The solution was stirred under a stream of air until it became a thick slurry (ca. 3 mL solvent remaining). Subsequent filtration afforded dioxopiperazine **1.38** as a colorless powder (1.7 g, 61% yield, single diastereomer, mp = 258–262 °C). R_f 0.58 (4:1 EtOAc:MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.33 (m, 3H), 7.12 (app d, *J* = 7.2, 2H), 4.91 (s, 1H), 4.40 (dd, *J* = 11.2, 6.6, 1H), 3.91 (q, *J* = 7.2, 1H), 3.05 (s, 3H), 2.79 (dd, *J* = 13.0, 11.2, 1H), 2.46 (dd, *J* = 13.0, 6.6, 1H), 1.69 (s, 3H), 1.48 (d, *J* = 7.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7 (C), 166.2 (C), 136.9 (C), 129.2 (2CH), 129.1 (2CH), 126.1 (CH), 119.9 (C), 69.8 (CH), 60.9 (CH), 56.3 (CH), 42.6 (C), 36.7 (CH_2), 32.2 (CH_3), 25.3 (CH_3), 15.4 (CH_3); IR (thin film): 2981, 2937, 2244, 1673 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calculated for $C_{17}H_{19}N_3O_2Na$, 320.1375; found, 320.1380. Characterization data are consistent with those previously reported.[42]



***Rac*-(3*R*,6*S*,7*S*,8a*S*)-6-(4-fluorophenyl)-2,3,7-trimethyl-1,4-dioxo-octahydropyrrolo-[1,2*a*] pyrazine-7-carbonitrile (1.39).** According to the procedure described for the synthesis of dioxopiperazine **1.38**, dioxopiperazine **1.39** was prepared from pyrrolidine **1.37** (2.5 g, 9.2 mmol, 1.0 equiv), 2-chloropropionyl chloride (1.1 mL, 11 mmol, 1.2 equiv), and $MeNH_2$ (18 mL, 40% in H_2O) and isolated as a colorless powder (1.6 g, 55% yield, ca. 8:1 mixture of C3-methyl epimers). The 8:1 epimeric mixture was carried forward in the next step without further purification. R_f 0.58 (4:1 EtOAc:MeOH); ^{1}H NMR (ca. 8:1 mixture of diastereomers, 500 MHz, $CDCl_3$): δ 7.13–7.05 (m, 4H), 4.90 (s, 1H), 4.39 (dd, *J* = 11.4, 6.6, 1H), 3.91 (q, *J* = 7.2, 1H), 3.06 (s, 3H), 2.76 (dd, *J* = 13.4, 11.4, 1H), 2.47 (dd, *J* = 13.4, 6.6, 1H), 1.69 (s, 3H), 1.49

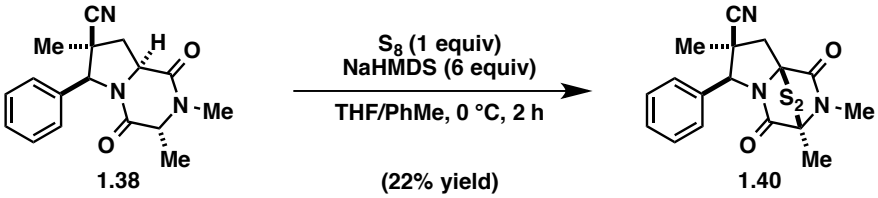
(d, J = 7.2, 3H); ^{13}C NMR (ca. 8:1 mixture of diastereomers, 125 MHz, $CDCl_3$): δ 166.8 (C), 166.1 (C), 163.0 (d, $J_{C–F}$ = 245.5, C), 132.8 (d, $J_{C–F}$ = 3.1, C), 127.9 (d, $J_{C–F}$ = 8.4, 2CH), 119.8 (C), 116.2 (d, $J_{C–F}$ = 21.8, 2CH), 69.2 (CH), 60.9 (CH), 56.3 (CH), 42.6 (C), 36.8 (CH_2), 32.2 (CH_3), 25.3 (CH_3), 15.4 (CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ –112.4; IR (thin film): 2989, 2940, 2241, 1681 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calculated for $C_{17}H_{18}FN_3O_2Na$, 338.1281; found, 338.1283. Characterization data are consistent with those previously reported.[42]



***Rac*-(3*R*,6*S*,7*S*,8*S*,8a*S*)-6-(benzo[*d*][1,3]dioxol-5-yl)-2,3,7,8-tetramethyl-1,4-dioxooctahydro-pyrrolo[1,2-*a*]pyrazine-7-carbonitrile (1.49).** A 25 mL round-bottom flask was charged with a magnetic stir bar, pyrrolidine **1.45** (320 mg, 1.0 mmol, 1.0 equiv), and hydroxylamine hydrochloride (69 mg, 1.0 mmol, 1.0 equiv). Pyridine (10 mL, 0.1 M) was added and the resulting solution was maintained at 75 °C for 2 h. After cooling to 23 °C, the solution was transferred to a separatory funnel with Et_2O (80 mL) and H_2O (15 mL). The layers of the resulting biphasic mixture were partitioned and the organic phase was extracted with sat. aq. NH_4Cl (15 mL) and sat. aq. $NaHCO_3$ (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Azeotropic removal of pyridine with PhMe afforded an oil that was transferred to a 50 mL round-bottom flask. The oil was dissolved in CH_2Cl_2 (2 mL) and the resulting solution was cooled to 0 °C in an ice-water bath. Et_3N (310 μL, 2.2 mmol, 2.2 equiv) was added in one portion, followed by the dropwise addition of 2-chloropropionyl chloride (210 μL, 2.2 mmol, 2.2 equiv). After 5 min, the reaction vessel was

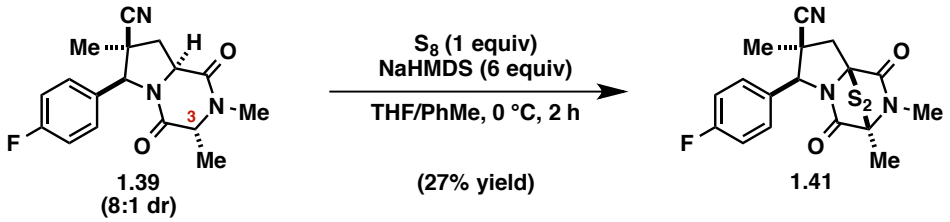
removed from the ice-water bath and the solution was maintained at 23 °C for 16 h. The reaction was quenched with H_2O (20 mL). The resulting phases were partitioned in a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting brown foam was dissolved in CH_2Cl_2 (2 mL) and a solution of $MeNH_2$ (2 mL, 40% in H_2O) was added. The biphasic mixture was vigorously stirred at 23 ºC for 16 h. The biphasic mixture was transferred to a separatory funnel with CH_2Cl_2 (20 mL) and H_2O (20 mL) and the phases were partitioned. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). Combined extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (10 mL) and MeOH (5 mL) was added. The solution was stirred under a stream of air until a precipitate formed. Filtration afforded impure dioxopiperazine **1.49** (43 mg, 12% yield, ca. 2:1 mixture of C3-methyl epimers) as a colorless powder which was carried forward without further purification. ^{1}H NMR (ca. 2:1 mixture of diastereomers, 600 MHz, $CDCl_3$): δ 6.78 (d, *J* = 8.0, 1H), 6.59 (dd, *J* = 8.0, 1.1, 1H), 6.54 (d, *J* = 1.1, 1H), 5.963 (s, 1H), 5.960 (s, 1H), 4.90 (s, 1H), 4.11 (q, *J* = 6.5, 1H), 3.84 (d, *J* = 10.3, 1H), 3.07 (s, 3H), 3.04–3.01 (m, 1H), 1.54 (d, *J* = 6.5, 3H), 1.52 (s, 3H), 1.41 (d, *J* = 6.5, 3H).

1.4.5 Synthesis of Epidithiodioxopiperazines

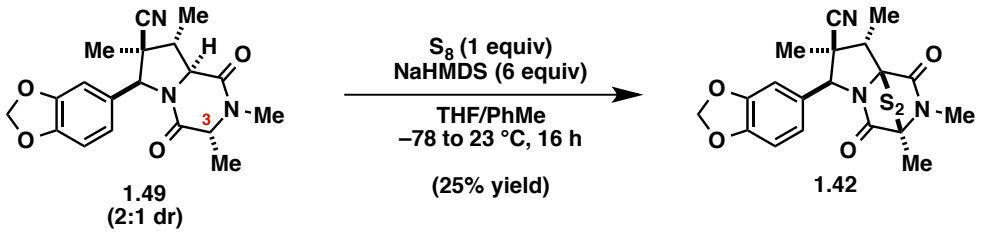


***Rac*-(3*S*,6*S*,7*S*,8a*S*)-2,3,7-trimethyl-1,4-dioxo-6-phenylhexahydro-6*H*-3,8a-epidithiopyrrolo-[1,2-*a*]pyrazine-7-carbonitrile (1.40).** Dioxopiperazine **1.38** (100 mg, 0.34 mmol, 1.0 equiv) and S_8 (90 mg, 0.34 mmol, 1.0 equiv) were added to a 25 mL round-bottom flask and

azeotropically dried with PhMe (3 x 3 mL). The solids were suspended in THF (3.4 mL, 0.10 M) and the heterogeneous mixture was sparged with Ar for 10 min. The suspension was cooled to 0 ºC for 5 min, then NaHMDS (0.60 M in PhMe, 3.4 mL, 2.0 mmol, 6.0 equiv) was added dropwise over 2 min with vigorous stirring. The reaction was maintained at 0 °C for 2 h, then quenched at 23 °C with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). Combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was dissolved in MeCN (15 mL) and washed with hexanes (3 x 10 mL) in a separatory funnel to remove HMDS-related byproducts. The MeCN layer was dried over Na_2SO_4, then concentrated in vacuo. Flash chromatography (2% EtOAc/CH_2Cl_2) afforded ETP **1.40** as a colorless powder (27 mg, 22% yield, mp = 243–246 °C). R_f 0.30 (3% EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.38 (m, 5H), 4.91 (s, 1H), 3.32 (d, *J* = 14.7, 1H), 3.09 (s, 3H), 3.00 (d, *J* = 14.7, 1H), 1.94 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7 (C), 162.2 (C), 133.8 (C), 129.6 (CH), 129.1 (2CH), 126.9 (2CH), 120.2 (C), 73.4 (C), 72.5 (CH), 44.5 (C), 43.0 (CH_2), 29.8 (C), 27.9 (CH_3), 24.9 (CH_3), 18.2 (CH_3); IR (thin film): 2917, 2849, 2240, 1705, 1680 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{17}H_{17}N_3O_2S_2Na$, 382.0660; found, 382.0671. Characterization data are consistent with those previously reported.[42]



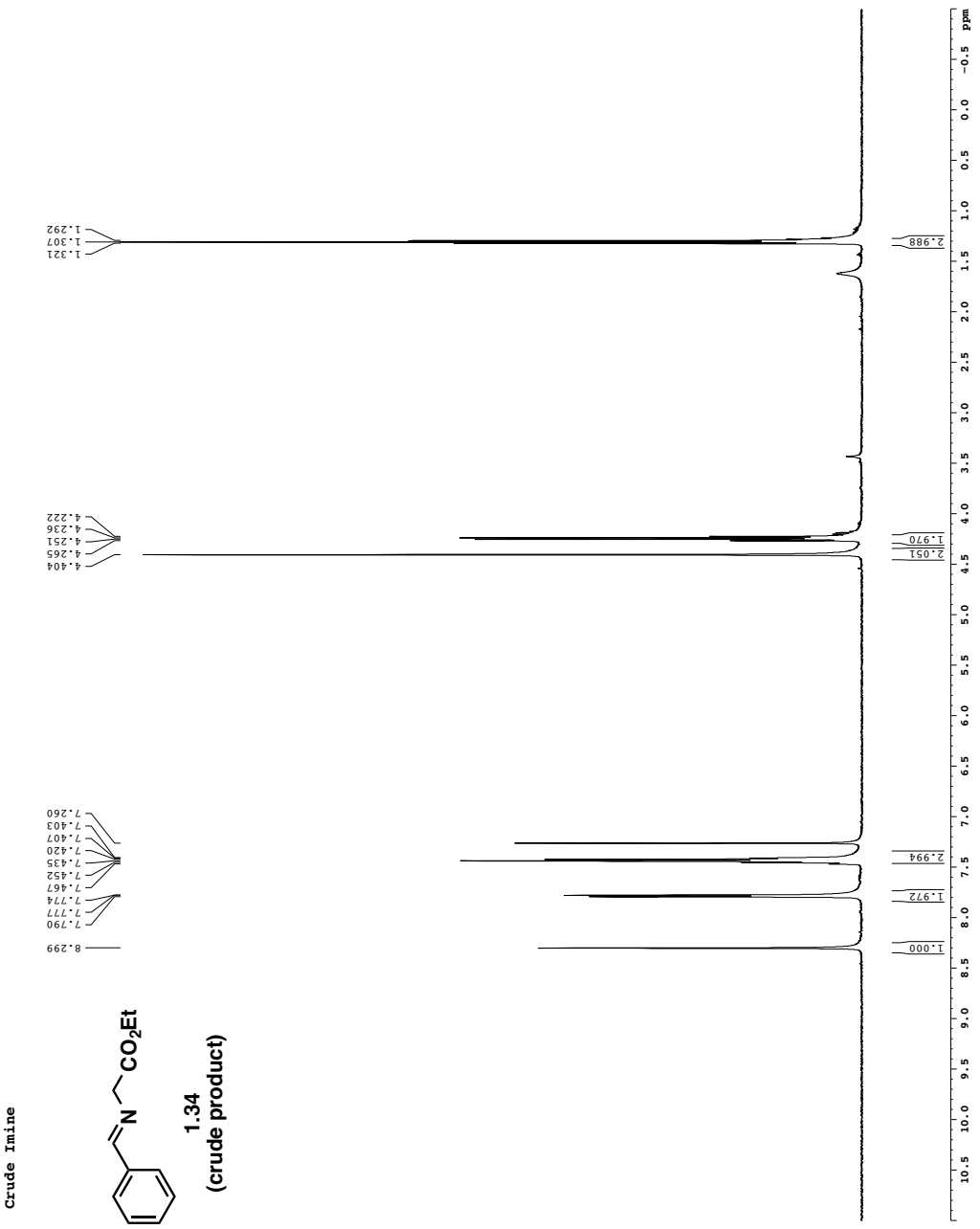
***Rac*-(3*S*,6*S*,7*S*,8a*S*)-6-(4-fluorophenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8a-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile (1.41).** According to the procedure described for the synthesis of ETP **1.40**, ETP **1.41** was prepared from dioxopiperazine **1.39** (110 mg, 0.34 mmol, 1.0 equiv) and accessed as a colorless powder (35 mg, 27% yield, mp = 221–223 ºC). R_f 0.18 (3% EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (app dd, J = 8.6, 5.2, 2H), 7.13 (app t, J = 8.6, 2H), 4.89 (s, 1H), 3.31 (d, J = 15.0, 1H), 3.08 (s, 3H), 2.99 (d, J = 15.0, 1H), 1.94 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6 (C), 163.4 (d, $J_{C–F}$ = 248.2, C), 162.2 (C), 129.6 (d, $J_{C–F}$ = 3.1, C), 128.8 (d, $J_{C–F}$ = 8.5, 2CH), 120.2 (C), 116.2 (d, $J_{C–F}$ = 22.1, 2CH), 73.52 (C), 73.46 (C), 71.9 (CH), 44.5 (C), 42.9 (CH_2), 27.9 (CH_3), 24.7 (CH_3), 18.2 (CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ –112.0; IR (thin film): 2988, 2926, 2239, 1703, 1687, 1511 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calculated for $C_{17}H_{16}FN_3O_2S_2Na$, 400.0566; found, 400.0559. Characterization data are consistent with those previously reported.[42]

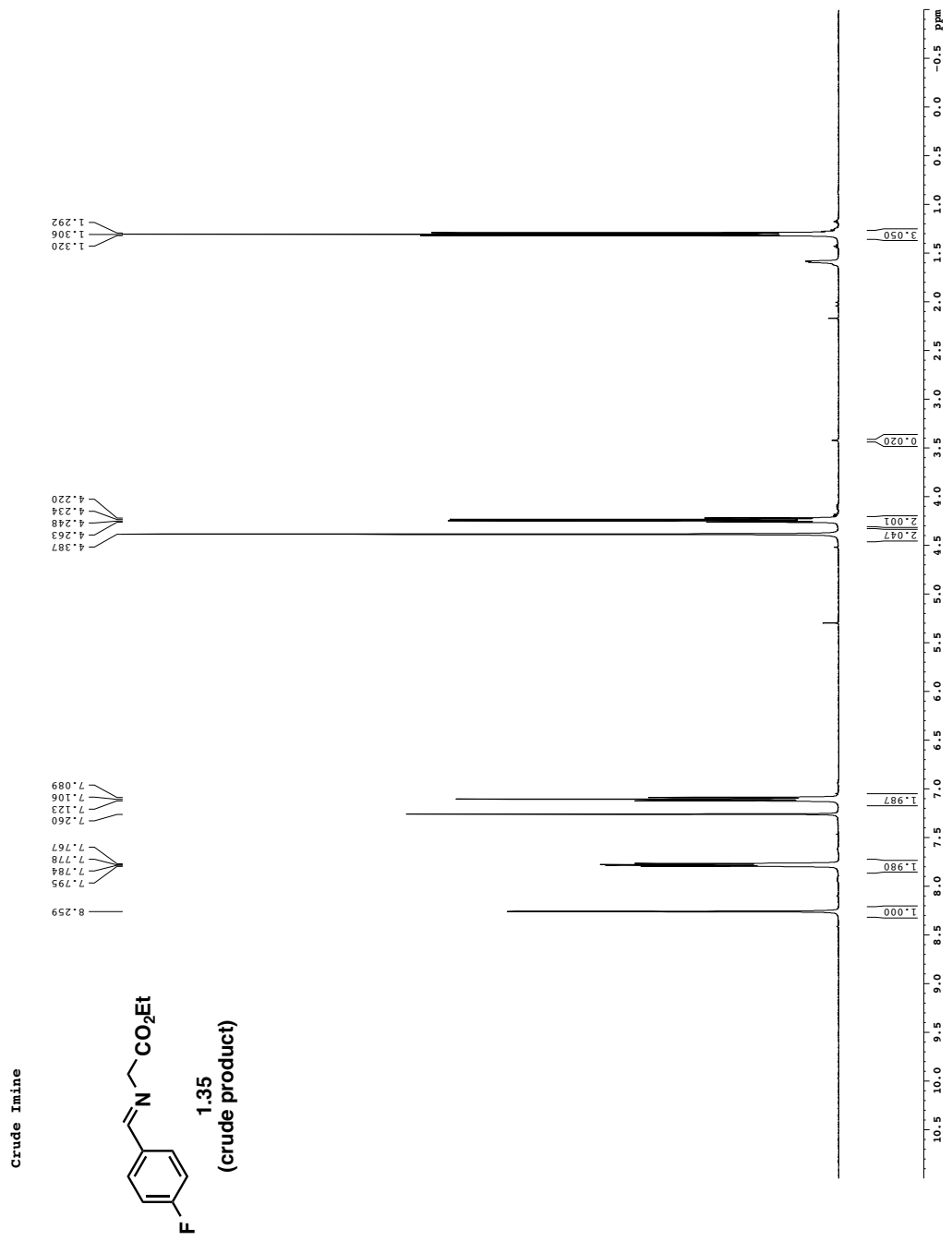


***Rac*-(3*S*,6*S*,7*S*,8*S*,8a*S*)-6-(benzo[*d*][1,3]dioxol-5-yl)-2,3,7,8-tetramethyl-1,4-dioxohexahydro-6*H*-3,8a-epithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile 9-sulfide (1.42).** A 15 mL round-bottom flask was charged with a magnetic stir bar, impure dioxopiperazine **1.49** (43 mg, 0.12 mmol, 1.0 equiv), S_8 (37 mg, 0.15 mmol, 1.2 equiv), and THF (1.2 mL, 0.10 M). The resulting

suspension was cooled to –78 °C for 5 min, then NaHMDS (0.60 M in PhMe, 1.2 mL, 0.73 mmol, 6.0 equiv) was added dropwise over 3 min with vigorous stirring. The resulting yellow-orange heterogeneous solution was slowly warmed to 23 °C and stirred for 16 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (5 mL). The resulting biphasic solution was transferred to a separatory funnel with CH_2Cl_2 (10 mL) and H_2O (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), then the organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure to yield an amorphous brown residue. This residue was dissolved in MeCN (10 mL) and washed with hexanes (3 x 20 mL) in a separatory funnel. The MeCN layer was dried over Na_2SO_4, then concentrated in vacuo. The residue was purified by PTLC (1% EtOAc/CH_2Cl_2). The desired ETP **1.42** was isolated as a colorless solid (12 mg, 25% yield, mp = 212–214 °C) after concentration in vacuo. R_f 0.47 (3% EtOAc/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.80 (d, J = 8.1, 1H), 6.58 (d, J = 8.1, 1H), 6.52 (s, 1H), 5.98 (s, 1H), 5.97 (s, 1H), 5.03 (s, 1H), 3.83 (q, J = 7.0, 1H), 3.10 (s, 3H), 1.96 (s, 3H), 1.90 (s, 3H), 1.50 (d, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3 (C), 162.5 (C), 148.62 (C), 148.58 (C), 129.9 (C), 119.7 (CH), 119.6 (C), 109.1 (CH), 106.2 (CH), 101.7 (C), 77.3 (C), 72.8 (C), 70.5 (CH), 47.8 (CH_2), 44.3 (CH), 27.8 (CH_3), 21.9 (CH_3), 18.3 (CH_3), 10.1 (CH_3); IR (thin film): 2984, 2917, 2849, 2244, 1695, 1505, 1491 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{19}H_{19}N_3O_4S_2Na$, 440.0715; found, 440.0719.

1.5 Appendix B: NMR Spectral Data

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(crude product)
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SOLVENT CDCl3
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DE 6.00 usec
TE 298.0 K
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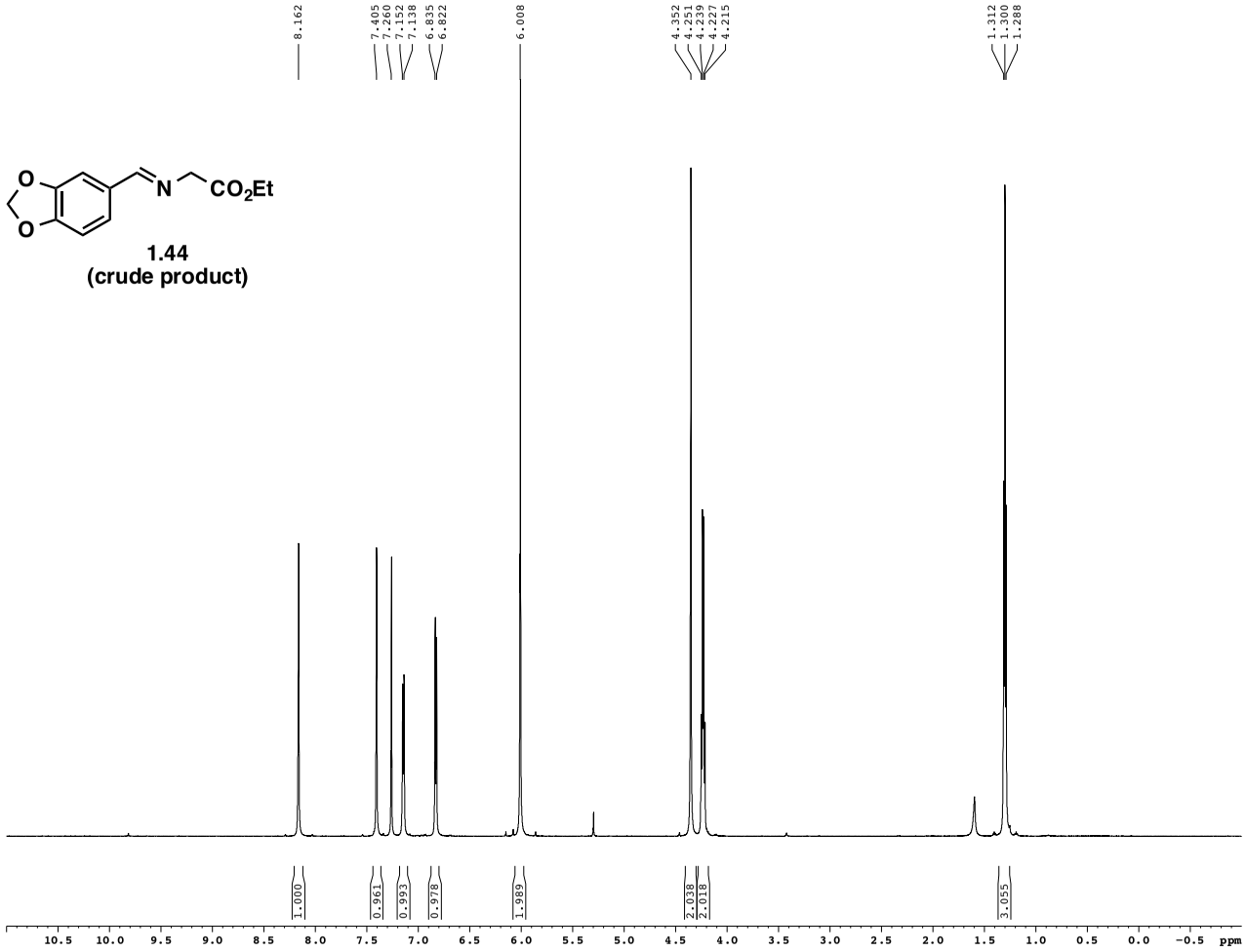
Crude Imine

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P1                         8.00 usec
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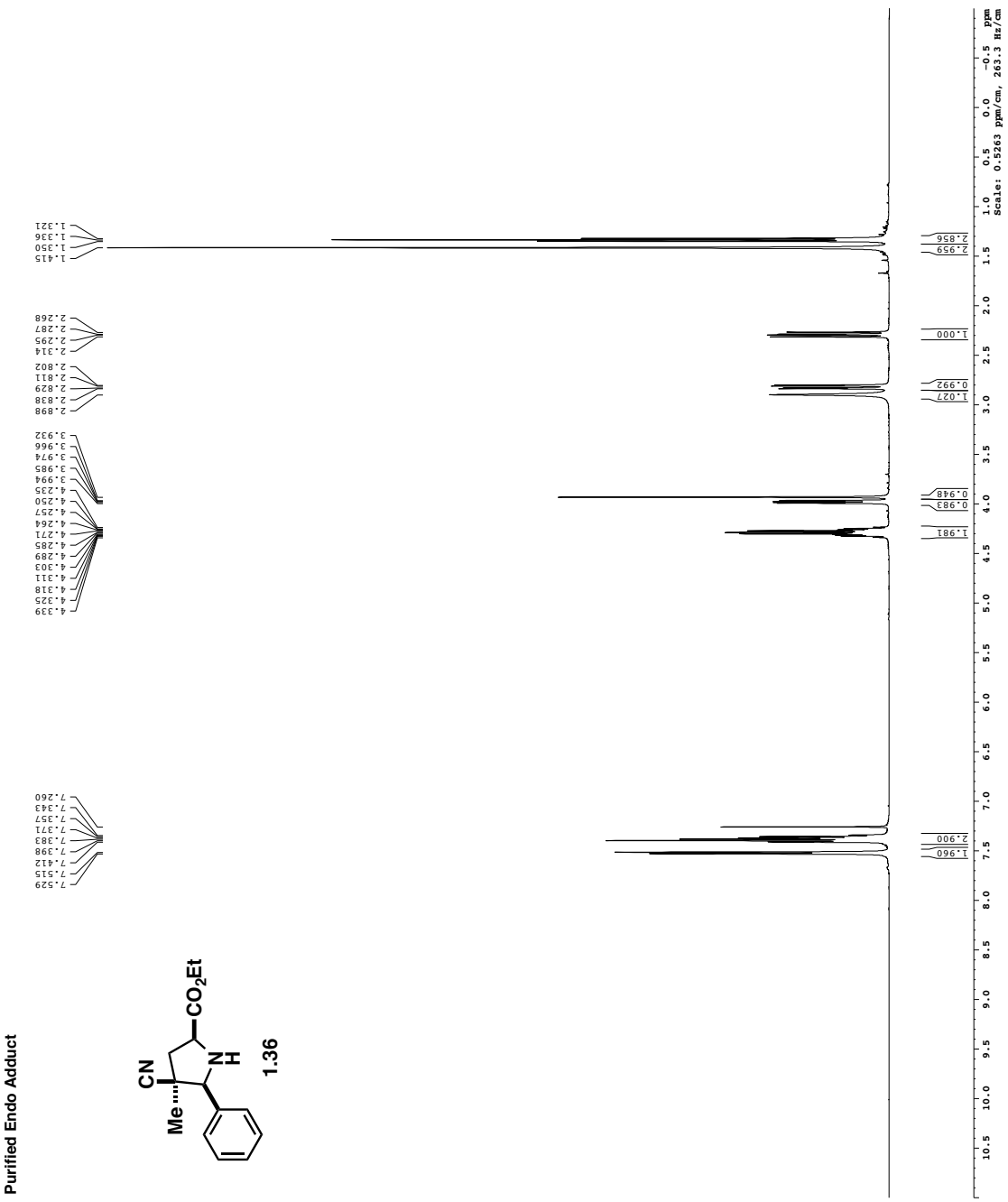
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DS 2
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FIDRES 0.098043 Hz
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RG 4
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DE 6.00 usec
TE 296.0 K
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MCWREK 0.01500000 sec
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2.287
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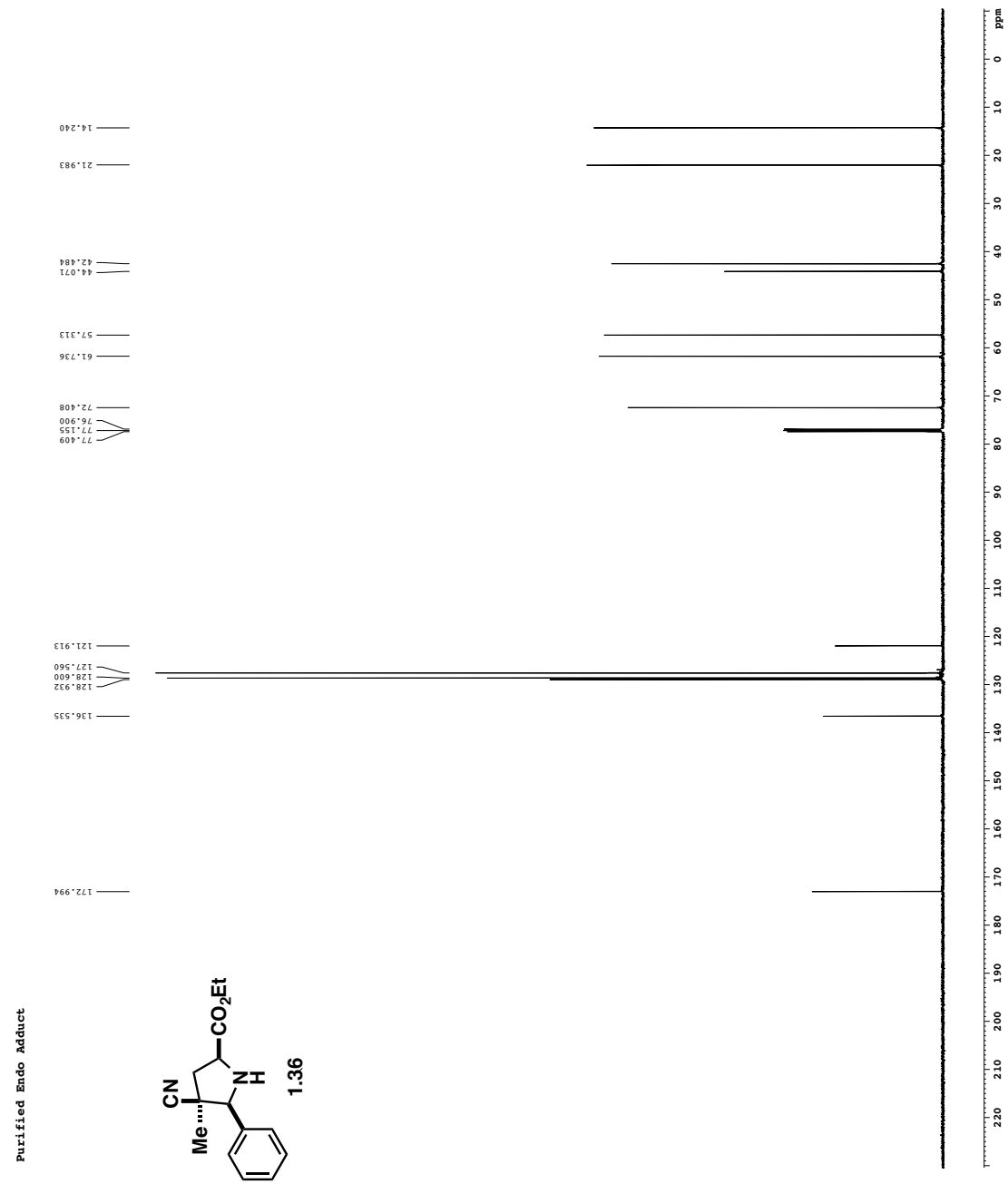
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SOLVENT CDCl3
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P11 500.00 usec
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GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
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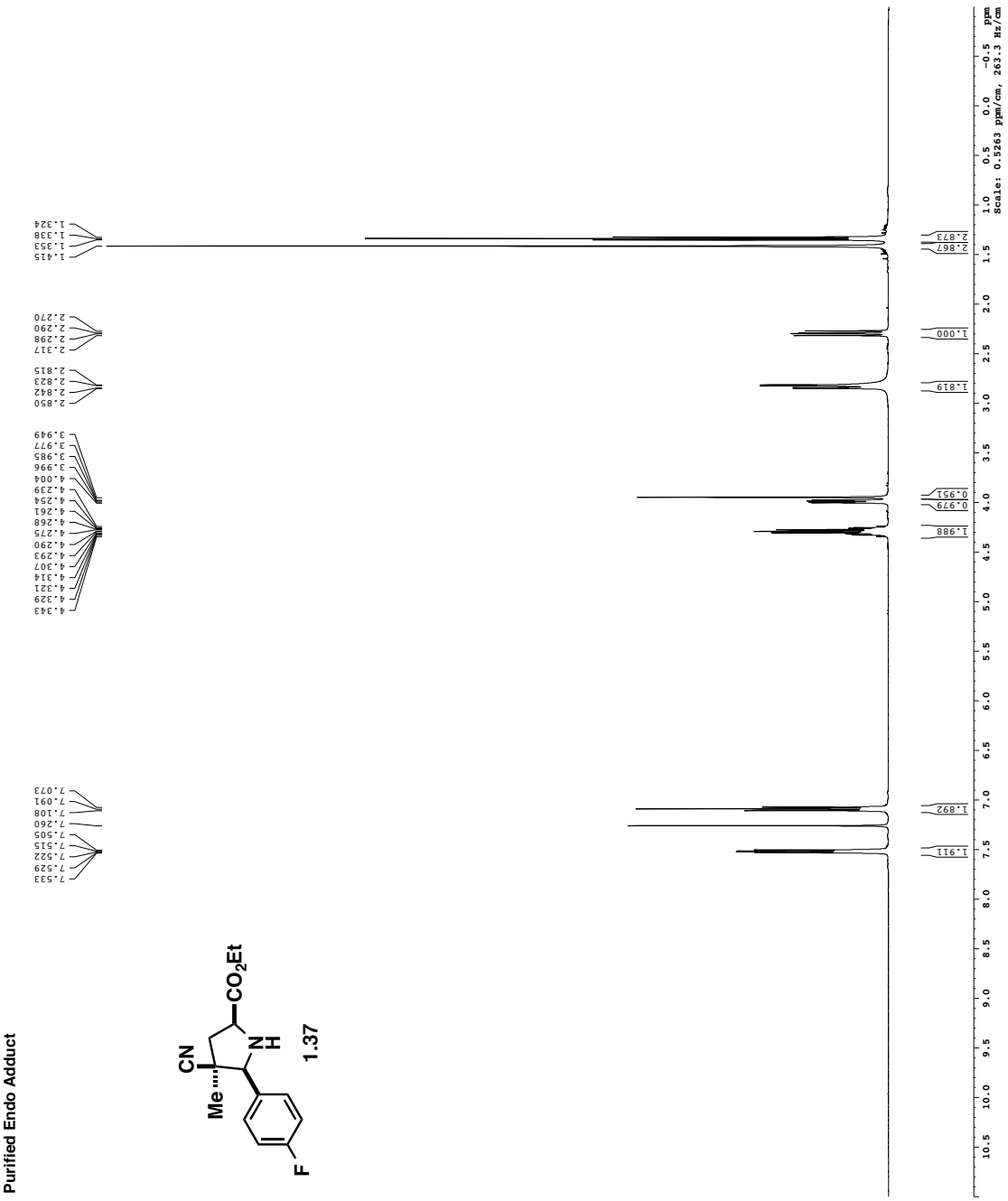
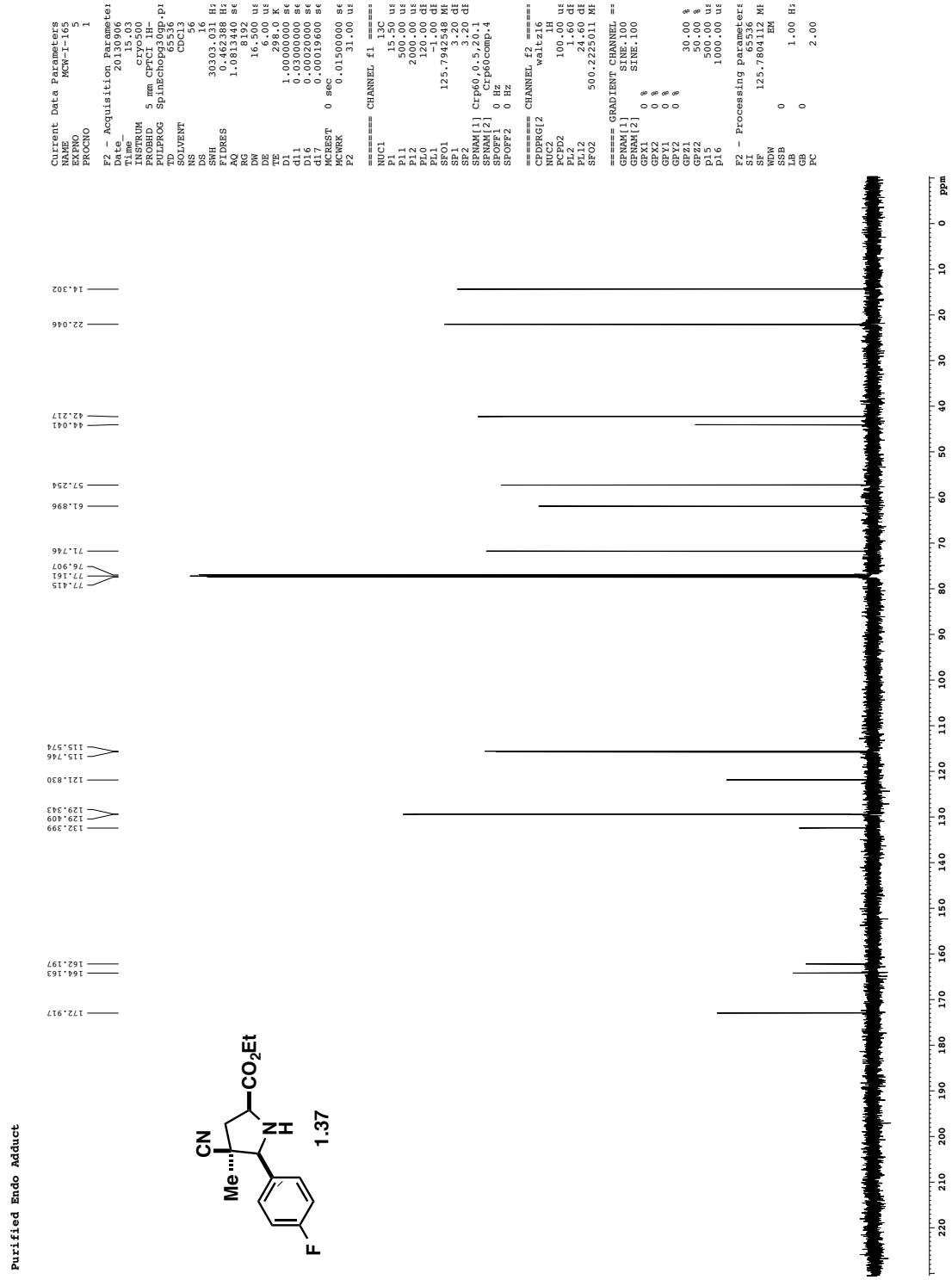
Purified Endo Adduct

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MCWRK 0.01500000 sec
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PL1 -1.00 dB
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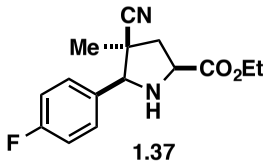
165b Endo – Purified Product



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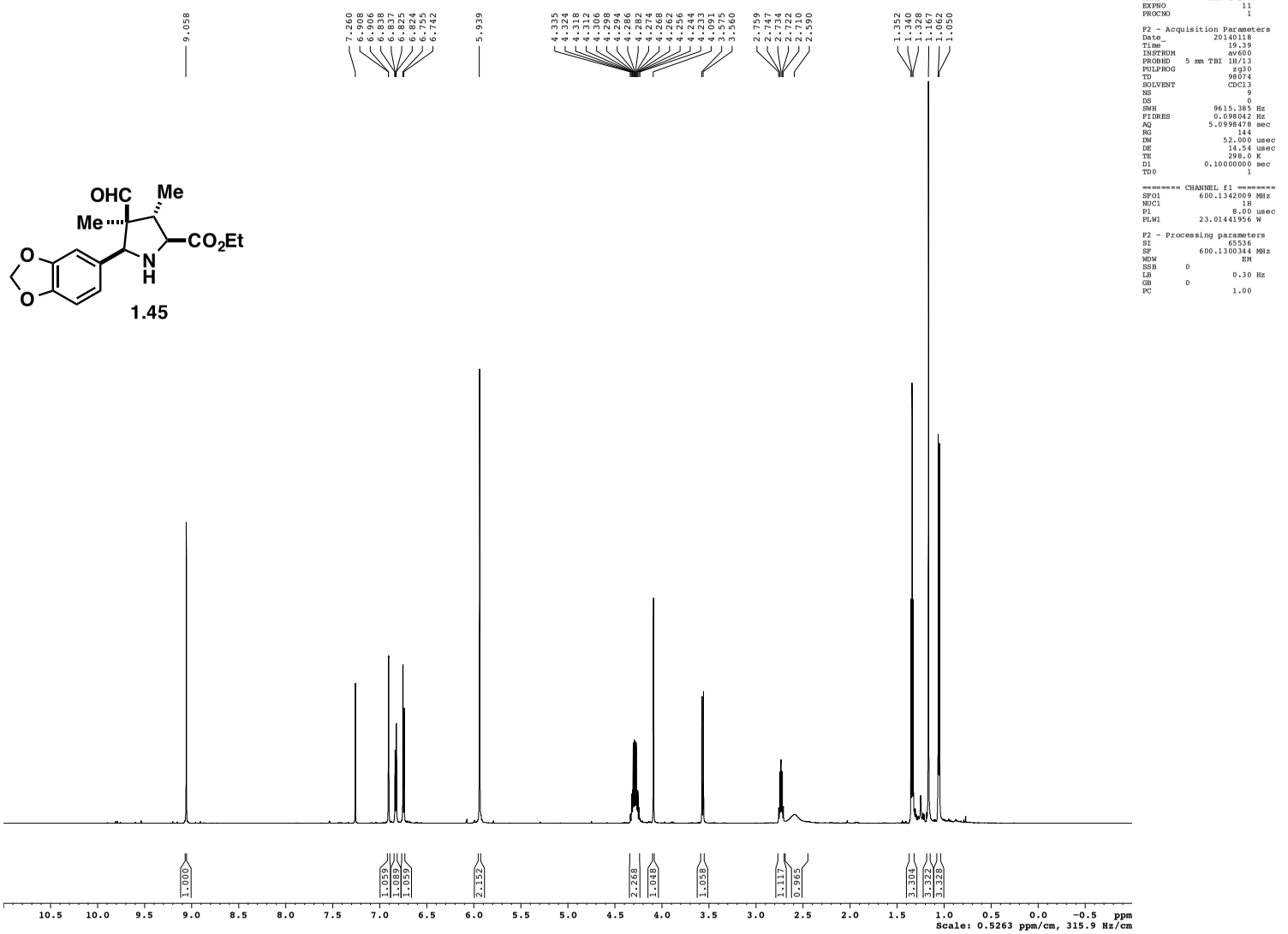
```

Endo Adduct



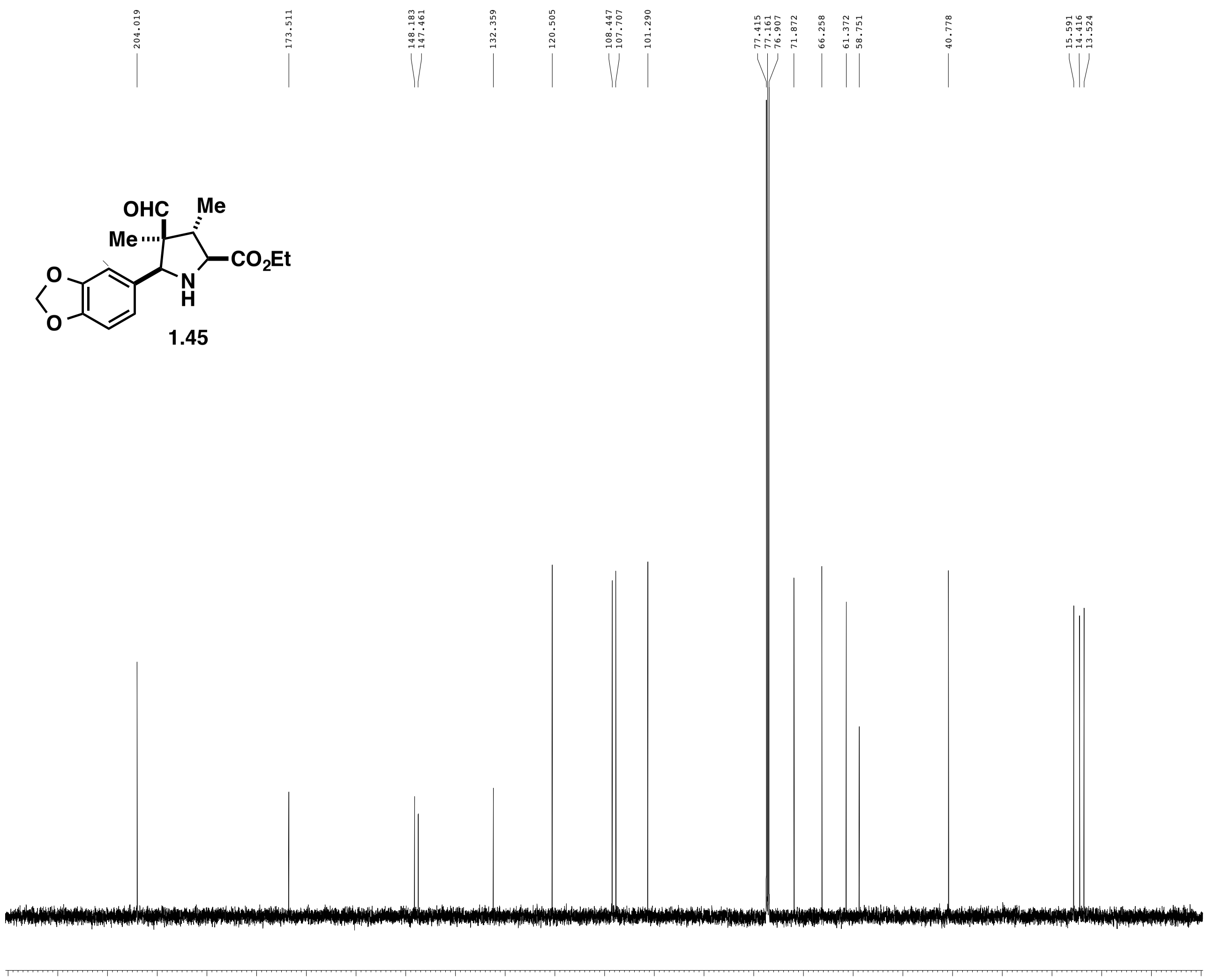

```
Current Data Parameters
NAME                  MCW-I-260
EXPNO                        11
PROCNO                        1

F2 - Acquisition Parameters
Date_               20140118
Time                     19.39
INSTRUM                  av600
PROBHD     5 mm TBI 1H/13
PULPROG                  zg30
TD                      98074
SOLVENT                 CDCl3
NS                           9
DS                           0
SWH                 9615.385 Hz
FIDRES              0.098042 Hz
AQ                  5.0998478 sec
RG                         144
DW                    52.000 usec
DE                    14.54 usec
TE                    298.0 K
D1                0.10000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1              600.1342009 MHz
NUC1                        1H
P1                        8.00 usec
PLW1             23.01441956 W

F2 - Processing parameters
SI                       65536
SF                600.1300344 MHz
WDW                         EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
```

Purified Endo Adduct




```
Current Data Parameters
NAME          MCW-I-260
EXPNO                10
PROCNO                1

F2 - Acquisition Parameter
Date_          20140118
Time              19.29
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.pr
TD                65536
SOLVENT           CDCl3
NS                  120
DS                   16
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ            1.0813440 se
RG               7298.2
DW               16.500 us
DE                 6.00 us
TE                298.0 K
D1           1.00000000 se
d11          0.03000000 se
D16          0.00020000 se
d17          0.00019600 se
MCREST   0 sec
MCWRK        0.01500000 se
P2                31.00 us

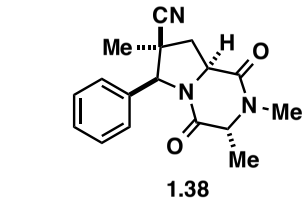
======== CHANNEL f1 ======
NUC1                13C
P1                15.50 us
P11              500.00 us
P12             2000.00 us
PL0              120.00 dB
PL1               -1.00 dB
SFO1        125.7942548 MH
SP1                3.20 dB
SP2                3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1   0 Hz
SPOFF2   0 Hz

======== CHANNEL f2 ======
CPDPRG[2        waltz16
NUC2                 1H
PCPD2            100.00 us
PL2                1.60 dB
PL12              24.60 dB
SFO2        500.2225011 MH

====== GRADIENT CHANNEL ==
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 us
p16             1000.00 us

F2 - Processing parameters
SI                65536
SF          125.7804092 MH
WDW                  EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 2.00
```

Purified Product



1.38

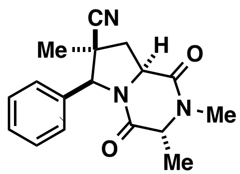

```
Current Data Parameters
NAME            MCW-I-171
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20130918
Time                17.10
INSTRUM             av600
PROBHD   5 mm TBI 1H/13
PULPROG             zg30
TD                 98074
SOLVENT            CDCl3
NS                    12
DS                     0
SWH             9615.385 Hz
FIDRES          0.098042 Hz
AQ              5.0998478 sec
RG                   101
DW                52.000 usec
DE                14.54 usec
TE                298.2 K
D1           0.10000000 sec
TD0                    1

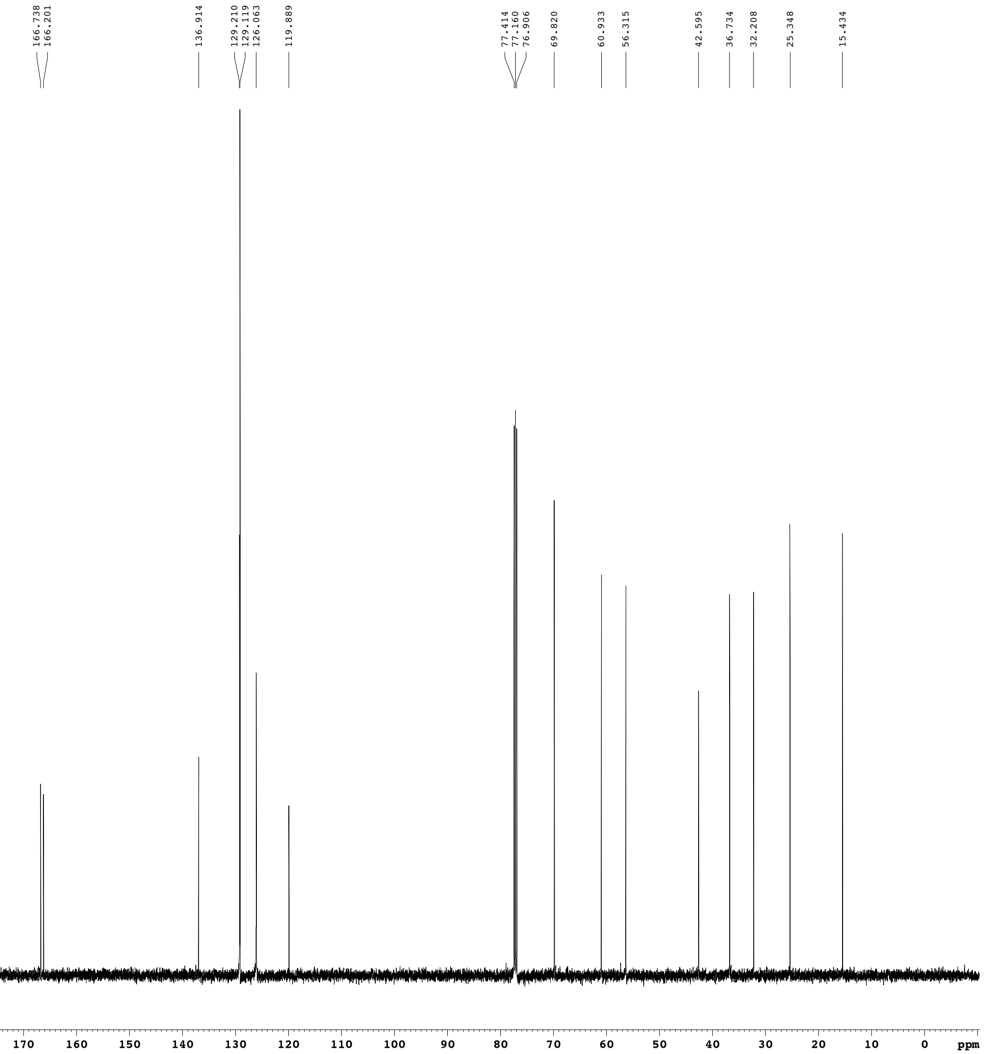
======== CHANNEL f1 ========
NUC1                  1H
P1                 8.00 usec
PLW1          23.01441956 W
SFO1          600.1342009 MHz

F2 - Processing parameters
SI                 65536
SF          600.1300346 MHz
WDW                   EM
SSB        0
LB                 0.30 Hz
GB         0
PC                 1.00
```

Purified Product



1.38




```
Current Data Parameters
NAME          MCW-I-171
EXPNO                 5
PROCNO                1

F2 - Acquisition Parameter
Date_          20130918
Time              17.42
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.pr
TD                65536
SOLVENT           CDCl3
NS                  104
DS                   16
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ            1.0813440 se
RG                 4096
DW               16.500 us
DE                 6.00 us
TE                298.0 K
D1           1.00000000 se
d11          0.03000000 se
D16          0.00020000 se
d17          0.00019600 se
MCREST   0 sec
MCWRK        0.01500000 se
P2                31.00 us

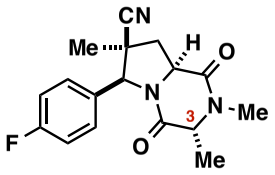
======== CHANNEL f1 ======
NUC1                13C
P1                15.50 us
P11              500.00 us
P12             2000.00 us
PL0              120.00 dB
PL1               -1.00 dB
SFO1        125.7942548 MH
SP1                3.20 dB
SP2                3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1   0 Hz
SPOFF2   0 Hz

======== CHANNEL f2 ======
CPDPRG[2        waltz16
NUC2                 1H
PCPD2            100.00 us
PL2                1.60 dB
PL12              24.60 dB
SFO2        500.2225011 MH

====== GRADIENT CHANNEL ==
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 us
p16             1000.00 us

F2 - Processing parameters
SI                65536
SF          125.7804141 MH
WDW                  EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 2.00
```

Purified Product



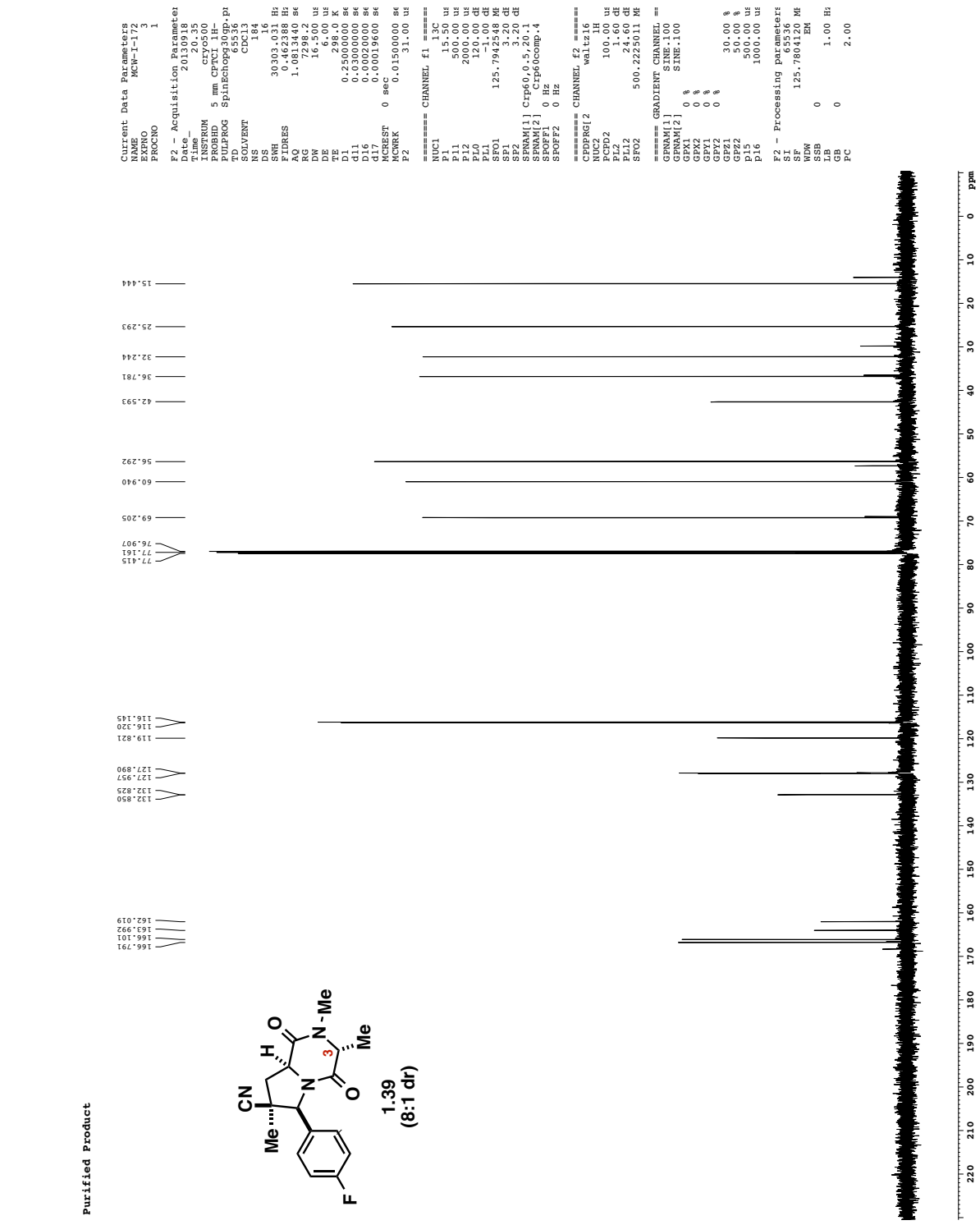
1.39
(8:1 dr)


```
Current Data Parameters
NAME              MCW-I-172
EXPNO                     2
PROCNO                    1

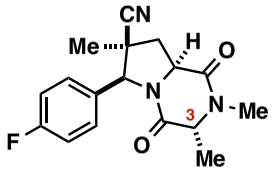
F2 - Acquisition Parameters
Date_           20130918
Time                20.32
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT            CDCl3
NS                     8
DS                     2
SWH              8012.820 Hz
FIDRES           0.098043 Hz
AQ               5.0998273 sec
RG                   5.7
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1           0.10000000 sec
MCREST    0 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 7.50 usec
PL1                1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF          500.2200308 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 4.00
```


Purified Product
Current Data Parameters
NAME MCW-I-172
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130918
Time 20.35
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG Spin2Echo@p5536.pi
TD 65536
SOLVENT CDCl3
NS 184
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCWGEST 0 sec 0.01500000 sec
MCWRK 31.00 usec
P2
======== CHANNEL f1 ======
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ======
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804120 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
15.444
25.293
32.244
36.781
42.593
56.292
60.940
69.205
76.907
77.161
77.415
116.145
116.320
119.821
127.890
127.957
132.825
132.850
162.019
163.992
166.101
166.791
ppm
1.39
(8:1 dr)

Purified Product {19F}



1.39
(8:1 dr)


```
Current Data Parameters
NAME                  MCW-I-172
EXPNO                        31
PROCNO                        1

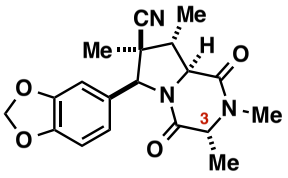
F2 - Acquisition Parameters
Date_               20131008
Time                    17.42
INSTRUM                 drx400
PROBHD    5 mm QNP H/F/P
PULPROG             zgfhigqn30
TD                       65536
SOLVENT                  CDCl3
NS                          24
DS                           4
SWH                 75187.969 Hz
FIDRES                1.147277 Hz
AQ                  0.4358144 sec
RG                     3649.1
DW                       6.650 usec
DE                       9.46 usec
TE                     298.0 K
D1                  2.00000000 sec
D11                 0.03000000 sec
D12                 0.00002000 sec

======== CHANNEL f1 ========
NUC1                       19F
P1                       22.50 usec
PL1                      -6.00 dB
SFO1               376.4646491 MHz

======== CHANNEL f2 ========
CPDPRG[2                waltz16
NUC2                       1H
PCPD2                    80.00 usec
PL2                       3.00 dB
PL12                     16.20 dB
SFO2               400.1320007 MHz

F2 - Processing parameters
SI                       65536
SF                 376.4983868 MHz
WDW                        EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
```

Precipitate



1.49
(2:1 dr, impure mixture)

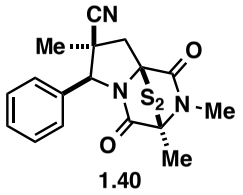

```
Current Data Parameters
NAME            MCW-I-298
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20140227
Time                15.02
INSTRUM             av600
PROBHD   5 mm TBI 1H/13
PULPROG             zg30
TD                 98074
SOLVENT            CDCl3
NS                     8
DS                     0
SWH             9615.385 Hz
FIDRES          0.098042 Hz
AQ              5.0998478 sec
RG                   512
DW                52.000 usec
DE                14.54 usec
TE                298.1 K
D1           0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1342009 MHz
NUC1                   1H
P1                  8.00 usec
PLW1        23.01441956 W

F2 - Processing parameters
SI                 65536
SF           600.1300344 MHz
WDW                   EM
SSB        0
LB                  0.30 Hz
GB         0
PC                  1.00
```

Purified Product



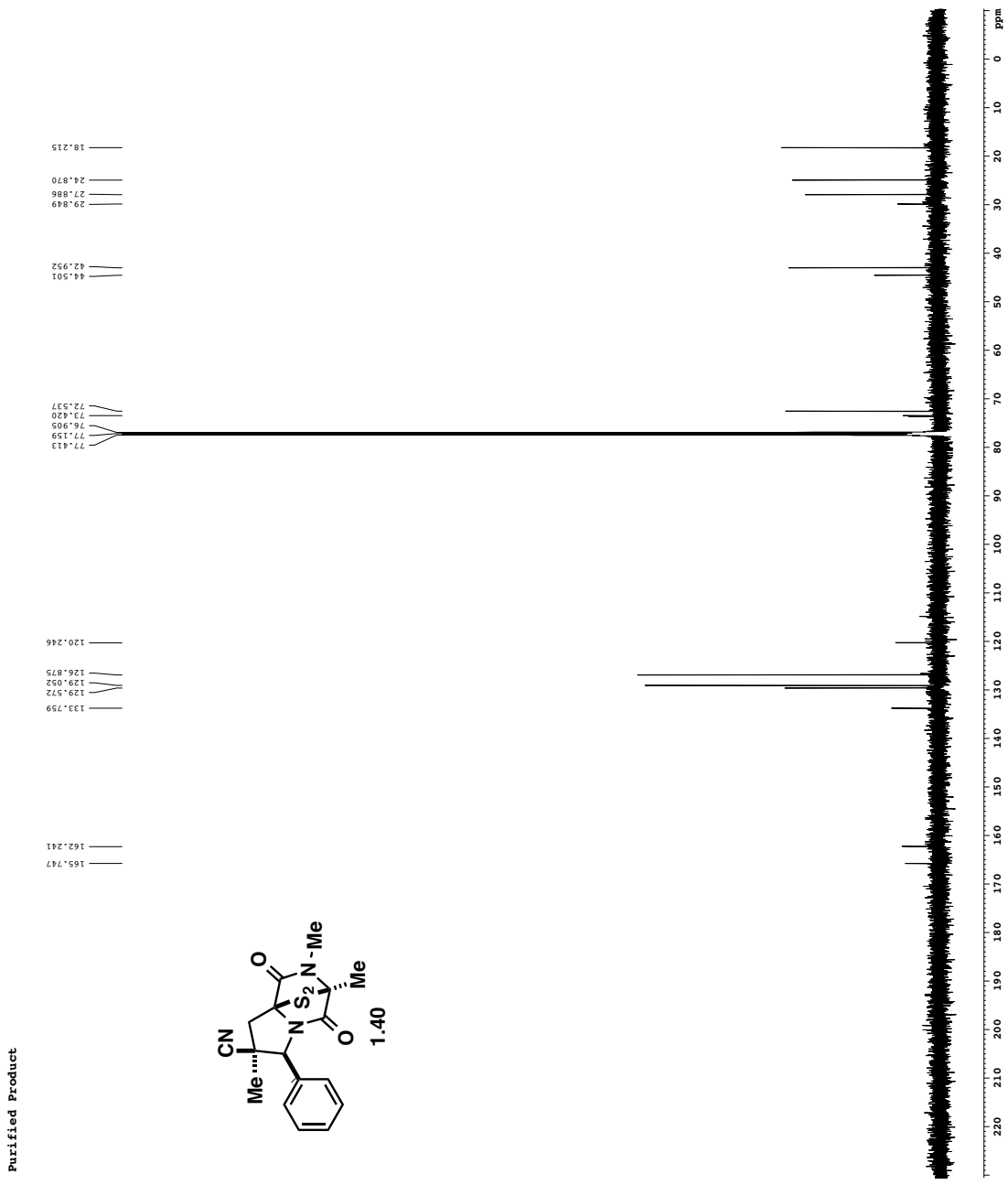
1.40

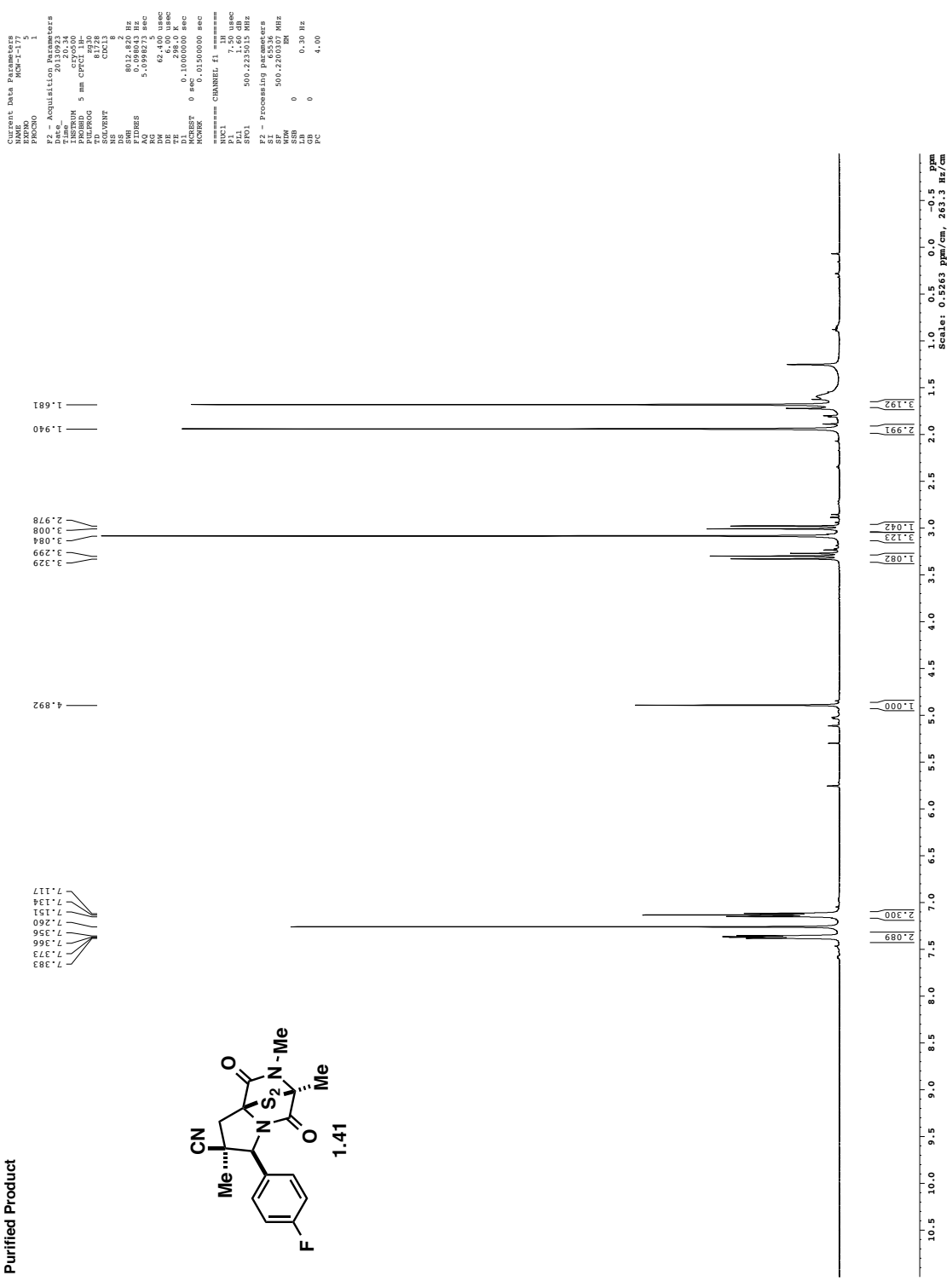

```
Current Data Parameters
NAME                  MCW-I-176
EXPNO                         4
PROCNO                        1

F2 - Acquisition Parameters
Date_               20130921
Time                      21.21
INSTRUM                 cryo500
PROBHD     5 mm CPTCI 1H-
PULPROG                   zg30
TD                       81728
SOLVENT                  CDCl3
NS                           16
DS                            0
SWH                   8012.820 Hz
FIDRES                0.098043 Hz
AQ                    5.0998273 sec
RG                          7.1
DW                       62.400 usec
DE                        6.00 usec
TE                       298.0 K
D1                  0.10000000 sec
MCREST     0 sec
MCWRK               0.01500000 sec

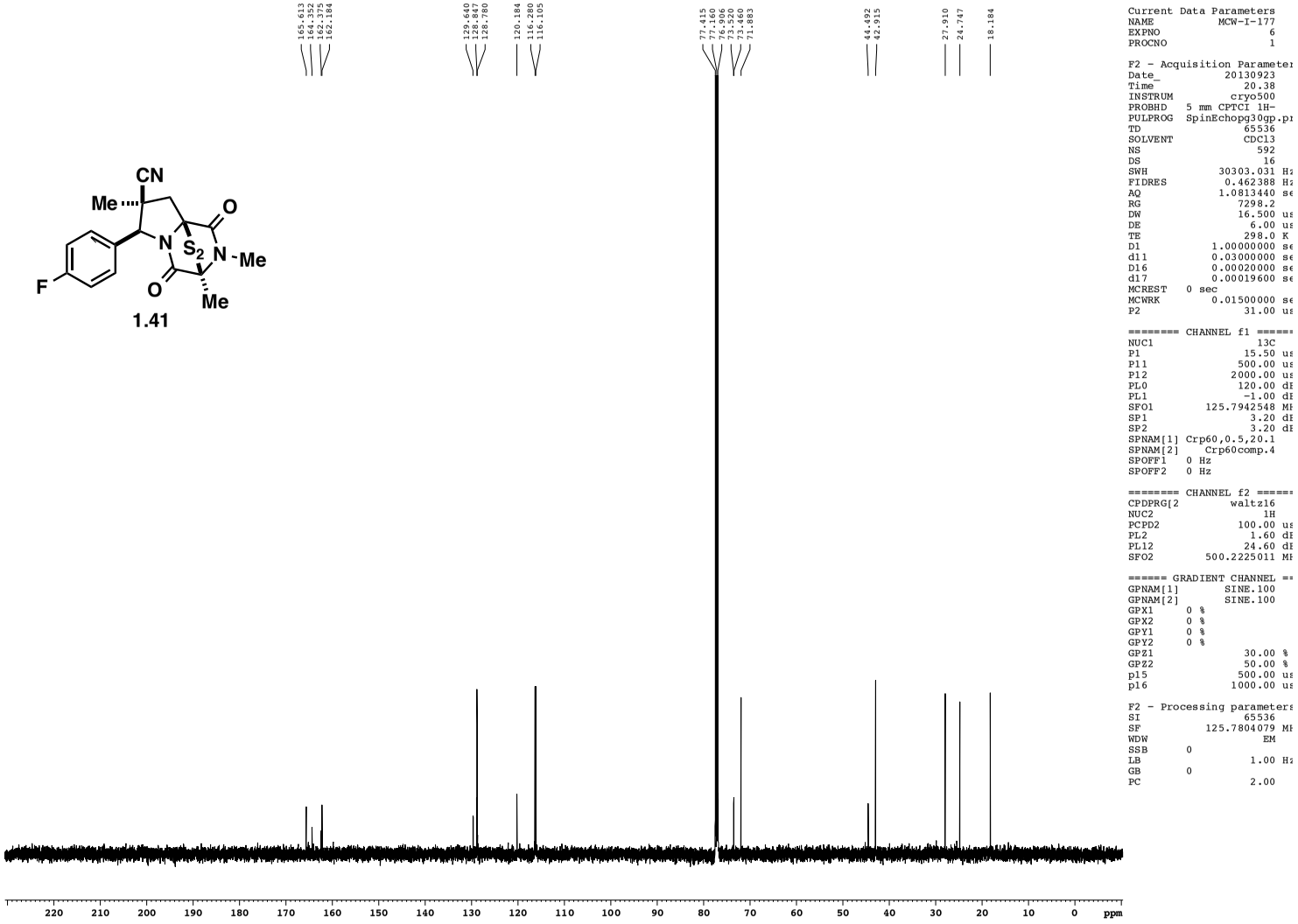
======== CHANNEL f1 ========
NUC1                         1H
P1                        7.50 usec
PL1                       1.60 dB
SFO1                500.2235015 MHz

F2 - Processing parameters
SI                           65536
SF                  500.2200308 MHz
WDW                             EM
SSB           0
LB                        0.30 Hz
GB            0
PC                        4.00
```


Purified Product
Current Data Parameters
NAME MCW-I-176
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130921
Time 21.24
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 3008
DS 0
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 459.6
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MC2REST 0 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
PL2 20000.00 dB
PL10 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804074 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
18.215
24.870
27.886
29.849
42.952
44.501
72.537
73.420
76.905
77.159
77.413
120.246
126.875
129.052
129.572
133.759
162.241
165.747
CN
Me
O
N
S2
N-Me
Me
O
1.40
ppm


Purified Product
Current Data Parameters
NAME MCM-I-177
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130923
Time 20.34
INSTRUM spect
PROBHD 5 mm CPPCI 1H
PULPROG zg30
TD 81928
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.099862 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCWREST 0 sec
MCWREK 0.01500000 sec
========== CHANNEL f1 ==========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200307 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
7.383
7.373
7.366
7.356
7.260
7.151
7.134
7.117
4.892
3.329
3.299
3.084
3.008
2.978
1.940
1.681
2.089
2.300
1.000
1.082
1.123
1.042
2.991
3.192
CN
Me
N
S2
N
Me
Me
O
O
F
1.41
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 ppm
Scale: 0.5263 ppm/cm, 263.3 Hz/cm

Purified Product




```
Current Data Parameters
NAME                  MCW-I-177
EXPNO                         6
PROCNO                        1

F2 - Acquisition Parameter
Date_                  20130923
Time                      20.38
INSTRUM                cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.pr
TD                         65536
SOLVENT                    CDCl3
NS                           592
DS                            16
SWH                  30303.031 Hz
FIDRES                0.462388 Hz
AQ                    1.0813440 se
RG                       7298.2
DW                        16.500 us
DE                         6.00 us
TE                        298.0 K
D1                    1.00000000 se
d11                   0.03000000 se
D16                   0.00020000 se
d17                   0.00019600 se
MCREST   0 sec
MCWRK                 0.01500000 se
P2                         31.00 us

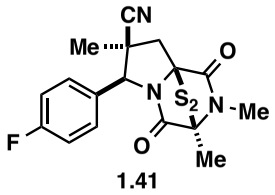
======== CHANNEL f1 ======
NUC1                         13C
P1                         15.50 us
P11                       500.00 us
P12                      2000.00 us
PL0                       120.00 dB
PL1                        -1.00 dB
SFO1                125.7942548 MH
SP1                        3.20 dB
SP2                        3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1   0 Hz
SPOFF2   0 Hz

======== CHANNEL f2 ======
CPDPRG[2                waltz16
NUC2                         1H
PCPD2                     100.00 us
PL2                        1.60 dB
PL12                      24.60 dB
SFO2                500.2225011 MH

====== GRADIENT CHANNEL ==
GPNAM[1]               SINE.100
GPNAM[2]               SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1                      30.00 %
GPZ2                      50.00 %
p15                      500.00 us
p16                     1000.00 us

F2 - Processing parameters
SI                         65536
SF                  125.7804079 MH
WDW                           EM
SSB      0
LB                         1.00 Hz
GB       0
PC                         2.00
```

Purified Product {19F}



1.41

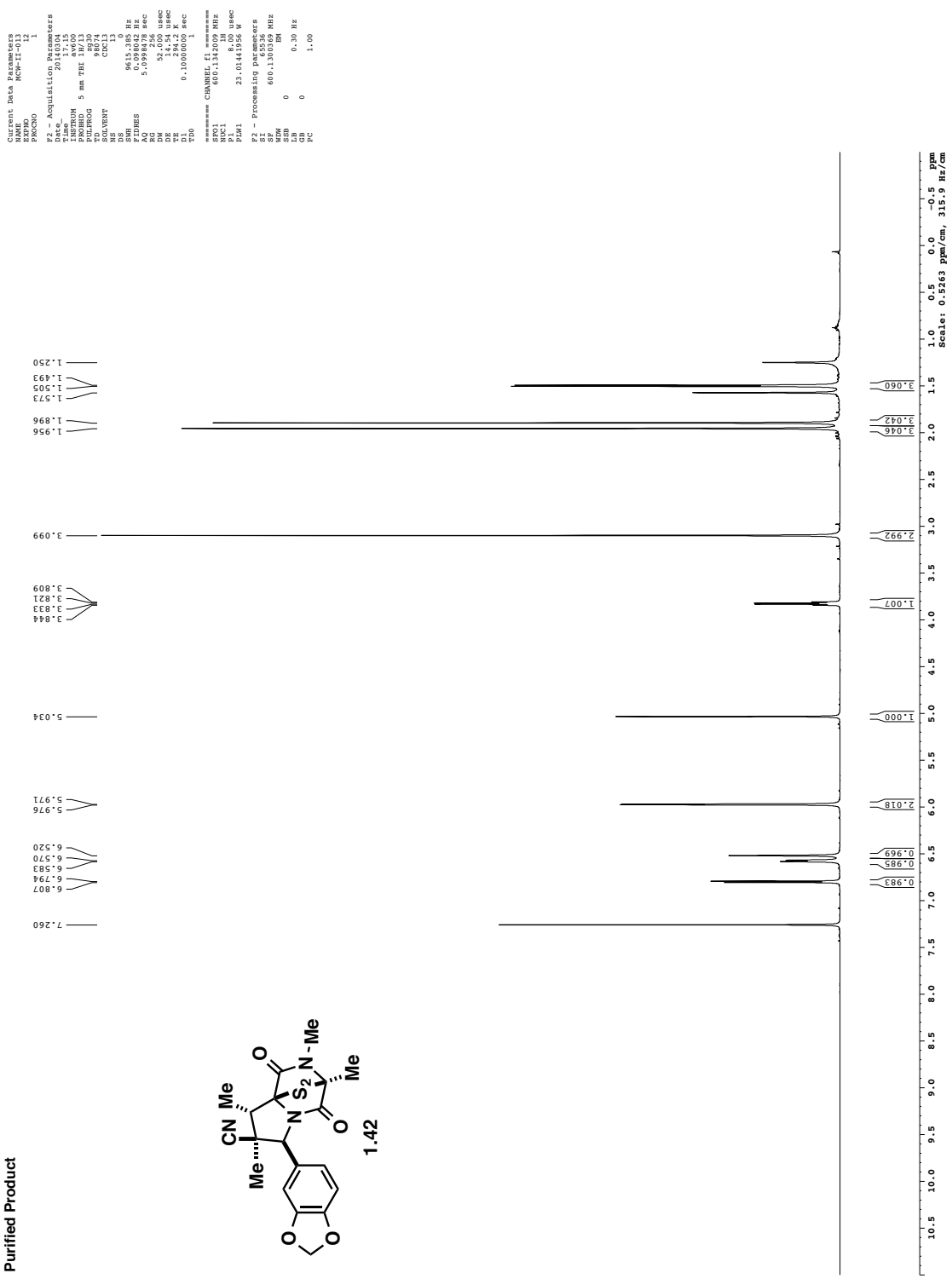

```
Current Data Parameters
NAME                  MCW-1-177
EXPNO                        31
PROCNO                        1

F2 - Acquisition Parameters
Date_               20131008
Time                    17.58
INSTRUM                 drx400
PROBHD    5 mm QNP H/F/P
PULPROG             zgfhigqn30
TD                       65536
SOLVENT                  CDCl3
NS                          32
DS                           4
SWH                 75187.969 Hz
FIDRES              1.147277 Hz
AQ                  0.4358144 sec
RG                     3649.1
DW                      6.650 usec
DE                      9.46 usec
TE                     298.0 K
D1                  2.00000000 sec
D11                 0.03000000 sec
D12                 0.00002000 sec

======== CHANNEL f1 ========
NUC1                       19F
P1                      22.50 usec
PL1                     -6.00 dB
SFO1              376.4646491 MHz

======== CHANNEL f2 ========
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                   80.00 usec
PL2                      3.00 dB
PL12                    16.20 dB
SFO2              400.1320007 MHz

F2 - Processing parameters
SI                       65536
SF                376.4983867 MHz
WDW                         EM
SSB           0
LB                       0.30 Hz
GB            0
PC                       1.00
```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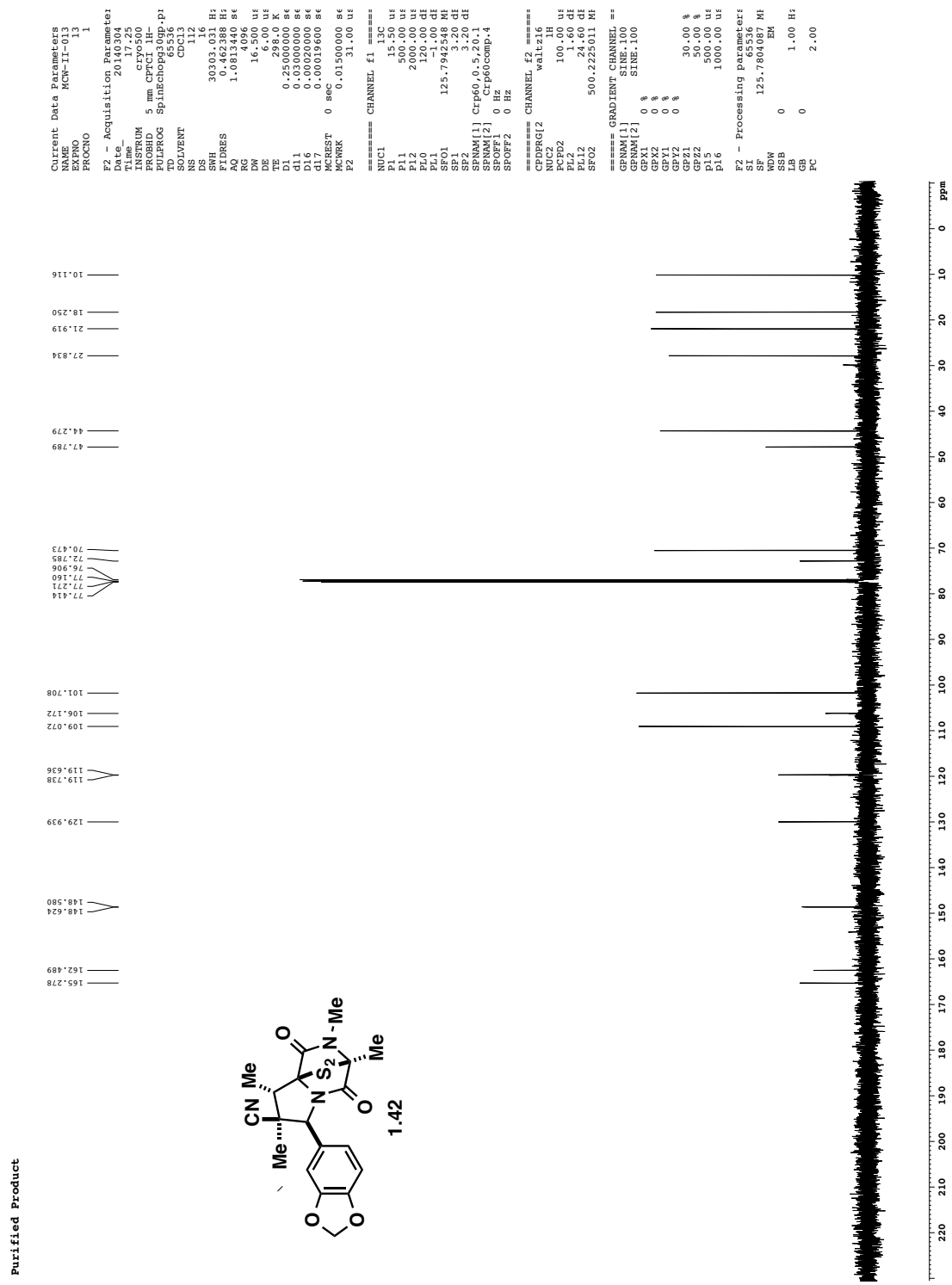
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GPZ1 30.00 %
GPZ2 50.00 %
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1.6 References and Notes

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[45] In contrast to the synthesis of tetrasulfide products accomplished by the Nicolaou and Reisman groups, we observed the disulfide derivative as the major sulfenylation product in our studies. We attribute this to the nonplanar topology of our ETP derivatives, which may not allow for the incorporation of a large tetrasulfide bridge. Alternatively, planar ETP products are common synthetic targets in the Nicolaou and Reisman groups, which may explain their observance of tetrasulfides as the major sulfenylation products (see references 44 and 46).

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[47] See Chapter 2 for studies relating the importance of relative and absolute stereochemistry to the potency of our novel ETP analogues.

[48] The sulfenylation procedure used resulted in the formation of many sulfenylated products. The desired epidithiodioxopiperazines were difficult to purely separate from the corresponding epitrithiodioxopiperazine products, resulting in low isolated yields of the target compounds.

[49] Baumann attempted twice to accomplish the desired 1,3-dipolar cycloaddition but in each case an overnight reaction resulted in 90% recovery of imine starting material **1.44** (unpublished studies, UC Irvine, MB2-141).

[50] As described previously by Baumann (unpublished studies, UC Irvine, MB2-148), treatment of imine **1.44** with 2-methyl-2-butenenitrile in MeCN at 85 °C for 6 h resulted in ca. 90% recovery of unreacted starting material.

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[52] Adapted from the procedure described by Quasdorf (unpublished studies, UC Irvine, KQ2-187).

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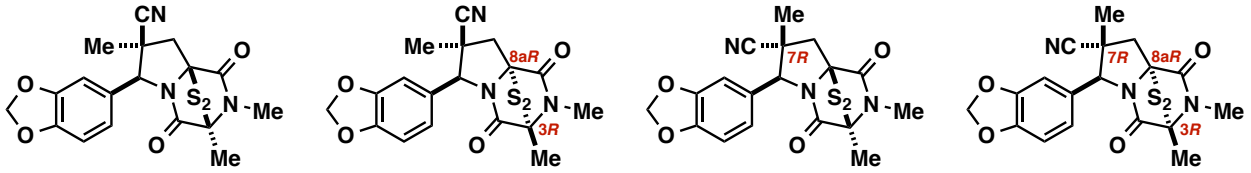
[55] Attempts to purify crude imine products to remove residual unreacted aldehyde (filtration through SiO_2, alumina, Celite, or Florisil, and bulb-to-bulb distillation) resulted in hydrolysis or dimerization of the desired material. If left concentrated for more than a few hours, slow decomposition of the imine was observed.

[56] Solidifies at –20 °C.

Chapter 2: Studies Toward the Development of a Diastereo- and Enantioselective Catalytic 1,3-Dipolar Cycloaddition for the Synthesis of Pyrrolidine Derivatives

2.1. Relative and Absolute Configuration are Important Factors in the Potency of Epidithiodioxopiperazine Analogues

As described in the previous chapter, the Overman group has developed a short synthetic sequence to access epipolythiodioxopiperazine (ETP) analogues that exhibit promising anticancer activity.[1] SAR studies identified ETP analogue **2.1** as the most potent analogue tested to date. Three additional diastereomers–**2.2**, **2.3**, and **2.4**–were synthesized and their anticancer activity was determined in order to investigate the effect of the relative configuration of the pyrrolidine ring substituents and the disulfide bridge on the corresponding IC_{50} value (Figure 2.1). Isomer **2.2**, where the disulfide bridge is trans to both the 3,4-methylenedioxyphenyl and nitrile groups, and congener **2.3**, which possesses a trans relationship between the nitrile group to both the disulfide bridge and the aryl group, both exhibited decreased potency against DU145 prostate cancer and A2058 melanoma cell lines compared to ETP **2.1**. Derivative **2.4**, a product retaining the cis relationship between the nitrile group and disulfide bridge but both of which are trans to the aryl group, exhibited the lowest potency of this series, with IC_{50} values of 2200 nM and 3750 nM against DU145 and A2058 cell lines, respectively. These data illustrated the importance of the relative configuration of the disulfide bridge, the 3,4-methylenedioxyphenyl group, and the nitrile substituent on the ETP skeleton.

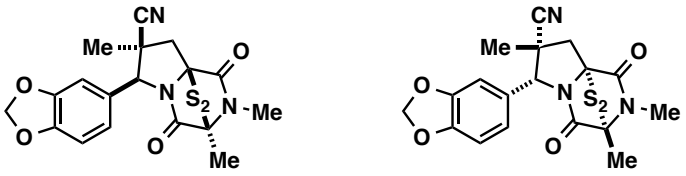


(±)-2.1	(±)-2.2	(±)-2.3	(±)-2.4
IC_{50} Values	IC_{50} Values	IC_{50} Values	IC_{50} Values
DU145: 100 nM A2058: 60 nM	DU145: 750 nM A2058: 220 nM	DU145: 870 nM A2058: 510 nM	DU145: 2200 nM A2058: 3750 nM

Figure 2.1. IC_{50} Values for Four ETP Diastereomers against Two Cancer Cell Lines

Racemic **2.1** was separated into its corresponding enantiomers using enantioselective HPLC.[1a] Growth inhibition assays were run using the resulting enantiopure ETPs, which demonstrated that enantiomer (+)-**2.1** is six times more potent at inhibiting DU145 prostate cancer cells than (–)-**2.1** and 13 times more potent against A2058 cells (Figure 2.2). Collectively, these experiments demonstrate, in addition to relative stereochemistry, that absolute stereochemistry is important in the anticancer activity in this series of ETP analogues.

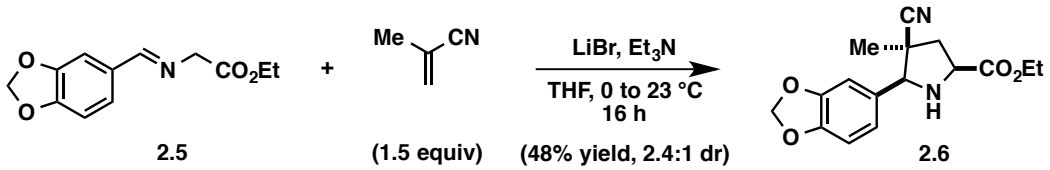
The synthetic route was reevaluated in order to more efficiently access ETP analogues in a diastereo- and enantioselective manner. As the 1,3-dipolar cycloaddition (1,3-DC) between imine **2.5** and methacrylonitrile is the first step in the sequence to **2.1** that introduces chiral centers (eq 2.1),[2] optimization of this step to synthesize endo pyrrolidine adduct **2.6** in a diastereo- and enantioselective fashion was initiated.



(+)-2.1	(–)-2.1
IC_{50} Values	IC_{50} Values
DU145: 130 nM A2058: 60 nM	DU145: 810 nM A2058: 750 nM

Figure 2.2. IC_{50} Values of Enantiopure (+)- and (–)-2.1 Against Two Cancer Cell Lines

Equation 2.1



2.2. Chiral Lewis Acids in 1,3-DCs of Azomethine Ylides

Grigg and coworkers pioneered the early development of metallo-azomethine ylides for regio- and stereoselective 1,3-DC reactions.[3,4] Ester-derived metallo-azomethine ylides adopt a "W-shaped" conformation when coordinated to a Lewis acid (LA, Figure 2.3).[5] Consequently, pyrrolidines formed via the endo transition state contain an all-*cis* relationship between substituents at C2, C4, and C5. In 1991, Grigg and Allway published the first report using a chiral Lewis acid to synthesize enantioenriched pyrrolidines from aryl aldehyde-derived imines.[6] The authors found that $CoCl_2$ and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol formed a suitable chiral catalyst that was used to synthesize pyrrolidine **2.7** in 83% yield and 96% ee (eq 2.2). Two major drawbacks exist in this method: The cobalt complex was used in stoichiometric amounts and, in order to prevent decomposition of the starting material, the dipolarophile methyl acrylate was used as the solvent. Nonetheless, this report inspired further investigations into the development of catalytic asymmetric 1,3-DC reactions.

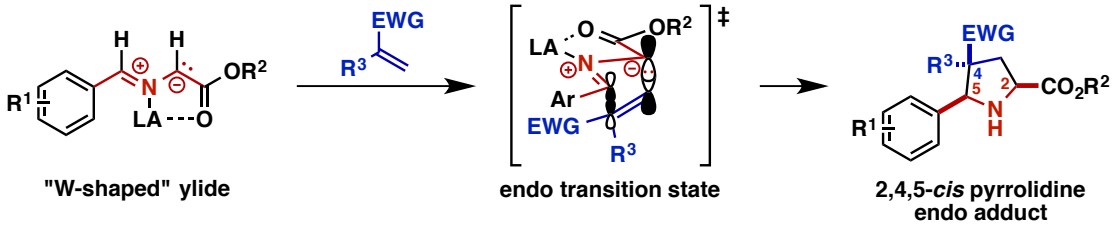
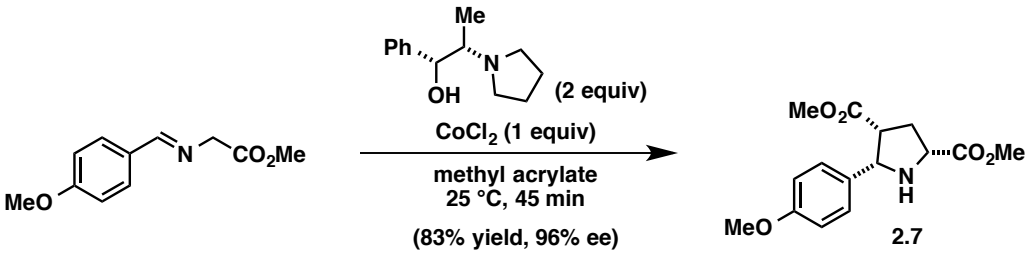
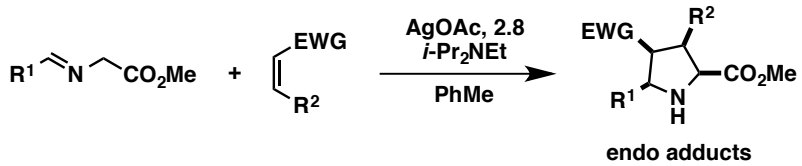


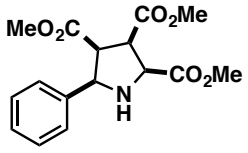
Figure 2.3. 1,3-DC between a "W-Shaped" Azomethine Ylide and an Electron-Deficient Olefin

Equation 2.2



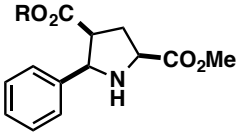
Eleven years after Grigg's development of an asymmetric synthesis of pyrrolidines by 1,3-DC,[6] the first reports of asymmetric 1,3-DC reactions using substoichiometric amounts of catalyst were independently described by the Zhang[7] and Jørgensen[8] groups. The Zhang group described endo adduct-selective syntheses of chiral pyrrolidines using the Ag(I)/xylyl-bis-ferrocenyl amide phosphine (FAP)[9] catalyst **2.8** (Figure 2.4). The authors noted increased enantioenrichment of pyrrolidine **2.9** when using bulky xylyl-FAP ligand **2.8** over FAP (**2.10**) as well as when more sterically demanding dipolarophiles like *tert*-butyl acrylate were employed (compare **2.11** to **2.12**). Using this method, Zhang and coworkers synthesized endo pyrrolidine adducts from 13 different imine substrates and six dipolarophiles with up to 97% ee.[7]





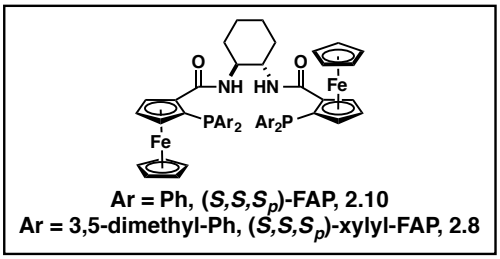
2.9

ligand	yield (%)	ee (%)
2.10	94	76
2.8	87	87



R = Me, 2.11
R = *t*-Bu, 2.12

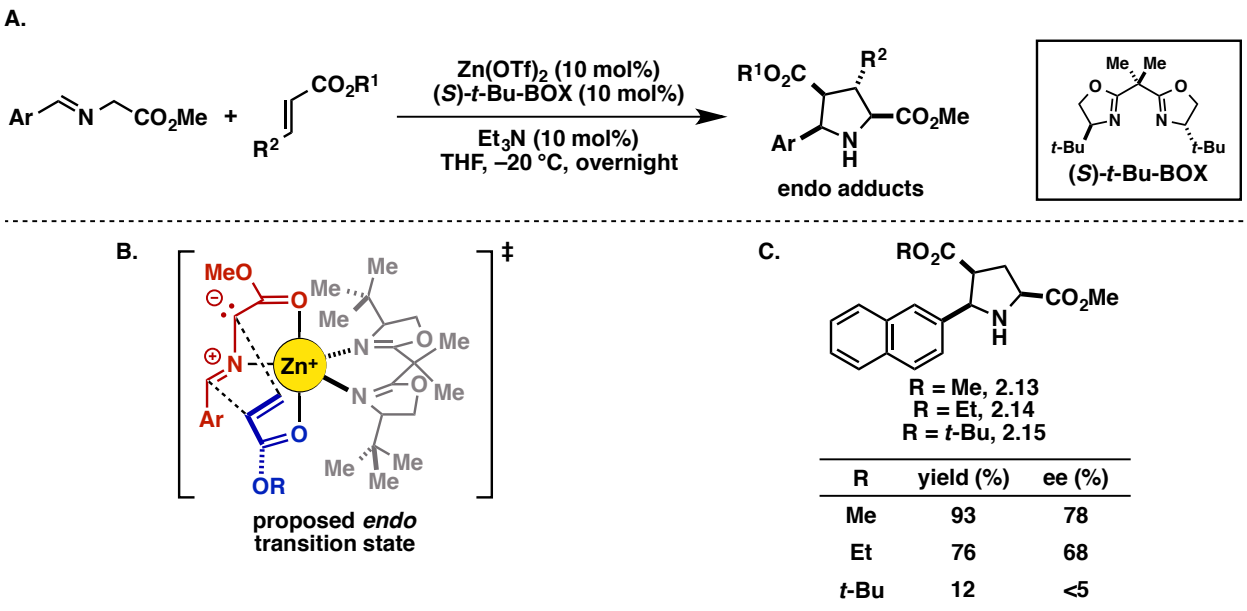
R	yield (%)	ee (%)
Me	90	60
t-Bu	85	93



Ar = Ph, (*S,S,Sp*)-FAP, 2.10
Ar = 3,5-dimethyl-Ph, (*S,S,Sp*)-xylyl-FAP, 2.8

Figure 2.4. Zhang's Ag(I)/xylyl-FAP-Catalyzed Synthesis of Enantioenriched Pyrrolidines

Alternatively, the Jørgensen group reported decreased optical purity of pyrrolidines accessed from acrylates by increasing steric bulk.[8] Using a Zn(II)/*t*-Bu-bisoxazoline (*t*-Bu-BOX) catalyst, endo pyrrolidine adducts were diastereoselectively synthesized from *N*-arylglycinates and acrylates or dimethyl fumarate (Figure 2.5A). The authors proposed a transition state model to explain both the diastereoselectivity and enantioselectivity trends observed in their experiments (Figure 2.5B). This model conforms to the hypothesis where the carbonyl group of the α,β-unsaturated dipolarophile occupies a coordination site on the metal, thereby activating the dipolarophile for the subsequent cycloaddition step. This model also rationalizes the effect of the acrylate bulkiness on yield and enantioenrichment of the corresponding pyrrolidine product (Figure 2.5C). Pyrrolidine **2.13** was synthesized from methyl acrylate in 93% yield with 78% ee. Using ethyl acrylate to access product **2.14**, however, resulted in a lower yield of 76% and a 10% drop in ee. Finally, cycloadduct **2.15** was formed in only 12% yield with enantioenrichment of <5%. The authors rationalize the proposed stabilized endo transition state by observing that acrylonitrile is an unsuitable dipolarophile for the developed reaction conditions, implying that sp^2 hybridization of the dipolarophile vinyl carbon is important in achieving high endo selectivity.[10] Although not supported by X-ray crystal structure analysis or theoretical calculations, the hypothesized endo transition state depicted in Jørgesen's report inspired the development of more selective 1,3-DCs using α,β-unsaturated carbonyl compounds as dipolarophiles.



R	yield (%)	ee (%)
Me	93	78
Et	76	68
t-Bu	12	<5

Figure 2.5. Jørgensen's Zn(II)/*t*-Bu-BOX Catalyst System

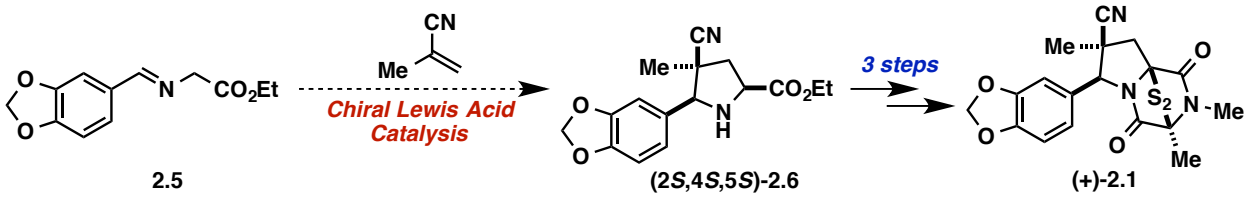
With an aim to develop a more available catalyst system for the asymmetric synthesis of pyrrolidine derivatives,[11] Schreiber and coworkers published a report in 2003 describing a Ag(I)/QUINAP[12] catalyst system.[13] This new catalyst proved to be highly reactive, as pyrrolidine products were synthesized from aryl imines and *tert*-butyl acrylate using only 3 mol % catalyst at –45 °C. Yields were typically high (89–95%) and up to 96% ee was reported. Notably, Schreiber's catalytic system allowed for the first synthesis of enantioenriched pyrrolidine products bearing a quaternary center at the C2 position, although higher reaction temperature and catalyst loading were required for this to be accomplished.

Currently, the catalytic asymmetric 1,3-DC literature utilizing azomethine ylides is dominated by the use of α,β-unsaturated carbonyl compounds as dipolarophiles and the pyrrolidine products formed are derived from the endo transition state in the majority of cases. A variety of different chiral Lewis acid complexes have been described to access optically active pyrrolidine products using salts of Ag(I),[14] Cu(I),[15] Cu(II),[16] Au(I),[17,18] Zn(II),[8,19] Ni(II),[20] or Ca(II).[21] Asymmetric oganocatalytic methods have also been reported.[3c,22] Many reports access

exo pyrrolidine adducts from α,β-unsaturated carbonyl dipolarophiles using Cu(I)[15a,c,d,g,i,j,l,n,p,u] and Cu(II)[16a,d–f,j,k] salts while others have found success using bulky ligands on Ag(I) such as TF-BIPHAMPhos,[14v] DTBM-SEGPHOS,[14w,x,ai;15y,16e] and atropisomeric amides.[14ak] However, far fewer examples exist of 1,3-DC reactions between azomethine ylides and α,β-unsaturated nitrile dipolarophiles.

The Overman lab aspires to selectively synthesize ETP (+)-**2.1** in large quantities in order to pursue more detailed biological studies. This goal can be quickly accomplished though elaboration of enantiopure pyrrolidine (2*S*,4*S*,5*S*)-**2.6** (Scheme 2.1). We wish to develop a diastereo- and enantioselective 1,3-DC between imine **2.5** and methacrylonitrile using chiral Lewis acid catalysis. The deficiency of reports describing the use and behavior of α,β-unsaturated nitrile dipolarophiles in catalytic asymmetric 1,3-DC reactions presents us with the opportunity to explore and better understand the reactivity of this underrepresented class of dipolarophile in catalytic asymmetric 1,3-DC reactions.

Scheme 2.1. Key Reaction to Develop a Highly Selective Synthesis of ETP (+)-2.1

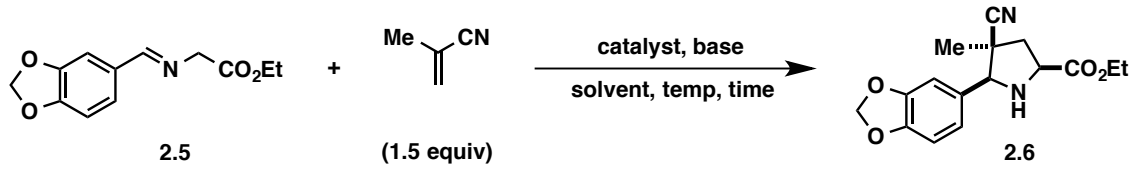


2.2.1 Ag(I)-Catalyzed 1,3-DC Reactions

Because Ag(I) salts are commonly used in catalytic asymmetric 1,3-DC reactions, initial efforts were focused on utilizing the conditions developed by Schreiber.[13] Thus, using 3 mol % Ag(I)/(*R*)-QUINAP catalyst, 1,3-DC between imine **2.5** and methacrylonitrile was attempted; however, no reaction proceeded under the precedented conditions (Table 2.1, entry 1). Reaction temperature (entry 2), catalyst loading (entries 3–9), superstoichiometric Lewis acid

(entries 10–14), solvent (entries 3–6), and organic base (entries 7, 10–14) were varied in order to accomplish the desired transformation. However, all attempts were met without success; unreacted starting material remained after each Ag(I)-catalyzed reaction tested. This indicated that the nitrile functionality of the dipolarophile might be poisoning the Ag(I) catalyst.

Table 2.1. Condition Screening for Ag(I)-Catalyzed 1,3-DC using Methacrylonitrile



2.5 (1.5 equiv) 2.6

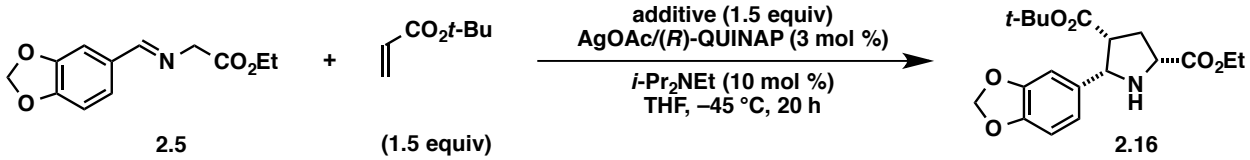
entry	catalyst (mol %)	base (mol %)	solvent	temp (°C)	time (h)	conversion (%)[a]	dr (endo:exo)
1	AgOAc/(*R*)-QUINAP (3)	*i*-Pr_2NEt (10)	THF	–45	20	0	–
2	AgOAc/(*R*)-QUINAP (3)	*i*-Pr_2NEt (10)	THF	0 to 23	16	0	–
3	AgOAc/(*R*)-QUINAP (5)	*i*-Pr_2NEt (17)	THF	–45	20	0	–
4	AgOAc/(*R*)-QUINAP (5)	*i*-Pr_2NEt (17)	PhMe	–45	20	0	–
5	AgOAc/(*R*)-QUINAP (5)	*i*-Pr_2NEt (17)	CH_2Cl_2	–45	20	0	–
6	AgOAc/(*R*)-QUINAP (5)	*i*-Pr_2NEt (17)	Et_2O	–45	20	0	–
7	AgOAc/(*S*)-QUINAP (5)	Et_3N (17)	THF	–45	20	0	–
8	AgOAc/(*S*)-QUINAP (5)	–	THF	–45	20	0	–
9	AgOAc/(*R*)-QUINAP (20)	*i*-Pr_2NEt (50)	THF	–45	20	0	–
10	LiBr (120)	Et_3N (120)	THF	–45	20	33	71:29
11	LiBr (120)	Et_3N (120)	THF	0 to 23	16	80	80:20
12	LiBr (120)	*i*-Pr_2NEt (120)	THF	0 to 23	16	25	75:25
13	AgOAc (120)	*i*-Pr_2NEt (120)	THF	0 to 23	16	0	–
14	AgOAc (120)	Et_3N (120)	THF	0 to 23	16	0	–

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture.

A set of competition experiments was designed in order to test whether the nitrile functionality of the dipolarophile was inhibiting the reactivity of the Ag(I)/QUINAP catalyst (Table 2.2). As the reaction between imine **2.5** and *tert*-butyl acrylate succeeded in 32% yield with exclusive formation of endo pyrrolidine adduct **2.16** (90% ee, entry 1),[23] this cycloaddition reaction was run with the inclusion of a nitrile-containing additive. Methacrylonitrile,

acetonitrile, and isobutyronitrile were chosen as the three additives, allowing the effect of both the nitrile functionality and steric hindrance on catalyst activity to be determined. No desired reactivity was observed with the inclusion of methacrylonitrile (entry 2). The addition of acetonitrile allowed for 5% pyrrolidine **2.16** to be formed, as determined by ^{1}H NMR (entry 3). Finally, the use of isobutyronitrile resulted in a 19% ^{1}H NMR yield of desired product **2.16** (entry 4).

Table 2.2. Competition Experiments to Test Nitrile–Ag(I) Compatibility



2.5 (1.5 equiv) 2.16

entry	additive	yield (%)[a]	ee (%)[b]
1	none	32	90
2	methacrylonitrile	0	–
3	acetonitrile	5	nd
4	isobutyronitrile[c]	19	nd

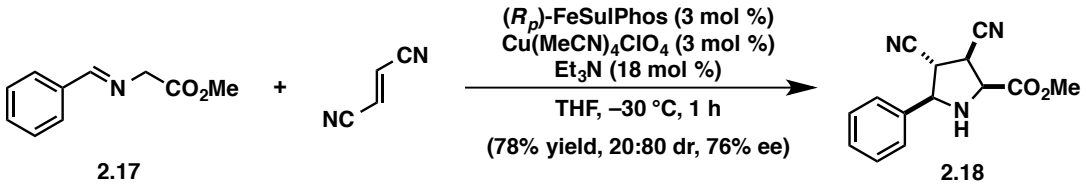
[a]Yield determined by ^{1}H NMR using DMF as an external standard. [b]Determined by enantioselective HPLC. [c]Reaction run using (*S*)-QUINAP. nd = not determined.

Collectively, the results of the competition experiments indicate that the nitrile functionality is interfering with the desired 1,3-DC reactivity and that dipolarophile sterics as well as conjugation are important factors in poisoning the silver catalyst. These results are consistent with a study by the Kühn group, who tested the effect of metal–nitrile bond strengths on the activity of a cyclopropanation catalyst with MeCN ligands.[24] Kühn's results indicated that the strong MeCN–Ag bond[25] inhibited reactivity while the weaker MeCN–Cu bond allowed Cu(I) complexes to be catalytically active. Thus, the focus of the reaction development was shifted to investigate the effectiveness of Cu(I) catalysts in the desired transformation.

2.2.2 Cu(I)-Catalyzed 1,3-DC Reactions

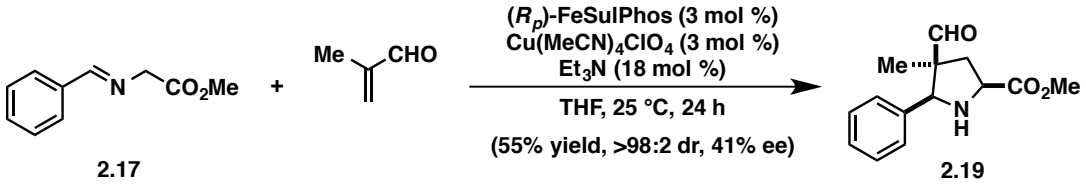
Carretero and coworkers accomplished asymmetric 1,3-DCs with fumaronitrile to form nitrile-containing pyrrolidines using $Cu(MeCN)_4ClO_4$ and enantiopure FeSulPhos ligands.[15b,e;26] Although the reaction of imine **2.17** with fumaronitrile preferentially formed exo pyrrolidine adduct **2.18** in 78% yield, 20:80 dr (endo:exo), and 76% ee (eq 2.3), Carretero showed that reaction of imine **2.17** with methacrolein selectively afforded endo adduct **2.19** in 55% yield and >98:2 dr (eq 2.4). Encouraged by Carretero's results using a nitrile-containing dipolarophile and separately an α-subsituted dipolarophile, the Cu(I)/(R_p)-FeSulPhos-catalyzed[27] 1,3-DC between imine **2.5** and methacrylonitrile was studied.

Equation 2.3



2.17 2.18

Equation 2.4



2.17 2.19

The Cu(I)/(R_p)-FeSulPhos-catalyzed 1,3-DC between imine **2.5** and methacrylonitrile resulted in the formation of the minor endo cycloadduct **2.6** in a 18:82 dr and 50% ee (eq 2.5). Based on conversion and diastereoselectivity of the 1,3-DC using 10 mol % Cu(I)/(R_p)-FeSulPhos catalyst, toluene (PhMe) was chosen as the solvent to be used in subsequent reactions (Table 2.3).

Equation 2.5

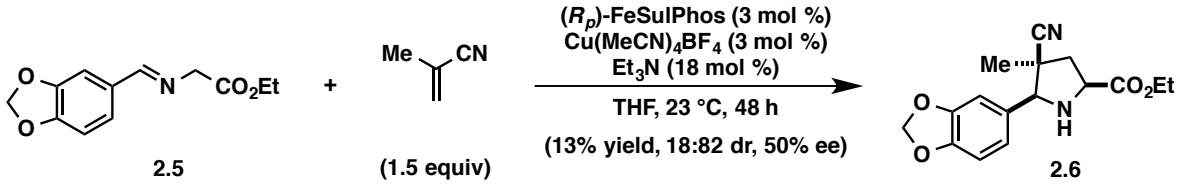
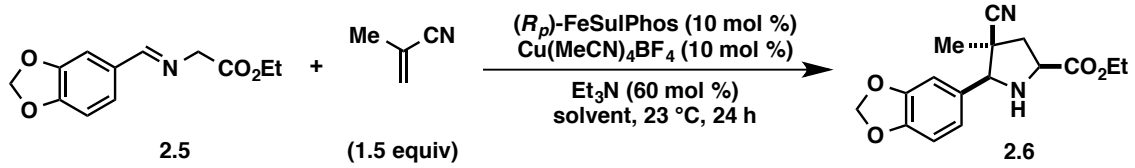


Table 2.3. Investigation of Solvent to Selectively Access Pyrrolidine 2.6



entry	solvent	conversion (%)[a]	dr (endo:exo)
1	THF	>95	17:83
2	DME	>95	17:83
3	Et_2O	95	21:79
4	CH_2Cl_2	94	14:86
5	PhMe	>95	29:71
6	PhH	89	33:67
7	MeOH	>95	28:72
8	MeCN	0	–
9	DMF	0	–

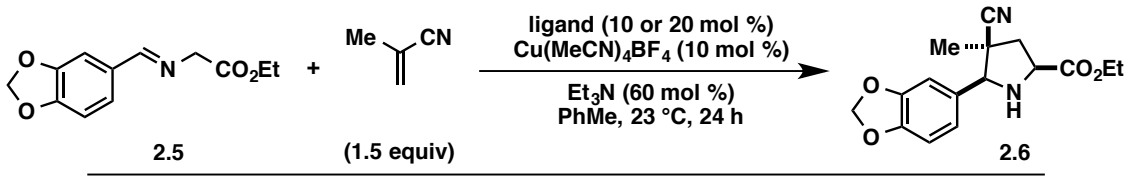
[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture.

2.3 Investigation of Ligand Types

A variety of different ligand types was investigated in order to identify a catalyst that exhibits the desired endo adduct selectivity in the 1,3-DC between imine **2.5** and methacrylonitrile (Table 2.4). Using a catalyst loading of 10 mol % and PhMe as the solvent, the 1,3-DC catalyzed by Cu(I)/(R_p)-FeSulPhos resulted in a 29:71 dr and a 38% ee of the endo pyrrolidine adduct **2.6** (entry 1). *P*,*N*-ligands (*S*)-QUINAP and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos) were also tested. These reactions offered low-to-no conversion to product and no diastereoselectivity (entries 2 and 3). Heteroatom-substituted

phosphine oxide (HASPO) ligand **2.20** and *N*-heterocyclic carbene (NHC) **2.21** were also examined in the 1,3-DC, both of which resulted in low conversion (entries 4 and 5).

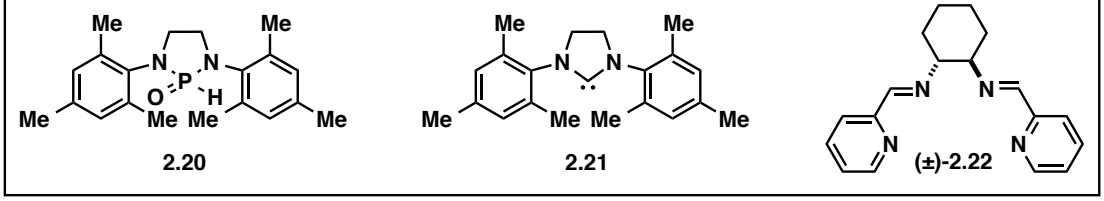
Table 2.4. *P,S*-, *P,N*-, HASPO, NHC, and Pyridine-Based Ligands



2.5 (1.5 equiv) 2.6

entry	ligand (mol %)	conversion (%)[a]	dr (endo:exo)	ee_{endo} (%)[b]
1	(R_p)-FeSulPhos (10)	>95	29:71	38
2	(*S*)-QUINAP (10)	0	–	nd
3	DavePhos (10)	57	50:50	–
4	HASPO 2.20 (20)	33	70:30	–
5	NHC 2.21 (20)[c]	31	60:40	–
6	bpy (10)	0	–	–
7	1,10-phenanthroline (10)	5	nd	–
8	(+)-PyBOX (10)	<5	nd	nd
9	(±)-2.22 (10)	22	74:26	–

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture. [b]Determined by enantioselective HPLC. [c]THF was used as the reaction solvent. nd = not determined.



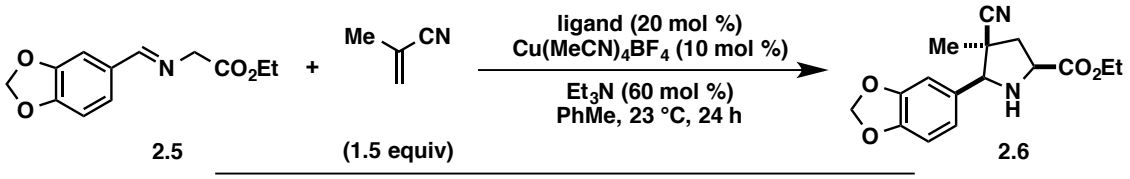
2.20 2.21 (±)-2.22

N,N'-Bidentate ligands are common in copper catalysis;[28] thus, the efficacy of select bipyridyl, bisoxazoline (BOX),[29] and diimine ligands were explored (Table 2.4). 2,2'-Bipyridyl (bpy), 1,10-phenanthroline, and (+)-PyBOX were ineffective ligands for the Cu(I)-catalyzed 1,3-DC, resulting in <5% conversion to desired product **2.6** (entries 6–8). The reaction run using racemic diimine ligand **2.22**[30] resulted in preferential formation of the endo cycloadduct (74:26 dr), but proceeded with a low 22% conversion (entry 9). As a result of the low reactivity

of pyridine-type ligands in the target reaction, the implementation of phosphorus-based ligands was studied next.

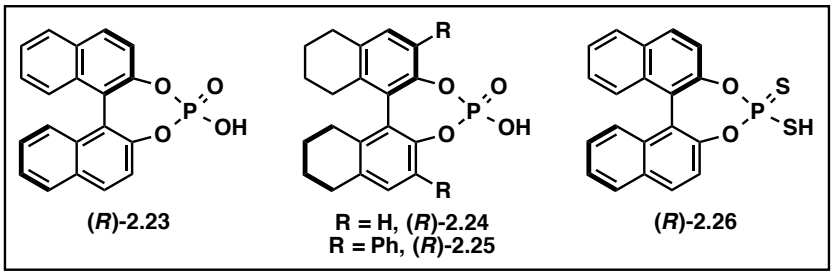
The effectiveness of chiral phosphoric acids as ligands was also explored (Table 2.5).[31] While reactions employing ligands (*R*)-**2.23**–(*R*)-**2.25** were selective for the endo adduct (ca. 85:15 dr), overall reactivity and resulting ee of product **2.6** were low (entries 1–3). Using dithiophosphoric acid ligand (*R*)-**2.26** resulted in no desired reactivity (entry 4). Thus, the reactivity of ligand classes other than chiral phosphoric acids was further explored.

Table 2.5. Chiral Phosphoric Acid Ligands



entry	ligand	conversion (%)[a]	dr (endo:exo)	ee_{endo} (%)[b]
1	(*R*)-2.23	33	86:14	0
2	(*R*)-2.24	49	84:16	2
3	(*R*)-2.25	51	87:13	0
4	(*R*)-2.26	<5	nd	nd

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture. [b]Determined by enantioselective HPLC. nd = not determined.

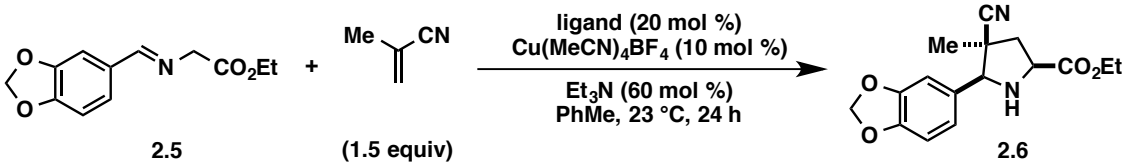


2.3.1 Phosphoramidite Ligands

Phosphoramidites are privileged ligands in asymmetric catalysis.[32] Their synthesis is robust and many research groups have accessed large libraries of chiral non-racemic phosphoramidite ligands.[33] Five phosphoramidite ligands were initially used in the Cu(I)-

catalyzed 1,3-DC reaction between imine **2.5** and methacrylonitrile (Table 2.6). Reactions run using BINOL-derived ligands (*S*)-Monophos,[34] (*S*)-**2.27**, and (*R,S*)-**2.28**[35] resulted in a non-selective mixture of endo and exo cycloadducts (ca. 62:38 dr) with 37–90% conversion and 22–43% ee of desired endo adduct **2.6** (entries 1–3). Using TADDOL-derived ligand[36,37] (*R,R*)-**2.29** resulted in no desired product (entry 4) and (*S*)-Metamorphos[35] proved to be an equally ineffective ligand (entry 5). In order to increase catalyst solubility and generalize the further use of phosphoramidite ligands, the reaction solvent was changed to THF.

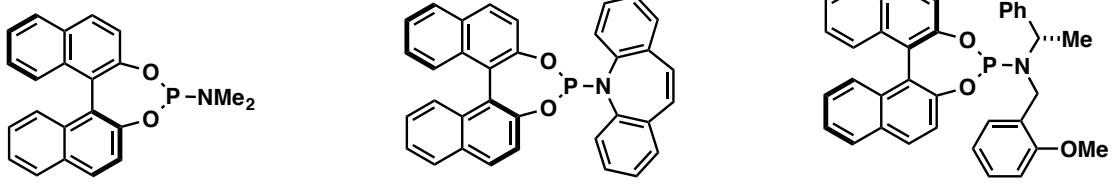
Table 2.6. Phosphoramidite Ligands Used with PhMe as the Reaction Solvent



2.5 (1.5 equiv) 2.6

entry	ligand (mol %)	conversion (%)[a]	dr (endo:exo)	ee_{endo} (%)[b]
1	(*S*)-Monophos	90	64:36	36
2	(*S*)-2.27	37	62:38	22
3	(*R,S*)-2.28	72	62:38	43
4	(*R,R*)-2.29	0	–	–
5	(*S*)-Metamorphos	<5%	nd	nd

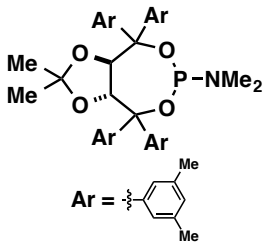
[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture. [b]Determined by enantioselective HPLC. nd = not determined.



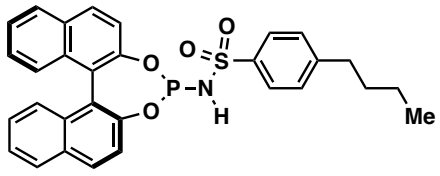
(*S*)-Monophos

(*S*)-2.27

(*R,S*)-2.28



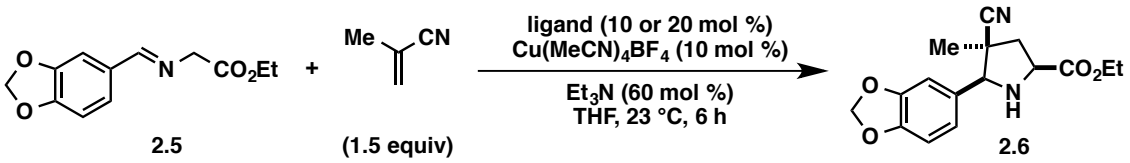
(*R,R*)-2.29



(*S*)-Metamorphos

After modifying the reaction between imine **2.5** and methacrylonitrile to run for 6 h in THF, a library of phosphoramidite ligands was tested (Table 2.7). Reactions performed using BINOL-achiral amine ligands resulted in poor diastereo- and enantioselectivity for endo adduct **2.6** (entries 1–4). The implementation of BINOL-chiral amine ligands resulted in reactions that were overall more selective for the exo cycloadduct (entries 5–8), yet pyrrolidine **2.6** was accessed with 58% ee when ligand (*R,R,R*)-**2.30** was used (entry 8). The highest ee was achieved when (*R,S*)-(1-Nph)-Quinaphos was used as the ligand (72% ee); however, this reaction was highly selective for the undesired exo cycloadduct (10:90 dr, entry 9). When the (*R*)-SIPHOS[38] ligand was used, product **2.6** was accessed with 26% ee but the reaction was not selective (49:51 dr, entry 10). The use of ligand (*R,R,R*)-**2.31** eroded the ee to 0% and the reaction favored the formation of the exo cycloadduct (29:71 dr, entry 11). Finally, when TADDOL-dimethylamine phosphoramidite (*R,R*)-**2.32** was used as the ligand, the reaction was not diastereoselective (45:55 dr), but endo adduct **2.6** was synthesized with 38% ee (entry 12). Although the reaction run using the Cu(I)/(*R,S*)-(1-Nph)-Quinaphos catalyst afforded desired product **2.6** in the highest ee, the diastereoselectivity was undesired. As a result, other ligand types were investigated using the new reaction conditions in THF.

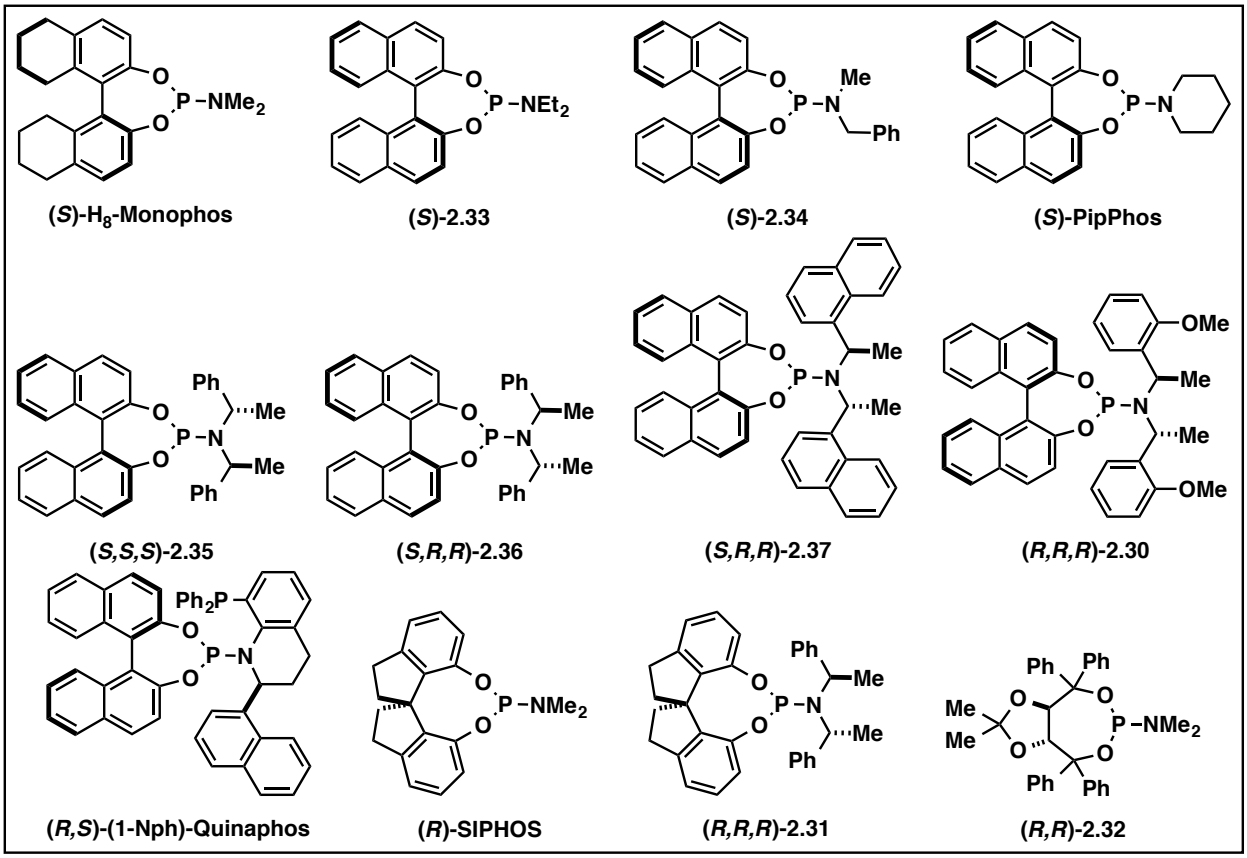
Table 2.7. Phosphoramidite Ligands Used with THF as the Reaction Solvent



2.5 (1.5 equiv) 2.6

entry	ligand (mol %)	conversion (%)[a]	dr (endo:exo)	ee_{endo} (%)[b]
1	(*S*)-H_8-Monophos (20)	74	35:65	8
2	(*S*)-2.33 (20)	28	45:55	nd
3	(*S*)-2.34 (20)	36	50:50	29
4	(*S*)-PipPhos (20)	11	50:50	nd
5	(*S,S,S*)-2.35 (20)	95	22:78	8
6	(*S,R,R*)-2.36 (20)	57	49:51	4
7	(*S,R,R*)-2.37 (20)	98	27:73	2
8	(*R,R,R*)-2.30 (20)	95	26:74	58
9	(*R,S*)-(1-Nph)-Quinaphos (10)	96	10:90	72
10	(*R*)-SIPHOS (20)	97	49:51	26
11	(*R,R,R*)-2.31 (20)	98	29:71	0
12	(*R,R*)-2.32 (20)	70	45:55	38

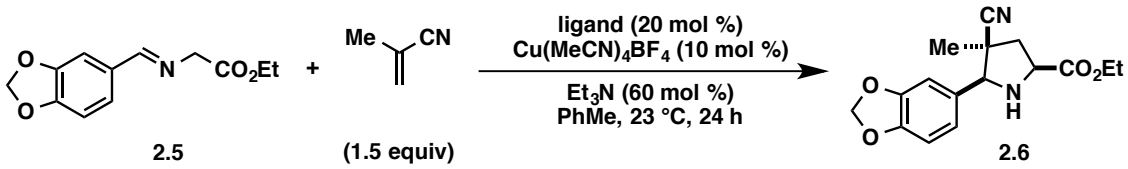
[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture. [b]Determined by enantioselective HPLC. nd = not determined.



2.3.2 Phosphine Ligands

Monodentate phosphines were next explored as ligands in the desired 1,3-DC reaction (Table 2.8). The use of triphenylphosphine as the ligand resulted in a low conversion to pyrrolidine products and a nonselective 58:42 dr (entry 1). A trend was observed when using fluorine-substituted ligands tris(*p*-fluorophenyl)phosphine and tris(pentafluorophenyl)phosphine. Conversions increased to over 90% and the diastereoselectivity of the reaction favored endo adduct **2.6** with increasing fluorine substitution on the ligand (entries 2 and 3). Three phosphines with substitution at the *ortho* position were also examined (entries 10–12). Ligands tri(*o*-tolyl)phosphine (entry 4) and tri(2-furyl)phosphine (entry 5) resulted in a 1,3-DC that proceeded in 52% and 68% conversion to product and 75:25 and 50:50 dr, respectively. The reaction run using (2-cyanophenyl)diphenylphosphine as the ligand proceeded with a low 29% conversion yet favored endo adduct **2.6** in a 79:21 dr (entry 6). Interestingly, the use of electron-rich tricyclohexylphoshpine as the ligand favored the exo pyrrolidine adduct in an 18:82 dr with a 98% conversion to product (entry 7). Finally, the reaction catalyzed by a Cu(I)/tris(hydroxymethyl)phosphine resulted in no desired reactivity (entry 8). This set of experiments revealed an interesting trend between ligand electronic effects and the diastereoselectivity of the 1,3-DC reaction. In order to further investigate this breakthrough observation, achiral and chiral polydentate phosphines were tested.

Table 2.8. Achiral Monodentate Phosphines



2.5 (1.5 equiv) 2.6

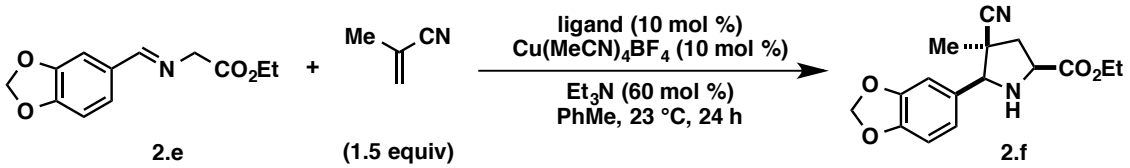
entry	ligand	conversion (%)[a]	dr (endo:exo)
1	triphenylphosphine	12	58:42
2	tris(*p*-fluorophenyl)phosphine	97	63:37
3	tris(pentafluorophenyl)phosphine	94	80:20
4	tri(*o*-tolyl)phosphine	52	75:25
5	tri(2-furyl)phosphine	68	50:50
6	(2-cyanophenyl)diphenylphosphine	29	79:21
7	tricyclohexylphosphine	98	18:82
8	tris(hydroxymethyl)phosphine	0	–

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture.

The selectivity trends of achiral polydentate phosphines in the targeted 1,3-DC were next explored (Table 2.9). The Cu(I)/1,2-bis(diphenylphosphino)ethane (dppe) complex catalyzed an endo adduct-selective 1,3-DC (entry 1). The use of the more electron-deficient variant 1,2-bis[bis(pentafluorophenyl)phosphino]ethane (dfppe) as the ligand resulted in a slower reaction and offered no improved endo selectivity (entry 2), unlike the trend observed with achiral monodentate phosphines. 1,3-Bis(diphenylphosphino)propane (dppp), whose extra methylene unit increased the bite angle to 91° (dppe = 85°), resulted in an erosion of endo selectivity (compare entries 1 and 3). Further increasing the bite angle of the ligand to 97° resulted in a dramatic loss of catalytic activity, as the reaction using a Cu(I)/1,4-bis(diphenylphosphino)butane (dppb) catalyst resulted in almost complete recovery of starting material (entry 4). The use of either 1,2-bis(diphenylphosphino)benzene (dppbz) or 1,1'-bis(diphenylphosphino)ferrocene (dppf) as the ligand resulted in low reactivity and endo selectivities near 70:30 dr (entries 5 and 6). As the bite angles of dppbz and dppf are 83° and 96°,

respectively, these studies do not indicate a trend relating diphosphine bite angle and reaction selectivity (entries 1–6).[39] DPEPhos and NIXANTPHOS were ineffective ligands to catalyze the reaction (entry 7 and 8), and XANTPHOS[40] and *t*-Bu-XANTPHOS promoted the desired transformation to only 26% and 48% conversion, respectively, after 24 h (entries 9 and 10).

Table 2.9. Achiral Bidentate Phosphine Ligands



2.e (1.5 equiv) 2.f

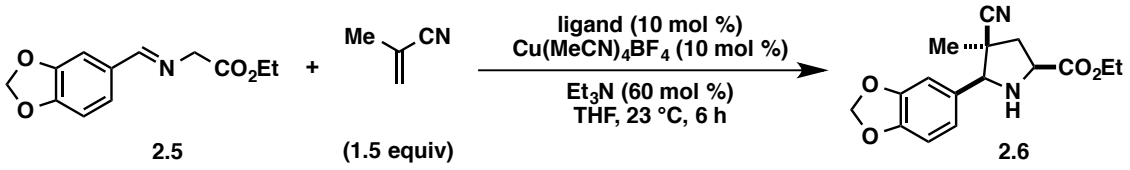
entry	ligand	conversion (%)[a]	dr (endo:exo)
1	dppe	92	81:19
2	dfppe	40	79:21
3	dppp	94	68:32
4	dppb	<5	nd
5	dpppbz	40	66:34
6	dppf	8	71:29
7	DPEPhos	0	–
8	NIXANTPHOS	0	–
9	XANTPHOS	26	69:31
10	*t*-Bu-XANTPHOS	48	48:52

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture. nd = not determined.

Bis(diphenylphosphine) ligands of various chain lengths and two tridentate phosphines were tested in THF (Table 2.10). Reactions that used dppe, dppp, and dppb as ligands resulted in high conversion to product and high endo selectivity (ca. 95% conversion and 85:15 dr, entries 1–3). Reactivity and endo selectivity were increased in the cases of dppp and dppb compared to the same reaction run in PhMe for 24 h (see Table 2.9, entries 3 and 4). Endo selectivity was lower for reactions using either 1,5-bis(diphenyl-phosphino)pentane (dpppe) or 1,6-bis(diphenylphosphino)hexane as the ligand (67:33 dr, entries 4 and 5). The diastereoselectivity was reversed when using either bis(2-diphenylphosphinoethyl)phenylphosphine (90:10 dr,

entry 6) or 1,1,1-tris(diphenylphosphinomethyl)ethane (8:92 dr, entry 7), although the nature of this switch is not well understood at this time. This set of experiments demonstrates the effectiveness of select achiral polydentate phosphine ligands to diastereoselectively access endo pyrrolidine adduct **2.6** in high conversion, although no clear trend relating structure and selectivity could be established.

Table 2.10. Achiral Polydentate Phosphine Ligands in THF



2.5 (1.5 equiv) 2.6

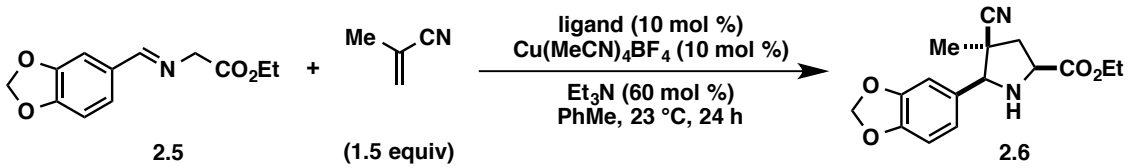
entry	ligand (mol %)	conversion (%)[a]	dr (endo:exo)
1	dppe	93	84:16
2	dppp	96	87:13
3	dppb	95	82:18
4	dpppe	96	67:33
5	1,6-bis(diphenylphosphino)hexane	94	67:33
6	bis(2-diphenylphosphinoethyl)phenylphosphine	97	90:10
7	1,1,1-tris(diphenylphosphinomethyl)ethane	95	8:92

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture.

The ability of chiral bisphosphine ligands to induce enantioselection in the Cu(I)-catalyzed 1,3-DC reaction was investigated next (Table 2.11). The reaction utilizing chiral ferrocenyldiphosphine Josiphos ligand[41] SL-J002-2 resulted in a 61% conversion to product, poor diastereoselectivity (42:58 dr), and a low 7% enantioenrichment of the desired endo adduct **2.6** (entry 1). While the use of ligand (*S,S*)-DIOP[42,43] in the reaction allowed for high conversion to the desired pyrrolidine products, the endo adduct diastereo- and enantioselectivities were low (entry 2). The use of (*R,R*)-Me-DUPHOS[44] resulted in lower reactivity and no diastereoselectivity; however the ee of the endo pyrrolidine adduct was increased to 44% (entry 3). The 1,3-DC reaction using (*S,S*)-DACH-phenyl Trost ligand[45] resulted in a 69:31 dr

and 50% ee of endo cycloadduct **2.6**. Cu(I)/(*S*)-BINAP[46,47] or Cu(I)/(*S*)-TolBINAP[48] complexes possessed high reactivity but favored the exo pyrrolidine cycloadduct in 26:74 or 30:70 dr, respectively (entries 5 and 6).

Table 2.11. Chiral Diphosphine Ligands Tested in the Cu(I)-Catalyzed 1,3-DC



2.5 (1.5 equiv) 2.6

entry	ligand	conversion (%)[a]	dr (endo:exo)	ee_{endo} (%)[b]
1	SL-J002-2	61	42:58	7
2	(*S,S*)-DIOP	92	40:60	25
3	(*R,R*)-Me-DUPHOS	37	60:40	44
4	(*S,S*)-DACH-phenyl	39	69:31	50
5	(*S*)-BINAP	93	26:74	42
6	(*R*)-TolBINAP	95	30:70	32
7	BIPHEP	96	34:66	–
8	(*R*)-MeOBIPHEP	94	27:73	6
9	(*R*)-3,5-*i*-Pr-MeOBIPHEP	83	11:89	36
10	(*R*)-3,5-xyl-MeOBIPHEP	22	73:27	2
11	(*R*)-SEGPHOS	9	32:68	nd
12	(*R*)-DIFLUOROPHOS	91	40:60	14

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture. [b]Determined by enantioselective HPLC. nd = not determined.

Substitution effects were examined using achiral BIPHEP[49] and three chiral MeOBIPHEP ligands[50] (Table 2.11, entries 7–10). Initially, it seemed that exo adduct selectivity improved with increasing bulkiness of the MeOBIPHEP ligand; however, the reaction catalyzed by the Cu(I)/(*R*)-3,5-xyl-MeOBIPHEP complex favored the endo adduct in a 73:27 dr, but with little enantioinduction (2% ee, entry 10). Finally, the effects of SEGPHOS[51] and DPEPhos[52] ligands were tested. While the introduction of difluoromethylene groups in (*R*)-DIFLUOROPHOS[53] increased the reactivity compared to using (*R*)-SEGPHOS, the

diastereoselectivity of the two reactions were similar, despite the difference in their electronic properties (entries 11 and 12). Of the polydentate phosphine ligands used, bis(2-diphenyl-phosphinoethyl)phenylphosphine resulted in the highest endo adduct selectivity (90:10 dr, Table 2.10, entry 6). The highest ee of endo adduct **2.6**, 44%, was achieved using (*R,R*)-Me-DUPHOS as the ligand on Cu(I), yet the overall reaction lacked diastereoselectivity (Table 2.11, entry 3).

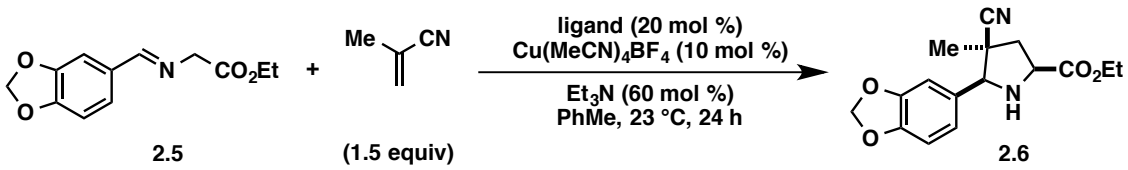
In summary, an interesting trend was discovered when achiral phosphine ligands were tested in the Cu(I)-catalyzed 1,3-DC reaction. Endo adduct selectivity increased with increased fluorine substitution on the triphenylphosphine backbone. It was also shown that electron-rich, bulky ligands like tricyclohexylphosphine were highly selective for the exo cycloadduct. Because no additional trends were recognized with the other phosphine ligands tested, phosphite ligands were chosen as the next ligand class to investigate.

2.3.3 Phosphite Ligands

Phosphite ligands are good π-acceptor ligands, which gives them a unique electron-withdrawing property that is not shared with phosphines.[54] High endo adduct selectivity was discovered while testing achiral monodentate phosphite ligands in the desired Cu(I)-catalyzed 1,3-DC reaction (Table 2.12). Using triphenyl phosphite as the ligand, pyrrolidine **2.6** was synthesized in 91% conversion with a 94:6 dr (entry 1). The use of either tris(2,4-di-*tert*-butylphenyl) phosphite or trimethyl phosphite resulted in slight erosion of endo selectivity to approximately 75:25 dr (entries 2 and 3). Dimethyl phosphite, a ligand which contains a P=O and P–H bond, did not allow for the desired transformation to occur (entry 4). Interestingly, the diastereoselectivity of the reaction was reversed to a 26:74 dr when the triisopropyl phosphite ligand was employed (entry 5). The highest endo adduct selectivity was achieved by using

tris(2,2,2-trifluoroethyl) phosphite as a monodentate ligand, where cycloadduct **2.6** was selectively synthesized in a >94:6 dr and 94% conversion (entry 6).

Table 2.12. Achiral Phosphite Ligands Used in the Cu(I)-Catalyzed 1,3-DC



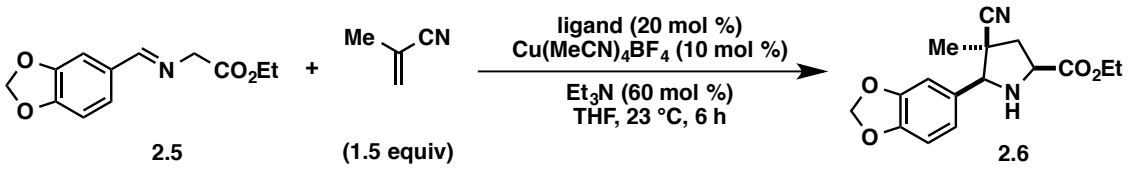
2.5 (1.5 equiv) **2.6**

entry	ligand (mol %)	conversion (%)[a]	dr (endo:exo)
1	triphenyl phosphite	91	94:6
2	tris(2,4-di-*tert*-butylphenyl) phosphite	94	75:25
3	trimethyl phosphite	83	76:24
4	dimethyl phosphite	0	–
5	triisopropyl phosphite	36	26:74
6	tris(2,2,2-trifluoroethyl) phosphite	94	>94:6

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture.

Achiral monodentate phosphite ligands were reexamined in the 1,3-DC between imine **2.5** and methacrylonitrile using THF instead of PhMe as the solvent and a reaction time of 6 h (Table 2.13). The endo adduct selectivities of reactions run using triphenyl phosphite, trimethyl phosphite, and tris(2,2,2-trifluoroethyl) phosphite were lower than those reactions run using the previous reaction conditions (compare Table 2.13, entries 1–3 to Table 2.12, entries 1, 3, and 6). Interestingly, the reaction run using triethyl phosphite as the ligand proceeded much more slowly and with a reversal of diastereoselectivity when compared to the same reaction run using electron-deficient tris(2,2,2-trifluoroethyl) phosphite (Table 2.13, compare entries 3 and 4). These experiments also indicate an important correlation between the electronic properties of the ligand and the resulting 1,3-DC reaction diastereoselectivity (see Table 2.8, entries 1–3). As a result of the observed drop in endo adduct selectivity for reactions run in THF, further studies were made with phosphite ligands using PhMe as the solvent.

Table 2.13. Achiral Monodentate Phosphite Ligands Run in THF



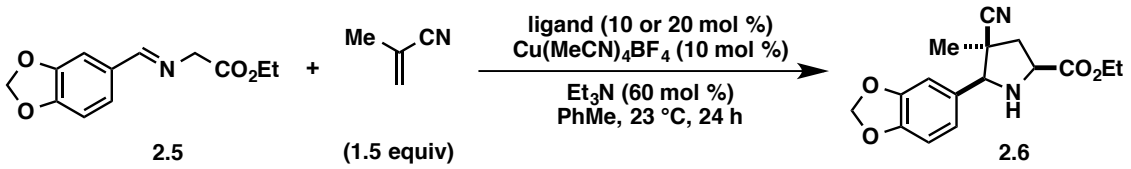
2.5 (1.5 equiv) 2.6

entry	ligand (mol %)	conversion (%)[a]	dr (endo:exo)
1	triphenyl phosphite	93	71:29
2	trimethyl phosphite	74	48:52
3	tris(2,2,2-trifluoroethyl) phosphite	96	93:7
4	triethyl phosphite	34	35:65
5	tributyl phosphite	87	68:32

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture.

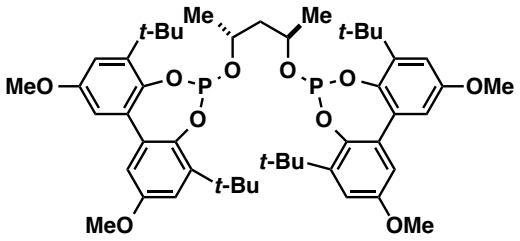
After demonstrating that phosphite ligands complexed with Cu(I) can be highly selective for the endo cycloadduct, three commercially available chiral phosphite ligands were chosen in order to investigate ee of pyrrolidine product **2.6** (Table 2.14). When using bulky bidentate (*R,R*)-Chiraphite, the reaction proceeded to only 50% conversion. Endo adduct **2.6** was formed selectively in a 78:22 dr, but without enantioenrichment (entry 1). SPINOL-derived[55,56] ligand (*R*)-ShiP allowed for 21% ee to be accomplished (entry 2), but using BINOL-derived[57] (*R*)-**2.38** resulted in only 8% ee of endo adduct **2.6** (entry 3).

Table 2.14. Chiral and Racemic Phosphite Ligands

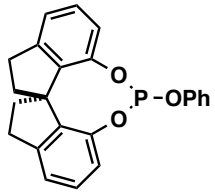


entry	ligand (mol %)	conversion (%)[a]	dr (endo:exo)	ee_{endo} (%)[b]
1	(*R,R*)-Chiraphite (10)	50	78:22	0
2	(*R*)-ShiP (20)	61	73:27	21
3	(*R*)-2.38 (20)	90	93:7	8
4	(±)-2.39 (20)	97	85:15	–
5	(±)-2.40 (20)	92	83:17	–

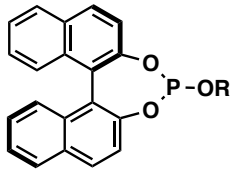
[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture. [b]Determined by enantioselective HPLC. nd = not determined.



(*R,R*)-Chiraphite



(*R*)-ShiP



R = *i*-Pr, (*R*)-2.38
R = Ph, (±)-2.39
R = 1-naphthyl, (±)-2.40

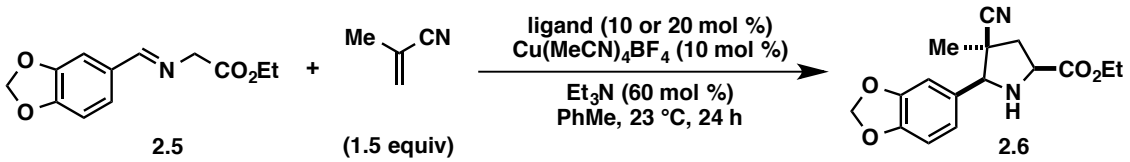
Because of the low selection and high price of commercial chiral phosphite ligands, the synthesis of a library of ligands was attempted by following the procedure described by Laschat and coworkers.[58,59] Purification of the desired phosphite ligands resulted in significant hydrolysis and only low yields of pure product were obtained, thus racemic BINOL was used in these early studies. Ligands (±)-**2.39** and (±)-**2.40** were successfully synthesized and used in the Cu(I)-catalyzed 1,3-DC reaction (Table 2.14, entries 4 and 5). While both reactions proceeded with >90% conversion and ca. 84:16 dr, attempts to prepare chiral phosphite ligands were suspended as a result of the difficulty of their synthesis and purification.

2.4 Conclusion

SAR studies have indicated the importance in accessing potent ETP analogue (+)-**2.1** in both a diastereo- and enantioselective manner. Over 75 ligands across a variety of ligand families were tested in our efforts to optimize the 1,3-DC step of the short ETP analogue synthesis. A positive correlation between the electron deficiency of the ligand and the 1,3-DC reaction endo adduct selectivity was observed. Achiral monodentate phosphite ligands have been identified as being able to accomplish the desired transformation with high endo adduct selectivity (>94:6 dr). This high selectivity may be attributed the π-accepting nature of this ligand class. Once chiral phosphite ligands are more readily accessible, an investigation of substitution pattern effects of chiral phosphite ligands on 1,3-DC reaction diastereo- and enantioselectivity will be initiated.

An interesting diastereodivergent trend was observed while investigating various ligand classes. We identified three ligands, each from a different class, which result in a different diastereomeric mixture of pyrrolidine products under otherwise identical reaction conditions (Table 2.15). This phenomenon is explained in further detail in Chapter 3.

Table 2.15. Ligand-Controlled Diastereodivergence



2.5 (1.5 equiv) 2.6

entry	ligand (mol %)	conversion (%)[a]	dr (endo:exo)
1	tris(2,2,2-trifluoroethyl) phosphite (20)	94	>94:6
2	tricyclohexylphosphine (20)	98	18:82
3	DavePhos (10)	57	50:50

[a]Conversion of starting material to product determined by relative integration in ^{1}H NMR spectrum of the crude reaction mixture.

2.5 Appendix A: Experimental Procedures

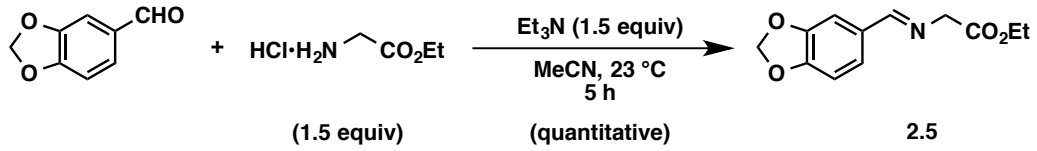
2.5.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame- or oven-dried glassware under a positive pressure of nitrogen (N_2) or argon (Ar) using anhydrous solvents (dried by passing through activated alumina columns under a positive pressure of Ar). Oxygen-sensitive reactions were carried out in solvents that were degassed by three freeze-pump-thaw cycles. Catalyst components and imine starting materials for the asymmetric 1,3-dipolar cycloaddition ligand screening reactions were weighed out in a MBraun Unilab 2000 glove box with a N_2 atmosphere. *tert*-Butyl acrylate and methacrylonitrile were distilled directly prior to use. All other commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator or Neslab Cryobath CB-80, and unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Analytical thin-layer chromatography (TLC) was conducted on EMD silica gel 60 F_{254} glass-backed plates (250 μm) and visualized by exposure to UV light (254 nm), or by potassium permanganate or ceric ammonium molybdate staining. Flash chromatography was performed using forced flow of the indicated solvent system on EMD Geduran® silica gel 60 (particle size 0.040–0.063 mm). Analytical enantioselective HPLC was performed on an Agilent 1100 Series HPLC utilizing Chiralcel columns (0.46 cm ϕ x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. NMR spectra were recorded at 298 K on Bruker FT-NMR spectrometers at the indicated frequencies. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual deuterated solvent signals ($CDCl_3$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant [*J*, reported in Hertz (Hz)], and integration. Splitting patters are abbreviated as follows: singlet (s), doublet (d),

triplet (t), quartet (q), multiplet (m), apparent (app), and broad (br). Carbon multiplicity was determined by a combination of DEPTQ and HMQC experiments. Chemical shifts (δ) for ^{31}P NMR spectra are reported in parts per million (ppm) and referenced to the corresponding calibrated ^{1}H NMR spectrum. Infrared (IR) spectra were recorded on a Varian 640-IR spectrometer as thin films in CH_2Cl_2 on KBr plates and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the UC Irvine Mass Spectrometry Facility with a Micromass LCT spectrometer. Melting points (mp) were determined on a melting point apparatus (Thomas Hoover, Uni-Melt) and are uncorrected. Abbreviations used can be found on the Internet at:

http://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf.

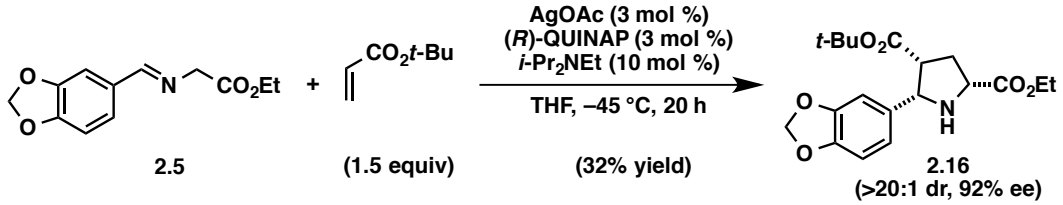
2.5.2 Synthesis of Imine 2.5



Ethyl (*E*)-2-((benzo[*d*][1,3]dioxol-5-ylmethylene)amino)acetate (2.5). A 50 mL round-bottom flask was charged with a magnetic stir bar, glycine ethyl ester hydrochloride (525 mg, 3.75 mmol, 1.50 equiv), and piperonal (375 mg, 2.50 mmol, 1.00 equiv). MeCN (4.2 mL, 0.6 M) and Et_3N (520 μL, 3.75 mmol, 1.50 equiv) were sequentially added and the resulting heterogeneous mixture was vigorously stirred at 23 °C for 5 h. Concentration of the reaction mixture under reduced pressure afforded an amorphous colorless solid, which was transferred to a separatory funnel using CH_2Cl_2 (15 mL) and H_2O (30 mL). The layers of the resulting biphasic mixture were partitioned and the organic layer was extracted with H_2O (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford imine **2.5** (590 mg, quantitative yield) as a light yellow oil.[60] Imine **2.5** was carried further in subsequent

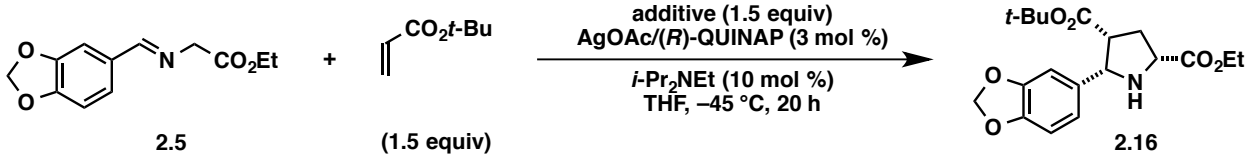
reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.41 (s, 1H), 7.15 (d, *J* = 7.9, 1H), 6.83 (d, *J* = 7.9, 1H), 6.01 (s, 2H), 4.35 (s, 2H), 4.23 (q, *J* = 6.8, 2H), 1.30 (t, *J* = 6.8, 3H).

2.5.3 Ag(I)-Catalyzed 1,3-DC Reactions



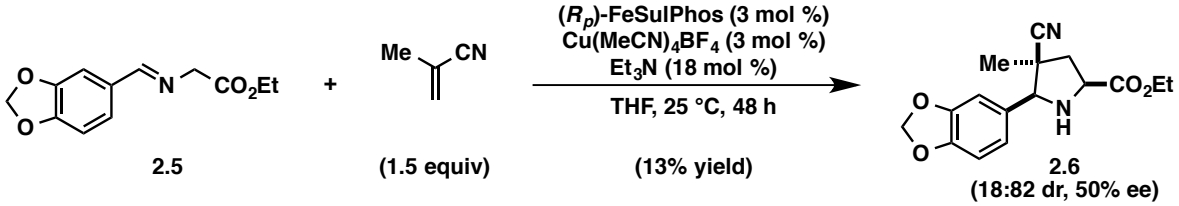
4-(*tert*-Butyl) 2-ethyl (2*R*,4*R*,5*S*)-5-(benzo[*d*][1,3]dioxol-5-yl)pyrrolidine-2,4-dicarboxylate (2.16). The enantioselective synthesis of pyrrolidine **2.16** was performed using the procedure reported by Schreiber and coworkers.[13] In the glove box, a foil-wrapped 1-dram vial was charged with a magnetic stir bar, AgOAc (1 mg, 0.005 mmol, 0.03 equiv), and (*R*)-QUINAP (2 mg, 0.005 mmol, 0.03 equiv). The vial was sealed with a Teflon-lined cap, removed from the glove box, and placed under an atmosphere of Ar. THF (0.52 mL) was added to the vial and the resulting catalyst solution was stirred at 23 °C for 5 h. The catalyst solution was then added to a vial containing a solution of imine **2.5** [41 mg, 0.17 mmol, 1.0 equiv; azeotropically dried with PhMe (3 x 0.5 mL)] in THF (1.2 mL) at –45 °C. *tert*-Butyl acrylate (38 μL, 0.26 mmol, 1.5 equiv) and *i*-Pr_2NEt (3 μL, 0.02 mmol, 0.1 equiv) were sequentially added and the reaction mixture was stirred at –45 °C for 20 h. The reaction mixture was quenched at 23 °C with 0.1 mL of a 10:1 v/v THF:glacial acetic acid solution, then concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and transferred to a separatory funnel with H_2O (10 mL). The layers of the resulting biphasic mixture were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash

chromatography (1:1 hexanes:EtOAc) to yield pyrrolidine **2.16** (20 mg, 32% yield) as a clear oil in >20:1 dr and 92% ee. Enantiomeric excess was determined by HPLC: Daicel Chiralpak AS, *i*-PrOH/*n*-hexane 60:40, flow rate 1.0 mL/min, λ = 254 nm, t_R = 9.2 min (major isomer), 12.5 min (minor isomer).[61] R_f 0.60 (1:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.83 (d, *J* = 7.9, 1H), 6.74 (d, *J* = 7.9, 1H), 5.91 (s, 2H), 4.42 (d, *J* = 7.9, 1H), 4.26 (q, *J* = 7.0, 2H), 3.91 (t, *J* = 8.5, 1H), 3.21 (q, *J* = 7.6, 1H), 2.97 (br s, 1H), 2.42–2.37 (m, 1H), 2.31–2.27 (m, 1H), 1.31 (t, *J* = 7.0, 3H), 1.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 171.7, 147.6, 146.9, 133.6, 120.6, 108.3, 108.0, 101.1, 80.8, 65.3, 61.4, 60.0, 50.4, 33.9, 27.8, 14.4; IR (thin film): 2978, 2932, 2904, 1730, 1489 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{19}H_{25}NO_6Na$, 386.1580; found, 386.1570.



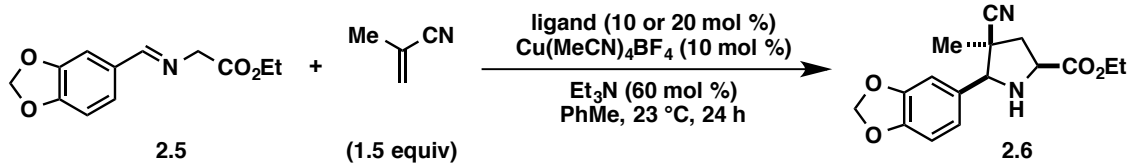
4-(*tert*-Butyl) 2-ethyl (2*R*,4*R*,5*S*)-5-(benzo[*d*][1,3]dioxol-5-yl)pyrrolidine-2,4-dicarboxylate (2.16). The competition experiments described in Table 2.2 were conducted following the procedure for the enantioselective synthesis of **2.16**. The additive [either methacrylonitrile (22 μL, 0.26 mmol, 1.5 equiv), acetonitrile (14 μL, 0.26 mmol, 1.5 equiv), or isobutyronitile (23 μL, 0.26 mmol, 1.5 equiv)] was introduced to the reaction vial simultaneously with *tert*-butyl acrylate. ^{1}H NMR yields were determined in $CDCl_3$ from the unpurified reaction residue using 3 μL DMF as the external standard.

2.5.4 Cu(I)-Catalyzed 1,3-DC Reactions



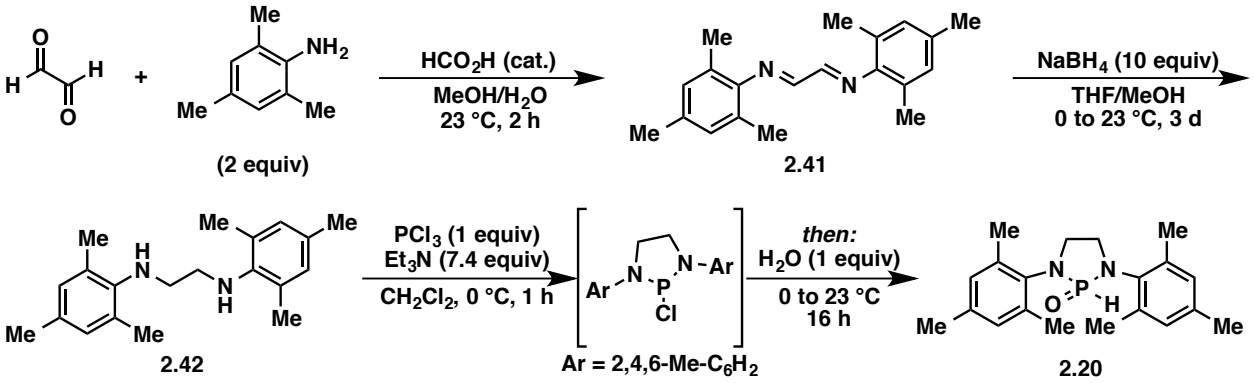
Ethyl (2*S*,4*S*,5*S*)-5-(benzo[*d*][1,3]dioxol-5-yl)-4-cyano-4-methylpyrrolidine-2-carboxylate (2.6). The enantioselective synthesis of pyrrolidine **2.6** was performed using the procedure reported by Carretero and coworkers.[15e] In the glove box, a 1-dram vial was charged with (R_p)-FeSulPhos (3 mg, 0.006 mmol, 0.03 equiv), $Cu(MeCN)_4BF_4$ (2 mg, 0.006 mmol, 0.03 equiv), and a magnetic stir bar. Also in the glove box, a second 1-dram vial was charged with imine **2.5** (47 mg, 0.20 mmol, 1.0 equiv). The vials were each sealed with a Teflon-lined cap, removed from the glove box, and placed under an atmosphere of Ar. THF (0.5 mL) was added to each vial. The vial containing the catalyst solution was cooled to –30 °C before the sequential addition of the imine solution, Et_3N (5.0 μL, 0.035 mmol, 0.18 equiv), and methacrylonitrile (25 μL, 0.30 mmol, 1.5 equiv). The reaction mixture stirred at –30 °C for 1 h, after which time TLC indicated no formation of product. The reaction mixture was then allowed to warm to 23 °C and product was detected by TLC after 1 h. The reaction mixture continued stirring at 23 °C for 48 h, after which time it was transferred to a separatory funnel with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers of the resulting biphasic mixture were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc) to afford pyrrolidine **2.6** (8 mg, 13% yield) as a yellow oil in 50% ee. Enantiomeric excess was determined by HPLC: Daicel Chiralpak OD-H III,

i-PrOH/*n*-hexane 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_R = 17.2 min (2*S*,4*S*,5*S*)-isomer, 19.8 min (2*S*,4*R*,5*S*)-isomer.



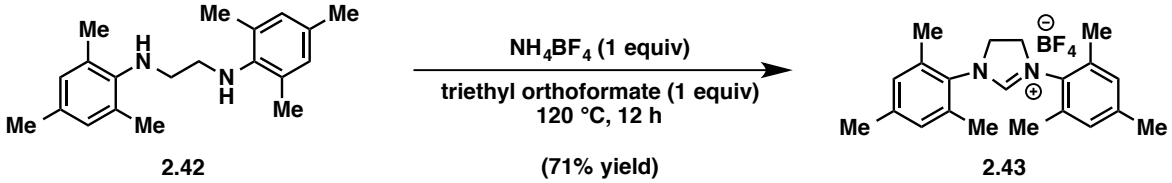
General Procedure for Investigating Cu(I) Catalysts. In the glove box, a 1-dram vial was charged with $Cu(MeCN)_4BF_4$ (3 mg, 0.01 mmol, 0.1 equiv), ligand (bi- or tridentate, 0.01 mmol, 0.1 equiv; monodentate, 0.02 mmol, 0.2 equiv), a magnetic stir bar, and PhMe (0.25 mL). Also in the glove box, a second 1-dram vial was charged with imine **2.5** (24 mg, 0.10 mmol, 1.0 equiv) and PhMe (0.25 mL). The vials were each sealed with a Teflon-lined cap, removed from the glove box, and placed under an atmosphere of Ar. To the vial containing catalyst solution was sequentially added the solution of imine **2.5**, Et_3N (8 μL, 0.06 mmol, 0.6 equiv), and methacrylonitrile (13 μL, 0.15 mmol, 1.5 equiv). After stirring for 24 h at 23 °C, the solution was filtered through 310 mg of SiO_2 with EtOAc (10 mL). After removal of the volatile components in vacuo, the resulting residues were analyzed by ^{1}H NMR to determine the starting material-to-product conversion and the endo:exo cycloadduct ratio via signal integration of the diagnostic pyrrolidine methylene group signals [endo adduct **2.6**: δ 2.81 (dd, *J* = 13.6, 4.3, 1H), δ 2.27 (dd, *J* = 13.6, 9.6, 1H); exo adduct: δ 2.72 (dd, *J* = 13.3, 9.9, 1H), δ 2.21 (dd, *J* = 13.5, 6.2, 1H)] against the imidoyl imine **2.5** signal [δ 8.16 (s, 1H)] and piperonal aldehidic signal [δ 9.81 (s, 1H); from hydrolysis of unreacted imine **2.5** starting material). Reactions represented in Tables 2.7, 2.10, and 2.13 were run in a similar manner to those described in this procedure, with modifications of the solvent (THF) and the reaction time (6 h). Enantiomeric excess was determined by HPLC: Daicel Chiralpak OD-H III, *i*-PrOH/*n*-hexane 10:90, flow rate 1.0 mL/min, λ = 254 nm, t_R = 32.9 min (2*S*,4*S*,5*S*)-isomer, 40.1 min (2*S*,4*R*,5*S*)-isomer.

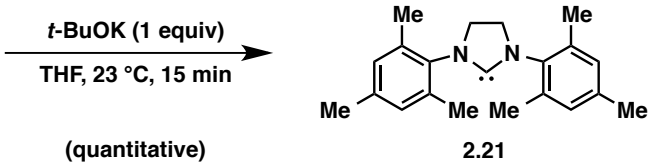
2.5.5 Ligand Synthesis



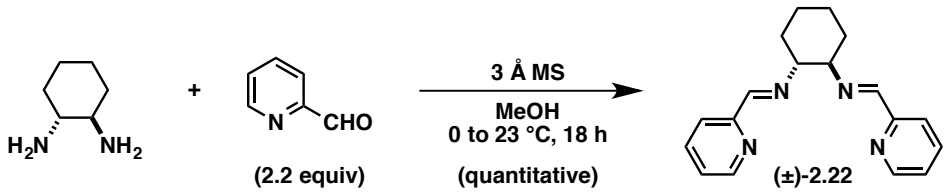
1,3-Dimesityl-1,3,2-diazaphospholidine 2-oxide (2.20). HASPO ligand **2.20** was prepared as described by Dieskau.[62] Glyoxal (2.3 mL, 20 mmol, 1.0 equiv, 40 wt % in H_2O) and 2,4,6-trimethylaniline (5.6 mL, 40 mmol, 2.0 equiv) were dissolved in a minimal amount of MeOH (0.4 mL) in a 250 mL round-bottom flask charged with a magnetic stir bar. Three drops of formic acid were added to initiate the formation of a dark brown precipitate. After stirring for 2 h, the brown precipitate was filtered through a Büchner funnel to afford diimine intermediate **2.41** as a bright yellow-orange solid, which was used immediately in the following transformation. A 250 mL three-neck flask was charged with diimine **2.41** (5.8 g, 20 mmol, 1.0 equiv) and a magnetic stir bar, followed by the addition of MeOH (40 mL) and THF (80 mL). The solution was cooled to 0 °C and $NaBH_4$ (7.60 g, 200 mmol, 10.0 equiv) was added portion-wise. The heterogeneous mixture was allowed to warm to 23 °C. After 3 days, the resulting clear solution was quenched with sat. aq. NH_4Cl (10 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 50 mL) and the organic layers were combined, washed with brine (100 mL), and dried over Na_2SO_4. The volatile components were removed under reduced pressure to afford diamine **2.42** (4.3 g, 73% yield over 2 steps) as a dark orange oil, which was used directly in the following transformation. A 25 mL round-bottom flask was charged with diamine **2.42** (1.5 g, 5.0 mmol, 1.0 equiv), a magnetic stir bar, and Et_3N (5.2 mL,

37 mmol, 7.4 equiv). The resulting mixture was dissolved in CH_2Cl_2 (8.3 mL) and cooled to 0 °C. PCl_3 (0.44 mL, 5.0 mmol, 1.0 equiv) was added dropwise over 20 min. The reaction temperature was maintained at 0 °C for 1 h before the dropwise addition of H_2O (90 μL, 5.0 mmol, 1.0 equiv). The resulting heterogeneous solution was allowed to warm to 23 °C and maintained at that temperature for 16 h. After filtration through Celite and concentration under reduced pressure, the residue was purified by flash chromatography (3:1 hexanes:EtOAc) to yield HASPO ligand **2.20** (1.6 g, 94%) as a colorless solid (mp = 160–162 °C). Spectral data match those previously reported.[63]

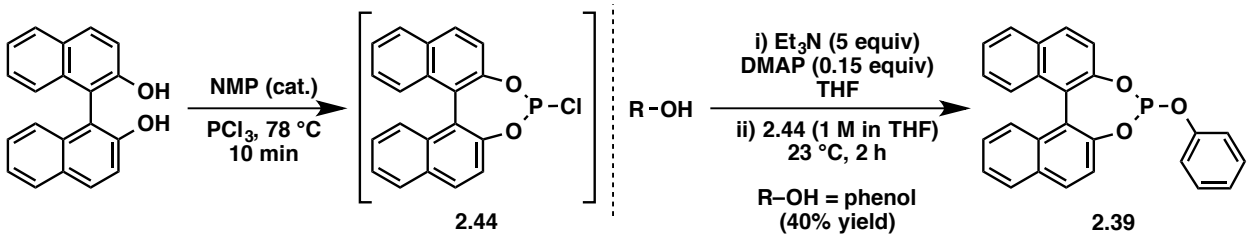




1,3-Dimesityl-4,5-dihydro-1*H*-imidazol-3-ium-2-ide (2.21). NHC ligand **2.21** was prepared following the procedure published by Kingsbury and Hoveyda.[64] A 10 mL round-bottom flask was charged with diamine **2.42** (1.8 g, 6.0 mmol, 1.0 equiv), ammonium tetrafluoroborate (0.60 g, 6.0 mmol, 1.0 equiv), and a magnetic stir bar. Triethyl orthoformate (1.0 mL, 6.0 mmol, 1.0 equiv) was then added and the resulting homogenous mixture was maintained at 120 °C for 12 h. Upon cooling to 23 °C, a purple solid formed, which was then suspended in EtOH (4 mL) and filtered with pentane, affording tetrafluoroborate salt **2.43** as a light purple solid (1.7 g, 71% yield). NHC ligand **2.21** was generated in situ immediately before use by stirring tetrafluoroborate salt **2.43** (8 mg, 0.02 mmol, 0.2 equiv) with *t*-BuOK (2 mg, 0.02 mmol, 0.2 equiv) in THF (0.25 mL, 0.40 M) for 15 min.

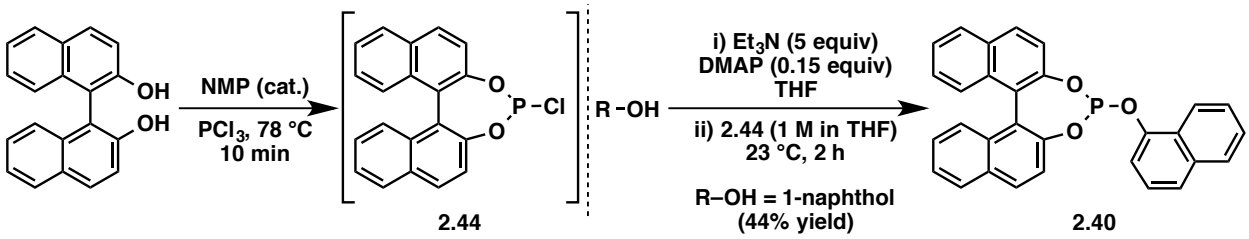


***Rac*-*N,N'*-(cyclohexane-1,2-diyl)bis(1-(pyridin-2-yl)methanimine) [(±)-2.22].** Diimine ligand (±)-**2.22** was prepared as described by Thomas and coworkers.[30] A 25 mL round-bottom flask was charged with a magnetic stir bar, 3 Å MS, (±)-*trans*-diaminocyclohexane (120 μL, 1.0 mmol, 1.0 equiv), and MeOH (2.5 mL, 0.4 M). The resulting heterogeneous mixture was cooled to 0 °C in an ice-water bath, then a methanolic solution of 2-pyridinecarboxaldehyde (210 μL, 2.2 mmol, 2.2 equiv in 2.5 mL MeOH) was added dropwise. The mixture was warmed to 23 °C and maintained at this temperature for 18 h. The reaction mixture was filtered through Celite with MeOH. Concentration of the filtrate afforded diimine ligand (±)-**2.22** (290 mg, quantitative yield) as an amorphous yellow solid, which was used without further purification.



***Rac*-4-phenoxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (2.39).** Phosphites **2.39** and **2.40** were prepared according to the procedure described by Laschat and coworkers.[58] A 10 mL round-bottom flask was charged with (±)-BINOL [570 mg, 2.0 mmol, 1.0 equiv; azeotropically dried with PhMe (3 x 2 mL)], a magnetic stir bar, PCl_3 (2 mL), and NMP (1 drop). The homogenous reaction mixture was heated at reflux for 10 min. The reaction mixture was cooled to 23 °C and excess PCl_3 was azeotropically removed under reduced pressure and inert atmosphere to yield **2.44** as an orange oil, which was then dissolved in THF (2 mL). A 15 mL round-bottom flask was charged with phenol (190 mg, 2.0 mmol, 1.0 equiv), DMAP

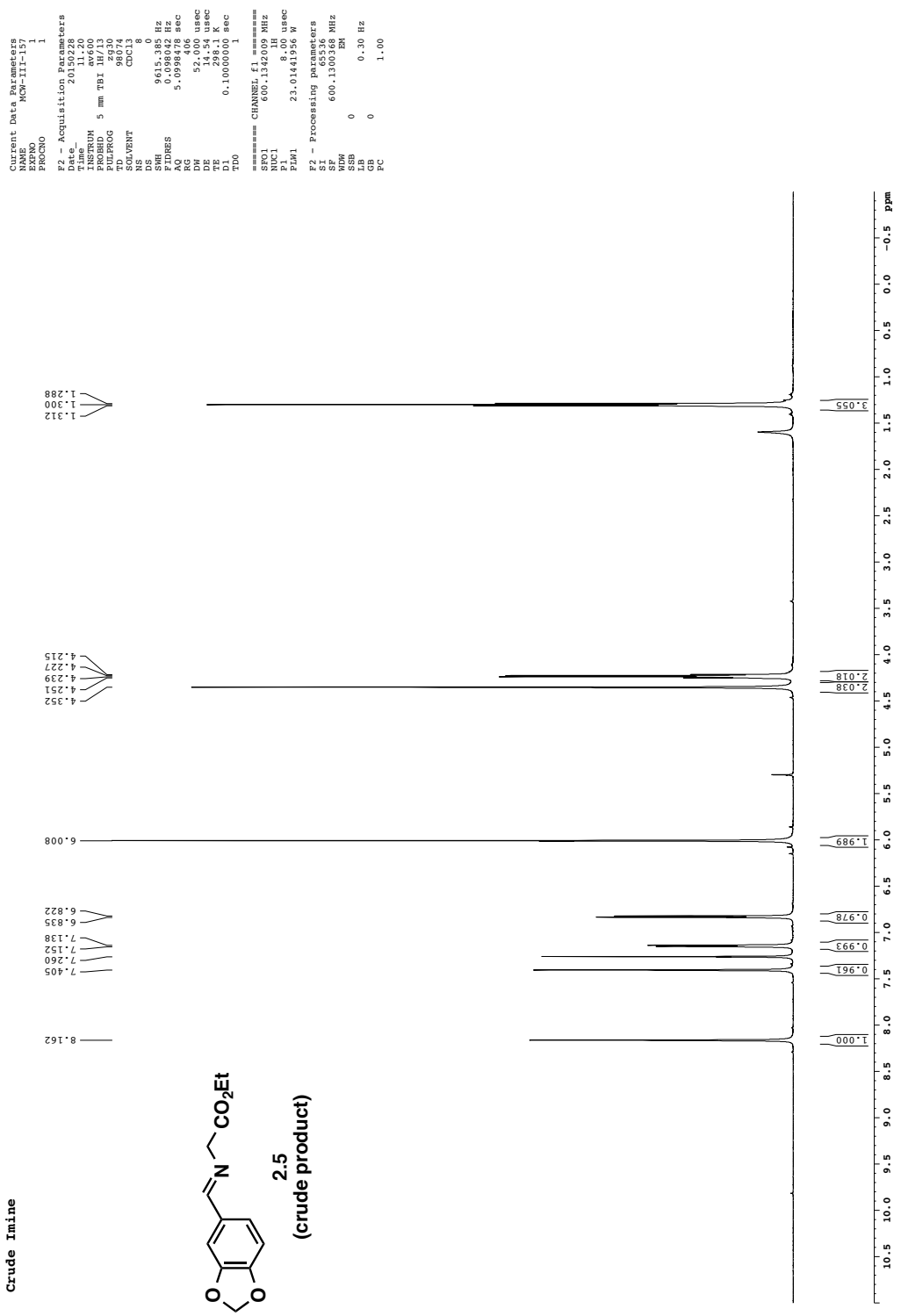
(37 mg, 0.30 mmol, 0.15 equiv), a magnetic stir bar, and Et_3N (1.4 mL, 10 mmol, 5.0 equiv). The solution of **2.44** was then added dropwise to the homogenous reaction mixture at 23 °C. The resulting homogenous reaction mixture stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (10:1 hexanes:EtOAc) to yield phosphite ligand **2.39** (165 mg, 40% yield) as an amorphous colorless solid. ^1H, ^{13}C, and ^{31}P NMR spectra of the product are consistent with those previously reported.[65]



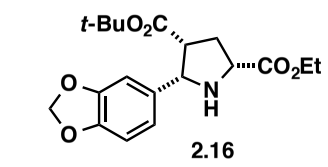
***Rac*-4-(naphthalen-1-yloxy)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (2.40).**

Phosphite ligand **2.40** was prepared following the procedure described for ligand **2.39** using 1-naphthol (290 mg, 2.0 mmol, 1.0 equiv) and accessed as an amorphous colorless solid (400 mg, 44% yield). ^1H, ^{13}C, and ^{31}P NMR spectra of the product are consistent with those previously reported.[59f]

2.6 Appendix B: NMR Spectral Data



Purified Product



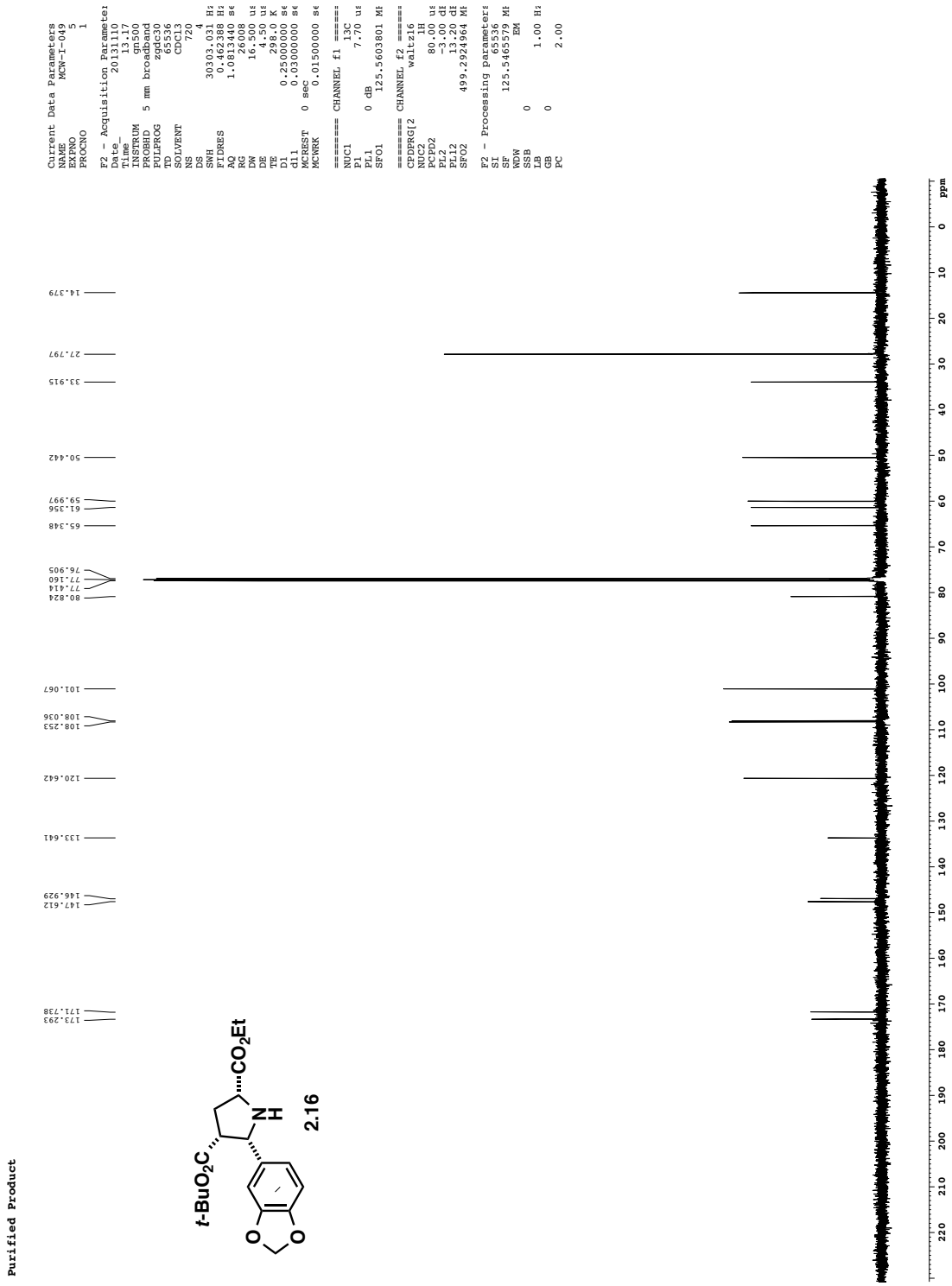
2.16


```
Current Data Parameters
NAME                  MCW-I-050
EXPNO                        19
PROCNO                        1

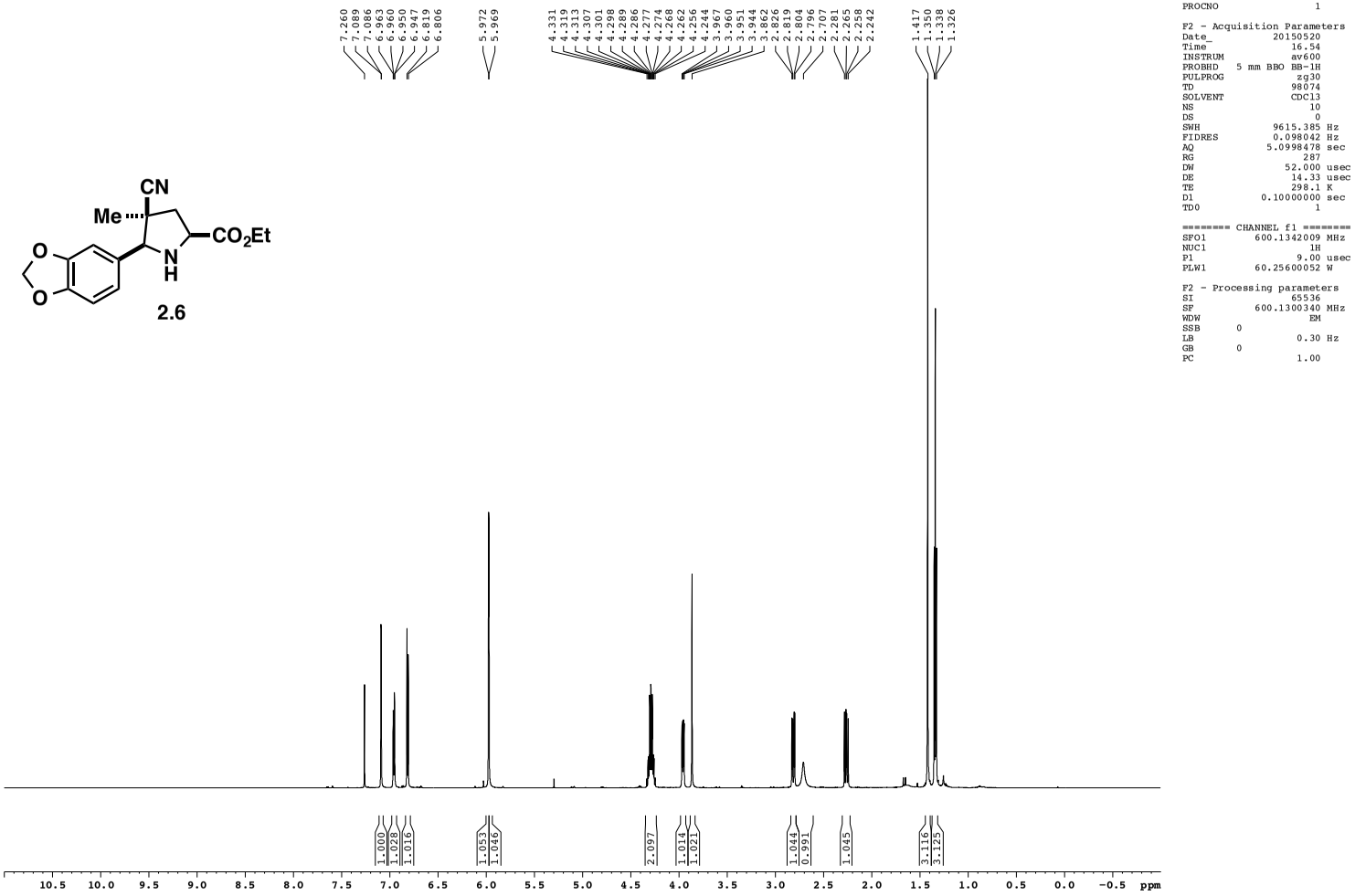
F2 - Acquisition Parameters
Date_                 20131110
Time                     13.02
INSTRUM                  av600
PROBHD   5 mm TBI 1H/13
PULPROG                  zg30
TD                       98074
SOLVENT                  CDC13
NS                          12
DS                           0
SWH                   9615.385 Hz
FIDRES                0.098042 Hz
AQ                    5.0998478 sec
RG                         114
DW                      52.000 usec
DE                      14.54 usec
TE                        298.4 K
D1                    0.10000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                       8.00 usec
PLW1                23.01441956 W
SFO1                600.1342009 MHz

F2 - Processing parameters
SI                        65536
SF                  600.1300353 MHz
WDW                          EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
```


Purified Product
Current Data Parameters
NAME MCW-I-049
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20131110
Time 13.17
INSTRUM qn500
PROBHD 5 mm broadband
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 720
DS 4
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 2048
DW 16.500 usec
DE 4.50 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
MCREST 0 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.70 usec
PL1 0 dB
SFO1 125.5603801 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 13.20 dB
SFO2 499.2924964 MHz
F2 - Processing parameters
SI 65536
SF 125.5465579 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
14.379
27.797
33.915
50.442
59.997
61.356
65.348
76.905
77.160
77.414
80.824
101.067
108.036
108.253
120.642
133.641
146.929
147.612
171.738
173.293
t-BuO2C
CO2Et
2.16
ppm

Endo Adduct



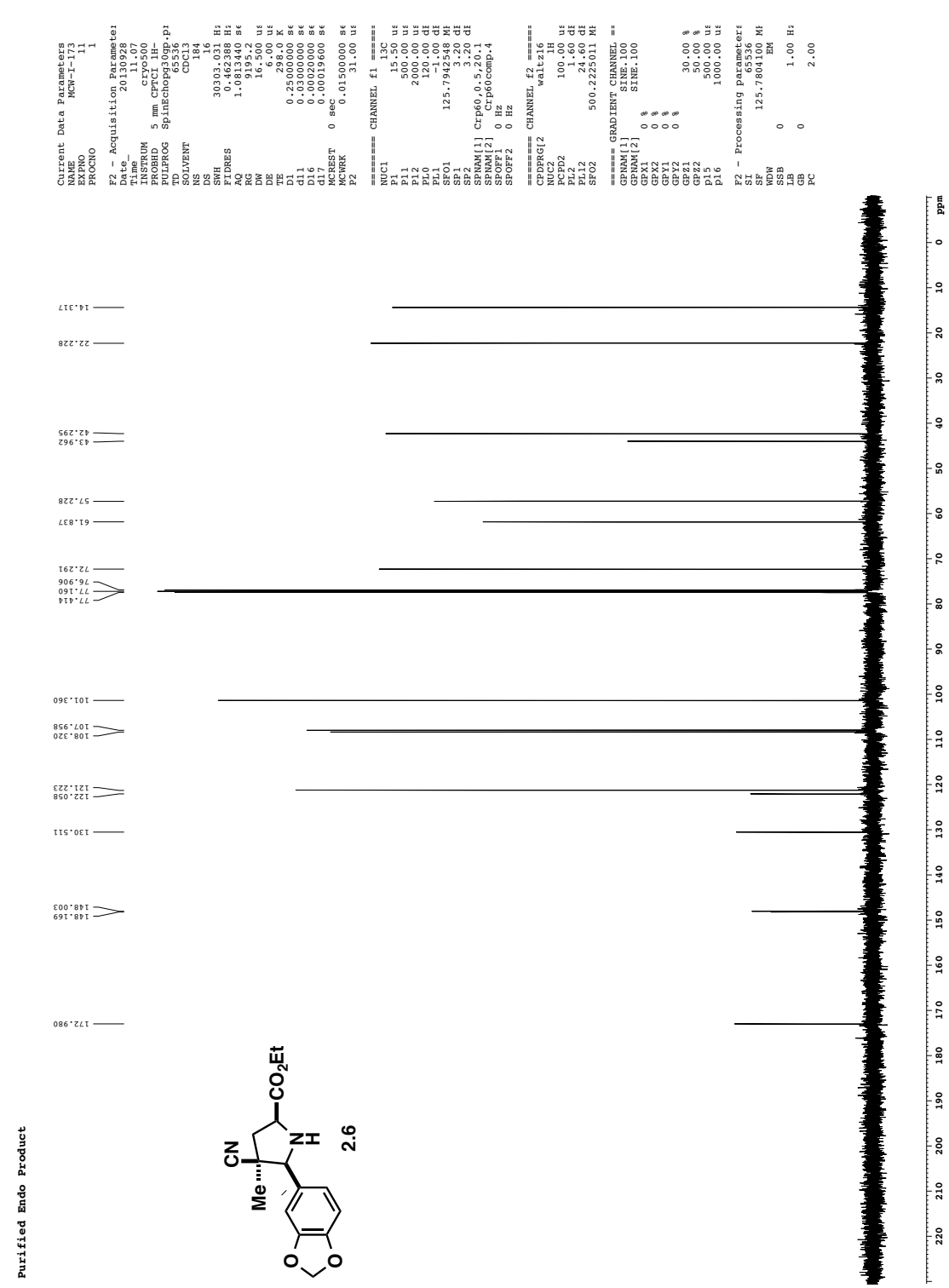
2.6

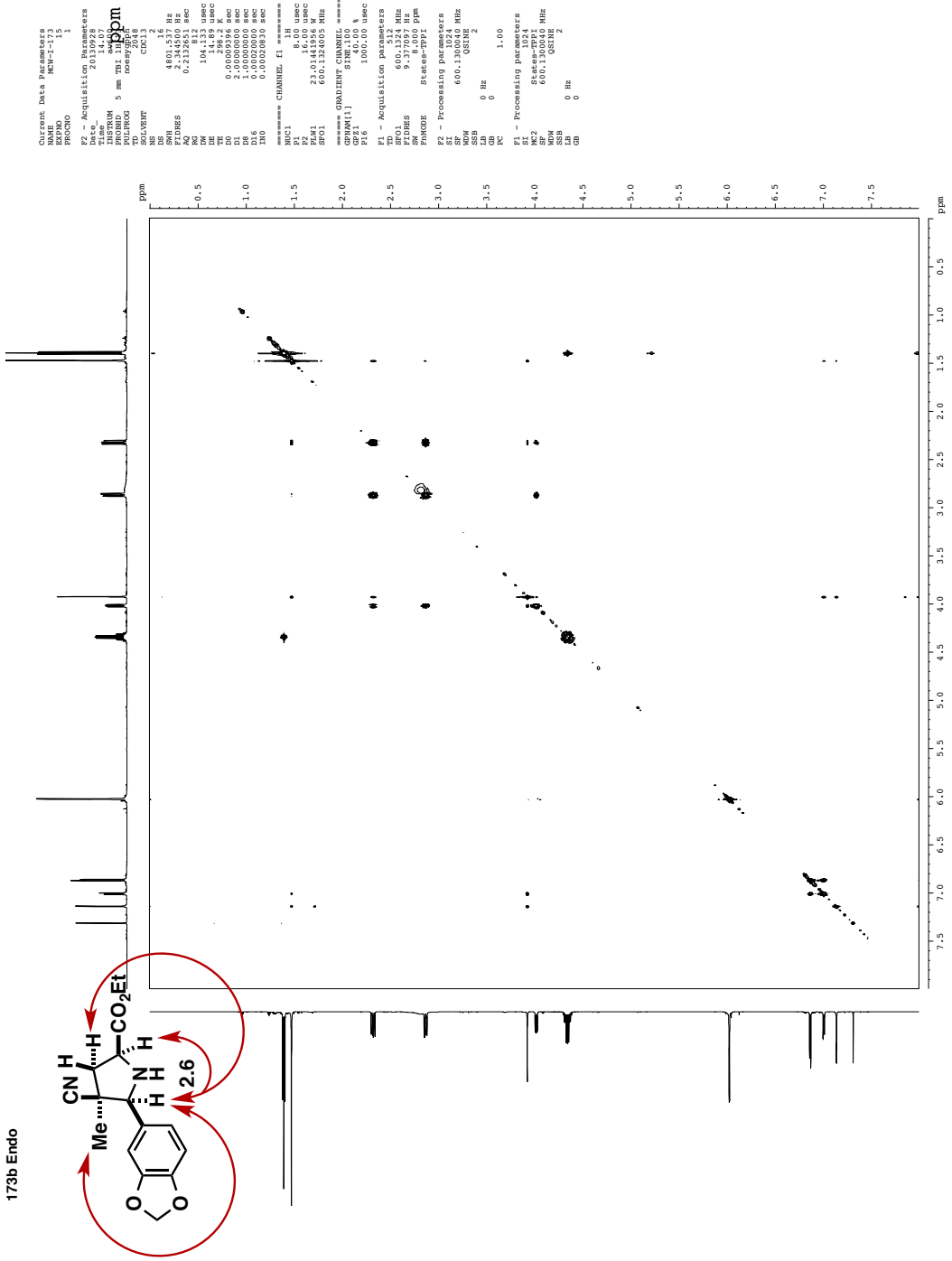
```
Current Data Parameters
NAME                  MCW-III-245
EXPNO                           6
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20150520
Time                        16.54
INSTRUM                    av600
PROBHD     5 mm BBO BB-1H
PULPROG                    zg30
TD                         98074
SOLVENT                    CDCl3
NS                             10
DS                              0
SWH                     9615.385 Hz
FIDRES                  0.098042 Hz
AQ                      5.0998478 sec
RG                            287
DW                         52.000 usec
DE                         14.33 usec
TE                         298.1 K
D1                    0.10000000 sec
TD0                             1

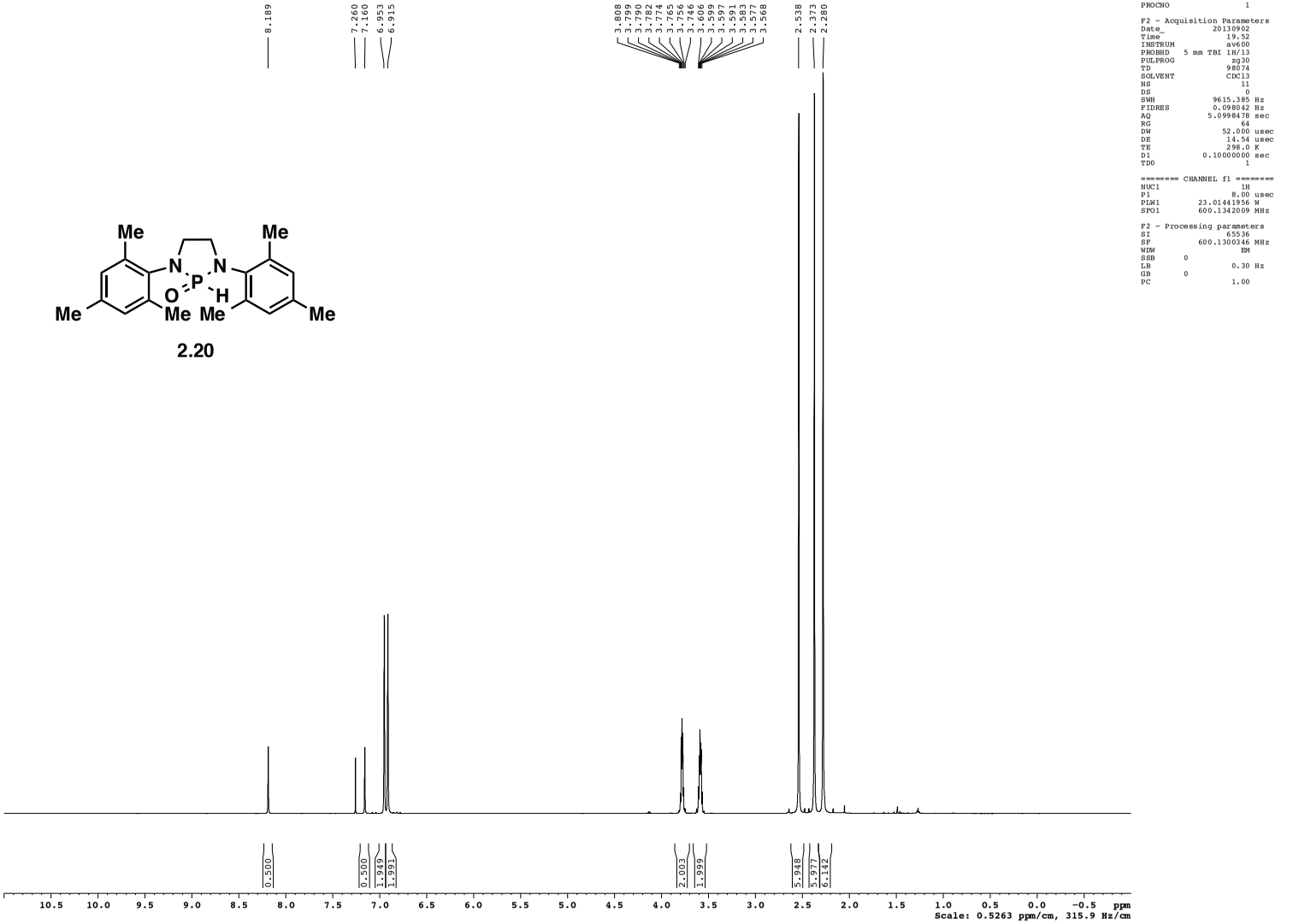
======== CHANNEL f1 ========
SFO1                 600.1342009 MHz
NUC1                           1H
P1                          9.00 usec
PLW1                60.25600052 W

F2 - Processing parameters
SI                             65536
SF                   600.1300340 MHz
WDW                            EM
SSB                0
LB                          0.30 Hz
GB                 0
PC                          1.00
```


Purified Endo Product
2.6
CN
Me
CO2Et
N
H
O
O
172.980
148.169
148.003
130.511
122.058
121.223
108.320
107.958
101.360
77.414
77.160
76.906
72.291
61.837
57.228
43.962
42.295
22.228
14.317
ppm


173b Endo
CN H
Me
H
CO2Et
N
H H
2.6
O
O
ppm
ppm

HASPO



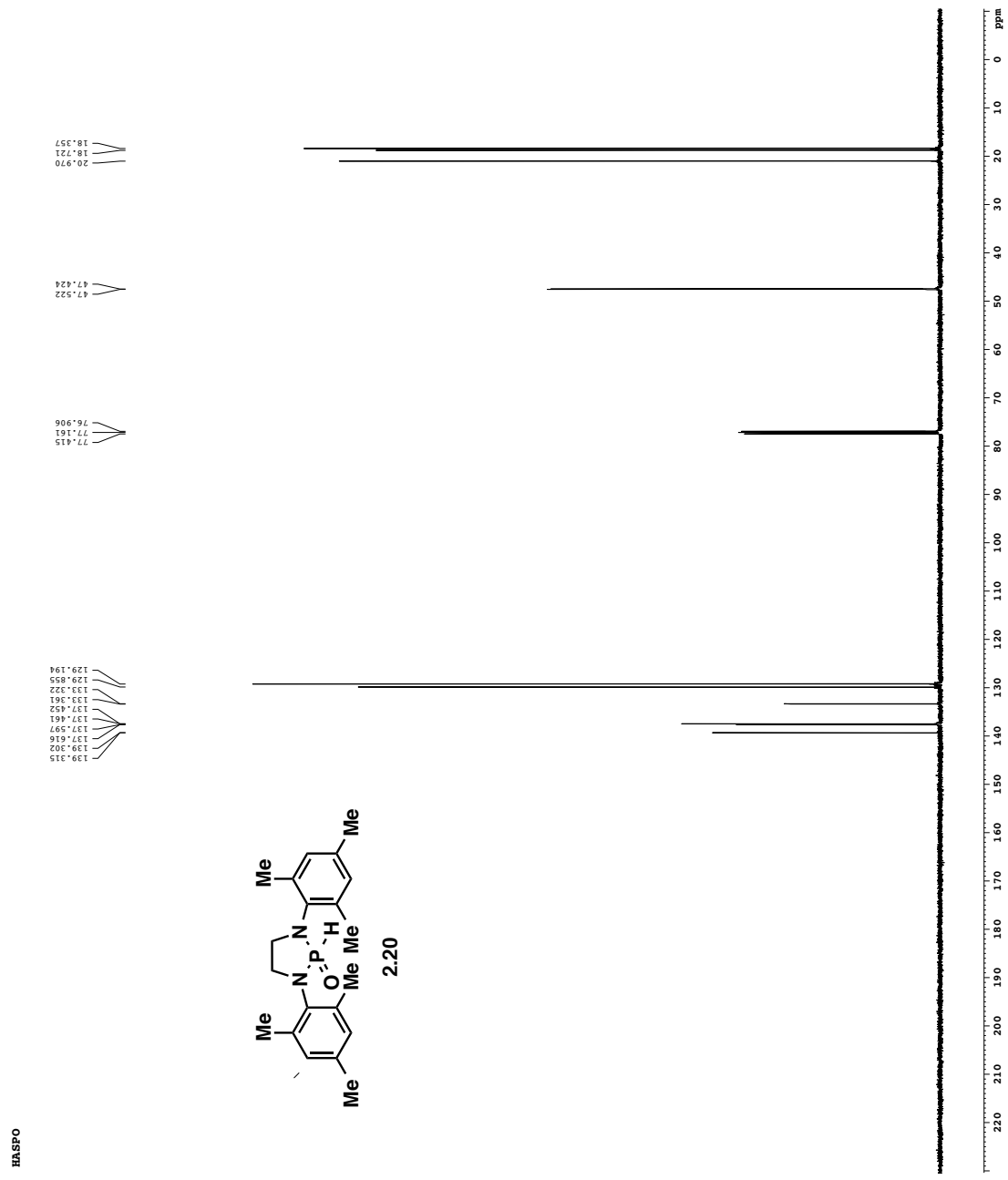
2.20

```
Current Data Parameters
NAME            MCW-I-145
EXPNO                   2
PROCNO                  1

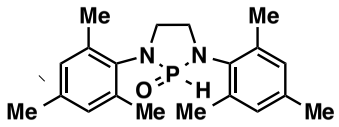
F2 - Acquisition Parameters
Date_            20130902
Time                19.52
INSTRUM             av600
PROBHD   5 mm TBI 1H/13
PULPROG                 zg30
TD                    98074
SOLVENT               CDCl3
NS                       11
DS                        0
SWH                9615.385 Hz
FIDRES             0.098042 Hz
AQ                 5.0998478 sec
RG                       64
DW                   52.000 usec
DE                   14.54 usec
TE                   298.0 K
D1              0.10000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                    8.00 usec
PLW1           23.01441956 W
SFO1           600.1342009 MHz

F2 - Processing parameters
SI                    65536
SF             600.1300346 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```


HASPO
Current Data Parameters
NAME MCW-I-145
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130903
Time 19.23
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3sp.p1
TD 65536
SOLVENT CDCl3
NS 72
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 72028.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MC4REST 0 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
PL2 20000.00 dB
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804256 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
20.970
18.721
18.357
47.522
47.424
77.415
77.161
76.906
139.315
139.302
137.616
137.597
137.461
137.452
133.361
133.322
129.855
129.194
Me
Me
Me
Me
Me
O
P
H
N
N
2.20
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

HASPO



2.20


```
Current Data Parameters
NAME                  MCW-I-145
EXPNO                        44
PROCNO                        1

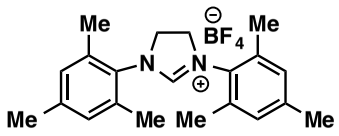
F2 - Acquisition Parameter
Date_                 20150721
Time                     16.55
INSTRUM                  av600
PROBHD    5 mm BBO BB-1H
PULPROG                 zgdc30
TD                       65536
SOLVENT                 CDCl3T
NS                           94
DS                            0
SWH                104166.664 Hz
FIDRES               1.589457 Hz
AQ                   0.3145728 se
RG                        2050
DW                       4.800 us
DE                       6.78 us
TE                      298.3 K
D1                 1.00000000 se
D11                0.03000000 se
TD0                           1

======== CHANNEL f1 ======
SFO1               242.9407211 MH
NUC1                       31P
P1                        9.00 us
PLW1              186.00000000 W

======== CHANNEL f2 ======
SFO2               600.1330006 MH
NUC2                       1H
CPDPRG[2                waltz16
PCPD2                    90.00 us
PLW2               60.25600052 W
PLW12               0.63826352 W

F2 - Processing parameters
SI                        65536
SF                 242.9370909 MH
WDW                          EM
SSB          0
LB                        2.00 Hz
GB           0
PC                        1.00
```

Crude Product



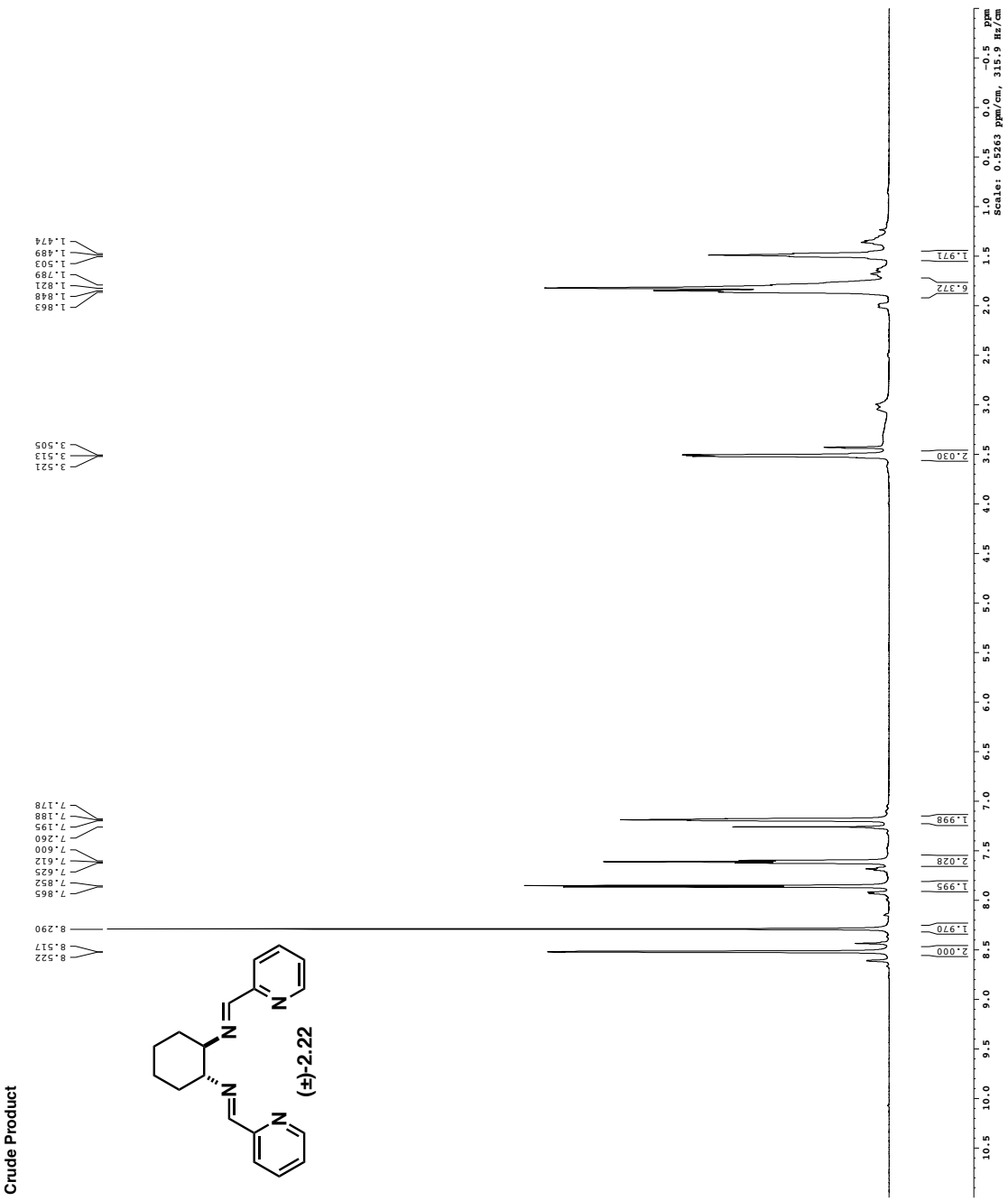
2.43


```
Current Data Parameters
NAME            MCW-I-144
EXPNO                   1
PROCNO                  1

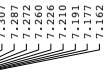
F2 - Acquisition Parameters
Date_            20130824
Time                11.25
INSTRUM             av600
PROBHD   5 mm TBI 1H/13
PULPROG             zg30
TD                 98074
SOLVENT            CDCl3
NS                     13
DS                      0
SWH             9615.385 Hz
FIDRES          0.098042 Hz
AQ              5.0998478 sec
RG                    724
DW                 52.000 usec
DE                 14.54 usec
TE                 298.1 K
D1            0.10000000 sec
TD0                     1

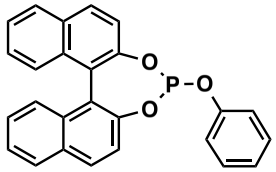
======== CHANNEL f1 ========
NUC1                   1H
P1                  8.00 usec
PLW1          23.01441956 W
SFO1          600.1342009 MHz

F2 - Processing parameters
SI                  65536
SF            600.1300346 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```


Crude Product
(±)-2.22
Current Data Parameters
NAME MCM-I-208
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20131011
Time 9.36
INSTRUM spect
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98304
SOLVENT CDCl3
NS 11
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.099968 sec
RG 322
DW 52.000 usec
DE 14.44 usec
TE 296.0 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 23.01441956 W
SFO1 600.1342009 MHz
F2 - Processing parameters
SI 65536
SF 600.1300358 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
8.522
8.517
8.290
7.865
7.852
7.625
7.612
7.600
7.260
7.195
7.188
7.178
3.521
3.513
3.505
1.863
1.848
1.821
1.789
1.503
1.489
1.474
2.000
1.970
1.995
2.028
1.998
2.030
6.372
1.971
Scale: 0.5263 ppm/cm, 315.9 Hz/cm
ppm

Purified Product





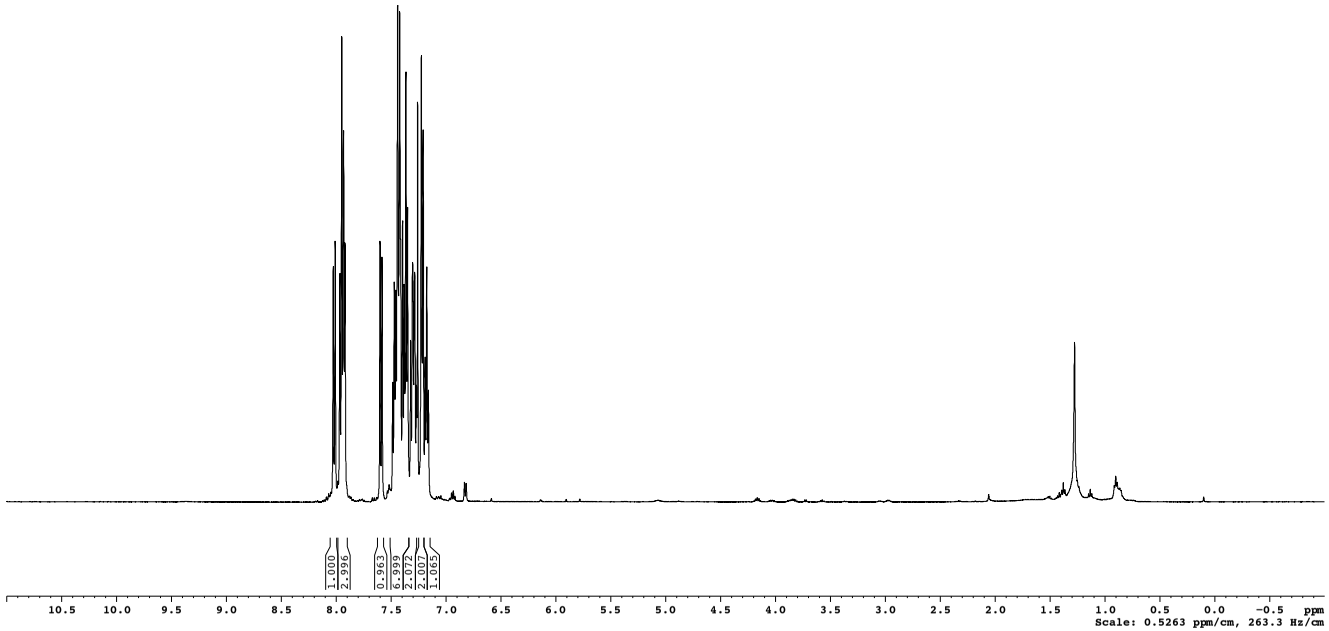
2.39

```
Current Data Parameters
NAME            MCW-I-237
EXPNO                   9
PROCNO                  1

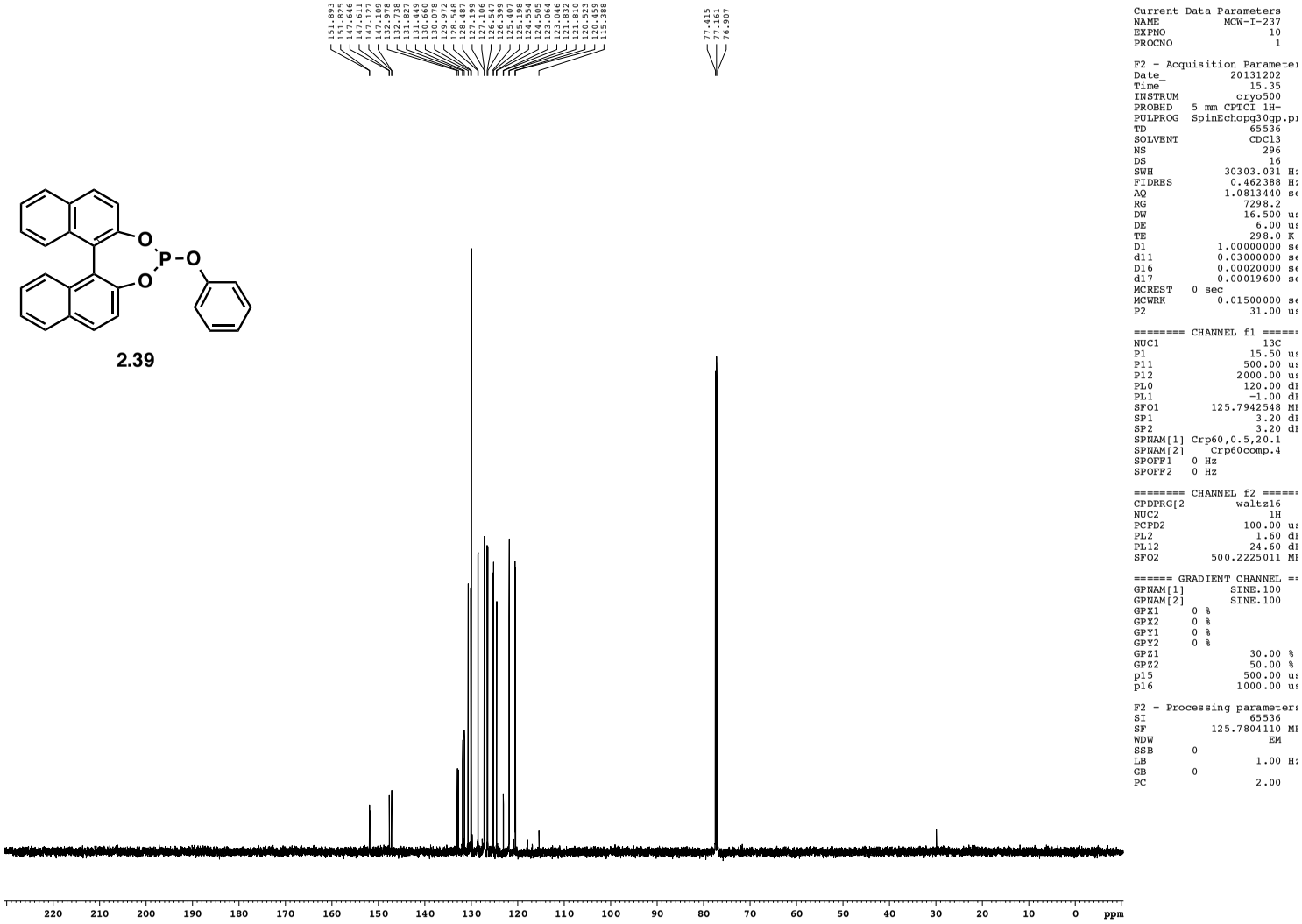
F2 - Acquisition Parameters
Date_            20131202
Time                15.31
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG               zg30
TD                   81728
SOLVENT              CDCl3
NS                       8
DS                       2
SWH              8012.820 Hz
FIDRES           0.098043 Hz
AQ               5.0998273 sec
RG                       8
DW                  62.400 usec
DE                   6.00 usec
TE                  298.0 K
D1              0.10000000 sec
MCREST    0 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   7.50 usec
PL1                  1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                      65536
SF            500.2200306 MHz
WDW                     EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   4.00
```



Purified Product




```
Current Data Parameters
NAME                  MCW-I-237
EXPNO                        10
PROCNO                        1

F2 - Acquisition Parameter
Date_                  20131202
Time                      15.35
INSTRUM                cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG   SpinEchopg30gp.pr
TD                         65536
SOLVENT                  CDCl3
NS                           296
DS                            16
SWH                  30303.031 Hz
FIDRES                0.462388 Hz
AQ                    1.0813440 se
RG                       7298.2
DW                       16.500 us
DE                        6.00 us
TE                       298.0 K
D1                   1.00000000 se
d11                  0.03000000 se
D16                  0.00020000 se
d17                  0.00019600 se
MCREST    0 sec
MCWRK                0.01500000 se
P2                       31.00 us

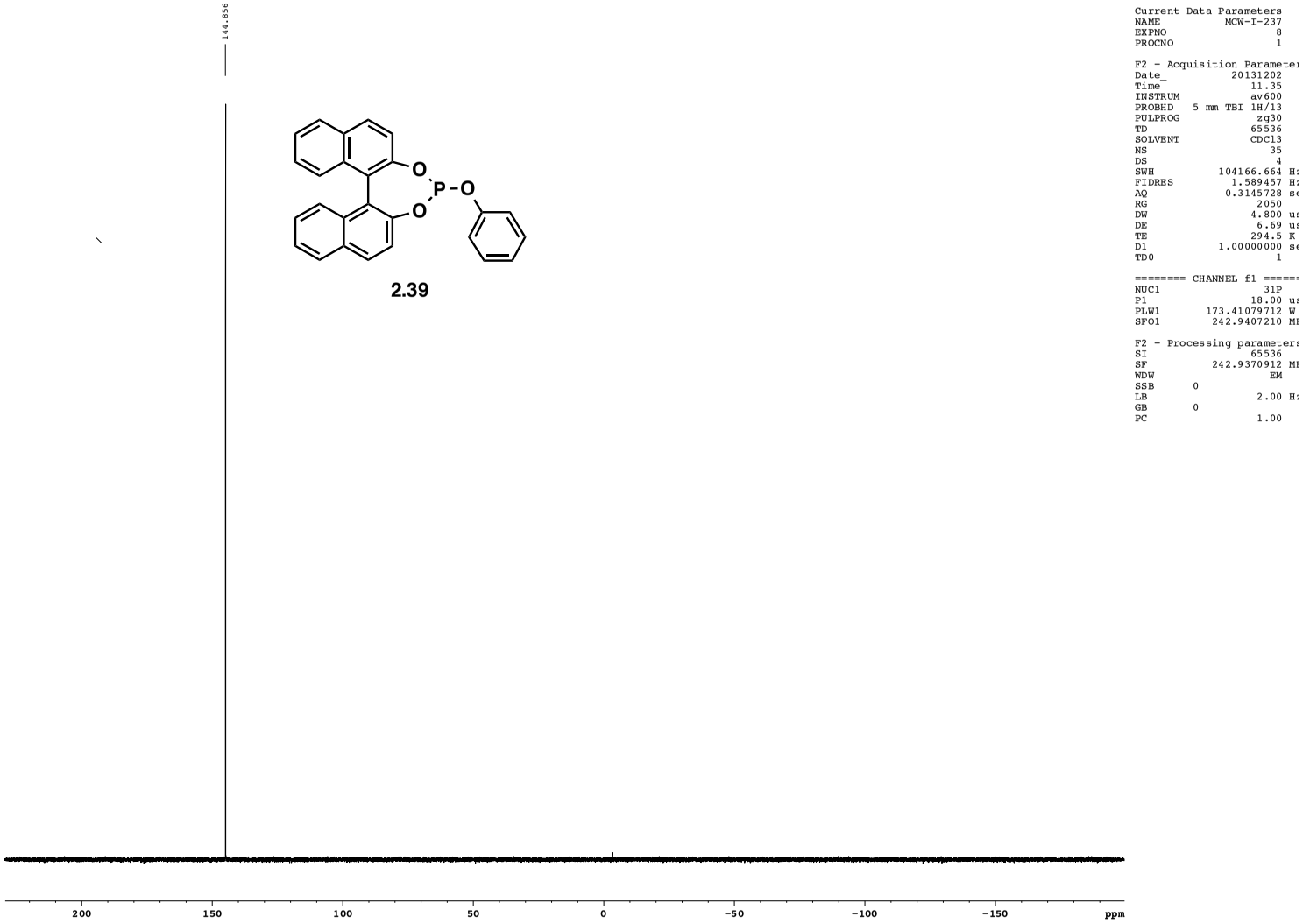
======== CHANNEL f1 ======
NUC1                        13C
P1                       15.50 us
P11                     500.00 us
P12                    2000.00 us
PL0                     120.00 dB
PL1                      -1.00 dB
SFO1                125.7942548 MH
SP1                       3.20 dB
SP2                       3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1    0 Hz
SPOFF2    0 Hz

======== CHANNEL f2 ======
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                   100.00 us
PL2                       1.60 dB
PL12                     24.60 dB
SFO2                500.2225011 MH

====== GRADIENT CHANNEL ==
GPNAM[1]              SINE.100
GPNAM[2]              SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                     30.00 %
GPZ2                     50.00 %
p15                     500.00 us
p16                    1000.00 us

F2 - Processing parameters
SI                         65536
SF                  125.7804110 MH
WDW                           EM
SSB       0
LB                        1.00 Hz
GB        0
PC                        2.00
```

Purified Product



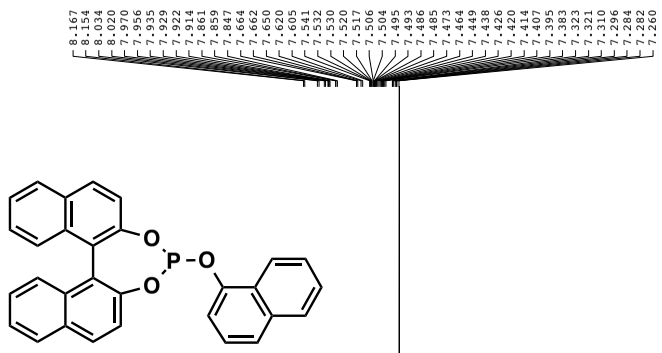

```
Current Data Parameters
NAME                  MCW-I-237
EXPNO                         8
PROCNO                        1

F2 - Acquisition Parameter
Date_                  20131202
Time                      11.35
INSTRUM                   av600
PROBHD   5 mm TBI 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           35
DS                            4
SWH                104166.664 Hz
FIDRES               1.589457 Hz
AQ                   0.3145728 se
RG                        2050
DW                       4.800 us
DE                       6.69 us
TE                       294.5 K
D1                  1.00000000 se
TD0                           1

======== CHANNEL f1 ======
NUC1                        31P
P1                        18.00 us
PLW1             173.41079712 W
SFO1              242.9407210 MH

F2 - Processing parameters
SI                        65536
SF                242.9370912 MH
WDW                         EM
SSB          0
LB                        2.00 Hz
GB           0
PC                        1.00
```

Purified Product



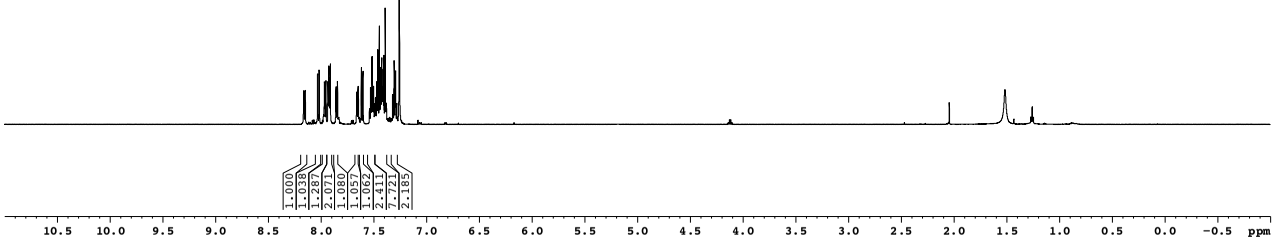
2.40

```
Current Data Parameters
NAME                  MCW-1-236
EXPNO                        20
PROCNO                        1

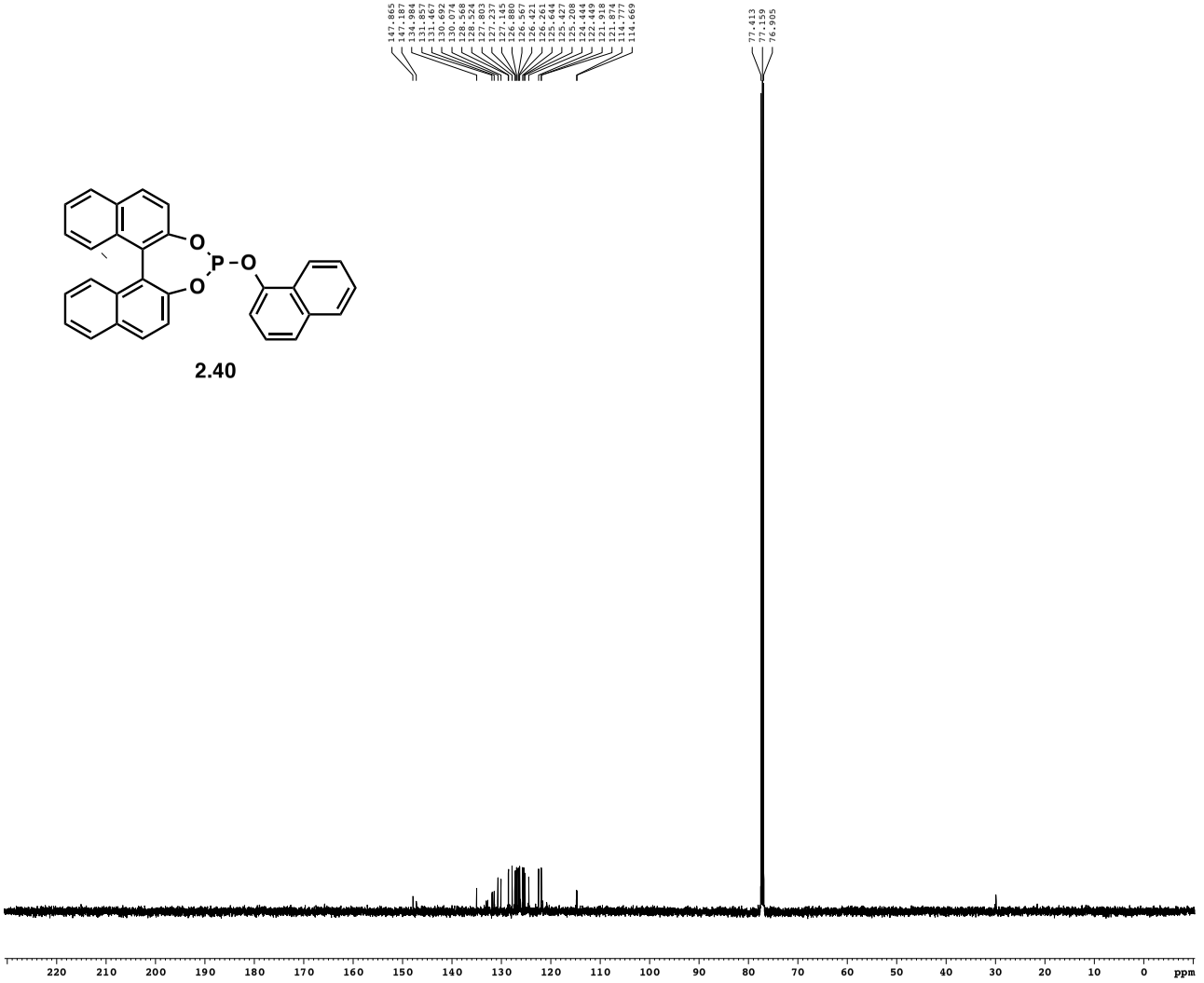
F2 - Acquisition Parameters
Date_               20131201
Time                      9.34
INSTRUM                 av600
PROBHD    5 mm TBI  1H/13
PULPROG                 zg30
TD                      98074
SOLVENT                 CDCl3
NS                           15
DS                            0
SWH                  9615.385 Hz
FIDRES               0.098042 Hz
AQ                   5.0998478 sec
RG                          575
DW                     52.000 usec
DE                     14.54 usec
TE                     298.1 K
D1                   0.10000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                        8.00 usec
PLW1                23.01441956 W
SFO1                600.1342009 MHz

F2 - Processing parameters
SI                        65536
SF                  600.1300352 MHz
WDW                          EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
```



Purified Product




```
Current Data Parameters
NAME            MCW-I-236
EXPNO                  23
PROCNO                  1

F2 - Acquisition Parameter
Date_            20131201
Time                12.04
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.pr
TD                  65536
SOLVENT             CDCl3
NS                    704
DS                     16
SWH            30303.031 Hz
FIDRES          0.462388 Hz
AQ             1.0813440 se
RG                 7298.2
DW                16.500 us
DE                 6.00 us
TE                298.0 K
D1            0.25000000 se
d11           0.03000000 se
D16           0.00020000 se
d17           0.00019600 se
MCREST   0 sec
MCWRK         0.01500000 se
P2                31.00 us

======== CHANNEL f1 ======
NUC1                  13C
P1                 15.50 us
P11               500.00 us
P12              2000.00 us
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MH
SP1                3.20 dB
SP2                3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1   0 Hz
SPOFF2   0 Hz

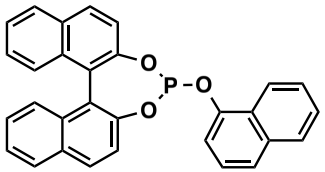
======== CHANNEL f2 ======
CPDPRG[2         waltz16
NUC2                  1H
PCPD2             100.00 us
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MH

====== GRADIENT CHANNEL ==
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 us
p16             1000.00 us

F2 - Processing parameters
SI                  65536
SF           125.7804073 MH
WDW                    EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 2.00
```

Purified Product

144.571



2.40

```
Current Data Parameters
NAME            MCW-I-236
EXPNO                  21
PROCNO                  1

F2 - Acquisition Parameter
Date_            20131201
Time                9.37
INSTRUM           av600
PROBHD   5 mm TBI 1H/13
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   54
DS                    4
SWH          104166.664 Hz
FIDRES         1.589457 Hz
AQ             0.3145728 se
RG                 2050
DW                4.800 us
DE                6.69 us
TE                298.0 K
D1            1.00000000 se
TD0                    1

======== CHANNEL f1 ======
NUC1                31P
P1                18.00 us
PLW1       173.41079712 W
SFO1        242.9407210 MH

F2 - Processing parameters
SI                 65536
SF          242.9369071 MH
WDW                   EM
SSB       0
LB                 2.00 Hz
GB        0
PC                 1.00
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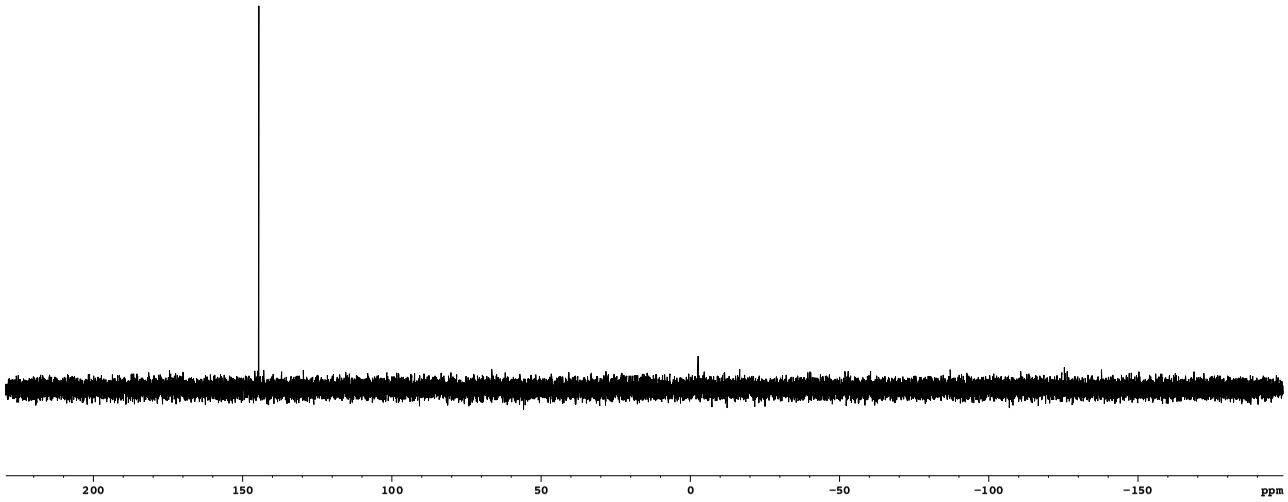
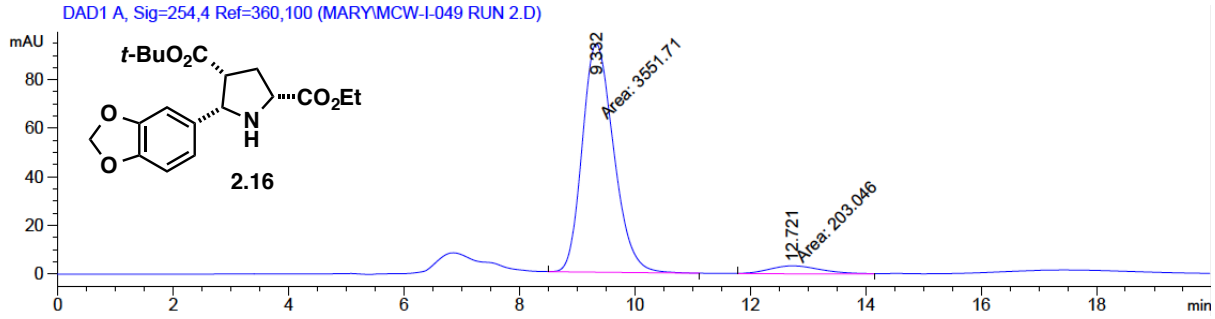


2.7 Appendix C: Enantioselective HPLC Chromatograms

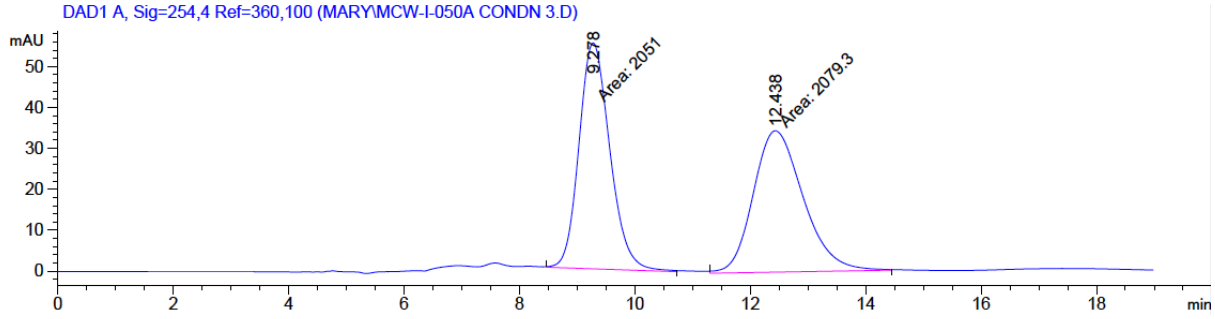
2.16, Table 2.2, entry 1 [(*R*)-QUINAP], 90% ee:

Daicel Chiralpak AS, *i*-PrOH/*n*-hexane 60:40, flow rate 1.0 mL/min, λ = 254 nm.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.332	MM	0.6301	3551.71265	93.94164	94.5923
2	12.721	MM	1.0344	203.04559	3.27167	5.4077

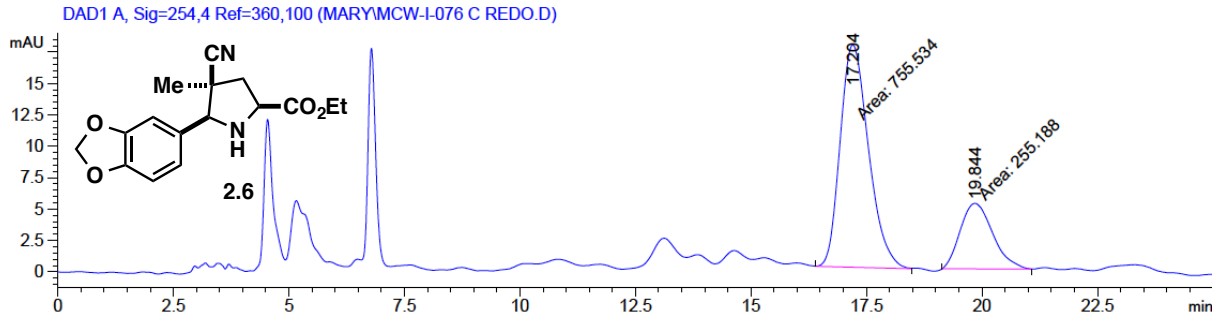
2.16, racemic standard:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.278	MM	0.6187	2051.00317	55.25095	49.6574
2	12.438	MM	1.0027	2079.30322	34.56282	50.3426

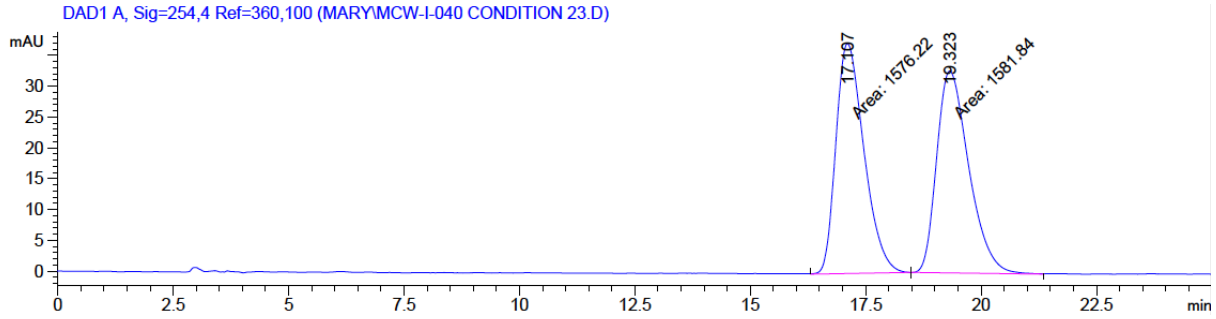
2.6, eq 2.5 [(R_p)-FeSulPhos], 50% ee:

Daicel Chiralpak OD-H III column; flow: 1.0 mL/min; 20:80 *i*-PrOH:*n*-hexane; λ = 254 nm.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.204	MM	0.7111	755.53387	17.70918	74.7519
2	19.844	MM	0.8149	255.18791	5.21936	25.2481

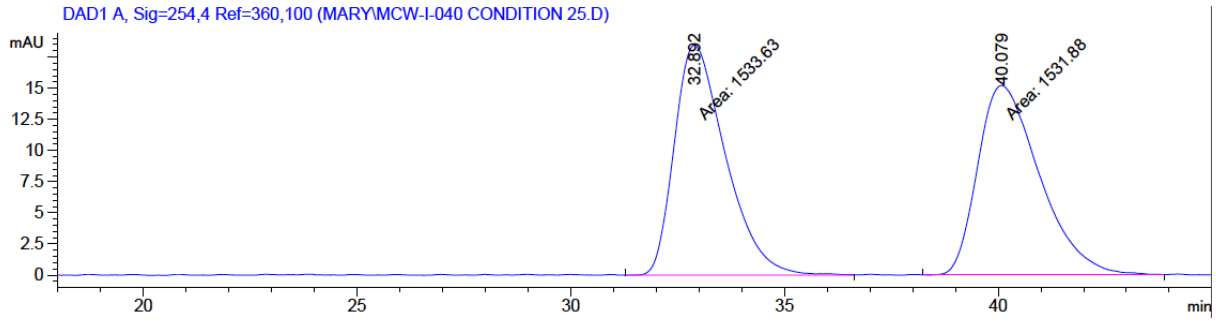
2.6, racemic standard:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.107	MM	0.7045	1576.21753	37.28816	49.9109
2	19.323	MM	0.8054	1581.84265	32.73400	50.0891

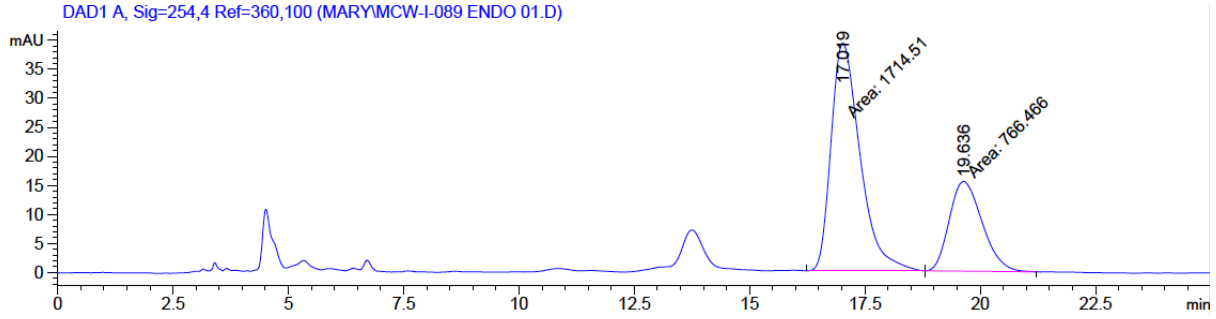
2.6, racemic standard:

Daicel Chiralpak OD-H III column; flow: 1.0 mL/min; 10:90 *i*-PrOH:*n*-hexane; λ = 254 nm.



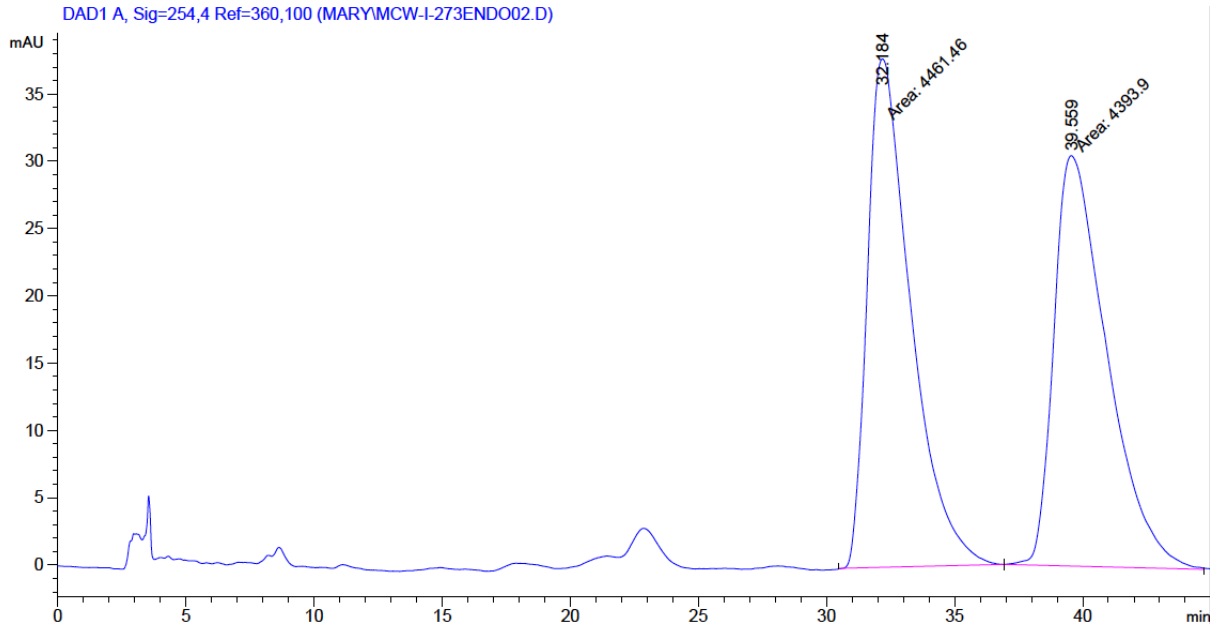
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.892	MM	1.3844	1533.63245	18.46268	50.0286
2	40.079	MM	1.6813	1531.87634	15.18501	49.9714

2.6, Table 2.4, entry 1 [(R_p)-FeSulPhos], 38% ee:



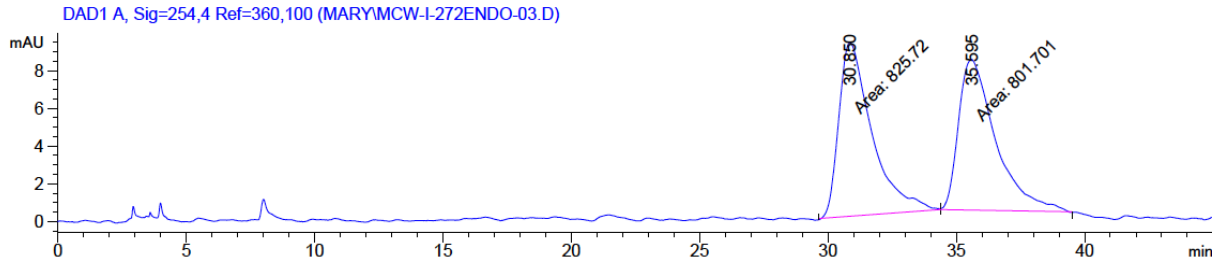
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.019	MM	0.7280	1714.50635	39.25321	69.1062
2	19.636	MM	0.8266	766.46637	15.45390	30.8938

2.6, Table 2.5, entry 1 [(*R*)-**2.23**], 0% ee:



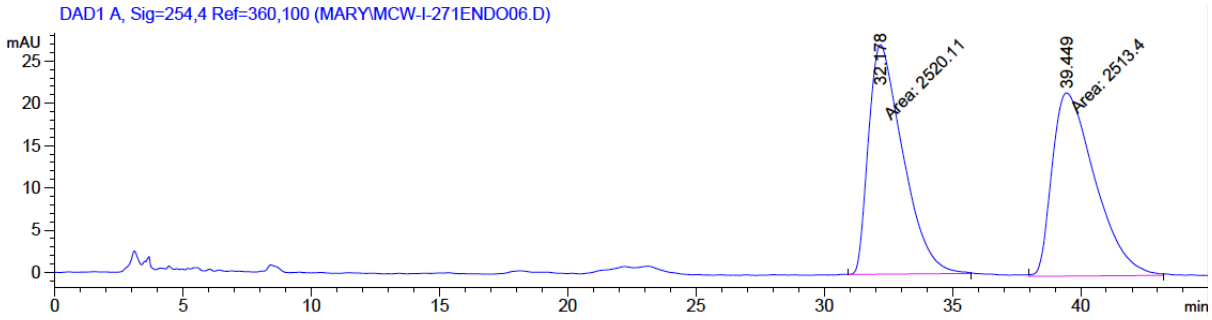
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.184	MM	1.9684	4461.46338	37.77616	50.3815
2	39.559	MM	2.4015	4393.89795	30.49405	49.6185

2.6, Table 2.5, entry 2 [(*R*)-**2.24**], 2% ee:



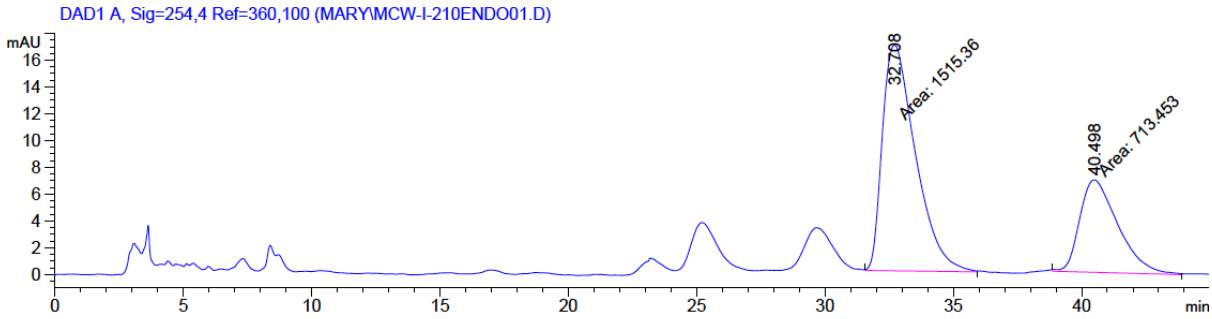
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.850	MM	1.4948	825.72034	9.20661	50.7380
2	35.595	MM	1.6719	801.70062	7.99176	49.2620

2.6, Table 2.5, entry 3 [(*R*)-**2.25**], 0% ee:



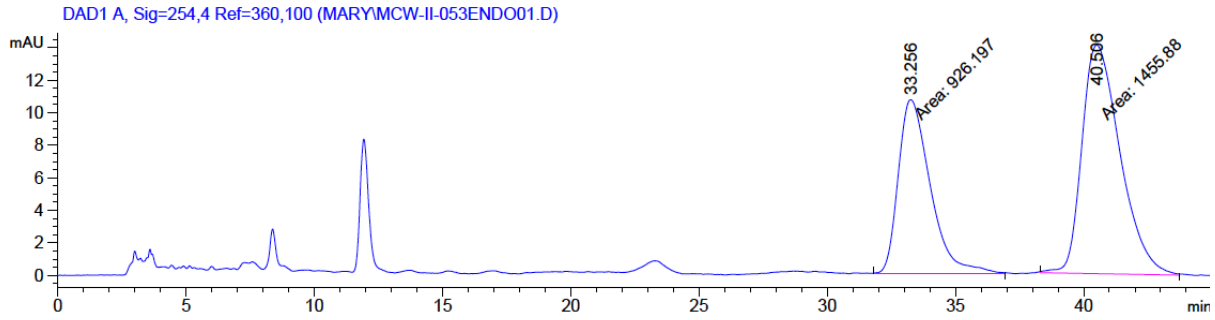
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.178	MM	1.5490	2520.10645	27.11579	50.0667
2	39.449	MM	1.9339	2513.39526	21.66064	49.9333

2.6, Table 2.6, entry 1 [(*S*)-Monophos], 36% ee:



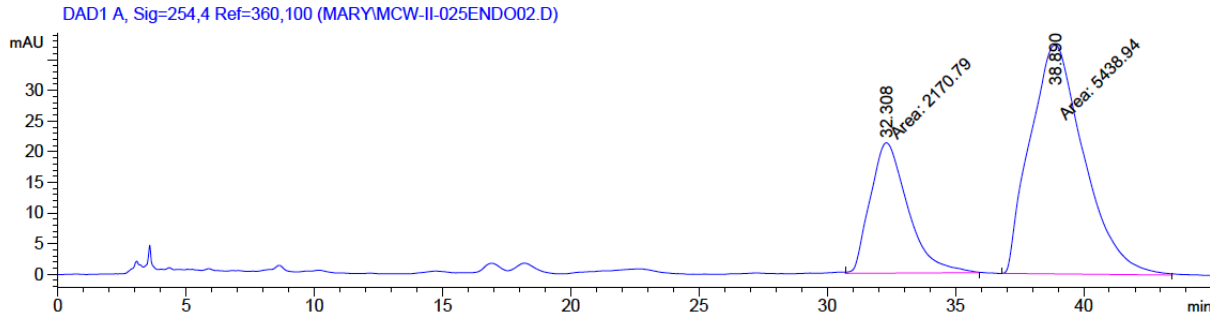
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.708	MM	1.4968	1515.36487	16.87351	67.9896
2	40.498	MM	1.7237	713.45319	6.89836	32.0104

2.6, Table 2.6, entry 2 [(*S*)-**2.27**], 22% ee:



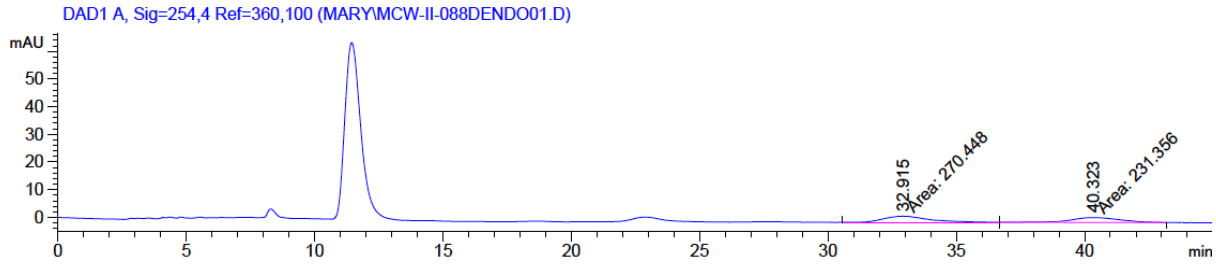
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.256	MM	1.4456	926.19733	10.67804	38.8819
2	40.506	MM	1.7254	1455.88086	14.06330	61.1181

2.6, Table 2.6, entry 3 [(*R,S*)-**2.28**], 43% ee:



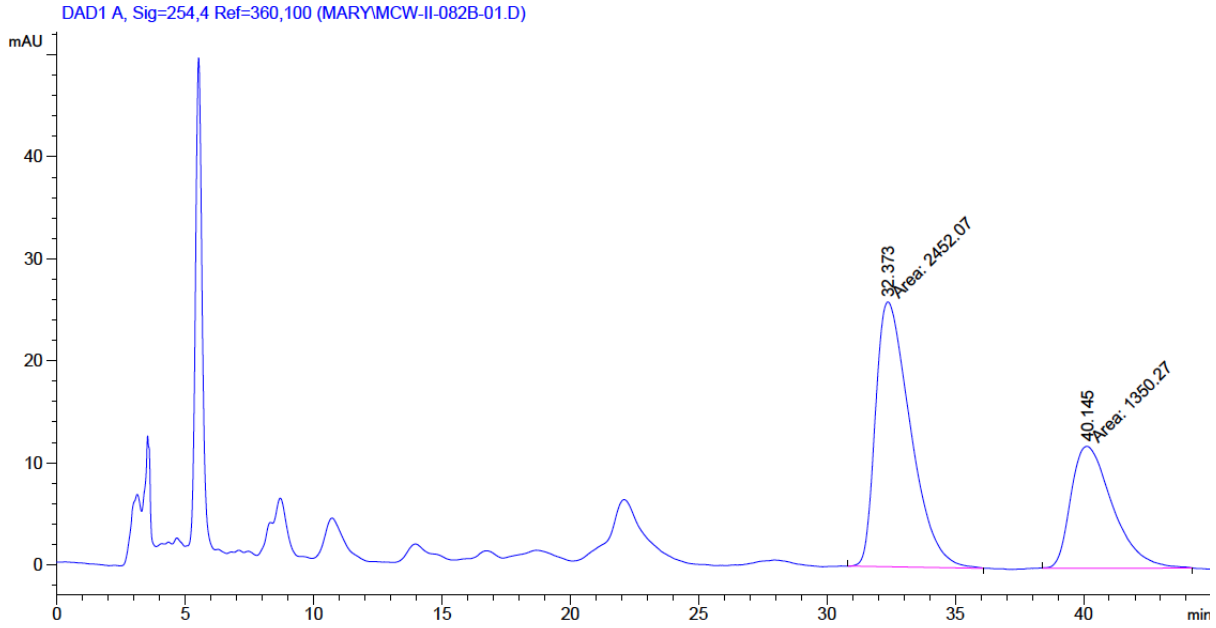
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.308	MM	1.7009	2170.79370	21.27077	28.5265
2	38.890	MM	2.4261	5438.94141	37.36426	71.4735

2.6, Table 2.7, entry 1 [(*S*)-H_8-Monophos], 8% ee:



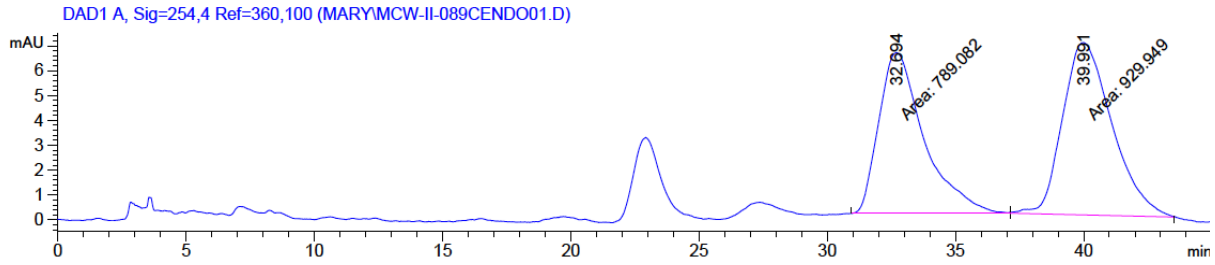
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.915	MM	2.0348	270.44794	2.21514	53.8951
2	40.323	MM	2.2183	231.35614	1.73826	46.1049

2.6, Table 2.7, entry 3 [(*S*)-**2.34**], 29% ee:



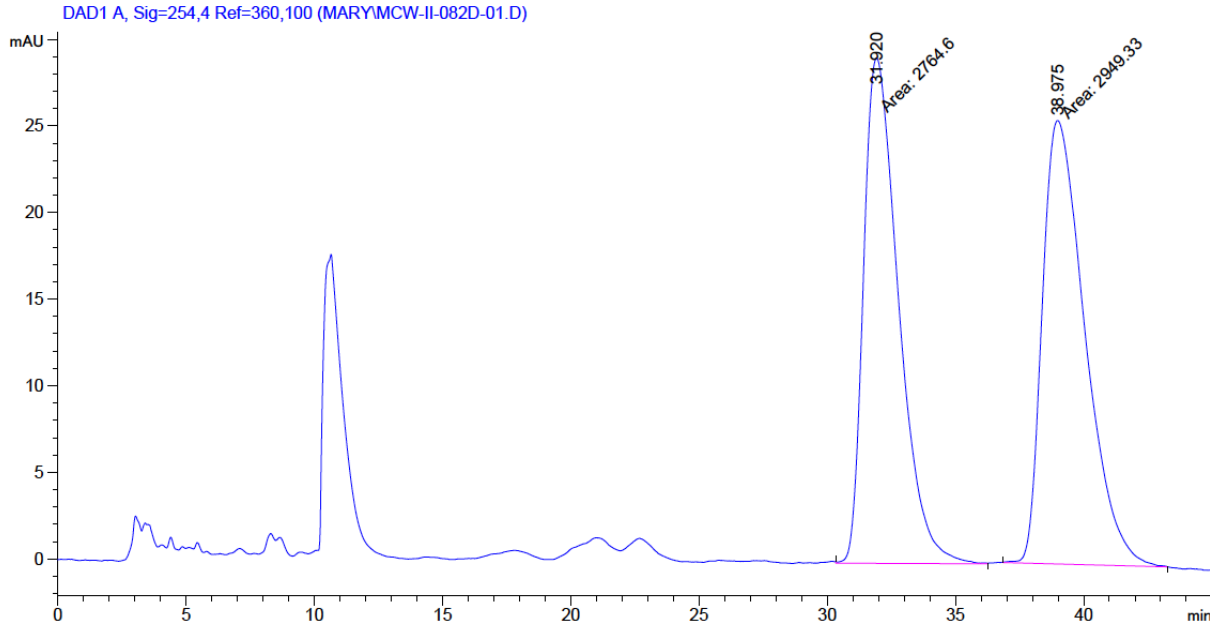
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.373	MM	1.5741	2452.07227	25.96318	64.4884
2	40.145	MM	1.8827	1350.27161	11.95354	35.5116

2.6, Table 2.7, entry 5 [(*S,S,S*)-**2.35**], 8% ee:



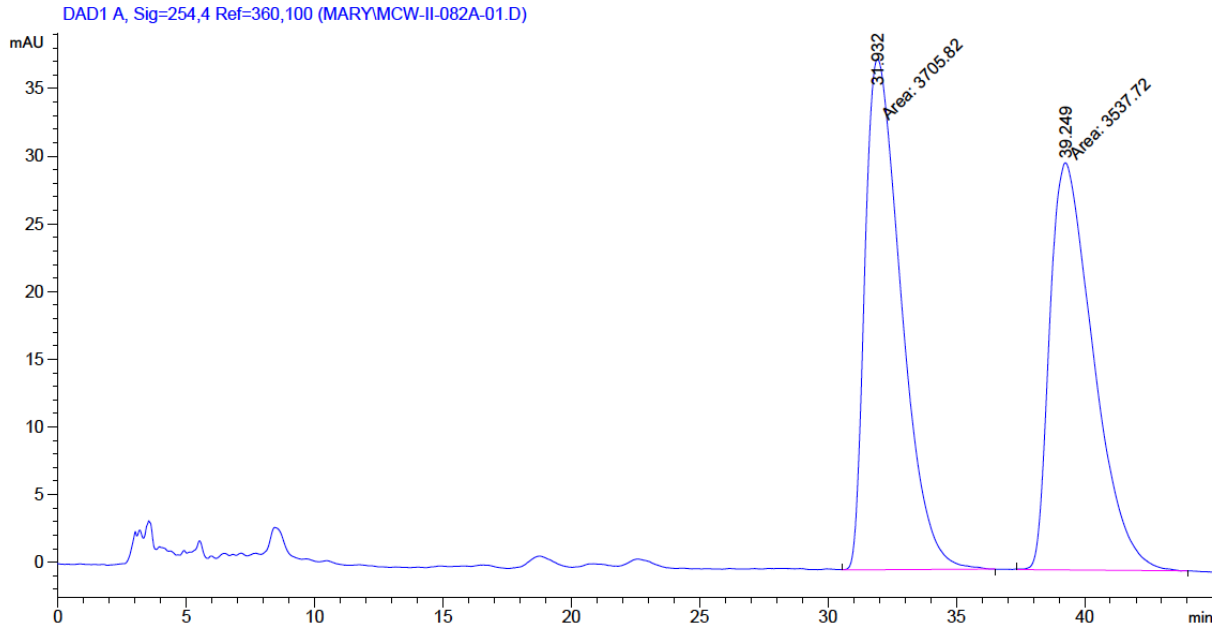
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.694	MM	2.0369	789.08209	6.45671	45.9027
2	39.991	MM	2.2350	929.94946	6.93469	54.0973

2.6, Table 2.7, entry 6 [(*S,R,R*)-**2.36**], 4% ee:



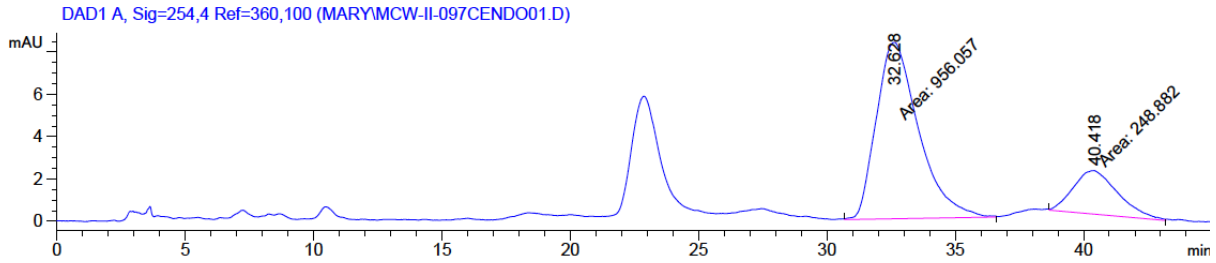
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.920	MM	1.5791	2764.60449	29.17932	48.3836
2	38.975	MM	1.9198	2949.32837	25.60496	51.6164

2.6, Table 2.7, entry 7 [(*S,R,R*)-**2.37**], 2% ee:



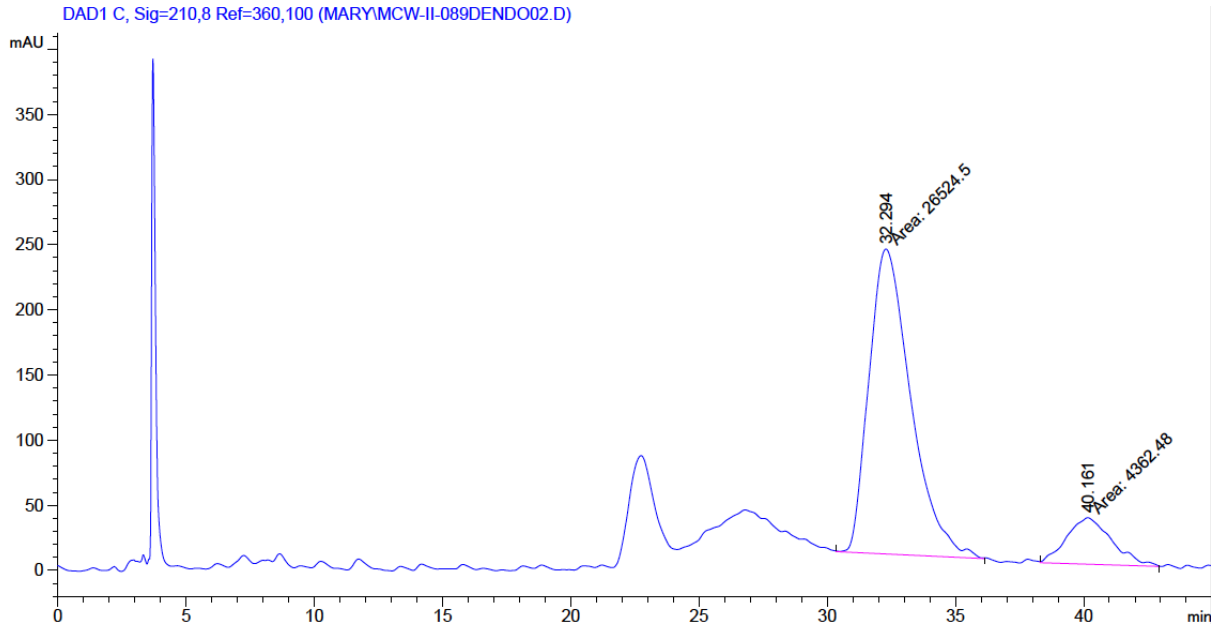
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.932	MM	1.6370	3705.82397	37.73063	51.1604
2	39.249	MM	1.9606	3537.71924	30.07359	48.8396

2.6, Table 2.7, entry 8 [(*R,R,R*)-**2.30**], 58% ee:



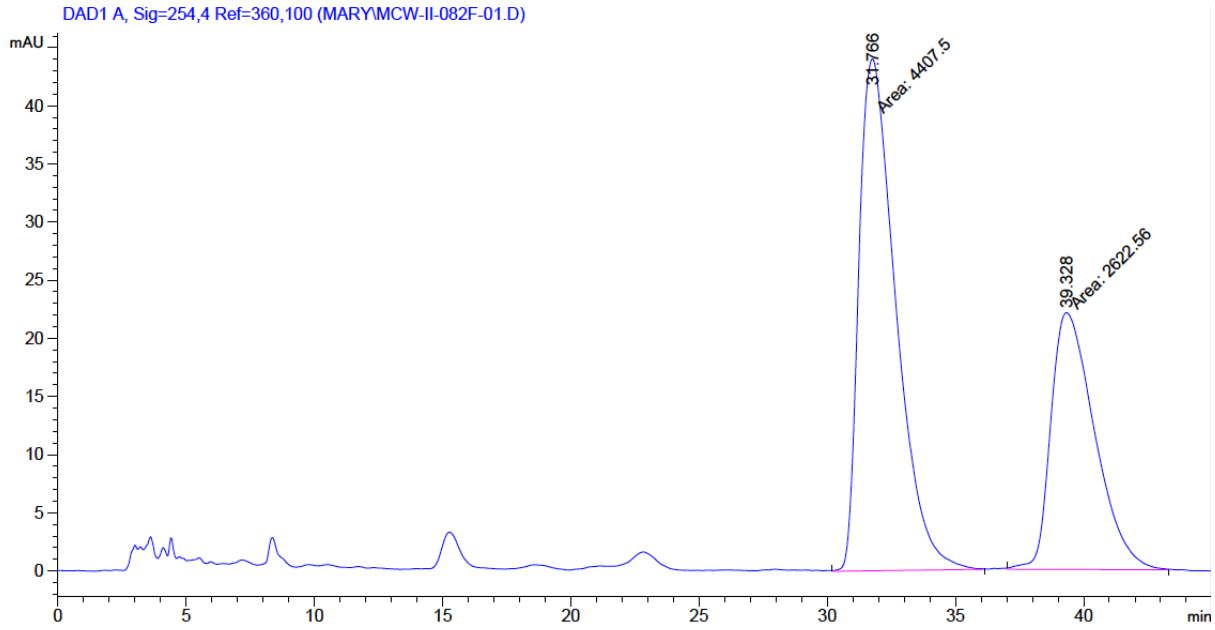
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.628	MM	1.9109	956.05695	8.33861	79.3449
2	40.418	MM	2.0147	248.88177	2.05893	20.6551

2.6, Table 2.7, entry 9 [(*R,S*)-(1-Nph)-Quinaphos], 72% ee:



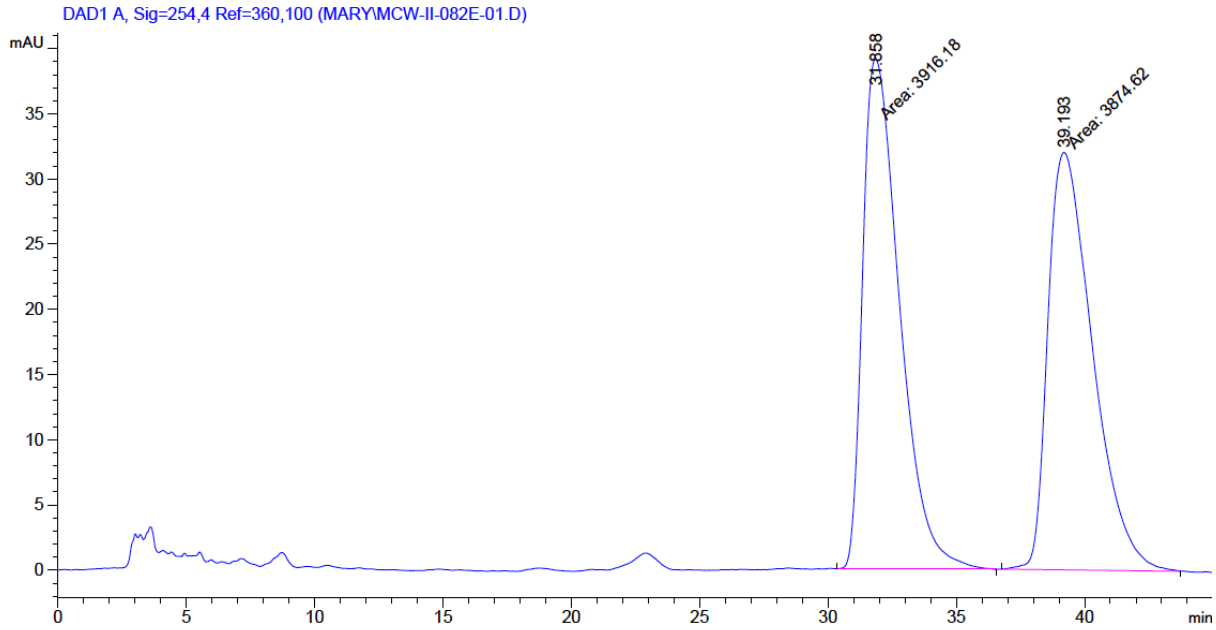
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.294	MM	1.8889	2.65245e4	234.04272	85.8760
2	40.161	MM	2.0394	4362.48047	35.65118	14.1240

2.6, Table 2.7, entry 10 [(*R*)-SIPHOS], 26% ee:



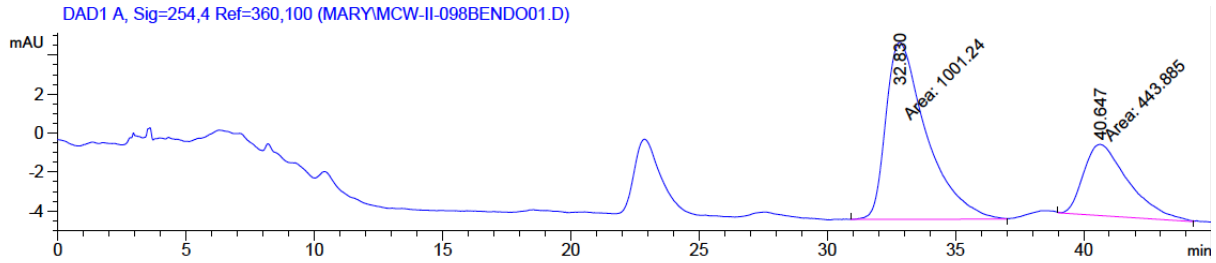
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.766	MM	1.6686	4407.50000	44.02386	62.6951
2	39.328	MM	1.9796	2622.55664	22.07989	37.3049

2.6, Table 2.7, entry 11 [(*R,R,R*)-**2.31**], 0% ee:



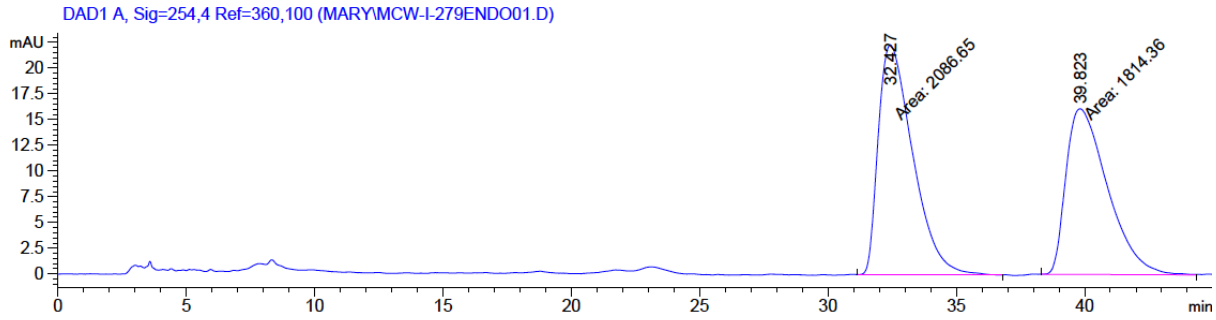
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.858	MM	1.6682	3916.18237	39.12510	50.2667
2	39.193	MM	2.0172	3874.61987	32.01261	49.7333

2.6, Table 2.7, entry 12 [(*R,R*)-**2.32**], 38% ee:



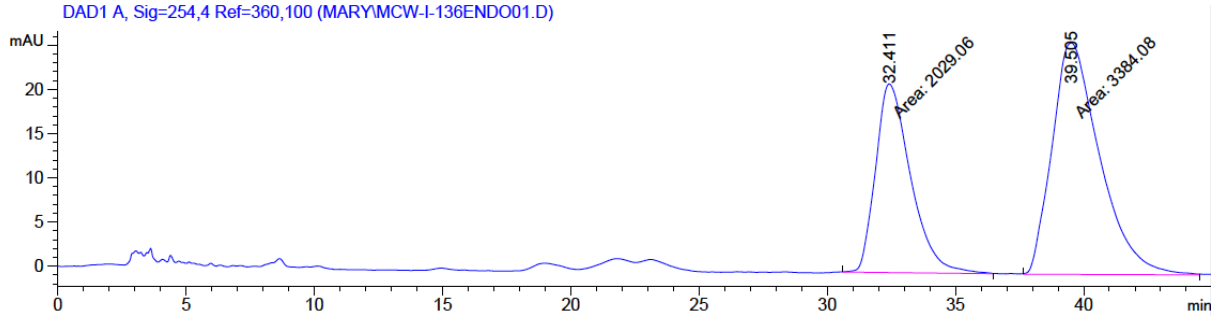
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.830	MM	1.8343	1001.23816	9.09723	69.2840
2	40.647	MM	2.0218	443.88452	3.65910	30.7160

2.6, Table 2.11, entry 1 (SL-J002-2), 7% ee:



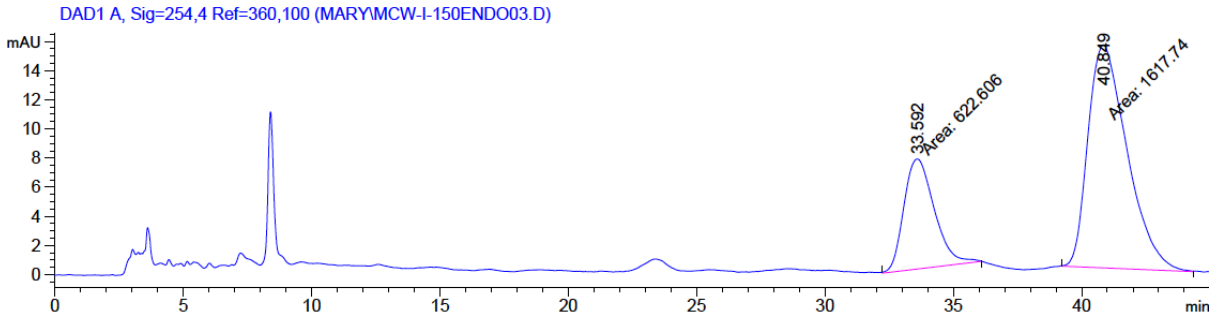
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.427	MM	1.5561	2086.65234	22.34980	53.4900
2	39.823	MM	1.8785	1814.36462	16.09728	46.5100

2.6, Table 2.11, entry 2 [(*S,S*)-DIOP], 25% ee:



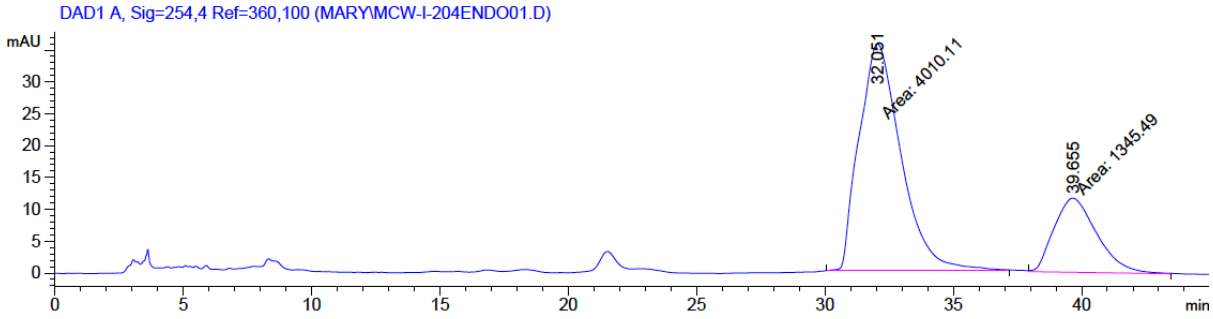
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.411	MM	1.5839	2029.05505	21.35107	37.4839
2	39.505	MM	2.1531	3384.07886	26.19565	62.5161

2.6, Table 2.11, entry 3 [(*R,R*)-Me-DUPHOS], 44% ee:



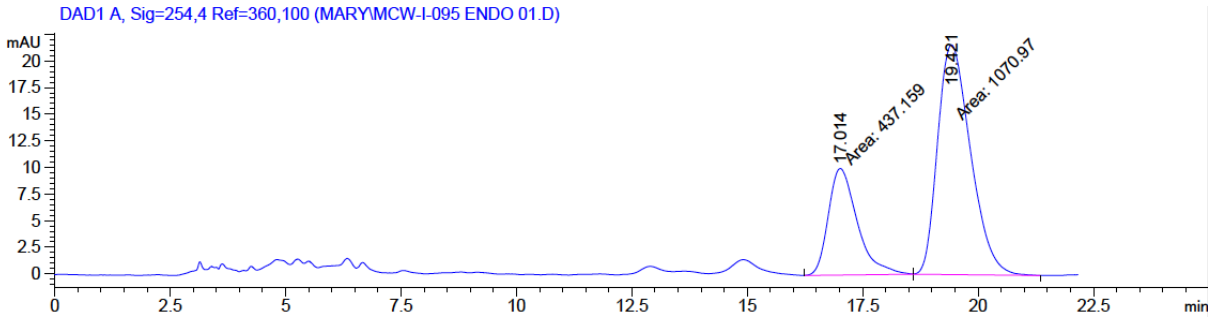
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.592	MM	1.3743	622.60614	7.55071	27.7906
2	40.849	MM	1.7623	1617.73853	15.29978	72.2094

2.6, Table 2.11, entry 4 [(*S,S*)-DACH-phenyl], 50% ee:



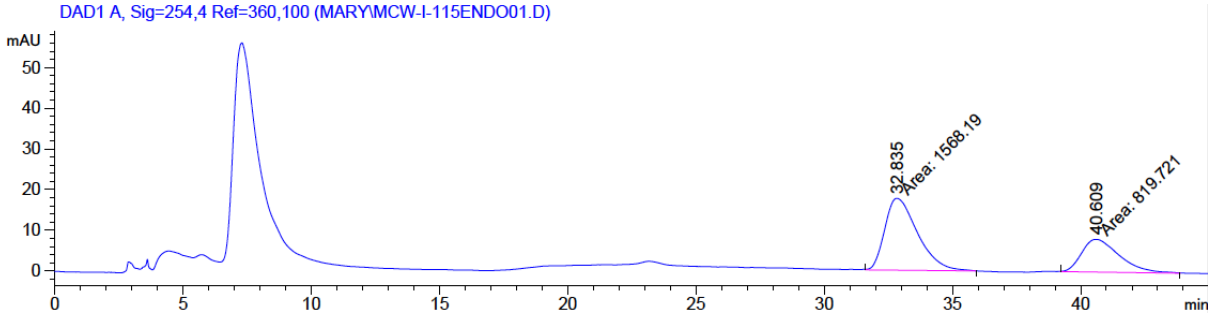
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.051	MM	1.8828	4010.11475	35.49694	74.8770
2	39.655	MM	1.9291	1345.48645	11.62436	25.1230

2.6, Table 2.11, entry 5 [(*S*)-BINAP], 42% ee:



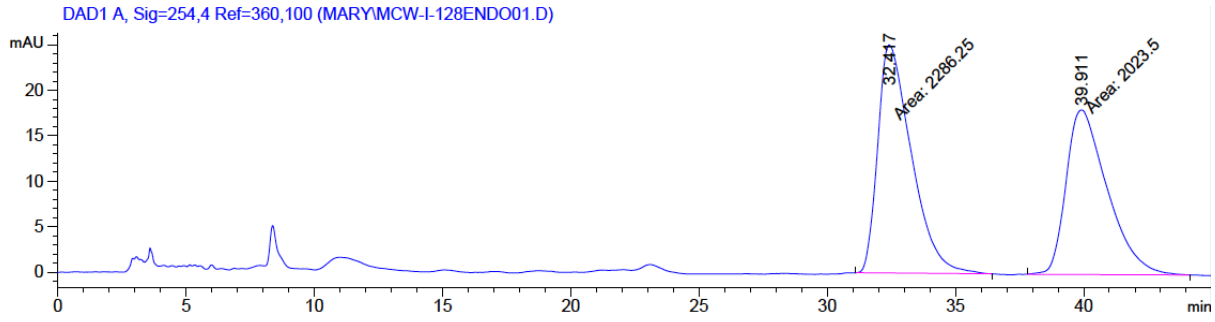
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.014	MM	0.7279	437.15881	10.00983	28.9868
2	19.421	MM	0.8269	1070.97400	21.58552	71.0132

2.6, Table 2.11, entry 6 [(*R*)-TolBINAP], 32% ee:



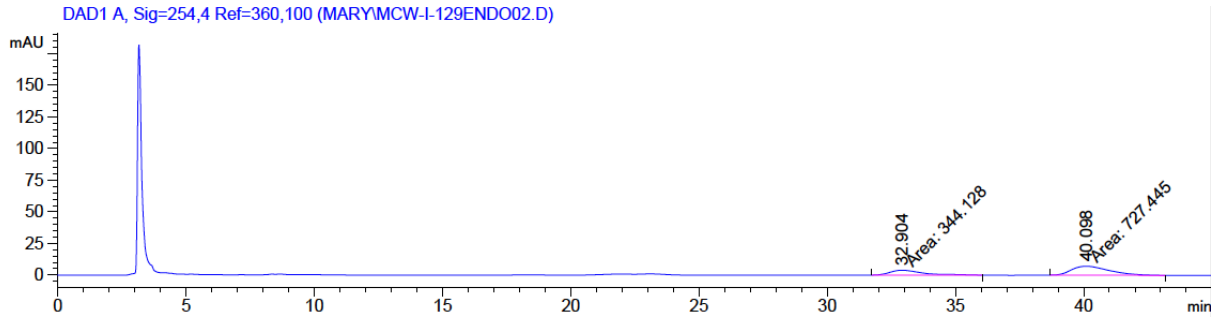
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.835	MM	1.4781	1568.19141	17.68276	65.6721
2	40.609	MM	1.6980	819.72076	8.04581	34.3279

2.6, Table 2.11, entry 8 [(*R*)-MeOBIPHEP], 6% ee:



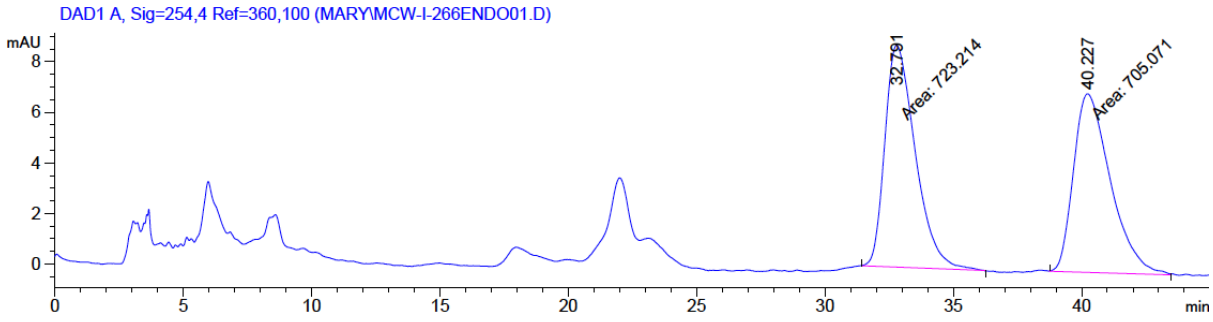
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.417	MM	1.5192	2286.24805	25.08135	53.0483
2	39.911	MM	1.8624	2023.50012	18.10879	46.9517

2.6, Table 2.11, entry 9 [(*R*)-3,5-*i*-Pr-MeOBIPHEP], 36% ee:



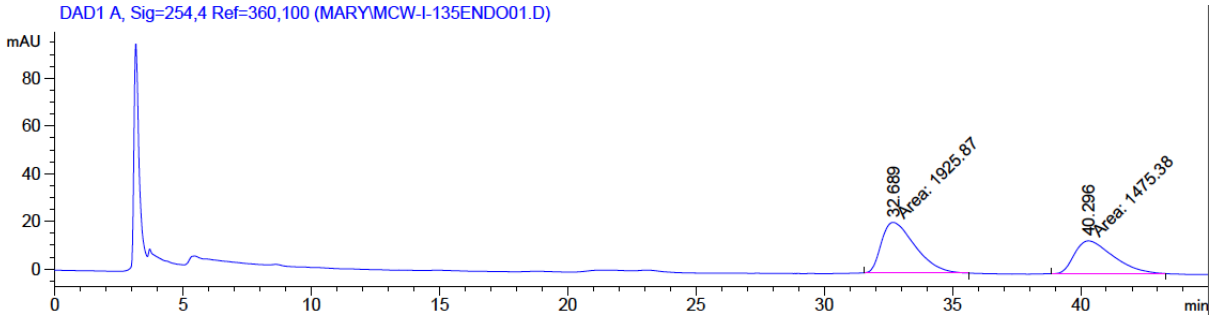
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.904	MM	1.4870	344.12750	3.85700	32.1143
2	40.098	MM	1.7098	727.44458	7.09090	67.8857

2.6, Table 2.11, entry 10 [(*R*)-3,5-xyl-MeOBIPHEP], 2% ee:



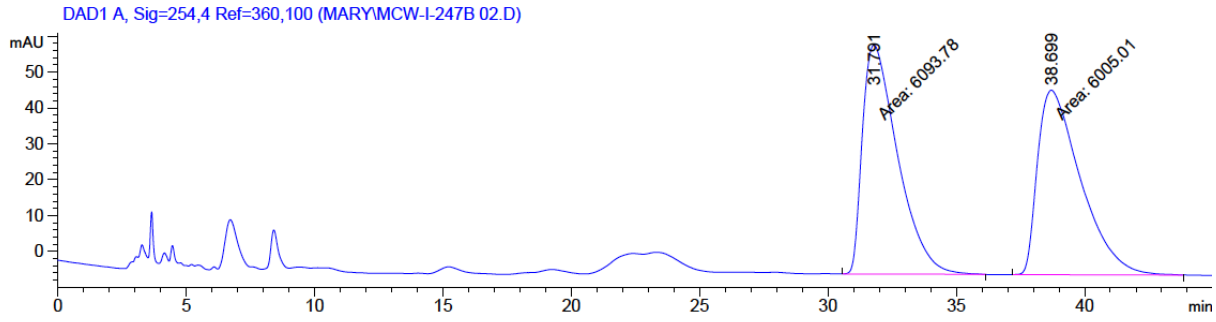
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.791	MM	1.3719	723.21393	8.78618	50.6351
2	40.227	MM	1.6646	705.07141	7.05926	49.3649

2.6, Table 2.11, entry 12 [(*R*)-DUFLUOROPHOS], 14% ee:



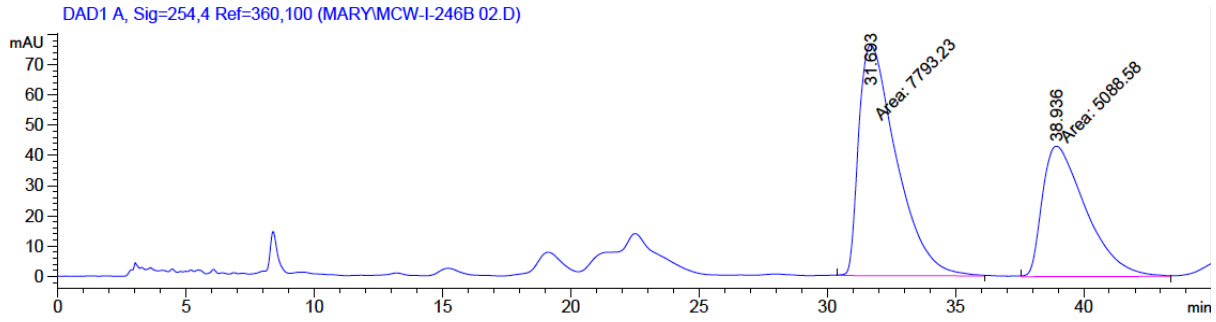
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.689	MM	1.5159	1925.86743	21.17435	56.6224
2	40.296	MM	1.7721	1475.37927	13.87638	43.3776

2.6, Table 2.14, entry 1 [(*R,R*)-Chiraphite], 0% ee:



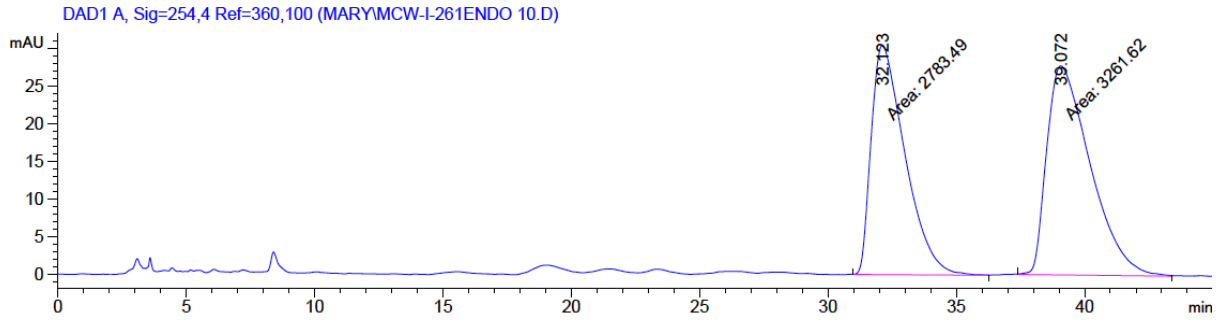
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.791	MM	1.5890	6093.77588	63.91776	50.3668
2	38.699	MM	1.9441	6005.01367	51.48040	49.6332

2.6, Table 2.14, entry 2 [(*R*)-ShiP], 21% ee:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.693	MM	1.7022	7793.23145	76.30497	60.4980
2	38.936	MM	1.9658	5088.57520	43.14257	39.5020

2.6, Table 2.14, entry 3 [(*R*)-**2.38**], 8% ee:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.123	MM	1.5222	2783.49048	30.47753	46.0453
2	39.072	MM	1.9594	3261.62134	27.74291	53.9547

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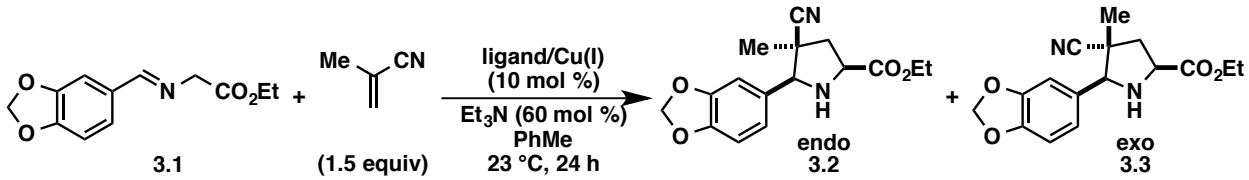
Chapter 3: Catalytic Diastereoselective Synthesis of Pyrrolidine Derivatives by 1,3-Dipolar Cycloaddition with Methacrylonitrile

3.1 Introduction

As described in Chapter 2, conditions for a Cu(I)-catalyzed 1,3-dipolar cycloaddition (1,3-DC) reaction between imine **3.1** and methacrylonitrile have been developed where the diastereoselectivity can be reversed by changing the ligand (Table 3.1). It was shown that when the electron-deficient π-accepting ligand tris(2,2,2-trifluoroethyl) phosphite [$P(OCH_2CF_3)_3$] was used, the reaction was selective for endo pyrrolidine product **3.2** (entry 1). Alternatively, utilization of the electron-rich σ-donating phosphine ligand tricyclohexylphoshine (PCy_3) yielded exo adduct **3.3** with high diastereoselectivity (entry 2). When *P,N*-ligand 2-dicyclohexylphosphino-2′-(*N,N*-dimethylamino)biphenyl (DavePhos) was the ligand employed, the 1,3-DC reaction afforded both diastereomers as a non-selective mixture (entry 3). The results of the studies described in Chapter 2 were of particular interest because such dramatic ligand effects on reaction diastereoselectivity have rarely been reported.[1,2,3]

Table 3.1. Ligand-Controlled Diastereodivergence



entry[a]	ligand	conversion (%)[d,e]	dr (endo:exo)[e]
1	tris(2,2,2-trifluoroethyl) phosphite[b]	94	>94:6
2	tricyclohexylphosphine[b]	98	18:82
3	DavePhos[c]	57	50:50

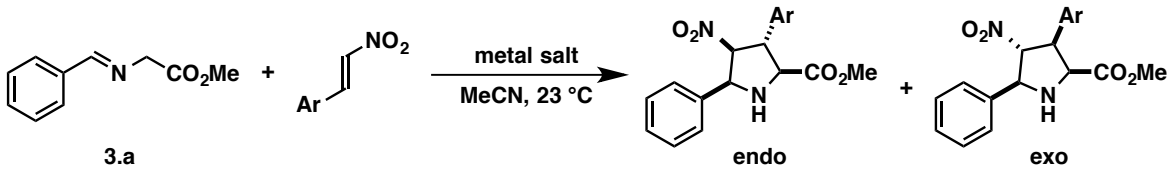
[a]Reactions were performed using imine 3.1 (0.10 mmol), methacrylonitrile (0.15 mmol), $Cu(MeCN)_4BF_4$ (10 mol %), and Et_3N (0.12 mmol) at a concentration of 0.2 M in PhMe. [b]Reactions were performed using 20 mol % ligand. [c]Reactions were performed using 10 mol % ligand. [d]Conversion is defined by comparing the relative amount of product to unreacted starting material. [e]Determined by relative integration in the ^1H NMR spectrum of the crude reaction mixture.

3.1.1 Switching 1,3-DC Diastereoselectivity by Changing the Metal Salt

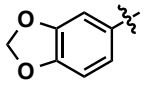
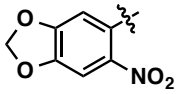
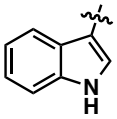
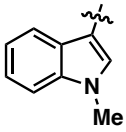
Early studies of metal-promoted 1,3-DC reactions reported success using Li(I)[4] or Ag(I) salts[5,6] in the formation of *N*-metalated azomethine ylide precursors. While these reports describe the selective synthesis of endo pyrrolidine cycloadducts using α,β-unsaturated carbonyl dipolarophiles, a report by Töke and coworkers described a difference in diastereoselectivity when either Li(I) or Ag(I) salts were used in 1,3-DC reactions between metallo-azomethine ylides and aryl nitroolefins.[7] Among the five examples listed, the greatest diastereoselectivity change was a 78:22 dr (endo:exo) when LiBr was used to promote the cycloaddition; instead, AgOAc induced a 30:70 dr, favoring the exo adduct (Table 3.2, entry 4). The authors propose that secondary orbital interactions of the dipolarophile aryl group with Ag(I) and dipolarophile coordination to Li(I)[4e] may result in the observed switch in diastereoselectivity.

Intrigued by the Töke report,[7] the Cossío group further investigated the effect of the metal on the diastereochemical outcome of 1,3-DC reactions involving nitroalkenes.[8] Through a combination of experimental and computational results, it was determined that the observed endo adduct selectivity of the reactions performed using $LiClO_4$ as the Lewis acid was indeed due to a lower energy endo transition state from coordination of the nitro group of the dipolarophile to the metal center. Competitive coordination for the metal binding sites was observed when the reactions were performed using AgOAc in acetonitrile; the nitrile groups of the solvent coordinated to Ag(I) more strongly than the nitro group of the dipolarophile. The corresponding lack of nitro group coordination resulted in a higher energy endo transition state when using Ag(I) compared to Li(I), explaining the exo adduct selectivity observed when utilizing AgOAc.

Table 3.2. Töke's Metal-Induced Diastereoselectivity Changes



3.a endo exo

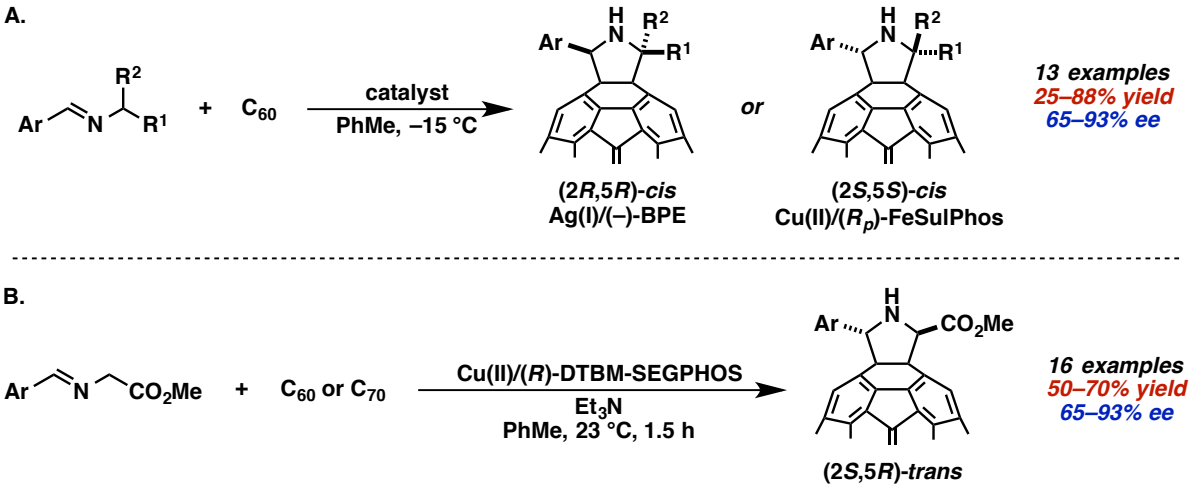
entry	dipolarophile Ar group	metal salt	yield (%)	dr (endo:exo)
1		LiBr	endo: 22	58:42
		AgOAc	exo: 17	56:44
2		LiBr	endo: 61	71:29
		AgOAc	exo: 42	37:63
3		LiBr	endo: 39	72:28
		AgOAc	exo: 44	34:66
4		LiBr	endo: 47	78:22
		AgOAc	exo: 36	30:70
5		LiBr	endo: 59	75:25
		AgOAc	exo: 51	30:70

3.1.2 Catalyst-Controlled Diastereoselectivity

Ag(I)[3a,9] and Cu(II)[1,2c,10] salts are common Lewis acids used in catalytic asymmetric 1,3-DC reactions. Martín and coworkers have studied the effects of switching the enantioselectivity of 1,3-DC reactions between azomethine ylides and fullerenes by using either a Ag(I)/(–)-BPE or a Cu(II)/(R_p)-FeSulPhos catalyst,[10a] resulting in the formation of (2*R*,5*R*)-*cis* or (2*S*,5*S*)-*cis* fulleropyrrolidines, respectively (Scheme 3.1A). Fullerenes are unique dipolarophiles as the π-system is noncoordinating and curved and the 1,3-DC endo/exo nomenclature does not apply to these systems. Therefore, the breakthrough discovery of a Cu(II)/(±)-BINAP[11] system[1] that synthesized 2,5-*trans* pyrrolidine fullerenes indicated a step-wise 1,3-DC reaction mechanism for this particular system. The Martín group further

elaborated this methodology using a Cu(II)/(*R*)-DTBM-SEGPHOS catalyst to synthesize enantioenriched 2,5-*trans* fulleropyrrolidines (Scheme 3.1B).[10d]

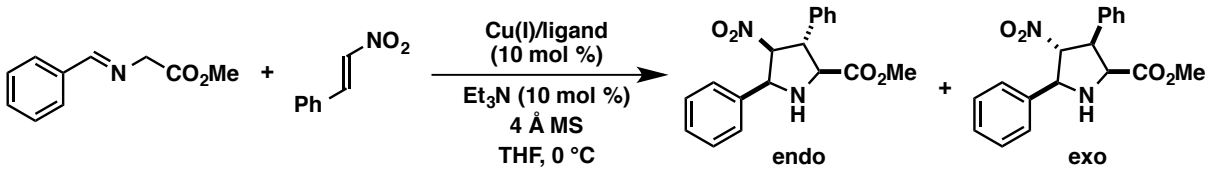
Scheme 3.1. Martín's Stereodifferentiation of Fulleropyrrolidines



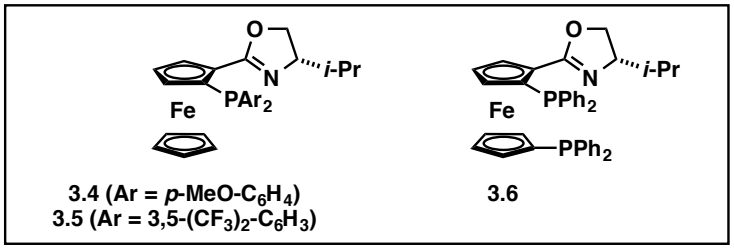
3.1.3 Ligand-Directed Diastereodivergence

In 2006, Hou and coworkers published a report where the endo/exo diastereoselectivity of a Cu(I)-catalyzed 1,3-DC between azomethine ylides and nitroalkenes could be switched by tuning electronics on the *P,N*-ferrocenyl ligand (Table 3.3).[12] When the aromatic group on the ligand phosphine moiety was electron-rich (**3.4**), the pyrrolidine exo adduct was selectively synthesized. Alternatively, the endo pyrrolidine adduct could be accessed by utilizing electron-deficient phosphine groups on the ligand (**3.5**). A non-selective mixture of both endo and exo pyrrolidine cycloadducts was formed when diphosphine ligand **3.6** was used. Yields were moderate (ca. 60%) due to competitive formation of the Michael addition product. While such electronic trends were observed in our diastereoselective 1,3-DC reaction, the reaction system developed by our group varies from that of the Hou group because we identified ligands from different ligand classes that accomplish the observed switches in endo/exo selectivity.

Table 3.3. Hou's *P,N*-Ferrocenyl Ligand-Induced Diastereoselectivity Changes



entry	ligand	yield (%)	dr (endo:exo)	ee (%)
1	3.4	65	exo only	98 (exo)
2	3.5	62	82:18	97 (endo)
3	3.6	37	51:49	15 (endo), 92 (exo)

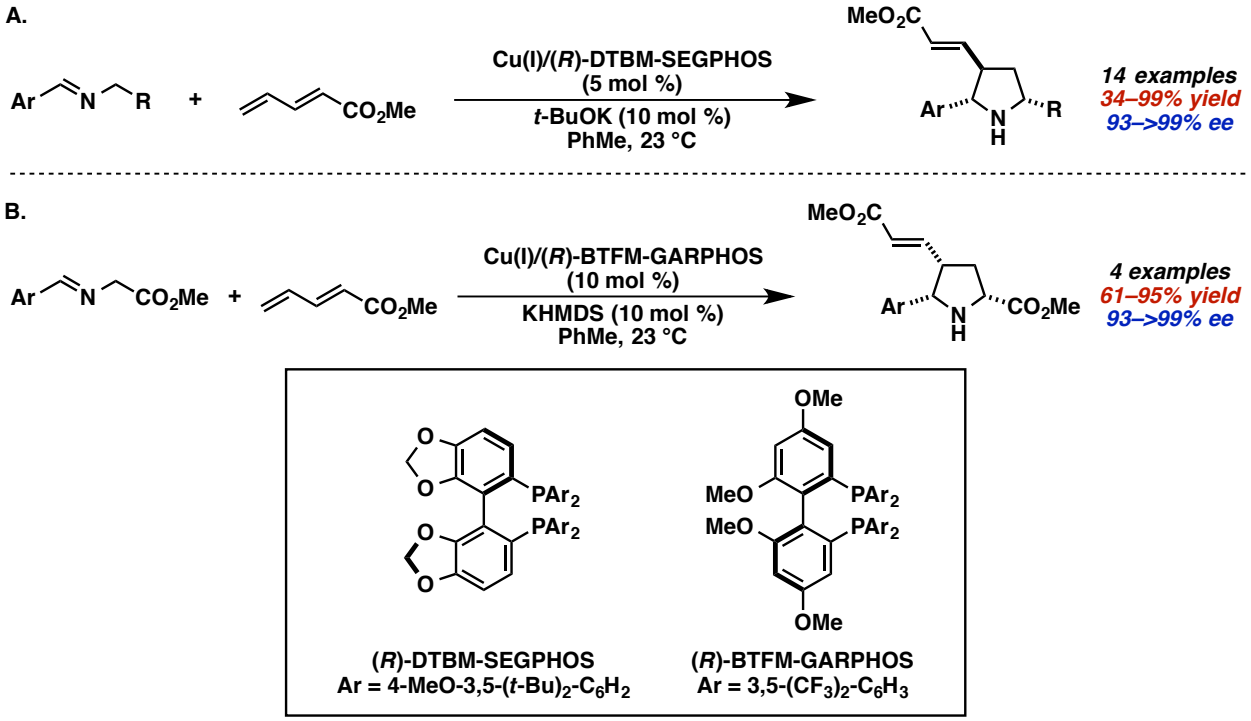


3.4 (Ar = *p*-MeO-C_6H_4)
3.5 (Ar = 3,5-$(CF_3)_2$-C_6H_3)

3.6

One final example is a recent report from the Carretero group where the diastereoselectivity of a Cu(I)-catalyzed 1,3-DC between azomethine ylides and acyclic 1,3-dienes was achieved using two different *P,P'*-biaryl phosphine ligands (Scheme 3.2).[13] Strong bases were required in order to accomplish selective reactivity at the terminal double bond of the diene. When Cs_2CO_3 was tested as the base, the 1,6-addition product was formed instead of the expected cycloadduct. This result suggested that this reaction proceeds step-wise. While no detailed discussion on the nature of diastereodivergence was provided in this report, it is possible that the diastereodetermining step is the Mannich-type cyclization, where the Cu(I) ligand can dictate the resulting C4 stereochemistry.

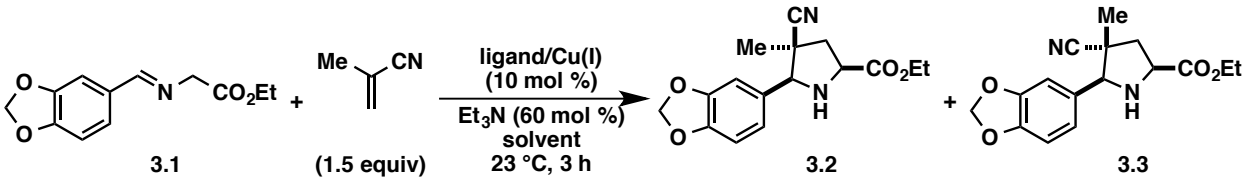
Scheme 3.2. Carretero's *P,P'*-Biaryl Ligand-Induced Diastereoselectivity Changes



3.2 Optimization of Reaction Conditions

After discovering the unique diastereoselectivity effects of different ligand types in the Cu(I)-catalyzed 1,3-DC (Table 3.1), reaction optimization was initiated. Higher yields and diastereoselectivity for reactions using $P(OCH_2CF_3)_3$ and PCy_3 were observed in THF than in PhMe or MeCN. (Table 3.4, entries 1–9). The reaction profiles using THF and CH_2Cl_2 were very similar (compare entries 1–3 and 10–12), but THF was chosen as the preferred solvent. With the exception of entry 6,[14,15] no reaction proceeds in the absence of Cu(I) salt, ligand, or base (Table 3.5). It was also demonstrated that the amount of the dipolarophile could be reduced to 1.1 equiv without compromising yield or altering the diastereoselectivity (Table 3.6).

Table 3.4. Solvent Screen

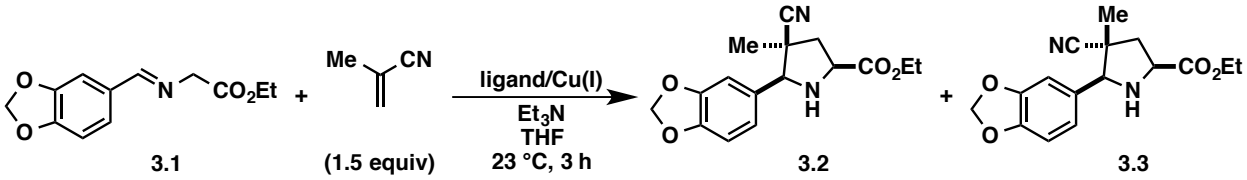


3.1 (1.5 equiv) 3.2 3.3

entry[a]	ligand	solvent	unreacted 3.1 (%)[d]	yield (%)[d]	dr (endo:exo)[e]
1	$P(OCH_2CF_3)_3$[b]		7	74	98:2
2	PCy_3[b]	THF	4	89	10:90
3	DavePhos[c]		4	85	41:59
4	$P(OCH_2CF_3)_3$[b]		99	0	–
5	PCy_3[b]	PhMe	7	89	16:84
6	DavePhos[c]		87	12	50:50
7	$P(OCH_2CF_3)_3$[b]		65	5	78:22
8	PCy_3[b]	MeCN	93	5	20:80
9	DavePhos[c]		83	7	62:38
10	$P(OCH_2CF_3)_3$[b]		20	77	96:4
11	PCy_3[b]	CH_2Cl_2	4	97	11:89
12	DavePhos[c]		21	74	40:60

[a]Reactions were performed using imine 3.1 (0.2 mmol), methacrylonitrile (0.3 mmol), $Cu(MeCN)_4BF_4$ (10 mol %), and Et_3N (0.12 mmol) at a concentration of 0.2 M in the indicated solvent. [b]Reactions were performed using 22 mol % ligand. [c]Reactions were performed using 11 mol % ligand. [d]GC yields using 1,3,5-trimethoxybenzene as external standard (± 5% error). [e]Ratios determined by GC-FID analysis.

Table 3.5. Negative Controls

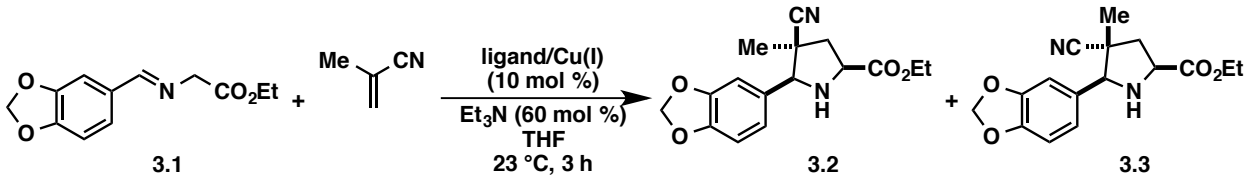


3.1 (1.5 equiv) 3.2 3.3

entry[a]	ligand	mol % Cu(I)	mol % Et_3N	unreacted 3.1 (%)[d]	yield (%)[d]	dr (endo:exo)[e]
1	none	0	60	98	0	–
2	$P(OCH_2CF_3)_3$[b]	0	60	93	0	–
3	PCy_3[b]	0	60	94	0	–
4	DavePhos[c]	0	60	93	0	–
5	$P(OCH_2CF_3)_3$[b]	10	0	89	0	–
6	PCy_3[b]	10	0	38	60	10:90
7	DavePhos[c]	10	0	88	0	–

[a]Reactions were performed using imine 3.1 (0.2 mmol) and methacrylonitrile (0.3 mmol) at a concentration of 0.2 M in THF. [b]Reactions were performed using 22 mol % ligand. [c]Reactions were performed using 11 mol % ligand. [d]GC yields using 1,3,5-trimethoxybenzene as external standard (± 5% error). [e]Ratios determined by GC-FID analysis.

Table 3.6. Equivalents of Dipolarophile

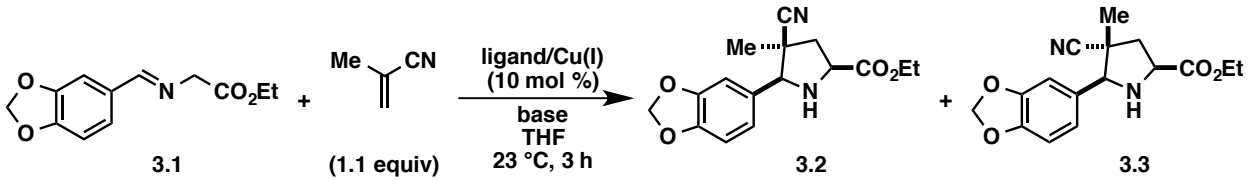


entry[a]	ligand	equiv methacrylonitrile	unreacted 3.1 (%)[d]	yield (%)[d]	dr (endo:exo)[e]
1	$P(OCH_2CF_3)_3$[b]		6	84	98:2
2	PCy_3[b]	1.1	4	93	10:90
3	DavePhos[c]		3	93	40:60
4	$P(OCH_2CF_3)_3$[b]		5	83	98:2
5	PCy_3[b]	1.5	4	90	10:90
6	DavePhos[c]		4	85	41:59
7	$P(OCH_2CF_3)_3$[b]		4	85	97:3
8	PCy_3[b]	2.0	3	97	10:90
9	DavePhos[c]		3	93	42:58

[a]Reactions were performed using imine 3.1 (0.2 mmol), $Cu(MeCN)_4BF_4$ (10 mol %), and Et_3N (0.12 mmol) at a concentration of 0.2 M in THF. [b]Reactions were performed using 22 mol % ligand. [c]Reactions were performed using 11 mol % ligand. [d]GC yields using 1,3,5-trimethoxybenzene as external standard (± 5% error). [e]Ratios determined by GC-FID analysis.

The effects of the nature of the base were next investigated (Table 3.7). When the strong organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead of Et_3N, yields of cycloadducts and diastereoselectivity eroded (entries 1–6). The efficacy of Cs_2CO_3 and KHMDS were also explored. Cs_2CO_3 proved to promote the 1,3-DC reaction well when ligands $P(OCH_2CF_3)_3$ and DavePhos were used (entries 7 and 9); however, the reaction run using PCy_3 as the ligand proceeded in a lower yield with a loss of diastereoselectivity compared to the same reaction using Et_3N (compare entries 2 and 8). Finally, the use of KHMDS resulted in very low yields of the desired products (entries 10–12). Using a catalytic amount of Et_3N maintained high conversion and desired diastereoselectivities (compare entries 1–3 to 13–15).

Table 3.7. Base Optimization

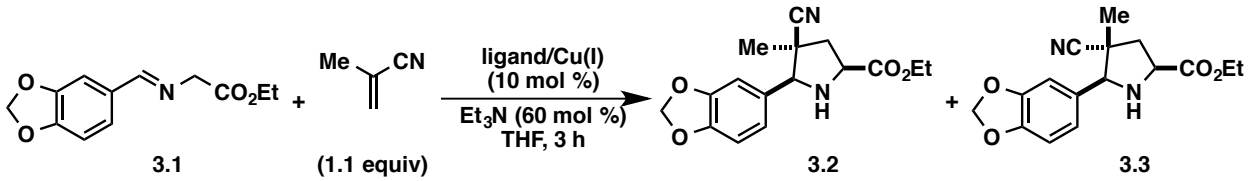


entry[a]	ligand	base (equiv)	unreacted 3.1 (%)[d]	yield (%)[d]	dr (endo:exo)[e]
1	$P(OCH_2CF_3)_3$[b]		6	84	98:2
2	PCy_3[b]	Et_3N (0.60)	4	93	10:90
3	DavePhos[c]		3	93	40:60
4	$P(OCH_2CF_3)_3$[b]		73	12	65:35
5	PCy_3[b]	DBU (0.60)	47	40	62:38
6	DavePhos[c]		13	67	45:55
7	$P(OCH_2CF_3)_3$[b]		6	82	97:3
8	PCy_3[b]	Cs_2CO_3 (0.60)	5	78	49:51
9	DavePhos[c]		2	86	47:53
10	$P(OCH_2CF_3)_3$[b]		1	20	94:6
11	PCy_3[b]	KHMDS (0.60)	13	6	nd
12	DavePhos[c]		1	2	nd
13[f]	$P(OCH_2CF_3)_3$[b]		5	81	98:2
14[f]	PCy_3[b]	Et_3N (1.1)	4	93	10:90
15[f]	DavePhos[c]		3	91	42:58

[a]Reactions were performed using imine 3.1 (0.20 mmol), methacrylonitrile (0.22 mmol), and $Cu(MeCN)_4BF_4$ (10 mol %) at a concentration of 0.2 M in THF. [b]Reactions were performed using 22 mol % ligand. [c]Reactions were performed using 11 mol % ligand. [d]GC yields using 1,3,5-trimethoxybenzene as external standard (± 5% error). [e]Ratios determined by GC-FID analysis. [f]Reactions run using 1.5 equiv methacrylonitrile. nd = not determined.

The 1,3-DC reaction was run at lower temperatures to determine whether an improvement of diastereoselectivity could be achieved (Table 3.8). Surprisingly, lower temperatures had no effect on the diastereoselectivity for any of the three reactions tested. Yields of the cycloadducts were lower as the reaction temperature was decreased (entries 1–6). Conveniently, ambient temperature proved to be the most effective temperature to carry out the desired transformation (entries 7–9).

Table 3.8. Temperature Effects on Yield and Diastereoselectivity



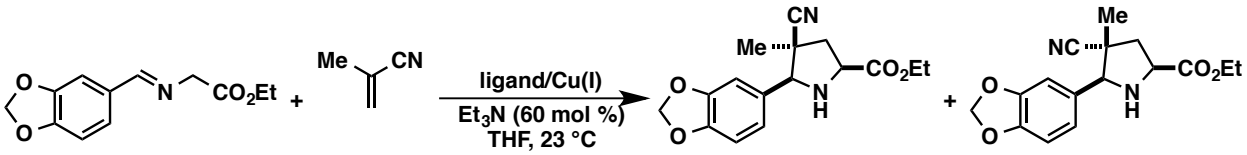
entry[a]	ligand	temp (°C)	unreacted 3.1 (%)[d]	yield (%)[d]	dr (endo:exo)[e]
1	$P(OCH_2CF_3)_3$[b]	–20	38	33	94:6
2	PCy_3[b]		44	56	9:91
3	DavePhos[c]		14	79	48:52
4	$P(OCH_2CF_3)_3$[b]	0	21	54	96:4
5	PCy_3[b]		15	81	10:90
6	DavePhos[c]		3	88	44:56
7	$P(OCH_2CF_3)_3$[b]	23	6	84	98:2
8	PCy_3[b]		4	93	10:90
9	DavePhos[c]		3	93	40:60

[a]Reactions were performed using imine 3.1 (0.20 mmol), methacrylonitrile (0.22 mmol), $Cu(MeCN)_4BF_4$ (10 mol %), and Et_3N (0.12 mmol) at a concentration of 0.2 M in THF. [b]Reactions were performed using 22 mol % ligand. [c]Reactions were performed using 11 mol % ligand. [d]GC yields using 1,3,5-trimethoxybenzene as external standard (± 5% error). [e]Ratios determined by GC-FID analysis.

The optimal catalyst loading, reaction time, and reaction concentration were next determined (Table 3.9). Running the reaction at a concentration of 0.2 M and using a 10 mol % catalyst loading for 1 h proved insufficient (entries 1–3), as did a 1 mol % catalyst loading for a reaction time of 12 h (entries 4–6). A catalyst loading of 5 mol % was adapted and the effect of concentration was explored over a 2 h reaction time (entries 7–24). Not surprisingly, yields increased as the reaction concentration was increased from 0.1 M to 1 M. Using $P(OCH_2CF_3)_3$ as the ligand, endo adduct selectivity slowly degraded as the reaction concentration was increased above 0.4 M (compare entry 13 to entries 16, 19, and 22). A concentration of 0.6 M was chosen for reactions run using the phosphite ligand as the results showed a reasonable compromise between yield and endo adduct selectivity. The reactions run using PCy_3 as the ligand showed good reactivity and exo adduct selectivity at a concentration of 1 M (entry 23), and a

concentration of 0.4 M was chosen to further study 1,3-DC reactions using DavePhos as the ligand (entry 15).

Table 3.9. Catalyst Loading and Reaction Concentration



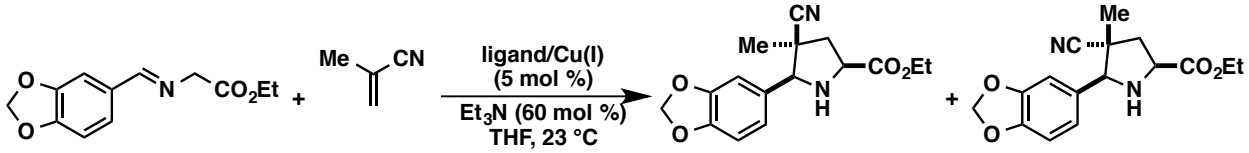
3.1 (1.1 equiv) 3.2 3.3

entry[a]	ligand	catalyst loading	concentration	time	unreacted 3.1 (%)[d]	yield (%)[d]	dr (endo:exo)[e]
1	$P(OCH_2CF_3)_3$[b]				50	25	96:4
2	PCy_3[b]	10 mol %	0.2 M	1 h	27	66	11:89
3	DavePhos[c]				4	86	40:60
4	$P(OCH_2CF_3)_3$[b]				65	7	97:3
5	PCy_3[b]	1 mol %	0.2 M	12 h	52	36	13:87
6	DavePhos[c]				80	1	nd
7	$P(OCH_2CF_3)_3$[b]				68	9	97:3
8	PCy_3[b]	5 mol %	0.1 M	2 h	27	62	12:88
9	DavePhos[c]				51	30	46:54
10	$P(OCH_2CF_3)_3$[b]				59	16	97:3
11	PCy_3[b]	5 mol %	0.2 M	2 h	13	76	11:89
12	DavePhos[c]				19	63	43:57
13	$P(OCH_2CF_3)_3$[b]				49	35	98:2
14	PCy_3[b]	5 mol %	0.4 M	2 h	7	88	10:90
15	DavePhos[c]				5	94	39:61
16	$P(OCH_2CF_3)_3$[b]				20	72	96:4
17	PCy_3[b]	5 mol %	0.6 M	2 h	6	98	10:90
18	DavePhos[c]				2	98	39:61
19	$P(OCH_2CF_3)_3$[b]				17	71	94:6
20	PCy_3[b]	5 mol %	0.8 M	2 h	3	97	10:90
21	DavePhos[c]				3	96	38:62
22	$P(OCH_2CF_3)_3$[b]				8	84	93:7
23	PCy_3[b]	5 mol %	1.0 M	2 h	3	99	9:91
24	DavePhos[c]				2	95	39:61

[a]Reactions were performed using imine 3.1 (0.20 mmol), methacrylonitrile (0.22 mmol), and Et_3N (0.12 mmol) with the indicated catalyst loading and at the indicated concentration in THF. [b]Reactions were performed using a 2.2:1 ligand-to-Cu(I) ratio. [c]Reactions were performed using a 1.1:1 ligand-to-Cu(I) ratio. [d]GC yields using 1,3,5-trimethoxybenzene as external standard (± 5% error). [e]Ratios determined by GC-FID analysis. nd = not determined.

Next, the reaction time was optimized using each of the three ligands based on the optimal concentration (Table 3.10). Focusing on four different time points, a reaction time of 5 h was chosen for reactions using the phosphite ligand as the highest conversion was achieved (entries 1–4). The high reactivity of the Cu(I)/PCy_3 catalyst was demonstrated by running the 1,3-DC for 0.5–2 h (entries 5–8) and a 1 h reaction time was chosen for this catalyst system. Finally, after probing the reactivity of the Cu(I)/DavePhos catalyst from 2–5 h at a concentration of 0.4 M, a 3 h reaction time was shown to accomplish desirable reactivity (entries 9–12).

Table 3.10. Optimization of Reaction Time



3.1 (1.1 equiv) 3.2 3.3

entry[a]	ligand	concentration	time	unreacted 3.1 (%)[d]	yield (%)[d]	dr (endo:exo)[e]
1	$P(OCH_2CF_3)_3$[b]	0.6 M	2 h	23	64	97:3
2			3 h	14	73	97:3
3			4 h	6	84	96:4
4			5 h	8	86	96:4
5	PCy_3[b]	1.0 M	30 min	14	86	9:91
6			60 min	5	95	9:91
7			90 min	4	>99	9:91
8			120 min	3	99	9:91
9	DavePhos[c]	0.4 M	2 h	7	91	38:62
10			3 h	3	95	38:62
11			4 h	3	96	37:63
12			5 h	2	96	38:62

[a]Reactions were performed using imine 3.1 (0.20 mmol), methacrylonitrile (0.22 mmol), Et_3N (0.12 mmol), and $Cu(MeCN)_4BF_4$ (5 mol %) for the indicated time and at the indicated concentration in THF. [b]Reactions were performed using 11 mol % ligand. [c]Reactions were performed using 5.5 mol % ligand. [d]GC yields using 1,3,5-trimethoxybenzene as external standard (± 5% error). [e]Ratios determined by GC-FID analysis.

3.3 Investigation of Imine Reactivity

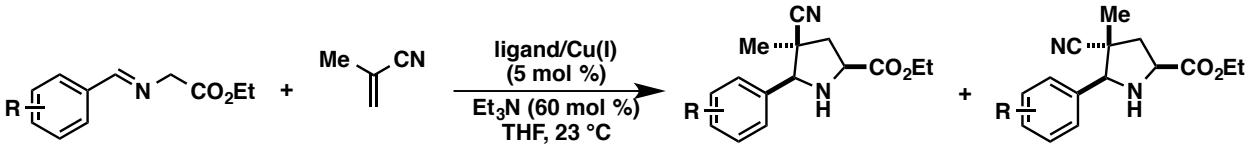
After optimizing the 1,3-DC reaction for each catalyst system at a 5 mol % catalyst loading, three different methods were developed: Method A, where $P(OCH_2CF_3)_3$ was used as the ligand (11 mol %) and the reaction was run at a concentration of 0.6 M for 5 h; method B,

where PCy_3 was used as the ligand (11 mol %) at a 1.0 M concentration for a 1 h reaction time; and method C, where ligand DavePhos (5.5 mol %), a 3 h reaction time, and a 0.4 M concentration were used. Relative configuration of the cycloadducts was assigned by 2D ^{1}H NMR experiments (see Appendix B for details).

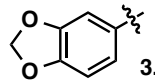
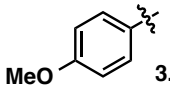
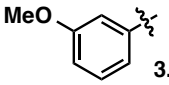
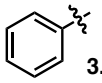
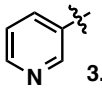
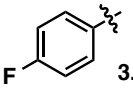
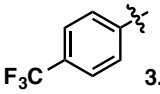
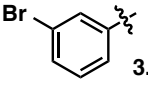
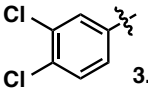
The results of cycloadditions of nine imine substrates with methacrylonitrile under these reaction conditions are summarized in Table 3.11. Electron-rich (**3.1**, **3.7**, **3.10**; entries 1–9), electron-neutral (**3.13**, entries 10–12), and electron-deficient (**3.16**, **3.19**, **3.22**, **3.25**, **3.28**; entries 13–27) aryl imines were used as substrates. Methods A and B preferentially provided the endo and exo cycloadducts, respectively. These results demonstrated that the diastereoselectivity trends are controlled by the catalyst.

As pyridyl groups are common ligands for copper,[16] it was not surprising that 3-pyridyl imine **3.16** was a poor substrate for this reaction (Table 3.11, entries 13–15). To test the hypothesis that the pyridyl group coordinates to the Cu(I) catalyst, the catalyst loading was increased from 5 mol % to 10 mol %, which resulted in increased yields of desired pyrrolidine products **3.17** or **3.18** (Table 3.12). Additionally, the three 1,3-DC reactions between phenyl imine **3.13** and methacrylonitrile were conducted in the presence of 1 equiv pyridine (Table 3.13). Compared to the results of these reactions run in the absence of pyridine, yields of pyrrolidine products **3.14** and **3.15** were significantly decreased. Collectively, these two sets of experiments indicate that pyridyl-derived imine substrates are not suitable for the Cu(I)-catalyzed 1,3-DC reaction, as they can reduce the activity of the catalyst.

Table 3.11. Diastereodivergence using Different Imines

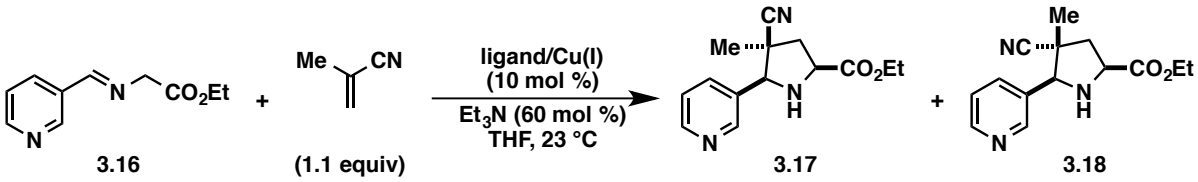


(1.1 equiv) endo adduct exo adduct

entry[a]	aryl group	method	GC yield (%)[e]	cycloadducts	dr (endo:exo)[f]	isolated yield (dr, endo:exo)[g]
1	 3.1	A[b]	88	endo = 3.2 exo = 3.3	96:4	79% (94:6)
2		B[c]	97		9:91	82% (11:89)
3		C[d]	95		39:61	
4	 3.7	A[b]	58	endo = 3.8 exo = 3.9	94:6	
5		B[c]	>99		12:88	
6		C[d]	96		35:65	
7	 3.10	A[b]	91	endo = 3.11 exo = 3.12	94:6	
8		B[c]	93		9:91	
9		C[d]	93		40:60	
10	 3.13	A[b]	76	endo = 3.14 exo = 3.15	98:2	76% (96:4)
11		B[c]	97		11:89	83% (12:88)
12		C[d]	94		38:62	
13	 3.16	A[b]	14	endo = 3.17 exo = 3.18	86:14	
14		B[c]	52		12:88	
15		C[d]	46		49:51	
16	 3.19	A[b]	84	endo = 3.20 exo = 3.21	96:4	
17		B[c]	>99		12:88	
18		C[d]	>99		41:59	
19	 3.22	A[b]	88	endo = 3.23 exo = 3.24	96:4	74% (96:4)
20		B[c]	92		14:86	78% (15:85)
21		C[d]	98		47:53	
22	 3.25	A[b]	78	endo = 3.26 exo = 3.27	96:4	
23		B[c]	95		12:88	
24		C[d]	98		56:44	
25	 3.28	A[b]	91	endo = 3.29 exo = 3.30	98:2	76% (98:2)
26		B[c]	>99		14:86	73% (15:85)
27		C[d]	>99		61:39	

[a]Reactions were performed using imine (0.20 mmol), methacrylonitrile (0.22 mmol), Et_3N (0.12 mmol), and $Cu(MeCN)_4BF_4$ (5 mol %), at the indicated concentration in THF. [b]Reactions run at 0.6 M for 5 h using $P(OCH_2CF_3)_3$ as the ligand (11 mol %). [c]Reactions run at 1.0 M for 1 h using PCy_3 as the ligand (11 mol %). [d]Reactions run at 0.4 M for 3 h using DavePhos as the ligand (5.5 mol %). [e]GC yields determined using 1,3,5-trimethoxybenzene as external standard (average of two experiments, ± 5% error). [f]Ratios determined by GC-FID analysis (average of two experiments). [g]Ratios determined by ^1H NMR analysis of the crude reaction mixture.

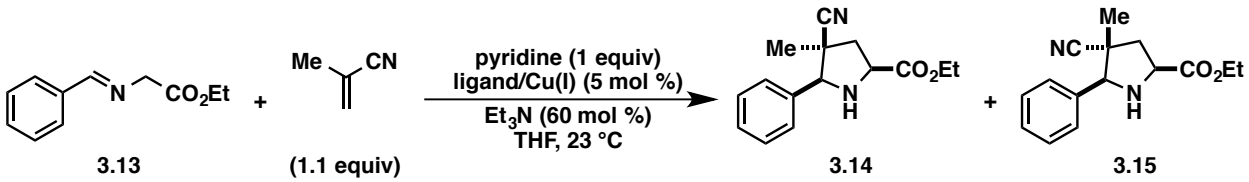
Table 3.12. Increased Catalyst Loading to Access Pyrrolidines 3.17 and 3.18



entry[a]	method	unreacted 3.16 (%)[e]	yield (%)[e]	dr (endo:exo)[f]
1	A[b]	52	39	76:24
2	B[c]	35	73	9:91
3	C[d]	33	67	44:56

[a]Reactions were performed using imine 3.16 (0.20 mmol), methacrylonitrile (0.22 mmol), Et_3N (0.12 mmol), and $Cu(MeCN)_4BF_4$ (10 mol %) at the indicated concentration in THF. [b]Reactions run at 0.6 M for 5 h using $P(OCH_2CF_3)_3$ as the ligand (22 mol %). [c]Reactions run at 1.0 M for 1 h using PCy_3 as the ligand (22 mol %). [d]Reactions run at 0.4 M for 3 h using DavePhos as the ligand (11 mol %). [e]GC yields determined using 1,3,5-trimethoxybenzene as external standard (± 5% error). [f]Ratios determined by GC-FID analysis.

Table 3.13. Pyridine Poisons Cu(I) Catalysts



entry[a]	method	unreacted 3.13 (%)[e]	yield (%)[e]	dr (endo:exo)[f]
1	A[b]	79	<5	nd
2	B[c]	45	49	10:90
3	C[d]	57	31	40:60

[a]Reactions were performed using imine 3.13 (0.20 mmol), methacrylonitrile (0.22 mmol), pyridine (0.20 mmol), Et_3N (0.12 mmol), and $Cu(MeCN)_4BF_4$ (5 mol %) at the indicated concentration in THF. [b]Reactions run at 0.6 M for 5 h using $P(OCH_2CF_3)_3$ as the ligand (11 mol %). [c]Reactions run at 1.0 M for 1 h using PCy_3 as the ligand (11 mol %). [d]Reactions run at 0.4 M for 3 h using DavePhos as the ligand (5.5 mol %). [e]GC yields determined using 1,3,5-trimethoxybenzene as external standard (± 5% error). [f]Ratios determined by GC-FID analysis. nd = not determined.

3.4 Transition State Calculations

A collaboration with the Houk group at UCLA was established in order to gain a better understanding of the catalyst control of the diastereoselectivity of the Cu(I)-catalyzed 1,3-DC reaction. Using the B3LYP-D3/6-311+G(d,p)/SDD,CPCM//B3LYP/6-31G*/LANL2DZ computational method, endo and exo adduct transition states were calculated for each Cu(I)-ligand-ylide complex.[17] The endo transition state was calculated to be 0.9 kcal/mol lower in energy than the corresponding exo transition state with the $P(OCH_2CF_3)_3$ ligand (Figure 3.1).

In the endo transitions state, a favorable electrostatic interaction between the ESP-negative nitrogen atom in methacrylonitrile and the ESP-positive methylene protons on the phosphite ligand was observed (Figure 3.2). This stabilizing interaction is absent in the exo transition state and therefore may account for the lower energy calculated for the endo transition state using $P(OCH_2CF_3)_3$ as the ligand.

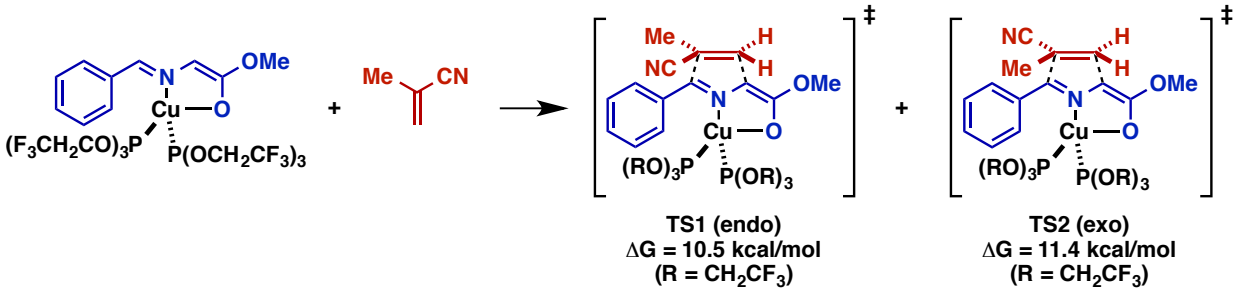


Figure 3.1. Transition State Energies Calculated for a Cu(I)-Phosphite-Ylide Complex

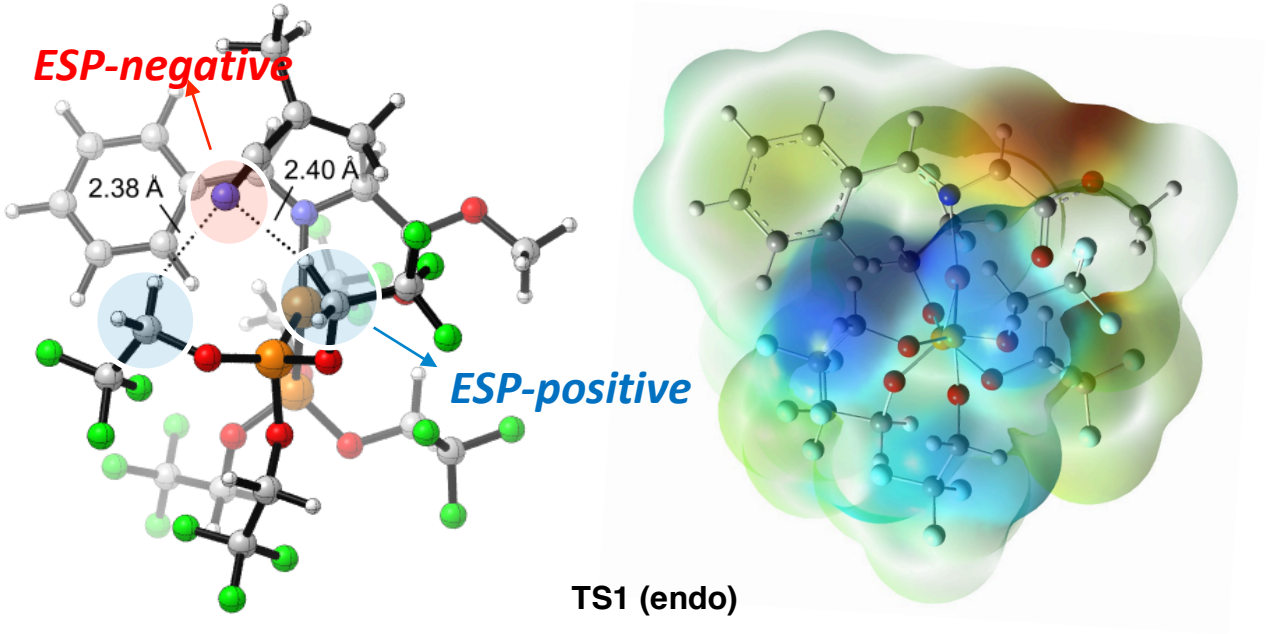
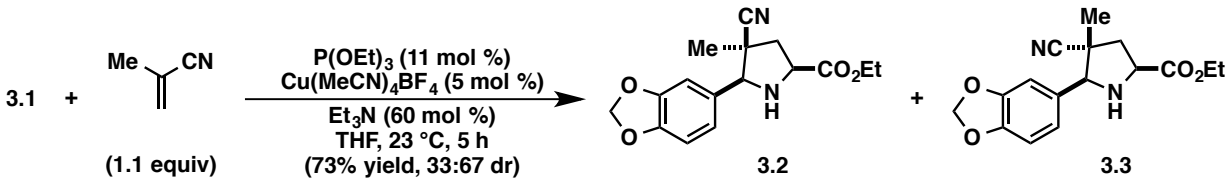


Figure 3.2. Calculated Endo Transition State with Phosphite Ligand

The endo transition state-stabilizing electrostatic interaction hypothesis was tested by running a similar calculation using triethyl phosphite [$P(OEt)_3$] as the ligand. The resulting endo and exo transition states were calculated to differ by only 0.5 kcal/mol and indicated a more

stable exo transition state; this difference is thought to be the result of the ESP-neutral character of the $P(OEt)_3$ methylene protons. This hypothesis was also tested experimentally (eq 3.1). The 1,3-DC reaction using $P(OEt)_3$ as the ligand accessed products **3.2** and **3.3** in a 73% yield and 33:67 dr (endo:exo). The disrupted endo adduct selectivity of this reaction supports the electrostatic interaction hypothesis.

Equation 3.1



The exo transition state was calculated to be 1.1 kcal/mol lower in energy than the endo transition state when PCy_3 was used as the ligand (Figure 3.3). This energy difference is proposed to be the result of steric interactions between the bulky cyclohexyl groups on the phosphine ligand and the nitrile group of the dipolarophile. These theoretical results are in corroboration with the experimental results using PCy_3 as the ligand.

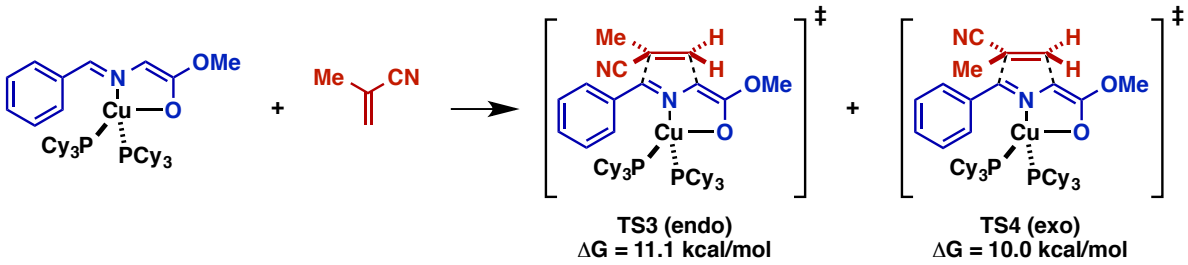
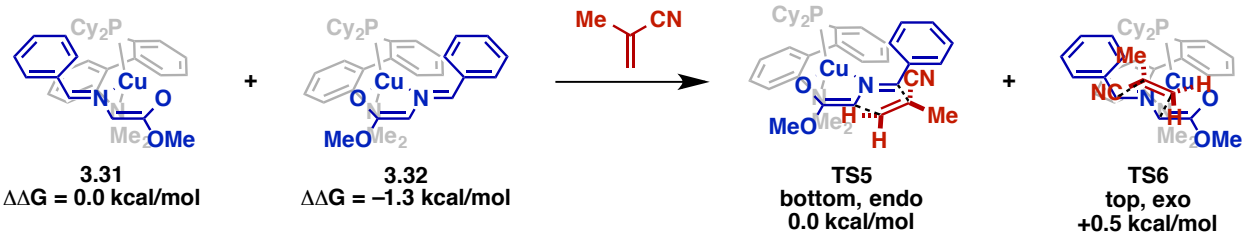


Figure 3.3. Transition State Energies Calculated for a Cu(I)-PCy_3-Ylide Complex

Eight transition states for the Cu(I)-DavePhos-ylide complex were found as a result of two diastereomeric Cu(I)/DavePhos complexes, **3.31** and **3.32**, and four possible approaches of the dipolarophile for each catalyst configuration (bottom or top approach and exo or endo coordination; Figure 3.4). The lowest energy endo and exo transition states, TS5 and TS6,

respectively, differed by only 0.5 kcal/mol. No significant stabilizing electrostatic or destabilizing steric interactions were detected. Collectively, the calculations performed on the Cu(I)-DavePhos-ylide complex offer an explanation for the poor diastereoselectivity that is observed experimentally.



3.31
ΔΔG = 0.0 kcal/mol

3.32
ΔΔG = –1.3 kcal/mol

TS5
bottom, endo
0.0 kcal/mol

TS6
top, exo
+0.5 kcal/mol

Figure 3.4. Transition State Energies Calculated for a Cu(I)-DavePhos-Ylide Complex

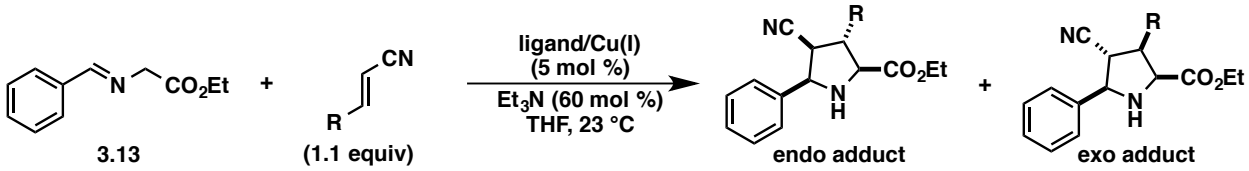
In summary, the theoretical calculations performed by the Houk group clearly demonstrate that the nitrile functionality of the dipolarophile is a key factor in differentiating the endo and exo transition states for the endo adduct-selective ligand $P(OCH_2CF_3)_3$ and the exo adduct-selective ligand PCy_3.

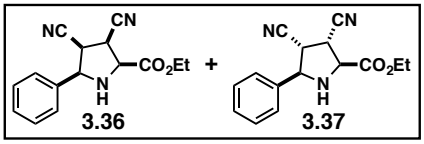
3.5 Utilization of Different Dipolarophiles

Nitrile-containing dipolarophiles are underrepresented in the catalytic 1,3-DC literature compared to α,β-unsaturated carbonyl compounds,[18] and the majority of such reports involve the use of either acrylonitrile[4e;9h,t,v,w,ah;10d,f;19] or highly electron-deficient fumaronitrile.[1,2a,6b,20,21] While the original goal to developing a highly diastereoselective 1,3-DC with methacrylonitrile was for the epidithiodioxopiperazine research program,[22] we embraced the opportunity to address the deficit of nitrile-containing dipolarophiles used in catalytic 1,3-DC reactions. The reaction between imine **3.13** and acrylonitrile was performed using the optimized conditions (Table 3.14). Endo adduct selectivity was not as pronounced as when methacrylonitrile was used (69:31 dr, entry 1).[23] As predicted by transition state calculations using methacrylonitrile, steric interactions with the α-methyl group increase the exo transition state energy when $P(OCH_2CF_3)_3$

is used as the ligand. The lack of substitution at the α-position on acrylonitrile may result in a relatively lower energy exo transition state, resulting in a less endo adduct-selective reaction using method A. However, using method B, exo pyrrolidine adduct **3.34** was selectively synthesized (8:92 dr, entry 2). This result was expected when considering the analogous lack of a stabilizing electrostatic interaction in the calculated endo transition state. Finally, in the reaction using DavePhos as the ligand, exo cycloadduct **3.34** was preferentially accessed in a 19:81 ratio (entry 3). This result also suggests the importance of α-substitution on the dipolarophile in the corresponding transition state energies.

Table 3.14. Nitrile-Containing Dipolarophiles



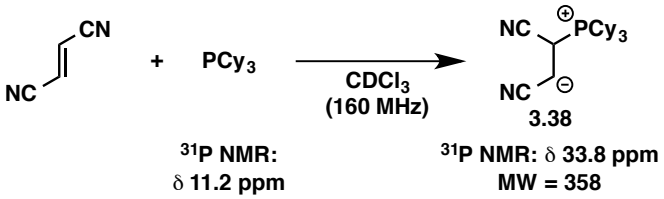
entry[a]	dipolarophile	method	yield (%)[e]	cycloadducts	dr (endo:exo)[f]
1	acrylonitrile (R = H)	A[b]	93[g]	endo = 3.33, exo = 3.34	69:31[g]
2		B[c]	85[g]		8:92[g]
3		C[d]	>99[g]		19:81[g]
4	fumaronitrile (R = CN)	A[b]	61 (3.35, exo)		
5		B[c]	65 (3.35, exo)		
6		C[d]	76 (3.35, exo)		

[a]Reactions were performed using imine 3.13 (0.20 mmol), dipolarophile (0.22 mmol), Et_3N (0.12 mmol), and $Cu(MeCN)_4BF_4$ (5 mol %), at the indicated concentration in THF. [b]Reactions run at 0.6 M for 5 h using $P(OCH_2CF_3)_3$ as the ligand (11 mol %). [c]Reactions run at 1.0 M for 1 h using PCy_3 as the ligand (11 mol %). [d]Reactions run at 0.4 M for 3 h using DavePhos as the ligand (5.5 mol %). [e]GC yields determined using 1,3,5-trimethoxybenzene as external standard (± 5% error). [f]Ratios determined by GC-FID analysis. [g]Average of two experiments.

Fumaronitrile was used as a dipolarophile in the optimized 1,3-DC reactions (Table 3.14). Despite the method used, exo cycloadduct **3.35** was accessed as the major product. The endo cycloadduct was not observed and additional diastereomers **3.36** and **3.37** were detected in small amounts (<10%),[24] indicating isomerization of the dipolarophile component.[25] Treatment of fumaronitrile with 1 equiv PCy_3 resulted in one signal observed by ^{31}P NMR and ESI-MS

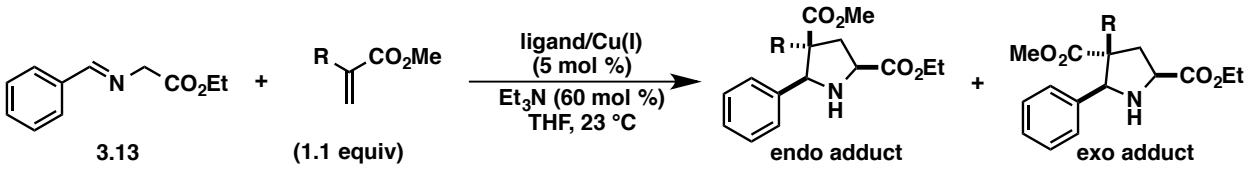
indicated the formation of zwitterionic species **3.38** (eq 3.2). These results indicate that either a stepwise Michael addition-intramolecular Mannich-type reaction pathway occurs when using fumaronitrile, or that the dipolarophile isomerizes prior to cycloaddition due to reaction with other reaction components. Thus, the use of fumaronitrile in this reaction was no longer pursued.

Equation 3.2



The reactivity of α,β-unsaturated carbonyl dipolarophiles methyl acrylate and methyl methacrylate were also examined in the Cu(I)-catalyzed reaction (Table 3.15). Reactions run using methyl acrylate resulted in preferential formation of endo pyrrolidine adduct **3.39** regardless of the method used (entries 1–3). While the reaction run using PCy_3 did not afford significant amounts of exo cycloadduct **3.40** (entry 2), pyrrolidine **3.40** was accessed non-selectively when method C was used (entry 3). Similar results were obtained using methyl methacrylate as the dipolarophile, but with lower overall yields (entries 4–6). While the Cu(I)-catalyzed 1,3-DC reaction with novel catalyst-controlled diastereoselectivity works well with acrylonitrile and methacrylonitrile dipolarophiles, reactions performed using acrylates with or without α-substitution were selective for the endo cycloadduct.

Table 3.15. Acrylate Dipolarophiles



3.13 (1.1 equiv) endo adduct exo adduct

entry[a]	dipolarophile	method	yield (%)[e]	cycloadducts	dr (endo:exo)[f]
1	methyl acrylate (R = H)	A[b]	87	endo = 3.39, exo = 3.40	97:3
2		B[c]	85		94:6
3		C[d]	93		69:31
4	methyl methacrylate (R = Me)	A[b]	61	endo = 3.41, exo = 3.42	99:1
5		B[c]	75		97:3
6		C[d]	87		78:22

[a]Reactions were performed using imine 3.13 (0.20 mmol), dipolarophile (0.22 mmol), Et_3N (0.12 mmol), and $Cu(MeCN)_4BF_4$ (5 mol %), at the indicated concentration in THF. [b]Reactions run at 0.6 M for 5 h using $P(OCH_2CF_3)_3$ as the ligand (11 mol %). [c]Reactions run at 1.0 M for 1 h using PCy_3 as the ligand (11 mol %). [d]Reactions run at 0.4 M for 3 h using DavePhos as the ligand (5.5 mol %). [e] ^1H NMR yields determined using 5,6-dibromo-1,3-benzodioxole as external standard (average of two experiments). [f]Ratios determined by ^1H NMR analysis of the crude reaction mixture (average of two experiments).

3.6 Conclusion

In conclusion, we have developed a catalytic 1,3-DC reaction to access nitrile-containing pyrrolidine products in high diastereoselectivity by changing only the ligand. Theoretical transition state energy calculations suggest a stabilizing electrostatic interaction in the endo transition state using $P(OCH_2CF_3)_3$ as the ligand and destabilizing steric interactions in the endo transition state when PCy_3 is used. The calculations explain the experimental selectivity trends using methacrylonitrile as the dipolarophile. The observed trends for acrylonitrile and methacrylonitrile dipolarophiles, however, did not apply to reactions using fumaronitrile or acrylates. Further development of this reaction to incorporate chiral ligands to achieve asymmetric induction is currently the future focus of this project.

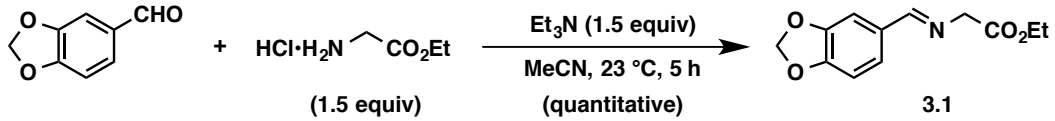
3.7 Appendix A: Experimental Procedures

3.7.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame- or oven-dried glassware under a positive pressure of nitrogen (N_2) or argon (Ar) using anhydrous solvents (dried by passing through activated alumina columns under a positive pressure of Ar). Oxygen-sensitive reactions were carried out in solvents that were degassed by three freeze-pump-thaw cycles. Catalyst components and imine starting materials for the 1,3-dipolar cycloaddition reactions were weighed out in an MBraun Unilab 2000 glove box with a N_2 atmosphere. Aldehydes were distilled neat prior to use. Methacrylonitrile, acrylonitrile, methyl acrylate, methyl methacrylate, and tris(2,2,2-trifluoroethyl) phosphite [$P(OCH_2CF_3)_3$] were sparged with Ar for 5 min before distilling neat prior to use. All other commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Analytical thin-layer chromatography (TLC) was conducted on EMD silica gel 60 F_{254} glass-backed plates (250 μm) and visualized by exposure to UV light (254 nm), or by Dragendorff–Munier and potassium permanganate staining. Flash chromatography was performed using forced flow of the indicated solvent system on EMD Geduran® silica gel 60 (particle size 0.040–0.063 mm). NMR spectra were recorded at 298 K on Bruker FT-NMR spectrometers at the indicated frequencies. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual deuterated solvent signals ($CDCl_3$ or acetone-d_6). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant [*J*, reported in Hertz (Hz)], and integration. Splitting patters are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), apparent (app), and broad (br). Carbon multiplicity was determined by

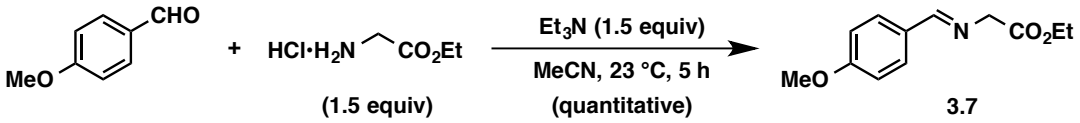
a combination of DEPTQ and HMQC experiments. Chemical shifts (δ) for ^{19}F and ^{31}P NMR spectra are reported in parts per million (ppm) and referenced to the corresponding calibrated ^{1}H NMR spectrum. GC-FID analysis was performed on an Agilent 7890A GC System equipped with a Flame Ionization Detector (FID) and Cyclodex-B capillary column (30 m length, 0.25 mm ID, 0.25 μM film). Infrared (IR) spectra were recorded on a Varian 640-IR spectrometer as thin films in CH_2Cl_2 on KBr plates and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the UC Irvine Mass Spectrometry Facility with a Micromass LCT spectrometer. Melting points (mp) were determined on a melting point apparatus (Thomas Hoover, Uni-Melt) and are uncorrected. Abbreviations used can be found on the Internet at: http://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf.

3.7.2 Synthesis of Imines

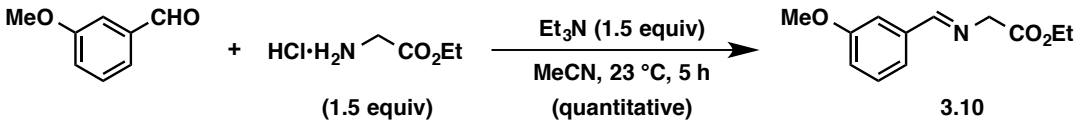


Ethyl (*E*)-2-((benzo[*d*][1,3]dioxol-5-ylmethylene)amino)acetate (3.1). A 50 mL round-bottom flask was charged with a magnetic stir bar and glycine ethyl ester hydrochloride (525 mg, 3.75 mmol, 1.50 equiv) and piperonal (375 mg, 2.50 mmol, 1.00 equiv). MeCN (4.2 mL, 0.6 M) and Et_3N (520 μL, 3.75 mmol, 1.50 equiv) were sequentially added and the resulting heterogeneous mixture was vigorously stirred at 23 °C for 5 h. Concentration of the reaction mixture under reduced pressure afforded an amorphous colorless solid, which was transferred to a separatory funnel using CH_2Cl_2 (15 mL) and H_2O (30 mL). The layers of the resulting biphasic mixture were partitioned and the organic layer was extracted with H_2O (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford imine **3.1** (588 mg, quantitative yield) as a light yellow oil.[26] Imine **3.1** was carried

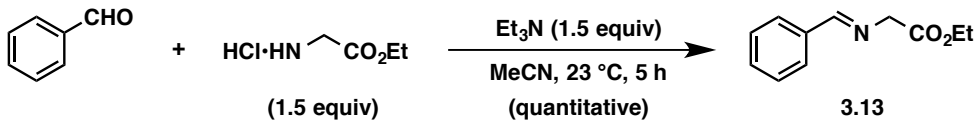
further in subsequent reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.41 (s, 1H), 7.15 (d, *J* = 7.9, 1H), 6.83 (d, *J* = 7.9, 1H), 6.01 (s, 2H), 4.35 (s, 2H), 4.23 (q, *J* = 6.8, 2H), 1.30 (t, *J* = 6.8, 3H).



Ethyl (*E*)-2-((4-methoxybenzylidene)amino)acetate (3.7). According to the procedure described for the synthesis of imine **3.1**, imine **3.7** was prepared from 4-methoxybenzaldehyde (300 μL, 2.5 mmol, 1.0 equiv) as a yellow oil (550 mg, quantitative yield). Imine **3.7** was carried further in subsequent reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.73 (app d, *J* = 8.6, 2H), 6.93 (app d, *J* = 8.6, 2H), 4.36 (s, 2H), 4.23 (q, *J* = 7.1, 2H), 3.85 (s, 3H), 1.30 (t, *J* = 7.1, 3H).

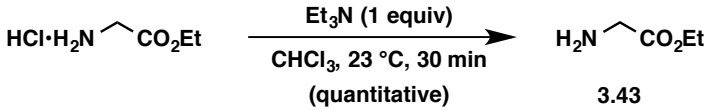


Ethyl (*E*)-2-((3-methoxybenzylidene)amino)acetate (3.10). According to the procedure described for the synthesis of imine **3.1**, imine **3.10** was prepared from 3-methoxybenzaldehyde (300 μL, 2.5 mmol, 1.0 equiv) as a light yellow oil (550 mg, quantitative yield). Imine **3.10** was carried further in subsequent reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.39 (br s, 1 H), 7.33 (t, *J* = 7.7, 1H), 7.29 (br d, *J* = 7.7, 1H), 7.01 (dd, *J* = 7.7, 1.8, 1H), 4.40 (s, 2H), 4.24 (q, *J* = 7.2, 2H), 3.85 (s, 3H), 1.31 (t, *J* = 7.2, 3H).

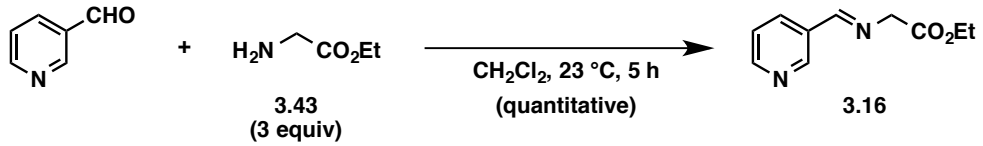


Ethyl (*E*)-2-(benzylideneamino)acetate (3.13). According to the procedure described for the synthesis of imine **3.1**, imine **3.13** was prepared from benzaldehyde (250 μL, 2.5 mmol,

1.0 equiv) as a clear oil (480 mg, quantitative yield). Imine **3.13** was carried further in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.79–7.77 (m, 2H), 7.47–7.40 (m, 3H), 4.40 (s, 2H), 4.24 (q, J = 7.2, 2H), 1.31 (t, J = 7.2, 3H).

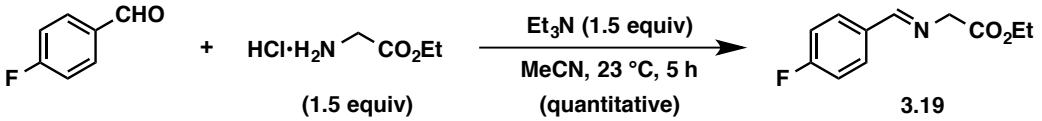


Glycine ethyl ester (3.43). Amine base **3.43** was prepared using modifications to the procedure of Al-Rawi and coworkers.[27] A 50 mL round-bottom flask was charged with a magnetic stir bar, glycine ethyl ester hydrochloride (1.7 g, 12 mmol, 1.0 equiv), and $CHCl_3$ (15 mL, 0.70 M). Et_3N (1.7 mL, 12 mmol, 1.0 equiv) was added in one portion and the resulting heterogeneous mixture stirred vigorously open to air at 23 °C for 30 min. The mixture was concentrated under reduced pressure and the resulting colorless solid was filtered through Celite using Et_2O (50 mL). Concentration of the filtrate afforded **3.43** as a light yellow oil which was carried forward without purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.19 (q, J = 7.1, 2H), 3.42 (s, 2H), 1.48 (br s, 2H), 1.28 (t, J = 7.1, 3H).

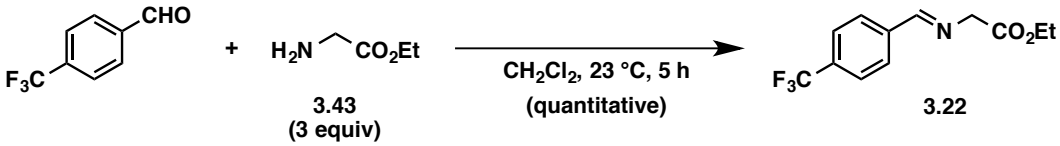


Ethyl (*E*)-2-((pyridin-3-ylmethylene)amino)acetate (3.16). A 50 mL round-bottom flask was charged with a magnetic stir bar, **3.43** (770 mg, 7.5 mmol, 3.0 equiv), and CH_2Cl_2 (4.2 mL, 0.6 M). 3-Pyridinecarboxaldehyde (230 μL, 2.5 mmol, 1.0 equiv) was then added in one portion. The resulting homogeneous mixture was maintained at 23 °C for 5 h. The reaction mixture was transferred to a separatory funnel using CH_2Cl_2 (10 mL) and H_2O (30 mL). The layers of the resulting biphasic mixture were partitioned and the organic layer was extracted with H_2O (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered, and

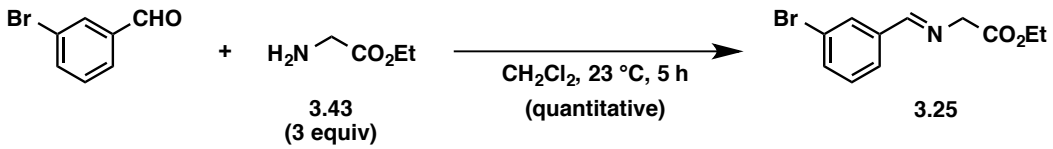
concentrated to afford imine **3.16** (480 mg, quantitative yield) as a light yellow oil. Imine **3.16** was carried further in subsequent reactions without further purification.[28] ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.89 (app d, *J* = 1.5, 1H), 8.68 (app dd, *J* = 4.8, 1.5, 1H), 8.35 (s, 1H), 8.19 (app dt, *J* = 7.9, 1.5, 1H), 7.37 (dd, *J* = 7.9, 4.8, 1H), 4.43 (s, 2H), 4.25 (q, *J* = 7.1, 2H), 1.31 (t, *J* = 7.1, 3H).



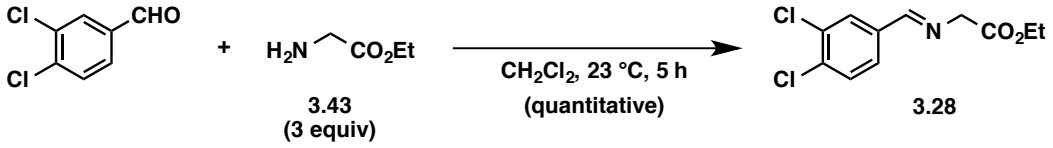
Ethyl (*E*)-2-((4-fluorobenzylidene)amino)acetate (3.19). According to the procedure described for the synthesis of imine **3.1**, imine **3.19** was prepared from 4-fluorobenzaldehyde (270 μL, 2.5 mmol, 1.0 equiv) as a light yellow oil (520 mg, quantitative yield). Imine **3.19** was carried further in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.78 (app dd, *J* = 8.6, 5.9, 2H), 7.11 (app t, *J* = 8.6, 2H), 4.39 (s, 2H), 4.24 (q, *J* = 7.2, 2H), 1.31 (t, *J* = 7.2, 3H).



Ethyl (*E*)-2-((4-(trifluoromethyl)benzylidene)amino)acetate (3.22). According to the procedure described for the synthesis of imine **3.16**, imine **3.22** was prepared from 4-(trifluoromethyl)benzaldehyde (340 μL, 2.5 mmol, 1.0 equiv) as a colorless semi-solid (650 mg, quantitative yield). Imine **3.22** was carried further in subsequent reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.90 (d, *J* = 8.1, 2H), 7.68 (d, *J* = 8.1, 2H), 4.44 (s, 2H), 4.25 (q, *J* = 7.1, 2H), 1.31 (t, *J* = 7.1, 3H).

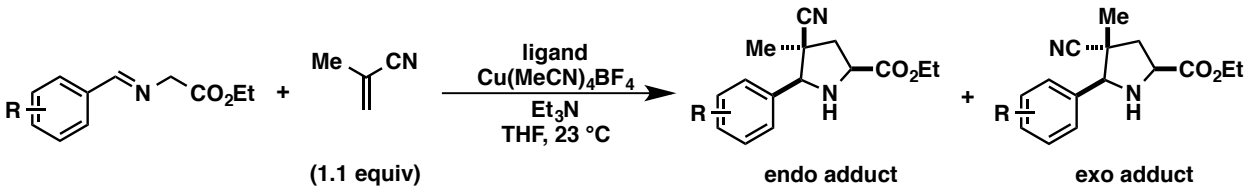


Ethyl (*E*)-2-((3-bromobenzylidene)amino)acetate (3.25). According to the procedure described for the synthesis of imine **3.16**, imine **3.25** was prepared from 3-bromobenzaldehyde (290 μL, 2.5 mmol, 1.0 equiv) as a yellow oil (670 mg, quantitative yield). Imine **3.25** was carried further in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.98 (br s, 1H), 7.67 (app d, J = 7.9, 1H), 7.57 (app d, J = 7.9, 1H), 7.30 (app t, J = 7.9, 1H), 4.40 (s, 2H), 4.25 (q, J = 7.1, 2H), 1.31 (t, J = 7.1, 3H).



Ethyl (*E*)-2-((3,4-dichlorobenzylidene)amino)acetate (3.28). According to the procedure described for the synthesis of imine **3.16**, imine **3.28** was prepared from 3,4-dichlorobenzaldehyde (440 mg, 2.5 mmol, 1.0 equiv) as a yellow oil (650 mg, quantitative yield). Imine **3.28** was carried further in subsequent reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.91 (d, J = 1.5, 1H), 7.59 (dd, J = 8.3, 1.5, 1H), 7.50 (d, J = 8.3, 1H), 4.40 (s, 2H), 4.25 (q, J = 7.1, 2H), 1.31 (t, J = 7.1, 3H).

3.7.3 Cu(I)-Catalyzed 1,3-DC Reaction Using Various Imine Substrates

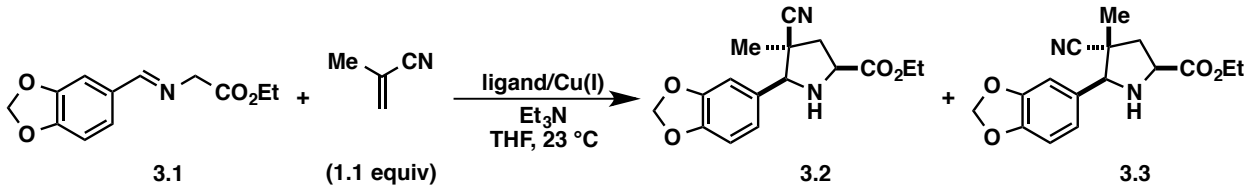


General Procedure 1. The catalyst and imine components of these reactions were partially prepared in separate 1-dram screw-top vials inside a glove box with a N_2 atmosphere. The reaction vial was charged with a magnetic stir bar and neat imine (0.20 mmol, 1.0 equiv). The catalyst and reaction vials were each sealed with a Teflon-lined cap, then brought outside the glove box where the Telfon-lined caps were each covered with an inverted 14/20 joint rubber septum under a balloon of Ar. **Method A:** In the glove box, the catalyst vial was charged with tetrakis(acetonitrile)copper(I) tetrafluoroborate (12.6 mg, 0.0400 mmol). Outside of the glove box, the catalyst vial was charged with THF (1.33 mL, freeze-pump-thawed) and tris(2,2,2-trifluoroethyl) phosphite (19.4 μL, 0.0880 mmol). An aliquot of the catalyst solution (0.33 mL, 0.60 M; 0.010 mmol, 0.050 equiv Cu(I) and 0.022 mmol, 0.11 equiv ligand), Et_3N (16.7 μL, 0.120 mmol, 0.600 equiv), and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) were added to the reaction vial via syringe. The resulting homogenous mixture was maintained at 23 °C for 5 h. The reaction was quenched by opening the vial to air and filtering the reaction mixture through a plug of SiO_2 (200 mg) using EtOAc (8.7 mL, HPLC grade). For yield and diastereomeric ratio analysis using GC-FID instrumentation, 1 mL of a GC standard solution [0.1 M solution of 1,3,5-trimethoxybenzene in EtOAc (HPLC grade)] was added to the filtrate. For analysis by ^1H NMR, ca. 28 mg 5,6-dibromo-1,3-benzodioxole was added to the filtrate as an external standard and the concentrated residue was analyzed in $CDCl_3$, acetone-d_6, C_6D_6, or CD_3OD. **Method B:** In the glove box, the catalyst vial was charged with

tetrakis(acetonitrile)copper(I) tetrafluoroborate (12.6 mg, 0.0400 mmol) and tricyclohexylphosphine (24.6 mg, 0.0880 mmol). Outside of the glove box, the catalyst vial was charged with THF (0.80 mL, freeze-pump-thawed). An aliquot of the catalyst solution (0.20 mL, 1.0 M; 0.010 mmol, 0.050 equiv Cu(I) and 0.022 mmol, 0.11 equiv ligand), Et_3N (16.7 μL, 0.120 mmol, 0.600 equiv), and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) were added to the reaction vial via syringe. The resulting homogenous mixture was maintained at 23 °C for 1 h. The reaction was quenched by opening the vial to air and filtering the reaction mixture through a plug of SiO_2 (200 mg) using EtOAc (8.2 mL, HPLC grade). For yield and diastereomeric ratio analysis using GC-FID instrumentation, 1 mL of a GC standard solution [0.1 M solution of 1,3,5-trimethoxybenzene in EtOAc (HPLC grade)] was added to the filtrate. For analysis by ^1H NMR, ca. 28 mg 5,6-dibromo-1,3-benzodioxole was added to the filtrate as an external standard and the concentrated residue was analyzed in $CDCl_3$, acetone-d_6, C_6D_6, or CD_3OD. **Method C:** In the glove box, the catalyst vial was charged with tetrakis(acetonitrile)-copper(I) tetrafluoroborate (12.6 mg, 0.0400 mmol) and DavePhos (17.3 mg, 0.0440 mmol). Outside of the glove box, the catalyst vial was charged with THF (2.0 mL, freeze-pump-thawed). An aliquot of the catalyst solution (0.50 mL, 0.4 M; 0.010 mmol, 0.050 equiv Cu(I) and 0.011 mmol, 0.055 equiv ligand), Et_3N (16.7 μL, 0.120 mmol, 0.600 equiv), and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) were added to the reaction vial via syringe. The resulting homogenous mixture was maintained at 23 °C for 3 h. The reaction was quenched by opening the vial to air and filtering the reaction mixture through a plug of SiO_2 (200 mg) using EtOAc (8.5 mL, HPLC grade). For yield and diastereomeric ratio analysis using GC-FID instrumentation, 1 mL of a GC standard solution [0.1 M solution of 1,3,5-trimethoxybenzene in EtOAc (HPLC grade)] was added to the filtrate. For analysis by ^1H NMR, ca. 28 mg

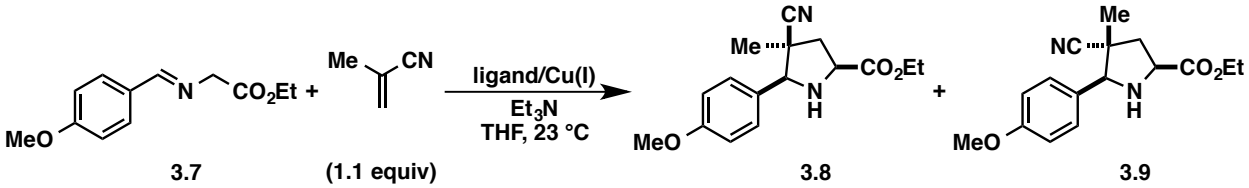
5,6-dibromo-1,3-benzodioxole was added to the filtrate as an external standard and the concentrated residue was analyzed in $CDCl_3$, acetone-d_6, C_6D_6, or CD_3OD. **Preparative Scale Experiments (General Procedure 2).** The imine and catalyst components of these reactions were partially prepared in separate 1-dram screw-top vials inside a glove box with a N_2 atmosphere. The reaction vial was charged with a magnetic stir bar and neat imine (0.50 mmol, 1.0 equiv). The catalyst and reaction vials were each sealed with a Teflon-lined cap, then brought outside the glove box where the Telfon-lined caps were each covered with an inverted 14/20 joint rubber septum under a balloon of Ar. **Method A:** In the glove box, the catalyst vial was charged with tetrakis(acetonitrile)copper(I) tetrafluoroborate (15.8 mg, 0.0500 mmol). Outside of the glove box, the catalyst vial was charged with THF (1.7 mL, freeze-pump-thawed) and tris(2,2,2-trifluoroethyl) phosphite (24 μL, 0.11 mmol). An aliquot of the catalyst solution (0.83 mL, 0.60 M; 0.025 mmol, 0.050 equiv Cu(I) and 0.055 mmol, 0.11 equiv ligand), Et_3N (42 μL, 0.30 mmol, 0.60 equiv), and methacrylonitrile (46 μL, 0.55 mmol, 1.1 equiv) were added to the reaction vial via syringe. The resulting homogenous mixture was maintained at 23 °C for 5 h. The reaction was quenched by opening the vial to air and filtering the reaction mixture through a plug of SiO_2 (400 mg) using EtOAc (15 mL). Concentration of the filtrate under reduced pressure afforded a residue that was purified by flash chromatography (2:1 hexanes:EtOAc). **Method B:** In the glove box, the catalyst vial was charged with tetrakis(acetonitrile)copper(I) tetrafluoroborate (15.8 mg, 0.0500 mmol) and tricyclohexylphosphine (30.8 mg, 0.110 mmol). Outside of the glove box, the catalyst vial was charged with THF (1.0 mL, freeze-pump-thawed). An aliquot of the catalyst solution (0.50 mL, 1.0 M; 0.025 mmol, 0.050 equiv Cu(I) and 0.055 mmol, 0.11 equiv ligand), Et_3N (42 μL, 0.30 mmol, 0.60 equiv), and methacrylonitrile (46 μL, 0.55 mmol, 1.1 equiv) were added to the

reaction vial via syringe. The resulting homogenous mixture was maintained at 23 °C for 1 h. The reaction was quenched by opening the vial to air and filtering the reaction mixture through a plug of SiO_2 (400 mg) using EtOAc (15 mL). Concentration of the filtrate under reduced pressure afforded a residue that was purified by flash chromatography (4:1 hexanes:EtOAc).



Ethyl *rac*-(2*S*,4*S*,5*S*)-5-(benzo[*d*][1,3]dioxol-5-yl)-4-cyano-4-methylpyrrolidine-2-carboxylate (3.2) and **ethyl *rac*-(2*S*,4*R*,5*S*)-5-(benzo[*d*][1,3]dioxol-5-yl)-4-cyano-4-methylpyrrolidine-2-carboxylate (3.3).** Using **General Procedure 1**, pyrrolidines **3.2** and **3.3** were accessed via various methods from imine **3.1** (47.0 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 88% yield, 96:4 dr; **Method B:** 97% yield, 9:91 dr; **Method C:** 95% yield, 39:61 dr. Using **General Procedure 2**, **Method A**, pyrrolidine **3.2** was isolated as a yellow oil (120 mg, 79% yield) from a crude reaction mixture with a 94:6 dr. Using **General Procedure 2**, **Method B**, pyrrolidine **3.3** was isolated as a yellow oil (123 mg, 82% yield) from a crude reaction mixture with a 11:89 dr. **3.2 (endo adduct):** R_f 0.12 (2:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 (d, *J* = 1.6, 1H), 6.96 (dd, *J* = 8.0, 1.6, 1H), 6.81 (d, *J* = 8.0, 1H), 5.97 (d, *J* = 1.9, 2H), 4.33–4.25 (m, 2H), 3.96 (dd, *J* = 9.6, 4.3, 1H), 3.87 (s, 1H), 2.81 (dd, *J* = 13.6, 4.3, 1H), 2.71 (br s, 1H), 2.27 (dd, *J* = 13.6, 9.6, 1H), 1.42 (s, 3H), 1.34 (t, *J* = 7.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0 (C), 148.2 (C), 148.0 (C), 130.5 (C), 122.1 (C), 121.2 (CH), 108.3 (CH), 108.0 (CH), 101.4 (CH_2), 72.3 (CH), 61.8 (CH_2), 57.2 (CH), 44.0 (C), 42.3 (CH_2), 22.2 (CH_3), 14.3 (CH_3); IR (thin film): 3351, 2980, 2901, 2234, 1734, 1490, 1445 cm^{-1};

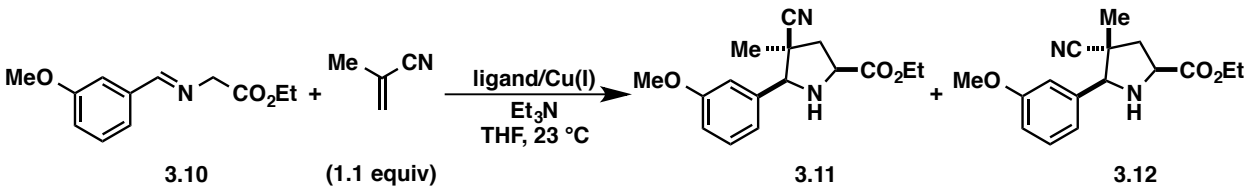
HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{16}H_{18}N_2O_4Na$, 325.1164; found, 325.1157. Spectral data match those previously reported.[22] **3.3 (exo adduct):** R_f 0.29 (2:1 hexanes:EtOAc); ^1H NMR (600 MHz, $CDCl_3$): δ 6.98 (d, *J* = 1.6, 1H), 6.93 (dd, *J* = 8.1, 1.4, 1H), 6.80 (d, *J* = 8.0, 1H), 5.96 (s, 2H), 4.50 (s, 1H), 4.24 (q, *J* = 7.1, 2H), 4.05–4.02 (m, 1H), 2.72 (dd, *J* = 13.3, 9.9, 1H), 2.63 (br s, 1H), 2.21 (dd, *J* = 13.5, 6.2, 1H), 1.31 (t, *J* = 7.3, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1 (C), 147.9 (C), 147.7 (C), 130.5 (C), 124.1 (C), 120.7 (CH), 108.4 (CH), 107.7 (CH), 101.3 (CH_2), 69.3 (CH), 61.7 (CH_2), 57.2 (CH), 41.5 (CH_2), 40.2 (C), 20.6 (CH_3), 14.3 (CH_3); IR (thin film): 3348, 2982, 2901, 2234, 1735, 1490, 1445 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{16}H_{18}N_2O_4Na$, 325.1164; found, 325.1156. Spectral data match those previously reported.[22]



3.7 3.8 3.9

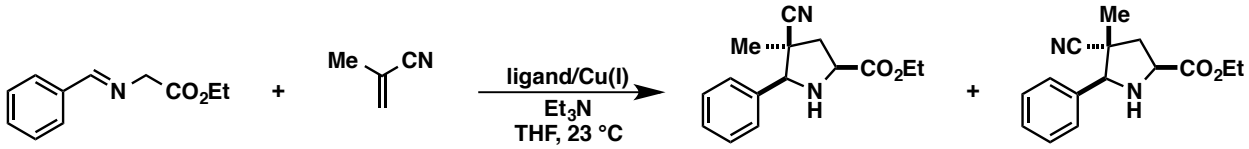
Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-5-(4-methoxyphenyl)-4-methylpyrrolidine-2-carboxylate (3.8) and **ethyl *rac*-(2*S*,4*R*,5*S*)-4-cyano-5-(4-methoxyphenyl)-4-methylpyrrolidine-2-carboxylate (3.9).** Using **General Procedure 1**, pyrrolidines **3.8** and **3.9** were accessed via various methods from imine **3.7** (44.2 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 58% yield, 94:6 dr; **Method B:** >99% yield, 12:88 dr; **Method C:** 96% yield, 35:65 dr. **3.8 (endo adduct):** R_f 0.30 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.8, 2H), 6.93 (d, *J* = 8.8, 2H), 4.35–4.24 (m, 2H), 3.97 (dd, *J* = 9.8, 1H), 3.89 (s, 1H), 3.81 (s, 3H), 2.82 (dd, *J* = 13.4, 4.1, 1H), 2.46 (br s, 1H), 2.28 (dd, *J* = 13.4, 9.8, 1H), 1.40 (s, 3H), 1.34 (t, *J* = 7.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2 (C), 160.1 (C), 128.8 ($2CH_2$), 128.5 (C), 122.2 (C),

144.1 ($2CH_2$), 72.2 (CH), 61.8 (CH_2), 57.4 (CH), 55.4 (CH_3), 44.1 (C), 42.5 (CH_2), 22.0 (CH_3), 14.3 (CH_3); IR (thin film): 3350, 2979, 2838, 2234, 1735, 1514, 1249 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{16}H_{20}N_2O_3Na$, 311.1372; found, 311.1362. Spectral data match those previously reported.[22] **3.9 (exo adduct):** R_f 0.50 (1:1 hexanes:EtOAc); ^1H NMR (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.6, 2H), 6.90 (d, *J* = 8.6, 2H), 4.53 (s, 1H), 4.25 (q, *J* = 7.1, 2H), 4.04 (dd, *J* = 9.7, 6.2, 1H), 3.81 (s, 3H), 2.74 (dd, *J* = 13.5, 9.7, 1H), 2.53 (br s, 1H), 2.21 (dd, *J* = 13.5, 6.2, 1H), 1.31 (t, *J* = 7.1, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3 (C), 159.7 (C), 128.6 (C), 128.4 (2CH), 124.2 (C), 114.0 (2CH), 69.2 (CH), 61.6 (CH_2), 57.3 (CH), 55.4 (CH_3), 41.8 (CH_2), 40.2 (C), 20.5 (CH_3), 14.3 (CH_3); IR (thin film): 3346, 2982, 2838, 2234, 1613, 1736, 1514, 1458, 1249 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{16}H_{20}N_2O_3Na$, 311.1372; found, 311.1371. Spectral data match those previously reported.[22]



Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-5-(3-methoxyphenyl)-4-methylpyrrolidine-2-carboxylate (3.11) and **ethyl *rac*-(2*S*,4*R*,5*S*)-4-cyano-5-(3-methoxyphenyl)-4-methylpyrrolidine-2-carboxylate (3.12).** Using **General Procedure 1**, pyrrolidines **3.11** and **3.12** were accessed via various methods from imine **3.10** (44.2 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 91% yield, 94:6 dr; **Method B:** 93% yield, 9:91 dr; **Method C:** 93% yield, 40:60 dr. **3.11 (endo adduct):** R_f 0.27 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.8, 1H), 7.13–7.12 (m, 1H), 7.09 (br d, *J* = 7.8, 1H), 6.91 (dd, *J* = 8.2, 2.2, 1H), 4.35–4.25 (m, 2H), 3.99 (dd, *J* = 9.6, 4.2, 1H), 3.91 (s, 1H), 3.84 (s, 3H), 2.83 (dd, *J* = 13.5, 4.2, 1H), 2.82

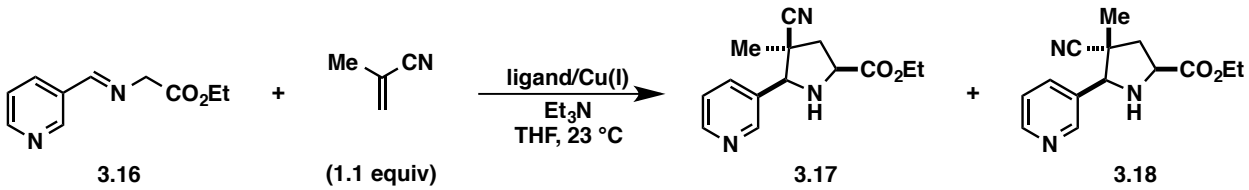
(br s, 1H), 2.29 (dd, J = 13.5, 9.6, 1H), 1.44 (s, 3H), 1.34 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1 (C), 159.8 (C), 138.3 (C), 129.7 (CH), 122.0 (C), 119.9 (CH), 114.6 (CH), 113.2 (CH), 72.5 (CH), 61.8 (CH_2), 57.5 (CH), 55.4 (CH_3), 44.1 (C), 42.6 (CH_2), 22.2 (CH_3), 14.3 (CH_3); IR (thin film): 3348, 2979, 2939, 2837, 2234, 1734, 1602, 1586, 1490, 1455 cm^{-1}; HRMS-CI (*m/z*) [M + H]$^+$ calculated for $C_{16}H_{21}N_2O_3$, 289.1552; found, 289.1551. Spectral data match those previously reported.[22] **3.12 (exo adduct):** R_f 0.54 (1:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (t, J = 8.0, 1H), 7.043 (d, J = 8.0, 1H), 7.036 (s, 1H), 6.87–6.86 (m, 1H), 4.55 (s, 1H), 4.25 (q, J = 7.0, 2H), 4.06 (dd, J = 9.6, 6.3, 1H), 3.82 (s, 3H), 2.74 (dd, J = 13.5, 9.6, 1H), 2.67 (br s, 1H), 2.22 (dd, J = 13.5, 6.3, 1H), 1.32 (t, J = 7.0, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2 (C), 159.9 (C), 138.5 (C), 129.7 (CH), 124.2 (C), 119.5 (CH), 113.9 (CH), 112.8 (CH), 69.4 (CH), 61.6 (CH_2), 57.4 (CH), 55.4 (CH_3), 41.8 (CH_2), 40.2 (C), 20.6 (CH_3), 14.3 (CH_3); IR (thin film): 3345, 2981, 2939, 2837, 2234, 1736, 1602, 1586, 1489, 1456 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calculated for $C_{16}H_{20}N_2O_3Na$, 311.1372; found, 311.1368. Spectral data match those previously reported.[22]



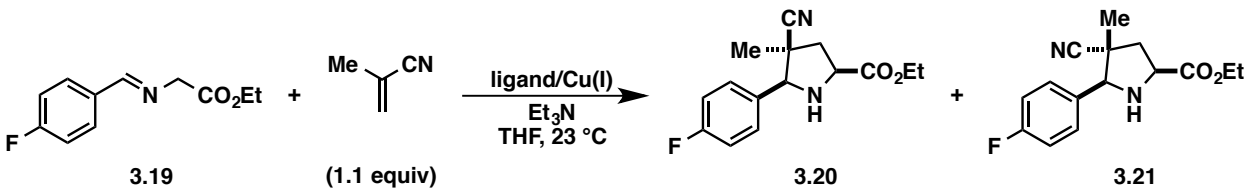
3.13 (1.1 equiv) 3.14 3.15

Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-4-methyl-5-phenylpyrrolidine-2-carboxylate (3.14) and **ethyl *rac*-(2*S*,4*R*,5*S*)-4-cyano-4-methyl-5-phenylpyrrolidine-2-carboxylate (3.15).** Using **General Procedure 1**, pyrrolidines **3.14** and **3.15** were accessed via various methods from imine **3.13** (38.2 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 76% yield, 98:2 dr; **Method B:** 97% yield, 11:89 dr; **Method C:** 94% yield, 38:62 dr. Using **General Procedure 2**,

Method A, pyrrolidine **3.14** was isolated as a clear oil (98 mg, 76% yield) from a crude reaction mixture with a 96:4 dr. Using **General Procedure 2**, **Method B**, pyrrolidine **3.15** was isolated as a colorless solid (107 mg, 83% yield; mp = 74–76 °C) from a crude reaction mixture with a 12:88 dr. **3.14 (endo adduct):** R_f 0.32 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (app d, *J* = 7.1, 2H), 7.41–7.34 (m, 3H), 4.34–4.24 (m, 2H), 3.98 (dd, *J* = 9.6, 4.2, 1H), 3.93 (s, 1H), 2.90 (br s, 1H), 2.82 (dd, *J* = 13.6, 4.2, 1H), 2.29 (dd, *J* = 13.6, 9.6, 1H), 1.42 (s, 3H), 1.34 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0 (C), 136.5 (C), 128.9 (CH), 128.6 (2CH), 127.6 (2CH), 121.9 (C), 72.4 (CH), 61.7 (CH_2), 57.3 (CH), 44.1 (C), 42.4 (CH_2), 22.0 (CH_3), 14.2 (CH_3); IR (thin film): 3348, 2980, 2234, 1734, 1454 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{18}N_2O_2Na$, 281.1266; found, 281.1263. Spectral data match those previously reported.[22] **3.15 (exo adduct):** R_f 0.25 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.3, 2H), 7.37–7.29 (m, 3H), 4.55 (s, 1H), 4.23 (q, *J* = 6.9, 2H), 4.04 (dd, *J* = 9.7, 6.2, 1H), 2.73 (dd, *J* = 13.4, 9.8, 1H), 2.67 (br s, 1H), 2.21 (dd, *J* = 13.5, 6.1, 1H), 1.30 (t, *J* = 7.1, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1 (C), 136.6 (C), 128.5 (CH), 128.3 (2CH), 127.1 (2CH), 124.0 (C), 69.4 (CH), 61.5 (CH_2), 57.2 (CH), 41.7 (C), 40.0 (CH_2), 20.4 (CH_3), 14.2 (CH_3); IR (thin film): 3346, 2982, 2235, 1736, 1455 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{18}N_2O_2Na$, 281.1266; found, 281.1275. Spectral data match those previously reported.[22]

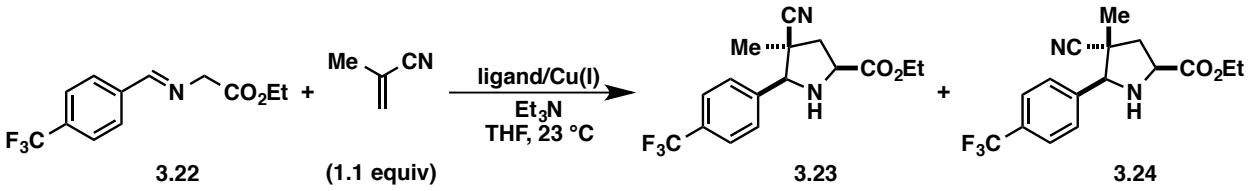


Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-4-methyl-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (3.17) and **ethyl *rac*-(2*S*,4*R*,5*S*)-4-cyano-4-methyl-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (3.18).** Using **General Procedure 1**, pyrrolidines **3.17** and **3.18** were accessed via various methods from imine **3.16** (38.4 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 14% yield, 86:14 dr; **Method B:** 52% yield, 12:88 dr; **Method C:** 46% yield, 49:51 dr. **3.17 (endo adduct):** R_f 0.24 (1:1 hexanes:acetone); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.57 (s, 1H), 8.08 (d, *J* = 7.7, 1H), 7.38–7.36 (m, 2H), 4.32–4.23 (m, 2H), 3.97 (dd, *J* = 9.3, 3.3, 1H), 3.95 (s, 1H), 2.85 (dd, *J* = 13.8, 3.3, 2H), 2.72 (br s, 1H), 2.31 (dd, *J* = 13.8, 9.3, 1H), 1.43 (s, 3H), 1.32 (t, *J* = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7 (C), 150.4 (CH), 149.3 (CH), 135.0 (CH), 132.6 (C), 123.7 (CH), 121.5 (C), 69.7 (CH), 61.7 (CH_2), 57.1 (CH), 43.9 (C), 41.9 (CH_2), 21.8 (CH_3), 14.2 (CH_3); IR (thin film): 3345, 2982, 2235, 1735, 1450, 1206 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{14}H_{17}N_3O_2Na$, 282.1219; found, 282.1216. **3.18 (exo adduct):** R_f 0.41 (1:1 hexanes:acetone); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.59 (d, *J* = 4.1, 1H), 7.83 (d, *J* = 8.1, 1H), 7.31 (dd, *J* = 4.1, 1H), 4.61 (s, 1H), 4.25 (q, *J* = 7.1, 2H), 4.09 (dd, *J* = 9.5, 6.1, 1H), 2.76 (dd, *J* = 13.5, 9.5, 1H), 2.54 (br s, 1H), 2.26 (dd, *J* = 13.5, 6.1, 1H), 1.31 (t, *J* = 7.1, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8 (C), 150.0 (CH), 148.9 (CH), 135.1 (CH), 132.6 (C), 123.54 (C), 123.52 (CH), 67.4 (CH), 61.7 (CH_2), 57.3 (CH), 41.4 (CH_2), 40.1 (C), 20.6 (CH_3), 14.3 (CH_3); IR (thin film): 3340, 2982, 2235, 1736, 1451, 1201 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{14}H_{17}N_3O_2Na$, 282.1219; found, 282.1223.



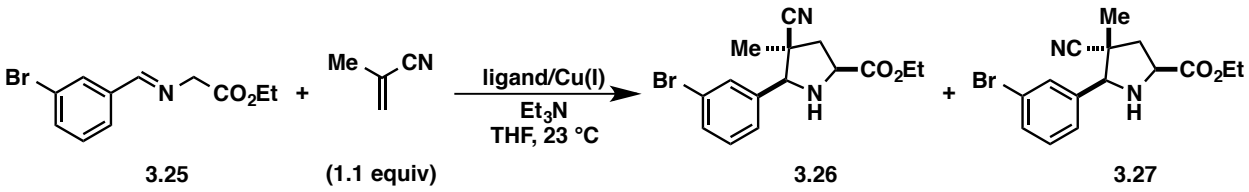
Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-5-(4-fluorophenyl)-4-methylpyrrolidine-2-carboxylate (3.20) and **ethyl *rac*-(2*S*,4*R*,5*S*)-4-cyano-5-(4-fluorophenyl)-4-methylpyrrolidine-2-carboxylate (3.21).** Using **General Procedure 1**, pyrrolidines **3.20** and **3.21** were accessed via various methods from imine **3.19** (41.8 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 84% yield, 96:4 dr; **Method B:** >99% yield, 12:88 dr; **Method C:** >99% yield, 41:59 dr. **3.20 (endo adduct):** R_f 0.29 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 8.7, 5.4, 2H), 7.09 (t, *J* = 8.7, 2H), 4.34–4.24 (m, 2H), 4.00 (dd, *J* = 9.6, 4.2, 1H), 3.95 (s, 1H), 2.83 (dd, *J* = 13.7, 4.2, 1H), 2.82 (br s, 1H), 2.30 (dd, *J* = 13.7, 9.6, 1H), 1.41 (s, 3H), 1.34 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9 (C), 163.2 (d, $J_{C–F}$ = 245.8, C), 132.4 (C), 129.4 (d, $J_{C–F}$ = 8.3, CH), 121.8 (C), 115.7 (d, $J_{C–F}$ = 21.5, CH), 71.7 (CH), 61.9 (CH_2), 57.3 (CH), 44.0 (C), 42.2 (CH_2), 22.0 (CH_3), 14.3 (CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ –112.7; IR (thin film): 3348, 2982, 2235, 1736, 1605, 1510 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{17}FN_2O_2Na$, 299.1172; found, 299.1177. Spectral data match those previously reported.[22] **3.21 (exo adduct):** R_f 0.28 (3:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 7.2, 4.5, 2H), 7.06 (t, *J* = 7.2, 2H), 4.56 (s, 1H), 4.24 (q, *J* = 6.0, 2H), 4.05 (dd, *J* = 8.1, 5.1, 1H), 2.74 (dd, *J* = 11.3, 8.1, 1H), 2.57 (br s, 1H), 2.23 (dd, *J* = 11.3, 5.1, 1H), 1.31 (t, *J* = 6.0, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1 (C), 162.8 (d, $J_{C–F}$ = 245.5, C), 132.5 (d, $J_{C–F}$ = 3.1, C), 128.9 (d, $J_{C–F}$ = 8.1, 2CH), 124.0 (C), 115.5 (d, $J_{C–F}$ = 21.3, 2CH), 68.8 (CH), 61.6 (CH_2), 57.2 (CH), 41.5 (CH_2), 40.0 (C), 20.5 (CH_3), 14.3 (CH_3); ^{19}F NMR

(376.5 MHz, $CDCl_3$): δ –113.7; IR (thin film): 3347, 2983, 2938, 2235, 1737, 1605, 1510 cm^{-1}; HRMS-CI (*m/z*) $[M + H]^+$ calculated for $C_{15}H_{18}FO_2N_2$, 277.1352; found, 277.1361. Spectral data match those previously reported.[22]



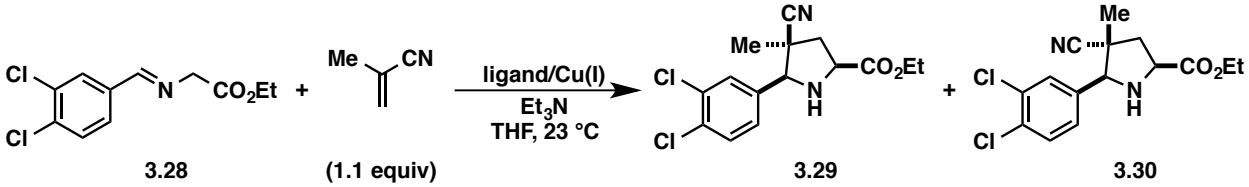
Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-4-methyl-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (3.23) and **ethyl *rac*-(2*S*,4*R*,5*S*)-4-cyano-4-methyl-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (3.24).** Using **General Procedure 1**, pyrrolidines **3.23** and **3.24** were accessed via various methods from imine **3.22** (51.8 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 88% yield, 96:4 dr; **Method B:** 92% yield, 14:86 dr; **Method C:** 98% yield, 47:53 dr. Using **General Procedure 2**, **Method A**, pyrrolidine **3.23** was isolated as a colorless solid (120 mg, 74% yield; mp = 98–100 °C) from a crude reaction mixture with a 96:4 dr. Using **General Procedure 2**, **Method B**, pyrrolidine **3.24** was isolated as a yellow solid (127 mg, 78% yield; mp = 69–71 °C) from a crude reaction mixture with a 15:85 dr. **3.23 (endo adduct):** R_f 0.31 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (app s, 4H), 4.35–4.25 (m, 2H), 4.03 (s, 1H), 4.02 (dd, *J* = 9.6, 3.8, 1H), 2.86 (dd, *J* = 13.5, 3.8, 1H), 2.79 (br s, 1H), 2.32 (dd, *J* = 13.5, 9.6, 1H), 1.45 (s, 3H), 1.35 (t, *J* = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8 (C), 141.0 (C), 131.2 (q, $J_{C–F}$ = 32.4, C), 128.1 (2CH), 125.7 (q, $J_{C–F}$ = 3.7, 2CH), 124.1 (q, $J_{C–F}$ = 273.1, C), 121.6 (C), 71.9 (CH), 61.9 (CH_2), 57.3 (CH), 44.1 (C), 42.2 (CH_2), 22.1 (CH_3), 14.3 (CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ –62.7; IR (thin film): 3351, 2983, 2907, 2878, 2236, 1738, 1620, 1326 cm^{-1}; HRMS-CI (*m/z*) $[M + H]^+$

calculated for $C_{16}H_{18}F_3N_2O_2$, 327.1320; found, 327.1310. **3.24 (exo adduct):** R_f 0.58 (1:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64–7.61 (m, 4H), 4.64 (s, 1H), 4.25 (q, *J* = 7.2, 2H), 4.08 (dd, *J* = 9.5, 6.5, 1H), 2.77 (dd, *J* = 13.3, 9.5, 1H), 2.66 (br s, 1H), 2.26 (dd, *J* = 13.3, 6.5, 1H), 1.31 (t, *J* = 7.2, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 173.0 (C), 141.1 (C), 130.8 (q, $J_{C–F}$ = 32.2, C), 127.8 (CH), 125.7 (q, $J_{C–F}$ = 3.7, C), 124.2 (q, $J_{C–F}$ = 272.2, C), 123.8 (CH), 69.0 (CH), 61.8 (CH_2), 57.3 (CH), 41.6 (CH_2), 40.1 (C), 20.7 (CH_3), 14.4 (CH_3); ^{19}F NMR (376.5 MHz, CDCl3): δ –62.6; IR (thin film): 3344, 2985, 2905, 2880, 2237, 1738, 1620, 1326 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{16}H_{17}F_3N_2O_2Na$, 327.1320; found, 327.1314.



Ethyl *rac*-(2*S*,4*S*,5*S*)-5-(3-bromophenyl)-4-cyano-4-methylpyrrolidine-2-carboxylate (3.26) and **ethyl *rac*-(2*S*,4*R*,5*S*)-5-(3-bromophenyl)-4-cyano-4-methylpyrrolidine-2-carboxylate (3.27).** Using **General Procedure 1**, pyrrolidines **3.26** and **3.27** were accessed via various methods from imine **3.25** (53.8 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 µL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 78% yield, 96:4 dr; **Method B:** 95% yield, 12:88 dr; **Method C:** 98% yield, 56:44 dr. **3.26 (endo adduct):** R_f 0.32 (1:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (br s, 1H), 7.52–7.49 (m, 2H), 7.28 (t, *J* = 8.0, 1H), 4.33–4.25 (m, 2H), 3.99 (dd, *J* = 9.7, 4.4, 1H), 3.92 (s, 1H), 2.83 (dd, *J* = 13.3, 4.4, 1H), 2.65 (br s, 1H), 2.29 (dd, *J* = 13.3, 9.7, 1H), 1.44 (s, 3H), 1.34 (t, *J* = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8 (C), 139.3 (C), 132.1 (CH), 130.9 (CH), 130.3 (CH), 126.2 (CH), 122.7 (C), 121.6 (C), 71.7 (CH), 61.9 (CH_2), 57.3 (CH), 44.0 (C),

42.2 (CH_2), 22.2 (CH_3), 14.3 (CH_3); IR (thin film): 3345, 2980, 2938, 2877, 2235, 1736, 1568, 1449, 1204 cm^{-1}; HRMS-CI (*m/z*) $[M + H]^+$ calculated for $C_{15}H_{18}BrN_2O_2$, 337.0552; found, 337.0555. **3.27 (exo adduct):** R_f 0.62 (1:1 hexanes:EtOAc); ^1H NMR (600 MHz, $CDCl_3$): δ 7.65 (br s, 1H), 7.47 (br d, *J* = 7.9, 1H), 7.41 (br d, *J* = 7.9, 1H), 7.25 (t, *J* = 7.9, 1H), 4.56 (s, 1H), 4.26 (q, *J* = 7.0, 2H), 4.07 (dd, *J* = 9.7, 6.3, 1H), 2.75 (dd, *J* = 13.4, 9.7, 1H), 2.68 (br s, 1H), 2.25 (dd, *J* = 13.4, 6.3, 1H), 1.33 (t, *J* = 7.0, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9 (C), 139.3 (C), 131.7 (CH), 130.2 (2CH), 126.1 (CH), 123.8 (C), 122.9 (C), 68.8 (CH_2), 61.7 (CH), 57.2 (CH_2), 41.4 (CH), 40.0 (C), 20.7 (CH_3), 14.3 (CH_3); IR (thin film): 3345, 2982, 2937, 2874, 2235, 1736, 1568, 1378 cm^{-1}; HRMS-CI (*m/z*) $[M + H]^+$ calculated for $C_{15}H_{18}BrN_2O_2$, 337.0552; found, 337.0546.

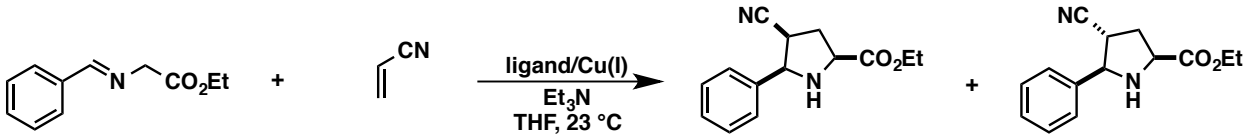


3.28 3.29 3.30

Ethyl *rac*-(2*S*,4*S*,5*S*)-4-cyano-5-(3,4-dichlorophenyl)-4-methylpyrrolidine-2-carboxylate (3.29) and **ethyl *rac*-(2*S*,4*R*,5*S*)-4-cyano-5-(3,4-dichlorophenyl)-4-methylpyrrolidine-2-carboxylate (3.30).** Using **General Procedure 1**, pyrrolidines **3.29** and **3.30** were accessed via various methods from imine **3.28** (51.8 mg, 0.200 mmol, 1.00 equiv) and methacrylonitrile (18.4 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 91% yield, 98:2 dr; **Method B:** >99% yield, 14:86 dr; **Method C:** >99% yield, 61:39 dr. Using **General Procedure 2**, **Method A**, pyrrolidine **3.29** was isolated as a colorless solid (124 mg, 76% yield; mp = 71–72 °C) from a crude reaction mixture with a 98:2 dr. Using **General Procedure 2**, **Method B**, pyrrolidine **3.30** was isolated as a clear oil (118 mg, 73% yield) from a crude reaction mixture with a 15:85 dr. **3.29 (endo adduct):** R_f 0.38

(1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.47 (d, *J* = 8.5, 1H), 7.42 (d, *J* = 8.5, 1H), 4.31–4.24 (m, 2H), 3.98 (dd, *J* = 9.5, 4.5, 1H), 3.92 (s, 1H), 2.83 (dd, *J* = 13.5, 4.5, 1H), 2.69 (br s, 1H), 2.28 (dd, *J* = 13.5, 9.5, 1H), 1.43 (s, 3H), 1.33 (t, *J* = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7 (C), 137.4 (C), 133.0 (C), 132.7 (C), 130.7 (CH), 129.7 (CH), 126.9 (CH), 121.5 (C). 71.0 (CH), 61.8 (CH_2), 57.1 (CH), 43.9 (C), 41.8 (CH_2), 22.2 (CH_3), 14.3 (CH_3); IR (thin film): 3350, 2981, 2938, 2236, 1737, 1469, 1205 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{16}Cl_2N_2O_2Na$, 349.0486; found, 349.0490. **3.30 (exo adduct):** R_f 0.59 (1:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.45 (d, *J* = 8.2, 1H), 7.33 (d, *J* = 8.2, 1H), 4.55 (s, 1H), 4.25 (q, *J* = 7.1, 2H), 4.09–4.06 (m, 1H), 2.75 (dd, *J* = 13.2, 9.5, 1H), 2.58 (br s, 1H), 2.25 (dd, *J* = 13.2, 6.1, 1H), 1.32 (t, *J* = 7.1, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8 (C), 137.4 (C), 133.0 (C), 132.6 (C), 130.6 (CH), 129.2 (CH), 126.7 (CH), 123.7 (C), 68.3 (CH), 61.7 (CH_2), 57.1 (CH), 41.3 (CH_2), 40.0 (C), 20.7 (CH_3), 14.3 (CH_3); IR (thin film): 3348, 2982, 2938, 2235, 1736, 1469, 1201 cm^{-1}; HRMS-CI (*m/z*) $[M + H]^+$ calculated for $C_{15}H_{17}Cl_2N_2O_2$, 327.0667; found, 327.0670.

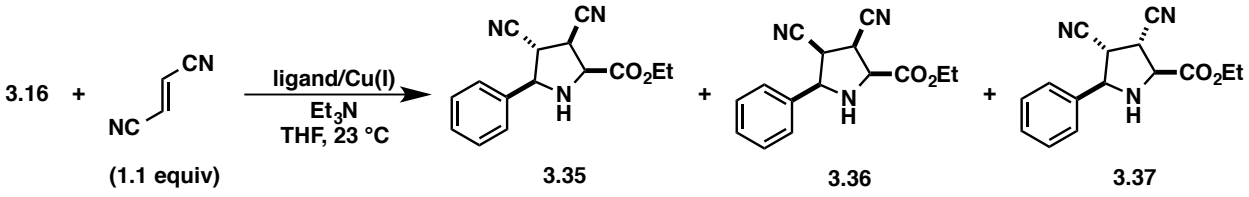
3.7.4 Cu(I)-Catalyzed 1,3-DC Reaction Using Various Dipolarophiles



3.16 (1.1 equiv) 3.33 3.34

Ethyl *rac*-(2*S*,4*S*,5*R*)-4-cyano-5-phenylpyrrolidine-2-carboxylate (3.33) and **ethyl *rac*-(2*S*,4*R*,5*R*)-4-cyano-5-phenylpyrrolidine-2-carboxylate (3.34).** Using **General Procedure 1**, pyrrolidines **3.33** and **3.34** were accessed via various methods from imine **3.16** (38.2 mg, 0.200 mmol, 1.00 equiv) and acrylonitrile (14.5 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 93% yield, 69:31 dr; **Method B:**

85% yield, 8:92 dr; **Method C:** >99% yield, 19:81 dr. **3.33 (endo adduct):** R_f 0.29 (1:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (app d, *J* = 7.6, 2H), 7.40 (app t, *J* = 7.6, 2H), 7.39 (app t, *J* = 7.6, 1H), 4.41 (d, *J* = 6.4, 1H), 4.33–4.23 (m, 2H), 3.96 (dd, *J* = 8.8, 6.4, 1H), 3.29–3.26 (m, 1H), 2.66 (br s, 1H), 2.63–2.56 (m, 1H), 2.51–2.47 (m, 1H), 1.33 (t, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6 (C), 137.8 (C), 128.7 (2CH), 128.6 (CH), 127.1 (2CH), 119.3 (C), 64.8 (CH), 61.7 (CH_2), 58.8 (CH), 36.0 (CH), 34.4 (CH_2), 14.2 (CH_3); IR (thin film): 3339, 2980, 2846, 2241, 1740, 1454, 1204 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{14}H_{16}N_2O_2Na$, 267.1110; found, 267.1114. **3.34 (exo adduct):** R_f 0.49 (1:1 hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (app d, *J* = 7.5, 2H), 7.39 (app t, *J* = 7.5, 2H), 7.34 (app t, *J* = 7.5, 1H), 4.38 (d, *J* = 9.0, 1H), 4.25 (q, *J* = 7.3, 2H), 4.07 (dd, *J* = 9.0, 4.8, 1H), 2.83 (q, *J* = 9.0, 1H), 2.59–2.50 (m, 2H), 2.39 (br s, 1H), 1.32 (t, *J* = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4 (C), 138.8 (C), 129.1 (2CH), 128.8 (CH), 126.8 (2CH), 119.8 (C), 67.5 (CH), 61.8 (CH_2), 58.8 (CH), 36.5 (CH), 34.6 (CH_2), 14.3 (CH_3); IR (thin film): 3350, 3062, 3031, 2983, 2917, 2849, 2243, 1734, 1455, 1378, 1273, 1206 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{14}H_{16}N_2O_2Na$, 267.1110; found, 267.1110.

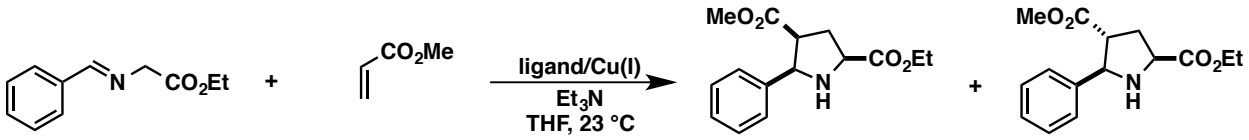


Ethyl *rac*-(2*S*,3*R*,4*R*,5*R*)-3,4-dicyano-5-phenylpyrrolidine-2-carboxylate (3.35). Exo pyrrolidine adduct **3.35** was synthesized using the following adaptations to **General Procedure 1**. The catalyst and imine components of these reactions were partially prepared in separate 1-dram screw-top vials inside a glove box with a N_2 atmosphere. The reagent vial was charged with neat imine **3.16** (38.2 mg, 0.200 mmol, 1.00 equiv). The catalyst and reagent vials were

each sealed with a Teflon-lined cap, then brought outside the glove box where the Telfon-lined caps were each covered with an inverted 14/20 joint rubber septum under a balloon of Ar. Outside of the glove box, a 1-dram vial was charged with fumaronitrile [17.2 mg, 0.220 mmol, 1.10 equiv; azeotropically dried with PhMe (3 x 2 mL)] and a magnetic stir bar, which was then sealed with a Teflon-lined cap and covered with an inverted 14/20 joint rubber septum under an atmosphere of Ar. **Method A:** In the glove box, the catalyst vial was charged with tetrakis(acetonitrile)copper(I) tetrafluoroborate (12.6 mg, 0.0400 mmol). Outside of the glove box, the catalyst vial was charged with THF (1.33 mL, freeze-pump-thawed) and tris(2,2,2-trifluoroethyl) phosphite (19.4 μL, 0.0880 mmol). An aliquot of the catalyst solution (0.33 mL, 0.60 M; 0.010 mmol, 0.050 equiv Cu(I) and 0.022 mmol, 0.11 equiv ligand) and Et_3N (16.7 μL, 0.120 mmol, 0.600 equiv) were added to the vial containing imine **3.16** via syringe. The homogenous mixture was transferred via syringe to the vial containing fumaronitrile. The resulting heterogeneous mixture was stirred at 23 °C for 5 h. The reaction was quenched by opening the vial to air and filtering the reaction mixture through a plug of SiO_2 (200 mg) using EtOAc (8.7 mL, HPLC grade). Exo adduct **3.35** was accessed in 61% yield as determined by GC-FID analysis by adding 1 mL of a GC standard solution [0.1 M solution of 1,3,5-trimethoxybenzene in EtOAc (HPLC grade)] to the filtrate. **Method B:** In the glove box, the catalyst vial was charged with tetrakis(acetonitrile)copper(I) tetrafluoroborate (12.6 mg, 0.0400 mmol) and tricyclohexylphosphine (24.6 mg, 0.0880 mmol). Outside of the glove box, the catalyst vial was charged with THF (0.80 mL, freeze-pump-thawed). An aliquot of the catalyst solution (0.20 mL, 1.0 M; 0.010 mmol, 0.050 equiv Cu(I) and 0.022 mmol, 0.11 equiv ligand) and Et_3N (16.7 μL, 0.120 mmol, 0.600 equiv) were added to the vial containing imine **3.16** via syringe. The homogenous mixture was transferred via syringe to the vial containing

fumaronitrile. The resulting heterogeneous mixture was stirred at 23 °C for 1 h. The reaction was quenched by opening the vial to air and filtering the reaction mixture through a plug of SiO_2 (200 mg) using EtOAc (8.2 mL, HPLC grade). Exo adduct **3.35** was accessed in 65% yield as determined by GC-FID analysis by adding 1 mL of a GC standard solution [0.1 M solution of 1,3,5-trimethoxybenzene in EtOAc (HPLC grade)] to the filtrate. **Method C:** In the glove box, the catalyst vial was charged with tetrakis(acetonitrile)copper(I) tetrafluoroborate (12.6 mg, 0.0400 mmol) and DavePhos (17.3 mg, 0.0440 mmol). Outside of the glove box, the catalyst vial was charged with THF (2.0 mL, freeze-pump-thawed). An aliquot of the catalyst solution (0.50 mL, 0.4 M; 0.010 mmol, 0.050 equiv Cu(I) and 0.011 mmol, 0.055 equiv ligand) and Et_3N (16.7 μL, 0.120 mmol, 0.600 equiv) were added to the vial containing imine **3.16** via syringe. The homogenous mixture was transferred via syringe to the vial containing fumaronitrile. The resulting heterogeneous mixture was stirred at 23 °C for 3 h. The reaction was quenched by opening the vial to air and filtering the reaction mixture through a plug of SiO_2 (200 mg) using EtOAc (8.5 mL, HPLC grade). Exo adduct **3.35** was accessed in 76% yield as determined by GC-FID analysis by adding 1 mL of a GC standard solution [0.1 M solution of 1,3,5-trimethoxybenzene in EtOAc (HPLC grade)] to the filtrate. In addition to exo adduct **3.35**, cycloadducts **3.36** and **3.37** were isolated by flash chromatography (4:1 hexanes:EtOAc to 100% EtOAc, gradient elution) but insufficient quantities of these two cycloadducts could be isolated for adequate characterization.[24] The endo cycloadduct was not detected. **3.35 (exo adduct):** Colorless solid (mp = 81–83 °C); R_f 0.54 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (app dd, *J* = 8.2, 1.2, 2H), 7.45–7.39 (m, 3H), 4.44–4.31 (m, 3H), 4.27 (app t, *J* = 7.4, 1H), 3.69 (app t, *J* = 8.6, 1H), 3.22 (app t, *J* = 8.6, 1H), 2.78 (app t, *J* = 7.8, 1H), 1.38 (t, *J* = 7.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3 (C), 136.5 (C), 129.6 (CH), 129.5 (2CH), 126.8

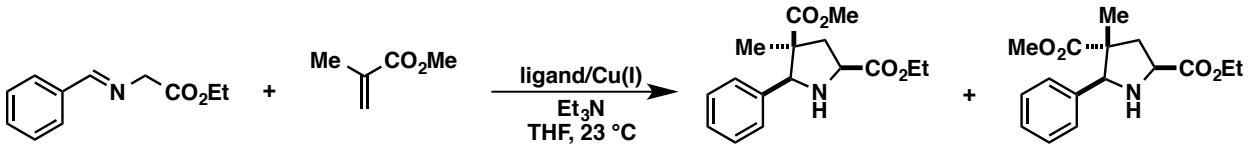
(2CH), 116.9 (C), 116.2 (C), 67.1 (CH), 63.0 (CH_2), 61.8 (CH), 41.6 (CH), 37.5 (CH), 14.2 (CH_3); IR (thin film): 3351, 3064, 3032, 2983, 2940, 2873, 2248, 1738, 1457, 1378, 1211 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{15}N_3O_2Na$, 292.1062; found, 292.1068. **3.36 (with minor impurities):** ^1H NMR (600 MHz, $CDCl_3$): δ 7.47–7.46 (m, 2H), 7.42–7.36 (m, 3H), 4.64 (dd, *J* = 9.1, 6.7, 1H), 4.33–4.29 (m, 2H), 3.74 (dd, *J* = 8.5, 5.1, 1H), 3.16 (app t, *J* = 9.1, 1H), 2.76 (app t, *J* = 6.4, 1H), 1.35 (t, *J* = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9 (C), 136.9 (C), 129.5 (CH), 129.3 (2CH), 126.7 (2CH), 116.6 (C), 115.9 (C), 66.1 (CH), 62.9 (CH_2), 62.8 (CH), 40.7 (CH), 35.9 (CH), 14.3 (CH_3); **3.37 (with minor impurities):** ^1H NMR (600 MHz, $CDCl_3$): δ 7.46–7.38 (m, 5H), 4.66 (app t, *J* = 6.1, 1H), 4.36 (q, *J* = 7.1, 2H), 4.18 (app t, *J* = 6.1, 1H), 3.72 (dd, *J* = 6.1, 4.4, 1H), 3.58 (dd, *J* = 6.1, 4.4, 1H), 2.82 (br s, 1H), 1.38 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0 (C), 135.4 (C), 129.5 (CH), 129.1 (2CH), 127.1 (2CH), 117.7 (C), 116.4 (C), 64.3 (CH), 63.2 (CH), 63.0 (CH_2), 41.0 (CH), 36.5 (CH), 14.3 (CH_3).



3.16 (1.1 equiv) 3.39 3.40

2-Ethyl 4-methyl *rac*-(2*S*,4*S*,5*R*)-5-phenylpyrrolidine-2,4-dicarboxylate (3.39) and **2-ethyl 4-methyl *rac*-(2*S*,4*R*,5*R*)-5-phenylpyrrolidine-2,4-dicarboxylate (3.40).** Using **General Procedure 1**, pyrrolidines **3.39** and **3.40** were accessed via various methods from imine **3.16** (38.2 mg, 0.200 mmol, 1.00 equiv) and methyl acrylate (19.8 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 87% yield, 97:3 dr; **Method B:** 85% yield, 94:6 dr; **Method C:** 93% yield, 69:31 dr. **3.39 (endo adduct):** R_f 0.27 (1:1 hexanes:EtOAc); ^1H NMR (600 MHz, $CDCl_3$): δ 7.33–7.29 (m, 4H), 7.26–7.23 (m, 1H), 4.54 (d, *J* = 7.8, 1H), 4.29 (q, *J* = 7.1, 2H), 3.96 (app t, *J* = 8.3, 1H), 3.32 (q, *J* = 7.8, 1H), 3.22

(s, 3H), 2.89 (br s, 1H), 2.45–2.37 (m, 2H), 1.34 (t, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4 (C), 173.0 (C), 139.2 (C), 128.2 (2CH), 127.6 (CH), 126.8 (2CH), 65.9 (CH), 61.2 (CH_2), 60.1 (CH), 51.3 (CH_3), 49.8 (CH), 33.4 (CH_2), 14.3 (CH_3); IR (thin film): 3346, 3062, 3028, 2983, 2950, 2906, 1735, 1454, 1437, 1203, 1168 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{15}H_{19}NO_4Na$, 300.1212; found, 300.1209. ^{1}H NMR spectral data are consistent with those previously reported.[19l] **3.40 (exo adduct):** R_f 0.40 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (app d, J = 7.6, 2H), 7.33 (app t, J = 7.6, 2H), 7.27 (app t, J = 7.6, 1H), 4.40 (d, J = 8.7, 1H), 4.23 (q, J = 7.1, 2H), 4.02 (dd, J = 8.9, 5.4, 1H), 3.63 (s, 3H), 2.91 (q, J = 8.9, 1H), 2.54–2.48 (m, 1H), 2.43 (br s, 1H), 2.40–2.35 (m, 1H), 1.30 (t, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3 (C), 173.9 (C), 141.2 (C), 128.7 (2CH), 127.9 (CH), 127.0 (2CH), 66.9 (CH), 61.4 (CH_2), 59.5 (CH), 52.0 (CH_3), 51.4 (CH), 34.9 (CH_2), 14.3 (CH_3); IR (thin film): 3345, 3028, 2982, 2953, 2904, 1732, 1437, 1196, 1168 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calculated for $C_{15}H_{20}NO_4$, 278.1392; found, 278.1384.



3.16 (1.1 equiv) 3.41 3.42

2-Ethyl 4-methyl *rac*-(2*S*,4*S*,5*S*)-4-methyl-5-phenylpyrrolidine-2,4-dicarboxylate (3.41) and **2-ethyl 4-methyl *rac*-(2*S*,4*R*,5*S*)-4-methyl-5-phenylpyrrolidine-2,4-dicarboxylate (3.42).** Using **General Procedure 1**, pyrrolidines **3.41** and **3.42** were accessed via various methods from imine **3.16** (38.2 mg, 0.200 mmol, 1.00 equiv) and methyl methacrylate (23.5 μL, 0.220 mmol, 1.10 equiv) in the following yields and diastereomeric ratios (endo:exo). **Method A:** 61% yield, 99:1 dr; **Method B:** 75% yield, 97:3 dr; **Method C:** 87% yield, 78:22 dr. **3.41 (endo adduct):** R_f 0.35 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.24 (m, 5H), 4.29

(q, J = 7.1, 2H), 4.06 (s, 1H), 4.02 (dd, J = 8.7, 7.2, 1H), 3.21 (s, 3H), 3.00 (br s, 1H), 2.72 (dd, J = 13.2, 7.2, 1H), 2.12 (dd, J = 13.2, 8.7, 1H), 1.41 (s, 3H), 1.33 (t, J = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9 (C), 174.0 (C), 138.9 (C), 128.3 (2CH), 128.0 (CH), 126.8 (2CH), 74.2 (CH), 61.3 (CH_2), 59.3 (CH), 54.9 (C), 51.5 (CH_3), 41.7 (CH_2), 22.8 (CH_3), 14.4 (CH_3); IR (thin film): 3348, 3028, 2981, 2878, 1734, 1455, 1240, 1217 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{16}H_{21}NO_4Na$, 314.1368; found, 314.1363. **3.42 (exo adduct):** R_f 0.61 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.30 (m, 4H), 7.27–7.24 (m, 1H), 4.70 (s, 1H), 4.25 (dq, J = 7.2, 1.1, 2H), 4.02 (dd, J = 9.1, 7.3, 1H), 3.74 (s, 3H), 2.76 (dd, J = 13.0, 9.1, 1H), 2.65 (br s, 1H), 1.97 (dd, J = 13.0, 7.3, 1H), 1.31 (t, J = 7.2, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.9 (C), 174.2 (C), 139.3 (C), 128.2 (2CH), 127.6 (CH), 127.4 (2CH), 68.9 (CH), 61.3 (CH_2), 58.1 (CH), 52.7 (C), 52.4 (CH_3), 42.0 (CH_2), 19.7 (CH_3), 14.4 (CH_3); IR (thin film): 3344, 3029, 2981, 2935, 1730, 1455, 1273, 1197 cm^{-1}; HRMS-CI (*m/z*) $[M + H]^+$ calculated for $C_{16}H_{22}NO_4$, 292.1549; found, 292.1553.

3.7.5 Verification of Cu(I)/PCy_3 Catalyst

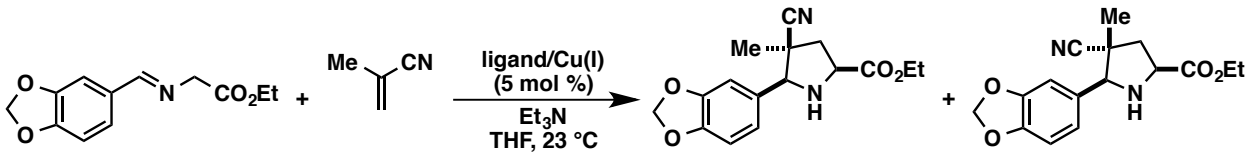
PCy_3 is a sensitive ligand because it readily oxidizes. A series of experiments was performed in order to verify that Cu(I)/PCy_3 was the active catalyst in the 1,3-DC reactions run using PCy_3 as the ligand. Tricyclohexylphosphonium tetrafluoroborate (PCy_3•HBF_4) is an air-stable salt from which PCy_3 is easily liberated by the addition of Et_3N (Table 3.16, entry 3). The 1,3-DC reaction was run using PCy_3•HBF_4 (Table 3.17, entry 2). The reaction proceeded more sluggishly but the dr was consistent with the reaction run using PCy_3. Increasing the reaction time to 19 h resulted in a higher yield (entry 3), but the yield did not compare to that using PCy_3 (entry 1). Pretreating the Cu(I)/PCy_3•HBF_4 catalyst solution with Et_3N (22 mol %) did not affect reactivity (entry 4). These results suggested that the Et_3N•HBF_4 byproduct may inhibit desired

reactivity. This hypothesis was supported by running the Cu(I)/PCy_3-catalyzed reaction with $Et_3N{\bullet}HBF_4$[29] as an additive. Yields were lower when increased amounts of $Et_3N{\bullet}HBF_4$ were added to the reaction but the dr was consistent at 10:90 (entries 5 and 6). Finally, it was shown that the reaction run using tricyclohexylphosphine oxide ($O{=}PCy_3$) was slower and less diastereoselective than running the same reaction with PCy_3 as the ligand (entry 7). Collectively, these results support that the reactions run in this report are indeed catalyzed by a Cu(I)/PCy_3 complex where the ligand has not been oxidized.

Table 3.16. ^{31}P NMR Shifts of PCy_3 Derivatives

entry	compound	^{31}P NMR (δ ppm in $CDCl_3$)
1	PCy_3	11.2
2	$PCy_3{\cdot}HBF_4$	27.8
3	$PCy_3{\cdot}HBF_4$ + Et_3N (1:1)	11.2
4	$O{=}PCy_3$	50.3

Table 3.17. Testing PCy_3 Ligands

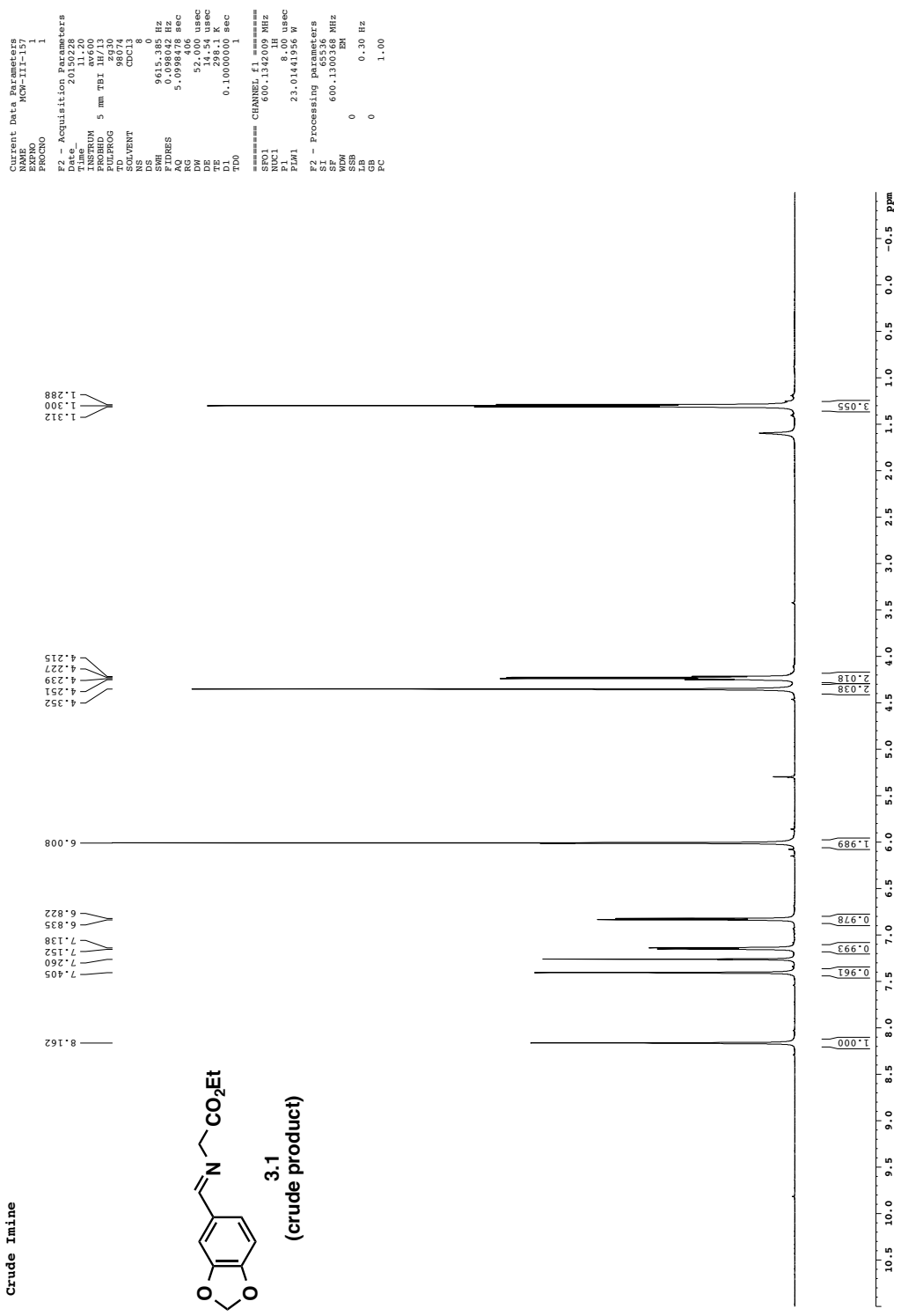


3.1 (1.1 equiv) 3.2 3.3

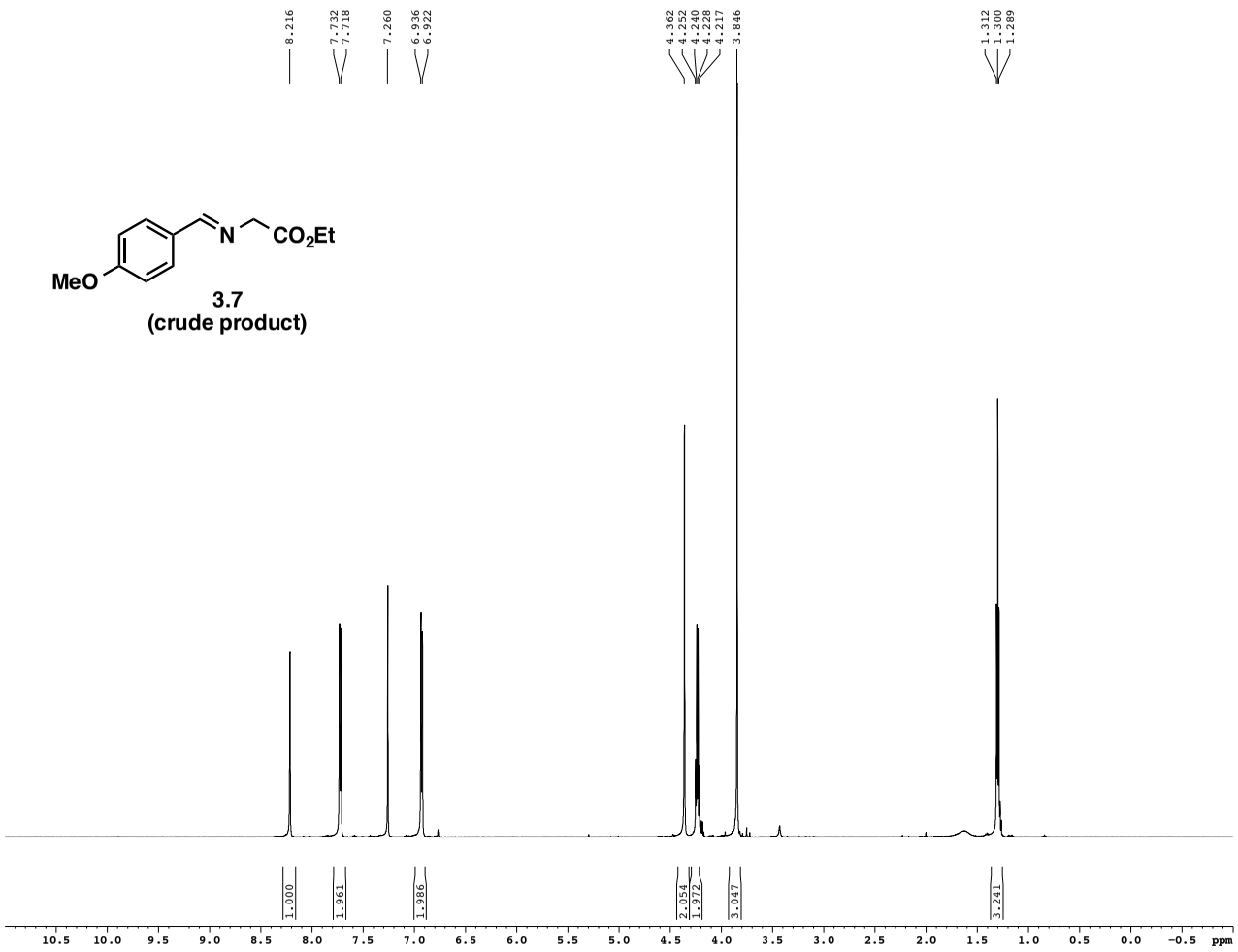
entry[a]	ligand (11 mol %)	additive	reaction time (h)	unreacted 3.1 (%)[b]	yield (%)[b]	dr (endo:exo)[c]
1	PCy_3	–	1	3	95	9:91
2	$PCy_3{\cdot}HBF_4$	–	1	69	25	9:91
3	$PCy_3{\cdot}HBF_4$	–	19	13	64	11:89
4	$PCy_3{\cdot}HBF_4$[d]	–	1	66	29	9:91
5	PCy_3	$Et_3N{\cdot}HBF_4$ (11 mol %)	1	38	57	10:90
6	PCy_3	$Et_3N{\cdot}HBF_4$ (22 mol %)	1	50	40	10:90
7	$O{=}PCy_3$	–	1	29	49	21:79

[a]Reactions were performed using imine 3.1 (0.20 mmol) and methacrylonitrile (0.22 mmol) at a concentration of 0.2 M in THF. [b]GC yields using 1,3,5-trimethoxybenzene as external standard (± 5% error). [c]Ratios determined by GC-FID analysis. [d]Pretreated catalyst solution with Et_3N (22 mol %).

3.8 Appendix B: NMR Spectral Data



Crude Imine

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PROCNO                         1

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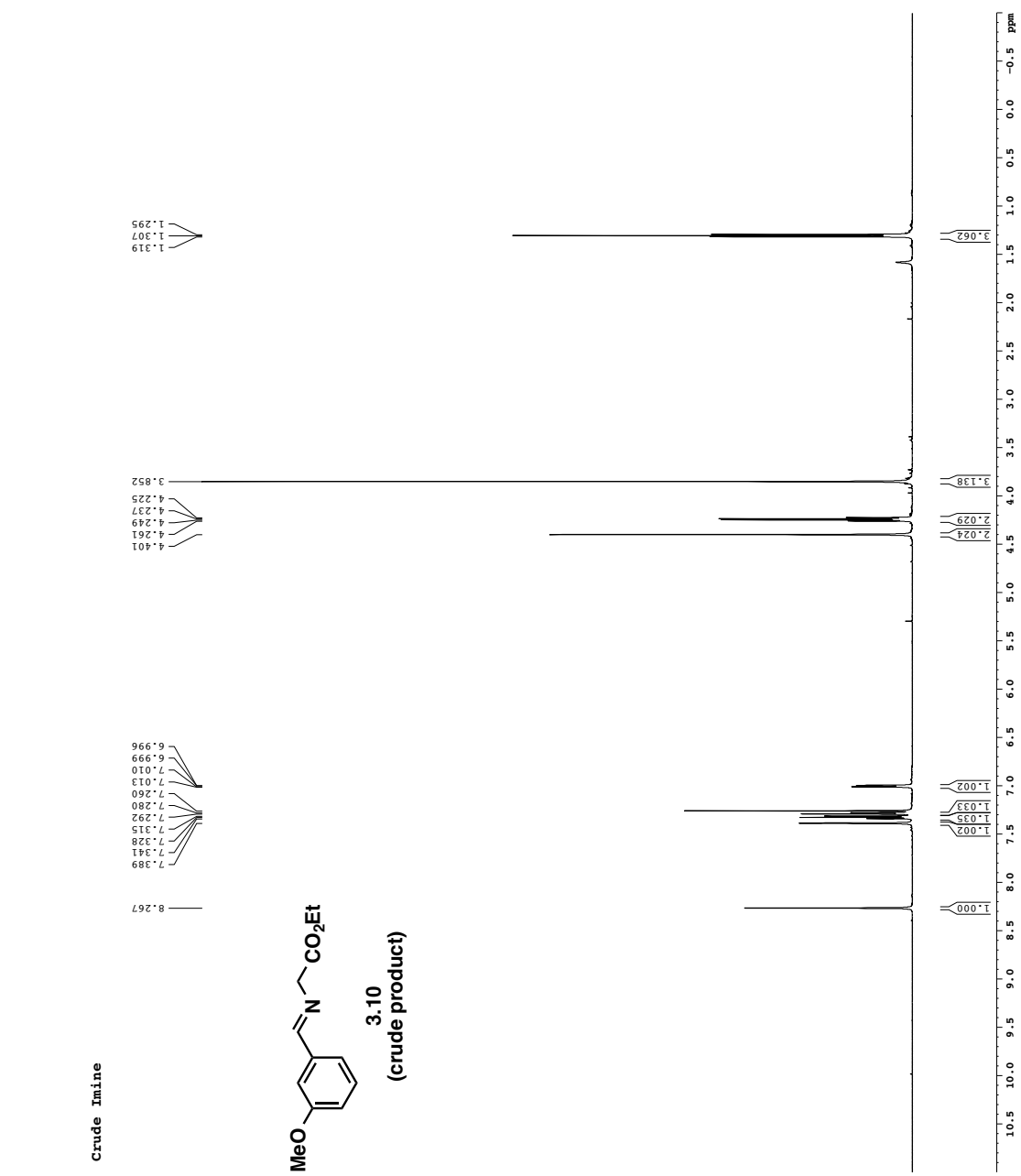
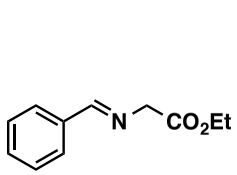
PROBHD    5 mm TBI 1H/13
PULPROG                    zg30
TD                        98074
SOLVENT                   CDCl3
NS                            10
DS                             0
SWH                    9615.385 Hz
FIDRES                 0.098042 Hz
AQ                     5.0998478 sec
RG                           512
DW                        52.000 usec
DE                        14.54 usec
TE                        298.0 K
D1                     0.10000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1                600.1342009 MHz
NUC1                        1H
P1                        8.00 usec
PLW1                23.01441956 W

F2 - Processing parameters
SI                         65536
SF                  600.1300346 MHz
WDW                           EM
SSB          0
LB                         0.30 Hz
GB           0
PC                         1.00
```


Crude Imine
MeO
CO2Et
3.10
(crude product)
8.267
7.389
7.341
7.328
7.315
7.292
7.280
7.260
7.013
7.010
6.999
6.996
4.401
4.261
4.249
4.237
4.225
3.852
1.319
1.307
1.295
1.000
1.002
1.033
1.035
1.002
2.024
2.029
3.138
3.062
ppm

Crude Imine



3.13
(crude product)


```
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PROCNO                         1

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PULPROG                    zg30
TD                         81728
SOLVENT                    CDCl3
NS                             8
DS                             0
SWH                     8012.820 Hz
FIDRES                  0.098043 Hz
AQ                      5.0998273 sec
RG                         1290.2
DW                         62.400 usec
DE                          6.00 usec
TE                         298.0 K
D1                      0.10000000 sec
MCREST     0 sec
MCWRK                   0.01500000 sec

======== CHANNEL f1 ========
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P1                         12.00 usec
PL1                        -5.80 dB
SFO1                499.2934950 MHz

F2 - Processing parameters
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PC                          1.00
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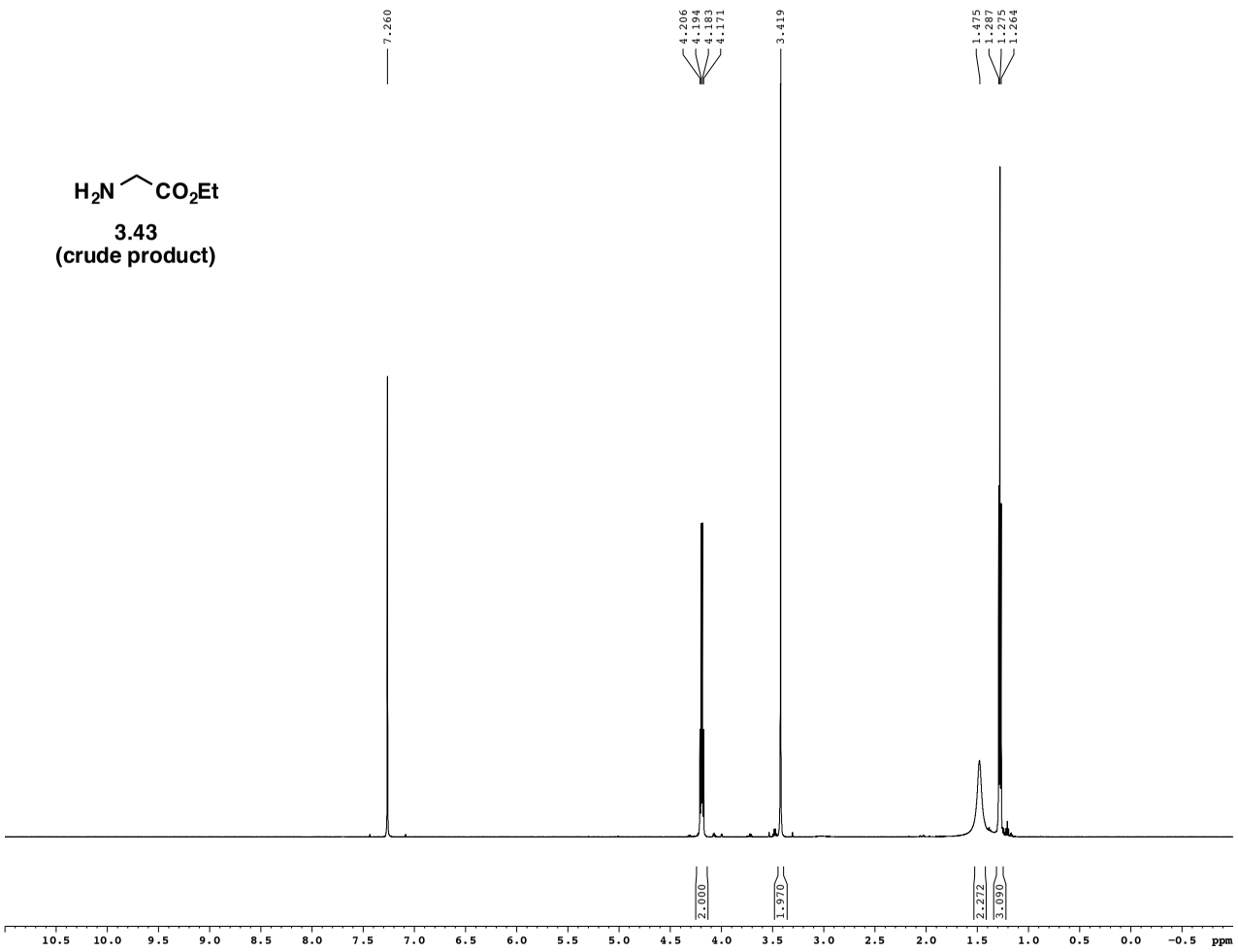
Crude Product



H_2N CO_2Et

3.43
(crude product)

```
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EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
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Time                18.14
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PROBHD   5 mm TBI 1H/13
PULPROG             zg30
TD                 98074
SOLVENT            CDCl3
NS                     8
DS                     0
SWH             9615.385 Hz
FIDRES          0.098042 Hz
AQ              5.0998478 sec
RG                   512
DW                52.000 usec
DE                14.54 usec
TE                298.0 K
D1            0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          600.1342009 MHz
NUC1                  1H
P1                 8.00 usec
PLW1          23.01441956 W

F2 - Processing parameters
SI                 65536
SF            600.1300344 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
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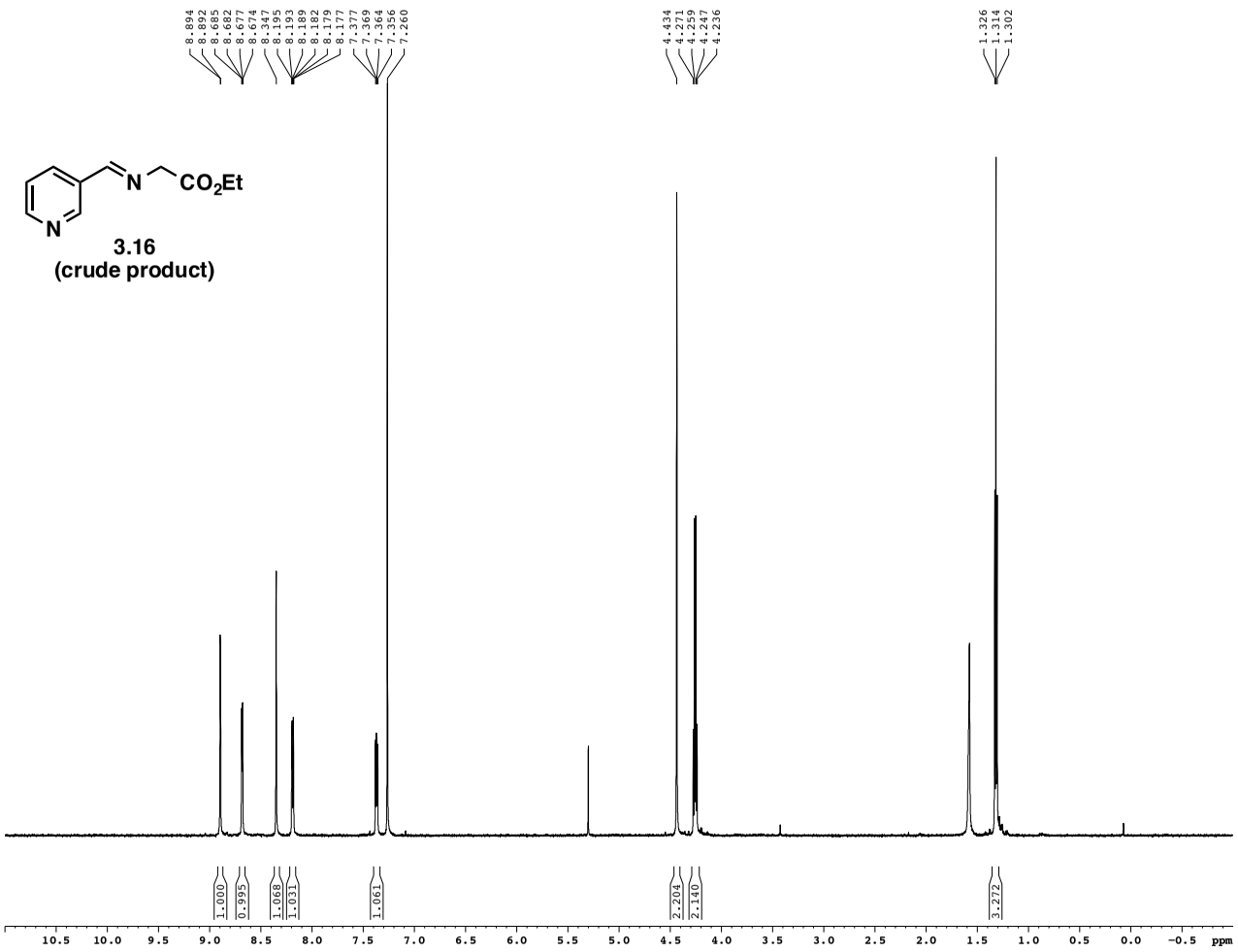
Crude Imine

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PROCNO                  1

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Time                9.23
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PROBHD   5 mm BBO BB-1H
PULPROG             zg30
TD                 38460
SOLVENT            CDCl3
NS                     8
DS                     0
SWH             9615.385 Hz
FIDRES          0.250010 Hz
AQ              1.9999200 sec
RG                   812
DW                52.000 usec
DE                14.33 usec
TE                298.4 K
D1            0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          600.1342009 MHz
NUC1                  1H
P1                 9.00 usec
PLW1          60.25600052 W

F2 - Processing parameters
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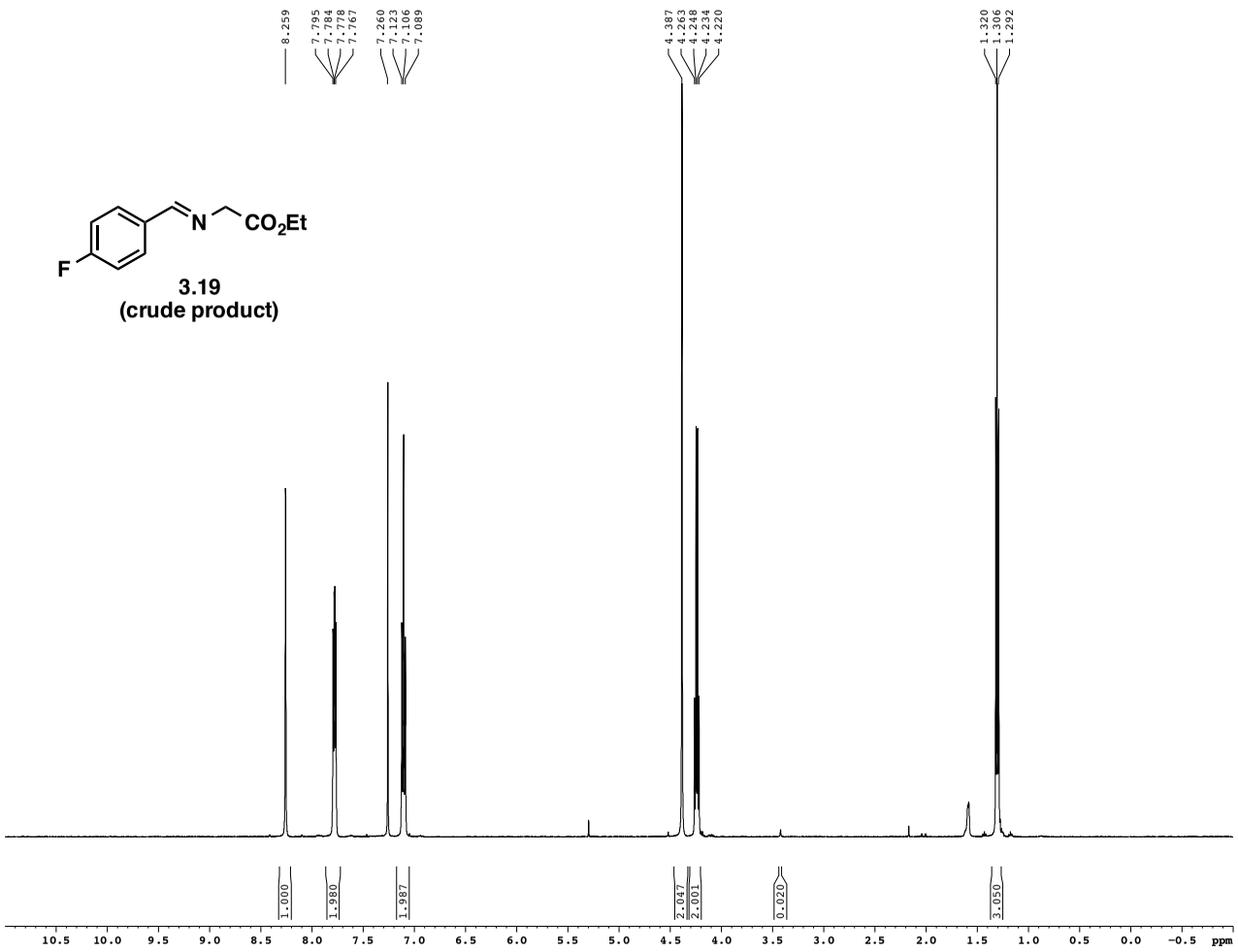
SF            600.1300339 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

Crude Imine

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PROCNO                         1

F2 - Acquisition Parameters
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PULPROG                    zg30
TD                        81728
SOLVENT                   CDCl3
NS                             8
DS                             0
SWH                     8012.820 Hz
FIDRES                  0.098043 Hz
AQ                      5.0998273 sec
RG                           4.5
DW                        62.400 usec
DE                         6.00 usec
TE                        298.0 K
D1                      0.10000000 sec
MCREST     0 sec
MCWRK                   0.01500000 sec

======== CHANNEL f1 ========
NUC1                          1H
P1                         7.50 usec
PL1                        1.60 dB
SFO1                500.2235015 MHz

F2 - Processing parameters
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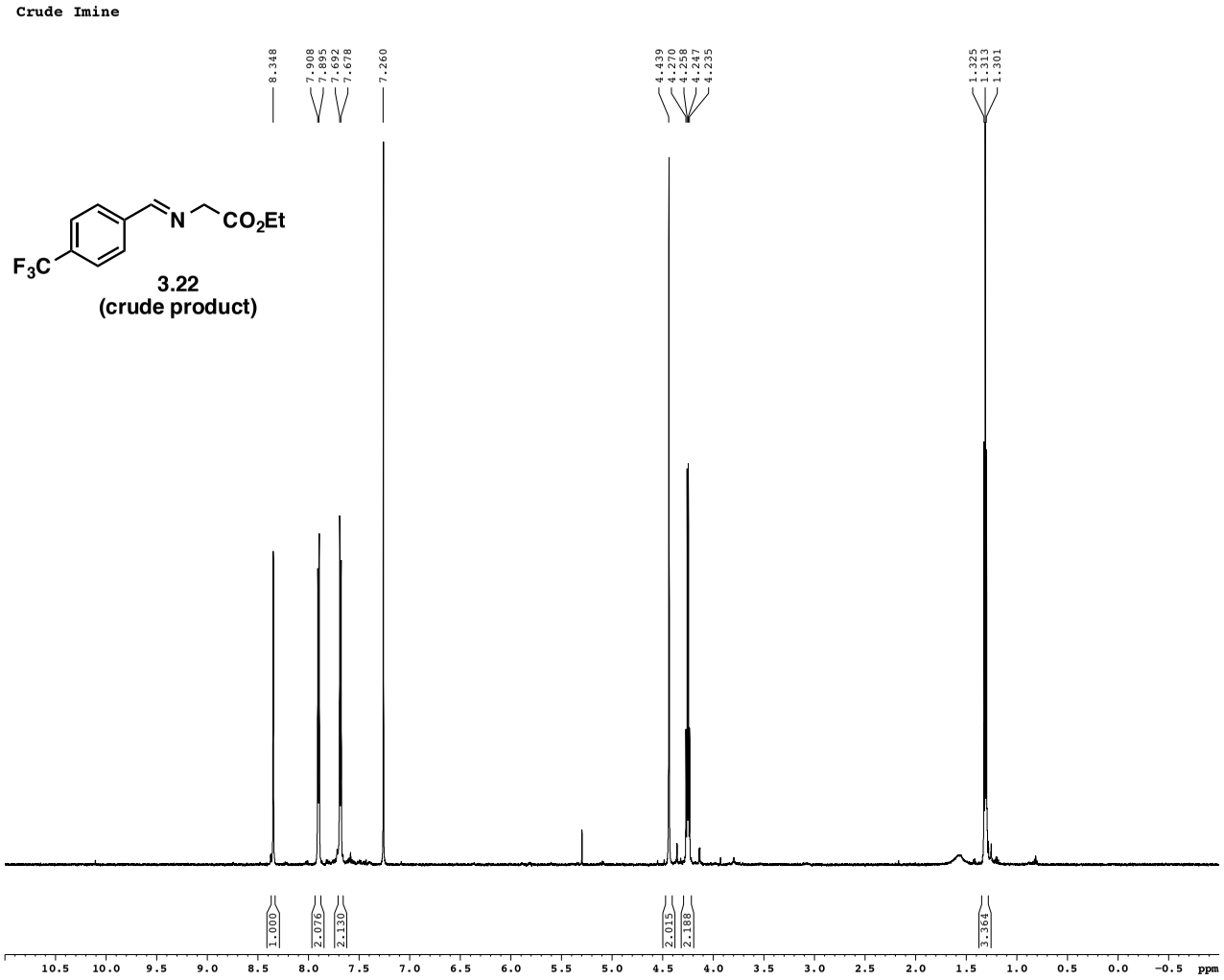
SF                  500.2200315 MHz
WDW                           EM
SSB        0
LB                         0.30 Hz
GB         0
PC                         4.00
```

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PROCNO                         1

F2 - Acquisition Parameters
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Time                        9.08
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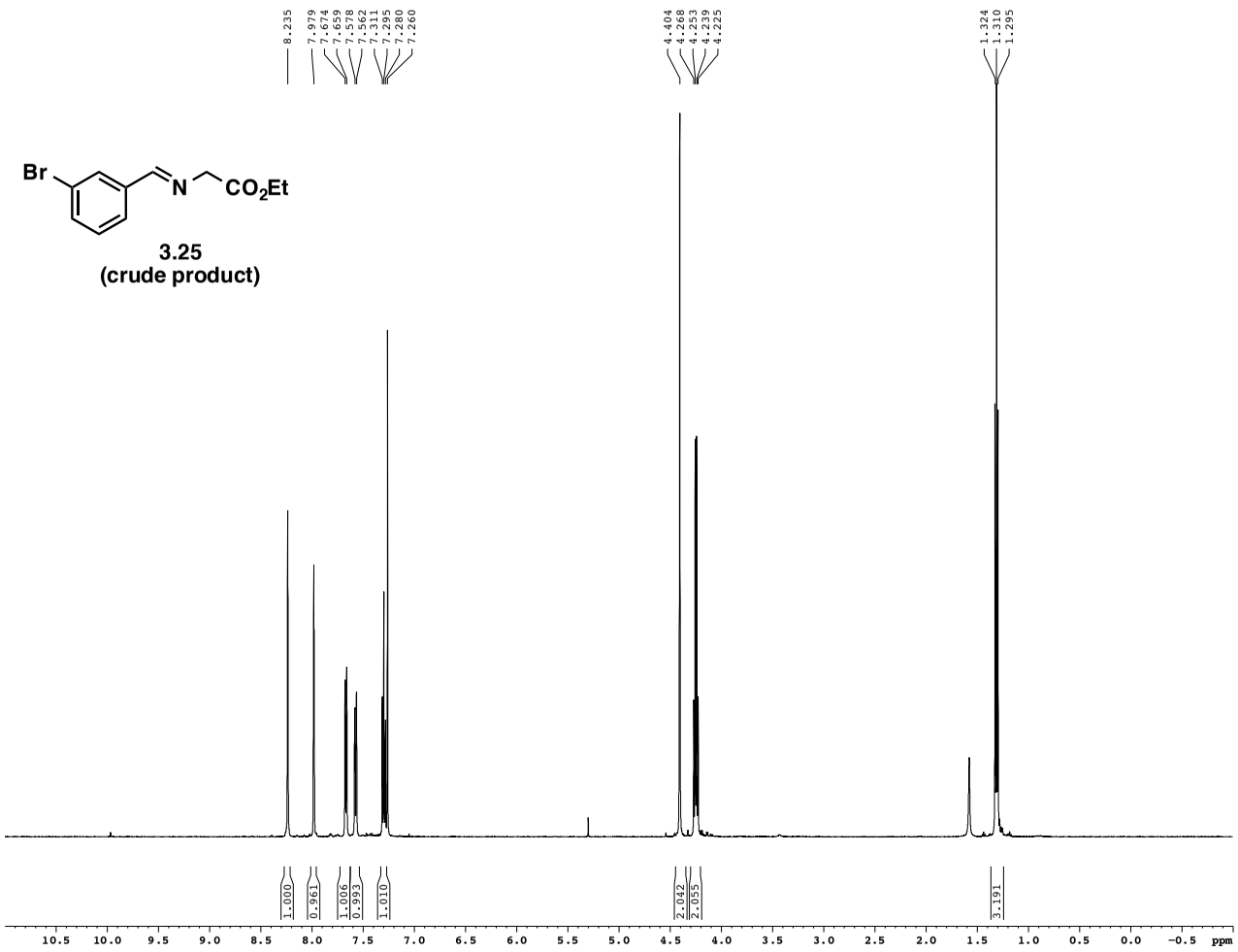
PULPROG                     zg30
TD                         98074
SOLVENT                    CDCl3
NS                             8
DS                             0
SWH                     9615.385 Hz
FIDRES                  0.098042 Hz
AQ                      5.0998478 sec
RG                          2050
DW                        52.000 usec
DE                        14.54 usec
TE                        298.0 K
D1                      0.10000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1                 600.1342009 MHz
NUC1                           1H
P1                         8.00 usec
PLW1                23.01441956 W

F2 - Processing parameters
SI                         65536
SF                   600.1300341 MHz
WDW                           EM
SSB          0
LB                         0.30 Hz
GB           0
PC                         1.00
```

Crude Imine

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PROCNO                  1

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PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT             CDCl3
NS                      8
DS                      0
SWH             8012.820 Hz
FIDRES          0.098043 Hz
AQ              5.0998273 sec
RG                    5.7
DW                 62.400 usec
DE                  6.00 usec
TE                 298.0 K
D1              0.10000000 sec
MCREST    0 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1         500.2235015 MHz

F2 - Processing parameters
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SSB       0
LB                  0.30 Hz
GB        0
PC                  4.00
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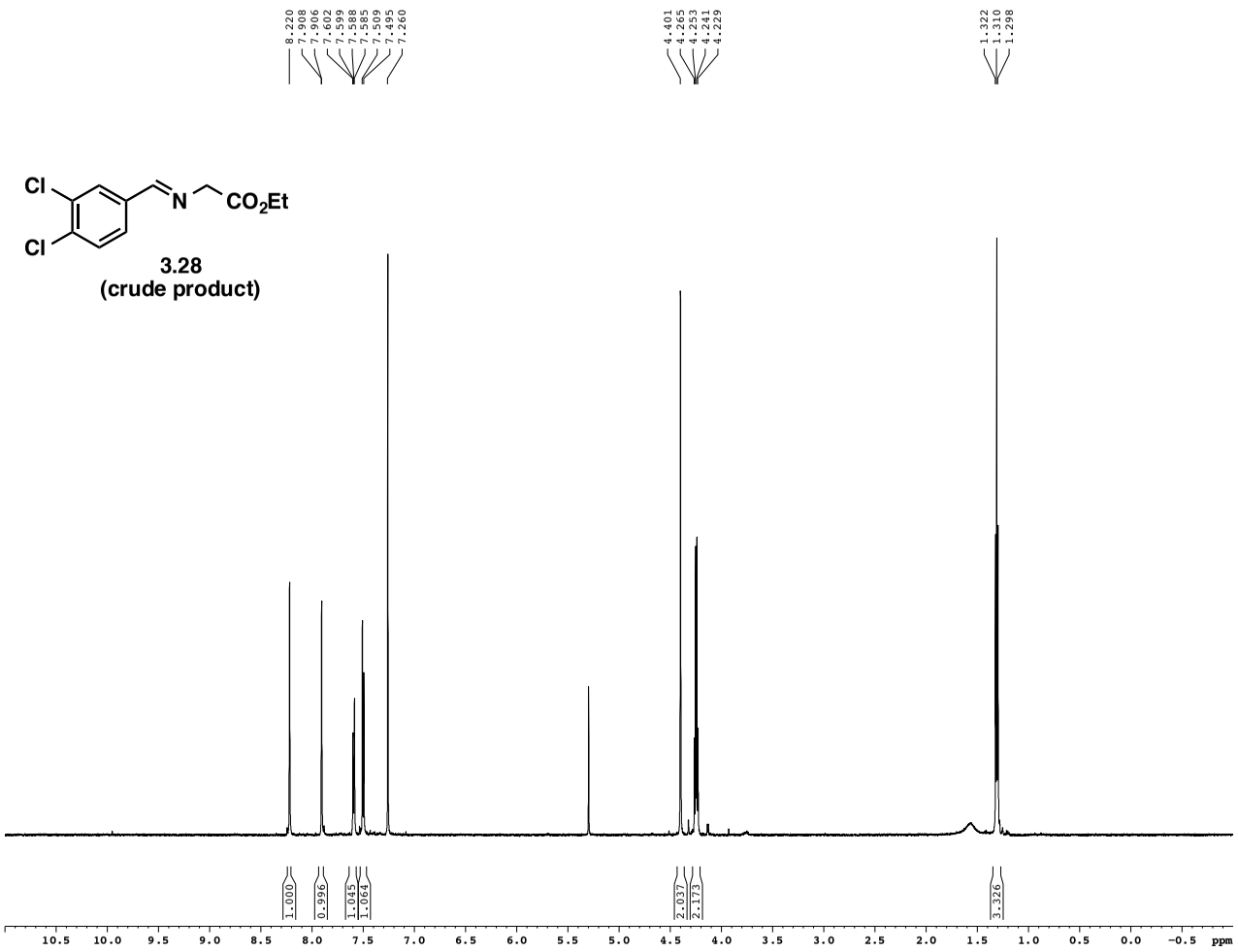
Crude Imine

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PROCNO                  1

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PULPROG            zg30
TD                98074
SOLVENT           CDCl3
NS                    8
DS                    0
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FIDRES        0.098042 Hz
AQ            5.0998478 sec
RG                 2050
DW               52.000 usec
DE               14.54 usec
TE               298.0 K
D1            0.10000000 sec
TD0                   1

======== CHANNEL f1 ========
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NUC1                  1H
P1                 8.00 usec
PLW1       23.01441956 W

F2 - Processing parameters
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WDW                  EM
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PC                1.00
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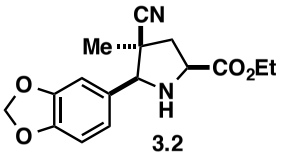
Endo Adduct



3.2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PROCNO                  1

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PULPROG             zg30
TD                 98074
SOLVENT             CDCl3
NS                     10
DS                      0
SWH            9615.385 Hz
FIDRES        0.098042 Hz
AQ            5.0998478 sec
RG                    287
DW               52.000 usec
DE               14.33 usec
TE                298.1 K
D1           0.10000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         600.1342009 MHz
NUC1                   1H
P1                   9.00 usec
PLW1         60.25600052 W

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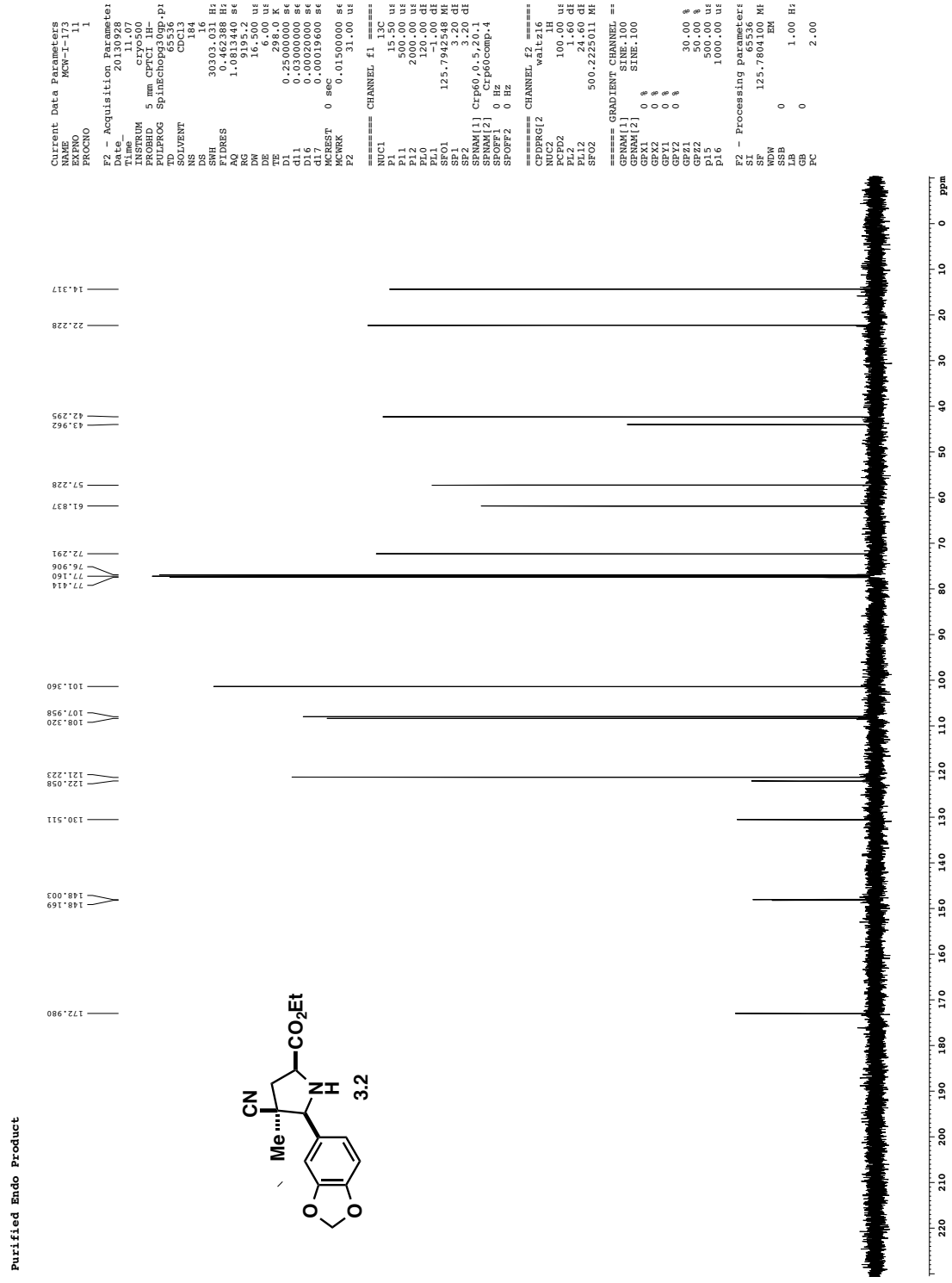
Purified Endo Product
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PROCNO 1
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PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchop3gp.p1
TD 65536
SOLVENT CDCl3
NS 184
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 91915.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MC4REST 0 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
PL2 20000.00 dB
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804100 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
14.317
22.228
42.295
43.962
57.228
61.837
72.291
76.906
77.160
77.414
101.360
107.958
108.320
121.223
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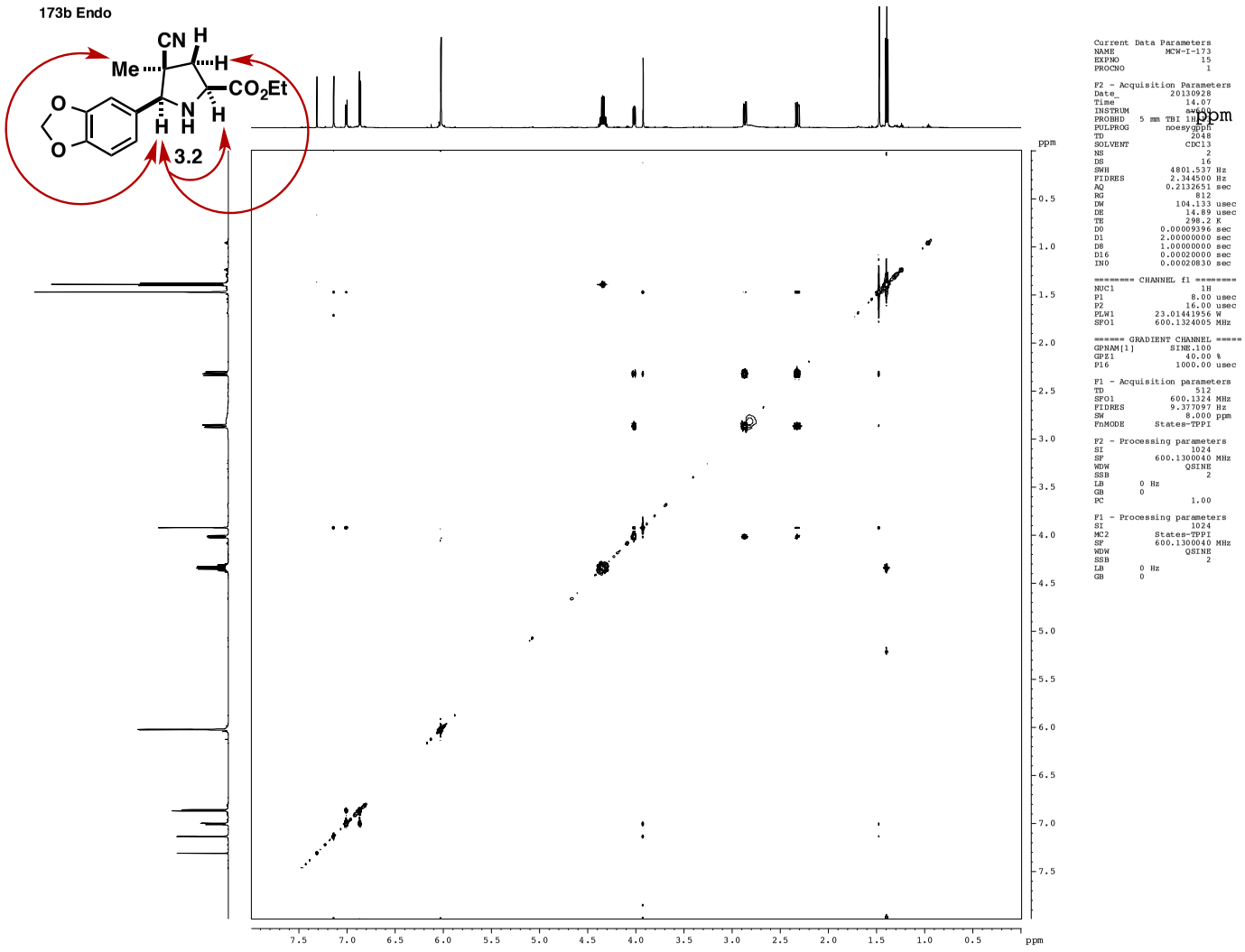
CN
Me
CO2Et
N
H
3.2
O
O
O
ppm


173b Endo
CN
H
Me
H
CO2Et
O
O
N
H
H
H
3.2
ppm
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PROCNO 1
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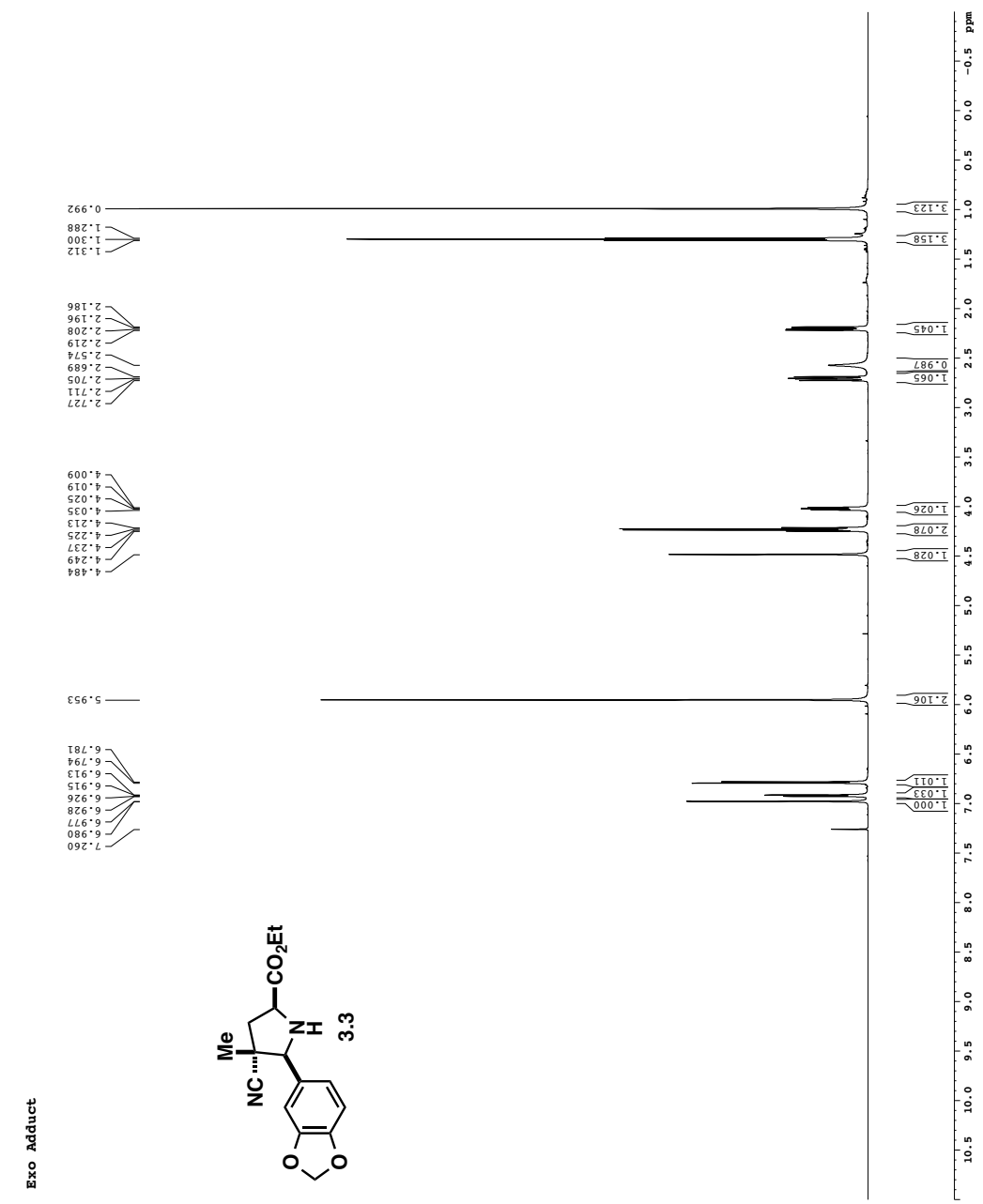
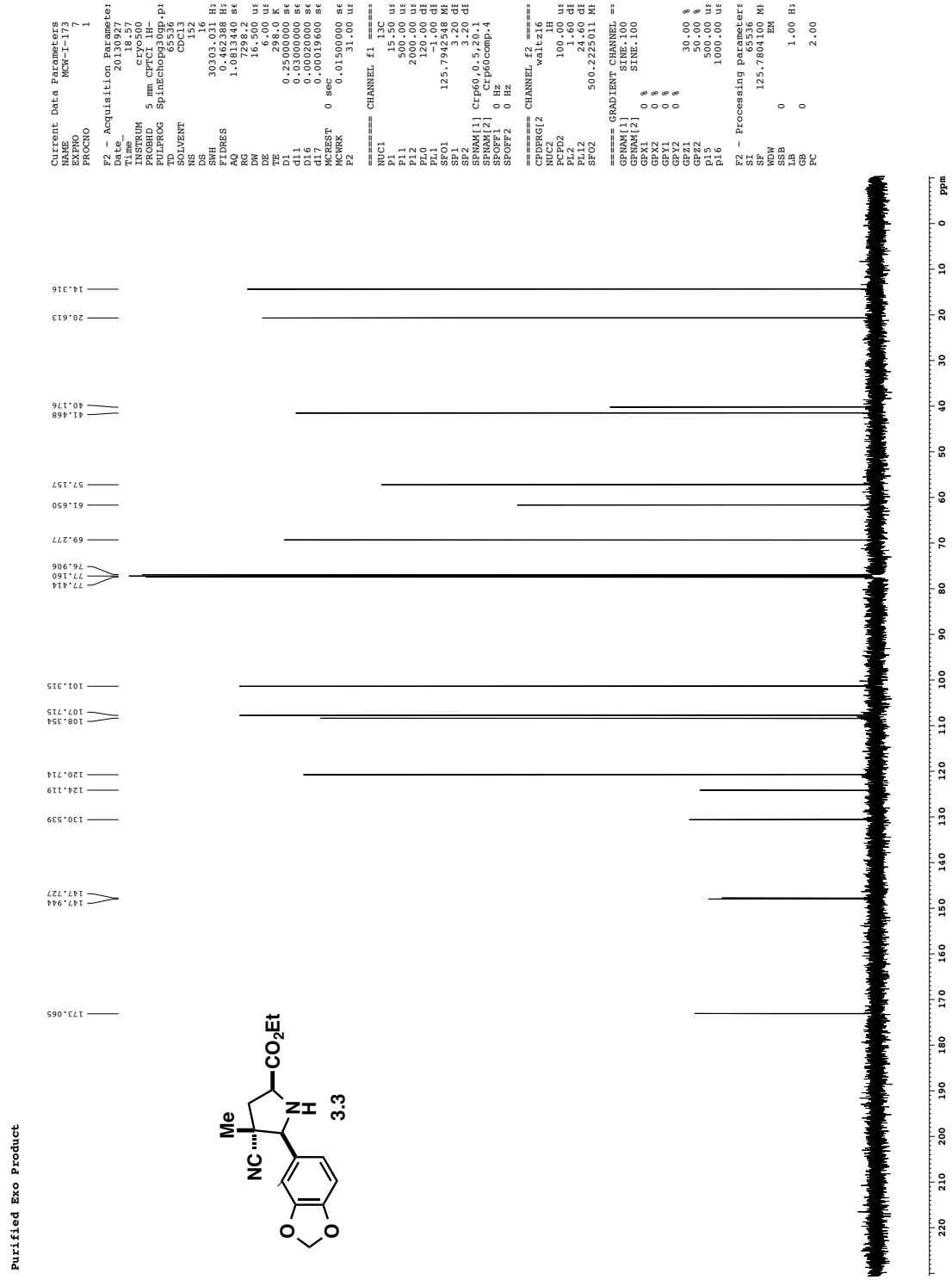
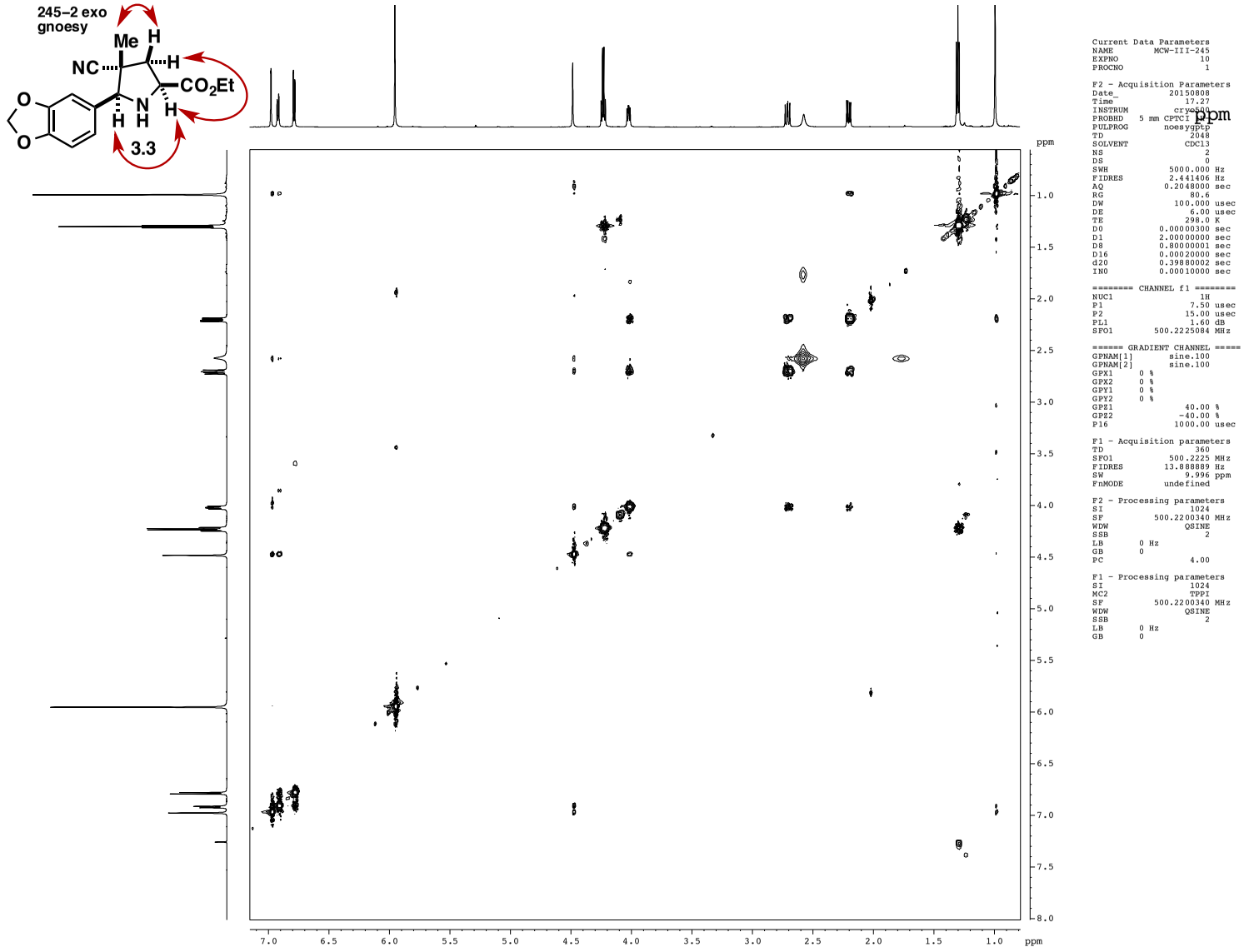
Time 14.07
INSTRUM av600
PROBHD 5 mm TBI 1H/
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 2
DS 16
SWH 4801.537 Hz
FIDRES 2.344500 Hz
AQ 0.2132651 sec
RG 812
DW 104.133 usec
DE 14.89 usec
TE 298.2 K
D0 0.00009396 sec
D1 2.00000000 sec
D8 1.00000000 sec
D16 0.00020000 sec
IN0 0.00020830 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
P2 16.00 usec
PLW1 23.01441956 W
SFO1 600.1324005 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPZ1 40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1324 MHz
FIDRES 9.377097 Hz
SW 8.000 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 1024
SF 600.1300040 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 States-TPPI
SF 600.1300040 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0


Exo Adduct
Current Data Parameters
NAME MCM-III-245
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150520
Time 16.58
INSTRUM av600
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 10
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.09988478 sec
RG 128
DW 52.000 usec
DE 14.33 usec
TE 298.2 K
D1 0.10000000 sec
1
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 9.00 usec
PLW1 60.25600052 W
F2 - Processing parameters
SI 65536
SF 600.1300340 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Me
NC
N
H
CO2Et
3.3
O
O
7.260
6.980
6.977
6.928
6.926
6.915
6.913
6.794
6.781
5.953
4.484
4.249
4.237
4.225
4.213
4.035
4.025
4.019
4.009
2.727
2.711
2.705
2.689
2.574
2.219
2.208
2.196
2.186
1.312
1.300
1.288
0.992
1.000
1.033
1.011
2.106
1.028
2.078
1.026
1.065
0.987
1.045
3.158
3.123
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
ppm


Purified Exo Product
Me
NC
CO2Et
N
H
3.3
O
O
173.065
147.944
147.727
130.539
124.119
120.714
108.354
107.715
101.315
77.414
77.160
76.906
69.277
61.650
57.157
41.468
40.176
20.613
14.316
ppm




```
Current Data Parameters
NAME            MCW-III-245
EXPNO                    10
PROCNO                    1

F2 - Acquisition Parameters
Date_             20150808
Time                 17.27
INSTRUM              cryo500
PROBHD    5 mm CPTCI 1H-13C
PULPROG          noesygpdp
TD                     2048
SOLVENT               CDCl3
NS                        2
DS                        0
SWH                5000.000 Hz
FIDRES             2.441406 Hz
AQ                 0.2048000 sec
RG                      80.6
DW                 100.000 usec
DE                   6.00 usec
TE                   298.0 K
D0                 0.00000300 sec
D1                 2.00000000 sec
D8                 0.80000001 sec
D16                0.00020000 sec
d20                0.39880002 sec
IN0                0.00010000 sec

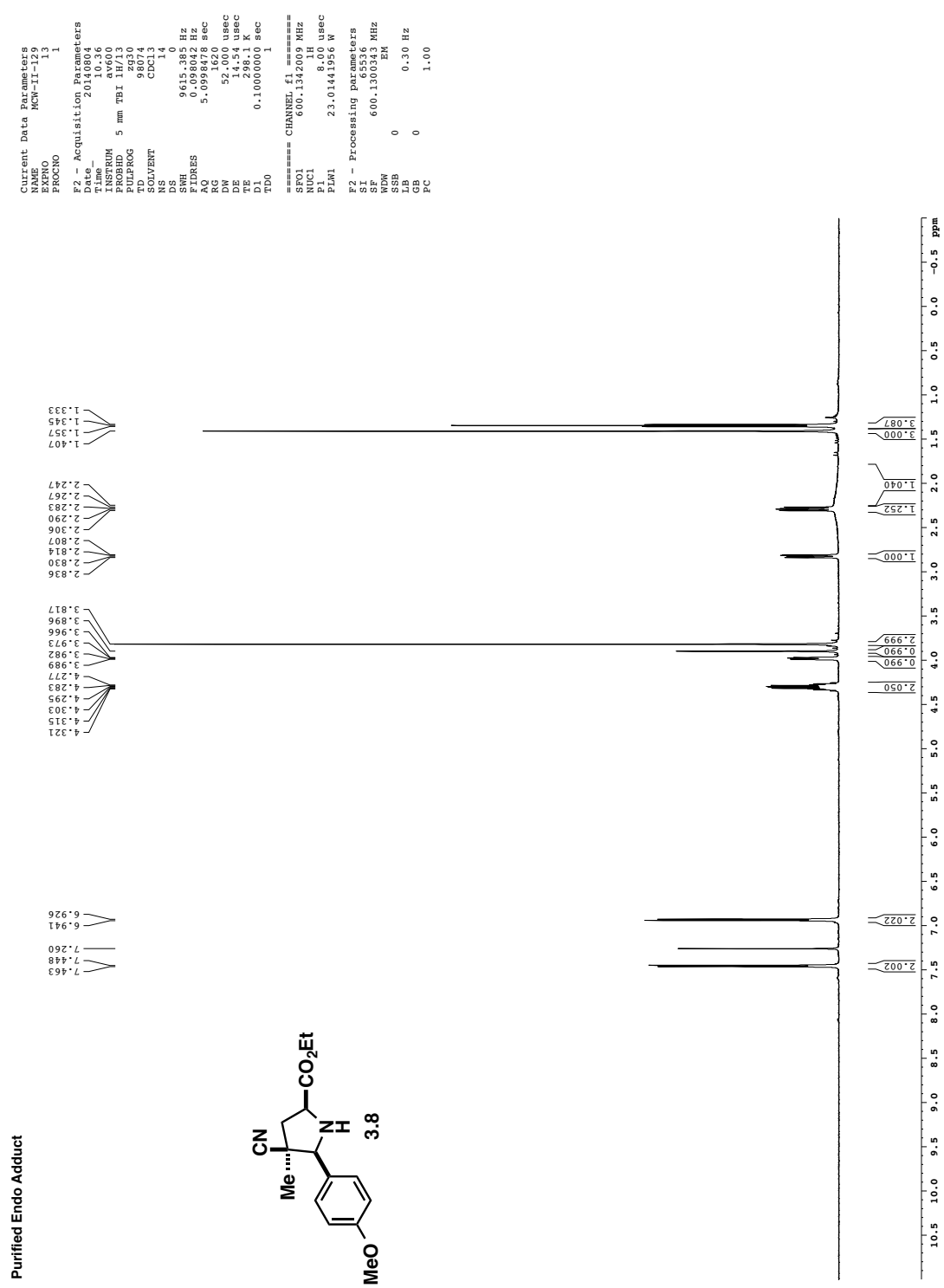
======== CHANNEL f1 ========
NUC1                      1H
P1                     7.50 usec
P2                    15.00 usec
PL1                    1.60 dB
SFO1           500.2225084 MHz

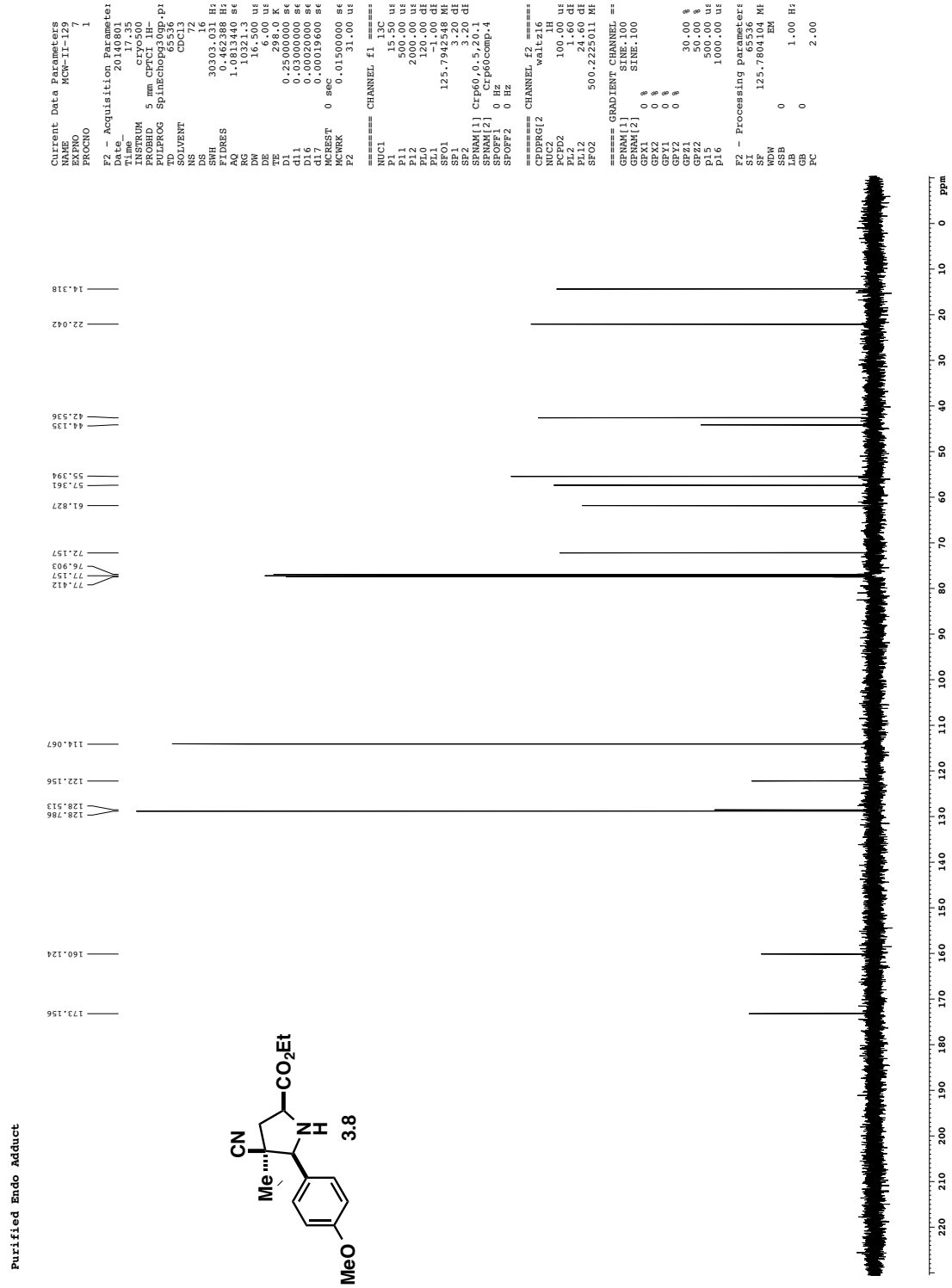
====== GRADIENT CHANNEL =====
GPNAM[1]             sine.100
GPNAM[2]             sine.100
GPX1          0 %
GPX2          0 %
GPY1          0 %
GPY2          0 %
GPZ1                  40.00 %
GPZ2                 -40.00 %
P16                1000.00 usec

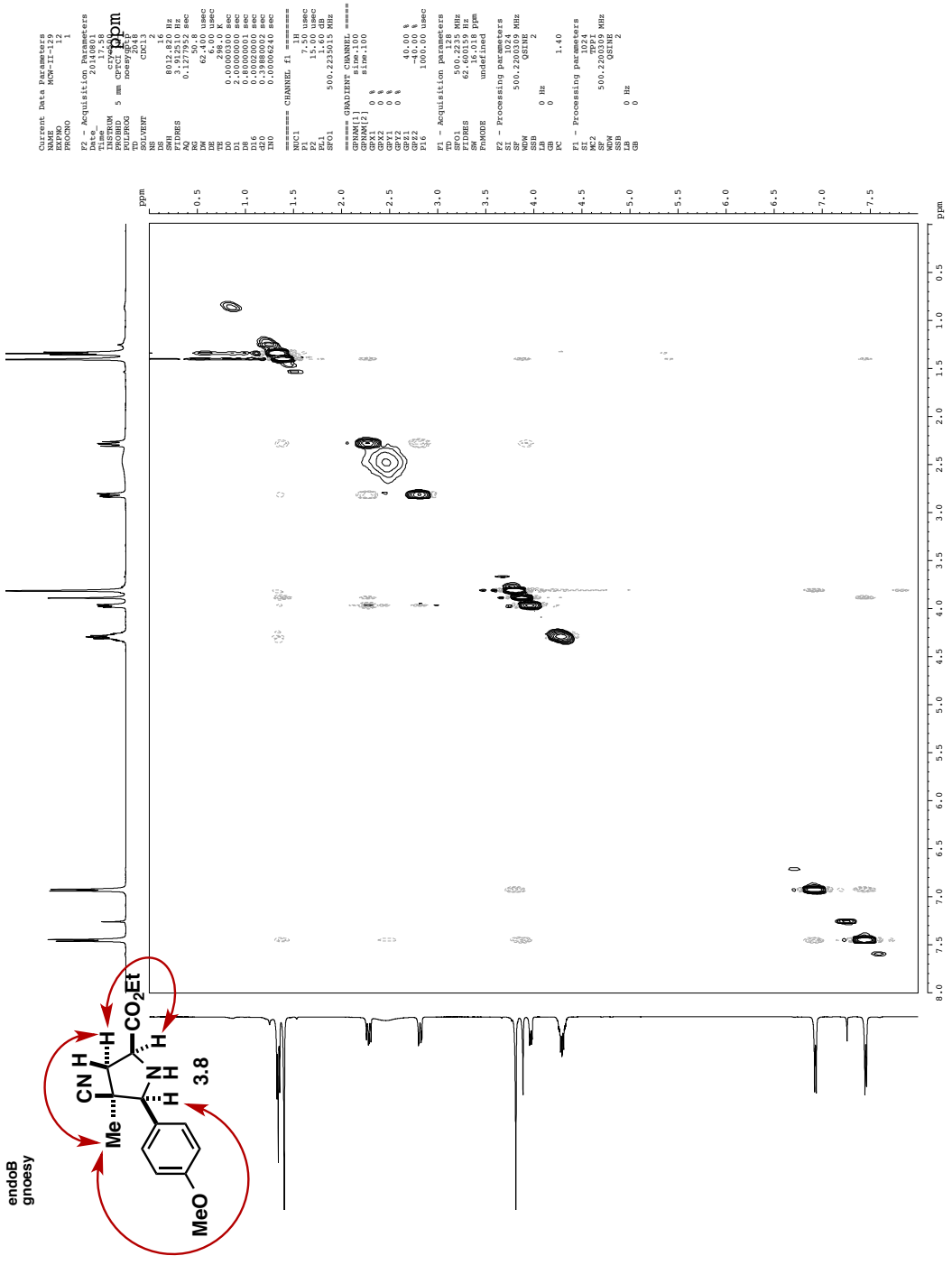
F1 - Acquisition parameters
TD                        360
SFO1               500.2225 MHz
FIDRES            13.888889 Hz
SW                     9.996 ppm
FnMODE            undefined

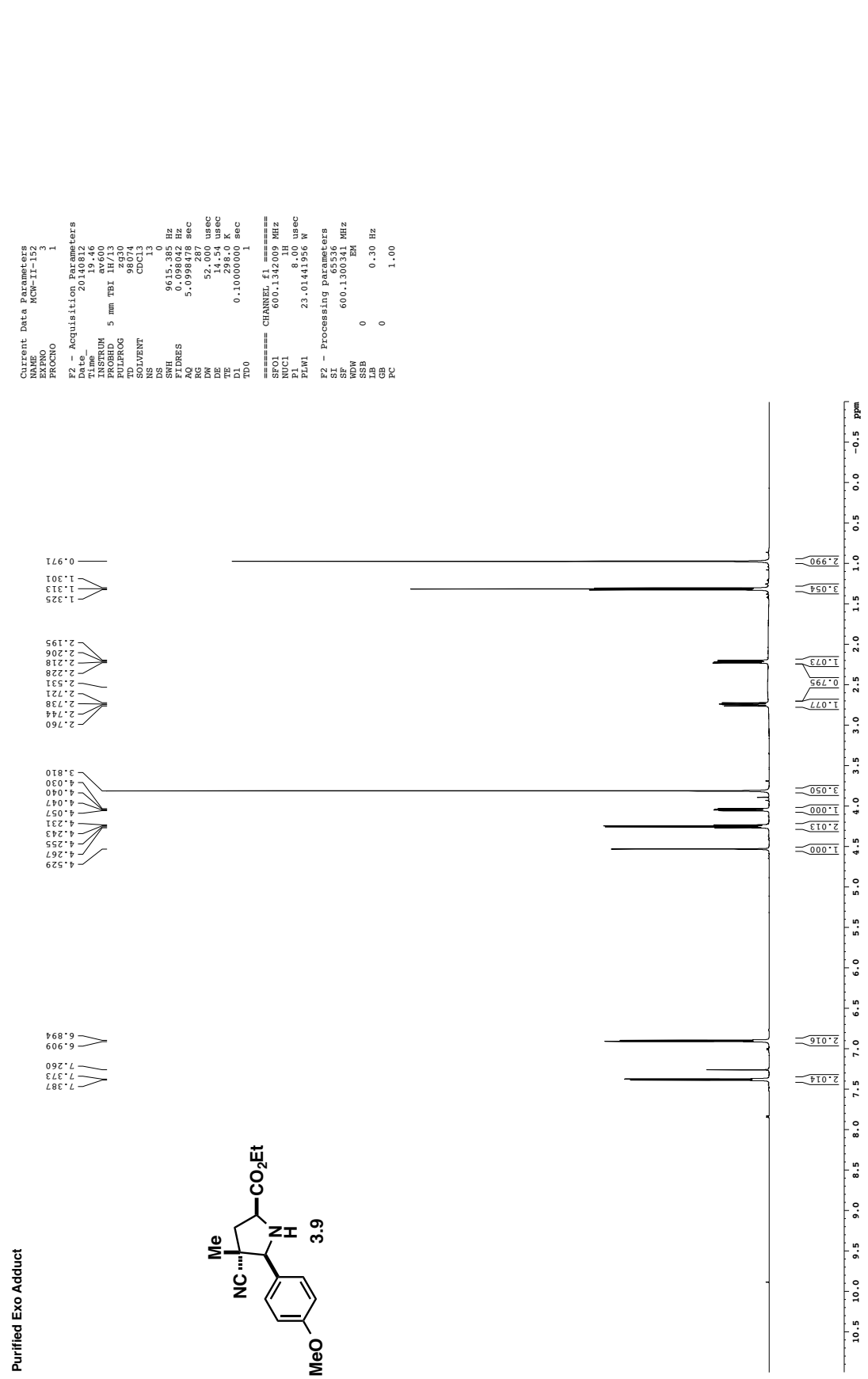
F2 - Processing parameters
SI                        1024
SF             500.2200340 MHz
WDW                     QSINE
SSB                        2
LB            0 Hz
GB            0
PC                     4.00

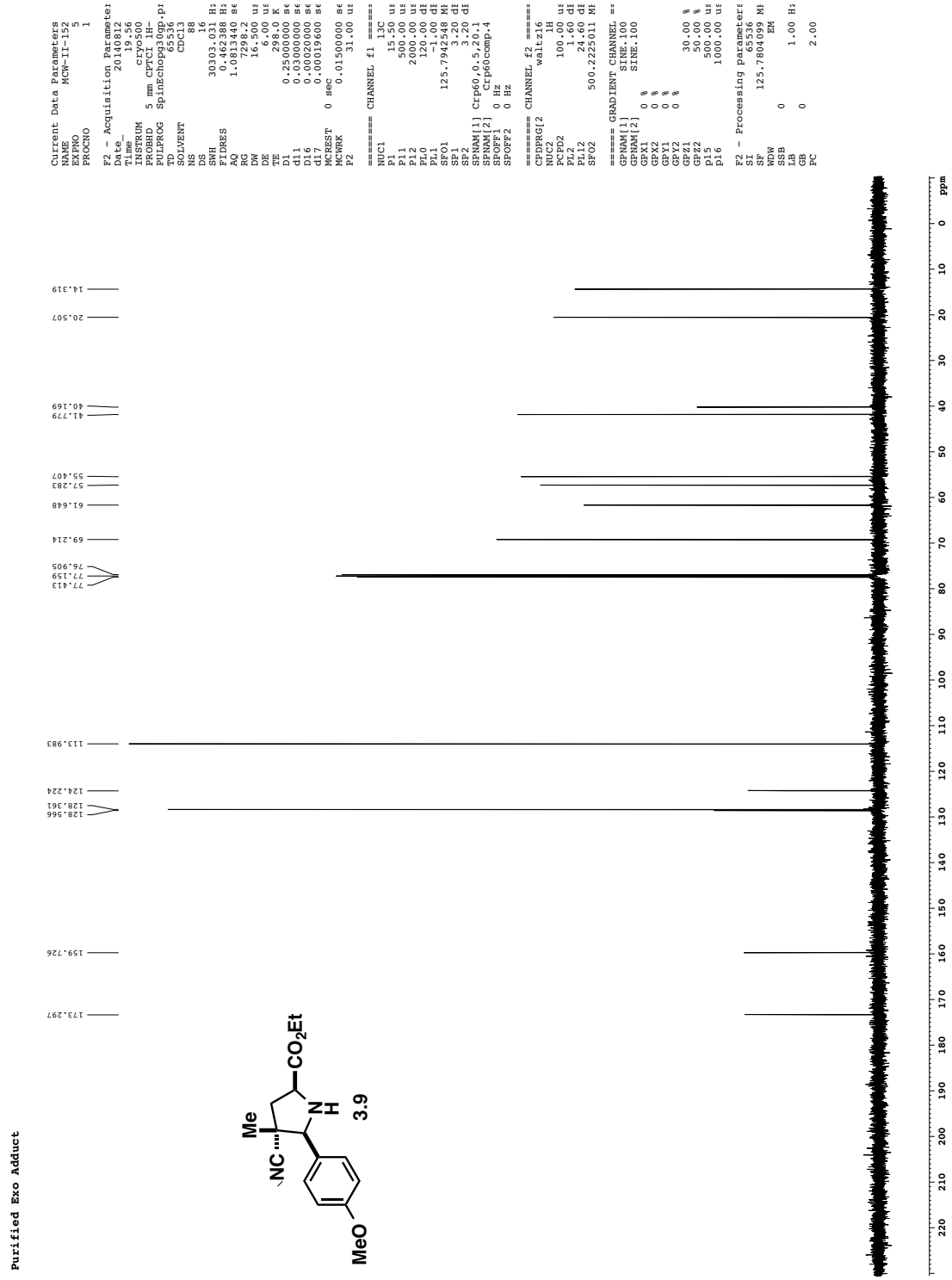
F1 - Processing parameters
SI                        1024
MC2                       TPPI
SF             500.2200340 MHz
WDW                     QSINE
SSB                        2
LB            0 Hz
GB            0
```

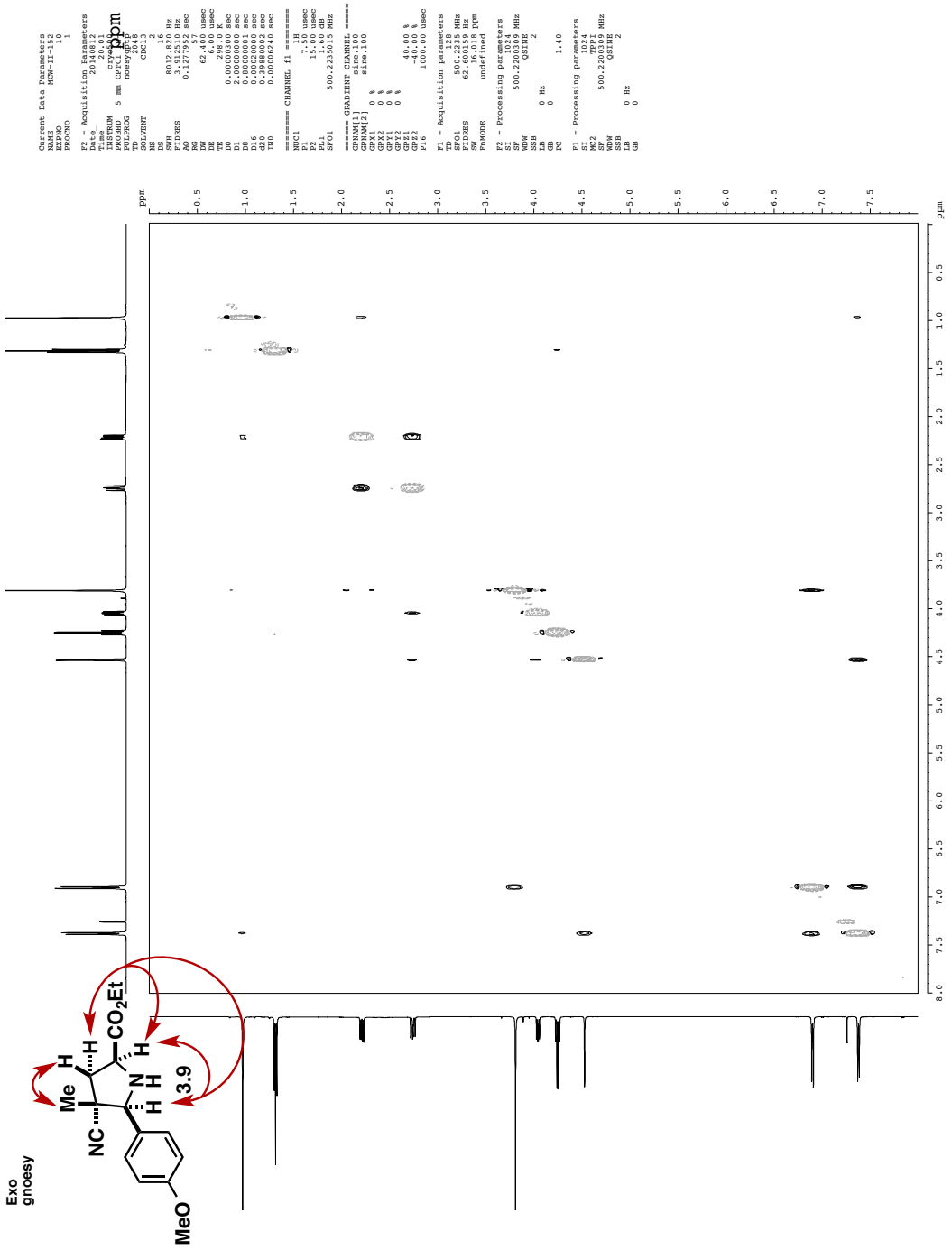

Purified Endo Adduct
Current Data Parameters
NAME MCW-II-129
EXPNO 13
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140804
Time 10.36
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98704
SOLVENT CDCl3
NS 14
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998478 sec
RG 160
DW 52.000 usec
DE 14.54 usec
TE 298.1 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300343 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.463
7.448
7.260
6.941
6.926
4.321
4.315
4.303
4.295
4.283
4.277
3.989
3.982
3.973
3.966
3.896
3.817
2.836
2.830
2.814
2.807
2.306
2.290
2.283
2.267
2.247
1.407
1.357
1.345
1.333
2.002
2.022
2.050
0.990
0.990
2.999
1.000
1.252
1.040
3.000
3.087
CN
Me
CO2Et
N
H
3.8
MeO
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
ppm

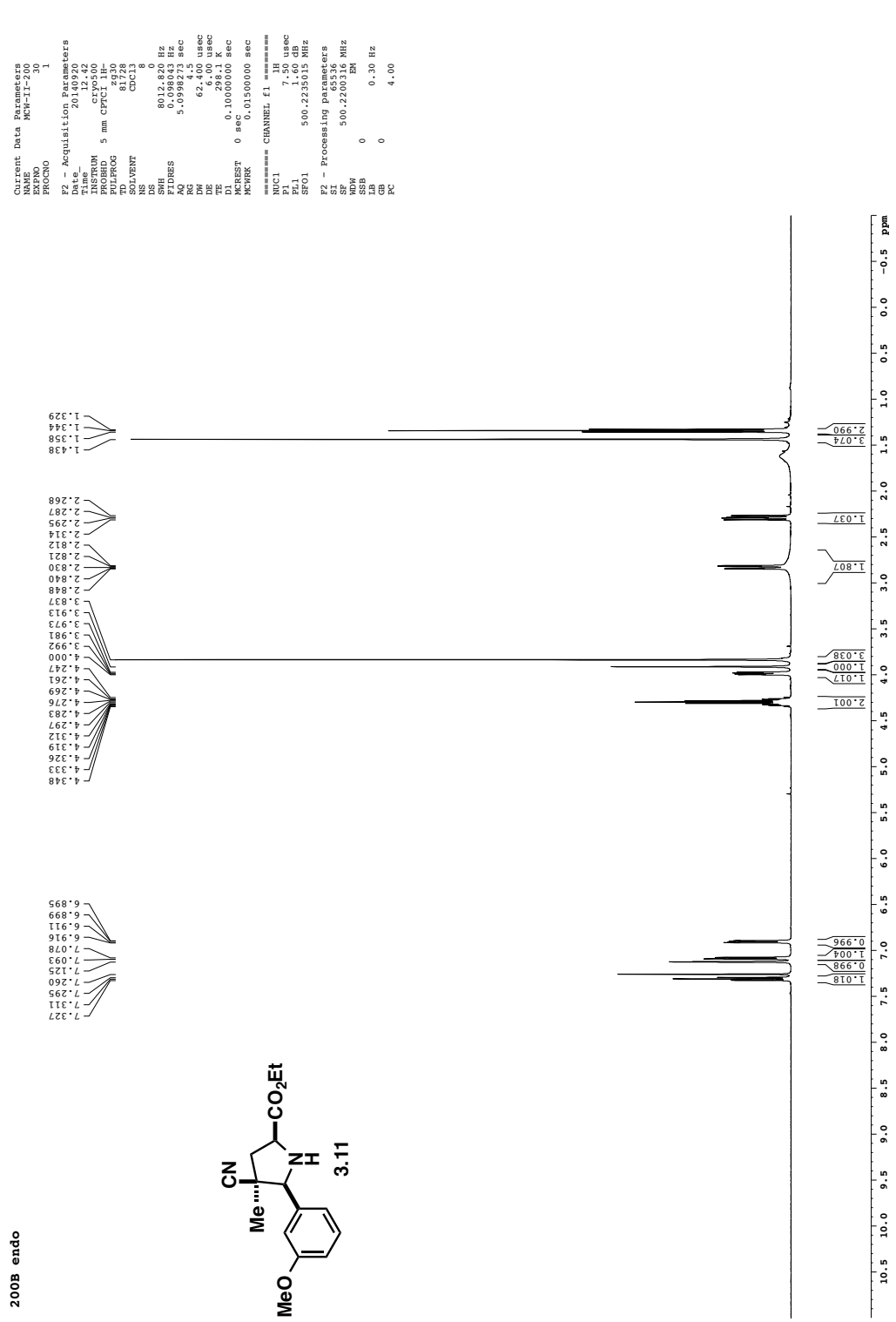

Purified Endo Adduct
Current Data Parameters
NAME MCW-II-129
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140801
Time 17.35
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchoPg3gp.p1
TD 65536
SOLVENT CDCl3
NS 72
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 1024.3
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCWREST 0 sec 0.01500000 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
PL1 500.00 usec
PL2 20000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804104 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
14.318
22.042
42.536
44.135
55.394
57.361
61.827
72.157
76.903
77.157
77.412
114.067
122.156
128.513
128.786
160.124
173.156
CN
Me
CO2Et
N
H
MeO
3.8
ppm


endoB
gnoesy
CN
H
Me
H
CO2Et
N
H
H
3.8
MeO
ppm

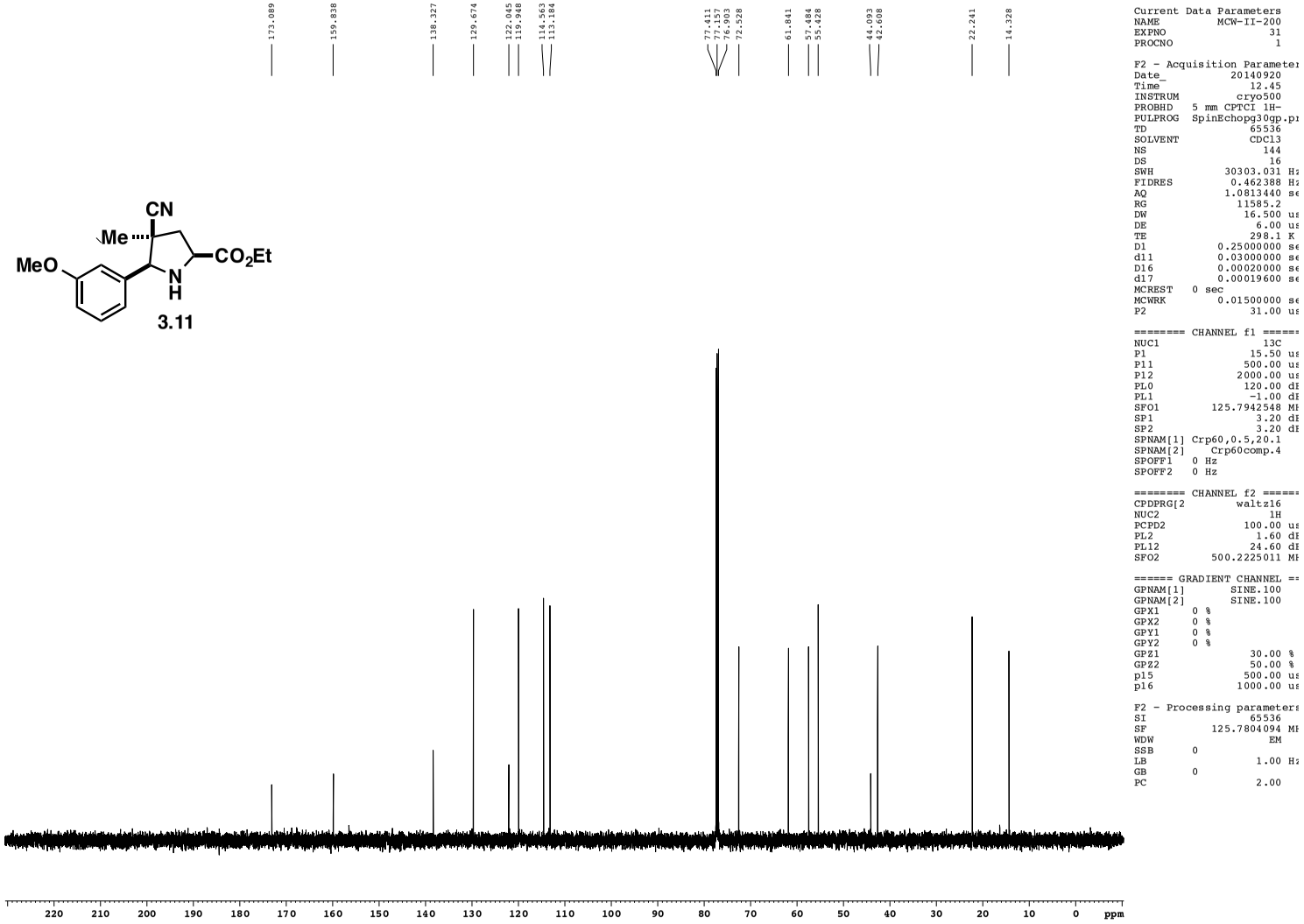

Purified Exo Adduct
Current Data Parameters
NAME MCW-II-152
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140812
Time 19.46
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 13
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998478 sec
RG 287
DW 52.000 usec
DE 14.54 usec
TE 298.0 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300341 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.971
1.301
1.313
1.325
2.195
2.206
2.218
2.228
2.531
2.721
2.738
2.744
2.760
3.810
4.030
4.040
4.047
4.057
4.231
4.243
4.255
4.267
4.529
6.894
6.909
7.260
7.373
7.387
2.990
3.054
1.073
0.795
1.077
3.050
1.000
2.013
1.000
2.016
2.014
Me
NC
CO2Et
N
H
MeO
3.9
ppm


Purified Exo Adduct
Me
NC
CO2Et
N
H
MeO
3.9
14.319
20.507
41.779
40.169
55.407
57.283
61.648
69.214
77.413
77.159
76.905
113.983
124.224
128.566
128.361
159.726
173.297
ppm


Exo
gnoesy
Me
H
NC
H
CO2Et
N
H
H
H
3.9
MeO
ppm


200B endo
Current Data Parameters
NAME MEW-II-200
EXPNO 30
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140930
Time 12.42
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 0
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 298.1 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200015 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1.438
1.358
1.344
1.329
2.990
3.074
2.868
2.287
2.295
2.314
2.812
2.821
2.830
2.840
2.848
1.037
1.807
3.837
3.913
3.973
3.981
3.992
4.000
4.247
4.261
4.269
4.276
4.283
4.297
4.312
4.319
4.326
4.333
4.348
3.038
1.000
1.017
2.001
7.327
7.311
7.295
7.260
7.125
7.078
7.093
6.916
6.911
6.899
6.895
1.018
0.998
1.004
0.996
CN
Me
CO2Et
N
H
MeO
3.11
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 ppm

200B endo




```
Current Data Parameters
NAME          MCW-II-200
EXPNO                 31
PROCNO                 1

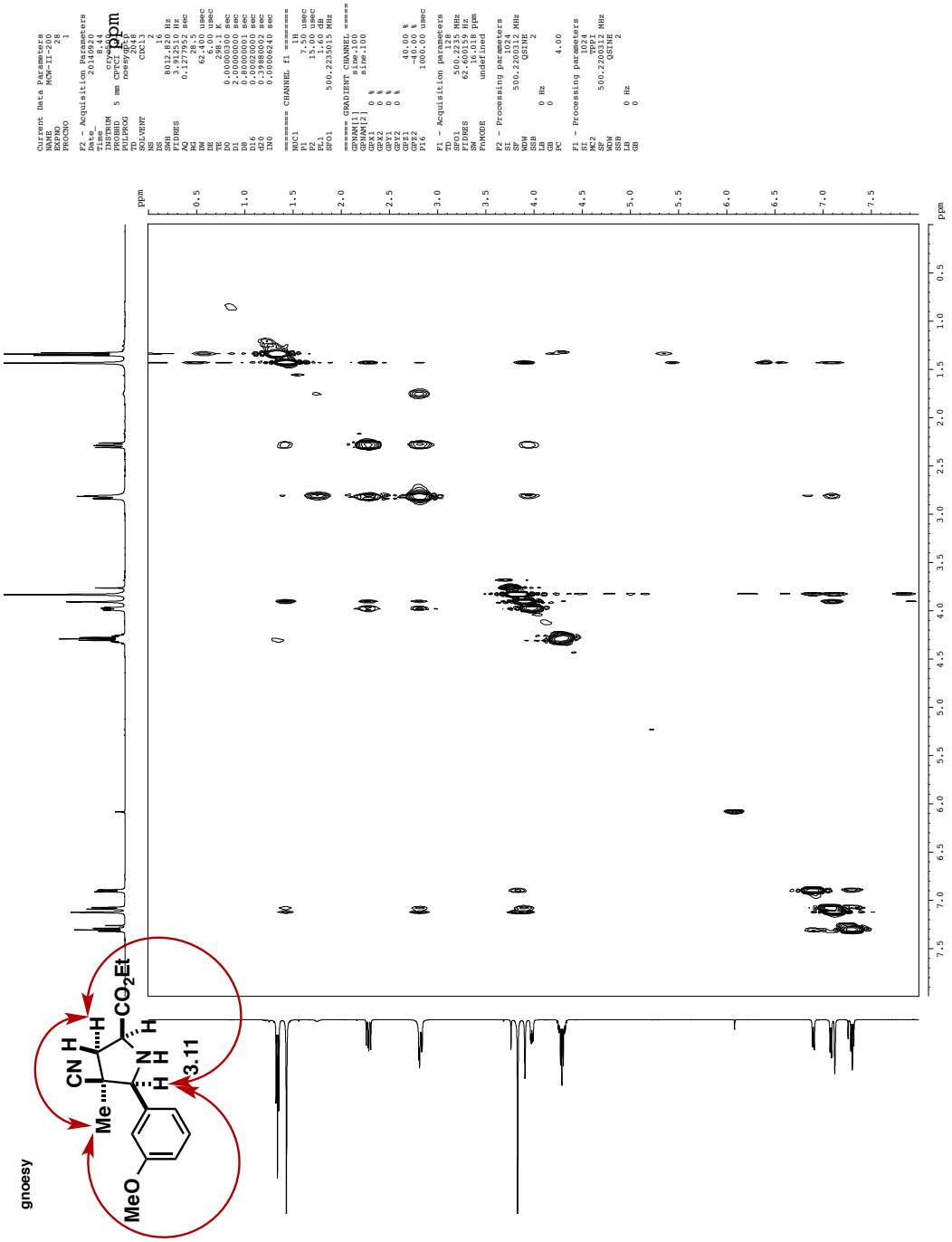
F2 - Acquisition Parameter
Date_           20140920
Time               12.45
INSTRUM          cryo500
PROBHD  5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.pr
TD                 65536
SOLVENT             CDCl3
NS                   144
DS                    16
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ            1.0813440 se
RG             11585.2
DW                16.500 us
DE                 6.00 us
TE                298.1 K
D1            0.25000000 se
d11           0.03000000 se
D16           0.00020000 se
d17           0.00019600 se
MCREST   0 sec
MCWRK         0.01500000 se
P2                31.00 us

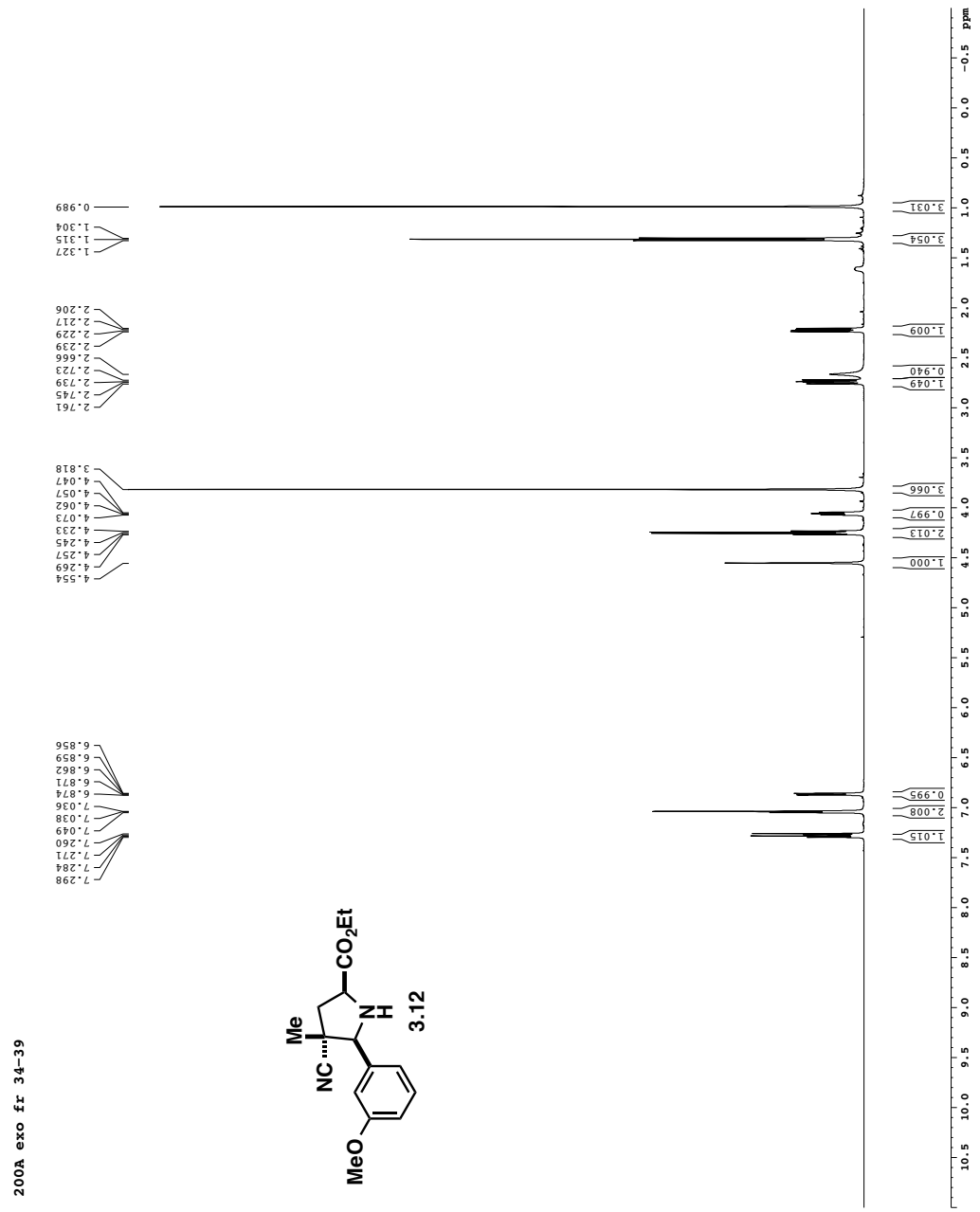
======== CHANNEL f1 ======
NUC1                13C
P1                15.50 us
P11              500.00 us
P12             2000.00 us
PL0              120.00 dB
PL1               -1.00 dB
SFO1        125.7942548 MH
SP1               3.20 dB
SP2               3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1   0 Hz
SPOFF2   0 Hz

======== CHANNEL f2 ======
CPDPRG[2         waltz16
NUC2                1H
PCPD2             100.00 us
PL2               1.60 dB
PL12              24.60 dB
SFO2        500.2225011 MH

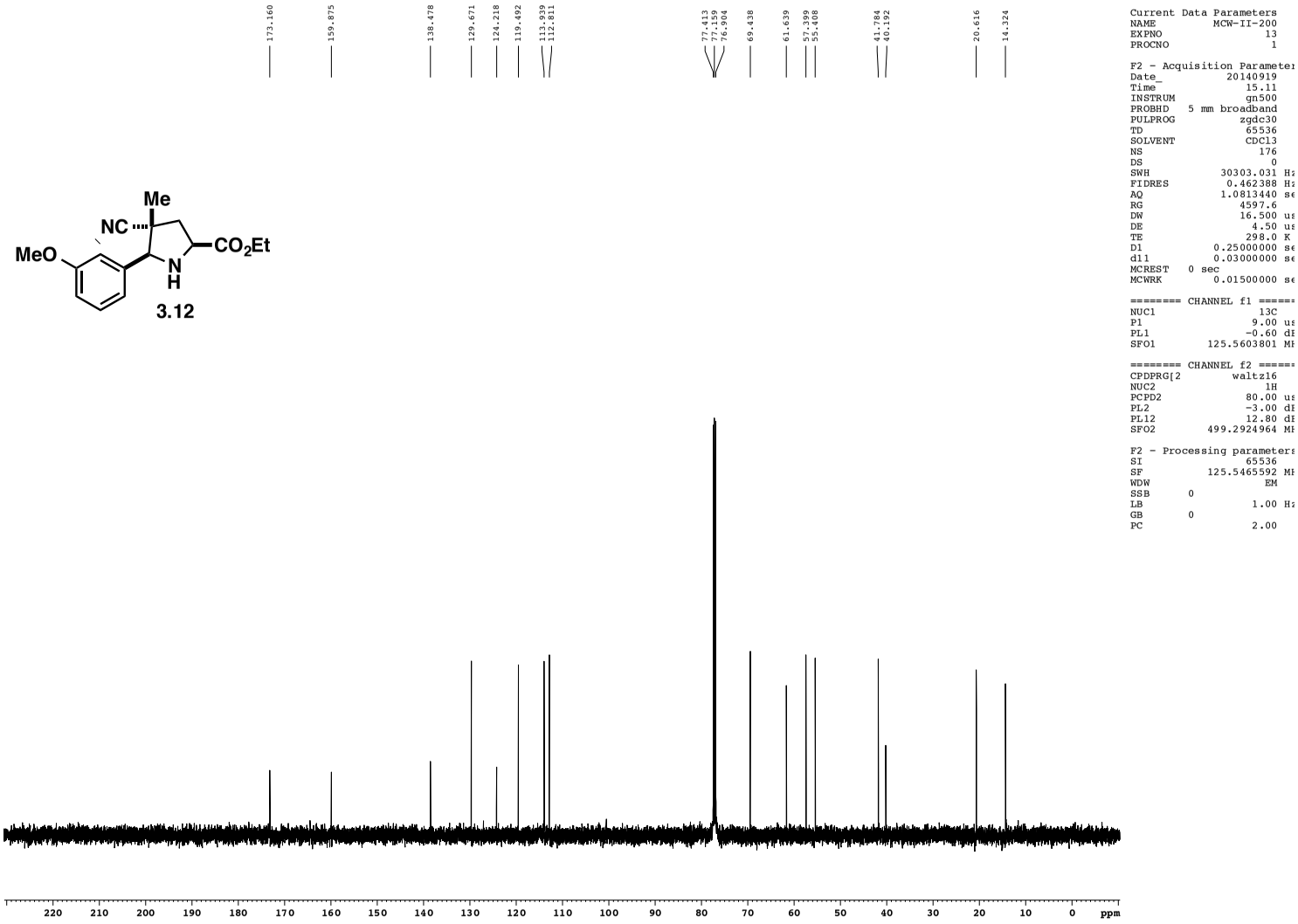
====== GRADIENT CHANNEL ==
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 us
p16             1000.00 us

F2 - Processing parameters
SI                 65536
SF          125.7804094 MH
WDW                   EM
SSB      0
LB                1.00 Hz
GB       0
PC                2.00
```


gnoesy
CN H
CO2Et
Me
N H
H
3.11
MeO
ppm


200A exo fr 34-39
Current Data Parameters
NAME MEW-II-200
EXPNO 12
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140919
Time 15.04
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 11
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.09988478 sec
RG 181
DW 52.000 usec
DE 14.54 usec
TE 298.1 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300341 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Me
NC
CO2Et
N
H
MeO
3.12
7.298
7.284
7.271
7.260
7.049
7.038
7.036
6.874
6.871
6.862
6.859
6.856
4.554
4.269
4.257
4.245
4.233
4.073
4.062
4.057
4.047
3.818
2.761
2.745
2.739
2.723
2.666
2.239
2.229
2.217
2.206
1.327
1.315
1.304
0.989
1.015
2.008
0.995
1.000
2.013
0.997
3.066
1.049
0.940
1.009
3.054
3.031
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
ppm

200A exo fr 34-39



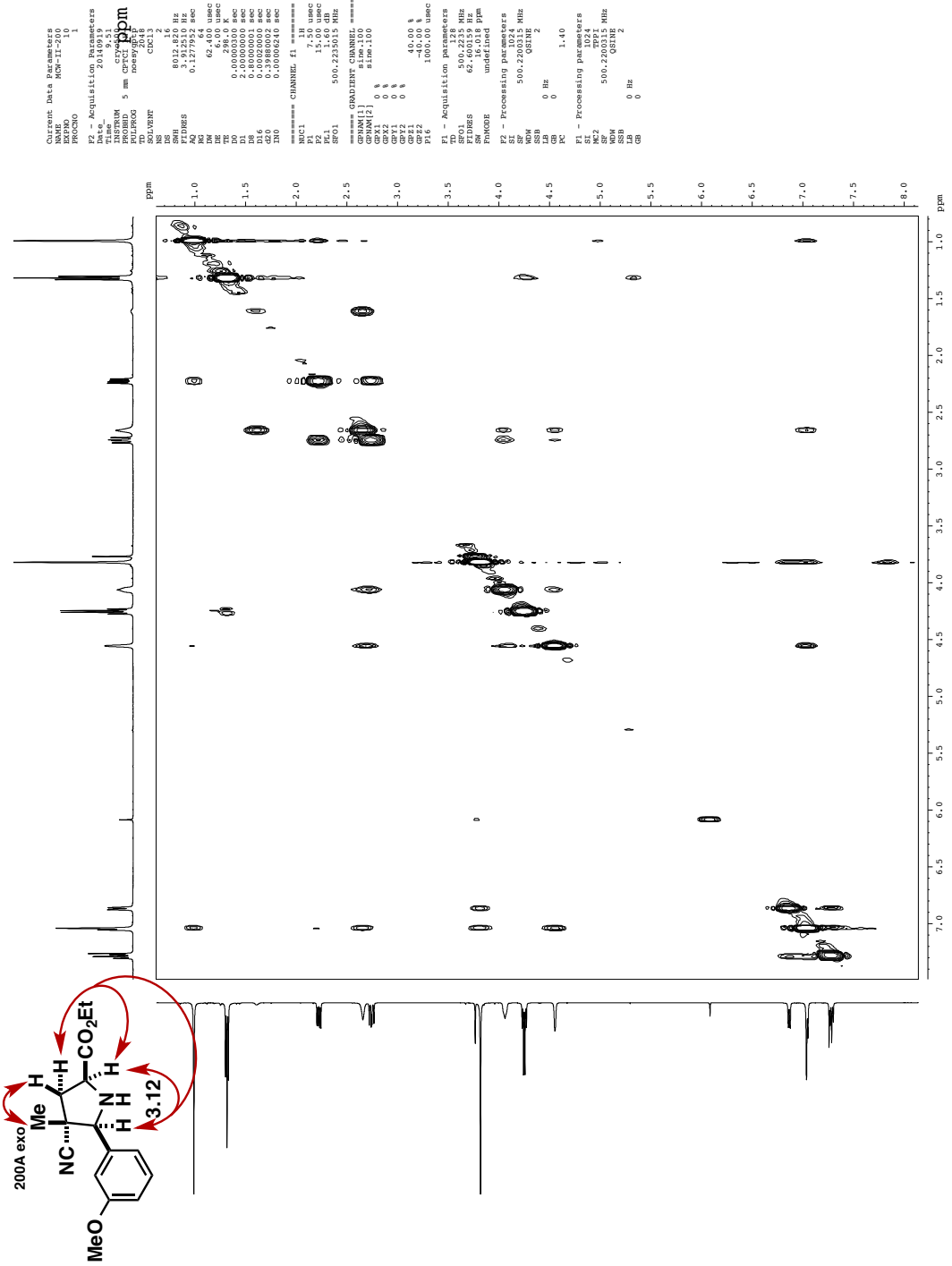

```
Current Data Parameters
NAME          MCW-II-200
EXPNO                 13
PROCNO                 1

F2 - Acquisition Parameter
Date_           20140919
Time               15.11
INSTRUM            gn500
PROBHD  5 mm broadband
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3
NS                  176
DS                    0
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ            1.0813440 se
RG               4597.6
DW                16.500 us
DE                 4.50 us
TE                298.0 K
D1           0.25000000 se
d11          0.03000000 se
MCREST   0 sec
MCWRK        0.01500000 se

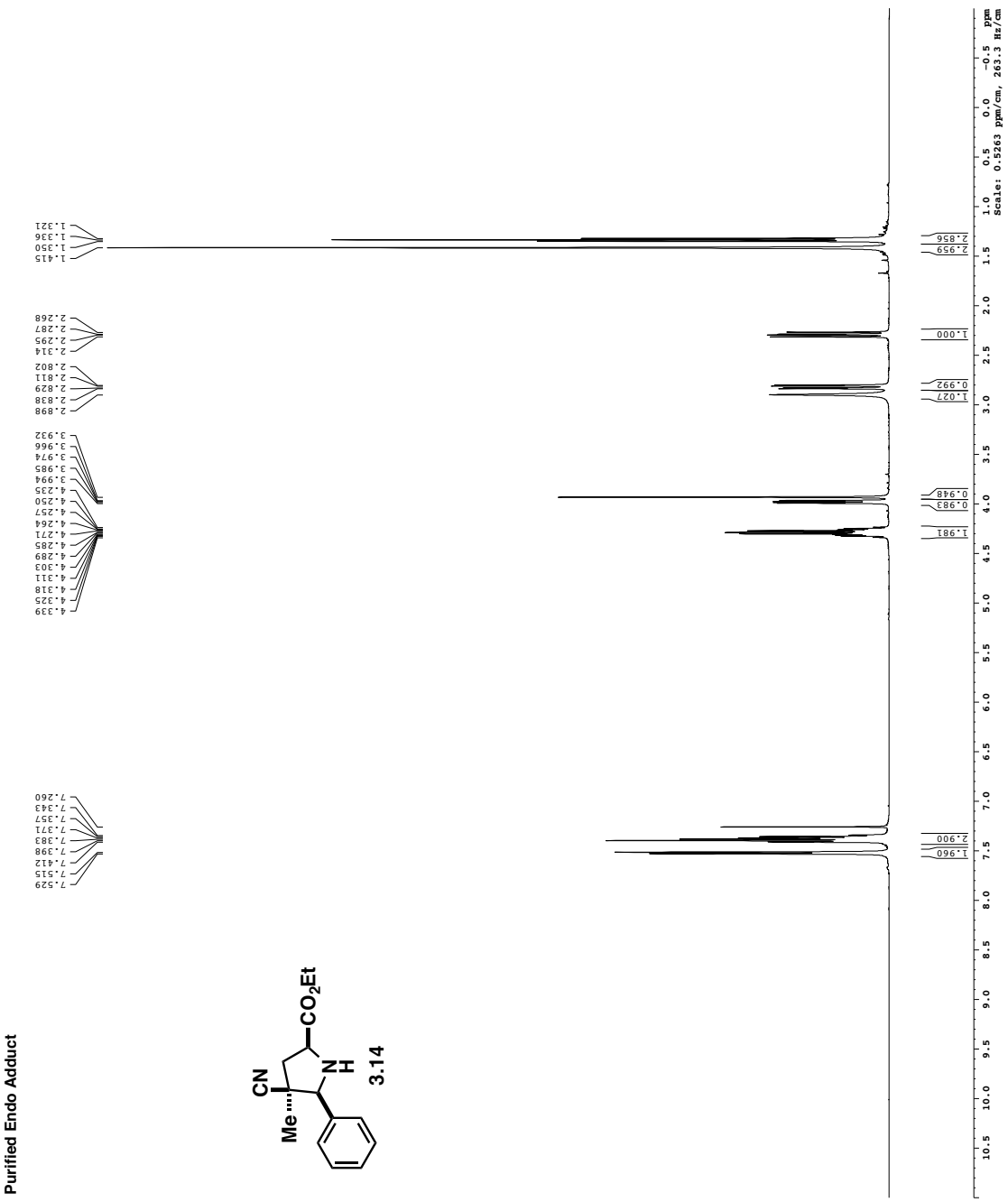
======== CHANNEL f1 ======
NUC1                13C
P1                 9.00 us
PL1               -0.60 dB
SFO1        125.5603801 MH

======== CHANNEL f2 ======
CPDPRG[2         waltz16
NUC2                1H
PCPD2              80.00 us
PL2                -3.00 dB
PL12               12.80 dB
SFO2        499.2924964 MH

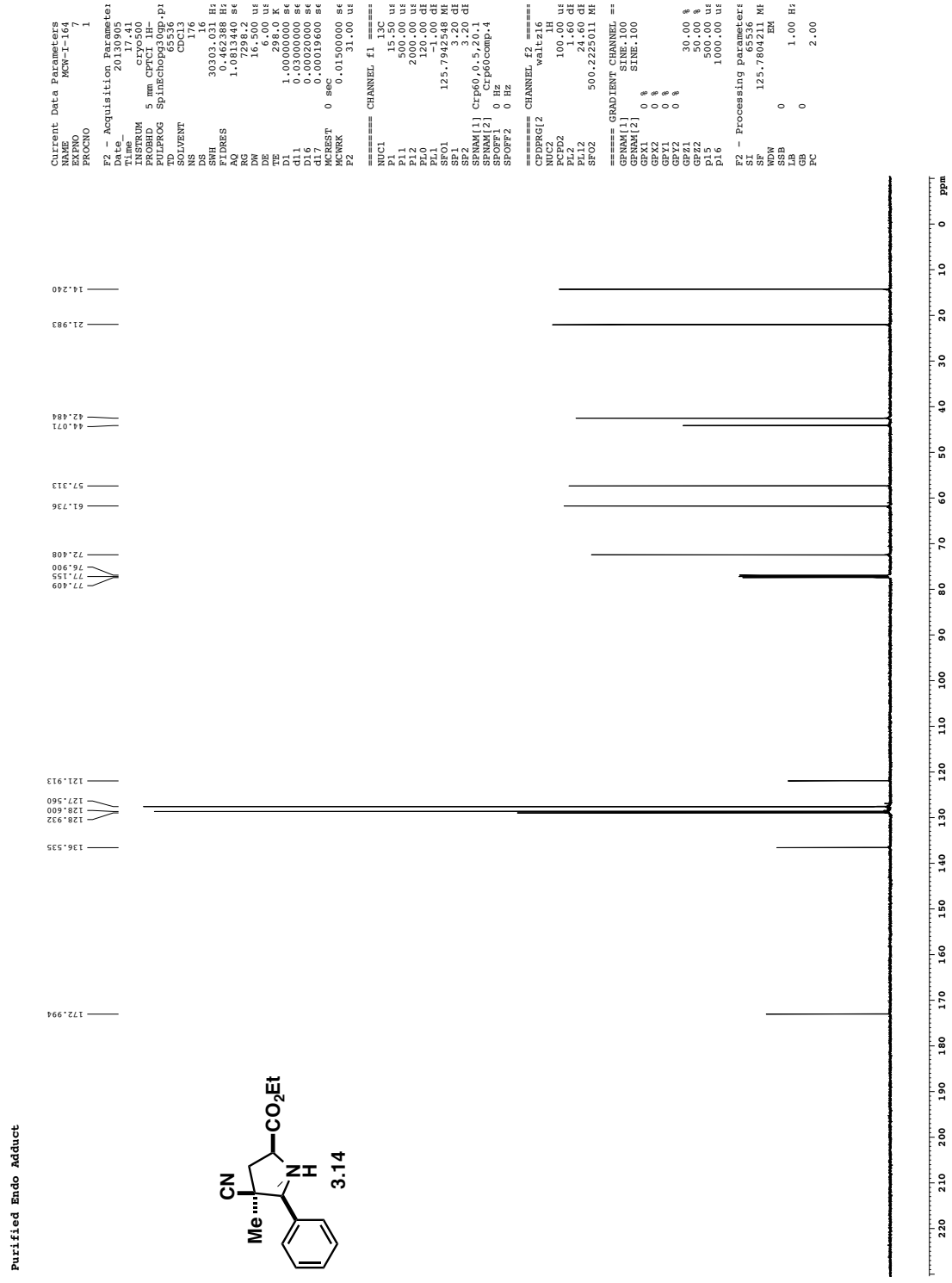
F2 - Processing parameters
SI                 65536
SF          125.5465592 MH
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 2.00
```


200A exo
Me
H
NC
CO2Et
H
N
H
H
3.12
MeO
ppm
ppm

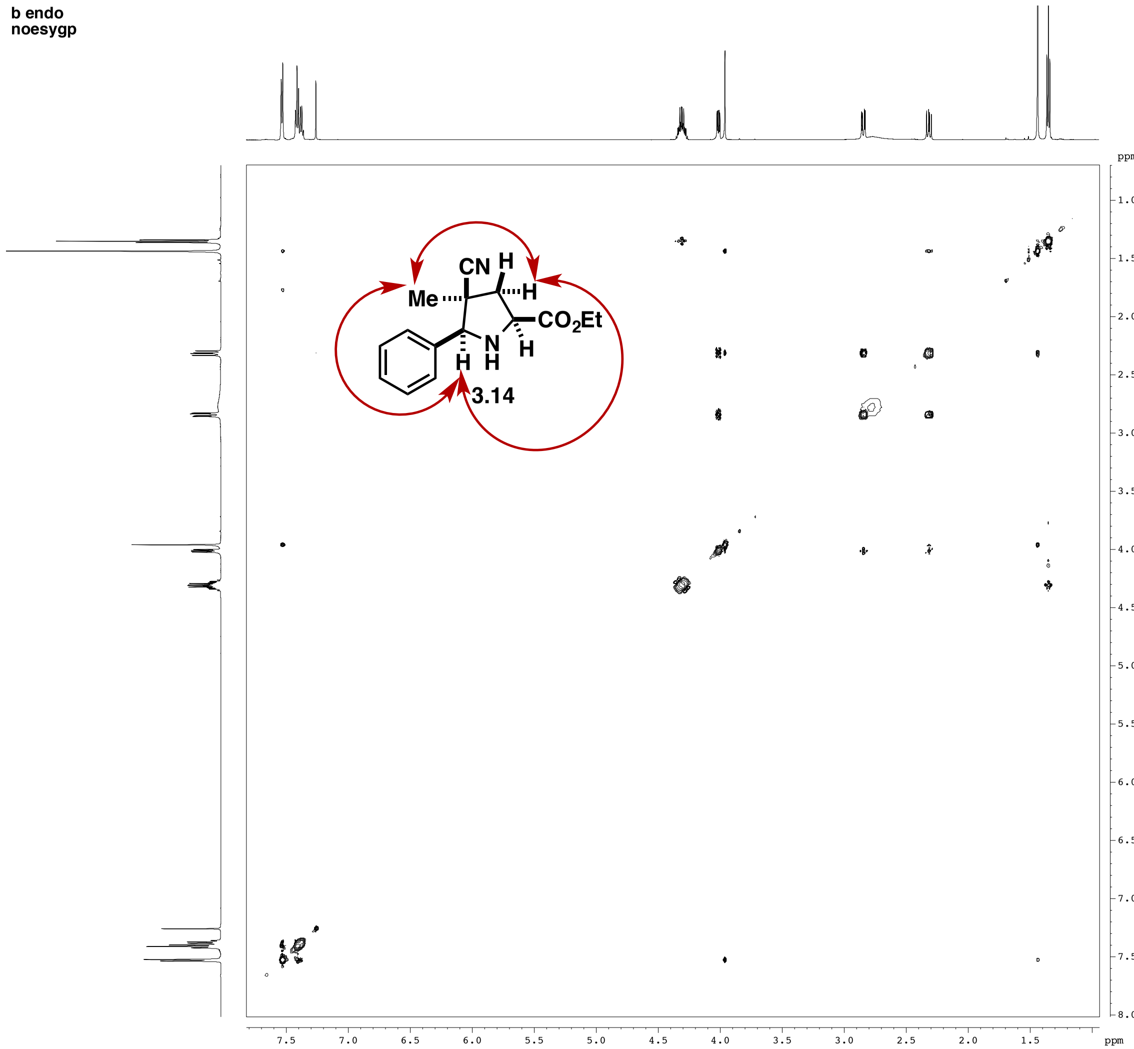
Purified Endo Adduct



3.14


Purified Endo Adduct
CN
Me
CO2Et
N
H
3.14
172.994
136.535
128.932
128.600
127.560
121.913
77.409
77.155
76.900
72.408
61.736
57.313
44.071
42.484
21.983
14.240
ppm

b endo
noesygp




```
Current Data Parameters
NAME          MCW-I-164
EXPNO                 9
PROCNO                1

F2 - Acquisition Parameters
Date_          20130914
Time              13.02
INSTRUM           av600
PROBHD   5 mm TBI 1H/
PULPROG       noesygpph
TD                 2048
SOLVENT           CDCl3
NS                    2
DS                   16
SWH            6002.401 Hz
FIDRES         2.930860 Hz
AQ            0.1705984 sec
RG                  912
DW               83.300 usec
DE                10.74 usec
TE                298.1 K
D0           0.00007311 sec
D1           2.00000000 sec
D8           1.00000000 sec
D16          0.00020000 sec
IN0          0.00016660 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 8.00 usec
P2                16.00 usec
PLW1        23.01441956 W
SFO1        600.1324005 MHz

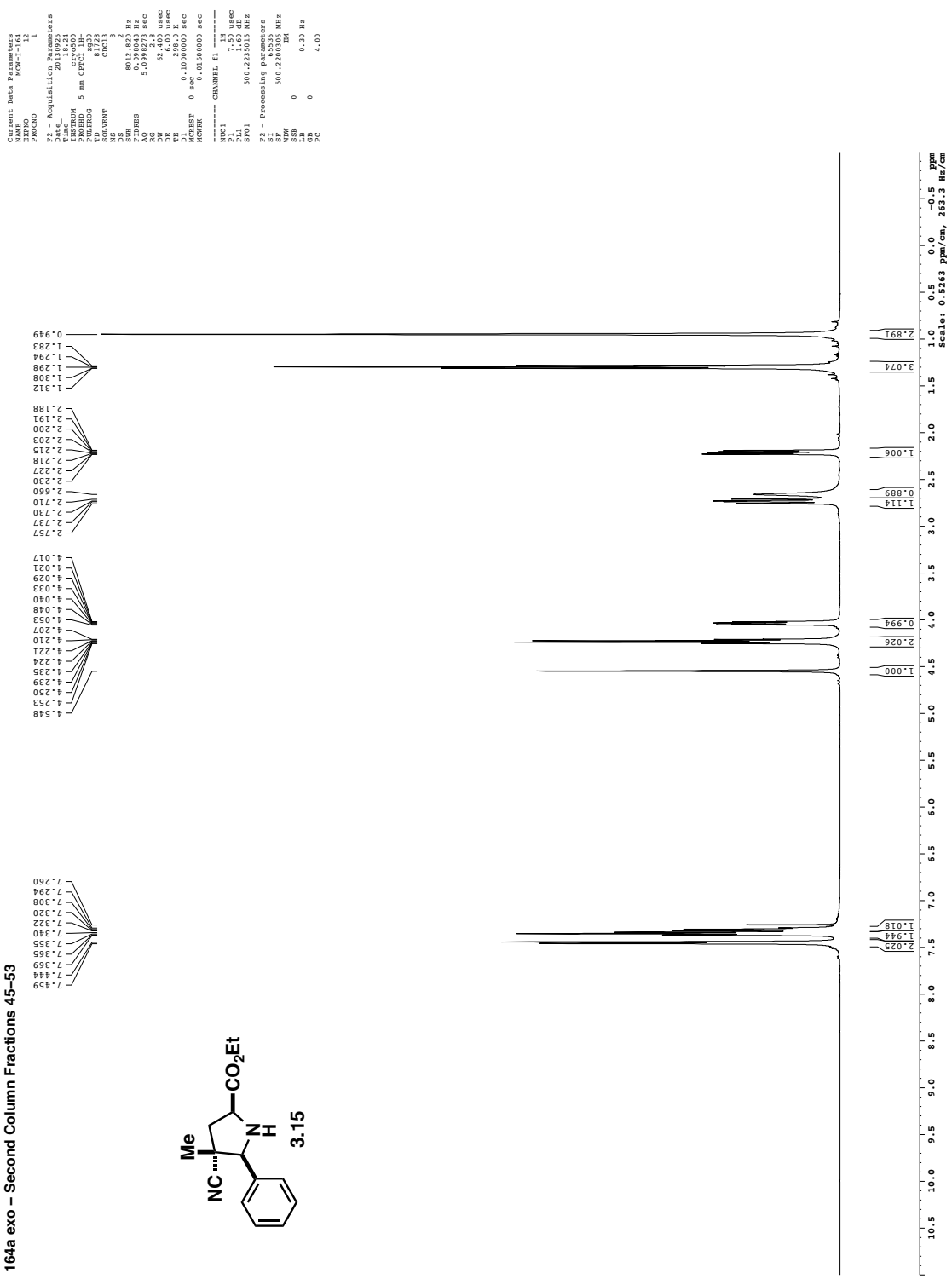
====== GRADIENT CHANNEL =====
GPNAM[1]       SINE.100
GPZ1              40.00 %
P16             1000.00 usec

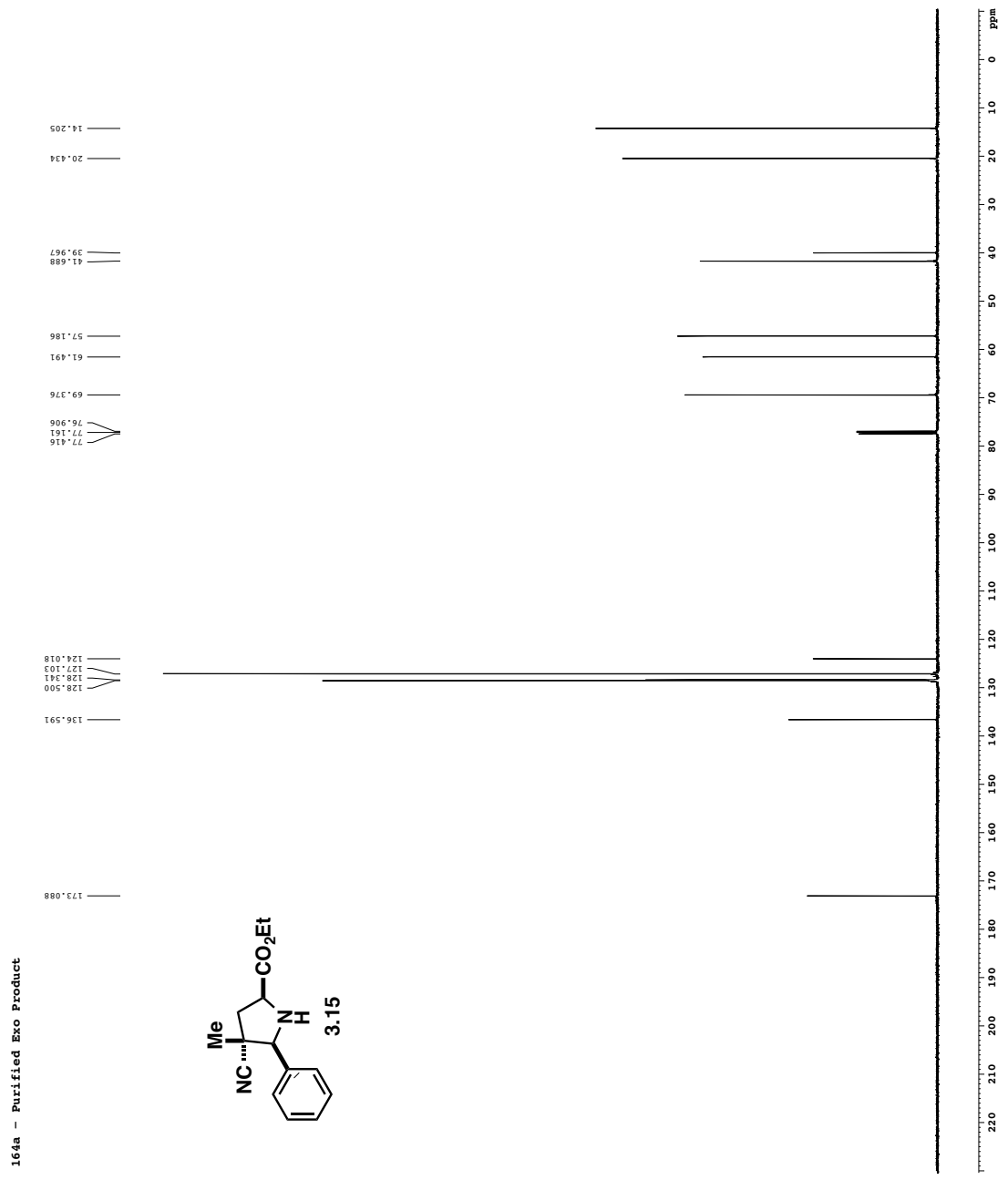
F1 - Acquisition parameters
TD                  512
SFO1           600.1324 MHz
FIDRES        11.723439 Hz
SW               10.002 ppm
FnMODE      States-TPPI

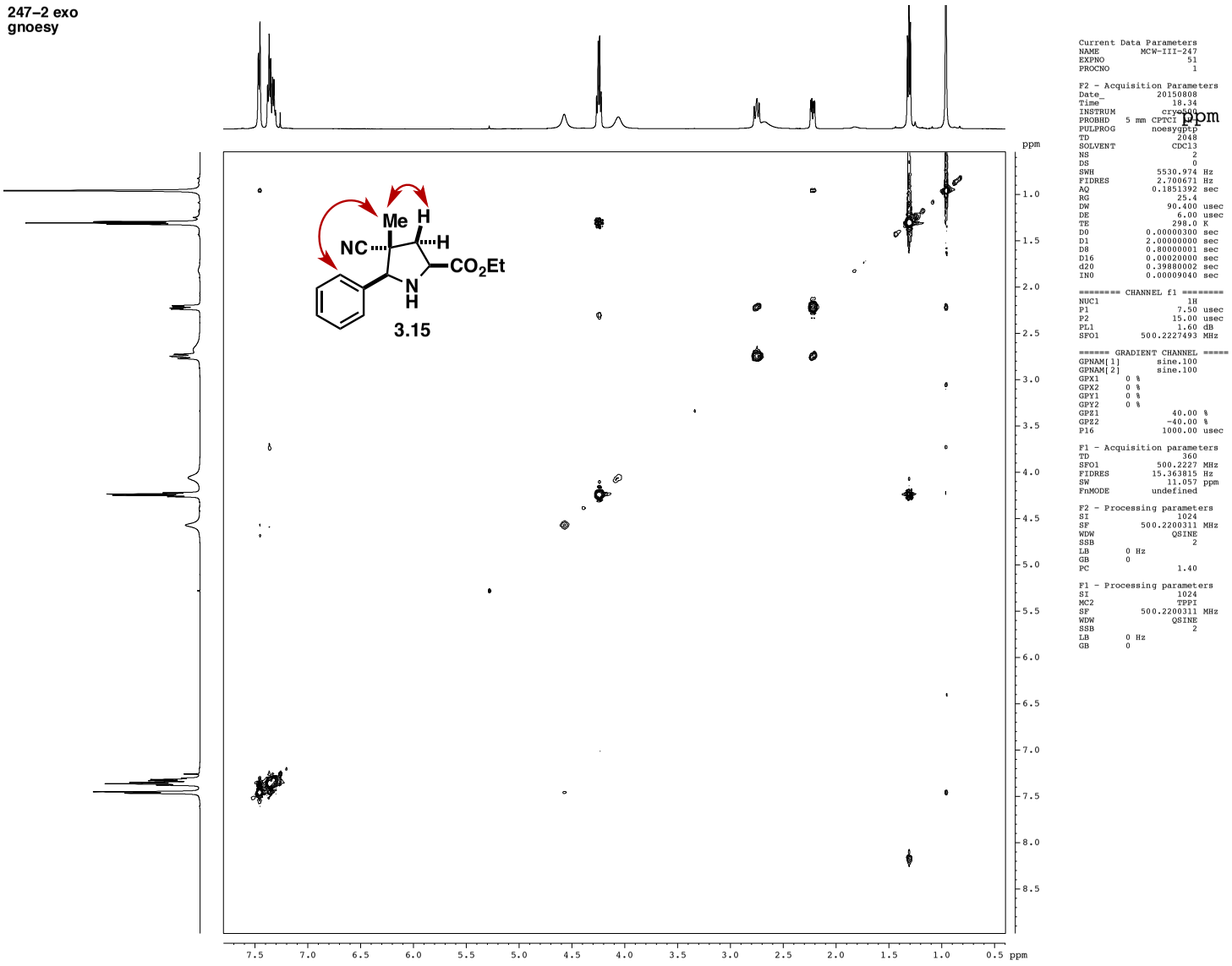
F2 - Processing parameters
SI                 1024
SF          600.1300350 MHz
WDW               QSINE
SSB                   2
LB                    0 Hz
GB                    0
PC                 1.00

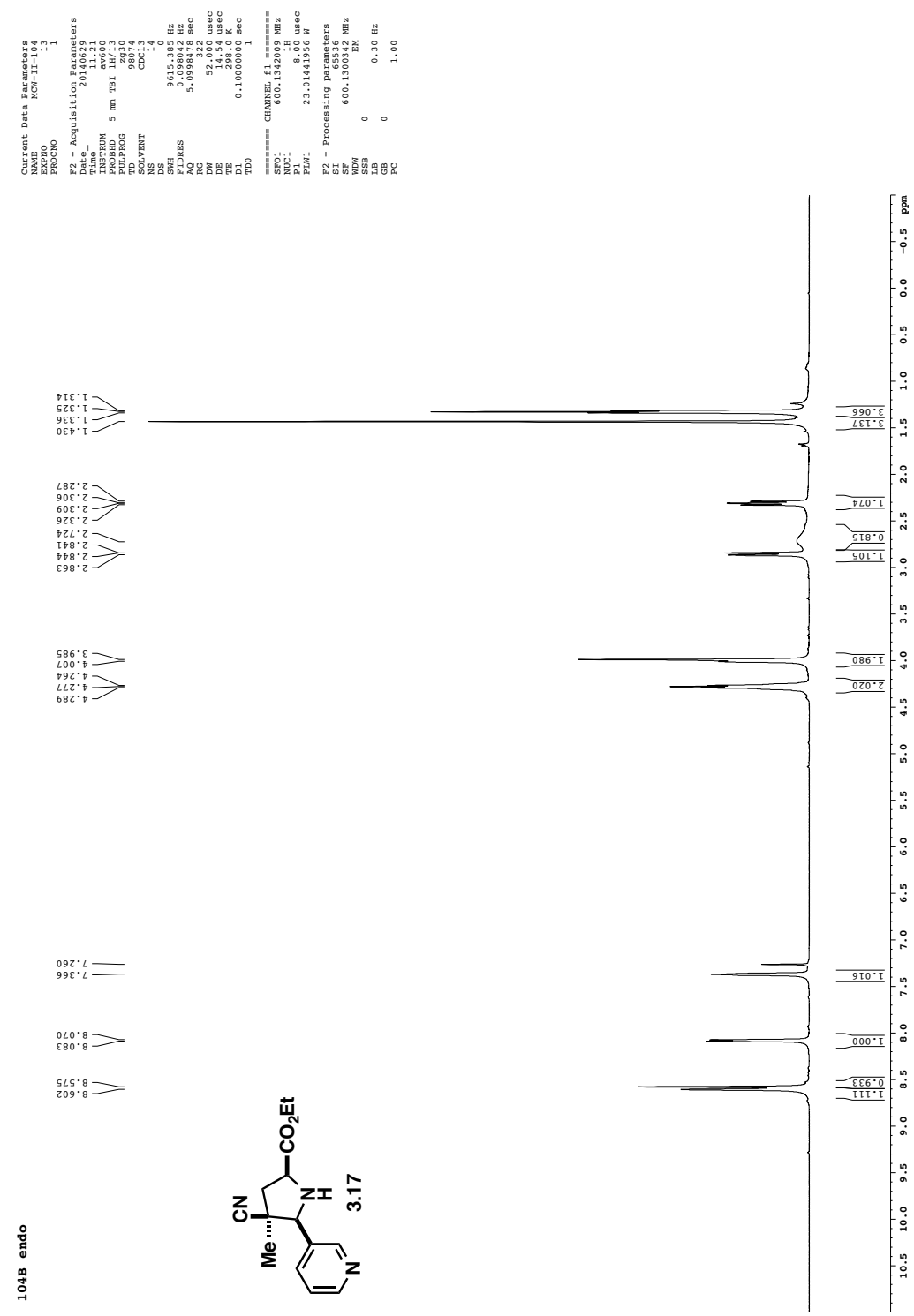
F1 - Processing parameters
SI                 1024
MC2         States-TPPI
SF          600.1300350 MHz
WDW               QSINE
SSB                   2
LB                    0 Hz
GB                    0
```

164a exo – Second Column Fractions 45–53

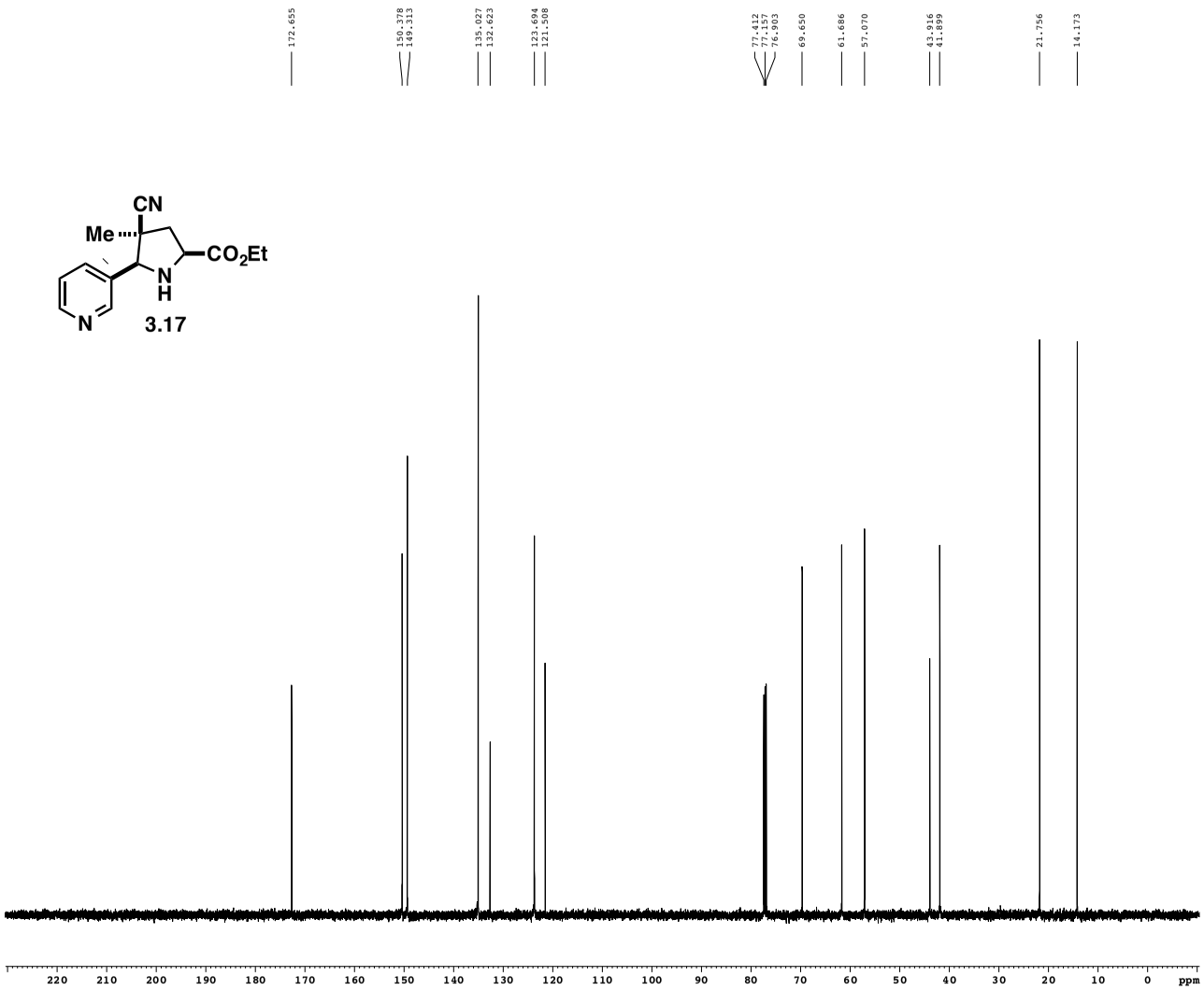



164a – Purified Exo Product
Me
NC
CO2Et
N
H
3.15
173.088
136.591
128.500
128.341
127.103
124.018
77.416
77.161
76.906
69.376
61.491
57.186
41.688
39.967
20.434
14.205
ppm


247–2 exo
gnoesy
Me
H
NC
H
CO2Et
N
H
3.15
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
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 ppm
f1 ppm
Current Data Parameters
NAME MCW-III-247
EXPNO 51
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150808
Time 18.34
INSTRUM cryo600
PROBHD 5 mm CPTCI 1H-
PULPROG noesygptp
TD 2048
SOLVENT CDCl3
NS 2
DS 0
SWH 5530.974 Hz
FIDRES 2.700671 Hz
AQ 0.1851392 sec
RG 25.4
DW 90.400 usec
DE 6.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D8 0.80000001 sec
D16 0.00020000 sec
d20 0.39880002 sec
IN0 0.00009040 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
P2 15.00 usec
PL1 1.60 dB
SFO1 500.2227493 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] sine.100
GPNAM[2] sine.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 40.00 %
GPZ2 -40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 360
SFO1 500.2227 MHz
FIDRES 15.363815 Hz
SW 11.057 ppm
FnMODE undefined
F2 - Processing parameters
SI 1024
SF 500.2200311 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1024
MC2 TPPI
SF 500.2200311 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0


104B endo
Current Data Parameters
NAME 104
EXPNO 13
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140629
Time 11.21
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 14
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998478 sec
RG 322
DW 52.000 usec
DE 14.54 usec
TE 298.0 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300342 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.602
8.575
8.083
8.070
7.366
7.260
4.289
4.277
4.264
4.007
3.985
2.863
2.844
2.841
2.724
2.326
2.309
2.306
2.287
1.430
1.336
1.325
1.314
1.111
0.933
1.000
1.016
2.020
1.980
1.105
0.815
1.074
3.137
3.066
CN
Me
CO2Et
N
H
N
3.17
ppm

Endo Adduct




```
Current Data Parameters
NAME          MCW-II-104
EXPNO                  6
PROCNO                 1

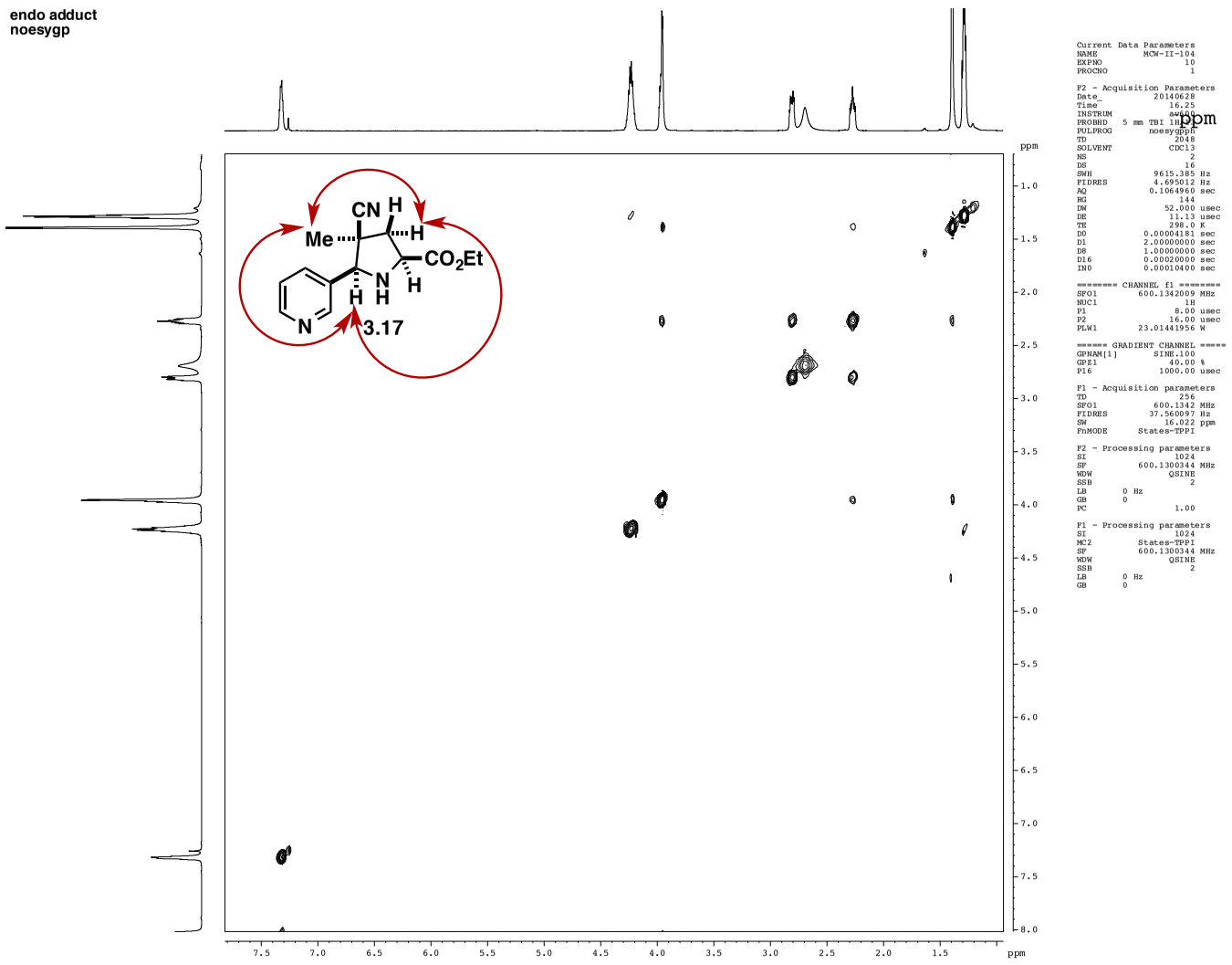
F2 - Acquisition Parameter
Date_           20140628
Time               15.42
INSTRUM          cryo500
PROBHD  5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.pr
TD                 65536
SOLVENT             CDCl3
NS                    72
DS                    16
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0813440 se
RG                  8192
DW                16.500 us
DE                 6.00 us
TE                298.0 K
D1            0.25000000 se
d11           0.03000000 se
D16           0.00020000 se
d17           0.00019600 se
MCREST   0 sec
MCWRK         0.01500000 se
P2                31.00 us

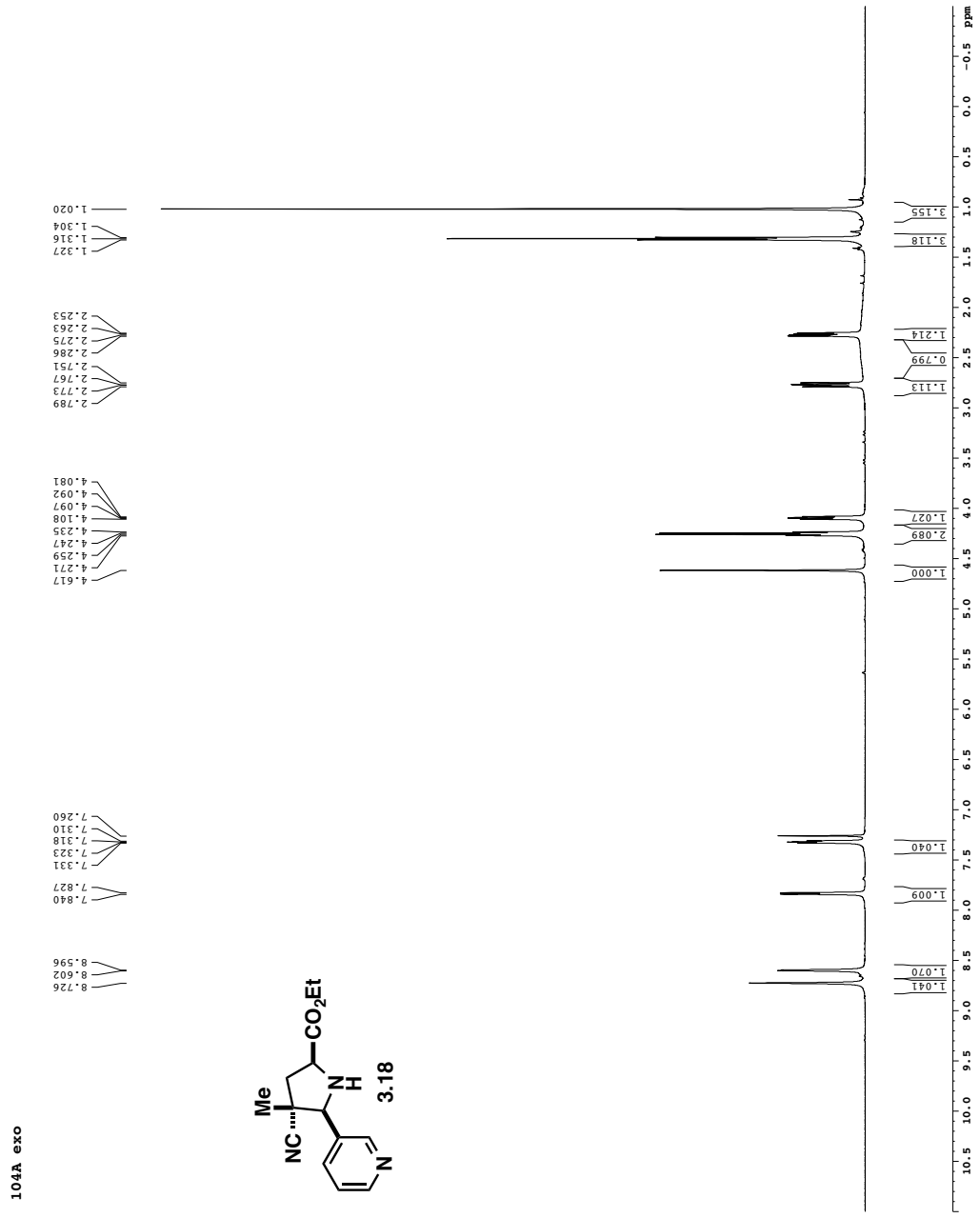
======== CHANNEL f1 ======
NUC1                 13C
P1                15.50 us
P11              500.00 us
P12             2000.00 us
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MH
SP1                3.20 dB
SP2                3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1   0 Hz
SPOFF2   0 Hz

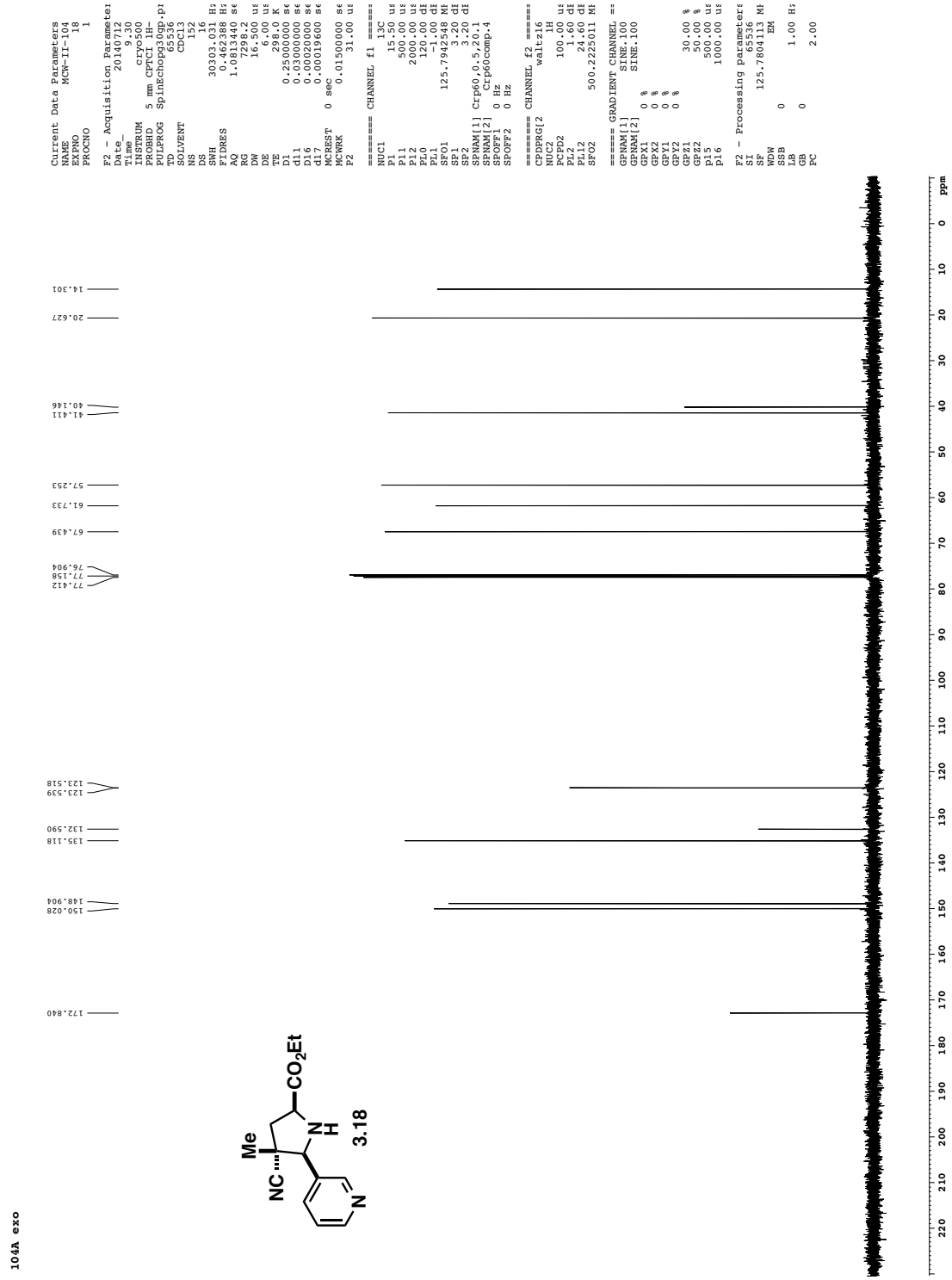
======== CHANNEL f2 ======
CPDPRG[2         waltz16
NUC2                 1H
PCPD2             100.00 us
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MH

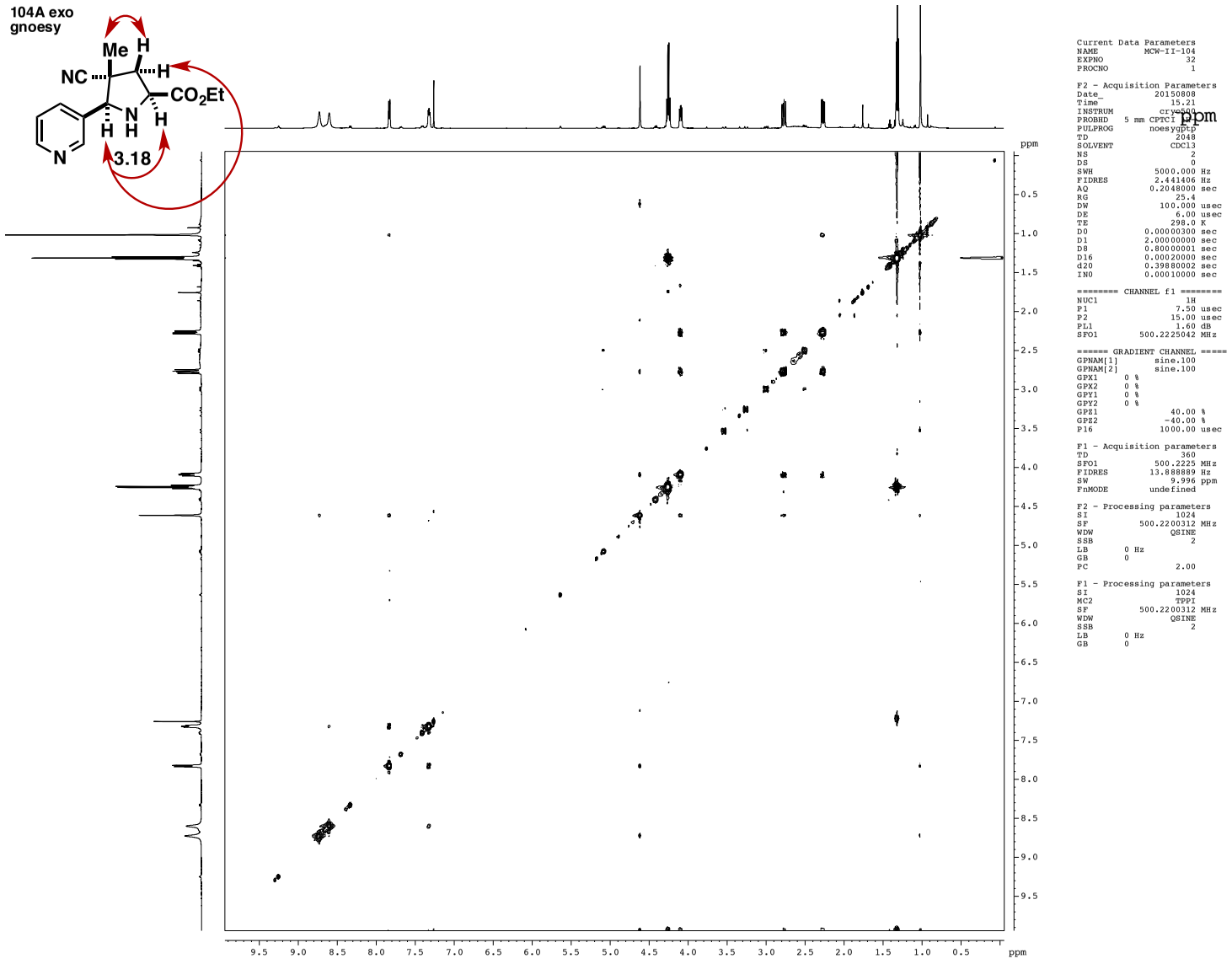
====== GRADIENT CHANNEL ==
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 us
p16             1000.00 us

F2 - Processing parameters
SI                 65536
SF          125.7804242 MH
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 2.00
```


endo adduct
noesygp
CN H
Me
H
CO2Et
N H
H H
N
3.17
3.9pm
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
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 ppm
Current Data Parameters
NAME MCW-II-104
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140628
Time 16.25
INSTRUM av600
PROBHD 5 mm TBI 1H/
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 2
DS 16
SWH 9615.385 Hz
FIDRES 4.695012 Hz
AQ 0.1064960 sec
RG 144
DW 52.000 usec
DE 11.13 usec
TE 298.0 K
D0 0.00004181 sec
D1 2.00000000 sec
D8 1.00000000 sec
D16 0.00020000 sec
IN0 0.00010400 sec
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
P2 16.00 usec
PLW1 23.01441956 W
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPZ1 40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 600.1342 MHz
FIDRES 37.560097 Hz
SW 16.022 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 1024
SF 600.1300344 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 States-TPPI
SF 600.1300344 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0


104A exo
Current Data Parameters
NAME MEW-IT-104
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140722
Time 16.41
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 10
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.09988478 sec
RG 256
DW 52.000 usec
DE 14.54 usec
TE 298.1 K
D1 0.10000000 sec
1
TD0
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300340 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.726
8.602
8.596
7.840
7.827
7.331
7.323
7.318
7.310
7.260
4.617
4.271
4.259
4.247
4.235
4.108
4.097
4.092
4.081
2.789
2.773
2.767
2.751
2.286
2.275
2.263
2.253
1.327
1.316
1.304
1.020
1.041
1.070
1.009
1.040
1.000
2.089
1.027
1.113
0.799
1.214
3.118
3.155
Me
NC
CO2Et
N
H
N
3.18
ppm


104A exo
Current Data Parameters
NAME MCW-II-104
EXPNO 18
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140712
Time 9.30
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 152
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 72793.2
DW 16.500 us
DE 6.00 us
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MC4REST 0 sec
MCWRK 0.01500000 sec
P2 31.00 us
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 us
P11 500.00 us
P12 2000.00 us
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 us
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 us
p16 1000.00 us
F2 - Processing parameters
SI 65536
SF 125.7804113 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
172.840
150.028
148.904
135.118
132.590
123.539
123.518
77.412
77.158
76.904
67.439
61.733
57.253
41.411
40.146
20.627
14.301
Me
NC
CO2Et
N
H
N
3.18
ppm




```
Current Data Parameters
NAME                  MCW-II-104
EXPNO                         32
PROCNO                         1

F2 - Acquisition Parameters
Date_               20150808
Time                      15.21
INSTRUM                   cryo500
PROBHD     5 mm CPTCI 1H-13C/15N
PULPROG             noesygpphp
TD                         2048
SOLVENT                   CDCl3
NS                            2
DS                            0
SWH                 5000.000 Hz
FIDRES              2.441406 Hz
AQ                  0.2048000 sec
RG                         25.4
DW                   100.000 usec
DE                     6.00 usec
TE                     298.0 K
D0                  0.00000300 sec
D1                  2.00000000 sec
D8                  0.80000001 sec
D16                 0.00020000 sec
d20                 0.39880002 sec
IN0                 0.00010000 sec

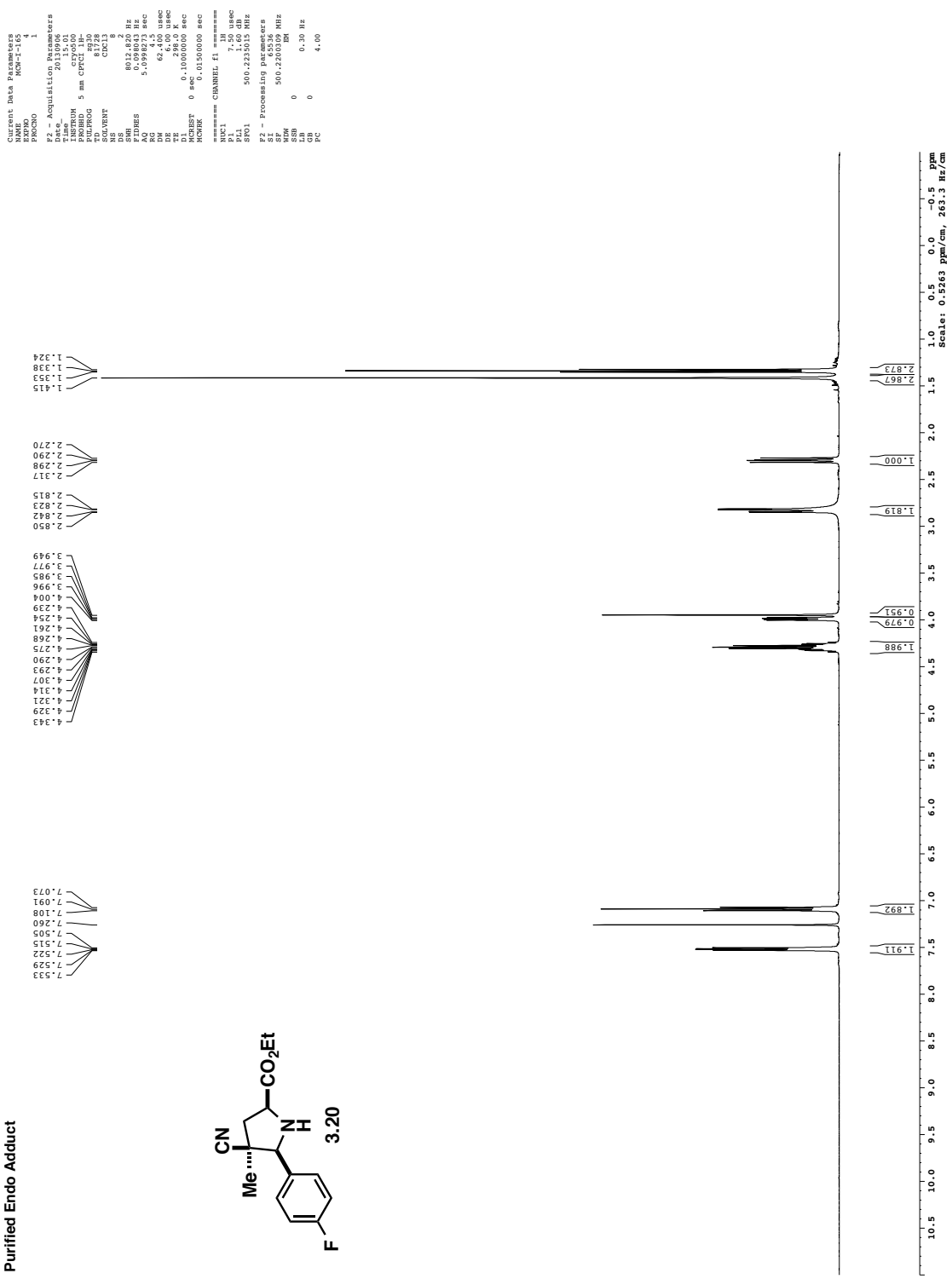
======== CHANNEL f1 ========
NUC1                       1H
P1                       7.50 usec
P2                      15.00 usec
PL1                      1.60 dB
SFO1              500.2225042 MHz

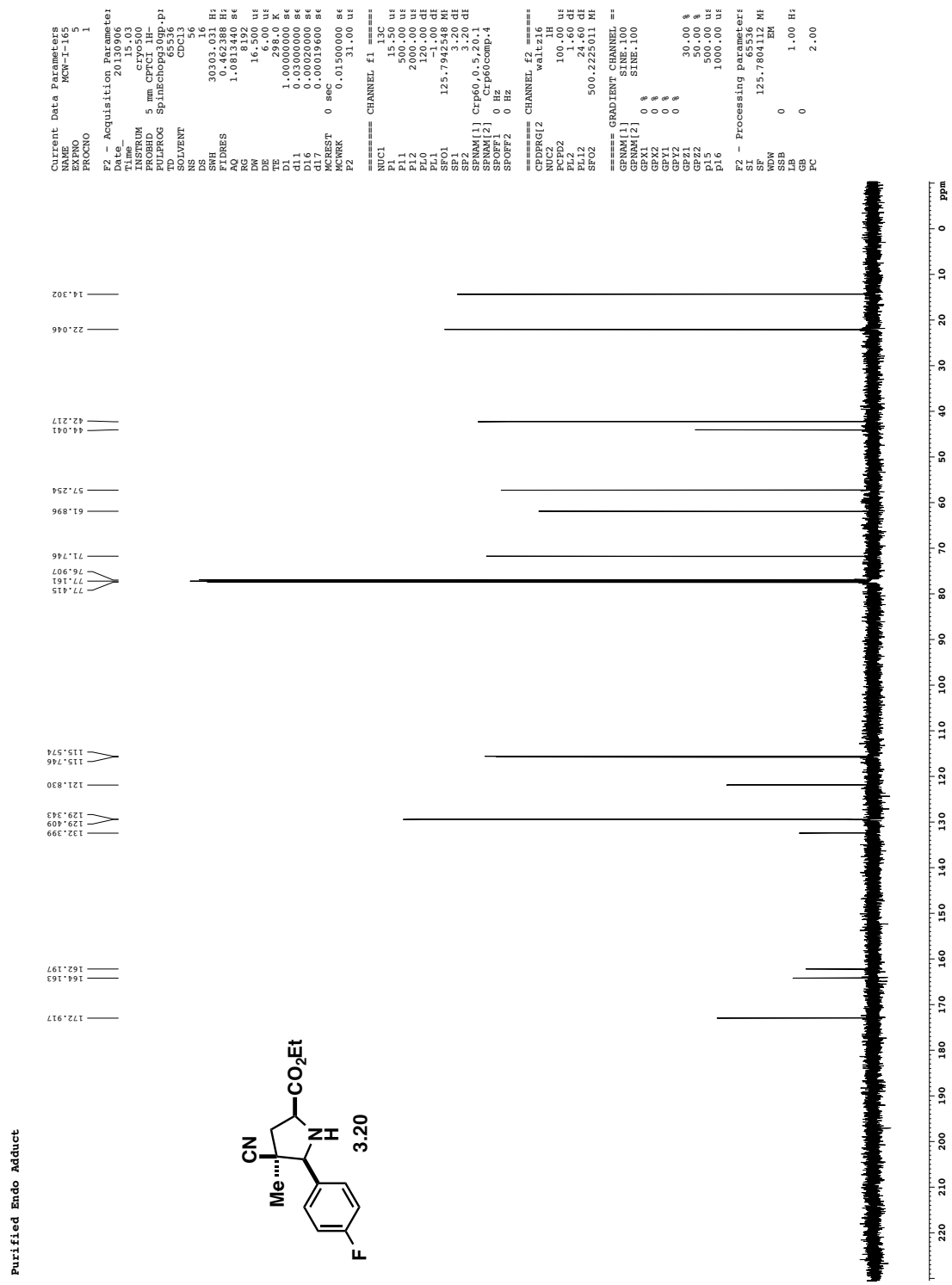
====== GRADIENT CHANNEL =====
GPNAM[1]              sine.100
GPNAM[2]              sine.100
GPX1        0 %
GPX2        0 %
GPY1        0 %
GPY2        0 %
GPZ1                    40.00 %
GPZ2                   -40.00 %
P16                  1000.00 usec

F1 - Acquisition parameters
TD                           360
SFO1                500.2225 MHz
FIDRES             13.888889 Hz
SW                      9.996 ppm
FnMODE              undefined

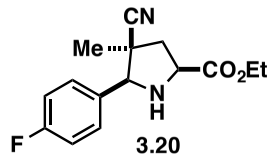
F2 - Processing parameters
SI                          1024
SF                500.2200312 MHz
WDW                       QSINE
SSB                           2
LB          0 Hz
GB          0
PC                         2.00

F1 - Processing parameters
SI                          1024
MC2                         TPPI
SF                500.2200312 MHz
WDW                       QSINE
SSB                           2
LB          0 Hz
GB          0
```


Purified Endo Adduct
CN
Me
CO2Et
N
H
F
3.20
Current Data Parameters
NAME MCM-I-165
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130906
Time 15.01
INSTRUM cpc-400
PROBHD 5 mm CPPC 1H
PULPROG zg30
TD 82928
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.099873 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 296.0 K
D1 0.10000000 sec
D11 0.03000000 sec
MCWREST 0 scans
MCWREK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200309 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
7.533
7.529
7.522
7.515
7.505
7.260
7.108
7.091
7.073
4.343
4.329
4.321
4.314
4.307
4.293
4.290
4.275
4.268
4.261
4.254
4.239
4.004
3.996
3.985
3.977
3.949
2.850
2.842
2.823
2.815
2.317
2.298
2.290
2.270
1.415
1.353
1.338
1.324
1.892
1.911
1.988
0.979
0.951
1.819
1.000
2.867
2.873
Scale: 0.5263 ppm/cm, 263.3 Hz/cm
ppm


Purified Endo Adduct
Current Data Parameters
NAME MCW-I-165
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130906
Time 15.03
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchoPg.p1
TD 65536
SOLVENT CDCl3
NS 56
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 8192
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCWREST 0 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
PL2 20000.00 dB
PL2 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804112 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
172.917
164.163
162.197
132.399
129.409
129.343
121.830
115.746
115.574
77.415
77.161
76.907
71.746
61.896
57.254
44.041
42.217
22.046
14.302
CN
Me
CO2Et
N
H
F
3.20
ppm

165b Endo – Purified Product



3.20

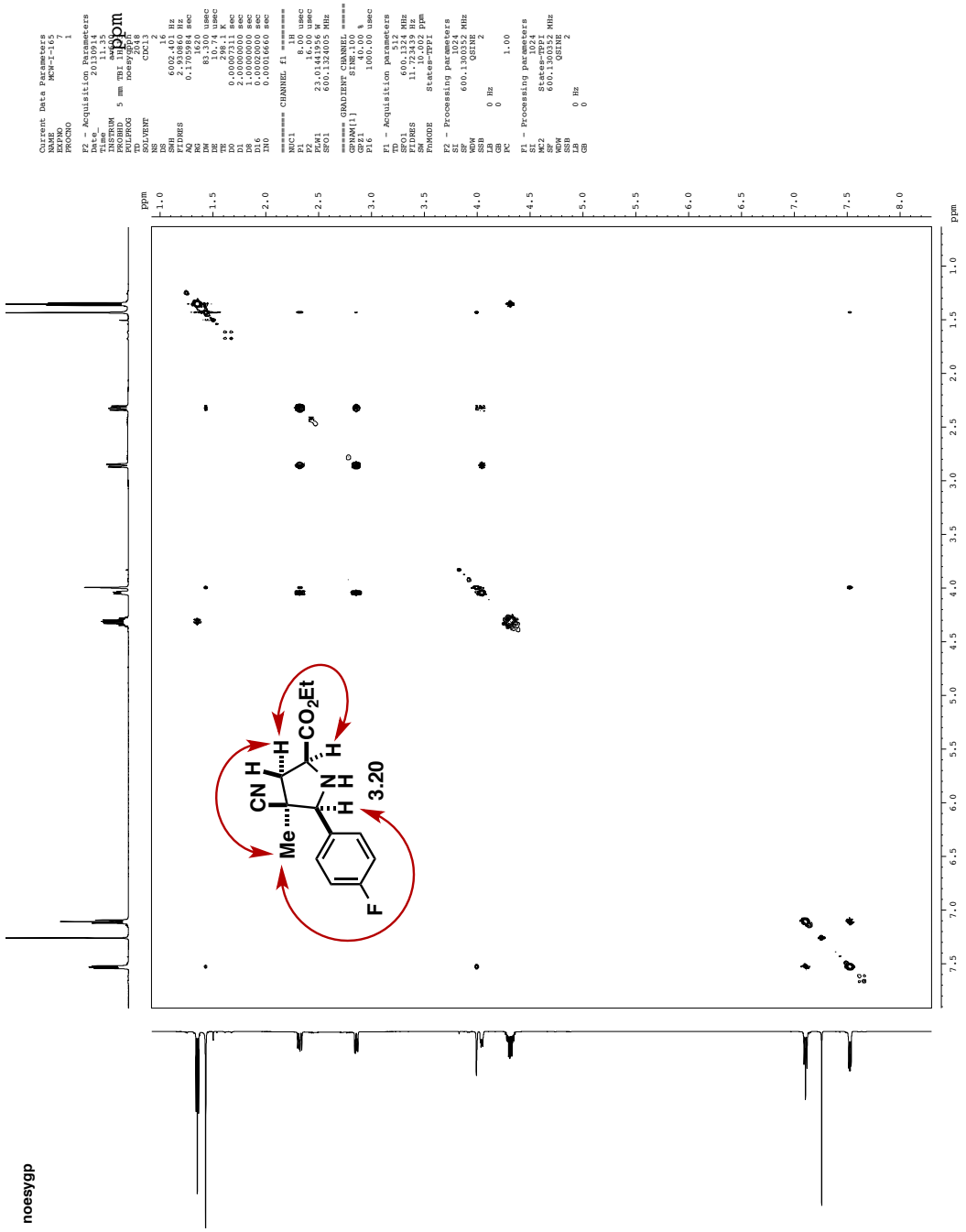

```
Current Data Parameters
NAME                  MCW-I-165
EXPNO                        32
PROCNO                        1

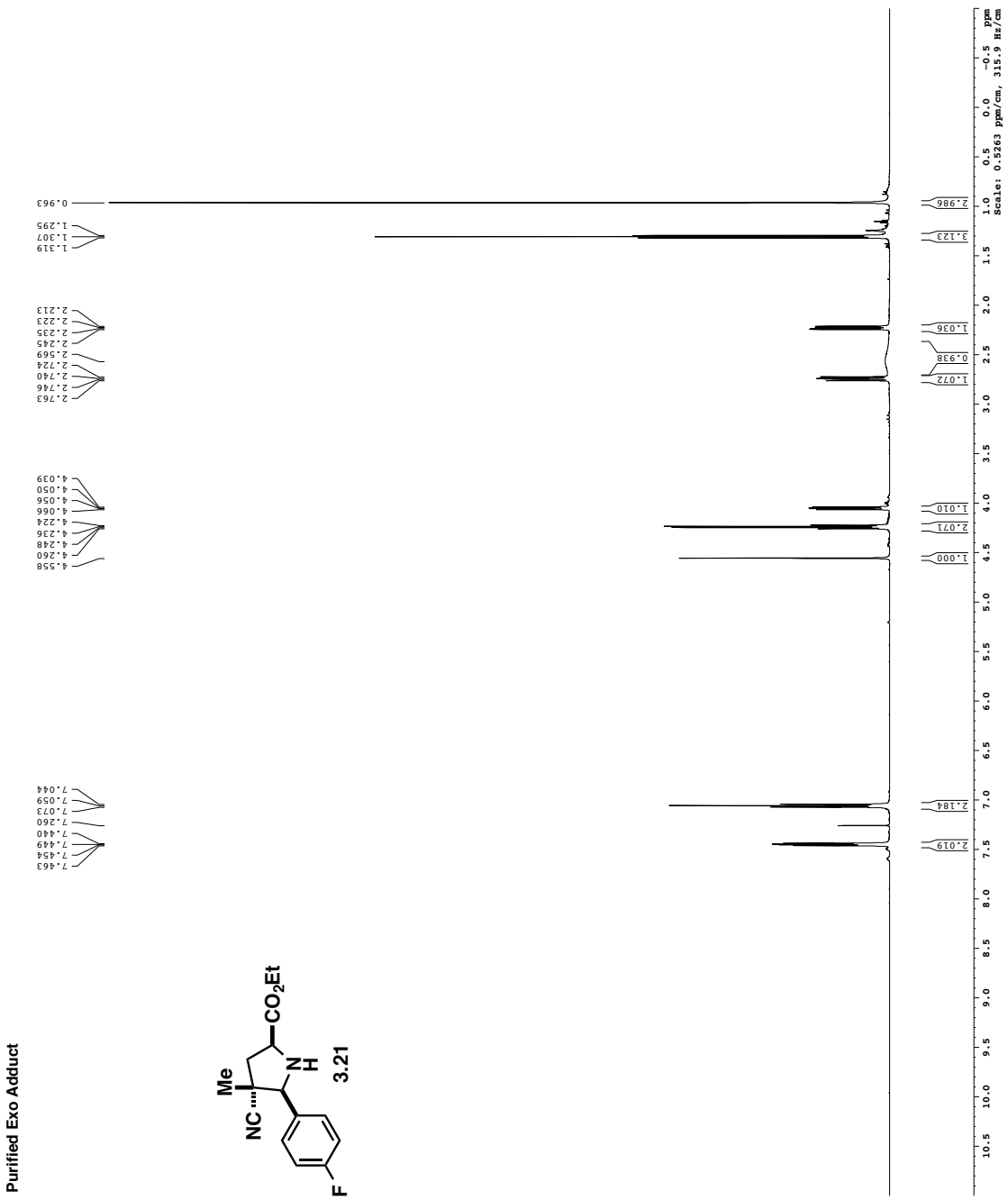
F2 - Acquisition Parameters
Date_              20131008
Time                    17.26
INSTRUM                drx400
PROBHD    5 mm QNP H/F/P
PULPROG            zgfhigqn30
TD                      65536
SOLVENT                 CDCl3
NS                         65
DS                          4
SWH                 75189.570 Hz
FIDRES              1.147302 Hz
AQ                  0.4358051 sec
RG                     3649.1
DW                      6.650 usec
DE                      9.46 usec
TE                      298.0 K
D1                  1.00000000 sec
D11                 0.03000000 sec
D12                 0.00002000 sec

======== CHANNEL f1 ========
NUC1                       19F
P1                      22.50 usec
PL1                     -6.00 dB
SFO1             376.4646491 MHz

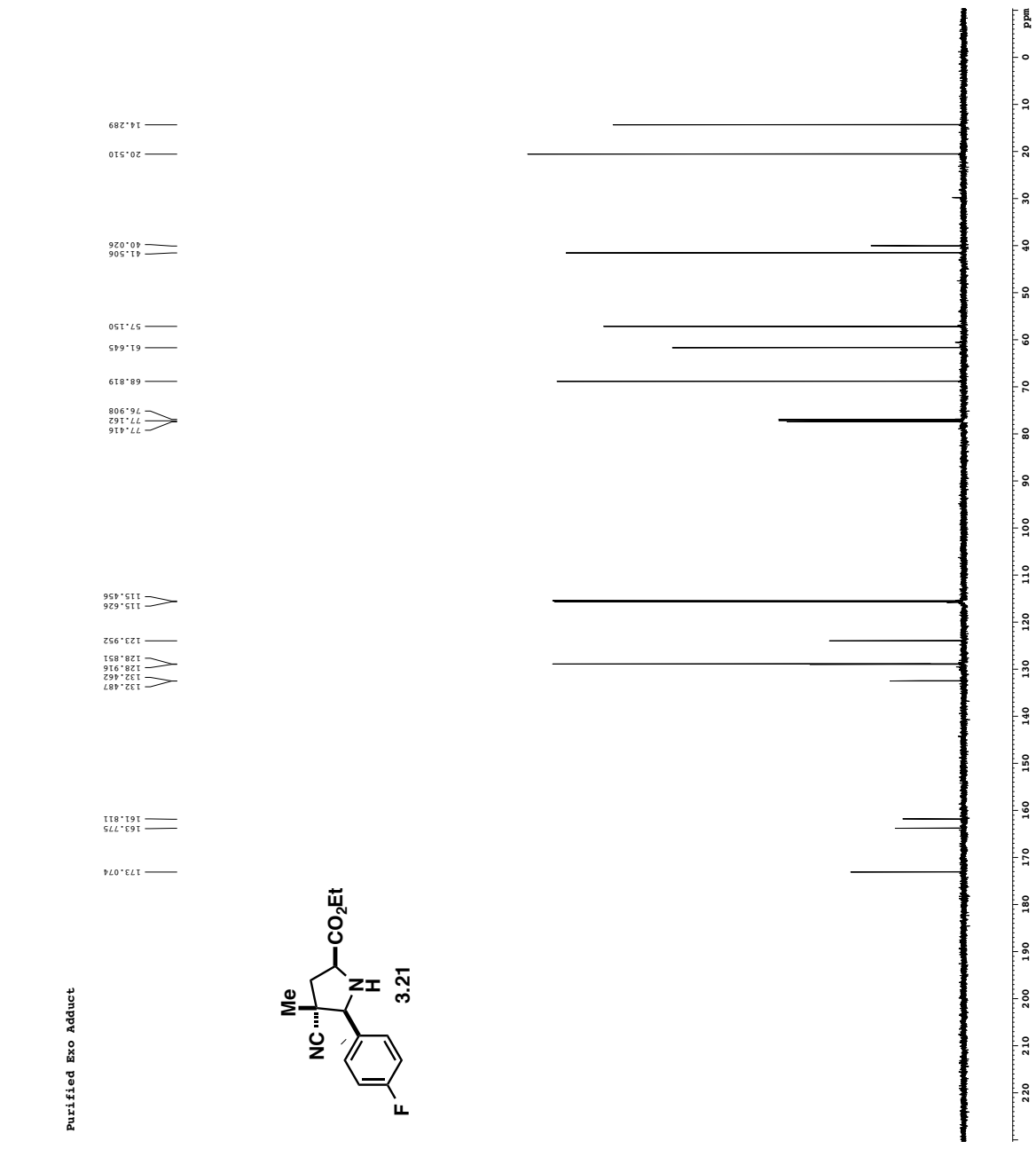
======== CHANNEL f2 ========
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                   80.00 usec
PL2                      3.00 dB
PL12                    16.20 dB
SFO2             400.1320007 MHz

F2 - Processing parameters
SI                        65536
SF               376.4983831 MHz
WDW                          EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
```

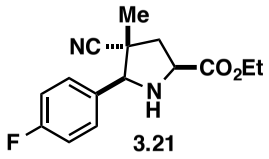

noesygp
Current Data Parameters
NAME MCM-I-165
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130914
Time 14.33
INSTRUM spect
PROBHD 5 mm TBI 1H/19F-
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 16
DS 16
SWH 6002.401 Hz
FIDRES 2.929884 Hz
AQ 0.1703984 sec
RG 1620
DW 83.300 usec
DE 10.74 usec
TE 298.1 K
D0 2.00000311 sec
D1 2.00000000 sec
D8 1.00000000 sec
D16 0.00020000 sec
ZH0 0.01016660 sec
====== CHANNEL f1 ======
NUC1 1H
P1 8.00 usec
PL1 6.00 usec
PL1W1 23.01444153 W
SFO1 600.1324005 MHz
===== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPZ1 40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1324 MHz
FIDRES 11.723439 Hz
SW 10.000 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 1024
SF 600.1300352 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 States-TPPI
SF 600.1300352 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
4.5ppm
3.20
CO2Et
CN
Me
F
ppm


Purified Exo Adduct
Me
NC
CO2Et
N
H
F
3.21
Scale: 0.5263 ppm/cm, 315.9 Hz/cm

Purified Exo Adduct



165a Exo – Purified Product



3.21

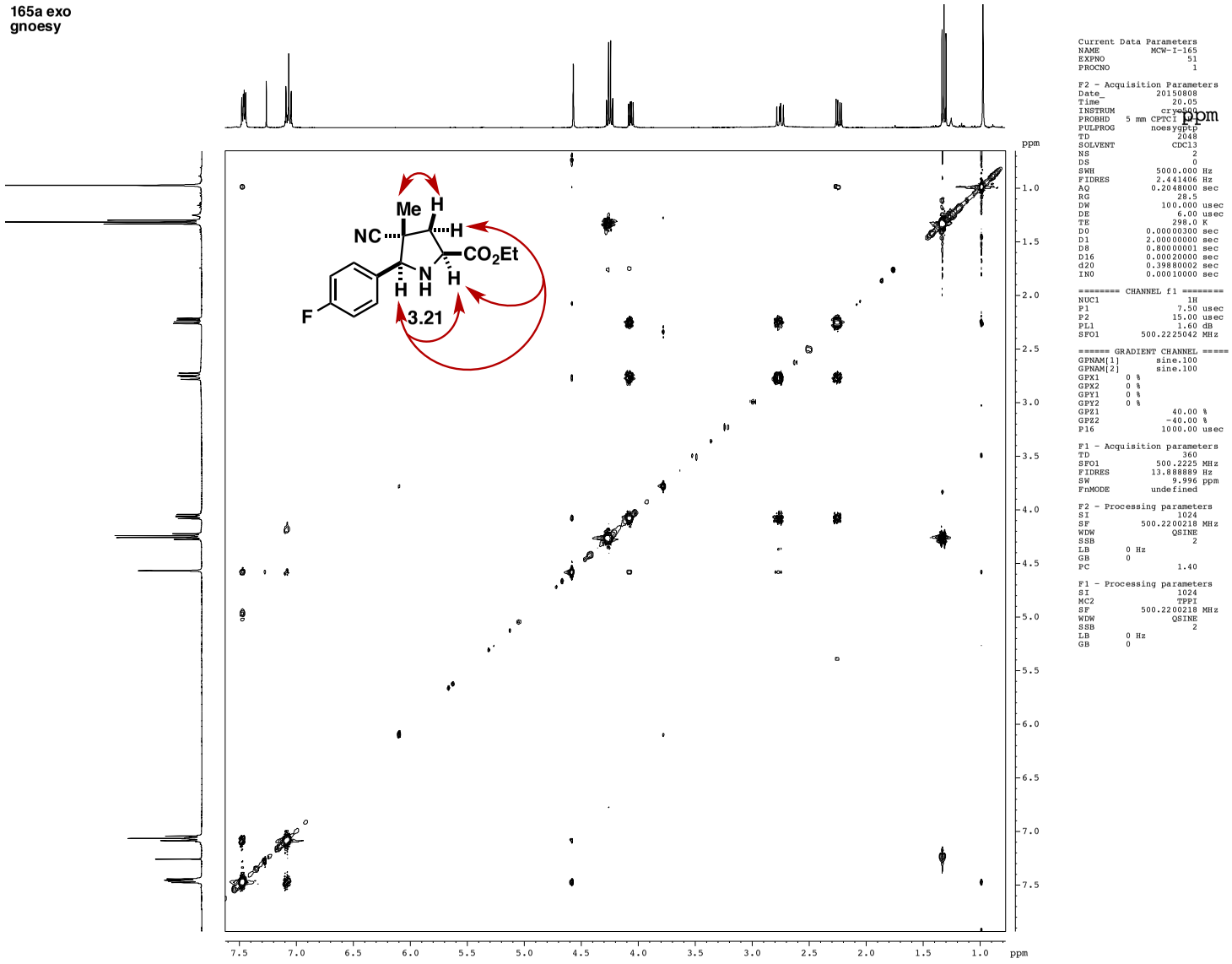

```
Current Data Parameters
NAME                  MCW-I-165
EXPNO                        35
PROCNO                        1

F2 - Acquisition Parameters
Date_               20131008
Time                    17.35
INSTRUM                drx400
PROBHD   5 mm QNP H/F/P
PULPROG            zgfhigqn30
TD                      65536
SOLVENT                 CDCl3
NS                         72
DS                          4
SWH                 75187.969 Hz
FIDRES                1.147277 Hz
AQ                  0.4358144 sec
RG                     3649.1
DW                      6.650 usec
DE                      9.46 usec
TE                      298.0 K
D1                 1.00000000 sec
D11                0.03000000 sec
D12                0.00002000 sec

======== CHANNEL f1 ========
NUC1                       19F
P1                      22.50 usec
PL1                     -6.00 dB
SFO1               376.4646491 MHz

======== CHANNEL f2 ========
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                   80.00 usec
PL2                      3.00 dB
PL12                    16.20 dB
SFO2               400.1320007 MHz

F2 - Processing parameters
SI                        65536
SF                 376.4983829 MHz
WDW                          EM
SSB             0
LB                       0.30 Hz
GB              0
PC                       1.00
```




```
Current Data Parameters
NAME                 MCW-I-165
EXPNO                       51
PROCNO                       1

F2 - Acquisition Parameters
Date_               20150808
Time                    20.05
INSTRUM                 cryo500
PROBHD     5 mm CPTCI 1H-13C/1
PULPROG             noesygpph
TD                       2048
SOLVENT                 CDCl3
NS                          2
DS                          0
SWH                 5000.000 Hz
FIDRES              2.441406 Hz
AQ                  0.2048000 sec
RG                       28.5
DW                  100.000 usec
DE                    6.00 usec
TE                    298.0 K
D0                  0.00000300 sec
D1                  2.00000000 sec
D8                  0.80000001 sec
D16                 0.00020000 sec
d20                 0.39880002 sec
IN0                 0.00010000 sec

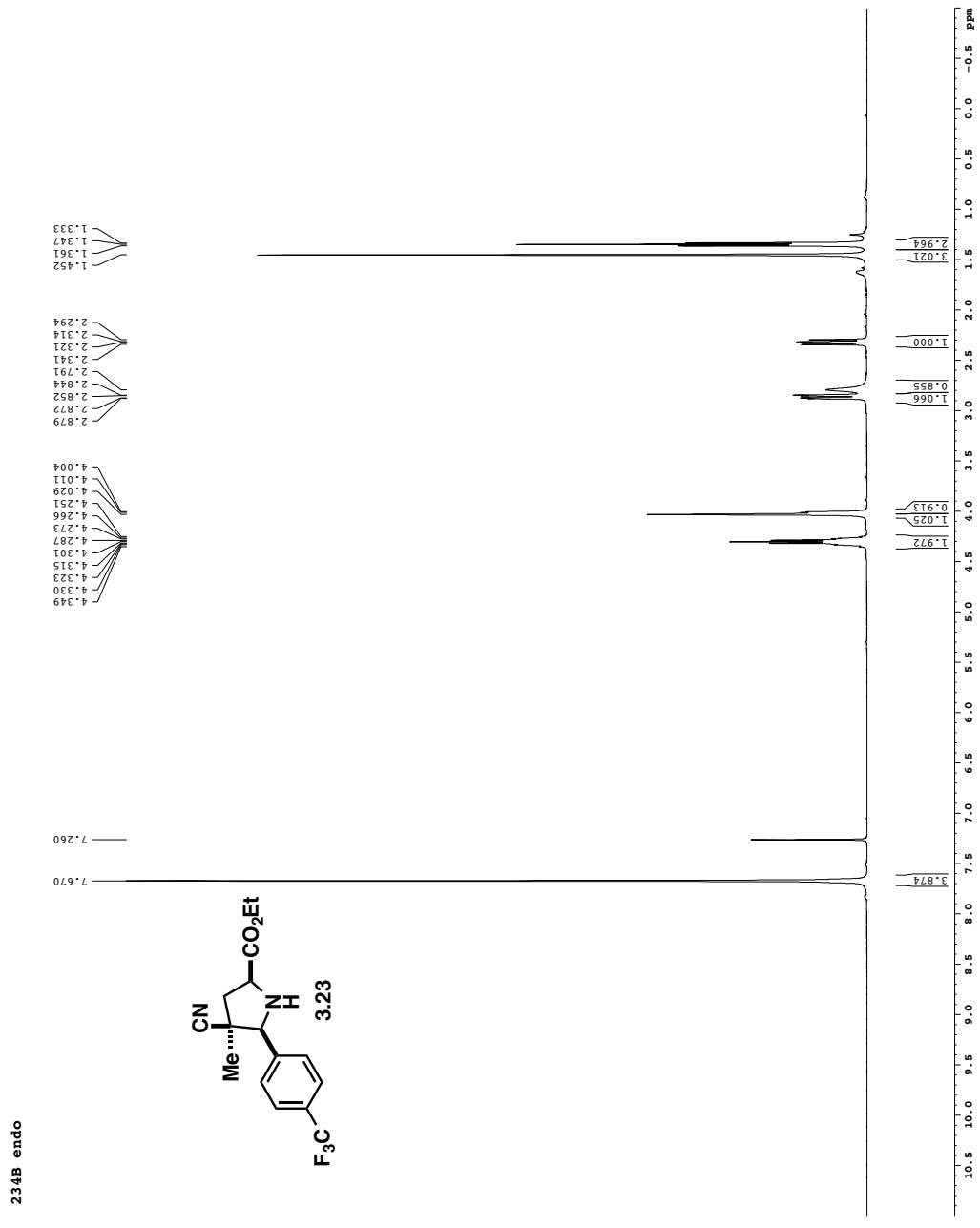
======== CHANNEL f1 ========
NUC1                        1H
P1                        7.50 usec
P2                       15.00 usec
PL1                       1.60 dB
SFO1             500.2225042 MHz

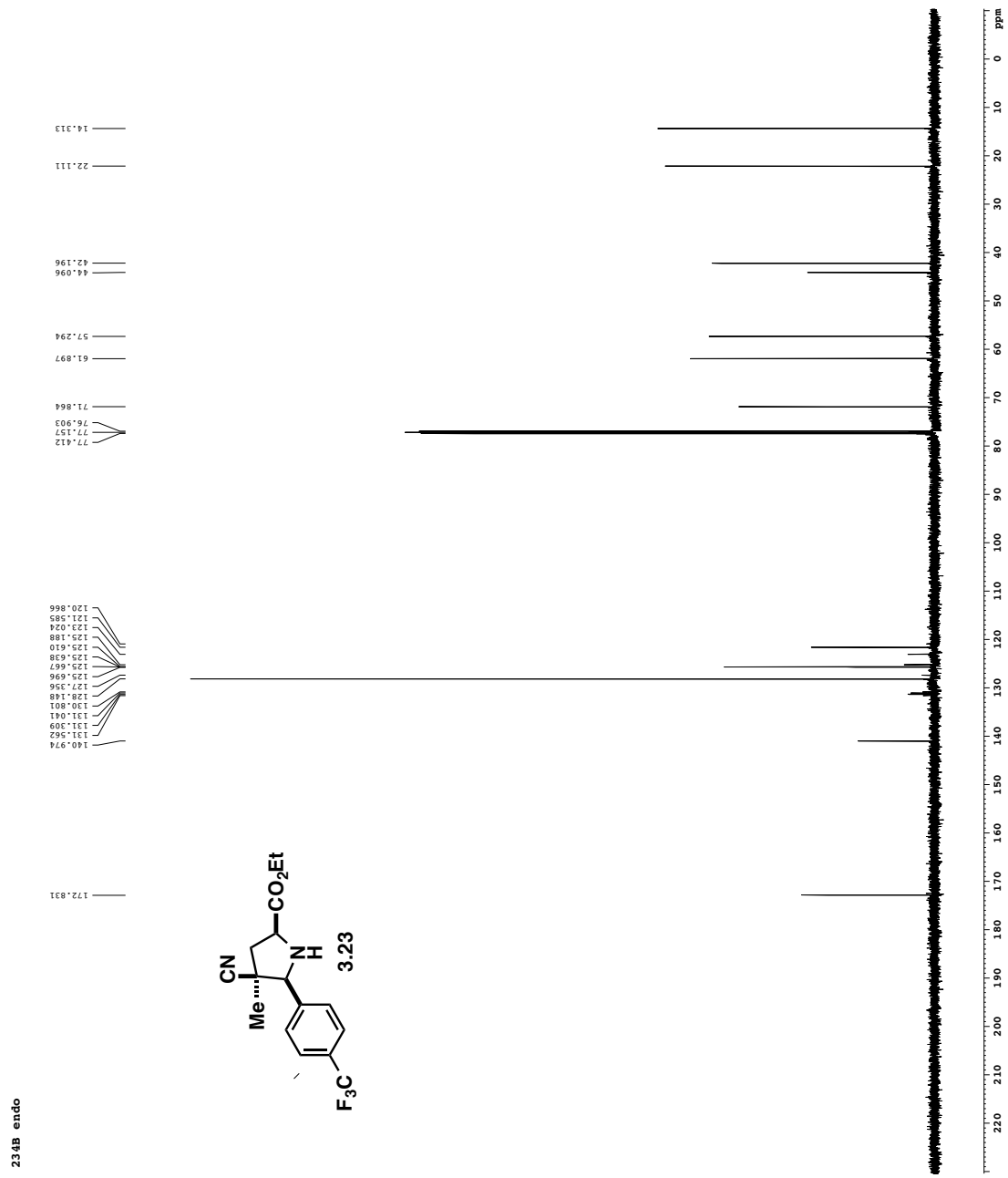
====== GRADIENT CHANNEL =====
GPNAM[1]              sine.100
GPNAM[2]              sine.100
GPX1        0 %
GPX2        0 %
GPY1        0 %
GPY2        0 %
GPZ1                     40.00 %
GPZ2                    -40.00 %
P16                   1000.00 usec

F1 - Acquisition parameters
TD                          360
SFO1                 500.2225 MHz
FIDRES              13.888889 Hz
SW                       9.996 ppm
FnMODE               undefined

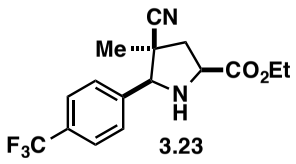
F2 - Processing parameters
SI                          1024
SF                500.2200218 MHz
WDW                       QSINE
SSB                          2
LB          0 Hz
GB          0
PC                        1.40

F1 - Processing parameters
SI                          1024
MC2                       TPPI
SF                500.2200218 MHz
WDW                       QSINE
SSB                          2
LB          0 Hz
GB          0
```


234B endo
Current Data Parameters
NAME MEW-II-234
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141004
Time 9.01
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 0
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 4
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200316 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
7.670
7.260
1.452
1.361
1.347
1.333
2.879
2.872
2.852
2.844
2.791
2.341
2.321
2.314
2.294
4.349
4.330
4.323
4.315
4.301
4.287
4.273
4.266
4.251
4.029
4.011
4.004
3.874
1.972
1.025
0.913
1.000
1.066
0.855
2.964
3.021
CN
Me
N
H
CO2Et
F3C
3.23
ppm


234B endo
Current Data Parameters
NAME MCW-II-234
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141004
Time 9.03
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 160
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 203.3
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MCWREST 0 sec 0.01500000 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL2 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804099 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
172.831
140.974
131.562
131.309
131.041
130.801
128.148
127.356
125.696
125.667
125.638
125.610
125.188
123.024
121.585
120.866
77.412
77.157
76.903
71.864
61.897
57.294
44.096
42.196
22.111
14.313
CN
Me
CO2Et
N
H
3.23
F3C
ppm

234B 19F{1H}



3.23

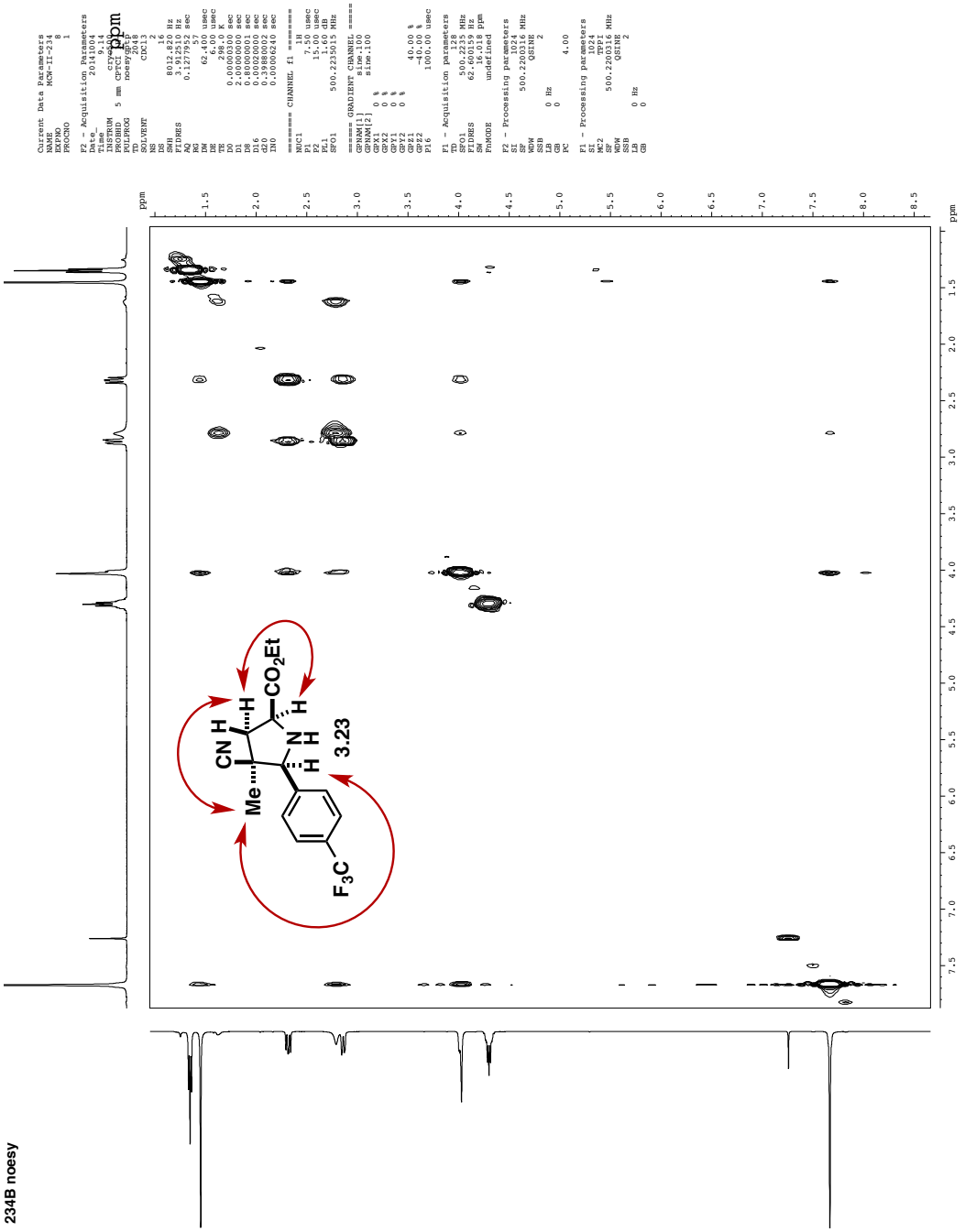

```
Current Data Parameters
NAME                  MCW-II-234
EXPNO                         13
PROCNO                         1

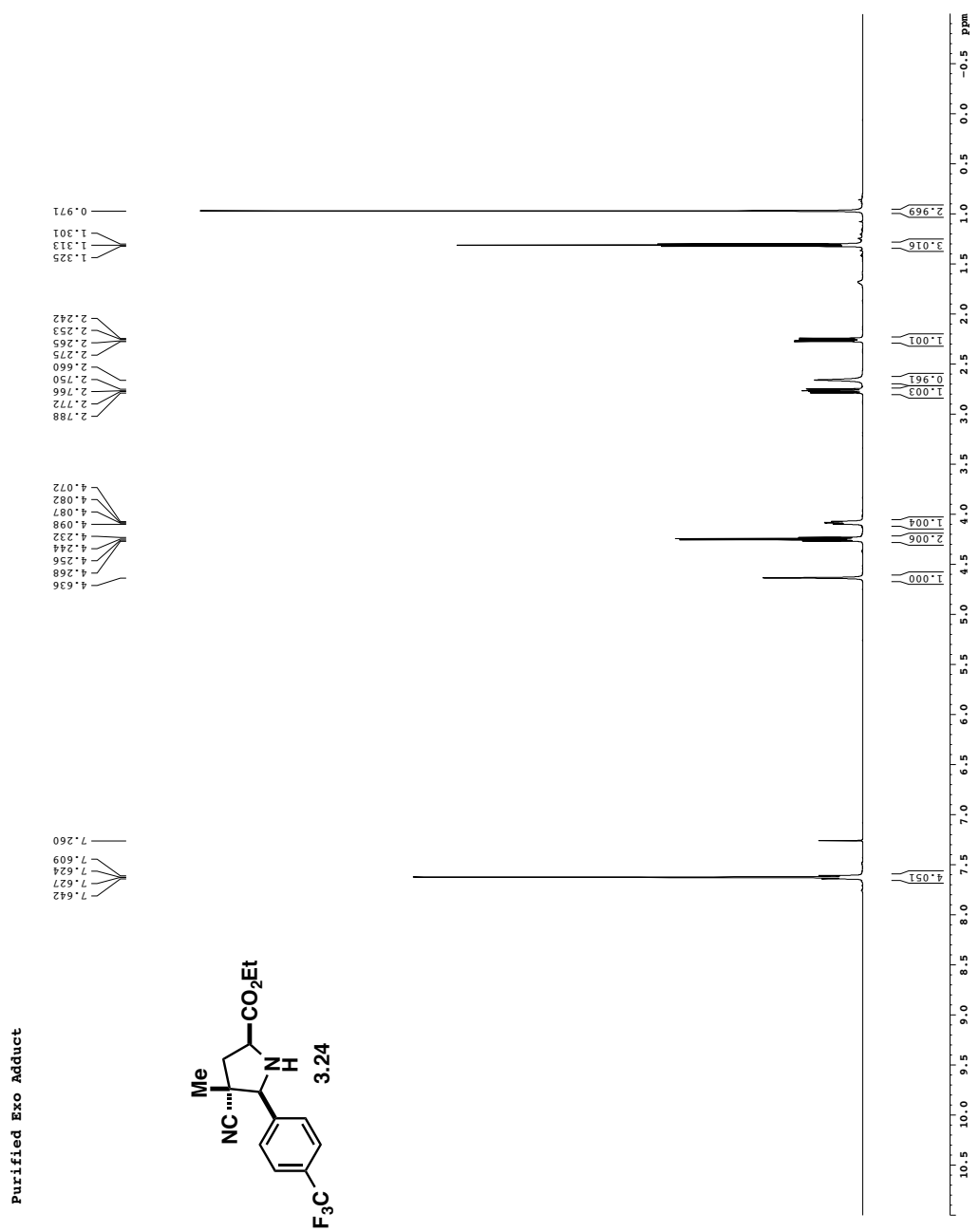
F2 - Acquisition Parameters
Date_               20141004
Time                      10.06
INSTRUM                 drx400
PROBHD    5 mm QNP H/F/P
PULPROG             zgfhigqn30
TD                       65536
SOLVENT                  CDCl3
NS                          24
DS                           4
SWH                  75187.969 Hz
FIDRES                1.147277 Hz
AQ                    0.4358144 sec
RG                       3649.1
DW                        6.650 usec
DE                        9.46 usec
TE                       298.0 K
D1                   2.00000000 sec
d11                  0.03000000 sec
d12                  0.00002000 sec

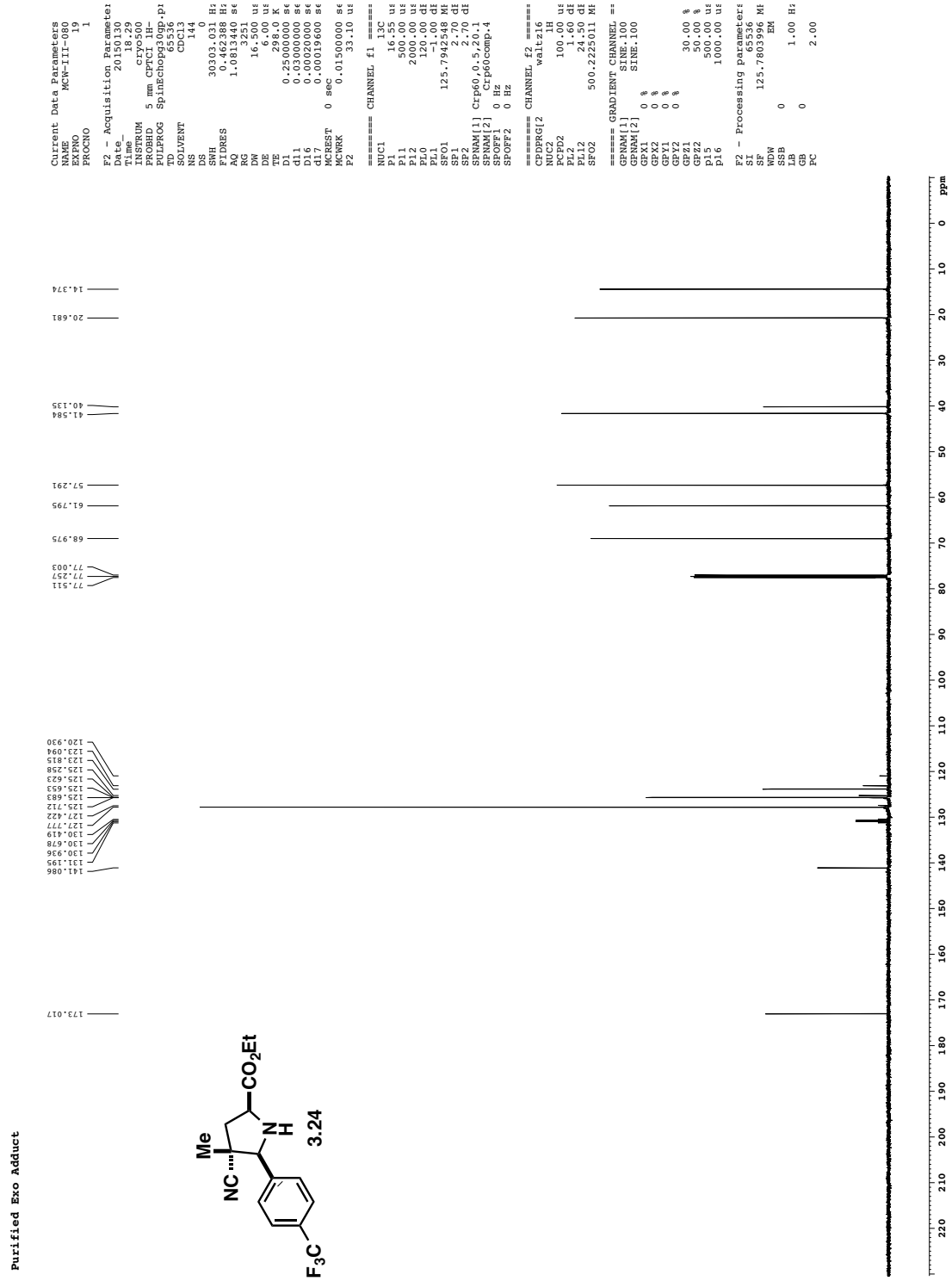
======== CHANNEL f1 ========
NUC1                        19F
P1                        22.50 usec
PL1                       -6.00 dB
SFO1               376.4646491 MHz

======== CHANNEL f2 ========
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                     90.00 usec
PL2                      120.00 dB
PL12                      17.70 dB
SFO2               400.1320007 MHz

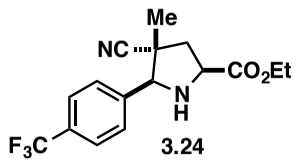
F2 - Processing parameters
SI                       65536
SF                 376.4983858 MHz
WDW                         EM
SSB             0
LB                        0.30 Hz
GB              0
PC                        1.00
```


234B noesy
ppm
ppm
ppm
CO2Et
CN
Me
F3C
3.23


Purified Exo Adduct
Current Data Parameters
NAME MCM-11F-080
EXPNO 16
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150130
Time 17.58
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 8
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.09988478 sec
RG 256
DW 52.000 usec
DE 14.54 usec
TE 298.0 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300356 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.642
7.627
7.624
7.609
7.260
4.636
4.268
4.256
4.244
4.232
4.098
4.087
4.082
4.072
2.788
2.772
2.766
2.750
2.660
2.275
2.265
2.253
2.242
1.325
1.313
1.301
0.971
4.051
1.000
2.006
1.004
1.003
0.961
1.001
3.016
2.969
Me
NC
CO2Et
N
H
3.24
F3C
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 ppm


Purified Exo Adduct
Me
NC
CO2Et
N
H
3.24
F3C
Current Data Parameters
NAME MCW-III-080
EXPNO 19
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150130
Time 18.29
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 144
DS 0
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 203
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MC2REST 0 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
PL2 20000.00 dB
PL2 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.59 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ===
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7803996 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
173.017
141.086
131.195
130.936
130.678
130.419
127.777
127.422
125.712
125.683
125.653
125.623
125.258
123.815
123.094
120.930
77.511
77.257
77.003
68.975
61.795
57.291
41.584
40.135
20.681
14.374
ppm

Purified Exo Adduct



3.24

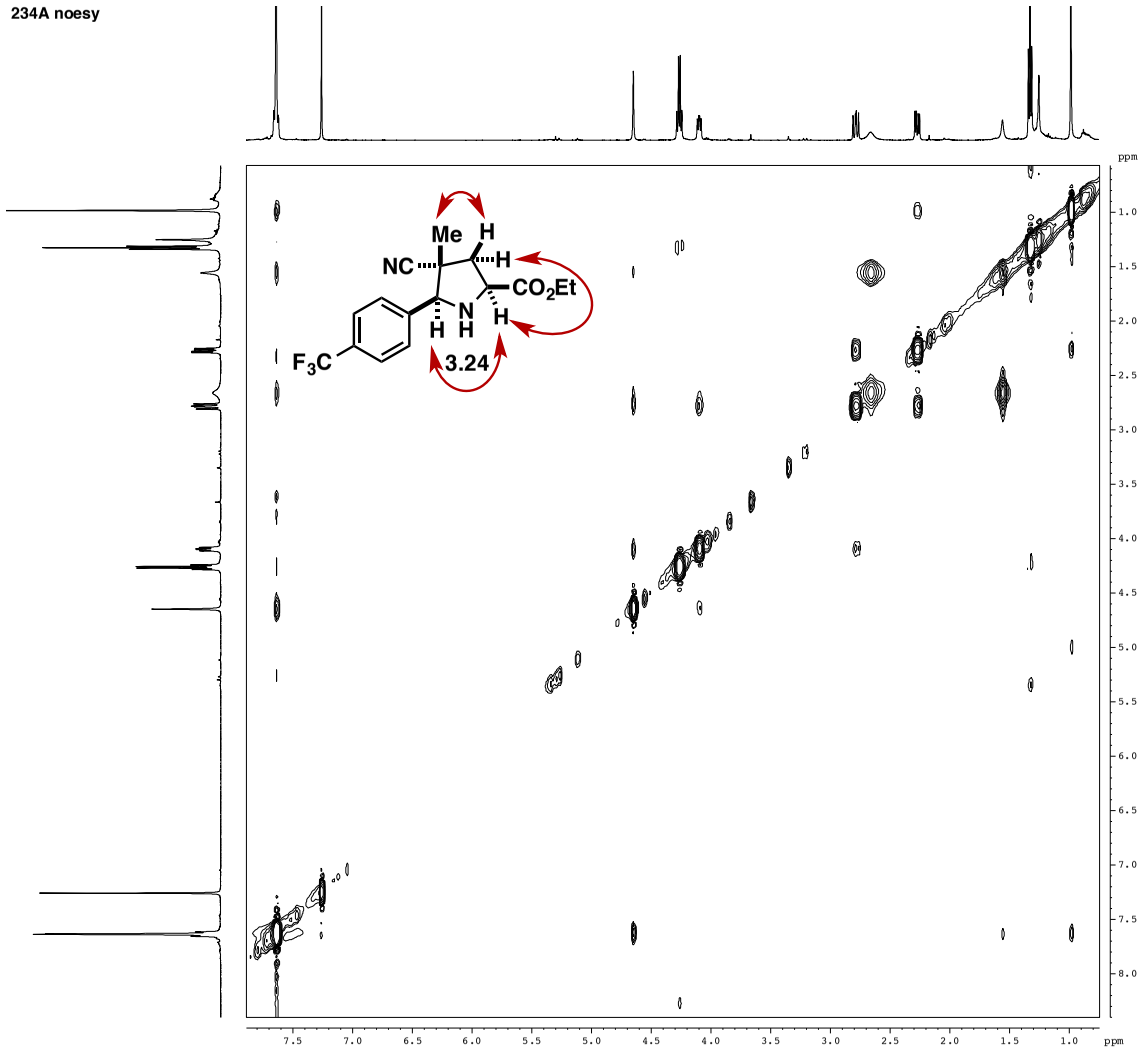

```
Current Data Parameters
NAME          MCW-III-080
EXPNO                  18
PROCNO                  1

F2 - Acquisition Parameters
Date_           20150130
Time               18.18
INSTRUM           drx400
PROBHD   5 mm QNP H/F/P
PULPROG       zgfhigqn30
TD                 65536
SOLVENT            CDCl3
NS                    12
DS                     4
SWH            75187.969 Hz
FIDRES             1.147277 Hz
AQ             0.4358144 sec
RG                1290.2
DW                 6.650 usec
DE                 9.46 usec
TE                298.0 K
D1             2.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

======== CHANNEL f1 ========
NUC1                  19F
P1                 22.50 usec
PL1                -6.00 dB
SFO1         376.4646491 MHz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PL2               120.00 dB
PL12               17.70 dB
SFO2         400.1320007 MHz

F2 - Processing parameters
SI                 65536
SF           376.4983857 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```




```
Current Data Parameters
NAME                 MCW-II-234
EXPNO                        21
PROCNO                        1

F2 - Acquisition Parameters
Date_               20141004
Time                   16.10
INSTRUM                cryo500
PROBHD   5 mm CPTCI 1H-13C/15N
PULPROG             noesygpph
TD                       2048
SOLVENT                 CDCl3
NS                           2
DS                          16
SWH                 8012.820 Hz
FIDRES              3.912510 Hz
AQ                  0.1277952 sec
RG                         128
DW                    62.400 usec
DE                     6.00 usec
TE                     298.0 K
D0                  0.00000300 sec
D1                  2.00000000 sec
D8                  0.80000001 sec
D16                 0.00020000 sec
d20                 0.39880002 sec
IN0                 0.00006240 sec

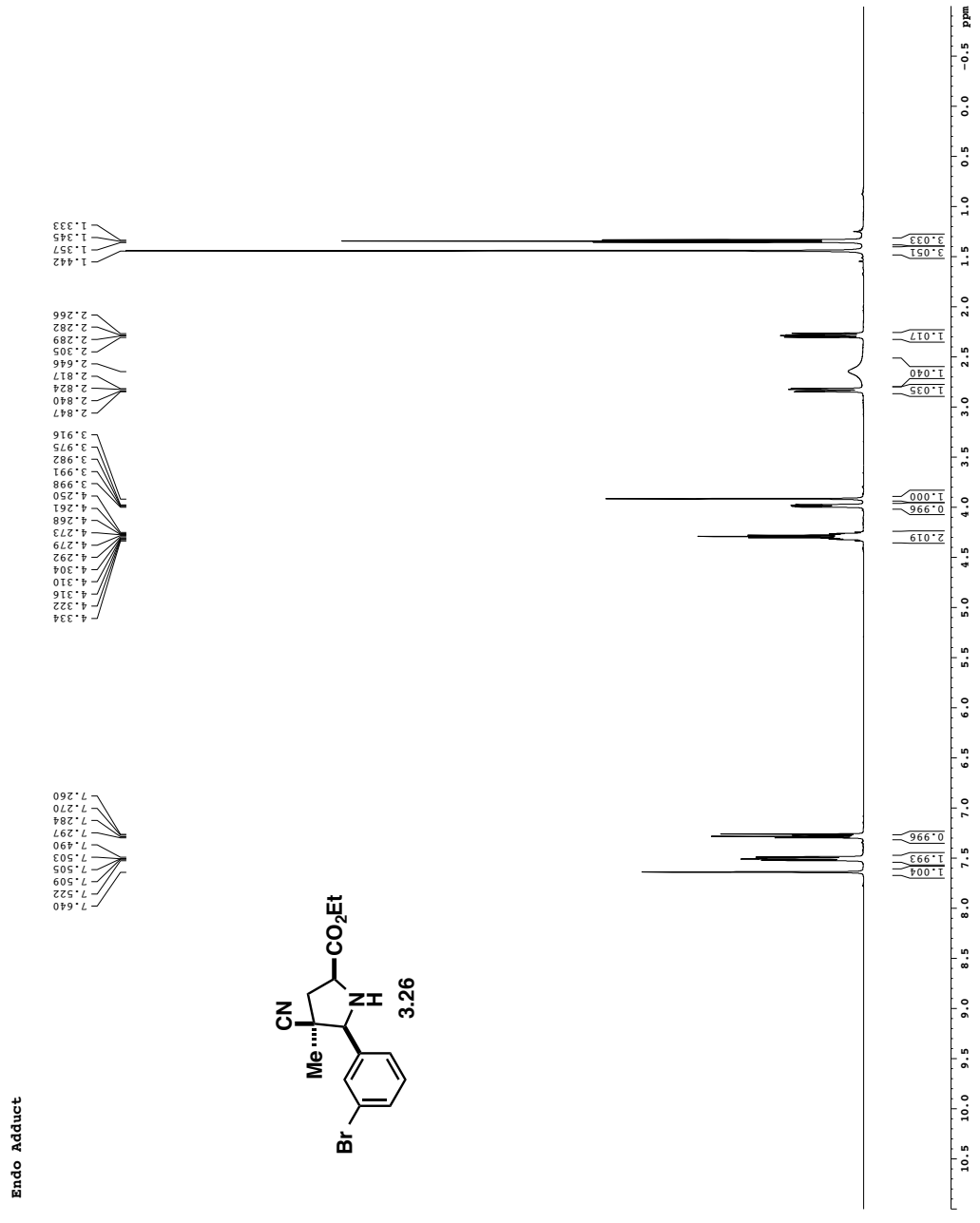
======== CHANNEL f1 ========
NUC1                       1H
P1                       7.50 usec
P2                      15.00 usec
PL1                      1.60 dB
SFO1               500.2235015 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]             sine.100
GPNAM[2]             sine.100
GPX1          0 %
GPX2          0 %
GPY1          0 %
GPY2          0 %
GPZ1                    40.00 %
GPZ2                   -40.00 %
P16                  1000.00 usec

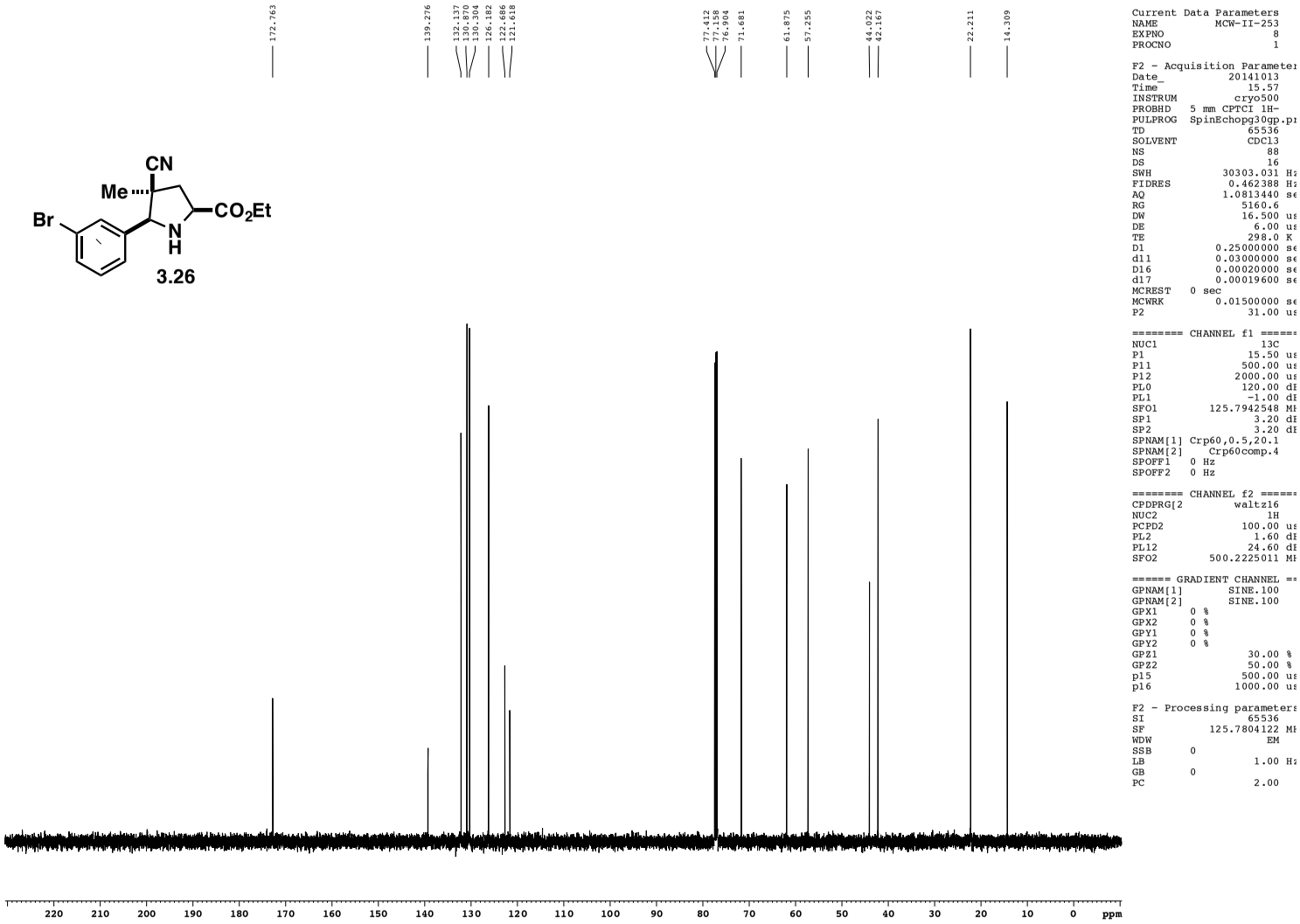
F1 - Acquisition parameters
TD                         128
SFO1               500.2235 MHz
FIDRES              62.601159 Hz
SW                     16.018 ppm
FnMODE               undefined

F2 - Processing parameters
SI                        1024
SF                 500.2200315 MHz
WDW                       QSINE
SSB                          2
LB            0 Hz
GB            0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2                       TPPI
SF                 500.2200315 MHz
WDW                       QSINE
SSB                          2
LB            0 Hz
GB            0
```


Endo Adduct
Current Data Parameters
NAME MEW-II-253
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141013
Time 15.24
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 8
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.09988478 sec
RG 181
DW 52.000 usec
DE 14.54 usec
TE 298.0 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300344 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.640
7.522
7.509
7.505
7.503
7.490
7.297
7.284
7.270
7.260
4.334
4.322
4.316
4.310
4.304
4.292
4.279
4.273
4.268
4.261
4.250
3.998
3.991
3.982
3.975
3.916
2.847
2.840
2.824
2.817
2.646
2.305
2.289
2.282
2.266
1.442
1.357
1.345
1.333
1.004
1.993
0.996
1.000
0.996
2.019
1.035
1.040
1.017
3.051
3.033
CN
Me
CO2Et
N
H
Br
3.26
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
ppm

Endo Adduct




```
Current Data Parameters
NAME            MCW-II-253
EXPNO                    8
PROCNO                   1

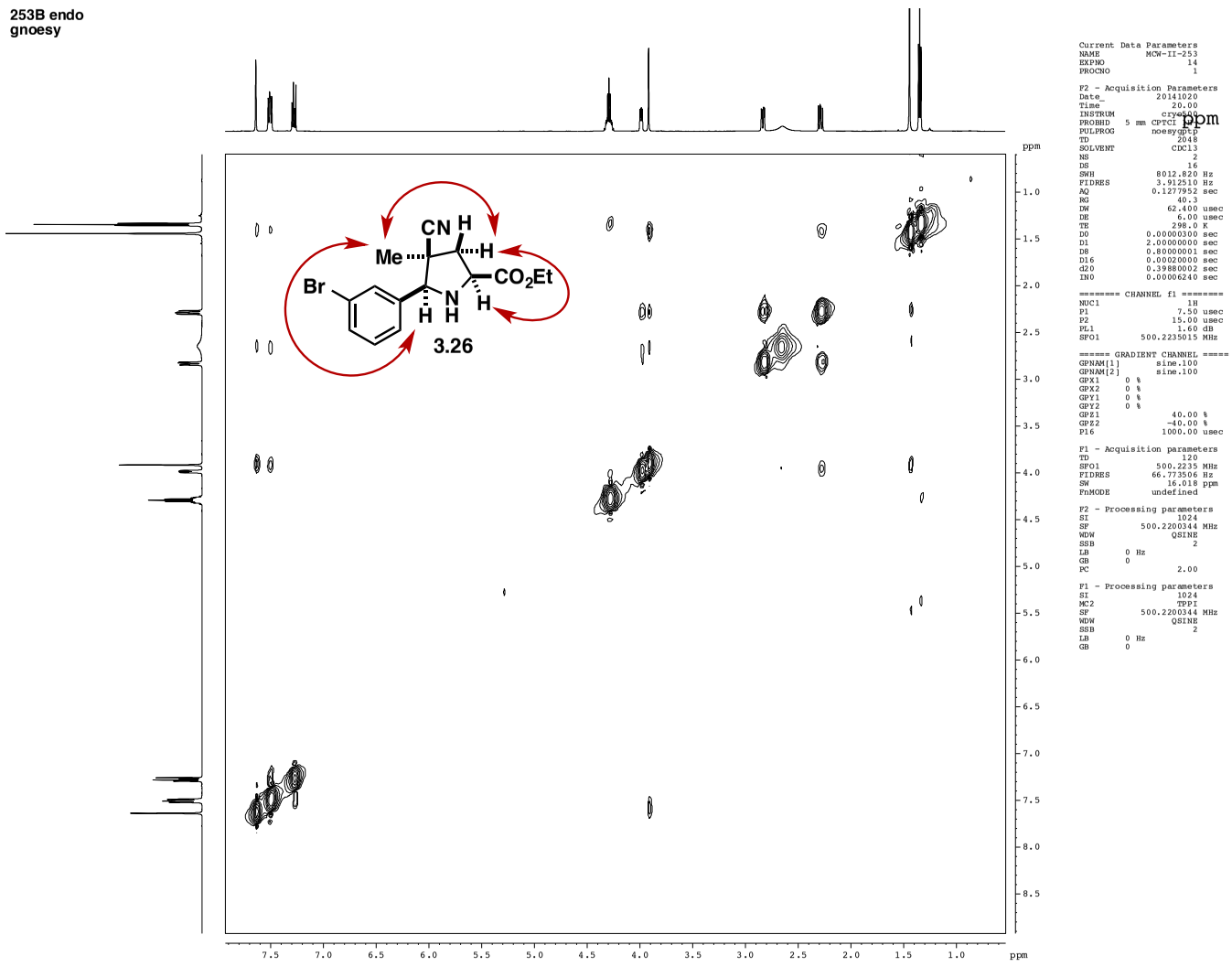
F2 - Acquisition Parameter
Date_             20141013
Time                 15.57
INSTRUM            cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.pr
TD                   65536
SOLVENT              CDCl3
NS                      88
DS                      16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813440 se
RG                  5160.6
DW                   16.500 us
DE                    6.00 us
TE                   298.0 K
D1              0.25000000 se
d11             0.03000000 se
D16             0.00020000 se
d17             0.00019600 se
MCREST    0 sec
MCWRK           0.01500000 se
P2                   31.00 us

======== CHANNEL f1 ======
NUC1                   13C
P1                   15.50 us
P11                 500.00 us
P12                2000.00 us
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1         125.7942548 MH
SP1                   3.20 dB
SP2                   3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1    0 Hz
SPOFF2    0 Hz

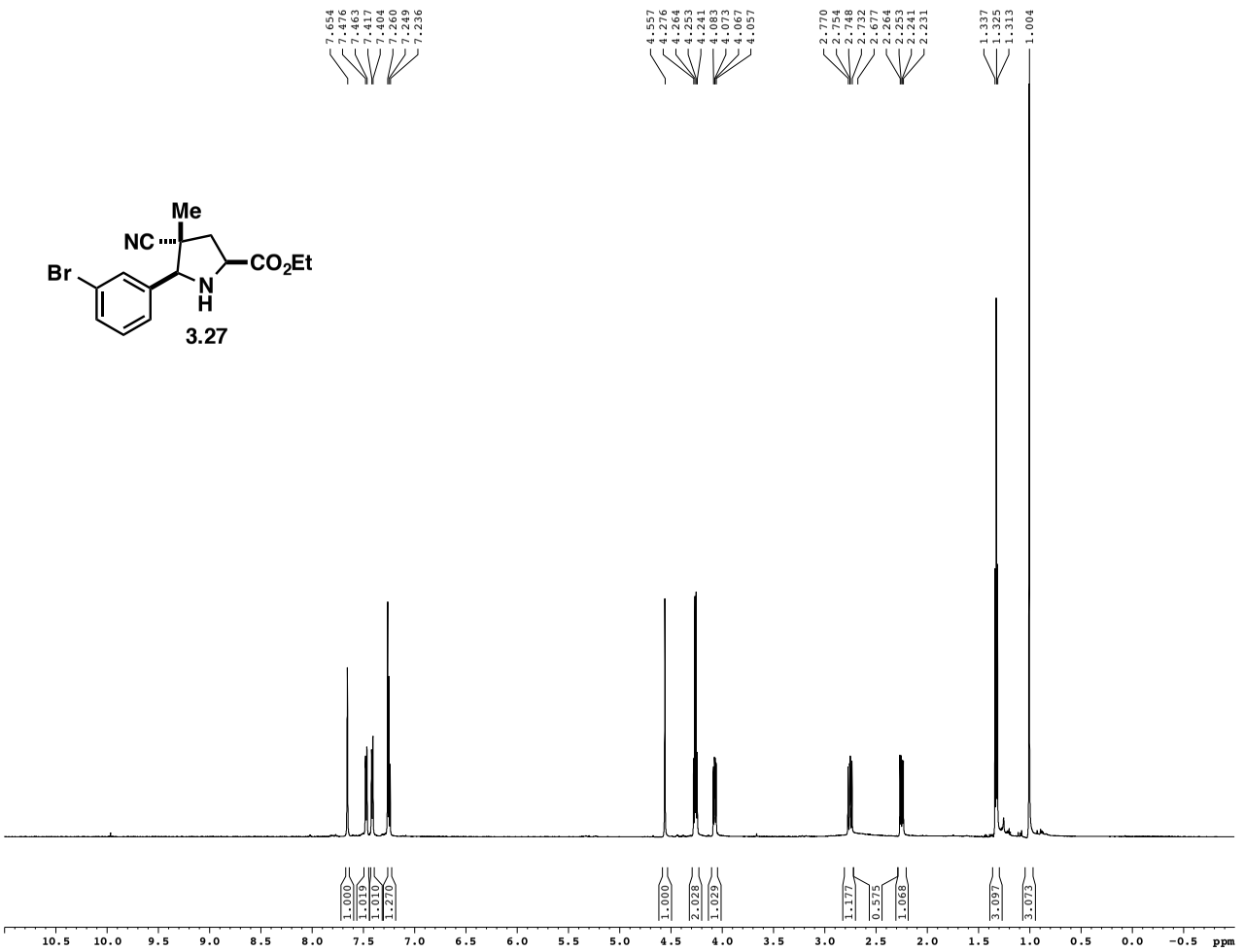
======== CHANNEL f2 ======
CPDPRG[2          waltz16
NUC2                   1H
PCPD2               100.00 us
PL2                   1.60 dB
PL12                 24.60 dB
SFO2         500.2225011 MH

====== GRADIENT CHANNEL ==
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                 30.00 %
GPZ2                 50.00 %
p15                 500.00 us
p16                1000.00 us

F2 - Processing parameters
SI                   65536
SF           125.7804122 MH
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    2.00
```


253B endo
gnoesy
CN H
Me
H
CO2Et
Br
N
H H
H
3.26
ppm
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
ppm
Current Data Parameters
NAME MCW-II-253
EXPNO 14
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141020
Time 20.00
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 2
DS 16
SWH 8012.820 Hz
FIDRES 3.912510 Hz
AQ 0.1277952 sec
RG 40.3
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D8 0.80000001 sec
D16 0.00020000 sec
d20 0.39880002 sec
IN0 0.00006240 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
P2 15.00 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] sine.100
GPNAM[2] sine.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 40.00 %
GPZ2 -40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 120
SFO1 500.2235 MHz
FIDRES 66.773506 Hz
SW 16.018 ppm
FnMODE undefined
F2 - Processing parameters
SI 1024
SF 500.2200344 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 2.00
F1 - Processing parameters
SI 1024
MC2 TPPI
SF 500.2200344 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0

Exo Adduct

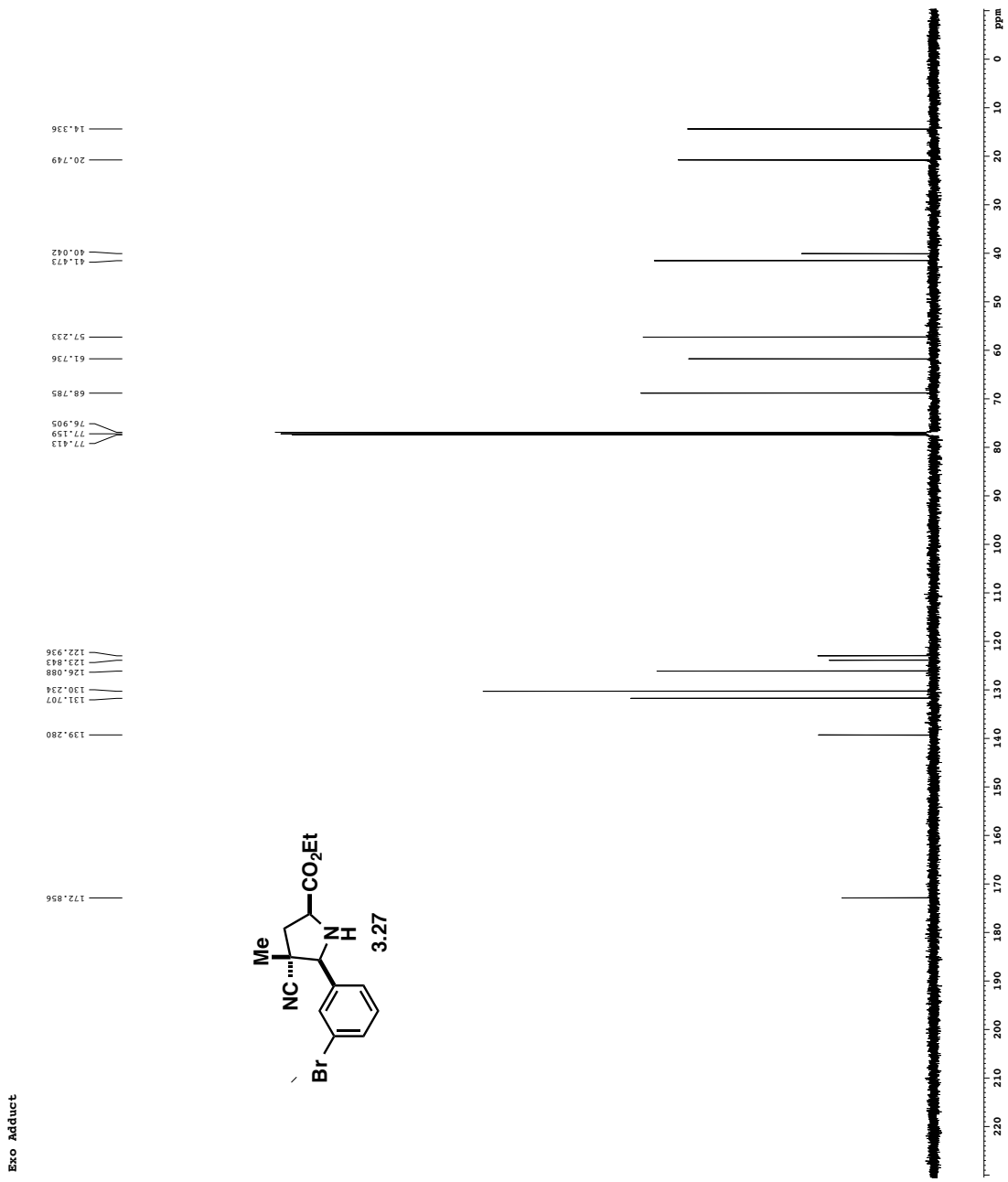


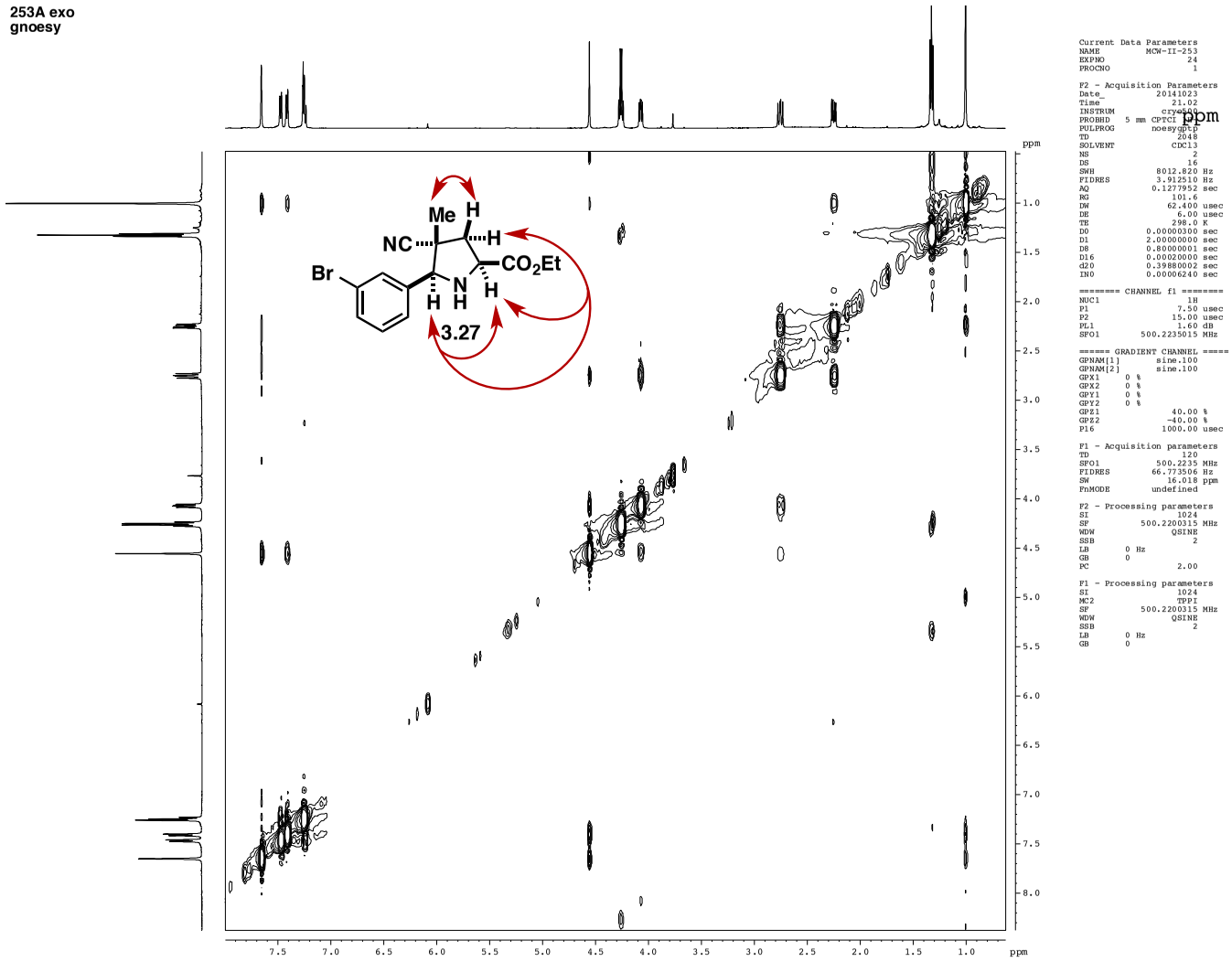

```
Current Data Parameters
NAME                  MCW-II-253
EXPNO                          4
PROCNO                         1

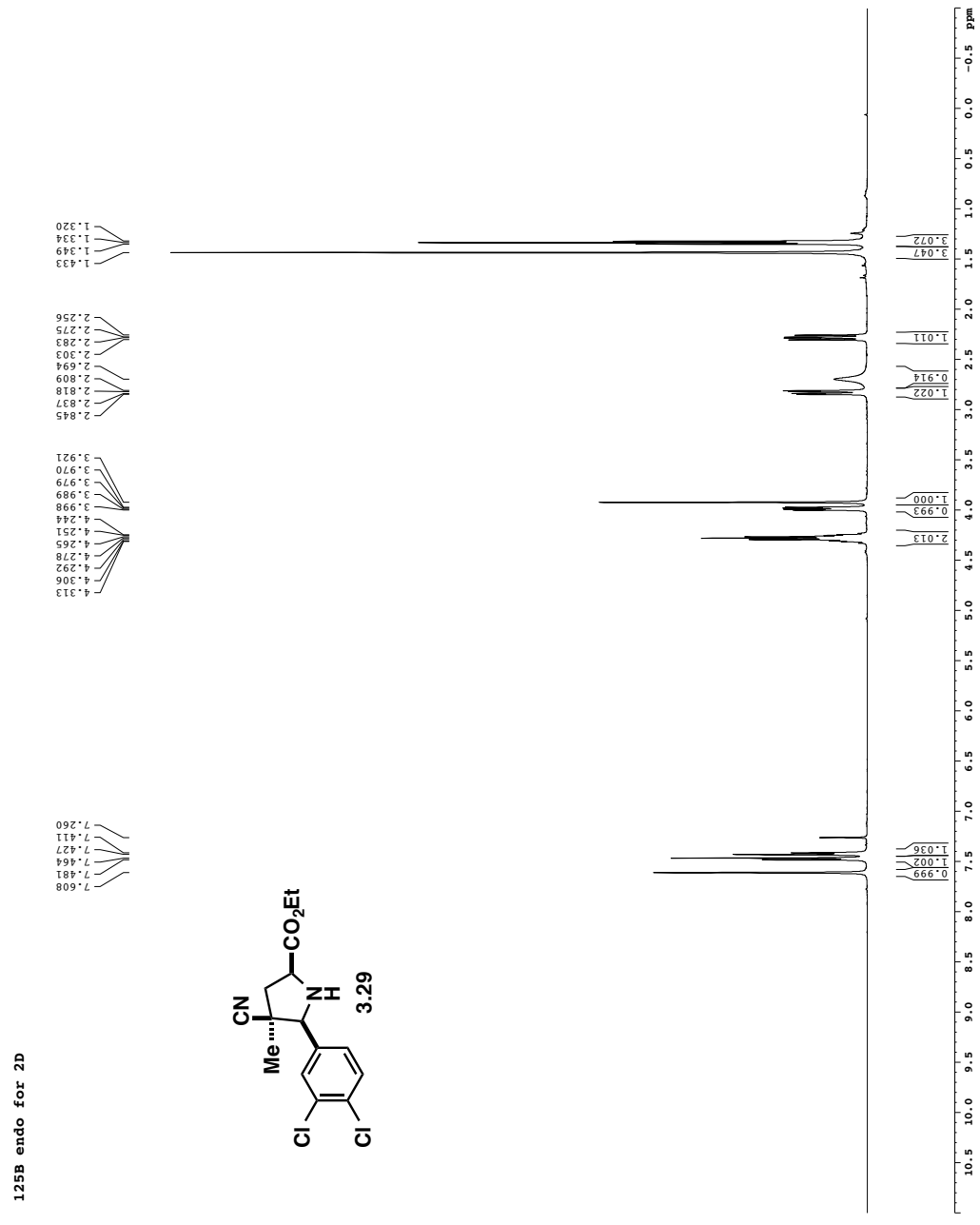
F2 - Acquisition Parameters
Date_               20141013
Time                      15.19
INSTRUM                  av600
PROBHD   5 mm TBI 1H/13
PULPROG                  zg30
TD                      98074
SOLVENT                  CDC13
NS                             8
DS                             0
SWH                  9615.385 Hz
FIDRES               0.098042 Hz
AQ                   5.0998478 sec
RG                           322
DW                        52.000 usec
DE                        14.54 usec
TE                        298.0 K
D1                   0.10000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1               600.1342009 MHz
NUC1                         1H
P1                        8.00 usec
PLW1               23.01441956 W

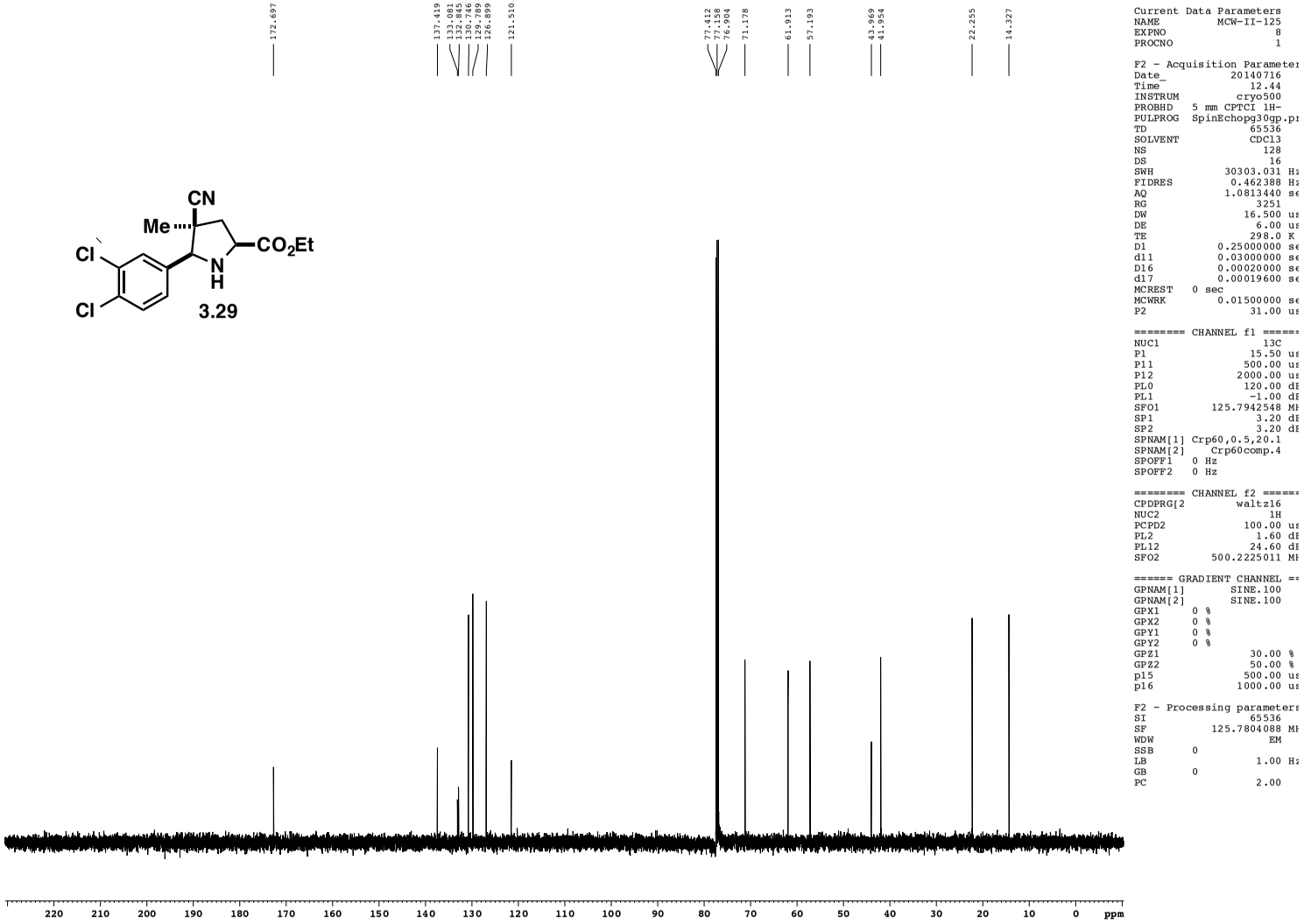
F2 - Processing parameters
SI                         65536
SF                 600.1300344 MHz
WDW                          EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
```


Exo Adduct
Current Data Parameters
NAME MCW-II-253
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141013
Time 15.46
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 240
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 4572
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MC2REST 0 sec
MCWRK 0.01500000 sec
P2 31.00 usec
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
PL2 20000.00 dB
PL2 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804091 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
Me
NC
CO2Et
N
H
Br
3.27
172.856
139.280
131.707
130.234
126.088
123.843
122.936
77.413
77.159
76.905
68.785
61.736
57.233
41.473
40.042
20.749
14.336
ppm


253A exo
gnoesy
Me
H
NC
H
CO2Et
Br
N
H
H
H
3.27
ppm
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
ppm
Current Data Parameters
NAME MCW-II-253
EXPNO 24
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141023
Time 21.02
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 2
DS 16
SWH 8012.820 Hz
FIDRES 3.912510 Hz
AQ 0.1277952 sec
RG 101.6
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D8 0.80000001 sec
D16 0.00020000 sec
d20 0.39880002 sec
IN0 0.00006240 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
P2 15.00 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] sine.100
GPNAM[2] sine.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 40.00 %
GPZ2 -40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 120
SFO1 500.2235 MHz
FIDRES 66.773506 Hz
SW 16.018 ppm
FnMODE undefined
F2 - Processing parameters
SI 1024
SF 500.2200315 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 2.00
F1 - Processing parameters
SI 1024
MC2 TPPI
SF 500.2200315 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0


125B endo for 2D
Current Data Parameters
NAME MEW-II-125
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140719
Time 10.18
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 0
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 6.3
DW 62.400 usec
DE 6.00 usec
TE 292.9 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200318 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
7.608
7.481
7.464
7.427
7.411
7.260
4.313
4.306
4.292
4.278
4.265
4.251
4.244
3.998
3.989
3.979
3.970
3.921
2.845
2.837
2.818
2.809
2.694
2.303
2.283
2.275
2.256
1.433
1.349
1.334
1.320
0.999
1.002
1.036
2.013
0.993
1.000
1.022
0.914
1.011
3.047
3.072
CN
Me
CO2Et
N
H
Cl
Cl
3.29
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
ppm

Endo Adduct




```
Current Data Parameters
NAME            MCW-II-125
EXPNO                    8
PROCNO                   1

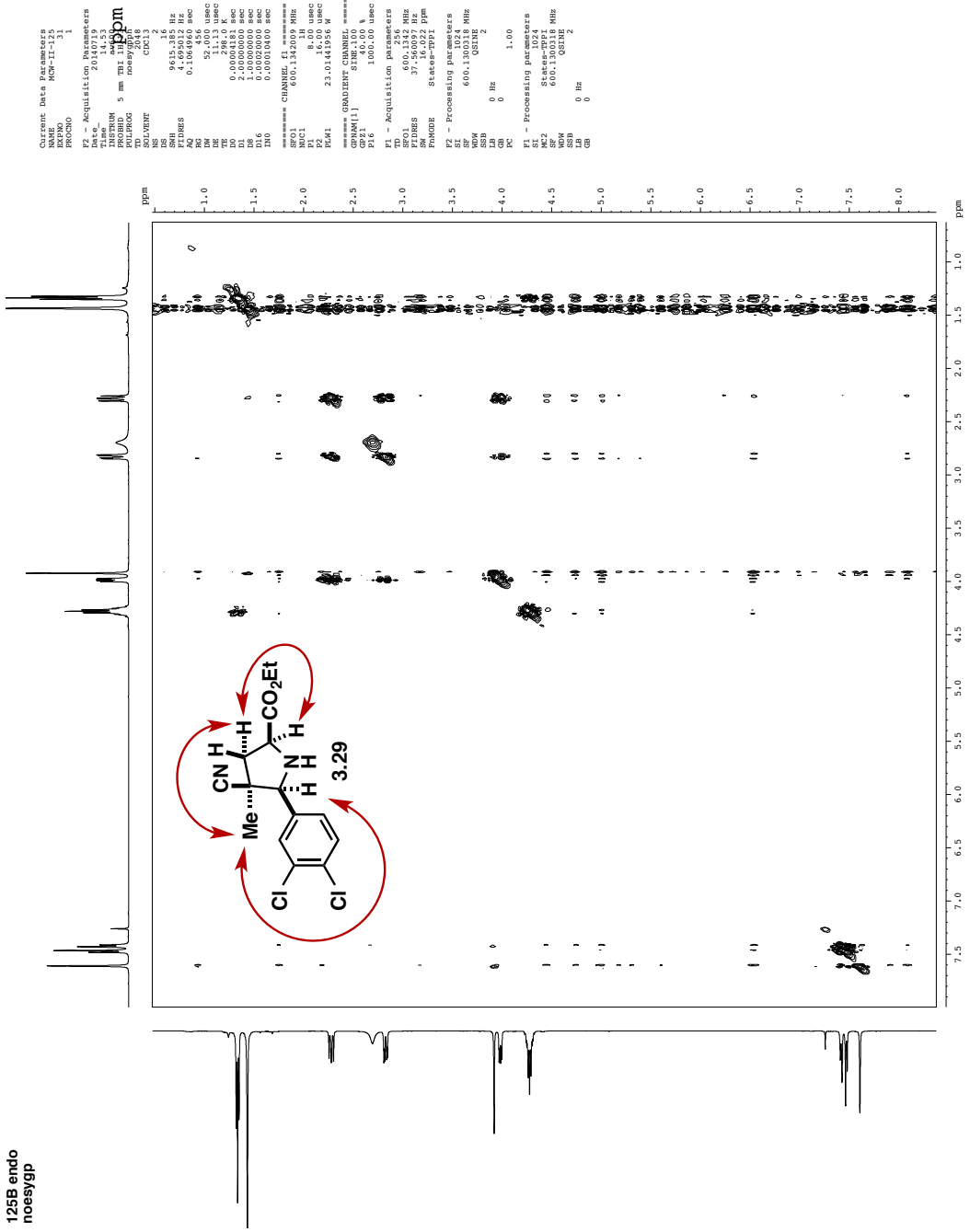
F2 - Acquisition Parameter
Date_             20140716
Time                 12.44
INSTRUM             cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.pr
TD                   65536
SOLVENT              CDCl3
NS                     128
DS                      16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0813440 se
RG                   3251
DW                 16.500 us
DE                  6.00 us
TE                 298.0 K
D1            0.25000000 se
d11           0.03000000 se
D16           0.00020000 se
d17           0.00019600 se
MCREST   0 sec
MCWRK         0.01500000 se
P2                 31.00 us

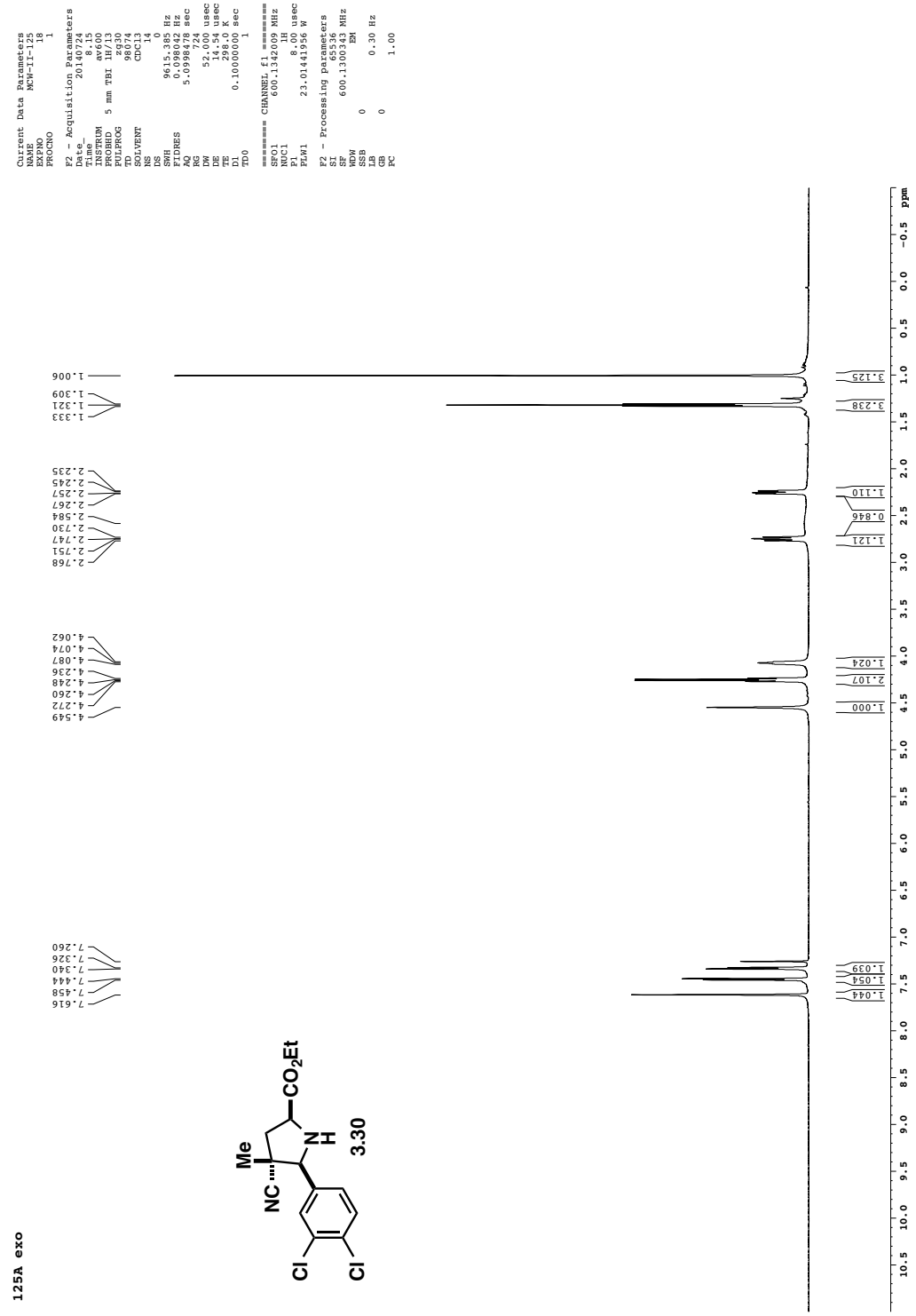
======== CHANNEL f1 ======
NUC1                 13C
P1                 15.50 us
P11               500.00 us
P12              2000.00 us
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MH
SP1                 3.20 dB
SP2                 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1   0 Hz
SPOFF2   0 Hz

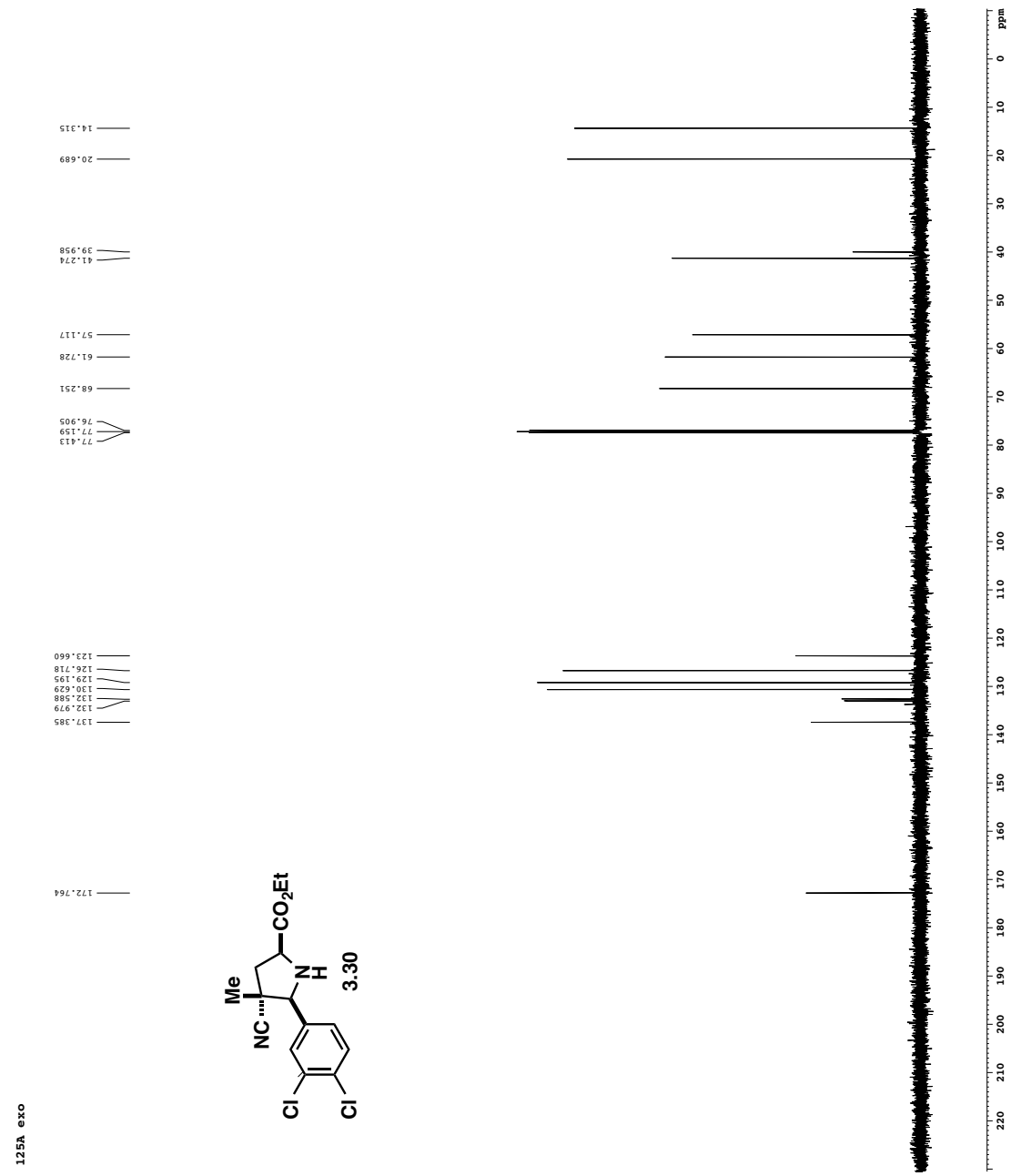
======== CHANNEL f2 ======
CPDPRG[2         waltz16
NUC2                 1H
PCPD2             100.00 us
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MH

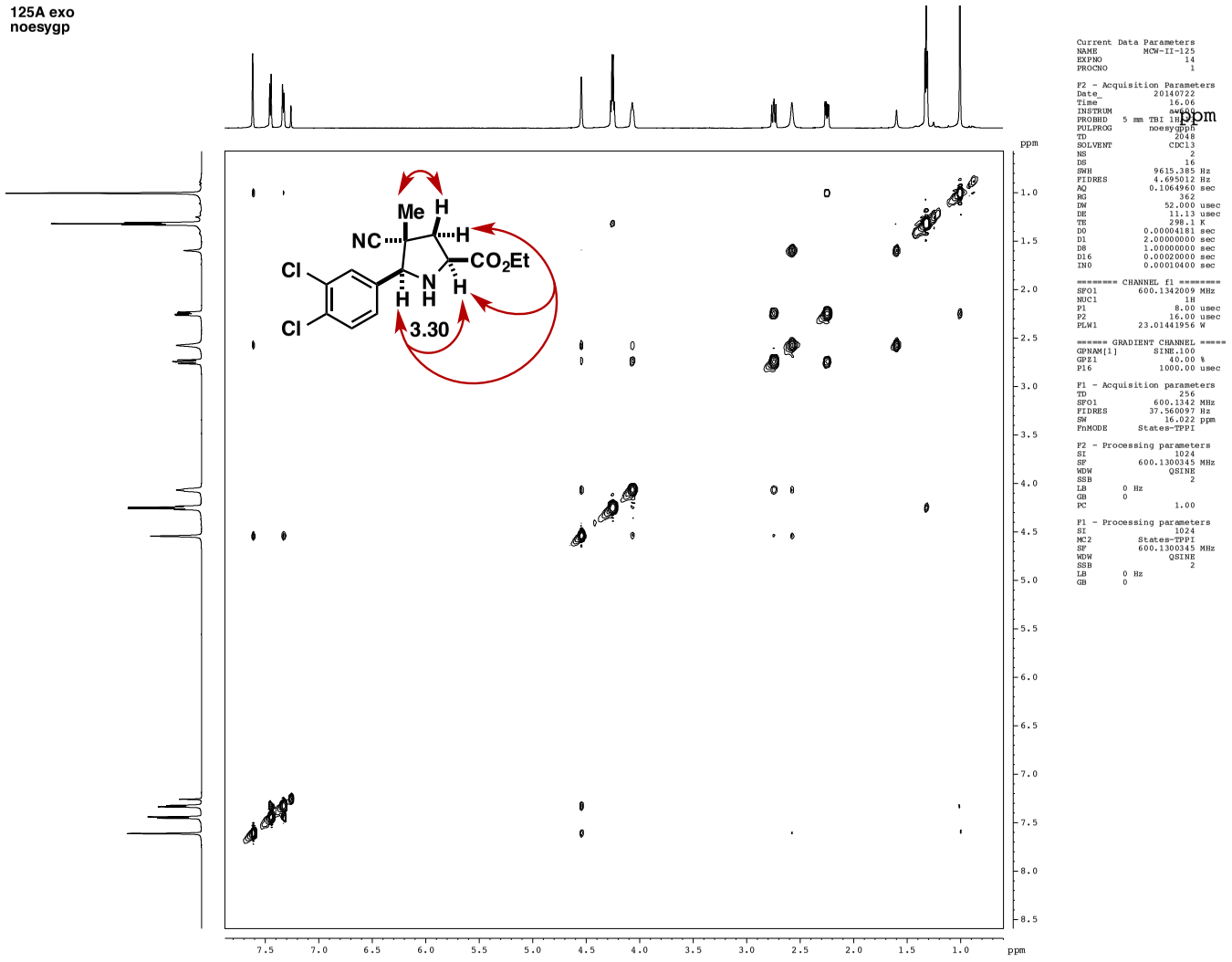
====== GRADIENT CHANNEL ==
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 us
p16              1000.00 us

F2 - Processing parameters
SI                   65536
SF          125.7804088 MH
WDW                     EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  2.00
```


125B endo
noesygp
Current Data Parameters
NAME MCM-II-31
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140719
Time 14.03
INSTRUM spect
PROBHD 5 mm TBI 1H/
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 16
DS 2
SWH 9615.385 Hz
FIDRES 4.695922 Hz
AQ 0.1064960 sec
RG 456
DW 52.000 usec
DE 11.13 usec
TE 298.0 K
D0 2.00004181 sec
D1 2.00000000 sec
D8 1.00000000 sec
D16 0.00020000 sec
ZH0 0.0010400 sec
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
P2 16.00 usec
PLW1 23.01441956 W
======== GRADIENT CHANNEL ====
GPNAM[1] SINE.100
GPZ1 40.00 %
DP16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 600.1342 MHz
FIDRES 37.560097 Hz
SW 16.022 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 1024
SF 600.1300318 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 States-TPPI
SF 600.1300318 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
ppm
CO2Et
CN
Me
Cl
Cl
3.29


125A exo
Current Data Parameters
NAME MEW-II-125
EXPNO 18
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140724
Time 8.15
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 14
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.09988478 sec
RG 724
DW 52.000 usec
DE 14.54 usec
TE 298.0 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300343 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.616
7.458
7.444
7.340
7.326
7.260
4.549
4.272
4.260
4.248
4.236
4.087
4.074
4.062
2.768
2.751
2.747
2.730
2.584
2.267
2.257
2.245
2.235
1.333
1.321
1.309
1.006
1.044
1.054
1.039
1.000
2.107
1.024
1.121
0.846
1.110
3.238
3.125
Me
NC
CO2Et
N
H
3.30
Cl
Cl
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 ppm


125A exo
Current Data Parameters
NAME MCW-II-125
EXPNO 38
PROCNO 1
F2 - Acquisition Parameter
Date_ 20140721
Time 18.13
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30.p1
TD 65536
SOLVENT CDCl3
NS 72
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 se
RG 155.2
DW 16.500 us
DE 6.00 us
TE 298.0 K
D1 0.25000000 se
d11 0.03000000 se
D16 0.00020000 se
d17 0.00019600 se
MC4REST 0 sec
MCWRK 0.01500000 se
P2 31.00 us
======== CHANNEL f1 ======
NUC1 13C
P1 15.50 us
P11 500.00 us
PL2 20000.00 dB
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MH
SP1 3.20 dB
SP2 3.20 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ======
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 us
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MH
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 us
p16 1000.00 us
F2 - Processing parameters
SI 65536
SF 125.7804108 MH
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
172.764
137.385
132.979
132.588
130.629
129.195
126.718
123.660
77.413
77.159
76.905
68.251
61.728
57.117
41.274
39.958
20.689
14.315
Me
NC
CO2Et
N
H
3.30
Cl
Cl
ppm




```
Current Data Parameters
NAME                  MCW-II-125
EXPNO                         14
PROCNO                         1

F2 - Acquisition Parameters
Date_               20140722
Time                      16.06
INSTRUM                   av600
PROBHD    5 mm TBI 1H,13C,15N Z-G
PULPROG             noesygpph
TD                        2048
SOLVENT                   CDCl3
NS                           2
DS                          16
SWH                   9615.385 Hz
FIDRES                4.695012 Hz
AQ                    0.1064960 sec
RG                          362
DW                       52.000 usec
DE                       11.13 usec
TE                       298.1 K
D0                    0.00004181 sec
D1                    2.00000000 sec
D8                    1.00000000 sec
D16                   0.00020000 sec
IN0                   0.00010400 sec

======== CHANNEL f1 ========
SFO1                600.1342009 MHz
NUC1                        1H
P1                        8.00 usec
P2                       16.00 usec
PLW1               23.01441956 W

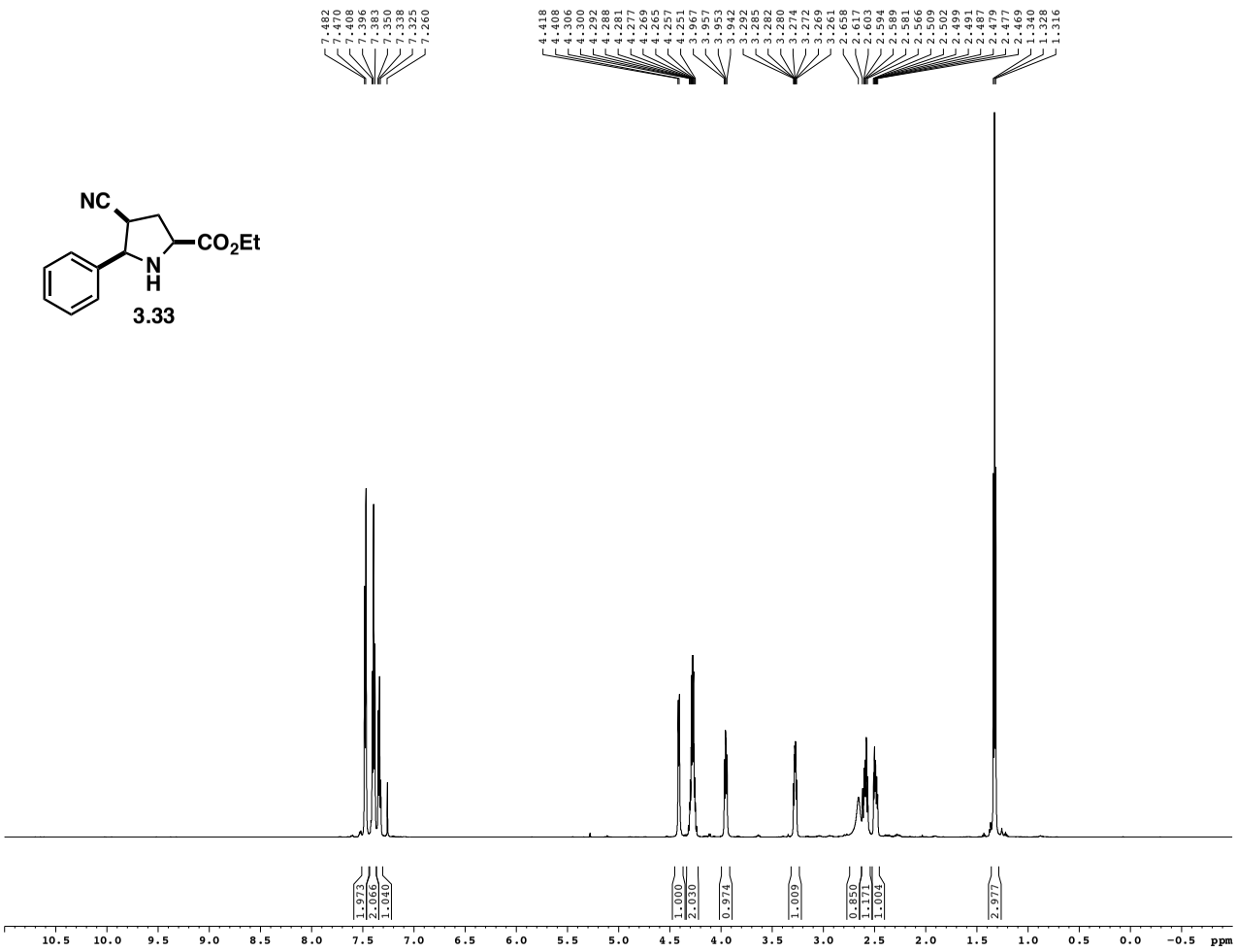
====== GRADIENT CHANNEL =====
GPNAM[1]               SINE.100
GPZ1                     40.00 %
P16                    1000.00 usec

F1 - Acquisition parameters
TD                          256
SFO1                600.1342 MHz
FIDRES               37.560097 Hz
SW                       16.022 ppm
FnMODE              States-TPPI

F2 - Processing parameters
SI                          1024
SF                  600.1300345 MHz
WDW                       QSINE
SSB                          2
LB              0 Hz
GB              0
PC                        1.00

F1 - Processing parameters
SI                          1024
MC2                 States-TPPI
SF                  600.1300345 MHz
WDW                       QSINE
SSB                          2
LB              0 Hz
GB              0
```

277B for 1H-1H 2D

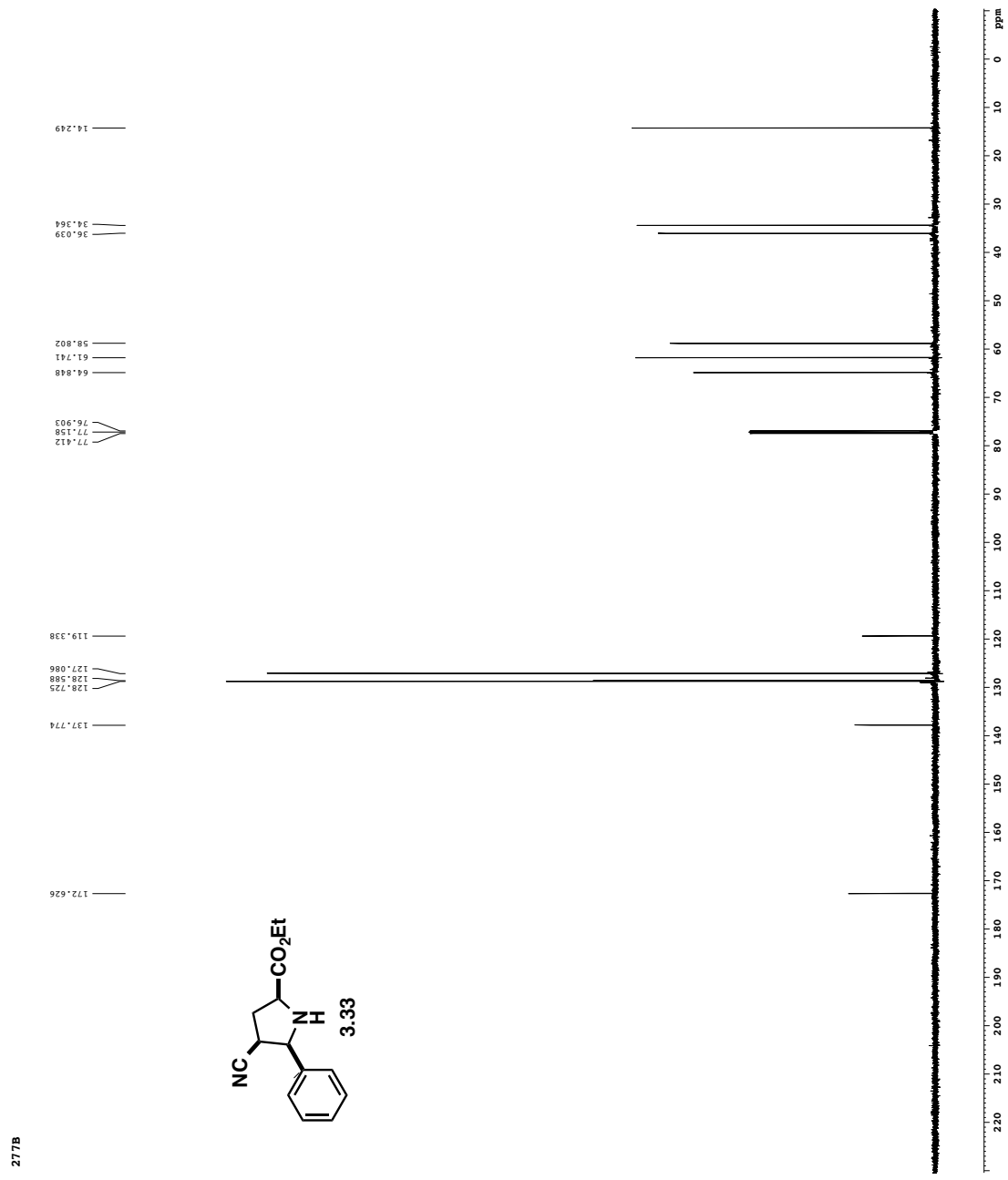


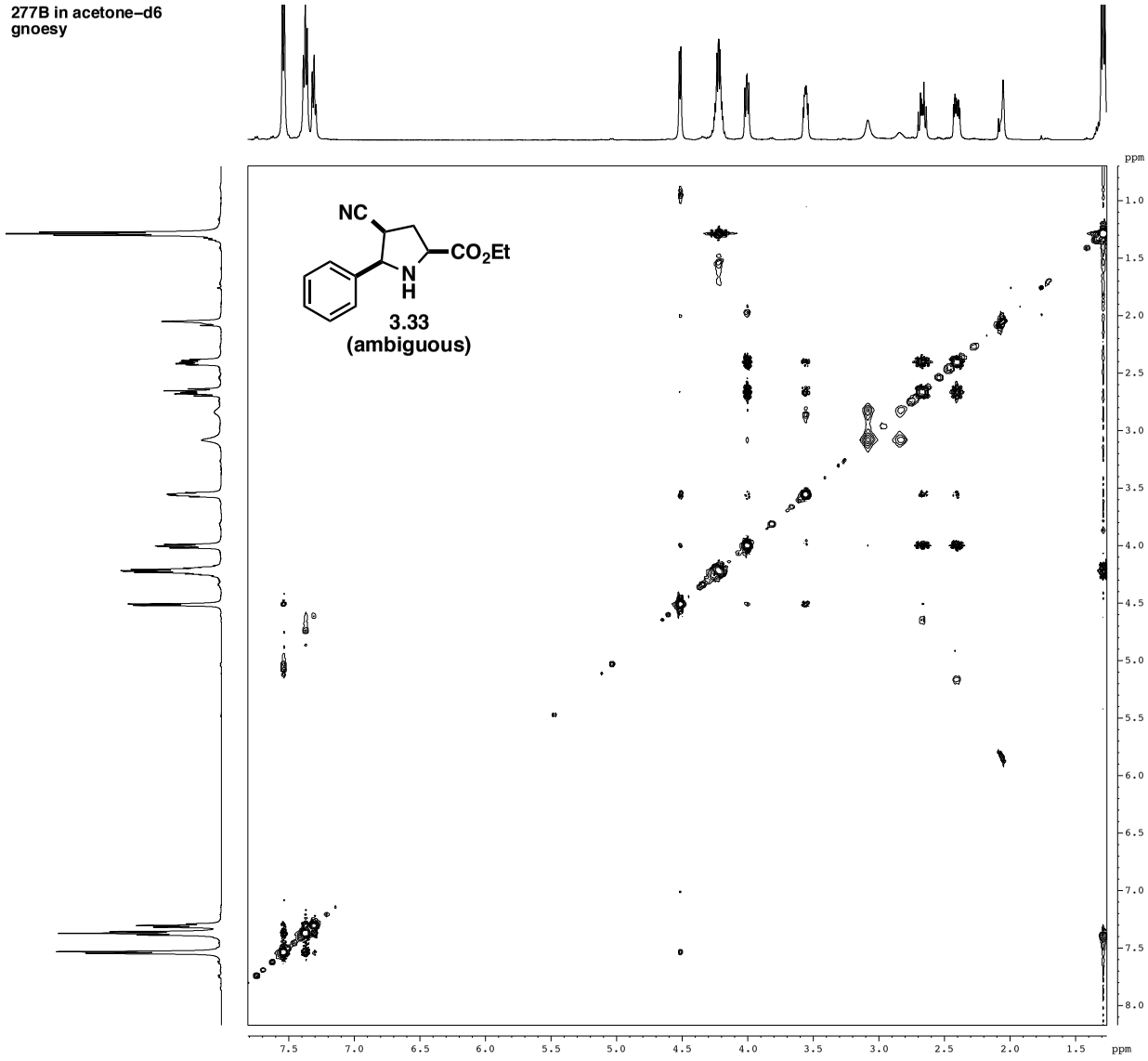

```
Current Data Parameters
NAME                  MCW-II-277
EXPNO                          9
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20141114
Time                       15.04
INSTRUM                    av600
PROBHD   5 mm TBI 1H/13
PULPROG                    zg30
TD                         98074
SOLVENT                    CDCl3
NS                             8
DS                             0
SWH                     9615.385 Hz
FIDRES                  0.098042 Hz
AQ                     5.0998478 sec
RG                           256
DW                        52.000 usec
DE                        14.54 usec
TE                          298.0 K
D1                    0.10000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1                600.1342009 MHz
NUC1                        1H
P1                        8.00 usec
PLW1                23.01441956 W

F2 - Processing parameters
SI                         65536
SF                  600.1300340 MHz
WDW                           EM
SSB                0
LB                         0.30 Hz
GB                 0
PC                         1.00
```


277B
Current Data Parameters
NAME MCW-II-277
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141114
Time 14.34
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 72
DS 0
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 155.2
DW 16.500 us
DE 6.00 us
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MC2REST 0 sec
MCWRK 0.01500000 sec
P2 33.10 us
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 us
P11 500.00 us
PL12 20000.00 dB
PL2 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 us
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 us
p16 1000.00 us
F2 - Processing parameters
SI 65536
SF 125.7804209 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
14.249
34.364
36.039
58.802
61.741
64.848
76.903
77.158
77.412
119.338
127.086
128.588
128.725
137.774
172.626
NC
CO2Et
N
H
3.33
ppm




```
Current Data Parameters
NAME                  MCW-II-277
EXPNO                         53
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20150809
Time                       8.49
INSTRUM                  cryo500
PROBHD     5 mm CPTCI 1H-13C/15N
PULPROG                noesygpph
TD                          2048
SOLVENT                  Acetone
NS                             2
DS                             0
SWH                   5000.000 Hz
FIDRES                2.441406 Hz
AQ                    0.2048000 sec
RG                         25.4
DW                     100.000 usec
DE                       6.00 usec
TE                       298.0 K
D0                    0.00000300 sec
D1                    2.00000000 sec
D8                    0.80000001 sec
D16                   0.00020000 sec
d20                   0.39880002 sec
IN0                   0.00010000 sec

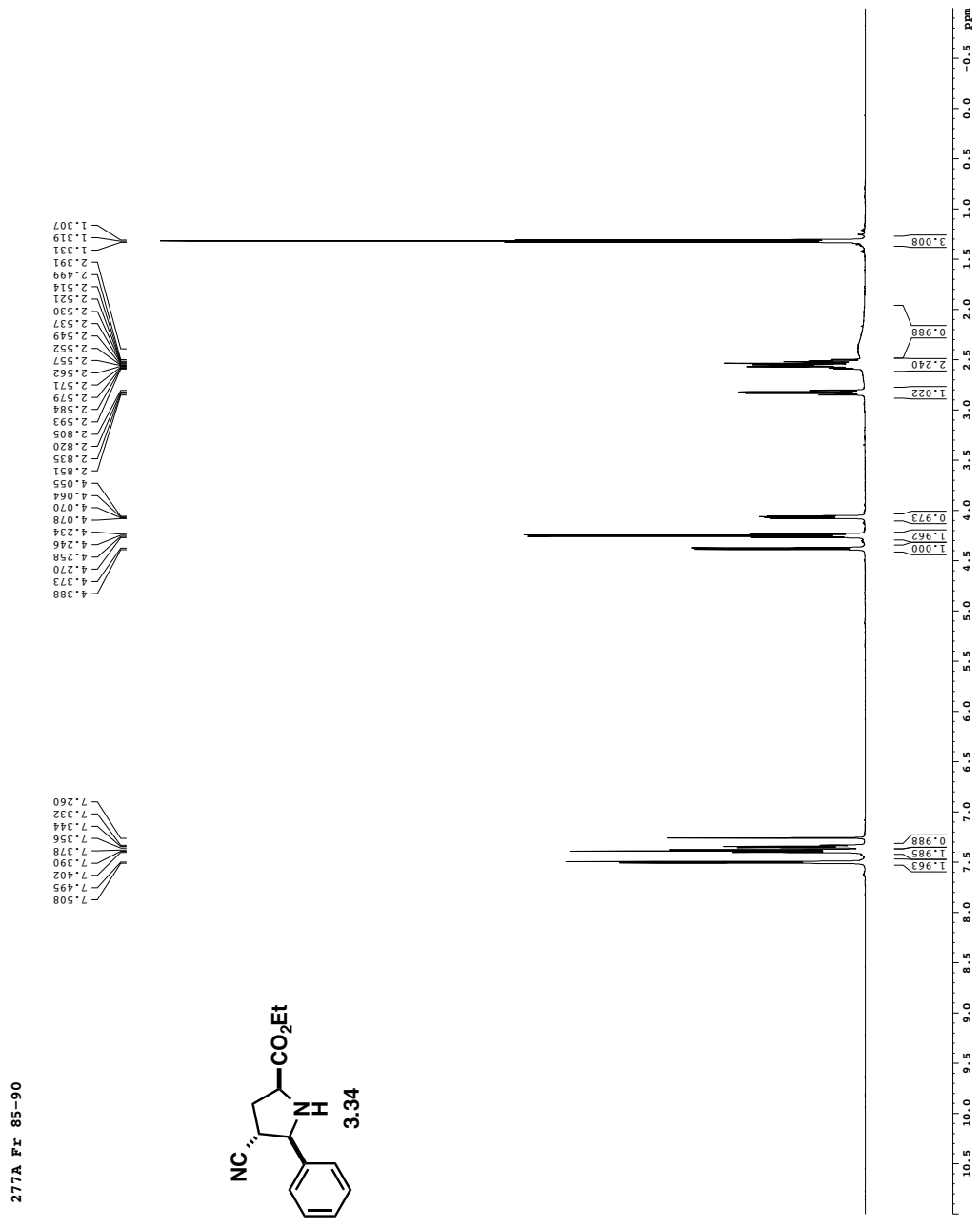
======== CHANNEL f1 ========
NUC1                         1H
P1                         7.50 usec
P2                        15.00 usec
PL1                        1.60 dB
SFO1                500.2225126 MHz

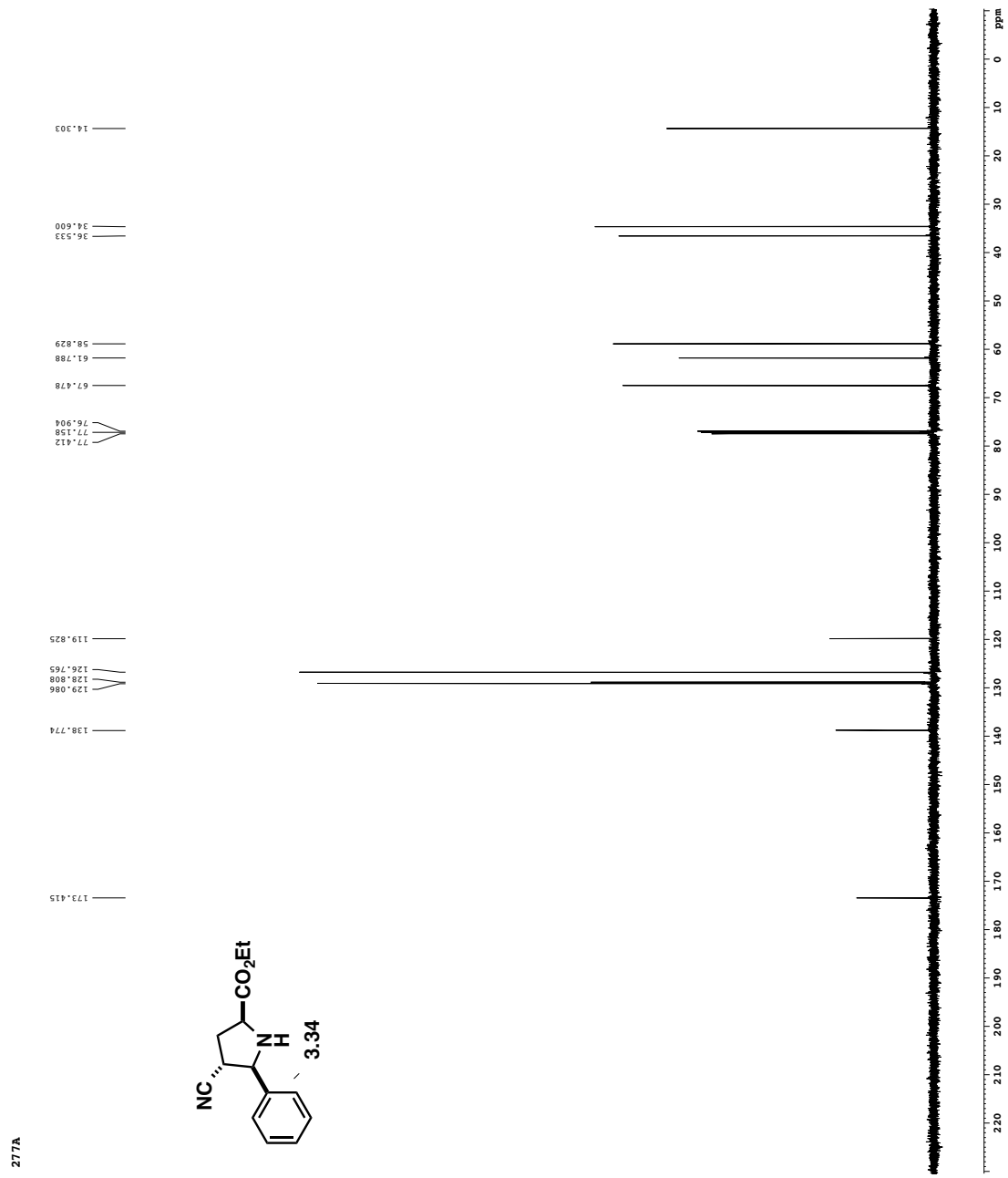
====== GRADIENT CHANNEL =====
GPNAM[1]                sine.100
GPNAM[2]                sine.100
GPX1          0 %
GPX2          0 %
GPY1          0 %
GPY2          0 %
GPZ1                       40.00 %
GPZ2                      -40.00 %
P16                     1000.00 usec

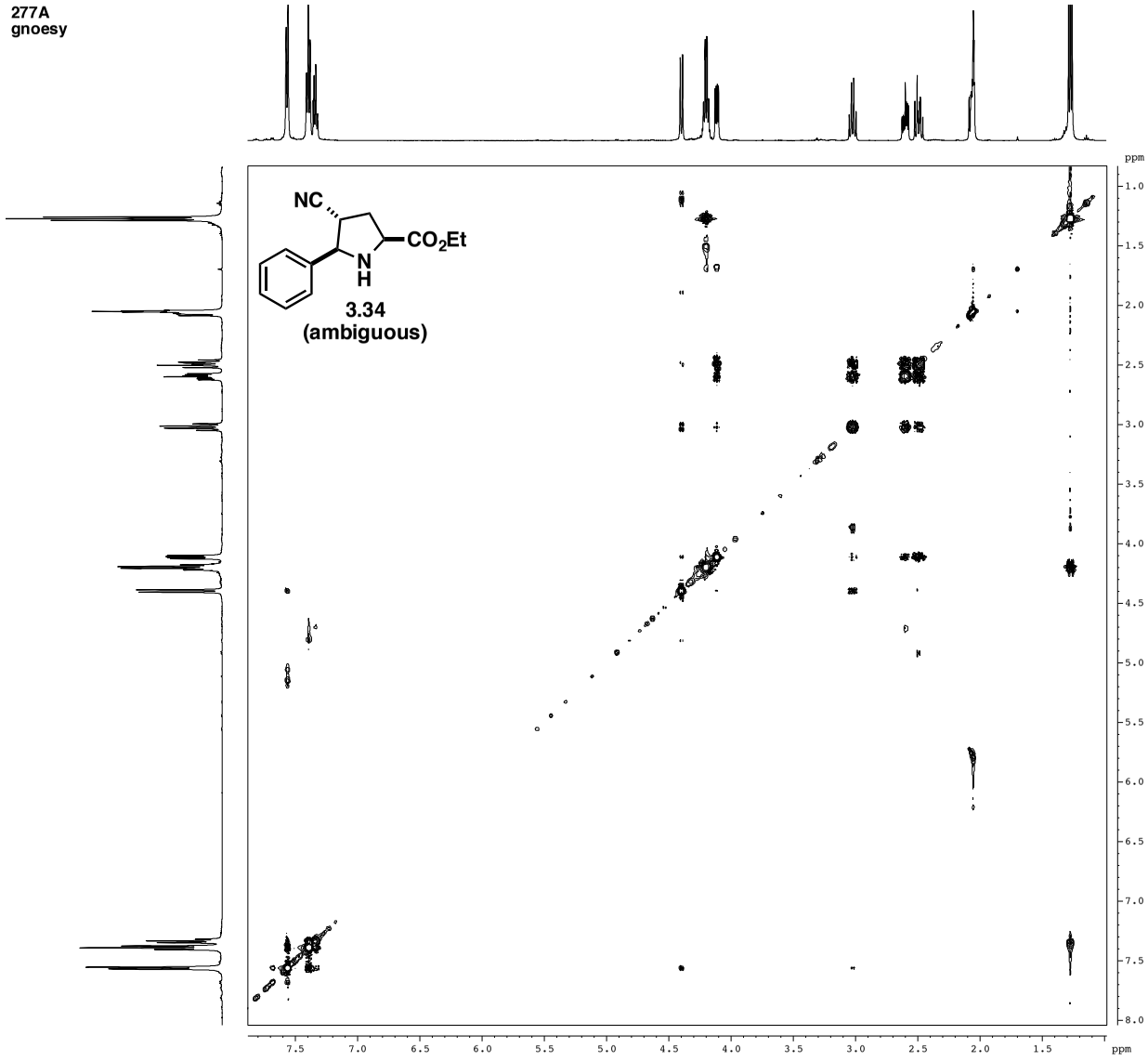
F1 - Acquisition parameters
TD                           560
SFO1                500.2225 MHz
FIDRES                8.928572 Hz
SW                        9.996 ppm
FnMODE                undefined

F2 - Processing parameters
SI                           1024
SF                  500.2200179 MHz
WDW                        QSINE
SSB                            2
LB            0 Hz
GB            0
PC                         1.40

F1 - Processing parameters
SI                           1024
MC2                          TPPI
SF                  500.2200179 MHz
WDW                        QSINE
SSB                            2
LB            0 Hz
GB            0
```


277A Fr 85-90
Current Data Parameters
NAME MEW-II-277
EXPNO 12
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141219
Time 17.40
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 8
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.09988478 sec
RG 203
DW 52.000 usec
DE 14.54 usec
TE 298.1 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
F2 - Processing parameters
SI 65536
SF 600.1300336 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.508
7.495
7.402
7.390
7.378
7.356
7.344
7.332
7.260
4.388
4.373
4.258
4.246
4.234
4.078
4.070
4.064
4.055
2.851
2.835
2.820
2.805
2.593
2.584
2.579
2.571
2.562
2.557
2.552
2.549
2.537
2.530
2.521
2.514
2.499
2.391
1.331
1.319
1.307
3.008
0.988
2.240
1.022
0.973
1.962
1.000
0.988
1.985
1.963
NC
CO2Et
N
H
3.34
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 ppm


277a
Current Data Parameters
NAME MCW-II-277
EXPNO 14
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141219
Time 17.49
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 96
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 459.6
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MCREST 0 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
PL2 20000.00 dB
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.59 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804131 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
14.303
34.600
36.533
58.829
61.788
67.478
76.904
77.158
77.412
119.825
126.765
128.808
129.086
138.774
173.415
NC
CO2Et
N
H
3.34
ppm




```
Current Data Parameters
NAME                 MCW-II-277
EXPNO                        51
PROCNO                        1

F2 - Acquisition Parameters
Date_              20150808
Time                    20.49
INSTRUM                cryo500
PROBHD     5 mm CPTCI 1H-13C/
PULPROG            noesygpph
TD                         2048
SOLVENT                 Acetone
NS                            2
DS                            0
SWH                 5000.000 Hz
FIDRES              2.441406 Hz
AQ                  0.2048000 sec
RG                           32
DW                   100.000 usec
DE                     6.00 usec
TE                    298.0 K
D0                  0.00000300 sec
D1                  2.00000000 sec
D8                  0.80000001 sec
D16                 0.00020000 sec
d20                 0.39880002 sec
IN0                 0.00010000 sec

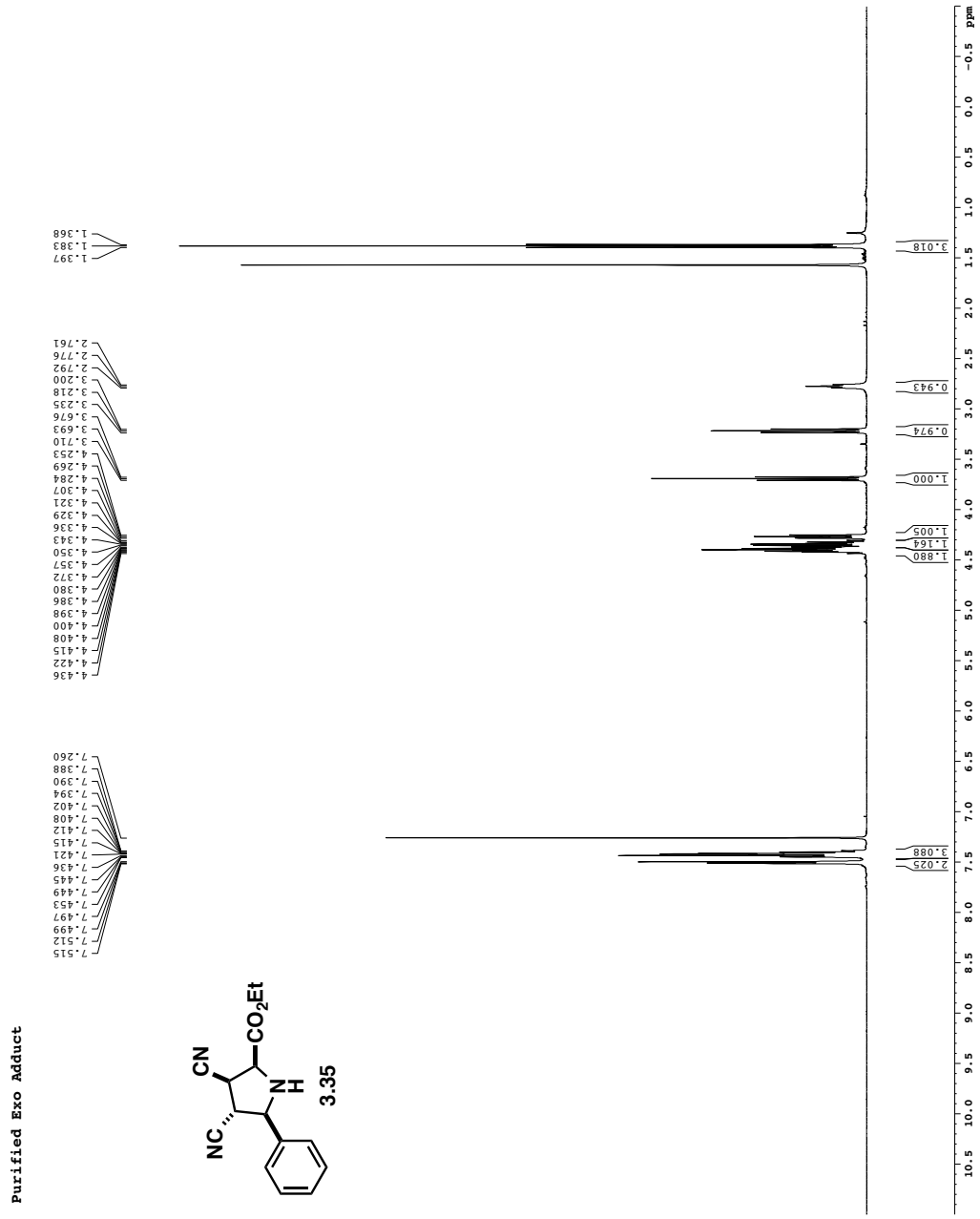
======== CHANNEL f1 ========
NUC1                       1H
P1                       7.50 usec
P2                      15.00 usec
PL1                      1.60 dB
SFO1             500.2224999 MHz

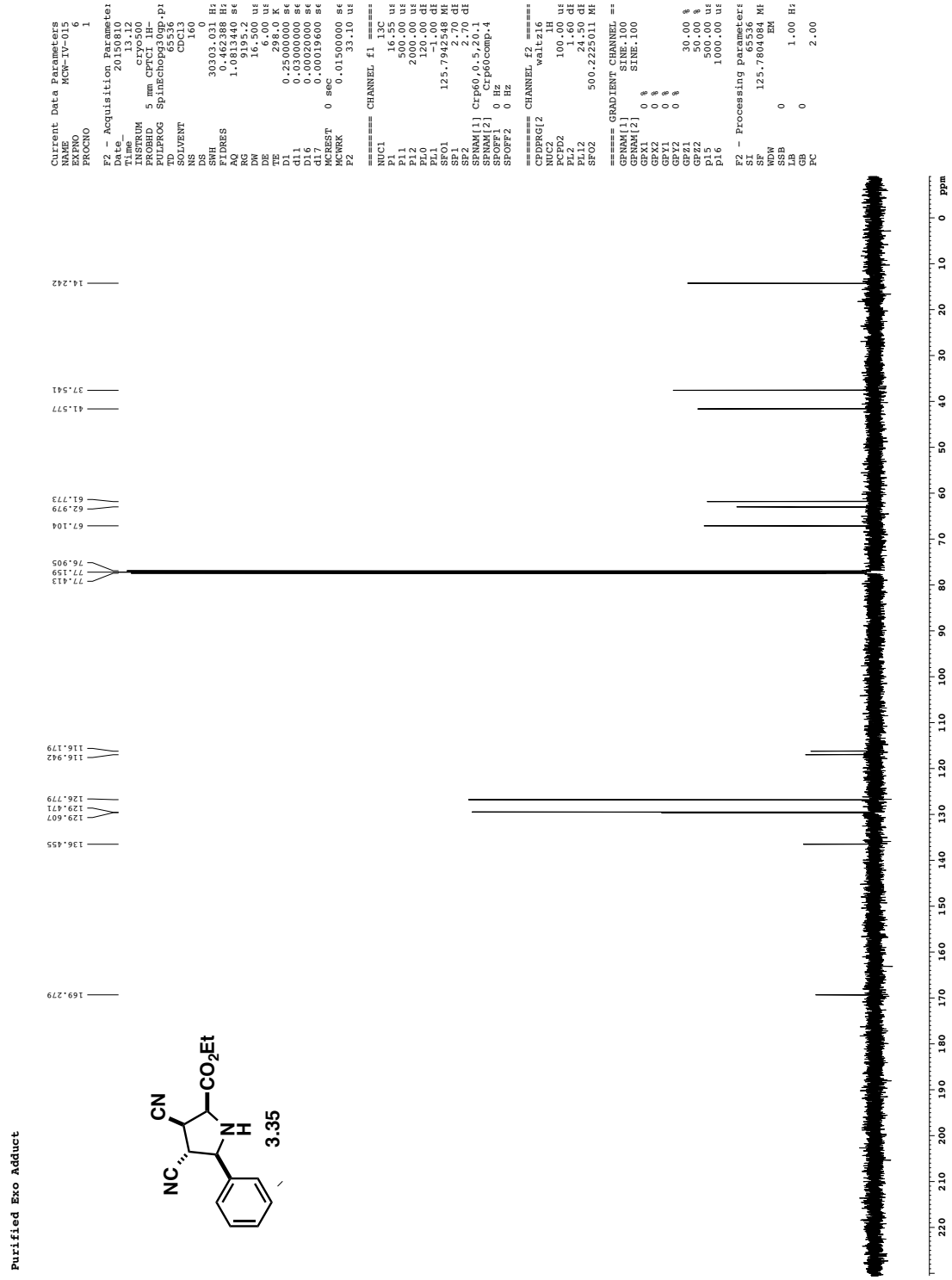
====== GRADIENT CHANNEL =====
GPNAM[1]              sine.100
GPNAM[2]              sine.100
GPX1        0 %
GPX2        0 %
GPY1        0 %
GPY2        0 %
GPZ1                    40.00 %
GPZ2                   -40.00 %
P16                  1000.00 usec

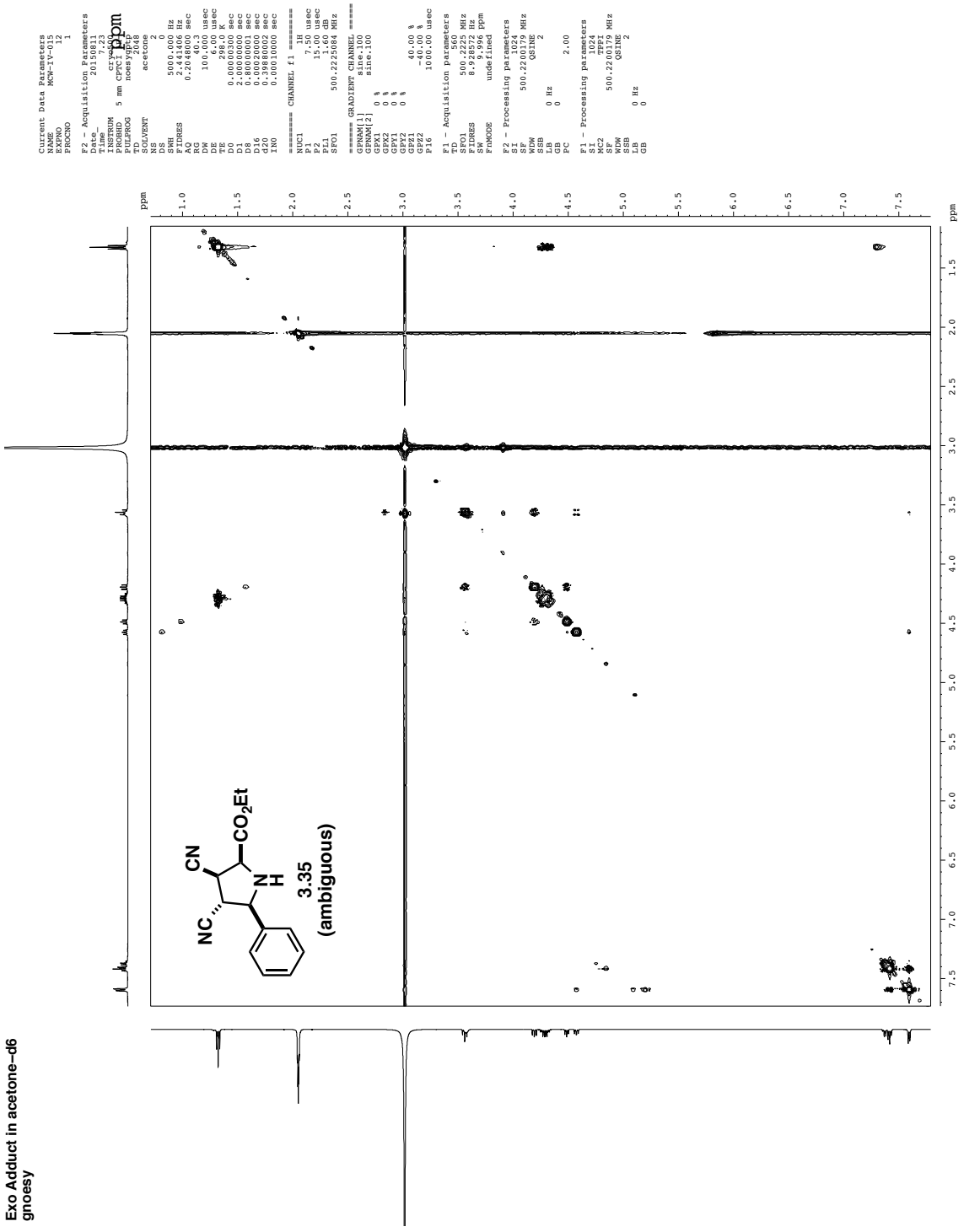
F1 - Acquisition parameters
TD                           560
SFO1                500.2225 MHz
FIDRES              8.928572 Hz
SW                      9.996 ppm
FnMODE              undefined

F2 - Processing parameters
SI                           1024
SF                500.2200180 MHz
WDW                        QSINE
SSB                           2
LB          0 Hz
GB          0
PC                        1.40

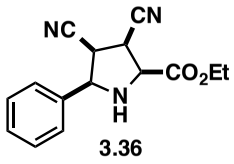
F1 - Processing parameters
SI                           1024
MC2                        TPPI
SF                500.2200180 MHz
WDW                        QSINE
SSB                           2
LB          0 Hz
GB          0
```


Purified Exo Adduct
Current Data Parameters
NAME MEW-IV-015
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150810
Time 13.12
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 0
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 8
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200312 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1.368
1.383
1.397
2.761
2.776
2.792
3.200
3.218
3.235
3.676
3.693
3.710
4.253
4.269
4.284
4.307
4.321
4.329
4.336
4.343
4.350
4.357
4.372
4.380
4.386
4.398
4.400
4.408
4.415
4.422
4.436
7.260
7.388
7.390
7.394
7.402
7.408
7.412
7.415
7.421
7.436
7.445
7.449
7.453
7.497
7.499
7.512
7.515
CN
CO2Et
NC
N
H
3.35
3.018
0.943
0.974
1.000
1.005
1.164
1.880
3.088
2.025
ppm


Purified Exo Adduct
Current Data Parameters
NAME MCW-1V-015
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150810
Time 13.12
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchop3gp.p1
TD 65536
SOLVENT CDCl3
NS 160
DS 0
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 91915.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCWREST 0 sec 0.01500000 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
PL1 500.00 usec
P12 2000.00 usec
PL2 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804084 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
169.279
136.455
129.607
129.471
126.779
116.942
116.179
77.413
77.159
76.905
67.104
62.979
61.773
41.577
37.541
14.242
CN
CO2Et
NC
N
H
3.35
ppm


Exo Adduct in acetone–d6
gnoesy
Current Data Parameters
NAME MCW-IV-015
EXPNO 12
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150811
Time 7.23
INSTRUM cryo400
PROBHD 5 mm CPTCI 1H-
PULPROG noesygpph
TD 32768
SOLVENT acetone
NS 2
DS 0
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 40.00
DW 100.000 usec
DE 6.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D8 0.80000001 sec
D16 0.00020000 sec
D20 0.03000000 sec
IN0 0.00010000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
P2 15.00 usec
PL1 1.60 dB
SFO1 500.2225084 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] sine.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 40.00 %
GPZ2 -40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 1024
SFO1 500.2225 MHz
FIDRES 8.928572 Hz
SW 4.996 ppm
FnMODE undefined
F2 - Processing parameters
SI 1024
SF 500.2200179 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 2.00
F1 - Processing parameters
SI 1024
MC2 TPPI
SF 500.2200179 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
ppm
CN
CO2Et
NC
N
H
3.35
(ambiguous)

Fr 94-99 redo



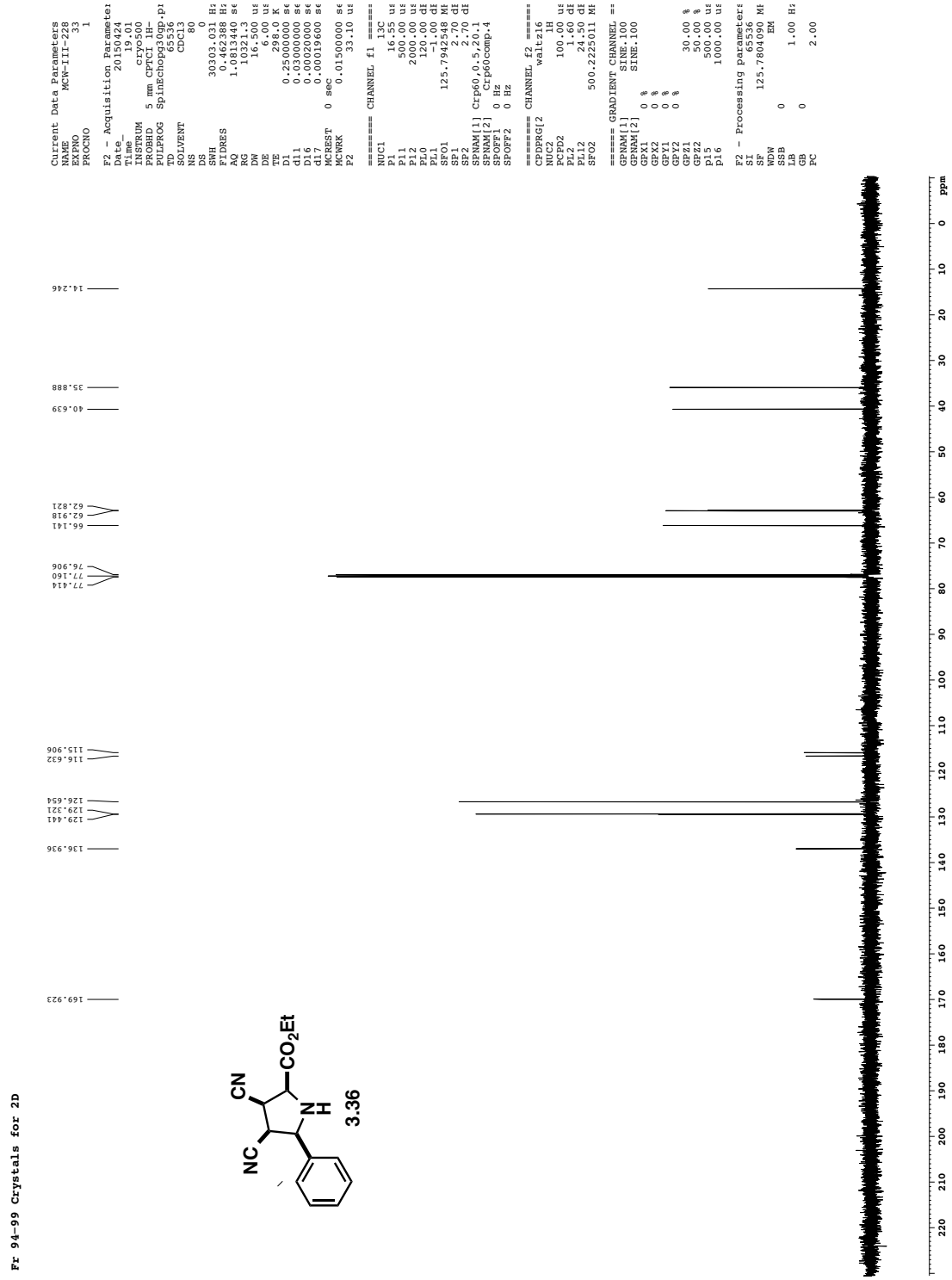
3.36

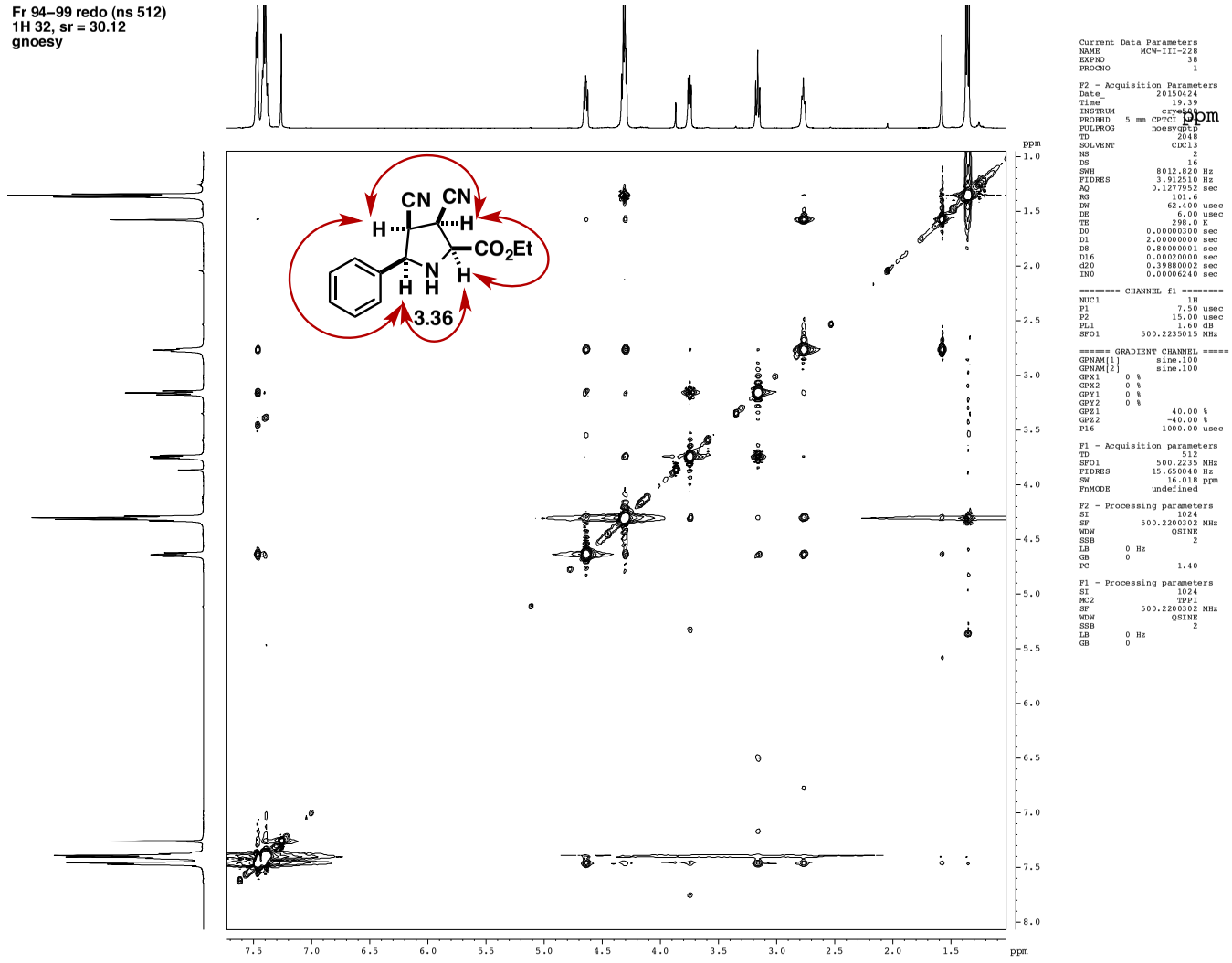

```
Current Data Parameters
NAME          MCW-III-228
EXPNO                  10
PROCNO                  1

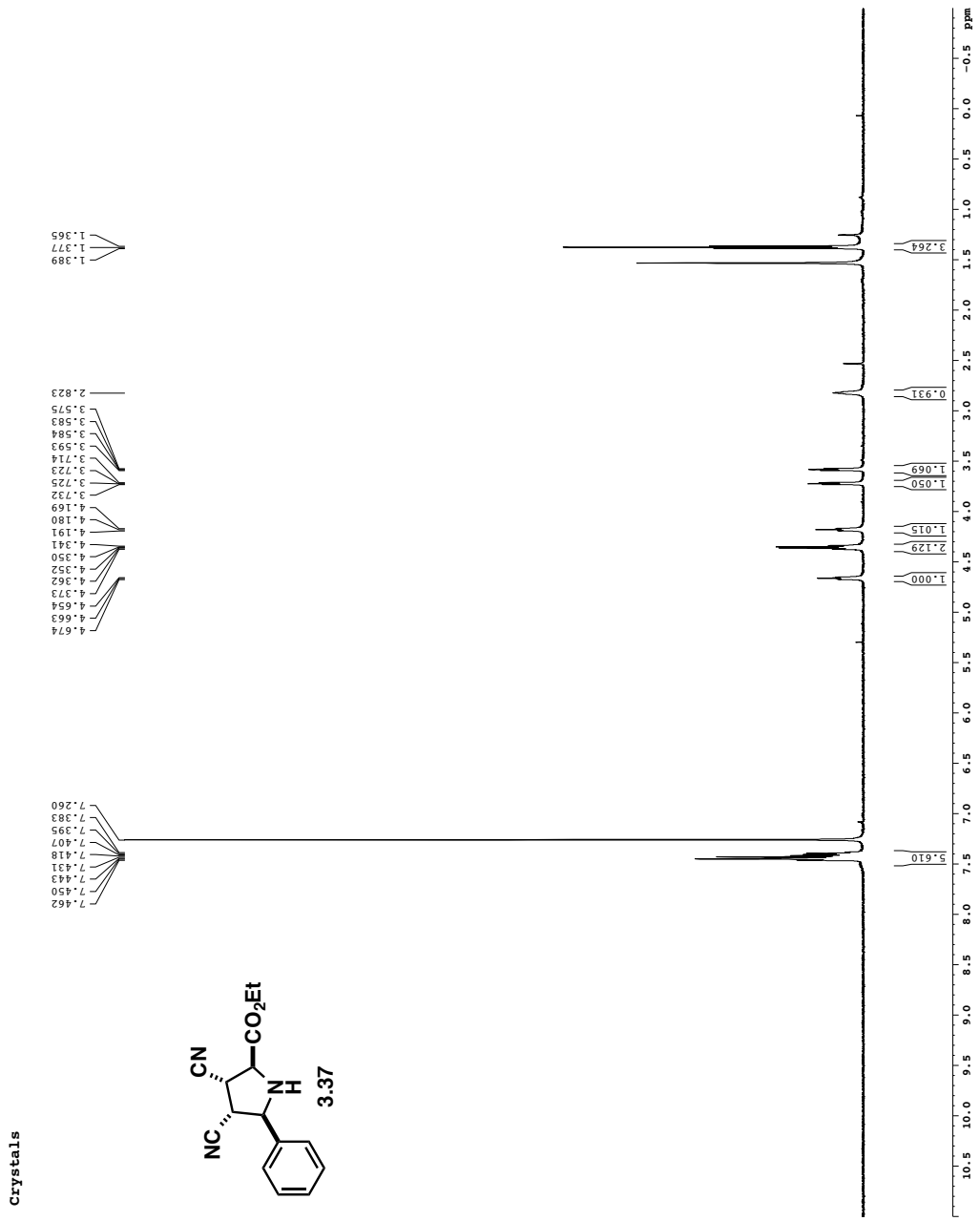
F2 - Acquisition Parameters
Date_            20150420
Time                15.29
INSTRUM           av600
PROBHD   5 mm BBO BB-1H
PULPROG             zg30
TD                 98074
SOLVENT            CDCl3
NS                     8
DS                     0
SWH             9615.385 Hz
FIDRES          0.098042 Hz
AQ              5.0998478 sec
RG                   456
DW                52.000 usec
DE                14.33 usec
TE                298.0 K
D1             0.10000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1342009 MHz
NUC1                   1H
P1                  9.00 usec
PLW1         60.25600052 W

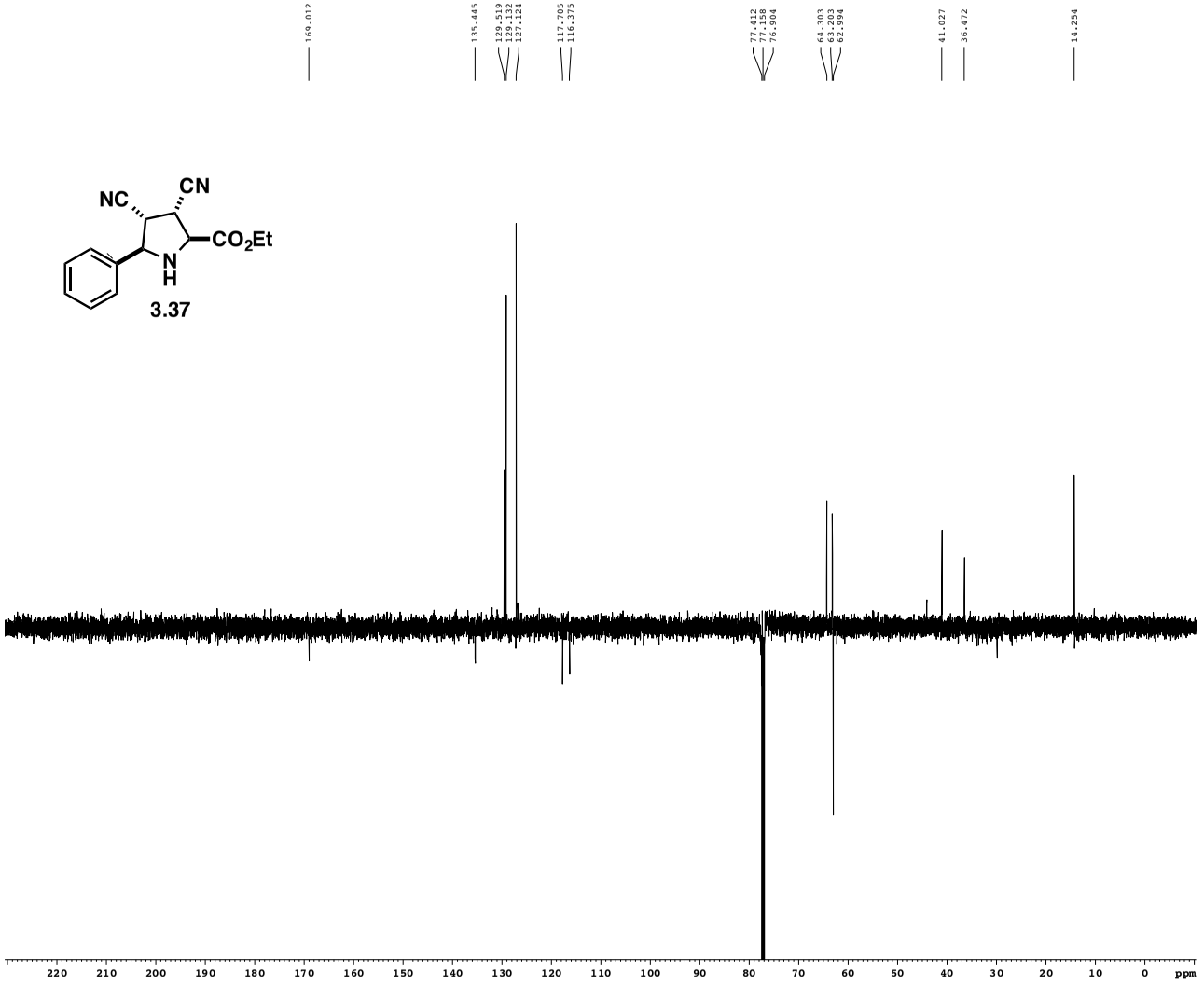
F2 - Processing parameters
SI                 65536
SF           600.1300341 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```


Fr 94-99 Crystals for 2D
Current Data Parameters
NAME MCW-III-228
EXPNO 33
PROCNO 1
F2 - Acquisition Parameter
Date_ 20150424
Time 19.01
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg.p
TD 65536
SOLVENT CDCl3
NS 80
DS 0
SWH 30303.031 H
FIDRES 0.462388 H
AQ 1.0813440 s
RG 1024.3
DW 16.500 u
DE 6.00 u
TE 298.0 K
D1 0.25000000 s
d11 0.03000000 s
D16 0.00020000 s
d17 0.00019600 s
MC4REST 0 sec
MCWRK 0.01500000 s
P2 33.10 u
======== CHANNEL f1 ======
NUC1 13C
P1 16.55 u
P11 500.00 u
P12 2000.00 u
PL2 120.00 d
PL1 -1.00 d
SFO1 125.7942548 M
SP1 2.70 d
SP2 2.70 d
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ======
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 u
PL2 1.60 d
PL12 24.00 d
SFO2 500.2225011 M
====== GRADIENT CHANNEL =
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 u
p16 1000.00 u
F2 - Processing parameter
SI 65536
SF 125.7804090 M
WDW EM
SSB 0
LB 1.00 H
GB 0
PC 2.00
CN
CO2Et
NC
N
H
3.36
169.923
136.936
129.441
129.321
126.654
116.632
115.906
77.414
77.160
76.906
66.141
62.918
62.821
40.639
35.888
14.246
ppm


Fr 94–99 redo (ns 512)
1H 32, sr = 30.12
gnoesy
CN
CN
H
H
CO2Et
N
H
H
H
3.36
ppm
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
Current Data Parameters
NAME MCW-III-228
EXPNO 38
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150424
Time 19.39
INSTRUM cryo500
PROBHD 5 mm CPTCI
PULPROG noesygpph
TD 2048
SOLVENT CDCl3
NS 2
DS 16
SWH 8012.820 Hz
FIDRES 3.912510 Hz
AQ 0.1277952 sec
RG 101.6
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D8 0.80000001 sec
D16 0.00020000 sec
d20 0.39880002 sec
IN0 0.00006240 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
P2 15.00 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] sine.100
GPNAM[2] sine.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 40.00 %
GPZ2 -40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 500.2235 MHz
FIDRES 15.650040 Hz
SW 16.018 ppm
FnMODE undefined
F2 - Processing parameters
SI 1024
SF 500.2200302 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1024
MC2 TPPI
SF 500.2200302 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0


Crystals
Current Data Parameters
NAME MCM-11-228
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150420
Time 10.25
INSTRUM av600
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 8
DS 0
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.09988478 sec
RG 1620
DW 52.000 usec
DE 14.33 usec
TE 298.3 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 600.1342009 MHz
NUC1 1H
P1 9.00 usec
PLW1 60.25600052 W
F2 - Processing parameters
SI 65536
SF 600.1300342 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.462
7.450
7.443
7.431
7.418
7.407
7.395
7.383
7.260
4.674
4.663
4.654
4.373
4.362
4.352
4.350
4.341
4.191
4.180
4.169
3.732
3.725
3.723
3.714
3.593
3.584
3.583
3.575
2.823
1.389
1.377
1.365
5.610
1.000
2.129
1.015
1.050
1.069
0.931
3.264
CN
CO2Et
NC
N
H
3.37
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 ppm

Crystals
deptq 13C spectrum with 1H decoupling (CH & CH3 one way up; C, CH2 and solvent the other)




```
Current Data Parameters
NAME          MCW-III-228
EXPNO                  13
PROCNO                  1

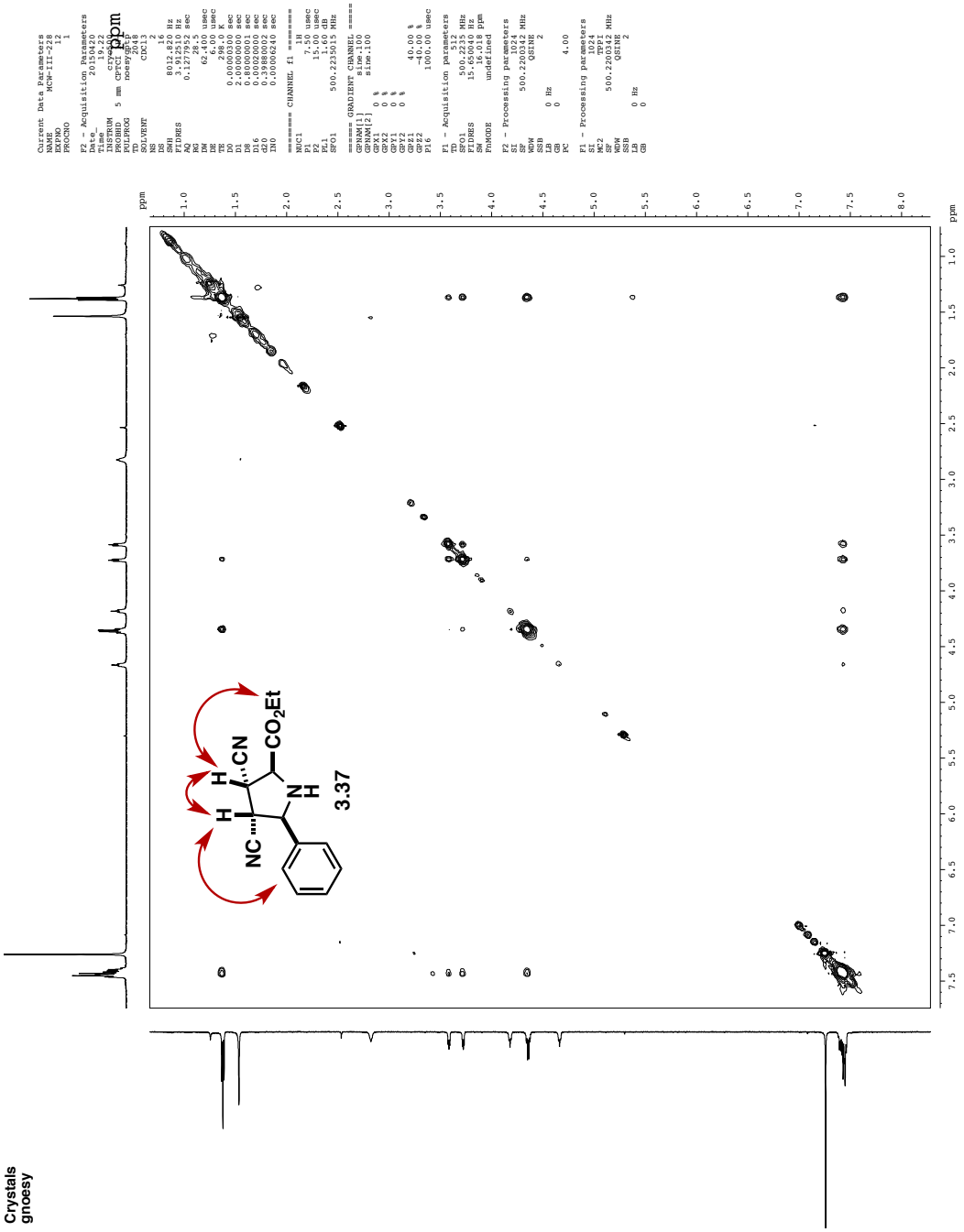
F2 - Acquisition Parameter
Date_            20150420
Time                20.26
INSTRUM           cryo500
PROBHD  5 mm CPTCI 1H-
PULPROG        deptqgpsp
TD                  65536
SOLVENT             CDCl3
NS                    720
DS                      0
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0813440 se
RG                7298.2
DW                16.500 us
DE                 6.00 us
TE                298.0 K
CNST2        145.0000000
CNST12         1.5000000
D1             1.00000000 se
d2             0.00344828 se
d12            0.00002000 se
D16            0.00020000 se
DELTA          0.00001707 se
DELTA1         0.00228023 se
DELTA2         0.00226483 se
DELTA3         0.00224828 se
MCREST   0 sec
MCWRK          0.01500000 se

======== CHANNEL f1 ======
NUC1                  13C
P1                 16.55 us
P12              2000.00 us
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MH
SP2                2.70 dB
SPNAM[2]    Crp60comp.4
SPOFF2   0 Hz

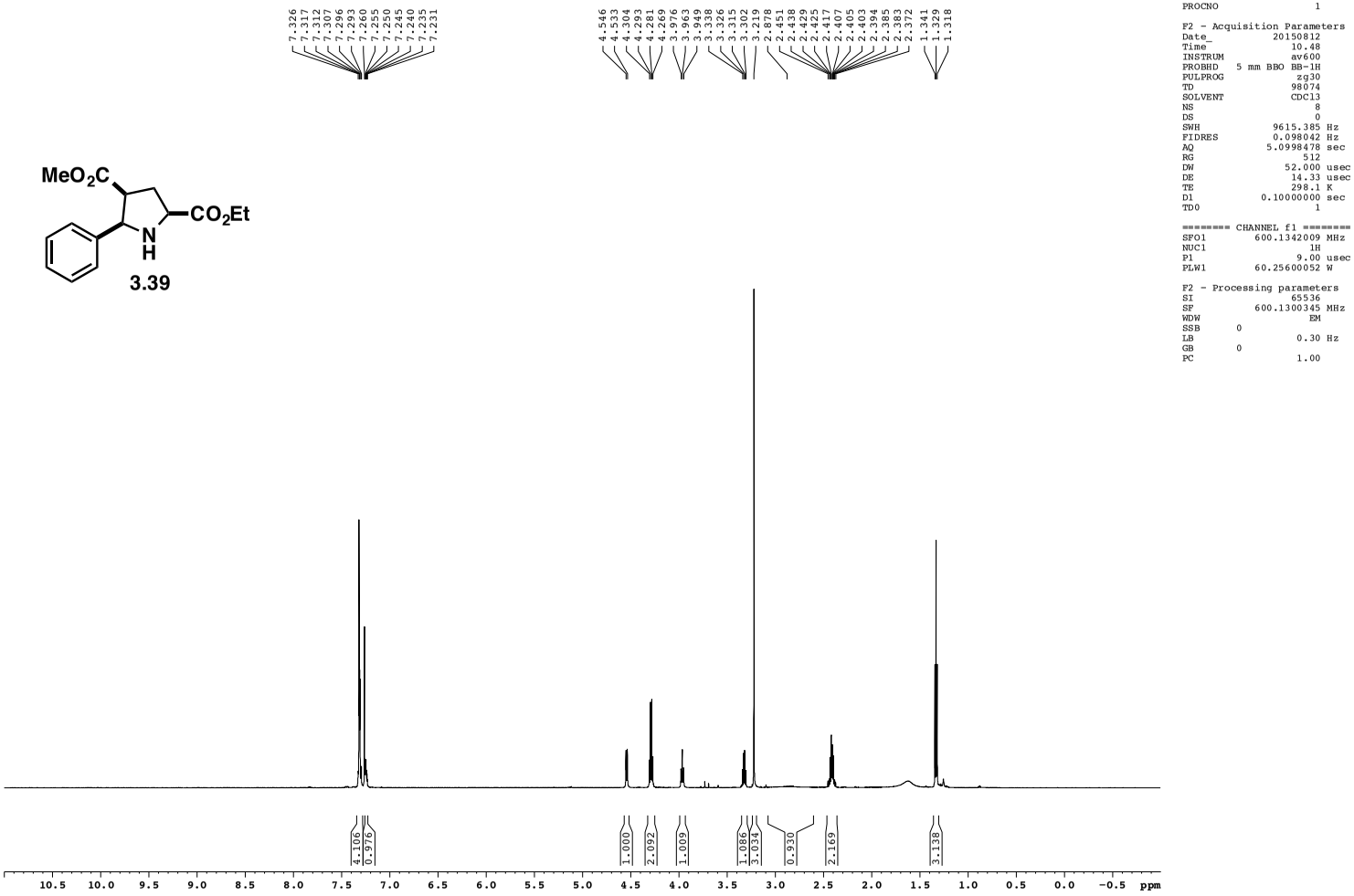
======== CHANNEL f2 ======
CPDPRG[2          waltz16
NUC2                  1H
p0                 11.55 us
P3                  7.70 us
p4                 15.40 us
PCPD2             100.00 us
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MH

====== GRADIENT CHANNEL ==
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPNAM[3]        SINE.100
GPX1     0 %
GPX2     0 %
GPX3     0 %
GPY1     0 %
GPY2     0 %
GPY3     0 %
GPZ1               31.00 %
GPZ2               31.00 %
GPZ3               31.00 %
P16              1000.00 us

F2 - Processing parameters
SI                  65536
SF           125.7804076 MH
WDW                    EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  2.00
```


Crystals
gnoesy
ppm
3.37
CO2Et
CN
H
N
NC

Fr 100-102

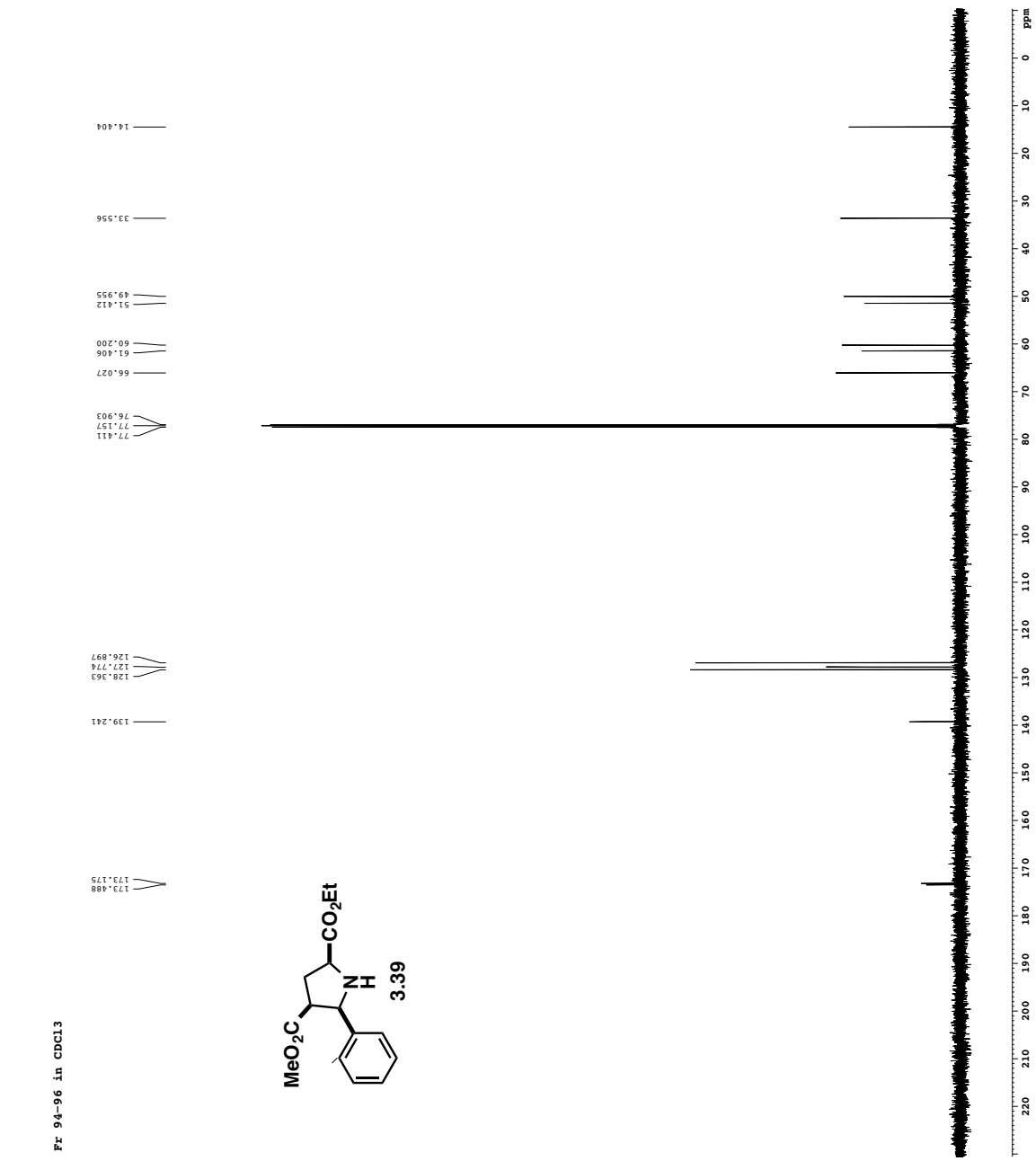


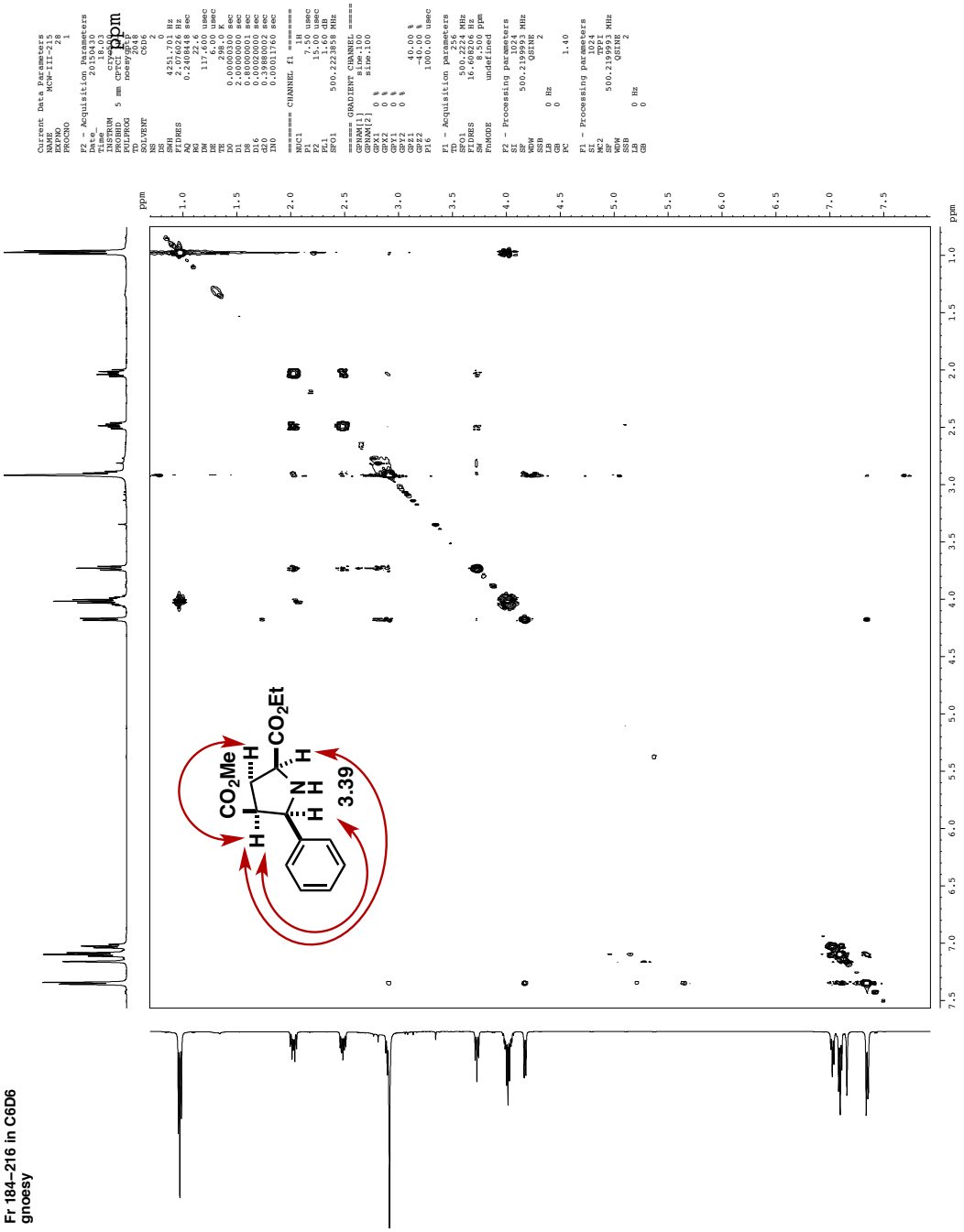

```
Current Data Parameters
NAME                  MCW-IV-017
EXPNO                          9
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20150812
Time                       10.48
INSTRUM                   av600
PROBHD    5 mm BBO  BB-1H
PULPROG                   zg30
TD                         98074
SOLVENT                   CDCl3
NS                             8
DS                             0
SWH                     9615.385 Hz
FIDRES                  0.098042 Hz
AQ                      5.0998478 sec
RG                           512
DW                        52.000 usec
DE                        14.33 usec
TE                        298.1 K
D1                      0.10000000 sec
TD0                            1

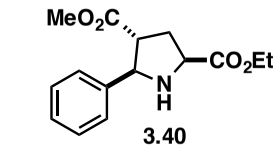
======== CHANNEL f1 ========
SFO1                 600.1342009 MHz
NUC1                         1H
P1                         9.00 usec
PLW1                60.25600052 W

F2 - Processing parameters
SI                           65536
SF                   600.1300345 MHz
WDW                           EM
SSB                0
LB                         0.30 Hz
GB                 0
PC                         1.00
```


Fr 94-96 in CDCl3
MeO2C
CO2Et
N
H
3.39
Current Data Parameters
NAME MCW-IV-017
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150811
Time 19.10
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 328
DS 0
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 722.2
DW 16.500 us
DE 6.00 us
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MC2REST 0 sec
MCWRK 0.01500000 sec
P2 33.10 us
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 us
P11 500.00 us
PL12 20000.00 dB
PL2 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 us
PL2 1.60 dB
PL12 24.00 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 us
p16 1000.00 us
F2 - Processing parameters
SI 65536
SF 125.7804080 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
14.404
33.556
49.955
51.412
60.200
61.406
66.027
76.903
77.157
77.411
126.897
127.774
128.363
139.241
173.175
173.488
ppm


Fr 184–216 in C6D6
gnoesy
ppm
CO2Me
CO2Et
3.39

Purified Product



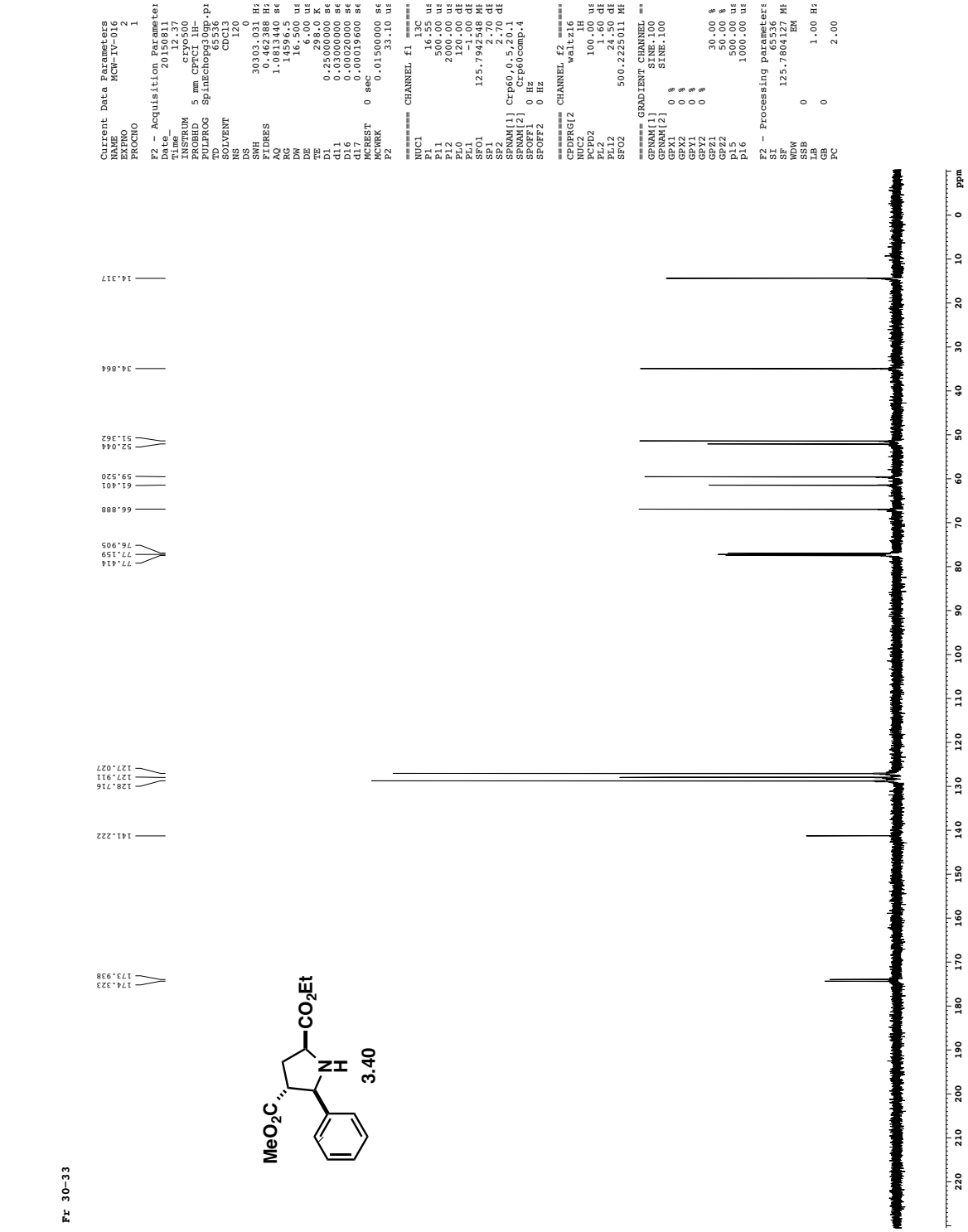
3.40


```
Current Data Parameters
NAME                  MCW-IV-016
EXPNO                          3
PROCNO                         1

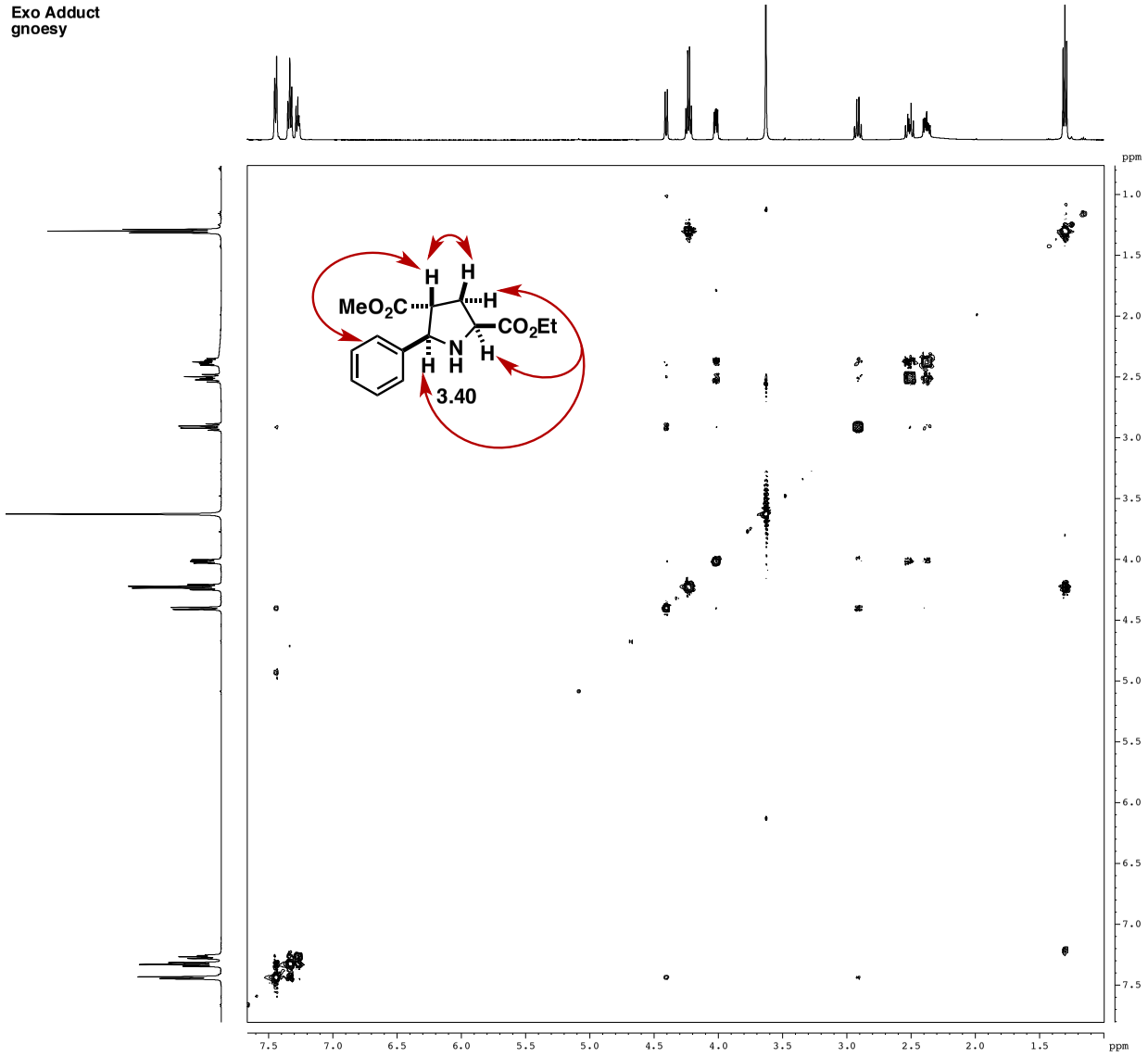
F2 - Acquisition Parameters
Date_                   20150811
Time                       13.53
INSTRUM                  cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG                    zg30
TD                        81728
SOLVENT                   CDCl3
NS                             8
DS                             0
SWH                     8012.820 Hz
FIDRES                  0.098043 Hz
AQ                    5.0998273 sec
RG                           7.1
DW                        62.400 usec
DE                         6.00 usec
TE                        298.0 K
D1                   0.10000000 sec
MCREST    0 sec
MCWRK               0.01500000 sec

======== CHANNEL f1 ========
NUC1                         1H
P1                        7.50 usec
PL1                       1.60 dB
SFO1                500.2235015 MHz

F2 - Processing parameters
SI                         65536
SF                  500.2200311 MHz
WDW                           EM
SSB               0
LB                        0.30 Hz
GB                0
PC                        4.00
```


Fr 30-33
Current Data Parameters
NAME MCW-IV-016
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150811
Time 12.37
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 120
DS 0
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 145.5
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MCWREST 0 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
PL2 20000.00 dB
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804127 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
14.317
34.864
51.362
52.044
59.520
61.401
66.888
76.905
77.159
77.414
127.027
127.911
128.716
141.222
173.938
174.323
MeO2C
CO2Et
N
H
3.40
ppm

Exo Adduct
gnoesy




```
Current Data Parameters
NAME                  MCW-IV-016
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_               20150811
Time                    20.02
INSTRUM                 cryo500
PROBHD     5 mm CPTCI 1H-13C/1
PULPROG             noesygpph
TD                       2048
SOLVENT                 CDCl3
NS                            2
DS                            0
SWH                 5000.000 Hz
FIDRES              2.441406 Hz
AQ                  0.2048000 sec
RG                         90.5
DW                   100.000 usec
DE                     6.00 usec
TE                     298.0 K
D0                  0.00000300 sec
D1                  2.00000000 sec
D8                  0.80000001 sec
D16                 0.00020000 sec
d20                 0.39880002 sec
IN0                 0.00010000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                       7.50 usec
P2                      15.00 usec
PL1                      1.60 dB
SFO1             500.2224999 MHz

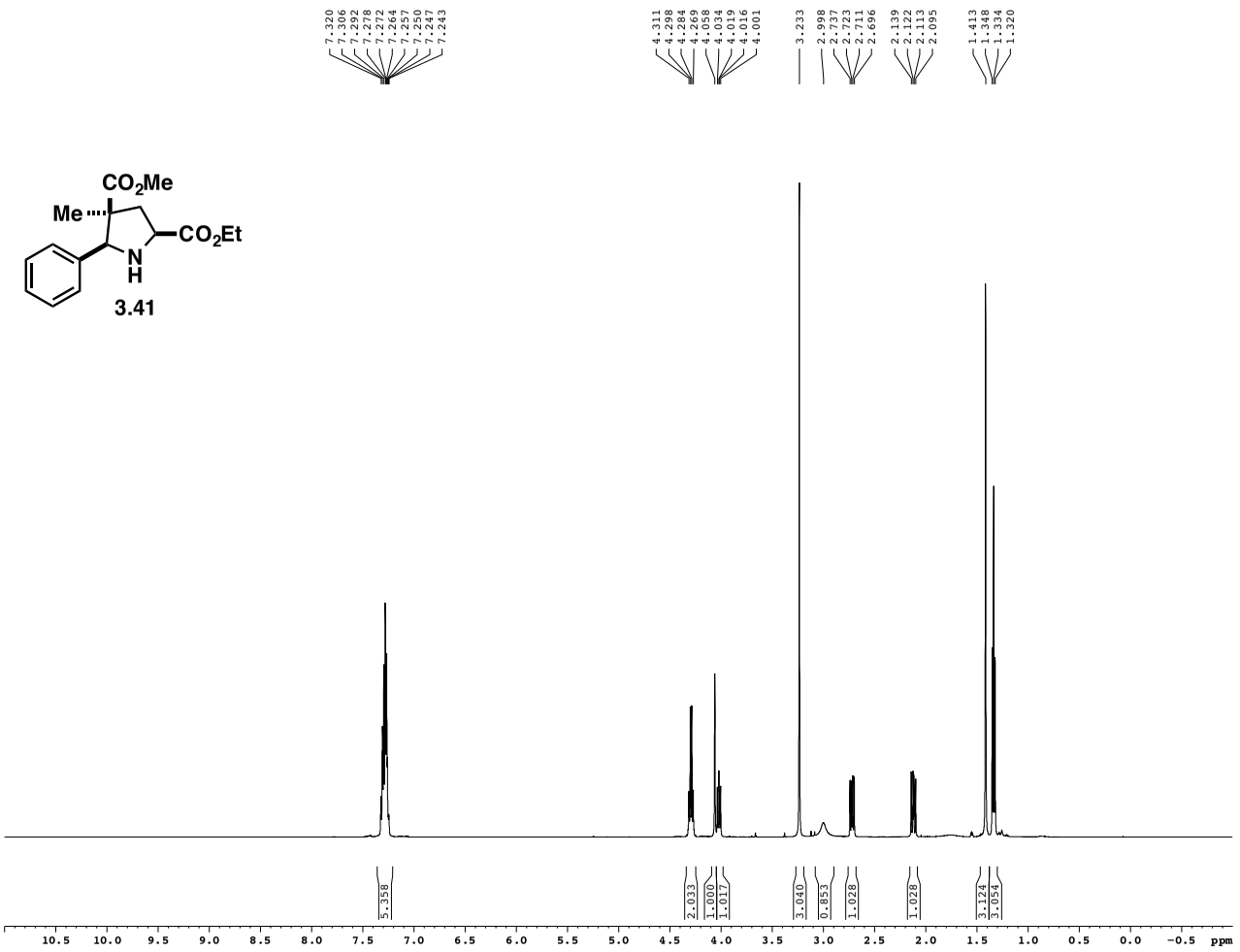
====== GRADIENT CHANNEL =====
GPNAM[1]             sine.100
GPNAM[2]             sine.100
GPX1        0 %
GPX2        0 %
GPY1        0 %
GPY2        0 %
GPZ1                    40.00 %
GPZ2                   -40.00 %
P16                  1000.00 usec

F1 - Acquisition parameters
TD                          560
SFO1                 500.2225 MHz
FIDRES               8.928572 Hz
SW                       9.996 ppm
FnMODE               undefined

F2 - Processing parameters
SI                          1024
SF                500.2200313 MHz
WDW                       QSINE
SSB                           2
LB          0 Hz
GB          0
PC                         2.00

F1 - Processing parameters
SI                          1024
MC2                         TPPI
SF                500.2200313 MHz
WDW                       QSINE
SSB                           2
LB          0 Hz
GB          0
```

Endo Adduct

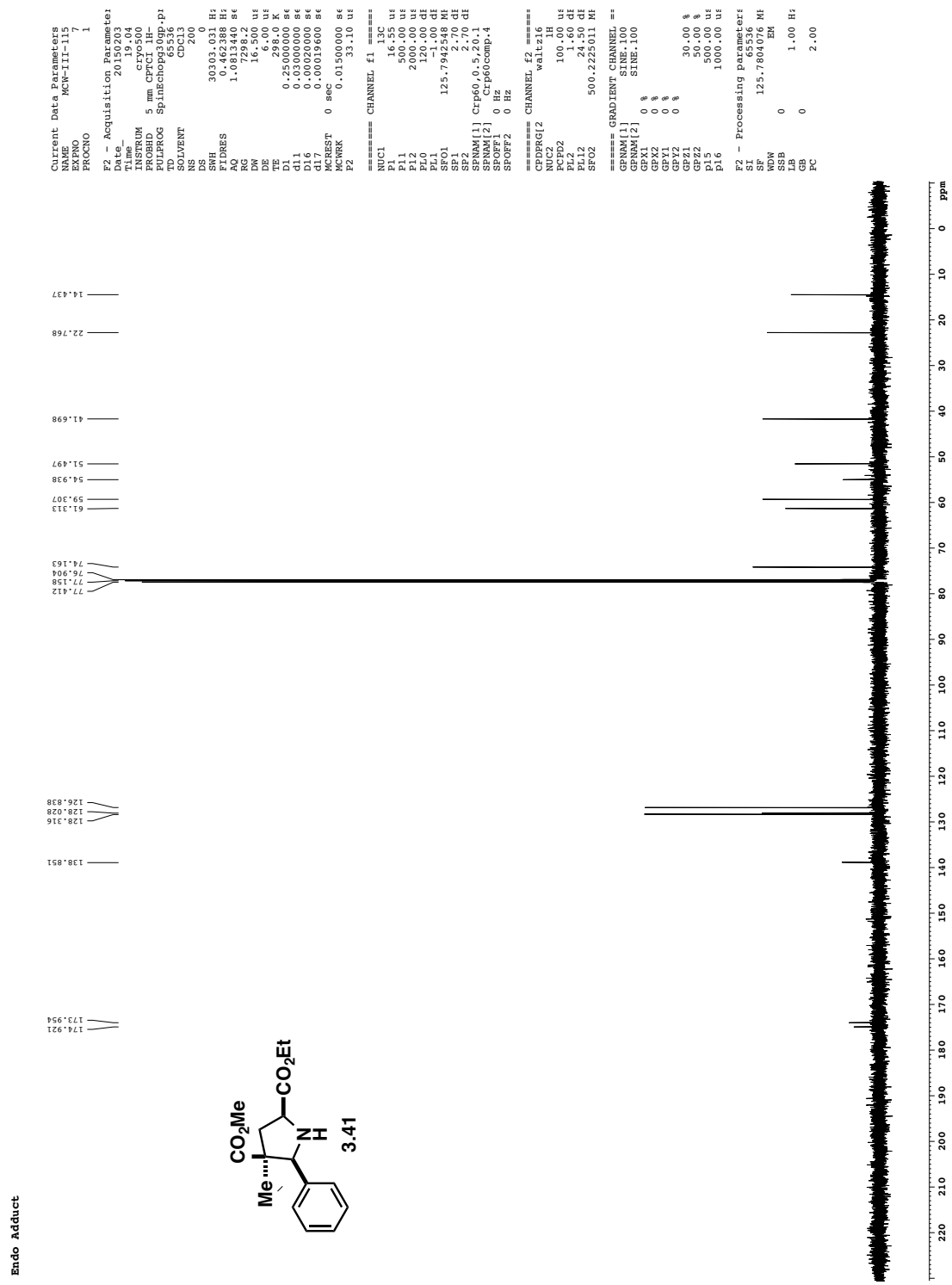


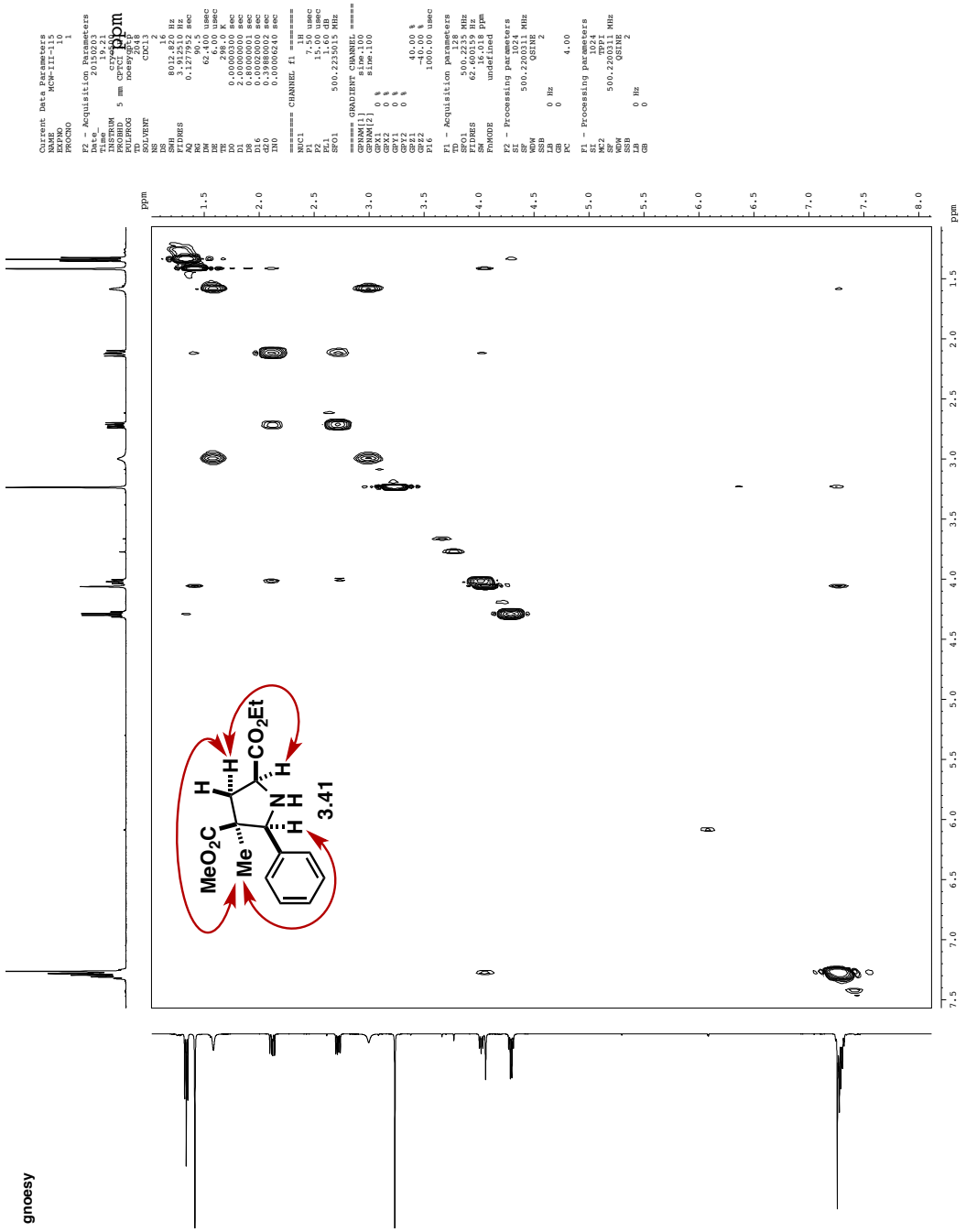

```
Current Data Parameters
NAME                  MCW-III-115
EXPNO                          39
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20150321
Time                        15.58
INSTRUM                   cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG                     zg30
TD                         81728
SOLVENT                    CDCl3
NS                             8
DS                             0
SWH                     8012.820 Hz
FIDRES                  0.098043 Hz
AQ                      5.0998273 sec
RG                             5
DW                         62.400 usec
DE                          6.00 usec
TE                         298.0 K
D1                      0.10000000 sec
MCREST    0 sec
MCWRK                   0.01500000 sec

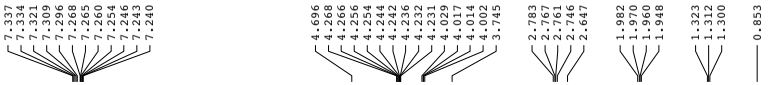
======== CHANNEL f1 ========
NUC1                           1H
P1                          7.50 usec
PL1                         1.60 dB
SFO1                500.2235015 MHz

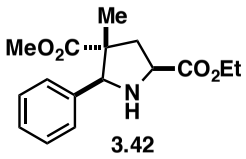
F2 - Processing parameters
SI                         65536
SF                  500.2200291 MHz
WDW                            EM
SSB                0
LB                          0.30 Hz
GB                 0
PC                          4.00
```


Endo Adduct
Current Data Parameters
NAME MCW-III-115
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150203
Time 19.04
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg3gp.p1
TD 65536
SOLVENT CDCl3
NS 200
DS 0
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 72792.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MCREST 0 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
PL1 500.00 usec
PL2 20000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ==
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804076 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
14.437
22.768
41.698
51.497
54.938
59.307
61.313
74.163
76.904
77.158
77.412
126.838
128.028
128.316
138.851
173.954
174.921
CO2Me
CO2Et
Me
N
H
3.41
ppm


gnoesy
ppm
MeO2C
Me
H
H
CO2Et
N
H
H
3.41

Fr 49-51





3.42

```
Current Data Parameters
NAME                  MCW-IV-021
EXPNO                          5
PROCNO                         1

F2 - Acquisition Parameters
Date_               20150815
Time                      15.15
INSTRUM                  av600
PROBHD    5 mm BBO BB-1H
PULPROG                  zg30
TD                      98074
SOLVENT                  CDCl3
NS                             8
DS                             2
SWH                 9615.385 Hz
FIDRES              0.098042 Hz
AQ                  5.0998478 sec
RG                            32
DW                    52.000 usec
DE                    14.33 usec
TE                      298.0 K
D1                  0.10000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1               600.1342009 MHz
NUC1                         1H
P1                        9.00 usec
PLW1               60.25600052 W

F2 - Processing parameters
SI                         65536
SF                 600.1300345 MHz
WDW                          EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
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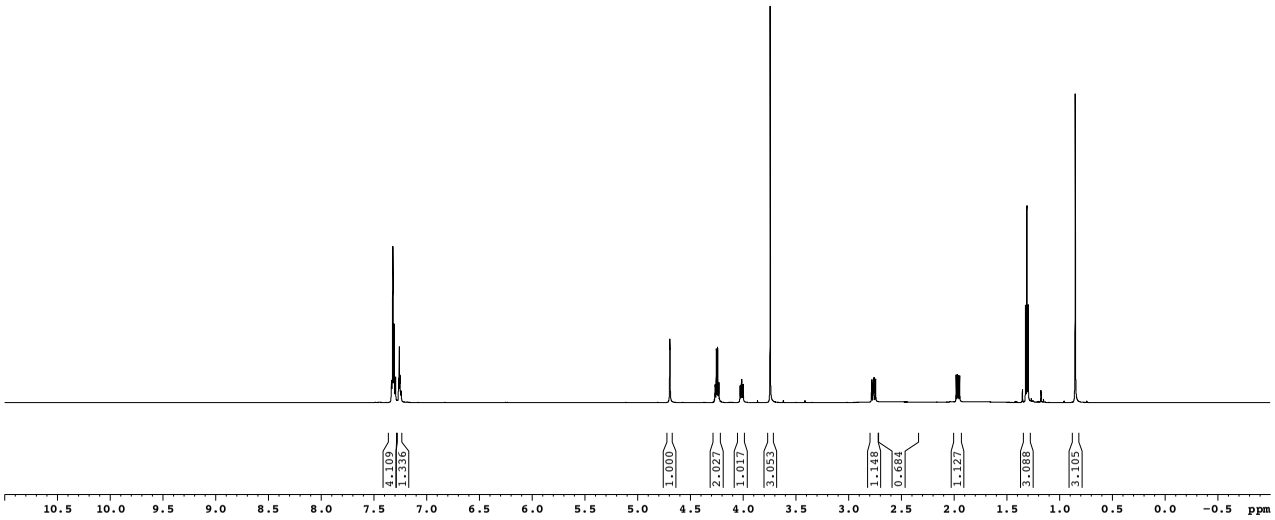

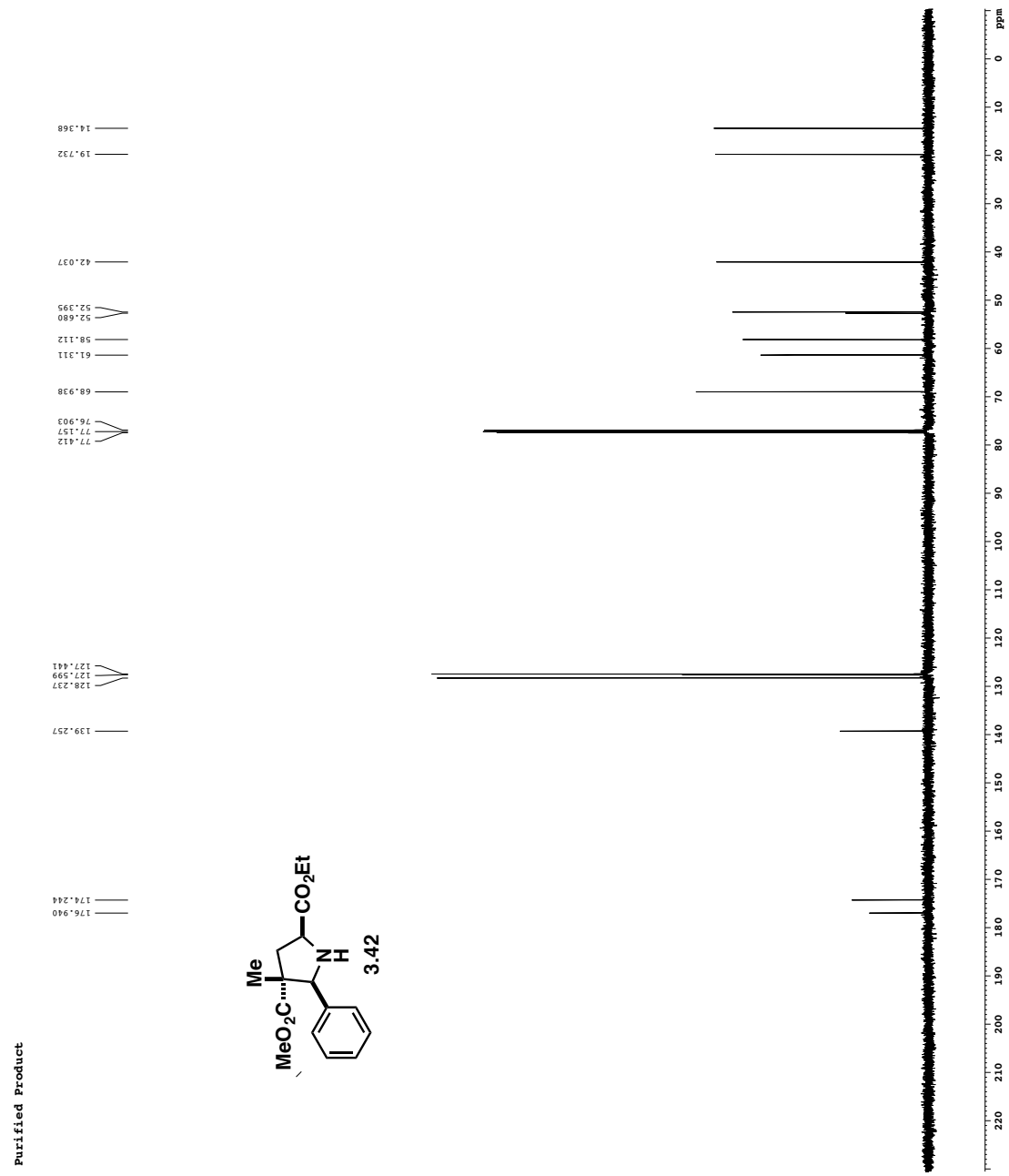
Purified Product
Current Data Parameters
NAME MCW-1V-021
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150815
Time 11.47
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zgpg30.pr
TD 65536
SOLVENT CDCl3
NS 240
DS 0
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813440 sec
RG 13004
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d12 0.00019600 sec
MCWREST 0 sec 0.01500000 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
PL2 20000.00 dB
PL10 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz
====== GRADIENT CHANNEL ====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804090 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
Me
MeO2C
CO2Et
N
H
3.42
14.368
19.732
42.037
52.680
52.395
58.112
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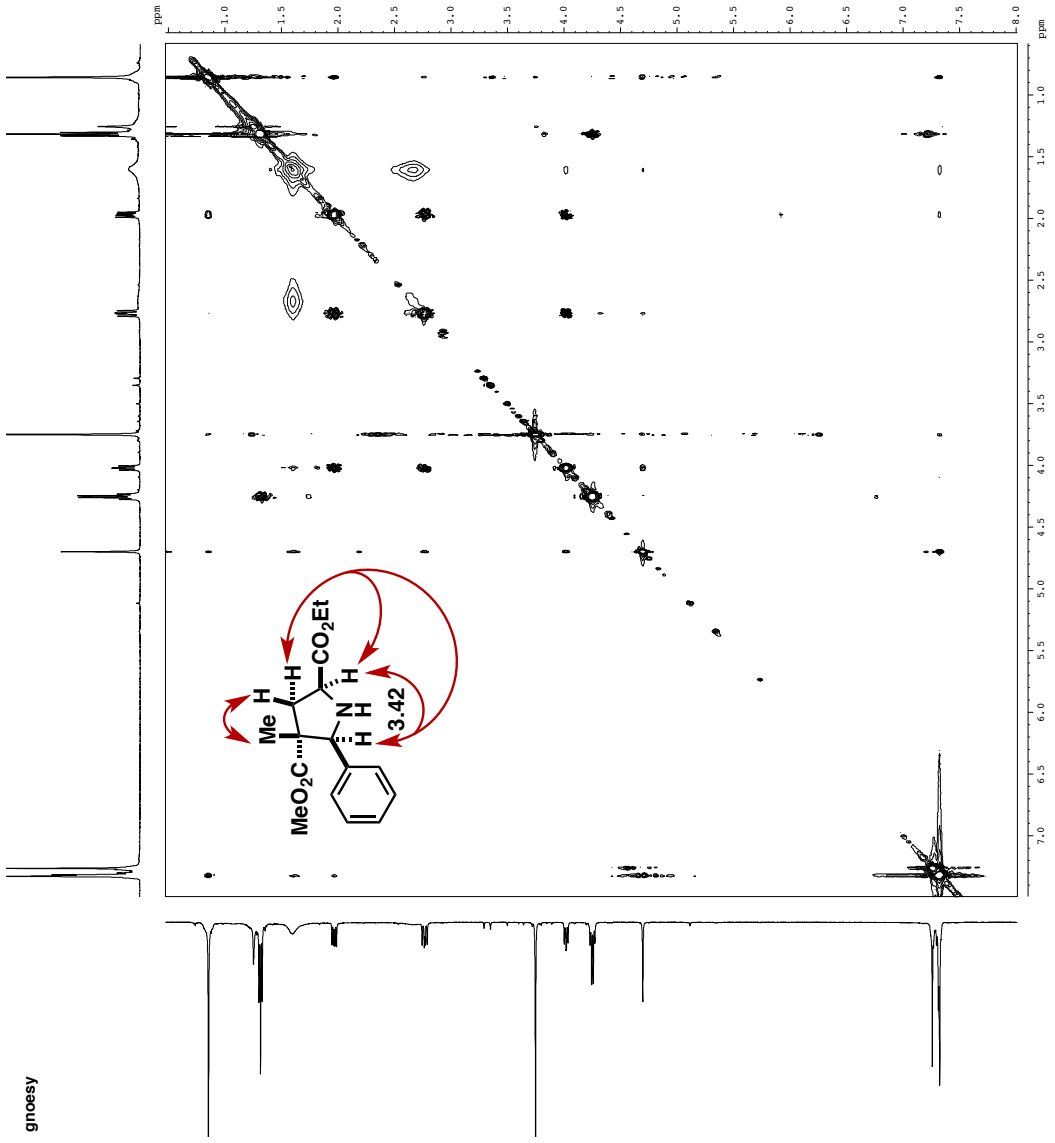
ppm


gnoesy
ppm
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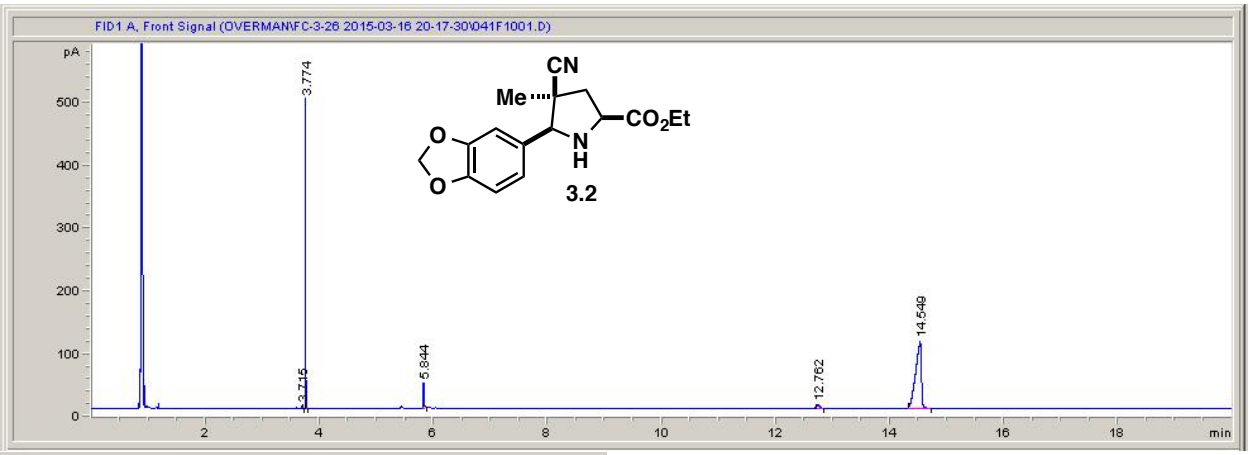
Me
H
MeO2C
CO2Et
N
H
H

3.9 Appendix C: Representative GC-FID Chromatograms

Table 3.18. GC-FID Response Factors for Starting Materials

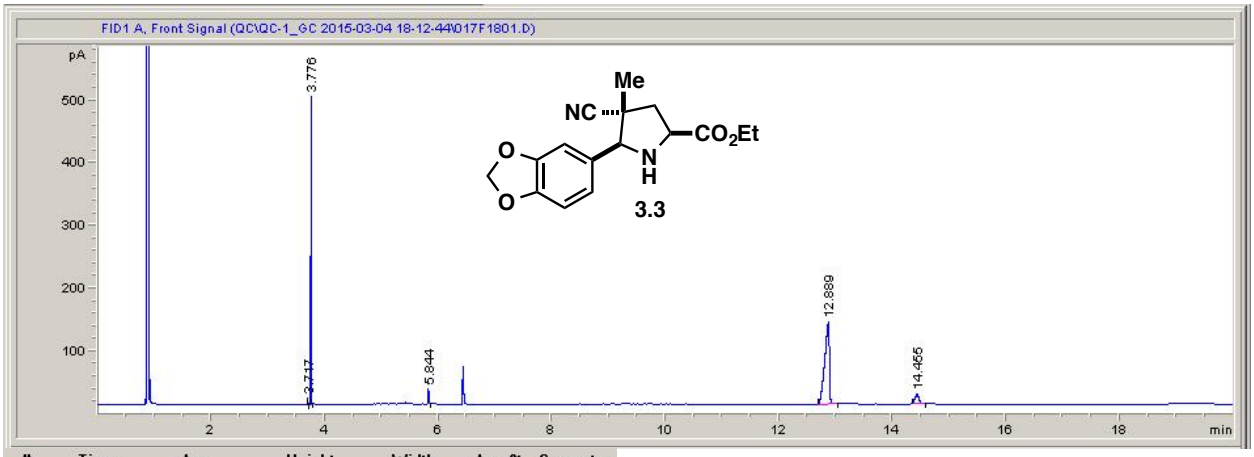
entry	compound	retention time (t_R)	response factor (F)
1	1,3,5-trimethoxybenzene	3.8 min	(standard)
2	piperonal	3.7 min	0.976 ± 0.059
3	3.1	5.8 min	1.143 ± 0.016
4	4-methoxybenzaldehyde	3.5 min	1.242 ± 0.036
5	3.7	5.5 min	1.235 ± 0.026
6	3-methoxybenzaldehyde	3.1 min	1.033 ± 0.006
7	3.10	5.1 min	1.323 ± 0.012
8	benzaldehyde	1.8 min	0.905 ± 0.026
9	3.13	4.2 min	1.340 ± 0.031
10	3-pyridinecarboxaldehyde	2.2 min	0.813 ± 0.029
11	3.16	4.6 min	0.822 ± 0.030
12	4-fluorobenzaldehyde	1.7 min	1.229 ± 0.028
13	3.19	4.2 min	1.180 ± 0.014
14	4-(trifluoromethyl)benzaldehyde	1.7 min	1.128 ± 0.013
15	3.22	4.1 min	1.487 ± 0.012
16	3-bromobenzaldehyde	3.1 min	1.104 ± 0.032
17	3.25	5.2 min	1.205 ± 0.041
18	3,4-dichlorobenzaldehyde	3.5 min	0.959 ± 0.035
19	3.28	5.6 min	1.043 ± 0.034

3.2, t_R = 14.6 min, F = 1.849 ± 0.084:



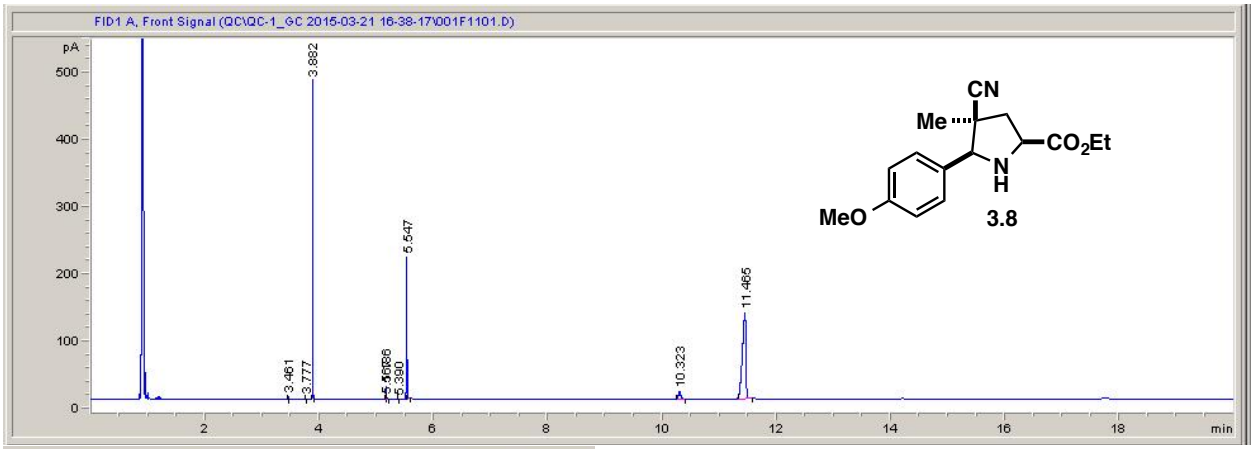
#	Time	Area	Height	Width	Area%	Symmetry
1	3.715	1.8	3.6	7.9776E-3	0.176	0.866
2	3.774	239.8	491.3	7.4932E-3	22.959	1.134
3	5.844	41.7	38.8	0.0165	3.992	0.909
4	12.762	22.2	5.5	0.0494	2.125	0.882
5	14.549	738.8	105.6	0.0908	70.748	3.192

3.3, t_R = 12.9 min, F = 1.778 ± 0.076:



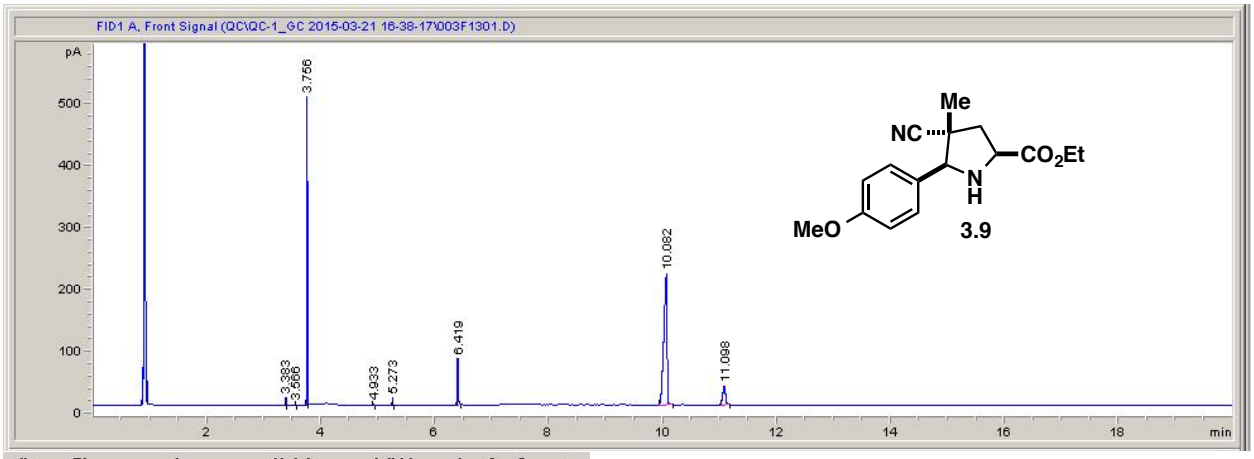
#	Time	Area	Height	Width	Area%	Symmetry
1	3.717	5	9.8	7.9259E-3	0.457	0.883
2	3.776	240.7	490.6	7.724E-3	22.016	1.126
3	5.844	24.3	23.4	0.0161	2.226	0.916
4	12.889	744.1	130	0.0736	68.062	3.287
5	14.455	79.1	15.4	0.0649	7.239	1.27

3.8, t_R = 11.5 min, F = 1.823 ± 0.057:



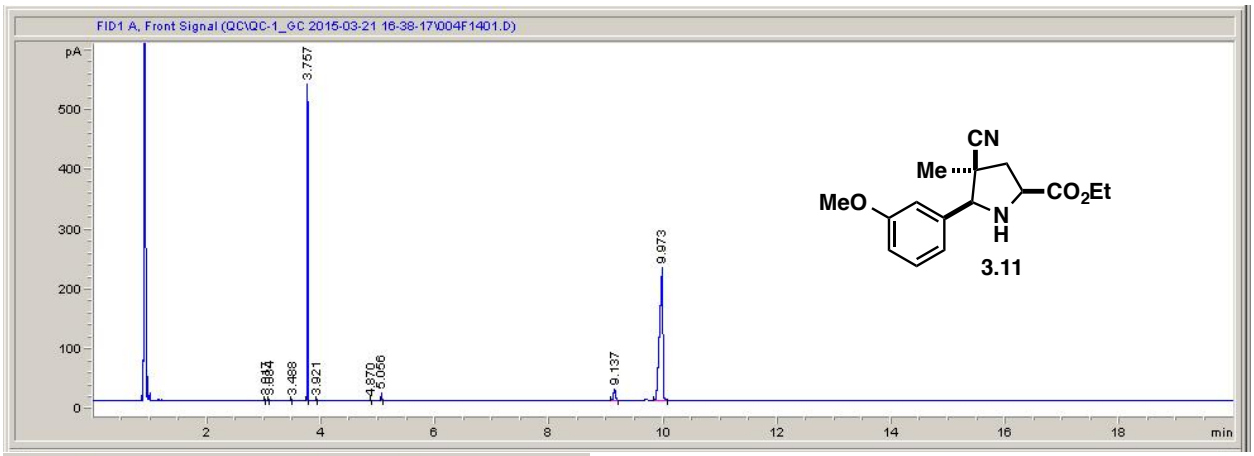
#	Time	Area	Height	Width	Area%	Symmetry
1	3.461	1.9	3.5	8.7079E-3	0.186	0.908
2	3.777	3.1E-1	6.1E-1	7.8441E-3	0.031	0.898
3	3.882	242.1	473.9	7.9595E-3	24.092	1.168
4	5.167	1.1	1.6	9.9488E-3	0.107	1.053
5	5.186	13.9	18.7	0.0113	1.384	0.751
6	5.39	4.2E-1	5.6E-1	9.0699E-3	0.041	0.937
7	5.547	172.9	211.4	0.0119	17.212	1.138
8	10.323	30.4	10.2	0.0376	3.022	0.994
9	11.465	541.8	127.7	0.0511	53.924	2.463

3.9, t_R = 10.1 min, F = 1.888 ± 0.064:



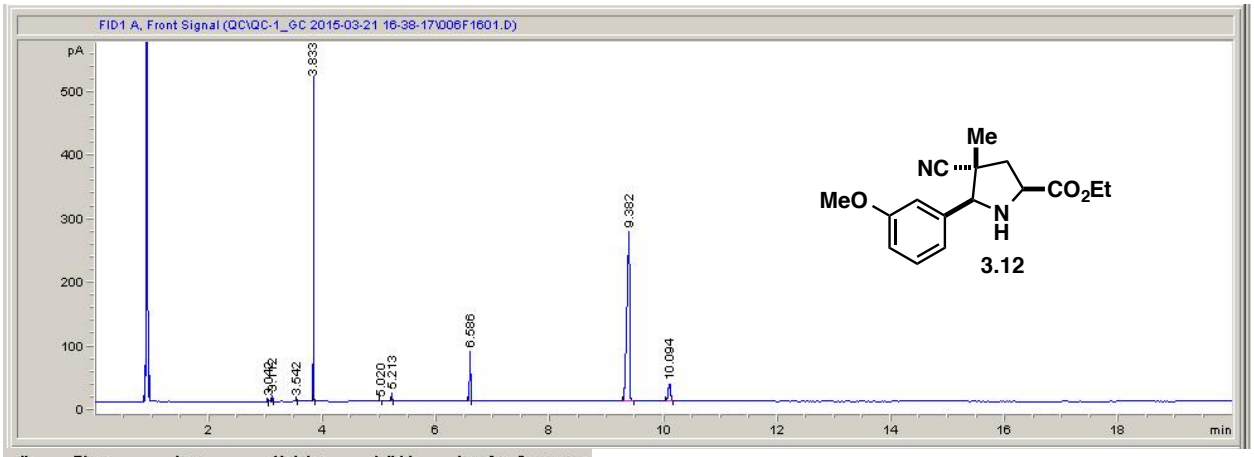
#	Time	Area	Height	Width	Area%	Symmetry
1	3.383	6	11.7	8.0158E-3	0.464	0.84
2	3.566	4.1E-1	6.3E-1	9.3337E-3	0.031	0.716
3	3.756	239.2	496.2	7.4245E-3	18.377	1.14
4	4.933	8.9E-1	1.2	0.0113	0.068	0.782
5	5.273	8.8	10.7	0.0127	0.674	0.868
6	6.419	99.5	74.9	0.0205	7.643	0.893
7	10.082	841.8	211.8	0.052	64.669	3.275
8	11.098	105.1	29.6	0.0499	8.073	1.234

3.11, t_R = 10.0 min, F = 2.000 ± 0.025:



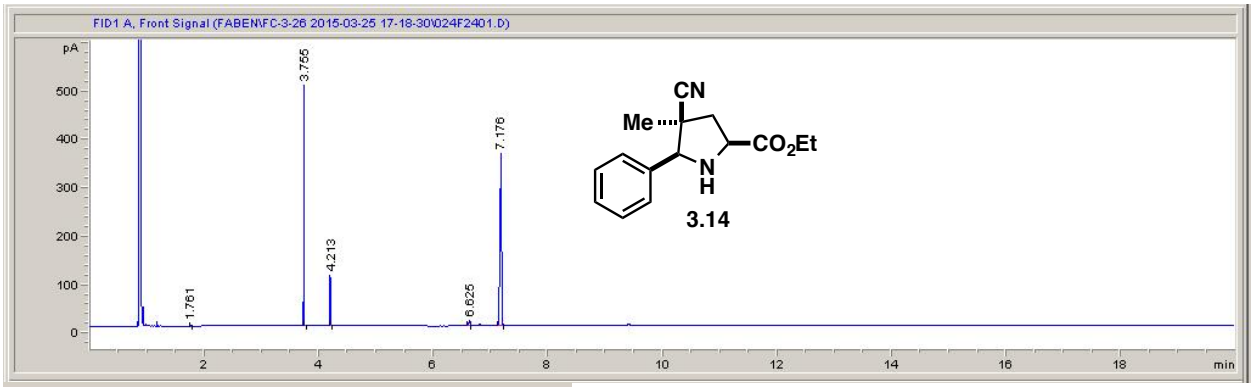
#	Time	Area	Height	Width	Area%	Symmetry
1	3.017	2	3.6	8.4707E-3	0.161	0.894
2	3.084	2.1	3.9	8.4812E-3	0.172	0.899
3	3.488	1.8	3.6	7.9536E-3	0.151	1.039
4	3.757	256.6	528.7	7.6616E-3	21.169	1.229
5	3.921	8.4E-1	1.8	7.2053E-3	0.069	0.946
6	4.87	6.7E-1	8.8E-1	0.0116	0.055	0.821
7	5.056	10.3	13.5	0.0116	0.847	0.795
8	9.137	48.2	18.9	0.034	3.978	0.911
9	9.973	889.6	220.9	0.0488	73.399	2.997

3.12, t_R = 9.4 min, F = 2.024 ± 0.032:



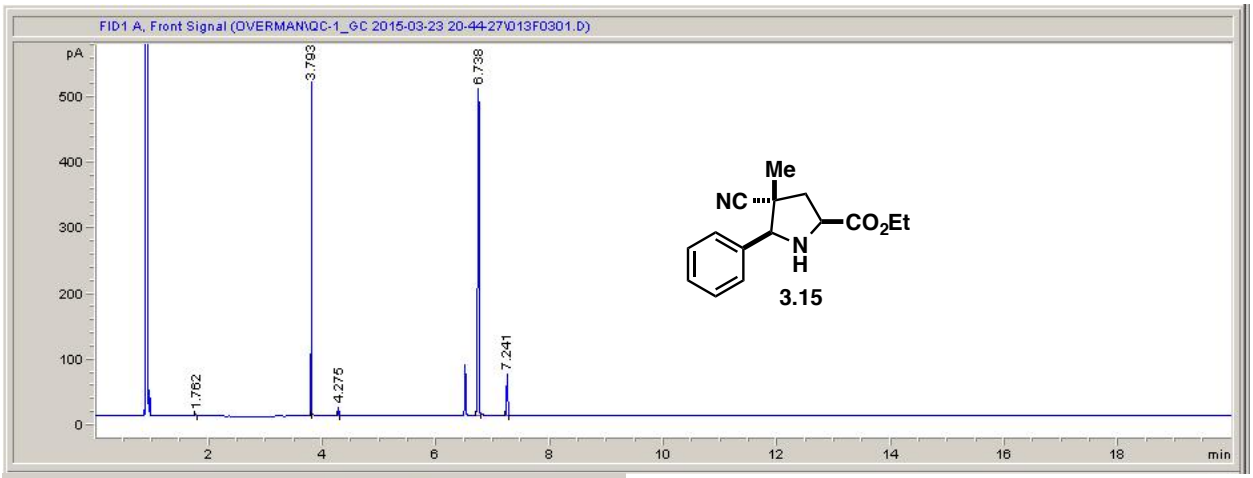
#	Time	Area	Height	Width	Area%	Symmetry
1	3.042	1.9	3.4	8.6899E-3	0.139	0.908
2	3.112	5.1	8.5	9.1741E-3	0.373	0.808
3	3.542	1.8	3.4	7.8E-3	0.131	0.975
4	3.833	253.9	508.3	8.0277E-3	18.735	1.12
5	5.02	6E-1	7.9E-1	0.0107	0.044	0.739
6	5.213	9.2	12.8	0.011	0.680	0.844
7	6.586	105.4	77.9	0.021	7.780	0.908
8	9.382	896.8	265.2	0.0455	66.173	3.248
9	10.094	80.6	27.3	0.0398	5.944	1.24

3.14, t_R = 7.2 min, F = 1.984 ± 0.044:



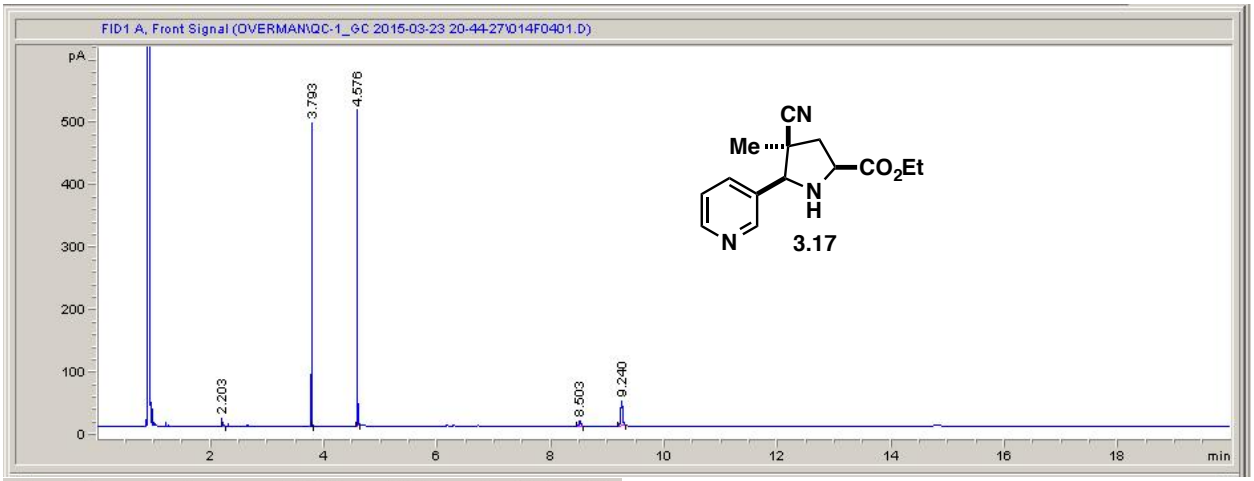
#	Time	Area	Height	Width	Area%	Symmetry
1	1.761	3.1	3.1	0.015	0.305	0.932
2	3.755	246.7	497.5	7.7862E-3	24.586	1.162
3	4.213	50.7	103.6	7.7092E-3	5.053	0.848
4	6.625	16.3	11.7	0.0208	1.628	0.908
5	7.176	686.7	354.7	0.029	68.429	2.091

3.15, t_R = 6.7 min, F = 1.978 ± 0.032:



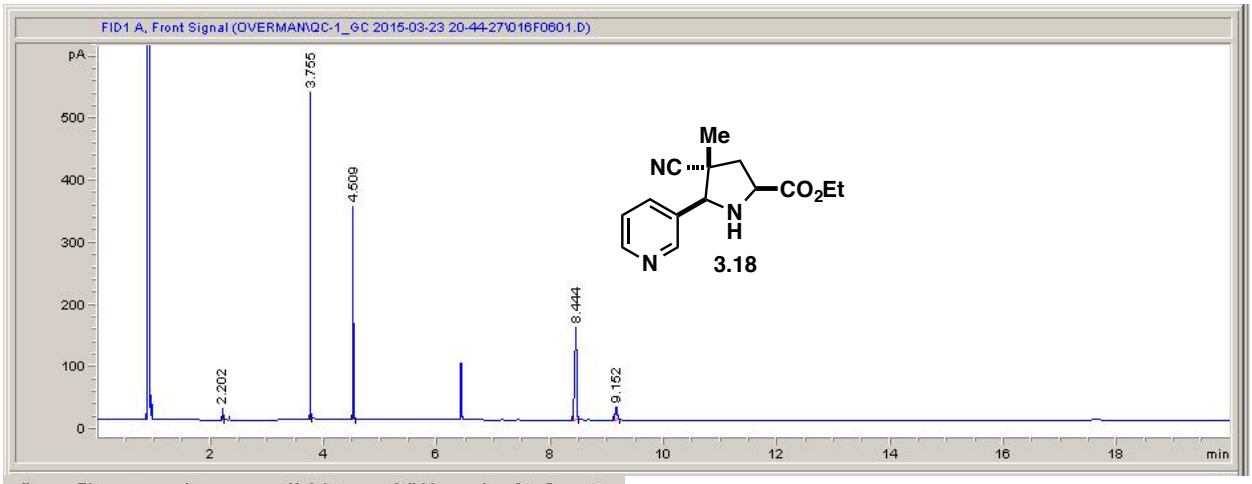
#	Time	Area	Height	Width	Area%	Symmetry
1	1.762	2.7	2.6	0.0149	0.227	0.77
2	3.793	241.1	507.8	7.3382E-3	20.558	1.084
3	4.275	6.8	12.6	8.5175E-3	0.584	0.911
4	6.738	820.8	497.8	0.023	70.004	2.177
5	7.241	101.1	63.6	0.0248	8.626	1.014

3.17, t_R = 9.2 min, F = 1.671 ± 0.066:



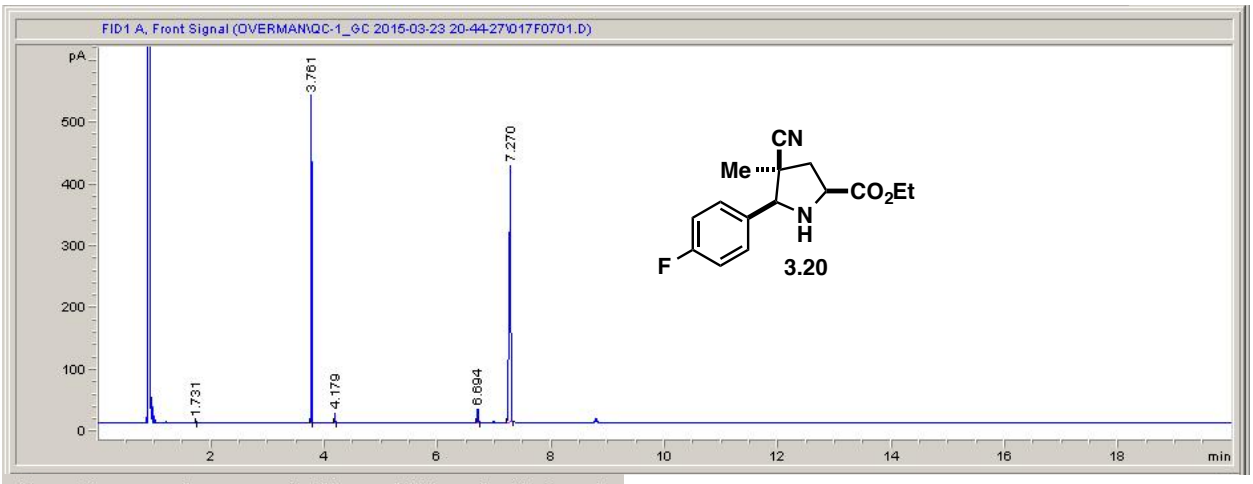
#	Time	Area	Height	Width	Area%	Symmetry
1	2.203	17.8	12.6	0.0199	2.697	0.36
2	3.793	236.3	485.7	7.4753E-3	35.824	1.152
3	4.576	288.4	504.5	8.6701E-3	43.730	1.072
4	8.503	16.6	7.4	0.0278	2.524	1.009
5	9.24	100.4	38.9	0.0349	15.224	1.053

3.18, t_R = 8.4 min, F = 1.600 ± 0.079:



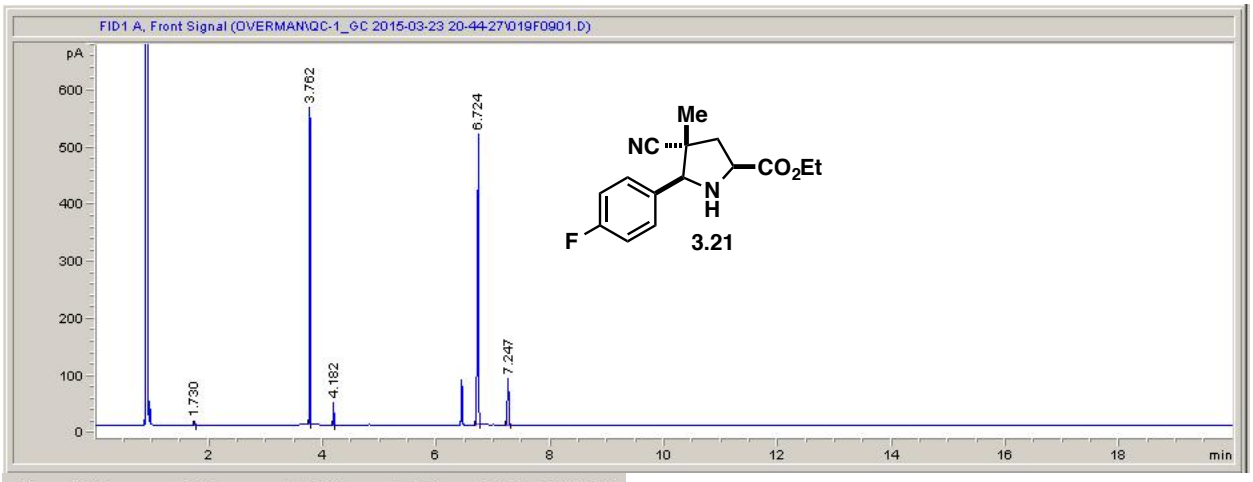
#	Time	Area	Height	Width	Area%	Symmetry
1	2.202	23	19.2	0.0186	2.616	0.471
2	3.755	242.1	525.4	7.1764E-3	27.538	1.067
3	4.509	194.4	343	8.6124E-3	22.115	0.921
4	8.444	366.6	149.4	0.0328	41.699	1.894
5	9.152	53	20.2	0.034	6.032	0.786

3.20, t_R = 7.3 min, F = 2.014 ± 0.042:



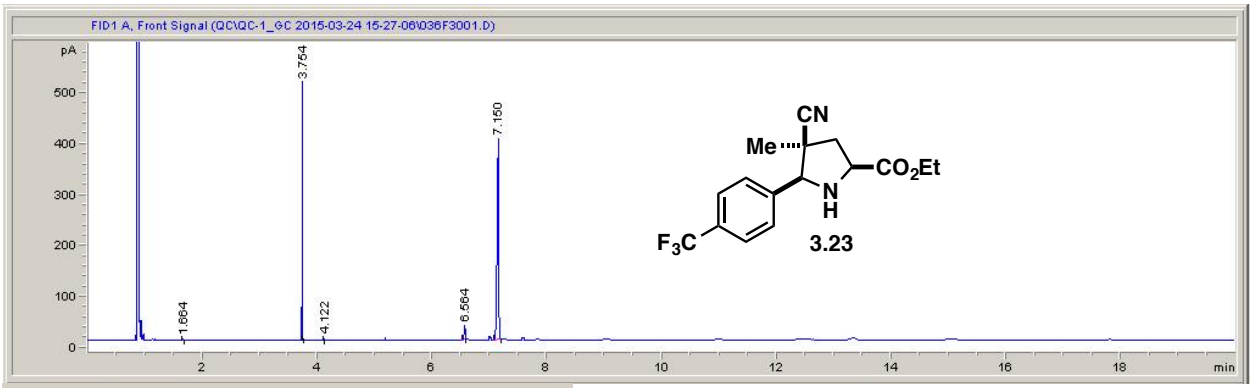
#	Time	Area	Height	Width	Area%	Symmetry
1	1.731	2.9	3.1	0.015	0.251	0.872
2	3.761	257.9	528.6	7.6915E-3	22.325	1.119
3	4.179	8	15.6	7.9632E-3	0.689	0.825
4	6.694	31	22.4	0.0219	2.687	0.994
5	7.27	855.3	414.9	0.0286	74.049	2.773

3.21, t_R = 6.7 min, F = 1.729 ± 0.017:



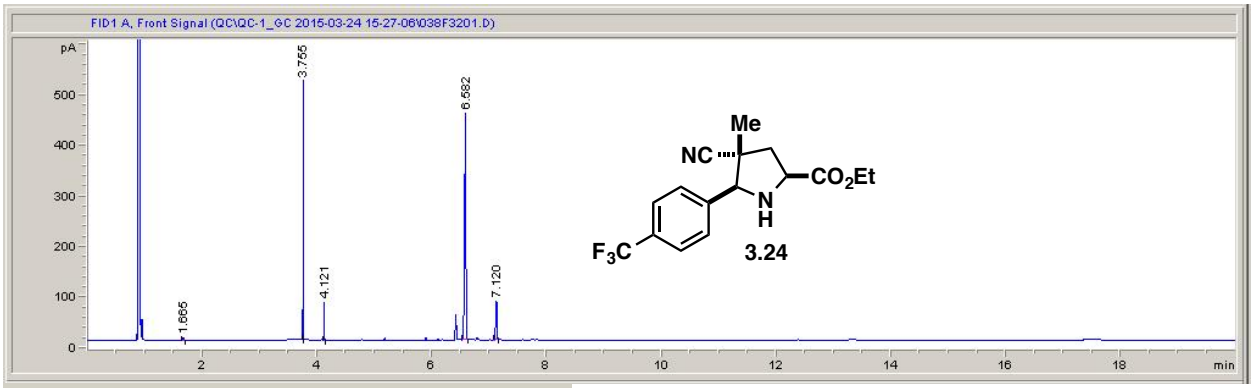
#	Time	Area	Height	Width	Area%	Symmetry
1	1.73	7.5	7.3	0.0153	0.592	0.701
2	3.762	261.3	554.1	7.3022E-3	20.595	1.127
3	4.182	18.8	38.8	7.4622E-3	1.484	0.866
4	6.724	841.7	508.4	0.0229	66.337	2.131
5	7.247	139.5	81.7	0.0255	10.992	1.178

3.23, t_R = 7.2 min, F = 1.943 ± 0.031:



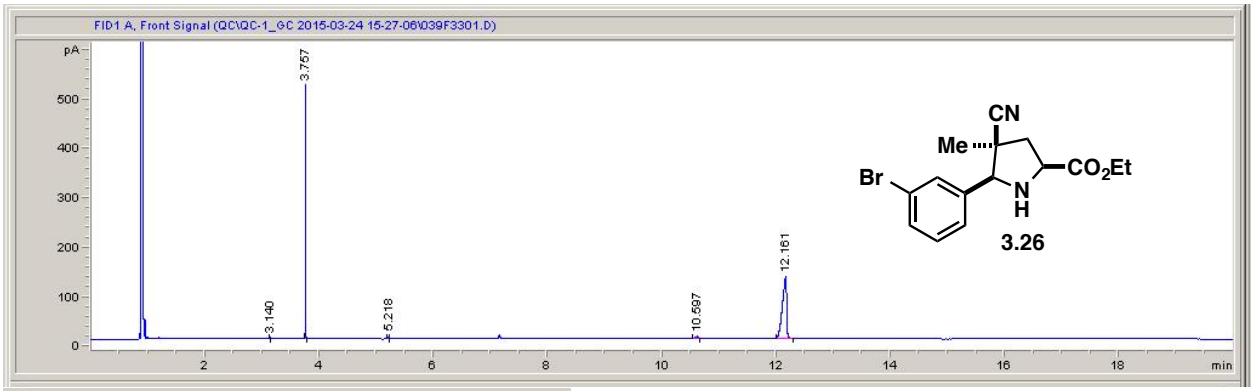
#	Time	Area	Height	Width	Area%	Symmetry
1	1.664	1.9	1.8	0.0141	0.173	0.666
2	3.754	237.6	505.3	7.2865E-3	22.119	1.144
3	4.122	2.2	4.1	8.2998E-3	0.204	0.806
4	6.564	38.9	28.5	0.0205	3.617	1.073
5	7.15	793.7	393.9	0.0271	73.887	2.49

3.24, t_R = 6.6 min, F = 1.919 ± 0.022:



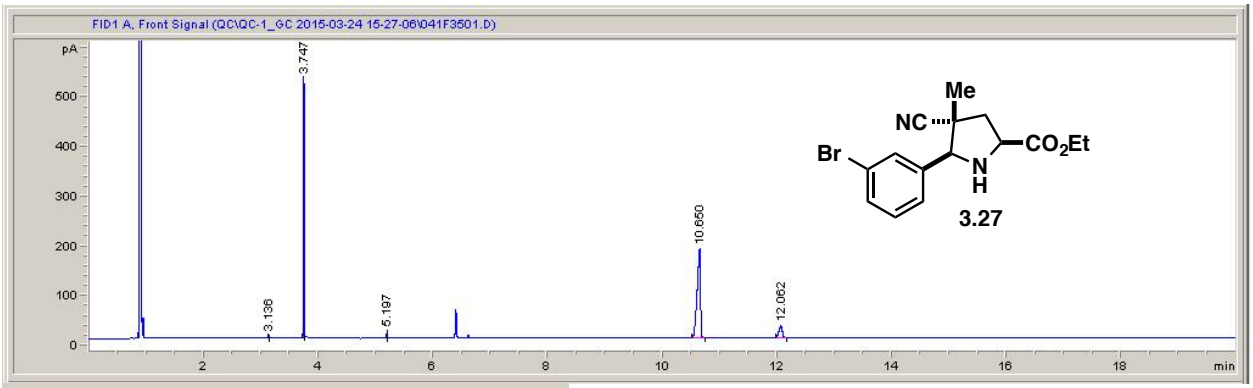
#	Time	Area	Height	Width	Area%	Symmetry
1	1.665	4.8	4.1	0.0165	0.421	0.58
2	3.755	246	510.5	7.4222E-3	21.545	1.128
3	4.121	34.6	75	6.9848E-3	3.032	0.923
4	6.582	731.9	448.5	0.0246	64.096	2.146
5	7.12	124.5	76.6	0.0252	10.906	1.132

3.26, t_R = 12.2 min, F = 1.837 ± 0.036:



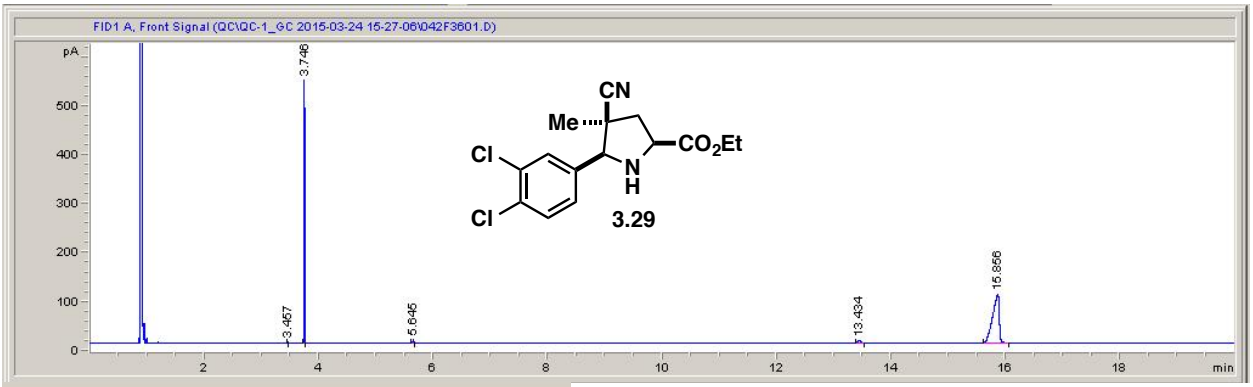
#	Time	Area	Height	Width	Area%	Symmetry
1	3.14	2.2	4.1	8.4186E-3	0.242	0.9
2	3.757	244	512.7	7.5535E-3	26.788	1.102
3	5.218	6.6	7.5	0.0137	0.723	0.853
4	10.597	15.9	5	0.0381	1.748	0.814
5	12.161	642.3	124.6	0.0675	70.500	2.944

3.27, t_R = 10.7 min, F = 1.770 ± 0.015:



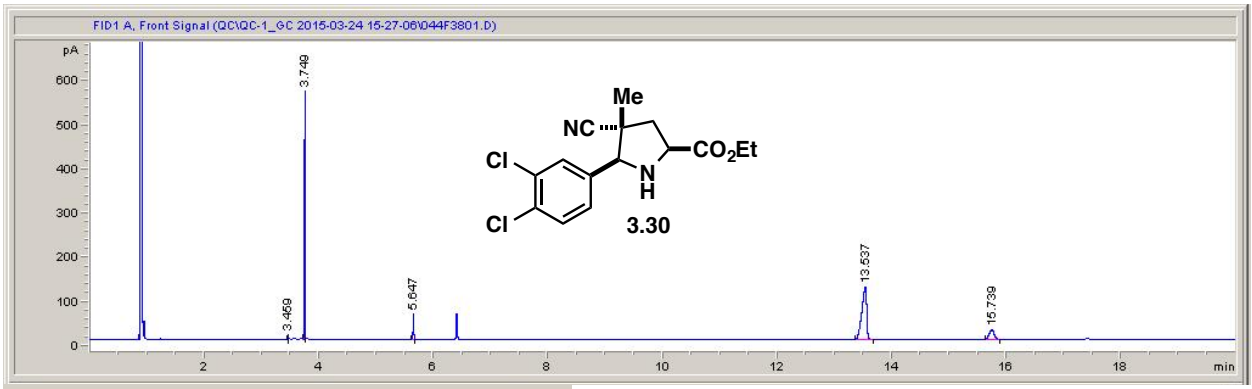
#	Time	Area	Height	Width	Area%	Symmetry
1	3.136	2.8	5	8.8797E-3	0.264	0.805
2	3.747	245.9	523.8	7.4775E-3	22.759	1.103
3	5.197	11.3	14.9	0.0118	1.047	0.902
4	10.65	724.5	178.8	0.0525	67.042	3.183
5	12.062	96.1	23.6	0.0496	8.889	1.214

3.29, t_R = 15.9 min, F = 1.758 ± 0.032:



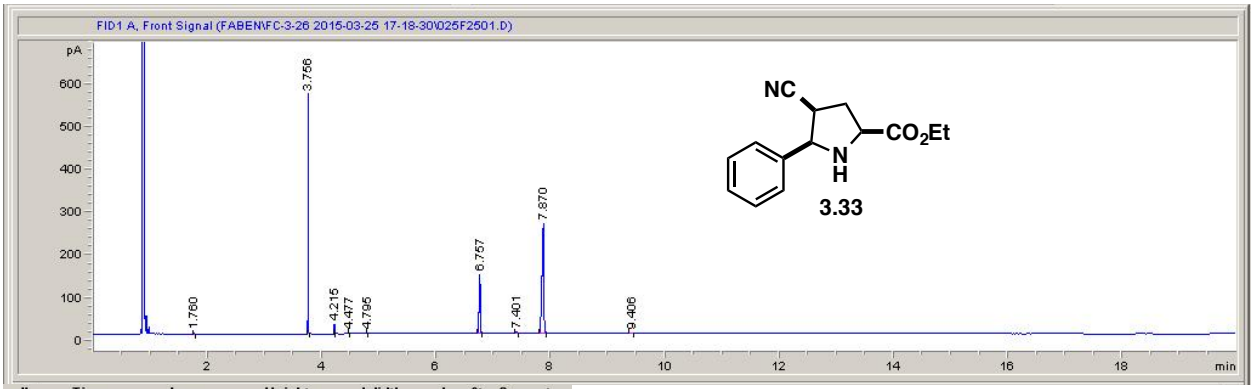
#	Time	Area	Height	Width	Area%	Symmetry
1	3.457	1.8	3.4	8.2131E-3	0.168	0.812
2	3.746	248.1	538.7	7.173E-3	23.133	1.181
3	5.645	8.1	7	0.0173	0.754	0.712
4	13.434	20.7	4.8	0.0531	1.925	0.789
5	15.856	793.9	99.2	0.0953	74.021	2.978

3.30, t_R = 13.5 min, F = 1.521 ± 0.099:



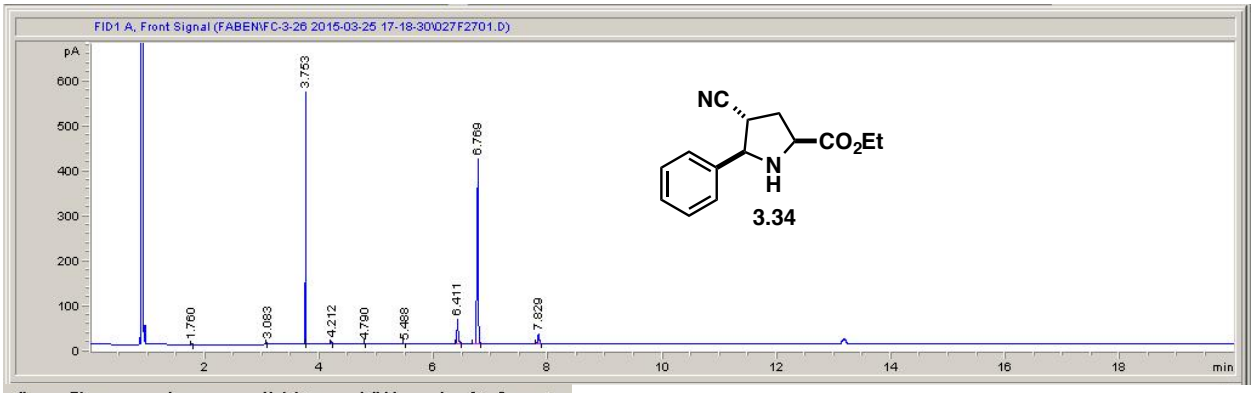
#	Time	Area	Height	Width	Area%	Symmetry
1	3.459	6	11.4	8.1584E-3	0.524	0.789
2	3.749	266.5	560.8	7.3439E-3	23.189	1.12
3	5.647	54.6	58.3	0.0145	4.749	1.035
4	13.537	695.5	119.5	0.0749	60.524	2.986
5	15.739	126.6	21.4	0.0713	11.015	1.027

3.33, t_R = 7.9 min, F = 1.681 ± 0.025:



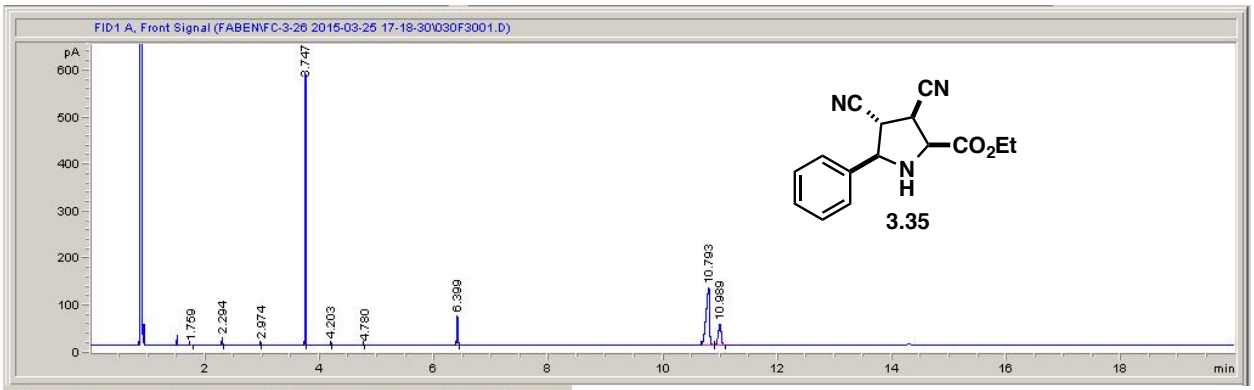
#	Time	Area	Height	Width	Area%	Symmetry
1	1.76	2.1	2.2	0.0145	0.188	0.914
2	3.756	264.6	561.1	7.3018E-3	24.287	1.193
3	4.215	11.3	21.6	7.8904E-3	1.033	0.782
4	4.477	3.3E-1	5.9E-1	8.0176E-3	0.030	0.974
5	4.795	3.8E-1	6E-1	0.0104	0.035	1.069
6	6.757	200.5	137.4	0.0222	18.399	1.337
7	7.401	4.8	2.7	0.0278	0.440	0.919
8	7.87	601.2	257	0.0327	55.180	2.425
9	9.406	4.4	1.8	0.0323	0.408	0.86

3.34, t_R = 6.8 min, F = 1.714 ± 0.034:



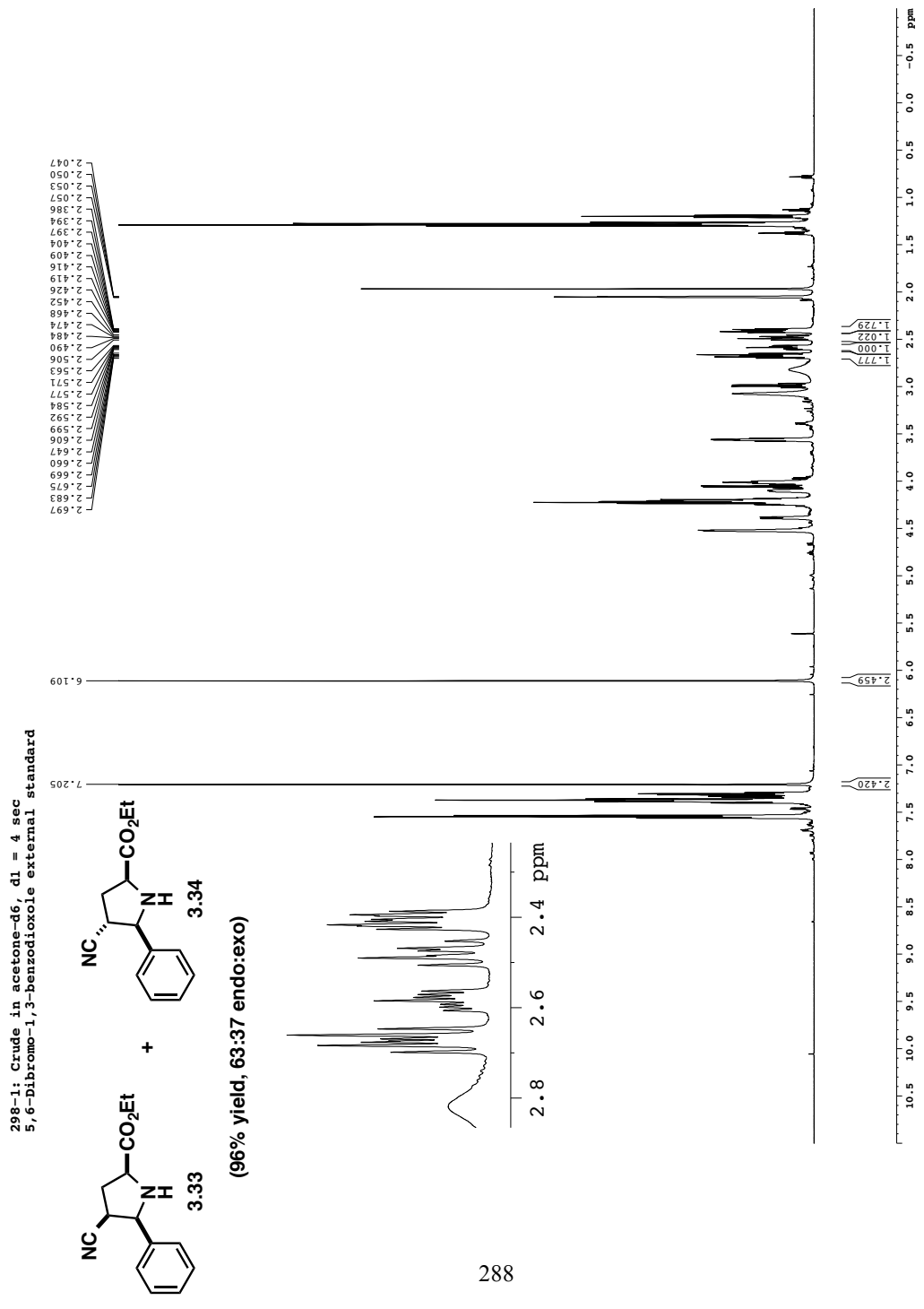
#	Time	Area	Height	Width	Area%	Symmetry
1	1.76	8E-1	8E-1	0.0129	0.073	0.801
2	3.083	1.7	3.3	8.3676E-3	0.157	0.915
3	3.753	267.9	558.5	7.3967E-3	24.327	1.147
4	4.212	3.6	6.9	7.9467E-3	0.329	0.757
5	4.79	6.6E-1	1	9.3878E-3	0.060	1.011
6	5.488	1.2	1.1	0.0158	0.105	0.722
7	6.411	86.5	53.7	0.0242	7.851	0.671
8	6.769	697.6	411.3	0.0232	63.349	2.238
9	7.829	41.3	21.4	0.0279	3.750	0.979

3.35, t_R = 11.0 min, F = 1.503 ± 0.026:

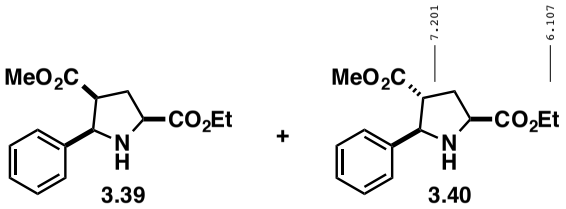


#	Time	Area	Height	Width	Area%	Symmetry
1	1.759	1.9	2.1	0.0142	0.180	0.89
2	2.294	12.3	16.6	0.0115	1.154	0.876
3	2.974	3.4	5.4	9.6053E-3	0.318	0.687
4	3.747	271.3	575.7	7.4981E-3	25.360	1.139
5	4.203	3.6	6.4	8.7356E-3	0.338	0.781
6	4.78	5.1E-1	8.3E-1	9.6267E-3	0.048	0.965
7	6.399	86	62.4	0.0215	8.043	0.804
8	10.793	524.8	122.2	0.0551	49.063	3.277
9	10.989	165.8	45.4	0.0534	15.496	1.452

3.10 Appendix D: Representative Analytical ^{1}H NMR Spectral Data



302-2: Crude in acetone-d6, d1 = 4 sec
5,6-Dibromo-1,2-benzodioxole external standard



3.39 + 3.40

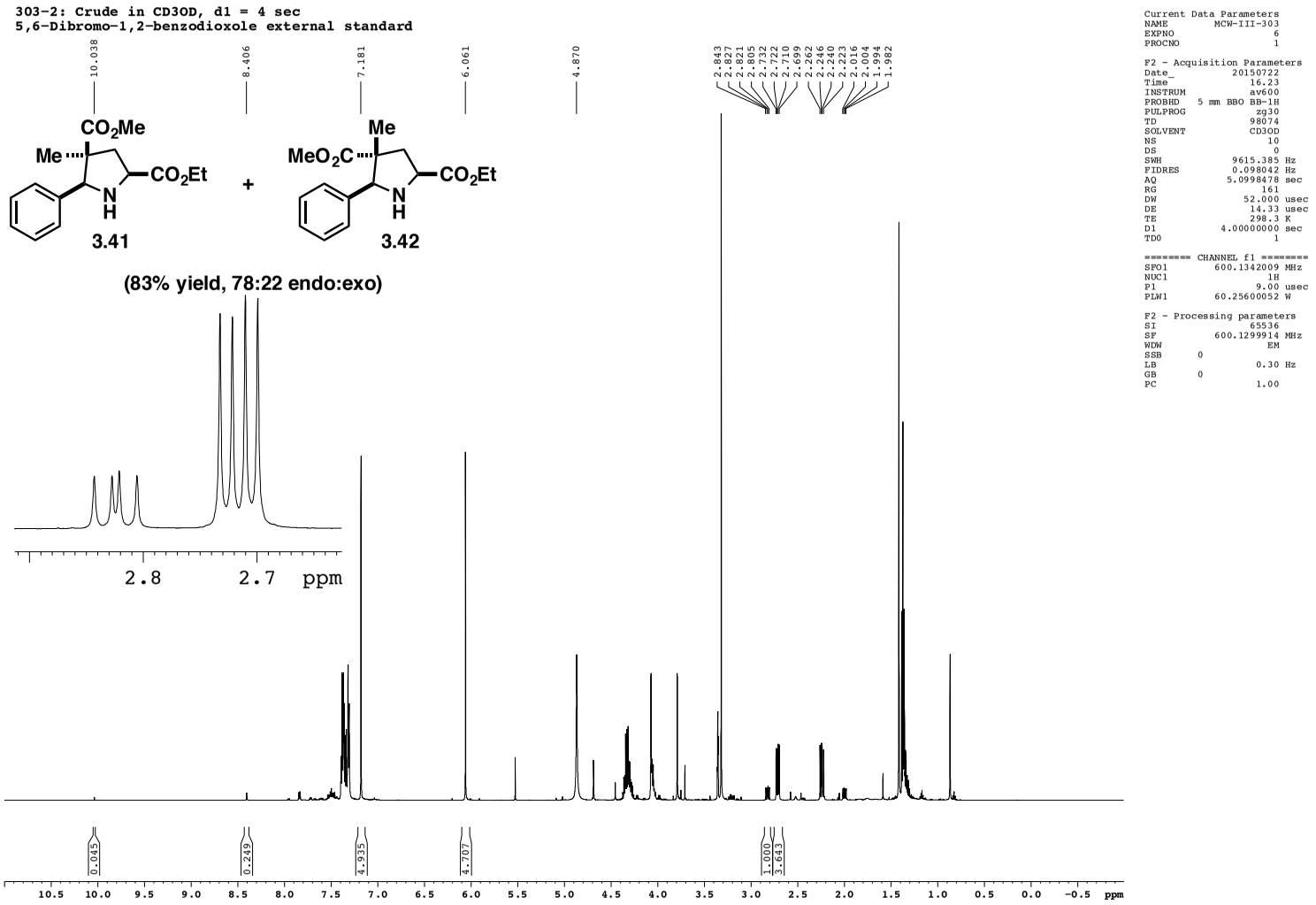
(93% yield, 68:32 endo:exo)


```
Current Data Parameters
NAME          MCW-III-302
EXPNO                   6
PROCNO                  1

F2 - Acquisition Parameters
Date_          20150722
Time               17.16
INSTRUM            av600
PROBHD   5 mm BBO BB-1H
PULPROG            zg30
TD                98074
SOLVENT         Acetone
NS                    10
DS                     0
SWH             9615.385 Hz
FIDRES          0.098042 Hz
AQ              5.0998478 sec
RG                   161
DW                52.000 usec
DE                14.33 usec
TE                298.1 K
D1             4.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          600.1342009 MHz
NUC1                  1H
P1                 9.00 usec
PLW1          60.25600052 W

F2 - Processing parameters
SI                 65536
SF            600.1300187 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```




```
Current Data Parameters
NAME          MCW-III-303
EXPNO                   6
PROCNO                  1

F2 - Acquisition Parameters
Date_           20150722
Time               16.23
INSTRUM            av600
PROBHD   5 mm BBO BB-1H
PULPROG             zg30
TD                 98074
SOLVENT            CD3OD
NS                    10
DS                     0
SWH             9615.385 Hz
FIDRES          0.098042 Hz
AQ              5.0998478 sec
RG                   161
DW                52.000 usec
DE                14.33 usec
TE                298.3 K
D1             4.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          600.1342009 MHz
NUC1                  1H
P1                 9.00 usec
PLW1          60.25600052 W

F2 - Processing parameters
SI                 65536
SF            600.1299914 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

3.11 References and Notes

[1] For an example where the diastereoselectivity of a Cu(II)-catalyzed 1,3-DC was switched by employing two different *P,P'*-biaryl ligands and fumaronitrile as the dipolarophile, see: Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett*. **2003**, *5*, 5043.

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