A base modulated synthesis of indoles and quinolines, an expedient synthesis of salviadione, and chemoselective couplings en route to indoles and pyrroloindoles

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A Base Modulated Synthesis of Indoles and Quinolines, An Expedient
Synthesis of Salviadione, and Chemoselective Couplings en route to
Indoles and Pyrroloindoles

Matthew Marshall Cummings

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in

Chemistry

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pyrroloindole

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ABSTRACT

A Base Modulated Synthesis of Indoles and Quinolines, An Expedient Synthesis of Salviadione, and Chemoselective Couplings en route to Indoles and Pyrroloindoles

Matthew Marshall Cummings

Palladium-catalyzed reductive N-heteroannulation of ortho-nitrostyrenes has become a synthetically useful method for the construction of indoles and indole-based heterocycles. Söderberg’s elaboration of this methodology has been utilized in the synthesis of indoles and quinolines from a common precursor. The same protocol has also been employed in the synthesis of the indole alkaloid Salviadione. A systematic investigation of chemoselectivity in Kosugi-Migita-Stille coupling reactions provided the basis for the synthesis of isomeric pyrroloindoles through palladium-catalyzed reductive double N-heteroannulation of dinitro-dialkenyl benzenes.
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Table of Contents

Title Page i
Abstract ii
Acknowledgements iii
Table of Contents iv
List of Figures viii
List of Schemes xvii
List of Tables xxiv

Chapter 1

Introduction to Indole, History of Indole, and Historical Routes to the Indole Core

1.1 Indole Background and Notable Indoles 2
1.2 Classical Routes to the Indole Core 6
1.3 Transition Metal Catalyzed Indole Synthesis 8
1.4 Indole Synthesis via Reductive Cyclization 10
1.5 Indole Preparation via Palladium-Catalyzed Reductive Heterocyclization 12

Chapter 2

A Base Modulated Synthesis of Indoles and Quinolines

2.1 Introduction 21
2.2 Results and Discussion 22
2.3 Conclusions 33
Chapter 3

An Expedient Synthesis of Salviadione

3.1 Salviadione Background 35
3.2 Expedient Synthesis of Salviadione 35
   3.2.1 Retrosynthetic Analysis 36
   3.2.2 Results and Discussion 37
3.3 Conclusions 43

Chapter 4

Investigation of Chemoselectivity in Kosugi-Migita-Stille Coupling Reactions

4.1 Kosugi-Migita-Stille Reaction Background 46
4.2 Chemoselective Stille Coupling Reactions 46
4.3 Investigation of Nitro Effect in Stille Coupling Reactions 48
   4.3.1 Preparation of Isomeric Substrates 49
   4.3.2 Results and Discussion 53
4.3 Conclusions 64

Chapter 5

Preparation of Pyrroloindoles via Palladium-Catalyzed Reductive Double N-Heterocyclization

5.1 Pyrroloindole Introduction and Background 67
5.2 Historical Routes to Pyrroloindoles of Type I 69
5.3 Pyrroloindole Preparation using Reductive Double N-Heterocyclization 73
5.3.1 Retrosynthetic Analysis
5.3.2 Banini Route to Pyrroloindoles
5.3.3 Synthesis of Symmetrical Pyrroloindoles
5.4 Synthesis of Non-Symmetrical Pyrroloindoles
5.4.1 Preparation of Cyclization Precursors
5.4.1.1 2,4-Dinitro-1,5-Dialkenyl Benzene Isomer
5.4.1.2 2,5-Dinitro-1,4-Dialkenyl Benzene Isomer
5.4.1.3 2,3-Dinitro-1,4-Dialkenyl Benzene Isomer
5.4.1.4 2,4-Dinitro-1,3-Dialkenyl Benzene Isomer
5.4.1.5 1,4-Dinitro-2,3-Dialkenyl Benzene Isomer
5.4.2 Pyrroloindole Synthesis via Reductive Double N-Heterocyclization
5.5 Conclusions

Chapter 6

Synthesis of Functionalized Aromatics

6.1 Brominations of 2-Nitrobenzaldehyde
6.1.1 Introduction
6.1.2 Results and Discussion
6.1.3 Conclusions
6.2 Synthesis of Functionalized Indoles
6.2.1 Synthesis of 6-Methyl-Nitroindoles
6.2.2 Synthesis of 5-Methoxy-Nitroindoles
6.2.3 Conclusions
Chapter 7

Supporting Information: Experimental Procedures

7.1 Supporting Information for Chapter 2: Indole/Quinoline 133
7.2 Supporting Information for Chapter 3: Salviadione 136
7.3 Supporting Information for Chapter 4: Chemoselective Coupling 145
7.4 Supporting Information for Chapter 5: Pyrroloindoles 166
7.5 Supporting Information for Chapter 6.1: 2-Nitrobenzaldehyde Brominations 182
7.6 Supporting Information for Chapter 6.2: Functionalized Indoles 187

References and Notes

Appendix

$^1$H and $^{13}$C NMR Spectra

- $^1$H and $^{13}$C NMR for Chapter 2: Indole/Quinoline 209
- $^1$H and $^{13}$C NMR for Chapter 3: Salviadione 218
- $^1$H and $^{13}$C NMR for Chapter 4: Chemoselective Coupling 232
- $^1$H and $^{13}$C NMR for Chapter 5: Pyrroloindoles 284
- $^1$H and $^{13}$C NMR for Chapter 6.1: Bromination 330
- $^1$H and $^{13}$C NMR for Chapter 6.2: Functionalized Indoles 340
List of Figures

Figure 1: Structure and Numbering of Indole 2
Figure 2: Structures of L-Tryptophan, Serotonin, and Melatonin 4
Figure 3: Structures of Dragmacidin, Eudistomin K, and Flustramine D 4
Figure 4: Structures of Sumatriptan, Tadalafil, Rizatriptan, and Fluvastatin 5
Figure 5: Structure and Atom Numbering of Salviadione 35
Figure 6: Types of Isomeric Pyrroloindoles 67
Figure 7: Physostigmine and Phenserine 67
Figure 8: CC-1065, Duocarmycin, and Yatakemycin 68
Figure 9: Isomeric Pyrroloindoles of Type I 69
Figure 10: Pyrroloindole Numbering 69
Figure 11: 2,4-Dinitro-1,5-Dialkenyl Benzene 79
Figure 12: Modified Work-up Procedure for Coupling of Phenol 84
Figure 13: 2,5-Dinitro-1,4-Dialkenyl Benzene 88
Figure 14: 2,3-Dinitro-1,4-Dialkenyl Benzene 93
Figure 15: 2,4-Dinitro-1,3-Dialkenyl Benzene 100
Figure 16: 1,4-Dinitro-2,3-Dialkenyl Benzene 106
Figure 17: $^1$H NMR of 3-Cyclohexyl-2-iodo-2-propenenitrile (110) 209
Figure 18: $^{13}$C NMR of 3-Cyclohexyl-2-iodo-2-propenenitrile (110) 210
Figure 19: $^1$H NMR of 3-Cyclohexyl-2-(nitrophenyl)-2-propenenitrile (111) 211
Figure 20: $^{13}$C NMR of 3-Cyclohexyl-2-(nitrophenyl)-2-propenenitrile (111) 212
Figure 21: $^1$H NMR of 3-Cyano-2-cyclohexylindole (112) 213
Figure 22: $^{13}$C NMR of 3-Cyano-2-cyclohexylindole (112) 214
Figure 23: $^1$H NMR of 3-cyano-2-(1-hydroxycyclohexyl)indole (113) 215

Figure 24: $^{13}$C NMR of 3-cyano-2-(1-hydroxycyclohexyl)indole (113) 216

Figure 25: $^1$H NMR of 5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (127) 217

Figure 26: $^{13}$C NMR of 5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (127) 218

Figure 27: $^1$H NMR of 10,10a-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthren-3(1$H,2H,9H$)-one (132) 219

Figure 28: $^{13}$C NMR of 10,10a-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthren-3(1$H,2H,9H$)-one (132) 220

Figure 29: $^1$H NMR of 10,10a-Dihydro-1,1-dimethyl-6-hydroxy-7-(1-methylethyl)-5-nitrophenanthren-3(1$H,2H,9H$)-one (125) 221

Figure 30: $^1$H NMR of 8$\alpha$,9,10,10a-Tetrahydro-1,1-dimethyl-8$\alpha$-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1$H,2H$)-dione (133) 222

Figure 31: $^{13}$C NMR of 8$\alpha$,9,10,10a-Tetrahydro-1,1-dimethyl-8$\alpha$-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1$H,2H$)-dione (133) 223

Figure 32: $^1$H NMR of 1,8$\alpha$,9$\alpha$,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-4$H$-benzo[def]carbazol-3(2$H$)-one (134) 224

Figure 33: $^{13}$C NMR of 1,8$\alpha$,9$\alpha$,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-4$H$-benzo[def]carbazol-3(2$H$)-one (134) 225

Figure 34: $^1$H NMR of 1,8$\alpha$,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-4$H$-benzo[def]carbazol-3(2$H$)-one (136) 226
Figure 35: $^{13}$C NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-$4H$-benzo[def]carbazol-3(2$H$)-one (136)

Figure 36: $^1$H NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-$4H$-benzo[def]carbazol-3(2$H$)-one (124)

Figure 37: $^{13}$C NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-4$H$-benzo[def]carbazol-3(2$H$)-one (124)

Figure 38: $^1$H NMR of Salviadione (123)

Figure 39: $^{13}$C NMR of Salviadione (123)

Figure 40: $^1$H NMR of 2-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (163)

Figure 41: $^{13}$C NMR of 2-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (163)

Figure 42: $^1$H NMR of 2-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene (166)

Figure 43: $^{13}$C NMR of 2-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene (166)

Figure 44: $^1$H NMR of 3-Bromo-2-trifluoromethanesulfonyloxy-nitrobenzene (151)

Figure 45: $^{13}$C NMR of 3-bromo-2-trifluoromethanesulfonyloxy-nitrobenzene (151)

Figure 46: $^1$H NMR of 3-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (157)

Figure 47: $^{13}$C NMR of 3-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (157)

Figure 48: $^1$H NMR of 4-Bromo-3-trifluoromethanesulfonyloxy-nitrobenzene (159)

Figure 49: $^{13}$C NMR of 4-Bromo-3-trifluoromethanesulfonyloxy-nitrobenzene (159)

Figure 50: $^1$H NMR of 2-Bromo-3-ethenyl-nitrobenzene (170)

Figure 51: $^{13}$C NMR of 2-Bromo-3-ethenyl-nitrobenzene (170)

Figure 52: $^1$H NMR of 2-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (171)

Figure 53: $^{13}$C NMR of 2-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (171)

Figure 54: $^1$H NMR of 2-Bromo-4-ethenyl-nitrobenzene (172)
Figure 55: $^{13}$C NMR of 2-Bromo-4-ethenyl-nitrobenzene (172) 247

Figure 56: $^1$H NMR of 2-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (173) 248

Figure 57: $^{13}$C NMR of 2-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (173) 249

Figure 58: $^1$H NMR of 2-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (175) 250

Figure 59: $^{13}$C NMR of 2-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (175) 251

Figure 60: $^1$H NMR of 2-Bromo-6-ethenyl-nitrobenzene (176) 252

Figure 61: $^{13}$C NMR of 2-Bromo-6-ethenyl-nitrobenzene (176) 253

Figure 62: $^1$H NMR of 3-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (177) 254

Figure 63: $^{13}$C NMR of 3-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (177) 255

Figure 64: $^1$H NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (178) 256

Figure 65: $^{13}$C NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (178) 257

Figure 66: $^1$H NMR of 3-Bromo-4-ethenyl-nitrobenzene (179) 258

Figure 67: $^{13}$C NMR of 3-Bromo-4-ethenyl-nitrobenzene (179) 259

Figure 68: $^1$H NMR of 3-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (180) 260

Figure 69: $^{13}$C NMR of 3-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (180) 261

Figure 70: $^1$H NMR of 3-Bromo-5-ethenyl-nitrobenzene (181) 262

Figure 71: $^{13}$C NMR of 3-Bromo-5-ethenyl-nitrobenzene (181) 263

Figure 72: $^1$H NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (182) 264

Figure 73: $^{13}$C NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (182) 265

Figure 74: $^1$H NMR of 5-Bromo-2-ethenyl-nitrobenzene (183) 266

Figure 75: $^{13}$C NMR of 5-Bromo-2-ethenyl-nitrobenzene (183) 267

Figure 76: $^1$H NMR of 4-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (184) 268

Figure 77: $^{13}$C NMR of 4-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (184) 269
Figure 78: $^1$H NMR of 4-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene (186) 270

Figure 79: $^{13}$C NMR of 4-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene (186) 271

Figure 80: $^1$H NMR of 4-Bromo-3-ethenyl-nitrobenzene (187) 272

Figure 81: $^{13}$C NMR of 4-Bromo-3-ethenyl-nitrobenzene (187) 273

Figure 82: $^1$H NMR of 3-Iodo-6-ethenyl-nitrobenzene (198) 274

Figure 83: $^{13}$C NMR of 3-Iodo-6-ethenyl-nitrobenzene (198) 275

Figure 84: $^1$H NMR of 3-Bromo-6-trifluoromethanesulfonyloxy acetophenone (201) 276

Figure 85: $^{13}$C NMR of 3-Bromo-6-trifluoromethanesulfonyloxy acetophenone (201) 277

Figure 86: $^1$H NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy acetophenone (202) 278

Figure 87: $^{13}$C NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy acetophenone (202) 279

Figure 88: $^1$H NMR of 6-Ethenyl-3-bromoacetophenone (203) 280

Figure 89: $^{13}$C NMR of 6-Ethenyl-3-bromoacetophenone (203) 281

Figure 90: $^1$H NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy anisole (209) 282

Figure 91: $^{13}$C NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy anisole (209) 283

Figure 92: $^1$H NMR of 2,3-dinitro-1,4-ethenylbenzene (241) 284

Figure 93: $^{13}$C NMR of 2,3-dinitro-1,4-ethenylbenzene (241) 285

Figure 94: $^1$H NMR of 2,3-dinitro-1,4-di(prop-1-en-2-yl)benzene (257) 286

Figure 95: $^{13}$C NMR of 2,3-dinitro-1,4-di(prop-1-en-2-yl)benzene (257) 287

Figure 96: $^1$H NMR of 5-iodo-2,4-dinitrophenol (263) 288

Figure 97: $^{13}$C NMR of 5-iodo-2,4-dinitrophenol (263) 289

Figure 98: $^1$H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenol (271) 290

Figure 99: $^{13}$C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenol (271) 291
Figure 100: $^1$H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenyl trifluoromethanesulfonate (261)

Figure 101: $^{13}$C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenyl trifluoromethanesulfonate (261)

Figure 102: $^1$H NMR of 1-chloro-2,4-dinitro-5-(prop-1-en-2-yl)benzene (273)

Figure 103: $^{13}$C NMR of 1-chloro-2,4-dinitro-5-(prop-1-en-2-yl)benzene (273)

Figure 104: $^1$H NMR of 1,5-dinitro-2,4-di(prop-1-en-2-yl)benzene (260)

Figure 105: $^{13}$C NMR of 1,5-dinitro-2,4-di(prop-1-en-2-yl)benzene (260)

Figure 106: $^1$H NMR of 1,5-dinitro-2-(prop-1-en-2-yl)-4-(prop-1- enyl)benzene (274)

Figure 107: $^{13}$C NMR of 1,5-dinitro-2-(prop-1-en-2-yl)-4-(prop-1- enyl)benzene (274)

Figure 108: $^1$H NMR of (E)-1,5-dinitro-2-(1-phenylprop-1-enyl)-4-(prop-1-en-2-yl)benzene (276)

Figure 109: $^{13}$C NMR of (E)-1,5-dinitro-2-(1-phenylprop-1-enyl)-4-(prop-1-en-2-yl)benzene (276)

Figure 110: $^1$H NMR of 2,5-dinitro-4-ethenylphenol (278)

Figure 111: $^{13}$C NMR of 2,5-dinitro-4-ethenylphenol (278)

Figure 112: $^1$H NMR of 2,5-dinitro-4-ethenylphenyl trifluoromethanesulfonate (277)

Figure 113: $^{13}$C NMR of 2,5-dinitro-4-ethenylphenyl trifluoromethanesulfonate (277)

Figure 114: $^1$H NMR of 4-bromo-2,3-dinitrophenol (292)

Figure 115: $^{13}$C NMR of 4-bromo-2,3-dinitrophenol (292)

Figure 116: $^1$H NMR of (Z)-methyl 2-(4-bromo-2,3-dinitrophenyl)but-2-enoate (301)

Figure 117: $^{13}$C NMR of (Z)-methyl 2-(4-bromo-2,3-dinitrophenyl)but-2-enoate (301)
Figure 118: $^1$H NMR of (Z)-methyl 2-(2,3-dinitro-4-(prop-1-en-2-yl)phenyl)but-2-enoate (302)

Figure 119: $^{13}$C NMR of (Z)-methyl 2-(2,3-dinitro-4-(prop-1-en-2-yl)phenyl)but-2-enoate (302)

Figure 120: $^1$H NMR of 1-iodo-3-methyl-2,4-dinitrobenzene (308)

Figure 121: $^{13}$C NMR of 1-iodo-3-methyl-2,4-dinitrobenzene (308)

Figure 122: $^1$H NMR of 2-(3-iodo-2,6-dinitrophenyl)ethanol (312)

Figure 123: $^{13}$C NMR of 2-(3-iodo-2,6-dinitrophenyl)ethanol (312)

Figure 124: $^1$H NMR of 1-iodo-2,4-dinitro-3-ethenylbenzene (313)

Figure 125: $^{13}$C NMR of 1-iodo-2,4-dinitro-3-ethenylbenzene (313)

Figure 126: $^1$H NMR of 1,3-dinitro-4-(prop-1-en-2-yl)-2-ethenylbenzene (314)

Figure 127: $^{13}$C NMR of 1,3-dinitro-4-(prop-1-en-2-yl)-2-ethenylbenzene (314)

Figure 128: $^1$H NMR of 3,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (326)

Figure 129: $^{13}$C NMR of 3,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (326)

Figure 130: $^1$H NMR of 3-methyl-2,6-dihydropyrrolo[2,3-g]indole (330)

Figure 131: $^{13}$C NMR of 3-methyl-2,6-dihydropyrrolo[2,3-g]indole (330)

Figure 132: $^1$H NMR of Methyl 2,6-dimethyl-1,8-dihydropyrrolo[3,2-g]indole-3-carboxylate (331): Figure 133: $^{13}$C NMR of Methyl 2,6-dimethyl-1,8-dihydropyrrolo[3,2-g]indole-3-carboxylate (331):

Figure 134: $^1$H NMR of 2,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (332)

Figure 135: $^{13}$C NMR of 2,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (332)

Figure 136: $^1$H NMR of 2,5-dimethyl-3-phenyl-1,7-dihydropyrrolo[3,2-f]indole (333) 310

Figure 118: 310

Figure 119: 311

Figure 120: 312

Figure 121: 313

Figure 122: 314

Figure 123: 315

Figure 124: 316

Figure 125: 317

Figure 126: 318

Figure 127: 319

Figure 128: 320

Figure 129: 321

Figure 130: 322

Figure 131: 323

Figure 132: 324

Figure 133: 325

Figure 134: 326

Figure 135: 327

Figure 136: 328
Figure 137: $^{13}$C NMR of 2,5-dimethyl-3-phenyl-1,7-dihydropyrrolo[3,2-f]indole (333) 329

Figure 138: $^1$H NMR of 3,4-dibromo-2-nitrobenzaldehyde (343) 330

Figure 139: $^{13}$C NMR of 3,4-dibromo-2-nitrobenzaldehyde (343) 331

Figure 140: $^1$H NMR of 4,5-dibromo-2-nitrobenzaldehyde (344) 332

Figure 141: $^{13}$C NMR of 4,5-dibromo-2-nitrobenzaldehyde (344) 333

Figure 142: $^1$H NMR of 3,4-dibromo-2-nitrobenzylalcohol (349) 334

Figure 143: $^{13}$C NMR of 3,4-dibromo-2-nitrobenzylalcohol (349) 335

Figure 144: $^1$H NMR of 4,5-dibromo-2-nitrobenzylalcohol (350) 336

Figure 145: $^{13}$C NMR of 4,5-dibromo-2-nitrobenzylalcohol (350) 337

Figure 146: $^1$H NMR of 3,6-dibromo-2-nitrobenzylalcohol (351) 338

Figure 147: $^{13}$C NMR of 3,6-dibromo-2-nitrobenzylalcohol (351) 339

Figure 148: $^1$H NMR of 2,3-dinitro-4-ethenyltoluene (355) 340

Figure 149: $^{13}$C NMR of 2,3-dinitro-4-ethenyltoluene (355) 341

Figure 150: $^1$H NMR of 6-methyl-7-nitroindole (356) 342

Figure 151: $^1$H NMR of 3,5-dinitro-4-ethenyltoluene (355) 343

Figure 152: $^{13}$C NMR of 3,5-dinitro-4-ethenyltoluene (355) 344

Figure 153: $^1$H NMR of 6-methyl-4-nitroindole (356) 345

Figure 154: $^{13}$C NMR of 6-methyl-4-nitroindole (356) 346

Figure 155: $^1$H NMR of 5-iodo-2,4-dinitroanisole (363) 347

Figure 156: $^{13}$C NMR of 5-iodo-2,4-dinitroanisole (363) 348

Figure 157: $^1$H NMR of 5-ethenyl-2,4-dinitroanisole (365) 349

Figure 158: $^{13}$C NMR of 5-ethenyl-2,4-dinitroanisole (365) 350

Figure 159: $^1$H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)anisole (369) 351
Figure 160: $^{13}$C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)anisole (369)  

Figure 161: $^1$H NMR of 3-methyl-5-methoxy-6-nitroindole (370)  

Figure 162: $^1$H NMR of 3-iodo-2,4-dinitroanisole (364)  

Figure 163: $^{13}$C NMR of 3-iodo-2,4-dinitroanisole (364)  

Figure 164: $^1$H NMR of 3-ethenyl-2,4-dinitroanisole (367)  

Figure 165: $^{13}$C NMR of 3-ethenyl-2,4-dinitroanisole (367)  

Figure 166: $^1$H NMR of 3-(prop-1-en-2-yl)-2,4-dinitroanisole (371)  

Figure 167: $^{13}$C NMR of 3-(prop-1-en-2-yl)-2,4-dinitroanisole (371)  

Figure 168: $^1$H NMR of 3-methyl-5-methoxy-4-nitroindole (372)  

Figure 169: $^{13}$C NMR of 3-methyl-5-methoxy-4-nitroindole (372)
**List of Schemes**

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial Preparation of Indole from Indigo</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Fischer Indole Synthesis</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Fischer Cyclization en route to Haplophytine</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Madelung Indole Synthesis</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>Houlihan Modification to Madelung Indole Synthesis</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>Madelung Methodology in the Synthesis of Penitrem D</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Hegedus Palladium-catalyzed Cyclization of o-Allylanilines</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>Larock Heteroannulation of Internal Alkyne with o-Iodoaniline</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>Baran’s Synthesis of Psychotrimine via Larock Cyclization</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>Buchwald Indole Synthesis via Intramolecular Amination</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>Reissert Method for Indole Preparation</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Leimgruber-Batcho Indole Synthesis</td>
<td>11</td>
</tr>
<tr>
<td>13</td>
<td>Cadogan and Sundberg’s Reductive Heterocyclization</td>
<td>11</td>
</tr>
<tr>
<td>14</td>
<td>Mechanism of Cadogan-Sundberg Indole Synthesis</td>
<td>12</td>
</tr>
<tr>
<td>15</td>
<td>Alternative Mechanism of Sundberg-Cadogan Cyclization</td>
<td>12</td>
</tr>
<tr>
<td>16</td>
<td>Watanabe Palladium(II)-Catalyzed Reductive Heterocyclization</td>
<td>13</td>
</tr>
<tr>
<td>17</td>
<td>Davies Reductive N-Heterocyclization of Isomeric Nitrostilbenes</td>
<td>14</td>
</tr>
<tr>
<td>18</td>
<td>Söderberg Reductive Heterocyclization</td>
<td>14</td>
</tr>
<tr>
<td>19</td>
<td>Proposed Mechanism(s) of Reductive N-Heteroannulation</td>
<td>16</td>
</tr>
<tr>
<td>20</td>
<td>Potential Palladium-Olefin Coordination-Mediated Reduction</td>
<td>17</td>
</tr>
<tr>
<td>21</td>
<td>$^{18}$O Labeling Study of Cadogan-Sundberg Reductive Cyclization</td>
<td>18</td>
</tr>
<tr>
<td>22</td>
<td>Deuterium-Labeling Study of [1,5]-Sigmatropic Rearrangement</td>
<td>19</td>
</tr>
</tbody>
</table>
Scheme 23: Initial Cyclization of Cyanoalkene

Scheme 24: Akazome’s Synthesis of Indoles and Quinolines

Scheme 25: Investigation of Cyclization Conditions

Scheme 26: Preparation of 2-Nitrostyrenes via Stille Coupling

Scheme 27: Preparation and Cyclization of Cyanoalkene 105

Scheme 28: Preparation and Cyclization of Cyanoalkene 111

Scheme 29: Attempt to Trap Reactive Intermediates

Scheme 30: Potential Mechanism(s) for Cyclization in Absence of Base

Scheme 31: Proposed Mechanism for Quinoline Formation

Scheme 32: Mechanistic Analysis of Quinoline Formation

Scheme 33: Proposed Mechanism Accounting for Fission, Oxidation, Elimination

Scheme 34: Proposed Retrosynthetic Outline for Salviadione

Scheme 35: Alkylation of Dimedone

Scheme 36: Preparation of Alkyliodide

Scheme 37: Preparation of Cyclization Precursor

Scheme 38: Acid-Induced Intramolecular Cyclization-Friedel-Crafts Alkylation

Scheme 39: Nitration of Tricyclic Diterpinoid Core

Scheme 40: Oxidation of Products to Quinole 133

Scheme 41: Palladium-Catalyzed Reductive N-Heteroannulation

Scheme 42: Attempted Cyclization of Quinole

Scheme 43: Benzylic Oxidation of Anisole Using DDQ

Scheme 44: DDQ Oxidation to Afford Salviadione

Scheme 45: Echavarren’s Chemoselective Stille Coupling Conditions
Scheme 46: Krolski Selective Coupling of 2-Bromo-3-Nitrophenyl Triflate

Scheme 47: Preparation of 2,4-Dinitro-5-Bromophenyl Triflate

Scheme 48: Attempted Selective Coupling of Dinitro-Bromophenyl Triflate

Scheme 49: Nitration of 2-Bromophenol

Scheme 50: Preparation of Isomeric Nitrophenyl Triflates

Scheme 51: Preparation of 2-Nitro-4-Bromophenyl Triflate

Scheme 52: Preparation of 3-Nitro-5-Bromophenyl Triflate

Scheme 53: Preparation of 2-Bromo-5-Nitrophenyl Triflate

Scheme 54: Preparation of 4-Bromo-3-Nitrophenyl Triflate

Scheme 55: Preparation of 3-Bromo-2-Nitrophenyl Triflate

Scheme 56: Preparation of 167 and 168

Scheme 57: Preparation of 2-Bromo-3-Nitrophenyl Triflate

Scheme 58: Preparation of Bromophenyl Triflates

Scheme 59: Echavarren’s Coupling of p-Iodophenyl Triflate

Scheme 60: Preparation of 4-Iodo-2-Nitrophenyl Triflate

Scheme 61: Coupling of 4-Iodo-2-Nitrophenyl Triflate

Scheme 62: Preparation of 5-Bromo-2-Trifloxy Acetophenone

Scheme 63: Selectivity Under Conditions A and B

Scheme 64: Bromine-Selective Coupling Under Conditions B

Scheme 65: Preparation of 3-Bromo-4-Trifloxy Anisole

Scheme 66: Selectivity Under Conditions A and B

Scheme 67: Berlin’s Approach to Pyrroloindoles

Scheme 68: Montmorillonite K-10 Catalyzed Synthesis of Pyrroloindoles
Scheme 69: Samsoniya Route to Isomeric Pyrroloindoles

Scheme 70: Pyrroloindole Preparation from Aminoindoline

Scheme 71: Oxidative Bicyclization of Diimines

Scheme 72: Intramolecular Hydroamination of Di-yne

Scheme 73: Retrosynthetic Analysis of Pyrroloindoles

Scheme 74: Banini Route to Pyrroloindoles of Class B

Scheme 75: Banini Route to Pyrroloindoles of Class C

Scheme 76: Failed Preparation of Benzyl Bromide

Scheme 77: Attempted Mono-Coupling of Dibromide

Scheme 78: Preparation of Dialkenyl-Dinitrobenzene

Scheme 79: Proposed Retrosynthetic Outline to Cyclization Precursor

Scheme 80: Nitration of 3-Iodophenol

Scheme 81: Nitration of 5-Iodo-2-Nitrophenol

Scheme 82: Nitration of 3-Iodo-4-Nitrophenol

Scheme 83: Preparation of Aryl Triflate

Scheme 84: Attempted Kosugi-Migita-Stille Coupling

Scheme 85: Kosugi-Migita-Stille Coupling of Iodophenol

Scheme 86: Conversion of Phenol to Triflate

Scheme 87: Attempted Kosugi-Migita-Stille Coupling of Aryl Triflate

Scheme 88: Conversion of Aryl Triflate to Aryl Chloride

Scheme 89: Kosugi-Migita-Stille Coupling of Aryl Chloride

Scheme 90: Kosugi-Migita-Stille Coupling of Aryl Triflate

Scheme 91: Preparation of Cyclization Precursor
Scheme 115: Attempted Coupling of Iodophenol 102
Scheme 116: Kawakami Methylation of 2,4-Dinitroaniline 103
Scheme 117: Preparation of Aryl Iodide 104
Scheme 118: Mundla’s Preparation of 2,6-Dinitrostyrene 104
Scheme 119: Synthesis of Styrene 105
Scheme 120: Kosugi-Migita-Stille Coupling of Aryl Iodide 105
Scheme 121: Attempted Condensation with Hexanal 105
Scheme 122: Proposed Retrosynthetic Outline to Cyclization Precursor 107
Scheme 123: Attempted Nitration of 2-Iodo-3-Nitrophenol 107
Scheme 124: Proposed ortho-Functionalization of Phenol 108
Scheme 125: Mechanism of ortho-Selective Nitration of Phenol 108
Scheme 126: Attempted ortho-Selective Nitration of Phenol 109
Scheme 127: Gaude’s ortho-Iodination of Phenol 109
Scheme 128: Attempted ortho-Iodination of Dinitrophenol 109
Scheme 129: Double Cyclization Using 1,10-phenanthroline/dppp 112
Scheme 130: Formation of Mixed Indole Dimer 115
Scheme 131: Intermolecular Dimerization of Pyrroloindole 115
Scheme 132: Proposed Substrate Preparation From Halobenzaldehyde 118
Scheme 133: Regioselective Bromination of 2-Nitrobenzaldehyde 119
Scheme 134: Bromination of 2-Nitrobenzaldehyde 120
Scheme 135: Sodium Borohydride Reduction of 340 122
Scheme 136: Reduction of Inseparable Mixture 122
Scheme 137: Reduction of Aldehyde to Confirm Structure 123
Scheme 138: Reduction of Aldehyde 344

Scheme 139: Reduction of Aldehyde 345

Scheme 140: Nitration of p-Bromotoluene 126

Scheme 141: Kosugi-Migita-Stille Coupling of Aryl Bromide 126

Scheme 142: Reductive N-Heterocyclization of Nitrostyrene 355

Scheme 143: Synthesis of 6-Methyl-4-Nitroindole 127

Scheme 144: Dinitration of 3-Haloanisole 128

Scheme 145: Preparation of 5-Methoxy-Nitroindoles 128

Scheme 146: Preparation of 3-Methyl-5-Methoxy-Nitroindoles 129
## List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Knoevenagel Condensation of 2-Arylacetonitrile</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Preparation of Ester-Substituted Alkenes</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Cyclizations to Afford Substituted Indoles and/or Quinolines</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>$^1$HNMR Shift Comparison Between Synthetic and Natural Salviadione</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>$^{13}$CNMR Shift Comparison Between Synthetic and Natural Salviadione</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>Isolated Yields From Reaction Under Conditions A and B</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>Selective Coupling of Bromophenyl Triflates</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>Reductive Double $N$-Heteroannulation</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>Reductive Double $N$-Heteroannulation Under Banini’s Conditions</td>
<td>110</td>
</tr>
<tr>
<td>10</td>
<td>Palladium-Catalyzed Reductive Double $N$-Heterocyclizations</td>
<td>112</td>
</tr>
<tr>
<td>11</td>
<td>Molar Ratios of Brominated Products</td>
<td>120</td>
</tr>
<tr>
<td>12</td>
<td>Isolated Yields of Brominated Products</td>
<td>121</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction to Indole, History of Indole, and Historical Routes to the Indole Core

1.1 Indole Background and Notable Indoles 2
1.2 Classical Routes to the Indole Core 6
1.3 Transition Metal Catalyzed Indole Synthesis 8
1.4 Indole Synthesis via Reductive Cyclization 10
1.5 Indole Preparation via Palladium-Catalyzed Reductive Heterocyclization 12
1.1 Indole Background and Notable Indoles

Indole (1) is the common name for the molecule featuring a pyrrole ring fused to a benzene ring along the 2- and 3-positions of the pyrrole. The name indole itself is in relation to indigo, which is the parent compound from which indole was originally isolated through treatment with oleum.

The atoms of indole are numbered according to the following scheme: the nitrogen atom is designated atom 1 and proceeds around the pyrrole portion of the molecule in a counter-clockwise fashion (Figure 1). The carbons where the pyrrole is fused to the benzene ring are often times denoted “3a” and “7a”.

**Figure 1: Structure and Numbering of Indole**

![Indole Structure](image)

Indole is a planar heteroaromatic molecule composed of a ten-electron pi-system made up of two electrons from the nitrogen atom and eight electrons from the remaining eight carbon atoms. Due to it having more pi-electrons than atoms, indole is often referred to as a “pi-excessive” aromatic compound. Typically, the 3-position of indole is highly reactive towards electrophilic species on the basis of pi-electron density, localization energy, and molecular orbital calculations. As expected, the amino-group of indoles is fairly acidic with a pKa of 17, possessing the ability to form an anion in the presence of a strong base. While the resulting electron pair of the anion does not lie within the pi-system, it still serves as a basis for the increased reactivity of the 3-position toward electrophiles.
The preparation of indoles and indole-based derivatives has been a topic of interest for more than a century, beginning with the initial development of indole triggered by the dye industry. Oxidation of indigo (2) to isatin (3) was achieved by Baeyer and Knopp, who then reduced isatin (3) to oxindole (4) (Scheme 1). Pyrolysis of 4 in the presence of zinc dust afforded indole (1). Baeyer first reported the formula of indole, which is still accepted today, in 1869.

**Scheme 1: Initial Preparation of Indole from Indigo**

The main use of indoles through the end of the 19th century was within the dyestuff industry. While the dye applications of indoles declined in the early 20th century, organic dyes still account for approximately $14.4 billion in global production.

Interest in indole-based molecules was re-ignited in the 1930’s as interest in alkaloid chemistry grew. The diverse structures of indole alkaloids leads to their wide range of biological activities and in turn triggered an increase in research toward the preparative methods of indoles.

A number of indole-based molecules are involved in processes within the human body. The amino acid L-tryptophan (5) is essential to the human diet while also functioning as a precursor for the neurotransmitter serotonin (6), which can be further converted to the neurohormone melatonin (7) (Figure 2).
Figure 2: Structures of L-tryptophan, Serotonin, and Melatonin

Indole alkaloids make up a quarter of the marine alkaloids and are considered to be the most structurally complex molecules of this class.\textsuperscript{13} Indole alkaloids have been isolated from a number of marine species, including sponges, tunicates, red algae, acorn worms, and symbiotic bacteria.\textsuperscript{13} In addition, marine alkaloids often possess structural features uncommon to terrestrial species, such as halides (Figure 3). Dragmacidin (8)\textsuperscript{14}, isolated from the deep water sponge Dragmacidin sp., has exhibited \textit{in vitro} cytotoxic activity against a number of cancer cell lines including lung, colon, and mammary.\textsuperscript{11} The novel oxathiazepine containing alkaloid Eudistomin K (9)\textsuperscript{15}, isolated from the Caribbean tunicate \textit{E. olivaceum}, inhibits herpes simplex virus-1 growth.\textsuperscript{13} Flustramine D (10)\textsuperscript{16}, isolated from the marine bryozoan \textit{F. foliacea}, exhibits inhibition of a wide spectrum of bacterial including \textit{E. coli}, \textit{S. typhimurium}, \textit{S. aureus}, and \textit{S. epidermidis}.\textsuperscript{13}

Figure 3: Structures of Dragmacidin, Eudistomin K, and Flustramine D

Synthetic indoles have also found applications in the medicinal field. Sumatriptan (11)\textsuperscript{17}, tadalafl (12)\textsuperscript{18}, rizatriptan (13)\textsuperscript{19}, and fluvastatin (14)\textsuperscript{20}, all containing an indole motif, accounted for over $3.2\ billion in sales in 2010 (Figure 4).\textsuperscript{21} Sumatriptan and rizatriptan have found use as anti-migrane drugs\textsuperscript{21}, tadalafl (commonly known as Cialis)
is used to treat erectile dysfunction\textsuperscript{22}, and fluvastatin is used to prevent cardiovascular disease\textsuperscript{23}.

**Figure 4: Structures of Sumatriptan, Tadalafil, Rizatriptan, and Fluvastatin**

Indoles have found applications in a number of areas. Their initial use as dyestuffs gradually progressed to exploration of their uses as biological compounds. With advances in isolation and characterization techniques, numerous novel indole alkaloids are reported annually. This has in turn triggered a heightened interest in preparative methods of indoles, which will be discussed in the following section.
1.2 Classical Routes to the Indole Core

One of the most widely applied methods for the preparation of indole intermediates en route to biologically active compounds\(^{25}\) is the Fischer indole synthesis.\(^{26,27}\) Developed in 1883, it allowed for the relatively simple conversion of enolizable \(N\)-arylhydrazones to indoles. In a simplistic example, condensation of aryl hydrazine 15 with 2-butane afforded intermediate hydrazone 16 which then underwent cyclization to afford indole 17 (Scheme 2). Addition of a protic or Lewis acid (typically \(\text{ZnCl}_2\)) served two purposes: to assist in the tautomerization in order to form the enehydrazine as well as to facilitate cleavage of the N-N bond.\(^4,25\)

**Scheme 2: Fischer Indole Synthesis**

\[
\begin{align*}
15 & \xrightarrow{\text{ZnCl}_2, \text{200 } ^\circ\text{C}, \text{60}\%} 16 & \rightarrow 17
\end{align*}
\]

A Fischer cyclization was employed as a key step in Fukuyama’s synthesis of haplophytine.\(^{28}\) Condensation of tricyclic ketone 18 with aryl hydrazine 19 followed by heating in the presence of \(p\)-toluenesulfonic acid afforded indoline 20 which was then converted to haplophytine in six additional steps (Scheme 3). The structural complexity of both substrates highlights the broad scope and functional group tolerance of the Fischer method.

**Scheme 3: Fischer Cyclization en route to Haplophytine**
The Madelung indole synthesis used high temperatures to convert N-phenylamides to indoles through intramolecular cyclization in the presence of a strong base.\textsuperscript{29} The first reported example prepared 2-methylindole (18) from o-methylacetanilide (21) through treatment with sodium amide and heating at 250°C (Scheme 4).\textsuperscript{30}

**Scheme 4: Madelung Indole Synthesis**

\[
\begin{align*}
\text{O} & \quad \text{NaNH}_2 \\
\text{21} & \quad 250 \degree C \\
& \quad \text{17}
\end{align*}
\]

One downfall of these conditions was that they were extremely harsh and in turn limited the scope of functionality.\textsuperscript{4} However, a number of modifications which utilized much milder conditions were also been reported. The Houlihan modification\textsuperscript{31} employed the use of either \textit{n}-butyllithium (\textit{n}-BuLi) or lithium \textit{N,N}-diisopropylamide (LDA) as the base and required much lower reaction temperatures. Using these conditions, \textit{N}-(4-chloro-2-methylphenyl)benzamide (22) was converted to 5-chloro-2-phenylindole (23) through treatment with two equivalents of \textit{n}-BuLi in tetrahydrofuran at -20°C (Scheme 5).\textsuperscript{32}

**Scheme 5: Houlihan Modification of Madelung Indole Synthesis**

\[
\begin{align*}
\text{22} & \quad n\text{-BuLi}, \text{THF} \\
& \quad -20 \degree C \text{ to r.t.} \\
& \quad > 90 \% \\
& \quad \text{Cl} \\
& \quad 23
\end{align*}
\]

An elegant application of the Madelung route was presented in the synthesis of penitrem D.\textsuperscript{33} This approach was daring in that it was applied at a late stage in the synthetic route. Condensation of aniline 24 with cyclic ester 25 was afforded heptacyclic indole 26 in excellent yield (Scheme 6).
Scheme 6: Madelung Methodology in the Synthesis of Penitrem D

1.3 Transition Metal Catalyzed Indole Synthesis

An early example of palladium-catalyzed indole preparation was reported by Hegedus et al. in 1976. This intramolecular elaboration of their earlier finding of palladium-assisted amination of olefins involved cyclization of an o-allylaniline in the presence of palladium (II) catalysts to afford 2-substituted indole (Scheme 7). The relatively mild reaction conditions accommodated a number of functional groups and was later applied in the preparation of ergot alkaloids.

Scheme 7: Hegedus Palladium-catalyzed Cyclization of o-Allylanilines

Larock et al. described a convenient preparation of 2,3-disubstituted indoles via palladium-catalyzed heteroannulation between o-iodoaniline (30) and internal alkynes (Scheme 8). This methodology allowed for the preparation of highly functionalized indoles with regioselective control based on the identities of the substituents on the alkyne. The reaction’s versatility has led to its application in the synthesis of a number of pharmaceutical compounds including Maxalt and Avitriptan. However, the Larock cyclization has been limited by the requirement of iodoaniline substrates, which are often
more expensive or not commercially-available in comparison to the corresponding bromo- or chloroanilines.  

**Scheme 8: Larock Heteroannulation of Internal Alkyne with o-Iodoaniline**

![Scheme 8: Larock Heteroannulation of Internal Alkyne with o-Iodoaniline](image)

A practical application of Larock methodology was in the synthesis of psychotrimine by Baran et al. Attempts to use pre-formed indoles as nucleophiles to prepare intermediate 33 were unsuccessful, however, a Larock cyclization between 2-iodoaniline derivative 32 and the properly substituted alkyne afforded bis-indole 33 in gram amounts (Scheme 9).

**Scheme 9: Baran’s Synthesis of Psychotrimine via Larock Cyclization**

![Scheme 9: Baran’s Synthesis of Psychotrimine via Larock Cyclization](image)

Buchwald’s aryl amination methodology has also been applied toward the synthesis of indoles and indole derivatives. Palladium-catalyzed intermolecular amination of aryl bromide with inexpensive benzophenone hydrazone 34 afforded hydrazone 35, which was converted to indole 36 upon heating under acidic conditions (Scheme 10). This method broadens the scope of the Fischer cyclization by providing an alterative method to prepare the requisite N-arylhydrazone precursors.
1.4 Indole Synthesis via Reductive Cyclization

An early example of indole synthesis via reductive heterocyclization was the Reissert method. In this route, an o-nitrobenzylcarbonyl compound 38, prepared through the condensation of an o-nitrotoluene (37) and an oxalic ester, underwent reductive cyclization the presence of zinc to afford indole-2-carboxylic acid derivatives, which then decarboxylated to give indole (1) (Scheme 11).

Another commonly used method in indole synthesis was the Leimgruber-Batcho route. This method, similar to the Reissert route, involved the condensation of o-nitrotoluenes 37 with dimethylformamide dimethyl acetal (DMFDMA), affording an intermediate B-(dimethylamino)-2-nitrostyrene 38 which then underwent reductive heterocyclization to afford indole (1) (Scheme 12). The success of the initial condensation was attributed to the increased acidity of the benzylic protons on account of the ortho nitro substituent. The addition of pyrrolidine resulted in the generation of
more reactive aminomethylenating reagent and was found to significantly shorten reaction times.\textsuperscript{44}

**Scheme 12: Leimgruber-Batcho Indole Synthesis**

Another method for indole synthesis that has received considerable attention involves reductive cyclization of \( o \)-nitrostyrenes. This method was pioneered by Cadogan\textsuperscript{45}, who used trivalent phosphorous compounds to form indoles through deoxygenation of nitroaromatics. An early example involved heating \( o \)-nitrostyrene \textsuperscript{39} in triethylphosphite, affording 2-phenylindole (\textsuperscript{40}) in good yield (Scheme 13).\textsuperscript{45}

**Scheme 13: Cadogan and Sundberg’s Reductive Heterocyclization**

While this method is broadly applicable, it has been limited to small-scale applications due to its requirement of high temperatures (>150 °C) as well as the generation of phosphorous waste. These conditions were also successful in preparing indoles from 2-nitrosobiphenyl compounds\textsuperscript{46}, lending mechanistic evidence to the cyclization of analogous nitroaromatics proceeding through a nitroso intermediate. It was presumed that this cyclization proceeded through a nitrene intermediate generated by the sequential deoxygenation of the nitro group\textsuperscript{45} (Scheme 14). Addition of triethyl phosphite to nitroaromatic \textsuperscript{39} followed by elimination of triethyl phosphite provides nitrosoarene \textsuperscript{41}, which was reduced to nitrene \textsuperscript{42} through repetition of the addition-
elimination sequence. Nitrene 42 then rapidly attacked the alkene to form heterocycle 43. Aromaticity was restored through [1,5]-sigmatropic rearrangement, producing indole 40.

**Scheme 14: Mechanism of Cadogan-Sundberg Indole Synthesis**

![Mechanism Diagram](image)

An alternative mechanism has been proposed based on the isolation of hydroxy- and ethoxy-indole by-products (Scheme 15). While the initial deoxygenation to afford nitroso compound 41 is widely accepted, the observation of oxy-indole side products could arise from direct cyclization of nitrosoaromatic 41 to afford hydroxyindole 44. It is then possible that hydroxyindole 44 could be further reduced to indole 40 by triethylphosphite.

**Scheme 15: Alternative Mechanism of Sundberg-Cadogan Cyclization**

![Alternative Mechanism Diagram](image)

1.5 *Indole Preparation via Palladium-Catalyzed Reductive Heterocyclization*

Within the past few decades, interest in methods for indole synthesis has led to the discovery of numerous transition-metal catalysts capable of inducing the reductive
heterocyclization of o-nitrostyrenes. While numerous metals have been found useful in such transformations, palladium-catalyzed routes employing carbon monoxide as a reducing agent have become the most popular. It is believed that these cyclizations proceed analogously to those reported by Cadogan and Sundberg, meaning that a nitrenoid intermediate likely forms via reduction of the nitro group by palladium/carbon monoxide. This transition-metal nitrene then attacks the ortho alkene to form the heterocycle, which undergoes [1,5]-sigmatropic rearrangement to give the indole. This mechanistic rationale is based on the proposed similarities between such reductive cyclizations and analogous cyclizations of azido aromatics.

An early palladium-catalyzed reductive N-heterocyclization route to indoles and indazoles was reported by Watanabe et al. This method improved on the previous routes by providing milder reaction conditions involving palladium(II) and tin(II) chloride catalysts along with pressurized carbon monoxide. Under these conditions, o-nitrostyrene (45) was converted to indole (1) in moderate yield (Scheme 16). A selection of substituted indoles were prepared using this method, although yields were moderate at best even under fairly high carbon monoxide pressures.

Scheme 16: Watanabe Palladium(II)-Catalyzed Reductive Heterocyclization

Davies reported an improved route for similar reductive heterocyclizations at significantly lower carbon monoxide pressures. Such reactions were achieved using 0.1% catalyst loadings under 1 atm carbon monoxide (as opposed to 20 atm used by Watanabe). It was also observed that the stereochemistry of the olefin did not have an
effect on the reaction. Reaction of a 1:1 mixture of both $E$- and $Z$-nitrostilbene isomers (39) afforded indole 40 in excellent yield (Scheme 17).

**Scheme 17: Davies Reductive $N$-Heterocyclization of Isomeric Nitrostilbenes**

![Scheme 17](image)

A similar transformation was reported by Söderberg in 1997. In an attempted methoxycarbonylation of styrene 46, indole 47 was isolated as the sole product (Scheme 18). While this result was unexpected, it was also not unprecedented based on the previously mentioned examples.

**Scheme 18: Söderberg Reductive Heterocyclization**

![Scheme 18](image)

Through a detailed optimization study of the reaction conditions, it was found that methanol and triethylamine were not required to induce the cyclization. It was also found that a number of solvents, including DMF, acetonitrile, and methanol, all resulted in formation of the desired indole product. Numerous palladium sources were also found successful, including Pd(OAc)$_2$, PdCl$_2$(MeCN)$_2$, Pd(dba)$_2$, and 10% Pd/C. The array of plausible conditions makes this method highly attractive and broadly applicable.

The Söderberg method provides a number of significant improvements over previously reported conditions. In comparison to Watanabe’s system, the Söderberg conditions require significantly lower temperatures while also eliminating the need for a Lewis acid additive. It is also an improvement over alternative routes involving aniline
derivatives\textsuperscript{34} in that (a) anilines are typically prepared through the reduction of the corresponding nitroarene, introducing an additional step to the route. In addition, the use of palladium (0) catalysts eliminates the need for an oxidant required when using palladium (II). From an environmental standpoint, the main by-product of the reaction is carbon dioxide, which is a significant improvement over previous routes using tin\textsuperscript{50} or phosphorous\textsuperscript{45} additives. This also leads to simplified workup procedures.

The plausible mechanisms for the reductive heterocyclization of \textit{o}-nitrostyrenes are presented in Scheme 19.\textsuperscript{53} The difficulty of isolating intermediates has prevented researchers from fully understanding the exact mechanism, so multiple plausible routes have been proposed based on numerous observations.

The mechanism initially proceeds through the palladium-catalyzed reduction of nitrostyrene \texttextsuperscript{45} by carbon monoxide to give intermediate \texttextsuperscript{48}. Carbon monoxide insertion into one of the palladium-oxygen bonds affords palladacycle \texttextsuperscript{49}, which, upon reductive elimination of carbon dioxide, affords palladium-bound nitrosarene \texttextsuperscript{50}. From this point, the mechanism could proceed in three ways:

Path A\textsuperscript{51} involves liberation of palladium from nitrosarene \texttextsuperscript{50} to afford nitrosostyrene \texttextsuperscript{51}, which can undergo 6-pi electrocyclization to afford nitronate \texttextsuperscript{52}. [1,5]-hydride shift of \texttextsuperscript{53} followed by isomerization of intermediate \texttextsuperscript{53} produces \textit{N}-hydroxyindole (\texttextsuperscript{54}). Reduction of \texttextsuperscript{54} by another equivalent of carbon monoxide then affords indole (1).

Path B begins with insertion of carbon monoxide to palladium-bound nitrosarene \texttextsuperscript{50} to give palladacycle \texttextsuperscript{55}. Subsequent reductive elimination of carbon dioxide produces palladium-bound nitrene \texttextsuperscript{56}, which could undergo 6 pi-electrocyclization to afford six-
membered palladacycle 57. Reductive elimination of palladium from 57 would furnish heterocycle 58, which could then isomerize to indole (1) through a [1,5]-hydrogen shift.

Path C is similar to Path B, although initial reductive elimination of palladium from 56 affords free nitrene 59. Nitrene 59 could then undergo an electrocyclization-isomerization process (as described for Path B) to ultimately afford indole (1).

**Scheme 19: Proposed Mechanism(s) of Reductive N-Heteroannulation**

While the exact mechanism of this transformation is not fully understood, several observations lend some evidence to potential intermediates. It is believed that the proximity of the nitro group to the alkene is crucial in facilitating the reaction, as observed for two isomeric nitrostilbenes. 52 While 2-nitrostilbene (39) reacts to give 2-phenylindole (40) in quantitative yield, 4-nitrostilbene (60) is recovered unchanged, also
in quantitative yield (Scheme 20). This result hints that initial coordination of the metal to the alkene is necessary for the initial reduction of the nitro group.\(^{52}\)

**Scheme 20: Potential Palladium-Olefin Coordination-Mediated Reduction**

The prevalence of \textit{N}-ethoxyindoles as side products of the Cadogan-Sundberg indole synthesis provides justification for path A.\(^{54,55}\) While the origin of these products was not initially studied, recent work by Peet \emph{et al.}\(^{47}\) determined through \(^{18}\)O labeling experiments that the oxygen found in the \textit{N}-alkoxyindole originates from the nitro group, not from triethylphosphite (Scheme 21). This means that the labeled nitro group of 61 is only reduced to the corresponding nitroso compound 62 and not further reduced to the nitrene. Nitroso intermediate 62 then cyclizes to afford intermediate 63, which could lose a proton to give deprotonated \textit{N}-hydroxyindole 64, which then attacks an ethyl group from the triethyl phosphate (produced in the initial deoxygenation of 61) to afford \textit{N}-ethoxyindole 65.
Watanabe postulated that formation of the free nitrene (path C, Scheme 19) was likely based on the evolution of carbon dioxide over the course of the reaction, although carbon dioxide is also generated in the initial reduction of the nitro group to the corresponding nitroso compound as well as in the reduction of nitrosarene to palladium-bound nitrene (path B, Scheme 19). This nitroso/nitrene species could then cyclize to form the five-membered ring, followed by a [1,5]-hydride shift to afford the indole product.

The aforementioned [1,5]-hydride shift was also studied by Watanabe (Scheme 22). Through deuterium labeling of \( o \)-nitrostyrene \( 65 \), it was determined that the 3-methyldindole product \( 67 \) was deuterated at both the 1- and 2-positions. This means that the nitrogen atom must abstract a deuterium from the \( \beta \)-carbon of the olefin during the cyclization process. This then became the basis for the proposed [1,5]-sigmatropic rearrangement of proposed intermediate \( 66 \) to afford indole \( 67 \).
Scheme 22: Deuterium-Labeling Study of [1,5]-Sigmatropic Rearrangement

Söderberg’s work over the past number of years has focused on applying this methodology toward the synthesis of a number of compounds including tryptophan derivatives, bicyclic heteroaromatics, carbazole alkaloids, mushroom metabolites, and various natural products. The ensuing sections will discuss novel applications of palladium-catalyzed reductive N-heterocyclizations in the preparation of indoles and indole derivatives.
Chapter 2

A Base Modulated Synthesis of Indoles and Quinolines

2.1 Introduction 21

2.2 Results and Discussion 22

2.3 Conclusions 33
2.1 Introduction

One of the most challenging tasks in synthetic organic chemistry is finding selectivity in reactions. Often times, researchers struggle to target one specific functional group in the presence of other similar functionalities. The ideal reaction would only alter the desired functionality while leaving other reactive moieties untouched. In the same sense, the ability to prepare different products from a common starting material is also of great use.

Through previous work within Söderberg’s group aimed at the preparation of 2,3-substituted indoles, an interesting result was obtained. Upon cyclization of cyano-substituted alkene 68, the expected indole 69 was isolated in moderate yield along with a small amount of quinoline 70 (Scheme 23). This unexpected result was of interest for it presented the potential for preparation of two different yet useful products from a common starting material.

**Scheme 23: Initial Cyclization of Cyanoalkene**

Upon examination of the literature, Akazome et al. reported a similar result. In the attempted cyclization of o-nitrocinnamaldehyde (71) using PdCl$_2$(PPh$_3$)$_2$ and SnCl$_2$ under carbon monoxide, quinoline 72 was isolated albeit in low yield (Scheme 24). Similar reaction of o-nitrochalcone (73) afforded both indole 74 and quinoline 75.
Although it can be envisioned that the aforementioned cyclizations may proceed through reduction of the nitro group to the corresponding aniline in a similar fashion to analogous indole syntheses reported by Hegedus, Akazome found that treatment of 2-aminostilbene with the established conditions afforded neither indole 74 or quinoline 75. This clearly demonstrates a different mechanism, likely involving the reduction of the nitro group to a nitroso or nitrile (as discussed in Chapter 1).

2.2 Results and Discussion

An investigative study was launched based on both Akazome’s results as well as Söderberg’s. The formation of quinoline 70 from cyanoalkene 68 was unexpected, however, upon consideration of the reaction conditions, it was proposed that the presence of a base, specifically 1,10-phenanthroline, could have altered the predicted selectivity. It was decided to examine whether simply varying the additives used in the reaction could alter the selectivity. In screening various conditions for the cyclization of 76, Banini et al. found that the combination of Pd(OAc)\(_2\) and PPh\(_3\) (deemed “conditions A”) produced exclusively indole 77, while the addition of DBU to the aforementioned conditions (deemed “conditions B”) afforded exclusively quinoline 78 (Scheme 25). This
led to the proposition that the reaction selectivity and product observed could be modulated through addition or exclusion of base in the reaction mixture.

Scheme 25: Investigation of Cyclization Conditions

![Scheme 25: Investigation of Cyclization Conditions]

To expand the scope of these findings, Banini et al. prepared a number of additional substrates to then subject to the two sets of cyclization conditions. Four unsaturated nitriles (81, 68, 83, 85) were prepared through Knoevenagel condensation of the corresponding 2-arylacetonitrile with ethanal or hexanal (Table 1).

Table 1: Knoevenagel Condensation of 2-Arylacetonitrile

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Aldehyde</th>
<th>Product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>MeCHO</td>
<td>81 (41%)</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>C_{5}H_{11}CHO</td>
<td>68 (89%)</td>
</tr>
</tbody>
</table>
Table 1: Knoevenagel Condensation of 2-Arylacetonitrile* (cont’d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Aldehyde</th>
<th>Product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="image1.png" alt="Image" /></td>
<td>MeCHO</td>
<td><img src="image2.png" alt="Image" /> 83 (21%)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image3.png" alt="Image" /></td>
<td>C₅H₅CHO</td>
<td><img src="image4.png" alt="Image" /> 85 (62%)</td>
</tr>
</tbody>
</table>

a) Conditions: AcOH, piperidine, PhH

In addition to the cyanoalkenes, two ester-functionalized alkenes (87, 89) were prepared using similar methodology65 (Table 2).

Table 2: Preparation of Ester-Substituted Alkenes*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Aldehyde</th>
<th>Product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image5.png" alt="Image" /></td>
<td>MeCHO</td>
<td><img src="image6.png" alt="Image" /> 87 (23%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image7.png" alt="Image" /></td>
<td>MeCHO</td>
<td><img src="image8.png" alt="Image" /> 89 (73%)</td>
</tr>
</tbody>
</table>

a) Conditions: AcOH, piperidine, PhH

Two additional substrates were prepared via Kosugi-Migita-Stille cross-coupling between 1-iodo-2-nitrobenzene (90) and either 1-propene-1-yltributyltin and 1-phenyl-1-propen-1-yltributyltin (Scheme 26).
Scheme 26: Preparation of 2-Nitrostyrenes via Stille Coupling

\[
\begin{align*}
\text{I} & \quad \text{SnBu}_3, \text{AsPh}_3 \quad \text{R} & \quad \text{PdCl}_2(\text{PhCN})_2 \quad \text{CuI, NMP} \\
\text{90} & \quad \text{91} & \quad \text{92} (R=\text{Ph}, 84\%) & \quad (R=\text{H}, 73\%)
\end{align*}
\]

With a number of substrates prepared, Banini et al. then examined the base-modulated cyclization. Cyclization of each ortho-nitrostyrene derivative using conditions A afforded exclusively indoles (69, 77, and 93-98, 17) in good isolated yields (Table 3, entries 1-6 and 10, 11, 13). The corresponding quinolines were not observed in the crude spectra from these reactions. Reaction of the same substrates using Conditions B gave different results depending on the substituent on the alkene. As anticipated, the cyano-substituted substrates furnished the corresponding quinolines 70, 78, 99-101 (entries 1-5). Disappointingly, ester 87 did not undergo cyclization to afford a quinoline under the basic conditions B. Three additional bases were examined for ester 87, however, indole 96 was formed in all cases (entries 6-9). This made it apparent that the formation of quinolines was limited to the cyano-substituted alkenes. In contrast, azaquinoline 103 was formed upon reaction of the pyridine derivative 89 (entry 10). In addition to 103, one additional product was isolated and identified as the azaindole 102. It is worth noting that 102 had lost a methyl group compared to azaindole 97 formed through reaction of 89 under conditions A. It was apparent that DBU was sufficiently basic to deprotonate all nitriles and esters examined as evidenced by the immediate change in color of the reaction mixtures upon addition of base, indicative of anion formation. In contrast, no color change was observed for the significantly less acidic substrates 91 and 92 upon addition of base. Reaction of 91 using DBU as the base furnished only indole 98 in 95%
yield (entry 11). However, reaction of 91 under conditions B using t-BuOK as the base (as opposed to DBU) initially produced a deep blue color (indicative of anion formation) and furnished quinoline 104 (entry 12). The least acidic substrate studied (92) afforded exclusively indole 17 under both conditions A and conditions B, regardless of what base was used (entry 13), indicating that neither t-BuOK nor DBU were basic enough to deprotonate the substrate.

Table 3. Cyclizations to Afford Substituted Indoles and/or Quinolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitroalkene</th>
<th>Conditions A&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conditions B&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76 (R=Et)</td>
<td>77 (79%)</td>
<td>78 (R'=Me, 88%)</td>
</tr>
<tr>
<td>2</td>
<td>81 (R=Me)</td>
<td>93 (82%)</td>
<td>99 (R'=H, 88%)</td>
</tr>
<tr>
<td>3</td>
<td>68 (R=Pent)</td>
<td>69 (91%)</td>
<td>70 (R'=Bu, 79%)</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>94 (80%)</td>
<td>100 (83%)</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>95 (74%)</td>
<td>101 (69%)</td>
</tr>
<tr>
<td>6</td>
<td>87</td>
<td>96 (85%)</td>
<td>96 (DBU, 87%)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>96 (NEt&lt;sub&gt;3&lt;/sub&gt;, 78%)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>96 (t-BuOK, 35%)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>96 (NaHMDS, 84%)</td>
</tr>
<tr>
<td>10</td>
<td>89</td>
<td>97 (89%)</td>
<td>102 (24%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>103 (63%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Table 3. Cyclizations to Afford Substituted Indoles and/or Quinolines (cont’d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitroalkene</th>
<th>Conditions A&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conditions B&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>91 (R=Ph)</td>
<td>98 (98%)</td>
<td>98 (95%)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>92 (R=H)</td>
<td>17 (96%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17 (89%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a) Conditions A: Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, DMF, CO (6 atm), 120 °C, 72 h.
b) Conditions B: Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, DBU, DMF, CO (6 atm), 120 °C, 72 h.
c) t-BuOK in place of DBU.
d) Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, MeCN, CO (4 atm), 70 °C, 15 h.

Two additional substrates 105 and 111, which cannot form fully aromatic quinolines without migration or loss of a carbon chain were also examined. Cyanoalkene 105 was prepared through condensation of 2-nitro-5-methoxy-1-cyanomethylbenzene (80) with 2-phenylpropanal (Scheme 27). Nitrile 105 was then subjected to reaction conditions A and B. Not surprisingly, under conditions A, the expected indole 106 was isolated in good yield (Scheme 27). In contrast, three different indoles, 107 and an inseparable mixture of 108 and 109 were obtained under the basic conditions B. The structures of 108 and 109 were elucidated using 2D NMR techniques including COSY, HMQC, HMBC, and NOESY. Interestingly, a significant part of the starting material was lost in the formation of indole 109.
Wittig reaction of cyclohexane carbaldehyde formed iodoalkene 110, which then underwent Kosugi-Migita-Stille cross-coupling with 2-nitrophenyl stannane to afford cyanoalkene 111 (Scheme 28). As anticipated, indole 112 was formed under conditions A, albeit in relatively low isolated yield. Under the basic conditions B, a low yield of indole 112 in addition to indole 113 featuring an oxidized cyclohexyl group were isolated. This outcome was interpreted as the result of a competing cyclization of 111 to 112 and cyclization of the anion formed through deprotonation of 111 to give 113.
The difference in chemoselectivity between the nitriles and the esters was puzzling. It was unclear why either indoles or quinolines were obtained from the nitrile-substituted substrates, while the esters afforded exclusively indoles under both sets of conditions. Presumably, the pKa for the substrates having either a nitrile or an ester moiety must be very similar in magnitude. For example, the pKa values for CH₃CN and CH₃CO₂Et have been reported as 24.5 and 25.0, respectively. In addition, the color changes observed upon addition of base to both the ester and nitrile-substituted substrates likely indicated that the conjugate base was formed, thus raising questions regarding the resonance forms of each anion.

To probe the electronic distribution of anions formed, two similar substrates 81 and 114, differing only in the electron-withdrawing group, CN vs. CO₂Et, respectively, were compared. Each substrate was deprotonated with t-BuOK in t-BuOH, then methyl iodide was added to the mixture with the intent of trapping the intermediate to determine the identity of the anion formed through the initial deprotonation (Scheme 29). In doing such, two different products were obtained. After workup and purification, ester 114 gave exclusively N-methoxyindole 115, while on the other hand, nitrile 81 furnished quinoline-N-oxide 116. As was noticed for two previous indole products (25 and 32), part of the alkyl chain was lost during the formation of indole 115. The drastically different results obtained through these two experiments under identical reaction conditions confirmed that esters and the nitriles have different chemoselectivity. The reason for this difference is presently unknown.
The mechanisms for the reactions leading to either indole or quinoline products and indoles wherein a carbon-carbon bond has been broken and/or a side-chain oxidized are not clear at this time. In the absence of a base, the reaction likely proceeds via a deoxygenation producing a nitroso compound followed by either a) a second deoxygenation to give a nitrenenoid intermediate and ultimately an indole or b) an electrocyclic ring closure to afford an N-hydroxy indole followed by a palladium-catalyzed deoxygenation as discussed in Chapter 1 (Scheme 30). However, this mechanistic rationale accounts for the formation of indoles without carbon-carbon bond cleavage or side-chain oxidation, both of which were observed in a few of the previously mentioned examples.

**Scheme 30: Potential Mechanism(s) for Cyclization in Absence of Base**

The mechanistic picture is slightly more complex in the presence of a base.

Addition of a sufficiently strong base to cyanoalkene 83 results in the formation of the conjugate base 117 as evidenced by the immediate formation of a deep blue solution.
(Scheme 31). The nitro group of 117 is likely deoxygenated by the catalyst system to form nitrosarene 118. Nucleophilic addition of the carbanion of 118 to the nitroso group followed by protonation-deprotonation and elimination of hydroxide (119 to 120) would furnish quinoline 100.

**Scheme 31: Proposed Mechanism for Quinoline Formation**

Makosza et al.\textsuperscript{67} have reported the formation of quinoline-N-oxides (such as 79, Scheme 25) by treatment of compound 76, and related substrates, with triethylamine and trimethylsilyl chloride (Scheme 32). This result raised the question of whether the base-modulated cyclization forming quinolines (conditions B) was simply a palladium-catalyzed reduction of the quinoline N-oxide 79 formed through nucleophilic attack of the initially formed carbanion to the nitro group of 76 without prior reduction of the nitro group to a nitrosarene. Submitting quinoline N-oxide 79 to conditions B did indeed furnish quinoline 76, however, the yield of quinoline 78 was only 24% after the same length of time required to produce quinoline 78 in 88% yield directly from 76 using our palladium-catalyzed methodology.
While this result is not conclusive, it indicates that the palladium-catalyzed reaction likely involves a different pathway than substrate (76) → quinoline-N-oxide (79) → quinoline (78). It is feasible that the palladium-catalyzed reduction of nitroaromatic 76, resulting in the formation of the nitroso-intermediate is faster in relation to nucleophilic addition to the nitro group in cases wherein a quinoline is formed. In the event, carbanion addition could then occur to the nitroso group (as depicted in Scheme 31) as opposed to the nitro group as reported by Makosza. Another explanation could be that nucleophilic addition to the nitro group may also be a reversible reaction under basic conditions while the reduction to a nitrosarene is not.

The final mechanistic question involved the formation of indoles with concurrent carbon-carbon bond fission (102, 109), oxidation (108, 113), or alkene formation (107). The transformation may occur via addition of allylic carbanion 117 to one of the nitro group oxygens, affording the seven-membered intermediate 118 (Scheme 33). Ring-opening of 118 would give nitrosarene 119, which following electrocyclic ring-closure would produce 120. Rearomatization of 120 either by loss of a proton would afford N-hydroxyindole 121 or through loss of acetophenone and subsequent protonation would provide N-hydroxyindole 122. Palladium-catalyzed deoxygenation of 121 would afford alcohol 107 after subsequent protonation. Elimination of water from 107 could then produce 108. Deoxygenation of 122 would result in the formation of indole 109.
The addition of the carbanion to the nitro group of 117 proposed in Scheme 33 is supported by related observations reported in the literature. Nyerges et al.\textsuperscript{68,69} reported novel 1,7 electrocyclizations of azomethine ylide to pendant nitro groups in their preparation of indazole-\(N\)-oxides. In addition, attack of carbanions to aromatic nitro groups has been proposed as one of the steps in the Bartoli indole synthesis using nitroarenes and excess alkenyl Grignard reagents.\textsuperscript{70}

### 2.3 Conclusions

A synthetic methodology for the formation of various 4-cyanoquinolines and 3-cyanoindoles from a common 1-cyano-1-(2-nitrophenyl)alkene precursor has been established. In the absence of a base, indoles are formed through palladium-catalyzed reductive \(N\)-heteroannulation. Quinolines are formed in the presence of a base, presumably through intramolecular nucleophilic addition of a carbanion to a nitrosarene. Analogous esters afford exclusively indoles regardless of the conditions used. Mechanistic rationales for the formation of both products and side products have been presented on the basis of literature precedence and experimental findings.
Chapter 3

An Expedient Synthesis of Salviadione

3.1 Salviadione Background 35
3.2 Expedient Synthesis of Salviadione 35
  3.2.1 Retrosynthetic Analysis 36
  3.2.2 Results and Discussion 37
  3.3 Conclusions 43
3.1 Introduction to Salviadione

Traditional Chinese folk medicine has employed the use of the dried root of *Salvia miltiorrhiza* as treatment for a wide array of illnesses as Danshen or Tanshen. A number of biologically active compounds have been isolated from the dried root and can be classified as either water-soluble phenolic acids or lipophilic abietane-type diterpenes. These compounds have shown biological activity ranging from antioxidant, anti-inflammatory, antifungal, anticoagulant, anti-HIV, antitumor, and antibacterial activity.\(^7^1\) Another structurally unique alkaloid, Salviadione, 1,1-dimethyl—6-(1-methylethyl)-1\(H\)-benzo[def]carbazole-3,5-(2\(H\),4\(H\))-dione (123), was also isolated from these dried roots in 2005 (Figure 5).\(^7^2\) It is believed that this is the only naturally isolated benzo[def]carbazole.\(^7^3\) and one of a small number prepared synthetically.\(^7^4\) The unique structure inspired us to commence a synthetic study.

**Figure 5: Structure and Atom Numbering of Salviadione**

3.2 Expedient Synthesis of Salviadione

The unique structure of Salviadione made it an attractive candidate for a synthetic study. It was proposed that formation of the \(N\)-heterocyclic ring of the molecule could result from a Söderberg palladium-catalyzed reductive \(N\)-heterocyclization reaction. The goal was to highlight this methodology as a key step in the synthetic route.
3.2.1 Retrosynthetic Analysis

The structure of Salviadione is deceptively complex, allowing us to propose a relatively concise synthetic route (Scheme 34). It was envisioned that Salviadione (123) could result from benzylic oxidation of phenol 124. The indole core of 124 could be prepared through reductive heterocyclization of nitroaromatic 125. Nitration of the tricyclic diterpenoid 126 would be expected to occur ortho to the methoxy group to give desired nitroaromatic 125. This tricyclic core could be prepared using the procedure previously outlined by Pan et al.75 Diterpenoid 126 would result from the acid-induced cyclization- Friedel-Craft’s alkylation of para-substituted anisole 127, which could be prepared through reaction between iodide 129 and the carbanion derived from 128. Iodide 129 could be achieved through a simple iodination of commercially available alcohol 131, while isopropyl enol ether 128 could be prepared from O-alkylation of 5,5-dimethyl-1,3-cyclohexanedione 130.
3.2.2 Results and Discussion

The synthetic route began with the alkylation of commercially available dimerdone (5,5-dimethyl-1,3-cyclohexanedione) 130 to afford isopropyl enol ether 131 through reaction with isopropanol and a catalytic amount of p-toluenesulfonic acid (Scheme 35).

Scheme 35: Alkylation of Dimedone

Alcohol 131 was then converted to the corresponding iodide 129 using typical Appel conditions (Scheme 36).
Scheme 36: Preparation of Alkyliodide

\[
\text{Iodide 129 then underwent alkylation with the carbanion formed through treatment of 128 with lithium N,N-diisopropylamine to give 127 (Scheme 37).}^{78,79}
\]

Scheme 37: Preparation of Cyclization Precursor

Intramolecular cyclization-Friedel-Crafts alkylation\(^7^5\) of 127 was achieved through heating in polyphosphoric acid, furnishing tricyclic terpenoid 126 (Scheme 38).

Scheme 38: Acid-Induced Intramolecular Cyclization-Friedel-Crafts Alkylation

The next major challenge was the nitration of tricyclic diterpenoid 126. The regioselectivity of the nitration was \textit{ortho} to the methoxy-group as was expected,\(^8^0\) however, the observed product(s) were very sensitive to reaction conditions, work-up procedure, and speed of chromatographic purification. Given these variables, it was very hard to control the outcome of a given reaction even when using similar conditions.
Nitration of 126 with a mixture of fuming nitric acid and sulfuric acid at -78 °C provided nitro-phenol 125 in addition to desired anisole product 132 (Scheme 39). The absence of demethylation product 125 in reactions where the starting material was not fully consumed leads us to believe that the demethylation must occur after introduction of the nitro-group. Though unexpected, the demethylation turned out to be beneficial, as nitrophenol 125 provided a more direct route to salviadione (123).

**Scheme 39: Nitration of Tricyclic Diterpinoid Core**

When the nitration was performed at -20 °C, nitro-phenol 125 was the major product observed along with a trace amount of 132. Upon separation by column chromatography, both 126 and 132 were moderately stable, however, exposure to acidic conditions and open air or leaving the products absorbed onto silica gel for an extended amount of time resulted in oxidation to quinole 133 as a mixture of diastereomers (14:1 ratio). As an example, treatment of 132 with acetic acid while absorbed on silica gel afforded quinole 133 in 88% yield. This product was also observed when the nitration of 126 was performed at 0 °C and allowed to warm to room temperature, after which the crude product was absorbed onto silica gel and left open to the air (Scheme 40).
The relative stereochemistry of the major diastereomer of **133** was concluded through NOE, COSY, and selective decoupling NMR experiments. The H9-axial proton and the hydroxy group displayed a four-bond spin-spin coupling ($J=1.5$ Hz), which is in accordance with values observed for similar compounds.$^{81}$

Each of the three nitration products (**125, 132, 133**) were subjected to the previously discussed palladium-catalyzed reductive $N$-heteroannulation conditions$^{60}$ in hope of obtaining the expected benzo[def]carbazoles. Reaction of both anisole **132** and phenol **125** with carbon monoxide in the presence of a catalytic amount of palladium bis(dibenzylidenacetone) and 1,10-phenanthroline provided **134** and **124** in 87% and 75% yield, respectively (Scheme 41). Unlike their precursors, both cyclization products were stable towards oxidation when treated with acetic acid, air, and when adsorbed onto silica gel.

**Scheme 41: Palladium-Catalyzed Reductive $N$-Heteroannulation**

Attempted palladium-catalyzed cyclization of quinole **133** was not as successful as the two previous cases. Although a small amount (10%) of salviadione (**123**) was isolated from a complex reaction mixture of which all of the starting material had been
consumed, none of the expected cyclization product 135 was obtained (Scheme 42). Multiple attempts to improve the yield of this direct route to salviadione (123) were unsuccessful.

**Scheme 42: Attempted Cyclization of Quinole**

![Scheme 42: Attempted Cyclization of Quinole](image)

Conditions: 1,10-phenanthroline, Pd(dba)$_2$, CO (6 atm), DMF, 120 °C

Methoxy-substituted compound 134 was also treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), resulting in benzylic oxidation to afford hydroxy substituted benzo[def]carbazole 136 (Scheme 43).$^{82}$ Interestingly, 136 possesses the same relative stereochemistry between the hydroxy group and the C9-axial proton as reported for a number of similar naturally occurring compounds.$^{83}$ In the case of 136, this relative stereochemistry was determined through NOE NMR experiments. Unfortunately, conversion of this compound to salviadione (123) would require demethylation, elimination of water, and oxidation, so the route was not pursued.

**Scheme 43: Benzylic Oxidation of Anisole Using DDQ**

![Scheme 43: Benzylic Oxidation of Anisole Using DDQ](image)

A more synthetically-useful route to salviadione (123) was achieved through treatment of hydroxy compound 124 with a four-fold excess of DDQ in tetrahydrofuran (THF), affording salviadione (123) in good yield (Scheme 44).
The structure of salviadione was confirmed through comparison of experimentally obtained melting point, IR, HRMS, and \( ^1H \) NMR data with that reported for the natural product.\(^{72} \) Table 4 provides a comparison of \( ^1H \) NMR data while \( ^{13}C \) NMR data is provided in Table 5. Every carbon resonance was found to be within 1 ppm of the natural product aside from one (C3a), which was 1.2 ppm off.

**Table 4: \( ^1H \)NMR Shift Comparison Between Synthetic and Natural Salviadione**

<table>
<thead>
<tr>
<th>Proton</th>
<th>( \delta ) (ppm)(^{a,c} )</th>
<th>( J ) (Hz)(^{a,c} )</th>
<th>( \Delta \delta ) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH</td>
<td>13.24 (14.23)(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-2</td>
<td>2.95 (2.95)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>H-6</td>
<td>7.55 (7.56)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>H-8</td>
<td>7.66 (7.66)</td>
<td>7.0 (7.5)</td>
<td>0</td>
</tr>
<tr>
<td>H-9</td>
<td>7.31 (7.30)</td>
<td>7.0 (7.5)</td>
<td>-0.01</td>
</tr>
<tr>
<td>iPr-CH</td>
<td>3.49 (3.54)</td>
<td>6.9 (7.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>iPr-Me</td>
<td>1.29 (1.31)</td>
<td>6.9 (7.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>1-Me</td>
<td>1.51 (1.49)</td>
<td>-0.02</td>
<td></td>
</tr>
</tbody>
</table>

a) In CDCl\(_3\), b) In DMSO-d\(_6\), c) Literature values in parenthesis.
Table 5: $^{13}$CNMR Shift Comparison Between Synthetic and Natural Salviadione

<table>
<thead>
<tr>
<th>Carbon</th>
<th>$\delta$ (ppm)$^a$</th>
<th>$\Delta \delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41.3 (41.3)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>57.3 (57.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>187.7 (188.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>3a</td>
<td>127.0 (128.2)</td>
<td>1.2</td>
</tr>
<tr>
<td>4a</td>
<td>126.7 (126.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>5</td>
<td>175.8 (175.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>6</td>
<td>151.3 (151.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>7</td>
<td>128.9 (129.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>7a</td>
<td>128.2 (127.9)</td>
<td>-0.3</td>
</tr>
<tr>
<td>8</td>
<td>129.5 (129.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>121.2 (121.0)</td>
<td>-0.2</td>
</tr>
<tr>
<td>9a</td>
<td>144.9 (145.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>9b</td>
<td>124.0 (123.9)</td>
<td>-0.1</td>
</tr>
<tr>
<td>9c</td>
<td>124.2 (124.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>iPr-Me</td>
<td>22.7 (22.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>iPr-CH</td>
<td>27.3 (27.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cl-Me</td>
<td>30.0 (30.1)</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

*a* In CDCl$_3$; Literature values in parenthesis.

To probe the potential biological uses of these compounds, salviadione (123), along with methoxy and hydroxy analogs 134 and 124, respectively, were tested for potential activity against liver cancer cell lines. However, initial results showed LD$_{50}$ values similar to those typical for DMSO, which was used as the carrier solvent in the assays. Therefore, any cell death was attributed to the DMSO rather than the synthesized compounds. However, this preliminary examination was very narrow in focus and it is possible that compounds 123, 124, and 134 possess other biological uses.

3.3 Conclusions

A novel, concise synthetic route to Salviadione and two related derivatives has been developed utilizing a key palladium-catalyzed reductive N-heterocyclization to form the indole core. Through an unexpected yet advantageous demethylation encountered in
the nitration of the tricyclic terpenoid intermediate, a more direct route than initially envisioned was established. This reaction sequence may allow facile preparation of additional structural analogues, which could prove useful in a wide array of biological applications.
Chapter 4

Investigation of Chemoselectivity in Kosugi-Migita-Stille Coupling Reactions

4.1 Kosugi-Migita-Stille Reaction Background 46
4.2 Chemoselective Stille Coupling Reactions 46
4.3 Investigation of Nitro Effect in Stille Coupling Reactions 48
   4.3.1 Preparation of Isomeric Substrates 49
   4.3.2 Results and Discussion 53
4.3 Conclusions 64
4.1 Kosugi-Migita-Stille Reaction Background

Carbon-carbon bond forming reactions have been a key focus of many synthetic organic chemists over the past number of decades. Kosugi, Shimizu, and Migita reported the first examples of palladium-catalyzed coupling between organotin compounds and carbon electrophiles in 1977. Stille’s first study of similar reactions was published in 1978. While his work was preceded by that of Kosugi, Shimizu, and Migita, the coupling of organotin reagents with carbon electrophiles using palladium catalysts is often referred to as simply the “Stille Coupling” reaction as Stille’s comprehensive mechanistic and synthetic investigations provided the basis for more recent studies.

4.2 Chemoselective Stille Coupling Reactions

Selectivity is an ever-important yet challenging issue when employing a particular reaction. Chemoselectivity refers to the ability to react with one particular functional group in the presence of other potentially reactive groups. A specific example of chemoselectivity was reported by Echavarren, who studied Stille cross-coupling reactions between organostannanes and arenes featuring both a halide and a triflate. Through use of different palladium catalysts and additives, selective couplings were achieved through either the carbon-halide or carbon-triflate bond of bromophenyl triflate. These results are summarized in Scheme 45. The use of tetrakis(triphenylphosphine)palladium(0) as the catalyst in 1,4-dioxane favored reaction with the bromine, affording styrene, while using bis(triphenylphosphine)palladium(II) dichloride as the catalyst along with a three-fold excess of lithium chloride in N,N-dimethylformamide (DMF) afforded exclusively styrene through reaction with the trifloxy group.
These initial studies suggest that using a palladium (II) catalyst as well as the addition of lithium chloride facilitates insertion of palladium into the carbon-oxygen bond of the triflate to afford bromostyrene 139. It was also proposed\textsuperscript{90} that coordination of the catalyst to the basic trifloxy group could direct the oxidative addition to occur into the triflate carbon-oxygen bond rather than to the carbon-bromine bond. The addition of lithium chloride facilitates ligand exchange of the trifluoromethanesulfonyloxy group for a chloride upon oxidative addition of palladium into the carbon-oxygen bond of the triflate, rendering the intermediate more reactive for subsequent transmetallation.\textsuperscript{91}

Only one example of a chemoselective coupling reaction involving a nitratated bromophenyl triflate has been reported by Krolski.\textsuperscript{92} Using conditions similar to those previously discussed\textsuperscript{90} for the selective coupling of aryl bromides, chemoselective coupling through the carbon-bromine bond of 2-bromo-3-nitrophenyl triflate (140) accomplished, affording styrene 141 (Scheme 46).

**Scheme 46: Krolski Selective Coupling of 2-Bromo-3-Nitrophenyl Triflate**

4.3 **Investigation of Nitro Effect in Stille Coupling Reactions**

Selective couplings were of interest for the potential use in the preparation of substrates en route to pyrroloindoles via reductive double \textit{N}-heteroannulations. The first
system examined was 2,4-dinitro-5-bromophenyl triflate (144), which was prepared in two steps from 3-bromophenol (142) (Scheme 47). Conversion of phenol 142 to the corresponding triflate 143 followed by nitration eliminated the formation of trinitrophenol as observed in the direct nitration of phenol 142.

**Scheme 47: Preparation of 2,4-Dinitro-5-Bromophenyl Triflate**

The application of Echavarren’s conditions that should result in coupling through the carbon-bromine bond (Conditions A) using substrate 144 afforded a near 1:1 mixture of triflate-coupled product 145 along with bromine-coupled 146 (Scheme 48).

**Scheme 48: Attempted Selective Coupling of Dinitro-Bromophenyl Triflate**

The lack of selectivity observed in the coupling of dinitroarene 144 was puzzling. It was concluded that additional factors must have been influencing the erosion of chemoselectivity observed for the dinitro substrate 144. Considering that electron-withdrawing substituents often enhance the reactivity of C-X bonds (with X referring to either a halide or pseudohalide) in coupling reactions, it was proposed that the nitro groups were the root of the eroded selectivity. The effect was believed to be due to the nitro groups being in conjugation with the ortho and para X-groups, reducing the electron density at those positions. The more electrophilic X-groups would then be more
prone to oxidative addition, potentially causing the observed loss of selectivity. Another proposal, based off Echavarren’s explanation\(^9^0\) for the selectivity observed under triflate-selective conditions B, was that the nitro-group could facilitate the oxidative addition into each C-X bond through coordination with the catalyst. In the case of substrate 144 where each C-X bond is ortho to a nitro group, potential coordination between palladium and the nitro group could facilitate oxidative addition into either C-X bond. To more explicitly examine the influence that placement of nitro groups had on coupling selectivity, it was deemed necessary to prepare each of the ten bromo-trifloxy nitrobenzene isomers in order to determine what effect the position of the nitro group relative to the triflate or bromine had on the selectivity of the coupling reaction. The plan was to subject each isomer to both the halide-selective conditions A (PPh\(_3\), Pd(PPh\(_3\))\(_4\), dioxane, reflux) and triflate-selective conditions B (PdCl\(_2\)(PPh\(_3\))\(_2\), LiCl, DMF, room temperature) as established by Echavarren.\(^9^0\)

### 4.3.1 Preparation of Isomeric Substrates

The first challenge was the preparation of the ten substitutional isomers using a variety of nitration and halogenation reactions.

2-bromo-4-nitrophenol 148 and 2-bromo-6-nitrophenol 149 were prepared through the nitration of 2-bromophenol 147 using sodium nitrite and oxalic acid along with wet silica gel (Scheme 49).\(^9^3\) The relatively mild reaction conditions provided solely mono-nitrated products with no evidence of di-nitration.
Scheme 49: Nitration of 2-Bromophenol

Conversion to the corresponding triflates 150 and 151 was then accomplished through treatment with pyridine and triflic anhydride (Scheme 50). Filtration of the crude reaction mixture removed the pyridine salt byproduct, and evaporation of solvent provided nearly pure product in both cases.

Scheme 50: Preparation of Isomeric Nitrophenyl Triflates

Nitration of 4-bromophenol (152) using the same conditions as above provided exclusively 2-nitro-4-bromophenol 153 (Scheme 51). Conversion to the corresponding triflate (as above) provided isomer 154.
Scheme 51: Preparation of 2-Nitro-4-Bromophenyl Triflate

3-nitro-5-bromophenol 156 was prepared in a two-step process from 2-amino-5-nitrophenol 155 (Scheme 52). Regioselective bromination using N-bromosuccinimide (NBS) followed by de-amination provided phenol 156, which was converted to triflate 157 through treatment with pyridine and triflic anhydride.

Scheme 52: Preparation of 3-Nitro-5-Bromophenyl Triflate

2-bromo-5-nitrophenyl triflate 159 was also prepared from 2-amino-5-nitrophenol (155) (Scheme 53). Initial halogenation with copper (II) bromide provided aryl bromide 158, which was subsequently converted to triflate 159 using previously established conditions.

Scheme 53: Preparation of 2-Bromo-5-Nitrophenyl Triflate

3-nitro-4-bromophenyl triflate 163 was prepared in three steps from 3-nitro-4-aminoanisole 160 (Scheme 54). Halogenation of aniline 160 using Sandmeyer-type
conditions provided aryl bromide 161, which was then treated with boron tribromide to cleave the phenyl methyl ether, providing phenol 162. Treatment of 162 with base and triflic anhydride afforded triflate 163.

**Scheme 54: Preparation of 4-Bromo-3-Nitrophenyl Triflate**

![Scheme 54](image)

Boron tribromide demethylation\textsuperscript{95} of anisole 164 provided phenol 165, which was then converted to triflate 166 using previously discussed conditions (Scheme 55).

**Scheme 55: Preparation of 3-Bromo-2-Nitrophenyl Triflate**

![Scheme 55](image)

Two additional isomers (167 and 168) were prepared through the mono-nitration of 3-bromophenyl triflate 143 (Scheme 56).

**Scheme 56: Preparation of 167 and 168**

![Scheme 56](image)

The final isomer 140 was prepared in near quantitative yield from phenol 169, which was on hand from previous work within the laboratory (Scheme 57).
4.3.2 Results and Discussion

With each of the possible structural isomers in hand, focus was turned to the coupling reaction, each substrate was treated with vinyl stannane in the presence of either bromine-selective conditions A (Pd(PPh₃)₄, dioxane, reflux) and triflate-selective conditions B (PdCl₂(PPh₃)₂, LiCl, DMF, r.t). The results of this systematic investigation are summarized in Table 6. In some cases, unreacted starting material and/or coupled product was isolated as the corresponding phenol due to hydrolysis during column chromatography. In addition, minor amounts of di-coupled products were also detected in some cases. All reactions were run for 24 hours to allow direct comparison between substrates by limiting potential variables. In a slight variation from Echavarren’s work which directly used Pd(PPh₃)₄, the same complex was generated in situ by mixing Pd(dba)₂ with PPh₃. For clarity, the substrates in Table 6 are arranged according to the position of the bromine relative to the nitro group. Entries 1-4 are isomers where the bromine is ortho to the nitro group, entries 5-8 possess a meta relationship between the bromine and nitro group, and entries 9-10 feature the bromine para to the nitro group.
**Table 6: Isolated Yields From Reaction Under Conditions A and B**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Br-coupling</th>
<th>TfO-coupling</th>
<th>Hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td><strong>140</strong></td>
<td><strong>141</strong> (36%)</td>
<td><strong>170</strong> (38%)</td>
<td><strong>169</strong> (62%)</td>
</tr>
<tr>
<td>1B</td>
<td>140 (27%)</td>
<td>141 (20%)</td>
<td>170 (38%)</td>
<td>169 (12%)</td>
</tr>
<tr>
<td>2A</td>
<td><strong>167</strong></td>
<td><strong>171</strong> (82%)</td>
<td><strong>172</strong> (37%)</td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td>167</td>
<td>171 (9%)</td>
<td>172 (37%)</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td><strong>163</strong></td>
<td><strong>173</strong> (68%)</td>
<td><strong>174</strong> (36%)</td>
<td></td>
</tr>
</tbody>
</table>
| 3B    | 163 (17%)
|        |            | **173** (23%)
|        |            | **174** (36%) |            |
| 4A    | **166**   | **175** (60%) | **176** (3%)  | **149** (18%) |
| 4B    | 166       | 175 (60%)   | 176 (3%)     | 149 (12%)  |
| 5A    | **151**   | **177** (24%) | **46** (5%)  | **149** (18%) |
| 5B    | 151 (5%)  | 177 (24%)   | 46 (5%)      | 149 (12%)  |
| 6A    | **150**   | **178** (22%) | **179** (57%) | **148** (8%) |
| 6B    | 150 (8%)  | 178 (22%)   | 179 (57%)    | 148 (16%)  |
| 7A    | **157**   | **180** (78%) | **181** (66%) |            |
| 7B    | 157       | 180 (78%)   | 181 (66%)    |            |
Table 6: Isolated Yields From Reaction Under Conditions A and B (cont’d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Br-coupling</th>
<th>TfO-coupling</th>
<th>Hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>8A</td>
<td><img src="image" alt="Structure" /></td>
<td>154 (10%)</td>
<td>182 (44%)$^a$</td>
<td>183 (3%)</td>
</tr>
<tr>
<td>8B</td>
<td>154</td>
<td></td>
<td></td>
<td>183 (78%)</td>
</tr>
<tr>
<td>9A</td>
<td><img src="image" alt="Structure" /></td>
<td>168</td>
<td>184 (64%)</td>
<td></td>
</tr>
<tr>
<td>9B</td>
<td>168</td>
<td></td>
<td>184 (26%)</td>
<td>185 (24%)</td>
</tr>
<tr>
<td>10A</td>
<td><img src="image" alt="Structure" /></td>
<td>159 (20%)$^a$</td>
<td>186 (48%)$^a$</td>
<td></td>
</tr>
<tr>
<td>10B</td>
<td>159 (31%)</td>
<td></td>
<td>186 (31%)$^a$</td>
<td>187 (7%)</td>
</tr>
</tbody>
</table>

**Cond. A**: vinyl stannane, PPh$_3$, Pd(dba)$_2$, 1,4-dioxane, 105 °C  
**Cond. B**: vinyl stannane, PdCl$_2$(PPh$_3$)$_2$, LiCl, DMF, r.t.

a) Yield calculated based on integration of $^1$H NMR spectrum; b) Also isolated was 31% di-coupled product

Under conditions A, all but one substrate featuring a bromine ortho to the nitro group (table 6, entries 1-4) exhibited high selectivity, affording exclusively bromine-coupled products (141, 171, 173). The only isomer of this group that was not completely selective was that which had both a bromine and a trifluoro group ortho to the nitro group (entry 4). In this case, a small amount of trifluoro-coupled product 176 was isolated in addition to the expected bromine-coupled product 175. This result could be explained by the trifluoro group also being activated toward oxidative addition through conjugation with the ortho nitro substituent.

Interestingly, substrates with a bromine meta to the nitro group (entries 5-8) also exhibited high selectivity under bromine-selective conditions A. Only isomer 151 (entry
5) was not completely selective for bromine coupling. It can be envisioned that the trifloxy group ortho to the nitro group would be activated through conjugation with the nitro group, while the bromine meta to the nitro group would not, leading to erosion of selectivity. However, substrates 150 and 154 (entries 6 and 8, respectively) in which the trifloxy group was also in conjugation with the nitro group do not exhibit the same erosion of selectivity. Also of interest is entry 7 where both the bromine and trifloxy group were meta to the nitro group. Surprisingly, the isolated yield of bromine-coupled 180 (78%) was among the highest of any isomer examined. This result may be attributed to the overall electron-deficient nature of the nitro-substituted aromatic system even though the nitro group was not in conjugation with the bromine or trifloxy group.

The last two substrates, 168 and 159 (entries 9 and 10, respectively), in which the bromine was positioned para to the nitro group were completely selective for bromine coupling under bromine-selective conditions A. This was surprising for isomer 168 in which the trifloxy group was activated ortho to the nitro group, although the bromine was in the para position, which would also be activated through conjugation with the nitro group. In this case, the observed selectivity could be attributed to a faster transmetalation between palladium and tin upon oxidative addition of the catalyst to the carbon-bromine bond as opposed to the carbon-oxygen bond of the triflate.91

Under triflate-selective conditions B, three of the four isomers in which the trifloxy group was ortho to the nitro group (entries 4, 5, 8) exhibited absolute selectivity for triflate coupling. In contrast, isomer 168 (entry 9) was actually counter-selective, affording bromine-coupled 184 in higher yield than triflate-coupled 185. This lack of selectivity could be attributed to the bromine being activated through conjugation with
the para nitro group, although the trifloxy group would also be activated ortho to the nitro group.

With the exception of entry 7 (where both the triflate and bromine were meta to the nitro group), isomers in which the trifloxy group was meta to the nitro group (entries 1, 3, 10) exhibited the lowest selectivities out of all of the substrates studied under conditions B. While this could be attributed to each substrate featuring an activated bromine ortho or para to the nitro group, it is also an indication that conditions B were not ideal for triflate-selective coupling. However, isomer 157 (entry 7) afforded exclusively triflate-coupled 181 on account of the bromine also being in an inactivated meta position relative to the nitro group.

The last two substrates were those where the trifloxy group was para to the nitro group (entries 2, 6). While isomer 150 was completely selective for triflate-coupling, isomer 167 exhibited eroded selectivity. This contrast could be attributed to the orientation of the bromine relative to the nitro group in each substrate, with the bromine of isomer 150 being in an unactivated meta position while the bromine of isomer 167 was activated by the ortho nitro group.

From the numerous examples presented in Table 6, it was apparent that the nitro group was key in influencing the selectivity of the reaction. In general, substrates in which the nitro group was ortho or para to the triflate or bromine exhibited significantly higher conditions-dependent selectivity than those where the nitro-group was meta relative to the targeted coupling moiety. In cases where the targeted C-X bond was meta to the nitro group, the selectivity was reduced and, in some cases, reversed from what was expected. The reversal of predicted selectivity in these cases could then attributed to electronic activation of the other C-X bond through conjugation with the nitro group.
In addition to the ten mono-nitrated cases mentioned above, two additional isomeric bromophenyl triflates 188 and 137 were prepared in near quantitative yield from the corresponding phenols (Scheme 58).

**Scheme 58: Preparation of Bromophenyl Triflates**

![Chemical reactions](image)

Each of these substrates (along with 3-bromophenyl triflate 143 from above) were then subjected to coupling conditions A and B. The selectivity observed in each of these reactions is summarized in Table 7.

**Table 7: Selective Coupling of Bromophenyl Triflates**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Br-coupling</th>
<th>Tfo-coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>188</td>
<td>189 (1.0)</td>
<td>190 (0.85)</td>
</tr>
<tr>
<td>1B</td>
<td>188</td>
<td>189 (0.15)</td>
<td>190 (0.85)</td>
</tr>
<tr>
<td>2A</td>
<td>143</td>
<td>191 (1.0)</td>
<td>192 (0.85)</td>
</tr>
<tr>
<td>2B</td>
<td>143</td>
<td>191 (0.15)</td>
<td>192 (0.85)</td>
</tr>
</tbody>
</table>
Table 7: Selective Coupling of Unsubstituted Bromophenyl Triflates (cont’d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Br-coupling</th>
<th>TfO-coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A</td>
<td>137</td>
<td>138 (0.85)</td>
<td>139 (0.15)</td>
</tr>
<tr>
<td>3B</td>
<td>137</td>
<td>138 (0.15)</td>
<td>139 (0.85)</td>
</tr>
</tbody>
</table>

Cond. A: PPh$_3$, Pd(dba)$_2$, 1,4-dioxane, 105 °C
Cond. B: PdCl$_2$(PPh$_3$)$_2$, LiCl, DMF, r.t.

Each of these substrates exhibited high selectivity under bromine-selective conditions A. However, conditions B were not as selective, with each substrate affording an approximately 6:1 ratio of the expected triflate-coupled product to the bromide-coupled product. This again demonstrated that conditions B were not ideal for selective coupling of triflates. Pure products were only isolated in some cases, however, due to the tendency of the styrene products to polymerize upon purification, particularly the bromostyrenes. In these cases, the coupled products were present in the NMR spectra obtained after work-up of the reaction mixture; however, no product was isolated upon purification using column chromatography regardless of whether silica gel, basic alumina, or neutral alumina were used as the stationary phase. For these substrates, the selectivities were inferred from integration of the $^1$H NMR spectra.

Echavarren$^{90}$ also examined the cross-coupling of iodophenyl triflate 193 (Scheme 59). In contrast to the results obtained for bromophenyl triflate 137, styrene 138 was the only product observed regardless of the catalyst conditions used. This was also in accordance with the established trend$^{97}$ that iodides undergo oxidative addition faster than triflates.
Scheme 59: Echavarren’s Coupling of \( p \)-Iodophenyl Trflate

4-iodo-2-nitrophenyl triflate 196 was prepared as a model to examine whether an iodide would still be more reactive than a trifloxy group even if the iodide was in an unactivated position (meta to the nitro group) and the trifloxy group was in an activated position (ortho to the nitro group). Nitration\(^{93}\) of 4-iodophenol (194) afforded nitrophenol 195, which was then converted to triflate 196 using previously established conditions (Scheme 60).

Scheme 60: Preparation of 4-Iodo-2-Nitrophenyl Trflate

Under both conditions A and B, iodine-coupled 197 was the major product isolated (Scheme 61). Even though the triflate was in an activated position ortho to the nitro group, the iodine was still more reactive towards coupling, even under triflate-selective conditions B, which afforded only a trace amount of triflate-coupled product 198. This result was drastically different than that observed for the analogous bromide 154 (table 6, entry 8), which afforded exclusively triflate-coupled 183 in 78% yield under conditions B. In addition, iodide 196 afforded exclusively iodine-coupled 197 under conditions A, whereas the analogous bromide 154 (table 6, entry 8) exhibited erosion of
selectivity under the same conditions. This direct comparison demonstrated the substantial difference in reactivity between aryl bromides and aryl iodides.

**Scheme 61: Coupling of 4-Iodo-2-Nitrophenyl Triflate**

![Scheme 61](image)

To examine whether the generalized chemoselectivity could be extended to electron-withdrawing substituents aside from a nitro group, 5-bromo-2-trifloxy acetophenone (201) was prepared (Scheme 62). Bromination of phenol 199 afforded the desired bromide 200, which was then converted to triflate 201.

**Scheme 62: Preparation of 5-Bromo-2-Trifloxy Acetophenone**

![Scheme 62](image)

Based on the observations for nitro-substituted arenes, it was proposed that coupling of 201 under conditions A would exhibit erosion of selectivity due to the triflate being activated by the ortho electron withdrawing substituent. However, conditions A afforded only 202 (albeit in poor yield), and conditions B afforded only 203, as expected (Scheme 63). This suggests that weaker electron-withdrawing substituents have little influence on the overall selectivity. However, it is also important to note that for the analogous nitro substrate 154 (Table 6, entry 8), conditions A were not completely selective for bromine-coupling, while conditions B were completely selective for triflate-
coupling. This result is in accordance with the weaker electron-withdrawing acetyl group present in 201 having a smaller activation effect relative to the nitro group in 154.

**Scheme 63: Selectivity Under Conditions A and B**

Previous work reported bromine-selective coupling under “Conditions B” for bromo-trifloxybenzene 204, affording 205 in moderate yield (Scheme 64). The observed selectivity was postulated to be due to the trifloxy group being deactivated by the ortho and para electron-donating methoxy and alkyl substituents, as well as the increased steric crowding around the triflate. The bromine positioned meta to the donating groups would be unaffected electronically, rendering it more reactive regardless of the catalyst conditions.

**Scheme 64: Bromine-Selective Coupling Under Conditions B**

To study the effect of electron-donating substituents in a more simple, direct example, 3-bromo-4-trifloxy anisole (208) was prepared (Scheme 65). Bromination of phenol 206 exhibited high regioselectivity, affording bromide 207, which was then converted to triflate 208.
Scheme 65: Preparation of 3-Bromo-4-Trifl oxy Anisole

Based on previously reported results,\textsuperscript{98} it was proposed that the electron-donating methoxy group would deactivate the para-trifl oxy substituent, while the meta-bromine would be unaffected since it was not in conjugation with the methoxy group. Indeed, bromine-coupled 209 was the only product observed under conditions A, while erosion of selectivity was observed under conditions B, resulting in a mixture of both 209 and 210 (Scheme 66). While the ratio of 210 : 209 under conditions B was nearly 11:1, it was apparent that the para-methoxy group did indeed deactivate the triflate.

Scheme 66: Selectivity Under Conditions A and B

While this study of the selectivity in Stille coupling reactions allowed direct comparison between numerous substituted aromatics, there are still some issues that remain. For one, the yield in some cases was moderate at best. Although the goal was to study the selectivity only using the previously established conditions,\textsuperscript{99} it would be careless to make broad generalizations based on examples that were completely selective, yet the coupled product was isolated in poor yield. In addition, the role of the different reaction conditions is not fully explained. Though conditions B use a palladium (II)
catalyst, this complex is presumably rapidly reduced to palladium (0) to afford a similar Pd(PPh$_3$)$_x$ species to that formed under conditions A.$^{99}$ Rather, the major difference between the two catalysts is the ratio of ligand : palladium in solution.$^{100}$ The use of a more polar solvent (DMF vs. dioxane) under conditions B may also play a key role in stabilizing the intermediate formed through oxidative addition of palladium to the carbon-oxygen bond of the triflate.$^{101}$ These numerous factors presumably had an effect on the observed selectivity.

4.4 Conclusions

Through this exhaustive study of selectivity in Stille coupling reactions, some important conclusions were drawn. It was clear that the presence of a nitro group as well as the positioning of the nitro group relative to the halide or trifloxy group had a direct effect on the chemoselectivity of the Stille coupling reaction. It was observed that reactivity was enhanced for groups positioned ortho and para to the nitro group, while groups meta to the nitro group were not affected. In the absence of a nitro group, selectivities were the direct result of the conditions themselves. In these cases, halide-selective conditions A were highly selective, while triflate-selective conditions B exhibited slight erosion of selectivity, affording approximately 6:1 ratios of the expected triflate-coupled products relative to the bromine-coupled products. In accordance with the general reactivity series, iodides were more reactive than triflates regardless of the conditions used and independent the location of a nitro group in the molecule. In contrast to nitro groups, the weaker deactivating acetyl group did not exhibit a similar trend in activating ortho and para groups towards coupling reaction. On the contrary, an electron-donating group such as a methoxy group was found to deactivate the ortho and
para positions through resonance. Based on these observations, the selectivity (or lack thereof) of a coupling reaction may be predicted.
Chapter 5
Preparation of Pyrroloindoles via Palladium-Catalyzed Reductive Double N-Heterocyclization

5.1 Pyrroloindole Introduction and Background 67
5.2 Historical Routes to Pyrroloindoles of Type I 69
5.3 Pyrroloindole Preparation using Reductive Double N-Heterocyclization 73
  5.3.1 Retrosynthetic Analysis 73
  5.3.2 Banini Route to Pyrroloindoles 74
  5.3.3 Synthesis of Symmetrical Pyrroloindoles 76
5.4 Synthesis of Non-Symmetrical Pyrroloindoles 79
  5.4.1 Preparation of Cyclization Precursors 79
    5.4.1.1 2,4-Dinitro-1,5-Dialkenyl Benzene Isomer 79
    5.4.1.2 2,5-Dinitro-1,4-Dialkenyl Benzene Isomer 88
    5.4.1.3 2,3-Dinitro-1,4-Dialkenyl Benzene Isomer 93
    5.4.1.4 2,4-Dinitro-1,3-Dialkenyl Benzene Isomer 100
    5.4.1.5 1,4-Dinitro-2,3-Dialkenyl Benzene Isomer 106
  5.4.2 Pyrroloindole Synthesis via Reductive Double N-Heterocyclization 110
5.5 Conclusions 115
5.1 Pyrroloindole Introduction and Background

Pyrroloindoles have been attractive synthetic targets over the past few decades particularly due to their wide array of potential uses as biological agents as well as electroconductive materials\(^{102}\) and bidentate ligands.\(^{103}\) The name pyrroloindole refers to a molecule that features a pyrrole moiety fused onto an indole core. This fusion can come in one of three ways: Type I are those in which the pyrrole is attached to the benzene portion of the indole, Type II feature a pyrrole fused to the nitrogen-containing heterocyclic portion of the indole, and Type III which involve a common nitrogen atom (Figure 6).

**Figure 6: Types of Isomeric Pyrroloindoles**

![Types of Isomeric Pyrroloindoles](image)

A number of pyrroloindoles have gained attention on account of their biological activities. Physostigmine (211), a natural product of Type II, is believed to possess therapeutic effects in the treatment of Alzheimer’s disease (Figure 7).\(^{104}\) Phenserine (212), also a natural product of Type II, was another potential Alzheimer drug, although it failed in Phase III development (Figure 7).

**Figure 7: Physostigmine and Phenserine**

![Physostigmine and Phenserine](image)

One field in which pyrroloindole based compounds of Type I have found recent application is in the preparation of biological agents, specifically in anti-tumor
Recent work focusing on the preparation of pyrroloindole based natural products CC-1065 (213), Duocarmycin (214) and Yatakemycin (215) has been reported by Boger et al (Figure 8). These compounds and their derivatives are members of a class of anti-tumor compounds whose mode of action centers around the sequence-selective alkylation of duplex DNA within the tumor through nucleophilic opening of the cyclopropane functionality of the anti-tumor agent.

**Figure 8: CC-1065, Duocarmycin, and Yatakemycin**

Recent work in Soderberg’s laboratory has focused on the preparation of pyrroloindoles of Type I in which the pyrrole is fused to the benzene portion of the indole. Within this class, there are five different isomers, which are shown in Figure 9.
Pyrroloindoles of type I are named based on the orientation of the pyrrole ring relative to the indole core (Figure 10). Similar to the numbering of the atoms of simple indole, the numbering ascends counter-clockwise around the heterocycle with the nitrogen being atom 1. In a similar fashion, each bond of the indole core is assigned a letter, with the bond between atoms 1 and 2 being bond A. The manner in which the pyrrole unit is fused to the indole core is represented by \([x, y-z]\), where \(x\) and \(y\) are the atoms of the pyrrole and \(z\) is the bond of the indole core that atoms \(x\) and \(y\) are attached to. For example, pyrroloindoles of class C are named 1,8-dihydropyrrolo[3,2-\(g\)]indoles.

**Figure 9: Isomeric Pyrroloindoles of Type I**

![Figure 9](image)

**Figure 10: Pyrroloindole Numbering**

![Figure 10](image)

### 5.2 Historical Routes to Pyrroloindoles of Type I

One of the earliest preparations of symmetrical pyrroloindoles was reported by Berlin et al. in 1987 in the study of oxidative polymerization to afford electroconductive materials.\(^{106}\) This two-step route involved condensation of di-nitro xylene (216) with \(N,N\)-dimethylformamide diethyl acetal (DMF-DEA) to give the bis-enamine 217 which then
underwent reductive cyclization catalyzed by palladium on carbon to afford dihydropyrroloindole 218 (Scheme 67). Although the route was concise, it was quite limited in scope in that only symmetrical, non-substituted pyrroloindoles were accessible.

**Scheme 67: Berlin’s Approach to Pyrroloindoles**

Shannon *et al.* prepared pyrrolo[3,2-f]- (220) and –[2,3-f]-indoles (221) through the Montmorillonite K-10 clay catalyzed Vilsmeier formylation of dipyrrrole 219 (Scheme 68). A mixture of isomers was obtained due to free-rotation about the methylene bridge.

**Scheme 68: Montmorillonite K-10 Catalyzed Synthesis of Pyrroloindoles**

Samsoniya *et al.* reported numerous methods to prepare and characterize isomeric pyrroloindoles. The first method utilized a Fischer-type bicyclization of bishydrazone 222 to form the two pyrrole rings (Scheme 69). The authors noted that due to the harsh conditions required for this transformation, a considerable amount of tar formed over the course of the reaction, presumably from decomposition of the reactants
and/or products. Another drawback was that due to the nature of the cyclization, one starting material 222 produced four isomeric pyrroloindole products (223-226) with little control over selectivity.

**Scheme 69: Samsoniya Route to Isomeric Pyrroloindoles**

![Scheme 69: Samsoniya Route to Isomeric Pyrroloindoles]

The second method reported by Samsoniya *et al.* circumvented the previously mentioned issue of isomer formation by using a pre-formed aminoindoline 227 (Scheme 70).<sup>109</sup> Fischer-type cyclization of hydrazone 227 produced two isomeric pyrroloindolines 228 and 229 with a preference for linear isomer 228. Hydrolysis of the ester and acetyl groups followed by decarboxylation and dehydrogenation then afforded the non-substituted pyrroloindoles 230 and 231.

**Scheme 70: Pyrroloindole Preparation from Aminoindoline**

![Scheme 70: Pyrroloindole Preparation from Aminoindoline]

Yoshikai *et al.* have applied their palladium-catalyzed aerobic oxidative bicyclization method to the preparation of pyrroloindoles from *N*-aryl imines.<sup>110</sup>
Palladium(II)-catalyzed dicyclization of diimines 232 and 234 afforded corresponding pyrroloindoles 233 and 235 (Scheme 71). While the authors did not attempt to prepare non-symmetrical compounds, the ease of preparation and wide range of aniline and ketone starting materials afford this method a very broad scope, although the yields of the pyrroloindole products were modest at best. In addition, the regioselectivities observed in the cyclizations were not explained.

**Scheme 71: Oxidative Bicyclization of Diimines**

Fujii and Ohno reported the preparation of mesylated pyrroloindole 237 through copper-catalyzed bis-cyclization of di-alkynyl-dimesylamide 236 (Scheme 72). The authors state that the cyclization was highly dependent on the substituents on the nitrogen atoms, with mesylates giving the highest conversion. In addition, this approach was limited to terminal alkynes, affording only non-substituted pyrroloindoles.

**Scheme 72: Intramolecular Hydroamination of Di-ylene**

One inherent limitation of many previous synthetic routes is that they only allow for preparation of symmetrical pyrroloindoles. This is in part due to limitations...
associated with the methods used to prepare the required starting materials, most of which also involve symmetrical compounds. Therefore, methods to prepare non-symmetrical substrates that can be converted to non-symmetrical pyrroloindoles are highly desirable.

5.3 Pyrroloindole Preparation via Reductive Double N-Heteroannulation

As discussed in the preceding chapters, Soderberg’s laboratory has studied the applications of palladium-catalyzed reductive N-heterocyclizations extensively. It was envisioned that this methodology could be applied in the synthesis of pyrroloindoles from dinitro-dialkenyl benzenes. The generally mild conditions used in such reactions could allow for broad functional group compatibility and offer significant improvements over the previously discussed methods.

5.3.1 Retrosynthetic Analysis

Retrosynthetically, it was proposed that each of the five isomeric pyrroloindoles of type I could be prepared through the palladium-catalyzed reductive double heterocyclization of the corresponding dinitro-dialkenyl benzene (Scheme 73).
5.3.2 Banini Route To Pyrroloindoles

Banini et al. successfully prepared pyrroloindoles using Soderberg’s palladium-catalyzed reductive \( N \)-heteroannulation methodology. Pyrroloindoles of class B such as 239 were achieved in six steps from \( p \)-bromotoluene (245) (Scheme 74). Nitration\(^{112}\) of 245 afforded a four-product mixture from which isomer 246 was separated and subjected to radical benzylic bromination\(^{113}\) using \( N \)-bromosuccinimide and benzyol peroxide. Benzyl bromide 247 was then converted to phosphine salt 248 before undergoing Wittig condensation to afford styrene 249. Kosugi-Migita-Stille coupling between bromide 249 and vinyl stannane then afforded dinitro-dialkenyl benzene 240. Reductive double \( N \)-heterocyclization was achieved through reaction with PPh\(_3\) and Pd(dba)\(_2\) in DMF at 120 °C in a sealed tube pressurized with carbon monoxide gas, affording pyrroloindole 239 in
excellent yield. In addition to symmetrical pyrroloindole 239, non-symmetrical pyrroloindoles were also prepared using this route.

**Scheme 74: Banini Route to Pyrroloindoles of Class B**

A slightly different approach was employed to prepare pyrroloindoles of class C (Scheme 75). Nitration of 1,4-dibromobenzene (250) provided three dinitrobenzene isomers, including 2,3-dinitro-1,4-dibromobenzene (251). Kosugi-Migita-Stille cross-coupling between 251 and vinyl stannane afforded bromostyrene 252, which underwent a second Kosugi-Migita-Stille coupling with α-stannyl ester to afford cyclization precursor 253. Exposure of 253 to altered Soderberg reductive heteroannulation conditions (PPh₃, Pd(OAc)₂) afforded pyrroloindole 254 in excellent yield.
5.3.3 Synthesis of Symmetrical Pyrroloindoles

Initial attempts to elaborate on Banini’s work encountered a number of issues. While Banini reported the benzylic bromination of dinitrotoluene 246 to afford benzyl bromide 247 in moderate yield, in our hands, the reaction afforded near quantitative recovery of starting material (Scheme 76).

Scheme 76: Failed Preparation of Benzyl Bromide

Replication of the reported mono-Kosugi-Migita-Stille cross-coupling of dinitro-dibromobenzene 251 with vinyl stannane was also unsuccessful (Scheme 77). While Banini achieved styrene 252 in moderate yield, in our hands, a mixture of mono- and di-coupled products 252 and 241 was obtained.
Scheme 77: Attempted Mono-Coupling of Dibromide

To circumvent this issue, the coupling reaction was attempted using a three-fold excess of stannane with the goal of preparing exclusively di-coupled arene 241. In the event, di-vinyl compound 241 was prepared in moderate yield (Scheme 78).

Scheme 78: Preparation of Dialkenyl-Dinitrobenzene

Reductive double N-heteroannulation of 241 was achieved using alternate conditions reported by Banini to afford pyrroloindole 218 in moderate yield (table 8, entry 1). Two additional cyclization precursors 255 and 257 were also prepared through dicoupling of 241 with propenyl- and isopropenyl stannane, respectively. Palladium-catalyzed cyclization of 255 afforded exclusively symmetrical pyrroloindole 256 in moderate yield (entry 2). Cyclization of 257 afforded solely indole 259 when the catalyst conditions were 1,10-phenanthroline and Pd(OAc)$_2$, however, pyrroloindole 258 was achieved through use of PPh$_3$ and Pd(dba)$_2$, although indole 259 was the major product.
### Table 8: Reductive Double N-Heteroannulation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1" alt="Substrate 241" /></td>
<td><img src="image2" alt="Product 218" /> (56%)</td>
</tr>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image3" alt="Substrate 255" /></td>
<td><img src="image4" alt="Product 256" /> (43%)</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image5" alt="Substrate 257" /></td>
<td><img src="image6" alt="Product 258" /> (25%) + <img src="image7" alt="Product 259" /> (12%)</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image8" alt="Substrate 257" /></td>
<td><img src="image6" alt="Product 258" /> (25%) + <img src="image7" alt="Product 259" /> (54%)</td>
</tr>
</tbody>
</table>

---

Dihydropyrroloindole 218 (entry 1) was isolated in moderate yield after 143 hours, although the cyclization was likely complete at an earlier time on account of the lack of unreacted starting material or mono-cyclized product. It was expected that the simple vinyl groups would present less steric repulsion toward the palladium in comparison to propenyl-substituted substrates 255 and 257 and would therefore react faster. Surprisingly, di-propenyl substrate 255 (entry 2) afforded pyrroloindole 256 in moderate yield after only 20 hours. On the contrary, 257 (entry 3) appeared to undergo mono-cyclization with ease, producing indole 259, however, the second cyclization to afford pyrroloindole 258 was much slower as evidenced by the significantly lower yield.
relative to indole 259. The decreased rate of the second cyclization could potentially be attributed to weaker coordination of the catalyst to the isopropenyl moiety of 259.

5.4.1 Synthesis of Non-Symmetrical Pyrroloindoles

While symmetrical pyrroloindoles were prepared using Soderberg’s palladium-catalyzed reductive double $N$-heteroannulation methodology, numerous limitations were apparent, including the inability to prepare non-symmetrical pyrroloindoles and the incomplete conversion to pyrroloindoles. In addition, only two of the five isomeric pyrroloindoles were achieved through the routes. Efforts to overcome the limitations in the preparation of non-symmetrical pyrroloindoles are presented in the sections hereafter.

5.4.1 Preparation of Cyclization Precursors

With the goal of preparing non-symmetrical pyrroloindoles using Soderberg’s reductive annulation methodology, efforts were made to establish routes to prepare the requisite dinitro-dialkenyl benzenes. Specifically, efforts focused on synthesizing non-symmetrical cyclization precursors in a controlled, sequential manner. For organizational clarity, each isomeric substrate is presented separately, although numerous commonalities were encountered in the preparation of each substrate.

5.4.1 2,4-Dinitro-1,5-Dialkenyl Benzene Isomer

The first and most extensively examined cyclization precursors were 2,4-dinitro-1,5-dialkenyl benzenes, such as 238 (Figure 11).

Figure 11: 2,4-Dinitro-1,5-Dialkenyl Benzene
Retrosynthetically, it was envisioned that dinitro-dialkenyl benzene 260 could be prepared through Kosugi-Migita-Stille coupling reaction of triflate 261 (Scheme 79). The isopropenyl moiety of 261 could be introduced by Kosugi-Migita-Stille cross coupling between aryl iodide 262 and isopropenyl stannane. Dinitrophenyl triflate 262 could arise from dinitrophenol 263, which could be prepared through the nitration of 3-iodophenol (264).

**Scheme 79: Proposed Retrosynthetic Outline to Cyclization Precursor**

Banwell *et al.*114 have reported the nitration of 3-iodophenol (264) using sodium nitrate in a solution of aqueous methanol and sulfuric acid, providing both 3-iodo-4-nitrophenol (265) and 5-iodo-2-nitrophenol (266) (Scheme 80). The relatively mild conditions employed prevent the formation of trinitrophenols as reported under harsher conditions.115,116

**Scheme 80: Nitration of 3-Iodophenol**
With isomers 265 and 266 in hand, a second nitration was examined. The methanol/water conditions used in the initial nitration (Scheme 80) proved to be too mild for a second nitration to occur, as evidenced by the absence of di-nitrated products. Therefore, a solution of sodium nitrate in sulfuric acid, believed to be slightly more acidic than the conditions used to introduce the first nitro group, yet milder than the fuming nitric acid/sulfuric acid system, was used. Gratifyingly, treatment of 5-iodo-2-nitrophenol (266) with sodium nitrate in sulfuric acid provided di-nitrophenols 263 and 267 with no evidence of tri-nitration (Scheme 81). It should be noted that in some cases, solely isomer 263 was formed, while in other cases, a near 1:1 mixture of isomers 263 and 267 was obtained.

**Scheme 81: Nitration of 5-Iodo-2-Nitrophenol**

\[
\text{O}_2\text{N} \quad \text{OH} \quad \text{NO}_2 \quad \text{I}
\]

\[\text{266} \quad \text{NaNO}_3, \text{H}_2\text{SO}_4 \quad 0 \degree \text{C to r.t.} \quad 32\%, 40\% \]

\[
\text{O}_2\text{N} \quad \text{OH} \quad \text{NO}_2 \quad \text{I}
\]

\[\text{263} \quad + \quad \text{O}_2\text{N} \quad \text{OH} \quad \text{NO}_2 \quad \text{I}
\]

\[\text{267} \]

Nitration of 3-iodo-4-nitrophenol (265) using these same conditions afforded dinitrophenols 263 and 268 (Scheme 82). Once again, 5-iodo-2,4-dinitrophenol (263) was the major product observed in most reactions, although in some cases, isomer 268 was also formed. Unfortunately, dinitrophenols 263 and 268 were nearly inseparable using column chromatography.

**Scheme 82: Nitration of 3-Iodo-4-Nitrophenol**

\[
\text{OH} \quad \text{NO}_2 \quad \text{I}
\]

\[\text{265} \quad \text{NaNO}_3, \text{H}_2\text{SO}_4 \quad 0 \degree \text{C to r.t.} \quad 69\%, 23\% \]

\[
\text{O}_2\text{N} \quad \text{OH} \quad \text{NO}_2 \quad \text{I}
\]

\[\text{263} \quad + \quad \text{OH} \quad \text{NO}_2 \quad \text{I}
\]

\[\text{268} \]
Subsequent treatment of dinitrophenol 263 with pyridine and triflic anhydride afforded aryl triflate 262 in near quantitative yield (Scheme 83).

Scheme 83: Preparation of Aryl Triflate

With the desired functionalized starting material in hand, focus was turned to the coupling reactions to prepare the target non-symmetrical dialkenyl-dinitrobenzenes. Attempts to selectively couple the iodine of substrate 262 were successful in producing styrene 146, however, purification using column chromatography resulted in the hydrolysis of the trifloxy group of 146 and lead to the isolation of phenol 247 (Scheme 84). Similar hydrolysis of electron-deficient aryl triflates has been documented in the literature.\textsuperscript{117}

Scheme 84: Attempted Kosugi-Migita-Stille Coupling

This counter-productive result forced reconsideration of the proposed synthetic route. While phenols are typically poor substrates for Stille coupling reactions due to the electron-rich nature of the aromatic system, the two nitro-groups of phenol 263 would potentially provide enough activation to allow for coupling of the dinitro-iodophenol and circumvent the issue of hydrolysis. This hypothesis was tested using 4,6-dinitro-3-iodophenol (263) (Scheme 85). Initially, attempted Kosugi-Migita-Stille coupling of
iodophenol 263 under conditions A\textsuperscript{80} (PPh\textsubscript{3}, Pd(dba)\textsubscript{2}, dioxane, reflux) afforded no product. Subsequently, copper (I) iodide was added and the solution was heated at reflux. Delightfully, complete conversion of the starting material to coupled phenol 271 was achieved in four hours. However, after workup with aqueous ammonia, no product was detected in the crude mixture via \textsuperscript{1}H NMR. On account of the ortho and para nitro groups, the acidity phenolic hydrogen of 271 was substantially lower than that of phenol itself, rendering the phenol soluble in aqueous base. In the event, lowering the pH of the aqueous phase from \textasciitilde10 to \textasciitilde4 followed by extraction provided the desired coupled phenol 271. Optimization of conditions led to shortened reaction times (3 hours) while affording phenol 271 in good yield.

**Scheme 85: Kosugi-Migita-Stille Coupling of Iodophenol**

![Scheme 85: Kosugi-Migita-Stille Coupling of Iodophenol](image)

This result not only afforded the desired compound, but it also resulted in purification of the product using a simple extraction process, which is depicted in Figure 12. Initially, the phenol product was extracted using an aqueous base, “washing” away the unwanted organic components from the reaction including dba and tributyltin iodide. Acidification of the aqueous phase protonated the phenoxide, allowing for extraction of the nearly pure phenol product prior to chromatography.
The success of the coupling reaction was attributed to the addition of copper iodide. The role of copper salts in Stille coupling reactions has been studied extensively. Liebeskind et al. reported significant rate enhancement when adding CuI to Pd(0)/PPh₃ catalyst systems, however, no rate enhancement was observed when using soft ligands such as AsPh₃. This has been attributed to CuI acting as a ligand scavenger, so the reported rate enhancement in the Pd(0)/PPh₃ system is presumably due to scavenging of excess PPh₃, as PPh₃ is known to inhibit the rate-limiting transmetalation step. Generation of organocopper species could also be generated through initial tin-copper transmetalation. The formed organocopper complex would then undergo tranmetalation to palladium faster in comparison to the initial stannane. Similar palladium-copper co-catalytic Stille conditions were employed by Hudgens et al. in the preparation of novel methylated tyrosine derivates.

Conversion of phenol 271 to triflate 261 was achieved using standard conditions (Scheme 86). Rapid purification using column chromatography afforded triflate 261 with no evidence of hydrolysis.
Initially, issues were encountered in applying conditions B\textsuperscript{90} (PdCl\(_2\)(PPh\(_3\))\(_2\), LiCl, DMF, r.t.) to couple the trifloxy group of 261. The attempted coupling of triflate 261 with stannane 272 afforded exclusively aryl chloride 273 (Scheme 87).

To probe the mechanism of this unexpected result, triflate 261 was treated with excess lithium chloride in DMF without the addition of palladium (Scheme 88). This would reveal whether the reaction involved a simple nucleophilic aromatic substitution mechanism or whether it was a palladium-catalyzed process. Interestingly, chloride 273 was achieved in moderate yield in the absence of a palladium catalyst, confirming the nucleophilic aromatic substitution mechanism. While unexpected, this result was reasonable considering highly activated nature of the trifloxy group on the basis of the \textit{ortho} and \textit{para} nitro substituents. Exploration of the literature also produced examples of similar observations.\textsuperscript{122}
Aryl chloride 273 was then coupled with isopropenyl stannane under conditions A\textsuperscript{90} to afford the desired dinitro-dialkenyl substrate 260 (Scheme 89). This result is significant in that aryl chlorides are typically sluggish in Kosugi-Migita-Stille reactions and often require more tailored catalyst and ligand systems. The electron-deficient nature of the system on account of the two nitro groups likely augments the reactivity of the chloride towards oxidative addition of palladium.

Scheme 89: Kosugi-Migita-Stille Coupling of Aryl Chloride

While the successful coupling of aryl chloride 273 was encouraging, the overall process was not atomically efficient in going from phenol 271 to triflate 261 then to chloride 273. Rather, direct coupling of triflate 261 was desired. Gratifyingly, use of conditions A\textsuperscript{90} in DMF rather than dioxane afforded coupled product 274 in good yield (Scheme 90). While the role of changing solvent was not investigated, the exclusion of lithium chloride from the reaction mixture avoided potential triflate replacement.
Scheme 90: Kosugi-Migita-Stille Coupling of Aryl Triflate

Similarly, cross-coupling between triflate 261 and α-phenyl alkenylstannane 275 afforded cyclization precursor 276 (Scheme 91).

Scheme 91: Preparation of Cyclization Precursor

Some of the advantages of Stille coupling reactions include the vast array of stannanes, their ease of preparation either from Grignard reagents\(^\text{123}\) or hydrostannation of alkynes,\(^\text{124}\) and their stability\(^\text{125}\) relative to alternative reagents. Rather than delve too far into these different options, only the readily available stannanes described above were employed. However, variation of the alkenyl stannane used in either coupling step would allow for preparation of a number of structurally diverse pyrroloindoles.

A straightforward method to prepare non-symmetrical 2,4-dinitro-1,5-dialkenyl benzene derivatives has been established. This concise process involving sequential Kosugi-Migita-Stille cross-coupling reactions overcomes a number of obstacles previously encountered in the preparation of the described substrates. In addition, the
generality of cross-coupling reaction allows for preparation of a diverse array of novel highly functionalized substrates.

5.4.2 2,5-Dinitro-1,4-Dialkenyl Benzene Isomer

The next isomeric cyclization precursor examined was 2,5-dinitro-1,4-dialkenyl benzene, such as divinylbenzene 240 (Figure 13). While Banini prepared compounds of this type (Section 3, this chapter), a more synthetically useful route was desired.

**Figure 13: 2,5-Dinitro-1,4-Dialkenyl Benzene**

![2,5-Dinitro-1,4-Dialkenyl Benzene](image)

Retrosynthetically, it was envisioned that cyclization precursor 240 could be prepared through Kosugi-Migita-Stille coupling between triflate 277 and vinyl stannane (Scheme 92). Triflate 277 could be achieved from phenol 278. Styrene 278 would result from Kosugi-Migita-Stille cross-coupling between iodophenol 279 and vinyl stannane. Dinitrophenol 279 could arise through the di-nitration of 4-iodophenol (194)

**Scheme 92: Proposed Retrosynthetic Outline to Cyclization Precursor**

![Scheme 92](image)
Preparation of isomer 240 was not as simple as initially proposed. It was envisioned that this isomer would be achieved through di-nitration of 4-iodophenol (194) (Scheme 93). However, after multiple attempts using a number of conditions, none of the desired di-nitrated product 279 was isolated. Rather, it appeared that the electron-donating hydroxy group para- to the iodine activated the iodine for ipso substitution, with 4-nitrophenol (280) being the isolated product. Under forcing conditions, 2,4-dinitrophenol (281) was also isolated. Similar substitutions of aryl halides has also been reported by Hodgson126 in his exhaustive examination of nitration reactions.

Scheme 93: Nitration of 4-Iodophenol

Based on these results, a revised route was proposed that capitalized on the position para- to the alcohol being activated through conjugation with the electron-donating hydroxyl group. The proposed route involved preparation of 2,5-dinitrophenol (283), then introducing the iodine in order to overcome the issue of ipso substitution encountered in the case of 4-iodophenol (194). Nitration of 3-nitrophenol (282) using sodium nitrate in sulfuric acid afforded both the desired 2,5-dinitrophenol (283) along with 2,3-dinitrophenol (284) (Scheme 94).127 Fortunately, these isomers were separable using column chromatography, as it was envisioned that isomer 284 could be used in the preparation of another substrate (Section 5.4.3).
Oxidative iodination of phenols has been reported using a number of oxidants, with one of the most recent being benzyltriphenylphosphonium peroxymonosulfate (BTPPMS) (286), prepared through treatment of benzyltriphenylphosphonium chloride (285) with Oxone (Scheme 95).\(^{128}\)

**Scheme 95: Preparation of Benzyltriphenylphosphonium Peroxymonosulfate**

Hajipour\(^{129}\) has reported the para-selective iodination of a number of phenols using potassium iodide (KI) and BTPPMS (286). In fact, it was reported that 4-iodo-2,5-dinitrophenol (279) was prepared in good yield from 2,5-dinitrophenol (283) using these conditions (Scheme 96).

**Scheme 96: Oxidative Iodination of 2,5-Dinitrophenol**

Attempts to replicate these results were unsuccessful in our hands. It was suspected that reagent 286 was highly impure and therefore not capable of oxidizing the substrate 283. The reported preparation of BTPPMS (286) (also reported by Hajipour\(^{128}\))
provided no specific work-up or characterization data, leaving questions regarding this reagent.

Iodination of deactivated aromatics using N-iodosuccinimide (NIS) under acidic conditions has been reported by Olah. Treatment of nitrobenzene (287) with NIS and two equivalents of trifluoromethanesulfonic acid afforded 3-nitroiodobenzene (288) in excellent yield, confirming that the reaction proceeded through an electrophilic mechanism based on the regioselectivity observed in the product (Scheme 97). It was proposed that a super electrophilic iodine-trifluoromethanesulfonate, generated in situ, was the highly reactive iodinating species.

**Scheme 97: Iodination of Deactivated Arene**

![Scheme 97: Iodination of Deactivated Arene](image)

In a slight modification of Olah’s protocol, treatment of 2,5-dinitrophenol (283) with NIS in sulfuric acid afforded the desired iodophenol 279 (Scheme 98). The ability to substitute expensive trifluoromethanesulfonic acid with sulfuric acid was an improvement to Olah’s conditions.

**Scheme 98: Electrophilic Iodination of 2,5-Dinitrophenol**

![Scheme 98: Electrophilic Iodination of 2,5-Dinitrophenol](image)

Coupling of iodophenol 279 was then attempted using the previously discussed modified Kosugi-Migita-Stille conditions (Scheme 85, Chapter 5). In the event, coupling
between iodophenol 279 and vinyl stannane afforded styrene 278 in good yield (Scheme 99). Typical radical inhibitor 2,6-di-\textit{t}-butyl-4-methylphenol (BHT) was added to the reaction in order to prevent polymerization of the styrene product.

**Scheme 99: Kosugi-Migita-Stille Coupling of 4-Iodo-2,5-Dinitrophenol**

![](image)

Phenol 278 was then converted to the corresponding triflate 277 using typical conditions (Scheme 100).

**Scheme 100: Preparation of Aryl Triflate**

![](image)

Kosugi-Migita-Stille cross-coupling of triflate 277 with vinyl stannane was achieved using typical conditions B.\(^9\) In contrast to the case of 261 (Scheme 87, Chapter 5), no chloride product was observed and the cross-coupled product 240 was achieved in moderate yield (Scheme 101).

**Scheme 101: Kosugi-Migita-Stille Coupling of Aryl Triflate**

![](image)
The established method employing sequential cross-coupling reactions offers a number of improvements in comparison to Banini’s method to prepare substrate 240 (Scheme 74, Chapter 5). Though both methods employed an initial nitration step, the nitration of 3-nitrophenol 282 (Scheme 94) afforded isomers 283 and 284 in moderate yield, whereas Banini’s nitration step afforded a mixture of four isomers, each in low yield. Additionally, 2,3-dinitrophenol (284) was of interest for preparation of another isomer. This method also avoids the often unsuccessful benzyl bromination step employed by Banini to convert dinitrotoluene 246 to benzyl bromide 247.

The desired 2,5-dinitro-1,4-diethenyl isomer 240 was achieved in five steps from 3-nitrophenol (282) using a series of electrophilic aromatic substitution and Kosugi-Migita-Stille coupling reactions. While only one symmetrical substrate was prepared, non-symmetrical cyclization precursors would be accessible by varying the stannane used in either coupling step.

5.4.3 2,3-Dinitro-1,4-Dialkenyl Benzene Isomer

Efforts were made to establish a synthetically useful route to prepare non-symmetrical 2,3-dinitro-1,4-dialkenyl cyclization precursors, such as divinylbenzene 241 (Figure 14).

Figure 14: 2,3-Dinitro-1,4-Dialkenyl Benzene

![2,3-Dinitro-1,4-Dialkenyl Benzene](image)

Initial attempts to prepare non-symmetrical substrates based on 241 through Kosugi-Migita-Stille coupling between 1,4-dibromo-2,3-dinitrobenzene (251) and vinyl
stannane failed due to the inability to achieve selectivity for mono-coupling (as discussed in Section 5.3.3). Based on the successful coupling of halophenols in the preparation of other isomers in this study (Sections 5.4.1 and 5.4.2), a route involving similar ideology was sought.

Retrosynthetically, it was envisioned that cyclization precursor 241 could be prepared through Kosugi-Migita-Stille coupling between aryl triflate 289 and vinyl stannane (Scheme 102). Aryl triflate 289 could arise from dinitrophenol 290. Styrene 290 could result from the Kosugi-Migita-Stille coupling between iodophenol 291 and vinyl stannane. Dinitrophenol 291 was envisioned through di-nitration of 4-iodophenol (194).

Scheme 102: Proposed Retrosynthetic Outline to Cyclization Precursor

Unfortunately, attempts to prepare 2,3-dinitro-4-iodophenol (291) through nitration of p-iodophenol (194) were unsuccessful (as discussed in Section 5.4.2). It became clear that iodoarenes were highly prone to substitution, therefore, alternative routes to prepare iodophenol 291 were explored. One such route involved using Hajipour’s methodology for the oxidative para iodination of phenols (described in
greater detail in Section 5.4.2). 2,3-dinitrophenol (284) was prepared through the nitration\(^{127}\) of 3-nitrophenol (282) using sodium nitrate in sulfuric acid (as also described in Section 5.4.2). However, treatment of dinitrophenol 284 with BTPPMS and potassium iodide failed to produce the desired iodophenol 291 (Scheme 103).

**Scheme 103: Attempted Oxidative Iodination of 2,3-Dinitrophenol**

![Scheme 103](image)

Similar to the analogous case of 2,5-dinitrophenol (283) (Section 5.4.2), electrophilic iodination of 284 was also attempted using N-iodosuccinimide in triflic acid\(^{130}\) (Scheme 104). While the crude \(^1\)H NMR spectrum appeared to show evidence of two iodinated products, neither was isolable through chromatographic purification. Trials using sulfuric acid in place of triflic acid were also unsuccessful.

**Scheme 104: Attempted Electrophilic Iodination of 2,3-Dinitrophenol**

![Scheme 104](image)

It was envisioned that the two nitro groups of 251 would render the bromines highly activated towards nucleophilic aromatic substitution (S\(_N\)Ar). Upon examination of the literature, examples of S\(_N\)Ar reactions using sodium hydroxide as a hydroxide source were discovered.\(^{116}\) Using this ideology, treatment of di-bromide 251 with excess sodium hydroxide provided 4-bromo-2,3-dinitrophenol 292 in good yield (Scheme 105).
Scheme 105: Preparation of 4-Bromo-2,3-Dinitrophenol

\[
\begin{align*}
\text{Br} & \quad \text{NO}_2 \
\text{Br} & \quad \text{NO}_2 \
\text{251} & \quad \text{NaOH, THF/H}_2\text{O} \
& \quad 80 \degree \text{C}, 81\% \\
\text{OH} & \quad \text{NO}_2 \
\text{Br} & \quad \text{NO}_2 \
\text{292} & 
\end{align*}
\]

With phenol 292 in hand, Kosugi-Migita-Stille coupling was attempted using modified conditions A\(^{90}\) (PPh\(_3\), Pd(dba)\(_2\), CuI, dioxane, reflux), which were successful in coupling 2,4-dinitro-5-iodophenol 263 (Section 5.4.1) as well as 2,5-dinitro-4-iodophenol 279 (Section 5.4.2). Regrettably, the established conditions proved unsuccessful in the coupling of bromophenol 292, returning only unreacted starting material (Scheme 106).

Interestingly, treatment of 292 with PdCl\(_2\)(PPh\(_3\))\(_2\) and CuI in toluene afforded isopropenyl-substituted phenol 293, albeit in poor yield.

Scheme 106: Kosugi-Migita-Stille Coupling of Bromophenol

The drastic difference in reactivity observed for bromophenol 292 compared to coupling of iodophenol 279 (Section 5.4.2) was puzzling. Both 292 and 279 were expected to be similar in electronics on account of the bromine of 292 and the iodine of 279 being ortho and meta to nitro groups and para to a hydroxy group. However, iodophenol 279 underwent coupling while the coupling of bromophenol 292 was extremely sluggish. Therefore, it was postulated that the difference in reactivity must have been the result of using an aryl bromide rather than an aryl iodide. It is widely accepted that aryl iodides are more reactive than aryl bromides under a range of typical
coupling conditions, so it was plausible that the combination of a less reactive aryl bromide that was also deactivated through conjugation with an electron-donating hydroxyl group caused the lack of reactivity observed for aryl bromide 292.

In an attempt to explore whether the analogous iodophenol would prove successful in the coupling step, a similar route to that previously presented was pursued using 1,4-diiodobenzene (294). Unfortunately, attempts to di-nitrate 294 afforded 4-nitriiodobenzene (295) as the lone product (Scheme 107).

**Scheme 107: Nitration of 1,4-Diiodobenzene**

![Scheme 107: Nitration of 1,4-Diiodobenzene](image)

This result provided more insight into the highly reactive nature of aryl iodides relative to bromides. Comparison of the nitrations of 1,4-dibromobenzene 250 and 1,4-diiodobenzene 294 provides a direct example. Di-nitration of dibromide 250 using mixed acid 90 °C afforded three di-nitrated isomers, whereas treatment of diiodide 294 with the same mixed acid conditions at room temperature resulted in ipso substitution of iodine by a nitro group. Considering these drastically different results, the differences in reactivity encountered in the aforementioned coupling reaction were not so surprising.

A revised route was sought to increase the reactivity of bromophenol 292 while limiting the number of additional steps required. It was envisioned that conversion of phenol 292 to tosylate 296 would decrease the electron-donor ability of the phenolic oxygen and potentially render the bromine less deactivated. This could then facilitate the oxidative addition necessary for coupling while also adding only one additional step as
tosylates are potentially suitable substrates for Kosugi-Migita-Stille coupling.\textsuperscript{132,133}

Phenol 292 was converted to the corresponding tosylate 296 through treatment with \( p \)-toluenesulfonyl chloride in the presence of triethylamine\textsuperscript{134} (Scheme 108). Unfortunately, Kosugi-Migita-Stille coupling between aryl bromide 296 and isopropenyl stannane using conditions A\textsuperscript{90} did not afford isopropenylbenzene 297. However, a more extensive examination of conditions may provide conditions capable of facilitating coupling reaction of this substrate.

**Scheme 108: Attempted Kosugi-Migita-Stille Coupling of Aryl Bromide**

\[
\begin{align*}
\text{OH} & \quad \text{TsCl, Et}_3\text{N} \quad \text{CH}_2\text{Cl}_2, 0 \degree \text{C to r.t.} \quad 80\% \quad \text{Br} \quad \text{NO}_2 \\
\begin{array}{c}
\text{NO}_2 \\
\text{Br}
\end{array} & \quad \rightarrow & \quad \begin{array}{c}
\text{OTs} \\
\text{NO}_2 \\
\text{Br}
\end{array} & \quad \text{SnBu}_3, \text{PPh}_3, \quad \text{Pd(dba)}_2, \text{dioxane} \\
\begin{array}{c}
\text{NO}_2 \\
\text{Br}
\end{array} & \quad \rightarrow & \quad \begin{array}{c}
\text{OTs} \\
\text{NO}_2 \\
\text{Br}
\end{array} & \quad \text{SnBu}_3, \text{PPh}_3, \quad \text{Pd(dba)}_2, \text{dioxane} \\
\begin{array}{c}
\text{NO}_2 \\
\text{Br}
\end{array} & \quad \rightarrow & \quad \begin{array}{c}
\text{OTs} \\
\text{NO}_2 \\
\text{Br}
\end{array}
\end{align*}
\]

Re-examination of previous work by Banini turned up an initially overlooked example. Kosugi-Migita-Stille coupling between dibromobenzene 251 and \( \alpha \)-stannyl ester 298 afforded exclusively mono-coupled product 299 (Scheme 109).

**Scheme 109: Selective Mono-Coupling of Dibromide by Banini**

\[
\begin{align*}
\text{Br} & \quad \text{NO}_2 \quad \text{CO}_2\text{Et} \quad \text{SnBu}_3 \quad \text{AsPh}_3, \text{Pd(dba)}_2, \text{THF} \quad 61\% \quad \text{Br} \quad \text{NO}_2 \\
\begin{array}{c}
\text{NO}_2 \\
\text{Br}
\end{array} & \quad \rightarrow & \quad \begin{array}{c}
\text{EtO}_2\text{C} \\
\text{NO}_2 \\
\text{Br}
\end{array} & \quad \begin{array}{c}
\text{Br} \\
\text{NO}_2 \\
\text{Br}
\end{array}
\end{align*}
\]

It was envisioned that the presence of an electron-withdrawing substituent on the benzyl position of 299 rendered the mono-coupled product less reactive towards a second coupling reaction. This was in contrast to other examples employing simple alkenyl
stannanes (as discussed in Section 5.3), in which the mono-coupled product appeared to be more reactive than the starting material (251) towards a second coupling reaction.

Gratifyingly, Kosugi-Migita-Stille coupling between 1,4-dibromo-2,3-dinitrobenzene 251 and α-stannyl ester 300 was achieved using Banini’s conditions afforded mono-coupled arene 301 in moderate yield with no detected di-coupling (Scheme 110). Though not employed in Banini’s example, it was also found that the addition of copper iodide aided the reaction, presumably through generation of a more reactive organocopper complex through tin-copper transmetalation.\textsuperscript{118}

**Scheme 110: Mono-Coupling Using α-Stannyl Ester**

While the requirement of an electron-deficient stannane such as 300 was viewed as a limitation of this route, the broad range of functional groups that could still be employed provide a wide range of possible substrates that could be prepared using this method.

Cross-coupling between substrate 301 and isopropenyl stannane was achieved using previously described Kosugi-Migita-Stille conditions,\textsuperscript{90} affording the desired non-symmetrical cyclization precursor 302 in moderate yield (Scheme 111).

**Scheme 111: Preparation of Non-Symmetrical Substrate**
Ultimately, non-symmetrical dinitro-dialkenyl benzene 302 was prepared in three steps from 1,4-dibromobenzene (250) through sequential Kosugi-Migita-Stille coupling reactions. While the first coupling step requires the use of an electron-withdrawing substituted stannane, a number of functional groups are still tolerated, providing a concise route to prepare otherwise inaccessible non-symmetrical substrates. The unusual reactivity of iodoarenes prevented the preparation of cyclization precursors such as 302 through coupling of 4-iodo-2,3-dinitrophenol (291).

### 5.4.4 2,4-Dinitro-1,3-Dialkenyl Benzene Isomer

The next target isomer was consisting of alternating nitro and alkenyl substituents, such as 242 (Figure 15). While this class could potentially lead to two different types of pyrroloindoles, they both faced the same obstacles in both the preparation of the substrate as well as the subsequent coupling steps.

**Figure 15: 2,4-Dinitro-1,3-Dialkenyl Benzene**

![Chemical Structure](image)

Retrosynthetically, it was initially envisioned that cyclization precursor 242 could be prepared through Kosugi-Migita-Stille coupling between aryl triflate 303 and vinyl stannane (Scheme 112). Aryl triflate 303 could be accessed through phenol 304. Styrene 304 would result from Kosugi-Migita-Stille coupling between iodophenol 268 and vinyl stannane. Dinitrophenol 268 was previously prepared through nitration of 3-iodophenol (264).
The sequential nitration\textsuperscript{114} of 3-iodophenol (264) (as discussed in Section 5.4.1) afforded a separable mixture of mono-nitrated isomers 265 and 266, which then underwent a second nitration using slightly stronger conditions (Scheme 113). Once again, 4,6-dinitro isomer 263 was the major product obtained, however, tailoring the conditions resulted in a slight increase in the amount of desired isomers 267 and 268 obtained (based on the starting material used). Unfortunately, the nitration of 3-iodo-4-nitrophenol (265) afforded an inseparable mixture of isomers 263 and 268. Surprisingly, in the nitration of 2-nitro-5-iodophenol (266), dinitro isomer 267 in which the nitro group adds to the more hindered carbon was the major product and was also separable from 263.

Scheme 113: Preparation of Dinitrophenol Isomers
A mixture of phenols 263 and 268 were subjected to coupling conditions A\textsuperscript{90} with the addition of copper (I) iodide (as discussed in Chapter 5.4.1) (Scheme 114). While coupled products 271 and 305 were isolated, the yield of desired phenol 305 was very low (8\%). Attempts to improve yields were futile, partially because the starting material consisted of two isomers, which made it difficult to optimize conditions.

**Scheme 114: Attempted Coupling of Isomeric Mixture**

![Scheme 114](image)

Attempted Kosugi-Migita-Stille coupling between 3-iodo-2,4-dinitrophenol (268) and isopropenyl stannane using conditions A\textsuperscript{90} in addition to copper (I) iodide afforded none of the coupled product (Scheme 115). Rather, 2,4-dinitrophenol (281) was isolated.

**Scheme 115: Attempted Coupling of Iodophenol**

![Scheme 115](image)

While it was suspected that the iodine of 3-iodo-2,4-dinitrophenol (268) would be highly activated towards oxidative addition on account the two ortho nitro substituents, it appeared that the neighboring nitro groups also provided steric hindrance, preventing the
transmetalation of the isopropenyl group from tin to palladium. However, the formation of dinitrophenol 281 was evidence that oxidative addition of palladium had occurred. The sensitivity of Kosugi-Migita-Stille reactions to steric demands has been previously noted.¹³⁵ This shortcoming, in addition to the difficulties discussed for isomer 267, resulted in this route’s abandonment.

Based on the issues encountered in the previously mentioned examples, a route was sought which did not require coupling of a group positioned between two nitro groups. The goal was to find examples of condensation reactions of toluene or benzaldehyde derivatives in order to overcome the issue of dehalogenation while also avoiding potential selectivity issues experienced when using sequential coupling reactions.

In a unique aromatic substitution reaction, Kawakami¹³⁶ reported the regioselective methylation of 2,4-dinitroaniline (306) through reaction with dimethyl sulfoxide (DMSO) and excess potassium tert-butoxide, affording 3-methyl-2,4-dinitroaniline (307) (Scheme 116). The mechanism involves deprotonation of the amine followed by formation of an imino-aromatic system, which is then attacked by the methanesulfonyl anion. Interestingly, the authors state that the analogous reaction using 2,4-dinitrophenol affords none of the desired methylated product, though a similar mechanism can be envisioned.

Scheme 116: Kawakami Methylation of 2,4-Dinitroaniline

\[
\begin{align*}
\text{NH}_2\text{NO}_2 \quad &\xrightarrow{r\text{BuOK, DMSO}} \quad \text{NH}_2\text{CH}_3\text{NO}_2 \\
\text{306} &\quad r.t., 86\% \quad \text{307}
\end{align*}
\]
Aniline 307 was then converted to aryl iodide 308 using modified Sandmeyer-type conditions\textsuperscript{137} (Scheme 117). The initially formed diazonium salt was displaced with potassium iodide in order to produce the more reactive aryl iodide for subsequent coupling reaction.

Scheme 117: Preparation of Aryl Iodide

\[
\begin{align*}
\text{307} & \xrightarrow{1. \text{NaNO}_2, \text{H}_2\text{SO}_4, \text{AcOH}, 10 \degree \text{C}} \text{I} \\
\text{308} & \xrightarrow{2. \text{KI}, \text{H}_2\text{O}, 10 \degree \text{C} \text{to} 50 \degree \text{C}} 86\%
\end{align*}
\]

Condensation reactions of 2,6-dinitrotoluene (309) as well as the subsequent elimination to afford di-nitrostyrene have been reported by Mundla (Scheme 118).\textsuperscript{138} The initial condensation of 309 with \textit{para}-formaldehyde in the presence of a catalytic amount of potassium hydroxide afforded alcohol 310. Conversion of alcohol 310 to mesylate 311 (which was not isolated) followed by subsequent elimination then afforded dinitrostyrene 311.

Scheme 118: Mundla’s Preparation of 2,6-Dinitrostyrene

\[
\begin{align*}
\text{309} & \xrightarrow{(\text{CH}_2\text{O})_n, \text{KOH, DMAc, r.t.} \text{ 95\%}} \text{310} \\
\text{310} & \xrightarrow{\text{Et}_3\text{N, MsCl, DMAc 0 \degree \text{C} \text{to} 90 \degree \text{C} \text{ 99\%}}} \text{311}
\end{align*}
\]

Employing Mundla’s methodology\textsuperscript{138} using toluene 308 afforded desired di-nitrostyrene 313 in moderate yield over two steps (Scheme 119).
Scheme 119: Synthesis of Styrene

Palladium-catalyzed Kosugi-Migita-Stille coupling between iodide 313 and isopropenyl stannane was achieved using typical conditions A,\(^{90}\) affording bis-alkenyl substrate 314 (Scheme 120).

Scheme 120: Kosugi-Migita-Stille Coupling of Aryl Iodide

Attempts to broaden the scope of Mundla’s\(^{138}\) methodology to prepare dinitrostyrenes sought to employ different aldehydes. However, substitution of para-formaldehyde with hexanal were unsuccessful, likely due to steric hinderance from the nitro groups neighboring the anion formed from 308 and the more bulky aldehyde, preventing the formation of alcohol 315 (Scheme 121).

Scheme 121: Attempted Condensation with Hexanal

Taking advantage of unique properties of dinitroarenes, a method was established to prepare non-symmetrical cyclization precursors in a straightforward manner. Initial
issues involving failed coupling of halides situated between two nitro groups were overcome through use of a condensation-elimination sequence to install the alkene moiety. While the condensation step is currently limited to formation of an ethenyl group, further investigations may allow more broad elaboration.

5.4.5 1,4-Dinitro-2,3-Dialkenyl Benzene Isomer

While four of the five desired cyclization precursors were successfully prepared, the final isomer has proved elusive. This cyclization precursor 244 would feature two nitro groups oriented \textit{para} to each other, as well as two neighboring alkenyl substituents (Figure 16).

\textbf{Figure 16: 1,4-Dinitro-2,3-Dialkenyl Benzene}

![Image of 1,4-Dinitro-2,3-Dialkenyl Benzene](image)

Retrosynthetically, dinitro-dialkenyl benzene 244 could result from Kosugi-Migita-Stille coupling between aryl triflate 316 and vinyl stannane (Scheme 122). Aryl triflate 316 could be achieved from dinitrophenol 317. Dinitrostyrene 317 could be envisioned from Kosugi-Migita-Stille coupling between iodophenol 318 and vinyl stannane. Dinitrophenol 318 could arise through either the nitration of 2-iodo-3-nitrophenol (319) or the iodination of 2,5-dinitrophenol (283).
It was initially envisioned that dinitrophenol 318 could be prepared through the nitration of 2-iodo-3-nitrophenol 319 (Scheme 123). In the event, it was found that rather forcing conditions were necessary for reaction to take place, as starting material was recovered in near quantitative yield in reactions using mixed acid at lower temperatures or under milder nitration conditions (such as NaNO₃, H₂SO₄). Unfortunately, attempts to force the reaction along by heating phenol 319 in mixed acid resulted in the decomposition of starting material and afforded none of the desired dinitrophenol product 318.

Ortho directed functionalization reactions of phenols were then examined as potential routes to prepare dinitrophenol 318. It was proposed that the electron-rich hydroxy substituent could be used to direct nitration¹³⁹ or iodination¹⁴⁰ to the positions ortho to it (Scheme 124).
Ortho-selective mono-nitration of substituted phenols using cerium (VI) ammonium nitrate (CAN) has been reported by Sathunuru et al.\textsuperscript{139} The regioselectivity of these reactions was attributed to the interaction of cerium with the hydroxyl oxygen of \textit{320}, leading to subsequent Fries-type rearrangement of intermediate \textit{321} to afford the \textit{o}-nitrophenol \textit{323} upon re-aromatization of intermediate \textit{322} (Scheme 125).

While Sathunuru’s study\textsuperscript{139} reported the successful nitration of a number of electron-withdrawing substituted phenols, the authors reported that cyano- and nitro-substituted phenols were unreactive, presumably due to the highly electron-deficient nature of arene. However, Sathunuru’s methodology\textsuperscript{139} was applied in an attempt to nitrate phenol \textit{319} (Scheme 126). In the event, the conditions appeared to be too mild and only unreacted starting material was recovered.
Scheme 126: Attempted ortho-Selective Nitration of Phenol

Similarly, ortho-selective halogenation of phenols was also explored. Previous work by Gaude et al. explored the halogenation and nitration of phenols by either iodine nitrate or bromine nitrate (generated in situ using silver nitrate and either iodine or bromine) and reported that in the presence of pyridine or triethylamine, selective ortho halogenation of phenol (320) was achieved, affording 2-iodophenol (324) (Scheme 127). In the absence of amine, a mixture of halogenated and nitrated products was isolated.

Scheme 127: Gaude’s ortho-Iodination of Phenol

Gaude’s methodology was applied to dinitrophenol 283 in hope of producing ortho-iodinated phenol 318 (Scheme 128). Unfortunately, no product was isolated, and starting material was recovered.

Scheme 128: Attempted ortho-Iodination of Dinitrophenol

Ultimately, attempts to prepare 1,4-dinitro-2,3-dialkenyl benzene isomer were unsuccessful. As apparent through the attempted routes, this isomer featuring
“mismatched” electronic effects was highly elusive. The mismatched electronics rendered intermediate substrates highly unreactive and posed an obstacle to prepare the targeted isomer. Although this isomer was not pursued further, the importance of pyrrolo[3,2-e]indole frameworks as demonstrated by their use in anti-tumor compounds such as CC-1065, duocarmycin, and yatakemycin makes this isomer still highly sought after.

5.4.2 Pyrroloindole Synthesis via Reductive Double N-Heteroannulation

With a number of isomeric substrates in hand, focus was turned to the palladium-catalyzed reductive double N-heterocyclizations to prepare each isomeric pyrroloindole. Using conditions previously established by Banini (PPh₃, Pd(dba)₂, CO (6 atm), DMF, 120 °C), pyrroloindoles were prepared, although mono-cyclized products were also isolated even after extended reaction times (5 days). These results are outlined in Table 9.

Table 9: Double Cyclization Using Banini’s Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /> <img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>260</td>
<td>325 (32%) 326 (59%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /> <img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>274</td>
<td>327 (34%) 328 (28%)</td>
</tr>
</tbody>
</table>

Conditions: PPh₃, Pd(dba)₂, CO (6 atm), 120 °C, 120 hours
While these initial cyclizations were not completely successful in producing the desired pyrroloindoles, useful insight was still gained. Substrate 260 (Table 9, entry 1) was converted to pyrroloindole 326 in moderate yield although a fair amount of indole 325 resulting from mono-cyclization was also isolated. The incomplete conversion of 260 to pyrroloindole 326 suggested that the second cyclization step was significantly slower than the initial cyclization, since no unreacted starting material was recovered. Substrate 274 (table 9, entry 2) provided insight into how substituents affect the rate of cyclization. Indole 327, formed through the cyclization of the propenyl moiety of 274, was isolated in slightly higher yield than indole 328, which was the result of cyclization of the isopropenyl substituent. Though the isolated yields were not drastically different, this result suggests that the propenyl substituent may provide less hinderance for coordination of palladium to induce the cyclization, meaning the propenyl substituent cyclizes faster than the isopropenyl group.

With the hope of shortening reaction times while at the same time improving the yield of pyrroloindole products, other ligand systems were also explored. Alternative Soderberg annulation conditions using a two ligand system comprised of 1,10-phenanthroline (1,10-phen) and 1,3-(bis)-diphenylphosphinopropane (dppp) as opposed to simply triphenylphosphine were employed in order to overcome potential catalyst degradation due to the longer time scale of these reactions. Under these modified conditions, diisopropenylarene 260 was converted to pyrroloindole 326 in good yield with no evidence of mono-cyclization (Scheme 129). In addition, the reaction time was reduced to 48 hours.
Scheme 129: Double Cyclization Using 1,10-phenanthroline/dppp

These modified Soderberg cyclization conditions were then applied to each of the substrates prepared in Chapter 5.4. The results of these reactions are summarized in Table 10.

Table 10: Reductive Double N-Heterocyclizations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="240b.png" alt="Image" /></td>
<td><img src="239.png" alt="Image" /> (78%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="314.png" alt="Image" /></td>
<td><img src="329.png" alt="Image" /> (47%)</td>
</tr>
<tr>
<td></td>
<td><img src="302.png" alt="Image" /></td>
<td><img src="330.png" alt="Image" /> (30%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="302.png" alt="Image" /></td>
<td><img src="331.png" alt="Image" /> (77%)</td>
</tr>
</tbody>
</table>
Table 10: Reductive Double N-Heterocyclizations*  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="https://example.com/substrate4.png" alt="Image of substrate" /></td>
<td><img src="https://example.com/product4.png" alt="Image of product" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="https://example.com/substrate5.png" alt="Image of substrate" /></td>
<td><img src="https://example.com/product5.png" alt="Image of product" /></td>
</tr>
</tbody>
</table>

* Conditions: 1,10-phenanthroline, dppp, Pd(dba)$_2$, CO (6 atm), DMF, 120 °C, 120 hrs  
* Reaction run for 87 hours  

Pyrroloindole 239 was obtained in moderate yield after 87 hours (Table 10, entry 1). It was anticipated that di-vinyl substrate 240 would cyclize faster than the other examples, which featured various substituents on the double bonds that could interfere with the coordination of palladium to the alkene. It is possible that the cyclization was complete in a shorter amount of time, however, difficulties in monitoring the reaction via TLC limited the certainty with which progress could be monitored. The modified catalyst conditions also improved on Banini’s preparation of 239 (which used PPh$_3$ and Pd(dba)$_2$ in DMF under CO (6 atm)) to obtain the pyrroloindole 239 in 84% yield after 144 hours. Although the yield was slightly lower in our hands, reducing the reaction time by nearly three days was a modest improvement.

In the case of vinyl-isopropenyl substrate 314 (Table 10, entry 2), it appeared as though the added steric bulk of the methyl group slowed down the cyclization of the
isopropenyl moiety as evidenced by the moderate amount of indole 329 isolated. However, desired pyrroloindole 330 was also isolated, albeit in poor yield on account of the isolation of indole 329. It is notable that the vinyl group of 314 reacts regioselectively with the 4-nitro group and not with the other neighboring nitro substituent. The structure of indole 329 was confirmed through observed NOE between the C7 proton of the indole core and the indole N-H. This inherent regioselectivity could potentially be attributed to the less hindered nitro group being more accessible to interaction with the palladium catalyst.

The cyclization of 2,3-dinitro substrate 302 (Table 10, entry 3) afforded pyrroloindole 331 in good yield with no detected mono-cyclization. In comparison to the cyclization of di-isopropenyl substrate 257 which afforded mono-cyclized indole 259 as the major product along with pyrroloindole 258 (Section 5.3.3), substrate 302 featuring more substituted double bond cyclized at a faster rate with no mono-cyclized product isolated. The rate enhancement could be attributed to the altered catalyst conditions with the two ligand system employed herein producing a more active catalyst.

Issues arose in the cyclization of propenyl-isopropenyl substrate 274 (Table 10, entry 4). While no starting material was detected or recovered at the end of three different trials, only trace amounts of pyrroloindole 332 was isolated. It is believed that the unsubstituted 3-position of the propenyl-cyclized portion of the product could render the pyrroloindole product prone to oligomerization, as evidenced by a substantial amount of insoluble brown material upon crude work-up. Studies on the acid-induced dimerization and oligomerization of indoles reported that the 3-position of 2-methylindole (17) is more nucleophilic than that of indole (1) on account of the added
electron-donating methyl group. Also reported is the reaction of 2-methylindole (17) and skatole (3-methylindole) (334) to afford mixed dimer 335 (Scheme 130).

Scheme 130: Formation of Mixed Indole Dimer

A similar transformation could be envisioned for pyrroloindole 332. In the event that pyrroloindole 332 is formed, intermolecular nucleophilic addition of the 2-methylindole portion of the molecule to the 3-methylindole portion of a second molecule would afford dimer 336 (Scheme 131). However, the inability to characterize the insoluble residue that was obtained prevented the confirmation of this dimerization.

Scheme 131: Intermolecular Dimerization of Pyrroloindole

The last substrate examined 276 (Table 10, entry 5) cyclized to afford pyrroloindole 333 in moderate yield. The added bulk on account of the phenyl and methyl substituents on the alkenyl group of 276 appeared to have little effect on the overall rate of the double annulation, as no mono-cyclized indole products were obtained.

5.5 Conclusions

Novel non-symmetrical pyrroloindoles were prepared from dialkenyl-dinitro benzenes. Four of the five highly functionalized isomeric cyclization precursors were
prepared through use of aromatic substitution along with Kosugi-Migita-Stille coupling reactions. Using Soderberg’s palladium-catalyzed reductive double \(N\)-heteroannulation methodology, the structurally complex cyclization precursors were converted to the corresponding pyrroloindoles. The generally mild catalyst conditions offer significant improvements over previously reported methods using harsh\(^{108,109}\) conditions. Catalyst degradation due to extended reaction times was also prevented through use of a two ligand system, protecting the integrity of the catalyst while also reducing the time needed for the double annulations to reach completion. This methodology provides synthetic routes to previously elusive highly functionalized non-symmetrical pyrroloindoles, which are of interest in a number of applications.
Chapter 6

Synthesis of Functionalized Aromatics

6.1 Brominations of 2-Nitrobenzaldehyde 118

6.1.1 Introduction 118

6.1.2 Results and Discussion 119

6.1.3 Conclusions 125

6.2 Synthesis of Functionalized Indoles 126

6.2.1 Synthesis of 6-Methyl-Nitroindoles 126

6.2.2 Synthesis of 5-Methoxy-Nitroindoles 127

6.2.3 Conclusions 130
6.1 Brominations of 2-Nitrobenzaldehyde

In the search for alternate routes to prepare non-symmetrical dinitro-dialkenyl aromatic compounds en route to the preparation of pyrroloindoles, the halogenation of nitrobenzaldehyde was explored. It was envisioned that the selectivity issues (discussed in Chapter 4) could be circumvented through use of a route that only required one coupling step. Therefore, halobenzaldehydes were sought as potential intermediates to prepare the desired cyclization precursors though Wittig condensation of the aldehyde and cross-coupling of the halide (Scheme 132).

Scheme 132: Proposed Substrate Preparation From Halobenzaldehyde

6.1.1 Introduction

A mild method for the bromination of deactivated aromatic compounds using N-bromosuccinimide (NBS) in sulfuric acid was reported by Saiganesh et al in 2007. Nine different substrates were examined and 60-92% yields of single products were reported. For eight of the starting materials, the directing effect of the functional groups present on the aromatic ring for electrophilic aromatic bromination coincided in the same position. Thus, the regioselectivity of the incoming electrophile was not an issue. The last substrate examined by the authors, 2-nitrobenzaldehyde (338), did not have this luxury. Nevertheless, 4-bromo-2-nitrobenzaldehyde (339) was reported as the only
product in over 60% yield (Scheme 133). In addition to the reaction of 338 with NBS in sulfuric acid, a related regioselective bromination using sodium bromide and sodium periodate in sulfuric acid – water to afford 339 in 88% isolated yield was reported by Kumar *et al* in 2012 (Scheme 133).\(^{144}\)

**Scheme 133: Regioselective Bromination of 2-Nitrobenzaldehyde**

![Chemical structure](attachment:image.png)

The experimental procedures, as described in the literature, were repeated a number of times. However, in our hands, the results reported could not be duplicated. The reactions with NBS gave a complex mixture of up to seven brominated products along with unreacted starting material. Reactions attempted using NaBr-NaIO₄ resulted only in quantitative recovery of starting material. The complex reaction mixtures obtained in the experiments using NBS were examined in order to assign structures to each product. It should be noted that each of the brominated products obtained are potentially useful building blocks in organic chemistry on account of their high degree of functionality, although each was obtained in relatively low yield.

6.1.2 **Results and Discussion**

In an attempt to deconvolute the complex reaction mixtures obtained, 2-nitrobenzaldehyde (338) was reacted with NBS in sulfuric acid at both the originally reported reaction temperature (25 °C) and at 60 °C. In addition, experiments employing different amounts of NBS were performed. Complex mixtures containing the four
possible monobrominated compounds (339-342) and three dibrominated products (343-345) were observed in the crude reaction mixtures in all cases (Scheme 134).

Scheme 134: Bromination of 2-Nitrobenzaldehyde

The molar ratios of products in each trial were extrapolated from integration of the crude $^1$H NMR spectra and are presented in Table 11. Purification of the crude mixtures afforded pure products along with two or three component mixtures. The isolated yields of each product in each trial are reported in Table 12.

Table 11: Molar Ratios of Brominated Products$^a$

<table>
<thead>
<tr>
<th>Equivalents NBS</th>
<th>338</th>
<th>339</th>
<th>340</th>
<th>341</th>
<th>342</th>
<th>343</th>
<th>344</th>
<th>345</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.25$^b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Reactions were performed at ambient temperature. Ratios were calculated from $^1$H NMR spectra of the crude reaction mixtures. b) Reaction at 60 °C.
Table 12: Isolated Yields of Brominated Products

<table>
<thead>
<tr>
<th>Equivalents NBS</th>
<th>338</th>
<th>339</th>
<th>340</th>
<th>341</th>
<th>342</th>
<th>343</th>
<th>344</th>
<th>345</th>
<th>Total Brominated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75</td>
<td>38</td>
<td>19</td>
<td>4</td>
<td>12</td>
<td>24</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>62%</td>
</tr>
<tr>
<td>1.25</td>
<td>17</td>
<td>21</td>
<td>4</td>
<td>9</td>
<td>20</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>63%</td>
</tr>
<tr>
<td>1.25b</td>
<td>4</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>36%</td>
</tr>
<tr>
<td>2.5</td>
<td>3</td>
<td>8</td>
<td>8</td>
<td>20</td>
<td>14</td>
<td>12</td>
<td>9</td>
<td>13</td>
<td>84%</td>
</tr>
<tr>
<td>5.0</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>19</td>
<td>17</td>
<td>64%</td>
</tr>
</tbody>
</table>

Starting material (338) was detected in all reactions aside from the reaction using 5 equivalents of NBS. Chromatographic separation using silica gel was partially successful in separating the isomers. Monobrominated isomer 340 was isolated from the mixture when five equivalents of NBS was added. Pure 344 was isolated regardless of the amount of NBS used, and pure 343 and 345 were separated from the crude mixture when five equivalents of NBS was used. Monobrominated compounds 339, 341, and 342 were always isolated as inseparable mixtures. The identities of compounds 340, 342, 344, and 345 were verified through comparison with literature NMR and/or melting point data.

In order to correctly identify each isomeric compound as well as to aide in the separation of the mixtures, all pure compounds and some of the mixtures were reduced to the corresponding benzylalcohols using sodium borohydride.

Reduction of 340 using sodium borohydride afforded known benzylalcohol 346 (Scheme 135). The aromatic 1H NMR splitting pattern consisting of two doublets and a triplet along with a nuclear Overhauser effect (nOe) between the methylene protons and one of the aromatic doublets confirmed the structure of 346 and thus of isomer 340. This
transformation also verified the structure of the other monobrominated product with the same doublet-doublet-triplet $^1$H NMR splitting pattern assigned as 342.

**Scheme 135: Sodium Borohydride Reduction of 340**

Aldehydes 339 and 341 were inseparable, however, treatment of the mixture with sodium borohydride provided a separable mixture of known benzylalcohols 347 and 348. These benzylalcohols also corroborated the structure of 339 and 341 by nOe experiments (Scheme 136).

**Scheme 136: Reduction of Inseparable Mixture**

Similarly, reduction of aldehyde 343 afforded benzylalcohol 349 (Scheme 137). The structure of 343 was then confirmed by and observed nOe between the benzyl protons and the ortho proton on the benzene ring of 349.
Aldehyde 344 was also reduced using sodium borohydride (Scheme 138). The structure of 350 and subsequently 344 were again confirmed through nOe experiments.

Similar reduction of aldehyde 345 afforded benzylalcohol 351 (Scheme 139). As expected, no nOe was observed between the methylene of 351 and any of the aromatic protons.

As anticipated, predominately monobrominated products were obtained from reactions using lower amounts of NBS and, not surprisingly, dibrominated products were
the major components when a large excess of NBS was used. Interestingly, the total yield of brominated products was roughly the same regardless of the amount of NBS used. A significantly lower yield was obtained from the reaction using 2.5 equivalents of NBS at 60 °C, even though little starting material was present in the crude mixture. The combination of elevated temperature and the acidic reaction medium may have caused decomposition of the starting material. Because only a small amount of dibrominated products were formed when less than one equivalent of NBS was used, the ratios of 339, 340, and 341 provided a measure of the reactivity of the different positions in 338 toward electrophilic aromatic bromination. The reactivity was normalized to compound 340, the minor monobrominated product, and was calculated to be 6.1 : 1 : 3.7 : 6.7 (in order from 339 to 342). This order of reactivity likely reflects the electron-withdrawing ability of the nitro group as compared to the aldehyde. Presumably the nitro group more effectively deactivates the meta positions (relative to the nitro group), in turn rendering the ortho and para positions (relative to the nitro group) more reactive. The results from the reactions using 0.75 and 5.0 equivalents of NBS also suggest that compounds 340, 341, and 342 undergo a second bromination at a much faster rate compared to 339, since a significant amount of the latter remains even at 5.0 equivalents of NBS. A rough order of reactivity for the second bromination of each monobrominated product was calculated by comparing the ratios of monobrominated products at 0.75 and 5.0 equivalents of NBS. The resulting order of 342 > 340 > 341 > 339 potentially reflects the minimized steric congestion of 342 and 340 relative to 339 and 340.
6.1.3 Conclusions

In summary, the reported results for the selective bromination of 2-nitrobenzaldehyde (338) using NBS in sulfuric acid to give 4-bromo-2-nitrobenzaldehyde (339) reported in the literature were unable to be duplicated. However, the complex mixture of four monobrominated and three dibrominated products obtained in the attempts were isolated and identified. Pure products were achieved through chromatographic separation along with reduction of the aldehydes to the corresponding benzylalcohols, also aiding in the structural elucidation of each isomer. Based on the ratios achieved in each trial, the relative reactivity of each position of 2-nitrobenzaldehyde towards electrophilic bromination was inferred and found to reflect the greater deactivating ability of the nitro group in comparison to the aldehyde. Each mono and dibrominated product possessed a high degree of functionality with the potential to be synthetically useful building blocks.
6.2 Synthesis of Functionalized Indoles

Through extensive efforts to prepare non-symmetrical cyclization precursors in the synthesis of pyrroloindoles, a number number of highly functionalized nitroaromatic compounds were prepared. While these compounds were ultimately not used in the established routes to prepare pyrroloindoles, it was envisioned that nitro-substituted indoles could be prepared from some of the intermediate compounds that were synthesized. These functionalized indoles would provide a diverse array of starting materials for a number of further transformations.

6.2.1 Synthesis of 6-Methyl-Nitroindoles

The first functionalized indoles that were prepared arose from the dinitration of \( p \)-bromotoluene (245) (Scheme 140). Due to the harsh conditions used in this reaction, all four possible dinitrated isomers 246 and 352-354 were observed. Although separation of isomers 246 and 353 proved to be very difficult, 352 and 354 were separable using column chromatography.

![Scheme 140: Nitration of \( p \)-Bromotoluene](attachment:image.png)

Under Kosugi-Migita-Stille cross-coupling conditions, aryl bromide 352 was coupled with vinyl stannane to afford dinitrostyrene 355 (Scheme 141).

![Scheme 141: Kosugi-Migita-Stille Coupling of Aryl Bromide](attachment:image.png)
Using modified Söderberg conditions, reductive N-heterocyclization of o-nitrostyrene \( \text{355} \) was achieved through treatment with triphenylphosphine and palladium (II) acetate in acetonitrile while heating in a sealed tube pressurized with carbon monoxide, affording 6-methyl-7-nitroindole (\( \text{356} \)), albeit in poor yield (Scheme 142).

**Scheme 142: Reductive N-Heterocyclization of Nitrostyrene 355**

![Chemical structure](image)

Similar methodology was applied to 3,5-dinitrotoluene isomer \( \text{354} \) (Scheme 143). Initial Kosugi-Migita-Stille coupling between aryl bromide \( \text{354} \) and vinyl stannane afforded styrene \( \text{357} \). Subsequent exposure of nitrostyrene \( \text{357} \) to the previously discussed reductive N-heterocyclization conditions afforded 6-methyl-4-nitroindole \( \text{358} \) in moderate yield over two steps.

**Scheme 143: Synthesis of 6-Methyl-4-Nitroindole**

![Chemical structure](image)

### 6.2.2 Synthesis of 5-Methoxy-Nitroindoles

In the attempted synthesis of pyrroloindoles starting from either 3-bromoanisole \( \text{359} \) or 3-iodoanisole \( \text{362} \), dinitro-haloanisoles \( \text{360}, \text{361}, \text{363}, \text{364} \) were prepared through treatment of the corresponding anisole with fuming nitric acid (Scheme 144). Interestingly, none of the 2,6-dinitroanisole product was formed from either substrate. On account of this, it was presumed that the first nitro group likely added to the 4-
position (relative to the methoxy group), then a second nitro group added to either of the positions ortho to the methoxy group. The substantial difference in the ratio of products 360:361 and 363:364 is also intriguing. While the iodine would be larger than the bromine and would pose a greater steric effect, the electronic effect in going from bromine to iodine likely influenced the observed differences in regioselectivity.

**Scheme 144: Dinitration of 3-Haloanisole**

These isomers were then subjected to previously discussed Kosugi-Migita-Stille coupling conditions in the presence of vinyl stannane to afford dinitrostyrenes 365 and 367, which were then cyclized using Söderberg’s palladium-catalyzed reductive N-heteroannulation conditions. This sequence afforded two isomeric methoxy-nitroindoles 366 and 368, albeit in low yield (Scheme 145). The structure of indole 368 was confirmed through the observed nOe between the C7 proton and the indole H.

**Scheme 145: Preparation of 5-Methoxy-Nitroindoles**
A similar route afforded 3-methylindoles 370 and 372 from intermediates 369 and 371, which resulted from Kosugi-Migita-Stille coupling between the requisite haloanisole and isopropenyl stannane (Scheme 146). The structure of indole 372 was again confirmed through the observed NOE between the C7 proton and the indole N-H.

**Scheme 146: Preparation of 3-Methyl-5-Methoxy-Nitroindoles**

While the yields of the indole products were moderate at best, a number of significant observations were made. As observed in prior cases, the ortho alkenyl group is necessary for reduction of a nitro group; nitro groups lacking an ortho alkenyl substituent were inert to the reductive conditions. The regioselectivity observed in the cyclization of isomers 367 and 371 was also of interest. While cyclization of these could occur through either of the two ortho nitro groups relative to the alkenyl substituent, only one indole product (368 and 372) was isolated in each case. This infers that steric influence the initial coordination-mediated nitro group reduction, as only the presumably more accessible nitro group reacted in these examples.
6.2.3 Conclusions

A number of substituted indoles were prepared through palladium-catalyzed reductive $N$-heterocyclization of the requisite $o$-nitrostyrene precursor. These examples expand the already broad substrate scope of Söderberg’s palladium-catalyzed reductive $N$-heteroaannulation methodology and exemplify the functional group compatibility of the relatively mild reaction conditions. Insight was also gained regarding the regioselectivity of the initial nitro group reduction, confirming previously proposed principles that a neighboring alkenyl group mediates nitro group reduction.
Chapter 7

Supporting Information: Experimental Procedures

7.1 Supporting Information for Chapter 2: Indole/Quinoline 133
7.2 Supporting Information for Chapter 3: Salviadione 136
7.3 Supporting Information for Chapter 4: Chemoselective Coupling 145
7.4 Supporting Information for Chapter 5: Pyrroloindoles 165
7.5 Supporting Information for Chapter 6.1: 2-Nitrobenzaldehyde Brominations 184
7.6 Supporting Information for Chapter 6.2: Functionalized Indoles 189
**General Procedures.** NMR spectra were determined in CDCl₃ at 600 MHz (¹H NMR) and 150 MHz (¹³C NMR), 400 MHz (¹H NMR) and 100 MHz (¹³C NMR), or at 270 MHz (¹H NMR) and 67.5 MHz (¹³C NMR). The chemical shifts are expressed in d values relative to SiMe₄ (0.0 ppm, ¹H and ¹³C) or CDCl₃ (77.0 ppm, ¹³C) internal standards. ¹H-¹H coupling constants are reported as calculated from spectra, thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually observed. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Hexanes and ethyl acetate were distilled from calcium hydride. Anhydrous acetonitrile, benzene, dichloromethane, 1,4-dioxane, $N,N$-dimethylformamide, and toluene were used as received. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure unless otherwise stated. Chromatography was performed on silica gel 60 (40-63 µm, Sorbtech). Melting points (uncorrected) were recorded directly from products obtained by chromatography.
3-Cyclohexyl-2-iodo-2-propenenitrile (110): To a solution of triphenylarsonium ethanenitrile (1.66 g, 3.90 mmol) in MeCN (15 mL) at 10 °C was added potassium carbonate (536 mg, 3.88 mmol) and iodine (997 mg, 3.93 mmol). The solution was stirred under a nitrogen atmosphere (ambient temp., 30 h) where after potassium carbonate (564 mg, 4.08 mmol), cyclohexylcarboxaldehyde (556 mg, 5.00 mmol) and H₂O (0.5 mL) were added. After an additional 48 h, the solvents were removed under reduced pressure and the resulting crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give 110 (171 mg, 0.65 mmol, 17%) as a brown oil. ^1H NMR δ 6.89 (d, J=10.2 Hz, 1H), 2.54 (qt, J=10.8, 3.6 Hz, 1H), 1.77-1.73 (m, 6H), 1.25-1.14 (m, 4H); ^13C NMR δ 167.3, 116.1, 49.7, 45.7, 45.0, 31.4, 25.3, 25.0; IR (ATR) 2935, 2851, 2211, 1447, 1148 cm⁻¹; HRMS (ESI) calcd for C₉H₁₂NaNi (M+Na⁺) 283.9912; found, 283.9906.

3-Cyclohexyl-2-(2-nitrophenyl)-2-propenenitrile (111): Reaction of tributyl(2-nitrophenyl) stannane (273 mg, 0.66 mmol), 110 (171 mg, 0.65 mmol), PdCl₂(PhCN)₂ (16 mg, 0.04 mmol), AsPh₃ (22 mg, 0.07 mmol) and CuI (22 mg, 0.12 mmol) in NMP (3 mL), as described for 91 (80 °C, 76 h), gave after chromatography (hexanes/EtOAc, 9:1) 111 (82 mg, 0.32 mmol, 48%, as a 14:1 mixture of isomers) as a pale brown oil. ^1H
NMR δ 8.03 (d, J=9.6 Hz, 1H), 7.65 (t, J=7.2 Hz, 1H), 7.55 (t, J=7.2 Hz, 1H), 7.41 (d, J=7.8 Hz, 1H), 6.31 (d, J=10.2 Hz, 1H), 2.78 (tq, J=4.2, 0.8 Hz, 1H), 1.87 (d, J=2.6 Hz, 2H), 1.79 (dt, J=13.8 Hz, 3.0 Hz, 2H), 1.72 (dt, J=13.2, 3.6 Hz, 1H), 1.40 (tq, J=12.6, 3.6 Hz, 2H), 1.23 (m, 3H); 13C NMR δ 156.7, 147.8, 133.5, 131.7, 129.9, 129.7, 124.9, 115.2, 110.6, 41.2, 31.6, 25.5, 25.1; IR (ATR) 2928, 2853, 2221, 1526, 1345, 854, 731 cm⁻¹; HRMS (ESI) calcd for C_{15}H_{16}NaN_{2}O_{2}(M+Na⁺) 279.1110; found 279.1104.

3-Cyano-2-cyclohexyindole (112): Reaction of 111 (73 mg, 0.31 mmol), PPh₃ (26.2 mg, 0.10 mmol), Pd(OAc) (7.6 mg, 0.03 mmol), and CO (6 atm) in DMF (5 mL), as described in for 77, gave after chromatography (hexanes/EtOAc, 7:3) 112 (34 mg, 0.15 mmol, 48%) as a pale yellow solid. mp 171-173 °C; ¹H NMR δ 8.54 (br s, 1H), 7.67 (d, J=4.8 Hz, 1H), 7.38 (d, J=7.2 Hz, 1H), 7.26-7.23 (m, 2H), 3.05 (tt, J=8.4, 3.6 Hz, 1H), 2.08 (d, J=12.0 Hz, 2H), 1.90 (dt, J=13.8, 3.0 Hz, 2H), 1.80 (d, J=12.6 Hz, 1H), 1.61 (dq, J=12.6, 3.6 Hz, 2H), 1.46 (tq, J=13.2, 3.6 Hz, 2H), 1.31 (tq, J=12.6, 3.6 Hz, 1H); ¹³C NMR δ 153.4, 134.1, 127.8, 123.3, 122.0, 119.0, 116.4, 111.3, 83.4, 37.6, 32.4, 26.1, 25.7; IR (ATR) 3227, 2919, 2849, 2215, 1439, 737 cm⁻¹; HRMS (ESI) calcd for C_{15}H_{16}NaN_{2}(M+Na⁺) 247.1211, found 247.1199.
3-Cyano-2-cyclohexylindole (112) and 3-cyano-2-(1-hydroxycyclohexyl)indole (113).

Reaction of 111 (82 mg, 0.32 mmol), PPh₃ (42 mg, 0.16 mmol), DBU (53 mg, 0.36 mmol), and Pd(OAc)₂ (10 mg, 0.05 mmol) in DMF (5 mL) as described for 78 gave after chromatography (hexanes/EtOAc, 8:2) 112 (5 mg, 0.02 mmol, 7%) and 113 (24 mg, 0.10 mmol, 31%) as a pale yellow oil. ¹H NMR δ 9.25 (br s, 1H), 7.68 (d, J=6.6 Hz, 1H), 7.40 (d, J=6.6 Hz, 1H), 7.25 (m, 2H), 2.47 (br s, 1H), 2.25 (dt, J=13.8, 4.8, 2H), 1.89 (d, J=13.8 Hz, 2H), 1.82-1.64 (m, J= 16.2 Hz, 5H), 1.43 (m, 1H); ¹³C NMR δ 154.6, 133.1, 129.2, 123.7, 122.3, 119.4, 116.8, 112.0, 80.7, 72.3, 37.4, 24.9, 21.6; IR (ATR) 3330, 2938, 2214, 1737, 1241, 1044 cm⁻¹; HRMS (ESI) calcd for C₁₅H₁₆NaN₂O (M+Na⁺) 263.1160, found 263.1155.
5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (127):  
5,5-Dimethyl-3-(1-methylethoxy)-2-cyclohexen-1-one (128)\(^{146}\) (4.133 g, 22.68 mmol) was dissolved in THF (25 mL) and cooled to -78 °C under a positive flow of nitrogen. Lithium diisopropylamide (2.0 M, 13.6 mL, 27.21 mmol) was added drop wise via a cannula over 15 min. The resulting yellow solution was stirred for 1 h at -78 °C before slowly adding the solution drop wise via a cannula to a solution of 1-(2-iodoethyl)-4-methoxybenzene (129)\(^{145}\) (7.132 g, 27.21 mmol) in THF (25 mL) cooled to -78 °C. The solution was allowed to stir up to ambient temperature (12 h) followed by addition of a solution of NH\(_4\)Cl (sat. aqueous, 50 mL) was carefully added and stirred for 5 min. The phases were separated and the aqueous portion was extracted with EtOAc (3 x 200 mL). The combined organic phases were dried (MgSO\(_4\)), filtered, and the solvents were removed under reduced pressure. The resulting orange oil was purified by chromatography (hexanes/EtOAc, 95:5 followed by 9:1) to afford 127 as a yellow oil (6.429 g, 20.32 mmol, 90%). \(^1\)H NMR (270 MHz) \(\delta\) 7.13 (d, \(J=8.5\) Hz, 2H), 6.82 (d, \(J=8.3\) Hz, 2H), 5.34 (s, 1H), 4.42 (sept, \(J=6.2\) Hz, 1H), 3.78 (s, 3H), 2.76 (ddd, \(J=13.4, 9.7, 5.7\) Hz, 1H), 2.54 (ddd, \(J=13.9, 9.7, 7.3\) Hz, 1H), 2.26 (d, \(J=17.6\) Hz, 1H), 2.18 (d, \(J=17.6\) Hz, 1H), 1.97 (dd, \(J=8.7, 4.3\) Hz, 1H), 1.83-1.69 (m, 2H), 1.28 (d, \(J=6.1\) Hz, 6H), 1.02 (s, 3H), 0.94 (s, 3H); \(^{13}\)C NMR (67.5 MHz) \(\delta\) 202.4 (+), 173.1 (+), 157.7 (+), 134.6 (+), 129.4 (-), 113.7 (-), 100.9 (-), 70.7 (-), 56.2 (-), 55.2 (-), 42.2 (+), 35.0 (+), 34.0 (+),
28.5 (-), 28.4 (+), 24.4 (-), 21.5 (-); IR (ATR) 2957, 2932, 1648, 1604, 1517, 1378, 1243, 1107 cm$^{-1}$.

10,10α-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthren-3(1H,2H,9H)-one (132) and 10,10α-Dihydro-1,1-dimethyl-6-hydroxy-7-(1-methylethyl)-5-nitrophenanthren-3(1H,2H,9H)-one (125): Fuming nitric acid (5.0 mL, 144 mmol) was cooled to -78 °C and concentrated sulfuric acid (13 drops) was slowly added dropwise. After stirring for 20 min, 126 (166 mg, 0.556 mmol) was added in one portion to the nitration solution. The resulting dark red solution was removed from the cold bath and allowed to stir for 10 min. at ambient temperature. The mixture was poured into 200 mL of ice, neutralized with Na$_2$CO$_3$ (s) and extracted with EtOAc (3 x 75 mL). The combined organic phases were dried (MgSO$_4$), filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography (hexanes/acetone, 6:4) to afford in order of elution 132 (47.9 mg, 0.140 mmol, 25%) as a colorless solid followed by 125 (59.6 mg, 0.181 mmol, 32%) as a yellow solid.

Analytical data for 132: mp 174-175 °C; $^1$H NMR (600 MHz) δ 7.15 (s, 1H), 6.14 (d, $J=0.8$ Hz, 1H), 3.83 (s, 3H), 3.30 (sept, $J=7.0$ Hz, 1H), 2.81 (dddd, $J=16.0, 7.3, 5.0, 0.6$, 1H), 2.71 (dddd, $J=16.0, 8.1, 5.0, 0.8$ Hz, 1H) 2.61 (dt, $J=7.1, 2.4$ Hz, 1H), 2.35 (dd, $J=16.0, 0.4$ Hz, 1H), 2.27 (dd, $J=16.0, 0.8$ Hz, 1H), 1.99 (dddd, $J=13.5, 7.3, 7.1, 7.1$ Hz, 1H), 1.87 (dddd, $J=13.5, 8.1, 5.0, 5.0$ Hz, 1H), 1.26 (d, $J=7.0$ Hz, 3H), 1.24 ($J=7.0$ Hz, 3H), 1.16 (s, 3H), 0.98 (s, 3H); $^{13}$C NMR (150 MHz) δ 198.5, 151.8, 147.5, 145.5, 144.4,
137.4, 127.6, 125.3, 124.8, 63.9, 51.6, 45.7, 37.1, 29.4, 28.9, 26.6, 23.4, 23.4, 23.2, 22.0; IR (ATR) 2968, 1664, 1525, 1283, 1254 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{20}\)H\(_{26}\)NO\(_4\) (M+H\(^+\)) 344.1862, found 344.1862. Analytical data for 125: mp 154-156 °C (dec); \(^1\)H NMR (270 MHz) \(\delta\) 9.20 (br s, 1H), 7.17 (s, 1H), 5.84 (d, \(J=2.2\) Hz, 1H), 3.37 (sept, \(J=6.9\) Hz, 1H), 2.82-2.57 (m, 4H), 2.40 (d, \(J=16.0\) Hz, 1H), 2.28 (d, \(J=15.8\) Hz, 1H), 2.04-1.97 (m, 1H), 1.26 (d, \(J=6.7\) Hz, 3H), 1.25 (d, \(J=6.9\) Hz, 3H), 1.23 (s, 3H), 1.02 (s, 3H); \(^{13}\)C NMR (67.5 MHz) \(\delta\) 198.2 (+), 154.2 (+), 149.2 (+), 139.7 (+), 134.0 (+), 133.6 (+), 130.4 (-), 129.0 (+), 125.3 (-), 50.8 (+), 45.3 (-), 37.2 (+), 28.7 (-), 28.6 (+), 27.2 (-), 23.4 (+), 22.7 (-), 22.2 (-), 22.0 (-); IR (ATR) 3280, 2959, 1660, 1645, 1544, 726 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{19}\)H\(_{24}\)NO\(_4\) (M+H\(^+\)) 330.1705; found, 330.1705.

**Alternative procedure to 125.** Fuming HNO\(_3\) (500 mL, 12.0 mmol) was stirred at -20 °C for 5 min before concentrated H\(_2\)SO\(_4\) (8 drops) was slowly added drop wise. The solution was stirred for 30 min before 126 (79 mg, 0.26 mmol) was added. The resulting dark red solution was stirred for 90 min before quenching with ice (30 mL). The mixture was neutralized with Na\(_2\)CO\(_3\) (aqueous, saturated) and extracted with EtOAc (3 x 50 mL). The combined organic phases were dried (MgSO\(_4\)), filtered and the solvent was removed under reduced pressure. The resulting brown oil was immediately purified by chromatography (hexanes/EtOAc, 9:1) affording 125 (66 mg, 0.20 mmol, 77%) as a yellow solid.
8a,9,10,10a-Tetrahydro-1,1-dimethyl-8a-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1H,2H)-dione (133): Fuming HNO₃ (6.9 mL, 164.0 mmol) was stirred at 0 °C for 5 min before concentrated H₂SO₄ (14 drops) was slowly added drop-wise. After 30 min at 0 °C, the solution was added drop wise via a pipette to 126 (1.078 g, 3.61 mmol) at ambient temperature. The resulting dark red solution was stirred for 4 h whereafter H₂O (5 mL) and NH₄Cl (sat., aqueous, 40 mL) was added sequentially. The precipitate was removed by filtration, dissolved in acetone (50 mL) and adhered to silica gel (≈1.0 g) and allowed to stand for 1 h. The solvent was removed under reduced pressure and purification by chromatography (hexanes/acetone, 9:1 followed by 7:3) gave 133 (0.832 g, 2.41 mmol, 67%, 14:1 diastereomeric ratio) as an orange solid. mp 239-240 °C; IR (ATR) 2952, 1663, 1530, 1266, 1253 cm⁻¹; HRMS (ESI) calcd for C₁₉H₂₄NO₅ (M+H⁺) 346.1654, found 346.1655. Spectral data of the major diastereomer 133 from the mixture: ¹H NMR (600 MHz, CDCl₃/DMSO-d₆) δ 6.66 (d, J=1.1 Hz, 1H), 6.02 (d, J=2.4 Hz, 1H), 5.49 (d, J=1.5 Hz, 1H), 2.94 (dsept, J=6.8, 1.0 Hz, 1H), 2.41 (ddd, J=12.3, 5.7, 2.4 Hz, 1H), 2.32 (ddd, J=13.8, 3.5, 2.3 Hz, 1H), 2.30 (d, J=15.3 Hz, 1H), 2.26 (d, J=15.3 Hz, 1H), 2.08 (dq, J=13.2, 4.0 Hz, 1H), 1.97-1.92 (m, 1H), 1.67 (ddt, J=13.2, 4.2, 1.2 Hz, 1H), 1.12 (d, J=7.2 Hz, 3H), 1.11 (d, J=7.2 Hz, 3H), 1.11 (s, 3H), 1.02 (s, 3H); ¹³C NMR (150 MHz, CDCl₃/DMSO-d₆) δ 198.0, 175.5, 152.1, 147.9, 145.6, 143.4, 142.2, 126.5, 68.9, 50.9, 49.0, 37.4, 35.6, 28.4, 26.4, 23.0, 21.3, 21.0, 20.5. Partial spectral data for minor diastereomer 133 from the mixture: ¹H NMR (600 MHz, CDCl₃/DMSO-d₆) δ 6.80 (d, J=1.0 Hz, 1H), 6.22 (d, J=2.8 Hz, 1H), 5.46 (s, 1H); ¹³C NMR (150 MHz, CDCl₃/DMSO-d₆) δ 198.1, 175.6, 153.4, 146.2, 145.8, 145.6, 139.8, 127.7, 67.7, 53.6, 45.1, 37.2, 37.1, 30.7, 28.7, 26.2, 23.0, 19.7, 19.6.
Alternative procedure to 133. To a solution of 132 (81 mg, 0.236 mmol) in acetone (5 mL) and acetic acid (1 mL) was added silica gel (0.5 g). The solvent was removed at reduced pressure and the yellow residue was allowed to stand open to air for 14 h. A slight yellow tint was noticed after this time and the residue was purified by chromatography (hexanes/acetone, 6:4) to afford 133 (72.0 mg, 0.208 mmol, 88%).

1,8,9,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methyl ethyl)-4H-benzo[def]carbazol-3(2H)-one (134): To a solution of 132 (22 mg, 0.065 mmol) in anhydrous DMF (1.0 mL) in a threaded ACE glass pressure tube was added 1,10-phenanthroline monohydrate (1.6 mg, 0.008 mmol), 1,3-bis(diphenylphosphino)propane (1.7 mg, 0.004 mmol), and bis(dibenzylideneacetone)palladium (2.3 mg, 0.004 mmol). The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (4 cycles of 6 atm). The reaction mixture was heated at 120 °C under carbon monoxide (6 atm) for 168 h. The solvent was removed via bulb-to-bulb distillation affording a brown residue. Water (5 mL) was added to this residue and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried (MgSO₄), filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography.
(hexanes/acetone, 9:1) to give 134 (17.3 mg, 0.057 mmol, 87%) as a yellow solid. mp 228-230 °C; \(^1\)H NMR (600 MHz) \(\delta\) 8.64 (br s, 1H), 6.81 (s, 1H), 3.94 (s, 3H), 3.52 (sept, \(J=7.0\) Hz, 1H), 3.03 (dd, \(J=12.1, 5.0\) Hz, 1H), 3.02-2.95 (m, 2H), 2.77 (d, \(J=15.8\) Hz, 1H), 2.33 (d, \(J=15.8\) Hz, 1H), 2.21 (m, 1H), 1.62 (m, 1H), 1.27 (d, \(J=7.0\) Hz, 3H), 1.27 (d, \(J=7.0\) Hz, 3H), 1.24 (s, 3H), 0.85 (s, 3H); \(^1^3\)C NMR \(\delta\) 190.0, 140.9, 140.4, 134.3, 130.0, 129.5, 127.6, 126.4, 115.7, 60.9, 55.8, 41.8, 41.2, 28.4, 27.4, 26.8, 25.1, 24.2, 23.9, 20.4; IR (ATR) 3264, 2958, 2930, 1653, 1620 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{20}\)H\(_{26}\)NO\(_3\) (M+H\(^+\)) 312.1964, found 312.1959.

\[\text{1,8,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-4H-benzo[def]carbazol-3(2H)-one (136):}\] To a solution of 134 (39.0 mg, 0.124 mmol) in THF (4 mL) was added DDQ (115 mg, 0.496 mmol) over a period of 5 min. The resulting mixture was allowed to stir at ambient temperature for 4 h where after the solvent was removed under reduced pressure. The color of the residue changed from purple to orange over 30 min. The crude product was purified by chromatography (hexanes/EtOAc, 7:3) to give 136 (36.0 mg, 87%) as a brown solid. mp = 141-143 °C; \(^1\)H NMR (600 MHz) \(\delta\) 8.60 (br s, 1H), 7.03 (s, 1H), 5.18 (t, \(J=2.7\) Hz, 1H), 3.95 (s, 3H), 3.53 (sept, \(J=7.2\) Hz, 1H), 3.37 (dd, \(J=12.0, 4.8\) Hz, 1H), 2.81 (d, \(J=5.2, 0.6\) Hz, 1H), 2.41 (ddd, \(J=13.8, 5.4, 3.0\) Hz, 1H), 2.37 (d, \(J=16.8\) Hz, 1H), 1.64 (ddd, \(J=16.8, 12.0, 3.0\) Hz, 1H), 1.60 (br s, 1H), 1.28 (d, \(J=7.2\) Hz, 3H), 1.27 (d, \(J=7.2\) Hz, 3H), 1.26 (s, 3H), 0.83 (s, 3H); \(^1^3\)C NMR (150 MHz) \(\delta\) 189.2, 143.0, 140.3, 132.8, 129.9, 128.9, 128.0, 125.5,
116.8, 67.7, 60.7, 55.9, 41.6, 35.7, 32.5, 28.3, 27.0, 24.1, 23.8, 20.7; IR (ATR) 3279 (br), 2959, 1650, 1624 cm⁻¹; HRMS (ESI) calcd for C₂₀H₂₆NO₃ (M+H⁺) 328.1913, found 328.1909.

189,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-4H-
benzo[def]carbazol-3(2H)-one (124): Reaction of 125 (140 mg, 0.566 mmol), bis(dibenzylideneacetone)palladium (20 mg, 0.034 mmol), 1,3-bis-(diphenylphosphino)propane (14 mg, 0.034 mmol), and 1,10-phenanthroline (13 mg, 0.068 mmol) were dissolved in anhydrous DMF (2 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction was heated at 120 °C under CO (6 atm) for 32 h. DMF was removed via vacuum distillation before water (10 mL) was added to the brown residue. The brown solution was extracted with ethyl acetate (3 x 40 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvent was removed. The resulting crude product was purified by chromatography (pentanes/acetone, 8:2 followed by 1:1) to afford 124 (91 mg, 0.423 mmol, 75%) as a light yellow solid. mp 234-236 °C; ¹H NMR (600 MHz, THF-d₈) δ 9.94 (s, 1H), 7.72 (s, 1H), 6.69 (s, 1H), 3.50 (sept, J=7.5 Hz, 1H), 3.03 (dd, J=12.6, 4.4 Hz, 1H), 2.96-2.88 (m, 2H), 2.7 (m, 1H), 2.20-2.14 (m, 2H), 1.53 (dq, J=11.9, 5.4 Hz, 1H), 1.24 (d, J=7.0 Hz, 3H), 1.22 (d, J=7.0 Hz, 3H), 1.19 (s, 3H), 0.78 (s, 3H); ¹³C NMR (150 MHz, THF-d₈) δ 187.9, 138.9, 133.6, 133.2, 129.5, 128.6, 126.8, 125.8, 115.7, 56.8, 42.4, 42.1, 28.7, 28.3,
27.8, 26.5, 24.0, 23.9, 20.6; IR (ATR) 3394 (br), 3260, 2962, 2928, 1617 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{19}\)H\(_{24}\)NO\(_2\) (M+H\(^+\)) 298.1807, found 298.1802.

**Salviadione (123):** To a solution of 124 (35 mg, 0.118 mmol) in THF (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (107 mg, 0.471 mmol) slowly in 2 approximately equal portions with a 5 min interval. The reaction mixture was stirred for 4 h at ambient temperature. The solvent was removed under reduced pressure from the resulting dark red-purple solution. The residue was dissolved in acetone (10 mL) and silica gel (\(\approx\)1.0 g) was added. The solvent was removed under reduced pressure and the resulting solid was allowed to stand open to the air (4 h). Purification by chromatography (hexanes/acetone, 9:1) gave salviadione (123) (28 mg, 0.095 mmol, 81%) as an orange solid. Physical (mp) and spectroscopical data (\(^1\)H, \(^{13}\)C, COSY, HMBC, HMQC) were in accordance with literature values. HRMS (ESI) calcd for C\(_{19}\)H\(_{20}\)NO\(_2\) (M+H\(^+\)) 294.1494, found 294.1494.

**Alternative method to 123** To a solution of 133 (101 mg, 0.29 mmol) in anhydrous DMF (7.0 mL) in a threaded ACE glass pressure tube was added dppp (7.7 mg, 0.019 mmol), phen (19 mg, 0.095 mmol) and Pd(dba)\(_2\) (15 mg, 0.027 mmol). The tube was
fitted with a pressure head and the solution was saturated with carbon monoxide (3 cycles of 6 atm). The reaction mixture was heated at 120 °C under carbon monoxide for 168 hours. The solvent was removed via bulb-to-bulb distillation affording a brown oil. Water (5 mL) was added to this residue and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were dried (MgSO₄), filtered, and solvent was removed under reduced pressure. The crude product was purified by chromatography (hexanes/ethyl acetate 7:3) to afford salviadione (123) (8.7 mg, 0.029 mmol, 10%).
7.3 Supporting Information for Chapter 4: Chemoselective Coupling

2-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (163): To an ice-cooled solution of 162 (269 mg, 1.23 mmol) in CH$_2$Cl$_2$ (5 mL) was added pyridine (200 µL, 2.48 mmol) and trifluoromethanesulfonic anhydride (Tf$_2$O, 250 µL, 1.48 mmol). The mixture was removed from the cold bath and allowed to stir at ambient temperature for 30 min. The resulting mixture was filtered through a small plug of silica gel and the solvent was removed under reduced pressure from the filtrate. Purification by chromatography (hexanes/EtOAc, 9:1) afforded 3 (391 mg, 1.12 mmol, 90%) as a yellow oil. $^1$H NMR δ 7.89 (d, $J$=9.0 Hz, 1H), 7.83 (d, $J$=3.0 Hz, 1H), 7.42 (dd, $J$=9.0, 3.0 Hz, 1H); $^{13}$C NMR δ 150.1, 147.9, 136.8, 126.3, 119.3, 118.6 (q, $J$=319 Hz, C-F), 114.6; IR (ATR) 3103, 1541, 1428, 1208, 1132 cm$^{-1}$. HRMS (ESI) calcd for C$_7$H$_3$BrNO$_5$F$_3$S (M+Na$^+$) 371.8759; found 371.8760.

2-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene (166): Treatment of 165 (298 mg, 1.37 mmol) in CH$_2$Cl$_2$ (5 mL) with pyridine (250 µL, 3.10 mmol) and Tf$_2$O (300 µL, 1.77 mmol), as described for 163, gave after chromatography (hexanes/EtOAc, 8:2) 166 (394 mg, 1.13 mmol, 80%) as a red solid. mp 52-53 °C; $^1$H NMR δ 7.73 (dd, $J$=6.6, 3.0 Hz, 1H), 7.49 (m, 2H); $^{13}$C NMR δ 144.3, 140.7, 133.4, 132.1, 121.6, 118.3 (q, $J$=319 Hz, 1H).
3-Bromo-2-trifluoromethanesulfonyloxy-nitrobenzene (151): Treatment of 149\(^{93}\) (189 mg, 0.87 mmol) in CH\(_2\)Cl\(_2\) (5 mL) with pyridine (150 µL, 1.85 mmol) and Tf\(_2\)O (200 µL, 1.18 mmol), as described for 163, gave after chromatography (hexanes/EtOAc, 7:3) 151 (299 mg, 0.85 mmol 98%) as a colorless oil. \(^1\)H NMR δ 8.04 (dd, J=8.4, 1.8 Hz, 1H), 7.99 (dd, J=8.4, 1.8 Hz, 1H), 7.46 (t, J=7.8 Hz, 1H); \(^{13}\)C NMR δ 143.6, 139.4, 139.1, 129.3, 125.6, 119.0, 118.4 (q, J=320 Hz, C-F); IR (ATR) 3093, 1588, 1542, 1427, 1344, 1210, 1134 cm\(^{-1}\); HRMS (ESI) calcd for C\(_7\)H\(_3\)BrNO\(_5\)F\(_3\)S (M+Na\(^+\)) 371.8759; found 371.8767.

3-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (157): Treatment of 156\(^{48}\) (329 mg, 1.51 mmol) in CH\(_2\)Cl\(_2\) (10 mL) with pyridine (250 µL, 3.10 mmol) and Tf\(_2\)O (300 µL, 1.78 mmol), as described for 163, gave after chromatography (hexanes/EtOAc, 7:3) 157 (316 mg, 0.90 mmol, 60%) as a red oil. \(^1\)H NMR δ 8.44 (t, J=1.8 Hz, 1H), 8.11 (t, J=1.8 Hz, 1H), 7.80 (t, J=1.8 Hz, 1H); \(^{13}\)C NMR δ 149.1, 149.0, 130.7, 126.7, 123.8, 118.5 (q, J=319 Hz, C-F), 116.0; IR (ATR) 3097, 1732, 1542, 1427, 1344, 1210, 1134 cm\(^{-1}\); HRMS (ESI) calcd for C\(_7\)H\(_3\)BrNO\(_5\)F\(_3\)S (M+Na\(^+\)) 371.8760; found 371.8764.
3-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene (154): Treatment of 153\(^{149}\) (353 mg, 1.60 mmol) in CH\(_2\)Cl\(_2\) (5 mL) with pyridine (260 \(\mu\)L, 3.22 mmol) and Tf\(_2\)O (330 \(\mu\)L, 1.95 mmol), as described for 163, gave after chromatography (hexanes/EtOAc, 7:3) 154 (540 mg, 1.54 mmol, 97\%) as a yellow oil. \(^1\)H NMR \(\delta\) 8.30 (d, \(J=2.4\) Hz, 1H), 7.88 (dd, \(J=9.0, 2.4\) Hz, 1H), 7.36 (d, \(J=9.0\) Hz, 1H); \(^{13}\)C NMR \(\delta\) 141.9, 140.5, 138.2, 129.7, 125.6, 122.3, 118.5 (q, \(J=319\) Hz, C-F); IR 3105, 1540, 1431, 1207, 1131 cm\(^{-1}\); HRMS (ESI) calcd for C\(_7\)H\(_3\)BrNO\(_5\)F\(_3\)S (M+Na\(^+\)) 373.8739; found 373.8740.

4-Bromo-3-trifluoromethanesulfonyloxy-nitrobenzene (159): Treatment of 158\(^{150}\) (119 mg, 0.55 mmol) in CH\(_2\)Cl\(_2\) (5 mL) with pyridine (90.0 \(\mu\)L, 1.12 mmol) and Tf\(_2\)O (120 \(\mu\)L, 0.71 mmol), as described for 163, gave without further purification 159 (188 mg, 0.54 mmol, 98\%) as a brown oil. \(^1\)H NMR \(\delta\) 8.22 (d, \(J=2.4\) Hz, 1H), 8.16 (dd, \(J=8.4, 2.4\) Hz, 1H), 7.93 (d, \(J=8.4\) Hz, 1H); \(^{13}\)C NMR \(\delta\) 147.7, 147.0, 135.2, 124.1, 123.9, 118.5 (q, \(J=319\) Hz, C-F), 118.4; IR (ATR) 3104, 1534, 1431, 1348, 1211, 1134 cm\(^{-1}\); HRMS (ESI) calcd for C\(_7\)H\(_3\)BrNO\(_5\)F\(_3\)S (M+Na\(^+\)) 373.8739; found 373.8740.
2-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene (141): To a solution of PPh₃ (6.5 mg, 0.03 mmol) and Pd(dba)₂ (3.7 mg, 0.006 mmol) in dioxane (1.5 mL), stirred for 5 min under an atmosphere N₂, was added 140 (105 mg, 0.30 mmol) and ethenyl(tributyl)stannane (119 mg, 0.38 mmol). The solution was heated at reflux for 24 h. The solvent was removed under reduced pressure. The resulting crude oil was dissolved in EtOAc (10 mL) and washed with NH₄OH (10% aq., 3 x 20 mL), H₂O (20 mL), and brine (20 mL). The organic phase was dried (MgSO₄), filtered, and solvents were removed under reduced pressure. Purification using chromatography (hexanes/EtOAc, 97:3) gave in order of elution, 141 (39.3 mg, 0.13 mmol, 36%) as a yellow oil, a mixture of 140 and dba (9.8 mg), and 169 (40.8 mg, 0.19 mmol, 62%). Spectral data were in accordance with literature values.

![Chemical Structure](image)

2-Bromo-3-ethenyl-nitrobenzene (170): To a solution of LiCl (40.9 mg, 0.96 mmol) and Pd(PPh₃)₂Cl₂ (4.8 mg, 0.007 mmol) in DMF (1.5 mL) under an atmosphere of N₂ was added 140 (110 mg, 0.32 mmol) and ethenyl(tributyl)stannane (123 mg, 0.39 mmol). The resulting solution was stirred at ambient temperature for 24 h. The solution was diluted with EtOAc (10 mL) and washed with NH₄OH (10% aq., 3 x 20 mL), H₂O (20 mL), and brine (20 mL). The organic phase was dried (MgSO₄), filtered, and solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 97:3) affording in order of elution, 11 (18.5 mg, 0.06 mmol, 20%), 170 (27.6 mg, 0.12 mmol, 38%) as a colorless oil. ^1H NMR δ 7.70 (d, J=7.8 Hz, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.42 (t, J=7.8 Hz, 1H), 7.10 (dd, J=16.8, 11.4 Hz, 1H), 5.76 (d, J=17.4 Hz, 1H).
Hz, 1H), 5.52 (dd, J=10.8 Hz, 1H); \(^{13}\)C NMR δ 147.2, 128.9, 128.3, 126.2, 125.7, 124.8, 123.8, 119.5; IR (ATR) 3110, 1533, 1423, 1358, 1210, 1135 cm \(^{-1}\); HRMS (ESI) calcd for C\(_8\)H\(_6\)NO\(_2\)Br (M+Na\(^{+}\)) 249.9474; found 249.9473.

2-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (171): Treatment of 167 (67.6 mg, 0.19 mmol) with ethenyl(tributyl)stannane (72.8 mg, 0.23 mmol), PPh\(_3\) (4.5 mg, 0.02 mmol) and Pd(dbac\(_2\)) (2.2 mg, 0.004 mmol) in dioxane (1.0 mL), as described for 141, gave after chromatography (hexanes/EtOAc, 97:3) 171 as a colorless oil (47.3 mg, 0.16 mmol, 82%). \(^1\)H NMR δ 8.06 (d, J= 9.0 Hz, 1H), 7.52 (d, J= 2.4 Hz, 1H), 7.34 (dd, J= 9.0, 3.0 Hz, 1H), 7.18 (dd, J= 16.8, 10.8 Hz, 1H), 5.81 (d, J= 17.4 Hz, 1H), 5.63 (d, J= 10.8 Hz, 1H); \(^{13}\)C NMR δ 151.7, 146.6, 136.4, 131.1, 127.0, 121.4, 121.3, 121.1, 118.7 (q, J= 319 Hz, C-F); IR (ATR) 3118, 1530, 1424, 1350, 1207, 1131 cm \(^{-1}\); HRMS (ESI) calcd for C\(_9\)H\(_6\)NO\(_5\)F\(_3\)S (M+Na\(^{+}\)) 319.9811; found 319.9809.

2-Bromo-4-ethenyl-nitrobenzene (172): Treatment of 167 (75.2 mg, 0.22 mmol) with ethenyl(tributyl)stannane (85.5 mg, 0.27 mmol), LiCl (28.1 mg, 0.66 mmol) and
Pd(PPh₃)₂Cl₂ (3.6 mg, 0.005 mmol) in DMF (1.0 mL), as described for 170, gave after chromatography (hexanes/EtOAc, 97:3) a mixture of 172 and 171 (calculated from ¹H NMR spectrum: 18.0 mg of 172, 0.08 mmol, 37%, 5.8 mg of 171, 9%) as a yellow oil. ¹H NMR δ 7.86 (d, J=7.8 Hz, 1H), 7.74 (d, J=1.2 Hz, 1H), 7.45 (dd, J=8.4, 1.8 Hz, 1H), 6.69 (dd, J= 18.0, 11.4 Hz, 1H), 5.90, (d, J=17.4 Hz, 1H), 5.52 (d, J=10.8 Hz, 1H); ¹³C NMR δ 142.9, 136.4, 133.7, 132.6, 126.1, 125.5, 119.3, 115.1; IR (ATR) 3095, 1573, 1526, 1346, 1217, 1139 cm⁻¹; HRMS (ESI) calcd for C₈H₆NO₂Br (M+Na⁺) 249.9474; found 249.9474.

2-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (173): Treatment of 163 (110 mg, 0.32 mmol) with ethenyl(tributyl)stannane (134 mg, 0.42 mmol), PPh₃ (6.9 mg, 0.03 mmol) and Pd(dba)₂ (3.6 mg, 0.006 mmol) in dioxane (1.5 mL), as described for 11, gave after chromatography (hexanes/EtOAc, 97:3) 15 (63.3 mg, 0.21 mmol, 68%) as a colorless oil. ¹H NMR δ 7.90 (d, J= 2.4 Hz, 1H), 7.74 (d, J= 9.0 Hz, 1H), 7.53 (dd, J= 9.0, 2.4 Hz, 1H), 7.18 (dd, J= 17.4, 10.8 Hz, 1H), 5.79 (d, J= 16.8 Hz, 1H), 5.61 (d, J= 10.8 Hz, 1H); ¹³C NMR δ 148, 147.7, 133.8, 131.1, 130.5, 126.2, 121, 118.6 (q, J= 319 Hz, C-F), 118; IR (ATR) 3110, 1533, 1426, 1351, 1208, 1133 cm⁻¹; HRMS (ESI) calcd for C₉H₆NO₅F₃S (M+Na⁺) 319.9811; found 319.9810.
**2-Bromo-5-ethenyl-nitrobenzene (174):** Treatment of 163 (120 mg, 0.34 mmol) with ethenyl(tributyl)stannane (135 mg, 0.43 mmol), LiCl (48.2 mg, 1.13 mmol) and Pd(PPh₃)₂Cl₂ (4.8 mg, 0.007 mmol) in DMF (1.5 mL), as described for 170, gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, 174 (27.8 mg, 0.12 mmol, 36%) as a colorless oil and a mixture of 173 and 163 (calculated from ¹H NMR spectrum 22 mg, 23% and 20 mg, 17%). Spectral data were in accordance with literature values.

![Chemical structure of 166 and 175](image)

**2-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (175):** Treatment of 166 (104 mg, 0.30 mmol) with ethenyl(tributyl)stannane (121 mg, 0.38 mmol), PPh₃ (6.7 mg, 0.03 mmol) and Pd(dba)₂ (3.7 mg, 0.006 mmol) in dioxane (1.5 mL) as described for 141, gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, 176 (2.3 mg, 0.01 mmol, 3%), and 175 (52.9 mg, 0.18 mmol, 60%) as a yellow solid. Spectral data for 175:

- mp=38-39 °C; ¹H NMR δ 7.67 (d, J= 8.4 Hz, 1H), 7.57 (t, J= 8.4 Hz, 1H), 7.41 (dd, J= 8.4, 1.2 Hz, 1H), 6.68 (dd, J= 17.4, 10.8 Hz, 1H), 5.91 (d, J= 17.4 Hz, 1H), 5.61 (d, J= 11.4 Hz, 1H); ¹³C NMR δ 142.0, 140.2, 133.2, 131.6, 128.6, 126.4, 121.9, 121.4, 118.4 (q, J= 319 Hz, C-F); IR (ATR) 3090, 1533, 1427, 1361, 1211, 1138 cm⁻¹. HRMS (ESI) calcd for C₉H₅NO₃F₃S (M+Na⁺) 319.9811; found 319.9809.

![Chemical structure of 166 and 176](image)

**2-Bromo-6-ethenyl-nitrobenzene (176):** Treatment of 166 (119 mg, 0.34 mmol) with ethenyl(tributyl)stannane (138 mg, 0.44 mmol), LiCl (45.6 mg, 1.08 mmol) and
Pd(PPh$_3$)$_2$Cl$_2$ (5.0 mg, 0.007 mmol) in DMF (1.5 mL) as described for 170 gave after chromatography (hexanes/EtOAc, 97:3) 176 as an off-white solid (47.1 mg, 0.21 mmol, 61%) (mp=42-44°C). $^1$H NMR δ 7.57 (d, $J$=7.8 Hz, 1H), 7.56 (d, $J$=7.8 Hz, 1H), 7.33 (t, $J$=7.8 Hz, 1H), 6.57 (dd, $J$=16.8, 11.4 Hz, 1H), 5.85 (d, $J$=16.8 Hz, 1H), 5.51 (d, $J$=10.8 Hz, 1H); $^{13}$C NMR δ 150.1, 132.6, 131.6, 130.9, 129, 125.6, 120.8, 112.9; IR (ATR) 3077, 1557, 1521, 1460, 1365, 1187 cm$^{-1}$. HRMS (ESI) calcd for C$_8$H$_6$NO$_2$Br (M+Na$^+$) 251.9454; found 251.9454.

3-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (177): Treatment of 151 (135 mg, 0.39 mmol) with ethenyl(tributyl)stannane (129 mg, 0.41 mmol), PPh$_3$ (8.2 mg, 0.03 mmol) and Pd(dba)$_2$ (4.5 mg, 0.008 mmol) in dioxane (2 mL) before adding as described for 141 gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, 46 and dicoupled (8.5 mg, 1:1 mixture, 5 mg Tf-coupled, 3.5 mg dicoupled), 149 (22.7 mg mixed with dba), and a mixture of 151 and 177 (95.1 mg). The latter fraction was re-chromatographed (hexanes/EtOAc, 97:3) to give in order of elution, 177 as a colorless oil (27.8 mg, 0.09 mmol, 24%) and 151 (12.3 mg, 0.04 mmol, 9%). Analytical data for 177: $^1$H NMR δ 7.98 (dd, $J$= 8.4, 1.8 Hz, 1H), 7.91 (dd, $J$= 8.4, 1.8 Hz, 1H), 7.48 (t, $J$= 8.4 Hz, 1H), 6.99 (dd, $J$= 17.4, 10.8 Hz, 1H), 5.95 (d, $J$= 17.4 Hz, 1H), 5.67 (d, $J$= 10.8 Hz, 1H); $^{13}$C NMR δ 143.0, 137.8, 134.4, 132, 128.5, 128.0, 125.5, 121.4, 118.3 (q, $J$= 319 Hz, C-F); IR (ATR) 3103, 1539, 1429, 1351, 1210, 1131 cm$^{-1}$; HRMS (ESI) calcd for C$_8$H$_6$NO$_2$F$_3$S (M+Na$^+$) 319.9811; found 319.9808.
3-Bromo-2-ethenyl-nitrobenzene (46): Treatment of 151 (99.8 mg, 0.29 mmol) with ethenyl(tributyl)stannane (97.5 mg, 0.31 mmol), LiCl (36.6 mg, 0.86 mmol) and Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (4.1 mg, 0.006 mmol) in DMF (1.5 mL) as described for 170 afforded after chromatography (hexanes/EtOAc, 9:1) in order of elution, 46 as a yellow oil (28.3 mg, 0.12 mmol, 43%), 149\textsuperscript{92} (7.4 mg, 0.03 mmol, 12%), and 151 (5.0 mg, 0.01 mmol, 5%). Spectral data were in accordance with literature values.

3-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (178): Treatment of 150 (102 mg, 0.29 mmol) with ethenyl(tributyl)stannane (116 mg, 0.37 mmol), PPh\textsubscript{3} (6.5 mg, 0.03 mmol) and Pd(dba\textsubscript{2}) (4.1 mg, 0.007 mmol) in dioxane (1.5 mL) as described for 141 gave after chromatography (hexanes/EtOAc, 97:3) order of elution, 178 (19.3 mg, 0.06 mmol, 22%) as a light pink oil, 150 (7.0 mg, 0.02 mmol, 7%), and 148\textsuperscript{93} (5.2 mg, 0.02 mmol, 7%). Analytical data for 178: \textsuperscript{1}H NMR δ 8.53 (d, J = 3.0 Hz, 1H), 8.21 (dd, J = 9.0, 2.4 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 6.94 (dd, J = 17.4, 11.4 Hz, 1H), 6.04 (d, J = 17.4 Hz, 1H), 5.70 (d, J = 11.4 Hz, 1H); \textsuperscript{13}C δ 149.9, 147.2, 132.7, 127.3, 124.0, 122.9, 122.7, 121.7, 118.5 (q, J = 319 Hz, C-F); IR (ATR) 3107, 1536, 1424, 1347, 1209, 1134 cm\textsuperscript{-1}; HRMS (ESI) calcd for C\textsubscript{9}H\textsubscript{6}NO\textsubscript{5}F\textsubscript{3}S (M+Na\textsuperscript{+}) 319.9811; found 319.9809.
3-Bromo-4-ethenyl-nitrobenzene (179): Treatment of 150 (110 mg, 0.32 mmol) with ethenyl(tributyl)stannane (138 mg, 0.43 mmol), LiCl (42.6 mg, 1.0 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (4.5 mg, 0.006 mmol) in DMF (1.5 mL) as described for 170 gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, 179 (40.7 mg, 0.18 mmol, 57%) as a yellow oil, 150 (8.7 mg, 0.02 mmol, 8%), and 148 (11.1 mg, 0.05 mmol, 16%).

Analytical data for 179: $^1$H NMR δ 8.43 (d, $J$=2.4 Hz, 1H), 8.14 (ddd, $J$= 8.4, 2.4, 0.6 Hz, 1H), 7.69 (d, $J$=9.0 Hz, 1H), 7.09 (dd, $J$=17.4, 11.4 Hz, 1H), 5.88 (d, $J$=18.0 Hz, 1H), 5.60 (dd, $J$=10.8, 0.6 Hz, 1H); $^{13}$C NMR δ 147.2, 143.7, 134.3, 128.2, 127.1, 123.4, 122.4, 120.9; IR (ATR) 3099, 1520, 1342, 1116, 1035 cm$^{-1}$; HRMS (ESI) calcd for C$_8$H$_6$NO$_2$Br (M+Na$^+$) 251.9454; found 251.9456.

3-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (180): Treatment of 157 (106 mg, 0.30 mmol) with ethenyl(tributyl)stannane (130 mg, 0.41 mmol), PPh$_3$ (6.4 mg, 0.02 mmol) and Pd(dba)$_2$ (3.4 mg, 0.006 mmol) in dioxane (1.5 mL) as described for 141 gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, 157 (4.1 mg, 0.01 mmol, 4%) and 180 (70.0 mg, 0.24 mmol, 78%) as a colorless oil. $^1$H NMR δ 8.30 (t, $J$= 1.8 Hz, 1H), 8.02 (t, $J$= 1.8 Hz, 1H), 7.61 (t, $J$= 1.8 Hz, 1H), 6.78 (dd, $J$= 17.4, 10.8 Hz, 1H), 5.98 (d, $J$= 17.4 Hz, 1H), 5.61 (d, $J$= 10.8 Hz, 1H); $^{13}$C
NMR δ 149.4, 149.2, 141.7, 133.2, 124.6, 120.6, 119.8, 118.6 (q, J= 319 Hz, C-F), 115.6; IR (ATR) 3103, 1540, 1425, 1348, 1213, 1132 cm⁻¹; HRMS (ESI) calcd for C₉H₆NO₂F₃S (M+Na⁺) 319.9811; found 319.9813.

3-Bromo-5-ethenyl-nitrobenzene (181): Treatment of 157 (109 mg, 0.31 mmol) with ethenyl(tributyl)stannane (139 mg, 0.44 mmol), LiCl (45.0 mg, 1.1 mmol) and Pd(PPh₃)₂Cl₂ (4.7 mg, 0.007 mmol) in DMF (1.5 mL) as described for 170 gave after chromatography (hexanes/EtOAc, 97:3) 181 (47.1 mg, 0.21 mmol, 66%) as an off-white solid. mp=37-39 °C; ¹H NMR δ 8.23 (t, J=1.8 Hz, 1H), 8.17 (t, J=1.8 Hz, 1H), 7.83 (t, J=1.8 Hz, 1H), 6.71 (dd, J=17.4, 10.8 Hz, 1H), 5.91 (d, J=17.4 Hz, 1H), 5.50 (d, J=11.4 Hz, 1H); ¹³C NMR δ 149, 140.8, 134.8, 133.6, 125.3, 122.9, 119.6, 118.5; IR (ATR) 3079, 1531, 1339, 1301, 1214 cm⁻¹; HRMS (ESI) calcd for C₈H₆NOBr (M+Na⁺) 251.9454; found 251.9452.

3-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (182): Treatment of 154 (103 mg, 0.29 mmol) with ethenyl(tributyl)stannane (112.4 mg, 0.35 mmol), PPh₃ (6.8 mg, 0.03 mmol) and Pd(dba)₂ (3.4 mg, 0.006 mmol) in dioxane (1.5 mL) as described for 141 gave after chromatography (hexanes/EtOAc, 9:1) in order of elution, 154 (10%) followed by 182 as a yellow oil mixed with dibenzylideneacetone (34.6 mg, 0.12 mmol, 44% based on ¹H NMR integration). Spectral data from the mixture of 182 and dba: ¹H NMR δ
8.15 (d, J= 2.4 Hz, 1H), 7.72 (dd, J= 9.0, 2.4 Hz, 1H), 7.41 (d, J= 9.0 Hz, 1H), 6.75 (dd, J= 17.4, 10.8 Hz, 1H), 5.92 (d, J= 17.4 Hz, 1H), 5.55 (d, J= 10.8 Hz, 1H); \(^{13}\)C NMR δ 141.7, 140.3, 139.2, 133.1, 132.2, 124.3, 123.8, 119.2, 118.5 (q, J= 319 Hz, C-F); IR (ATR) 3094, 1541, 1429, 1346, 1205, 1134 cm\(^{-1}\); HRMS (ESI) calcd for C\(_9\)H\(_6\)NO\(_5\)F\(_3\)S (M+Na\(^{+}\)) 319.9811; found 319.9812.

5-Bromo-2-ethenyl-nitrobenzene (183): Treatment of 154 (111 mg, 0.32 mmol) with ethenyl(tributyl)stannane (131 mg, 0.41 mmol), LiCl (44.5 mg, 0.86 mmol) and Pd(PPh\(_3\))\(_2\)Cl\(_2\) (4.2 mg, 0.006 mmol) in DMF (1.5 mL) as described for 170 gave after chromatography (hexanes/EtOAc, 9:1) 183 as a yellow solid (56.3 mg, 0.25 mmol, 78%). mp=40-41°C; \(^1\)H NMR δ 8.07 (d, J=2.4 Hz, 1H), 7.70 (dd, J= 8.4, 2.4 Hz, 1H), 7.51 (d, J=8.4 Hz, 1H), 7.11 (dd, J=17.4, 11.4 Hz, 1H), 5.76 (d, J=17.4 Hz, 1H), 5.55 (d, J=11.4 Hz, 1H); \(^{13}\)C NMR δ 148.0, 136.1, 132.2, 131.5, 129.7, 127.3, 121.4, 119.7; IR (ATR) 3097, 1552, 1514, 1341, 1149 cm\(^{-1}\); HRMS (ESI) calcd for C\(_8\)H\(_6\)NO\(_2\)Br (M+Na\(^{+}\)) 251.9454; found 251.9455.

4-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (184): Treatment of 168\(^{12}\) (104 mg, 0.29 mmol) with ethenyl(tributyl)stannane (121 mg, 0.38 mmol), PPh\(_3\) (6.8 mg, 0.03 mmol) and Pd(dba\(_2\)) (3.4 mg, 0.006 mmol) in dioxane (1.5 mL) as described for 141 gave
after chromatography (hexanes/EtOAc, 97:3) a mixture of 184 and dba (62.3 mg, calculated 55.9 mg, 64% 184 and 6.6 mg dba) as a yellow oil. Analytical data for 184: $^1$H NMR δ 8.16 (d, $J= 8.4$ Hz, 1H), 7.55 (dd, $J= 8.4$, 1.8 Hz, 1H), 7.41 (d, $J= 1.8$ Hz, 1H), 6.76 (dd, $J= 17.4$, 10.8 Hz, 1H), 5.97 (d, $J= 17.4$ Hz, 1H), 5.63 (d, $J= 10.8$ Hz, 1H); $^{13}$C NMR δ 145.2, 141.9, 140.1, 133.4, 127.1, 126.2, 121.4, 120.9, 118.6 (q, $J= 319$ Hz, C-F); IR (ATR) 3114, 1587, 1529, 1429, 1341, 1209 cm$^{-1}$; HRMS (ESI) calcd for C$_9$H$_6$NO$_2$F$_3$S (M+Na$^+$) 319.9811; found 319.9808.

4-Bromo-2-ethenyl-nitrobenzene (185):$^{152}$ Treatment of 168 (99.5 mg, 0.29 mmol) with ethenyl(tributyl)stannane (98.1 mg, 0.31 mmol), LiCl (37.0 mg, 0.87 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (4.0 mg, 0.006 mmol) in DMF (1.5 mL) as described for 170 gave after chromatography (hexanes/EtOAc, 9:1) in order of elution, 185 (11.0 mg, 0.05 mmol, 17%) as an off-white solid, 168 (22.9 mg, 0.07 mmol, 22%) and 184 (19.4 mg, 0.07 mmol, 23%). Spectral data for 185 were in accordance with literature values.

4-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene (186): Treatment of 159 (74.7 mg, 0.21 mmol) with ethenyl(tributyl)stannane (83.2 mg, 0.26 mmol), PPh$_3$ (5.0 mg, 0.02 mmol) and Pd(dba)$_2$ (2.7 mg, 0.005 mmol) in dioxane (1.5 mL) as described for 141 gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, 159 (14.8 mg, 0.04
mmol, 20%) and 186 (30.2 mg, 0.10 mmol, 48%) as a yellow oil. Analytical data for 186:

\( ^1H \text{ NMR } \delta 8.25 (dd, J= 8.4, 1.8 \text{ Hz}, 1H), 8.17 (d, J= 1.8 \text{ Hz}, 1H), 7.83 (d, J= 8.4 \text{ Hz}, 1H), 6.98 (dd, J= 17.4, 10.8 \text{ Hz}, 1H), 6.05 (d, J= 17.4 \text{ Hz}, 1H), 5.75 (d, J= 10.8 \text{ Hz}, 1H); \)

\( ^{13}C \text{ NMR } \delta 147.4, 146, 137.5, 127.9, 127.6, 123.3, 122.9, 118.5 (q, J C-F=319 \text{ Hz}, C-F), \)

117.8; IR (ATR) 3118, 1528, 1425, 1346, 1210, 1132 cm\(^{-1}\); HRMS (ESI) calcd for C\(_9\)H\(_6\)NO\(_2\)F\(_3\)S (M+Na\(^+\)) 319.9811; found 319.9809.

4-Bromo-3-ethenyl-nitrobenzene (187): Treatment of 159 (85.9 mg, 0.25 mmol) with ethenyl(tributyl)stannane (98.2 mg, 0.31 mmol), LiCl (32.2 mg, 0.76 mmol) and Pd(PPh\(_3\))\(_2\)Cl\(_2\) (3.6 mg, 0.005 mmol) in DMF (1.5 mL) as described for 170 gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, 187 (3.8 mg, 0.02 mmol, 7\%) as an off-white solid, 159 (27.0 mg, 0.08 mmol, 31\%) and 186 (22.4 mg, 0.08 mmol, 31\%). Spectral data for 186: mp=38-40 \^\text{\textdegree}C; \(^1H \text{ NMR } \delta 8.39 (d, J=2.4 \text{ Hz}, 1H), 7.97 (dd, J=8.4, 2.4 \text{ Hz}, 1H), 7.74 (d, J=9.0 \text{ Hz}, 1H), 7.06 (dd, J=17.4, 10.8 \text{ Hz}, 1H), 5.99 (d, J=17.4 \text{ Hz}, 1H), 5.56 (d, J=10.8 \text{ Hz}, 1H); \(^{13}C \text{ NMR } \delta 143.5, 139.1, 134.2, 133.9, 131.4, 123.1, 121.5, 119.7; IR (ATR) 3099, 2926, 1525, 1341, 1030 cm\(^{-1}\); HRMS (ESI) calcd for C\(_8\)H\(_6\)NO\(_2\)Br (M+Na\(^+\)) 251.9454; found 251.9452.
2-ethenyl-trifluoromethanesulfonyloxybenzene (189): Treatment of 188 (96.5 mg, 0.32 mmol) with ethenyl(tributyl)stannane (124 mg, 0.39 mmol), PPh₃ (7.2 mg, 0.03 mmol) and Pd(db)₂ (3.5 mg, 0.006 mmol) in dioxane (1 mL) as described for 141 afforded after chromatography (hexanes/EtOAc, 97:3) a mixture of 189 and unreacted 188 (32.0 mg) (calculated from ¹H NMR spectrum 8.0 mg, 10% and 24.0 mg, 24%) as a colorless oil. ¹H NMR d 7.65 (dd, J=7.2, 2.4 Hz, 1H), 7. (dd, J=8.4, 1.8 Hz, 1H), 7.48 (t, J=8.4 Hz, 1H), 6.93 (dd, J=17.4, 11.4 Hz, 1H), 5.85 (dd, J=17.4, 0.6 Hz, 1H), 5.49 (d, J=10.8, 0.6 Hz, 1H); ¹³C NMR d 146.9, 131.1, 129.3, 128.9, 128.4, 127.3, 121.6, 118.6, 118.5 (q, J=319.1 Hz, C-F); IR (ATR) 2963, 1469, 1258, 1135, 875 cm⁻¹.

2-ethenyl-bromobenzene (190): Treatment of 188 (88.3 mg, 0.25 mmol) with vinyl(tributyl)stannane (98.0 mg, 0.31 mmol), LiCl (32.2 mg, 0.76 mmol) and Pd(PPh₃)₂Cl₂ (3.8 mg, 0.005 mmol) in DMF (1 mL) as described for 170 afforded crude yellow oil (108 mg) which was purified by column chromatography (hexanes/ethyl acetate, 9:1), however, the product reacted on the silica gel so no product was isolated. Crude spectral data were in accordance with literature values with a 6:1 ratio of triflate-coupled 190 to bromine-coupled 189.

3-ethenyl-trifluoromethanesulfonyloxybenzene (191): Treatment of 143 (105 mg, 0.34 mmol) with vinyl(tributyl)stannane (127 mg, 0.40 mmol), PPh₃ (7.6 mg, 0.03 mmol), and
Pd(dba)$_2$ (4.0 mg, 0.007 mmol) in dioxane (1.5 mL) as described for 141 afforded after chromatography (hexanes/ethyl acetate, 97:3) a mixture of 191 and unreacted 143 (49.2 mg) (calculated from $^1$H NMR spectrum 28.8 mg, 33% and 20.2 mg, 19%) as a colorless oil. $^1$H NMR d 7.40 (m, 2H), 7.29 (d, $J$=0.6 Hz, 1H), 7.15 (dt, $J$=7.2, 1.8 Hz, 1H), 6.60 (dd, $J$=17.4, 10.8 Hz, 1H), 5.80 (d, $J$=18.0 Hz, 1H), 5.38 (d, $J$=10.8 Hz, 1H); $^{13}$C NMR d 149.9, 140.3, 135.0, 130.3, 126.1, 120.2, 118.8, 118.7 (q, $J$=319.1 Hz, C-F), 116.5; IR (ATR) 3103, 1539, 1429, 1351, 1210, 1131 cm$^{-1}$.

3-bromostyrene (192): Treatment of 143 (108 mg, 0.36 mmol) with vinyl(tributyl)stannane (141 mg, 0.44 mmol), LiCl (45.6 mg, 1.08 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (5.4 mg, 0.008 mmol) in DMF (1.5 mL) as described for 170 afforded crude yellow oil (175 mg) which was purified by column chromatography (hexanes/ethyl acetate, 9:1), however, the product reacted on the silica gel so no product was isolated. Crude spectral data were in accordance with literature values with a 6:1 ratio of triflate-coupled 192 to bromine-coupled 191.

4-ethenyl-trifluoromethanesulfonoylbenzene (138)$^{90}$: Treatment of 137 (102 mg, 0.34 mmol) with vinyl(tributyl)stannane (128 mg, 0.40 mmol), PPh$_3$ (7.5 mg, 0.03 mmol), and Pd(dba)$_2$ (4.3 mg, 0.007 mmol) in dioxane (1.5 mL) as described for 141
afforded after chromatography (hexanes/ethyl acetate, 97:3) **138** (25.2 mg, 0.10 mmol, 30%) as a colorless oil. Spectral data were in accordance with literature values.

![Diagram of 4-bromostyrene (137) to 4-bromostyrene (139)]

**4-bromostyrene (139)**: Treatment of **137** (108 mg, 0.35 mmol) with vinyl(tributyl)stannane (141 mg, 0.44 mmol), LiCl (45.5 mg, 1.07 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (4.7 mg, 0.007 mmol) in DMF (1.5 mL) as described for **170** afforded crude yellow oil which was purified by column chromatography (hexanes/ethyl acetate, 9:1), however, the product reacted on the silica gel so no product was isolated. Crude spectral data were in accordance with literature values with a 6:1 ratio of triflate-coupled **139** to bromine-coupled **138**.

![Diagram of iodo-6-ethenyl-nitrobenzene (196) to iodo-6-ethenyl-nitrobenzene (198)]

**3-Iodo-6-ethenyl-nitrobenzene (198)**: Treatment of **196** (116 mg, 0.29 mmol) with ethenyl(tributyl)stannane (120 mg, 0.38 mmol), LiCl (39.7 mg, 0.94 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (4.1 mg, 0.006 mmol) in DMF (1.5 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **198** (3.2 mg, 0.01 mmol, 4%) as a brown oil, 195 (8.7 mg, 0.03 mmol, 14%), and a mixture of **196** and **197** (67.1 mg). Spectral data for **198**: $^1$H NMR $\delta$ 8.25 (d, $J=1.8$ Hz, 1H), 7.89 (dd, $J=7.8$, 1.8 Hz, 1H), 7.35 (d, $J=7.8$ Hz, 1H), 7.10 (dd, $J=16.8$, 10.8 Hz, 1H), 5.77 (d, $J=16.8$ Hz, 1H), 5.52 (d,
$J=10.8 \text{ Hz, 1H}$; $^{13}$C NMR δ 148.0, 142.0, 133.0, 132.8, 131.6, 129.8, 119.7, 91.8; IR (ATR) 3094, 2925, 1519, 1341, 1261, 1086 cm$^{-1}$; HRMS (ESI) calcd for C$_8$H$_6$NO$_2$I (M+Na$^+$) 297.9335; found 297.9333.

3-Bromo-6-trifluoromethanesulfonyloxy acetophenone (201): Treatment of 200 (381 mg, 1.77 mmol) in CH$_2$Cl$_2$ (10 mL) with pyridine (275 µL, 3.41 mmol) and Tf$_2$O (325 µL, 1.92 mmol) as described for 163, gave without further purification 201 (590 mg, 1.70 mmol, 96%) as an orange oil. $^1$H NMR δ 7.92 (d, $J=2.4$ Hz, 1H), 7.72 (dd, $J=8.4$, 2.4 Hz, 1H), 7.23 (d, $J=8.4$ Hz, 1H), 2.63 (s, 3H); $^{13}$C NMR δ 195.1, 145.5, 136.4, 133.5, 133.4, 124.3, 122.0, 118.4 (q, $J=320$ Hz, C-F), 29.2; IR (ATR) 3101, 1701, 1424, 1202, 1133 cm$^{-1}$.

3-Ethenyl-6-trifluoromethanesulfonyloxy acetophenone (202): Treatment of 201 (101 mg, 0.29 mmol) with ethenyl(tributyl)stannane (116 mg, 0.37 mmol), PPh$_3$ (6.4 mg, 0.02 mmol) and Pd(dba)$_2$ (3.8 mg, 0.007 mmol) in dioxane (2 mL) as described for 141 gave after chromatography (hexanes/EtOAc, 9:1) 202 (11.6 mg, 0.04 mmol, 14%) as a colorless oil. $^1$H NMR δ 7.78 (d, $J=2.4$ Hz, 1H), 7.61 (dd, $J=8.4$, 2.4 Hz, 1H), 7.30 (d, $J=8.4$ Hz, 1H), 6.73 (dd, $J=17.4$, 10.8 Hz, 1H), 5.83 (d, $J=17.4$ Hz, 1H), 5.44 (d, $J=$
10.8 Hz, 1H), 2.65 (s, 3H); $^{13}$C NMR δ 196.6, 145.9, 138.1, 134.3, 132.3, 130.7, 128.3, 122.9, 118.5 (q, $J=319$, Hz, C-F), 117.3, 29.6; IR (ATR) 3096, 1698, 1421, 1202, 1134 cm$^{-1}$;

![Diagram](image)

**6-Ethenyl-3-bromoacetophenone (203):** Treatment of 201 (112 mg, 0.32 mmol) with ethenyl(tributyl)stannane (129 mg, 0.41 mmol), LiCl (43.5 mg, 1.03 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (4.8 mg, 0.007 mmol) in DMF (2 mL) as described for 170 gave after chromatography (hexanes/EtOAc, 8:2) 203 (42.6 mg, 0.19 mmol, 58%) as a colorless oil.

$^1$H NMR δ 7.73 (d, $J=1.8$, Hz, 1H), 7.57 (dd, $J=8.4$, 1.8 Hz, 1H), 7.43 (d, $J=8.4$, Hz, 1H), 7.09 (dd, $J=17.4$, 10.8 Hz, 1H), 5.64 (dd, $J=17.4$, 1.2 Hz, 1H), 5.37 (dd, $J=11.4$, 1.2 Hz, 1H), 2.56 (s, 3H); $^{13}$C NMR δ 200.5, 138.9, 136.4, 134.7, 134.4, 131.3, 129.1, 121.1, 117.4, 29.8; IR (ATR) 3088, 1686, 1472, 1355, 1235, 830 cm$^{-1}$;

![Diagram](image)

**3-Ethenyl-4-trifluoromethanesulfonyloxy anisole (209):** Treatment of 208$^{153}$ (106 mg, 0.32 mmol) with vinyl(tributyl)stannane (126 mg, 0.40 mmol), PPh$_3$ (7.0 mg, 0.03 mmol) and Pd(db$_2$) (3.7 mg, 0.006 mmol) in dioxane (2 mL) as described for 141 gave after chromatography (hexanes/EtOAc, 9:1) 209 (29.6 mg, 0.10 mmol, 33%) as a colorless oil.

$^1$H NMR δ 7.18 (d, $J=9.0$, Hz, 1H), 7.09 (d, $J=3.0$, Hz, 1H), 6.89 (dd, $J=17.4$, 11.4 Hz, 1H), 6.84 (dd, $J=9.0$, 3.0 Hz, 1H), 5.83 (d, $J=18.0$, Hz, 1H), 5.49 (d, $J=11.4$, Hz, 1H),
3.84 (s, 1H); $^{13}$C NMR $\delta$ 158.9, 140.5, 132.1, 129.1, 122.6, 118.6, 118.3 (q, $J= 319$ Hz, C-F), 114.5, 111.6, 55.7; IR (ATR) 2968, 1485, 1419, 1206, 1137, 868 cm$^{-1}$;

3-Bromo-4-ethylanisole (210). Treatment of 208 (103 mg, 0.31 mmol) with ethenyl(tributyl)stannane (119 mg, 0.38 mmol), LiCl (38.9 mg, 0.92 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (4.5 mg, 0.006 mmol) in DMF (2 mL) as described for 170 gave after chromatography (hexanes/EtOAc, 9:1) in order of elution, 210 (26.3 mg, 0.12 mmol, 43%) as an orange oil and 209 (3.3 mg, 0.01 mmol, 4%). Spectral data were in accordance with literature values.
7.4: Supporting Information for Chapter 5: Pyrroloindoles

**2,3-dinitro-1,4-ethenylbenzene (241):** To a solution of PPh$_3$ (42.3 mg, 0.16 mmol) and Pd(dba)$_2$ (14.8 mg, 0.03 mmol) in toluene (5 mL) were added 251 (99.2 mg, 0.30 mmol) and a solution of tributyl(vinyl) stannane (274.8 mg, 0.87 mmol) in toluene (2 mL). Mixture heated at 110°C for 68 hours. Resulting brown solution filtered through Celite, diluted with EtOAc (20 mL), washed with NH$_4$OH (10% aq, 3x30 mL), H$_2$O (30 mL), then brine (30 mL). Organic layer dried (MgSO$_4$), filtered, then solvent removed under reduced pressure. The resulting crude brown oil was purified using column chromatography (hexanes:EtOAc, 8:2) to afford 241 (32.5 mg, 0.15 mmol, 49%) as a yellow solid. $^1$H NMR (CDCl$_3$) $\delta$ 7.78 (s, 2H), 6.74 (dd, 2H, $J=17.5, 11.1$ Hz), 5.93 (d, 2H, $J= 17.2$ Hz), 5.64 (d, 2H, $J= 11.1$ Hz); HRMS (ESI) calcd for C$_{10}$H$_8$N$_2$O$_4$Na (M+Na$^+$) 243.0376, found 243.0375.

**1,8-dihydropyrrolo[3,2-g]indole (218)**: In an oven-dried ACE glass pressure tube was mixed 241 (31.5 mg, 0.14 mmol), Pd(OAc)$_2$ (3.2 mg, 0.01 mmol), 1,10-phenanthroline (1.8 mg, 0.01 mmol), and anhydrous DMF (3 mL). The tube was fitted with a pressure head, and the solution was saturated with CO (four cycles, 6 atm). The
tube was then allowed to heat at 120 °C for 143 h. The solvent was then removed by a bulb-to-bulb resulting in a dark brown crude material which was subsequently diluted with H2O (15 mL) and extracted with EtOAc (3x25 mL). Combined organic layers dried (MgSO4), filtered, then solvent removed under reduced pressure. Resulting crude brown oil purified by chromatography (hexanes: EtOAc, 85:15, then 7:3) to give 218 (12.3 mg, 0.08 mmol, 56%) as a dark grey solid. HRMS (ESI) calcd for C10H8N2H (M+H+) 157.0760, found 157.0758.

2,3-dinitro-1,4-di(prop-1-enyl)benzene (255): To a solution of PPh3 (56.7 mg, 0.22 mmol) and Pd(dba)2 (20.9 mg, 0.04 mmol) in toluene (5 mL) were added 251 (154 mg, 0.47 mmol) and a solution of tributyl(prop-1-enyl)stannane (430 mg, 1.3 mmol) in toluene (5 mL). Mixture heated at 110°C for 72 hours. Resulting brown solution filtered through Celite, diluted with EtOAc (20 mL), washed with NH4OH (10% aq, 3x30 mL), H2O (30 mL), then brine (30 mL). Organic layer dried (MgSO4), filtered, then solvent removed under reduced pressure. The resulting crude brown oil was purified using column chromatography (hexanes:EtOAc, 9:1) to afford 255 (75.8 mg, 0.31 mmol, 65%) as a yellow solid. 1H NMR (CDCl3) δ 7.50 (s, 2H), 6.42 (dd, J= 11.4, 1.8 Hz, 2H), 6.08 (dq, 2H, J= 11.4, 6.6 Hz), 1.78 (dd, 6H, J= 7.2, 1.8 Hz); 13C NMR δ 133.5, 132.9, 131.0, 122.4, 14.8; IR (ATR) 3041, 2954, 1649, 1528, 1358, 859, 820 cm−1; HRMS (ESI) calcd for C12H12N2O4Na (M+Na+) 271.0689, found 271.0688.
2,7-dimethyl-1,8-dihydropyrrolo[3,2-g]indole (256): In an oven-dried ACE glass pressure tube was mixed 255 (29.9 mg, 0.12 mmol), Pd(OAc)$_2$ (3.1 mg, 0.01 mmol), 1,10-phenanthroline (2.9 mg, 0.01 mmol), and anhydrous DMF (3 mL). The tube was fitted with a pressure head, and the solution was saturated with CO (four cycles, 6 atm). The tube was then allowed to heat at 120 °C for 20 h until all starting material was consumed as judged by TLC. The solvent was then removed by a bulb-to-bulb resulting in a dark brown crude which was subsequently diluted with H$_2$O (15 mL) and extracted with EtOAc (3x25 mL). Combined organic layers dried (MgSO$_4$), filtered, then solvent removed under reduced pressure. Resulting crude brown oil purified by chromatography (hexanes: EtOAc, 8:2) to give 256 (9.5 mg, 0.05 mmol, 43.0%) as a dark grey solid. HRMS (ESI) calcd for C$_{12}$H$_{12}$N$_2$H (M+H$^+$) 185.1073, found 185.1071.

2,3-dinitro-1,4-di(prop-1-en-2-yl)benzene (257): To a solution of PPh$_3$ (64.9 mg, 0.25 mmol) and Pd(dba)$_2$ (28.2 mg, 0.05 mmol) in toluene (10 mL) were added 251 (198 mg, 0.61 mmol) and a solution of tributyl(prop-1-en-2-yl)stannane (487 mg, 1.47 mmol). Mixture heated at 110 °C for 45 hours. Resulting brown solution filtered through Celite,
diluted with EtOAc (30 mL), washed with NH₄OH (10% aq, 3x30 mL), H₂O (30 mL), then brine (30 mL). Organic layer dried (MgSO₄), filtered, then solvent removed under reduced pressure. The resulting crude green residue was purified using column chromatography (hexanes:EtOAc, 7:3) to afford 257 (93.0 mg, 0.37 mmol, 64%) as a yellow solid (mp= 135-137 °C). ¹H NMR (CDCl₃) δ 7.44 (s, 2H), 5.27 (m, 2H), 5.03 (m, 2H), 2.11 (m, 6H); ¹³C NMR δ 142.1, 139.2, 137.4, 131.5, 118.1, 23.1; IR (ATR) 3094, 2973, 1643, 1543, 1526, 1355, 911, 847 cm⁻¹

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\begin{align*}
\text{257} & \quad \text{258} \quad \text{259}
\end{align*}
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3,6-dimethyl-1,8-dihydropyrrolo[3,2-g]indole (258): In an oven-dried ACE glass pressure tube was mixed 257 (26.3 mg, 0.11 mmol), Pd(dba)₂ (4.8 mg, 0.008 mmol), PPh₃ (12.1 mg, 0.05 mmol), and anhydrous DMF (3 mL). The tube was fitted with a pressure head, and the solution was saturated with CO (four cycles, 6 atm). The tube was heated at 120 °C for 96 hours until all starting material was consumed as judged by TLC. The solvent was then removed by a bulb-to-bulb resulting in a dark brown crude material which was subsequently diluted with H₂O (15 mL) and extracted with EtOAc (3x25 mL). Combined organic layers dried (MgSO₄), filtered, then solvent removed under reduced pressure. Resulting crude brown oil was purified by chromatography (hexanes: EtOAc, 8:2) to afford in order of elution 258 (5.1 mg, 0.03 mmol, 25%) as a dark grey solid and 259 (12.9 mg, 0.06 mmol, 54%) as a brown solid (mp= 72-74 °C). HRMS of 258 (ESI) calcd for C₁₂H₁₂N₂H (M+H⁺) 185.1073, found 185.1071.
To an ice-cooled solution of 265 (256 mg, 1.45 mmol) in H$_2$SO$_4$ (4 mL) was added NaNO$_3$ (215 mg, 2.53 mmol). The resulting brown solution was stirred at ambient temperature (4 hours). Solution quenched with ice, then extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO$_4$), filtered, then the solvents were removed under reduced pressure. Purification using column chromatography (Hexanes/EtOAc, 8:2) afforded in order of elution 263 (307 mg, 0.99 mmol, 69%) and 268 (103 mg, 0.33 mmol, 23%). Spectral data for 263: $^1$H NMR (600 MHz) δ 10.74 (s, 1H), 8.78 (s, 1H), 7.97 (s, 1H); $^{13}$C NMR (150 MHz) δ 155.9, 134.1, 133.7, 122.7, 122.5, 97.2; IR (ATR) 3268, 3098, 1607, 1567, 1520, 1315 cm$^{-1}$; HRMS (ESI) calcd for C$_6$H$_3$N$_2$O$_4$I (M-H) 308.90084, found 308.90105. Spectral data for 268: $^1$H NMR (600 MHz) δ 7.83 (d, J= 9.0 Hz, 1H), 7.24 (d, J= 9.0 Hz, 1H); $^{13}$C NMR (150 MHz) δ 152.4, 145.2, 127.9, 127.2, 117.3, 81.5; IR (ATR) 3232, 3097, 1525, 1336, 1296 cm$^{-1}$;

2,4-dinitro-5-(prop-1-en-2-yl)phenol (271): To a solution of 263 (363 mg, 1.17 mmol) in dioxane (4 mL) was added PPh$_3$ (24.7 mg, 0.09 mmol), Pd(dba)$_2$ (13.3 mg, 0.02 mmol), CuI (225 mg, 1.18 mmol), BHT (26.8 mg, 0.12 mmol), and tributyl(prop-1-en-2-yl)stannane (396 mg, 1.2 mmol). The resulting solution was heated at 105 °C (16 hours).
Solvents were removed under reduced pressure, then the residue was purified using column chromatography (hexanes/EtOAc, 1:1 with 5% Et$_3$N followed by hexanes/EtOAc, 9:1 with 5% AcOH) to afford 271 (44.7 mg, 0.20 mmol, 17%) as a brown solid. $^1$H NMR (600 MHz) $\delta$ 10.83 (s, 1H), 8.83 (s, 1H), 7.11 (s, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 2.08 (s, 3H); $^{13}$C NMR (150 MHz) $\delta$ 157.2, 148.8, 141.5, 140.1, 131.4, 122.8, 121.9, 116.6, 22.7. IR (ATR) 3115, 2960, 1582, 1330 cm$^{-1}$; HRMS (ESI) calcd for C$_9$H$_8$N$_2$O$_5$ (M-H) 223.03550, found 223.03562.

2,4-dinitro-5-(prop-1-en-2-yl)phenyl trifluoromethanesulfonate (261): To an ice-cooled solution of 271 (118 mg, 0.52 mmol) in CH$_2$Cl$_2$ (5 mL) was added pyridine (90.0 $\mu$L, 1.11 mmol), and Tf$_2$O (100 $\mu$L, 0.59 mmol) and the solution stirred while warming to ambient temperature over 30 minutes. Solvents were removed under reduced pressure and the crude product purified using column chromatography (hexanes/EtOAc, 85:15) to afford 261 (160 mg, 45 mmol, 86%) as a yellow oil. $^1$H NMR (600 MHz) $\delta$ 8.71 (s, 1H), 7.45 (s, 1H), 5.39 (d, $J$= 1.8 Hz, 1H), 5.11 (s, 1H), 2.13 (s, 3H); $^{13}$C (150 MHz) $\delta$ 146.3, 146.2, 143.1, 139.8, 139.6, 126.7, 123.2, 118.9, 118.5 (q, $J$= 319 Hz), 22.5; IR (ATR) 3144, 2928, 1590, 1538, 1435, 1340 cm$^{-1}$.
1,5-dinitro-2,4-di(prop-1-en-2-yl)benzene (260): To a solution of 261 (149 mg, 0.34 mmol) in DMF (2 mL) was added PdCl$_2$(PPh$_3$)$_2$ (5.3 mg, 0.007 mmol), LiCl (50.3 mg, 1.19 mmol), BHT (7.0 mg, 0.03 mmol), and tributyl(prop-1-en-2-yl)stannane (293 mg, 0.88 mmol). The resulting solution was heated at 60 °C (16 hours). The resulting brown solution was quenched with NH$_4$OH (10% aq., 15 mL), then extracted with EtOAc (20 mL). The organic layer was washed with NH$_4$OH (10% aq., 20 mL), H$_2$O (20 mL), and brine (20 mL), then dried (MgSO$_4$), filtered, then solvents were removed under reduced pressure. Purification using column chromatography (hexanes/EtOAc, 85:15) afforded 260 (73.3 mg, 0.29 mmol, 87%) as a white solid (mp= 77-78 °C). $^1$H NMR (600 MHz) δ 8.45 (s, 1H), 7.33 (s, 1H), 5.29 (d, $J= 1.2$ Hz, 2H), 5.03 (d, $J= 1.2$ Hz, 2H), 2.11 (d, $J= 1.2$ Hz, 6H); $^{13}$C NMR (150 MHz) δ 146.3, 143.3, 141.1, 133.0, 120.6, 117.0, 22.9; IR (ATR) 3101, 2983, 1584, 1525, 1345 cm$^{-1}$;

1,5-dinitro-2-(prop-1-en-2-yl)-4-(prop-1-enyl)benzene (274): Reaction of 261 (86.3 mg, 0.24 mmol), tributyl(prop-1-enyl)stannane (117 mg, 0.35 mmol), PdCl$_2$(PPh$_3$)$_2$ (4.3 mg, 0.006 mmol), LiCl (38.6 mg, 0.91 mmol) in DMF (2 mL) as described for 260 afforded after purification using column chromatography (hexanes/EtOAc, 9:1) 274 (52.1
mg, 0.21 mmol, 87%) as a yellow oil (~2:1 ratio of Z/E isomers). $^1$H NMR for Z-isomer (400 MHz) δ 8.61 (s, 1H), 7.38 (s, 1H), 6.76 (dq, $J = 11.6, 2.0$ Hz, 1H), 6.11 (dq, $J = 11.6, 7.2$ Hz, 1H), 5.29 (t, $J = 1.6$ Hz, 1H), 5.03 (t, $J = 1.2$ Hz, 1H), 2.11 (t, $J = 1.2$ Hz, 3H), 1.80 (dd, $J = 7.6, 2.0$ Hz, 3H); $^1$H NMR for E-isomer (400 MHz) δ 8.52 (s, 1H), 7.55 (s, 1H), 6.94 (dq, $J = 15.6, 1.6$ Hz, 1H), 6.47 (dq, $J = 15.6, 6.8$ Hz, 1H), 5.28 (t, $J = 1.2$ Hz, 1H), 5.02 (t, $J = 1.2$ Hz, 1H), 2.11 (t, $J = 0.8$ Hz, 3H), 2.01 (dd, $J = 7.2, 2.0$ Hz, 3H); $^{13}$C NMR (combined isomers, 100 MHz) δ 146.2, 145.8, 145.4, 145.2, 143.4, 143.1, 141.6, 141.3, 137.6, 137.1, 136.0, 134.3, 131.7, 130.7, 124.7, 124.5, 121.3, 121.2, 116.9, 116.6, 23.0, 22.9, 19.1, 14.6; IR (ATR) 3105, 2978, 1581, 1520, 1341 cm$^{-1}$;  

(\textit{E})-1,5-dinitro-2-(1-phenylprop-1-enyl)-4-(prop-1-en-2-yl)benzene (276): Reaction of 261 (83.5 mg, 0.23 mmol), (\textit{E})-tributyl(1-phenylprop-1-enyl)stannane (117 mg, 0.29 mmol), PPh$_3$ (13.4 mg, 0.05 mmol), and Pd(dba)$_2$ (7.3 mg, 0.01 mmol) in DMF (2 mL) at 50 °C as described for 260 afforded after purification using column chromatography (hexanes/EtOAc, 85:15) 276 (34.9 mg, 0.11 mmol, 46%) as a yellow solid (mp = 92-94 °C). $^1$H NMR (400 MHz) δ 8.33 (s, 1H), 7.39 (s, 1H), 7.34-7.29 (m, 3H), 7.17-7.15 (m, 2H), 6.01 (q, $J = 7.6$ Hz, 1H), 5.27 (m, 1H), 5.03 (m, 1H), 2.11 (m, 3H), 1.93 (d, $J = 7.6$ Hz, 3H); $^{13}$C NMR (100 MHz) δ 147.3, 146.0, 143.1, 142.8, 141.2, 137.2, 136.4, 134.5, 129.8, 129.7, 128.2, 127.9, 120.7, 117.0, 23.0, 15.7; IR (ATR) 2954, 1583, 1525, 1346 cm$^{-1}$;
1-chloro-2,4-dinitro-5-(prop-1-en-2-yl)benzene (273): To a solution of 261 (198 mg, 0.55 mmol) in DMF (1 mL) was added LiCl (79.0 mg, 1.86 mmol) and the solution stirred at 60 °C (8 hours). The resulting solution was diluted with EtOAc (15 mL) and washed with H₂O (5 x 20 mL). The organic phase was dried (MgSO₄), filtered, and solvents were removed. Purification using column chromatography (hexanes/EtOAc, 7:3) afforded 273 (64.2 mg, 0.26 mmol, 48%) as a white solid (mp= 128-130 °C). ¹H NMR (400 MHz) δ 8.50 (s, 1H), 7.59 (s, 1H), 5.33 (s, 1H), 5.07 (s, 1H), 2.11 (s, 3H); ¹³C NMR (100 MHz) δ 145.8, 145.7, 143.9, 140.1, 134.2, 131.7, 122.1, 117.8, 22.6; IR (ATR) 3091, 1593, 1568, 1507, 1338 cm⁻¹.

2,5-dinitro-4-ethylphenol (278): Reaction of 279¹²⁹ (122 mg, 0.39 mmol), PPh₃ (10.3 mg, 0.04 mmol), Pd(dbac)₂ (5.2 mg, 0.01 mmol), CuI (74.3 mg, 0.39 mmol), BHT (9.7 mg, 0.04 mmol), and tri-n-butyl(ethenyl)stannane (168 mg, 0.64 mmol in dioxane (3 mL) 105 °C (5 hours) as described for 271 afforded after purification using column chromatography (hexanes/EtOAc, 95:5 w/ 5% AcOH) 278 (55.8 mg, 0.27 mmol, 68%) as a yellow solid (mp= 97-98 °C). ¹H NMR (600 MHz) δ 10.44 (s, 1H), 8.40 (s, 1H), 7.64 (s, 1H), 6.93 (dd, J= 17.4, 10.8 Hz, 1H), 5.80 (d, J= 16.8 Hz, 1H), 5.55 (d, J= 11.4 Hz,
1H); $^{13}$C NMR (150 MHz) δ 153.7, 152.3, 135.3, 129.4, 125.1, 125.0, 120.0, 115.9; IR (ATR) 2245, 2080, 1630, 1525, 1263 cm$^{-1}$;

2,5-dinitro-4-vinylphenyl trifluoromethanesulfonate (277): Reaction of 278 (56.3 mg, 0.27 mmol), Et$_3$N (100 µL, 0.72 mmol), and Tf$_2$O (60 µL, 0.36 mmol) in CH$_2$Cl$_2$ (5 mL) as described for 261 afforded after purification using column chromatography (hexanes/EtOAc, 7:3) 277 (90.8 mg, 0.26 mmol, 98%) as an orange oil. $^1$H NMR (400 MHz) δ 8.40 (s, 1H), 8.02 (s, 1H), 7.16 (dd, $J$ = 17.2, 11.2 Hz, 1H), 5.99 (d, $J$ = 17.2 Hz, 1H), 5.80 (d, $J$ = 11.2 Hz, 1H); $^{13}$C NMR (100 MHz) δ 148.8, 143.4, 139.5, 126.7, 123.8, 121.6, 120.6, 118.5, 118.2 (q, $J$ = 319 Hz, C-F); IR (ATR) 3117, 1557, 1436, 1344, 1225 cm$^{-1}$; HRMS

2,5-dinitro-1,4-diethenylbenzene (240): Reaction of 277 (92.9 mg, 0.27 mmol), tri-n-butyl(ethenyl)stannane (105 mg, 0.33 mmol), PdCl$_2$(PPh$_3$)$_2$ (4.2 mg, 0.006 mmol), and LiCl (39.1 mg, 0.92 mmol) in DMF (3 mL) at ambient temperature (18 hours) as described for 260 afforded after purification using column chromatography (hexanes/EtOAc, 9:1) 240 (38.8 mg, 0.18 mmol, 65%) as a yellow solid (mp= 140-141 °C). $^1$H NMR (600 MHz) δ 8.14 (s, 2H), 7.10 (dd, $J$ = 17.4, 10.8 Hz, 2H), 5.91 (d, $J$ = 17.4
Hz, 2H), 5.65 (d, J= 10.8 Hz, 2H); $^{13}$C NMR (150 MHz) δ 149.3, 132.9, 129.9, 124.2, 121.5; IR (ATR) 3112, 3075, 1517, 1348, 1283 cm$^{-1}$;

4-bromo-2,3-dinitrophenol (292): To a solution of 251$^{155}$ (730 mg, 2.24 mmol) in THF (8 mL) and H$_2$O (0.5 mL) was added NaOH (1.04 g, 26.1 mmol). Solution heated at 80 °C in sealed pressure tube for 18 hours. Resulting brown solution diluted with H$_2$O (25 mL) and acidified with HCl then extracted with EtOAc (3x30 mL). Combined organic layers dried (MgSO$_4$), filtered, and solvents removed under reduced pressure. Crude brown oil was purified using column chromatography (hexanes/EtOAc, 7:3 w/ 5% AcOH) to afford 292 (554 mg, 2.11 mmol, 94%) as a yellow solid (mp= 59-61 °C). $^1$H NMR (400 MHz) δ 7.55 (d, J= 8.4 Hz, 1H), 7.20 (d, J= 8.8 Hz, 1H); $^{13}$C NMR (100 MHz) δ149.0, 138.3, 136.1, 126.5, 114.5, 111.5; IR (ATR) 3391, 1566, 1535, 1456, 1374 cm$^{-1}$; HRMS (ESI) calcd for C$_6$H$_3$N$_2$O$_5$Br (M-H) 260.91471, found 260.91484.

(Z)-methyl 2-(4-bromo-2,3-dinitrophenyl)but-2-enoate (301)

To a solution of 251$^a$ (309 mg, 0.95 mmol) in THF (5 mL) was added (E)-methyl 2-(tributylstanny1)but-2-enoate (599 mg, 1.54 mmol), AsPh$_3$ (115 mg, 0.38 mmol), Pd(dba)$_2$ (46.2 mg, 0.08 mg), and CuI (187 mg, 0.98 mmol). The resulting solution was
heated at 80 °C (42 hours). The resulting brown solution was diluted with Et₂O (25 mL) and washed with 10% aq. NH₄OH (3 x 20 mL), H₂O (20 mL), and brine (20 mL). The organic phase was dried (MgSO₄), filtered, and solvents were removed under reduced pressure. The resulting brown oil was purified using column chromatography (hexanes/EtOAc, 7:3) to afford 301 (101 mg, 0.29 mmol, 31%) as a yellow solid (mp= 132-134 °C). ¹HNMR (400 MHz) 7.86 (d, J= 8.4 Hz, 1H), 7.37 (d, J= 8.4 Hz, 1H), 6.50 (q, J= 7.6 Hz, 1H), 3.69 (s, 3H), 2.30 (d, J= 7.6 Hz, 3H); ¹³C 164.0, 147.0, 136.8, 136.6, 134.8, 134.2, 131.7, 128.3, 121.5, 114.3, 51.8, 16.4; IR (ATR) 3089, 2956, 1726, 1534, 1350, 1215 cm⁻¹;

(Z)-methyl 2-(2,3-dinitro-4-(prop-1-en-2-yl)phenyl)but-2-enoate (302)

Reaction of 301 (99.0 mg, 0.29 mmol), tributyl(prop-1-en-2-yl)stannane (120 mg, 0.36 mmol), PPh₃ (15.8 mg, 0.06 mmol), and Pd(dba)₂ (8.8 mg, 0.15 mmol) in toluene (3 mL) at 110 °C (24 hours) as described for 271 afforded after purification using column chromatography (hexanes/EtOAc, 8:2) 302 (57.6 mg, 0.19 mmol, 66%) as a yellow oil. ¹H NMR (400 MHz) δ 7.54 (d, J= 8.0 Hz, 1H), 7.36 (d, J= 8.0 Hz, 1H), 7.34 (q, J= 7.2 Hz, 1H), 5.30 (s, 1H), 5.08 (s, 1H), 3.73 (s, 3H), 2.14 (s, 3H), 1.77 (d, J= 6.8 Hz, 3H); ¹³C NMR (100 MHz) δ 164.9, 146.4, 144.1, 142.7, 139.0, 138.3, 133.7, 132.0, 129.9, 128.8, 118.4, 52.3, 23.1, 15.7; IR (ATR) 2952, 1726, 1552, 1354, 1205 cm⁻¹;
1-iodo-3-methyl-2,4-dinitrobenzene (308): To a solution of 2,4-dinitro-3-methylaniline 307 (492 mg, 2.5 mmol) in AcOH (8 mL) cooled to 10 °C, slowly added a solution of NaNO₂ (226 mg, 3.3 mmol) in H₂SO₄ (conc., 1.5 mL). Resulting red/brown solution stirred at 10 °C for 1 hour before adding a solution of KI (600 mg, 3.6 mmol) in H₂O (5 mL). Resulting brown suspension heated at 50 °C for 15 minutes. Suspension neutralized with NaHCO₃ (sat. aq.) and extracted with EtOAc (3x30 mL). Combined organic layers were washed with NaHSO₃ (sat. aq., 50 mL) and brine (50 mL), then organic layers dried (MgSO₄), filtered, and solvents removed under reduced pressure. The resulting red solid was purified using column chromatography (hexanes/EtOAc, 8:2) to afford 308 (647 mg, 2.10 mmol, 86%) as an orange solid (mp= 91-92 °C) (Lit. 90 °C)

¹HNMR (600 MHZ) δ 7.93 (d, J= 9.0 Hz, 1H), 7.71 (d, J= 9.0 Hz, 1H), 2.47 (s, 3H);

¹³CNMR δ 157.1, 149.9, 138.5, 126.4, 126.2, 91.1, 14.9; IR (ATR) 1594, 1529, 1344, 902 cm⁻¹;

2-(3-iodo-2,6-dinitrophenyl)ethanol (312): To a solution of 308 (221 mg, 0.71 mmol) in N,N-dimethylacetamide (5 mL) was added para-formaldehyde (30.0 mg, 1.00 mmol) and potassium hydroxide (10.2 mg, 0.18 mmol). The resulting brown solution was stirred at
ambient temperature (5 hours). The resulting brown solution was diluted with EtOAc (20 mL) and washed with H₂O (4 x 25 mL) and brine (25 mL). The organic phase was dried (MgSO₄), filtered, and solvents were removed under reduced pressure. The resulting orange solid was purified using column chromatography (hexanes/EtOAc, 7:3) to afford 312 (176 mg, 0.52 mmol, 72%) as a light yellow solid (mp= 137-140 °C). ¹H NMR (400 MHz) δ 7.98 (d, J= 8.4 Hz, 1H), 7.72 (d, J= 8.4 Hz, 1H), 3.87 (t, J= 6.4 Hz, 2H), 3.17 (t, J= 6.4 Hz, 2H), 2.10 (s, 1H); ¹³C NMR (100 MHz) δ 157.1, 150.7, 139.2, 127.1, 126.5, 91.4, 61.8, 31.2; IR (ATR) 3391, 3083, 1531, 1357, 1031 cm⁻¹;

1-iodo-2,4-dinitro-3-ethenylbenzene (313): To an ice-cooled solution of 312 (164 mg, 0.48 mmol) in N,N-dimethylacetamide (5 mL) was added methanesulfonyl chloride (75 µL, 0.97 mmol) and triethylamine (200 µL, 1.43 mmol). The resulting cloudy solution was stirred while warming to ambient temperature (2 hours), then heated at 90 °C (22 hours). The resulting light brown solution was diluted with EtOAc (15 mL) and washed with H₂O (5 x 20 mL) and brine (20 mL). The organic phase was dried (MgSO₄), filtered, and solvents were removed under reduced pressure. The resulting brown oil was purified using column chromatography (hexanes/EtOAc, 7:3) to afford 313 (118 mg, 0.37 mmol, 77%) as a yellow solid (mp= 86-88 °C). ¹H NMR (400 MHz) δ 8.02 (d, J= 8.8 Hz, 1H), 7.80 (d, J= 8.4 Hz, 1H), 6.85 (dd, J= 18.4, 11.6 Hz, 1H), 5.59 (d, J= 12 Hz, 1H),
5.49 (d, J = 18.4 Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 148.2, 140.1, 139.7, 127.9, 126.8, 125.8, 123.4, 91.6; IR (ATR) 30.87, 2891, 1522, 1337, 837 cm$^{-1}$;

![Diagram](image)

**1,3-dinitro-4-(prop-1-en-2-yl)-2-ethenylbenzene (314):** Reaction of 313 (109 mg, 0.34 mmol), tributyl(prop-1-en-2-yl)stannane (132 mg, 0.40 mmol), PPh$_3$ (18.2 mg, 0.07 mmol), Pd(dba)$_2$ (9.9 mg, 0.02 mmol), and BHT (2 pieces) in dioxane (3 mL) at 75 °C (23 hours) as described for 271 afforded after purification using column chromatography (hexanes/EtOAc, 85:15) 314 (51.2 mg, 0.22 mmol, 64%) as a yellow solid (mp= 48-50 °C). $^1$H NMR (400 MHz) $\delta$ 8.04 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 6.90 (dd, J = 18.0, 12.0 Hz, 1H), 5.55 (d, J = 12.0 Hz, 1H), 5.45 (dd, J = 17.6, 0.8 Hz, 1H), 5.31 (m, 1H), 5.07 (m, 1H), 2.10 (s, 3H); $^{13}$C NMR (100 MHz) $\delta$ 149.8, 147.0, 140.9, 138.9, 128.7, 127.3, 127.2, 125.2, 122.4, 118.8, 23.3; IR (ATR) 3096, 2981, 1524, 1345, 918 cm$^{-1}$;

![Diagram](image)

**3,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (326)** In an oven-dried ACE glass pressure tube was mixed 260 (47.5 mg, 0.19 mmol), 1,10-phenanthroline (6.4 mg, 0.032 mmol), dppp (6.2 mg, 0.015 mmol), and Pd(dba)$_2$ (7.8 mg, 0.013 mmol) and dry DMF (2 mL). The tube was fitted with a pressure head, and the vessel was saturated with CO (three cycles, 6 atm). The tube was heated at 120 °C for 48 hours, then the solvent was
removed by bulb-to-bulb and the resulting dark brown crude mixture afforded after column chromatography (hexanes/EtOAc, 1:1) 326 (25.2 mg, 0.14 mmol, 73%) as a brown solid (mp= 195-200 °C). $^1$H NMR (600 MHz) $\delta$ 7.63 (s, 1H), 7.56 (s, 2H), 7.18 (s, 1H), 6.91 (s, 2H), 2.39 (s, 3H); $^{13}$C NMR $\delta$ 135.3, 124.7, 121.1, 111.0, 106.7, 90.9, 10.1; IR (ATR) 3275, 2920, 1668, 1631, 1507, 1255 cm$^{-1}$;

1,5-dihydropyrrolo[2,3-f]indole (239) Reaction of 240 (29.6 mg, 0.13 mmol), 1,10-phenanthroline (3.4 mg, 0.017 mmol), dppt (3.5 mg, 0.008 mmol), and Pd(dba)$_2$ (5.0 mg, 0.008 mmol) in DMF (2 mL) under carbon monoxide (3 cycles, 6 atm) for 87 hours as described for 326 afforded after column chromatography (hexanes/EtOAc, 85:15) 239 (15.9 mg, 0.10 mmol, 78%) as an off white solid. Spectral data were in accordance with literature values.$^{106}$

3-methyl-2,6-dihydropyrrolo[2,3-g]indole (330) Reaction of 314 (87.9 mg, 0.37 mmol), 1,10-phenanthroline (9.3 mg, 0.047 mmol), dppt (9.2 mg, 0.022 mmol), and Pd(dba)$_2$ (13.8 mg, 0.024 mmol) in DMF (3 mL) under carbon monoxide (3 cycles, 6 atm) for 110 hours as described for 326 afforded after column chromatography (hexanes/EtOAc, 1:1) in order of elution 330 (19.4 mg, 0.11 mmol, 30%) as brown solid (mp= 89-91 °C) and
(35.5 mg, 0.17 mmol, 47%) as a brown solid. Spectral data for 330: \(^1\)H NMR (400 MHz) \(\delta\) 8.24 (br s, 1H), 8.11 (br s, 1H), 7.39 (d, \(J= 8.4\) Hz, 1H), 7.18 (dd, \(J= 8.8\) Hz, 0.8 Hz, 1H), 7.14 (t, \(J= 2.8\) Hz, 1H), 6.87 (m, 1H), 6.63 (m, 1H), 2.38 (s, 3H); \(^13\)C NMR (100 MHz) \(\delta\) 133.0, 128.9, 128.4, 121.9, 121.0, 117.8, 113.9, 112.7, 104.5, 98.5, 10.1; IR (ATR) 3398, 2924, 1632, 1402, 724 cm\(^{-1}\);

Methyl 2,6-dimethyl-1,8-dihydropyrrolo[3,2-g]indole-3-carboxylate (331): Reaction of 302 (46.9 mg, 0.15 mmol), 1,10-phenanthroline (3.8 mg, 0.019 mmol), dppp (4.1 mg, 0.010 mmol), and Pd(dba)_2 (5.6 mg, 0.010 mmol) in DMF (2 mL) under carbon monoxide (3 cycles, 6 atm) for 110 hours as described for 326 afforded after column chromatography (hexanes/EtOAc, 1:1) 331 (28.6 mg, 0.12 mmol, 77%) as an off-white solid that turned green/brown upon dissolving in CDCl\(_3\). \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 10.75 (s, 1H), 9.57 (s, 1H), 7.76 (d, \(J= 8.4\) Hz, 1H), 7.32 (d, \(J=8.4\) Hz, 1H), 3.92 (s, 3H), 2.75 (s, 3H), 2.36 (s, 3H); \(^13\)C NMR (100 MHz) \(\delta\) 166.6, 139.9, 123.5, 122.1, 121.8, 120.9, 118.3, 112.4, 112.2, 111.6, 104.3, 50.1, 113.9, 9.6; IR (ATR) 3381, 1655, 1446, 1419, 1198, 1109 cm\(^{-1}\);
2,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (332): Reaction of 274 (67.8 mg, 0.27 mmol), 1,10-phenanthroline (6.5 mg, 0.032 mmol), dppp (6.8 mg, 0.016 mmol), and Pd(dba)$_2$ (10.0 mg, 0.017 mmol) in DMF (2.5 mL) under carbon monoxide (3 cycles, 6 atm) for 110 hours as described for 326 afforded after column chromatography (hexanes/EtOAc, 1:1) 332 (12.3 mg, 0.07 mmol, 24%) as a brown solid (mp= 183-185 °C). $^1$H NMR (600 MHz) $\delta$ 11.9 (br s, 1H), 8.76 (s, 1H), 8.50 (d, $J= 1.8$ Hz, 1H), 8.28 (br s, 1H), 8.12 (s, 1H), 6.25 (d, $J= 1.2$ Hz, 1H), 2.72 (s, 3H), 2.45 (s, 3H); $^{13}$C NMR (150 MHz) $\delta$ 159.8, 139.5, 137.5, 134.5, 128.9, 124.8, 124.4, 116.7, 102.8, 101.4, 14.1, 13.7; IR (ATR) 3197, 2924, 2857, 1677, 1625, 1504 cm$^{-1}$;

2,5-dimethyl-3-phenyl-1,7-dihydropyrrolo[3,2-f]indole (333): Reaction of 276 (25.6 mg, 0.079 mmol), Pd(dba)$_2$ (3.2 mg, 0.005 mmol), 1,10-phenanthroline (2.5 mg, 0.012 mmol), dppp (2.4 mg, 0.006 mmol), in DMF (1.5 mL) under carbon monoxide (3 cycles, 6 atm) for 120 hours as described for 326 afforded after column chromatography (hexanes: EtOAc, 1:1) 333 (4.8 mg, 0.02 mmol, 17%) as a brown residue. $^1$H NMR (600 MHz) $\delta$ 11.95 (s, 1H), 8.78 (s, 1H), 8.49 (s, 1H), 8.20 (s, 1H), 7.53-7.45 (m,
5H), 3.28 (s, 3H), 2.67 (s, 3H); $^{13}$C NMR (150 MHz) $\delta$ 159.8, 134.3, 131.2, 130.0, 129.8, 129.3, 128.8, 128.5, 127.6, 127.1, 126.4, 125.3, 124.0, 122.1, 15.5, 12.5; IR (ATR) 3383, 2918, 2850, 1706, 1602, 1495 cm$^{-1}$;
7.5 Supporting Information Chapter 6.1: 2-Nitrobenzaldehyde Brominations

Bromination of 2-nitrobenzaldehyde (338) using 0.75 equivalents of NBS. To a solution of 338 (986 mg, 6.53 mmol) in H₂SO₄ (conc. 5.0 mL) was added N-bromosuccinimide (NBS) (878 mg, 4.93 mmol). The resulting mixture was stirred at ambient temperature (3 h). The reaction was quenched with ice and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with saturated NaCl (aqueous, 30 mL), dried (MgSO₄), filtered through a silica gel plug, and the solvents were evaporated under reduced pressure. The resulting brown oil was purified by column chromatography (hexanes/EtOAc, 8:2) to afford the following fractions in order of elution: (I) 4-bromo-2-nitrobenzaldehyde (339)¹⁵⁸ (216 mg, 19%), 5-bromo-2-nitrobenzaldehyde (341)¹⁵⁹ (134 mg, 12%), and 4,5-dibromo-2-nitrobenzaldehyde (344) (18 mg, 1%) as a yellow solid; (II) 6-bromo-2-nitrobenzaldehyde (342) (268 mg, 24%),¹⁶₀ 3,6-dibromo-2-nitrobenzaldehyde (345) (25 mg, 2%),¹⁶¹ and 338 (409 mg, 41%) as a yellow oil; (III) 3-bromo-2-nitrobenzaldehyde (340)¹⁶² as a yellow solid (60 mg, 0.26 mmol, 4%). 340: mp = 73-74 °C (Lit. mp = 75-77 °C).

Bromination of 338 using 1.25 equivalents of NBS. Reaction of 338 (1.01 g, 6.71 mmol) and NBS (1.48 g, 8.32 mmol) in H₂SO₄ (5.0 mL) as described above afforded the
following fractions in order of elution: (I) 344 (28 mg, 0.09 mmol, 1%) as an off-white solid; (II) 339 (328 mg, 21%), 341 (140 mg, 9%), and 3,4-dibromo-2-nitrobenzaldehyde (343) (94 mg, 5%); (III) 342 (310 mg, 20%), 345 (65 mg, 3%), 338 (168 mg, 17%); (IV) 340 (54 mg, 0.23 mmol, 4%).

Data for 343: mp = 105-106 °C (Lit. mp = 105-107 °C); $^{1}H$ NMR $\delta$ 10.39 (s, 1H), 8.39 (s, 1H), 8.19 (s, 1H); $^{13}C$ NMR $\delta$ 185.9, 147.7, 134.3, 132.5, 130.8, 130.4, 129.6; IR (ATR) 3088, 2890, 1687, 1525, 1338, 1178 cm$^{-1}$

**Bromination of 338 using 1.25 equivalents of NBS at 60 °C.** Reaction of 338 (459 mg, 3.03 mmol) and NBS (677 mg, 3.80 mmol) in H$_2$SO$_4$ (3.0 mL) at 60 °C as described above afforded the following fractions in order of elution: (I) 344 (21 mg, 0.07 mmol, 2%); (II) 339 (66 mg, 9%) and 341 (24 mg, 3%); (III): 339 (5 mg, 0.7%) and 343 (85 mg, 9%); (IV) 342 (59 mg, 8%), 345 (13 mg, 1%),$^{162}$ and 338 (18 mg, 4%); (V) 340 (20 mg, 0.09 mmol, 3%).

**Bromination of 338 using 2.5 equivalents of NBS.** Reaction of 338 (504 mg, 3.33 mmol) and NBS (1.48 g, 8.30 mmol) in H$_2$SO$_4$ (3.0 mL) as described above provided after purification by chromatography (hexanes/EtOAc, 85:15) the following fractions in order of elution: (I) 344 (65 mg, 0.21 mmol, 9%); (II) 339 (58 mg, 8%), 341 (153 mg, 20%), and 343 (128 mg, 12%); (III) 342 (108 mg, 14%), 345 (129 mg, 13%), and 338 (17 mg, 3%); (IV) 340 (57 mg, 0.25 mmol, 8%).

**Bromination of 338 using 5.0 equivalents of NBS.** Reaction of 338 (504 mg, 3.33 mmol) and N-bromosuccinimide (2.94 g, 16.5 mmol) in H$_2$SO$_4$ (3.0 mL) as described above afforded the following in order of elution: (I) 344 (193 mg, 0.62 mmol, 19%); (II) 343 (247 mg, 24%) and 339 (32 mg, 4%); (III) 345 (174 mg, 0.56 mmol, 17%).
Data for **343**: mp = 98-99 °C (white solid); $^1$H NMR $\delta$ 10.21 (s, 1H), 7.94 (d, $J$= 9.0 Hz, 1H), 7.93 (d, $J$= 8.4 Hz, 1H); $^{13}$C NMR $\delta$ 187.8, 146.2, 135.9, 135.5, 133.6, 123.9, 123.8; IR (ATR) 3112, 3075, 1702, 1522, 1342 cm$^{-1}$; HRMS (ESI) calcd for C$_7$H$_3$Br$_2$NO$_3$ (M+H$^+$) 307.8552; found 307.8556.

**3-Bromo-2-nitrobenzylalcohol (346).**$^{164}$ To a solution of **340** (105 mg, 0.46 mmol) in THF (3 mL) and H$_2$O (1 mL) was added sodium borohydride (37 mg, 0.98 mmol). The resulting solution was stirred at ambient temperature (20 min), water was added (20 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried (MgSO$_4$), filtered, and the solvents were evaporated under reduced pressure to give **346** (87 mg, 0.37 mmol, 81%) as a pale yellow oil. No further purification was required. Spectral data are in accordance with literature data.

**4-Bromo-2-nitrobenzylalcohol (347) and 5-bromo-2-nitrobenzylalcohol (348).**$^{164}$ Reaction of a mixture of **339** and **341** (1.40 g, 64:36 ratio, 6.09 mmol) in dry THF (15 mL) and H$_2$O (5 mL) was added sodium borohydride (405 mg, 10.7 mmol), as described for **346**, afforded after work up and purification by chromatography (hexanes/EtOAc, 8:2) in order of elution **5-bromo-2-nitrobenzylalcohol 348** (476 mg, 2.04 mmol) and **4-bromo-2-nitrobenzylalcohol 347** (713 mg, 3.07 mmol) both as faint yellow solids. Spectral data were in accordance with literature data.

**Fraction II:**

To a mixture of 6-bromo-2-nitrobenzaldehyde (342), 3,6-dibromo-2-nitrobenzaldehyde (345), and 2-nitrobenzaldehyde (338) (150 mg, 0.68 : 0.09 : 0.23) in THF (5 mL) and H$_2$O (3 mL) was added sodium borohydride (49.8 mg, 1.32 mmol) as described for **346** afforded after purification by chromatography (hexanes/EtOAc, 8:2) in order of elution: a
mixture of 6-bromo-2-nitrobenzyl alcohol\textsuperscript{166} and 3,6-dibromo-2-nitrobenzyl alcohol (148 mg) followed by 2-nitrobenzyl alcohol\textsuperscript{167} (36 mg, 0.23 mmol).

\[
\begin{array}{c}
\text{CHO} \\
\text{Br} \\
\text{Br}
\end{array} \rightarrow \begin{array}{c}
\text{CH}_2\text{OH} \\
\text{Br} \\
\text{Br}
\end{array}
\]

**3,4-Dibromo-2-nitrobenzylalcohol (349).** Reaction of 343 (101 mg, 0.33 mmol) with sodium borohydride (42.6 mg, 1.13 mmol) in THF (3 mL) and H\textsubscript{2}O (1 mL) as described for 346 afforded after purification by chromatography (hexanes/EtOAc, 7:3) 349 (48 mg, 0.16 mmol, 47\%) as an off-white solid. mp 76-78 °C; \textsuperscript{1}H NMR \(\delta\) 7.78 (d, \(J=9.0\) Hz, 1H), 7.69 (d, \(J=8.4\) Hz, 1H), 4.99 (s, 2H), 2.72 (br s, 1H); \textsuperscript{13}C NMR \(\delta\) 149.8, 136.2, 133.6, 132.2, 130.1, 124.0, 62.8; IR (ATR) 3554, 3073, 1518, 1339, 1028 cm\textsuperscript{-1}; HRMS (ESI) calcd for C\textsubscript{7}H\textsubscript{5}NO\textsubscript{3}Br (M+Na\textsuperscript{+}) 333.8508; found 333.8508.

\[
\begin{array}{c}
\text{CHO} \\
\text{Br} \\
\text{Br}
\end{array} \rightarrow \begin{array}{c}
\text{CH}_2\text{OH} \\
\text{Br} \\
\text{Br}
\end{array}
\]

**4,5-Dibromo-2-nitrobenzylalcohol (350).** Reaction of 344 (292 mg, 0.94 mmol) with sodium borohydride (71.8 mg, 1.90 mmol) in THF (3 mL) and H\textsubscript{2}O (1 mL) as described for 346 afforded after purification by chromatography (hexanes/EtOAc, 8:2) 350 (136 mg, 0.44 mmol, 46\%) as an off-white solid. mp 112-113 °C; \textsuperscript{1}H NMR \(\delta\) 8.36 (s, 1H), 8.11 (s, 1H), 4.98 (s, 2H), 2.41 (br s, 1H); \textsuperscript{13}C NMR \(\delta\) 145.8, 137.3, 134.1, 132.2, 129.7, 124.1,
61.5; IR (ATR) 3225, 3089, 1505, 1336, 1035 cm\(^{-1}\); HRMS (ESI) calcd for C\(_7\)H\(_5\)NO\(_3\)Br (M+Na\(^+\)) 333.8508; found 333.8509.

3,6-Dibromo-2-nitrobenzylalcohol (351). Reaction 345 (130 mg, 0.42 mmol) and sodium borohydride (30 mg, 0.79 mmol) in THF (3 mL) and H\(_2\)O (1 mL) as described for 346 afforded after purification by chromatography (hexanes/EtOAc, 7:3) 351 (99 mg, 0.32 mmol, 76%) as a white solid. mp 75-76 °C; \(^1\)H NMR \(\delta\) 7.62 (d, \(J=9.0\) Hz, 1H), 7.51 (d, \(J=9.0\) Hz, 1H), 4.76 (d, \(J=6.6\) Hz, 2H), 2.23 (t, \(J=7.2\) Hz, 1H); \(^13\)C NMR \(\delta\) 152.0, 135.7, 134.3, 133.4, 124.5, 112.5, 61.6; IR (ATR) 3194, 1539, 1356, 1076, 1043 cm\(^{-1}\); HRMS (ESI) calcd for C\(_7\)H\(_5\)NO\(_3\)Br (M+Na\(^+\)) 333.8508; found 333.8510.
2,3-dinitro-4-ethenyltoluene (355): To a solution of 352 (155 mg, 0.60 mmol) in toluene (5 mL) was added (ethenyl)tri-n-butylstannane (203 mg, 0.64 mmol), PPh₃ (62.9 mg, 0.24 mmol), Pd(dba)₂ (29.3 mg, 0.05 mmol) and the solution was heated at 110° C for 66 hours. The resulting brown solution was filtered through Celite, diluted with ethyl acetate (20 mL), washed with NH₄OH (10% aq, 3 x 30 mL), H₂O (30 mL), and brine (30 mL). The organic layer was dried (MgSO₄), filtered, then solvents removed under reduced pressure. Purification using column chromatography (hexanes/EtOAc, 8:2) afforded 355 (82.3 mg, 0.40 mmol, 66%) as a brown solid (mp= 68-71 °C) ¹H NMR (600 MHz) δ 7.70 (d, J= 8.4 Hz, 1H), 7.46 (d, J= 8.4 Hz, 1H), 6.73 (dd, J= 17.4, 11.4 Hz, 1H), 5.87 (d, J= 16.8 Hz, 1H), 5.60 (d, J= 11.4 Hz, 1H), 2.46 (s, 3H); ¹³C NMR (150 MHz) δ 143.5, 142.1, 134.1, 132.2, 130.3, 129.1, 128.5, 121.5, 18.1; IR (ATR) 3031, 2963, 1612, 1558, 1341 cm⁻¹

6-methyl-7-nitroindole (356): Reaction of 355 (82.3 mg, 0.40 mmol), PPh₃ (26.3 mg, 0.10 mmol), Pd(OAc)₂ (5.7 mg, 0.02 mmol) in MeCN (2 mL) under pressurized CO (g)
(3 cycles, 90 psi) at 70 °C for 168 hours afforded after column chromatography (hexanes/EtOAc, 9:1) **356** (3.9 mg, 0.02 mmol, 6%) as a yellow solid.

HNMR (270 MHz) δ 9.97 (br s, 1H), 7.80 (d, J= 7.9 Hz, 1H), 7.33 (t, J= 2.8 Hz, 1H), 7.07 (d, J= 7.9 Hz, 1H), 6.65 (t, J= 2.8 Hz, 1H), 2.83 (s, 3H); IR (ATR) 3376, 2927, 1475, 1312, 1267 cm⁻¹

**3.5-dinitro-4-ethenyltoluene (357):** Reaction of **354** (148 mg, 0.57 mmol), (ethenyl)tri-n-butylstannane (206 mg, 0.65 mmol), PPh₃ (60.9 mg, 0.23 mmol), Pd(dba)₂ (26.0 mg, 0.04 mmol) in toluene (5 mL) at 110 °C for 48 hours as described for 355 afforded after column chromatography (hexanes/EtOAc, 8:2) **357** (67.2 mg, 0.32 mmol, 57%) as a brown solid (mp= 59-61 °C) ¹H NMR (600 MHz) δ 7.84 (s, 2H), 7.00 (dd, J= 17.4, 11.4 Hz, 1H), 5.49 (dd, J= 11.4, 0.6 Hz, 1H), 5.31 (dd, J= 18.0, 0.6 Hz, 1H), 2.52 (s, 3H); ¹³C NMR (150 MHz) δ 149.9, 140.1, 128.1, 127.6, 125.8, 121.1, 20.9; IR (ATR) 3015, 2971, 1629, 1538, 1352 cm⁻¹

![3.5-dinitro-4-ethenyltoluene](image)

**6-methyl-4-nitroindole (358):** Reaction of **357** (67.2 mg, 0.32 mmol), PPh₃ (21.0 mg, 0.08 mmol), Pd(OAc)₂ (4.4 mg, 0.02 mmol) in MeCN (2 mL) under pressurized CO (g) (3 cycles, 90 psi) at 70 °C for 18 hours afforded after column chromatography
(hexanes/EtOAc, 9:1) 358 (34.0 mg, 0.19 mmol, 60%) as an orange solid (mp=169-171 °C); HNMR 8.52 (br s, 1H), 8.00 (s, 1H), 7.52 (s, 1H), 7.40 (t, J= 2.4 Hz, 1H), 7.24 (t, J= 2.4 Hz, 1H), 2.54 (s, 3H); CNMR 140.1, 138.2, 131.3, 127.8, 120.2, 119.0, 118.1, 103.2, 21.3; IR (ATR) 3364, 3115, 2915, 1504, 1346, 1277 cm⁻¹;

5-bromo-2,4-dinitroanisole (360)168 and 3-bromo-2,4-dinitroanisole (361): To fuming nitric acid (5 mL) cooled to -78 °C was added 359 (309 mg, 1.7 mmol). Solution removed from cold bath upon addition of starting material and allowed to warm to ambient temperature over 30 minutes. Resulting yellow solution poured over 100 mL ice, causing off-white solid to form. Aqueous mixture extracted with ethyl acetate (3 x 40 mL), then combined organic layers washed with sodium carbonate (sat. aq, 50 mL), dried over MgSO₄, filtered, and solvents removed to give yellow solid. Purification via column chromatography (hexanes/EtOAc, 85:15) afforded in order of elution 361 (white solid, 26.1 mg, 6%) and 360 (off-white solid, 407 mg, 89%)168. Spectral data for 361: $^{1}$HNMR δ 7.97 (d, J= 8.9 Hz, 1H), 7.57 (d, J= 8.9 Hz, 1H), 4.04 (s, 3H);

5-iodo-2,4-dinitroanisole (363) 3-iodo-2,4-dinitroanisole (364): To a solution of fuming nitric acid (10 mL) cooled to -78 °C was added 362 (3.02 g, 12.9 mmol). Solution removed from cold bath upon addition of starting material and allowed to warm
to ambient temperature over 30 minutes. Resulting brown solution poured over 100 mL ice, causing off-white solid to form. Aqueous mixture extracted with ethyl acetate (3 x 40 mL), then combined organic layers washed with sodium carbonate (sat. aq, 50 mL), dried over MgSO₄, filtered, and solvents removed to give yellow solid. Purification via column chromatography (hexanes/EtOAc, 7:3) afforded in order of elution 364 (yellow solid, 454.6 mg, 10.9%) and 363 (yellow solid, 742.6 mg, 17.7%)

Spectral data for 364: mp= 154-157 °C, ¹H NMR δ 8.08 (d, J= 9.0 Hz, 1H), 7.13 (d, J= 9.6 Hz, 1H), 4.01 (s, 3H); ¹³C NMR δ 154.0, 148.6, 146.3, 128.0, 112.5, 82.0, 57.6; IR (ATR) 1575, 1520, 1342, 1283, 1020 cm⁻¹

Spectral data for 363: mp= 113-115 °C, ¹H NMR δ 8.58 (s, 1H), 7.76 (s, 1H), 4.09 (s, 3H); ¹³C NMR δ 155.0, 144.2, 138.2, 127.3, 123.4, 94.3, 57.9; IR (ATR) 1594, 1526, 1339, 1247, 987 cm⁻¹; HRMS (ESI) calc’d for C₁₇H₁₅N₂O₅I (M+Na)= 346.9135, found 346.9139.

**2,4-dinitro-5-ethenylanisole (365):** Reaction of 360 (159 mg, 0.58 mmol), (ethenyl)tri-n-butylstannane (304 mg, 0.96 mmol), PPh₃ (68.6 mg, 0.26 mmol), and Pd(dba)₂ (27.4 mg, 0.05 mmol) in toluene (6 mL) for 48 hours as described for 355 afforded after purification using column chromatography (hexanes/EtOAc, 8:2) 365 (55.8 mg, 38%) as a yellow solid (mp= 72-74 °C). ¹H NMR δ 8.69 (s, 1H), 7.36 (dd, J= 17.2, 10.8 Hz, 1H),
7.20 (s, 1H), 5.82 (d, J= 17.2 Hz, 1H), 5.68 (d, J= 10.9 Hz, 1H), 4.12 (s, 3H); $^{13}$C NMR δ 156.0, 140.7, 132.5, 124.0, 123.7, 121.8, 115.3, 112.9, 57.3; IR (ATR) 3108, 3060, 1607, 1579, 1516, 1338, 1277, 1249 cm$^{-1}$;

2,4-dinitro-3-ethenylanisole (367): To a solution of 364 (240.3 mg, 0.74 mmol) in toluene (10 mL) was added (ethenyl)tri-n-butylstannane (342.1 mg, 1.07 mmol), PPh$_3$ (85.3 mg, 0.32 mmol), and Pd(dba)$_2$ (35.2 mg, 0.06 mmol) and 2,6-di-t-butyl-4-methylphenol (18.7 mg, 0.08 mmol) for 48 hours as described for 355 afforded after purification using column chromatography (hexanes/EtOAc, 7:3) gave 367 (135.6 mg, 82%) as a brown solid. $^1$HNMR δ 8.04 (d, J=8.4 Hz, 1H), 7.48 (d, J=8.4 Hz, 1H), 6.60 (dd, J=17.4, 10.8 Hz, 1H), 6.00 (d, J=17.4 Hz, 1H), 5.69 (d, J= 11.4 Hz, 1H), 4.02 (s, 3H); $^{13}$CNMR δ 146.9, 136.0, 129.2, 128.6, 128.2, 127.1, 123.8, 121.5, 65.0; IR (ATR) 3109, 2958, 1672, 1577, 1519, 1340, 1286 cm$^{-1}$;

5-methoxy-6-nitroindole (366)$^{169}$: In an oven-dried ACE glass pressure tube dissolved 365 (41.5 mg, 0.19 mmol), 1,10-phenanthroline (7.4 mg, 0.04 mmol), and Pd(OAc)$_2$ (4.1 mg, 0.02 mmol) in N,N-dimethylformamide (3 mL). Tube fitted with pressure head and
pressurized with carbon monoxide (4 cycles, 6 atm), then placed in aluminum heating block at heated at 120\(^{\circ}\) C for 28 hours. Brown solution diluted with H\(_2\)O (25 mL), then extracted with ethyl acetate (4 x 40 mL). Combined organic layers dried over MgSO\(_4\), filtered, then solvents removed under reduced pressure. Purification of crude brown residue via column chromatography (hexanes/EtOAc, 1:1) afforded \(366\) (10.3 mg, 28\%) as a brown residue. Spectral data were in accordance with literature values.

\[ \text{5-methoxy-4-nitroindole (368)}^{169} : \text{In an oven-dried ACE glass pressure tube dissolved 367 (55.7 mg, 0.25 mmol), 1,10-phenanthroline (9.8 mg, 0.05 mmol), and Pd(OAc)\(_2\) (5.3 mg, 0.024 mmol) in N,N-dimethylformamide (3 mL). Tube fitted with pressure head and pressurized with carbon monoxide (4 cycles, 6 atm), then placed in aluminum heating block at heated at 120\(^{\circ}\) C for 24 hours. Solvent removed via bulb-to-bulb distillation. Purification of crude brown residue via column chromatography (hexanes/EtOAc afforded 368 (10.9 mg, 23\%) as a yellow solid. Spectral data were in accordance with literature values.} \]

\[ \text{2,4-dinitro-5-(prop-1-en-2-yl)anisole (369): Reaction of 363 (257 mg, 0.79 mmol), tributyl(prop-1-en-2-yl)stannane (312 mg, 0.94 mmol), PPh\(_3\) (57.0 mg, 0.22 mmol), and Pd(dba)\(_2\) (35.4 mg, 0.06 mmol) in toluene (10 mL) for 41 hours as described for 355} \]
afforded after purification using column chromatography (hexanes/EtOAc, 8:2) **369** (68.8 mg, 0.29 mmol, 37%) as a yellow oil. $^1$HNMR $\delta$ 8.61 (s, 1H), 6.97 (s, 1H), 5.27 (s, 1H), 5.01 (s, 1H), 4.08 (s, 3H), 2.11 (s, 3H); $^{13}$CNMR $\delta$ 156.0, 146.5, 142.5, 139.5, 137.4, 123.4, 226.4, 115.5, 57.5, 23.1; IR (ATR) 3114, 3045, 1615, 1579, 1516, 1338 cm$^{-1}$.

3-methyl-5-methoxy-6-nitroindole (370): Reaction of **369** (68.8 mg, 0.29 mmol), PPh$_3$ (33.2 mg, 0.13 mmol), and Pd(OAc)$_2$ (7.8 mg, 0.03 mmol) in MeCN (3 mL) under CO (g) (3 cycles, 90 psi) at 120 °C (48 hrs) afforded after purification using column chromatography (hexanes/EtOAc, 8:2) **370** (4.3 mg, 0.02 mmol, 7%) as a yellow solid (mp = 127-129 °C). $^1$HNMR $\delta$ 8.11 (br s, 1H), 8.00 (s, 1H), 7.21 (t, $J$ = 1.2 Hz, 1H), 7.10 (s, 1H), 4.01 (s, 3H), 2.32 (d, $J$ = 1.2 Hz, 3H); $^{13}$CNMR $\delta$ 148.1, 136.4, 132.6, 129.2, 128.1, 112.4, 109.8, 102.3, 57.4, 9.7; IR (ATR) 3289, 3098, 2945, 1524, 1340, 1271 cm$^{-1}$; HMRS (ESI) calc’d for C$_{10}$H$_{10}$N$_2$O$_3$ (M+Na) 229.0583, found 229.0583.

2,4-dinitro-3-(prop-1-en-2-yl)anisole (371): Reaction of **361** (204 mg, 0.74 mmol), tributyl(prop-1-en-2-yl)stannane (519 mg, 1.57 mmol), PPh$_3$ (79.9 mg, 0.30 mmol), and Pd(dba)$_2$ (34.6 mg, 0.06 mmol) in toluene (20 mL) for 47 hours as described for **355** afforded after purification using column chromatography (hexanes/EtOAc, 9:1) **371** (37.0
mg, 0.16 mmol, 21%) as a brown oil. $^1$H NMR $\delta$ 8.25 (d, $J=9.6$ Hz, 1H), 7.08 (d, $J=9.6$ Hz, 1H), 5.30 (m, 1H), 4.98 (m, 1H), 4.01 (s, 3H), 2.11 (s, 3H); $^{13}$C NMR $\delta$ 154.4, 141.4, 140.3, 137.2, 134.2, 128.2, 118.3, 111.1, 57.3, 23.3; IR (ATR) 3113, 2954, 1662, 1581, 1345, 1275 cm$^{-1}$;

3-methyl-5-methoxy-4-nitroindole (372): Reaction of 371 (34.8 mg, 0.15 mmol), 1,10-phenanthroline (6.6 mg, 0.04 mmol), and Pd(OAc)$_2$ (3.1 mg, 0.01 mmol) in DMF (3 mL) under CO (g) (3 cycles, 90 psi) at 120 °C (43 hrs) afforded after purification using column chromatography (hexanes/EtOAc, 7:3) 372 (16.5 mg, 0.08 mmol, 53%) as a brown solid (mp= 152-154 °C). $^1$H NMR $\delta$ 8.07 (br s, 1H), 7.39 (d, $J=9.0$ Hz, 1H), 7.06 (t, $J=0.6$ Hz, 1H), 6.94 (d, $J=9.0$ Hz, 1H), 3.93 (s, 3H), 2.18 (d, $J=1.2$ Hz, 3H); $^{13}$C NMR $\delta$ 145.6, 133.5, 133.0, 126.2, 120.1, 114.1, 109.9, 108.9, 58.2, 10.1; IR (ATR) 3348, 2984, 1521, 1322, 1242 cm$^{-1}$; HMRS (ESI) calc’d for C$_{10}$H$_{10}$N$_2$O$_3$ (M+Na) 229.0583, found 229.0583.
References and Notes


27. Fischer, E.; Hess, O. *Ber.* **1884**, *17*, 559.


43. Reissert, A.; Ber. 1897, 30, 1030.


73. The parent compound has been isolated from for example coal tar pitch, in sediment samples, and in smoke from a variety of sources. For example, see: Kruber, O.; Grigoleit, G. *Chem. Ber.* **1954**, 87, 1895-1905.


79. The compound has been reported without any spectral data, see: Ref. 3.


158. For a synthesis, mp, and spectral data, see: Seo, J. H.; Artman III, G. D.; Weinreb, S. M. 


Appendix

$^1$H and $^{13}$C NMR Spectra

- $^1$H and $^{13}$C NMR for Chapter 2: Indole/Quinoline 209
- $^1$H and $^{13}$C NMR for Chapter 3: Salviadione 218
- $^1$H and $^{13}$C NMR for Chapter 4: Chemoslective Coupling 232
- $^1$H and $^{13}$C NMR for Chapter 5: Pyrroloindoles 284
- $^1$H and $^{13}$C NMR for Chapter 6.1: Bromination 330
- $^1$H and $^{13}$C NMR for Chapter 6.2: Functionalized Indoles 340
$^1$H and $^{13}$C NMR for Chapter 2: Indole/Quinoline

Figure 17: $^1$H NMR of 3-Cyclohexyl-2-iodo-2-propenitrile (110)
Figure 18: $^{13}$C NMR of 3-Cyclohexyl-2-iodo-2-propenitrile (110)
Figure 19: $^1$H NMR of 3-Cyclohexyl-2-(2-nitrophenyl)-2-propenenitrile (111)
Figure 20: $^{13}$C NMR of 3-Cyclohexyl-2-(2-nitrophenyl)-2-propenitrile (111)
Figure 21: $^1$H NMR of 3-Cyano-2-cyclohexylindole (112)
Figure 22: $^{13}$C NMR of 3-Cyano-2-cyclohexylindole (112)
Figure 23: $^1$H NMR of 3-cyano-2-(1-hydroxycyclohexyl)indole (113)
Figure 24: $^{13}$C NMR of 3-cyano-2-((1-hydroxycyclohexyl)indole (113)
Figure 25: $^1$H NMR of 5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (127)
Figure 26: $^{13}$C NMR of 5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (127)
Figure 27: $^1$H NMR of 10,10α-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthren-3($1H,2H,9H$)-one (132)
Figure 28: $^{13}$C NMR of 10,10α-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthrene-3(1$H$,2$H$,9$H$)-one (132)
Figure 29: $^1$H NMR of 10,10α-Dihydro-1,1-dimethyl-6-hydroxy-7-(1-methylethyl)-5-nitrophenanthren-3(1H,2H,9H)-one (125)
Figure 30: $^1$H NMR of 8a,9,10,10a-Tetrahydro-1,1-dimethyl-8a-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1H,2H)-dione (133)
Figure 31: $^{13}$C NMR of $8a,9,10,10a$-Tetrahydro-1,1-dimethyl-$8a$-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1H,2H)-dione (133)
Figure 32: $^1$H NMR of 1,8,9,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-4H-
benzo[de]carbazol-3(2H)-one (134)
Figure 33: $^{13}$C NMR of 1,8,9,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-4H-benzo[def]carbazol-3(2H)-one (134)
Figure 34: $^1$H NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-4H-benzo[def]carbazol-3(2H)-one (136)
Figure 35: $^{13}$C NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-4H-benzo[def]carbazol-3(2H)-one (136)
Figure 36: $^1$H NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-
$4H$-benzo[def]carbazol-3(2$H$)-one (124)
Figure 37: $^{13}$C NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-
$4H$-benzo$[def]$carbazol-3($2H$)-one (124)
Figure 38: $^1$H NMR of Salviadione (123)
Figure 39: $^{13}$C NMR of Salviadione (123)
$^1$H and $^{13}$C NMR for Chapter 4: Chemoselective Coupling

Figure 40: $^1$H NMR of 2-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (163)
Figure 41: $^{13}$C NMR of 2-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (163)
Figure 42: $^1$H NMR of 2-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene (166)
Figure 43: $^{13}$C NMR of 2-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene (166)
Figure 44: $^1$H NMR of 3-Bromo-2-trifluoromethanesulfonyloxy-nitrobenzene (151)
Figure 45: $^{13}$C NMR of 3-bromo-2-trifluoromethanesulfonyloxy-nitrobenzene (151)
Figure 46: \(^1\)H NMR of 3-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (157)
Figure 47: $^{13}$C NMR of 3-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (157)
Figure 48: $^1$H NMR of 4-Bromo-3-trifluoromethanesulfonyloxy-nitrobenzene (159)
Figure 49: $^{13}$C NMR of 4-Bromo-3-trifluoromethanesulfonyloxy-nitrobenzene (159)
Figure 50: $^1$H NMR of 2-Bromo-3-ethenyl-nitrobenzene (170)
Figure 51: $^{13}$C NMR of 2-Bromo-3-ethynyl-nitrobenzene (170)
Figure 52: $^1$H NMR of 2-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (171)
Figure 53: $^{13}$C NMR of 2-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (171)
Figure 54: $^1$H NMR of 2-Bromo-4-ethenyl-nitrobenzene (172)
Figure 55: $^{13}$C NMR of 2-Bromo-4-ethenyl-nitrobenzene (172)
Figure 56: $^1$H NMR of 2-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (173)
Figure 57: $^{13}$C NMR of 2-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (173)
Figure 58: $^1$H NMR of 2-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (175)
Figure 59: $^{13}$C NMR of 2-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (175)
Figure 60: $^1$H NMR of 2-Bromo-6-ethenyl-nitrobenzene (176)
Figure 61: $^{13}$C NMR of 2-Bromo-6-ethenyl-nitrobenzene (176)
Figure 62: $^1$H NMR of 3-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (177)
Figure 63: $^{13}$C NMR of 3-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (177)
Figure 64: $^1$H NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (178)
Figure 65: $^{13}$C NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (178)
Figure 66: $^1$H NMR of 3-Bromo-4-ethenyl-nitrobenzene (179)
Figure 67: $^{13}$C NMR of 3-Bromo-4-ethenyl-nitrobenzene (179)
Figure 68: $^1$H NMR of 3-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (180)
Figure 69: $^{13}$C NMR of 3-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (180)
Figure 70: $^1$H NMR of 3-Bromo-5-ethenyl-nitrobenzene (181)
Figure 71: $^{13}$C NMR of 3-Bromo-5-ethynyl-nitrobenzene (181)
Figure 72: $^1$H NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (182)
Figure 73: $^{13}\text{C}$ NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (182)
Figure 74: $^1$H NMR of 5-Bromo-2-ethenyl-nitrobenzene (183)
Figure 75: $^{13}\text{C}$ NMR of 5-Bromo-2-ethenyl-nitrobenzene (183)
Figure 76: $^1$H NMR of 4-Ethynyl-2-trifluoromethanesulfonyloxy-nitrobenzene (184)
Figure 77: $^{13}$C NMR of 4-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (184)
Figure 78: $^1$H NMR of 4-Ethynyl-3-trifluromethanesulfonyloxy-nitrobenzene (186)
Figure 79: $^{13}$C NMR of 4-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene (186)
Figure 80: $^1$H NMR of 4-Bromo-3-ethenyl-nitrobenzene (187)
Figure 81: $^{13}$C NMR of 4-Bromo-3-ethenyl-nitrobenzene (187)
Figure 82: $^1$H NMR of 3-iodo-6-ethenyl-nitrobenzene (198)
Figure 83: $^{13}$C NMR of 3-Iodo-6-ethenyl-nitrobenzene (198)
Figure 84: $^1$H NMR of 3-Bromo-6-trifluoromethanesulfonyloxy acetophenone (201)
Figure 85: $^{13}$C NMR of 3-Bromo-6-trifluoromethanesulfonyloxy acetophenone (201)
Figure 86: $^1$H NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy acetophenone (202)
Figure 87: $^{13}$C NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy acetophenone (202)
Figure 88: $^1$H NMR of 6-Ethenyl-3-bromoacetophenone (203)
Figure 89: $^{13}$C NMR of 6-Ethenyl-3-bromoacetophenone (203)
Figure 90: $^1$H NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy anisole (209)
Figure 91: $^{13}$C NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy anisole (209)
Figure 92: $^1$H NMR of 2,3-dinitro-1,4-ethenylbenzene (241)
Figure 93: $^{13}$C NMR of 2,3-dinitro-1,4-ethenylbenzene (241)
Figure 94: $^1$H NMR of 2,3-dinitro-1,4-di(prop-1-en-2-yl)benzene (257)
Figure 95: $^{13}$C NMR of 2,3-dinitro-1,4-di(prop-1-en-2-yl)benzene (257)
Figure 96: $^1$H NMR of 5-iodo-2,4-dinitrophenol (263)
Figure 97: $^{13}$C NMR of 5-iodo-2,4-dinitrophenol (263)
Figure 98: $^1$H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenol (271)
Figure 99: $^{13}$C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenol (271)
Figure 100: $^1$H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenyl trifluoromethanesulfonate (261)
Figure 101: $^{13}$C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenyl trifluoromethanesulfonate (261)
Figure 102: $^1$H NMR of 1-chloro-2,4-dinitro-5-(prop-1-en-2-yl)benzene (273)
Figure 103: $^{13}$C NMR of 1-chloro-2,4-dinitro-5-(prop-1-en-2-yl)benzene (273)
Figure 104: $^1$H NMR of 1,5-dinitro-2,4-di(prop-1-en-2-yl)benzene (260)
Figure 105: $^{13}$C NMR of 1,5-dinitro-2,4-di(prop-1-en-2-yl)benzene (260)
Figure 106: $^1$H NMR of 1,5-dinitro-2-(prop-1-en-2-yl)-4-(prop-1-enyl)benzene (274)
Figure 107: $^{13}$C NMR of 1,5-dinitro-2-(prop-1-en-2-yl)-4-(prop-1-enyl)benzene (274)
Figure 108: $^1$H NMR of (E)-1,5-dinitro-2-(1-phenylprop-1-enyl)-4-(prop-1-en-2-yl)benzene (276)
Figure 109. $^{13}$C NMR of (E)-1,5-dinitro-2-(1-phenylprop-1-enyl)-4-(prop-1-en-2-yl)benzene (276)
Figure 110. $^1$H NMR of 2,5-dimino-4-ethenylphenol (278)
Figure 111: $^{13}$C NMR of 2,5-dinitro-4-ethenylphenol (278)
Figure 112: $^1$H NMR of 2,5-dinitro-4-ethenylphenyl trifluoromethanesulfonate (277)
Figure 113: $^{13}$C NMR of 2,5-dinitro-4-ethenylphenyl trifluoromethanesulfonate (277)
Figure 114: $^1$H NMR of 4-bromo-2,3-dinitrophenol (292)
Figure 115: $^{13}$C NMR of 4-bromo-2,3-dinitrophenol (292)
Figure 116: \(^1\)H NMR of (Z)-methyl 2-(4-bromo-2,3-dinitrophenyl)but-2-enoate (301)
Figure 117: $^{13}$C NMR of (Z)-methyl 2-(4-bromo-2,3-dinitrophenyl)but-2-enoate (301)
Figure 118: $^1$H NMR of (Z)-methyl 2-(2,3-dinitro-4-(prop-1-en-2-yl)phenyl)but-2-enoate

(302)
Figure 119: $^{13}$C NMR of (Z)-methyl 2-(2,3-dinitro-4-(prop-1-en-2-yl)phenyl)but-2-enoate (302)
Figure 120: $^1$H NMR of 1-iodo-3-methyl-2,4-dinitrobenzene (308)
Figure 121: $^{13}$C NMR of 1-iodo-3-methyl-2,4-dinitrobenzene (308)
Figure 122: \textsuperscript{1}H NMR of 2-(3-iodo-2,6-dinitrophenyl)ethanol (312)
Figure 123: $^{13}$C NMR of 2-(3-iodo-2,6-dinitrophenyl)ethanol (312)
Figure 124: $^1$H NMR of 1-iodo-2,4-dinitro-3-ethenylbenzene (313)
Figure 125. $^{13}$C NMR of 1-iodo-2,4-dinitro-3-ethenylbenzene (313)
Figure 126: $^1$H NMR of 1,3-dinitro-4-(prop-1-en-2-yl)-2-ethenylbenzene (314)
Figure 127: $^{13}$C NMR of 1,3-dinitro-4-(prop-1-en-2-yl)-2-ethenylbenzene (314)
Figure 128: 1H NMR of 3,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (326)
Figure 129: $^{13}$C NMR of 3,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (326)
Figure 130: $^1$H NMR of 3-methyl-2,6-dihydropyrrolo[2,3-g]indole (330)
Figure 131: $^{13}$C NMR of 3-methyl-2,6-dihydropyrrolo[2,3-g]indole (330)
Figure 132: $^1$H NMR of Methyl 2,6-dimethyl-1,8-dihydropyrrolo[3,2-g]indole-3-carboxylate (331):
Figure 133: $^{13}$C NMR of Methyl 2,6-dimethyl-1,8-dihydropyrrolo[3,2-g]indole-3-carboxylate (331):
Figure 134: $^1$H NMR of 2,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (332)
Figure 135: $^{13}$C NMR of 2,5-dimethyl-1,7-dihydropyrrolo[3,2-f]indole (332)
Figure 136: $^1$H NMR of 2,5-dimethyl-3-phenyl-1,7-dihydropyrrolo[3,2-f]indole (333)
Figure 137: $^{13}$C NMR of 2,5-dimethyl-3-phenyl-1,7-dihydropyrrolo[3,2-f]indole (333)
Figure 138: $^1$H NMR of 3,4-dibromo-2-nitrobenzaldehyde (343)
Figure 139: $^{13}$C NMR of 3,4-dibromo-2-nitrobenzaldehyde (343)
Figure 140: $^1$H NMR of 4,5-dibromo-2-nitrobenzaldehyde (344)
Figure 141: $^{13}$C NMR of 4,5-dibromo-2-nitrobenzaldehyde (344)
Figure 142: $^1$H NMR of 3,4-dibromo-2-nitrobenzylalcohol (349)
Figure 143: $^{13}$C NMR of 3,4-dibromo-2-nitrobenzylalcohol (349)
Figure 144: $^1$H NMR of 4,5-dibromo-2-nitrobenezylalcohol (350)
Figure 145: $^{13}$C NMR of 4,5-dibromo-2-nitrobenzylalcohol (350)
Figure 146: $^1$H NMR of 3,6-dibromo-2-nitrobenzylalcohol (351)
Figure 147: $^{13}$C NMR of 3,6-dibromo-2-nitrobenzylalcohol (351)
Figure 148: 'H NMR of 2,3-dinitro-4-ethenyltoluene (355)
Figure 149: $^{13}$C NMR of 2,3-dinitro-4-ethenyltoluene (355)
Figure 150: $^1$H NMR of 6-methyl-7-nitroindole (356)
Figure 151: $^1$H NMR of 3,5-dinitro-4-ethenyltoluene (355)
Figure 152: $^{13}$C NMR of 3,5-dinitro-4-ethenyltoluene (355)
Figure 153: $^1$H NMR of 6-methyl-4-nitroindole (356)
Figure 154: $^{13}$C NMR of 6-methyl-4-nitroindole (356)
Figure 155: $^1$H NMR of 5-iodo-2,4-dinitroanisole (363)
Figure 156: $^{13}$C NMR of 5-iodo-2,4-dinitroanisole (363)
Figure 157: $^1$H NMR of 5-ethenyl-2,4-dinitroanisole (365)
Figure 158: $^{13}$C NMR of 5-ethenyl-2,4-dinitroanisole (365)
Figure 159: $^1$H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)anisole (369)
Figure 160: $^{13}$C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)anisole (369)
Figure 161: H NMR of 3-methyl-5-methoxy-6-nitroindole (370)
Figure 162: $^1$H NMR of 3-iodo-2,4-dinitroanisole (364)
Figure 163: $^{13}$C NMR of 3-iodo-2,4-dinitroanisole (364)
Figure 164: $^1$H NMR of 3-ethenyl-2,4-dinitroanisole (367)
Figure 165: $^{13}$C NMR of 3-ethenyl-2,4-dinitroanisole (367)
Figure 166: $^1$H NMR of 3-(prop-1-en-2-yl)-2,4-dinitroanisole (371)
Figure 167: $^{13}$C NMR of 3-(prop-1-en-2-yl)-2,4-dinitroanisole (371)
Figure 168: $^1$H NMR of 3-methyl-5-methoxy-4-nitroindole (372)
Figure 169: $^{13}$C NMR of 3-methyl-5-methoxy-4-nitroindole (372)