2008

Synthesis of azaindoles, diazaindoles, and advanced carbazole alkaloid intermediates via palladium-catalyzed reductive N-heteroannulation

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**Synthesis of Azaindoles, Diazaindoles, and Advanced Carbazole Alkaloid
Intermediates *via* Palladium-Catalyzed Reductive *N*-Heteroannulation**

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Thesis submitted to the
Eberly College of Arts and Sciences
at West Virginia University
in partial fulfillment of the requirements
for the degree of

Master of Science
in
Chemistry

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2008

Keywords: Pd-Catalyzed *N*-Heteroannulations, Azaindoles, Diazaindoles
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Abstract

Synthesis of Azaindoles, Diazaindoles, and Advanced Carbazole Alkaloid Intermediates *via* Palladium-Catalyzed Reductive *N*-Heteroannulation

Grissell M. Carrero-Martínez

Over the years, azaindoles and diazaindoles have generated an increased interest due to their structural similarities with indoles and their potential as pharmacologically active compounds. A mild and efficient methodology has been developed for the synthesis of azaindoles and diazaindoles. This novel procedure includes a palladium-catalyzed reductive *N*-heteroannulation as the key step. This methodology was successfully applied to the synthesis of 4-azaindole, 2-phenyl-5-azaindole, 2-phenyl-6-azaindole, and 7-azaindole. In addition, this method was efficiently utilized to synthesize 2-phenyl-4,6-diazaindole and 2-phenyl-4,5-diazaindole. The reductive *N*-heteroannulation was carried out in the presence of Pd(dba)₂, 1,10-phenanthroline, and carbon monoxide (6 atm) in DMF at 120 °C.

A number of carbazole alkaloids have been synthesized and are of great interest due to the wide array of biological activity these compounds exhibit. Advanced intermediates of carbazole alkaloids were prepared utilizing a Stille coupling to afford the cyclization precursors, 2-(2-nitroarene)-2-cyclohexenones. These precursors were subjected to the palladium-catalyzed cyclization developed, smoothly affording the desired carbazolones. Utilizing this method, the cyclization precursor of an advanced carbazolone intermediate of (+)-Aspidospermidine was obtained in good yield. Reductive cyclizations of Stille coupling products, 2-(2-nitroarene)-2-cyclohexenones, using Pd/C and 1 atm of hydrogen yielded the corresponding 1,2,3,4-tetrahydrocarbazole derivatives.

Acknowledgements

I would like to express my gratitude to my research advisor, Dr. Björn C. G. Söderberg, for his guidance, encouragement, knowledge, and patience. I would also like to thank the members of my committee, Dr. Kung K. Wang and Dr. John H. Penn for their time and assistance. I would also like to express my appreciation to Dr. Novruz Akhmedov for all his help with the data acquisition.

I am very grateful for the help, support, and friendship of my laboratory coworkers. My special thanks go to Chris Dacko, Amy Aylor, Rachel Byerly, and Jeremiah Hubbard, their encouragement, love, and friendship made my graduate experience enjoyable and unforgettable.

I want to thank my family and friends for their love, encouragement, patience, and for always believing in me. I would like to give my special thanks to my mom, María Migdalia, my brother, Franklin, and my sister-in-law Julie because their advice and guidance made this possible. I am certain that I wouldn't be here without any of them.

The financial support of the C. Eugene Bennett Department of Chemistry at West Virginia University and the National Science Foundation is also gratefully acknowledged.

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Part I

Synthesis of Pyrrolopyridines and Pyrrolodiazines
via Palladium-Catalyzed Reductive *N*-Heteroannulation

1. Introduction

Naturally occurring pyrrolopyridines, or azaindoles, are relatively scarce. These indole analogs have created considerable interest as they are essential building blocks in many pharmaceutically relevant drugs. Some azaindole derivatives have shown numerous biological activities such as anthelmintic,¹ non-narcotic antitussive,² antimalarial,³ HIV-1 inhibitory, 5-HT₆ antagonist, and antagonist of gonadotropin releasing hormone,⁴ among others. In addition, these molecules have also found applications in coordination chemistry and material synthesis.⁵ Similarly, pyrrolodiazines have sparked significant interest since they are of ample value as pharmaceutical agents. Some derivatives of pyrrolodiazines have shown antitumor activity,⁶ potent inhibitors of purine nucleoside phosphorylase,⁷ antibiotic,⁸ citostatic, antiviral,⁹ antiglucoma, and anticancer activities.¹⁰

1.1 Pyrrolopyridines

Numerous synthetic methods have been developed for the preparation of substituted indoles, but relatively few have been used for the synthesis of azaindoles (Fig. 1). This may be due to the electron-deficient nature of the pyridine ring which alters the π -system in such a way that those methods either do not work or give poor results.¹¹ In recent

years, thanks to improvements made to classical indole synthesis methods and the development of the organometallic chemistry field, new routes have been developed and reported in the literature for the synthesis of azaindoles.

Figure 1. Structures of 4-, 5-, 6-, and 7-azaindoles **1-4**

Several conditions have been used for the formation of azaindoles; among them is the Reissert synthesis. Originally used for indoles, a 2-nitropicoline and diethyl oxalate are reacted in the presence of sodium ethoxide followed by a reduction/cyclization (Scheme 1)¹¹ to obtain a 2-substituted azaindole.

Scheme 1. Reissert synthesis

Another method which was previously used to prepare azaindoles is the Madelung synthesis. It requires a base and high temperatures for the cyclization of *o*-amido-picolines (Scheme 2).¹² Some of the disadvantages of this method include: (a) the limited

application for azaindole synthesis due to the harsh conditions, (b) the reaction is subject to variables such as quality of reagents, and purity of starting materials, among others, and (c) yields are often erratic and irreproducible.¹³

Scheme 2. Madelung synthesis of 7-azaindole

Extensively used for the synthesis of indoles, the Bartoli cyclization offers an alternate method. It was anticipated that this reaction would provide an efficient pathway to the preparation of azaindoles due to the similarities with indoles. Wang and co-workers reported syntheses of 4- and 6-azaindoles (Scheme 3) using nitropyridines and a large excess of vinyl Grignard.¹⁴ The yields were low to moderate, but comparable to the results obtained in the preparation of indoles. It was also noted that the presence of a large substituent or a halogen next to the nitro moiety gave higher yields of azaindoles.

Scheme 3. Bartoli cyclization

The first example of a Hemetsberger-Knittel synthesis of an azaindole derivative was carried out by Fresneda and co-workers in 2000. A few years later, Roy and co-workers studied the generality of this reaction for a series of substituted 5-, 6-, and 7-azaindoles.¹⁵ This method requires the conversion of a pyridine carboxaldehyde into the azidopyridine acrylate, followed by thermal cyclization (Scheme 4).

Scheme 4. Hemetsberger-Knittel synthesis

Tyler and co-workers used the Batcho-Leimgruber method for the synthesis of aza-C-nucleoside immucillins **20** (Scheme 5).¹¹ Condensation of *o*-nitropicoline with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA), followed by a reductive cyclization of the enamine affords the azaindole.

Scheme 5. Batcho-Leimgruber synthesis of immucillin analog **20**

Scheme 7. Internal and terminal alkynes in the preparation of azaindoles

Based on observations made by McLaughlin and co-workers, they were able to develop an innovative procedure for Sonogashira couplings, as shown in Scheme 8.¹⁷ Reductive amination of the inexpensive 3-amino-2-chloropyridine (**31**) with a ketone or aldehyde, followed by Sonogashira coupling and cyclization, afforded the desired N-protected azaindole derivative **33**.

Scheme 8. Synthesis of 4-azaindole derivative **33**

Kumar *et al*¹⁸ carried out a Suzuki reaction between iodide **34** and vinyl borate **35** followed by acidic hydrolysis to give azaindole **36** (Scheme 9).

Scheme 9. Suzuki coupling for the synthesis of 7-azaindole derivative **36**

Yamanaka *et al*¹⁹ reported the Stille couplings of halonitro- and nitrotriflyloxypyridines with (Z)-1-ethoxy-2-tributylstannylethene using 0.03 equivalents of $\text{PdCl}_2(\text{PPh}_3)_2$, 1.0 equivalent of Et_4NCl in acetonitrile to construct nitrovinylpyridines (Scheme 10). In some instances both, E and Z, isomers were obtained. Subsequent reduction of the nitro moiety in **38** provided aminopyridine, which was successfully cyclized under acidic conditions in good yield.

Scheme 10. Yamanaka's azaindole synthesis

A noteworthy reaction path was investigated and drastically improved by Boehringer-Ingelheim.¹¹ Nitrostyrylpyridines were reduced in the presence of stannous chloride, providing a hydroxylamine intermediate, which was oxidized to the corresponding 1-hydroxy-2-phenylazaindole (Scheme 11). The N-hydroxyindole could be reduced to afford the azaindole in good to excellent yield.

Scheme 11. Boehringer-Ingelheim azaindole synthesis

1.2 Pyrrolodiazines

Pyrrolodiazines, or diazaindoles, are heterocyclic compounds having a pyrrole ring fused to a six-membered aromatic ring containing two nitrogen atoms (Fig 2). In comparison, the pyrrolodiazines have not been studied as extensively as the azaindoles. Most of the methods described in the literature involve a Sonogashira coupling or a condensation reaction with a methyldiazine.

Figure 2. Diazaindoles **43-48**

It is evident that the interest for pyrrolodiazines is increasing, but synthetic routes are scarce. Efforts towards the synthesis of pyrrolopyrazines have been centered on the lithiation of a 2-alkyl substituted pyrazine followed by reaction with aryl nitrile (Scheme 12).²⁰ Disadvantages of this method are the limited amount of commercially available 2-alkyl substituted pyrazines and the low reaction yields, which varies depending on the substituent in the aryl nitrile partner.²¹

Scheme 12. Synthesis of 4,7-diazaindole derivative **50**

Hopkins *et al*²² reported the Sonogashira coupling of readily available 2-amino-3-chloropyrazine (**51**) with phenylacetylene followed by base-induced cyclization (Scheme

13), as well as the one-pot heteroannulation with 2-chloro-3-(*N*-methanesulfonamide)-pyrazine (**53**) (Scheme 14).

Scheme 13. Synthesis of **50** *via* Sonogashira coupling

Scheme 14. One-pot synthesis of **50**

A different methodology was reported by Meltzer and co-workers.²³ Their reaction involved the treatment of 2-amino-3-methylpyrazine (**54**) with the Vilsmeier reagent, followed by hydrolysis of the immonium salt **55** to afford the desired product **56** (Scheme 15). All the couplings reported in the literature involve an aminopyrazine. To our knowledge, there is no published report for a nitropyrazine coupling.

Scheme 15. Synthesis of 4,7-diazaindole derivative **56**

Annulation of a pyrrole ring onto a pyrimidine, construction of a pyrimidine ring onto an aminopyrrole or the transformation of a bicyclic heterocycle are the most commonly used methods for the synthesis of pyrrolopyrimidines.⁶ According to Tumkevicius *et al.*,²⁴ only a few reports exist in the literature regarding the synthesis of 4,5-diazaindole (**45**) from 5-nitro-pyrimidines. Tumkevicius and co-workers developed two-step (Scheme 16) and one-pot (Scheme 17) routes using a Sonogashira coupling for the synthesis of **59**. Comparing both ways, even though there is no intermediate purification, a lower yield was the main disadvantage of the one-pot synthesis.

Scheme 16. Two-step reaction synthesis of **59**

Scheme 17. One-pot synthesis of **59**

The method reported by Townsend *et al.*⁶ started with bromination of 2,4-dimethoxy-6-methyl-5-nitropyrimidine (**60**) (Scheme 18). Bromide displacement was carried out by reaction of sodium cyanide in cold aqueous methanol, followed by cyclization to give the

desired product **63**. In an alternate route (Scheme 19), **60** was treated with *tert*-butoxybis(dimethylamino)-methane (BBDM) to obtain the cyclization precursor **64**. This was catalytically hydrogenated with Raney nickel to get diazaindoles **63**. Low cyclization yield is the major drawbacks for both pathways.

Scheme 18. Synthesis of 4,6-diazaindole derivative **63**

Scheme 19. Synthesis of pyrrolo[3,2-*d*]pyrimidine derivative **63**

Similar reports were described by Tkachenko *et al*²⁵ and Müller *et al*,²⁶ in which various 5-nitro-6-styryluracil derivatives were submitted to reductive cyclization in the presence of zinc (Scheme 20) and triethyl phosphite (Scheme 21), respectively.

Scheme 20. Tkachenko's synthesis of **67**

Scheme 21. Müller's preparation of 4,6-diazaindole derivative **69**

It is worth mentioning the 1,3-dipolar cycloaddition reaction of fervenulin 4-oxide (**70**) with dimethyl acetylenedicarboxylate (DMAD) described by Senga and co-workers (Scheme 22),²⁷ in which they obtained **71** in good yields.

Scheme 22. Senga's synthesis of derivative **71**

A number of pyrrolopyridazines have been prepared. Castle *et al*²⁸ described the synthesis of pyrrolo[3,2-*c*]pyridazine derivative **74**. As shown in Scheme 23, 4-amino-3-methylpyridazine (**72**) was treated with triethyl orthoformate and anhydrous HCl to

obtain **73**. This was treated with diethyl oxalate and potassium ethoxide to obtain the enolate that readily cyclized to **74**, which was obtained in good yield.

Scheme 23. Synthesis of ethyl pyrrolo[3,2-*c*]pyridazine-6-carboxylate 2-oxide **74**

Another method employed is the cyclization of *ortho*-(Boc-amino)alkynylpyridazines. Described by Riether *et al.*,²⁹ this methodology (Scheme 24) utilizes a Sonogashira coupling reaction to obtain the cyclization precursor (**76**). This precursor is submitted to a DBU-mediated cyclization to obtain the desired pyrrolopyridazines in excellent yields.

Scheme 24. Synthesis of 4,5-diazaindole derivative **77**

1.3 Reductive *N*-Heteroannulation Reactions

A new methodology for the synthesis of indoles was developed in our group.³⁰ This procedure involves the palladium-catalyzed reductive *N*-heteroannulation of 2-nitrostyrenes (Scheme 25). The presence of three reagents was found to be critical in this reaction: a palladium catalyst, a ligand (usually a phosphine), and carbon monoxide. This reaction has been successful in the synthesis of a variety of functionalized indoles, carbazoles, and benzimidazoles, among others.

Scheme 25. Palladium-catalyzed *N*-heteroannulation

Similar procedures have been reported in the literature. Watanabe *et al*³¹ published a related procedure in which annulations of nitroarenes with unsaturated groups in the *ortho* position lead to indole formation in the presence of catalytic amount of PdCl₂(MeCN)₂, triphenylphosphine, excess tin dichloride, and 20 atm of carbon monoxide (Scheme 26). Another similar example was reported by Cenini *et al*³² using Pd(TMB)₂/TMPhen (TMBH = 2,4,6-trimethylbenzoic acid; TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline) as the catalyst (Scheme 27).

Scheme 26. Watanabe's indole synthesis

Scheme 27. Cenini's indole synthesis

All previously described methods generally produce good yields of indoles.

Nevertheless, compared to the procedure developed in Söderberg's group, most of these methods employ very harsh reaction conditions. The conditions developed are much milder, proceed at significantly lower pressure and temperature, and do not require the addition of a Lewis Acid such as tin dichloride. Due to the success obtained in the synthesis of a variety of indole, carbazole, and benzimidazole derivatives, we decided to apply this new method to the synthesis of pyrrolopyridines and different pyrrolodiazines. The synthesis and attempted synthesis of these compounds is presented herein.

2. Results and Discussion

2.1 Synthesis of Pyrrolopyridines

It was envisioned that azaindoles could be prepared employing one or two successive palladium-catalyzed reactions. Azaindoles precursors could be prepared by condensation of an *o*-methylnitropyridine and benzaldehyde or utilizing a Stille coupling, similar to the one previously described by Yamanaka, between an *o*-halonitropyridine and vinyltributyl stannane. The precursors could then be submitted to the palladium-catalyzed *N*-heteroannulation, which could provide the corresponding azaindoles, as shown in Scheme 28.

Scheme 28. Strategy for azaindole preparation

Commercially available 2-chloro-3-nitropyridine was subjected to two consecutive palladium-catalyzed reactions. Following the procedure reported by Li *et al.*,³³ 2-vinyl-3-nitropyridine (**84**) was obtained and subsequent cyclization in the presence of Pd(dba)₂, 1,10-phenanthroline and 6 atm of carbon monoxide, afforded the desired 4-azaindole (**1**) (Scheme 29). As shown in Scheme 30, 2-nitro-3-trifluoromethane-sulfonyloxy pyridine

(**85**) was formed by reaction of commercially available 3-hydroxy-2-nitropyridine with trifluoromethanesulfonic anhydride in pyridine. A similar protocol to that described for **1**, a Stille coupling followed by cyclization, was used on **85** to obtain 7-azaindole (**4**) in moderate yield.

Scheme 29. Synthesis of 4-azaindole **1**

Scheme 30. Synthesis of 7-azaindole **4**

The synthesis of 2-phenyl-5-azaindole (**89**) started with nitration of the commercially available 3-picoline N-oxide (Scheme 31). Condensation of the nitrated product **87** with benzaldehyde followed by palladium-catalyzed *N*-heteroannulation afforded the desired deoxygenated azaindole, as confirmed by X-ray crystallography, in excellent yield. In the same manner, condensation of 3-nitro-4-picoline with benzaldehyde gave **90**, which was cyclized to 2-phenyl-6-azaindole (**91**) in excellent yield (Scheme 32).

Scheme 31. Synthesis of 2-phenyl-5-azaindole **89**

Scheme 32. Synthesis of 2-phenyl-6-azaindole **91**

2.2 Synthesis of Pyrrolopyrimidines

The synthesis to a pyrrolo[3,2-*d*]pyrimidine derivative commenced with the treatment of commercially available 4,6-dihydroxy-5-nitropyrimidine with phosphorus oxychloride and *N,N*-diethylaniline to obtain 4,6-dichloro-5-nitropyrimidine (**92**) in good yield (Scheme 33).

Scheme 33. Synthesis of 4,6-dichloro-5-nitropyrimidine **92**

The next step was a coupling reaction to obtain a vinyl group *ortho* to the nitro moiety. As shown in Table 1, all the coupling attempts to obtain the desired product were ineffective. Variations of the Stille and Suzuki couplings were attempted with **92** but all failed. In an effort to obtain a more reactive substituent, it was also attempted to get halogens and triflates but these endeavors were futile.

Entry	X	R	Conditions (% Yield)	Temp (°C)	Time (h)
1	Cl	vinyl	CH ₂ CHSnBu ₃ , PdCl ₂ (PPh ₃) ₂ , Et ₄ NCl, CH ₃ CN	110	73
2 ³⁴	Cl	vinyl	CH ₂ CHSnBu ₃ , PdCl ₂ (PPh ₃) ₂ , PPh ₃ , PhCH ₃ , N ₂	110	96
3	Cl	vinyl	CH ₂ CHSnBu ₃ , Pd(dba) ₂ , PPh ₃ , CuI, DMF	rt	43
4	Cl	vinyl	CH ₂ CHSnBu ₃ , Pd(dba) ₂ , PPh ₃ , CuI, DMF	80	48
5 ³⁵	Cl	vinyl	22 , Pd(OAc) ₂ , PPh ₃ , Na ₂ CO ₃ , DME	85	18
6 ³⁶	Cl	vinyl	22 , PdCl ₂ (PPh ₃) ₂ , K ₃ PO ₄ •7H ₂ O, THF	70	20.5
7 ³⁷	Cl	vinyl	22 , Pd(dba) ₂ , PPh ₃ , K ₂ CO ₃ , H ₂ O/DME	90	23
8 ³⁸	Cl	I	HI	rt	24
9	OH	OTf	OTf ₂ , Et ₃ N, N ₂	rt	21
10	OH	OTf	OTf ₂ , <i>i</i> Pr ₂ Net, CH ₂ Cl ₂ , N ₂	0	3
11 ³⁹	OH	Br	P ₂ O ₅ , TBAB, PhCH ₃	100	3

Table 1. Coupling conditions evaluated

The difficulty of the couplings led us to examine the condensation reaction previously used with the pyridines. Remennikov *et al*⁴⁰ reported the conversion of **92** to 4-methoxy-6-methyl-5-nitropyrimidine (**94**), which would allow the condensation reaction to occur. Decarboxylation of **93** and subsequent condensation of the resulting compound **94** with benzaldehyde afforded the desired 4-methoxy-5-nitro-6-styrylpyrimidine (**95**). Treatment of this compound with Pd(dba)₂ in the presence of 1,10-phenanthroline and DMF gave the corresponding 4-methoxy-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (**96**) in high yield.

Scheme 34. Synthesis of 5*H*-pyrrolo[3,2-*d*]pyrimidine derivative **96**

For the synthesis of the 7*H*-pyrrolo[2,3-*d*]pyrimidine derivative, due to the very limited starting material availability, the only plausible route was condensation of 2,4-dihydroxy- or 2,4-dichloro-5-methyl-6-nitropyrimidine, followed by standard cyclization conditions. As shown in Scheme 35, various attempts were made, but no nitration of either thymine or 2,4-dichloro-5-methylpyrimidine (**97**) occurred.

Scheme 35. Attempted synthesis of 6-nitro-substituted pyrimidine

Taking into consideration other work with diazines, it was believed that the nitration could proceed with little or no problem with thymine N-oxide or 2,4-dichloro-5-methylpyrimidine N-oxide. Two reaction conditions were tried, but failed to give any N-oxide (Scheme 36).

Scheme 36. Attempted preparation of pyrimidine N-oxides

Due to the lack commercial availability and difficulty in preparation of a suitable pyrimidine, it was not feasible to design a reaction route for the synthesis of 7*H*-pyrrolo[2,3-*d*]pyrimidine or a derivative.

2.3 Synthesis of Pyrrolopyridazines

The efforts started with 3-chloro-6-methylpyridazine, due to the limited commercially available starting materials. To obtain the cyclization precursors, it was envisioned that it was possible to perform either one of the procedures previously described with a nitro-3-chloro-6-methylpyridazine. After the initial nitration attempt (Scheme 37)³⁵ failed and reviewing the literature, it was concluded that it was necessary to oxidize a nitrogen for

the nitration reaction to proceed. It is important to note that nitration occurs *para* to the N-oxide. At this early stage in the synthesis, it was not relevant which nitrogen was oxidized, considering that nitration at either carbon would allow us to carry on with the synthesis.

Scheme 37. Failed nitration of 3-chloro-6-methylpyridazine

Abiding by the procedure described by Hideo and co-workers,⁴¹ a separable mixture of three products was obtained, all in very low yields. After several trials to increase the yields or to get one predominant product and after extensive NMR studies, it was concluded that the mixture consisted of **98**, **99**, and **100** (Scheme 38). In addition, when submitting **98** to the conditions shown in Scheme 37, no nitrated product was obtained.

Scheme 38. Pyridazine N-oxides **98-100**

Re-evaluation of the data acquired and the literature, led to the synthesis of the symmetrical 3,6-dimethylpyridazine (**101**), which would give only one N-oxide. Following the publications of Foote *et al*⁴² and Fariña *et al*⁴³ the desired pyridazine was obtained (Scheme 39), which gave excellent results for the oxidation. Nitration of the

resulting N-oxide **102** gave good yield and was treated with benzaldehyde to afford the desired 6-methyl-4-nitro-3-styrylpyridazine 1-oxide (**104**). Palladium-catalyzed reductive *N*-heteroannulation of **104** gave 3-methyl-6-phenyl-5*H*-pyrrolo[3,2-*c*]pyridazine (**105**) in good yield.

Scheme 39. Synthesis of 4,5-diazaindole derivative **105**

2.4 Attempted Synthesis of Pyrrolopyrazine

It was envisioned that the synthesis towards 5*H*-pyrrolo[2,3-*b*]pyrazine or a derivative could begin using the procedure reported by Kaupp *et al*⁴⁴ to obtain 1,4-dihydroquinoxaline-2,3-dione (**106**). As shown in Scheme 40, *o*-phenylenediamine was reacted with benzil to make the desired product **106**. This was treated with phosphorus oxychloride and phosphorus pentachloride to form 2,3-dichloroquinoxaline (**107**) in good yield. Dry ammonia was bubbled through to get **108**. According to Kaupp, they

followed Hartman and Schwering⁴⁵ methodology to obtain 2-chloro-3-nitroquinoxaline. This was done by reacting 2-amino-3-chloroquinoxaline with trifluoromethanesulfonic anhydride and dimethylsulfoxide, followed by oxidation with m-CPBA and then ozone. It was decided not to follow this procedure on account of the reaction conditions and also because Kaupp and co-workers reported a low yield. In an effort to find an alternate oxidation route, two ways were evaluated, one utilizing peroxyacetic acid in CHCl₃ and the other using hydrogen peroxide, and titanium superoxide (**109**)⁴⁶ in methanol but these efforts were unsuccessful.

Scheme 40. Initial attempt towards 1*H*-pyrrolo[2,3-*b*]quinoxaline

The next trial involved the synthesis of 2-hydroxy-3-nitro-5,6-diphenylpyrazine (**111**). Following the procedure reported by Kaftory and co-workers,⁴⁷ glycineamide hydrochloride was reacted with benzil under basic conditions to obtain 3-hydroxy-5,6-diphenylpyrazine (**110**), which was nitrated to obtain **111**⁴⁸ in good yield (Scheme 41). Formation of the coupling precursors **112** and **113** were accomplished in good and quantitative yields, respectively.

Scheme 41. Synthesis of coupling precursors **112** and **113**

As shown in Table 2, several Stille and Suzuki couplings were attempted. Reaction of **112** with vinyltributyl stannane (Entry 1) gave the desired product, but it was not possible to obtain a pure sample. In an effort to circumvent this problem, a *N*-heteroannulation of the crude sample of the Stille coupling was attempted, but no cyclization product was observed.

Entry	X	R	Conditions (% Yield)	Temp (°C)	Time (h)
1	OTf	H	CH ₂ CHSnBu ₃ , PdCl ₂ (PPh ₃) ₂ , Et ₄ NCl, CH ₃ CN (54)	100	92
2	OTf	H	CH ₂ CHSnBu ₃ , PdCl ₂ (PhCN) ₂ , Ph ₃ As, CuI, NMP	80	23
3	OTf	CO ₂ Et	, PdCl ₂ (PPh ₃) ₂ , Et ₄ NCl, CH ₃ CN	100	67
4 ⁴⁴	OTf	H	22 , Pd(dba) ₂ , PPh ₃ , K ₂ CO ₃ , H ₂ O/DME	90	20
5	OTf	H	22 , Pd(dba) ₂ , PPh ₃ , LiCl, K ₂ CO ₃ , H ₂ O/DME	90	16
6 ⁴⁹	Cl	H	22 , Pd(OAc) ₂ , CH ₃ ONa, CH ₃ OH	rt	72

Table 2. Stille and Suzuki coupling attempts

After the ineffective trials with the Stille and Suzuki coupling, we tried to obtain a methylpyrazine to perform a condensation with benzaldehyde. In an effort to obtain 2-methyl-3-nitro-5,6-diphenylpyrazine, various routes were attempted. The first involved the procedure reported by Remennikov *et al*, which gave excellent results with pyrimidine. The second route, employing trimethyl aluminum, was described by Ohta and co-workers.⁵⁰ Unfortunately, both methods failed to give the desired products (Scheme 42).

Scheme 42. Attempts towards a methyl pyrazine

In a different attempt, the methodology described by Guo⁵¹ was followed to obtain the desired **115** (Scheme 43). This compound was treated with fuming nitric acid and glacial acetic acid, but no nitration product was observed. Also, **115** was heated in a fuming nitric acid and concentrated sulfuric acid mixture. This attempt also failed to produce the desired nitrated product.

Scheme 43. Synthesis of 5-methyl-2,3-diphenylpyrazine **115**

Our final attempts involved Sonogashira couplings between **112** or **113** and phenyl-acetylene or trimethylsilylacetylene. Table 3 shows the different conditions utilized in the Sonogashira reaction.

Entry	X	R	Conditions	Temp (°C)	Time (h)
1	OTf	Ph	Phenylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N/THF	rt	19
2	OTf	Ph	Phenylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, NMP	50	87
3	OTf	Ph	Phenylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N, N ₂	60	48
4	OTf	Ph	Phenylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	70	91
5	Cl	Ph	Phenylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	rt	22
6	Cl	Ph	Phenylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	80	42
7	Cl	Ph	Phenylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	70	92
8	OTf	TMS	Trimethylsilylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	90	23
9	OTf	TMS	Trimethylsilylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	90	92
10	OTf	TMS	Trimethylsilylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	90	180
11	OTf	TMS	Trimethylsilylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	90	180
12	Cl	TMS	Trimethylsilylacetylene, PdCl ₂ (PPh ₃) ₂ , CuI, Et ₃ N	90	22

Table 3. Sonogashira coupling conditions

3. Conclusion

The methodology developed by the Söderberg group was successfully applied for the synthesis of various azaindoles and pyrrolodiazines. Total synthesis of 4-, 5-, 6-, and 7-azaindoles (**1-4**) have been achieved using a condensation reaction with benzaldehyde or

a Stille coupling followed by palladium-catalyzed reductive *N*-heteroannulation as the key step. Similarly, syntheses of 5*H*-pyrrolo[3,2-*d*]pyrimidine derivative (**96**) and 5*H*-pyrrolo[3,2-*c*]pyridazine derivative (**105**) have been achieved. The ability to synthesize certain compounds was severely impaired by the limited availability and/or the difficulty in preparing suitable starting materials. It can be concluded that the developed methodology will be successful in the synthesis of the remaining diazaindoles when adequate cyclization precursors become available either by viable commercial starting materials or by appropriate synthesis.

Part II

Synthesis of Carbazolones as an Advanced Intermediate to (+)-Aspidospermidine

1. Introduction

Carbazole alkaloids have been of great interest due to their pharmacological potential and variety of biological activities. These natural products show properties such as antitumor, antifungal, antibiotic, as well as having inhibitory effects on mitosis and antimalarial activity.⁵² Most of these compounds have a one-carbon substituent in the 3-position and an oxygenated functionality in the 1- or 2- position. The Söderberg group has been interested in a number of these compounds, many of which are part are found in plants of the genus *Murraya* and *Aspidosperma*.

Carbazolones are carbazole derivatives that, like carbazole alkaloids, are interesting synthetic targets because of their biological activity. Tetrahydrocarbazolones have been greatly used as advanced intermediates in synthetic efforts towards a number of naturally occurring carbazole alkaloids (Figure 3). A variety of methods have been used to prepare carbazolones. A common approach to the preparation of these types of compounds is *via* the Fischer indole synthesis. A Japp-Klingemann condensation of diazonium salts with 2-(hydroxymethylene)-1-cyclohexanones can be used to obtain hydrazones, which can be subjected to the Fischer indole synthesis to get the desired tetrahydrocarbazolone.⁵³ The downside of this method is the highly acidic reaction

conditions and regioisomeric product formation when asymmetrical or 3-substituted analogs are used.

Figure 3. Carbazole alkaloids

Palladium-catalyzed Heck-type reactions (Scheme 44)⁵⁴ and aryne condensation of enamines in the presence of NaNH_2 -*t*BuONa (Scheme 45)⁵⁵ have also been used to produce carbazolones.

Scheme 44. Formation of carbazolone derivative **117**

Scheme 45. Preparation of carbazolone **119**

(+)-Aspidospermidine (Figure 3), the parent compound of the *Aspidosperma* alkaloids, has been the fundamental target for most of the efforts regarding this family of compounds. This basic structure retains the characteristic pentacyclic skeleton, but is not of pharmacological relevance and contains no sensitive functional groups. This is the main reason why this compound is frequently used as a stepping stone for the development of new synthetic pathways that might aid in the construction of more complex *Aspidosperma* alkaloids. Among the pioneering methods developed for this purpose are the Stork's Fischer-indole,⁵⁶ Harley-Mason's indoloquinolizidine rearrangement,⁵⁷ Büchi's Diels-Alder,⁵⁸ and Overman's aza-Cope rearrangement. More recent methodologies include the one published by Aubé and co-workers,⁵⁹ featuring an intramolecular Schmidt reaction (Scheme 46).

Scheme 46. Aubé's synthesis of (+)-Aspidospermidine

Another method recently developed was reported by Heathcock *et al*,⁶⁰ in which the key step is an intramolecular cascade reaction that simultaneously forms three rings (Scheme 47). Also, a short six-step synthesis (Scheme 48) was reported by Coldham and co-workers,⁶¹ in which three of the five rings are constructed in one step. ($\pm$)-Aspidospermidine was obtained in 40% overall yield.

Scheme 47. Heathcock's synthesis of (±)-Aspidospermidine

While there are many methods for the preparation of carbazolones and carbazoles, these methods have some drawbacks. Some of the traditional methods lack regioselectivity and/or employ harsh conditions that may affect some functional groups. Another disadvantage is the availability of starting materials. Regioselectivity is not a problem in the method developed by the Söderberg group and numerous functional groups tolerate

the milder reaction conditions. A new synthesis of tetrahydrocarbazolones used as advanced intermediates in the synthesis of (+)-Aspidospermidine is herein reported.

Scheme 48. Short synthesis of (±)-Aspidospermidine

2. Results and Discussion

Carbazolones could be prepared *via* the *N*-heteroannulation of 2-(2-nitrophenyl)-2-cycloalkenones (Scheme 49), but it was necessary to develop a method to synthesize a variety of substituted 2-(2-nitrophenyl)-2-cycloalkenones.

Scheme 49. General synthetic strategy

It was decided that the best route to obtain cyclization precursors was utilizing a Stille coupling reaction between cycloalkenones and nitrobenzenes (Scheme 50). This type of coupling, between 2-iodocycloalkenones and aryl stannanes using bis(benzonitrile)-palladium dichloride ($\text{PdCl}_2(\text{PhCN})_2$), triphenylarsine (Ph_3As) and copper iodide (CuI) in *N*-methylpyrrolidinone (NMP), was reported by Johnson *et al.*⁶² This methodology was successfully adapted by the Söderberg group to obtain a number of Stille coupling products.⁶² The coupling products could be easily cyclized to get the desired carbazolones in good yields.

Scheme 50. General Stille coupling strategy

Efforts towards the synthesis of (+)-Aspidospermidine centered in obtaining **142**. This key carbazolone intermediate was part of the synthesis reported by Desmaele and co-workers, as previously described.⁶³ As shown in Scheme 51, with a slight modification of literature procedures, it was possible to obtain cyclohexenone **139** in good yield. This compound was treated with iodine and pyridine in carbon tetrachloride to get **140** in 73% yield. Stille coupling between **140** and **141** was successfully accomplished utilizing the previously described conditions.

Scheme 51. Synthesis of carbazolone precursor **142**

3. Conclusion

We have effectively applied the methodology to the synthesis of (+)-Aspidospermidine key intermediate **142**. This methodology can be use as a stepping stone to obtain other compounds of the *Aspidosperma* family. The synthesis has been achieved using a Stille coupling reaction followed by a palladium-mediated reductive *N*-heteroannulation as the

key steps. These new conditions provide a generally more efficient and higher yielding than previous methods utilized for the synthesis of these alkaloids.

Part III

Synthesis of Advanced Intermediates of Tetrahydrocarbazole Derivatives *Via* Palladium-Catalyzed Hydrogenation Reactions

1. Introduction

TiCl₃ reduction of compounds analogous to **143** has been reported by various groups.⁶⁴

Reaction of **143** with aqueous TiCl₃ in acetone gave 1,2,3,4-tetrahydrocarbazole (**144**) in good yield, as shown in Scheme 52.

Scheme 52. Reduction with TiCl₃

Other conventional methods used in the formation of carbazoles such as the Fischer indoles synthesis⁶⁵ and palladium-catalyzed annulations between iodoanilines and ketones often suffer from a lack of regioselectivity and produce isomers (Scheme 53).

Scheme 53. Synthesis of methyl-substituted 1,2,3,4-tetrahydrocarbazoles

There is only one example in the literature reported by Tanaka and co-workers,⁶⁶ in which a nitrobenzene and an α,β -unsaturated ketone are successfully cyclized to the indole in the presence of PtO_2 and hydrogen (Scheme 54).

Scheme 54. Tanaka's indole synthesis of **149**

In a study performed in the Söderberg group, it was discovered that it is possible to obtain 1,2,3,4-tetrahydrocarbazoles from direct reduction of the nitro group in 2-(2-nitrophenyl)-2-cyclohexen-1-ones in the presence of Pd/C and 1 atm of hydrogen (Scheme 55). The synthesis of advanced carbazole alkaloid intermediates *via* reductive cyclization is herein reported.

Scheme 55. General reductive cyclization

2. Results and Discussion

The synthesis of the advanced intermediate **152** was effectively accomplished (Scheme 56). Silylation of 4-methylcyclohexanone with trimethylsilyl chloride in the presence of triethylamine and DMF afforded **150** in excellent yield. This was followed by a palladium-catalyzed dehydrosilylation, Saegusa oxidation,⁶⁷ to obtain 4-methyl-2-cyclohexen-1-one (**151**). A reason for the seemingly low yield might be the volatility of the compound. Iodination of **151** was accomplished in the presence of iodine and carbon tetrachloride in pyridine. This intermediate can be coupled with a nitroarene utilizing a Stille coupling or an Ullman-type coupling, similar to the one described by Banwell and co-workers.⁶⁸ Finally, the coupling product can be submitted to a palladium-catalyzed reductive cyclization in the presence of Pd/C and hydrogen (1 atm) to obtain the desired 3-methyl-1,2,3,4-tetrahydrocarbazole.

Scheme 56. Synthesis of advanced intermediate **152**

As shown in Scheme 57, reaction of 2-cyclohexenone in the presence of iodine and carbon tetrachloride in pyridine afforded **153** in high yield. This was submitted to a palladium-mediated Ullman cross-coupling with *o*-bromonitrobenzene, to obtain the desired coupling product **154** in good yield. Instead of utilizing a palladium-catalyzed cyclization, it was decided to follow the TiCl_3 cyclization procedure reported by Buchwald and co-workers.⁶⁹ Treatment of **154** with TiCl_3 in the presence of ammonium acetate in ethanol gave the carbazolone product **155** in low yield, the desired carbazole was not observed. This method was more successful for the synthesis of 2,3-substituted indoles than for the formation of tetrahydrocarbazole and tetrahydrocarbazolone **155**.

Scheme 57. Synthesis of carbazalone **155**

Synthesis of 8-methyl-1,2,3,4-tetrahydrocarbazole (**161**) started with commercially available 3-methyl-2-nitrobenzoic acid, which was treated with thionyl chloride to obtain the corresponding acid chloride, followed by addition of sodium azide afforded **156** (Scheme 58). This was heated in acetic acid to give 3-methyl-2-nitroaniline (**157**) in quantitative yield. A Sandmeyer reaction was performed to get **158** in 35% yield. Conversion to aryl stannane **159** was achieved by reaction of **158** with hexabutyltin in the presence of $\text{Pd(PPh}_3)_4$, formed *in situ*, in toluene. Stille coupling between **153** and **159**, using $\text{PdCl}_2(\text{PhCN})_2$, Ph_3As , and CuI in NMP, gave **160** in 76% yield. Reductive cyclization of the coupling product was achieved using Pd/C and hydrogen (1 atm) in methanol. Under these conditions we obtained **161** and **162**, which indicates that the reduction of the cyclohexenone double bond occurs prior to the nitro group reduction. It has been demonstrated that submitting **162** to Pd/C-H_2 conditions gives **161**.⁷⁰

Scheme 58. Synthesis of carbazole **161**

3. Conclusion

We have successfully developed a mild and efficient reaction pathway to carbazole derivatives. The key steps in this route are two consecutive palladium-catalyzed reactions, a Stille coupling followed by reductive cyclization in the presence of palladium on carbon and H_2 .

Part IV

Experimental Section

1. General Procedures

All NMR spectra were determined in CDCl_3 at 600 MHz (^1H NMR) and 150 MHz (^{13}C NMR) unless otherwise stated. The chemical shifts are expressed in δ values relative to Me_4Si (0.00, ^1H and ^{13}C) or CDCl_3 (7.26, ^1H and 77.00, ^{13}C) 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 obtained. Results of APT (attached proton test) ^{13}C NMR experiments are shown in parenthesis, where relative to CDCl_3 , (-) denotes CH_3 or CH , and (+) denotes CH_2 or C .

Tetrahydrofuran (THF), toluene, and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Pyridine, triethylamine, hexanes, acetonitrile, diisopropylamine, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time they are used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure or by bulb-to-bulb distillation under reduced pressure. Chromatography was performed on silica gel 60 (35-75 μm , VWR). Melting points were determined on a MelTemp and are uncorrected. Elemental analyses were

performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.

2. Experimental Details

1*H*-pyrrolo[3,2-*b*]pyridine²⁴ (**1**)

To an oven-dried, threaded ACE glass pressure tube was added 3-nitro-2-vinylpyridine⁴⁰ (**84**) (190 mg, 1.27 mmol), Pd(dba)₂ (36.1 mg, 0.0628 mmol), 1,10-phenanthroline (25.0 mg, 0.126 mmol), and anhydrous DMF (4 mL). The tube was fitted with a pressure head, the solution saturated with CO (four cycles to 6 atm) and heated to 120 °C (42h). The solvent was removed by bulb-to-bulb distillation under reduced pressure. The crude product was purified by flash chromatography (Hexanes/EtOAc, 3:7) to give **1** (97.6 mg, 0.826 mmol, 65%) as a light yellow solid. mp 126-128 °C (Lit. 125-126 °C).

2-nitro-3-vinylpyridine (**86**)

A mixture of 2-nitro-3-trifluoromethanesulfonyloxy pyridine²⁴ (**85**) (507 mg, 1.86 mmol) vinyl tri-*n*-butyl stannane (700 mg, 2.21 mmol), tetraethylammonium chloride (305 mg, 1.84 mmol), PdCl₂(PPh₃)₂ (16.8 mg, 0.0239 mmol) in CH₃CN (10 mL) was heated to reflux (67h). The mixture was diluted in CHCl₃ (10 mL) and H₂O (10 mL) and filtered

through Celite. The filtrate was extracted with CHCl_3 (30 mL) and washed with 10% NH_4OH (3 x 15 mL). The organic layer was dried (MgSO_4) and concentrated under vacuum. The crude was purified by flash chromatography (Hexanes/EtOAc, 8:2) to give **86** (236 mg, 1.57 mmol, 85%) as a yellow solid. mp 34-36 °C. ^1H NMR (CDCl_3 , 600 MHz): δ 5.61 (d, J = 10.8 Hz, 1H), 5.86 (d, J = 17.4 Hz, 1H), 6.98 (dd, J = 11.4, 17.4 Hz, 1H), 7.58 (dd, J = 4.2, 7.8 Hz, 1H), 8.09 (dd, J = 1.8, 7.8 Hz, 1H), 8.46 (dd, J = 1.8, 4.8 Hz, 1H). ^{13}C NMR (CDCl_3 , 150 MHz): δ 121.2(+), 126.9(+), 127.7(-), 129.5(-), 137.6(-), 147.5(-). IR (neat) 1531 cm^{-1} . Anal. Calcd for $\text{C}_7\text{H}_6\text{N}_2\text{O}_2$: C, 56.00; H, 4.03. Found: C, 56.28; H: 4.23.

1H-pyrrolo[2,3-*b*]pyridine² (4)

Reaction of 2-nitro-3-vinylpyridine (**86**) (506 mg, 3.37 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (95.8 mg, 0.167 mmol), 1,10-phenanthroline (67.1 mg, 0.338 mmol), and DMF (4 mL), as described for **1** (7.5d), gave, after chromatography (EtOAc/MeOH, 9:1), **4** (163 mg, 1.38 mmol, 41%) as a light yellow solid. mp 103-104 °C (Lit. 105-106 °C).

2-phenyl-1H-pyrrolo[3,2-*c*]pyridine¹ (89)

A mixture of 4-nitro-3-styrylpyridine N-oxide⁷¹ (**88**) (102 mg, 0.421 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (11.5 mg, 0.0200 mmol), 1,10-phenanthroline (8.3 mg, 0.042

mmol), and anhydrous DMF (5 mL), was heated to 120 °C (22h) as described for **1**. The crude product was purified by flash chromatography (EtOAc) to give **89** (74.4 mg, 0.383 mmol, 91%) as yellow crystals. mp 282-283 °C (Lit.¹ 282-283 °C).

2-phenyl-1H-pyrrolo[2,3-c]pyridine⁷² (91)

Reaction of 3-nitro-4-styrylpyridine³³ (**90**) (131 mg, 0.579 mmol) in the presence of Pd(dba)₂ (16.6 mg, 0.0289 mmol), 1,10-phenanthroline (11.6 mg, 0.0585 mmol), and anhydrous DMF (4 mL), as described for **1** (24h), gave, after chromatography (EtOAc/MeOH, 9:1) **91** (98.5 mg, 0.507 mmol, 87%) as a light yellow solid. mp 224-226 °C (Lit.¹ 223-225 °C).

4-acetylaceton-6-chloro-5-nitropyrimidine⁴⁷ (93)

To a suspension of NaH (104 mg, 4.33 mmol) in anhydrous THF (10mL) under nitrogen, 2,4-pentanedione (0.445 mL, 4.33 mmol) was added and stirred until all the H₂ evolved (30 min). 4,6-dichloro-5-nitropyrimidine⁷³ (**92**) (500 mg, 2.58 mmol) was added and stirred under nitrogen (1h). An additional portion of NaH (62.0 mg, 2.58 mmol) was added to the reaction mixture (3h). The THF was removed to give **93** (425 mg, 1.65 mmol, 64%) as a light brown solid. mp 118-122 °C (Lit.⁴⁷ 120-122 °C).

4-methoxy-6-methyl-5-nitropyrimidine⁴⁷ (**94**)

A mixture of 4-acetylacetone-6-chloro-5-nitropyrimidine (**93**) (2.01 g, 7.80 mmol), KOH (875 mg, 15.6 mmol) in CH₃OH (35 mL) was heated to reflux (4h). The crude was purified by flash chromatography (Hexanes/EtOAc, 1:1) to give **94** (907 mg, 5.36 mmol, 69%) as a light yellow solid. mp 75-76 °C (Lit. 81-83 °C).

4-methoxy-5-nitro-6-styrylpyrimidine (**95**)

A mixture of 4-methoxy-6-methyl-5-nitropyrimidine (**94**) (163 mg, 0.964 mmol), benzaldehyde (0.125 mL, 1.23 mmol), and piperidine (0.050 mL, 0.506 mmol) in CH₃OH (5 mL) was heated to reflux (15.5h). The precipitate was dissolved in acetone and purified by flash chromatography (Hexanes/EtOAc, 6:4) to give **95** (101 mg, 0.393 mmol, 41%) as a light yellow solid. mp 135-137 °C. ¹H NMR (CDCl₃, 600 MHz): δ 4.12 (s, 3H), 7.02 (d, *J* = 15.0 Hz, 1H), 7.39-7.42 (m, 3H), 7.59 (dd, *J* = 7.8, 2.4 Hz, 2H), 8.17 (d, *J* = 15.6 Hz, 1H), 8.74 (s, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ 55.3 (-), 117.5 (-), 128.3 (-), 129.0 (-), 130.4 (-), 134.8 (+), 142.1 (-), 142.1 (+), 154.2 (+), 157.3 (-), 161.4 (+). IR (neat): 1637, 1572, 1521 cm⁻¹.

4-methoxy-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine (**96**)

Reaction of 4-methoxy-5-nitro-6-styrylpyrimidine (**95**) (251 mg, 0.976 mmol), Pd(dba)₂ (27.7 mg, 0.0482 mmol) and 1,10-phenanthroline (19.3 mg, 0.973 mmol) in DMF (5 mL), as described for **1** (24h), gave, after chromatography (Hexanes/EtOAc, 2:8; EtOAc; EtOAc/MeOH, 9:1; successively) **96** (180 mg, 0.799 mmol, 82%) as a white solid. mp 222-223 °C. ¹H NMR (DMSO-d₆, 600 MHz): δ 4.11 (s, 3H), 7.05 (d, *J* = 1.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 8.4 Hz, 2H), 8.01 (dd, *J* = 9.0, 1.2 Hz, 2H), 8.41 (s, 1H), 12.3 (br s, 1H); ¹³C NMR (DMSO-d₆, 150 MHz): δ 53.1 (-), 99.3 (-), 115.5 (+), 126.1 (-), 128.7 (-), 128.9 (-), 131.0 (+), 142.4 (+), 149.4 (-), 150.8 (+), 155.2 (+). IR (neat): 2754, 1624, 1526, 1457, 1393, 1345, 1293, 1120 cm⁻¹. Anal. Calcd for C₁₃H₁₁N₃O: C, 69.32; H, 4.92. Found: C, 69.61; H, 5.19.

3,6-dimethylpyridazine^{50,51} (**101**)

To a solution of 2,5-dimethylfuran (3.01g, 31.3 mmol) in methanol (150 mL) at 0 °C, hydrogen peroxide was added (50%, 6.00 mL, 103 mmol). The solution was stirred and NaOCl (5%, 21 mL, 14.1 mmol) was slowly added and stirred (15 min). Hydrazine hydrate (51%, 5.90 mL, 96.5 mmol) was added and allowed to warm up to room temperature. The methanol was removed under reduced pressure and the residue extracted with chloroform (4 x 75 mL). The organic layer was washed with brine (3 x 45

mL), dried (MgSO₄) and concentrated to obtain **101** (1.01 g, 9.34 mmol, 67%) as a clear oil.

6-methyl-4-nitro-3-styrylpyridazine 1-oxide (**104**)

A solution of 3,6-dimethyl-4-nitropyridazine 1-oxide (**103**)⁷⁴ (123 mg, 0.727 mmol), benzaldehyde (99.9 mg, 0.941 mmol), and piperidine (0.038 mL, 0.386 mmol) in CH₃OH (4.0 mL) was heated to reflux (21h). The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the organic layer was dried (MgSO₄) and concentrated under vacuum. After purification by flash chromatography (Hexanes/EtOAc, 6:4) **104** (56.5 mg, 0.220 mmol, 30%) was obtained as a yellow solid. mp 170-172 °C. ¹H NMR (CDCl₃-d₆, 600 MHz): δ 2.56 (s, 3H), 7.39-7.44 (m, 3H), 7.63 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.76 (d, *J* = 16.2 Hz, 1H), 8.06 (d, *J* = 15.6 Hz, 1H), 8.25 (s, 1H); ¹³C NMR (CDCl₃-d₆, 150 MHz): δ 17.7(-), 116.7(-), 128.3(-), 129.0(-), 129.4(-), 130.3(-), 134.2(+), 135.1(-), 141.8(+), 143.1(+), 149.6(+). IR (neat): 3057, 2666, 1314, 1214 cm⁻¹. Anal. Calcd for C₁₃H₁₁N₃O₃: C, 60.70; H, 4.31; N, 16.33. Found: C, 61.07; H, 4.68; N, 16.28.

6-methyl-2-phenyl-5H-pyrrolo[3,2-c]pyridazine (105)

Reaction of 6-methyl-4-nitro-3-styrylpyridazine (**104**) (45.9 mg, 0.178 mmol), Pd(dba)₂ (5.40 mg, 0.00939 mmol), and 1,10-phenanthroline (3.80 mg, 0.0192 mmol) in DMF (4 mL), as described for **1** (14h), gave, after chromatography (EtOAc, followed by EtOAc/CH₃OH, 9:1) **105** (22.8 mg, 0.109 mmol, 61%) as a yellow solid. mp >250 °C. ¹H NMR (DMSO-d₆, 600 MHz): δ 2.45 (s, 3H), 7.01 (s, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.87 (s, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 12.3 (br s, 1H); ¹³C NMR (DMSO-d₆, 150 MHz): δ 18.6 (-), 95.5 (+), 115.4 (-), 124.4 (+), 125.8 (-), 129.0 (-), 129.1 (-), 130.4 (-), 137.4 (+), 144.4 (+), 146.1 (+). IR (neat): 3057, 2666, 1314, 1214 cm⁻¹.

2-trifluoromethanesulfonyloxy-3-nitro-5,6-diphenylpyrazine (112)

To a solution of 2-hydroxy-3-nitro-5,6-diphenylpyrazine⁵⁶ (**111**) (1.89 g, 6.44 mmol) and N,N-diisopropylethylamine (3.20 mL, 18.4 mmol) in CH₂Cl₂ (100 mL) at 0 °C under N₂ atmosphere, trifluoromethanesulfonic anhydride (1.52 mL, 9.05 mmol) was slowly added and stirred (3h). Cold water was added to the reaction mixture and extracted with CH₂Cl₂ (3 x 50 mL). The organic layer was dried (MgSO₄) and concentrated under vacuum. The crude was purified by flash chromatography (Hexanes/EtOAc, 9:1) to give **112** (2.70 g, 6.35 mmol, 98%) as a light yellow solid. mp 112-114 °C. ¹H NMR (CDCl₃, 600 MHz): δ

7.35-7.39 (m, 4H), 7.44-7.48 (m, 2H), 7.53-7.56 (m, 4H); ^{13}C NMR (CDCl_3 , 150 MHz): δ 115.3 (+), 117.4 (+), 119.5 (+), 121.7 (+), 128.8 (-), 128.9 (-), 129.8 (-), 129.9 (-), 130.1 (-), 130.6 (-), 131.3 (-), 134.4 (+), 134.7 (+), 140.8 (+), 141.2 (+), 151.4 (+), 155.6 (+). IR (neat): 1431, 1209 cm^{-1} .

2-chloro-3-nitro-5,6-diphenylpyrazine (**113**)

A mixture of 2-hydroxy-3-nitro-5,6-diphenylpyrazine⁵⁶ (**111**) (251 mg, 0.856 mmol), N,N-diethylaniline (0.270 mL, 1.70 mmol), and phosphorus oxychloride (5 mL) was heated to reflux (4.5h). The reaction mixture was poured into ice and the precipitate filtered and washed with cold H_2O . Product **112** (264 mg, 0.847 mmol, 99%) was obtained as a brown solid. No further purification was required. mp 167-168 $^{\circ}\text{C}$. ^1H NMR (CDCl_3 , 270 MHz): δ 7.25-7.46 (m, 8H).

Methyl (+)-(S)-1-ethyl-2-oxo-3-cyclohexene-1-propanoate (**139**)⁶³

To a solution of methyl (+)-(S)-1-ethyl-2-oxocyclohexane-1-propanoate⁶³ (**137**) (2.89 g, 13.6 mmol) in anhydrous DMF (25 mL) was added Et_3N (10.0 mL, 71.7 mmol). Trimethylsilyl chloride (5.20 mL, 41.0 mmol) was slowly added and it was heated to 100 $^{\circ}\text{C}$ (72h). The reaction mixture was diluted with hexanes (50 mL) and poured into cold

water (50 mL) and then extracted with hexanes. The combined organic layers were dried (MgSO_4) and concentrated under reduced pressure.

To the crude silyl enol ether (**138**) (3.45 g, 12.1 mmol) in DMSO (50 mL) was added $\text{Pd}(\text{OAc})_2$ (466 mg, 2.08 mmol). The reaction was flushed and kept under oxygen (1 atm) while being heated to 40 °C (72h). An additional portion of $\text{Pd}(\text{OAc})_2$ (285 mg, 1.27 mmol) was added and heated to 60 °C (25h). The reaction mixture was cooled and diluted with ethyl acetate (150 mL) and washed with water (3 x 50 mL). The combined organic layers were dried (MgSO_4) and concentrated. The crude was purified by flash chromatography (Hexanes/EtOAc, 7:3) to give **139** (1.92 g, 9.13 mmol, 75%) as a colorless oil.

4-methyl-2-cyclohexen-1-one (151)⁷⁵

To a solution of **150** (1.54 g, 8.35 mmol) in DMSO (50 mL) was added $\text{Pd}(\text{OAc})_2$ (181 mg, 0.806 mmol). The reaction was flushed and kept under oxygen (1 atm) while being heated to 40 °C (24h). The reaction mixture was cooled and diluted with ethyl acetate (100 mL) and washed with water (3 x 40 mL). The combined organic layers were dried (MgSO_4) and concentrated. The crude was purified by flash chromatography (Hexanes/EtOAc, 9:1) to afford **151** (382 mg, 3.47 mmol, 42%) as a colorless oil.

2-(2nitrophenyl)-2-cyclohexen-1-one (154**)**⁶⁸

A solution of 2-iodo-2-cyclohexen-1-one (**153**)⁷⁶ (1.11 g, 5.00 mmol), *o*-bromonitrobenzene (2.02 g, 10.0 mmol), Pd(dba)₂ (130 mg, 0.226 mmol), Cu (1.57 g, 24.7 mmol) in DMSO (17 mL) was heated to 70 °C (1.5 h) under nitrogen. The reaction mixture was diluted with ether (150 mL) and filtered through Celite. The filtrate was washed with brine (2 x 150 mL) and H₂O (1 x 150 mL). The organic phase was dried (MgSO₄) and concentrated at reduced pressure. The crude product was purified by flash chromatography (Hexanes/EtOAc, 9:1, 7:3, 1:1, successively) to give **154** (823 mg, 3.79 mmol, 76%) as a yellow solid. mp 91-93 °C (Lit.⁶⁸ 92-95 °C).

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Appendix

Figure 4: ^1H NMR of 2-nitro-3-vinylpyridine **86**

Figure 5: ^{13}C NMR of 2-nitro-3-vinylpyridine **86**

Figure 6: ^1H NMR of 4-methoxy-5-nitro-6-styrylpyrimidine **95**

Figure 7: ^{13}C NMR of 4-methoxy-5-nitro-6-styrylpyrimidine **95**

Figure 8: ^1H NMR of 4-methoxy-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine **96**

Figure 9: ^{13}C NMR of 4-methoxy-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine **96**

Figure 10: ^1H NMR of 6-methyl-4-nitro-3-styrylpyridazine 1-oxide **104**

Figure 11: ^{13}C NMR of 6-methyl-4-nitro-3-styrylpyridazine 1-oxide **104**

Figure 12: ^1H NMR of 6-methyl-2-phenyl-5*H*-pyrrolo[3,2-*c*]pyridazine **105**

Figure 13: ^{13}C NMR of 6-methyl-2-phenyl-5*H*-pyrrolo[3,2-*c*]pyridazine **105**

Figure 14: ^1H NMR of 2-triflate-3-nitro-5,6-diphenylpyrazine **112**

Figure 15: ¹³C NMR of 2-triflate-3-nitro-5,6-diphenylpyrazine **112**

Figure 16: ^1H NMR of 2-chloro-3-nitro-5,6-diphenylpyrazine **113**