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Jeremiah W. Hubbard
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Synthesis of Substituted 2-Vinyl and 2-Phenylbenzimidazoles and Progress towards the Synthesis of Natural Products ht-13-A and ht-13-B

Jeremiah W. Hubbard

Dissertation submitted to the
Eberly College of Arts and Sciences
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in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy
in
Chemistry

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N-Heteroannulations, Heck reaction

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Synthesis of 2-alkenyl and 2-arylbenzimidazoles, having a variety of functional groups, has been accomplished *via* a novel palladium-catalyzed reductive N-heteroannulation of 2-nitro-*N*-alkyl or *N*-benzyl benzenamines. The cyclization precursors are readily prepared from commercially available compounds by a variety of methods. In addition, the first total synthesis of ht-13-A has been studied. The key steps of the synthesis are a Mitsunobu reaction, an intramolecular Heck reaction, and a reductive N-heteroannulation.

**Dedicated to my Parents,
George and Kathryn Hubbard**

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Chapter 1 Introduction

A. Benzimidazoles and 2-Substituted Benzimidazoles

The benzimidazole core may have been reported in the literature as early as 1872¹, but was clearly identified by 1899² and the interest from synthetic chemists continues today³. The general structures of benzimidazoles consist of a benzene ring fused to the 4 and 5 positions of an imidazole ring. The numbering of benzimidazole starts with the protonated nitrogen of the imidazole ring and progresses towards the other nitrogen. Some confusion could occur since the proton can shift between the two nitrogen atoms and consequently changes the numbering of the compound (Scheme 1). The benzimidazole with the lowest numbered substituents will be used in this document except in cases describing the work of others that use an alternate numbering system. If the imidazole nitrogen is substituted then the numbering will always start with that nitrogen and continue around the imidazole ring.

Scheme 1 Numbering of Benzimidazoles

The benzimidazole core is of interest to synthetic chemists because of its wide range of biological activities and its framework forming the base of some current pharmaceuticals. For example, compounds containing a benzimidazole core have shown biological activity such as anti-infective, anticancer, antibacterial, antifungal,

anthelmintic, antiretroviral, antiallergic, and antitumor^{3a, 4, 5}. Possibly the most well known pharmaceuticals containing the benzimidazole core are the proton pump inhibitors Prevacid[®], Prilosec[®], and Nexium[®] (Figure 1). While these compounds with a bulky

Figure 1

substituent in the 2-position are used in the treatment of peptic ulcers (proton pump inhibitors), compounds with a small substituent in the 2-position are usually anthelmintics (anti-worm). Benzimidazole anthelmintics are used in both veterinary medicines to treat a wide range of animals⁶ and in human medicine. Examples of current anthelmintics drugs include fenbendazole for animals⁶ and mebendazole for humans⁷. Other drugs with a 2-substituted benzimidazole core in use today include antihistaminics⁸ such as mizolastine, anticoagulant Dabigatran⁹, and potential drugs such as the antitumor class of compounds pyrrolo[1,2-*a*]benzimidazoles¹⁰ (PBI) as seen in Figure 2.

In addition to pharmaceuticals and veterinary medicines, the benzimidazole core can be found in commercially available fungicides. Examples of these types of compounds can be seen in Figure 3 and include the fungicides Fuberidazole and

Figure 2

Thiabendazole as well as the acaricide (pesticide targeting mites) Fenzaflor¹¹.

Unfortunately, fungicide resistance has become a problem for the most commonly used benzimidazole fungicides¹².

The benzimidazole core can be seen in a wide variety of synthetic compounds, but there are very few examples of benzimidazoles in nature. One of the few compounds isolated from a natural source, Kealiiquinone¹³ is a benzimidazole alkaloid isolated from a Micronesian sponge species of *Leucetta* (Figure 4). Another benzimidazole found in

Figure 3

Fuberidazole

Thiabendazole

Fenzaflor

nature is an axial ligand¹⁴ to cobalt found in Vitamin B12. The ligand is named *N*-ribosyl-dimethylbenzimidazole and the structure can be seen in Figure 4.

Figure 4

Kealiiquinone

Adenosylcobalamin

R = CH₃

Methylcobalamin

R = OH

Hydroxocobalamin

R = CN

Cyanocobalamin

Vitamin B₁₂ Family

B. 2-Vinyl and 2-Phenylbenzimidazoles

While 2-vinylbenzimidazoles can be found in the literature as early as 1952¹⁵, there are very few articles published since that time. Some possible reasons for this could be that 2-vinylbenzimidazoles have a tendency to polymerize¹⁶ and were prepared in low isolated yields¹⁷. The tendency to polymerize was exploited with homopolymerization¹⁸ as well as 2-vinylbenzimidazole copolymerized with a wide variety of compounds¹⁵.

Despite these limitations, the recent literature has shown a number of substituted 2-vinylbenzimidazoles with promising biological activities. Some examples of these styryl derivatives include fluorescent chemosensors for heparin detection¹⁹, possible HIV-1 (human immunodeficiency virus) integrase binding inhibitors²⁰, possible inhibitors of monoamine oxidase B²¹, GTP-selective fluorescent chemosensors²², and fluorescent disperse dyes²³ (Figure 5).

In contrast to the 2-vinylbenzimidazoles, numerous articles have been published on 2-phenylbenzimidazole and substituted 2-phenylbenzimidazoles. Probably the most recognized commercial use of a substituted 2-phenylbenzimidazole is in sunscreens²⁴. The purpose of the benzimidazoles in sunscreens is to act as UV filters with 2-phenylbenzimidazole-4,6-disulfonic acid²⁵ and 2-phenyl-5-sulfonic acid²⁶ being two examples. However, with newer methods of detection^{26, 27}, questions about the safety of these compounds have been introduced. Minimal reports of adverse reactions to phenylbenzimidazole sulfonic acid can be seen in the literature such as photocontact reactions²⁸ or allergic and photoallergic reactions²⁹ and a five year study reported only

Figure 5

Heparin Orange
Fluorescent Chemosensor

HIV-1 Integrase Binding Inhibitor

Inhibitor of Monoamine Oxidase B

Fluorescent Disperse Dye

GTP-Selective Fluorescent Chemosensor

one case of allergic reaction and considered it an exception³⁰. Other reports links 2-phenylbenzimidazole and 2-phenylbenzimidazole-5-sulfonic acid to photosensitization of Guanine-specific DNA damage³¹ as well as DNA damage in the HaCaT keratinocytes with light irradiation, but no damage without light³². The use of substituted 2-phenylbenzimidazoles in cosmetics³³ is also widespread. The function of 2-

phenylbenzimidazole-5-sulfonic acid in cosmetics is the same as in sunscreens, namely that of a UV filter³⁴.

Substituted 2-phenylbenzimidazoles have been tested for a wide range of biological activities. A small sampling of the published results of substituted 2-phenylbenzimidazoles for biological activity includes antibacterial activity against methicillin resistant *Staphylococcus aureus*³⁵, AMP-activated protein kinase activators to fight obesity³⁶, as topoisomerase I poisons³⁷, disrupting of Golgi processing and potent activity against IgE³⁸, as a novel peptide coupling reagent³⁹, for antitumor activity⁴⁰, for antimicrobial and antifungal activity⁴¹, for antioxidant properties⁴², and as inhibitors of HIV-1 reverse transcriptase⁴³. A few of the other possible uses of substituted 2-phenylbenzimidazoles include their use in the indirect fluorescent determination of pharmaceutical compounds⁴⁴, as accelerators for curing of epoxy resin⁴⁵, in a complex with iridium to form an organic light emitting diode⁴⁶, as an additive in electrolytic solution to effect dye-sensitized solar cell performance⁴⁷, and as intermediates in organic reactions forming triazines⁴⁸, diketones⁴⁹, or benzotriazoles⁵⁰. A variety of the above discussed substituted 2-phenylbenzimidazoles can be seen in Figure 6.

Figure 6

UV Filter in Sunscreens

AMP-Activated Protein Kinase Activator

Inhibitor of HIV-1 Reverse Transcriptase

Topoisomerase I Poison

Accelerator for Curing Epoxy Resin

Organic Light Emitting Diode

C. Formation of 2-Substituted Benzimidazoles

While there are numerous ways to prepare 2-substituted benzimidazoles⁵¹, two procedures are the most widely used. The first is the Philips synthesis involving a condensation of 1,2-diaminobenzenes with a carboxylic acid or acid derivatives in the presence of an acid⁵² (Scheme 2, path A) and the other method involves the oxidative condensation of 1,2-diamines with aromatic aldehydes (Scheme 2, path B)⁵³. Advances in both pathways of the synthesis of 2-substituted benzimidazoles can be seen in the recent literature.

Scheme 2 Common Paths to 2-Substituted Benzimidazoles

There have been many reports of updated syntheses since the original Phillips work condensing 1,2-diaminobenzenes with carboxylic acids. Some of the most recent examples include the use of microwave heating⁵⁴, a resin to avoid strong acids with microwave heating⁵⁵, the alternative condensing agent *N,N*-dimethylchlorosulfitemethaniminium chloride⁵⁶, cyclocondensation with catalytic BF₃·Et₂O⁵⁷, an enzymatic catalyst⁵⁸, and the two step reactions between 1,2-diaminobenzene and one equivalent of an acid chloride before employing BF₃·Et₂O as a

selective reagent for cyclodehydration⁵⁹ or two equivalents of an acid chloride then cyclized using *p*-toluenesulfonic acid⁶⁰ (Scheme 3).

Scheme 3 2-Substituted Benzimidazoles from 1,2-Aminobenzenes and Acid Chlorides

While the use of carboxylic acids with 1,2-diaminobenzenes was discussed in a wide range of articles from earlier years, the use of aldehydes with 1,2-diaminobenzenes seems to be the current method of choice when forming 2-substituted benzimidazoles. A few of the results from the large number of papers published recently include the reaction of *o*-phenylenediamine derivatives and aldehydes in the presence of the organic salt ammonium acetate⁶¹, with air oxidation after condensation⁶², using (bromodimethyl)sulfonium bromide for oxidative dehydrogenation after condensation⁶³, oxidation by hypervalent iodine⁶⁴, and catalyzed by *p*-toluenesulfonic acid⁶⁵, iron(III)/iron(II) redox cycle⁶⁶, or Oxone^{®67}. In general, the recent references listed above use aromatic aldehydes to form substituted 2-phenylbenzimidazoles (Scheme 4).

Scheme 4 2-Substituted Benzimidazoles from 1,2-Aminobenzenes and Aldehydes

Other recent improvements include the development of environmentally friendly reactions to 2-substituted benzimidazoles. Examples include the use of iodine as a green oxidant⁶⁸, oxidation with activated carbon and molecular oxygen⁶⁹, the oxidative condensation promoted by KHSO_4 ⁷⁰, use of zeolites⁷¹, and the use of sulfamic acid as an eco-friendly catalyst⁷². There are also a few methods that do not use 1,2-diaminobenzenes when forming 2-substituted benzimidazoles. These include the use of *N*-arylamidines with hypochlorite and base⁷³ and the tosylation of *N*-arylamidoximes in the presence of triethylamine⁷⁴ (Scheme 5).

Scheme 5 2-Substituted Benzimidazoles Without Using 1,2-Aminobenzenes

There have also been a few metal-catalyzed syntheses to form 2-substituted benzimidazoles. A few examples include the reactions of amidines with lead tetraacetate oxidation⁷⁵, a palladium-catalyzed reaction⁷⁶, or an iron-catalyzed oxidation⁷⁷ (Scheme

Scheme 6 2-Substituted Benzimidazoles Using Metal Catalysts

6). In addition, an annulation to form 2-vinylbenzimidazole using a ruthenium-catalyst has been reported⁷⁸. It is interesting to note that with acetonitrile as the solvent only the benzimidazole was formed, but in cyclooctene both a higher yield of the benzimidazole and the side product 2-methylquinoxaline were observed (Scheme 7). An alternate published procedure to 2-vinylbenzimidazoles uses an anion-exchange resin with substituted pyridinium salts⁷⁹.

Scheme 7 2-Vinylbenzimidazoles Using Ruthenium-Catalyst

D. Developed Method

With the number of diverse uses for 2-substituted benzimidazoles, a mild and efficient synthetic method would be useful. The previously discussed reactions all suffer from one or more problems such as a lack of diversity in the starting materials, strongly acidic or harsh dehydrating conditions, high temperatures, prolonged reaction times, toxic solvents, use of a large amount of oxidant, tedious work-ups, poor yields, or side products. Thus, based on a relatively mild palladium-catalyzed N-heteroannulations to give indoles recently developed in our laboratories⁸⁰, we attempted to use similar reaction conditions for the formation of benzimidazoles. In addition to indoles, the developed reaction has been used to form quinoxalines and quinoxalinones⁸¹, carbazoles⁸², carbazolones⁸³, and β -carbolines⁸⁴. The N-heteroannulation for each system consists of a palladium source, ligand, and carbon monoxide, but the reaction conditions are slightly different in each system to improve yields and the conditions have yet to be fully optimized.

In our original experiment, *N*-2-(propen-1-yl)benzenamine was prepared by nucleophilic aromatic substitution of methyl 2-bromo-3-nitrobenzoate (**3**) with 1-amino-2-propene. Reductive N-heteroannulation of the benzenamine **5** gave the substituted 2-vinylbenzimidazole (**27**) in 34% yield (Scheme 8). Encouraged by the results from the initial reaction sequence, the scope and limitations of the palladium-catalyzed formation of 2-substituted benzimidazoles from *N*-allyl or *N*-benzyl-2-nitrobenzenamines was studied.

Scheme 8 Original Experiment Forming Substituted 2-Vinylbenzimidazole

E. Natural Product Syntheses of ht-13-A and ht-13-B

In a recent patent⁸⁵, a number of compounds were isolated from *Streptomyces sp.* PA-48561 that have an affinity for serotonin receptors. The patent claims that the compounds are useful as remedies for central nervous system diseases such as anxiety neuroses, depression, schizophrenia, cerebral apoplexy, dementia, pain, and Parkinson's disease. Of the compounds isolated, two were of synthetic interest for the utilization of the reductive N-heteroannulation developed in our laboratories. The structure of ht-13-A and ht-13-B (Figure 7) has a similar motif to compounds we previously synthesized⁸⁰, such as the indole core and a ring fused to the three and four positions of the indole. The envisioned synthetic route would be similar to the methodology developed using a Heck reaction followed by a reductive N-heteroannulation to form the indole ring. The Heck precursor would be formed from a Mitsunobu reaction which would set the stereochemistry of the molecule. To date, no synthesis of either ht-13-A or ht-13-B has been reported in the literature.

Figure 7

To apply the developed 3,4-fused indole methodology to a natural product synthesis a number of possible targets having this core were considered. The fused ring

of the possible targets include those with a heteroatom, usually oxygen or nitrogen, as well as rings that are all carbon based. Possible compounds included pibocin A⁸⁶, an ergoline marine alkaloid, hyrtiazepine⁸⁷, an azepino-indole-type alkaloid, clavicipitic acid⁸⁸, an intermediate in ergot alkaloid formation, or novel indoloazepine derivatives⁸⁹ which could be used as vasopressin V2 receptor antagonists (Figure 8). ht-13-A and ht-13-B were chosen as the targets for the natural product over the other possibilities for a number of reasons. While all of the possible targets include a fused ring and an indole core the other substituents were a factor in choosing a target. The pyrrolidine ring on ht-13-A and ht-13-B could be made following literature procedures while the other targets had no clear path to the substituents. Also, the retrosynthetic sequence for ht-13-A and ht-13-B was hoped to be only three key steps from known starting materials while all the other targets looked to include many more synthetic steps. In the developed methodology, the Heck reaction forming a seven member fused ring, as well as the indole cyclization, gave the best results so a target with a seven membered ring was favored. Finally, since no other routes are known to either ht-13-A or ht-13-B a synthesis would supplement the natural source and allow them to be tested for a wide range of biological activity.

Figure 8

Pibocin A

Hyrtiazepine

Clavicipitic Acid

Indoloazepine derivative

Chapter 2 Results and Discussion

A. Preparation of *N*-Allyl and *N*-Benzyl-2-Nitrobenzenamines

Our general route to 2-vinyl or 2-phenyl substituted benzimidazoles includes the synthesis of *N*-allyl or *N*-benzyl-2-nitrobenzenamines followed by the recently developed N-heterocyclization. In order to examine the palladium-catalyzed N-heteroannulation to give benzimidazoles, a variety of *N*-allyl or *N*-benzyl-2-nitrobenzenamines were synthesized. The compounds were selected to introduce a variety of substituents such as a halide (chloride), electron withdrawing groups (ester and nitro), and an electron donating group (methoxy) on the benzimidazole. Further diversity was accomplished by the selection of compounds such as those that include the use of a pyridine ring in the place of the benzene ring, compounds that can be used to form isomers, and compounds where more than one position could participate in the N-heteroannulation.

The original method utilized to form *N*-allyl or *N*-benzyl-2-nitrobenzenamines was nucleophilic aromatic substitution⁹⁰ using 2-halo-1-nitroarenes and amines. The three substrates synthesized in this manner were methyl 3-nitro-2-(*N*-(2-propen-1-yl))aminobenzoate (**5**), *N*-(2-propen-1-yl) 2-(*N*-(2-propen-1-yl))amino-3-nitrobenzamide (**6**), and methyl 2-(*N*-benzylamino)-3-nitrobenzoate (**7**) as seen in Table 1. Compound **5** was formed by stirring methyl 2-bromo-1-nitrobenzoate (**3**) with allylamine and sulfuric acid. Stirring of **3** with benzylamine yielded compound **7** without the need of the sulfuric acid catalyst. The nitrobenzamide **6** was produced from the double addition of allylamine to 2-bromo-3-nitrobenzoic acid (**4**) when they were reacted in the presence of oxalyl chloride. While these methods worked well for a few compounds it did not give

satisfactory yields for all the substrates examined and not all starting materials were readily available.

Table 1 Nucleophilic Aromatic Substitution Forming 2-Nitrobenzenamines^a

Entry	Nitrobenzene	Amine	Product	Yield
1	3		5	87%
2	4		6	48%
3	3		7	79%

^a See Chapter 3 for experimental details

An alternate procedure to nucleophilic aromatic substitution was needed and a search of the literature led to the reductive amination⁹¹ of 2-nitrobenzenamines with aldehydes. Three more substrates were synthesized in this manner, specifically *N*-benzyl-2-nitrobenzenamine **8**, *N*-4-nitrobenzyl-2-nitrobenzenamine **9**, and *N*-benzyl-5-chloro-2-nitrobenzenamine **10** (Table 2). Compounds **8** and **10** were synthesized using the appropriate amine, benzaldehyde, and acetic acid stirring at room temperature then reduced with sodium triacetoxyborohydride. However, the synthesis of compound **9** did not require acid, but instead a Dean-Stark trap was utilized to remove water forming the

condensation product which was subsequently reduced by sodium triacetoxyborohydride. Unfortunately, after a good yield in forming **8**, the yields for the other two compounds fell dramatically driving the need for another method that would give higher yields.

Table 2 Reductive Amination Forming *N*-Benzyl-2-nitrobenzenamines^a

Entry	Nitrobenzene	Aldehyde	Product	Yield
1			8	83%
2			9	25%
3			10	35%

^a See Chapter 3 for experimental details

After the nucleophilic aromatic substitution and reductive amination methods did not provide satisfactory results, the annulation precursors were prepared using a Buckwald-Hartwig-type palladium-catalyzed amination of 2-halo-1-nitroarenes⁹². This method of preparation gave the best yields for the majority of precursors and the results can be seen in Table 3. Typical reaction conditions consist of heating the proper 2-halo-1-nitroarenes and amines with palladium diacetate, racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (binap), and cesium carbonate to form the corresponding *N*-allyl or *N*-

Table 3 Buckwald-Hartwig-Type Reactions Forming 2-Nitrobenzenamines^a

Entry	Nitrobenzene	Amine	Product	Yield
1			11	81%
2			12	92%
3			13	74%
4			14	58%
5			15	54%
6			16	83%

Table 3 (*continued*)

Entry	Nitrobenzene	Amine	Product	Yield
7				85%
8				75%
9				68%
10				84%

^a See Chapter 3 for experimental details

benzyl-2-nitrobenzenamine. Exact reaction conditions and amounts of material used for all reactions can be found in the experimental section.

In addition to the methods listed above, a number of compounds were synthesized by following published routes. The four compounds produced in this way are *N*-cinnamyl-2-nitrobenzenamine (**21**), 2-nitro-*N*-phenethylbenzenamine (**22**), *N*-benzyl-4-

chloro-2-nitrobenzenamine (**23**), and *N*-benzyl-3-nitropyridin-2-amine (**24**) which are shown in Figure 9.

Figure 9

Finally, to test the capability of the N-heteroannulation using an amide instead of an amine, compound **25** was synthesized according to a literature procedure⁹³. *N*-Benzyl-2-nitrobenzenamine (**8**) was reacted with acetyl chloride with catalytic sulfuric acid in acetic anhydride to give amide **25** with a yield of 91% (Scheme 9).

Scheme 9 Formation of *N*-Benzyl-*N*-(2-nitrophenyl)acetamide

B. Formation of 2-Substituted Benzimidazoles

With a variety of *N*-benzyl and *N*-allyl-2-nitroarenes available, *N*-benzyl-2-nitrobenzenamine (**8**) was used as a model system for the initial screening of the reaction conditions for the N-heteroannulation. This compound was chosen because the product, 2-phenylbenzimidazole (**30**), is substantially more stable when compared with the 2-ethenylbenzimidazoles such as **26**. As discussed in the introduction, the 2-vinylbenzimidazoles are very prone to polymerization. The screening reactions were performed at 120 °C for 20-24 hours in all cases, and the amount of product was determined after purification by column chromatography. Starting material (**8**) was obtained in varying amounts, but since it co-elutes with bis(dibenzylidene)acetone (dba) the amount was not quantified.

The initial screen of the reaction conditions included examining the palladium catalyst, ligands, solvent, pressure, and pressurizing gas (Table 4). While the study is by no means exhaustive it did lead to reaction conditions that gave quality yields in most cases. In the initial reaction attempted (Scheme 8) both bis(1,3-diphenylphosphino)propane (dppp) and 1,10-phenanthroline (phen) were used as ligands. This combination has previously been employed successfully in the synthesis 3,4-fused indoles⁸⁰, 1,2-dihydro-4(3*H*)-carbazolones⁸³, and β -carboline⁸⁴. However, for the transformation of **8** to **30**, a much higher yield was achieved using only 1,10-phenanthroline as the ligand (Table 4, entry 2). Palladium diacetate (Pd(OAc)₂) was examined as a catalyst in place of bis(dibenzylidene)acetone palladium (Pd(dba)₂), but did not perform as well as the original catalyst (entry 3). The absence of any palladium catalyst resulted in a 96% recovery of starting material (entry 4).

Table 4 Optimization of the N-Heteroannulation Reaction^a

Entry	Catalyst	Ligands	Solvent	Pressure (atm)	Yield of 30 (%)
1	Pd(dba) ₂	dppp/phen	DMF	6	20
2	Pd(dba)₂	phen	DMF	6	83
3	Pd(OAc) ₂	phen	DMF	6	28
4	—	phen	DMF	6	0 ^b
5	Pd(dba) ₂	phen	MeCN	6	26
6	Pd(dba) ₂	phen	NMP	6	30
7	Pd(dba) ₂	phen	PhMe	6	34
8	Pd(dba) ₂	phen	DMF	1	19 ^c
9	Pd(dba) ₂	phen	DMF	3	33
10	Pd(dba) ₂	phen	DMF	10	52
11	Pd(dba) ₂	phen	DMF	14	40
12	Pd(dba) ₂	dppp/phen	DMF	14	28
13	Pd(dba) ₂	phen	DMF	20	23
14	Pd(dba) ₂	phen	DMF	2 ^d	0

^a The temperature for all reactions was 120 °C^b Compound **8** was recovered in 96%^c 2-Nitrobenzenamine was also isolated in 22%^d Argon was used in place of carbon monoxide

Dimethyl formamide (DMF) was used in the original sequence, but a variety of other solvents were explored. Acetonitrile (MeCN), *N*-methylpyrrolidinone (NMP), and toluene were all tested under the same reaction conditions (entries 5, 6, 7). Nonetheless, DMF was shown to be the best of the solvents tested for the reaction conditions. Previous work⁹⁴ has shown DMF to be the optimal solvent for the cyclization of 2-nitro-1-alkenylarenes to give indoles.

Carbon monoxide is integral to the reaction as replacing it with an argon atmosphere (entry 14) resulted in no reaction. A carbon monoxide pressure of 6 atm. was found to be optimal for this reaction as lowering or raising the pressure only resulted in

diminishing yields (entries 8-13). In contrast to the $\text{Ru}_3(\text{CO})_{12}$ catalyst discussed in the introduction (Scheme 7), no quinoxaline was observed under any reaction conditions for any of the substrates examined including using cyclooctene as the solvent. Reaction of **8** in cyclooctene resulted in quantitative recovery of the starting material.

After discovering the best conditions and with an array of substrates available, the scope and limitations of the annulation reactions were examined. All *N*-substituted-2-nitroarenes were subjected to the developed reaction conditions for relatively long reaction times (2-8 days) until completion as monitored by TLC. The results of the *N*-heteroannulation can be seen in Table 5.

All four *N*-allylated-2-nitrobenzenamines examined underwent annulations to give 2-alkenyl-substituted benzimidazoles (entries 1-4). Likewise, the vast majority of *N*-benzyl-2-nitrobenzenamines reacted to form the corresponding substituted benzimidazole (entries 5-15 and 17-21). Functional groups were mostly tolerated on both the benzyl ring (entries 6 and 7) and the 2-nitrobenzenamine ring (entries 8-14 and 17-18). However, having a nitro-group on either ring resulted in no recovered starting material and no identifiable products formed (entries 7 and 9). This lack of formed product and loss of starting material was also seen from the reaction of the pyridine derivative **24** (entry 15). This is not entirely surprising as previous studies have shown that groups containing nitrogen can poison palladium catalysts⁹⁵. In addition to these examples, reaction of *N*-substituted-2-nitroarenes leading to fused systems worked well in some cases (entries 19-20), but not as well in others (entries 17-18). Unfortunately, the amide did not react under the standard conditions to form the substituted benzimidazole (entry 21).

Table 5 N-Heterocyclization of 2-Nitroarenes Forming Benzimidazoles^a

Entry	N-Substituted-2-nitroarene	Benzimidazole	Yield
1	11	26	46%
2	5	27	74%
3	6	28	22%
4	21^b	29	54%
5	8	30	83%
6	12	31	56%

Table 5 (continued)

Entry	N-Substituted-2-nitroarene	Benzimidazole	Yield
7	<p>9</p>	<p>32</p>	0% ^c
8	<p>13</p>	<p>33</p>	76%
9	<p>16</p>	<p>34</p>	0% ^c
10	<p>14</p>	<p>35</p>	52%
11	<p>15</p>	<p>36</p>	60% ^d
12	<p>10</p>	<p>37</p>	58%

Table 5 (continued)

Entry	N-Substituted-2-nitroarene	Benzimidazole	Yield
13	<p>23^b</p>	<p>37</p>	64%
14	<p>7</p>	<p>38</p>	45%
15	<p>24^b</p>	<p>37</p>	0% ^c
16	<p>22^b</p>	<p>40</p>	0% ^c
17	<p>17</p>	<p>41</p>	-- ^e
18	<p>18</p>	<p>42</p>	3%

Table 5 (*continued*)

Entry	<i>N</i> -Substituted-2-nitroarene	Benzimidazole	Yield
19	19	43	44%
		44	6%
20	20	45	64%
21	25	46	0% ^c

^a See Chapter 3 for experimental details^b Prepared according to literature procedure^c No benzimidazole, starting material, or any other identified products were observed^d In addition, 28% of **15** was also isolated^e Approximately 90% pure; the yield was not calculated

It is evident, from examples in Table 5, that in order for a methylene group to participate in the cyclization it must be activated by an adjacent aryl or alkenyl group. To begin with, having a two carbon chain, such as in *N*-(2-phenyl-1-ethyl)-2-

nitrobenzenamine, did not lead to the benzimidazole being formed under the reaction conditions, but did produce minute quantities of a number of unidentified products (entry 16). In addition, no reaction of the N-substituted methyl groups of either **14** or **15** was observed while the expected benzimidazoles were formed (entries 10 and 11). Finally, when two different methylenes were present in the same molecule (**19**), only the benzylic methylene reacted to form the benzimidazole nucleus (entry 19).

The mechanism of the N-heteroannulation to form benzimidazoles is presently unclear. However, a palladium bound nitrene could be the possible reactive species based on similar suggested mechanisms (Scheme 10). For example, a metal-bound

Scheme 10 Possible Mechanism to Palladium Bound Nitrene

nitrene followed by carbon-hydrogen bond insertion was suggested for the ruthenium-catalyzed reaction seen in Scheme 7. Also, ruthenium⁹⁶ and palladium⁹⁷ in the presence of carbon monoxide have been shown to catalyze the formation of nitrogen containing heterocycles. In addition, selenium⁹⁸ and ruthenium⁹⁹ with carbon monoxide has also been shown to catalyze the formation of 2-arylbenzimidazoles from 2-nitro-N-

(phenylmethylene)benzenamine, the imine derived from the reaction of 2-nitrobenzenamine and benzaldehyde.

Given the literature precedence, an oxidation of the amine to an imine followed by cyclization was initially considered as a possible reaction path. However, reaction of preformed 2-nitro-*N*-(phenylmethylene)benzenamine under the developed reaction conditions did not produce the corresponding 2-phenylbenzimidazole (**30**), but only resulted in hydrolysis of the imine back to the original starting materials (Scheme 11).

Scheme 11 Possible Reaction of Oxidation of Amine to Imine

Another mechanistic possibility is a base mediated cyclization to form a *N*-hydroxybenzimidazole followed by a palladium-catalyzed deoxygenation. This does not appear to be the case since no reaction is observed in the absence of palladium (Table 4, entry 4) and the starting material is recovered unchanged even after prolonged reaction times. Quenching the reaction before complete consumption of starting material only gave recovered starting material and product, but did not lead to any identifiable intermediates.

C. Methodology of 2-Vinyl and 2-Phenylbenzimidazoles Conclusion

The developed methodology to substituted benzimidazoles was shown to be not only a viable route, but also a successful one. The method is a relative mild and expedient palladium-catalyzed synthesis of 2-alkenyl or 2-aryl-substituted benzimidazoles starting from readily available *N*-allyl or *N*-benzyl-2-nitrobenzenamines. The reaction involves, at least formally, an unusual insertion into a sp^3 -hybridized carbon-hydrogen bond. The reaction sequence is flexible and a variety of functional groups are tolerated. Although numerous methods for the preparation of benzimidazoles exist, the presented reaction may offer an advantage when acid sensitive or oxidation prone functional groups are present in the target molecule.

D. Preparation of Starting Materials for Natural Product Synthesis

Retrosynthetically, the final key step in the synthesis of natural products ht-13-A and ht-13-B (Scheme 12) will be the developed palladium-catalyzed N-heteroannulation to form the indole ring. The precursor to this reaction would come from a Heck-type reaction and the precursor for the Heck reaction will be formed by a Mitsunobu reaction between phenol **47** (X=Br) or **48** (X=I) and the proper alcohol (Scheme 12). The proposed route requires a variety of starting materials to be synthesized, including 2-bromo or 2-iodo-3-nitrophenol and the proper pyrrolidine ring.

Scheme 12 Retrosynthesis of ht-13-A (**1**) and ht-13-B (**2**)

Literature procedures were followed to form the needed pyrrolidine rings as well as the 2-halo-3-nitrophenol starting materials. Following literature procedures, 2-amino-3-nitrophenol was transformed into 2-bromo-3-nitrophenol¹⁰⁰ (**47**) or 2-iodo-3-nitrophenol¹⁰¹ (**48**) using a Sandmeyer-type reaction (Scheme 13). Both compounds were

synthesized with the idea of obtaining the best possible yield in the Heck reaction later in the synthetic sequence.

Scheme 13 Synthesis of 2-Bromo-3-nitrophenol and 2-Iodo-3-nitrophenol

^aPrepared by colleague Christopher Dacko

A small number of different routes were attempted for the synthesis of the pyrrolidine ring. Reasons for the different approaches include the failure of the ring to react under Mitsunobu reaction, failure to react to form the correct ring, and lack of literature precedence to form the correct stereoisomer. The original method used for the construction of the pyrrolidine ring was following a literature procedure¹⁰², although forming the enantiomer of the publisher sequence (Scheme 14). The synthesis starts from commercially available (*R*)-malic acid reacting with acetyl chloride and methylamine to form the imide **49**. Anhydrous hydrogen chloride gas was used to remove the acetyl group followed by protection of the resulting alcohol using *t*-butyl dimethyl silyl chloride (TBSCl). The regiospecific reduction of one carbonyl group was achieved by sodium borohydride. A mixture of isomers was formed in this reaction, but the mixture of isomers does not affect later reactions to set the stereochemistry at that position.

Employing a Williamson ether synthesis using sodium hydride to deprotonate followed

Scheme 14 Original Synthesis of Pyrrolidine Ring

Starting from commercially available D-(+)-malic acid diethyl ester, the alcohol was protected using dihydropyran and pyridinium *p*-toluenesulfonate (PPTS). After protection of the alcohol, the two ester groups were reduced to the diol **60** using lithium aluminum hydride (LAH). The alcohol groups in **60** were reacted with methane sulfonylchloride (MsCl) in the presence of a base forming **61** which was then reacted with methane sulfonic acid (MsOH) to remove the tetrahydropyran (THP) protecting group. It was hoped that compound **62** would successfully undergo the Mitsunobu reaction then cyclize to the pyrrolidine ring and lead to both ht-13-A and ht-13-B. Although that reaction worked, later steps in the sequence failed (see Chapter 2, section E).

After two unsuccessful ventures, a route that led to positive results was found. Instead of trying to form one starting material leading to both ht-13-A and ht-13-B, it was decided that separate pyrrolidine rings were needed for each compound. The target ring that would lead to ht-13-A was partially made in the original synthesis (Scheme 16). Compound **57** was reduced using LAH, but was found to not be stable upon storing. Thus, once formed it was reacted under the Mitsunobu reaction conditions as quickly as possible.

Scheme 16 Synthesis of Pyrrolidine **63** Leading to ht-13-A

The route to the pyrrolidine ring that would lead to ht-13-B is a collection of literature procedures leading to ring **73** (Scheme 17). The synthesis starts with the transformation of trans-4-hydroxy-L-proline to the methyl ester **64** using thionyl chloride in methanol¹⁰⁴. The amine is then protected using di-*tert*-butyl dicarbonate anhydride (Boc₂O) followed by protection of the alcohol with a TBS group giving compound **66**¹⁰⁵. After the two protections, the methyl ester was reduced using sodium borohydride and lithium chloride to yield the alcohol **67**¹⁰⁶. The formed alcohol was then converted to the methanesulfonyl ether **68** and reduced to the pyrrolidine **69** using lithium triethylborohydride¹⁰⁵. Oxidation of the methylene in **69** to a carbonyl was accomplished using ruthenium oxide and sodium periodate to yield the amide **70**¹⁰⁷. The amide carbonyl was reduced, using lithium triethylborohydride, to an alcohol that was transformed to the methyl ether by PPTS and methanol giving compound **71**¹⁰⁷. The allyl group was then introduced as previously shown using allyl trimethylsilane and titanium tetrachloride, but the Boc protecting group was unexpectedly removed. The deprotected mixture of isomers (**72**) was reprotected using Boc₂O to give the desired allylation products (**73**). Finally, the mixture of isomers was subjected to TBAF to remove the TBS protecting group and separated¹⁰⁸ to give compounds **74** and **75**.

In addition to the loss of a Boc group, the loss of another protecting group was experienced (Scheme 18). In one attempted sequence to get to pyrrolidine **63** that was later abandoned, the TBS protecting group was inadvertently removed in two separate steps. During the allylation reaction of pyrrolidinone **53** the loss of the TBS group was observed as a mixture of isomers in addition to obtaining the desired products **54** and **55**. The free alcohols were reprotected and separated to give the desired TBS ethers.

Scheme 17 Synthesis of Pyrrolidine **74** Leading to ht-13-B

Reduction of the cis-isomer again leads to unintended removal of the TBS protecting group in addition to the desired pyrrolidine **63**. As the next step in the sequence is the removal of the TBS group, the crude mixture was subjected to the deprotection conditions giving the desired pyrrolidine **63**.

Scheme 18 Loss of Protecting Group

E. Formation of Ether (Mitsunobu Reaction)

The Mitsunobu reaction was developed in its most recognized form by Professor Oyo Mitsunobu in 1967¹⁰⁹. The usual protocol involves the reaction of an alcohol and an acid/pronucleophile promoted by a phosphane and an azodicarboxylate or azodicarboxamide under mild conditions (Scheme 19). Many acid/pronucleophiles have been used such as carboxylic acids, phenols, and imides to prepare esters, ethers, or carbon-nitrogen bonds. The Mitsunobu reaction is popular due to its stereoselectivity, ability to tolerate a large range of functional groups, and the mild conditions. The main drawback of the Mitsunobu is that the by-products phosphane oxide and hydrazinedicarboxylate or hydrazinedicarboxamide tend to co-elute with the desired product. A wide range of uses of the Mitsunobu reaction has been published since the original manuscript¹¹⁰ and current studies towards improvements are ongoing¹¹¹. While the numerous uses of the Mitsunobu reaction are found in the synthesis of steroids, carbohydrates, or nucleosides, a relatively small number of papers report the use in preparation of alkaloidal compounds¹¹².

Scheme 19 Mitsunobu Reaction

Using the originally synthesized cis-pyrrolidinone **57** and 2-bromo-3-nitrophenol (**47**), the Mitsunobu reaction was attempted. Initially, diethylazodicarboxylate (DEAD) and triphenylphosphine were the reagents used in the reaction, but no product was formed (**76**). Given that DEAD is no longer commercially available, the use of

diisopropylazodicarboxylate (DIAD) with triphenylphosphine was next attempted, but again no product was seen. Lowering of the temperature to -20 °C with DIAD and triphenylphosphine still yielded no product. To be sure that steric hindrance was not the problem, the diastereomer (**56**) of pyrrolidinone **57** was reacted under the DIAD and triphenylphosphine conditions, but once more no product was observed (**77**). Finally, the

Scheme 20 Failed Coupling Reactions

Possible Side Reaction:

mesylate **58** was reacted in a S_N2 type reaction with cesium carbonate or sodium hydride as a base. These reactions also did not lead to any of the desired ether (Scheme 20). It is thought that the slightly basic conditions of the Mitsunobu reaction give the elimination product forming an alkene (**78**) as shown in Scheme 20. This is not unlikely as a recent paper¹¹³ describes similar elimination products from β -thioalkoxy alcohols (Scheme 21).

Scheme 21 Elimination Reaction of β -Thioalkoxy Alcohols

Given that the pyrrolidinone ring failed to react under the Mitsunobu reaction conditions, mostly likely because of the acidic proton, an alternate method was needed. Compound **62** was constructed knowing that the protons would be much less acidic and thus it would be more likely to form the desired ether. Subjecting the alcohol **62** to the Mitsunobu conditions with 2-bromo-3-nitrophenol (**47**), triphenylphosphine, and DIAD lead to the desired ether (**79**) in excellent yield. To form the pyrrolidine ring and further the reaction sequence, literature procedures¹¹⁴ were followed to form **80** in two steps. The dimesylate **79** was transformed to the cyclic hydroxylamine which was then oxidized to the nitron **80**. An allylation of the nitron was attempted following two separate literature procedures. The first attempted was made using allyl TMS and titanium tetrachloride¹⁰², but no product (**81**) was seen. Likewise, no product (**81**) was formed when nitron **80** was reacted with a Grignard reagent¹¹⁵, allyl magnesium chloride (Scheme 22).

Scheme 22 Failed Allylation Reactions

Finally, after removal of the carbonyl group in pyrrolidinone **57** either by reduction (Scheme 16) or by changing routes (Scheme 17), the Mitsunobu reaction was accomplished successfully. Using the conditions previously attempted, 2-halo-3-nitrophenol, DIAD, and triphenylphosphine were reacted to give the desired ethers in good yields. Both 2-bromo and 2-iodo-3-nitrophenol were used in the reaction so that the next step in the sequence, the Heck reaction, could be examined for the best possible results. The pyrrolidine ring (**63**) that would lead to ht-13-A and the ring (**74**) that would lead to ht-13-B were both reacted under the Mitsunobu conditions and gave the corresponding ethers in good yields (Scheme 23).

Scheme 23 Successful Mitsunobu Reactions

F. Intramolecular Heck Reaction

The Heck reaction has become one of the most versatile methods for the preparation of carbon-carbon bonds since it was first introduced¹¹⁶. The Heck reaction is the second key step in our general scheme to the natural products ht-13-A (**1**) and ht-13-B (**2**). It is used to form the fused ring and to position the double bond for cyclization to the indole while not affecting the stereochemistry of the molecules (Scheme 24). Our previous methodology⁸⁰ to fused indoles demonstrated the feasibility of using the Heck reaction to form a seven member heterocyclic ring and leading into the N-heteroannulation to form the indole ring.

Scheme 24 Possible Heck Reaction Products

The initial attempt of the Heck reaction was utilizing the same conditions developed during the methodology, namely the substrate (**85**), palladium diacetate, and tri-*o*-tolylphosphine in triethylamine at 120 °C. However, these conditions only result in recovered starting material (Table 6, entry 1). A recent paper¹¹⁷ provided alternate reaction conditions that gave promising results. The reaction of the same substrate (**85**) with palladium diacetate, triphenylphosphine, and silver carbonate in DMF gave the

desired product in 31% yield (entry 2). The same conditions using the bromo-substituted substrate (**84**) gave a similar 35% yield (entry 4). Unfortunately, the same conditions with substrate **83** gave no product, starting material, or other isolatable products (entry 5). Reacting compound **84** under the original conditions ($\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tolyl})_3$, NEt_3) gave a similar yield to the other reactions (entry 3).

Table 6 Heck Reaction Results

Entry	Substrate	Conditions	Yield
1		$\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tolyl})_3$, NEt_3 , 120 °C	recovered starting material
2	85	$\text{Pd}(\text{OAc})_2$, PPh_3 , Ag_2CO_3 , DMF, 120 °C	87 , 35%
3		$\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tolyl})_3$, NEt_3 , 120 °C	87 , 29%
4	84	$\text{Pd}(\text{OAc})_2$, PPh_3 , Ag_2CO_3 , DMF, 120 °C	87 , 31%
5		$\text{Pd}(\text{OAc})_2$, PPh_3 , Ag_2CO_3 , DMF, 120 °C	86 , not observed
	83		

G. Reductive N-Heteroannulation

Our previously published methodology⁸⁰ gave yields from 33-83% for the reductive N-heteroannulation forming 3,4-fused indoles. The cyclization conditions of this methodology consist of bis(dibenzylidenacetone)palladium, 1,10-phenanthroline, and 1,3-bis(diphenylphosphino)propane in DMF under carbon monoxide at six atmospheres. Subjecting compound **87** to these conditions did not give the expected indole or any other identifiable products (Table 7). Other heterocycles have been synthesized in our group using alternate conditions or palladium diacetate and 1,10-phenanthroline under a carbon monoxide atmosphere with good results. Attempting these conditions gave promising results in the crude mixture, but with the small amounts used and the difficulty in the separation no product was able to be isolated.

Table 7 N-Heteroannulation Results

Entry	Substrate	Conditions	Yield
1		Pd(dba) ₂ , phen, dppp, DMF, 120 °C, 6 atm CO	no product isolated
2	87	Pd(OAc) ₂ , phen, DMF, 120 °C, 6 atm CO	no product isolated

H. Natural Products ht-13-A and ht-13-B Conclusions

The envisioned routes to ht-13-A and ht-13-B hold promise with the short, concise total synthesis. However, the total syntheses have not been completed. The key steps of a Mitsunobu reaction, Heck reaction, and indole cyclization utilizing a reductive N-heteroannulation have all shown potential, but optimization is still in progress. Now that the Mitsunobu reaction and Heck reaction are effective a larger amount of precursor compounds for the N-heteroannulation should be possible and allow for reactions to be performed on a larger scale. A larger scale should also help in finding the best method to purify the natural product ht-13-A and the *N*-Boc protected precursor to ht-13-B.

Chapter 3 Experimental

A. General Procedures

All NMR spectra were determined in CDCl_3 at 600 MHz (^1H NMR) and 150 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to Me_4Si (0.00, ^1H and ^{13}C) or CDCl_3 (77.00, ^{13}C) internal standards. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Toluene, hexanes, and EtOAc were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed in oven-dried glassware under an argon atmosphere unless otherwise stated. Solvents were removed from crude reaction mixtures and products on a rotary evaporator at water aspirator pressure. Melting points were determined on a MelTemp and are uncorrected. Elemental analyses were performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.

B. Experimental

Methyl 3-nitro-2-(*N*-(2-propen-1-yl))aminobenzoate (5)

To a solution of methyl 2-bromo-3-nitrobenzoate (1.12 g, 4.31 mmol) in dichloromethane (50 mL) was added 2-propen-1-ylamine (350 mL, 4.66 mmol) and the reaction mixture was stirred at ambient temperature (23 h). Concentrated sulfuric acid (5 drops) was added and three portions of 2-propen-1-ylamine (330 mL, 4.40 mmol) were added (immediately, after 21.5 h, and after 24 h). The solution was heated at 50 °C for this entire period and for an additional 23 h after the last addition. The solvents were removed

on a rotary evaporator at water aspirator pressure and the residue was purified by chromatography (hexanes/EtOAc, 9:1) to give **5** (890 mg, 3.77, 87%) as a pale brown solid. Mp 60–61 °C; ^1H NMR: δ 8.56 (br s, 1H), 8.08 (dd, $J=7.2, 1.2$ Hz, 1H), 7.97 (dd, $J=7.8, 1.8$ Hz, 1H), 6.69 (t, $J=7.8$ Hz, 1H), 5.85–5.91 (m, 1H), 5.32 (d, $J=16.8$ Hz, 1H), 5.22 (d, $J=10.2$ Hz, 1H), 3.91 (s, 3H), 3.61 (s, 2H); ^{13}C NMR: δ 167.7, 145.3, 137.4, 136.9, 133.6, 131.5, 118.0, 116.8, 114.6, 52.4, 49.1; IR (neat): 1687, 1523, 1344, 1121 cm^{-1} ; Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4$: C, 55.93; H, 5.12. Found: C, 56.05; H, 5.58; HRMS calcd for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 237.0875, found: 237.0870.

***N*-(2-Propen-1-yl) 2-(*N*-(2-propen-1-yl))amino-3-nitrobenzamide (**6**)**

To a solution of 2-bromo-3-nitrobenzoic acid (2.06 g, 8.37 mmol) in benzene (20 mL) at 0 °C was added oxalyl chloride (4.0 mL, 45.9 mmol) via syringe. The resulting solution was stirred (0 °C, 10 min, ambient temperature, 1 h, and at reflux, 1 h), and the solvent and excess reagents were removed. The crude product was dissolved in benzene (20 mL), *N*-(2-propen-1-yl)amine (2.0 mL, 26.7 mmol) in benzene (10 mL) was added via pipette, and the resulting solution was stirred at ambient temperature (68 h). The solvent was removed on a rotary evaporator at water aspirator pressure and the crude product was purified by chromatography (hexanes/EtOAc, 6:4) to give **6** (1.05 g, 4.02 mmol, 48%) as a yellow solid followed by *N*-(2-propen-1-yl) 2-bromo-3-nitrobenzamide (740 mg, 2.60, 31%) as a yellow solid. Data for **6**: mp 59–60 °C; ^1H NMR: δ 8.16 (dd, $J=9.0, 1.2$ Hz, 1H), 7.76 (dd, $J=7.8, 1.2$ Hz, 1H), 7.64 (br s, 1H), 6.85 (t, $J=7.8$ Hz, 1H), 6.72 (br s, 1H), 5.96–5.84 (m, 2H), 5.29–5.25 (m, 2H), 5.23–5.18 (m, 2H), 4.07 (t, $J=6.0$ Hz, 2H), 3.80 (t, $J=6.0$ Hz, 2H); ^{13}C NMR: δ 167.2, 143.7, 137.8, 136.4, 133.8, 133.4, 128.7, 126.6, 117.6,

117.5, 117.5, 50.6, 42.5; IR (neat): 3311, 1637, 1488, 1270, 925 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_3$: C, 59.76; H, 5.79. Found: C, 59.43; H, 6.06.

Methyl 2-(*N*-benzylamino)-3-nitrobenzoate (7**)¹¹⁸**

A solution of methyl 2-bromo-3-nitrobenzoate (261 mg, 1.00 mmol) and benzylamine (230 μL , 2.11 mmol) in dichloromethane (10 mL) was stirred at ambient temperature (23 h). Additional benzylamine (12 μL , 1.10 mmol) was added and the solution was stirred at ambient temperature (24 h). The solution was washed with sodium carbonate (4 $\times$ 10 mL) and then the organic phase was dried (MgSO_4), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 9:1) gave **7** (225 mg, 0.791 mmol, 79%) as a yellow solid. Mp 96–97 $^{\circ}\text{C}$; ^1H NMR: δ 8.77 (br s, 1H), 8.09 (dd, $J=7.8$, 1.8 Hz, 1H), 7.99 (dd, $J=8.4$, 1.8 Hz, 1H), 7.34 (t, $J=7.8$ Hz, 2H), 7.30–7.28 (m, 3H), 6.71 (t, $J=7.8$ Hz, 1H), 4.16 (d, $J=4.2$ Hz, 2H), 3.88 (s, 3H); ^{13}C NMR: δ 167.7, 145.3, 137.6, 137.3, 136.9, 131.6, 128.9, 127.9, 127.9, 116.9, 114.7, 52.4, 51.0; IR (neat): 1699, 1577, 1490, 1259, 1105 cm^{-1} ; Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4$: C, 62.93; H, 4.93. Found: C, 63.28; H, 5.30.

***N*-Benzyl-2-nitrobenzenamine (**8**)**

To a solution of 2-nitrobenzenamine (300 mg, 2.17 mmol), benzaldehyde (420 μL , 4.13), glacial acetic acid (750 μL , 13.1 mmol), and dichloromethane (10 mL) was added sodium triacetoxyborohydride (1.29 g, 6.09 mmol) and the reaction mixture was stirred at ambient temperature (90.5 h). Additional benzaldehyde (210 μL , 2.06 mmol) was added and the solution was stirred at ambient temperature (28.75 h). Additional sodium

triacetoxyborohydride (648 mg, 3.06 mmol) was added and the solution was stirred at ambient temperature (23.5 h). The mixture was diluted with aqueous sodium bicarbonate (10 mL) and washed with EtOAc (4×10 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure. The crude product was purified by chromatography (hexanes then hexanes/EtOAc, 95:5) to give **8** (409 mg, 1.80 mmol, 83%) as an orange solid. Mp 73–74 °C (lit.¹¹⁹ 72 °C).

***N*-4-Nitrobenzyl-2-nitrobenzenamine (9)**

A solution of 2-nitrobenzenamine (552 mg, 4.00 mmol), 4-nitrobenzaldehyde (605 mg, 4.01 mmol), and benzene (50 mL) was heated at reflux (110 °C, 47 h followed by 130 °C for 67 h) while removing water via a Dean–Stark trap. After cooling to ambient temperature, dichloromethane (20 mL) and sodium triacetoxyborohydride (2.37 g, 11.2 mmol) were added and the reaction mixture was stirred at ambient temperature (23.25 h). Workup as described for **8** gave after chromatography (hexanes/EtOAc, 9:1) **9** (270 mg, 0.988 mmol, 25%) as a yellow solid. Mp 127–129 °C (lit.⁹³ 133–135 °C).

***N*-Benzyl-5-chloro-2-nitrobenzenamine (10)**

5-Chloro-2-nitrobenzenamine (599 mg, 3.47 mmol), benzaldehyde (68 µL, 6.68 mmol), and acetic acid (1.2 mL, 21.0 mmol), in dichloromethane (20 mL) with sodium triacetoxyborohydride (2.07 g, 9.77 mmol), were reacted as described for **7**. Additional benzaldehyde (340 µL, 3.34 mmol, after 19.75 h), sodium triacetoxyborohydride (1.03 g, 4.86 mmol, after 20 h), benzaldehyde (340 µL, 3.34 mmol, after 26.5 h), and

triacetoxyborohydride (1.03 g, 4.86 mmol, after 27 h) were added, and the reaction mixture was stirred for an additional 20.25 h. Workup as described for **8** gave after chromatography (hexanes then hexanes/EtOAc, 98:2) **10** (322 mg, 1.23 mmol, 35%) as an orange solid. Mp 96–98 °C (lit.¹²⁰ 100–101 °C).

***N*-(2-Propen-1-yl)-2-nitrophenylamine (11)**

A solution of 1-iodo-2-nitrobenzene (124 mg, 0.498 mmol), *N*-(2-propen-1-yl)amine (50 µL, 0.666 mmol), palladium diacetate (Pd(OAc)₂, 11.7 mg, 0.052 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (binap, 47.1 mg, 0.076 mmol), and cesium carbonate (228 mg, 0.700 mmol) in toluene (6 mL) was stirred (30 min) under argon atmosphere followed by heating at 80 °C (44.75 h). The mixture was cooled to ambient temperature, diluted with EtOAc (6 mL), filtered (Celite), and the Celite was washed with a few milliliter of EtOAc. The solvents were removed on a rotary evaporator at water aspirator pressure and the crude product was purified by column chromatography on silica (hexanes/EtOAc, 9:1) to give **11** (72.2 mg, 0.405 mmol, 81%) as an orange oil. Analytical data are in complete agreement with published values^{90a}.

***N*-(4-Methoxybenzyl)-2-nitrobenzenamine (12)**

A solution of 2-bromo-1-nitrobenzene (230 mg, 1.14 mmol), 4-methoxybenzylamine (170 µL, 1.31 mmol), Pd(OAc)₂ (23.6 mg, 0.105 mmol), binap (94.0 mg, 0.151 mmol), and cesium carbonate (460 mg, 1.41 mmol) in toluene (6 mL) was reacted, as described for **11** (rt, 30 min; 80 °C, 28.5 h), to give after purification by chromatography

(hexanes/EtOAc, 9:1) **12** (270 mg, 1.05 mmol, 92%) as a yellow solid. Mp 94–95 °C (lit.¹²¹ 81–82 °C).

***N*-Benzyl-4-methoxy-2-nitrobenzenamine (13)**

Reaction of 4-bromo-3-nitro-1-methoxybenzene (461 mg, 2.00 mmol), benzylamine (290 μ L, 2.66 mmol), Pd(OAc)₂ (45.1 mg, 0.201 mmol), binap (188 mg, 0.302 mmol), and cesium carbonate (914 mg, 2.81 mmol) in toluene (6 mL), as described for **11** (30 min at rt, 16.5 h at 80 °C), gave after dilution, filtration, and chromatography (hexanes then hexanes/EtOAc, 98:2) **13** (380 mg, 1.48 mmol, 74%) as a red solid. Mp 104–105 °C (lit.¹²² 105–106 °C); ¹H NMR: δ 8.35 (br s, 1H), 7.65 (d, J =2.4 Hz, 1H), 7.37–7.33 (m, 4H), 7.29 (t, J =6.6 Hz, 1H), 7.08 (dd, J =9.6, 3.0 Hz, 1H), 6.78 (d, J =9.6 Hz, 1H), 4.54 (d, J =5.4 Hz, 2H), 3.78 (s, 3H); ¹³C NMR: δ 149.9, 141.1, 137.6, 131.4, 128.9, 127.6, 127.1, 127.0, 115.6, 107.3, 55.9, 47.3; IR (neat): 1569, 1515, 1281, 1031 cm⁻¹; Anal. Calcd for C₁₄H₁₄N₂O₃: C, 65.11; H, 5.46. Found: C, 65.01; H, 5.73.

***N*-Benzyl-*N*-methyl-4-methoxy-2-nitrobenzenamine (14)**

A solution of 2-bromo-5-methoxy-1-nitrobenzene (500 mg, 2.16 mmol), *N*-benzyl-*N*-methyl amine (370 μ L, 2.87 mmol), Pd(OAc)₂ (49.3 mg, 0.220 mmol), binap (202 mg, 0.325 mmol), and cesium carbonate (984 mg, 3.02 mmol) in toluene (6 mL), as described for **11** (30 min at rt, 19.75 h at 80 °C), gave after dilution, filtration, and chromatography (hexanes/EtOAc, 95:5) **14** (340 mg, 1.25 mmol, 58%) as a dark red oil. ¹H NMR: δ 7.29–7.27 (m, 4H), 7.22–7.20 (m, 2H), 7.11 (d, J =9.6 Hz, 1H), 6.98 (dd, J =9.0, 3.0 Hz, 1H), 4.14 (s, 2H), 3.73 (s, 3H), 2.64 (s, 3H); ¹³C NMR: δ 154.0, 143.9, 139.7, 137.5, 128.2,

128.0, 127.1, 123.4, 119.8, 109.0, 60.2, 55.6, 41.1; IR (neat): 1519, 1496, 1452, 1292, 1033, 863, 696 cm^{-1} ; Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$: C, 66.16; H, 5.92. Found: C, 66.31; H, 6.21.

***N*-Benzyl-(5-methoxy-2-nitrophenyl)-*N*-methylamine (15)**

Reaction of 2-iodo-4-methoxy-1-nitrobenzene (500 mg, 1.79 mmol), *N*-benzyl-*N*-methylamine (300 μL , 2.33 mmol), $\text{Pd}(\text{OAc})_2$ (40.7 mg, 0.181 mmol), binap (168 mg, 0.269 mmol), and cesium carbonate (819 mg, 2.51 mmol) in toluene (6 mL), as described for **11** (45.5 h at 80 $^{\circ}\text{C}$, 23.25 h at 120 $^{\circ}\text{C}$), gave after dilution, filtration, and chromatography (hexanes/EtOAc, 98:2) **15** (262 mg, 0.962 mmol, 54%) as a yellow solid. Mp 97–99 $^{\circ}\text{C}$; ^1H NMR: δ 7.85 (d, $J=9.6$ Hz, 1H), 7.32–7.22 (m, 5H), 6.45 (d, $J=1.8$ Hz, 1H), 6.38 (dd, $J=9.6, 2.4$ Hz, 1H), 4.33 (s, 2H), 3.74 (s, 3H), 2.74 (s, 3H); ^{13}C NMR: δ 163.4, 148.3, 136.8, 133.8, 128.9, 128.4, 127.4, 127.2, 105.0, 104.0, 58.5, 55.5, 40.3; IR (neat): 1613, 1567, 1501, 1450, 1415, 1216 cm^{-1} ; Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$: C, 66.16; H, 5.92. Found: C, 65.94; H, 6.22.

***N*-Benzyl-2,4-dinitrobenzenamine (16)**

Reaction of 1-bromo-2,4-dinitrobenzene (494 mg, 2.00 mmol), benzylamine (290 μL , 2.66 mmol), $\text{Pd}(\text{OAc})_2$ (45.5 mg, 0.203 mmol), binap (197 mg, 0.316 mmol), and cesium carbonate (914 mg, 2.81 mmol) in toluene (6 mL), as described for **11** (30 min at rt, 19.5 h at 80 $^{\circ}\text{C}$), gave after dilution, filtration, and chromatography (hexanes/EtOAc, 9:1 then 8:2) **16** (454 mg, 1.66 mmol, 83%) as a yellow solid. Mp 115–117 $^{\circ}\text{C}$ (lit.¹²³ 115–116 $^{\circ}\text{C}$).

2-(4-Methoxy-2-nitrophenyl)-2,3-dihydro-1H-isoindole (17)

Reaction of 2-bromo-5-methoxy-1-nitrobenzene (375 mg, 1.62 mmol), isoindoline (255 mg, 2.14 mmol), Pd(OAc)₂ (36.2 mg, 0.161 mmol), binap (151 mg, 0.242 mmol), and cesium carbonate (738 mg, 2.27 mmol) in toluene (6 mL), as described for **11** (30 min at rt, 19.5 h at 80 °C) gave after dilution, filtration, and chromatography (hexanes/EtOAc, 9:1) **17** (374 mg, 1.38 mmol, 85%) as a red solid. Mp 103–104 °C (lit.¹²⁴ 112 °C).

2-(2-Nitro-1-phenyl)-1,2,3,4-tetrahydroisoquinoline (19)

Reaction of 2-bromo-1-nitrobenzene (404 mg, 2.00 mmol), 1,2,3,4-tetrahydroisoquinoline (330 µL, 2.64 mmol), Pd(OAc)₂ (45.5 mg, 0.203 mmol), binap (187 mg, 0.301 mmol), and cesium carbonate (915 mg, 2.81 mmol) in toluene (6 mL), as described for **11** (6 h at rt, 40.75 h at 80 °C), gave after dilution, filtration, and chromatography (hexanes/EtOAc, 95:5) **19** (344 mg, 1.35 mmol, 68%) as an orange solid. Mp 98–100 °C (lit.¹²⁵ 100–102 °C).

2-(2-Nitrophenyl)-2,3-dihydro-1H-benzo[de]isoquinoline (20)

Reaction of 2-iodonitrobenzene (124 mg, 0.498 mmol), 2,3-dihydro-1H-benzo[de]isoquinoline (109 mg, 0.644 mmol), Pd(OAc)₂ (11.8 mg, 0.053 mmol), binap (46.7 mg, 0.075 mmol), and cesium carbonate (229 mg, 0.703 mmol) in toluene (6 mL), as described for **11** (30 min at rt, 91.25 h at 80 °C), gave after dilution, filtration, and chromatography (hexanes/EtOAc, 6:4) **20** (121 mg, 0.417 mmol, 84%) as a yellow solid. Mp 104–108 °C; ¹H NMR: δ 7.77 (d, *J*=7.8 Hz, 1H), 7.71 (d, *J*=8.4 Hz, 2H), 7.41 (t,

$J=7.8$ Hz, 2H), 7.31 (t, $J=8.4$ Hz, 1H), 7.21 (d, $J=6.6$ Hz, 2H), 7.14 (d, $J=9.0$ Hz, 1H), 6.96 (t, $J=7.8$ Hz, 1H), 4.63 (s, 4H); ^{13}C NMR: δ 145.3, 143.3, 133.4, 132.1, 128.0, 126.6, 126.0, 125.8, 121.8, 121.7, 121.7, 55.2; IR (neat): 1602, 1520, 1355, 1214, 802, 752 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2$: C, 74.47; H, 4.86. Found: C, 74.23; H, 5.23.

N-Benzyl-N-(2-nitrophenyl)acetamide⁹³ (25)

To a solution of **8** (116 mg, 0.51 mmol) in acetic anhydride (1 ml) was added acetyl chloride (0.04 ml, 0.56 mmol) and H_2SO_4 (1 drop) with heating until **8** dissolved. The resulting mixture was stirred at room temperature for 24 h. To the reaction mixture was added H_2O (5 ml) then extracted with EtOAc (3x5 ml). The combined organic phase was dried (MgSO_4) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 7:3) gave **25** (126 mg, 0.47 mmol, 92%).

2-Ethenyl-1H-benzimidazole (26)

To a threaded ACE Glass pressure tube were added **11** (72.2 mg, 0.405 mmol), bis(dibenzylideneacetone)palladium ($\text{Pd}(\text{dba})_2$, 14.1 mg, 0.025 mmol), and 1,10-phenanthroline monohydrate (8.40 mg, 0.047 mmol) in DMF (6 mL). The tube was fitted with a pressure head and after the solution was saturated with CO (four cycles to 6 atm of CO) the reaction mixture was heated at 120 $^\circ\text{C}$ under CO (6 atm, 47 h). The mixture was diluted with EtOAc (10 mL) and washed with water (4x10 mL). The combined organic phases were dried (MgSO_4), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc,

2:8) gave **26** (27.1 mg, 0.188 mmol, 46%) as a pale brown solid. Mp 149–153 °C (lit.⁷⁹ 184 °C).

Methyl 2-ethenyl-1*H*-benzimidazole-4-carboxylate (27)

Reaction of **5** (37.8 mg, 0.160 mmol), Pd(dba)₂ (7.30 mg, 0.013 mmol), and 1,10-phenanthroline monohydrate (4.0 mg, 0.022 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 70.5 h), gave after extraction and chromatography (hexanes/EtOAc, 7:3) **27** (24.1 mg, 0.119 mmol, 74%) as a red solid. Mp 64–71 °C; ¹H NMR: δ 7.94 (dd, *J*=7.8, 0.6 Hz, 1H), 7.88 (dd, *J*=7.8, 1.2 Hz, 1H), 7.29 (t, *J*=7.8 Hz, 1H), 6.85 (dd, *J*=18.0, 11.4 Hz, 1H), 6.26 (d, *J*=18.0 Hz, 1H), 5.73 (d, *J*=11.4 Hz, 1H), 3.98 (s, 3H); ¹³C NMR: δ 167.0, 151.3, 144.5, 134.4, 126.1, 125.0, 125.0, 121.9, 121.7, 113.2, 52.1; IR (neat): 1702, 1431, 1291, 1137, 931 cm⁻¹; HRMS calcd for C₁₁H₁₁N₂O₂ (M+H⁺): 203.0821, found: 203.0815.

***N*-(2-Propen-1-yl) 2-ethenyl-1*H*-benzimidazole-4-carboxamide (28)**

Reaction of **6** (261 mg, 1.00 mmol), Pd(dba)₂ (34.8 mg, 0.061 mmol), and 1,10-phenanthroline monohydrate (21.7 mg, 0.120 mmol) in DMF, (6 mL) as described for **26** (CO, 120 °C, 47 h), gave after extraction and chromatography (hexanes/EtOAc, 6:4) **28** (50.1 mg, 0.221 mmol, 22%) as a 7:1 mixture of rotamers as a pale yellow solid. Mp 192–195 °C; major rotamer: ¹H NMR (DMSO-*d*₆): δ 13.11 (br s, 1H), 9.91 (br s, 1H), 7.86 (d, *J*=7.8 Hz, 1H), 7.68 (d, *J*=7.8 Hz, 1H), 7.33 (t, *J*=7.8 Hz, 1H), 6.85 (dd, *J*=18.0, 11.4 Hz, 1H), 6.38 (d, *J*=14.4 Hz, 1H), 6.01 (10-line ddt, *J*=17.4, 10.8, 5.4 Hz, 1H), 5.80 (d, *J*=11.4 Hz, 1H), 5.30 (dd, *J*=17.4, 1.2 Hz, 1H), 5.15 (dd, *J*=10.2, 1.2 Hz, 1H), 4.09 (t,

$J=5.4$ Hz, 2H); ^{13}C NMR: δ 164.3, 151.2, 140.8, 135.3, 134.5, 126.1, 122.8, 122.6, 122.5, 122.0, 115.0, 114.8, 41.1; IR (neat): 1637, 1610, 1554, 1429, 1251 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}$: C, 68.70; H, 5.77. Found: C, 68.81; H, 6.01. Minor rotamer: ^1H NMR ($\text{DMSO}-d_6$): δ 12.42 (br s, 1H), 8.81 (br s, 1H), 7.73 (t, $J=8.4$ Hz, 2H), 7.22 (t, $J=7.8$ Hz, 1H), 6.96 (dd, $J=18.0$, 11.4 Hz, 1H), 6.43 (d, $J=17.4$ Hz, 1H), 5.60–5.92 (m, 1H), 5.62 (d, $J=11.4$ Hz, 1H), 5.21 (d, $J=17.4$ Hz, 1H), 5.11 (d, $J=10.2$ Hz, 1H), 3.98 (br s, 2H).

2-(2-Phenyl-1-ethenyl)-1H-benzimidazole (29)

Reaction of **21** (267 mg, 1.05 mmol), $\text{Pd}(\text{dba})_2$ (37.0 mg, 0.064 mmol), and 1,10-phenanthroline monohydrate (22.8 mg, 0.127 mmol) in DMF (6 mL), as described for **26** (CO, 120 $^\circ\text{C}$, 92.75 h), gave after extraction and chromatography (hexanes/EtOAc, 6:4) **29** (126 mg, 0.570 mmol, 54%) as a yellow-brown solid. Mp 202–204 $^\circ\text{C}$ (lit.¹²⁶ 201–202 $^\circ\text{C}$).

2-Phenyl-1H-benzimidazole (30)

Reaction of **8** (114 mg, 0.502 mmol), $\text{Pd}(\text{dba})_2$ (17.7 mg, 0.031 mmol), and 1,10-phenanthroline monohydrate (10.4 mg, 0.058 mmol) and DMF (6 mL), as described for **26** (CO, 120 $^\circ\text{C}$, 139.75 h), gave after extraction and chromatography (hexanes/EtOAc, 9:1) **30** (80.7 mg, 0.416 mmol, 83%) as a white solid. Mp 302–303 $^\circ\text{C}$ (lit.^{76,127} 285–286 $^\circ\text{C}$).

2-(4-Methoxyphenyl)-1*H*-benzimidazole (31)

Reaction of **12** (250 mg, 0.968 mmol), Pd(dba)₂ (33.7 mg, 0.059 mmol), and 1,10-phenanthroline monohydrate (21.3 mg, 0.118 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 65.5 h), gave after extraction and chromatography (hexanes/EtOAc, in order 8:2, 1:1) **31** (121 mg, 0.540 mmol, 56%) as a pale brown solid. Mp 222–225 °C (lit.⁷⁶ 222–225 °C).

5-Methoxy-2-phenyl-1*H*-benzimidazole (33)

Reaction of **13** (128 mg, 0.498 mmol), Pd(dba)₂ (17.7 mg, 0.031 mmol), 1,10-phenanthroline monohydrate (10.7 mg, 0.060 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 193.75 h), gave after extraction and chromatography (hexanes/EtOAc, 7:3) **33** (85.5 mg, 0.378 mmol, 76%) as a faint yellow solid. Mp 142–143 °C (lit.¹²⁸ 143–144 °C).

5-Methoxy-1-methyl-2-phenyl-1*H*-benzimidazole (35)

Reaction of **14** (136 mg, 0.499 mmol), Pd(dba)₂ (17.8 mg, 0.031 mmol), and 1,10-phenanthroline monohydrate (10.9 mg, 0.061 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 67.75 h), gave after extraction and chromatography (hexanes/EtOAc, 9:1 then 1:1) **35** (61.4 mg, 0.258 mmol, 52%) as a white solid¹²⁹. Mp 123–126 °C; ¹H NMR: δ 7.75 (d, *J*=7.8 Hz, 2H), 7.53–7.48 (m, 3H), 7.30 (s, 1H), 7.27 (d, *J*=9.0 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H); ¹³C NMR: δ 156.4, 153.9, 143.6, 131.3, 130.2, 129.6, 129.3, 128.6, 112.8, 110.0, 101.9, 55.8, 31.7; IR (neat): 1467, 1158, 1025,

833, 803, 770 cm^{-1} ; Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$: C, 75.61; H, 5.92. Found: C, 75.49; H, 6.42; HRMS calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$): 239.1184, found: 239.1179.

6-Methoxy-1-methyl-2-phenyl-1*H*-benzimidazole (36)

Reaction of **15** (134 mg, 0.492 mmol), $\text{Pd}(\text{dba})_2$ (17.4 mg, 0.030 mmol), and 1,10-phenanthroline monohydrate (10.6 mg, 0.059 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 115.5 h), gave after extraction and chromatography (hexanes/EtOAc, in order 9:1, 7:3, 3:7) **15** (38.1 mg, 0.140 mmol, 28%) followed by **36** (70.6 mg, 0.296 mmol, 60%) as a white solid. Mp 145–147 °C; ^1H NMR: δ 7.70 (t, $J=7.2$ Hz, 3H), 7.48–7.43 (m, 3H), 6.93 (dd, $J=9.0, 2.4$ Hz, 1H), 6.78 (s, 1H), 3.85 (s, 3H), 3.74 (s, 3H); ^{13}C NMR: δ 156.6, 152.8, 137.3, 130.2, 129.3, 129.1, 128.5, 120.1, 111.5, 93.1, 55.7, 31.5; IR (neat): 1462, 1216, 1084, 1023, 809 cm^{-1} ; Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$: C, 75.61; H, 5.92. Found: C, 75.38; H, 6.43. HRMS calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$): 239.1184, found: 239.1179.

5-Chloro-2-phenyl-1*H*-benzimidazole (37)

Reaction of *N*-benzyl-4-chloro-2-nitrobenzenamine (**23**)¹³⁰ (131 mg, 0.499 mmol), $\text{Pd}(\text{dba})_2$ (17.2 mg, 0.030 mmol), and 1,10-phenanthroline monohydrate (11.0 mg, 0.061 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 46.5 h), gave after extraction and chromatography (hexanes/EtOAc, 9:1 then 1:1) **37** (72.9 mg, 0.319 mmol, 64%) as a pale brown solid. Mp 210–212 °C (lit.⁷⁶ 206–210 °C).

Alternative procedure: Reaction of **10** (131 mg, 0.499 mmol), Pd(dba)₂ (18.0 mg, 0.031 mmol), and 1,10-phenanthroline monohydrate (11.6 mg, 0.064 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 74 h), gave after extraction and chromatography (hexanes/EtOAc, 1:1) **37** (67.4 mg, 0.295 mmol, 59%) as a pale brown solid.

Methyl 2-phenyl-1H-benzimidazole-4-carboxylate (38)

Reaction of **7** (143 mg, 0.503 mmol), Pd(dba)₂ (17.6 mg, 0.031 mmol), and 1,10-phenanthroline monohydrate (11.0 mg, 0.061 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 139.5 h), gave after extraction and chromatography (hexanes/EtOAc, 9:1 then 7:3) **38** (56.7 mg, 0.225 mmol, 45%) as a pale brown solid. Mp 123–126 °C (lit.¹³¹ 125–127 °C).

Alternative procedure: Reaction of **7** (99.3 mg, 0.349 mmol), Pd(dba)₂ (12.6 mg, 0.022 mmol), 1,10-phenanthroline monohydrate (7.8 mg, 0.043 mmol), and 1,3-bis(diphenylphosphino)propane (8.9 mg, 0.022 mmol) in DMF (5 mL), as described for **26** (CO, 120 °C, 138.5 h), gave after extraction and chromatography (hexanes/EtOAc, 9:1 then 7:3) **38** (47.4 mg, 0.188 mmol, 54%) as a pale brown solid.

7-Methoxy-11H-isoindolo[2,1-a]benzimidazole (41)

Reaction of **17** (113 mg, 0.418 mmol), Pd(dba)₂ (15.1 mg, 0.026 mmol), and 1,10-phenanthroline monohydrate (8.9 mg, 0.050 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 76 h), gave after extraction and chromatography (hexanes/EtOAc, 7:3) **41** (34.3 mg, approximately 90% pure by ¹H NMR)¹³². Spectral data from impure **41**: ¹H

NMR: δ 7.96 (d, $J=7.2$ Hz, 1H), 7.49 (d, $J=7.2$ Hz, 1H), 7.46 (t, $J=7.2$ Hz, 1H), 7.41 (dt, $J=7.2$, 1.2 Hz, 1H), 7.26 (d, $J=2.4$ Hz, 1H), 7.24 (dd, $J=7.2$, 1.8 Hz, 1H), 6.87 (dd, $J=6.6$, 1.8 Hz, 1H), 4.91 (s, 2H), 3.84 (s, 3H); ^{13}C NMR: δ 158.7, 156.1, 149.1, 143.3, 129.4, 129.2, 128.6, 127.3, 123.9, 121.7, 112.6, 109.8, 103.2, 55.8, 47.3; HRMS calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$): 237.1028, found: 237.1023.

5,6-Dihydrobenz[4,5]imidazo[2,1-*a*]isoquinoline (43) and benz[4,5]imidazo[2,1-*a*]isoquinoline (44)

Reaction of **19** (127 mg, 0.499 mmol), $\text{Pd}(\text{dba})_2$ (17.3 mg, 0.030 mmol), and 1,10-phenanthroline monohydrate (11.1 mg, 0.062 mmol) in DMF (6 mL), as described for **26** (CO, 120 °C, 67.5 h), gave after extraction and chromatography (hexanes/EtOAc, 9:1) **44** (6.6 mg, 0.030 mmol, 6%) as a pale yellow solid followed by **43** (48.9 mg, 0.222 mmol, 44%) as a pale brown solid¹²⁹. Data for **44**: mp 107–108 °C (lit.^{133,134} 129–130 °C). Data for **43**: mp 148–149 °C; ^1H NMR: δ 8.30 (dd, $J=7.8$, 1.8 Hz, 1H), 7.84–7.81 (m, 1H), 7.42–7.34 (m, 3H), 7.31–7.25 (m, 3H), 4.32 (t, $J=7.2$ Hz, 2H), 3.27 (t, $J=7.2$ Hz, 2H); ^{13}C NMR: δ 149.1, 144.0, 134.7, 134.2, 130.1, 128.0, 127.7, 126.7, 125.6, 122.6, 122.4, 119.8, 109.0, 40.4, 28.2; IR (neat): 1482, 1448, 1326, 775, 734 cm^{-1} ; Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2$: C, 81.79; H, 5.49. Found: C, 81.49; H, 5.92.

7H-Benzimidazo[2,1-*a*]benz[*de*]isoquinoline (45)

Reaction of **20** (102 mg, 0.351 mmol), $\text{Pd}(\text{dba})_2$ (11.3 mg, 0.020 mmol), and 1,10-phenanthroline monohydrate (8.0 mg, 0.044 mmol) in DMF (6 mL), as described above for **26** (CO, 120 °C, 112 h), gave after extraction and chromatography (hexanes/EtOAc,

7:3 then 1:1) **45** (54.9 mg, 0.214 mmol, 61%) as a yellow solid. Mp 210–212 °C (lit.¹³⁵ 212–213 °C).

2-Bromo-3-nitrophenol¹⁰⁰ (47)

2-Amino-3-nitrotoluene (11.9 g, 77.2 mmol) was dissolved in 60 ml H₂O and 30 ml of 1,4-dioxane and heated to reflux. Hydrobromic acid (34 ml, 48%) was added dropwise over a 20 min. period, after which the mixture was heated at reflux an additional 15 min. The reaction was cooled to 0 °C and sodium nitrite (5.34 g, 77.4 mmol) in 40 ml of H₂O was added dropwise over a 30 min. period followed by stirring 15 min. at 0 °C. The mixture was added dropwise to a stirring solution of copper(I) bromide (11.2 g, 78.1 mmol) in 60 ml H₂O and 34 ml HBr (48%) at 0 °C. The reaction was stirred for 15 min. at 0 °C, warmed to 60 °C, stirred 15 min., then cooled to room temperature, and stirred overnight. The reaction mixture was transferred to a separatory funnel and extracted with diethyl ether (4x300 ml). The combined organic phases were dried (MgSO₄), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, in order 98:2, 95:5, 9:1, 8:2) gave **47** (5.45 g, 25.0 mmol, 32%) as a yellow solid.

(R)-1-Methyl-2,5-dioxopyrrolidin-yl acetate¹⁰² (49)

A mixture of D-malic acid (5.31 g, 39.6 mmol) and AcCl (13 ml) was heated at 45 °C for 1 h. then another 15 ml of AcCl was added and heated for another 4 h. The solvent was removed in vacuo, the residue was dissolved in CH₂Cl₂ (90 ml) and cooled to -20 °C. To this was added a solution of methanamine (1.5 g, 48.3) in CH₂Cl₂ (60 ml) at -78 °C. The

resulting mixture was allowed to warm to room temperature and stirred for 5.5 h. The solvents were removed on a rotary evaporator at water aspirator pressure and AcCl (50 ml) was added. The resulting mixture stirred at 50 °C for 11 h. The AcCl was removed and purification by chromatography (hexanes/EtOAc, 1:1) gave **49** (6.55 g, 38.3 mmol, 97%) as a clear liquid.

(R)-3-Hydroxy-1-methylpyrrolidine-2,5-dione¹⁰² (50)

To a solution of **49** (6.55 g, 38.3 mmol) in absolute ethanol (50 ml) was bubbled dry HCl gas at 50 °C for 1 h. The solvent was removed to dryness and the residue was purified by chromatography (hexanes/EtOAc, 1:3) giving **50** (4.45 g, 34.5, 90%) as a white solid.

(R)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-methylpyrrolidine-2,5-dione¹⁰² (51)

To a stirred solution of **50** (4.28 g, 33.2 mmol) in DMF (10 ml) was added *tert*-butylchlorodimethylsilane (6.03 g, 40.0 mmol) and imidazole (2.38 g, 35.0 mmol). The mixture was stirred at room temperature for 23.75 h. then H₂O (30 ml) was added. The mixture was extracted with EtOAc (4x15 ml), dried (MgSO₄), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure giving **51** (7.68 g, 31.6 mmol, 95%) as a white solid.

(R)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-1-methylpyrrolidin-2-one¹⁰² (52)

To a solution of **51** (5.65 g, 23.2 mmol) in MeOH (20 ml) was added sodium borohydride (2.63 g, 69.5 mmol) in one portion at -10 °C. After stirring for 10 min., saturated NH₄Cl (20 ml) was added and the solution was extracted with EtOAc (4x10 ml). The combined

organic phases were dried (MgSO_4), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure giving **52** (4.94 g, 20.1 mmol, 87%) as a white solid.

(R)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-methoxy-1-methylpyrrolidin-2-one¹⁰² (53**)**

To a suspension of NaH (80%, 651 mg, 27.1 mmol) in THF (8 ml) at 0 °C was dropwise added a solution of **52** (5.29 g, 21.6 mmol) in THF (8 ml). After stirring 0.5 h., methyl iodide (2.15 ml, 34.5 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed on a rotary evaporator at water aspirator pressure and purification by chromatography (hexanes/EtOAc, 2:1) gave **53** (4.43 g, 17.1 mmol, 79%) as a yellow liquid.

(4R, 5S)-5-Allyl-4-[(*tert*-butyldimethylsilyl)oxy]-1-methylpyrrolidin-2-one (54**) and**

(4R, 5R)-5-allyl-4-[(*tert*-butyldimethylsilyl)oxy]-1-methylpyrrolidin-2-one¹⁰² (55**)**

A solution of **53** (1.01 g, 3.89 mmol) and allyltrimethylsilane (2.45 ml, 15.4 mmol) in CH_2Cl_2 (20 ml) at -78 °C was stirred for 15 min. TiCl_4 (0.85 ml, 7.7 mmol) in CH_2Cl_2 (10 ml) was slowly added and after 5 min. the cooling bath was removed and the mixture was stirred for 2 h. then quenched by pouring into a stirred slurry of $\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O}$ (13g) in CH_2Cl_2 (15 ml). After 15 min., MgSO_4 was added and the mixture was 0.5 h. The filtered organic phase was removed on a rotary evaporator at water aspirator pressure and purification by chromatography (hexanes/EtOAc, 1:1) gave **54** (156 mg, 0.58 mmol, 15%) followed by **55** (748 mg, 2.78 mmol, 71%).

(4R, 5S)-5-Allyl-4-hydroxy-1-methylpyrrolidin-2-one¹⁰² (56)

To a solution of **54** (134 mg, 0.50 mmol) was added dropwise a solution of tetrabutylammonium fluoride (1 M in THF, 0.60 ml). After stirring for 12.5 h., the solvents were removed on a rotary evaporator at water aspirator pressure and purification by chromatography (EtOAc, EtOAc/ MeOH, 95:5, MeOH) gave **56** (100 mg, 0.64 mmol, quant.)

(4R, 5R)-5-Allyl-4-hydroxy-1-methylpyrrolidin-2-one¹⁰² (57)

To a solution of **55** (353 mg, 1.31 mmol) was added dropwise a solution of tetrabutylammonium fluoride (1 M in THF, 1.57 ml). After stirring for 7 h., the solvents were removed on a rotary evaporator at water aspirator pressure and purification by chromatography (EtOAc, EtOAc/ MeOH, 9:1) gave **57** (197 mg, 1.27 mmol, 97%).

(4R, 5R)-5-Allyl-4-methanesulfoxy-2-pyrrolidone¹³⁶ (58)

To a solution of **57** (155 mg, 1.0 mmol) in 10 ml CH₂Cl₂ were added at 0 °C methanesulfonyl chloride (85 µl, 1.1 mmol) and triethylamine (185 µl, 1.3 mmol). The solution was stirred at 0 °C for 1 h. and was then allowed to warm to rt. After stirring overnight, water (10 ml) was added and the mixture was extracted with CH₂Cl₂ (4x10 ml). The crude solid was redissolved in 10 ml CH₂Cl₂ and methanesulfonyl chloride (85 µl, 1.1 mmol) and triethylamine (185 µl, 1.3 mmol) were added at 0 °C. The solution was stirred at 0 °C for 1 h. and was then allowed to warm to rt. After stirring overnight, water (10 ml) was added and the mixture was extracted with CH₂Cl₂ (4x10 ml). The combined organic phases were dried (MgSO₄), filtered, and the solvents were removed

on a rotary evaporator at water aspirator pressure. Purification by chromatography (EtOAc then EtOAc/MeOH, in order 95:5, 8:2, then MeOH) gave **58** (159 mg, 0.68 mmol, 68%).

(R)-Diethyl 2-(tetrahydro-2H-pyran-2-yloxy)succinate¹⁰³ (59)

Dihydropyran (12.3 ml, 134.8 mmol) was added to a solution of D-malic acid diethyl ester (8.3 g, 43.6 mmol) and pyridinium *p*-toluenesulfonate (1.2 g, 4.8 mmol) in CH₂Cl₂ (220 ml). After stirring (rt) for 4 h., the reaction mixture was diluted with CH₂Cl₂ (100 ml), washed with half-saturated brine (2x100 ml), dried (MgSO₄), and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc 7:3) gave **59** (11.9 g, 43.4 mmol, quant.).

(R)-2-(Tetrahydro-2H-pyran-2-yloxy)butane-1,4-diol¹⁰³ (60)

A suspension of lithium aluminum hydride (1.3 g, 34.3 mmol) in 30 ml of THF was warmed at 55 °C for 1 h. Compound **59** (4.7 g, 17.1 mmol) in 15 ml THF was added dropwise and the resulting mixture was stirred at 55 °C for 24 h. before cautious, sequential addition of water (2 ml), 10% NaOH (3 ml), and water (2 ml). After filtration (diethyl ether wash), the filtrate was dried (MgSO₄) and the solvents were removed in vacuo, affording **60** (2.7 g, 14.2 mmol, 83%).

(R)-2-(Tetrahydro-2H-pyran-2-yloxy)butane-1,4-dimethanesulfonate¹⁰³ (61)

A solution of **60** (2.7 g, 14.2 mmol) in CH₂Cl₂ (55 ml) cooled to -15 °C was treated sequentially with triethylamine (7.25 ml, 52.0 mmol) and methanesulfonyl chloride (3.7

ml, 47.8 mmol). After 45 min. at -15 °C the reaction mixture was poured over crushed ice and stirred for 5 min. before the organic layer was washed 5% HCl (50 ml), saturated NaHCO₃ (50 ml), and H₂O (50 ml), dried (MgSO₄), and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (diethyl ether) gave **61** (1.96 g, 5.7 mmol, 40%). Starting material (**60**, 0.97 g) was also recovered.

(R)-1,2,4-Butanetriol 1,4-bis(methanesulfonate)¹⁰³ (62)

A solution of **61** (3.8 g, 11.0 mmol) in absolute ethanol (20 ml) containing 0.3 ml of methanesulfonic acid was warmed at 50 °C for 2 h. The cooled mixture was stirred at 0 °C for 16 h. and filtered (cold EtOH wash), affording **62** (2.3 g, 8.3 mmol, 75%).

(2R, 3R)-2-Allyl-1-methylpyrrolidin-3-ol¹³⁷ (63)

To a solution of **57** (284 mg, 1.8 mmol) in THF (8 ml) was added LiAlH₄ (514 mg, 13.5 mmol). The suspension was stirred at 65 °C for 19 h., then cooled to room temperature and H₂O (2 ml), 3M aqueous solution of NaOH (2 ml), and H₂O (2 ml) were added successively. The mixture was extracted with EtOAc (3x25 ml), dried (MgSO₄), and the solvents were removed on a rotary evaporator at water aspirator pressure to give crude **63** (217 mg, 1.54 mmol, 86%). ¹H NMR δ 5.90 (ddt, *J*=17.4, 9.6, 6.6 Hz, 1H), 5.16 (dq, *J*=17.4, 1.8 Hz, 1H), 5.06 (dpent, *J*=10.2, 1.2 Hz, 1H), 4.13 (ddd, *J*=7.2, 4.8, 2.4 Hz, 1H), 3.73 (br s, 1H), 3.15 (dt, *J*=9.0, 3.0 Hz, 1H), 2.34-2.40 (m, 1H), 2.30-2.33 (m, 1H), 2.28 (s, 3H), 2.18 (dddd, *J*=13.8, 9.6, 7.2, 3.0 Hz, 1H), 2.02-2.07 (m, 1H), 1.93 (dt, *J*=9.6, 4.6 Hz, 1H), 1.69 (ddt, *J*=13.8, 9.0, 1.8 Hz, 1H); ¹³C δ 135.7 (-), 116.5 (+), 72.1 (-), 70.9 (-),

54.6 (+), 40.1 (-), 33.0 (+), 31.7 (+); IR (neat) 3366, 2944, 2787, 1455, 1128 cm^{-1} ; $[\alpha]^{25}_{\text{D}}$ = -95.4 ± 1.2 ($c = 1.0$, CHCl_3); HRMS (ESI) calcd for $\text{C}_8\text{H}_{15}\text{NO}$ ($\text{M}+\text{H}^+$) 142.12326, found 142.12264.

(2S, 4R)-Methyl 4-hydroxypyrrolidine-2-carboxylate¹⁰⁴ (64)

To a stirred suspension of *trans*-4-hydroxy-L-proline (99.7 g, 0.76 mol) in methanol (400 ml) at 0 °C was added thionyl chloride (60 ml, 0.82 mmol). The reaction mixture was stirred at 0 °C for 1 h. then refluxed for 38.75 h. The reaction mixture was allowed to cool and then precipitated with diethyl ether. The precipitate was collected by filtration and washed with diethyl ether to give **64** (122.5 g, 0.68 mol, 89%) as a white solid.

(2S, 4R)-1-*tert*-Butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate¹⁰⁵ (65)

To a suspension of **64** (38.1 g, 0.21 mol) and CH_2Cl_2 (300 ml) was added triethylamine (88 ml, 0.63 mol), and the system was immersed in an ice-salt bath. To the mixture was added di-*tert*-butyl dicarbonate (50.1 g, 0.23 mol), and the reaction mixture was stirred for 20.5 h. during which time the ice bath expired. The reaction mixture was washed with 1 M H_3PO_4 (2x150 ml) and saturated NaHCO_3 (2x150ml), dried (MgSO_4), and the solvents were removed on a rotary evaporator at water aspirator pressure giving **65** (50.7 g, 0.207 mol, 98%).

(2S, 4R)-1-(*tert*-Butoxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-carbomethoxypyrrolidine¹⁰⁵ (66)

To a stirring solution of **65** (50.0 g, 0.20 mol) and DMF (80 ml) were added imidazole (28.9 g, 0.42 mol) and *tert*-butylchlorodimethylsilane (34.0 g, 0.23 mol). The reaction mixture was stirred at room temperature for 1.5 h., diluted with diethyl ether (150 ml), and washed with H₂O (150 ml), 1 M H₃PO₄ (150 ml), and saturated NaHCO₃ (150 ml). The ether solution was dried (MgSO₄) and the solvents were removed on a rotary evaporator at water aspirator pressure giving **66** (71.8 g, 0.20 mol, quant.).

(2S, 4R)-1-(*tert*-Butyoxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-(hydroxymethyl)pyrrolidine¹⁰⁶ (67)

Lithium chloride (128 mg, 3.02 mmol) and NaBH₄ (118 mg, 3.12 mmol) were added to a solution of **66** (307 mg, 0.85 mmol) in THF (0.5 ml) and MeOH (0.5 ml) at room temperature. After stirring for 22 h., the mixture was concentrated, EtOAc (1 ml) was added to the residue and washed with 10% HCl (5 ml). The aqueous layer was extracted with EtOAc (2x1 ml) and the combined organic phases were washed with NaHCO₃ (5 ml) and brine (5 ml). The organic layer was dried (MgSO₄), and the solvents were removed on a rotary evaporator at water aspirator pressure giving **67** (273 mg, 0.82 mmol, 97%).

(2S, 4R)-(tert-Butoxycarbonyl)-4-[(tert-butyldimethylsilyl)oxy]-2-methylpyrrolidine¹⁰⁵ (69)

To a solution of **67** (2.0 g, 6.0 mmol) and CH₂Cl₂ (5 ml) was added triethylamine (1.7 ml, 12.2 mmol). The system was cooled in an ice-salt bath and methanesulfonyl chloride was added via an addition funnel. The reaction mixture was stirred for 16.5 h., during which the ice bath expired. The reaction mixture was partitioned between EtOAc (15 ml) and H₂O (15 ml). The organic phase was washed 1 M H₃PO₄ (30 ml), and saturated NaHCO₃ (30 ml), dried (MgSO₄), and the solvents were removed on a rotary evaporator at water aspirator pressure. The crude product was dissolved in THF (15 ml) and cooled in an ice bath and lithium triethylborohydride in THF (1.0 M solution, 24 ml) was added. The cold bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc (15 ml) and washed with H₂O (30 ml), 1 M H₃PO₄ (30 ml), saturated NaHCO₃ (30 ml), and brine (30 ml). The organic phase was dried (MgSO₄) and the solvents were removed on a rotary evaporator at water aspirator pressure to give **69** (2.0 g, 6.3 mmol, quant.).

(3R, 5S)-(tert-Butoxycarbonyl)-3-[(tert-butyldimethylsilyl)oxy]-5-methyl-2-pyrrolidinone¹⁰⁷ (70)

A solution of **69** (219 mg, 0.69 mmol) in EtOAc (3 ml) was added to a mixture of RuO₂·xH₂O (12.5 mg, 0.09 mmol) and 10% NaIO₄ (4 ml). The solution was stirred vigorously for 3 h. at room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (2x3 ml). The combined extracts was treated with 2-propanol (2 drops) and the precipitated solid was filtered off. The filtrate was washed with brine

(3x1 ml), dried (MgSO₄), and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 9:1) gave **70** (112 mg, 0.34 mmol, 49%).

(3R, 5S)-(tert-Butoxycarbonyl)-3-[(tert-butyldimethylsilyl)oxy]-5-methyl-2-methoxypyrrolidine¹⁰⁷ (71)

Lithium triethylborohydride in THF (1.0 M solution, 1.52 ml) was added to a solution of **70** (0.42 mg, 1.27 mmol) in THF (5 ml) at -78 °C. After 30 min., the reaction was quenched with saturated aqueous NaHCO₃ (10 ml) and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (2x10 ml), dried (MgSO₄) and the solvents were removed on a rotary evaporator at water aspirator pressure. The crude product was dissolved in methanol (5 ml), pyridinium *p*-toluenesulfonate (27.8 mg, 0.11 mmol) was added, and the reaction mixture was stirred for 15.5 h. at room temperature. The mixture was diluted with EtOAc (10 ml) and the organic layer was washed successively with 10% citric acid (10 ml), saturated NaHCO₃ (10 ml), and brine (10 ml). The organic phase was dried (MgSO₄) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 6:1) gave **71** (376 mg, 1.09 mmol, 86%) as a mixture of isomers.

(3R, 5R)-2-Allyl-3-[(tert-butyldimethylsilyl)oxy]-methylpyrrolidine¹⁰² (72)

A solution of **71** (376 mg, 1.09 mmol) and allyltrimethylsilane (0.69 ml, 4.34 mmol) in CH₂Cl₂ (15 ml) at -78 °C was stirred for 15 min. TiCl₄ (0.24 ml, 2.2 mmol) in CH₂Cl₂ (5 ml) was slowly added and after 5 min. the cooling bath was removed and the mixture was

stirred for 2.5 h. then quenched by pouring into a stirred slurry of $\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O}$ (13g) in CH_2Cl_2 (15 ml). After 15 min., MgSO_4 was added and the mixture was 0.5 h. The filtered organic phase was removed on a rotary evaporator at water aspirator pressure giving the crude mixture of isomers **72** (225 mg, 0.88 mmol, 81%).

Spectral data for major rotamer of **72**

^1H NMR δ 5.82 (ddt, $J=16.8, 10.2, 6.6$ Hz, 1H), 5.09 (d, $J=17.4$ Hz, 1H), 5.02 (d, $J=10.2$ Hz, 1H), 4.20 (s, 1H), 3.58 (dt, $J=14.4, 7.2$ Hz, 1H), 3.13 (dt, $J=7.1, 3.4$ Hz, 1H), 2.33 (pent, $J=6.6$ Hz, 1H), 2.26 (pent, $J=7.2$ Hz, 1H), 1.92 (dd, $J=12.6, 6.6$ Hz, 1H), 1.49 (ddd, $J=13.2, 9.0, 4.8$ Hz, 1H), 1.18 (d, $J=6.6$ Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C δ 136.0 (-), 116.5 (+), 73.9 (-), 62.9 (-), 51.3 (-), 43.8 (+), 33.7 (+), 25.8 (-), 22.1 (-), 18.0 (+), -4.4 (-), -5.0 (-).

Partial spectral data for minor rotamer of **72**

^1H NMR δ 3.87 (pent, $J=4.2$ Hz, 1H), 3.37 (ddd, $J=15.0, 12.6, 6.0$ Hz, 2H), 2.95 (dt, $J=7.6, 5.3$ Hz, 1H), 2.14 (pent, $J=7.4$ Hz, 1H), 1.75 (ddd, $J=13.2, 6.6, 3.6$ Hz, 1H), 1.15 (d, $J=6.6$ Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C δ 135.7 (-), 116.9 (+), 67.0 (-), 52.3 (-), 43.5 (+), 38.3 (+), 21.3 (-), 18.0 (+), -4.5 (-), -4.7 (-).

(3R, 5R)-2-Allyl-1-(tert-butoxycarbonyl)-3-[(tert-butyldimethylsilyl)oxy]-5-methylpyrrolidine¹⁰⁵ (73)

To a suspension of **72** (497 mg, 1.95 mmol) and CH_2Cl_2 (5 ml) was added triethylamine (0.81 ml, 5.81 mmol), and the system was immersed in an ice-salt bath. To the mixture

was added di-*tert*-butyl dicarbonate (479 mg, 2.19 mmol), and the reaction mixture was stirred for 22 h. during which time the ice bath expired. The reaction mixture was washed with 1 M H₃PO₄ (2x5 ml) and saturated NaHCO₃ (2x5ml), dried (MgSO₄), and the solvents were removed on a rotary evaporator at water aspirator pressure giving **73** (625 mg, 1.76 mmol, 90%).

Spectral data for major rotamer of **73**

¹H NMR δ 5.86 (pent, *J*=8.0 Hz, 1H), 5.02 (d, *J*=18.6 Hz, 1H), 4.95 (d, *J*=9.6 Hz, 1H), 4.43-4.45 (m, 1H), 3.76-4.03 (m, 2H), 2.49-2.61 (m, 1H), 2.24-2.26 (m, 1H), 1.93-2.08 (m, 1H), 1.65-1.69 (m, 1H), 1.47 (s, 9H), 1.19 (d, *J*=6.0 Hz, 3H), 0.90 (s, 9H), 0.67 (s, 6H).

Partial spectral data for minor rotamer of **73**

¹H NMR δ 5.78 (pent, *J*=8.6 Hz, 1H), 1.45 (s, 9H), 1.15 (d, *J*=6.0 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

Spectral data for mixture of **73**

¹³C δ 154.0, 146.7, 136.7 (-), 136.5 (-), 135.1 (-), 116.9 (+), 116.3 (+), 85.1, 79.2, 78.9, 78.9, 70.8 (-), 70.2 (-), 67.2, 60.4 (-), 60.1 (-), 52.4 (-), 51.7 (-), 50.6 (-), 50.4 (-), 40.0 (+), 39.0 (+), 33.7 (+), 32.3 (+), 28.6 (-), 28.5, 27.4 (-), 25.8 (-), 25.7 (-), 22.3 (-), 21.2 (-), 18.1, 17.9, -4.9 (-); IR (neat) 2957, 2930, 1693, 1383, 1364, 1067 cm⁻¹.

(2R, 3R, 5R)-2-Allyl-1-(tert-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine (74)
and (2S, 3R, 5R)-2-allyl-1-(tert-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine¹⁰⁸
(75)

Tetrabutylammonium fluoride (1 M in THF, 9.5 ml) was added to a solution of **72** (1.58 g, 4.44 mmol) in THF (20 ml) at 0 °C. The reaction mixture was stirred for 45.5 h., during which the ice bath expired. The reaction mixture was poured into H₂O (100 ml), extracted with EtOAc (4x100ml), dried (MgSO₄), and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 7:3) gave **74** (795 mg, 3.29 mmol, 74%) followed by **75** (153 mg, 0.63, 14%).

Spectral data for rotameric mixture 74

¹H NMR δ 5.88-5.95 (m, 1H), 5.10 (d, *J*=17.4 Hz, 1H), 5.02 (d, *J*=10.2 Hz, 1H), 4.54 (s, 1H), 3.89 (br s, 2H), 2.91 (br s, 1H), 2.55 (s, 1H), 2.37 (s, 1H), 2.04-2.08 (m, 1H), 1.78-1.82 (m, 1H), 1.47 (s, 9H), 1.19 (br s, 3H); ¹³C δ 154.0 (+), 136.3 (-), 116.5 (+), 79.3 (+), 70.4 (-), 70.1 (-), 59.5 (-), 50.5 (-), 39.2 (+), 38.2 (+), 33.6 (+), 32.3 (+), 28.4 (-), 21.8 (-), 20.7 (-); IR (neat) 3436, 1663, 1366, 1172, 1063 cm⁻¹; [α]_D²⁵ = -39.6 (*c* = 1.02, CHCl₃); HRMS (ESI) calcd for C₁₃H₂₃NO₃ (M+H⁺) 242.17569, found 242.17507.

Partial spectral data for rotameric mixture 74 at (-20 °C)

¹H NMR δ 5.92 (ddt, *J*=24.6, 9.6, 7.2 Hz, 1H), 5.11 (dd, *J*=17.4, 7.8 Hz, 1H), 5.03 (d, *J*=10.2 Hz, 1H), 4.54 (dt, *J*=10.2, 6.6 Hz, 1H), 3.97 (dt, *J*=7.2, 3.0 Hz, 0.5H), 3.82-3.91 (m, 1.5H), 3.69 (br s, 0.5H), 3.62 (br s, 0.5H), 2.57 (pent, *J*=7.2, 0.5 Hz, 0.5H), 2.51

(pent, $J=7.2$, 0.5 Hz, 0.5H), 2.42-2.45 (m, 0.5H), 2.30-2.33 (m, 0.5H), 2.07 (ddt, $J=15.6$, 11.4, 9.0 Hz, 1H), 1.82 (dt, $J=12.6$, 6.0 Hz, 1H), 1.47 (d, $J=6.6$ Hz, 9H), 1.46 (s, 9H), 1.18 (dd, $J=16.8$, 6.0 Hz, 3H); ^{13}C δ 154.0, 153.9, 136.3, 136.1, 116.7, 116.6, 79.4, 79.2, 70.0, 69.6, 59.4, 59.1, 50.5, 50.1, 38.5, 37.6, 33.6, 32.2, 28.3, 21.7, 20.6

Partial spectral data for rotameric mixture **74** at (+60 °C)

^1H NMR δ 5.91 (ddt, $J=24.6$, 10.2, 7.2 Hz, 1H), 5.11 (dq, $J=17.4$, 1.8 Hz, 1H), 5.02 (d with further fine splitting, $J=10.2$ Hz, 1H), 4.51 (dt, $J=16.8$, 7.2 Hz, 1H), 3.93 (br s, 1H), 3.87 (pent, $J=6.6$ Hz, 1H), 2.54 (pent, $J=7.2$ Hz, 1 Hz, 0.5H), 2.45 (br s, 1H), 2.21 (br s, 1H), 2.04 (ddt, $J=12.0$, 10.8, 9.0 Hz, 1H), 1.79 (ddd, $J=12.0$, 6.6, 1.8 Hz, 1H), 1.47 (s, 9H), 1.19 (d, $J=6.0$ Hz, 3H); ^{13}C δ 154.1, 136.5, 129.9, 116.5, 79.3, 70.6, 59.7, 50.7, 39.2, 33.0, 28.5, 28.4, 21.3

Spectral data for rotameric mixture **75**

^1H NMR δ 5.77-5.84 (m, 1H), 5.06-5.09 (m, 2H), 4.11 (s, 1H), 4.00 (br s, 1H), 3.78 (s, 1H), 2.42 (br s, 1H), 2.06-2.09 (m, 3H), 1.74-1.79 (m, 1H), 1.47 (s, 9H), 1.27 (br s, 3H); ^{13}C δ 155.1 (+), 134.8 (-), 117.2 (+), 79.3 (+), 73.2 (-), 66.8 (-), 52.1 (-), 40.6 (+), 38.6 (+), 28.5 (-), 21.9 (-); IR (neat) 3405, 1664, 1390, 1169, 1096 cm^{-1} ; $[\alpha]^{25}_{\text{D}} = -8.1 \pm 0.7$ ($c = 5.75$, MeOH); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{23}\text{NO}_3$ ($\text{M}+\text{H}^+$) 242.17569, found 242.17507.

Partial spectral data for rotameric mixture **75** at (-55 °C)

^1H NMR δ 5.77-5.84 (m, 1H), 5.07-5.10 (m, 2H), 4.10 (br s, 1H), 4.00 (bs, 1H), 3.94-4.01 (m, 2H), 3.78-3.83 (m, 1H), 2.37-3.39 (m, 0.5H), 2.28-2.31 (m, 0.5H), 2.07-2.16 (m, 1.5H), 2.00 (dt, $J=13.8, 9.0$ Hz, 0.5H), 1.46 (s, 9H), 1.28 (dd, $J=15.6, 6.0$ Hz, 3H); ^{13}C δ 115.2, 115.0, 134.7, 117.3, 117.2, 79.4, 72.8, 71.9, 66.3, 66.2, 51.9, 51.9, 39.8, 39.6, 38.4, 38.3, 28.2, 22.4, 21.6.

Partial spectral data for rotameric mixture **75** at (+60 °C)

^1H NMR δ 5.81 (ddt, $J=16.8, 10.2, 6.9$ Hz, 1H), 5.05-5.09 (m, 2H), 4.11 (t, $J=1.2$ Hz, 1H), 4.00 (q, $J=6.6$ Hz, 1H), 3.76 (br s, 1H), 2.42-2.44 (m, 1H), 2.09 (dt with further fine splitting, $J=15.0, 7.8$ Hz, 1H), 2.05 (dddd, $J=13.7, 7.4, 2.7, 1.3$ Hz, 1H), 1.76 (ddd, $J=13.8, 8.4, 4.8$ Hz, 1H), 1.73 (br s, 1H), 1.47 (s, 9H), 1.26 (d, $J=6.6$ Hz, 3H); ^{13}C δ 155.1, 134.9, 117.1, 79.3, 73.7, 67.0, 52.3, 40.8, 38.6, 28.6, 22.1.

(S)-2-(2-Bromo-3-nitrophenoxy)butane-1,4-dimethanesulfonate¹¹⁴ (79)

To a solution of **62** (581 mg, 2.09 mmol) in THF (5 ml) were added triphenylphosphine (827 mg, 3.15 mmol) and **47** (685 mg, 3.14 mmol). The solution was cooled to 0 °C and DIAD (0.63 ml, 3.18 mmol) was added dropwise. The cold bath was removed and the mixture was stirred 2 h, concentrated, diluted with CH_2Cl_2 (10 ml), washed with 1 M NaOH (10 ml) and 1 M HCl (10 ml), and dried (MgSO_4). Purification by chromatography (hexanes/EtOAc, 1:9) gave **79** (936 mg, 2.02 mmol, 97%). ^1H NMR δ 7.45 (dt, $J=7.8, 1.8$ Hz, 1H), 7.39 (d, $J=7.8$ Hz, 1H), 7.28 (d, $J=8.4$ Hz, 1H), 4.89 (pent, $J=5.4$ Hz, 1H), 4.41-4.47 (m, 4H), 3.03 (d, $J=1.8$ Hz, 3H), 2.99 (d, $J=1.8$ Hz, 3H), 2.29

(q, $J=5.4$ Hz, 2H); ^{13}C δ 155.2, 151.8, 129.0, 118.1, 118.0, 105.8, 74.6, 69.0, 65.3, 37.5, 37.2, 30.8; IR (neat) 1532, 1346, 1167, 961, 794 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -24.3$ ($c = 1.0$, CHCl_3); Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{BrNO}_9\text{S}_2$: C, 31.18; H, 3.49. Found: C, 31.51; H, 3.66.

(S)-4-(2-Bromo-3-nitrophenoxy)-3,4-dihydro-2H-pyrrole N-oxide¹¹⁴ (80)

A suspension of **79** (216 mg, 0.47 mmol) and hydroxylamine hydrochloride (149 mg, 2.14 mmol) in triethylamine (5 ml) was heated at reflux for 2.5 h. The solvents were removed and the resulting crude material was washed with diethyl ether (4x5 ml). The ethereal extracts were concentrated, dissolved in CH_2Cl_2 (5 ml), and cooled to 0 °C. MnO_2 (61.3 mg, 0.71 mmol) was added, the cold bath was removed, and the solution was stirred at room temperature for 2 h. The solution was filtered through a short pad of Celite and MgSO_4 . The solvents were removed on a rotary evaporator at water aspirator pressure and purification by chromatography (hexanes/EtOAc, 1:1) gave **80** (35 mg, 0.12 mmol, 25%). ^1H NMR δ 7.43 (t, $J=8.4$ Hz, 1H), 7.40 (d, $J=7.8$ Hz, 1H), 7.11 (s, 1H), 7.09 (d, $J=7.8$ Hz, 1H), 5.53 (d, $J=7.8$ Hz, 1H), 4.35 (pent, $J=8.4$ Hz, 1H), 4.01 (ddd, $J=13.8, 9.0, 4.2$ Hz, 1H), 2.81 (ddt, $J=14.4, 8.4, 7.2$ Hz, 1H), 2.49-2.54 (m, 1H); ^{13}C δ 155.0 (+), 152.2 (+), 130.7 (-), 128.8 (-), 118.1 (-), 117.5 (-), 106.5 (+), 79.6 (-), 61.4 (+), 27.4 (+); IR (neat) 3232, 1582, 1531, 1455, 1107 cm^{-1} .

(2R, 3S)-2-Allyl-3-(2-bromo-3-nitrophenoxy)-1-methylpyrrolidine¹¹⁴ (82)

To a solution of **63** (265 mg, 1.88 mmol) in THF (5 ml) were added triphenylphosphine (739 mg, 2.82 mmol) and **47** (614 mg, 2.82 mmol). The solution was cooled to 0 °C and DIAD (0.56 ml, 2.82 mmol) was added dropwise. The cold bath was removed and the

mixture was stirred 10 h., concentrated, diluted with CH₂Cl₂ (25 ml), washed with 1 M NaOH (25 ml) and 1 M HCl (25 ml), and dried (MgSO₄). Purification by chromatography (MeOH) gave **82** (187 mg, 0.55 mmol, 29%).

(2R, 3S)-2-Allyl-3-(2-iodo-3-nitrophenoxy)-1-methylpyrrolidine¹¹⁴ (83)

To a solution of **63** (92.7 mg, 0.66 mmol) in THF (2 ml) were added triphenylphosphine (284 mg, 1.08 mmol) and **48** (282 mg, 1.06 mmol). The solution was cooled to 0 °C and DIAD (0.21 ml, 1.06 mmol) was added dropwise. The cold bath was removed and the mixture was stirred 2 h, concentrated, diluted with CH₂Cl₂ (10 ml), washed with 1 M NaOH (10 ml) and 1 M HCl (10 ml), and dried (MgSO₄). Purification by chromatography (hexanes/EtOAc, 3:7 then 1:9) gave **83** (129 mg, 0.33 mmol, 50%). ¹H NMR δ 7.38 (t, *J*=8.4 Hz, 1H), 7.27 (dd, *J*=7.8 Hz, 1.2, 1H), 6.88 (dd, *J*=8.4 Hz, 1.2, 1H), 5.87 (ddt, *J*=17.0, 10.0, 7.0 Hz, 1H), 5.11 (dq, *J*=16.8 Hz, 1.2, 1H), 5.05 (d with other fine splitting, *J*=10.8 Hz, 1H), 4.56 (ddd, *J*=6.6, 4.2, 1.8 Hz, 1H), 3.09 (t, *J*=8.4 Hz, 1H), 2.67-2.70 (m, 1H), 2.58-2.62 (m, 1H), 2.46-2.51 (m, 1H), 2.45 (s, 3H), 2.28 (dt, *J*=14.4, 7.2 Hz, 1H), 2.18 (ddt, *J*=13.8, 11.4, 7.2 Hz, 1H), 1.80 (dd, *J*=13.8, 6.6 Hz, 1H); ¹³C δ 158.0 (+), 155.8 (+), 134.5 (-), 129.8 (-), 117.3 (+), 116.7 (-), 115.5 (-), 83.7 (-), 81.2 (+), 70.8 (-), 55.0 (+), 40.7 (-), 36.2 (+), 30.2 (+); HRMS (ESI) calcd for C₁₄H₁₇IN₂O₃ (M+H⁺) 389.03629, found 389.03566.

(2R, 3S, 5R)-2-Allyl-1-(tert-butoxycarbonyl)-3-(2-bromo-3-nitrophenoxy-5-methylpyrrolidine¹¹⁴ (84)

To a solution of **74** (295 mg, 1.22 mmol) in THF (5 ml) were added triphenylphosphine (482 mg, 1.84 mmol) and **47** (400 mg, 1.83 mmol). The solution was cooled to 0 °C and DIAD (0.37 ml, 1.87 mmol) was added dropwise. The cold bath was removed and the mixture was stirred 3 h, concentrated, diluted with CH₂Cl₂ (10 ml), washed with 1 M NaOH (10 ml) and 1 M HCl (10 ml), and dried (MgSO₄). Purification by chromatography (hexanes/EtOAc, 7:3 then 1:1) gave **84** (224 mg, 0.51 mmol, 41%) followed by starting material **74** (134 mg).

Spectral data for rotameric mixture 84

¹H NMR δ 7.38 (t, *J*=7.8 Hz, 0.5H), 7.35 (t, *J*=7.2 Hz, 0.5H), 7.30 (d, *J*=9.0 Hz, 0.5H), 7.29 (d, *J*=8.4 Hz, 1H), 5.80-5.90 (m, 1H), 5.19 (d, *J*=16.8 Hz, 1H), 5.18 (d, *J*=10.8 Hz, 1H), 4.70 (s, 0.5H), 4.69 (s, 0.5H), 3.96-4.14 (m, 2H), 2.77 (d, *J*=13.2 Hz, 0.5H), 2.62 (d, *J*=9.6 Hz, 0.5H), 2.44-2.52 (m, 1H), 2.14-2.20 (m, 1H), 1.96-2.04 (m, 1H), 1.48 (s, 9H); ¹³C δ 155.3, 155.2, 153.8, 153.3, 152.2, 152.2, 134.3 (-), 134.0 (-), 128.4 (-), 128.3 (-), 118.7 (+), 118.6 (+), 116.6 (-), 116.5 (-), 116.1 (-), 116.0 (-), 105.5, 105.3, 82.4 (-), 81.1 (-), 79.6, 79.6, 62.9 (-), 62.7 (-), 60.3, 53.2 (-), 53.1 (-), 37.4 (+), 36.4 (+), 36.1 (+), 35.5 (+), 28.4 (-), 21.7 (-), 20.5 (-); IR (neat) 2976, 1682, 1534, 1387, 1269 cm⁻¹; [α]_D²⁵ = +0.12 ±0.01 (*c* = 1.0, MeOH); HRMS (ESI) calcd for C₁₉H₂₅BrN₂O₅ (M+H⁺) 441.10258, found 441.10227.

(2R, 3S, 5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-(2-iodo-3-nitrophenoxy-5-methylpyrrolidine¹¹⁴ (85**)**

To a solution of **74** (240 mg, 1.0 mmol) in THF (5 ml) were added triphenylphosphine (395 mg, 1.51 mmol) and **48** (398 mg, 1.50 mmol). The solution was cooled to 0 °C and DIAD (0.30 ml, 1.51 mmol) was added dropwise. The cold bath was removed and the mixture was stirred 4 h, concentrated, diluted with CH₂Cl₂ (10 ml), washed with 1 M NaOH (10 ml) and 1 M HCl (10 ml), and dried (MgSO₄). Purification by chromatography (hexanes/EtOAc, 1:1 then EtOAc) gave **85** (315 mg, 0.65 mmol, 65%).

Spectral data for rotameric mixture 85

¹H NMR δ 7.39 (t, *J*=7.8 Hz, 0.5H), 7.37 (t, *J*=7.8 Hz, 0.5H), 7.27 (d, *J*=7.2 Hz, 0.5H), 7.26 (d, *J*=7.8 Hz, 0.5H), 6.94 (d, *J*=8.4 Hz, 1H), 5.81-5.90 (m, 1H), 5.18 (d, *J*=16.8 Hz, 1H), 5.18 (d, *J*=10.2 Hz, 1H), 4.66 (s, 0.5H), 4.66 (s, 0.5H), 4.00-4.19 (m, 2H), 2.77 (d, *J*=12.0 Hz, 0.5H), 2.61 (d, *J*=10.8 Hz, 0.5H), 2.46-2.54 (m, 1H), 2.15-2.23 (m, 1H), 1.98-2.04 (m, 1H), 1.51-1.54 (m, 3H), 1.48 (s, 9H); ¹³C δ 159.9, 158.0, 157.9, 156.2, 156.1, 153.9, 153.4, 134.3 (-), 134.1 (-), 129.8 (-), 129.7 (-), 118.7 (+), 118.6 (+), 116.8 (-), 116.8 (-), 115.0 (-), 114.9 (-), 82.8 (-), 81.5 (-), 81.0, 80.8, 79.7, 79.7, 74.3, 63.0 (-), 62.9 (-), 60.3, 53.3 (-), 53.2 (-), 37.5 (+), 36.5 (+), 36.1 (+), 35.6 (+), 28.5 (-), 22.1 (-), 21.9 (-), 21.7 (-), 21.6 (-), 21.0, 20.9, 14.2; IR (neat) 1680, 1532, 1364, 1110, 1020 cm⁻¹; [α]_D²⁵ = +30.7 ± 0.91 (*c* = 1.05, MeOH); HRMS (ESI) calcd for C₁₉H₂₅IN₂O₅ (M+H⁺) 489.08871, found 489.08809.

Tricyclic compound **87**¹¹⁷

A solution of **85** (95.9 mg, 0.20 mmol), Pd(OAc)₂ (4.6 mg, 0.02 mmol), PPh₃ (4.9 mg, 0.02 mmol), and Ag₂CO₃ (112 mg, 0.41 mmol) in DMF (5 ml) was stirred at 120 °C for 64.5 h. The solvents were removed on a rotary evaporator at water aspirator pressure, dissolved in CH₂Cl₂ (20 ml), filtered (Celite), concentrated, and the residue was purified by chromatography (hexanes/EtOAc, 7:3 then 1:1) to give **87** (26.7 mg, 0.07 mmol, 35%).

Alternate procedure: A solution of Pd(OAc)₂ (7.4 mg, 0.03 mmol) and tri(o-tolyl)phosphine (39.4 mg, 0.13 mmol) in triethylamine (3 ml) was stirred (5 min.) at ambient temperature. Compound **84** (200 mg, 0.45 mmol) in triethylamine (4 ml) was added and the resulting mixture was heated at 120 °C (31 h). The solvents were removed on a rotary evaporator at water aspirator pressure and the residue was purified by chromatography (hexanes/EtOAc, 9:1) to give **87** (46.8 mg, 0.13 mmol, 29%).

Alternate procedure: A solution of **84** (114 mg, 0.26 mmol), Pd(OAc)₂ (6.9 mg, 0.03 mmol), PPh₃ (4.7 mg, 0.02 mmol), and Ag₂CO₃ (146 mg, 0.53 mmol) in DMF (5 ml) was stirred at 120 °C for 67 h. The solvents were removed on a rotary evaporator at water aspirator pressure, dissolved in CH₂Cl₂ (20 ml), filtered (Celite), concentrated, and the residue was purified by chromatography (hexanes/EtOAc, 9:1) to give **87** (29.9 mg, 0.08 mmol, 31%).

Spectral data for rotameric mixture **87**

^1H NMR δ 7.63 (dd, $J=7.2, 2.4$ Hz, 1H), 7.24-7.28 (m, 2H), 6.08 (br s, 1H), 5.83 (br s, 0.5H), 5.73 (br s, 0.5H), 4.90 (br s, 1H), 3.80 (ddt, $J=16.8, 10.2, 7.2$ Hz, 3H), 3.29 (dd, $J=12.6, 7.2$ Hz, 1H), 2.57 (br s, 1H), 1.93 (dt, $J=12.6, 10.8$ Hz, 1H), 1.48 (s, 9H), 1.45 (s, 3H); ^{13}C δ 158.8, 153.9, 149.9, 136.2, 134.3, 133.2, 128.4, 128.2, 127.7 (-), 127.3 (-), 126.8, 125.9, 120.6, 120.5, 87.3, 86.8 (-), 80.0, 61.8 (-), 56.4, 52.2 (-), 51.6 (-), 40.3 (+), 37.4 (+), 28.4 (-), 26.4 (+), 21.8, 20.1; IR (neat) 1691, 1528, 1154, 1031, 712 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = -159.0 \pm 0.6$ ($c = 1.0$, MeOH).

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Appendix

Figure 10: ¹H NMR of Methyl 3-nitro-2-(N-(2-propen-1-yl))aminobenzoate **5**

Figure 11: ^{13}C NMR of Methyl 3-nitro-2-(*N*-(2-propen-1-yl))aminobenzoate **5**

Figure 12: DEPT of Methyl 3-nitro-2-(*N*-(2-propen-1-yl))aminobenzoate **5**

Figure 13: ¹H NMR of *N*-(2-Propen-1-yl) 2-(*N*-(2-propen-1-yl))amino-3-nitrobenzamide **6**

Figure 14: ^{13}C NMR of *N*-(2-Propen-1-yl) 2-(*N*-(2-propen-1-yl))amino-3-nitrobenzamide **6**

Figure 15: DEPT of *N*-(2-Propen-1-yl) 2-(*N*-(2-propen-1-yl))amino-3-nitrobenzamide **6**

Figure 16: ¹H NMR of Methyl 2-(*N*-benzylamino)-3-nitrobenzoate **7**

Figure 17: ¹³C NMR of Methyl 2-(N-benzylamino)-3-nitrobenzoate **7**

Figure 18: DEPT of Methyl 2-(*N*-benzylamino)-3-nitrobenzoate **7**

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Figure 20: ^{13}C NMR of *N*-Benzyl-4-methoxy-2-nitrobenzenamine **13**

Figure 21: DEPT of *N*-Benzyl-4-methoxy-2-nitrobenzenamine **13**

Figure 22: ¹H NMR of *N*-Benzyl-*N*-methyl-4-methoxy-2-nitrobenzenamine **14**

Figure 23: ¹³C NMR of *N*-Benzyl-*N*-methyl-4-methoxy-2-nitrobenzenamine **14**

Figure 24: DEPT of *N*-Benzyl-*N*-methyl-4-methoxy-2-nitrobenzenamine **14**

Figure 25: ¹H NMR of *N*-Benzyl-(5-methoxy-2-nitrophenyl)-*N*-methylamine **15**

Figure 26: ^{13}C NMR of *N*-Benzyl-(5-methoxy-2-nitrophenyl)-*N*-methylamine **15**

Figure 27: DEPT of *N*-Benzyl-(5-methoxy-2-nitrophenyl)-*N*-methylamine **15**

Figure 28: ¹H NMR of 2-(6-Methoxy-2-nitrophenyl)-2,3-dihydro-1H-isoindole **18**

Figure 29: ¹³C NMR of 2-(6-Methoxy-2-nitrophenyl)-2,3-dihydro-1H-isoindole **18**

Figure 30: DEPT of 2-(6-Methoxy-2-nitrophenyl)-2,3-dihydro-1H-isoinidole **18**

Figure 31: ¹H NMR of 2-(2-Nitrophenyl)-2,3-dihydro-1*H*-benzo[de]isoquinoline **20**

Figure 32: ^{13}C NMR of 2-(2-Nitrophenyl)-2,3-dihydro-1H-benzo[de]isoquinoline **20**

Figure 33: ¹H NMR of 2-Ethenyl-1H-benzimidazole **26**

Figure 34: ^{13}C NMR of 2-Ethenyl-1H-benzimidazole **26**

Figure 35: DEPT of 2-Ethenyl-1*H*-benzimidazole **26**

Figure 36: ¹H NMR of Methyl 2-ethenyl-1H-benzimidazole-4-carboxylate **27**

Figure 37: ¹³C NMR of Methyl 2-ethenyl-1H-benzimidazole-4-carboxylate **27**

Figure 38: DEPT of Methyl 2-ethenyl-1*H*-benzimidazole-4-carboxylate **27**

Figure 39: ¹H NMR of *N*-(2-Propen-1-yl) 2-ethenyl-1*H*-benzimidazole-4-carboxamide **28**

Figure 40: ¹³C NMR of *N*-(2-Propen-1-yl) 2-ethenyl-1*H*-benzimidazole-4-carboxamide **28**

Figure 41: DEPT of *N*-(2-Propen-1-yl) 2-ethenyl-1*H*-benzimidazole-4-carboxamide **28**

Figure 42: ¹H NMR of 5-Methoxy-1-methyl-2-phenyl-1H-benzimidazole **35**

Figure 43: ^{13}C NMR of 5-Methoxy-1-methyl-2-phenyl-1H-benzimidazole **35**

Figure 44: DEPT of 5-Methoxy-1-methyl-2-phenyl-1*H*-benzimidazole **35**

Figure 45: ¹H NMR of 6-Methoxy-1-methyl-2-phenyl-1H-benzimidazole **36**

Figure 46: ^{13}C NMR of 6-Methoxy-1-methyl-2-phenyl-1H-benzimidazole **36**

Figure 47: DEPT of 6-Methoxy-1-methyl-2-phenyl-1*H*-benzimidazole **36**

Figure 48: ¹H NMR of 7-Methoxy-11H-isoindolo[2,1-a]benzimidazole **41**

Figure 49: ^{13}C NMR of 7-Methoxy-11H-isindolo[2,1-a]benzimidazole **41**

Figure 50: DEPT of 7-Methoxy-11*H*-isoindolo[2,1-*a*]benzimidazole **41**

Figure 51: ¹H NMR of 5,6-Dihydrobenz[4,5]imidazo[2,1-*a*]isoquinoline **43**

Figure 52: ¹³C NMR of 5,6-Dihydrobenz[4,5]imidazo[2,1-a]isoquinoline **43**

Figure 53: DEPT of 5,6-Dihydrobenz[4,5]imidazo[2,1-*a*]isoquinoline **43**

Figure 54: ¹H NMR of (R)-1,2,4-Butanetriol 1,4-bis(methanesulfonate) **62**

Figure 55: ^{13}C NMR of (R)-1,2,4-Butanetriol 1,4-bis(methanesulfonate) **62**

Figure 56: ¹H NMR of (S)-2-(2-Bromo-3-nitrophenoxy)butane-1,4-dimethanesulfonate **79**

Figure 57: ¹³C NMR of (S)-2-(2-Bromo-3-nitrophenoxy)butane-1,4-dimethanesulfonate **79**

Figure 58: ¹H NMR of (S)-4-(2-Bromo-3-nitrophenoxy)-3,4-dihydro-2H-pyrrole N-oxide **80**

Figure 59: ^{13}C NMR of (S)-4-(2-bromo-3-nitrophenoxy)-3,4-dihydro-2H-pyrrole N-oxide **80**

Figure 60: DEPT of (S)-4-(2-Bromo-3-nitrophenoxy)-3,4-dihydro-2H-pyrrole N-oxide **80**

Figure 61: ¹H NMR of (3R, 5R)-2-Allyl-3-[(*tert*-butyldimethylsilyl)oxy]-methylpyrrolidine **72**

Figure 62: ¹³C NMR of (3R, 5R)-2-Allyl-3-[(*tert*-butyldimethylsilyl)oxy]-methylpyrrolidine **72**

Figure 63: DEPT of (3R, 5R)-2-Allyl-3-[(*tert*-butyldimethylsilyl)oxy]-methylpyrrolidine **72**

Figure 64: ¹H NMR of (3R, 5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-[(*tert*-butyl)dimethylsilyl]oxy]-5-methylpyrrolidine **73**

Figure 65: ¹³C NMR of (3R, 5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-[(*tert*-butyl)dimethylsilyl]oxy]-5-methylpyrrolidine **73**

Figure 66: DEPT of (3R, 5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-5-methylpyrrolidine **73**

Figure 67: ¹H NMR of (2R,3R)-2-Allyl-1-methylpyrrolidin-3-ol **63**

Figure 68: ^{13}C NMR of (2R,3R)-2-Allyl-1-methylpyrrolidin-3-ol **63**

Figure 69: DEPT of (2R,3R)-2-Allyl-1-methylpyrrolidin-3-ol **63**

Figure 70: ¹H NMR of (2R,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **74**

Figure 71: ¹H NMR (-20 °C) of (2R,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **74**

Figure 72: ¹³C NMR of (2R,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **74**

Figure 73: ¹³C NMR (-20 °C) of (2R,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **74**

Figure 74: DEPT of (2R,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **74**

Figure 75: ¹H NMR of (2S,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **75**

Figure 76: ¹H NMR (-55 °C) of (2S,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **75**

Figure 77: ^{13}C NMR of (2S,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **75**

Figure 78: ¹³C NMR (-60 °C) of (2S,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **75**

Figure 79: DEPT of (2S,3R,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-hydroxy-5-methylpyrrolidine **75**

Figure 80: ¹H NMR of (2R,3S,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-(2-iodo-3-nitrophenoxy)-5-methylpyrrolidine **85**

Figure 81: ¹³C NMR of (2R,3S,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-(2-iodo-3-nitrophenoxy)-5-methylpyrrolidine **85**

Figure 82: DEPT of (2R,3S,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-(2-iodo-3-nitrophenoxy)-5-methylpyrrolidine **85**

Figure 83: ¹H NMR of (2R,3S,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-(2-bromo-3-nitrophenoxy)-5-methylpyrrolidine **84**

Figure 84: ¹³C NMR of (2R,3S,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-(2-bromo-3-nitrophenoxy)-5-methylpyrrolidine **84**

Figure 85: DEPT of (2R,3S,5R)-2-Allyl-1-(*tert*-butoxycarbonyl)-3-(2-bromo-3-nitrophenoxy)-5-methylpyrrolidine **84**

Figure 86: ¹H NMR of (2R,3S)-2-Allyl-3-(2-iodo-3-nitrophenoxy)-1-methylpyrrolidine **83**

Figure 87: ^{13}C NMR of (2R,3S)-2-Allyl-3-(2-iodo-3-nitrophenoxy)-1-methylpyrrolidine **83**

Figure 88: DEPT of (2R,3S)-2-Allyl-3-(2-iodo-3-nitrophenoxy)-1-methylpyrrolidine **83**

Figure 89: ¹H NMR of tricyclic compound **87**

Figure 90: ¹H NMR (-40 °C) of tricyclic compound **87**

Figure 91: ^{13}C NMR of tricyclic compound **87**

Figure 92: ^{13}C NMR (-40°C) of tricyclic compound **87**

Figure 93: DEPT of tricyclic compound **87**