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Reaction Discovery Using Nickel Catalysis and Total Syntheses of Indolactam Alkaloids

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Noah Frederick Fine Nathel

2015

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ABSTRACT OF THE DISSERTATION

Reaction Discovery Using Nickel Catalysis and Total Syntheses of Indolactam Alkaloids

by

Noah Frederick Fine Nathel

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2015

Professor Neil Kamal Garg, Chair

Transition metal-catalyzed cross-coupling reactions are useful tools to assemble carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds. Traditionally, electrophilic halides and pseudohalides have been cross-coupled to their nucleophilic counterparts with palladium. Recently, however, the implementation of nickel as a catalyst for cross-coupling reactions has enabled the use of less reactive cross-coupling partners, such as carbamates, sulfamates, and amides. This dissertation describes the development of nickel-catalyzed cross-couplings of untraditional electrophiles to forge carbon–heteroatom (C–X) bonds. Additionally, the total syntheses of four indolactam alkaloids, indolactam V, pendolmycin, lyngbyatoxin A, and

teleocidin A-2, using both a key distortion-controlled indolyne reaction and palladium-catalyzed sp^2–sp^3 C–C bond construction, are described.

Chapters one and two describe the development of nickel-catalyzed amination reactions of aryl electrophiles to form carbon–nitrogen (C–N) bonds. The amination reaction of aryl carbamates to form aryl amines is discussed. Subsequently, the development of green cross-couplings of aryl sulfamates and chlorides to similarly form aryl amines is reported.

Chapter three introduces a means to accomplish a controlled cine substitution. This two-step process is comprised of a carbamate-directed ortho-lithiation/functionalization of an arene, followed by a nickel-catalyzed reductive deoxygenation of the directing group. This sequence provides a new strategy for synthesis and complements the more commonly employed ipso substitution in arene functionalization.

Chapter four concerns the utility of amides as electrophilic cross-coupling partners. These traditionally unreactive moieties are activated by nickel and coupled to alcohols to form acyl C–O bonds. This study suggests that amides may serve as useful building blocks to construct C–X and C–C bonds.

Chapter five describes the total syntheses of (–)-indolactam V and its C7-substituted natural product derivatives, (–)-pendolmycin, (–)-lyngbyatoxin A, and (–)-teleocidin A-2. The C4–N linkage is constructed with a distortion-controlled indolyne functionalization. The total synthesis of (–)-indolactam V provides a platform for the divergent syntheses of the other three natural products via a palladium-catalyzed cross-coupling to functionalize C7 and introduce a quaternary center.

The dissertation of Noah Frederick Fine Nathel is approved.

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Neil Kamal Garg, Committee Chair

University of California, Los Angeles

2015

For Dr. Howard Nathel, Ms. Lisa H. Fine, Mr. Patrick J. Henry, Mathilde, Cosmo, Dybbuk, Gezunt, and Shegetz

TABLE OF CONTENTS

Abstract ii

Committee Page iv

Dedication Page v

Table of Contents vi

List of Figures xii

List of Tables xxvi

List of Abbreviations xxviii

Acknowledgements xxxii

Biographical Sketch xlii

CHAPTER ONE: Nickel-Catalyzed Amination of Aryl Carbamates and Sequential Site-Selective Cross-Couplings 1

1.1 Abstract 1

1.2 Introduction 1

1.3 Optimization and Substrate Scope 3

1.4 Computational Studies 8

1.5 Site-Selective Cross-Couplings and Synthetic Applications 10

1.6 Conclusions 12

1.7 Experimental Section 13

1.7.1 Materials and Methods 13

1.7.2 Experimental Procedures 14

1.7.2.1 Synthesis of Aryl Carbamate Substrates 14

1.7.2.2 Aminations of Aryl Carbamates 17
1.7.2.3 Experiments Involving Carbamate and Sulfamate Substrates 25
1.7.2.4 Key Optimization Studies 33
1.7.3 Computational Methods 33
1.7.3.1 Complete Reference of Gaussian 09 34
1.7.3.2 Single Point Calculations using Other DFT Methods and Basis Sets 35
1.7.3.3 The Cartesian Coordinates (**Å**), and Gibbs Free Energies at 298K for the Optimized Structures 36
1.8 Notes and References 68
1.9 Spectra Relevant to Chapter One 77

CHAPTER TWO: Nickel-Catalyzed Amination of Aryl Chlorides and Sulfamates in 2-Me-THF 122
2.1 Abstract 122
2.2 Introduction 122
2.3 Optimization and Substrate Scope 123
2.4 Gram-Scale Couplings 130
2.5 Conclusion 131
2.6 Experimental Section 132
2.6.1 Materials and Methods 132
2.6.2 Experimental Procedures 133
2.6.2.1 Syntheses of Aryl Pseudohalide Substrates 133

2.6.2.2 Solvent Optimization and Scope of Electrophile.....133
2.6.2.3 Aminations of Aryl Sulfamates and Chlorides.....134
2.6.2.4 Isolation Experiments.....142
2.7 Notes and References.....145
2.8 Spectra Relevant to Chapter Two.....152

CHAPTER THREE: Cine Substitution of Arenes using the Aryl Carbamate as a Removable Directing Group.....174
3.1 Abstract.....174
3.2 Introduction.....174
3.3 Cine Substitution of Para Substituted Aryl Carbamates.....176
3.4 Cine Substitution of Indoles.....177
3.5 Cross-Coupling Approaches to Ipso and Cine Substituted Products.....178
3.6 Substrate Scope of Reductive Cleavage or Aryl Carbamates.....179
3.7 Conclusion.....180
3.8 Experimental Section.....182
3.8.1 Materials and Methods.....182
3.8.2 Experimental Procedures.....183
3.8.2.1 Synthesis of Aryl Carbamate Substrates.....183
3.8.2.2 Reduction of Aryl Carbamates.....195
3.8.2.3 Cross Coupling Approaches to Ipso and Cine Substituted Products.....203
3.9 Notes and References.....206

3.10 Spectra Relevant to Chapter Three

CHAPTER FOUR: Conversion of Amides to Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds 264

4.1 Abstract 264

4.2 Introduction 265

4.3 Optimization and Substrate Scope 268

4.4 Computation Studies 273

4.5 Selective Amide Bond Cleavages 274

4.6 Conclusion 276

4.7 Experimental Section 277

4.7.1 Materials and Methods 277

4.7.2 Experimental Procedures 278

4.7.2.1 Syntheses of Amide Substrates 278

4.7.2.2 Methanolysis Control Experiments 283

4.7.2.3 Screening of Amide Substrates 284

4.7.2.4 Comparison of Ligands and Relevant Control Experiments 285

4.7.2.5 Scope of Methodology 287

4.7.2.6 Selective Cleavage of Tertiary over Secondary Amide 298

4.7.2.7 Selective Cleavage of Aryl Amide Over Alkyl Amide 300

4.7.2.8 Selective Cleavage Aryl Amide in the Presence of an Ester 303

4.7.3 Verification of Enantiopurity 306

4.7.3.1 Racemic Compound Syntheses 306

4.7.3.2 Chiral SFC Assays 308
4.7.4 Computational Methods 314
4.7.4.1 Complete Reference to Gaussian 09 314
4.7.4.2 Transition State Structures for Decarbonylation Pathway 315
4.7.4.3 Comparison of Acyl C–N and Aryl C–N Bond Activation Pathway 315
4.7.4.4 Analysis of Amides Derived from Alkyl Carboxylic Acids 316
4.7.4.5 Analysis of *N*-Me,Boc Amide Esterification 318
4.7.4.6 Free Energy and Enthalpy of Amide and Ester Formation 319
4.7.4.7 Energies, Enthalpies, and Free Energy of the Calculated Structures 321
4.7.4.8 Cartesian Coordinates for the Optimized Structures 322
4.8 Notes and References 443
4.9 Spectra Relevant to Chapter Four 448

CHAPTER FIVE: Total Syntheses of Indolactam Alkaloids (–)-Indolactam V, (–)-Pendolmycin, (–)-Lyngbyatoxin A, and (–)-Teleocidin A-2 500
5.1 Abstract 500
5.2 Introduction 500
5.3 Optimization and Substrate Scope 504
5.3.1 Optimization of the Total Synthesis of Indolactam V (**5.1**) 504
5.3.2 Cross-Coupling to Introduce the C7 sp^2–sp^3 Linkage and the Key Quaternary Carbon 505

5.3.3 Total Synthesis of (–)-Pendolmycin (**5.2**) 507

5.3.4 Total Synthesis of Lyngbyatoxin A (**5.3**) and Teleocidin A-2 (**5.4**) 509

5.4 Conclusion 512

5.5 Experimental Section 512

5.5.1 Materials and Methods 512

5.5.2 Experimental Procedures 514

5.5.2.1 Optimization of the Total Synthesis of Indolactam V (**5.1**) 514

5.5.2.2 Cross-Coupling to Introduce the C7 sp^2–sp^3 Linkage 522

5.5.2.3 Total Synthesis of (–)-Pendolmycin (**5.2**) 524

5.5.2.4 Total Syntheses of (–)-Lyngbyatoxin A (**5.3**) and (–)-Teleocidin A-2 (**5.4**) 529

5.6 Notes and References 539

5.7 Spectra Relevant to Chapter Five 546

LIST OF FIGURES

CHAPTER ONE

Figure 1.1. Known C–C and Proposed C–N Bond Formation Reactions using Aryl Carbamates as Substrates 2

Figure 1.2. Gibbs Free Energy Diagram of Ni-Catalyzed Amination of *N*,*N*,-Dimethylphenylcarbamate and Dimethylamine 8

Figure 1.3. Carbamate Functionalization and Low Reactivity of Carbamates and Sulfamates toward Conventional Pd- and Cu-Catalyzed Couplings 11

Figure 1.4. Synthesis of Polysubstituted Arenes using Sequential Sulfamate / Carbamate Couplings 12

Figure 1.5. Comparison of Single Point Energies Using Varied DFT Methods and Basis Sets 35

Figure 1.6. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.23** 78

Figure 1.7. Infrared spectrum of compound **1.23** 79

Figure 1.8. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.23** 79

Figure 1.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.25** 80

Figure 1.10. Infrared spectrum of compound **1.25** 81

Figure 1.11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.25** 81

Figure 1.12. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.27** 82

Figure 1.13. Infrared spectrum of compound **1.27** 83

Figure 1.14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.27** 83

Figure 1.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.28** 84

Figure 1.16. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1.30** 85

Figure 1.17. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.32** 86

Figure 1.18. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.34** 87

Figure 1.19. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.36** 88

Figure 1.20. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.38** 89

Figure 1.21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.40** 90

Figure 1.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.42** 91

Figure 1.23. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.44** 92

Figure 1.24. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.45** 93

Figure 1.25. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.47** 94

Figure 1.26. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.48** 95

Figure 1.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.49** 96

Figure 1.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.51** 97

Figure 1.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.52** 98

Figure 1.30. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.53** 99

Figure 1.31. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **1.54** 100

Figure 1.32. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.55** 101

Figure 1.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.56** 102

Figure 1.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.57** 103

Figure 1.35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.58** 104

Figure 1.36. ^{1}H NMR (500 MHz, C_6D_6) of compound **1.59** 105

Figure 1.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.14** 106

Figure 1.38. Infrared spectrum of compound **1.14** 107

Figure 1.39. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.14** 107

Figure 1.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.15** 108

Figure 1.41. Infrared spectrum of compound **1.15**.....109

Figure 1.42. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.15** 109

Figure 1.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.16** 110

Figure 1.44. Infrared spectrum of compound **1.16**.....111

Figure 1.45. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.16** 111

Figure 1.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.17** 112

Figure 1.47. Infrared spectrum of compound **1.17**.....113

Figure 1.48. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.17** 113

Figure 1.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.18** 114

Figure 1.50. Infrared spectrum of compound **1.18**.....115

Figure 1.51. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.18** 115

Figure 1.52. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.19** 116

Figure 1.53. Infrared spectrum of compound **1.19**.....117

Figure 1.54. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.19** 117

Figure 1.55. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.20** 118

Figure 1.56. Infrared spectrum of compound **1.20**.....119

Figure 1.57. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.20** 119

Figure 1.58. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.21** 120

Figure 1.59. Infrared spectrum of compound **1.21**.....121

Figure 1.60. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.21** 121

CHAPTER TWO

Figure 2.1. Amination of (Hetero)aryl Chlorides and Sulfamates in a Green Solvent Using Nickel 123

Figure 2.2. Coupling of (Hetero)aryl Sulfamates with Morpholine in 2-Me-THF 127

Figure 2.3. Coupling of (Hetero)aryl Chlorides with Morpholine in 2-Me-THF 128

Figure 2.4. Scope of Amine Component in the Coupling Reaction.....129

Figure 2.5. Gram-Scale Couplings of Trifluoromethyl-Containing Substrates 130

Figure 2.6. Gram-Scale Couplings of Heterocyclic Substrates.....131

Figure 2.7. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.4** 153

Figure 2.8. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.6** 154

Figure 2.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.7** 155

Figure 2.10. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.8** 156

Figure 2.11. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.9** 157

Figure 2.12. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.10** 158

Figure 2.13. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.11** 159

Figure 2.14. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.12** 160

Figure 2.15. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.13** 161

Figure 2.16. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.14** 162

Figure 2.17. Infrared spectrum of compound **2.14**.....163

Figure 2.18. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.14** 163

Figure 2.19. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.15** 164

Figure 2.20. Infrared spectrum of compound **2.15**.....165

Figure 2.21. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.15** 165

Figure 2.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.16** 166

Figure 2.23. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.17** 167

Figure 2.24. Infrared spectrum of compound **2.17**.....168

Figure 2.25. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.17** 168

Figure 2.26. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.18** 169

Figure 2.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.19** 170

Figure 2.28. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.20** 171

Figure 2.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.21** 172

Figure 2.30. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.26** 173

CHAPTER THREE

Figure 3.1. Cine Substitution of Aryl *O*-Carbamates.....175

Figure 3.2. Cine Substitution of *Para*-methoxycarbamate **3.3** to give *Meta*-substituted Products **3.5a–c**.....177

Figure 3.3. Cine Substitution of Indolylcarbamate **3.6** 178

Figure 3.4. Cross-Coupling Approaches to Ipso or Cine Substituted Products from Carbamate **3.6** 179

Figure 3.5. Reductive Cleavage of Aryl Carbamates.....180

Figure 3.6. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.4a** 213

Figure 3.7. Infrared spectrum of compound **3.4a**.....214

Figure 3.8. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.4a** 214

Figure 3.9. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3.4b** 215

Figure 3.10. Infrared spectrum of compound **3.4b**.....216

Figure 3.11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.4b** 216

Figure 3.12. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.4c**.....217

Figure 3.13. Infrared spectrum of compound **3.4c** 218

Figure 3.14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.4c**.....218

Figure 3.15. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3.29** 219

Figure 3.16. Infrared spectrum of compound **3.29**.....220

Figure 3.17. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.29** 220

Figure 3.18. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.7** 221

Figure 3.19. Infrared spectrum of compound **3.7**.....222

Figure 3.20. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.7** 222

Figure 3.21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.8** 223

Figure 3.22. Infrared spectrum of compound **3.8**.....224

Figure 3.23. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.8** 224

Figure 3.24. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.9** 225

Figure 3.25. Infrared spectrum of compound **3.9**.....226

Figure 3.26. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.9** 226

Figure 3.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.30** 227

Figure 3.28. Infrared spectrum of compound **3.30**.....228

Figure 3.29. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.30** 228

Figure 3.30. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.32** 229

Figure 3.31. Infrared spectrum of compound **3.32**.....230

Figure 3.32. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.32** 230

Figure 3.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.34** 231

Figure 3.34. Infrared spectrum of compound **3.34** 232

Figure 3.35. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.34** 232

Figure 3.36. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.36** 233

Figure 3.37. Infrared spectrum of compound **3.36** 234

Figure 3.38. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.36** 234

Figure 3.39. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.38** 235

Figure 3.40. Infrared spectrum of compound **3.38** 236

Figure 3.41. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.38** 236

Figure 3.42. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.40** 237

Figure 3.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.41** 238

Figure 3.44. Infrared spectrum of compound **3.41** 239

Figure 3.45. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.41** 239

Figure 3.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.18** 240

Figure 3.47. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.5a** 241

Figure 3.48. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.5b** 242

Figure 3.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.5c** 243

Figure 3.50. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.10** 244

Figure 3.51. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.11** 245

Figure 3.52. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3.12** 246

Figure 3.53. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.13** 247

Figure 3.54. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.19** 248

Figure 3.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.20** 249

Figure 3.56. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.21** 250

Figure 3.57. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.22** 251

Figure 3.58. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.23** 252

Figure 3.59. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.24** 253

Figure 3.60. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.25** 254

Figure 3.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.26** 255

Figure 3.62. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.27** 256

Figure 3.63. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.28** 257

Figure 3.64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.14** 258

Figure 3.65. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.15** 259

Figure 3.66. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.16** 260

Figure 3.67. Infrared spectrum of compound **3.16** 261

Figure 3.68. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.16** 261

Figure 3.69. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.17** 262

Figure 3.70. Infrared spectrum of compound **3.17** 263

Figure 3.71. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.17** 263

CHAPTER FOUR

Figure 4.1. Natural, Synthetic, and Proposed Methods for Amide Bond Cleavage 266

Figure 4.2. Gibbs Free Energy Diagram of Ni-Catalyzed Esterification of Amide **4.15** with Methanol 274

Figure 4.3. Mild and Selective Esterifications of Bis- and Valine-Derived Amides 275

Figure 4.4. Analysis of Competing Pathways for Esterification of *N*-Me,Boc Substrate **4.108**.....318

Figure 4.5. Substitution Effects on Equilibrium of Amide Esterification.....319

Figure 4.6. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.39** 449

Figure 4.7. Infrared spectrum of compound **4.39**.....450

Figure 4.8. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.39** 450

Figure 4.9. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.41** 451

Figure 4.10. Infrared spectrum of compound **4.41**.....452

Figure 4.11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.41** 452

Figure 4.12. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.43** 453

Figure 4.13. Infrared spectrum of compound **4.43**.....454

Figure 4.14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.43** 454

Figure 4.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.45** 455

Figure 4.16. Infrared spectrum of compound **4.45**.....456

Figure 4.17. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.45** 456

Figure 4.18. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.47** 457

Figure 4.19. Infrared spectrum of compound **4.47**.....458

Figure 4.20. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.47** 458

Figure 4.21. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.8** 459

Figure 4.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.48** 460

Figure 4.23. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.50** 461

Figure 4.24. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.52** 462

Figure 4.25. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.54** 463

Figure 4.26. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.56** 464

Figure 4.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.57** 465

Figure 4.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.59** 466

Figure 4.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.61** 467

Figure 4.30. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.62** 468

Figure 4.31. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.63** 469

Figure 4.32. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.64** 470

Figure 4.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.72** 471

Figure 4.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.74** 472

Figure 4.35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.76** 473

Figure 4.36. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **4.78** 474

Figure 4.37. Infrared spectrum of compound **4.78**.....475

Figure 4.38. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.78** 475

Figure 4.39. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.80** 476

Figure 4.40. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.29** 477

Figure 4.41. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.82** 478

Figure 4.42. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.84** 479

Figure 4.43. Infrared spectrum of compound **4.84**.....480

Figure 4.44. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.84** 480

Figure 4.45. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.86** 481

Figure 4.46. Infrared spectrum of compound **4.86**.....482

Figure 4.47. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.86** 482

Figure 4.48. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.88** 483

Figure 4.49. Infrared spectrum of compound **4.88**.....484

Figure 4.50. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.88** 484

Figure 4.51. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.27** 485

Figure 4.52. Infrared spectrum of compound **4.27**.....486

Figure 4.53. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.27** 486

Figure 4.54. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.30** 487

Figure 4.55. Infrared spectrum of compound **4.30**.....488

Figure 4.56. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.30** 488

Figure 4.57. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.91** 489

Figure 4.58. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.94** 490

Figure 4.59. Infrared spectrum of compound **4.94**.....491

Figure 4.60. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.94** 491

Figure 4.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.31** 492

Figure 4.62. Infrared spectrum of compound **4.31**.....493

Figure 4.63. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.31** 493

Figure 4.64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.32** 494

Figure 4.65. Infrared spectrum of compound **4.32**.....495

Figure 4.66. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.32** 495

Figure 4.67. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.34** 496

Figure 4.68. Infrared spectrum of compound **4.34**.....497

Figure 4.69. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.34** 497

Figure 4.70. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.33** 498

Figure 4.71. Infrared spectrum of compound **4.33**.....499

Figure 4.72. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.33** 499

CHAPTER FIVE

Figure 5.1. Indolactam Alkaloids **5.1**–**5.4** 502

Figure 5.2. Synthetic Strategy Toward **5.1** and C7 Substituted Indolactam Alkaloids.503

Figure 5.3. Optimized Synthesis of Indolactam V (**5.1**) and **5.14**.....505

Figure 5.4. C7 Functionalization of **5.14** and Introduction of Key sp^2–sp^3 Linkage with a Quaternary Carbon Substituent 508

Figure 5.5. Total Synthesis of (–)-Pendolmycin (**5.2**).....509

Figure 5.6. Synthesis of Morpholine Amide **5.29** and Cross-Coupling to Access Diastereomeric Adducts **3.31** and **3.32** Possessing the Necessary All-Carbon Quaternary Stereocenters 510

Figure 5.7. Total Synthesis of (–)-Lyngbyatoxin A (**5.3**) 511

Figure 5.8. Total Synthesis of (–)-Teleocidin A-2 (**5.4**) 512

Figure 5.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.14** 547

Figure 5.10. Infrared spectrum of compound **5.14**.....548

Figure 5.11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.14** 548

Figure 5.12. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.16b** 549

Figure 5.13. Infrared spectrum of compound **5.16b**.....550

Figure 5.14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.16b** 550

Figure 5.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.16c**.....551

Figure 5.16. Infrared spectrum of compound **5.16c** 552

Figure 5.17. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.16c**.....552

Figure 5.18. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.24** 553

Figure 5.19. Infrared spectrum of compound **5.24**.....554

Figure 5.20. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.24** 554

Figure 5.21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.25** 555

Figure 5.22. Infrared spectrum of compound **5.25**.....556

Figure 5.23. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.25** 556

Figure 5.24. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.26** 557

Figure 5.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.27** 558

Figure 5.26. Infrared spectrum of compound **5.27**.....559

Figure 5.27. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.27** 559

Figure 5.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.2** 560

Figure 5.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.29** 561

Figure 5.30. Infrared spectrum of compound **5.29**.....562

Figure 5.31. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.29** 562

Figure 5.32. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.31** 563

Figure 5.33. Infrared spectrum of compound **5.31**.....564

Figure 5.34. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.31** 564

Figure 5.35 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.33** 565

Figure 5.36 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.34** 566

Figure 5.37. Infrared spectrum of compound **5.34**.....567

Figure 5.38. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.34** 567

Figure 5.39. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.3** 568

Figure 5.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.32** 569

Figure 5.41. Infrared spectrum of compound **5.32**.....570

Figure 5.42. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.32** 570

Figure 5.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.46** 571

Figure 5.44. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.47** 572

Figure 5.45. Infrared spectrum of compound **5.47**.....573

Figure 5.46. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.47** 573

Figure 5.47. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.4** 574

LIST OF TABLES

CHAPTER ONE

Table 1.1. Amination of Aryl Carbamates with Morpholine....4

Table 1.2. Amination of *o*-Substituted and Heterocyclic Carbamates....5

Table 1.3. Amination of Aryl Carbamates with Various Amines....7

Table 1.4. Optimization of Ligand, Base, and Temperature....33

Table 1.5. Comparison of Single Point Energies Using Varied DFT Methods and Basis Sets....35

CHAPTER TWO

Table 2.1. Examination of Solvents in the Amination of 1-Chloronapthalene....124

Table 2.2. Evaluation of Various Electrophiles....125

CHAPTER FOUR

Table 4.1. Computational and Experimental Substrate Optimization....270

Table 4.2. Scope of Amide Substrate and Alcohol Nucleophile....271

Table 4.3. Attempted Conversion of Amide **4.15** to Methyl Benzoate Under Various Reaction Conditions....283

Table 4.4. Survey of Amide Substrates....284

Table 4.5. Ligand Screening for Nickel-Catalyzed Esterification....286

Table 4.6. Comparison of Aryl vs. Alkyl Amide Substrates....316

Table 4.7. Energies, Enthalpies, and Free Energies of the Structures Calculated at the M06/SDD,6-311+G(d,p)(SMD^{toluene})//B3LYP/LANL2DZ,6-31G(d) 321

CHAPTER FIVE

Table 5.1. C7 sp^2–sp^3 Cross-Coupling on Model Substrate **5.15** 507

LIST OF ABBREVIATIONS

Å	angstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl, acetate
AcOH	acetic acid
AIBN	Azobisisobutyronitrile
α	alpha
app.	apparent
aq.	aqueous
atm	atmosphere
Bz	benzoyl
Bn	benzyl
β	beta
br	broad
Boc	*tert*-butoxycarbonyl
BTPP	(*tert*-butylimino)tris(pyrrolidino)phosphorane
Bu	butyl
i-Bu	isobutyl
n-Bu	butyl (linear)
t-Bu	*tert*-butyl
t-BuOH	*tert*-butyl alcohol
BHT	butylated hydroxytoluene
c	concentration for specific rotation measurements
°C	degrees Celsius
CAN	Cerium (IV) ammonium nitrate
calcd	calculated
cat.	catalytic
CCDC	Cambridge Crystallographic Data Centre
COD	1,5-cyclooctadiene
d	doublet
DCB	1,2-dichlorobenzene
DCE	1,2-dichloroethane
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether

DIC	*N,N*′-Diisopropylcarbodiimide
dig	digonal
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
ee	enantiomeric excess
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
g	gram(s)
Glc	glucosyl
h	hour(s)
HMPA	Hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared (spectroscopy)
J	coupling constant
L	liter
LiHMDS	lithium hexamethyldisilazide
M	molecular mass
m	multiplet or milli
m	meta
m/z	mass to charge ratio
μ	micro
*m*CPBA	3-chloroperbenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl ether

mp	melting point
MS	molecular sieves
NF-κB	Nuclear Factor kappa B
NIS	*N*-iodosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
[O]	oxidation
p	para
π	pi
PCC	pyridinium chlorochromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
Piv	pivaloyl
PMP	1,2,2,6,6-Pentamethylpiperidine
PPh_3	triphenylphosphine
ppm	parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
PSI	Pounds per square inch
pyr	pyridine
q	quartet
rt	room temperature
R_f	retention factor
s	singlet
sat.	saturated
SGLT2	sodium-glucose linked transporter 2
t	triplet
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TEBA	Benzyltriethylammonium
TES	triethylsilyl

Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsiyl triflate
trig	trigonal
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet

ACKNOWLEDGEMENTS

First, I would like to thank my advisor, Professor Neil Garg, for his unconditional support and direction during my graduate studies. Neil's encouragement was integral in helping me overcome obstacles I faced during my time at UCLA. His commitment to scientific and professional excellence has been extremely influential to the members of our research group and has provided me with the confidence to go forward as a scientist. I left my original graduate program, and it was difficult to re-enter the field due to a stigma toward transfer students. Neil gave me a second chance at chemistry and I will always be grateful.

Professor Ken Houk has also been a tremendous mentor and collaborator. Professor Houk served on my oral exam committee and taught me everything there is to know about Physical Organic Chemistry, my favorite subfield. He challenged me during oral and written exams to help me grow as a critical thinker. I would also like to acknowledge Professors Richard L. Weiss and Andrea M. Kasko for taking time out of their schedules to serve on my candidacy and dissertation committees. I would also like to thank my computational collaborators, Xin Hong, Dr. Peng Liu, and Yu-Fang Yang, for their expertise and vital contributions to our projects.

Professor Geoff W. Coates and Dr. Peter Widger (my graduate mentor) provided me with my first academic research experience when I was an undergraduate at Cornell University. Both have supported my academic and professional development well after I graduated from college. Geoff has an amazingly elegant and creative research program, of which I was honored to be a part, and inspired my interest in metal catalysis. Pete was a most patient mentor, helping me overcome discomfort and build confidence working in the lab environment. To this day, I still use the customized techniques he taught me, including air-sensitive reaction set-up and

specialized recrystallization. Thank you Geoff and Pete - I am touched by your unwavering support.

Thank you to Dr. Pascal Dube, my mentor at Pfizer during a summer internship. Although he was only responsible for directing me in completing a quick project, he went way beyond the call of duty, teaching me the fundamentals of organic chemistry and things I missed in my classes. Thanks to Pascal, I came to understand what was really happening from a molecular orbital point of view. Pascal was so patient, kind and encouraging; after a summer under his guidance, I knew I wanted to be a chemist.

During my semester at University of Michigan, I worked as a rotation student in Professor Melanie Sanford's research group. Besides providing fundamentals of organometallics, Professor Sanford was very helpful in promoting my future in chemistry. I will always appreciate her support.

During my years at UCLA, I was lucky to have a slew of supportive friends. Their constant support, encouragement, and fellowship are what helped me forge on when I was frustrated to the brink of quitting. I will always remember my classmates with fondness. Joel - one of the most unique people I've ever met, will be a lifelong friend. He has unique and vivid intuition for chemistry. I often couldn't keep up with his conversations about complex molecule synthesis and recently developed reactions, but am happy that someone with such capabilities will be the future of chemistry. I know the field of total synthesis will be in good hands and I know he will achieve his goal of becoming a professor. Besides being an outstanding thinker, I can call Joel one of my best friends. We supported one other through very difficult times and I will never forget how much his companionship meant to me, including but not limited to: a variety of jokes only we could appreciate; movies only we could appreciate; and food we could

only appreciate. And Evan (or Vern), whenever I think of phosphines, I think of you (because we stayed up countless hours memorizing phosphine ligands for one of our synthesis exams). As the night before a big test turned to day, the lines blurred between humor and reality. Thank you for sharing those less-than-comfortable experiences with me.

The upperclassmen were pivotal to my survival in this program. Dr. Kyle Quasdorf, you are a quiet and thoughtful person for whom I have the utmost respect. You are a brilliant chemist and the world of Pharma is lucky to have you. Thank you for doing my first *ortho*-lithiation. It was really intimidating, but ultimately I got the hang of it. Dr. Ben Boal's serene nature is in stark contrast to my anxious one, and I truly enjoyed his company and good humor. Ben has a very lucky wife and new daughter. Dr. Sarah Bronner, on the other hand, was just about as anxious as I was. This, however, got her far and I can only appreciate it more. She mentored me when I started work on my first total synthesis project, and it was she who set the stage for solving its key step and ultimate completion. Sarah, I will miss going to Native Foods with you. We're the only two people in all of Los Angeles who like it.

To the Dean Empress (a.k.a. the Dean Goddess, Dr. Tehetena Mesganaw, etc.), you were my very first co-worker/influencer. I can't begin to thank you for the support and guidance you gave me from the day I started the program, all the way through the end of your tenure at UCLA. Besides being a meticulous chemist, you were very motherly and kind. I really needed that during my first few years here and I credit you with giving me the strength to get through the tough of times. To Dr. Alex Schammel, master of purification and one of my best friends: you were the first person to make me feel welcome here. I wasn't sure if I could make it in grad school; you made being at work fun and you helped me overcome some of my worst fears. You helped me resolve almost every technical problem I encountered in lab. When I felt embarrassed

over having a meltdown, you were always a trusted confidant. I thank you for this and apologize for any trauma I likely caused. I enjoyed exploring L.A. with you and watching more movies with you than I can count. You will always be one of my closest friends and I will never forget what you did for me.

Dr. Alex Huters and I share interests in elegant dining and T.V. shows; I will always think fondly of our conversations on these subjects. Thank you too for your help with classes, cumes and chemistry. Alex, you are a wealth of knowledge and hope you're enjoying the high life in Chicago. I hear it's "SOOOOOOO" good.

I would like to thank the class above mine. Dr. Grace Chiou, thank you for your constant optimism, Chinese food tips, and telling me to "pump oil". Dr. Adam Goetz, thank you for your help in solving problems and for handling difficult situations with such grace and tranquility. I wish I got to hang out with you more, because I know we appreciate similar things. Maybe I'll see you in Seattle one day. Dr. Stephen Ramgren, you took me under your wing when I first got to grad school. I was scared to do a lot of intimidating things in lab, but you made them seem easy and gave me an enormous confidence boost. I always thought of you as the go-to person in our group (and many people agree). I also take comfort in knowing that Snapper Jack's exists. To Dr. Amanda Silberstein: you always had a calming effect on me (no easy task). Besides being the zookeeper for our room, you were always helpful with chemistry and with solving problems. You have a great sense of humor and it was an honor and pleasure working next to you. You were also the only person I knew who had molecules jumping off prep plates! Amazing. The undergraduates that you will mentor as budding assistant professor are lucky indeed. You will be a valued asset to your institution.

I overlapped with some amazing underclassmen. Liana Hie was a great and thoughtful friend and an excellent coworker. I wouldn't have been able to get much done without her perseverance and talent. Liana, I consider you a very close friend. I will miss exploring odd ethnic foods with you. You taught me the true meaning of "sushi". Tejas Shah was another long-term project partner and great friend. We climbed hills to make natural products and learned a lot about Schwartz's reagent. I decomposed a lot of his precious material, and I don't think he holds a grudge. Tejas, it was an honor working with you. I couldn't have finished the project without you. I also thank you for sharing your uncanny talent for fixing software problems.

Nick Weires, it was great getting to know you better during my last year here. You are a thoughtful, meticulous and helpful co-worker with a great talent for mentoring younger students, and you are one of the funniest people I've ever met. I wish you the best of luck in the future. Jose Medina, Mr. JACS: you are a great guy. I truly respect your ability to focus on the important things in life and not let trivia impede your path. Your work ethic is inspiring and subtle sense of humor appreciated. It was fun working with you and hope to stay in touch. Jesus Moreno - the one true other horror movie connoisseur; we share a similar sense of humor as well as outlook on life. I respect your organization and technical talents. You are one of the nicest people I've met, a very loyal friend, and I anticipate your great success in the future. I expect Bagul will be standing not so far behind. Finally, Michael (topolus) Corsello deserves a lot of credit in helping me get through the program. Mike, I am so happy to have met you. Your passion for knowledge – be it chemistry, biology, philosophy - is inspiring. Your passion for psychology came in very handy – thanks for taking the time to listen to me. I knew you'd be a great friend from the very start and know you'll be one for a lifetime. One word of advice: when you become a professor, try not to stick your chin out.

For the past few years or so, I've had the pleasure of getting to know the youngest members of our group. Junyong Kim, it was an honor working with you on your first project. You are a great coworker, friend, and a very funny individual. Ring Ring. Elias Picazo, I've never met such an optimist (what's *wrong* with you?). Seriously, I have a lot of respect for that attitude, which will take you far. Your assessments of scary films are astute and will make many top ten lists. Emma Baker, your smile is what drives me to come to work every day. Kidding – but it HAS been wonderful working next to you and getting to know you this past year, even if the movies I go to are too late for you. GJGJG. Joyann Barber, it was great sitting next to you and thank you for tolerating me. If you can do that, you can do anything. I wish you the best of luck with the rest of your Ph.D. Lucas Morill, you're a really nice and smart person. Good luck, keep drinking the IPA, and don't get my fume hood too dirty. Bryan Simmons, it was really nice getting to know you and Chloe in the short time we overlapped. The lab is lucky to have you and I wish you the best here at UCLA. I would also like to thank Travis McMahon, our fearless postdoc. Just remember, Travis, the commissioner called an out for the hole in one.

Finally this thesis would not have been possible without the support of close friends and family. Ryan Cary, my best friend growing up, you've always been there for me, even when I've egregiously failed to return your calls for weeks. Thank you for believing in me, sticking up for me, and being a great friend. To my cousins Joshua, Daniel, Adam, Harris and Hailey Nathel and Jesse Tyma; aunts and uncles Marilyn and Mark Tyma, Michele and Michael Nathel, Allison and Matthew Nathel – thank you for sticking by my side and understanding when I dropped off the face of the planet to complete my degree. I am back on Earth now.

To my wonderful and supportive girlfriend, Courtney Roberts. Thank you for always being there for me. Literally… you moved in. I'm so lucky to have you nearby at work and,

although we keep chemistry talk to a minimum, I'm lucky that you understand what I do. You are one of the most thoughtful and kind people I've ever met. You've tolerated my less-than-optimal schedule, and I can't thank you more. I look forward to spending our Saturdays off together. We have so much fun trying new coffee places (most of which you discovered), food places (most of which I discovered), and watching movies. I love sharing our common interests and humor and love you so much. You are my girlfriend and my best friend. Thank you for being in my life. Additionally, Bew.

I would like to give a special thanks to my grandparents, Arlene and Julian Fine, may you rest in peace. I am sad that you are not here to see what your grandchildren have chosen for their paths, but your legacy lives on. The combination of your amiable and sardonic personalities, respectively, have been fully translated to your successors, and I will always love you both for that. My best memories of you were in Reno and Connecticut. Papa would gamble with such passion that Nana and I would buy out the casino with the points he earned. You were the most down-to-earth people ever. Both of you were loved my so many people, but especially your family. We miss you greatly. To my grandparents, Harriet and Gerald Nathel, your love and support from across the country influence my happiness and success. You are amazing people, parents and grandparents. Your generosity to your children and grandchildren knows no bounds. Some of my fondest memories are when you would come out to California and we would go to Napa Valley. I credit you both for my lavish and unaffordable taste in food and, more importantly, the family values I cherish. Thank you for always being there for us no matter what. We all love you so much and couldn't be luckier to have you in our lives.

Undoubtedly, I owe the most to my parents. Jeff Henry, my stepfather, who has been in my life since I was 10 years old. He's been very supportive of my mom and me. I will always

appreciate his down-to-earth nature, willingness to adapt to a completely different culture, and ability to get things done efficiently. Jeff is an outlier in our country. He transcended all professional ceilings and made it to the upper echelon by sheer intellect and personality. Jeff, I will always look up to you.

To Dr. Howard Nathel, my father, I wouldn't be in the position I'm in if it weren't for you. From an academic point of view, I saw you as a role model to do what I really wanted to do: science. In retrospect, I think it was the trips to Lawrence Livermore National Laboratory where you worked that compelled me to enter the field. Although you moved on to bigger and better things, your advice about the field, graduate school, and life have been crucial for the ascension through my degree. Some of the darkest times in my life, where I struggled with a learning disability, you were there to keep me from derailing. I will always remember the time and effort you put in. When I was leaving my first graduate program, you were supportive of my decision because my happiness was more important to you than my career path. When I was a mischievous teenager, you were stern but compassionate, and identified with me by recalling stories from your own youth. When I was a child, you were always there with homework help and advice on interpersonal issues. You provide whatever I needed, whenever I needed it. You were also the best thing to happen to Cosmo, and even if he was a sociopath, he's appreciating your love from the great beyond. I am very proud of my father for his contribution to the generation beyond mine. He volunteers in one of the most perilous parts of our country, tutoring, training, and standing up for underprivileged youth. Oakland, California is hanging on by a string, and he's the one holding it. Thank you, Dad, for everything you do.

To Lisa Fine, my mother. I don't know where to start, but I suppose I could begin with the baby pictures. You were holding me up and supporting me from the time I was born. When I

was young, we would walk with Mathilde in Terrace Park, Tilden Park and Point Isabel. Those may be my earliest memories. You taught me that pets are family members and it speaks very well to your character. Every creature under your care lives better than British Royalty. Some of my greatest memories are the ones I've had in your company. Going to Great America and Santa Cruz Beach Boardwalk, to name a few. Scandia was probably my favorite. Thank you for giving me enough quarters to finish some of those longer arcade games. You always listened to my stories, especially the ones that you really didn't have any interest in. For instance, the plot of Mortal Kombat, which I made you watch four hundred times; or alternatively, the chemistry I'm learning now. No matter the subject, you have always made an effort to make me feel good about my interests and pursue whatever I wanted (as long as my title had some form of "doctor" in it). During the darkest times in my life, you have been a platform to stand upon. I always felt I could show my true emotions around you without being judged. You definitely got that from Nana. And on the other hand, I owe all of my less-than-palatable humor to you, which ultimately came from Nana's counterpart. It was these gifts that gave me the power to get to where I am today and I don't have the words to express my gratitude. I look up to you for your interpersonal skills. When my mother took me to work, it provided me a glimpse of how to treat people, no matter their corporate position. I don't know where I would be without these lessons and I wish to convey that she will always be a role model in my life. Love you, Mom.

Chapter 1 is a version of Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Fine Nathel, N. F.; Hong, X.; Liu, P.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766–1771. Mesganaw, Silberstein, Ramgren and Fine Nathel were responsible for experimental work. Hong and Liu were responsible for computational work.

Chapter 2 is a version of Fine Nathel, N. F.; Kim, J.; Hie, L.; Jiang, X.; Garg, N. K. *ACS Catal.* **2014**, *4*, 3289–3292. Fine Nathel, Kim, Hie, and Jiang were responsible for experimental work.

Chapter 3 is a version of Mesganaw, T.; Fine Nathel, N. F.; Garg, N. K. *Org. Lett.* **2012**, *14*, 2918–2921. Mesganaw and Fine Nathel were responsible for experimental work.

Chapter 4 is a version of Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *in press*. Hie, Fine Nathel, Shah and Baker were responsible for experimental work. Hong, Yang, and Liu were responsible for computational work.

Chapter 5 is a version of Fine Nathel, N. F.[†]; Shah, T. K.[†]; Bronner, S. M.; Garg, N. K. *Chem. Sci.* **2014**, *5*, 2184–2190. Fine Nathel, Shah, and Bronner were responsible for experimental work.

BIOGRAPHICAL SKETCH

Education

University of California, Los Angeles, CA

- Doctoral Candidate, Organic Chemistry
- Graduate Research Assistant, July 2010 to present
- Current GPA: 3.99/4.00

Cornell University, Ithaca, NY

- Bachelor of Arts, Chemistry and Chemical Biology, *Magna Cum Laude*, May 2009
- Cumulative GPA: 3.66/4.00

Professional and Academic Experience

Graduate Research Assistant: University of California, Los Angeles, CA

- July 2010 to present under the direction of Professor Neil K. Garg
- Discovered the nickel-catalyzed amination of *O*-aryl carbamates.
- Developed conditions for the nickel-catalyzed reductive cleavage of aryl carbamates, expanded the methodology's scope, and established its utility for the syntheses of meta-substituted arenes.
- Determined the substrate scope for the amination of aryl sulfamates and chlorides with an air-stable nickel precatalyst using the green solvent 2-Me-THF.
- Established the amine scope in the nickel-catalyzed amidations of unactivated aryl esters.
- Determined the scope of compatible alcohols for the nickel-catalyzed esterifications of aryl amides.
- Completed the enantiospecific total syntheses of three indolactam alkaloids: pendolmycin, lyngbyatoxin A, and teleocidin A-2, via a divergent route stemming from indolactam V.
- Determined the relative electrophilicities for a range of aryne intermediates.

Teaching Assistant: University of California, Los Angeles, CA

- Led discussions for undergraduate organic chemistry (September 2010 to June 2011), explaining topics such as structure, spectroscopy, and reactivity.
- Supervised and taught undergraduate experimental organic chemistry topics, including analytical and preparative chromatography, distillation, extraction, recrystallization, spectroscopy, titration and error analysis (January 2011 to March 2011).

Undergraduate Research Assistant: Cornell University, Ithaca, NY

- Investigated the effect of benzoate co-catalysts in the reactivity of cobalt-catalyzed enantioselective polymerizations under the guidance of Professor Geoffrey W. Coates (January 2008 – May 2009).

Summer Intern:

- Merck, Inc., Rahway, NJ (July 2009 – August 2009)
  -Determined the scope of specific catalytic enzymes in Merck's biocatalysis division under the direction of Dr. Jacob Janey.
- Pfizer, Inc., Groton, CT (June 2008 – August 2008)

-Established the substrate scope for the carbonyldiimidazole-mediated Lossen rearrangement in the process chemistry department under the supervision of Dr. Pascal Dube.

- Amgen, Inc., South San Francisco, CA (May 2007 – August 2007)
  -Synthesized a ligand for metal-catalyzed asymmetric cyclopropanation reactions in the medicinal chemistry department under the direction of Dr. Zice Fu.

Honors and Awards

- Ruth L. Kirschstein NRSA Predoctoral Fellowship, 2012–Present.
- Excellence in Second Year Academics and Research Award, 2012.
- NSF Graduate Research Fellowship Honorable Mention, 2011 and 2012.

Publications

Undergraduate Studies

1. Dube, P.; Fine Nathel, N. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. "Carbonyldiimidazole-Mediated Lossen Rearrangement" *Org. Lett.* **2009**, *2*, 1766–1771.

Graduate Studies

2. Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Fine Nathel, N. F.; Hong, X.; Liu, P.; Garg, N. K. "Nickel-Catalyzed Amination of Aryl Carbamates and Sequential Site-Selective Cross-Couplings" *Chem. Sci.* **2011***, 2*, 1766–1771.

3. Mesganaw, T.; Fine Nathel, N. F.; Garg, N. K. "Cine Substitution of Arenes Using the Aryl Carbamate as a Removable Directing Group" *Org. Lett.* **2012**, *14*, 2918–2921.

4. Fine Nathel, N. F.; Shah, T. K.; Bronner, S. M.; Garg, N. K. "Total Syntheses of Indolactam Alkaloids (–)-Indolactam V, (–)-Pendolmycin, (–)-Lyngbyatoxin A, and (–)-Teleocidin A-2" *Chem. Sci*. **2014**, *5*, 2184–2190.

5. Fine Nathel, N. F.; Kim, J.; Hie, L.; Jiang, X.; Garg, N. K. "Nickel-Catalyzed Amination of Aryl Chlorides and Sulfamates in 2-Me-THF" *ACS Catal.* **2014**, *4*, 3289–3293. (**Featured in C&E News**)

6. Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. "Conversion of Amides to Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds" *Nature* **2015**, *in press*.

Presentations

1. **Amination of Aryl Sulfamates and Carbamates (Poster).** Stephen D. Ramgren, Amanda L. Silberstein, Tehetena Mesganaw, Noah F. Fine Nathel, Liana Hie, and Neil K. Garg, *Western Regional ACS Meeting,* Pasadena, CA, November 2011.

2. **Amination of Aryl Sulfamates and Carbamates (Poster).** Amanda L. Silberstein, Stephen D. Ramgren, and Neil K. Garg, *ACS National Meeting*, San Diego, CA, March 2012.

3. **The Total Synthesis of C7 Substituted Indolactam Alkaloids (Poster).** Amanda L. Silberstein, Stephen D. Ramgren, and Neil K. Garg, *Seaborg Symposium (UCLA)*, Los Angeles, CA, October 2013.

4. **Enantiospecific Total Syntheses of Indolactam Alkaloids (Talk).** Noah F. Fine Nathel, Tejas K. Shah, Sarah M. Bronner, and Neil K. Garg, *ACS National Meeting*, San Francisco, CA, August 2014.

CHAPTER ONE

Nickel-Catalyzed Amination of Aryl Carbamates and Sequential Site-Selective Cross-Couplings

1.1 Abstract

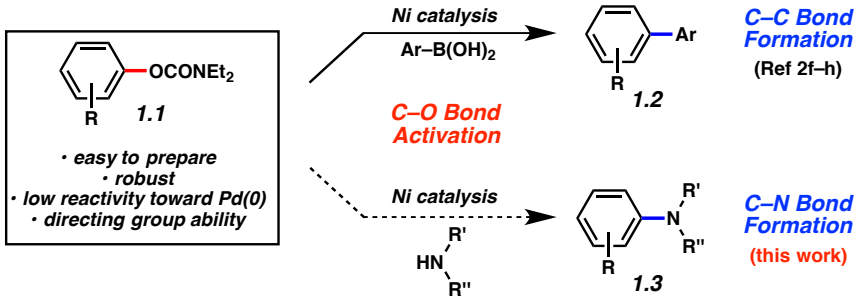
We report the amination of aryl carbamates using nickel-catalysis. The methodology is broad in scope with respect to both coupling partners and delivers aminated products in synthetically useful yields. Computational studies provide the full catalytic cycle of this transformation, and suggest that reductive elimination is the rate-determining step. Given that carbamates are easy to prepare, robust, inert to Pd-catalysis, and useful for arene functionalization, these substrates are particularly attractive partners for use in synthesis. The sequential use of carbamate functionalization / site-selective cross-couplings processes highlights the utility of this methodology.

1.2 Introduction

The discovery of methods for the assembly of carbon–nitrogen bonds continues to be an active area of research. Among the numerous tactics available for C–N bond formation, transition metal-catalyzed processes, led by Buchwald and Hartwig, have become some of the most widely used methods in chemical synthesis.[1] Recent efforts have focused on the catalytic amination of phenol derivatives[2,3,4,5] as phenols are readily available, with certain analogs being ideally poised for the synthesis of polysubstituted arenes.[6]

One particularly attractive class of electrophilies are the *N,N*-dialkyl aryl *O*-carbamates (**1.1**, Figure 1.1). Features of these substrates include their ease of preparation,[7] pronounced stability, and low reactivity toward Pd(0). Furthermore, aryl carbamates can be used for arene functionalization,[8] prior to a cross-coupling event, using either electrophilic aromatic substitution,[9] directed *o*-metallation,[10] or recently described Pd- or Ir-catalyzed methods.[11]

Figure 1.1. Known C–C and Proposed C–N Bond Formation Reactions using Aryl Carbamates as Substrates.



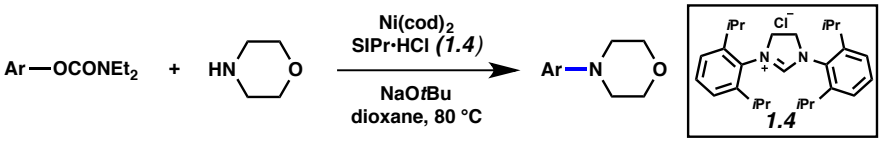
Although aryl carbamates have been employed in C–C bond forming processes (Figure 1.1, **1.1** → **1.2**),[12,13] their use in amination reactions (**1.1** → **1.3**), has been less explored. Specifically, during the course of our own studies, only a single example of carbamate amination was reported using the *N,N*-diethylcarbamate derivative of phenol.[4] Considering the importance of transition metal-catalyzed amination reactions in modern synthetic chemistry,[1] coupled with the salient features of carbamate electrophiles, we sought to develop a general method for carbamate amination. In this thesis, we report the broad scope of carbamate amination methodology, as well as a computational study of the full catalytic cycle. In addition, we demonstrate the value of these reaction partners for the synthesis of polysubstituted aryl amines using sequential carbamate functionalization / site-selective cross-coupling methodologies.

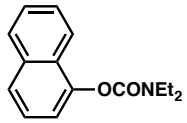
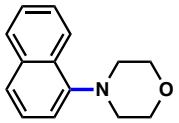
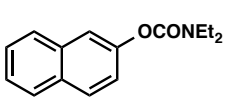
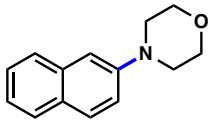
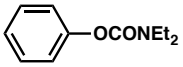
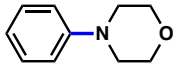
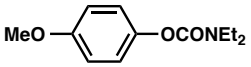
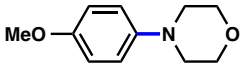
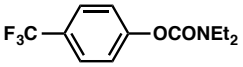
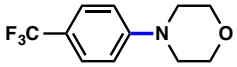
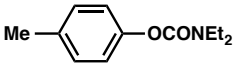
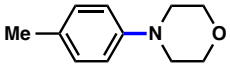
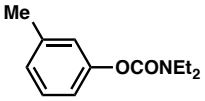
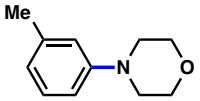
1.3 Optimization and Substrate Scope

To initiate studies, we attempted the amination of diethyl naphthylcarbamates with morpholine under a variety of reaction conditions. Although Ni / PCy_3-based conditions have been useful for achieving C–C bond formation, it was not possible to achieve amination using related procedures.[14] After conducting an extensive survey of reaction parameters (e.g., nickel catalysts, ligands, solvents, bases, temperature, etc.), it was observed that combinations of Ni catalysts and *N*-heterocyclic carbene ligands promoted the desired amination. Our laboratory and Chatani's have previously noted analogous findings in couplings of sulfamates and pivalates, respectively.[4,5]

We identified the use of catalytic $Ni(cod)_2$, SIPr•HCl (**1.4**),[15] and NaO*t*Bu, in dioxane at 80 °C as optimal reaction conditions for amination and investigated the carbamate substrate scope (Table 1.1).[16,17] Naphthyl carbamates, which typically function well in the Suzuki–Miyaura coupling, were excellent substrates for the amination (entries 1 and 2). Non-fused aromatics were also tolerated by the methodology (entries 3–7). The electron-donating methoxy group (entry 4) and the electron-withdrawing trifluoromethyl group (entry 5) were suitable substrates. Methyl substituents at the para and meta positions were tolerated as well (entries 6 and 7).

Table 1.1. Amination of Aryl Carbamates with Morpholine.[a]



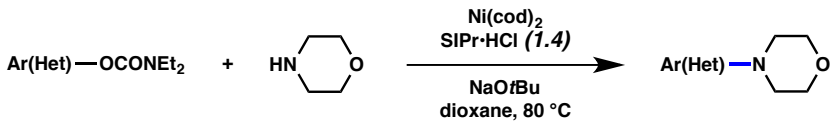
entry	Ar–OCONEt$_2$	product	yield[b]
1			91%
2			92%
3			90%
4[c]			74%
5			90%
6[d]			77%
7			80%

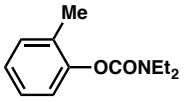
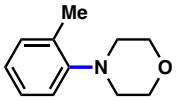
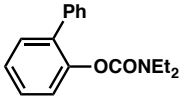
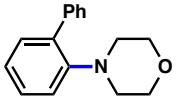
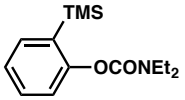
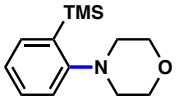
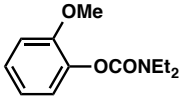
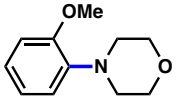
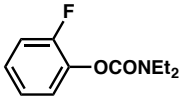
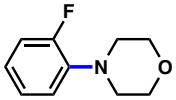
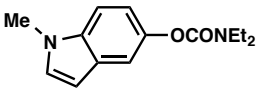
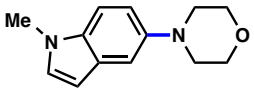
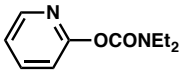
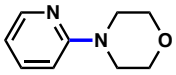
[a] Conditions unless otherwise stated: Ni(cod)$_2$ (5 mol%), **1.4** (10 mol%), carbamate substrate (1 equiv), morpholine (1.2 equiv), NaO*t*Bu (1.4 equiv), 3 h. [b] Isolated yields. [c] Ni(cod)$_2$ (15 mol%), **1.4** (30 mol%), morpholine (1.8 equiv), NaO*t*Bu (2.2 equiv). [d] Ni(cod)$_2$ (10 mol%), **1.4** (20 mol%).

The feasibility of coupling *o*-substituted carbamates, in addition to heterocyclic substrates, was examined (Table 1.2).[17] Of note, *o*-substituted aryl carbamates are readily accessible by functionalization of the parent carbamate (using directed metallation[10] or transition metal-catalyzed processes[11]), but have proven to be exceptionally challenging substrates in the recently discovered nickel-catalyzed Suzuki–Miyaura coupling.[12] We were delighted to find that a range of *o*-substituted phenylcarbamates could be employed in our amination methodology.[18] Carbon substituents were well-tolerated (entries 1 and 2), as were heteroatoms (entries 3–5).

Furthermore, heterocyclic substrates containing indole or pyridine underwent coupling with morpholine under nickel catalysis (entries 6 and 7).

Table 1.2. Amination of *o*-Substituted and Heterocyclic Carbamates.[a]

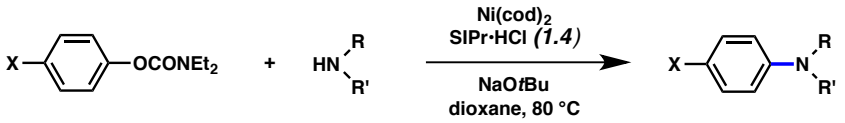


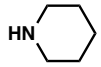
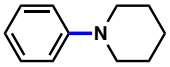
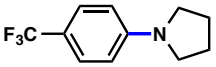
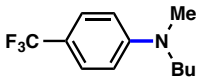
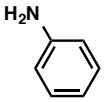
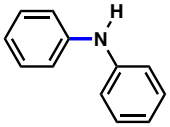
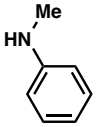
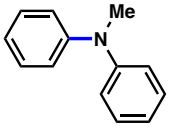
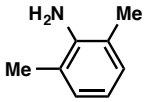
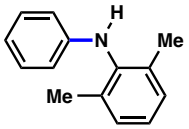
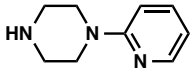
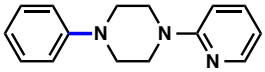
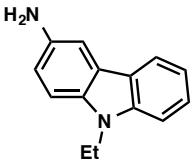
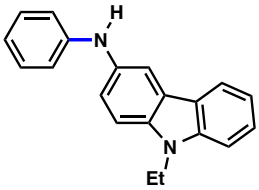
entry	Ar–OCONEt$_2$	product	yield[b]
1[c]			65%
2[d]			53%
3[e]			61%
4[d]			55%
5[f]			84%
6[g]			55%
7			78%

[a] Conditions unless otherwise stated: Ni(cod)$_2$ (5 mol%), **1.4** (10 mol%), carbamate substrate (1 equiv), morpholine (1.2 equiv), NaO*t*Bu (1.4 equiv), 3 h. [b] Isolated yields. [c] Ni(cod)$_2$ (15 mol%), **1.4** (30 mol%), morpholine (1.8 equiv), NaO*t*Bu (2.2 equiv). [d] Ni(cod)$_2$ (15 mol%), **1.4** (30 mol%), morpholine (2.4 equiv), NaO*t*Bu (2.2 equiv). [e] Ni(cod)$_2$ (20 mol%), **1.4** (40 mol%), morpholine (1.2 equiv), NaO*t*Bu (1.7 equiv), 120 °C. [f] Ni(cod)$_2$ (10 mol%), **1.4** (20 mol%). [g] Ni(cod)$_2$ (20 mol%), **1.4** (40 mol%), morpholine (1.8 equiv), NaO*t*Bu (2.2 equiv).

As shown in Table 1.3, a variety of amines can be employed in the carbamate amination.[17,19] Both cyclic and acyclic secondary amines were tolerated (entries 1–3), in addition to anilines (entries 4–6). Of note, use of the sterically congested 2,6-dimethylaniline delivered the corresponding aminated product in 92% yield (entry 6). The methodology also allows for the coupling of amines with appended heterocycles (entries 7 and 8).

Table 1.3. Amination of Aryl Carbamates with Various Amines.[a]

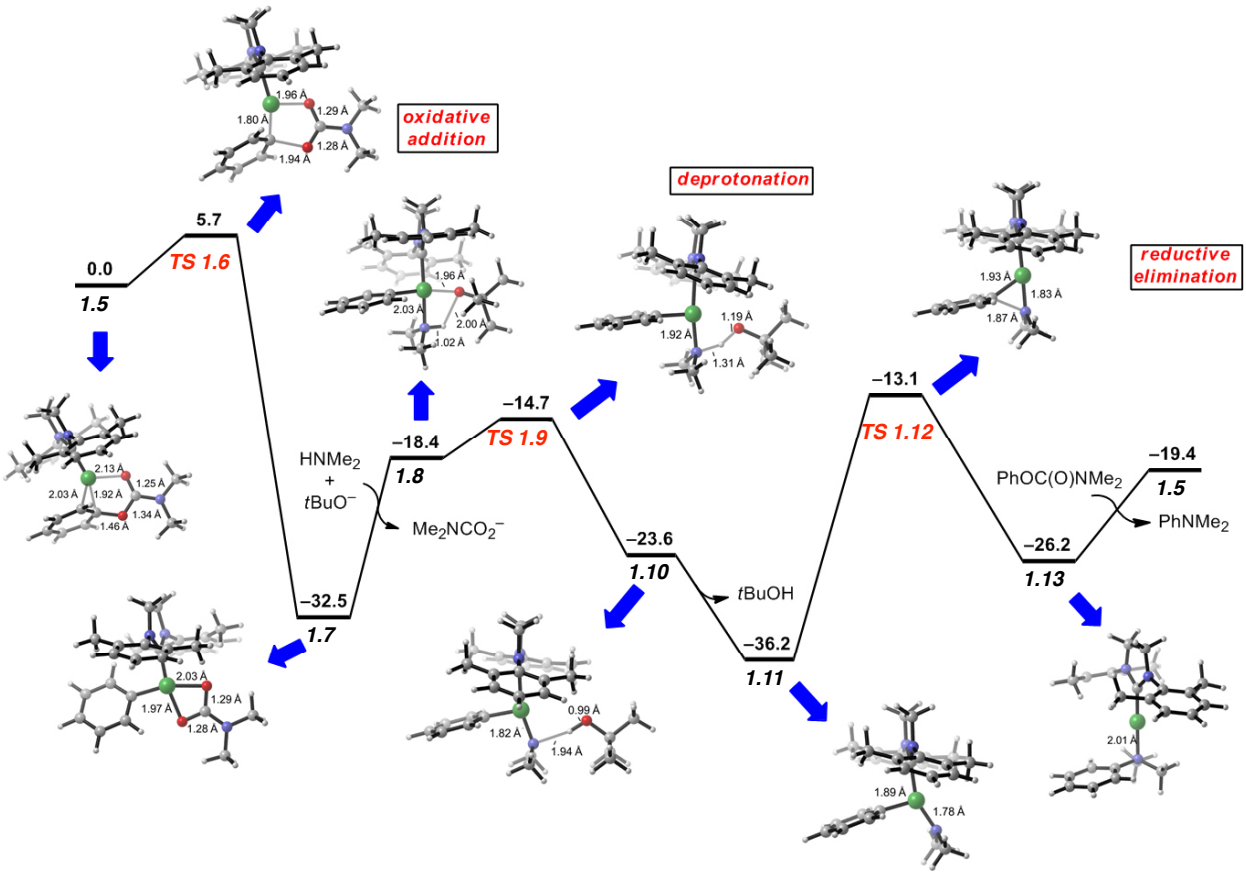


entry	amine	product	yield[b]
1[c]			96%
2			91%
3			86%
4[d]			84%
5[d]			70%
6[e]			92%
7[c]			94%
8[c]			93%

[a] Conditions unless otherwise stated: $Ni(cod)_2$ (5 mol%), **1.4** (10 mol%), carbamate substrate (1 equiv), amine (1.2 equiv), NaO*t*Bu (1.4 equiv), 3 h. [b] Isolated yields. [c] $Ni(cod)_2$ (10 mol%), **1.4** (20 mol%). [d] $Ni(cod)_2$ (15 mol%), **1.4** (30 mol%), amine (1.8 equiv), NaO*t*Bu (2.2 equiv). [e] $Ni(cod)_2$ (15 mol%), **1.4** (30 mol%), amine (2.4 equiv), NaO*t*Bu (2.2 equiv).

1.4 Computational Studies

Figure 1.2. Gibbs Free Energy Diagram of Ni-Catalyzed Amination of *N,N*-Dimethylphenylcarbamate and Dimethylamine. Energies are given in kcal/mol.



Although the mechanism of palladium-based aminations has been studied computationally,[20,21,22] no theoretical studies of nickel-catalyzed aminations have been reported. Furthermore, computational studies involving unconventional phenol-based electrophiles (e.g., esters, carbamates, sulfamates) are rare and have only been examined in the context of C–C bond formation.[23] Accordingly, we conducted a DFT study of the nickel-catalyzed carbamate amination, using *N,N*-dimethyl phenylcarbamate and dimethylamine as substrates.[24]

The results of this computational study are shown in Figure 1.2 in the form of a Gibbs free energy diagram, which in turn, provides the full catalytic cycle for carbamate amination. Analogous to Pd-catalyzed amination, three fundamental steps occur: oxidative addition, deprotonation, and reductive elimination.[25] Previous mechanistic and theoretical studies on similar Pd- and Ni-catalyzed reactions suggested that the oxidative addition initiates via a monoligated η^2 complex **1.5**.[21,26,27] The oxidative addition occurs through a five-centered transition state **TS 1.6**, in which the carbonyl oxygen in the carbamate is coordinated with Ni.[28] The electron-rich NHC ligand facilitates the oxidative addition, which requires only 5.7 kcal/mol with respect to the η^2 complex **1.5**.[29] Similar oxidative additions with phosphine ligands require much higher activation energies ($\Delta G^{\ddagger}$ = 13.5 kcal/mol when PCy_3 ligand is used).[23b]

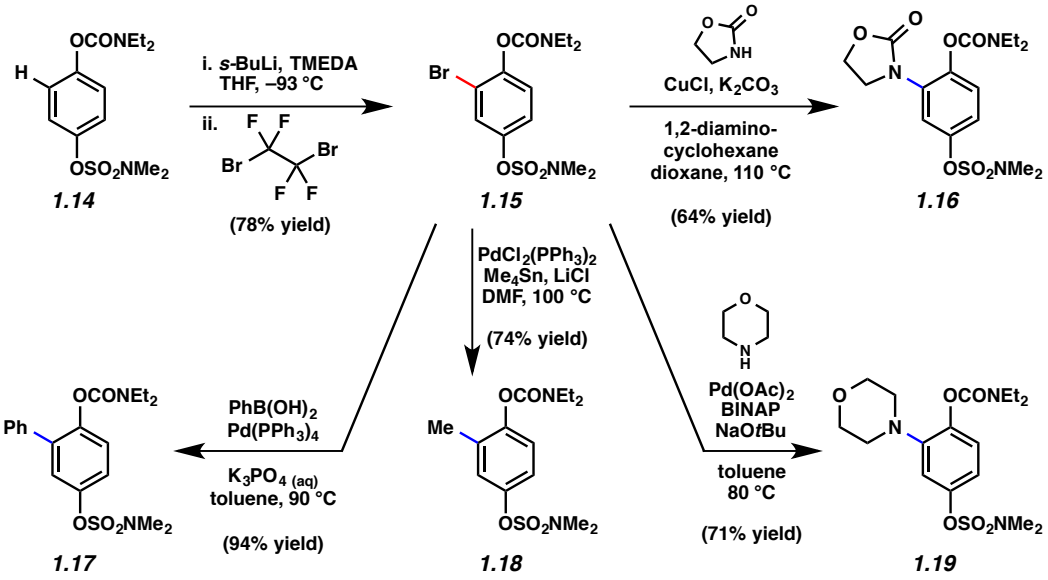
The oxidative addition leads to a stable intermediate (phenyl)nickel(II) carbamate intermediate **1.7** (–32.5 kcal/mol). Complex **1.7** undergoes ligand exchange with dimethylamine and *tert*-butoxide to liberate carbamate anion and form intermediate **1.8** (–18.4 kcal/mol). This ligand exchange process is endergonic, mainly due to entropic effects. The proton transfer from the coordinated amine to *tert*-butoxide (**TS 1.9**) requires only 3.7 kcal/mol activation energy from complex **1.8**.[30] Subsequent dissociation of *tert*-butanol gives the (phenyl)(amino)nickel(II) complex **1.11** (–36.2 kcal/mol). Reductive elimination then occurs through **TS 1.12** (–13.1 kcal/mol), which gives the product complex **1.13** (–26.2 kcal/mol). The reductive elimination from **1.11** to **TS 1.12** requires 23.1 kcal/mol and is the rate-limiting step in the catalytic cycle. Thus, the overall energy span[31] of the catalytic cycle is 23.1 kcal/mol, in agreement with the experimental observations that the amination reaction readily occurs under slightly elevated temperatures. The barrier for reductive elimination with the Ni(NHC) catalyst is much higher compared to that of Pd-phosphine catalysts.[20b,22e] Following the reductive elimination, the

reactant complex **1.5** can be regenerated by ligand exchange from the product complex **1.13** to initiate another catalytic cycle. The whole catalytic cycle is exergonic by 19.4 kcal/mol.[32]

1.5 Site-Selective Cross-Couplings and Synthetic Applications

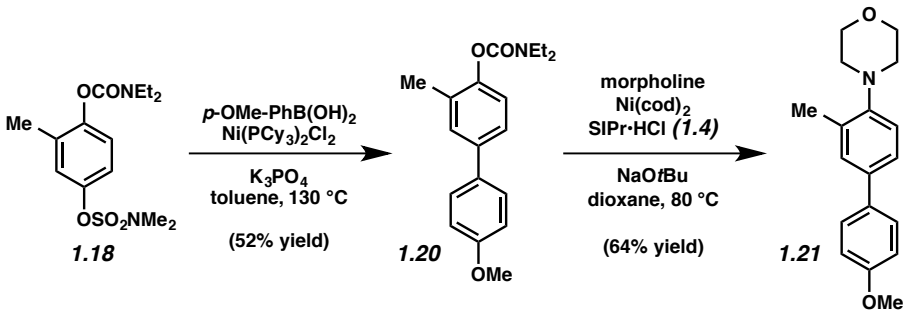
Figure 1.3 highlights a series of experiments that were undertaken to explore carbamate directing group ability and the low reactivity of these substrates to conventional catalytic transformations. The key substrate for our studies, dihydroquinone derivative **1.14**, was selected with the aim of simultaneously probing the reactivity of aryl sulfamates, which have also proven to be extremely useful electrophiles in nickel-catalyzed couplings. Lithiation and bromination of substrate **1.14** provided trisubstituted arene **1.15**. In accord with literature precedent by Snieckus,[13f] the lithiation proceeded selectively adjacent to the carbamate with the sulfamate remaining intact. Bromoarene **1.15** was subsequently employed in a series of C–C and C–heteroatom bond constructions. Pd-catalyzed arylation (**1.15 → 1.17**), alkylation (**1.15 → 1.18**), and amination (**1.15 → 1.19**) proceeded smoothly, as did Cu-catalyzed C–N bond formation (**1.15 → 1.16**). In all cases, the sulfamate and carbamate were not disturbed.

Figure 1.3. Carbamate Functionalization and Low Reactivity of Carbamates and Sulfamates toward Conventional Pd- and Cu-Catalyzed Couplings.



Having demonstrated the robust nature of carbamates and sulfamates to a variety of conditions, we examined the subsequent cross-couplings of these functional groups (Figure 1.4). *o*-Methylated derivative **1.18**, prepared by either *o*-bromination and Stille coupling (see Figure 1.3) or direct *o*-methylation of **1.14**, was used in this study. We have found that the sulfamate of **1.18** is more reactive compared to the carbamate, and that high degrees of selectivity can be obtained in arylation.[33] Suzuki–Miyaura coupling of **1.18** furnished carbamate **1.20** in 52% yield. Subsequently, carbamate **1.20** was employed in our nickel-catalyzed amination to furnish polysubstituted aryl amine **1.21**. We expect that the ability to consecutively cross-couple bromides, sulfamates, and carbamates will be useful in the synthesis of complex molecules.

Figure 1.4. Synthesis of Polysubstituted Arenes using Sequential Sulfamate / Carbamate Couplings.



1.6 Conclusion

In summary, we have found that aryl carbamates are excellent substrates for the nickel-catalyzed amination reaction. The scope of the methodology is broad with respect to both coupling partners, and includes the coupling of electron-rich, heterocyclic, and sterically congested carbamates. DFT calculations reveal the full catalytic cycle of the nickel-catalyzed carbamate amination and suggest that reductive elimination (23.1 kcal/mol barrier) is the rate-determining step. Moreover, we have demonstrated that aryl carbamates are outstanding precursors for the synthesis of polysubstituted aryl amines using sequential carbamate functionalization and site-selective coupling processes. The use of this methodology in natural product synthesis will be reported in due course.

1.7 Experimental Section

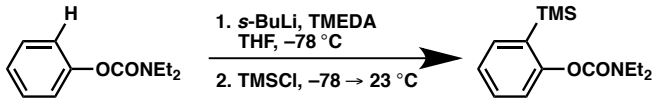
1.7.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). Unless otherwise stated, commercially obtained reagents were used as received. Amines were purified by filtration over basic Brockman Grade I 58 Å Al_2O_3 (Activity 1), followed by distillation over calcium hydride, prior to use. $Ni(cod)_2$ was obtained from Strem Chemicals and SIPr•HCl was obtained from Sigma Aldrich. Dioxane was purified by distillation over sodium benzophenone ketyl radical and degassed by the freeze-pump-thaw method. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, iodine, vanillin, and potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 300, 400, 500, 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (d ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{19}F NMR (at 300, 400 MHz) spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Melting points are uncorrected and were obtained on a Laboratory Devices

Mel-Temp II instrument. High resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility.

1.7.2 Experimental Procedures

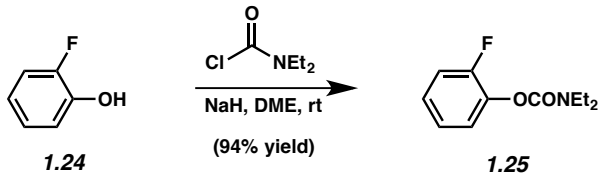
1.7.2.1 Synthesis of Aryl Carbamate Substrates



1.22 *1.23*

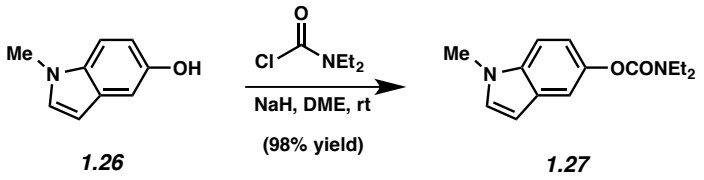
1.23 (Table 1.2, entry 3). To a solution of phenyl carbamate **1.22** (1.0 g, 4.82 mmol, 1 equiv) in THF (24 mL) was added TMEDA (0.79 mL, 5.31 mmol, 1.1 equiv) at 0 °C. The solution was cooled to –78 °C and *s*-BuLi (1.04 M in Hexanes, 5.11 mL, 5.31 mmol, 1.1 equiv) was added dropwise over 15 min. The mixture was stirred at –78 °C for 1 h and then TMSCl (0.80 ml, 6.3 mmol, 1.3 equiv) was added dropwise over 10 min. The resulting mixture was stirred at –78 °C for 45 min and then allowed to warm to 23 °C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (5 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and then evaporated to dryness. The crude residue was purified by flash chromatography (5:1 Hexanes:EtOAc) to furnish 2-(trimethylsilyl)phenyl carbamate **1.23** as a colorless solid (1.17 g, 85% yield). R_f 0.41 (5:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, J = 7.5, 1.5, 1H), 7.37 (ddd, J = 7.5, 1.5, 1.0, 1H), 7.18 (td, J = 7.0, 1.0, 1H), 7.04 (dd, J = 8.0, 0.5, 1H), 3.49 (q, J = 7.5, 2H), 3.49 (q, J = 7.5, 2H), 3.40 (q, J = 7.5, 2H), 1.26 (t, J = 7.5, 3H), 1.20 (t, J = 7.5, 3H), 0.29 (s, 9H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 156.5, 154.6,

135.0, 131.7, 130.5, 124.9, 122.4, 42.1, 41.7, 14.3, 13.4, –0.7; IR (film): 2972, 1714, 1412, 1258, 1152 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{14}H_{23}NO_2SiNa$, 288.1396; found, 288.1393.



1.24 *1.25*

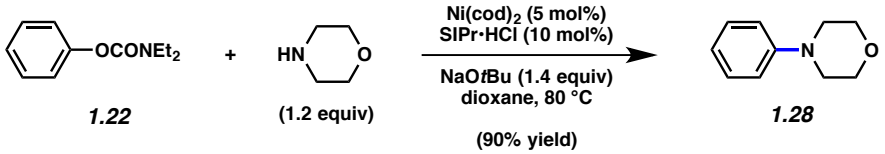
1.25 (Table 1.2, entry 5). To a round bottom flask containing NaH (0.85 g, 21.4 mmol, 1.2 equiv, 60% dispersion in oil) was added a solution of 2-flurophenol (**1.24**) (2.0 g, 17.8 mmol, 1 equiv) in DME (71 mL) via cannula transfer. A solution of diethylcarbamoyl chloride (2.15 mL, 16.9 mmol, 0.95 equiv) in DME (10 mL) was then added dropwise via cannula to the reaction vessel. The reaction mixture was allowed to stir for 15 h and was then quenched with H_2O (10 mL). The volatiles were removed under reduced pressure, and Et_2O (50 mL) and H_2O (20 mL) were added. The layers were separated, and the organic layer was washed successively with 1 M KOH (20 mL) and H_2O (20 mL). The combined aqueous layers were extracted with Et_2O (3 x 25 mL). The combined organic layers were then washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5:1 Hexanes:EtOAc) to yield 2-flurophenylsulfamate **1.25** as a clear oil (3.35 g, 94% yield). R_f 0.27 (5:1 Hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.21–7.09 (m, 4H), 3.46 (q, J = 6.5, 2H), 3.39 (q, J = 6.5, 2H), 1.27 (t, J = 6.5, 3H) 1.21 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6 (d, J = 246.5), 153.2, 139.0 (d, J = 12.1), 126.2 (d, J = 7.0), 124.2, 124.1 (d, J = 3.9), 116.3 (d, J = 18.4), 42.4, 42.0, 13.9, 13.2; IR (film): 2977, 1720, 1600, 1502, 1417, 1255 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{11}H_{14}FNO_2Na$, 234.0906; found, 234.0912.



1.26 *1.27*

1.27 (Table 1.2, entry 6). To a round bottom flask containing NaH (0.33 g, 8.15 mmol, 1.2 equiv, 60% dispersion in oil) was added a solution of *N*-methyl-5-hydroxyindole (**1.26**) (1.0 g, 6.79 mmol, 1 equiv) in DME (27 mL) via cannula transfer. A solution of diethylcarbamoyl chloride (0.875 mL, 6.45 mmol, 0.95 equiv) in DME (15 mL) was then added dropwise via cannula to the reaction vessel. The reaction was allowed to stir for 3.5 d, and then quenched with H_2O (10 mL). The volatiles were removed under reduced pressure, and then Et_2O (50 mL) and H_2O (15 mL) were added. The layers were separated, and the organic layer was washed successively with 1 M KOH (20 mL) and H_2O (20 mL). The combined aqueous layers were extracted with Et_2O (3 x 20 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (9:1 Benzene:Et_2O) to yield carbamate **1.27** as a white solid (1.55g, 98% yield). R_f 0.44 (9:1 Benzene:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 2.5, 1H), 7.26 (d, J = 9.0, 1H), 7.05 (d, J = 3.0, 1H), 6.98 (dd, J = 8.5, 2.3, 1H), 6.43 (dd, J = 3.0, 0.5, 1H), 3.78 (s, 3H), 3.47 (m, 2H), 3.41 (m, 2H), 1.27 (m, 3H), 1.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 145.1, 134.5, 129.8, 128.7, 116.3, 113.2, 109.4, 101.1, 42.3, 41.9, 33.1, 14.4, 13.6; IR (film): 2972, 1708, 1467, 1418, 1218, 1159 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{14}H_{18}N_2O_2Na$, 269.1266; found, 269.1267.

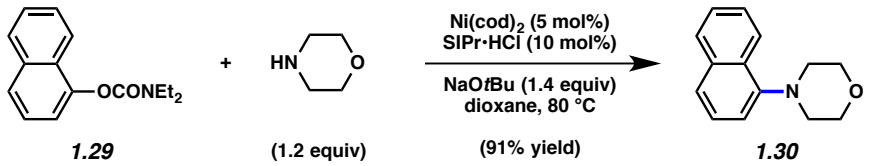
1.7.2.2 Aminations of Aryl Carbamates



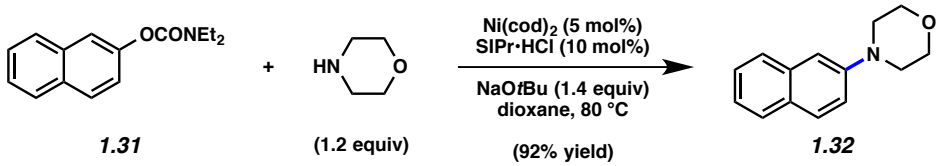
1.22 (1.2 equiv) (90% yield) *1.28*

Representative Procedure (coupling of phenylcarbamate 1.22, Table 1.1, entry 3) is used as an example). 1.28. A 20 mL reaction vial was charged with $Ni(cod)_2$ (6.8 mg, 0.025 mmol, 5 mol%), SIPr•HCl (21.2 mg, 0.05 mmol, 10 mol%), anhydrous powdered NaO*t*Bu (67.2 mg, 0.7 mmol, 1.4 equiv), and a magnetic stir bar, all in a glove box. Subsequently, a solution of carbamate substrate **1.22** (96.6 mg, 0.50 mmol, 1 equiv) and morpholine (52.4 mL, 0.60 mmol, 1.2 equiv) in dioxane (2.5 mL) was added. The vessel was removed from the glove box, and then heated to 80 °C for 3 h. After cooling the reaction vessel to 23 °C and concentrating under reduced pressure, the crude residue was loaded onto a silica gel column (2.5 x 10 cm) and purified by flash chromatography (9:1 Hexanes: EtOAc) to yield aminated product **1.28** (73.4 mg, 90% yield) as a white solid. R_f 0.29 (9:1 Hexanes:EtOAc). Spectral data match those previously reported.[34]

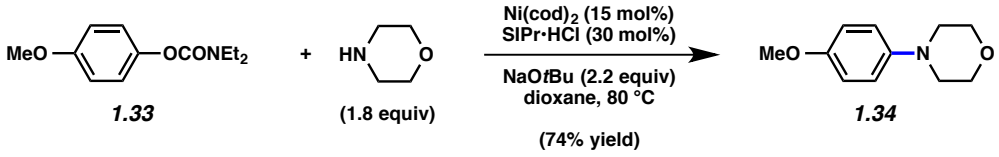
Any modifications of the conditions shown in this representative procedure are specified in the following schemes, which depict all of the results shown in Tables 1.1, 1.2, and 1.3.



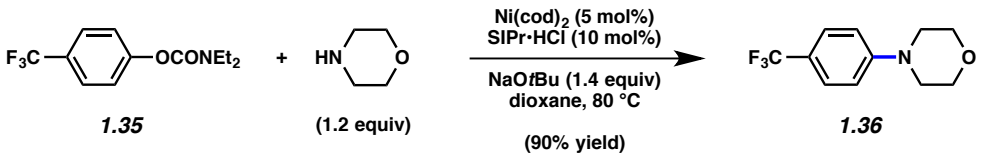
1.30 (Table 1.1, entry 1). Purification by flash chromatography (9:1 Hexanes:EtOAc) afforded aminated product **1.30** (91% yield) as a white solid. R_f 0.38 (9:1 Hexanes:EtOAc). Spectral data match those previously reported.[35]



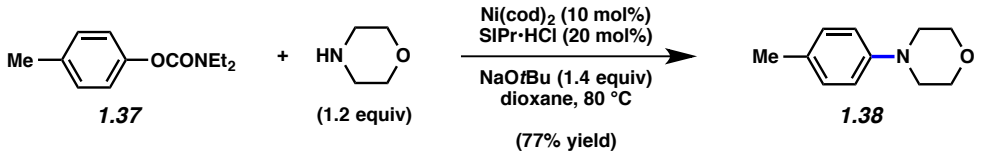
1.32 (Table 1.1, entry 2). Purification by flash chromatography (9:1 Hexanes:EtOAc) afforded aminated product **1.32** (92% yield) as a white solid. R_f 0.32 (9:1 Hexanes:EtOAc). Spectral data match those previously reported.[36]



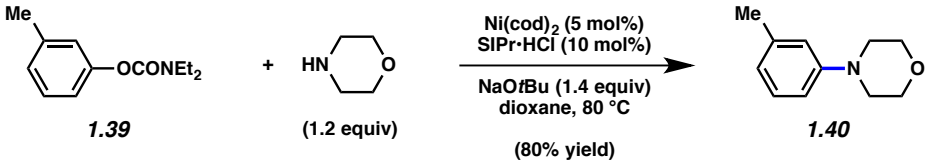
1.34 (Table 1.1, entry 4). Purification by flash chromatography (10:1:1 Benzene:Et_2O:CH_2Cl_2) afforded aminated product **1.34** (74% yield) as a white solid. R_f 0.18 (10:1:1 Benzene:Et_2O:CH_2Cl_2). Spectral data match those previously reported.[37]



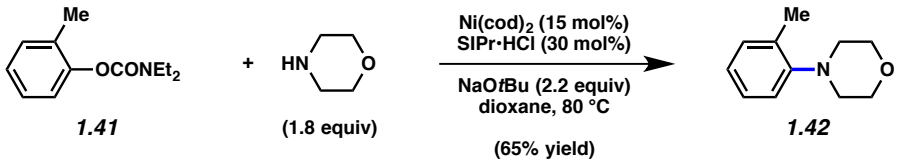
1.36 (Table 1.1, entry 5). Purification by flash chromatography (30:1 Benzene:Et_2O) afforded aminated product **1.36** (90% yield) as a white solid. R_f 0.30 (30:1 Benzene:Et_2O). Spectral data match those previously reported.[38]



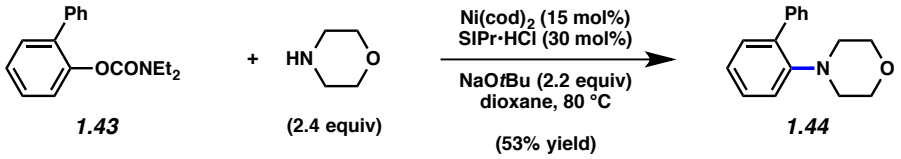
1.38 (Table 5.1, entry 6). Purification by flash chromatography (19:1 Benzene:Et_2O) afforded aminated product **1.38** (77% yield) as a white solid. R_f 0.53 (19:1 Benzene:Et_2O). Spectral data match those previously reported.[39]



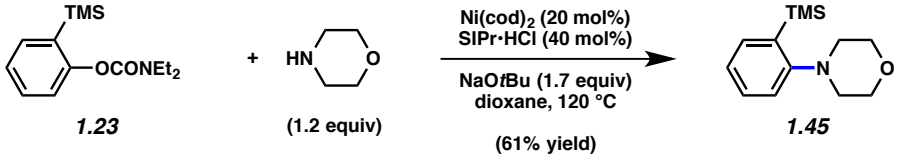
1.40 (Table 1.1, entry 7). Purification by flash chromatography (19:1 Benzene:Et_2O) afforded aminated product **1.40** (80% yield) as a yellow oil. R_f 0.49 (19:1 Benzene:Et_2O). Spectral data match those previously reported.[39]



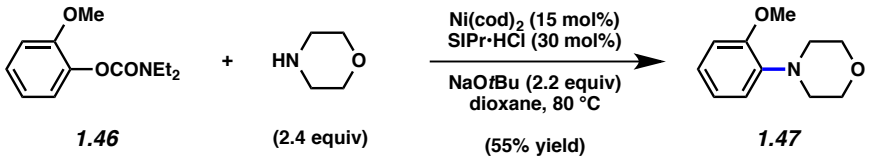
1.42 (Table 1.2, entry 1). Purification by flash chromatography (19:1 Hexanes:EtOAc) afforded aminated product **1.42** (65% yield) as a yellow oil. R_f 0.37 (19:1 Hexanes:EtOAc). Spectral data match those previously reported.[39]



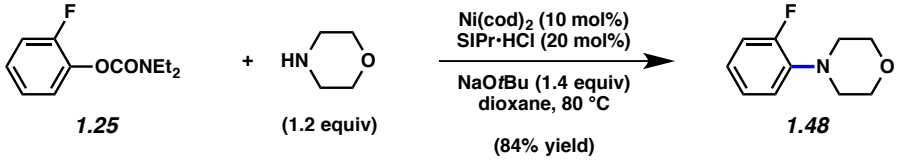
1.44 (Table 1.2, entry 2). Purification by flash chromatography (100% Benzene) afforded aminated product **1.44** (53% yield) as an off-white solid. R_f 0.53 (100% Benzene). Spectral data match those previously reported.[5a]



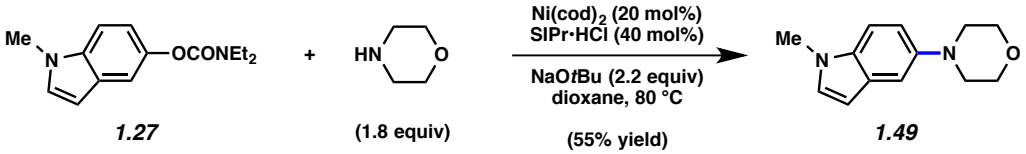
1.45 (Table 1.2, entry 3). Purification by flash chromatography (5:1 Benzene:Hexanes) afforded aminated product **1.45** (61% yield) as a white solid. R_f 0.31 (100% Benzene). Spectral data match those previously reported.[5a]



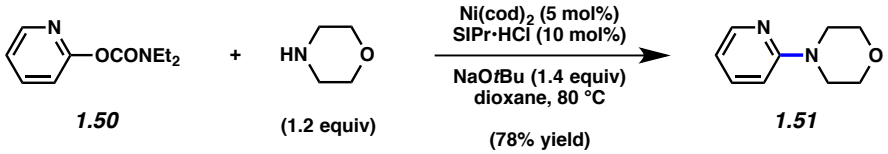
1.47 (Table 1.2, entry 4). Purification by flash chromatography (9:1 Benzene:Et_2O) afforded aminated product **1.47** (55% yield) as a yellow oil. R_f 0.23 (9:1 Benzene:Et_2O). Spectral data match those previously reported.[40]



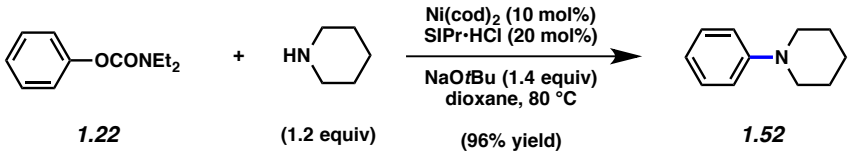
1.48 (Table 1.2, entry 5). Purification by flash chromatography (40:1 Benzene:Et_2O) afforded aminated product **1.48** (84% yield) as an off-white solid. R_f 0.22 (40:1 Benzene:Et_2O). Spectral data match those previously reported.[41]



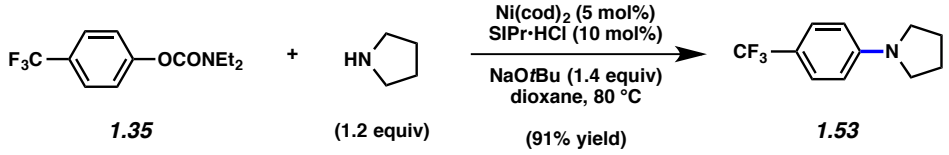
1.49 (Table 1.2, entry 6). Purification by flash chromatography (6:1:1 Benzene:Et_2O:CH_2Cl_2) afforded aminated product **1.49** (55% yield) as a off-white solid. R_f 0.21 (10:1:1 Benzene:Et_2O:CH_2Cl_2). Spectral data match those previously reported.[5a]



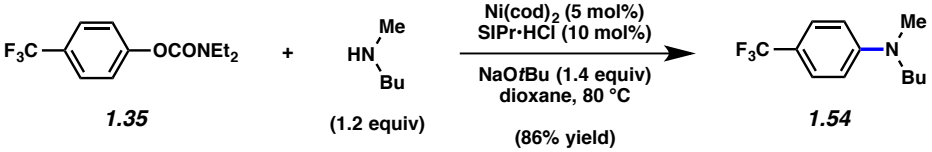
1.51 (Table 1.2, entry 7). Purification by flash chromatography (2:1 Hexanes:EtOAc) afforded aminated product **1.51** (78% yield) as a pale yellow oil. R_f 0.28 (9:1 Benzene:Et_2O). Spectral data match those previously reported.[42]



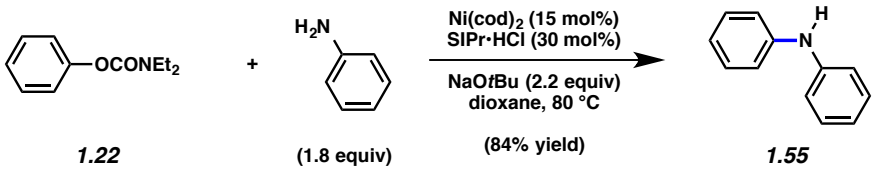
1.52 (Table 1.3, entry 1). Purification by flash chromatography (50:1 Hexanes:EtOAc) afforded aminated product **1.52** (96% yield) as a clear oil. R_f 0.29 (50:1 Hexanes:EtOAc). Spectral data match those previously reported.[43]



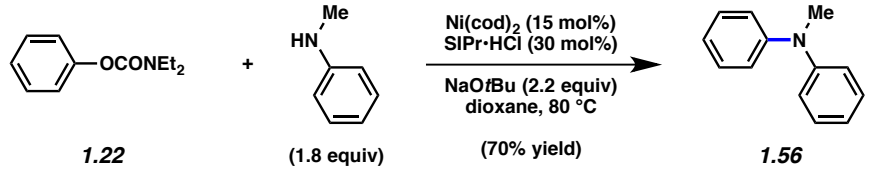
1.53 (Table 1.3, entry 2). Purification by flash chromatography (50:1 Hexanes:Et_2O) afforded aminated product **1.53** (91% yield) as a white solid. R_f 0.28 (50:1 Hexanes:Et_2O). Spectral data match those previously reported.[44]



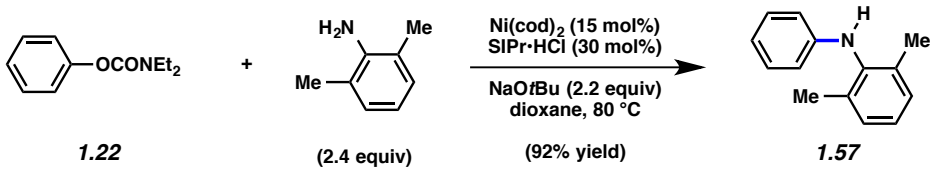
1.54 (Table 1.3, entry 3). Purification by flash chromatography (50:1 Hexanes:Et_2O) afforded aminated product **1.54** (86% yield) as a clear oil. R_f 0.32 (50:1 Hexanes:Et_2O). Spectral data match those previously reported.[5a]



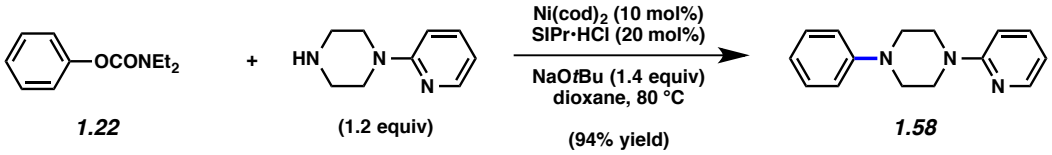
1.55 (Table 1.3, entry 4). Purification by flash chromatography (4:1 Hexanes:CH_2Cl_2) afforded aminated product **1.55** (84% yield) as a yellow solid. R_f 0.28 (4:1 Hexanes:CH_2Cl_2). Spectral data match those previously reported.[39]



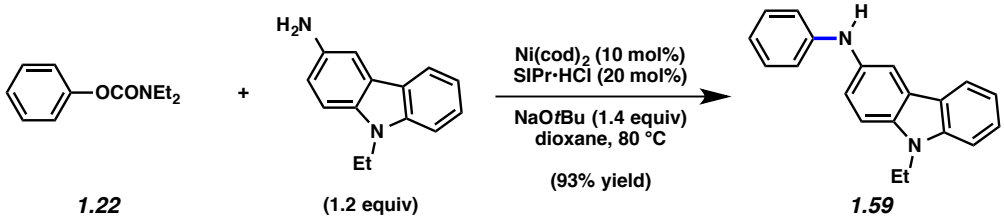
1.56 (Table 1.3, entry 5). Purification by flash chromatography (100:1 Hexanes:Et_2O) afforded aminated product **1.56** (70% yield) as a yellow oil. R_f 0.12 (100:1 Hexanes:Et_2O). Spectral data match those previously reported.[39]



1.57 (Table 1.3, entry 6). Purification by flash chromatography (20:1 Hexanes:Et_2O) afforded aminated product **1.57** (92% yield) as a clear oil. R_f 0.41 (20:1 Hexanes:Et_2O). Spectral data match those previously reported.[39]

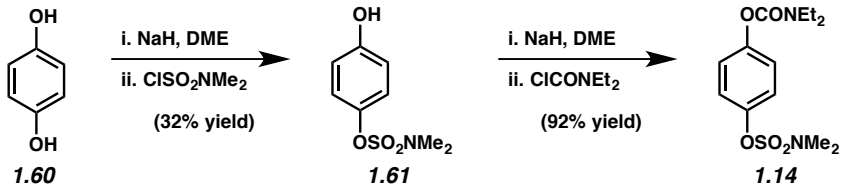


1.58 (Table 1.3, entry 7). Purification by flash chromatography (8:1 Hexanes:EtOAc) afforded aminated product **1.58** (94% yield) as a white solid. R_f 0.30 (8:1 Hexanes:EtOAc). Spectral data match those previously reported.[43]



1.59 (Table 1.3, entry 8). Purification by flash chromatography (300:150:1 Hexanes:CH_2Cl_2:Et_3N) afforded aminated product **1.59** (93% yield) as a white solid. R_f 0.30 (2:1 Hexanes:CH_2Cl_2). Spectral data match those previously reported.[5a]

1.7.2.3 Experiments Involving Carbamate and Sulfamate Substrates

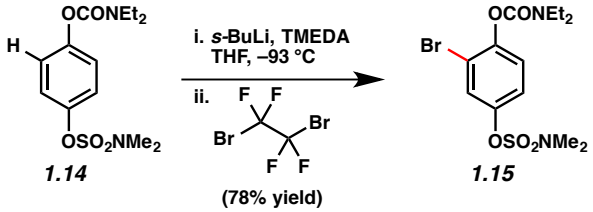


1.60 *1.61* *1.14*

Carbamate Sulfamate 1.14. To a round bottom flask containing NaH (0.308 g, 25.9 mmol, 1.2 equiv, 60% dispersion in oil) was added a solution of hydroquinone (**1.60**) (3.0 g, 27.3 mmol, 1 equiv) in DME (60 mL) via cannula transfer. A solution of dimethylsulfamoyl chloride (2.76 mL, 25.9 mmol, 1.2 equiv) in DME (60 mL) was then added immediately via cannula transfer. The reaction was allowed to stir for 12 h and the reaction was quenched with deionized H_2O (20 mL). The volatiles were removed under reduced pressure, and then Et_2O (50 mL) and H_2O (20 mL) were added. The layers were separated and the organic phase was washed with H_2O (3 x 30 mL). The combined aqueous layers were extracted with Et_2O (3 x 50 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (7:1:1 Benzene:CH_2Cl_2:Et_2O) to yield sulfamate **1.61** as a white solid (1.77 g, 32% yield).

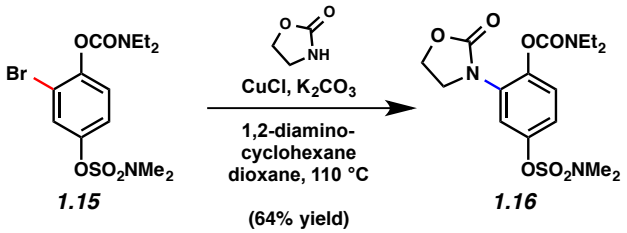
To a round bottom flask containing NaH (0.560 g, 14.0 mmol, 1.2 equiv, 60% dispersion in oil) was added a solution of **1.61** (2.53 g, 11.7 mmol, 1 equiv) in DME (23 mL). A solution of diethylcarbamoyl chloride (1.45 mL, 11.0 mmol, 0.95 equiv) in DME (23 mL) was then added dropwise to the reaction vessel. After stirring for 12 h, the reaction mixture was quenched with deionized H_2O (9 mL). The solvent was removed under reduced pressure and then Et_2O (22 mL) was added. The organic layer was washed with H_2O (3 x 9 mL). The combined aqueous layers were back-extracted with Et_2O (3 x 22 mL). The combined organic layers were washed with brine (9 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue

was purified by flash chromatography (1:1 Hexanes:EtOAc) to yield carbamate sulfamate **1.14** as a white solid (3.39 g, 92% yield). R_f 0.54 (7:1:1 Benzene:Et_2O:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.27 (d, J = 8.5, 2H), 7.14 (d, J = 9, 2H), 3.41 (m, 4H), 2.69 (s, 6H), 1.25 (t, J = 7, 3H), 1.20 (t, J = 7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 153.9, 149.9, 147.1, 123.1, 122.7, 42.5, 42.1, 38.9, 14.4, 13.5; IR (film): 2983, 2939, 1721, 1474, 1357, 1273, 1156 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{13}H_{20}N_2O_5SNa$, 339.0991; found 339.0988.



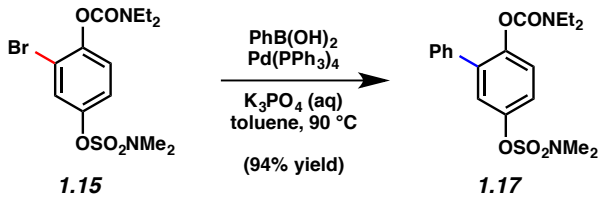
Bromide 1.15. To a solution of carbamate **1.14** (280.7 mg, 0.887 mmol, 1.0 equiv) and TMEDA (0.145 mL, 0.976 mmol, 1.1 equiv) in THF (4.4 mL) at –93 °C was added *s*-BuLi (0.720 mL, 0.976 mmol, 1.1 equiv) dropwise. After stirring for 45 min, 1,2-dibromotetrafluoroethane (0.148 mL, 1.242 mmol, 1.4 equiv) was added dropwise and the reaction was allowed to warm to 23 °C over 15 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL) and stirred at 23 °C for 60 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (1 x 5 mL), dried by passage over a plug of silica gel, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (3:1:1 Hexanes:CH_2Cl_2:Et_2O) to yield brominated product **1.15** (272.0 mg, 78% yield) as an off-white solid. R_f 0.17 (3:1:1 Hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.54 (t, J = 1.5, 1H), 7.26 (d, J = 1.5, 2H), 3.50 (q, J = 7.0, 2H), 3.40 (q, J = 7.0, 2H), 2.99 (s, 6H), 1.31 (t, J = 7.0, 3H), 1.23 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 152.9, 147.6, 147.3, 126.5, 124.8, 121.7, 116.9, 42.6, 42.3, 38.9, 14.4, 13.4; IR (film):

2977, 1724, 1592, 1472, 1372, 1148 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{13}H_{19}BrN_2O_5SNa$, 417.0096; found 417.0107.

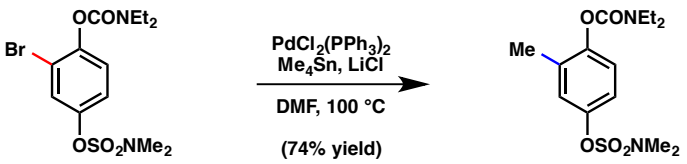


Oxazolidinone 1.16. A 1 mL vial was charged with K_2CO_3 (55.7 mg, 0.404 mmol, 2 equiv) and a magnetic stir bar. The vial and contents were flame-dried under reduced pressure, and then allowed to cool under N_2. Bromide **1.15** (80.0 mg, 0.202 mmol, 1 equiv) and 2-oxazolidinone (17.6 mg, 0.202 mmol, 1 equiv) were added. The vial was then evacuated and backfilled with N_2 three times and brought into a glove box. CuCl (2.0 mg, 0.020 mmol, 10 mol%) was added and the reaction vessel was removed from the glove box and placed under an atmosphere of N_2. (±)-trans-1,2-diaminocyclohexane (4.8 mL, 0.040mmol, 20 mol%) was then added, followed by anhydrous dioxane (110 mL). The reaction vessel was shielded from light, sealed with a Teflon-coated cap, and heated to 110 °C. After 13 h, the reaction was allowed to cool to 23 °C. The residue was diluted in EtOAc (1 mL) and filtered over a pad of celite (EtOAc eluent, 7 mL). Concentration under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:1 Benzene:EtOAc) to yield oxazolidinone **1.16** as a yellow oil (51.9 mg, 64% yield). R_f 0.28 (1:1 Benzene:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.32 (dd, J = 2.0, 1.0, 1H), 7.23 (d, J = 2.0, 2H), 4.44 (t, J = 8.0, 2H), 3.98 (t, J = 7.8, 2H), 3.44 (q, J = 7.2, 2H), 3.36 (q, J = 7.0, 2H), 2.96 (s, 6H), 1.23 (t, J = 7.0, 3H), 1.19 (t, J = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 156.1, 153.2, 147.2, 145.4, 131.1, 124.9, 121.9, 120.7, 62.8, 47.2, 42.5, 42.2,

38.9, 14.2, 13.4; IR (film): 2977, 1753, 1717, 1611, 1504, 1367, 1146 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{16}H_{23}N_3O_7SNa$, 424.1154; found 424.1150.

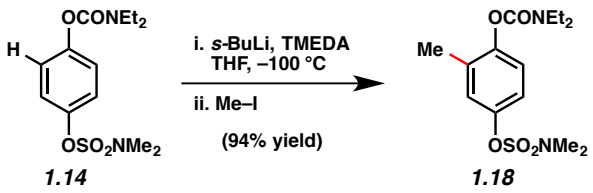


Biaryl 1.17. A 20 mL scintillation vial was charged with a magnetic stir bar, K_3PO_4 (1 mL, 2 M aqueous) and toluene (1.7 mL), and the resulting biphasic mixture was sparged with N_2 for 1 h. To the solution were added bromide **1.15** (150 mg, 0.379 mmol, 1 equiv), phenylboronic acid (56 mg, 0.455 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (66 mg, 0.057 mmol, 15 mol%). The resulting mixture was sparged with N_2 for 10 min. The vial was sealed with a Teflon-coated screw-cap and heated at 90 °C for 14 h. After cooling to 23 °C, dichloromethane (10 mL) and Na_2SO_4 were added and the mixture was allowed to stand for 30 min. The crude mixture was then filtered over silica gel and concentrated under reduced pressure. The crude residue was purified by flash chromatography (3:1:1 Hexanes:CH_2Cl_2:Et_2O) to yield biaryl **1.17** as a yellow oil (140 mg, 94% yield). R_f 0.22 3:1:1 Hexanes:CH_2Cl_2:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.40–7.22 (m, 8H), 3.23 (m, 4H), 2.99 (s, 6H), 1.04 (t, *J* = 6.8, 3H), 0.99 (t, *J* = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 153.8, 147.2, 146.9, 137.0, 136.7, 129.1, 128.3, 127.8, 124.6, 123.8, 121.5, 42.2, 41.8, 38.9, 14.0, 13.2; IR (film): 2976, 1714, 1471, 1367, 1141 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{19}H_{24}N_2O_5SNa$, 415.1304; found 415.1297.

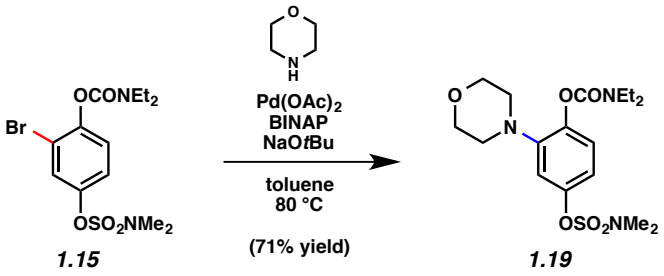


1.15 *1.18*

Sulfamate 1.18. Procedure A. To a 4 mL vial charged with anhydrous lithium chloride (53.6 mg, 1.265 mmol, 5 equiv) was added a solution of bromide **1.15** (100.0 mg, 0.253 mmol, 1 equiv) in *N,N*-dimethylformamide (2.5 mL) that had been rigorously sparged with N_2, all in a glove box. Next, $PdCl_2(PPh_3)_2$ (4.2 mg, 0.006 mmol, 2.5 mol%) was added and the mixture was stirred until a yellow solution formed. To this solution was added neat tetramethyltin (87.7 μL, 0.633 mmol, 2.5 equiv) dropwise. The reaction vial was sealed, removed from the glove box, and heated to 100 °C for 16 h. The reaction was allowed to cool to 23 °C and was then quenched by the addition of H_2O (2.5 mL). The aqueous layer was extracted with EtOAc (5 x 6 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was redissolved in EtOAc (5 mL) and then washed sequentially with aqueous 1 M KF (3 x 5 mL), saturated aqueous NH_4Cl (1 x 5 mL), and H_2O (1 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield sulfamate **1.18** as a white solid (62.1 mg, 74% yield). R_f 0.39 (5:1 Benzene:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.14 (bs, 1H), 7.10–7.05 (m, 2H), 3.45 (q, J = 7.0, 2H), 3.37 (q, J = 6.5, 2H), 2.94 (s, 6H), 2.21 (s, 3H), 1.26 (t, J = 6.5, 3H), 1.19 (t, J = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 153.7, 148.4, 147.0, 132.4, 124.0, 123.3, 119.9, 42.4, 42.0, 38.8, 16.5, 14.3, 13.4; IR (film): 2976, 1714, 1416, 1367, 1273, 1134 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{14}H_{22}N_2O_5SNa$, 353.1147; found 353.1142.

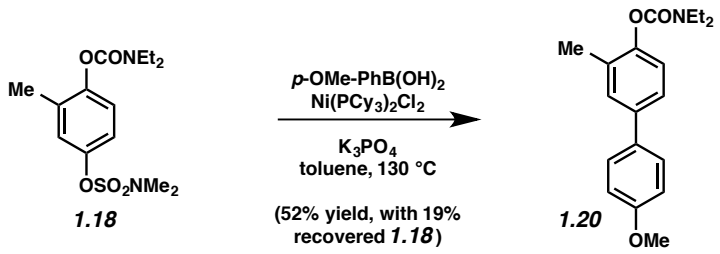


Sulfamate 1.18. Procedure B. To a solution of carbamate **1.14** (900 mg, 2.85 mmol, 1.0 equiv) and TMEDA (0.47 mL, 3.129 mmol, 1.1 equiv) in THF (14.4 mL) at –100 °C was added *s*-BuLi (2.44 mL, 3.129 mmol, 1.1 equiv) dropwise. After stirring for 50 min, methyl iodide (0.42 mL, 6.83 mmol, 2.4 equiv) was added dropwise and stirred for 5 min before warming to 23 °C over 45 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (27 mL) and stirred at 23 °C for 60 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried by passage over a plug of silica gel, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (9:1 Benzene:Et_2O) to yield methylated product **1.18** (884.5 mg, 94% yield) as an off-white solid. Spectral data matched procedure A, see above.



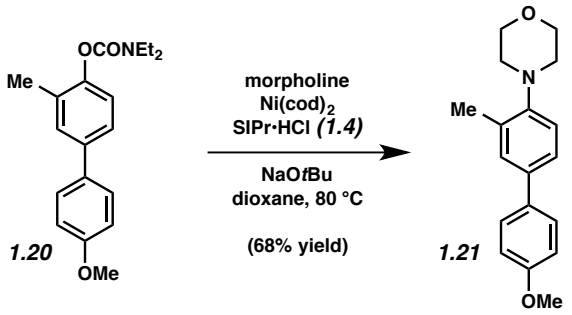
Amine 1.19. A 4 mL reaction vial was charged with $Pd(OAc)_2$ (5.7 mg, 0.025 mmol, 10 mol%), BINAP (17.4 mg, 0.028 mmol, 11 mol%), anhydrous powdered NaO*t*Bu (34.0 mg, 0.354 mmol, 1.4 equiv), bromide **1.15** (100.0 mg, 0.253 mmol, 1 equiv), morpholine (26.6 μL, 0.304 mmol, 1.2 equiv) and a magnetic stir bar, all in a glove box. Subsequently, toluene (1.0 mL) that had been rigorously sparged with N_2, was added. The vessel was sealed under an atmosphere of

argon, and then heated to 80 °C for 16 h. After cooling to 23 °C, the crude mixture was diluted with Et_2O, filtered over a plug of celite with additional Et_2O (10 mL), and concentrated under reduced pressure. The crude residue was purified by flash chromatography (1:1 Benzene:Et_2O) to furnish aminated product **1.19** (72.1 mg, 71% yield) as a yellow oil. R_f 0.33 (1:1 Benzene:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.06 (d, *J* = 8.0, 1H), 6.96–6.92 (m, 2H), 3.79 (t, *J* = 4.8, 4H), 3.45 (q, *J* = 7.0, 2H), 3.38 (q, *J* = 7.0, 2H), 3.00 (t, *J* = 4.5, 4H), 2.95 (s, 6H), 1.25 (t, *J* = 7.0, 3H), 1.21 (t, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 153.6, 147.8, 145.9, 143.5, 124.5, 116.2, 113.7, 67.2, 51.6, 42.3, 41.8, 38.9, 14.4, 13.5; IR (film): 2972, 1716, 1608, 1584, 1498, 1413, 1367, 1139 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{27}N_3O_6SNa$, 424.1518; found 424.1508.



Carbamate 1.20. A 4 mL vial containing K_3PO_4 (0.324 g, 1.53 mmol, 7.2 equiv) was flame-dried and cooled to 23 °C. The $Ni(PCy_3)_2Cl_2$ (25.3 mg, 0.042 mmol, 20 mol%), boronic acid (0.161 g, 1.06 mmol, 5 equiv) and sulfamate **1.18** (70 mg, 0.212 mmol, 1 equiv) were added to the vial. Toluene (0.7 mL) was added, and the resulting mixture was stirred at 23 °C for 1 h. The reaction was then heated at 130 °C for 8 h. The reaction was then cooled to 23 °C and purified by flash chromatography (9:1 Benzene:CH_2Cl_2 → 8:1:1 Hexanes:EtOAc:CH_2Cl_2) to produce carbamate **1.20** (34.7 mg, 52% yield) as a white solid, along with recovered sulfamate **1.18** (13.3 mg, 19% yield). R_f 0.24 (8:1:1 Hexanes:EtOAc:CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): d 7.48 (d,

J = 9, 2H), 7.37 (s, 1H), 7.35 (d, J = 9.6, 1H), 7.10 (d, J = 8.4, 1H) 6.95 (d, J = 8.4, 2H), 3.85 (s, 3H), 3.49 (m, 2H), 3.41 (m, 2H), 2.27 (s, 3H), 1.25 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): d 159.1, 154.1, 149.2, 138.2, 133.5, 130.7, 129.4, 128.2, 125.2, 122.5, 114.2, 55.4, 42.4, 42.0, 16.6, 14.4, 13.5; IR (film): 2973, 2931, 1711, 1608, 1416, 1213, 1153 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{19}H_{23}NO_3Na$, 336.1576; found 336.1567.

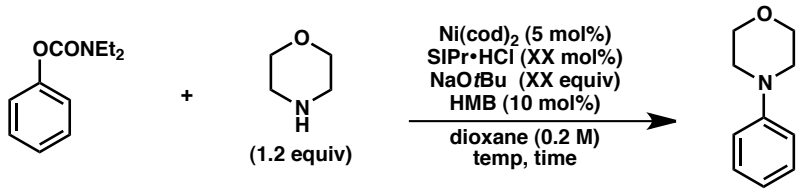


Amine 1.21. A 4 mL vial was charged with carbamate **1.20** (45.5 mg, 0.145 mmol, 1 equiv), $Ni(cod)_2$ (4.1 mg, 0.015 mmol, 10 mol%), SIPr•HCl (12.8 mg, 0.03 mmol, 20 mol%), anhydrous powdered NaO*t*Bu (30.6 mg, 0.319 mmol, 2.2 equiv), and a magnetic stir bar, all in a glove box. Subsequently, morpholine (30.5 mL, 0.348 mmol, 2.4 equiv) and dioxane (0.73 mL) were added. The vessel was sealed and removed from the glove box, and then heated to 80 °C for 3 h. After cooling the reaction vessel to 23 °C, the reaction mixture was filtered over a pad of silica, washed with EtOAc (10 mL) and evaporated to dryness. The crude residue was dissolved in CH_2Cl_2 (0.5 mL), and the resulting solution was layered with benzene (0.1 mL) and hexanes (1.5 mL). The hexane and benzene layers mixed upon standing, and the resulting mixture was placed in a freezer (ca. –10 °C) overnight. After 12 h, the crystals that were formed were collected by filtration and washed with cold hexanes (4 mL) to yield amine **1.21** (27.8 mg, 68% yield) as a yellow solid. R_f 0.39 (8:1:1 Hexanes:EtOAc:CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): d 7.49 (d, J = 7.8, 2H), 7.39 (s, 1H), 7.36 (d, J = 7.8, 1H), 7.07 (d, J = 7.8, 1H) 6.96 (d, J = 7.8, 2H), 3.87

(bs, 4H), 3.85 (bs, 3H), 2.95 (bs, 4H), 2.37 (bs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 158.9, 150.3, 136.0, 133.7, 133.0, 130.0, 128.0, 125.0, 119.3, 114.3, 67.6, 55.5, 52.4, 18.2; IR (film): 2990, 2963, 2854, 2836, 1718, 1605, 1581, 1496, 1224, 1116, 1023 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{21}NO_2H$, 284.1650; found 284.1648.

1.7.2.4 Key Optimization Studies

Table 1.4. Optimization of Ligand, Base and Temperature.



Entry	SIPr•HCl (mol%)	NaO*t*Bu (equiv)	temp	time	Conversion (%)
1	2.5	1.313	rt	24 h	59
2	5	1.325	rt	24 h	73
3	10	1.4	rt	24 h	92
4	30	1.6	rt	24 h	>95%
5	10	1.4	80 °C	3 h	>95%

1.7.3 Computational Methods

N,N-dimethyl phenylcarbamate and dimethyl amine are used as representatives of experimental substrates. *N,N'*-bis(2,6-dimethylphenyl)4,5-dihydroimidazol-2-ylidene is used as model for the experimental ligand, *N,N'*-bis(2,6-diisopropylphenyl)4,5-dihydroimidazol-2-ylidene (SIPr). Geometry optimizations and frequency calculations were performed using B3LYP and a mixed basis set employing SDD for metal and 6-31G(d) for other atoms. Single point energies were calculated with B3LYP and a mixed basis set of SDD for metal and 6-311+G(2d,p) basis set for other atoms. Energies reported are Gibbs free energies in solution,

which involve zero-point vibrational energy corrections, thermal corrections to Gibbs free energy at 298 K, and solvation free energy corrections computed by singlet point CPCM calculations with B3LYP/SDD–6-311+G(2d,p) on gas-phase optimized geometries. In CPCM calculations, 1,4-dioxane was used as solvent. The molecular cavities were built up using the United Atom Topological Model (UAHF). Vibrational frequencies were calculated for all optimized structures to confirm the nature of the stationary points. All calculations were performed using Gaussian 09 package.

1.7.3.1 Complete Reference of Gaussian 09

Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.

1.7.3.2 Single Point Calculations using Other DFT Methods and Basis Sets

We performed single point calculations for the energy profiles shown in Figures 1.2 in the manuscript using other DFT methods and basis sets. The geometries were optimized using B3LYP and a mixed basis set of SDD for metal and 6-31G(d) for other atoms. Different DFT methods (B3LYP, B3P86, B3PW91) and basis sets (6-31G(d), 6-311+G(2d,p)) were used to calculate the single point energies and solvation energy corrections for all species (shown in Figure 1.5 and Table 1.5).

Figure 1.5. Comparison of Single Point Energies Using Varied DFT Methods and Basis Sets.

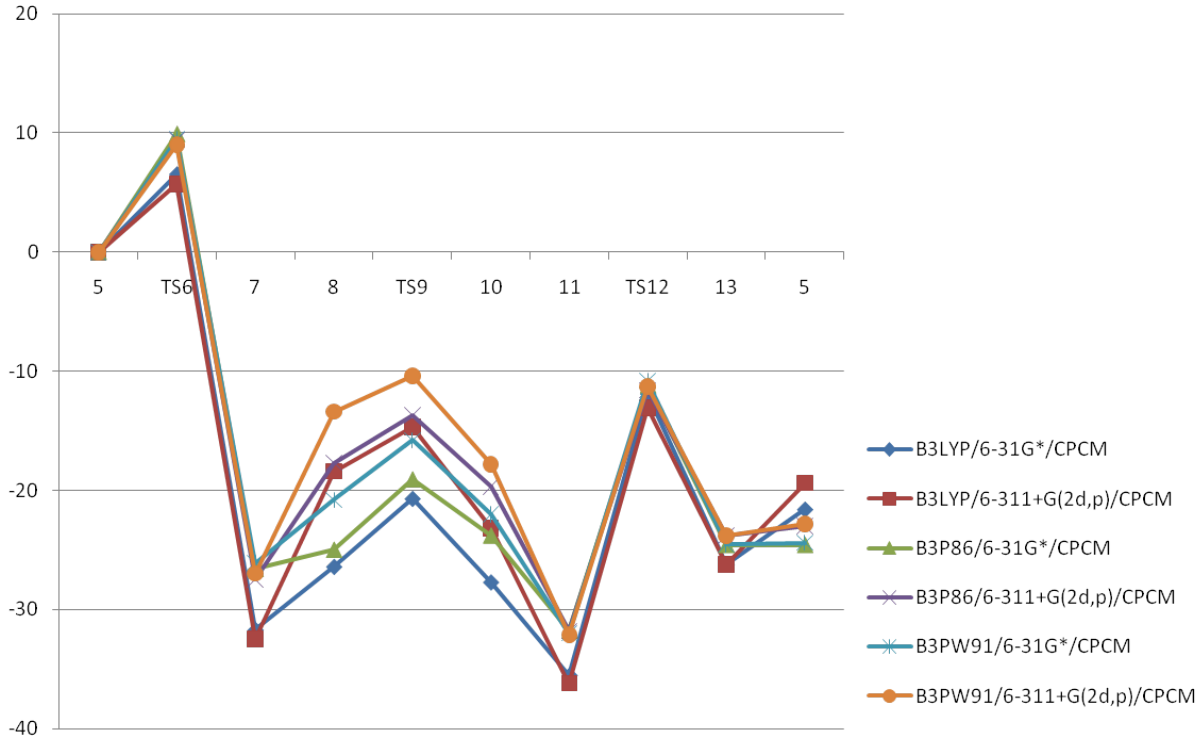


Table 1.5. Comparison of Single Point Energies Using Varied DFT Methods and Basis Sets.

-	**1.5**	**TS 1.6**	**1.7**	**1.8**	**TS 1.9**	**1.10**	**1.11**	**TS 1.12**	**1.13**	**1.5**
	0.0	6.5	-31.7	-26.4	-20.7	-27.7	-35.5	-11.9	-26.2	-21.6

B3LYP /6-311+G(2d,p)/CPCM	0.0	5.7	-32.5	-18.4	-14.7	-23.2	-36.2	-13.1	-26.2	-19.4
B3P86 /6-31G*/CPCM	0.0	9.9	-26.6	-25.0	-19.1	-23.8	-31.8	-11.2	-24.6	-24.6
B3P86 /6-311+G(2d,p)/CPCM	0.0	9.4	-27.5	-17.7	-13.7	-19.7	-31.8	-11.6	-23.8	-23.0
B3PW91 /6-31G*/CPCM	0.0	9.5	-26.1	-20.8	-15.8	-22.0	-32.0	-10.8	-24.5	-24.4
B3PW91 /6-311+G(2d,p)/CPCM	0.0	9.0	-27.0	-13.4	-10.4	-17.8	-32.1	-11.3	-23.8	-22.8

1.7.3.3 The Cartesian coordinates (Å), and Gibbs free energies at 298K for the optimized structures.

For transition state structures, one imaginary frequency was observed and given below. For all minimum structures, no imaginary frequencies were observed.

1.5

Total SCF energy: -1572.50113709 a.u.

Enthalpy at 298K: -1571.908190 a.u.

Gibbs free energy at 298K: -1572.014494 a.u.

Free energy in solution at 298K: -1572.458643 a.u.

Cartesian coordinates

ATOM	X	Y	Z
C	-0.41142000	1.91417000	1.53913500
C	1.36290900	1.90276200	3.21553400
C	-0.34955500	0.18778100	3.29867800
C	-0.96022300	0.70565600	2.11292100
H	-0.82116900	-0.65607900	3.79884900

C	0.78955400	0.75491200	3.82842700
H	1.24276900	0.34141700	4.72575200
H	-1.99320100	0.43162600	1.90213400
C	0.76238300	2.49168300	2.12454600
O	-1.30555300	2.88485100	0.90518900
C	-1.28374900	2.85234600	-0.43397100
O	-0.64872200	1.99267700	-1.07397200
H	1.15635000	3.41149500	1.69846600
H	2.26775500	2.34008300	3.63061600
Ni	-0.05263000	0.48757700	0.31068100
N	-2.01780300	3.82997300	-1.02560300
C	-2.76058200	4.83706800	-0.28136100
H	-3.83666900	4.74226800	-0.47975500
H	-2.58251500	4.71639100	0.78455100
H	-2.44192300	5.84153500	-0.58927000
C	-2.11353900	3.88690400	-2.47556300
H	-1.51984200	3.08153800	-2.90424900
H	-3.15899000	3.77869000	-2.79366700
H	-1.73884400	4.85079700	-2.84407900
C	0.40258700	-1.19786900	-0.38592500
N	-0.40520000	-2.28207800	-0.57864200
N	1.64334200	-1.57458500	-0.81013800
C	0.26193900	-3.42676000	-1.22639800

C	-1.81633400	-2.29835100	-0.33880200
C	1.73366000	-2.97584900	-1.25828500
C	2.80724400	-0.74023700	-0.76200500
H	0.11600700	-4.34818300	-0.65202800
C	-2.29648900	-2.89450700	0.84315700
C	-2.69477000	-1.75941500	-1.29883900
H	2.17445100	-3.03963700	-2.25957100
C	3.11754200	0.05914000	-1.87859700
C	3.63140400	-0.76363700	0.37936500
C	-3.67951500	-2.94280900	1.05274700
C	-1.34203400	-3.44511200	1.87614600
C	-4.07132900	-1.82782800	-1.05132000
C	-2.17594400	-1.09540700	-2.55220700
C	4.28327100	0.83278700	-1.83989400
C	2.19888300	0.11189400	-3.07641200
C	4.78987000	0.02180900	0.37648300
C	3.25895600	-1.57730400	1.59599600
C	-4.56316200	-2.41502300	0.11295900
H	-4.06191000	-3.39558600	1.96442800
H	-1.88344600	-3.76286400	2.77290500
H	-0.78777100	-4.31586100	1.50226200
H	-0.60267700	-2.69112600	2.16593600
H	-4.76108300	-1.41626900	-1.78446600

H	-1.43403100	-1.71486600	-3.06915400
H	-2.99525000	-0.89857800	-3.25148600
H	-1.68797200	-0.14281800	-2.31428400
C	5.11731200	0.81232100	-0.72365600
H	4.53383500	1.45638700	-2.69471100
H	2.63333000	0.72839000	-3.86989000
H	2.00644700	-0.88420800	-3.49321800
H	1.22808600	0.54038100	-2.80150400
H	5.43468600	0.01563600	1.25191600
H	2.32052900	-1.21522300	2.03122800
H	3.12156100	-2.63939200	1.35918400
H	4.03932800	-1.50626800	2.36025300
H	-5.63496400	-2.46119500	0.28809400
H	6.02127700	1.41590200	-0.70932200
H	-0.14612200	-3.59282000	-2.23246800
H	2.36419500	-3.56385400	-0.57873200

TS 1.6

Total SCF energy:	-1572.48623239 a.u.
Enthalpy at 298K:	-1571.894822 a.u.
Gibbs free energy at 298K:	-1572.000684 a.u.
Free energy in solution at 298K:	-1572.449576 a.u.
Imaginary frequency:	-194.54 cm^{-1}

Cartesian coordinates

ATOM	X	Y	Z
C	-0.12043700	1.77464900	1.67640100
C	1.26056900	2.19695900	3.61631800
C	-0.57945300	0.63003600	3.79176800
C	-0.91030600	0.86527400	2.43475600
H	-1.20510300	-0.03327100	4.38652400
C	0.49865700	1.27720400	4.37283100
H	0.74818100	1.09999700	5.41573100
H	-1.85157000	0.48556800	2.04185000
C	0.94530300	2.47470000	2.29733300
O	-1.07140700	3.10013900	0.62737000
C	-0.85726400	2.83253300	-0.60327400
O	-0.33887000	1.73576700	-1.03050600
H	1.52136400	3.19686400	1.72573600
H	2.11048400	2.69546200	4.07817000
Ni	0.01019700	0.48424400	0.43212300
C	0.25028700	-1.25728000	-0.39694400
N	-0.70811100	-2.17445900	-0.66715200
N	1.42305000	-1.76630600	-0.83825400
C	-0.20727400	-3.38309100	-1.35458800
C	1.30543400	-3.10384000	-1.45552100
H	-0.68346400	-3.49120100	-2.33603800

H	-0.43329000	-4.28330900	-0.77241200
H	1.66361500	-3.08266800	-2.49089600
H	1.90846700	-3.83735700	-0.90809000
N	-1.19085900	3.78784000	-1.53427400
C	-1.91513400	4.98533000	-1.14279900
H	-1.51117700	5.85319700	-1.67937100
H	-2.98729900	4.90570200	-1.38090400
H	-1.80221900	5.13595100	-0.07099000
C	-1.12780100	3.50534600	-2.95675900
H	-0.44104300	2.67965100	-3.13224600
H	-2.11615600	3.23979200	-3.36451000
H	-0.76952300	4.39386700	-3.49147200
C	-2.10205600	-2.01870200	-0.36474400
C	-2.60278300	-2.55157000	0.83863800
C	-2.93826200	-1.36663000	-1.29043900
C	-3.97201800	-2.42539200	1.10037700
C	-4.30172600	-1.26236500	-0.98928900
C	-4.81720000	-1.78806400	0.19356900
H	-4.37326300	-2.82826700	2.02700100
H	-4.96083000	-0.75963400	-1.69257100
H	-5.87831200	-1.69871900	0.41073200
C	2.69333100	-1.10583900	-0.73859300
C	3.10981200	-0.26133800	-1.78435300

C	3.50210100	-1.34687900	0.38756000
C	4.37362700	0.33301500	-1.68861500
C	4.75837800	-0.73274700	0.44363100
C	5.19435000	0.09775500	-0.58728900
H	4.71085200	0.98958200	-2.48681900
H	5.39385600	-0.90548900	1.30858000
H	6.17343200	0.56616500	-0.52978400
C	2.20615700	0.03743700	-2.95696400
H	1.82552600	-0.87538200	-3.43087500
H	1.33803000	0.62335000	-2.63238400
H	2.74283400	0.61030500	-3.71975300
C	3.01832800	-2.21246800	1.52715400
H	2.11328500	-1.79166200	1.98031000
H	2.77474200	-3.23154600	1.20156000
H	3.78312000	-2.28782100	2.30598600
C	-2.38167300	-0.75594500	-2.55442200
H	-1.74183200	0.10270800	-2.31803900
H	-1.77369600	-1.46873200	-3.12439300
H	-3.19236000	-0.41354200	-3.20547400
C	-1.68656700	-3.20909600	1.84383500
H	-1.15349400	-4.06931800	1.42048800
H	-0.92822900	-2.50348200	2.20232700
H	-2.25507200	-3.56631200	2.70795000

1.7

Total SCF energy: -1572.55602277 a.u.

Enthalpy at 298K: -1571.894822 a.u.

Gibbs free energy at 298K: -1572.065526 a.u.

Free energy in solution at 298K: -1572.510379 a.u.

Cartesian coordinates

ATOM	X	Y	Z
Ni	0.12795100	0.64169300	0.52753200
C	-0.10170700	-0.88518000	-0.54790800
C	-0.99135300	-2.38729000	-2.13656400
C	0.35171400	-2.93531600	-1.62950300
H	-1.81278500	-3.09651800	-2.00801000
H	0.23858800	-3.86534400	-1.05977300
N	0.82620100	-1.85203100	-0.74034300
N	-1.19064900	-1.19082600	-1.28997700
H	1.07219100	-3.11649700	-2.43225500
H	-0.95807200	-2.09293400	-3.19291600
C	-1.11658800	0.09956900	1.85787900
C	-1.79684400	1.14094700	2.52191100
C	-1.38352300	-1.20797100	2.30086300
C	-2.68754600	0.88692600	3.56904200

H	-1.61417200	2.17060400	2.22903300
C	-2.25810900	-1.47029600	3.36341000
H	-0.90603400	-2.05228100	1.81270900
C	-2.91876600	-0.42104400	4.00158200
H	-3.19546000	1.71763600	4.05578700
H	-2.42533400	-2.49712300	3.68481400
H	-3.60275100	-0.61810400	4.82386600
O	0.61706400	2.36438200	1.34744500
C	1.39645400	2.59490100	0.35613000
O	1.45507400	1.70759000	-0.57451400
N	2.13008300	3.73935100	0.28961200
C	2.09150600	4.71487400	1.36505500
H	3.07983500	4.81269200	1.83566800
H	1.79645200	5.69968200	0.97837200
H	1.36958700	4.39001200	2.11279000
C	3.03127000	3.99417200	-0.81805000
H	2.78995100	4.95367700	-1.29538000
H	4.07382300	4.03712200	-0.47213300
H	2.93101200	3.19391700	-1.54973400
C	2.20423200	-1.83852200	-0.31307200
C	3.15782100	-1.24022400	-1.16462800
C	2.58838300	-2.49690700	0.87018000
C	4.50304300	-1.27647300	-0.78360900

C	3.94756100	-2.50737200	1.21117500
C	4.89837700	-1.89787800	0.39894700
H	5.24547800	-0.81324100	-1.42843900
H	4.25492200	-3.00785000	2.12590100
H	5.94825200	-1.91880000	0.67912900
C	-2.32449600	-0.33469800	-1.53087900
C	-3.58524900	-0.70726800	-1.02307000
C	-2.16581800	0.80531600	-2.34582600
C	-4.67961500	0.12096100	-1.29745300
C	-3.28954200	1.60452500	-2.58955900
C	-4.53554600	1.27425500	-2.06402200
H	-5.65392500	-0.14707500	-0.89726100
H	-3.17884500	2.49047500	-3.20973300
H	-5.39616500	1.90753300	-2.26256400
C	2.76230200	-0.55789800	-2.45205400
H	2.13641900	-1.19510400	-3.08862300
H	2.20506400	0.35930400	-2.24061400
H	3.65330600	-0.29304900	-3.03001000
C	1.59815600	-3.17414400	1.78609000
H	1.13862000	-2.45353200	2.47129900
H	0.78478700	-3.65846000	1.23691500
H	2.09805900	-3.93771400	2.39061000
C	-3.78536000	-1.96323300	-0.21009900

H	-4.78694800	-1.97618300	0.22974500
H	-3.69160100	-2.86819100	-0.82608000
H	-3.06039700	-2.03168800	0.60450700
C	-0.84017500	1.17619300	-2.96863300
H	-0.14819000	1.60618100	-2.23613600
H	-0.33718900	0.30673000	-3.40789400
H	-0.99114500	1.90994900	-3.76698100

5.7

Total SCF energy: -1617.61569826 a.u.

Enthalpy at 298K: -1616.892203 a.u.

Gibbs free energy at 298K: -1617.003548 a.u.

Free energy in solution at 298K: -1617.459161 a.u.

Cartesian coordinates

ATOM	X	Y	Z
Ni	0.27367100	0.23273500	0.85607000
C	0.57760900	-0.00948900	-3.32150100
C	-0.94925500	-0.10216200	-3.22909200
H	1.02281100	-0.84450100	-3.86991100
H	-1.33970000	-1.06007200	-3.59216400
C	-0.14393900	-1.58750800	1.26533300
C	0.72561900	-2.69193100	1.19603700

C	-1.40315900	-1.81986800	1.85867600
C	0.36411400	-3.95630200	1.68104800
H	1.71599800	-2.56841800	0.76395300
C	-1.77193500	-3.07568000	2.35240100
H	-2.11954200	-1.00325200	1.93850200
C	-0.88874200	-4.15523400	2.26222900
H	1.06702800	-4.78463700	1.60713000
H	-2.75181600	-3.21103500	2.80741900
H	-1.17242800	-5.13405700	2.64175400
N	1.16730500	0.41760100	2.67440900
H	1.28210900	1.42124000	2.51342900
O	0.61150300	2.16516000	0.77827600
C	-0.13047300	3.25950100	1.26408500
C	-1.57764000	2.87528100	1.63919500
C	0.55664800	3.85553100	2.52274000
C	-0.14894100	4.37171900	0.18909900
H	-2.10593700	2.45345600	0.78086200
H	-1.58001500	2.11696200	2.43172100
H	-2.14706700	3.74113400	2.00374400
H	1.61055800	4.06549800	2.30577700
H	0.08058700	4.79067600	2.84564100
H	0.51096300	3.16165700	3.37253300
H	-0.72546600	5.24883400	0.51211500

H	0.87477300	4.69895500	-0.02688300
H	-0.58319000	4.00091300	-0.74371300
C	2.50410600	-0.20269400	2.70240200
H	2.39927000	-1.28941400	2.74080300
H	3.04780800	0.06904400	1.79412500
H	3.07797100	0.13047800	3.58039600
C	0.42766900	0.17510300	3.92237300
H	-0.51423700	0.72846200	3.90234400
H	0.19985500	-0.88958100	4.00836500
H	1.00980300	0.49127500	4.80075900
C	-0.05775100	0.03944600	-1.03351700
N	-1.19379000	0.02551100	-1.77586900
N	0.98397100	-0.03952700	-1.90167600
H	-1.45778900	0.69979300	-3.77245900
H	0.91694400	0.92266100	-3.78835200
C	-2.55647600	-0.05760800	-1.32168800
C	-3.34331100	1.11042900	-1.30450300
C	-3.11539400	-1.32285300	-1.04264500
C	-4.67459900	1.01130800	-0.88076300
C	-4.45012900	-1.37495100	-0.62426300
C	-5.22139900	-0.21856200	-0.52539100
H	-5.28429500	1.91071400	-0.84208200
H	-4.88731800	-2.34079700	-0.38456600

H	-6.25387300	-0.27975000	-0.19138700
C	2.37796900	-0.20568000	-1.58248100
C	3.19629400	0.92722600	-1.39795700
C	2.91466600	-1.51089700	-1.58302200
C	4.55004100	0.71747900	-1.10132400
C	4.27271700	-1.67106300	-1.28166400
C	5.08335300	-0.56723700	-1.02593800
H	5.19022600	1.58136300	-0.94150100
H	4.69444500	-2.67299200	-1.26087600
H	6.13550100	-0.70746500	-0.79152500
C	2.65092300	2.32541200	-1.52161700
H	2.15159000	2.47632800	-2.48756800
H	1.91420900	2.51671200	-0.72813400
H	3.46149100	3.05824800	-1.45022100
C	2.08783800	-2.71875100	-1.96220800
H	2.00544100	-2.80979100	-3.05460900
H	2.55802300	-3.63842700	-1.60080700
H	1.07629900	-2.67766900	-1.55381700
C	-2.34830900	-2.60655900	-1.25584700
H	-1.33241300	-2.55447100	-0.86223700
H	-2.85013800	-3.44054500	-0.75812200
H	-2.29050300	-2.85058300	-2.32625600
C	-2.81155200	2.43211100	-1.80450900

H	-3.01199000	2.54536400	-2.87968100
H	-3.29768600	3.27146200	-1.29823200
H	-1.73490200	2.52020200	-1.65462900

TS 1.9

Total SCF energy: -1617.59749836 a.u.

Enthalpy at 298K: -1616.880462 a.u.

Gibbs free energy at 298K: -1616.995999 a.u.

Free energy in solution at 298K: -1617.453272 a.u.

Imaginary frequency: -915.73 cm^{-1}

Cartesian coordinates

ATOM	X	Y	Z
Ni	0.06798100	0.25408800	0.74762500
C	0.63890500	-1.24424600	-3.16919900
C	-0.88397600	-1.03503700	-3.18180100
H	0.92388700	-2.28618200	-3.34539600
H	-1.43689000	-1.94965900	-3.41565100
C	-0.21754800	-1.39231300	1.60651700
C	0.85086800	-2.22614700	1.97978200
C	-1.51132400	-1.77583200	2.00272600
C	0.63570800	-3.39724700	2.71639800
H	1.86902800	-1.96248800	1.70368100
C	-1.72832600	-2.94604000	2.73980800
H	-2.36694900	-1.15775700	1.74128500
C	-0.65552100	-3.76391200	3.10008400
H	1.48387100	-4.02026900	2.99469400
H	-2.74086300	-3.21392200	3.03634900

H	-0.82294700	-4.67146800	3.67499200
N	0.30201900	1.19808400	2.39771200
H	0.44824400	2.17268200	1.54043500
O	0.49876100	2.64993400	0.44943900
C	0.44829700	4.07271600	0.43913800
C	-0.89721400	4.55965400	1.01643400
C	1.60718600	4.61565700	1.30148600
C	0.60936500	4.58726500	-1.00175600
H	-1.73259000	4.17194400	0.42331800
H	-1.02380600	4.20779600	2.04687100
H	-0.96153100	5.65540800	1.02372400
H	2.56571700	4.25127100	0.91536400
H	1.63109500	5.71302800	1.30738200
H	1.50852600	4.27415200	2.33879400
H	0.55896100	5.68292600	-1.03570500
H	1.57567800	4.28071900	-1.41565600
H	-0.17968700	4.19266500	-1.64989500
C	1.51082700	0.91243600	3.16627000
H	1.44547000	-0.04834100	3.69708500
H	2.37687400	0.87500000	2.49685900
H	1.69312300	1.70025200	3.91600600
C	-0.86123500	1.35035600	3.26678200
H	-1.73242300	1.65038800	2.67433000

H	-1.10972500	0.41590200	3.79009100
H	-0.68330700	2.12644700	4.02996400
C	-0.04665400	-0.45100500	-1.04400700
N	-1.16039400	-0.59680200	-1.79648600
N	1.00928600	-0.83117600	-1.79823100
H	-1.19859600	-0.25906300	-3.88860700
H	1.16033600	-0.62093000	-3.90316600
C	-2.51744600	-0.35942100	-1.38485600
C	-3.02682300	0.95228400	-1.42000700
C	-3.32540700	-1.46017100	-1.03637900
C	-4.36206600	1.15277400	-1.04954400
C	-4.65621900	-1.21314300	-0.67817600
C	-5.17108100	0.08141800	-0.67691400
H	-4.76728900	2.16128700	-1.06406500
H	-5.28948500	-2.05015200	-0.39533900
H	-6.20555900	0.25463400	-0.39238500
C	2.38129800	-0.92410600	-1.37507900
C	3.19374700	0.22482100	-1.42304100
C	2.89775600	-2.18297900	-1.00543400
C	4.53398800	0.10094000	-1.03592100
C	4.24397600	-2.25882300	-0.62816800
C	5.05574600	-1.12652600	-0.63445800
H	5.17126600	0.98115900	-1.05964100

H	4.65327300	-3.21987400	-0.32698600
H	6.09793200	-1.20330400	-0.33587000
C	2.64772500	1.55623700	-1.87179900
H	2.10025700	1.47226500	-2.81884900
H	1.95596600	1.97204600	-1.12838500
H	3.46336100	2.27132000	-2.02041200
C	2.05084400	-3.43443700	-1.02349200
H	1.93689200	-3.82951000	-2.04257300
H	2.51810600	-4.22228200	-0.42534700
H	1.05280900	-3.25683100	-0.61542500
C	-2.79487300	-2.87468400	-1.04605700
H	-1.82663000	-2.94501000	-0.54353100
H	-3.48710800	-3.54672000	-0.53057000
H	-2.67488800	-3.25695700	-2.06899600
C	-2.16432100	2.11278500	-1.84786400
H	-1.72871300	1.94801300	-2.84183600
H	-2.75512400	3.03293700	-1.89413500
H	-1.33372000	2.27215700	-1.15161300

1.10

Total SCF energy:	-1617.60755966 a.u.
Enthalpy at 298K:	-1616.886029 a.u.

Gibbs free energy at 298K: -1617.005198 a.u.

Free energy in solution at 298K: -1618.06911822 a.u.

ATOM	X	Y	Z
Ni	0.01811400	-0.00789400	0.73710000
C	-1.46147700	-0.65556900	-3.17658300
C	-1.36713800	0.88052500	-3.16521300
H	-2.47123400	-1.01615700	-3.39540700
H	-2.33843500	1.36219300	-3.31909900
C	-1.59029000	0.13341800	1.69822200
C	-2.28243500	-1.01246600	2.12834700
C	-2.07867400	1.38458100	2.11371200
C	-3.42461400	-0.91112100	2.93171100
H	-1.92911400	-2.00112600	1.84335600
C	-3.22052600	1.48756500	2.91712700
H	-1.56350600	2.29548400	1.81695100
C	-3.90078400	0.33985000	3.32929300
H	-3.93859100	-1.81591700	3.25153000
H	-3.57392300	2.46996000	3.22567800
H	-4.78625800	0.41894100	3.95542100
N	1.17413500	-0.09719100	2.13350200
H	2.67683600	-0.23504700	0.91238700
O	3.27783200	-0.30710800	0.12449300
C	4.65312400	-0.37342700	0.51945100

C	5.04658500	0.91428800	1.26296500
C	4.88367800	-1.60527000	1.41097300
C	5.44908300	-0.50255800	-0.78415700
H	4.85866200	1.78916500	0.63106600
H	4.45936000	1.02661400	2.18186100
H	6.10792300	0.90863500	1.53986100
H	4.56843900	-2.51488100	0.88824400
H	5.94115400	-1.71040700	1.68263000
H	4.30464700	-1.52887400	2.33887100
H	6.52542300	-0.55634300	-0.58511400
H	5.15086300	-1.40772100	-1.32444200
H	5.25904000	0.35947700	-1.43289200
C	1.19092800	-1.29158100	2.97149400
H	0.40146200	-1.26826600	3.74184000
H	1.04419900	-2.18898900	2.36180500
H	2.15529100	-1.39465500	3.49893200
C	1.38718900	1.09362400	2.94908400
H	1.39258400	1.99087200	2.32173700
H	0.60298700	1.21668400	3.71523800
H	2.35419500	1.04547800	3.47984200
C	-0.69728100	0.05232200	-1.04722700
N	-0.85847900	1.16043000	-1.80578100
N	-1.06625400	-1.01121300	-1.79693500

H	-0.67331400	1.27045600	-3.91768200
H	-0.77501600	-1.11746700	-3.89558400
C	-0.53896600	2.50409000	-1.40966500
C	0.79324300	2.94986400	-1.51596600
C	-1.57756500	3.35886300	-0.98838500
C	1.07627500	4.27000000	-1.14123800
C	-1.24697200	4.66934000	-0.62523100
C	0.06967100	5.12150900	-0.69230700
H	2.09963600	4.62969600	-1.21338800
H	-2.03451600	5.33789500	-0.28689200
H	0.30894000	6.14207900	-0.40521400
C	-0.99116200	-2.38922300	-1.39660400
C	0.23987500	-3.06784700	-1.48814900
C	-2.17161400	-3.04149900	-0.98705900
C	0.27405000	-4.41787500	-1.11416800
C	-2.08872500	-4.39051100	-0.62448000
C	-0.87514200	-5.07377200	-0.68007600
H	1.21622100	-4.95670700	-1.17542600
H	-2.98806800	-4.90533900	-0.29620600
H	-0.82803900	-6.12141700	-0.39474800
C	1.49768200	-2.38825500	-1.97666400
H	1.30501400	-1.74316600	-2.84115900
H	1.96557600	-1.76118100	-1.20737300

H	2.23639000	-3.13746700	-2.28018100
C	-3.49628900	-2.31717300	-0.93158500
H	-3.84949900	-2.03336400	-1.93170800
H	-4.26429000	-2.95690400	-0.48661100
H	-3.42836600	-1.40563600	-0.33036400
C	-3.01369900	2.89355000	-0.92818300
H	-3.10563500	1.93495300	-0.41006300
H	-3.63036200	3.62276000	-0.39452900
H	-3.44513200	2.77789800	-1.93167800
C	1.89909200	2.05525700	-2.02481900
H	1.57534300	1.45447900	-2.88222800
H	2.75429700	2.65914900	-2.34595100
H	2.26039500	1.35487600	-1.26127800

1.11

Total SCF energy: -1383.92420628 a.u.

Enthalpy at 298K: -1383.349281 a.u.

Gibbs free energy at 298K: -1383.451204 a.u.

Free energy in solution at 298K: -1383.82905792 a.u.

Cartesian coordinates

ATOM	X	Y	Z
Ni	-0.00651200	0.32201300	1.11357500

C	-0.75425200	-2.29259400	-2.09268600
C	0.78083500	-2.36467000	-2.01544700
H	-1.23527300	-3.26116800	-1.92012100
H	1.14046100	-3.34407100	-1.67621900
C	-0.00458600	1.95291700	0.16508500
C	-1.20620000	2.61324000	-0.15162300
C	1.19795100	2.61813900	-0.13850700
C	-1.20690400	3.87909100	-0.74934800
H	-2.16075200	2.14219700	0.07476900
C	1.19996100	3.88403300	-0.73671100
H	2.15210200	2.15168100	0.09927500
C	-0.00320600	4.52125400	-1.04668700
H	-2.15371800	4.36587400	-0.97751400
H	2.14722700	4.37441600	-0.95500500
H	-0.00271400	5.50534800	-1.50935100
C	0.00387800	-0.81407000	-0.40013500
N	-1.08459400	-1.35294800	-1.00105000
N	1.09907100	-1.33216300	-1.00751300
H	-1.10541000	-1.90641800	-3.05552700
H	1.26406500	-2.14247500	-2.97131200
N	-0.01767300	0.65911300	2.86413400
C	-1.21923200	1.05233400	3.58131600
H	-1.26678700	0.57098100	4.57424300

H	-1.25903900	2.14372000	3.75062100
H	-2.11378600	0.76185800	3.02175400
C	1.17190100	1.06156700	3.59595900
H	1.20083600	2.15315600	3.76611300
H	1.21145400	0.58017600	4.58922800
H	2.07552100	0.77888500	3.04701600
C	-2.45148700	-1.09223600	-0.64742600
C	-3.00804500	-1.75180400	0.46637100
C	-3.21936000	-0.22910900	-1.45452200
C	-4.35244000	-1.51288900	0.77443000
C	-4.56118900	-0.02319500	-1.11127500
C	-5.12548800	-0.65557800	-0.00560200
H	-4.79347700	-2.01209400	1.63352200
H	-5.16331100	0.64754500	-1.71889200
H	-6.16807300	-0.48178300	0.24699500
C	2.46354600	-1.07937800	-0.63768300
C	3.23939400	-0.23092400	-1.45228500
C	3.01041000	-1.72844700	0.48654500
C	4.58071400	-0.02798700	-1.10695500
C	4.35518200	-1.49234000	0.79724900
C	5.13620100	-0.64930000	0.00984000
H	5.18975400	0.63011600	-1.72137600
H	4.78988900	-1.98307100	1.66446600

H	6.17892900	-0.47921400	0.26441700
C	2.64762900	0.46793100	-2.65355300
H	1.78116900	1.07378100	-2.36922000
H	3.38673500	1.13122900	-3.11285000
H	2.32055300	-0.23988300	-3.42577900
C	2.18311900	-2.64717000	1.35480800
H	1.44582300	-2.08260500	1.93878300
H	1.62858000	-3.38543800	0.76371100
H	2.82299300	-3.19144400	2.05609300
C	-2.18927100	-2.68801200	1.32359300
H	-1.44973200	-2.13717100	1.91774600
H	-2.83440300	-3.23862100	2.01500500
H	-1.63776200	-3.41937500	0.72113900
C	-2.62754800	0.47447500	-2.65323100
H	-2.48094100	-0.21074400	-3.49898100
H	-3.29407100	1.27102100	-2.99707300
H	-1.66121200	0.92756500	-2.41389500

TS 1.12

Total SCF energy:	-1383.89159731 a.u.
Enthalpy at 298K:	-1383.317527 a.u.
Gibbs free energy at 298K:	-1383.349281 a.u.

Free energy in solution at 298K: -1383.792104 a.u.

Imaginary frequency: -386.75 cm^{-1}

Cartesian coordinates

ATOM	X	Y	Z
Ni	-0.00109900	0.42569300	0.99488900
C	-0.77285500	-2.85314000	-1.50021200
C	0.76795800	-2.85430100	-1.50007500
H	-1.19523000	-3.76552100	-1.06242200
H	1.18888800	-3.76744200	-1.06248000
C	0.00349100	2.21436800	0.27025900
C	-1.20317200	2.74160100	-0.25975400
C	1.21485400	2.73773400	-0.25287500
C	-1.19111200	3.70148900	-1.27155600
H	-2.15939100	2.37462000	0.10075100
C	1.21158900	3.69772500	-1.26465300
H	2.16785400	2.36746200	0.11276000
C	0.01249800	4.19377000	-1.78507700
H	-2.13869900	4.06672900	-1.66376900
H	2.16255500	4.05998800	-1.65141000
H	0.01592200	4.94761100	-2.56747400
C	-0.00122400	-1.03168800	-0.17677200
N	-1.09240900	-1.68136000	-0.66215900
N	1.08912300	-1.68322900	-0.66160100

H	-1.19369900	-2.74077400	-2.50575200
H	1.18919100	-2.74223200	-2.50549200
N	-0.00240000	1.88059300	2.10566600
C	-1.21022900	2.44382700	2.69724600
H	-1.19619700	2.28049100	3.78385100
H	-1.29784000	3.52832100	2.51183200
H	-2.09863500	1.94849700	2.30130200
C	1.20261600	2.44200000	2.70468900
H	1.29310800	3.52632100	2.51965400
H	1.18149900	2.27889300	3.79121200
H	2.09275200	1.94522300	2.31444800
C	-2.45535100	-1.32936200	-0.38659100
C	-3.07366400	-1.83157800	0.77468500
C	-3.15761300	-0.53358900	-1.31204000
C	-4.41786300	-1.51424800	1.00134500
C	-4.50178500	-0.24306600	-1.04899700
C	-5.12930800	-0.72753500	0.09718100
H	-4.90738600	-1.89172500	1.89575500
H	-5.05622200	0.37305500	-1.75252400
H	-6.17377600	-0.49302800	0.28535500
C	2.45257900	-1.33382600	-0.38507800
C	3.15689000	-0.53907800	-1.30983900
C	3.06908300	-1.83738200	0.77658400

C	4.50139100	-0.25102000	-1.04572000
C	4.41366500	-1.52250700	1.00432000
C	5.12719000	-0.73689100	0.10082700
H	5.05745500	0.36427400	-1.74869200
H	4.90186500	-1.90102200	1.89901600
H	6.17194500	-0.50430000	0.28981900
C	-2.47914700	0.02623300	-2.53979000
H	-1.66824000	0.70771000	-2.26052900
H	-2.04785000	-0.75954600	-3.17162900
H	-3.19336800	0.58571300	-3.15175400
C	-2.30462300	-2.66685000	1.76990600
H	-1.81371300	-3.52543500	1.29637400
H	-1.51685200	-2.07273100	2.24964900
H	-2.96839300	-3.04863400	2.55181000
C	2.48016300	0.02250600	-2.53772400
H	3.19579300	0.58071300	-3.14919200
H	2.04747600	-0.76218700	-3.16996500
H	1.67059100	0.70557300	-2.25849000
C	2.29775800	-2.67154300	1.77095800
H	1.51117900	-2.07591500	2.25079000
H	1.80499700	-3.52862100	1.29662300
H	2.96032600	-3.05542400	2.55285300

1.13

Total SCF energy: -1383.91740982 a.u.

Enthalpy at 298K: -1383.341905 a.u.

Gibbs free energy at 298K: -1383.437013 a.u.

Free energy in solution at 298K: -1383.813068 a.u.

Cartesian coordinates

ATOM	X	Y	Z
Ni	-0.00066800	0.37762900	0.70290000
C	-0.75518700	-3.15373300	-1.29347900
C	0.78662100	-3.15961400	-1.27005700
H	-1.18458600	-4.03027400	-0.79273000
H	1.19219300	-4.02007800	-0.72236100
C	-0.01519200	3.07540800	0.58505300
C	-1.23292300	3.53284900	0.04866200
C	1.17841800	3.56747300	0.02576900
C	-1.24993300	4.43044700	-1.01803000
H	-2.17683800	3.17885500	0.44210100
C	1.14922400	4.46472200	-1.04138400
H	2.13963400	3.24244900	0.40187200
C	-0.06211100	4.90537200	-1.57422600
H	-2.20790800	4.75942400	-1.41243100
H	2.08971800	4.82096200	-1.45390700
H	-0.08007600	5.60695500	-2.40325400

C	0.00598800	-1.18726600	-0.16772200
N	-1.08346500	-1.91682200	-0.56705100
N	1.10277000	-1.89876900	-0.58023500
H	-1.15648900	-3.12769600	-2.31477200
H	1.22042100	-3.17637500	-2.27761600
N	0.00698200	2.12767900	1.68903000
C	-1.18930600	2.20936700	2.56519500
H	-1.05518000	1.50847000	3.39001100
H	-1.32029200	3.22856300	2.96241000
H	-2.08276100	1.90525500	2.02204300
C	1.22853500	2.21967900	2.52765400
H	1.35783400	3.23763000	2.92892200
H	1.13012600	1.51042600	3.35025300
H	2.10849000	1.93247400	1.95390700
C	-2.44561000	-1.53130500	-0.35759400
C	-3.12118800	-1.98932000	0.78993300
C	-3.10043100	-0.75223600	-1.33137900
C	-4.47031000	-1.65303800	0.94922300
C	-4.45054400	-0.43839500	-1.13672300
C	-5.13432700	-0.88616400	-0.00715500
H	-5.00121100	-1.99673500	1.83396400
H	-4.96624400	0.16521800	-1.88003100
H	-6.18391700	-0.63702000	0.12783900

C	2.46129200	-1.50389300	-0.36480500
C	3.11747900	-0.73335600	-1.34448100
C	3.13349900	-1.94409200	0.79217000
C	4.46437300	-0.40853000	-1.14599100
C	4.47967200	-1.59720500	0.95467900
C	5.14422600	-0.83779500	-0.00715400
H	4.98055000	0.18888400	-1.89388800
H	5.00740400	-1.92712800	1.84652200
H	6.19126600	-0.58017700	0.13100500
C	-2.35328600	-0.23043500	-2.53455000
H	-1.52350400	0.41385000	-2.21950400
H	-1.92179000	-1.03923600	-3.13705100
H	-3.01697600	0.35048600	-3.18297900
C	-2.39661300	-2.78938500	1.84499100
H	-2.01405500	-3.74068200	1.45401000
H	-1.53424800	-2.22891400	2.22579300
H	-3.06137800	-3.01914200	2.68391100
C	2.37422200	-0.23332800	-2.55929600
H	3.03780500	0.34331100	-3.21163200
H	1.95237700	-1.05384700	-3.15288800
H	1.53761600	0.40914900	-2.25912300
C	2.40858000	-2.73626900	1.85310900
H	1.53979900	-2.17726000	2.22151000

H	2.03570100	-3.69523500	1.47163100
H	3.07019500	-2.95053000	2.69857400

1.8 Notes and References

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(7) Aryl *N*,*N*-diethylcarbamates are readily prepared from aryl alcohols and commercially available *N*,*N*-diethylcarbamoyl chloride. The latter reagent costs approximately $20–25 per mol ($0.15–$0.20 per gram) from common chemical suppliers, such as Alfa Aesar and Aldrich Chemical Co., Inc.

(8) Other phenol-based amination partners cannot be used effectively for directed metallation / functionalization. Specifically, aryl sulfonates and pivalates are not suitable substrates,

whereas aryl methyl ethers are poor metalation substrates. Aryl sulfamates can be used in *ortho*-lithiation, but the sulfamate directing group ability is approximately 20x less compared to carbamates; see ref. 13f.

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(13) For C–C bond forming processes involving aryl pivalates, methyl ethers, or sulfamates, see: (*a*) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc*. **2008**, *130*, 14422–14423. (*b*) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468–

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(14) This finding is likely not surprising since C–N and C–C bond forming processes would proceed through fairly different mechanistic pathways (although the initial oxidative addition step would be common to both processes).

(15) SIPr•HCl (**1.4**), is commercially available (CAS# 258278-25-0).

(16) Although these conditions are broadly useful, aminations of certain substrates proceed even at ambient temperature. For example, *N,N*-diethyl phenylcarbamate undergoes coupling with morpholine in 24 h at 23 °C using 5 mol% catalyst (~90% conversion based on ^{1}H NMR analysis with internal standard).

(17) For certain substrates, the use of standard reaction conditions led to slow conversion to aminated product. In these cases, higher catalyst, ligand, and/or amine loadings could be used to expedite reaction progress as indicated in Tables 1.1–1.3. The formation of undesired byproducts is not typically observed.

(18) The carbamate derived from 2,6-dimethylphenol fails to undergo amination under our reaction conditions.

(19) Attempts to effect the amination of primary aliphatic amines, such as benzyl amine and *n*-butylamine, led to the recovery of starting material, albeit with some non-specific decomposition.

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(23) (*a*) Li, Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815–8823. (*b*) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352–6363.

(24) All geometries were optimized using the B3LYP functional and a mixed basis set of SDD for Ni and 6-31G(d) for other atoms. A larger base set, SDD for Ni and 6-311 + G(2d,p) for other atoms was used for single point energy calculations and solvation energy corrections using the CPCM model. Single point calculations using the B3P86 and B3PW91 functionals were also performed and give comparable results to the B3LYP calculations (see section 1.7.3). The isopropyl groups on the SIPr ligand were replaced with methyls in the calculations to reduce computational cost. All calculations were performed using Gaussian 09. Gaussian 09, revision B.01, M. J. Frisch *et al.* Gaussian, Inc., Wallingford CT, 2010.

(25) The Ni-catalyzed amination of aryl carbamates is not inhibited by the presence of galvinoxyl radical or BHT; thus, we propose that a Ni(I)/Ni(III) catalytic cycle is likely not operative. For examples where additives such as galvinoxyl radical or BHT are used to probe the presence of Ni(I) intermediates, see: (*a*) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319–6332. (*b*) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547–7560. (*c*) Kochi, J. *Pure Appl. Chem.* **1980**, *52*, 571–605. (*d*) Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139–2144. (*e*) Kamigaito, M.; Ando; T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689–3745. (*f*) Zhou, J. Ph.D. Thesis, Massachusetts Institute of Technology, 2005. (*g*) Phapale, V. B.; Guisan-Ceinos, M.; Bunuel, E.; Cardenas, D. J. *Chem. Eur. J.* **2009**, *15*, 12681–12688. For recent examples of catalytic reactions that proceed via Ni(I)/Ni(III) cycles, see: (*h*) Zhang, K.; Conda-Sheridan, M.; Cooke, S. R.; Louie, J. *Organometallics* **2011**, *30*, 2546–2552. (*i*) Miyazaki, S.; Koga, Y.; Matsumoto, T.; Matsubara, K. *Chem. Commun.* **2010**, *46*, 1932–1934.

(26) The monoligated oxidative addition is suggested as a preferred pathway in most Pd- and Ni-catalyzed oxidative additions with phosphine and NHC ligands: (*a*) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 4746–4748. (*b*) Stambuli, J. P.; Buehl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346–9347. (*c*) Stambuli, J. P.; Incarvito, C. D.; Buehl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184–1194. (*d*) Yamashita, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5344–5345. (*e*) Green, J. C.; Herbert, B. J.; *J. Organomet. Chem.* **2005**, *690*, 6054–6067. (*f*) Gooßen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *Organometallics* **2006**, *25*, 54–67. (*g*) Sergeev, A. G.; Zapf, A.; Spannenberg, A.; Beller, M. *Organometallics* **2008**, *27*, 297–300. (*h*) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141–8154. (*i*) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 3387–3389.

(27) We calculate that $Ni(NHC)_2$ is 22.6 kcal/mol more stable in solution compared to **1.5**. However, increasing the concentration of the NHC ligand does not suppress the amination reaction (see section 1.7.3), suggesting that $Ni(NHC)_2$ is not the catalyst resting state. Although not presently well-understood, it is likely that the dissociation of one NHC ligand from $Ni(NHC)_2$ is facilitated by other species in the reaction mixture. For similar hypotheses involving NHC dissociation from $Ni(NHC)_2$ complexes, see: (*a*) Zimmerman, P. M.; Paul, A.; Zhang, Z.; Musgrave, C. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 2201–2205. (*b*) Zimmerman, P. M.; Paul, A.; Musgrave, C. B. *Inorg. Chem.* **2009**, *48*, 5418–5433.

(28) An alternative pathway involving three-centered oxidative addition transition state requires much higher activation energy than the five-centered pathway via **TS 1.6**. Similar effects are observed in oxidative additions of carbamates and sulfamates with $Ni(PR_3)$; see ref. 23b.

(29) Similar effects of ligands have been reported previously: (*a*) Corbet, J. P.; Mignani, G. *Chem. Rev*. **2006**, *106*, 2651–2710. (*b*) Ahlquist, M.; Norrby, P. *Organometallics* **2007**, *26*, 550–553. (*c*) Marion, N.; Nolan, S. P.; *Acc. Chem. Res.* **2008**, *41*, 1440–1449. (*d*) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596.

(30) Since the mechanism involves charged species, the energetics of the deprotonation step is expected to be strongly affected by solvation effects. We have tested a number of DFT methods and basis sets with the CPCM solvation model. These results (see section 1.7.3) all indicate that deprotonation is not the rate-limiting step. This also agrees with the experimental observations that the choice of bases does not affect the rate of the reaction. For a related study of effects of bases in Pd-catalyzed aminations, see: Shekhar, S.; Hartwig, J. F. *Organometallics* **2006**, *26*, 340–351.

(31) Kozuch, S.; Shaik, S. *Acc. Chem. Res.* **2011**, *44*, 101–110.

(32) The energy difference (–19.4 kcal/mol) between complex **1.5** at the beginning and end of the Figure 1.2 plot represents the energy released in the catalytic cycle. For a pertinent discussion, see ref 31.

(33) Competition experiments between phenol-derived carbamates and sulfamates indicate that sulfamates are inherently more reactive than carbamates in both the nickel-catalyzed Suzuki–Miyaura coupling and amination. The preference for sulfamate coupling seen in the conversion of **1.18→1.20** is likely heightened because of the carbamate's *ortho* substituent.

(34) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598–15599.

(35) Desmarets, C.; Champagne, B.; Walcarius, A.; Bellouard, C.; Omar-Amrani, R.; Ahajji, A.; Fort, Y.; Schneider, R. *J. Org. Chem*. **2006**, *71*, 1351–1361.

(36) Gao, C.; Yang, L. *J. Org. Chem.* **2008**, *73*, 1624–1627.

(37) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133–1135.

(38) Guo, D.; Huang, H.; Xu, J.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, *10*, 4513–4516.

(39) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029–3036.

(40) Li, J.; Cui, M.; Yu, A.; Wu, Y. *J. Organomet. Chem.* **2007**, *692*, 3732–3742.

(41) Fasani, E.; Tilocca, F.; Protti, S.; Merli, D.; Albini, A. *Org. Biomol. Chem.* **2008**, *6*, 4634–4642.

(42) Wagaw, S.; Buchwald, S. L. *J. Org. Chem*. **1996**, *61*, 7240–7241.

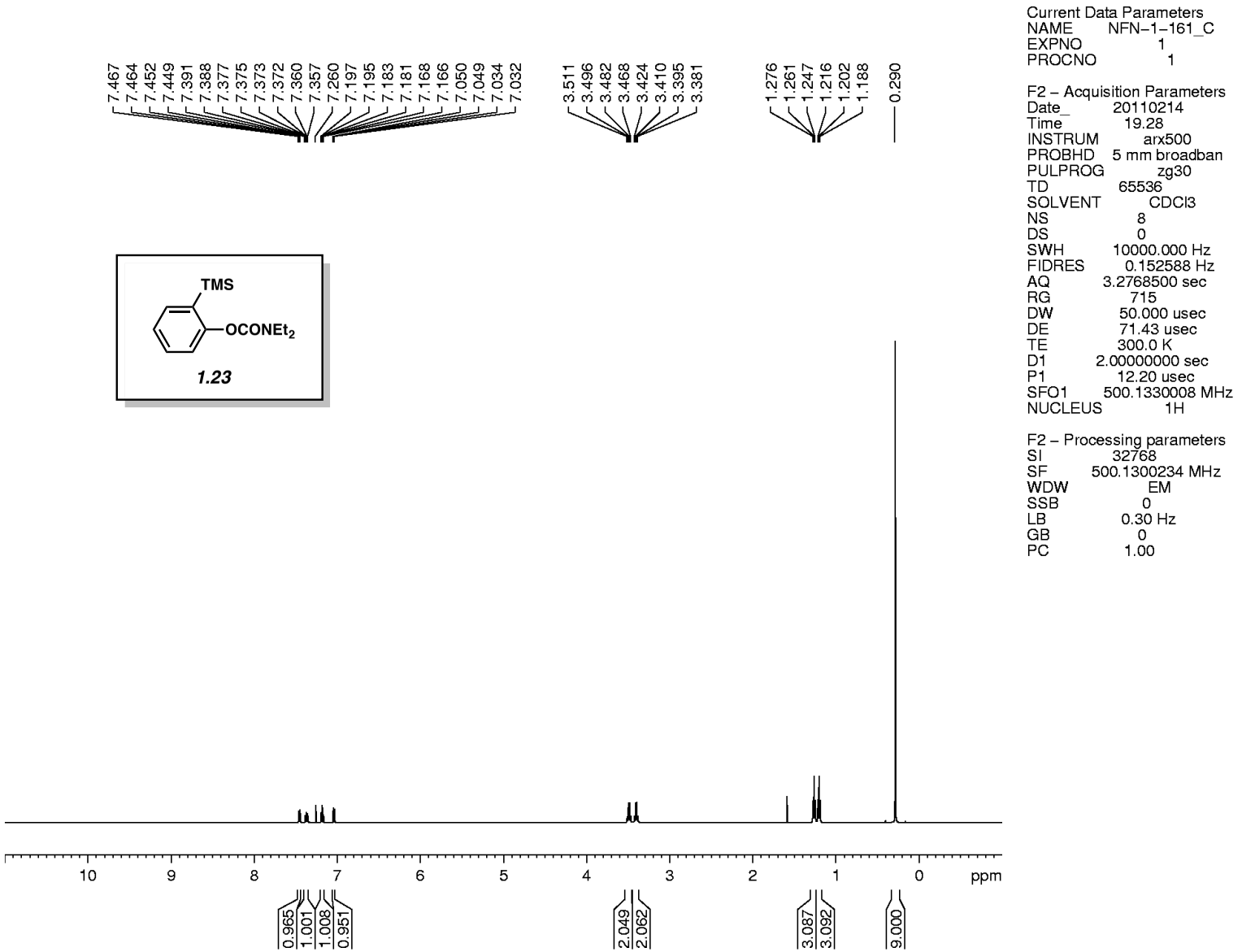
(43) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 2929–2932.

(44) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829–12842.

Spectra Relevant to Chapter One:

Nickel-Catalyzed Amination of Aryl Carbamates and

Sequential Site-Selective Cross-Couplings



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PROCNO 1

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PROBHD 5 mm broadban
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 715
DW 50.000 usec
DE 71.43 usec
TE 300.0 K
D1 2.00000000 sec
P1 12.20 usec
SFO1 500.1330008 MHz
NUCLEUS 1H

F2 – Processing parameters
SI 32768
SF 500.1300234 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure 1.6. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.23**.

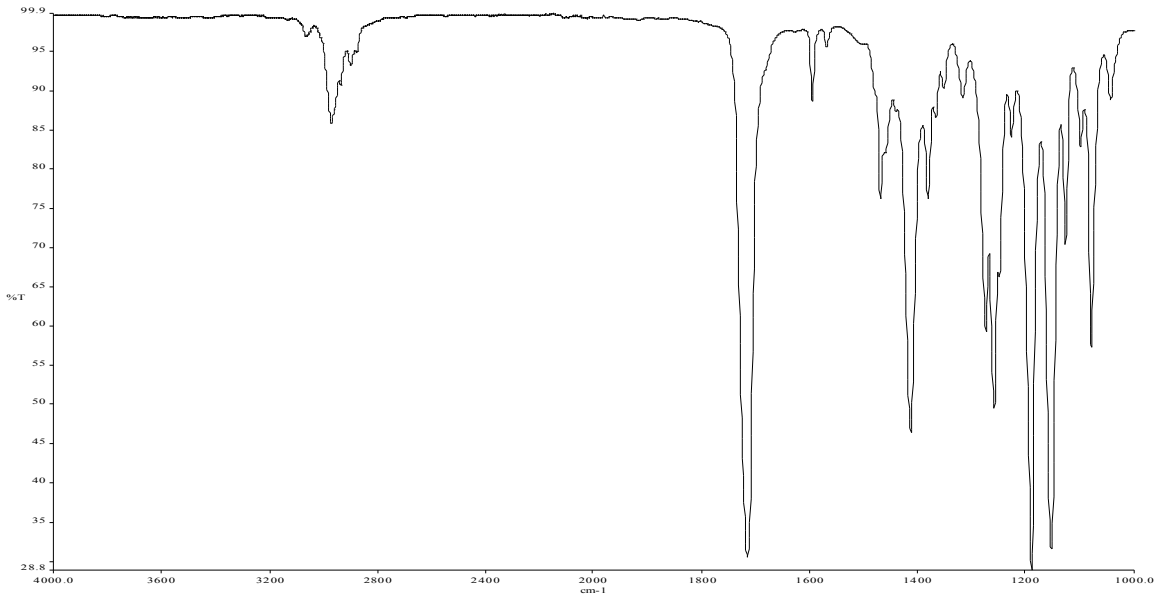


Figure 1.7. Infrared spectrum of compound **1.23**.

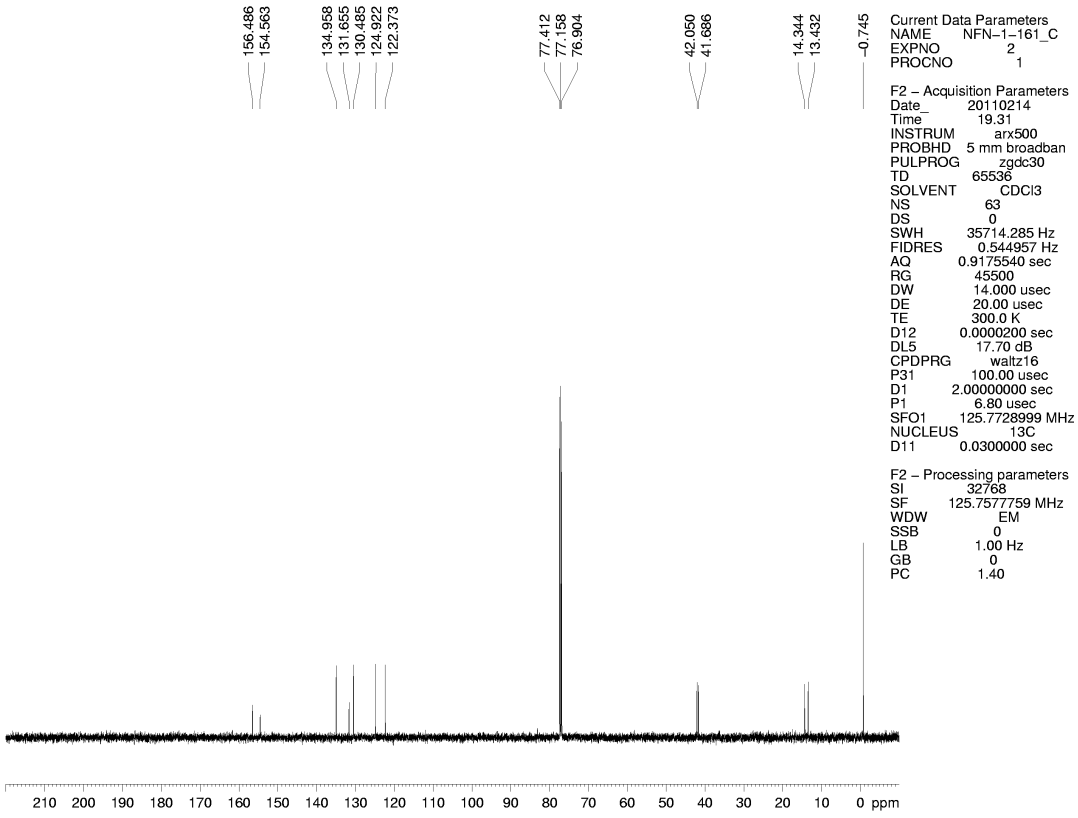
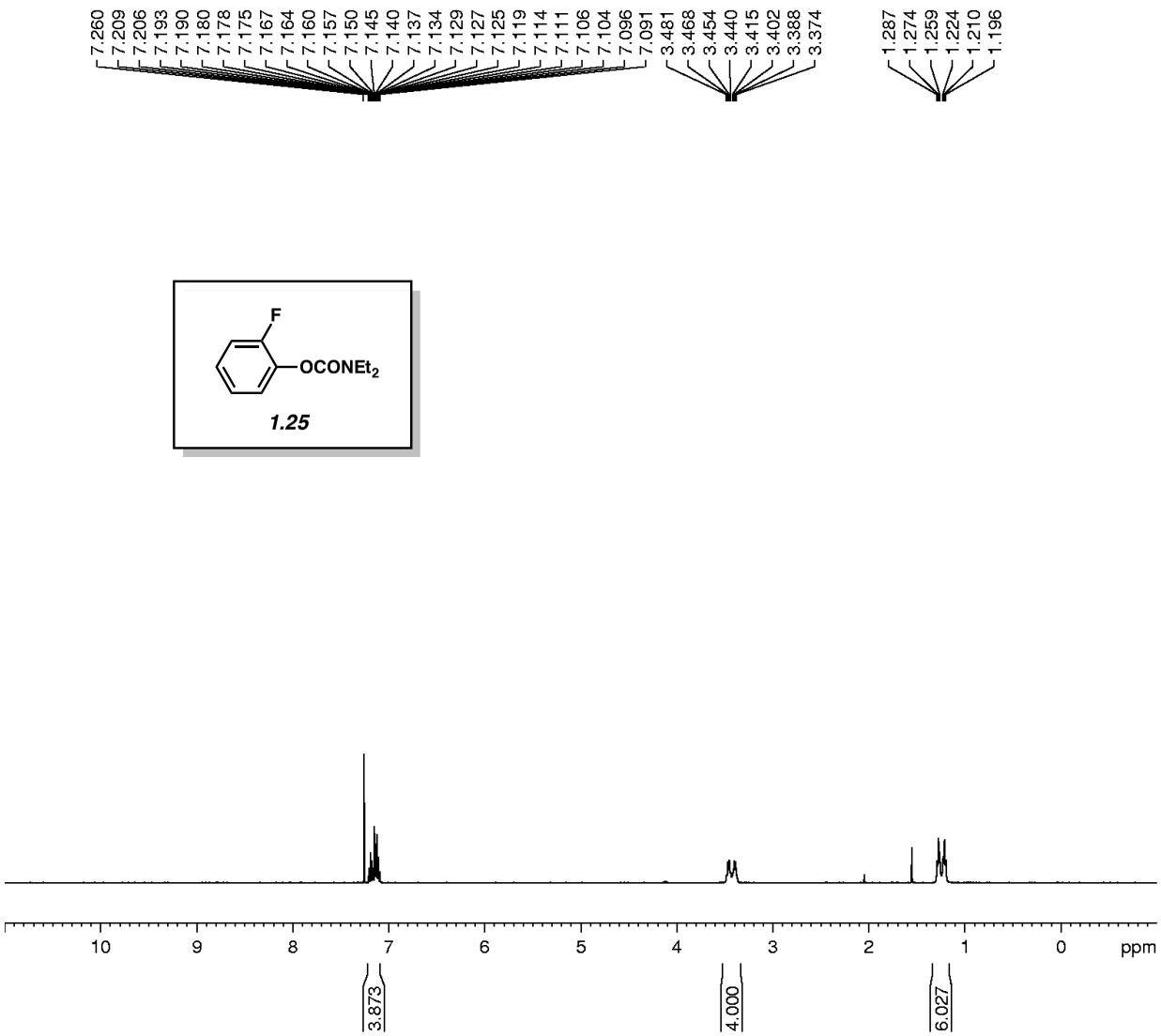


Figure 1.8. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.23**.



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PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 2860
DW 50.000 usec
DE 71.43 usec
TE 300.0 K
D1 2.00000000 sec
P1 11.00 usec
SFO1 500.1330008 MHz
NUCLEUS 1H

F2 – Processing parameters
SI 32768
SF 500.1300237 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Figure 1.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.25**.

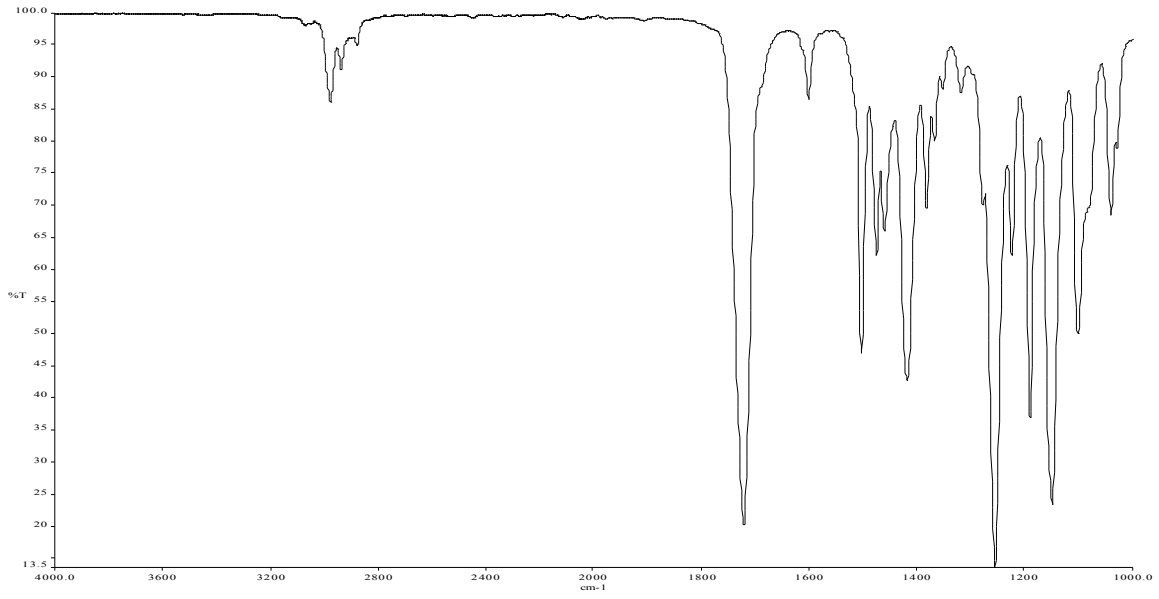


Figure 1.10. Infrared spectrum of compound **1.25**.

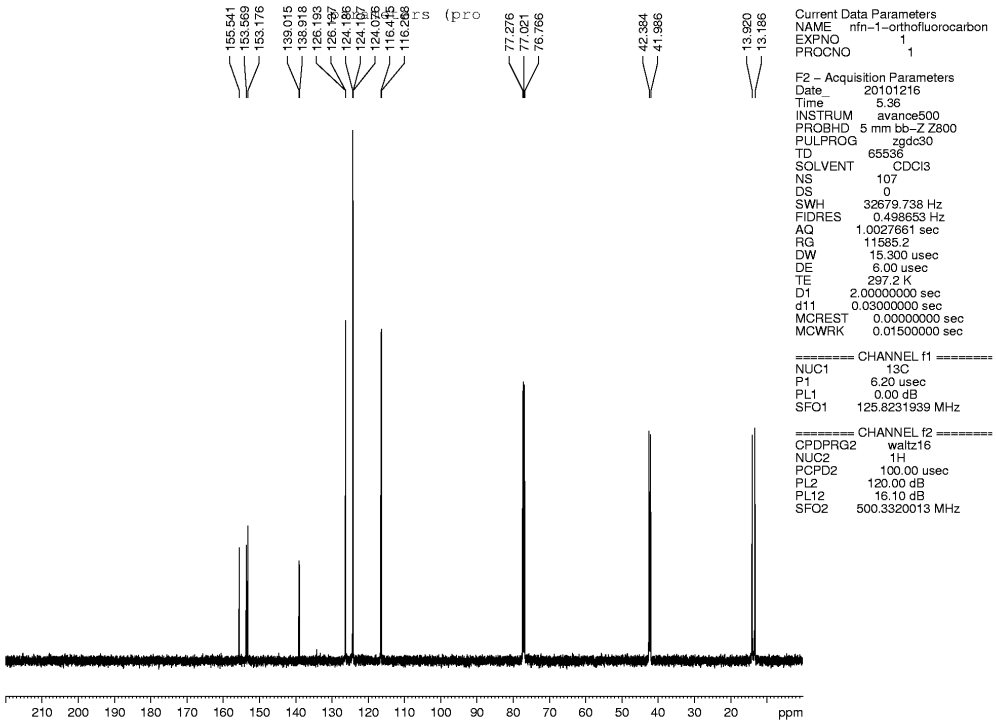
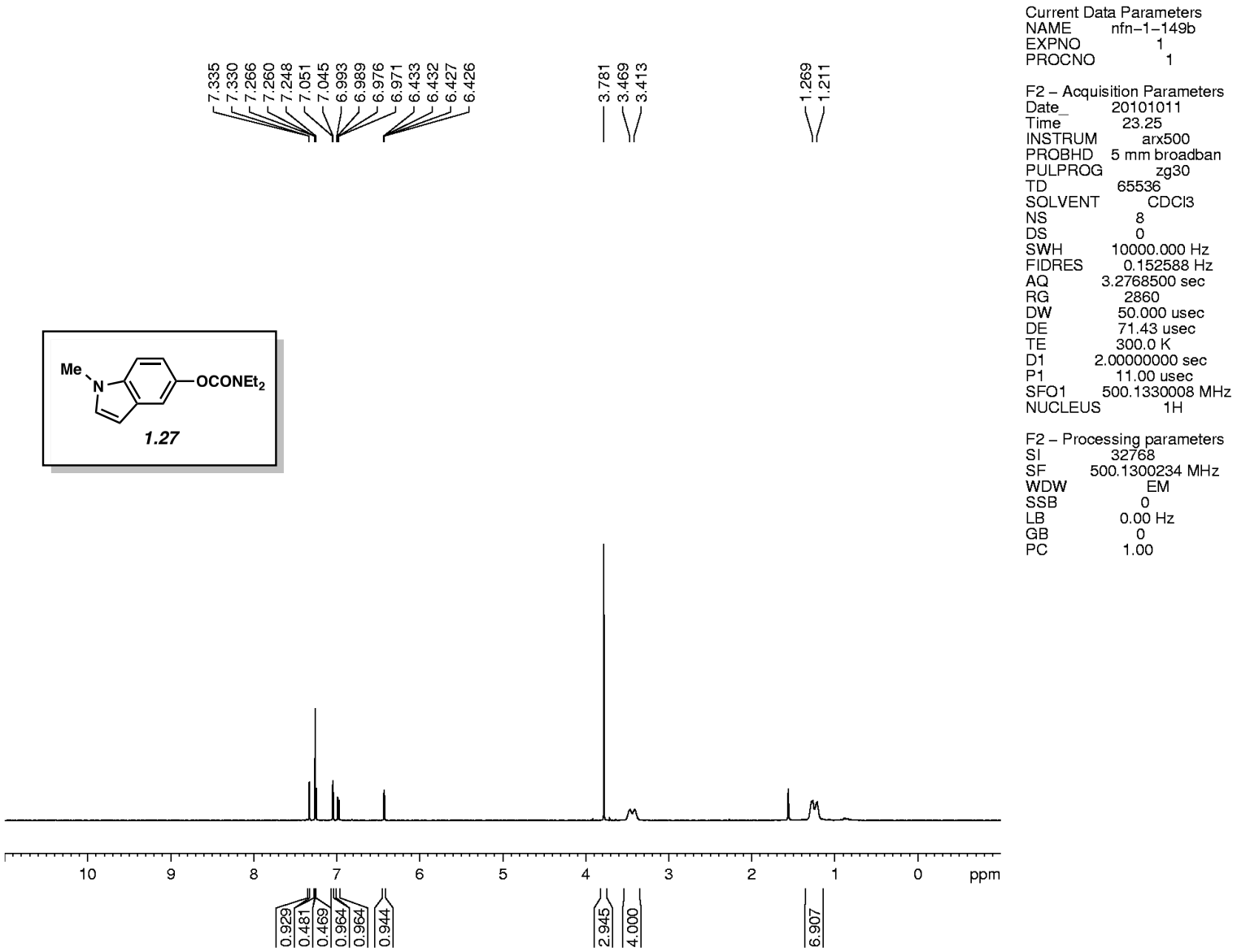


Figure 1.11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.25**.



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PROCNO 1

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PROBHD 5 mm broadban
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 2860
DW 50.000 usec
DE 71.43 usec
TE 300.0 K
D1 2.00000000 sec
P1 11.00 usec
SFO1 500.1330008 MHz
NUCLEUS 1H

F2 – Processing parameters
SI 32768
SF 500.1300234 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Figure A1.12. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.27**.

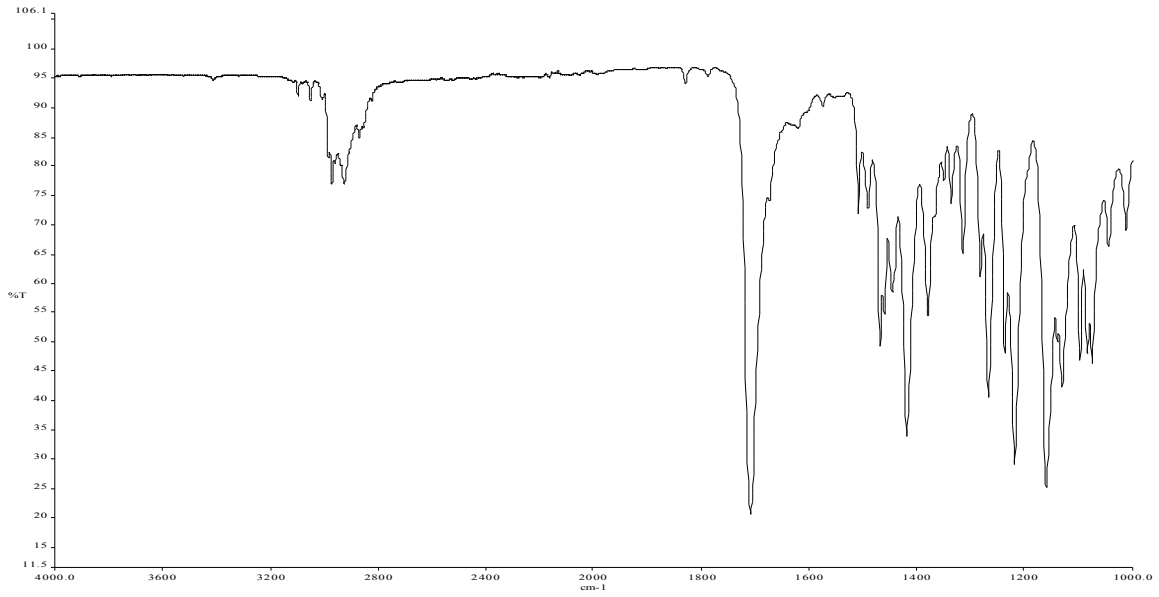


Figure 1.13. Infrared spectrum of compound **1.27**.

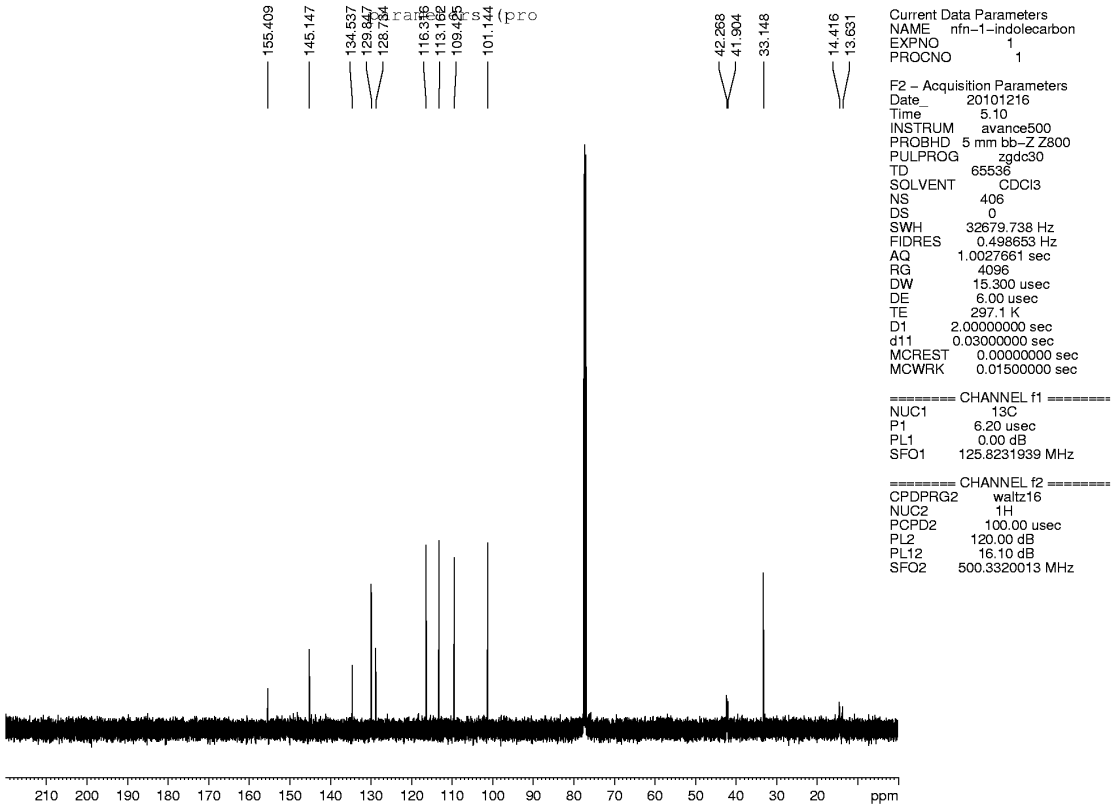


Figure 1.14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.27**.

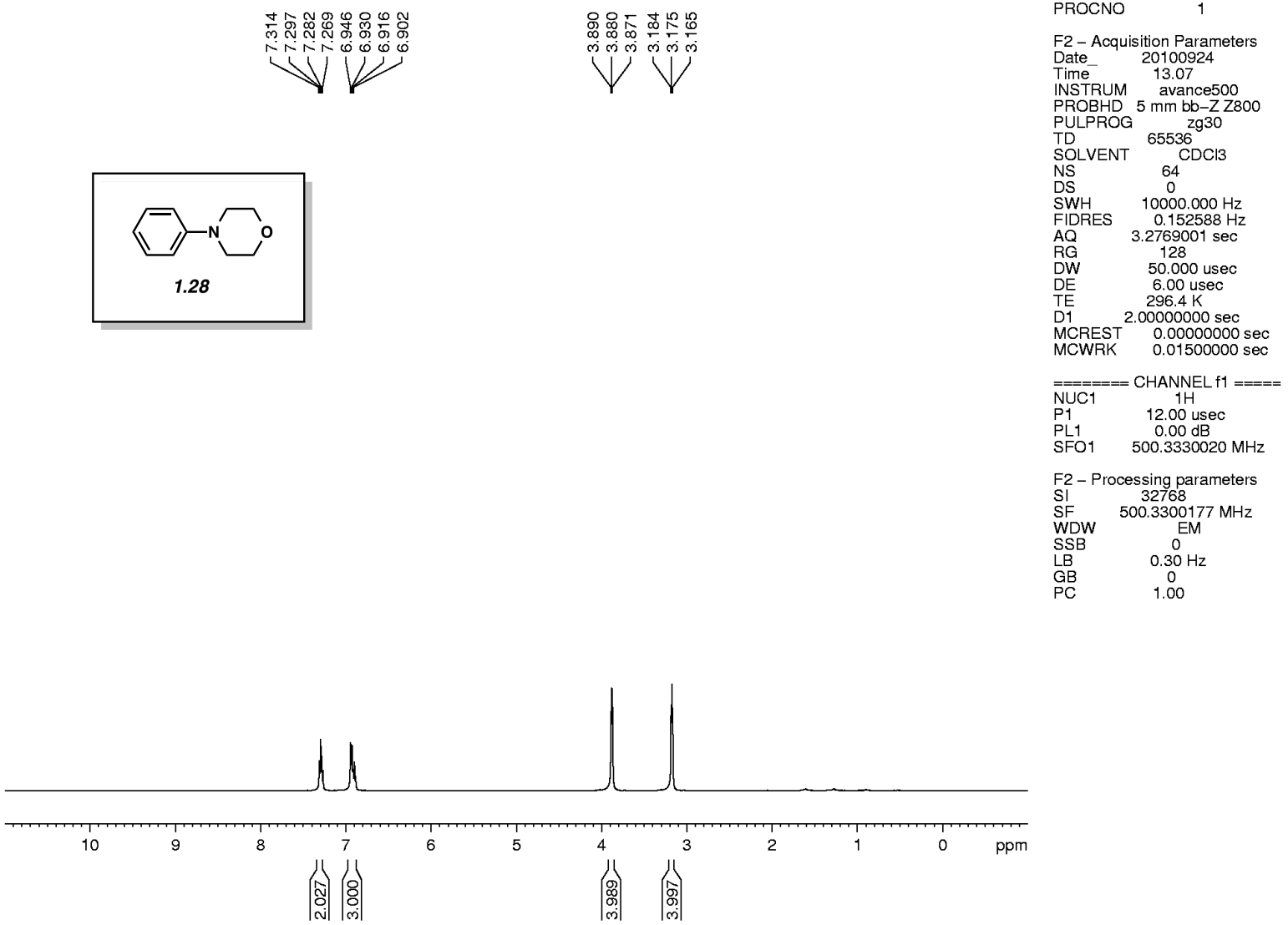


Figure 1.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.28**.

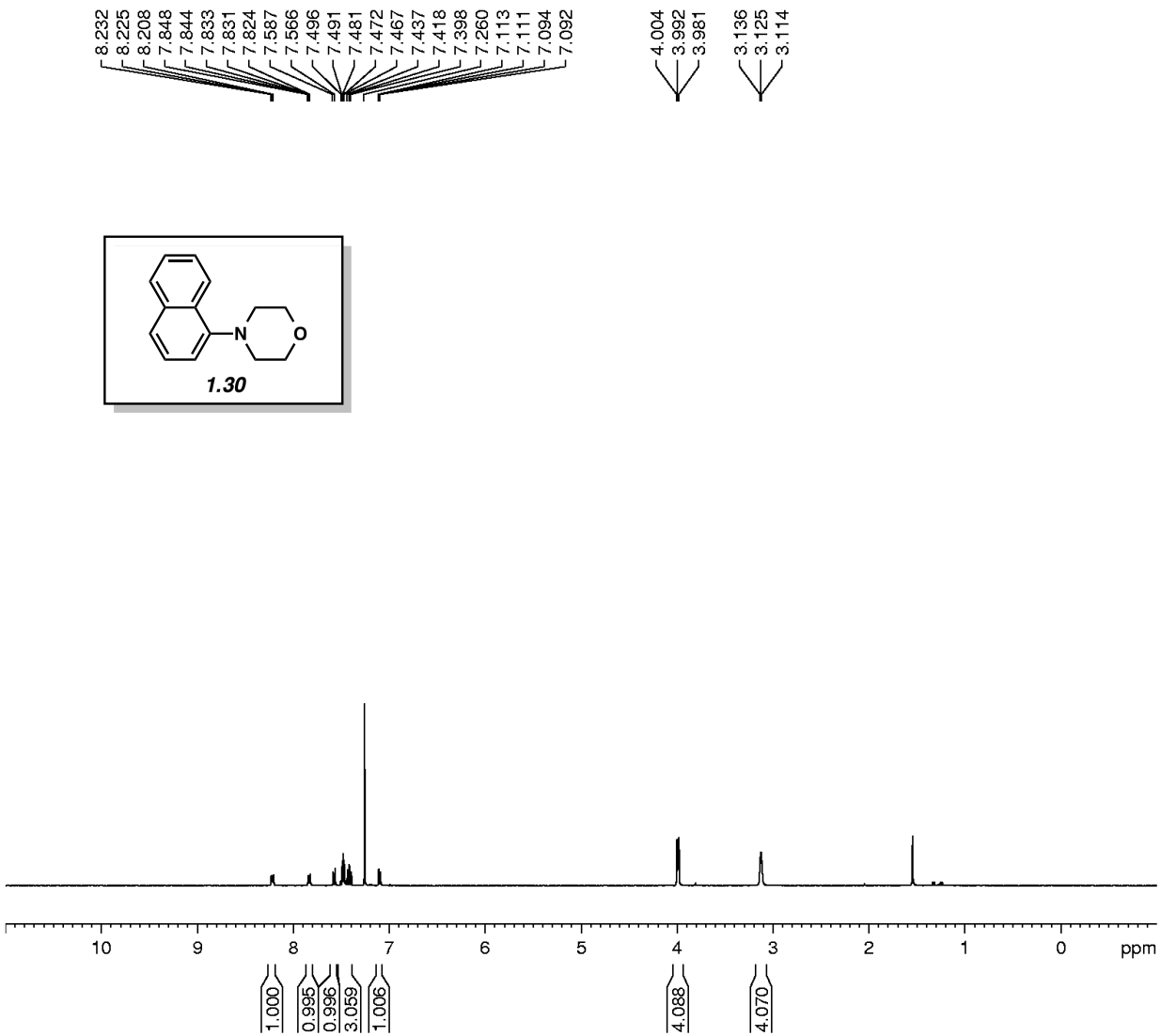


Figure 1.16. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1.30**.

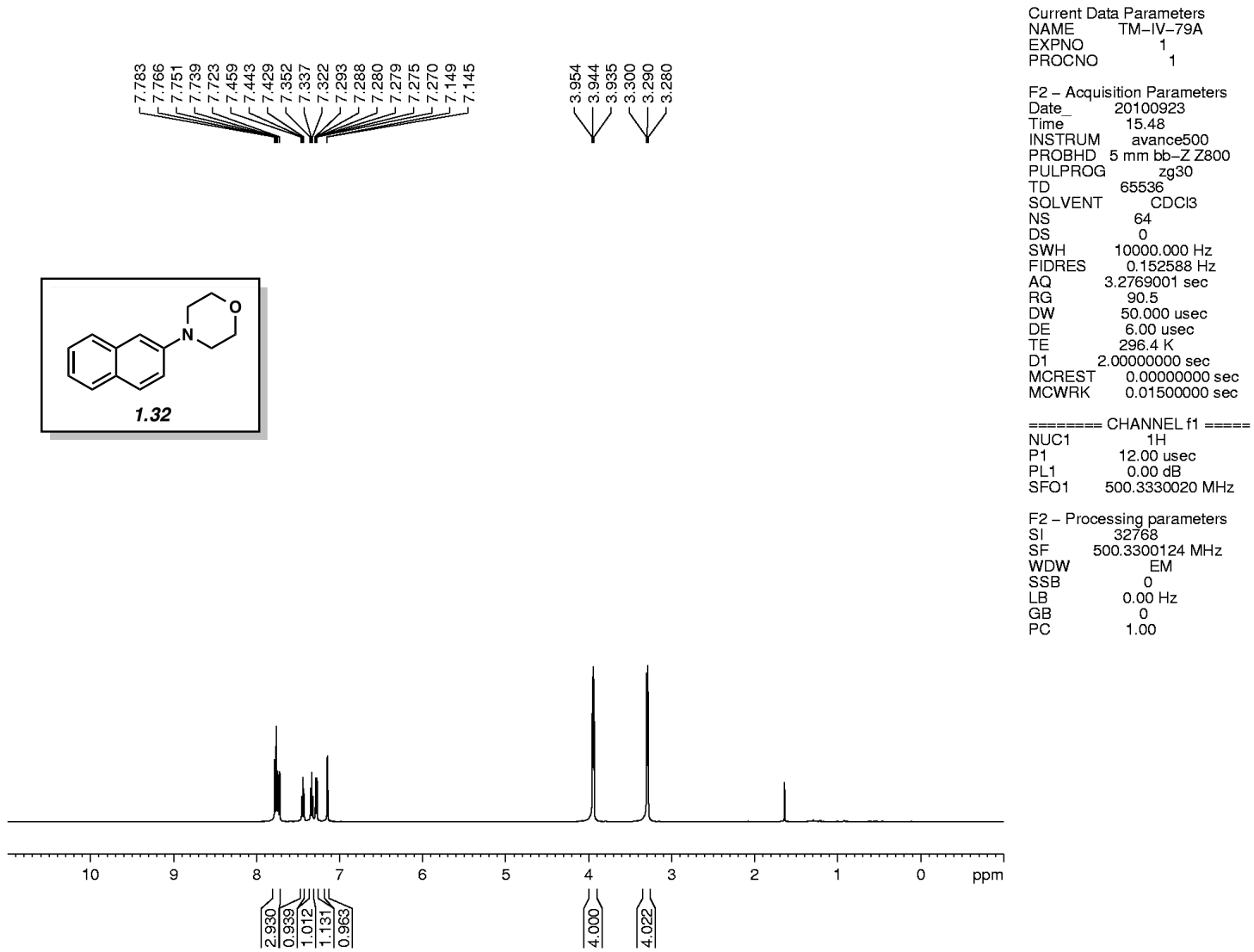
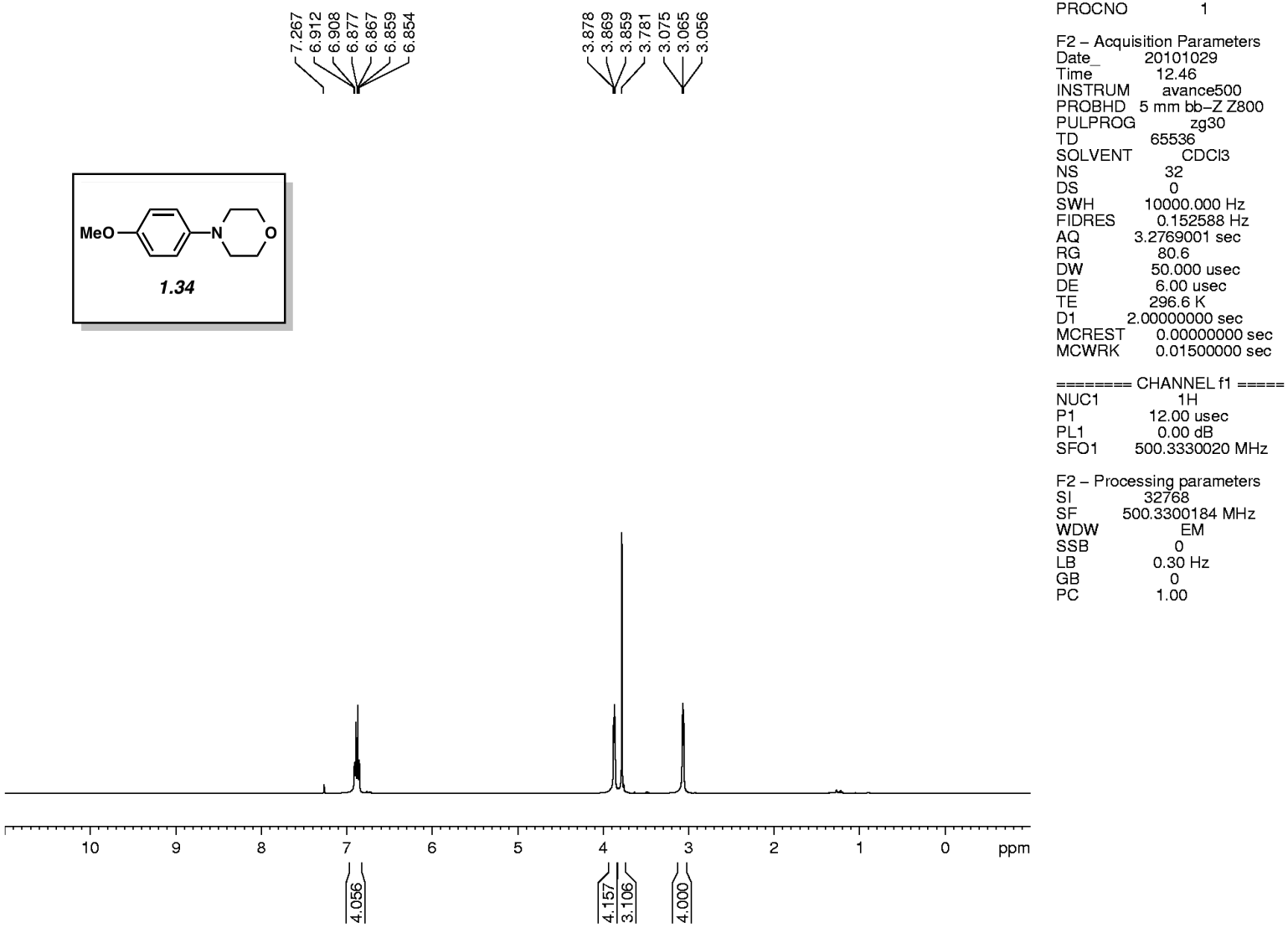


Figure 1.17. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.32**.



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PROCNO 1

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TD 65536
SOLVENT CDCl3
NS 32
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SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 80.6
DW 50.000 usec
DE 6.00 usec
TE 296.6 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
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SF 500.3300184 MHz
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LB 0.30 Hz
GB 0
PC 1.00

Figure 1.18. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.34**.

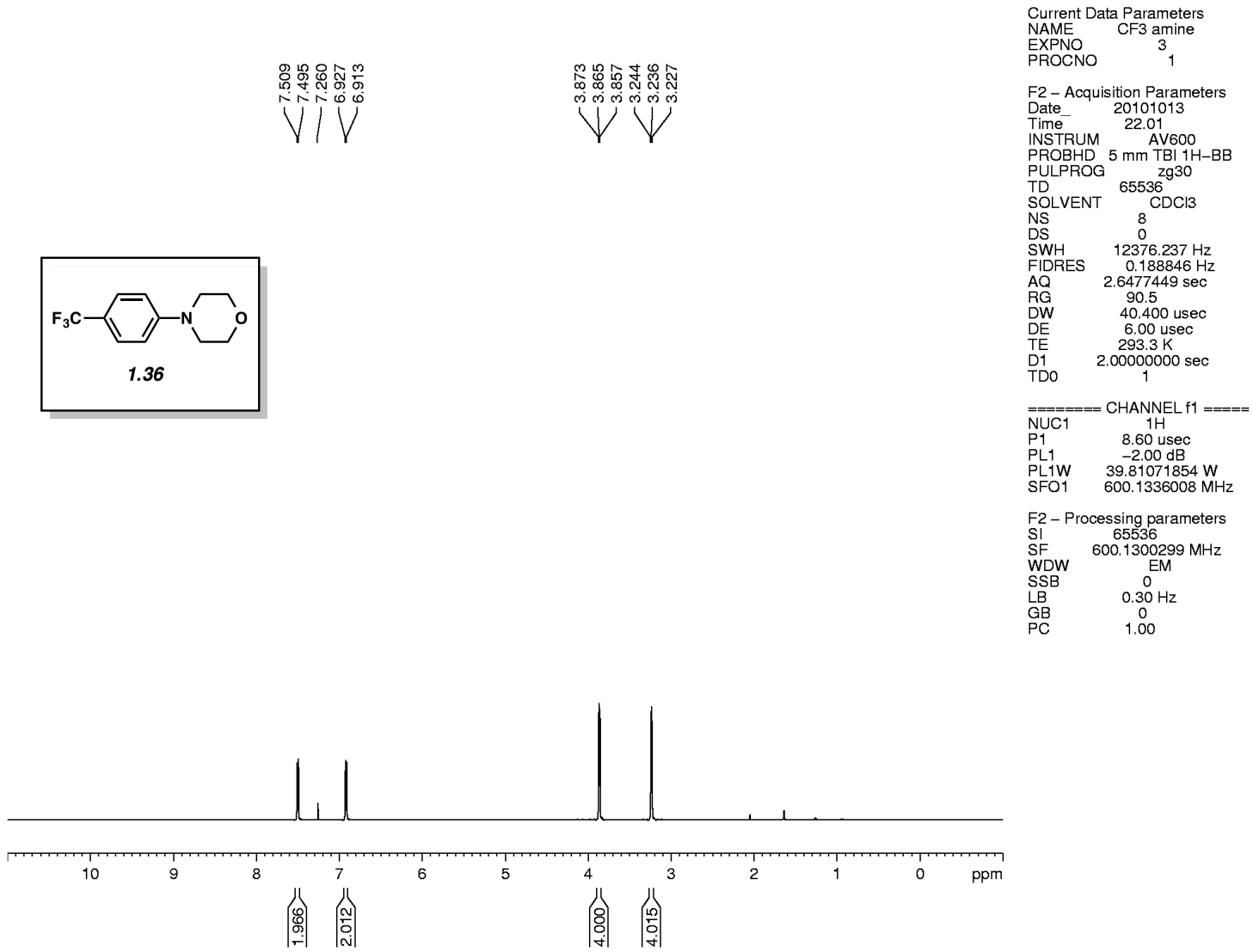
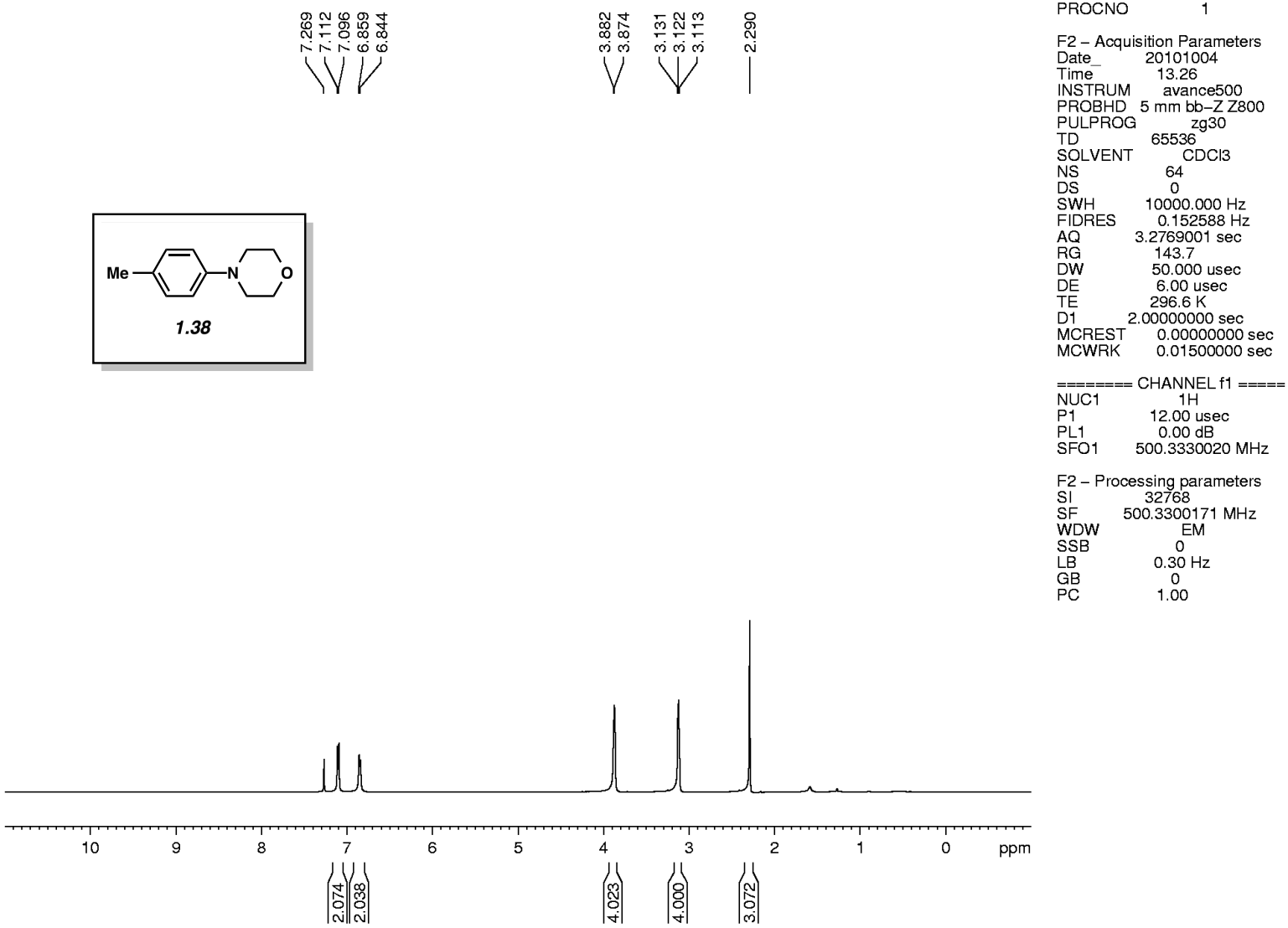


Figure 1.19. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.36**.



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PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 64
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 143.7
DW 50.000 usec
DE 6.00 usec
TE 296.6 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
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P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
SI 32768
SF 500.3300171 MHz
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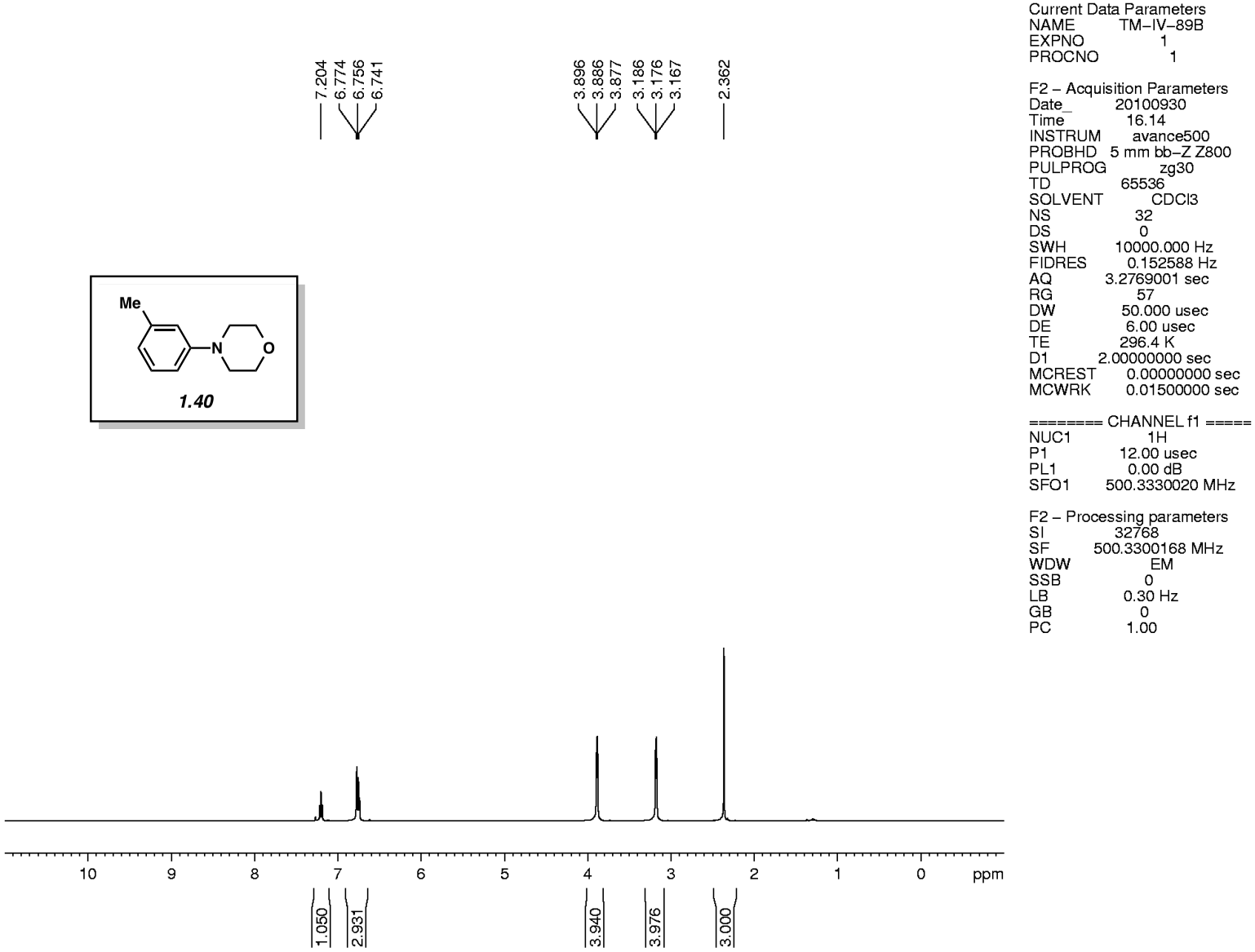
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure 1.20. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.38**.



Current Data Parameters
NAME TM–IV–89B
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PROCNO 1

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TD 65536
SOLVENT CDCl3
NS 32
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 57
DW 50.000 usec
DE 6.00 usec
TE 296.4 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
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PC 1.00

Figure 1.21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.40**.

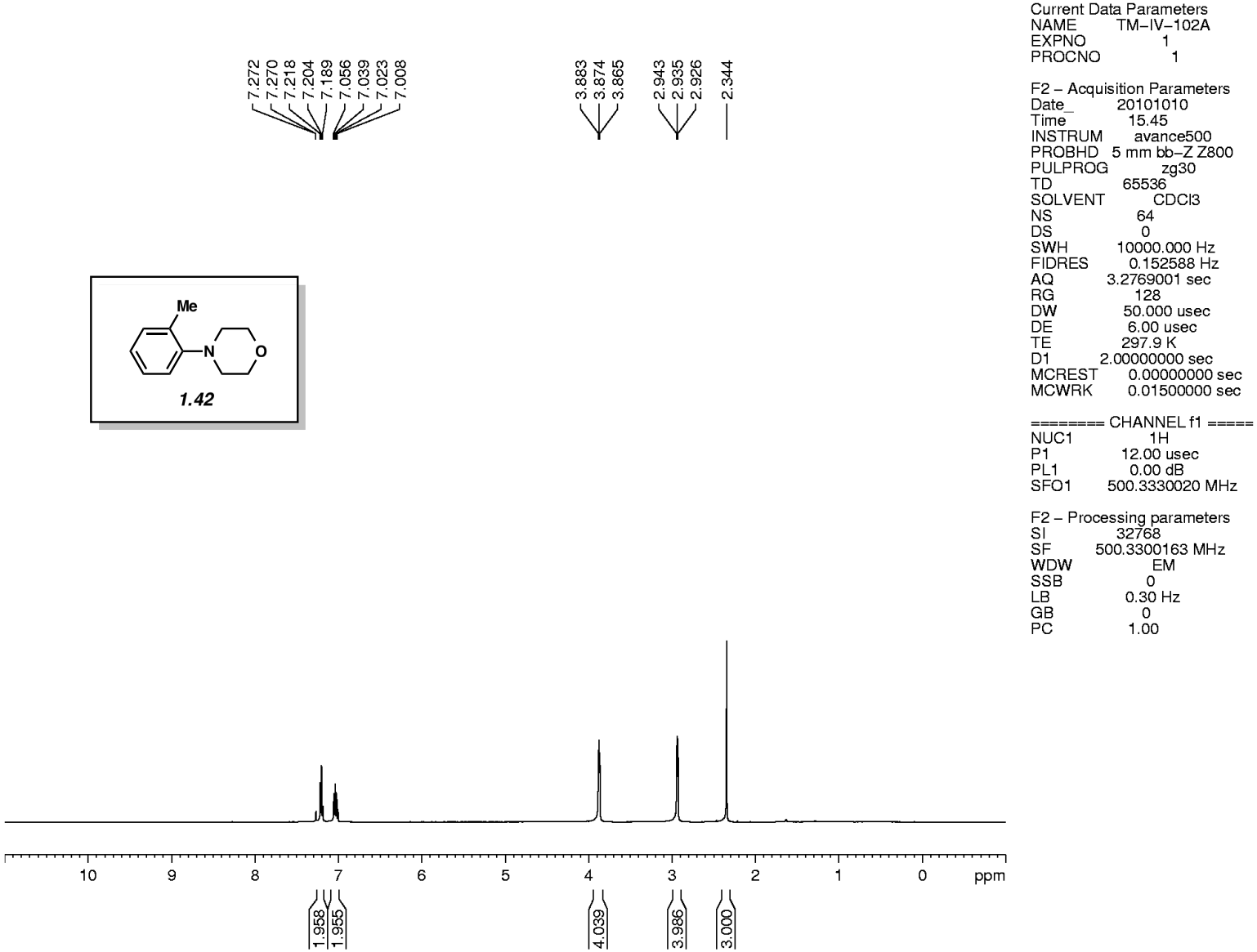


Figure 1.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.42**.

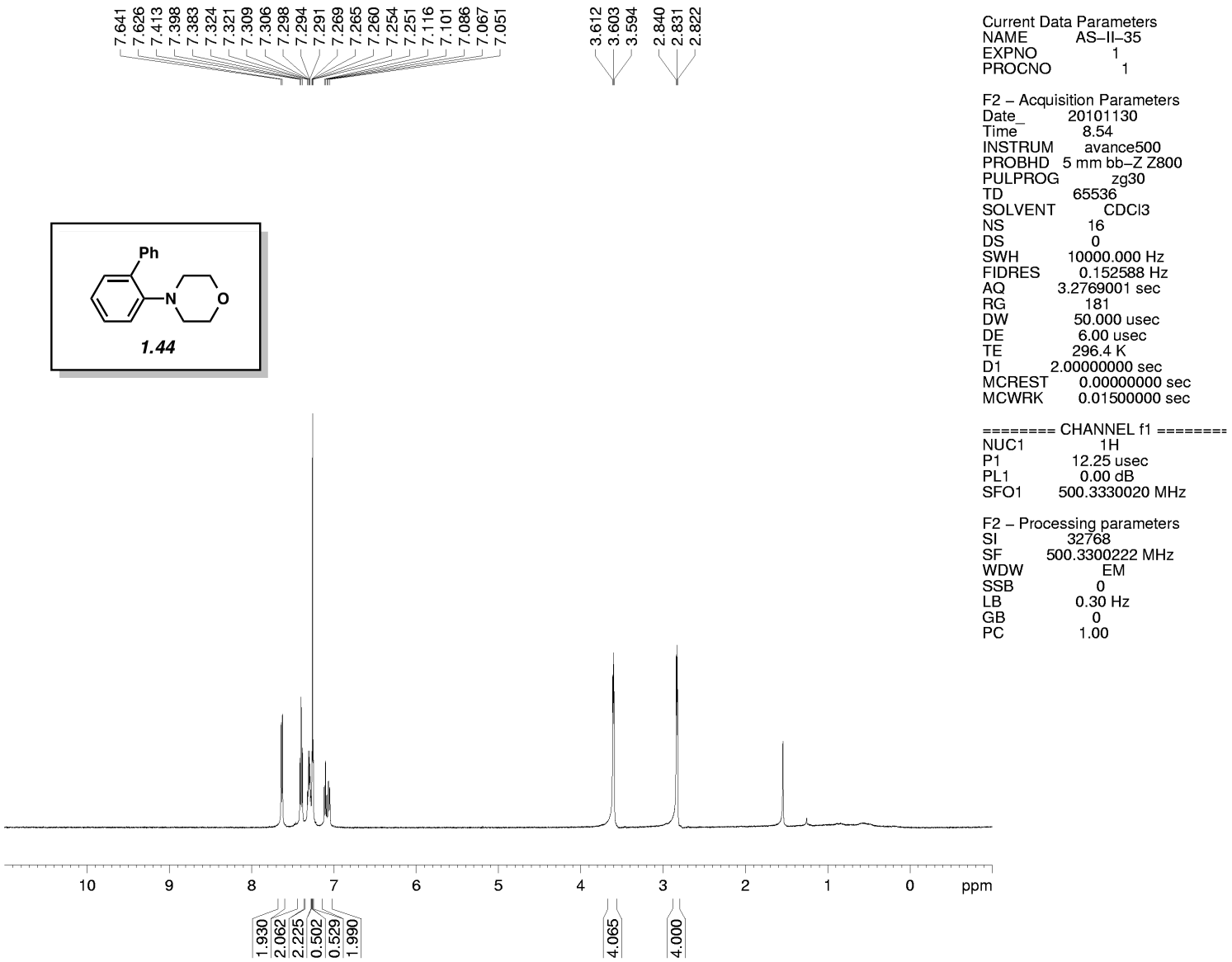


Figure 1.23. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.44**.

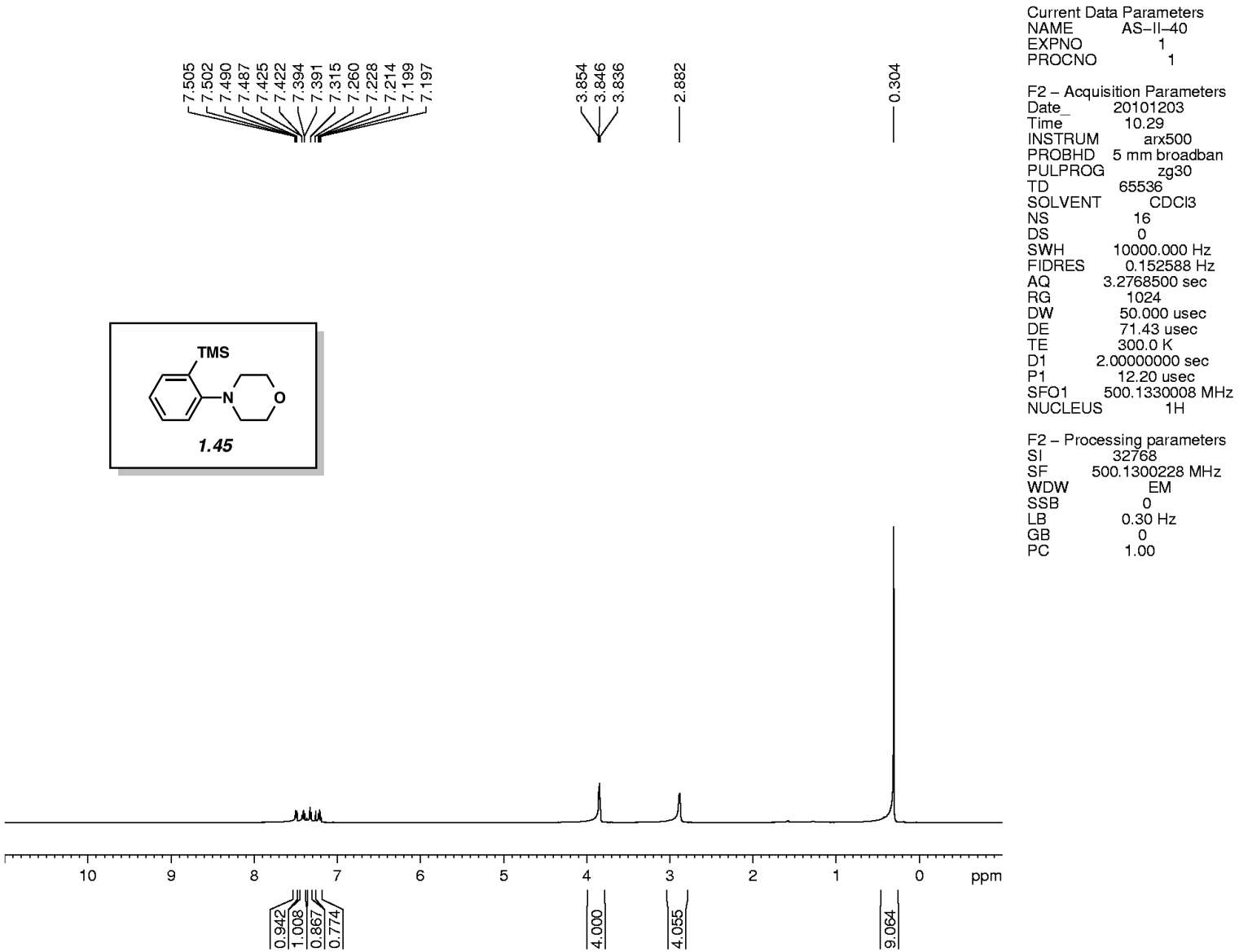


Figure 1.24. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.45**.

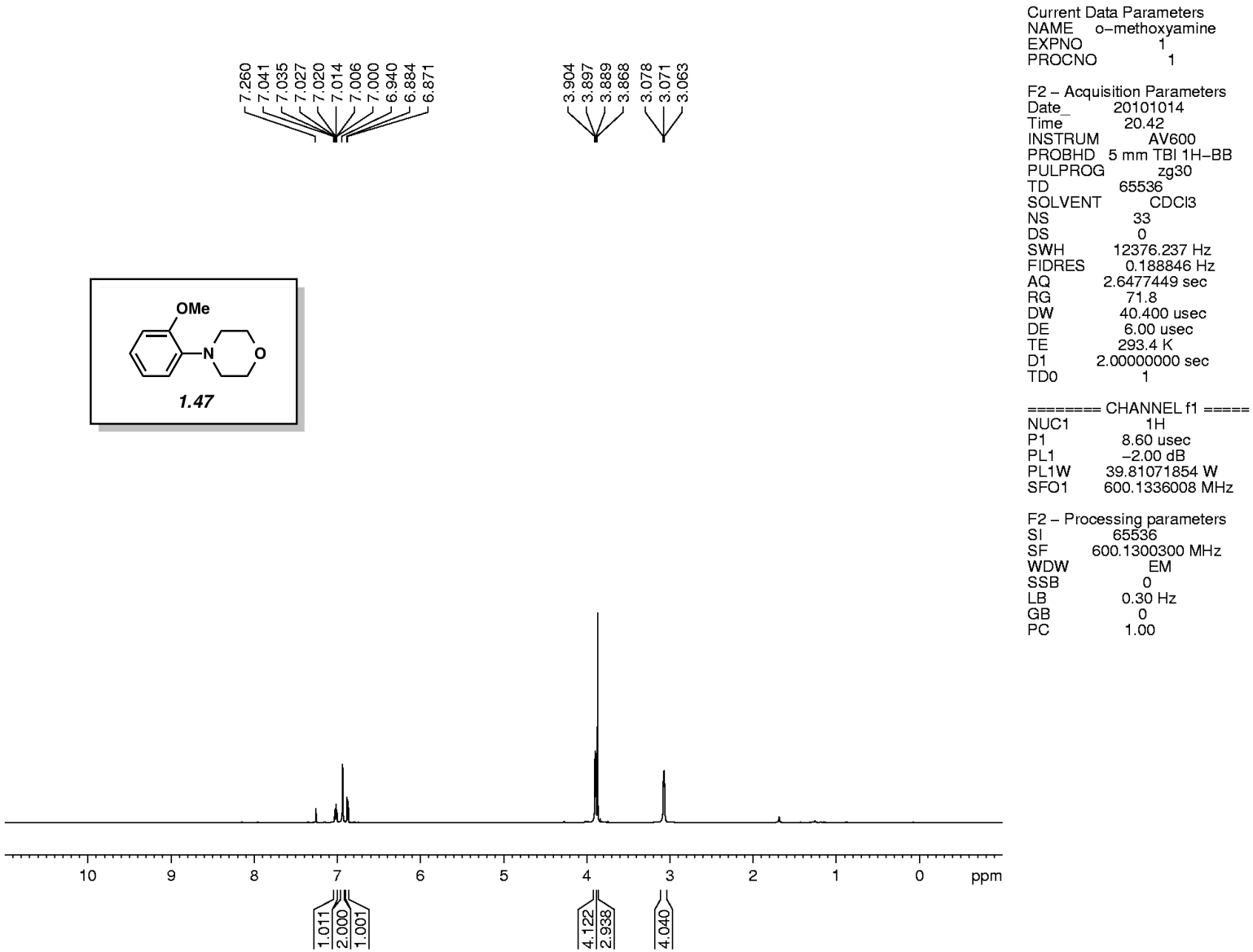


Figure 1.25. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.47**.

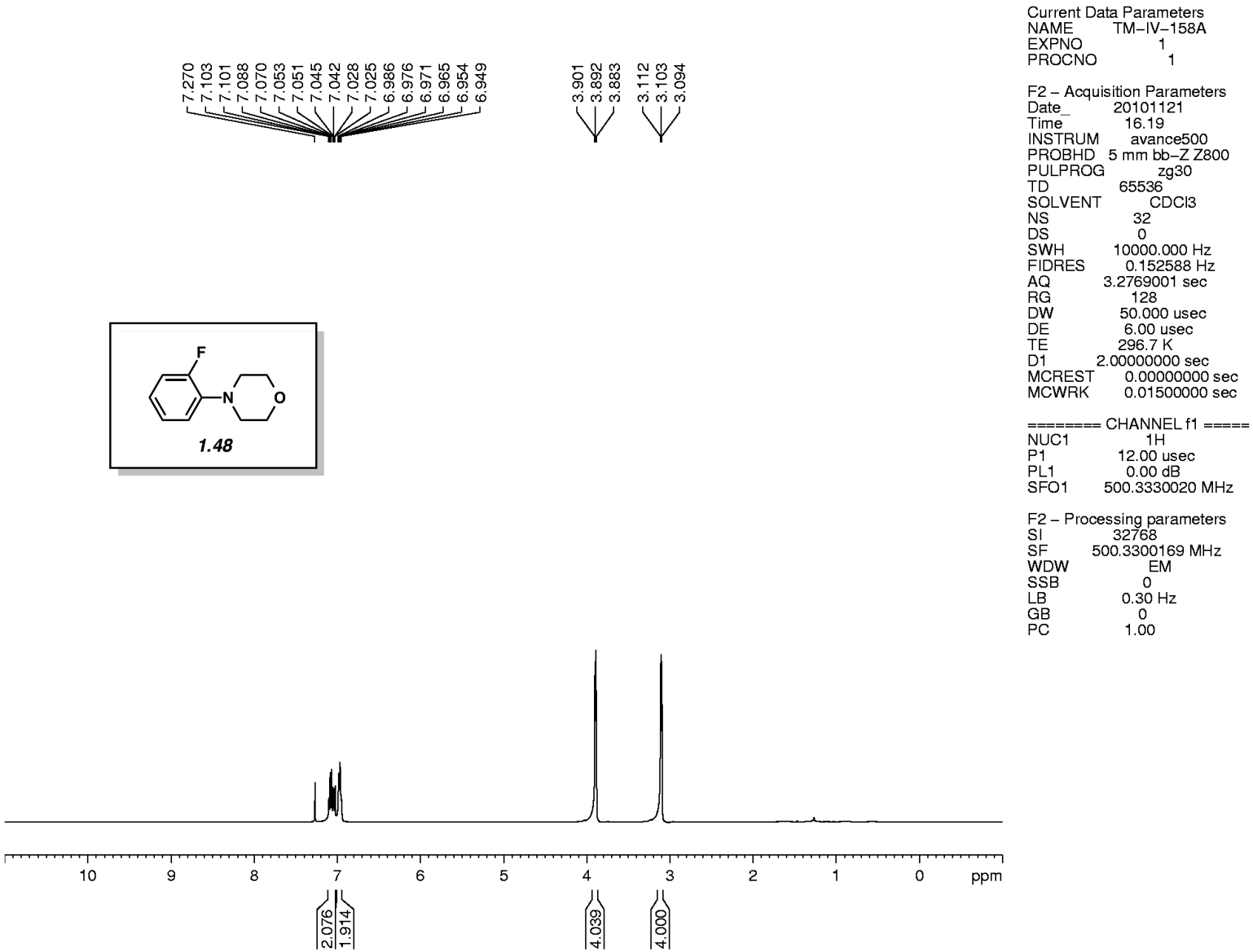
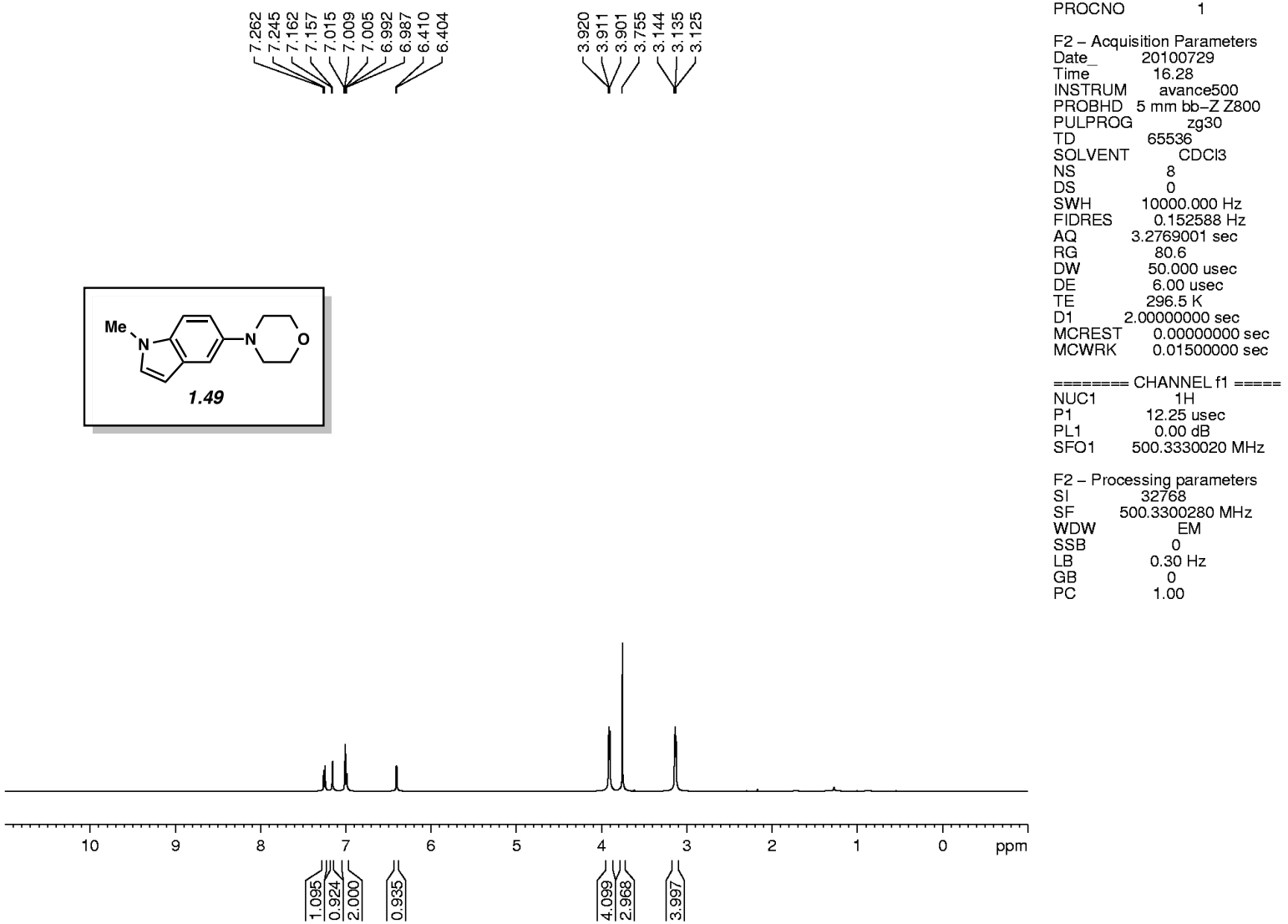


Figure 1.26. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.48**.



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PROCNO 1

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TD 65536
SOLVENT CDCl3
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2769001 sec
RG 80.6
DW 50.000 usec
DE 6.00 usec
TE 296.5 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =====
NUC1 1H
P1 12.25 usec
PL1 0.00 dB
SFO1 500.3330020 MHz

F2 – Processing parameters
SI 32768
SF 500.3300280 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Figure 1.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.49**.

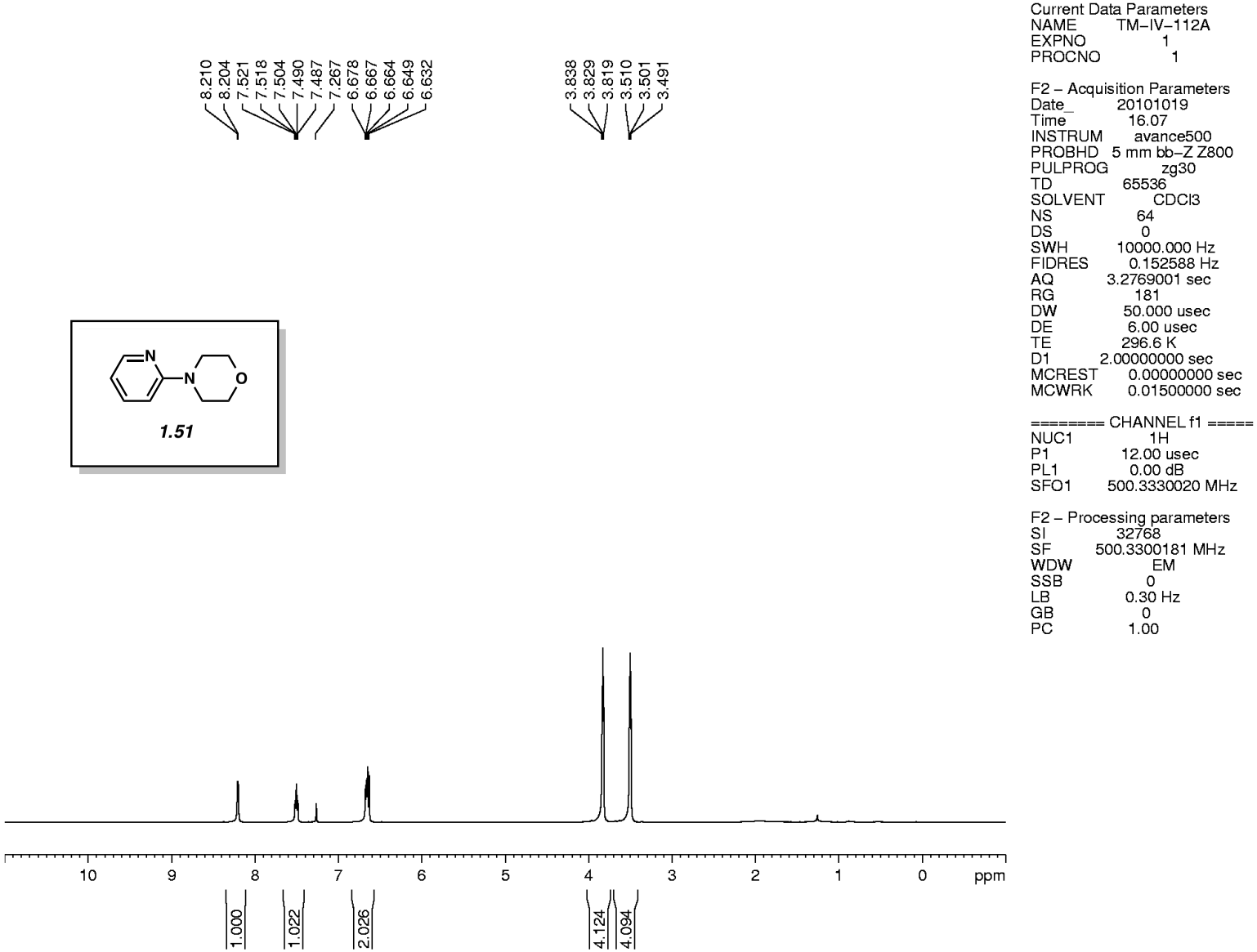

Figure 1.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.51**.

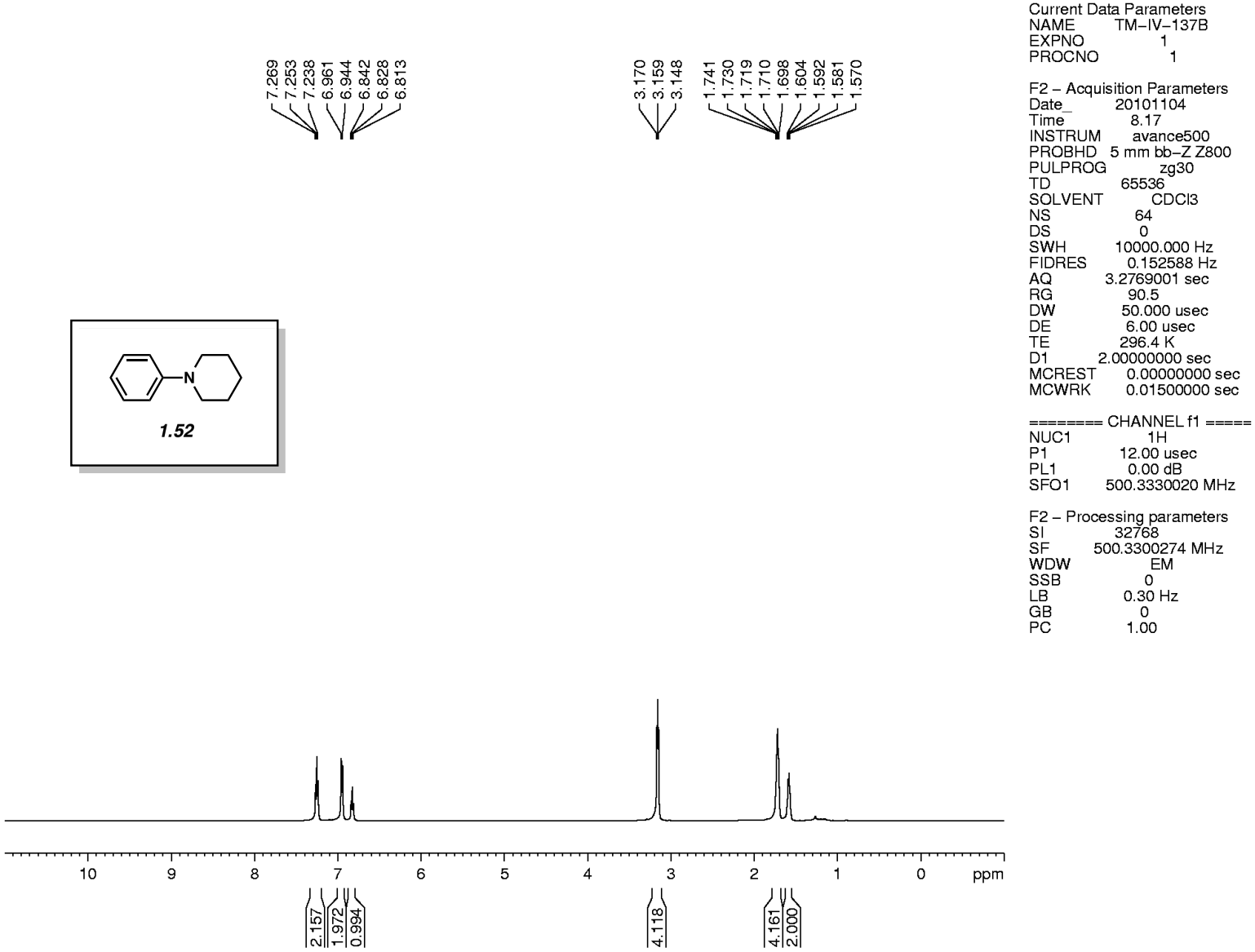

Figure 1.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.52**.

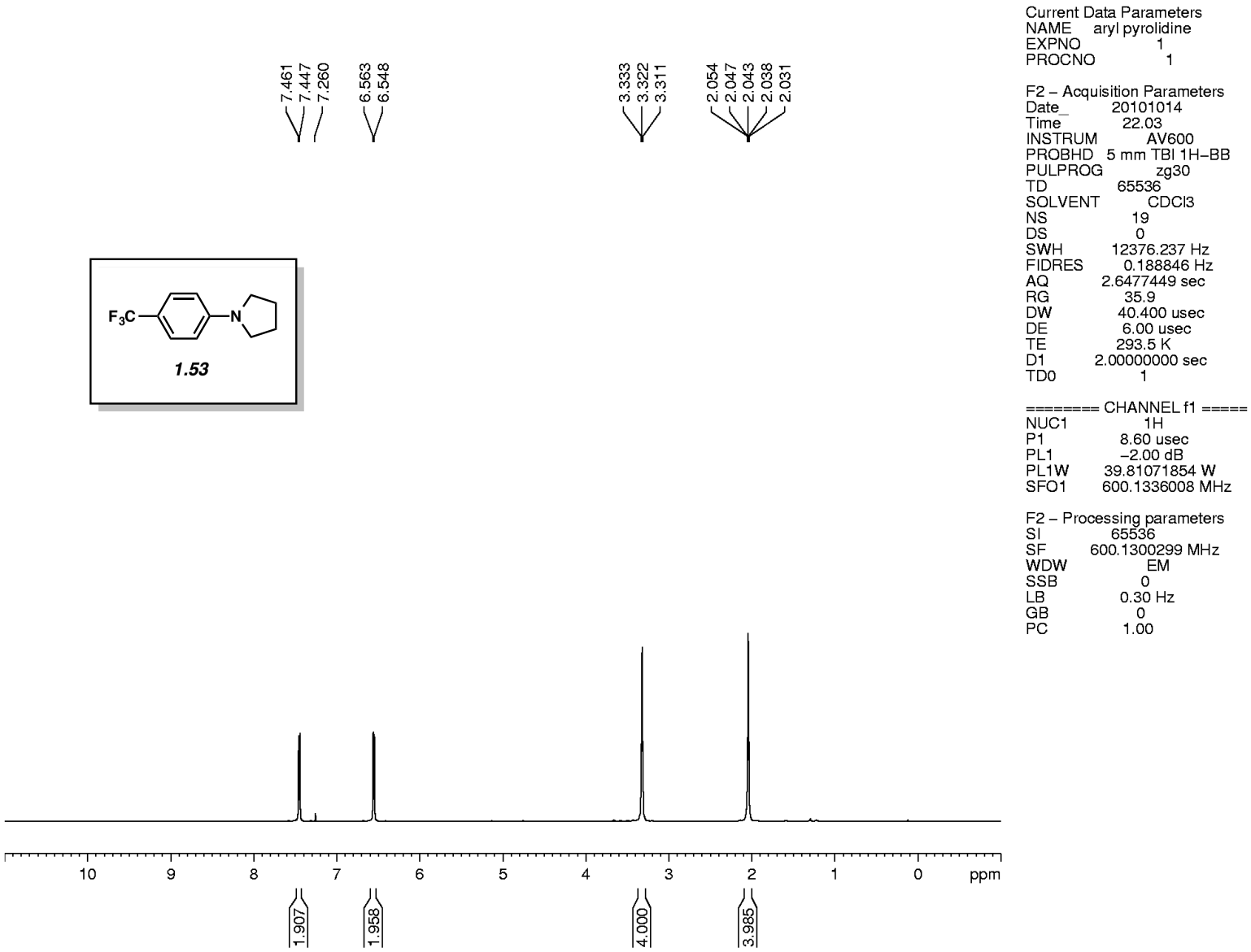

Figure 1.30. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.53**.

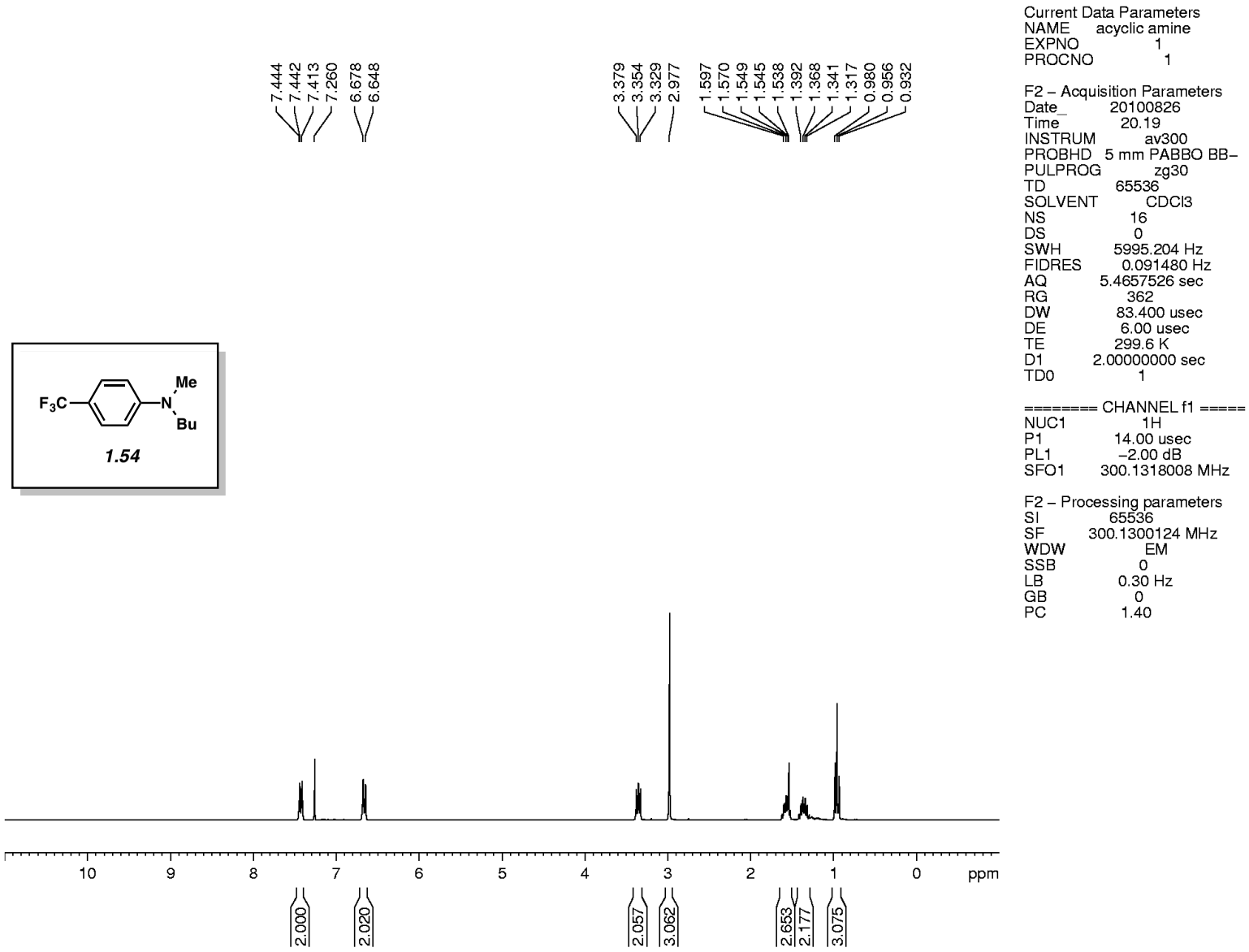

Figure 1.31. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **1.54**.

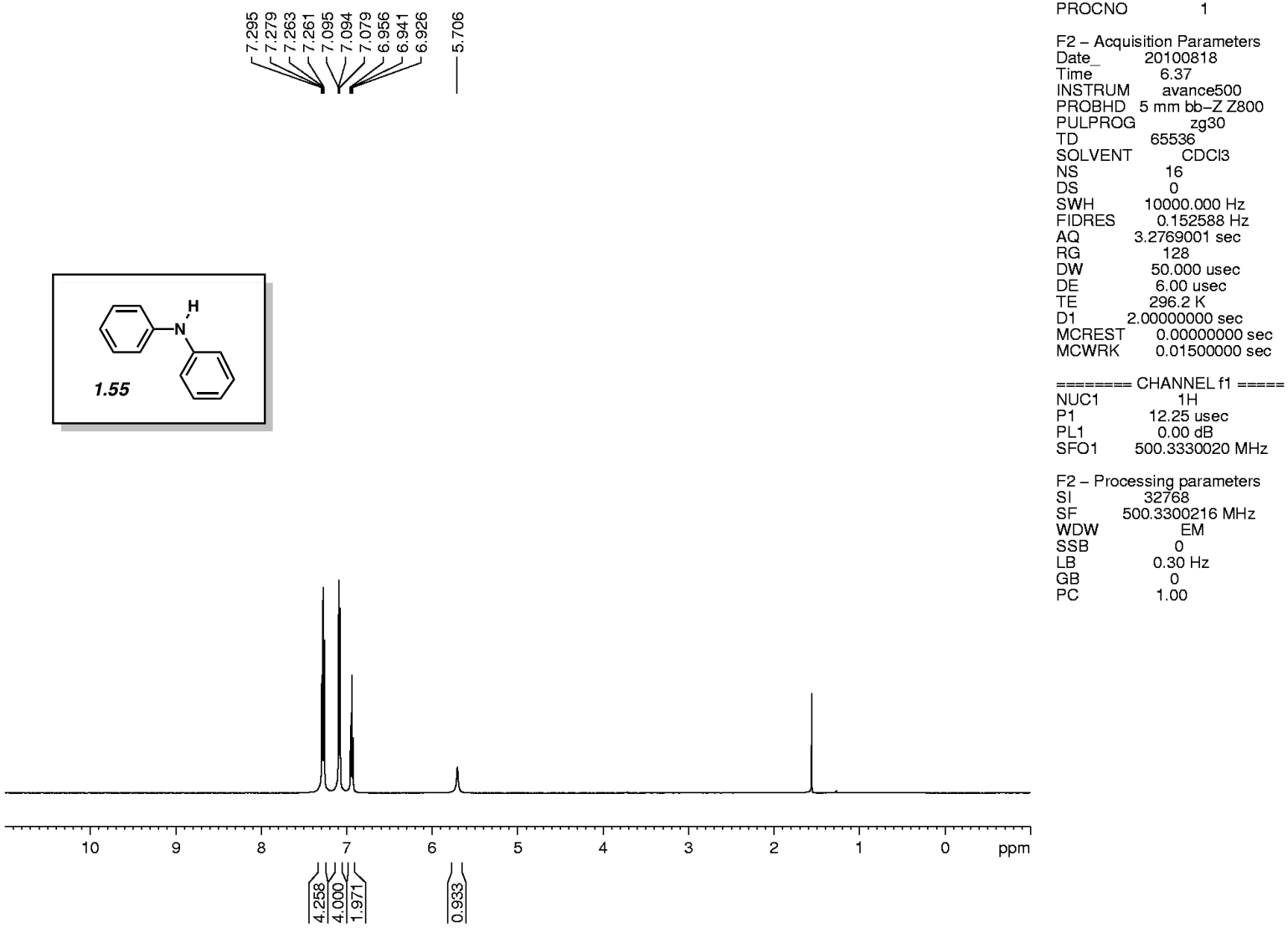

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Figure 1.32. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.55**.

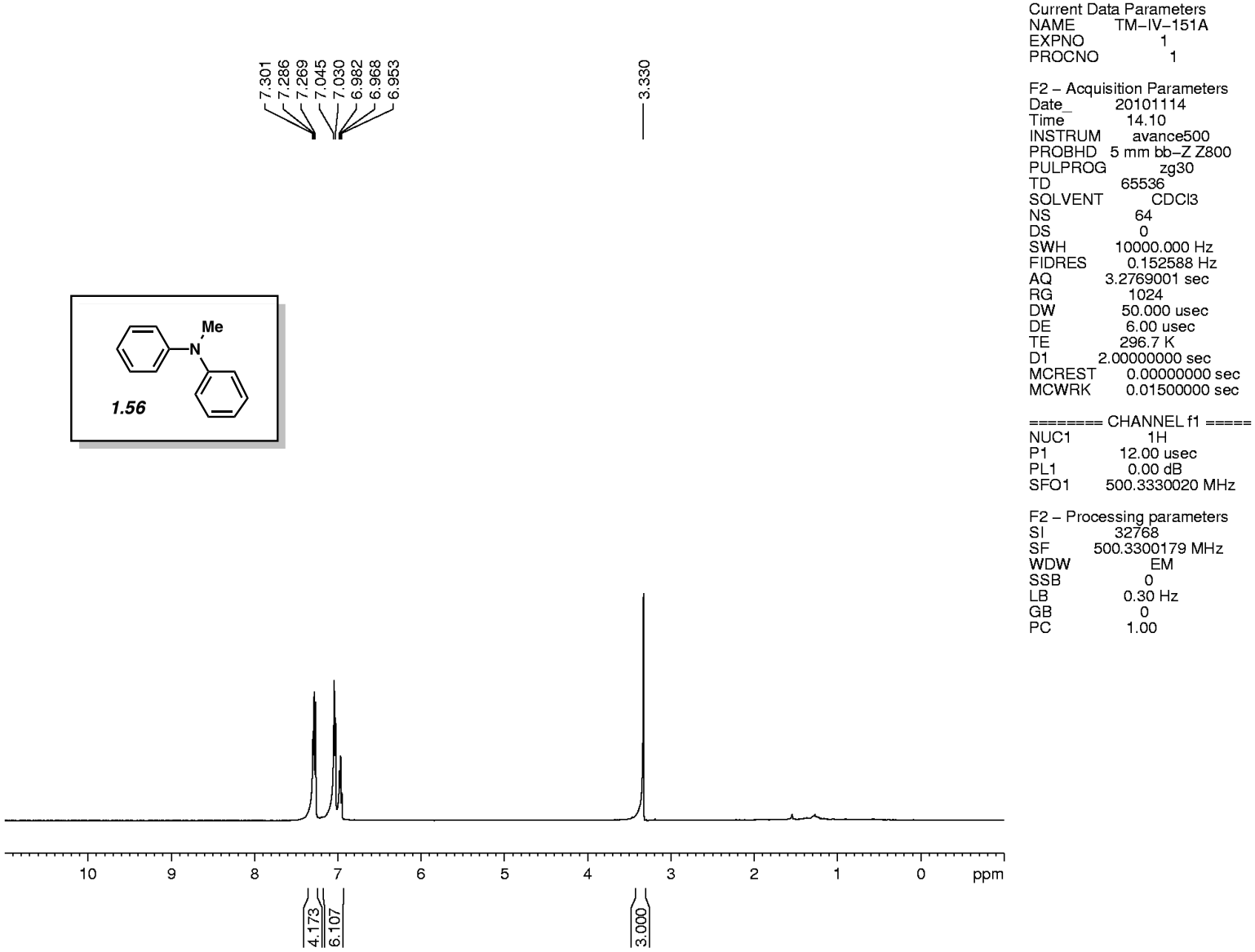


Figure 1.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.56**.

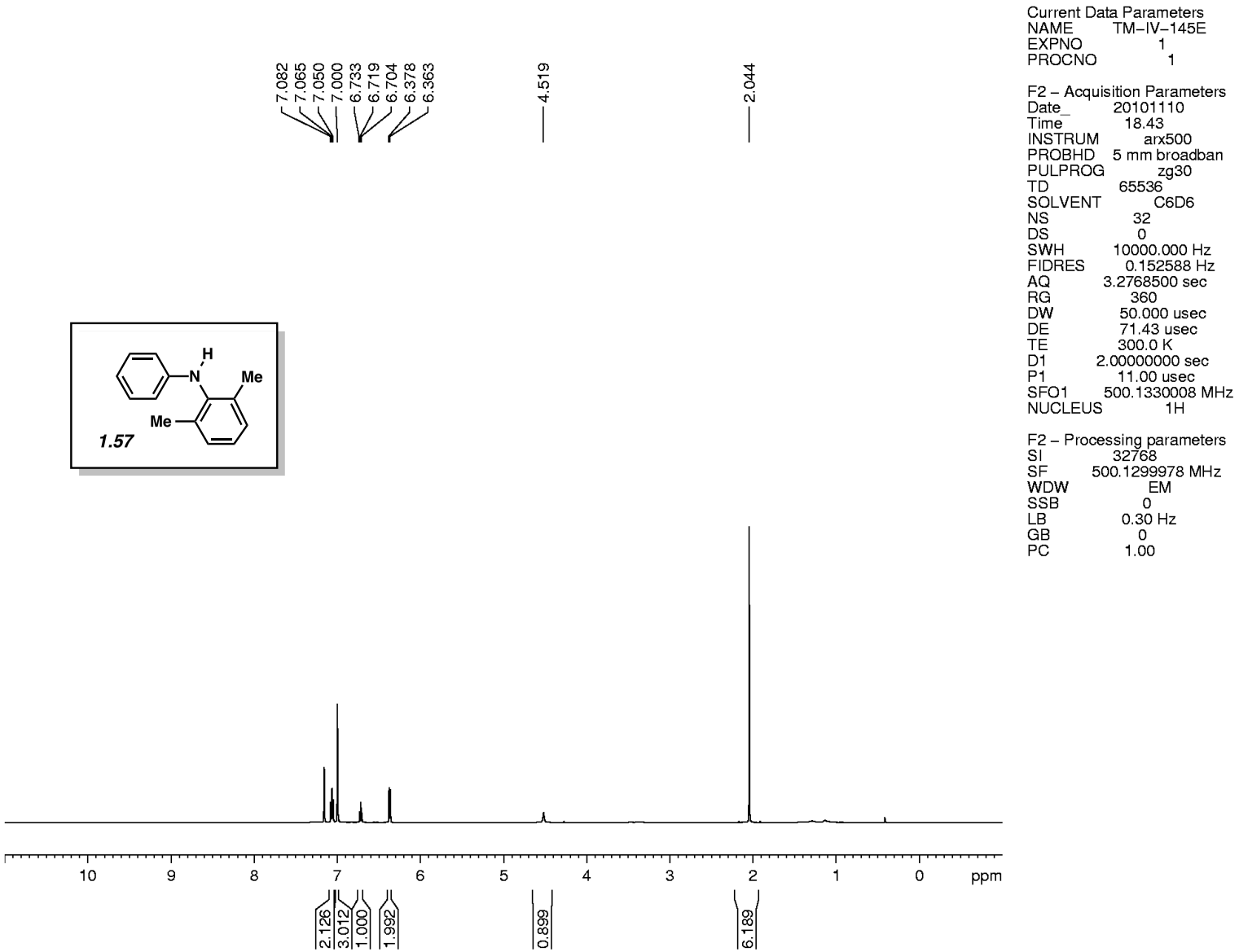


Figure 1.34. ^{1}H NMR (500 MHz, C_6D_6) of compound **1.57**.

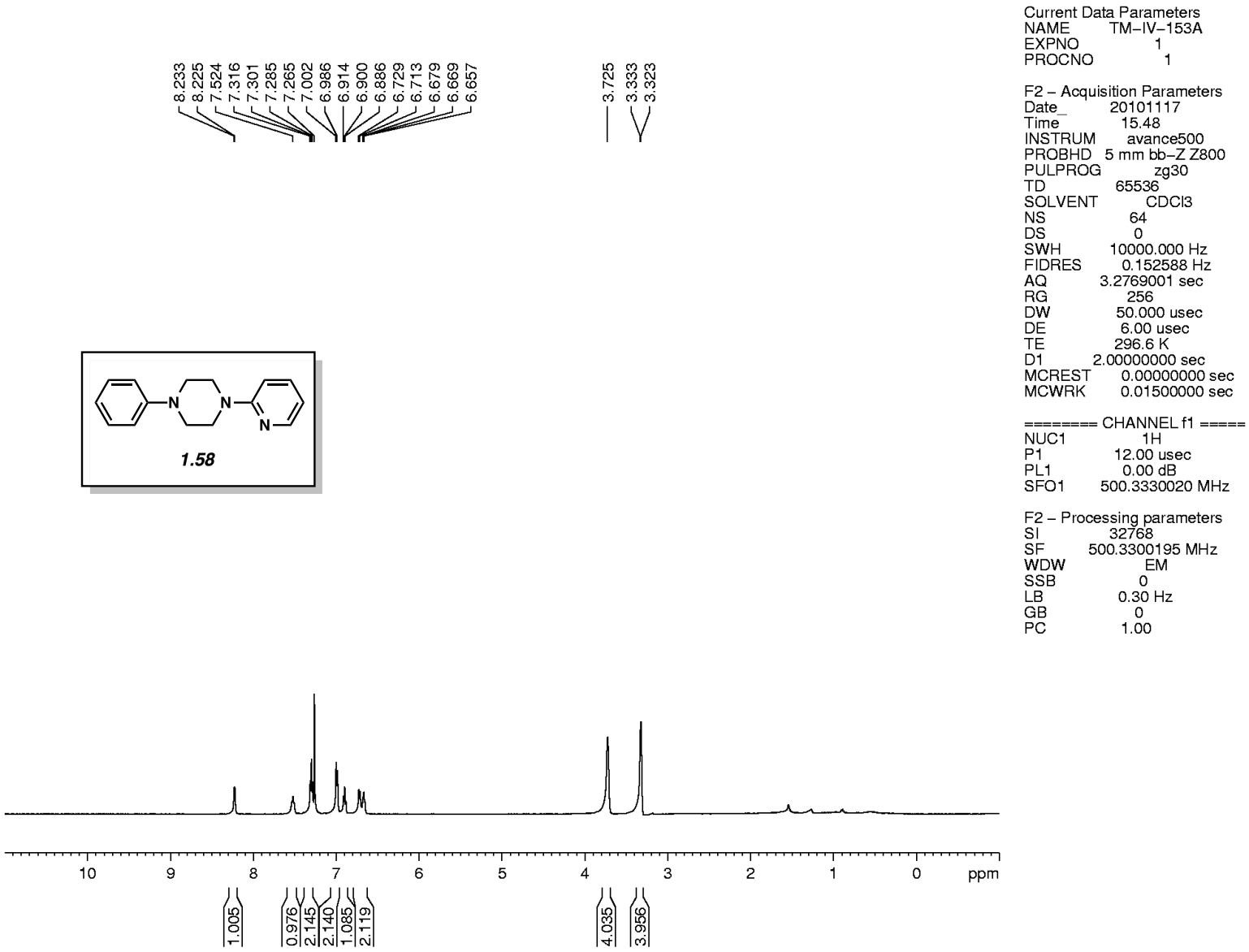


Figure 1.35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.58**.

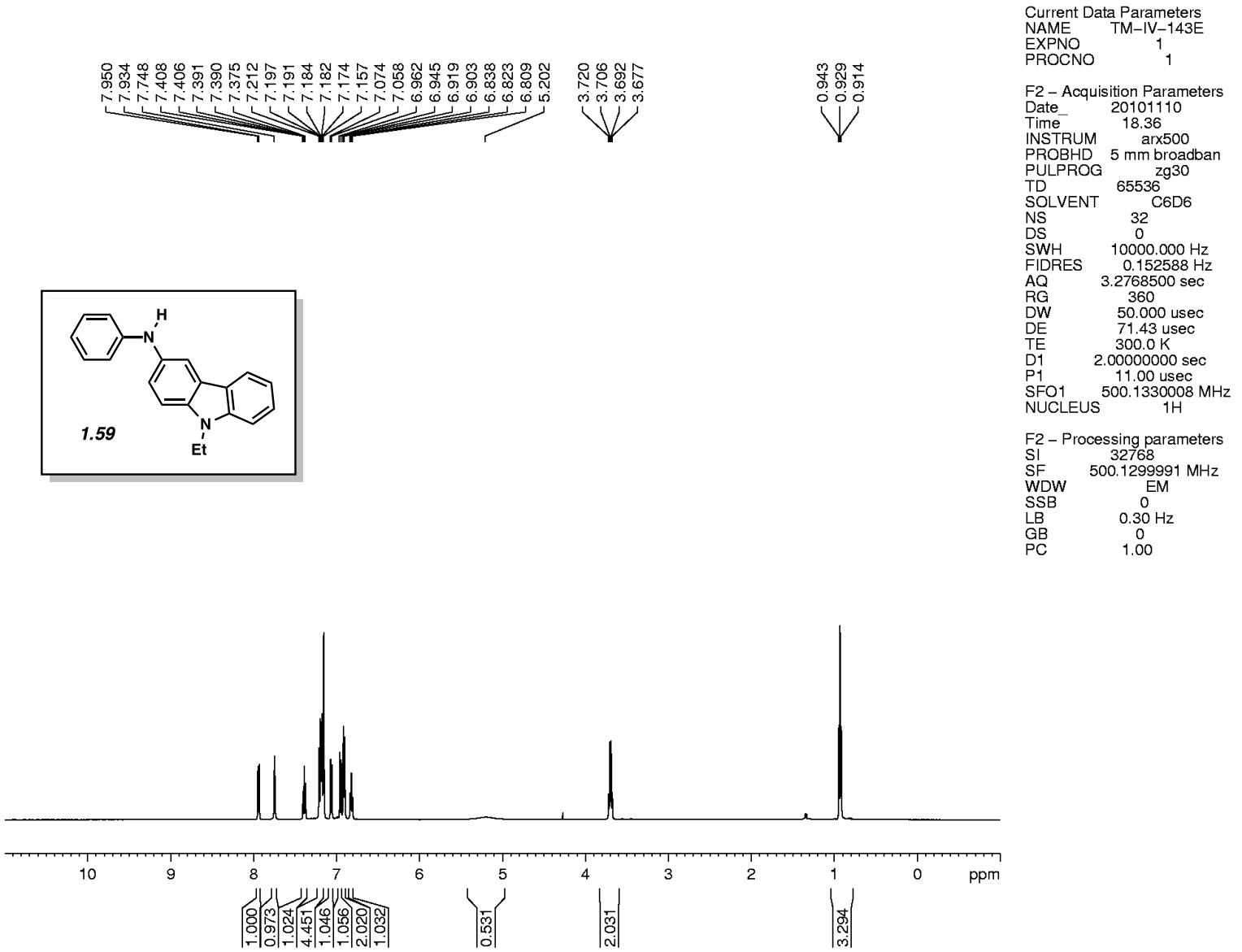


Figure 1.36. ^{1}H NMR (500 MHz, C_6D_6) of compound **1.59**.

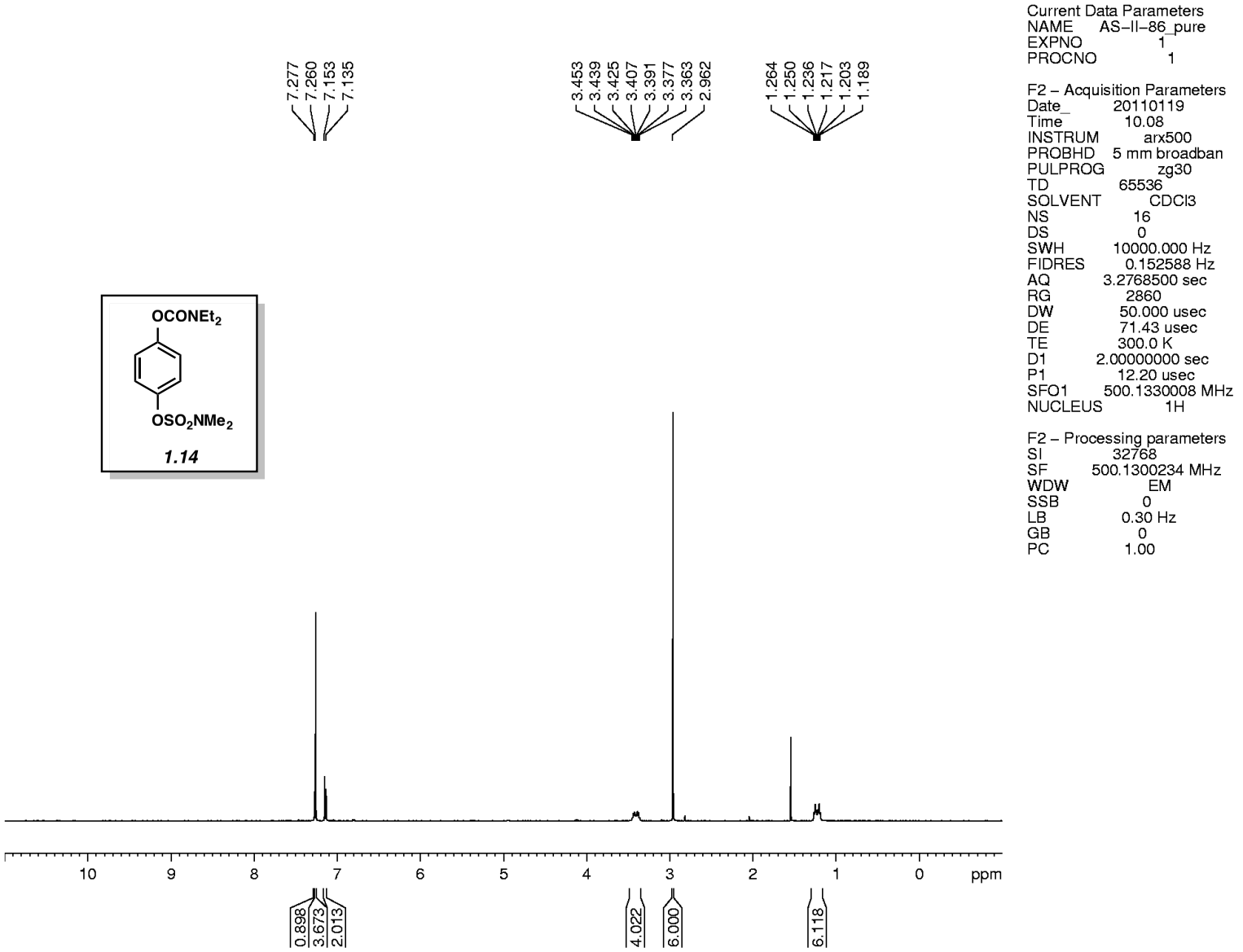


Figure 1.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.14**.

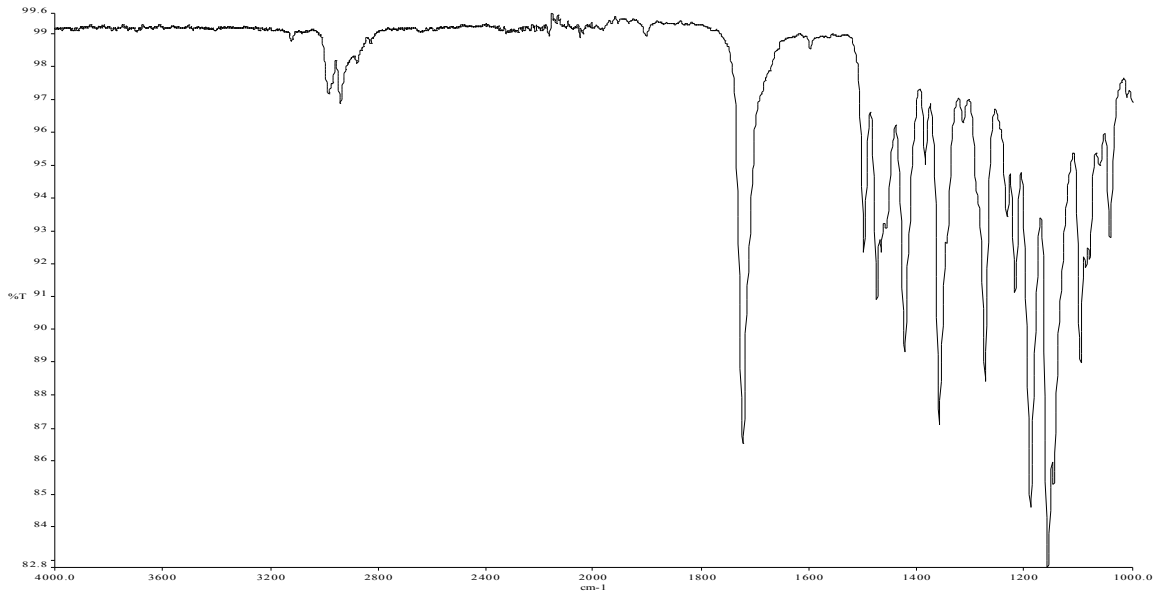


Figure 1.38. Infrared spectrum of compound **1.14**.

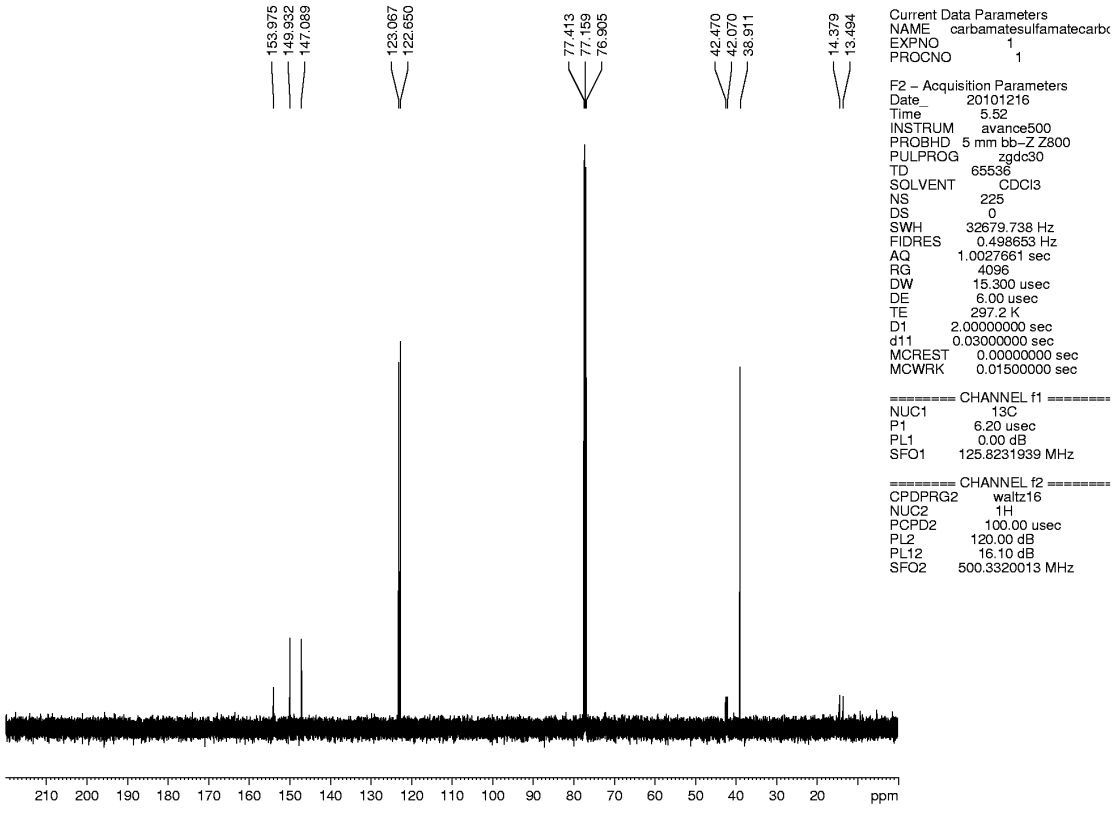
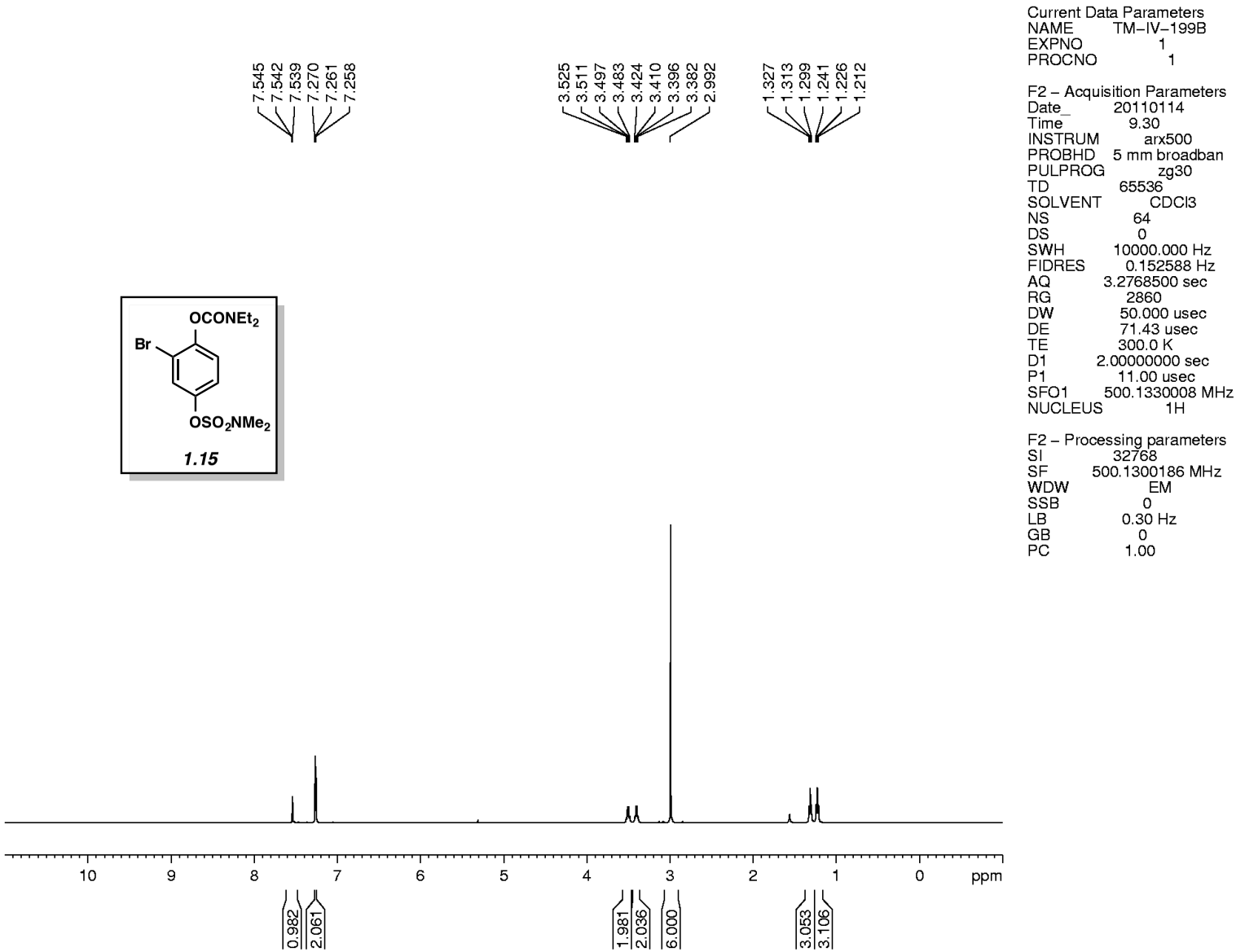


Figure 1.39. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.14**.



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PC 1.00

Figure 1.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.15**.

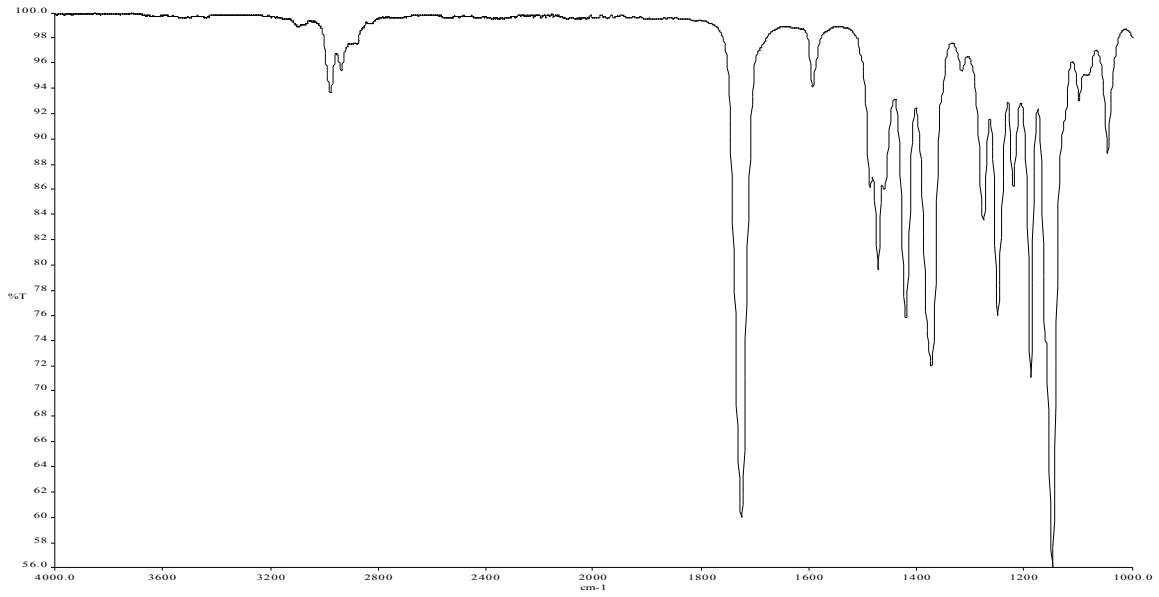

Figure 1.41. Infrared spectrum of compound **1.15**.

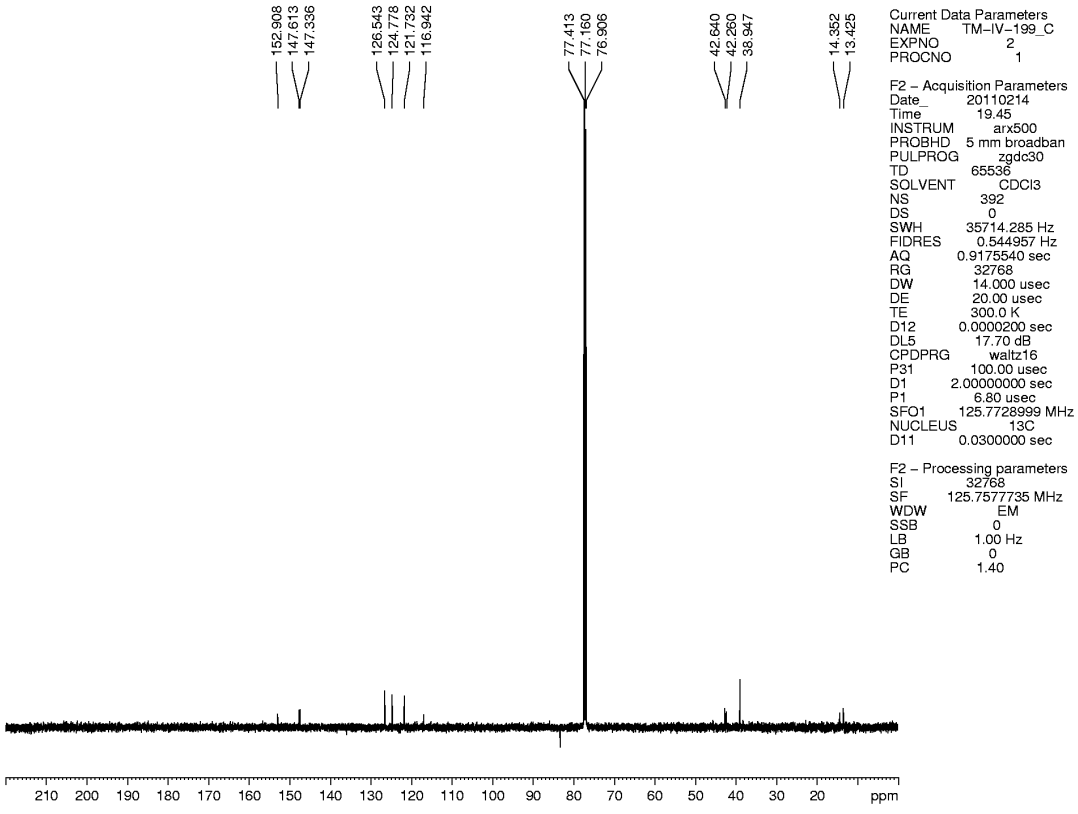

Figure 1.42. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.15**.

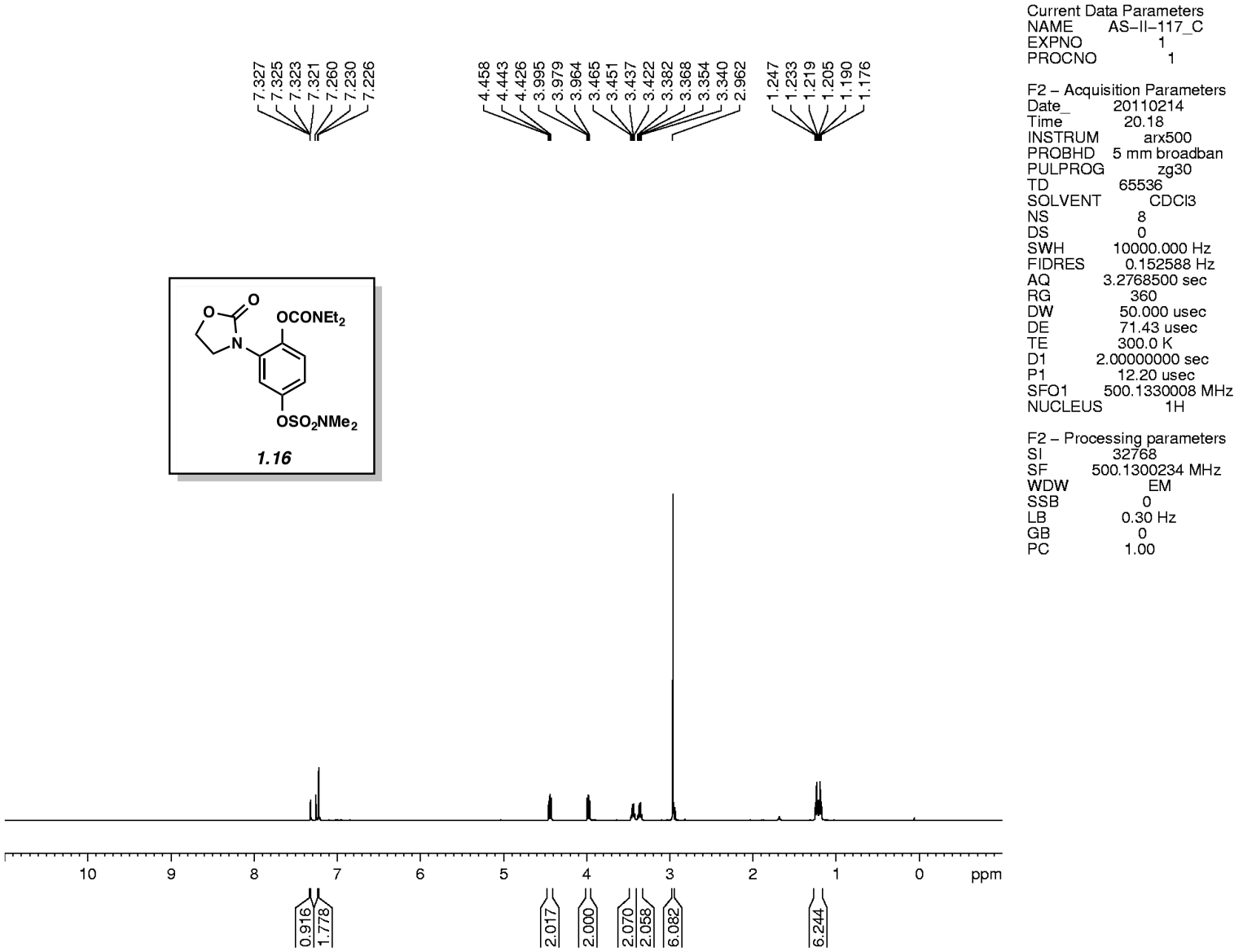

Figure 1.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.16**.

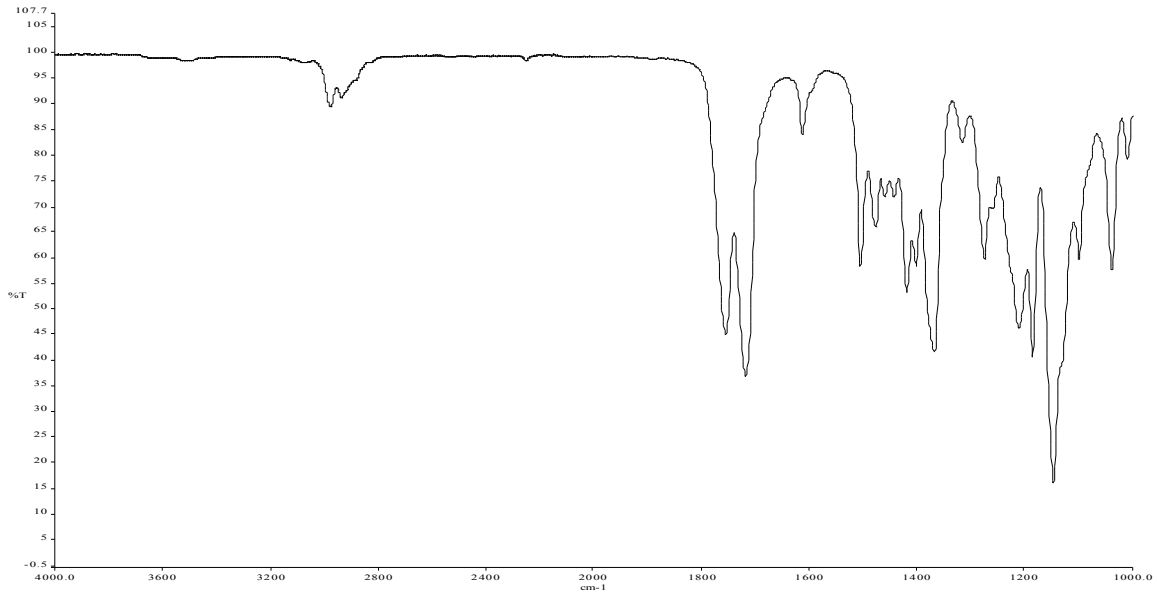

Figure 1.44. Infrared spectrum of compound **1.16**.

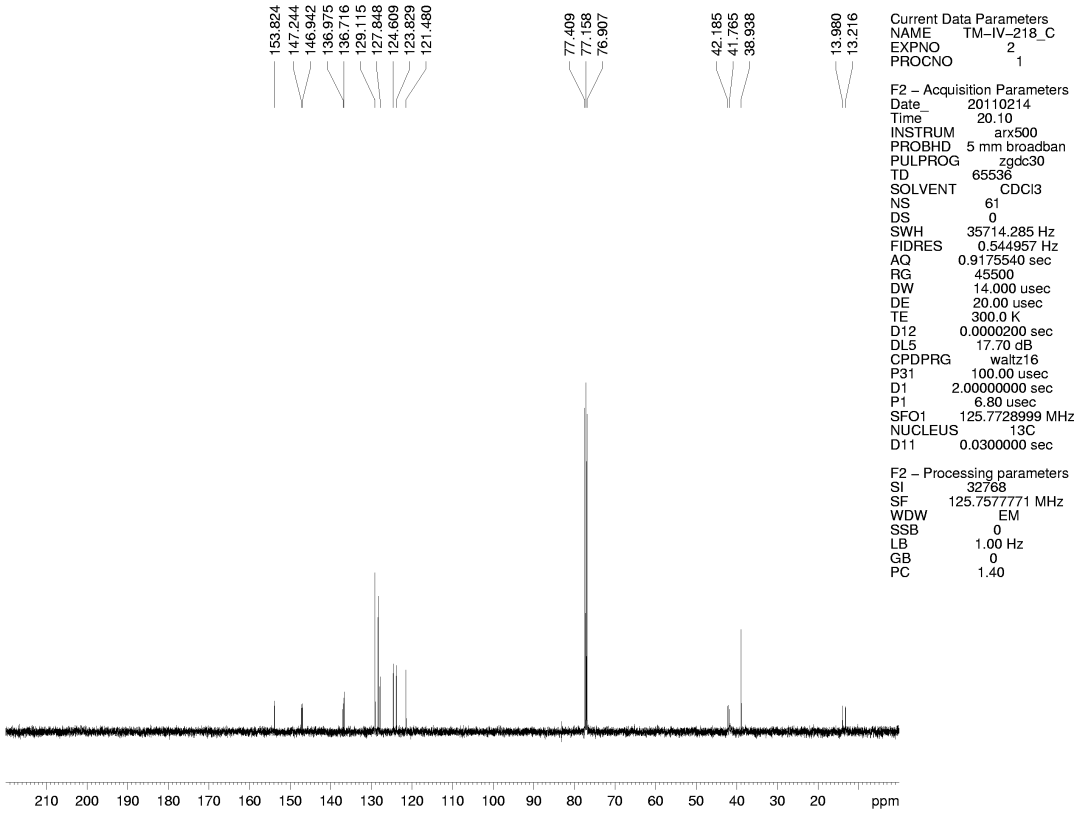

Figure 1.45. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.16**.

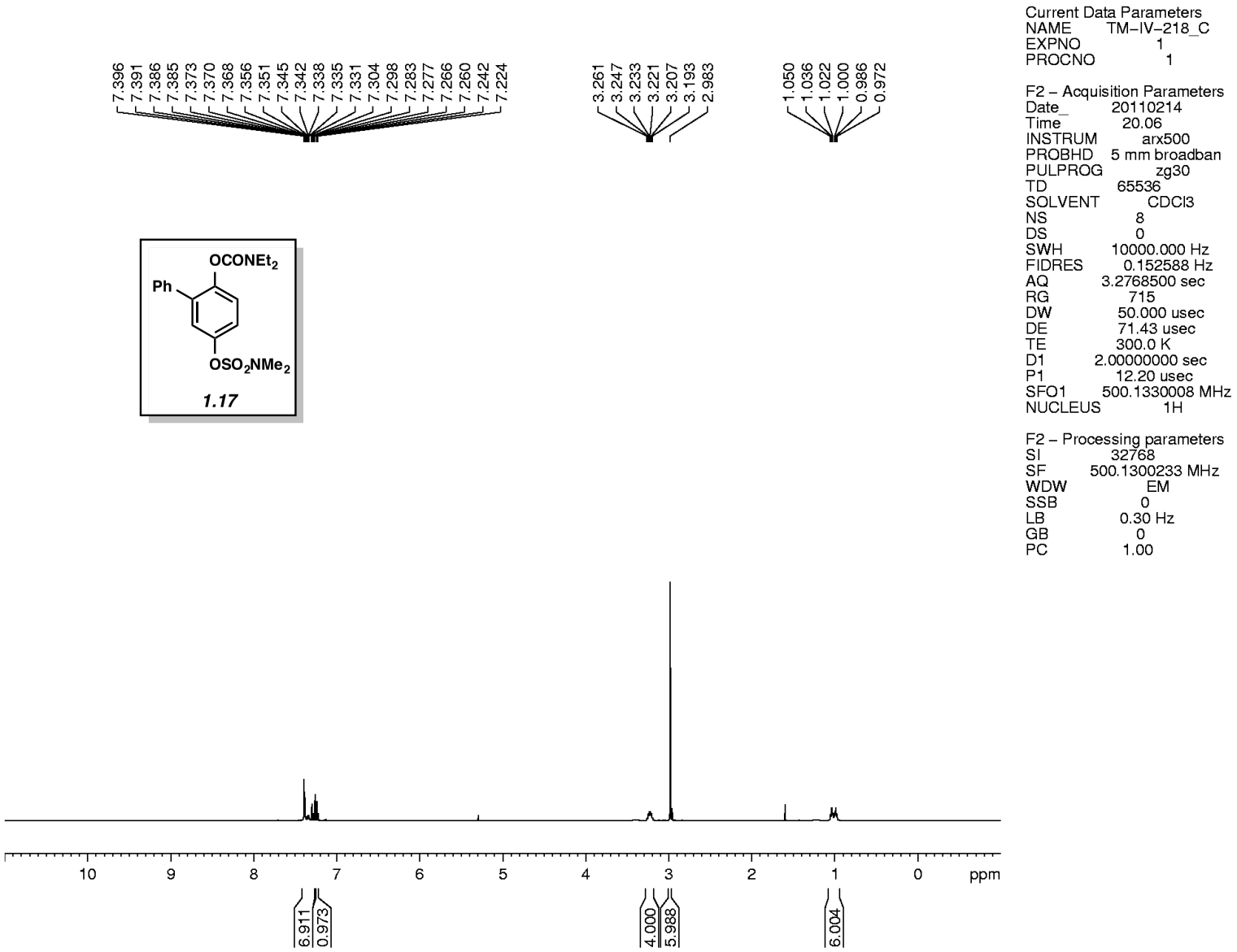

Figure 1.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.17**.

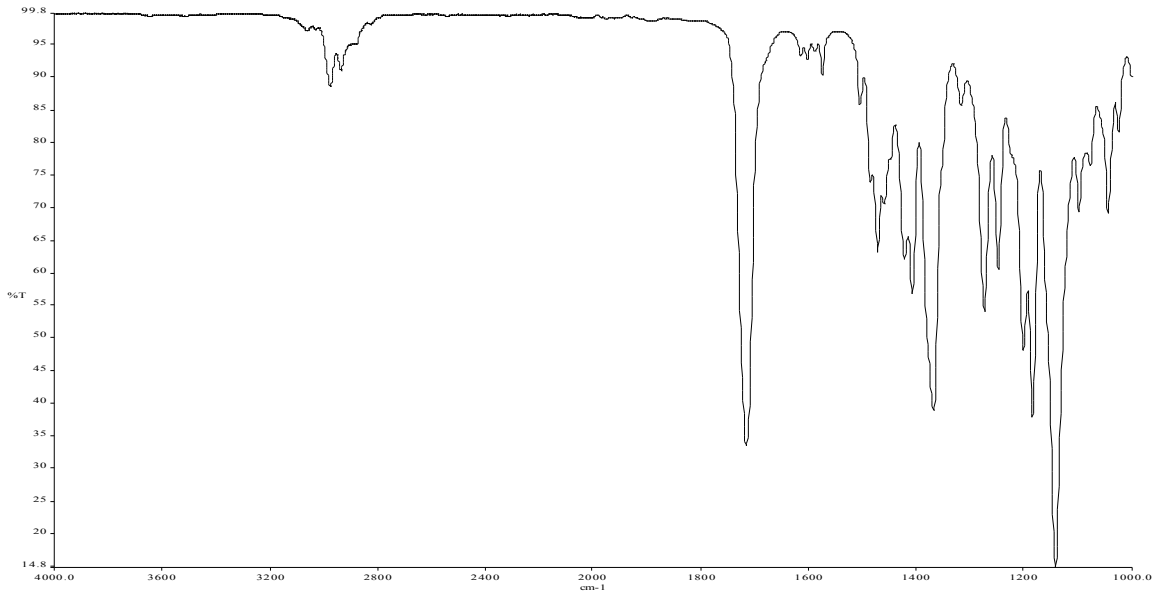

Figure 1.47. Infrared spectrum of compound **1.17**.

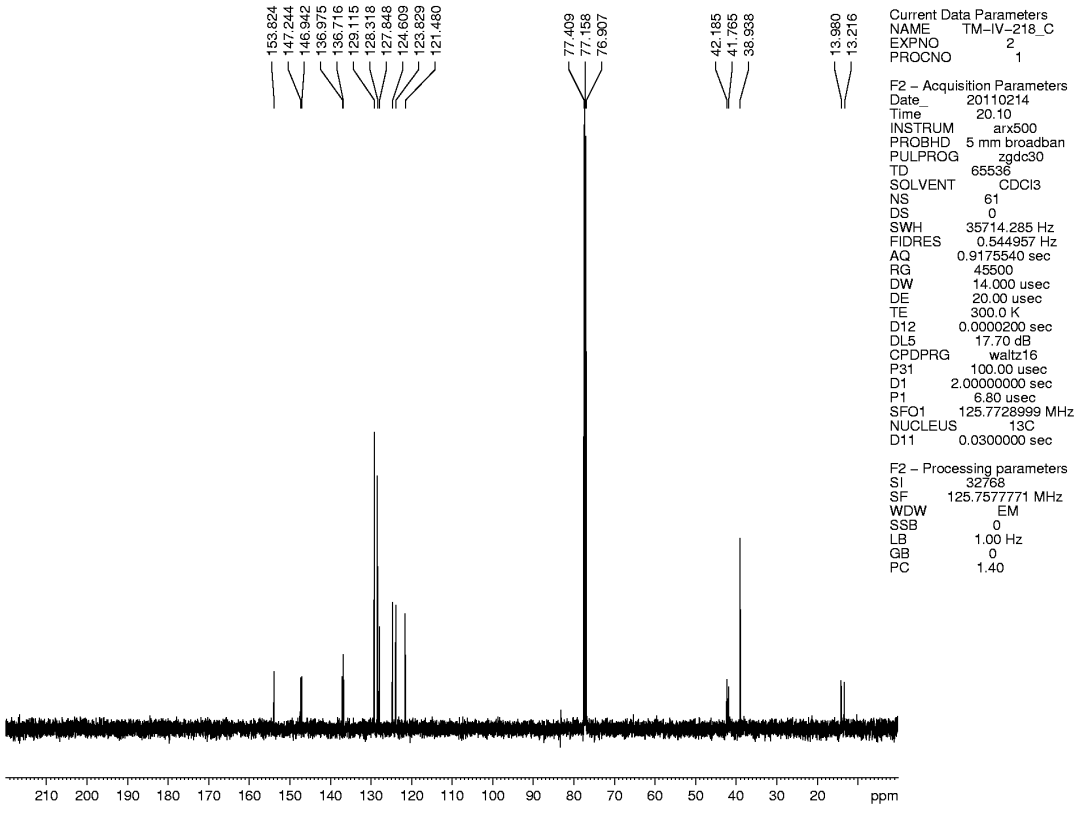

Figure 1.48. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.17**.

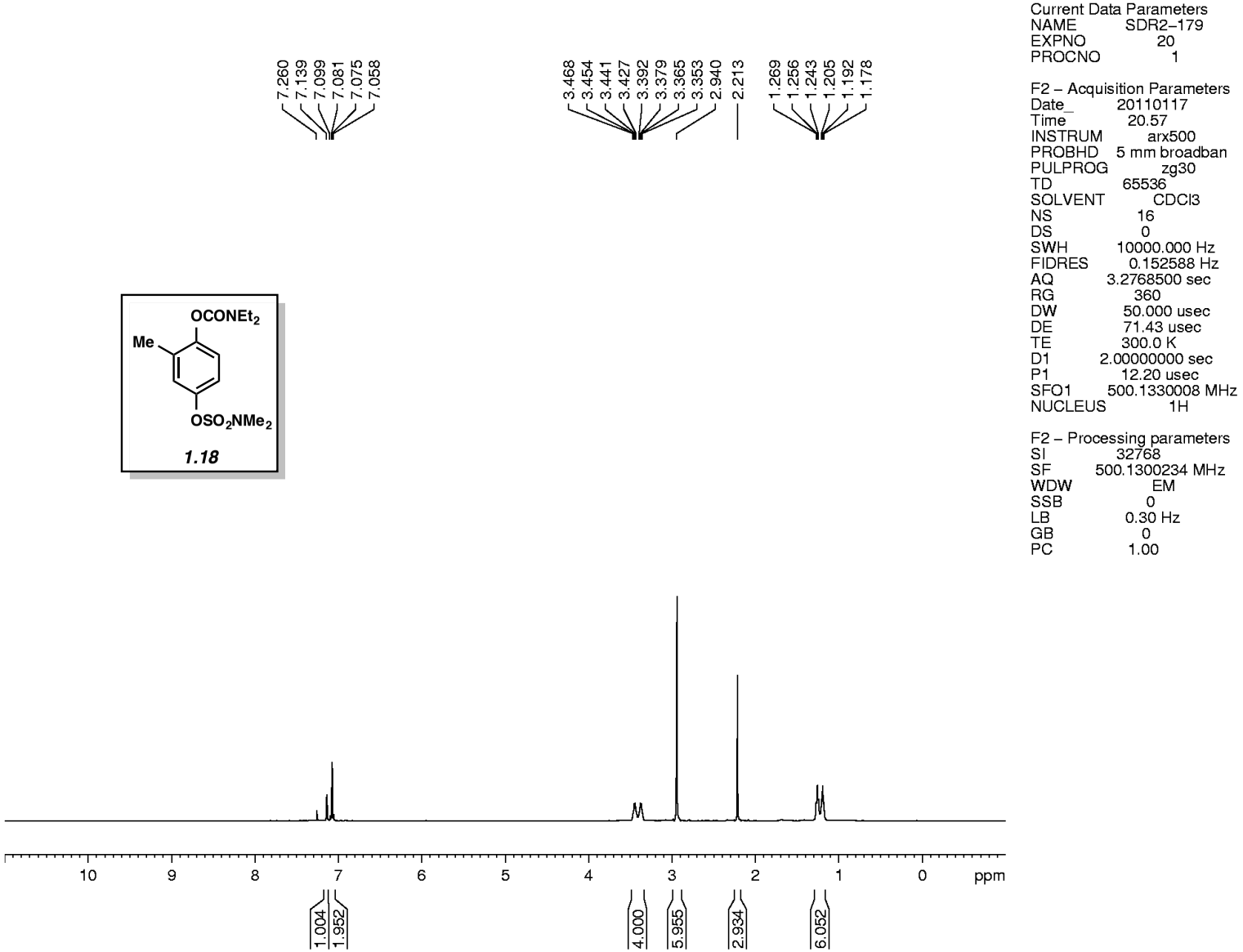

Figure 1.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.18**.

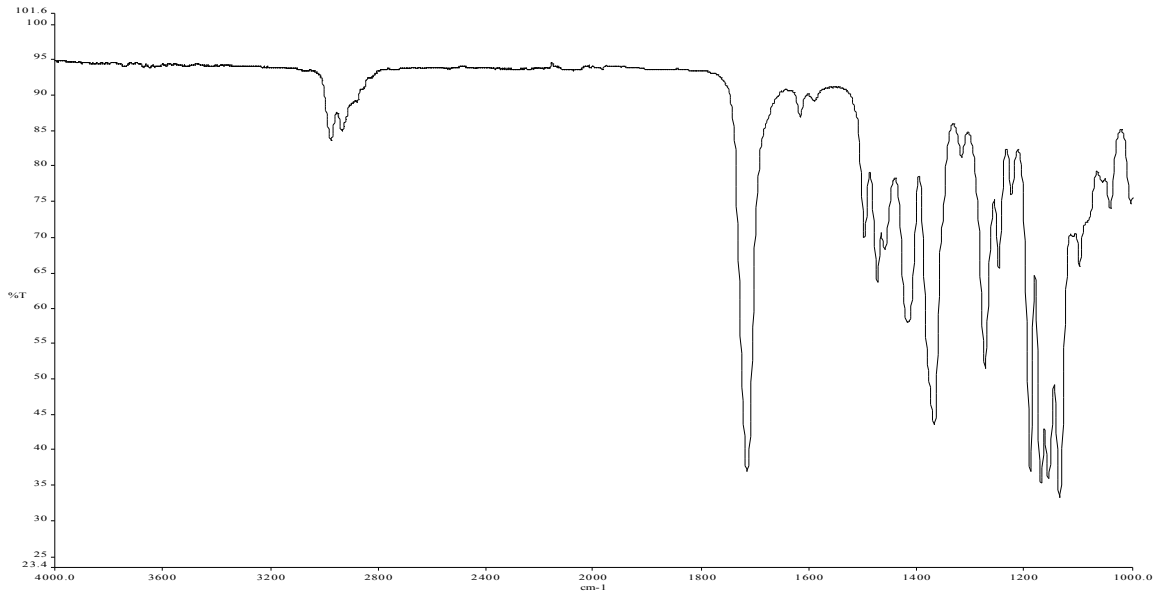

Figure 1.50. Infrared spectrum of compound **1.18**.

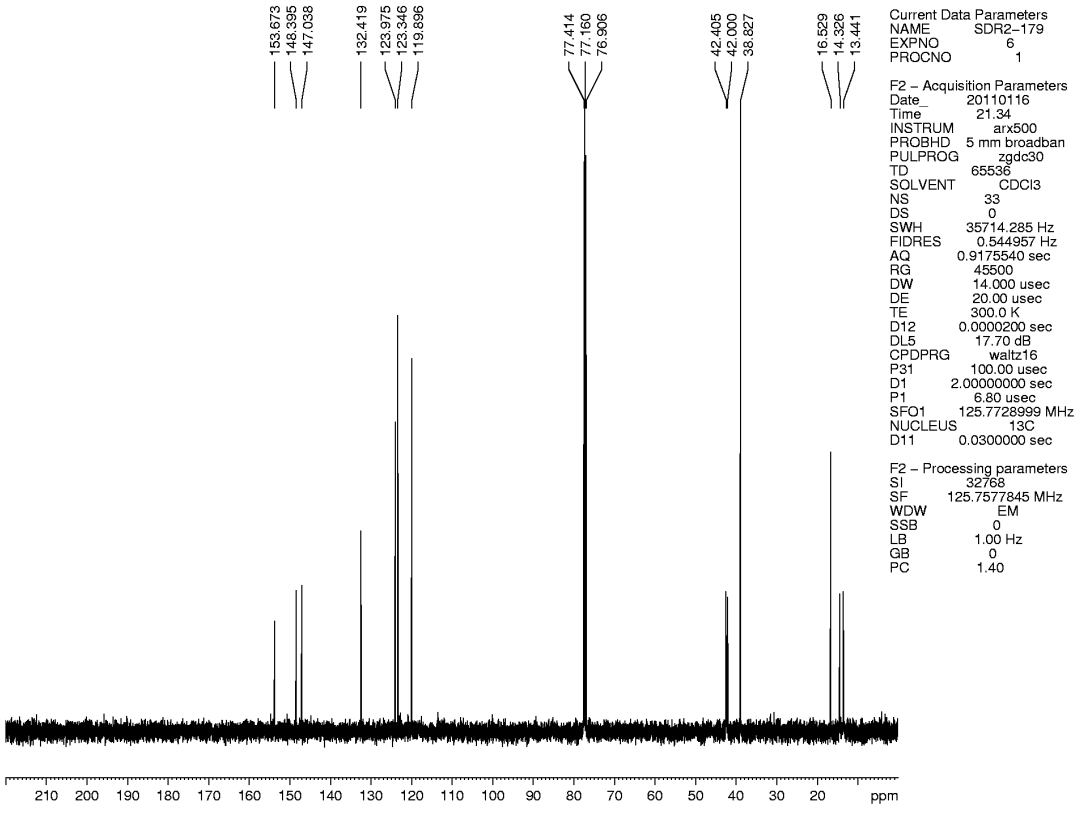

Figure 1.51. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.18**.

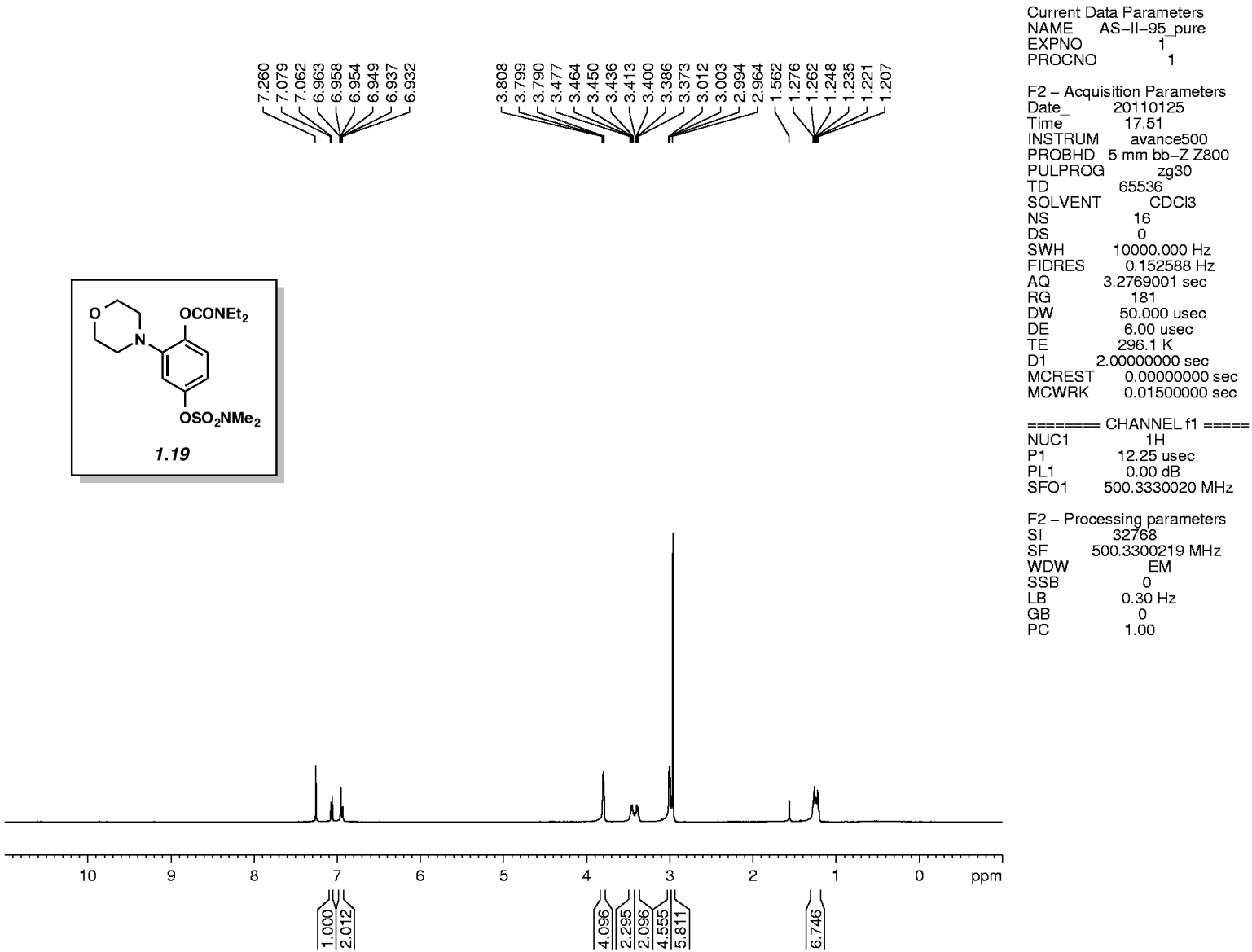

Figure 1.52. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **1.19**.

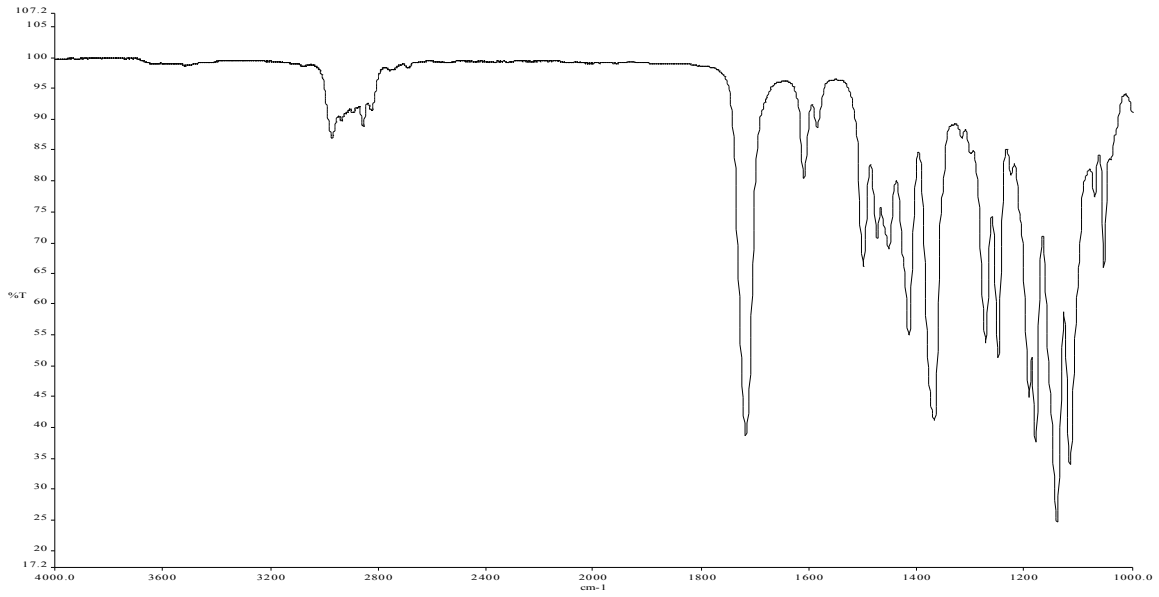

Figure 1.53. Infrared spectrum of compound **1.19**.

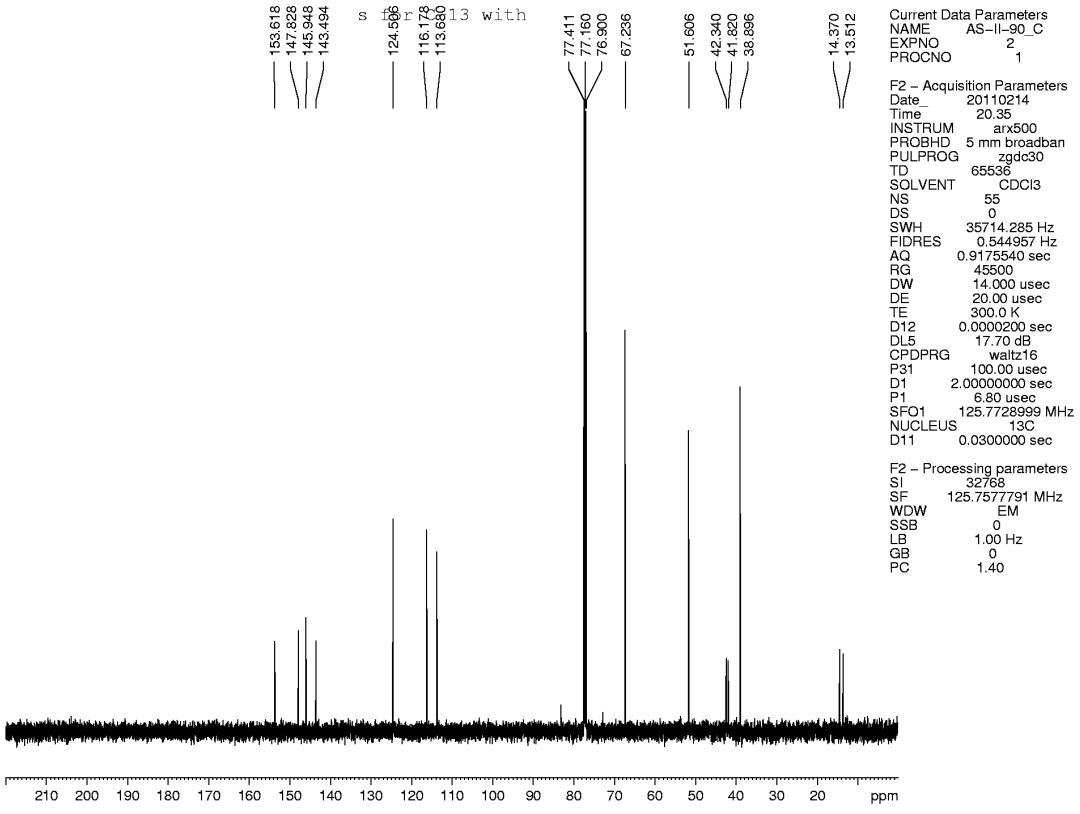

Figure 1.54. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.19**.

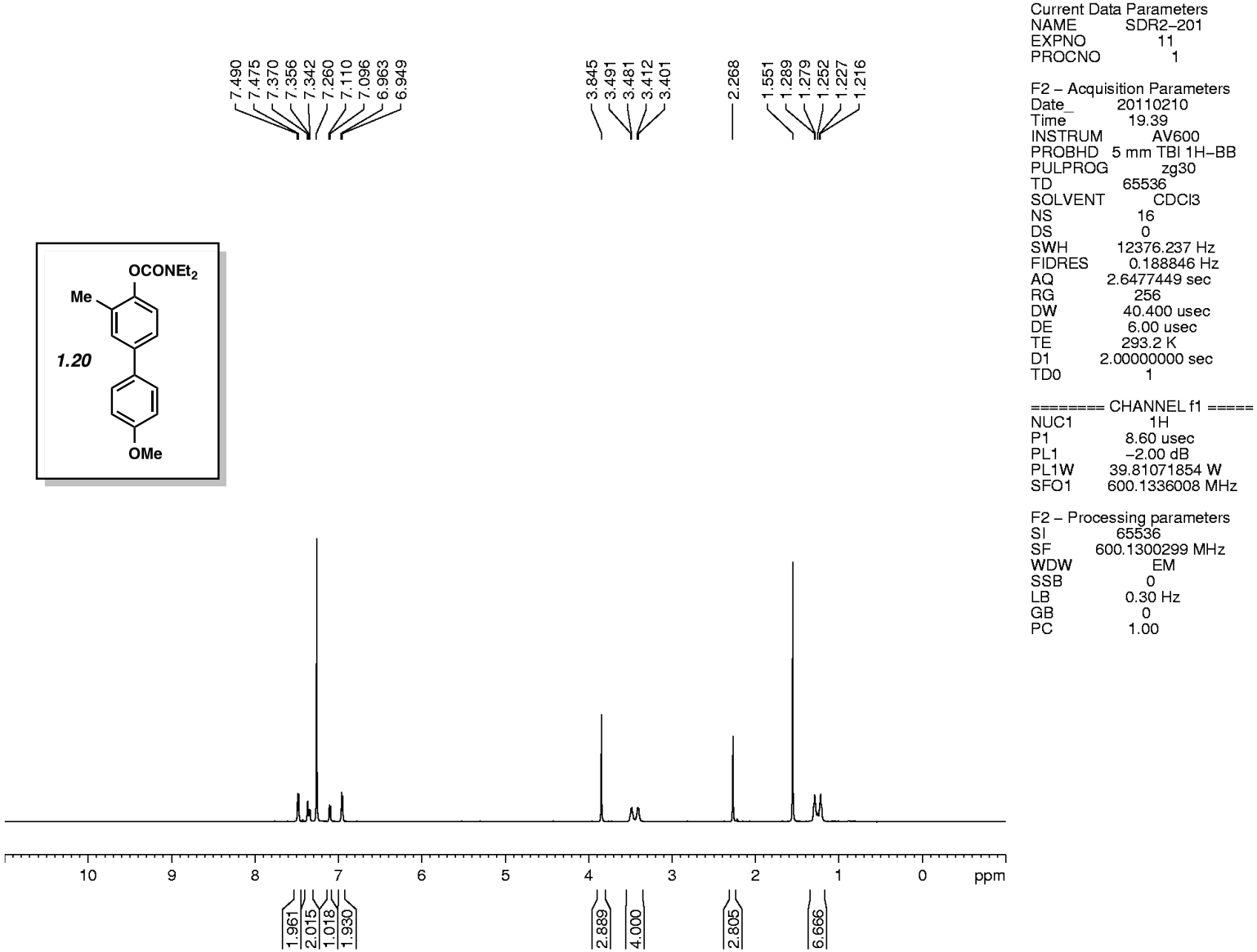

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Figure 1.55. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.20**.

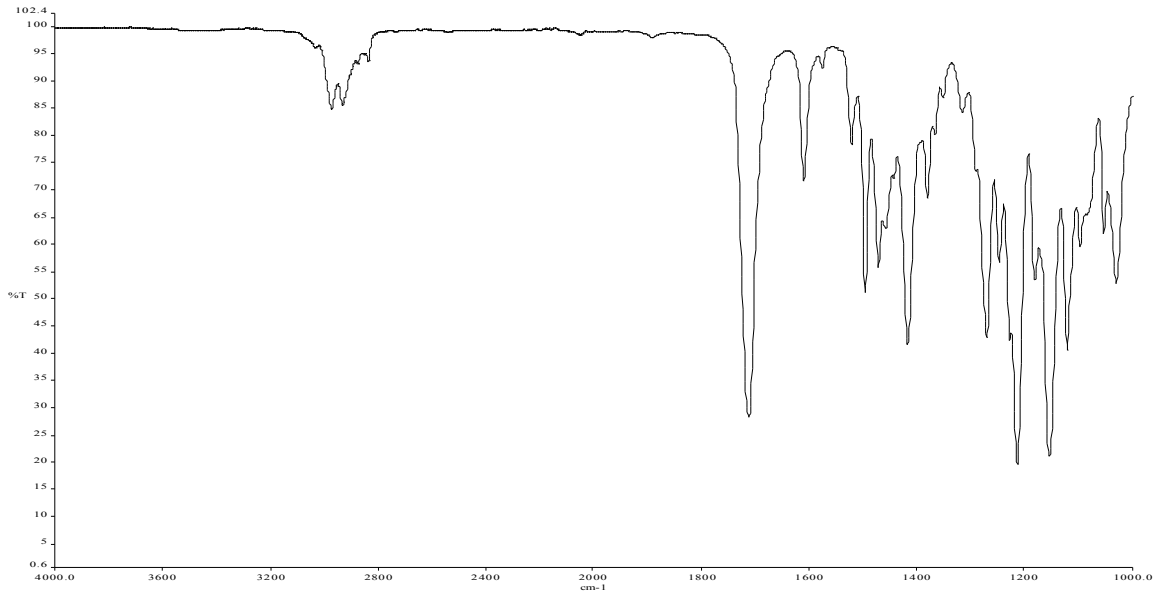


Figure 1.56. Infrared spectrum of compound **1.20**.

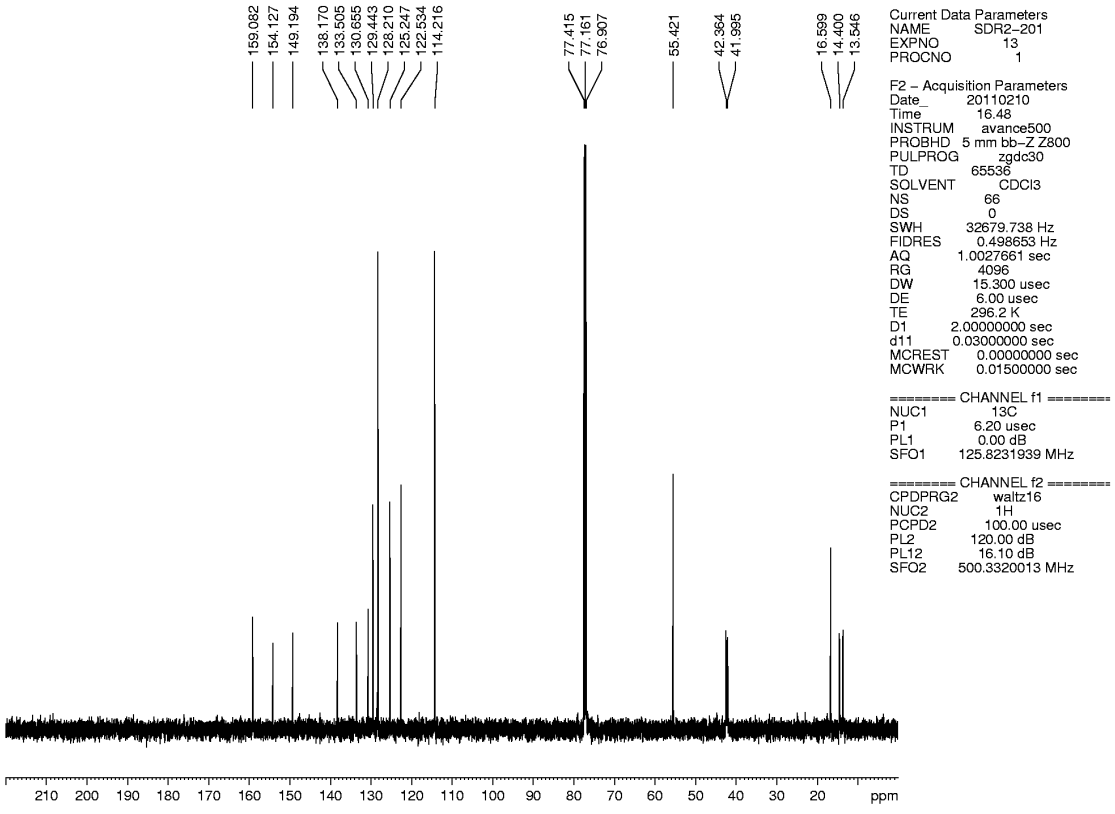


Figure 1.57. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.20**.

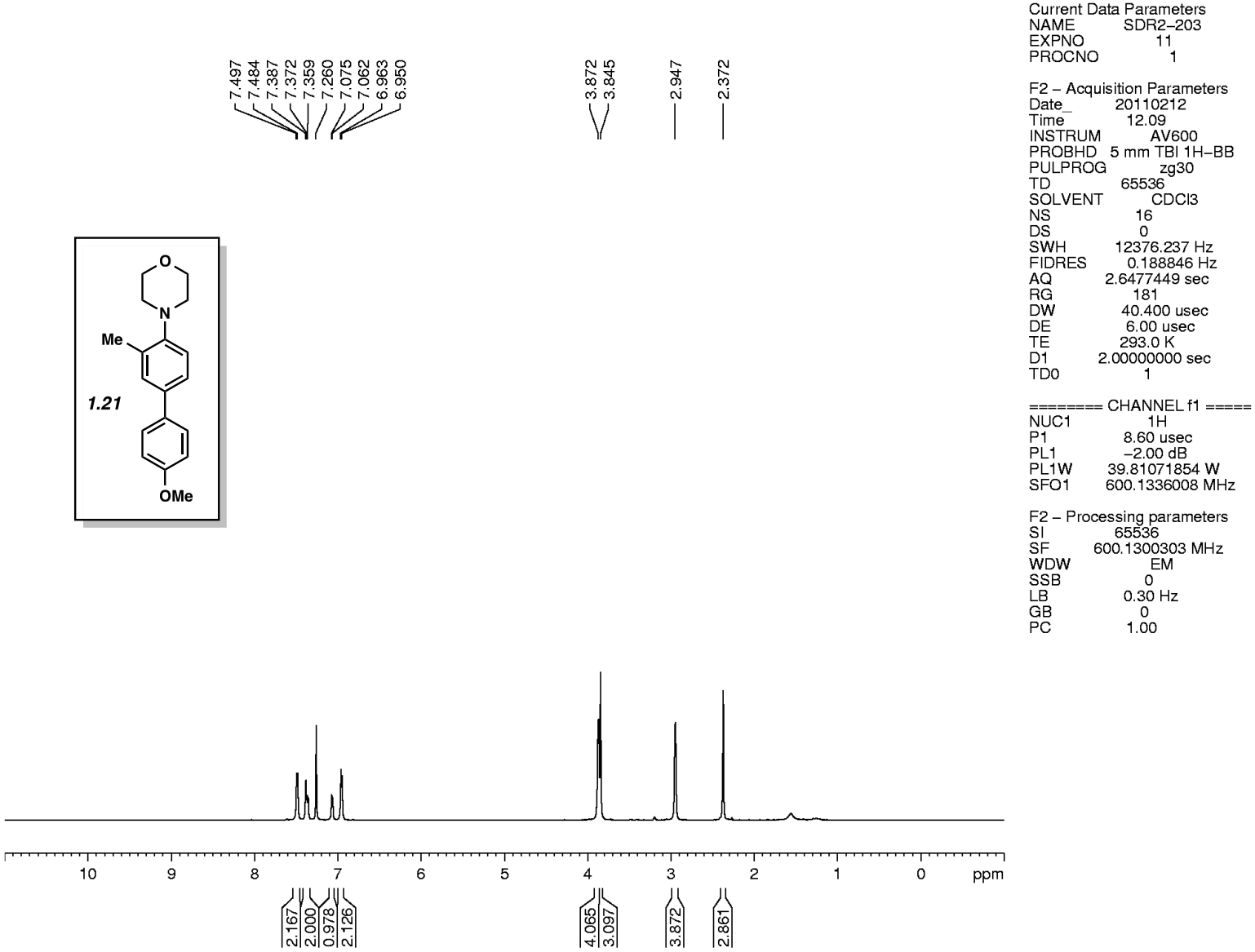


Figure 1.58. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **1.21**.

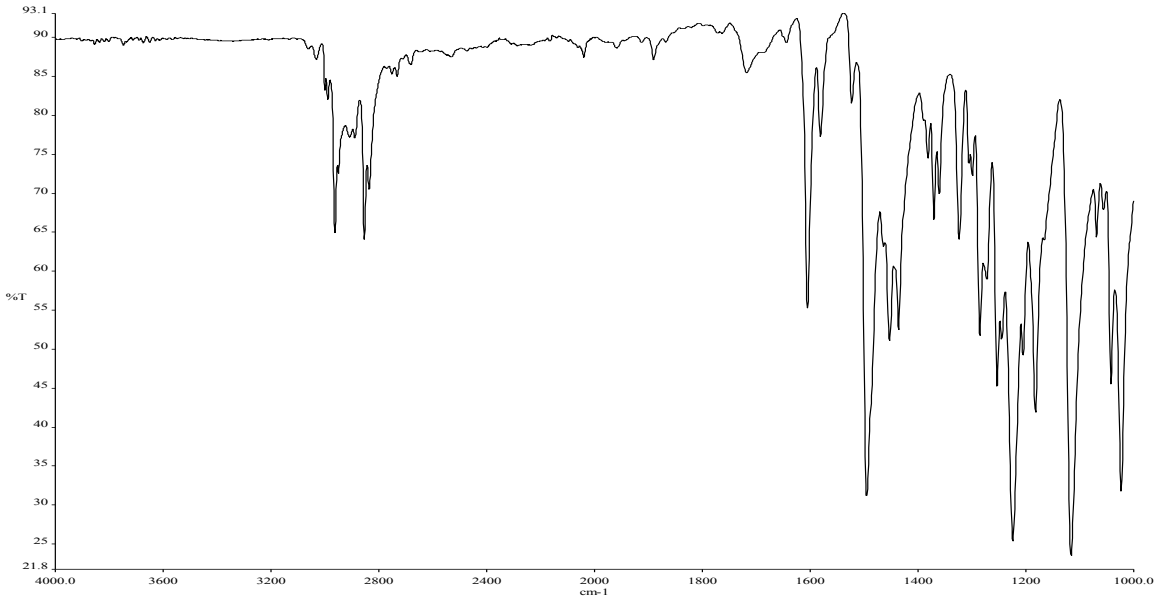


Figure 1.59. Infrared spectrum of compound **1.21**.

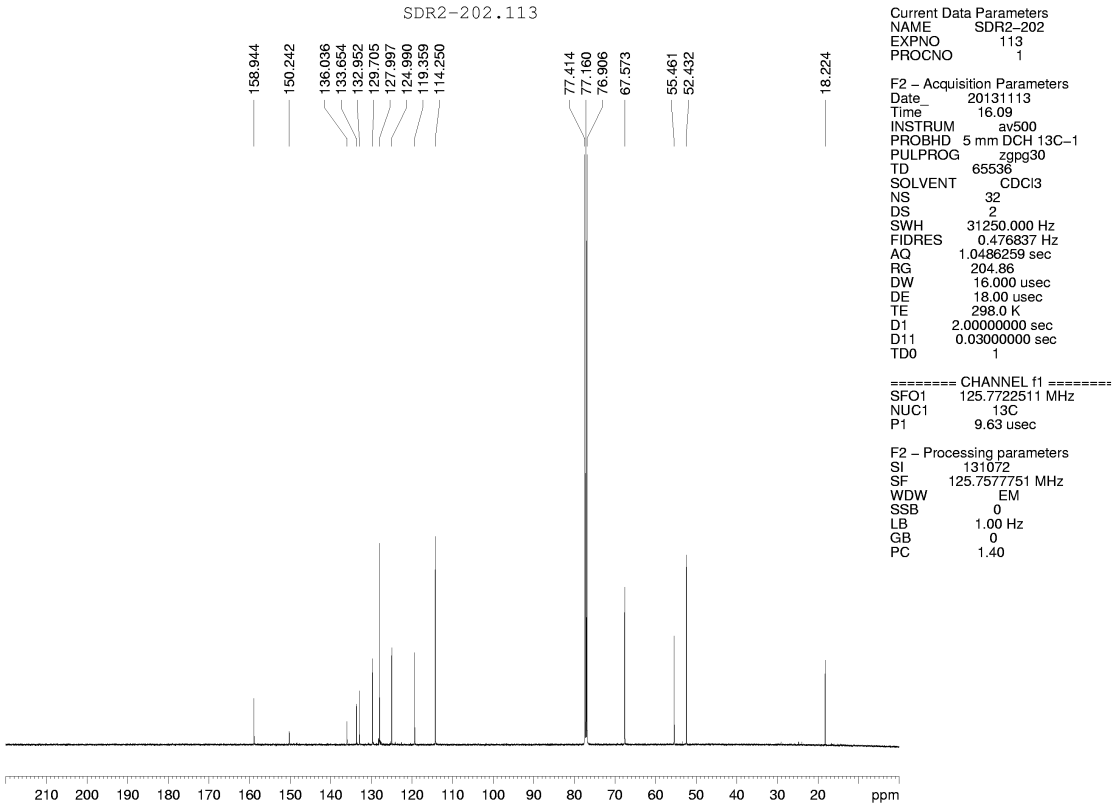


Figure 1.60. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **1.21**.

CHAPTER TWO

Nickel-Catalyzed Amination of Aryl Chlorides and Sulfamates in 2-Me-THF

2.1 Abstract

The nickel-catalyzed amination of aryl *O*-sulfamates and chlorides using the green solvent 2-methyl-THF is reported. This methodology employs the commercially available and air-stable pre-catalyst $NiCl_2$(DME), is broad in scope, and provides access to aryl amines in synthetically useful yields. The utility of this methodology is underscored by examples of gram-scale couplings conducted with catalyst loadings as low as 1 mol % nickel. Moreover, the nickel-catalyzed amination described is tolerant of heterocycles and should prove useful in the synthesis of pharmaceutical candidates and other heteroatom-containing compounds.

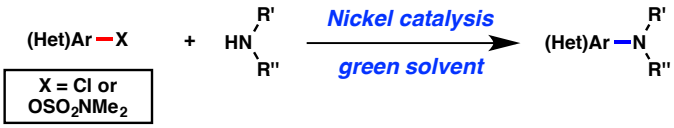
2.2 Introduction

Transition metal-catalyzed cross-couplings have had a profound impact on chemical synthesis.[1] As mild and useful alternatives to classical fragment couplings, cross-couplings have become one of the most frequently employed transformations for the construction of carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds in both academic and industrial settings.[1] Although palladium-catalyzed couplings dominate the field, there has been growing interest in the development of related couplings that employ non-precious metals.[2] Nickel, in particular, is very attractive in part due to its wide availability and low cost.[2d–h] Additionally, certain nickel catalysts have the unique ability to activate a wide range of electrophilic coupling partners, well beyond the scope of traditional cross-couplings that use palladium catalysis.[2d–h] Moreover, in

addition to cost and reactivity benefits, nickel catalysis has shown great promise for operating under green reaction conditions,[3] particularly in green solvents.[4]

Our research group and others have developed new protocols for aryl C–C and C–N bond formation[5] using nickel catalysis.[2d–h,4,6,7,8] These procedures not only enable the desired bond formations, but also utilize air and moisture stable Ni(II) precatalysts that do not require glove box handling. To render these transformations more practical, we have recently focused our efforts on developing greener variants. This has led to a general nickel-catalyzed Suzuki–Miyaura coupling procedure that takes place in a variety of green solvents, is scalable at low catalyst loadings, and possesses an unusually broad substrate scope.[4] Herein, we report a complementary procedure for the efficient formation of aryl C–N bonds that proceeds in a green solvent using nickel catalysis (Figure 2.1).

Figure 2.1. Amination of (hetero)aryl chlorides and sulfamates in a green solvent using nickel catalysis.

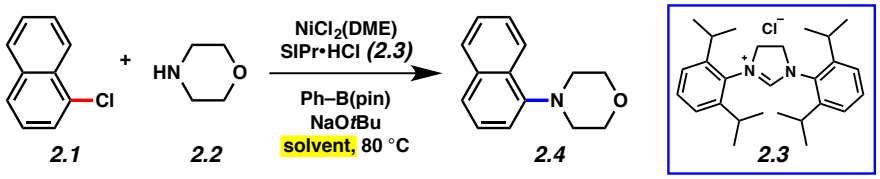


2.3 Optimization and Substrate Scope

Having previously established the nickel-catalyzed amination of aryl sulfamates,[7g,j] albeit not in a green solvent, we sought to first develop the corresponding coupling of aryl chlorides. We chose naphthyl chloride **2.1** for our studies and tested its coupling with morpholine (**2.2**) using nickel catalysis (Table 2.1). Indeed, upon exposure of **2.1** and **2.2** to our previously disclosed sulfamate amination conditions,[7g,7j,9,10] product **2.4** was obtained when toluene was

used as the solvent (entry 1). Other solvents that are considered environmentally attractive were also tested.[11,12] The use of DMF, which ranks favorably with regard to safety and some environmental considerations,[11] gave **2.4** in 50% yield (entry 2). We also examined alcohol solvents. Although the desired coupling did not take place when *n*-butanol was employed (entry 3), we found that the use of *t*-amyl alcohol gave the aminated product in good yield (entry 4). Ethereal solvents were also tested. Fortunately, the use of THF, MTBE, CPME,[13] or 2-Me-THF (entries 5–8, respectively) uniformly furnished **2.4** in excellent yield.

Table 2.1. Examination of Solvents in the Amination of 1-Chloronaphthalene.[a]



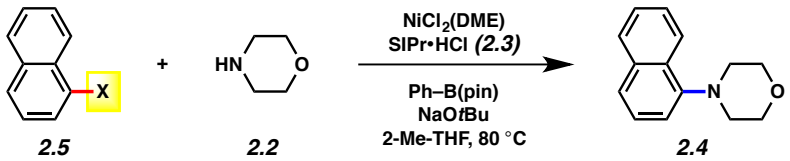
Entry	Solvent	Yield[b]	Entry	Solvent	Yield[b]
1	toluene	95%	5	THF	88%
2	DMF	50%	6	MTBE	96%
3	*n*-BuOH	0%	7	CPME	100%
4	*t*-amyl alcohol	78%	8	2-Me-THF	95%

[a] Reactions were carried out with $NiCl_2$(DME) (5 mol %), SIPr•HCl (10 mol %), Ph-B(pin) (0.55 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.80 equiv), NaOtBu (1.85 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. [b] Yields were determined using hexamethylbenzene as an internal standard.

Of the solvents surveyed, we elected to focus on the use of 2-Me-THF for our subsequent studies.[14] 2-Me-THF has gained attention as a promising solvent for industrial applications[15] due to several salient features, including that: a) it is not easily oxidized; b) it readily phase-separates from aqueous layers (in contrast to THF); c) it is obtained from furfural, which, in turn comes from renewable feedstock; d) it has a higher boiling point compared to THF, which can be advantageous in some instances; and e) it poses minimal health risks.

After establishing suitable reaction conditions for the amination of **2.1** with morpholine (**2.2**) we probed the use of other 1-naphthyl-based electrophilic coupling partners **2.5** in this methodology (Table 2.2). We were delighted to find that 1-bromonaphthalene could also be employed (entry 2). However, the corresponding iodide and triflate substrates gave only modest yields of **2.4** (entries 3 and 4). The use of a tosylate coupling partner, on the other hand, led to the desired product in 71% yield (entry 5). Finally, whereas the pivalate ester substrate failed (entry 6), we found that the corresponding carbamate and sulfamate substrates could be employed in the methodology (entries 7 and 8). Overall, the chloride and sulfamate substrates gave the best yields of product **2.4**; thus, we elected to evaluate the scope of the methodology for these two types of electrophiles.[16,17]

Table 2.2. Evaluation of Various Electrophiles.[a]



2.5 *2.2* *2.4*

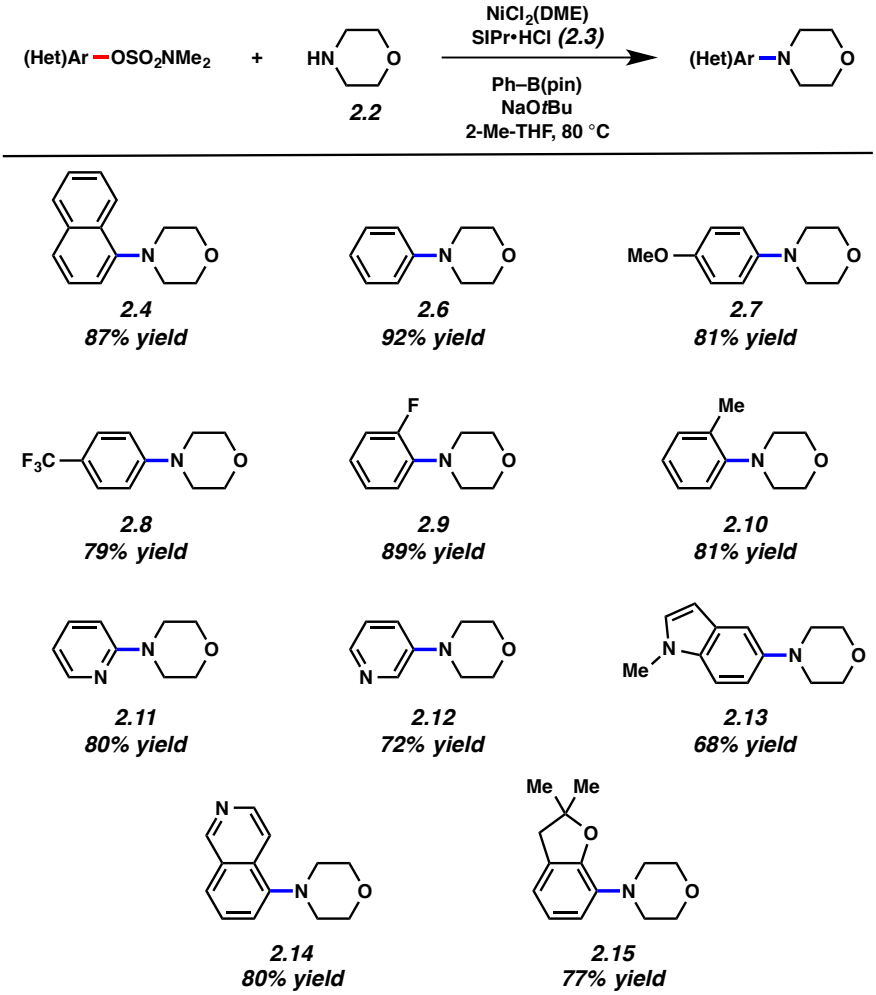
Entry	*X*	*Yield*[b]	*Entry*	*X*	*Yield*[b]
1	Cl	95%	5	OTs	71%
2	Br	62%	6	OPiv	4%
3	I	27%	7	$OC(O)NEt_2$	76%
4	OTf	6%	8	OSO_2NMe_2	87%

[a] Reactions were carried out with $NiCl_2$(DME) (5 mol %), SIPr•HCl (10 mol %), Ph–B(pin) (0.55 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.80 equiv), NaOtBu (1.85 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. [b] Yields were determined using hexamethylbenzene as an internal standard.

Figure 2.2 highlights the scope of the methodology with regard to the coupling of aryl sulfamate substrates using morpholine (**2.2**) as the amine partner and 2-Me-THF as solvent. Simple aryl hydrocarbon substrates, such as naphthyl and phenyl sulfamates, were readily aminated as demonstrated by the high yielding formation of **2.4** and **2.6**, respectively.

Additionally, the generation of products **2.7**–**2.10** in good yields shows the methodology's tolerance of electron-donating, electron-withdrawing, and ortho substituents. Given the prevalence of heterocycles in pharmaceuticals, where amination reactions are widely employed, we also tested several heterocyclic sulfamate substrates. 2- and 3-substituted pyridines were well tolerated, as demonstrated by the formation of products **2.11** and **2.12**, respectively. Moreover, indole-, isoquinoline-, and dihydrobenzofuran-containing substrates were suitable coupling partners, as judged by the formation of **2.13**–**2.15** in synthetically useful yields.

Figure 2.2. Coupling of (hetero)aryl sulfamates with morpholine in 2-Me-THF.[a]

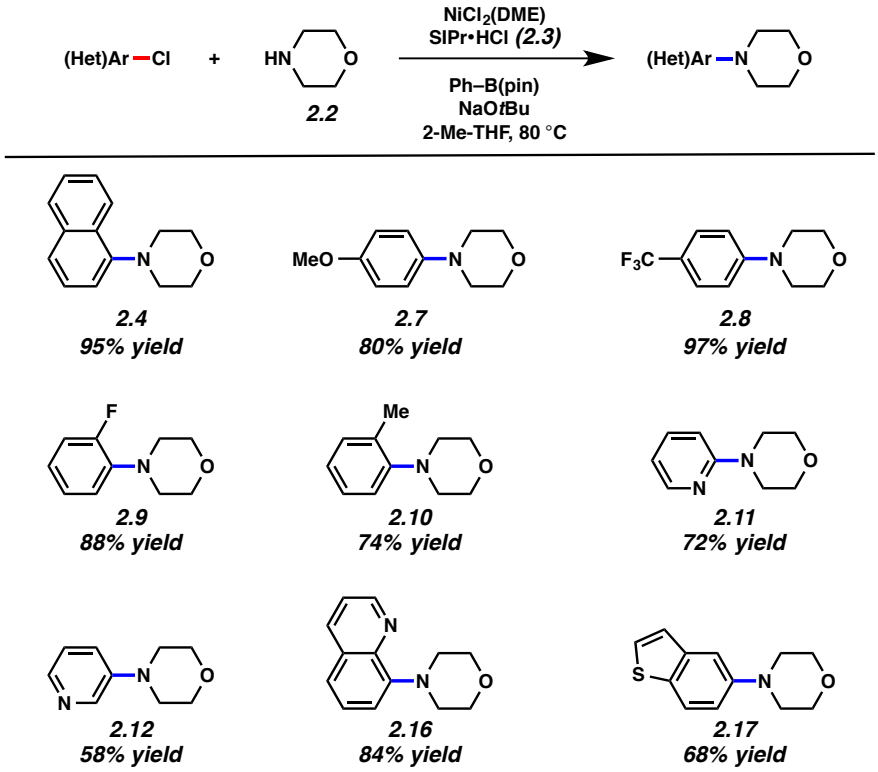


[a] Reactions were carried out with $NiCl_2$(DME) (5–15 mol %), SIPr•HCl (10–30 mol %), Ph–B(pin) (0.30–0.45 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.80 equiv), NaO*t*Bu (2.25–2.55 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. Yields were determined using hexamethylbenzene as an internal standard.

Similarly, an array of aryl chlorides underwent the nickel-catalyzed amination reaction with morpholine (**2.2**) in 2-Me-THF (Figure 2.3). Non-heterocyclic substrates, including those containing electronically or sterically biasing substituents, coupled smoothly, as shown by the formation of adducts **2.4** and **2.7**–**2.10**. Of note, commercially available heterocyclic aryl

chlorides could also be employed, thus giving rise to products **2.11**, **2.12**, **2.16**, and **2.17**. The tolerance of the methodology to pyridines, quinolines, and benzothiophenes suggests the utility of our coupling conditions for applications in drug discovery.

Figure 2.3. Coupling of (hetero)aryl chlorides with morpholine in 2-Me-THF.[a]

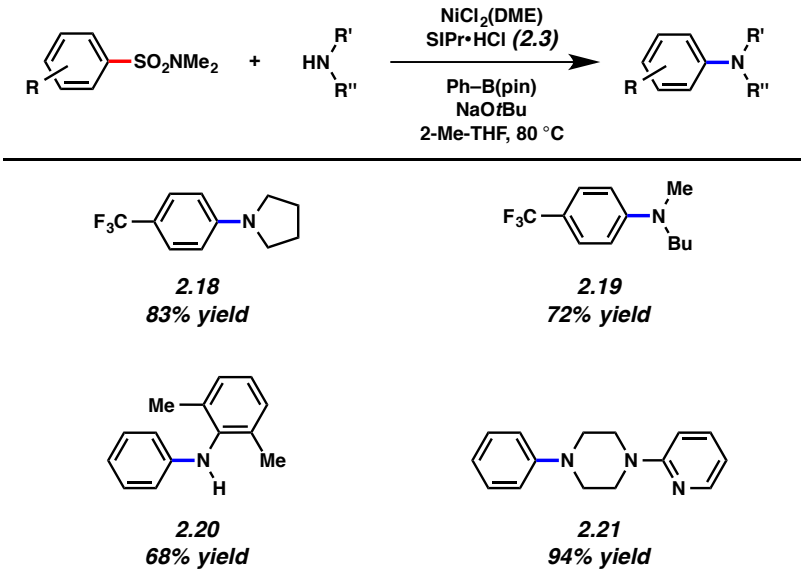


[a] Reactions were carried out with $NiCl_2$(DME) (5–15 mol %), SIPr•HCl (10–30 mol %), Ph–B(pin) (0.35–0.70 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.80 equiv), NaOtBu (2.25–2.70 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. Yields were determined using hexamethylbenzene as an internal standard.

As shown in Figure 2.4, the scope of this amination methodology is not limited to the use of morpholine as the amine coupling partner. For example, pyrrolidine could be employed to give aminated product **2.18**. As demonstrated by the formation of **2.19**, the acyclic amine n-methylbutylamine was also tolerated in this methodology. Additionally, we found that 2,6-

dimethylaniline, despite its steric hindrance, underwent the desired amination to give the unsymmetrical biaryl amine product **2.20**. We were also delighted to find that a piperazine nucleophile bearing a pyridine ring coupled smoothly to give product **2.21** in 94% yield.

Figure 2.4. Scope of amine component in the coupling reaction.[a]

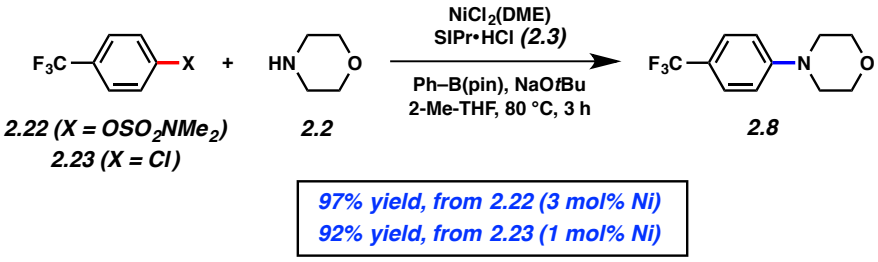


[a] Reactions were carried out with NiCl2(DME) (5–15 mol %), SIPr•HCl (10–30 mol %), Ph–B(pin) (0.35–0.75 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.20–2.40 equiv), NaOtBu (2.10–3.45 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. Yields were determined using hexamethylbenzene as an internal standard.

2.4 Gram-Scale Couplings

One general limitation pertaining to nickel-catalyzed cross-couplings is the frequent use of high catalyst loadings (i.e., often >10%).[2d–h] Whereas progress has been made in rendering nickel-catalyzed Suzuki–Miyaura couplings more efficient,[4,6i] corresponding achievements in nickel-mediated amination reactions have been lacking. To address this challenge, we tested the coupling of trifluoromethyl-containing sulfamate and chloride substrates **2.22** and **2.23**, respectively, in the amination reaction with **2.2** using 2-Me-THF as solvent (Figure 2.5). Using 3 and 1 mol% Ni, respectively, we found that gram-scale couplings could be achieved to give the arylated morpholine product **2.8** in excellent yields.

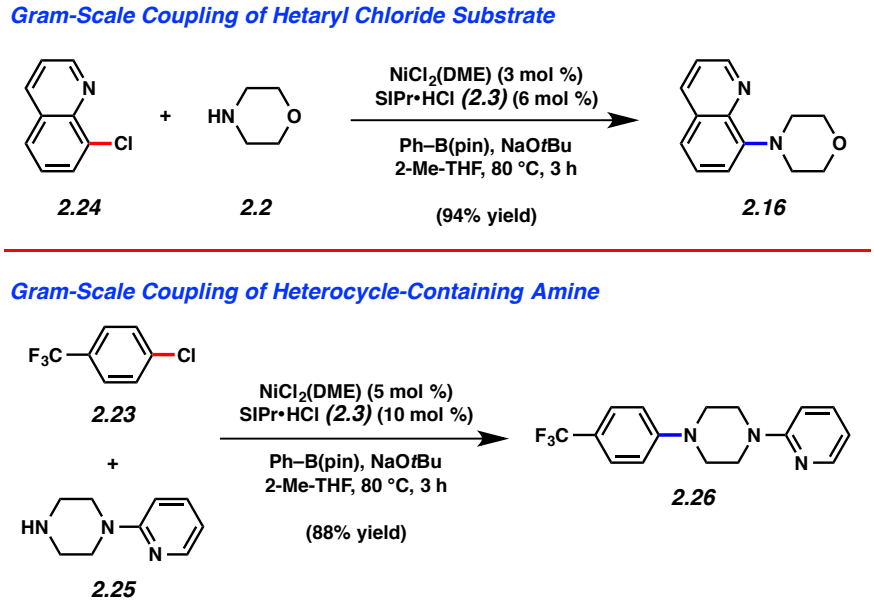
Figure 2.5. Gram-scale couplings of trifluoromethyl-containing substrates.



As noted earlier, the amination of heterocyclic substrates in 2-Me-THF provides a promising tool for the synthesis of pharmaceutical candidates. To further probe this notion, we tested the gram-scale couplings of heterocycle-containing substrates, as shown in Figure 2.6. Chloroquinoline **2.24** underwent facile coupling with morpholine (**2.2**) to generate aminated product **2.16** in 94% yield. This coupling was performed on gram-scale using 3 mol % Ni. Finally, we tested the gram-scale coupling of trifluoromethylated aryl chloride **2.23** with pyridyl

piperazine derivative **2.25**. This reaction provided adduct **2.26** in 88% yield; of note, **2.26** contains two heterocycles and a trifluoromethyl group, all of which are motifs commonly seen in pharmaceuticals.

Figure 2.6. Gram-scale couplings of heterocyclic substrates.



2.5 Conclusion

In summary, we have developed the nickel-catalyzed coupling of a variety of electrophilic substrates (e.g., halides and pseudohalides) with amines using the attractive, green solvent 2-Me-THF. The couplings of aryl *O*-sulfamates and aryl chlorides proceed in the highest yields, and may be achieved using an air-stable nickel precatalyst. The methodology has a broad scope and is tolerant of electronically biasing substituents, sterics, and even pharmaceutically-relevant heterocycles. The scalability of the nickel-catalyzed amination in 2-Me-THF using low catalyst loading bodes well for future synthetic applications in drug discovery and other arenas.

2.6 Experimental Section

2.6.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen and commercially obtained reagents were used as received. Amines were purified by filtration over basic Brockman Grade I 58 Å Alumina (Activity 1), followed by distillation over calcium hydride prior to use. $NiCl_2$(DME) was obtained from Strem Chemicals. NaO*t*Bu, the amines, SIPr•HCl, and Ph–B(pin) were obtained from Sigma-Aldrich and Alfa Aesar. Halogenated substrates were obtained from Combi-Blocks, Sigma-Aldrich, and Oakwood Products, Inc. 2-Me-THF was obtained from Acros Organics [2-Methyltetrahydrofuran, 99+%, pure, stabilized] and used without further purification. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm for analytical chromatography and 0.5 mm for preparative chromatography) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, iodine, vanillin, and potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 400, 500, and 600 MHz) and are reported relative to residual solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration and are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$. Data for ^{13}C NMR are reported in terms of chemical shift (at 125 MHz) and are referenced to the residual solvent peak 77.16 for $CDCl_3$. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency absorption (cm^{-1}). Uncorrected melting points were measured using a Digimelt MPA160 melting

point apparatus. High-resolution mass spectra were obtained from the UCLA Mass Spectrometry Facilities.

2.6.2 Experimental Procedures

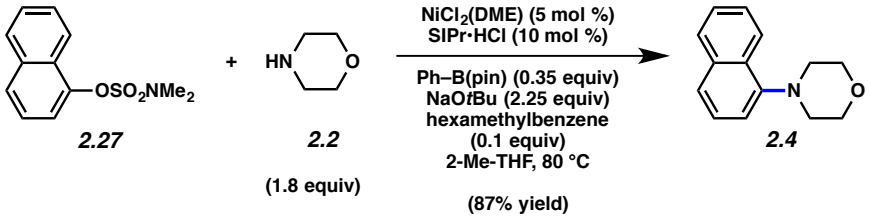
2.6.2.1 Syntheses of Aryl Pseudohalide Substrates

Note: Experimental procedures for the syntheses of the aryl triflates,[18] tosylates,[19] pivalates,[20] carbamates,[21] and sulfamates[21a,22] shown in Table 2.2 and Figures 2.2, 2.4, and 2.5 have previously been reported.

2.6.2.2 Solvent Optimization and Scope of Electrophile

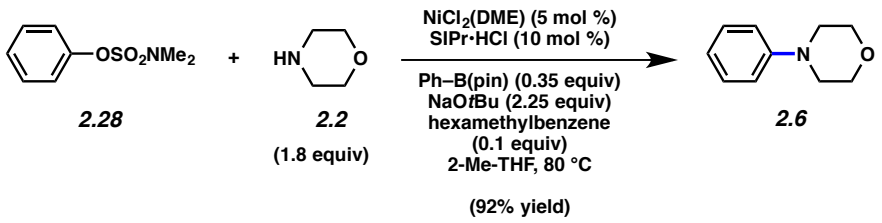
Representative Procedure for Amination of Electrophiles from Table 2.1 (coupling of naphthylchloride 2.1 is used as an example). A 4 mL reaction vial with a magnetic stir bar was charged with Ph–B(pin) (57.5 mg, 0.275 mmol, 0.55 equiv), anhydrous powdered NaO*t*Bu (88.9 mg, 0.925 mmol, 1.85 equiv), $NiCl_2$(DME) (5.5 mg, 0.025 mmol, 5 mol %), hexamethylbenzene (8.1 mg, 0.050 mmol, 0.1 equiv), and SIPr•HCl (21.7 mg, 0.0506 mmol, 10 mol %). Subsequently, toluene (2.5 ml), naphthylchloride **2.1** (81.3 mg, 0.500 mmol, 1.0 equiv), and morpholine (87.1 μL, 0.900 mmol, 1.8 equiv) were added sequentially. The resulting heterogenous mixture was stirred for 1 min while purging with N_2, and the vial was sealed with a Teflon-lined screw cap. The mixture was stirred at 23 °C for 1 h, and then at 80 °C for 3 h in a preheated aluminum block. The reaction vessel was allowed to cool to 23 °C and the mixture was filtered by passage through a plug of silica gel (EtOAC eluent, 5 mL), and then concentrated under reduced pressure. The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[23]

2.6.2.3 Aminations of Aryl Sulfamates and Chlorides



Representative Procedure (coupling of naphthylsulfamate 2.27 is used as an example). A 4 mL reaction vial with a magnetic stir bar was charged with Ph–B(pin) (36.6 mg, 0.175 mmol, 0.35 equiv), anhydrous powdered NaO*t*Bu (108.1 mg, 1.125 mmol, 2.25 equiv), $NiCl_2$(DME) (5.5 mg, 0.025 mmol, 5 mol %), hexamethylbenzene (8.1 mg, 0.050 mmol, 0.1 equiv), and SIPr•HCl (21.7 mg, 0.0506 mmol, 10 mol %). Subsequently, 2-Me-THF (2.5 ml), naphthylsulfamate **2.27** (125.7 mg, 0.5002 mmol, 1.0 equiv), and morpholine (87.1 μL, 0.900 mmol, 1.8 equiv) were added, sequentially. The resulting heterogenous mixture was stirred for 1 min while purging with N_2, and the vial was sealed with a Teflon-lined screw cap. The mixture was stirred at 23 °C for 1 h, and then at 80 °C for 3 h in a preheated aluminum heating block. The reaction vessel was allowed to cool to 23 °C and the mixture was filtered by passage over a plug of silica gel (EtOAC eluent, 5 mL), and then concentrated under reduced pressure. The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[23]

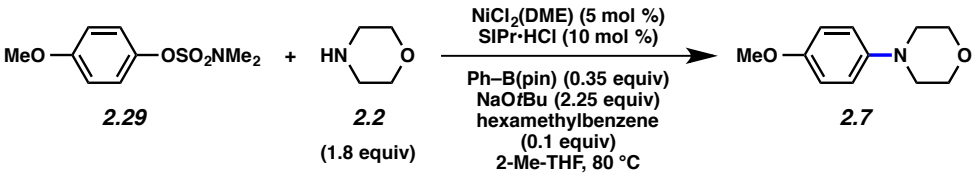
Any modifications of the conditions shown in the representative procedure above are specified in the following schemes, which depict all of the results shown in Figures 2.2–2.4.



2.28 *2.2* (1.8 equiv) *2.6*

(92% yield)

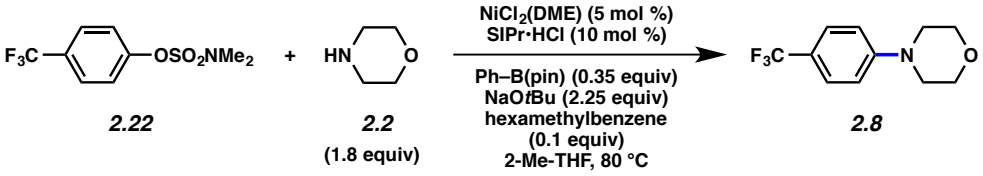
2.6 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[24]



2.29 *2.2* (1.8 equiv) *2.7*

(81% yield)

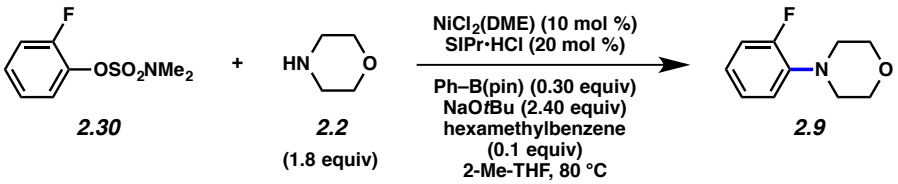
2.7 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbezene as an internal standard. Spectral data match those previously reported.[25]



2.22 *2.2* (1.8 equiv) *2.8*

(79% yield)

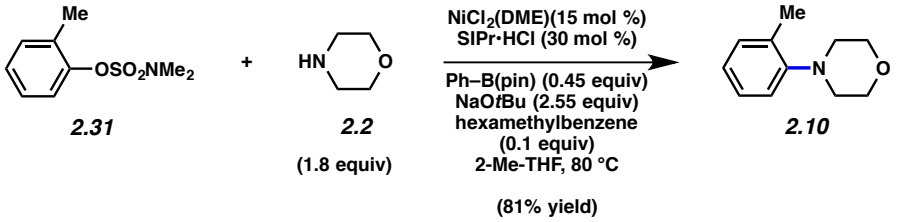
2.8 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[26]



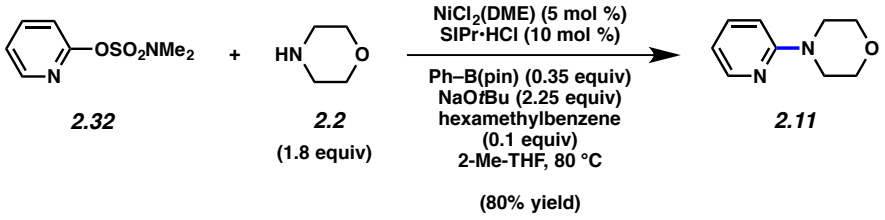
2.30 *2.2* (1.8 equiv) *2.9*

(89% yield)

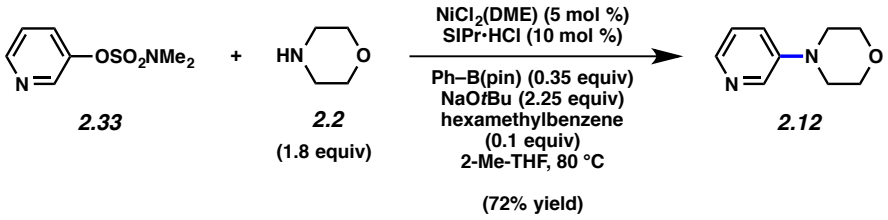
2.9 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[27]



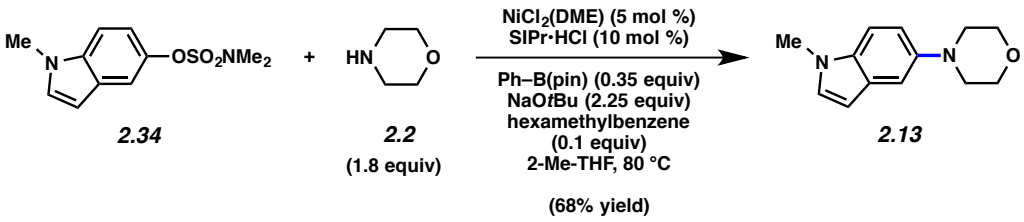
2.10 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[10e]



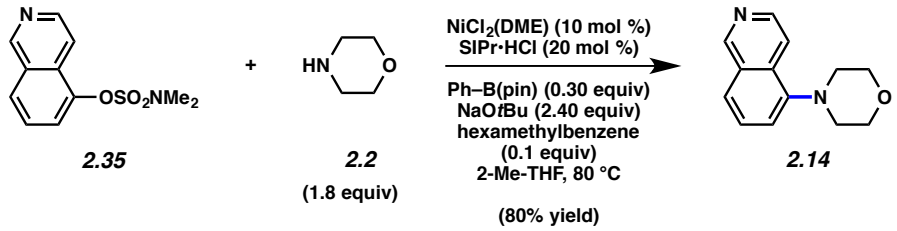
2.11 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[28]



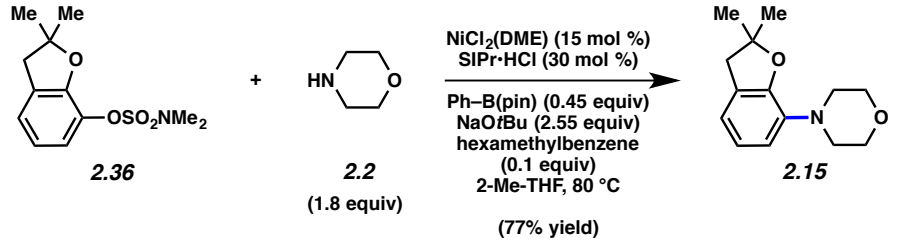
2.12 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[28]



2.13 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[29]

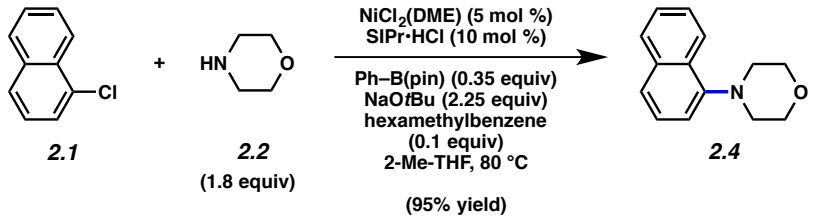


2.14 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. An analytic sample of **2.14** was prepared by filtration of the reaction mixture through a plug of silica gel (EtOAc eluent, 5 mL), evaporation of the solvent under reduced pressure, and purification of an aliquot of the crude residue by preparative thin-layer chromatography (5:1 Hexanes:EtOAC, 20x20 cm). R_f 0.18 (1:1 Hexanes:EtOAc); ^{1}H NMR: (400 MHz, $CDCl_3$): δ 9.23 (s, 1H), 8.53 (d, J = 6.0, 1H), 7.93 (d, J = 6.0, 1H), 7.68 (d, J = 8.0, 1H), 7.54 (app t, J = 8.0, 1H), 7.27 (t, J = 7.5, 1H), 3.99 (t, J = 4.5, 4H), 3.11 (t, J = 4.5, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.1, 147.6, 141.8, 130.8, 129.1, 126.5, 122.0, 117.7, 115.5, 66.4, 52.4; IR (film): 2966, 2825, 1617, 1582, 1489, 1454, 1433, 1387, 1263, 1115, 1055, 1033 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{13}H_{15}N_2O$, 215.11789; found 215.11741.

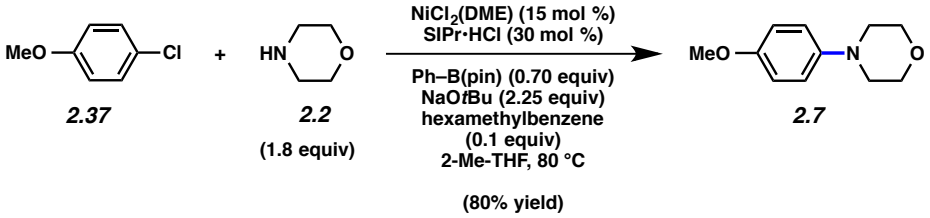


2.15 (Figure 2.2). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. An analytic sample of **2.15** was prepared by filtration of the reaction mixture

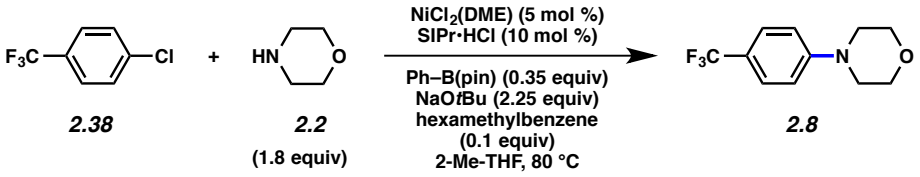
through a plug of silica gel (EtOAc eluent, 5 mL), evaporation of the solvent under reduced pressure, and purification of an aliquot of the crude residue by preparative thin-layer chromatography (5:1 Hexanes:EtOAC, 20x20 cm). R_f 0.27 (9:1 Hexanes:EtOAc); ^{1}H NMR: (400 MHz, $CDCl_3$): δ 6.81–6.77 (m, 3H), 6.68 (dd, J = 6.7, 2.2, 1H), 3.88 (t, J = 4.5, 4H), 3.13 (t, J = 4.5, 4H), 2.99 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 136.4, 128.0, 120.7, 118.6, 115.3, 86.8, 67.1, 50.0, 43.2, 28.4; IR (film): 2968, 2854, 1608, 1455, 1269, 1119, 1006 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.14886; found 234.14766.



2.4 (Figure 2.3). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[23]



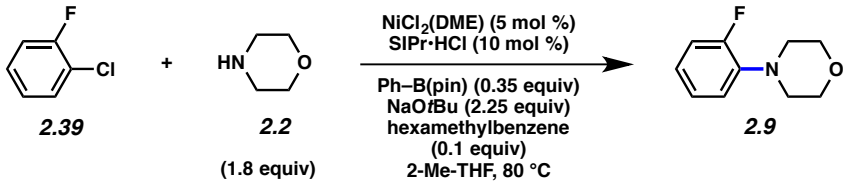
2.7 (Figure 2.3). The yield was determined by 1H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[25]



2.38 *2.2* (1.8 equiv) *2.8*

(97% yield)

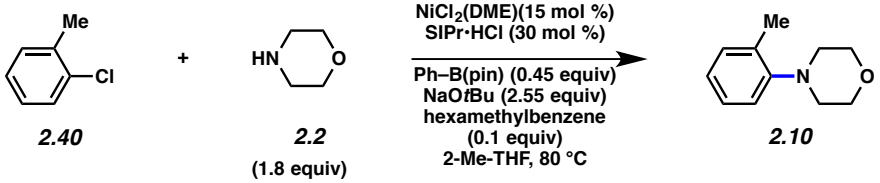
2.8 (Figure 2.3). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[26]



2.39 *2.2* (1.8 equiv) *2.9*

(88% yield)

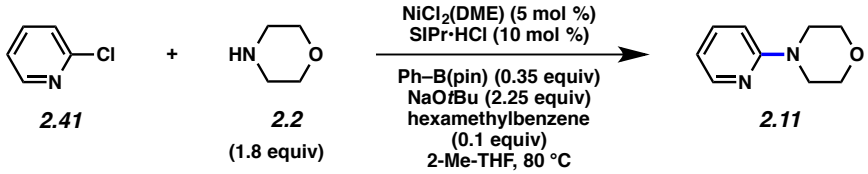
2.9 (Figure 2.3). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[27]



2.40 *2.2* (1.8 equiv) *2.10*

(74% yield)

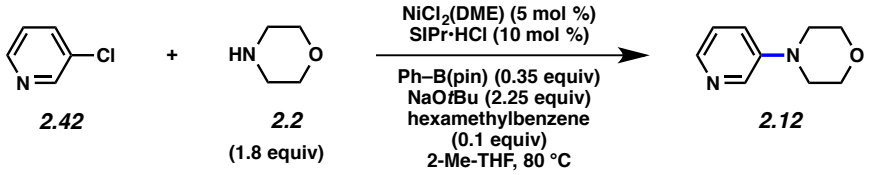
2.10 (Figure 2.3). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[10e]



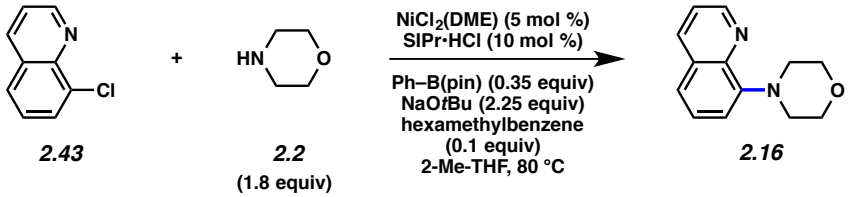
2.41 *2.2* (1.8 equiv) *2.11*

(72% yield)

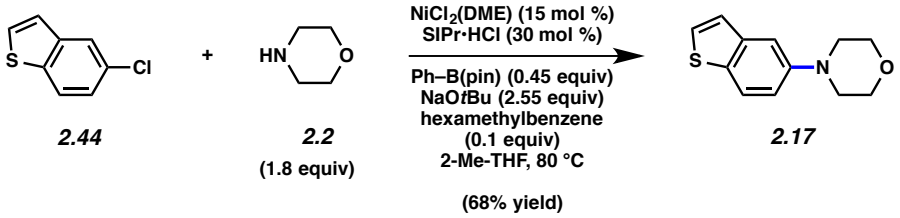
2.11 (Figure 2.3). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[28]



2.12 (Figure 2.3). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[28]

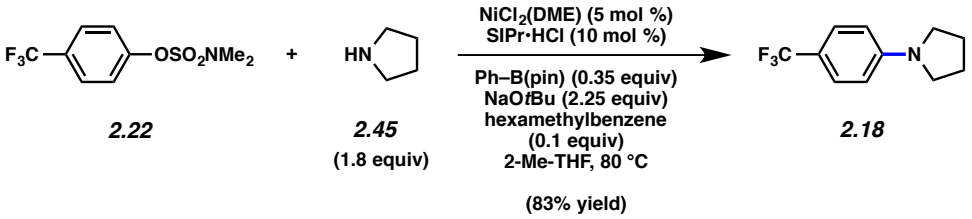


2.16 (Figure 2.3). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[30]

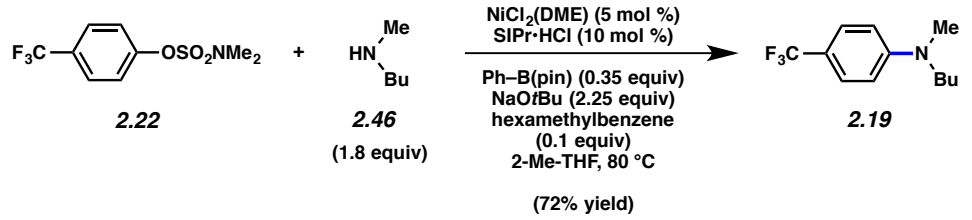


2.17 (Figure 2.3). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. An analytic sample of **2.17** was prepared by filtration of the reaction mixture through a plug of silica gel (EtOAc eluent, 5 mL), evaporation of the solvent under reduced pressure, and purification of an aliquot of the crude residue by preparative thin-layer chromatography (5:1 Hexanes:EtOAC, 20x20 cm). R_f 0.21 (9:1 Hexanes:EtOAc); ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.8, 1H), 7.41 (d, J = 5.4, 1H), 7.29 (br s, 1H), 7.24 (d, J = 5.4, 1H), 7.07 (dd, J = 8.8, 2.2, 1H), 3.90 (t, J = 4.5, 4H), 3.20 (t, J = 4.5, 4H); ^{13}C NMR (125 MHz,

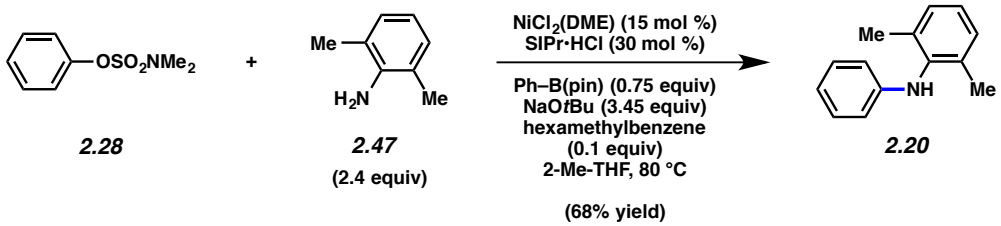
$CDCl_3$): δ 149.2, 140.8, 132.3, 127.3, 123.8, 123.0, 116.3, 109.7, 67.1, 50.8; IR (film): 2966, 2909, 2829, 1595, 1444, 1262, 1233, 1120 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{12}H_{14}SNO$, 220.07906; found 220.07835.



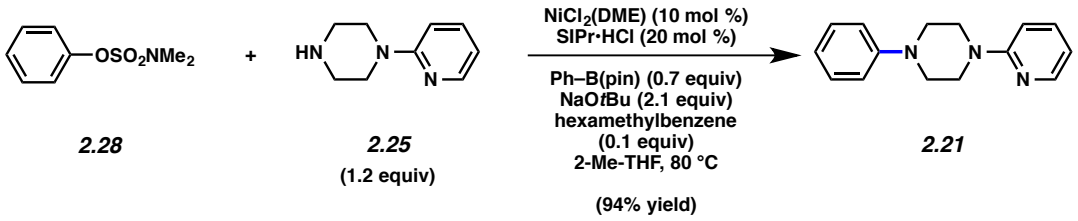
2.18 (Figure 2.4). The yield was determined by ^1H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[31]



2.19 (Figure 2.4). The yield was determined by ^1H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[29]

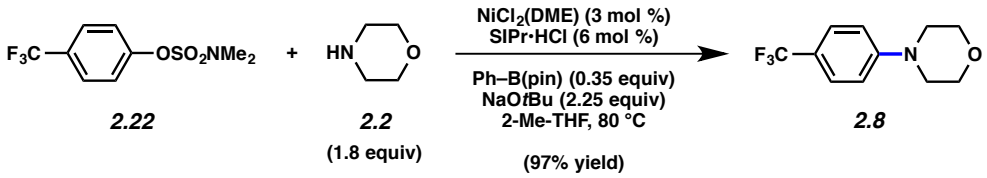


2.20 (Figure 2.4). The yield was determined by ^1H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[10e]



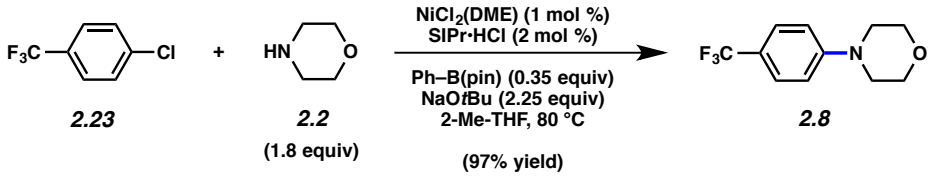
2.21 (Figure 2.4). The yield was determined by ^{1}H NMR analysis with hexamethylbenzene as an internal standard. Spectral data match those previously reported.[7e]

2.6.2.4 Isolation Experiments

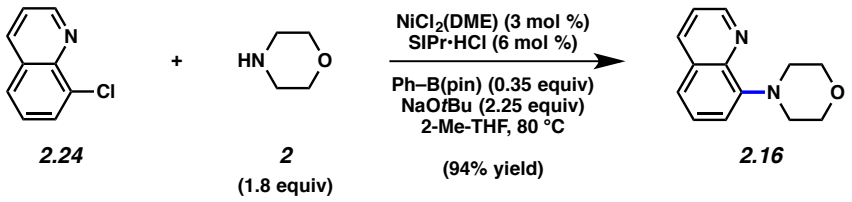


2.8 (Figure 2.5). A 100 mL round bottom flask with a magnetic stir bar was charged with Ph–B(pin) (271.5 mg, 1.30 mmol, 0.35 equiv), anhydrous powdered NaO*t*Bu (802.2 mg, 8.35 mmol, 2.25 equiv), $NiCl_2$(DME) (24.5 mg, 0.11 mmol, 3 mol %), and SIPr•HCl (95.5 mg, 0.22 mmol, 6 mol %). Subsequently, 2-Me-THF (18.6 ml), trifluorobenzosulfamate **2.22** (1.0 g, 3.71 mmol, 1.0 equiv), and morpholine (578 μL, 6.69 mmol, 1.8 equiv) were added, sequentially. The resulting heterogenous mixture was stirred for 1 min while purging with N_2, and then under an atmosphere of N_2 for 1 h. The reaction was then equipped with a reflux condenser and placed in an oil bath, preheated to 80 °C, for 3 h. The reaction flask was allowed to cool to 23 °C and the mixture was filtered by passage over a plug of silica gel (EtOAC eluent, 5 mL). After concentration under reduced pressure, the crude residue was purified by flash chromatography (4:1 Hexanes:EtOAc)

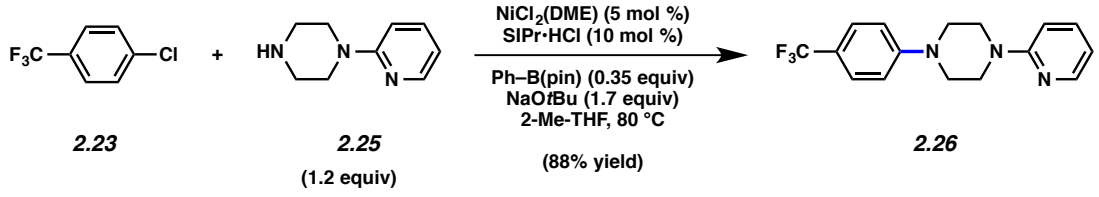
to yield amine **2.8** (832.1 mg, 97%) as a white solid. Spectral data match those previously reported.[26]



2.8 (Figure 2.5). A 100 mL round bottom flask with a magnetic stir bar was charged with Ph–B(pin) (405.4 mg, 1.94 mmol, 0.35 equiv), anhydrous powdered NaO*t*Bu (1.20 g, 12.47 mmol, 2.25 equiv), $NiCl_2$(DME) (12.2 mg, 0.06 mmol, 1 mol %), and SIPr•HCl (47.5 mg, 0.111 mmol, 2 mol %). Subsequently, 2-Me-THF (27.7 ml), trifluorobenzochloride **2.23** (1.0 g, 5.54 mmol, 1.0 equiv), and morpholine (863 μL, 9.97 mmol, 1.8 equiv) were added, sequentially. The resulting heterogenous mixture was stirred for 1 min while purging with N_2, and then under an atmosphere of N_2 at 23 °C for 1 h. The reaction was then equipped with a reflux condenser and placed in an oil bath, preheated to 80 °C, for 3 h. The reaction flask was allowed to cool to 23 °C and the mixture was filtered by passage through a plug of silica gel (EtOAC eluent, 5 mL). After concentration under reduced pressure, the crude residue was purified by flash chromatography (4:1 Hexanes:EtOAc) to yield amine **2.8** (1.18 g, 97%) as a white solid. Spectral data match those previously reported.[26]



2.16 (Figure 2.6). A 100 mL round bottom flask was charged with a magnetic stir bar, flame-dried under reduced pressure, and allowed to cool under N_2. The flask was then charged with Ph–B(pin) (447.1 mg, 2.14 mmol, 0.35 mol), anhydrous powdered NaO*t*Bu (1.32 g, 13.8 mmol, 2.25 equiv), $NiCl_2$(DME) (40.2 mg, 0.183 mmol, 3 mol %), and SIPr•HCl (157.3 mg, 0.367 mmol, 6 mol %). Subsequently, 2-Me-THF (30.6 mL), chloroquinoline **2.24** (1.0 g, 6.11 mmol, 1.0 equiv), and morpholine (95.1 μL, 11.0 mmol, 1.8 equiv) were added, sequentially. The resulting heterogenous mixture was stirred for 1 min while purging with N_2, and then under an atmosphere for 1 h. The reaction was then equipped with a reflux condenser and placed in an oil bath, preheated to 80 °C, for 3 h. The reaction flask was allowed to cool to 23 °C and the mixture was filtered by passage through a plug of silica gel (EtOAC eluent, 5 mL). After concentration under reduced pressure, the crude residue was purified by flash chromatography (2:1 Hexanes:EtOAc) to yield morpholino quinoline **2.16** (1.23 g, 94%) as a clear viscous oil. Spectral data match those previously reported.[30]



2.26 (Figure 2.6). A 100 mL round bottom flask was charged with a magnetic stir bar, flame-dried under reduced pressure, and allowed to cool under N_2. The flask was then charged with Ph–B(pin) (426.0 mg, 1.94 mmol, 0.35 equiv), anhydrous powdered NaO*t*Bu (904.9 mg, 9.42

mmol, 1.7 equiv), $NiCl_2$(DME) (60.9 mg, 0.277 mmol, 5 mol %), and SIPr•HCl (237.7 mg, 0.554 mmol, 10 mol %). Subsequently, 2-Me-THF (27.7 ml), 4-trifluoro (**21b**) (1.0 g, 5.54 mmol, 1.0 equiv), and 1-(2-pyridyl)piperizine (1.01 mL, 6.65 mmol, 1.2 equiv) were added, sequentially. The resulting heterogenous mixture was stirred for 1 min while purging with N_2, and then under an atmosphere of N_2 for 1 h. The reaction was then equipped with a reflux condenser and placed in an oil bath, preheated to 80 °C, for 3 h. The reaction flask was allowed to cool to 23 °C and the mixture was filtered by passage through a plug of silica gel (EtOAC eluent, 5 mL). After concentration under reduced pressure, the crude residue was purified by flash chromatography (8:1 Hexanes:EtOAc) to yield piperizine **2.26** (1.49 g, 88%) as an off-white solid. Spectral data match those previously reported.[32]

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(16) Aryl chlorides are attractive substrates as they are often available commercially or are easily synthesized. Additionally, aryl chlorides are often robust enough to be carried through multiple synthetic operations.

(17) Aryl sulfamates bear many notable features. They are easily synthesized from their corresponding phenols, which are often commercially available, and are generally stable to acidic and basic reaction conditions. Moreover, aryl sulfamates may be used to direct arene functionalization through electrophilic aromatic substitution or *ortho*-lithiation processes. For a discussion of these features, see: (*a*) Snieckus, V. *Chem. Rev*. **1990**, *90*, 879–933. (*b*) Hartung, C. G.; Snieckus V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: New York, 2002; pp. 330–367. (*c*) Macklin, T. K., Snieckus, V. *Org. Lett*. **2005**, *7*, 2519–

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Spectra Relevant to Chapter Two:

Nickel-Catalyzed Amination of Aryl Chlorides and Sulfamates

in 2-Me-THF

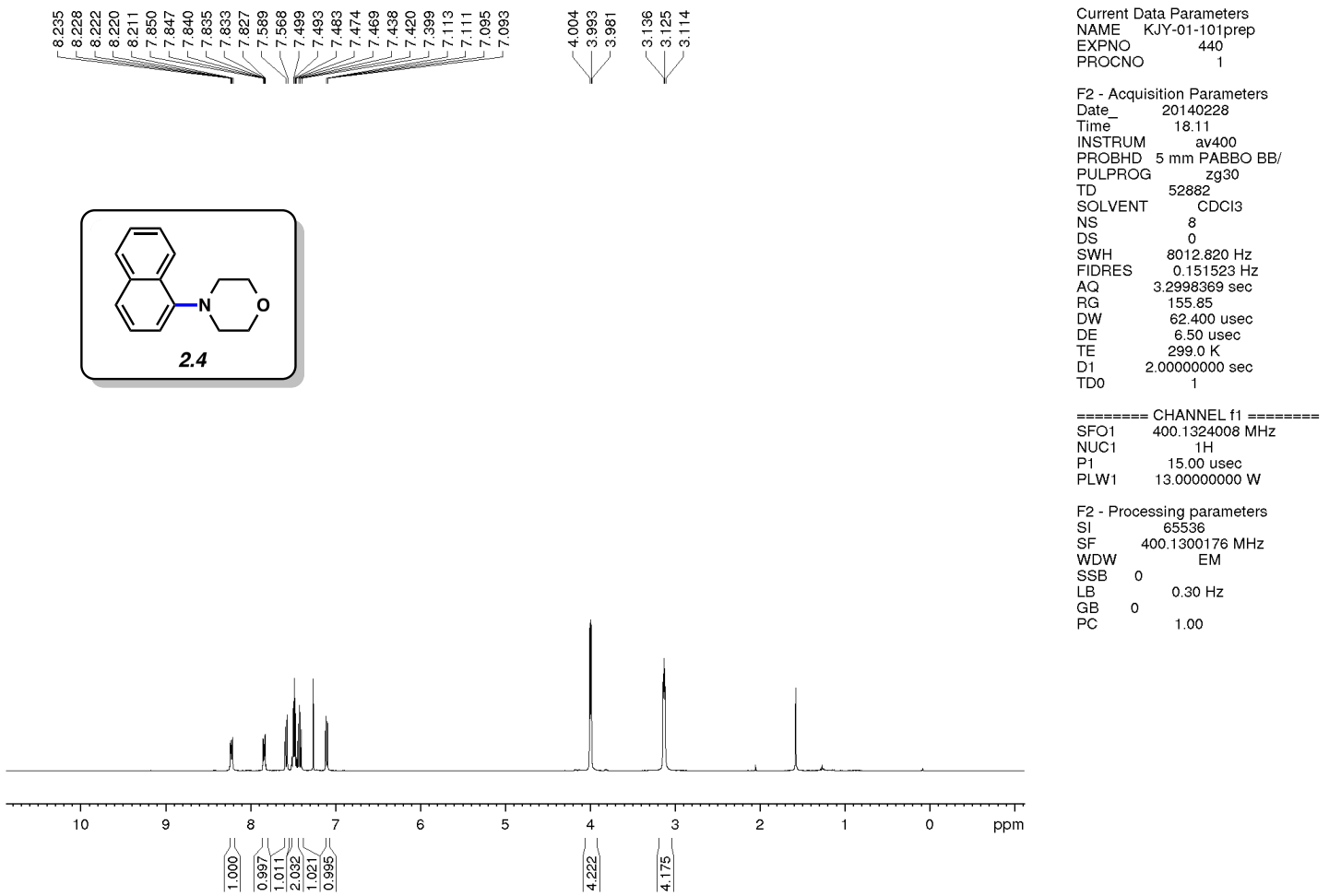


Figure 2.7. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.4**.

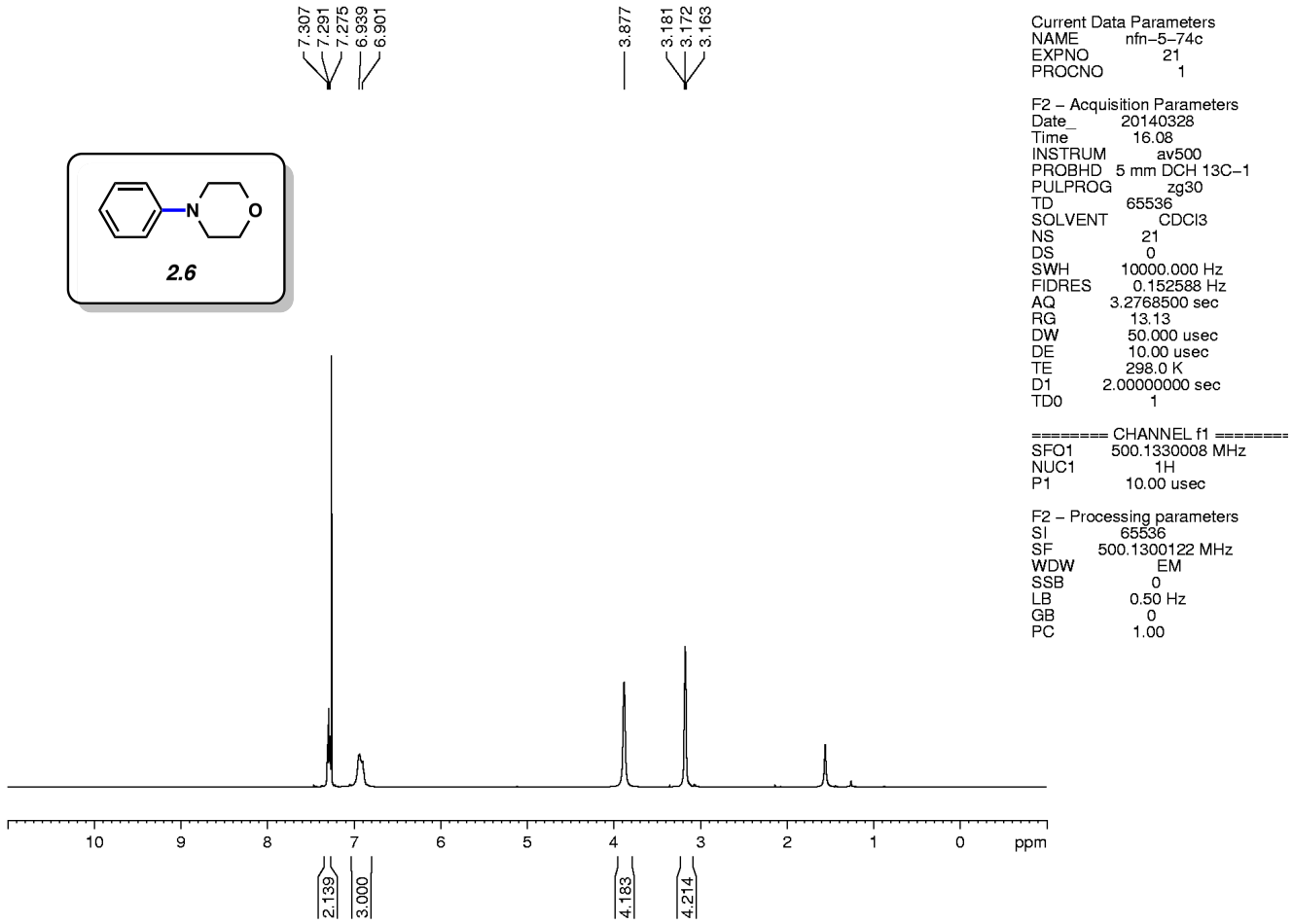
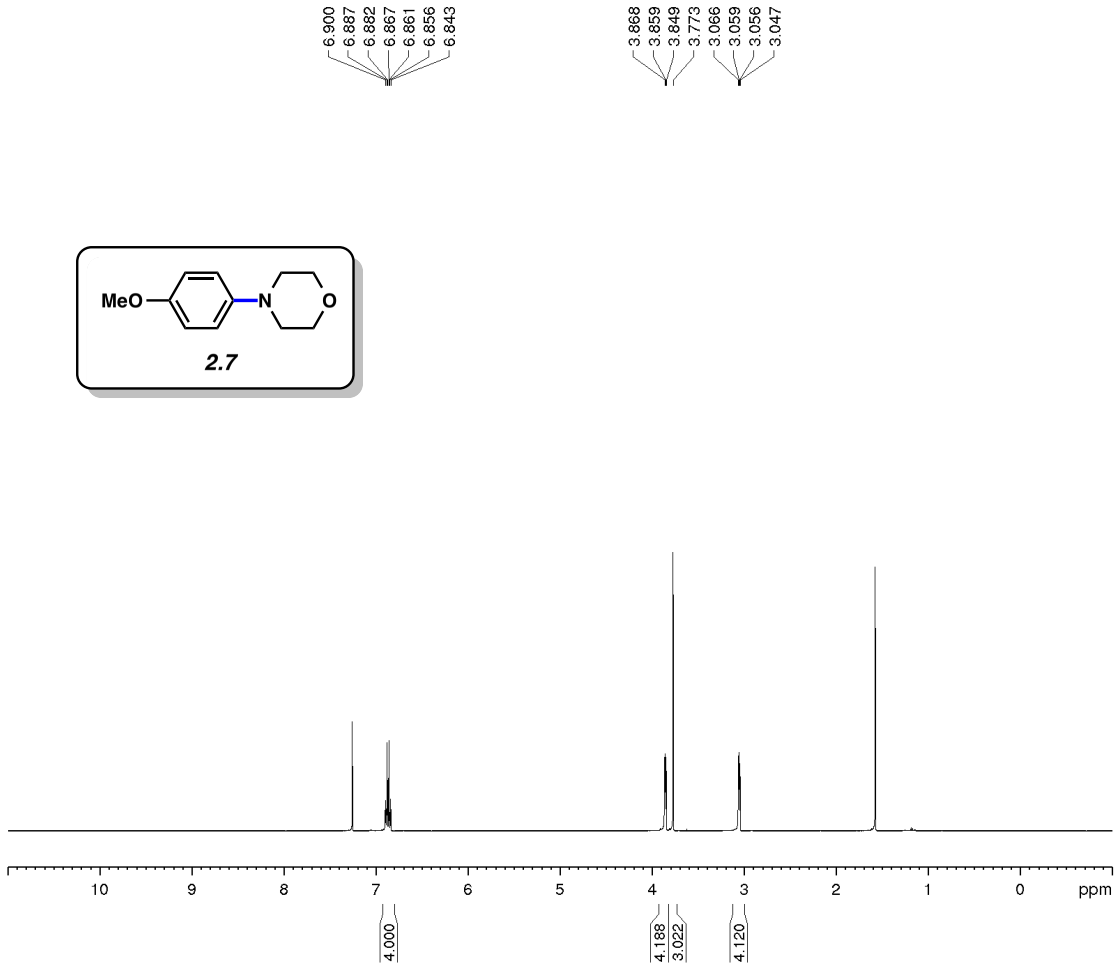


Figure 2.8. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.6**.



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PROCNO 1

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SOLVENT CDCl3
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FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 181
DW 50.000 usec
DE 6.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
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F2 - Processing parameters
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GB 0
PC 1.00

Figure 2.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.7**.

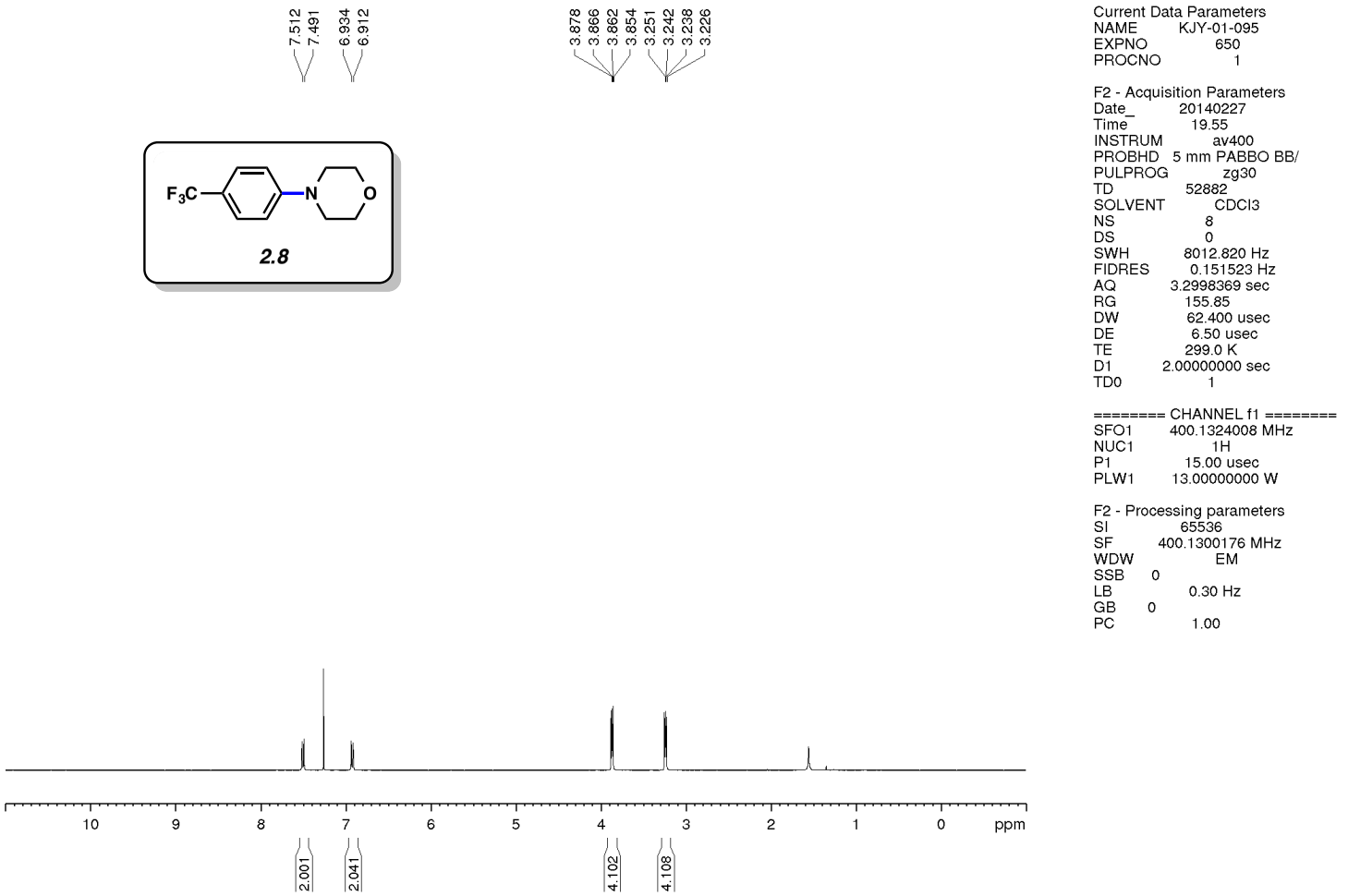


Figure 2.10. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.8**.

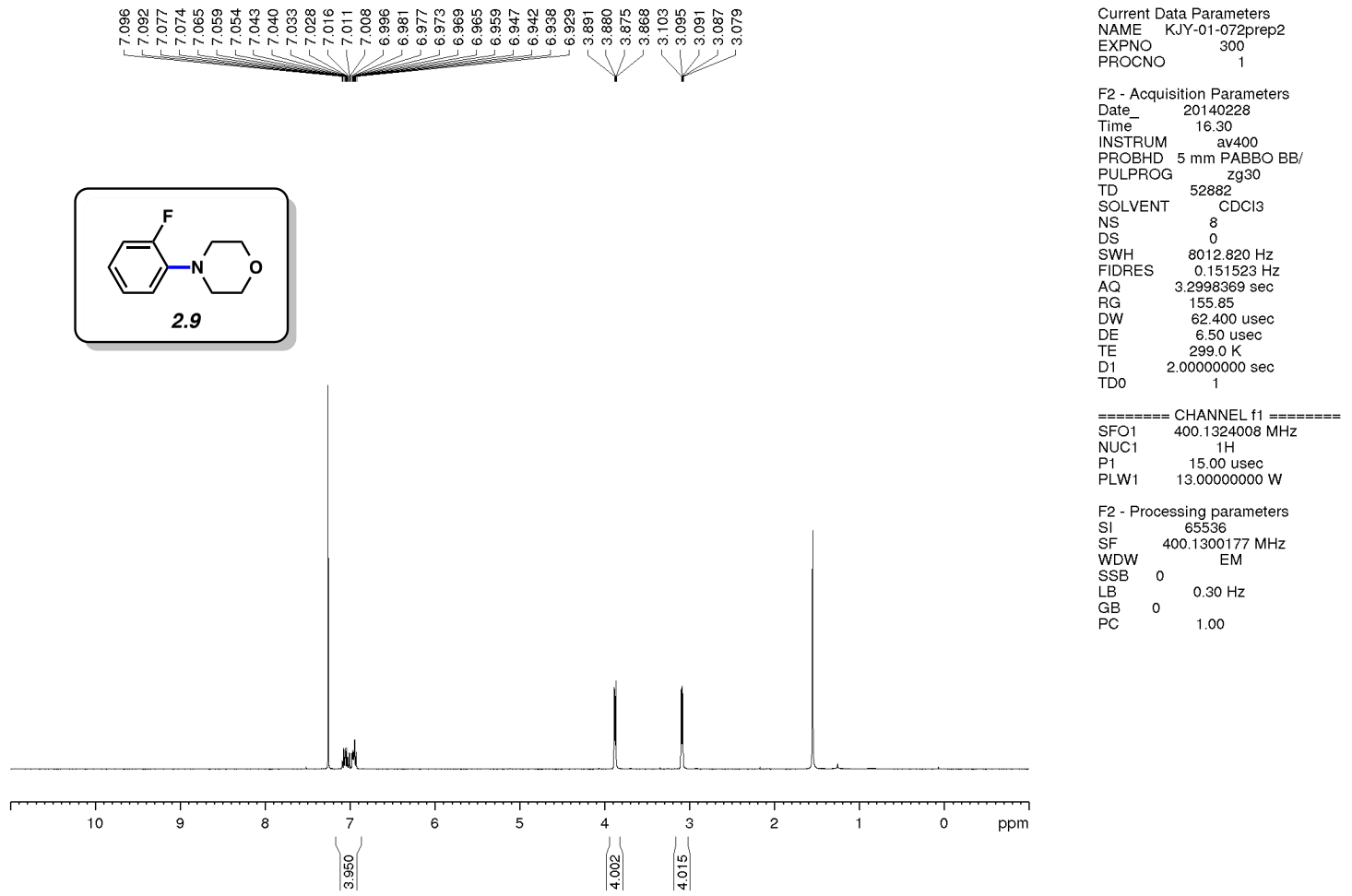


Figure 2.11. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.9**.

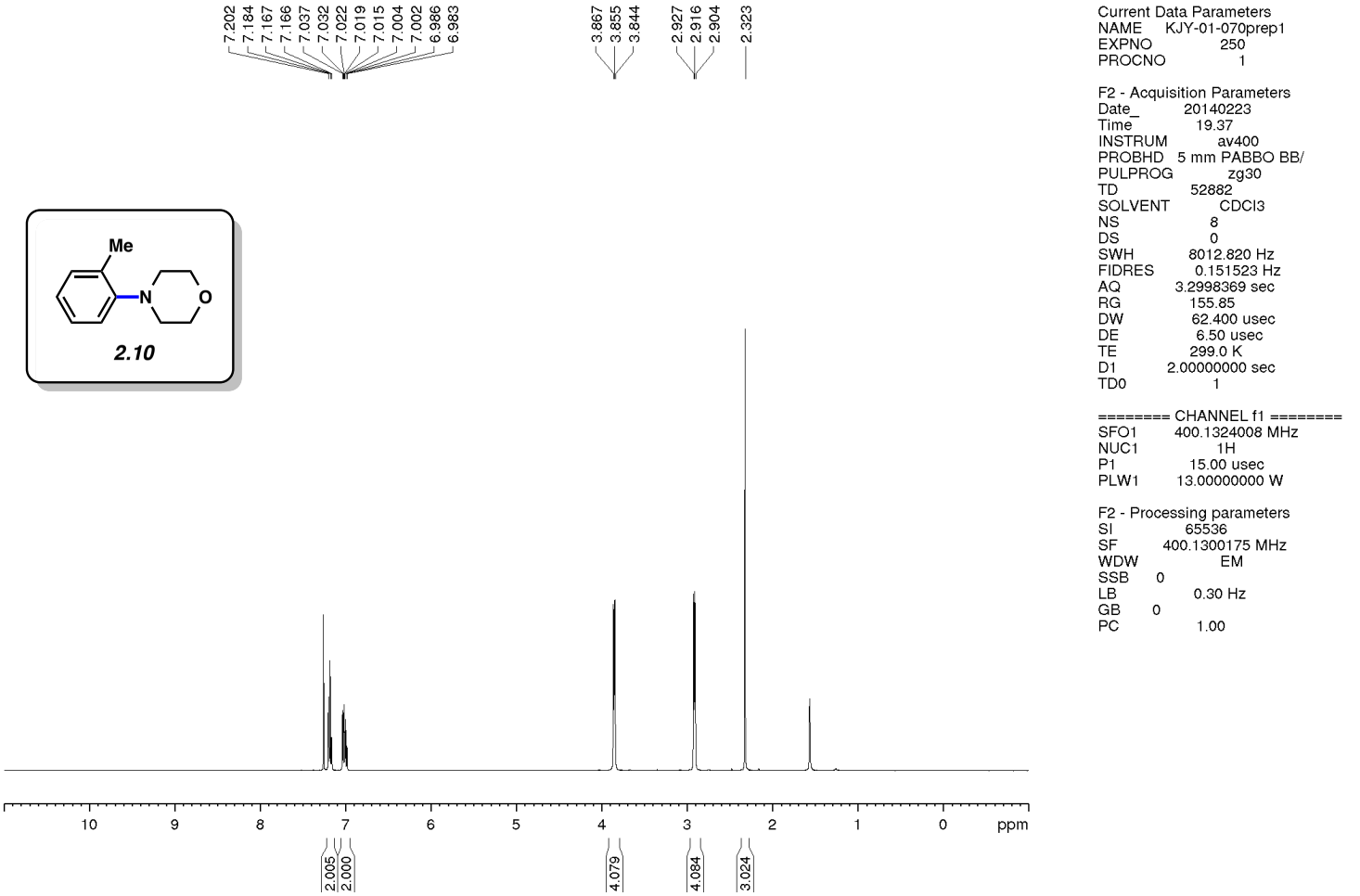
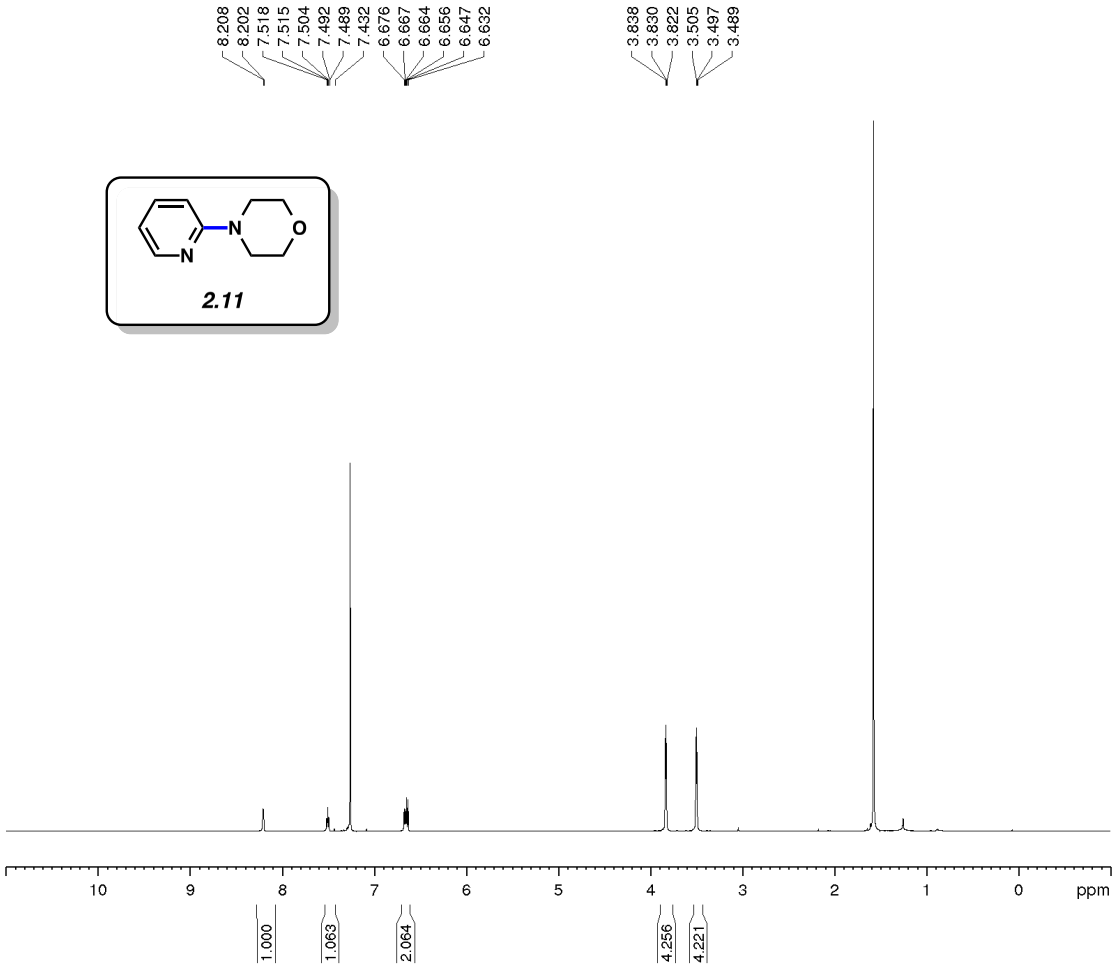


Figure 2.12. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.10**.



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AQ 2.6476543 sec
RG 256
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DE 6.50 usec
TE 680.7 K
D1 2.00000000 sec
TD0 1

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PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1336008 MHz

F2 - Processing parameters
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SF 600.1300297 MHz
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SSB 0
LB 1.00 Hz
GB 0
PC 1.00

Figure 2.13. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.11**.

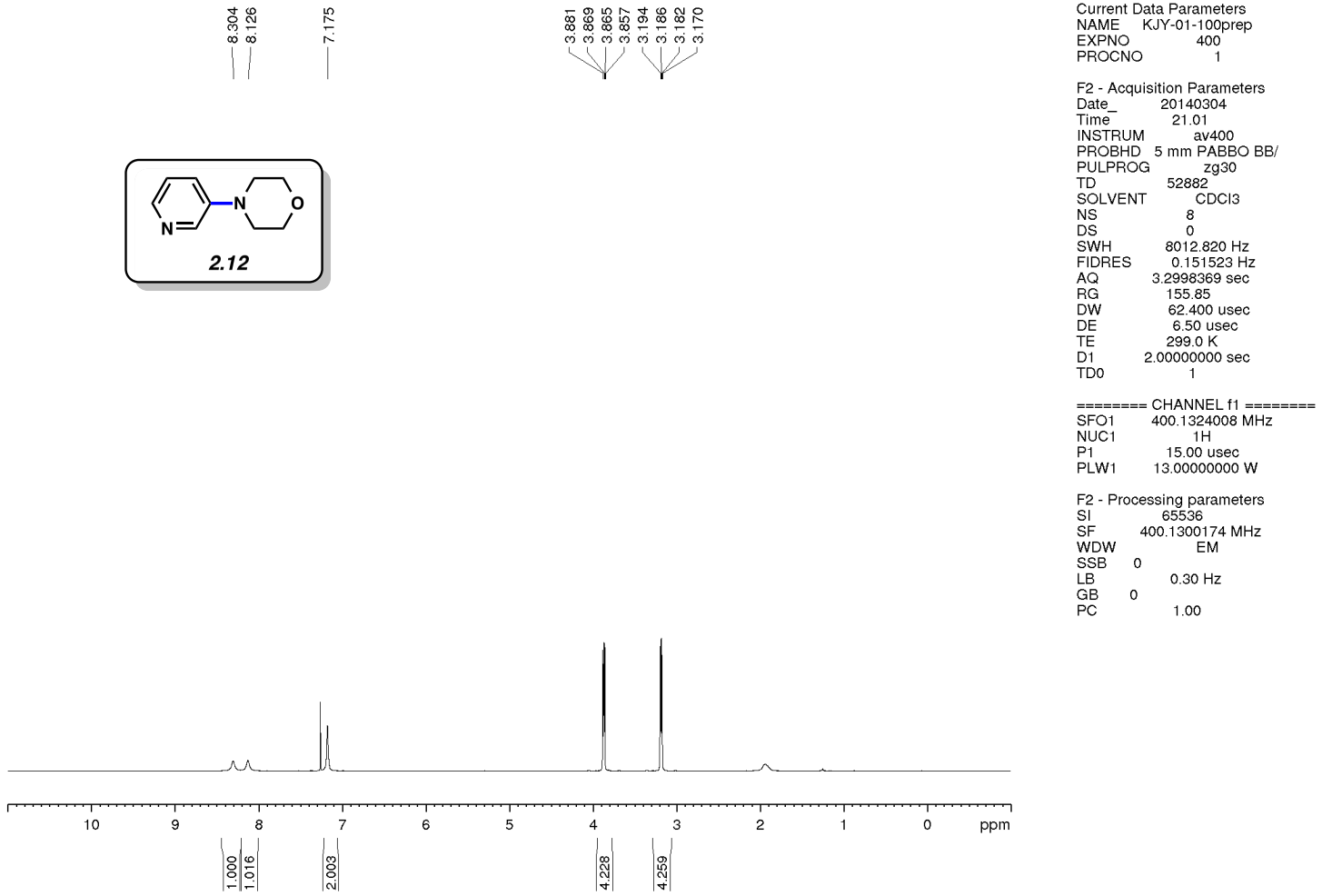

Figure 2.14. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.12**.

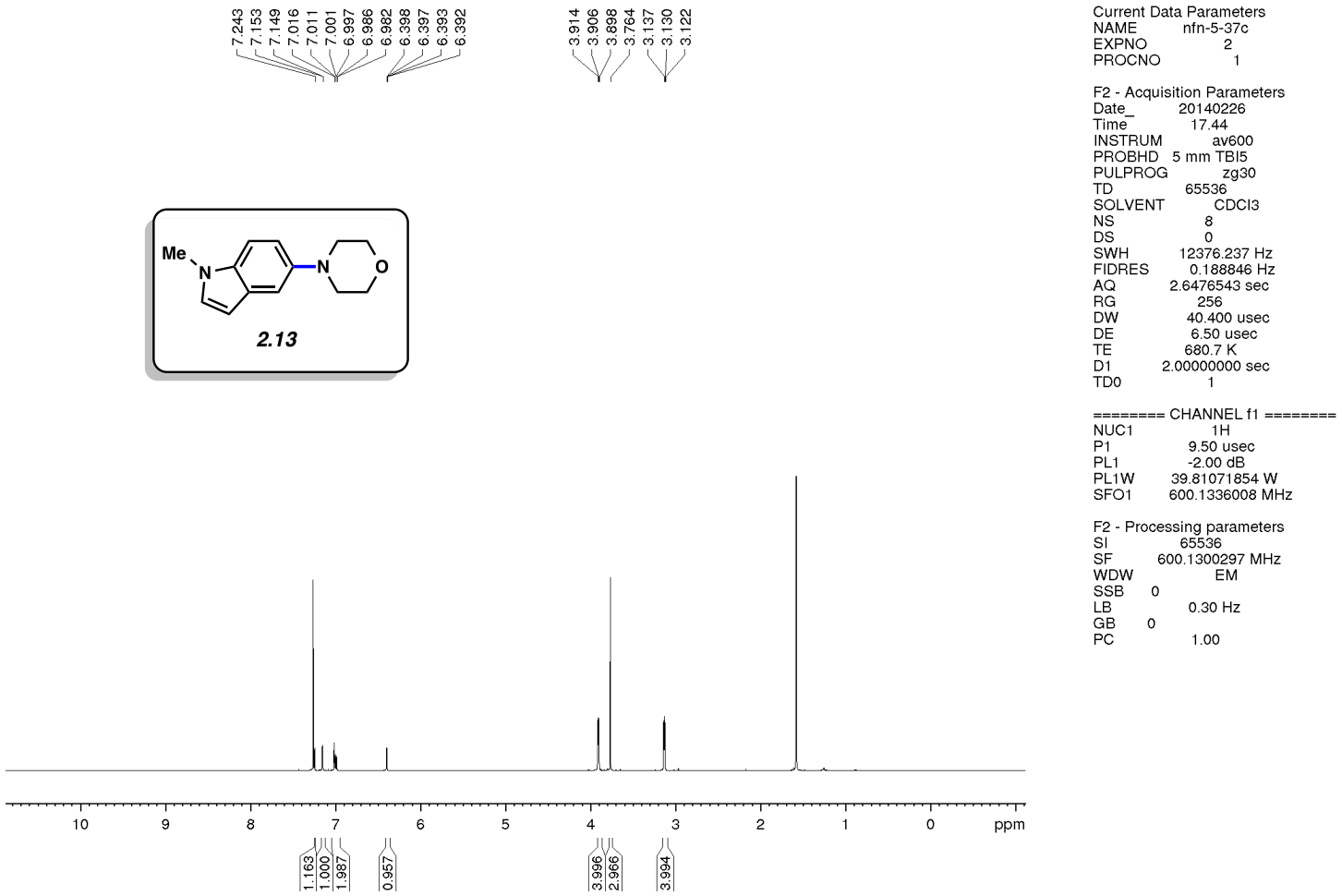

Figure 2.15. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.13**.

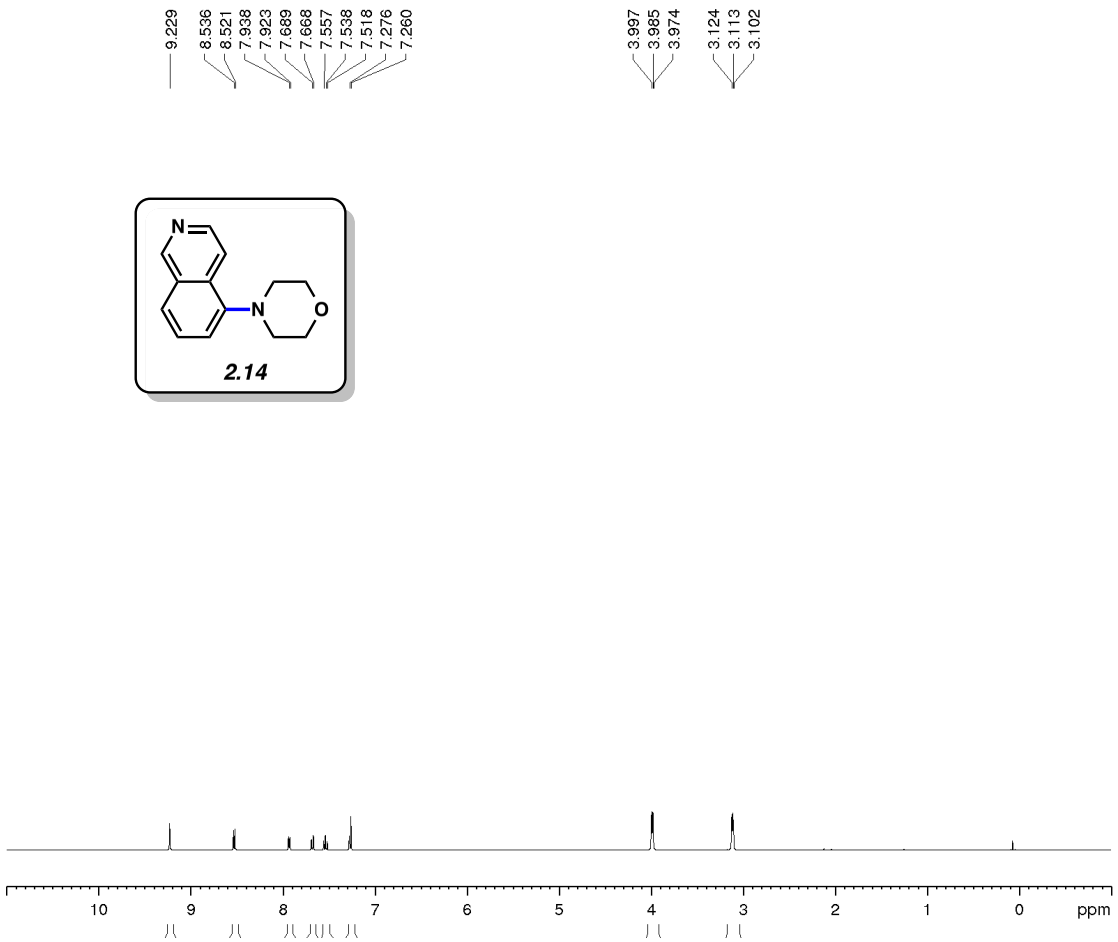

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Figure 2.16. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.14**.

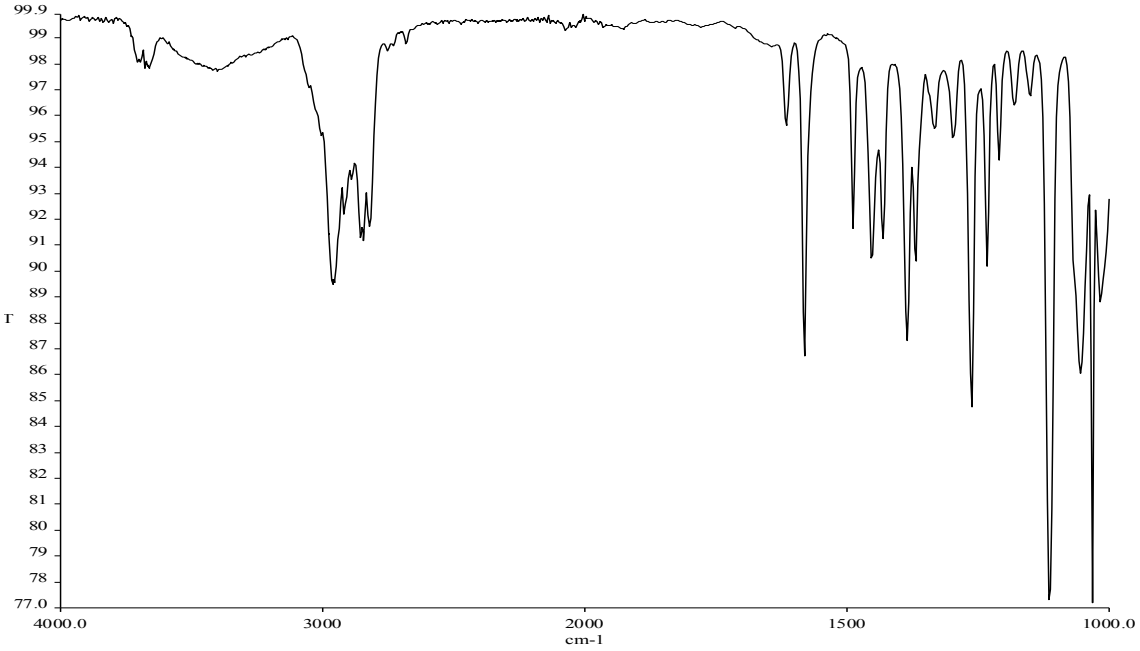


Figure 2.17. Infrared spectrum of compound **2.14**.

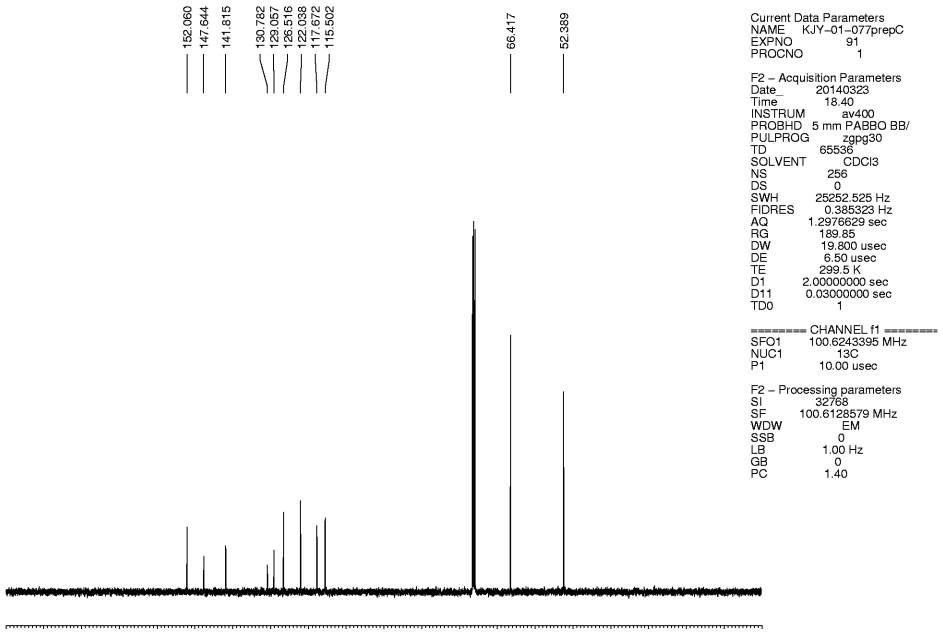


Figure 2.18. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.14**.

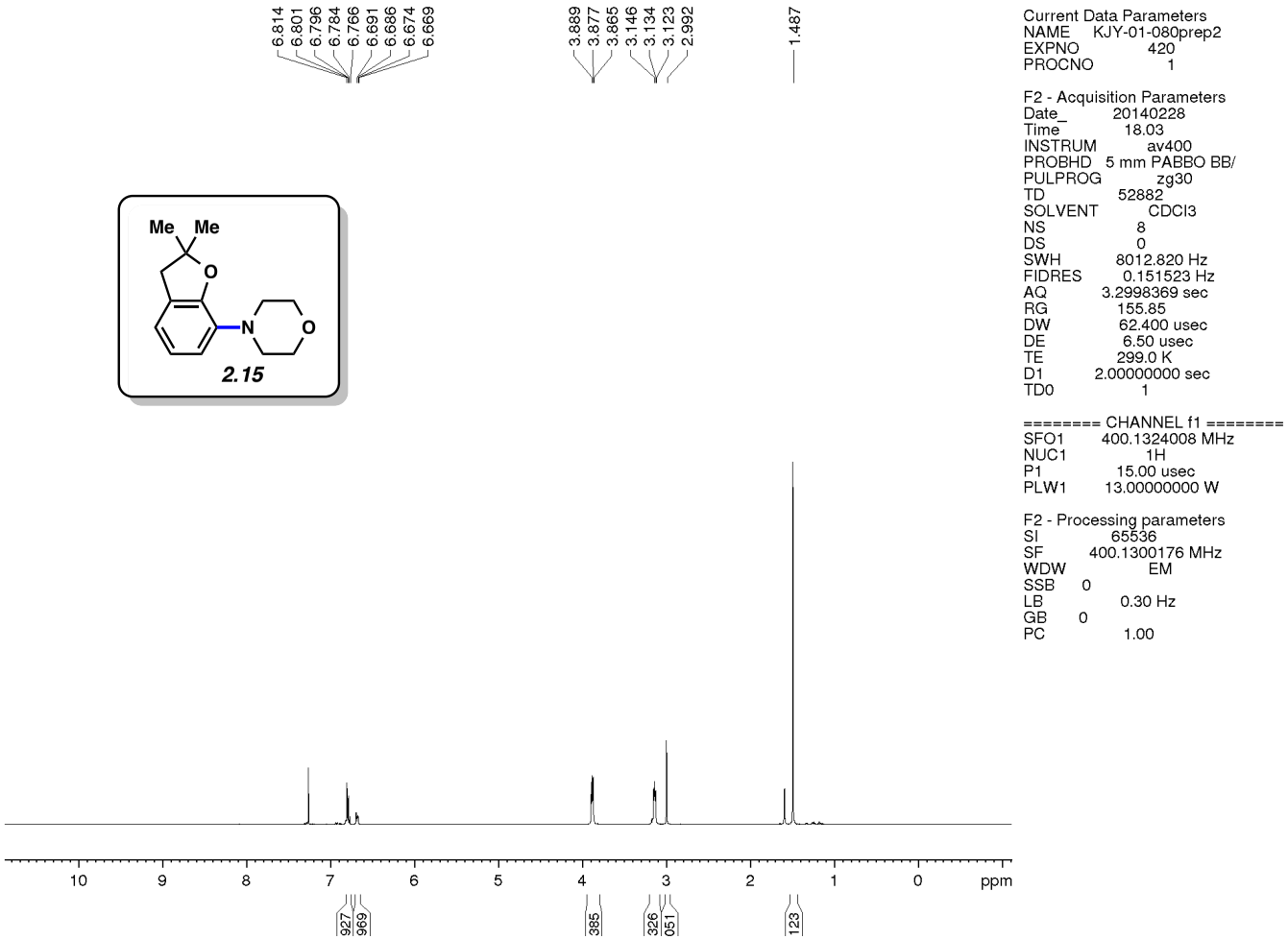


Figure 2.19. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.15**.

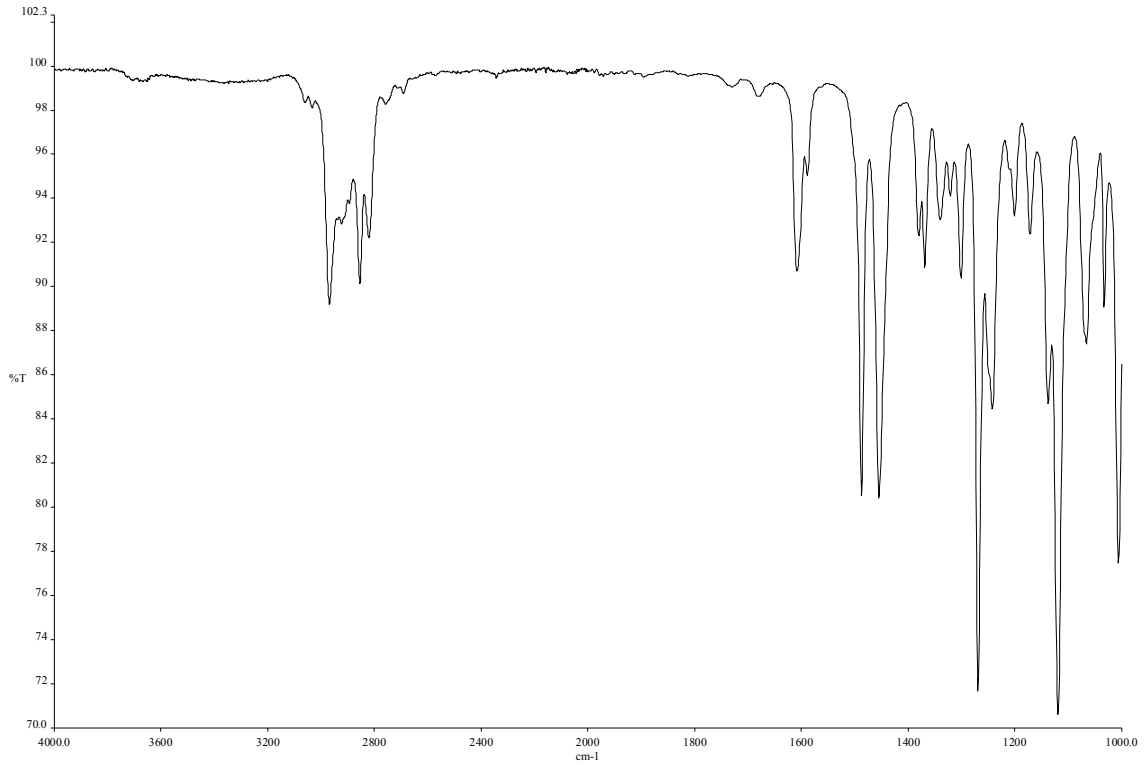


Figure 2.20 Infrared spectrum of compound **2.15**.

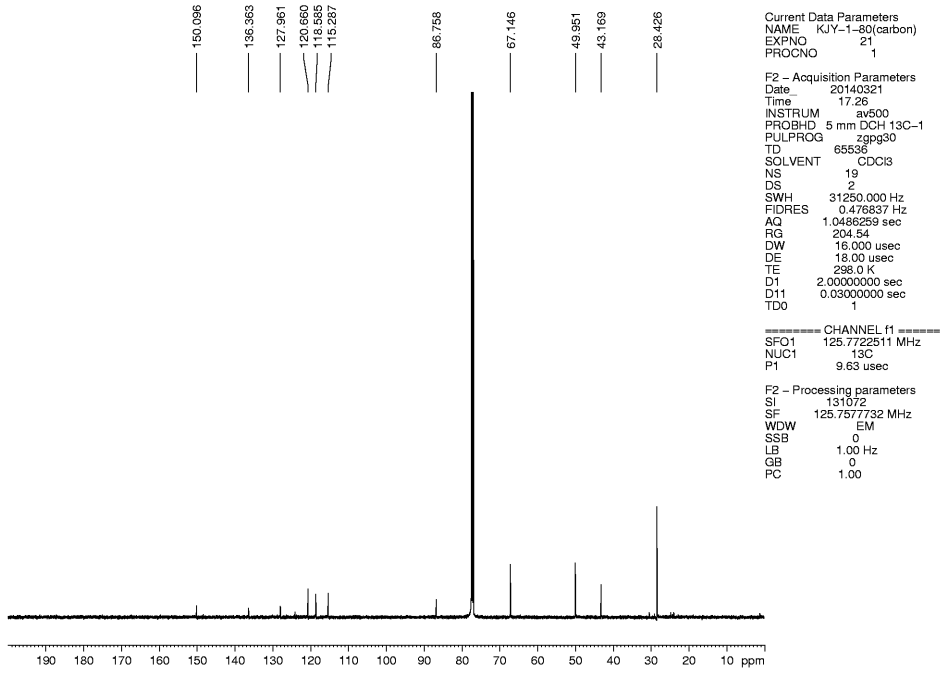


Figure 2.21. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.15**.

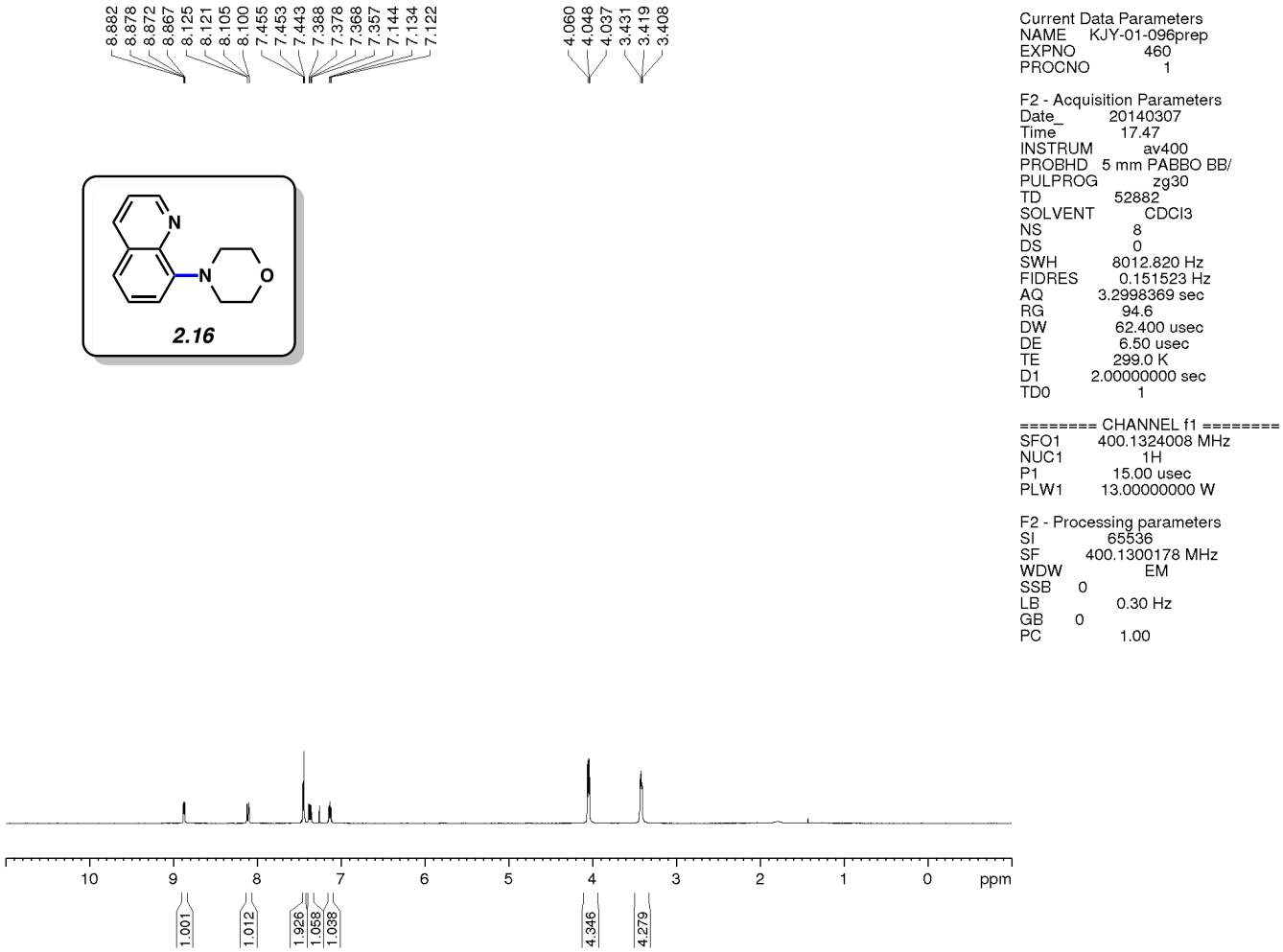


Figure 2.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.16**.

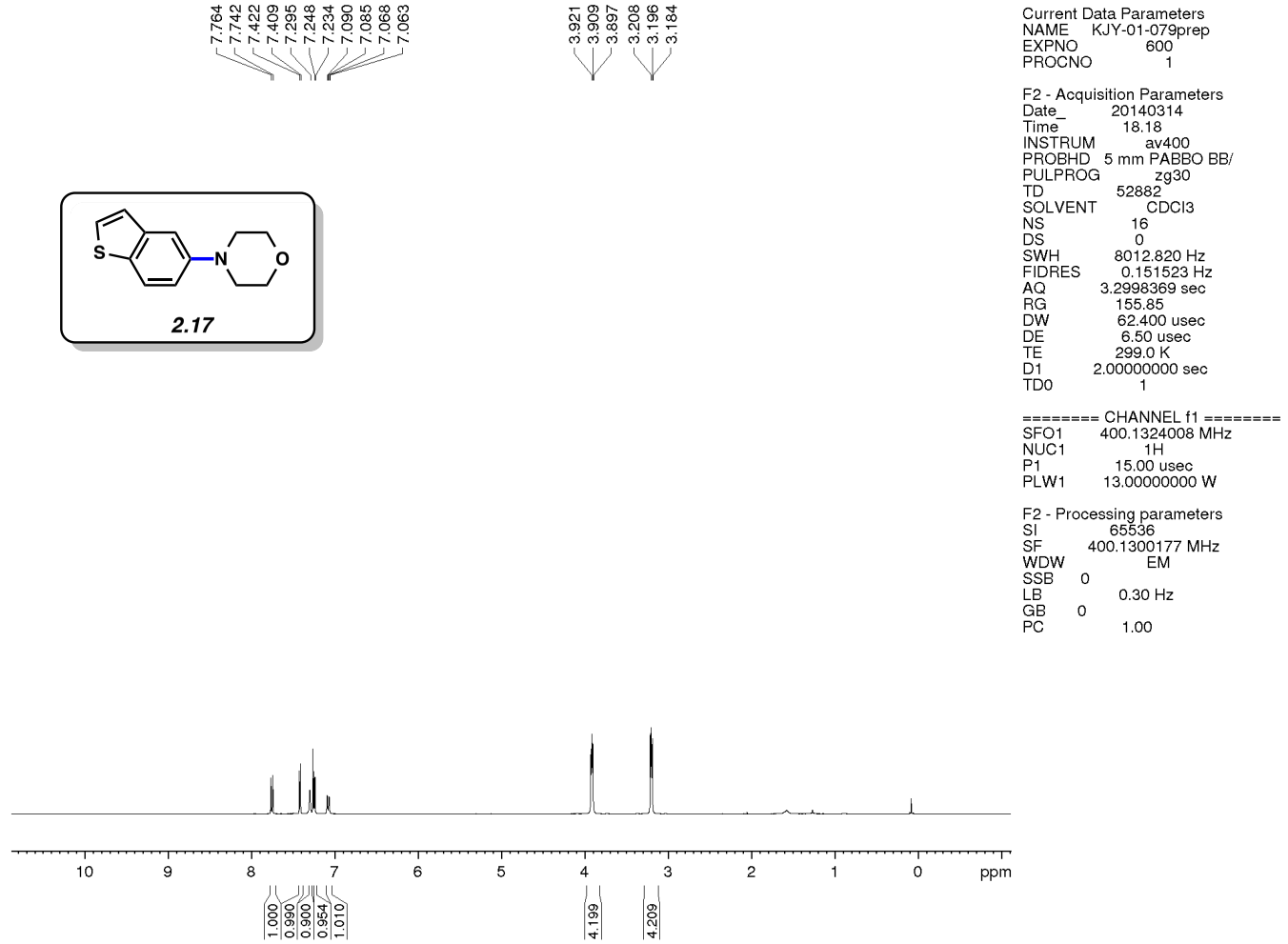


Figure 2.23. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **2.17**.

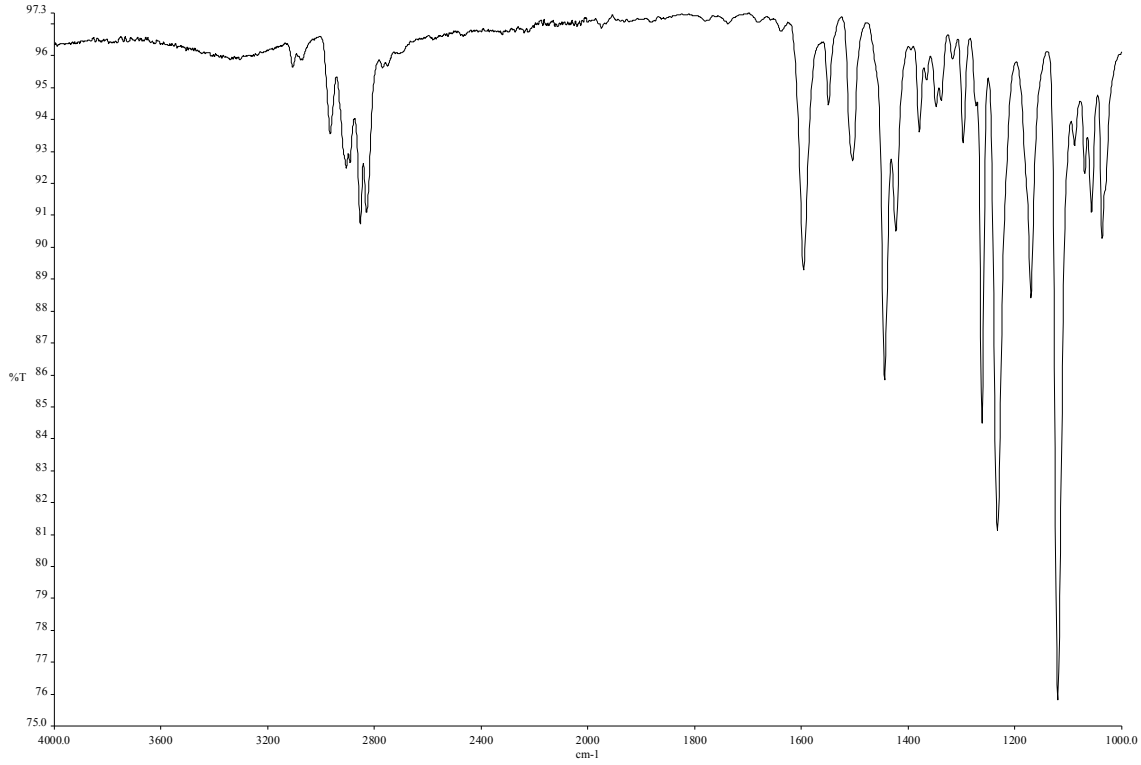


Figure 2.24. Infrared spectrum of compound **2.17**.

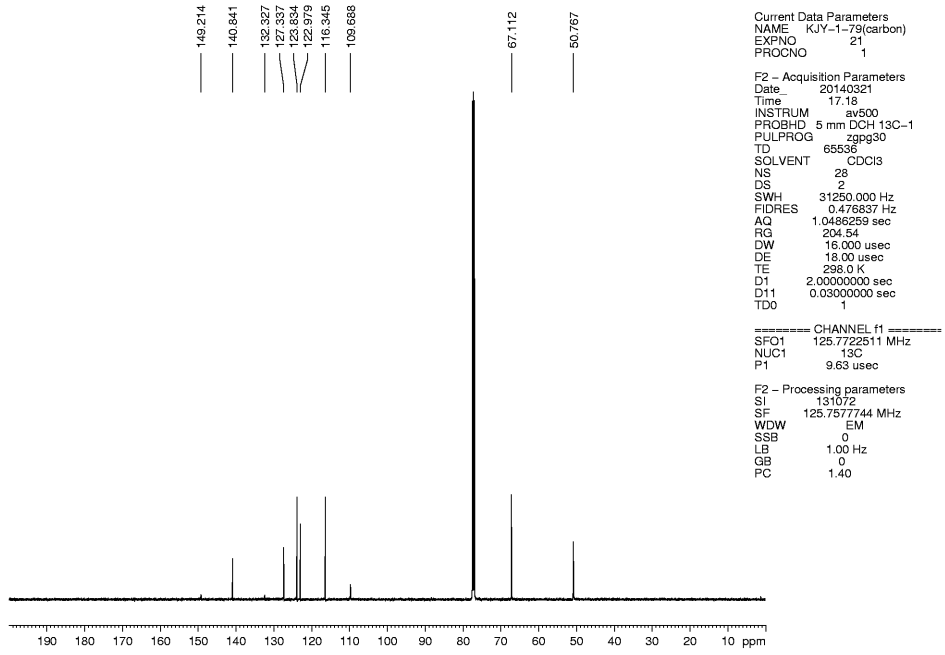
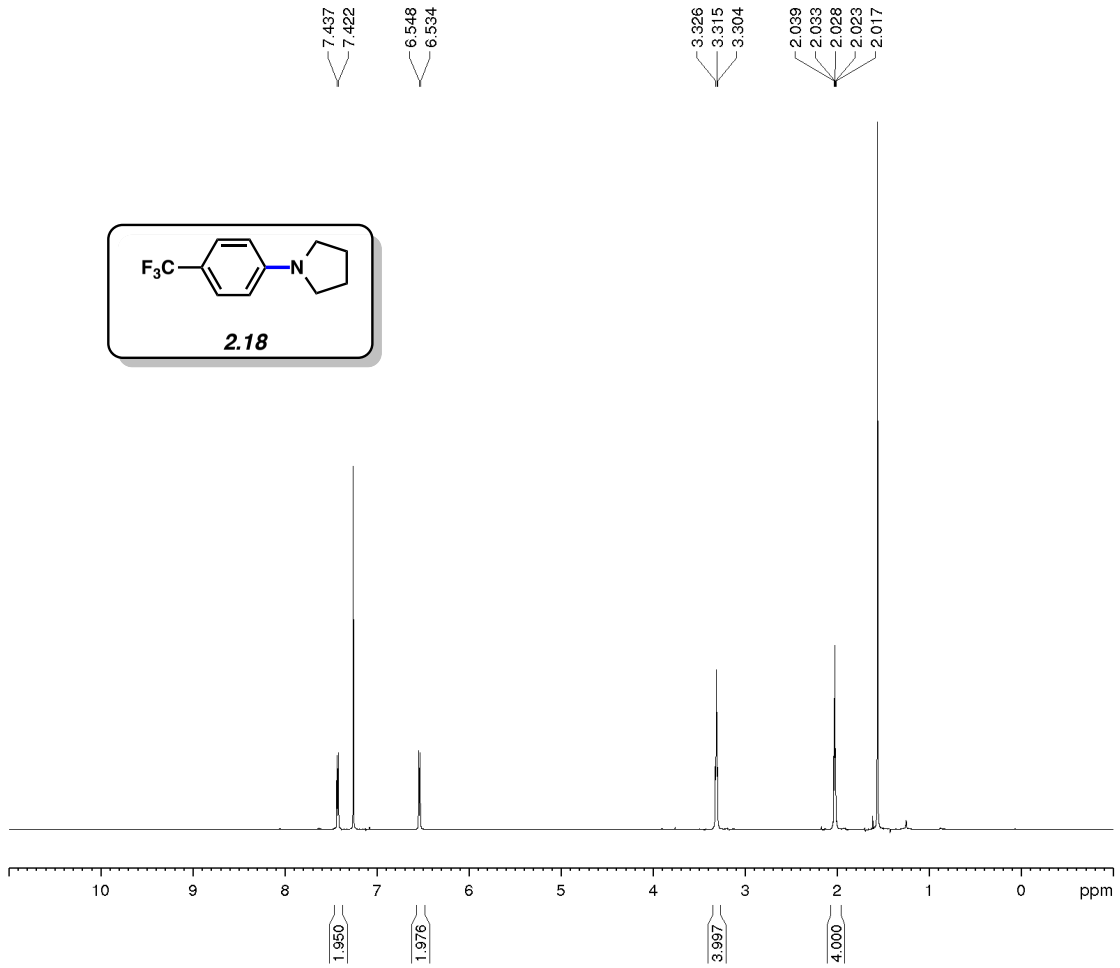


Figure 2.25. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **2.17**.



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FIDRES 0.188846 Hz
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RG 256
DW 40.400 usec
DE 6.50 usec
TE 680.7 K
D1 2.00000000 sec
TD0 1

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F2 - Processing parameters
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GB 0
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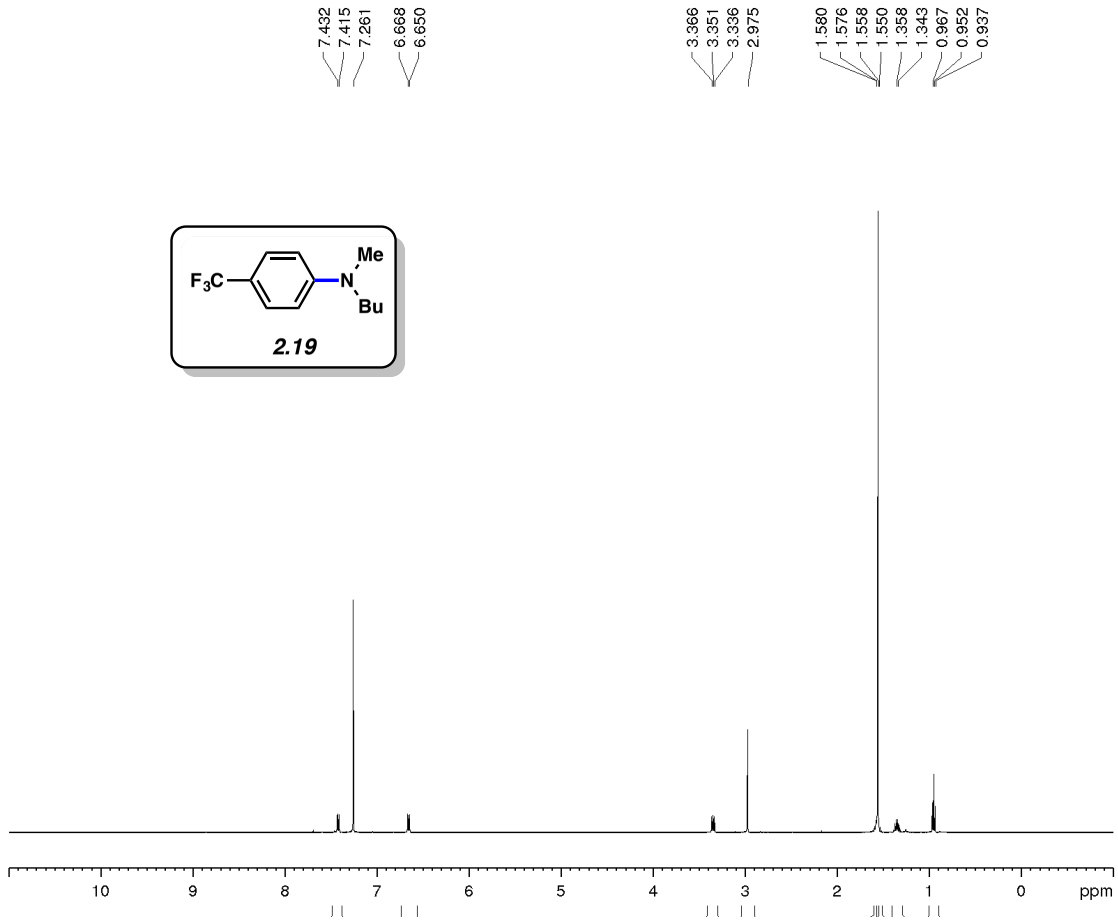
Figure 2.26. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.18**.

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TD              65536
SOLVENT          CDCl3
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DS                  0
SWH          10000.000 Hz
FIDRES        0.152588 Hz
AQ           3.2767999 sec
RG                181
DW             50.000 usec
DE              6.00 usec
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======== CHANNEL f1 ========
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F2 - Processing parameters
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LB       0 Hz
GB       0
PC               1.00
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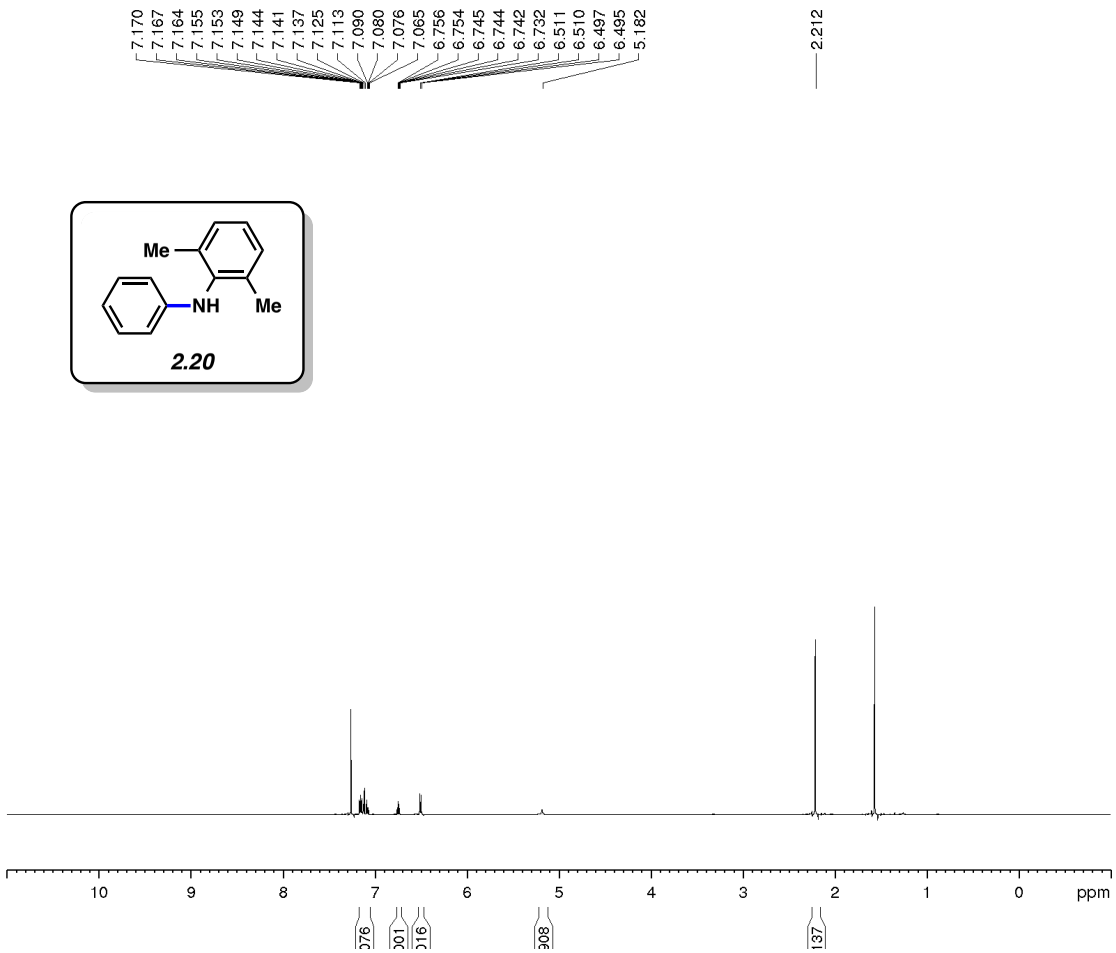
Figure 2.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.19**.



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FIDRES 0.188846 Hz
AQ 2.6476543 sec
RG 256
DW 40.400 usec
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TE 680.9 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 9.50 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1336008 MHz

F2 - Processing parameters
SI 65536
SF 600.1300297 MHz
WDW EM
SSB 0
LB 0.30 Hz
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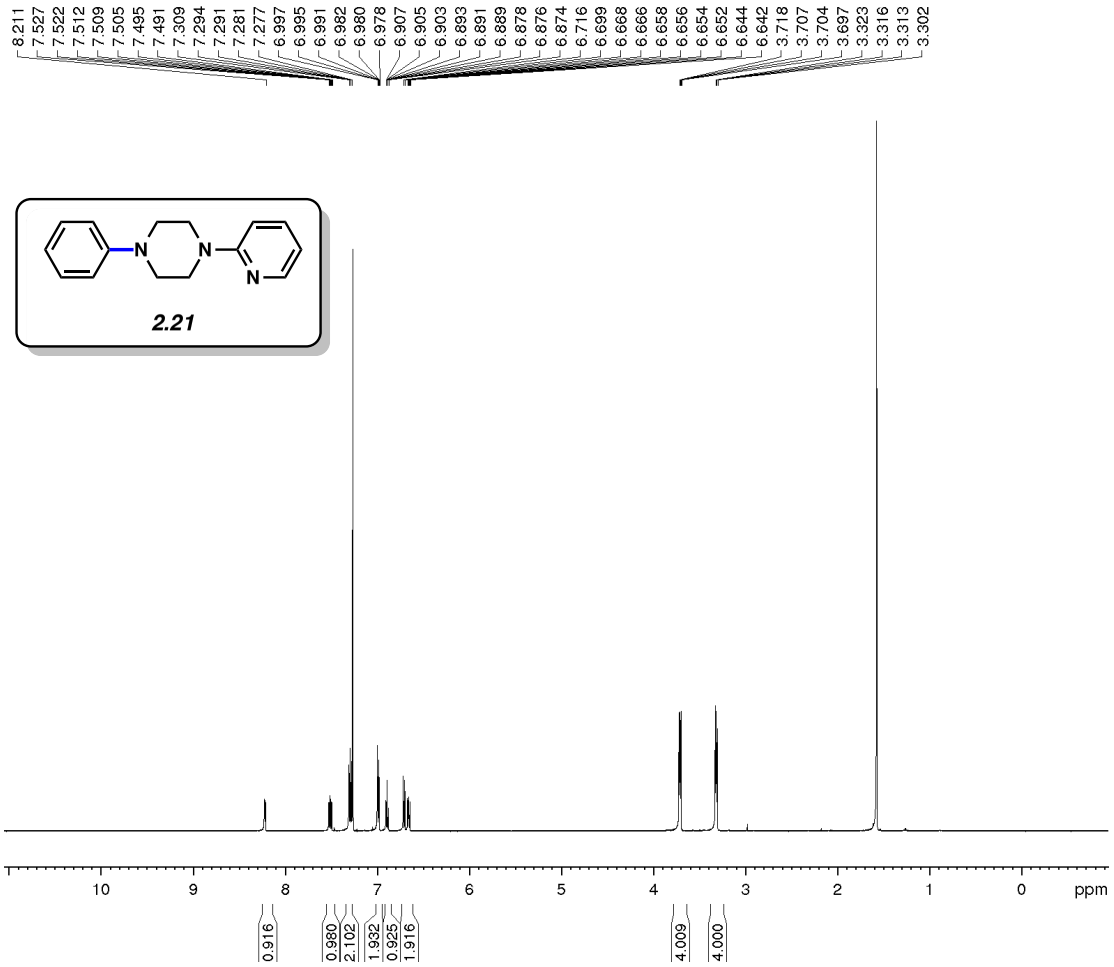
PC 1.00

Figure 2.28. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.20**.



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PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 31
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 181
DW 50.000 usec
DE 6.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
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PL1 0 dB
SFO1 500.3330020 MHz

F2 - Processing parameters
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SSB 0
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GB 0
PC 1.00

Figure 2.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.21**.

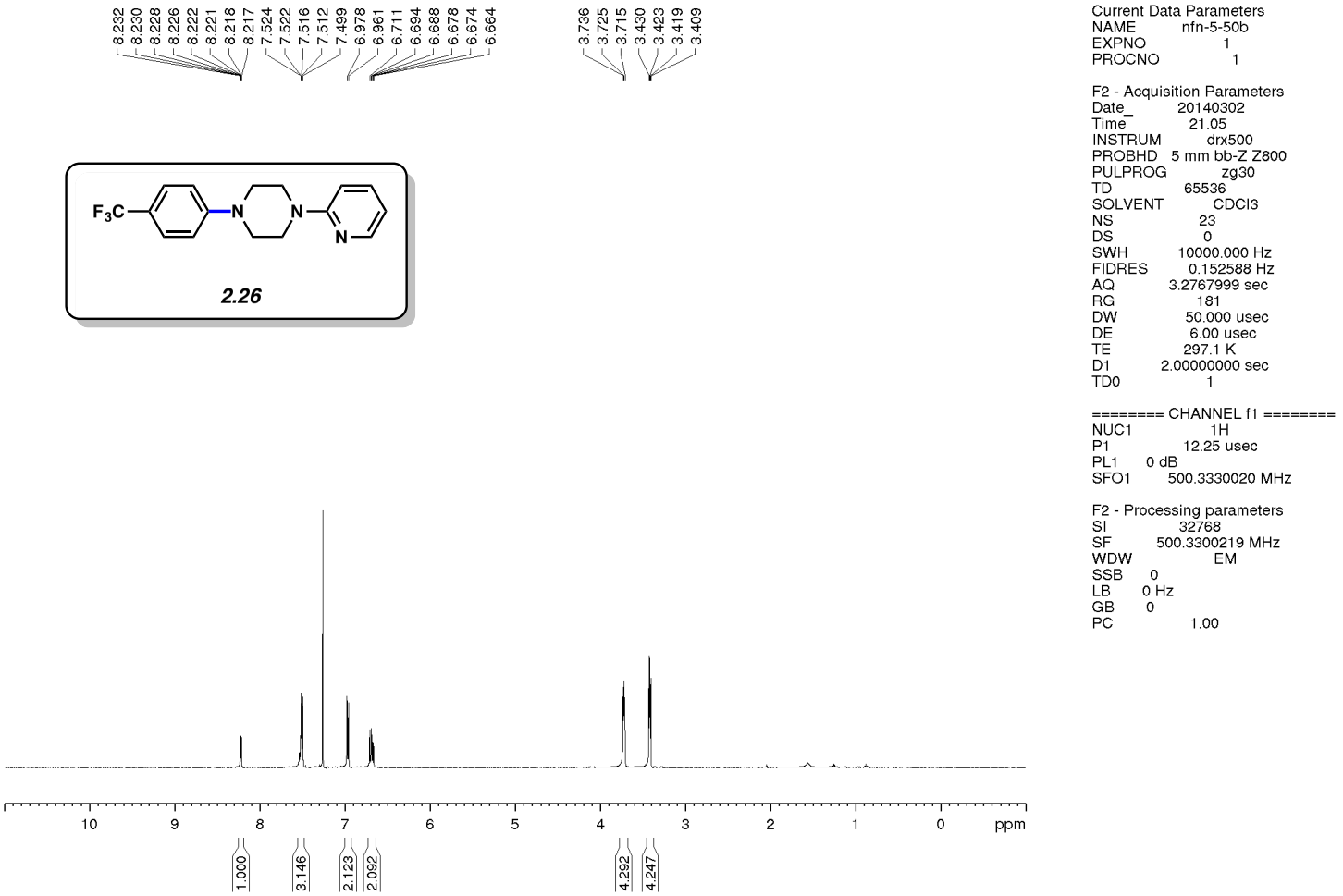


Figure 2.30. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **2.26**.

CHAPTER THREE

Cine Substitution of Arenes using the Aryl Carbamate as a Removable Directing Group

3.1 Abstract

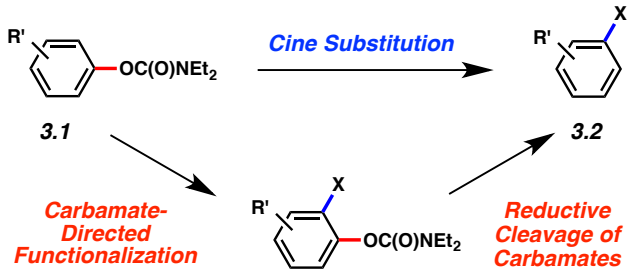
An efficient and controlled means to achieve a rare cine substitution of arenes is reported. The methodology relies on the strategic use of aryl *O*-carbamates as readily removable directing groups for arene functionalization. The removal of aryl carbamates is achieved by employing an air-stable Ni(II) precatalyst, along with an inexpensive reducing agent, to give synthetically useful yields across a range of substrates. The net cine substitution process offers a fundamentally new strategy for analogue synthesis, which complements the well-established logic for achieving arene functionalization by ipso substitution.

3.2 Introduction

Arene substitution processes are some of the most important and frequently used transformations in organic synthesis.[1] Whereas ipso substitution can be readily achieved through numerous means, including metal-catalyzed cross-coupling [2] and nucleophilic aromatic substitution,[3] methods to achieve other patterns of arene substition are rare. For example, cine substitution of aromatics,[4] where a new substituent is introduced adjacent to the position of the departing leaving group, has seen little use beyond reactions of nitroaromatics[5] and in reactions that invoke aryne[6] intermediates. A controlled and selective method to achieve the net cine

substitution of arenes would provide a valuable means for arene functionalization and a versatile new tool for analogue synthesis.

Figure 3.1. Cine substitution of aryl *O*-carbamates.



Bearing in mind the unique ability of aryl carbamates[7,8] to participate efficiently in directed metalation reactions,[9] most commonly using organolithium chemistry pioneered by Snieckus,[10] we considered the net arene cine substitution process shown in Figure 3.1. Aryl carbamates **3.1** would undergo ortho-functionalization, followed by reductive aryl C–O bond cleavage to afford the net cine substituted products **3.2**. Although methods for aryl C–O bond cleavage of aryl sulfonates are well known,[11] and recent examples pertaining to phenol-derived esters[12,13] and ethers have been reported,[12,14,15] no methodology exists for the reductive removal of synthetically useful aryl carbamates. In fact, the cleavage of aryl carbamates through C–O bond reduction has only been observed as a minor undesired reaction pathway in the attempted coupling of aryl carbamates with alkyl Grignard reagents.[16]

We report the first method to achieve the reductive cleavage of aryl *O*-carbamates, which utilizes an air-stable Ni(II) precatalyst and an inexpensive silane reducing agent. When employed subsequently to carbamate-directed arene functionalization, this methodology provides an efficient means to achieve the desired arene cine substitution process. Our approach provides an

intrinsically new method for analogue synthesis, which augments the conventional logic for achieving arene functionalization by ipso substitution.

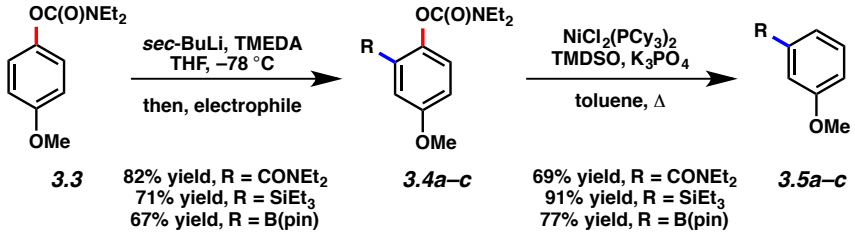
3.3 Cine Substitution of Para Substituted Aryl Carbamates

We first explored the sequential ortho-functionalization / reduction of methoxycarbamate **3.3** to give cine substituted products **3.5** (Figure 3.2). Carbamate-directed lithiation of **3.3** proceeded smoothly, without competitive metalation ortho to the methoxy substituent. This observation, which is consistent with literature data,[17] reflects the superior directing group ability of carbamates compared to ethers. Quenching of the lithiated intermediate with various electrophiles gave products **3.4a–c**.

Next, we developed conditions for the unexplored aryl carbamate cleavage. We,[18] and others,[16,19] have shown that the aryl C–O bond of aryl carbamates may be activated by specific Ni-ligand combinations to ultimately construct C–C or C–N bonds.[20] The Ni(II) precatalyst $NiCl_2(PCy_3)_2$,[21] which was used in the Suzuki–Miyaura coupling of aryl carbamates, was considered ideal because of its low cost and pronounced stability to air and water.[22] Despite the fact that this complex has not been used in reductive aryl C–O bond cleavage reactions, we tested its performance in the desired transformation using **3.4a** as the substrate, in conjunction with various reducing agents. After considerable experimentation, it was found that reductive cleavage occurred efficiently using cat. $NiCl_2(PCy_3)_2$, 1,1,3,3-tetramethyldisiloxane (TMDSO),[23] and K_3PO_4 in toluene at 115 °C to afford meta substituted arene **3.5a** in 69% yield (Figure 3.2). Of note, the methoxy substituent remained intact despite the fact that aryl ethers have been shown to be removable under Ni-based reductive conditions.[14] Removal of the carbamate from

ortho-substituted substrates **3.4b** and **3.4c** using our Ni-catalyzed conditions provided meta-substituted products **3.5b** and **3.5c**, respectively. Given the rich precedent for the controlled ortho functionalization of aryl carbamates and the efficiency of the carbamate removal methodology (vida infra), this cine substitution process provides a useful tool for the conversion of para to meta substituted arenes.

Figure 3.2. Cine substitution of *para*-methoxycarbamate **3.3** to give *meta*-substituted products **3.5a–c**.

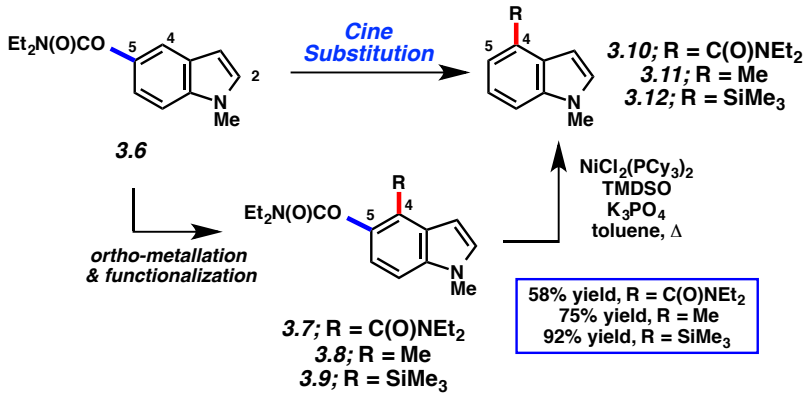


3.4 Cine Substitution of Indoles

The cine substitution sequence was also tested on 5-hydroxyindole derivative **3.6** (Figure 3.3). Lithiation of **3.6** proceeded selectively at C4; subsequent functionalization of the resulting organolithium species gave ortho-substituted carbamate products **3.7**–**3.9**. Amide **3.7** was obtained through a Fries rearrangement / carbamoylation sequence, whereas products **3.8** and **3.9** came from direct quenching of the intermediate lithiated species with MeI or TMSCl, respectively. Reductive cleavage of **3.7**–**3.9** under our Ni-catalyzed reaction conditions furnished the desired products **3.10**–**3.12**. The cine substitution of indolylcarbamate **3.6** demonstrates: (a) the unrivaled directing group ability of the *N,N*-diethylalkylcarbamate, as competitive C2 lithiation was not observed,[24,25] (b) that the Ni-catalyzed carbamate removal methodology may

be used on heterocyclic, ortho-substituted substrates, and (c) that C4-substituted indoles can be readily synthesized from more accessible C5-substituted precursors.[26]

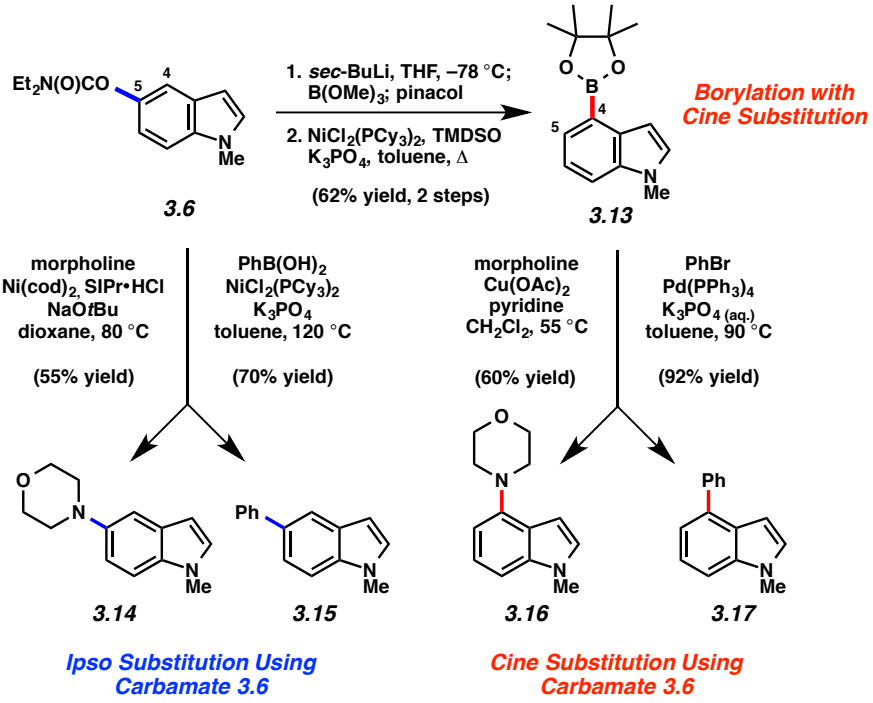
Figure 3.3. Cine substitution of indolylcarbamate **3.6**.



3.5 Cross-Coupling Approaches to Ipso and Cine Substituted Products

Figure 3.4 highlights the ability to employ carbamates in either ipso or cine substitution reactions, in a highly controlled manner, using transition metal-catalyzed reactions. Using Ni-catalysis, direct coupling of carbamate **3.6** affords products **3.14** or **3.15**, via C–N[18c] or C–C[18a,b] bond formation, respectively. Alternatively, borylation of **3.6** with cine substitution, provides boronic ester **3.13**. Boronate **3.13** could be elaborated to either amine **3.16** or arylated product **3.17**, via Chan–Lam[27] or Suzuki–Miyaura couplings, respectively. Given the widespread use of transition-metal catalyzed reactions in medicinal chemistry,[28] we expect the complementary means to achieve C–C and C–N bond formation using aryl carbamates, with controlled ipso or cine substitution, will add to the arsenal of tools needed to efficiently synthesize analogues of lead compounds.

Figure 3.4. Cross-coupling approaches to ipso or cine substituted products from carbamate **3.6**.

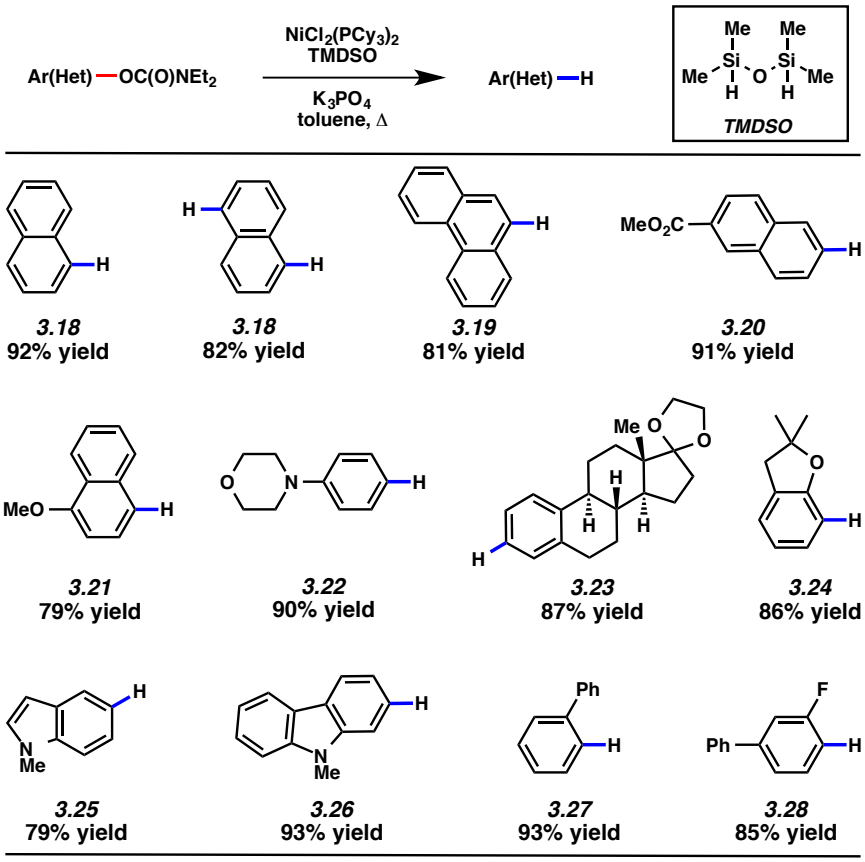


3.6 Substrate Scope of Reductive Cleavage of Aryl Carbamates

Finally, we explored the generality of our reaction conditions for the reductive cleavage of various carbamate substrates, as no general methodology exists for this transformation (Figure 3.5). Fused aromatics were excellent substrates, giving rise to products **3.18**–**3.21**. Of note, a double-decarbamoylation proceeded smoothly to give naphthalene (**3.18**) in 82% yield. Non-fused aromatics were also tolerated, as were a variety of functional groups. For instance, an electron-deficient ester survived the transformation to provide **3.20**, and electron-donating substituents did not cause difficulty as suggested by the smooth formation of **3.21** and **3.22**, respectively. The successful reduction of an estrone derivative demonstrates the use of this methodology on a complex system bearing a ketal protecting group to furnish **3.23**. Several heterocyclic substrates were evaluated to provide **3.24**–**3.26** in synthetically useful yields. Two

additional ortho-substituted carbamates were examined to give **3.27** and **3.28**, which demonstrate that both phenyl and fluoro substituents positioned ortho to the carbamate are tolerated by this methodology.

Figure 3.5. Reductive cleavage of aryl carbamates.[a,b]



[a] Aryl carbamate (1 equiv), $NiCl_2(PCy_3)_2$ (5–20 mol%), TMDSO (2.5 equiv), K_3PO_4 (4.5 equiv), toluene (0.27 M), 115–125 °C for 15 h. [b] Isolated yields.

3.7 Conclusion

In summary, we have developed an efficient means to achieve a rare arene cine substitution process. The methodology relies on the strategic use of aryl *O*-carbamates as readily removable directing groups for arene functionalization. We expect that our parent method for carbamate removal will prove useful for aryl C–O bond cleavage reactions. Moreover, the cine

substitution process offers a fundamentally new tool for arene functionalization that is intended to complement the prevalent logic of arene ipso substitution as a means to prepare analogues of important scaffolds.

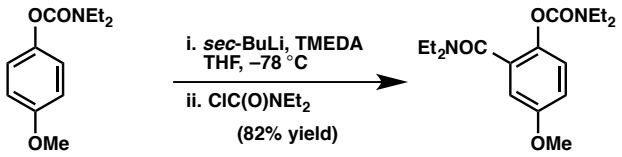
3.8 Experimental Section

3.8.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). Unless otherwise stated, commercially obtained reagents were used as received. $NiCl_2(PCy_3)_2$ was obtained from Strem Chemicals, 1,1,3,3-tetramethyldisiloxane (TMDSO) was obtained from Sigma Aldrich and potassium phosphate was obtained from VWR (manufactured by Acros Organics). Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, iodine, vanillin, and potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 300, 400, 500, 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{19}F NMR (at 300, 400 MHz) spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Melting points are uncorrected and were obtained on a Laboratory Devices Mel-Temp II instrument. High resolution mass spectra were obtained from both the UC Los Angeles and Irvine Mass Spectrometry Facility.

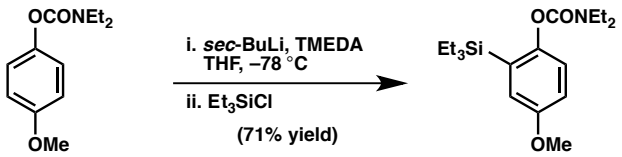
3.8.2 Experimental Procedures

3.8.2.1 Synthesis of Aryl Carbamate Substrates



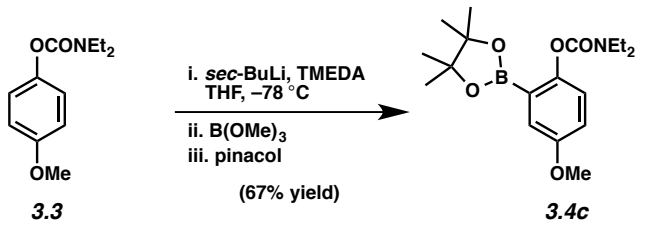
3.3 *3.4a*

3.4a. To a solution of carbamate **3.3**[32] (0.1 g, 0.448 mmol, 1.0 equiv) and TMEDA (0.087 mL, 0.582 mmol, 1.3 equiv) in THF (2.2 mL) at –78 °C was added *sec*-BuLi (0.525 mL, 0.582 mmol, 1.3 equiv) over 15 min. After stirring for 1 h, $ClC(O)NEt_2$ (0.074 mL, 0.582 mmol, 1.3 equiv) was added over 10 min. The reaction was stirred at –78 °C for 1 h, allowed to warm to 23 °C, and then quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was diluted with H_2O (5 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (3:1 Hexanes:EtOAc) to yield amide product **3.4a** (0.118 g, 82% yield) as a light yellow oil. R_f 0.12 (3:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, J = 9.0, 1H), 6.90 (dd, J = 9.0, 3.0, 1H), 6.78 (d, J = 3.0, 1H), 3.80 (s, 3H), 3.74 (bs, 1H), 3.44–3.23 (m, 6H), 3.13 (s, 1H), 1.21 (atd, J = 7.0, 1.5 6H), 1.17 (t, J = 7.0, 3H), 1.07 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 156.6, 153.9, 140.8, 131.3, 124.3, 115.0, 111.5, 55.7, 42.8, 42.2, 42.0, 38.6, 14.2, 13.9, 13.4, 12.7; IR (film): 2973, 2936, 1714, 1634, 1197, 1152 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{26}N_2O_4H$, 323.1971; found, 323.1971.

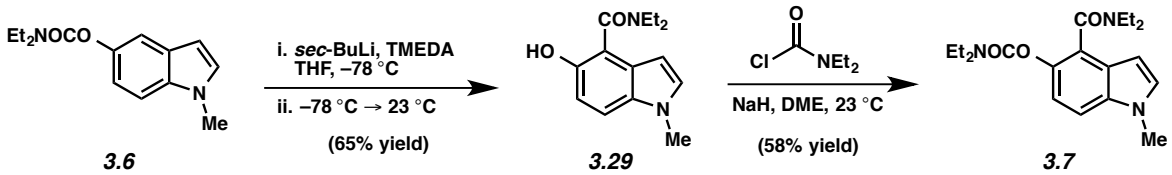


3.3 *3.4b*

3.4b. To a solution of carbamate **3.3**[32] (0.1 g, 0.448 mmol, 1.0 equiv) and TMEDA (0.087 mL, 0.582 mmol, 1.3 equiv) in THF (2.2 mL) at –78 °C was added *sec*-BuLi (0.525 mL, 0.582 mmol, 1.3 equiv) over 15 min. After stirring for 1 h, Et_3SiCl (0.098 mL, 0.582 mmol, 1.3 equiv) was added over 10 min. The reaction was stirred at –78 °C for 1 h, allowed to warm to 23 °C, and then quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was diluted with H_2O (5 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20:1 Hexanes:EtOAc) to yield silyl product **3.4b** (0.107 g, 71% yield) as a clear oil. R_f 0.52 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97–6.87 (m, 3H), 3.81 (s, 3H), 3.47 (q, J = 6.8, 2H), 3.40 (q, J = 7.2, 2H), 1.25 (t, J = 7.2, 3H), 1.19 (t, J = 6.8, 3H), 0.96 (at, J = 8.0, 9H), 0.81 (aq, J = 8.0, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 154.9, 150.2, 130.1, 123.2, 121.1, 114.9, 55.7, 41.9, 41.5, 14.3, 13.4, 7.6, 3.5; IR (film): 2954, 2876, 1715, 1264, 1186, 1153 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{31}NO_3SiH$, 338.2151; found, 338.2153.



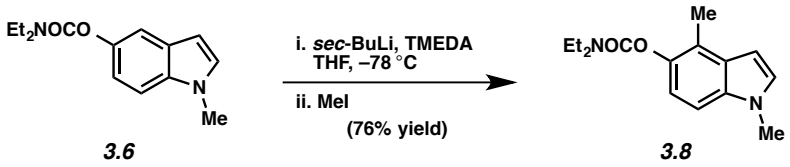
3.4c. To a solution of carbamate **3.3**[32] (0.1 g, 0.448 mmol, 1.0 equiv) and TMEDA (0.087 mL, 0.582 mmol, 1.3 equiv) in THF (2.2 mL) at –78 °C was added *sec*-BuLi (0.525 mL, 0.582 mmol, 1.3 equiv) over 15 min. After stirring for 1 h, trimethyl borate (0.065 mL, 0.582 mmol, 1.3 equiv) was added over 10 min. The reaction was stirred at –78 °C for 1 h, allowed to warm to 23 °C, and then quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was diluted with H_2O (5 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was dissolved in MeOH (30 ml) with pinacol (0.069 g, 0.582 mmol), concentrated in vacuo, and purified by flash chromatography (5:1 Hexanes:EtOAc) to yield pinacolborane product **3.4c** (0.105 g, 67% yield) as a clear oil. R_f 0.44 (3:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (ad, *J* = 3.0, 1H), 6.99–6.95 (m, 2H), 3.50 (q, *J* = 7.0, 2H), 3.38 (q, *J* = 7.0, 2H), 1.31 (s, 12H), 1.29 (t, *J* = 7.5, 3H), 1.20 (t, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 155.3, 150.0, 123.3, 119.8, 118.4, 83.7, 55.8, 42.1, 41.7, 25.0, 14.2, 13.6; IR (film): 2977, 2935, 1712, 1410, 1194, 1156 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{28}BNO_5H$, 350.2142; found, 350.2144.



Amide Carbamate 3.7. To a solution of indole carbamate **3.6**[29] (1.5 g, 6.09 mmol, 1.0 equiv) and TMEDA (1.0 mL, 6.70 mmol, 1.1 equiv) in THF (30 mL) at –78 °C was added *sec*-BuLi (6.0 mL, 6.70 mmol, 1.1 equiv) over 15 min. After stirring for 45 min the reaction was allowed to warm to 23 °C and stirred for 3 h. The reaction was quenched with H_2O (30 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (7:1 → 5:1 → 4:1 → 2:1 → 1:1 → 1:2 Hexanes:Acetone) to yield the amide hydroxyindole product **3.29** (0.980 g, 65% yield) as a colorless amorphous solid. R_f 0.13 (5:1 Hexanes:Acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 8.5, 1H), 7.23 (at, J = 7.5, 1H), 7.07–7.09 (m, 2H), 6.44 (dd, J = 0.5, 3.0, 1H), 3.81 (s, 3H), 3.65 (as, 2H), 3.22 (as, 2H), 1.31 (as, 3H), 1.02 (as, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 136.9, 129.7, 129.7, 125.6, 121.4, 117.2, 109.9, 99.9, 43.2, 38.9, 33.1, 14.6, 13.3; IR (film): 3160, 1596, 1577, 1309, 1255 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{18}N_2O_2H$, 247.1447; found, 247.1448.

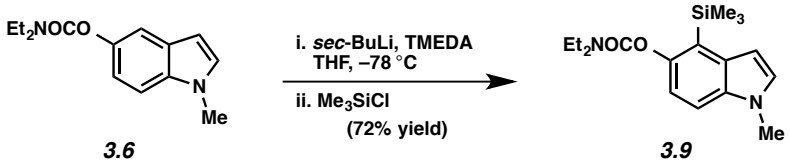
A round bottom flask was charged with NaH (0.175 g, 4.38 mmol, 1.2 equiv, 60% dispersion in oil). A solution of amide hydroxyindole **3.29** (0.90 g, 3.65 mmol, 1 equiv) in DME (15 mL) and DMSO (5 mL) was warmed to 50 °C to fully dissolve the amide hydroxyindole. The homogeneous solution was added dropwise via cannula to the sodium hydride. Diethylcarbamoyl chloride (0.44 mL, 3.47 mmol, 0.95 equiv) was then added dropwise to the reaction vessel. The reaction was stirred for 41 h. The reaction was diluted with H_2O (25 mL)

and EtOAc (25 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organic layers were then washed with H_2O (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, and evaporated to dryness. The crude residue was purified by flash chromatography (6:1 → 4:1 Hexanes:Acetone) to yield amide carbamate **3.7** (0.700 g, 58% yield) as a yellow oil. R_f 0.31 (4:1 Hexanes:Acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 5.0, 1H), 7.06–7.05 (m, 2H), 6.36 (d, *J* = 3.0, 1H), 3.79 (s, 3H), 3.72 (sextet, *J* = 7.0, 1H), 3.53 (sextet, *J* = 7.0, 1H), 3.50–3.31 (m, 4H), 3.28 (sextet, *J* = 7.0, 1H), 3.11 (sextet, *J* = 7.0, 1H), 1.27 (t, *J* = 7.0, 3H), 1.23 (t, *J* = 7.0, 3H), 1.17 (t, *J* = 7.0, 3H), 0.98 (t, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 154.7, 140.6, 134.4, 130.2, 125.8, 121.8, 117.4, 109.9, 100.0, 43.0, 42.2, 42.1, 38.5, 33.3, 14.3, 14.2, 13.6, 13.1; IR (film): 2974, 1714, 1632, 1417, 1220, 1160 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{27}N_3O_3H$, 346.2131; found, 346.2130.



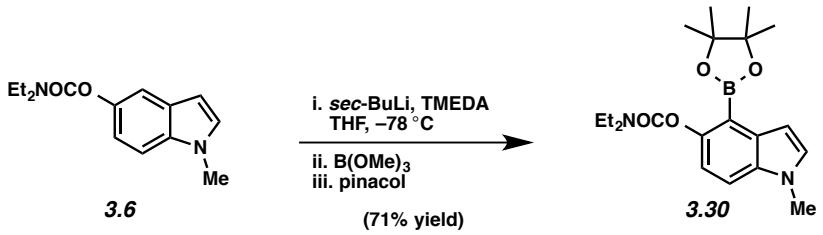
Methyl Carbamate 3.8. To a solution of indole carbamate **3.6**[29] (1.0 g, 4.06 mmol, 1.0 equiv) and TMEDA (0.67 mL, 4.47 mmol, 1.1 equiv) in THF (20 mL) at –78 °C was added *sec*-BuLi (3.6 mL, 4.47 mmol, 1.1 equiv) over 15 min. After stirring for 1 h, methyl iodide (0.30 mL, 4.87 mmol, 1.2 equiv) was added dropwise over 1 min and stirred for 1 h. The reaction was allowed to warm to 23 °C over 1 h and quenched with saturated aqueous NH_4Cl (10 mL). The reaction mixture was diluted with H_2O (20 mL) and EtOAc (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (7:1 → 5:1 Hexanes:EtOAc) to afford the methyl

carbamate **3.8** (0.80 g, 76% yield) as a white solid. R_f 0.30 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.5, 1H), 7.03 (d, *J* = 3.0, 1H), 6.94 (d, *J* = 8.5, 1H), 6.46 (d, *J* = 3.0, 1H), 3.76 (s, 3H), 3.51 (ad, *J* = 6.0, 2H), 3.41 (ad, *J* = 6.0, 2H), 2.37 (s, 3H), 1.30 (as, 3H), 1.21 (as, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1, 142.8, 134.3, 129.3, 129.1, 121.6, 116.8, 107.1, 99.9, 42.2, 41.9, 33.2, 17.4, 14.5, 12.7; IR (film): 2972, 1708, 1467, 1418, 1218, 1159 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{20}N_2O_2Na$, 283.1422; found, 283.1420.



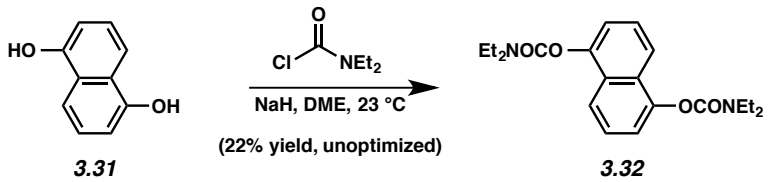
Silyl Carbamate 3.9. To a solution of indole carbamate **3.6**[29] (1.0 g, 4.06 mmol, 1.0 equiv) and TMEDA (0.67 mL, 4.47 mmol, 1.1 equiv) in THF (20 mL) at –78 °C was added *sec*-BuLi (3.6 mL, 4.47 mmol, 1.1 equiv) over 15 min. After stirring for 1 h, Me_3SiCl (0.67 mL, 4.87 mmol, 1.2 equiv) was added dropwise over 1 min and stirred for 2 h. The reaction was allowed to warm to 23 °C over 20 min and then quenched with saturated aqueous NH_4Cl (10 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (19:1 → 9:1 → 5:1 Hexanes:EtOAc) to yield silyl carbamate product **3.9** (0.933 g, 72% yield) as an off-white solid. R_f 0.20 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.5, 1H), 7.09 (d, *J* = 3.0, 1H), 6.88 (d, *J* = 8.5, 1H), 6.64 (dd, *J* = 3.0, 0.5, 1H), 3.78 (s, 3H), 3.52 (q, *J* = 7.0, 2H), 3.42 (q, *J* = 7.0, 2H), 1.28 (t, *J* = 7.0, 3H), 1.21 (q, *J* = 7.0, 3H), 0.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 150.4, 133.7, 132.7, 129.3, 122.2, 116.9, 111.1, 102.6, 41.8, 41.5, 33.2, 14.4, 14.5, 1.1; IR

(film): 2972, 1707, 1601, 1401, 1210, 1157 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{26}N_2O_2ASiNa$, 341.1661; found, 341.1660.



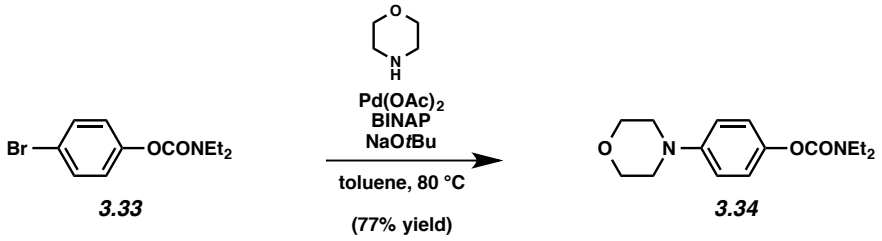
3.30. To a solution of indole carbamate **3.6**[29] (1.0 g, 4.06 mmol, 1.0 equiv) and TMEDA (0.67 mL, 4.47 mmol, 1.1 equiv) in THF (20 mL) at –78 °C was added *sec*-BuLi (4.0 mL, 4.47 mmol, 1.1 equiv) over 15 min. After stirring for 45 min, trimethylborate (0.54 mL, 4.87 mmol, 1.2 equiv) was added dropwise and stirred for 1.5 h. The reaction was allowed to warm to 23 °C over 30 min and then quenched with saturated aqueous NH_4Cl (15 mL) and a drop of H_2O. The reaction mixture was diluted with H_2O (30 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in dry MeOH (40 mL) and pinacol (0.53g, 4.47 mmol, 1.1 equiv) was added. The solution was evaporated to dryness over 10 min. The crude residue was purified by flash chromatography (15:1 Hexanes:Acetone) to generate boronic ester indole carbamate product **3.30** (1.08 g, 71% yield) as a yellow oil. R_f 0.25 (5:1 Hexanes:Acetone); ^1H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, *J* = 9.0, 1H), 7.07 (d, *J* = 3.0, 1H), 6.94–6.92 (m, 2H), 3.77 (s, 3H), 3.54 (q, *J* = 7.0, 2H), 3.40 (q, *J* = 7.0, 2H), 1.34 (s, 12H), 1.33–1.29 (m, 3H), 1.20 (t, *J* = 6.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 150.8, 138.0, 134.1, 133.8, 130.0, 129.2, 125.4, 116.7, 112.3, 103.5, 83.1, 42.0, 41.6, 33.1, 25.2, 25.0, 21.6, 14.3, 13.7; IR (film): 2976, 2933,

1709, 1412, 1275, 1214, 1162 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{29}BN_2O_4H$, 373.2303; found, 373.2305.

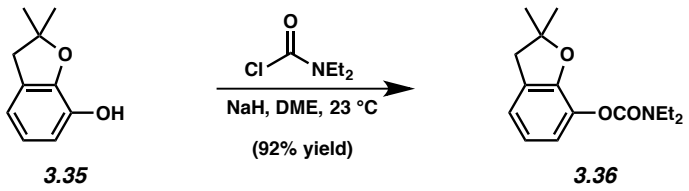


3.31 *3.32*

3.32. A round bottom flask was charged with NaH (0.60 g, 14.98 mmol, 2.4 equiv, 60% dispersion in oil). A solution of 1,5-dihydroxynaphthalene (**3.31**) (1.0 g, 6.24 mmol, 1 equiv) in DME (25 mL) was added dropwise via cannula to the sodium hydride. Diethylcarbamoyl chloride (1.50 mL, 11.86 mmol, 1.9 equiv) was then added dropwise to the reaction vessel. The reaction was allowed to stir for 20 h. The volatiles were removed under reduced pressure and then EtOAc (30 mL) and H_2O (20 mL) were added. The layers were separated, and the organic layer was washed successively with 1 M KOH (20 mL) and H_2O (20 mL). The combined aqueous layers were extracted with EtOAc (3 x 50 mL). The combined organic layers were then washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5:1 Benzene:Et_2O) to yield biscarbamate naphthalene **3.32** as a red amorphous solid (0.50 g, 22% yield). R_f 0.30 (5:1 Benzene:Et_2O); ^1H NMR (500 MHz, $CDCl_3$): d 7.79 (d, *J* = 8.5, 2H), 7.45 (t, *J* = 8.0, 2H), 7.31 (d, *J* = 7.5, 2H), 3.61 (q, *J* = 7.0, 4H), 3.45 (q, *J* = 7.0, 4H), 1.38 (t, *J* = 7.0, 6H), 1.25 (t, *J* = 7.0, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 147.6, 129.0, 126.0, 118.8. 118.6, 42.5, 42.2, 14.6, 13.6; IR (film): 2975, 1709, 1394, 1242, 1153 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{20}H_{26}N_2O_4Na$, 381.1790; found, 381.1790.

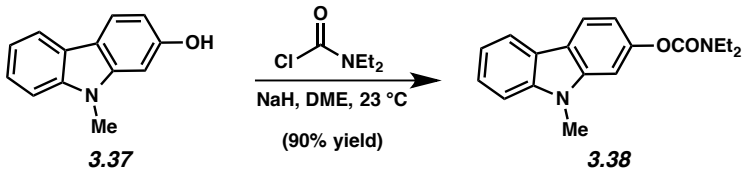


3.34. A 50 mL round bottom flask was charged with $Pd(OAc)_2$ (83.0 mg, 0.37 mmol, 10 mol%), BINAP (0.24 g, 0.40 mmol, 11 mol%), anhydrous powdered NaO*t*Bu (0.59 g, 5.14 mmol, 1.4 equiv), bromide **3.33**[30] (1.0 g, 3.67 mmol, 1 equiv), morpholine (0.39 mL, 4.4 mmol, 1.2 equiv) and a magnetic stir bar, all in a glove box. Subsequently, toluene (15 mL) that had been rigorously sparged with N_2 was added. The vessel was sealed under an atmosphere of argon and then heated at 80 °C for 24 h. After cooling the reaction vessel to 23 °C, the crude mixture was diluted with Et_2O (10 mL), filtered over a plug of celite with additional Et_2O (10 mL) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5:1 Hexanes:EtOAc) to yield aminated carbamate **3.34** (0.7835 g, 77% yield) as a gray amorphous solid. R_f 0.10 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02 (d, J = 9.0, 2H), 6.89 (d, J = 9.0, 2H), 3.85 (t, J = 4.5, 4H), 3.42–3.38 (m, 4H), 3.10 (q, J = 4.5, 4H), 1.24–1.19 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 154.8, 148.9, 145.1, 122.4, 116.8, 67.1, 50.2, 42.3, 41.9, 14.4, 13.5; IR (film): 2971, 2834, 1713, 1512, 1418, 1210 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{22}N_2O_3H$, 279.1709; found, 279.1710.

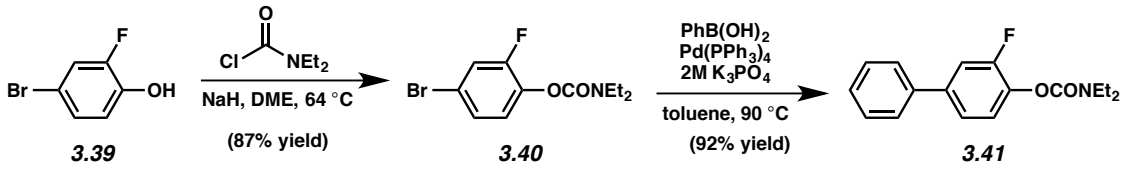


3.35 *3.36*

3.36. A round bottom flask was charged with NaH (0.88 g, 21.92 mmol, 1.2 equiv, 60% dispersion in oil). A solution of dihydrobenzofuranol **3.35** (3.0 mL, 18.27 mmol, 1 equiv) in DME (40 mL) was added dropwise via cannula to the sodium hydride. A solution of diethyl carbamoyl chloride (2.2 mL, 17.36 mmol, 0.95 equiv) in DME (30 mL) was then added dropwise via cannula to the reaction vessel. The reaction was stirred at 23 °C for 45 h. The volatiles were removed under reduced pressure and then Et_2O (30 mL) and H_2O (20 mL) were added. The layers were separated and the organic layer was washed successively with 1 M KOH (20 mL) and H_2O (20 mL). The combined aqueous layers were extracted with Et_2O (3 x 20 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, and evaporated to dryness. The crude residue was purified by flash chromatography (7:1 Hexanes:EtOAc) to yield carbamate **3.36** as a clear oil (1.0 g, 92% yield). R_f 0.4 (Benzene); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (dd, J = 7.5, 1.5, 1H), 6.91 (ad, J = 8.0, 1H), 6.76 (at, J = 7.5, 1H), 3.44–3.38 (m, 4H), 3.01 (s, 2H), 1.47 (s, 6H), 1.26–1.20 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8, 150.6, 135.4, 129.3, 121.9, 121.8, 119.9, 87.8, 43.1, 42.3, 42.1, 28.2, 14.1, 13.4; IR (film): 2974, 2934, 1718, 1416, 1152, 1052 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{21}NO_3Na$, 286.1419; found, 286.1420.



3.38. A round bottom flask was charged with NaH (122 mg, 3.04 mmol, 1.2 equiv, 60% dispersion in oil). A solution of 2-hydroxycarbazole **3.37**[32] (500 mg, 2.54 mmol, 1 equiv) in DME (10 mL) was added dropwise via cannula to the sodium hydride. Diethyl carbamoyl chloride (0.31 mL, 2.41 mmol, 0.95 equiv) was then added dropwise to the reaction vessel. The reaction was stirred at 23 °C for 13 h. The reaction was diluted with H_2O (10 mL) and the volatiles were removed under reduced pressure. EtOAc (30 mL) and H_2O (20 mL) were added and the layers were separated. The organic layer was washed successively with 1 M KOH (20 mL) and H_2O (20 mL). The combined aqueous layers were extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (2:1 Hexanes:EtOAc) to generate carbazole carbamate **3.38** as a white solid (0.643 g, 90% yield). R_f 0.15 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.0, 1H), 8.04 (d, J = 8.5, 1H), 7.46–7.44 (m, 1H), 7.39 (d, J = 8.0, 1H), 7.25–7.21 (m, 2H), 6.99 (dd, J = 8.5, 2.0, 1H), 3.81 (s, 3H), 3.52 (q, J = 7.0, 2H), 3.44 (q, J = 7.0, 2H), 1.32 (t, J = 7.0, 3H), 1.25 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 150.3, 141.6, 141.6, 125.4, 122.7, 120.7, 120.3, 120.2, 119.2, 113.3, 108.5, 102.2, 42.4, 42.0, 29.4, 14.5, 13.6; IR (film): 3055, 2978, 1710, 1602, 1417, 1266, 1154 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{18}H_{20}N_2O_2Na$, 319.1422; found, 319.1421.



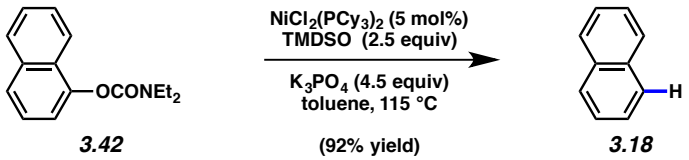
3.41. A round bottom flask was charged with NaH (0.188 g, 4.70 mmol, 1.2 equiv, 60% dispersion in oil). A solution of phenol **3.39** (0.43 mL, 6.24 mmol, 1 equiv) in DME (7 mL) was added dropwise via cannula to the sodium hydride. A solution of diethylcarbamoyl chloride (0.47 mL, 3.73 mmol, 0.95 equiv) in DME (9 mL) was then added dropwise via cannula to the reaction vessel. The reaction was stirred at 64 °C for 1.5 h. The reaction was stopped and cooled to 23 °C. The volatiles were removed under reduced pressure and then Et_2O (30 mL) and H_2O (20 mL) were added. The layers were separated, and the organic layer was washed successively with 1 M KOH (20 mL) and H_2O (20 mL). The combined aqueous layers were extracted with Et_2O (3 x 20 mL). The combined organic layers were then washed with brine (20 mL), dried over $MgSO_4$, and evaporated to dryness. The crude residue was purified by flash chromatography (7:1 Hexanes:EtOAc) to yield carbamate **3.40** (1.0 g, 87% yield) as a clear oil. Spectral data match those previously reported.[31]

A 20 mL scintillation vial was charged with a magnetic stir bar, K_3PO_4 (2.2 mL, 2 M aqueous) and toluene (4.3 mL) and the biphasic solution was sparged with N_2 for 1 h. To the solution was added bromide **3.40** (250 mg, 0.86 mmol, 1 equiv), phenylboronic acid (126 mg, 1.03 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (149 mg, 0.13 mmol, 15 mol%) and the resulting mixture was sparged with N_2 for 10 min. The vial was sealed with a Teflon-coated screw-cap and heated at 90 °C for 18 h. After cooling to 23 °C, CH_2Cl_2 (10 mL) and Na_2SO_4 were added and the mixture was allowed to stand for 30 min. The crude mixture was then filtered over silica and concentrated under reduced pressure. The crude residue was purified by flash chromatography

(15:1 → 10:1 Hexanes: EtOAc) to yield fluorobiphenyl carbamate **3.41** (140 mg, 92% yield) as a clear oil. R_f 0.05 (Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.51 (m, 2H), 7.46–7.41 (m, 2H), 7.38–7.31 (m, 3H), 7.26 (t, *J* = 8.0, 1H), 3.48 (q, *J* = 7.0, 2H), 3.42 (q, *J* = 7.0, 2H), 1.29 (t, *J* = 7.0, 3H), 1.23 (t, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 155.6, 153.7, 153.3, 134.0, 139.9, 139.6, 128.9, 127.7, 127.1, 124.4, 122.8, 115.2, 42.6, 42.1, 14.1, 13.3; IR (film): 2976, 1714, 1471, 1367, 1141 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{18}FNO_2H$, 288.1400; found 288.1399.

Note: Experimental procedures for the syntheses of the aryl carbamates shown in Figure 3.5 have previously been reported.[32]

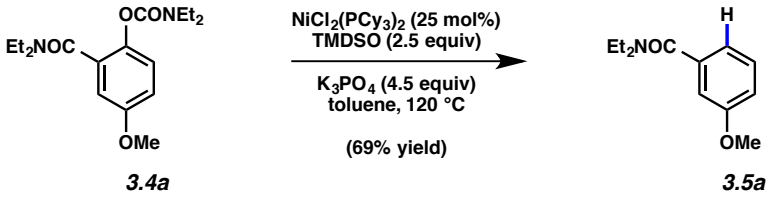
3.8.2.2 Reduction of Aryl Carbamates



Representative Procedure (reduction of naphthylcarbamate 3.42, Figure 3.5 is used as an example). Naphthalene (3.18, Figure 3.5). A 4-mL vial was charged with anhydrous powdered K_3PO_4 (0.379 g, 1.8 mmol, 4.5 equiv) and a magnetic stir bar. The vial and contents were flame-dried under reduced pressure, then allowed to cool under N_2. Naphthyl carbamate **3.42**[32] (96.8 mg, 0.4 mmol, 1 equiv) and $NiCl_2(PCy_3)_2$ (13.8 mg, 0.02 mmol, 5 mol%) were added. Subsequently, tetramethyldisiloxane (TMDSO) (0.17 mL, 1.0 mmol, 2.5 equiv) and toluene (1.5 mL) were added. The septum cap was replaced with a Teflon-lined screw cap. The

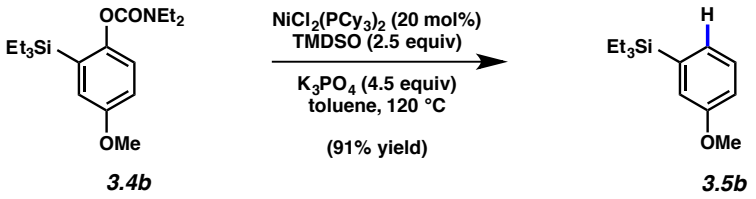
heterogeneous mixture was stirred at 115 °C for 15 h. The reaction vessel was cooled to 23 °C. The reaction mixture was diluted with EtOAc (5 mL), filtered over a pad of celite (eluted with an additional 5 mL of EtOAc), and evaporated to dryness. The crude residue was purified by flash chromatography (100% Hexanes) to yield deoxygenated product **3.18** (47.2 mg, 92% yield) as a white amorphous solid. R_f 0.52 (100% Hexanes). Spectral data match those previously reported.[33]

Any modifications of the conditions shown in this representative procedure are specified in the following schemes, which depict all of the results shown in Figures 3.2, 3.3, 3.4, and 3.5.



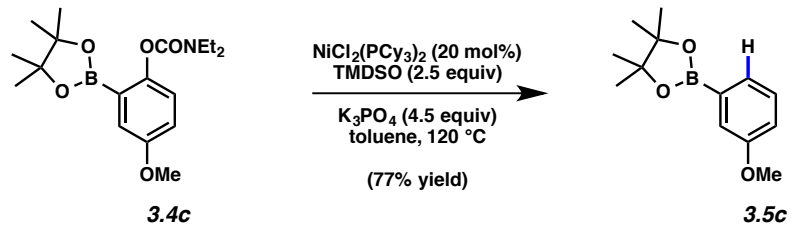
3.4a *3.5a*

Amide 3.5a (Figure 3.2). Purification by flash chromatography (3:1 Hexanes:EtOAc) generated deoxygenated product **3.5a** (91% yield) as a clear oil. R_f 0.28 (1:1 Hexanes:EtOAc). Spectral data match those previously reported.[34]



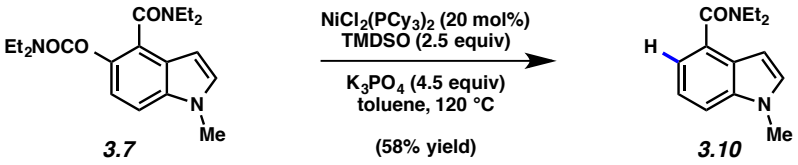
3.4b *3.5b*

Silane 3.5b (Figure 3.2). Purification by flash chromatography (19:1 Hexanes:EtOAc) generated deoxygenated product **3.5b** (91% yield) as a clear oil. R_f 0.44 (19:1 Hexanes:EtOAc). Spectral data match those previously reported.[35]



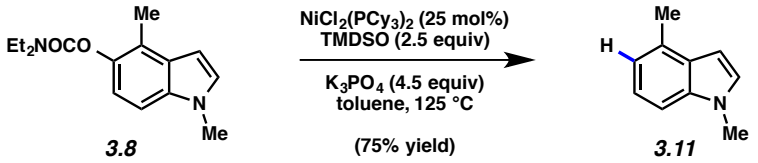
3.4c *3.5c*

Boronic Ester 3.5c (Figure 3.2). Purification by flash chromatography (19:1 Hexanes:EtOAc) afforded deoxygenated product **3.5c** (77% yield) as a clear oil. R_f 0.30 (19:1 Hexanes:EtOAc). Spectral data match those previously reported.[36]

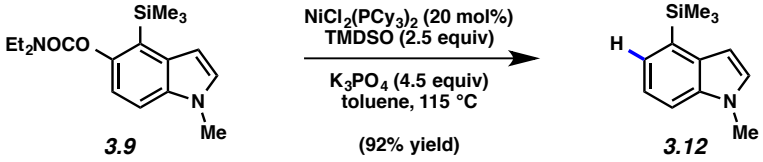


3.7 *3.10*

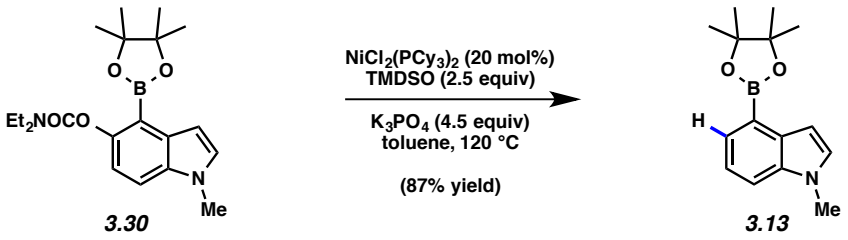
Amide Indole 3.10 (Figure 3.3). Purification by flash chromatography (7:1 Hexanes:Acetone) yielded deoxygenated product **3.10** (58% yield) as a pale green solid. R_f 0.09 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (ad, J = 8.5, 1H), 7.22 (at, J = 7.5, 1H), 7.09–7.07 (m, 2H), 6.44 (dd, J = 3.0, 0.5, 1H), 3.81 (s, 3H), 3.65 (as, 2H), 3.22 (as, 2H), 1.31 (as, 3H), 1.02 (as, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 136.9, 129.7, 129.7, 125.6, 121.4, 117.2, 109.9, 99.9, 43.2, 38.9, 33.1, 14.6, 13.3; IR (film): 2972, 1624, 1427, 1288, 1113 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{18}N_2OH$, 231.1497; found, 231.1495.



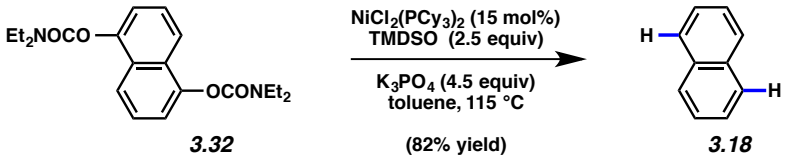
Methylindole 3.11 (Figure 3.3). Purification by flash chromatography (20:1 Hexanes:EtOAc) generated deoxygenated product **3.11** (75% yield) as a light yellow liquid. R_f 0.42 (20:1 Hexanes:EtOAc). Spectral data match those previously reported.[42]



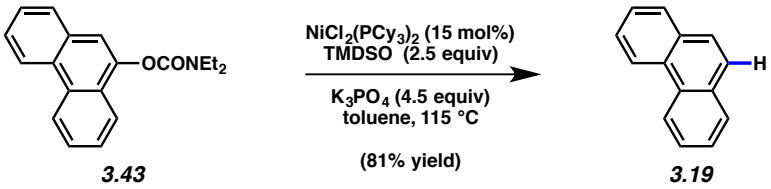
Silylindole 3.12 (Figure 3.3). Purification by flash chromatography (5:1 Hexanes:EtOAc) yielded deoxygenated product **3.12** (92% yield) as a pale green solid. R_f 0.47 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (ad, J = 8.0, 1H), 7.29–7.22 (m, 2H), 7.11 (d, J = 3.5, 1H), 6.62 (dd, J = 2.5, 1.0, 1H), 3.87 (s, 3H), 0.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 132.4, 132.2, 128.7, 125.4, 121.2, 110.4, 102.1, 32.9, 0.42; IR (film): 3044, 2956, 1518, 1406, 1248 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{17}NSiH$, 204.1208; found, 204.1213.



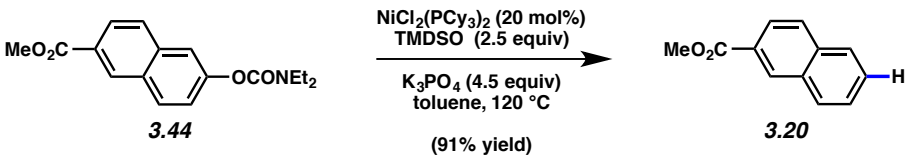
Boronic Ester Indole 3.13 (Figure 3.4). Purification by flash chromatography (10:1 Hexanes:EtOAc) generated deoxygenated product **3.13** (87% yield) as a white solid. R_f 0.37 (10:1 Hexanes:EtOAc). Spectral data match those previously reported.[37]



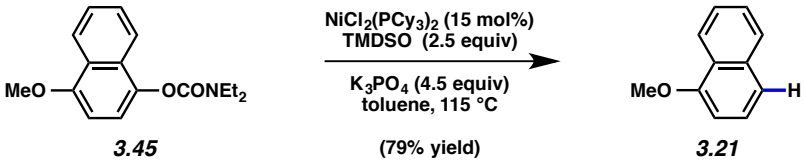
Naphthalene (3.18, Figure 3.5). Purification by flash chromatography (100% Hexanes) yielded deoxygenated product **3.18** (82% yield) as a white amorphous solid. R_f 0.52 (100% Hexanes). Spectral data match those previously reported.[33]



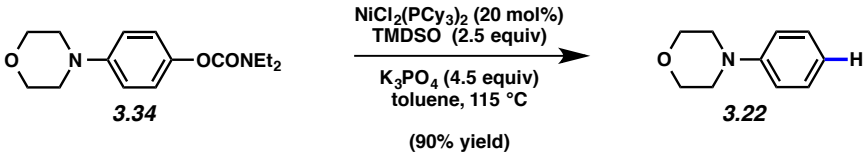
Phenanthrene (3.19, Figure 3.5). Purification by flash chromatography (100% Hexanes) afforded deoxygenated product **3.19** (81% yield) as a white amorphous solid. R_f 0.35 (100% Hexanes). Spectral data match those previously reported.[33]



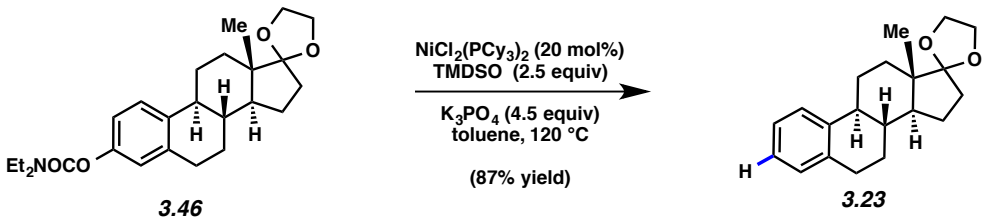
Naphthyl Ester 3.20 (Figure 3.5). Purification by flash chromatography (9:1 Hexanes:EtOAc) afforded deoxygenated product **3.20** (91% yield) as a white amorphous solid. R_f 0.37 (9:1 Hexanes:EtOAc). Spectral data match those previously reported.[33]



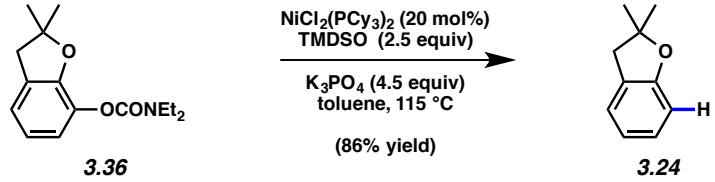
Naphthyl Ether 3.21 (Figure 3.5). Purification by flash chromatography (19:1 Hexanes:EtOAc) afforded deoxygenated product **3.21** (79% yield) as a white solid. R_f 0.48 (19:1 Hexanes:EtOAc). Spectral data match those previously reported.[38]



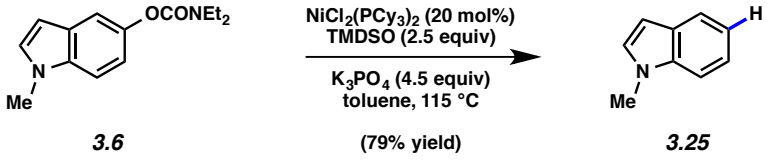
Arylamine 3.22 (Figure 3.5). Purification by flash chromatography (9:1 Hexanes:EtOAc) afforded deoxygenated product **3.22** (90% yield) as a white amorphous solid. R_f 0.29 (9:1 Hexanes:EtOAc). Spectral data match those previously reported.[39]



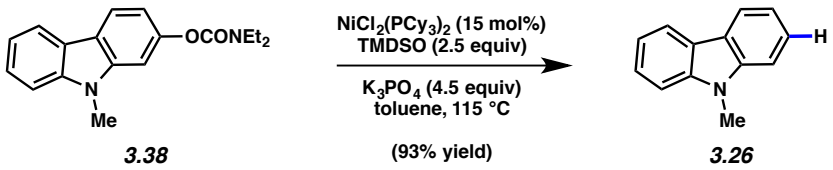
Estrone 3.23 (Figure 3.5). Purification by flash chromatography (10:1 Hexanes:EtOAc) generated deoxygenated product **3.23** (87% yield) a white solid. R_f 0.48 (10:1 Hexanes:EtOAc). Spectral data match those previously reported.[40]



Dihydrobenzofuran 3.24 (Figure 3.5). Purification by flash chromatography (10:1 Hexanes:EtOAc) afforded deoxygenated product **3.24** (86% yield) as a pale yellow oil. R_f 0.52 (10:1 Benzene:Et_2O). Spectral data match those previously reported.[41]

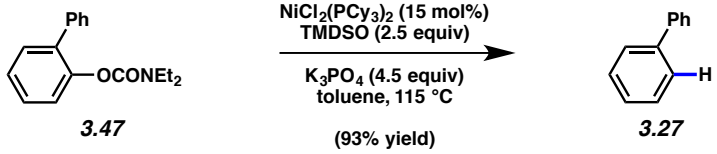


Indole 3.25 (Figure 3.5). Purification by flash chromatography (7:1 Hexanes:EtOAc) yielded deoxygenated product **3.25** (79% yield) as a light yellow liquid. R_f 0.53 (7:1 Hexanes:EtOAc). Spectral data match those previously reported.[42]



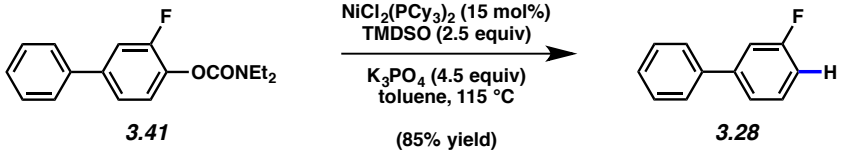
3.38 *3.26*

Carbazole 3.26 (Figure 3.5). Purification by flash chromatography (10:1 Hexanes:EtOAc) yielded deoxygenated product **3.26** (93% yield) as a white solid. R_f 0.48 (10:1 Hexanes:EtOAc). Spectral data match those previously reported.[33]



3.47 *3.27*

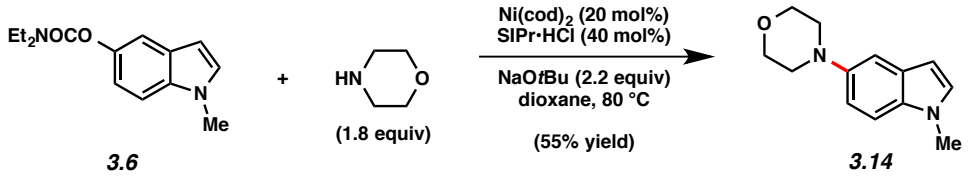
Biphenyl (3.27, Figure 3.5). Purification by flash chromatography (9:1 Hexanes:EtOAc) afforded deoxygenated product **3.27** (93% yield) as a white solid. R_f 0.62 (9:1 Hexanes:EtOAc). Spectral data match those previously reported.[33]



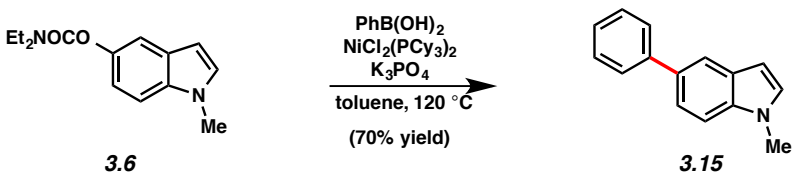
3.41 *3.28*

Flurobiphenyl (3.28, Figure 3.5). Purification by flash chromatography (100% Hexanes) yielded deoxygenated product **3.28** (85% yield) as a white amorphous solid. R_f 0.50 (100% Hexanes). Spectral data match those previously reported.[43]

3.8.2.3 Cross Coupling Approaches to Ipso and Cine Substituted Products

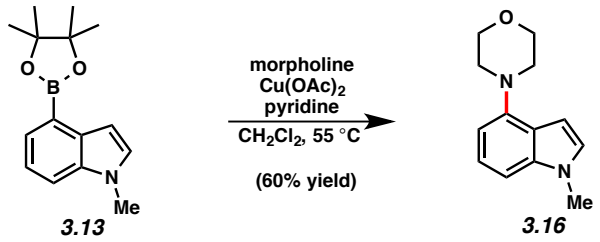


5-Morpholine Indole 3.14. A 20 mL scintillation vial was charged with $Ni(cod)_2$ (27.5 mg, 0.1 mmol, 20 mol%), SIPr•HCl (85.4 mg, 0.2 mmol, 40 mol%), anhydrous powdered NaO*t*Bu (105.7 mg, 1.1 mmol, 2.2 equiv), and a magnetic stir bar, all in a glove box. Subsequently, a solution of carbamate substrate **3.6** (123.2 mg, 0.50 mmol, 1 equiv) and morpholine (79.0 mL, 0.9 mmol, 1.8 equiv) in dioxane (2.5 mL) was added. The vessel was removed from the glove box and then heated to 80 °C for 3 h. After cooling the reaction vessel to 23 °C and concentrating under reduced pressure, the crude residue was loaded onto a silica gel column (2.5 x 10 cm) and purified by flash chromatography (6:1:1 Benzene:Et_2O:CH_2Cl_2) to yield aminated product **3.14** (47.6 mg, 55% yield) as a white solid. R_f 0.21 (10:1:1 Benzene:Et_2O:CH_2Cl_2). Spectral data match those previously reported.[39]



5-Phenylindole 3.15. A 4-mL vial was charged with anhydrous powdered K_3PO_4 (611 mg, 2.88 mmol, 7.2 equiv) and a magnetic stir bar. The vial and the contents were flame-dried under reduced pressure and then allowed to cool under N_2. Phenyl boronic acid (195 mg, 1.6 mmol, 4.5

equiv), $NiCl_2(PCy_3)_2$ (27.6 mg, 0.04 mmol, 10 mol%), and indole carbamate **3.6** (98.5 mg, 0.4 mmol, 1 equiv) were added. The vial was then evacuated and backfilled with N_2. Toluene (1.4 mL) was added and the vial was sealed with a Teflon-lined screw cap and stirred at 23 °C for 1 h. The heterogeneous mixture was then heated at 120 °C for 14 h. The reaction vessel was allowed to cool to 23 °C. The mixture was diluted with EtOAc (5 mL) and filtered over a pad of silica (eluted with an additional 5 mL of EtOAc). The crude residue was purified by flash chromatography (20:1 Hexanes:EtOAc) to yield coupled product **3.15** (88.0 mg, 70% yield) as a white solid. R_f 0.53 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[32a]



4-Morpholine Indole 3.16. A 4-mL dram vial equipped with a magnetic stir bar was flame-dried under reduced pressure and backfilled with N_2. After cooling to 23 °C, the indole boronic ester **3.13** (0.050 g, 0.194 mmol, 1 equiv) and copper acetate (0.212g, 1.167 mmol, 6 equiv) were added to the vial. Morpholine (0.050 mL, 0.583 mmol, 3 equiv), pyridine (0.063 mL, 0.778 mmol, 4 equiv) and CH_2Cl_2 (0.5 mL) were then added to the solids. The septum cap was replaced with a Teflon-coated cap and the reaction was stirred at 55 °C for 2 d. The reaction vessel was removed from the heating block and cooled to 23 °C. The solution was loaded directly onto a silica gel column and purified by flash chromatography (5:1 hexanes:EtOAc) to yield 4-morpholine indole **3.16** (0.025g, 60% yield) as a light yellow solid. R_f 0.42 (5:1

Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (t, *J* = 8.0, 1H), 7.04 (d, *J* = 8.0, 1H), 7.02 (d, *J* = 3.0, 1H), 6.61 (d, *J* = 8.0, 1H), 6.48 (d, *J* = 3.0, 1H), 3.9 (t, *J* = 5.0, 4H), 3.79 (s, 3H), 3.26 (t, *J* = 5.0, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.8, 138.0, 127.5, 122.4, 121.7, 106.3, 104.5, 99.5, 67.8, 52.0, 33.2; IR (film): 2963, 2858, 1575, 1498, 1235, 1117 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{16}N_2OH$, 217.1341; found, 217.1347.

3.13 *3.17*

4-Phenylindole 3.17. A 20 mL scintillation vial was charged with a magnetic stir bar, K_3PO_4 (3 mL, 2 M aqueous) and toluene (1.5 mL). The biphasic solution was then sparged with N_2 for 1 h. To the solution was added indole boronic ester **3.13** (150 mg, 0.583 mmol, 1 equiv), phenylboronic acid (123 mg, 1.167 mmol, 2 equiv) and $Pd(PPh_3)_4$ (101 mg, 0.088 mmol, 15 mol%) and the resulting mixture was sparged with N_2 for 10 min. The vial was sealed with a Teflon-coated screw-cap and heated at 90 °C for 14 h. After cooling to 23 °C, CH_2Cl_2 (5 mL) and Na_2SO_4 were added and the mixture was allowed to stand for 30 min. The crude mixture was then filtered over silica and concentrated under reduced pressure. The crude residue was purified by flash chromatography (7:1 Hexanes:EtOAc) to yield 4-phenylindole **3.17** as a light yellow oil (112 mg, 92% yield). R_f 0.41 (7:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): d 7.72 (d, *J* = 7.5, 2H), 7.50 (t, *J* = 7.5, 2H), 7.40–7.32 (m, 3H), 7.22 (dd, *J* = 6.5, 1.5, 1H), 7.12 (d, *J* = 3.5, 1H), 6.80 (d, *J* = 3.0, 1H) 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d 141.4, 137.2, 134.5, 129.2, 128.8, 128.5, 127.0, 126.7, 121.9, 119.3, 108.5, 100.4, 32.8; IR (film): 3053, 2909,

1603, 1513, 1413, 1286 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{13}NOH$, 208.1126; found 208.1128.

3.9 Notes and References

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Spectra Relevant to Chapter Three:

Cine Substitution of Arenes using the Aryl Carbamate as a Removable Directing Group

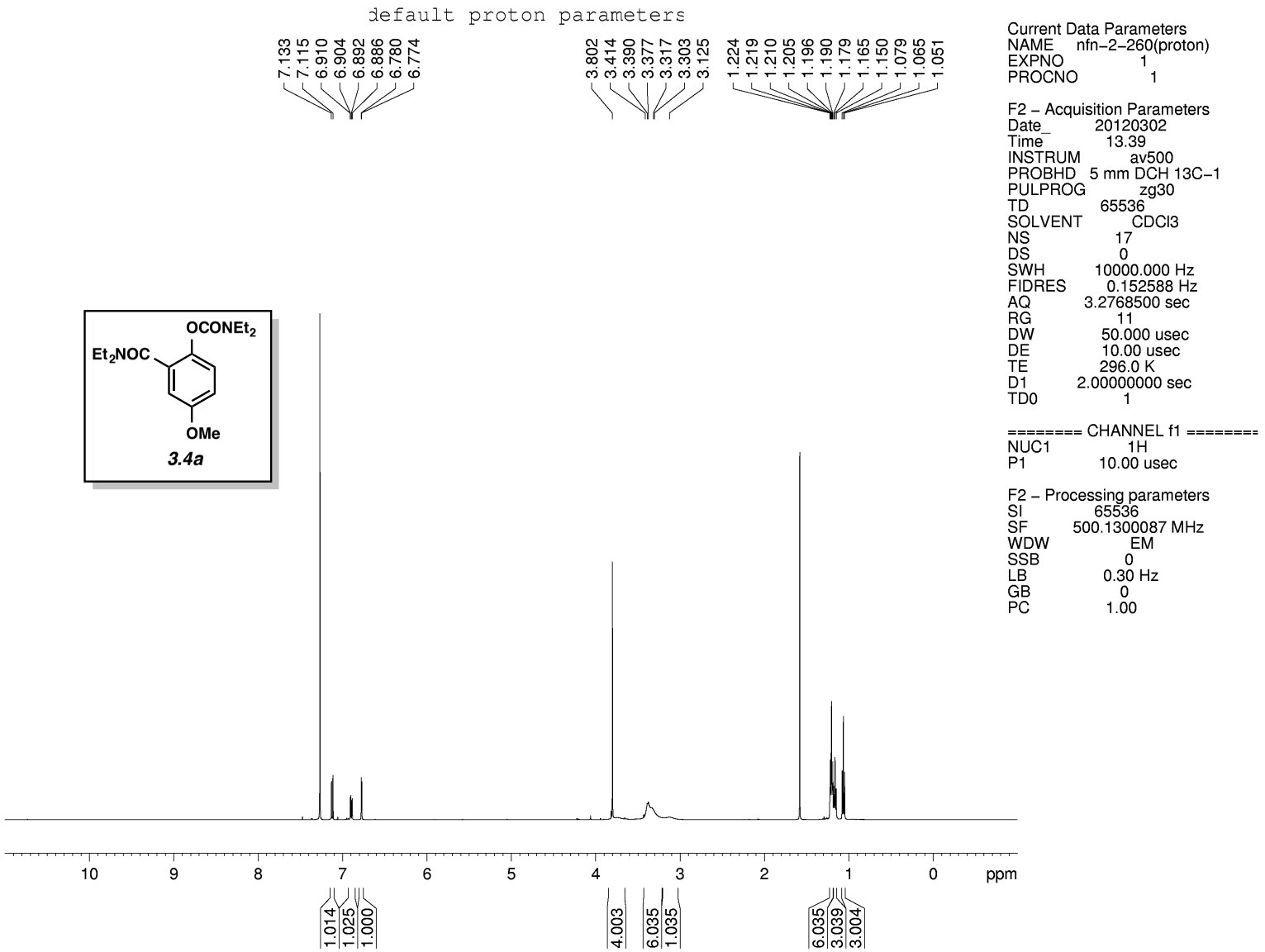


Figure 3.6. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.4a**.

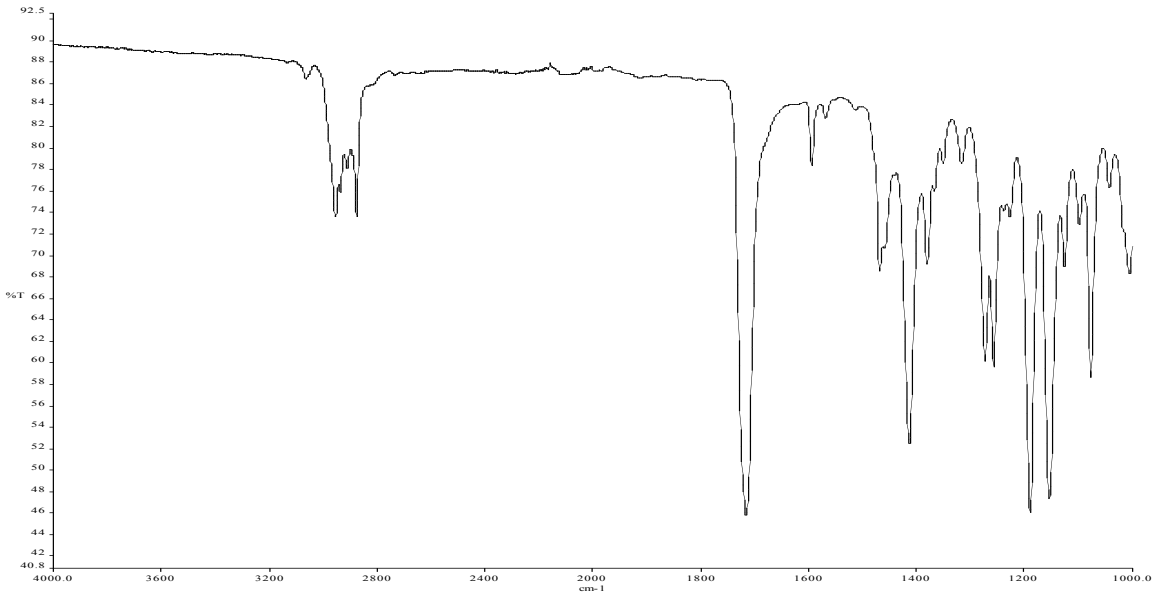


Figure 3.7. Infrared spectrum of compound **3.4a**.

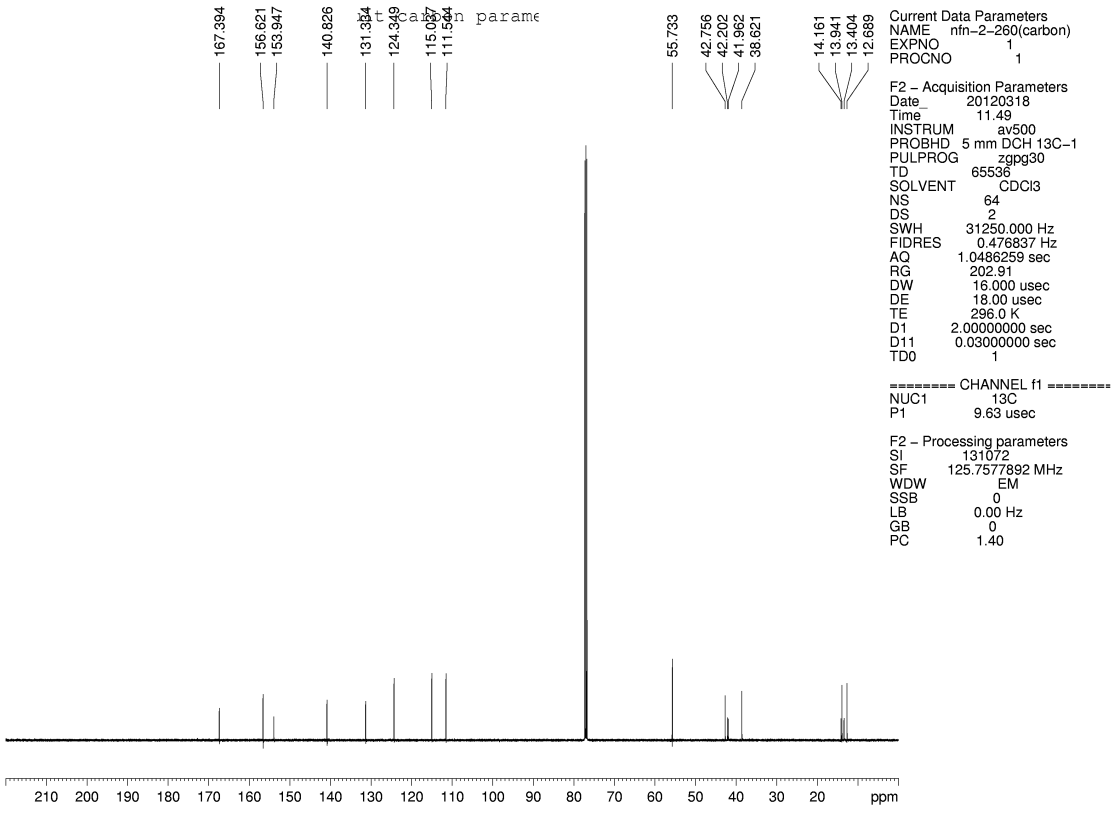


Figure 3.8. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.4a**.

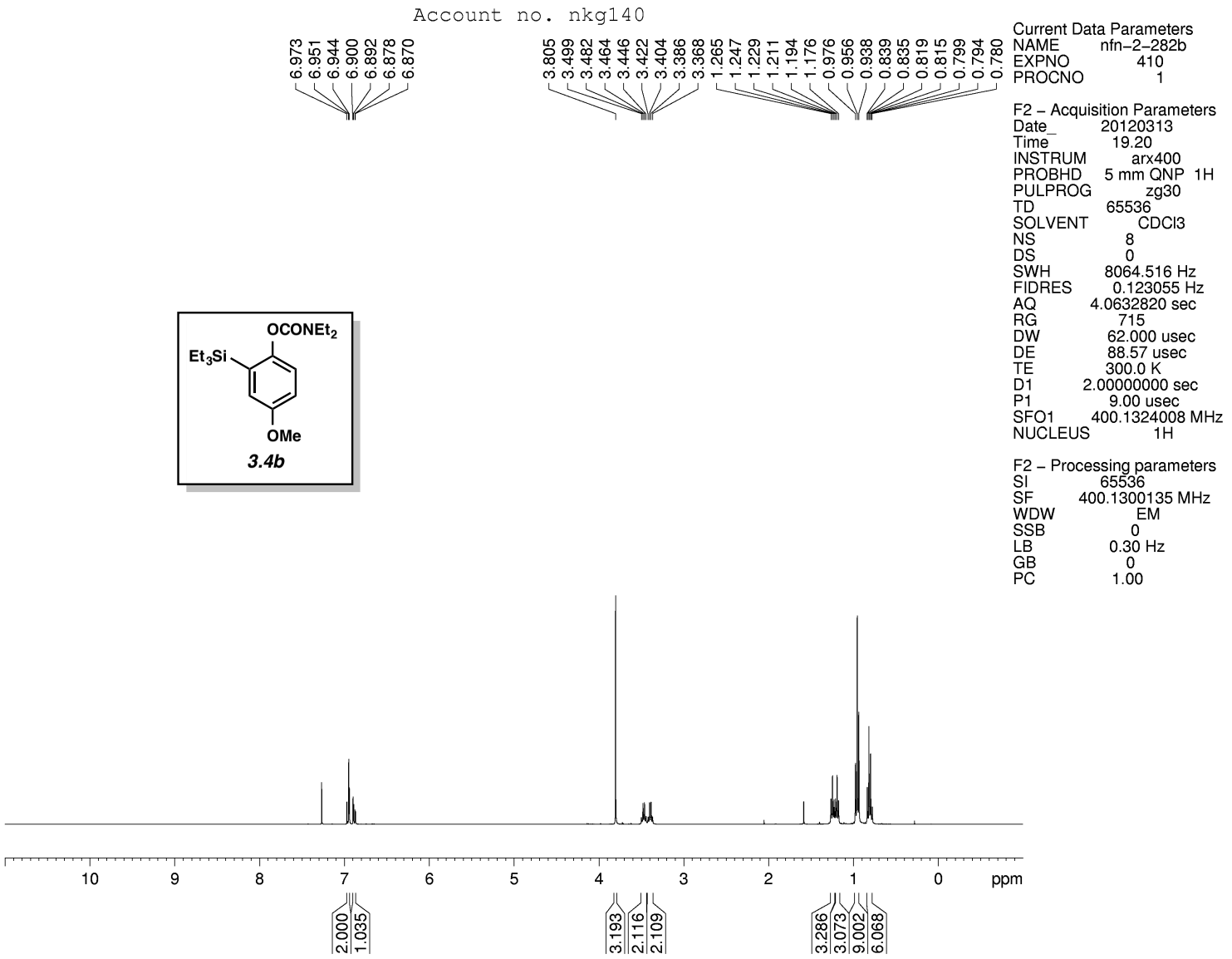


Figure 3.9. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3.4b**.

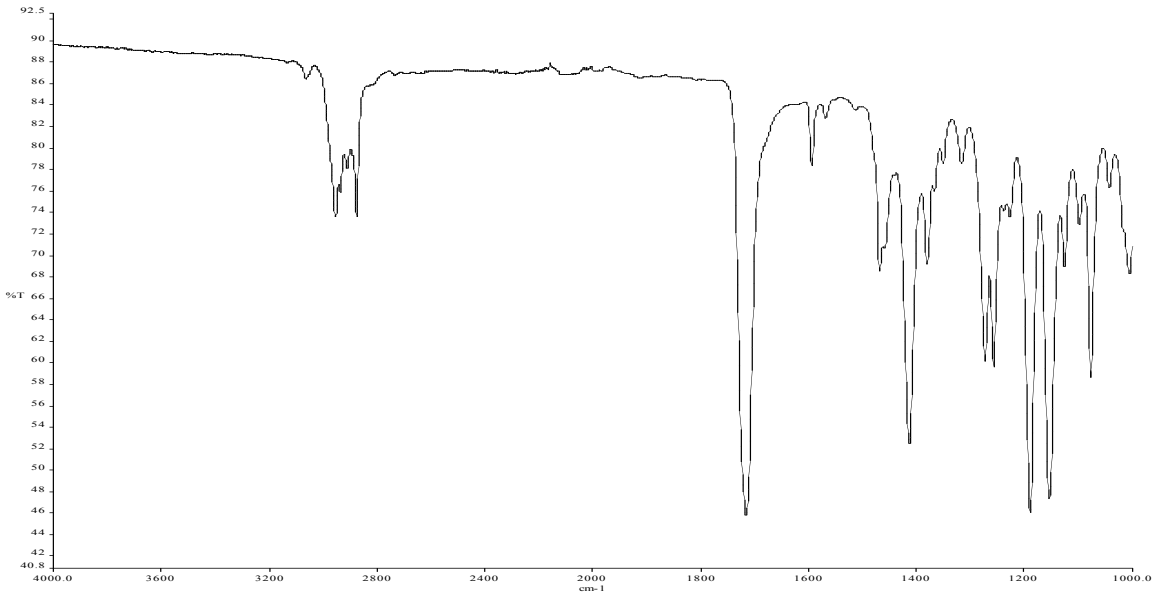


Figure 3.10. Infrared spectrum of compound **3.4b**.

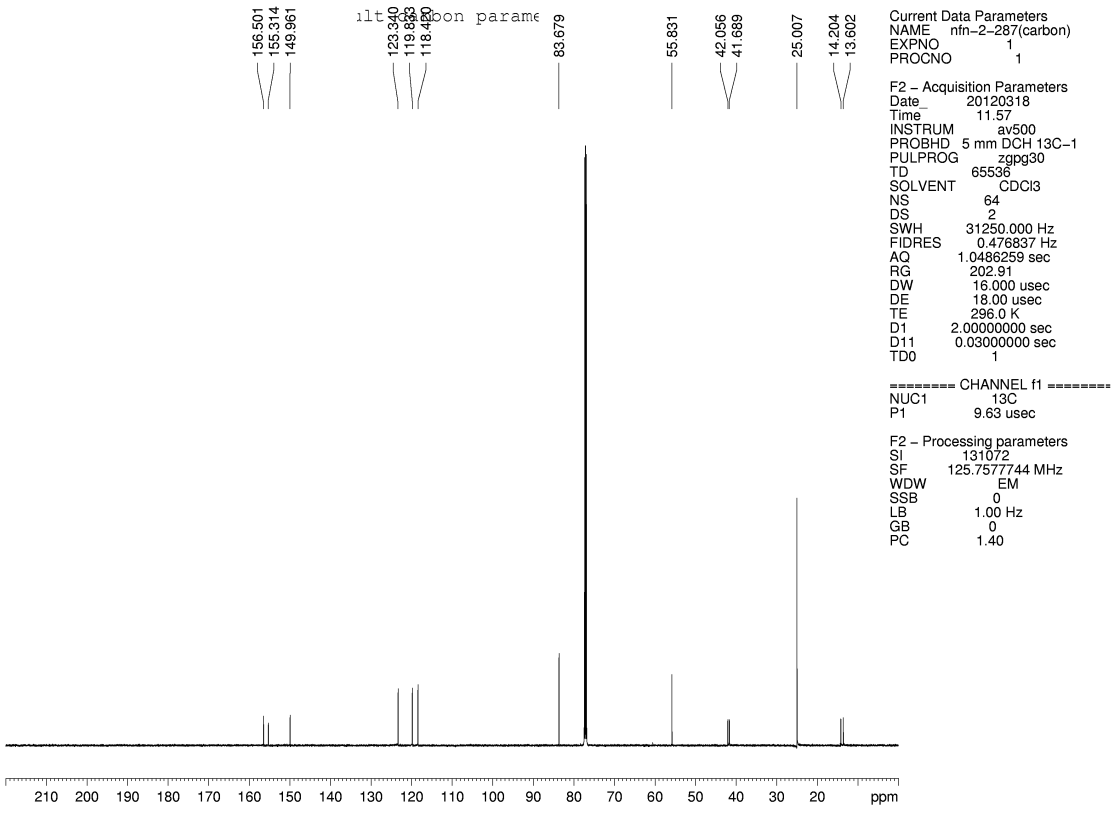


Figure 3.11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.4b**.

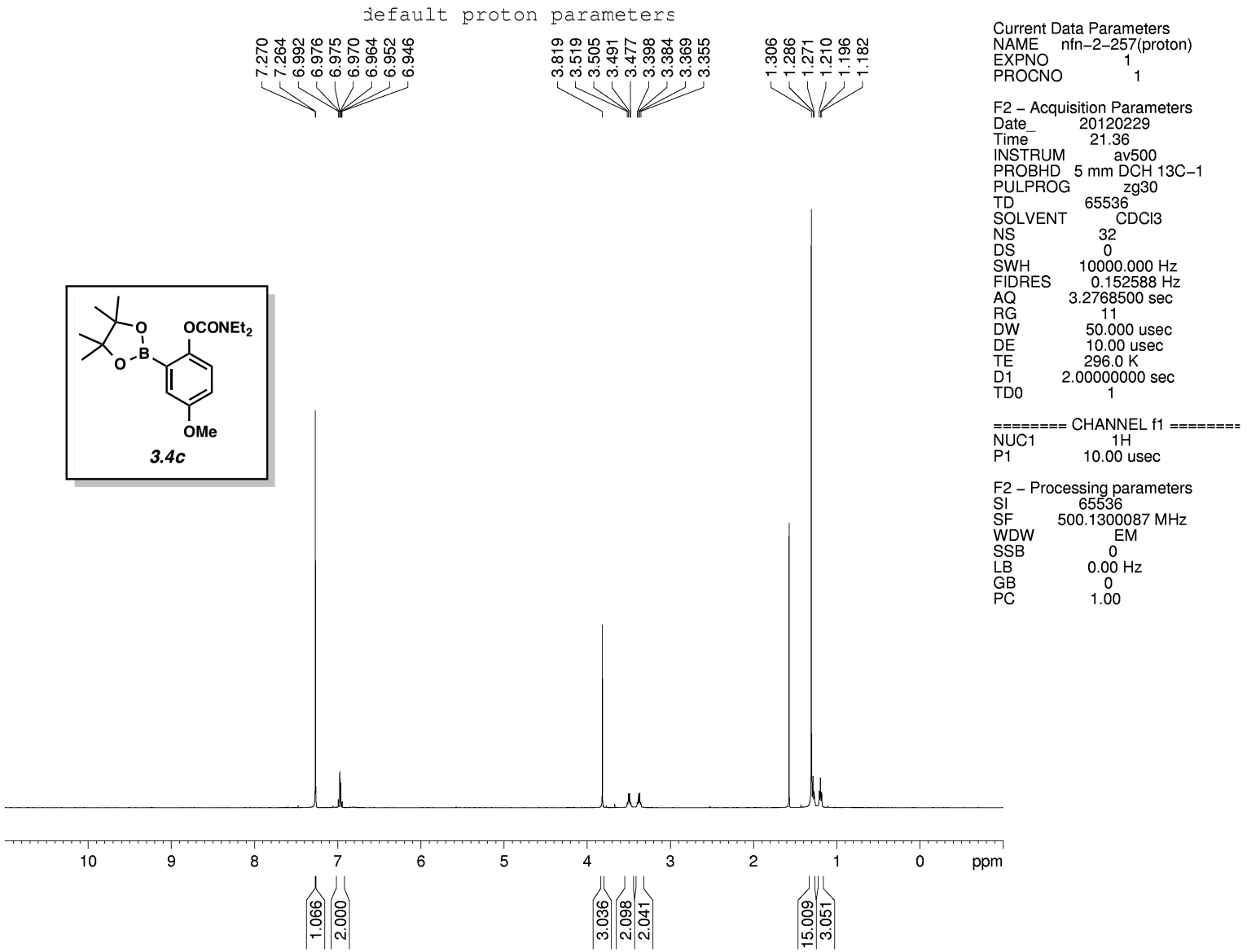


Figure 3.12. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.4c**.

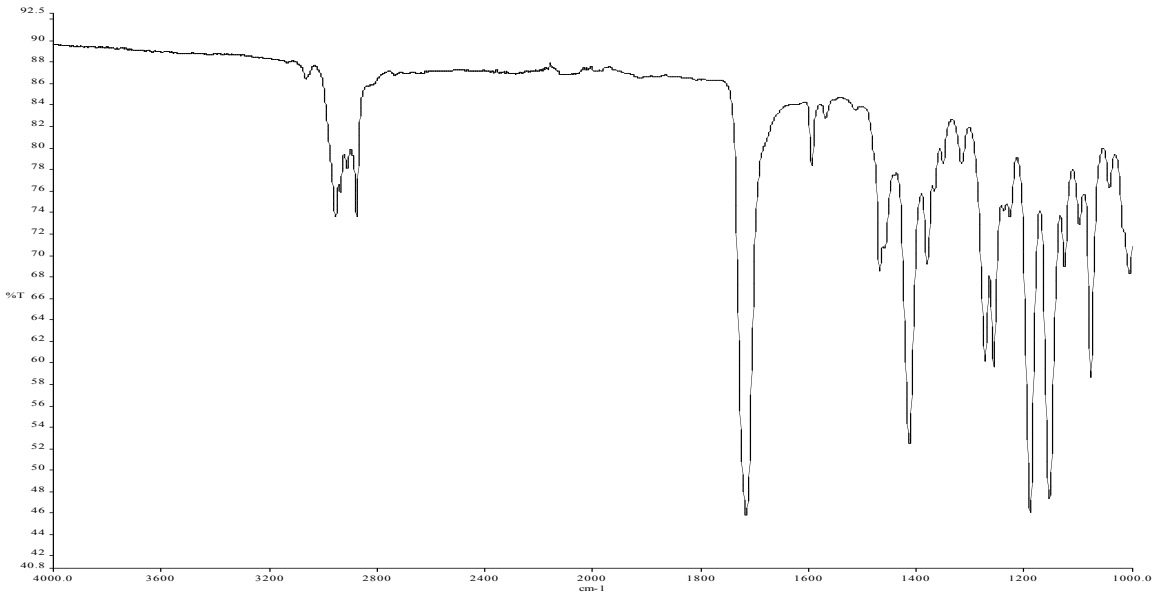


Figure 3.13. Infrared spectrum of compound **3.4c**.

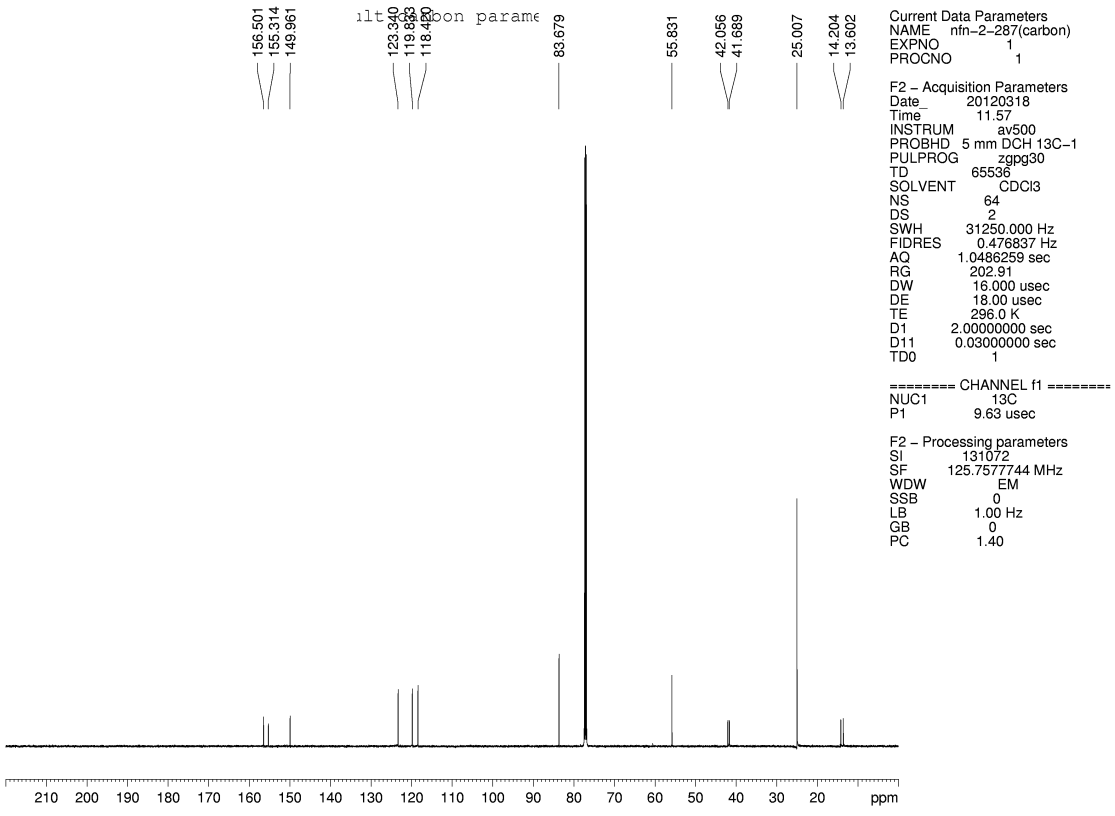


Figure 3.14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.4c**.

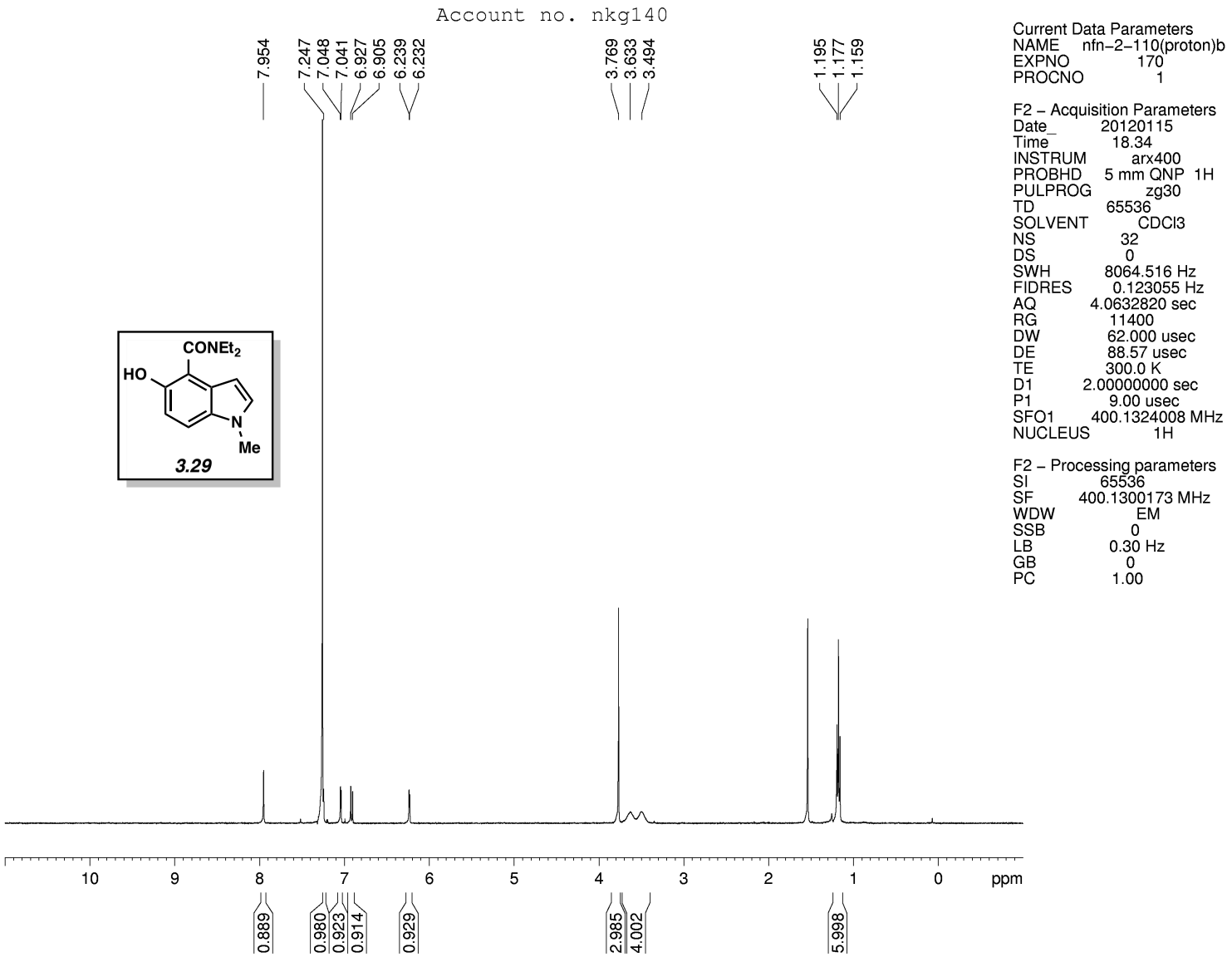


Figure 3.15. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3.29**.

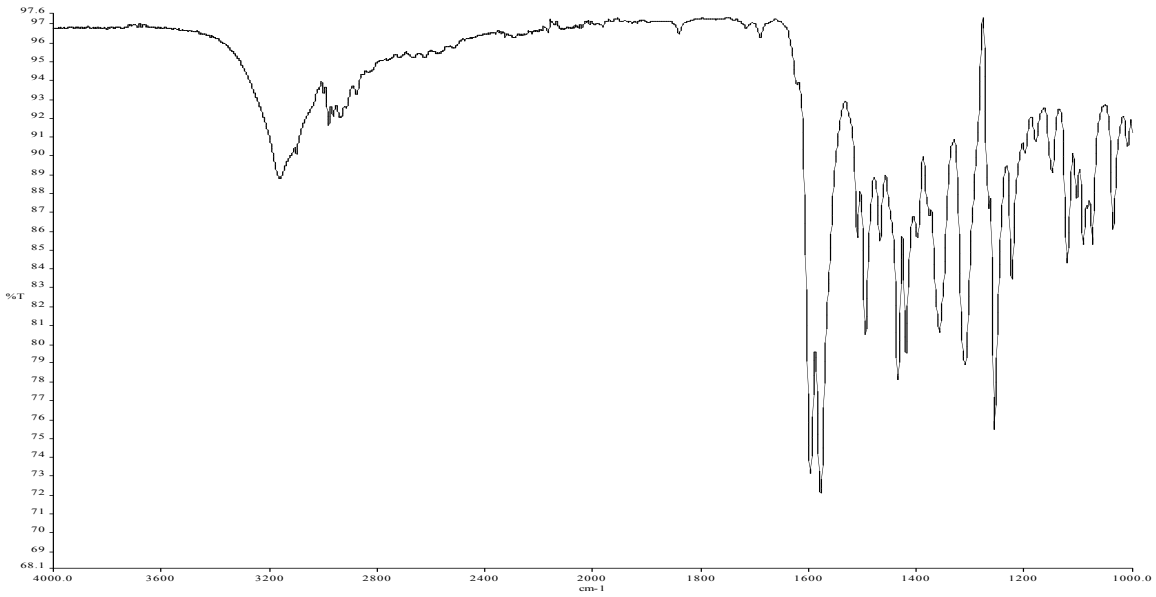


Figure 3.16. Infrared spectrum of compound **3.29**.

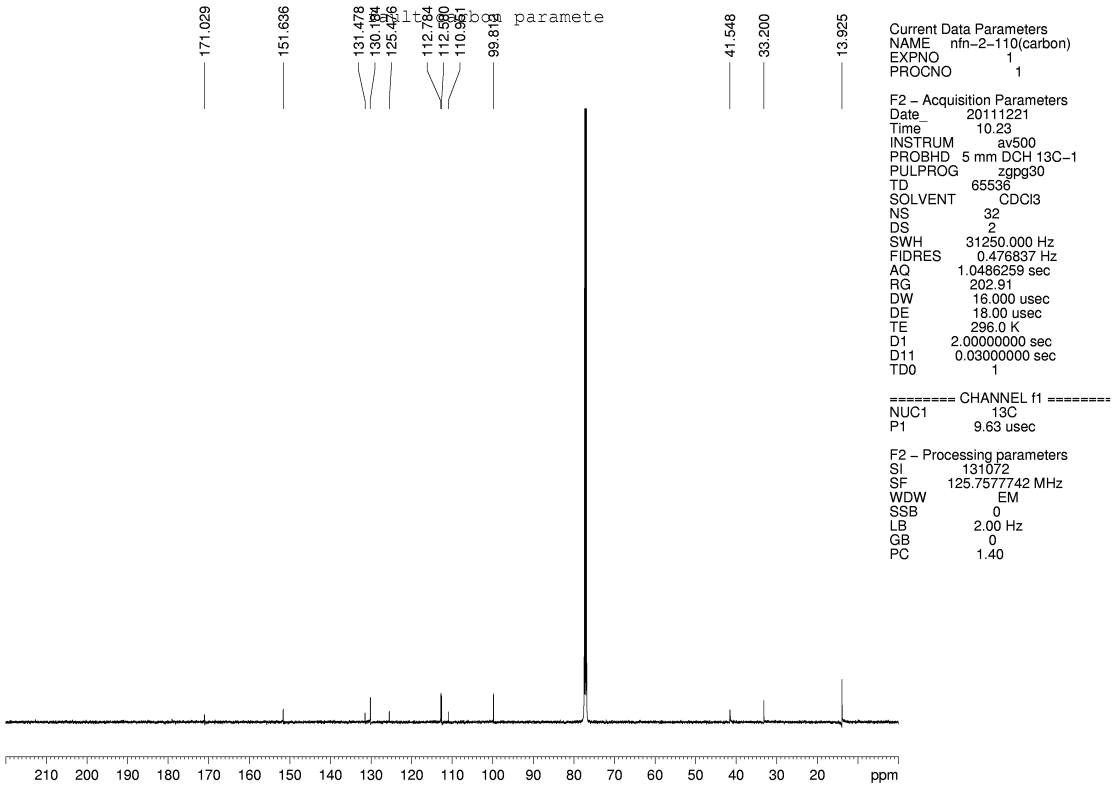


Figure 3.17. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.29**.

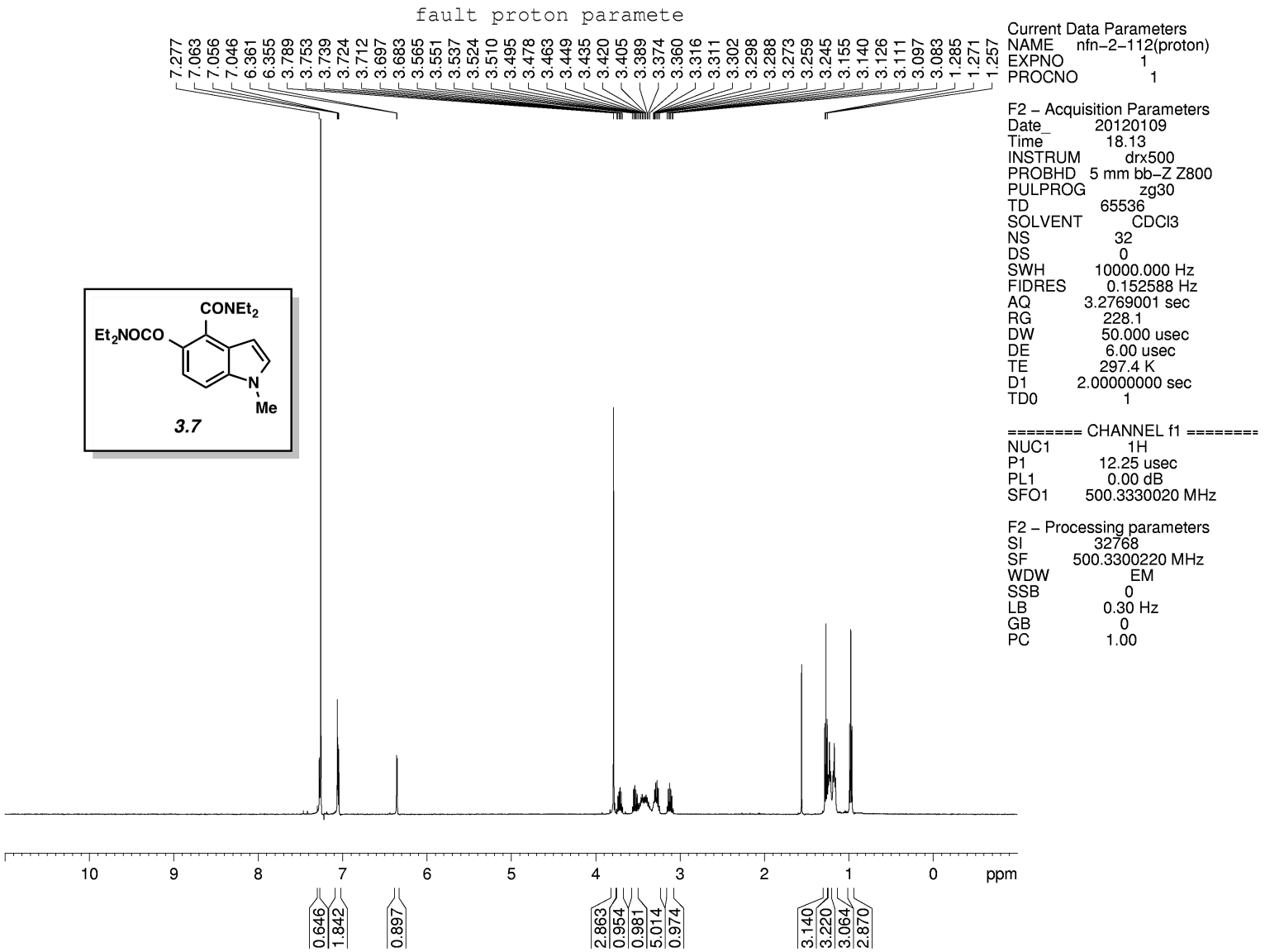


Figure 3.18. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.7**.

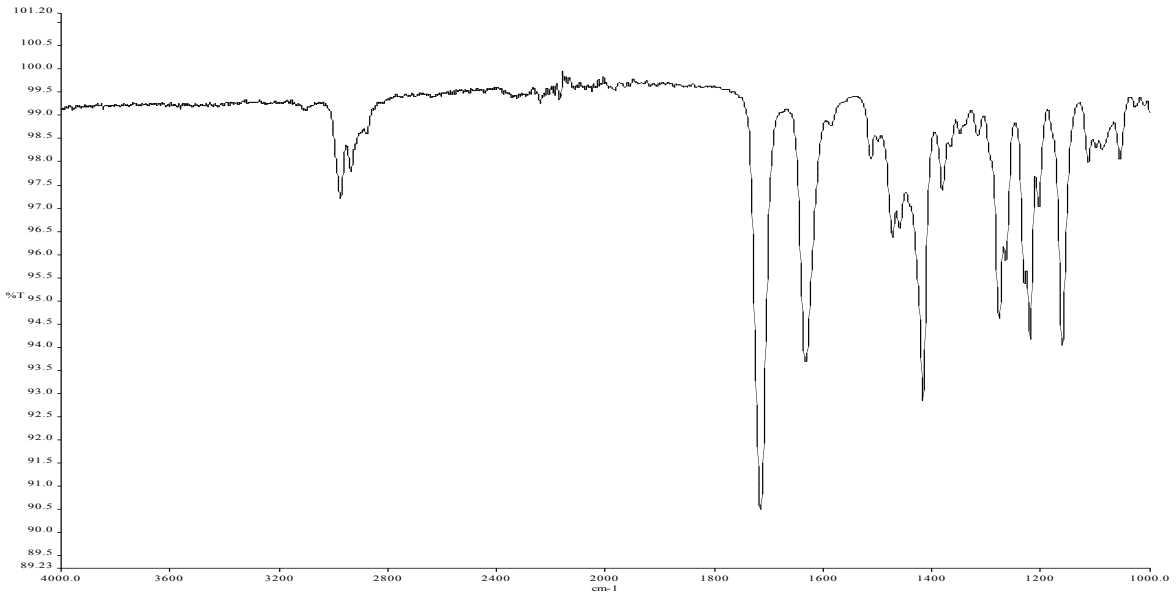


Figure 3.19. Infrared spectrum of compound **3.7**.

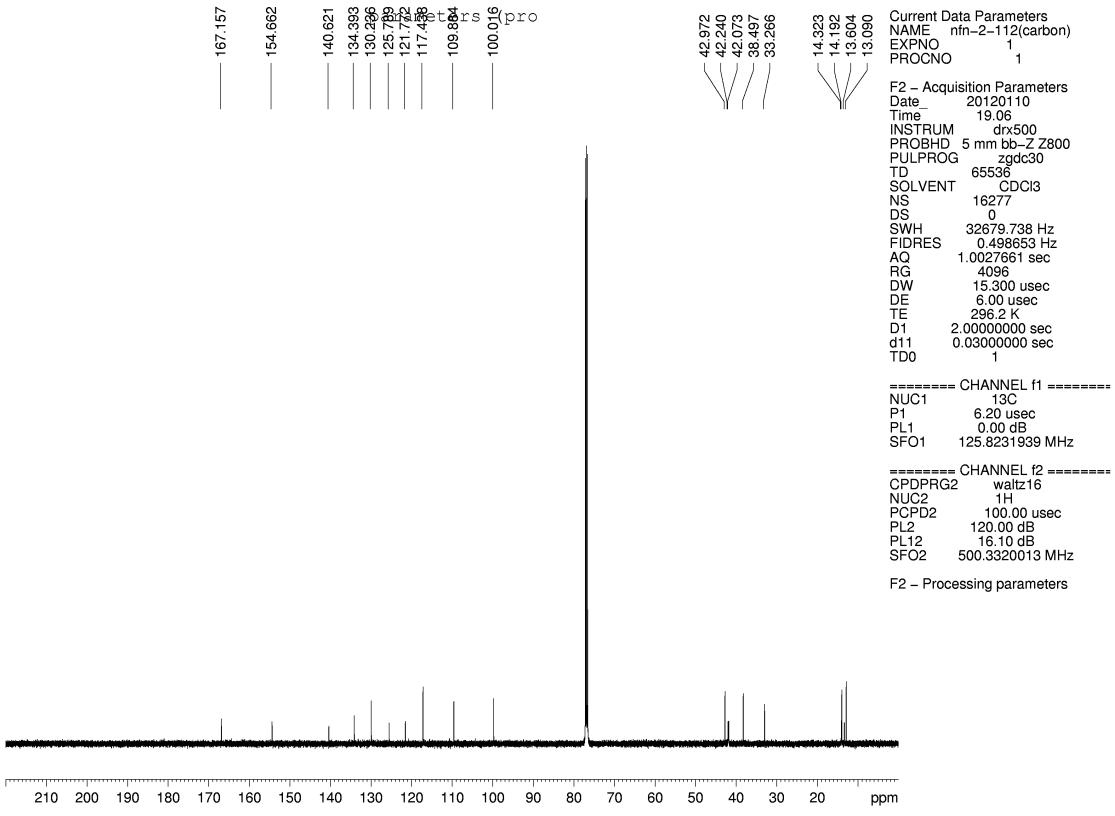


Figure 3.20. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.7**.

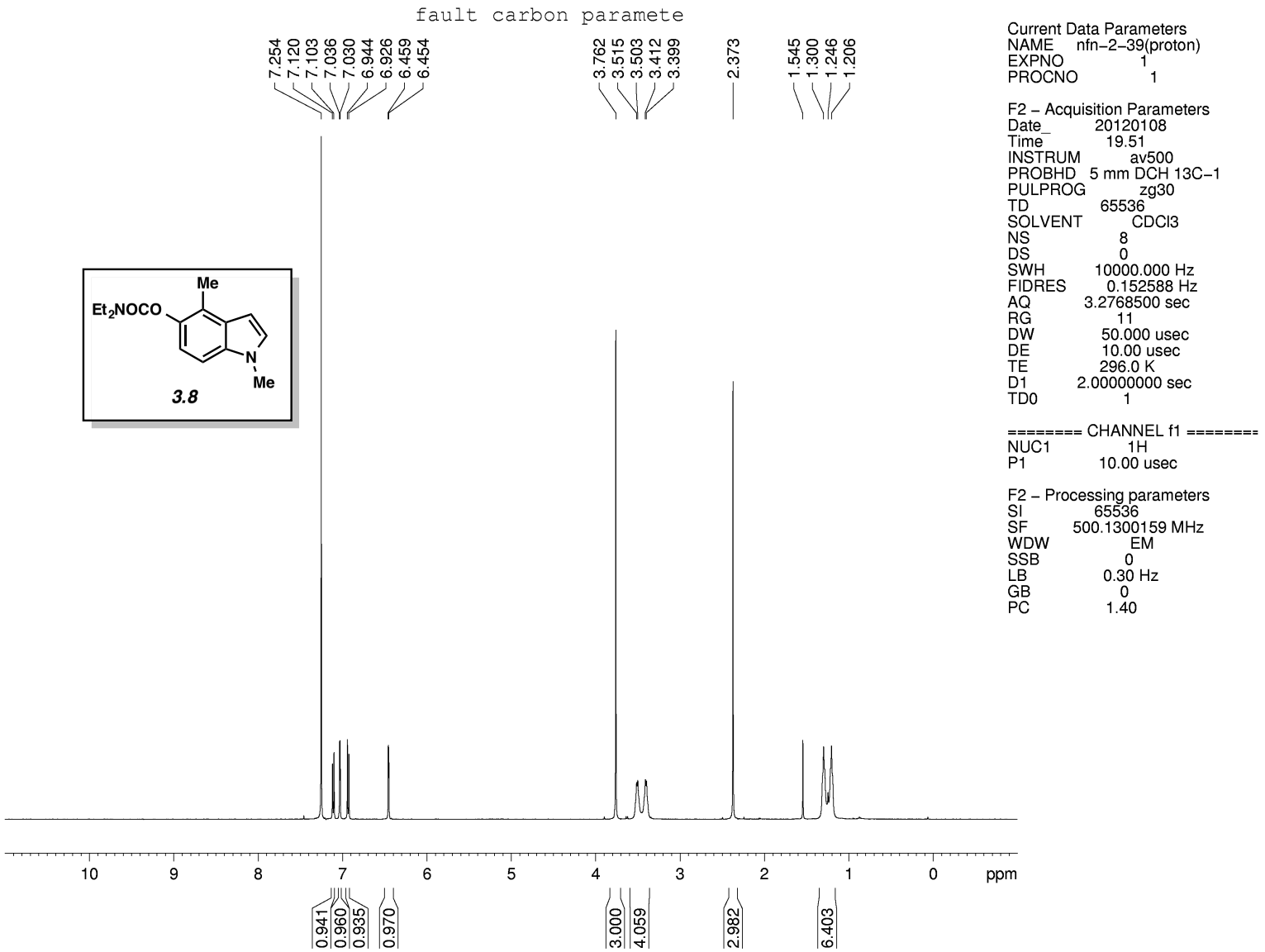


Figure 3.21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.8**.

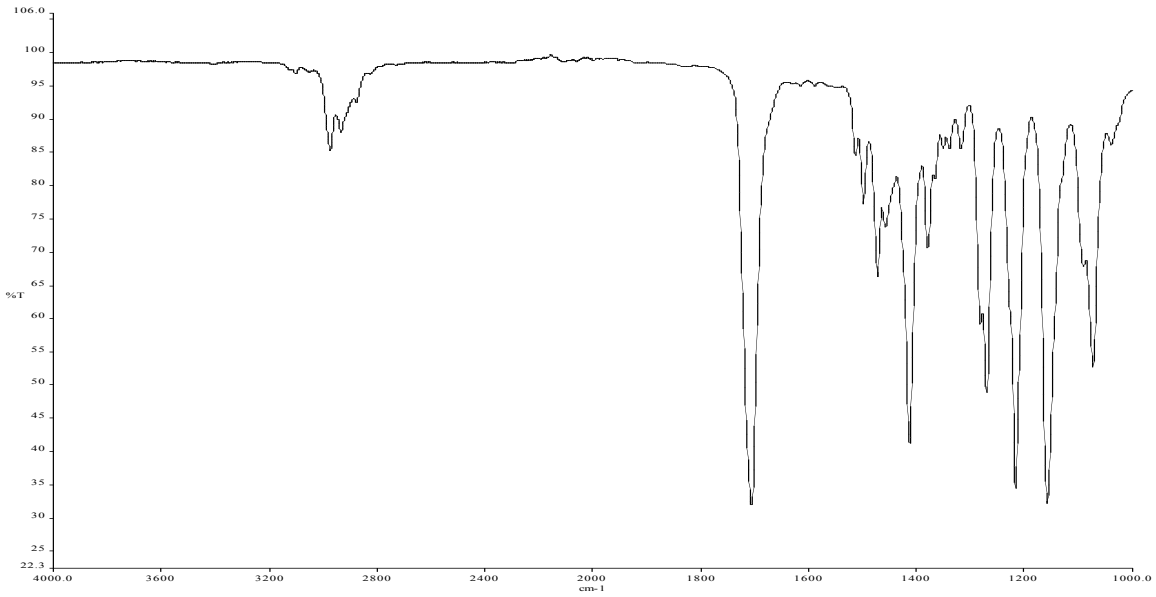


Figure 3.22. Infrared spectrum of compound **3.8**.

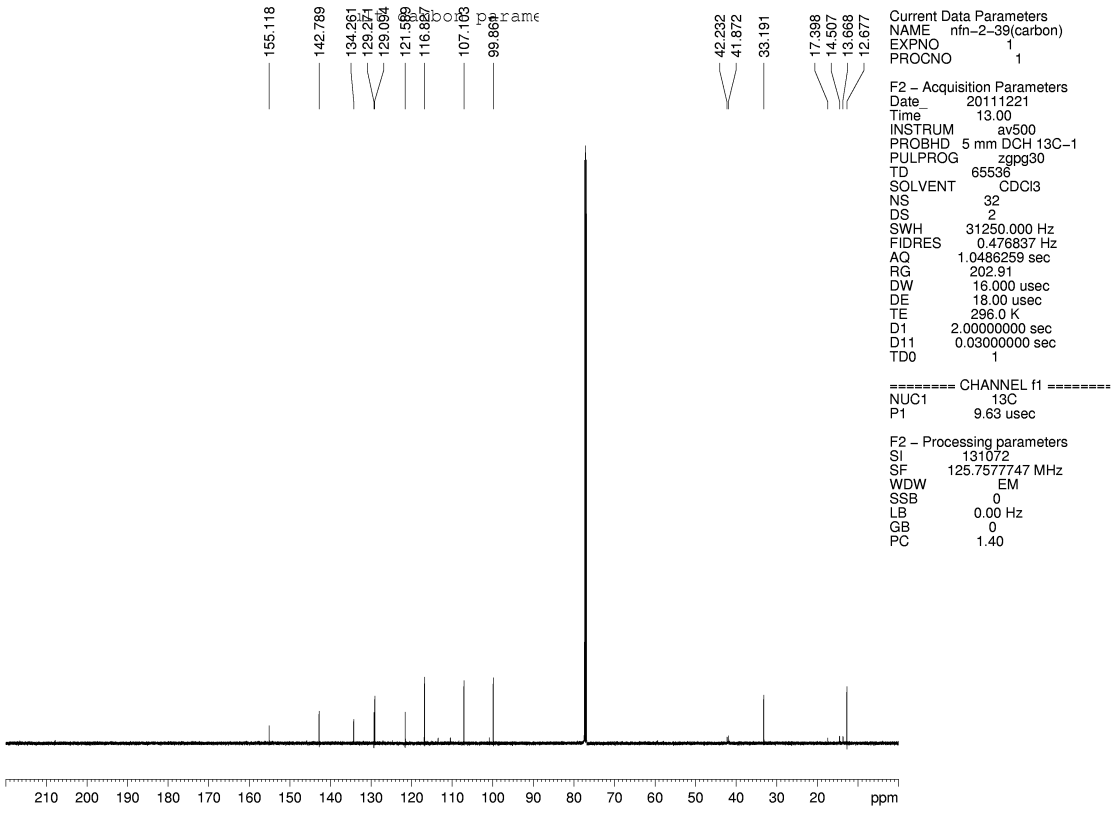


Figure 3.23. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.8**.

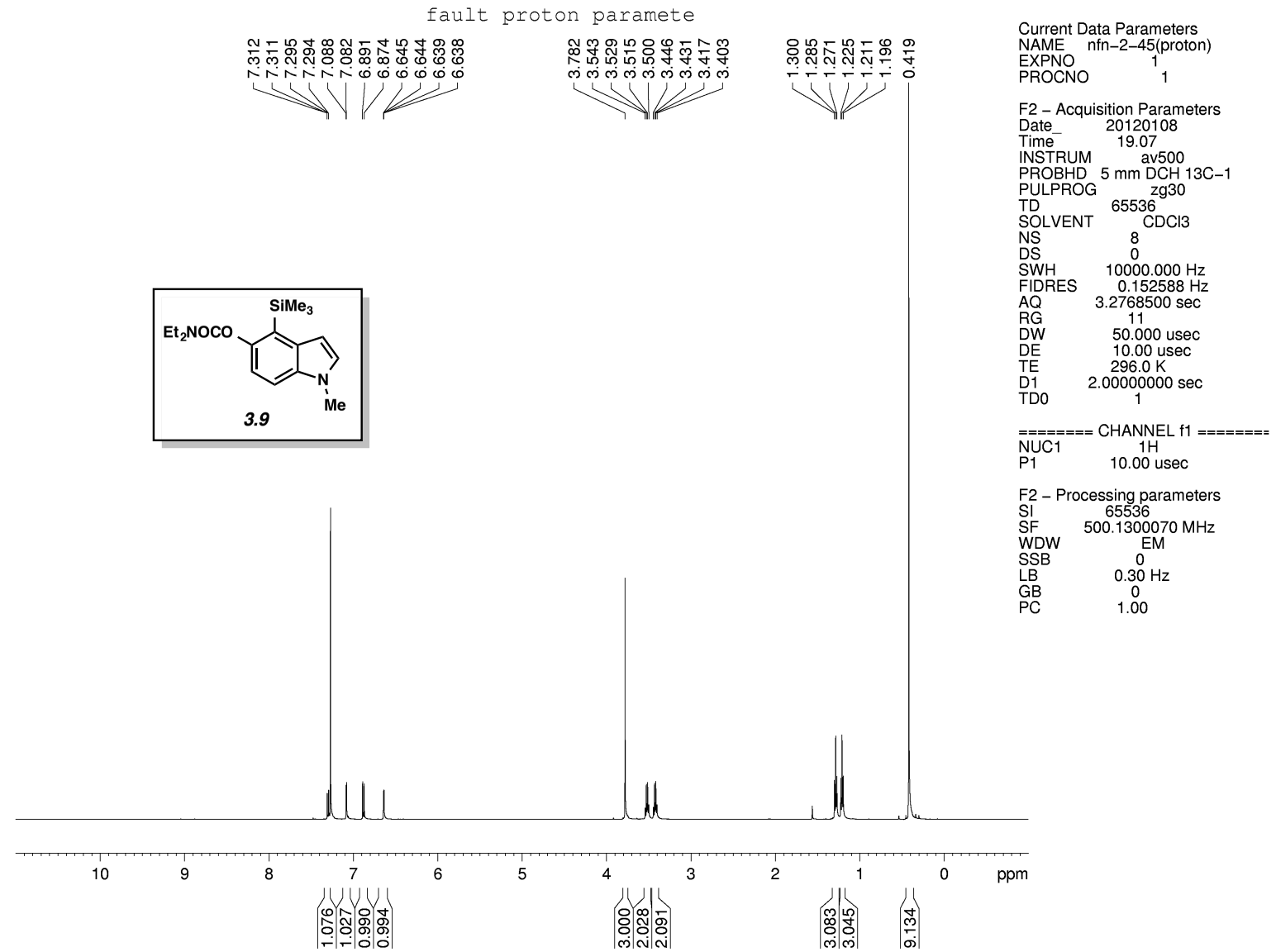


Figure 3.24. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.9**.

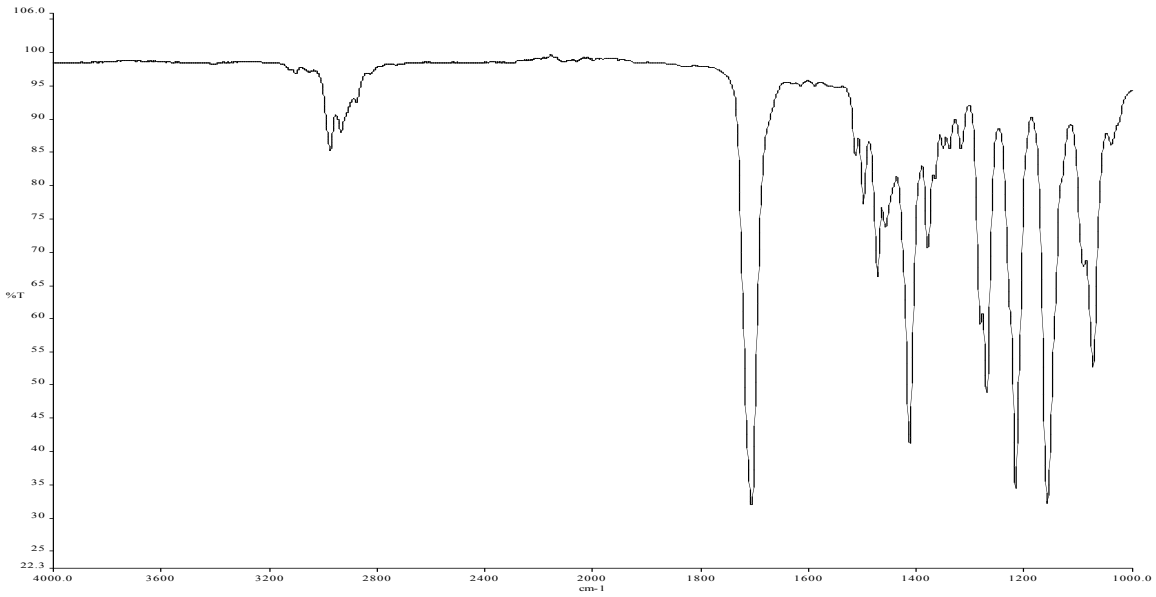


Figure 3.25. Infrared spectrum of compound **3.9**.

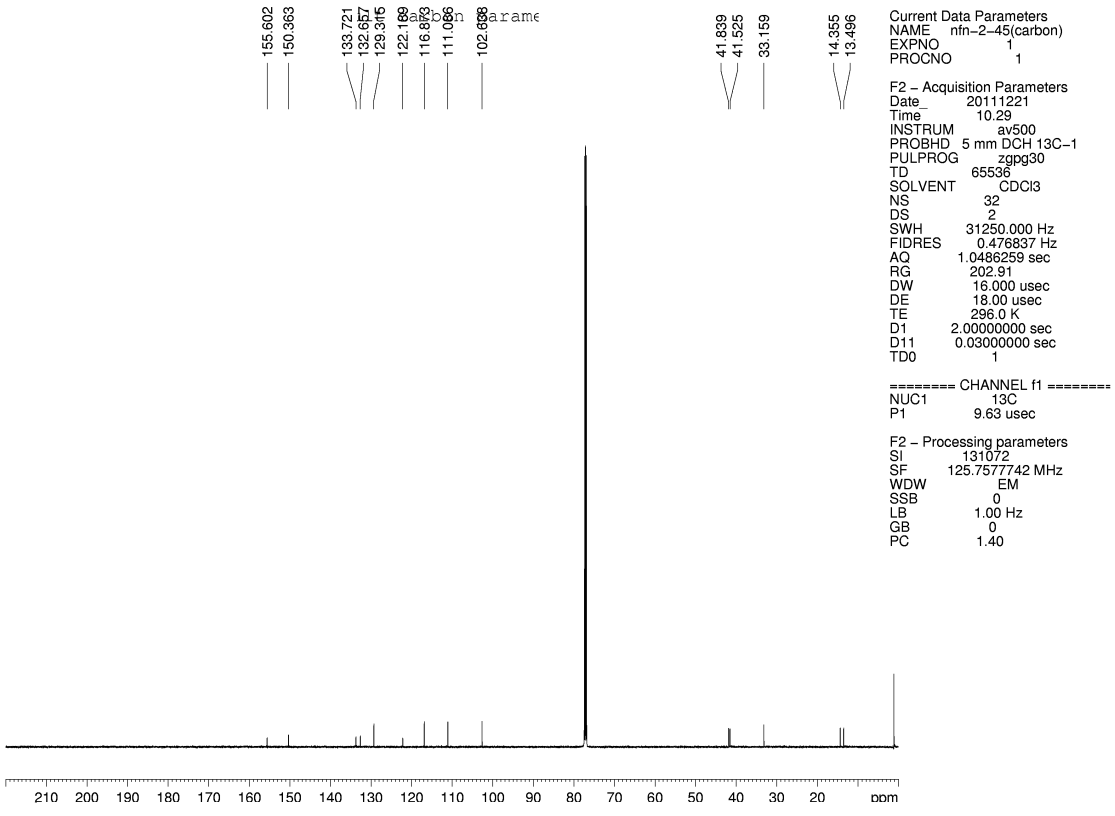


Figure 3.26. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.9**.

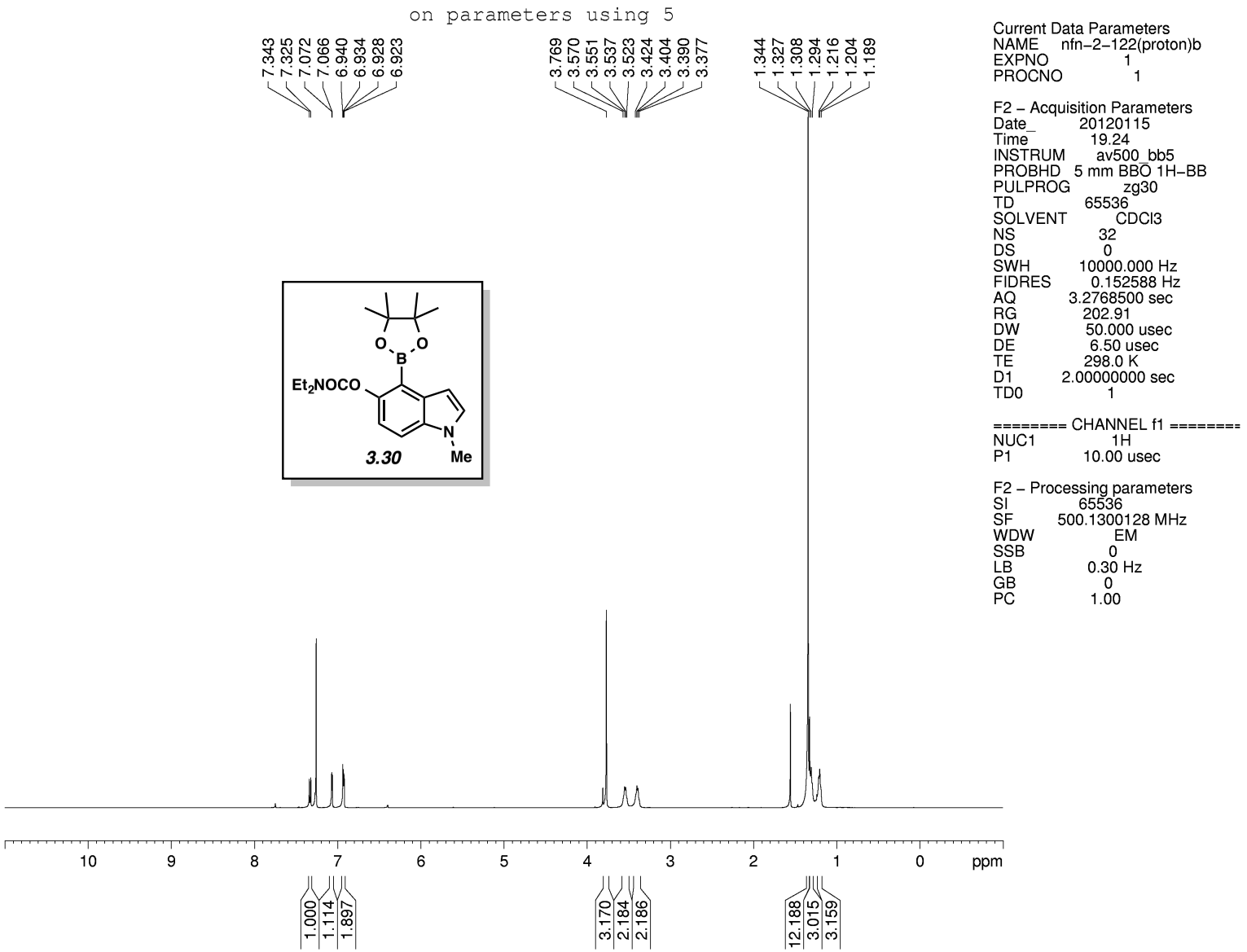


Figure 3.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.30**.

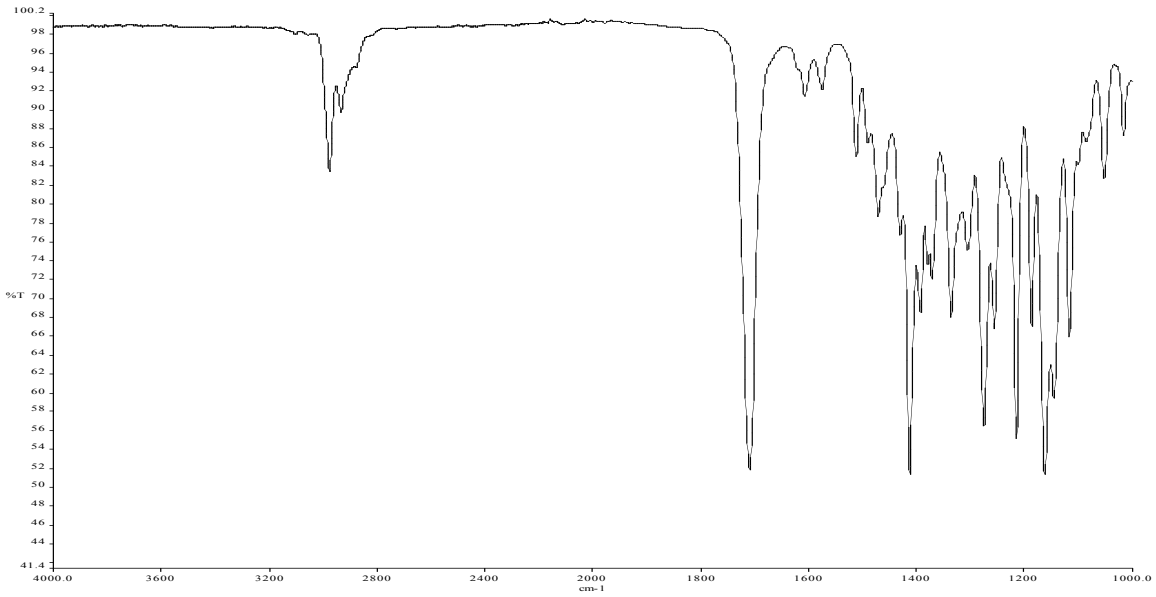


Figure 3.28. Infrared spectrum of compound **3.30**.

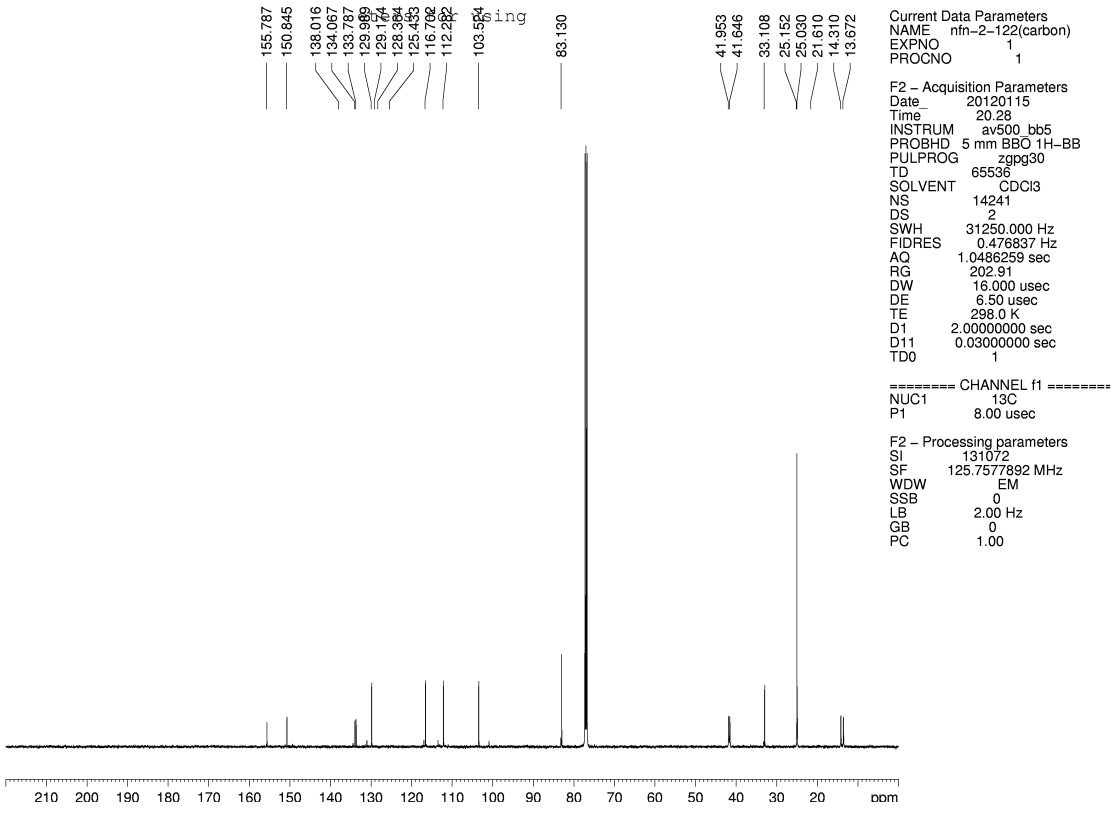


Figure 3.29. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.30**.

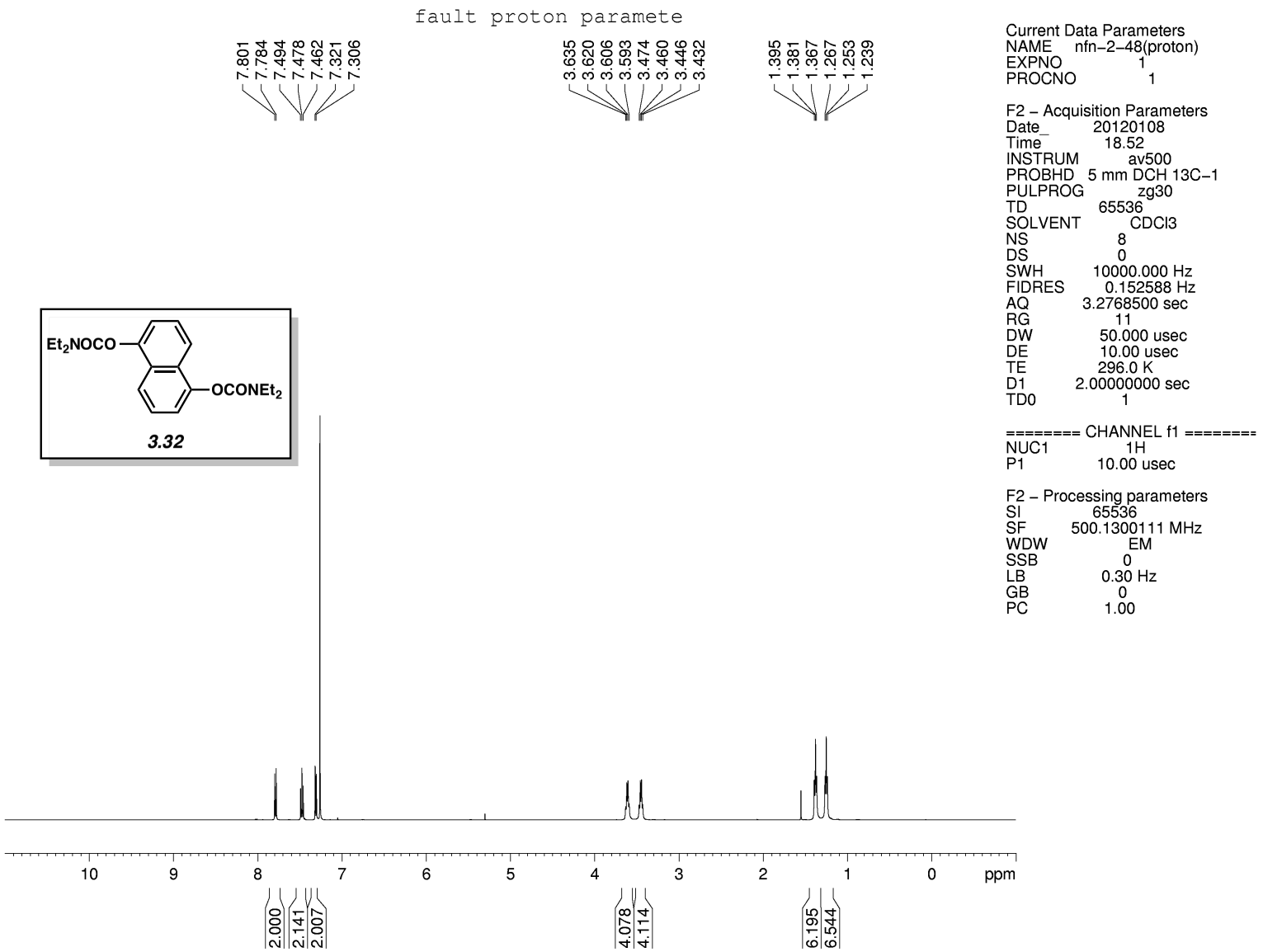


Figure 3.30. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.32**.

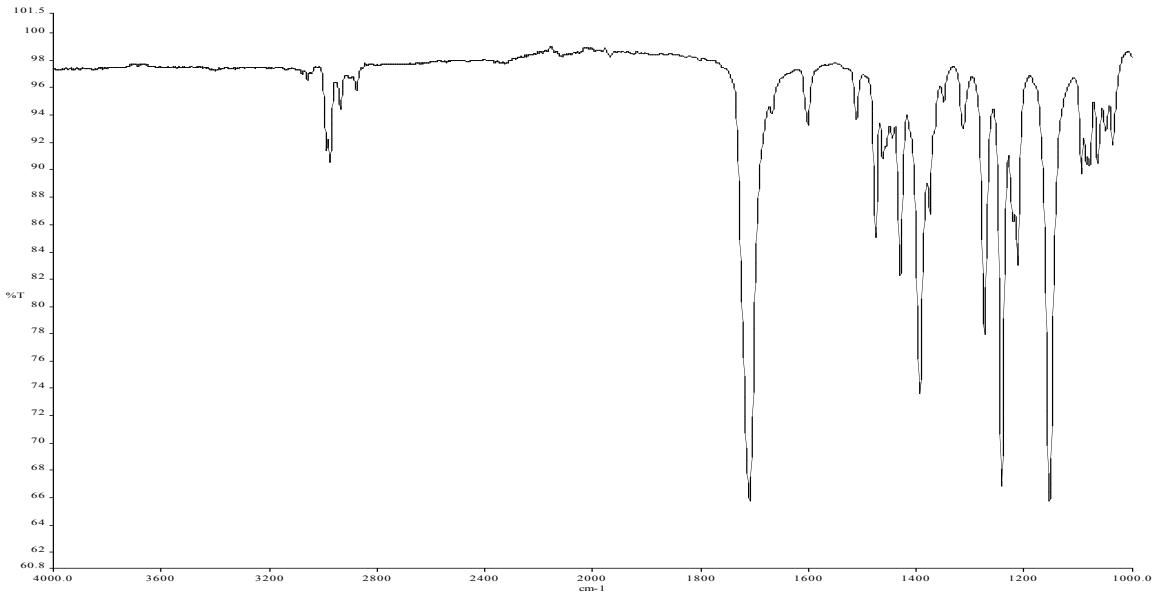


Figure 3.31. Infrared spectrum of compound **3.32**.

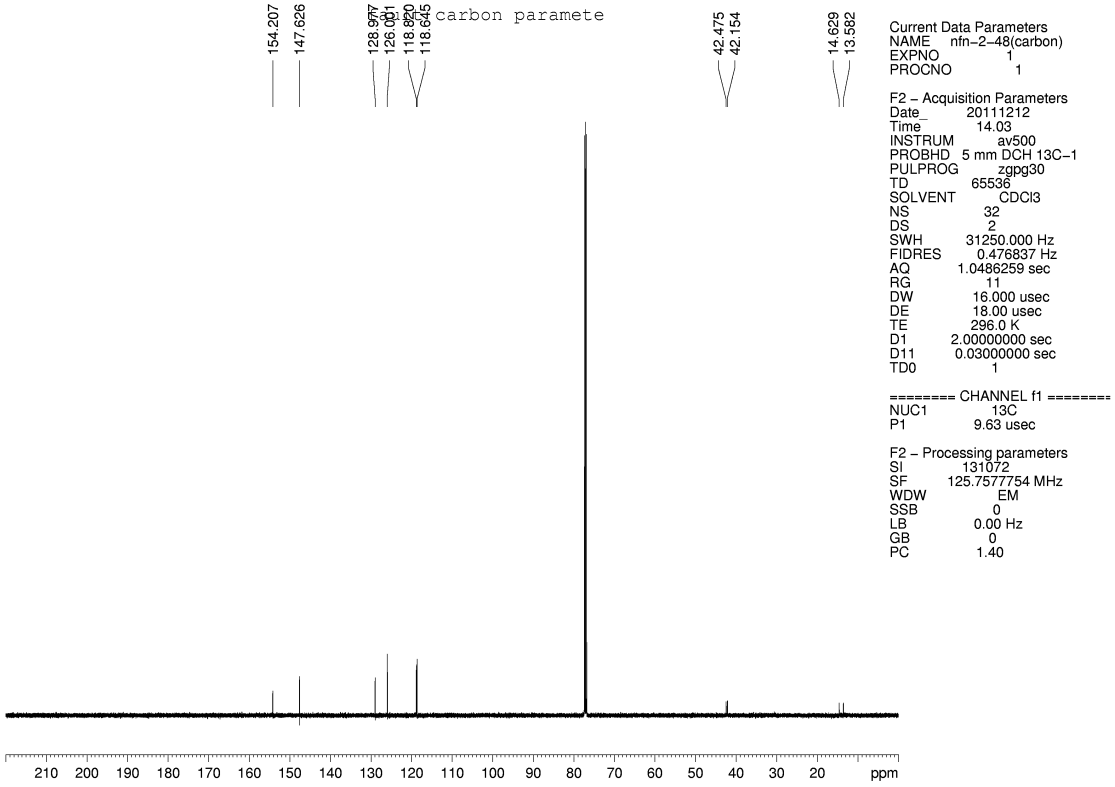


Figure 3.32. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.32**.

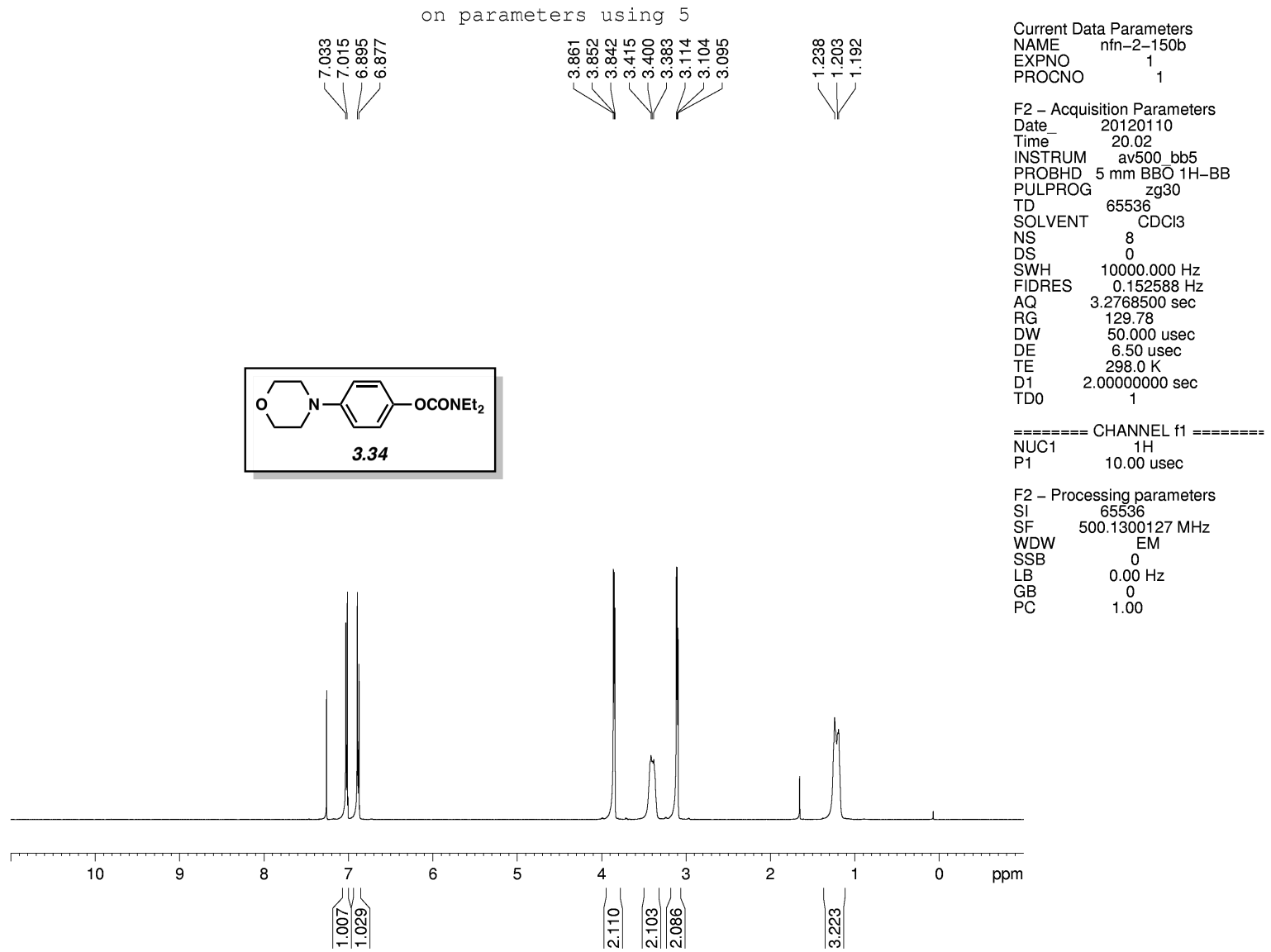


Figure 3.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.34**.

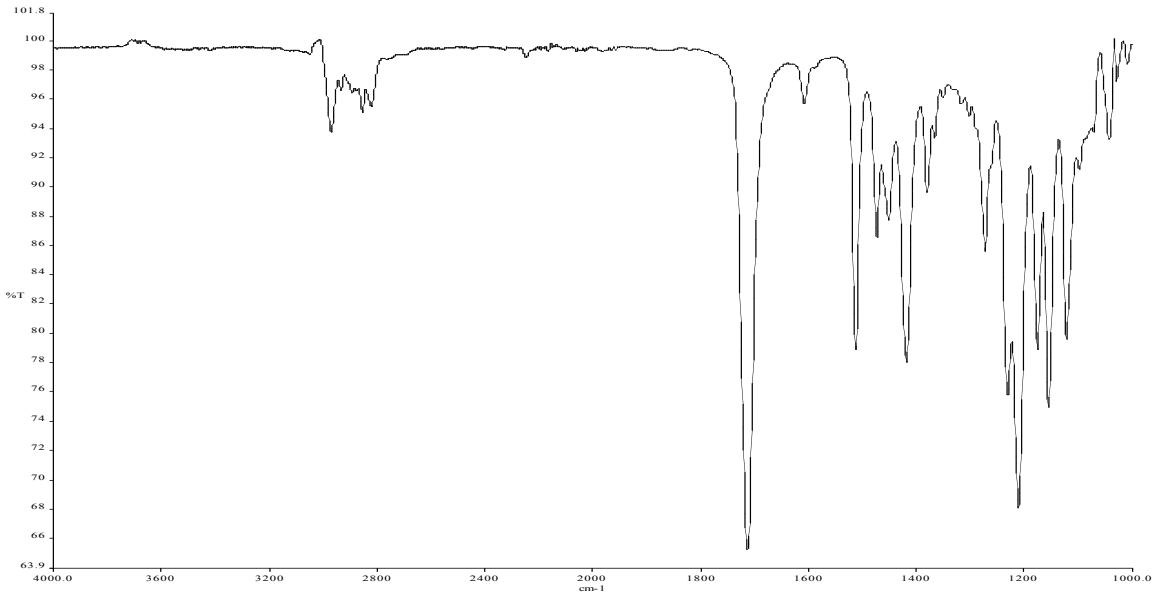


Figure 3.34. Infrared spectrum of compound **3.34**.

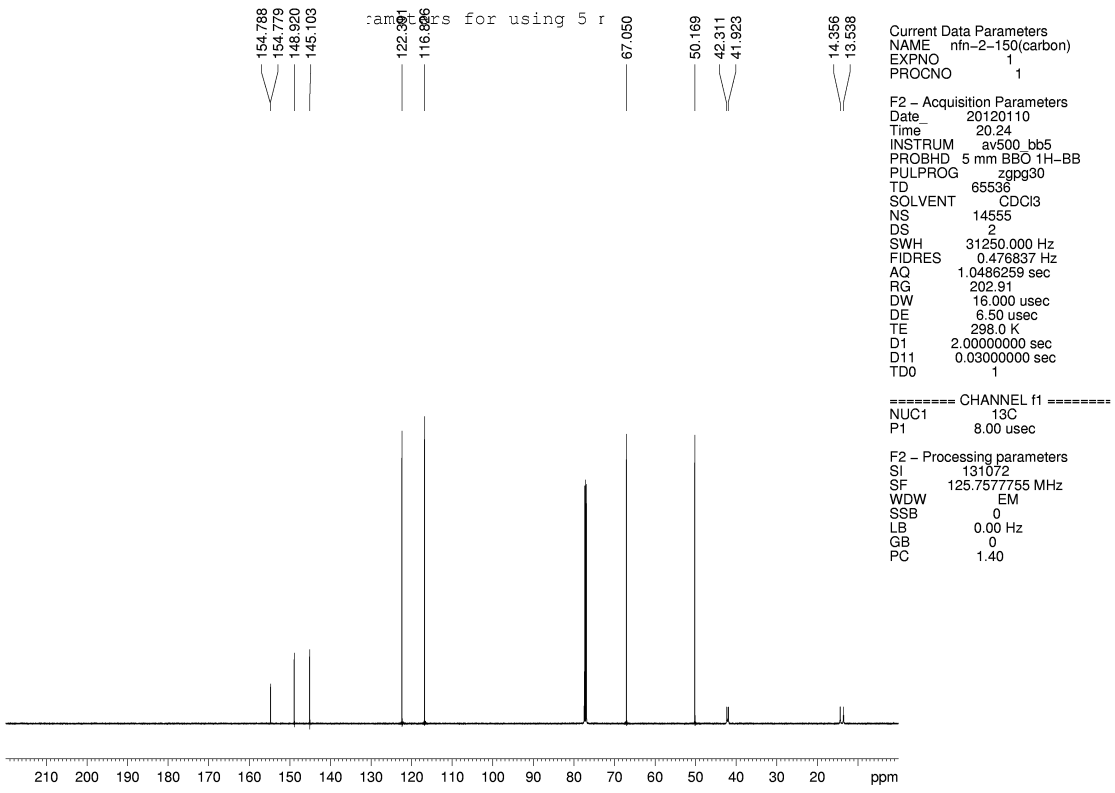


Figure 3.35. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.34**.

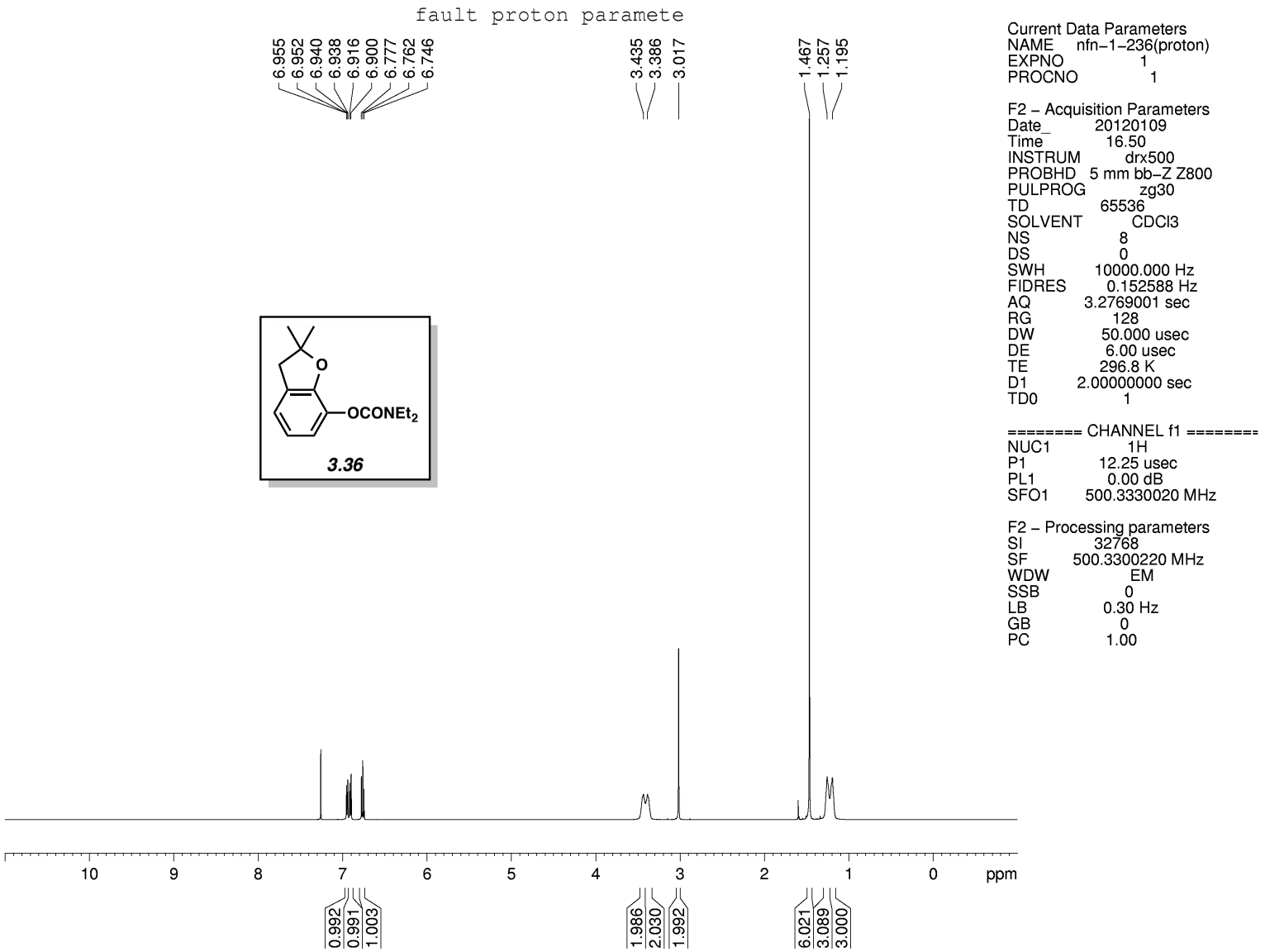


Figure 3.36. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.36**.

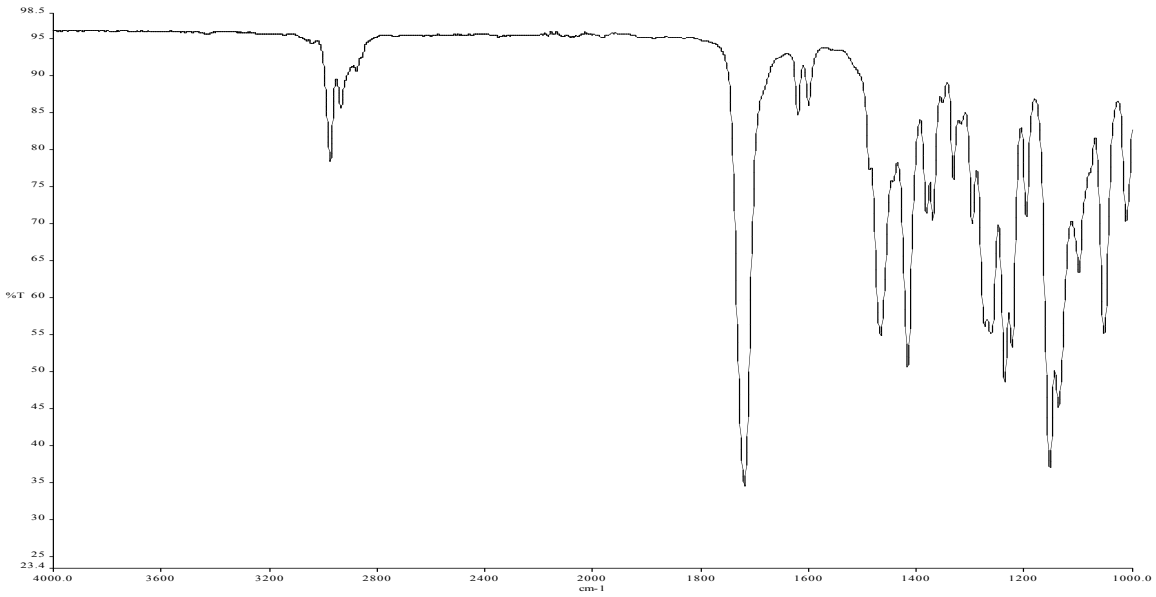


Figure 3.37. Infrared spectrum of compound **3.36**.

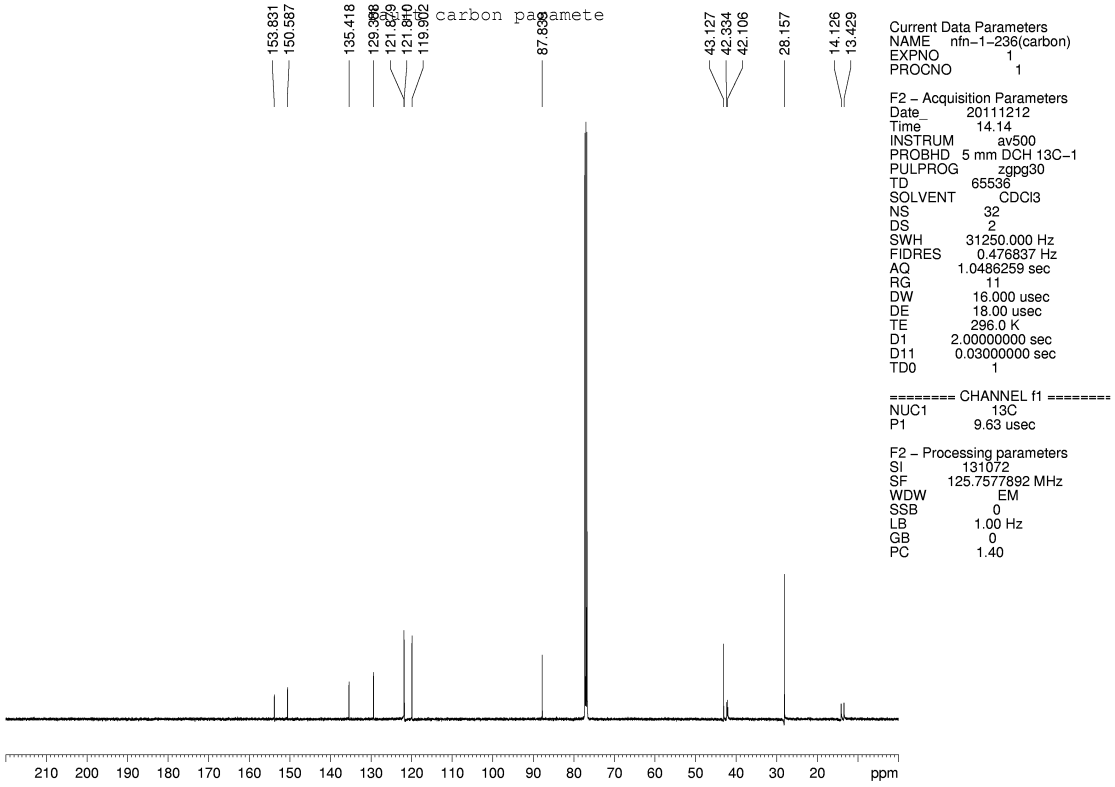


Figure 3.38. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.36**.

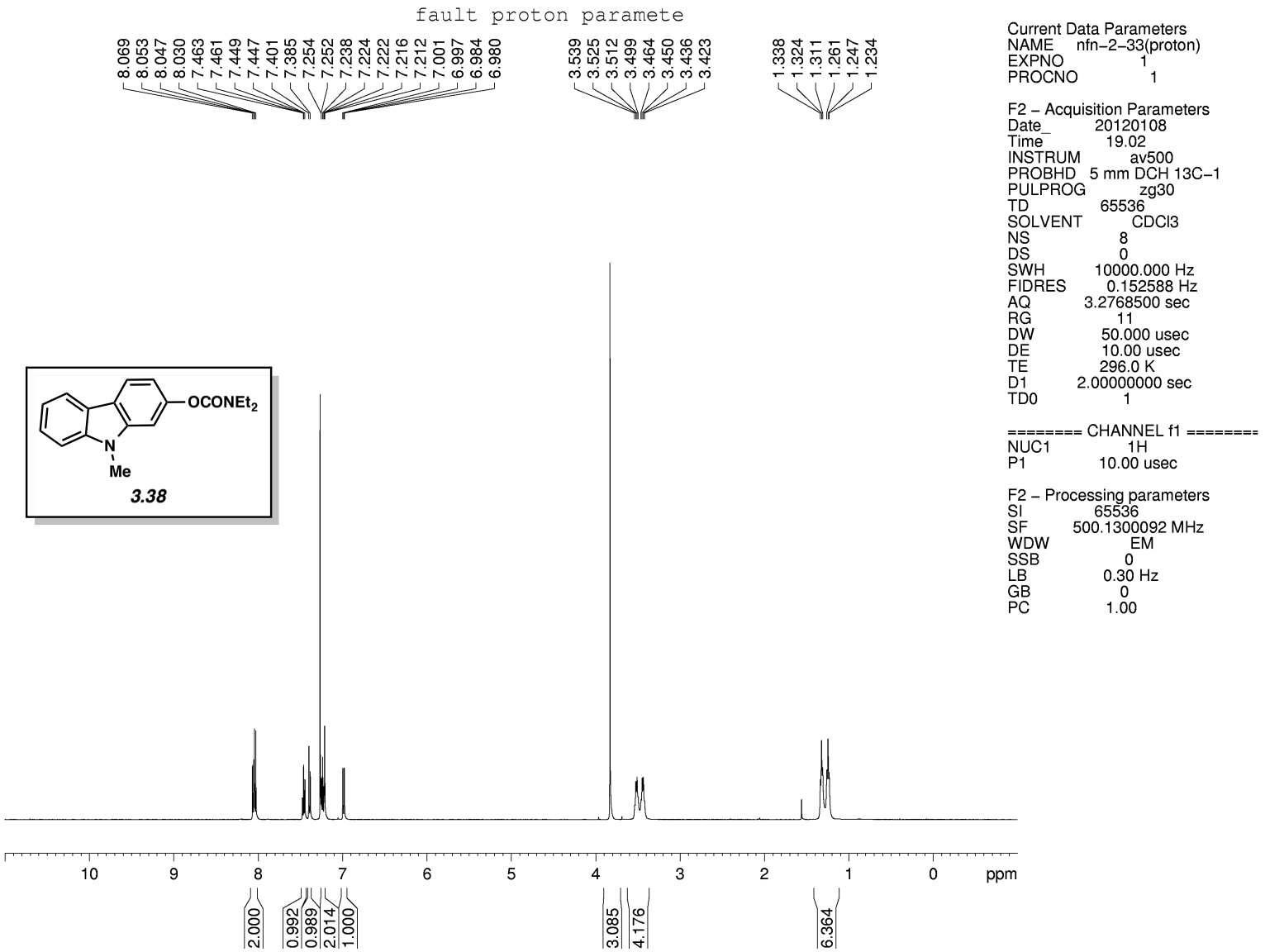


Figure 3.39. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.38**.

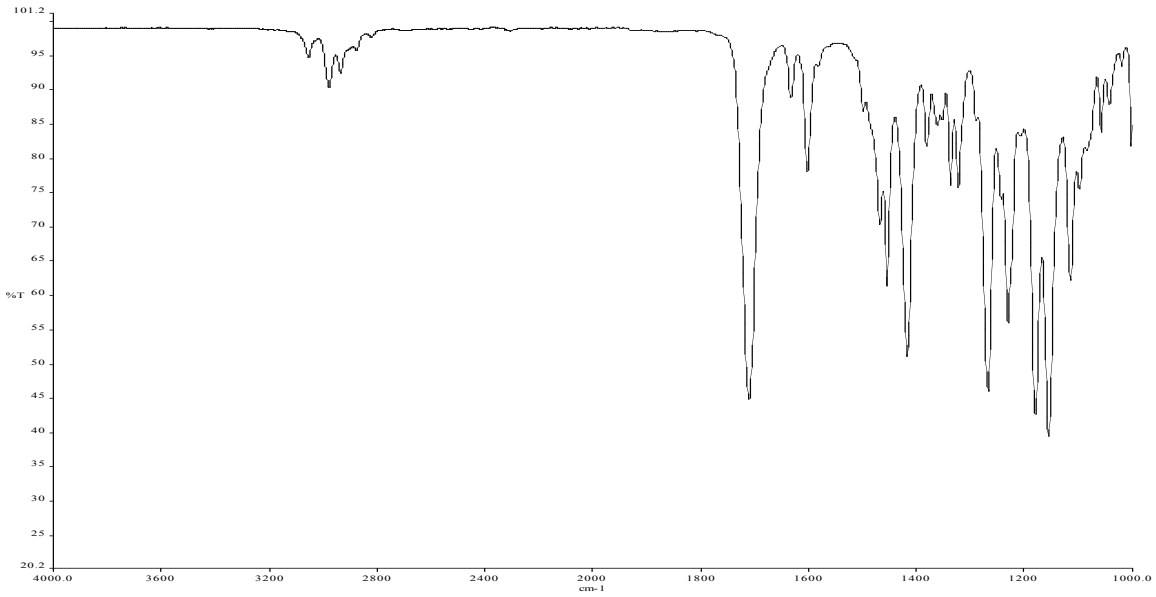


Figure 3.40. Infrared spectrum of compound **3.38**.

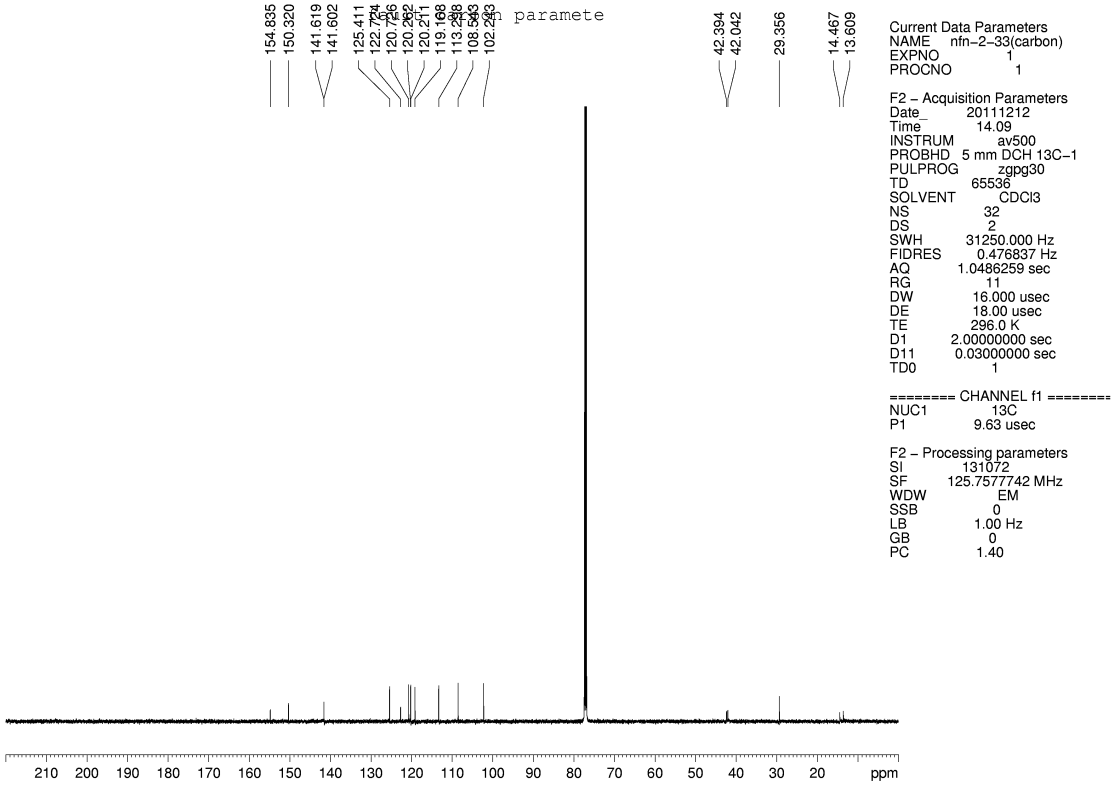


Figure 3.41. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.38**.

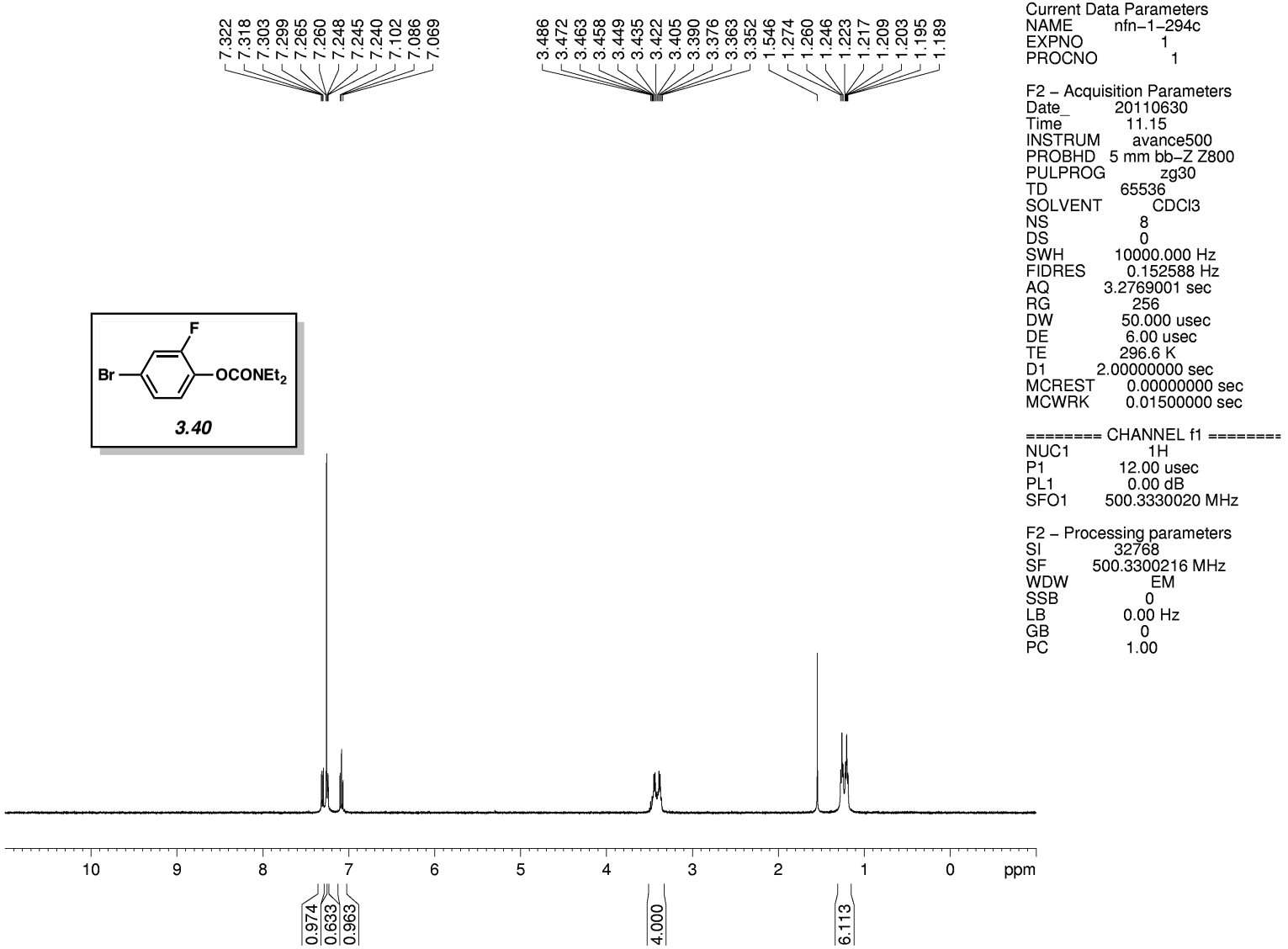


Figure 3.42. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.40**.

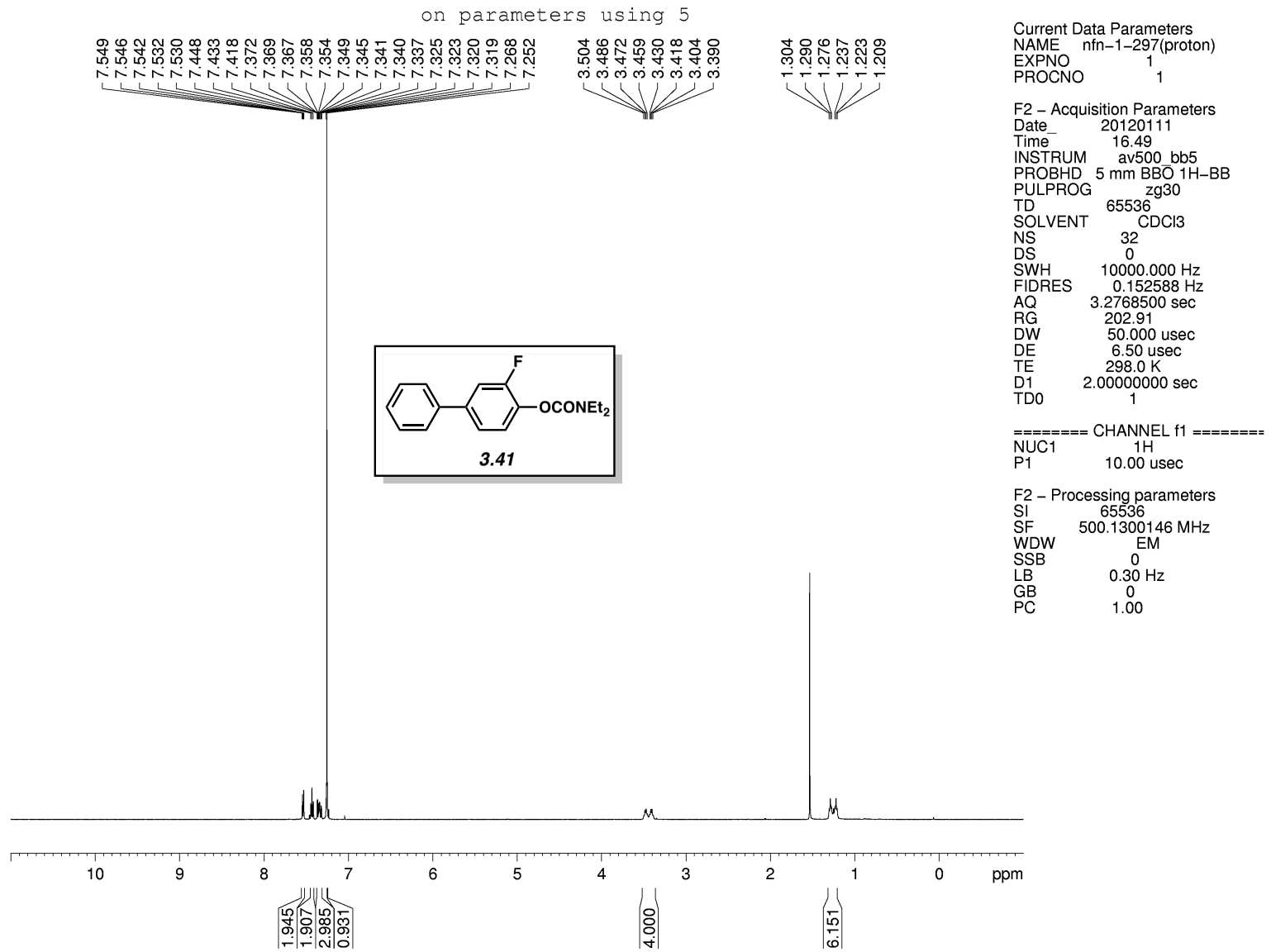


Figure 3.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.41**.

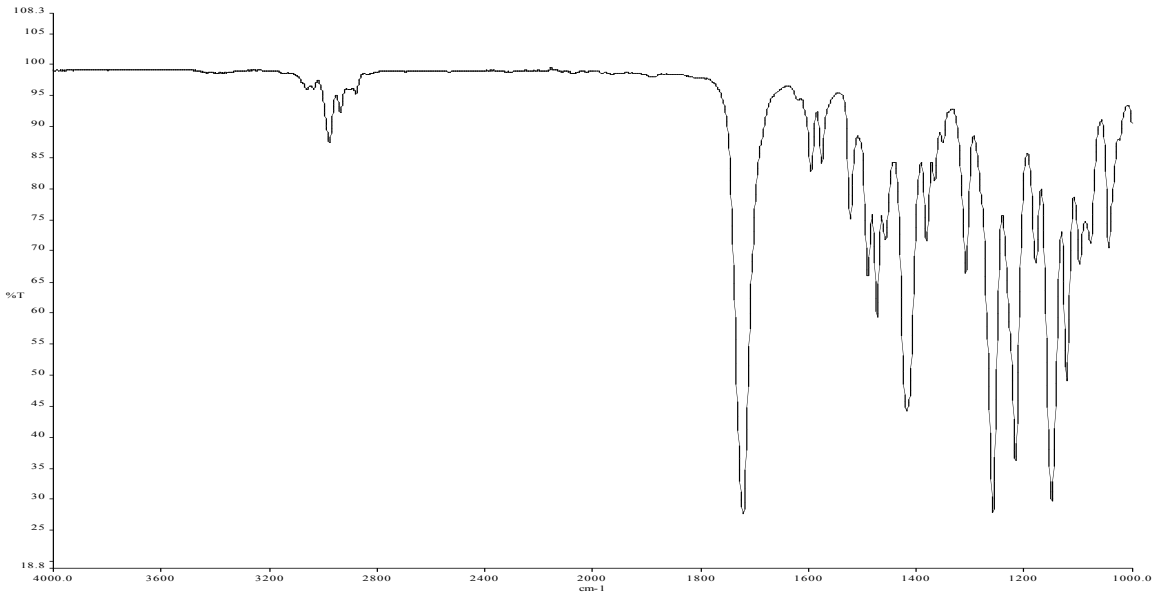


Figure 3.44. Infrared spectrum of compound **3.41**.

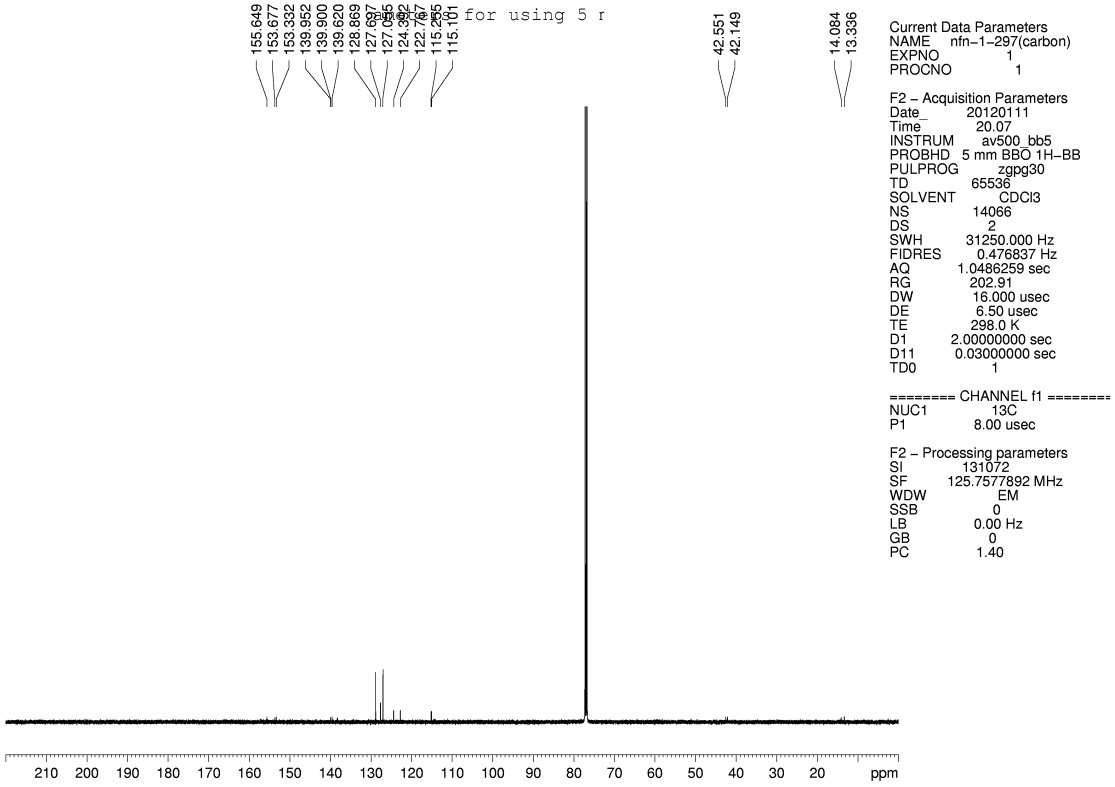


Figure 3.45. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.41**.

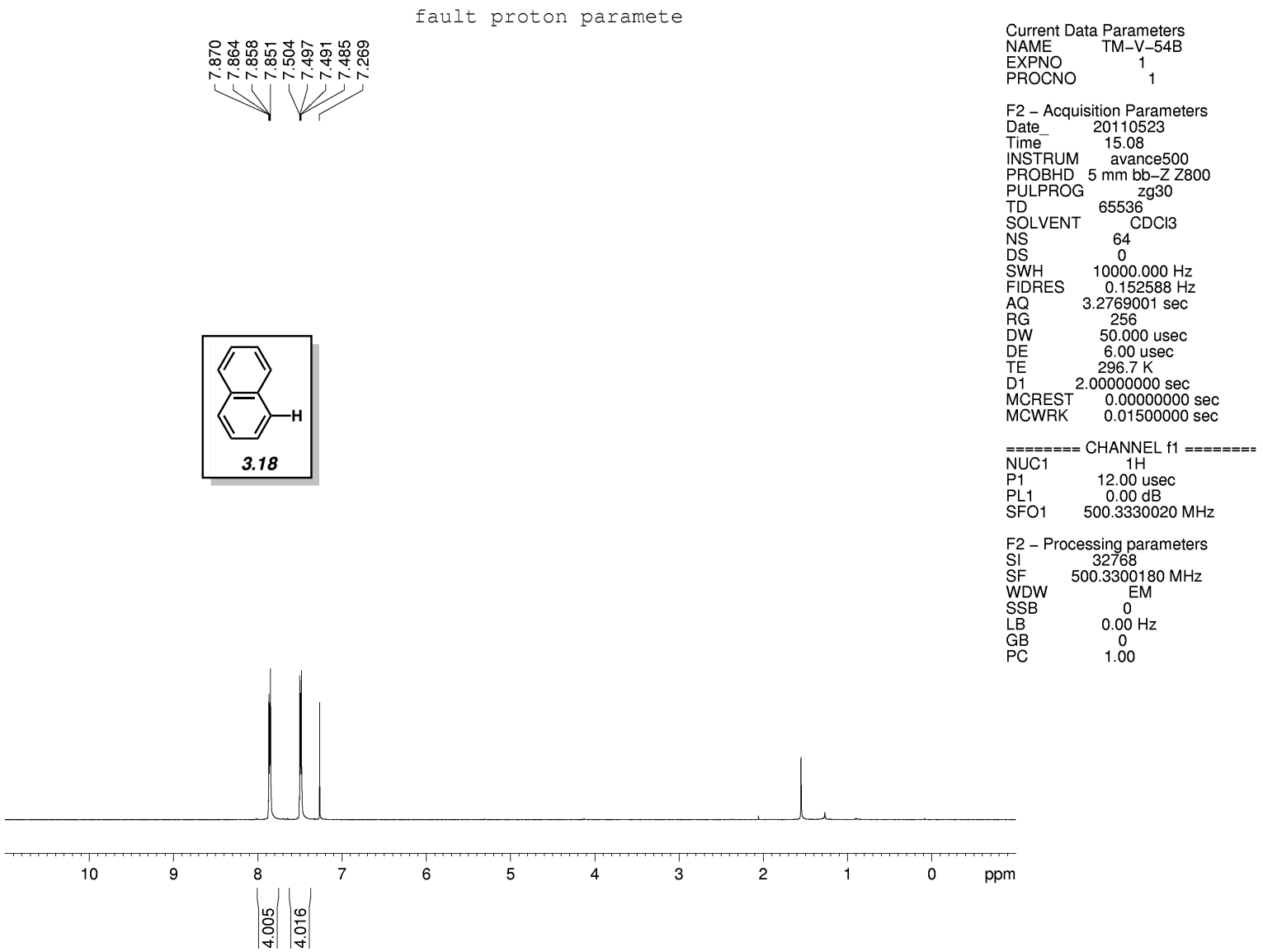


Figure 3.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.18**.

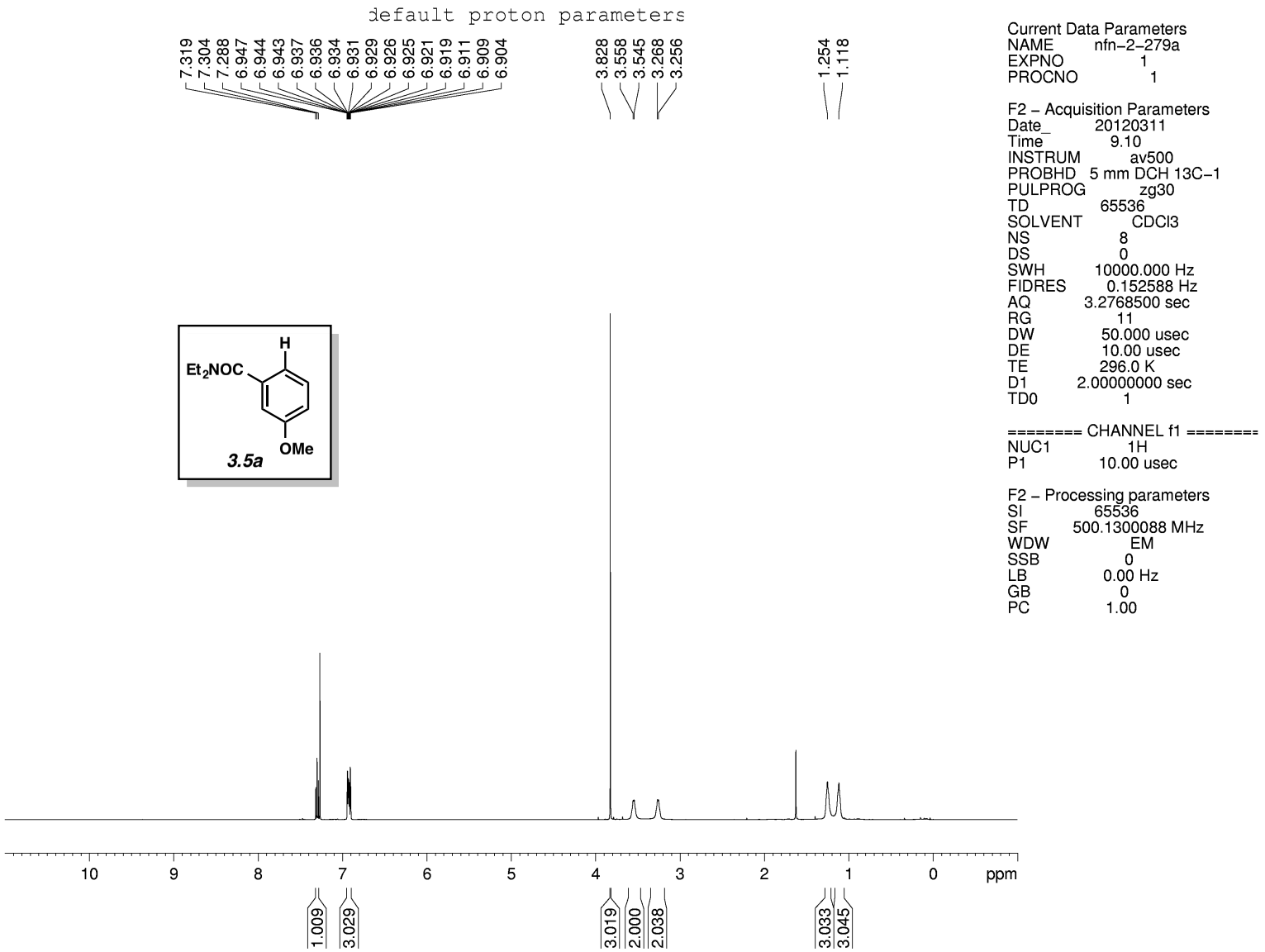


Figure 3.47. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.5a**.

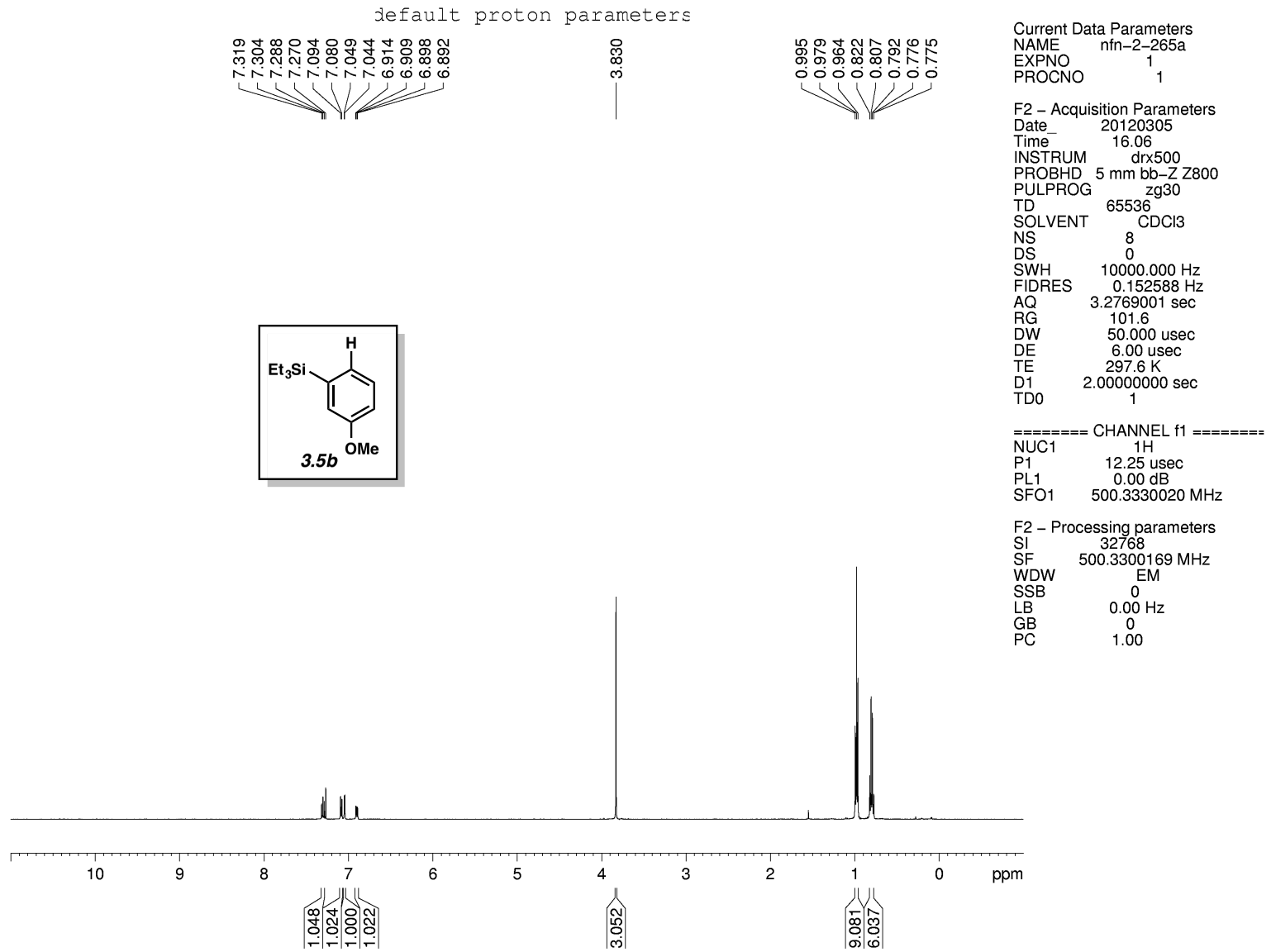


Figure 3.48. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.5b**.

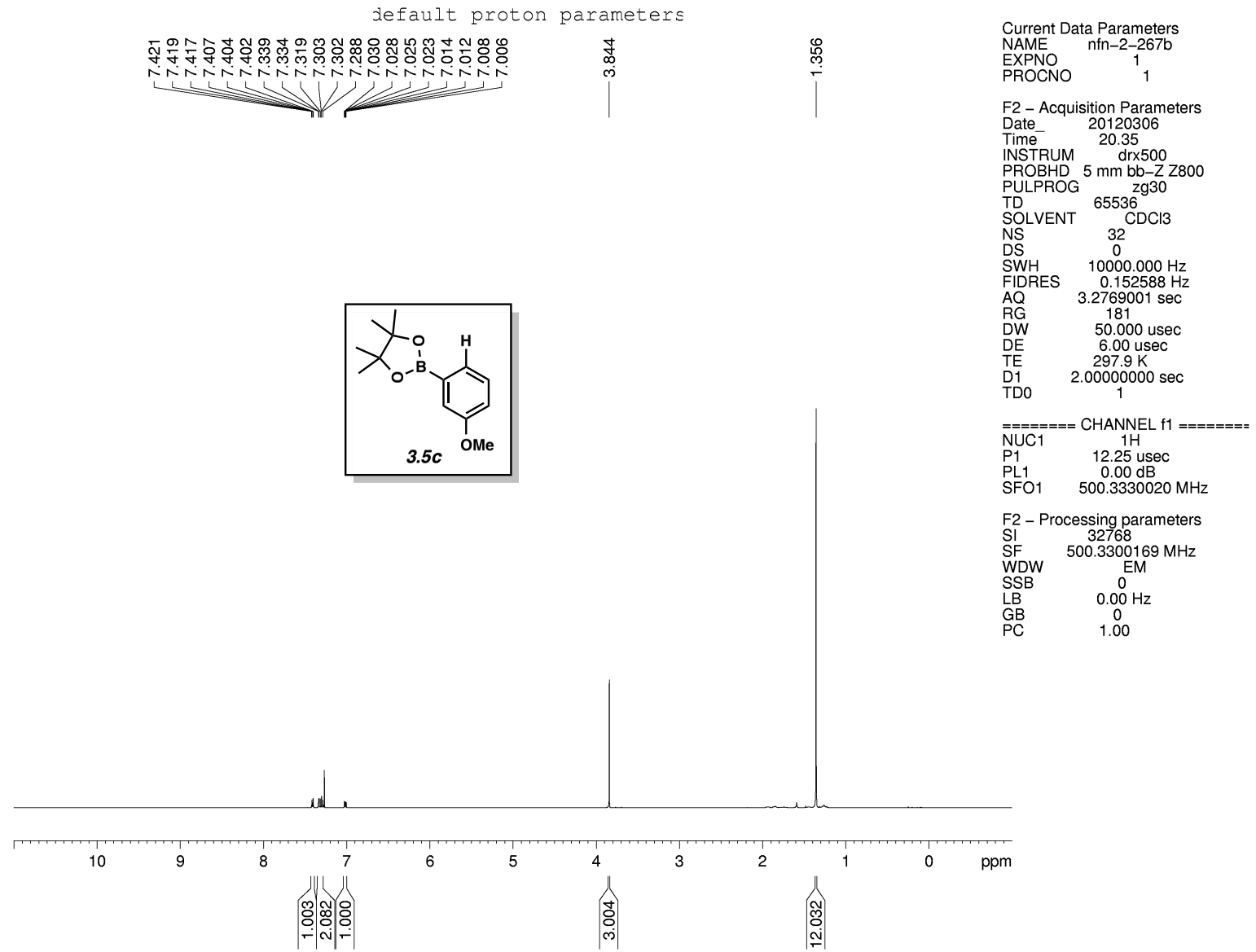


Figure 3.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.5c**.

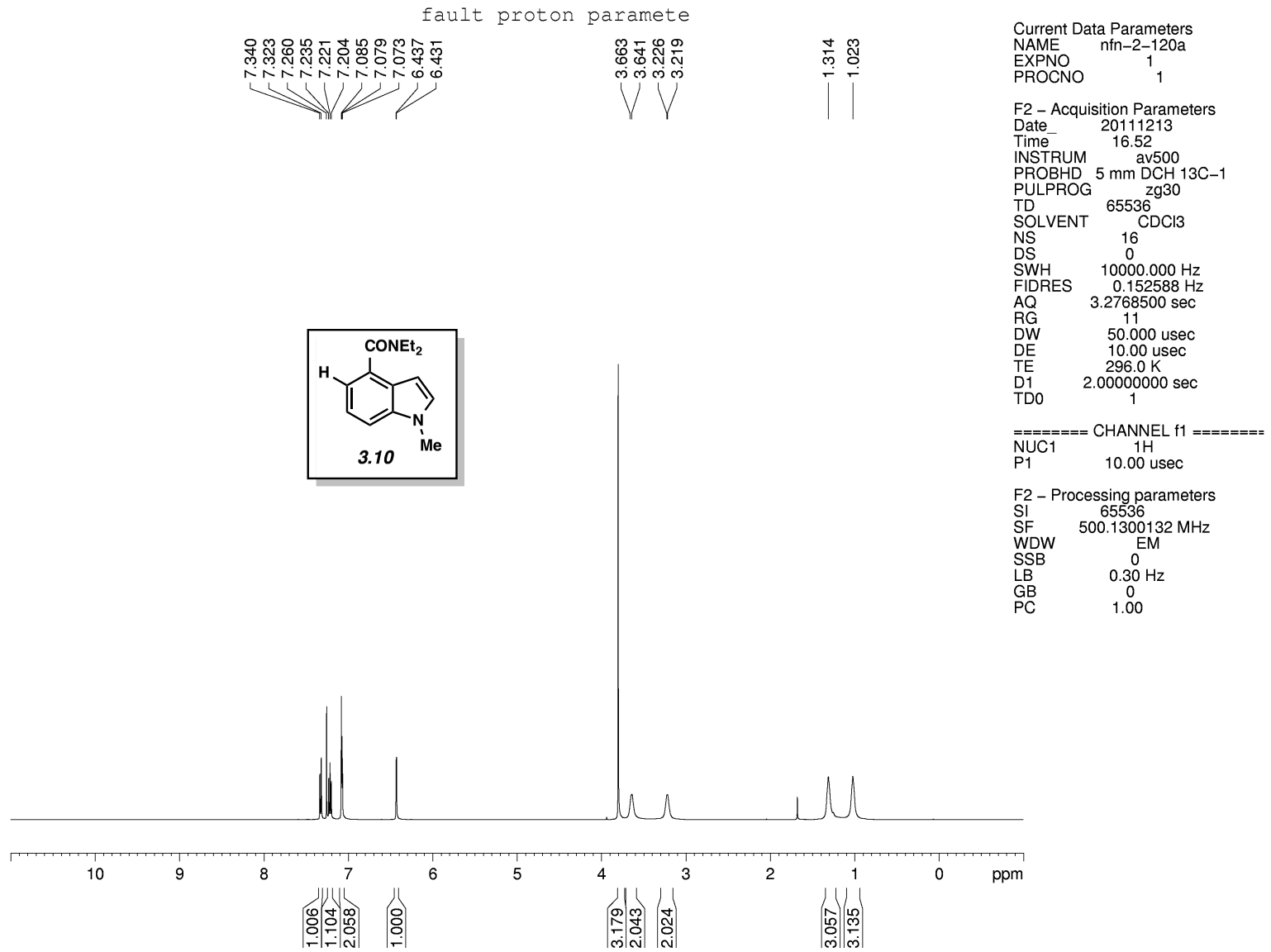


Figure 3.50. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.10**.

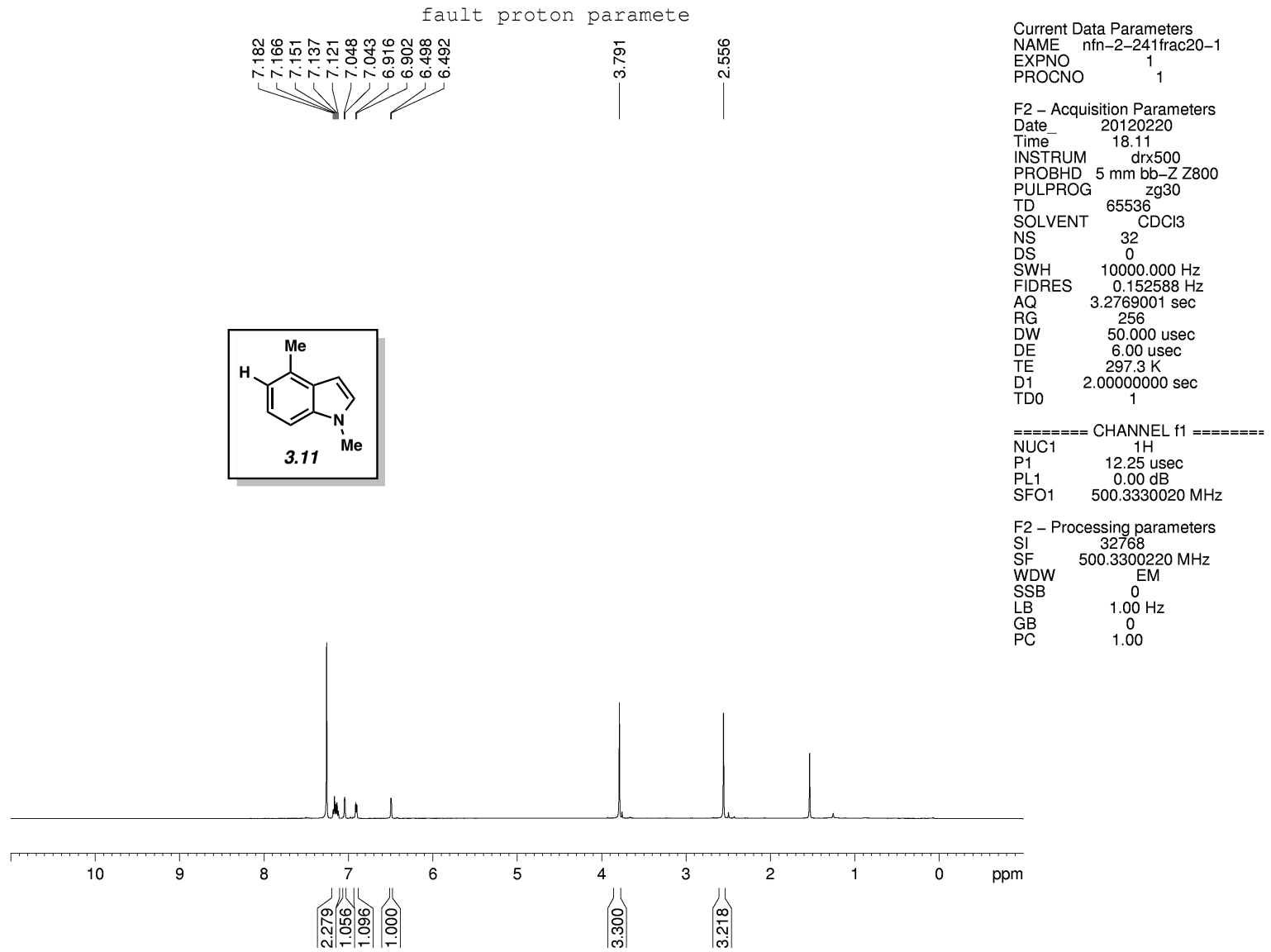


Figure 3.51. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.11**.

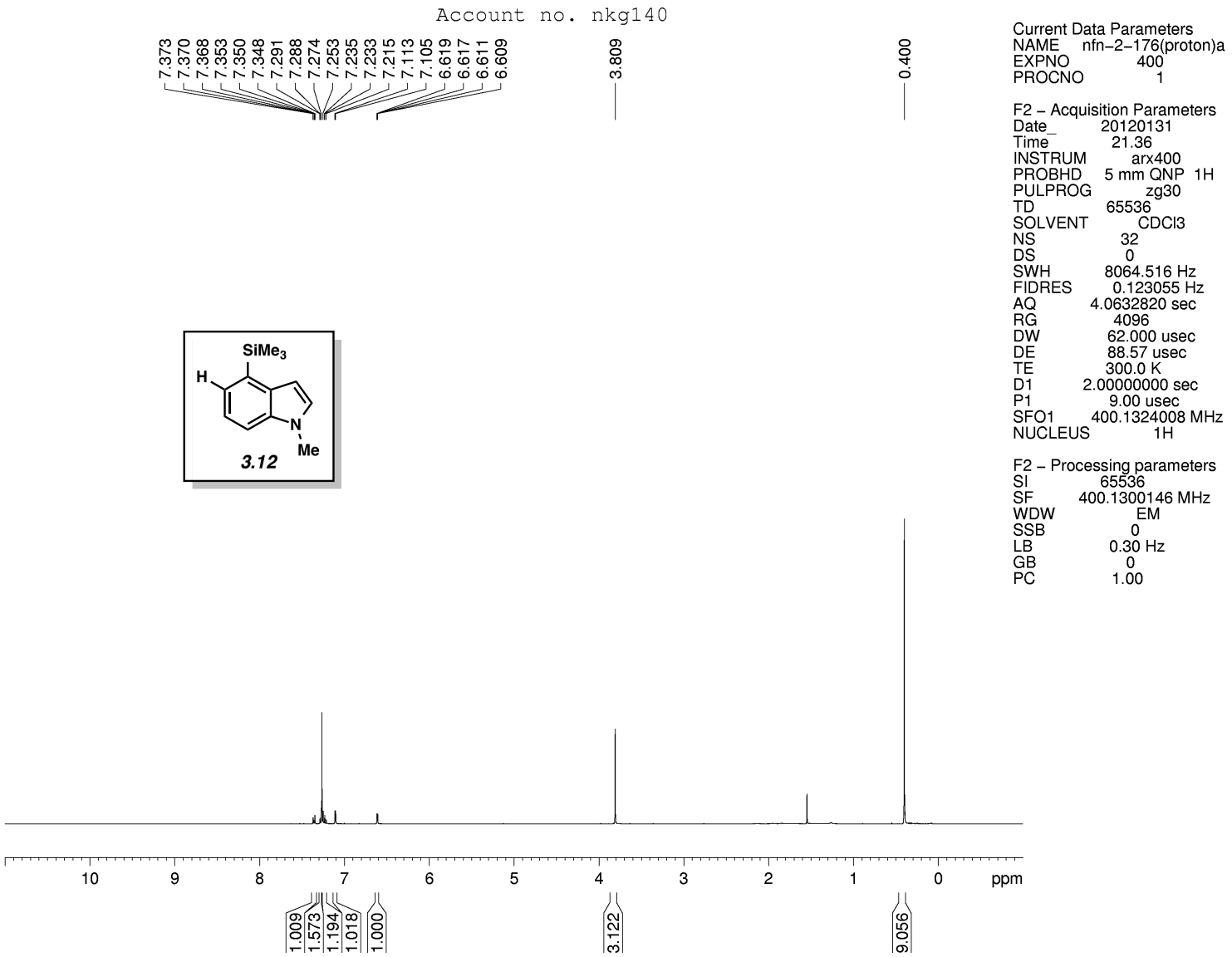


Figure 3.52. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3.12**.

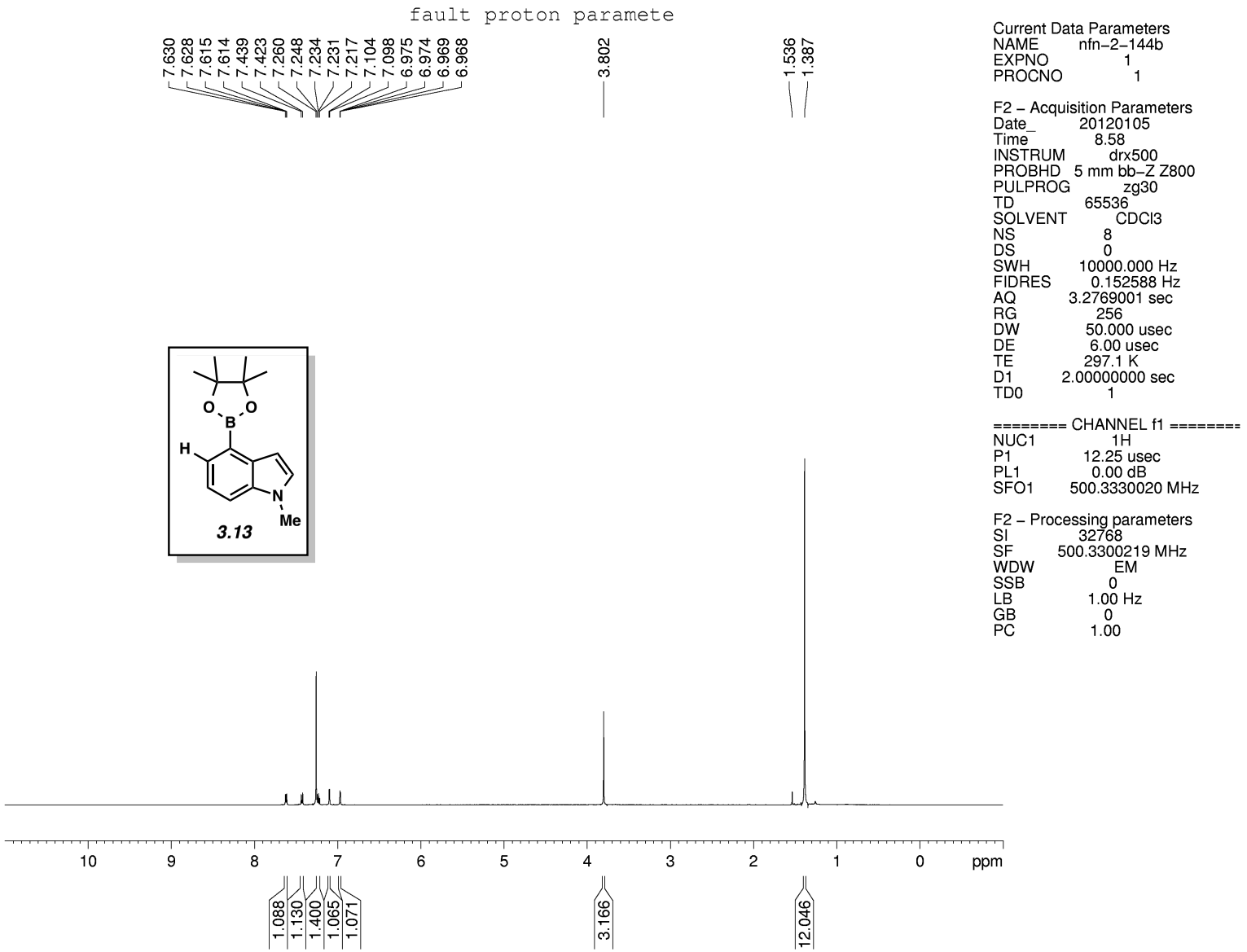


Figure 3.53. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.13**.

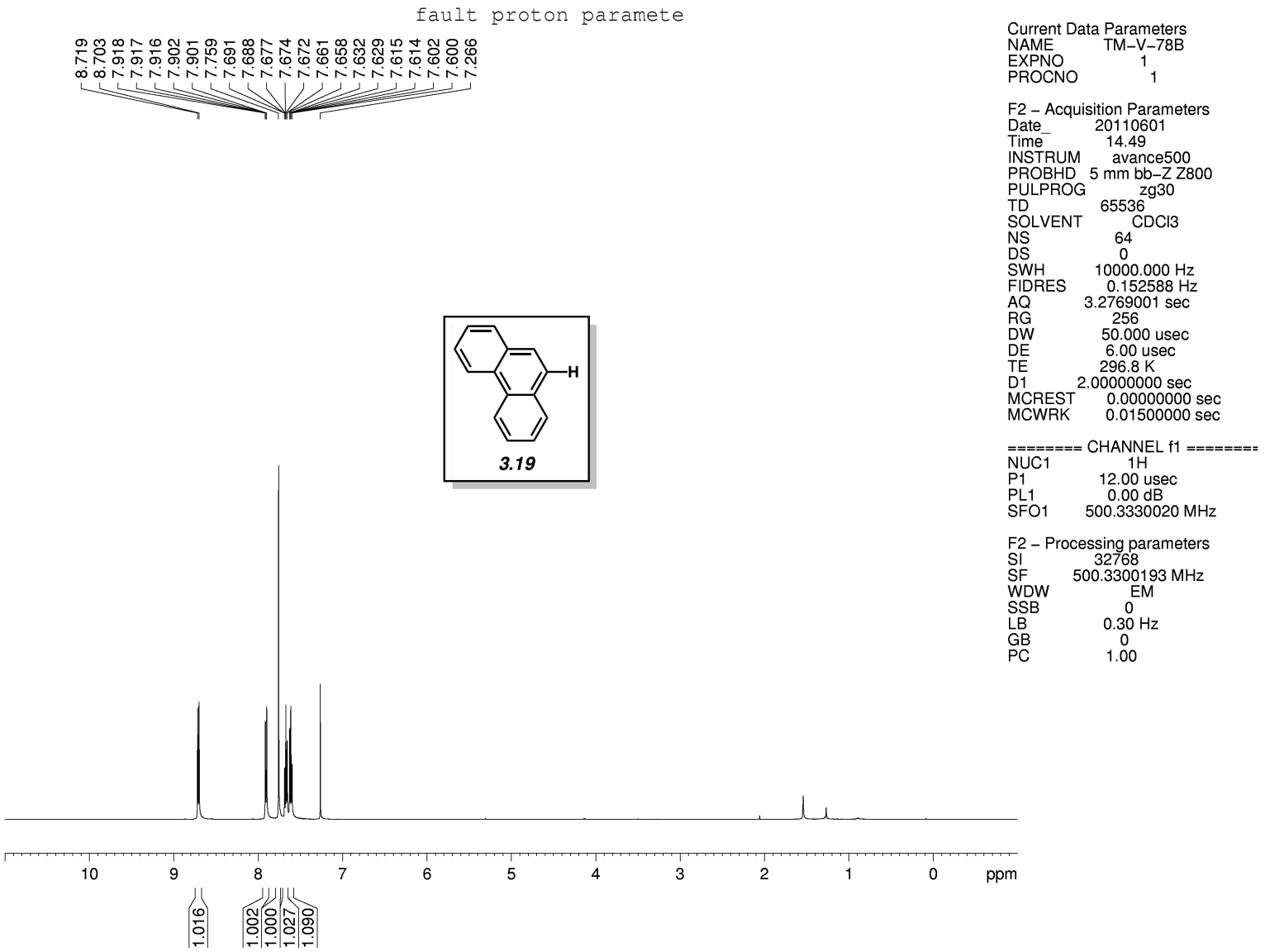


Figure 3.54. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.19**.

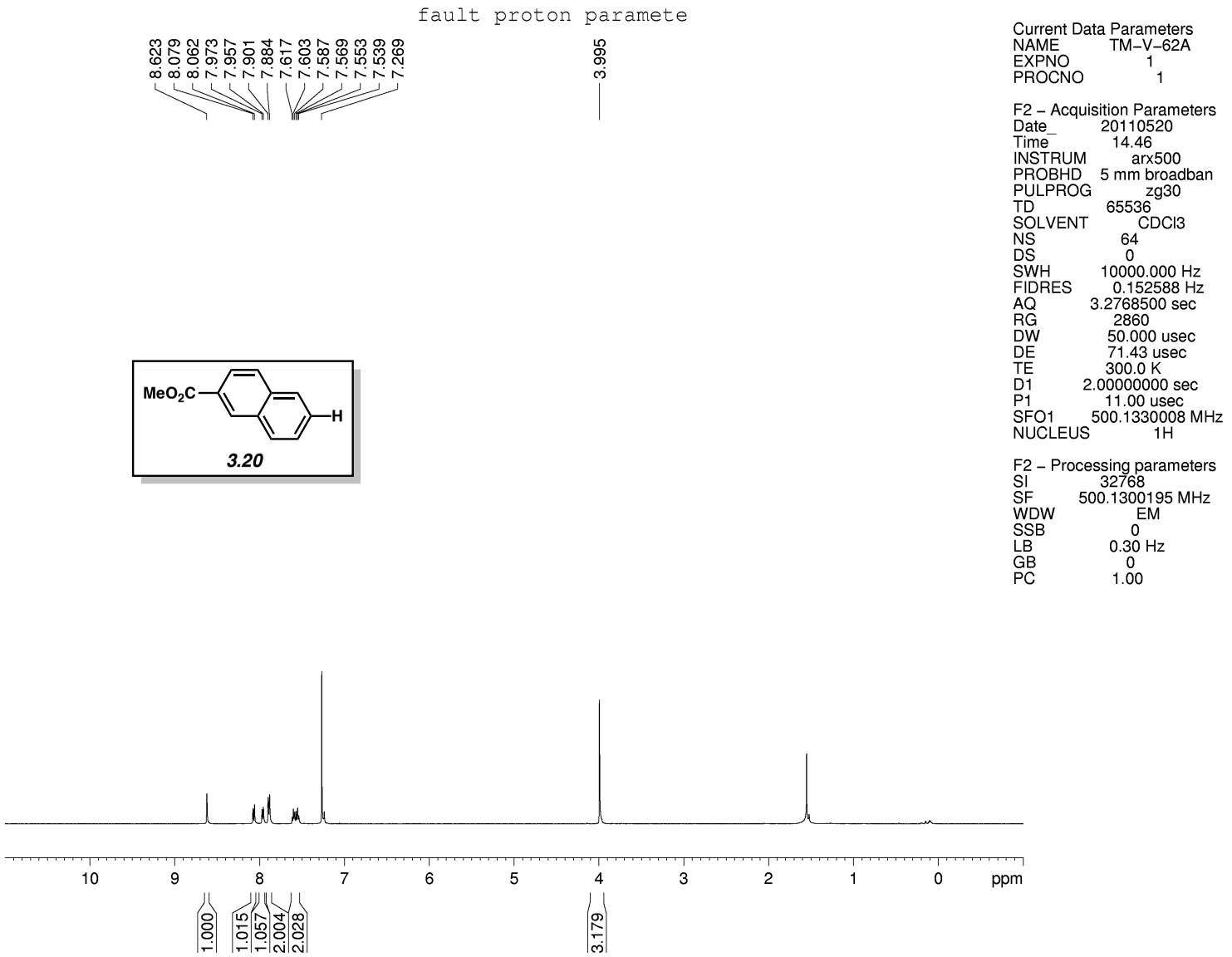


Figure 3.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.20**.

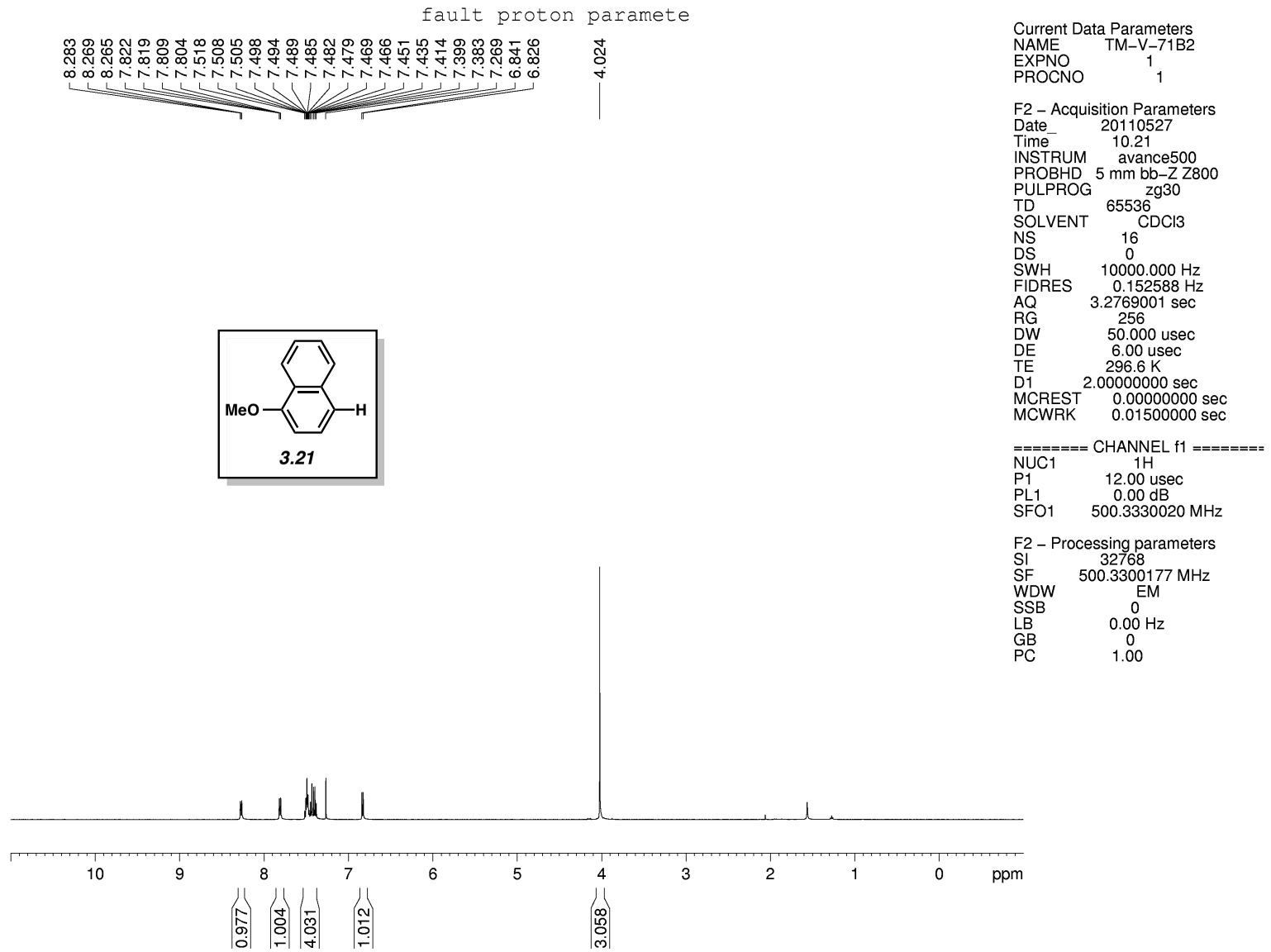


Figure 3.56. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.21**.

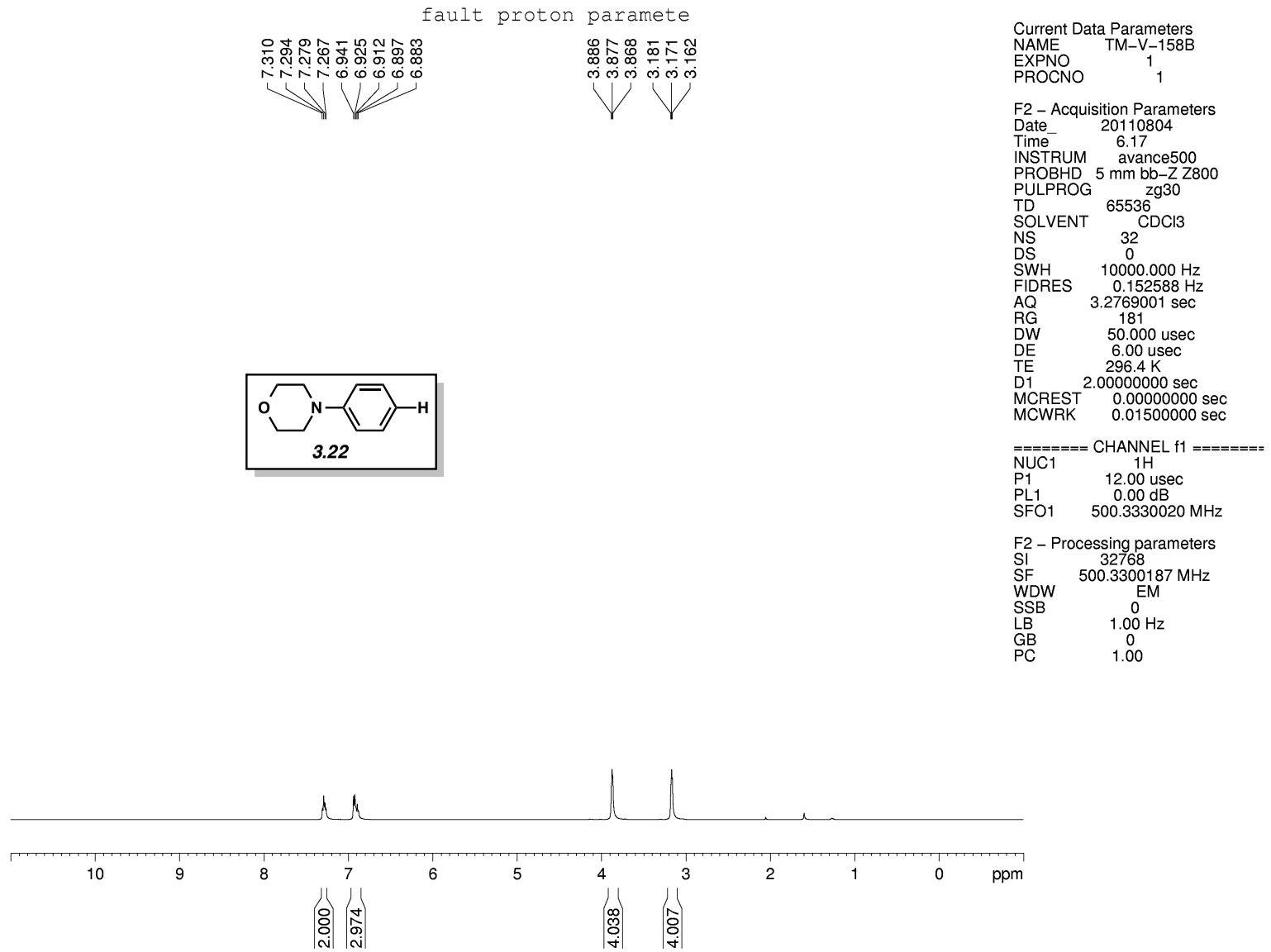


Figure 3.57. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.22**.

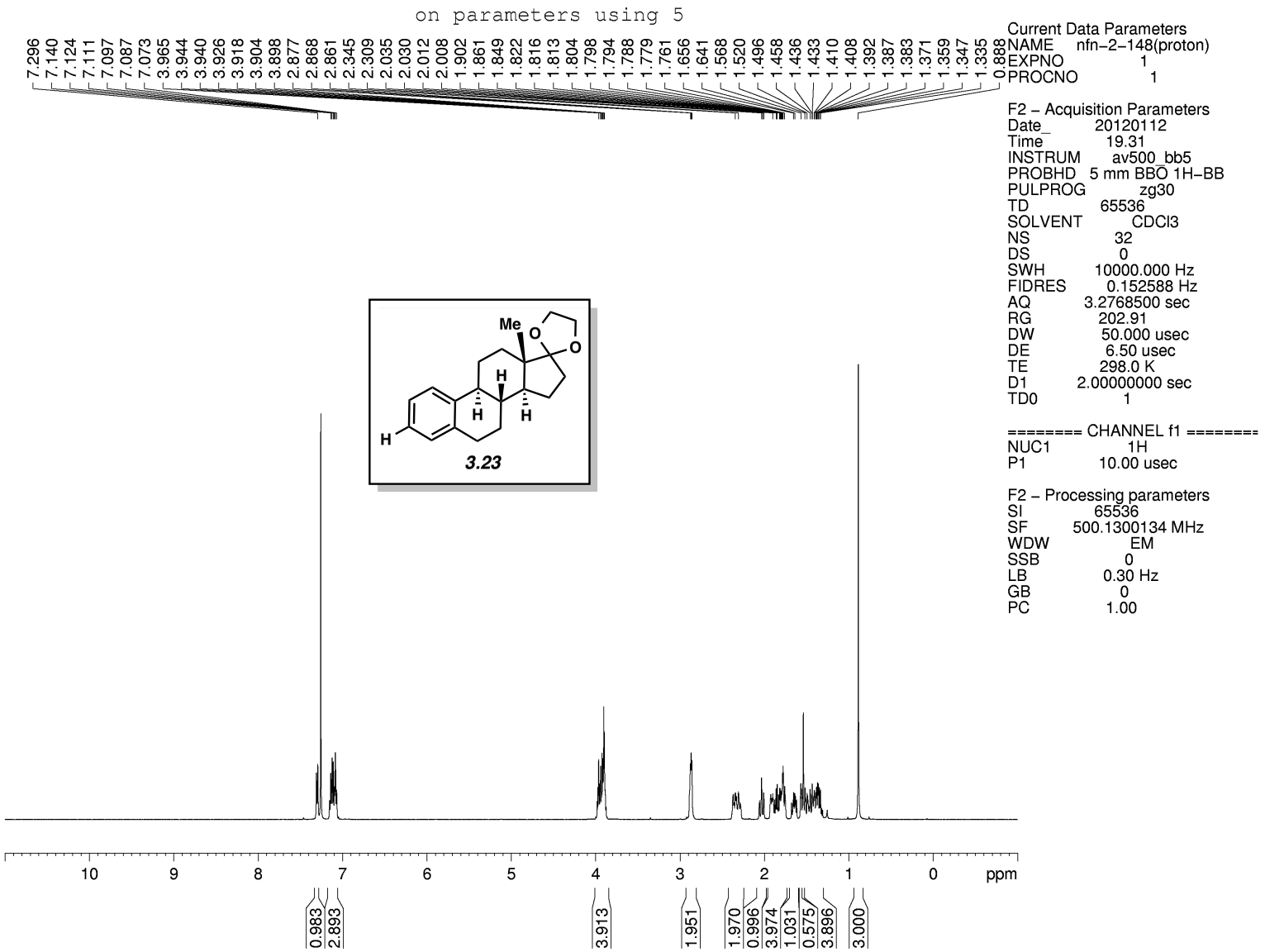


Figure 3.58. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.23**.

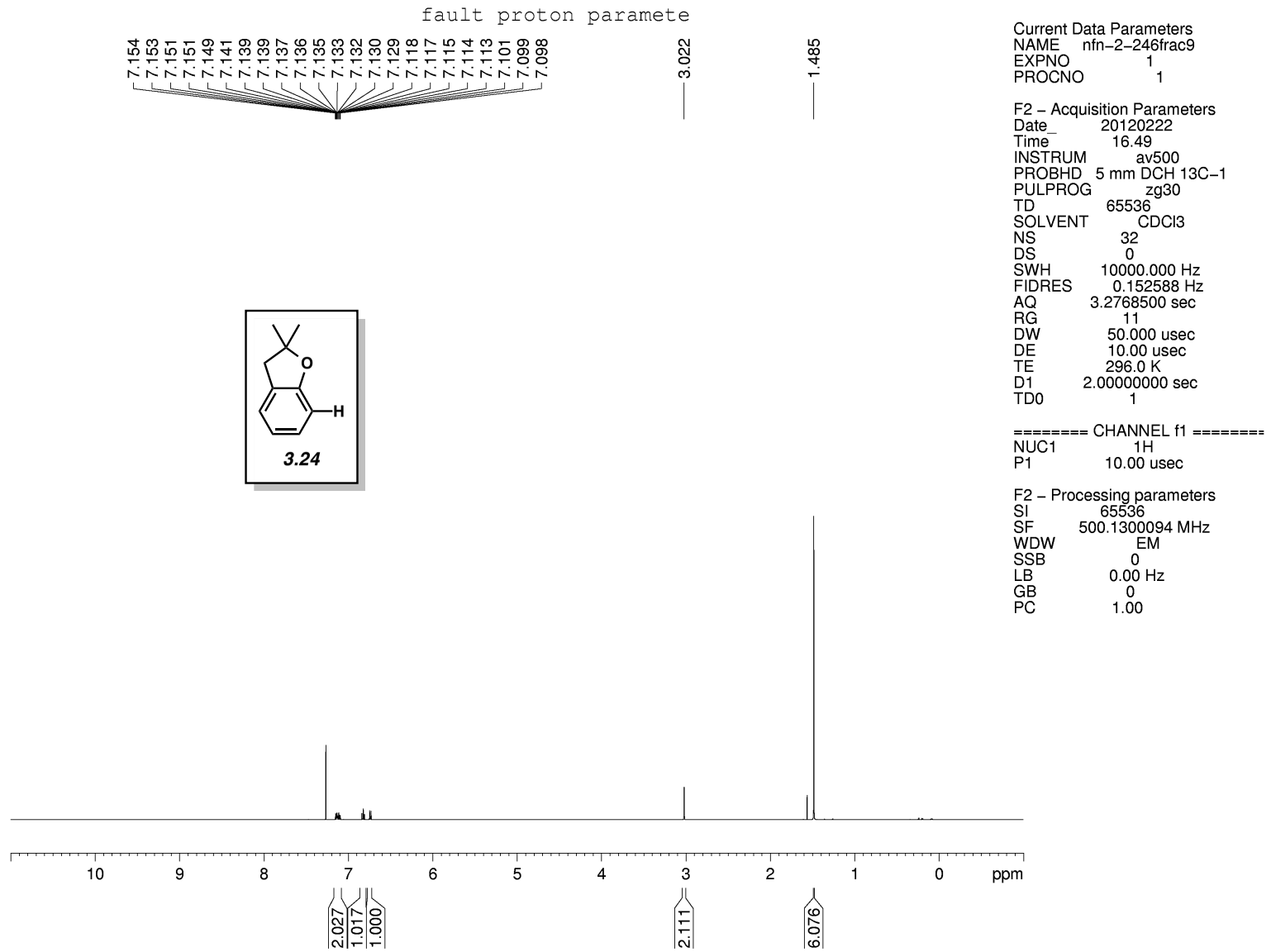


Figure 3.59. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.24**.

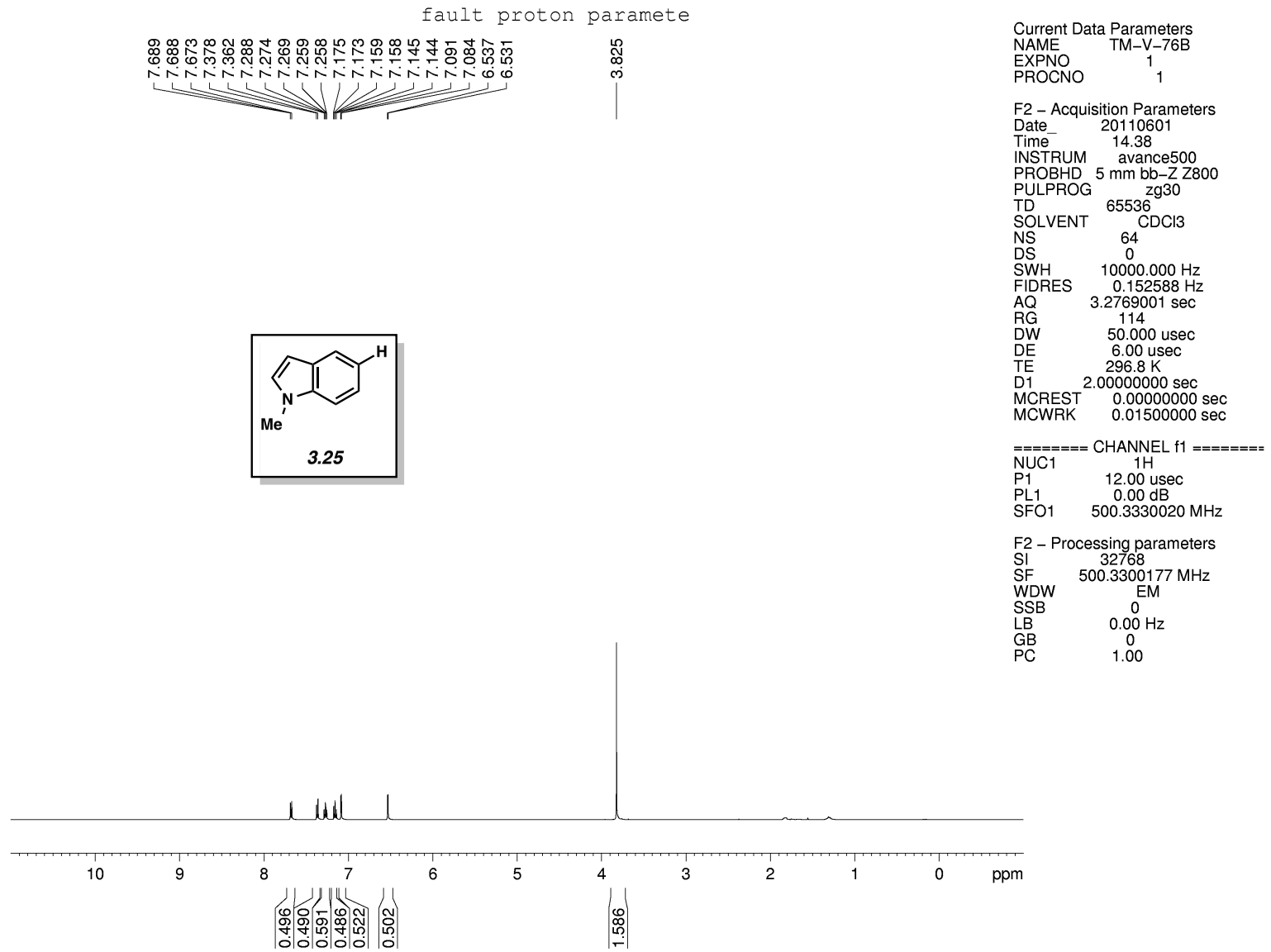


Figure 3.60. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.25**.

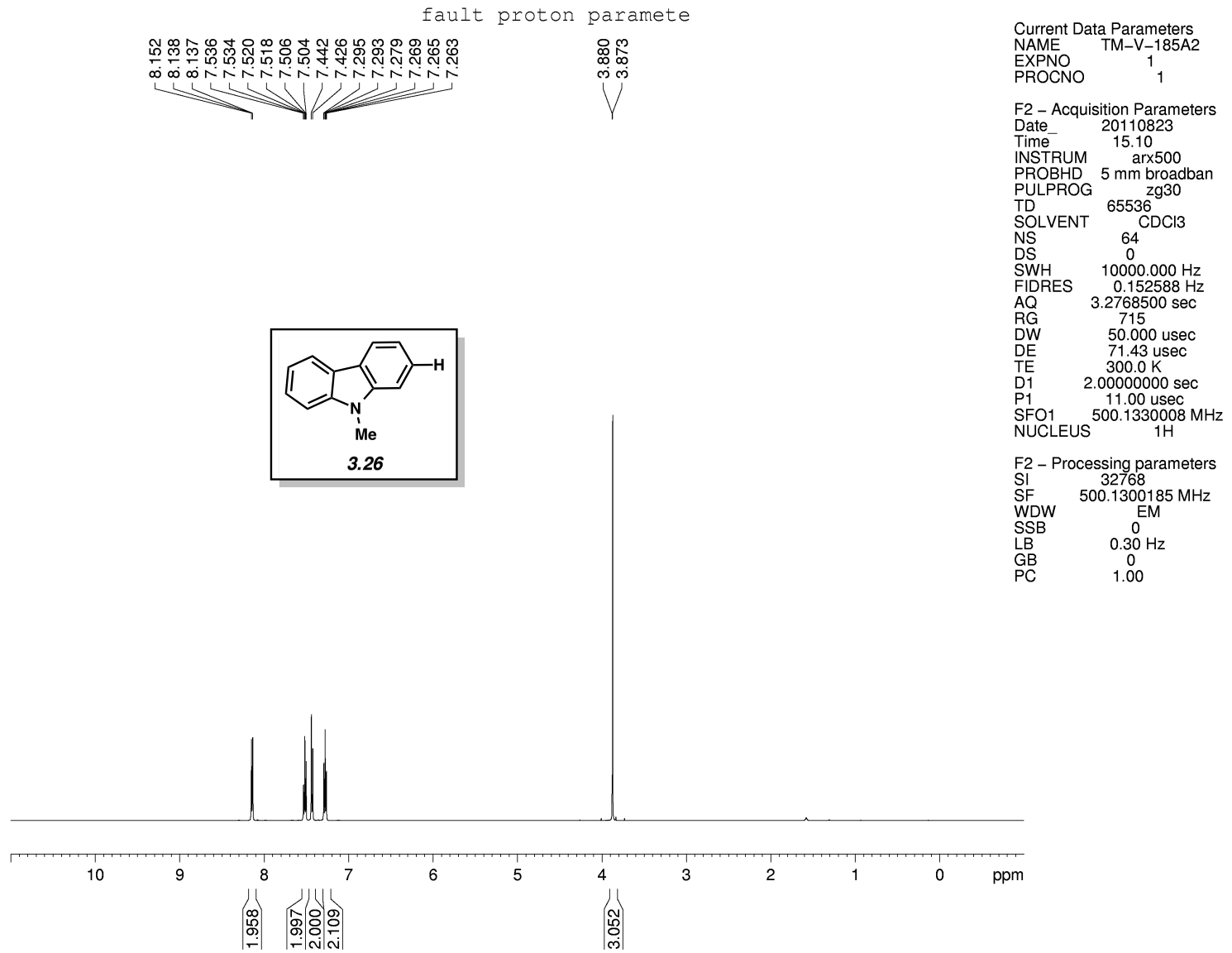


Figure 3.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.26**.

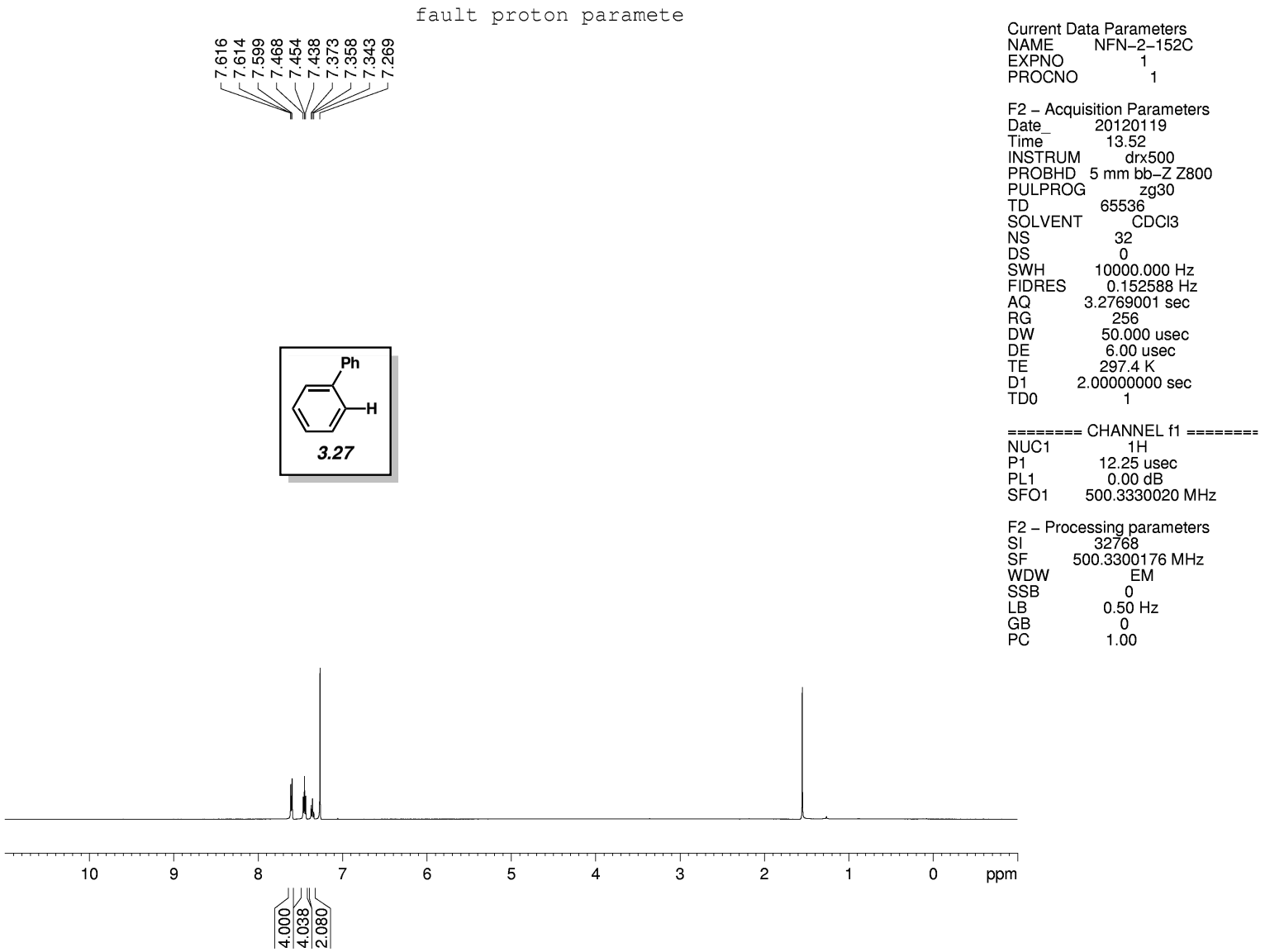


Figure 3.62. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.27**.

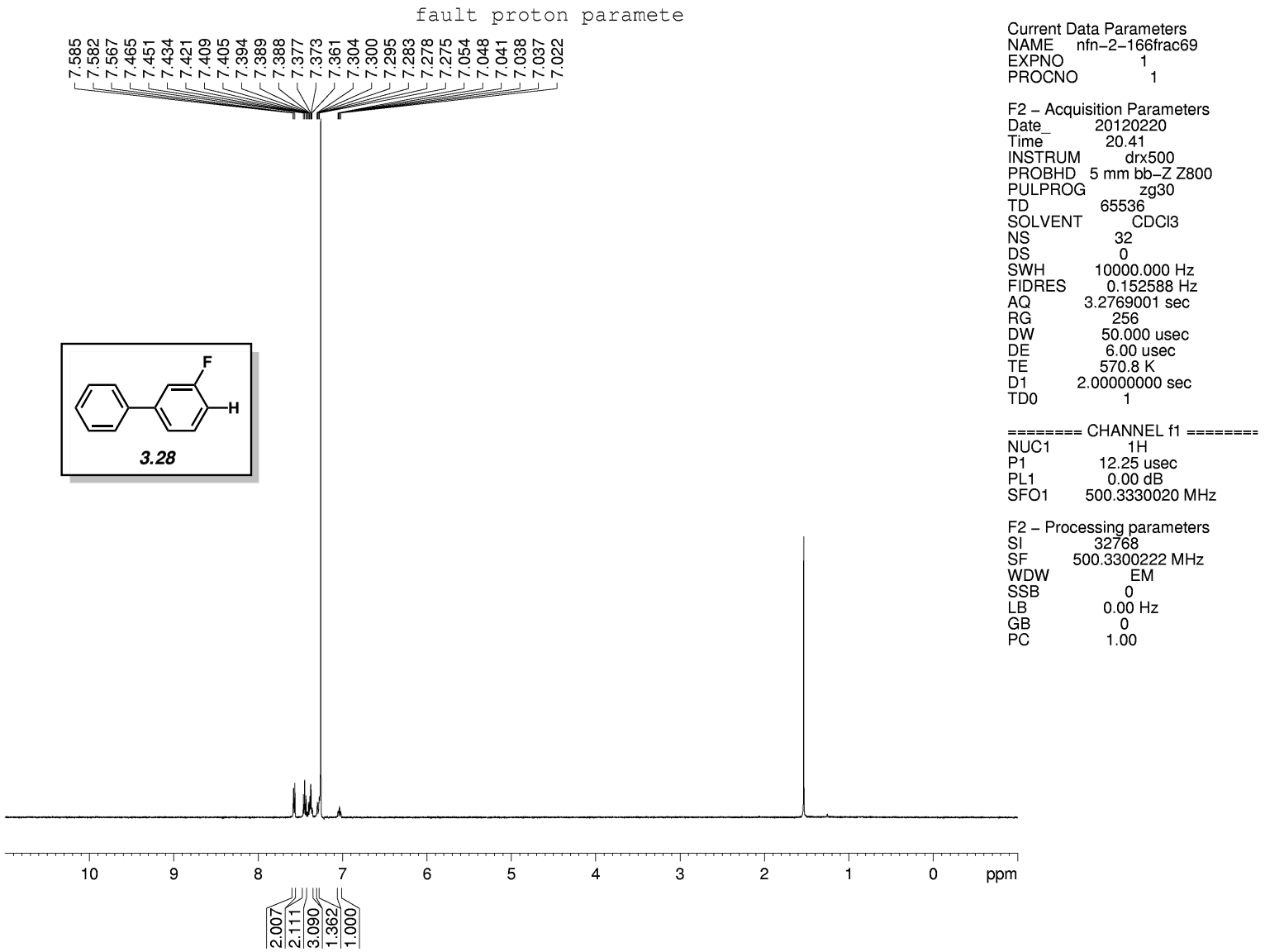
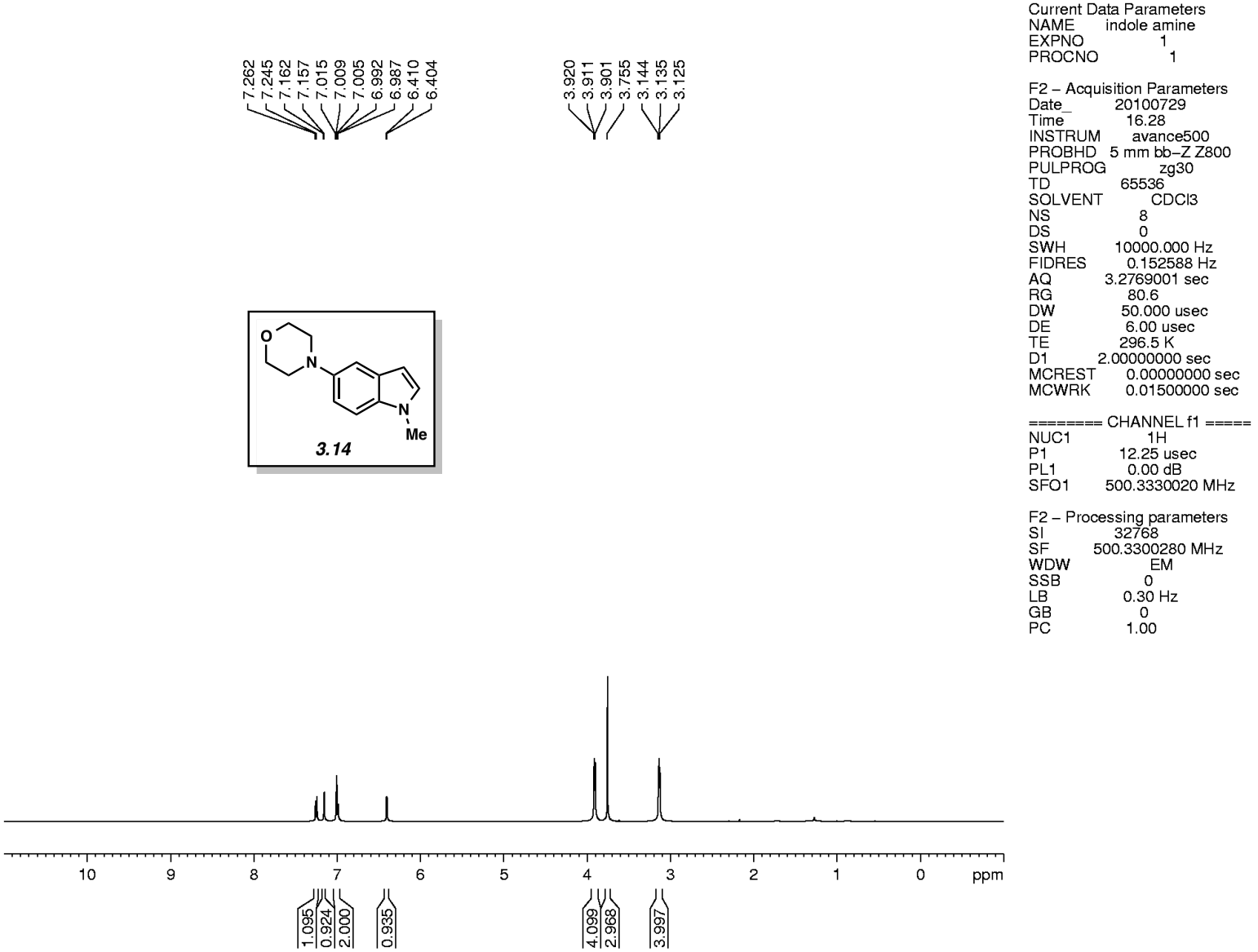


Figure 3.63. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.28**.



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PROCNO 1

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Figure 3.64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.14**.

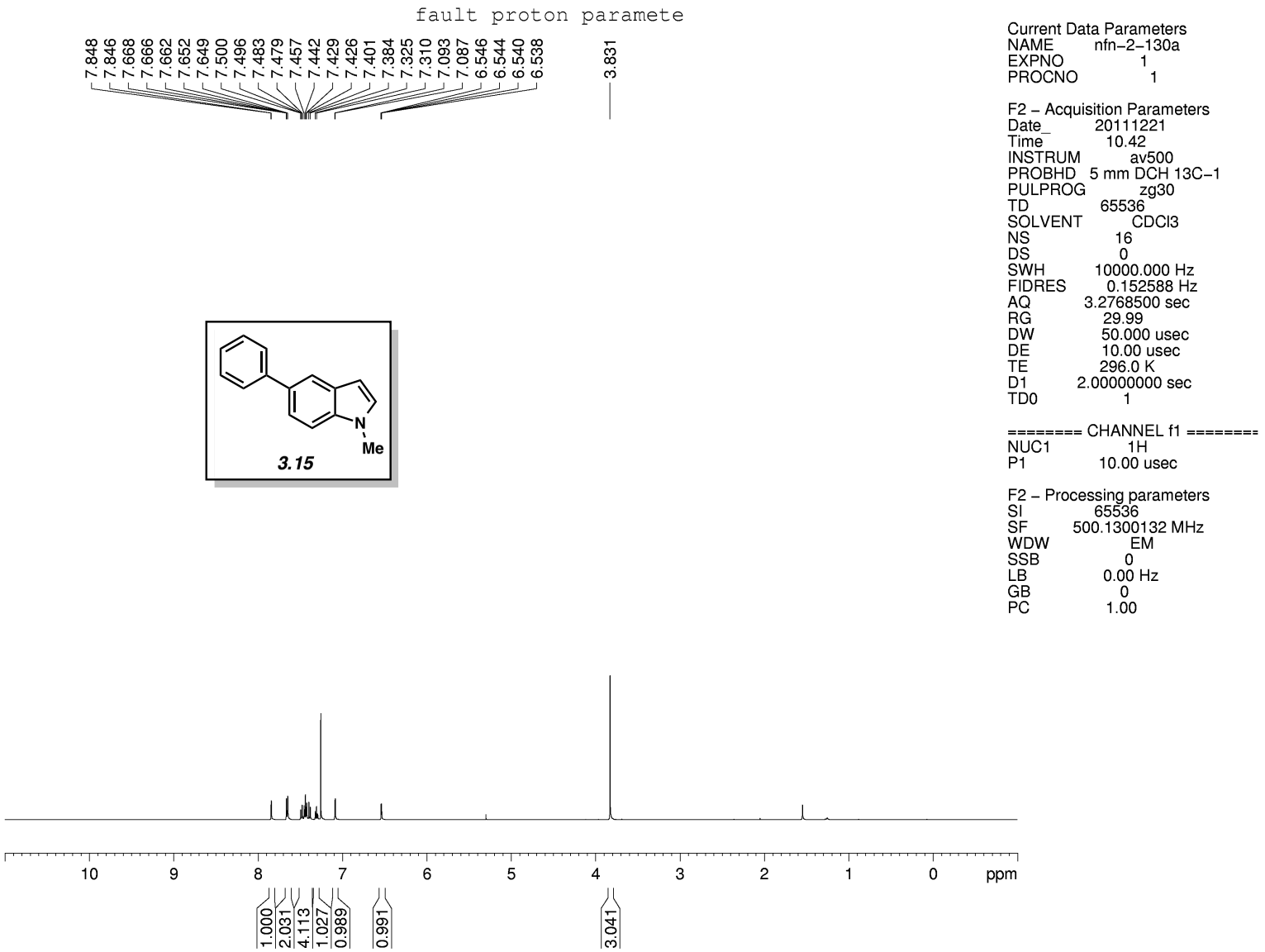


Figure 3.65. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.15**.

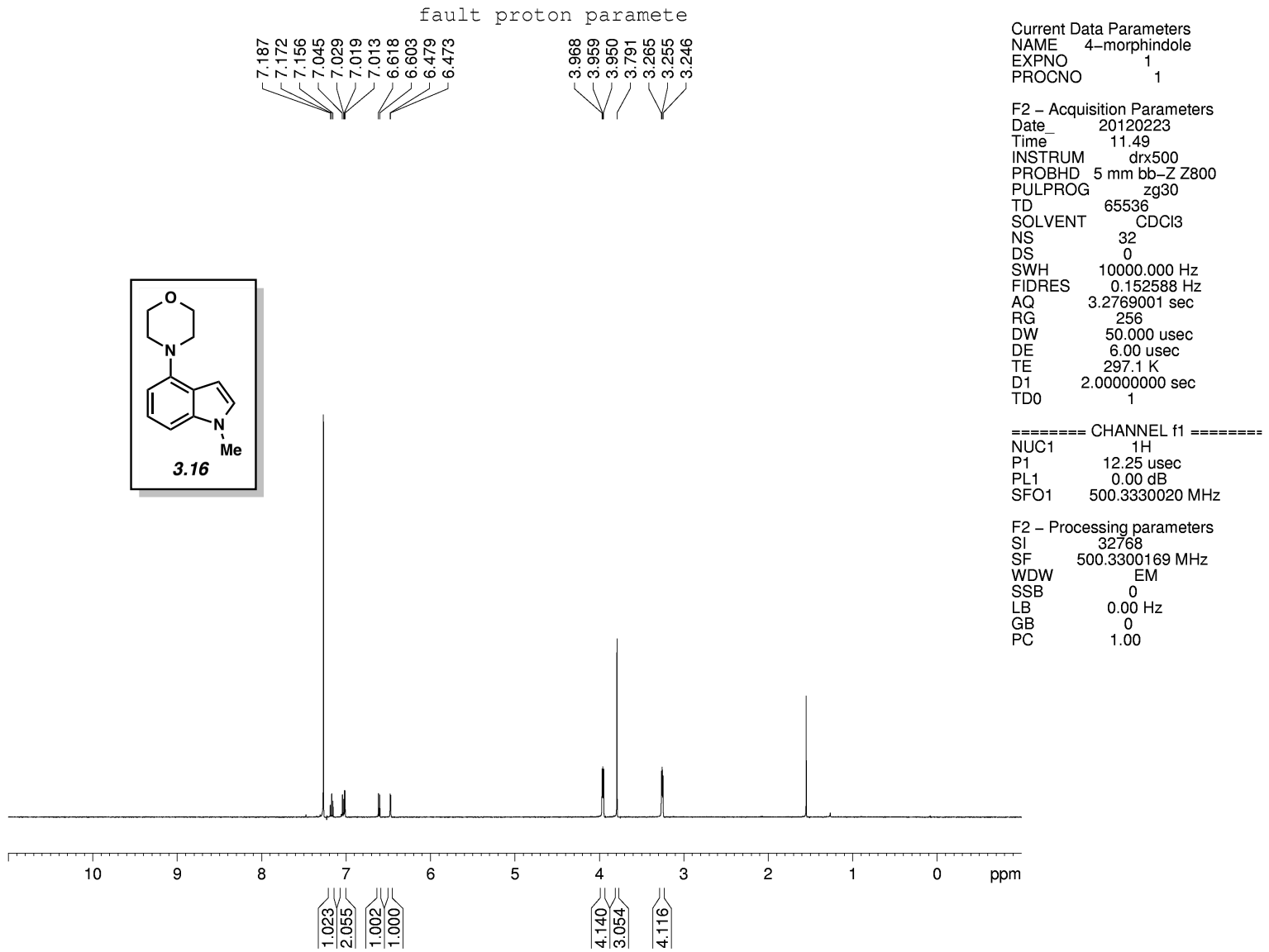


Figure 3.66. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.16**.

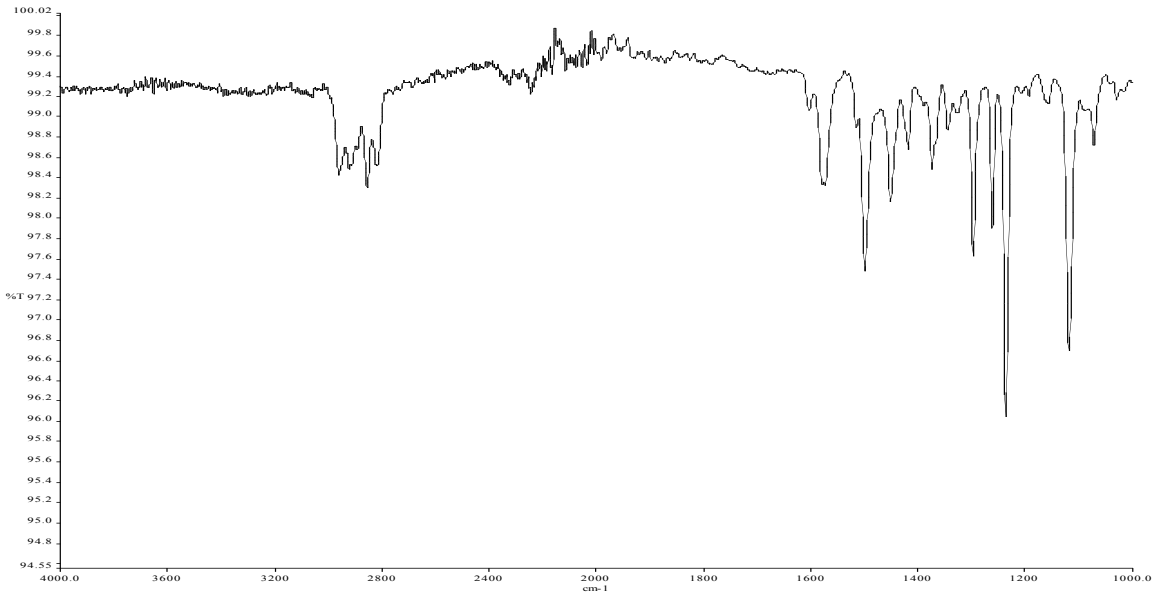


Figure 3.67. Infrared spectrum of compound **3.16**.

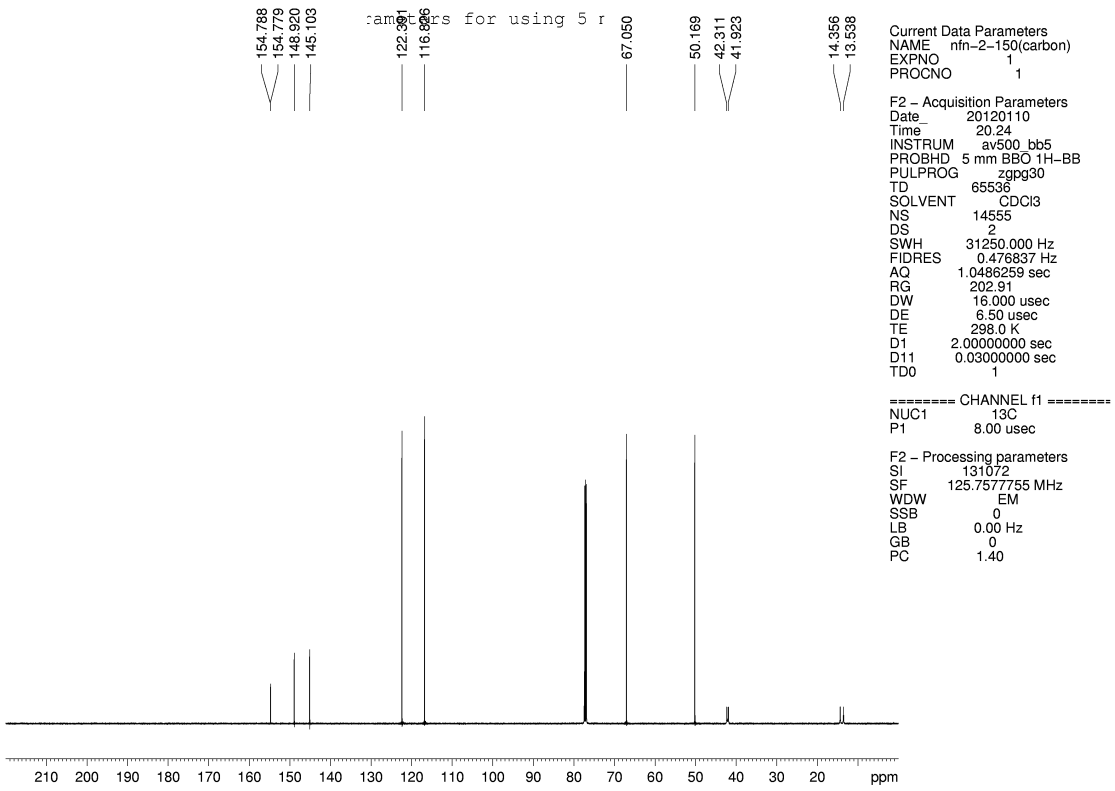


Figure 3.68. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.16**.

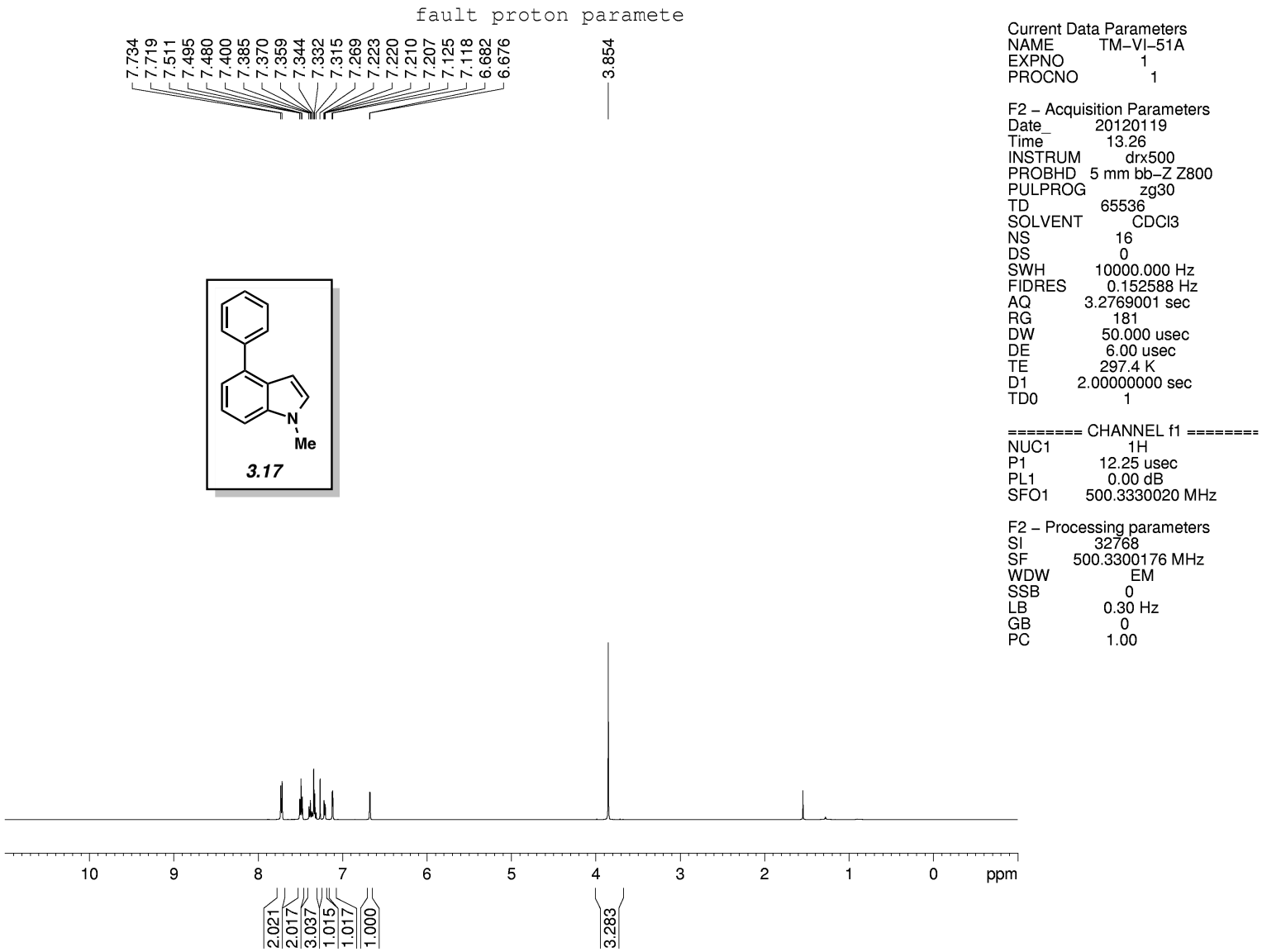


Figure 3.69. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.17**.

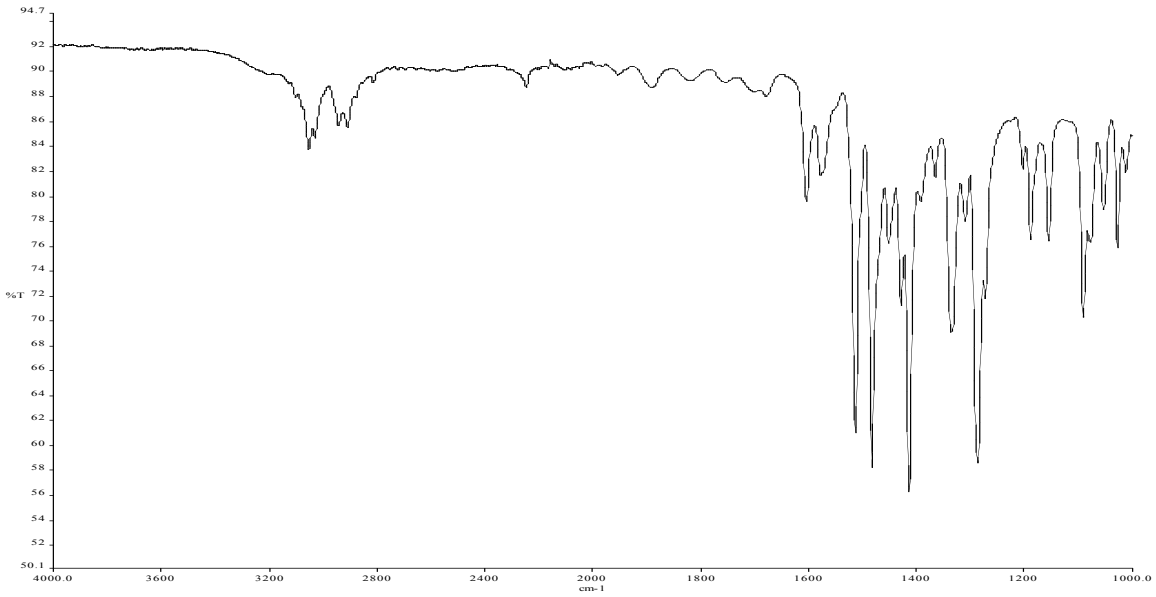


Figure 3.70. Infrared spectrum of compound **3.17**.

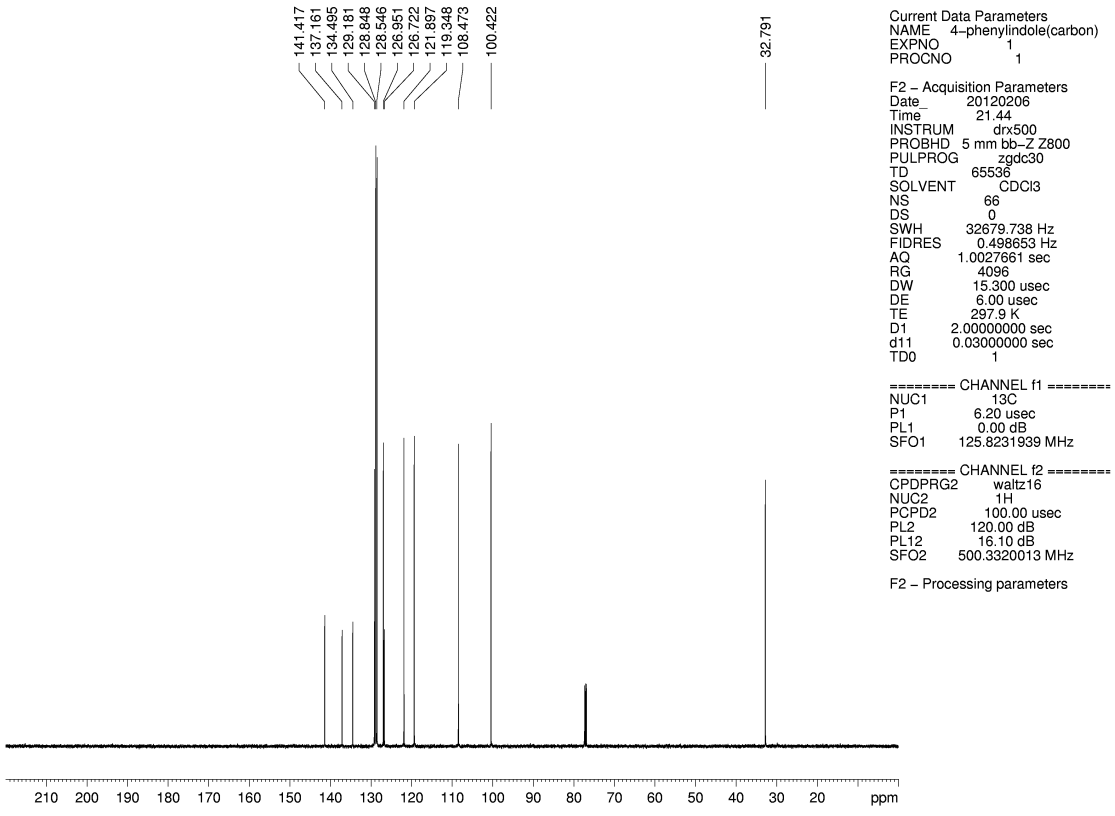


Figure 3.71. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **3.17**.

CHAPTER FOUR

Conversion of Amides to Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds

4.1 Abstract

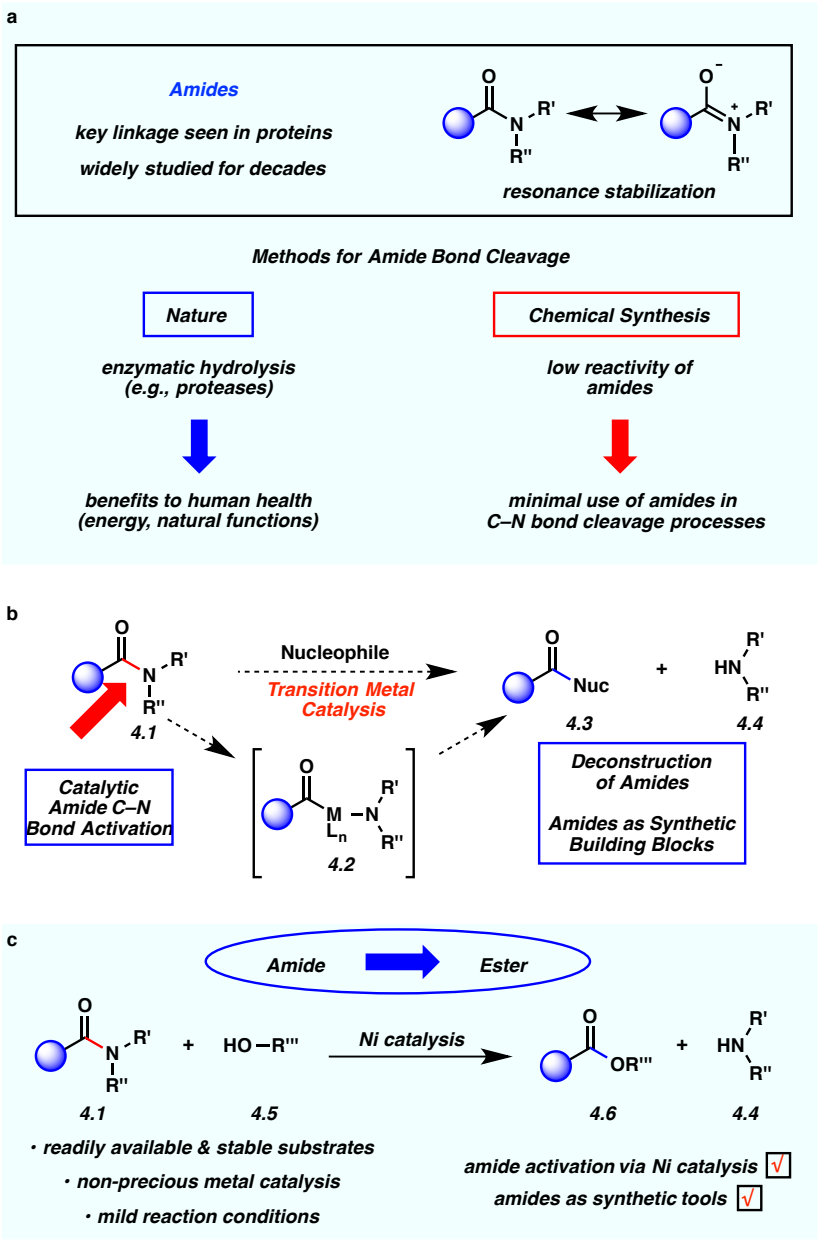
Amides are prevalent functional groups that serve as the key building blocks of proteins. Whereas Nature can masterfully cleave amides through the action of enzymes, such as proteases, the ability to break the C–N bond of amides using synthetic chemistry remains a challenge. The modest synthetic utility of amides as electrophiles can be traced to their low reactivity, which in turn is derived from the well-known resonance stability of amides. We describe a new strategy to harness amide functional groups as synthons, which relies on the nickel-catalyzed activation of amide C–N bonds. This approach has been validated through the conversion of amides to esters, which is a challenging and underdeveloped transformation. The reaction methodology proceeds under exceptionally mild reaction conditions, and avoids the use of a large excess of an alcohol nucleophile. DFT calculations provide insight into the thermodynamics and catalytic cycle for this unique transformation. These studies are expected to fuel the further use of amides as valuable building blocks for the construction of C–heteroatom or C–C bonds using non-precious metal catalysis.

4.2 Introduction

The ability to interconvert functional groups lies at the cornerstone of both synthetic chemistry and countless biological processes. As a result of decades of research, chemists have learned to strategically harness the reactivity of almost any functional group through the development of innovative methodologies.[1,2] Likewise, breakthroughs in biochemistry have allowed us to understand how Nature manipulates functional groups in order to regulate physiological processes.[3]

One particularly interesting dichotomy exists in considering the amide functional group,[4] which is the key component of all proteins and is therefore of tremendous importance (Figure 4.1). Sparked by Schwann's initial discovery of pepsin in 1836, the first enzyme discovered, scientists have been intrigued by the remarkable ability of enzymes to break down amide linkages.[5] Such amide cleavage processes govern many cellular regulatory functions and are also responsible for the degradation of proteins to amino acids.[4,5] In contrast, the synthetic chemistry of amide bond cleavage has remained largely underdeveloped, despite that amides are well suited for use in multistep synthesis because of their pronounced stability to a variety of reaction conditions. The most commonly employed methods to break amide C–N bonds include the reductive conversion of amides to aldehydes using Schwartz's reagent[6] and the interception of Weinreb's *N*-OMe-*N*-Me amides with organometallic reagents en route to ketones.[7] Following Pauling's seminal postulate regarding amide planarity,[8] the poor reactivity of amides is now well understood by the strength of the resonance-stabilized amide C–N bond.[4]

Figure 4.1. Natural, Synthetic, and Proposed Methods for Amide Bond Cleavage.



To circumvent the long-standing problem involving the low reactivity of amides and their modest synthetic utility in C–N bond cleavage processes, we conceived of the general approach shown in Figure 4.1b. The C–N bond of amide **4.1** would undergo activation by a transition metal catalyst. Following oxidative addition, the resulting acyl metal species **4.2** would be

trapped by an appropriate nucleophile to furnish product **4.3**, with the release of amine **4.4**. The success of this approach would allow for the breakdown of amides, and would also render amides useful synthetic building blocks. Although examples exist for the metal-catalyzed C–heteroatom bond activation of acid chlorides,[9] anhydrides,[9] and 2-pyridyl esters,[10] to our knowledge, the direct metal-catalyzed activation of C–N bonds of amides is unknown. This is notable given the rampant use of transition metal catalysis in organic synthesis, where there exist countless examples of catalytic transformations occurring smoothly in the presence of amide linkages.

This manuscript describes the validation of the strategy outlined in Figure 4.1b through the conversion of amides to esters (Figure 4.1c). Amide to ester conversion, much like transamidation,[11,12] has remained a challenging and underdeveloped synthetic transformation. It is often the case that amides are sufficiently stable such that esterification is difficult and requires the use of harsh acidic or basic conditions, while employing a large excess of nucleophile (e.g., using the alcohol nucleophile as solvent).[4] Perhaps the most promising protocol to achieve amide to ester conversions is Keck's methylation / hydrolysis sequence,[13] although this methodology is limited to the synthesis of methyl esters. Esterifications using acyl aziridines[14] and *N*-methylamides (albeit with activation by nitrosation)[15] have also been reported. Here, we demonstrate the Ni-catalyzed conversion of amides to esters, which proceeds under exceptionally mild reaction conditions. In addition to establishing the scope of this methodology, we use DFT calculations to predict whether the amide to ester conversion, or the reverse, is thermodynamically favored. DFT calculations are also used to predict a full catalytic cycle. These experimental and computational studies not only substantiate the notion of utilizing non-precious metal catalysis for the activation of amide C–N bonds, but also lay the foundation for

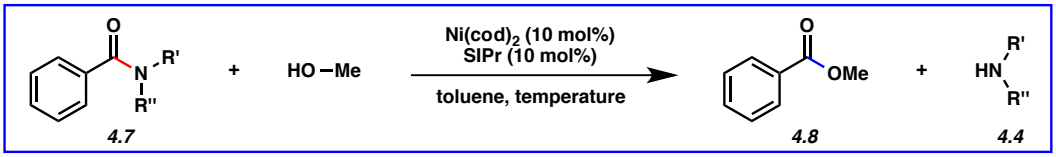
further studies aimed at the strategic manipulation of amides as synthetic building blocks using catalysis.

4.3 Optimization and Substrate Scope

To initiate our studies, we examined the conversion of benzamides **4.7** to methyl benzoate **4.8** using both computations and experiments (Table 4.1). As amides are well known for their pronounced stability, we assessed if the amide to ester conversion could be rendered thermodynamically favorable by the judicious choice of amide *N*-substituents. Using DFT methods, the **Δ**G for the reaction of amides **4.7** with methanol to give esters **4.8** and amines **4.4** was calculated. Whether this transformation is favorable or not indeed depends on the nature of the *N*-substituents (entries 1–8). Methanolysis of Weinreb amide **4.12** (entry 4) and *N*-arylated substrates **4.14** and **4.15** (entries 6–8) were found to be the most favorable energetically. In contrast, esterifications of *N*-alkyl amides **4.9**, **4.10**, and **4.13** were deemed thermodynamically unfavorable. This is in line with the experimentally measured equilibrium constant for the reaction of *N*,*N*-dimethylbenzamide **4.10** and methanol (entry 2), in which the reverse reaction is thermodynamically favored (see Supplementary Information for further discussion). [16] Encouraged by the unique ability of Ni to catalyze the activation of strong *aryl*–heteroatom bonds,[17,18,19] particularly those in phenol-,[19] aniline-,[20,21,22] and phthalimide derivatives,[23] we also calculated the activation energies for *acyl* C–N bond oxidative addition of each amide substrate using Ni catalysis. The calculated barriers using the commercially available *N*-heterocyclic carbene (NHC) ligand SIPr (entries 1–8) reveal that the oxidative addition barriers are reasonable in most cases. Simultaneously, we studied these reactions experimentally using 10 mol% $Ni(cod)_2$, 10 mol% SIPr, 2.0 equivalents of methanol, and toluene as solvent at 110 °C for 12 h,

and established strong correlations between our observations and computational predictions. No reaction or low yields were seen for substrates **4.9**–**4.13** (entries 1–5). However, in cases where the calculated **Δ**G and the oxidative addition barrier were favorable, significant formation of product **4.8** was observed (entries 6 and 7). Coupling of substrate **4.15** gave a quantitative yield of product (entry 7), and further optimization showed that even with only 1.2 equivalents of methanol and a temperature of 80 °C, product formation occurred smoothly (entry 8) to give complete conversion to **4.8**. Importantly, no reaction takes place if either the precatalyst or ligand are omitted, while the use of alternate NHC or phosphine ligands typically leads to lower yields or no reaction. We conclude that nickel catalysis is indeed operative in the amide activation / esterification process.

Table 4.1. Computational and Experimental Substrate Optimization.

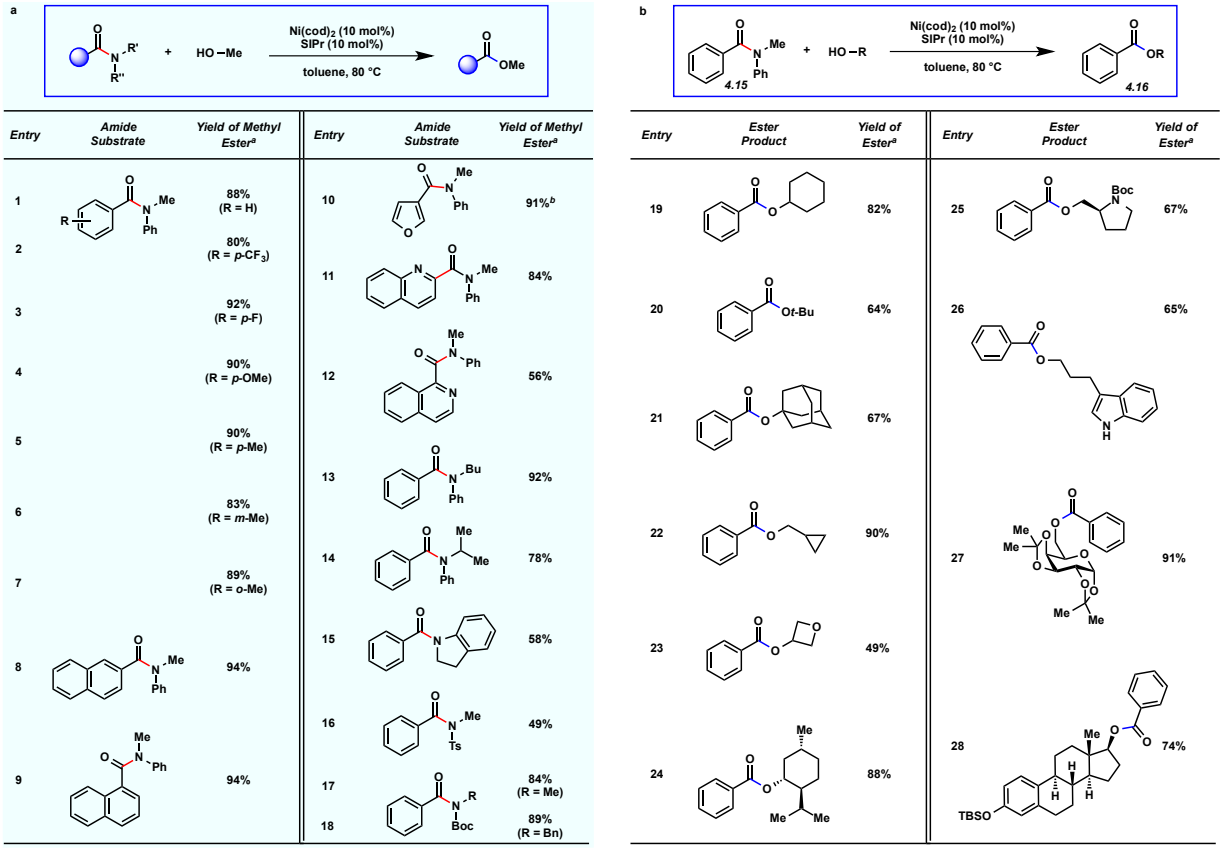


Entry		Calculated DG[a] (kcal/mol)	Calculated oxidative addition barrier with Ni /SIPr (kcal/mol)[b]	Temp	Equivalents of MeOH	Yield of ester[c]
1	4.9	+2.4	36.8	110 °C	2.0	0%
2	4.10	0.0	36.2	110 °C	2.0	0%
3	4.11	–1.1	34.0	110 °C	2.0	23%
4	4.12	–6.1	31.9	110 °C	2.0	22%
5	4.13	+3.1	39.0	110 °C	2.0	0%
6	4.14	–4.3	30.6	110 °C	2.0	55%
7	4.15	–6.8	26.0	110 °C	2.0	>99%
8				80 °C	1.2	>99%

With optimized conditions in hand, we examined the scope of the transformation with regard to the amide substrate (Table 4.2a). In addition to the parent benzamide (entry 1), substrates containing the electron-withdrawing trifluoromethyl or fluoride substituents (entries 2 and 3) or the electron-donating methoxy or methyl substituents (entries 4 and 5) were well tolerated. In addition, the transformation proceeded smoothly using *meta*- and *ortho*-methyl-substituted substrates to give the desired esters in excellent yields (entries 6 and 7). Beyond the use of phenyl derivatives, we examined naphthyl and heterocyclic substrates. Indeed, naphthyl

compounds readily coupled (entries 8 and 9), as did furan, quinoline, and isoquinoline substrates (entries 10–12, respectively). It should be noted, however, that amides derived from alkyl carboxylic acids do not undergo the nickel-catalyzed esterification under our reaction conditions. As shown later in this manuscript (see Figure 4.3), this attribute provides opportunities to realize selective amide C–N bond cleavages in more complex substrates.

Table 4.2. Scope of Amide Substrate and Alcohol Nucleophile.



Entry	Amide Substrate	Yield of Methyl Ester[a]
1		88% (R = H)
2		80% (R = *p*-CF_3)
3		92% (R = *p*-F)
4		90% (R = *p*-OMe)
5		90% (R = *p*-Me)
6		83% (R = *m*-Me)
7		89% (R = *o*-Me)
8		94%
9		94%
10		91%[b]
11		84%
12		56%
13		92%
14		78%
15		58%
16		49%
17		84% (R = Me)
18		89% (R = Bn)

Entry	Ester Product	Yield of Ester[a]
19		82%
20		64%
21		67%
22		90%
23		49%
24		88%
25		67%
26		65%
27		91%
28		74%

A variety of *N*-substituents were also surveyed, as shown in Table 4.2a. In addition to the longer *N*-Bu and the branched *N*-*i*Pr alkyl chains (entries 13 and 14, respectively), we found that a cyclic amide derived from indoline was tolerated by the methodology (entry 15). Lastly,

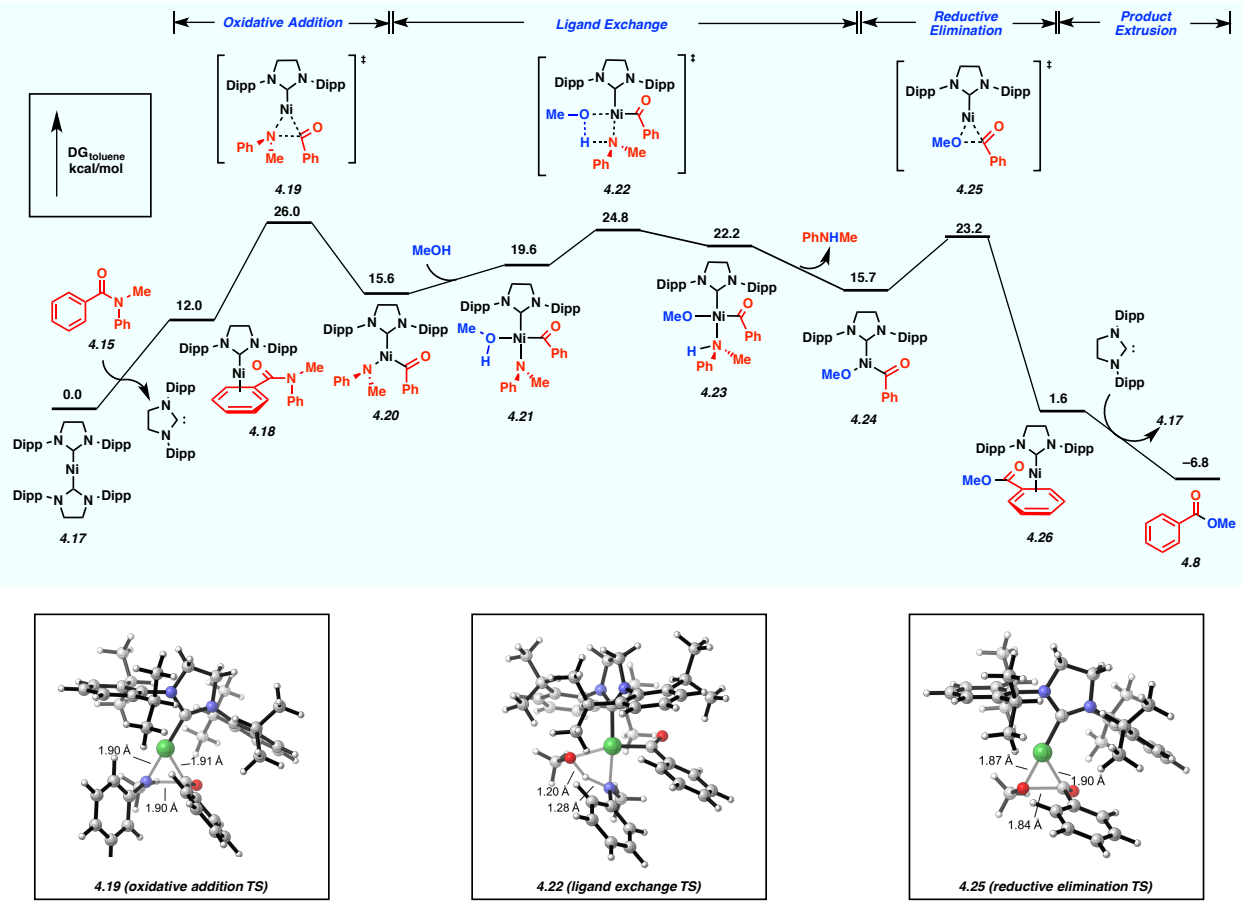
protected *N*-alkyl benzamides were tested. Although use of the *N*-Ts derivative gave the corresponding ester in modest yield (entry 16), the corresponding *N*-Boc substrate more efficiently underwent conversion to ester **4.8** (entry 17). The analogous *N*-Bn,Boc substrate was also evaluated and gave the desired ester in 89% yield (entry 18). These latter results show that the methodology is not restricted to anilide substrates, as long as the overall reaction energetics are thermodynamically favorable (see Supplementary Information for energetics involving *N*-Boc,Me substrate). Moreover, one can strategically employ secondary benzamides as substrates for esterification, following a straightforward activation step (i.e., Boc-protection).

Using amide **4.15** as the substrate, we also evaluated the scope of the methodology with respect to the alcohol nucleophile (Table 4.2b). As shown, synthetically useful yields of product were obtained using only 1.2 equivalents of the alcohol, even when significantly complex and hindered alcohols were utilized. Cyclohexanol, *t*-butanol, and 1-adamantol coupled smoothly to give the corresponding esters (entries 19–21, respectively). It should be noted that *t*-butyl esters can readily be hydrolyzed to carboxylic acids under acidic conditions. Similarly, we found that cyclopropyl carbinol and an oxetane-derived alcohol could be employed in the esterification reaction (entries 22 and 23, respectively). The use of the hindered secondary alcohol (–)-menthol was also tested. To our delight, the desired ester was obtained in 88% yield (entry 24). Furthermore, we found that Boc-L-prolinol was tolerated in the methodology (entry 25), in addition to an indole-containing alcohol (entry 26), thus further demonstrating the promise our methodology holds for reactions of heterocyclic substrates. As shown in entries 27 and 28, respectively, a complex sugar-containing alcohol bearing two acetals and an estrone-derived steroidal alcohol also underwent the desired esterification reaction.

4.4 Computational Studies

Although nickel-catalyzed aryl and acyl C–O bond activation processes have been previously studied computationally,[24,25,26,27,28] no analogous studies involving C–N bond activation have been reported. Thus, to shed light on the mechanism of the facile amide to ester conversion, the catalytic cycle was computed using DFT calculations. Figure 4.2 provides the free energy profile using amide substrate **4.15**. The [Ni(SIPr)$_2$] complex, **4.17**, is believed to be the resting state of the catalytic cycle. Dissociation of one carbene ligand from complex **4.17** provides a coordination site for amide **4.15**. Following coordination to give intermediate **4.18**, oxidative addition occurs via transition state **4.19**. This key event cleaves the amide C–N bond and produces acyl nickel species **4.20**. The next step of the catalytic cycle is ligand exchange, which proceeds by coordination of methanol to give intermediate **4.21**. Subsequent ligand exchange via transition state **4.22** facilitates the deprotonation of methanol, giving nickel complex **4.23**. Dissociation of *N*-Me-aniline produces acyl nickel species **4.24**, which in turn, undergoes reductive elimination via transition state **4.25** to deliver the ester-coordinated complex **4.26**. Finally, the ester product **4.8** is released to regenerate catalyst **4.17**. The rate-determining step in the catalytic cycle is the oxidative addition (transition state **4.19**) with an overall barrier of 26.0 kcal/mol relative to the resting state **4.17**. The overall reaction is thermodynamically favored by –6.8 kcal/mol. As decarbonylation of acyl nickel species has been observed,[29,30] we also calculated the kinetic barrier for decarbonylation events (see computational methods). Consistent with experiments, decarbonylation pathways from acyl nickel species **4.20** or **4.24** were found to be less favorable compared to product formation pathways.

Figure 4.2. Gibbs Free Energy Diagram of Ni-Catalyzed Esterification of Amide **4.15** with Methanol. Energies are given in kcal/mol.

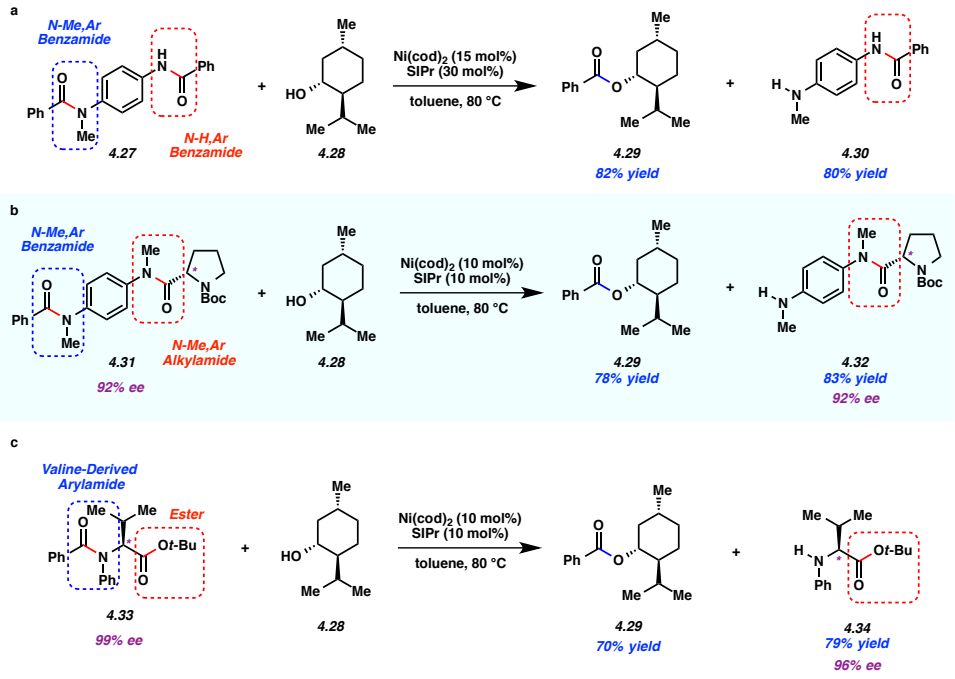


4.5 Selective Amide Bond Cleavages

As highlighted by the experiments shown in Figure 4.3, the nickel-catalyzed conversion of amides to esters can be used to achieve selective and mild amide bond cleavages. In the first example, guided by our earlier computational and experimental observations (see Table 4.1), we performed the esterification of bis(amide) substrate **4.27** using the hindered alcohol (–)-menthol (Figure 4.3a). Although both amides are *N*-arylated benzamides, only the tertiary amide was cleaved to give ester **4.29**, while also releasing aminoamide **4.30**. Additionally, bis(amide) **4.31**, which possesses two tertiary amides was studied in the nickel-catalyzed esterification reaction

(Figure 4.3b). In this case, the tertiary L-proline-derived alkyl amide was not disturbed, while the tertiary benzamide underwent cleavage to give ester **4.29** and aminoamide **4.32** in good yields. Lastly, we prepared L-valine derivative **4.33**, which also bears an ester (Figure 4.3c). Upon exposure of **4.33** to 1.2 equiv of (–)-menthol and the nickel-catalyzed conditions, ester **4.29** and aminoester **4.34** were obtained in 70% and 79% yields, respectively. It is believed that the ester functionality withstands the reaction conditions because it is not attached to an arene, analogous to the lack of reactivity seen in our attempts to esterify amides derived from alkyl carboxylic acids (e.g., **4.31**). It should be noted that **4.32** and **4.34** were obtained in high enantiomeric excess, thus highlighting the mild nature of the reaction conditions, which avoid any significant epimerization of the a stereocenters.

Figure 4.3. Mild and Selective Esterifications of Bis- and Valine-Derived Amides.



4.6 Conclusion

We have discovered an efficient means to achieve the conversion of amides to esters. The methodology circumvents the classic problem of amides being poorly reactive functional groups by using nickel catalysis to achieve the previously unknown catalytic activation of amide C–N bonds. DFT calculations support a catalytic cycle that involves a rate-determining oxidative addition step, followed by ligand exchange and reductive elimination. The methodology is broad in scope, particularly with respect to the alcohol nucleophiles, and proceeds under exceptionally mild reaction conditions using just 1.2 equivalents of the alcohol nucleophile. Moreover, selective amide bond cleavage can be achieved in the presence of other functional groups, including less reactive amides and esters, without the epimerization of stereocenters. Many future advances pertaining to this methodology can be envisioned, such as the catalytic esterification of primary amides, additional *N,N*-disubstituted amides, amides derived from alkyl or vinyl carboxylic acids, and perhaps even polyamide substrates bearing multiple stereocenters. We hope this study will also fuel the further harnessing of amides as valuable building blocks for the construction of C–heteroatom or C–C bonds using non-precious metal catalysis.

4.7 Experimental Section

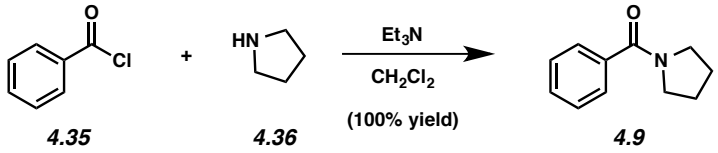
4.7.1 Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen and commercially obtained reagents were used as received. Non-commercially available substrates were synthesized following protocols specified in Section A in the Experimental Procedures. Alcohols and toluene were purified by distillation and taken through five freeze-pump-thaw cycles or recrystallized prior to use. Carboxylic acid **4.46**, amine **4.89**, and ester **4.96** were obtained from Combi-Blocks. Acid chlorides **4.35**, **4.37**, **4.40**, **4.42**, **4.44**, alcohols **4.71**, **4.73**, **4.75**, **4.77**, **4.79**, **4.81**, **4.83**, **4.85**, **4.87**, **4.28**, amines **4.36**, **4.38**, **4.90**, acid **4.92**, amide **4.10**, benzamide and ligand SIMes were obtained from Sigma-Aldrich. Boronic acid **4.95** was obtained from Oakwood Products, Inc. $Ni(cod)_2$, SIPr, IMes, IPr, PCy_3, dppe, and dppf were obtained from Strem Chemicals. Amide **4.13**, ligands PPh_3, PPh_2Cy, and PCy_2Ph were obtained from Alfa Aesar. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm for analytical chromatography and 0.50 mm for preparative chromatography) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, iodine, vanillin, and potassium permanganate staining techniques. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 300, 400, 500, and 600 MHz) and are reported relative to residual solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (at 75 and 125 MHz). IR spectra were recorded on a Perkin-Elmer 100

spectrometer and are reported in terms of frequency absorption (cm^{-1}). High-resolution mass spectra were obtained on Thermo Scientific™ Exactive Mass Spectrometer with DART ID-CUBE. Determination of enantiopurity was carried out on a Mettler Toledo SFC (supercritical fluid chromatography) using a Daicel ChiralPak OJ-H column.

4.7.2 Experimental Procedures

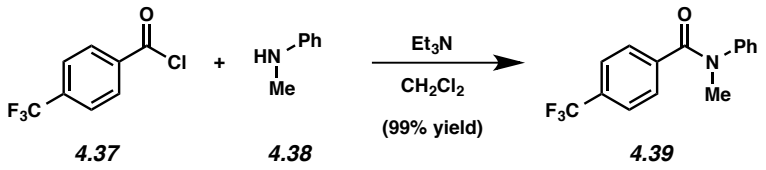
4.7.2.1 Syntheses of Amide Substrates



Representative procedure for the synthesis of amide substrates from Table 4.1 and 4.2 (synthesis of amide 4.9 is used as an example). To a solution of pyrrolidine **4.36** (1.3 mL, 15.7 mmol, 1.1 equiv), triethylamine (2.5 mL, 17.8 mmol, 1.25 equiv), and dichloromethane (28.5 mL, 0.5 M) at 0 °C, was added acid chloride **4.35** (2.0 g, 14.2 mmol, 1.0 equiv). The reaction mixture was gradually warmed to 23 °C over 30 min and then stirred for 1 h. The reaction mixture was diluted with EtOAc (50 mL), and then washed successively with 1.0 M HCl (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude solid material was purified by flash chromatography (1:1 Hexanes:EtOAc) to yield amide product **4.9** (2.5 g, 100% yield) as a white solid. Spectral data matched those previously reported.[31a]

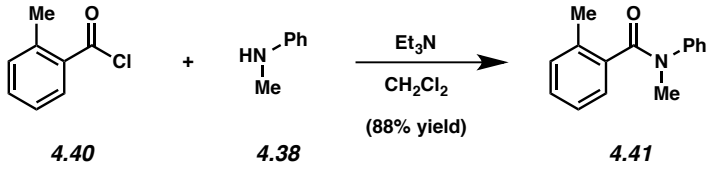
Note: Experimental procedures for the syntheses of amides shown in Table 1 and 2 have previously been reported: **4.9**,[31a] **4.11**,[31b] **4.12**,[31c] **4.14**,[31d] **4.15**,[31e] **4.49**,[31f] **4.51**,[31f] **4.53**,[31f] **4.55**,[31g] **4.58**,[31g] **4.59**,[31h] **4.65**,[31f] **4.66**,[31e] **4.67**,[31i] **4.68**,[31j] **4.69**,[31k] and **4.70**,[31l] with the exception of *p*-

trifluoromethyl amide **4.39**, *o*-methyl amide **4.41**, furan **4.43,** quinoline **4.45**, and isoquinoline **4.47**. Syntheses for these latter compounds are as follows:



4.37 ***4.38*** ***4.39***

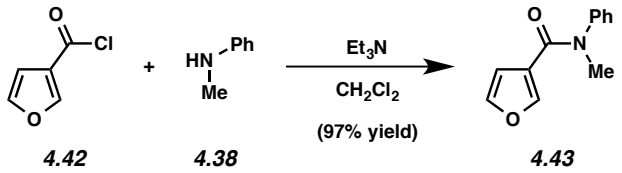
To a solution of triethylamine (2.1 mL, 15 mmol, 1.25 equiv) and *N*-Me aniline (1.43 mL, 13.2 mmol, 1.1 equiv) in dichloromethane (24.0 mL, 0.5 M) at 0 °C, was added acid chloride **4.37** (2.5 g, 12.0 mmol, 1.0 equiv). The resulting heterogeneous mixture was allowed to stir at 23 °C for 12 h. The mixture was then diluted with EtOAc (30 mL) and 1.0 M HCl (40 mL). The organic layer was washed with brine (2 x 40 mL) and then dried over Na_2SO_4. The volatiles were removed under reduced pressure, and the crude oil was purified by flash chromatography (5:1 Hexanes:EtOAc) to yield amide product **4.39** (3.3 g, 99% yield) as a white solid. Amide **4.39**: R_f 0.27 (5:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 7.44 (q, J = 8.4, 4H), 7.24–7.23 (m, 2H), 7.19 (t, J = 7.4, 1H), 7.03 (d, J = 7.55, 2H), 3.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 144.3, 139.6, 131.4 (q, J_{C-F} = 32.6 Hz), 129.5, 129.1, 127.2, 127.0, 124.9 (q, J_{C-F} = 3.8 Hz), 122.7, 120.5, 38.5 ; IR (film): 2971, 1738, 1639, 1596, 1496, 1371, 1322, 1165, 1122, 1108, 1065, 1019 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{15}H_{13}F_3NO$, 280.09492; found 280.09339.



4.40 ***4.38*** ***4.41***

To a solution of acid chloride **4.40** (2.5 g, 16.0 mmol, 1.0 equiv) and dichloromethane (10 mL) at 0 °C, was added a solution of triethylamine (2.1 mL, 15 mmol, 1.25 equiv) and *N*-Me aniline

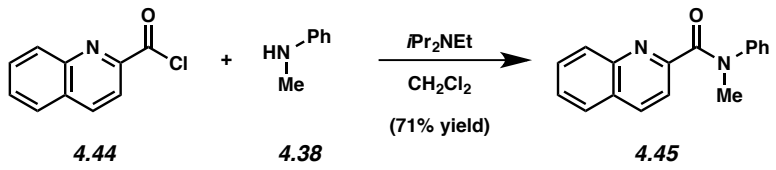
(1.43 mL, 13.2 mmol, 1.1 equiv) in dichloromethane (22 mL). The resulting heterogeneous mixture was warmed to 23 °C and allowed to stir for 12 h. The mixture was then diluted with EtOAc (30 mL) and 1.0 M HCl (50 mL). The organic layer was washed with brine (50 mL) and then dried over Na_2SO_4. The volatiles were removed under reduced pressure, and the crude oil was purified by flash chromatography (5:1 Hexanes:EtOAc) to yield amide product **4.41** (3.2 g, 88% yield) as a white solid. Amide **4.41**: R_f 0.30 (5:1 Hexanes:EtOAc); ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.18–7.03 (m, 9H), 3.49 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 143.9, 136.7, 134.8, 130.3, 129.0, 128.7, 127.6, 126.7, 126.6, 125.2, 37.4, 19.6; IR (film): 3062, 2924, 1643, 1594, 1494, 1456, 1417, 1364, 1303, 1280, 1180, 1121, 1097, 1028 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{15}H_{16}NO$, 226.12319; found 226.12159.



4.42 ***4.38*** ***4.43***

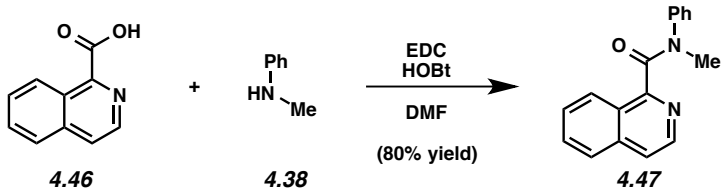
To a flask containing a solution of *N*-Me aniline (1.3 mL, 12.3 mmol, 1.6 equiv) and triethylamine (1.1 mL, 7.7mmol, 1.0 equiv) in dichloromethane (11.5 mL, 0.67 M) at 0 °C, was added acid chloride **4.42** (1.0 g, 7.7 mmol, 1.0 equiv). The resulting heterogeneous mixture was warmed to 23 °C over 30 min and then heated to reflux for 1 h. After cooling to 23 °C, the reaction mixture was stirred for 12 h and then quenched with 1.0 M HCl (10 mL). The organic layer was washed with brine (30 mL) and then dried over Na_2SO_4. The volatiles were removed under reduced pressure, and the crude solid was purified by flash chromatography (5:1 Hexanes:EtOAc) to yield amide product **4.43** (1.5 g, 97% yield) as a white solid. Amide **4.43**: R_f 0.24 (5:1 Hexanes:EtOAc); ^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.44–7.36 (m, 3H), 7.23–7.19 (m, 2H), 7.14 (t, *J* = 1.78, 1H), 6.89–6.87 (m, 1H), 6.11–6.10 (m, 1H), 3.41 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 163.2, 145.7, 144.1, 141.9, 129.7, 128.1, 127.8, 121.9, 111.0, 38.2; IR (film): 3481, 3129, 2970, 1739, 1630, 1593, 1561, 1497, 1379, 1354, 1157, 1074, 1040 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{12}H_{12}NO_2$, 202.08680; found 202.08580.



4.44 ***4.38*** ***4.45***

To a solution of *N*-Me aniline (1.2 mL, 11.5 mmol, 1.1 equiv) and *N*,*N*-diisopropylethylamine (9.1 mL, 52.2 mmol, 5.0 equiv) in dichloromethane (100 mL, 0.1 M) at 0 °C, was added acid chloride **4.44** (2.0 g, 10.4 mmol, 1.0 equiv). The resulting heterogeneous mixture was allowed to stir at 23 °C. After 17 h, additional *N*-Me aniline (1.2 mL, 11.5 mmol, 1.1 equiv) and *N*,*N*-diisopropylethylamine (6.0 mL, 34.4 mmol, 3.3 equiv) were added sequentially. After stirring at 23 °C for 6 h, the reaction mixture was quenched with 1.0 M HCl (50 mL). The organic layer was washed with brine (50 mL) and then dried over Na_2SO_4. The volatiles were removed under reduced pressure, and the crude oil was purified by flash chromatography (5:1 Hexanes:EtOAc) to yield amide product **4.45** (2.0 g, 71% yield) as a white solid. Amide **4.45**: R_f 0.40 (5:1 Hexanes:EtOAc); ^1H NMR: (500 MHz, $CDCl_3$): δ 8.03 (br s, 1H), 7.85 (br s, 1H), 7.77–7.58 (m, 2H), 7.57–7.43 (m, 2H), 7.24–6.99 (m, 5H), 3.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 154.2, 146.9, 144.4, 136.4, 129.9, 129.8, 129.1, 127.7, 127.5, 127.5, 127.0, 126.7, 120.6, 38.2; IR (film): 3457, 2971, 1739, 1642, 1594, 1495, 1375.55, 1229, 1217, 1121, 1104 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{17}H_{15}N_2O$, 263.11844; found 263.11718.



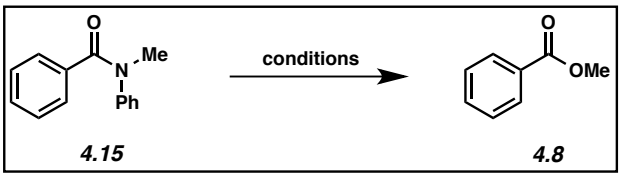
4.46 *4.38* *4.47*

To a mixture of carboxylic acid **4.46** (1.0 g, 4.0 mmol, 1.0 equiv), EDC (0.7 g, 4.4 mmol, 1.1 equiv), HOBt (0.6 g, 4.4 mmol, 1.1 equiv), and DMF (60.0 mL, 0.067 M) was added *N*-Me aniline (0.5 mL, 4.4 mmol, 1.1 equiv). The resulting mixture was stirred at 23 °C for 12 h, and then diluted with deionized water (100 mL) and EtOAc (100 mL). The aqueous layer was separated and the organic layer was extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine (150 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude oil was purified by flash chromatography with (1:1 Hexanes:EtOAc) to yield amide product **4.47** (0.9 g, 80% yield) as a white solid. Amide **4.47**: R_f 0.50 (1:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$): (major rotamer) δ 8.25 (d, J = 5.8, 1H), 8.18–8.17 (m, 1H), 7.74–7.72 (m, 1H), 7.66–7.60 (m, 2H), 7.46 (d, J = 5.8, 1H), 7.04–6.97 (m, 5H), 3.65 (s, 3H); (minor rotamer) [10/14 protons were discernable] δ 8.60–8.58 (m, 1H), 7.96–7.84 (m, 1H), 7.59–7.49 (m, 5H), 3.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ168.4, 155.8, 143.4, 141.4, 136.2, 130.5, 128.9, 128.0, 127.1, 126.9, 126.7, 126.0, 125.9, 121.1, 37.3; IR (film): 3060, 2939, 1651, 1595, 1561, 1496, 1460, 1431, 1399 1372, 1119, 1054, 1033 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{17}H_{15}N_2O$, 263.11844; found 263.11768.

*Note: **4.47** was obtained as a 7.5:1 mixture of rotamers. These data represent empirically observed chemical shifts and coupling constants from the ^{1}H NMR spectrum*

4.7.2.2 Methanolysis Control Experiments

Table 4.3. Attempted Conversion of Amide **4.15** to Methyl Benzoate Under Various Reaction Conditions.[a]



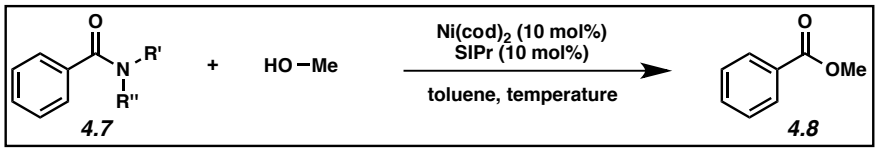
4.15 ***4.8***

	Experimental Results	
Reaction Conditions	***Recovered 4.15***	***8a***
Conc. HCl (5.13 equiv), MeOH (0.12 M) 23 °C (2 h) → 75 °C (2 h) → 100 °C (17 h)	100%	0%
NaOMe (2.0 equiv), MeOH (0.12 M) 23 °C (4 h) → 80 °C (4 h) → 110 °C (13.5 h)	93%	7%
NaOMe (10.0 equiv), MeOH (0.12 M) 23 °C (1.5 h) → 80 °C (4 h) → 110 °C (14 h)	94%	6%
K_2CO_3 (1.0 equiv), MeOH (0.12 M) 23 °C (7 h) → 110 °C (12 h)	95%	5%

[a] Yields were determined by ^1H NMR analysis using hexamethylbenzene as an internal standard

4.7.2.3 Screening of Amide Substrates

Table 4.4. Survey of Amide Substrates.[a]

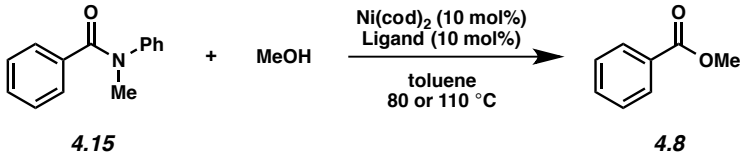


Entry		*Temp*	*Equivalents of MeOH*	*Yield of ester*	*Remainder of the mass*
1	***4.9***	110 °C	2.0	0%	***4.9*** (100%)
2	***4.10***	110 °C	2.0	0%	***4.10*** (100%)
3	***4.11***	110 °C	2.0	23%	***4.11*** (77%)
4	***4.12***	110 °C	2.0	22%	***4.12*** (72%) + ***4.13*** (6%)
5	***4.13***	110 °C	2.0	0%	***4.13*** (100%)
6	***4.14***	110 °C	2.0	55%	***4.14*** (45%)
7	***4.15***	110 °C	2.0	quant.	-
8		80 °C	1.2	quant.	-

[a] Yields were determined by ^{1}H NMR analysis using hexamethylbenzene as an internal standard.

Note: The attempted esterification of benzamide using MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), SIPr (10 mol%), and toluene (1.0 M) at 110 °C led to no reaction.

4.7.2.4 Comparison of Ligands and Relevant Control Experiments

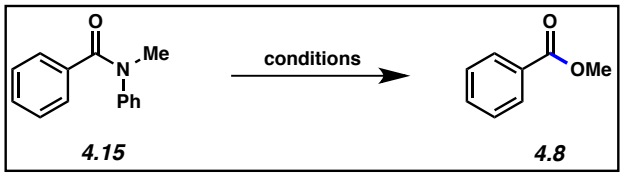


4.15 *4.8*

Representative Procedure for Esterifications of Benzamides from Table 4.4 and 4.5 (coupling of amide 4.15 is used as an example). A 1-dram vial containing amide **4.15** (50.0 mg, 0.24 mmol, 1.0 equiv), hexamethylbenzene (7.8 mg, 0.48 mmol, 0.2 equiv), and a magnetic stir bar was charged with $Ni(cod)_2$ (6.6 mg, 0.024 mmol, 10 mol%) and ligand (0.024 mmol, 10 mol%) in a glove box. Subsequently, toluene (0.24 mL, 1.0 M) and then methanol (19.4 μL, 0.48 mmol, 2.0 equiv) were added. The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and stirred at 80 or 110 °C for 12 h. After cooling to 23 °C, the mixture was diluted with hexanes (0.5 mL) and filtered over a plug of silica gel (10 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the yield was determined by ^1H NMR analysis with hexamethylbenzene as an internal standard.

Any modifications of the conditions shown in the representative procedure above are specified in the following Table 4.4 and 4.5.

Table 4.5. Ligand Screening for Nickel-Catalyzed Esterification.[a]

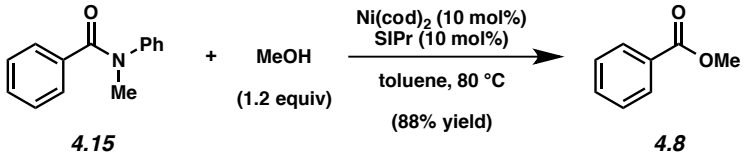


4.15 ***4.8***

Reaction Conditions	***Experimental Results*** ***4.15***	***4.8***
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), SIPr (10 mol%) toluene (1.0 M), 110 °C, 12 h	0%	100%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), IPr (10 mol%) toluene (1.0 M), 110 °C, 12 h	0%	100%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), SIMes (10 mol%) toluene (1.0 M), 110 °C, 12 h	0%	0%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), IMes (10 mol%) toluene (1.0 M), 110 °C, 12 h	63%	37%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), PPh_3 (10 mol%) toluene (1.0 M), 110 °C, 12 h	100%	0%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), PPh_2Cy (10 mol%) toluene (1.0 M), 110°C, 12 h	100%	0%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), PCy_3 (10 mol%) toluene (1.0 M), 110 °C, 12 h	85%	15%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), $PhPCy_2$ (10 mol%) toluene (1.0 M), 110 °C, 12 h	97%	3%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), dppe 10 mol%) toluene (1.0 M), 110 °C, 12 h	100%	0%
MeOH (2.0 equiv), $Ni(cod)_2$ (10 mol%), dppf (10 mol%) toluene (1.0 M), 110 °C, 12 h	100%	0%
Control Experiments:		
MeOH (1.2 equiv), $Ni(cod)_2$ (10 mol%), SIPr (10 mol%) toluene (1.0 M), 80 °C, 12 h	0%	100%
MeOH (1.2 equiv), toluene (1.0 M), 80 °C, 12 h	100%	0%
MeOH (1.2 equiv), SIPr (10 mol%) toluene (1.0 M), 80 °C, 12 h	100%	0%
MeOH (1.2 equiv), $Ni(cod)_2$ (10 mol%) toluene (1.0 M), 80 °C, 12 h	100%	0%

[a] Yields were determined by ^1H NMR analysis using hexamethylbenzene as an internal standard.

4.7.2.5 Scope of Methodology

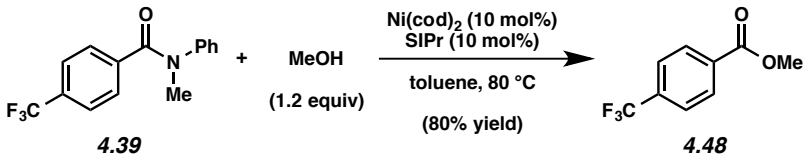


4.15 *4.8*

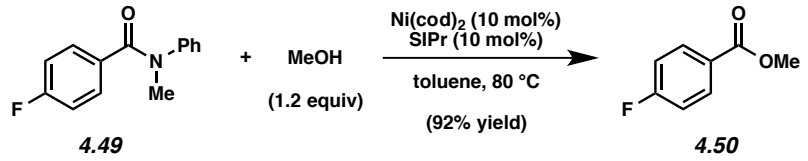
Representative Procedure (coupling of amide 4.15 and methanol is used as an example). Ester 4.8 (Table 4.2a, entry 1). A 1-dram vial containing amide **4.15** (100.0 mg, 0.47 mmol, 1.0 equiv) and a magnetic stir bar was charged with $Ni(cod)_2$ (13.0 mg, 0.047 mmol, 10 mol%) and SIPr (18.4 mg, 0.047 mmol, 10 mol%) in a glove box. Subsequently, toluene (0.47 mL, 1.0 M) and then methanol (23.0 μL, 0.56 mmol, 1.2 equiv) were added. The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and stirred at 80 °C for 12 h. After cooling to 23 °C, the mixture was diluted with hexanes (0.5 mL) and filtered over a plug of silica gel (10 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (20:1 Hexanes:EtOAc) to yield ester product **4.8** (88% yield, average of two experiments) as a clear oil. Ester **4.8**: R_f 0.41 (20:1 Hexanes:EtOAc). Spectral data match those previously reported.[32]

Any modifications of the conditions shown in the representative procedure above are specified in the following schemes, which depict all of the results shown in Table 4.2.

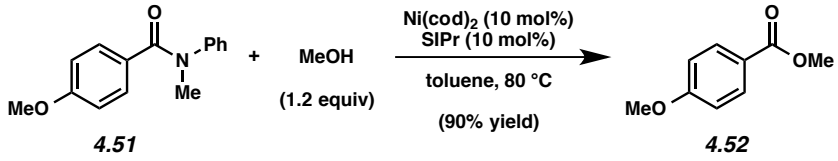
For each of the nickel-catalyzed reactions described herein, control experiments were performed concurrently where $Ni(cod)_2$ or both $Ni(cod)_2$ and SIPr were omitted from the reactions. In all cases, these control experiments led to the recovery of the amide substrates with no detectable conversion to the corresponding esters.



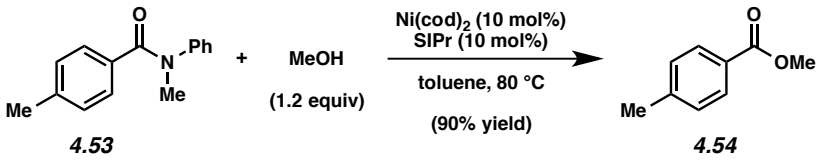
Ester 4.48 (Table 4.2a, entry 2). Purification by flash chromatography (10:1 Hexanes:EtOAc) generated ester **4.48** (80% yield, average of two experiments) as a clear oil. Ester **4.48**: R_f 0.59 (10:1 Hexanes:EtOAc). Spectral data match those previously reported.[33]



Ester 4.50 (Table 4.2a, entry 3). Purification by flash chromatography (20:1 Hexanes:EtOAc) generated ester **4.50** (92% yield, average of two experiments) as a clear oil. Ester **4.50**: R_f 0.37 (20:1 Hexanes:EtOAc). Spectral data match those previously reported.[34]

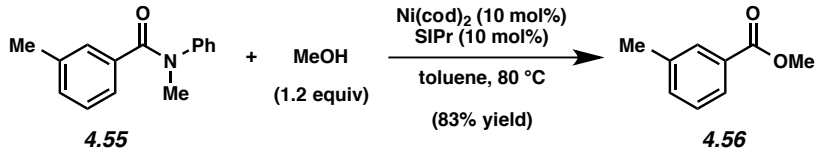


Ester 4.52 (Table 4.2a, entry 4). Purification by flash chromatography (5:1 Hexanes:EtOAc) generated ester **4.52** (90% yield, average of two experiments) as a white solid. Ester **4.52**: R_f 0.59 (10:1 Hexanes:EtOAc). Spectral data match those previously reported.[35]



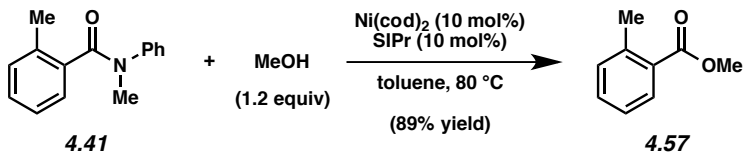
4.53 *4.54*

Ester 4.54 (Table 4.2a, entry 5). Purification by flash chromatography (15:1 Hexanes:EtOAc) generated ester **4.54** (90% yield, average of two experiments) as a clear oil. Ester **4.54**: R_f 0.60 (20:1 Hexanes:EtOAc). Spectral data match those previously reported.[35]



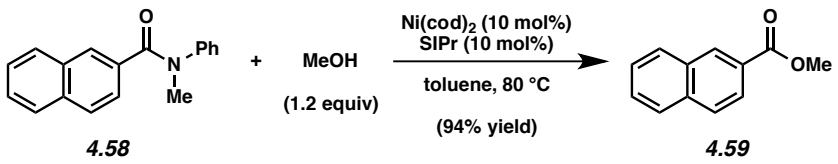
4.55 *4.56*

Ester 4.56 (Table 4.2a, entry 6). Purification by flash chromatography (20:1 Hexanes:Et_2O) generated ester **4.56** (83% yield, average of two experiments) as a clear oil. Ester **4.56**: R_f 0.52 (15:1 Hexanes:EtOAc). Spectral data match those previously reported.[36]

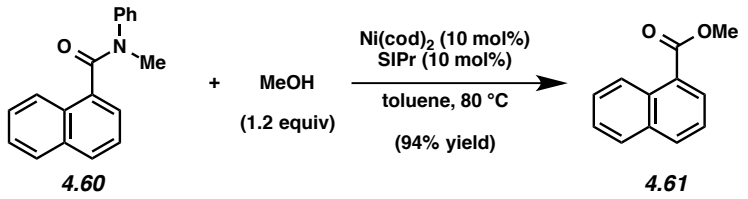


4.41 *4.57*

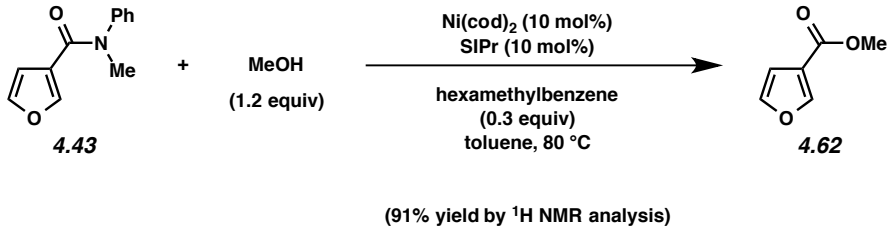
Ester 4.57 (Table 4.2a, entry 7). Purification by flash chromatography (15:1 Hexanes:EtOAc) generated ester **4.57** (89% yield, average of two experiments) as a clear oil. Ester **4.57**: R_f 0.69 (15:1 Hexanes:EtOAc). Spectral data match those previously reported.[34]



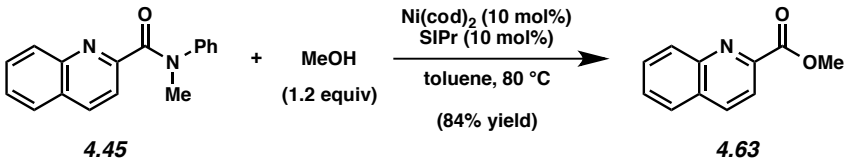
Ester 4.59 (Table 4.2a, entry 8). Purification by flash chromatography (20:1 Hexanes:EtOAc) generated ester **4.59** (94% yield, average of two experiments) as a white solid. Ester **4.59**: R_f 0.69 (10:1 Hexanes:EtOAc). Spectral data match those previously reported.[37]



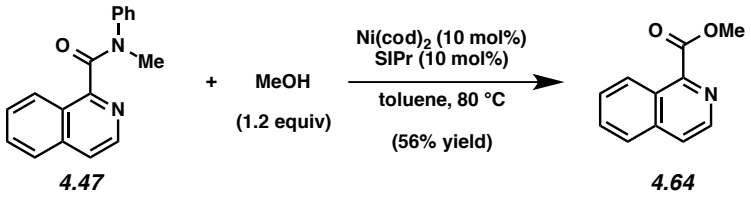
Ester 4.61 (Table 4.2a, entry 9). Purification by flash chromatography (15:1 Hexanes:EtOAc) generated ester **4.61** (94% yield, average of two experiments) as a clear oil. Ester **4.61**: R_f 0.57 (15:1 Hexanes:EtOAc). Spectral data match those previously reported.[38]



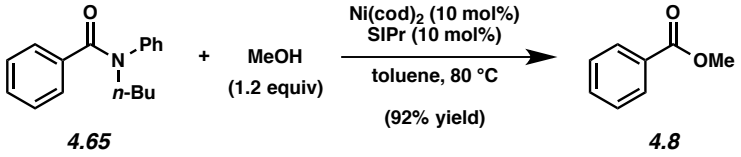
Ester 4.62 (Table 4.2a, entry 10). ^{1}H NMR: (300 MHz, $CDCl_3$): δ 8.02–8.01 (m, 1H), 7.43–7.42 (m, 1H), 6.76–6.74 (m, 1H), 3.85 (s, 3H). Ester **4.62**: Spectral data of the crude mixture of ester **4.62** match those previously reported.[39]



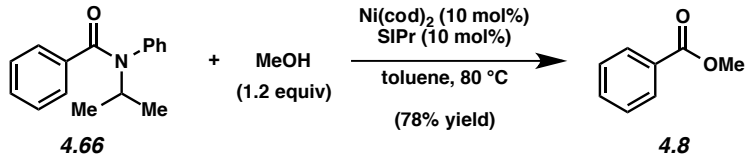
Ester 4.63 (Table 4.2a, entry 11). Purification by flash chromatography (1:1 Hexanes:EtOAc) generated ester **4.63** (84% yield, average of two experiments) as a white solid. Ester **4.63**: R_f 0.39 (1:1 Hexanes:EtOAc). Spectral data match those previously reported.[40]



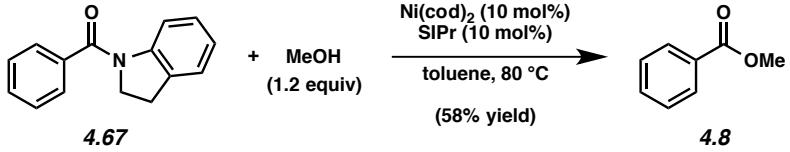
Ester 4.64 (Table 4.2a, entry 12). Purification by flash chromatography (1:1 Hexanes:EtOAc) generated ester **4.64** (56% yield, average of two experiments) as a clear oil. Ester **4.64**: R_f 0.43 (1:1 Hexanes:EtOAc). Spectral data match those previously reported.[41]



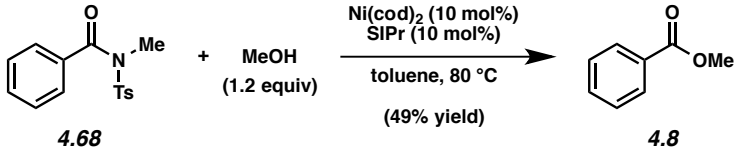
Ester 4.8 (Table 4.2a, entry 13). Purification by flash chromatography (10:1 Hexanes:Et_2O) generated ester **4.8** (92% yield, average of two experiments) as a clear oil. Ester **4.8**: R_f 0.44 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[32]



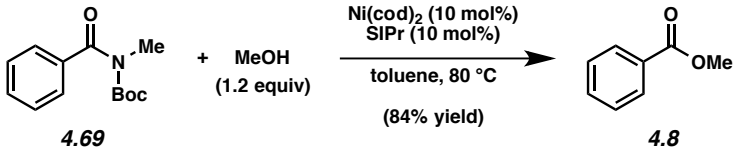
Ester 4.8 (Table 4.2a, entry 14). Purification by flash chromatography (10:1 Hexanes:Et_2O) generated ester **4.8** (78% yield, average of two experiments) as a clear oil. Ester **4.8**: R_f 0.44 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[32]



Ester 4.8 (Table 4.2a, entry 15). Purification by flash chromatography (10:1 Hexanes:Et_2O) generated ester **4.8** (58% yield, average of two experiments) as a clear oil. Ester **4.8**: R_f 0.44 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[32]

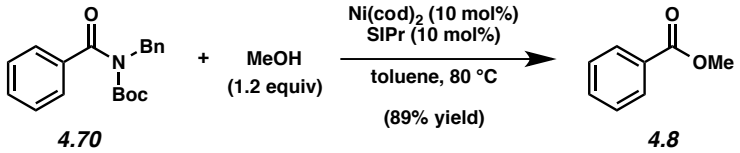


Ester 4.8 (Table 4.2a, entry 16). Purification by flash chromatography (10:1 Hexanes:Et_2O) generated ester **4.8** (49% yield, average of two experiments) as a clear oil. Ester **4.8**: R_f 0.44 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[32]



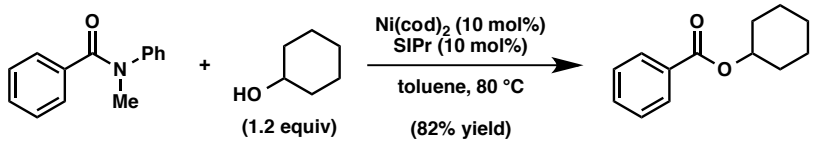
4.69 *4.8*

Ester 4.8 (Table 4.2a, entry 17). Purification by flash chromatography (10:1 Hexanes:Et_2O) generated ester **4.8** (84% yield, average of two experiments) as a clear oil. Ester **4.8**: R_f 0.44 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[32]



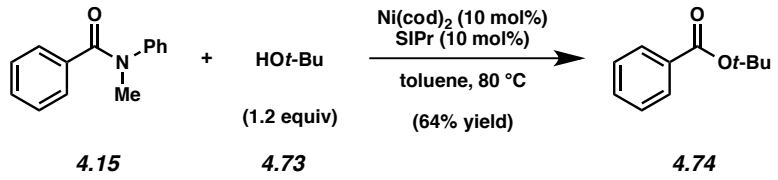
4.70 *4.8*

Ester 4.8 (Table 4.2a, entry 18). Purification by flash chromatography (10:1 Hexanes:Et_2O) generated ester **4.8** (89% yield, average of two experiments) as a clear oil. Ester **4.8**: R_f 0.44 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[32]

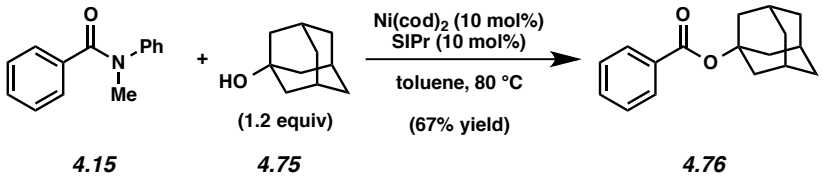


4.15 *4.71* *4.72*

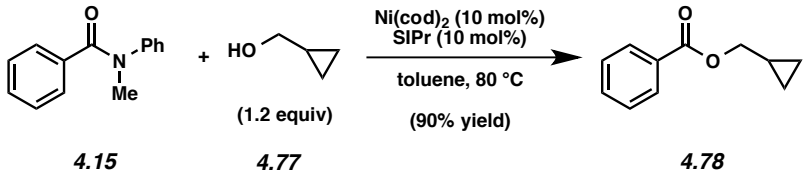
Ester 4.72 (Table 4.2b, entry 19). Purification by flash chromatography (100:1 Hexanes:EtOAc) generated ester **4.72** (82% yield, average of two experiments) as a clear oil. Ester **4.72**: R_f 0.59 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[42]



Ester 4.74 (Table 4.2b, entry 20). Purification by flash chromatography (100:1 Hexanes:EtOAc) generated ester **4.74** (64% yield, average of two experiments) as a clear oil. Ester **4.74**: R_f 0.71 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[43]

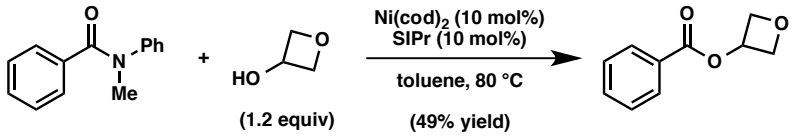


Ester 4.76 (Table 4.2b, entry 21). Purification by flash chromatography (100:1 Hexanes:EtOAc) generated ester **4.76** (67% yield, average of two experiments) as a clear oil. Ester **4.76**: R_f 0.76 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[44]

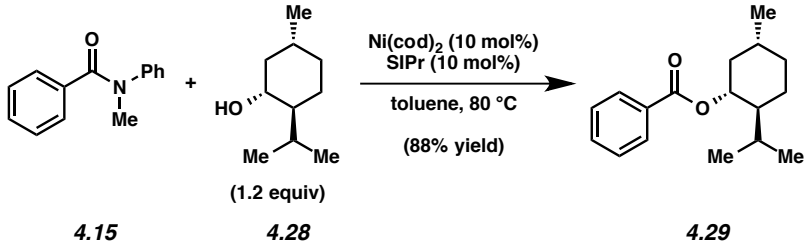


Ester 4.77 (Table 4.2b, entry 22). Purification by flash chromatography (20:1 Hexanes:Et_2O) generated ester **4.78** (90% yield, average of two experiments) as a clear oil. Ester **4.78**: R_f 0.88 (5:1 Hexanes:EtOAc); ^{1}H NMR: (600 MHz, $CDCl_3$): δ 8.09–8.05 (m, 2H), 7.57–7.54 (m, 1H), 7.46–7.42 (m, 2H), 4.16 (d, J = 7.2, 2H), 1.30–1.23 (m, 1H), 0.64–0.57 (m, 2H), 0.41–0.32 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 132.9, 130.7, 129.7, 128.4, 69.8, 10.0, 3.4; IR (film):

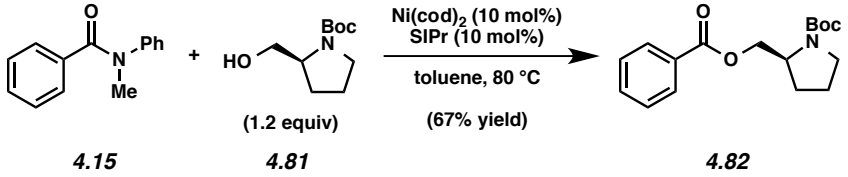
3079, 1451, 1712, 1272, 1114 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{11}H_{13}O2$, 177.09101; found 177.09057.



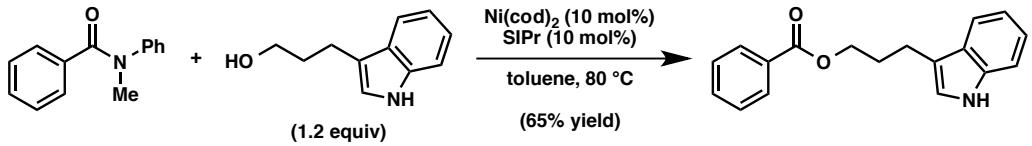
Ester 4.80 (Table 4.2b, entry 23). Purification by flash chromatography (10:1 Hexanes:Et_2O) generated ester **4.80** (49% yield, average of two experiments) as a clear oil. Ester **4.80**: R_f 0.41 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[45]



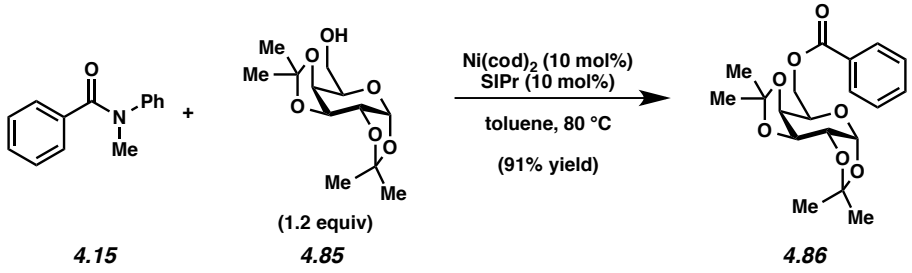
Ester 4.29 (Table 4.2b, entry 24). Purification by flash chromatography (100:1 Hexanes:EtOAc) generated ester **4.29** (88% yield, average of two experiments) as a white solid. Ester **4.29**: R_f 0.59 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[46]



Ester 4.82 (Table 4.2b, entry 25). Purification by flash chromatography (5:1 Hexanes:EtOAc) generated ester **4.82** (67% yield, average of two experiments) as a clear oil. Ester **4.82**: R_f 0.81 (5:1 Hexanes:EtOAc). Spectral data match those previously reported.[47]

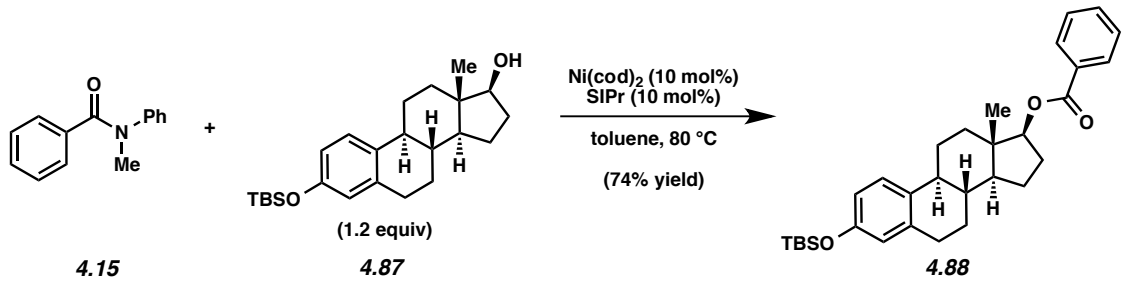


Ester 4.84 (Table 4.2b, entry 26). Purification by flash chromatography (100:1 Benzene:Acetone) generated ester **4.84** (65% yield, average of two experiments) as a clear oil. Ester **4.84**: R_f 0.26 (5:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 8.06–8.03 (m, 2H), 8.00–7.90 (br s, 1H), 7.64–7.60 (m, 1H), 7.56 (tt, *J* = 7.3, 1.4, 1H), 7.48–7.42 (m, 2H), 7.37 (dt, *J* = 8.1, 0.92, 1H), 7.20 (ddd, *J* = 11.6, 7.5, 1.2, 1H), 7.12 (ddd, *J* = 11.6, 7.5, 1.2, 1H), 7.04–7.02 (m, 1H), 4.40 (t, *J* = 6.40, 2H), 2.98–2.92 (m, 2H) 2.24–2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 136.5, 133.0, 130.6, 129.7, 128.5, 127.5, 122.2, 121.6, 119.4, 118.9. 115.5, 111.3, 64.7, 29.2, 21.8; IR (film): 3411, 2360, 1702, 1273, 1117 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{18}H_{18}NO_2$, 280.13321; found 280.13205.



Ester 4.86 (Table 4.2b, entry 27). Purification by flash chromatography (10:1 Hexanes:Et_2O) generated ester **4.86** (91% yield, average of two experiments) as a clear oil. Ester **4.86**: R_f 0.25 (5:1 Hexanes:Et_2O); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 8.07–8.03 (m, 2H), 7.58–7.53 (m, 1H), 7.46–7.41 (m, 2H), 5.57 (d, *J* = 4.9, 1H), 4.65 (dd, *J* = 7.9, 2.5, 1H), 4.53 (dd, *J* = 11.5, 4.9, 1H), 4.43 (dd, *J* = 11.5, 7.5, 1H), 4.35 (dd, *J* = 5.0, 2.5, 1H), 4.33 (dd, *J* = 7.9, 2.0, 1H), 4.19 (ddd, *J* = 7.5, 5.0, 2.0, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 166.6, 133.1, 130.2, 129.9, 128.5, 109.9, 109.0, 96.5, 71.3, 70.9, 70.7, 66.3, 64.0, 26.2, 26.1, 25.1, 24.7; IR (film): 2989, 1720, 1276 1108, 1070 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{19}H_{25}O_7$, 365.15948; found 365.15835; $[a]^{22.0}_D$ –70.4° (*c* = 1.000, CH_2Cl_2).

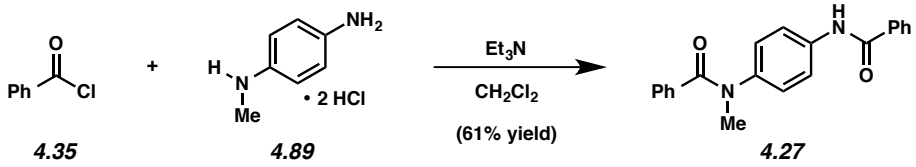


4.15 *4.87* *4.88*

Ester 4.88 (Table 4.2b, entry 28). Purification by flash chromatography (100:1 Hexanes:EtOAc) generated ester **4.88** (74% yield, average of two experiments) as a clear oil. Ester **4.88**: R_f 0.67 (5:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 8.09–8.03 (m, 2H), 7.59–7.53 (m, 1H), 7.49–7.41 (m, 2H), 7.15–7.10 (m, 1H), 6.64–6.59 (m, 1H), 6.58–6.54 (m, 1H), 5.13–4.90 (m, 1H), 2.90–2.76 (m, 2H), 2.48–2.17 (m, 3H), 2.02–1.63 (m, 5H), 1.60–1.28 (m, 6H), 0.99–0.86 (m, 11H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 166.3, 153.5, 153.5, 138.0, 137.9, 133.1, 133.1, 132.9, 131.0, 130.9, 129.7, 129.7, 128.5, 128.5, 126.3, 126.3, 120.1, 120.1, 117.3, 83.4, 82.8, 50.0, 49.7, 45.5, 44.0, 43.9, 43.5, 39.2, 38.7, 37.2, 32.3, 30.4, 29.9, 29.8, 28.2, 27.9, 27.4, 25.9, 24.6, 23.6, 18.3, 17.0, 12.5, -4.2; IR (film): 2928, 1717, 1496, 1274, 1256, 1116 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{31}H_{43}O_3Si$, 491.28866; found 491.29615; $[a]^{22.0}_D$ +56.2° (*c* = 1.000, CH_2Cl_2).

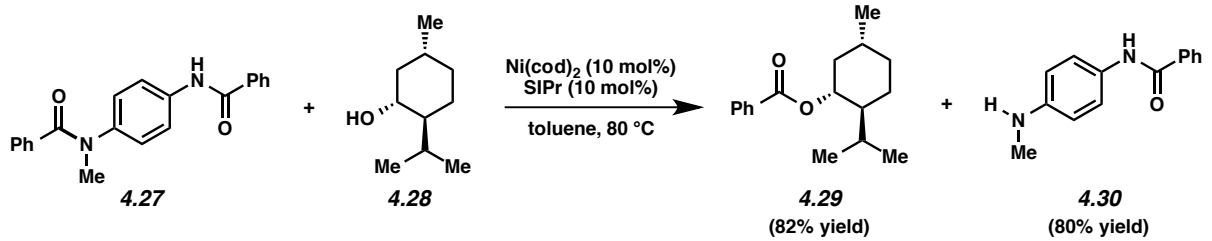
*Note: **4.88** was obtained as mixture of rotamers. These data represent empirically observed chemical shifts from the ^{13}C NMR spectrum.*

4.7.2.6 Selective Cleavage of Tertiary over Secondary Amide



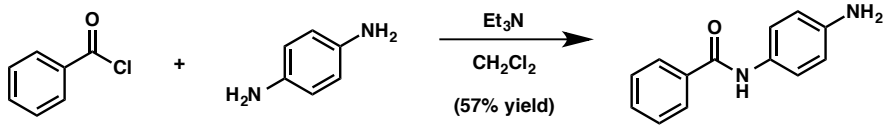
4.35 *4.89* *4.27*

Amide 4.27 (Figure 4.3a). A mixture of amine salt **4.89** (3.1 g, 16.0 mmol, 1.0 equiv), dichloromethane (96.0 mL, 0.5 M), and triethylamine (8.9 mL, 64.0 mmol, 8.9 mL) was stirred at 23 °C for 30 min. The reaction vessel was cooled to 0 °C and benzoyl chloride (5.6 mL, 48.0 mmol, 3.0 equiv) was added dropwise over 15 min with stirring. The resulting heterogeneous mixture was warmed to 23 °C over 30 min and stirred for 18 h. The reaction mixture was then diluted with EtOAc (50 mL) and then washed sequentially with 1.0 M HCl (50 mL) and brine (50 mL. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified via flash chromatography (1:1 Hexanes:EtOAc) to give amide **4.27** (3.2 g, 61% yield) as a white solid. Amide **4.27**: R_f 0.34 (1:1 Hexanes:EtOAc); ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.85–7.80 (m, 2H), 7.76 (br s, 1H), 7.58–7.44 (m, 5H), 7.34–7.30 (m, 2H), 7.25–7.22 (m, 1H), 7.21–7.15 (m, 2H), 7.05 (d, J = 8.9 Hz, 2H), 3.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 166.0, 141.0, 140.9, 136.7, 136.6, 136.0, 134.8, 132.1, 132.1, 129.8, 128.9, 128.8, 128.8, 128.0, 127.6, 127.5, 127.2, 127.2, 120.9, 120.8, 38.6; IR (film): 3299, 2971, 2245, 1737, 1625, 1602, 1578, 1509, 1372, 1316, 1292, 1244, 1101 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{19}N_2O_2$, 331.14465; found 331.14229.



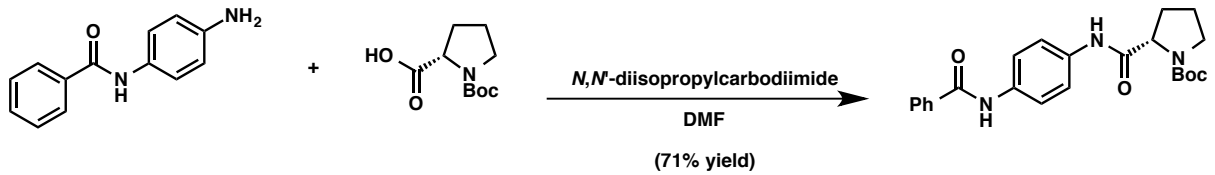
Ester 4.29 and Aminoamide 4.30 (Figure 4.3a). A 1-dram vial containing amide **4.27** (100.0 mg, 0.30 mmol, 1.0 equiv) and a magnetic stir bar was charged with $Ni(cod)_2$ (12.4 mg, 0.045 mmol, 15 mol%) and SIPr (35.2 mg, 0.045 mmol, 30 mol%) in a glove box. Subsequently, toluene (0.45 mL, 1.0 M) and then (–)-menthol **4.28** (56.0 mg, 0.36 mmol, 1.2 equiv) were added. The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and stirred at 80 °C for 12 h. After cooling to 23 ºC, the mixture was diluted with hexanes (0.5 mL) and filtered over a plug of silica gel (10 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (10:1 → 1:1 Hexanes:EtOAc) generated ester **4.29** (82% yield, average of two experiments) as a white solid and aminoamide **4.30** (80% yield, average of two experiments) as a white solid. Ester **4.29**: R_f 0.90 (1:1 Hexanes:EtOAc). Spectral data matched those previously reported.[46] Aminoamide **4.30**: R_f 0.30 (1:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, DMSO): δ 9.89 (s, 1H), 7.93 (d, J = 7.6, 2H), 7.58–7.40 (m, 5H), 6.52 (d, J = 8.4, 2H), 5.50 (br s, 1H), 2.66 (d, J = 4.9, 3H); ^{13}C NMR (125 MHz, DMSO): δ 164.6, 146.7. 135.3, 131.1, 128.3, 128.0, 127.4, 122.2, 111.3, 30.0; IR (film): 3268, 1639, 1535, 1517, 1468, 1402, 1310, 1246, 1177, 1026 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{14}H_{15}N_2O$, 227.11844; found 227.11649.

4.7.2.7 Selective Cleavage of Aryl Amide Over Alkyl Amide



4.35 *4.90* *4.91*

Amide 4.91 (Figure 4.3b). To a solution of amine **4.90** (7.7g, 71.1 mmol, 2.0 equiv) and triethylamine (6.2 mL, 44.5 mmol, 1.25 equiv) in dichloromethane (356.0 mL, 0.1 M) was added benzoyl chloride **4.35** (5.0 g, 35.6 mL, 1.0 equiv) dropwise over 15 min. After stirring at 23 °C for 12 h, the reaction mixture was then diluted with deionized water (200 mL) and dichloromethane (200 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting red solid was purified by flash chromatography (1:1 Hexanes: EtOAc → 100% EtOAc) to give a white solid (4.3 g, 57% yield). Amide **4.91**: R_f 0.31 (1:1 Hexanes:EtOAc). Spectral data matched those previously reported.[48]

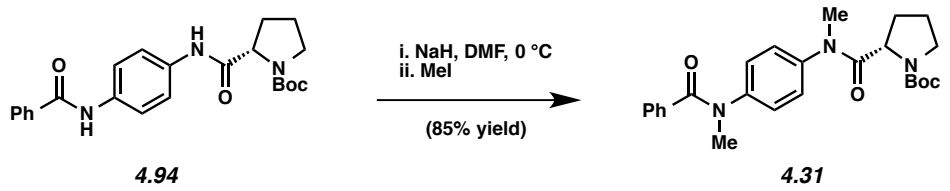


4.91 *4.92* *4.93*

Amide 4.93 (Figure 4.3b). To a mixture of amide **4.91** (1.5 g, 7.1 mmol, 1.0 equiv) and carboxylic acid **4.92** (1.52 g, 7.1 mmol, 1.0 equiv) in dry DMF (2.7 mL, 2.6 M) at 0 °C was added *N*,*N*'-diisopropylcarbodiimide (1.3 mL, 8.5 mmol, 1.2 equiv) dropwise over 5 min. The reaction was then stirred at 0 °C for 10 min and 23 °C for 12 h. The crude reaction mixture was poured into 1:1 H_2O/MeOH solution (1 L). The resulting solid was collected to afford amide

4.93 (2.1 g, 71% yield) as a white solid. Amide **4.93**: R_f 0.69 (3:1 Acetone:Benzene); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 9.53 (m, 1H), 7.90–7.84 (m, 2H), 7.76 (br s, 1H), 7.65–7.52 (m, 5H), 7.52–7.46 (m, 2H), 4.59–3.18 (m, 3H), 2.68–1.74 (m, 4H), 1.50 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 165.7, 156.7, 135.4, 135.1, 133.8, 131.9, 128.9, 127.2, 121.2, 120.3, 81.1, 60.6, 47.4, 28.6, 27.4, 24.8; IR (film): 3295, 1668, 1515, 1405, 1308, 1162 cm^{-1}; HRMS-ESI (*m/z*) [M-H] calcd for $C_{23}H_{26}O_4N_3$, 408.19178; found 408.19340; $[a]^{22.0}_D$ –50.0° (*c* = 0.100, $CHCl_3$).

*Note: **4.93** was obtained as mixture of rotamers. These data represent empirically observed chemical shifts and coupling constants from the ^{1}H NMR and ^{13}C NMR spectra.*

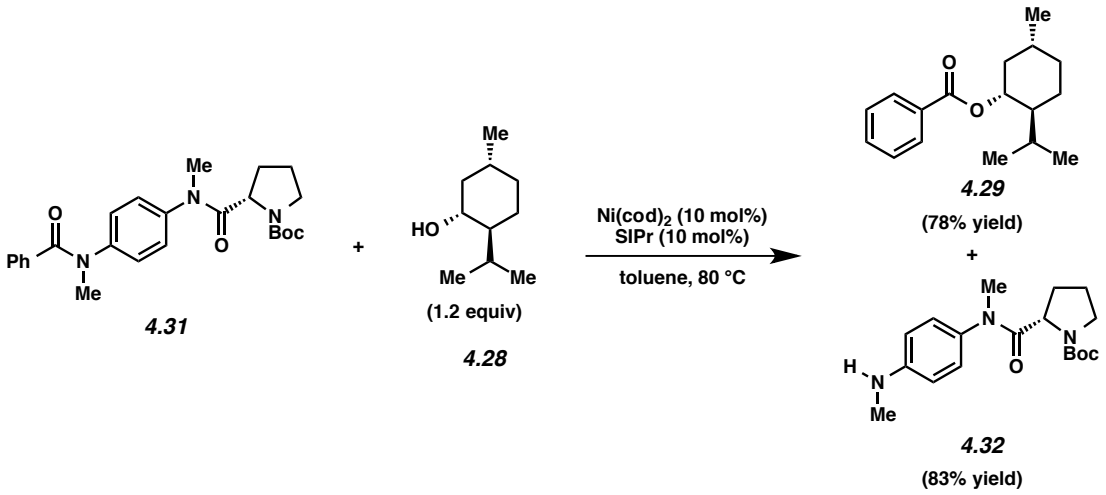


4.94 ***4.31***

Amide 4.31 (Figure 4.3b). To a solution of amide **4.94** (300.0 mg, 0.73 mmol) in dry DMF (12.0 mL, 0.06 M) at 0 °C, was added NaH (60% in oil dispersion, 62.0 mg, 1.5 mmol, 2.1 equiv). The mixture was stirred at 0 °C for 1 h and then MeI (91.0 mL, 1.5 mmol, 2.0 equiv) was added. The solution was stirred at 0 °C for an additional hour and then warmed to 23 °C over 30 min. After 14 h, the reaction was quenched with a solution of saturated aqueous NH_4Cl (5 mL) and diluted with deionized water (50 mL). The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic layers were washed succesively with water (4 x 50 mL) and brine (50 mL), and then dried over $MgSO_4$. After concentration under reduced pressure, the crude residue was purified by flash chromatography (2:1 → 1:1 Hexanes/EtOAc) to provide amide **4.31** (272.0 mg, 85% yield) as a clear oil. Amide **4.31**: R_f 0.33 (1:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 7.91–7.37 (m, 1H), 7.33–7.24 (m, 2H), 7.24–7.14 (m, 6H), 4.25–3.98 (m, 1H), 3.59–

3.48 (m, 3H), 3.52 (app d, J = 8.6, 1H), 3.48–3.33 (m, 1H), 3.29–3.17 (m, 3H), 2.02–1.59 (m, 4H), 1.45 (app d, J = 3.2, 9H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 172.5, 170.8, 154.5, 153.9, 144.6, 144.4, 141.7, 141.4, 135.9, 135.8, 130.1, 129.9, 128.8, 128.8, 128.5, 128.2, 127.9, 127.9, 127.2, 79.9, 79.5, 57.2, 56.9, 47.3, 47.2, 38.3, 37.8, 37.7, 31.6, 30.3, 28.8, 28.7, 24.4, 23.6, 1.2; IR (film): 2974, 2876, 1643, 1509, 1364, 1119 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{25}H_{32}O_4N_3$, 438.23873; found 438.23824; $[a]^{22.0}_D$ +76.0° (*c* = 0.100, $CHCl_3$).

*Note: **4.31** was obtained as mixture of rotamers. These data represent empirically observed chemical shifts and coupling constants from the ^{1}H NMR and ^{13}C NMR spectra.*

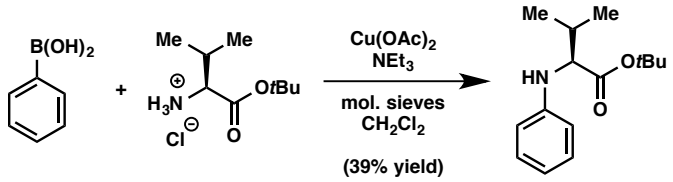


Ester 4.29 and Amine 4.32 (Figure 4.3b). A 1-dram vial containing amide **4.31** (100.0 mg, 0.23 mmol, 1.0 equiv) and a magnetic stir bar was charged with $Ni(cod)_2$ (6.3 mg, 0.023 mmol, 10 mol%) and SIPr (8.9 mg, 0.023 mmol, 10 mol%) in a glove box. Subsequently, toluene (0.23 mL, 1.0 M) and then (–)-menthol **4.28** (42.9 mg, 0.27 mmol, 1.2 equiv) were added. The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and stirred at 80 °C for 12 h. After cooling to 23 °C, the mixture was diluted with hexanes (0.5 mL) and filtered over a plug of silica gel (10 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the

crude residue was purified by flash chromatography (100:1 to 1:1 Hexanes:EtOAc) provided ester **4.29** (78% yield, average of two experiments) as a white solid and amine **4.32** (83% yield, average of two experiments) as a clear oil. Ester **4.29**: R_f 0.90 (1:1 Hexanes:EtOAc). Spectral data matched those previously reported.[46] Amine **4.32**: R_f 0.18 (1:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 7.16 (d, *J* = 7.5, 1H), 7.03 (d, *J* = 8.5, 1H), 6.63 (t, *J* = 8.5, 2H), 4.60–3.25 (m, 4H), 3.22 (s, 3H), 2.86 (app d, *J* = 7.3, 3H), 2.03–1.59 (m, 4H), 1.47 (app d, *J* = 14.4, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.9, 128.7, 79.6, 79.2, 57.3, 57.0, 47.4, 47.2, 38.0, 31.8, 30.9, 30.6, 28.8, 28.7, 24.4, 23.7; IR (film): 3368, 2976, 1649, 1524, 1390, 1160, 1119 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{18}H_{28}N_3O_3$, 334.21252; found 334.21195; $[a]^{22.0}_D$ +66.00° (*c* = 0.100, $CHCl_3$).

*Note: **4.32** was obtained as mixture of rotamers. These data represent empirically observed chemical shifts and coupling constants from the ^{1}H NMR and ^{13}C NMR spectra.*

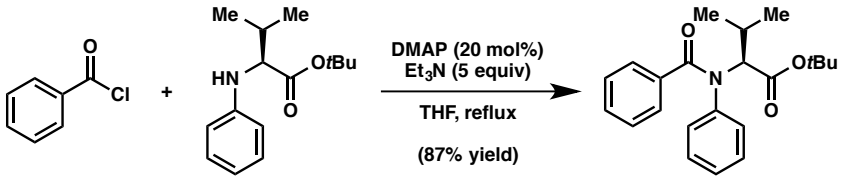
4.7.2.8 Selective Cleavage of Aryl Amide in the Presence of an Ester



4.95 ***4.96*** ***4.34***

Amine 4.34 (Figure 4.3c). A round bottom flask was charged with 4Å molecular sieves (14.0 g, 2.0 equiv), ester **4.96** (7.0 g, 33.4 mmol, 1.0 equiv), boronic acid **4.95** (8.1 g, 66.8 mmol, 2.0 equiv), and $Cu(OAc)_2$ (6.7 g, 36.7 mmol, 1.1 equiv). The flask was evacuated by vacuum, backfilled with O_2, and then held under an O_2 atmosphere by balloon. Dichloromethane (333.0 mL, 0.1 M) and triethylamine (9.3 mL, 66.8 mmol, 2.0 equiv) were added sequentially, and the

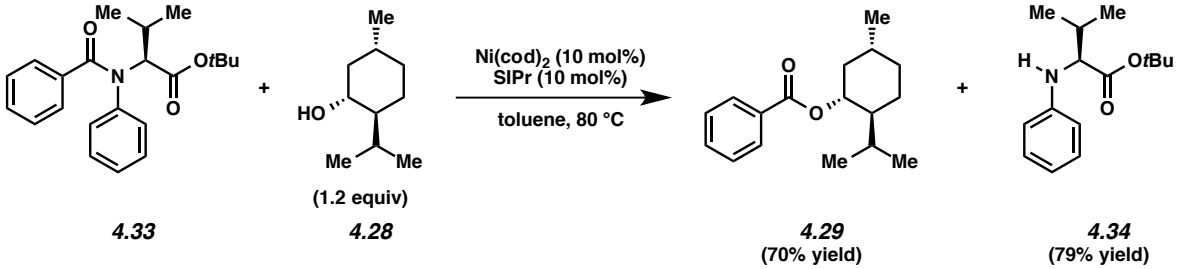
reaction mixture was stirred at 23 °C for 14 h. The reaction mixture was then quenched with a solution of NH_3 in MeOH (6N, 15 mL). After removing the volatiles under reduced pressure, the crude mixture was purified via flash chromatography (10:1 Hexanes:EtOAc) to give amine **4.34** as a white solid (3.2 g, 39% yield). Amide **4.34**: R_f 0.65 (5:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 7.18–7.13 (m, 2H), 6.71 (tt, *J* = 7.3, 1.0, 1H), 6.66–6.61 (m, 2H), 4.15 (br s, 1H), 3.75 (d, *J* = 5.6, 1H), 2.15–2.05 (m, 1H), 1.42 (s, 9H), 1.03 (dd, *J* = 11.3, 7.0, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 147.7, 129.4, 118.1, 113.8, 81.6, 63.0, 31.6, 28.2, 19.1, 18.8; IR (film): 3383, 2970, 1708, 1605, 1368, 1156 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{15}H_{24}N_1O_2$, 250.18016; found 250.17955; $[a]^{22.0}_D$ –26.00° (*c* = 0.100, $CHCl_3$)



4.35 *4.34* *4.33*

Amide 4.33 (Figure 4.3c). To a solution of amine **4.34** (887 mg, 3.55 mmol) in THF (35.5 mL, 0.1 M) was added DMAP (86.7 mg, 0.71 mmol, 0.2 equiv) and triethylamine (2.46 mL, 17.75 mmol, 5 equiv). Then, benzoyl chloride (2.05 mL, 17.75 mmol, 5 equiv) was added dropwise into the flask over 5 min and then refluxed. After 18 h, the reaction mixture was cooled to 23 °C, quenched with 1.0 M HCl (20 mL), extracted with EtOAc (3 X 50 mL), and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the crude residue was purified via flash chromatography (30:1 Hexanes:EtOAc) to give amide **4.33** as a yellow solid (1.09 g, 87% yield). Amide **4.33**: R_f 0.43 (5:1 Hexanes:EtOAc); ^{1}H NMR: (500 MHz, $CDCl_3$): δ 7.26–7.25 (m, 2H), 7.21–7.10 (m, 8H), 4.56 (d, *J* = 9.7, 1H), 2.59–2.56 (m, 1H), 1.43 (s, 9H), 1.09 (d, *J* = 6.9, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 169.7, 143.2, 136.4, 129.6, 128.8, 128.7, 128.6, 127.8,

126.9, 81.6, 68.9, 28.8, 28.2, 21.4, 20.3; IR (film): 2973, 1734, 1649, 1493, 1368, 1153 cm^{-1}; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{15}H_{24}N_1O_2$, 354.20692; found 354.20591; $[a]^{22.0}_D$ –76.00° (*c* = 0.100, $CHCl_3$).

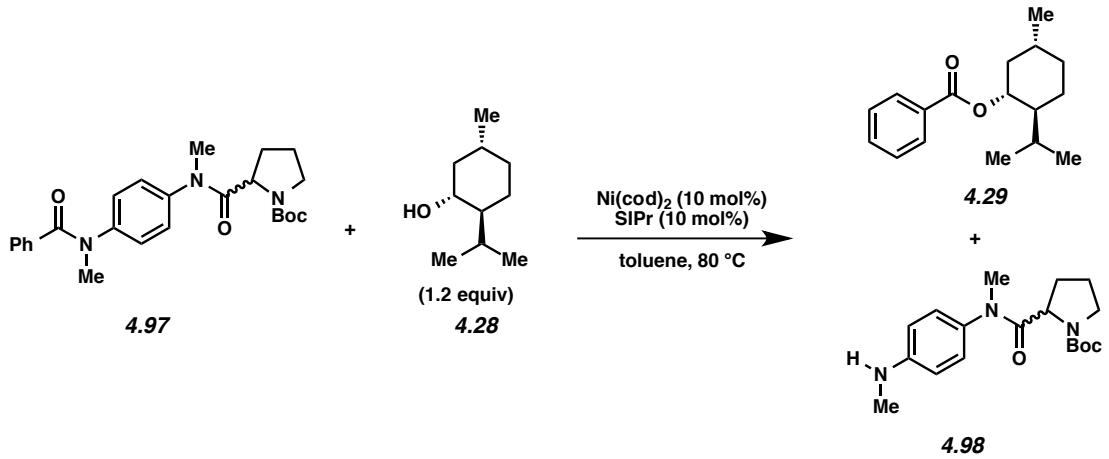


4.33 ***4.28*** ***4.29*** (70% yield) ***4.34*** (79% yield)

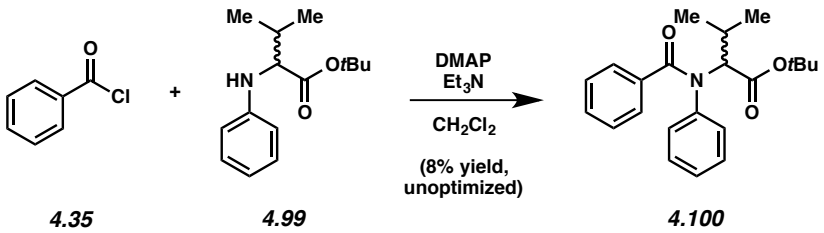
Ester 4.29 and Amide 4.34 (Figure 4.3c). A 1-dram vial containing amide **4.33** (100.0 mg, 0.28 mmol, 1.0 equiv) and a magnetic stir bar was charged with $Ni(cod)_2$ (7.8 mg, 0.028 mmol, 10 mol%) and SIPr (11.1 mg, 0.028 mmol, 10 mol%) in a glove box. Subsequently, toluene (0.28 mL, 1.0 M) and then (–)-menthol **4.28** (53.1 mg, 0.34 mmol, 1.2 equiv) were added. The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and stirred at 80 °C for 12 h. After cooling to 23 °C, the mixture was diluted with hexanes (0.5 mL) and filtered over a plug of silica gel (10 mL of EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (100:1 Hexanes:EtOAc) generated ester **4.29** (70% yield) as a white solid and amide **4.34** (79% yield) as a clear oil. Ester **4.29**: R_f 0.90 (1:1 Hexanes:EtOAc). Spectral data matched those previously reported.[46] Amide **4.34**: Spectral data of amide **4.34** matched the characterization data shown in page 303.

4.7.3 Verification of Enantiopurity

4.7.3.1 Racemic Compound Syntheses



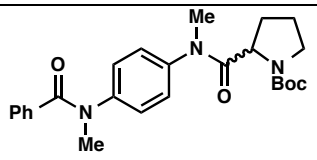
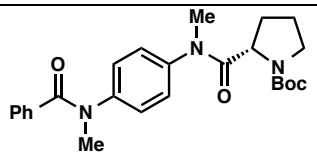
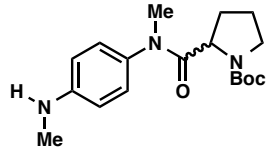
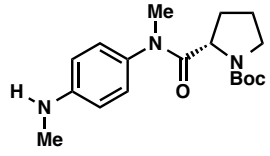
***rac*-Amine 4.98 (Figure 4.3b). 4.98** was prepared using the procedure described earlier to synthesize **4.32** (see pages 300–301), but using the racemic Boc-proline **4.92**. A 1-dram vial containing **4.97** (40.0 mg, 0.09 mmol, 1.0 equiv) and a magnetic stir bar was charged with $Ni(cod)_2$ (3.1 mg, 0.011 mmol, 12.5 mol%) and SIPr (4.5 mg, 0.011 mmol, 12.5 mol%) in a glove box. Subsequently, toluene (0.11 mL, 0.8 M) and then (–)-menthol **4.28** (21.4 mg, 0.24 mmol, 1.5 equiv) were added. The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and stirred at 80 °C for 12 h. After cooling to 23 °C, the mixture was diluted with hexanes (0.5 mL) and filtered over a plug of silica gel (10 mL of EtOAc eluent). The volatiles were removed under reduced pressure. The crude residue was purified by preparative thin-layer chromatography (1:1 Hexanes:EtOAc) to give amine **4.98** (13.2 mg, 43% yield) as a clear oil. Spectral data matched those reported in the experimental procedure on page 302.



4.35 *4.99* *4.100*

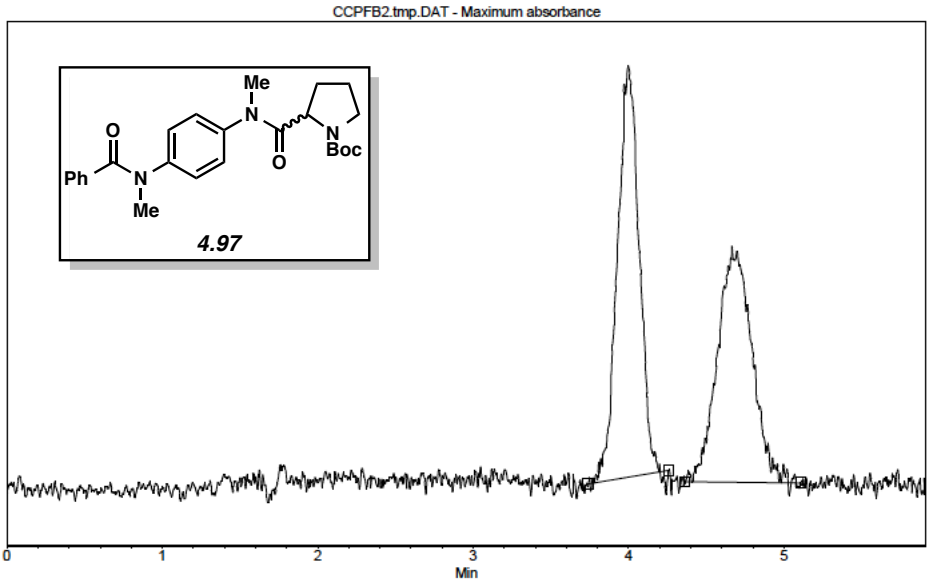
***rac*-Amide 4.100 (Figure 4.3b). 4.99** was prepared using the procedure described earlier to synthesize **4.34** (see page 303), but using racemic ester **4.34**. A 1-dram vial containing a magnetic stir bar, aniline **4.99** (20.0 mg, 0.080 mmol, 1.05 equiv), and CH_2Cl_2 (0.8 mL) was added Et_3N (14 mL, 0.10 mmol, 1.3 equiv) and benzoyl chloride (8.9 mL, 0.076 mmol). The mixture was stirred at 23 °C for 2 d and then diluted in water (25 mL). After extraction with EtOAc (4 x 25 mL), the combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude residue was purified by preparative thin-layer chromatography (5:1 EtOAc/Hexanes) to give **4.100** (2.2 mg, 8% yield, unoptimized) as a clear oil.

4.7.3.2 Chiral SFC Assays

Compound	Method Column /Temp	Polar Cosolvent	Method Flow Rate	Rentention Times	Enantiomeric Ratio (er)
 ***4.97***	Daicel ChiralPak OJ-H / 35°C	7% MeOH	2.00 mL/min	4.00/4.67 min	52:48
 ***4.31***	Daicel ChiralPak OJ-H / 35°C	7% MeOH	2.00 mL/min	4.53/5.27 min	**96:4**
 ***4.98***	Daicel ChiralPak OJ-H / 35°C	15 % *i*-PrOH	1.00 mL/min	7.96/9.09	52:48
 ***4.32***	Daicel ChiralPak OJ-H / 35°C	15 % *i*-PrOH	1.00 mL/min	7.60/8.78	**96:4**

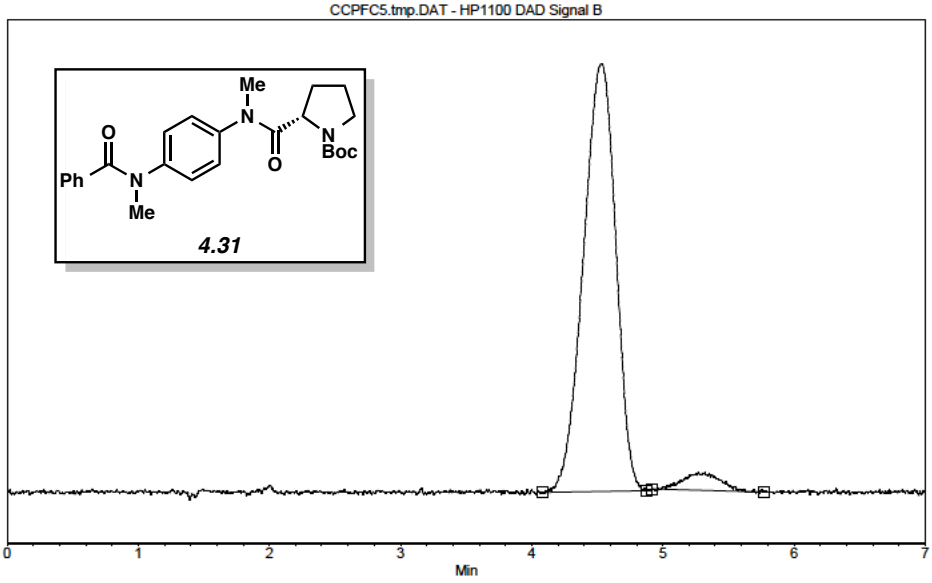
No stereochemical erosion occurs during the nickel-catalyzed esterification.

Date:12/16/2014
Sample:nfn-6-199b-bbb1
Method Name:NOT DEFINED
Run Info:N.A.



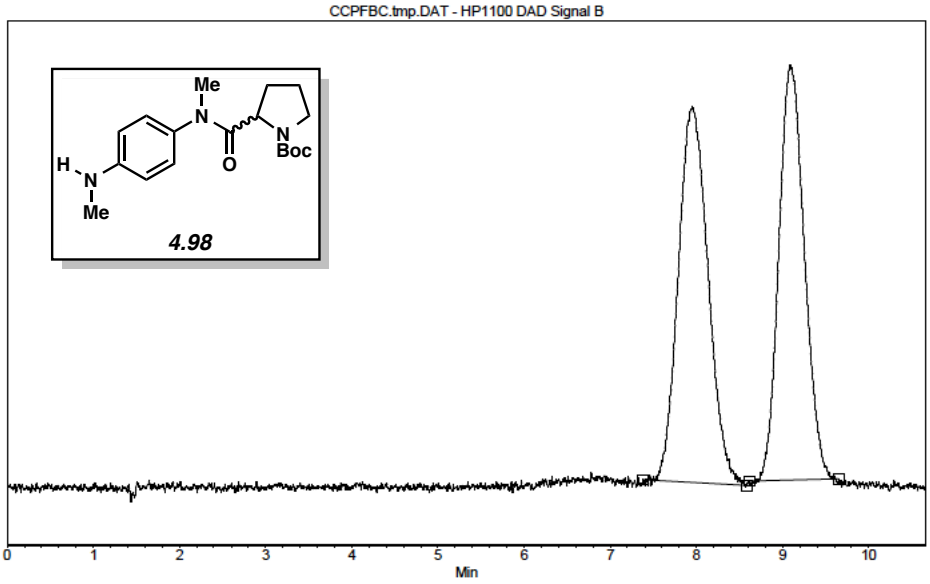
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	3.74	4.00	4.26	0.00	52.37	119.3	19.2	52.367
2	UNKNOWN	4.36	4.67	5.11	0.00	47.63	68.6	17.5	47.633
Total						100.00	187.9	36.7	100.000

Date:12/16/2014
Sample:nfn-6-107b1
Method Name:OJiso7%MeOH
Run Info:N.A.



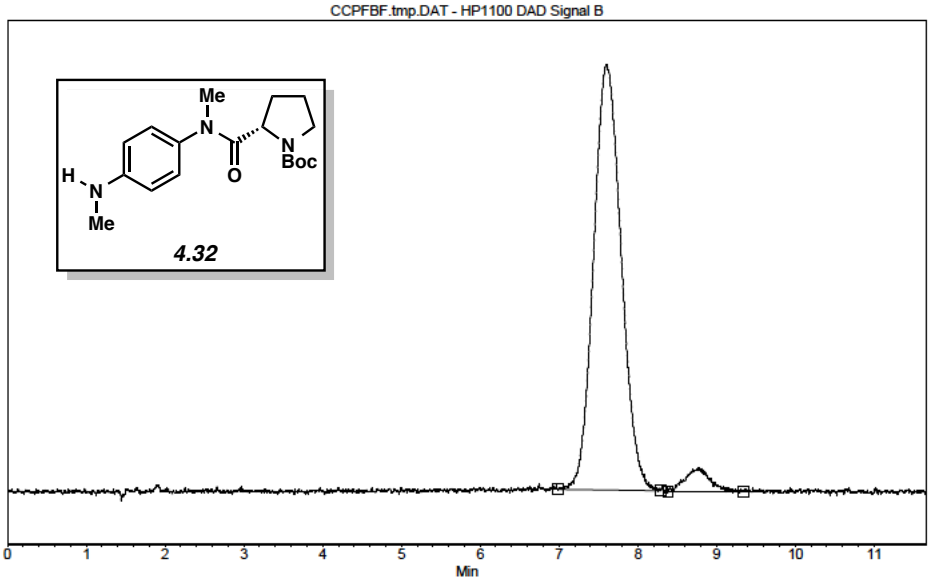
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	4.08	4.53	4.87	0.00	95.57	311.2	89.1	95.569
2	UNKNOWN	4.92	5.27	5.77	0.00	4.43	13.3	4.1	4.431
Total						100.00	324.5	93.2	100.000

Date:12/16/2014
Sample:nfn-6-197b-71
Method Name:OJiso15%iPrOH-A
Run Info:N.A.

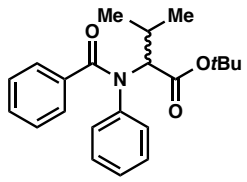
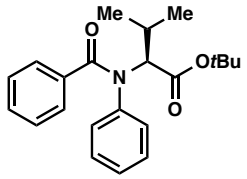
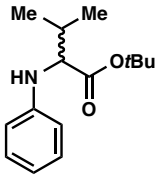
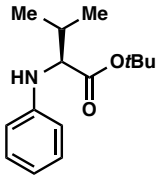


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	7.38	7.96	8.59	0.00	51.46	112.9	45.2	51.463
2	UNKNOWN	8.61	9.09	9.65	0.00	48.54	124.9	42.7	48.537
Total						100.00	237.8	87.9	100.000

Date:12/16/2014
Sample:nfn-6-197b-61
Method Name:OJiso15%iPrOH-A
Run Info:N.A.

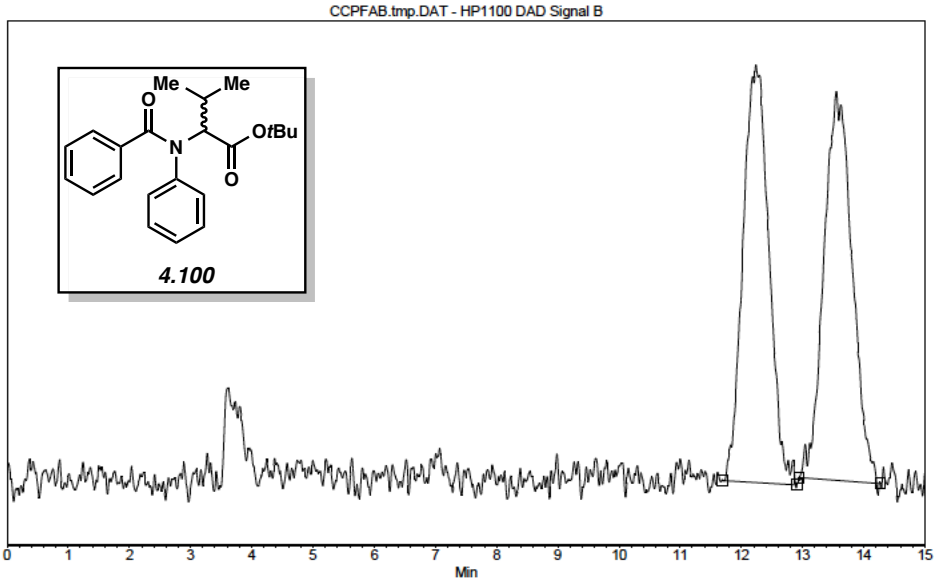


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.99	7.60	8.29	0.00	95.51	208.2	84.5	95.512
2	UNKNOWN	8.39	8.78	9.35	0.00	4.49	11.3	4.0	4.488
Total						100.00	219.5	88.5	100.000

Compound	Method Column /Temp	Polar Cosolvent	Method Flow Rate	Rentention Times	Enantiomeric Ratio (er)
 ***4.100***	Daicel ChiralPak OJ-H / 35°C	0.5 % MeOH	0.5 mL/min	12.24/13.55 min	50:50
 ***4.33***	Daicel ChiralPak OJ-H / 35°C	0.5 % MeOH	0.5 mL/min	12.23 min	**100:0**
 ***4.99***	Daicel ChiralPak OJ-H / 35°C	5 % *i*-PrOH	2.00 mL/min	4.73/4.95 min	50:50
 ***4.34***	Daicel ChiralPak OJ-H / 35°C	5 % *i*-PrOH	2.00 mL/min	4.77/4.99 min	**98:2**

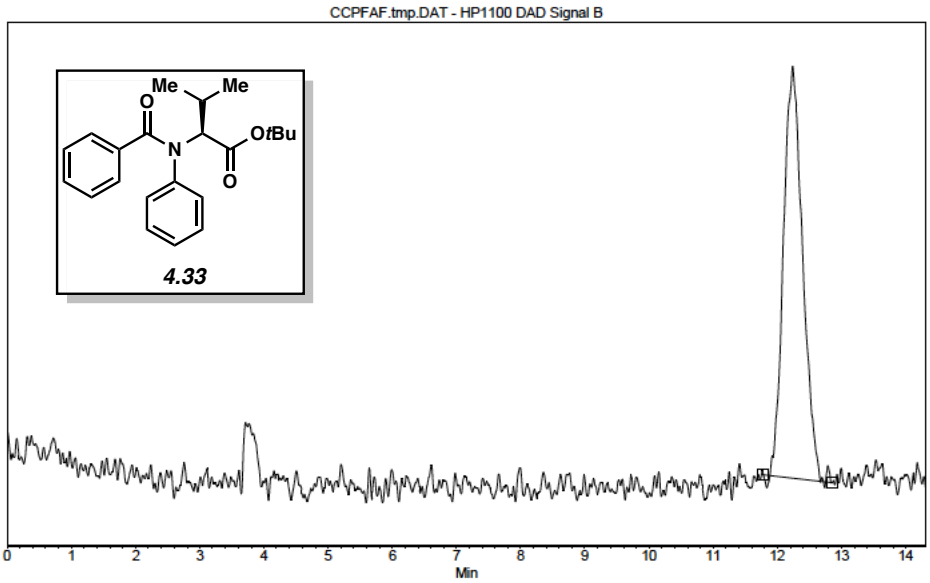
Minimal stereochemical erosion during the nickel-catalyzed esterification was observed.

Date:12/16/2014
Sample:nfn-6-201f-bb1
Method Name:OJiso.5iPrOH
Run Info:N.A.



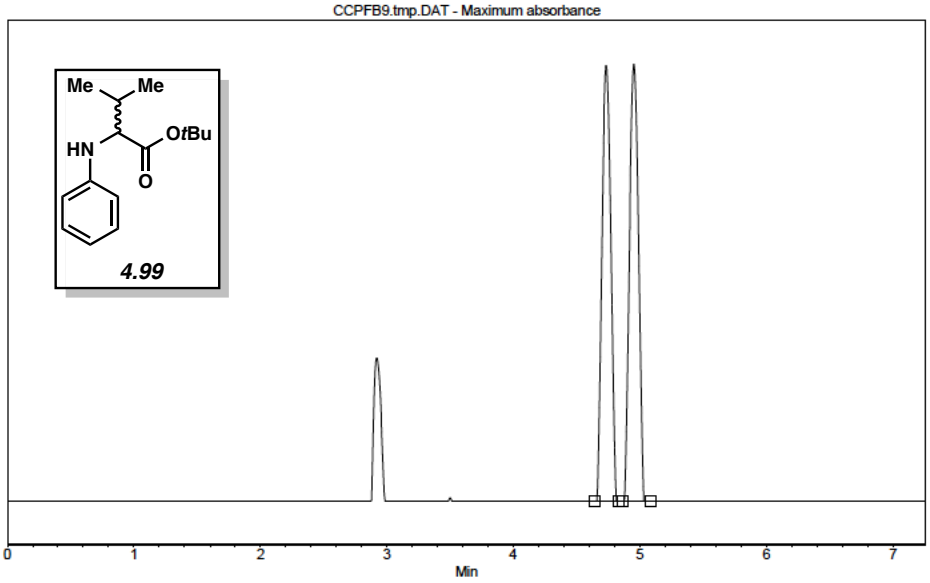
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.70	12.24	12.91	0.00	49.67	91.0	44.6	49.672
2	UNKNOWN	12.94	13.55	14.28	0.00	50.33	84.6	45.2	50.328
Total						100.00	175.6	89.8	100.000

Date:12/16/2014
Sample:nfn-6-171a-k0
Method Name:OJisopoint5flow1-3
Run Info:N.A.



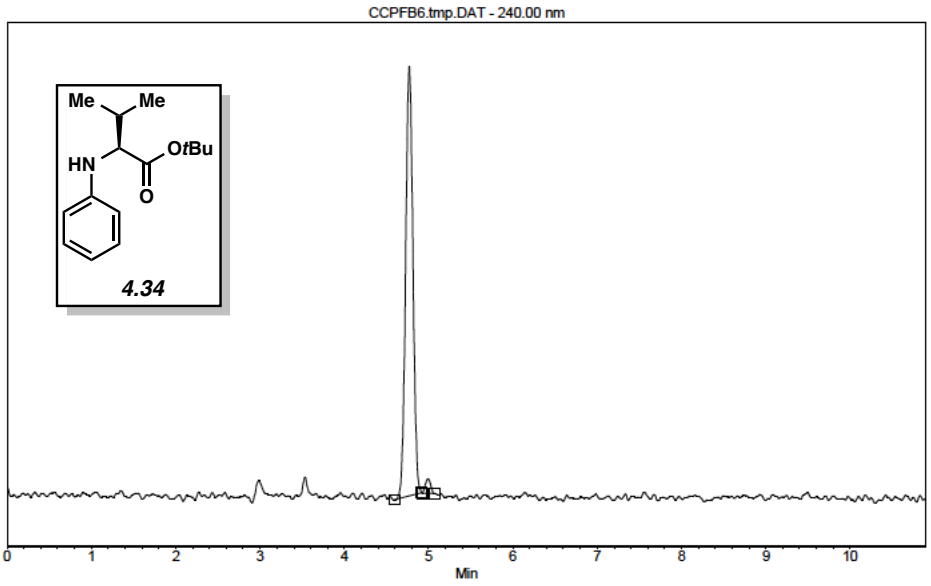
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.78	12.23	12.85	0.00	100.00	100.4	34.7	100.000
Total						100.00	100.4	34.7	100.000

Date:12/16/2014
Sample:NFN-6-195bb1
Method Name:NOT DEFINED
Run Info:N.A.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	4.64	4.73	4.83	0.00	49.64	137.3	11.2	49.644
2	UNKNOWN	4.87	4.95	5.09	0.00	50.36	137.6	11.3	50.356
Total						100.00	274.9	22.5	100.000

Date:12/16/2014
Sample:nfn-6-195rrr1
Method Name:NOT DEFINED
Run Info:N.A.



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	4.59	4.77	4.92	0.00	97.64	509.0	50.9	97.643
2	UNKNOWN	4.93	4.99	5.07	0.00	2.36	17.4	1.2	2.357
Total						100.00	526.4	52.2	100.000

4.7.4 Computational Methods

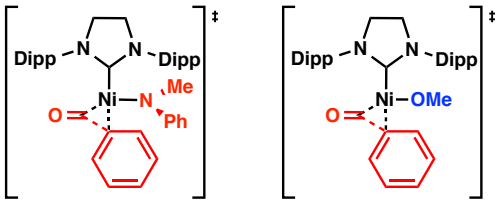
All the calculations were carried out with the Gaussian 09 package. Geometry optimizations were performed with B3LYP.[49] The LANL2DZ basis set[50] with ECP was used for Ni, and the 6-31G(d) basis set[51] was used for other atoms. Frequency analysis was conducted at the same level of theory to verify the stationary points to be minima or saddle points. The single-point energies and solvent effects in toluene were computed with M06[52]/SDD[53]-6-311+G(d,p) basis sets by using SMD solvation model.[54] Computed structures are illustrated using CYLView.[55]

4.7.4.1 Complete Reference of Gaussian 09

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J.

J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Rev. D.01*; Gaussian, Inc., Wallingford, CT, **2010**.

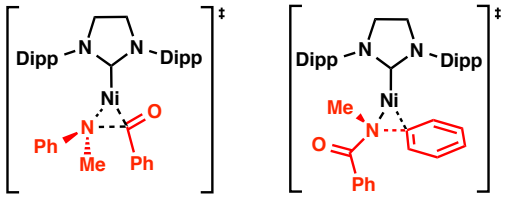
4.7.4.2 Transition State Structures for Decarbonylation Pathway



4.101
28.6 kcal/mol

4.102
24.1 kcal/mol

4.7.4.3 Comparison of Acyl C–N and Aryl C–N Bond Activation Pathway



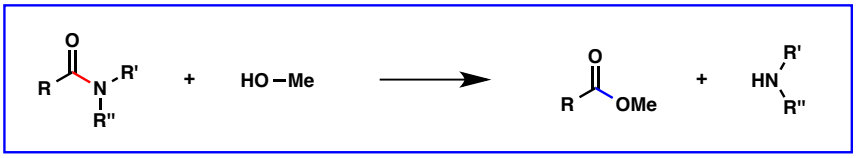
4.19
26.0 kcal/mol

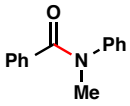
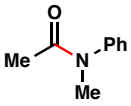
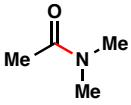
4.103
35.3 kcal/mol

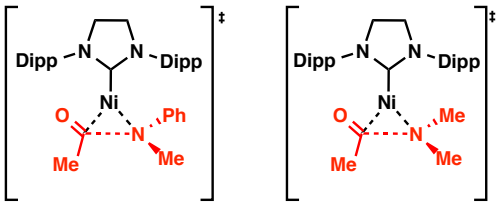
*Calculations were performed on the competing aryl C–N bond cleavage transition state. Transition state **4.103** was found to be 9.3 kcal/mol higher compared to the barrier for acyl C–N bond cleavage, via **4.19**.*

4.7.4.4 Analysis of Amides Derived from Alkyl Carboxylic Acids

Table 4.6. Comparison of Aryl vs. Alkyl Amide Substrates.



Entry	*Amide*		*Calculated ΔG (kcal/mol)*	*Calculated oxidative addition barrier with Ni /SIPr (kcal/mol)*
1		*4.15*	–6.8	26.0 (see 4.19)
2		*4.104*	–3.6	31.8 (see 4.105)
3		*4.106*	+2.3	36.7 (see 4.107)



4.105
31.8 kcal/mol

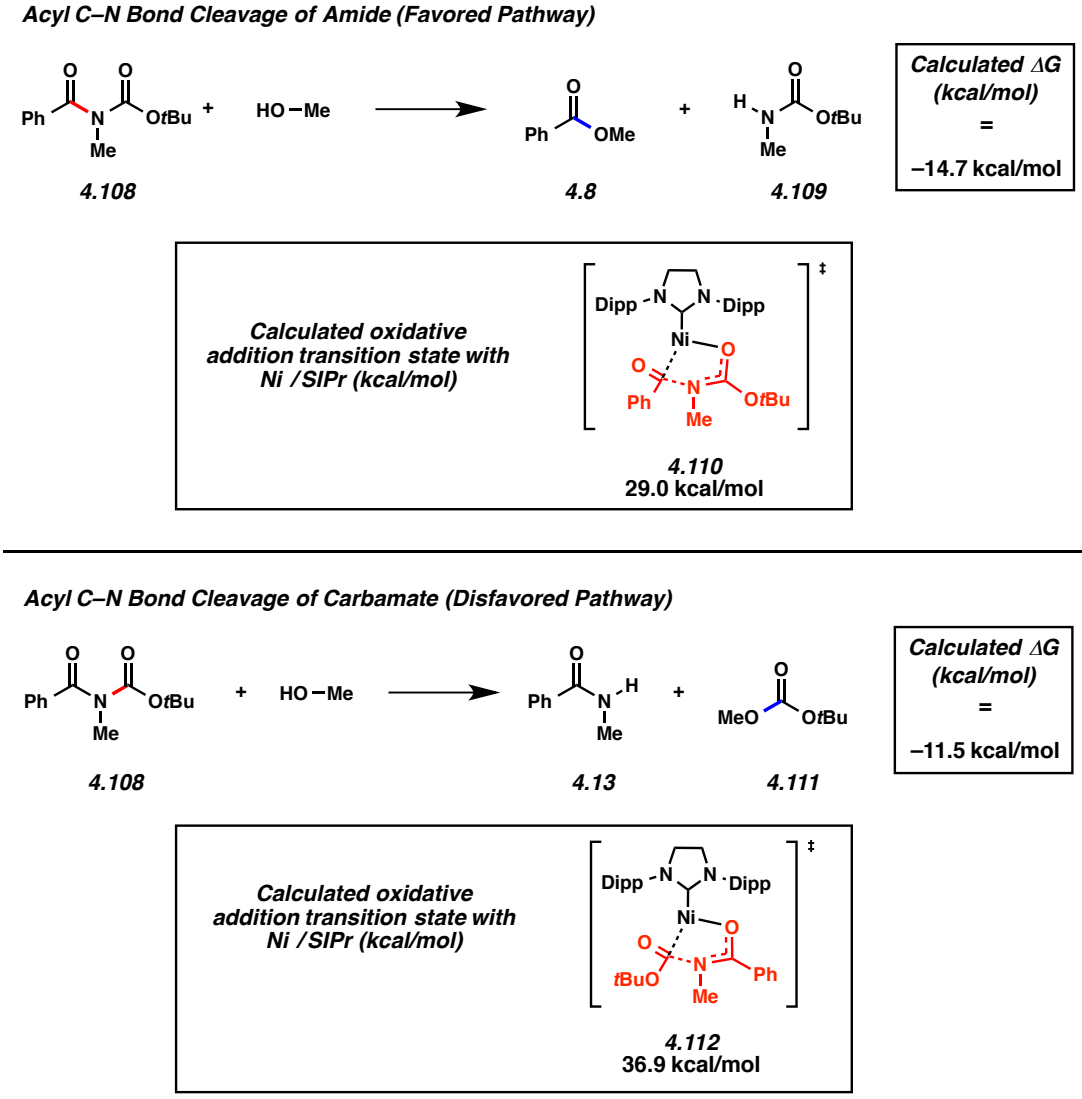
4.107
36.7 kcal/mol

We have performed computations involving two additional substrates: *N*-Me-*N*-phenylacetamide (**4.104**) and *N*,*N*-dimethylacetamide (**4.106**). In the case of *N*-Me-*N*-phenylacetamide, the oxidative addition barrier (transition state **4.105**) was found to be 31.8

kcal/mol with respect to the $Ni(SIPr)_2$ resting state. Similarly, for *N*,*N*-dimethylacetamide, the oxidative addition barrier (transition state **4.107**) was found to be 36.7 kcal/mol with respect to the $Ni(SIPr)_2$ resting state. These high kinetic barriers are likely responsible for the inability of alkyl carboxylic acids to participate in our nickel-catalyzed esterifications. Also, in the case of substrate **4.106**, the amide to methyl ester conversion is not energetically favorable.

4.7.4.5 Analysis of *N*-Me,Boc Amide Esterification

Figure 4.4. Analysis of Competing Pathways for Esterification of *N*-Me,Boc Substrate **4.108**.

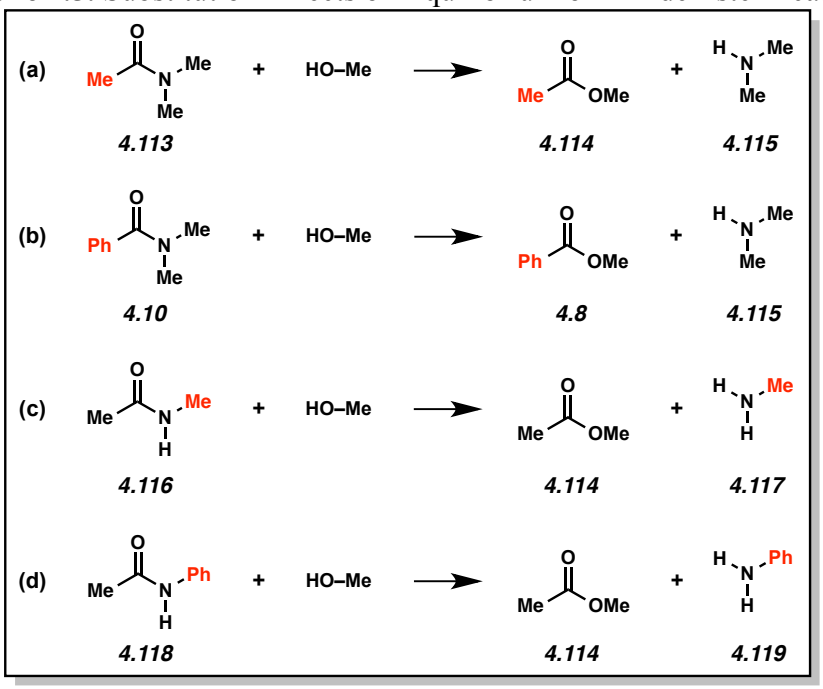


The calculations show that the desired esterification of substrate **4.108** with MeOH is thermodynamically favorable by 14.7 kcal/mol. The oxidative addition transition state (transition state **4.110**) was found to be 29.0 kcal/mol with respect to the $Ni(SIPr)_2$ resting state. We have also performed computations of a plausible competitive process involving cleavage of the carbamate acyl C–N bond. This transformation is also thermodynamically favorable (11.5

kcal/mol). However, the oxidative addition barrier (transition state **4.112**) was found to be 36.9 kcal/mol with respect to the $Ni(SIPr)_2$ resting state. Accordingly, carbamate C–N bond cleavage is not observed and the desired esterification occurs smoothly.

4.7.4.6 Free Energy and Enthalpy of Amide and Ester Formation

Figure 4.5. Substitution Effects on Equilibrium of Amide Esterification.



Reaction	Δ_rH(gas)[a]	Δ_rH(cond.)[d]	Δ_rH(methanol)[e]	Δ_rG(methanol)[f]	Δ_rH(calc.)[g]	Δ_rG(calc.)[g]
(a)	+5.3[b]	+11.4			+2.3	+2.3
(b)	-0.3	+10.6	+3.6	+3.3	0.0	0.0
(c)	+3.8	+14.0			+3.4	+3.9
(d)	+0.2[c]	+8.0			-3.0	-2.6

[a] Reaction enthalpy calculated using gas phase standard enthalpy of formation data.[56]
[b] Gas phase enthalpy of formation for the amide **4.113** is calculated from liquid phase standard enthalpy of formation and enthalpy of vaporization.[56]
[c] Gas phase enthalpy of formation for the amide **4.118** is calculated from solid phase standard enthalpy of formation and enthalpy of sublimation.[56]
[d] Reaction enthalpy calculated using condensed phase standard enthalpy of formation data. Solid phase enthalpies of formation were used for amides **4.10** and **4.118**. Liquid phase enthalpies of formation were used for other compounds.[56]
[e] Reaction enthalpy calculated from enthalpies of reaction and solution.[16]
[f] Reaction free energy derived from the equilibrium constant of ester aminolysis in methanol.[16]
[g] Energies are calculated with M06/6-311+G(d,p)/SMD(toluene)//B3LYP/6-31G(d).

[h] All energies are in kcal/mol.

Figure 4.5 shows how substituents affect the equilibrium of amide esterification. We performed DFT calculations on the reaction enthalpies and free energies of the esterification of four amides, for which the experimental enthalpy of formation data are available. The enthalpies of reaction are also calculated using experimental enthalpy of formation data in the gas phase ($\Delta_r H$(gas)) and in the condensed phase ($\Delta_r H$(cond.)).[56] Interestingly, the esterification reaction is significantly more endothermic if condensed phase enthalpy of formation data were used. One of the major factors that contribute to this deviation is the greater intermolecular stabilizing forces in neat methanol liquid. The equilibrium of reaction (b) in methanol has been investigated by Guthrie *et al*.[16] The standard free energy of reaction derived from equilibrium constant ($\Delta_r G$(methanol)) and the standard enthalpy of reaction in methanol solution derived from enthalpies of solution data both indicate the amide esterification is less endothermic than the prediction by $\Delta_r H$(cond.). Based on these considerations, we postulate that the gas phase thermodynamic data ($\Delta_r H$(gas)) would better represent the experimental conditions with the non-polar toluene solvent. Unfortunately, the gas phase enthalpies of formation for amides **4.113** and **4.118** are not available, and were derived from liquid and solid phase enthalpies of formation and enthalpies of vaporization and sublimation, respectively. Thus, larger experimental errors are expected for $\Delta_r H$(gas) of reactions (a) and (d).

The DFT calculations with the SMD solvation model in toluene (1.0 M, 298 K) predicted very close reaction enthalpies compared to $\Delta_r H$(gas) for reactions (b) and (c). Larger deviations from $\Delta_r H$(gas) were obtained for (a) and (d), which may be attributed to the greater experimental error as described above. Thus, the DFT predicted enthalpies of reactions ($\Delta_r H$(calc)) are used to

analyze the substituent effects. Phenyl substitution at the carbonyl and N position significantly favors the esterification (a vs. b and c vs. d), while the esterification of *N*-methylacetamide is much less favorable than that of *N,N*-dimethylacetamide. This further confirms the expectation that mostly the reverse reaction (i.e. amidation) should be favorable, but the judicious use of varied substrates can perturb the equilibrium.

4.7.4.7 Energies, Enthalpies, and Free Energy of the Calculated Structures

Table 4.7. Energies, Enthalpies, and Free Energies of the Structures Calculated at the M06/SDD,6-311+G(d,p)(SMD^{toluene})//B3LYP/LANL2DZ,6-31G(d).

Structures	ZPE	DE	DH	DG	E	H	G	Imaginary	DDG
MeOH	0.051473	0.054761	0.055705	0.028756	-115.691065	-115.63536	-115.662309	—	—
4.4a	0.130353	0.135268	0.136212	0.102291	-212.479801	-212.343589	-212.377510	—	—
4.4b	0.093028	0.097390	0.098334	0.067601	-135.098988	-135.000654	-135.031387	—	—
4.4c	0.135967	0.141254	0.142199	0.107525	-287.686445	-287.544246	-287.578920	—	—
4.4d	0.097148	0.102641	0.103585	0.069012	-210.253121	-210.149536	-210.184109	—	—
4.4e	0.064450	0.067831	0.068775	0.041555	-95.816309	-95.747534	-95.774754	—	—
4.4f	0.117436	0.123214	0.124158	0.088289	-287.465710	-287.341552	-287.377421	—	—
4.4g	0.145946	0.153153	0.154097	0.114653	-326.747411	-326.593314	-326.632758	—	—
4.9	0.221898	0.232888	0.233832	0.184277	-556.741196	-556.507364	-556.556919	—	—
4.10	0.184539	0.195044	0.195988	0.148064	-479.354994	-479.159006	-479.206930	—	—
4.11	0.227243	0.238874	0.239819	0.188374	-631.941051	-631.701232	-631.752677	—	—
4.12	0.188279	0.199798	0.200742	0.150388	-554.500325	-554.299583	-554.349937	—	—
4.13	0.156359	0.165575	0.166519	0.121160	-440.076464	-439.909945	-439.955304	—	—
4.14	0.209470	0.221355	0.222299	0.169869	-631.715959	-631.493660	-631.546090	—	—
4.15	0.237383	0.250756	0.2517	0.195805	-670.987803	-670.736103	-670.791998	—	—
4.9_TS	0.817159	0.862147	0.863091	0.73669	-1888.379615	-1887.516524	-1887.642925	-221.285	**36.8**
4.10_TS	0.779705	0.824113	0.825057	0.700324	-1810.994261	-1810.169204	-1810.293937	-243.236	**36.2**
4.11_TS	0.822386	0.868066	0.869011	0.741075	-1963.584228	-1962.715217	-1962.843153	-192.983	**34.0**
4.12_TS	0.78317	0.828976	0.82992	0.701265	-1886.145139	-1885.315219	-1885.443874	-144.322	**31.9**
4.13_TS	0.751675	0.79476	0.795704	0.673483	-1771.711376	-1770.915672	-1771.037893	-265.940	**39.0**
4.14_TS	0.805092	0.850906	0.85185	0.722942	-1963.364955	-1962.513105	-1962.642013	-234.989	**30.6**

4.15_TS (4.19)	0.832519	0.880023	0.880968	0.749155	-2002.644449	-2001.763481	-2001.895294	-226.879	**26.0**
4.8	0.144145	0.152933	0.153878	0.109776	-459.947621	-459.793743	-459.837845	—	—
4.17	1.194703	1.259623	1.260567	1.092339	-2492.357024	-2491.096457	-2491.264685	—	**0.0**
4.18	0.834665	0.882315	0.883259	0.750844	-2002.668552	-2001.785293	-2001.917708	—	**12.0**
4.19	0.832519	0.880023	0.880968	0.749155	-2002.644449	-2001.763481	-2001.895294	-226.879	**26.0**
4.20	0.833357	0.881423	0.882367	0.749078	-2002.661012	-2001.778645	-2001.911934	—	**15.6**
4.21	0.887528	0.939803	0.940747	0.797540	-2118.365280	-2117.424533	-2117.567740	—	**19.6**
4.22	0.884746	0.935623	0.936567	0.799931	-2118.359517	-2117.422950	-2117.559586	-880.974	**24.8**
4.23	0.890480	0.941197	0.942141	0.806427	-2118.370107	-2117.427966	-2117.563680	—	**22.2**
4.24	0.740176	0.783680	0.784625	0.661525	-1791.602890	-1790.818265	-1790.941365	—	**15.7**
4.25	0.740041	0.782667	0.783611	0.662388	-1791.591727	-1790.808116	-1790.929339	-178.698	**23.2**
4.26	0.741023	0.784452	0.785396	0.661905	-1791.625676	-1790.840280	-1790.963771	—	**1.6**
4.101	0.831324	0.878890	0.879834	0.749575	-2002.640735	-2001.760901	-2001.891160	24.100	**28.6**
4.102	0.738576	0.781652	0.782596	0.660871	-1791.588769	-1790.806173	-1790.927898	-141.606	**24.1**
4.103	0.832584	0.880133	0.881077	0.747983	-2000.935468	-2000.934524	-2001.067618	-285.50	**35.3**
4.105	0.780187	0.824315	0.825259	0.702244	-1810.187123	-1810.186179	-1810.309194	-262.54	**31.8**
4.107	0.726324	0.767748	0.768692	0.651647	-1617.596856	-1617.595911	-1617.712957	-261.49	**36.7**
4.108	0.283512	0.300766	0.30171	0.237711	-785.774018	-785.472308	-785.536307	—	—
4.109	0.192446	0.203738	0.204682	0.15551	-441.544868	-441.340186	-441.389358	—	—
4.110	0.878983	0.930354	0.931298	0.791429	-2117.431420	-2116.500122	-2116.639991	-127.940	**29.0**
4.111	0.180461	0.191201	0.192146	0.144843	-461.411697	-461.219551	-461.266854	—	—
4.112	0.879394	0.930259	0.931203	0.793358	-2117.420778	-2116.489575	-2116.627420	-181.425	**36.9**

4.7.4.8 Cartesian Coordinates for the Optimized Structures

Structure **MeOH**

C	0.66202700	-0.01964300	0.00001500
H	1.07978400	0.99092600	-0.00029300
H	1.03670200	-0.54413900	-0.89306500
H	1.03669300	-0.54359300	0.89342100
O	-0.74868300	0.12252300	-0.00003300
H	-1.13587500	-0.76552300	0.00010800

Structure **4.4a**

N	-0.00027200	-1.16976800	-0.35546600
C	1.16153700	-0.44896000	0.17194400
C	-1.16180900	-0.44838800	0.17177500
C	0.77918100	1.02907700	-0.05696000
H	1.32562700	-0.62816800	1.25225700
C	-0.77861900	1.02952600	-0.05673800
H	-2.07563700	-0.74223100	-0.35666300
H	1.20090600	1.67724100	0.71747700
H	-1.19971500	1.67761700	0.71810400
H	-1.32627300	-0.62771200	1.25200800
H	-1.16100600	1.37868400	-1.02064600
H	1.16146600	1.37758300	-1.02114500
H	2.07533600	-0.74339600	-0.35621300
H	-0.00053800	-2.14877600	-0.07705200

Structure **4.4b**

N	0.00000100	0.56565200	-0.14997900
H	0.00000100	1.32851400	0.52364400
C	-1.21340600	-0.22277100	0.02051900
H	-1.27349300	-0.76817300	0.98256200
H	-2.09042400	0.42835100	-0.06015100
H	-1.27701500	-0.96758900	-0.78242200

C	1.21340400	-0.22277100	0.02051900
H	2.09042400	0.42835300	-0.06012100
H	1.27348100	-0.76819800	0.98255000
H	1.27703100	-0.96757100	-0.78243800

Structure **4.4c**

N	-0.66985300	1.23234300	0.00000000
O	0.64393300	-1.26966100	0.00000000
C	0.00575700	0.74607600	1.20515000
H	-0.53601900	1.10023000	2.09062900
H	1.05354800	1.09453000	1.28293400
C	0.00575700	-0.78183100	1.17435600
H	-1.03320500	-1.14752200	1.22075200
H	0.56413400	-1.19192100	2.02151600
C	0.00575700	-0.78183100	-1.17435600
H	-1.03320500	-1.14752200	-1.22075200
H	0.56413400	-1.19192100	-2.02151600
C	0.00575700	0.74607600	-1.20515000
H	1.05354800	1.09453000	-1.28293400
H	-0.53601900	1.10023000	-2.09062900
H	-0.69757700	2.24929600	0.00000000

Structure **4.4d**

N	-0.52451800	0.53504500	-0.27257800
H	-0.73379800	1.44953200	0.13222200
C	-1.67445700	-0.33703300	-0.04443500
H	-1.92619200	-0.46353800	1.01911500
H	-2.53327900	0.09697500	-0.56960100
H	-1.46704200	-1.32147700	-0.47403900
O	0.53744800	0.05042500	0.57854700
C	1.68310500	-0.18681200	-0.22103600
H	2.05440000	0.73657000	-0.68660900
H	2.44267000	-0.58030200	0.46223500
H	1.48339200	-0.92341300	-1.01082700

Structure **4.4e**

N	-0.75214100	-0.00000400	-0.12565000
H	-1.14352800	0.81274400	0.34714800
C	0.70576100	0.00000300	0.01756900
H	1.11564700	0.88167700	-0.48738500
H	1.08618900	0.00002300	1.05455200
H	1.11565500	-0.88171200	-0.48732200
H	-1.14354700	-0.81272300	0.34714400

Structure **4.4f**

C	-1.17206100	-1.20286000	0.00342200
C	0.22125000	-1.20847200	-0.00518300
C	0.93933100	0.00002900	-0.01060800
C	0.22126200	1.20847800	-0.00516400
C	-1.17209400	1.20283200	0.00342100
C	-1.88223000	0.00000200	0.00828300
H	-1.70581000	-2.15013600	0.00912900
H	0.76346000	-2.15196500	-0.01301100
H	0.76339300	2.15201800	-0.01294400
H	-1.70583000	2.15011700	0.00912800
H	-2.96822000	-0.00001000	0.01652100
N	2.33777800	-0.00002600	-0.07872500
H	2.77789600	-0.83504400	0.28880100
H	2.77792200	0.83515000	0.28842200

Structure **4.4g**

C	-1.87903000	-0.99599700	0.04404700
C	-0.52306200	-1.29859000	-0.00645300
C	0.44389000	-0.27364900	-0.06110900
C	0.00116300	1.06189100	-0.05755500
C	-1.36394100	1.35128800	-0.01155300
C	-2.31524800	0.33317000	0.04074600
H	-2.60221900	-1.80678700	0.08702800

H	-0.19630100	-2.33695600	-0.01040600
H	0.71818900	1.87532700	-0.09269000
H	-1.68111900	2.39140500	-0.01127000
H	-3.37503800	0.56698000	0.08004800
N	1.79315600	-0.60933700	-0.15169000
H	2.00222900	-1.54218400	0.17725900
C	2.83605400	0.36453900	0.10851500
H	2.73975200	0.86180100	1.08807400
H	3.80454800	-0.14120900	0.06920400
H	2.83892100	1.14107400	-0.66524300

Structure **4.9**

C	0.25657200	0.96086400	-0.24121900
O	0.35784400	2.18385400	-0.34863500
C	-1.09875000	0.31915800	-0.11054100
C	-2.08116900	1.03344300	0.59081100
C	-1.44471300	-0.89297400	-0.72344600
C	-3.37278200	0.52594600	0.71201300
H	-1.81311400	1.99103100	1.02536100
C	-2.74442900	-1.39188500	-0.61822700
H	-0.70894500	-1.43625300	-1.30830300
C	-3.70750300	-0.68958500	0.10815100
H	-3.00485900	-2.32626300	-1.10838500

H	-4.12224400	1.08174700	1.26914300
H	-4.71718000	-1.08217800	0.19545600
N	1.37121100	0.16191500	-0.24835400
C	1.49185000	-1.21587700	0.26028400
C	2.68693900	0.82296000	-0.33859900
C	2.90181800	-1.24990700	0.86847500
H	0.70219500	-1.43867500	0.98180700
C	3.68967000	-0.30434000	-0.05272400
H	2.81771800	1.28539600	-1.32191900
H	2.87748600	-0.85030600	1.88960300
H	4.61364300	0.06886500	0.39878700
H	2.74272300	1.62746000	0.40491000
H	3.95828000	-0.82260000	-0.98159400
H	3.31327300	-2.26313400	0.91088600
H	1.41476400	-1.94615100	-0.55805300

Structure **4.10**

C	-0.99865900	0.63422200	-0.18488700
O	-1.28619700	1.78372800	-0.51294300
C	0.44899100	0.23134600	-0.07539700
C	1.34027800	1.15672300	0.48532600
C	0.95223700	-0.96054700	-0.61593500
C	2.70405700	0.87709200	0.54413200

H	0.94795100	2.09615900	0.86171300
C	2.32104600	-1.23111400	-0.57510000
H	0.27630300	-1.66606300	-1.09100500
C	3.19780700	-0.31841000	0.01433400
H	2.70220700	-2.15200800	-1.00843400
N	-1.96911200	-0.32111400	0.03866400
C	-3.35572900	0.05826000	-0.19920400
H	-3.84622900	0.39144800	0.72711100
H	-3.38204000	0.87566200	-0.91840600
H	-3.90569700	-0.80515200	-0.59123400
C	-1.79340400	-1.50819300	0.86429400
H	-2.10665100	-2.41208700	0.32510400
H	-0.75296400	-1.62124400	1.16400000
H	-2.40648900	-1.42811100	1.77370500
H	4.26260800	-0.53236600	0.05183300
H	3.38460900	1.59546500	0.99313800

Structure **4.11**

C	0.02314100	0.97226500	-0.28580500
O	0.14027600	2.19514800	-0.23015500
C	-1.33370100	0.34441600	-0.10547600
C	-2.17783700	0.88496500	0.87431400
C	-1.82304700	-0.66154400	-0.95088700

C	-3.47385700	0.39860400	1.03493900
H	-1.80578200	1.69394100	1.49498100
C	-3.12799100	-1.13423100	-0.80252200
H	-1.19144800	-1.05743600	-1.74134300
C	-3.95175000	-0.61284800	0.19702700
H	-3.50210200	-1.90488900	-1.47112800
N	1.09646300	0.14803500	-0.56228900
O	3.50526200	-0.87244300	0.54738100
C	2.39086800	0.76584100	-0.86642100
H	2.22691200	1.83259600	-1.02232700
H	2.78087200	0.31599200	-1.78969000
C	3.38143000	0.51903600	0.27130900
H	3.05007900	1.05701600	1.17453200
H	4.38144500	0.87043900	-0.00009200
C	2.25654400	-1.43211800	0.91874800
H	1.88719700	-0.95996600	1.84527400
H	2.43535500	-2.49418800	1.11477600
C	1.20704900	-1.26379100	-0.18809600
H	1.51202700	-1.84775800	-1.06786900
H	0.24225100	-1.63723600	0.15603600
H	-4.11586900	0.81563300	1.80611700
H	-4.96557600	-0.98559500	0.31616400

Structure **4.12**

C	-0.66807200	0.61549400	0.05806800
O	-1.03258600	1.76706900	-0.12469300
C	0.78359000	0.23304900	-0.01296400
C	1.72115200	1.16547500	0.45278000
C	1.23255100	-0.95844000	-0.60141600
C	3.08505500	0.89391400	0.36694400
H	1.36261600	2.10003300	0.87230800
C	2.59936800	-1.22148500	-0.70046400
H	0.51228600	-1.66431800	-1.00428200
C	3.52696200	-0.30083400	-0.20840500
H	2.93931300	-2.14134200	-1.16853500
N	-1.57706000	-0.43623100	0.22704500
C	-1.39814000	-1.49890300	1.21294800
H	-1.93660900	-2.39289200	0.88595200
H	-0.33886800	-1.73160700	1.31563400
H	-1.79502000	-1.18065400	2.18527900
O	-2.91964200	-0.00462300	0.30379200
C	-3.47627500	0.12983400	-1.00305300
H	-4.52844400	0.37433900	-0.83528800
H	-2.99353400	0.94300300	-1.55392400
H	-3.39730100	-0.80914000	-1.56538500
H	4.59105300	-0.50884400	-0.28195800

H	3.80460800	1.61685500	0.74146000

Structure **4.13**

C	-1.23440800	0.38832700	-0.10996200
O	-1.66597900	1.50533400	-0.38235500
C	0.24260900	0.10595700	-0.04934000
C	1.09742200	1.19955400	0.14351500
C	0.79460400	-1.17443200	-0.20051700
C	2.47645700	1.01401400	0.21280100
H	0.65575600	2.18650300	0.23329200
C	2.17642300	-1.35903000	-0.13898300
H	0.15469900	-2.02878600	-0.40543500
C	3.01923000	-0.26645200	0.07464700
H	2.59434000	-2.35387900	-0.26738100
N	-2.06069200	-0.67527000	0.14990000
C	-3.50402900	-0.51945300	0.19648900
H	-3.86732400	-0.32403300	1.21464300
H	-3.76910100	0.33206900	-0.43111300
H	-3.99099700	-1.42221400	-0.18609500
H	4.09515600	-0.41118600	0.12436700
H	3.12979400	1.86785800	0.37078000
H	-1.65949400	-1.49302400	0.58458600

Structure **4.14**

C	0.48098900	-0.66798400	-0.08292500
O	0.21930500	-1.85957900	-0.20887000
C	1.90409900	-0.17928200	-0.04416700
C	2.88435600	-1.10135500	0.34889000
C	2.29416100	1.11809300	-0.40850400
C	4.22399000	-0.72487400	0.40837300
H	2.57140200	-2.10894100	0.60166200
C	3.63770500	1.49175200	-0.35761700
H	1.56250400	1.83409500	-0.77482100
C	4.60384100	0.57388600	0.05839600
H	3.92940800	2.49592300	-0.65272400
N	-0.47468800	0.31720700	0.05142500
C	-1.88078000	0.19749600	0.04058900
C	-2.55327200	-1.00807100	-0.21523900
C	-2.62402700	1.36319200	0.29046300
C	-3.94857500	-1.02435400	-0.21620400
H	-1.98202100	-1.90618500	-0.40088000
C	-4.01558400	1.32895700	0.28677000
H	-2.10604100	2.30017600	0.48808200
C	-4.68898800	0.13226800	0.03250800
H	-4.45992200	-1.96269400	-0.41463300
H	-4.57220300	2.24143800	0.48298600

H	-5.77476500	0.10289200	0.02918900
H	-0.13098300	1.23949800	0.27933900
H	5.64952900	0.86639100	0.10033900
H	4.97398300	-1.44475100	0.72446000

Structure **4.15**

C	-0.44972400	0.62256400	-0.09407900
O	-0.14422700	1.72565100	-0.53383000
C	-1.90618300	0.22982000	-0.06393200
C	-2.82939600	1.18812100	0.37784600
C	-2.37702700	-0.98203500	-0.58816800
C	-4.19659300	0.92170400	0.33736600
H	-2.46071900	2.14199200	0.74183300
C	-3.74745100	-1.23843300	-0.65094100
H	-1.67388900	-1.71664200	-0.96997900
C	-4.65880300	-0.29237100	-0.17804300
H	-4.10238200	-2.17493900	-1.07267800
N	0.48707400	-0.29906300	0.35932600
C	1.89052000	-0.11872800	0.12729300
C	2.50755500	1.14183200	0.16594100
C	2.67933300	-1.25499200	-0.11368200
C	3.88276600	1.24817300	-0.04275400
H	1.91151000	2.02456600	0.34344900

C	4.05419100	-1.13653100	-0.31377200
H	2.21881800	-2.23666300	-0.15856100
C	4.66482900	0.11721500	-0.28174900
H	4.34476100	2.23140800	-0.00996500
H	4.64417700	-2.02971700	-0.50170100
H	5.73552000	0.21158200	-0.44008100
H	-5.72546800	-0.49592800	-0.21959600
H	-4.90286700	1.66530300	0.69650100
C	0.10618400	-1.45826000	1.17598100
H	-0.86863800	-1.28648900	1.63081200
H	0.05598400	-2.39054000	0.60024400
H	0.84628400	-1.58417400	1.97124400

Structure **4.9_TS**

C	-1.42905700	1.29394000	-1.07880600
O	-2.10229500	0.76928200	-1.95764900
Ni	0.31787100	0.65195100	-0.72575900
C	0.44592500	-0.90671300	0.35478200
N	1.64325400	-1.21322200	0.92752000
N	-0.39705300	-1.93166800	0.62728000
C	1.65610100	-2.50705600	1.63685000
C	2.83117900	-0.40635800	0.85653700
C	0.25817100	-3.06178700	1.32275100

C	-1.74515600	-2.10930600	0.15277000
H	2.46365500	-3.14443600	1.26061900
H	1.81787700	-2.35594600	2.71064300
C	3.70265800	-0.55780900	-0.24685300
C	3.14115600	0.46699900	1.92479700
H	0.28928900	-3.93560700	0.66090200
H	-0.30029400	-3.33920300	2.22097700
C	-2.81458900	-1.89416100	1.05116100
C	-1.96441400	-2.59471000	-1.15523500
C	4.87733600	0.20467200	-0.26982500
C	3.41706800	-1.52004400	-1.39546500
C	4.33300900	1.19764000	1.85646600
C	2.23510600	0.62363300	3.14223500
C	-4.11469600	-2.15281200	0.60153500
C	-2.60165100	-1.42550700	2.48821100
C	-3.28489700	-2.83247500	-1.55453000
C	-0.82974600	-2.89360900	-2.12960600
C	5.19392300	1.07368000	0.76941200
H	5.55582100	0.11102200	-1.11319700
C	4.49772700	-2.61500200	-1.49841300
C	3.25488600	-0.77424400	-2.73397700
H	2.46463600	-2.01680800	-1.18860000
H	4.59038000	1.87551000	2.66541300

C	1.87873100	2.09730400	3.41765300
C	2.86875900	-0.01577800	4.39557600
H	1.29810000	0.09834000	2.93121600
C	-4.35186400	-2.61382200	-0.68977300
H	-4.95322900	-1.98965700	1.27260200
C	-2.90918200	-2.55521800	3.49421800
C	-3.43174900	-0.17279800	2.82592300
H	-1.54617600	-1.15442400	2.59790700
H	-3.47803300	-3.19403600	-2.56045600
C	-0.98796100	-2.11853800	-3.45185100
C	-0.70199300	-4.40890100	-2.38916900
H	0.10517300	-2.55583800	-1.67339500
H	6.11270000	1.65318700	0.73405900
H	4.60043800	-3.17026300	-0.55861900
H	5.47907600	-2.19048900	-1.74051400
H	4.24120300	-3.32935900	-2.28959700
H	2.46170500	-0.02196800	-2.66837600
H	2.99565200	-1.47917500	-3.53298500
H	4.18119100	-0.26500800	-3.02547000
H	1.46425000	2.58033100	2.52737400
H	2.75578000	2.67462000	3.73239400
H	1.13722700	2.16268000	4.22274000
H	3.10533800	-1.07412900	4.23745800

H	2.18781300	0.05707700	5.25207500
H	3.80202600	0.49238000	4.66574800
H	-5.36927200	-2.80429400	-1.02146400
H	-2.31764900	-3.45639100	3.29476300
H	-3.96630600	-2.84291100	3.44985300
H	-2.69555400	-2.22786500	4.51906100
H	-3.23554800	0.63879100	2.12109200
H	-3.18546600	0.18144200	3.83433700
H	-4.50696200	-0.38615900	2.80802900
H	-1.13110400	-1.05248800	-3.25709900
H	-1.85099700	-2.47758500	-4.02588300
H	-0.09743500	-2.25618200	-4.07771600
H	-0.54643300	-4.97134000	-1.46040600
H	0.14437500	-4.61344000	-3.05623700
H	-1.60533900	-4.80638200	-2.86685900
C	-3.30830200	3.93926700	1.76428900
C	-3.97082100	3.55931400	0.59216300
H	-1.50912700	3.73583100	2.93782900
C	-2.02567700	3.45162300	2.02434000
C	-3.35232900	2.70179400	-0.31555700
C	-2.05712900	2.21700400	-0.06878100
C	-1.40643200	2.59438700	1.11286300
H	-3.85450300	2.38811600	-1.22546400

H	-0.41523700	2.19539300	1.31229100
H	-3.79219800	4.60715000	2.47250100
H	-4.97228000	3.93122600	0.38958400
C	0.54363500	3.53535000	-1.47948600
C	0.12848000	2.05786900	-3.30343300
C	-0.13444200	4.36593200	-2.57904800
H	1.62950700	3.74114700	-1.47008700
H	0.16646600	3.76261200	-0.47791700
C	0.13375500	3.51690300	-3.83202100
H	0.94250600	1.47642300	-3.76171900
H	-0.80955100	1.53698600	-3.54169200
H	0.25902000	5.38595400	-2.65589600
H	-1.21104400	4.42872500	-2.37823700
H	1.11822100	3.76741700	-4.24733500
H	-0.60550600	3.67379000	-4.62469200
N	0.27532500	2.14237300	-1.84413000

Structure **4.10_TS**

C	1.41254000	-0.75473500	-1.77120600
O	2.02681200	0.13062100	-2.35187600
C	-0.23361100	-0.56164900	-4.02031700
H	0.38066600	-1.10796300	-4.75934100
H	-1.23392000	-0.41946100	-4.46423800

H	0.22128900	0.42118400	-3.87471100
Ni	-0.32864200	-0.38586400	-1.11430100
C	-0.45801700	0.56756400	0.52379100
N	-1.66428500	0.59382500	1.15655400
N	0.37096800	1.38192600	1.21992100
C	-1.69314400	1.44442600	2.36087900
C	-2.84008700	-0.11540900	0.72990400
C	-0.30249300	2.09711000	2.32743400
C	1.72840300	1.73697000	0.89482000
H	-2.50878000	2.17299500	2.29974800
H	-1.85217800	0.83462800	3.25850300
C	-3.71922500	0.50165500	-0.18948500
C	-3.12505000	-1.38467900	1.28436000
H	-0.34573300	3.16994200	2.10495700
H	0.24985500	1.96922700	3.26229400
C	2.77812400	1.14563100	1.63380600
C	1.97682300	2.73396200	-0.07459900
C	-4.87680800	-0.19290300	-0.56288300
C	-3.45539700	1.88377300	-0.77874100
C	-4.30176300	-2.02984800	0.88668100
C	-2.20616100	-2.05681200	2.29946900
C	4.08837200	1.55721000	1.36310100
C	2.53317000	0.11165500	2.72940900

C	3.30636600	3.10592000	-0.30692300
C	0.86344900	3.44111300	-0.84107300
C	-5.16954000	-1.44515200	-0.03181500
H	-5.56015400	0.25730100	-1.27758100
C	-4.57509300	2.87863200	-0.41421200
C	-3.24595100	1.81629700	-2.30407700
H	-2.52553900	2.26294300	-0.34400000
H	-4.54061300	-3.00581900	1.29967200
C	-1.79986000	-3.47726800	1.86251800
C	-2.84757400	-2.08607200	3.70219900
H	-1.28797700	-1.46419100	2.36147800
C	4.35407400	2.52524800	0.39977700
H	4.91169600	1.11291400	1.91528200
C	2.82553000	0.70049400	4.12610800
C	3.34932600	-1.17669900	2.51431500
H	1.47458400	-0.16693800	2.69508200
H	3.52243700	3.86270500	-1.05532400
C	1.08267400	3.39263300	-2.36523300
C	0.69912700	4.89738600	-0.35755900
H	-0.07332400	2.91425600	-0.63731300
H	-6.07553500	-1.96528800	-0.33159100
H	-4.71230800	2.95039100	0.67122400
H	-5.53607700	2.58148300	-0.85005100

H	-4.33461000	3.87868700	-0.79390700
H	-2.42303100	1.13851200	-2.55518500
H	-3.00701400	2.81049400	-2.70058600
H	-4.14718900	1.45947200	-2.81673900
H	-1.36685100	-3.47348300	0.85721900
H	-2.65649500	-4.16115600	1.85444900
H	-1.05725300	-3.88908400	2.55624600
H	-3.11252200	-1.08031000	4.04807600
H	-2.15803400	-2.52653900	4.43233400
H	-3.76508600	-2.68656000	3.70434800
H	5.37869000	2.82884900	0.20126300
H	2.24174900	1.60763400	4.32160300
H	3.88450400	0.96706300	4.22470800
H	2.59108100	-0.03020100	4.90984200
H	3.16116700	-1.60833400	1.52815000
H	3.08170900	-1.92296200	3.27248800
H	4.42612000	-0.99168900	2.60426200
H	1.26250700	2.36592900	-2.69435300
H	1.94122800	4.00417200	-2.66867800
H	0.20092600	3.78981700	-2.88342000
H	0.50170000	4.95232400	0.71983500
H	-0.13270200	5.38445500	-0.88098100
H	1.60542800	5.48227100	-0.55480800

N	-0.30591900	-1.26911600	-2.75838000
C	3.48847900	-4.33372700	-0.54979500
C	4.04909300	-3.46477800	-1.49129200
H	1.80887100	-4.70318700	0.75345700
C	2.24508500	-4.03681600	0.01331800
C	3.36835800	-2.30921100	-1.86976900
C	2.11118600	-2.01121400	-1.32054900
C	1.56244100	-2.88141100	-0.37106100
H	3.79173200	-1.61774200	-2.59158000
H	0.60222800	-2.63238500	0.07291100
H	4.02013700	-5.23456900	-0.25372800
H	5.01961600	-3.68902400	-1.92724300
C	-0.58570200	-2.68169600	-2.92931600
H	-1.58978700	-2.83961300	-3.36019200
H	0.13926400	-3.17059600	-3.60609000
H	-0.55721900	-3.20538000	-1.97092200

Structure **4.11_TS**

C	-1.41178700	1.36989200	-0.74919900
O	-2.01955900	1.05949800	-1.76442700
Ni	0.33485400	0.70007600	-0.48020100
C	0.46408400	-1.07607500	0.19433100
N	1.66880600	-1.48878700	0.67480900

N	-0.36679800	-2.14489800	0.23286800
C	1.69818700	-2.90408100	1.08829100
C	2.84649200	-0.66935500	0.77393300
C	0.30546800	-3.39313300	0.66184300
C	-1.71714700	-2.22695300	-0.26268300
H	2.51135000	-3.43692300	0.58371200
H	1.86181400	-2.98429300	2.16960000
C	3.71938800	-0.58505400	-0.33492400
C	3.14073900	-0.02085000	1.99573900
H	0.34444100	-4.09977100	-0.17554200
H	-0.24594800	-3.86768200	1.47791400
C	-2.78146100	-2.23519000	0.66728700
C	-1.94333200	-2.40049400	-1.64646300
C	4.88129900	0.18590100	-0.20264100
C	3.44753600	-1.30356700	-1.65270700
C	4.32015700	0.72853200	2.07711900
C	2.23236900	-0.12776200	3.21644900
C	-4.08305400	-2.39798900	0.17841700
C	-2.56127300	-2.11200800	2.17277500
C	-3.26516300	-2.55621100	-2.08060200
C	-0.81510400	-2.46192800	-2.67183900
C	5.18244700	0.83720600	0.98935300
H	5.56012400	0.27381000	-1.04629500

C	4.55117600	-2.33094300	-1.97479300
C	3.26172300	-0.30638700	-2.81271500
H	2.50773200	-1.85398100	-1.54847500
H	4.56642200	1.23642900	3.00529500
C	1.83387900	1.25538700	3.76563500
C	2.88376600	-0.98120400	4.32458700
H	1.31055600	-0.62914600	2.90432500
C	-4.32689200	-2.55396100	-1.18236700
H	-4.91683300	-2.40409200	0.87461600
C	-2.84121200	-3.45206300	2.88645000
C	-3.40882900	-0.99016900	2.80195700
H	-1.50953900	-1.85361400	2.33694000
H	-3.46408800	-2.68033000	-3.14097800
C	-1.02493400	-1.46656400	-3.82860300
C	-0.63348300	-3.89698700	-3.20913300
H	0.11278800	-2.17360800	-2.16978800
H	6.09067100	1.42826100	1.07236300
H	4.67248400	-3.05961100	-1.16454700
H	5.52142600	-1.84493000	-2.12990700
H	4.30536100	-2.87951200	-2.89175500
H	2.44945600	0.39611900	-2.59778500
H	3.01861300	-0.84002300	-3.73934600
H	4.17375000	0.27540100	-2.99148900

H	1.39665200	1.88158800	2.98157100
H	2.69559600	1.79200000	4.17902400
H	1.09771100	1.14622800	4.57088100
H	3.14866800	-1.98147300	3.96320300
H	2.20025200	-1.09603700	5.17437800
H	3.80279400	-0.51204000	4.69563900
H	-5.34508100	-2.67556400	-1.54272200
H	-2.23667600	-4.27086100	2.47928200
H	-3.89371700	-3.73976400	2.77829400
H	-2.62578800	-3.37051000	3.95881100
H	-3.23774100	-0.03237000	2.30464300
H	-3.15382500	-0.87622500	3.86268300
H	-4.48023100	-1.21559500	2.74670100
H	-1.21737900	-0.46307900	-3.44051000
H	-1.87263300	-1.75631500	-4.46152300
H	-0.13427300	-1.44221600	-4.46873200
H	-0.44175100	-4.61539700	-2.40296100
H	0.20832800	-3.94073800	-3.91089100
H	-1.53030300	-4.23420600	-3.74242200
C	-3.48596700	3.27837700	2.51614300
C	-4.08185000	3.16787200	1.25540300
H	-1.74597300	2.82382900	3.70866800
C	-2.20966800	2.75202900	2.72794300

C	-3.40231300	2.54284400	0.21181500
C	-2.11141400	2.02727300	0.41139300
C	-1.52964300	2.12734300	1.68083500
H	-3.85039400	2.44447600	-0.77200300
H	-0.54429900	1.69728700	1.83944000
H	-4.01665600	3.76675200	3.32947200
H	-5.07843300	3.56925400	1.08870300
C	0.69754500	3.61706300	-0.43531900
C	0.29963100	2.65717900	-2.62617000
C	-0.04545400	4.87423600	-0.89814400
H	1.78290000	3.79387900	-0.55481200
H	0.51389400	3.46157900	0.63289100
C	-0.42929900	3.94852600	-3.00738500
H	1.33683900	2.71607300	-3.00462500
H	-0.18941300	1.81151000	-3.11998900
H	0.36615000	5.76932900	-0.41794800
H	-1.11416000	4.79299700	-0.63609100
H	-0.30328800	4.16968600	-4.07308800
H	-1.50589200	3.84126200	-2.79431300
N	0.29774700	2.43126900	-1.18628600
O	0.09252700	5.06956900	-2.30015900

Structure **4.12_TS**

C	1.43883900	-0.82162600	-1.53683800
O	2.08172000	0.06096600	-2.08399900
Ni	-0.31565400	-0.42051800	-0.95794500
C	-0.45533400	0.61401700	0.63811500
N	-1.67278200	0.68500300	1.23752800
N	0.36987700	1.45211400	1.30276800
C	-1.73191900	1.63368900	2.36598500
C	-2.84188500	-0.03162400	0.80381100
C	-0.30484600	2.20952700	2.38121600
C	1.73626700	1.76759100	0.97581700
H	-2.49785700	2.39635100	2.18585200
H	-1.98716600	1.11183300	3.29524200
C	-3.64910800	0.51565000	-0.22038600
C	-3.18827800	-1.23958100	1.45246400
H	-0.27762900	3.28158000	2.15558000
H	0.20524800	2.05351700	3.33656400
C	2.77101400	1.16324600	1.72396700
C	2.00527200	2.73423800	-0.01760200
C	-4.79993100	-0.18936900	-0.59685400
C	-3.33006100	1.84199600	-0.90343200
C	-4.35397700	-1.89726100	1.04414200
C	-2.34613300	-1.83168700	2.57841500
C	4.09067600	1.53283000	1.43895000

C	2.49908200	0.15920600	2.84099600
C	3.34312500	3.06481200	-0.26352800
C	0.90619300	3.44825700	-0.79850800
C	-5.15271600	-1.38198800	0.02648900
H	-5.43044200	0.20721800	-1.38754300
C	-4.41088300	2.89830200	-0.59382000
C	-3.13580200	1.68096600	-2.42418400
H	-2.38448700	2.21214400	-0.49583600
H	-4.63937500	-2.82721800	1.52794900
C	-1.93207500	-3.28727900	2.29019300
C	-3.07710500	-1.73602300	3.93355300
H	-1.42535200	-1.24418300	2.65079500
C	4.37753600	2.47171600	0.45261500
H	4.90454700	1.07866700	1.99721100
C	2.80857700	0.77004100	4.22431600
C	3.27722900	-1.15646900	2.65178500
H	1.43302600	-0.09046400	2.81410000
H	3.57601900	3.79749100	-1.03082200
C	1.06985800	3.28301100	-2.32166800
C	0.83224100	4.93967300	-0.40931700
H	-0.05023100	2.99017000	-0.53014200
H	-6.05223200	-1.91000300	-0.27900400
H	-4.53791900	3.04382600	0.48566500

H	-5.38466900	2.60658600	-1.00464300
H	-4.13867200	3.86307900	-1.03801000
H	-2.33789700	0.96980300	-2.66254100
H	-2.87160800	2.64727500	-2.87066000
H	-4.05553400	1.33392200	-2.91044800
H	-1.42055100	-3.36905100	1.32600800
H	-2.79784100	-3.95912500	2.26689100
H	-1.25373200	-3.65042700	3.07129900
H	-3.35235500	-0.70257000	4.17364600
H	-2.44131600	-2.11600600	4.74222100
H	-3.99992300	-2.32826200	3.92773500
H	5.40919100	2.74252800	0.24322000
H	2.24748000	1.69557500	4.39929600
H	3.87400600	1.01204800	4.31650600
H	2.55656800	0.06282200	5.02396500
H	3.07324700	-1.60437000	1.67586600
H	2.99133600	-1.87780600	3.42709800
H	4.35922600	-1.00043900	2.73372500
H	1.13927700	2.22641400	-2.59215900
H	1.97316500	3.78925900	-2.68371600
H	0.21276300	3.73028800	-2.84033500
H	0.67341500	5.07377900	0.66785100
H	0.00814400	5.43322400	-0.93865000

H	1.75825500	5.46455300	-0.67255400
N	-0.23598300	-1.35169300	-2.57451100
C	3.36155100	-4.46558600	-0.26633800
C	4.00787300	-3.57838700	-1.13316700
H	1.57663400	-4.84752100	0.88456200
C	2.07951800	-4.16731200	0.20159000
C	3.37382400	-2.40401900	-1.53376500
C	2.07919800	-2.10516100	-1.08091800
C	1.44526500	-2.99122600	-0.20161200
H	3.86238200	-1.69911200	-2.19930700
H	0.45609800	-2.73790600	0.17144100
H	3.85728100	-5.38083700	0.04716100
H	5.00847500	-3.80375100	-1.49404000
O	-0.46866400	-0.46887900	-3.67789800
C	0.51578000	-0.61996000	-4.70234400
H	0.48475500	-1.62219700	-5.15188800
H	0.24933200	0.11498400	-5.46861900
H	1.51826000	-0.41357600	-4.31997400
C	-0.75742100	-2.67433900	-2.86117700
H	-1.85054600	-2.66847900	-3.00163500
H	-0.30082900	-3.12111800	-3.75827200
H	-0.52255700	-3.32388900	-2.01327900

Structure **4.13_TS**

C	1.41336900	-0.42363400	-1.93842700
O	1.90217300	0.57784100	-2.44391000
C	-0.38544400	-0.32685600	-4.14444500
H	-1.37823000	0.12974500	-4.25995900
H	0.35916100	0.48611300	-4.15377600
H	-0.20668100	-0.95323300	-5.02862600
Ni	-0.32410800	-0.38977300	-1.20769500
C	-0.52304000	0.38561500	0.52074300
N	-1.74188400	0.31906100	1.12146800
N	0.28563800	1.09490300	1.34334200
C	-1.79986400	0.97787700	2.43956000
C	-2.89611100	-0.34277300	0.57719800
C	-0.41079300	1.62872500	2.53540800
C	1.63579700	1.51916700	1.07918100
H	-2.61738300	1.70610500	2.47235100
H	-1.97495800	0.23760300	3.22988600
C	-3.77929000	0.38783300	-0.24988600
C	-3.15371400	-1.68748900	0.92767300
H	-0.45300600	2.72305000	2.48320600
H	0.12496600	1.35508500	3.44872700
C	2.70066700	0.81793700	1.68800900
C	1.85943300	2.67590700	0.29982200

C	-4.91452700	-0.26778800	-0.74221800
C	-3.53534800	1.84684300	-0.62206100
C	-4.30718600	-2.29258200	0.41551300
C	-2.22989700	-2.48459300	1.84273100
C	4.00376700	1.27977400	1.46821600
C	2.47465800	-0.38187100	2.60441600
C	3.18259100	3.09134500	0.10891300
C	0.72594200	3.50526200	-0.29720800
C	-5.17915300	-1.59420300	-0.41521100
H	-5.60043400	0.26973900	-1.39083100
C	-4.69808900	2.75428500	-0.17428100
C	-3.25838900	2.00250700	-2.13002900
H	-2.63659400	2.18160500	-0.09516400
H	-4.52416400	-3.32675800	0.66828500
C	-1.72213900	-3.77195000	1.16595200
C	-2.91394300	-2.80744100	3.18686700
H	-1.35129900	-1.86669400	2.05274100
C	4.24640100	2.40155200	0.68107300
H	4.83920200	0.75384100	1.92149000
C	2.75858800	-0.01105400	4.07587400
C	3.30842000	-1.60946800	2.19392800
H	1.42026900	-0.66715000	2.52574000
H	3.38063200	3.96964400	-0.49848000

C	0.87055000	3.68732700	-1.82011500
C	0.61376900	4.87217100	0.41086600
H	-0.21175000	2.96727300	-0.12859400
H	-6.06695500	-2.08419600	-0.80629300
H	-4.88817900	2.66456200	0.90172600
H	-5.62928100	2.50631100	-0.69682100
H	-4.46671400	3.80345100	-0.39296100
H	-2.39606000	1.39935400	-2.43278300
H	-3.04695500	3.05061600	-2.37375700
H	-4.11995900	1.68519600	-2.72955900
H	-1.24023100	-3.54542300	0.20971600
H	-2.53816600	-4.47775300	0.97191400
H	-0.99249200	-4.27750900	1.80959800
H	-3.25386200	-1.89838800	3.69662400
H	-2.22146500	-3.33363700	3.85474200
H	-3.79015600	-3.45029500	3.04100100
H	5.26587100	2.74156000	0.51799800
H	2.16512200	0.85021900	4.40421600
H	3.81465500	0.24791000	4.21771600
H	2.52977700	-0.85505300	4.73798900
H	3.12121300	-1.89094600	1.15493600
H	3.05629100	-2.46483200	2.83274100
H	4.38303200	-1.42406700	2.30705100

H	0.98869600	2.71997400	-2.31503400
H	1.74164500	4.30591600	-2.06875300
H	-0.01550800	4.19506800	-2.22151000
H	0.46973300	4.76334600	1.49277700
H	-0.23281200	5.44283500	0.01012900
H	1.52010200	5.47022400	0.25909600
N	-0.29398100	-1.10779300	-2.91931200
C	3.91442900	-3.86588200	-1.20064900
C	4.46055200	-2.67589300	-1.69144100
H	2.11477300	-4.86437100	-0.55049300
C	2.54455100	-3.94271800	-0.93499200
C	3.64164800	-1.57153200	-1.92125000
C	2.26420000	-1.64042400	-1.66028900
C	1.72710600	-2.83394400	-1.15794400
H	4.04445900	-0.64096000	-2.30837600
H	0.66329600	-2.88163600	-0.93809800
H	4.55308600	-4.72771700	-1.02415400
H	5.52636100	-2.61212400	-1.89717600
H	0.04313000	-2.04809400	-3.09192500

Structure **4.14_TS**

C	0.95646800	1.90304400	-0.33630000
O	1.21851300	2.42510400	0.73887900

Ni	-0.42386000	0.58180600	-0.38279700
C	-0.13093000	-1.15545200	0.33138200
N	-1.12061000	-2.08114000	0.21083500
N	0.87005900	-1.73191900	1.03661200
C	-0.78642800	-3.39162600	0.80032300
C	-2.36081000	-1.87850600	-0.48820500
C	0.53686800	-3.09061800	1.52017100
C	2.08401800	-1.10482600	1.49084600
H	-1.57688700	-3.72556600	1.47972400
H	-0.67576600	-4.14656000	0.01170800
C	-3.49521000	-1.45029500	0.23943800
C	-2.43673800	-2.17257400	-1.86917900
H	0.42873500	-3.08032300	2.61104800
H	1.33165400	-3.79681700	1.26500600
C	3.28248700	-1.36234700	0.78817500
C	2.06824900	-0.32834200	2.67123100
C	-4.70310200	-1.29834000	-0.45266400
C	-3.45333800	-1.17950400	1.74029100
C	-3.66951400	-2.00667300	-2.51121200
C	-1.23851200	-2.67805600	-2.66621500
C	4.46519500	-0.79098100	1.27220200
C	3.33614100	-2.27120400	-0.43707100
C	3.27945900	0.22000700	3.10961200

C	0.80807800	-0.11496300	3.50573900
C	-4.79297400	-1.57092000	-1.81421000
H	-5.58581500	-0.96250600	0.08399400
C	-4.26754900	-2.23645100	2.51528500
C	-3.93175500	0.24239300	2.09035800
H	-2.41178700	-1.25917200	2.06647900
H	-3.75153500	-2.22225300	-3.57285500
C	-0.94976000	-1.79560000	-3.89512600
C	-1.42748900	-4.15058000	-3.08534900
H	-0.35728300	-2.62448400	-2.01959900
C	4.46587600	-0.00133000	2.41796300
H	5.39831600	-0.96938100	0.74545600
C	4.04421100	-3.60207400	-0.10424500
C	4.00646200	-1.59698900	-1.64793400
H	2.30554700	-2.50208200	-0.72694500
H	3.29160800	0.83068800	4.00736300
C	0.54992000	1.36977200	3.82453000
C	0.86711300	-0.94579500	4.80570200
H	-0.04701200	-0.46876000	2.92134900
H	-5.74010100	-1.44656600	-2.33249900
H	-3.91575400	-3.25350100	2.30511200
H	-5.32991600	-2.19401800	2.24738600
H	-4.18853200	-2.06537700	3.59545400

H	-3.35667500	1.00319700	1.55366100
H	-3.81844300	0.42318000	3.16600900
H	-4.99002900	0.38571300	1.84303600
H	-0.83759700	-0.74661500	-3.60313700
H	-1.75553500	-1.85366500	-4.63610900
H	-0.02457800	-2.11909200	-4.38639400
H	-1.59701100	-4.79907300	-2.21797900
H	-0.54014100	-4.51661000	-3.61564400
H	-2.28817500	-4.26517600	-3.75493200
H	5.39378000	0.43733000	2.77580000
H	3.57194200	-4.11811300	0.73995500
H	5.09373800	-3.43175900	0.16360800
H	4.02534800	-4.27616900	-0.96932600
H	3.51241500	-0.65694800	-1.90547700
H	3.96001600	-2.26032700	-2.52047400
H	5.06443500	-1.38229300	-1.45752700
H	0.54999500	1.96842900	2.91053600
H	1.31281900	1.77587300	4.49985600
H	-0.41847700	1.47848100	4.32883700
H	1.01534000	-2.01404400	4.60679600
H	-0.06258600	-0.83141700	5.37620000
H	1.69394100	-0.61438900	5.44518000
N	-0.73526300	2.30677800	-1.07121700

C	3.80467800	2.07692500	-3.57675300
C	4.07520300	2.67674400	-2.34369500
H	2.38548600	0.91772700	-4.71759700
C	2.59947100	1.39465800	-3.76435800
C	3.14461700	2.60400500	-1.30821000
C	1.92774500	1.92956000	-1.49079000
C	1.67174800	1.31536800	-2.72525200
H	3.33342400	3.06915700	-0.34621700
H	0.74784800	0.75891500	-2.86250400
H	4.52925900	2.13648500	-4.38478100
H	5.01266600	3.20578600	-2.19094500
H	-0.58352500	2.45586300	-2.06460500
C	-1.41228100	3.37811400	-0.48274900
C	-1.71263800	3.38186100	0.89311200
C	-1.79970200	4.49388300	-1.25202900
C	-2.38316500	4.46029000	1.46745000
H	-1.40520700	2.53842700	1.50076300
C	-2.48115500	5.56010800	-0.67102900
H	-1.56807800	4.51218700	-2.31581500
C	-2.77865500	5.55461600	0.69456400
H	-2.60024400	4.44211100	2.53302900
H	-2.77766500	6.40337000	-1.29053600
H	-3.30709400	6.38888100	1.14743600

Structure **4.15_TS (4.19)**

C	-0.41090300	1.70452500	-1.30793600
O	-1.27877500	1.65703600	-2.17617600
Ni	0.40830600	0.05859500	-0.79369300
C	-0.53308900	-1.13628300	0.34505000
N	0.15780700	-2.15078600	0.93539700
N	-1.83734300	-1.30647600	0.66644700
C	-0.68304300	-3.07704700	1.71682700
C	1.57716800	-2.35308900	0.83382500
C	-2.09673600	-2.54569400	1.43420300
C	-2.96286200	-0.52956700	0.21462100
H	-0.53815800	-4.10860600	1.37789700
H	-0.42030400	-3.03111500	2.78002800
C	2.08717200	-3.11180400	-0.24469400
C	2.42592900	-1.84503100	1.84541200
H	-2.69528700	-3.23785500	0.83039200
H	-2.65683900	-2.32401400	2.34680100
C	-3.55317100	0.39068700	1.11003500
C	-3.51242900	-0.77510400	-1.06328900
C	3.47029500	-3.32500500	-0.30641500
C	1.19037100	-3.71011500	-1.32425800
C	3.79929400	-2.09592300	1.74037400

C	1.89350300	-1.06190100	3.04194300
C	-4.69676000	1.07914700	0.68864900
C	-3.01286000	0.63289800	2.51699000
C	-4.65638200	-0.05810600	-1.43374400
C	-2.93533500	-1.80423000	-2.03028000
C	4.32099200	-2.82392000	0.67386700
H	3.88448800	-3.89625400	-1.13257300
C	1.28131300	-5.24905300	-1.34504000
C	1.49793900	-3.11678000	-2.71246600
H	0.15577400	-3.44557100	-1.08591200
H	4.47102800	-1.71488500	2.50428900
C	2.62911200	0.27674500	3.24435000
C	1.96061200	-1.90720700	4.33151100
H	0.84273100	-0.82655500	2.84525200
C	-5.24443500	0.86130200	-0.57160900
H	-5.16393600	1.79610700	1.35775100
C	-3.96749200	0.05938000	3.58581400
C	-2.73968500	2.12348200	2.79164800
H	-2.05510600	0.10855900	2.60157300
H	-5.09128600	-0.22271400	-2.41521600
C	-2.65645100	-1.20127200	-3.42025200
C	-3.85587200	-3.03762900	-2.14119000
H	-1.97356900	-2.14006300	-1.63159900

H	5.39098500	-3.00302900	0.60940500
H	1.03563200	-5.67965900	-0.36719600
H	2.28801400	-5.59033000	-1.61288800
H	0.58409900	-5.66209400	-2.08357000
H	1.38283600	-2.02760200	-2.70540400
H	0.81274300	-3.52855500	-3.46310400
H	2.52125800	-3.34744900	-3.03173000
H	2.63569000	0.87514000	2.32834500
H	3.67068900	0.12408000	3.55066000
H	2.13900300	0.85935500	4.03317400
H	1.41662800	-2.85310700	4.22897100
H	1.52968000	-1.35632100	5.17604400
H	2.99874600	-2.15199000	4.58602100
H	-6.13135100	1.40786800	-0.88161800
H	-4.16319500	-1.00854900	3.43357700
H	-4.93529500	0.57422500	3.56267700
H	-3.54481700	0.18842600	4.58965700
H	-2.07017100	2.55128400	2.04186100
H	-2.27418300	2.24535200	3.77734800
H	-3.66655200	2.70878900	2.79364400
H	-2.06038300	-0.28973200	-3.32775600
H	-3.58658400	-0.95037700	-3.94463800
H	-2.11711600	-1.92608300	-4.04280200

H	-4.03074700	-3.50794600	-1.16591900
H	-3.41316000	-3.78916100	-2.80630100
H	-4.83442800	-2.76287800	-2.55284400
N	1.31556500	1.25219000	-1.96042000
C	-0.27787200	5.08122600	1.37270300
C	-1.09686200	5.09137400	0.23975600
H	1.14063800	3.94141300	2.53235800
C	0.50534000	3.95847100	1.65043100
C	-1.12532000	3.98916700	-0.61272000
C	-0.33044700	2.86220900	-0.34827600
C	0.47501200	2.85488300	0.79735800
H	-1.75876800	3.97706300	-1.49394700
H	1.07343000	1.97699800	1.01613600
H	-0.25402000	5.94115700	2.03744200
H	-1.71433100	5.95957800	0.02233100
C	2.45629400	1.99245800	-1.54673900
C	2.69125800	3.30005200	-2.01373700
C	3.38404800	1.43514300	-0.64904100
C	3.80774200	4.01991700	-1.59403500
H	1.97658400	3.75864400	-2.69115000
C	4.49714500	2.16271200	-0.22262300
H	3.22657600	0.41867700	-0.29900500
C	4.71750200	3.45791400	-0.69355000

H	3.96153900	5.03158200	-1.96190100
H	5.20045700	1.70706100	0.47064700
H	5.58646100	4.02259500	-0.36618100
C	1.19625700	1.05476500	-3.40518200
H	1.43076100	1.96913800	-3.96677300
H	1.87374900	0.26168500	-3.75246000
H	0.16705400	0.77408200	-3.63869000

Structure **4.8**

C	1.23502800	0.39113300	-0.00000800
O	1.97337600	-0.74367700	0.00001000
O	1.73031000	1.50174400	-0.00002600
C	3.39455500	-0.54791800	0.00001000
H	3.70670000	0.00651200	0.88924400
H	3.82782600	-1.54873600	0.00006000
H	3.70671000	0.00642500	-0.88927500
C	-0.23032800	0.11919200	-0.00000300
C	-1.09864200	1.21976300	-0.00002700
C	-0.75333600	-1.18174400	0.00002600
C	-2.47731300	1.02167000	-0.00002300
H	-0.67215900	2.21745600	-0.00004800
C	-2.13401100	-1.37560100	0.00003100

H	-0.07783300	-2.02976100	0.00004400
C	-2.99650900	-0.27618600	0.00000700
H	-2.53761800	-2.38436900	0.00005300
H	-4.07230500	-0.43076900	0.00001000
H	-3.14746800	1.87685400	-0.00004200

Structure **4.17**

C	0.00382900	-1.89545200	-0.11266300
N	0.98201500	-2.69732100	-0.65779400
N	-0.96164100	-2.77787600	0.32270100
C	0.70100800	-4.14525000	-0.61264900
C	-0.67441000	-4.20013900	0.04905100
H	1.47011900	-4.66797200	-0.03184200
H	0.70547700	-4.56923500	-1.62378700
H	-0.67777500	-4.78130800	0.97812900
H	-1.44267800	-4.62406200	-0.60885800
C	-2.28284700	-2.50293600	0.80885200
C	-3.34378300	-2.38510500	-0.11894000
C	-2.53475200	-2.56055700	2.19913600
C	-4.64802300	-2.25730400	0.37377100
C	-3.85942700	-2.45127400	2.64067800
C	-4.90912000	-2.29298900	1.74061800
H	-5.47277200	-2.14799300	-0.32541200

H	-4.07119900	-2.49512000	3.70559800
H	-5.93050700	-2.20814400	2.10340200
C	2.28712200	-2.34086000	-1.13403800
C	3.37968500	-2.38683300	-0.23702400
C	2.49123800	-2.15793300	-2.52074400
C	4.66861000	-2.18896000	-0.74668100
C	3.80155400	-1.98250100	-2.98331200
C	4.88334600	-1.99222200	-2.10777000
H	5.51762900	-2.20801900	-0.06858100
H	3.97671000	-1.84048200	-4.04644200
H	5.89300500	-1.85469800	-2.48680600
C	3.20024500	-2.67969600	1.24890700
C	3.94966900	-3.95905300	1.67263600
C	3.62300600	-1.48148500	2.11316400
H	2.13387400	-2.84024100	1.43112400
H	3.64826300	-4.82610900	1.07299300
H	5.03455100	-3.84452900	1.56236500
H	3.74739600	-4.18748500	2.72615800
H	3.04766700	-0.59253600	1.84448900
H	3.45210700	-1.69619200	3.17554100
H	4.68639100	-1.24690200	1.98681800
C	1.34118800	-2.18022700	-3.52185100
C	1.27095000	-0.87971700	-4.34152000

C	1.42934100	-3.40573800	-4.45423600
H	0.40969800	-2.25316000	-2.95247500
H	1.16226400	-0.01216600	-3.68390800
H	2.17065700	-0.73581900	-4.95203900
H	0.41095400	-0.90428500	-5.02108400
H	1.45685900	-4.34462800	-3.88918500
H	0.56372900	-3.43939900	-5.12702200
H	2.33257300	-3.36968600	-5.07536000
C	-1.42089300	-2.77679600	3.21794600
C	-1.41014200	-1.68906100	4.30701300
C	-1.51439700	-4.17603900	3.86181500
H	-0.46854400	-2.71036100	2.68289700
H	-1.32985400	-0.69248200	3.86442800
H	-2.32020900	-1.71775000	4.91845200
H	-0.55678100	-1.83384900	4.98013600
H	-1.50165200	-4.97296800	3.10971700
H	-0.67373400	-4.34208700	4.54657700
H	-2.44113800	-4.28426500	4.43844500
C	-3.11401900	-2.43328200	-1.62598500
C	-3.88940000	-3.59168200	-2.28526600
C	-3.45423600	-1.09006300	-2.28937800
H	-2.04791000	-2.60873000	-1.79592100
H	-3.64764200	-4.55729100	-1.82518900

H	-4.97361100	-3.45005700	-2.20419600
H	-3.64464500	-3.65301300	-3.35265400
H	-2.84686800	-0.28853300	-1.86148300
H	-3.25910600	-1.13517300	-3.36822300
H	-4.50896400	-0.82664900	-2.15108800
Ni	-0.00166600	-0.00001600	0.00004600
C	0.00400400	1.89542300	0.11267300
N	-0.96138300	2.77790800	-0.32275400
N	0.98226300	2.69723900	0.65775000
C	-0.67402200	4.20016400	-0.04920400
C	-2.28261600	2.50306200	-0.80888300
C	0.70138800	4.14519100	0.61250700
C	2.28732400	2.34069000	1.13405400
H	-1.44225400	4.62420300	0.60867300
H	-0.67733000	4.78126600	-0.97832400
C	-3.34357100	2.38542400	0.11891300
C	-2.53450800	2.56062400	-2.19917000
H	0.70589300	4.56924600	1.62361500
H	1.47054900	4.66780200	0.03166500
C	3.37993300	2.38662200	0.23709500
C	2.49136300	2.15772900	2.52076600
C	-4.64782200	2.25773800	-0.37379500
C	-3.11381200	2.43371100	1.62595600

C	-3.85919400	2.45146800	-2.64071200
C	-1.42061900	2.77667800	-3.21798400
C	4.66882500	2.18868500	0.74681100
C	3.20058200	2.67952400	-1.24884000
C	3.80164800	1.98222300	2.98339500
C	1.34126500	2.18006400	3.52181600
C	-4.90890900	2.29335900	-1.74064700
H	-5.47258800	2.14857700	0.32539000
C	-3.88909200	3.59223800	2.28513300
C	-3.45415400	1.09058100	2.28946300
H	-2.04768900	2.60907800	1.79588500
H	-4.07095600	2.49527300	-3.70563600
C	-1.40999900	1.68888400	-4.30699300
C	-1.51394100	4.17590200	-3.86191900
H	-0.46828100	2.71015100	-2.68292600
C	4.88348400	1.99191100	2.10790700
H	5.51787900	2.20771800	0.06875500
C	3.95003000	3.95889200	-1.67249000
C	3.62339900	1.48133500	-2.11310100
H	2.13422100	2.84007200	-1.43111700
H	3.97674500	1.84017600	4.04653100
C	1.27091200	0.87954400	4.34145800
C	1.42944100	3.40555300	4.45422900

H	0.40980800	2.25305800	2.95239400
H	-5.93030400	2.20861100	-2.10343000
H	-3.64724600	4.55778400	1.82497000
H	-4.97331500	3.45070300	2.20407500
H	-3.64433200	3.65364200	3.35251600
H	-2.84684700	0.28896200	1.86164700
H	-3.25903600	1.13576900	3.36830600
H	-4.50890200	0.82724300	2.15118100
H	-1.32981100	0.69232000	-3.86435400
H	-2.32007500	1.71763800	-4.91841700
H	-0.55663300	1.83354300	-4.98013700
H	-1.50108300	4.97286300	-3.10985600
H	-0.67326000	4.34180500	-4.54669500
H	-2.44067000	4.28422600	-4.43854800
H	5.89311700	1.85433300	2.48699200
H	3.64858400	4.82593300	-1.07284400
H	5.03490500	3.84436800	-1.56215400
H	3.74782200	4.18735000	-2.72601900
H	3.04805400	0.59237500	-1.84447400
H	3.45255200	1.69606400	-3.17548200
H	4.68678000	1.24676000	-1.98670600
H	1.16223000	0.01200900	3.68382500
H	2.17056900	0.73559200	4.95203700

H	0.41087100	0.90413900	5.02096400
H	1.45704300	4.34445300	3.88920000
H	0.56379700	3.43925100	5.12697300
H	2.33264000	3.36943400	5.07539700

Structure **4.18**

C	-2.14961700	-1.77703200	-1.22473900
Ni	0.28742500	-0.37159500	-0.76876300
O	-2.19030300	-2.90546000	-0.73641200
C	1.22838000	0.61157200	0.54171900
N	2.39069700	0.20948100	1.12724100
N	0.90710600	1.80755200	1.10953600
C	2.84545800	1.09452800	2.21755500
C	1.93137800	2.31638700	2.04390900
H	3.90735800	1.33649200	2.10943500
H	2.70708900	0.60340400	3.18993100
H	2.45684600	3.17301200	1.60058100
H	1.47648400	2.64823400	2.98251600
C	-0.21015900	2.62890700	0.74341000
C	-1.36387000	2.60730300	1.55874700
C	-0.11508700	3.48099900	-0.37979100
C	-2.43448900	3.44088900	1.21189700
C	-1.21747000	4.28840200	-0.68871600
C	-2.36731700	4.27177200	0.09638900

H	-3.33329200	3.43712300	1.82269600
H	-1.16961500	4.94680300	-1.55197800
H	-3.20898400	4.91098000	-0.15781000
C	3.02317100	-1.05958400	0.90165600
C	4.13272700	-1.12029500	0.03023200
C	2.55460900	-2.20446800	1.58542900
C	4.74563000	-2.36292500	-0.17300900
C	3.19990100	-3.42352900	1.34282400
C	4.28120100	-3.50753600	0.46953000
H	5.59808500	-2.43461400	-0.84323400
H	2.85364100	-4.31935600	1.85081700
H	4.76743500	-4.46419700	0.29661200
C	4.68316700	0.11630300	-0.67411000
C	6.10440600	0.45430800	-0.17937100
C	4.65582900	-0.02605600	-2.20763700
H	4.03240000	0.95897300	-0.42081000
H	6.13161300	0.59209400	0.90803200
H	6.81323900	-0.34464500	-0.42739800
H	6.46570000	1.37712700	-0.64909800
H	3.64069300	-0.22459600	-2.56472700
H	5.01338300	0.89720600	-2.67998200
H	5.30309500	-0.84284200	-2.54934000
C	1.41850400	-2.14819200	2.60417200

C	0.25938000	-3.10344000	2.26322400
C	1.95258600	-2.42312400	4.02610400
H	1.00583900	-1.13506900	2.59456800
H	-0.19536500	-2.85777800	1.29931800
H	0.58913700	-4.14847900	2.22931100
H	-0.52121000	-3.03104400	3.03034800
H	2.75866300	-1.73071200	4.29679600
H	1.14887200	-2.31721600	4.76466100
H	2.35094000	-3.44105100	4.11140700
C	1.14193500	3.56618200	-1.24036400
C	0.87120800	3.14743800	-2.69792800
C	1.76862300	4.97372200	-1.17444200
H	1.87365500	2.85902300	-0.83902500
H	0.49476000	2.12047000	-2.74491400
H	0.13734600	3.80677100	-3.17725600
H	1.79659700	3.19834900	-3.28435000
H	1.98871400	5.26828000	-0.14154300
H	2.70533100	5.00171600	-1.74392500
H	1.09992000	5.73203500	-1.59847900
C	-1.47570800	1.71027500	2.78826000
C	-1.67448100	2.53338500	4.07664800
C	-2.58941300	0.65811700	2.62625000
H	-0.53293600	1.16354100	2.88713400

H	-0.87064000	3.26604100	4.21572300
H	-2.62286400	3.08313900	4.06170400
H	-1.68914800	1.87363600	4.95231800
H	-2.41753400	0.03505900	1.74308100
H	-2.62394700	0.00196900	3.50426300
H	-3.57566000	1.12603700	2.52394000
C	-0.95229800	-1.37318900	-2.04942300
C	0.27103000	-2.08913800	-1.79271900
C	-1.06111400	-0.67511600	-3.29811300
C	1.31672200	-2.06417300	-2.75782400
H	0.27989300	-2.85814800	-1.02596200
C	-0.02903000	-0.67512500	-4.21494200
H	-1.99386500	-0.18797000	-3.56170000
C	1.17624200	-1.36663400	-3.94189700
H	-0.15295700	-0.15879600	-5.16339400
N	-3.20370200	-0.87359700	-1.06335500
C	-3.06977900	0.55764300	-1.35164800
H	-2.01663800	0.83850800	-1.32431100
H	-3.48557100	0.84183700	-2.32693600
H	-3.59338400	1.12443400	-0.57790900
C	-4.47169000	-1.29774300	-0.55304700
C	-5.63588300	-0.71649900	-1.08257100
C	-4.59896100	-2.24016600	0.48154600

C	-6.89459500	-1.06778400	-0.59558900
H	-5.56198300	0.00511400	-1.88964800
C	-5.86355300	-2.58893500	0.95561900
H	-3.71372800	-2.70102400	0.89334300
C	-7.01769700	-2.00919000	0.42625200
H	-7.77978900	-0.60634500	-1.02597000
H	-5.94116800	-3.32067400	1.75586700
H	-7.99778600	-2.28665100	0.80459700
H	2.22120800	-2.63348900	-2.56019200
H	1.97669700	-1.36796100	-4.67736800

Structure **4.19**

C	-0.41090300	1.70452500	-1.30793600
O	-1.27877500	1.65703600	-2.17617600
Ni	0.40830600	0.05859500	-0.79369300
C	-0.53308900	-1.13628300	0.34505000
N	0.15780700	-2.15078600	0.93539700
N	-1.83734300	-1.30647600	0.66644700
C	-0.68304300	-3.07704700	1.71682700
C	1.57716800	-2.35308900	0.83382500
C	-2.09673600	-2.54569400	1.43420300
C	-2.96286200	-0.52956700	0.21462100
H	-0.53815800	-4.10860600	1.37789700

H	-0.42030400	-3.03111500	2.78002800
C	2.08717200	-3.11180400	-0.24469400
C	2.42592900	-1.84503100	1.84541200
H	-2.69528700	-3.23785500	0.83039200
H	-2.65683900	-2.32401400	2.34680100
C	-3.55317100	0.39068700	1.11003500
C	-3.51242900	-0.77510400	-1.06328900
C	3.47029500	-3.32500500	-0.30641500
C	1.19037100	-3.71011500	-1.32425800
C	3.79929400	-2.09592300	1.74037400
C	1.89350300	-1.06190100	3.04194300
C	-4.69676000	1.07914700	0.68864900
C	-3.01286000	0.63289800	2.51699000
C	-4.65638200	-0.05810600	-1.43374400
C	-2.93533500	-1.80423000	-2.03028000
C	4.32099200	-2.82392000	0.67386700
H	3.88448800	-3.89625400	-1.13257300
C	1.28131300	-5.24905300	-1.34504000
C	1.49793900	-3.11678000	-2.71246600
H	0.15577400	-3.44557100	-1.08591200
H	4.47102800	-1.71488500	2.50428900
C	2.62911200	0.27674500	3.24435000
C	1.96061200	-1.90720700	4.33151100

H	0.84273100	-0.82655500	2.84525200
C	-5.24443500	0.86130200	-0.57160900
H	-5.16393600	1.79610700	1.35775100
C	-3.96749200	0.05938000	3.58581400
C	-2.73968500	2.12348200	2.79164800
H	-2.05510600	0.10855900	2.60157300
H	-5.09128600	-0.22271400	-2.41521600
C	-2.65645100	-1.20127200	-3.42025200
C	-3.85587200	-3.03762900	-2.14119000
H	-1.97356900	-2.14006300	-1.63159900
H	5.39098500	-3.00302900	0.60940500
H	1.03563200	-5.67965900	-0.36719600
H	2.28801400	-5.59033000	-1.61288800
H	0.58409900	-5.66209400	-2.08357000
H	1.38283600	-2.02760200	-2.70540400
H	0.81274300	-3.52855500	-3.46310400
H	2.52125800	-3.34744900	-3.03173000
H	2.63569000	0.87514000	2.32834500
H	3.67068900	0.12408000	3.55066000
H	2.13900300	0.85935500	4.03317400
H	1.41662800	-2.85310700	4.22897100
H	1.52968000	-1.35632100	5.17604400
H	2.99874600	-2.15199000	4.58602100

H	-6.13135100	1.40786800	-0.88161800
H	-4.16319500	-1.00854900	3.43357700
H	-4.93529500	0.57422500	3.56267700
H	-3.54481700	0.18842600	4.58965700
H	-2.07017100	2.55128400	2.04186100
H	-2.27418300	2.24535200	3.77734800
H	-3.66655200	2.70878900	2.79364400
H	-2.06038300	-0.28973200	-3.32775600
H	-3.58658400	-0.95037700	-3.94463800
H	-2.11711600	-1.92608300	-4.04280200
H	-4.03074700	-3.50794600	-1.16591900
H	-3.41316000	-3.78916100	-2.80630100
H	-4.83442800	-2.76287800	-2.55284400
N	1.31556500	1.25219000	-1.96042000
C	-0.27787200	5.08122600	1.37270300
C	-1.09686200	5.09137400	0.23975600
H	1.14063800	3.94141300	2.53235800
C	0.50534000	3.95847100	1.65043100
C	-1.12532000	3.98916700	-0.61272000
C	-0.33044700	2.86220900	-0.34827600
C	0.47501200	2.85488300	0.79735800
H	-1.75876800	3.97706300	-1.49394700
H	1.07343000	1.97699800	1.01613600

H	-0.25402000	5.94115700	2.03744200
H	-1.71433100	5.95957800	0.02233100
C	2.45629400	1.99245800	-1.54673900
C	2.69125800	3.30005200	-2.01373700
C	3.38404800	1.43514300	-0.64904100
C	3.80774200	4.01991700	-1.59403500
H	1.97658400	3.75864400	-2.69115000
C	4.49714500	2.16271200	-0.22262300
H	3.22657600	0.41867700	-0.29900500
C	4.71750200	3.45791400	-0.69355000
H	3.96153900	5.03158200	-1.96190100
H	5.20045700	1.70706100	0.47064700
H	5.58646100	4.02259500	-0.36618100
C	1.19625700	1.05476500	-3.40518200
H	1.43076100	1.96913800	-3.96677300
H	1.87374900	0.26168500	-3.75246000
H	0.16705400	0.77408200	-3.63869000

Structure **4.20**

C	-0.79598300	1.63253100	-1.06324600
O	-1.62465100	1.56196200	-1.95177800
Ni	0.39493800	0.21509700	-0.84333000
C	-0.54627600	-1.03856200	0.28790800
N	0.18951300	-1.97623100	0.94276800
N	-1.84844100	-1.36417600	0.46093600
C	-0.61911200	-3.02084400	1.60258200
C	1.62347900	-2.01568900	1.05703400
C	-2.04595200	-2.63927100	1.18729600
C	-3.01543400	-0.67742700	-0.02931800
H	-0.32065000	-4.01279000	1.24786100
H	-0.46996300	-2.99078600	2.68775500
C	2.38013400	-2.67826300	0.06305800
C	2.23225700	-1.47226700	2.21276100
H	-2.50484500	-3.37737700	0.51985600
H	-2.71457100	-2.49420600	2.04037200
C	-3.72014200	0.17010700	0.85518000
C	-3.48559400	-0.94601800	-1.33289300
C	3.76735300	-2.75790600	0.23941800
C	1.74363300	-3.33493300	-1.15852600
C	3.62137400	-1.58920200	2.34179900
C	1.43315200	-0.79114500	3.32074700

C	-4.88892900	0.78198700	0.38648600
C	-3.28932900	0.39434200	2.30347100
C	-4.66193400	-0.31174800	-1.74827800
C	-2.78293400	-1.91387800	-2.27999300
C	4.38500800	-2.22156100	1.36458900
H	4.37133200	-3.25208900	-0.51574800
C	1.83155200	-4.87265700	-1.06433700
C	2.35644200	-2.82857300	-2.47838700
H	0.68307900	-3.06424300	-1.17156700
H	4.11197700	-1.17836900	3.21980700
C	1.92828700	0.64042600	3.60194200
C	1.44961300	-1.62867000	4.61679200
H	0.39412200	-0.71029200	2.98575200
C	-5.35506100	0.54972400	-0.90394100
H	-5.44457800	1.44416900	1.04467000
C	-4.28624500	-0.26467100	3.28113200
C	-3.10946200	1.88376400	2.65063800
H	-2.31529900	-0.08616500	2.44364800
H	-5.03796600	-0.49381700	-2.75073100
C	-2.48244100	-1.27653900	-3.64984700
C	-3.60025900	-3.21191300	-2.44917000
H	-1.82010900	-2.18207700	-1.83414400
H	5.46283900	-2.29649400	1.48059200

H	1.36607700	-5.25214000	-0.14670600
H	2.87472300	-5.21016400	-1.06848900
H	1.32679600	-5.33790700	-1.91936300
H	2.29787500	-1.73731600	-2.54063900
H	1.81572900	-3.25820600	-3.33047400
H	3.40809500	-3.12314000	-2.57530100
H	1.91795000	1.25073800	2.69439000
H	2.95020300	0.64390700	3.99838200
H	1.28380900	1.12373300	4.34558500
H	1.07376000	-2.64491900	4.45081500
H	0.82778000	-1.15699000	5.38698100
H	2.46652800	-1.71679600	5.01672500
H	-6.26409400	1.03519600	-1.24943600
H	-4.42048300	-1.33272500	3.07336900
H	-5.27356000	0.20699800	3.21254400
H	-3.93742300	-0.15952300	4.31556100
H	-2.38349100	2.36429700	1.99041400
H	-2.75688800	1.98811600	3.68392100
H	-4.05439400	2.43363400	2.57031800
H	-1.95591700	-0.32749200	-3.52324500
H	-3.40208700	-1.08368900	-4.21541400
H	-1.86492100	-1.95393900	-4.25219500
H	-3.78918300	-3.70545700	-1.48823900

H	-3.06784100	-3.91965100	-3.09607200
H	-4.57412700	-3.00652000	-2.90918000
N	1.64499000	0.85103200	-2.06110100
C	-0.51241900	5.20990700	1.31046900
C	-1.57591000	5.03335400	0.41812800
H	1.30225000	4.36453300	2.11561100
C	0.46712000	4.22224400	1.43513400
C	-1.65863500	3.87225100	-0.34576600
C	-0.68201800	2.86993900	-0.21607500
C	0.38001700	3.05401800	0.67646900
H	-2.47131500	3.71517700	-1.04798000
H	1.14839100	2.29130300	0.74712700
H	-0.44570500	6.11916900	1.90261100
H	-2.33551400	5.80470000	0.31855700
C	2.78814700	1.55341500	-1.68758200
C	3.41970300	2.52388600	-2.50256200
C	3.39948300	1.27683200	-0.43761300
C	4.57362700	3.18452700	-2.07677100
H	3.00292300	2.77358700	-3.47154500
C	4.54163300	1.94704600	-0.01916800
H	2.96779600	0.50085500	0.18875900
C	5.14509500	2.91312600	-0.83420800
H	5.02665000	3.92650700	-2.73121100

H	4.97784700	1.69924300	0.94640200
H	6.04424200	3.43025700	-0.51065200
C	1.20132400	1.04467200	-3.43675600
H	0.90411200	2.08203400	-3.66199900
H	1.99365700	0.76683000	-4.14946800
H	0.33473800	0.40935300	-3.63090400

Structure **4.21**

C	1.08039100	0.00658900	-1.61567600
O	-2.27793600	-3.38491800	0.82424500
O	0.64929800	0.69673500	-2.52569700
C	-3.12216600	-4.19899800	0.03870100
H	-3.60401500	-3.64514800	-0.78307600
H	-2.59266700	-5.06454300	-0.39141000
H	-3.91302000	-4.58399200	0.69170600
C	2.51891100	-0.42474500	-1.59783400
C	3.15238100	-0.83785000	-0.42046800
C	3.24024800	-0.41452500	-2.80459000
C	4.49287400	-1.22267500	-0.44226700
H	2.59349700	-0.84950400	0.50838500
C	4.57323500	-0.81676800	-2.82809500
H	2.73699800	-0.08835700	-3.70971400
C	5.20239000	-1.21808700	-1.64482400

H	5.12400700	-0.81693800	-3.76532200
Ni	-0.10927300	-0.64980300	-0.33788200
C	-0.70220500	1.09693700	0.25422800
N	-1.99977200	1.46711400	0.14806100
N	-0.01585100	2.15309000	0.75431900
C	-2.22457100	2.89016500	0.47891000
C	-3.09923000	0.64835600	-0.30111800
C	-0.89859400	3.27882200	1.13642800
C	1.37715700	2.19840400	1.11699300
H	-2.42070600	3.45778200	-0.43858700
H	-3.08349100	3.00409400	1.14382000
C	-3.40925700	0.58662300	-1.67998200
C	-3.89723600	0.00160800	0.67209500
H	-0.50217600	4.22756500	0.77024200
H	-0.97270800	3.33615700	2.22925300
C	1.80787900	1.59320800	2.32177900
C	2.26594700	2.93785400	0.30095800
C	-4.51335300	-0.18458800	-2.06497700
C	-2.64244100	1.37844300	-2.73633300
C	-4.98910400	-0.75374200	0.22826300
C	-3.65000700	0.14556300	2.17217400
C	3.16425300	1.69267200	2.65654500
C	0.84757300	0.91711800	3.29875700

C	3.60950300	3.00834100	0.68904700
C	1.80551500	3.71155700	-0.93381600
C	-5.29241500	-0.85430000	-1.12570000
H	-4.77215200	-0.25303300	-3.11731400
C	-3.45554200	2.61703900	-3.17344800
C	-2.26475500	0.53613400	-3.96770800
H	-1.70118700	1.71772500	-2.29724100
H	-5.60834300	-1.26969800	0.95572200
C	-3.63922000	-1.20493600	2.91396400
C	-4.69286900	1.09145400	2.80757000
H	-2.66268600	0.60020300	2.30614700
C	4.06057800	2.38373800	1.84684100
H	3.52167600	1.23137400	3.57211100
C	0.52917300	1.85879600	4.48128600
C	1.37046600	-0.42960500	3.83091700
H	-0.08912800	0.71248400	2.77163200
H	4.31200200	3.56242600	0.07371000
C	2.65484500	3.42574300	-2.18598200
C	1.79663800	5.22959800	-0.64533900
H	0.78333100	3.39690600	-1.16546700
H	-6.14425700	-1.44682000	-1.44952600
H	-3.72180400	3.25708600	-2.32413200
H	-4.39105600	2.31983800	-3.66293000

H	-2.88038100	3.21988100	-3.88639500
H	-1.67359300	-0.33703300	-3.68204000
H	-1.65561900	1.13684300	-4.65185400
H	-3.14810000	0.19600100	-4.52142100
H	-2.99644900	-1.93505200	2.41434000
H	-4.64716300	-1.63437100	2.97139500
H	-3.29476800	-1.05852300	3.94525600
H	-4.70839700	2.07798400	2.32948200
H	-4.48181300	1.23383300	3.87432200
H	-5.70169900	0.67096100	2.71987300
H	5.10899200	2.44646600	2.12627700
H	0.12079200	2.81833900	4.14489900
H	1.43445800	2.07304000	5.06172200
H	-0.20131000	1.39555400	5.15525600
H	1.64847200	-1.10607500	3.01817500
H	0.59424200	-0.91994400	4.42993700
H	2.24549700	-0.29991300	4.47847400
H	2.64174600	2.36522800	-2.44266200
H	3.69659700	3.73975800	-2.05221000
H	2.25155200	3.98394500	-3.03918400
H	1.20361300	5.48364600	0.24086200
H	1.38518100	5.77978900	-1.49996500
H	2.81434400	5.59848700	-0.46990400

N	-0.00759000	-2.47526100	-0.75877100
C	0.94442100	-3.29761400	-0.13669000
C	1.05052600	-3.26235200	1.27392000
C	1.79272600	-4.19158400	-0.82556100
C	1.97915300	-4.04288800	1.95262800
H	0.35294800	-2.63852000	1.82561200
C	2.71696300	-4.97893100	-0.13594200
H	1.74820200	-4.26016800	-1.90684900
C	2.82744900	-4.90903400	1.25256100
H	2.02468400	-3.99474900	3.03834700
H	3.36081700	-5.65201600	-0.69792600
H	3.54512900	-5.52907400	1.78276500
C	-0.33366100	-2.83669500	-2.13956700
H	-1.19203800	-2.24617900	-2.47105800
H	0.49179700	-2.65214400	-2.84580400
H	-0.60108400	-3.90141900	-2.22005400
H	-1.55579100	-3.03305400	0.25338200
H	4.97756900	-1.53962700	0.47674200
H	6.24327900	-1.53123600	-1.66263800

Structure **4.22**

C	1.03646800	-0.08072400	-1.53652100
O	-1.05458800	-2.37315900	0.94761400

O	0.46663300	0.30960300	-2.55037900
C	-2.12349300	-3.22540200	0.56930900
H	-2.58545800	-2.93360900	-0.38330600
H	-1.77017300	-4.26495600	0.47222300
H	-2.90848500	-3.22004900	1.33355500
C	2.54205900	-0.09627900	-1.50242700
C	3.25704200	-0.05656100	-0.30072600
C	3.24547600	-0.14590400	-2.71878800
C	4.65207500	-0.04448400	-0.31020600
H	2.71756600	-0.02373000	0.63922900
C	4.63833400	-0.15965700	-2.72744000
H	2.67918200	-0.16681000	-3.64520500
C	5.34423200	-0.10266100	-1.52106500
H	5.17571200	-0.20951600	-3.67133600
Ni	-0.01041000	-0.88164900	-0.19715700
C	-1.03157700	0.76228200	0.06102900
N	-2.36255200	0.89051400	-0.15244200
N	-0.56009400	1.99494400	0.38442000
C	-2.81890300	2.29725600	-0.12035600
C	-3.35877500	-0.12388300	-0.37630700
C	-1.63923200	2.99660700	0.54347000
C	0.76331000	2.36369100	0.81351000
H	-2.99484100	2.64800400	-1.14487400

H	-3.75129200	2.38910600	0.44117800
C	-3.62928100	-0.57373000	-1.68679500
C	-4.14444400	-0.52476900	0.72964500
H	-1.37385900	3.93838600	0.06259500
H	-1.80847300	3.19048000	1.61019300
C	1.20784700	2.00064800	2.10806900
C	1.53658400	3.19947000	-0.02803100
C	-4.68450200	-1.48118900	-1.85792500
C	-2.86635800	-0.06143000	-2.90493100
C	-5.18592600	-1.43047100	0.49951800
C	-3.91583800	0.01267500	2.14211100
C	2.47325200	2.44430400	2.51325600
C	0.34170200	1.22352200	3.09845500
C	2.79175800	3.61477900	0.43302900
C	1.03330500	3.72006900	-1.37496700
C	-5.45336300	-1.90978600	-0.77991900
H	-4.91376000	-1.84710500	-2.85453000
C	-3.73132400	0.93630100	-3.70494600
C	-2.37600400	-1.19463300	-3.82339100
H	-1.97068600	0.45974900	-2.56036400
H	-5.79628000	-1.76526300	1.33393400
C	-3.44395500	-1.08024300	3.12090000
C	-5.16989600	0.73071300	2.68157500

H	-3.11119500	0.75247200	2.09383100
C	3.26361200	3.23532300	1.68478600
H	2.84051600	2.17613200	3.49924500
C	-0.29350800	2.18228800	4.12936600
C	1.11093400	0.10685800	3.82710900
H	-0.46742500	0.73977500	2.54492700
H	3.40753700	4.24728800	-0.19941200
C	2.01283500	3.46372200	-2.53521800
C	0.71908000	5.23073900	-1.28679700
H	0.11036400	3.18615900	-1.62085100
H	-6.26754700	-2.61236800	-0.93808800
H	-4.06263600	1.77828000	-3.08573300
H	-4.62996900	0.45050100	-4.10482500
H	-3.16230600	1.34075200	-4.55029700
H	-1.76422800	-1.91339400	-3.27076100
H	-1.75600200	-0.77738100	-4.62404200
H	-3.20587100	-1.73779300	-4.29152300
H	-2.50898400	-1.53270200	2.77718300
H	-4.19540100	-1.87183300	3.22972500
H	-3.27885900	-0.64534600	4.11478800
H	-5.50937100	1.52437300	2.00504600
H	-4.95850500	1.18303100	3.65781400
H	-6.00579300	0.03450100	2.81575700

H	4.24226600	3.56712400	2.02159600
H	-0.88384200	2.97117400	3.64972100
H	0.47918900	2.67261600	4.73378100
H	-0.95369900	1.63094400	4.80970300
H	1.62265400	-0.55355200	3.12219000
H	0.41404600	-0.50051700	4.41582700
H	1.85880000	0.50903200	4.52060300
H	2.19940500	2.39758200	-2.67083000
H	2.97356300	3.96731600	-2.37654100
H	1.58738300	3.85391200	-3.46750300
H	0.03086000	5.47004100	-0.46786800
H	0.27030900	5.58331000	-2.22312000
H	1.63460800	5.81006100	-1.11801800
N	0.92178900	-2.68365000	-0.39323600
C	2.12042900	-3.01483300	0.27682000
C	2.15565600	-2.90515200	1.68370500
C	3.26809500	-3.49845300	-0.37601300
C	3.30067000	-3.23983100	2.39936300
H	1.25503200	-2.58666000	2.20032900
C	4.41161100	-3.83700400	0.35126500
H	3.28057200	-3.59330600	-1.45625400
C	4.44306200	-3.70649100	1.73901700
H	3.29556700	-3.15263900	3.48357900

H	5.28700600	-4.20300500	-0.18031300
H	5.33460000	-3.97417200	2.29955900
C	0.74714200	-3.26553300	-1.72484100
H	-0.29358200	-3.12887100	-2.03267400
H	1.38342100	-2.79054000	-2.48389500
H	0.96857500	-4.34312700	-1.72273600
H	-0.08858100	-2.80021700	0.37976100
H	5.19689800	-0.00633500	0.62884700
H	6.43142300	-0.10819800	-1.52668800

Structure **4.23**

C	1.05024100	0.03393300	-1.59671100
O	-1.07582600	-1.77382700	1.06485400
O	0.55090900	0.50477500	-2.61926700
C	-1.79676600	-2.91702700	0.74298000
H	-2.27130100	-2.88781300	-0.25706700
H	-1.18981600	-3.85717800	0.78478200
H	-2.61743500	-3.09315200	1.45870800
C	2.56595900	0.00456100	-1.50848900
C	3.22614100	-0.13051300	-0.28236100
C	3.32875400	0.10388900	-2.68572600
C	4.62108100	-0.14351200	-0.22483300
H	2.64122000	-0.21035700	0.62796900

C	4.72028200	0.06530900	-2.63386900
H	2.80425100	0.21788500	-3.63030500
C	5.36963500	-0.05261500	-1.39952100
H	5.30202500	0.13356700	-3.55011800
Ni	-0.01640600	-0.83805100	-0.26877000
C	-0.98380900	0.79324500	0.03053700
N	-2.30814000	0.93550700	-0.21012800
N	-0.51154800	1.99945400	0.43499700
C	-2.74715600	2.34564000	-0.12910100
C	-3.30303300	-0.07663800	-0.45789700
C	-1.59213000	2.99367600	0.62587800
C	0.80119100	2.31035800	0.93483600
H	-2.86317100	2.75176300	-1.14165500
H	-3.70486500	2.42788700	0.38841100
C	-3.51540000	-0.56304600	-1.76560100
C	-4.13078100	-0.46035000	0.62334500
H	-1.30937100	3.96527300	0.22032300
H	-1.80062900	3.11396900	1.69655100
C	1.21640500	1.80018500	2.18957900
C	1.60138900	3.21870500	0.20136600
C	-4.55152100	-1.48864900	-1.95776800
C	-2.70660600	-0.07153200	-2.96162500
C	-5.14668700	-1.38943400	0.37412000

C	-3.98121200	0.11536600	2.03124000
C	2.47548600	2.18850400	2.66536000
C	0.32673800	0.91898000	3.06671800
C	2.84733900	3.57449000	0.73144400
C	1.14088400	3.86500400	-1.10569400
C	-5.35587900	-1.90515300	-0.90185500
H	-4.73596800	-1.87999700	-2.95376700
C	-3.48068000	1.02008200	-3.73163500
C	-2.30813100	-1.20424200	-3.92458400
H	-1.77305800	0.36446900	-2.59905000
H	-5.78429700	-1.71297600	1.19242800
C	-3.55861000	-0.94786600	3.06210100
C	-5.26620400	0.84309800	2.47746500
H	-3.17508900	0.85369300	2.01059200
C	3.28761600	3.06056100	1.94621700
H	2.82001200	1.80963900	3.62252200
C	-0.37724800	1.77204300	4.14501100
C	1.08687400	-0.24098800	3.73389000
H	-0.43982300	0.45557000	2.44183800
H	3.48111700	4.26442000	0.18198900
C	2.14678700	3.68692600	-2.25788600
C	0.84843700	5.36727400	-0.89506300
H	0.21738900	3.36963000	-1.41999800

H	-6.15189600	-2.62507900	-1.07460600
H	-3.74215100	1.86757900	-3.08780600
H	-4.41542400	0.62246100	-4.14696400
H	-2.87575100	1.40198800	-4.56264200
H	-1.85462800	-2.04210100	-3.38479000
H	-1.57630500	-0.83123100	-4.64899500
H	-3.16416700	-1.59519400	-4.48820800
H	-2.59030800	-1.36758000	2.77577200
H	-4.29647800	-1.75632800	3.13362200
H	-3.47224200	-0.49116000	4.05657800
H	-5.57035300	1.61618800	1.76112400
H	-5.11253800	1.32289500	3.45150600
H	-6.10641200	0.14695700	2.58266300
H	4.25967800	3.34751500	2.33903700
H	-0.96418000	2.58767700	3.70765200
H	0.35448500	2.22408400	4.82606700
H	-1.05520500	1.14984900	4.74136800
H	1.62706300	-0.84264500	2.99788500
H	0.37292200	-0.89931400	4.24104500
H	1.80364200	0.10873200	4.48700900
H	2.31605100	2.63118900	-2.47507200
H	3.11232500	4.15483800	-2.03284300
H	1.75476600	4.16094000	-3.16573600

H	0.13693000	5.54497500	-0.08032500
H	0.43724600	5.81021400	-1.81004300
H	1.76690000	5.91173300	-0.64519600
N	0.84513100	-2.70932100	-0.77058800
C	1.90226100	-3.18293400	0.10486000
C	1.62699000	-3.25573100	1.47954400
C	3.15488600	-3.57696000	-0.37397800
C	2.59977200	-3.73121700	2.35590600
H	0.66326900	-2.89164900	1.82968300
C	4.12446900	-4.04575400	0.51797800
H	3.39349200	-3.51512000	-1.42913500
C	3.85313300	-4.13185100	1.88191700
H	2.37616100	-3.78545300	3.41833300
H	5.09558600	-4.34635000	0.13353300
H	4.60791800	-4.50379600	2.56943300
C	1.03601600	-2.98631300	-2.20907700
H	0.12996100	-2.68822300	-2.73744500
H	1.86606400	-2.39732300	-2.59995200
H	1.23531300	-4.05101200	-2.38978200
H	-0.00081400	-3.19509400	-0.47929100
H	5.12117600	-0.23517400	0.73548500
H	6.45585000	-0.07494500	-1.35632200

Structure **4.24**

C	1.04086100	-0.55147800	-1.66674900
O	-0.56470900	-2.84935800	-0.93087500
O	0.86179300	0.45101200	-2.33794100
C	-1.06820100	-3.33474800	-2.14506300
H	-1.45896800	-4.35517900	-1.99978200
H	-1.88950900	-2.72300500	-2.55599800
H	-0.28192100	-3.39784700	-2.91815100
C	2.31927700	-1.34264800	-1.78138900
C	3.43129700	-0.72861900	-2.38434300
C	2.42918600	-2.65909000	-1.31181800
C	4.63733900	-1.41422400	-2.49814200
H	3.33181500	0.28473100	-2.75849500
C	3.63642800	-3.34793400	-1.44337100
H	1.54687900	-3.13444100	-0.89026800
C	4.74271900	-2.72678800	-2.02601200
H	3.71195300	-4.37353100	-1.09076200
Ni	-0.29063600	-1.13334100	-0.50956800
C	-0.54579700	0.50170500	0.46280100
N	-1.81243800	0.92827400	0.66565000
N	0.28053900	1.31576000	1.15402700
C	-1.89768400	2.13835200	1.50762500
C	-2.98373600	0.37400600	0.03679500

C	-0.44823300	2.29057800	1.99758800
C	1.70490400	1.16661100	1.28731100
H	-2.23219900	2.99350600	0.90796800
H	-2.61375100	1.99180500	2.32198400
C	-3.42473100	0.91418700	-1.19238600
C	-3.68665600	-0.66254000	0.69074800
H	-0.05417200	3.30019100	1.85864000
H	-0.33114400	2.02062000	3.05476200
C	2.22569600	0.15721100	2.12724600
C	2.54600100	2.08286500	0.61524400
C	-4.59371000	0.38788900	-1.75528900
C	-2.68582700	2.03770900	-1.91427500
C	-4.84776600	-1.15291300	0.08108600
C	-3.23160200	-1.25854500	2.01969400
C	3.61796600	0.04904900	2.23459700
C	1.34249500	-0.77615300	2.95118300
C	3.92943400	1.93509500	0.76792200
C	2.00162100	3.24203900	-0.21730900
C	-5.30093900	-0.63386100	-1.12791300
H	-4.95226900	0.78194400	-2.70205500
C	-3.54293000	3.31897100	-1.97505500
C	-2.22729600	1.61182800	-3.32225200
H	-1.77770000	2.26820500	-1.34891100

H	-5.40182000	-1.95523400	0.55993700
C	-2.96913400	-2.77415500	1.90716300
C	-4.23941400	-0.95163500	3.14594800
H	-2.28221400	-0.78600900	2.29183800
C	4.46420400	0.92231500	1.55904600
H	4.04359900	-0.72745700	2.86383000
C	1.51598200	-0.50656900	4.46045200
C	1.59293200	-2.26014300	2.62514100
H	0.29812300	-0.56728000	2.70090300
H	4.59772400	2.62250500	0.25719000
C	2.56440400	3.27157900	-1.65039100
C	2.26209200	4.58861300	0.49186000
H	0.91916800	3.10816100	-0.30897500
H	-6.20501200	-1.02847700	-1.58427400
H	-3.85763300	3.64611700	-0.97666600
H	-4.45002100	3.16398800	-2.57096700
H	-2.97666800	4.13527800	-2.43879300
H	-1.54181300	0.76258500	-3.26681700
H	-1.69458100	2.43788100	-3.80791900
H	-3.07752500	1.34212800	-3.95973000
H	-2.24671300	-2.99529300	1.11416300
H	-3.89275000	-3.32367600	1.68887900
H	-2.57490600	-3.15827500	2.85608600

H	-4.40378800	0.12669100	3.25961200
H	-3.87495000	-1.34340100	4.10310900
H	-5.21316300	-1.41443000	2.94665700
H	5.54173500	0.81918400	1.65588000
H	1.31049700	0.54123200	4.70982600
H	2.53693900	-0.73014200	4.79155400
H	0.83210600	-1.13614100	5.04223500
H	1.42742600	-2.46186900	1.56284500
H	0.91088500	-2.89445000	3.20378900
H	2.61768100	-2.56088700	2.87341300
H	2.29984300	2.35867900	-2.18915500
H	3.65485100	3.38571200	-1.65708500
H	2.14265900	4.12332200	-2.19783700
H	1.86115300	4.60068200	1.51239300
H	1.80117100	5.41241700	-0.06622000
H	3.33686900	4.79408500	0.56193900
H	5.68388000	-3.26355200	-2.11805300
H	5.49556100	-0.93034400	-2.95798200

Structure **4.25**

C	1.23638800	-0.49444800	-2.13130800
O	-0.23740300	-1.40840100	-2.74058400
O	1.54281000	0.50217400	-2.76432500

C	-0.78643300	-0.81048800	-3.90092300
H	-0.66406300	-1.50321800	-4.74506000
H	-1.85815200	-0.60387600	-3.77276800
H	-0.26723300	0.12854900	-4.13984200
C	2.22378200	-1.56949300	-1.77606100
C	3.57331900	-1.19568000	-1.68614300
C	1.86356000	-2.90327600	-1.53184900
C	4.54639500	-2.13936600	-1.35701700
H	3.84329300	-0.16363400	-1.88340100
C	2.84117500	-3.84517600	-1.21155700
H	0.82512200	-3.19600800	-1.63032500
C	4.18416000	-3.46706300	-1.11962400
H	2.55494400	-4.87998600	-1.04046200
Ni	-0.37241900	-0.49181300	-1.11320300
C	-0.54000500	0.43400700	0.52282100
N	-1.76522100	0.44395500	1.11505500
N	0.28341900	1.17306200	1.30066400
C	-1.80005600	1.15629900	2.40493200
C	-2.90902400	-0.26876300	0.61648400
C	-0.40243400	1.79675100	2.45397900
C	1.66121200	1.48836200	1.03532000
H	-2.60903700	1.89417200	2.42166700
H	-1.97003100	0.44889000	3.22685300

C	-3.83570800	0.41526900	-0.20286700
C	-3.10093000	-1.62017600	0.98376700
H	-0.43504700	2.88528500	2.32665600
H	0.13397300	1.58082400	3.38291200
C	2.66314100	0.72795000	1.67726200
C	1.97573100	2.59311400	0.21269600
C	-4.95127600	-0.29173900	-0.66749100
C	-3.65255800	1.87765600	-0.59605600
C	-4.23417000	-2.27991600	0.49312700
C	-2.12606100	-2.37075900	1.88556100
C	4.00000700	1.06993000	1.44119800
C	2.33631600	-0.41275000	2.63714400
C	3.32887000	2.89026600	0.00899600
C	0.90692800	3.49649700	-0.39692000
C	-5.15067600	-1.62665300	-0.32627500
H	-5.67166100	0.21029600	-1.30735600
C	-4.83307400	2.74856900	-0.12298700
C	-3.42384200	2.02809000	-2.11261600
H	-2.74996200	2.24675300	-0.09935900
H	-4.39915700	-3.32128000	0.75527000
C	-1.48288200	-3.56567000	1.15567600
C	-2.80120200	-2.81891800	3.19725900
H	-1.31452300	-1.68543300	2.14841700

C	4.33264000	2.13555600	0.60976300
H	4.78966200	0.49395200	1.91574300
C	2.77719900	-0.06914100	4.07517900
C	2.94295800	-1.75347600	2.18543100
H	1.24930900	-0.54172900	2.64489800
H	3.59923400	3.72821200	-0.62677500
C	1.07706100	3.68739000	-1.91553700
C	0.87806300	4.86204800	0.32324100
H	-0.06510600	3.01714800	-0.24311700
H	-6.02243500	-2.15850400	-0.69829100
H	-4.98640600	2.66541800	0.95938300
H	-5.77006500	2.45933700	-0.61296700
H	-4.64778000	3.80266900	-0.36098900
H	-2.54476700	1.45894100	-2.43257500
H	-3.26227500	3.08112100	-2.37243700
H	-4.28759400	1.67017000	-2.68555600
H	-0.96370100	-3.23334400	0.25087100
H	-2.23276300	-4.31079100	0.86504800
H	-0.75372700	-4.06123200	1.80769600
H	-3.23207900	-1.96885500	3.73933600
H	-2.07216600	-3.30777200	3.85434900
H	-3.61006800	-3.53453600	3.00907500
H	5.37646600	2.38463200	0.43638300

H	2.33296700	0.87101800	4.42341900
H	3.86624100	0.03832200	4.14157700
H	2.47887500	-0.86462500	4.76874000
H	2.59460900	-2.03091200	1.18731600
H	2.65839400	-2.54952700	2.88471500
H	4.03787700	-1.71328500	2.15861300
H	1.10095600	2.72345800	-2.42976000
H	2.00130700	4.22817200	-2.15314600
H	0.24324300	4.28179200	-2.30973900
H	0.72504500	4.75449500	1.40386400
H	0.07060900	5.48846300	-0.07489800
H	1.82129000	5.40225400	0.17841600
H	4.94271700	-4.20430800	-0.86880100
H	5.58930900	-1.83886400	-1.29229500

Structure **4.26**

C	-1.93085400	2.24212300	-1.99308500
Ni	-0.04918400	0.94964200	-0.48307300
O	-3.00955200	2.67873800	-1.29167300
O	-2.03786600	1.59390800	-3.02292600
C	-4.28335100	2.29804200	-1.82514700
H	-4.41824200	1.21494800	-1.75942900
H	-5.02339500	2.80798200	-1.20643100

H	-4.37484200	2.60901100	-2.86935800
C	0.25785300	-0.70386300	0.37213600
N	1.44515100	-1.33608800	0.57768300
N	-0.70592800	-1.51514300	0.88735300
C	1.32537200	-2.64602500	1.24739500
C	-0.18922900	-2.75381200	1.50204900
H	1.91273700	-2.66063600	2.17277800
H	1.70248900	-3.44633900	0.59913200
H	-0.43719300	-2.78398800	2.57016600
H	-0.63563300	-3.63559700	1.02933500
C	-2.11405200	-1.23727900	0.88694500
C	-2.91428000	-1.73665400	-0.16562000
C	-2.67747900	-0.52922300	1.97184400
C	-4.29356700	-1.49867000	-0.11392700
C	-4.06072200	-0.31089600	1.97111200
C	-4.86457000	-0.79107100	0.94100300
H	-4.92877100	-1.87591800	-0.91076900
H	-4.51432800	0.23849700	2.79171800
H	-5.93755500	-0.61760900	0.96221000
C	2.73010100	-0.84277200	0.17277800
C	3.48173200	-0.05606900	1.07264600
C	3.23694300	-1.20222500	-1.09527800
C	4.74132900	0.39607500	0.66058000

C	4.50123800	-0.72353900	-1.46047300
C	5.24765800	0.07194600	-0.59513100
H	5.33405300	1.00941500	1.33396100
H	4.90720500	-0.97934200	-2.43558900
H	6.22734700	0.43362300	-0.89694500
C	2.97251300	0.29845400	2.46608500
C	3.86407800	-0.31804500	3.56288500
C	2.83129500	1.81977600	2.65901200
H	1.97096500	-0.12915200	2.57343100
H	3.94725500	-1.40556300	3.45083300
H	4.87947600	0.09487600	3.53372200
H	3.44944700	-0.10867900	4.55637300
H	2.16376400	2.24794500	1.90558800
H	2.41891900	2.03902900	3.65168100
H	3.80097800	2.32703100	2.58423200
C	2.45949600	-2.08744500	-2.06472400
C	2.09037600	-1.33161100	-3.35506700
C	3.22441500	-3.38774800	-2.38215700
H	1.51787700	-2.36611900	-1.58212600
H	1.48165400	-0.45310700	-3.12300900
H	2.98369800	-0.99885600	-3.89711800
H	1.51366500	-1.97908900	-4.02651800
H	3.47311700	-3.94187600	-1.46936200

H	2.61940000	-4.04007100	-3.02312600
H	4.16313500	-3.18380500	-2.91054500
C	-1.83512300	-0.00947400	3.13283100
C	-1.86635700	1.52859700	3.21535100
C	-2.26169700	-0.64582800	4.47075800
H	-0.79581000	-0.29682100	2.94655300
H	-1.49721800	1.97417800	2.28609900
H	-2.88199600	1.90135200	3.39447500
H	-1.23209300	1.87826900	4.03922400
H	-2.21862200	-1.74055200	4.42763000
H	-1.60290400	-0.31053200	5.28081800
H	-3.28686100	-0.36651000	4.74118000
C	-2.33051200	-2.53378600	-1.32806900
C	-2.78075700	-4.00833700	-1.27156600
C	-2.67336100	-1.91185700	-2.69540300
H	-1.24079800	-2.51082300	-1.23006700
H	-2.51842300	-4.47923700	-0.31669100
H	-3.86724300	-4.09516300	-1.39296600
H	-2.30913300	-4.58462700	-2.07663300
H	-2.35631800	-0.86668700	-2.75566600
H	-2.17228700	-2.47010500	-3.49578500
H	-3.75096100	-1.95208200	-2.89689600
C	-0.64942600	2.64428000	-1.36854400

C	0.57872000	2.21560500	-1.97704000
C	-0.58122900	3.58552600	-0.29085100
C	1.79992400	2.82362800	-1.58218100
H	0.53146000	1.64382200	-2.89875900
C	0.62881400	4.14526400	0.08004700
H	-1.50263500	3.89824500	0.18796300
C	1.82565600	3.77865900	-0.58102000
H	0.65710300	4.88084800	0.87983100
H	2.71857600	2.53434200	-2.08585200
H	2.76518400	4.24244500	-0.29273500

Structure **4.101**

C	0.83329900	-1.28293200	1.72382600
O	1.48444300	-1.37055400	2.69781600
Ni	-0.08074100	-0.80881600	0.31270500
C	0.65865700	0.85937300	-0.32930600
N	-0.01347600	2.01042200	-0.54931800
N	1.94387400	1.04489900	-0.72925000
C	0.87195400	3.10372400	-1.01094000
C	-1.33345100	2.36393500	-0.08541900
C	2.14203100	2.34789300	-1.40159000
C	3.06433600	0.15610000	-0.53744400
H	0.41981200	3.64207600	-1.84540500
H	1.03702800	3.81473900	-0.19094300
C	-2.37481700	2.50386700	-1.03018700
C	-1.52351200	2.68144700	1.27935100
H	2.22093100	2.19763700	-2.48554000
H	3.05703100	2.83145800	-1.05433800
C	3.89197200	0.34814000	0.59665600
C	3.37426200	-0.81491500	-1.51673100
C	-3.62031800	2.94749400	-0.57205100
C	-2.18329600	2.22165700	-2.51690300
C	-2.79358700	3.11516700	1.68206900
C	-0.41081200	2.61000800	2.32274200

C	4.97598600	-0.51967200	0.77407700
C	3.70798800	1.50877400	1.57338400
C	4.47117600	-1.65618700	-1.28704700
C	2.62726900	-0.91168000	-2.84297400
C	-3.83393700	3.24801400	0.76945800
H	-4.43892400	3.05171100	-1.27740000
C	-2.11025500	3.53515400	-3.32642100
C	-3.28879200	1.31680500	-3.09261700
H	-1.23471000	1.68835100	-2.63163700
H	-2.96489900	3.35908100	2.72679000
C	-0.77109300	1.67556700	3.49375500
C	-0.04253900	4.01494700	2.84350600
H	0.48116400	2.19167800	1.84890500
C	5.25569200	-1.52506500	-0.14597700
H	5.61462100	-0.40094900	1.64414500
C	4.78508200	2.58945300	1.32706400
C	3.72811400	1.08192300	3.05299900
H	2.72976700	1.96030300	1.38101100
H	4.72244800	-2.41545200	-2.02144000
C	2.24307200	-2.35339700	-3.22149500
C	3.46226700	-0.27073100	-3.97372200
H	1.70046500	-0.33798500	-2.74986800
H	-4.81171100	3.58538100	1.10276200

H	-1.32300400	4.20813700	-2.96685500
H	-3.05787900	4.08356900	-3.26411600
H	-1.91700200	3.32325800	-4.38501300
H	-3.40798600	0.40968600	-2.49686400
H	-3.03638400	1.03028100	-4.12073900
H	-4.25566700	1.83288700	-3.12924400
H	-1.02214300	0.67248600	3.13562000
H	-1.62735900	2.05396600	4.06389200
H	0.07607900	1.58681500	4.18355000
H	0.24818100	4.68628000	2.02686400
H	0.79433000	3.95493700	3.54975500
H	-0.88676000	4.47975000	3.36587300
H	6.09892600	-2.19147200	0.01501000
H	4.79727500	2.93683600	0.28762100
H	5.78476000	2.19883100	1.55079900
H	4.61226300	3.45750700	1.97437300
H	2.98446800	0.30887600	3.25532900
H	3.51590000	1.94888600	3.69041500
H	4.71096100	0.69727500	3.34961800
H	1.65790900	-2.83473500	-2.43274100
H	3.12684300	-2.97112100	-3.41793900
H	1.63712700	-2.35268600	-4.13457600
H	3.72492800	0.76884700	-3.74715700

H	2.90398400	-0.28359700	-4.91740700
H	4.39853400	-0.81993300	-4.12882600
N	-1.52719400	-1.00122000	-0.99337700
C	-1.03264900	-5.35885200	1.34124200
C	0.07508500	-5.01077200	0.56321000
H	-2.58731100	-4.64529300	2.65633500
C	-1.72524500	-4.37562800	2.05215300
C	0.48484900	-3.67892100	0.49498200
C	-0.22229600	-2.68199200	1.18718700
C	-1.31816100	-3.04290200	1.98425400
H	1.36465500	-3.41445400	-0.08700200
H	-1.86884800	-2.28538900	2.53155000
H	-1.35107500	-6.39650200	1.39897500
H	0.62148100	-5.77579000	0.01709600
C	-2.77543500	-1.32873300	-0.51421900
C	-3.66680600	-2.24043400	-1.14645500
C	-3.25862700	-0.70748800	0.67267100
C	-4.93597500	-2.49554800	-0.62511500
H	-3.35777100	-2.76577200	-2.04347900
C	-4.52142500	-0.97711700	1.18421000
H	-2.62315100	0.02507100	1.16349500
C	-5.38308300	-1.87601000	0.54266800
H	-5.58239300	-3.20169800	-1.14384700

H	-4.84511700	-0.46640900	2.08972500
H	-6.37335600	-2.08086300	0.94016300
C	-1.15570000	-1.59658600	-2.25874300
H	-0.98493100	-2.69030900	-2.21380300
H	-1.91905000	-1.42873200	-3.03689500
H	-0.22933100	-1.13817900	-2.61790300

Structure **4.102**

C	0.53445100	1.54491300	-1.56975400
O	0.88546400	1.54733400	-2.70178800
Ni	0.02610100	1.09295800	0.02621300
C	-0.05981200	-0.81051700	0.04103500
N	-1.18274600	-1.55367700	-0.00190400
N	0.99703900	-1.64101100	0.15286500
C	-0.90211500	-3.00642800	-0.01560500
C	-2.53377700	-1.07610500	-0.14484800
C	0.58873700	-3.05144600	0.34126600
C	2.38450700	-1.26307800	0.23612000
H	-1.53215700	-3.53021000	0.70755500
H	-1.10992800	-3.41523900	-1.01219600
C	-3.36024500	-1.05479500	0.99983100
C	-3.02186900	-0.71997900	-1.42303500
H	0.76268800	-3.35056300	1.38172200

H	1.16453500	-3.71476700	-0.30795900
C	3.19861200	-1.45483300	-0.90473500
C	2.91498200	-0.78973500	1.45914100
C	-4.68440900	-0.62703500	0.84477000
C	-2.87555100	-1.48932100	2.37956900
C	-4.35486600	-0.30063100	-1.51941900
C	-2.17976900	-0.83114800	-2.69144100
C	4.55751600	-1.13300500	-0.80554600
C	2.66744000	-2.03408400	-2.21441800
C	4.28140700	-0.48047300	1.49685000
C	2.08226600	-0.66344300	2.73272200
C	-5.17886500	-0.24733000	-0.39885000
H	-5.33509700	-0.58905300	1.71392300
C	-3.66430000	-2.71231200	2.89016800
C	-2.91741000	-0.32545500	3.38585300
H	-1.82424200	-1.77893200	2.29265700
H	-4.75575500	-0.01942600	-2.48872100
C	-2.27447800	0.41945400	-3.58484700
C	-2.57014800	-2.08954100	-3.49648400
H	-1.13157000	-0.93317700	-2.39782600
C	5.09606100	-0.64499200	0.38071100
H	5.20143500	-1.26880100	-1.66978400
C	3.23013100	-3.45138700	-2.45614200

C	2.95755600	-1.12862900	-3.42665300
H	1.57863900	-2.11382400	-2.13091800
H	4.71523400	-0.11293300	2.42157400
C	2.34117700	0.65280000	3.48576700
C	2.33321800	-1.87143400	3.66097200
H	1.02513700	-0.63887700	2.46039500
H	-6.20967400	0.08329500	-0.49734700
H	-3.61874600	-3.55326400	2.18687900
H	-4.72279900	-2.47142200	3.04389300
H	-3.26016400	-3.05059400	3.85175700
H	-2.25233900	0.46770500	3.03600600
H	-2.57420200	-0.66710100	4.37056400
H	-3.93296600	0.07119700	3.50594500
H	-2.04739700	1.32955500	-3.02243400
H	-3.27210700	0.53110500	-4.02534700
H	-1.55537400	0.34748400	-4.40784600
H	-2.47406300	-3.00292300	-2.89817200
H	-1.93069400	-2.19319600	-4.38129200
H	-3.61052600	-2.02917300	-3.83789100
H	6.15347900	-0.39955200	0.43812500
H	3.02349800	-4.12544200	-1.61640200
H	4.31772600	-3.42439400	-2.59215800
H	2.79202400	-3.88938400	-3.36101900

H	2.51318700	-0.13869200	-3.29822300
H	2.53526100	-1.57596600	-4.33479200
H	4.03438300	-1.00756600	-3.59295900
H	2.18640800	1.51239300	2.82924100
H	3.35388100	0.70378900	3.90454900
H	1.63505200	0.74256300	4.31816500
H	2.11400300	-2.82473400	3.16536100
H	1.70283000	-1.80271000	4.55559300
H	3.37974400	-1.90720800	3.98858000
C	0.34582000	5.79266100	-0.18962600
C	1.50885500	5.04614500	0.02138000
H	-1.71955500	5.75064100	-0.81480500
C	-0.81666300	5.16814100	-0.65044300
C	1.50979500	3.67391800	-0.22814700
C	0.34396400	3.03711800	-0.68235500
C	-0.81650600	3.79581700	-0.90063500
H	2.41643500	3.09361100	-0.07471100
H	-1.71879800	3.31079900	-1.26498500
H	0.34676900	6.86268400	0.00126400
H	2.41212700	5.53448300	0.37808700
O	-0.46888700	1.23624000	1.81268500
C	-0.60021900	2.48208400	2.43087100
H	-1.31824700	3.15346900	1.92426000

H	-0.96727000	2.35065400	3.46521900
H	0.35275000	3.03962100	2.50434900

Structure **4.103**

C	2.92953200	-0.98360200	0.33111100
O	2.43710900	-1.28023300	1.41925800
C	4.41855700	-1.08658700	0.15113900
C	5.24900900	-0.58382100	1.16310100
C	4.99193600	-1.77668900	-0.92669300
C	6.63188700	-0.73331900	1.07910900
H	4.79614600	-0.08372200	2.01370000
C	6.37507200	-1.94824900	-0.99563800
H	4.35520200	-2.20478700	-1.69552100
C	7.19817200	-1.41709400	-0.00047900
H	6.80894800	-2.49928600	-1.82581200
N	2.12950000	-0.60531300	-0.75298200
C	0.90893900	-1.67776300	-1.20053300
C	0.74051300	-2.87098100	-0.44365100
C	0.66638600	-1.74720500	-2.59952500
C	0.31831500	-4.04327000	-1.05974400
H	0.92869100	-2.85764100	0.62140500
C	0.24672200	-2.93825200	-3.19337300
H	0.77432800	-0.86454000	-3.21944600

C	0.07068100	-4.09839000	-2.43757200
H	0.17325100	-4.93065500	-0.44750600
H	0.05072400	-2.94957900	-4.26386300
H	-0.25262800	-5.02304800	-2.90692900
H	8.27602500	-1.54259300	-0.06098600
H	7.26812400	-0.32709200	1.86095500
C	2.75089200	0.11828300	-1.87875800
H	3.60721700	0.68863500	-1.51626000
H	3.07882600	-0.55775400	-2.67752900
H	2.02843500	0.82440900	-2.29138300
Ni	0.35788000	-0.03805500	-0.27574700
C	-1.29941700	0.72350600	0.25271700
N	-1.48440200	2.07144000	0.31682600
N	-2.44407000	0.15304800	0.70596500
C	-2.80198000	2.47973800	0.83937400
C	-0.51763300	3.05193800	-0.08794500
C	-3.46735800	1.12567500	1.14398800
C	-2.67409700	-1.25425800	0.88140100
H	-2.68629700	3.10711200	1.73092700
C	0.40625100	3.54332000	0.86084900
C	-0.54438000	3.53625900	-1.41487500
H	-4.40084700	0.97867800	0.59049400
C	-3.36816400	-1.96416700	-0.12302200

C	-2.26700400	-1.87606100	2.08248400
C	1.33469100	4.50326500	0.43884800
C	0.41755200	3.07058100	2.31137200
C	0.40544500	4.49528100	-1.78629900
C	-1.55192500	3.03002900	-2.44251200
C	-3.61082600	-3.32737300	0.08217900
C	-3.88870600	-1.28675800	-1.38726700
C	-2.52931300	-3.24336000	2.23457300
C	-1.61260100	-1.10770500	3.22733900
C	1.34092500	4.97311600	-0.87170900
H	2.06289200	4.88799700	1.14770600
C	0.15782500	4.23739700	3.28550300
C	1.72248800	2.33192400	2.66604400
H	-0.39719900	2.35047100	2.43427100
H	0.41335000	4.87324200	-2.80500900
C	-0.86862600	2.15146400	-3.50825800
C	-2.34743600	4.17851400	-3.09162400
H	-2.26790200	2.38793800	-1.92041300
C	-3.18919200	-3.96590500	1.24493200
H	-4.13580800	-3.89628900	-0.68003300
C	-5.42928800	-1.19801500	-1.37043200
C	-3.39963800	-1.97683300	-2.67322300
H	-3.49371400	-0.26598700	-1.40312700

H	-2.21713000	-3.74651400	3.14564100
C	-0.23582500	-1.67752000	3.61550000
C	-2.55061500	-1.05324600	4.45198200
H	-1.44725600	-0.07948800	2.89138600
H	2.07104900	5.71741200	-1.17921000
H	-0.77865100	4.75745200	3.05156100
H	0.09377700	3.86663900	4.31543600
H	0.96476700	4.97881800	3.25124600
H	1.85055600	1.44062300	2.04367200
H	2.59833300	2.97851800	2.53153600
H	1.70249400	2.01072500	3.71446700
H	-0.38314500	1.29177200	-3.03481100
H	-1.60617200	1.77448200	-4.22727900
H	-0.11122100	2.71515100	-4.06674100
H	-2.84676400	4.79758000	-2.33724100
H	-1.70232200	4.83600600	-3.68586600
H	-3.11425700	3.77650700	-3.76440500
H	-3.38280200	-5.02657200	1.38360000
H	-5.79830700	-0.68194000	-0.47621900
H	-5.79363800	-0.65583000	-2.25161000
H	-5.88248200	-2.19657300	-1.38251500
H	-2.30823800	-2.03048900	-2.70236700
H	-3.79034700	-2.99783900	-2.75909900

H	-3.74498300	-1.41901800	-3.55278500
H	0.47078500	-1.61928500	2.78344000
H	0.18290900	-1.10437900	4.45222700
H	-0.30836600	-2.72283900	3.93950500
H	-3.52868800	-0.62753900	4.19687500
H	-2.72545800	-2.05421900	4.86415300
H	-2.10825700	-0.43956500	5.24610100
H	-3.35054600	3.06246100	0.08932000
H	-3.68470400	0.99241300	2.21005000

Structure **4.105**

C	-1.00232100	0.90731000	-1.93443100
O	-0.60475300	0.37222000	-2.96655000
Ni	0.13873900	0.76442800	-0.42285100
C	0.29901500	-0.91322600	0.43708000
N	1.52368400	-1.31092500	0.86944800
N	-0.58291400	-1.87337100	0.80418800
C	1.52576400	-2.60858500	1.56944900
C	2.74590800	-0.61657900	0.56988500
C	0.03271100	-2.98672000	1.55971600
C	-1.99653900	-1.87884600	0.54687300
H	2.15015700	-3.33338700	1.03397500

H	1.93012900	-2.49956500	2.58230600
C	3.44531500	-0.93991200	-0.61557300
C	3.23126500	0.34770400	1.48028000
H	-0.15982900	-3.94219200	1.06113300
H	-0.39481900	-3.03999000	2.56749800
C	-2.87027500	-1.25502400	1.46526100
C	-2.48278900	-2.57436700	-0.58347600
C	4.63475000	-0.25094100	-0.88145000
C	2.95710100	-2.00420100	-1.59536900
C	4.42753100	1.00496000	1.16701600
C	2.49676800	0.69343500	2.77174200
C	-4.24550000	-1.30862800	1.20678000
C	-2.37289000	-0.56758400	2.73357700
C	-3.86772600	-2.60007200	-0.79258700
C	-1.56644600	-3.32244800	-1.54875000
C	5.12293300	0.71302400	-0.00291300
H	5.18647100	-0.47111500	-1.79127000
C	3.98815600	-3.14216000	-1.74098500
C	2.59150300	-1.40791300	-2.96943500
H	2.04030400	-2.44261600	-1.18934200
H	4.81799300	1.75687100	1.84724200
C	2.03460900	2.16366100	2.78484400
C	3.34985500	0.36997600	4.01423500

H	1.59599100	0.07306600	2.81958700
C	-4.74291700	-1.96977700	0.08755000
H	-4.93661100	-0.82949700	1.89456400
C	-2.76900400	-1.37267500	3.98900300
C	-2.86697400	0.88644100	2.84474300
H	-1.28004800	-0.53299700	2.69080800
H	-4.26476500	-3.12312600	-1.65787300
C	-1.74789300	-2.87255400	-3.01106600
C	-1.76627500	-4.84766500	-1.41762300
H	-0.53212300	-3.09500800	-1.27189300
H	6.04827400	1.23600900	-0.23001200
H	4.24433200	-3.58363200	-0.77037600
H	4.91889200	-2.78585200	-2.19753100
H	3.58920700	-3.93644700	-2.38275000
H	1.75302000	-0.70831900	-2.89441400
H	2.29411700	-2.20871700	-3.65761200
H	3.44537000	-0.88647200	-3.41883000
H	1.39776000	2.38521800	1.92136400
H	2.88649500	2.85329700	2.75806300
H	1.46305400	2.37609200	3.69653000
H	3.66010300	-0.68144000	4.02621600
H	2.78112600	0.56783400	4.93066500
H	4.25792000	0.98316100	4.04953600

H	-5.81383700	-1.99919000	-0.09569300
H	-2.39830500	-2.40332100	3.94259900
H	-3.85865000	-1.42022300	4.10169200
H	-2.35989400	-0.90374600	4.89203700
H	-2.58760100	1.46673200	1.96060300
H	-2.42717200	1.36902500	3.72589300
H	-3.95674000	0.93872400	2.95146600
H	-1.53282300	-1.80676900	-3.12979200
H	-2.76534100	-3.06942600	-3.37003500
H	-1.06054200	-3.43159400	-3.65787400
H	-1.61741000	-5.19380700	-0.38763100
H	-1.05941400	-5.38288000	-2.06280400
H	-2.77903000	-5.14124700	-1.71841900
N	0.01944900	2.38171100	-1.43885100
C	-2.47842600	1.16127800	-1.67906900
H	-2.89446000	1.73818900	-2.51561900
H	-2.98402000	0.19133100	-1.64517500
H	-2.66935200	1.69505900	-0.74878100
C	1.02678900	2.56716100	-2.48769800
H	0.58218900	2.73243300	-3.47941300
H	1.67174400	3.41817600	-2.23805300
H	1.64357600	1.67111500	-2.55831200
C	-0.67783700	3.54006500	-1.03954400

C	-0.88224800	4.63636700	-1.90321300
C	-1.20111800	3.63284100	0.26682200
C	-1.59070000	5.76003500	-1.47708500
H	-0.49194300	4.60853000	-2.91493600
C	-1.92117500	4.75075600	0.68037400
H	-1.01633600	2.81007700	0.95239600
C	-2.12239200	5.82735500	-0.18812300
H	-1.73152200	6.58948300	-2.16642300
H	-2.31194400	4.78815000	1.69474000
H	-2.67307600	6.70541500	0.13765600

Structure **4.107**

C	-0.77134400	0.58028200	2.46091800
O	-0.46232700	1.74371400	2.67189600
Ni	0.28784200	-0.43814000	1.29386100
C	0.02215600	-0.02809400	-0.53544700
N	1.09417200	0.13651100	-1.35306600
N	-1.08575800	0.08877800	-1.30857700
C	0.74347700	0.40494000	-2.76001700
C	2.45864900	0.18713400	-0.90306600
C	-0.78984300	0.26668700	-2.74626900
C	-2.44442300	-0.03872400	-0.86330400
H	1.07455500	1.40849100	-3.05325100

H	1.23021800	-0.31774000	-3.42415400
C	3.01776800	1.43364300	-0.54110600
C	3.21547100	-1.00487900	-0.86909000
H	-1.30073100	1.15037200	-3.14120500
H	-1.13930900	-0.60561500	-3.31257100
C	-3.01361500	-1.32435600	-0.73188000
C	-3.19538400	1.13410100	-0.62302100
C	4.35376100	1.45491900	-0.12299200
C	2.22942600	2.73928100	-0.60212800
C	4.54698500	-0.92716900	-0.44309300
C	2.62853500	-2.35595200	-1.26501700
C	-4.34464700	-1.41386300	-0.30509300
C	-2.23890500	-2.60047500	-1.04901900
C	-4.52639800	0.98829000	-0.21190400
C	-2.61934800	2.53371900	-0.82331400
C	5.11310800	0.28898700	-0.07125800
H	4.80452900	2.39943000	0.16875000
C	2.85731900	3.71881800	-1.61520400
C	2.08021300	3.39566300	0.78481400
H	1.21781400	2.50805800	-0.94978500
H	5.14688100	-1.83206100	-0.39957200
C	2.57969900	-3.32171300	-0.06458400
C	3.38618600	-2.98380600	-2.45135900

H	1.59511600	-2.18933300	-1.58510900
C	-5.09578400	-0.27125800	-0.04460900
H	-4.80075900	-2.39228900	-0.18145500
C	-2.93469600	-3.42768500	-2.14834600
C	-1.99633700	-3.44950000	0.21342900
H	-1.25534700	-2.31001900	-1.43119800
H	-5.12345100	1.87474400	-0.01645700
C	-2.68754600	3.39271600	0.45440900
C	-3.31503700	3.24891000	-2.00067500
H	-1.55960900	2.42582600	-1.07556500
H	6.14804400	0.32867600	0.25847800
H	2.94738900	3.27003100	-2.61188000
H	3.86094000	4.02969300	-1.30229000
H	2.24309500	4.62286900	-1.70202600
H	1.51061500	2.75940400	1.46898700
H	1.54269300	4.34728900	0.69057800
H	3.05715800	3.61177200	1.23401300
H	2.00886800	-2.88836600	0.76440000
H	3.58629300	-3.55255700	0.30397600
H	2.10496500	-4.26740600	-0.35375000
H	3.40231600	-2.31324800	-3.31852400
H	2.90837700	-3.92285500	-2.75521300
H	4.42628400	-3.21178500	-2.19041900

H	-6.12815700	-0.36209600	0.28302500
H	-3.10166300	-2.83277100	-3.05380800
H	-3.90868900	-3.80517200	-1.81600400
H	-2.32031400	-4.29485800	-2.41859900
H	-1.42210900	-2.88227800	0.95374500
H	-1.43055700	-4.35524900	-0.03678000
H	-2.94122000	-3.76124200	0.67446200
H	-2.11808600	2.94045800	1.27163300
H	-3.72230500	3.53981900	0.78679200
H	-2.26346400	4.38490000	0.25742300
H	-3.26440100	2.65946900	-2.92405000
H	-2.84468800	4.22113500	-2.19011400
H	-4.37482300	3.42932000	-1.78473300
N	0.64852500	-0.79082400	3.08950700
C	1.64662800	-0.02937000	3.81489200
H	1.27378600	0.30801300	4.80003800
H	2.55594300	-0.62818000	3.99360700
H	1.93020800	0.86059100	3.24807100
C	-2.14109900	0.04132600	2.85345200
H	-2.26232100	0.12158500	3.94149500
H	-2.90632700	0.66413000	2.37889600
H	-2.29377000	-0.99448700	2.54809500
C	0.08837100	-1.86111100	3.88840000

H	0.86810900	-2.58973200	4.17287000
H	-0.36690200	-1.49909500	4.83067500
H	-0.67480100	-2.40945000	3.32903900

Structure **4.108**

C	1.09120400	-0.88662600	-0.16707500
O	0.95965100	-2.09134900	-0.10256700
C	2.44050900	-0.24277000	-0.04067800
C	3.56145900	-0.99114100	-0.42847700
C	2.62292900	1.02113600	0.53914400
C	4.84328200	-0.47114900	-0.26675400
H	3.40663800	-1.98008800	-0.84776500
C	3.90824100	1.53319400	0.71645300
H	1.76028400	1.59023000	0.87252000
C	5.01872800	0.79207500	0.30607900
H	4.04290900	2.50719900	1.17875200
N	-0.01817100	-0.00773000	-0.35018400
C	0.06126900	1.09182100	-1.32437900
H	-0.26615400	2.03621000	-0.88104100
H	1.09382400	1.19347300	-1.65618000
H	-0.57060600	0.87810700	-2.19095200
C	-1.26304200	-0.37141100	0.19027200
H	5.70668600	-1.05181800	-0.57949100
H	6.01941400	1.19459600	0.43878300

O	-1.41590400	-1.18670900	1.07262500
O	-2.23251400	0.36926000	-0.39146500
C	-3.63765300	0.24780100	0.04242400
C	-4.14306200	-1.17478300	-0.21912700
C	-3.76902300	0.65239700	1.51469100
C	-4.35055300	1.25472100	-0.86418400
H	-3.99443700	-1.44460100	-1.27050400
H	-3.62138500	-1.89887200	0.40818500
H	-5.21625800	-1.22697000	-0.00318800
H	-3.35832800	1.65595100	1.67325500
H	-4.82817100	0.67202400	1.79508400
H	-3.24681400	-0.05119900	2.16460400
H	-5.42222500	1.26803500	-0.63964800
H	-3.95254500	2.26349200	-0.71217400
H	-4.22122400	0.98713800	-1.91803400

Structure 4.109

N	2.08650500	-0.70125800	-0.00016400
C	3.43654800	-0.17759100	0.00012000
H	3.99052900	-0.49649600	0.89192600
H	3.99125600	-0.49782700	-0.89073400
H	3.36569800	0.91107100	-0.00068600
C	0.98462000	0.10568200	-0.00009800
O	1.01609100	1.32651100	-0.00004600

O	-0.13015500	-0.67204700	-0.00021000
C	-1.46902400	-0.06957600	0.00002200
C	-1.67491000	0.75987200	1.27304200
C	-1.67523400	0.76001400	-1.27285400
C	-2.38649300	-1.29602300	0.00007900
H	-1.48668600	0.14558800	2.16083900
H	-1.00587000	1.62156400	1.29142500
H	-2.71090300	1.11487600	1.31925800
H	-1.48719000	0.14583300	-2.16076100
H	-2.71124200	1.11501300	-1.31880800
H	-1.00620300	1.62171300	-1.29128800
H	-3.43557200	-0.98191700	0.00019100
H	-2.20866600	-1.91147000	-0.88796400
H	-2.20849200	-1.91152400	0.88805000
H	1.92728000	-1.69759600	-0.00010900

Structure **4.110**

C	0.45566500	-1.35373400	-1.08357100
O	0.86463800	-0.81472300	-2.10000200
Ni	-0.48328800	-0.24755500	0.15534600
N	-1.40159200	-2.22771100	-1.53754800
C	2.43475100	-4.87847700	0.45936400
C	2.82632700	-4.29907400	-0.74856700

H	1.06457400	-4.76313700	2.12257900
C	1.37954400	-4.31563500	1.18295700
C	2.17153100	-3.16367300	-1.22671800
C	1.11163000	-2.59401500	-0.50644500
C	0.72340600	-3.18168500	0.70593200
H	2.46488200	-2.70962400	-2.16679600
H	-0.10682300	-2.75756000	1.26086700
H	2.94531300	-5.76202700	0.83437700
H	3.64308600	-4.73182400	-1.32148800
C	-2.20817700	-2.16785300	-0.51930100
C	-1.62753000	-3.09524700	-2.67070000
H	-2.61213100	-2.93040300	-3.12995900
H	-0.85967500	-2.87552500	-3.42082400
H	-1.55640100	-4.16120300	-2.40802000
O	-1.94398000	-1.41955200	0.49781000
O	-3.32973800	-2.92940600	-0.54285500
C	-4.36546900	-2.87263200	0.49177700
C	-3.80507200	-3.34265400	1.83967700
C	-4.96349800	-1.46294600	0.57072900
C	-5.40675400	-3.86883900	-0.03041200
H	-4.61711800	-3.42099300	2.57222800
H	-3.34580000	-4.33182400	1.73317600
H	-3.05529700	-2.64471900	2.21493800

H	-5.32496100	-1.14984500	-0.41519200
H	-5.81395100	-1.45795000	1.26278500
H	-4.22230000	-0.74098200	0.91724900
H	-6.25599000	-3.92726400	0.65905800
H	-5.77643700	-3.55878500	-1.01327600
H	-4.96828400	-4.86735100	-0.12819000
C	0.59158800	1.33343100	0.10810300
N	1.90820700	1.62317200	0.20488700
N	-0.07778900	2.50799100	0.00636300
C	2.16721700	3.07786000	0.30812600
C	2.97318800	0.69222400	0.46580000
C	0.80822600	3.68565500	-0.06451900
C	-1.49577700	2.63450900	-0.20650900
H	2.47029700	3.32456700	1.33403500
C	3.11866100	0.14409200	1.75985600
C	3.89699500	0.41396900	-0.56764600
H	0.79771500	4.10359100	-1.07907900
C	-2.01249800	2.57751700	-1.52096100
C	-2.32813400	2.86895600	0.91104900
C	4.17652400	-0.74732500	1.97894500
C	2.22123000	0.53230700	2.93264700
C	4.94208300	-0.47413600	-0.28867300
C	3.83155000	1.08980700	-1.93567500

C	-3.39025200	2.76508400	-1.68827200
C	-1.13470000	2.32685400	-2.74367300
C	-3.69896400	3.04351700	0.68669500
C	-1.78794100	2.91490000	2.33694500
C	5.07601000	-1.06183200	0.96579600
H	4.30214500	-1.19295100	2.96170200
C	3.01259800	1.34598400	3.97851400
C	1.54423200	-0.68481100	3.58831400
H	1.42150300	1.17487600	2.55363300
H	5.66154000	-0.71096400	-1.06726300
C	3.85385300	0.09184700	-3.10759600
C	4.97547100	2.11693400	-2.08406500
H	2.87835900	1.62386500	-1.99812300
C	-4.22725600	2.99733900	-0.60027500
H	-3.81307400	2.72354600	-2.68789100
C	-1.06002500	3.58103500	-3.63880200
C	-1.60594100	1.10057200	-3.54893500
H	-0.12321500	2.09680100	-2.39815300
H	-4.36015500	3.21769300	1.53131000
C	-2.33403300	1.74452700	3.17945400
C	-2.07317600	4.26780100	3.01769400
H	-0.70099900	2.79564400	2.28680700
H	5.88876400	-1.75763200	1.15671000

H	3.47180300	2.23710500	3.53436800
H	2.35252600	1.67215200	4.79152500
H	3.81716800	0.74726600	4.42134900
H	0.96704000	-1.25273100	2.85360400
H	2.27868800	-1.36256300	4.03884600
H	0.86439900	-0.35659800	4.38405800
H	2.99550500	-0.58053900	-3.05069700
H	3.80087600	0.63636200	-4.05848300
H	4.77631500	-0.50095800	-3.12234700
H	4.98181700	2.85064400	-1.26915100
H	5.95217100	1.61844900	-2.07897800
H	4.88347200	2.66039900	-3.03217100
H	-5.29363800	3.13929800	-0.75555400
H	-0.68969700	4.45457000	-3.08822400
H	-0.38837200	3.40388700	-4.48707200
H	-2.04568700	3.84119100	-4.04322300
H	-1.61676500	0.20255700	-2.92515500
H	-2.60795100	1.25323400	-3.96857400
H	-0.91832200	0.91934000	-4.38262000
H	-2.10302000	0.77952800	2.71508400
H	-1.89333700	1.75764800	4.18382500
H	-3.42284900	1.80860800	3.29153700
H	-1.66395800	5.10342000	2.43787900

H	-3.14910500	4.44199800	3.13435000
H	-1.62356300	4.29471500	4.01739200
H	2.97046500	3.38223500	-0.36623600
H	0.47886100	4.46466700	0.62987800

Structure **4.111**

C	0.98799300	-0.04878700	0.00014600
O	1.08204600	-1.25963100	-0.00001800
O	-0.12324500	0.69276400	0.00045600
C	-1.45308200	0.05477900	-0.00002100
C	-1.63309500	-0.77731700	-1.27393900
C	-1.63358000	-0.77799000	1.27339500
C	-2.39397200	1.26205900	0.00009800
H	-1.45724300	-0.15816100	-2.16056200
H	-0.94752800	-1.62632100	-1.29266800
H	-2.66045900	-1.15537900	-1.32237200
H	-1.45817400	-0.15926600	2.16040700
H	-2.66091200	-1.15621900	1.32120400
H	-0.94789600	-1.62690300	1.29196200
H	-3.43596400	0.92558800	-0.00012400
H	-2.22759000	1.88051600	0.88779400
H	-2.22732900	1.88090400	-0.88727800
O	2.03327600	0.80028400	0.00008300

C	3.31847800	0.16467300	-0.00005800
H	4.04297400	0.97984400	-0.00013100
H	3.44361600	-0.45821800	0.88997100
H	3.44343600	-0.45823300	-0.89009900

Structure **4.112**

C	-0.00873400	-1.53272700	0.77024700
O	-0.44040900	-1.34633900	1.90302300
Ni	0.40280500	-0.08341500	-0.39319800
N	1.91330500	-1.92569800	0.97670300
C	2.62808000	-1.49497200	-0.03074900
C	2.40210800	-2.42146800	2.24224700
H	3.41303100	-2.06716000	2.47742500
H	1.71338600	-2.06144300	3.01592600
H	2.40535000	-3.52069600	2.29323400
O	2.05699200	-0.81103300	-0.96331400
C	-1.01844300	1.16865200	-0.12904900
N	-2.36451100	1.14802300	-0.23450400
N	-0.64327300	2.46302700	0.02973900
C	-2.96469800	2.50251400	-0.26851800
C	-3.21043700	0.01765500	-0.50905000
C	-1.77224500	3.41251200	0.06556400
C	0.70205600	2.89564700	0.30391900
H	-3.37510800	2.69532100	-1.26748100

C	-3.28986600	-0.49689900	-1.82190900
C	-4.02848000	-0.47487600	0.53246800
H	-1.85452800	3.87030800	1.05870200
C	1.12910400	2.99402400	1.64754000
C	1.54476800	3.25165600	-0.77284400
C	-4.20145900	-1.53168400	-2.06608300
C	-2.44064400	0.03047000	-2.97398600
C	-4.92553900	-1.50687800	0.23162100
C	-3.98756700	0.08740300	1.95140600
C	2.43572700	3.43520700	1.88796400
C	0.22372600	2.65177800	2.82748100
C	2.84102000	3.69020100	-0.47513900
C	1.09349600	3.17440500	-2.22826800
C	-5.01593300	-2.03165600	-1.05460000
H	-4.27570300	-1.94877000	-3.06653200
C	-3.31271000	0.61827800	-4.10116600
C	-1.48972700	-1.05598600	-3.51382300
H	-1.81327800	0.84022200	-2.59028100
H	-5.56317700	-1.90175300	1.01764400
C	-3.60302100	-0.98601100	2.98741800
C	-5.32533400	0.75970500	2.32414200
H	-3.20355700	0.85006900	1.98794600
C	3.28629400	3.77920100	0.84064600

H	2.79174800	3.50878400	2.91178400
C	-0.01488100	3.88675500	3.72070800
C	0.76448400	1.46458200	3.64815700
H	-0.74683200	2.33767300	2.43190700
H	3.51001800	3.96364000	-1.28632000
C	1.98931400	2.23251100	-3.05803400
C	1.02310500	4.57535000	-2.86865300
H	0.08216000	2.75560500	-2.24183800
H	-5.72039300	-2.83140300	-1.26849300
H	-3.97175500	1.41246200	-3.73026900
H	-2.68017200	1.04194400	-4.89054700
H	-3.94661700	-0.14829000	-4.56193800
H	-0.85745000	-1.45190500	-2.71318600
H	-2.04897300	-1.89101500	-3.95324000
H	-0.84202100	-0.64095200	-4.29565300
H	-2.60972600	-1.38652800	2.76902500
H	-3.58418800	-0.54591800	3.99235500
H	-4.32768800	-1.80942000	3.00241500
H	-5.60737400	1.54005700	1.60677400
H	-6.14325500	0.02990500	2.35048400
H	-5.25869800	1.21822300	3.31798100
H	4.29693100	4.11953500	1.05091100
H	-0.41698300	4.73104700	3.14755600

H	-0.72673200	3.64653000	4.51918300
H	0.91336400	4.22430700	4.19651900
H	0.77590500	0.55088300	3.04760900
H	1.77587100	1.66204900	4.02343900
H	0.11642300	1.28550000	4.51474900
H	2.05579200	1.23701800	-2.60649500
H	1.58786600	2.12649500	-4.07318900
H	3.00811300	2.62877600	-3.14757500
H	0.35776000	5.24238400	-2.30775000
H	2.01188800	5.04769400	-2.90276400
H	0.65020000	4.50864900	-3.89772900
H	-3.78102900	2.58448700	0.45394900
H	-1.62629500	4.21391800	-0.66604100
O	-0.43088500	-2.51505000	-0.09687700
C	-0.68477000	-3.92124800	0.26271700
C	0.55218700	-4.72460700	-0.16199000
C	-1.00935800	-4.14900900	1.74258800
C	-1.88689400	-4.30544100	-0.60600800
H	0.77786600	-4.54037200	-1.21730900
H	1.42719500	-4.44031600	0.42689100
H	0.37488400	-5.79847500	-0.02590700
H	-1.89077700	-3.58246600	2.04992700
H	-1.21500600	-5.21732000	1.88890900

H	-0.18197200	-3.86769700	2.39637200
H	-2.11685500	-5.37132700	-0.48841900
H	-2.76738600	-3.72206700	-0.32339600
H	-1.67165000	-4.11230000	-1.66192100
C	4.09976300	-1.72939200	-0.18941500
C	4.88811200	-0.71221300	-0.74896200
C	4.70609800	-2.94180300	0.16738700
C	6.25823800	-0.89607100	-0.92451200
H	4.41006000	0.21708900	-1.04063400
C	6.07542400	-3.13137800	-0.02471800
H	4.10309900	-3.74715500	0.57428200
C	6.85567000	-2.10706600	-0.56391800
H	6.86074400	-0.09747000	-1.34968800
H	6.53135500	-4.08054400	0.24444000
H	7.92318700	-2.25300900	-0.70734200

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Spectra Relevant to Chapter Four:

Conversion of Amides to Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds

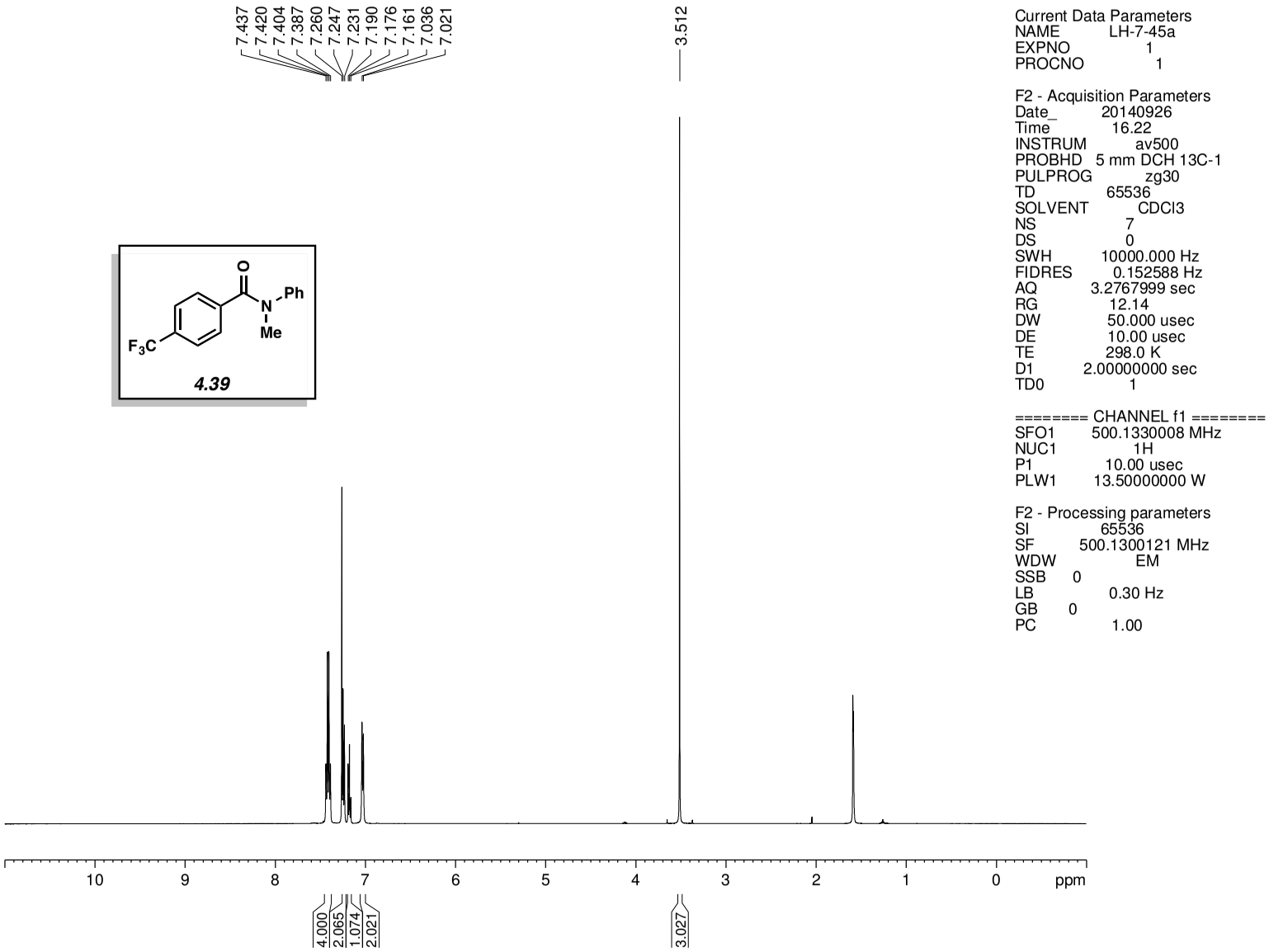


Figure 4.6. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.39**.

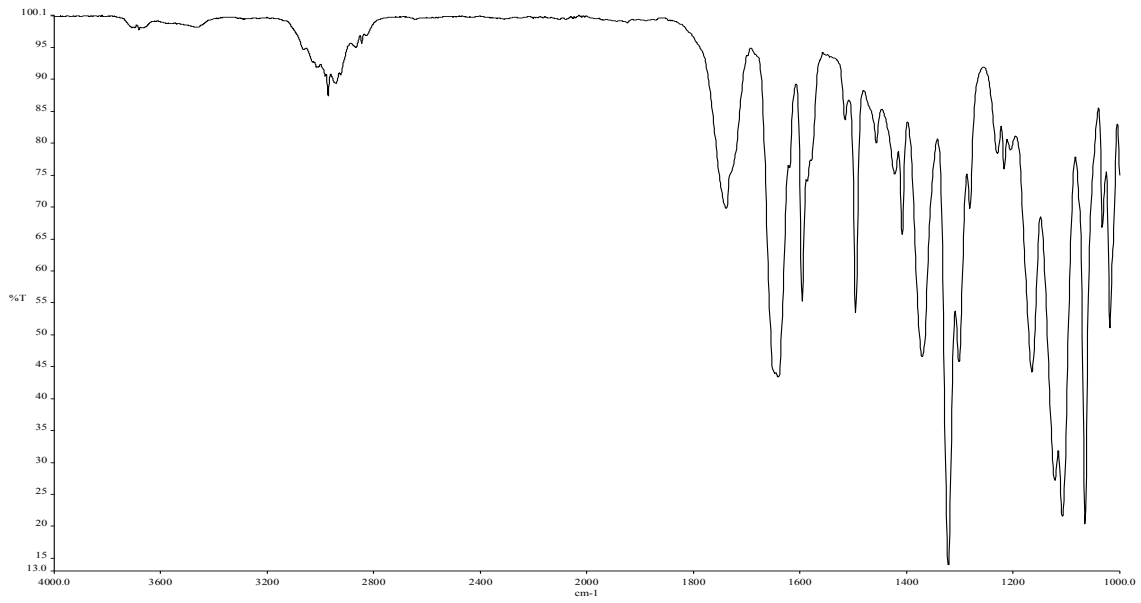


Figure 4.7. Infrared spectrum of compound **4.39**.

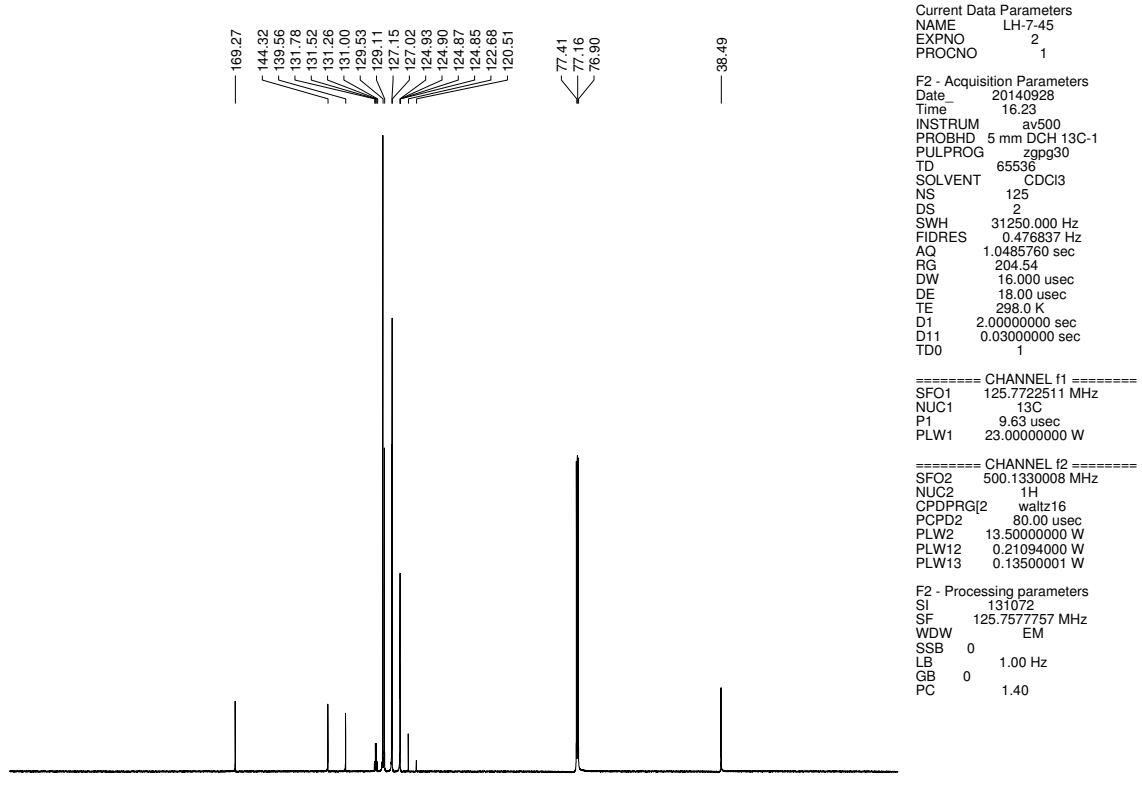


Figure 4.8. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.39**.

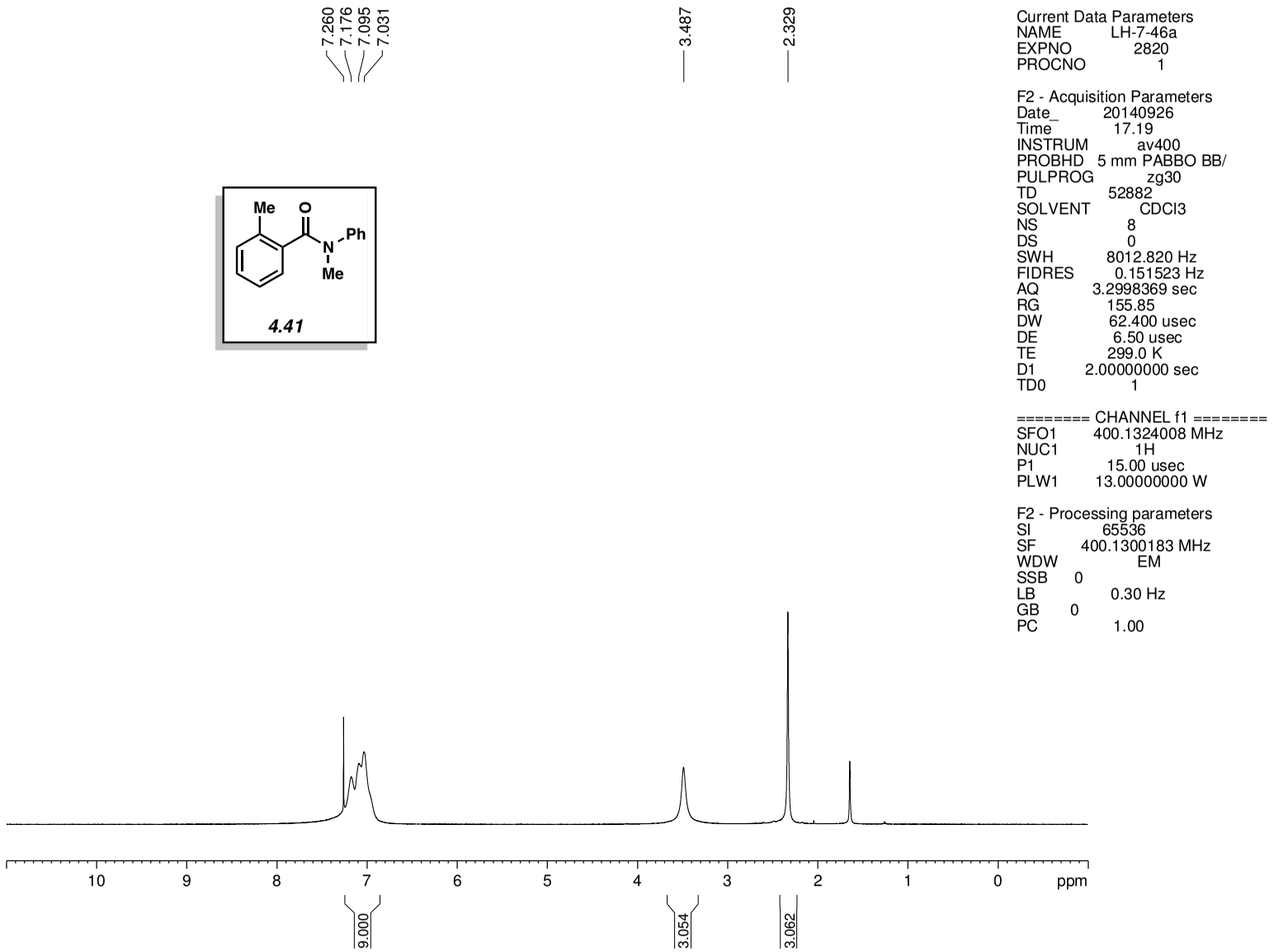


Figure 4.9. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.41**.

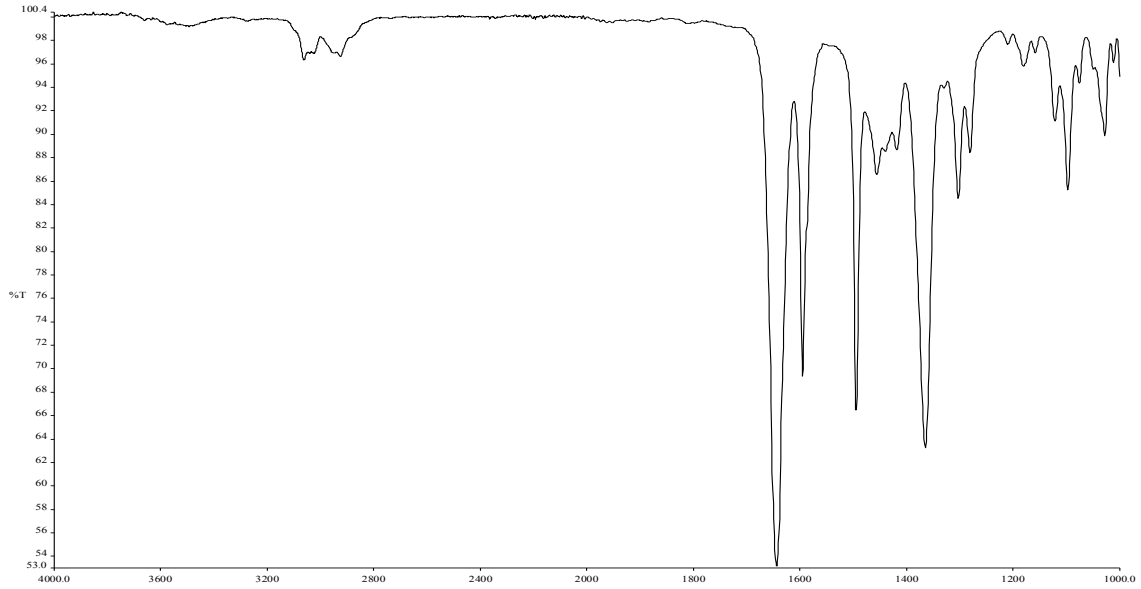


Figure 4.10. Infrared spectrum of compound **4.41**.

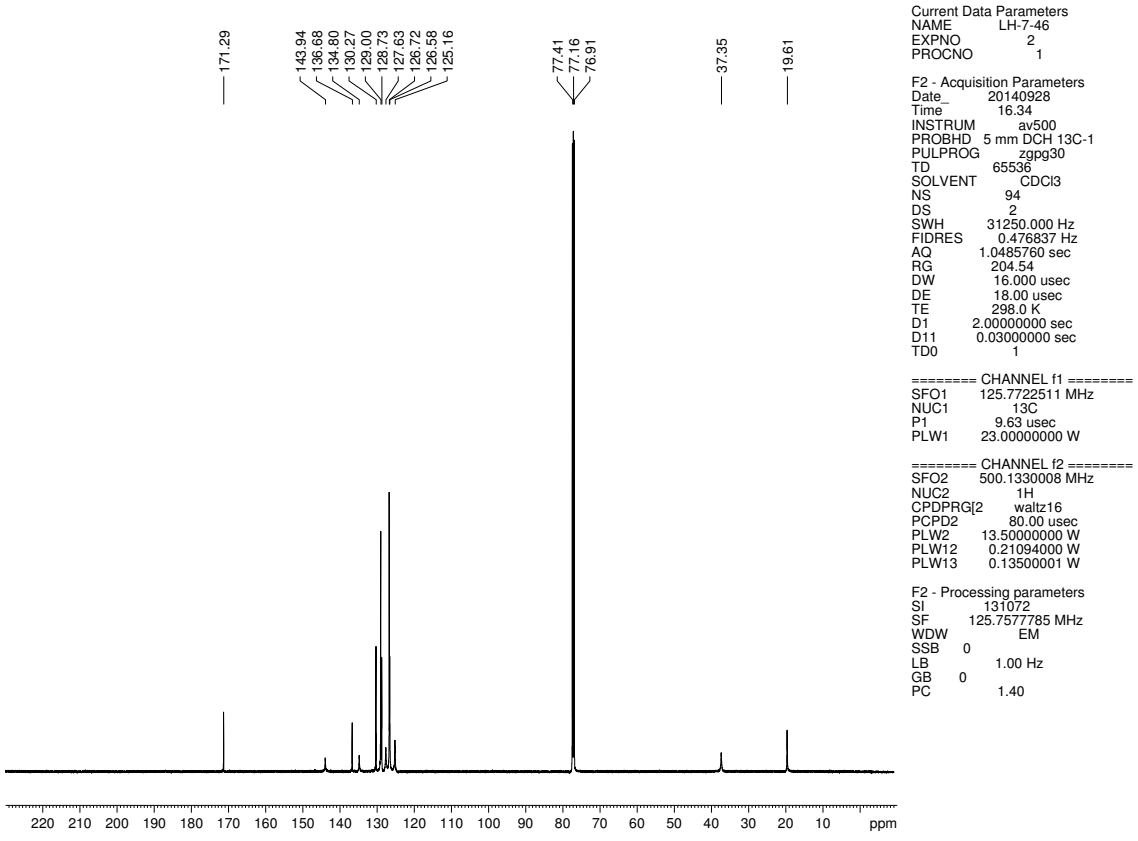


Figure 4.11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.41**.

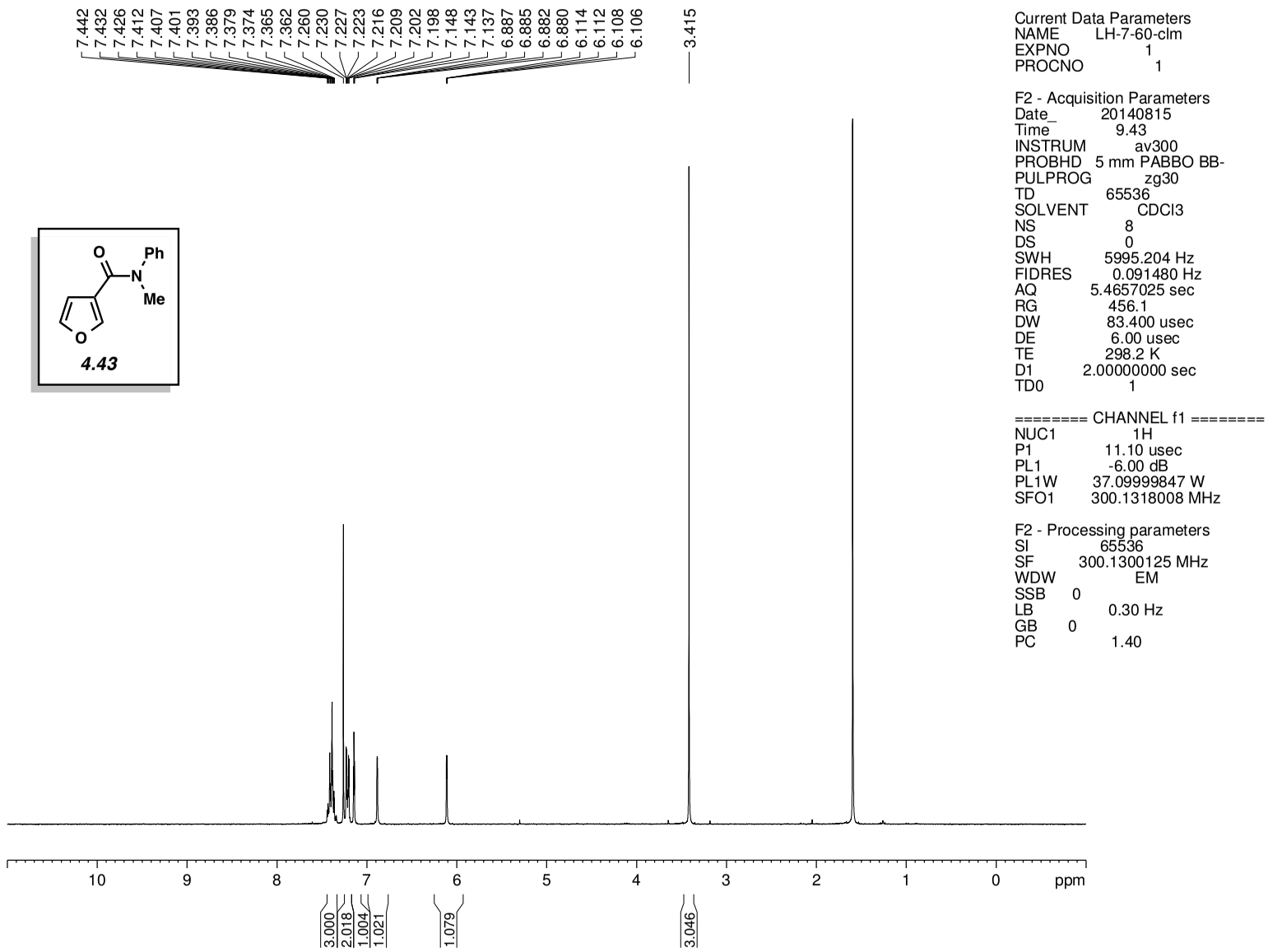


Figure 4.12. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.43**.

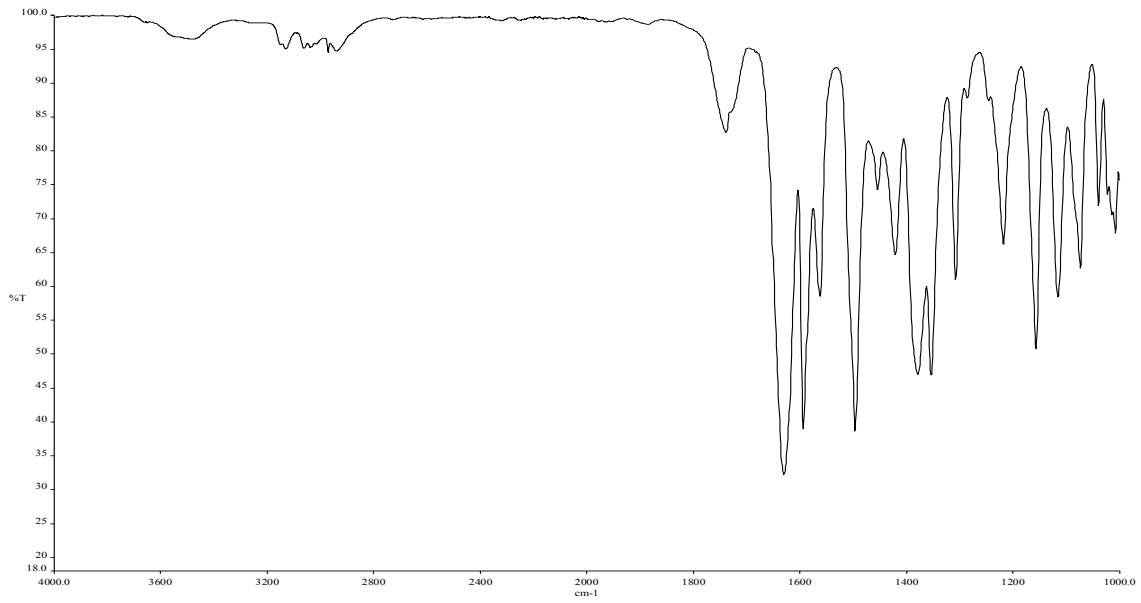


Figure 4.13. Infrared spectrum of compound **4.43**.

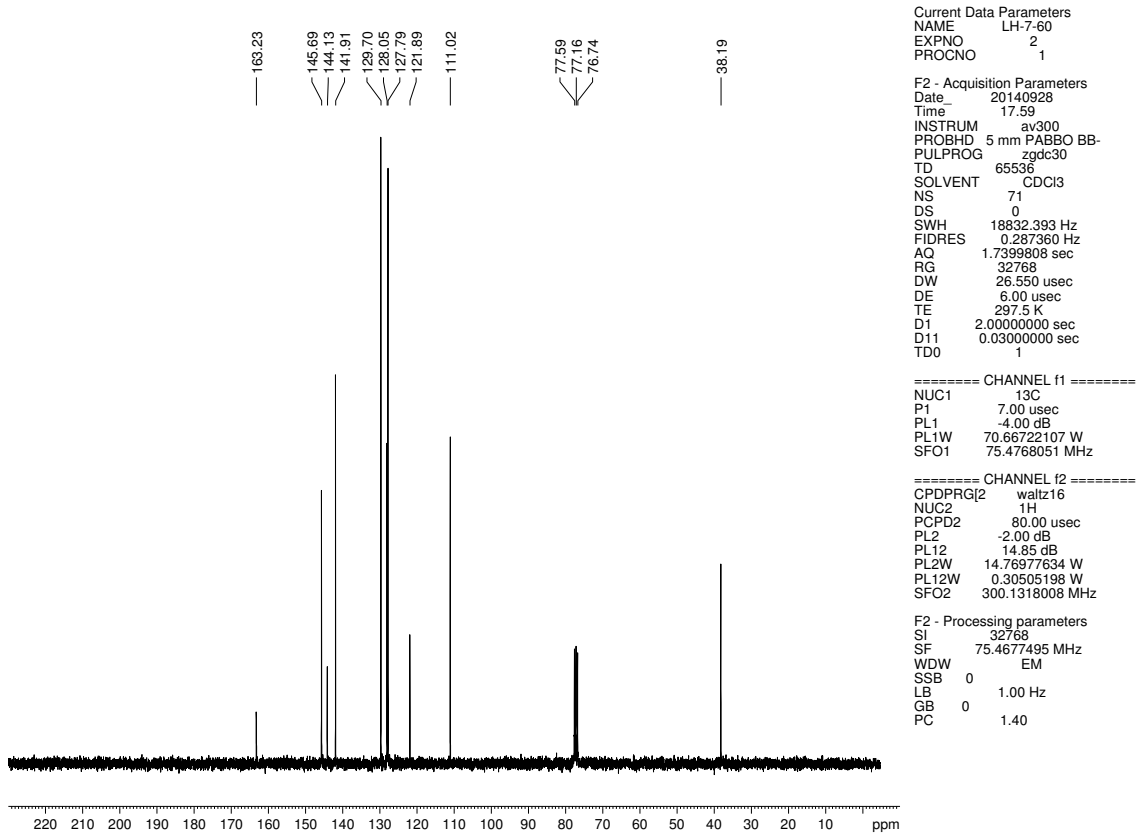


Figure 4.14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.43**.

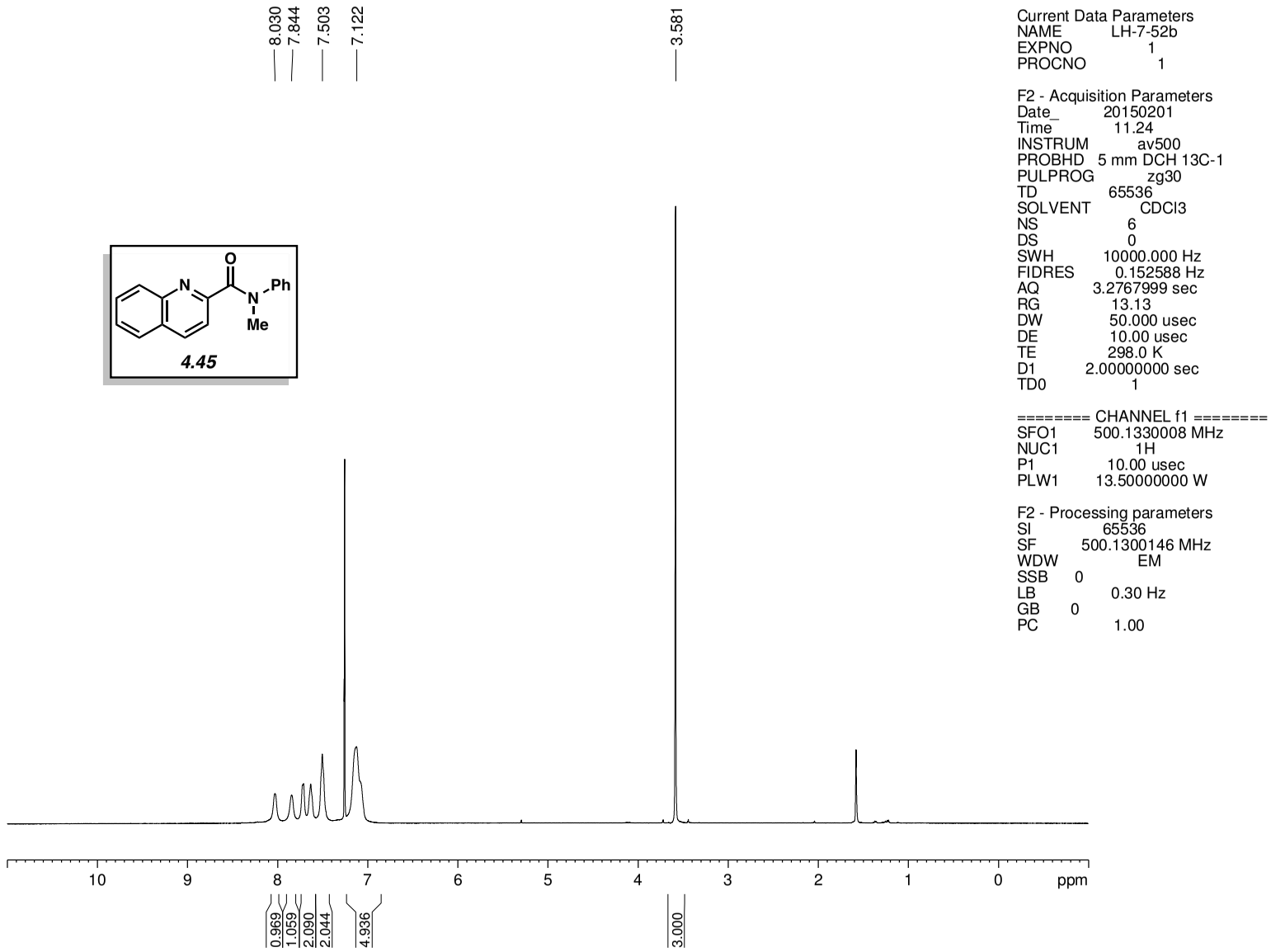


Figure 4.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.45**.

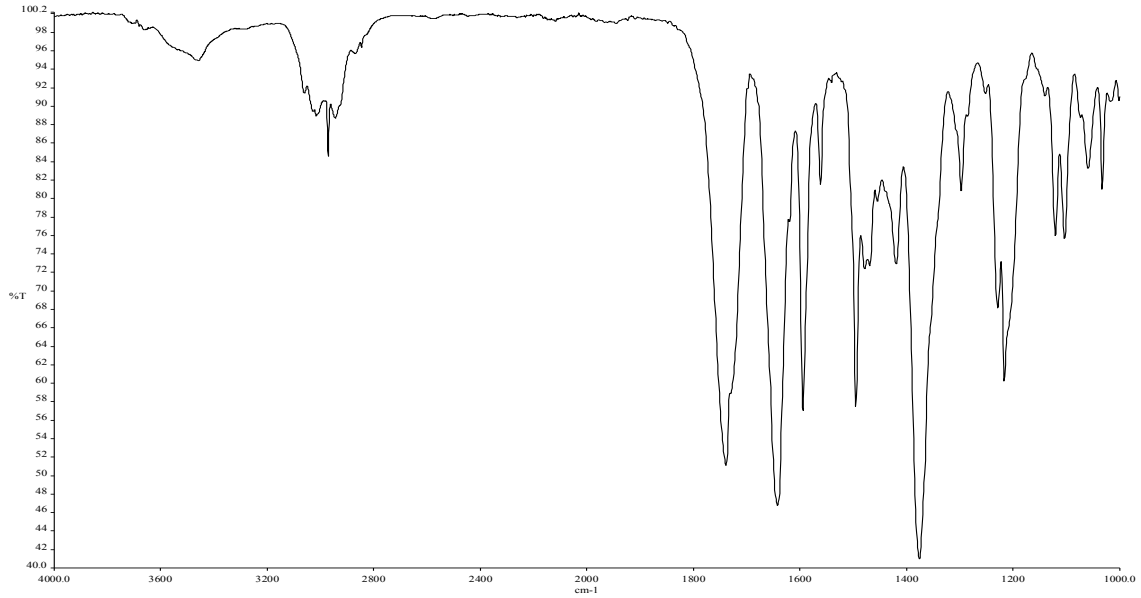


Figure 4.16. Infrared spectrum of compound **4.45**.

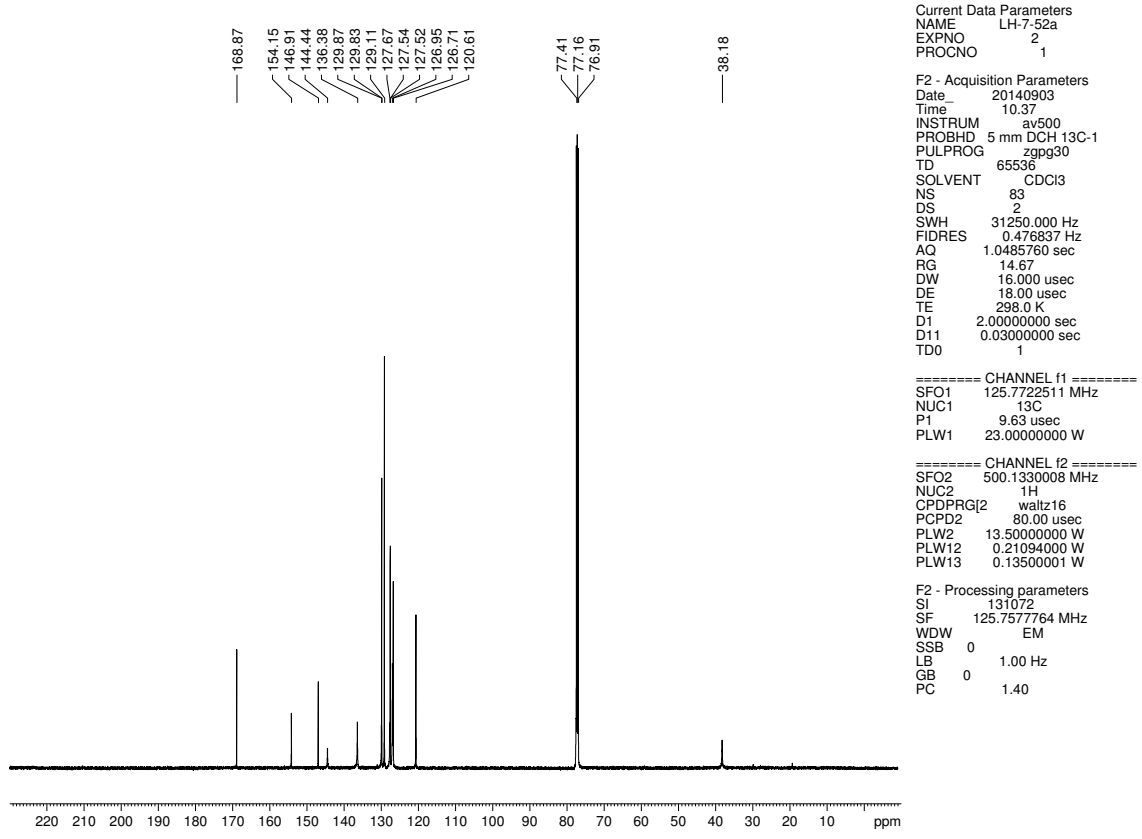


Figure 4.17. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.45**.

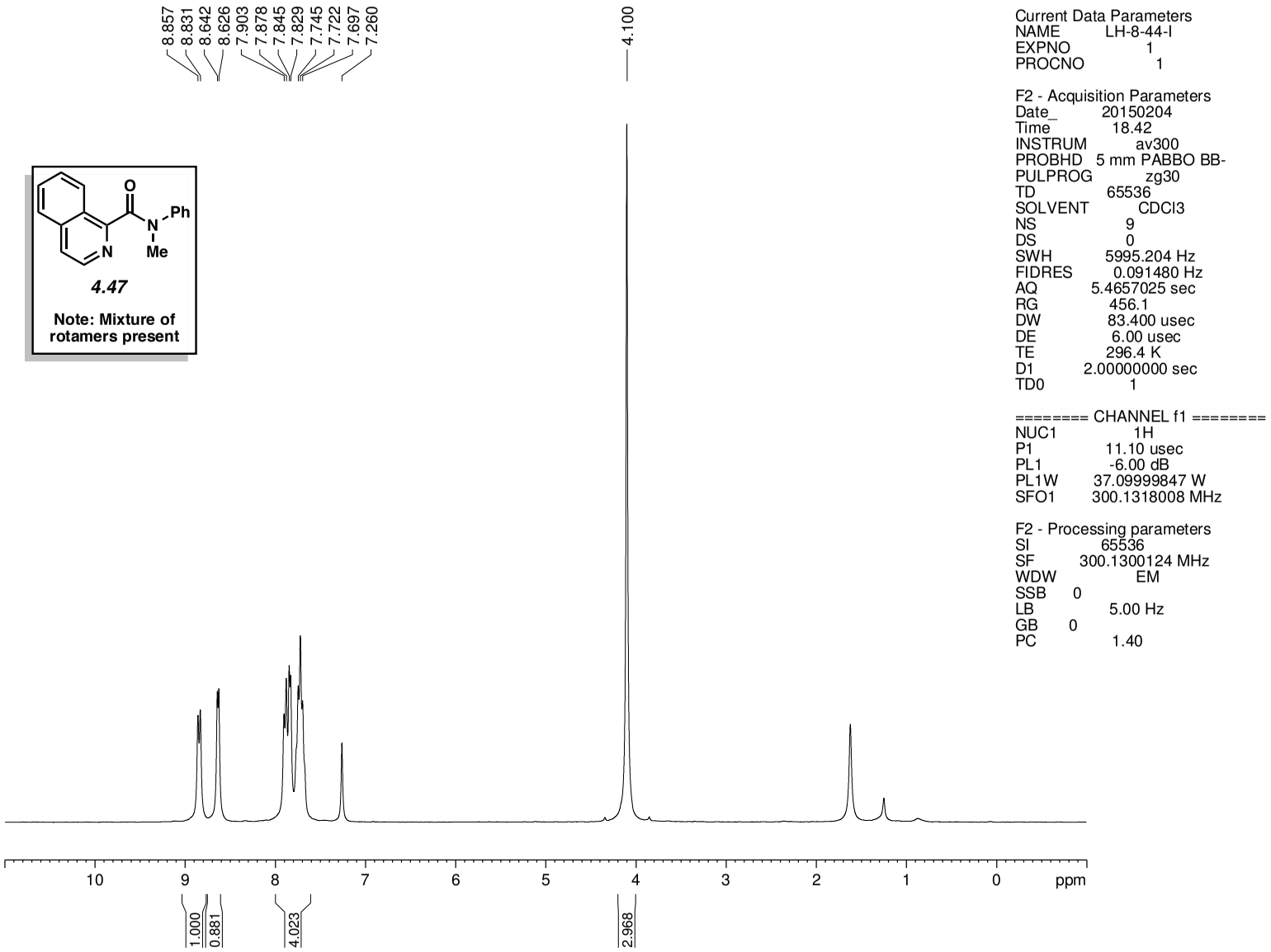


Figure 4.18. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.47**.

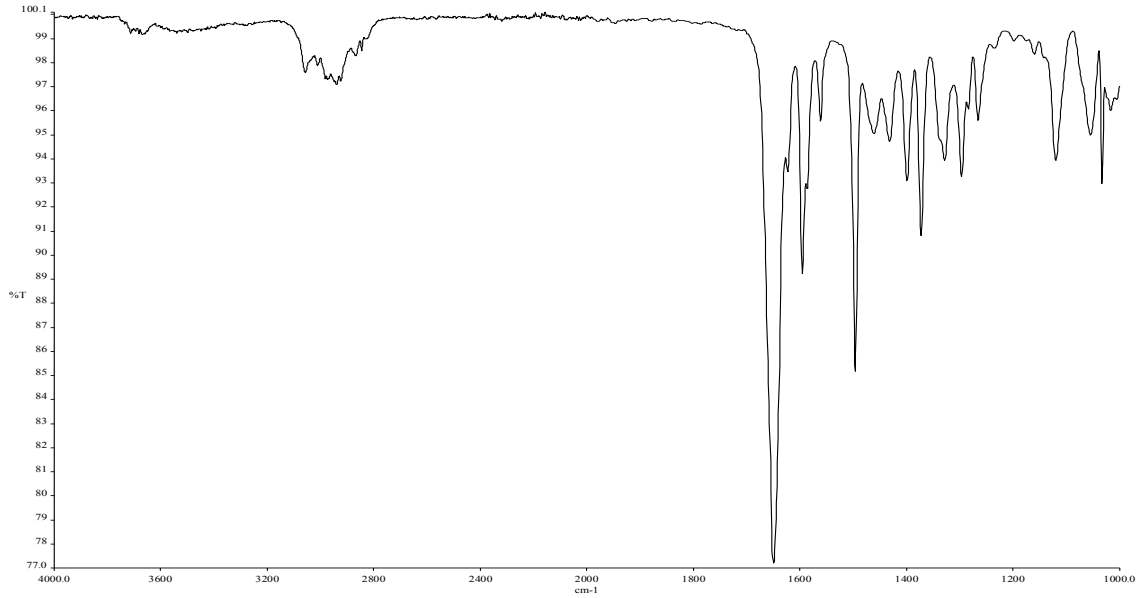


Figure 4.19. Infrared spectrum of compound **4.47**.

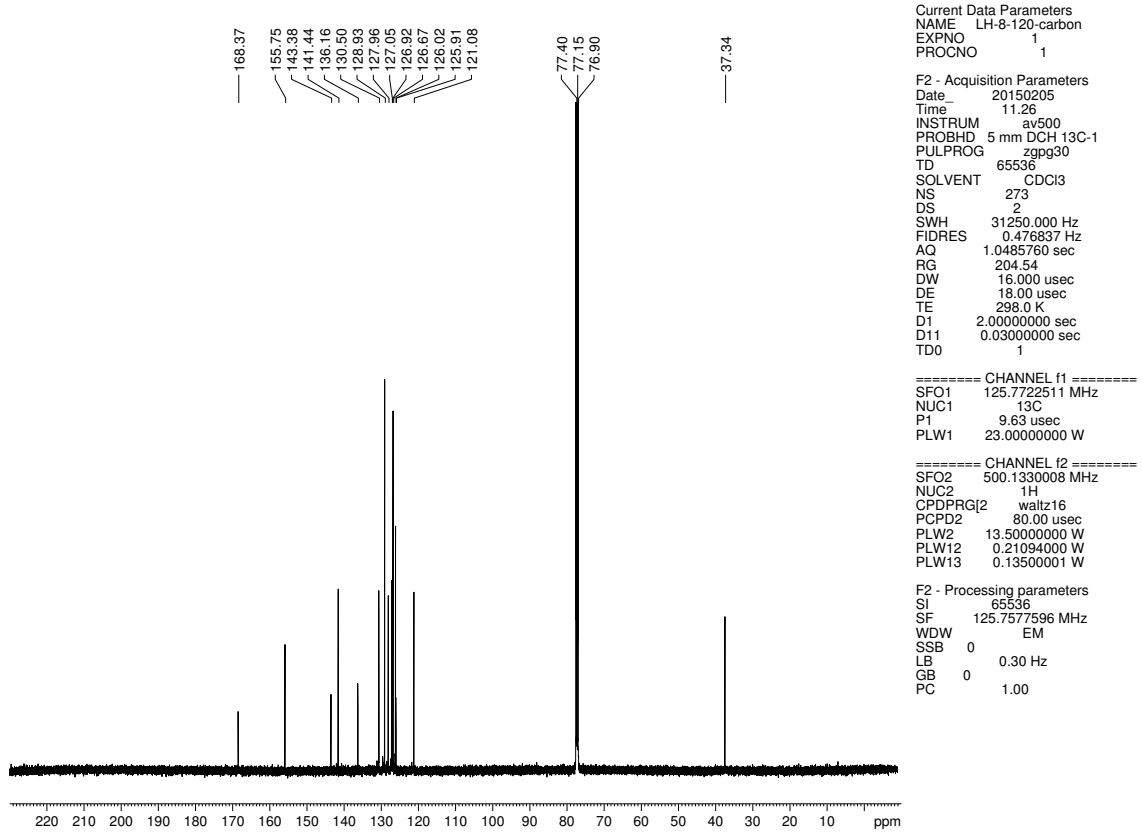


Figure 4.20. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.47**.

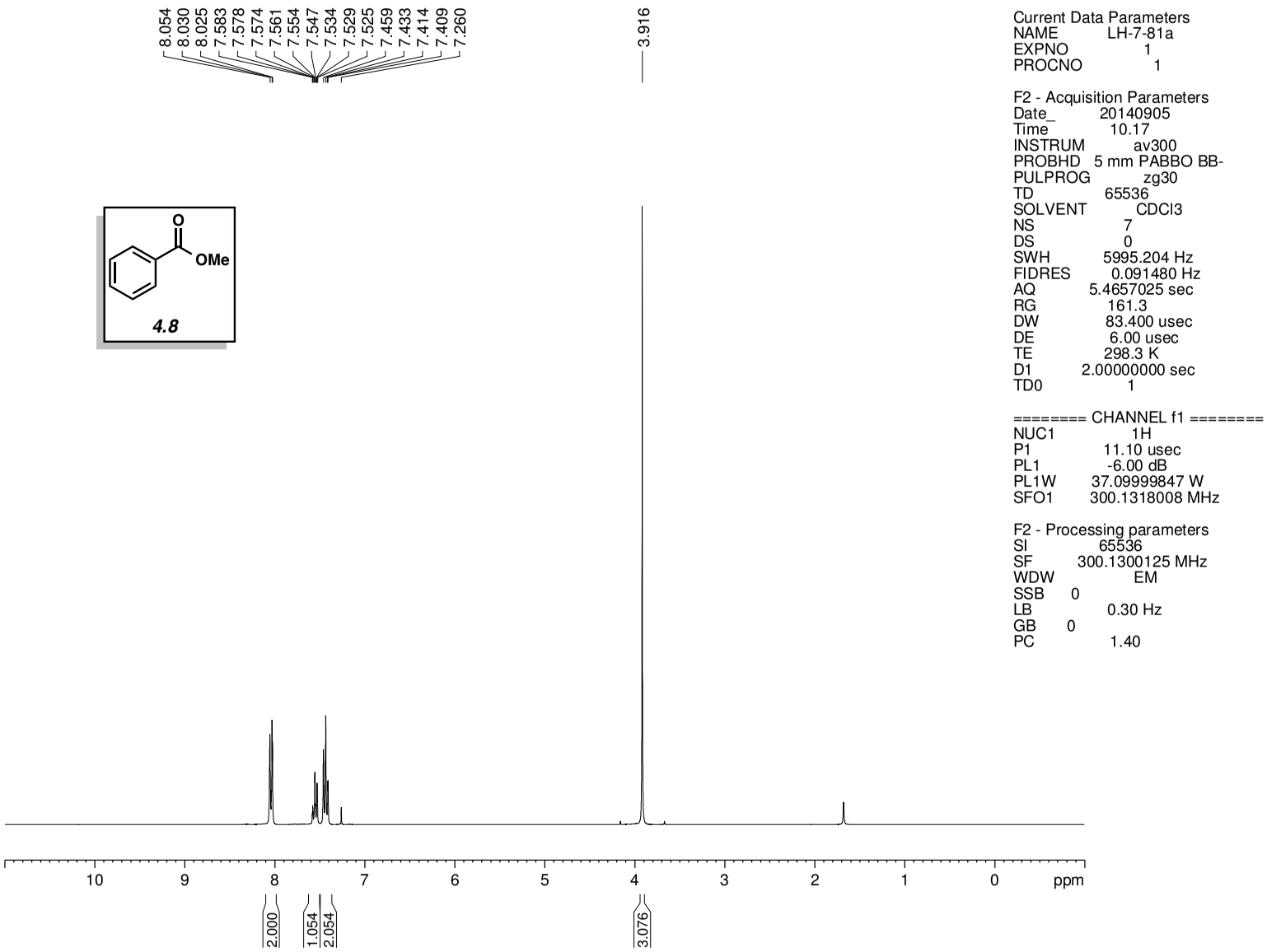


Figure 4.21. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.8**.

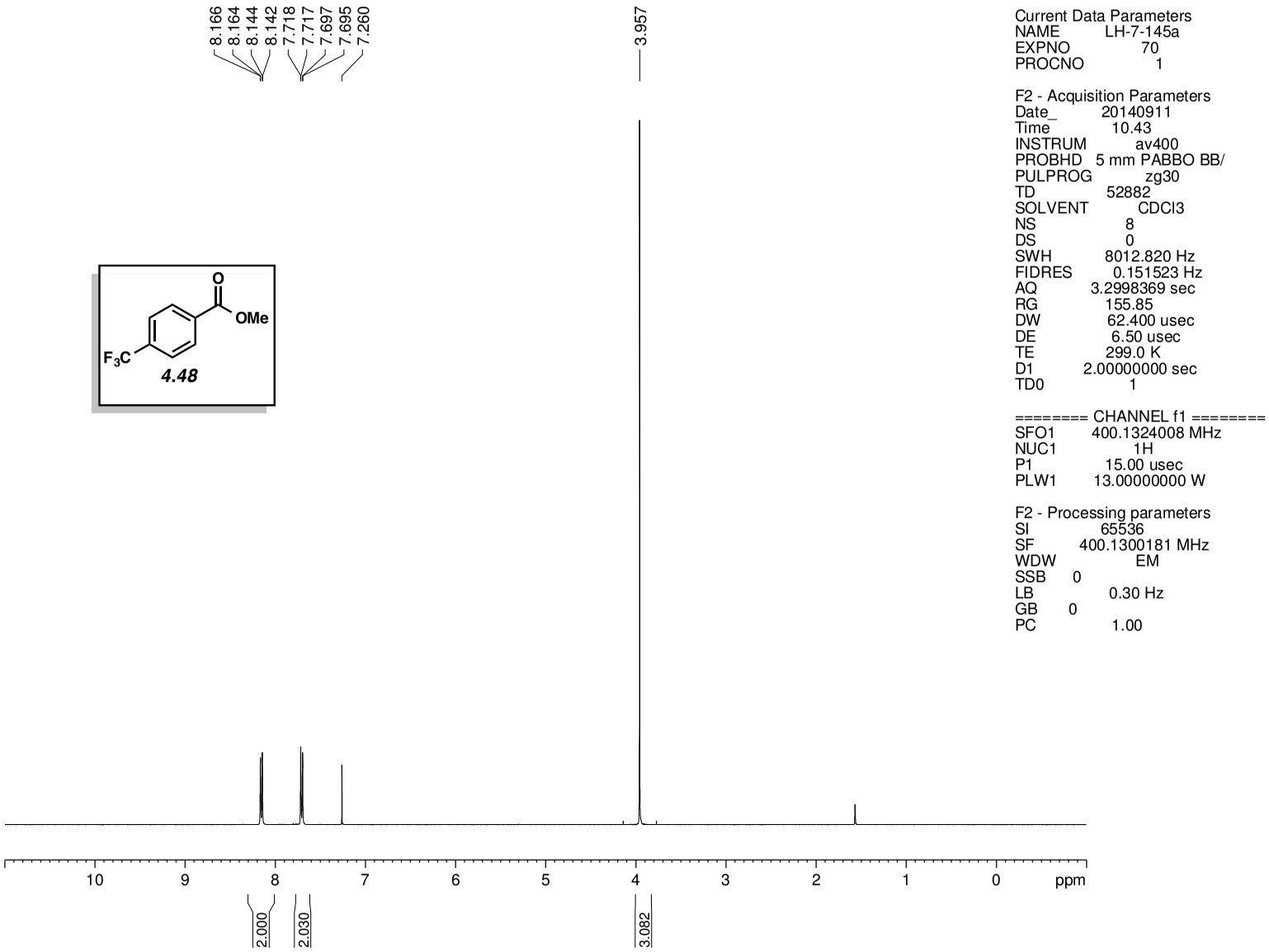


Figure 4.22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.48**.

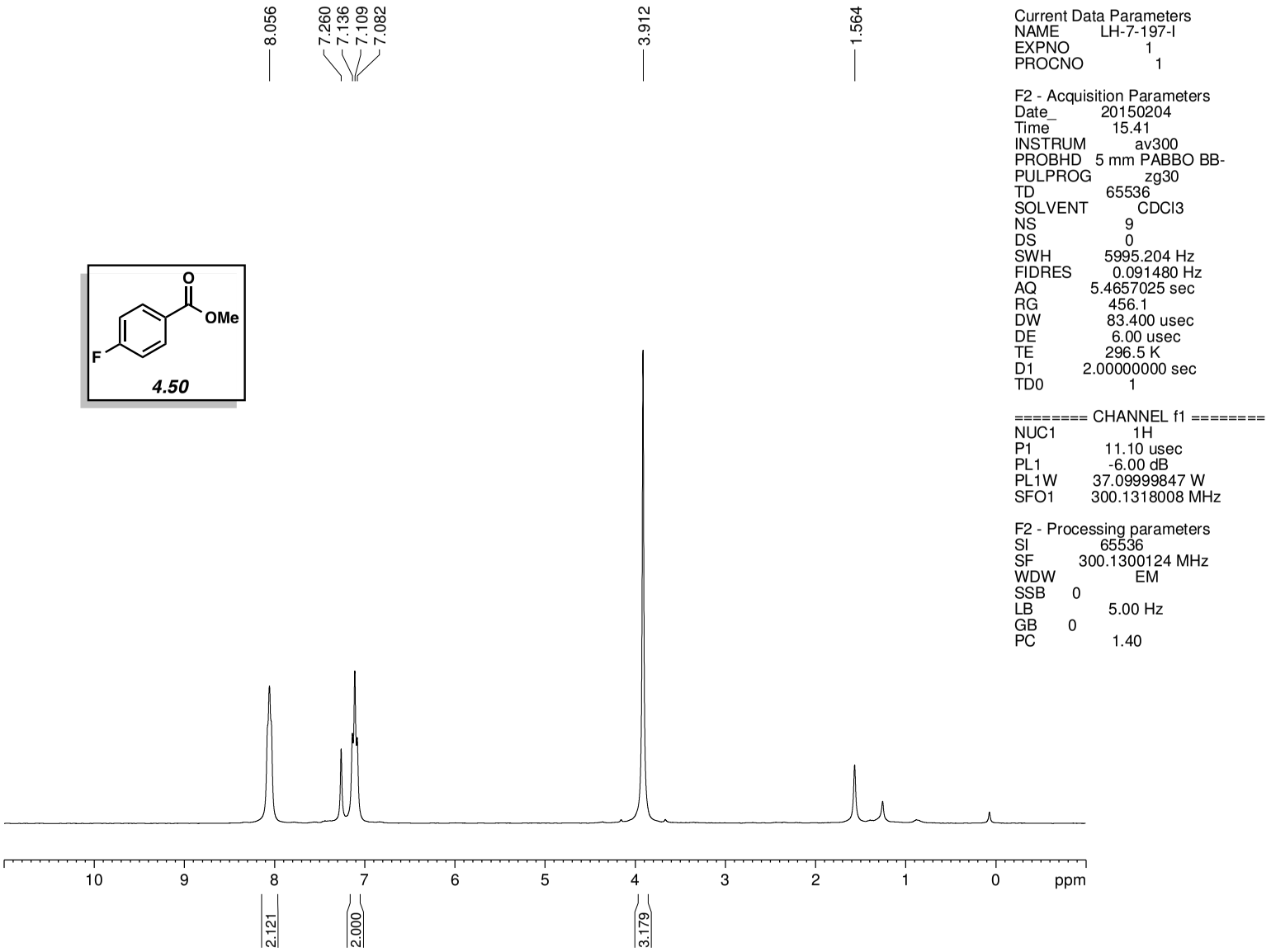


Figure 4.23. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.50**.

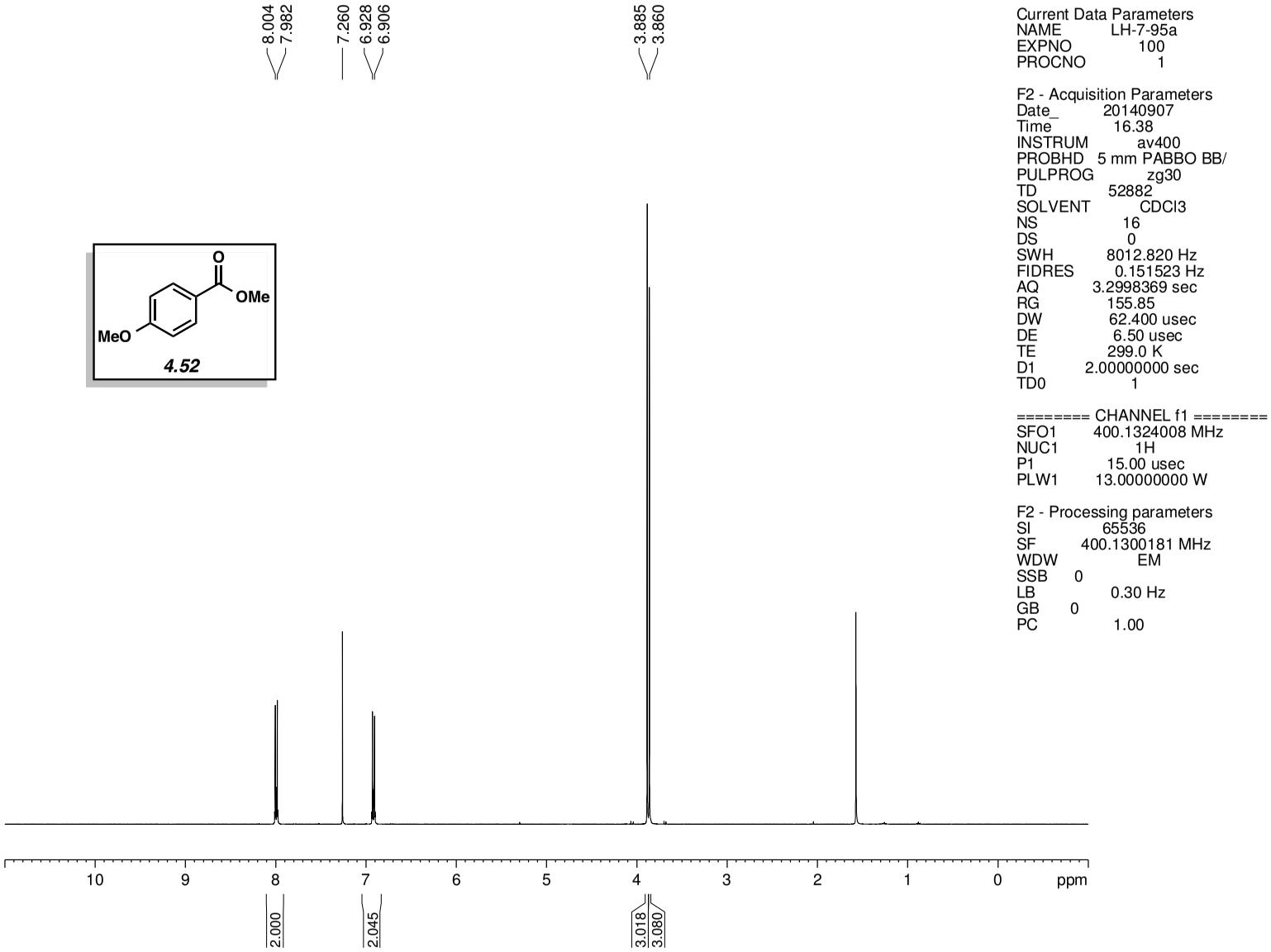


Figure 4.24. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.52**.

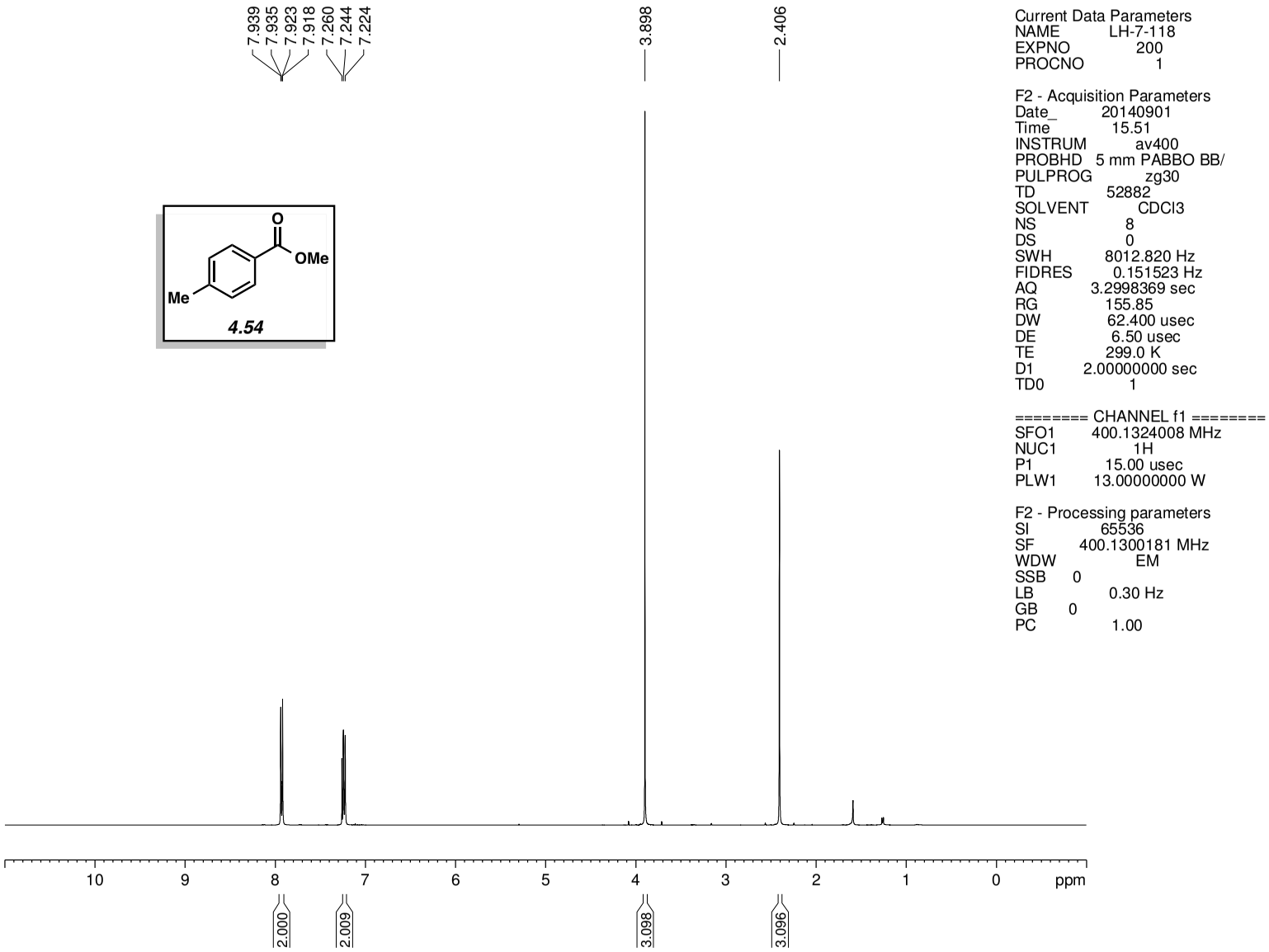


Figure 4.25. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.54**.

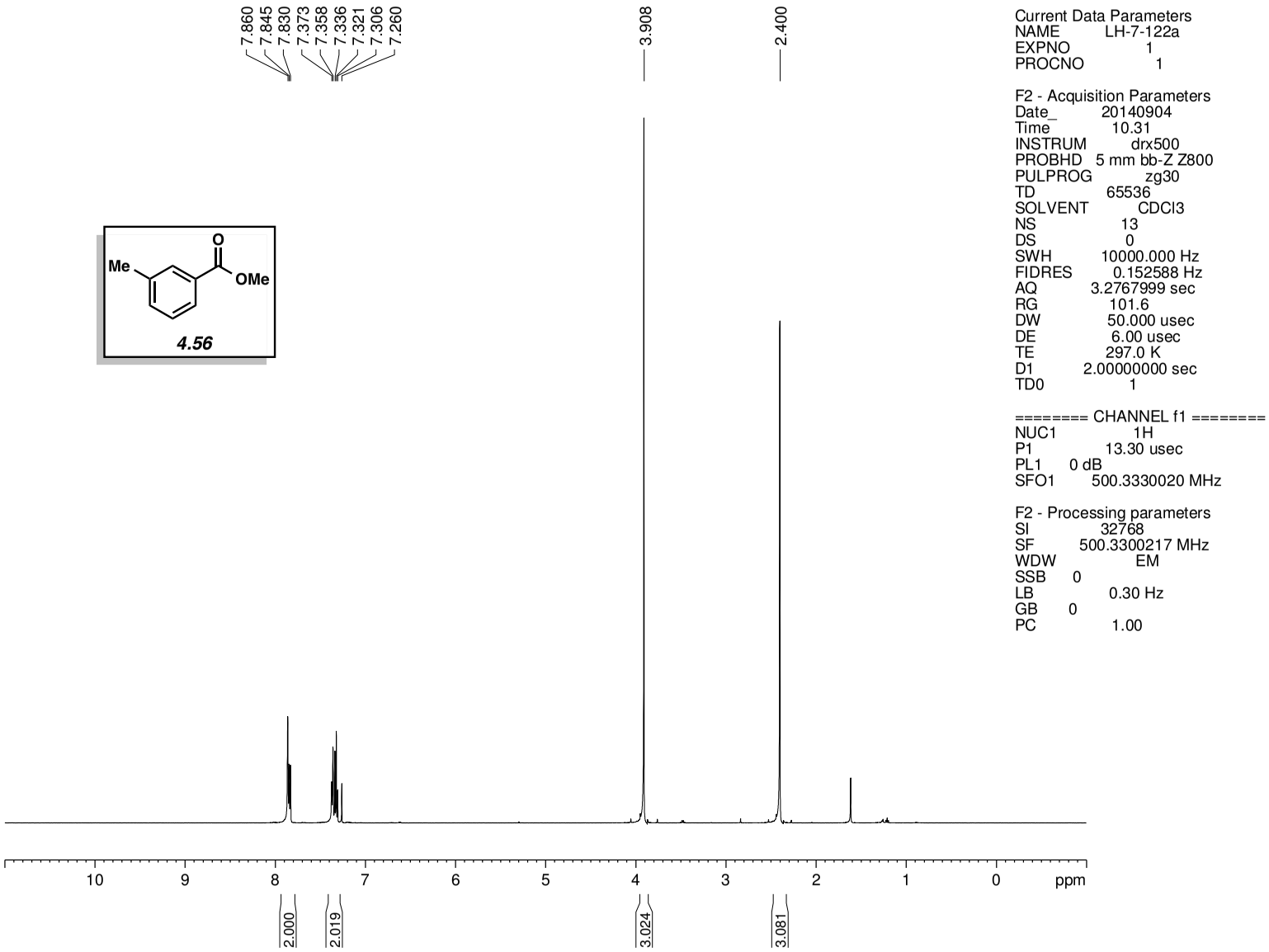


Figure 4.26. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.56**.

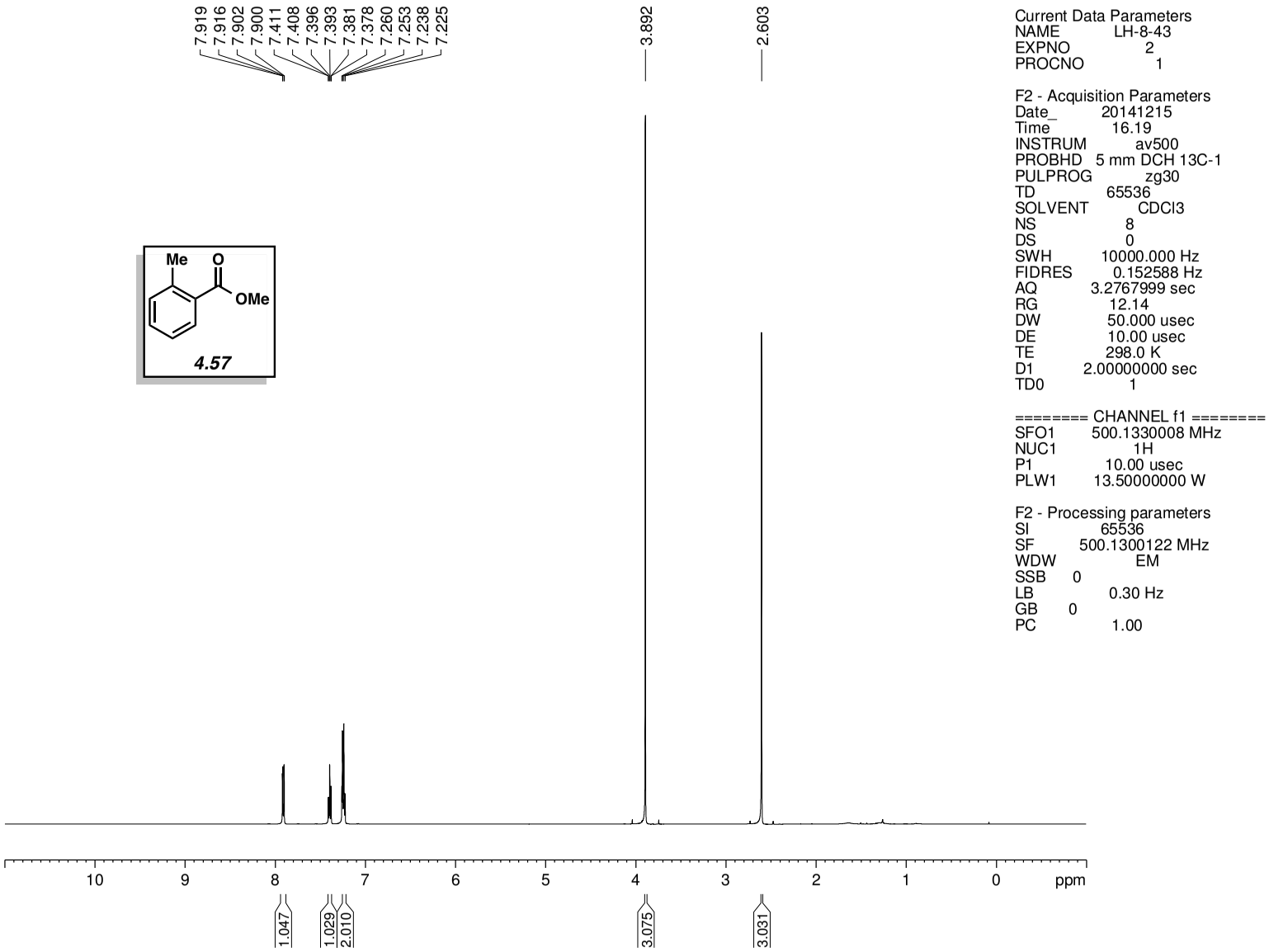


Figure 4.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.57**.

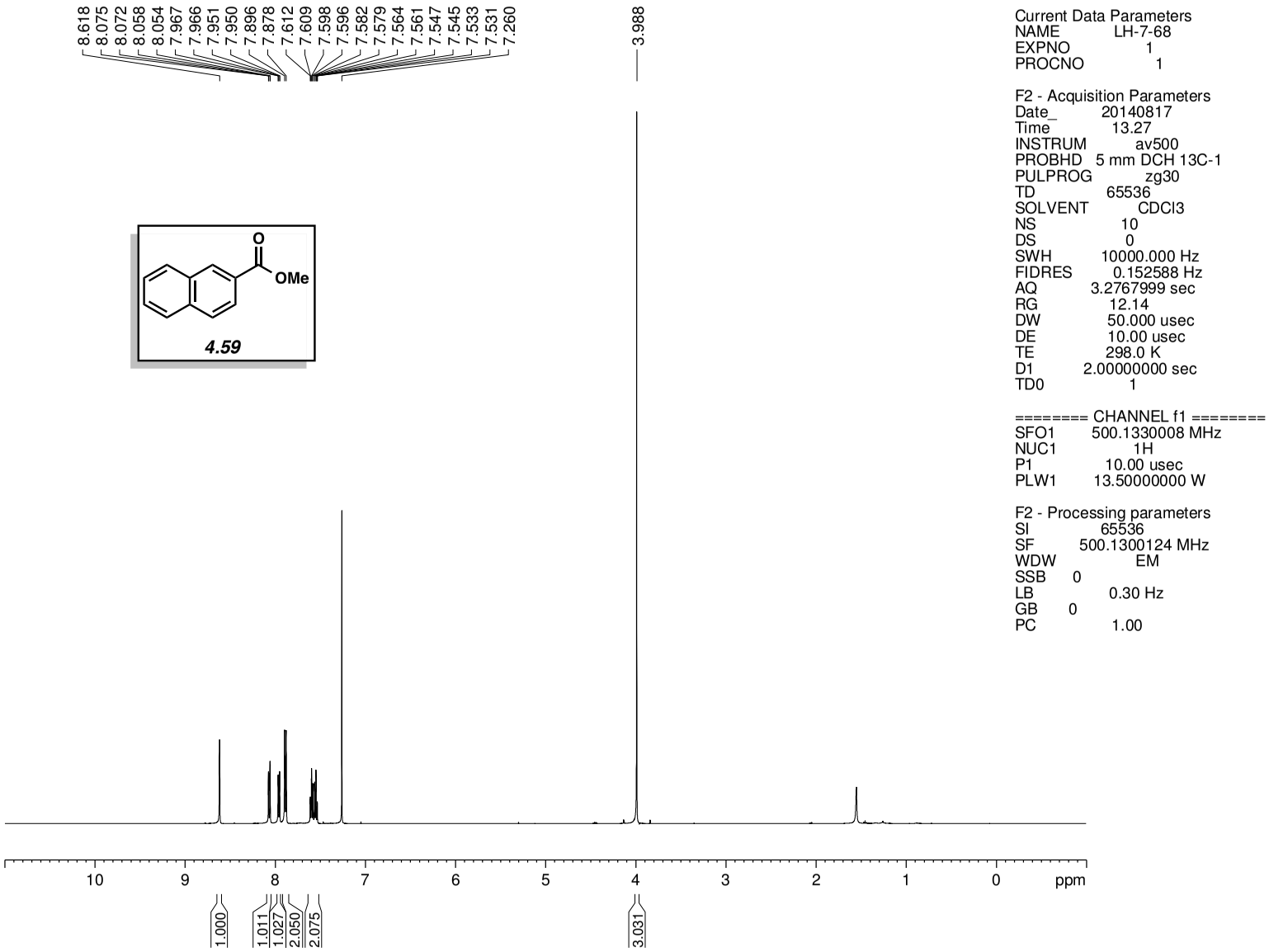


Figure 4.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.59**.

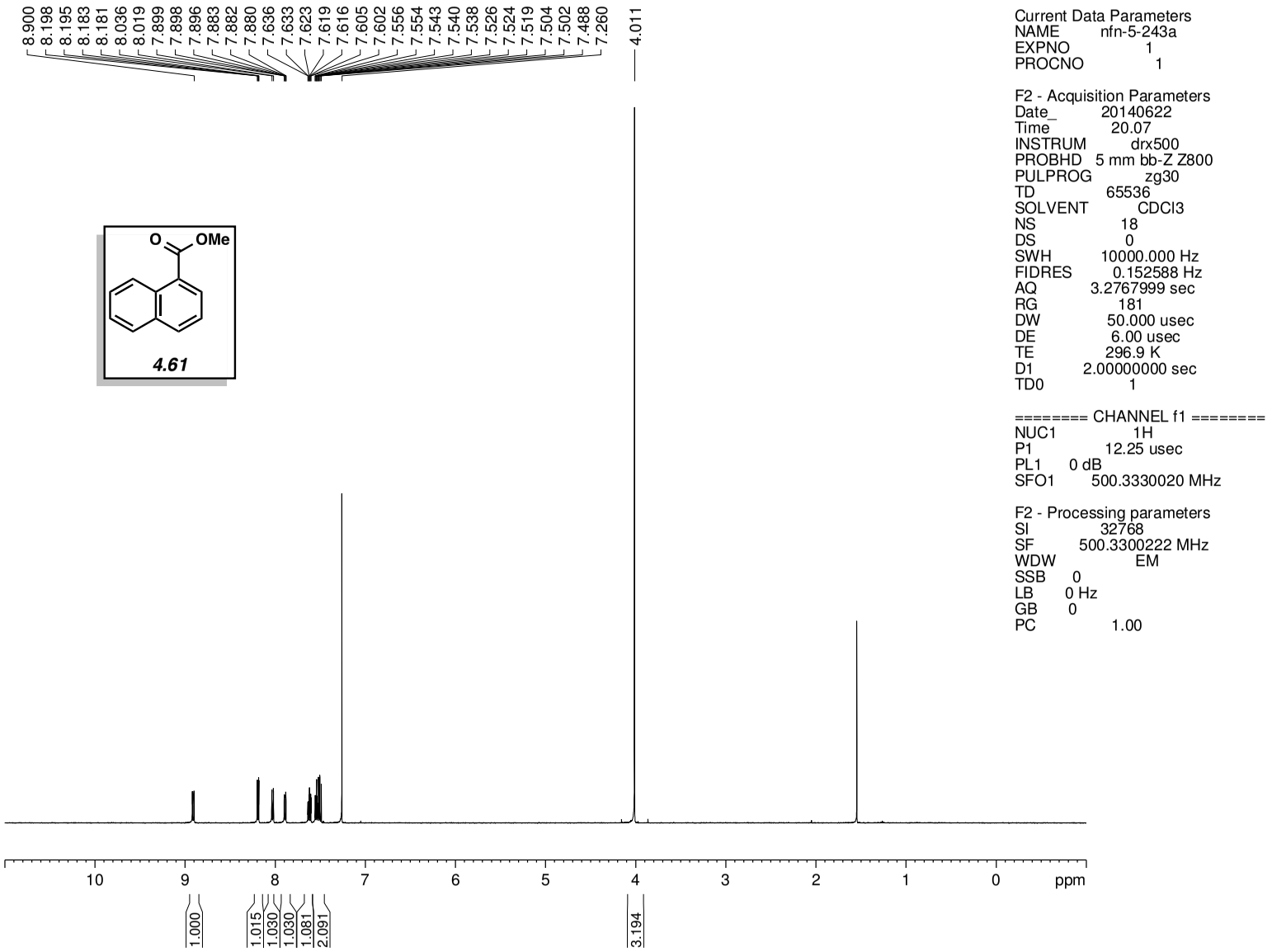


Figure 4.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.61**.

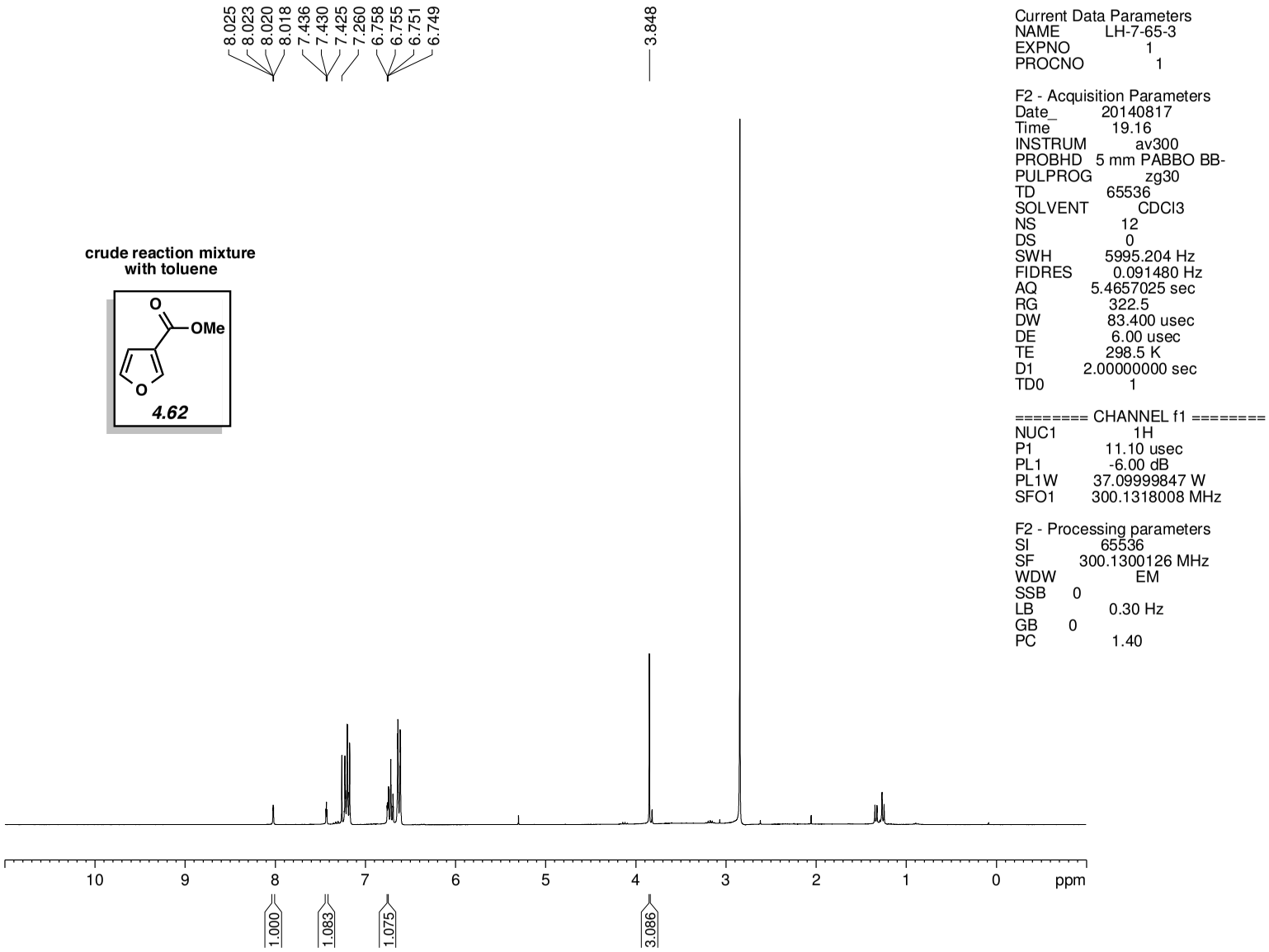


Figure 4.30. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.62**.

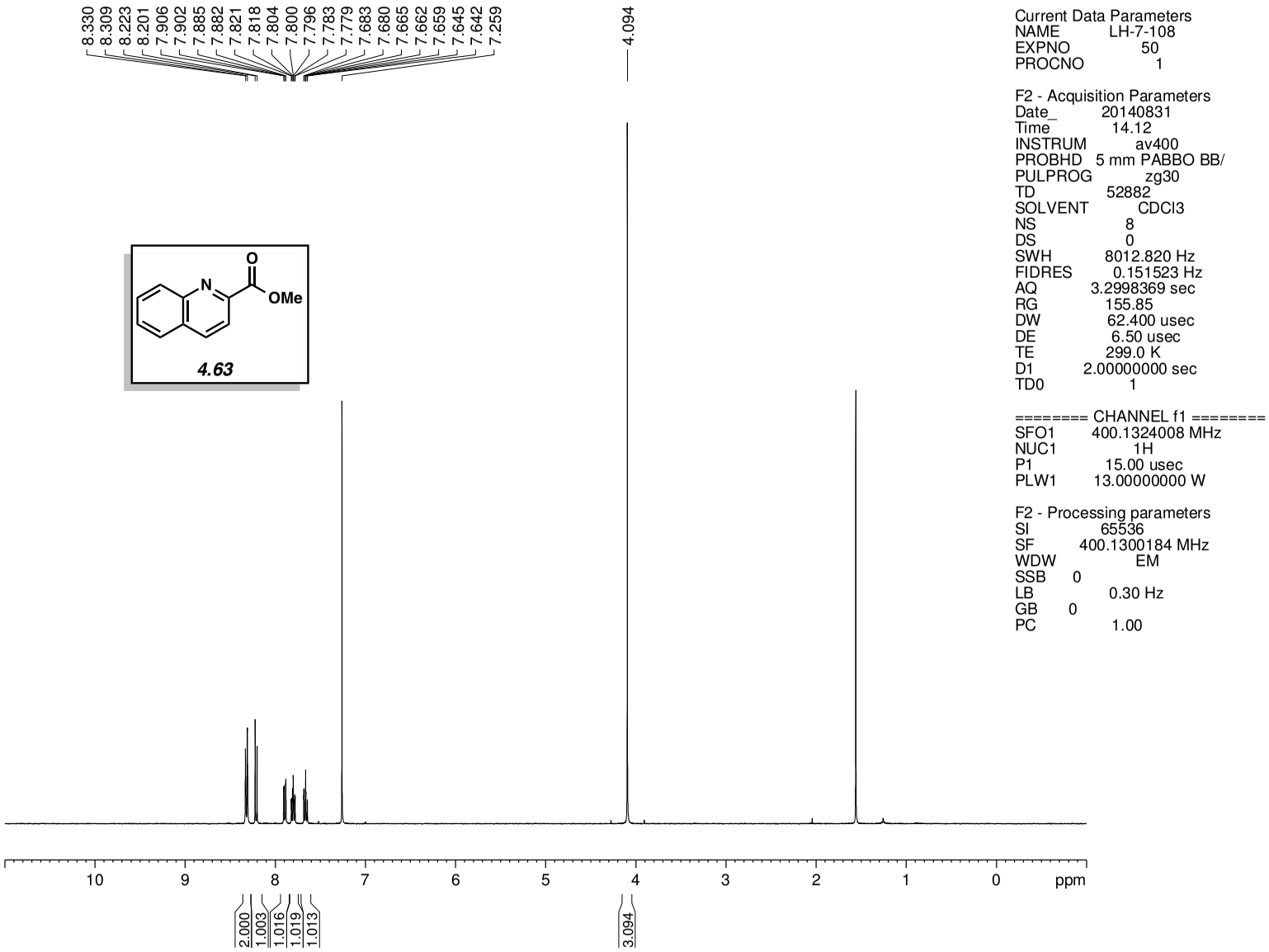


Figure 4.31. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.63**.

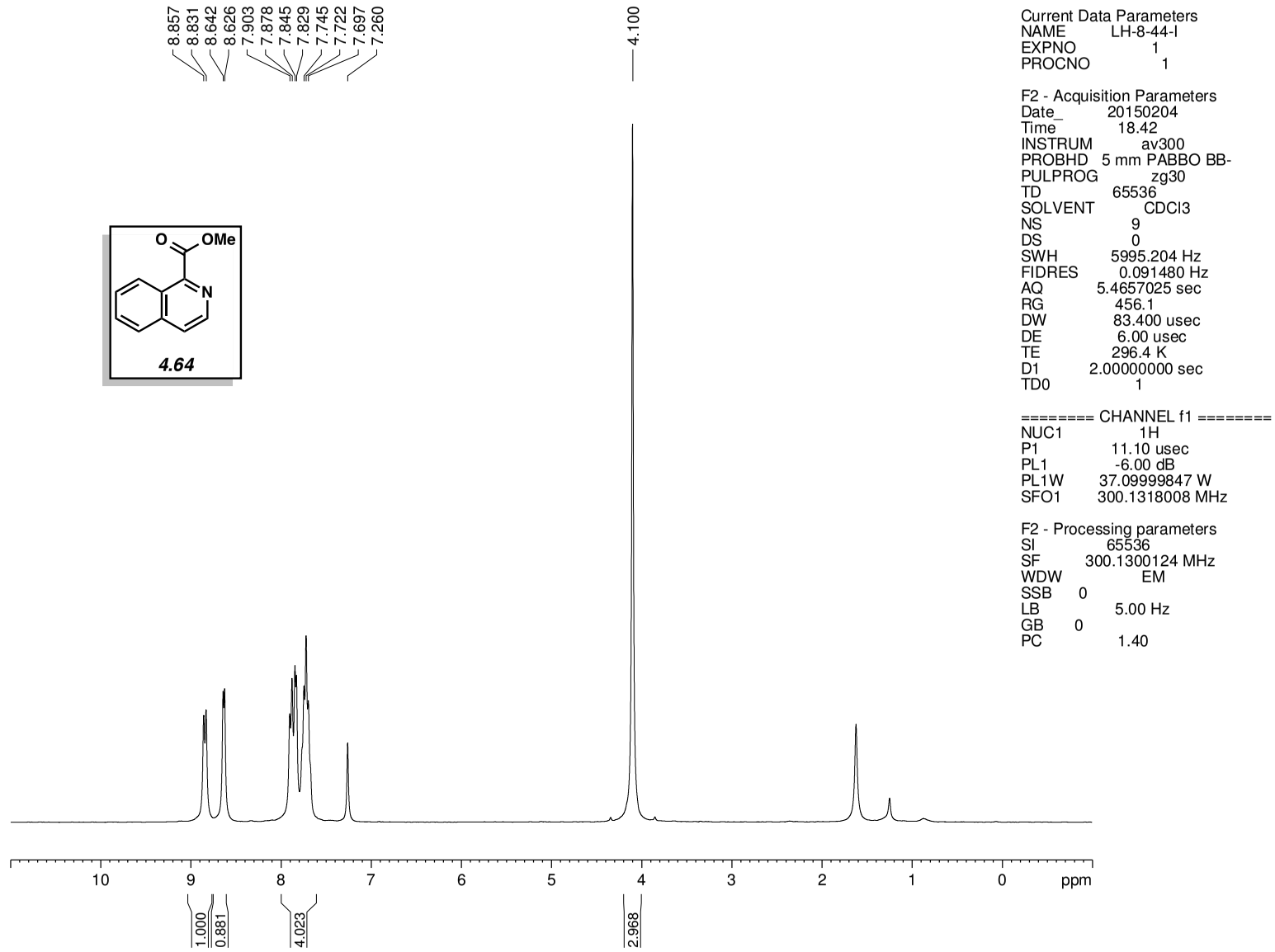


Figure 4.32. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.64**.

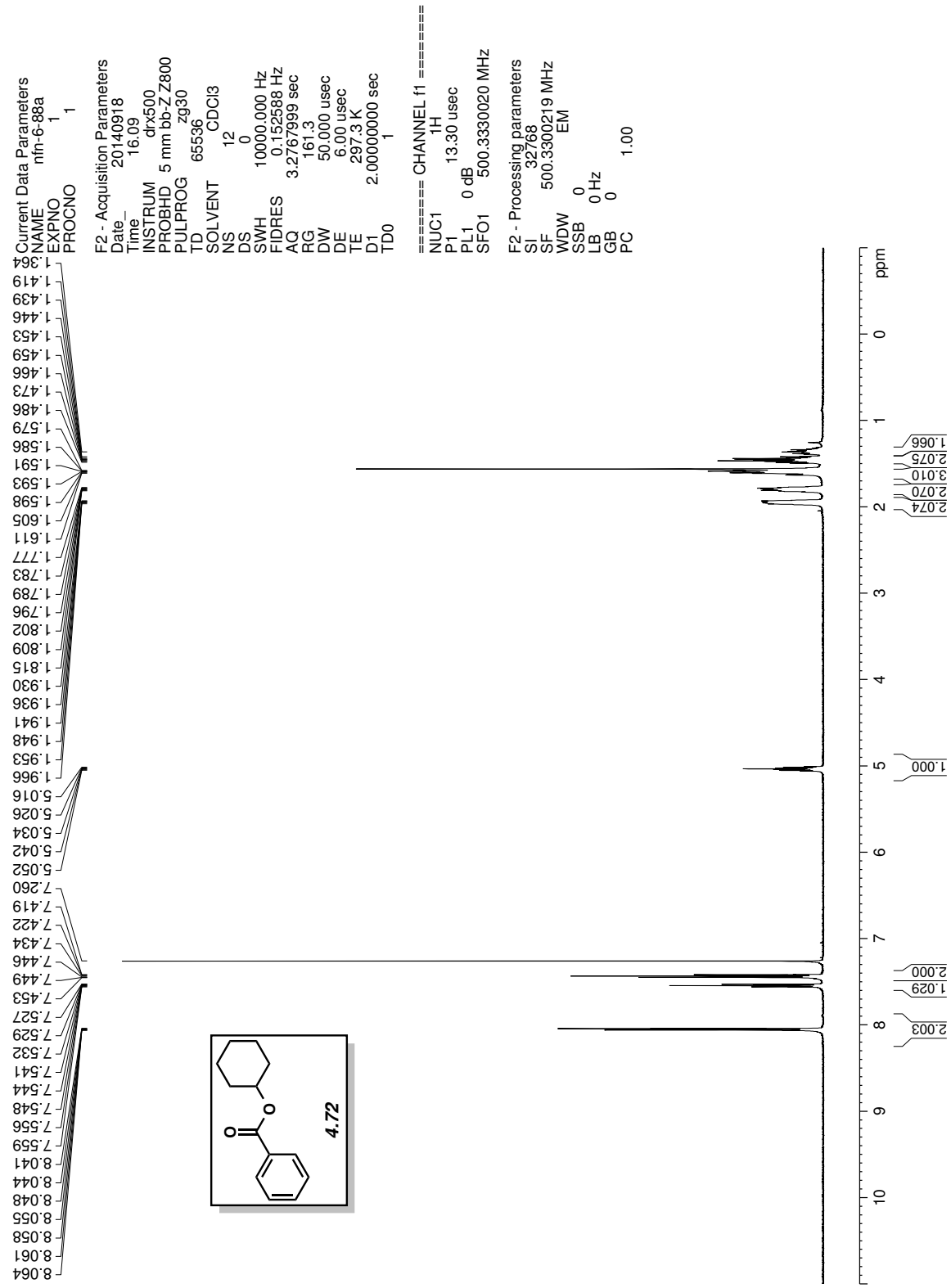


Figure 4.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.72**.

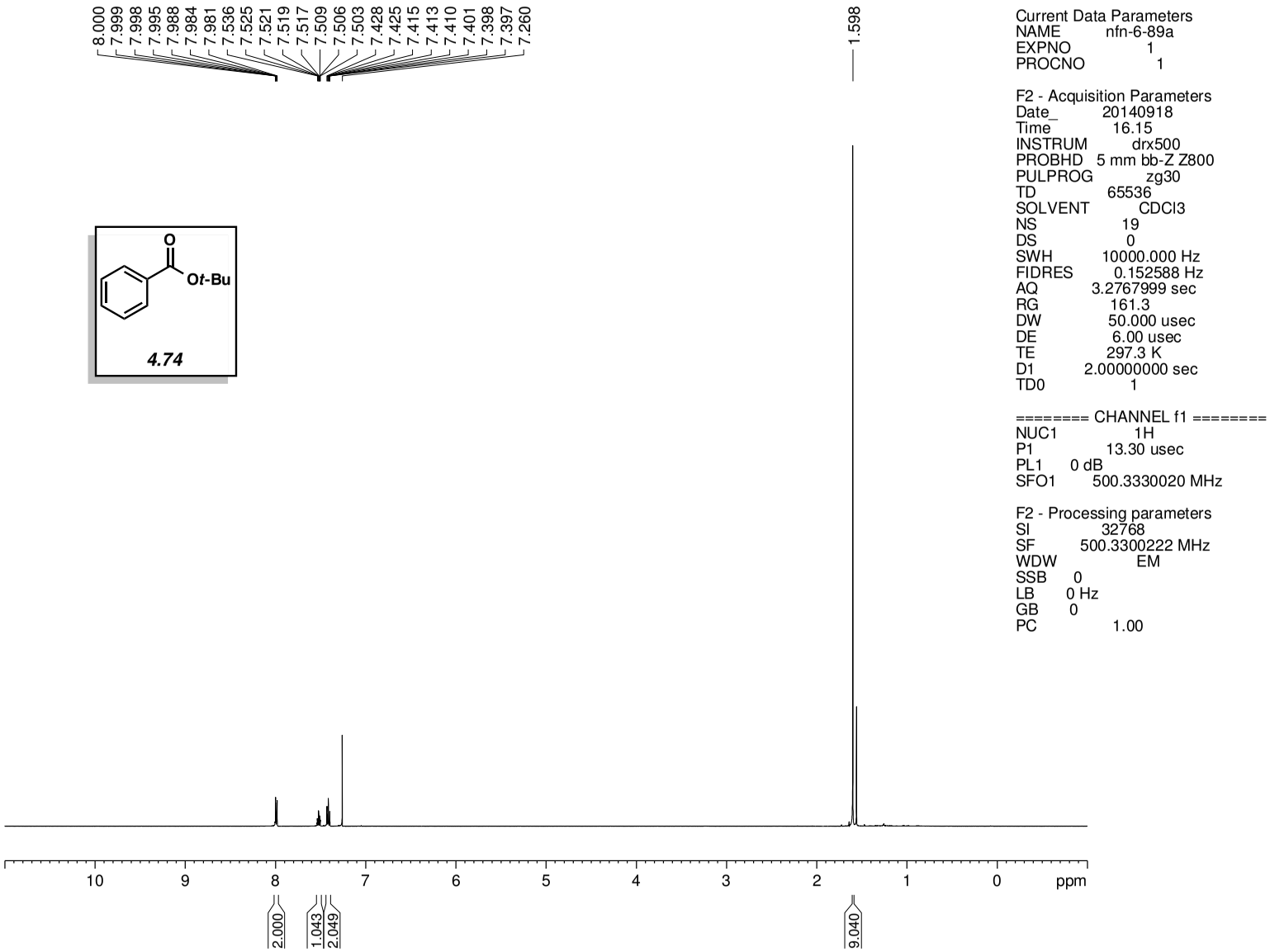


Figure 4.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.74**.

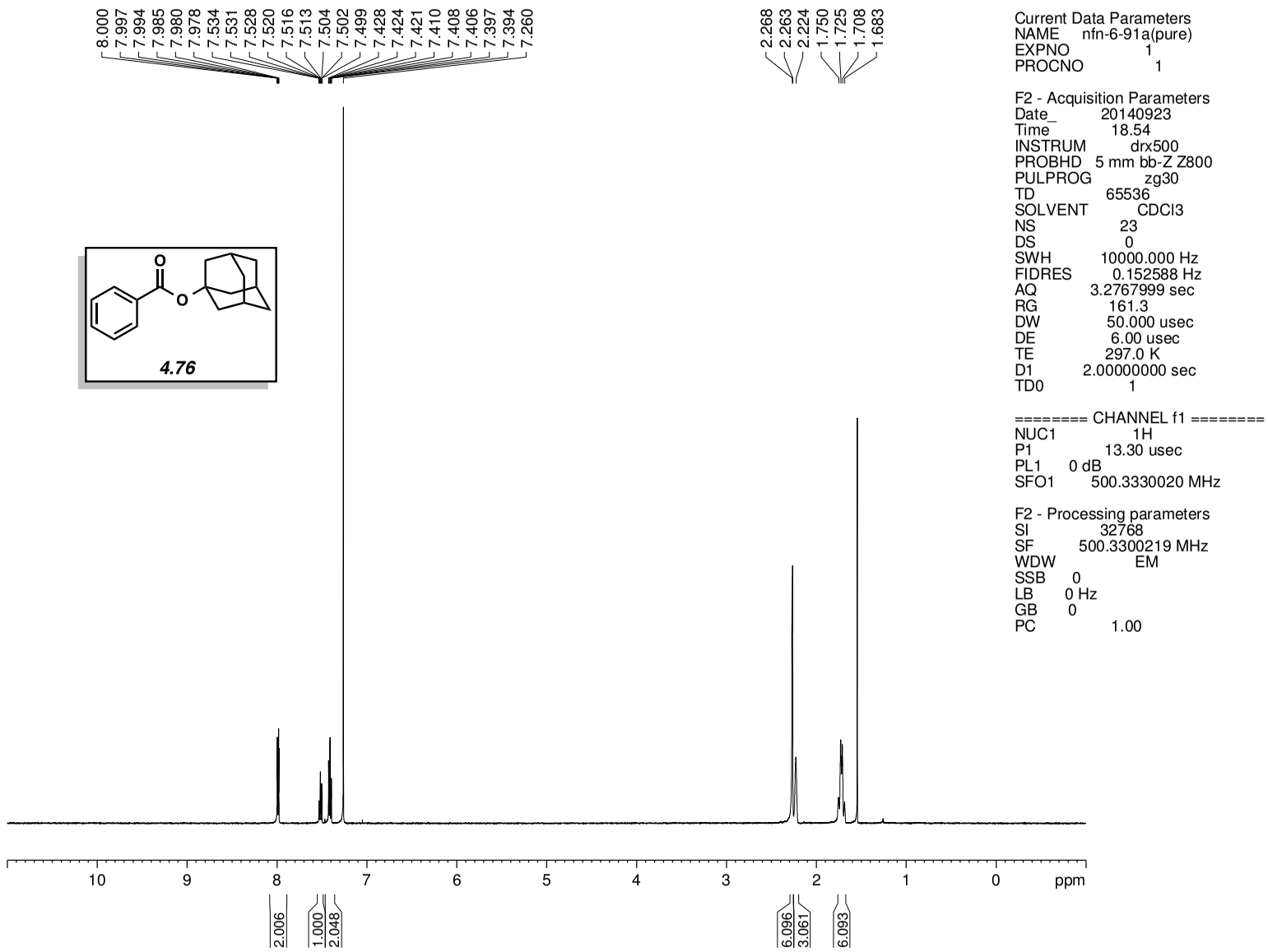


Figure 4.35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.76**.

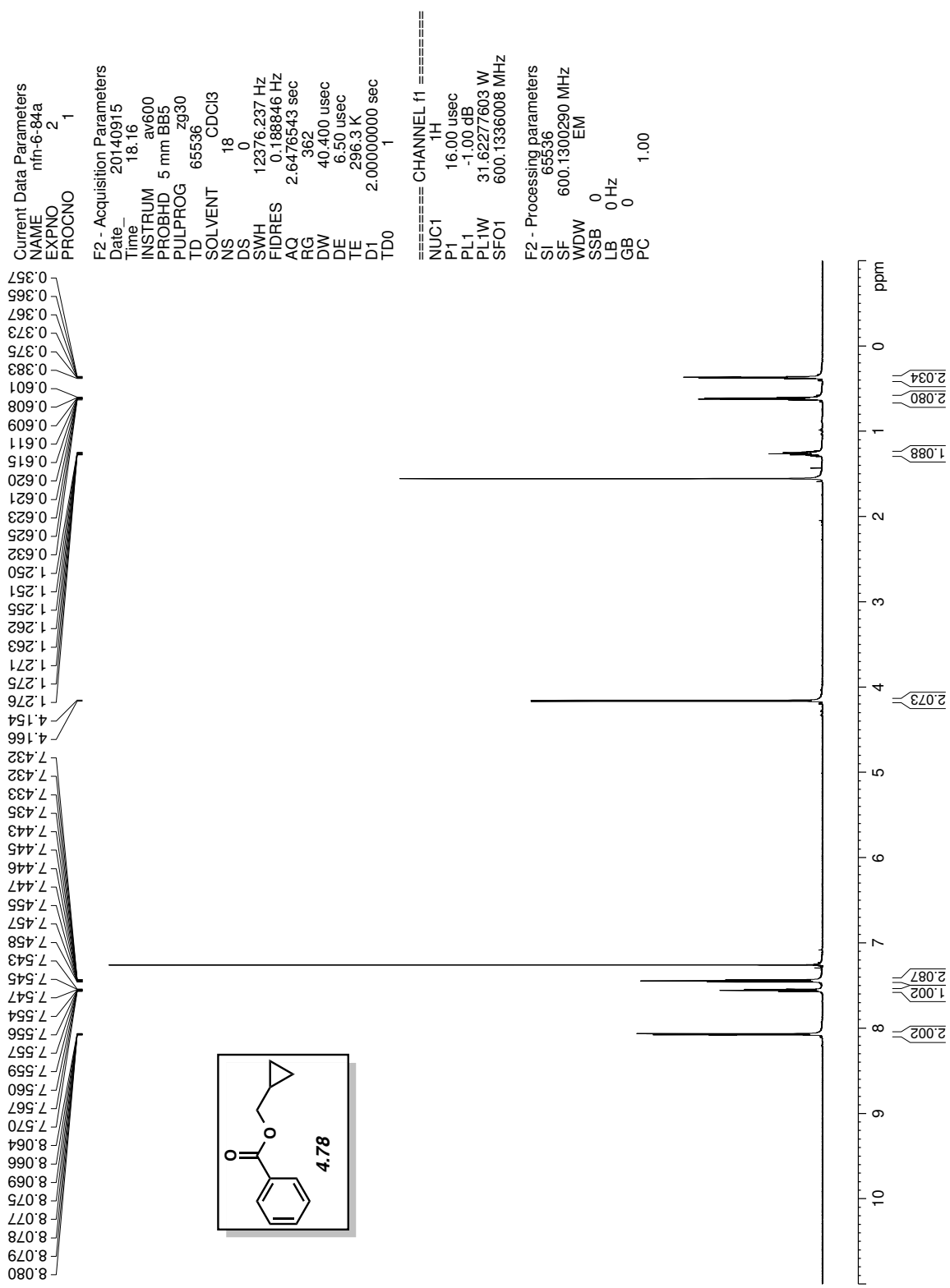


Figure 4.36. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **4.78**.

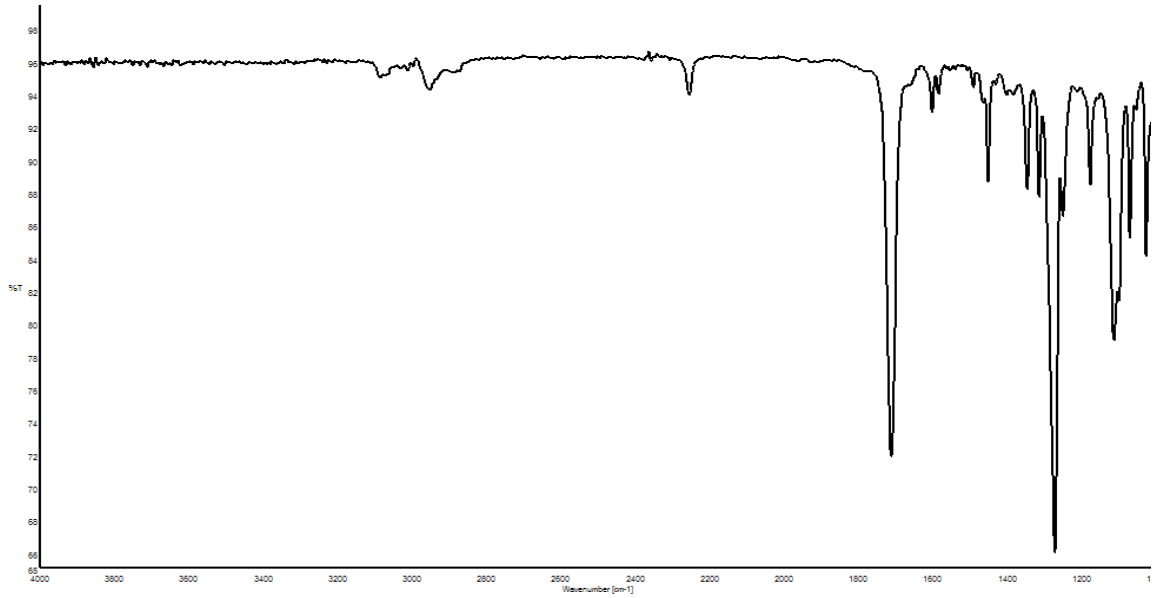


Figure 4.37. Infrared spectrum of compound **4.78**.

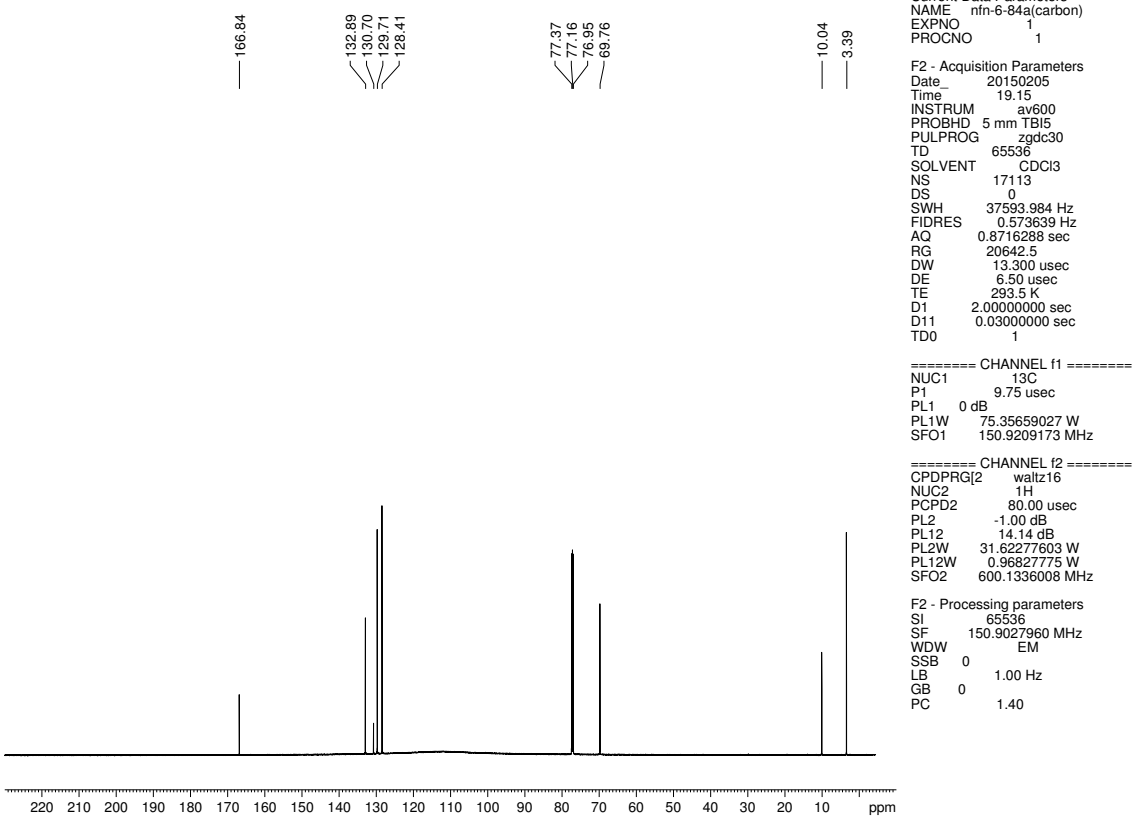


Figure 4.38. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.78**.

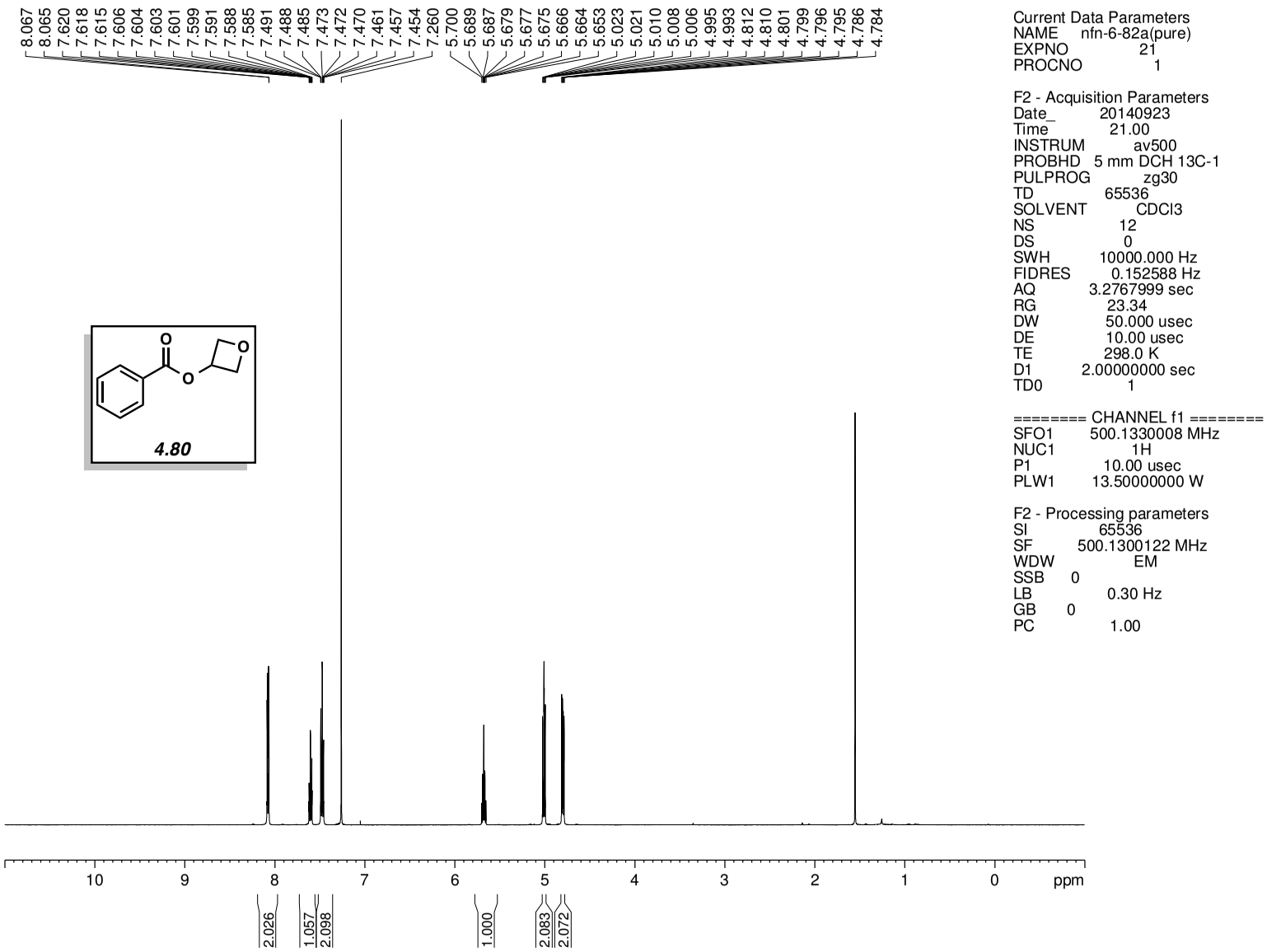


Figure 4.39. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.80**.

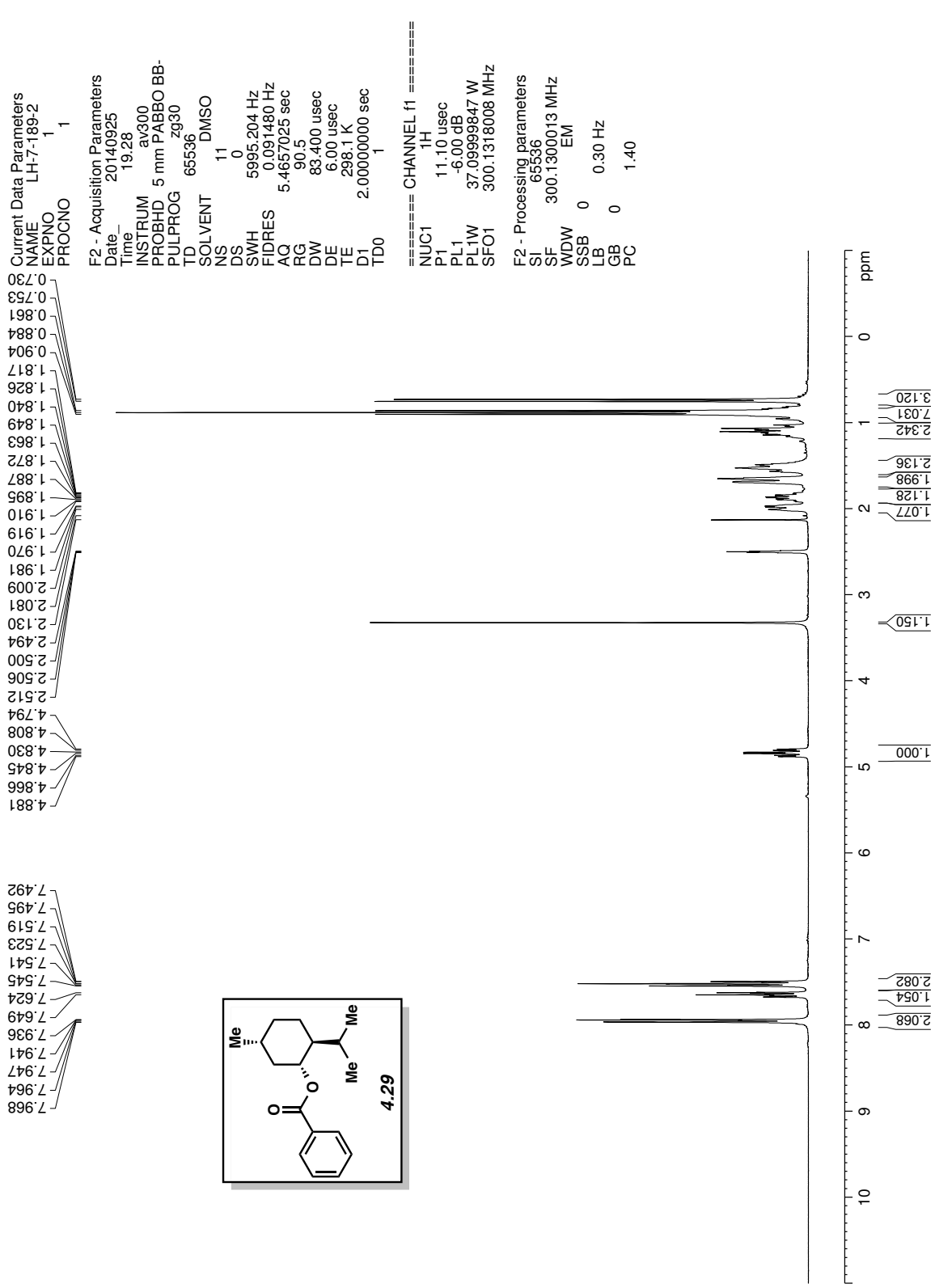


Figure 4.40. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **4.29**.

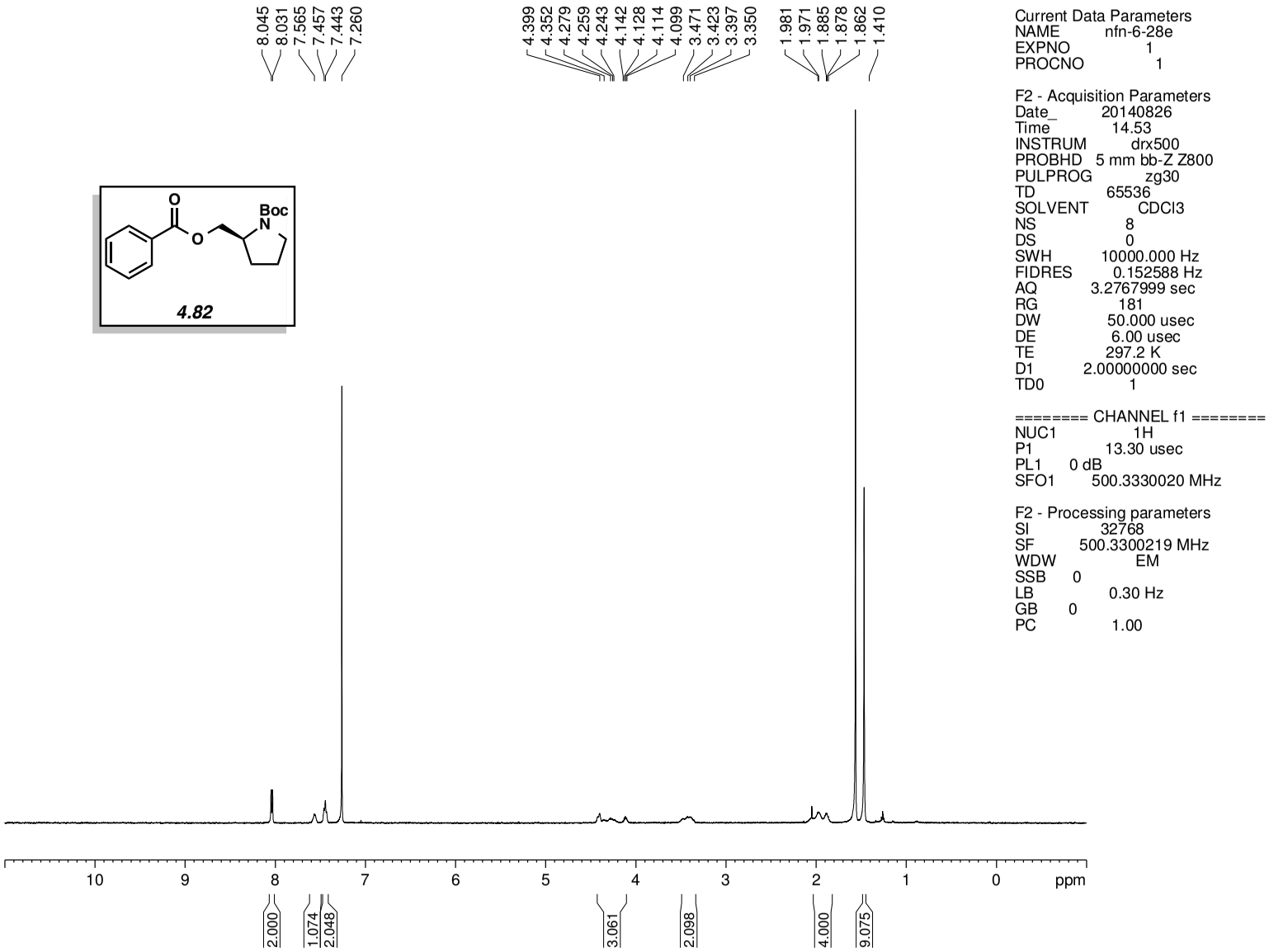


Figure 4.41. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.82**.

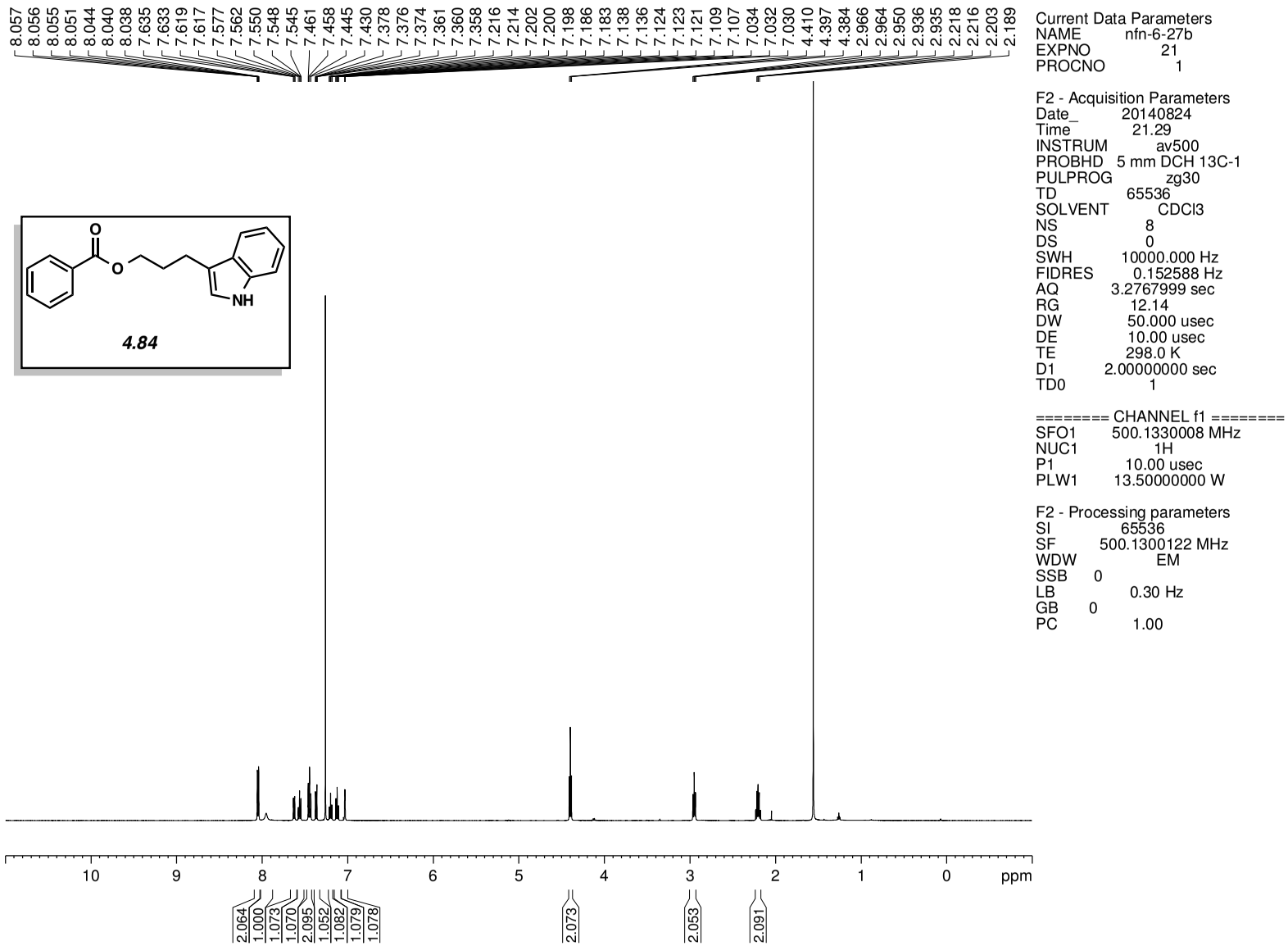


Figure 4.42. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.84**.

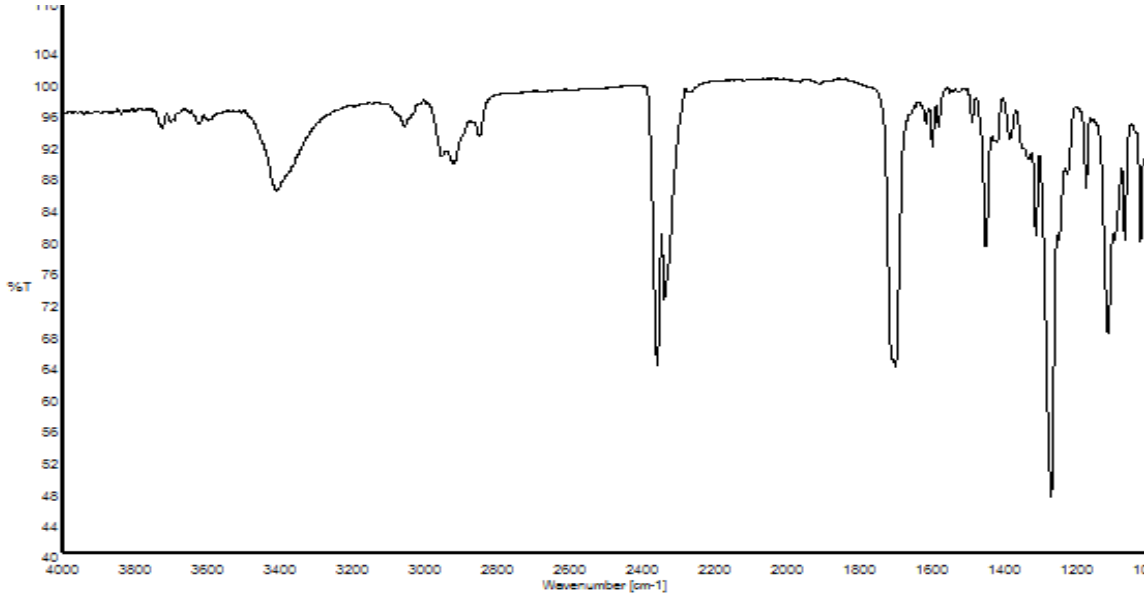


Figure 4.43. Infrared spectrum of compound **4.84**.

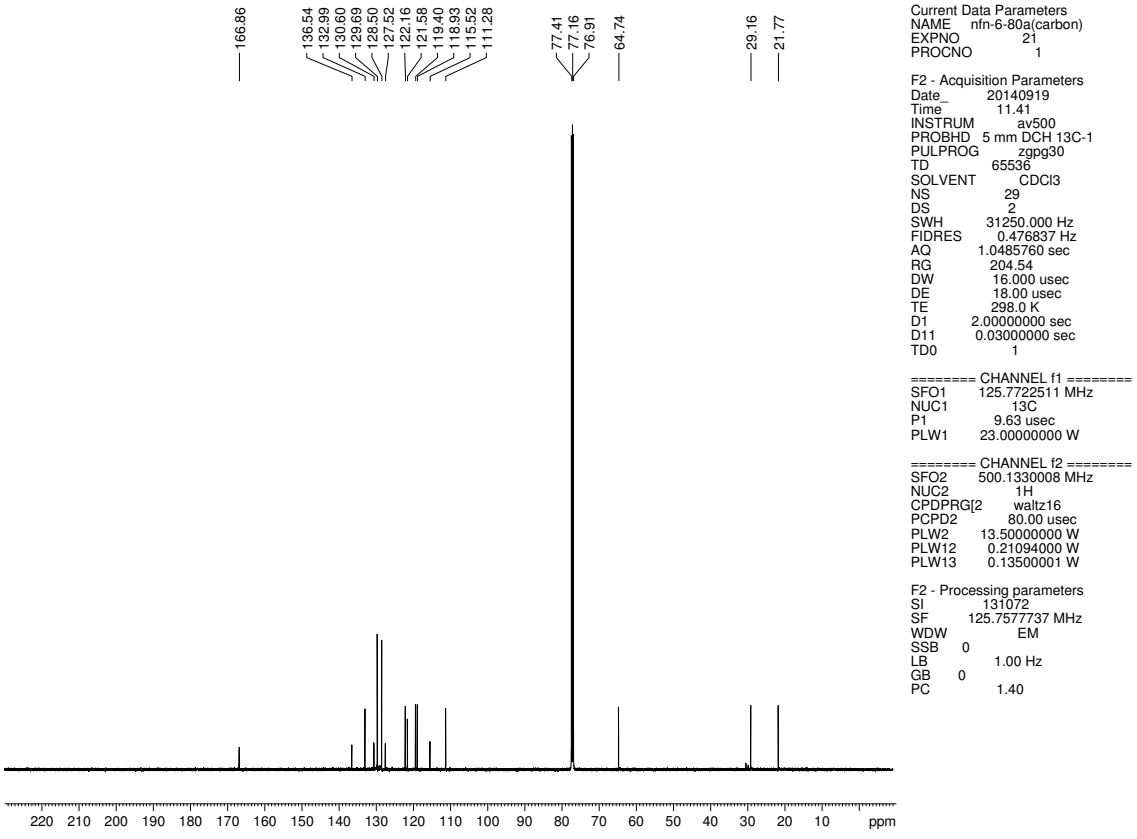


Figure 4.44. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.84**.

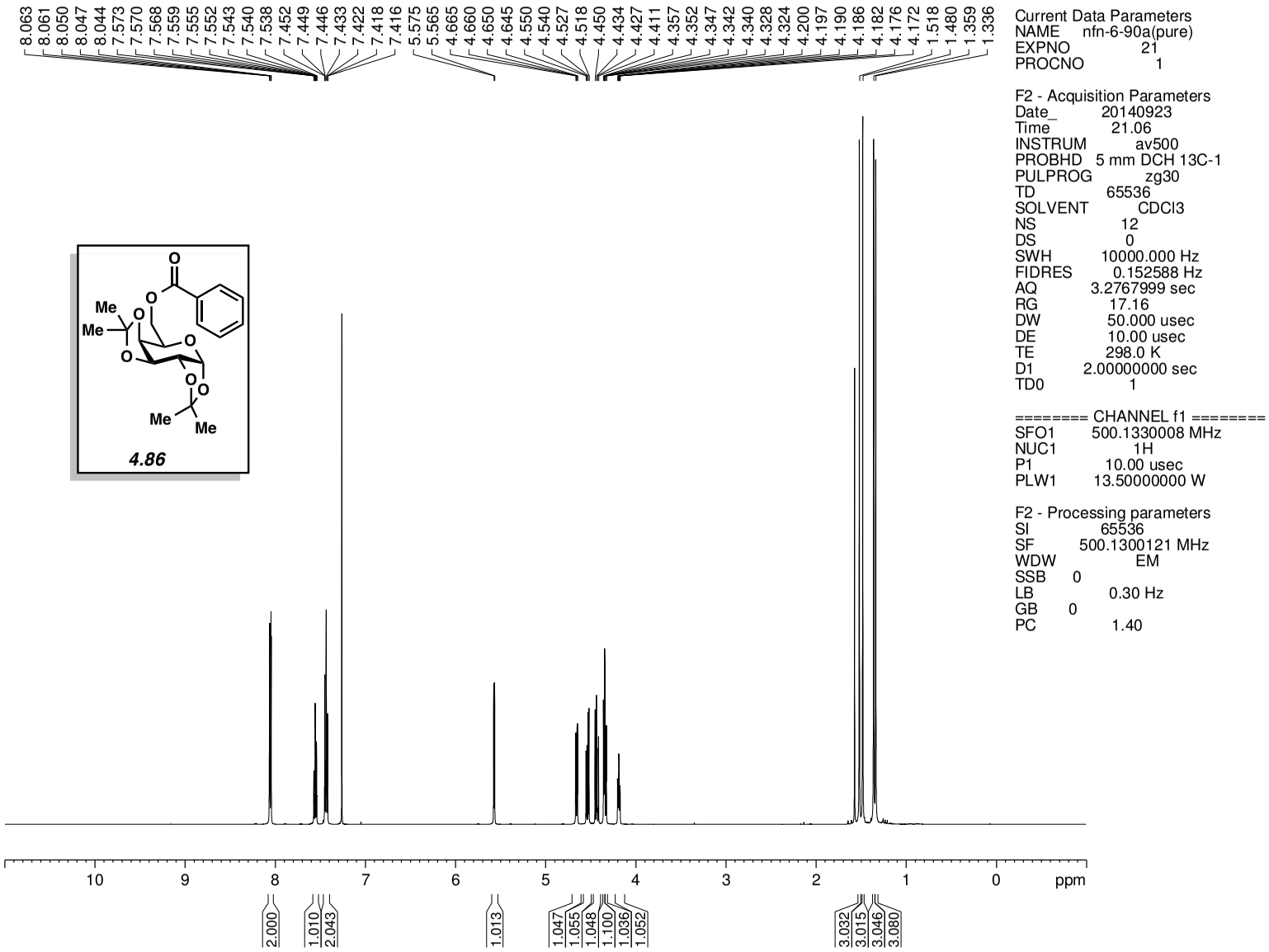


Figure 4.45. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.86**.

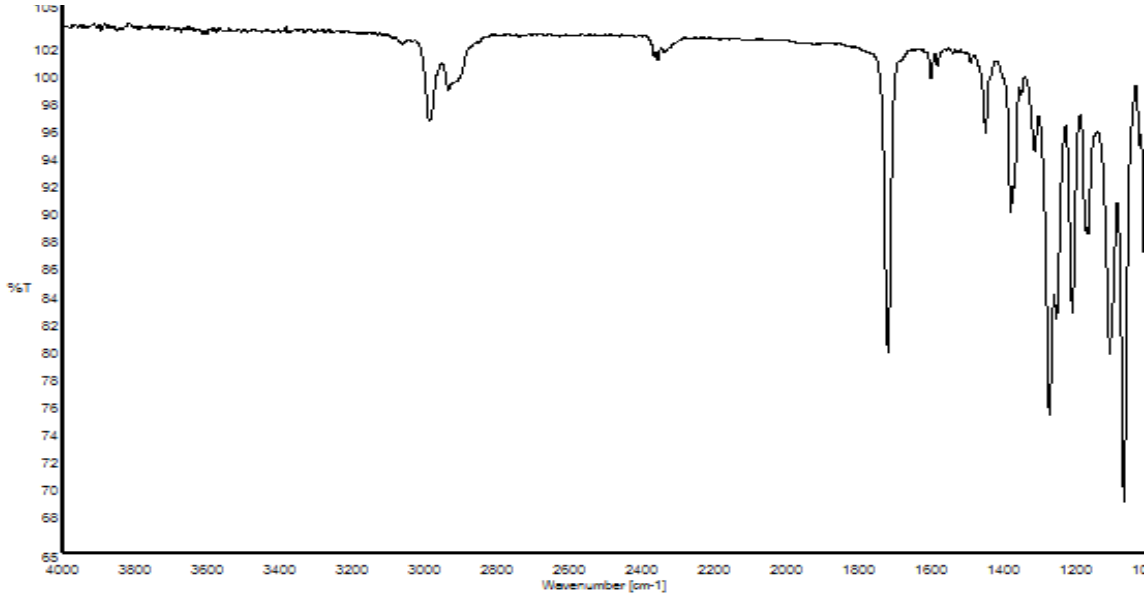


Figure 4.46. Infrared spectrum of compound **4.86**.

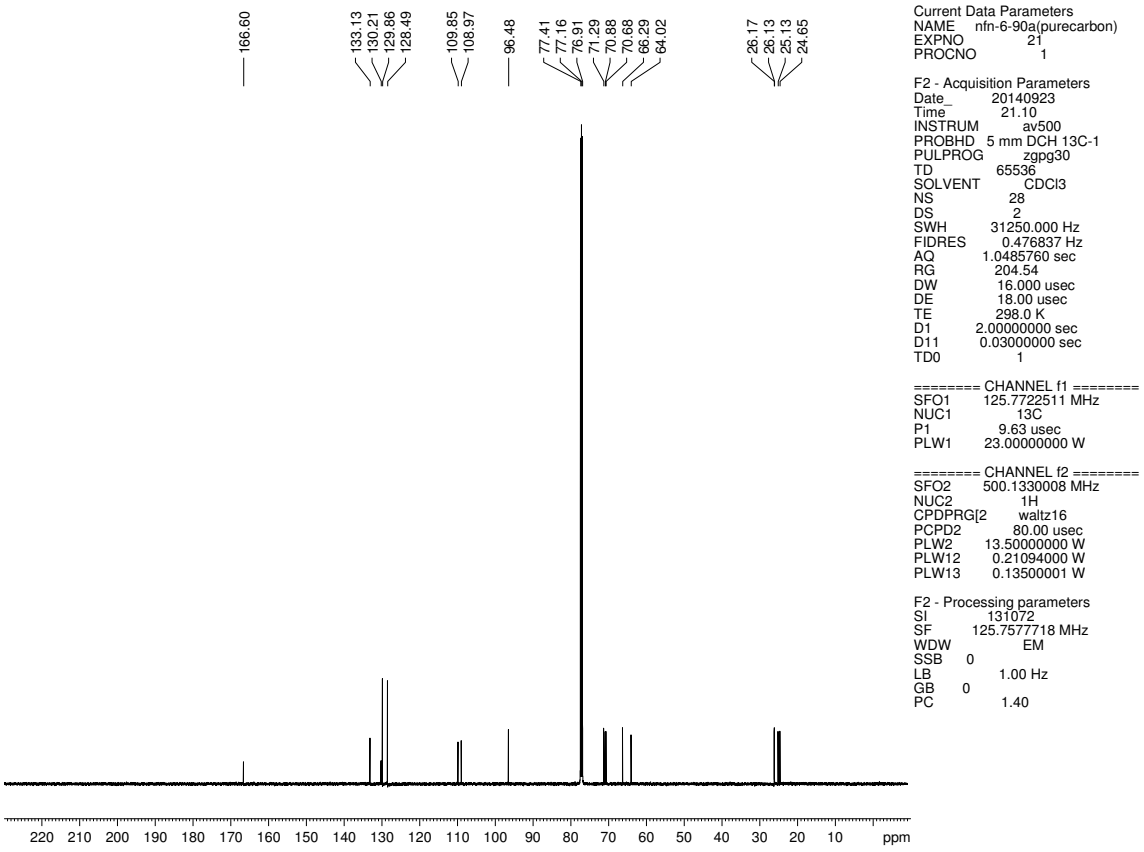


Figure 4.47. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.86**.

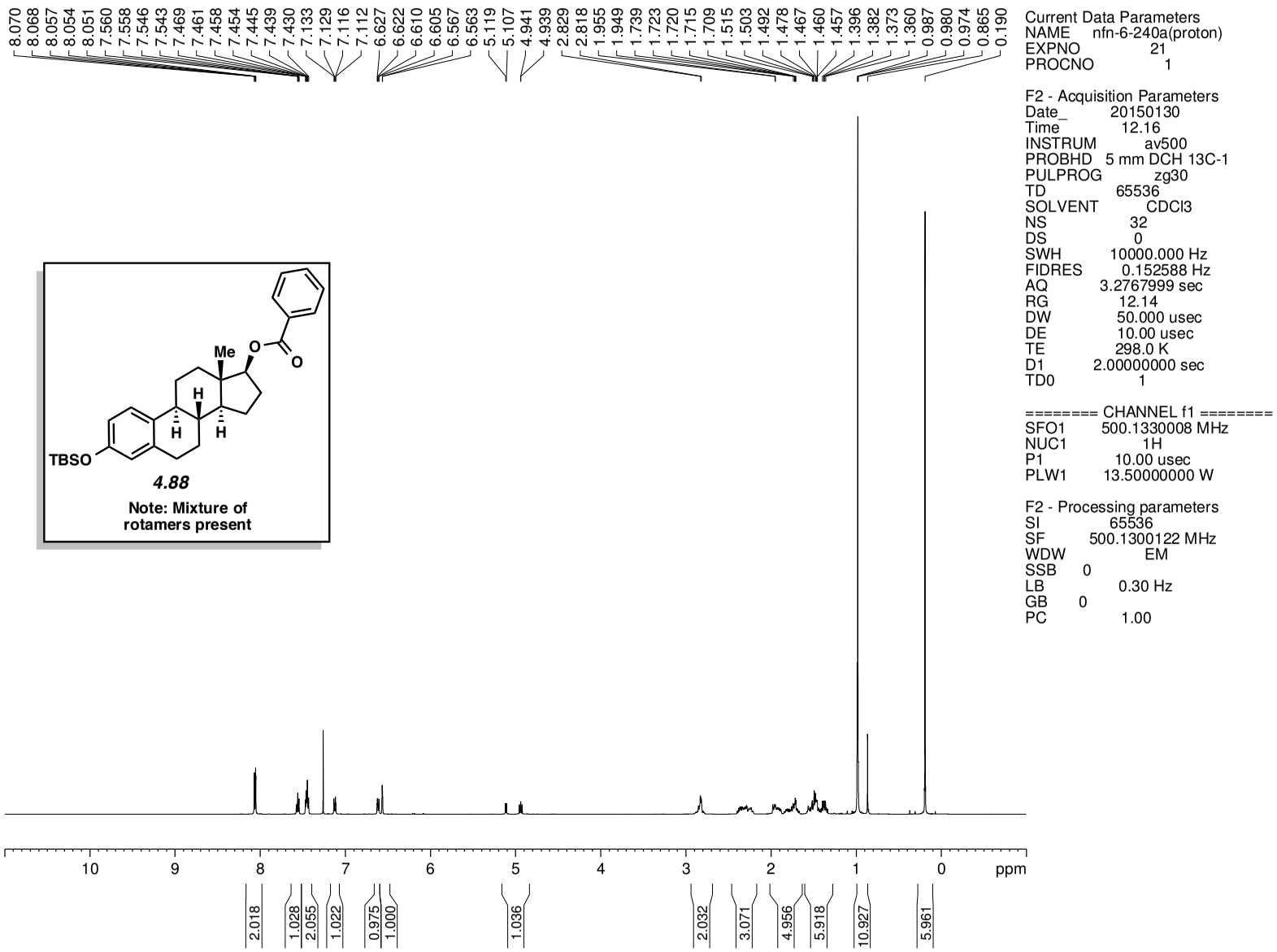


Figure 4.48. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.88**.

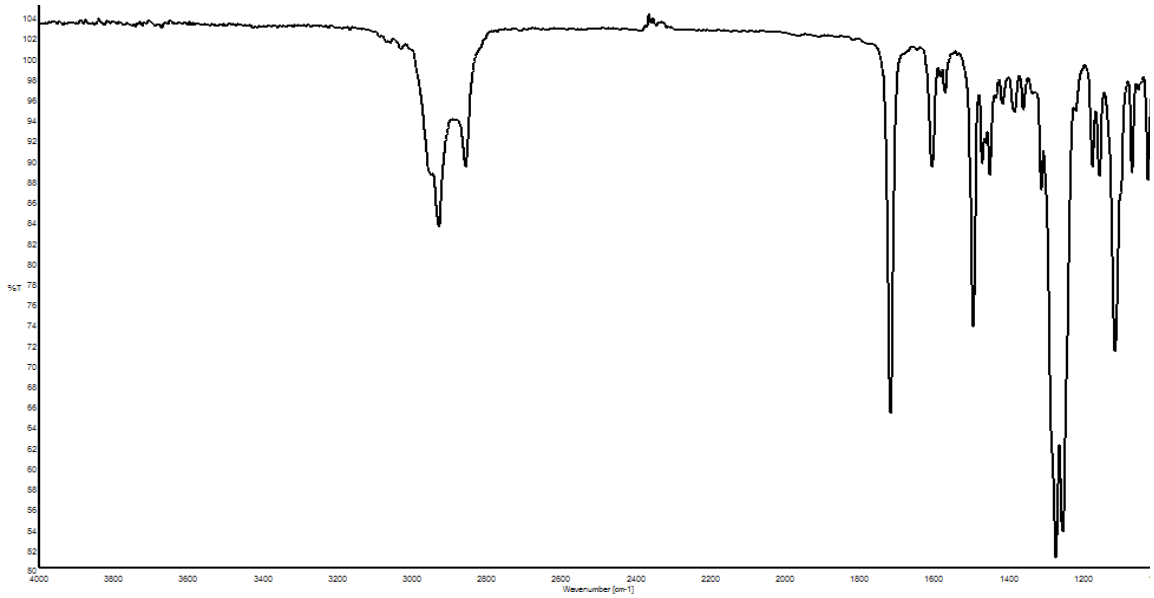


Figure 4.49. Infrared spectrum of compound **4.88**.

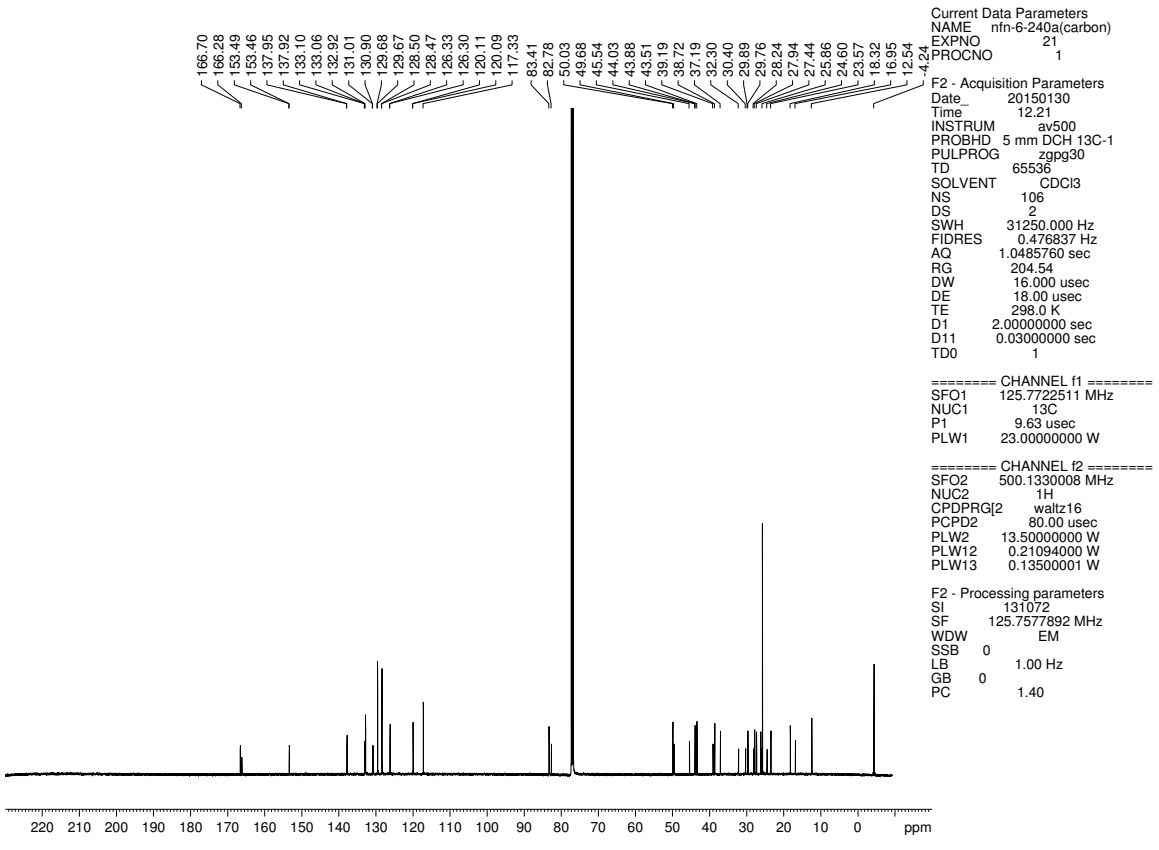


Figure 4.50. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.88**.

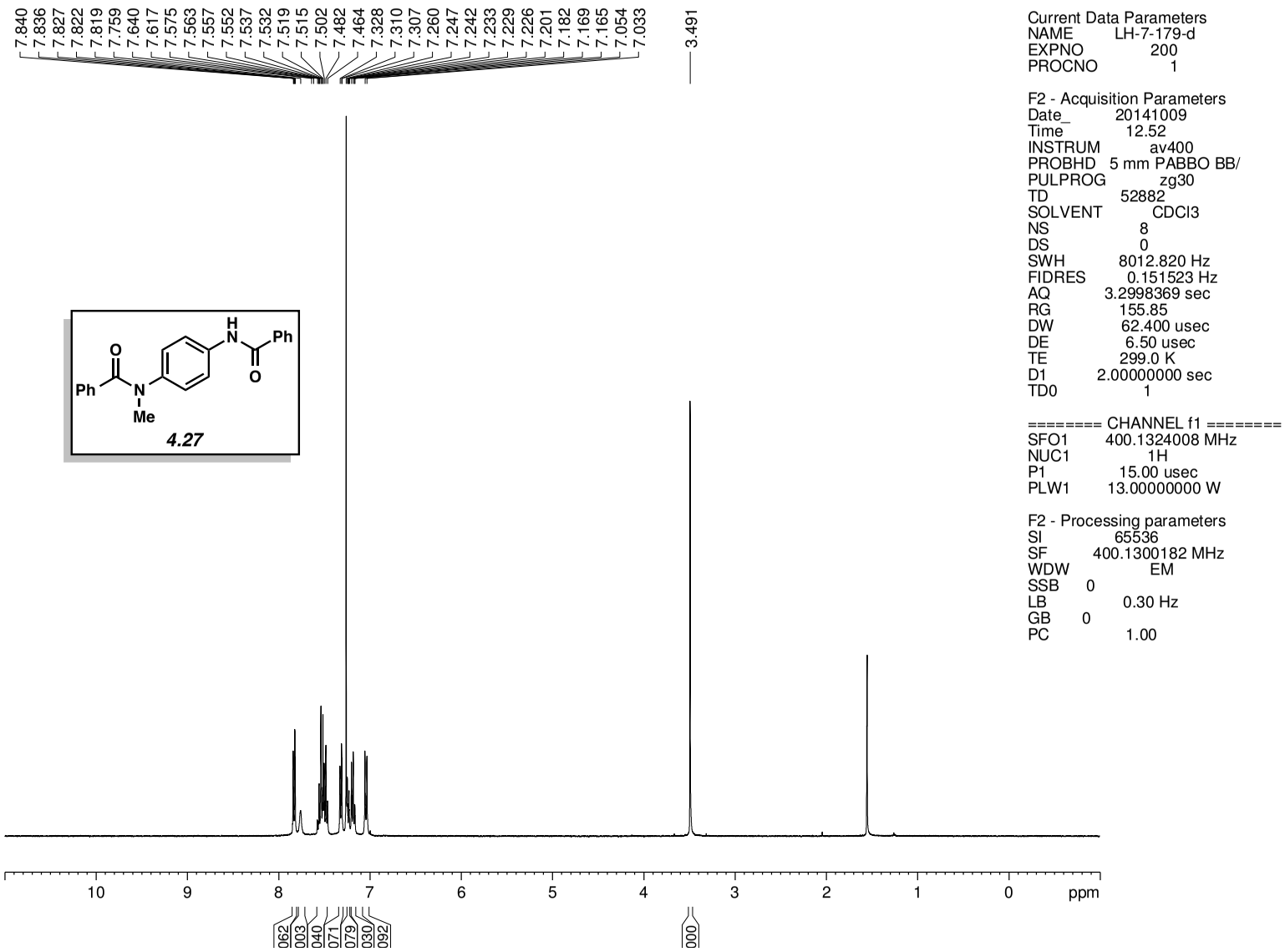


Figure 4.51. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.27**.

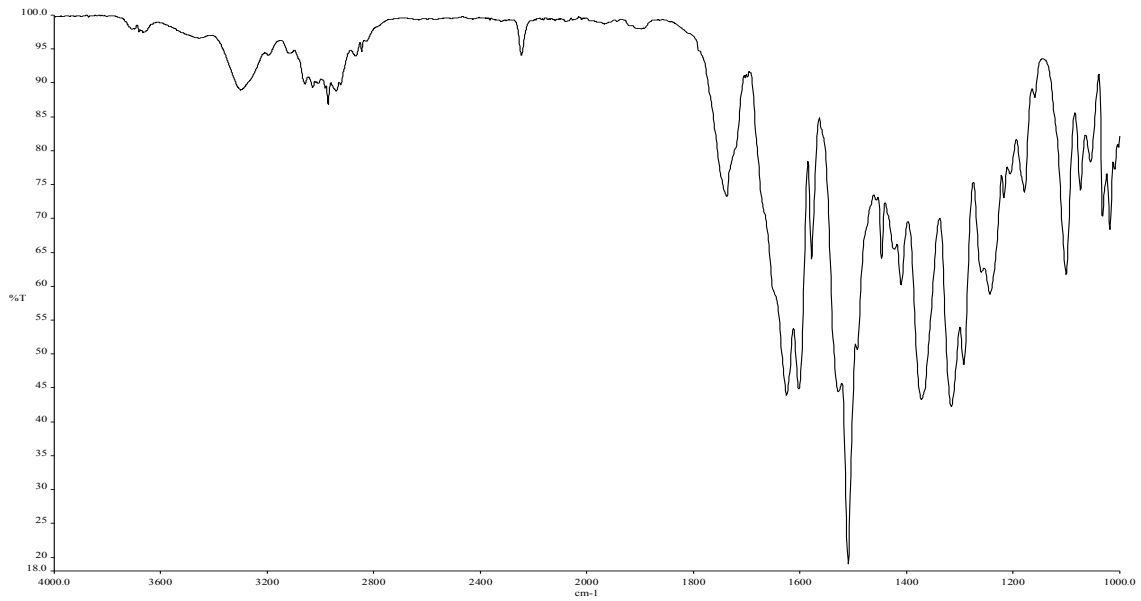


Figure 4.52. Infrared spectrum of compound **4.27**.

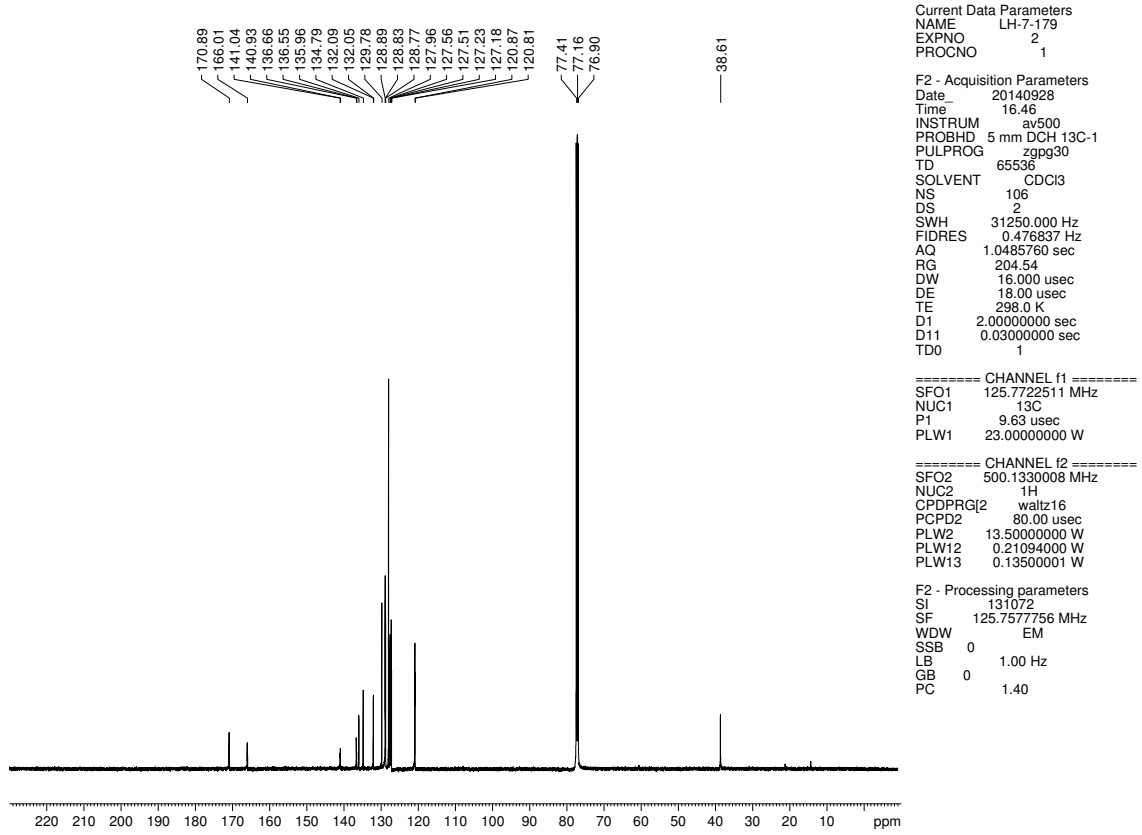


Figure 4.53. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.27**.

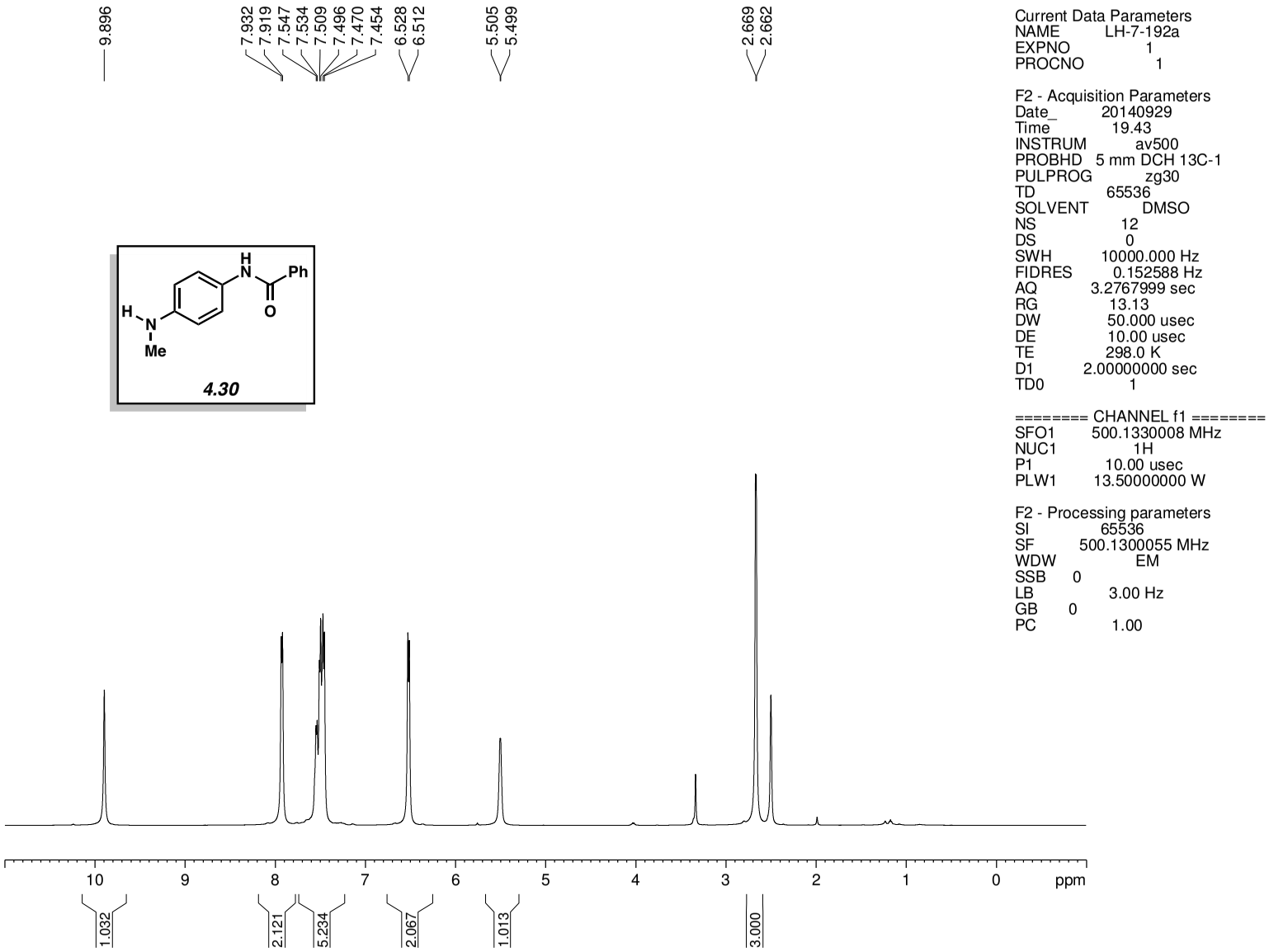


Figure 4.54. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.30**.

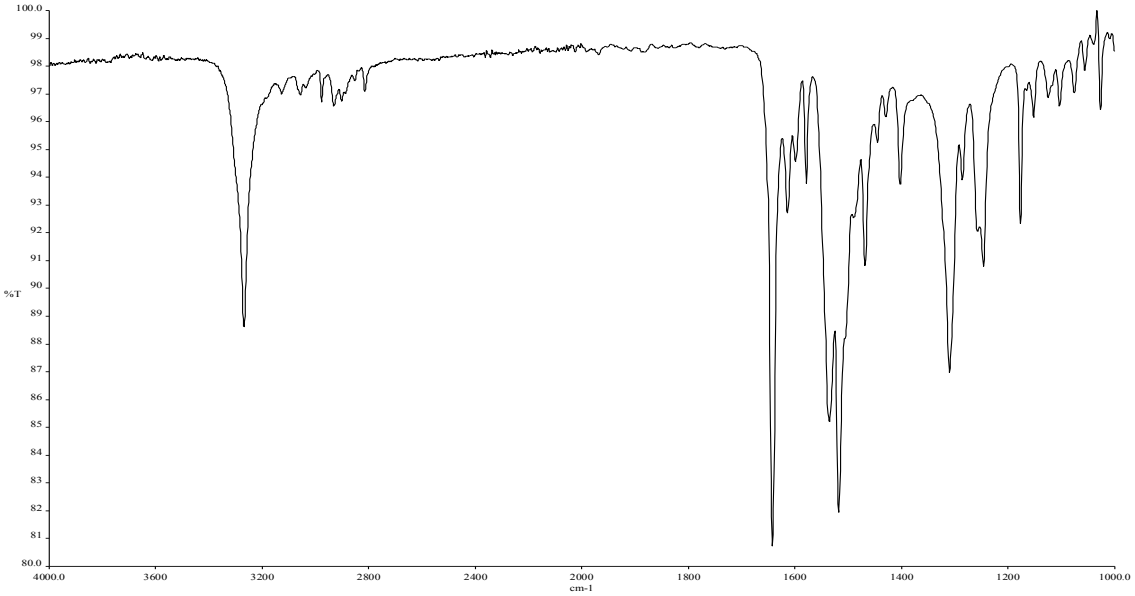


Figure 4.55. Infrared spectrum of compound **4.30**.

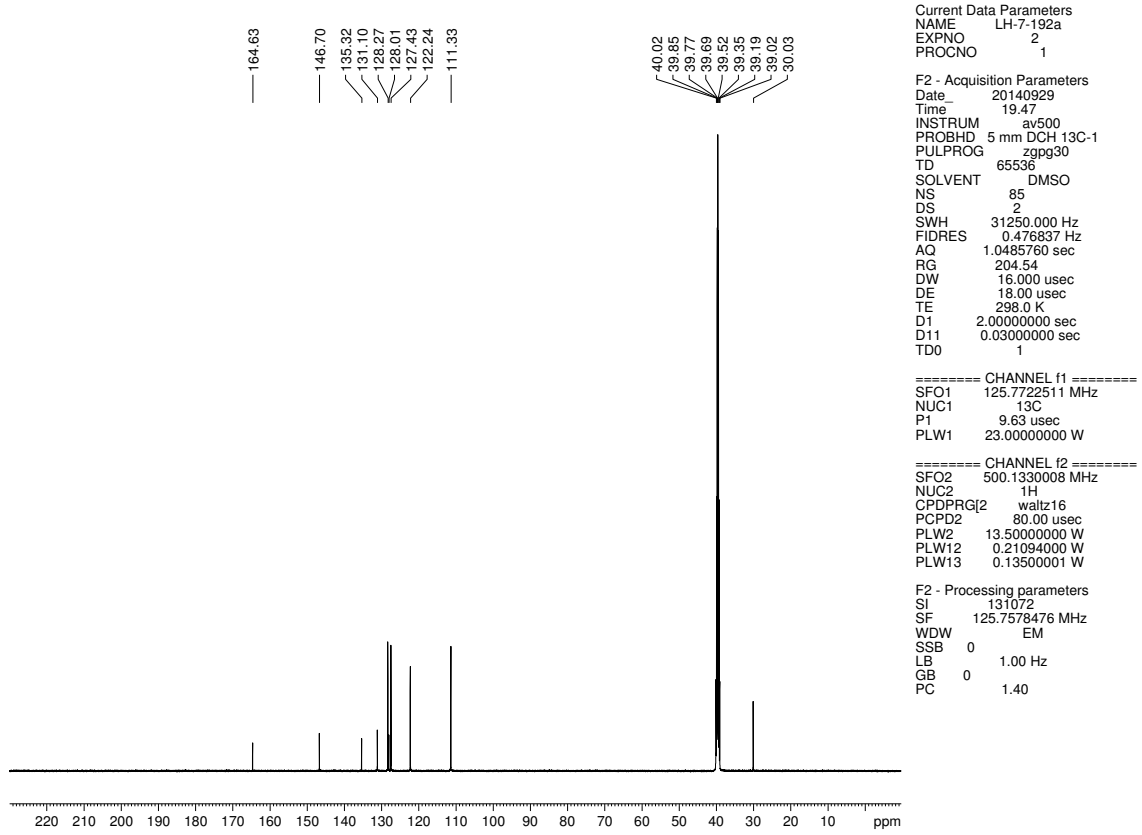


Figure 4.56. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.30**.

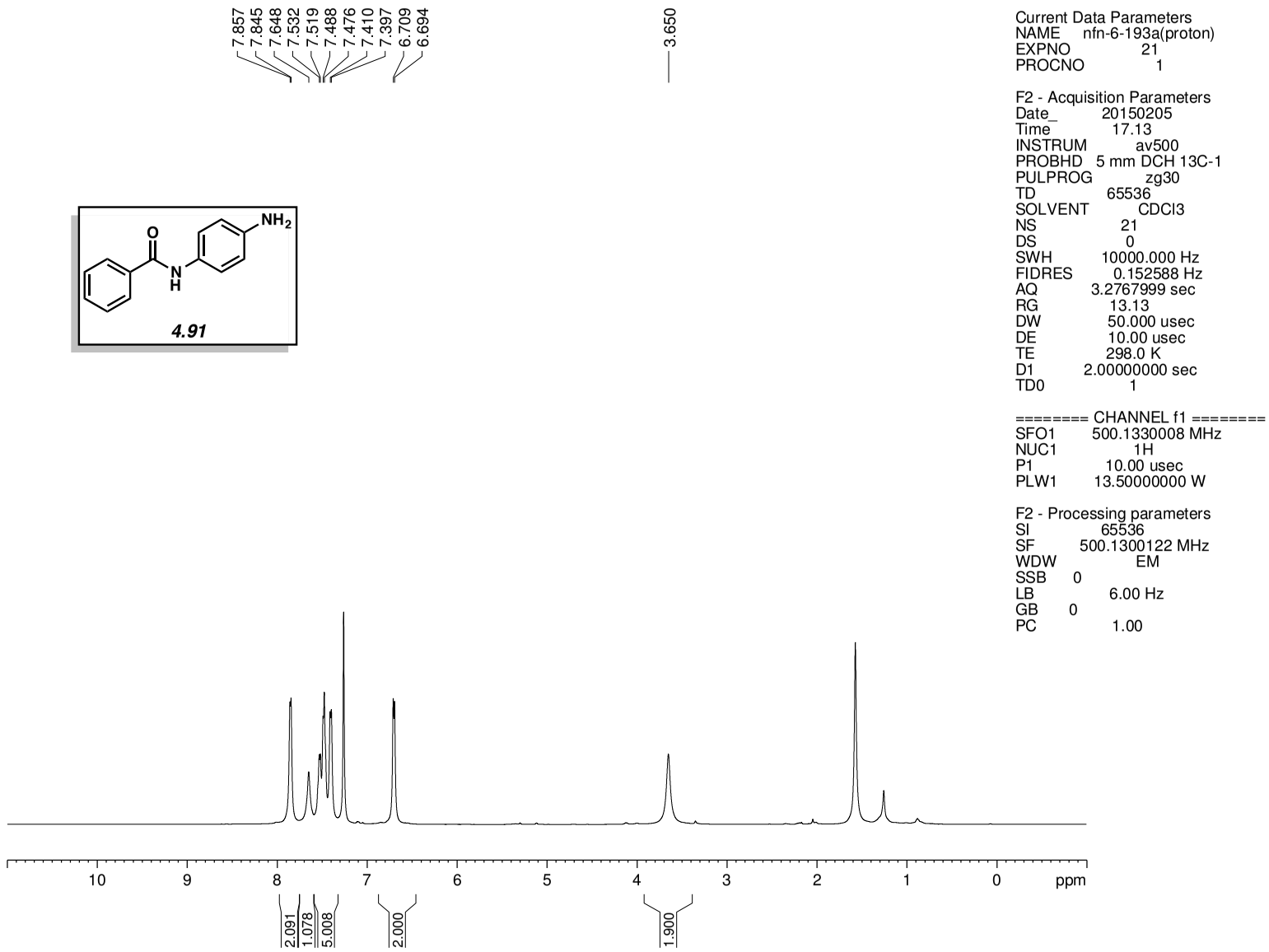


Figure 4.57. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.91**.

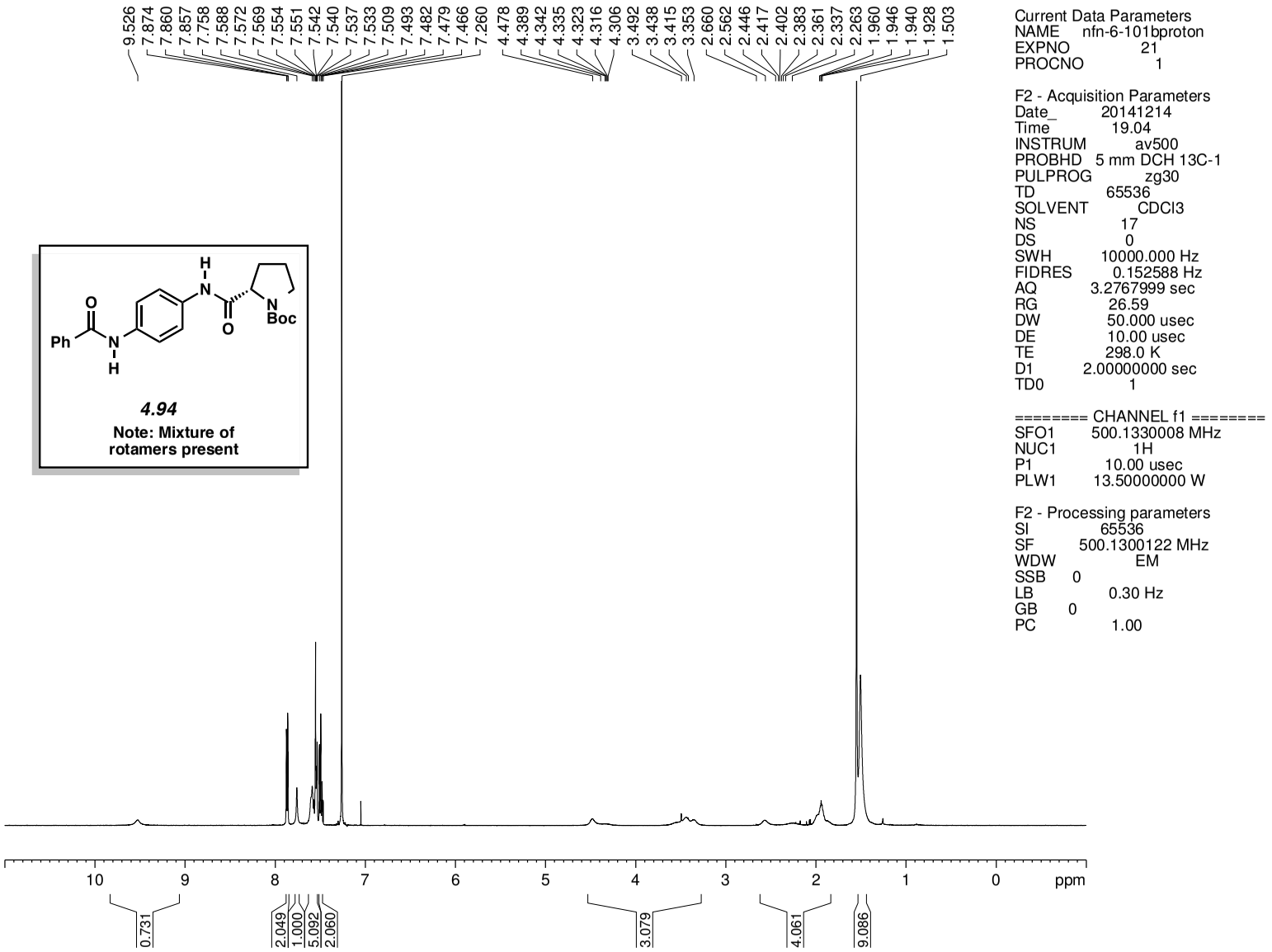


Figure 4.58. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.94**.

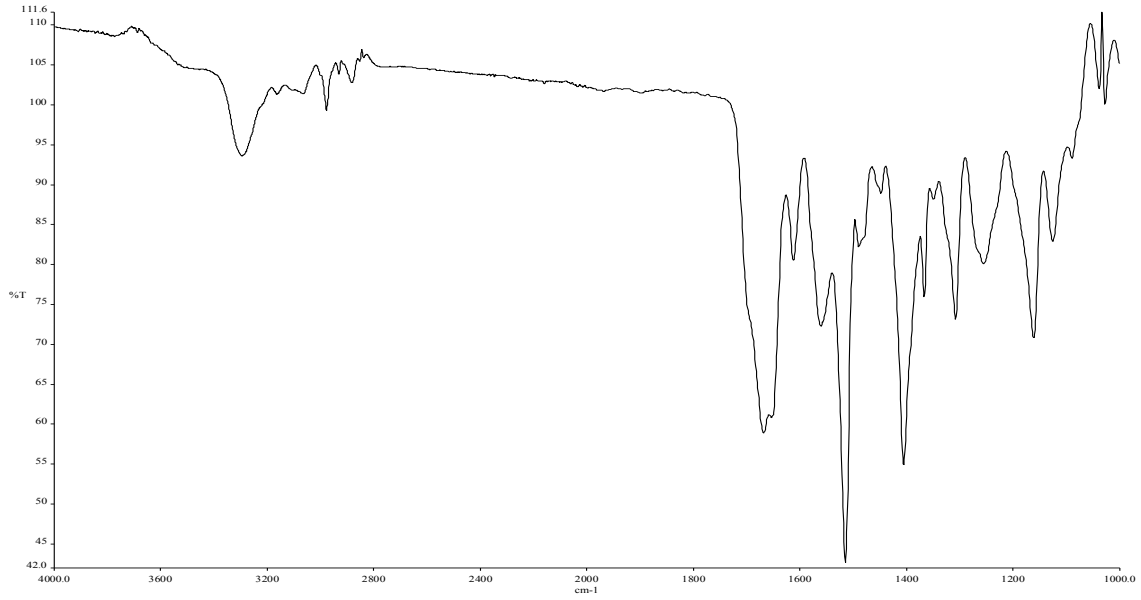


Figure 4.59. Infrared spectrum of compound **4.94**.

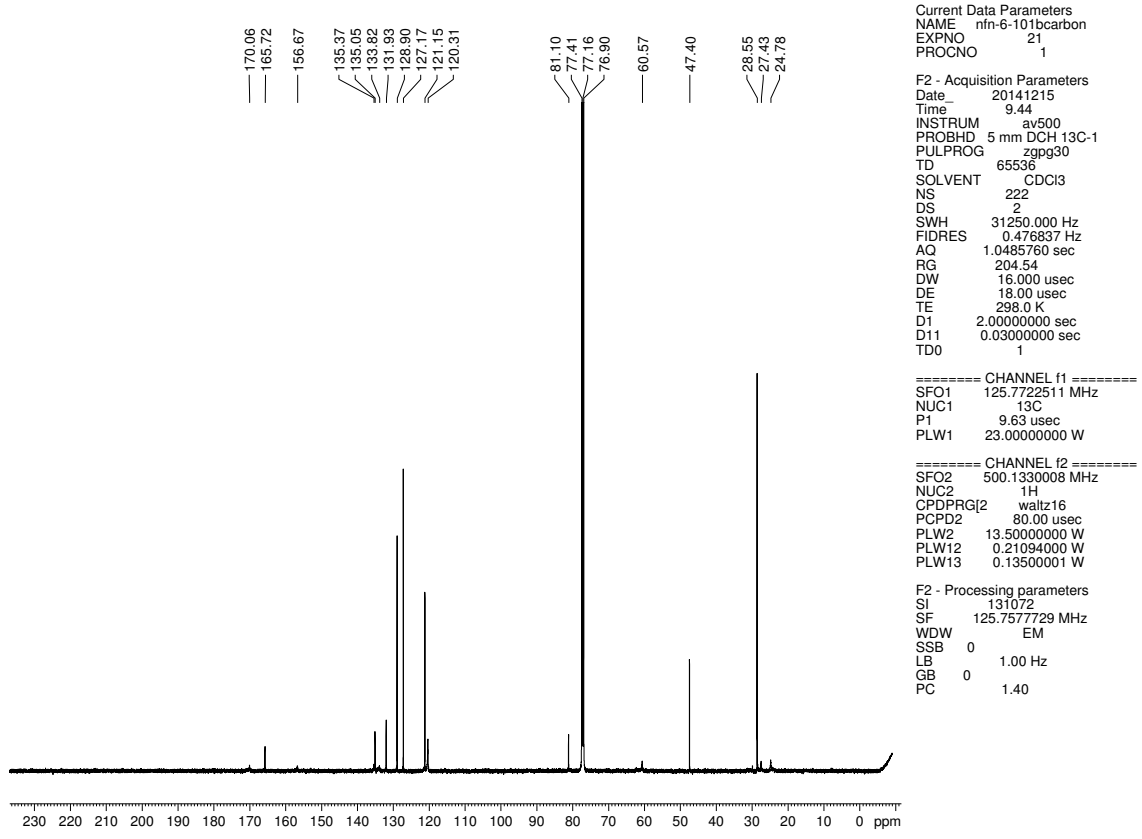


Figure 4.60. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.94**.

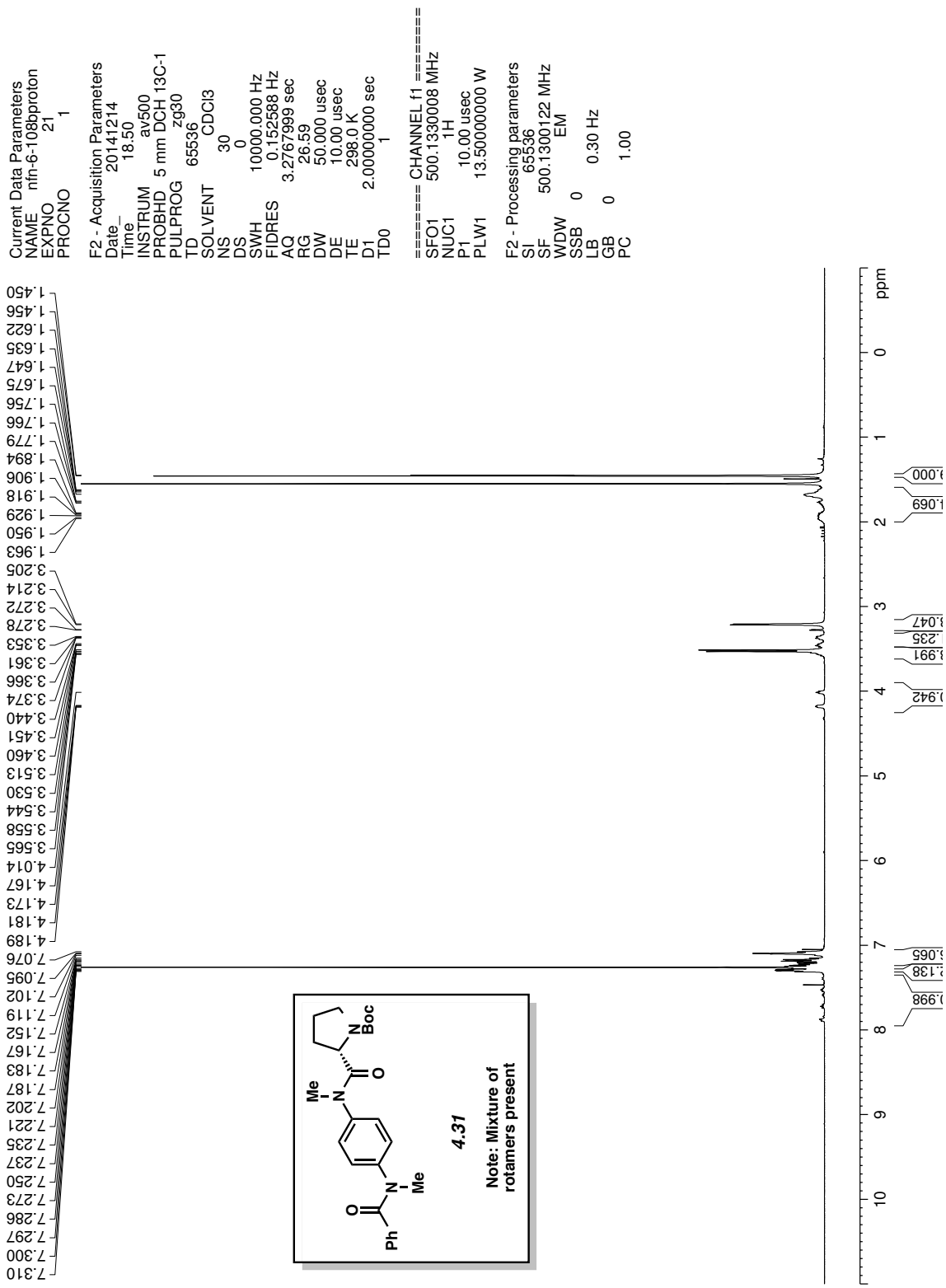


Figure 4.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.31**.

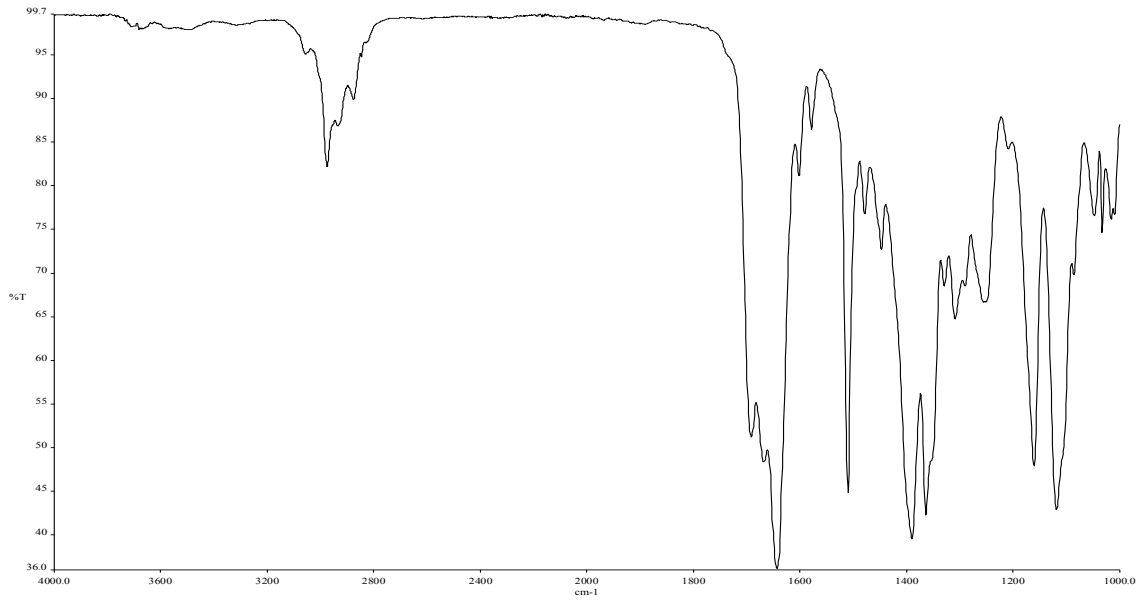


Figure 4.62. Infrared spectrum of compound **4.31**.

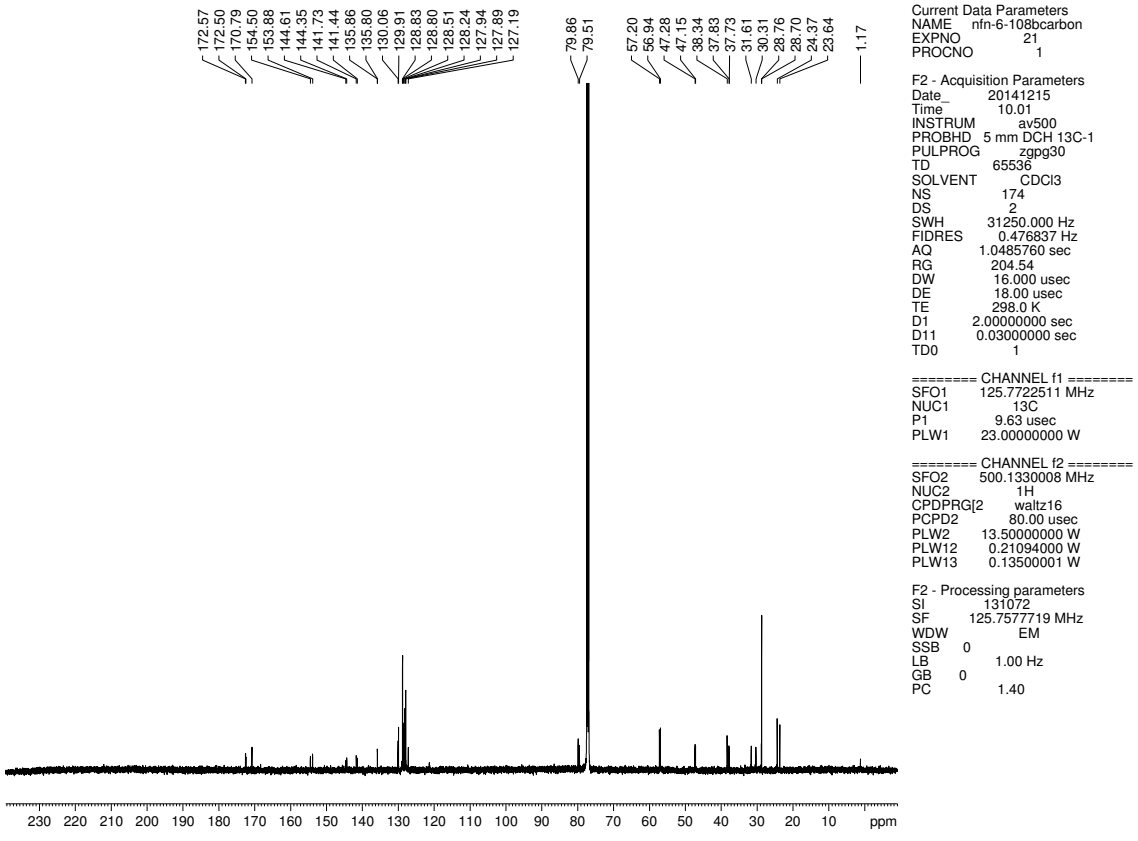


Figure 4.63. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.31**.

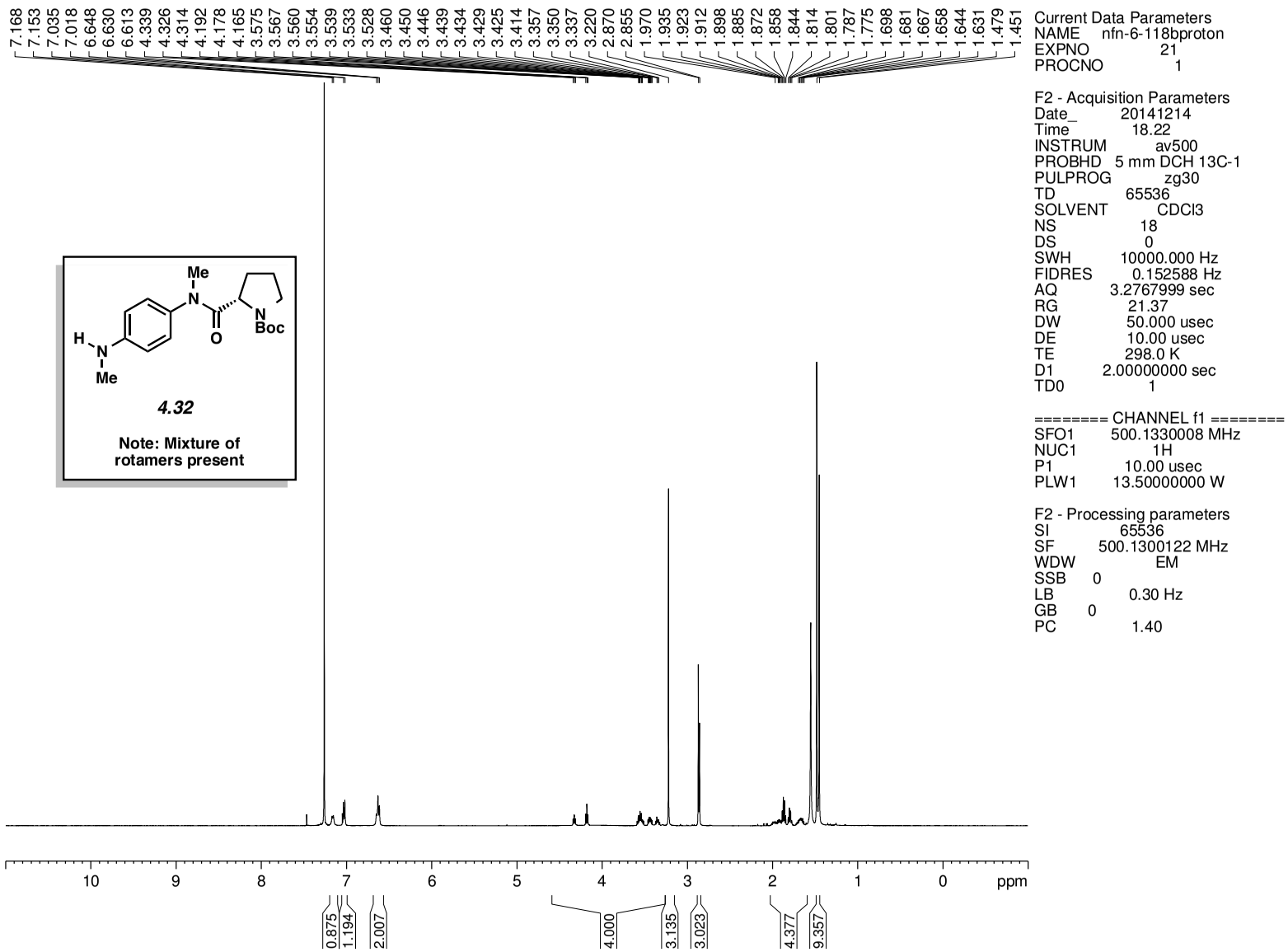


Figure 4.64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.32**.

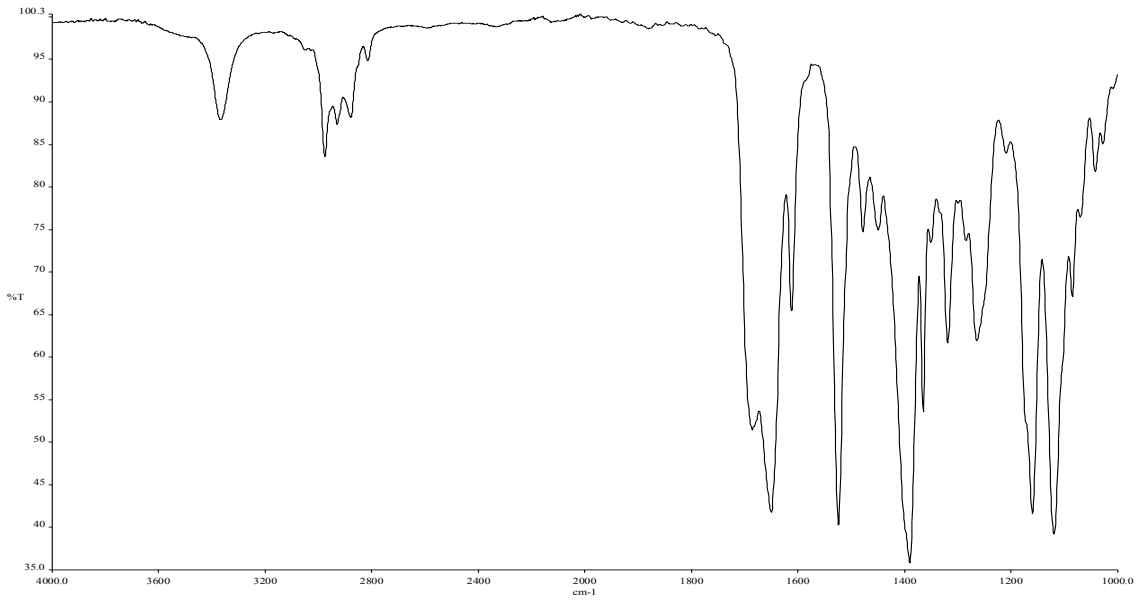


Figure 4.65. Infrared spectrum of compound **4.32**.

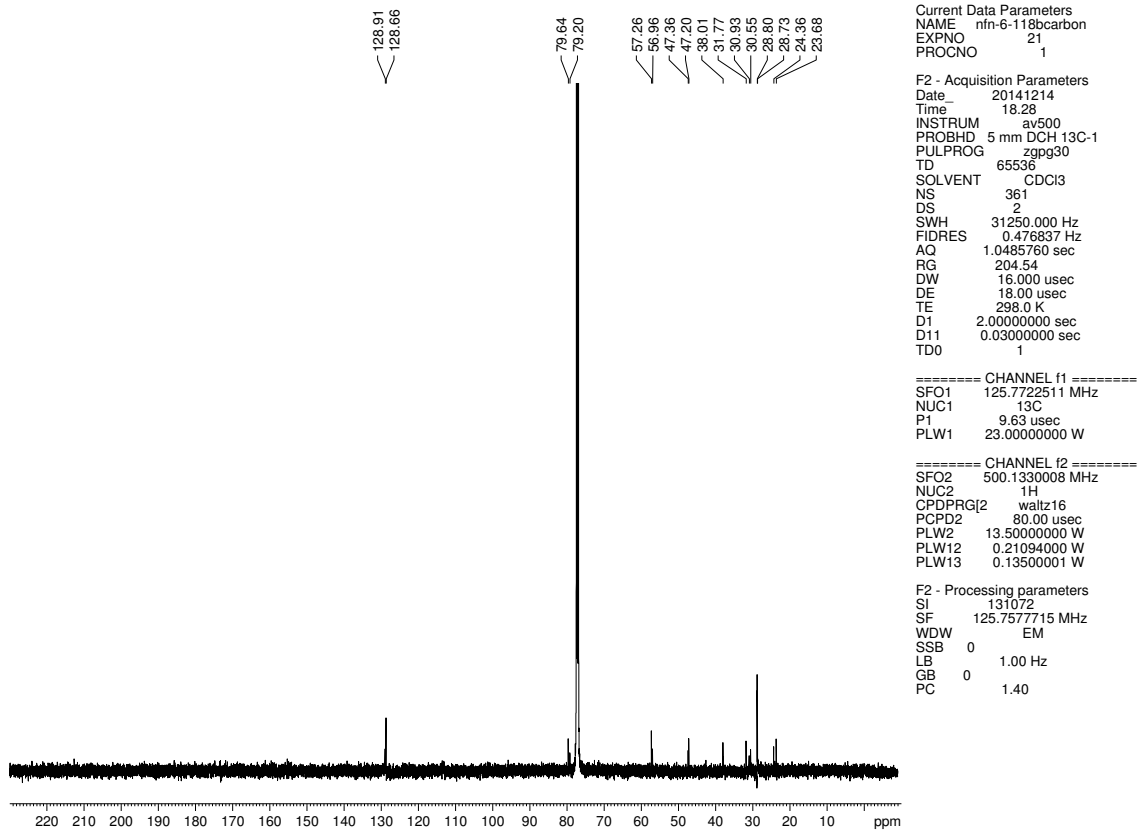


Figure 4.66. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.32**.

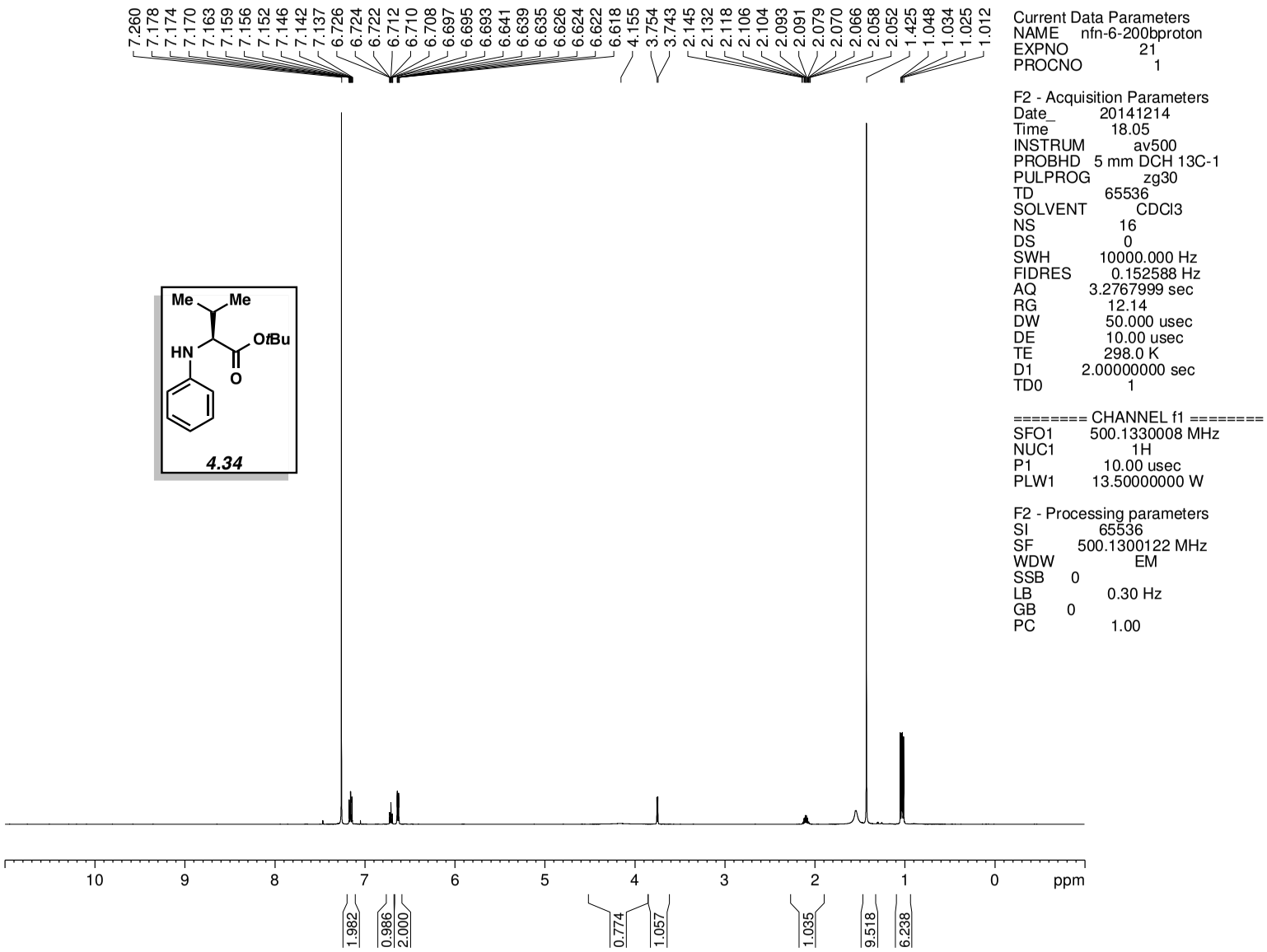


Figure 4.67. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.34**.

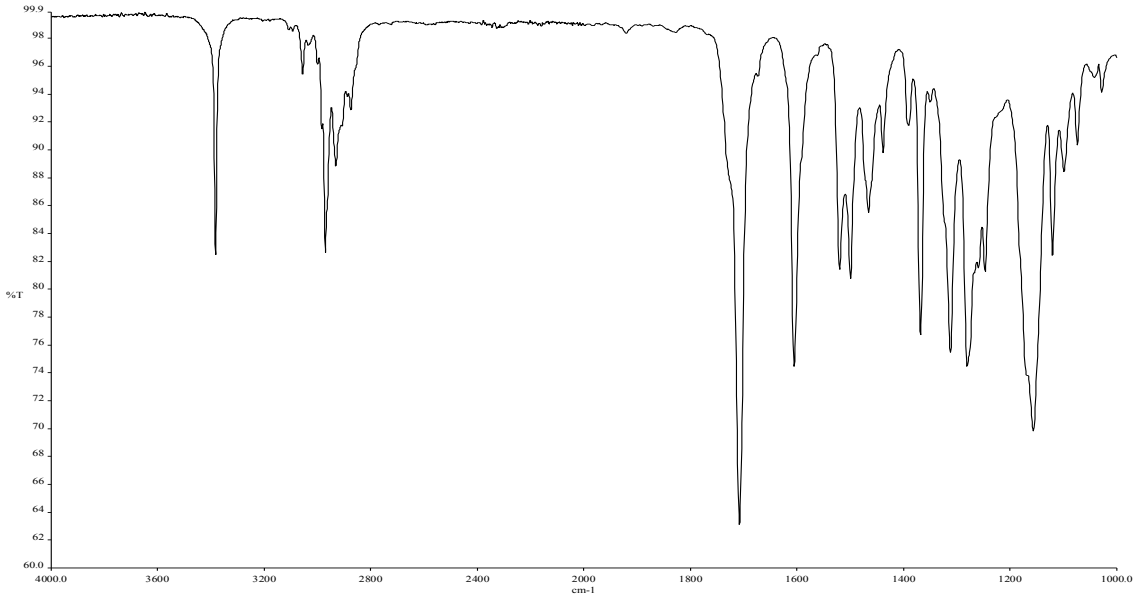


Figure 4.68. Infrared spectrum of compound **4.34**.

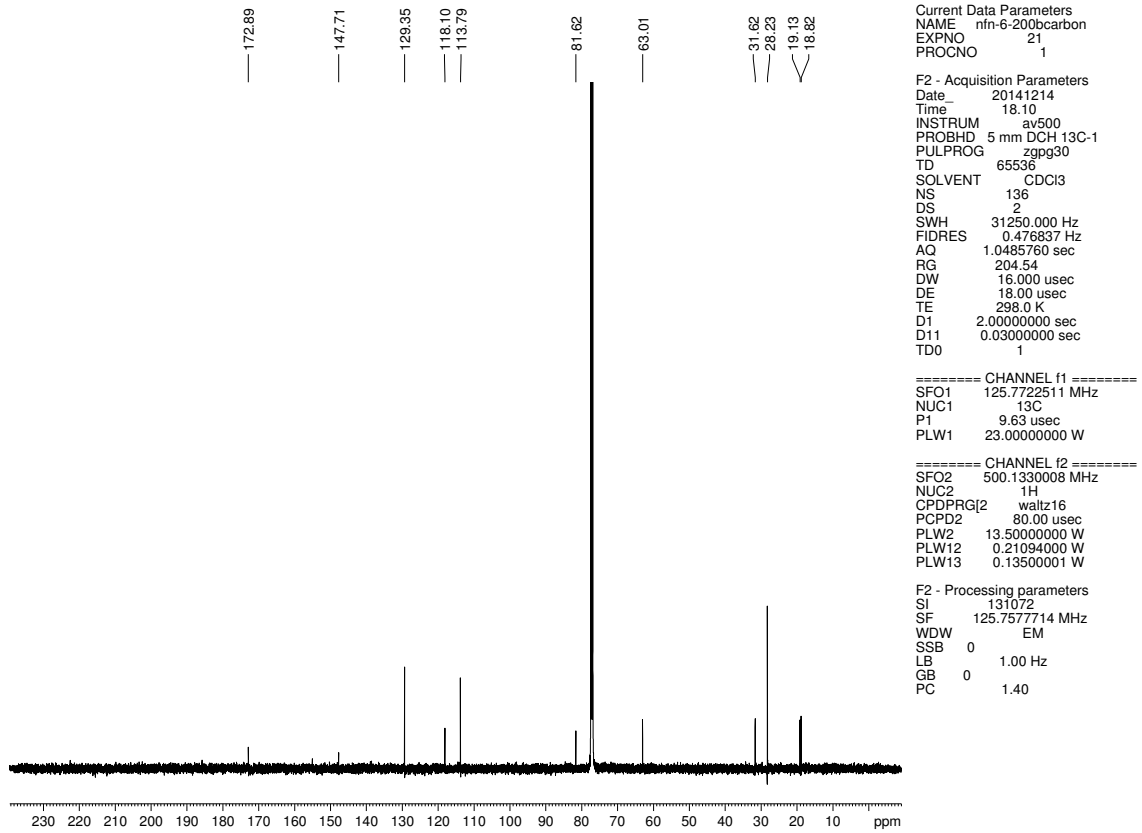


Figure 4.69. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.34**.

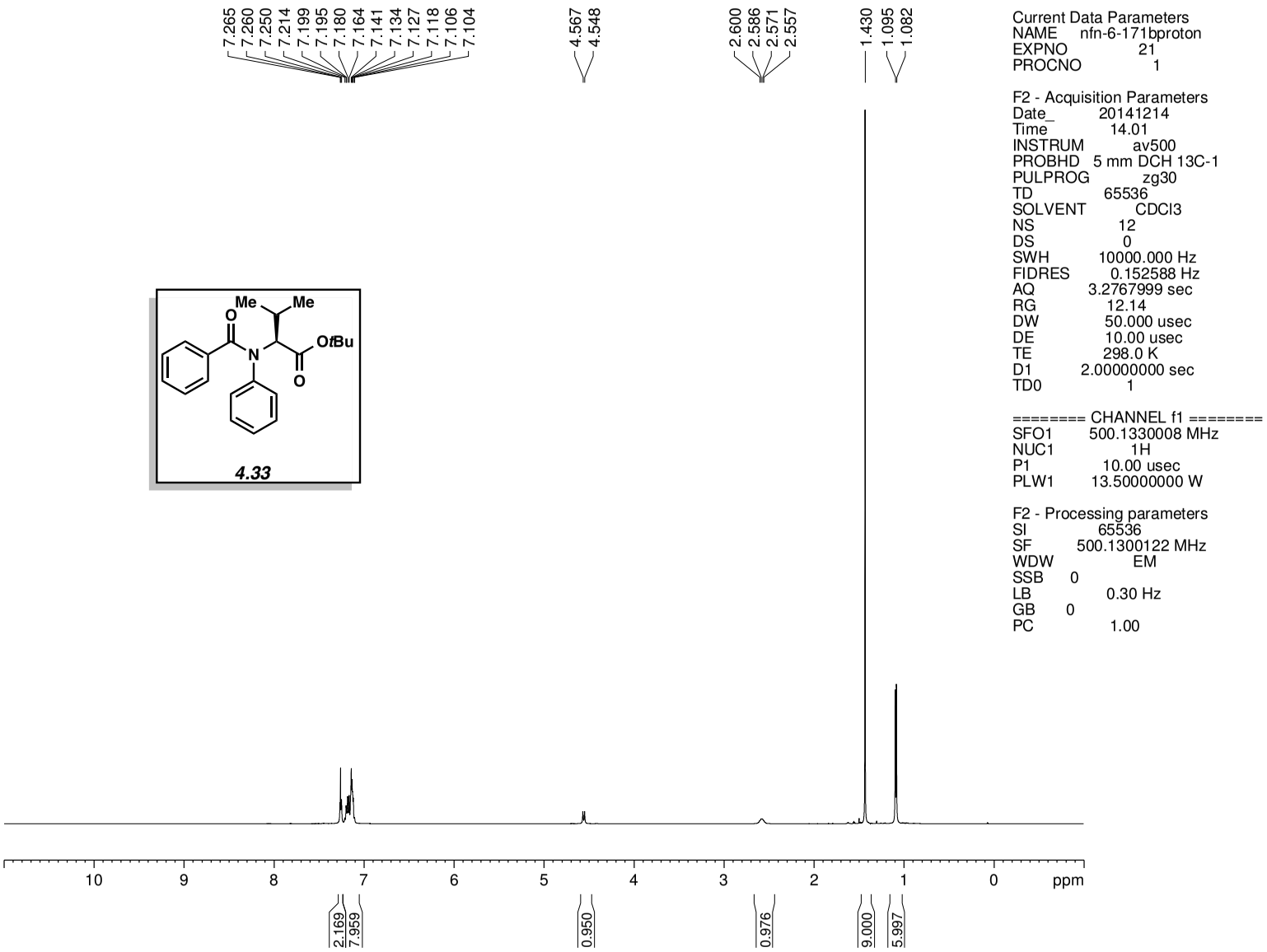


Figure 4.70. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.33**.

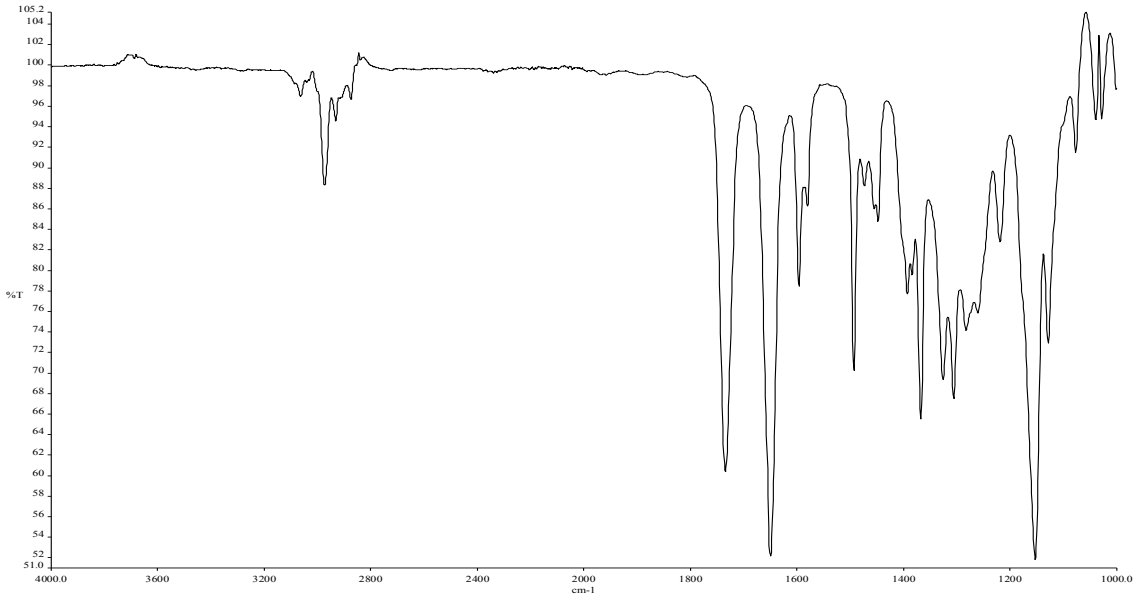


Figure 4.71. Infrared spectrum of compound **4.33**.

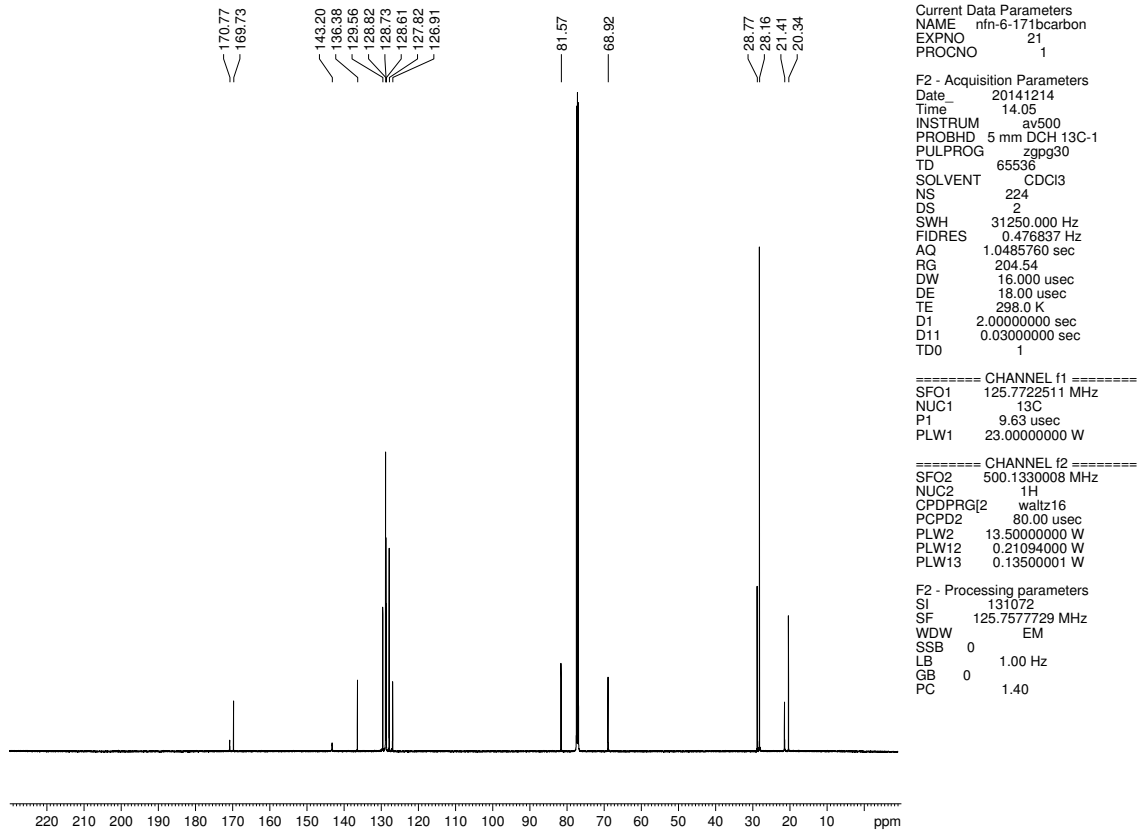


Figure 4.72. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4.33**.

CHAPTER FIVE

Total Syntheses of Indolactam Alkaloids (–)-Indolactam V, (–)-Pendolmycin, (–)-Lyngbyatoxin A, and (–)-Teleocidin A-2

5.1 Abstract

We report the total syntheses of (–)-indolactam V and the C7-substituted indolactam alkaloids (–)-pendolmycin, (–)-lyngbyatoxin A, and (–)-teleocidin A-2. The strategy for preparing indolactam V relies on a distortion-controlled indolyne functionalization reaction to establish the C4–N linkage, in addition to an intramolecular conjugate addition to build the conformationally-flexible nine-membered ring. The total synthesis of indolactam V then sets the stage for the divergent synthesis of the other targeted alkaloids. Specifically, late-stage sp^2–sp^3 cross-couplings on an indolactam V derivative are used to introduce the key C7 substituents and the necessary quaternary carbons. These challenging couplings, in addition to other delicate manipulations, all proceed in the presence of a basic tertiary amine, an unprotected secondary amide, and an unprotected indole. Thus, our approach not only enables the enantiospecific total syntheses of four indolactam alkaloids, but also serves as a platform for probing complexity-generating and chemoselective transformations in the context of alkaloid total synthesis.

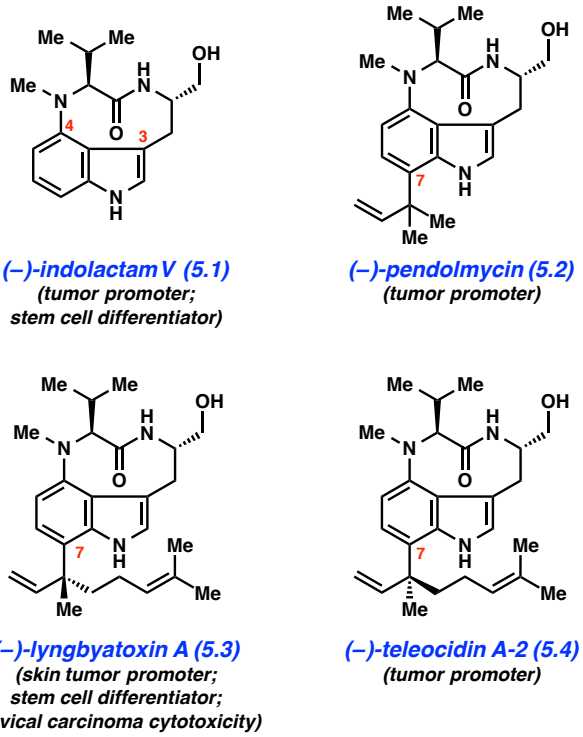
5.2 Introduction

Natural products belonging to the family of indolactam alkaloids[1] (e.g., **5.1**–**5.4**, Figure 5.1) have been widely studied for their pharmacological properties. The most well-known of these compounds is indolactam V (**5.1**), which was first isolated in 1984.[2] Indolactam V (**5.1**)

functions as an efficient tumor promoter as a result of its ability to bind to protein kinase C (PKC). Accordingly, **5.1** has been used in a variety of studies to better understand mammalian tumor growth.[3,4] Similarly, C7-substituted indolactams **5.2**–**5.4** have been valued for their tumor-promoting abilities. It should be noted that each of **5.1**–**5.4** and their derivatives exhibit biological functions which range from stem-cell differentiation[5] to anti-bacterial,[6] anti-malarial[7] and anti-cancer[8] activities.

The attractive biological profiles of indolactam alkaloids have prompted numerous synthetic investigations. These efforts have led to several total syntheses of **5.1**,[9,10] as well as completed syntheses of **5.2**–**5.4**.[11,12] A central challenge to accessing each of these alkaloids involves assembly of the parent 3,4-disubstituted indole framework possessing a conformationally-flexible[13] 9-membered lactam. To this end, most strategies to access the medium-sized ring have involved amide bond formation as the key step.[9] With regard to **5.2**–**5.4**, introduction of the C7 sp^2–sp^3 linkage presents an additional challenge. The few successful approaches to **5.2**–**5.4** all involve early introduction of the C7-linked quaternary carbon, followed by assembly of the indole core.[11,12]

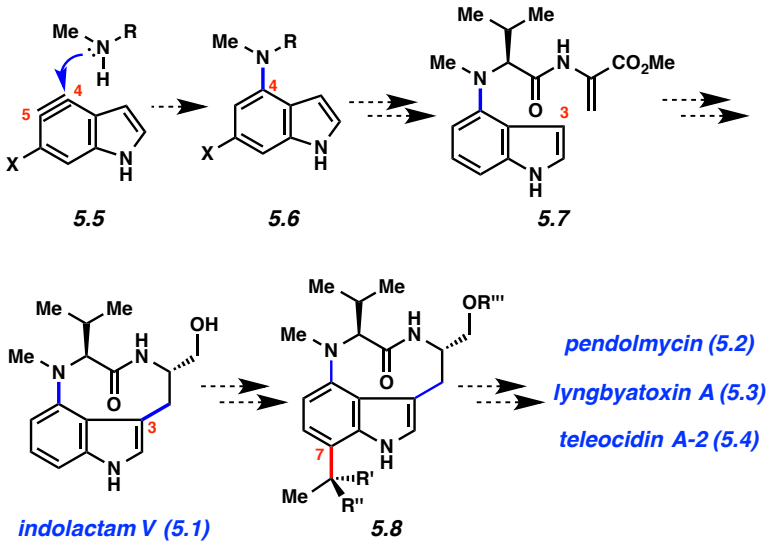
Figure 5.1. Indolactam Alkaloids **5.1**–**5.4**.



We envisioned a strategically distinct approach to indolactam V (**5.1**) and related C7-substituted alkaloids **5.2**–**5.4**, which is summarized in Figure 5.2. Specifically, the 9-membered ring would be introduced through two key steps from an appropriate indole building block: namely, intermolecular assembly of the C4–N bond and ring closure at C3. This would be implemented in practice by accessing an indolyne *in situ*,[14,15,16] which would undergo selective C4-trapping by an amine nucleophile (**5.5**→**5.6**). Elaboration of adduct **5.6** to ester **5.7** would be followed by a challenging conjugate addition at C3 to forge the 9-membered ring en route to **5.1**. We hypothesized that **5.1** could be used as a precursor to the C7-substituted indolactam alkaloids, without the use of *N*-protecting groups. Our unique divergent strategy would require the use of efficient cross-couplings to build the sp^2–sp^3 C–C linkages and introduce the quaternary carbons (**5.1**→**5.8**→**5.2**–**5.4**). Achieving alkylative cross-couplings at C7 of indoles

can be difficult, and only a few such examples are known in the presence of unprotected indole nitrogens.[17] Moreover, to our knowledge, there are no examples of sp^2–sp^3 cross-couplings to introduce quaternary C7 substituents on indole substrates in the literature.

Figure 5.2. Synthetic Strategy Toward **5.1** and C7 Substituted Indolactam Alkaloids **5.2**–**5.4**.



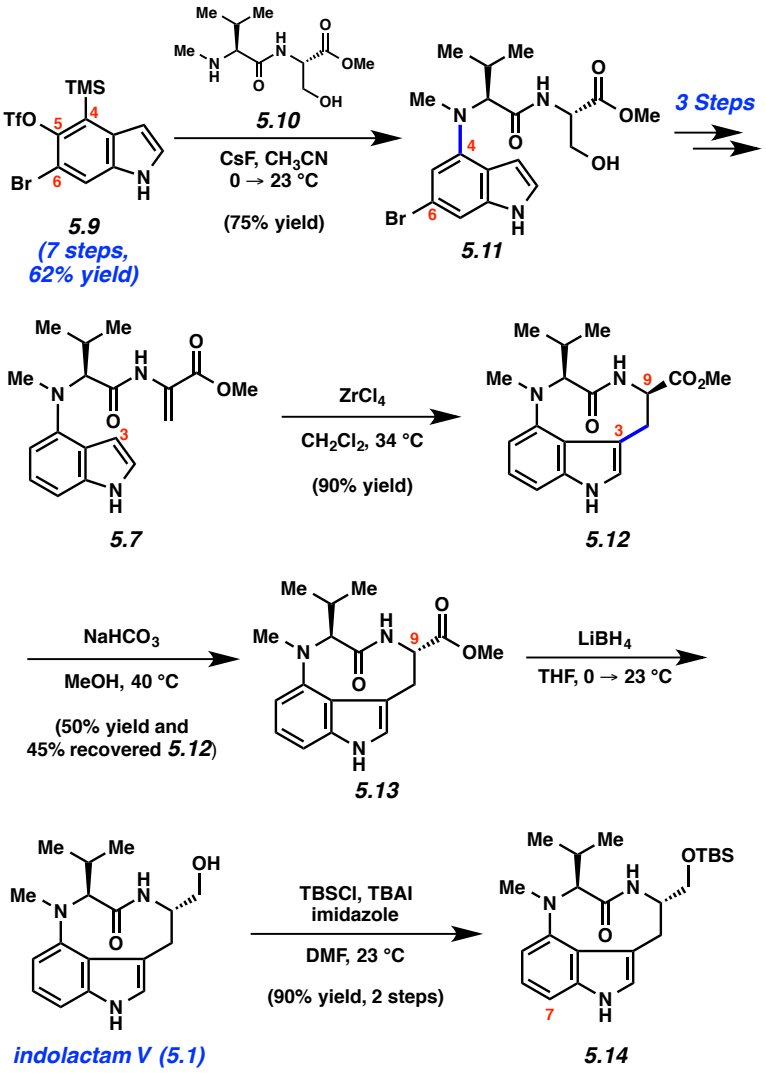
We herein describe the enantiospecific total syntheses of indolactam alkaloids **5.1**–**5.4**. As we have previously reported a formal total synthesis of **5.1**,[10] aside from a brief discussion of optimization of key steps, this manuscript focuses on C7 functionalization studies and the divergent total syntheses of the less well-studied targets **5.2**–**5.4**. This study not only leads to the generation of several natural products enantiospecifically, but also serves as an exercise aimed at probing complexity-generating and chemoselective transformations in alkaloid total synthesis.

5.3 Optimization and Substrate Scope

5.3.1 Optimization of the Total Synthesis of Indolactam V (5.1)

Although our previous studies toward **5.1** validated our approach, we sought to improve several key steps of our formal synthesis[10] and render the route suitable for scale-up (Figure 5.3). We first optimized the synthesis of indolyne precursor **5.9**, which can now be obtained in 7 steps from commercially available materials in 62% overall yield (previously 27% yield, over 7 steps).[18] Next, treatment of silyltriflate **5.9** with peptide **5.10** in the presence of CsF in acetonitrile efficiently furnished indolyne adduct **5.11** and established the key C4–N linkage.[19,20] The regioselectivity in the indolyne trapping is governed by aryne distortion,[15a,b] which arises from the presence of the inductively-withdrawing C6 bromide substituent.[10] After elaborating **5.11** to α,β-unsaturated ester **5.7**, $ZrCl_4$-mediated cyclization[21] provided **5.12** as a single diastereomer in 90% yield.[22] As **5.12** possesses the undesired stereochemical configuration at C9, we developed optimal conditions to facilitate its epimerization based on the protocol reported by Nakatsuka.[9c] Treatment of **5.12** with $NaHCO_3$ in MeOH at 40 °C delivered a separable mixture of recovered **5.12** and the desired epimer **5.13**. Reduction of **5.13** delivered indolactam V (**5.1**), which was subsequently protected to give silyl ether **5.14** in 90% yield over two steps. Using our optimized route, we have prepared over 500 mg of **5.14** for use in subsequent functionalization efforts.

Figure 5.3. Optimized Synthesis of Indolactam V (**5.1**) and **5.14**.



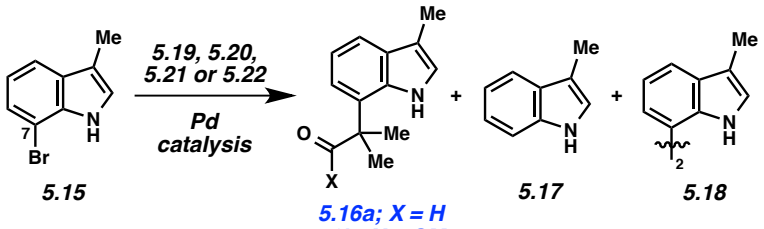
5.3.2 Cross-Coupling to Introduce the C7 sp^2–sp^3 Linkage and the Key Quaternary Carbon

With access to late-stage compound **5.14**, we turned our attention to the previously unexplored divergent approach to alkaloids **5.2**–**5.4**. One of the most challenging aspects of this strategy involves functionalization of C7. Importantly, the methodology would have to build a new sp^2–sp^3 C–C linkage, containing a quaternary center, on an unprotected indole. In general, sp^2–sp^3 couplings are far less common compared to their sp^2–sp^2 counterparts and, as mentioned

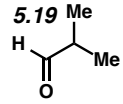
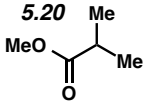
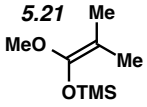
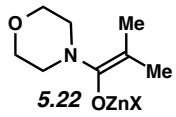
previously, no examples of such couplings to introduce quaternary carbons at C7 of indoles are available.

We tested the viability of our alkylative coupling strategy using readily available unprotected bromoindole substrate **5.15** (Table 5.1). Enolate precursors **5.19**–**5.22** were examined, as the carbonyls in the presumed products could plausibly be elaborated to the olefins present in **5.2**–**5.4**. Unfortunately, attempts to use isobutyraldehyde (**5.19**) as the coupling partner[23] led predominantly to the recovery of starting material **5.15** with or without formation of desbromo indole **5.17** (entries 1[24] and 2, respectively). We also tested ester **5.20** as a coupling partner,[25] but only observed recovered substrate **5.15** (entries 3 and 4). Next, silylketene acetal **5.21** was employed in the desired coupling.[26] To our delight, using 1 mol% $Pd(dba)_2$, some of the desired product **5.16b** was formed, albeit with recovered substrate **5.15** (entry 5). By simply increasing the catalyst loading to 5 mol%, full conversion to product **5.16b** was observed (entry 6). Zinc enolate **5.22**, which was generated in situ from the corresponding a-bromoamide, was also evaluated as a potential coupling partner using Hartwig's methodology.[27] Although no reaction was observed using literature conditions (entry 7), we found that the desired product **5.16c** could be obtained under more forcing conditions (i.e., 15 mol% Pd and 80 °C) (entry 8). It should be noted that desbromo compound **5.17** and dimer **5.18** were also formed in minor quantities. To our knowledge, the successful formation of **5.16b** and **5.16c** represents the first simultaneous formation of an sp^2–sp^3 bond and quaternary center at the C7 position of an indole with an unprotected nitrogen.

Table 5.1. C7 sp^2–sp^3 Cross-Coupling on Model Substrate **5.15**.



5.15 ***5.16a; X = H*** ***5.16b; X = OMe*** ***5.16c; X = morpholine*** ***5.17*** ***5.18***

entry	*cross-coupling partner*	*conditions*[a]	*ratio*[b] *5.15:5.16:5.17:5.18*
1	***5.19*** 	2 mol% $Pd(OAc)_2$, Ligand ***5.23***[c] Cs_2CO_3, dioxane, 80 °C	3.7 : 0 : 1 : 0
2		2 mol% $Pd(OAc)_2$, Ligand ***5.23***[c] $LiNCy_2$, dioxane, 80 °C	1 : 0 : 0 : 0
3	***5.20*** 	1 mol% $Pd(dba)_2$, P(*t*-Bu)$_3$ $LiNCy_2$, toluene, 23 °C	1 : 0 : 0 : 0
4		5 mol% $Pd(dba)_2$, P(*t*-Bu)$_3$ $LiNCy_2$, toluene, 23 °C	1 : 0 : 0 : 0
5	***5.21*** 	1 mol% $Pd(dba)_2$, P(*t*-Bu)$_3$ ZnF_2, DMF, 80 °C	1 : 3 : 0 : 0
6		5 mol% $Pd(dba)_2$, P(*t*-Bu)$_3$ ZnF_2, DMF, 80 °C	0 : 1 : 0 : 0
7	 ***5.22***	2.5 mol% $[P(t\text{-Bu})_3PdBr]_2$ toluene, 23 °C	1 : 0 : 0 : 0
8		15 mol% $[P(t\text{-Bu})_3PdBr]_2$ toluene, 80 °C	0 : 11.3 : 2.1 : 1

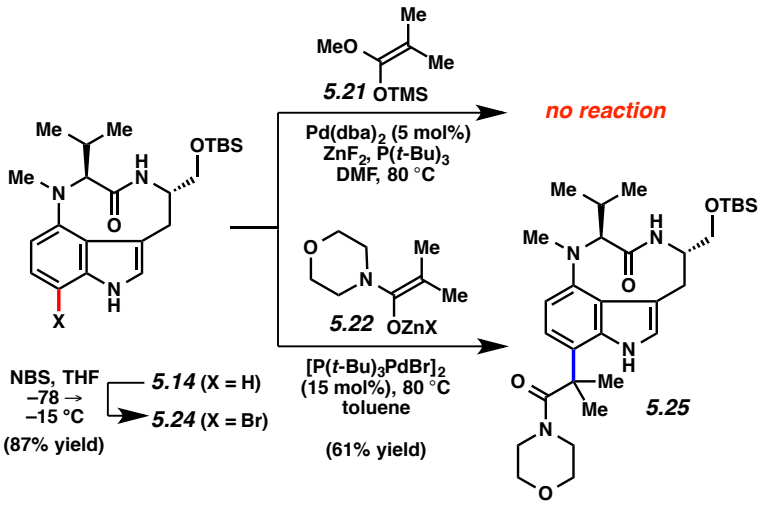
[a] For detailed reaction conditions, see the experimental procedures. [b] Ratios determined by ^1H NMR analysis of the crude reaction mixtures. [c] Ligand 5.23 = diisopropyl[2'-methoxy-1,1'-binaphthalen]-2-yl.

5.3.3 Total Synthesis of (–)-Pendolmycin (5.2)

Our promising results for the cross-coupling on the model system prompted us to shift our efforts to the complex indolactam scaffold (Figure 5.4). Treatment of **5.14** with NBS led to C7 bromination to furnish **5.24**.[28] Next, the critical coupling reactions using the aforementioned conditions (see Table 5.1, entries 6 and 8) were tested. Despite our previous success in coupling

silylketene acetal **5.21**, attempts to effect the corresponding coupling on indolylbromide **5.24** led to no reaction. However, the coupling of bromide **5.24** with zinc enolate **5.22** delivered cross-coupled product **5.25** in 61% yield. As this complexity-generating transformation proceeds on an advanced late-stage intermediate in the presence of two free NHs and a tertiary amine to introduce an sp^2–sp^3 linkage with a quaternary carbon, its success demonstrates the exceptional tolerance and utility of Hartwig's parent methodology.[27]

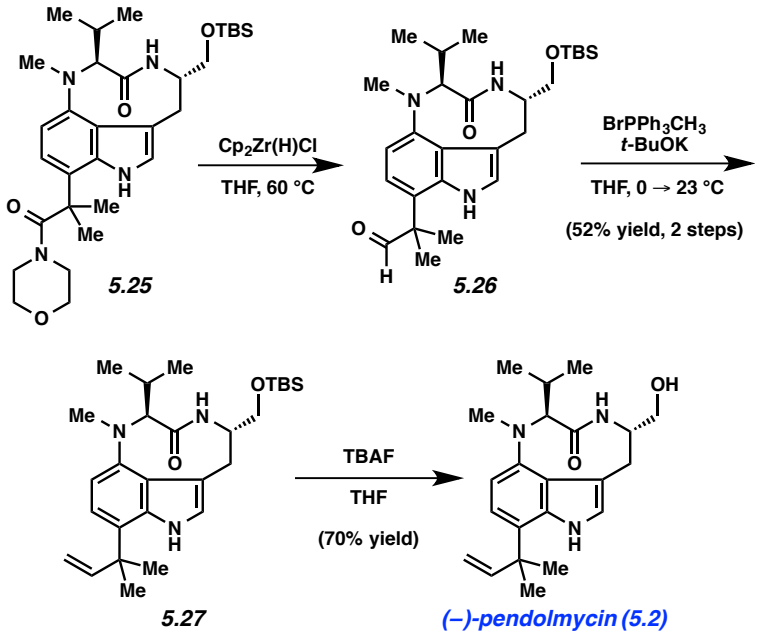
Figure 5.4. C7 Functionalization of **5.14** and Introduction of Key sp^2–sp^3 Linkage with a Quaternary Carbon Substituent.



Having installed the necessary C7 substituent and the key quaternary carbon, we were able to complete the total synthesis of pendolmycin (**5.2**), as shown in Figure 5.5. The morpholine amide of **5.25**, which neighbors the sterically-congested quaternary carbon, was selectively reduced with the Schwartz reagent (i.e., $Cp_2Zr(H)Cl$)[29] to furnish aldehyde **5.26**. Of note, competitive reduction of the secondary amide was not observed.[30] Subsequent Wittig olefination of **5.26** provided the penultimate compound **5.27**. Finally, exposure of **5.27** to TBAF

in THF revealed the primary alcohol to deliver (–)-pendolmycin (**5.2**). This three-step sequence provides a concise means to convert amide **5.25** to the natural product (**5.2**), without the use of *N*-protecting groups.

Figure 5.5. Total Synthesis of (–)-Pendolmycin (**5.2**).



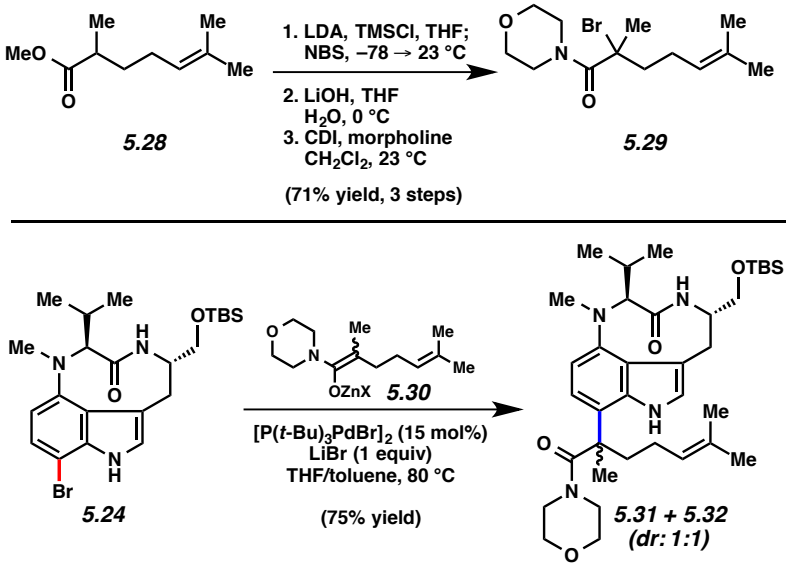
5.3.4 Total Synthesis of Lyngbyatoxin A (5.3) and Teleocidin A-2 (5.4)

Although structurally similar to pendolmycin (**5.2**), lyngbyatoxin A (**5.3**) and teleocidin A-2 (**5.4**) present additional degrees of complexity. Specifically, the sidechains appended to C7 of the indole each contain a quaternary stereocenter, in addition to an electron-rich olefin. We envisioned that both natural products **5.3** and **5.4** could be obtained from bromoindole **5.24** (see Figure 5.4) and a prochiral cross-coupling partner.

To enable this approach, we prepared amide **5.29** and tested the key cross-coupling reaction (Figure 5.6). Ester **5.28**, which was obtained from commercial sources, first underwent

α-bromination under standard conditions.[31] Subsequent saponification,[32] followed by CDI-mediated coupling with morpholine, afforded amide **5.29**.[33] Reaction of amide **5.29** with Zn metal resulted in conversion to the corresponding zinc enolate **5.30**. Gratifyingly, treatment of bromoindole **5.24** with in situ-generated enolate **5.30** under Pd-catalyzed coupling conditions gave the desired diastereomeric products **5.31** and **5.32** in 75% combined yield (d.r. = 1:1 by ^{1}H NMR analysis).[34] Isomers **5.31** and **5.32** were separable by silica gel chromatography.[35] The formation of **5.31** and **5.32** represents the first implementation of Hartwig's amide enolate coupling methodology in the assembly of stereogenic quaternary carbons.[27]

Figure 5.6. Synthesis of Morpholine Amide **5.29** and Cross-Coupling to Access Diastereomeric Adducts **5.31** and **5.32** Possessing the Necessary All-Carbon Quaternary Stereocenters.



With coupled products **5.31** and **5.32** in hand, we completed the total syntheses of (–)-lyngbyatoxin A (**5.3**) and (–)-teleocidin A-2 (**5.4**), respectively (Figures 5.7 and 5.8). Amide **5.31** was reduced to aldehyde **5.33**, which in turn, underwent Wittig homologation to give **5.34**

(Figure 5.7). To complete the total synthesis of (–)-lyngbyatoxin (**5.3**), it was necessary to deprotect the primary alcohol in **5.34**. Although attempts to employ TBAF led to decomposition, we found that exposure of **5.34** to $LiBF_4$ and camphorsulfonic acid (CSA) in THF at ambient temperature afforded natural product **5.3**.[28,36] We were delighted to find that the analogous 3-step reaction sequence facilitated the conversion of diastereomer **5.32** to (–)-teleocidin A-2 (**5.4**) as summarized in Figure 5.8. Spectral data for our synthetic samples of natural products **5.2**–**5.4** matched literature reports.[11,12]

Figure 5.7. Total Synthesis of (–)-Lyngbyatoxin A (**5.3**).

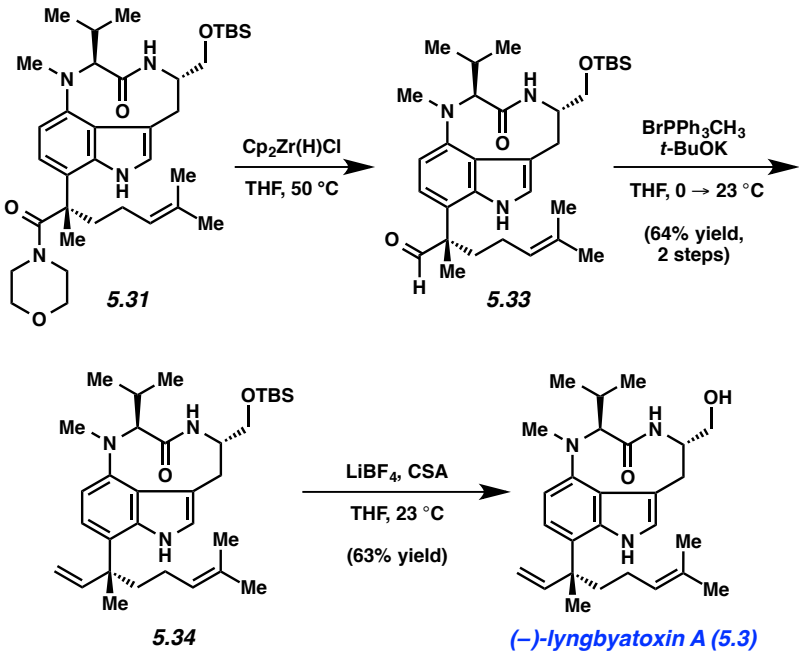
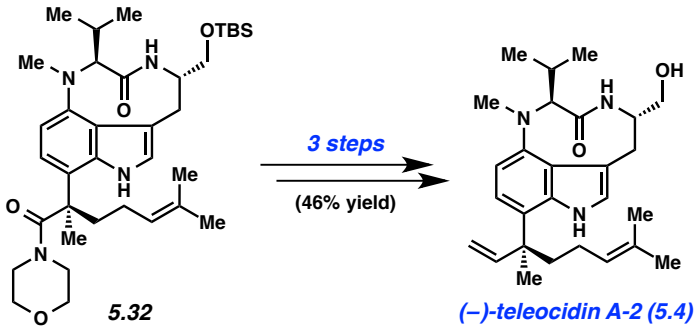


Figure 5.8. Total Synthesis of (–)-Teleocidin A-2 (**5.4**).



5.4 Conclusion

We have completed the total syntheses of four indolactam alkaloids: (–)-indolactam V, (–)-pendolmycin, (–)-lyngbyatoxin A, and (–)-teleocidin A-2. Our approach to these alkaloids features a number of key features, including: a) a distortion-controlled indolyne functionalization reaction to assemble a key C–N bond; b) a Lewis acid-mediated cyclization to assemble the nine-membered lactam; and specifically, for the divergent syntheses of **5.2**–**5.4**; c) late-stage sp^2–sp^3 cross-couplings to introduce the C7 sidechains and the challenging quaternary carbons; and d) a series of delicate functional group manipulations in the absence of *N*-protecting groups. Our studies demonstrate that indolynes serve as valuable electrophilic indole surrogates and provide an unconventional tactic for use in total synthesis. Moreover, these efforts showcase a series of complexity-generating (e.g., sp^2–sp^3 cross-couplings) and chemoselective transformations in the context of alkaloid synthesis.

5.5 Experimental Section

5.5.1 Materials and Methods

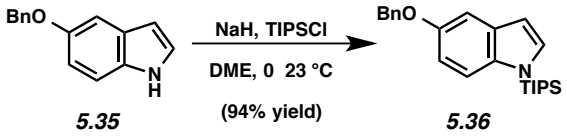
Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere

of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. 6-Benzyloxyindole was obtained from Combi-Blocks, Inc. Cesium fluoride (CsF), di-μ-bromobis(tri-*tert*-butylphosphino)dipalladium(I) ($[P(t\text{-}Bu)_3PdBr]_2$), tris(dibenzylideneacetone)dipalladium ($Pd(dba)_2$), and bis(cyclopentadienyl)zirconium(IV) chloride hydride (Schwartz's reagent) were purchased from Strem Chemicals. Tri-*tert*-butylphosphine and methyl trimethyl dimethylketene acetal was purchased from Sigma-Aldrich. The following reagents were distilled prior to use: chlorotrimethylsilane (TMSCl), *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), and tetramethylethylenediamine (TMEDA); 1,2-dibromoethane was passed over basic Brockman Grade I 58 Å activated alumina and then stirred over 4 Å molecular sieves for 7 h before distillation. Diethylamine (Et_2NH) was stirred over KOH for 1 h and then passed over basic Brockman Grade I 58 Å activated alumina prior to use. DBU was stirred over 4 Å molecular sieves for 3 h and then passed over basic Brockman Grade I 58 Å. *N*-pentane was dried over $MgSO_4$. *N*-bromosuccinamide (NBS) was purified by recrystallization from deionized water. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Melting points were determined using a MEL TEMP II melting point apparatus. Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, iodine, vanillin, ninhydrin, and potassium permanganate staining. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^1H NMR spectra were recorded on Bruker spectrometers (at 500 MHz or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^1H NMR spectra are reported as follows: chemical

shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 125 or 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured with a Rudolf Autopol III Automatic Polarimeter. High-resolution mass spectra were obtained from the UC Irvine Mass Spectrometry Facility and the UCLA Molecular Instrumentation Center.

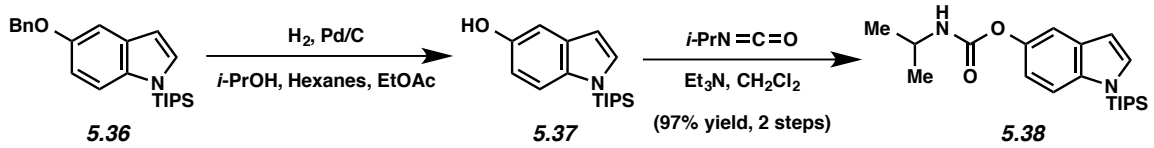
5.5.2 Experimental Procedures

5.5.2.1 Optimization of the Total Synthesis of Indolactam V (5.1)



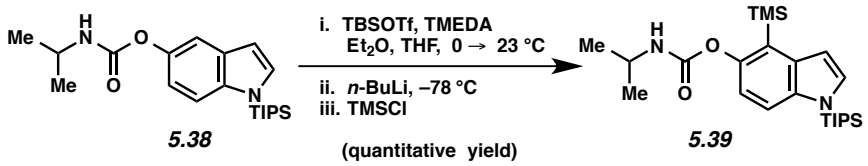
5.35 *5.36*

***N*-TIPS benzyloxyindole 5.36.** To a flask containing NaH (60% dispersion in mineral oil, 0.700 g, 17.5 mmol, 1.3 equiv) at 0 °C was added a solution of 5-benzyloxyindole **5.35** (3.00 g, 13.5 mmol) in 1,2-dimethoxyethane (40 mL). The resulting solution was stirred at 0 °C for 20 min, then TIPSCl (4.34 mL, 20.3 mmol, 1.5 equiv) was added dropwise over 5 min. The resulting mixture was removed from the 0 °C bath and allowed to warm to 23 °C. After stirring for an additional 90 min, the reaction was quenched with H_2O (2 mL). The biphasic mixture was concentrated under reduced pressure, then further diluted with Et_2O (50 mL) and H_2O (10 mL). The layers were separated, and then the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash chromatography (3:1 Hexanes:CH_2Cl_2) to afford known **5.36**[15b] (4.82 g, 94% yield) as a white solid.



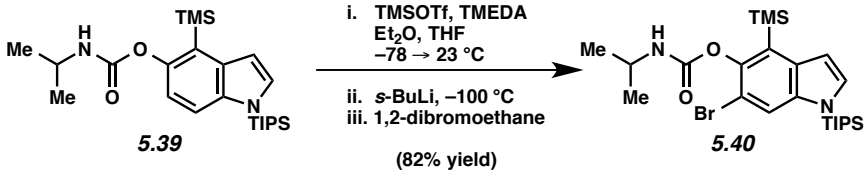
***N*-TIPS carbamate 5.38.** Carbamate **5.38** was prepared following the general procedure described by Igarashi.[37] To a solution of *N*-TIPS benzyloxyindole (4.72 g, 12.4 mmol) in 1:1:1 *i*-PrOH:Hexanes:EtOAc (108 mL) was added 5% Pd/C (0.67 g, 0.32 mmol, 2.6 mol% Pd). The mixture was placed under an atmosphere of hydrogen (double-balloon), stirred for 2.5 h at 23 °C, and then filtered over celite (EtOAc eluent). Evaporation of the solvent under reduced pressure afforded crude **5.37** as a pink solid, which was used in the subsequent step without further purification.

To a solution of crude **5.37** in CH_2Cl_2 (60.0 mL) and Et_3N (0.518 mL, 3.72 mmol, 0.3 equiv), was added *i*-PrNCO (3.64 mL, 37.2 mmol, 3 equiv. The solution was stirred at 23 °C for 24 h, then concentrated to dryness under reduced pressure. Purification by flash chromatography (2:1 Hexanes:Et_2O) provided known *N*-TIPS carbamate **5.38**[15b] (4.48 g, 97% yield, 2 steps) as a white solid.



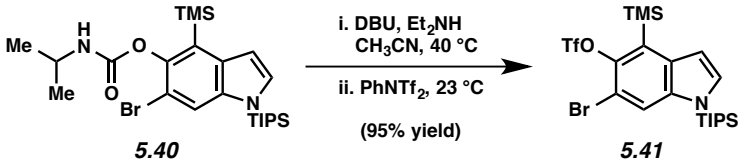
***N*-TIPS silylcarbamate 5.39.** Silyl carbamate **5.39** was prepared following the general procedure described by Hoppe and Snieckus for *o*-lithiation of isopropyl carbamates, with minor modifications.[38,39] To a solution of *N*-TIPS carbamate **5.38** (4.48 g, 11.98 mmol) and TMEDA (2.51 mL, 16.8 mmol, 1.4 equiv) in 3:1 Et_2O:THF (120 mL) at 0 °C was added a solution of TBSOTf in *n*-pentane (1.30 M, 17.3 mL, 14.4 mmol, 1.2 equiv). After stirring for 5 min, the

white suspension was allowed to warm to 23 °C over 30 min. TMEDA (6.28 mL, 41.9 mmol, 3.5 equiv) was added, and the mixture was cooled to –78 °C. A solution of *n*-BuLi in hexanes (1.43 M, 29.3 mL, 41.9 mmol, 3.5 equiv) was added dropwise over 55 min. The mixture was stirred at –78 °C for 3 h, then neat TMSCl (10.6 mL, 83.9 mmol, 7 equiv) was added dropwise over 1 h. The resulting mixture was stirred at –78 °C for 1 h, quenched with 1 M $NaHSO_4$ (50 mL), and allowed to warm to 23 °C over 45 min with vigorous stirring. The biphasic mixture was further diluted with Et_2O (50 mL), the layers were separated, and then the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash chromatography (2:1 Hexanes:Et_2O) to afford known silylcarbamate **5.39**[15b] (5.33 g, quantitative yield) as a white solid.

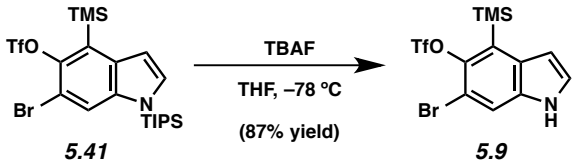


6-Bromo silylcarbamate 5.40. 6-Bromo silylcarbamate **5.40** was prepared following the general procedure described by Snieckus for *o*-lithiation, with modifications.[40] To a solution of silylcarbamate **5.39** (2.19 g, 4.90 mmol) in 3:1 Et_2O:THF (69.6 mL) at –78 °C was added TMEDA (1.02 mL, 6.86 mmol, 1.4 equiv), followed by a solution of TMSOTf in *n*-pentane (1.30 M, 3.91 mL, 5.90 mmol, 1.2 equiv). After stirring for 5 min, the white suspension was allowed to warm to 23 °C over 28 min, by which time TMEDA·TfOH had formed as an oil on the bottom of the flask. The mixture was placed in a hexanes and liquid nitrogen bath at –100 °C and TMEDA (2.56 mL, 17.2 mmol, 3.5 equiv) was added. A solution of *sec*-BuLi in cyclohexane (1.18 M,

37.4 mL, 44.1 mmol, 9 equiv) was added dropwise over 1.2 h. The mixture was stirred at –100 °C for 4.5 h, then neat 1,2-dibromoethane (5.09 mL, 58.8 mmol, 12.0 equiv) was added dropwise over 10 min. The resulting mixture was stirred at –100 °C for 3 h, quenched with 0.5 M aqueous $NaHSO_4$ (50 mL), and warmed to 23 °C over 40 min with vigorous stirring. The layers were separated, and the organic layer was washed successively with 1 M aqueous $NaHSO_4$ (50 mL) and brine (50 mL), then dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (5:1 Benzene:CH_2Cl_2) to afford known 6-bromo silylcarbamate **5.40**[10] (2.12 g, 82% yield) as a white solid.

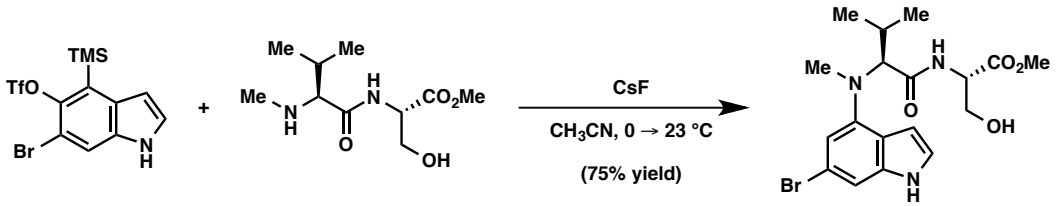


***N*-TIPS 6-bromo silyltriflate 5.41.** To a solution of 6-bromo silylcarbamate **5.40** (0.636 g, 1.21 mmol) in MeCN (24 mL) were added DBU (0.427 mL, 3.03 mmol, 2.5 equiv) and Et_2NH (0.187 μL, 1.82 mmol, 1.5 equiv). The resulting mixture was placed in a heating bath maintained at 40 °C for 15 min, then allowed to cool to 23 °C. Next, a solution of $PhNTf_2$ (0.650 g, 1.82 mmol, 1.5 equiv) in MeCN (2.1 mL) was added. After stirring for 25 min, the reaction mixture was passed over a plug of silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (30:1 Hexanes:Et_2O) to provide known *N*-TIPS 6-bromo silyltriflate **5.41**[10] (0.654 g, 95% yield) as a white solid.



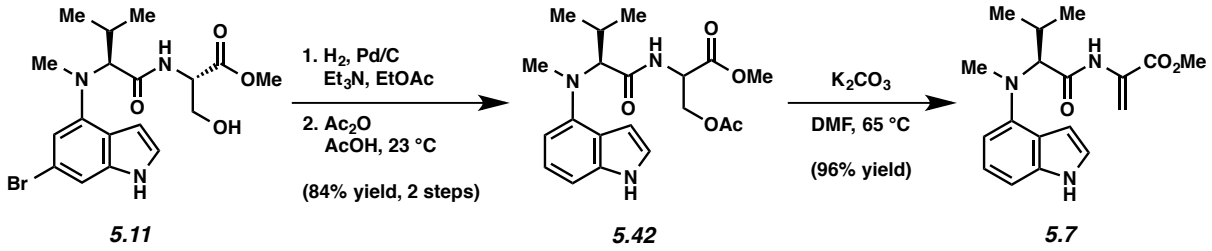
5.41 *5.9*

***N*-H 6-bromo silyltriflate 5.9.** To a solution of *N*-TIPS 6-bromo silyltriflate **5.41** (0.143 g, 0.250 mmol) in THF (9.4 mL) at –78 °C was added a solution of TBAF in THF (1.0 M, 250 μL, 0.250 mmol, 1 equiv) dropwise over 3 min. The solution was stirred for 15 min, then quenched with H_2O (12 mL). The biphasic mixture was further diluted with EtOAc (12 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (2 × 12 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (2.5:1 Hexanes:CH_2Cl_2) to provide known bromo silyltriflate **5.9**[10] (90.9 mg, 87% yield) as a white solid.



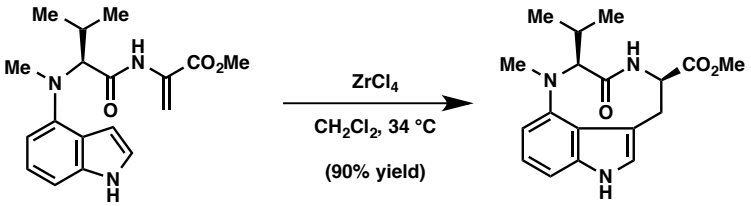
5.9 *5.10* *5.11*

Indolyne adduct 5.11. To a stirred solution of *N*-H 6-bromo silyltriflate **5.9** (52.1 mg, 0.125 mmol) and peptide **5.10**[10] (87.1 mg, 0.375 mmol, 3 equiv) in MeCN (1.25 mL) was placed in a 0 °C bath and added CsF (38.0 mg, 0.250 mmol, 2 equiv). The reaction mixture was stirred at 0 °C for 12 h, and was then allowed to warm to 23 °C. After stirring for an additional 12 h, the reaction mixture was filtered over silica gel (EtOAc eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:0.7:0.7 Hexanes:CH_2Cl_2:Et_2O) to provide known indolyne adduct **5.11**[10] (40.0 mg, 75% yield) as a clear oil.



5.11 *5.42* *5.7*

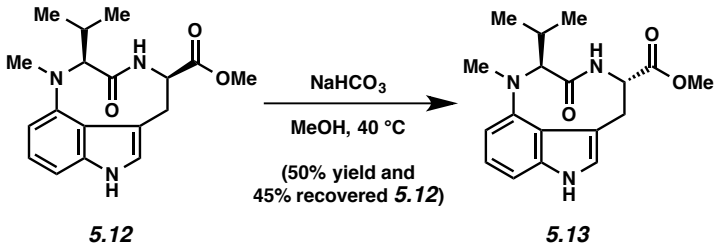
Unsaturated ester 5.7. Indolyne adduct **5.11** was converted to **5.42** in 84% yield using our previously reported two-step procedure.[10] To a solution of **5.42** (98.2 mg, 0.252 mmol) in DMF (2.5 mL) was added K_2CO_3 (69.7 mg, 0.504 mmol, 2 equiv). The resulting mixture was placed in a heating bath maintained at 65 °C for 10 h, then allowed to cool to 23 °C. The reaction mixture was passed over a plug of cotton (EtOAc eluent). Evaporation at 60 °C under reduced pressure afforded the crude product, which was further purified by flash chromatography (5:1 Hexanes:EtOAc) to provide known ester **5.7**[10] (79.7 mg, 96% yield) as a white solid.



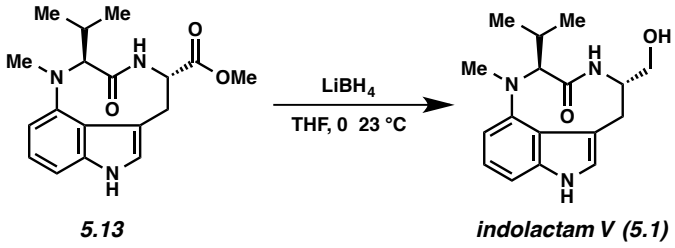
5.7 *5.12*

Tricycle 5.12. A modification of Piersanti's procedure for alkylation of indoles was employed to construct the desired 9-membered ring.[21] Inside a glove box, $ZrCl_4$ (336.5 mg, 1.45 mmol, 15 equiv) and then CH_2Cl_2 (0.96 mL) were added to a vial containing **5.7** (31.7 mg, 0.096 mmol). The reaction vessel was placed into an aluminum block maintained at 34 °C. After 16 h, the vial was transferred out of the glove box and the reaction mixture was added dropwise to saturated aqueous $NaHCO_3$ (15 mL) at 0 °C. The resulting solids were removed by filtration over celite (EtOAc eluent). The layers were separated and the aqueous layer was extracted with EtOAc (15

mL). The combined organic layers were dried over Na_2SO_4. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (5:1 → 2:1 Hexanes:EtOAc) to afford known tricycle **5.12**[10] (28.5 mg, 90% yield) as a white solid.

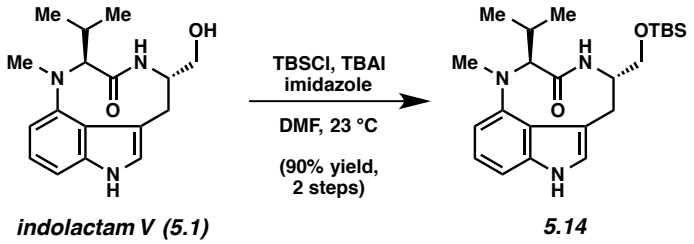


Ester 5.13. Tricycle **5.12** was epimerized following the protocol described by Nakatsuka, with modifications.[9d] To a solution of **5.12** (42.1 mg, 0.128 mmol) in MeOH (8.5 mL) was added $NaHCO_3$ (294.4 mg, 3.5 mmol, 27.4 equiv). The resulting mixture was placed in a heating bath maintained at 40 °C for 3 d, then allowed to cool to 23 °C. The reaction mixture was concentrated and diluted with EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated, and then the organic layer was washed with brine (50 mL), and dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude mixture, which was purified by flash chromatography (95:5 → 90:10 Benzene:CH_3CN) to afford known ester **5.13**[9d] (21.0 mg, 50% yield) and recovered epimer **5.12**[9d] (19.0 mg, 45% yield) as a white solid.



Indolactam V (5.1). Ester **5.13** was reduced following the protocol described by Nakatsuka, with modifications.[9d] Inside a glove box, a vial was charged with **5.13** (125.4 mg, 0.381 mmol),

$LiBH_4$ (54.8 mg, 2.515 mmol, 6.6 equiv) and THF (0.381 mL). The vial was removed from the glove box and allowed to stir for 2 h at 23 °C. After 2 h, the reaction mixture was poured into ice water (5 mL). The mixture was then extracted with CH_2Cl_2 (50 mL). The organic layers were combined, washed with brine (15 mL), and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded crude indolactam V (**5.1**), which was used in the subsequent step without further purification. Spectral data match those previously reported.[9d]

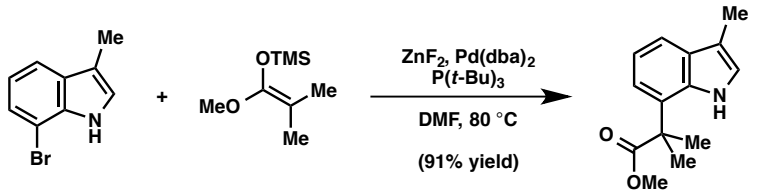


indolactam V (5.1) ***5.14***

Silylether 5.14. Indolactam V (**5.1**) was silyl protected following the protocol described by Kishi.[36] To a stirred solution of indolactam V (**5.1**) (41.7 mg, 0.317 mmol) in DMF (1.4 mL) was added TBSCl (20.6 mg, 0.137 mmol, 1.0 equiv), imidazole (46.5 mg, 0.684 mmol, 5.0 equiv), and TBAI (5.0 mg, 0.014 mmol, 0.1 equiv). The resulting mixture was allowed to stir at 23 °C. After 12 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with EtOAc (10 mL). The organic layer was separated, and then the organic layer was washed with brine (50 mL), and dried over Na_2SO_4. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (4:1 Hexane:EtOAc) to afford known silylether **5.14** (118.5 mg, 90% yield over two steps) as a white solid. Silylether **5.14**: Mp = 192-195 °C; R_f 0.65 (1:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (br s, 1H), 7.08 (t, J = 7.9, 1H), 6.91 (d, J = 8.0, 1H), 6.89 (s, 1H), 6.52 (d, J = 7.7, 1H), 6.19 (br s, 1H), 4.38 (d, J = 10.2, 1H), 4.24 (d, J = 3.9, 1H), 3.65 (dd, J = 10.1, 4.3, 1H), 3.48 (t, J = 9.5, 1H), 3.17 (d, J = 17.4, 1H), 2.95–2.88 (m, 4H), 2.65–2.61 (m, 1H), 0.94 (d, J = 6.4, 3H), 0.91 (s, 3H), 0.89 (s,

9H), 0.64 (d, J = 6.7, 3H), 0.06 (s, 3H) 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 148.0, 139.5, 123.0, 121.4, 118.1, 114.7, 106.4, 104.0, 71.3, 65.5, 55.2, 34.2, 33.0, 28.7, 26.0, 21.7, 19.6, 18.4, -5.2, -5.3; IR (film): 3320, 2928, 1643, 1251 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calculated for $C_{23}H_{37}N_3O_2SiNa$, 438.2553; found, 438.2554; $[\alpha]^{20}_D$ –124.00° (c 0.10 CH_2Cl_2).

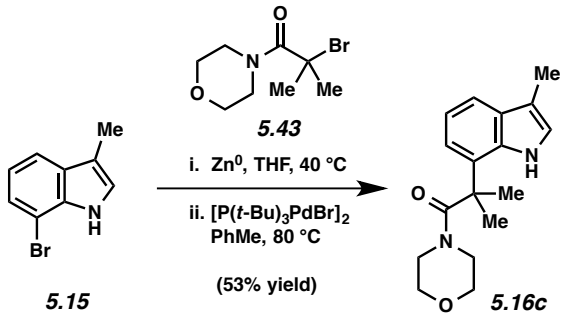
5.5.2.2 Cross-Coupling to Introduce the C7 sp^2–sp^3 Linkage



5.15 *5.21* *5.16b*

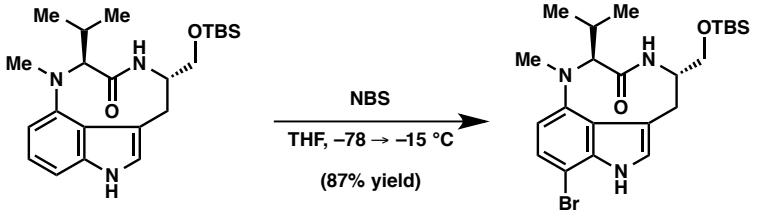
Ester 5.16b. Ester **5.16b** was prepared following the general coupling protocol described by Hartwig for the cross-coupling of silyl ketene acetals with aryl bromides, with modifications.[26] A flame-dried vial under N_2, containing 7-bromoskatol (**5.15**)[41] (9.9 mg, 0.047 mmol), was transferred to a glovebox. A magnetic stir bar was added, followed by P(tBu)$_3$ (4.7 µl, 4.7 µmol, 0.1 equiv), ZnF_2 (2.5 mg, 0.025 mmol, 0.5 equiv), and a solution of $Pd(dba)_2$ (1.4 mg, 2.4 µmol, 0.05 equiv) in DMF (0.47 mL). Trimethylsilyldimethylketene (**5.21**) (14.4 µl, 0.071 mmol, 1.5 equiv) was added and the vial was sealed with a teflon-coated cap and removed from the glovebox. The reaction was stirred at 80 °C for 12 h, cooled to 23 °C, and then filtered over silica (100% EtOAc eluent) and concentrated in vacuo. The crude residue was purified by preparative thin layer chromatography (3:1:1 Hexanes:CH_2Cl_2:EtO_2) to afford ester **5.16b** (9.9 mg, 91%) as an amorphous tan solid. Ester **5.16b**: R_f 0.6 (3:1:1 Hexanes:CH_2Cl_2: EtO_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (br s, 1H), 7.52 (ddd, J = 7.8, 1.0, 1.0, 1H), 7.19 (dd, J = 7.5, 1.0 1H), 7.12 (dd, J = 7.8, 7.5 1H), 6.96 (ddd, J = 1.0, 1.0, 1.0, 1H), 3.61 (s, 3H), 2.32 (d, J = 1.0, 3H), 1.71 (s, 6H),; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.7, 134.1, 129.2, 126.5, 121.9, 119.2,

118.4, 117.9, 111.4, 52.8, 45.3, 25.2, 9.8; IR (film): 3428, 2950, 1713, 1434, 1264, 1152 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calculated for $C_{14}H_{18}NO_2$, 232.1332; found, 232.1328.



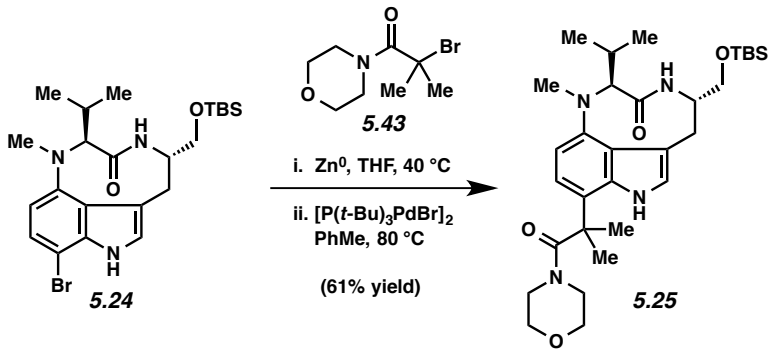
Morpholine amide 5.16c. Amide **5.16c** was prepared following the general protocol for the cross-coupling of α-bromoamides with aryl bromides described by Hartwig, with modifications.[27] Inside a glove box, a vial was charged with morpholine amide **5.43** (390.0 mg, 1.65 mmol, 5 equiv), activated zinc dust (112.0 mg, 1.71 mmol, 5.2 equiv) and THF (1.4 mL). The vial was sealed and placed into a heating block maintained at 40 °C for 4 h. This heterogeneous solution was removed from the heat and immediately added to a solution of 7-bromoskatol **5.15**[41] (69.0 mg, 0.33 mmol) and $[P(t\text{-Bu})_3PdBr]_2$ (38.3 mg, 0.05 mmol, 0.15 equiv) in toluene (3.2 mL). The resulting solution was stirred at 80 °C for 12 h. After cooling to 23 °C, the reaction mixture was loaded directly onto a silica gel column and separated by flash chromatography (5:1 Hexane:EtOAc) to afford morpholine amide **5.16c** (50.3 mg, 53% yield) as a clear oil. Morpholine Amide **16c**: R_f 0.08 (5:1 Hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 8.35 (br s, 1H), 7.51–7.46 (m, 1H), 7.12–7.08 (m, 2H), 6.95–6.93 (m, 1H), 3.89–2.45 (br m, 8H), 2.32 (d, J = 1.1, 3H), 1.67 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 133.7, 129.3, 128.1, 121.9, 119.6, 118.0, 116.1, 111.6, 67.1, 65.8, 47.5, 45.3, 43.7, 9.8; IR (film): 3365, 2920, 1619, 1426, 1245, 1112 cm^{-1}; HRMS-ESI (*m/z*) $[M - H]^-$ calculated for $C_{17}H_{21}N_2O_2$, 285.1609; found, 285.1610.

5.5.2.3 Total Synthesis of (–)-Pendolmycin (5.2)



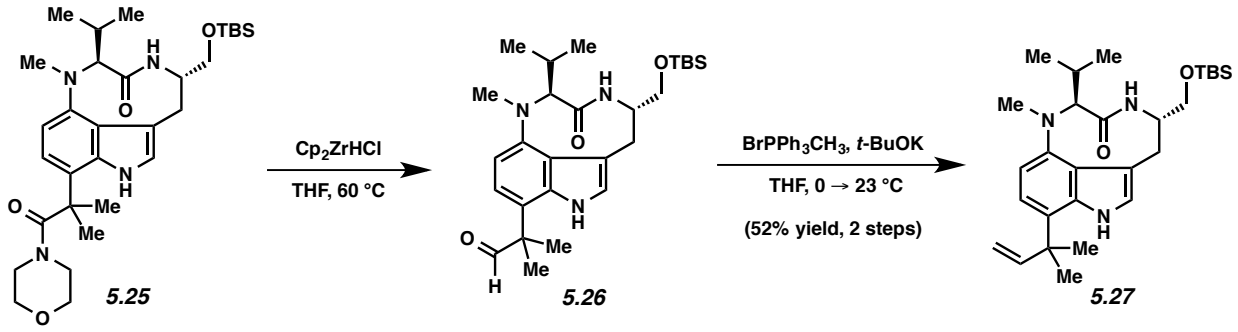
5.14 *5.24*

Bromoindole 5.24. Silylether **5.14** was functionalized following the general protocol described by Kishi, with modification.[28] To a stirred solution of silylether **5.14** (9.5 mg, 0.023 mmol) in THF (2.3 mL) at –78 °C was added *N*-bromosuccinimide (4.1 mg, 0.023 mmol, 1.0 equiv) in THF (2.3 mL). After 10 min, the reaction warmed to –15 °C and stirred for an additional 10 min. The reaction was quenched with water (1 mL), diluted with EtOAc (10 mL) and then washed sequentially with water (10 mL), and brine (5 mL). The organic layers were combined and dried over Na_2SO_4. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (3:1 Hexane:EtOAc) to afford bromoindole **5.24** (6.8 mg, 87% yield) as a white solid. Bromoindole **5.24**: Mp: 188–190 °C; R_f 0.6 (2:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (br s, 1H), 7.18 (d, J = 8.3, 1H), 6.94 (t, J = 1.8, 1H), 6.41 (d, J = 8.3, 1H), 6.16 (s, 1H), 4.30 (d, J = 10.2, 1H), 4.18–4.14 (m, 1H), 3.65 (dd, J = 10.2, 4.4, 1H), 3.48 (dd, J = 10.0, 9.1 1H), 3.17–3.10 (m, 1H), 2.93–2.87 (m, 4H), 2.66–2.55 (m, 1H) 0.93 (d, J = 6.3, 3H), 0.90–0.88 (m, 9H), 0.62 (d, J = 6.8, 3H), 0.04 (d, J = 11.9, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 147.6, 137.3, 125.1, 121.8, 119.1, 116.1, 107.6, 95.9, 71.5, 65.4, 55.0, 34.1, 33.0, 28.7, 26.0, 21.7, 19.7, 18.4, -5.2, -5.3; IR (film): 3369, 3325, 2928, 2857, 1647, 1502, 1251, 1104 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{23}H_{36}BrN_3O_2SiNa$, 516.1658; found, 516.1659; $[\alpha]^{20}_D$ –384.00° (c 0.10 CH_2Cl_2).



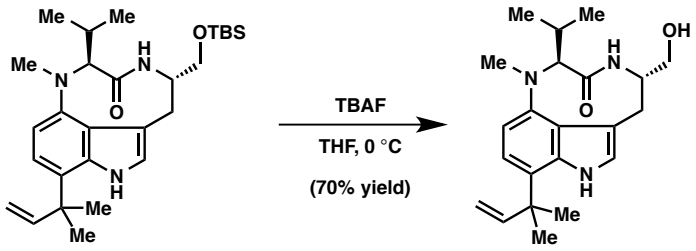
Morpholine amide 5.25. Amide **5.25** was prepared following the general protocol described by Hartwig for the cross-coupling of α-bromoamides with aryl bromides, with modifications.[27] Inside a glove box, a vial was charged with morpholine amide **5.43** (19.1 mg, 0.081 mmol, 10.0 equiv), activated zinc dust (5.5 mg, 0.084 mmol, 10.4 equiv) and THF (0.3 mL). The vial was sealed and placed into a heating block maintained at 40 °C for 4 h. This heterogeneous solution was removed from the heat and immediately added to a solution of bromoindole **5.24** (4.0 mg, 8 μmol) and $[P(t\text{-Bu})_3PdBr]_2$ (0.9 mg, 1 μmol, 15 mol%) in toluene (0.2 mL). The resulting solution was stirred at 80 °C for 12 h. After cooling to 23 °C, the reaction mixture was loaded directly onto a silica gel column and separated by flash chromatography (1:1 Hexane:EtOAc) to afford morpholine amide **5.25** (2.8 mg, 61% yield) as a light yellow oil. Morpholine amide **5.25**: R_f 0.4 (1:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 6.96 (d, J = 8.0, 1H), 6.86 (s, 1H), 6.49 (d, J = 8.0, 1H), 6.16 (br s, 1H), 4.33 (d, J = 10.0, 1H), 4.25–4.16 (m, 1H), 3.70–3.56 (m, 4H), 3.47 (t, J = 10.0, 1H), 3.39–3.20 (m, 3H), 3.14 (d, J =17.4, 3H), 2.66–2.55 (m, 1H), 1.70 (s, 3H), 1.42 (s, 3H), 1.10 (d, J = 6.6, 3H), 0.93 (d, J = 6.6, 4H), 0.88 (s, 9H), 0.55 (d, J = 6.6, 3H), 0.05 (d, J = 12.5, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 172.9, 170.9, 147.0, 136.7, 122.0, 120.5, 118.7, 117.2, 114.3, 106.3, 71.2, 65.5, 56.7, 55.0, 44.8, 36.4, 34.1, 32.9, 28.7, 26.0, 23.4, 21.7, 20.7, 19.7, 18.4 -5.2, -5.3; IR (film): 3375, 2956, 2928, 2857, 1665,

1620, 1508 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{31}H_{50}N_4O_4SiNa$, 593.3498; found, 593.3499; $[\alpha]^{22}_D$ 317.80° (c 0.10 CH_2Cl_2).



Olefin 5.27. Aldehyde **5.26** was prepared following the general protocol described by Georg for the reduction of tertiary amides, with modifications.[29] Inside a glove box, Cp_2ZrHCl (33.9 mg, 0.131 mmol, 5 equiv) and THF (0.7 mL) were added to a vial containing **5.25** (15.0 mg, 0.026 mmol). The reaction vessel was placed in an aluminum block maintained at 60 °C. After stirring for 2 h, the vial was transferred out of the glove box and the reaction mixture was quenched with H_2O (5 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. Evaporation under reduced pressure afforded the crude product, which was used in the subsequent step without further purification. Aldehyde **5.26**: R_f 0.8 (1:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.33 (s, 1H), 8.39 (br s, 1H), 7.07 (d, *J* = 8.2, 1H), 6.85 (s, 1H), 6.56 (d, *J* = 8.2, 1H), 6.15 (s, 1H), 4.33 (d, *J* = 10.1, 1H), 4.21–4.12 (m, 1H), 3.62 (dd, *J* = 10.1, 4.2, 1H), 3.45 (t, *J* = 10.1, 1H), 3.17–3.10 (m, 1H), 2.92 (s, 3H), 2.90–2.86 (m, 1H), 2.66–2.57 (m, 1H) 1.56 (s, 3H), 0.93 (d, *J* = 6.3, 3H), 0.87 (s, 9H), 0.62 (d, *J* = 6.7, 3H), 0.09–0.0 (m, 9H).

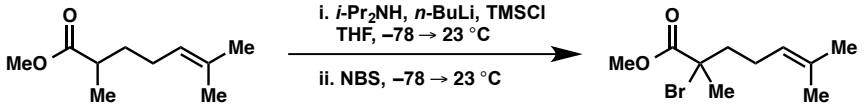
To a solution of methyl triphenylphosphonium bromide (48.8 mg, 0.137 mmol, 12 equiv) in THF (0.29 mL) at 0 °C was added potassium *tert*-butoxide (15.3 mg, 0.137 mmol, 12 equiv). The resulting mixture was stirred at 0 °C for 30 min then warmed 23 °C. After 30 min the vial was cooled to 0 °C and a solution of aldehyde **5.26** (5.5 mg, 0.011 mmol) in THF (0.29 mL) was added. After 1 h, the reaction was warmed to 23 °C for 2 h. The reaction is quenched with water (5 mL) and diluted with EtOAc (10 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (4:1 Hexanes:EtOAc + 2% Et_3N) to provide olefin **5.27** (2.9 mg, 52% yield) as a light yellow oil. Olefin **5.27**: R_f 0.3 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): 8.47 (br s, 1H), 7.01 (d, J = 8.0, 1H), 6.85–6.79 (m, 1H), 6.53–6.46 (m, 1H), 6.24–6.10 (m, 2H), 5.33 (dd, J = 17.8, 1.2, 1H), 5.22 (dd, J = 10.5, 1.2 1H), 4.32 (d, J = 10.5, 1H) 4.29–4.21 (m, 1H) 3.63 (dd, J = 10.5, 4.2, 1H), 3.49–3.41 (m, 1H), 3.15 (app d, J = 17.8, 1H), 2.91 (s, 3H), 2.89–2.72 (m, 1H), 2.68–2.57 (m, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 0.95–0.90 (m, 3H), 0.87 (s, 9H), 0.65 (d, J = 6.5, 3H), 0.05 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 149.8, 146.8, 137.6, 122.8, 121.2, 119.2, 118.8, 114.3, 111.4, 106.5, 71.3, 65.5, 55.1, 40.3, 34.1, 33.1, 28.7, 27.4, 26.9, 26.0, 21.7, 19.7, 18.4, -5.2, -5.3; IR (film): 3452, 3380, 2956, 2929, 2858, 1656, 1507 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{28}H_{45}N_3O_2SiNa$, 506.3179; found, 506.3182; $[\alpha]^{20}_D$ –126.00° (c 0.10 CH_2Cl_2).



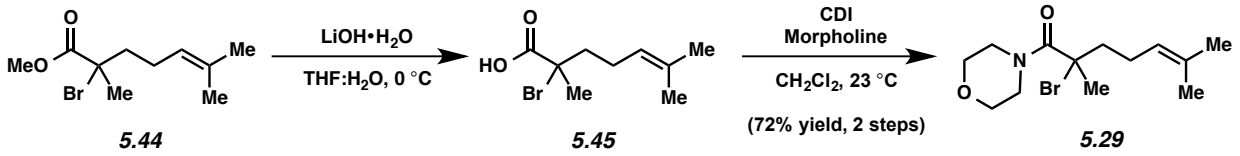
5.27 *pendolmycin (5.2)*

Pendolmycin (5.2). To a solution of olefin **5.27** (6.7 mg, 0.014 mmol) in THF (0.276 mL) at 0 °C was added a solution of TBAF in THF (1.0 M, 138 μL, 0.138 mmol, 10 equiv) dropwise over 3 min. The solution was stirred for 15 min, and then quenched with H_2O (2 mL). The biphasic mixture was further diluted with EtOAc (10 mL) and H_2O (5 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (5:1 CH_2Cl_2:CH_3OH) to provide pendolmycin (**5.2**) (3.6 mg, 70% yield) as a viscous oil. Spectral data for synthetic **5.2** was consistent with literature reports.[11] Pendolmycin (**5.2**): R_f 0.2 (5:1 CH_2Cl_2:CH_3OH); ^1H NMR (500 MHz, $CDCl_3$): Major conformer: δ 8.48 (br s, 1H), 7.01 (d, *J* = 8.0, 1H), 6.86–6.82 (m, 1H), 6.48 (d, *J* = 8.0, 1H), 6.19 (dd, *J* = 17.8, 10.5, 1H), 5.32 (dd, *J* = 17.8, 1.4, 1H), 5.21 (dd, *J* = 10.5, 1.0, 1H), 4.34 (d, *J* = 10.0, 1H), 4.36–4.29 (m, 1H), 3.74 (app d, *J* = 12.0, 1H), 3.62–3.39 (m, 2H), 3.39–3.32 (m, 1H), 3.17 (app d, *J* = 17.0, 1H), 3.08 (dd, *J* = 17.0, 4.0, 1H), 2.9 (s, 3H), 2.65–2.55 (m, 1H) 1.51 (s, 3H), 1.48 (s, 3H), 0.92 (d, *J* = 7.0, 3H), 0.64 (d, *J* = 7.0, 3H); Minor conformer [26/31 protons were discernable]: δ 8.72 (br s, 1H), 7.12 (d, *J* = 7.8, 1H), 7.02 (d, *J* = 7.8, 1H), 6.97 (d, *J* = 2.0, 1H), 6.21 (dd, 17.8, 10.5, 1H), 5.37 (dd, *J* =17.8, 1.4, 1H), 5.27 (dd, *J* =10.5, 1.4, 1H), 4.48–4.39 (m, 1H), 3.43 (app d, *J* =7.2, 1H), 3.44–3.39 (dd, *J* =1.8, 1.4, 1H), 2.99 (d, *J* =10.5, 1.4, 1H), 2.80 (dd, *J* = 15.0, 2.0, 1H), 2.73 (s, 3H), 2.44–2.31 (m, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.25 (d, *J* =6.7, 1H), 0.94 (d, *J* =6.7, 3H).

5.5.2.4 Total Syntheses of (–)-Lyngbyatoxin A (5.3) and (–)-Teleocidin A-2 (5.4)



Bromo ester 5.44. α-Bromo methyl ester **5.44** was prepared following the known protocol described by Webber for the α-bromination of esters, with modifications.[31] A flask containing THF (33.4 mL) and diisopropylamine (2.81 mL, 20.03 mmol, 2.4 equiv) was cooled to –78 °C and then a solution of *n*-BuLi (8.8 mL, 2.55 M in hexanes, 2.7 equiv) was added dropwise over 5 min. The reaction was stirred for an additional 10 min at –78 °C and then warmed to 23 °C over 1 h. The mixture was cooled to –78 °C and TMSCl (2.8 mL, 21.8 mmol, 2.61 equiv) was added dropwise over 5 min. To the resulting clear solution was added ester **5.28** (1.42 g, 8.35 mmol) as a solution in THF (41.7 mL) over 10 min. The resulting yellow solution was stirred at –78 °C for 20 min and *N*-bromosuccinamide (3.86 g, 21.7 mmol, 2.6 equiv) was added quickly under a stream of nitrogen. The flask was purged with nitrogen for 1 min and allowed to warm to 23 °C in the absence of light over 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) and further diluted with water (200 mL) and Et_2O (200 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The organics were combined, washed with brine (50 mL), and dried over $MgSO_4$. Evaporation under reduced pressure provided a crude light yellow oil, which was purified by flash chromatography (60:1 Hexane:Et_2O) to afford bromo ester **5.44** (2.03 g, 98% yield) as a yellow oil. Bromo ester **5.44**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.12–5.06 (m, 1H), 3.78 (s, 3H), 2.18–1.96 (m, 4H), 1.91 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H).

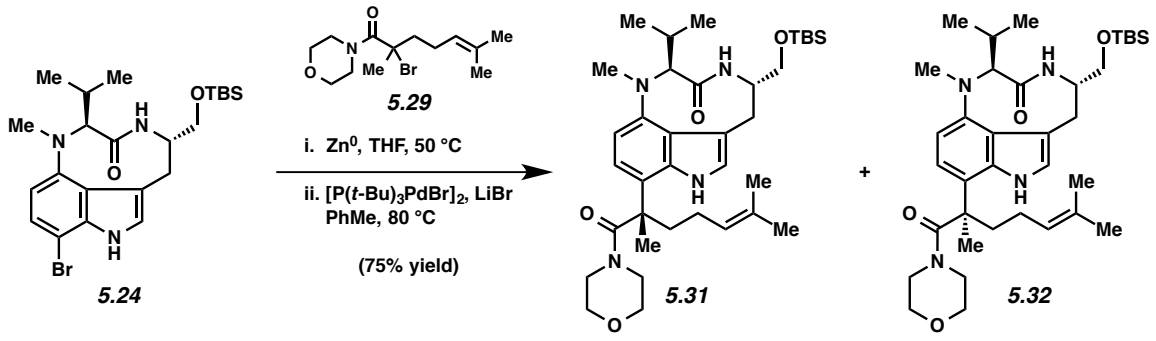


5.44 *5.45* *5.29*

α-Bromo amide 5.29. Carboxylic acid **5.45** was prepared following the general protocol by Xia for the saponification of methyl esters, with modifications.[42] To a stirred solution of α-bromo methyl ester **5.44** (12.50 g, 50.1 mmol) in THF (157 mL) at –15 °C was added a solution of lithium hydroxide monohydrate (3.13 g, 74.6 mmol, 1.4 equiv) in H_2O (133 mL) dropwise via syringe pump. After 7 h, the reaction was quenched with 1 M HCl (100 mL) and then diluted with EtOAc (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded crude **5.45**, which was used in the subsequent step without further purification.

Amide **5.29** was prepared from crude **5.45** following a general protocol for the coupling of esters to amines using 1,1'-carbonyldiimidazole, with modifications.[33] To a solution of crude **5.45** in CH_2Cl_2 (250 mL) was added 1,1'-carbonyldiimidazole (12.99 g, 80.16 mmol, 1.6 equiv). After stirring for 15 min, morpholine (10.83 mL, 125.25 mmol, 2.5 equiv) was added and the reaction was allowed to stir for 6 h. The reaction was quenched with 5% citric acid (400 mL), concentrated in vacuo, and then diluted with H_2O (150 mL) and Et_2O (150 mL). The organic layer was separated, washed with brine (50 mL), and then dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was purified by flash chromatography (5:1 Hexanes:EtOAc) to afford α-bromo amide **5.29** (11.0 g, 72% yield, over two steps) as a yellow oil. α-bromo amide **5.29**: R_f 0.7 (1:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.11–5.05 (m, 1H), 4.00–3.66 (m, 8H), 2.30–1.90 (m, 7H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 133.1, 122.3, 66.6, 61.4, 43.0, 30.5, 25.7, 24.7, 17.7; IR (neat): 2967, 2916,

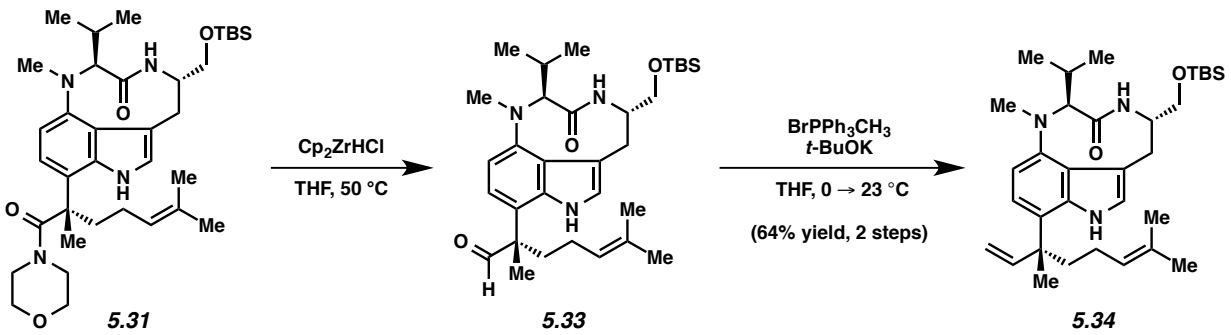
2855, 1635, 1418 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calculated for $C_{13}H_{22}BrNO_2$, 304.0907; found, 304.0901.



Morpholine amides 5.31 and 5.32. Amides **5.31** and **5.32** were prepared following the general protocol described by Hartwig for the cross-coupling of α-bromoamides with aryl bromides, with modifications.[27] Inside a glove box, a vial was charged with a magnetic stir bar, α-bromo amide **5.29** (41.2 mg, 0.135 mmol, 10 equiv), activated zinc dust (8.8 mg, 0.134 mmol, 9.9 equiv), and THF (0.32 mL). The vial was sealed and placed into a heating block maintained at 50 °C for 12 h. This clear, pale yellow solution was removed from the heat and immediately added to a solution of bromoindole **5.24** (6.7 mg, 0.0135 mmol), LiBr (1.2 mg, 0.0135 mmol, 1.0 equiv) and $[P(t\text{-}Bu)_3PdBr]_2$ (1.6 mg, 2 μmol, 15 mmol%) in toluene (0.2 mL). The resulting solution was stirred at 80 °C for 12 h. The reaction mixture was passed through a silica gel plug (EtOAc eluent) and concentrated in vacuo. The crude residue was separated by preparatory thin layer chromatography (2:1 Hexane:EtOAc) to afford two separate diastereomeric amides **5.31** (1.8 mg, 43% yield) and **5.32** (2.4 mg, 32% yield) as light yellow viscous oils. Morpholine amide **5.31**: R_f 0.7 (2:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 6.89 (d, J = 8.2, 1H), 6.82 (br s, 1H), 6.46 (d, J = 8.2, 1H), 6.13 (br s, 1H), 4.40–4.00 (m, 1H), 4.31 (d, J = 10.2, 1H), 4.28–4.20 (m, 1H), 3.65 (dd, J = 10.2, 4.3, 2H), 3.48 (t, J = 9.9, 1H), 3.39–2.70 (m, 14H), 2.69–

2.50 (m, 1H), 2.45–1.66 (m, 10H), 0.94–0.91 (m, 4H), 0.88 (s, 9H), 0.54 (br s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 146.9, 136.8, 124.5, 121.8, 118.7, 114.1, 106.2, 71.3, 67.2, 65.9, 65.6, 61.6, 55.1, 54.5, 47.5, 46.0, 43.7, 38.8, 34.1, 32.9, 29.9, 28.7, 26.0, 25.8, 23.2, 21.7, 20.3, 19.7, 17.6, -5.2, -5.3; IR (film): 3383, 2928, 1664, 1508, 1115 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calculated for $C_{36}H_{59}N_4O_4Si$, 639.4305; found, 639.4301; $[\alpha]^{22}_D$ – 108.00 (c 0.10 CH_2Cl_2). Morpholine amide **5.32**: R_f 0.7 (2:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (br s, 1H), 6.95 (d, *J* = 8.2, 1H), 6.84 (br s, 1H), 6.46 (d, *J* = 8.2, 1H), 6.14 (br s, 1H), 5.25–5.00 (m, 1H), 4.32 (d, *J* = 10.0, 1H), 4.24–4.16 (br m, 1H), 3.70–3.42 (m, 1H) 3.64 (dd, *J* = 10.0, 4.1, 2H), 3.46 (t, *J* = 9.9, 1H), 3.40–3.0 (m, 6H), 2.90 (dd, *J* = 17.9, 4.1, 1H) 2.90 (s, 3H), 2.66–2.51 (m, 1H), 2.35–1.81 (m, 5H), 1.79–1.58 (m, 8H), 0.96–0.89 (m, 4H), 0.87 (s, 9H), 0.52 (d, *J* = 6.6, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) [28/36 carbons were discernable]: δ 175.5, 172.9, 171.3, 147.0, 136.6, 118.7, 114.2, 106.2, 71.2, 67.2, 65.9, 65.5, 60.6, 55.0, 47.5, 34.2, 32.9, 29.8, 29.4, 28.8, 26.0, 21.7, 21.2, 19.7, 18.4, 14.4, -5.2, -5.3; IR (film): 3375, 2928, 1666, 1508, 1115 cm^{-1}; HRMS-ESI (*m/z*) $[M - H]^-$ calculated for $C_{36}H_{57}N_4O_4Si$, 637.4149; found, 637.4147; $[\alpha]^{22}_D$ –106.00 (c 0.10 CH_2Cl_2).

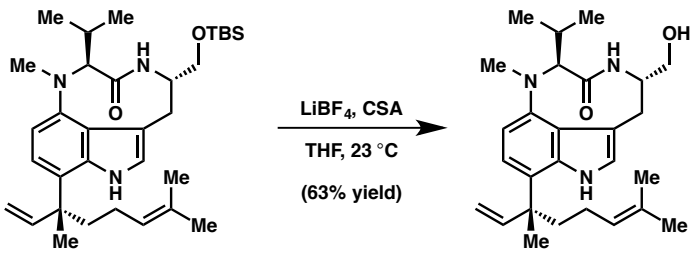
Note: ^{1}H NMR and ^{13}C NMR integrations and peaks were complicated by the presence of major and minor conformers.[13] Empirical data is therefore reported for compounds **5.31**–**5.34**, **5.46** and **5.47**. Absolute stereochemical configuration for amides **5.31** and **5.32** were determined by subjecting each compound to the subsequent synthetic steps and matching each resulting compound to known spectral data for the natural products **5.3** and **5.4**.



Olefin 5.34. Aldehyde **5.33** was prepared following the general protocol described by Georg for the reduction of tertiary amides, with modifications.[29] Inside a glove box, Cp_2ZrHCl (7.3 mg, 0.03 mmol, 10 equiv) and THF (0.3 mL) were added to a vial containing **5.31** (1.8 mg, 3 μmol). The reaction vessel was placed into an aluminum block maintained at 50 °C. After stirring for 12 h, the vial was transferred out of the glove box. The reaction mixture was quenched with silica gel (10.0 mg) and EtOAc with 2% Et_3N (1.0 mL), and then stirred for 1 h. The mixture was eluted through a plug of silica gel (EtOAc with 2% Et_3N eluent). Evaporation under reduced pressure afforded crude **5.33**, which was used in the subsequent step without further purification. Aldehyde **5.33**: R_f 0.9 (1:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.33 (s, 1H), 8.5 (br s, 1H), 7.05 (d, J = 8.2, 1H), 6.83 (b s, 1H), 6.55 (d, J = 8.2, 1H), 6.16 (s, 1H), 5.18–5.01 (m, 1H), 4.33 (d, J = 9.9, 1H), 4.26–4.08 (m, 1H), 3.78–3.68 (m, 1H), 3.63 (dd, J = 10.9, 4.8, 1H), 3.45 (t, J = 9.9, 1H), 3.11–3.06 (m, 1H), 2.91 (s, 3H), 2.79–2.49 (m, 2H), 2.43–1.76 (m, 5H), 1.65 (s, 2H), 1.63 (s, 2H), 1.42–1.40 (m, 1H), 0.94–0.88 (m, 9H), 0.86–0.80 (m, 3H), 0.82 (dd, J = 9.9, 6.7, 2H) 0.58 (d, J = 6.7, 3H), 0.05 (s, 3H), 0.02 (s, 3H).

A vial was charged with methyl triphenylphosphonium bromide (266.5 mg, 0.746 mmol, 265 equiv) and placed in a 0 °C bath. To this vial was added a solution of potassium *tert*-butoxide (79.0 mg, 0.704 mmol, 250 equiv) in THF (1.0 mL) dropwise over 2 min, and the resulting yellow mixture was allowed to warm to 23 °C over 30 min. After 1 h, an aliquot of the

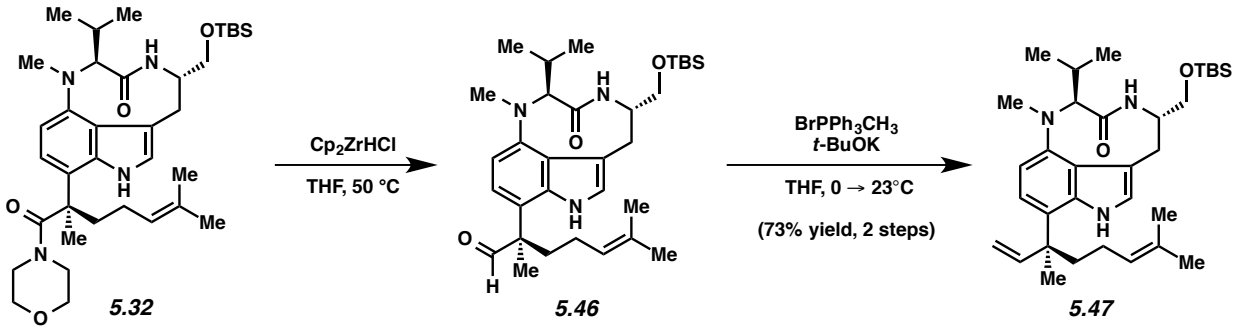
resulting ylide stock solution (20.0 µl, 5 equiv) was added dropwise to a solution of aldehyde **5.33** (3 µmol) in THF (0.3 mL) at 0 °C. After 1 h, the reaction was warmed up to 23 °C and stirred for 12 h. The reaction was quenched with water (1 mL) and EtOAc (1 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:199 Acetone:Benzene) to provide olefin **5.34** (1.0 mg, 64% yield over two steps) as a viscous light yellow oil. Olefin **5.34**: R_f 0.5 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54–8.47 (m, 1H), 6.97 (d, J = 8.1, 1H), 6.80 (br s, 1H), 6.48 (d, J = 8.1, 1H), 6.17 (dd, J = 17.6, 10.6, 1H), 6.15 (br s, 1H), 5.36–5.23 (m, 3H), 5.13–5.03 (m, 1H), 4.31 (d, J = 10.0, 1H), 4.24 (dd, J = 10.0, 3.6, 1H), 3.63 (dd, J = 10.0, 3.6, 1H), 3.46 (t, J = 10.0, 1H), 3.13 (d, J = 17.6, 1H), 3.00–2.85 (s, 5H), 2.85–2.73 (m, 1H), 2.65–2.57 (m, 1H), 2.55–1.73 (m, 5H), 1.65 (app s, 2H), 1.49–1.44 (m, 6H), 0.88 (s, 9H), 0.64 (d, J = 6.8, 3H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 148.6, 146.7, 137.7, 131.6, 124.8, 121.6, 121.0 120.1, 118.9, 114.2, 112.6, 106.5, 71.3, 65.5, 55.1, 43.4, 39.8, 38.7, 34.1, 33.0, 32.1, 28.7, 26.0, 24.2, 23.2, 21.7, 19.7, 18.4, 17.7, 14.3, -5.2, -5.3; IR (film): 2927, 2856, 1662, 1508, 1105 cm^{-1}; HRMS-ESI (*m/z*) $[M - H]^-$ calculated for $C_{33}H_{52}N_3O_2Si$, 550.38233; found, 550.38368; $[\alpha]^{20}_D$ –98.00 (c 0.10 CH_2Cl_2).



5.34 *lyngbyatoxin A (5.3)*

Lyngbyatoxin A (5.3). Lyngbyatoxin A (**5.3**) was prepared following the general protocol for desilylation described by Kishi, with modifications.[36] A vial was charged with lithium tetrafluoroborate (85.0 mg, 0.91 mmol, 500 equiv) and CH_3CN (0.91 mL). An aliquot of the resulting mixture (1.0 M, 9 μL, 9 μmol, 5 equiv) was added dropwise to a solution of **5.34** (1.0 mg, 1.8 μmol) in THF (0.25 mL) over 1 min. After the solution was stirred for 20 min, (±)-camphorsulfonic acid (2.1 mg, 9 μmol, 5 equiv) was added and the reaction was stirred for 24 h at 23 °C. The mixture was diluted with EtOAc (1 mL) and H_2O (1 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (17:2:1 Hexanes:$CHCl_3$:*i*PrOH) to provide lyngbyatoxin A (**5.3**) (0.5 mg, 63% yield) as a viscous light yellow oil. Lyngbyatoxin A (**5.3**): R_f 0.6 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ (major conformer) 8.52 (br s, 1H), 6.97 (d, *J* = 8.2, 1H), 6.83–6.77 (m, 1H), 6.48 (d, *J* = 8.2, 1H), 6.34 (s, 1H), 6.18 (dd, *J* = 18.0, 10.5, 1H), 5.32 (d, *J* = 18.0, 1H), 5.28 (d, *J* = 10.5, 1H), 5.12–5.02 (m, 1H), 4.30 (d, *J* = 10.0, 1H), 4.29– 4.20 (m, 1H), 3.75 (dd, *J* = 10.7, 4.2 1H), 3.54–3.50 (m, 1H), 3.18 (br d, *J* = 17.0, 1H), 2.99 (dd, *J* = 15.0, 11.0, 1H), 2.91 (s, 3H), 2.58 (dqq, *J* = 10.7, 6.5, 6.5, 1H), 2.04–2.16 (m, 5H), 1.65 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H) 0.92 (d, *J* = 6.5, 3H), 0.64 (d, *J* = 6.5, 3H); δ (minor conformer) [27/39 protons were discernable] 8.76 (br s, 1H), 7.10 (d, *J* = 8.0, 1H), 7.01 (d, *J* = 8.0, 1H), 5.34 (d, *J* = 18.0, 1H), 4.46–4.40 (m, 1H), 3.46 (dd, *J* = 11.0, 6.7, 1H), 3.38 (dd, *J* =

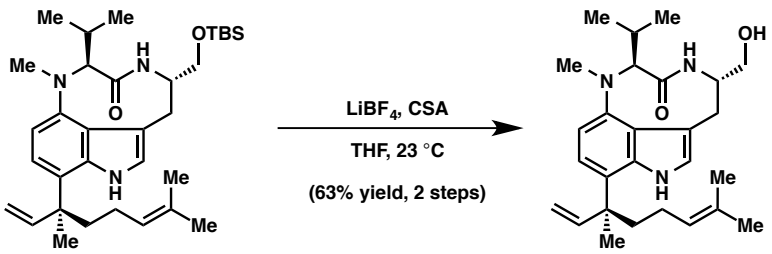
11.0, 6.7, 1H), 2.80 (dd, *J* = 15.0, 1.5, 1H), 2.74 (s, 3H), 2.39 (dqq, *J* = 10.8, 6.5, 6.5, 1H), 1.63 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.25 (d, *J* = 6.5, 3H), 0.97 (d, *J* = 6.5, 3H).



Olefin 5.47. Aldehyde **5.46** was prepared following the general protocol described by Georg for the reduction of tertiary amides, with modifications.[29] Inside a glove box, Cp_2ZrHCl (7.7 mg, 0.03 mmol, 10 equiv) and THF (0.3 mL) were added to a vial containing **5.32** (1.9 mg, 3 μmol). The reaction vessel was placed into an aluminum block maintained at 50 °C. After stirring for 12 h, the vial was transferred out of the glove box. The reaction mixture was quenched with silica gel (10.0 mg) and EtOAc with 2% Et_3N (1.0 mL), and then stirred for 1 h. The mixture was eluted through a plug of silica gel (EtOAc with 2% Et_3N eluent). Evaporation under reduced pressure afforded crude **5.46**, which was used in the subsequent step without further purification. Aldehyde **5.46**: R_f 0.9 (1:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.33 (s, 1H), 8.5 (br s, 1H), 7.04 (d, *J* = 8.4, 1H), 6.84 (m, 1H), 6.55 (d, *J* = 8.4, 1H), 6.16 (s, 1H), 5.15–4.98 (m, 1H), 4.47–3.97 (m, 2H), 4.43 (d, *J* = 10.0, 1H), 3.78–3.68 (m, 1H), 3.61 (dd, *J* = 10.0, 4.3, 2H), 3.44 (t, *J* = 10.0, 1H), 3.17–3.10 (m, 2H), 2.91 (s, 3H), 2.79–2.54 (m, 3H), 2.23–1.81 (m, 5H), 1.41 (s, 3H), 0.87 (m, 9H), 0.77 (dd, *J* = 10.0, 6.7, 3H) 0.57 (d, *J* = 6.7, 3H), 0.05 (s, 3H), 0.02 (s, 3H).

A vial was charged with methyl triphenylphosphonium bromide (117.0 mg, 0.328 mmol, 110 equiv) and placed in a 0 °C bath. To this vial was added a solution of potassium *tert*-

butoxide (33.3 mg, 0.297 mmol, 100 equiv) in THF (1.0 mL) dropwise over 2 min and the resulting yellow mixture was allowed to warm to 23 °C over 30 min. After 1 h, an aliquot of the resulting ylide stock solution (50.0 μl, 5 equiv) was added dropwise to a solution of aldehyde **5.46** (3 μmol) in THF (0.3 mL) at 0 °C. After 1 h, the reaction was warmed up to 23 °C and stirred for 12 h. The reaction was quenched with water (1 mL) and EtOAc (1 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (1:199 Acetone:Benzene) to provide olefin **5.47** (1.2 mg, 73% yield over two steps) as a viscous light yellow oil. Olefin **5.47**: R_f 0.5 (5:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (br m, 1H), 6.98 (d, *J* = 8.1, 1H), 6.82 (br s, 1H), 6.49 (d, *J* = 8.1, 1H), 6.21 (dd, *J* = 17.6, 10.6, 1H), 6.15 (br s, 1H), 5.32–5.22 (m, 2H), 5.13–5.01 (m, 1H), 4.31 (d, *J* = 10.1, 1H), 4.25 (m, 1H), 3.63 (dd, *J* = 10.1, 4.5, 1H), 3.45 (t, *J* = 10.1, 1H), 3.13 (d, *J* = 17.7, 1H), 2.91 (s, 3H), 2.88–2.74 (m, 2H), 2.66–2.54 (m, 1H), 2.10–1.70 (m, 3H), 1.65–1.61 (m, 2H), 1.45 (s, 2H), 1.43 (s, 1H), 1.38 (s, 2H), 0.88 (s, 9H), 0.85 (dd, *J* = 6.8, 4.5, 2H), 0.83–0.78 (m, 1H), 0.75 (dd, *J* = 4.5, 6.8, 2H), 0.60 (d, *J* = 6.8, 3H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 149.3, 146.7, 137.6, 131.6, 124.7, 121.2, 120.4, 118.7, 114.1, 112.2, 106.0, 71.3, 65.5, 55.0, 43.5, 39.6, 38.1, 34.2, 32.9, 32.1, 28.7, 26.0, 24.9, 23.3, 22.7, 21.8, 19.6, 18.4, 17.5, 14.3, -5.2, -5.3; IR (film): 2927, 2854, 1662, 1466, 1105 cm^{-1}; HRMS-ESI (*m/z*) $[M - H]^-$ calculated for $C_{33}H_{52}N_3O_2Si$, 550.38233; found, 550.38371; $[\alpha]^{20}_D$ –136.00 (c 0.10 CH_2Cl_2).



5.47 *teleocidin A-2 (5.4)*

Teleocidin A-2 (5.4). Teleocidin A-2 (**5.4**) was prepared following the general protocol for desilylation described by Kishi, with modifications.[36] A vial was charged with lithium tetrafluoroborate (63.7 mg, 0.68 mmol, 250 equiv) and CH_3CN (0.68 mL). An aliquot of the resulting mixture (1.0 M, 14 μL, 14 μmol, 5 equiv) was added dropwise to a solution of **5.47** (1.5 mg, 3 μmol) in THF (0.25 mL) over 1 min. After the solution was stirred for 20 min, (±)-camphorsulfonic acid (3.2 mg, 14 μmol, 5 equiv) was added and the reaction was stirred for 24 h at 23 °C. The mixture was diluted with EtOAc (1 mL) and H_2O (1 mL). The layers were separated, and then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (17:2:1 Hexanes:$CHCl_3$:*i*PrOH) to provide teleocidin A-2 (**5.4**) (0.5 mg, 63% yield) as a viscous light yellow oil. Teleocidin A-2 (**5.4**): R_f 0.6 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ (major conformer) 8.53 (br s, 1H), 6.98 (d, *J* = 8.1, 1H), 6.83–6.80 (m, 1H), 6.49 (d, *J* = 8.1, 1H), 6.20 (dd, *J* = 18.0, 10.5, 1H), 5.30 (d, *J* = 18.0, 1H), 5.26 (d, *J* = 10.5, 1H), 5.10–5.05 (m, 1H), 4.34 (d, *J* = 10.5, 1H), 4.37– 4.30 (m, 1H), 3.72 (dd, *J* = 10.8, 4.0 1H), 3.54–3.44 (m, 1H), 3.18 (br d, *J* = 17.0, 1H), 2.96 (dd, *J* = 17.0, 4.0 1H), 2.92 (s, 3H) 2.60 (dqq, *J* = 10.8, 6.5, 6.5, 1H), 2.51–1.69 (m, 6H), 1.62 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H) 0.92 (d, *J* = 6.5, 3H), 0.60 (d, *J* = 6.5, 3H); δ (minor conformer) [31/39 protons were discernable] 8.75 (br s, 1H), 7.09 (d, *J* = 8.0, 1H), 7.01 (d, *J* = 8.0, 1H), 6.97 (s, 1H), 6.22 (dd, *J* = 17.9, 10.3, 1H), 5.35 (*J* = 17.9, 1H), 5.33 (d, *J* = 11.0, 1H), 5.12–5.02 (m, 1H)

4.48–4.39 (m, 1H), 3.46 (dd, *J* = 11.0, 6.5, 1H), 3.39 (dd, *J* = 11.0, 6.5, 1H), 2.80 (dd, *J* = 15.0, 1.5, 1H), 2.73 (s, 3H), 2.39 (dqq, *J* = 11.0, 6.5, 6.5, 1H), 1.65 (s, 3H), 1.47 (s, 3H), 1.42 (s, 3H), 1.25 (d, *J* = 6.5, 3H), 0.94 (d, *J* = 6.5, 3H).

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(20) Less than 5% of the corresponding C5-substituted product was detected.

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Spectra Relevant to Chapter Five:

Total Syntheses of Indolactam Alkaloids (–)-Indolactam V, (–)-Pendolmycin, (–)-Lyngbyatoxin A, and (–)-Teleocidin A-2

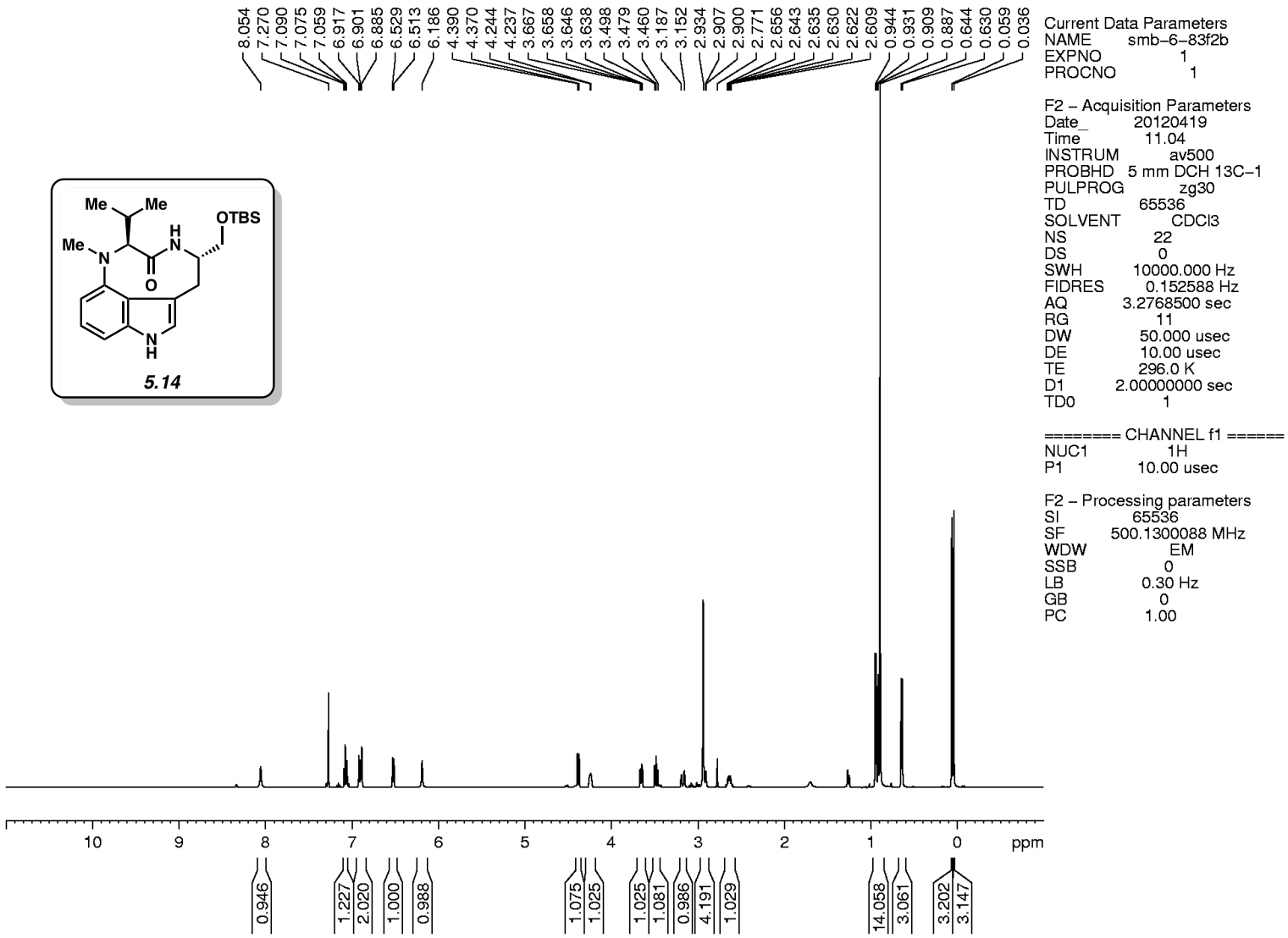

Figure 5.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.14**.

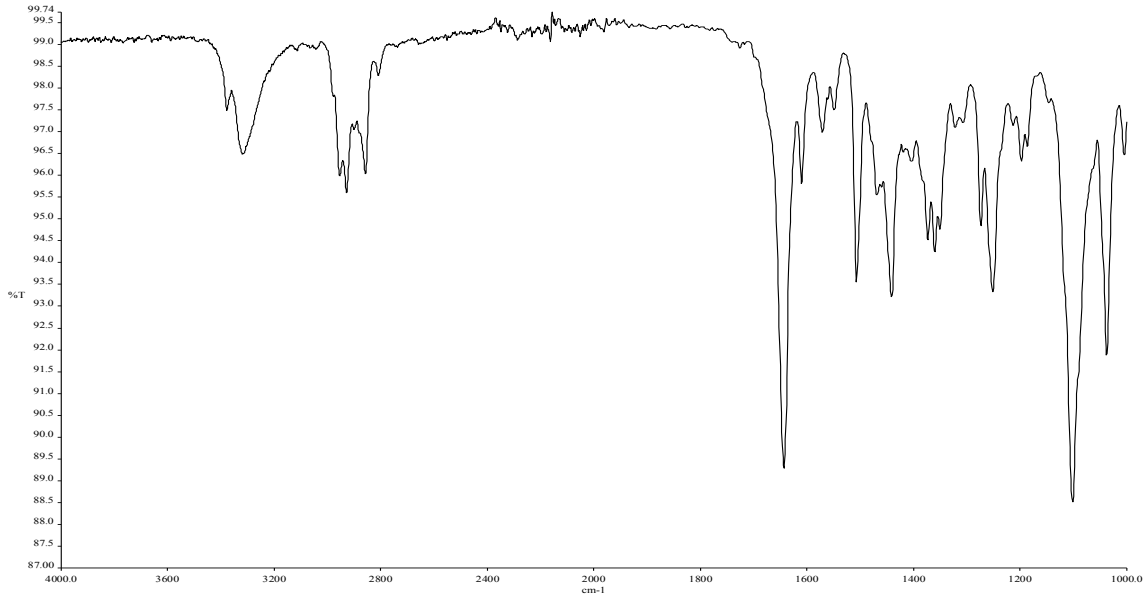

Figure 5.10. Infrared spectrum of compound **5.14**.

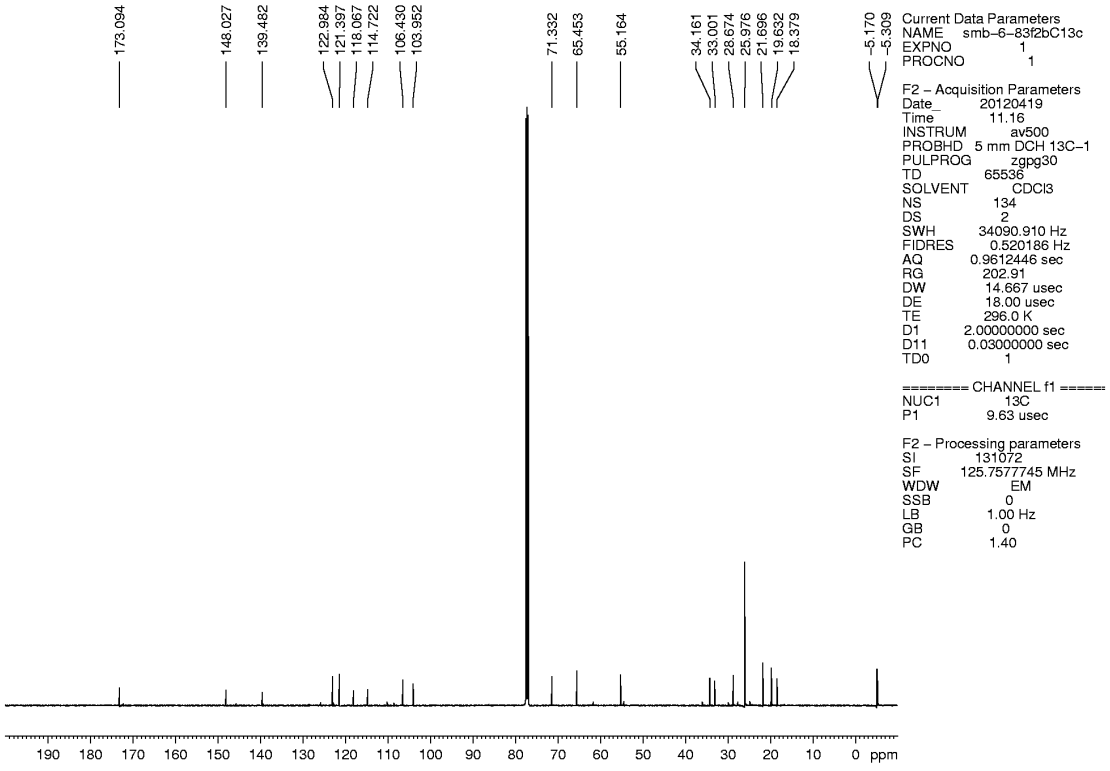

Figure 5.11. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.14**.

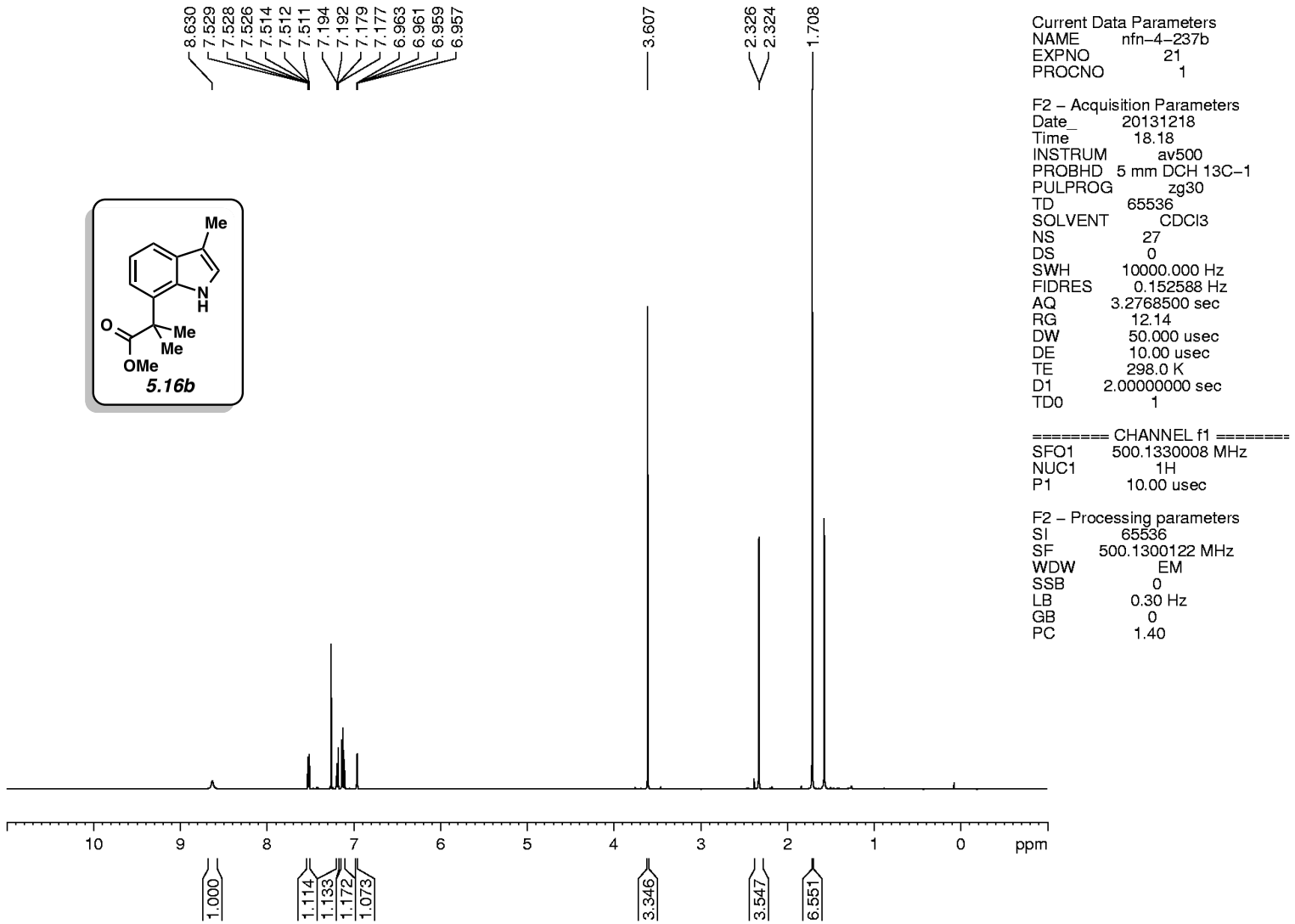

Figure 5.12. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.16b**.

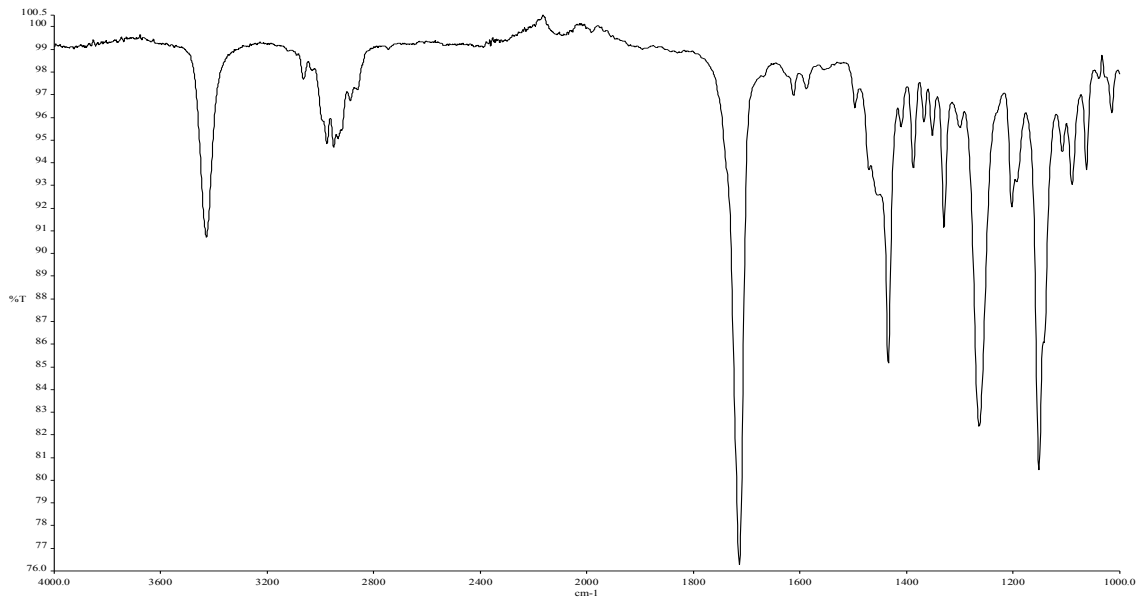

Figure 5.13. Infrared spectrum of compound **5.16b**.

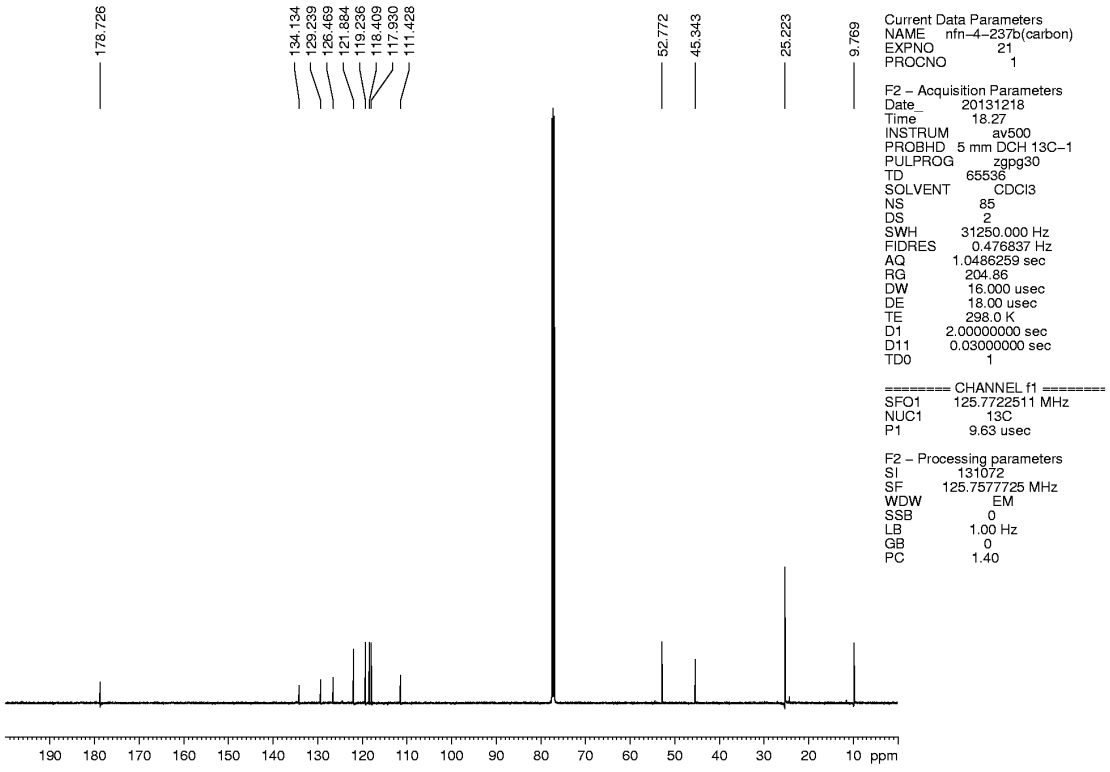

Figure 5.14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.16b**.

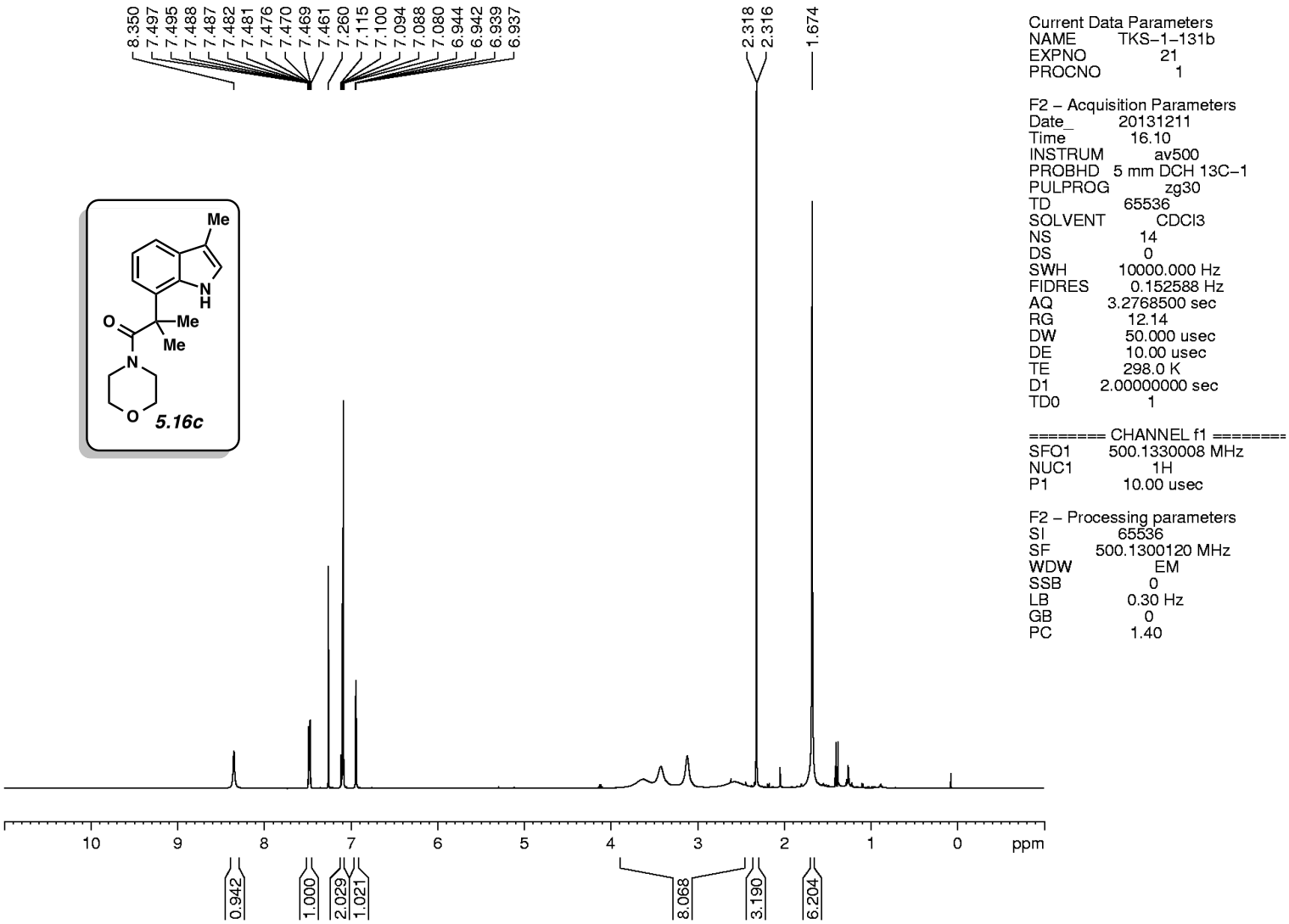

Figure 5.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.16c**.

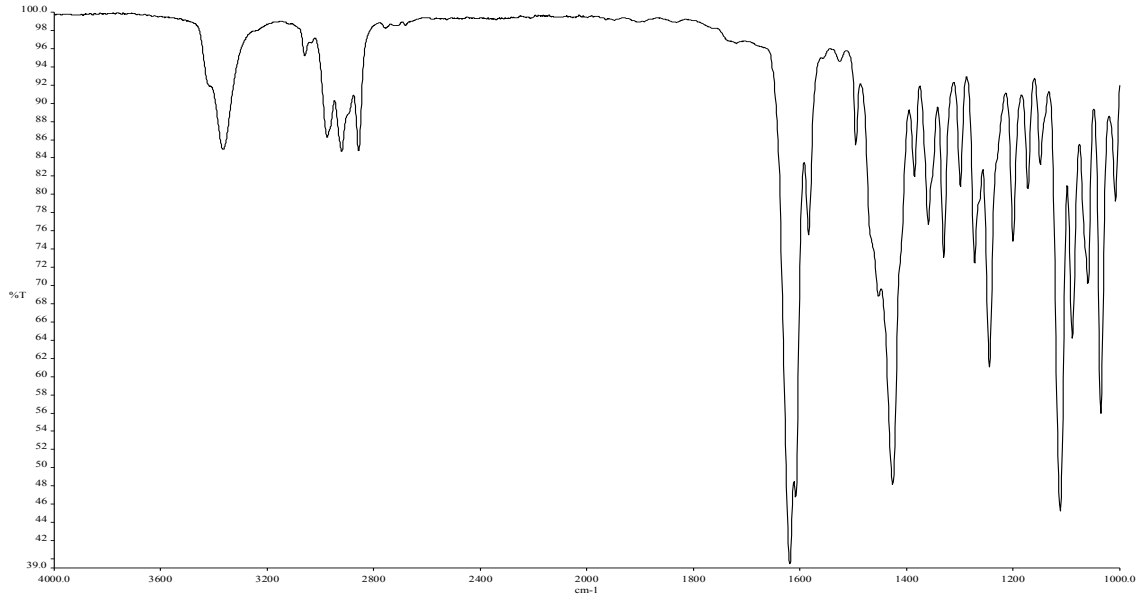

Figure 5.16. Infrared spectrum of compound **5.16c**.

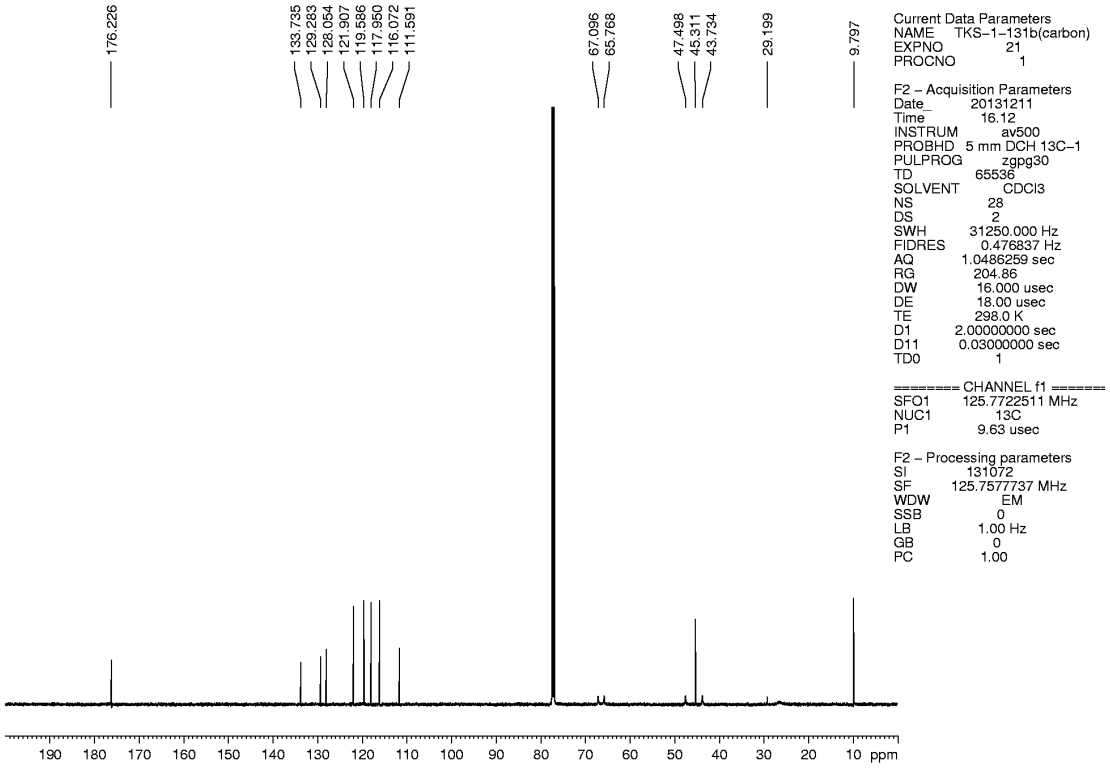

Figure 5.17. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.16c**.

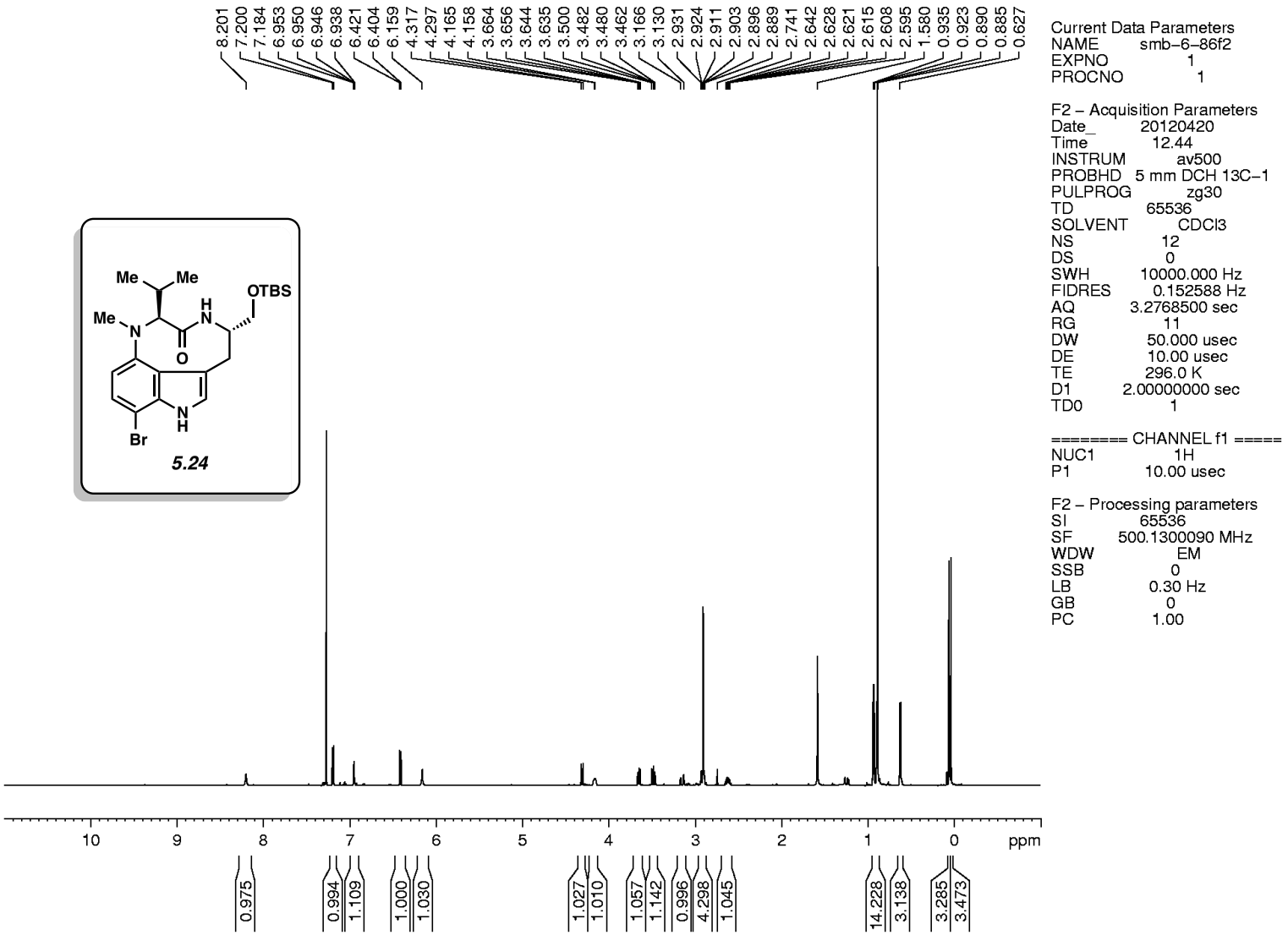

Figure 5.18. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.24**.

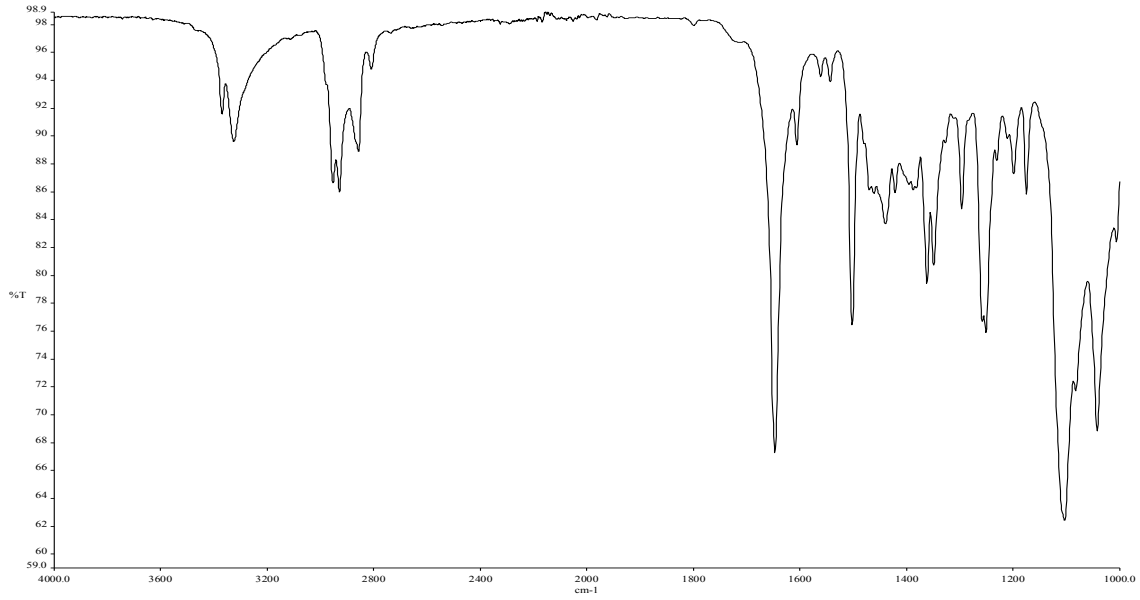

Figure 5.19. Infrared spectrum of compound **5.24**.

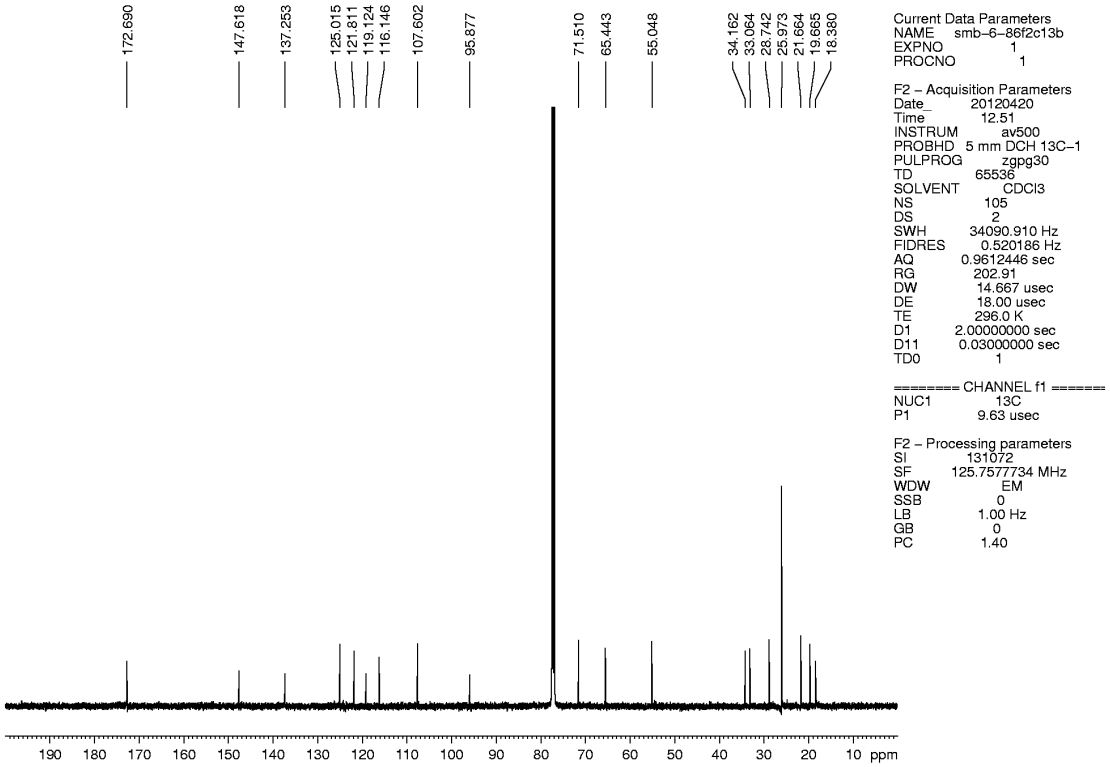

Figure 5.20. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.24**.

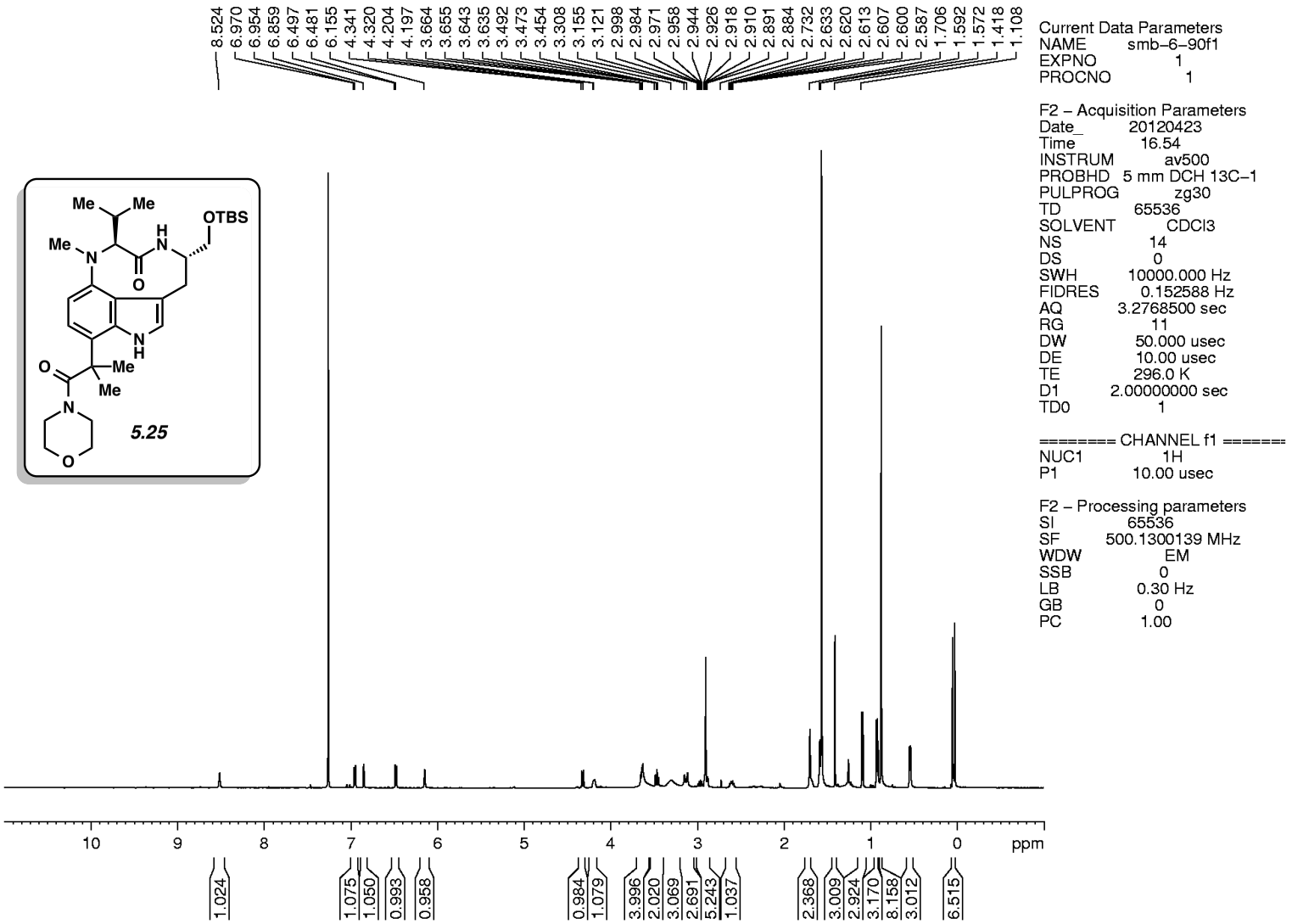

Figure 5.21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.25**.

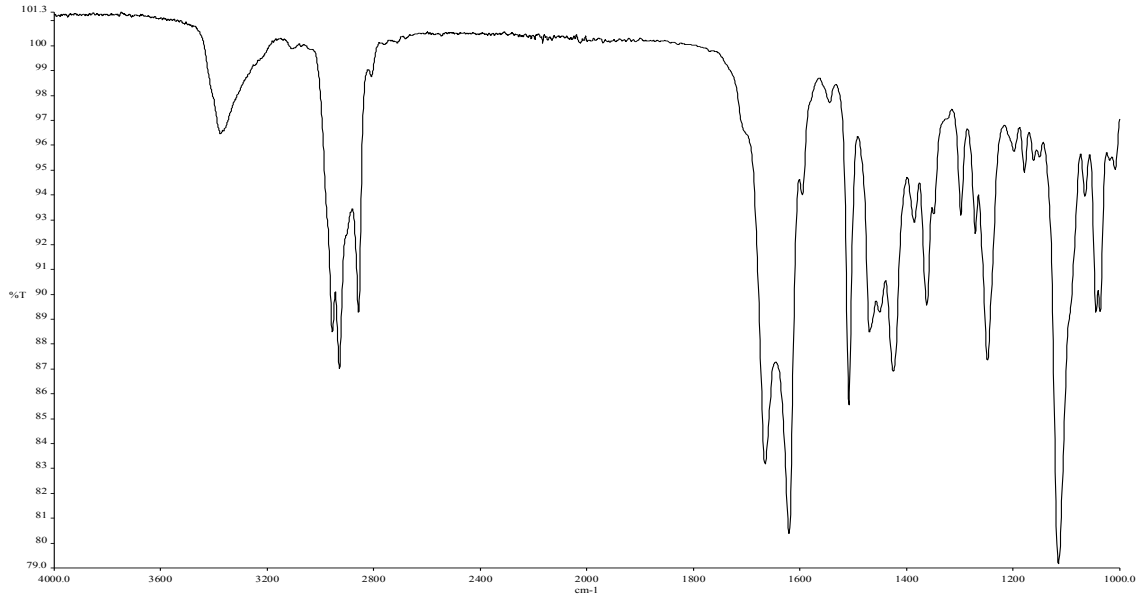

Figure 5.22. Infrared spectrum of compound **5.25**.

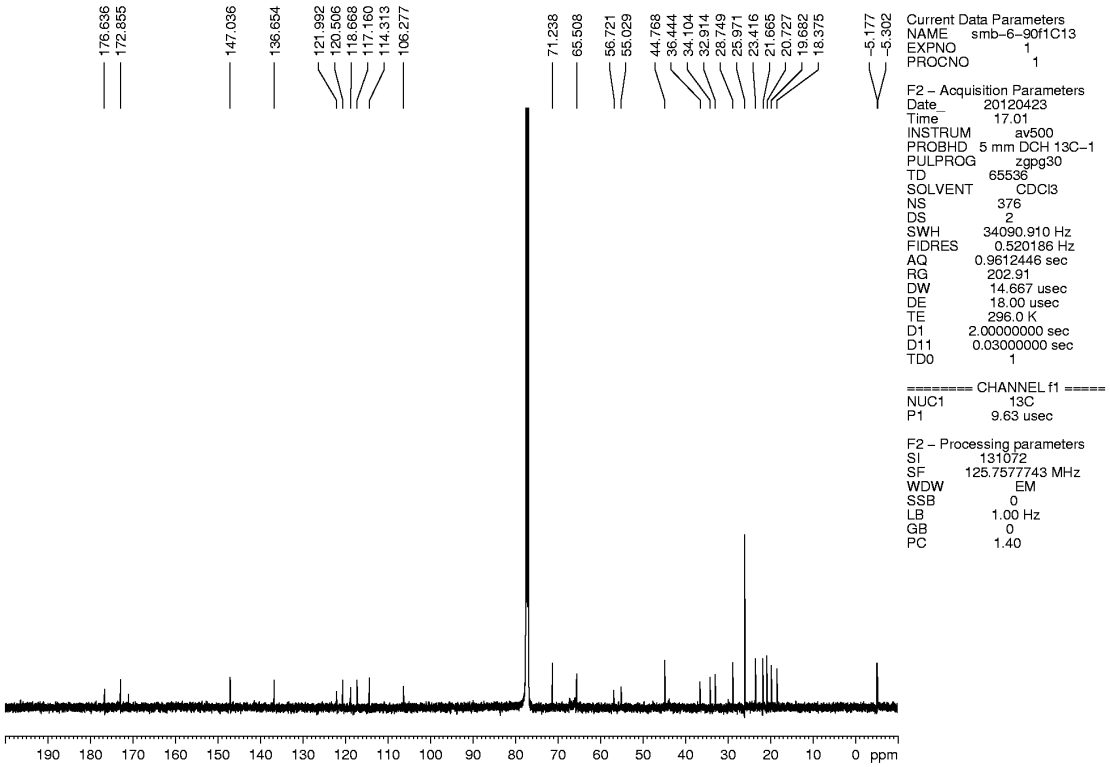

Figure 5.23. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.25**.

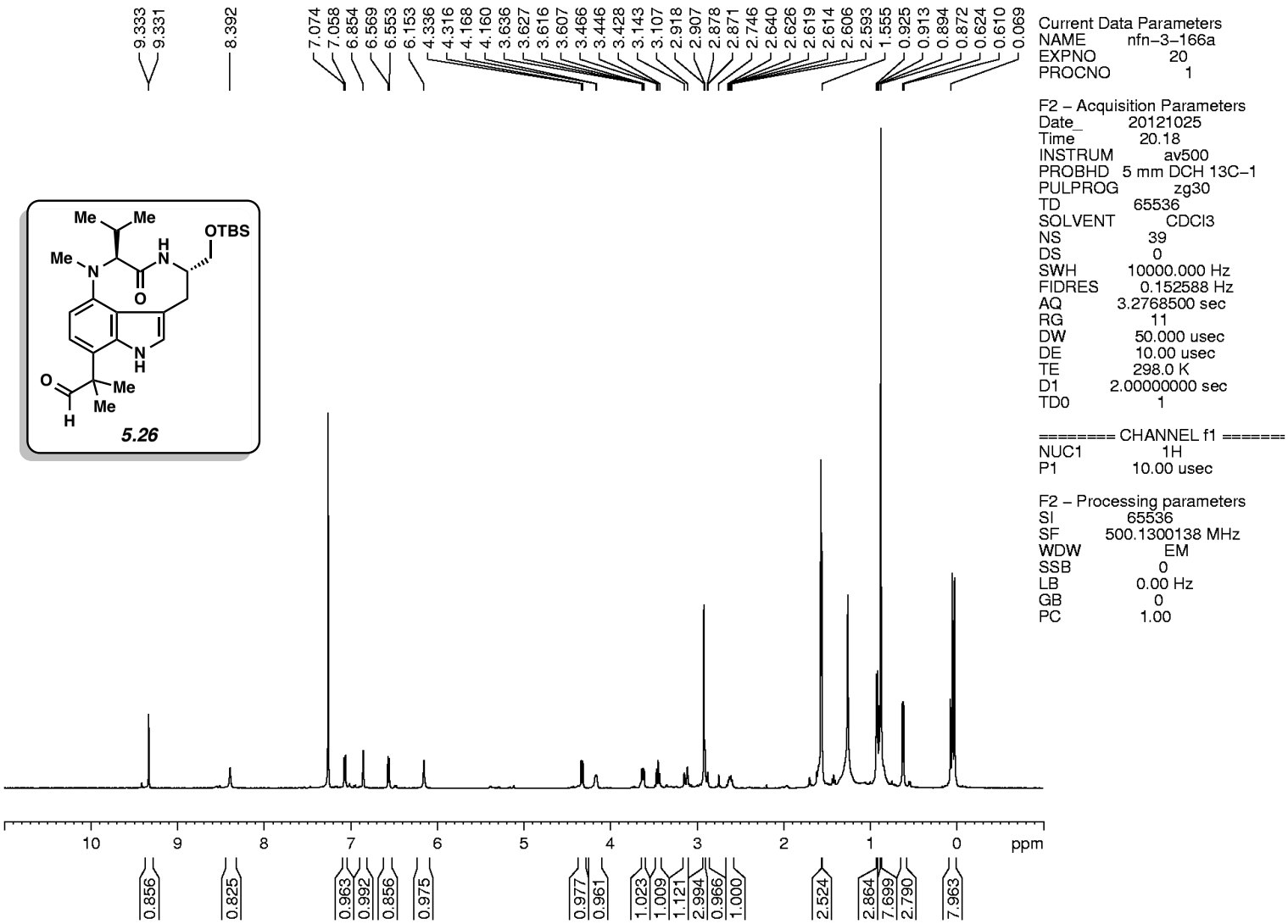

Figure 5.24. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.26**.

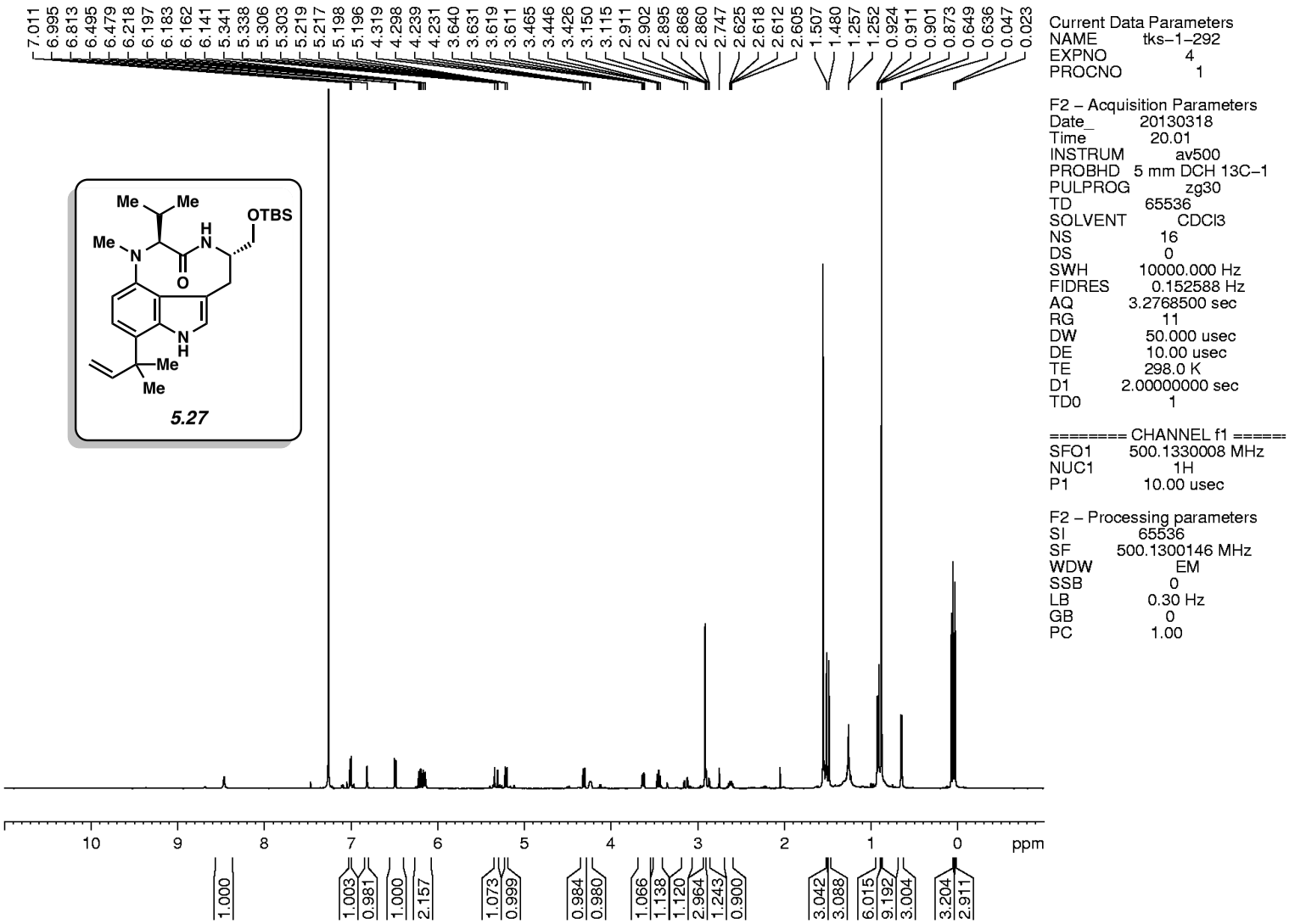

Figure 5.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.27**.

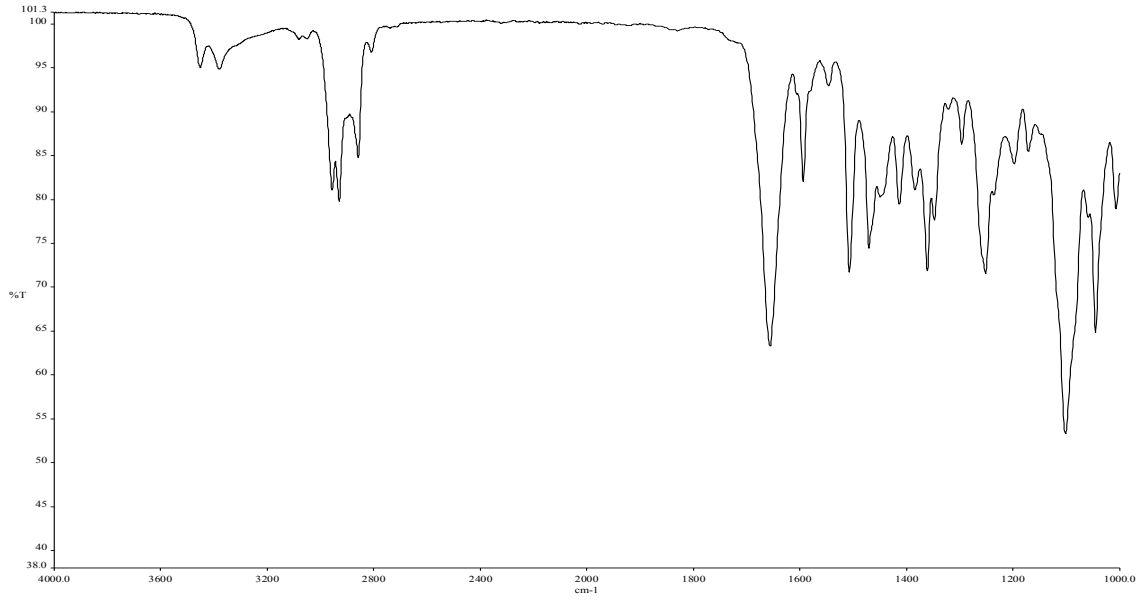

Figure 5.26. Infrared spectrum of compound **5.27**.

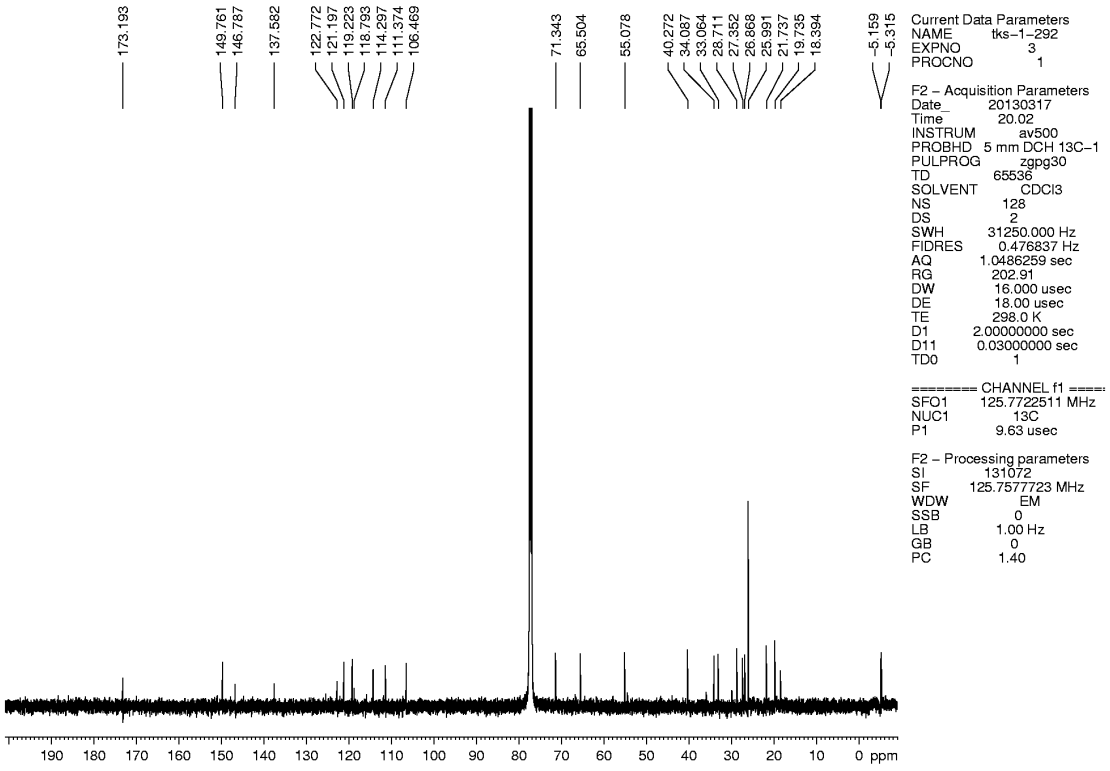

Figure 5.27. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.27**.

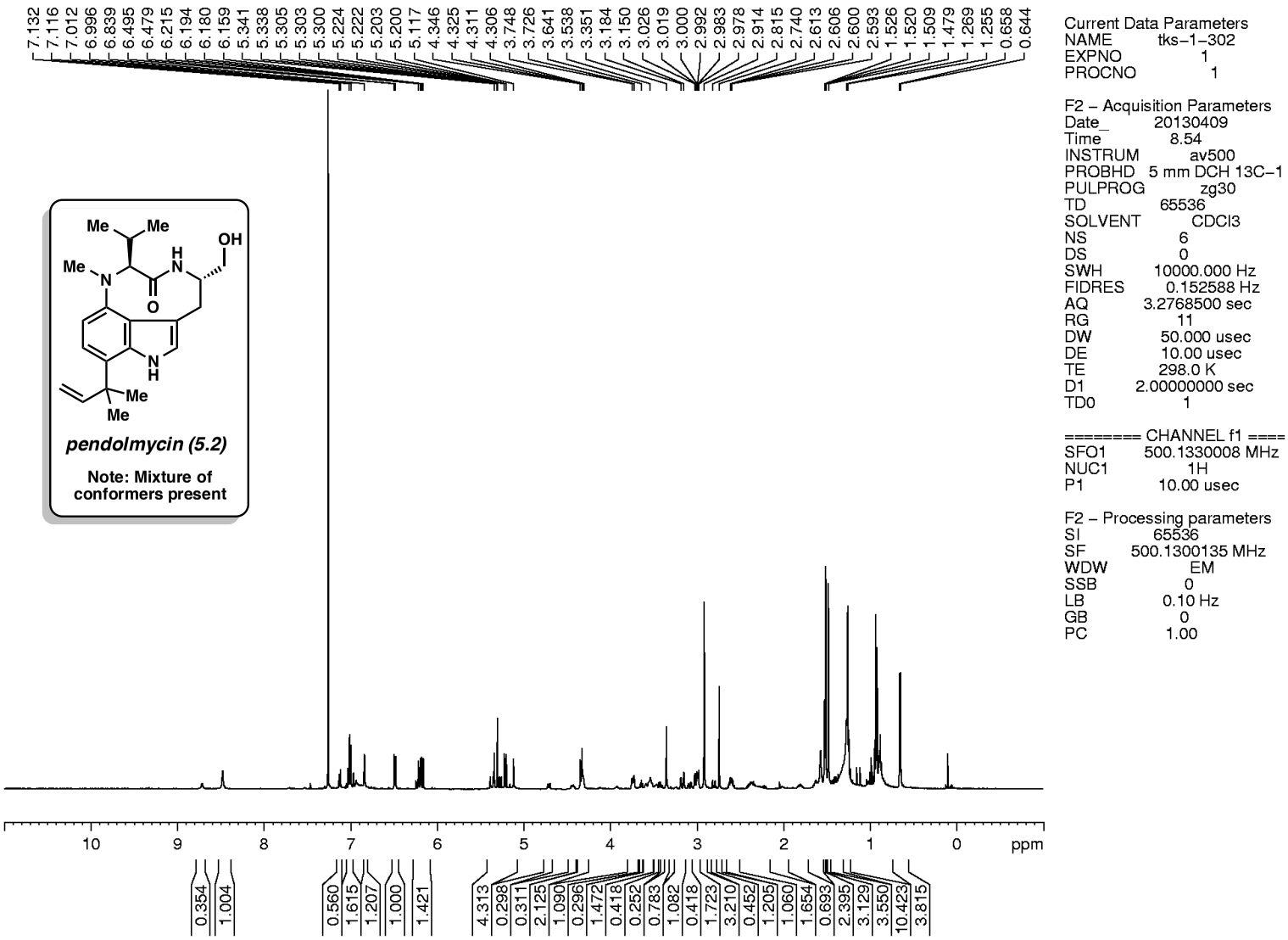

Figure 5.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.2**.

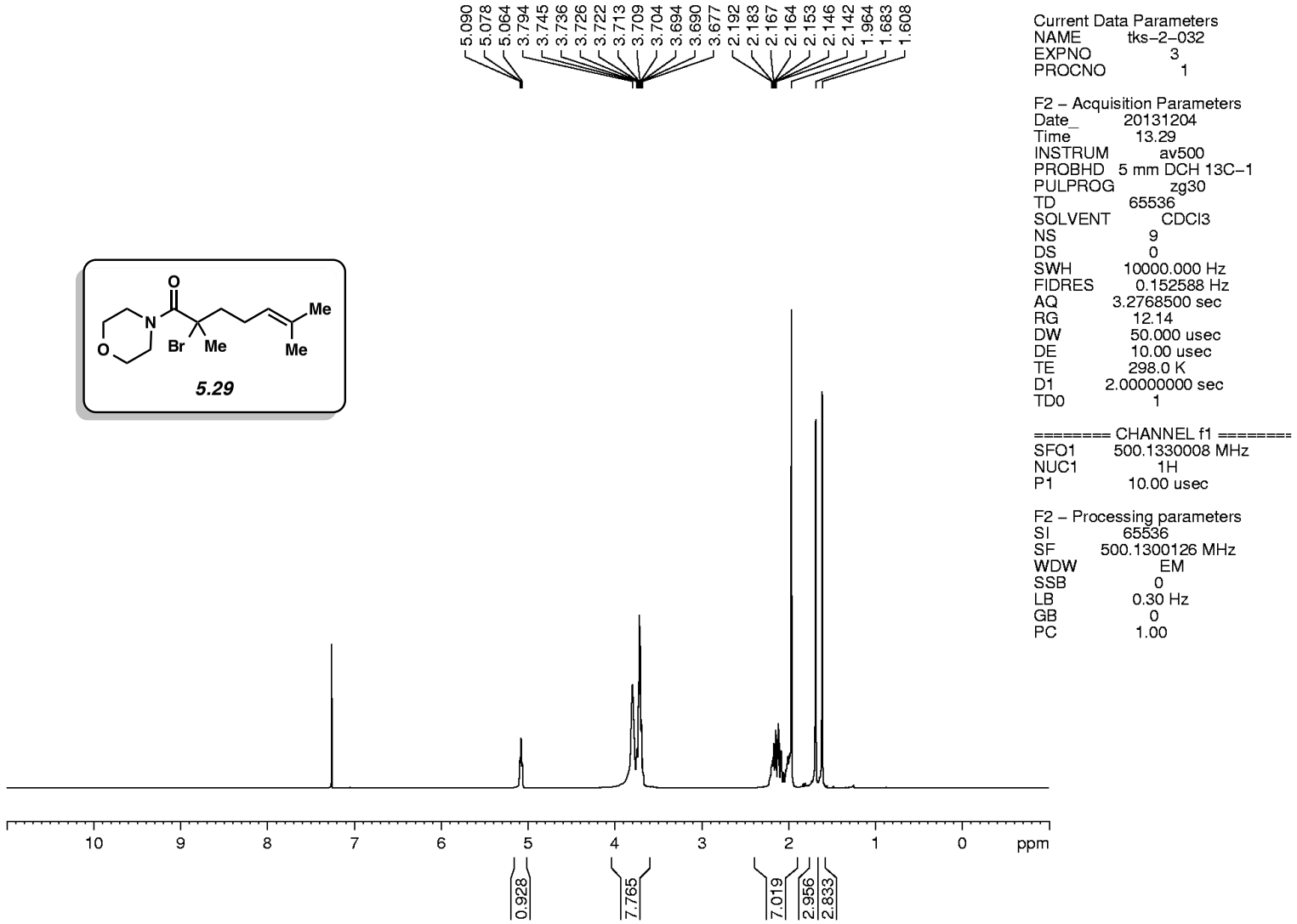

Figure 5.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.29**.

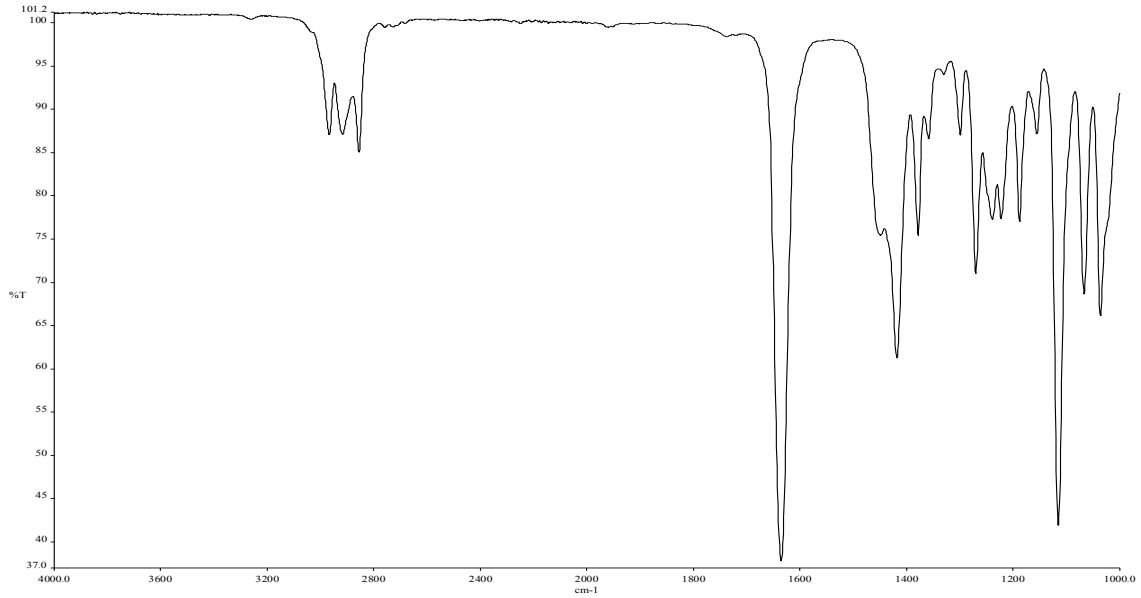

Figure 5.30. Infrared spectrum of compound **5.29**.

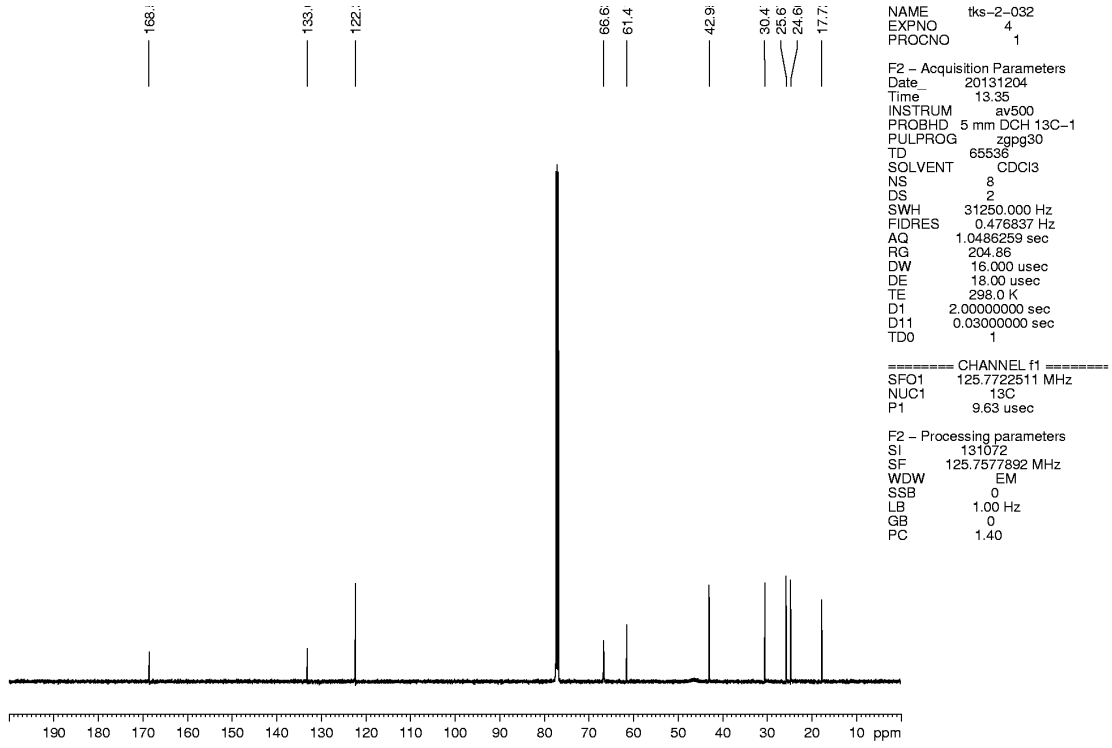

Figure 5.31. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.29**.

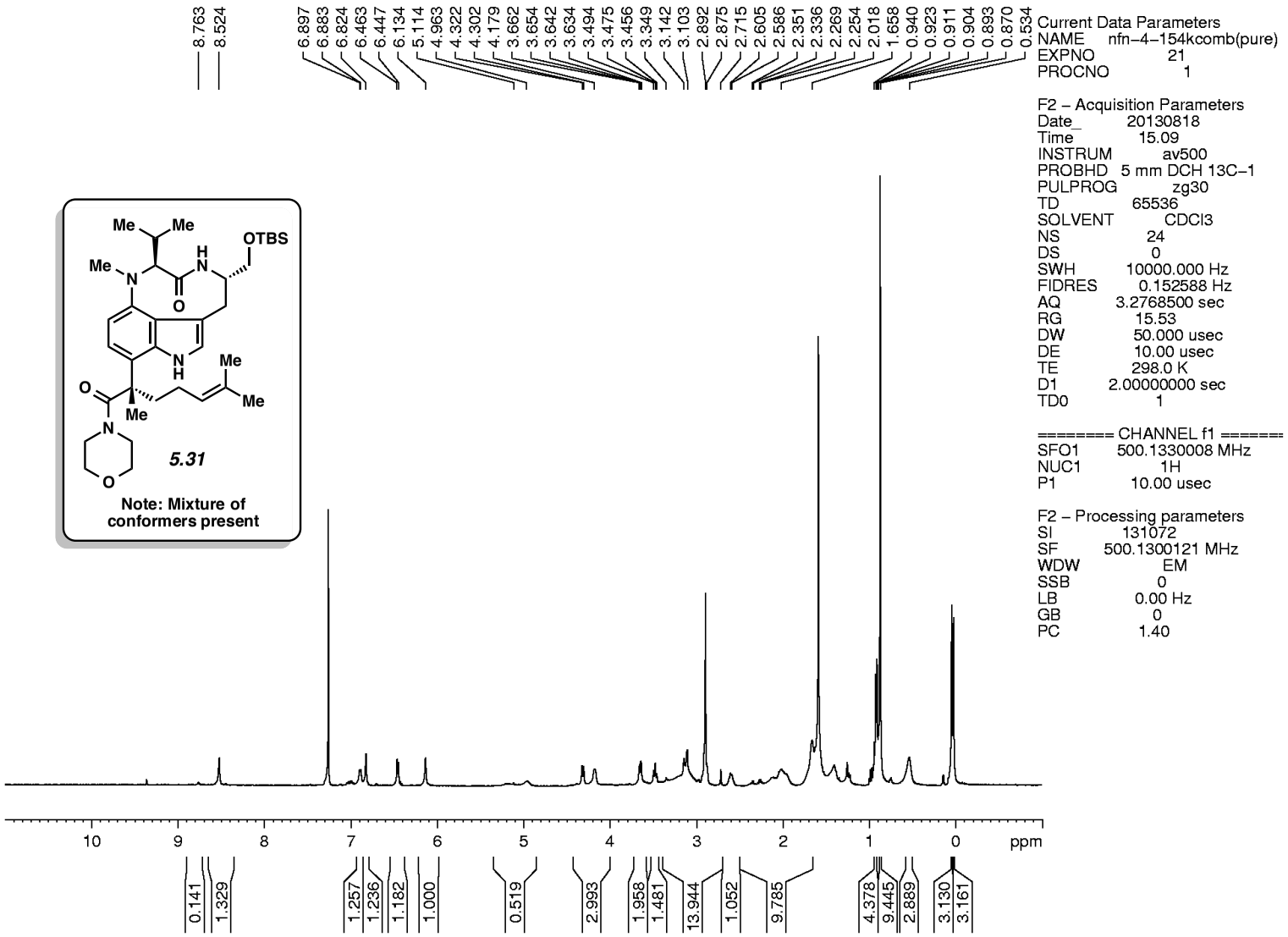

Figure 5.32. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.31**.

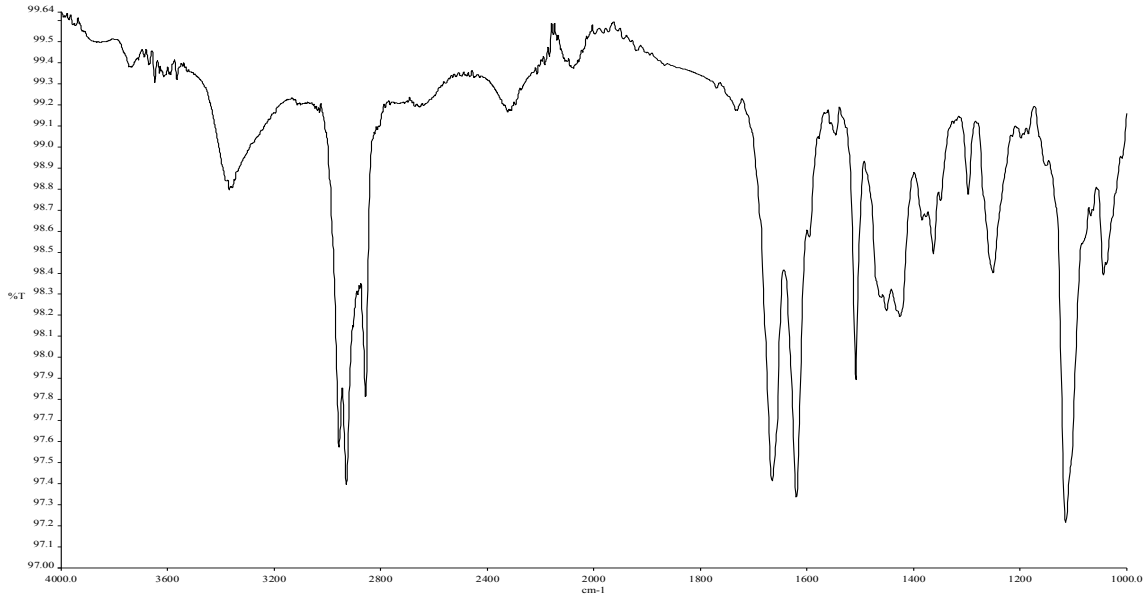

Figure 5.33. Infrared spectrum of compound **5.31**.

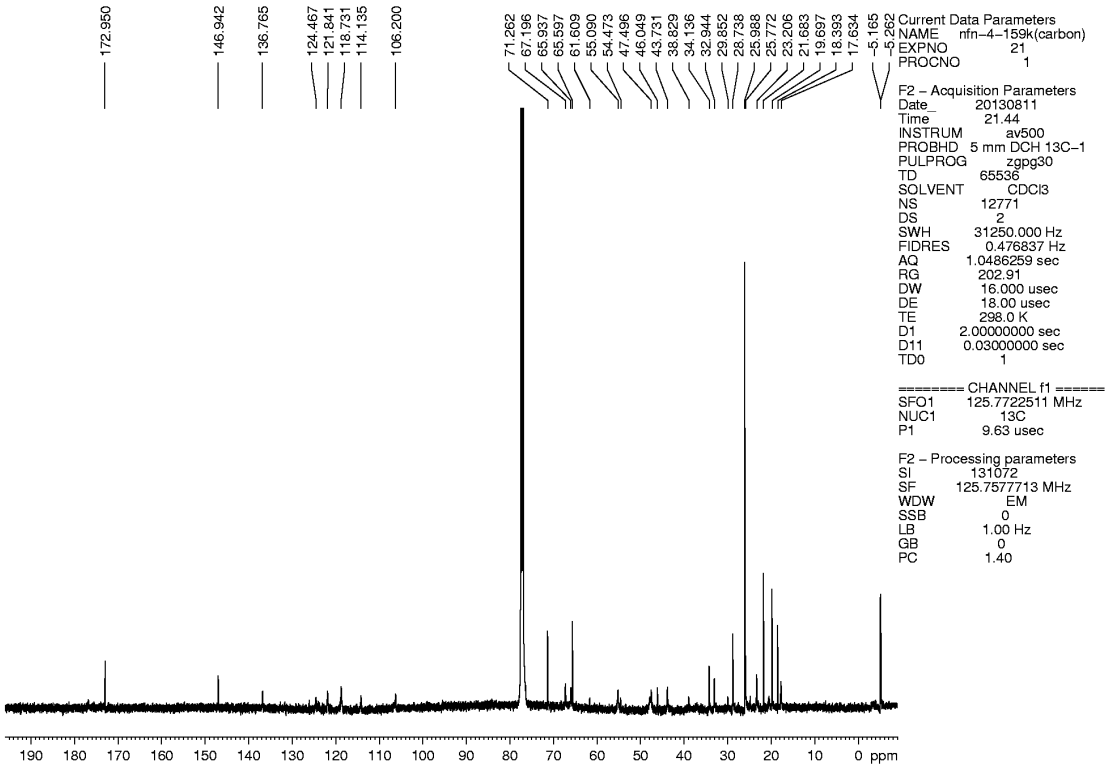

Figure 5.34. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.31**.

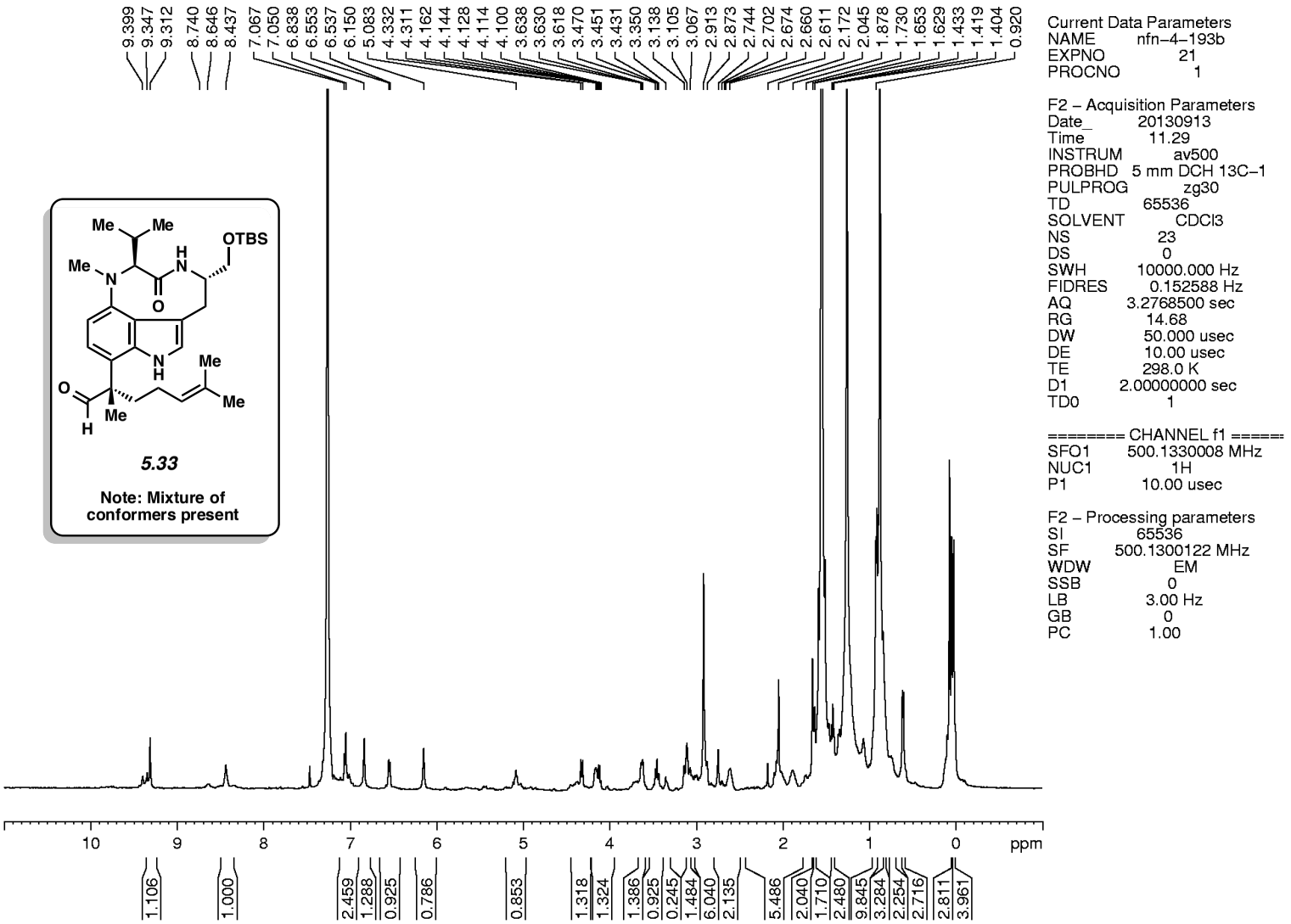

Figure 5.35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.33**.

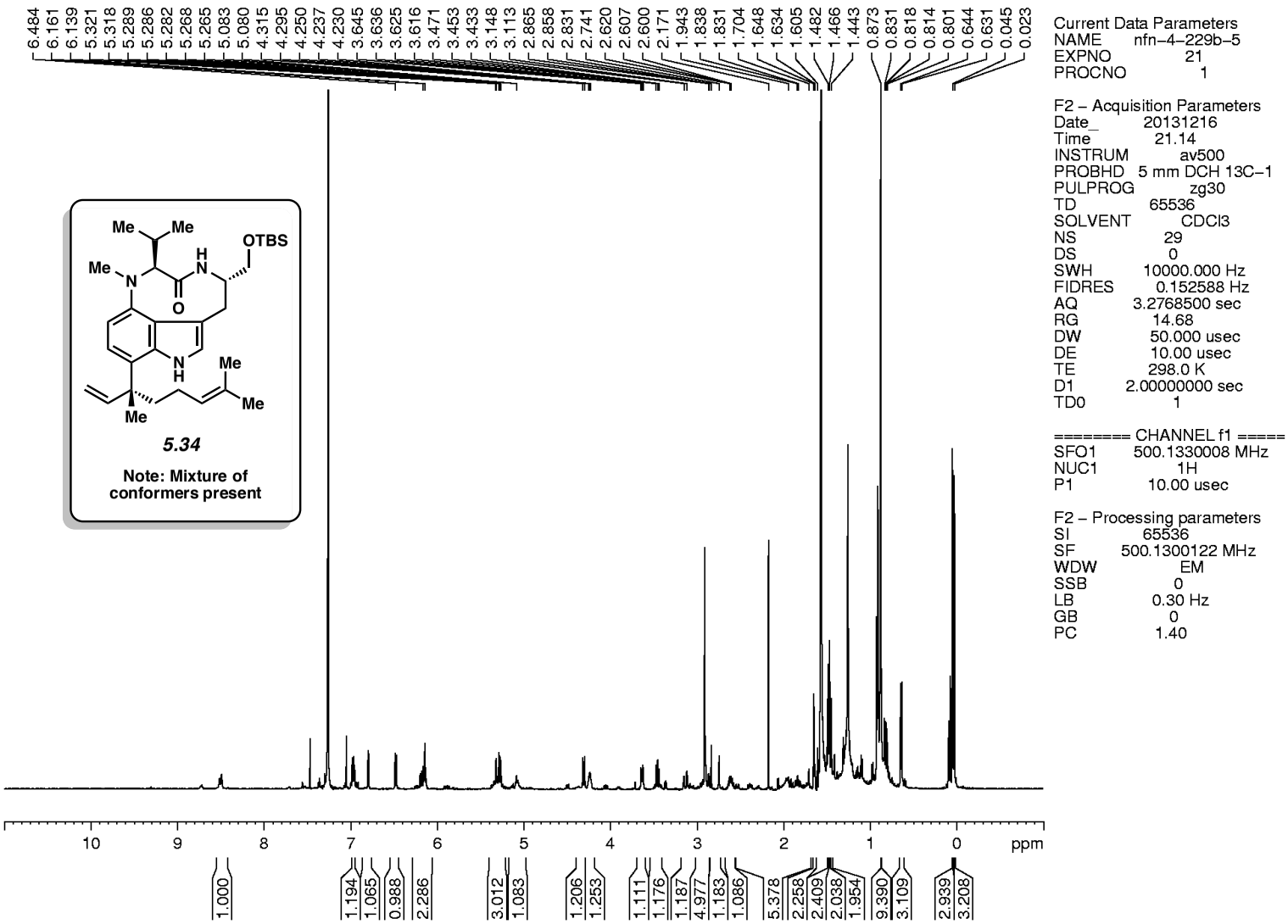

Figure 5.36. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.34**.

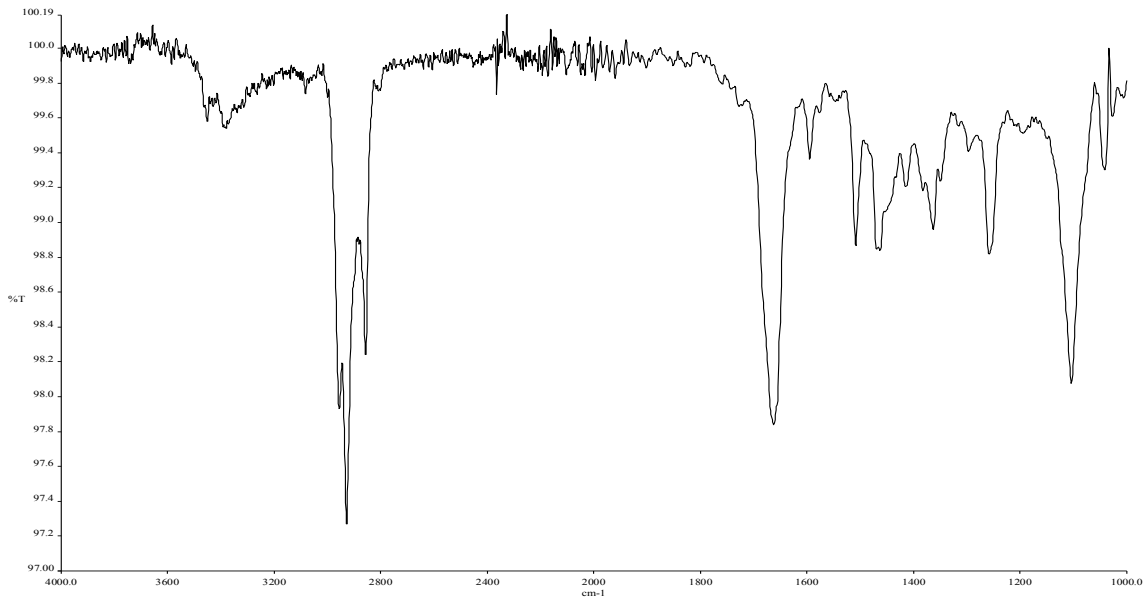

Figure 5.37. Infrared spectrum of compound **5.34**.

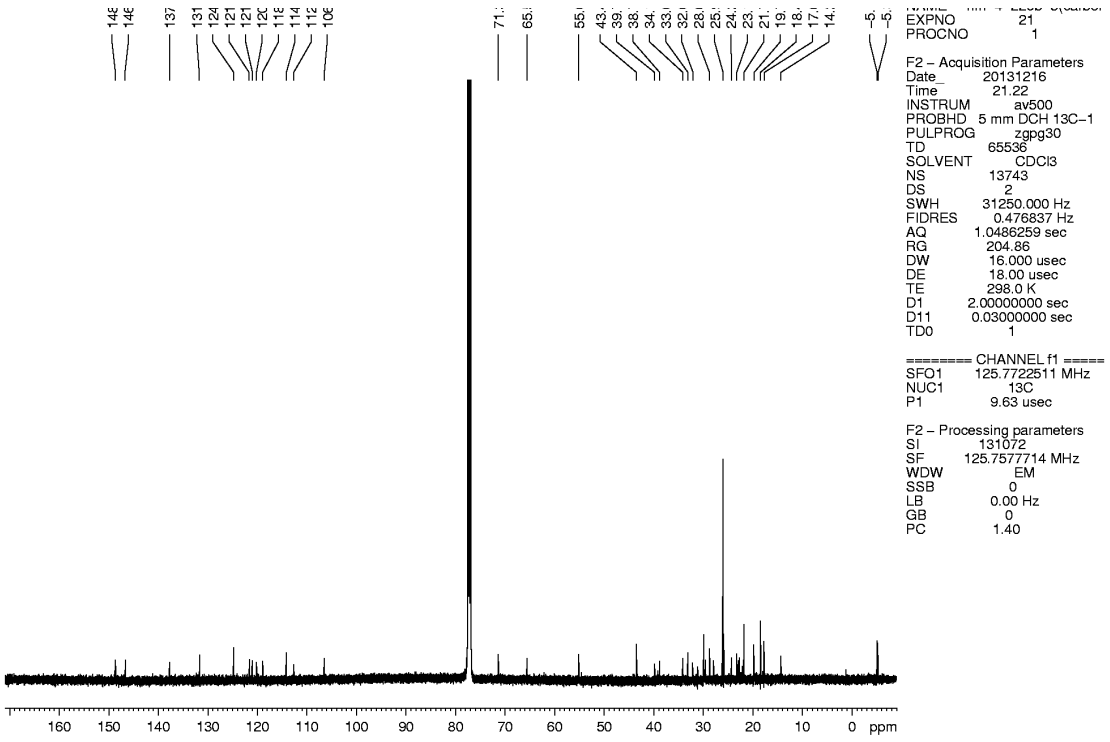

Figure 5.38. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.34**.

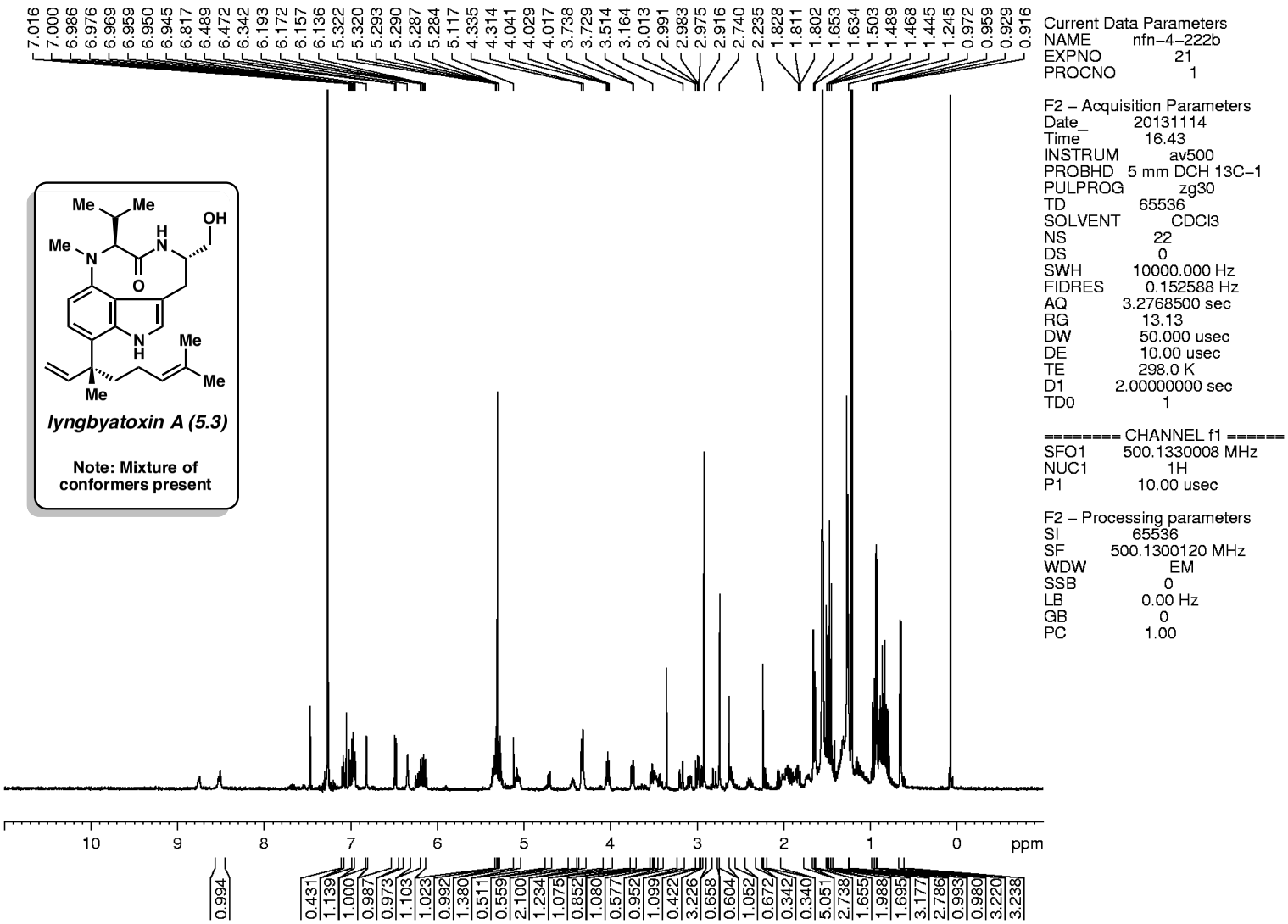

Figure 5.39. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.3**.

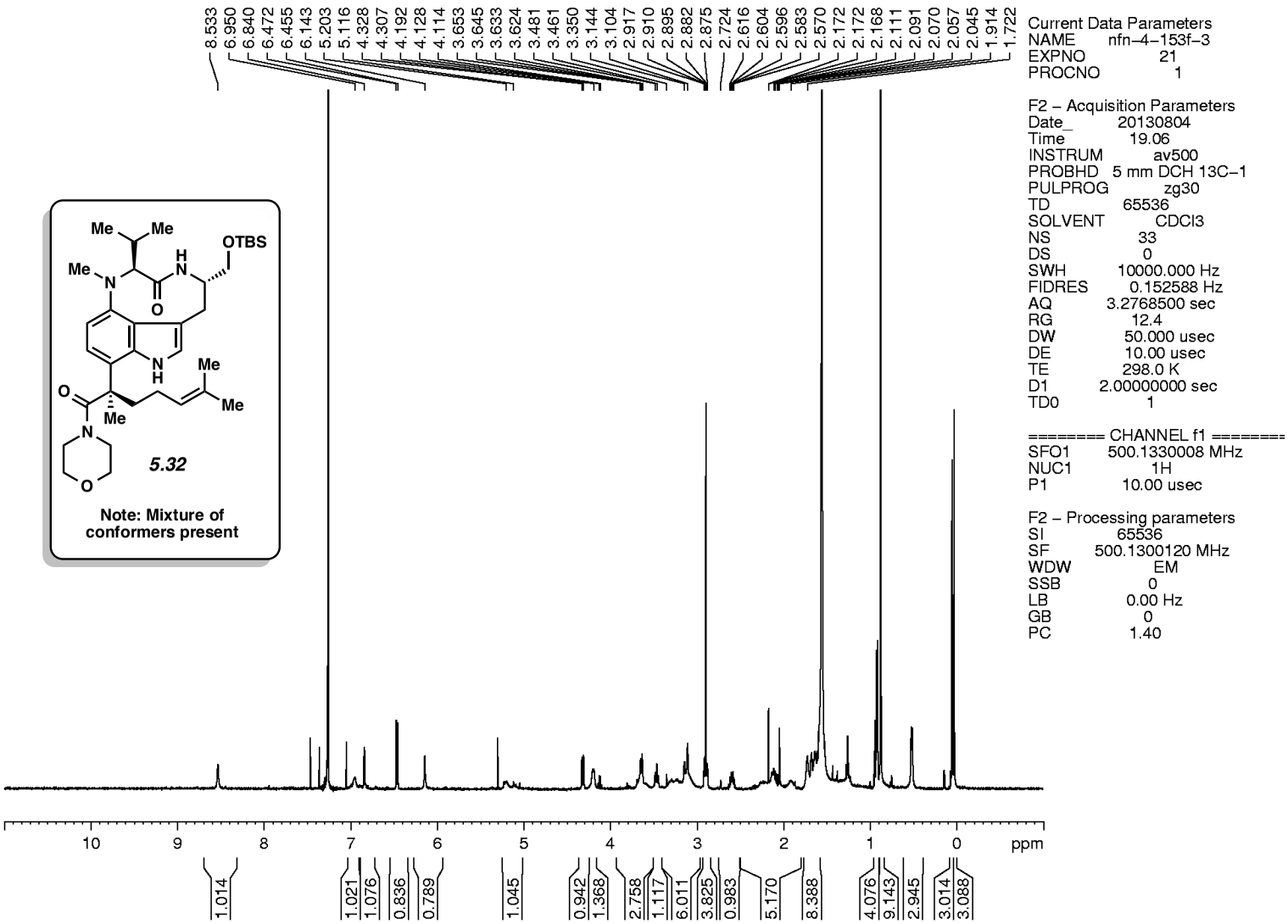

Figure 5.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.32**.

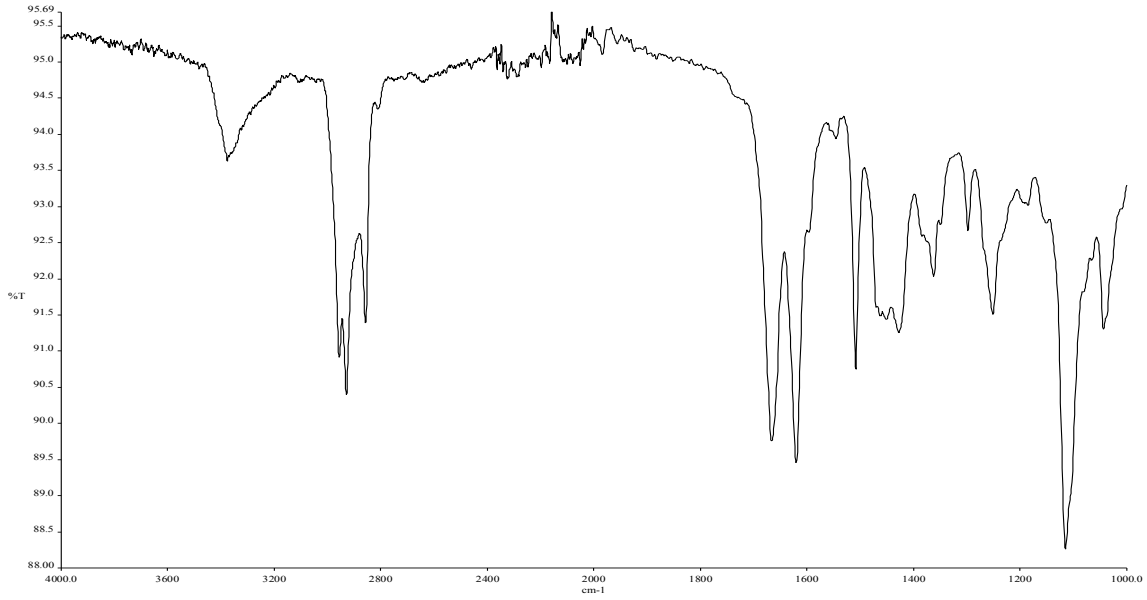

Figure 5.41. Infrared spectrum of compound **5.32**.

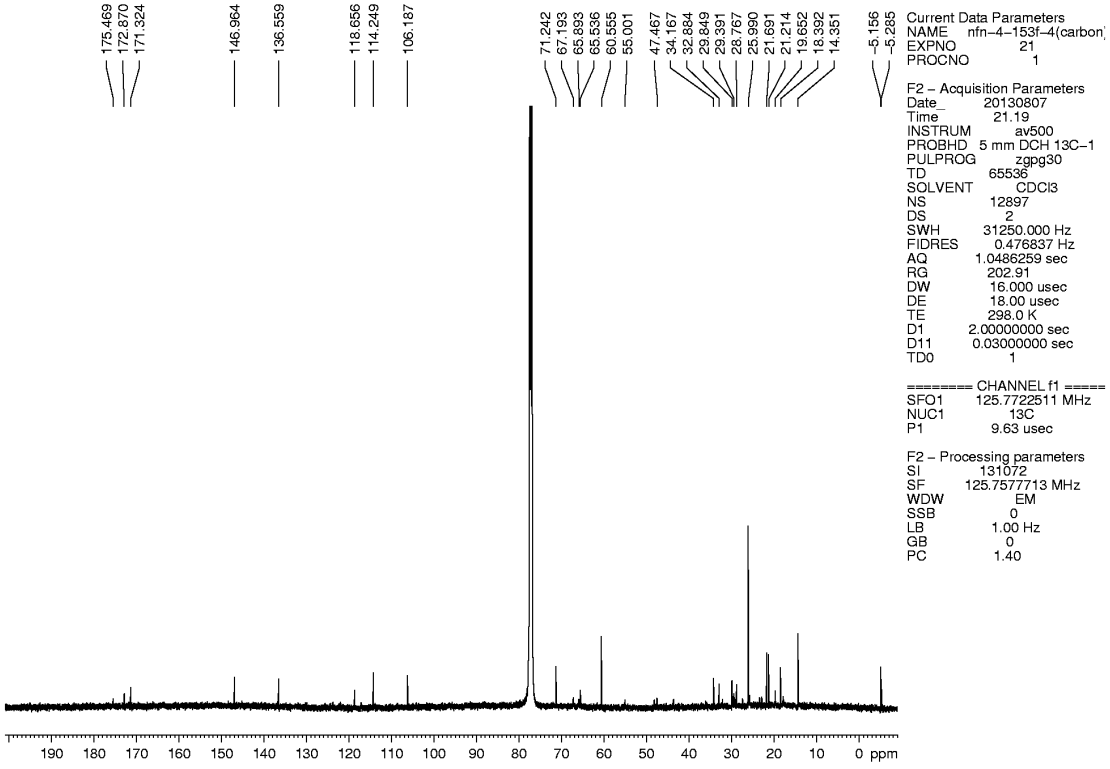

Figure 5.42. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.32**.

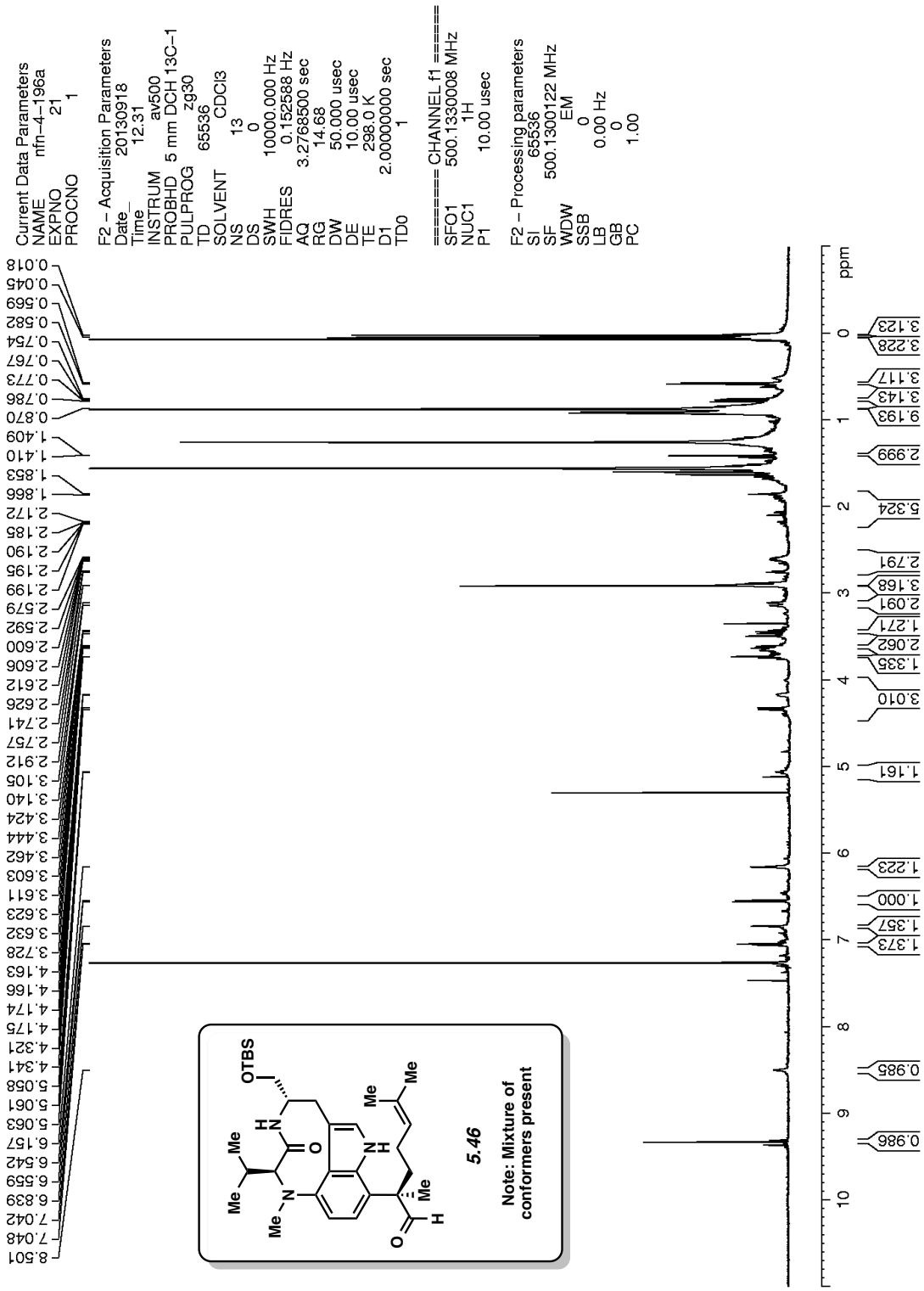

Figure 5.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.46**.

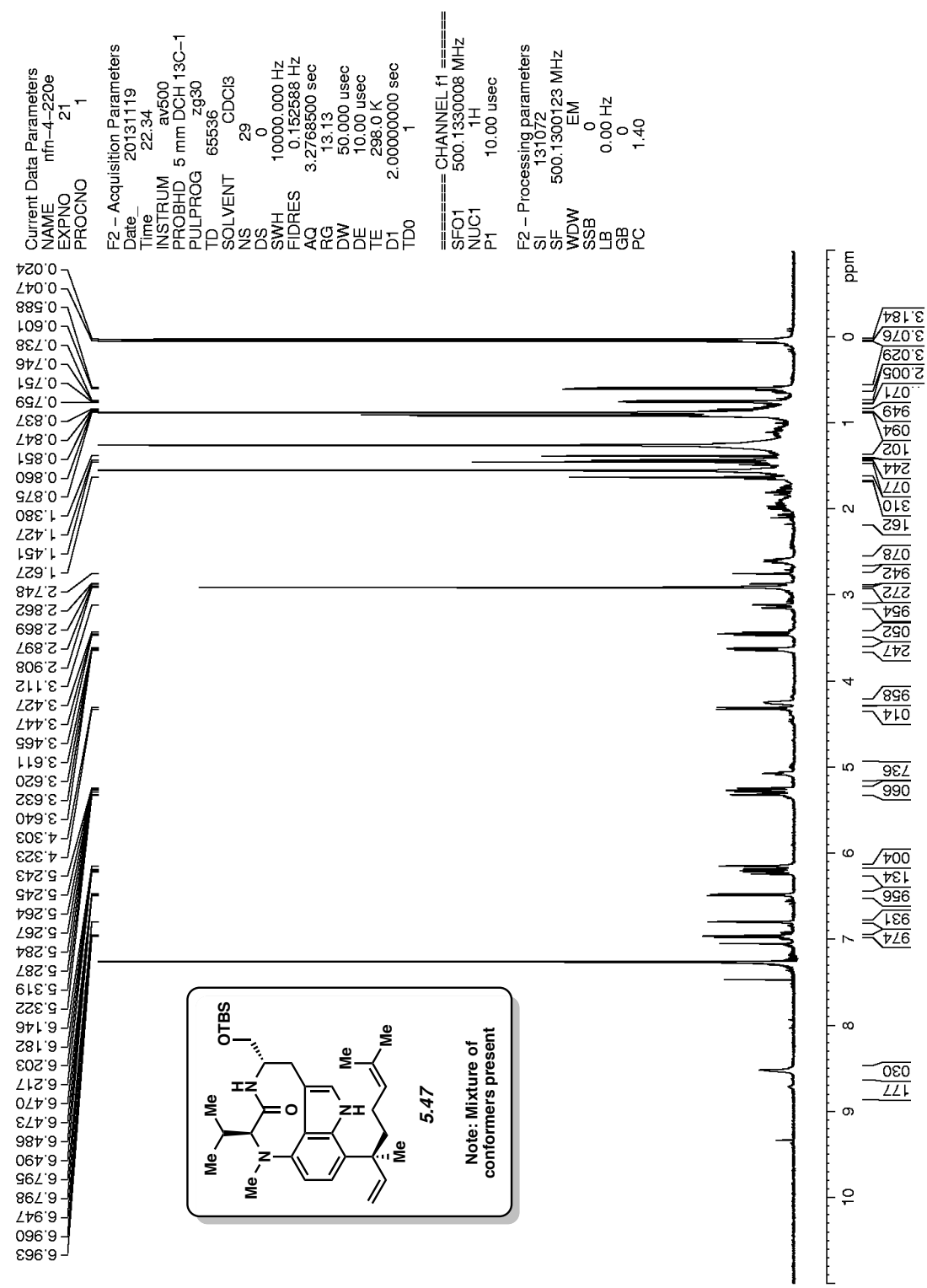

Figure 5.44. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.47**.

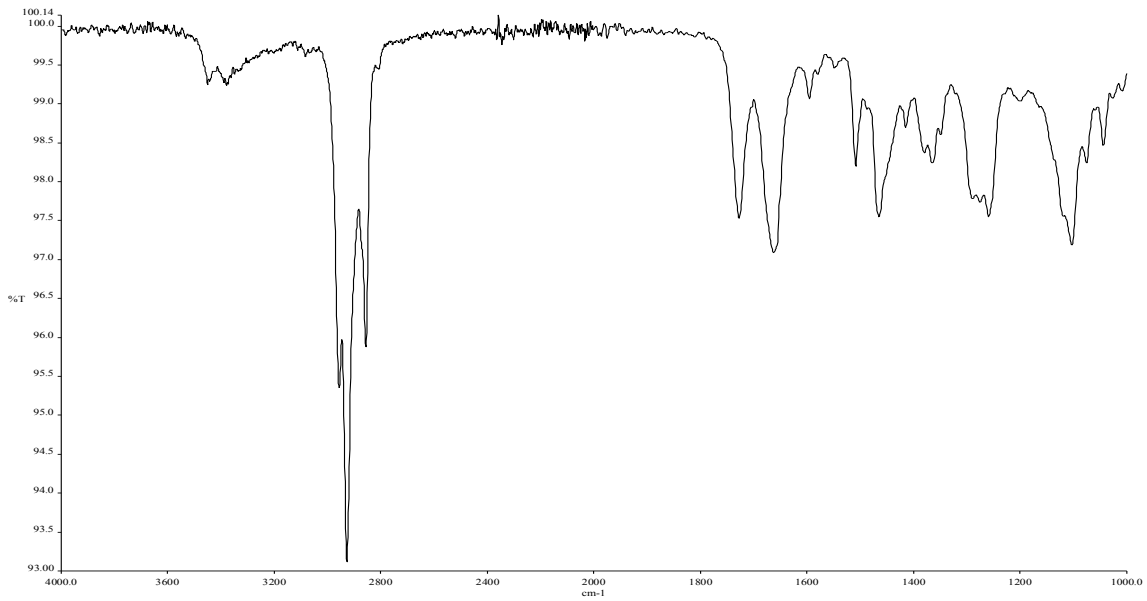

Figure 5.45. Infrared spectrum of compound **5.47**.

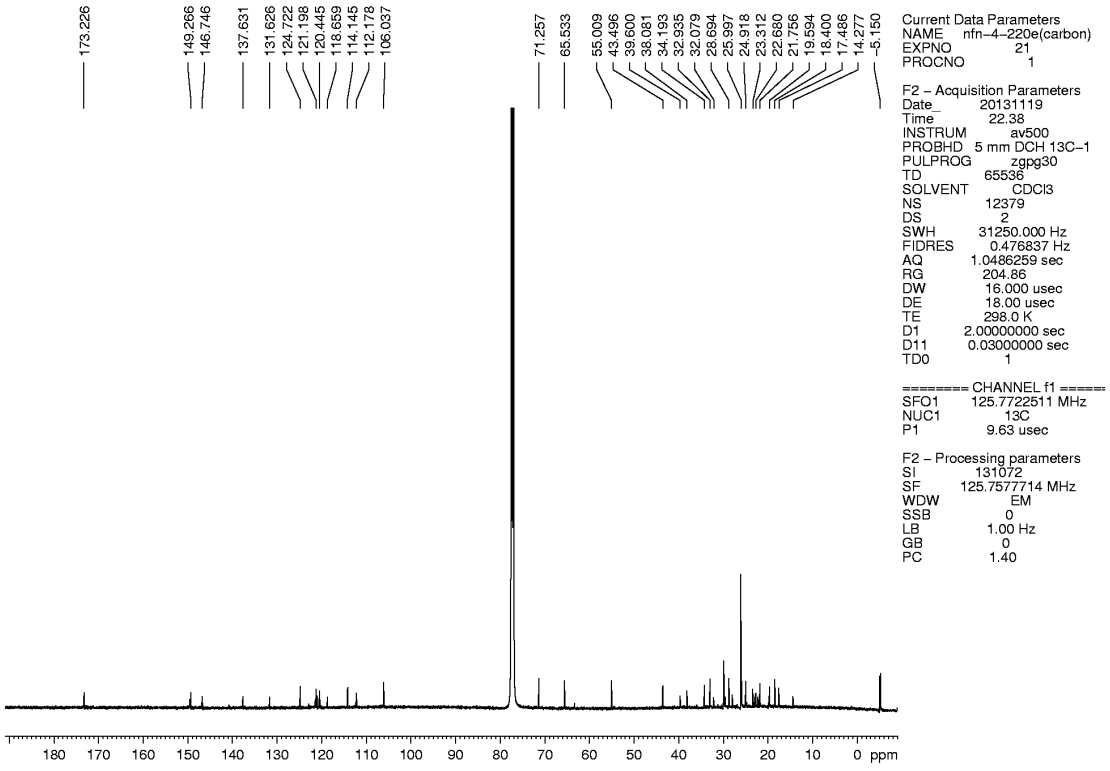

Figure 5.46. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5.47**.

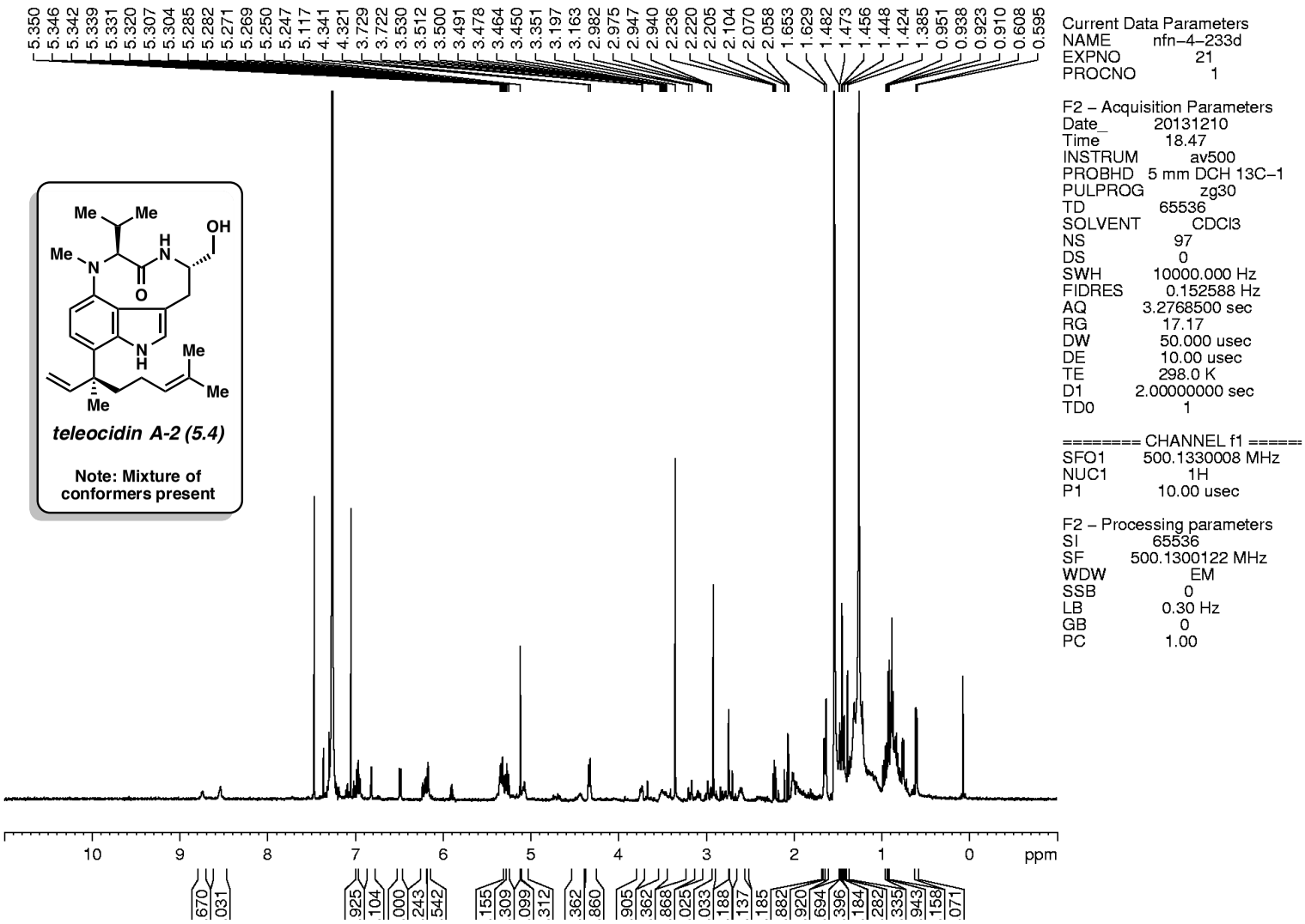

Figure 5.47. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.4**.