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Novel syntheses of indoles, quinoxalines, 2-quinoxalinones, 2-alkylbenzimidazoles and other heterocycles

Jeffery M. Wallace
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Novel Syntheses of Indoles, Quinoxalines, 2-Quinoxalinones, 2-Alkylbenzimidazoles and Other Heterocycles

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Dissertation

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Abstract

Using a palladium-catalyzed reductive *N*-heteroannulation methodology previously discovered in our labs, a 20 mmol synthetic route to methyl indole-4-carboxylate has been developed. Methyl indole-4-carboxylate is synthesized in four steps, with the key step being the reductive cyclization of methyl 2-ethenyl-3-nitrobenzoate in good overall yield. This cyclization method has been modified and applied to the preparation of quinoxalines, 2-quinoxalinones and other heterocyclic compounds. We also propose a possible mechanism for these transformations.

In addition, a novel method to 2-alkylbenzimidazoles has been developed. The thermal reactions of 2-azidonitrobenzenes with various aldehydes give 2-alkylbenzimidazoles generally in moderate yield.

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Part I

Synthesis of Methyl Indole-4-carboxylate by Reductive *N*-Heteroannulation of Methyl 2-Ethenyl-3-nitrobenzoate

1. Introduction

The indole ring system can be found in many physiologically active compounds both naturally occurring and non-naturally occurring. Two of the more well known biologically active indoles are strychnine, a potent toxin, and sumatriptan, an antimigraine medicine marketed by GlaxoSmithKline under the name Imitrex (Figure 1). Other indole-containing compounds exhibit biological properties including antibacterial,¹ antiallergy² and antitumor³ activity. The development of synthetic routes to indoles is therefore a worthwhile goal of researchers.

Figure 1. Strychnine and Sumatriptan (Imitrex)

strychnine

sumatriptan (Imitrex)

One of the more commonly known routes is the Fischer indole synthesis (Scheme 1).⁴ This method involves the reaction of an arylhydrazine (**1**) and a ketone (**2**) to form an arylhydrazone (**3**) which is then treated with a Lewis acid such as ZnCl_2 to form the indole (**4**). A potential drawback of the Fischer method is if the substrate contains an unsymmetrically

substituted aryl ring, the reaction could lead to regioisomers. The potential for regioisomers also exists if some unsymmetrical ketones are used.

Scheme 1. Fischer Indole Synthesis

Another named route to indoles is the Madelung synthesis (Scheme 2).⁵ In this method, 2-tolylacetamide (5) is treated with base to form the benzyl carbanion, which then reacts with the carbonyl and, upon elimination, forms the indole (6). A strong base, such as an alkyllithium, is usually required for this reaction making it unsuitable for molecules with certain functional groups.

Scheme 2. Madelung Indole Synthesis

The Bischler method of indole preparation⁶ involves the reaction of aminobenzenes (7) with α -haloketones (8) to form α -(*N*-arylamino)ketones (9) which are then cyclized in the

presence of an acid catalyst to form the corresponding indoles (**10**) (Scheme 3). Just as with the Fischer method, regiochemistry becomes a problem with substrates containing unsymmetrically substituted aryl rings.

Scheme 3. Bischler Indole Synthesis

1.1. Palladium-Catalyzed Indole Syntheses

Recently, a new method for the preparation of indoles was developed in our group.⁷ This procedure, detailed in Scheme 4, involved the reductive *N*-heteroannulation of 2-nitrostyrenes (**11**) in the presence of a palladium catalyst, a phosphine and carbon monoxide to give indoles (**12**) in good yields. With no strong acid or base required in this reaction and no regiochemical issues, this method is potentially more useful than many others.

Scheme 4. Palladium-catalyzed Cyclization of 2-Nitrostyrenes

Other palladium-catalyzed routes to indoles include the reaction of 2-allylaminobenzenes (**13**) with $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ as the catalyst and benzoquinone as the reoxidant to give indoles (**14**) generally in good yields (Scheme 5).⁸

Scheme 5. Palladium-catalyzed Cyclization of 2-Allylaminobenzenes

In addition to the reactions of alkenes, some methods have been developed that involve the cyclization of arylalkynes. One such method uses $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ as a catalyst to convert 2-alkynylanilides (**15**) to *N*-acylated indoles⁹ (**16**) as described in Scheme 6.

Scheme 6. Palladium-catalyzed Cyclization of 2-Alkynylanilides

Most of the indole-forming reactions of the type described in Scheme 4 were performed on a relatively small scale (1-2 mmol) in a glass pressure tube (20-40 mL). We wanted to know if it was feasible to produce indoles on a larger scale (20-50 mmol) using our method and so a

scaled-up procedure was developed. That procedure was used to synthesize methyl indole-4-carboxylate and it is presented.

2. Results and Discussion

The synthesis of methyl indole-4-carboxylate is detailed in Scheme 7. Methyl 2-methyl-3-nitrobenzoate (**17**) was previously synthesized in our laboratory according to a literature procedure.¹⁰ Compound **18** was prepared easily from **17** *via* radical bromination. The bromide was transformed into triphenylphosphonium bromide **19** by reaction with triphenylphosphine. Treatment with triethylamine formed the ylide necessary for the subsequent Wittig reaction with formaldehyde to form **20** in 71% from bromide **18**. Because of the increased scale of the reaction and to avoid the explosion of a smaller glass pressure vessel (the pressure we used was approaching the upper limit of the manufacturer rating), it was necessary to use a large stainless steel high pressure Parr reactor for the conversion of **20** to **21**. The reaction of **20** (4.10 g, 20.00 mmol) in the presence of Pd(OAc)₂ (269 mg, 1.2 mmol), triphenylphosphine (1.30 g, 4.8 mmol) and CO (6 atm) at 90 °C in acetonitrile (100 mL) for 27 h gave methyl indole-4-carboxylate (**21**) (3.06 g, 17.5 mmol) in 87% yield.

Scheme 7. Synthesis of Methyl Indole-4-carboxylate (21)

3. Conclusions

We have developed a mild and efficient multi-mmol synthesis of methyl indole-4-carboxylate. The key step of this synthetic route is the reductive *N*-heteroannulation of methyl 2-ethenyl-3-nitrobenzoate using a protocol previously developed in our laboratory.

Part II

Synthesis of Quinoxalines and 2-Quinoxalinones by Palladium-Catalyzed *N*-Heteroannulation Reactions

1. Introduction

The quinoxaline structure is a moiety found in many compounds exhibiting biological activity. Examples of biologically active quinoxalines are riboflavine, also known as vitamin B₂, an important nutritional factor, and oxythioquinox, an antifungal agent (Figure 2). Other quinoxalines exhibit antifungal,¹¹ antituberculosis,¹² antiepilepsy,¹³ antibacterial¹⁴ and antitumor¹⁵ activities. This wide range of physiological activity makes the quinoxaline ring system an attractive synthetic target.

Figure 2. Riboflavine and Oxythioquinox

Most previous syntheses of quinoxalines involve the Hinsberg condensation of substituted 1,2-diaminobenzenes with 1,2-dicarbonyl compounds. This method generally resulted in the formation of isomeric products from unsymmetrical starting materials. Katoh *et*

al reported the synthesis of quinoxalines **24** and **25** by the reaction of methyl 3,4-diaminobenzoate (**22**) and ethyl pyruvate (**23**) (Scheme 8).¹⁶ The products were obtained in 87% as a 1:1 mixture of regioisomers.

Scheme 8. The Work of Katoh *et al*

It is possible, however, to achieve some degree of selectivity in the production of regioisomers if the nucleophilicity of the amino groups or the electrophilicity of the carbonyls is sufficiently different. Ammar *et al* described the formation of quinoxalines **28** and **29** as a 2:1 mixture from 4-benzoyl-1,2-diaminobenzene (**26**) and pyruvic acid (**27**) (Scheme 9).¹⁷ In this case the benzoyl moiety deactivates the *para*-amino group leaving the *meta*-amino group to react with the more reactive ketone to form **28** as the major isomer.

Scheme 9. The Work of Ammar *et al*

It is also possible to utilize substituent effects and reaction conditions simultaneously to achieve selectivity. The work of Paglietti *et al* is detailed in Scheme 10. In this example, substituted 1,2-diaminobenzenes (**30**) are reacted with phenyl glyoxal (**31**) to form quinoxalines **32** and **33** in different ratios if the reaction was performed in neutral, acidic or basic conditions.¹⁸

Scheme 10. The Work of Paglietti *et al*

<u>Conditions</u>	<u>R</u>	<u>yield</u>	<u>Ratio (32:33)</u>
neutral	OCH ₃	59%	1 : 8
neutral	NO ₂	79%	5 : 1
acidic	OCH ₃	61%	1.1 : 1
acidic	NO ₂	79%	5 : 1
basic	NO ₂	84%	1 : 4

The Hinsberg-type condensation reactions of 1,2-diaminobenzenes with 1,2-dielectrophiles are not limited to 1,2-dicarbonyl compounds. Kano *et al* reported the synthesis of quinoxalines **32** and **33** in 27-30% yield from the condensation of substituted 1,2-diaminobenzenes (**30**) and phenacyldimethylsulfonium iodide (**34**) (Scheme 11).¹⁹ Selectivity was achieved by using the appropriate substituents on the aryl ring. When the substituent was electron withdrawing, the *para*-amino group was deactivated and the *meta*-amino group reacted with the preferred α -methylene carbon of the sulfonium salt to form only **32**. Conversely, when

the substituent was electron donating, the *para*-amino group reacted at this preferred site to form only **33**.

Scheme 11. The Work of Kano *et al*

<u>R</u>	<u>Ratio (32:33)</u>
Cl	1 : 2
OCH ₃	all 33
NO ₂	all 32

McKillop *et al* reported the formation of aminoquinoxalines **36** and **37** from the reaction of substituted 1,2-diaminobenzenes (**30**) and ethyl carboethoxyformimidate (**35**) (Scheme 12).²⁰ As in the previous examples, selectivity can be achieved in this reaction depending on the electronic nature of the substituent.

Scheme 12. The Work of McKillop *et al*

<u>R</u>	<u>Ratio (36:37)</u>
CH ₃	1 : 1
NO ₂	all 37

Other variations of the 1,2-dielectrophiles are acetylenedicarboxylates. Iwanami described the reaction of 1,2-diaminobenzene (**38**) with diethyl acetylenedicarboxylate (**39**) to form **40** in almost quantitative yield (Scheme 13).²¹ In this reaction, one amine reacts with an ester and the other amine is in position to react in a Michael-fashion. The yield of this reaction is good; however, the use of unsymmetrical starting materials would lead to the formation of regioisomers.

Scheme 13. The Work of Iwanami

Makino *et al* reported the reaction of **41** with diketene (**42**) to give *N*-oxide **43** in 70% yield. Subsequent reduction of **43** with sodium hydrogensulfite gives quinoxalinone **44** in 75% yield (Scheme 14).²²

Scheme 14. The Work of Makino *et al*

Krchňák *et al* reported the synthesis of **46** on solid support *via* the reduction of **45** to the aryl amine and subsequent intramolecular reaction with the ester (Scheme 15).²³ After cleavage of the solid support, **46** could be easily oxidized to the corresponding fully aromatic quinoxaline.

Scheme 15. The Work of Krchňák *et al*

Quinoxalines of type **49** have been synthesized in good to moderate yields by the reaction of 1-(2-isocyanophenyl)pyrrole (**47**) with Eschenmoser's salts (**48**), as reported by Kobayashi *et al* (Scheme 16).²⁴

Scheme 16. The Work of Kobayashi *et al*

Kundu *et al* described the synthesis of 2-arylquinoxalines (**51**) by the copper iodide-catalyzed cyclization of alkyne **50** (Scheme 17).²⁵ The products are formed in moderate yields with the lowest yields reported when the aryl group on the alkyne contains an electron donating substituent in the *para* position (ex. $Ar = p\text{-CH}_3\text{O-C}_6\text{H}_4$). This is presumably because the alkyne is more electron rich and, therefore, is a less favorable position for the amine to attack.

Scheme 17. The Work of Kundu *et al*

There are many synthetic routes to the quinoxaline ring system; however, many of these methods have limitations. In most cases, regiochemistry is an issue unless one of only a few functional groups is used. Often another limitation is low yields. We have developed a synthetic method to quinoxalines and 2-quinoxalinones *via* *N*-heteroannulation of *N*-(2-nitroaryl)enamines. Regioselectivity is not an issue in our method and a variety of functional groups are compatible with the reaction conditions. Also, our reactions typically proceeded smoothly in high conversion. The novel synthesis of an array of quinoxalines and 2-quinoxalinones is presented.

2. Results and Discussion

Our initial goal was to utilize the aforementioned palladium-catalyzed cyclization conditions (Scheme 4) to prepare a series of benzimidazoles from a variety of imines (Scheme 18). Compound **54** was prepared in moderate yield from the condensation of 2-nitroaminobenzene (**52**) and 4-nitrobenzaldehyde (**53**). The subsequent cyclization, however, failed. Even after numerous attempts to refine the cyclization conditions by employing Pd(dba)₂ (dba = dibenzylideneacetone), 1,3-bis(diphenylphosphino)propane (dppp) and *N,N*-dimethylformamide (DMF), the reactions were still met with no success.

Scheme 18. Synthesis of 54 and Cyclization Attempt

Next, we tried to prepare an aryl imine with an aliphatic substituent. However, the reaction of 2-nitroaminobenzene (**52**) and 2-methylpropanal (**55**) produced enamine **56** instead of the expected imine. Since the mechanism for the cyclization reaction is not well established, we decided to react **56** under CO atmosphere and in the presence of Pd(dba)₂ and dppp in the hopes of getting the corresponding 2-isopropylbenzimidazole. Instead, this reaction afforded quinoxaline **57** and quinoxalinone **58** in 71% and 11%, respectively (Scheme 19).

Scheme 19. Novel Synthesis of Quinoxalines and 2-Quinoxalinones

With this result in hand, we set out to determine the scope and limitations of this novel cyclization reaction. First, we needed to synthesize a variety of enamines as precursors to cyclization. Most of the enamines were prepared by the condensation of a commercially available substituted 2-nitroaminobenzene and an α,α -disubstituted aldehyde, most commonly 2-

methylpropanal. Most of the reactions were carried out at ambient temperature under inert atmosphere in the presence of 4 Å molecular sieves with benzene or CH₂Cl₂ as the solvent.

Table 1 shows the results of the condensation reactions. Some modifications of the reaction conditions were made for the synthesis of compounds **56**, **68** and **70**. Initially, for compound **56**, the reaction mixture was cooled to -20 °C to avoid hydrolysis of the product. This reaction produced **56** in 73% yield, but it was later determined that the cooling was unnecessary and it was abandoned on future reactions. The yields of compounds **68** and **70** were improved by heating the reaction mixture in a standard microwave oven. Compound **82** was isolated in 85% yield as an inseparable mixture of *cis* and *trans* isomers.

Generally, the condensation reactions produced the desired enamines in very good yields. The lower yield of **68** may be attributed to the increased steric bulk around the amino group. Also, slightly lower yields were obtained when the substituent on the aryl ring was an electron withdrawing group. This served to deactivate the amine and render it a much poorer nucleophile. By the same token, the nucleophilicity of the amine was increased when the substituent was an electron donating group, producing generally higher yields of enamines. It also seems that enamines from a 2-nitroaminobenzene and a straight-chain aliphatic aldehyde cannot be formed by this method. Starting material was recovered unchanged from the reaction of **52** and **83** (Table 1, Entry 14).

Table 1. Synthesis of Enamines by Condensation Reactions

Entry	Aniline	Aldehyde	Enamine
1	52	55	56 (73%)^a
2	59	55	60 (89%)
3	61	55	62 (95%)
4	63	55	64 (100%)
5	65	55	66 (88%)

Table 1 (continued)

Entry	Aniline	Aldehyde	Enamine
6	67	55	68 (5%)^b
7	69	55	70 (78%)^b
8	71	55	72 (36%)
9	73	55	74 (20%)
10	75	55	76 (74%)

Table 1 (continued)

Entry	Aniline	Aldehyde	Enamine
11	61	77	78 (88%)
12	61	79	80 (91%)
13	63	81	82 (85%)^c
14	52	83	not observed

a) Reaction temperature was -20°C. b) Reactions were heated in a microwave oven. c) Product was isolated as a 1:1 mixture of *cis* and *trans* isomers.

Since compounds **71** and **75** are not commercially available, it was necessary to prepare them for the condensation reactions. Compound **71** was prepared *via* Curtius rearrangement of

3-methyl-2-nitrobenzoic acid (**84**) (Scheme 20). Compound **75** was prepared by the acid-promoted esterification of 4-amino-3-nitrobenzoic acid (**85**) (Scheme 21).

Scheme 20. Curtius Rearrangement of 3-Methyl-2-nitrobenzoic Acid

Scheme 21. Esterification of 4-Amino-3-nitrobenzoic Acid

As well as pursuing substrates with a substituted aryl ring, we also synthesized an aryl enamine containing the pyridine moiety. Scheme 22 shows the condensation of 2-amino-3-nitropyridine (**86**) and 2-methylpropanal (**55**). This reaction gave the desired compound **87**, but in low yield. Another product of the reaction was compound **88**, which resulted from the attack of a second amine on the imine intermediate.

Scheme 22. Synthesis of 87 and 88

In order to expand the scope of the methodology, we decided to synthesize enamines containing an α,β -unsaturated carbonyl moiety. Scheme 23 details the preparation of two of these compounds. Compound **90** was prepared in 32% yield by the condensation of 2-nitroaminobenzene (**52**) and 1,2-cyclohexandione (**89**). Compound **92** was prepared in the same way in 70% yield by the reaction of 2-nitroaminobenzene (**52**) and 1,3-cyclohexandione (**91**).

Scheme 23. Synthesis of 90 and 92

The synthesis of compounds **95**, **96** and **97** is described in Scheme 24. The enamines were prepared *via* an addition-elimination reaction of the corresponding 2-nitroaminobenzene and (*E*)-4-methoxy-3-buten-2-one (**94**), which was prepared according to Neuenschwander's procedure.²⁶ It is interesting to note that only the *cis* isomer in each case is formed. According to Fedor *et al*, the *cis* isomer is the thermodynamically more stable isomer when the possibility for hydrogen bonding exists between the carbonyl and amino groups.²⁷ These reactions proceeded smoothly and afforded the desired products in high yields.

Scheme 24. Addition Elimination Reactions

With the preparation of several enamines, we now could test the scope of the cyclization reaction. The first attempted cyclization of enamine **56** using $Pd(dba)_2$ (6 mol%), dppp (6 mol%) and carbon monoxide (4 atm) in acetonitrile at 70 °C gave quinoxaline **57** and quinoxalinone **58** in 71% and 11%, respectively (Scheme 19). Despite the success of this reaction, attempts to cyclize other enamines under the same conditions failed. With further refining of the reaction conditions, we found that the following worked the best: $Pd(dba)_2$ (6 mol%), dppp (6 mol%), 1,10-phenanthroline monohydrate (phen) (12 mol%), CO (6 atm) in DMF at 70 °C.

We tested these reaction conditions on the substrates shown in Table 1. The results of these cyclizations are summarized in Table 2. Most of the reactions proceeded smoothly to give a mixture of quinoxalines and 2-quinoxalinones in high total yields. The cyclization of **62** gave compounds **100** and **101** in 76% and 11%, respectively. It is interesting to note that this reaction was performed again under seemingly identical conditions and the yields of **100** and **101** were 57% and 40%, respectively. This result has since been irreproducible. Lower yields were typically seen in the cases that had an electron withdrawing group on the aryl ring; no evidence of either expected product was seen in the attempted cyclization of **70**. The cyclization of **74** produced a product that was tentatively assigned as **110** (Table 2, Entry 9). Numerous attempts to purify compound **110** by column chromatography failed and the assignment was based on the interpretation of the ^1H NMR and ^{13}C NMR spectra. The cyclization of **76** gave an inseparable mixture of **111** and **112** (Table 2, Entry 10). The yields of these two compounds were calculated from the ^1H NMR spectrum. It is interesting to note that the cyclization of compound **80** produced only the quinoxaline and none of the quinoxalinone was seen (Table 2, Entry 12). The cyclization of **82** gave slightly different products than the other reactions in that both **116** and **117** are fully aromatic (Table 2, Entry 13).

The differences in the NMR spectra of quinoxalines and 2-quinoxalinones are quite clear. For example, in the ^1H NMR spectra, the *gem*-dimethyl signal for the quinoxalinone is generally more downfield than that of the quinoxaline. For 3,4-dihydro-3,3,6-trimethyl-2-quinoxalinone (**99**), this signal appears at 1.40 ppm, while for 1,2-dihydro-2,2,7-trimethylquinoxaline (**98**), this signal is at 1.30 ppm. The C-*H* on the nitrogen-containing ring of **98** shows an NMR signal at 7.23 ppm, while **99** shows no such signal. In the ^{13}C NMR, the aliphatic quaternary carbon of compound **99** appears at 55.4 ppm, while the analogous carbon in **98** appears at 50.3 ppm.

Table 2.^a Synthesis of Quinoxalines and 2-Quinoxalinones

Entry	Enamine	Quinoxaline	Quinoxalinone
1	<p>56</p>	<p>57 (71%)^b</p>	<p>58 (11%)^b</p>
2	<p>60</p>	<p>98 (50%)</p>	<p>99 (45%)</p>
3	<p>62</p>	<p>100 (76%)</p>	<p>101 (11%)</p>
4	<p>64</p>	<p>102 (56%)</p>	<p>103 (16%)</p>
5	<p>66</p>	<p>104 (29%)</p>	<p>105 (45%)</p>

Table 2 (continued)

Entry	Enamine	Quinoxaline	Quinoxalinone
6	<p>68</p>	<p>106 (27%)</p>	<p>107 (42%)</p>
7	<p>70</p>	<p>not observed</p>	<p>not observed</p>
8	<p>72</p>	<p>108 (63%)</p>	<p>109 (12%)</p>
9	<p>74</p>	<p>110 (<52%)</p>	<p>not observed</p>
10	<p>76</p>	<p>111 (3%)^c</p>	<p>112 (2%)^c</p>

Table 2 (continued)

Entry	Enamine	Quinoxaline	Quinoxalinone
11	78	113 (70%)	114 (13%)
12	80	115 (69%)	not observed
13	82	116 (25%)	117 (14%)
14	87	118 (34%)	119 (6%)

a) General conditions: Pd(dba)₂ (6 mol%), dppp (6 mol%), phen (12 mol%), CO (6 atm), DMF, 70°C. For more exact details, see: Experimental Section. b) Conditions: Pd(dba)₂ (6 mol%), dppp (6 mol%), CO (4 atm), CH₃CN, 70°C. c) Products were isolated as an inseparable mixture. Yields were estimated from the ¹H NMR spectrum.

Next, we examined the cyclization of enamines derived from the condensation of 2-nitroaminobenzenes and ketones. Compound **90** formed a mixture of three products when subjected to the reaction conditions (Scheme 25). Naturally occurring 1-hydroxyphenazine (**120**) is formed from the reaction in low yield. Compounds **121** and **122** were also formed in low yields. Compound **122** was aromatized using Pd/C (12.5 mol% Pd), 1,2,4-trimethylbenzene (10 eq) in diphenyl ether at 230 °C for 20 h to give **120** in 20% yield. This leads us to believe that the product of the cyclization reaction is **122**. In the reaction mixture, compound **122** is dehydrogenated by catalytic Pd(0) to give **120**. Compound **90** may also undergo reduction of the nitro group to an amine and subsequent reaction of the amine with the carbonyl. Ultimately, this compound will tautomerize to form **121**.

Scheme 25. Cyclization of 90 and Aromatization of 122

The reaction of **92** under slightly modified cyclization conditions gave **120** in relatively low yield (Scheme 26). The only modification to the conditions in this case was the increased temperature (120 °C). Although it could be envisioned that **122** could be formed in this reaction, it was not observed.

Scheme 26. Cyclization of **92**

Acetylquinoxalines have also been prepared in low yields using our cyclization conditions. The reactions generally lead to the formation of the products in low yield. However, it is our hope that with small modifications to the procedure, our method will be a viable synthetic route to acetylquinoxalines. The reaction of **95** under the cyclization conditions gave **122** in 6% yield. Something interesting was discovered when the aryl ring was functionalized. When **96** was subjected to the same conditions, a mixture of regioisomers **124** and **125** were obtained in 13% yield. Similarly, when **97** was cyclized, a mixture of the same isomers was obtained in 4% yield. When the results of the reactions are compared, the ratios of products are not the same indicating that the mixture formed in each case is not the thermodynamic mixture, but the kinetic mixture. The results of these reactions are shown in Scheme 27.

Scheme 27. Synthesis of Acetylquinoxalines

We propose that the cyclization reactions proceed *via* the formation of a palladium-bound nitrene intermediate. The formation of this intermediate will be discussed in Part III. We also propose that the regioisomeric products formed in the above examples arise from the migration of the four carbon unit from one nitrogen to the other, resulting in the formation of isomeric nitrenes **126** and **130** (Scheme 28). These nitrenes should react in the same manner as discussed later in Part III to form the appropriate quinoxalines **125** and **124**. It is assumed in each case that the major product arises from the initially formed nitrene and not the nitrene formed from the migration.

Scheme 28. Formation of Isomeric Nitrenes

As previously discussed, our attempts to form enamines by the condensation of 2-nitroaminobenzenes and straight-chain aliphatic aldehydes failed. This result led us to try a different route. It is known that azides react with triphenylphosphine *via* the Staudinger reaction to form iminophosphoranes.²⁸ These iminophosphoranes can then undergo aza-Wittig reactions with aldehydes and ketones to form imines. We decided to react 2-nitrophenylazides with triphenylphosphine, and then an aldehyde, in the hopes of isolating the corresponding imine or enamine. The reaction of 2-azidonitrobenzene (**131**), triphenylphosphine and heptanal (**83**) in the manner described above gave a red mixture which is a typical characteristic of the formation of

an enamine. An attempt to purify the enamine by column chromatography resulted in complete decomposition of the product. It was then decided to form the expected enamine and subject the crude product to the cyclization conditions without further purification. Scheme 29 describes this two-step sequence that produced 2-pentylquinoxaline (**132**), 2-pentylquinoxaline-1-oxide (**133**) and 2-hexylbenzimidazole (**134**) in 25%, 8% and 14%, respectively. These results indicate that the aza-Wittig reaction first forms an imine, which would be expected to undergo nitrene insertion to produce benzimidazole **134**. The imine might also isomerize to the enamine, which upon reaction with the nitrene would give quinoxaline **132**. The mass spectrum of the compound designated to be **133** shows a peak at $m/z = 199$. This peak would correspond to $[M-17]^+$, or the loss of OH, since the molecular weight of the *N*-oxide is 216. According to Bartoszek *et al*,²⁹ quinoxaline-*N*-oxides substituted at the *ortho* position to the NO group give characteristic $[M-OH]^+$ fragments. This, along with the rest of the fragmentation pattern and spectral data, led us to the conclusion that we did, in fact, isolate compound **133**.

Scheme 29. Synthesis of **132**, **133** and **134**

The reaction to form enamine **68** proceeded, although in very low yield (Table 1, Entry 6). It was our idea that a reaction of 2-azido-3-nitrotoluene (**135**) and 2-methylpropanal (**55**) in the manner described above might give a higher two-step yield of the cyclization products. In

fact, the reaction gave **67**, **106** and **136** in 8%, 11% and 62%, respectively, and is described in Scheme 30.

Scheme 30. Synthesis of 67, 106 and 136

For the above study, it was necessary to synthesize two aryl azides for the Staudinger/aza-Wittig sequences. Compounds **131** and **135** were prepared in good yields *via* diazotization of the corresponding aminobenzene followed by treatment with sodium azide. The results of these reactions are shown in Scheme 31.

Scheme 31. Preparation of Azides 131 and 135

In most of the cyclization reactions two products – a quinoxaline and a 2-quinoxalinone – are formed in appreciable yields. We wanted to test various changes in the reaction conditions to

see if one product could be formed exclusively. First, we subjected enamine **62** to the cyclization conditions and varied only the CO pressure. The reaction conditions for this set of experiments was Pd(dba)₂ (6 mol%), dppp (6 mol%), phen (12 mol%), CO (various pressures), DMF, 70 °C, 18 h (Scheme 32). The results of this study are summarized in Table 3. The results show that carbon monoxide is crucial for the reaction to take place. In the absence of carbon monoxide, the reaction did not proceed (Table 3, Entry 1). It is also interesting to note that the reaction proceeded well under ambient carbon monoxide pressure, indicating that for some substrates, higher pressures may not be necessary. It also seems that overall yields increase as the pressure is increased.

Scheme 32. Cyclization Reactions under Various CO Pressures

Table 3.^a Results of Cyclization Reactions under Various CO Pressures

Entry	CO pressure (atm)	100	101
1	0 ^b	0%	0%
2	ambient ^c	70%	10%
3	2	60%	9%
4	4	86%	6%
5	6	76%	11%
6	8	88%	3%
7	16	99%	1%

a) Isolated yields of **100** and **101** are reported.

b) No carbon monoxide was added to the reaction vessel.

c) The reaction vessel was flushed with carbon monoxide.

Next, we varied the reaction times for the cyclizations. The reaction conditions for this set of experiments was Pd(dba)₂ (6 mol%), dppp (6 mol%), phen (12 mol%), CO (6 atm), DMF, 70 °C (Scheme 33). The results of this study are summarized in Table 4. It was determined that longer reaction times served no benefit and any differences in the yields of products were probably within standard error.

Scheme 33. Cyclization Reactions with Various Reaction Times

Table 4. Results of Cyclization Reactions with Various Reaction Times

Entry	reaction time (h)	100	101
1	1	73%	10%
2	4	77%	2%
3	18	76%	11%
4	36	88%	1%

We also tested the effect of H₂O in the reaction mixture. The reaction conditions for this set of experiments was Pd(dba)₂ (6 mol%), dppp (6 mol%), phen (12 mol%), CO (6 atm), 70 °C, 18 h (Scheme 34). The results of this study are summarized in Table 5. When the reaction was performed using H₂O as the solvent no reaction took place (Table 5, Entry 1). This result may be because of a limited solubility of the enamine and other reagents in H₂O. When the reaction was performed in a 1:1 mixture of DMF/H₂O an increased yield of quinoxaline **100** was seen, while no **101** was isolated (Table 5, Entry 2). The most interesting result was obtained when the reaction was performed in DMF, but 6 equivalents of H₂O were added to the reaction mixture (Table 5, Entry 3). In this experiment **100** was isolated in 80% yield, while **101** was not seen.

Scheme 34. Cyclization Reactions with Various Solvent Mixtures

Table 5. Results of Cyclization Reactions with Various Solvent Mixtures

Entry	Solvent ^a	100	101
1	H ₂ O	0%	0%
2	DMF/H ₂ O (1:1)	37%	0%
3	DMF ^b	80%	0%

a) General conditions: Pd(dba)_2 (6 mol%), dppp (6 mol%), phen (12 mol%), CO (6 atm), 70°C, 18 h. The solvent used is listed. b) 6 equivalents of H₂O was added to the reaction mixture.

Encouraged by the previous results, we decided to attempt the cyclization of more substrates under the conditions described in Table 5, Entry 3. The results of these reactions are shown in Scheme 35. When enamine **64** was subjected to these new conditions, quinoxaline **102** was obtained in 96% yield, while quinoxalinone **103** was obtained in 4% yield. The quinoxaline/quinoxalinone yield was 56%/16% when the reaction was performed without the addition of H₂O (Table 2, Entry 4). Similarly, when **66** was reacted under the conditions that included the addition of 6 eq of H₂O, **104** and **105** were obtained in 81% and 18%, respectively. This result is especially interesting given that the same reaction performed under the original

conditions gave quinoxalinone **105** as the major product (Table 2, Entry 5). Further investigation is planned to determine the scope of these reaction conditions.

Scheme 35. Cyclization Reactions with the Addition of Excess Water

3. Conclusions

A mild and efficient route to quinoxalines and 2-quinoxalinones using a palladium-catalyzed cyclization reaction was developed. A variety of functional groups and substitution patterns are tolerated by this reaction. However, generally lower yields are obtained for substrates containing an electron withdrawing group. Also, it appears as if the ratio of products obtained in the reaction can be manipulated by slightly changing the reaction conditions, namely the addition of H₂O to the reaction mixture.

Part III

Investigation into the Mechanism of the Palladium-Catalyzed *N*-Heteroannulation Reactions

1. Mechanistic Investigation

The mechanism of the cyclizations of *N*-(2-nitroaryl)enamines to quinoxalines and 2-quinoxalinones has been investigated. Transition metal-catalyzed deoxygenation of organic nitro compounds has been proposed to proceed *via* the formation of nitrene, or nitrenoid, intermediates.³⁰ Carbon monoxide is crucial for the reaction to proceed, functioning as a reducing agent to give a metal-bound nitrene and carbon dioxide. Metal-bound nitrenes have been previously reported. For example, a ruthenium-bound derived from 2-nitrosobiphenyl has been isolated and characterized by X-ray crystallography.³¹ Decomposition of this complex gave the expected nitrene insertion product. We propose a mechanism for the formation of a palladium-bound nitrene intermediate under our reaction conditions. This mechanism is detailed in Scheme 36.

Scheme 36. Proposed Mechanism for the Formation of a Palladium-bound Nitrene

The mechanism for the formation of the quinoxaline/quinoxalinone products is unclear; however, we propose possible mechanisms for their respective formations. The proposed mechanism for the formation of quinoxalines is detailed in Scheme 37. In this mechanism, the partially negative carbon of the enamine reacts with the partially positive nitrogen of the palladium-bound nitrene in a formal [2 + 2] intramolecular cycloaddition to form bicyclic species **144**. Sequential β -hydride elimination to give **145** followed by reductive elimination would form the quinoxaline (**57**) and regenerate the palladium(0) catalyst.

Scheme 37. Proposed Mechanism for the Formation of Quinoxalines

Our proposed mechanism for the formation of 2-quinoxalinones is detailed in Scheme 38. Before complete deoxygenation to give the palladium-bound nitrene, insertion of the alkene into the intermediately formed metallacycle **146** (a palladium-bound nitrosoarene) occurs. Two different insertion products can be envisioned; one resulting from the insertion of the alkene into the Pd-O bond (**147**) and the other from the insertion into the N-O bond (**148**) of the metallacycle. The latter seems to be the species more likely formed since a simple β -hydride elimination-reductive elimination sequence would give a 2-quinoxalinone. Intramolecular

insertions of alkenes into metal-bound nitrosoarenes, the first step in this sequence, have been proposed.³²

Scheme 38. Proposed Mechanism for the Formation of 2-Quinoxalinones

By subjecting compound **102** to the cyclization conditions we have shown that oxidation of the quinoxaline does not lead to the 2-quinoxalinone; compound **102** was recovered unchanged from the reaction mixture. By an analogous reaction of **105**, we have also shown that the 2-quinoxalinone is not reduced under the same conditions. These studies are illustrated in Scheme 39.

Scheme 39. Reaction of **102** and **105** under Cyclization Conditions

It is established that a nitrene species is formed upon the thermolysis of azides.³⁰ Therefore, in order to further investigate the mechanism of the cyclization reactions, we attempted to prepare *N*-(2-azidoaryl)enamines. The attempted condensation of 2-azidoaminobenzenes with aldehydes in the presence of molecular sieves under previously described conditions was met with no success. However, the condensation of 2-azidoaminobenzene and various aryl aldehydes in the presence of catalytic acetic acid in refluxing ethanol to form the corresponding imine is described by Alajarín *et al.*³³ Although the product isolated by Alajarín was an imine, we thought that by using aliphatic aldehydes and considering our previous experience with the condensations of aminobenzenes and, for example, 2-methylpropanal, that it might be possible to form the enamine under these conditions.

The condensation of 2-azido-4-chloroaminobenzene (**150**) (the synthesis of **150** will be discussed in the next section) and 2-methylpropanal (**55**) was attempted. The only isolated product was 5-chloro-2-isopropylbenzimidazole (**151**) in 61% yield. This result indicates that if

a nitrene is formed upon heating, it reacts with the initially formed imine from the condensation reaction to give the benzimidazole. The benzimidazole is the expected nitrene insertion product from such a reaction according to Krbecek *et al.*³⁴ The result of this reaction is described in Scheme 40. The formation of 2-alkylbenzimidazoles under these conditions was pursued further and the results are described in the next section.

Scheme 40. Synthesis of Benzimidazole 151

We still desired to isolate a *N*-(2-azidoaryl)enamine, but it was clear that the condensation of an aminobenzene and an aldehyde was not the route to take. We attempted the addition-elimination reaction of 2-azido-4-methylaminobenzene (**152**) (the synthesis of **152** will be discussed in the next section) and (*E*)-4-methoxy-3-buten-2-one (**94**) to form (*Z*)-4-(2-azido-4-methylphenylamino)-3-buten-2-one (**153**). This reaction proceeded smoothly to give the desired product in 78% yield (Scheme 41).

Scheme 41. Preparation of 153

With this result in hand, compound **153** was refluxed in ethanol in the presence of catalytic p -toluenesulfonic acid. This reaction produced an inseparable mixture (6:1) of quinoxalines **125** and **124** (Scheme 42) similar to the cyclizations of N -(2-nitroaryl)enamines **96** and **97** (Scheme 27, Part II). This indicates that a nitrene intermediate is a possibility in the palladium-catalyzed N -heteroannulations of N -(2-nitroaryl)enamines to form quinoxalines and 2-quinoxalinones.

Scheme 42. Synthesis of 124 and 125

It has been reported that organic azides react with a variety of transition metals, such as Mo,³⁵ W³⁶ and Fe,³⁷ to form metal-bound nitrenes. We decided to react compound **153** with a Pd(0) catalyst in the hopes of forming the palladium-bound nitrene species. The reaction of

compound **153** with Pd(dba)₂ and dppp in DMF at ambient temperature produced a product that is tentatively designated as **154** in 18% yield (Scheme 43). This result also supports the hypothesis that a nitrene intermediate is involved in the formation of the quinoxaline ring system by the palladium-catalyzed *N*-heteroannulations of *N*-(2-nitroaryl)enamines.

Scheme 43. Synthesis of 154

In our proposed mechanism for the formation of a nitrene intermediate (Scheme 36), it can be envisioned that species **140**, which is formally palladium coordinated to a nitroso group, could also exist as the “free” nitroso group (Scheme 44). It is also curious if this “free” nitroso group is part of the catalytic cycle. To test this, 2-nitrosoaminobenzene (**157**) was prepared according to Haddadin *et al*³⁸ and then reacted with 2-methylpropanal (**55**) in DMF at 80 °C. This reaction produced only 2-isopropylbenzimidazole (**158**) in 16% yield (Scheme 45). This result indicates that the “free” nitroso group is not part of the catalytic cycle in the reactions forming quinoxalines and 2-quinoxalinones.

Scheme 44. Illustration of 140 as an Aryl Nitroso Group

Scheme 45. Reaction of 2-Nitrosoaminobenzene with 2-Methylpropanal

2. Conclusions

We have proposed a reasonable mechanism for the palladium-catalyzed *N*-heteroannulation of *N*-(2-nitroaryl)enamines to quinoxalines and 2-quinoxalinones that involves the formation of a palladium-bound nitrene as a key step. We have designed several experiments to test the viability of our proposed mechanism and the results of all of them have been in support.

Part IV

Novel Synthesis of 2-Alkylbenzimidazoles

1. Introduction

The benzimidazole nucleus is present in many physiologically active compounds. Examples of benzimidazoles possessing biological activity are omeprazole, an antiulcerative marketed by AstraZeneca under the names Prilosec (racemic) and Nexium (magnesium salt of the *S*-isomer), and thiabendazole, a veterinary anthelmintic and fungicide for spoilage control of citrus fruit and for the prevention of Dutch elm disease (Figure 3). Other benzimidazoles exhibit antifertility,³⁹ antitumor,⁴⁰ anthelmintic,⁴¹ fungicidal,⁴² antiviral⁴³ and antiarrhythmic⁴⁴ activity. This variety of physiological activity makes the benzimidazole ring structure a worthwhile synthetic target for researchers.

Figure 3. Omeprazole and Thiabendazole

A wide variety of synthetic methods for the preparation of benzimidazoles have been reported. Bárzana *et al* reports the synthesis of benzimidazoles (**161**) and 1-hydroxybenzimidazoles (**160**) from 4-alkyl-2-nitroacetanilides (**159**) by reductive cyclization with baker's yeast (Scheme 46).⁴⁵ The *ortho* nitro group of **159** is reduced by the yeast to the

corresponding hydroxylamine which then undergoes an intramolecular reaction with the amide carbonyl to give the 1-hydroxybenzimidazole (**160**). The hydroxylamine could also undergo a second reduction to the amine, which then undergoes an analogous cyclization to the benzimidazole (**161**). Interestingly, when the substituent on the aryl ring is a nitro group (R = NO₂), only the nitro in the *ortho* position is reduced. High conversion rates are generally associated with this reaction. However, a potential drawback is that the reaction only works when the substituent is an electron withdrawing group.

Scheme 46. The Work of Bárzana *et al*

It has been shown by Grenda *et al* that the reaction of *N*-arylamidine hydrochlorides (**162**) with sodium hypochlorite and base form benzimidazoles (**163**) in moderate to good yield (Scheme 47).⁴⁶ This sequence can be used to form 2-alkyl and 2-arylbenzimidazoles with better yields generally accompanying the latter. These reactions require the formation of an amidine from the reaction of an aryl amine with a nitrile or an imide prior to cyclization. A possible

drawback of this procedure is that if the aryl ring were substituted the cyclization will most likely give regioisomeric products.

Scheme 47. The Work of Grenda *et al*

The synthesis of 2-alkylbenzimidazoles by TiO₂-mediated photocatalysis is reported by Li *et al.* In this example, alcoholic solutions of 1,2-dinitrobenzenes (**164**) are irradiated in the presence of TiO₂ to form 2-alkylbenzimidazoles (**165**) in good yield (Scheme 48).⁴⁷ The reaction involves the oxidation of the alcohol solvent to the corresponding aldehyde and the reduction of the dinitrobenzene to a 2-nitroaminobenzene. This is followed by intermolecular condensation to form the corresponding imine. Further reduction of the nitro group on the imine to the hydroxylamine followed by intramolecular cyclization and dehydration gives 2-alkylbenzimidazoles. Solvents, and therefore aldehydes, were limited to ethanol and 1-propanol to give methyl and ethyl substituted benzimidazoles, respectively. It seems that this procedure is limited to alcohols that serve as good solvents for the reaction. Also, substrates possessing an electron withdrawing group tended to give lower yields of benzimidazoles.

Scheme 48. The Work of Li *et al*

Another transition metal-catalyzed preparation of benzimidazoles is reported by Perry *et al.*⁴⁸ In this sequence, described in Scheme 49, aryl halides (**166**) are reacted with 1,2-diaminobenzenes (**30**) in the presence of carbon monoxide, a palladium catalyst and a base to form 2-arylbenzimidazoles (**167**) in good yields. This procedure tolerates a variety of functional groups on either of the aromatic rings. Some side products are seen in the reaction, such as bisamides, resulting from the reaction of both amino groups with two Ar-C(O)-Pd-X species. However, these products seem to be sufficiently diminished or eliminated by changing the base or solvent.

Scheme 49. The Work of Perry *et al*

Thomas *et al* reported the synthesis of benzimidazoles by the tin(II) chloride reduction of 2-nitroaminobenzenes followed by condensation with alkanolic anhydrides (Scheme 50).⁴⁹ For example, fluoro substituted 2-nitroaminobenzene **168** is reduced with SnCl₂ followed by the reaction with pentanoic anhydride to give the corresponding benzimidazole (**169**) in 48% yield. The low yield of this reaction along with the need for 5 equivalents of SnCl₂ does not serve to make this method of benzimidazole preparation the most efficient.

Scheme 50. The Work of Thomas *et al*

The reaction of 1,2-diaminobenzenes (**30**) with aliphatic selenonesters (**170**) to produce 2-alkylbenzimidazoles (**171**) is reported by Cohen *et al.*⁵⁰ This method is described in Scheme 51. The reaction proceeds smoothly in the unsubstituted system as well as with an electron donating substituent (R = CH₃) on the aryl ring to afford the corresponding 2-alkylbenzimidazole in 92% and 86% yields, respectively. However, the yield of the reaction drops sharply with an electron withdrawing group (R = Cl) on the aryl ring. Another potential drawback of this method is the production of moderately toxic hydrogen selenide as a byproduct.

Scheme 51. The Work of Cohen *et al*

A ruthenium-catalyzed route to benzimidazoles is reported by Cenini *et al* (Scheme 52).⁵¹ The reaction of 2-nitroaminobenzene (**52**) with aliphatic or aromatic aldehydes (**172**) in the presence of Ru₃(CO)₁₂ (2.5 mol%) and carbon monoxide (49 atm) gives 2-alkyl and 2-arylbenzimidazoles (**163**) in moderate to good yield. The reaction is proposed to proceed through an imine intermediate followed by the formation of a ruthenium-bound nitrene. The nitrene then inserts into the C-H bond of the imine to form the benzimidazole.

Scheme 52. The Work of Cenini *et al*

Another route to benzimidazoles that probably proceeds through a nitrene intermediate is the reductive cyclization of *N*-benzilidene-2-nitroaminobenzenes (**173**) by triethyl phosphite (Scheme 53). The formation of a nitrene species by phosphorus-promoted deoxygenation of aromatic nitro compounds has been proposed.³⁰ This reaction, reported by Cadogan *et al*,⁵² forms 2-phenylbenzimidazoles (**174**) in moderate to low yields.

Scheme 53. The Work of Cadogan *et al*

The thermolysis of aromatic azides is also known to form nitrenes.³⁰ The work of Hall *et al*⁵³ is described in Scheme 54. In this sequence, imines (**177**) are prepared in moderate to good yields by the reaction of 2-azidoaminobenzenes (**175**) with aromatic aldehydes (**176**). Thermolysis of these azido imines at 130 °C in DMF presumably forms the nitrene intermediate, which undergoes C-H insertion to form the 2-arylbenzimidazoles (**178**). The two-step yields in these reactions are generally moderate to low.

Scheme 54. The Work of Hall *et al*

There are many different methods of forming the benzimidazole ring system. Many of these methods are not without limitations. Some require the multi-step formation of a cyclization precursor which lowers overall yields. Many methods are intolerant of certain functional groups. We have developed an extremely mild single-step route to 2-alkylbenzimidazoles *via* sequential condensation-nitrene insertion reactions. Our method tolerates a variety of substituents (electron-donating and withdrawing) as well as different substitution patterns. Also, our reactions typically give 2-alkylbenzimidazoles in moderate to good yields. The novel synthesis of a variety of 2-alkylbenzimidazoles is presented.

2. Results and Discussion

Encouraged by the results of the reaction described in Scheme 40 (Part III), we decided to pursue the preparation of 2-alkylbenzimidazoles by reacting 2-azidoaminobenzenes with aldehydes in refluxing ethanol. It was necessary to first prepare a number of substituted 2-azidoaminobenzenes. Compounds **186** and **150** were prepared by the method of Hall *et al* (Scheme 55).⁵⁴ First, the appropriate 2-nitroaminobenzenes (**65** and **63**) were melted with phthalic anhydride (**179**) to form the corresponding 2-phthalamidonitrobenzenes (**180** and **181**). Despite the relatively low yields of these reactions we decided to move forward in the sequence.

Subsequent reduction of **180** and **181** by iron and acetic acid produced **182** and **183**, respectively, in good yields. Next, the 2-phthalamidoaminobenzenes (**182** and **183**) were subjected to diazotization conditions followed by treatment with sodium azide. This sequence produced 2-phthalamidophenylazides **184** and **185** in 75% and 59% yields, respectively. The final step of the series was the removal of the phthalamide protecting group. This was performed using hydrazine hydrate and gave compounds **186** and **150** in 54% and 62% yields, respectively.

Scheme 55. Preparation of 186 and 150

Due to the low yields of some of the reactions, namely on the first and last steps, we decided to modify the protocol for the formation of our 2-azidoaminobenzenes. The formation of compounds **152**, **197** and **198** was achieved a little differently (Scheme 56). The appropriate *o*-aminonitroarenes (**59**, **67** and **86**) were reacted with phthaloyl chloride (**187**) and pyridine in refluxing toluene to give the corresponding *o*-phthalamidonitroarenes (**188**, **189** and **190**) in excellent yields. Subsequent hydrogenation using 10% Pd/C as the catalyst afforded *o*-aminophthalamidoarenes **191**, **192** and **193** in 88%, 75% and 50% yields, respectively. The hydrogenation reactions seemed to proceed more smoothly and cleaner than the iron reductions discussed above. Compounds **191**, **192** and **193** were then subjected to slightly modified diazotization conditions and treatment with sodium azide to give *o*-azidophthalamidoarenes (**194**, **195** and **196**) in acceptable yields. Also slightly modified were the deprotection reactions. These reactions worked better with longer reaction times and using THF/ethanol as co-solvents. Compounds **152**, **197** and **198** were prepared according to this improved method in 98%, 60% and 96% yields, respectively.

Scheme 56. Preparation of 152, 197 and 198

With several compounds in hand, it was now possible to examine the scope of the benzimidazole-forming reaction. During the condition optimization process, we tried several approaches. The set of conditions that generally provided the highest benzimidazole yields are as follows: 1.0 equivalent of azide and 1.2 equivalents of aldehyde (added dropwise to avoid

aldol condensation side products) in refluxing ethanol for 24 h. Shorter reaction times led to lower conversion to benzimidazoles and the isolation of azide starting materials. We also attempted to promote the formation of imines by the addition of glacial acetic acid to the reaction mixture. Generally, the addition of acid led to the rapid decomposition of the azides and, therefore, lower yields of benzimidazoles.

Next, we reacted our previously prepared azides with a variety of aldehydes under these “optimized” reaction conditions. The results of these reactions are summarized in Table 6. Generally, the reactions of azides with 2-methylpropanal (**55**) and heptanal (**83**) proceeded smoothly to give 2-alkylbenzimidazoles in moderate yields. However, the reactions of azides with some of the other aldehydes were met with limited success. The reaction of **152** with phenylacetaldehyde (**81**) (Table 6, Entry 6) gave only 10% of the benzyl-substituted benzimidazole (**202**), while **203** was formed in 40% yield. The product ratio changed somewhat when glacial acetic acid (25 μ L) was added to the reaction mixture. In this reaction **202** and **203** were formed in 19% and 30% yields, respectively. The reaction of **152** with trimethylacetaldehyde (**205**) (Table 6, Entry 8) formed 5-methyl-2-*tert*-butylbenzimidazole in 25% yield. This diminished yield may be attributed to the steric bulk around the electrophilic carbonyl. In the reaction of **198** with 2-methylpropanal (**55**), the major product is 2,3-diaminopyridine (**213**), presumably from the hydrogen abstraction of the nitrene intermediate. Imidazopyridine **212** is the minor product in this reaction, isolated in only 7% yield (Table 6, Entry 12).

Table 6.^a Synthesis of 2-Alkylbenzimidazoles

Entry	Azide	Aldehyde	Product(s)
1	186	55	151 (76%)
2 ^b	150	55	151 (66%)
3	186	83	199 (63%)
4	152	55	200 (71%)
5	152	83	201 (75%)

Table 6 (continued)

Entry	Azide	Aldehyde	Product(s)
6 ^c	152	81	202 (10%) + 203 (40%)
7	152	CH_2O 204	203 (18%)
8	152	205	206 (25%)
9	152	207	208 (33%)

Table 6 (continued)

Entry	Azide	Aldehyde	Product(s)
10	152	209	210 (14%)
11	197	55	136 (69%) + 211 (8%)
12	198	55	212 (7%) + 213 (33%)

a) General conditions: 1.0 eq azide, 1.2 eq aldehyde, ethanol, reflux, approx. 24 h. b) An additional reaction was performed using 2.75 eq aldehyde and 0.5 mL acetic acid; yield: **151** (61%). c) An additional reaction was performed with 0.025 mL acetic acid added to reaction mixture; yields: **202** (19%), **203** (30%)

The thermal reactions of 2-azidoaminobenzenes with aldehydes to form benzimidazoles are thought to occur by the mechanism described in Scheme 57. At least initially, the reaction is thought to form an imine from the condensation of an amine and an aldehyde. This is followed by the thermally-driven loss of N₂ to give a nitrene.³⁰ The imine-nitrene may then react in an electrocyclic fashion followed by spontaneous isomerization to form the benzimidazole. In some of our reactions, benzimidazoles unsubstituted in the 2-position were obtained (Table 6, Entries 6 and 11). The reason for the formation of these products is unclear at this point.

Scheme 57. Proposed Mechanism for the Formation of Benzimidazoles

As a study of the mechanism of the formation of benzimidazoles, we attempted to prepare a 2-cyclopropylmethylbenzimidazole. Our thought was that if a radical mechanism existed, one of the intermediates might react in such a way causing the cyclopropyl ring to open. Examination of the product(s) might give us some insight into the structure(s) of the intermediate(s). A slightly different procedure was employed in the synthesis of 2-cyclopropylmethyl-5-methylbenzimidazole (**217**) (Scheme 58). First, 2-cyclopropylethanol (**216**) was oxidized to the aldehyde with pyridinium chlorochromate. Without purification, to the aldehyde solution was added 2-azido-4-methylaminobenzene (**152**) and the mixture was heated at 100 °C in a sealed reaction vessel for 24 h. This method, gave only benzimidazole **217** in 11% yield. No other products were recovered and so no insight into the mechanism was gained.

Scheme 58. Synthesis of 217

3. Conclusions

We have developed a novel route to 2-alkylbenzimidazoles from the condensation-cyclization reaction of 2-azidoaminobenzenes and aldehydes. The best results were achieved when 2-methylpropanal or heptanal was used. Other aldehydes gave considerably lower yields of benzimidazoles. The reaction can also be expanded to include the pyridine moiety; however, the yield was greatly diminished. We have also proposed a mechanism for the transformations to occur involving a nitrene intermediate.

Part V

Synthesis of Other Heterocyclic Ring Systems *via N-Heteroannulation* Reactions

1. Synthesis of Alloxazines

The family of compounds known as the alloxazines is characterized by the ring system shown in Figure 4. Many members of this class of compounds exhibit a wide range of biological activity.⁵⁵ One of the more notable biologically active alloxazines is the nutritional factor riboflavine. It was our desire to expand the palladium-catalyzed *N*-heteroannulation methodology to include the synthesis of alloxazines.

Figure 4. Alloxazine and Riboflavine

In order to test our reaction conditions, it was necessary to synthesize the cyclization precursors. Cyclization precursors would generally have to fit the model shown in Figure 5. We attempted many methods in our quest to synthesize compounds of this type; however, in the end, we were unable to succeed at our task. Various attempted procedures are presented.

Figure 5. General Structure of an Alloxazine Precursor

First we attempted to prepare a cyclization precursor by various reactions of 2-nitroaminobenzene (**52**) and 6-halouracils (Scheme 59). The details of these reactions are summarized in Table 7. Addition-elimination type reactions were attempted with **52** and 6-chlorouracil (**218**) using two different solvents, 1-butanol and chloroform (Table 7, Entries 1 and 2). Neither reaction produced the desired product. Next, we attempted the coupling by following a literature protocol using *N,N*-dimethylaminobenzene and acetic acid.⁵⁶ We tried this reaction using the chloro, bromo and iodo-substituted uracil (Table 7, Entries 3, 4 and 5). None of these reactions were successful. Finally, a copper-promoted coupling was attempted according to a literature procedure (Table 7, Entry 6).⁵⁷ In this example, the coupling of **52** and **218** failed to give the desired result.

Scheme 59. General Reaction of 2-Nitroaminobenzene and 6-Halouracils

Table 7. Conditions for the Reactions of 2-Nitroaminobenzene and 6-Halouracils

Entry		Conditions
1	218 , R=Cl	1-butanol, pyridine, reflux
2	218 , R=Cl	CHCl ₃ , pyridine, reflux
3	218 , R=Cl	PhN(CH ₃) ₂ , AcOH, 180°C
4	219 , R=Br	PhN(CH ₃) ₂ , AcOH, 180°C
5	220 , R=I	PhN(CH ₃) ₂ , AcOH, 180°C
6	218 , R=Cl	Cu, Li ₂ CO ₃ , DMSO, 150°C

Next, a series of palladium-catalyzed reactions were attempted according to literature protocols (Scheme 60).⁵⁸ The details of these reactions are summarized in Table 8. The reaction of 2-nitroaminobenzene (**52**) with 6-iodouracil (**220**) under these conditions failed to give the desired product (Table 8, Entry 1). When we attempted the coupling using 6-aminouracil (**222**) and aryl halides, the reactions failed as well (Table 8, Entries 2 and 3).

Scheme 60. General Palladium-catalyzed Reactions to Form Cyclization Precursors

Table 8. Conditions for the Palladium-catalyzed Reactions

Entry			Conditions
1	52 , X= NH_2 , Y=H	220 , Z=I	$\text{Pd}(\text{dba})_2$, BINAP, KO t -Bu, toluene, 80°C
2	221 , X=I, Y=H	222 , Z= NH_2	$\text{Pd}(\text{OAc})_2$, BINAP, Cs_2CO_3 , toluene, 80°C
3	223 , X=Br, Y= OCH_3	222 , Z= NH_2	$\text{Pd}(\text{OAc})_2$, BINAP, Cs_2CO_3 , toluene, 80°C

It was necessary to synthesize three different 6-halouracils for the previously described coupling reactions. Scheme 61 describes the syntheses of 6-chlorouracil (**218**), 6-iodouracil (**220**) and 6-bromouracil (**219**). Compound **218** was prepared by the reaction of 1,3-dimethylbarbituric acid (**224**) with phosphorus oxychloride in 78% yield. Compound **220** was prepared in 64% yield from the reaction of **218** and sodium iodide. This reaction was performed in a sealed pressure tube in acetone at 120 °C. The reaction of 1,3-dimethylbarbituric acid (**224**) with phosphorus tribromide gave compound **219** in 33% yield.

Scheme 61. Preparation of 218, 219 and 220

The synthesis of cyclization precursors was attempted by a few other methods, as well. Scheme 62 describes three such methods. First, it was thought that the reaction of 2-nitroaminobenzene (**52**) and 1,3-dimethylbarbituric acid (**224**) would produce the desired product by the condensation of the amino group and one of the less hindered carbonyls. This reaction, however, failed to give the product. The reaction of 2-nitroaminobenzene (**52**) and 6-aminouracil (**222**) under acidic conditions was thought would proceed through an addition-elimination pathway and result in the formation of the desired product and ammonia. This reaction, too, failed. Finally, we proposed that the reaction of 2-azidonitrobenzene (**131**) with triphenylphosphine would form the corresponding iminophosphorane. This species would then react in an aza-Wittig fashion with one of the less hindered carbonyls to form the desired

compound. When the reaction was performed in tetrahydrofuran (THF), the only product isolated from this sequence was 2-nitroaminobenzene (**52**) in 94% yield. However, when diethyl ether was used for the formation of the iminophosphorane, then CHCl_3 for the aza-Wittig, no reaction occurred.

Scheme 62. Other Reactions to Form Cyclization Precursors

2. Synthesis of an Indole-fused Pyrimidine Derivative

Heterocyclic compounds having the general structure shown in Figure 6 are known to exhibit physiological properties such as blood sugar-lowering activity.⁵⁹ It was our desire to

explore the possibility of preparing such compounds using our palladium-catalyzed *N*-heteroannulation method.

Figure 6. General Structure of an Indole-fused Pyrimidine Derivative

indole-fused pyrimidine derivatives

In order to test the reaction, we first needed to synthesize an appropriate cyclization precursor. We chose to prepare our precursor *via* a Stille coupling of tributyl(2-nitrophenyl)stannane (**225**) and 6-iodouracil (**220**) (Scheme 63). Aryl stannane **225** was previously synthesized in our labs according to a literature procedure.⁶⁰ The reaction of **225** and **220** in the presence of $\text{PdCl}_2(\text{PhCN})_2$, Ph_3As and CuI in *N*-methylpyrrolidinone (NMP) at 80 °C gave the desired coupling product **226** and homocoupling product **227** in 48% and 36% yields, respectively.

Scheme 63. Preparation of 226 and 227

With compound **226** in hand, we attempted the cyclization according to our method. The reaction of **226** in the presence of $\text{Pd}(\text{dba})_2$, dppp, phen and carbon monoxide in DMF at 70°C gave the desired cyclization product **228** in 9% yield (Scheme 64).

Scheme 64. Synthesis of 228

3. Conclusions

Despite numerous attempts and the use of many different methods we were unsuccessful in the synthesis of alloxazine precursors. It is our belief that if this type of compound can be prepared that it will undergo cyclization under our conditions to form the desired alloxazine. More research is planned in this area.

We were able to synthesize an interesting heterocyclic compound that is analogous to compounds known to exhibit biological activity. This compound was synthesized in relatively low yield; however, with adjustments to the protocol, it is our belief that our method of cyclization can be expanded and become a viable synthetic route to compounds of this type. This is an area that will be researched further in our labs.

Part VI

Experimental Section

1. General Procedures

All NMR spectra were determined in CDCl_3 at 270 MHz (^1H NMR) and 67.5 MHz (^{13}C NMR) unless otherwise noted. The chemical shifts are expressed in δ values relative to $(\text{CH}_3)_4\text{Si}$ (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 in $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test) ^{13}C NMR experiments are shown in parentheses, where relative to CDCl_3 , (-) denotes CH_3 or CH and (+) denotes CH_2 or C .

Benzene, toluene and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Pyridine, triethylamine, hexanes, acetonitrile, ethyl acetate and dichloromethane were distilled from calcium hydride. Chemicals prepared according to literature procedures have been referenced the first time they are used; all other reagents were obtained from commercial sources and used as received. Silica gel (200-400 mesh) was used for flash chromatography. Solvents were removed using a rotary evaporator at water aspirator pressure unless otherwise noted. Infrared (IR) spectra were recorded using NaCl plates. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. High Resolution Mass Spectra (HRMS) were performed at the University of California Riverside Mass Spectrometry Center.

2. Experimental Details

Methyl 2-bromomethyl-3-nitrobenzoate⁷ (18).

To a solution of methyl 2-methyl-3-nitrobenzoate (**17**) (9.60 g, 49.1 mmol) and benzoyl peroxide (0.60 g, 2.6 mmol) in CCl₄ (100 mL) was added dropwise a solution of bromine (3.0 mL, 58.6 mmol) dissolved in CCl₄ (20 mL) with stirring. The mixture was illuminated with a 100 Watt flood lamp and was heated at reflux for 24 h. The reaction was diluted with CH₂Cl₂ (50 mL) and washed with NaHCO₃ (saturated, aqueous, 3 X 50 mL). The organic phase was dried (MgSO₄), filtered and concentrated. Compound **18** (13.46 g, 49.1 mmol, 100%) was obtained as pale yellow crystals.

(2-Carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide⁷ (19).

To a solution of **18** (13.50 g, 49.1 mmol) in CHCl₃ (150 mL) was added triphenylphosphine (14.80 g, 56.5 mmol) with stirring. The reaction was heated at reflux for 2 h. The resulting orange solution was then poured into diethyl ether (anhydrous, 400 mL) and a white precipitate formed. After cooling in the freezer (approx. -20 °C) for 1 h, (2-carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide (**19**) was collected by filtration and used without further purification in the next procedure.

Methyl 2-ethenyl-3-nitrobenzoate⁷ (20).

Paraformaldehyde (20.00 g, 667 mmol) was placed in a 250 mL, 2-necked, round-bottomed flask. An argon inlet was connected to one of the necks. The other neck was connected to a 1 L, 2-necked, round-bottomed flask via Tygon tubing (2 cm id) and two male

24/40 joints. In the 1 L flask, the crude (2-carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide from the previous procedure was dissolved in CH₂Cl₂ (500 mL). A glass tube was attached to the Tygon tubing such that the end extended several cm into the solution. Triethylamine (30.0 mL, 215 mmol) was added to the 1 L flask and resulted in the immediate formation of a deep blue/purple solution; a condenser was attached to the second neck of the flask. Argon was then passed over the paraformaldehyde so that a steady stream of gas was constantly bubbling through the purple ylide solution. The paraformaldehyde was then heated to 160 °C in order to generate formaldehyde which flowed through the solution. Upon completion of the addition of formaldehyde, the purple color of the ylide slowly changed to brown over a period of 1-2 h. The resulting solution was poured into hexanes (500 mL) and the resulting solid (triphenylphosphine oxide) was removed by filtration. The filtrate was concentrated and the crude product was purified by flash chromatography (hexanes/EtOAc, 8:2) to give **20** (7.30 g, 35.0 mmol, 71% over 2 steps) as a white solid.

Methyl indole-4-carboxylate^{7,10} (21**).**

To a solution of **20** (4.10 g, 20.0 mmol) and triphenylphosphine (1.30 g, 4.8 mmol) dissolved in acetonitrile (100 mL) in a 300 mL glass liner of a stainless steel reaction vessel was added palladium diacetate (269 mg, 1.2 mmol). The glass liner was placed in the reaction vessel and the vessel was flushed 3 times with CO. The reaction was heated and stirred at 90 °C under CO (6 atm) for 27 h. The reaction mixture was filtered through Celite and washed with CH₂Cl₂. The filtrate was concentrated and the product was purified by flash chromatography (hexanes/CH₂Cl₂, 7:3, then 1:1) to give **21** (3.06 g, 17.5 mmol, 87%) as a pale yellow solid.

2-Nitro-*N*-[(4-nitrophenyl)methylene]benzenamine⁶¹ (54**).**

To a solution of 2-nitroaminobenzene (**52**) (502 mg, 3.6 mmol) and 4-nitrobenzaldehyde (**53**) (552 mg, 3.7 mmol) dissolved in benzene (anhydrous, 10 mL) under argon atmosphere was added 4 Å molecular sieves (3 g; the molecular sieves were charged by heating to 120 °C under vacuum overnight and then stored under argon atmosphere). The reaction proceeded at ambient temperature without stirring for 23 h. The molecular sieves were removed by filtration and then rinsed with CH₂Cl₂. The filtrate was concentrated and the product was recrystallized from EtOAc to give **54** (532 mg, 1.96 mmol, 54%) as a fluffy yellow solid: ¹H NMR δ 8.51 (s, 1 H), 8.36 (d, *J* = 8.7 Hz, 2 H), 8.09 (d, *J* = 8.7 Hz, 2 H), 8.02 (dd, *J* = 8.1 and 1.4 Hz, 1 H), 7.64 (dt, *J* = 7.9 and 1.4 Hz, 1 H), 7.38 (dt, *J* = 7.8 and 1.2 Hz, 1 H), 7.08 (d, *J* = 7.9 Hz, 1 H); ¹³C NMR δ 159.3 (-), 149.6 (+), 145.8 (+), 142.8 (+), 140.5 (+), 134.1 (-), 129.9 (-), 126.3 (-), 124.8 (-), 124.0 (-), 120.5 (-).

2-Nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (56**).**

To a solution of 2-nitroaminobenzene (**52**) (502 mg, 3.6 mmol) and 2-methylpropanal (**55**) (0.33 mL, 3.6 mmol) dissolved in benzene (anhydrous, 10 mL) at -20 °C under argon atmosphere was added 4 Å molecular sieves (4 g; the molecular sieves were charged by heating to 120 °C under vacuum overnight and then stored under argon atmosphere). The reaction proceeded at -20 °C for 14 days. The molecular sieves were removed by filtration and then rinsed with CH₂Cl₂. The filtrate was concentrated and the product was purified by flash chromatography (hexanes/EtOAc, 95:5) to give **56** (510 mg, 2.7 mmol, 73%) as a red solid: mp 38-40°C; ¹H NMR δ 9.64 (br s, 1 H), 8.18 (dd, *J* = 8.4 and 1.5 Hz, 1 H), 7.44 (dt, *J* = 8.6 and 1.5 Hz, 1 H), 7.05 (d, *J* = 8.7 Hz, 1 H), 6.70 (dt, *J* = 6.9 and 1.2 Hz, 1 H), 6.27 (dm, *J* = 8.2 and 1.2

Hz, 1 H), 1.82 (s, 3 H), 1.80 (s, 3 H); ^{13}C NMR δ 141.3 (+), 136.0 (-), 131.6 (+), 126.7 (-), 118.4 (+), 118.2 (-), 116.3 (-), 114.1 (-), 22.5 (-), 16.6 (-); IR (neat) 1639, 1577, 1208 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$ 192.0899, found 192.0899.

1,2-Dihydro-2,2-dimethylquinoxaline⁶² (57) and 3,4-dihydro-3,3-dimethyl-2-quinoxalinone⁶³ (58).

2-Nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (**56**) (102 mg, 0.53 mmol), $\text{Pd}(\text{dba})_2$ (20 mg, 0.035 mmol), 1,3-bis(diphenylphosphino)propane (dppp) (15 mg, 0.036 mmol) and acetonitrile (5 mL) were combined in a threaded pressure tube fitted with a pressure head. The tube was flushed 3 times with CO. The reaction was heated and stirred at 70 °C under CO (4 atm) for 20 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 . The filtrate was concentrated and the product was purified by flash chromatography (hexanes/EtOAc, 7:3) to give **57** (60 mg, 0.375 mmol, 71%) and **58** (10 mg, 0.057 mmol, 11%) as off-white solids.

4-Methyl-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (60).

The same procedure as described for **56** was repeated except that a mixture of 4-methyl-2-nitroaminobenzene (**59**) (501 mg, 3.3 mmol), 2-methylpropanal (**55**) (0.30 mL, 3.3 mmol), benzene (anhydrous, 10 mL) and 4 Å molecular sieves (4 g) at ambient temperature was reacted for 20 h. Purification by flash chromatography (hexanes/EtOAc, 95:5) gave **60** (601 mg, 2.9 mmol, 89%) as a red solid: mp 53-55°C; ^1H NMR δ 9.56 (br s, 1 H), 7.98 (s, 1 H), 7.27 (dd, J = 8.6 and 2.2 Hz, 1 H), 6.96 (d, J = 8.9 Hz, 1 H), 6.27 (dm, J = 9.6 Hz, 1 H), 2.28 (s, 3 H), 1.81 (s, 3 H), 1.79 (s, 3 H); ^{13}C NMR δ 139.4 (+), 137.5 (-), 131.1 (+), 126.0 (+), 125.8 (-), 118.4 (-),

117.4 (+), 114.1 (-), 22.4 (-), 19.9 (-), 16.6 (-); IR (neat) 1632, 1572, 1519, 1341, 1166 cm^{-1} ;

Anal. calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$: C, 64.06; H, 6.84, found: C, 64.18; H, 6.70.

4-Methoxy-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (62).

The same procedure as described for **56** was repeated except that a mixture of 4-methoxy-2-nitroaminobenzene (**61**) (506 mg, 3.0 mmol), 2-methylpropanal (**55**) (0.30 mL, 3.3 mmol), benzene (anhydrous, 10 mL) and 4 Å molecular sieves (4 g) at ambient temperature was reacted for 20 h. Purification by flash chromatography (hexanes/EtOAc, 98:2) gave **62** (635 mg, 2.9 mmol, 95%) as a red solid: mp 57-59°C; ^1H NMR δ 9.61 (d, J = 8.2 Hz, 1 H), 7.60 (d, J = 2.7 Hz, 1 H), 7.15 (dd, J = 9.4 and 3.0 Hz, 1 H), 7.02 (d, J = 9.4 Hz, 1 H), 6.27 (dm, J = 9.6 Hz, 1 H), 3.81 (s, 3 H), 1.81 (s, 3 H), 1.79 (s, 3 H); ^{13}C NMR δ 150.2 (+), 137.0 (+), 130.6 (+), 127.1 (-), 118.5 (-), 117.5 (+), 115.5 (-), 106.5 (-), 55.6 (-), 22.4 (-), 16.6 (-); IR (neat) 1638, 1520, 1162, 1122 cm^{-1} ; Anal. calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3$: C, 59.45; H, 6.35, found: C, 59.18; H, 6.42.

4-Chloro-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (64).

The same procedure as described for **56** was repeated except that a mixture of 4-chloro-2-nitroaminobenzene (**63**) (505 mg, 2.9 mmol), 2-methylpropanal (**55**) (0.27 mL, 2.9 mmol), benzene (anhydrous, 10 mL) and 4 Å molecular sieves (4 g) at ambient temperature was reacted for 26 h. No further purification was needed and **64** (660 mg, 2.9 mmol, 100%) was obtained as a red solid: mp 109-110°C; ^1H NMR δ 9.58 (d, J = 8.2 Hz, 1 H), 8.17 (d, J = 2.7 Hz, 1 H), 7.38 (dd, J = 9.2 and 2.5 Hz, 1 H), 7.01 (d, J = 9.1 Hz, 1 H), 6.22 (dm, J = 9.6 and 1.2 Hz, 1 H), 1.82 (s, 3 H), 1.79 (s, 3 H); ^{13}C NMR δ 140.0 (+), 136.2 (-), 131.5 (+), 125.9 (-), 121.2 (+), 119.9 (+),

118.0 (-), 115.7 (-), 22.5 (-), 16.8 (-); IR (neat) 1641, 1198, 1124 cm^{-1} ; Anal. Calc for $\text{C}_{10}\text{H}_{11}\text{ClN}_2\text{O}_2$: C, 52.99; H, 4.89, found: C, 53.08; H, 4.82.

5-Chloro-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (66).

The same procedure as described for **56** was repeated except that a mixture of 5-chloro-2-nitroaminobenzene (**65**) (504 mg, 2.9 mmol), 2-methylpropanal (**55**) (0.30 mL, 3.3 mmol), CH_2Cl_2 (anhydrous, 15 mL) and 4 Å molecular sieves (4 g) at ambient temperature was reacted for 24 h. No further purification was needed and **66** (585 mg, 2.6 mmol, 88%) was obtained as a red solid: mp 99-100°C; ^1H NMR δ 9.60 (br s, 1 H), 8.13 (d, $J = 9.2$ Hz, 1 H), 7.02 (d, $J = 2.2$ Hz, 1 H), 6.66 (dd, $J = 9.2$ and 2.2 Hz, 1 H), 6.19 (d, $J = 9.4$ Hz, 1 H), 1.83 (s, 3 H), 1.79 (s, 3 H); ^{13}C NMR δ 142.8 (+), 141.8 (+), 130.3 (+), 128.2 (-), 120.5 (+), 117.8 (-), 116.9 (-), 113.8 (-), 22.5 (-), 16.8 (-); IR (neat) 3326, 3112, 2927, 1570, 1494, 1410, 1190, 1064 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{10}\text{H}_{11}\text{ClN}_2\text{O}_2$ 226.0509, found 226.0500.

6-Methyl-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (68).

To a solution of 2-methyl-6-nitroaminobenzene (**67**) (1.03 g, 6.8 mmol) and 2-methylpropanal (**55**) (2.0 mL, 22.0 mmol) dissolved in 1,2-dichloroethane (20 mL) in a threaded pressure tube was added 4 Å molecular sieves until the level of the sieves was just below that of the solvent (the molecular sieves were charged by heating to 120 °C under vacuum overnight and then stored under argon atmosphere). The pressure tube was capped tightly with a threaded Teflon plug. The reaction was heated in a standard microwave oven for 30 seconds then allowed to cool for 3-5 minutes. This was repeated until the total heating time reached 15 minutes. The molecular sieves were removed by filtration and washed with CH_2Cl_2 . The filtrate was

concentrated and the product was purified by flash chromatography (hexanes/EtOAc, 9:1) to give **68** (71 mg, 0.34 mmol, 5%) as a red paste: ^1H NMR δ 8.75 (d, J = 5.9 Hz, 1 H), 7.95 (d, J = 8.6 Hz, 1 H), 7.30 (d, J = 7.4 Hz, 1 H), 6.76 (t, J = 7.7 Hz, 1 H), 5.98 (d, J = 8.4 Hz, 1 H), 2.40 (s, 3 H), 1.76 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR δ 141.5 (+), 138.2 (-), 137.3 (+), 129.4 (+), 124.2 (-), 124.1 (-), 118.5 (-), 114.6 (+), 22.2 (-), 20.9 (-), 16.3 (-); IR (neat) 1634, 1519, 1339 cm^{-1} .

2,4-Dinitro-*N*-[(2-methyl)-1-propenyl]benzenamine (70).

The same procedure as described for **68** was repeated except that a mixture of 2,4-dinitroaminobenzene (**69**) (1.00 g, 5.5 mmol), 2-methylpropanal (**55**) (1.0 mL, 13.9 mmol) and 1,2-dichloroethane (20 mL) was reacted for a total of 15 minutes. Purification by flash chromatography (hexanes/EtOAc, 9:1) gave **70** (1.00 g, 4.3 mmol, 78%) as a red solid: mp 113-115°C; ^1H NMR δ 10.06 (d, J = 8.2 Hz, 1 H), 9.16 (d, J = 2.5 Hz, 1 H), 8.27 (dd, J = 9.6 and 2.7 Hz, 1 H), 7.12 (d, J = 9.6 Hz, 1 H), 6.32 (d, J = 9.4 Hz, 1 H), 1.88 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR δ 143.8 (+), 136.5 (+), 130.0 (-), 129.9 (+), 124.1 (-), 124.0 (+), 117.0 (-), 114.4 (-), 22.5 (-), 16.8 (-); IR (neat) 1590, 1461, 1426, 1330, 1307 cm^{-1} ; Anal. calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_4$: C, 50.63; H, 4.67, found: C, 50.79; H, 4.77.

3-Methyl-2-nitroaminobenzene⁶⁴ (71).

To a solution of 3-methyl-2-nitrobenzoic acid (**84**) (4.90 g, 27.0 mmol) dissolved in 1,2-dichloroethane (100 mL) was added SOCl_2 (10.0 mL, 137 mmol) and *N,N*-dimethylformamide (DMF) (1 drop). The reaction refluxed under argon atmosphere for 3 h and was then concentrated by vacuum distillation. The resulting material was added to acetone (75 mL, 0 °C). To this solution was added NaN_3 (10.1 g, 155 mmol in 40 mL H_2O) and the mixture stirred for

10 minutes. This solution was added to H₂O (300 mL) and the resulting solid (acyl azide) was collected by filtration and used without further purification.

The crude acyl azide was dissolved in AcOH/distilled H₂O (10:1, 330 mL) and refluxed for 2 h. The reaction was concentrated by vacuum distillation. The resulting solid was recrystallized from AcOH to give **71** (2.48 g, 16.3 mmol, 60%): ¹H NMR δ 7.14 (t, *J* = 7.7 Hz, 1 H), 6.65 (d, *J* = 8.3 Hz, 1 H), 6.58 (d, *J* = 7.3 Hz, 1 H), 5.15 (br s, 2 H), 2.47 (s, 3 H); ¹³C NMR (150 MHz) δ 142.9 (+), 136.1 (+), 135.0 (+), 132.7 (-), 120.7 (-), 116.0 (-), 20.9 (-).

3-Methyl-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (72).

The same procedure as described for **56** was repeated except that a mixture of 3-methyl-2-nitroaminobenzene (**71**) (500 mg, 3.3 mmol), 2-methylpropanal (**55**) (0.50 mL, 5.5 mmol), benzene (anhydrous, 20 mL) and 4 Å molecular sieves (15 g) at ambient temperature was reacted for 3 days. Purification by flash chromatography (hexanes) gave **72** (241 mg, 1.17 mmol, 36%) as a red paste: ¹H NMR δ 8.24 (d, *J* = 8.4 Hz, 1 H), 7.23 (t, *J* = 7.9 Hz, 1 H), 6.84 (d, *J* = 8.6 Hz, 1 H), 6.58 (d, *J* = 7.4 Hz, 1 H), 6.12 (d, *J* = 9.4 Hz, 1 H), 2.49 (s, 3 H), 1.78 (s, 3 H), 1.73 (s, 3 H); ¹³C NMR δ 140.3 (+), 135.9 (+), 135.5, 133.3 (-), 120.5 (-), 119.4 (-), 116.8 (+), 112.3 (-), 22.5 (-), 21.6 (-), 16.6 (-).

[4-(2-Methylpropenylamino)-3-nitrophenyl]phenylmethanone (74).

The same procedure as described for **56** was repeated except that a mixture of 3-nitro-4-aminobenzophenone (**73**) (500 mg, 2.1 mmol), 2-methylpropanal (**55**) (0.30 mL, 3.3 mmol), CH₂Cl₂ (anhydrous, 40 mL) and 4 Å molecular sieves (15 g) at ambient temperature was reacted for 12 days. Purification by flash chromatography (hexanes/EtOAc, 9:1) gave **74** (120 mg, 0.41

mmol, 20%) as a red solid: ^1H NMR δ 9.96 (d, J = 9.4 Hz, 1 H), 8.66 (d, J = 2.0 Hz, 1 H), 8.04 (dd, J = 9.1 and 2.0 Hz, 1 H), 7.75 (dd, J = 8.4 and 1.5 Hz, 2 H), 7.60 (t, 1 H), 7.50 (t, 2 H), 7.14 (d, J = 9.1 Hz, 1 H), 6.34 (d, J = 9.4 Hz, 1 H), 1.86 (s, 3 H), 1.84 (s, 3 H); ^{13}C NMR δ 193.4 (+), 143.4 (+), 137.4 (+), 136.8 (-), 132.3 (-), 130.7 (-), 130.5 (+), 129.4 (-), 128.5 (-), 125.5 (+), 121.8 (+), 117.6 (-), 114.3 (-), 22.6 (-), 16.9 (-); IR (neat) 1650, 1612, 1209, 1132 cm^{-1} .

Methyl 4-amino-3-nitrobenzoate⁶⁵ (75).

Methanol (30.0 mL, 741 mmol), 4-amino-3-nitrobenzoic acid (**85**) (2.00 g, 11.0 mmol), H_2SO_4 (concentrated, 1.0 mL) and benzene (anhydrous, 100 mL) were combined in a round-bottomed flask fitted with a Dean-Stark trap and a reflux condenser. The reaction was heated and stirred at reflux for 13 h. The reaction mixture was then concentrated and added to CHCl_3 (100 mL). The solution was washed with NaHCO_3 (20% aqueous solution, 2 X 100 mL). The organic phase was dried (MgSO_4), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 9:1, 8:2 and 7:3) gave **75** (1.50 g, 7.6 mmol, 69%) as a yellow solid.

Methyl 4-(2-methylpropenylamino)-3-nitrobenzoate (76).

The same procedure as described for **56** was repeated except that a mixture of methyl 4-amino-3-nitrobenzoate (**75**) (500 mg, 2.6 mmol), 2-methylpropanal (**55**) (5.0 mL, 55.1 mmol), camphor sulfonic acid (10 mg), CH_2Cl_2 (anhydrous, 150 mL) and 4 Å molecular sieves (50 g) at ambient temperature was reacted for 11 days. Purification by flash chromatography (hexanes/EtOAc, 95:5) gave **76** (470 mg, 1.88 mmol, 74%) as a red solid: mp 121-124 $^\circ\text{C}$; ^1H NMR δ 9.87 (d, J = 11.4 Hz, 1 H), 8.89 (d, J = 2.0 Hz, 1 H), 8.05 (dd, J = 9.2 and 1.5 Hz, 1 H),

7.06 (d, $J = 9.2$ Hz, 1 H), 6.30 (d, $J = 9.4$ Hz, 1 H), 3.91 (s, 3 H), 1.85 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR δ 165.4 (+), 143.4 (+), 136.1 (-), 131.0 (+), 129.4 (-), 121.2 (+), 118.1 (+), 117.6 (-), 113.9 (-), 52.1 (-), 22.6 (-), 16.8 (-); IR (neat) 1707, 1615, 1523, 1437, 1287, 1217 cm^{-1} .

4-Methoxy-2-nitro-*N*-(cyclohexylmethylene)benzenamine (78).

The same procedure as described for **56** was repeated except that a mixture of 4-methoxy-2-nitroaminobenzene (**61**) (508 mg, 3.0 mmol), formylcyclohexane (**77**) (0.360 mL, 3.2 mmol), benzene (anhydrous, 10 mL) and 4 Å molecular sieves (4 g) at ambient temperature was reacted for 2.5 h. No further purification was needed and **78** (696 mg, 2.7 mmol, 88%) was obtained as a red solid: mp 46-48°C; ^1H NMR δ 9.68 (br s, 1 H), 7.60 (d, $J = 2.7$ Hz, 1 H), 7.15 (dd, $J = 9.4$ and 3.2 Hz, 1 H), 7.05 (d, $J = 9.2$ Hz, 1 H), 6.22 (d, $J = 9.4$ Hz, 1 H), 3.81 (s, 3 H), 2.30-1.50 (m, 10 H); ^{13}C NMR δ 150.3 (+), 137.4 (+), 130.6 (+), 127.2 (-), 126.1 (+), 115.6 (-), 115.5 (-), 106.6 (-), 55.7 (-), 33.6 (+), 28.3 (+), 27.5 (+), 26.9 (+), 26.6 (+); IR (neat) 2929, 2360, 1572, 1517, 1411, 1283, 1214 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$ 262.1317, found 262.1310.

4-Methoxy-2-nitro-*N*-(2,2-diphenylethenyl)benzenamine (80).

The same procedure as described for **56** was repeated except that a mixture of 4-methoxy-2-nitroaminobenzene (**61**) (304 mg, 1.8 mmol), diphenylacetaldehyde (**79**) (0.40 mL, 2.3 mmol), CH_2Cl_2 (anhydrous, 30 mL) and 4 Å molecular sieves (15 g) at ambient temperature was reacted for 3 days. Purification by flash chromatography (hexanes/EtOAc, 9:1) gave **80** (572 mg, 1.7 mmol, 91%) as a red solid: mp 152-153°C; ^1H NMR δ 9.93 (d, $J = 11.6$ Hz, 1 H), 7.53 (d, $J = 2.7$ Hz, 1 H), 7.48-7.05 (m, 13 H), 3.74 (s, 3 H); ^{13}C NMR δ 151.3 (+), 140.7 (+),

137.4 (+), 135.1 (+), 132.2 (+), 129.7 (-), 129.3 (-), 128.4 (-), 127.9 (-), 126.6 (-), 126.5 (two overlapping peaks; both -), 124.0 (+), 121.6 (-), 115.8 (-), 107.4 (-), 55.8 (-); IR (neat) 3055, 1517, 1283, 1218, 1139, 1062 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3$ 346.1317, found 346.1306.

(*E*)-4-Chloro-2-nitro-*N*-(2-phenylethylene)benzenamine (82-*E***) and (*Z*)-4-chloro-2-nitro-*N*-(2-phenylethylene)benzenamine (**82-*Z***).**

The same procedure as described for **56** was repeated except that a mixture of 4-chloro-2-nitroaminobenzene (**63**) (1.00 g, 5.8 mmol), phenylacetaldehyde (**81**) (0.70 mL, 6.0 mmol), CH_2Cl_2 (anhydrous, 35 mL) and 4 Å molecular sieves (15 g) at ambient temperature was reacted for 20 h. A virtually inseparable mixture of **82-*E*** and **82-*Z*** (1.35 g, 4.9 mmol, 85%) resulted as a red solid: **82-*Z*** mp 104-106°C; ^1H NMR δ 10.41 (d, J = 10.6 Hz, 1 H), 8.20 (d, J = 2.5 Hz, 1 H), 7.50-7.40 (m, 5 H), 7.27 (tt, J = 6.9 and 1.7 Hz, 1 H), 7.18 (d, J = 9.2 Hz, 1 H), 6.64 (dd, J = 11.1 and 9.4 Hz, 1 H), 5.83 (d, J = 9.2 Hz, 1 H); ^{13}C NMR δ 138.9 (+), 136.3 (-), 135.2 (+), 132.7 (+), 129.1 (-), 127.7 (-), 127.1 (-), 126.1 (-), 122.9 (+), 122.5 (-), 115.8 (-), 111.5 (-); IR (neat) 3317, 2352, 1640, 1619, 1567, 1513, 1341 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{O}_2$ 274.0509, found 274.0513; **82-*E*** ^1H NMR δ 9.87 (d, J = 11.9 Hz, 1 H), 8.14 (d, J = 2.5 Hz, 1 H), 7.60-7.20 (m, 6 H), 7.06 (d, J = 15.8 Hz, 1 H), 6.98 (d, J = 11.4 Hz, 1 H), 6.16 (d, J = 15.6 Hz, 1 H).

3-Nitro-*N*-[(2-methyl)-1-propenyl]-2-pyridinamine (87) and *N*-(1-(3-nitropyridin-2-ylamino)-2-methylpropyl)-3-nitropyridin-2-amine (88).

The same procedure as described for **56** was repeated except that a mixture of 2-amino-3-nitropyridine (**86**) (505 mg, 3.6 mmol), 2-methylpropanal (**55**) (0.35 mL, 3.9 mmol), CH₂Cl₂ (anhydrous, 35 mL) and 4 Å molecular sieves (15 g) at ambient temperature was reacted for 5 days. Purification by flash chromatography (hexanes/EtOAc, 9:1) gave **87** (139 mg, 0.7 mmol, 20%) as a red solid and **88** (258 mg, 0.8 mmol, 44%) as a yellow solid: **87** mp 62-64°C; ¹H NMR δ 9.87 (br s, 1 H), 8.50-8.40 (m, 2 H), 7.08 (d, *J* = 8.2 Hz, 1 H), 6.80-6.60 (m, 1 H), 1.84 (s, 3 H), 1.82 (s, 3 H); ¹³C NMR δ 155.8 (-), 148.4 (+), 135.4 (-), 127.6 (+), 117.3 (-), 116.8 (+), 112.8 (-), 22.7 (-), 16.8 (-); IR (neat) 3364, 2917, 1678, 1604, 1574, 1494, 1444 cm⁻¹; Anal. calcd for C₉H₁₁N₃O₂: C, 55.95; H, 5.74, found: C, 56.06; H, 5.69; **88** mp 101-103 °C; ¹H NMR δ 8.81 (d, *J* = 7.9 Hz, 2 H), 8.45-8.35 (m, 4 H), 6.73-6.67 (m, 2 H), 6.29 (quartet, *J* = 7.6 Hz, 1 H), 2.63 (octet, *J* = 6.9 Hz, 1 H), 1.11 (d, *J* = 6.7 Hz, 6 H); ¹³C NMR δ 155.2 (-), 151.7 (+), 135.1 (-), 128.1 (+), 112.4 (-), 64.2 (-), 32.0 (-), 18.4 (-); IR (neat) 3372, 1600, 1569, 1481, 1443, 1245 cm⁻¹.

2-(2-Nitrophenylamino)-2-cyclohexen-1-one (90).

2-Nitroaminobenzene (**52**) (2.00 g, 14.5 mmol), 1,2-cyclohexanedione (**89**) (1.90 g, 16.9 mmol), benzene (anhydrous, 40 mL) and concentrated H₂SO₄ (5 drops) were combined in a round-bottomed flask fitted with a Dean-Stark trap and a reflux condenser. The reaction was heated and stirred at reflux for 21 h. The reaction mixture was then concentrated. Purification by flash chromatography (hexanes/EtOAc, 9:1, then 8:2) gave **90** (1.07 g, 4.6 mmol, 32%) as an orange solid: mp 75-77 °C; ¹H NMR δ 9.38 (br s, 1 H), 8.18 (dd, *J* = 8.7 and 1.5 Hz, 1 H), 7.43

(ddd, $J = 8.7, 7.4$ and 1.7 Hz, 1 H), 7.31 (dd, $J = 8.7$ and 1.5 Hz, 1 H), 6.87-6.77 (m, 2 H), 2.65-2.54 (m, 4 H), 2.10 (pentet, $J = 6.2$ Hz, 2H); ^{13}C NMR δ 194.6 (+), 140.6 (+), 135.2 (-), 134.8 (+), 134.6 (+), 129.7 (-), 126.7 (-), 118.1 (-), 116.8 (-), 37.7 (+), 25.0 (+), 22.4 (+); IR (neat) 3294, 2944, 1672, 1571, 1430, 1246, 1155 cm^{-1} .

3-(2-Nitrophenylamino)-2-cyclohexen-1-one⁶⁶ (92).

The same procedure as described for **90** was repeated except that a mixture of 2-nitroaminobenzene (**52**) (1.26 g, 9.1 mmol), 1,3-cyclohexanedione (**91**) (1.00 g, 8.9 mmol), benzene (anhydrous, 30 mL) and concentrated H_2SO_4 (3 drops) was reacted for 22 h. The product was recrystallized from EtOAc to give **92** (1.45 g, 6.3 mmol, 70%) as a yellow solid: ^1H NMR (600 MHz) δ 8.66 (br s, 1 H), 8.17 (dd, $J = 8.4$ and 1.8 Hz, 1 H), 7.68 (dd, $J = 7.8$ and 1.2 Hz, 1 H), 7.58 (dt, $J = 7.2$ and 1.8 Hz, 1 H), 7.15 (dt, $J = 7.2$ and 1.2 Hz, 1 H), 5.97 (s, 1 H), 2.60 (t, $J = 6.0$ Hz, 2 H), 2.43 (t, $J = 6.0$ Hz, 2 H), 2.10 (pentet, $J = 6.6$ Hz, 2 H); ^{13}C NMR (150 MHz) δ 198.7, 158.0, 138.7, 135.7, 135.0, 126.4, 123.4, 123.1, 105.0, 36.6, 30.6, 21.5.

(Z)-4-(2-Nitrophenylamino)-3-buten-2-one⁶⁷ (95).

2-Nitroaminobenzene (**52**) (1.50 g, 10.9 mmol), (*E*)-4-methoxy-3-buten-2-one²⁶ (**94**) (1.0 mL, 9.8 mmol), *p*-toluenesulfonic acid (10 mg) and CH_2Cl_2 (anhydrous, 10 mL) were combined, heated and stirred at reflux for 9 h. The reaction mixture was then concentrated. Purification by flash chromatography (hexanes/EtOAc, 9:1) gave **95** (1.98 g, 9.6 mmol, 98%) as a yellow solid: ^1H NMR δ 13.11 (br s, 1 H), 8.24 (dd, $J = 8.4$ and 1.5 Hz, 1 H), 7.59 (t, $J = 7.2$ Hz, 1 H), 7.36 (d, $J = 8.7$ Hz, 1 H), 7.24 (dd, $J = 11.8$ and 8.1 Hz, 1 H), 7.08 (t, $J = 8.4$ Hz, 1 H), 5.55 (d, $J = 8.1$

Hz, 1 H), 2.24 (s, 3 H); ^{13}C NMR (150 MHz) δ 199.0, 138.6, 137.4, 136.0, 135.5, 126.8, 121.5, 115.4, 102.4, 30.0.

(Z)-4-(4-Methyl-2-nitrophenylamino)-3-buten-2-one (96).

The same procedure as described for **95** was repeated except that a mixture of 4-methyl-2-nitroaminobenzene (**59**) (2.00 g, 13.1 mmol), (*E*)-4-methoxy-3-buten-2-one²⁶ (**94**) (1.4 mL, 13.7 mmol), *p*-toluenesulfonic acid (10 mg) and CH_2Cl_2 (anhydrous, 15 mL) reacted at reflux for 7 h. The product was recrystallized from ethanol to give **96** (2.48 g, 11.2 mmol, 86%) as a yellow solid: mp 135-137 °C; ^1H NMR δ 13.00 (br s, 1 H), 8.04 (s, 1 H), 7.41 (d, J = 8.6 Hz, 1 H), 7.25-7.15 (m, 2 H), 5.52 (d, J = 7.9 Hz, 1 H), 2.37 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR δ 198.8 (+), 139.1 (-), 136.5 (-), 135.7 (+), 135.1 (+), 131.8 (+), 126.3 (-), 115.4 (-), 101.7 (-), 29.9 (-), 20.2 (-); IR (neat) 1646, 1564, 1528, 1460, 1345, 1269, 1196 cm^{-1} .

(Z)-4-(5-Methyl-2-nitrophenylamino)-3-buten-2-one (97).

The same procedure as described for **95** was repeated except that a mixture of 5-methyl-2-nitroaminobenzene (**93**) (2.00 g, 13.1 mmol), (*E*)-4-methoxy-3-buten-2-one²⁶ (**94**) (1.4 mL, 13.7 mmol), *p*-toluenesulfonic acid (10 mg) and CH_2Cl_2 (anhydrous, 15 mL) reacted at reflux for 12 h. The product was recrystallized from ethanol to give **97** (2.07 g, 9.4 mmol, 71%) as an orange solid: mp 124-126 °C; ^1H NMR δ 13.10 (d, J = 9.9 Hz, 1 H), 8.14 (d, J = 8.6 Hz, 1 H), 7.25 (dd, J = 11.9 and 8.3 Hz, 1 H), 7.14 (s, 1 H), 6.87 (d, J = 8.6 Hz, 1 H), 5.54 (d, J = 7.9 Hz, 1 H), 2.43 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR (150 MHz) δ 198.8 (+), 147.2 (+), 138.6 (-), 137.2 (+), 133.7 (+), 126.6 (-), 122.6 (-), 115.3 (-), 102.1 (-), 29.9 (-), 21.9 (-); IR (neat) 1654, 1595, 1500, 1334, 1195, 1168 cm^{-1} .

1,2-Dihydro-2,2,7-trimethylquinoxaline (98) and 3,4-dihydro-3,3,6-trimethyl-2-quinoxalinone⁶³ (99).

The same procedure as described for **57** was repeated except that a mixture of 4-methyl-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (**60**) (102 mg, 0.49 mmol), Pd(dba)₂ (18 mg, 0.031 mmol), dppp (14 mg, 0.034 mmol), 1,10-phenanthroline monohydrate (phen) (12 mg, 0.067 mmol) and DMF (5 mL) was reacted at 70 °C under CO (6 atm) for 2 h. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and washed with brine (3 X 30 mL). The combined aqueous phases were extracted with CH₂Cl₂ (1 X 30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 7:3) gave **98** (43 mg, 0.25 mmol, 50%) and **99** (42 mg, 0.22 mmol, 45%) as off-white solids: **98** mp 112-115°C; ¹H NMR δ 7.23 (s, 1 H), 7.13 (d, *J* = 7.7 Hz, 1 H), 6.53 (d, *J* = 7.7 Hz, 1 H), 6.31 (s, 1 H), 3.87 (d, *J* = 4.2 Hz, 1 H), 2.42 (s, 3 H), 1.30 (s, 6 H); ¹³C NMR δ 159.5 (-), 139.0 (+), 136.4 (+), 129.2 (+), 127.4 (-), 119.2 (-), 114.1 (-), 50.3 (+), 27.1 (-), 21.4 (-); IR (neat) 3240, 2964, 1610, 1482, 1453, 1322, 1246 cm⁻¹; HRMS (EI) calc. for C₁₁H₁₄N₂ 174.1157, found 174.1163; **99** ¹H NMR δ 8.46 (br s, 1 H), 6.64 (d, *J* = 7.9 Hz, 1 H), 6.57 (d, *J* = 8.6 Hz, 1 H), 6.49 (s, 1 H), 3.87 (br s, 1 H), 2.24 (s, 3 H), 1.40 (s, 6 H); ¹³C NMR (150 MHz) δ 171.5, 133.4, 132.7, 123.2, 119.9, 115.0, 114.9, 55.4, 25.5, 21.0.

1,2-Dihydro-2,2-dimethyl-7-methoxyquinoxaline (100) and 3,4-dihydro-3,3-dimethyl-6-methoxy-2-quinoxalinone⁶⁸ (101).

The same procedure as described for **57** was repeated except that a mixture of 4-methoxy-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (**62**) (200 mg, 0.90 mmol), Pd(dba)₂ (31 mg, 0.05 mmol), dppp (22 mg, 0.05 mmol), phen (19 mg, 0.10 mmol) and DMF (3 mL) was

reacted at 70 °C under CO (6 atm) for 18 h. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and washed with brine (3 X 40 mL). The combined aqueous phases were extracted with CH₂Cl₂ (1 X 40 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 8:2 and 6:4) gave **100** (130 mg, 0.68 mmol, 76%) and **101** (20 mg, 0.10 mmol, 11%) as off-white solids: **100** mp 65-66°C; ¹H NMR δ 7.20-7.10 (m, 2 H), 6.26 (dd, *J* = 8.6 and 2.5 Hz, 1 H), 6.02 (d, *J* = 2.5 Hz, 1 H), 3.85 (s, 1 H), 3.74 (s, 3 H), 1.30 (s, 6 H); ¹³C NMR δ 160.1 (+), 157.7 (-), 137.8 (+), 128.6 (-), 125.7 (+), 103.4 (-), 98.9 (-), 55.2 (-), 50.1 (+), 27.1 (-); IR (neat) 3362, 3260, 2963, 1619, 1583, 1454, 1249, 1209, 1166, 1035 cm⁻¹; HRMS (EI) calc. for C₁₁H₁₄N₂O 190.1106, found 190.1103; **101** ¹H NMR δ 7.81 (br s, 1 H), 6.62 (d, *J* = 8.4 Hz, 1 H), 6.32 (dd, *J* = 8.4 and 2.5 Hz, 1 H), 6.26 (d, *J* = 2.5 Hz, 1 H), 3.75 (s, 3 H), 3.67 (br s, 1 H), 1.41 (s, 6 H); ¹³C NMR (150 MHz) δ 170.6, 156.5, 134.0, 119.4, 115.4, 104.1, 100.8, 55.5, 55.4, 25.5.

7-Chloro-1,2-dihydro-2,2-dimethylquinoxaline (102) and 6-chloro-3,4-dihydro-3,3-dimethyl-2-quinoxalinone⁶⁸ (103).

The same procedure as described for **57** was repeated except that a mixture of 4-chloro-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (**64**) (100 mg, 0.44 mmol), Pd(dba)₂ (17 mg, 0.029 mmol), dppp (12 mg, 0.029 mmol), phen (12 mg, 0.067 mmol) and DMF (5 mL) was reacted at 70 °C under CO (6 atm) for 2 h. The reaction mixture was diluted with CH₂Cl₂ (30 mL) and washed with brine (3 X 30 mL). The combined aqueous phases were extracted with CH₂Cl₂ (1 X 40 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 7:3) gave **102** (48 mg, 0.25 mmol, 56%) and **103** (15 mg, 0.070 mmol, 16%) as off-white solids: **102** mp 136-138°C; ¹H NMR δ 7.26 (s,

1 H), 7.14 (d, J = 8.2 Hz, 1 H), 6.67 (dd, J = 8.4 and 2.2 Hz, 1 H), 6.48 (d, J = 2.2 Hz, 1 H), 3.75 (s, 1 H), 1.33 (s, 6 H); ^{13}C NMR δ 160.3 (-), 137.6 (+), 133.8 (+), 129.9 (+), 128.7 (-), 118.2 (-), 113.3 (-), 50.3 (-), 27.2 (-); IR (neat) 3229, 2972, 1600, 1480, 1451, 1238 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{10}\text{H}_{11}\text{ClN}_2$ 194.0611, found 194.0611; **103** ^1H NMR δ 7.48 (br s, 1 H), 6.73 (dd, J = 8.4 and 2.2 Hz, 1 H), 6.67 (d, J = 2.2 Hz, 1 H), 6.60 (d, J = 8.2 Hz, 1 H), 3.76 (br s, 1 H), 1.41 (s, 6 H); ^{13}C NMR (150 MHz) δ 170.9, 133.9, 128.6, 124.2, 119.1, 115.8, 114.1, 55.5, 25.6.

6-Chloro-1,2-dihydro-2,2-dimethylquinoxaline (104) and 7-chloro-3,4-dihydro-3,3-dimethyl-2-quinoxalinone⁶⁸ (105).

The same procedure as described for **57** was repeated except that a mixture of 5-chloro-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (**66**) (200 mg, 0.88 mmol), $\text{Pd}(\text{dba})_2$ (30 mg, 0.052 mmol), dppp (23 mg, 0.056 mmol), phen (21 mg, 0.117 mmol) and DMF (10 mL) was reacted at 70 °C under CO (6 atm) for 5.5 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with brine (3 X 30 mL). The combined aqueous phases were extracted with CH_2Cl_2 (1 X 40 mL). The combined organic phases were dried (MgSO_4), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 8:2) gave **104** (50 mg, 0.26 mmol, 29%) and **105** (84 mg, 0.40 mmol, 45%) as off-white solids: **104** mp 112-114°C; ^1H NMR δ 7.29 (d, J = 1.7 Hz, 1 H), 7.23 (d, J = 2.5 Hz, 1 H), 6.96 (dd, J = 8.4 and 2.2 Hz, 1 H), 6.42 (d, J = 8.4 Hz, 1 H), 3.78 (br s, 1 H), 1.31 (s, 6 H); ^{13}C NMR δ 161.5 (-), 135.3 (+), 132.1 (+), 128.4 (-), 127.3 (-), 122.5 (+), 114.5 (-), 50.4 (+), 27.0 (-); IR (neat) 3249, 2970, 1600, 1485, 1455 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{10}\text{H}_{11}\text{ClN}_2$ 194.0611, found 194.0619; **105** ^1H NMR δ 8.59 (br s, 1 H), 6.85 (dd, J = 8.4 and 2.2 Hz, 1 H), 6.76 (d, J = 2.0 Hz, 1 H), 6.59 (d, J = 8.4 Hz, 1 H), 3.72 (br s,

1 H), 1.41 (s, 6 H); ^{13}C NMR (150 MHz) δ 171.3, 131.5, 126.6, 124.1, 123.4, 115.1, 115.0, 55.5, 25.5.

1,2-Dihydro-2,2,5-trimethylquinoxaline (106) and 3,4-dihydro-3,3,8-trimethyl-2-quinoxalinone⁶⁸ (107).

The same procedure as described for **57** was repeated except that a mixture of 6-methyl-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (**68**) (43 mg, 0.21 mmol), Pd(dba)₂ (7 mg, 0.012 mmol), dppp (7 mg, 0.017 mmol), phen (7 mg, 0.039 mmol) and DMF (5 mL) was reacted at 70 °C under CO (6 atm) for 2 h. The reaction mixture was diluted with CH₂Cl₂ (30 mL) and washed with brine (3 X 30 mL). The combined aqueous phases were extracted with CH₂Cl₂ (1 X 30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 8:2) gave **106** (10 mg, 0.057 mmol, 27%) and **107** (17 mg, 0.089 mmol, 42%) as off-white solids: **106** mp 79-81°C; ^1H NMR δ 7.29 (s, 1 H), 6.91 (t, J = 7.7 Hz, 1 H), 6.58 (d, J = 7.7 Hz, 1 H), 6.35 (d, J = 7.7 Hz, 1 H), 3.65 (br s, 1 H), 2.41 (s, 3 H), 1.31 (s, 6 H); ^{13}C NMR (150 MHz) δ 158.8 (-), 136.5 (+), 135.6 (+), 129.8 (+), 128.1 (-), 119.9 (-), 111.6 (-), 49.5 (+), 26.7 (-), 17.2 (-); IR (neat) 3275, 2960, 1590, 1464, 1289, 1160 cm⁻¹; **107** ^1H NMR δ 7.51 (br s, 1 H), 6.81 (t, J = 7.6 Hz, 1 H), 6.63 (d, J = 6.9 Hz, 1 H), 6.55 (d, J = 7.9 Hz, 1 H), 3.68 (br s, 1 H), 2.22 (s, 3 H), 1.40 (s, 6 H); ^{13}C NMR (150 MHz) δ 171.0, 132.7, 123.8, 123.2, 122.6, 121.2, 112.5, 55.3, 25.4, 16.4.

Alternate procedure for 2-methyl-6-nitroaminobenzene⁶⁹ (67), 1,2-dihydro-2,2,5-trimethylquinoxaline (106) and 2-isopropyl-4-methylbenzimidazole⁷⁰ (136). To a solution of 2-azido-3-nitrotoluene (**135**) (1.00 g, 5.6 mmol) dissolved in diethyl ether (anhydrous, 40 mL) was added triphenylphosphine (1.5 g, 5.7 mmol). The mixture stirred under argon atmosphere at

ambient temperature for 1 h. The reaction was then concentrated. To the resulting solid was added CHCl_3 (40 mL) and 2-methylpropanal (**55**) (7.0 mL, 77.0 mmol). The reaction mixture stirred at reflux under argon atmosphere for 6 days. The red color of the reaction, as well as TLC, indicated that the desired enamine had been formed. The reaction was concentrated and the crude solid was used without further purification.

To a solution of the crude enamine dissolved in DMF (8 mL) in a threaded pressure tube fitted with a pressure head was added $\text{Pd}(\text{dba})_2$ (190 mg, 0.3 mmol), dppp (140 mg, 0.3 mmol) and phen (120 mg, 0.7 mmol). The tube was flushed 3 times with CO. The reaction was heated and stirred at 70 °C under CO (6 atm) for 21 h. The reaction mixture was concentrated and the product was purified by flash chromatography (hexanes/EtOAc, 9:1, 8:2, 1:1, 3:7 and EtOAc) to give **67** (71 mg, 0.47 mmol, 8%) as a yellow solid, **106** (106 mg, 0.6 mmol, 11%) as a pale yellow solid and **136** (603 mg, 3.46 mmol, 62%) as a tan solid.

1,2-Dihydro-2,2,8-trimethylquinoxaline (108) and 3,4-dihydro-3,3,5-trimethyl-2-quinoxalinone⁶⁸ (109).

The same procedure as described for **57** was repeated except that a mixture of 3-methyl-2-nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (**72**) (228 mg, 1.1 mmol), $\text{Pd}(\text{dba})_2$ (38 mg, 0.067 mmol), dppp (27 mg, 0.065 mmol), phen (24 mg, 0.13 mmol) and DMF (3 mL) was reacted at 70 °C under CO (6 atm) for 14 h. The solvent was removed under high vacuum. Purification by flash chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3 and 1:1) gave **108** (120 mg, 0.69 mmol, 63%) and **109** (26 mg, 0.14 mmol, 12%) as off-white solids: **108** mp 95-97°C; ^1H NMR δ 7.28 (d, J = 2.0 Hz, 1 H), 7.14 (d, J = 7.9 Hz, 1 H), 6.93 (d, J = 7.4 Hz, 1 H), 6.65 (t, J = 7.7 Hz, 1 H), 3.53 (br s, 1 H), 2.10 (s, 3 H), 1.34 (s, 6 H); ^{13}C NMR δ 159.7 (-), 134.5 (+), 130.7

(+), 129.8 (-), 125.5 (-), 120.8 (+), 117.3 (-), 50.2 (+), 27.3 (-), 16.0 (-); IR (neat) 2964, 1624, 1600, 1497, 1280, 1082 cm^{-1} ; **109** mp 182-184 °C; ^1H NMR δ 8.82 (br s, 1 H), 6.79 (dd, J = 6.7 and 2.0 Hz, 1 H), 6.73-6.63 (m, 2 H), 3.58 (br s, 1 H), 2.17 (s, 3 H), 1.43 (s, 6 H); ^{13}C NMR (150 MHz) δ 171.4, 130.9, 125.2, 125.1, 122.1, 118.8, 113.2, 55.4, 25.8, 16.6.

(3,4-Dihydro-3,3-dimethylquinoxalin-6-yl)phenylmethanone (110).

The same procedure as described for **57** was repeated except that a mixture of [4-(2-methylpropenylamino)-3-nitrophenyl]phenylmethanone (**74**) (120 mg, 0.40 mmol), $\text{Pd}(\text{dba})_2$ (14 mg, 0.024 mmol), dppp (10 mg, 0.024 mmol), phen (9 mg, 0.048 mmol) and DMF (5 mL) was reacted at 70 °C under CO (6 atm) for 18 h. The reaction mixture was filtered through Celite with EtOAc and the filtrate was concentrated. After numerous attempts to purify the product by flash chromatography, the yellow solid that was isolated was tentatively determined to be **110** (<56 mg, <0.2 mmol, <52%): ^1H NMR δ 7.79 (dd, J = 8.4 and 1.5 Hz, 2 H), 7.57 (t, J = 7.4 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.39 (d, J = 1.7 Hz, 1 H), 7.30 (d, J = 7.9 Hz, 1 H), 7.08 (dd, J = 7.9 and 1.8 Hz, 1 H), 7.03 (d, J = 1.7 Hz, 1 H), 4.08 (br s, 1 H), 1.34 (s, 6 H); ^{13}C NMR δ 196.4 (+), 163.0 (-), 137.6 (+), 137.5 (+), 136.8 (+), 134.3 (+), 132.2 (-), 129.9 (-), 128.1 (-), 127.1 (-), 120.8 (-), 115.0 (-), 50.5 (+), 27.1 (-).

Methyl 3,4-dihydro-3,3-dimethylquinoxaline-6-carboxylate (111) and methyl 1,2,3,4-tetrahydro-3,3-dimethyl-2-oxoquinoxaline-6-carboxylate (112).

The same procedure as described for **57** was repeated except that a mixture of methyl 4-(2-methylpropenylamino)-3-nitrobenzoate (**76**) (250 mg, 1.0 mmol), $\text{Pd}(\text{dba})_2$ (35 mg, 0.061 mmol), dppp (25 mg, 0.061 mmol), phen (22 mg, 0.12 mmol) and DMF (5 mL) was reacted at 70

°C under CO (6 atm) for 17 h. The reaction mixture was then concentrated. Purification by flash chromatography (hexanes/EtOAc, 8:2 and 6:4) gave an inseparable mixture of **111** (6 mg, 0.03 mmol, 3%) and **112** (5 mg, 0.02 mmol, 2%) as a tan solid⁷¹: data for the mixture ¹H NMR δ 8.93 (s, 1 H), 8.53 (s, 1 H), 7.97 (d, *J* = 8.2 Hz, 1 H), 7.56 (dd, *J* = 8.2 and 1.5 Hz, 1 H), 7.49 (dd, *J* = 8.2 and 1.5 Hz, 1 H), 7.29 (d, *J* = 1.2 Hz, 1 H), 6.98 (d, *J* = 8.2 Hz, 1 H), 4.08 (br s, 1 H), 3.94 (br s, 1 H), 3.88 (s, 6 H), 1.81 (s, 6 H), 1.71 (s, 6 H) (Note: One proton signal is missing. It is most likely masked by the solvent residual peak at 7.27 ppm).

7'-Methoxy-spiro[cyclohexane-1,2'(1'H)quinoxaline] (113) and 1',4'-dihydro-7'-methoxy-spiro[cyclohexane-1,2'(3'H)quinoxalin]3'-one (114).

The same procedure as described for **57** was repeated except that a mixture of 4-methoxy-2-nitro-*N*-(cyclohexylmethylene)benzenamine (**78**) (201 mg, 0.77 mmol), Pd(dba)₂ (27 mg, 0.047 mmol), dppp (19 mg, 0.046 mmol), phen (19 mg, 0.105 mmol) and DMF (10 mL) was reacted at 70 °C under CO (6 atm) for 4.5 h. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and washed with brine (4 X 50 mL). The combined aqueous phases were extracted with CH₂Cl₂ (1 X 50 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 7:3) gave **113** (123 mg, 0.534 mmol, 70%) and **114** (24 mg, 0.097 mmol, 13%) as off-white solids: **113** mp 141-142°C; ¹H NMR δ 7.23 (s, 1 H), 7.15 (d, *J* = 8.4 Hz, 1 H), 6.27 (dd, *J* = 8.4 and 2.5 Hz, 1 H), 6.08 (d, *J* = 2.7 Hz, 1 H), 4.06 (br s, 1 H), 3.76 (s, 3 H), 1.80-1.30 (m, 10 H); ¹³C NMR δ 160.0 (+), 157.7 (-), 137.7 (+), 128.5 (-), 126.5 (+), 103.4 (-), 99.0 (-), 55.1 (-), 51.4 (+), 34.7 (+), 25.1 (+), 20.3 (+); IR (neat) 3243, 2927, 1612, 1582, 1466, 1308, 1257, 1102 cm⁻¹; HRMS (EI) calc. for C₁₄H₁₈N₂O 230.1419, found 230.1410; **114** mp 260-263°C; ¹H NMR (DMSO-*d*₆) δ 9.93 (s,

1H), 6.59 (d, $J = 8.4$ Hz, 1 H), 6.52 (d, $J = 2.5$ Hz, 1 H), 6.17 (dd, $J = 8.6$ and 2.5 Hz, 1 H), 5.96 (s, 1 H), 3.63 (s, 3 H), 1.7- 1.4 (m, 10 H); ^{13}C NMR (DMSO- d_6) δ 169.5 (+), 155.3 (+), 134.4 (+), 120.0 (+), 116.6 (-), 102.8 (-), 100.3 (-), 55.6 (+), 54.9 (-), 31.4 (+), 25.0 (+), 19.9 (+); IR (neat) 3368, 2929, 1672, 1518, 1259, 1015 cm^{-1} ; HRMS (EI) calc for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$ 246.1368, found 246.1371.

1,2-Dihydro-2,2-diphenyl-7-methoxyquinoxaline (115).

The same procedure as described for **57** was repeated except that a mixture of 4-methoxy-2-nitro-*N*-(2,2-diphenylethenyl)benzenamine (**80**) (96 mg, 0.28 mmol), $\text{Pd}(\text{dba})_2$ (10 mg, 0.017 mmol), dppp (7 mg, 0.017 mmol), phen (7 mg, 0.039 mmol) and DMF (4 mL) was reacted at 70 °C under CO (6 atm) for 18 h. The solvent was removed under high vacuum. Purification by flash chromatography (hexanes/EtOAc, 8:2) gave **115** (60 mg, 0.19 mmol, 69%) as a tan solid: mp 164-166°C; ^1H NMR δ 7.59 (d, $J = 2.5$ Hz, 1 H), 7.40-7.25 (m, 10 H), 7.19 (d, $J = 8.7$ Hz, 1 H), 6.27 (dd, $J = 8.4$ and 2.5 Hz, 1 H), 6.09 (d, $J = 2.5$ Hz, 1 H), 4.43 (br s, 1 H), 3.75 (s, 3 H); ^{13}C NMR δ 160.5 (+), 153.3 (-), 144.1 (+), 136.5 (+), 129.1 (-), 128.6 (-), 127.6 (-), 127.4 (-), 124.7 (+), 103.8 (-), 98.4 (-), 62.5 (+), 55.2 (-); IR (neat) 3232, 2998, 2930, 1594, 1486, 1293, 1224, 1174, 1033 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}$ 314.1419, found 314.1409.

7-Chloro-2-phenylquinoxaline¹⁹ (116) and 6-chloro-3-phenyl-2-quinoxalinol⁷² (117).

The same procedure as described for **57** was repeated except that a mixture of (*E*) and (*Z*)-4-chloro-2-nitro-*N*-(2-phenylethylene)benzenamine (**82**) (106 mg, 0.39 mmol), $\text{Pd}(\text{dba})_2$ (13 mg, 0.023 mmol), dppp (10 mg, 0.024 mmol), phen (10 mg, 0.055 mmol) and DMF (10 mL) was reacted at 70 °C under CO (6 atm) for 48 h. The reaction mixture was diluted with CH_2Cl_2 (20

mL) and washed with brine (3 X 30 mL). The combined aqueous phases were extracted with CH₂Cl₂ (1 X 30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 9:1) gave **116** (23 mg, 0.096 mmol, 25%) and **117** (14 mg, 0.055 mmol, 14%) as off-white solids: **116** ¹H NMR δ 8.91 (s, 1 H), 8.69 (d, *J* = 2.2 Hz, 1 H), 8.08 (d, *J* = 8.9 Hz, 1 H), 8.00-7.95 (m, 2 H), 7.76 (dd, *J* = 8.9 and 2.2 Hz, 1 H), 7.62-7.51 (m, 3 H); ¹³C NMR (150 MHz) δ 147.5 (-), 143.0 (+), 139.8, 137.8, 137.0 (+), 132.2 (-), 131.4 (-), 130.6 (-), 129.5 (+), 129.4 (-), 128.8 (-), 119.0 (-); **117** ¹H NMR δ 9.32 (s, 1 H), 8.22-8.18 (m, 2 H), 8.16 (d, *J* = 2.2 Hz, 1 H), 8.06 (d, *J* = 8.9 Hz, 1 H), 7.69 (dd, *J* = 8.9 and 2.2 Hz, 1 H), 7.60-7.56 (m, 3 H); ¹³C NMR (150 MHz) δ 152.6, 143.4, 142.7, 140.1, 136.3, 136.1, 130.6, 130.5, 130.4, 129.2, 128.5, 127.6.

1,2-Dihydro-2,2-dimethylpyrido[2,3-*b*]pyrazine (118) and 1,2-dihydro-2,2-dimethylpyrido[2,3-*b*]pyrazin-3-one (119).

The same procedure as described for **57** was repeated except that a mixture of 3-nitro-*N*-[(2-methyl)-1-propenyl]-2-pyridinamine (**87**) (100 mg, 0.52 mmol), Pd(dba)₂ (18 mg, 0.031 mmol), dppp (14 mg, 0.034 mmol), phen (13 mg, 0.072 mmol) and DMF (5 mL) was reacted at 70 °C under CO (6 atm) for 6 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with brine (3 X 30 mL). The combined aqueous phases were extracted with EtOAc (1 X 30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 7:3) gave **118** (28 mg, 0.17 mmol, 34%) and **119** (5 mg, 0.028 mmol, 6%) as off-white solids: **118** ¹H NMR δ 9.28 (s, 1 H), 7.57 (dd, *J* = 4.7 and 1.5 Hz, 1 H), 6.85-6.70 (m, 2 H), 4.03 (br s, 1 H), 1.81 (s, 6 H); ¹³C NMR δ 157.5 (-), 146.2 (+), 137.5 (-), 131.9 (+), 119.6 (-), 115.2 (-), 80.0 (+), 27.5 (-); IR (neat) 2976, 1674,

1609, 1444, 1343, 1245 cm^{-1} ; **119** mp 202-205°C; ^1H NMR δ 9.24 (br s, 1 H), 7.83 (dd, J = 4.9 and 1.5 Hz, 1 H), 6.94 (dd, J = 7.9 and 1.5 Hz, 1H), 6.84 (dd, J = 7.7 and 4.9 Hz, 1 H), 3.72 (br s, 1 H), 1.45 (s, 6 h); ^{13}C NMR δ 171.0 (+), 140.3 (+), 137.9 (-), 128.5 (+), 120.2 (-), 119.1 (-), 56.0 (+), 26.1(-); IR (neat) 3310, 1683, 1558, 1458, 1289 cm^{-1} ; HRMS (EI) calc. for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}$ 177.0902, found 177.0899.

1-Hydroxyphenazine⁶⁹ (120), 1,2,3,4-tetrahydrophenazine⁷³ (121) and 3,4-dihydrophenazin-1(2H)-one⁷⁴ (122).

The same procedure as described for **57** was repeated except that a mixture of 2-(2-nitrophenylamino)-2-cyclohexen-1-one (**90**) (100 mg, 0.4 mmol), $\text{Pd}(\text{dba})_2$ (15 mg, 0.026 mmol), dppp (11 mg, 0.027 mmol), phen (10 mg, 0.061 mmol) and DMF (2 mL) was reacted at 70 °C under CO (6 atm) for 22 h. The solvent was removed under high vacuum. Purification by flash chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1 and 3:7) gave **120** (5 mg, 0.025 mmol, 6%), **121** (6 mg, 0.033 mmol, 8%) and **122** (13 mg, 0.066 mmol, 15%) as brown solids: **122** ^1H NMR δ 8.33 (dd, J = 8.4 and 1.5 Hz, 1 H), 8.07 (dd, J = 8.2 and 1.5 Hz, 1 H), 7.88 (dt, J = 6.9 and 1.5 Hz, 1 H), 7.81 (dt, J = 6.9 and 1.5 Hz, 1 H), 3.43 (t, J = 6.2 Hz, 2 H), 3.01 (t, J = 6.2 Hz, 2 H), 2.37 (pentet, J = 6.4 Hz, 2 H).

Alternate procedure A for 120. Compound **122** (25 mg, 0.13 mmol), 10% Pd/C (20 mg, 0.02 mmol Pd), 1,2,4-trimethylbenzene (0.15 mL, 1.1 mmol) and diphenyl ether (1.0 mL) were combined in a threaded pressure tube fitted with a Teflon cap. The reaction was heated and stirred at 230 °C for 20 h. The mixture was then filtered through silica gel and washed with EtOAc. The filtrate was then concentrated. The remaining diphenyl ether was removed by bulb-to-bulb distillation to give **120** (5 mg, 0.025 mmol, 20%) as a brown solid.

Alternate procedure B for 120. The same procedure as described for **57** was repeated except that a mixture of 3-(2-nitrophenylamino)-2-cyclohexen-1-one (**92**) (302 mg, 1.3 mmol), Pd(dba)₂ (45 mg, 0.08 mmol), dppp (33 mg, 0.08 mmol), phen (30 mg, 0.17 mmol) and DMF (4 mL) was reacted at 120 °C under CO (6 atm) for 22 h. The mixture was then filtered through Celite and the filtrate was concentrated under high vacuum. Purification by flash chromatography (hexanes/EtOAc, 8:2, 7:3, 1:1 and EtOAc) gave **120** (67 mg, 0.34 mmol, 26%) as a brown solid.

2-Acetylquinoxaline (123).

The same procedure as described for **57** was repeated except that a mixture of (*Z*)-4-(2-nitrophenylamino)-3-buten-2-one (**95**) (200 mg, 1.0 mmol), Pd(dba)₂ (33 mg, 0.06 mmol), dppp (24 mg, 0.06 mmol), phen (23 mg, 0.13 mmol) and DMF (10 mL) was reacted at 90 °C under CO (6 atm) for 44 h. The mixture was diluted with CH₂Cl₂ (30 mL) and washed with H₂O (3 X 30 mL). The combined aqueous phases were extracted with CH₂Cl₂ (30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 8:2, 7:3, 1:1) gave **123** (10 mg, 0.06 mmol, 6%) as a brown solid: ¹H NMR δ 9.51 (s, 1 H), 8.23-8.17 (m, 2 H), 7.94-7.84 (m, 2 H), 2.87 (s, 3 H); ¹³C NMR (150 MHz) δ 199.8, 146.6, 143.9, 143.1 (-), 141.1, 132.2 (-), 130.7 (-), 130.5 (-), 129.4 (-), 25.5.

2-Acetyl-6-methylquinoxaline (124) and 2-acetyl-7-methylquinoxaline (125).

The same procedure as described for **57** was repeated except that a mixture of (*Z*)-4-(4-methyl-2-nitrophenylamino)-3-buten-2-one (**96**) (100 mg, 0.45 mmol), Pd(dba)₂ (16 mg, 0.03 mmol), dppp (11 mg, 0.03 mmol), phen (10 mg, 0.06 mmol) and DMF (2 mL) was reacted at 70

°C under CO (6 atm) for 21 h. The solvents were removed under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave an inseparable mixture of **124** and **125** (11 mg, 0.06 mmol, 13%) as a pale yellow solid: data for the mixture ¹H NMR δ 9.46 (s, 1 H), 9.43 (s, 1 H), 8.08 (d, *J* = 8.6 Hz, 1 H), 8.06 (d, *J* = 8.7 Hz, 1 H), 7.98 (s, 1 H), 7.94 (s, 1 H), 7.71 (apparent dt, *J* = 9.1 and 2.0 Hz, 2 H), 2.85 (s, 6 H), 2.65 (s, 6 H); ¹³C NMR (150 MHz) δ 199.9, 199.8, 146.6, 146.0, 144.0, 143.1, 142.4, 142.2, 141.4, 141.2, 139.5, 134.6, 133.1, 130.0, 129.2, 128.9, 128.4, 128.3, 25.5, 25.5, 22.1, 21.8.

Alternate procedure A for 124 and 125. The same procedure as described for **57** was repeated except that a mixture of (*Z*)-4-(5-methyl-2-nitrophenylamino)-3-buten-2-one (**97**) (500 mg, 2.3 mmol), Pd(dba)₂ (78 mg, 0.14 mmol), dppp (56 mg, 0.14 mmol), phen (49 mg, 0.27 mmol) and DMF (2 mL) was reacted at 70 °C under CO (6 atm) for 20 h. The solvents were removed under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave an inseparable mixture of **124** and **125** (15 mg, 0.08 mmol, 4%) as a pale yellow solid.

Alternate procedure B for 124 and 125. Compound **153** (205 mg, 0.95 mmol), *p*-toluenesulfonic acid (10 mg) and ethanol (50 mL) were combined and heated to reflux for 27 h. The reaction mixture was then concentrated. Purification by flash chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 6:4 and 1:1) gave an inseparable mixture of **124** and **125** (11 mg, 0.06 mmol, 6%) as a pale yellow solid.

2-Azido-1-nitrobenzene⁷⁵ (131).

To a solution of 2-nitroaminobenzene (**52**) (5.00 g, 36.2 mmol) dissolved in H₂O (300 mL) at 0 °C was added HCl (concentrated, 75 mL). Small amounts of ice were added

periodically to keep the solution at 0 °C. The solution of amine hydrochloride stirred for 5 minutes. NaNO₂ (3.00 g, 43.5 mmol in 10 mL H₂O) was added to the cold solution and the reaction stirred for 3 h. The remaining insoluble solid was removed by filtration. To the filtrate was added NaN₃ (2.90 g, 44.6 mmol in 10 mL H₂O). Small amounts of diethyl ether were used to stop the foaming that resulted. The solution was stirred for 2 h. The resulting solid was removed by filtration and washed with cold diethyl ether to give **131** (4.75 g, 29.0 mmol, 80%) as an off-white solid: ¹H NMR δ 7.95 (dd, *J* = 8.2 and 1.2 Hz, 1 H), 7.63 (dt, *J* = 7.8 and 1.5 Hz, 1 H), 7.35 (dd, *J* = 8.2 and 1.0 Hz, 1 H), 7.27 (dt, *J* = 7.8 and 1.0 Hz, 1 H); ¹³C NMR (150 MHz) δ 140.8 (+), 134.7 (+), 134.0 (-), 126.0 (-), 124.9 (-), 120.7 (-).

2-Pentylquinoxaline (132), 2-pentylquinoxaline-1-oxide (133) and 2-hexylbenzimidazole⁷⁶ (134).

To a solution of 2-azidonitrobenzene (**131**) (500 mg, 3.1 mmol) dissolved in diethyl ether (anhydrous, 20 mL) was added triphenylphosphine (800 mg, 3.1 mmol). The mixture stirred under argon atmosphere at ambient temperature for 1 h. The reaction was then concentrated. To the resulting solid was added CHCl₃ (25 mL) and heptanal (**83**) (4.0 mL, 29.8 mmol). The reaction mixture stirred at reflux under argon atmosphere for 7 days. The red color of the reaction, as well as TLC, indicated that the desired enamine had been formed. The reaction was concentrated and the crude solid was used without further purification.

To a solution of the crude enamine dissolved in DMF (10 mL) in a threaded pressure tube fitted with a pressure head was added Pd(dba)₂ (110 mg, 0.2 mmol), dppp (80 mg, 0.2 mmol) and phen (70 mg, 0.4 mmol). The tube was flushed 3 times with CO. The reaction was heated and stirred at 70 °C under CO (6 atm) for 72 h. The reaction mixture was concentrated and the

product was purified by flash chromatography (hexanes/EtOAc, 8:2, 7:3, 6:4, 1:1 and 3:7) to give **132** (153 mg, 0.76 mmol, 25%) as a yellow oil, **133** (54 mg, 0.25 mmol, 8%) as an off-white solid and **134** (84 mg, 0.42 mmol, 14%) as a tan solid: **132** ^1H NMR δ 8.75 (s, 1 H), 8.06 (apparent triplet with further fine splitting, $J = 9.4$ Hz, 2 H), 7.76 (dt, $J = 6.7$ and 1.7 Hz, 1H) partially overlapping 7.71 (dt, $J = 6.9$ and 1.7 Hz, 1 H), 3.02 (t, $J = 7.7$ Hz, 2 H), 1.86 (pentet, $J = 7.6$ Hz, 2 H), 1.47-1.32 (m, 4 H), 0.91 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (150 MHz) δ 157.6 (+), 145.7 (-), 142.1 (+), 141.1 (+), 129.8 (-), 129.1 (-), 128.8 (-), 128.7 (-), 36.4 (+), 31.5 (+), 29.1 (+), 22.4 (+), 13.9 (-); IR (neat) 2957, 2927, 2857, 1561, 1492, 1126, 761 cm^{-1} ; **133** mp 32-34 $^{\circ}\text{C}$; ^1H NMR δ 8.69 (s, 1 H), 8.61 (apparent doublet with further fine splitting, $J = 10.1$ Hz, 1 H), 8.10 (apparent doublet with further fine splitting, $J = 9.7$ Hz, 1 H), 7.81-7.71 (m, 2 H), 3.08 (t, $J = 7.7$ Hz, 2 H), 1.84 (pentet, $J = 7.4$ Hz, 2 H), 1.48-1.38 (m, 4 H), 0.93 (t, $J = 6.9$ Hz, 3 H); ^{13}C NMR (150 MHz) δ 146.8 (-), 144.4 (+), 143.0 (+), 137.0 (+), 130.5 (-), 130.0 (-), 129.9 (-), 118.7 (-), 31.7 (+), 28.7 (+), 25.2 (+), 22.3 (+), 13.9 (-); IR (neat) 2957, 2927, 2860, 1579, 1494, 1359, 1302, 766 cm^{-1} .

2-Azido-3-nitrotoluene⁷⁷ (**135**).

The same procedure as described for **131** was repeated except that a mixture of 2-methyl-6-nitroaminobenzene (**67**) (3.00 g, 19.7 mmol), H_2O (100 mL), HCl (concentrated, 100 mL), NaNO_2 (1.70 g, 24.6 mmol) and NaN_3 (2.50 g, 38.5 mmol) gave **135** (2.62 g, 14.7 mmol, 75%) as a pale yellow solid: ^1H NMR δ 7.80 (d, $J = 8.2$ Hz, 1 H), 7.45 (d, $J = 7.4$ Hz, 1 H), 7.21 (t, $J = 7.9$ Hz, 1 H), 2.43 (s, 3 H); ^{13}C NMR (150 MHz) δ 143.8 (+), 135.5 (-), 135.3 (+), 132.1 (+), 125.4 (-), 123.4 (-), 18.1 (-).

2-Azido-4-chloroaminobenzene⁷⁸ (150).

To a solution of **185** (5.50 g, 18.2 mmol) dissolved in methanol (35 mL) was added hydrazine hydrate (85% aqueous solution, 1.1 mL). The reaction proceeded at ambient temperature with occasional stirring for 30 minutes. The resulting paste was added to an aqueous NaOH solution (0.25 M, 330 mL). The insoluble solid was removed by filtration and added to ethanol (150 mL) with stirring. The insoluble solid was removed by filtration and the filtrate was added to H₂O (500 mL). The resulting solid was removed by filtration to give **150** (1.90 g, 11.3 mmol, 62%) as an off-white solid.

5-Chloro-2-isopropylbenzimidazole⁷⁹ (151).

To a refluxing solution of 2-azido-5-chloroaminobenzene (**186**) (300 mg, 1.8 mmol) dissolved in ethanol (absolute, 50 mL) was added dropwise a solution of 2-methylpropanal (**55**) (0.195 mL, 2.2 mmol) dissolved in ethanol (absolute, 20 mL). The reaction was stirred at reflux for 24 h, then concentrated. The crude solid was purified by column chromatography (hexanes/EtOAc, 8:2, 7:3, 1:1 and 3:7) to give **151** (262 mg, 1.4 mmol, 76%) as a brown solid: ¹H NMR δ 7.51 (d, *J* = 1.7 Hz, 1 H), 7.43 (d, *J* = 8.7 Hz, 1 H), 7.18 (dd, *J* = 8.7 and 2.0 Hz, 1 H), 3.28 (septet, *J* = 6.9 Hz, 1 H), 1.46 (d, *J* = 6.9 Hz, 6 H); ¹³C NMR δ 161.2, 127.8, 122.7, 114.5 (broad signal), 29.1, 21.5 (Note: three carbons were not observed due to the slow exchange of the N-H proton, which causes these signals to be broadened).

Alternate procedure A for compound 151. Compound **151** was also prepared according to the method above except that a mixture of 2-azido-4-chloroaminobenzene (**150**) (174 mg, 1.0 mmol), ethanol (absolute, 70 mL total) and 2-methylpropanal (**55**) (0.115 mL, 1.3

mmol) after 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1 and 3:7) gave **151** (132 mg, 0.68 mmol, 66%) as a brown solid.

Alternate procedure B for compound 151. 2-azido-4-chloroaminobenzene (**150**) (405 mg, 2.4 mmol), ethanol (absolute, 20 mL total) and 2-methylpropanal (**55**) (0.600 mL, 6.6 mmol) were reacted as described above with the following change: Glacial acetic acid (0.5 mL) was added to the azide solution before heating to reflux. After 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1 and 3:7), **151** (287 mg, 1.5 mmol, 61%) was isolated as a brown solid.

2-Azido-4-methylaminobenzene⁷⁸ (152).

To a solution of **194** (9.50 g, 34.1 mmol) dissolved in THF (200 mL) and ethanol (35 mL) was added hydrazine hydrate (85% aqueous solution, 14 mL). The reaction stirred at ambient temperature for 20 h. The insoluble solid was removed by filtration and washed with cold ethanol. The filtrate was added to H₂O (0°C, 700 mL) and extracted with diethyl ether (6 X 150 mL). The organic phase was dried (MgSO₄), filtered and concentrated to give **152** (4.90 g, 33.3 mmol, 98%) as an off-white solid.

(Z)-4-(2-Azido-4-methylphenylamino)-3-buten-2-one (153).

The same procedure as described for **95** was repeated except that a mixture of 2-azido-4-methylaminobenzene (**152**) (600 mg, 4.1 mmol), (*E*)-4-methoxy-3-buten-2-one²⁶ (**94**) (0.5 mL, 4.9 mmol), *p*-toluenesulfonic acid (10 mg) and CH₂Cl₂ (anhydrous, 25 mL) reacted at ambient temperature for 72 h. Purification by flash chromatography (hexanes/EtOAc, 9:1) gave **153** (684 mg, 3.2 mmol, 78%) as an orange solid: mp 66-68 °C; ¹H NMR (600 MHz) δ 11.65 (d, *J* = 11.4

Hz, 1 H), 7.15 (dd, $J = 12.6$ and 7.8 Hz, 1 H), 6.98 (d, $J = 8.4$ Hz, 1 H), 6.91 (s, 1 H), 6.89 (d, $J = 8.4$ Hz, 1 H), 5.31 (d, $J = 7.2$ Hz, 1 H), 2.31 (s, 3 H), 2.16 (s, 3 H); ^{13}C NMR (150 MHz) δ 198.7 (+), 141.6 (-), 133.4 (+), 129.4 (+), 127.6 (+), 126.2 (-), 119.1 (-), 113.4 (-), 97.8 (-), 29.4 (-), 20.7 (-); IR (neat) 2115, 1641, 1601, 1559, 1471, 1280 cm^{-1} .

2-Acetyl-1,4-dihydro-7-methylquinoxaline (**154**).

Compound **153** (200 mg, 0.9 mmol), $\text{Pd}(\text{dba})_2$ (32 mg, 0.06 mmol), dppp (46 mg, 0.1 mmol) and DMF (5 mL) were combined and reacted at ambient temperature for 3 days. The reaction mixture was then concentrated under high vacuum. Purification by flash chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1 and 3:7) gave **154** (31 mg, 0.16 mmol, 18%) as an off-white solid: ^1H NMR δ 8.34 (s, 1 H), 7.10 (d, $J = 7.9$ Hz, 1 H), 7.02 (s, 1 H), 6.83 (d, $J = 8.2$ Hz, 1 H), 4.38 (br s, 2 H), 2.76 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (150 MHz) δ 192.6 (+), 147.7 (+), 138.2 (+), 131.5 (-), 128.3 (+), 125.9 (-), 124.6 (-), 122.3 (+), 118.0 (-), 27.2 (-), 20.1 (-); IR (neat) 1687, 1632, 1519, 1242, 1030 cm^{-1} .

2-Isopropylbenzimidazole⁶⁹ (**158**).

To a solution of 2-nitrosoaminobenzene³⁸ (**157**) (100 mg, 0.8 mmol) dissolved in DMF (5 mL) in a threaded pressure tube fitted with a Teflon cap was added 2-methylpropanal (**55**) (0.15 mL, 1.7 mmol). The reaction stirred at 80 °C for 72 h and the solvent was removed under high vacuum. Purification by flash chromatography (hexanes/EtOAc, 9:1, 8:2, 1:1, 3:7 and EtOAc) gave **158** (21 mg, 0.131 mmol, 16%).

4-Chloro-2-phthalamidonitrobenzene⁸⁰ (**180**).

The method of Hall *et al*⁵⁴ was employed to transform 5-chloro-2-nitroaminobenzene (**65**) (17.50 g, 101.6 mmol) and phthalic anhydride (**179**) (15.10 g, 101.8 mmol) into **180** (10.00 g, 33.1 mmol, 33%) as a yellow solid: ¹H NMR δ 8.17 (d, *J* = 8.6 Hz, 1 H), 8.02-7.95 (m, 2 H), 7.88-7.81 (m, 2 H), 7.60 (dd, *J* = 8.9 and 2.5 Hz, 1 H), 7.55 (d, *J* = 2.2 Hz, 1 H); ¹³C NMR (150 MHz) δ 165.9 (+), 143.9, 140.2 (+), 134.9 (-), 131.6 (+), 130.9 (-), 129.7 (-), 126.9 (-), 126.8 (+), 124.3 (-).

5-Chloro-2-phthalamidonitrobenzene⁸⁰ (**181**).

The same procedure as described for **180** was repeated except that a mixture of 4-chloro-2-nitroaminobenzene (**63**) (17.50 g, 101.4 mmol) and phthalic anhydride (**179**) (14.90 g, 100.6 mmol) gave **181** (9.27 g, 30.6 mmol, 30%) as a yellow solid: ¹H NMR δ 8.19 (d, *J* = 2.5 Hz, 1 H), 8.02-7.94 (m, 2 H), 7.88-7.81 (m, 2 H), 7.76 (dd, *J* = 8.4 and 2.5 Hz, 1 H), 7.50 (d, *J* = 8.6 Hz, 1 H); ¹³C NMR (150 MHz) δ 166.0, 145.8, 135.5, 134.9, 134.1, 131.8, 131.7, 126.0, 124.3, 124.1.

4-Chloro-2-phthalamidoaminobenzene⁸⁰ (**182**).

The reduction of **180** was performed according to the method of Hall *et al*.⁵⁴ The mixture of **180** (7.60 g, 25.1 mmol), iron powder (18.00 g, 322.5 mmol), acetone (200 mL) and acetic acid/ H₂O (1:1, 40 mL) reacting at reflux with stirring for 2.5 h gave **182** (6.28 g, 23.0 mmol, 92%) as a yellow solid: ¹H NMR δ 7.98-7.95 (m, 2 H), 7.83-7.79 (m, 2 H), 7.22 (dd, *J* = 8.6 and 2.2 Hz, 1 H), 7.14 (d, *J* = 2.5 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 3.76 (br s, 2 H); ¹³C NMR (150

MHz) δ 166.9, 142.1, 134.6, 131.8, 130.1, 129.0, 124.0, 123.5, 118.7 (Note: one carbon is not seen, possibly due to two overlapping signals).

5-Chloro-2-phthalamidoaminobenzene⁸⁰ (183).

The same procedure as described for **182** was repeated except that a mixture of **181** (9.00 g, 29.7 mmol), iron powder (21.00 g, 376 mmol), acetone (250 mL) and acetic acid/ H₂O (1:1, 50 mL) after 15 h gave **183** (6.75 g, 24.8 mmol, 83%) as a yellow solid: ¹H NMR (600 MHz) δ 7.96-7.94 (m, 2 H), 7.81-7.79 (m, 2 H), 7.03 (d, J = 7.8 Hz, 1 H), 6.88 (s, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 3.83 (br s, 2 H); ¹³C NMR (150 MHz) δ 167.1 (+), 144.4 (+), 135.7 (+), 134.6 (-), 131.9 (+), 130.3 (-), 123.9 (-), 119.3 (-), 117.4 (-), 116.4 (+).

4-Chloro-2-phthalamidophenylazide⁸⁰ (184).

The same procedure as described for **131** was repeated except that a mixture of **182** (6.25 g, 22.9 mmol), H₂O (150 mL), HCl (concentrated, 25 mL), NaNO₂ (1.60 g, 23.2 mmol) and NaN₃ (1.50 g, 23.1 mmol) gave **184** (5.10 g, 17.2 mmol, 75%) as an off-white solid: ¹H NMR δ 8.00-7.93 (m, 2 H), 7.85-7.78 (m, 2 H), 7.49 (dd, J = 8.7 and 2.5 Hz, 1 H), 7.32 (d, J = 2.2 Hz, 1 H), 7.25 (d, J = 8.7 Hz, 1 H).

5-Chloro-2-phthalamidophenylazide⁸⁰ (185).

The same procedure as described for **131** was repeated except that a mixture of **183** (6.75 g, 24.8 mmol), H₂O (100 mL), HCl (concentrated, 25 mL), NaNO₂ (1.80 g, 26.1 mmol) and NaN₃ (1.70 g, 26.3 mmol) gave **185** (4.40 g, 14.6 mmol, 59%) as an off-white solid: ¹H NMR δ

7.99-7.92 (m, 2 H), 7.84-7.77 (m, 2 H), 7.30 (d, $J = 2.0$ Hz, 1 H), 7.26-7.23 (m, 2 H); ^{13}C NMR (150 MHz) δ 166.6, 139.1, 136.3, 134.5, 131.8, 131.5, 125.6, 123.9, 121.2, 119.6.

2-Azido-5-chloroaminobenzene⁸⁰ (186).

The same procedure as described for **150** was repeated except that a mixture of **184** (5.10 g, 16.9 mmol), methanol (35 mL), hydrazine hydrate (85% aqueous solution, 1.2 mL) and NaOH (0.25 M, 220 mL) gave **186** (1.50 g, 9.1 mmol, 54%) as an off-white solid: ^1H NMR δ 6.93 (d, $J = 8.4$ Hz, 1 H), 6.74 (dd, $J = 8.4$ and 2.2 Hz, 1 H), 6.67 (d, $J = 2.2$ Hz, 1 H), 3.88 (br s, 2 H); ^{13}C NMR (150 MHz) δ 139.1, 130.7, 123.8, 119.2, 118.7, 115.4.

5-Methyl-2-phthalamidonitrobenzene⁸¹ (188).

To a refluxing solution of phthaloyl chloride (**187**) (15 mL, 104 mmol) dissolved in toluene (100 mL) was added dropwise a solution of 4-methyl-2-nitroaminobenzene (**59**) (15.00 g, 98.6 mmol), pyridine (20.0 mL, 247 mmol) and toluene (100 mL). The reaction was stirred at reflux for 20 h. The solution was filtered while hot through an oven-heated fritted funnel and the filtrate was concentrated. The product was purified by recrystallization from acetic acid to give **188** (26.60 g, 94.2 mmol, 96%) as a yellow solid: ^1H NMR δ 8.02 (d, $J = 1.2$ Hz, 1 H), 8.00-7.78 (m, 2 H), 7.85-7.78 (m, 2 H), 7.59 (dd, $J = 8.2$ and 1.2 Hz, 1 H), 7.40 (d, $J = 8.2$ Hz, 1 H); ^{13}C NMR (150 MHz) δ 166.4 (+), 145.2 (+), 140.6 (+), 134.7 (-), 134.6 (-), 131.7 (+), 130.5 (-), 126.0 (-), 123.9 (-), 122.8 (+), 21.0 (-).

3-Methyl-2-phthalamidonitrobenzene⁸² (189).

The same procedure as described for **188** was repeated except that a mixture of phthaloyl chloride (**187**) (1.5 mL, 10.4 mmol), 6-methyl-2-nitroaminobenzene (**67**) (1.50 g, 9.9 mmol), pyridine (2.0 mL, 24.7 mmol) and toluene (100 mL total) was reacted for 40 h. Recrystallization from acetic acid gave **189** (2.45 g, 8.7 mmol, 88%) as a yellow solid.

3-Nitro-2-phthalamidopyridine (190).

The same procedure as described for **188** was repeated except that a mixture of phthaloyl chloride (**187**) (4.0 mL, 27.7 mmol), 2-amino-3-nitropyridine (**86**) (3.00 g, 21.6 mmol), pyridine (6.0 mL, 74.2 mmol) and toluene (100 mL total) was reacted for 42 h. Recrystallization from acetic acid gave **190** (5.56 g, 20.7 mmol, 96%) as a yellow solid: mp 171-173°C; ¹H NMR δ 8.94 (dd, *J* = 4.9 and 1.7 Hz, 1 H), 8.56 (dd, *J* = 8.2 and 1.5 Hz, 1 H), 8.03-7.98 (m, 2 H), 7.90-7.80 (m, 2 H), 7.65 (dd, *J* = 8.2 and 4.7 Hz, 1 H); ¹³C NMR δ 165.5 (+), 153.3 (-), 142.5 (+), 139.1 (+), 134.9 (-), 134.5 (-), 131.7 (+), 124.6 (-), 124.3 (-); IR (neat) 1786, 1735, 1592, 1541, 1355 cm⁻¹.

5-Methyl-2-phthalamidoaminobenzene⁸³ (191).

Compound **188** (26.30 g, 93.2 mmol), 10% Pd/C (4.60 g, 4.3 mmol Pd) and ethanol (absolute, 225 mL) were combined in a threaded pressure tube fitted with a teflon cap attached to a hydrogenation apparatus. The tube was flushed 3 times with H₂. The reaction was stirred at ambient temperature under H₂ (4 atm) for 15 h. After releasing the pressure, the open flask was heated gently to dissolve the solid product. The hot solution was filtered through an oven-heated fritted funnel packed with Celite and washed with boiling ethyl acetate. The filtrate was

concentrated and the product was purified by recrystallization from ethanol to give **191** (20.60 g, 81.7 mmol, 88%) as a yellow solid: ^1H NMR δ 7.97-7.91 (m, 2 H), 7.82-7.75 (m, 2 H), 7.00 (d, J = 8.6 Hz, 1 H), 6.74-6.71 (m, 2 H), 3.67 (br s, 2 H), 2.32 (s, 3 H); ^{13}C NMR (150 MHz) δ 167.4, 143.0, 140.3, 134.3, 132.0, 128.8, 123.7, 120.2, 118.3, 115.3, 21.2.

3-Methyl-2-phthalamidoaminobenzene⁸² (192).

The same procedure as described for **191** was repeated except that a mixture of **189** (2.30 g, 8.2 mmol), 10% Pd/C (500 mg, 0.47 mmol Pd), ethanol (absolute, 100 mL) and H_2 (3 atm) after 44 h at 60 °C gave **192** (1.50 g, 6.1 mmol, 75%) as a yellow solid.

3-Amino-2-phthalamidopyridine (193).

The same procedure as described for **191** was repeated except that a mixture of **190** (3.50 g, 12.9 mmol), 10% Pd/C (700 mg, 0.66 mmol Pd), ethanol (absolute, 50 mL) and H_2 (4 atm) after 25 h at 60 °C gave **193** (1.50 g, 6.4 mmol, 50%) as a yellow solid: mp 204-206°C; ^1H NMR δ 8.10 (t, J = 3.0 Hz, 1 H), 8.00-7.93 (m, 2 H), 7.83-7.77 (m, 2 H), 7.23 (d, J = 3.2 Hz, 2 H), 3.85 (br s, 2 H); ^{13}C NMR δ 166.9 (+), 140.0 (+), 139.8 (-), 134.5 (-), 132.8 (+), 132.1 (+), 125.5 (-), 125.3 (-), 124.0 (-); IR (neat) 3434, 1716, 1469, 1377 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_2$ 239.0695, found 239.0703.

5-Methyl-2-phthalamidophenylazide (194).

The same procedure as described for **131** was repeated except that a mixture of **191** (10.00 g, 39.7 mmol), H_2O (300 mL), HCl (concentrated, 75 mL), NaNO_2 (3.30 g, 47.8 mmol) and NaN_3 (3.10 g, 47.7 mmol) gave **194** (9.90 g, 35.5 mmol, 90%) as an off-white solid: mp

161-163°C; ^1H NMR δ 7.97-7.92 (m, 2 H), 7.82-7.76 (m, 2 H), 7.17 (d, J = 7.9 Hz, 1 H), 7.12-7.07 (m, 2 H), 2.44 (s, 3 H); ^{13}C NMR δ 166.9 (+), 141.1 (+), 137.1 (+), 134.1 (-), 131.8 (+), 130.0 (-), 126.1 (-), 123.6 (-), 119.8 (+), 119.6 (-), 21.2 (-); IR (neat) 2110, 1734, 1714, 1514, 1383 cm^{-1} .

3-Methyl-2-phthalamidophenylazide (**195**).

The same procedure as described for **131** was repeated except that a mixture of **192** (1.37 g, 5.4 mmol), H_2O (100 mL), HCl (concentrated, 25 mL), NaNO_2 (450 mg, 6.5 mmol) and NaN_3 (425 mg, 6.54 mmol) gave **195** (1.10 g, 4.1 mmol, 75%) as an off-white solid: mp 142-144°C; ^1H NMR δ 7.99-7.94 (m, 2 H), 7.83-7.78 (m, 2 H), 7.41 (t, J = 7.4 Hz, 1 H), 7.16-7.13 (m, 2 H), 2.21 (s, 3 H); ^{13}C NMR δ 166.9 (+), 139.4 (+), 138.2 (+), 134.3 (-), 132.0 (+), 130.4 (-), 126.9 (-), 123.8 (-), 121.7 (+), 116.6 (-), 17.9 (-); IR (neat) 2361, 2124, 1742, 1717, 1469, 1374 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{15}\text{H}_{10}\text{N}_4\text{O}_2$ 278.0804, found 278.0801.

3-Azido-2-phthalamidopyridine (**196**).

The same procedure as described for **131** was repeated except that a mixture of **193** (1.50 g, 6.1 mmol), H_2O (60 mL), HCl (concentrated, 15 mL), NaNO_2 (500 mg, 7.3 mmol) and NaN_3 (485 mg, 7.5 mmol) gave **196** (970 mg, 3.7 mmol, 60%) as an off-white solid: mp 167-169°C; ^1H NMR δ 8.47 (dd, J = 1.5 and 4.7 Hz, 1 H), 8.00-7.94 (m, 2 H), 7.85-7.78 (m, 2 H), 7.68 (dd, J = 8.2 and 1.5 Hz, 1 H), 7.50 (dd, J = 8.2 and 4.7 Hz, 1 H); ^{13}C NMR δ 166.3, 145.6 (-), 137.2, 135.3, 134.5 (-), 132.0 (+), 127.9 (-), 125.6 (-), 124.0 (-); IR (neat) 2126, 1723, 1455, 1374 cm^{-1} .

2-Azido-6-methylaminobenzene⁸⁴ (197).

The same procedure as described for **152** was repeated except that a mixture of **195** (1.10 g, 3.9 mmol), THF (50 mL), ethanol (10 mL) and hydrazine hydrate (85% aqueous solution, 1.5 mL) was reacted at ambient temperature for 48 h. The product was purified by column chromatography (hexanes/EtOAc, 8:2) to give **197** (343 mg, 2.3 mmol, 60%) as an off-white solid: ¹H NMR δ 6.93 (d, *J* = 8.7 Hz, 1 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 6.72 (t, *J* = 7.7 Hz, 1 H), 3.76 (br s, 2 H), 2.16 (s, 3 H); ¹³C NMR (150 MHz) δ 136.3, 126.7, 124.8, 123.4, 118.4, 115.9, 17.3.

2-Amino-3-azidopyridine (198).

The same procedure as described for **152** was repeated except that a mixture of **196** (840 mg, 3.2 mmol), THF (20 mL), ethanol (5 mL) and hydrazine hydrate (85% aqueous solution, 1.5 mL) was reacted at ambient temperature for 26 h. The insoluble solid was removed by filtration and the filtrate was condensed. The resulting solid was added to HCl (10%, 100 mL) and the insoluble solid was removed by filtration. The filtrate was washed with diethyl ether (3 X 50 mL). The aqueous layer was made basic with NaOH (3 M) and was then extracted with diethyl ether (4 X 50 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated to give **198** (412 mg, 3.1 mmol, 96%) as a brown solid: mp 71-73°C; ¹H NMR δ 7.86 (dd, *J* = 4.9 and 1.5 Hz, 1 H), 7.23 (dd, *J* = 7.7 and 1.5 Hz, 1 H), 6.70 (dd, *J* = 7.7 and 4.9 Hz, 1 H), 4.74 (br s, 2 H); ¹³C NMR δ 150.9 (+), 143.4 (-), 124.5 (-), 120.3 (+), 113.4 (-); IR (neat) 3453, 2120, 1629, 1487, 1257 cm⁻¹; HRMS (EI) calc. for C₅H₅N₅ 135.0545, found 135.0542.

5-Chloro-2-hexylbenzimidazole (**199**).

The same procedure as described for **151** was repeated except that a mixture of 2-azido-5-chloroaminobenzene (**186**) (302 mg, 1.8 mmol), ethanol (absolute, 70 mL total) and heptanal (**83**) (0.290 mL, 2.2 mmol) after 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2 and 7:3) gave **199** (266 mg, 1.1 mmol, 63%) as a brown solid: mp 120-122 °C; ^1H NMR δ 12.01 (br s, 1 H), 7.53 (d, J = 2.0 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.19 (dd, J = 8.6 and 2.0 Hz, 1 H), 2.97 (t, J = 7.6 Hz, 2 H), 1.85 (pentet, J = 7.4 Hz, 2 H), 1.40-1.10 (m, 6 H), 0.79 (t, J = 6.9 Hz, 3 H); ^{13}C NMR δ 157.3 (+), 139.3 (+), 137.0 (+), 127.7 (+), 122.6 (-), 115.1 (-), 114.4 (-), 31.3 (+), 29.3 (+), 28.9 (+), 28.4 (+), 22.3 (+), 13.8 (-); IR (neat) 2921, 2360, 1450, 1024 cm^{-1} ; HRMS (EI) calc. for $\text{C}_{13}\text{H}_{17}\text{ClN}_2$ 236.1080, found 236.1071.

2-Isopropyl-5-methylbenzimidazole⁸⁵ (**200**).

The same procedure as described for **151** was repeated except that a mixture of 2-azido-4-methylaminobenzene (**152**) (300 mg, 2.0 mmol), ethanol (absolute, 70 mL total) and 2-methylpropanal (**55**) (0.220 mL, 2.4 mmol) after 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave **200** (249 mg, 1.4 mmol, 71%) as a brown solid: ^1H NMR δ 7.44 (d, J = 8.2 Hz, 1 H), 7.35 (s, 1 H), 7.02 (dd, J = 8.2 and 1.2 Hz, 1 H), 3.33 (septet, J = 6.9 Hz, 1 H), 2.43 (s, 3 H), 1.48 (d, J = 6.9 Hz, 6 H); ^{13}C NMR δ 160.0, 138.5 (broad signal), 137.0 (broad signal), 131.8, 123.4, 114.5 (broad signal), 114.0 (broad signal), 29.1, 21.7, 21.6.

2-Hexyl-5-methylbenzimidazole⁸⁶ (**201**).

The same procedure as described for **151** was repeated except that a mixture of 2-azido-4-methylaminobenzene (**152**) (305 mg, 2.1 mmol), ethanol (absolute, 70 mL total) and heptanal

(**83**) (0.330 mL, 2.5 mmol) after 24 h and chromatography (hexanes/EtOAc, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave **201** (334 mg, 1.5 mmol, 75%) as a brown solid: ^1H NMR δ 12.03 (br s, 1 H), 7.47 (d, $J = 8.2$ Hz, 1 H), 7.38 (s, 1 H), 7.04 (dd, $J = 8.2$ and 1.2 Hz, 1 H), 2.99 (t, $J = 7.7$ Hz, 2 H), 2.45 (s, 3 H), 1.87 (pentet, $J = 7.4$ Hz, 2 H), 1.38-1.15 (m, 6 H), 0.79 (t, $J = 6.7$ Hz, 3 H); ^{13}C NMR δ 155.0, 131.8, 123.5, 114.5 (broad signal), 31.4, 29.3, 29.0, 28.3, 22.5, 21.6, 14.0 (Note: three carbons were not observed due to the slow exchange of the N-H proton, which causes these signals to be broadened).

2-Benzyl-5-methylbenzimidazole⁸⁷ (202) and 5-methylbenzimidazole⁶⁹ (203).

The same procedure as described for **151** was repeated except that a mixture of 2-azido-4-methylaminobenzene (**152**) (300 mg, 2.0 mmol), ethanol (absolute, 70 mL total) and phenylacetaldehyde (**81**) (0.280 mL, 2.4 mmol) after 24 h and chromatography (hexanes/EtOAc, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave **202** (47 mg, 0.21 mmol, 10%) as a brown solid and **203** (107 mg, 0.81 mmol, 40%) as an off-white solid.

Alternate procedure for 202 and 203. 2-azido-4-methylaminobenzene (**152**) (300 mg, 2.0 mmol), ethanol (absolute, 70 mL total) and phenylacetaldehyde (**81**) (0.300 mL, 2.6 mmol) were reacted as described for **151** with the following change: Glacial acetic acid (25 μL) was added to the azide solution before heating to reflux. After 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc), **202** (87 mg, 0.39 mmol, 19%) was isolated as a brown solid and **203** (79 mg, 0.60 mmol, 30%) as an off-white solid.

Alternate procedure for 203. The same procedure as described for **151** was repeated except that a mixture of 2-azido-4-methylaminobenzene (**152**) (306 mg, 2.1 mmol), ethanol (absolute, 70 mL total) and paraformaldehyde (78 mg, 2.6 mmol) after 24 h and chromatography

(hexanes/EtOAc, 6:4, 1:1, 3:7 and EtOAc) gave **203** (49 mg, 0.37 mmol, 18%) as an off-white solid.

5-Methyl-2-*tert*-butylbenzimidazole⁸⁸ (206).

The same procedure as described for **151** was repeated except that a mixture of 2-azido-4-methylaminobenzene (**152**) (300 mg, 2.0 mmol), ethanol (absolute, 70 mL total) and trimethylacetaldehyde (**205**) (0.270 mL, 2.5 mmol) after 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave **206** (94 mg, 0.5 mmol, 25%) as a brown solid.

2,5-Dimethylbenzimidazole⁶⁹ (208).

The same procedure as described for **151** was repeated except that a mixture of 2-azido-4-methylaminobenzene (**152**) (302 mg, 2.0 mmol), ethanol (absolute, 70 mL total) and acetaldehyde (**207**) (0.140 mL, 2.5 mmol) after 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave **208** (99 mg, 0.7 mmol, 33%) as a brown solid.

(*E*)-5-Methyl-2-(1-propenyl)benzimidazole⁸⁹ (210).

The same procedure as described for **151** was repeated except that a mixture of 2-azido-4-methylaminobenzene (**152**) (308 mg, 2.1 mmol), ethanol (absolute, 70 mL total) and crotonaldehyde (**209**) (0.20 mL, 2.4 mmol) after 24 h and chromatography (hexanes/EtOAc, 95:5, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave **210** (50 mg, 0.29 mmol, 14%).

2-Isopropyl-4-methylbenzimidazole⁷⁰ (136) and 4-methylbenzimidazole⁹⁰ (211).

The same procedure as described for **151** was repeated except that a mixture of 2-azido-6-methylaminobenzene (**197**) (280 mg, 1.9 mmol), ethanol (absolute, 70 mL total) and 2-methylpropanal (**55**) (0.210 mL, 2.3 mmol) after 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave **136** (226 mg, 1.3 mmol, 69%) as a brown solid and **211** (21 mg, 0.16 mmol, 8%) as an off-white solid: **211** ¹H NMR δ 8.60 (br s, 1 H), 8.12 (s, 1 H), 7.49 (d, J = 7.9 Hz, 1 H), 7.20 (t, J = 7.4 Hz, 1 H), 7.93 (d, J = 7.4 Hz, 1 H), 2.62 (s, 3 H).

Alternate procedure for 136. See page 90.

2-Isopropylimidazo[*b*]pyridine⁹¹ (212) and 2,3-diaminopyridine⁶⁹ (213).

The same procedure as described for **151** was repeated except that a mixture of 2-amino-3-azidopyridine (**198**) (302 mg, 2.2 mmol), ethanol (absolute, 70 mL total) and 2-methylpropanal (**55**) (0.250 mL, 2.8 mmol) after 24 h and chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1, 3:7 and EtOAc) gave **212** (27 mg, 0.17 mmol, 7%) and **213** (81 mg, 0.74 mmol, 33%) as brown solids: **212** mp 140-142 °C; ¹H NMR δ 8.36 (dd, J = 4.9 and 1.5 Hz, 1 H), 8.07 (d, J = 7.9 Hz, 1 H), 7.25 (dd, J = 7.9 and 4.9 Hz, 1 H), 3.40 (septet, J = 7.2 Hz, 1 H), 1.58 (d, J = 7.2 Hz, 6 H); ¹³C NMR δ 162.4 (+), 149.2 (+), 141.6 (-), 136.0 (+), 127.1 (-), 117.7 (-), 29.7 (-), 21.3 (-); IR (neat) 2971, 2750, 1609, 1410, 1271 cm⁻¹.

2-Cyclopropylmethyl-5-methylbenzimidazole (217).

A mixture of 2-cyclopropylethanol (**216**) (300 mg, 3.5 mmol) and PCC (980 mg, 4.6 mmol) dissolved in CH₂Cl₂ (anhydrous, 50 mL) stirred at ambient temperature for 7 h. The solution was then filtered through a fritted funnel packed with a thin layer of silica gel. To the

filtrate (crude aldehyde) in a threaded pressure vessel fitted with a teflon cap was added 2-azido-4-methylaminobenzene (**152**) (310 mg, 2.1 mmol). The reaction was stirred at 100 °C for 24 h and the mixture was then concentrated. Purification by column chromatography (hexanes/EtOAc, 9:1, 8:2, 7:3, 1:1 and 3:7) gave **217** (73 mg, 0.39 mmol, 11%): mp 155-157°C; ¹H NMR δ 7.45 (d, *J* = 8.2 Hz, 1 H), 7.34 (s, 1 H), 7.03 (d, *J* = 8.2 Hz, 1 H), 2.87 (d, *J* = 7.2 Hz, 2 H), 2.44 (s, 3 H), 1.29-1.13 (m, 1 H), 0.58-0.50 (m, 2 H), 0.28-0.22 (m, 2 H); ¹³C NMR δ 154.8 (+), 138.5 (+), 137.0 (+), 131.6 (+), 123.3 (-), 114.4 (-), 114.1 (-), 34.0 (+), 21.5 (-), 9.5 (-), 4.8 (+); IR (neat) 3005, 2919, 2865, 1449, 1282 cm⁻¹; HRMS (EI) calc. for C₁₂H₁₄N₂ (M-H⁺) 185.1079, found 185.1078.

6-Chloro-1,3-dimethyluracil⁶⁹ (218).

To a solution of 1,3-dimethylbarbituric acid (**224**) (6.50 g, 41.6 mmol) and H₂O (2 mL) was added dropwise phosphorus oxychloride (50.0 ml, 536 mmol) (Note: a violent reaction occurred during the addition of the first few mL). The reaction was stirred at reflux for 75 minutes and then the phosphorus oxychloride was removed by distillation. To the resulting material was added H₂O (300 mL). This solution was extracted with CHCl₃ (4 X 75 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. The product was purified by recrystallization from H₂O to give **218** (5.64 g, 32.3 mmol, 78%) as a pale yellow solid.

6-Bromo-1,3-dimethyluracil⁹² (219).

A solution of 1,3-dimethylbarbituric acid (**224**) (1.00 g, 6.4 mmol) and phosphorus tribromide (5.0 ml, 53.0 mmol) was heated at reflux for 75 minutes. The solution was poured

onto ice (100 mL) and extracted with EtOAc (5 X 30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (hexanes/EtOAc, 8:2, 6:4 and 1:1) gave **219** (458 mg, 2.1 mmol, 33%) as a brown solid: ¹H NMR δ 6.16 (s, 1 H), 3.63 (s, 3 H), 3.33 (s, 3 H); ¹³C NMR (150 MHz) δ 160.7 (+), 150.7 (+), 136.5 (+), 105.9 (-), 36.5 (-), 28.2 (-).

6-Iodo-1,3-dimethyluracil⁹³ (220).

To a solution of NaI (3.04 g, 20.3 mmol) dissolved in acetone (10 mL) in a threaded pressure vessel was added 6-chloro-1,3-dimethyluracil (**218**) (500 mg, 2.9 mmol). The reaction vessel was then sealed with a Teflon cap and heated to 130 °C for 81 h. The mixture was concentrated and H₂O (75 mL) was added. This solution was extracted with EtOAc (4 X 30 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. The product was purified by recrystallization from EtOAc to give **220** (490 mg, 1.8 mmol, 64%) as a brown solid.

2,2'-Dinitrobiphenyl⁶⁹ (227) and 6-(2-nitrophenyl)-1,3-dimethyluracil (226).

To a solution of 6-iodo-1,3-dimethyluracil (**220**) (267 mg, 1.0 mmol) and 2-(tri-*n*-butylstannyl)-1-nitrobenzene⁶⁰ (**225**) (494 mg, 1.2 mmol) dissolved in *N*-methylpyrrolidinone (3 mL) under argon atmosphere was added PdCl₂(PhCN)₂ (23 mg, 0.06 mmol), triphenylarsine (34 mg, 0.11 mmol) and CuI (21 mg, 0.11 mmol). The reaction was stirred at reflux for 20 h. The solution was diluted with EtOAc (50 mL) and washed with NH₄OH (10%, 3 X 20 mL) and H₂O (2 X 20 mL). The combined aqueous layers were extracted with EtOAc (2 X 25 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated. Purification by flash

chromatography (hexanes/EtOAc, 9:1, 8:2, 6:4, 1:1, 3:7 and EtOAc) gave **227** (53 mg, 0.22 mmol, 36%) as a brown solid and **226** (126 mg, 0.48 mmol, 48%) as a tan solid: **226** ^1H NMR δ 8.28 (dd, $J = 7.9$ and 1.2 Hz, 1 H), 7.86-7.72 (m, 2 H), 7.44 (dd, $J = 7.2$ and 1.7 Hz, 1 H), 5.60 (s, 1 H), 3.43 (s, 3 H), 3.13 (s, 3 H); ^{13}C NMR δ 162.1, 151.3, 146.6, 134.5, 131.5, 130.6, 128.4, 125.3, 101.4, 33.6, 28.1 (Note: one carbon signal is missing).

1,3-Dimethyl-1H-pyrimido[5,4-b]indole-2,4(3H,5H)dione (228).

The same procedure as described for **57** was repeated except that a mixture of 6-(2-nitrophenyl)-1,3-dimethyluracil (**226**) (120 mg, 0.5 mmol), $\text{Pd}(\text{dba})_2$ (16 mg, 0.03 mmol), dppp (11 mg, 0.03 mmol), phen (10 mg, 0.06 mmol) and DMF (5 mL) was reacted at 70°C under CO (6 atm) for 24 h. The reaction mixture was then concentrated. Purification by flash chromatography (hexanes/EtOAc, 9:1, 7:3, 1:1, 3:7 and EtOAc) gave **228** (9 mg, 0.04 mmol, 9%) as a tan solid: ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 12.00 (s, 1 H), 8.08 (d, $J = 7.8$ Hz, 1 H), 7.47 (d, $J = 8.4$ Hz, 1 H), 7.40 (dt, $J = 6.6$ and 0.6 Hz, 1 H), 7.15 (dt, $J = 7.5$ and 0.6 Hz, 1 H), 3.84 (s, 3 H), 3.33 (s, 3 H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 155.9, 151.0, 138.1, 126.8, 126.6, 121.7, 119.8, 115.3, 113.9, 113.0, 32.5, 28.0.

References

1. Pardasani, R.T.; Jain, S.K.; Yadav, S.K.; Sharma, I. *Indian Journal of Heterocyclic Chemistry* **2002**, *12*, 179-180.
2. Menciu, C.; Duflos, M.; Fouchard, F.; Le Baut, G.; Emig, P.; Achterrath, U.; Szelenyi, I.; Nickel, B.; Schmidt, J.; Kutscher, B.; Guenther, E. *J. Med. Chem.* **1999**, *42*, 638-648.
3. Chaturvedula, V.S.P.; Sprague, S.; Schilling, J.K.; Kingston, D.G.I. *J. Nat. Prod.* **2003**, *66*, 528-531.
4. (a) Robinson, B. *Chem. Rev.* **1969**, *69*, 227-250. (b) Robinson, B. *Chem. Rev.* **1963**, *63*, 373-401.
5. Allen, C.F.H.; Van Allan, J. *Org. Synth.* **1955**, *Coll. Vol. 3*, 597-599.
6. Bashford, K.E.; Cooper, A.L.; Kane, P.D.; Moody, C.J.; Muthusamy, S.; Swann, E. *J. Chem. Soc., Perkin Trans. 1* **2002**, *14*, 1672-1687.
7. Söderberg, B.C.; Shriver, J.A. *J. Org. Chem.* **1997**, *62*, 5838-5845.
8. Hegedus, L.S.; Allen, G.F.; Bozell, J.J.; Waterman, E.L. *J. Am. Chem. Soc.* **1978**, *100*, 5800-5807.
9. Taylor, E.C.; Katz, A.H.; Salgado-Zamora, H.; McKillop, A. *Tetrahedron Lett.* **1985**, *26*, 5963-5966.
10. Ponticello G.S.; Baldwin J.J. *J. Org. Chem.* **1979**, *44*, 4003-4005.
11. Romer, D.R.; Aldrich, B.L.; Pews, R.G.; Walter, R.W., Jr. *Pesticide Science* **1995**, *43*, 263-266.
12. Ortega, M.A.; Montoya, M.E.; Jaso, A.; Zarranz, B.; Tirapu, I.; Aldana, I.; Monge, A. *Pharmazie* **2001**, *56*, 205-207.
13. Zarnowski, T.; Kleinrok, Z.; Turski, W.A.; Czuczwar, S.J. *Neuropharmacology* **1993**, *32*, 895-900.
14. Metzner, J.; Lippmann, E.; Weber, F.G.; Westphal, G. *Pharmazie* **1981**, *36*, 368-370.
15. (a) Toshima, K.; Kimura, T.; Takano, R.; Ozawa, T.; Ariga, A.; Shima, Y.; Umezawa, K.; Matsumura, S. *Tetrahedron* **2003**, *59*, 7057-7066. (b) Vitale, G.; Corona, P.; Loriga, M.; Paglietti, G. *Farmaco* **1998**, *53*, 150-159.

16. Katoh, A.; Yoshida, T.; Ohkanda, J. *Heterocycles* **2000**, *52*, 911-920.
17. Ali, M.M.; Ismail, M.M.F.; El-Gaby, M.S.A.; Zahran, M.A.; Ammar, Y.A. *Molecules* **2000**, *5*, 864-873.
18. Loriga, M.; Nuvole, A.; Paglietti, G. *J. Chem. Res. Synop.* **1989**, 202-203.
19. Kano, S.; Yuasa, Y. *Heterocycles* **1981**, *16*, 1449-1452.
20. McKillop, A.; Chattopadhyay, S.K.; Henderson, A.; Avendano, C. *Synthesis* **1997**, *3*, 301-304.
21. (a) Kurasawa, Y.; Takada, A. *Heterocycles* **1985**, *23*, 2083-2119. (b) Iwanami, Y. *J. Chem. Soc. Japan, Pure Chem. Soc.* **1961**, *82*, 778-780.
22. Makino, K.; Sakata, G.; Morimoto, K. *Heterocycles* **1985**, *23*, 1729-1734.
23. Krchňák, V.; Szabo, L.; Vágner, J. *Tetrahedron Lett.* **2000**, *41*, 2835-2838.
24. Kobayashi, K.; Matsumoto, T.; Irisawa, S.; Yoneda, K.; Morikawa, O.; Konishi, H. *Heterocycles* **2001**, *55*, 973-980.
25. Mukhopadhyay, R.; Kundu, N. *Tetrahedron Lett.* **2000**, *41*, 9927-9930.
26. (a) Kozmin, S.A.; Janey, J.M.; Rawal, V.H. *J. Org. Chem.* **1999**, *64*, 3039-3047. (b) Lienhard, U.; Fahrni, H.-P.; Neuenschwander, M. *Helv. Chim. Acta* **1978**, *61*, 1609-1621.
27. (a) Chu, J.H.; Murty, B.S.R.; Fedor, L. *J. Am. Chem. Soc.* **1976**, *98*, 3632-3635. (b) Dudek, G.O.; Holm, R.H. *J. Am. Chem. Soc.* **1962**, *84*, 2691-2696.
28. (a) Molina, P.; Arques, A.; Vinader, M.V. *J. Org. Chem.* **1988**, *53*, 4654-4663. (b) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635-646.
29. Bartoszek, M.; Salzwedel, D.; Stumm, G.; Niclas, H.-J. *Organic Mass Spectrometry* **1987**, *22*, 259-268.
30. Söderberg, B.C.G. *Curr. Org. Chem.* **2000**, *4*, 727-764.
31. Crotti, C.; Cenini, S.; Bassoli, A.; Rindone, B.; Demartin, F. *J. Mol. Catal.* **1991**, *70*, 175-187.
32. Ragaini, F.; Cenini, S.; Tollari, S.; Tummollilo, G.; Beltrami, R. *Organometallics* **1999**, *18*, 928.
33. Alajarín, M.; Vidal, A.; Tovar, F.; Conesa, C. *Tetrahedron Lett.* **1999**, *40*, 6127-6130.

34. Krbeček, L.; Takimoto, H. *J. Org. Chem.* **1964**, 29, 3630-3632.
35. Fourquet, J.L.; LeBlanc, M.; Saravanamuthu, A.; Bruce, M.R.M.; Bruce, A.E. *Inorg. Chem.* **1991**, 30, 3241-3243.
36. Massey, S.T.; Mansour, B.; McElwee-White, L. *J. Organomet. Chem.* **1995**, 485, 123-126.
37. Abramovitch, R.A.; Azogu, C.I.; Sutherland, R.G. *Tetrahedron Lett.* **1971**, 20, 1637-1640.
38. (a) Haddadin, M.J.; Bitar, H.E.; Issidorides, C.H. *Heterocycles* **1979**, 12, 323-327. (b) Nazer, M.Z.; Haddadin, M.J.; Petridou, J.P.; Issidorides, C.H. *Heterocycles* **1977**, 6, 541-545.
39. Pandey, V.K.; Raj, N. *Current Science* **1986**, 55, 848-850.
40. Skibo, E.B. *Current Medicinal Chemistry* **1996**, 3, 47-78.
41. Townsend, L.B.; Wise, D.S. *Parasitology Today* **1990**, 6, 107-112.
42. Langcake, P.; Kuhn, P.J.; Wade, M. *Progress in Pesticide Biochemistry and Toxicology* **1983**, 3, 1-109.
43. Holmes, D.S.; Bethell, R.C.; Cammack, N.; Clemens, I.R.; Kitchin, J.; McMeekin, P.; Mo, C.L.; Orr, D.C.; Patel, B.; Paternoster, I.L.; Storer, R. *J. Med. Chem.* **1993**, 36, 3129-3136.
44. Ellingboe, J.W.; Spinelli, W.; Winkley, M.W.; Nguyen, T.T.; Parsons, R.W.; Moubarak, I.F.; Kitzen, J.M.; Von Engen, D.; Bagli, J.F. *J. Med. Chem.* **1992**, 35, 705-716.
45. Navarro-Ocaña, A.; Olguín, L.F.; Luna, H.; Jiménez-Estrada, M.; Bárzana, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 21, 2754-2756.
46. Grenda, V.J.; Jones, R.E.; Gal, G.; Slettinger, M. *J. Org. Chem.* **1965**, 30, 259-261.
47. Wang, H.; Partch, R.E.; Li, Y. *J. Org. Chem.* **1997**, 62, 5222-5225.
48. Perry, R.J.; Wilson, B.D. *J. Org. Chem.* **1993**, 58, 7016-7021.
49. Thomas, A.P.; Allott, C.P.; Gibson, K.H.; Major, J.S.; Masek, B.B.; Oldham, A.A.; Ratcliffe, A.H.; Roberts, D.A.; Russell, S.T.; Thomason, D.A. *J. Med. Chem.* **1992**, 35, 877-885.
50. Cohen, V.I.; Pourabass, S. *J. Heterocycl. Chem.* **1977**, 14, 1321-1323.

51. Crotti, C.; Cenini, S.; Ragaini, F.; Porta, F.; Tollari, S. *J. Mol. Catal.* **1992**, 72, 283-298.
52. Cadogan, J.I.G.; Marshall, R.; Smith, D.M.; Todd, M.J. *J. Chem. Soc. (C)* **1970**, 18, 2441-2443.
53. Hall, J.H.; Kamm, D.R. *J. Org. Chem.* **1965**, 30, 2092-2093.
54. Hall, J.H.; Patterson, E. *J. Am. Chem. Soc.* **1967**, 89, 5856-5861.
55. (a) Song, Y.; Coupar, I.M.; Iskander, M.N. *Quantitative Structure-Activity Relationships* **2001**, 20, 23-30. (b) Shin, H.K.; Shin, Y.W.; Hong, K.W. *American Journal of Physiology* **2000**, 278, H339-H344. (c) Mallesh, K.; Kavitha, T.; Reddy, V.M. *Acta Ciencia Indica, Physics* **1989**, 15, 67-74.
56. Cowden, W.B.; Halladay, P.K.; Cunningham, R.B.; Hunt, N.H.; Clark, I.A. *J. Med. Chem.* **1991**, 34, 1818-1822.
57. Gorvin, J.H. *J. Chem. Soc., Perkin Trans. I* **1988**, 6, 1331-1335.
58. (a) Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* **2000**, 65, 1144-1157. (b) De Riccardis, F.; Bonala, R.R.; Johnson, F. *J. Am. Chem. Soc.* **1999**, 121, 10453-10460.
59. Ishida, A.; Inage, M.; Akatsuka, H.; Inamasu, M.; Mitsui, T. *Jpn. Kokai Tokkyo Koho* **1994**, JP06220059.
60. Kosugi, M.; Ohya, T.; Migita, T. *Bull. Chem. Soc. Japan* **1983**, 56, 3855-3856.
61. Johnston, D.; Smith, D.M. *J. Chem. Soc., Perkin Trans. I* **1976**, 4, 399-404.
62. Battistini, M.; Erba, E.; Pocar, D. *J. Chem. Soc., Perkin Trans. I* **1993**, 3, 339-342.
63. Lai, J.T. *Synthesis* **1982**, 1, 71-74.
64. Newman, M.S.; Kannan, R. *J. Org. Chem.* **1976**, 41, 3356-3359.
65. Makosza, M.; Bia-lecki, M. *J. Org. Chem.* **1998**, 63, 4878-4888.
66. Suzuki, K.; Komatsu, T.; Ina, S.; Fujii, K.; Kojima, J.; Yamana, K. *Jpn. Kokai Tokkyo Koho* **1992**, JP04282314.
67. Inouye, G. *Nippon Kagaku Zasshi* **1954**, 75, 732-734.
68. Meichsner, C.; Riess, G.; Kleim, J.P.; Roesner, M.; Paessens, A.; Blunck, M. *Eur. Pat. Appl.* **1995**, 657166.
69. Commercially available.

70. Roth, T.; Morningstar, M.L.; Boyer, P.L.; Hughes, S.H.; Buckheit, R.W., Jr.; Michejda, C.J. *J. Med. Chem.* **1997**, *40*, 4199-4207.
71. Yields were calculated from ^1H NMR.
72. Abdulla, R.F. *Tetrahedron Lett.* **1974**, *40*, 3559-3562.
73. Petukhov, P.A.; Tkachev, A.V. *Tetrahedron* **1997**, *53*, 9761-9768.
74. Glombik, H.; Utz, R.; Lang, H.J.; Geisen, K.; Beyhl, F.E. *Eur. Pat. Appl.* **1988**, EP288898.
75. Capperucci, A.; Degl'Innocenti, A.; Funicello, M.; Mauriello, G.; Scafato, P.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 2254-2256.
76. Tan, K.L.; Bergman, R.G.; Ellman, J.A. *J. Am. Chem. Soc.* **2002**, *124*, 13964-13965.
77. Visentin, S.; Amiel, P.; Fruttero, R.; Boschi, D.; Roussel, C.; Giusta, L.; Carbone, E.; Gasco, A. *J. Med. Chem.* **1999**, *42*, 1422-1427.
78. Novak, M.; Kahley, M.J.; Lin, J.; Kennedy, S.A.; James, T.G. *J. Org. Chem.* **1995**, *60*, 8294-8304.
79. Benchidmi, M.; El Kihel, A.; Essassi, E.M.; Knouzi, N.; Toupet, L.; Danion-Bougot, R.; Carrie, R. *Bulletin des Societes Chimiques Belges* **1995**, *104*, 605-611.
80. Amenta, D.S.; Mallory, F.B. *J. Org. Chem.* **1980**, *45*, 5236-5238.
81. Hannout, I.B.; Hassan, E.A.; Islam, A.M.; Ismail, I.M. *United Arab Republic Journal of Chemistry* **1970**, *13*, 199-212.
82. Vamecq, J.; Bac, P.; Herrenknecht, C.; Maurois, P.; Delcourt, P.; Stables, J.P. *J. Med. Chem.* **2000**, *43*, 1311-1319.
83. Stead, C.V. (Imperial Chemical Industries Ltd.) *Brit. Pat. Appl.* **1962**, GB19590923.
84. Hall, J.; Dolan, F.W. *J. Org. Chem.* **1978**, *43*, 4608-4612.
85. Bhangadia, R.; Khadikar, P.V.; Agrawal, J.K. *Indian Journal of Chemistry, Section A* **1999**, *38A*, 170-172.
86. Suo, R.; Wang, G.; Pang, Z. *Beijing Huagong Daxue Xuebao* **1999**, *26*, 27-30.
87. Chaudhury, S.; Debroy, A.; Mahajan, M.P. *Can. J. Chem.* **1982**, *60*, 1122-1126.
88. Russell, G.A.; Wang, L.; Rajaratnam, R. *J. Org. Chem.* **1996**, *61*, 8988-8991.

89. Hasan, M.; Mali, F.; Alvarez, M.C.G.; Yunus, U.; Rashid, N.; Maqbool, Z. *J. Chem. Soc. Pak.* **1990**, *12*, 80-83.
90. Mathias, L.J.; Overberger, C.G. *J. Org. Chem.* **1978**, *43*, 3526-3530.
91. Dubey, P.K.; Ratnam, C.V. *Indian Journal of Chemistry, Section B* **1978**, *16B*, 531-533.
92. Szilagyi, G.; Wamhoff, H. *Synthesis* **1981**, *9*, 701-702.
93. Saito, I.; Ikehira, H.; Matsuura, T. *J. Org. Chem.* **1986**, *51*, 5148-5153.

Appendix

Figure 7: ¹H NMR of Compound 56

Figure 8: ¹³C NMR of Compound 56

Figure 9: ^1H NMR of Compound 60

Figure 10: ¹³C NMR of Compound 60

Figure 11: ^1H NMR of Compound 62

Figure 12: ¹³C NMR of Compound 62

Figure 13: ¹H NMR of Compound 64

Figure 14: ^{13}C NMR of Compound 64

Figure 15: ¹H NMR of Compound 66

Figure 16: ¹³C NMR of Compound 66

Figure 17: ¹H NMR of Compound 68

Figure 18: ¹³C NMR of Compound 68

Figure 19: ¹H NMR of Compound 70

Figure 20: ¹³C NMR of Compound 70

Figure 21: ¹H NMR of Compound 72

Figure 22: ¹³C NMR of Compound 72

Figure 23: ¹H NMR of Compound 74

Figure 24: ¹³C NMR of Compound 74

Figure 25: ^1H NMR of Compound 76

Figure 26: ¹³C NMR of Compound 76

Figure 27: ¹H NMR of Compound 78

Figure 28: ^{13}C NMR of Compound 78

Figure 29: ¹H NMR of Compound 80

Figure 30: ¹³C NMR of Compound 80

Figure 31: ^1H NMR of Compound **82-Z**

Figure 32: ¹³C NMR of Compound 82-Z

Figure 33: ^1H NMR of Compound **82-E**

Figure 34: ¹H NMR of Compound 87

Figure 35: ^{13}C NMR of Compound 87

Figure 36: ¹H NMR of Compound 88

Figure 37: ^{13}C NMR of Compound 88

Figure 38: ¹H NMR of Compound 90

Figure 39: ¹³C NMR of Compound 90

Figure 40: ^1H NMR of Compound 96

Figure 41: ^{13}C NMR of Compound 96

Figure 42: ¹H NMR of Compound 97

Figure 43: ^{13}C NMR of Compound 97

Figure 44: ^1H NMR of Compound 98

Figure 45: ^{13}C NMR of Compound 98

Figure 46: ^1H NMR of Compound 100

Figure 47: ¹³C NMR of Compound 100

Figure 48: ¹H NMR of Compound 102

Figure 49: ^{13}C NMR of Compound **102**

Figure 50: ¹H NMR of Compound 104

Figure 51: ¹³C NMR of Compound 104

Figure 52: ^1H NMR of Compound 106

Figure 53: ¹³C NMR of Compound 106

Figure 54: ^1H NMR of Compound 108

Figure 55: ¹³C NMR of Compound 108

Figure 56: ¹H NMR of Compound 110

Figure 57: ¹³C NMR of Compound 110

Figure 58: ^1H NMR of Compounds 111 and 112

Figure 59: ¹H NMR of Compound 113

Figure 60: ^{13}C NMR of Compound 113

Figure 61: ^1H NMR of Compound 114

Figure 62: ¹³C NMR of Compound 114

Figure 63: ¹H NMR of Compound 115

Figure 64: ^{13}C NMR of Compound 115

Figure 65: ¹H NMR of Compound 118

Figure 66: ^{13}C NMR of Compound **118**

Figure 68: ^{13}C NMR of Compound 119

Figure 69: ¹H NMR of Compound 123

Figure 70: ^{13}C NMR of Compound 123

Figure 71: ^1H NMR of Compounds 124 and 125

Figure 72: ^{13}C NMR of Compounds 124 and 125

Figure 73: ¹H NMR of Compound 132

Figure 74: ^{13}C NMR of Compound 132

Figure 75: ¹H NMR of Compound 133

Figure 76: ¹³C NMR of Compound 133

Figure 77: ¹H NMR of Compound 153

Figure 78: ¹³C NMR of Compound **153**

Figure 79: ¹H NMR of Compound 154

154

Figure 80: ¹³C NMR of Compound 154

Figure 81: ^1H NMR of Compound 190

Figure 82: ¹³C NMR of Compound 190

Figure 83: ¹H NMR of Compound 193

Figure 84: ¹³C NMR of Compound **193**

Figure 85: ¹H NMR of Compound 194

Figure 86: ¹³C NMR of Compound 194

Figure 87: ^1H NMR of Compound 195

Figure 88: ¹³C NMR of Compound 195

Figure 89: ¹H NMR of Compound 196

Figure 90: ¹³C NMR of Compound 196

Figure 91: ^1H NMR of Compound 198

Figure 92: ^{13}C NMR of Compound **198**

Figure 93: ^1H NMR of Compound 199

Figure 94: ^{13}C NMR of Compound 199

Figure 95: ^1H NMR of Compound **217**

Figure 96: ^{13}C NMR of Compound **217**

Figure 97: ¹H NMR of Compound 226

Figure 98: ¹³C NMR of Compound 226

Figure 99: ¹H NMR of Compound 228

Figure 100: ¹³C NMR of Compound 228