A CONVENIENT SYNTHESIS OF PYRROLNITRIN AND RELATED HALOGENATED PHENYLPYRROLES

by

Matthew Daniel Morrison

A thesis submitted to the Department of Chemistry

In conformity with the requirements for

the degree of Master of Science

Queen's University

Kingston, Ontario, Canada

September, 2009

Abstract

This thesis details a straightforward synthetic route to the antifungal compound pyrrolnitrin **1.2**, along with several analogous halogenated phenylpyrroles. The proposed synthetic protocol involved the Suzuki-Miyaura cross-coupling of appropriately halogenated pyrrole pinacolboronate esters and aryl compounds.

In the efforts towards preparing the cross-coupling partners, we report a regiospecific and high yielding synthesis of a 3-chloro pyrrole compound **2.14**, its brominated analog **2.16**, an iodinated analog **2.17**, and the corresponding pinacolboronate ester **2.18**. We also report a generalized reaction sequence (lithiation/carboxylation/Schmidt reaction/oxidation) for the preparation of halogenated benzoic acids, anilines and nitrobenzenes. In particular, we synthesized the desired halogenated nitrobenzene coupling partner **3.27** in excellent yield. We were also able to show that the conditions employed in this sequence were mild enough to allow preparation of the 2-bromo-6-iodo compound **3.33**.

Once the coupling partners were prepared, we developed the optimal conditions for our Suzuki-Miyaura cross-coupling reactions. In doing so, we were able to prepare our target compound **1.2** and several halogenated analogs in good yields. We also prepared brominated and deuterated arylpyrroles **4.27** and **4.28**, respectively, for future use in mechanistic studies of the pyrrolnitrin biosynthetic enzymes, PrnB, Prn C and PrnD. This required preparation of the corresponding brominated and deuterated pyrrole pinacolboronate esters **4.24** and **4.26**.

Acknowledgements

First and foremost, I would like to thank my supervisor, Dr. Derek Pratt, for giving me the opportunity to be a part of this incredible, diverse, and truly unique research group. Your guidance, support, understanding and relentless patience inspired me to push through the low points (inevitable in any research project) until I had achieved my goals and found success. But most of all, it was the example you set through your diligence and passion for your own work that had the greatest impact in shaping me into the chemist I am today. Though, I only worked under your wing for two years, I matured more as an academic and a person in that short time than I ever could have imagined. I will always look back on my time with the Pratt group with fond memories, and sincere gratitude.

I could not have achieved half of my accomplishments without the help and advice from many of the brilliant and selfless academics in the department. I need to thank the people of the Baird group (Emily, Goran, John, and Greg) who were always available to keep my spirits high. People of the Crudden group (John, Jenny, Yonek, Jeremy, Ben, Tom, Chris, and all the rest), I never could have made it without you. Wang group, thanks for all the solvent! I could not forget Todd Macklin of the Snieckus group, whose priceless advice I sought after on many occasions.

A special thanks goes out to all my fellow members of the Pratt group: Jay, Johan, Susheel, Mukund, Rami, Di, and Chris Witiw. Jay, you're "one guy" that I'll never forget. Johan, you ensured that no group meeting or night out on the town was ever dull. Susheel, you saved my chemistry life on a daily basis. As for all the rest, I'll miss you guys a lot! I'd also like to thank the members of Dr. Dave Zechel's research group: Dave, Ryan (a guy from Thunder Bay, ON, with only two things on his mind), Meagan, Anupam, and Katie. I'll miss all of you! Special thanks goes out to Dave, whose great energy, smile and outlook on life made everyone's time in the lab that much more enjoyable.

Table of Contents

Abstract ii

Acknowledgements iii

Table of Contents iv

List of Figures and Schemes vi

List of Tables x

Chapter 1 – Introduction 1

1.1 Halogenating Enzymes 2

1.1.1 Background 2

1.1.2 Haloperoxidases 3

1.1.2.1 Heme-Dependent Haloperoxidases 4

1.1.2.2 Vanadium-Dependent Haloperoxidases 5

1.1.2.3 Non-Heme Iron Haloperoxidases 6

1.1.3 O_2-Dependent Halogenases 7

1.1.3.1 α-Ketoglutarate-Dependent Halogenases 8

1.1.3.2 Flavin-Dependent Halogenases 10

1.2 Synthetic Methodology 15

1.2.1 The Directed *ortho* Metalation (D*o*M) Reaction 15

1.2.1.1 Mechanism of the D*o*M Reaction 15

1.2.1.2 Directed Metalation Groups (DMGs) 20

1.2.1.3 Cooperative Metalation Effects 21

1.2.1.4 Scope of D*o*M Chemistry 23

1.2.2 Lithium-Halogen Exchange 24

1.2.2.1 Mechanism of Lithium-Halogen Exchange 26

1.2.2.1.1 Four-Center Transition State Model 27

1.2.2.1.2 Radical-Mediated Mechanisms 28

1.2.2.1.3 Nucleophilic Mechanisms 31

1.2.3 Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds: The Suzuki-Miyaura Reaction 33

1.2.3.1 Application to Natural Product Synthesis 36

1.3 Outline of Research Project 38

Chapter 2 – Syntheses of 3- and 3,4-Disubstituted Pyrroles 43
2.1 Background 44
2.1.1 Direction by a Removable 2-Substituent 45
2.1.2 Direction by a Removable 1-Substituent 46
2.1.3 Halogen-Metal Interchange of 1-(TIPS)-3-Bromopyrrole 50
2.2 Steps Towards a 3,4-Disubstituted Pyrrole 51
2.3 Conclusions 55

Chapter 3 – Syntheses of 2,6-Dihaloanilines and 2,6-Dihalonitrobenzenes 56
3.1 Background 57
3.2 Syntheses of 2-Chloro-6-Haloanilines (and 2-Chloro-6-Halonitrobenzenes) 59
3.3 Conclusions 65

Chapter 4 – Cross-Coupling Between Halogenated Pyrroles and 1,2,3-Trisubstituted Aromatics 67
4.1 Background 68
4.2 Cross-Couplings of 1-(TIPS)-3-(BPin)pyrrole with Various Aryl Bromides 71
4.3 Cross-Couplings of 1-(TIPS)-3-Chloro-4-(BPin)pyrrole with Various Aryl Bromides 74
4.4 Syntheses of Brominated and Deuterated Arylpyrroles 75
4.5 Conclusions 77

Chapter 5 – Experimental Methods 79
5.1 General Methods 80
5.2 General Procedures 81
5.3 Specific Experimental Procedures 86

References 98

List of Figures and Schemes

Figure 1.1: Biologically active organohalogens. 3

Figure 1.2: Hierarchy of DMGs. 20

Scheme 1.1: Reaction mechanism of a heme-containing chloroperoxidase. Only the heme iron without the porphyrin ring system is shown. 5

Scheme 1.2: Intermediates in the mechanism of vanadium-dependent haloperoxidases. 6

Scheme 1.3: Oxidation of indole, indolylacetic acid and tryptophan by chloroperoxidases. 7

Scheme 1.4: Mechanism of α-ketoglutarate halogenases. 9

Scheme 1.5: Nucleophilic mechanism of flavin-dependent halogenases. 11

Scheme 1.6: Electrophilic mechanism of flavin-dependent halogenases. 11

Scheme 1.7a: Chlorination mechanism of PrnA. 13

Scheme 1.7b: Proposed mechanism of RebH (and PrnA) with chloramine intermediate. 14

Scheme 1.8: The directed *ortho* metalation (D*o*M) reaction. 15

Scheme 1.9: Inductive effect explanation of the D*o*M reaction mechanism. 16

Scheme 1.10: Complex-induced proximity effect (CIPE) for a lithiation/substitution sequence. 17

Scheme 1.11: CIPE process in the β-lithiation of γ,δ-unsaturated tertiary amides. 18

Scheme 1.12: Base-dependent selectivity of the D*o*M reaction. 18

Scheme 1.13: *n*-BuLi dimers in the D*o*M reaction 19

Scheme 1.14: Electrostatically favorable arrangement of charges during a simultaneous complexation/proton abstraction step in D*o*M reactions. 20

Scheme 1.15: Deprotonation at the common site between two *meta* DMGs. 21

Scheme 1.16: D*o*M in the synthesis of an enantiopure aromatic sulfoxide 23

Scheme 1.17: An application of D*o*M in combination with Suzuki-Miyaura cross-coupling 24

Scheme 1.18: Production of lithiated intermediate in lithium-halogen exchange. 24

Scheme 1.19: Demonstration of necessity for *o*-lithiated intermediate in a Li-X exchange reaction. 25

Scheme 1.20: Competing mechanisms in Li-X exchange reactions. 25

Scheme 1.21: Example of predominance of Wurtz-type coupling in a Li-X exchange reaction. 26

Scheme 1.22: Four-center transition state model of Li-X exchange. 27

Scheme 1.23: Single-electron transfer in Li-X exchange. 29

Scheme 1.24: Use of a cyclizable probe in the study of the Li-X exchange mechanism. 30

Scheme 1.25: Use of 6-bromo-1-phenyl-1-hexyne as a radical probe in the study of the Li-X exchange mechanism. 30

Scheme 1.26: Temperature-dependent isomerization of 5-hexen-1-yllithium. 31

Scheme 1.27: Nucleophilic mechanism of Li-X exchange. 31

Scheme 1.28: Formation of the “ate-complex” intermediate in Li-X exchange. 32

Scheme 1.29: Isolation of a Li-X exchange “ate-complex” intermediate. 33

Scheme 1.30: Mechanism of Suzuki-Miyaura cross-coupling. 35

Scheme 1.31: Synthesis of the antitumor alkaloid, narciclasin. 36

Scheme 1.32: Synthesis of an isochroman analogue of michellamines. 37

Scheme 1.33: Synthesis of retinoid receptor ligands. 38

Scheme 1.34: Proposed biosynthetic pathway to pyrrolnitrin. 39

Scheme 1.35: Total synthesis of pyrrolnitrin by Nakano et al. 40

Scheme 1.36: Total synthesis of pyrrolnitrin by Gosteli. 41

Scheme 2.1: Positions on a pyrrole ring. 44

Scheme 2.2: Selective formation of a 3-substituted pyrrole. 45

Scheme 2.3: Examples of 2-substituted pyrroles used for β-directed substitution reactions. 46

Scheme 2.4: Demonstration of favorable β:α product ratio when using a *N*-substituent on pyrrole. 47

Scheme 2.5: Formation of 1-(TIPS)pyrrole. 48

Scheme 2.6: Proposed retrosynthetic approach to pyrrolnitrin. 52

Scheme 2.7: Synthesis of 1-(TIPS)-3-chloropyrrole. 53

Scheme 2.8: Synthesis of 1-(TIPS)-3-(BPin)pyrrole. 53

Scheme 2.9: Route to 1-(TIPS)-3-chloro-4-(BPin)pyrrole. 54

Scheme 2.10: Metalation/electrophile quench of 3,4-dihalo-1-(TIPS)pyrroles 55

Scheme 3.1: Metalation of *N*-pivaloylaniline. 57

Scheme 3.2: Reaction of a Piv-protected aniline with various electrophiles. 58

Scheme 3.3: Metalation of *N*-(Boc)aniline. 59

Scheme 3.4: Preparation of 2-bromo-6-chloroaniline by Ayyangar et al. 60

Scheme 3.5: Reaction of Piv- and Boc-protected anilines with iodine electrophile. 60

Scheme 3.6: Formation of 2,6-difluoroaniline by Roe et al. 62

Scheme 3.7: Decomposition products of lithiated 2-bromo-6-chlorobenzene. 62

Scheme 3.8: Synthesis of 2-bromo-6-chlorobenzoic acid. 63

Scheme 3.9: Comparison between different metalation/carboxylation conditions. 65

Scheme 3.10: Structure of 2,6-difluoronitrosobenzene. 65

Scheme 4.1: Cross-coupling of a 2-substituted pyrrole boronic acid. 69

Scheme 4.2: Cross-coupling of a 3-substituted pyrrole boronic acid. 70

Scheme 4.3: Cross-coupling of a 3,4-disubstituted pyrrole bispinacolboronate ester. 71

Scheme 4.4: Unexpected bis-coupling product of 1-(TIPS)-3-(BPin)pyrrole with 2-

bromo-6-chloronitrobenzene. 74

Scheme 4.5: Synthesis of 1-(TIPS)-3-bromo-4-(BPin)pyrrole. 76

Scheme 4.6: Synthesis of 1-(TIPS)-3-deuterio-4-(BPin)pyrrole. 76

List of Tables

Table 1.1: Metalation of 1,3-disubsituted benzenes followed by electrophile quench. 22

Table 2.1: Reaction of TIPS-pyrrole with electrophilic reagents. 49

Table 2.2: Reaction of a lithiopyrrole intermediate with various electrophiles. 51

Table 3.1: Hydrolytic conditions for the removal of Piv 61

Table 3.2: Generalized lithiation/carboxylation/Schmidt reaction/oxidation Sequence. 64

Table 4.1: Various catalytic conditions for Suzuki-Miyaura cross-coupling of 3-(BPin)-1-(TIPS)pyrrole with 2-bromoaniline. 72

Table 4.2: Suzuki-Miyaura cross-coupling of **2.15** with aryl bromides. 73

Table 4.3: Suzuki-Miyaura cross-coupling of **2.18** with aryl bromides. 75

Table 4.4: Suzuki-Miyaura cross-coupling of **4.24** and **4.26** with aryl bromides. 77

Chapter 1 – Introduction

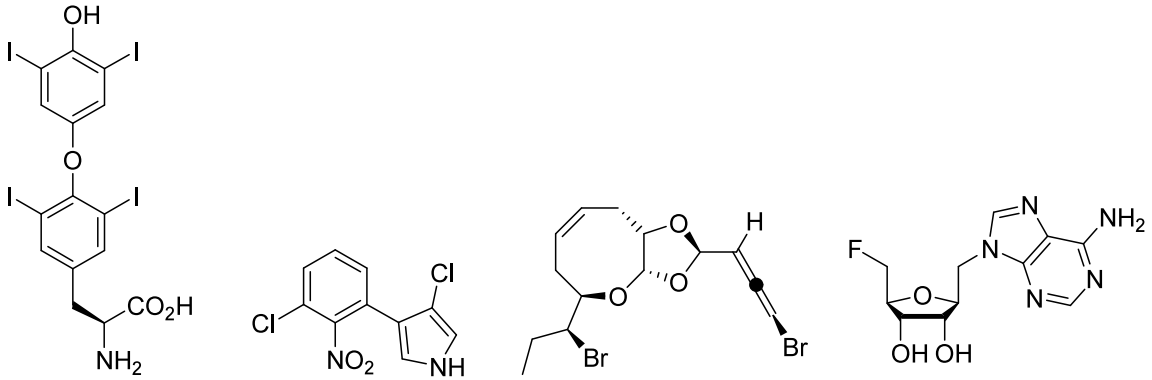
1.1 Halogenating Enzymes

1.1.1 Background

Natural products bearing halogen atoms have, historically, played an important role in the discovery and development of medicinal agents. Such biologically active organohalogens are synthesized by marine organisms, bacteria, terrestrial plants, and higher life forms including humans.[1] These products display distinct physiological and biochemical roles in the organisms that produce them, for example, thyroxine (**1.1**) is an aryl iodide required for human metabolic control and homeostasis;[2] pyrrolnitrin (**1.2**), which contains two carbon-chlorine bonds, is a biocontrol agent produced by several strains of *Pseudomonas*;[3] laurallene (**1.3**) is a terpenoid product containing two carbon-bromine bonds;[4] and 5'-fluoro-5'-deoxyadenosine (5'-FDA, **1.4**), produced by *Streptomyces cattleya,* is one of relatively fewer fluorine-containing natural products (Figure 1.1).[5] The halogen atom incorporated into the organic substrate is commonly determined by the relative abundance of halide in the surrounding environment. Thus, natural organohalogens synthesized by marine organisms typically contain more bromine than chlorine due to the abundance of marine bromide, while those produced by terrestrial organisms predominately contain chlorine on account of the relatively high chloride content in soil.[1] A great number of such halogenating enzymes—known as halogenases—have been isolated, characterized, and studied, but few biosynthetic pathways have been elucidated.[6] The most common enzymatic strategies used for biological bromination, chlorination, and iodination are predominantly oxidative, in that the abundant ionic species Cl^-, Br^-, and I^- are oxidized in order to react not as nucleophiles but as electrophilic or radical species. However, one of the greatest contributors to the formation of halogenated environmental pollutants (e.g. CH_3Cl, CH_3Br and CH_3I) are *S*-adenosylmethionine-dependent halide methyltransferases found predominantly in

plants and marine algae.[7] The quantity produced of these organohalides is on the scale of megatons per year. Interestingly, the mechanism of halogenation here relies on a nucleophilic mechanism, whereby the halide ions act as nucleophiles.

Of the known oxidative halogenases, there are three main classes: haloperoxidases, flavin-dependent halogenases, and α-ketoglutarate-dependent halogenases. Enzymes that catalyze C-F bond formation (e.g. fluorinase)[8] do so by a mechanism distinct from those employed by enzymes which install other halogens (Cl, Br, or I), that is, a nucleophilic substitution mechanism is used, and they will not be discussed any further here.



thyroxine, **1.1** pyrrolnitrin, **1.2** laurallene, **1.3** 5'-FDA, **1.4**

Figure 1.1: Biologically active organohalogens.

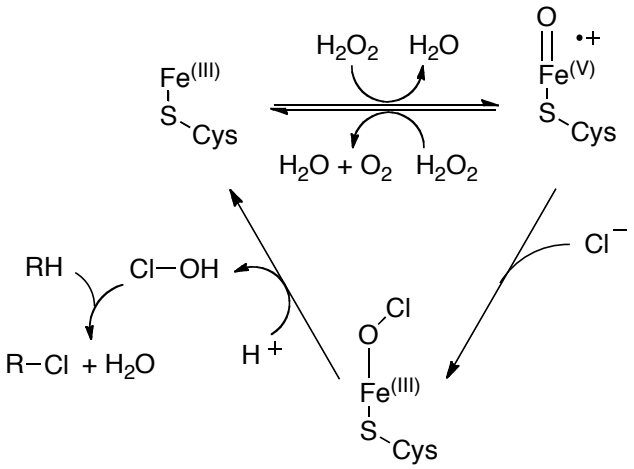
1.1.2 Haloperoxidases

Haloperoxidases are a class of enzymes capable of halogenating substrates in the presence of halide ions and peroxides such as hydrogen peroxide (H_2O_2). Three distinct groups of these enzymes are currently known, each with their own unique mechanism: (i) heme-dependent haloperoxidases, (ii) vanadium-dependent haloperoxidases, and (iii) non-heme iron haloperoxidases.

1.1.2.1 Heme-Dependent Haloperoxidases

Haloperoxidases whose prosthetic group interacts with a heme-iron co-factor for their halogenating activity are known as heme-dependent haloperoxidases. In order to catalyze halogenation reactions, these haloperoxidases require H_2O_2 and halide ions (Cl^-, Br^-, or I^-, but not F^-). This class of enzymes is best depicted by the well-known fungal enzyme chloroperoxidase (CPO)—named for the most electronegative halogen it can oxidize. CPO, which was isolated and extensively characterized by Hager and colleagues,[9] catalyzes the chlorination, bromination, and iodination of various organic compounds through electrophilic substitution[10] and addition mechanisms.[11] By elucidating the 3-D structure of this enzyme,[12] a reaction mechanism could be inferred, as it showed an axially coordinated hypochlorite ion (ClO^-) was the halogenating agent (Scheme 1.1—porphyrin ring system not shown).[13, 14] The Fe^{III}–OCl species, which arises when Cl^- captures an Fe^{IV}=O/porphyrin-thiolate radical, acts as a "Cl^+" equivalent. Alternatively, Sundaramoorthy *et al.* demonstrated that the metal-bound hypohalite ion dissociates to form free hypohalous acid (HOX), where in solution it reacts with substrate.[12]

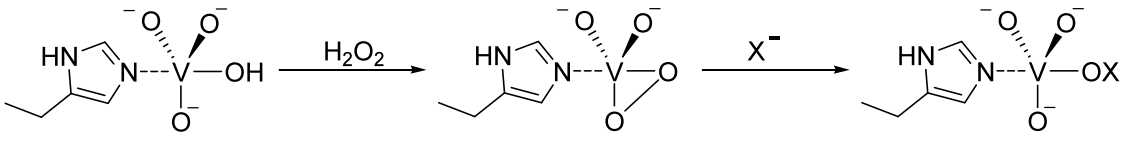
Scheme 1.1[13]



1.1.2.2 Vanadium-Dependent Haloperoxidases

Vanadium-dependent haloperoxidases also catalyze the oxidation of halides (except fluoride) by hydrogen peroxide. These enzymes are also classified according to the most electronegative halide they can oxidize, and thus, vanadium chloroperoxidases (V-CPOs) can oxidize chloride, bromide, and iodide, whereas vanadium bromoperoxidases (V-BrPOs) oxidize bromide and iodide. V-CPOs have been isolated from certain fungi, but not yet from marine organisms, whereas V-BrPOs have been isolated from all the various classes of green, red, and brown marine algae.[15] The redox cofactor of a vanadium-dependent haloperoxidases is anchored in the active site when the vanadate ion ligates to a single protein ligand, the imidazole ring of a histidine residue (Scheme 1.2).[16] In order to generate the electrophilic –OX ("X^+"), incoming hydrogen peroxide coordinates to the vanadate ion and it is this complex that oxidizes the halide ion. With these haloperoxidases, unlike with heme-dependent haloperoxidases, there is no change in the oxidation state at the metal center during generation of the halogenating species. Similarly to heme-dependent haloperoxidases, however, the hypohalite ion had also been proposed to dissociate from the metal center, yielding free hypohalous acid in solution for reaction with substrate.[17]

Scheme 1.2[16]

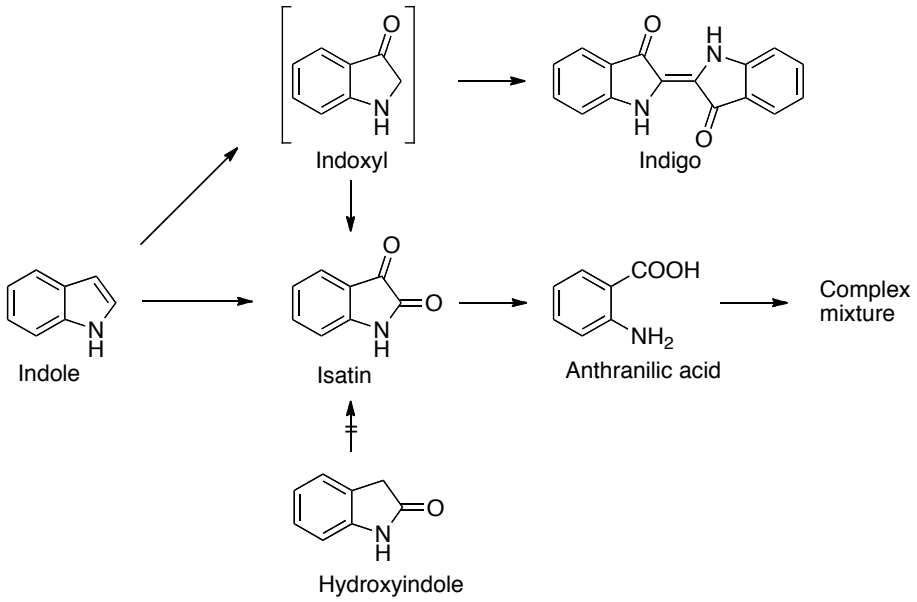


In general, both heme-dependent and vanadium-dependent haloperoxidases utilize H_2O_2 to generate high-valent metal-oxo species that react with various halides to generate –OX ("X^+" equivalents) in their active sites. These electrophilic halogen species are then delivered onto electron-rich organic substrates, either by direct reaction with nucleophiles or by first dissociating to free hypohalous acid in solution. In either case, the result is poor regioselectivity and substrate specificity.

1.1.2.3 Non-Heme Haloperoxidases

Haloperoxidases that appear to depend on non-heme ferric iron have been isolated from algae and *Pseudomonas* species.[18] In 2001, van Pee and co-workers[19] used CPOs isolated from strains of *Streptomyces lividans* and *Pseudomonas pyrrocinia* to oxidize indole, indolylacetic acid and tryptophan. In doing so, they isolated indigo (indoxyl), isatin, and anthranilic acid (intermediate products of oxidative degradation of indole and indole derivatives) from the reaction medium (Scheme 1.3). These results showed that bacterial non-heme haloperoxidases were capable of oxidative degradation of indole and indole derivatives. In contrast to heme-containing haloperoxidases, the primary target of the oxidation reaction catalyzed by non-heme CPOs was found to be the β-carbon atom of the pyrrole cycle.

Scheme 1.3[19]



1.1.3 O_2-Dependent Halogenases

Until 1997, haloperoxidases were believed to be responsible for all enzyme-mediated halogenations.[20] It is now clear that haloperoxidases play less of a role in the biosynthesis of more complex halogenated compounds in microorganisms. Rather, two new classes of enzymes with halogenase activity have been identified as major players in the introduction of halogen atoms into activated substrates: flavin-dependent halogenases, and α-ketoglutarate dependent halogenases. In both of these enzyme classes, O_2 is required as well as a cosubstrate that is reduced during the catalytic cycle. The first member to be discovered in the flavin-dependent class was the enzyme responsible for inserting chlorine at C_7 of the tetracycline nucleus during chlortetracycline biosynthesis.[21] Since then, many homologues of this enzyme have been discovered, including the halogenases responsible for chlorinating electron-rich aromatic side chains of natural products such as pyrrolnitrin **1.2**,[3, 22] and pyoluteorin.[23] The second class of O_2-dependent halogenases consists of non-heme Fe^{2+} enzymes which are homologous to the two-His,

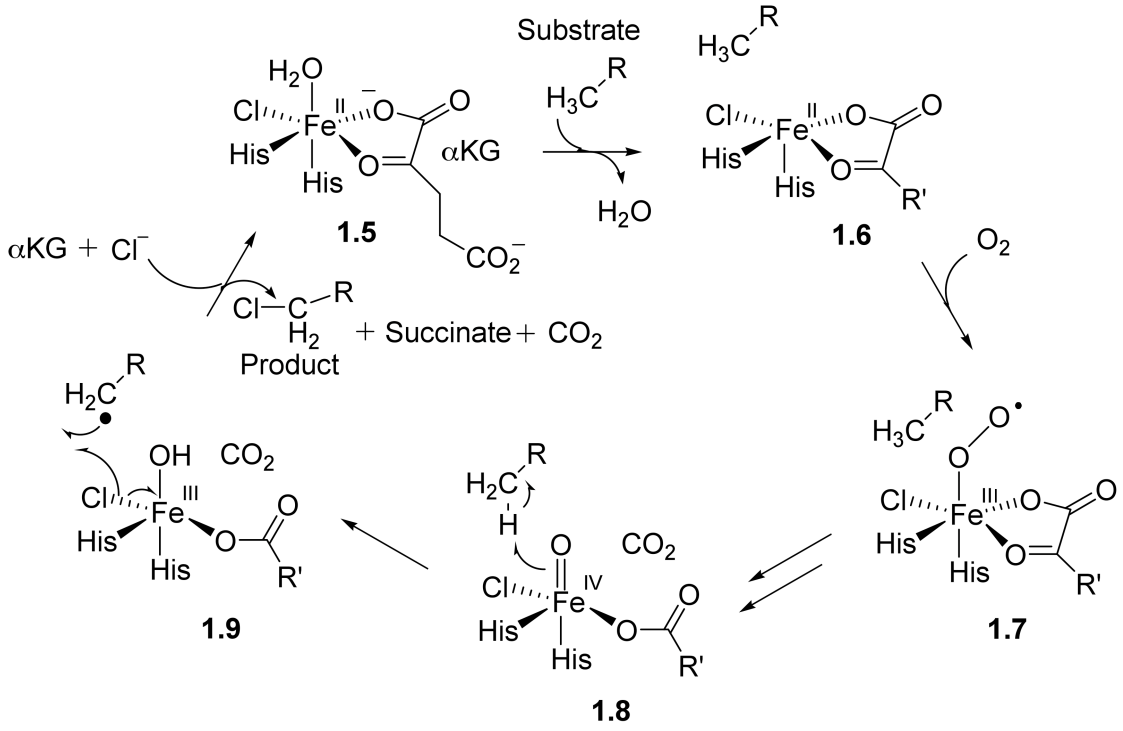
one-carboxylate family of non-heme Fe^{2+} oxygenases that require α-ketoglutarate as a cosubstrate.[24] The redox power of α-ketoglutarate-dependent halogenases is stronger than that of flavin-dependent halogenases, meaning that these stronger iron-based oxo reagents are capable of halogenating less reactive carbon sites.[16]

1.1.3.1 α-Ketoglutarate-Dependent Halogenases

Identification of halogenated molecules containing C-X bonds on unactivated aliphatic carbons (e.g., barbamide),[25] as opposed to the electron-rich aromatic rings of flavin-dependent halogenase substrates, suggested that another class of enzymatic catalysts existed. Unlike haloperoxidases and flavin-dependent halogenases, this type of halogenase is able to install halogen atoms on substrates lacking double bonds. This class came to be known as α-ketoglutarate (αKG)-dependent halogenases. Typically, to introduce functionality at unactivated carbon sites, nature will utilize iron enzymes and generate high-valent oxoiron species[26] as powerful oxidants, as it does in biological hydroxylation reactions.[27] Iron can perform catalytic oxygenation of this sort as the familiar heme-dependent monooxygenases best depicted by cytochrome P450s,[28] or as non-heme iron enzymes which decarboxylate the cosubstrate αKG.[29] Studies on the latter class of enzymes have shown that catalytic halogenation of aliphatic carbons can also be performed in the presence of halogenase, Fe^{II}, and three small-molecule co-substrates: αKG, O_2, and X^-.[30] After the binding of dioxygen in the active site of non-heme αKG-dependent enzymes (**1.7** in Scheme 1.4),[31] the decarboxylation of αKG follows to yield a high-energy ferryl-oxo intermediate **1.8** used for substrate hydrogen-atom abstraction. Whereas, the coordination sphere of iron in αKG-dependent oxygenases usually contains a 2-His, 1-carboxylate motif, forming what is known as the 'facial triad', the iron center of αKG-dependent halogenases have the carboxylate ligand replaced by a halide ion (X = Cl, or Br). Once the Fe^{IV}=O species **1.8** has

abstracted H•, the resulting substrate CH_2• radical is in proximity to the X• radical in the active site **1.9**.[31] Radical rebound involving transfer of OH• or X• to the methylene radical then yields an alcohol or halogenated product, respectively, with concomitant regeneration of the starting Fe^{II} oxidation state. Competition between transfer of OH• or X• is expected, but in certain cases only a single product is observed. For example, in SyrB2, a novel αKG-dependent halogenase, catalytic chlorination trumps hydroxylation due to specific orientation of the substrate-derived radical and iron-bound Cl in the active site.[31] The lower potential of Cl• versus OH• has also been used to explain similar reactivity in model complexes.[30, 32]

Scheme 1.4[31]

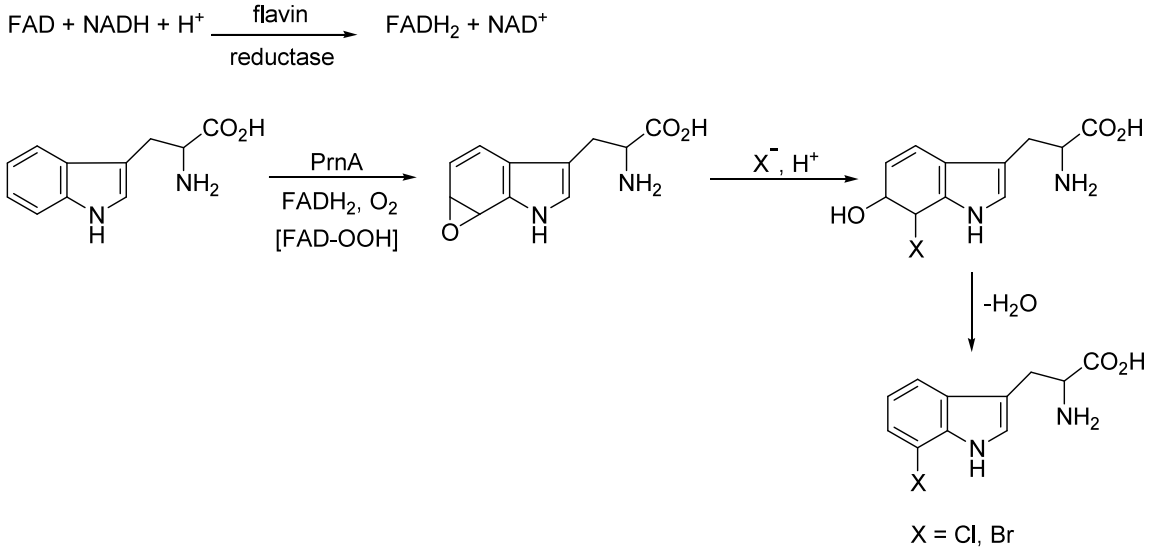


1.1.3.2 Flavin-Dependent Halogenases

This class of flavin-dependent halogenases was defined by van Pée and colleagues when they successfully reconstituted the *in vitro* activity of the flavin adenine dinucleotide (FAD)-dependent tryptophan-7-halogenase (PrnA) as the first step of pyrrolnitrin **1.2** biosynthesis in *Pseudomonas fluorescens*.[33] To date, *in vitro* halogenating activity of flavin-dependent halogenases has only been shown for a handful of enzymes,[34] including PltA from pyoluteorin biosynthesis in *P. fluorescens* Pf-5,[23] and RebH from the chemotherapeutic agent rebeccamycin biosynthesis in *Lechevalieria aerocolonigenes*.[35] All of these enzymes require reduced $FADH_2$ (provided by reaction of FAD with a flavin reductase), halide ion (X^-) and O_2 as co-substrates for the halogenation reaction. It has been shown that there is not a specific interaction between the reductase and the halogenase, which is typical of such two-component systems. In the halogenase active site, an intermediate 4α-hydroperoxyflavin (FAD-4α-OOH)—the same intermediate used by flavin-dependent monooxygenase enzymes[36]—was presumed to form by the reaction of $FADH_2$ with O_2.[20] This flavin intermediate forms independently of substrate, as proposed by Walsh and colleagues who showed that the rates of FAD-4α-OOH formation in RebH were comparable in the presence and absence of tryptophan.[37]

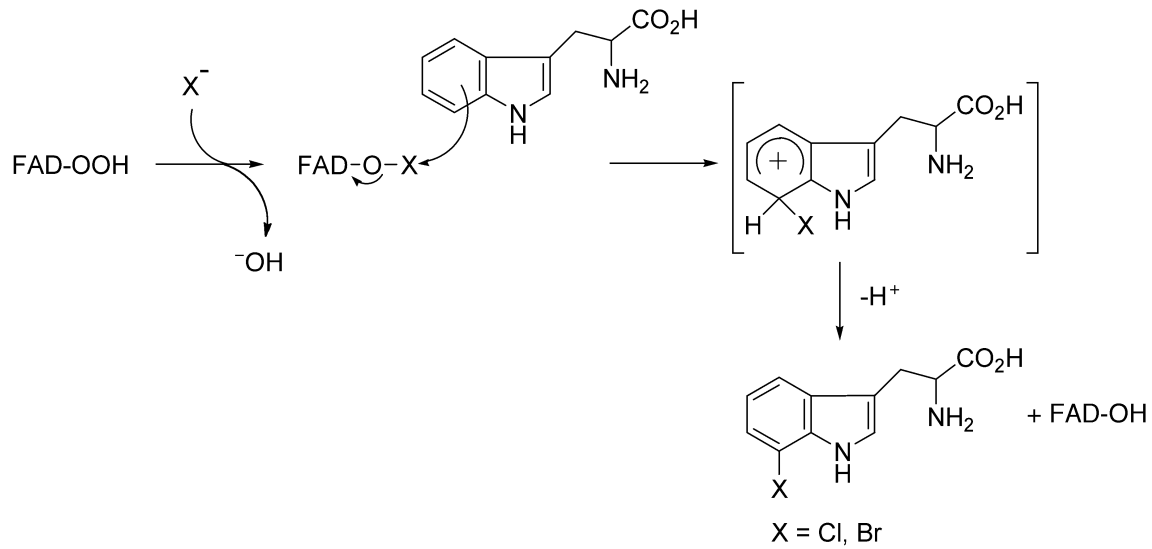
There have been two proposed mechanisms for this class of enzymes. The first is of nucleophilic nature, in which the substrate reacts with FAD-4α-OOH to form an epoxide, followed by the regioselective incorporation of a nucleophilic halide ion to form a halohydrin, which yields the halogenated product after dehydration (Scheme 1.5).[33]

Scheme 1.5[33]



The second is an electrophilic mechanism, suggested by Hubbard and Walsh,[38] that proposes the formation of a flavin-bound, activated electrophilic halide species (Scheme 1.6). This FAD-4α-OX intermediate (formed by attack of X^- on FAD-OOH) is attacked by substrate aromatic π electrons, yielding a halogenated product after the subsequent deprotonation step.

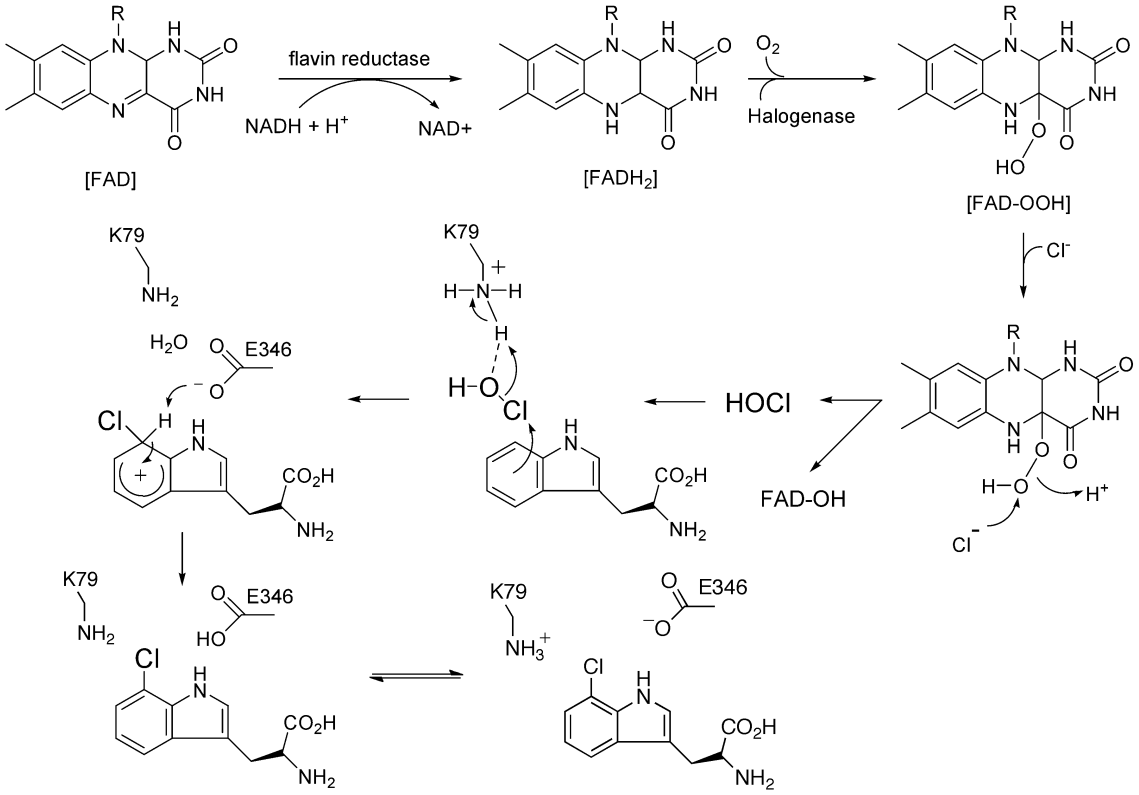
Scheme 1.6[34]



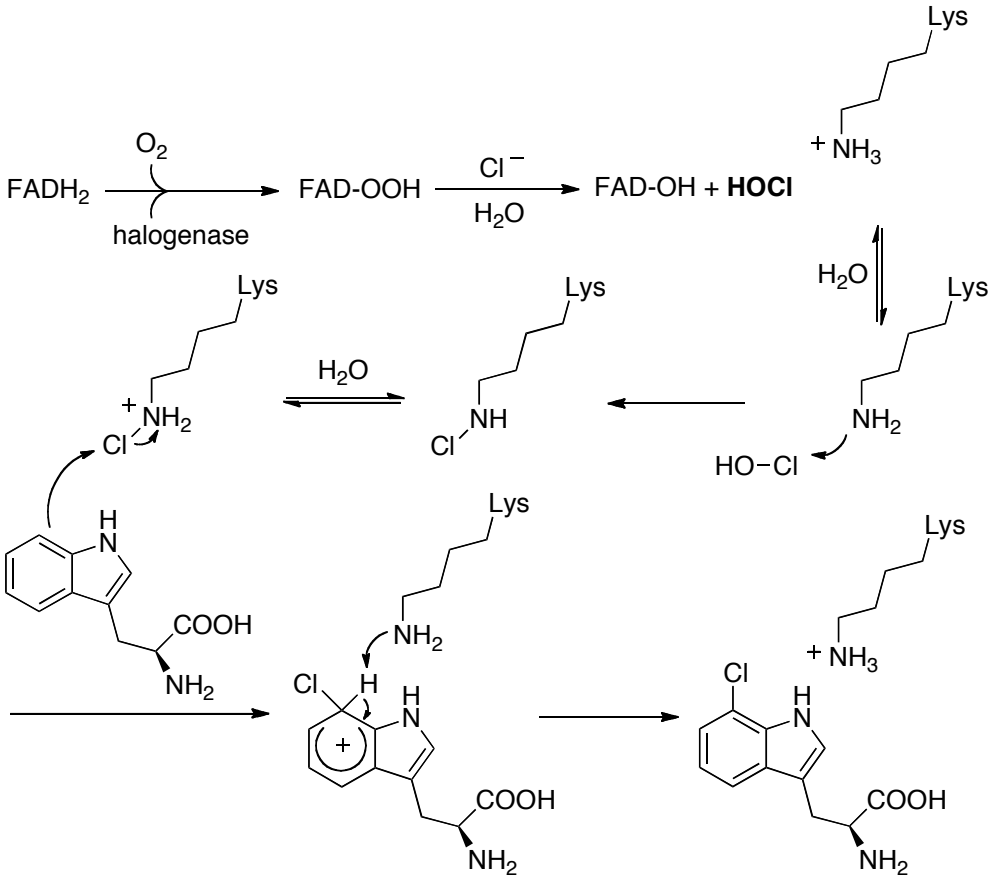
The elucidation of the 3-D structure[39] of PrnA, the first enzyme from the pyrrolnitrin biosynthetic gene cluster, suggested that both of these mechanisms were incorrect. Previously, the use of HOX as the halogenating agent in flavin-dependent halogenase reactions was discounted due to its high reactivity and poor substrate specificity, which did not agree with observed results, but structural characterization of tryptophan 7-halogenase (PrnA) revealed otherwise. In fact, the crystal structure of PrnA indicated that HOCl could very well be the active halogenating agent. How this highly reactive agent was able to chlorinate tryptophan regioselectively was explained by a 10 Å long tunnel which channeled the HOCl from the site of formation directly onto the 7-position of the substrate, tryptophan. HOCl formation took place by nucleophilic attack of Cl^- on the FAD-4α-OOH intermediate (Scheme 1.7a). The side chain of residue K79 provides a hydrogen bond to the HOCl, positioning it in a controlled spatial orientation for reaction with substrate and also activating Cl by increasing its electrophilicity. The Wheland intermediate formed after electrophilic addition of Cl to tryptophan is stabilized by a glutamate residue (E346) in the substrate binding site. This residue then deprotonates the intermediate, yielding the product, 7-chlorotryptophan.

Walsh and co-workers[144] demonstrated the existence of a long-lived chloramine intermediate in the chlorination of tryptophan by an enzyme similar to PrnA, RebH of the rebeccamycin gene cluster. The reaction of $FADH_2$, Cl^-, and O_2 in the active site generates the oxidizing agent HOCl, as with PrnA, which then reacts with a lysine residue Lys79 in the active site to form a lysine chloramine (Lys-εNH-Cl) intermediate (Scheme 1.7b). It was shown that this covalent enzyme chloramine formed in the absence of tryptophan substrate and remained on the enzyme even after the removal of FAD. The identity of this intermediate was suggested by the X-ray crystal structure of RebH, which revealed an active site Lys79 located in a central position between flavin and tryptophan binding sites located 4.1 Å above the C7 position of tryptophan.

Scheme 1.7a[39]



Scheme 1.7b[144]



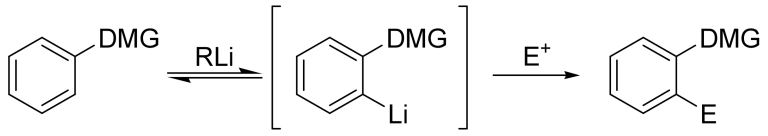
It should be noted that although flavin-dependent enzymes appear to be ubiquitous, mechanistic and crystallographic studies are still quite limited.

1.2 Synthetic Methodology

1.2.1 The Directed *ortho* Metalation (D*o*M) Reaction

Many modern synthetic targets of interest for pharmaceutical and agrochemical preparations require regiospecific construction of polysubstituted aromatic or heteroaromatic components.[40] In cases where contiguously substituted systems (1,2,3-, and 1,2,3,4-) are sought after, a powerful synthetic protocol for the synthetic chemist is the D*o*M reaction, discovered in 1939-1940 by Wittig[41, 42] and Gilman.[43] The reaction involves deprotonation of an aromatic substrate **1.10** at a site *ortho* to a heteroatom-containing directed metalation group (DMG) by a strong base, such as alkyllithium, phenyllithium[44], or lithium amides[45], yielding a lithiated intermediate **1.11**. Subsequent treatment with electrophilic reagents yields *ortho*-substituted products **1.12** (Scheme 1.8).

Scheme 1.8[46]



1.10 **1.11** **1.12**

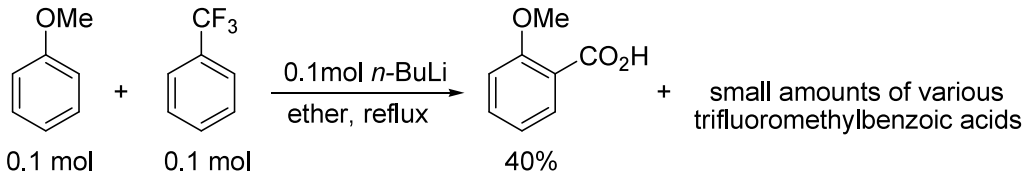
DMG = Cl, Br, I, NR_2, F, CO_2Li, SO_2NR_2, $CONR_2$, $OCONR_2$, $OPO(NEt_2)_2$

1.2.1.1 Mechanism of the D*o*M Reaction

Roberts and Curtin[47] pioneered mechanistic studies of the D*o*M reaction with their studies on the metalation of benzotrifluoride. In their work, a competitive metalation experiment was carried out in which a 1:1 mixture of benzotrifluoride and anisole were subjected to metalation

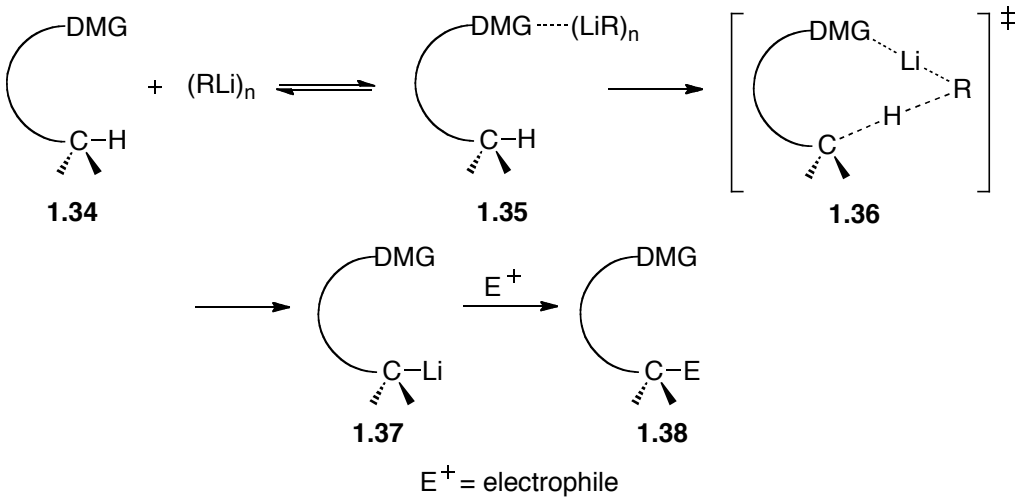
conditions (i.e., *n*-BuLi, ether, reflux) with subsequent carboxylation (Scheme 1.9).[47] They found products consistent with almost exclusive *ortho* metalation of the anisole. From this finding, they proposed that the product distribution was due to the greater activating ability of the methoxyl substituent on the benzene nucleus of anisole compared to that of the trifluoromethyl group of benzotrifluoride, that is, the inductive effect of the methoxyl group caused a greater increase in acidity of the ring hydrogens. Furthermore, and more importantly, they rationalized that the regioselectivity of the metalation could be accounted for by an initial coordination of the metallic atom (i.e., Li) of the metalating agent with a lone pair on the directing group (i.e., –OMe). This coordination step was thought to aid the reaction in two ways: (i) by increasing the polarization of the C-Li bond of the metalating agent (e.g., *n*-BuLi), and (ii) by enhancing the inductive effect of the DMG on the substrate. Eventually, this mechanistic hypothesis came to be known as the complex induced proximity effect (CIPE), whereby the formation of a prelithiation complex brings reactive groups into proximity for directed deprotonation.[48, 49]

Scheme 1.9[47]



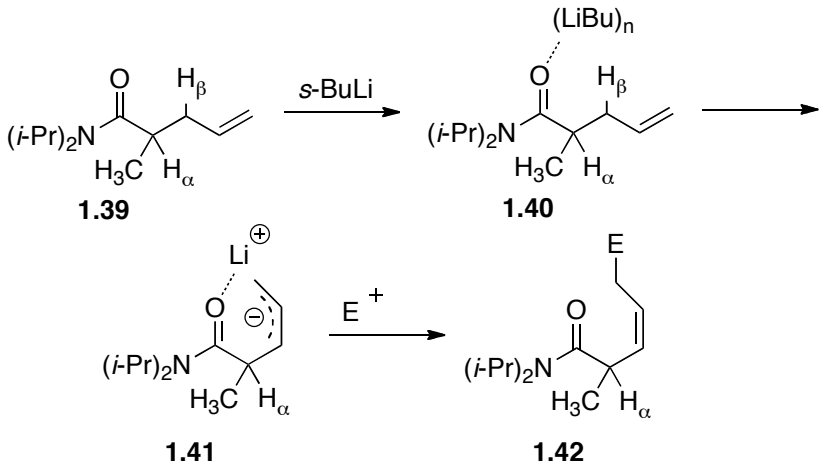
A general CIPE for a lithiation/substitution sequence is shown in Scheme 1.10.[50] The complex **1.35** is provided after association of **1.34** with an organolithium reagent. Subsequent directed lithiation of **1.35** via **1.36** leads to **1.37**, which can react with an electrophile (E^+) to provide **1.38**.

Scheme 1.10[50]



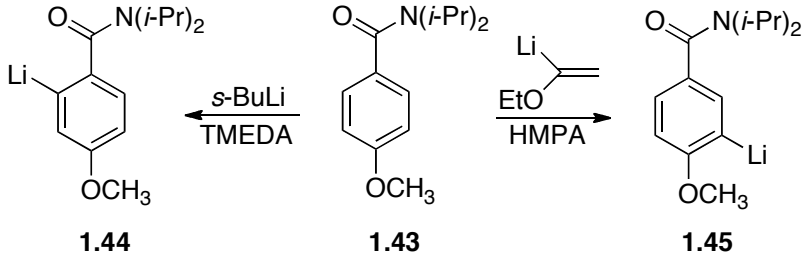
A clear demonstration of dominance by a CIPE process is the β-lithiation of γ,δ-unsaturated tertiary amides. In their work, Beak and Meyers[51] showed that the reaction of **1.39** with *s*-BuLi to give **1.42** required kinetic removal of the β-proton in the presence of the much more acidic α-proton (Scheme 1.11). It was shown using control and isotopic substitution experiments that no α-deprotonation or dianion formation was involved in this reaction, contrary to what resonance and inductive effects would predict. Thus, the observed loss of a β-proton indicates regiocontrol by a CIPE process.

Scheme 1.11[51]



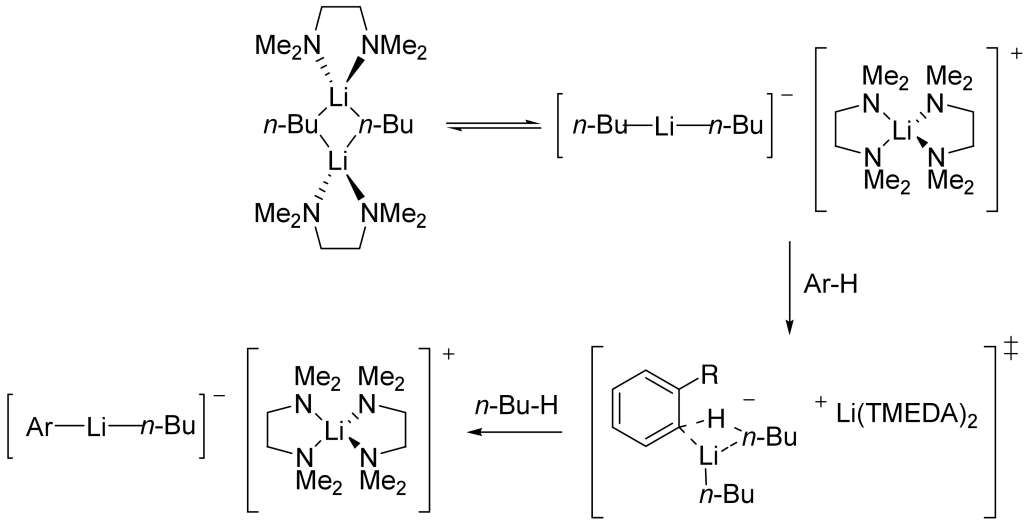
By altering the balance of inductive and association effects, CIPE can provide remarkable regioselectivity in D*o*M reactions. For example, Shimano and Meyers[52] showed that the directed lithiation of **1.43** with *s*-BuLi·TMEDA provided lithiation at the position *ortho* to the strongly complexing carboxamide, yielding **1.44**. Alternatively, when lithiation of **1.43** was performed using a precoordinated α-ethoxyvinyllithium (EVL) / hexamethylphosphoramide (HMPA) complex, coordination to the carboxamide was inhibited leaving the strong inductive effect of the methoxy group to drive the reaction towards **1.45** (Scheme 1.12).[50] This latter example supports a mechanism for D*o*M which is driven solely by inductive effects.[53, 54]

Scheme 1.12[50]



Schlosser and co-workers have thoroughly examined and supported the importance of inductive effects as the driving force in D*o*M reactions.[55] Using Schlosser's work as a platform, Collum and colleagues determined rate laws for the *n*-BuLi/TMEDA-mediated ortholithiations of a variety of alkoxy-substituted arenes and provided evidence for a common mechanism entailing *n*-BuLi dimers.[54] They proposed a triple-ion-based model (Scheme 1.13) that depended largely upon inductive effects. Using this model, *ab initio* calculations afforded strong theory-experimental correlations. In fact, the calculations suggested that orienting the oxygen lone pairs of the alkoxy moiety (e.g. R = OMe) towards the lithium was marginally stabilizing at best and may actually have been destabilizing, which did not support a mechanism relying on CIPE processes. However, it was noted that extrapolating these results to other classes of ortholithiation should be done with caution, especially when strongly coordinating substituents such as carboxamides are involved.

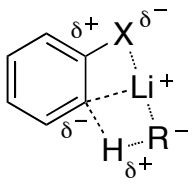
Scheme 1.13[54]



Schleyer and colleagues[56] proposed a third mechanism for the D*o*M reaction known as "kinetically enhanced metalation" (KEM), which emphasizes that the directing and activating

effects of electronegative substituents are transition-state phenomena. *Ab initio* calculations of the mechanism for lithium hydride-mediated metalation of benzene, phenol, and fluorobenzene were not in agreement with a pre-equilibrium complexation, but instead suggested that complexation and proton abstraction occurred in a single step. In this mechanism, electronegative *ortho* substituents are believed to stabilize the transition states for aromatic lithiation in two ways: (i) an electrostatically favorable arrangement of charges is provided (Scheme 1.14), and (ii) through strong coordination of lithium to electron-rich substituents (*e.g.* O–Li, and F–Li). With these two effects working in combination, the activation energy is decreased substantially. It appears that this combination of effects adequately explains the strong preference for *ortho* metalations and other regioselective metalations (i.e., CIPE processes).[51]

Scheme 1.14[56]



1.2.1.2 Directed Metalation Groups (DMGs)

DMGs are typically classified as either carbon-based or heteroatom-based, according to the DMG atom directly connected to the aromatic ring. A variety of DMGs are available to the synthetic chemist, each with different degrees of synthetic utility, and most importantly, lability under acidic conditions. Since DMGs are designed to endure strong basic conditions, they are usually removed in acidic media, but some DMGs require harsher removal conditions to which functional groups may be sensitive. For this reason, DMGs with mild hydrolytic lability such as cumyl amide,[57] *N*-silyl-protected *O*-aryl-*N*-monoalkylcarbamate,[58] and sulfonamide[57] can be useful synthetic tools.

Some of the most noteworthy DMGs, in terms of metalation power and synthetic utility, are the tertiary amide,[59] *O*-carbamate,[60] tertiary sulphonamide,[50] and the oxazoline.[61] Some of the weaker DMGs are *tert*-butoxycarbonyl (Boc), pivaloyl (Piv), diethylamine, and halogen atoms, as depicted in Figure 1.2.

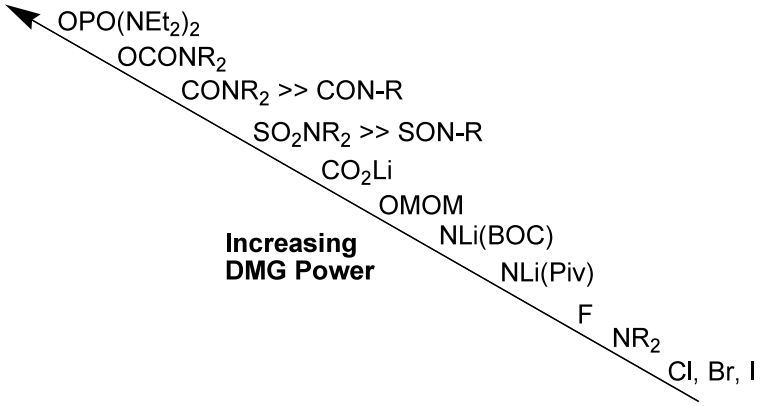


Figure 1.2: Hierarchy of DMGs

1.2.1.3 Cooperative Metalation Effects

A noteworthy feature of the D*o*M reaction is the cooperative effect of 1,3-interrelated DMGs in promoting metalation at their common site (Scheme 1.15). By exploiting this effect, it is possible to prepare contiguously substituted aromatic systems that may otherwise be difficult to obtain. A variety of reactions involving the metalation of 1,3-disubsituted benzenes followed by electrophile quench are shown in Table 1.1.[46]

Scheme 1.15

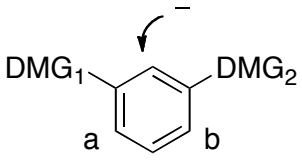
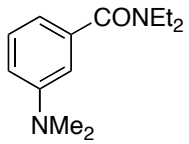
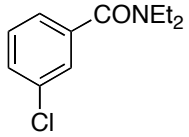
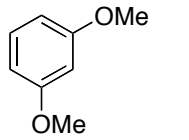
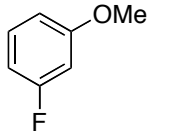
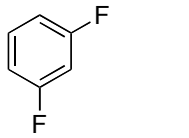


Table 1.1[46]

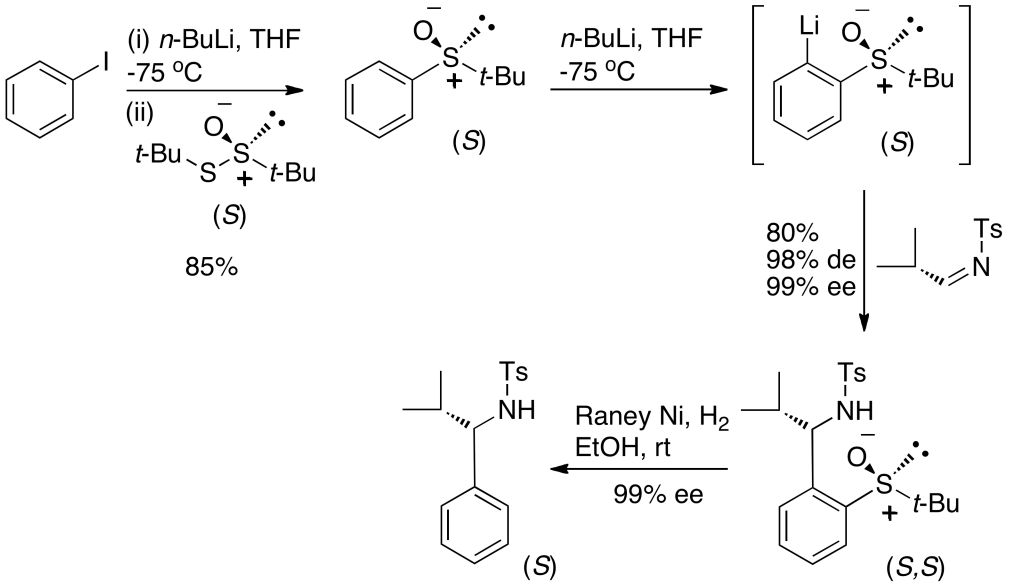
entry	substrate	metalation conditions	electrophile	yield, %
1		*sec*-BuLi/TMEDA/THF/-78 °C	PhCHO	77-79
2		*sec*-BuLi/TMEDA/THF/-78 °C	MeOD	80
3		*n*-BuLi/Et_2O/+35 to -78 °C	$Me_2CHCOCl$	78
4		*n*-BuLi/THF/-65 °C	$B(OMe)_3/H_2O_2$/HOAc	53
5		*n*-BuLi/THF/-65 °C	CO_2	88

Of the entries shown, it is interesting to note that metalation and subsequent electrophile quench of the substrate in entry 1 occurred readily, providing the 1,2,3-trisubstituted product in 77-79% yield, despite the steric bulk around the common site and the use of a bulky base. Under the same conditions, metalation of the substrate in entry 2 provided almost the same yield even though there was less steric hindrance around the common site. Both the methoxy and fluoro DMGs also proved to be quite effective in directing metalation to the common site, with the best yield (88%) obtained when using 1,3-difluorobenzene.

1.2.1.4 Scope of D*o*M Chemistry

Directed *ortho* metalation has been applied to the synthesis of enantiopure aromatic (phenyl, naphthyl) and heteroaromatic (pyridyl, quinolyl, diazinyl) sulfoxides, as shown in the work of Fur et al.[62] For example, they reacted iodobenzene with *n*-BuLi followed by quench with (*S*)-*tert*-butyl *tert*-butanethiosulfoxide to yield the enatiopure sulfoxide in 85% yield (Scheme 1.16).[62] Subsequent D*o*M of the sulfoxide followed by quench with *N*-tosylimine afforded the enantiopure aromatic sulfoxide in 80% yield with 99% ee. Removal of the sulfoxide group was afforded by hydrogenation with Raney nickel.

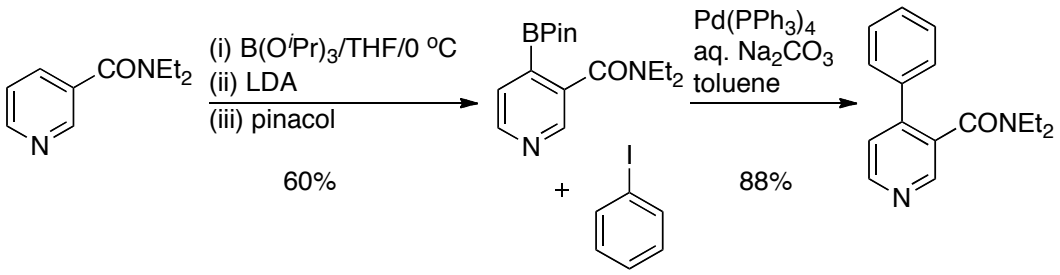
Scheme 1.16[62]



The application of D*o*M in combination with Sukuzki-Miyaura cross-coupling (see Section 1.2.3) for the synthesis of complex natural and non-natural products has been demonstrated in the work of Snieckus and co-workers.[63] For example, in their one-pot procedure for the synthesis of azabiaryls, Snieckus and co-workers used a D*o*M-boronation-Suzuki-Miyaura cross-coupling sequence. In Scheme 1.17, a DMG-bearing pyridine is subjected to the *in situ*

LDA-B(O^iPr)$_3$ procedure and the resulting boronate intermediate is isolated as the pinacolate compound. Subsequent application of standard Suzuki-Miyaura conditions on the isolated nicotinamide pinacolboronate proceeded smoothly to give the product azabiaryl in 88% yield.

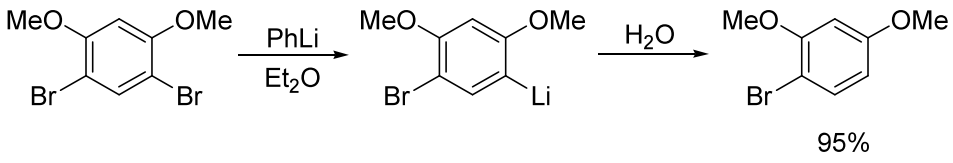
Scheme 1.17[63]



1.2.2 Lithium-Halogen Exchange

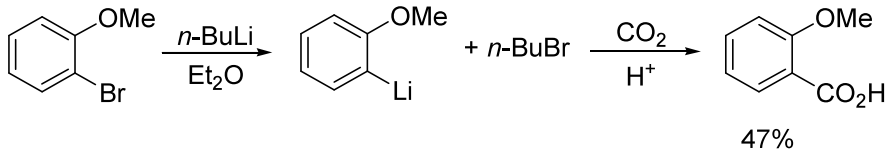
As early as 1927, there were reports of lithium-halogen exchange reactions in which treatment of an aryl halide with an alkyllithium reagent (*e.g.*, *n*-BuLi), followed by quench with a proton source, gave dehalogenated product.[64] However, no documented attempts were made to exploit this reaction until the work of Wittig and co-workers in 1938.[41] In their seminal work, Wittig and co-workers[41] described the treatment of 4,6-dibromo-1,3-dimethoxybenzene with phenyllithium (PhLi) in diethyl ether to produce 4-bromo-1,3-dimethoxybenzene in 95% yield after hydrolysis (Scheme 1.18). It was concluded that the monobromide product could only have been produced via a lithiated intermediate.

Scheme 1.18[41]



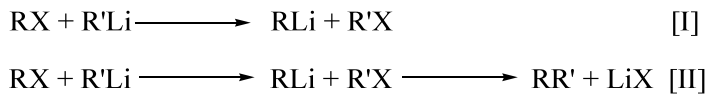
The introduction of a carboxyl group onto a phenyl ring via lithium-halogen exchange was later reported by Gilman.[43] In this reaction, *n*-BuLi was added to a solution of *o*-bromoanisole in diethyl ether, followed by carboxylation and subsequent proton quench (Scheme 1.19). It was postulated that the existence of an *o*-lithioanisole intermediate, derived from lithium-bromine exchange, was necessary for product formation.

Scheme 1.19[43]



The early observations of Gilman on lithium-halogen (Li-X) exchange provide a generalized guide to understanding the reaction. Some of his observations were as follows: (i) aryl fluorides do not undergo exchange,[65] (ii) the rates of exchange of aryl halides decrease in the order of I>Br>Cl,[66] and (iii) exchange is a reversible process leading to an equilibrium mixture favoring the more stable organolithium.[67] Gilman and colleagues[66] stated that two competing reactions exist in solution: metal-halogen exchanges [I], and Wurtz-type couplings [II] (Scheme 1.20).[66]

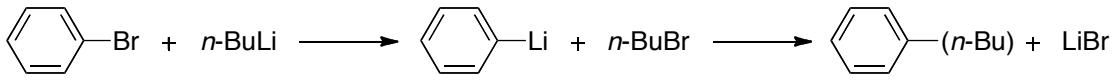
Scheme 1.20[66]



When the reaction is between aryl halides and alkyllithium compounds, the latter reaction, [II], is slower, and follows the exchange reaction, [I]. However, if the reaction is not quenched with electrophile (E^+) soon enough, reaction [II] predominates and essentially consumes all the

RLi. For example, the treatment of bromobenzene with *n*-BuLi produces *n*-butyl bromide that will eventually react with the phenyllithium to give *n*-butylbenzene (Scheme 1.21).[65]

Scheme 1.21[65]



In this example, the coupling reaction of an alkyl halide with an aryllithium compound is faster than the coupling reaction of an aryl halide with an alkyllithium compound. However, this reaction pathway can be made highly unfavorable under properly controlled experimental conditions.[66]

1.2.2.1 Mechanism of Lithium-Halogen Exchange

A complicating factor in the study of the mechanism of Li-X exchange is that most organolithium compounds exist as aggregates in solution, although choice of reaction solvent (*e.g.*, tetrahydrofuran, THF) or addition of chelating ligands (*e.g.*, tetramethylethylenediamine, TMEDA) can often minimize the degree of aggregation.[68] It is believed that a lower degree of association provides a more reactive organolithium species, but difficulty in identifying the active organolithium species has made this subject to controversy. For example, McGarrity and co-workers[49] claimed that dimers are the most reactive species, at least when *n*-BuLi is employed, while Waack and Doran[69] provided evidence that monomers are the most reactive. The nature of the organolithium species (*i.e.*, monomer, dimer, tetramer, etc.) in solution needs to be considered when studying the reaction of an organolithium with a substrate. However, the difficulty in obtaining such data, even for simple systems, has resulted in a lacking number of studies that unambiguously demonstrate the relationship between organolithium association and observed reactivity. It is often convenient when describing proposed mechanisms of Li-X exchange to

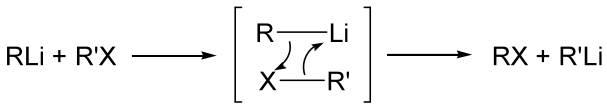
depict organolithiums as monomeric species [*e.g.*, RLi or $(RLi)_n$] for the sake of pictoral clarity. This convention shall be used in the schemes that follow, but should not be taken to imply the actual structure of the reagents.

The mechanism of Li-X exchange has been described by three principal mechanistic schemes: (1) the four-center transition state model; (2) radical-mediated mechanisms; and (3) nucelophilic attack on halogen.

1.2.2.1.1 Four-Center Transition State Model

In their study of the reaction between phenyllithium (PhLi) and allyl chloride, Magid and Welch[70] found that it followed second-order kinetics (first order in each component), which suggested a concerted mechanism. Studies on the reaction of organolithiums with bromo-,[71] and iodobenzene[72] also supported such a mechanism. A concerted process, with a four-center transition state is depicted in Scheme 1.22.[73]

Scheme 1.22[73]

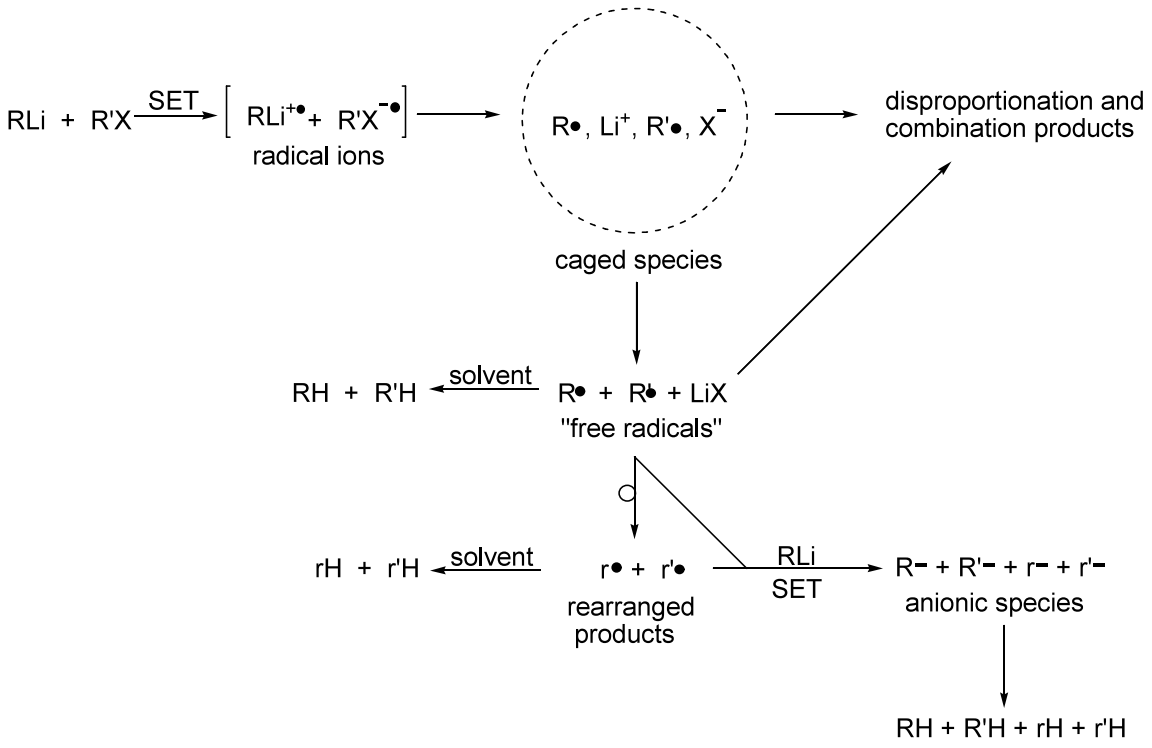


This model involves a "head-to-tail" association of RLi and R'X followed by concerted bond-breaking and bond-making. Rather than providing a mechanistic pathway, this model serves as more of a description of the reaction. Thus, although this model is often used to illustrate the metal-halogen exchange reaction, there is sparse direct evidence to support such a mechanism.

1.2.2.1.2 Radical-Mediated Mechanisms

It is generally accepted that radicals produced in organometallic processes are mediated by mechanisms involving single-electron transfer (SET). For example, when SET from an organolithium compound (RLi) to an organohalide (R'X) occurs, a radical-cation ($RLi^{+\bullet}$) and a radical-anion ($R'X^{-\bullet}$) form within the solvent cage (Scheme 1.23).[73] These species can then follow one of two pathways: (i) within the solvent cage, loss of Li^+ and X^- occurs resulting in two carbon-centered radicals which may undergo combination and/or disproportionation; (ii) diffusion of the radical ions from the solvent cage followed by loss of Li^+ and X^-, yielding highly reactive carbon-centered "free radicals" available for a variety of reactions. Some radicals may even undergo skeletal rearrangements, either within the solvent cage prior to combination and/or disproportionation or as "free radicals." The rearranged and unrearranged species may both lose radical character by hydrogen atom abstraction from the solvent or by reduction to carbanions by SET from the organolithium reagent. The newly formed carbanions may then react with a suitable electrophile, such as a proton.

Scheme 1.23[73]

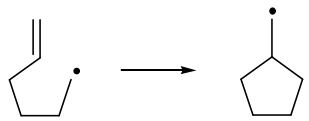


Direct evidence for the involvement of radical species in Li-X exchange reactions can be demonstrated using electron-spin resonance (ESR) spectroscopy and/or radical probes. For example, Fischer[74] used ESR spectroscopy to study the reactions of several alkyl halides with a variety of organolithiums and found that the reactions of alkyl halides with 2^o and 3^o alkyllithiums generated radical intermediates. No radicals were observed in reactions of 1^o alkyllithiums or PhLi with alkyl halides.[74] However, using ESR spectroscopy, Russell and Lamson[75] were able to detect radicals in the reactions of *n*-BuLi, a 1^o alkyllithium, with various alkyl bromides and iodides when the ratio of Et_2O (solvent) to TMEDA was one-to-one.

Although the generation of radicals in Li-X exchange reactions was demonstrated by these ESR studies, the data did not, however, clearly reveal the involvement of radicals as intermediates in these processes.

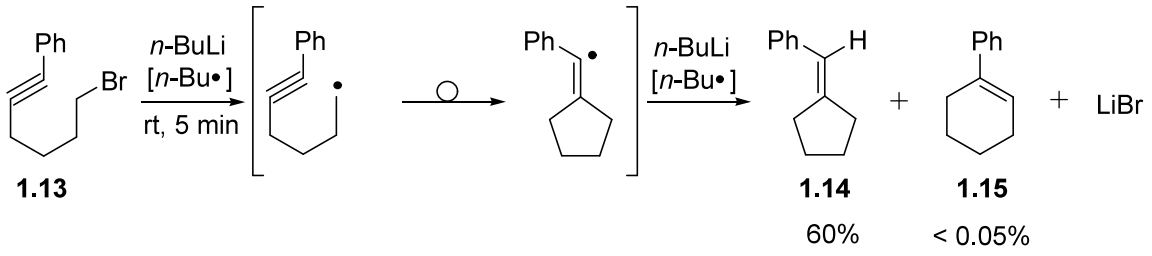
Radical probes—species that, when converted to a radical during a reaction, undergo a characteristic intramolecular rearrangement—have also been used to provide support for the existence of radical intermediates in Li-X exchange reactions.[76] Cyclizable probes, such as the 5-hexen-1-yl radical (Scheme 1.24),[73] were first used in 1967 by Ward[77] to study Li-X exchange.

Scheme 1.24[73]



In his work,[77] Ward treated 6-bromo-1-phenyl-1-hexyne (**1.13** in Scheme 1.25) in a 5:1 mixture of hexane–ether with excess *n*-butyllithium. Following aqueous quench, benzylidene-cyclopentane **1.14** was found in 60% yield along with coupling, reduction, and elimination products. The alternative cyclization product, 1-phenylcyclohexene **1.15**, if formed at all, was present in less than 0.05%.

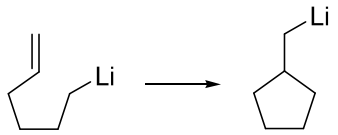
Scheme 1.25



The use of radical probes in mechanistic studies of organometallic reactions is often, however, fraught with difficulties. In the study of Li-X exchange, the product alkyllithium may be capable of a rearrangement that mimics that of a radical, and anionic rearrangement may thus lead to non-negligible quantities of isomerized product. For example, 5-hexen-1-yllithium undergoes isomerization analogous to that of the 5-hexen-1-yl radical at a rate that is a strong

function of temperature (Scheme 1.26)[78]: the alkenyllithium is indefinitely stable at T ≤ -78 °C, but undergoes rapid cyclization at higher temperatures (*e.g.*, at 23 °C, $t_{1/2}$ = 5.5 min)[78]

Scheme 1.26[78]

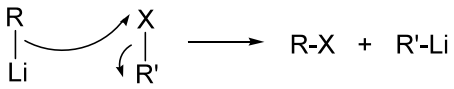


The fact that some so-called radical probes can form rearranged products via lithiated intermediates demonstrates that the observation of rearranged products is not, in itself, sufficient evidence to implicate the involvement of radical intermediates in Li-X reactions. To firmly establish the existence of radical intermediates, it must be shown that, under the conditions of the study, the carbanionic species cannot undergo the same rearrangement as the corresponding radical species to give rearranged products. When this can be done, product analysis alone may allow the identification of those species which were derived from radicals in a complex reaction mixture.

1.2.2.1.3 Nucleophilic Mechanisms

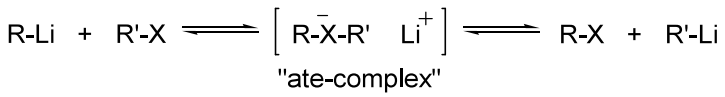
Sunthankar and Gilman[79] were the first to propose a mechanism for Li-X exchange, in which the organolithium reagent nucleophilically attacks the halogen of the organic halide. This was an unusual mechanistic suggestion, in that it involved a carbanionic leaving group (Scheme 1.27).[73]

Scheme 1.27



This process may come as surprising since it is normally expected that, in nucleophilic reactions, attack should occur at carbon with subsequent loss of a halogen leaving group. In their studies, Wittig and Schöllkopf[80] postulated that such a mechanism may reversibly proceed through an "ate-complex" intermediate (Scheme 1.28).[80]

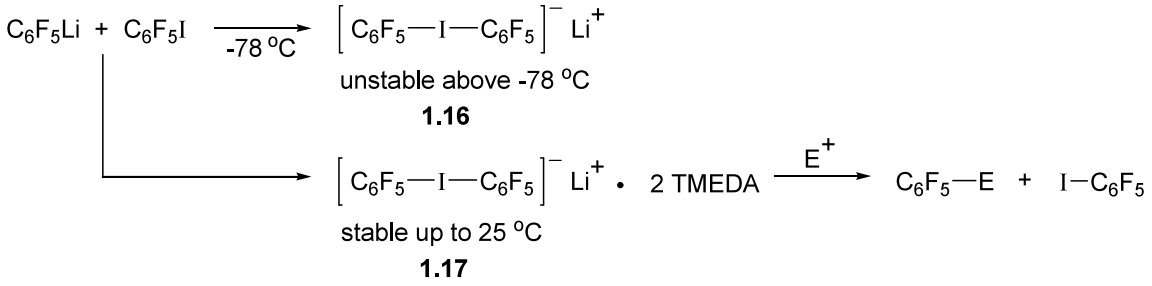
Scheme 1.28[80]



A number of researchers have since presented evidence for the intermediacy of an "ate-complex" in Li-X exchange reactions.[81, 82] In fact, Farnham and Calabrese[82] were able to isolate and provide structural characterization for a hypervalent iodine species which served as a model for the Li-X exchange "ate-complex" intermediate. In their work, treatment of (pentafluorophenyl)lithium with 1 equivalent of pentafluorophenyl iodide at -78 ^{o}C resulted in the unstable lithium bis(pentafluorophenyl)iodinanide. The lithium salt of this anion (**1.16**, Scheme 1.29)[82] was isolated at -78 ^{o}C, but underwent vigorous exothermic decomposition at higher temperatures. A more stable, complexed lithium salt **1.17**,[82] which was isolable under an inert atmosphere at room temperature, was generated by the addition of 2 equiv of TMEDA to the complex at -78 ^{o}C. This complex was not stable in solution at room temperature, but suitable crystals for single-crystal X-ray diffraction analysis were grown by dissolving the complex in ether at 25 ^{o}C, followed by rapid cooling to -20 to -30 ^{o}C. X-ray diffraction analysis of **1.17** revealed a nearly linear C-I-C angle of 175^{o} as well as long carbon-iodine bond distances, which corresponded with a hypervalent 10-I-2 system. Each lithium ion was shown to be coordinated by two TMEDA molecules, as expected. The ability of this complex to react with electrophiles was also

demonstrated, whereby **1.17** was found to deliver a nucleophilic C_6F_5 along with equimolar quantities of pentafluorophenyl iodide.

Scheme 1.29[82]



1.2.3 Palladium-Catalyzed Cross-Coupling Reactions of Organo-boron Compounds: The Suzuki-Miyaura Reaction

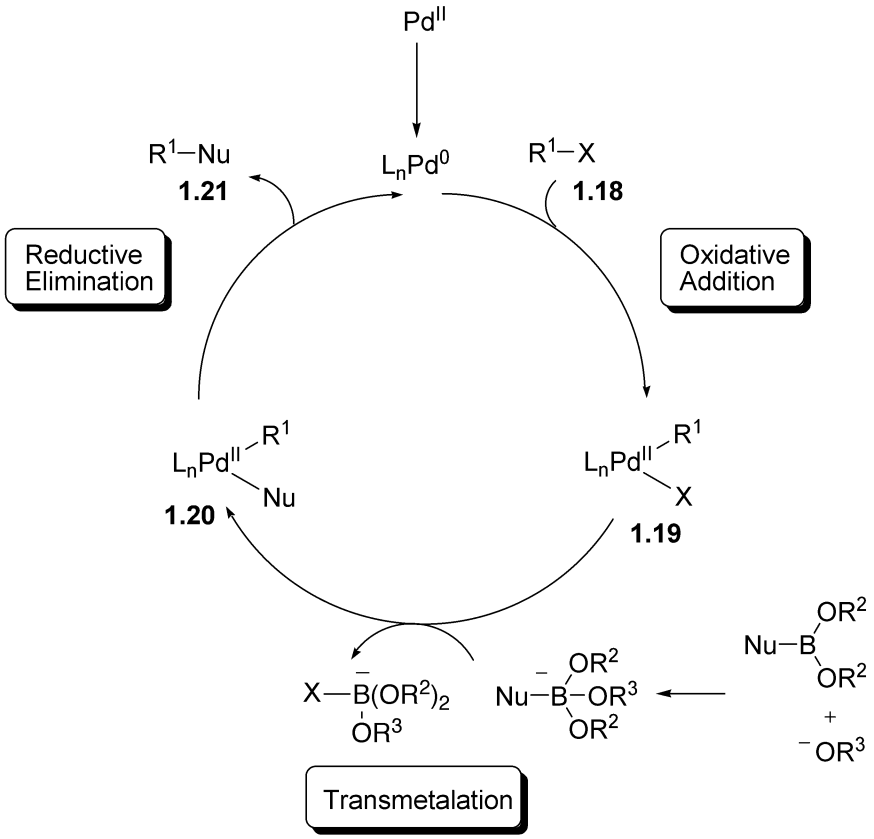
Since the 1970s, when cross-coupling reactions employing various organometallic nucleophiles were first described,[83] many nucleophilic reagents have proven to be highly useful for the cross-coupling reaction, e.g., organolithiums by Murahashi,[84] organostannans by Migita[85] and Stille,[86] and organosilicon compounds by Hiyama.[87] The Suzuki-Miyaura cross-coupling reaction in particular utilizes highly electrophilic organoboron compounds, but the organic groups on boron are weakly nucleophilic and require coordination of a negatively charged base to the boron atom. This pre-coordination step, however, is known to sufficiently increase the nucleophilicity of the organic group on boron.

Organoboron reagents such as organoboronic acids and esters have sufficiently enough reactivity for the transmetalation to other metals. Though transmetalations to metals such as silver(I),[88] magnesium(II),[84] zinc(II),[89] aluminum(II),[90] tin(IV),[91] copper(I),[92] and mercury(II)[93] halides have much precedent in the literature, palladium(II)[94] is the metal-of-choice in the Suzuki-Miyaura cross-coupling reaction. When activated with suitable bases, organoboron reagents thus

undergo cross-coupling reactions via transmetalation to palladium(II) halides (or triflates) and have been proven to be a general technique for a wide range of selective carbon-carbon bond formation.[95] The main advantages to organoboron compounds over other organometallic nucleophiles is that they are generally thermally stable and inert to water and oxygen, which allows for their handling without special precautions. For purification, the boronic esters can be isolated by distillation and the acids, by crystallization. Alternatively, the pinacol esters of boronic acids may be isolated by flash chromatography over silica gel.[96]

There are many processes involved in cross-coupling reactions of organometallics, some of which are less understood (*i.e.* ligand exchanges), but a general catalytic cycle involving oxidative addition–transmetalation–reductive elimination sequences gives a basic outline of the processes involved (Scheme 1.30).[94]

Scheme 1.30



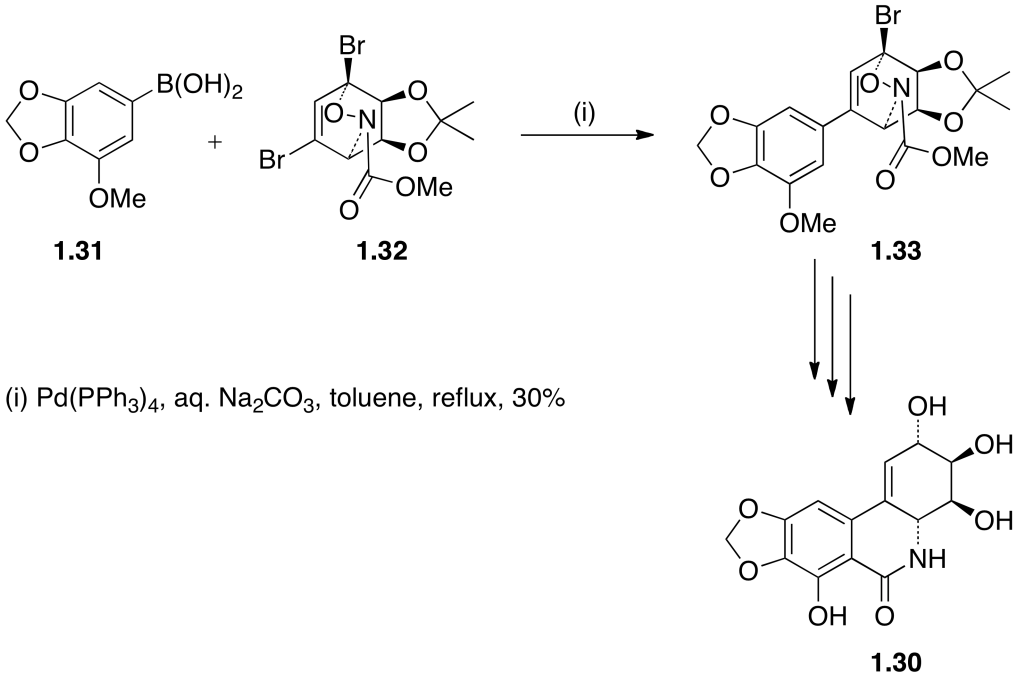
The active catalyst, which is thought to be a Pd(0) species, undergoes oxidative addition with the organoelectrophile **1.18** to yield a stable *trans*-σ-Pd(II) complex **1.19**. In the transmetalation step, the base is used to increase polarizability of the C-B bond, forming a more active nucleophilic species which attacks palladium leading to formation of complex **1.20**. After reductive elimination, the product **1.21** is produced along with regenerated Pd(0) catalyst.

In most cases, the oxidative addition step is rate-limiting, and the relative reactivity for organoelectrophiles is as follows: I > OTf > Br >> Cl.[94] Commonly used palladium catalysts are $Pd(PPH_3)_4$, $PdCl_2(PPh_3)_2$, or $Pd(OAc)_2$ with a variety of different phosphine ligands.[97]

1.2.3.1 Application to Natural Product Synthesis

The Suzuki-Miyaura cross-coupling reaction has found wide application in the synthesis of natural products, non-natural products, and other bioactive compounds. For example, Hudlicky and co-workers[98] have reported a synthesis of the antitumour alkaloid, narciclasin **(1.30**, Scheme 1.31), in which they used Pd-catalyzed cross-coupling of the dibromo compound **1.31** and boronic acid **1.32** to give the key intermediate **1.33**. After subsequent transformations, they obtained **1.30** in 20% overall yield (30% yield for the coupling step).

Scheme 1.31[98]



1.31 **1.32** **1.33**

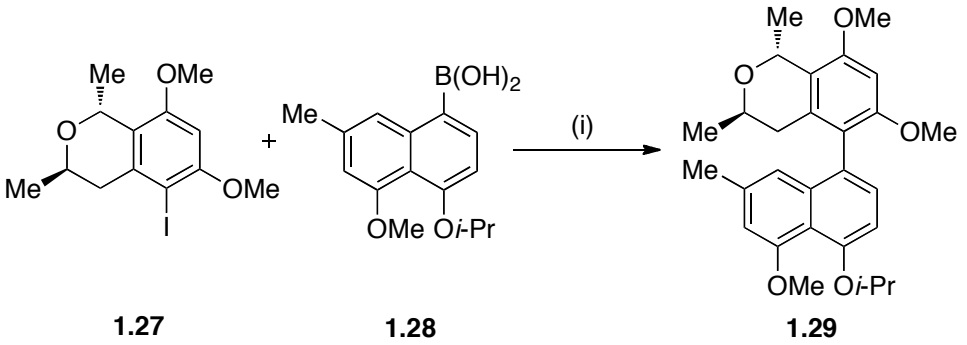
(i) $Pd(PPh_3)_4$, aq. Na_2CO_3, toluene, reflux, 30%

1.30

Dawson et al.[99] have reported the stereospecific preparation of the anti-HIV compounds michellamine A and C via a Suzuki-Miyaura cross-coupling reaction. In a similar way, de Koning and co-workers were able to synthesize an isochroman analogue (**1.26**, Scheme 1.32) of

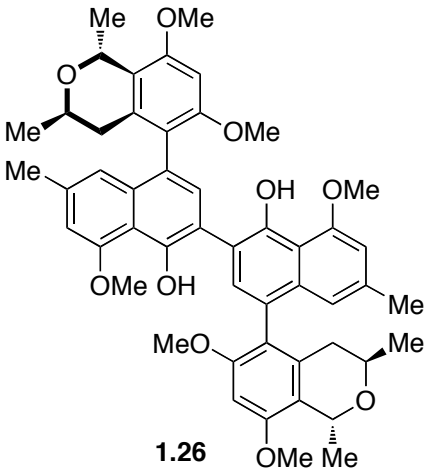
michellamines by using the $Pd(PPh_3)_4$-catalyzed cross-coupling reaction of 5-iodo-6,8-dimethoxy-1,3-trans-dimethylisochroman **1.27** with the appropriate naphthaleneboronic acid **1.28** to give **1.29** followed by further transformations.

Scheme 1.32[99]



1.27 **1.28** **1.29**

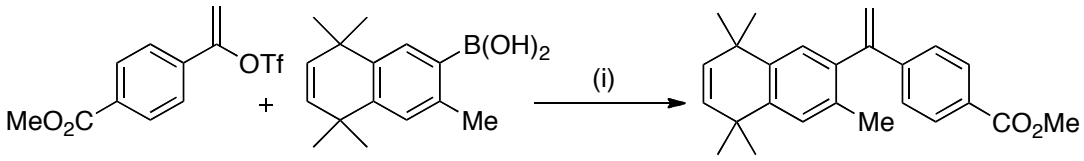
(i) $Pd(PPh_3)_4$, K_3PO_4, DMF, 100 °C, 85%



1.26

Medically important compounds such as retinoid receptor ligands—useful for their structural similarity with vitamin A—have also been synthesized using Suzuki-Miyaura cross-coupling. Faul and co-workers[100] have reported the synthesis of these compounds by the cross-coupling reaction as shown in Scheme 1.33.

Scheme 1.33[100]

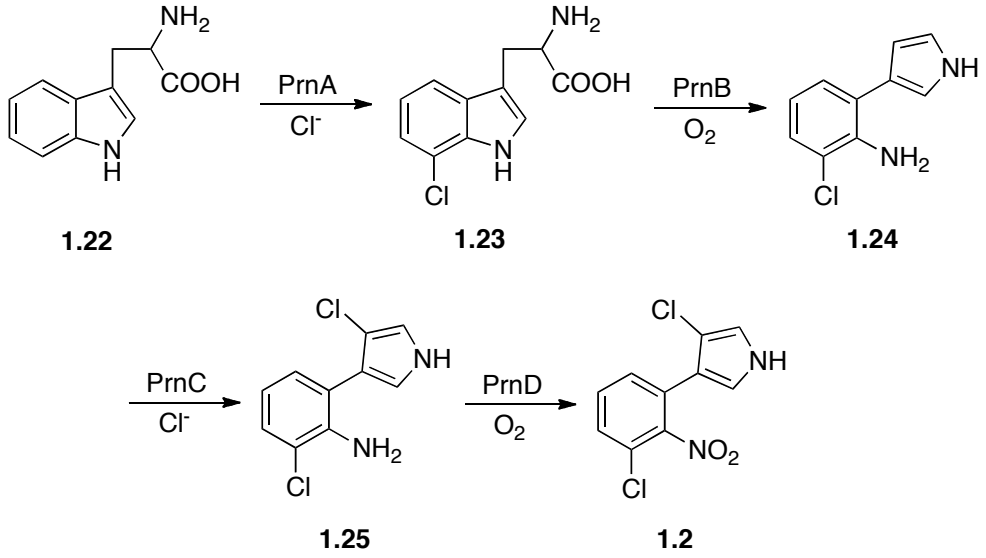


(i) $Pd(OAc)_2$, P(*o*-tol)$_3$, DMF, Et_3N, 50 °C, 81%

1.3 Outline of Research Project

Of the two relatively newly discovered classes of halogenases, α-ketoglutarate-dependent and flavin-dependent, few have been fully characterized in terms of molecular structure and mechanism of halogenation. We were interested in the mechanisms of such enzymes from the viewpoint of organic chemists, whereby enzymatic transformations were able to deliver "unexpected" regioisomers that would otherwise not be obtainable by standard methods in organic synthesis. For example, in the biosynthesis of pyrrolnitrin **1.2** two chlorination steps by the enzymes PrnA and PrnC place chlorine atoms in unusual positions (Scheme 1.34).[101] Chemical chlorination of **1.22** is not possible by standard chemical means, which makes the enzymatic chlorination of **1.22** by PrnA a specific and unusual reaction, although there are a number of naturally produced antibiotics that are derived from **1.23**.[102] Also, electrophilic addition of chlorine to the pyrrole ring of **1.24** would be expected to occur at one of the two available α positions, but PrnC allows the regioselective addition of chlorine to the less active β position.[3]

Scheme 1.34[101]



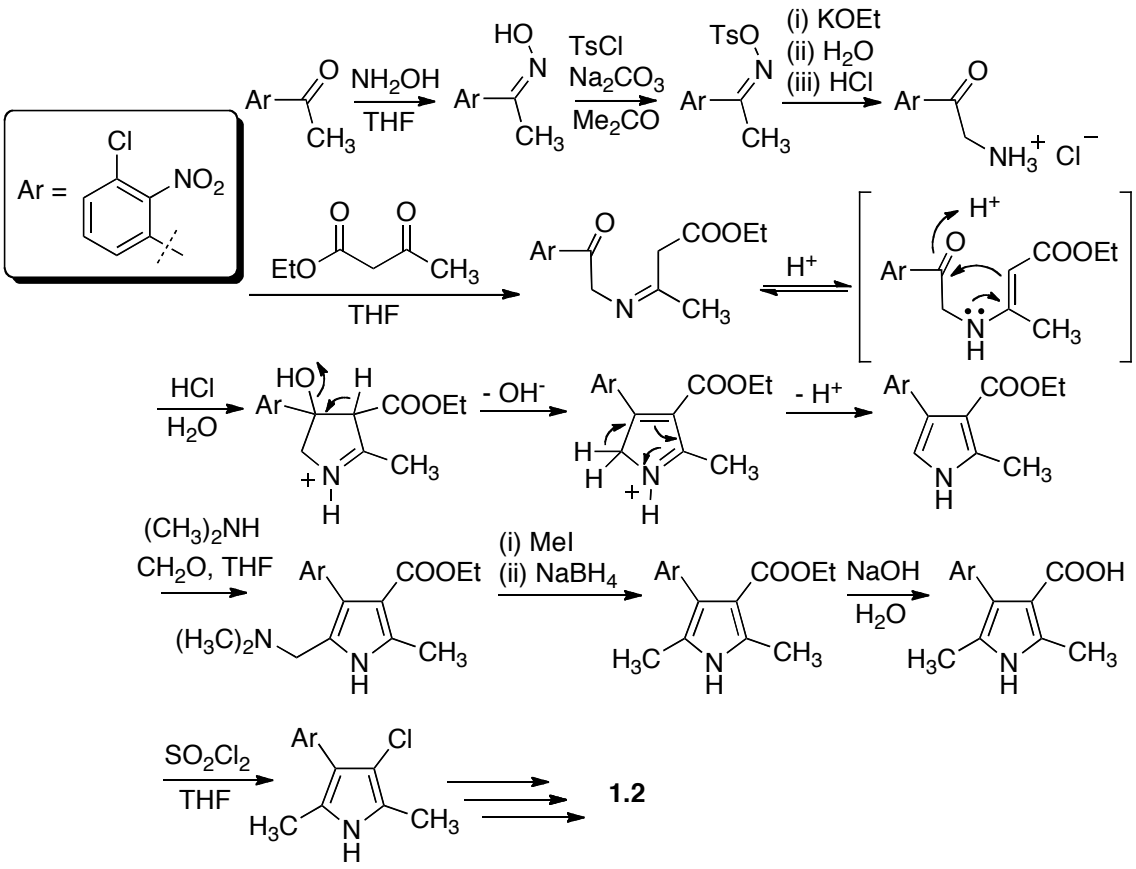
1.22 **1.23** **1.24**

1.25 **1.2**

In order to study the mechanisms of PrnC and the other pyrrolnitrin biosynthetic enzymes PrnB and PrnD (PrnA has been studied extensively[39]), we would require the putative biosynthetic products **1.23**, **1.24**, **1.25** and **1.2**, but there is a lack of commercial availability and documented chemical syntheses for these compounds in the literature. There have been, however, two reported total syntheses of **1.2**,[103] but they are cumbersome and rely upon *de novo* construction of the substituted pyrrole ring (see Scheme 1.35 and 1.36), thus precluding easy access to analog compounds that would be useful for mechanistic studies (e.g. brominated or deuterated analogs of **1.2**, **1.24** and **1.25**).

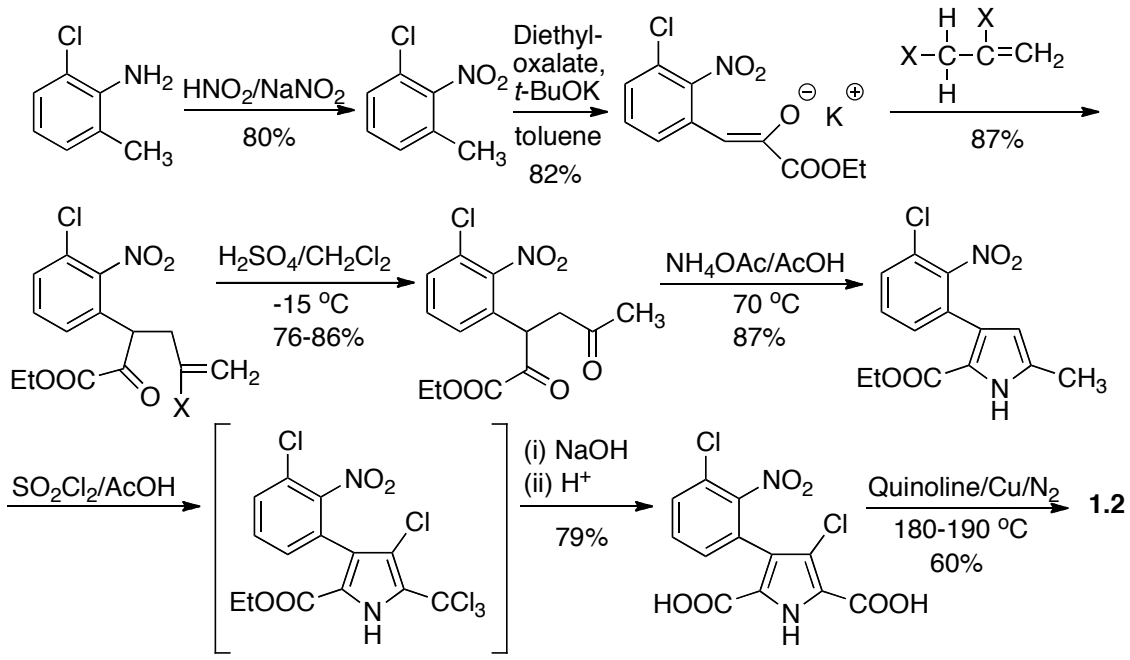
Scheme 1.35

Total Synthesis of **1.2** by Nakano et al.[134] (1966):



Scheme 1.36

Total Synthesis of **1.2** by Gosteli[135] (1972):



The two syntheses shown in Scheme 1.35 and Scheme 1.36 were designed for the preparation of **1.2** alone. Though it may be possible to synthesize compounds **1.24** and **1.25** via slightly modified versions of either method, the preparation of brominated and deuterated analogs would require starting from the earlier steps in either sequence (with the appropriate starting materials) due to the streamline nature of these protocols. Our objective for this project was to develop a more versatile synthetic approach to **1.2** which allowed for easier access to a variety of analog compounds to be used in mechanistic studies of PrnC (and PrnB and PrnD). To accomplish this, we proposed the following:

i) We will devise a synthesis to **1.2** involving Suzuki-Miyaura cross-coupling of an appropriately halogenated pyrrole pinacolboronate ester with an appropriately halogenated aryl halide (see Scheme 2.7).

ii) We will develop strategies towards our necessary pyrrole and aryl cross-coupling partners such that they could be easily modified to give brominated or deuterated analogs.

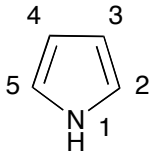
iii) We will use Suzuki-Miyaura cross-coupling to prepare analogs of **1.2**, **1.24** and **1.25**.

Chapter 2 – Syntheses of 3- and 3,4-Disubstituted Pyrroles

2.1 Background

In solution, pyrrole (**2.1**, Scheme 2.1) is known to undergo predominant or exclusive kinetic electrophilic substitution at the 2(α) position with most electrophilic reagents due to its electron-rich structure.[104, 105] Finding reliable and efficient procedures to functionalize the less readily accessible 3(β) position of pyrroles has thus been the objective of numerous investigations in the past.[106] 3-Substituted pyrroles can be useful in the synthesis of complex natural products (e.g. pyrrolnitrin, **1.2**), whereas synthetic routes towards such products have historically relied upon low-yielding ring closure reactions to generate the pyrrole ring (see Scheme 1.35). A variety of methods now exist for the preparation of 3-substituted pyrroles without reliance on the ring closure approach.[106]

Scheme 2.1

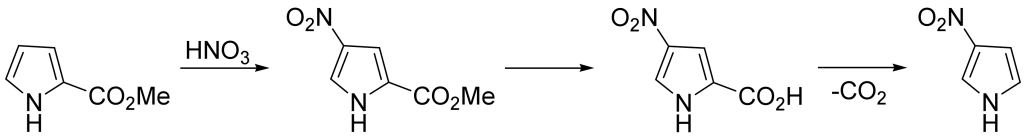


2.1

2.1.1 Direction by a Removable 2-Substituent

Dating back to as early as the 1930s, a systematic pathway existed for the preparation of a 3-substituted pyrrole from "naked" pyrrole.[107] In his work, Rinkes demonstrated that nitration of 2-acetylpyrrole, methyl pyrrole-2-carboxylate, pyrrole-2-carboxylic acid, and 2-nitropyrrole gave mixtures of the corresponding 4- and 5-nitro derivatives.[107] It was shown that more electron-withdrawing (i.e., *meta*-directing) substituents in the 2-position gave predominantly the 2,5-isomer while less electron-withdrawing groups gave mostly the 2,4-isomer. Preparation of 4-nitropyrrole-2-carboxylic acid (**2.4**, Scheme 2.2) from the methyl ester (**2.3**) followed by subsequent decarboxylation afforded 3-nitropyrrole (**2.5**), albeit in low yield. A pathway had thus been established for 3-substituted products.

Scheme 2.2[106]

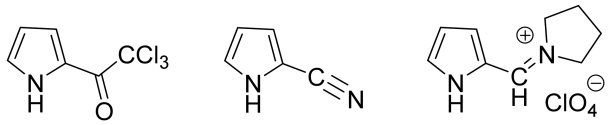


2.2 **2.3** **2.4** **2.5**

Further exploration of the introduction of removable directing groups into the 2-position and the subsequent substitution reactions of these compounds revealed that the best directing groups were acid or ester, cyano, formyl, acetyl, and trichloroacetyl derivatives. Investigation of the substitution reactions of this type of pyrrole derivative showed that a variety of 2,4-disubstituted compounds could be prepared in high yield with minimal 2,5-isomer formation.[106] It was evident that certain substrates were much less useful and versatile than others, with some giving low yields, and others unfavorable product mixtures. The most satisfactory results,

however, were obtained with the 2-trichloroacetyl (**2.6**, Scheme 2.3), 2-cyano- (**2.7**), and 2-azafulvenium salt (**2.8**) derivatives, which were each obtainable in good yield from pyrrole.[106]

Scheme 2.3



2.6 **2.7** **2.8**

To be synthetically useful, the directing group on pyrrole needed to be easily removed after the desired substitution reaction. Normally, directing groups that could be converted to the carboxylic acid were used, due to the facile decarboxylation reaction. For example, 4-substituted-2-trichloroacetyl derivatives may be easily converted to the corresponding 4-substituted-2-carboxylic acids and then decarboxylated to yield 3-substituted products. Other examples include 4-substituted-2-nitriles[108, 109] and 4-substituted-2-aldehydes,[110] which may both be converted to the corresponding acids in mediocre to excellent yields.

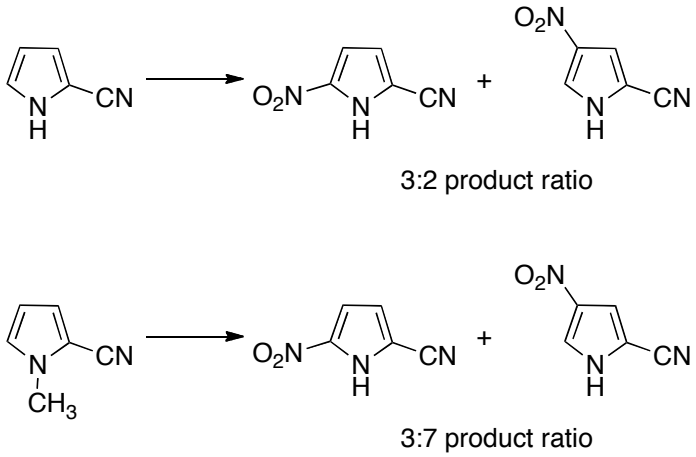
There are a variety of electron-withdrawing groups that may be installed in the 2-position of pyrrole, but these reactions suffer from poor yields, and some directing groups are not easily removable. The main drawback to this approach to 3-substituted pyrroles is the reliance on the final decarboxylation step for removal of the 2-substituent. This step limits the directing groups used to acid or ester, cyano, formyl, acetyl, and trichloroacetyl derivatives, and also limits the final yields obtained.

2.1.2 Direction by a Removable 1-Substituent

Following the observation by Anderson[108] that the nitration of 1-methyl-2-pyrrolecarbonitrile (Scheme 2.4) gave a higher proportion of the 4-substituted product than did

the nitration of 2-pyrrolecarbonitrile, an attempt was made to exploit this effect. A bulkier and presumably removable 1-substituent, a benzyl group, was introduced in hopes that the greater steric bulk around the 2-positions would direct substitution to the 3- and/or 4-positions. While nitration and bromination reactions on 1-benzylpyrrole provided a greater proportion of 3-substituted product, the subsequent reaction for removal of the benzyl group (catalytic hydrogenation over Raney nickel) proved unsuccessful.[111] Other directing groups were found to be highly effective in directing substitution to the 3-position. Of these, the most effective was *t*-butyl, followed closely by 1-aryl groups.[111] However, no attempts were made to remove these 3-directing groups after the substitution step.

Scheme 2.4[108]

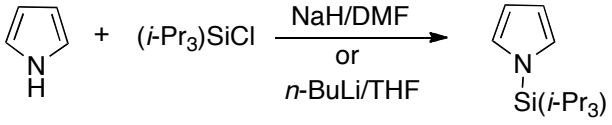


It was not until the work of Muchowski and co-workers[105] that a sterically demanding, stable and easily cleavable 3-directing 1-substituent on pyrrole was discovered. Expanding upon the work of Corey *et al.*[112] in which the remarkable steric requirements of the triisopropylsilyl (TIPS) moiety were first recorded, Muchowski and co-workers employed this moiety for the task of blocking the α positions of the pyrrole nucleus. Molecular modeling studies predicted that the steric shielding of the α positions by the TIPS moiety would allow for almost exclusive

substitution at the β positions. Knowing this, along with the known facile tetraalkylammonium fluoride induced cleavage of trialkylsilyl moieties,[113] made the study of TIPS-pyrrole as a progenitor of β-substituted pyrroles even more attractive.

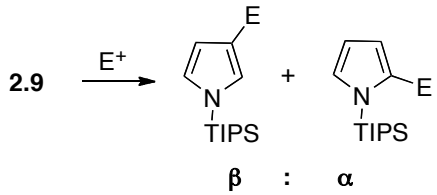
Preparation of TIPS-pyrrole proceeds in high yield by the simple reaction between the sodium or lithium salt of pyrrole and triisopropylsilyl chloride (Scheme 2.5). With the β-directing group in place, a variety of reactions of **2.9** with electrophilic reagents can be performed, as summarized in Table 2.1.

Scheme 2.5



2.9

Table 2.1: Reaction of TIPS-pyrrole 2.9 with electrophilic reagents



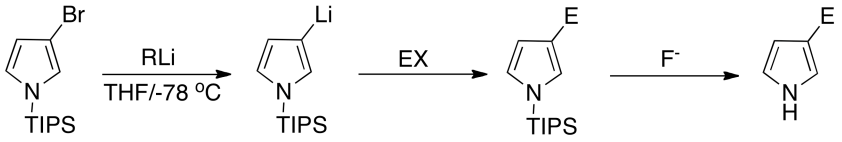
Reaction	Reagent	Equivalents	Product	β:α ratio
Bromination	NBS	1 equiv	3-bromo-1-TIPS-pyrrole	25:1
		2 equiv	3,4-dibromo-1-TIPS-pyrrole	19:1
Chlorination	NCS	1 equiv	3-chloro-1-TIPS-pyrrole	0.74:1
Iodination	I_2/mercuric acetate	1 equiv/ 1 equiv	3-iodo-1-TIPS-pyrrole	---
		2 equiv/ 2 equiv	3,4-diiodo-1-TIPS-pyrrole	---
Nitration	Acetyl nitrate	1 equiv	3-nitro-1-TIPS-pyrrole	11:1
Acylation	Ethyl oxalyl chloride	1 equiv	3-acyl-1-TIPS-pyrrole	---
	Trichloroacetyl chloride	1 equiv	3-acyl-1-TIPS-pyrrole	---

2.1.3 Halogen-Metal Interchange of 1-(TIPS)-3-Bromo-pyrrole

Anderson and Griffiths were the first to successfully perform a lithium-halogen exchange on a 3-substituted pyrrole.[111] In their work, they treated 1-benzyl-3-bromopyrrole with lithium metal to generate 1-benzyl-3-lithiopyrrole. After carboxylation of the organolithium product, they obtained an acid which they converted to the corresponding methyl ester and characterized as methyl 1-benzyl-3-pyrrolecarboxylate. This was a significant discovery, in that it demonstrated the potential for functionalization with a diverse array of electrophiles at the 3-position of pyrrole. The main drawback to their approach, however, was that it was not possible to remove the N-substituent, a benzyl group in this case, after functionalization. It was not until the application of the TIPS protecting group on pyrrole by Muchowski and co-workers that this problem was overcome.[105]

By treating 1-(TIPS)-3-bromopyrrole **2.10** with 1 equiv of *n*-butyllithium or 2 equiv of *tert*-butyllithium in THF at -78 ^{o}C, Muchowski and co-workers were able to obtain the desired lithiopyrrole **2.11** (Table 2.2). It was shown that the lithiopyrrole derivative **2.11** reacted with a broad spectrum of electrophilic reagents. The reagents examined included alkyl halides, carbon dioxide, a variety of carbonyl compounds, and trimethylsilyl chloride. The products **2.12** were obtained in very good yields for most reagents, and in some cases the products were desilylated to the 3-substituted pyrroles **2.13**. Some of the notable substituents installed at the 3-position of pyrrole were methyl (Me), *n*-butane (*n*-Bu), trimethylsilane (Me_3Si), an aldehyde (CHO), an alcohol (CH_2OH), a cyclic hydrocarbon (cyclohexen-1-yl), and a ketone (COMe). No attempts were made, however, to install a halogen atom such as chlorine (not achievable with great selectivity via the electrophilic reaction using NCS; see Table 2.1) or fluorine.

Table 2.2[105]



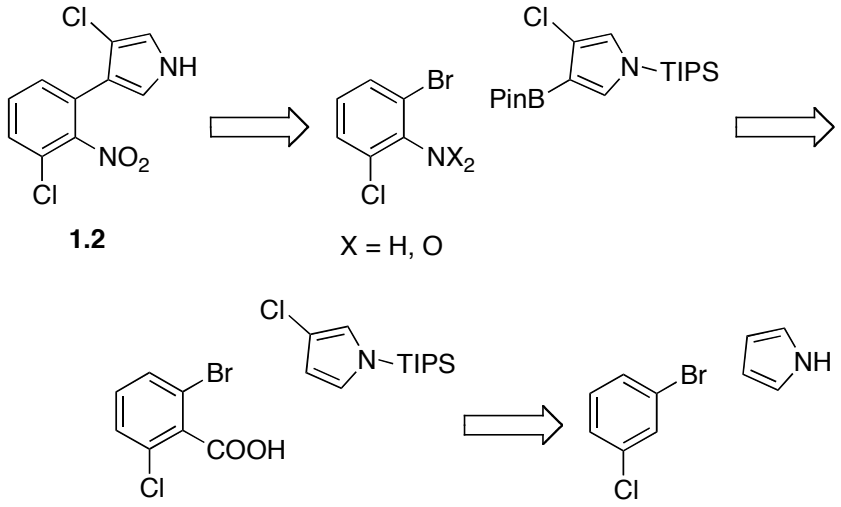
2.10 **2.11** **2.12** **2.13**

RLi (equiv)	EX	E in products	**2.12**	**2.13**
t-BuLi (2)	MeI	Me	92	
t-BuLi (2)	Me_3SiCl	Me_3Si	87	
t-BuLi (2)	CO_2 (gas)	COOH	88	88
n-BuLi (1)	DMF	CHO	82	86
t-BuLi (2)	MeCON(OMe)Me	COMe	61	84

2.2 Steps Towards a 3,4-Disubstituted Pyrrole

In our efforts towards a synthesis of pyrrolnitrin **1.2**, we needed to functionalize both β positions of pyrrole: the first with a chlorine atom, and the other with an aryl moiety. Since there was some precedent in the literature for Suzuki-Miyaura cross-coupling reactions between TIPS-protected 3-substituted pyrrole boronic acids (or the corresponding pinacolboronate esters, BPin) and phenyl/aryl halides, we devised the retrosynthetic approach shown in Scheme 2.6.

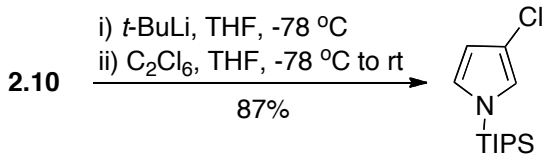
Scheme 2.6[114]



The challenge, then, was the regioselective installation of chlorine on pyrrole, as well as some other halogen that would allow access to the organolithium compound for subsequent conversion to the organoboron species.

Our initial efforts to chlorinate the 3-position of 1-(TIPS)pyrrole with both sulfuryl chloride and NCS[105] were to no avail. Product mixtures contained plenty of starting material along with small quantities of the 2-chloro, 3-chloro, and 2,3-dichloro compounds. We decided next to react the organolithium compound **2.11** (generated from **2.10** using the procedure of Muchowski and co-workers[105]) with hexachloroethane, an electrophilic chlorine source. The result was a nearly quantitative conversion of the 3-bromo compound **2.10** to 1-(TIPS)-3-chloropyrrole **2.14** (Scheme 2.7). We also carried out the lithiation/electrophile quench sequence on 1-(TIPS)-3-iodopyrrole (prepared by the protocol of Muchowski and co-workers[115]) and found similar yields. This was the first of two major obstacles in the synthesis of the pyrrole moiety to be used in cross-coupling experiments.

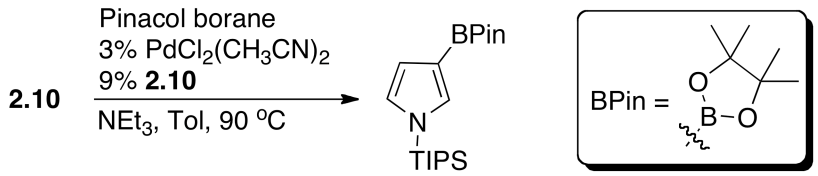
Scheme 2.7



2.14

The next challenge was installation of the boron electrophile at the remaining β position on **2.14**. A quick review of the literature showed that pinacolboronate esters could be prepared in high yield and purified by column chromatography.[116] Further investigations revealed the work of Billingsly and Buchwald,[117] in which they prepared 1-(TIPS)-3-(BPin)pyrrole from **2.10** in 79% yield (Scheme 2.8). It should be noted that we chose to work with the pyrrole pinacolboronate ester after initial attempts to prepare the corresponding boronic acid failed to produce product in high enough yield or purity.

Scheme 2.8[117]



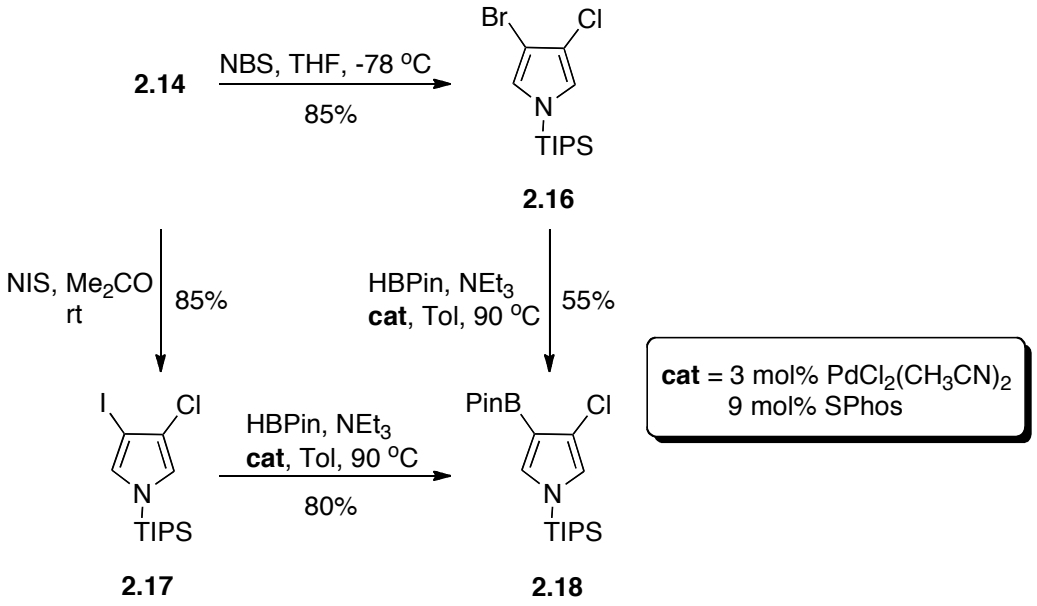
2.15

We planned to generate our own 1-(TIPS)-3-chloro-4-(BPin)pyrrole **2.18** (Scheme 2.9) from 3-bromo-4-chloro compound **2.16**, but first we needed to prepare **2.16**. We initially attempted to perform the Li-X exchange reaction on the 3,4-dibromo compound. However, due to difficulties in purifying the dibromo compound, we chose to abandon this route (see Scheme 2.10). Instead, we prepared **2.16** in high yield and good purity by simply brominating the monochloro compound

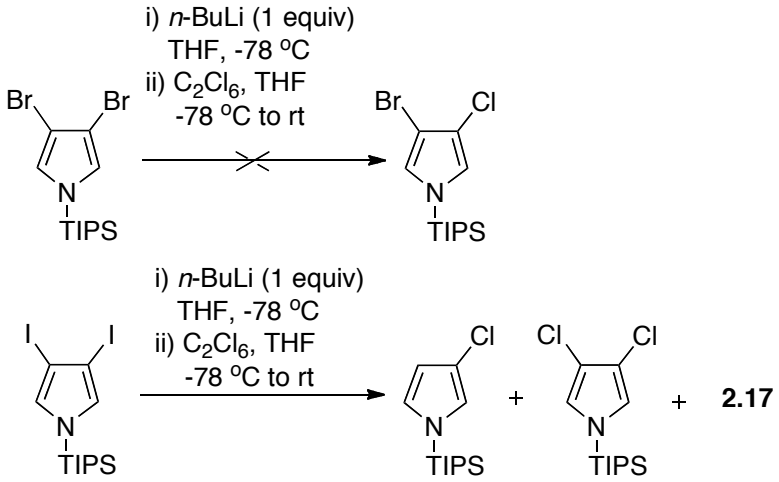
2.14 (Scheme 2.9). We then subjected this compound to the conditions of Billingsley and Buchwald[117] to form **2.18**, but the reaction was sluggish and delivered poor yields (~55%).

By subjecting the 3-chloro-4-iodo compound **2.17** to the same conditions, we hoped to receive better yields of **2.18** due to the more reactive iodine atom. To prepare **2.17**, we initially attempted the Li-X reaction on the diiodo compound, but received product mixtures of the monochloro and dichloro compounds (Scheme 2.10) with only small quantities of **2.17**. We then tried to iodinate the 4-position of **2.14** and obtained **2.17** in excellent yield. After subjecting **2.17** to the conditions of Billingsley and Buchwald, we obtained the desired product **2.18** in 80% yield (Scheme 2.9). We had thus succeeded in synthesizing one of the two necessary cross-coupling partners for our approach to pyrrolnitrin **1.2** and suitable analogs.

Scheme 2.9



Scheme 2.10



2.3 Conclusions

In our efforts to prepare a 3,4-disubstituted pyrrole for the syntheses of **1.2** and various analogs needed for mechanistic studies, we overcame many obstacles. We first developed a method to regioselectively chlorinate 1-(TIPS)pyrrole in the β position (**2.14** in Scheme 2.7) by quenching the lithiopyrrole derivative with hexachloroethane. Then, in our attempts to install Br **2.16** or I **2.17** in the remaining β position—allowing later access to the pinacol boronate ester **2.18**—we found that treatment of **2.14** with NIS to give the iodinated product **2.17** was the best route. The subsequent Pd-catalyzed reaction for the installation of BPin was carried out, giving access to our desired pyrrole pinacolboronate ester **2.18** necessary for our future cross-coupling experiments.

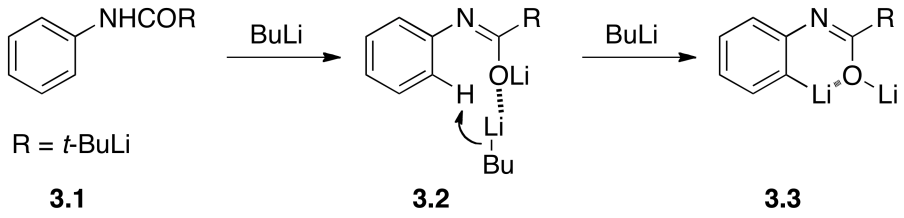
Chapter 3 – Syntheses of 2,6-Dihaloanilines and 2,6-Dihalonitrobenzenes

3.1 Background

Though it is possible to perform electrophilic substitution on anilines, usually via their *N*-acylated derivatives, such reactions are complicated by the formation of regioisomers and low yields.[118] Methods to perform regiospecific *ortho* alkylation of aromatic amines have historically included the use of anilinodichloroboranes,[119] and metalation reactions on phenyl isocyanides (protected primary anilines).[120] Unsatisfied with the results provided by these techniques, Fuhrer and Gschwend explored the use of a pivaloyl (Piv) protecting group on aniline for *ortho* metalation reactions.[118]

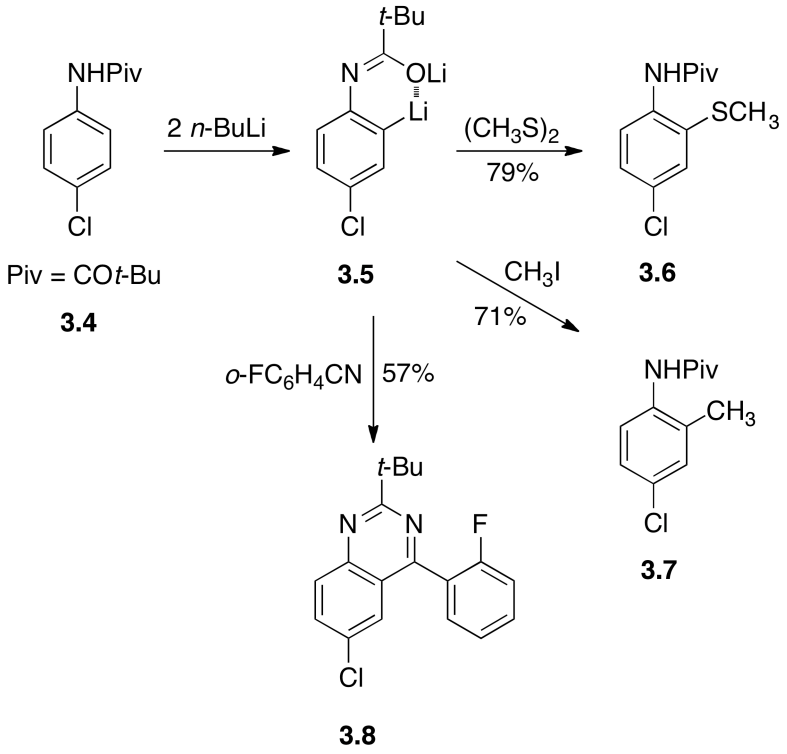
The *ortho*-directing ability of the nitrogen atom varies according to its degree of substitution. While there is a lack of reports on the successful *ortho* metalation of primary anilines and tertiary anilides are regarded as one of the weakest *ortho*-directing groups,[118] secondary anilides have been shown to provide high yields and remarkable regioselectivity in *ortho*-metalation reactions.[118] Fuhrer and Gschwend demonstrated the utility of *N*-pivaloylanilides **3.1** (Scheme 3.1).

Scheme 3.1[118]



After initial deprotonation by one equivalent of BuLi, the oxygen atom in the deprotonated species **3.2** serves as a ligand for a second equivalent of lithiating agent. This coordination of the second equivalent of base facilitates a regiospecific attack on the *o*-hydrogen and formation of the dilithio intermediate **3.3**. The choice of *t*-Bu as the R group was ideal as there were no acidic α protons available for attack by the lithiating agent. The facile reactivity of the *p*-chloro derivative **3.4** with n-BuLi in THF at 0 ^{o}C is illustrated in Scheme 3.2.

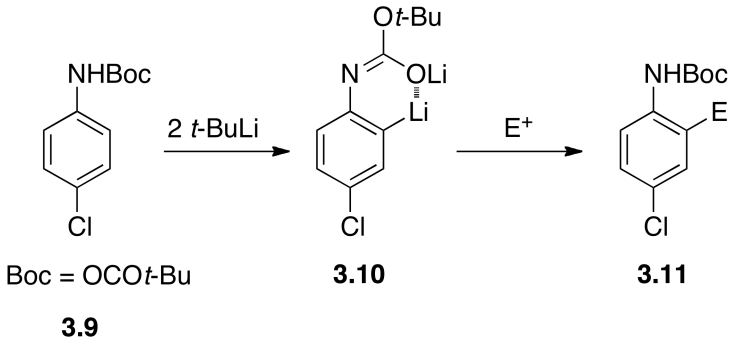
Scheme 3.2[118]



Another highly useful protecting group used in D*o*M reactions on anilines is the *tert*-butoxycarbonyl group (Scheme 3.3).[121] Although *tert*-butoxycarbonyl (Boc) differs from the Piv protecting group by only one oxygen atom, it is much more easily removed once the desired metalation reaction has been performed. Fuhrer and Gschwend reported that Piv could be

removed hydrolytically in HCl or Et_3OBF_4/H_2O, but such harsh conditions are not always compatible with the survival of newly introduced functional groups on anilines. This was the motivation for the development of the more acid labile Boc protecting group by Muchowski and Venuti.[121] The more cleavable protecting group comes, however, at the cost of *ortho*-directing ability in D*o*M reactions; that is, Boc is more easily cleaved but Piv is a superior DMG. In any case, these two protecting groups allow for superior regioselectivity and high yields in *ortho*-lithiation reactions on anilines.

Scheme 3.3[121]



Boc = OCO*t*-Bu

3.9

3.10

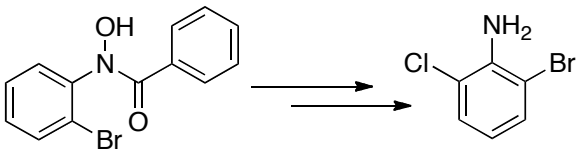
3.11

3.2 Syntheses of 2-Chloro-6-Haloanilines (and 2-Chloro-6-Halonitrobenzenes)

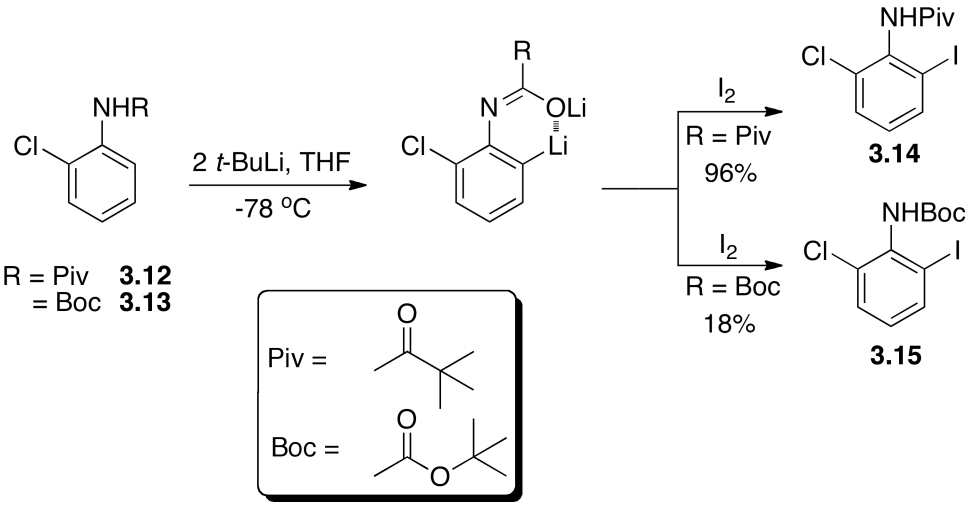
Our approach to the synthesis of pyrrolnitrin **1.2** required preparation of a nitrobenzene compound with a chlorine atom in one *ortho* position and either bromine or iodine in the other so that the compound could be cross coupled with our 1-(TIPS)-3-chloro-4-(BPin)pyrrole **2.18**. To access the nitrobenzene moiety, we planned to make the appropriately substituted aniline and oxidize the product with *meta*-chloroperoxybenzoic acid (*m*-CPBA). Our first target was 2-bromo-6-chloroaniline. Our attempts to reproduce the procedure of Ayyangar and co-workers,[122] in which *N*-(2-bromophenyl) benzohydroxamic acid was treated with thionyl chloride and the

resulting anilide was subsequently hydrolyzed to 2-bromo-6-chloroaniline, were unsuccessful (Scheme 3.4). We next attempted *ortho* metalation reactions on 2-chloroaniline with both the Piv and Boc protecting groups (Scheme 3.5). We found that the use of I_2 as the electrophile rather than our Br electrophile (dibromotetrafluoroethane) provided the best yields (96% vs. 23%).

Scheme 3.4



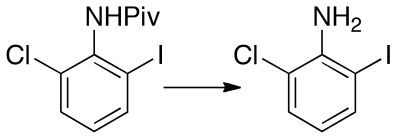
Scheme 3.5



As expected, metalation of **3.12** provided the iodine-substituted product in much higher yield than could be achieved with **3.13**. However, we were unable to remove the Piv group from the product using the conditions described by Fuhrer and Gschwend.[118] The harsh acidic conditions would merely strip the product of its iodine substituent, leaving a mixture of **3.12** and unreacted material **3.14**. The variety of hydrolytic conditions used are shown in Table 3.1. The low yield of the metalation/halogenation of **3.13** precluded its use in our synthetic strategy toward **1.2**, despite

facile removal of the Boc protecting group under the conditions of Muchowski and Venuti.[118] It was evident that we were in need of an alternate route to 2-chloro-6-halonitrobenzene.

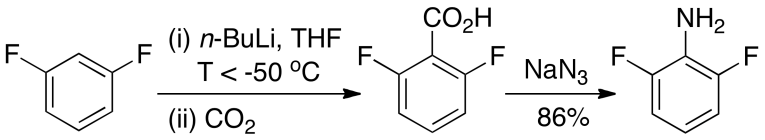
Table 3.1



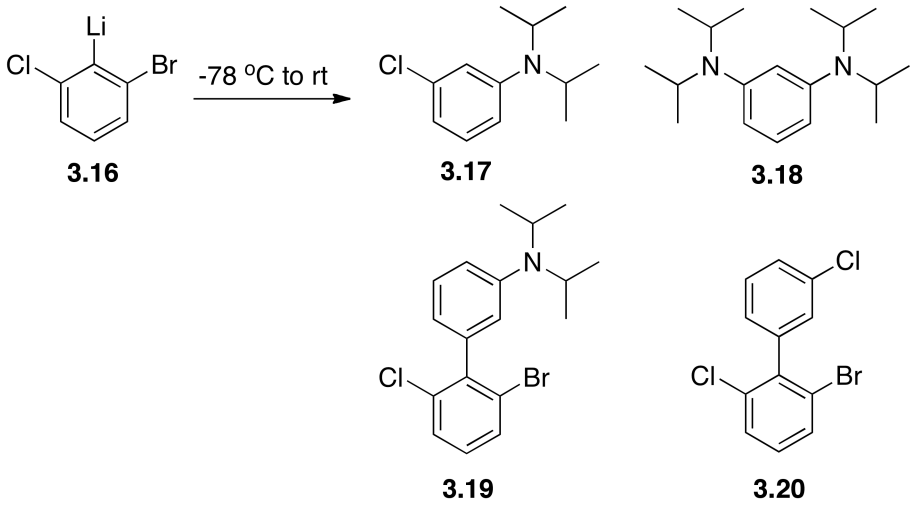
Reagent	Solvent	Temp (°C)	Time	Yield (%)
1M NaOH	MeOH	rt	18 h	0
20% H_2SO_4	EtOH	reflux	48 h	0
20% H_2SO_4	EtOH	reflux	72 h	0
6M HCl	dioxane	reflux	24 h	0
48% HBr	n/a	reflux	5 h	0
LAH	ether	rt	2 h	0

We then came across the work of Roe,[123] which showed that 1,3-difluorobenzene and 1,3-dichlorobenzene could be converted to 2,6-difluorobenzoic acid and 2,6-dichlorobenzoic acid in 81% and 75% yield, respectively. In this procedure, the 2,6-dihalobenzene was taken up in THF, treated with *n*-BuLi at below -50 °C to generate an aryllithium intermediate, then subjected to carboxylation to yield the corresponding 2,6-dihalobenzoic acid. A subsequent Schmidt rearrangement was shown to afford the 2,6-difluoroaniline in 86% yield (Scheme 3.6).[124] This sequence appeared ideal for our preparation of 2-bromo-6-chloroaniline. Further investigations led to our discovery of the work of Hickey and co-workers,[125] in which they showed that significant benzyne-type decomposition of 2-bromo-6-chlorophenyl lithium **3.16** (Scheme 3.7) occurred at temperatures above -70 °C.

Scheme 3.6[123]

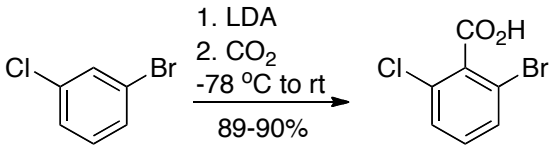


Scheme 3.7[125]



In their studies, 2-bromo-6-chlorobenzene was taken up in THF, cooled to -78 °C, then treated with lithium di-*iso*-propylamide (LDA) according to the procedure of Schlosser[126] to generate **3.16**. The reaction mixture was then allowed to slowly warm, and by only -70 °C the solution had begun to darken. Within 30–45 seconds, the reaction temperature had spiked to 65 °C and the solution was refluxing. An assay of the product mixture revealed complete consumption of **3.16** and generation of the four major products shown in Scheme 3.5. These products formed due to nucleophilic attack on the benzyne intermediate by LDA, di-*iso*-propyl amine (DIPA), and **3.16**. Hickey and co-workers found that by maintaining the reaction temperature between -85 and -70 °C, they could minimize benzyne-type decomposition and thus generate 2-bromo-6-chlorobenzoic acid **3.22** (Scheme 3.8) in 89–90% yield.

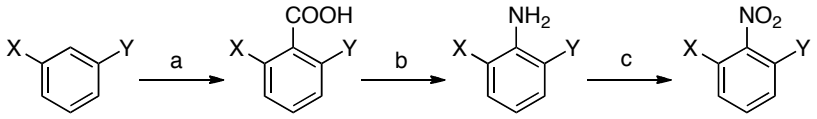
Scheme 3.8



3.21 **3.22**

When we experimented with these conditions in our own work, we were fortunately able to obtain **3.22** in excellent yield. Then, after subjecting the acid to Schmidt conditions, we obtained the corresponding aniline in 92% yield. A subsequent oxidation reaction using *m*-CPBA in dichloroethane (DCE) afforded the target nitrobenzene **3.27** needed for our cross-coupling experiments in 94% yield (Table 3.2). This was a great accomplishment for us, as we had struggled with this compound for a long time. It was interesting to see how after little success in our earlier efforts with D*o*M reactions on protected anilines, a simple modification of the DMG(s) used was all it took to provide our target compound. The cooperative effect of the Cl and Br DMGs led to facile lithiation at the common site of **3.21**, allowing for installation of the carboxyl group. This reaction was ideal for the fact that a basic extraction on the crude product was enough to deliver **3.22** is high purity, thus avoiding the need for crystallization. We thought that the subsequent Schmidt reaction might have been problematic due to the steric bulk around the common site between the halogen atoms, but the reaction proceeded smoothly. Column chromatography on the crude aniline was enough to deliver **3.26** in great yield and high purity. The final step, oxidation to the nitrobenzene, proceeded without problems to afford the crude product. Column chromatography of the crude material gave the pure target compound **3.27** in great yield.

Table 3.2



aryl halide	yield (product)	yield (product)	yield (product)
X, Y = Br, F	92 (**3.23**)	86 (**3.24**)	88 (**3.25**)
X, Y = Br, Cl	99 (**3.22**)	92 (**3.26**)	94 (**3.27**)
X, Y = Br, Br	85 (**3.28**)	78 (**3.29**)	82 (**3.30**)
X, Y = Br, I	80 (**3.31**)	83 (**3.32**)	78 (**3.33**)

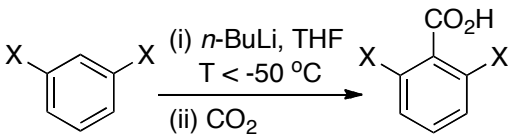
[a] (i) LDA, THF, -78 °C, 1 h; (ii) CO_2, -78 °C to rt, 2 h (-100 °C to rt for **3.31**). [b] (i) H_2SO_4, 60 °C, 1.5 h; (ii) NaN_3, rt, 42 h. [c] *m*-CPBA, DCE, 70 °C, 2h.

Our lithiation-carboxylation-Schmidt-oxidation sequence enabled us to prepare not only our target compound for cross-coupling with 1-(TIPS)-3-chloro-4-(BPin)pyrrole **2.18**, but also several other previously unreported 2,6-dihaloanilines and 2,6-dihalonitrobenzenes. Most notably, the preparation of 2-bromo-6-iodobenzoic acid **3.31** (along with the corresponding aniline and nitrobenzene) was achieved in good yield by simply dropping the reaction temperature to -100 °C to ensure minimal benzyne-type decomposition of the unstable 2-bromo-6-iodophenyl lithium species. We did find, however, a 5:1 mixture of the desired 2-bromo-6-iodo compound **3.31** and deiodinated product (2-bromobenzoic acid) due to Li-X exchange.

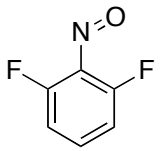
We were able to improve on Roe's yields of 2,6-difluorobenzoic acid and 2,6-dichlorobenzoic acid using our lithiation/carboxylation conditions (Scheme 3.9). We were able to convert the difluoro and dichloro compounds to the corresponding anilines in good yields (86% and 88%, respectively) but the subsequent oxidation reaction for the difluoro compound was fraught with difficulties. The compound would stall out at the nitroso stage (Scheme 3.10) and not progress to the nitrobenzene. We believed that this was due to the high electronegativity of the fluoro groups, which reduced the nucleophilicity of the aniline. Regardless, with our target

nitrobenzene needed for the synthesis of **1.2** and several interesting new 2,6-dihaloaniline and 2,6-dihalonitrobenzene compounds in hand, we were ready to begin our cross-coupling experiments.

Scheme 3.9



Scheme 3.10



2,6-difluoronitrosobenzene

3.3 Conclusions

Our efforts towards a 2-chloro-6-haloaniline (and the corresponding 2-chloro-6-halonitrobenzene) involved experiments with D*o*M chemistry. We found that by protecting the amine group of 2-chloroaniline with either Piv **3.12** or Boc **3.13** DMGs, we could perform *ortho* metalation and subsequently install an iodine atom at the 6-position (**3.14** and **3.15**, respectively). We had much better success using **3.12**, but we were unable to remove the Piv DMG after our desired transformation. A variety of hydrolytic conditions were tried, but none were successful in

removing the Piv group (Table 3.1). We then utilized a different set of DMGs on a completely different molecule **3.21** and found that we could metalate at the common site between the Cl and Br atoms and subsequently carboxylate this position **3.22**. We carried **3.22** forward and, using a Schmidt reaction, were able to generate our desired 2-bromo-6-chloroaniline **3.26**. Conversion of **3.26** to the desired nitrobenzene compound **3.27** occurred readily by oxidation with *m*-CPBA. We further experimented with our lithiation-carboxylation-Schmidt-oxidation sequence and found that we were able to apply it to a number of dihalobenzenes to prepare novel dihaloanilines and nitrobenzenes (Table 3.2). Most notably, we were able to synthesize the 2-bromo-6-iodobenzoic acid **3.31** (and the corresponding aniline **3.32** and nitrobenzene **3.33** compounds) by modifying our reaction conditions (T = -100 ^{o}C) to minimize benzyne-type decomposition. We did, however, find a 5:1 ratio of our desired product **3.31** and the deiodinated material (2-bromoaniline).

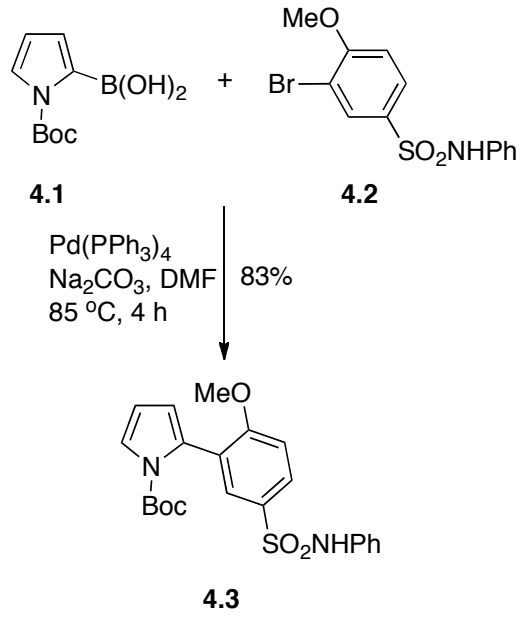
Chapter 4 – Cross-Coupling Between Halogenated Pyrroles and 1,2,3-Trisubstituted Aromatics

4.1 Background

Amongst the various processes available for the palladium-catalyzed cross-coupling between aryl moieties and intact pyrroles, including Buchwald-Hartwig,[127] Heck,[128] Negishsi,[129] Sonogashira,[130] Suzuki-Miyaura,[131] and Ullmann[132] reactions, the Suzuki-Miyaura reaction leads the field. This particular reaction is especially useful given the ease with which pyrroles can be converted into the corresponding boronic acid derivatives.[133] Many papers report on the ability of *N*-substituted pyrroles to be used in directed metalation reactions, in which the lithio-species is formed regiospecifically at the C2 position and, following trapping with a boron electrophile

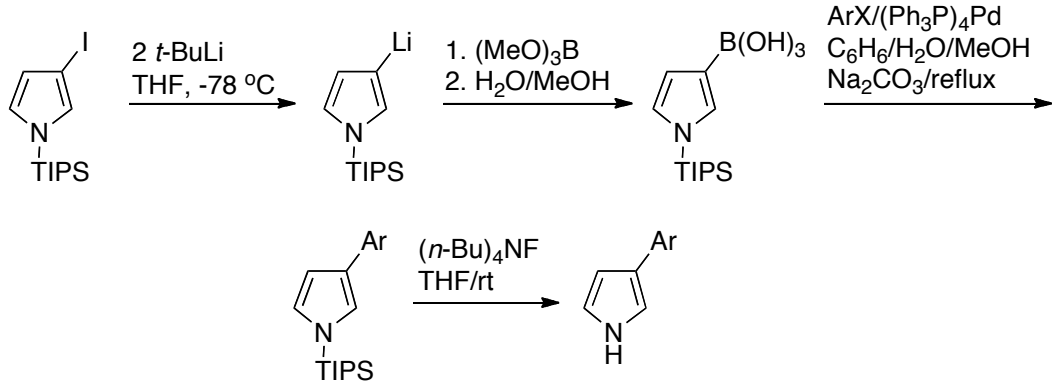
(typically trimethoxyborane), the C2-boronic acid is generated. These acids are then used in cross-coupling reactions with aryl halides. A good example of this is demonstrated in the work of Johnson *et al*.,[134] where they cross-coupled pyrrole boronic acids with aryl bromides to prepare novel agonists of the dopamine D3 receptor (Scheme 4.1).

Scheme 4.1[134]



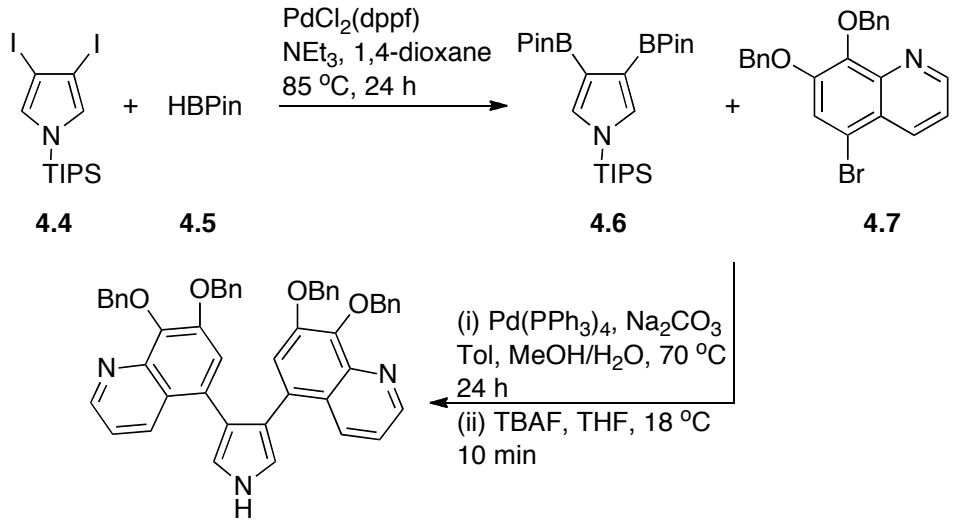
The corresponding C3-boronic acid derivatives have also been described by various groups including Muchowski and co-workers[115] who showed that these systems, having the boronic acid substituent in the 3-position of pyrrole, could undergo cross-coupling reactions with a variety of aryl and heteroaryl bromides and iodides (Scheme 4.2).

Scheme 4.2



Pyrroles bearing more than one boronic acid (or pinacolboronate ester) have been described to undergo tandem Suzuki-Miyaura cross-coupling reactions, as shown by Steglich and co-workers[133] in their total synthesis of the cytotoxic marine alkaloid halitulin **4.8** (Scheme 4.3). In their work, Steglich and co-workers showed that the 3,4-diiodinated pyrrole **4.4** could be converted to the corresponding bispinacolboronate ester **4.6** under Masuda's[135] conditions. Compound **4.6** was then shown to undergo a tandem reaction with 2 equivalents of the C5-brominated quinoline **4.7**, yielding product **4.8** after removal of the TIPS protecting group.

Scheme 4.3[133]

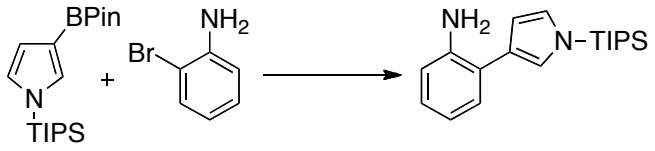


4.2 Cross-Couplings of 1-(TIPS)-3-(BPin)pyrrole with Various Aryl Bromides

With the necessary coupling partners for **1.24**, **1.25**, **1.2** and several analogous halogenated phenylpyrroles in hand, Suzuki-Miyaura cross-couplings of the pyrrole pinacolboronate esters and various aryl bromides were initiated. To begin, we chose to use the more easily prepared pyrrole boronate ester **2.15** (produced in just 1 step from **2.10** versus 3 steps from **2.10** for **2.18**) for cross-coupling reactions with commercially available 2-bromoaniline under various catalytic conditions (Table 4.1). Using the $Pd(PPh_3)_4$ catalyst provided modest yields at best regardless of base or solvent system used, whereas the conditions tried for the $PdCl_2$(dppf) catalyst did not result in product formation. When we tried Pd_2dba_3 catalyst in combination with the SPhos ligand developed by Billingsley and Buchwald,[117] we found greatly improved yields. When we used the same SPhos ligand in combination with $Pd(OAc)_2$ catalyst,

the yields were very good, and we thus chose to work with this catalyst system for our cross-coupling reactions using the other pyrrole pinacolboronate esters and aryl halides.

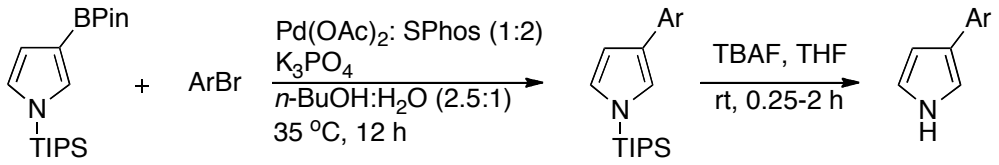
Table 4.1

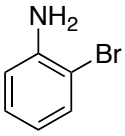
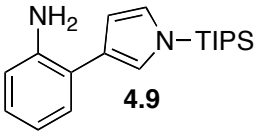
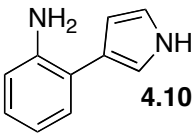
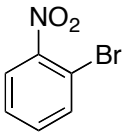
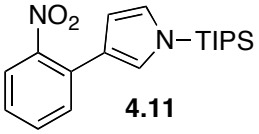
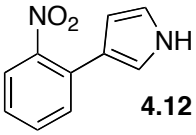
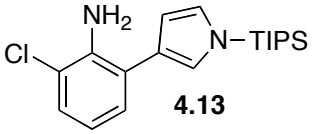
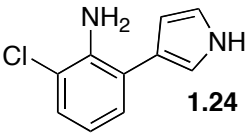
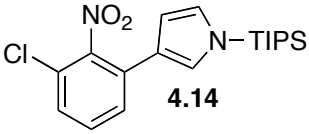
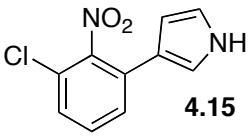


catalyst	base	solvent	temp (°C)	yield (%)
$Pd(PPh_3)_4$	K_3PO_4	DMF	100	26
$Pd(PPh_3)_4$	Na_2CO_3	toluene	reflux	22
$Pd(PPh_3)_4$	Na_2CO_3	toluene/MeOH/H_2O	reflux	30
$PdCl_2$(dppf)	NEt_3	1,4-dioxane	85	0
Pd_2dba_3/SPhos	K_3PO_4	*n*-BuOH	100	75
$Pd(OAc)_2$/SPhos	K_3PO_4	*n*-BuOH/H_2O	100	85

A key to the success of Billingsley and Buchwald's protocol, was the use of an *n*-butanol:H_2O solvent system in a ratio of 2.5:1. Billingsley and Buchwald found that this co-solvent ratio minimized the amount of reduced aryl halide formed during the course of cross-coupling reactions with **2.15**. In our experiments, we were pleased to find that **2.15** also cross-coupled with the various aryl bromides to yield, after subsequent fluorodesilylations, **4.10**,[136] **4.12**,[136] **4.15**[137] and monodechloroaminopyrrolnitrin **1.24**[138] in good yields (Table 4.2). Whereas the reaction of 2-bromoaniline with **2.15** required heating to 100 °C in an overnight reaction, the remaining aryl bromides coupled much more readily; so readily for the highly active **3.27**, in fact, that this reaction needed to be cooled to 0 °C to minimize the amount of 2,6-bis-(1-TIPS-pyrrole)nitrobenzene **4.22** formed (Scheme 4.4). It is clear that the electron-withdrawing nitro group of **3.27** was responsible for the high activity of this compound since the analogous aniline compound **3.26** was not observed to undergo bis-coupling with **2.15**.

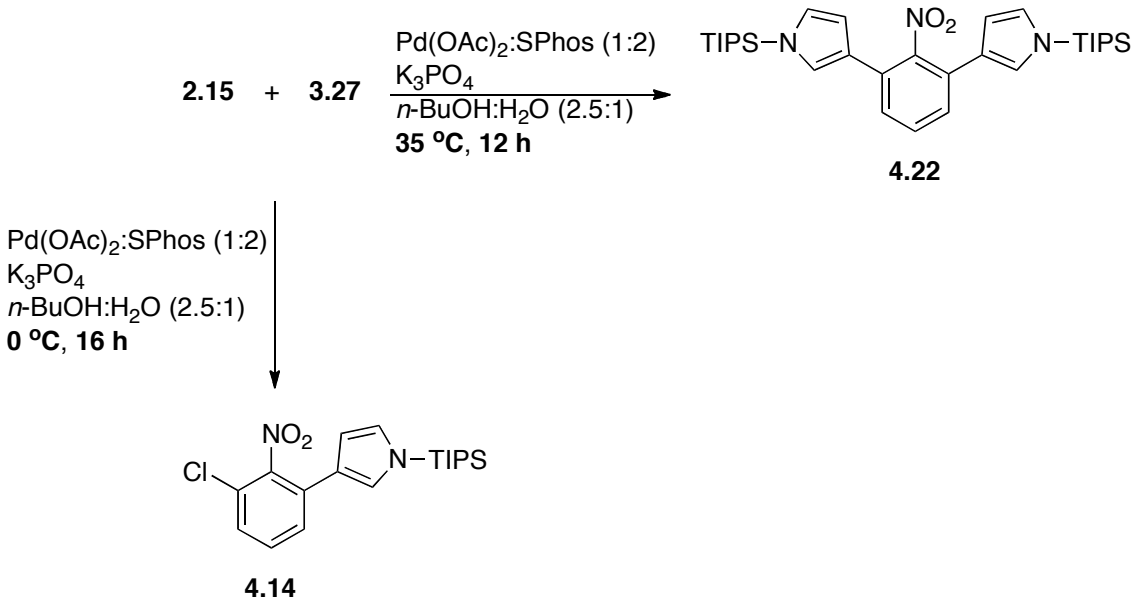
Table 4.2



pyrrole	ArBr	product	yield (%)	product	yield (%)
2.15		 **4.9**	85[a]	 **4.10**	79
2.15		 **4.11**	81	 **4.12**	81
2.15	**3.26**	 **4.13**	82	 **1.24**	80
2.15	**3.27**	 **4.14**	87[b]	 **4.15**	64

[a] Carried out at 100 °C for 16 h. [b] Carried out at 0 °C for 16 h.

Scheme 4.4

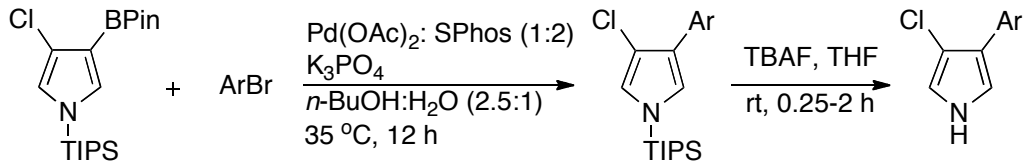


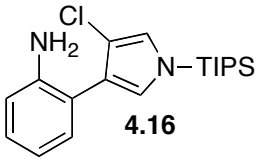
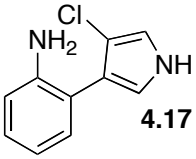
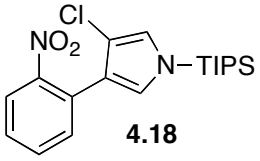
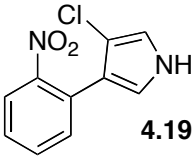
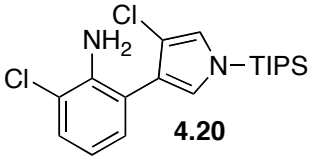
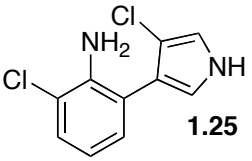
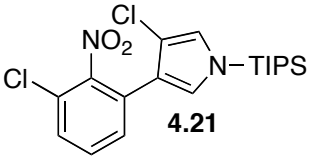
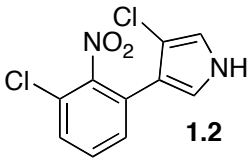
4.3 Cross-Couplings of 1-(TIPS)-3-Chloro-4-(BPin)pyrrole with Various Aryl Bromides

Since our Suzuki-Miyaura cross-coupling reactions using **2.15** were a success, we next used our 1-(TIPS)-3-chloro-4-(BPin)pyrrole **2.18** to cross-couple with the various aryl bromides. Under the conditions of Billingsley and Buchwald,[117] we were able to produce arylpyrroles **4.17** and **4.19**,[139] as well as aminopyrrolnitrin **1.25**[140] and our target pyrrolnitrin **1.2** in good yields after their respective fluorodesilylations (Table 4.3). We had thus accomplished two of our three outlined goals (see Section 1.3: Outline of Research Project), in that we had devised a synthetic approach to pyrrolnitrin **1.2** relying upon the cross-coupling of easily modified pyrrole and aryl halides; we had also successfully prepared several analogs of **1.24** and **1.25** to be used in mechanistic studies of the pyrrolnitrin biosynthetic enzymes PrnB–D. The remaining goal, was

thus to prepare several arylpyrroles with bromine or deuterium incorporated into their molecular structure.

Table 4.3



pyrrole	ArBr	product	yield (%)	product	yield (%)
2.18		 **4.16**	81[a]	 **4.17**	75
2.18		 **4.18**	86	 **4.19**	78
2.18	**3.26**	 **4.20**	82	 **1.25**	73
2.18	**3.27**	 **4.21**	89[b]	 **1.2**	74

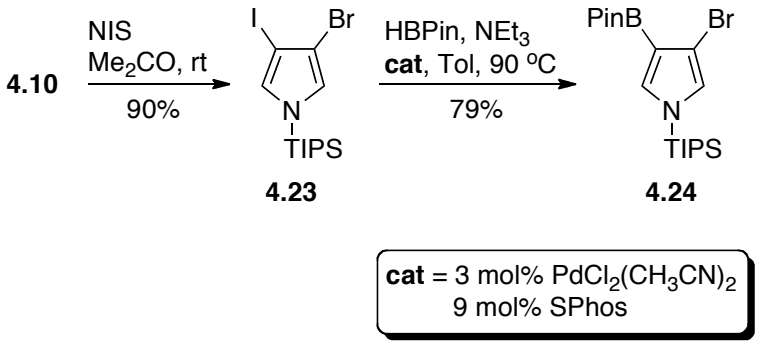
[a] Carried out at 100 °C for 5 h. [b] Carried out at 0 °C for 16 h.

4.4 Syntheses of Brominated and Deuterated Arylpyrroles

Given the recent interest[141] in the potential for chlorinating enzymes such as PrnA and PrnC to also perform biological brominations, we sought after brominated analogs of compounds **1.24** and **1.25** in order to help study the mechanism and crystal structure of PrnC. To do so, we

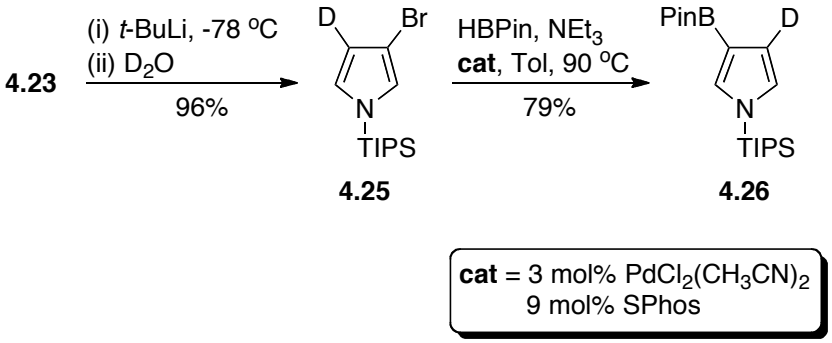
required the brominated analog **4.24** of our pyrrole pinacolboronate ester **4.18**, which we were able to prepare in good yield from our newly synthesized 3-bromo-4-iodo pyrrole moiety **4.23** (Scheme 4.5).

Scheme 4.5



In an analogous approach, we also obtained the deuterated pyrrole pinacolboronate ester **4.26**, whose cross-coupling product with **3.27** could be used in mechanistic (kinetic isotope effect) studies with PrnC (Scheme 4.6).

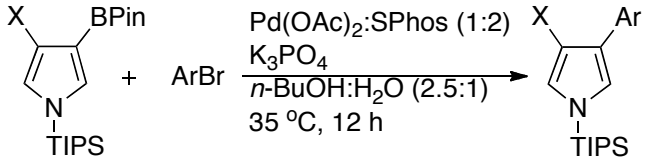
Scheme 4.6

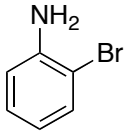
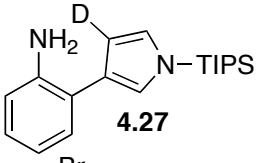
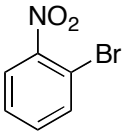
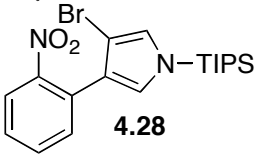


As we expected, cross-coupling reactions between **4.26** and the various halogenated anilines and nitrobenzenes gave arylpyrrole products with similar yields to those achieved using the analogous pyrrole pinacolboronate ester **4.15** (Table 4.4). However, the yields for the

reactions employing the brominated pyrrole pinacolboronate ester **4.24** were surprisingly low due to its competing homo-coupling reaction. Attempts to optimize the conditions to favor the cross-coupling over the homo-coupling pathway are underway in our lab.

Table 4.4



pyrrole	ArBr	product	yield (%)
X=D **4.26**		 **4.27**	90
X=Br **4.24**		 **4.28**	18

4.5 Conclusions

We had thus succeeded in accomplishing our goals outlined in Section 1.3: Outline of Research Project. To summarize, we:

- regioselectively installed chlorine in the β position of pyrrole via our tandem lithium-halogen exchange/electrophilic chlorination pathway
- generalized a lithiation/carboxylation/Schmidt reaction/oxidation sequence for the preparation of 2,6-dihaloanilines (and the corresponding 2,6-dihalonitrobenzenes) bearing bromides and iodides

- determined optimal conditions for the cross-coupling of chlorinated aryl bromides and boronated pyrroles and, in doing so, developed a novel synthetic route to the antifungal agent pyrrolnitrin **1.2**
- prepared precursors to **1.2** along with related halogenated arylpyrroles

Our future efforts will involve:

i) Using our brominated and deuterated arylpyrroles in kinetic and mechanistic studies of heterologously overexpressed pyrrolnitrin biosynthetic enzymes

ii) Optimizing the conditions for the cross-coupling of **4.24** with aryl bromides so as to minimize the homo-coupling pathway

Chapter 5 – Experimental

GENERAL METHODS.

^{1}H 300, 400, and 500 MHz NMR spectra were obtained on an Avance-300, Avance- 400, or Avance-500 spectrometer referenced to $(CD_3)_2CO$ at 2.05 ppm.[142] ^{13}C 300, 400, and 500 MHz NMR spectra were obtained on an Avance-300, Avance 400, or Avance 500 MHz spectrometer referenced to $(CD_3)_2CO$ at 2.05 ppm.[142] High resolution mass spectra were obtained on a Waters / Micromass GCT mass spectrometer (Manchester, UK) in EI mode. THF was dried with a Solvent Purification System from Pure Solv. Butylliuthiums (*n*- and *t*-) were purchased from Sigma-Aldrich and stored in septum-sealed containers under nitrogen atmosphere. Most chemicals (catalysts, ligands, reagents) were purchased from Sigma-Aldrich. For low temperature measurements, a Digi-Sense Dual JTEK Thermocouple Thermometer was used.

All experiments were carried out under nitrogen in oven dried glassware, using syringe-septum cap techniques. Flash column chromatography was carried out using Silicycle Ultra Pure Silica Gel (particle size: 40-63 μm).

Standard Work-up:

The reaction mixture was quenched with 5–10 mL of saturated ammonium chloride (NH_4Cl) solution and the resulting biphasic mixture was transferred to a separatory funnel. The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (EtOAc, 3 x 10–20 mL). The organic layers were combined and washed with saturated sodium chloride (NaCl, 1 x 10–20 mL), dried with magnesium sulfate ($MgSO_4$) and concentrated under reduced pressure to afford the crude product.

GENERAL PROCEDURES

General Procedure 1. Preparation of 2,6-Dihalobenzoic acids:

To a solution of *n*-BuLi (1.4 equiv) in dry THF (2.0 mL/mmol dihalobenzene) at 0 ^{o}C was added diisopropylamine (DIPA, 1.5 equiv), and the mixture was stirred at this temperature for 15 min before cooling to -100 ^{o}C (ethyl ether/CO_2). To the mixture at -100 ^{o}C was added dihalobenzene (1.0 equiv) dropwise while maintaining T < -90 ^{o}C. After 1 h of reaction time, $CO_{2(g)}$ was added subsurface via syringe/needle (place dry ice pellet in empty 10 mL syringe and plug needle with septum to accumulate $CO_{2(g).}$) The addition of $CO_{2(g)}$ was continued until $\Delta T < 0.2$ ^{o}C, and the reaction was then left to warm to room temperature (*c.a.* 1 h). The mixture was diluted with water (5–10 mL) and transferred to a separatory funnel where the mixture was extracted with sodium hydroxide (NaOH, 0.1 N, 3 x 10–20 mL). The aqueous layers were collected and then back-extracted with EtOAc (10–20 mL). This organic layer was discarded. The aqueous layer was then acidified to pH 1 using 6 N hydrochloric acid (HCl), and subsequently extracted with EtOAc (3 x 10–20 mL). This organic layer was washed with sodium chloride (NaCl, 10–20 mL), dried over $MgSO_4$, and reduced *in vacuo* to afford the product in high purity.

General Procedure 2. Preparation of 2,6-Dihaloanilines:

A solution of 2,6-dihalobenzoic acid (1.0 equiv) in concentrated sulfuric acid (H_2SO_4, 2.5 mL/mmol dihalobenzoic acid) was heated to 60 ^{o}C for 1.5 h. The solution was then cooled for 15 min at rt before addition of sodium azide (NaN_3). The resulting mixture was left to stir at rt for 48 h before cooling to 0 ^{o}C and basifying with concentrated ammonium hydroxide (NH_4OH). A subsequent extraction (see standard work-up procedure) was performed to yield the product in high purity.

General Procedure 3. Preparation of 2,6-Dihalonitrobenzenes:

To a solution of 2,6-dihaloaniline (1.0 equiv) in anhydrous dichloroethane (DCE, 2.0 mL/mmol dihaloaniline) was added *meta*-chloroperbenzoic acid (*m*-CPBA, 4.0 equiv). The resulting mixture was heated at 70 ^{o}C for 2 h (monitored reaction progress by TLC and GC/MS) while the reaction vessel was wrapped in aluminum foil to minimize light exposure. After the 2 h reaction period, the mixture was diluted with EtOAc (5 mL), transferred to a separatory funnel and extracted with 0.1 N NaOH (3–5 x 10–20 mL) to remove residual perbenzoic and benzoic acids. After rinsing with brine (10–20 mL), and drying over $MgSO_4$, the organic phase was reduced *in vacuo* to yield the product in high purity.

General Procedure 4. Preparation of TIPS-Protected Phenylpyrroles by Suzuki-Miyaura Cross-Coupling:

In an over-dried Schlenk flask, the solid starting materials (SMs) were combined: phenyl halide (1.0 equiv), *N*-(TIPS)pyrrole pinacol boronate (1.2 equiv), palladium acetate [$Pd(OAc)_2$, 0.05 equiv], 2-Dicyclohexyl-phosphino-2′,6′-dimethoxybiphenyl (SPhos, 0.10 equiv), and potassium phosphate (K_3PO_4, 2.0 equiv). Note: when one of the starting materials was an oil at room temperature, it was dissolved in reaction solvent (*e.g. n*-butanol) and added with the rest of the solvent at a later stage. The Schlenk flask containing the solid materials was evacuated and back-filled with nitrogen (3 times), followed by addition of the solvent system (2.0 mL/mmol aryl halide), consisting of degassed *n*-butanol (*n*-BuOH) and degassed deionized water in the ratio of 2.5:1. The resulting mixture was heated at 35 ^{o}C for 12 h. The crude reaction mixture was then filtered through a plug of silica gel using EtOAc eluent and reduced *in vacuo*. Purification by column chromatography over deactivated silica gel (5% triethylamine, NEt_3) provided the desired TIPS-protected phenylpyrrole.

General Procedure 5. Preparation of Iodinated *N*-(TIPS)pyrroles:

To a solution of the starting *N*-(TIPS)pyrrole (1.0 equiv) in acetone (2.0 mL/mmol SM) was added *N*-iodosuccinimide (NIS, 1.0 equiv). The reaction flask was covered in aluminum foil and the mixture was stirred at room temperature for 7–12 h. Note: on TLC plates, the iodinated products often had a very similar R_f to the starting material, so it was useful to monitor the reaction progress by GC-MS. To do this, a pipette tip full of reaction mixture was filtered through a micro-plug of cotton and silica in a separate pipette using EtOAc eluent. Once the reaction had finished, the crude mixture was reduced *in vacuo*. The product was then taken up in either hexane or pentane, filtered through a plug of neutral alumina, and reduced *in vacuo* to give the product in high purity.

General Procedure 6. Preparation of Brominated *N*-(TIPS)pyrroles:

To a solution of the starting *N*-(TIPS)pyrrole (1.0 equiv) in THF (2.0 mL/mmol SM) at -78 ^{o}C was added *N*-bromosuccinimide (NIS, 1.0 equiv). While the reaction mixture remained exposed to light and air, stirring was continued at -78 ^{o}C for 1–2 h. Note: on TLC plates, the brominated products often had a very similar R_f to the starting material, so it was useful to monitor the reaction progress by GC-MS. To do this, a pipette tip full of reaction mixture was filtered through a micro-plug of cotton and silica in a separate pipette using EtOAc eluent. Once the reaction had finished, the crude mixture was reduced *in vacuo*. The product was then taken up in either hexane or pentane, filtered through a plug of neutral alumina, and reduced *in vacuo*.

General Procedure 7. Metalation of Halogenated *N*-(TIPS)pyrroles:

To a solution of 3-X-*N*-(TIPS)pyrrole (1.0 equiv, X = Br or I) in THF (2.0 mL/mmol SM) at -78 ^{o}C, was added *t*-BuLi (2.05 equiv of a 1.7 M solution in hexanes) dropwise. This mixture was kept at -78 ^{o}C for 0.5 h (X = I) or 1 h (X = Br). A solution of the electrophile (2.0 equiv) in THF (3.0 mL/mmol SM) was then added dropwise, and the resulting mixture was left to react at -78 ^{o}C for 0.5 h before warming to RT (*c.a.* 1 h). The reaction mixture was worked-up (see Standard Work-up) and reduced *in vacuo* to give the crude product. The crude product was purified by column chromatography over deactivated silica gel (5% NEt_3) using pentane eluent.

General Procedure 8. Preparation of *N*-(TIPS)pyrrole pinacol boronates:

In an oven-dried Schlenk flask, the solid SMs were combined: 3-X-*N*-(TIPS)pyrrole (1.0 equiv, X = Br or I), bis(acetonitrile)dichloropalladium(II) [$PdCl_2(CH_3CN)_2$, 0.03 equiv], and SPhos (0.09 equiv). Note: when one of the starting materials was an oil at room temperature, it was dissolved in reaction solvent (*e.g.* toluene) and added with the rest of the solvent at a later stage. The Schlenk flask containing the solid SMs was evacuated and back-filled with nitrogen (3 times), followed by addition of dry toluene (2.0 mL/mmol 3-X-*N*-(TIPS)pyrrole), degassed NEt_3 (2.5 equiv), and finally pinacol borane (HBPin, 1.2 equiv). The resulting mixture was heated at 90 ^{o}C for *c.a.* 3 h. The crude reaction mixture was then filtered through a plug of neutral alumina using EtOAc eluent and reduced *in vacuo*. Purification by column chromatography over deactivated silica gel (5% NEt_3) provided the desired *N*-(TIPS)pyrrole pinacol boronate. Note: column chromatography must be performed quickly to minimize product decomposition. It is helpful to use shorter and thicker column lengths of silica gel.

General Procedure 9. Fluoride-Induced Desilylation of TIPS-Protected Phenylpyrroles:

To a solution of TIPS-protected phenylpyrrole (1.0 equiv) in THF (2.0 mL/mmol SM) at room temperature was added tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 2.0 equiv) dropwise. With the reaction vessel was covered in aluminum foil to minimize light exposure, the mixture was stirred at room temperature for *c.a.* 1 h (reaction progress monitored by TLC). Standard work-up, and subsequent purification by column chromatography over deactivated silica gel (5% NEt_3) afforded the desilylated product. It was necessary to further purify some deprotected phenylpyrroles using a normal phase SunFire^{TM} Prep Silica column (5 μm particle size, 10 x 150 mm column) with a UV detector (254 nm), isocratic mobile phase (hexane:EtOAc, 2.5:1), and 1.2 mL/min flow rate.

3-Chloro-*N*-(TIPS)pyrrole (2.14):

Following General Procedure 7, **2.14** was prepared from 3-bromo-*N*-(TIPS)pyrrole (6.00 g, 19.9 mmol). The crude residue was purified by column chromatography, affording **2.14** as a colorless oil in 87% yield. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm1H NMR (400 MHz, *Solvent*) d ppm 1.10 (d, *J* = 8.78 Hz, 18H), 1.58-1.47 (m, 3H), 6.21 (dd, *J* = 2.51, 1.75 Hz, 1H), 6.81 (dd, *J* = 3.09, 1.93 Hz, 2H); ^{13}C NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.115, 19.022, 112.505, 115.365, 122.596, 126.248; HRMS (EI) *m/z*: calcd for $C_{13}H_{24}ClNSi$: 257.1367. Found: 257.1376.

3-Bromo-4-chloro-*N*-(TIPS)pyrrole (2.16):

Following General Procedure 6,[105] **2.16** was prepared from **2.14** (2.50 g, 9.70 mmol). Recrystallization from methanol afforded **2.16** as a white solid in 85% yield. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.14-1.09 (m, 18H), 1.56 (td, *J* = 14.99, 7.51, 7.51 Hz, 3H), 6.95 (t, *J* = 8.8, 8.8 Hz, 2H); ^{13}C NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 12.925, 18.928, 99.968, 116.121, 123.426, 125.729; HRMS (EI) *m/z*: calcd for $C_{13}H_{23}BrClNSi$: 335.0472. Found 335.0482.

3-Chloro-4-iodo-*N*-(TIPS)pyrrole (2.17):

Following General Procedure 5, **2.17** was prepared from **2.14** (2.50 g, 9.70 mmol). The title compound was a white solid. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.12 (d, *J* = 8.78 Hz, 18H), 1.55 (tt, *J* = 7.34, 7.34, 5.21, 5.21 Hz, 3H), 6.97 (dd, *J* = 10.22, 2.46 Hz, 2H); ^{13}C NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 12.944, 18.942, 67.994, 120.072, 123.282, 130.950; HRMS (EI) *m/z*: calcd for $C_{13}H_{23}ClINSi$: 383.0333. Found 383.0344.

3-Chloro-4-(4',4',5',5'-tetramethyl-1',3',2'-dioxaborolan-2'-yl)-*N*-(TIPS)pyrrole (2.18):

Following General Procedure 8, **2.18** was prepared from 3-chloro-4-iodo-*N*-(TIPS)pyrrole (4.45 g, 11.6 mmol). The crude residue was purified by column chromatography, affording **2.18** as an off-white solid in 80% yield. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.12-1.10 (m, 18H), 1.29 (s,

12H), 1.57-1.53 (m, 3H), 6.85 (d, J = 2.32 Hz, 1H), 7.11 (d, J = 2.32 Hz, 1H); ^{13}C NMR [500 MHz, *$(CD_3)_2CO$*] δ ppm 13.075, 19.002, 26.179, 84.463, 112.496, 120.941, 124.162, 135.683; HRMS (EI) *m/z*: calcd for $C_{19}H_{35}BClNO_2Si$: 383.2219. Found 383.2222.

2-Bromo-6-fluorobenzoic acid (3.23):

Following General Procedure 1, **3.23** was prepared from 1-bromo-3-fluorobenzene (2.23 g, 10.0 mmol). The white crystalline product was obtained in 92% yield. ^{1}H NMR [400 MHz, *$(CD_3)_2CO$*] δ ppm 7.56 (d, J = 7.9 Hz, 1H), 7.48 (td, J = 5.9, 8.2 Hz, 1H), 7.33 (dd, J = 4.7, 12.8 Hz, 1H). ^{13}C NMR [400 MHz, *$(CD_3)_2CO$*] δ ppm 164.78, 161.23, 158.73, 133.07, 129.64, 120.00, 115.84.

2-Bromo-6-fluoroaniline (3.24):

Following General Procedure 1, **3.24** was prepared from **3.23** (860 mg, 4.5 mmol). The white crystalline product was obtained in 86% yield. ^{1}H NMR (400 MHz, Acetone) δ 7.22 (dd, J = 1.0, 8.1, 1H), 7.06 – 6.95 (m, 1H), 6.57 (td, J = 5.5, 8.2, 1H), 4.86 (s, 2H) ^{13}C NMR (400 MHz, acetone) δ 152.21, 149.81, 134.69, 127.83, 117.21, 113.97.

2-Bromo-6-fluoronitrobenzene (3.25):

Following General Procedure 1, **3.25** was prepared from **3.24** (322 mg, 1.46 mmol). The white crystalline product was obtained in 88% yield. ^{1}H NMR (400 MHz, CDCl3) δ 7.54 – 7.48 (m, 1H), 7.40 (td, J = 5.5, 8.3, 1H), 7.30 – 7.23 (m, 1H). ^{13}C NMR (400 MHz, CDCl3) δ 155.40, 152.81, 132.31, 129.29, 116.23, 114.30.

2-Bromo-6-chlorobenzoic acid (3.22):

Following General Procedure 1, **3.22** was prepared from 1-bromo-3-chlorobenzene (5.00 g, 26.1 mmol). The off-white crystalline product was obtained in quantitative yield. The analytical and spectral data were in accordance with those previously reported.[125]

2-Bromo-6-chloroaniline (3.26):

Following General Procedure 2, **3.26** was prepared from 2-bromo-6-chlorobenzoic acid (5.00 g, 24.2 mmol). The crude crystalline material was purified by column chromatography, affording **3.26** as a light brown solid in 92% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 5.10 (s, 2H), 6.58 (t, *J* = 8.00, 8.00 Hz, 1H), 7.26 (dd, *J* = 7.97, 1.16 Hz, 1H), 7.38 (dd, *J* = 8.01, 1.19 Hz, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 110.201, 119.971, 120.375, 130.453, 133.046, 143.863; HRMS (EI) *m/z*: calcd for C_6H_5BrClN: 204.9294. Found 204.9295.

2-Bromo-6-chloronitrobenzene (3.27):

Following General Procedure 3, **3.27** was prepared from 2-bromo-6-chloroaniline (5.00 g, 21.2 mmol). The crude crystalline material was purified by column chromatography, affording **3.27** as an orange solid in 94% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 7.59 (t, *J* = 8.21, 8.21 Hz, 1H), 7.76-7.74 (m, 1H), 7.85 (dd, *J* = 8.18, 0.92 Hz, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 115.016, 127.193, 131.927, 134.483, 134.519, 151.650; HRMS (EI) *m/z*: calcd for $C_6H_3BrClNO_2$: 234.9036. Found 234.9047.

2,6-Dibromobenzoic acid (3.28):

Following General Procedure 1, **3.28** was prepared from 1,3-dibromobenzene (3.00 g, 12.7 mmol). The off-white crystalline product was obtained in 85% yield. The analytical and spectral data were in accordance with those previously reported.[143]

2,6-Dibromoaniline (3.29):

Following General Procedure 2, **3.29** was prepared from 2,6-dibromobenzoic acid (2.50 g, 8.93 mmol). The crude crystalline material was purified by column chromatography, affording **3.29** as an off-white solid in 78% yield. The analytical and spectral data were in accordance with those previously reported by AIST: Integrated Spectral Database System of Organic Compounds.

2,6-Dibromonitrobenzene (3.30):

Following General Procedure 3, **3.30** was prepared from 2,6-dibromoaniline (2.00 g, 7.12 mmol). The crude crystalline material was purified by column chromatography, affording **3.30** as an orange solid in 82% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 7.31 (t, *J* = 8.10, 8.10 Hz, 1H), 7.68 (d, *J* = 8.11 Hz, 2H); ^{13}C NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 119.976, 132.941, 132.977, 139.765, 167.272; HRMS (EI) *m/z*: calcd for $C_6H_3Br_2NO_2$: 278.8531. Found 278.8544.

2-Bromo-6-iodobenzoic acid (3.31):

Following General Procedure 1, **3.31** was prepared from 1-bromo-3-iodobenzene (3.00 g, 10.6 mmol). The off-white crystalline product was obtained in 80% yield. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 7.13 (t, *J* = 8.03, 8.03 Hz, 1H), 7.72-7.69 (m, 1H), 7.94-7.91 (m, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 93.150, 119.717, 133.625, 133.725, 134.196, 140.132; HRMS (EI) *m/z*: calcd for $C_7H_4BrIO_2$: 325.8439. Found 325.8427.

2-Bromo-6-iodoaniline (3.32):

Following General Procedure 2, **3.32** was prepared from 2-bromo-6-chlorobenzoic acid (2.30 g, 7.04 mmol). The crude crystalline material was purified by column chromatography, affording **3.32** as a white solid in 58% yield. ^{1}H NMR [400 MHz, *CDCl$_3$*] δ ppm 7.60 (dd, *J* = 5.41, 1.32 Hz, 1H), 7.41 (dd, *J* = 1.33, 6.60 Hz, 1H), 6.33 (t, *J* = 7.90 Hz, 1H) ^{13}C NMR [500 MHz, *(CDCl$_3$)*] δ ppm 144.457, 138.626, 133.164, 120.759, 107.727, 83.492; HRMS (EI) *m/z*: calcd for C_6H_5BrIN: 296.8650. Found 296.8648.

2-Bromo-6-iodonitrobenzene (3.33):

Following General Procedure 3, **3.33** was prepared from 2-bromo-6-iodoaniline (1.50 g, 5.04 mmol). The crude crystalline material was purified by column chromatography, affording **3.33** as a color solid in 56% yield. ^{1}H NMR [400 MHz, *CDCl$_3$*] δ ppm 7.84 (d, *J* = 7.97 Hz, 1H), 7.64 (d, *J* = 8.10 Hz, 1H), 7.06 (t, *J* = 8.04, 8.04 Hz, 1H); ^{13}C NMR [500 MHz, *(CDCl$_3$)*] δ ppm 155.690,

139.424, 138.889, 132.308, 113.292, 85.900; HRMS (EI) *m/z*: calcd for $C_6H_3BrINO_2$: 326.8392. Found 326.8391.

3-(2'-aminophenyl)-*N*-(TIPS)pyrrole (4.9):

Following General Procedure 4, **4.9** was prepared from **2.15** (125 mg, 0.357 mmol) and commercially available 2-bromoaniline (Sigma-Aldrich, 65.3 mg, 0.298 mmol). The crude residue was purified by column chromato-graphy, affording **4.9** as a light yellow oil in 85% yield. ^{1}H NMR [400 MHz, *$(CD_3)_2CO$*] δ 1.16 (d, *J* = 8.78 Hz, 18H), 1.57 (td, *J* = 14.95, 7.51, 7.51 Hz, 3H), 4.45 (s, 2H), 6.50 (dd, *J* = 2.60, 1.40 Hz, 1H), 6.63 (d, *J* = 1.00 Hz, 1H), 6.77-6.73 (m, 1H), 6.97-6.92 (m, 2H), 7.04 (s, 1H), 7.17 (dd, *J* = 7.57, 1.35 Hz, 1H); ^{13}C NMR [400 MHz, *$(CD_3)_2CO$*] δ ppm 11.771, 17.621, 110.889, 115.450, 117.604, 122.159, 124.957, 126.848, 129.506, 145.104; HRMS (EI) *m/z*: calcd for $C_{19}H_{30}N_2Si$: 314.2178. Found 314.2193.

3-(2'-aminophenyl)pyrrole (4.10):

Following General Procedure 9, **4.10** was prepared from **4.9** (79.6 mg, 0.253 mmol). The crude residue was purified by column chromatography, affording **4.10** as a light yellow oil in 79% yield. ^{1}H NMR [500 MHz, *$(CD_3)_2CO$*] δ ppm 4.46 (s, 2H), 6.34 (dd, *J* = 4.13, 2.51 Hz, 1H), 6.62 (dt, *J* = 7.43, 7.40, 1.15 Hz, 1H), 6.74 (dd, *J* = 7.92, 1.00 Hz, 1H), 6.88 (dd, *J* = 4.67, 2.59 Hz, 1H), 6.93 (dt, *J* = 7.90, 7.90, 1.53 Hz, 1H), 7.01 (dd, *J* = 4.09, 1.83 Hz, 1H), 7.15 (dd, *J* = 7.55, 1.46 Hz, 1H), 10.19 (s, 1H); ^{13}C NMR [500 MHz, *$(CD_3)_2CO$*] δ ppm 109.446, 116.915, 117.768, 119.089, 120.143, 123.588, 123.995, 128.181, 131.031, 146.670; HRMS (EI) *m/z*: calcd for $C_{10}H_{10}N_2$: 158.0844. Found 158.0845.

3-(2'-nitrophenyl)-*N*-(TIPS)pyrrole (4.11):

Following General Procedure 4, **4.11** was prepared from **2.15** (125 mg, 0.357 mmol) and commercially available 2-bromonitrobenzene (Sigma-Aldrich, 60.2 mg, 0.298 mmol). The crude residue was purified by column chromatography, affording **4.11** as a light yellow oil in 81%

yield. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.13 (t, *J* = 8.78, 8.78 Hz, 18H), 1.58-1.52 (m, 3H), 6.41 (dd, *J* = 2.80, 1.50 Hz, 1H), 6.93-6.91 (m, 1H), 7.06-7.04 (m, 1H), 7.42-7.38 (m, 1H), 7.58 (dt, *J* = 7.80, 7.59, 1.33 Hz, 1H), 7.66 (ddd, *J* = 4.82, 3.23, 1.05 Hz, 2H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.231, 19.073, 111.937, 122.744, 124.638, 124.718, 127.144, 128.232, 130.977, 132.273, 133.197, 151.275; HRMS (EI) *m/z*: calcd for $C_{19}H_{28}N_2O_2Si$: 344.1920. Found 344.1922.

3-(2'-nitrophenyl)pyrrole (4.12):

Following General Procedure 9, **4.12** was prepared from **4.11** (83.0 mg, 0.241 mmol). The crude residue was purified by column chromatography, affording **4.12** as a light yellow oil in 81% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 6.27-6.24 (m, 1H), 6.87 (dd, *J* = 2.76, 1.81 Hz, 1H), 7.07-7.04 (m, 1H), 7.40-7.36 (m, 1H), 7.57 (dt, *J* = 7.96, 7.67, 1.25 Hz, 1H), 7.63 (dd, *J* = 7.95, 1.12 Hz, 2H), 10.39 (s, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 109.045, 118.734, 120.062, 120.988, 124.664, 127.982, 131.307, 132.200, 133.145; HRMS (EI) *m/z*: calcd for $C_{10}H_8N_2O_2$: 188.0586. Found 188.0585.

3-(2'-amino-3'-chlorophenyl)-*N*-(TIPS)pyrrole (4.13):

Following General Procedure 4, **4.13** was prepared from **2.15** (125 mg, 0.357 mmol) and **3.26** (61.5 mg, 0.298 mmol). The crude residue was purified by column chromatography, affording **4.13** as a light yellow oil in 82% yield. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.15 (d, *J* = 7.50 Hz, 18H), 1.62-1.54 (m, 3H), 4.69 (s, 2H), 6.51 (dd, *J* = 2.67, 1.44 Hz, 1H), 6.65 (t, *J* = 7.78, 7.78 Hz, 1H), 7.00-6.95 (m, 1H), 7.07 (t, *J* = 8.78, 8.78 Hz, 1H), 7.13 (ddd, *J* = 8.11, 6.61, 1.43 Hz, 3H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 11.846, 17.699, 110.916, 118.003, 119.111, 122.764, 124.076, 124.101, 125.445, 127.103, 128.458, 141.460; HRMS (EI) *m/z*: calcd for $C_{19}H_{29}ClN_2Si$: 348.1789. Found 348.1785.

3-(2'-amino-3'-chlorophenyl)pyrrole (1.24):

Following General Procedure 9, **1.24** was prepared from **4.13** (85.2 mg, 0.244 mmol). The crude residue was purified by column chromatography, affording **4.13** as a light yellow oil in 80% yield. The analytical and spectral data were in accordance with those previously reported.[140]

3-(3'-chloro-2'-nitrophenyl)-*N*-(TIPS)pyrrole (4.14):

Following General Procedure 4, **4.14** was prepared from **2.15** (125 mg, 0.357 mmol) and **3.27** (70.5 mg, 0.298 mmol). The crude residue was purified by column chromatography, affording **4.14** as a light yellow oil in 87% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.12 (d, *J* = 7.52 Hz, 18H), 1.54 (dd, *J* = 15.00, 7.49 Hz, 3H), 6.47 (dd, *J* = 2.69, 1.48 Hz, 1H), 6.96-6.94 (m, 1H), 7.08 (d, *J* = 1.51 Hz, 1H), 7.49 (dd, *J* = 8.03, 1.16 Hz, 1H), 7.56 (t, *J* = 7.96, 7.96 Hz, 1H), 7.68 (dd, *J* = 7.87, 1.18 Hz, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.209, 19.102, 111.588, 121.397, 124.723, 124.967, 125.972, 127.533, 127.801, 130.278, 132.132, 132.899; HRMS (EI) *m/z*: calcd for $C_{19}H_{27}ClN_2O_2Si$: 378.1530. Found 378.1526.

3-(3'-chloro-2'-nitrophenyl)pyrrole (4.15):

Following General Procedure 9, **4.15** was prepared from **4.14** (98.2 mg, 0.259 mmol). The crude residue was purified by column chromatography, affording **4.15** as a light yellow oil in 64% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 6.35-6.30 (m, 1H), 6.91 (dd, *J* = 4.66, 2.57 Hz, 1H), 7.09 (d, *J* = 1.07 Hz, 1H), 7.48 (dd, *J* = 7.99, 1.11 Hz, 1H), 7.55 (d, *J* = 7.97 Hz, 1H), 7.64 (dd, *J* = 7.90, 1.10 Hz, 1H), 10.539 (s, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 108.832, 118.792, 119.070, 121.558, 125.981, 128.597, 130.248, 132.558, 132.906; HRMS (EI) *m/z*: calcd for $C_{10}H_7ClN_2O_2$: 222.0196. Found 222.0192.

3-Chloro-4-(2'-aminophenyl)-*N*-(TIPS)pyrrole (4.16):

Following General Procedure 4, **4.16** was prepared from **2.18** (137 mg, 0.357 mmol) and commercially available 2-bromoaniline (Sigma-Aldrich, 65.3 mg, 0.298 mmol). The crude

residue was purified by column chromatography, affording **4.16** as a light yellow oil in 81% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.15 (d, *J* = 7.56 Hz, 18H), 1.57 (td, *J* = 14.96, 7.51, 7.51 Hz, 3H), 4.34 (s, 2H), 6.68-6.64 (m, 1H), 6.78 (dd, *J* = 8.01, 0.95 Hz, 1H), 6.91 (d, *J* = 2.46 Hz, 1H), 6.98 (d, *J* = 2.47 Hz, 1H), 7.04 (dt, *J* = 7.99, 7.98, 1.55 Hz, 1H), 7.11 (dd, *J* = 7.53, 1.47 Hz, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.080, 19.092, 115.217, 116.653, 118.559, 120.297, 123.607, 124.930, 129.712, 132.934, 147.801; HRMS (EI) *m/z*: calcd for $C_{19}H_{29}ClN_2Si$: 348.1789. Found 348.1772.

3-Chloro-4-(2'-aminophenyl)pyrrole (4.17):

Following General Procedure 9, **4.17** was prepared from **4.16** (84.1 mg, 0.241 mmol). The crude residue was purified by column chromatography, affording **4.17** as a light yellow oil in 75% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 4.38 (s, 2H), 6.64 (dt, *J* = 7.41, 7.41, 1.14 Hz, 1H), 6.77 (dd, *J* = 8.01, 0.98 Hz, 1H), 6.90-6.87 (m, 1H), 6.95 (t, *J* = 2.60, 2.60 Hz, 1H), 7.02 (dt, *J* = 8.01, 7.97, 1.56 Hz, 1H), 7.08 (dd, *J* = 7.52, 1.49 Hz, 1H), 10.38 (s, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 112.569, 116.575, 118.027, 118.459, 119.036, 120.559, 120.834, 129.577, 133.076, 147.940; HRMS (EI) *m/z*: calcd for $C_{10}H_9ClN_2$: 192.0454. Found 192.0452.

3-Chloro-4-(2'-nitrophenyl)-*N*-(TIPS)pyrrole (4.18):

Following General Procedure 4, **4.18** was prepared from **2.18** (137 mg,0.357 mmol) and commercially available 2-bromonitrobenzene (Sigma-Aldrich, 60.2 mg, 0.298 mmol). The crude residue was purified by column chromatography, affording **4.18** as a light yellow oil in 86% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.15 (d, *J* = 7.51 Hz, 18H), 1.57 (td, *J* = 11.59, 7.50, 7.50 Hz, 3H), 6.96 (dd, *J* = 5.82, 2.46 Hz, 2H), 7.58 (dd, *J* = 11.84, 4.46 Hz, 2H), 7.73-7.69 (m, 1H), 7.96-7.88 (m, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 11.579, 17.532, 113.446, 120.632, 122.335, 123.681, 124.156, 128.068, 128.433, 132.414, 133.230; HRMS (EI) *m/z*: calcd for $C_{19}H_{27}ClN_2O_2Si$: 344.1920. Found 344.1922.

3-Chloro-4-(2'-nitrophenyl)pyrrole (4.19):

Following General Procedure 9, **4.19** was prepared from **4.18** (97.0 mg, 0.256 mmol). The crude residue was purified by column chromatography, affording **4.19** as a light yellow oil in 78% yield. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 6.95 (td, *J* = 5.21, 2.35, 2.35 Hz, 2H), 7.55 (ddd, *J* = 6.59, 5.46, 3.84 Hz, 2H), 7.70 (dd, *J* = 7.58, 6.23 Hz, 1H), 7.90 (dd, *J* = 7.98, 0.88 Hz, 1H), 10.53 (s, 1H); ^{13}C NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 112.459, 118.333, 119.314, 119.426, 125.637, 129.711, 129.830, 133.868, 134.830; HRMS (EI) *m/z*: calcd for $C_{10}H_7ClN_2O_2$: 222.0196. Found 222.0194.

3-Chloro-4-(2'-amino-3'-chlorophenyl)-*N*-(TIPS)pyrrole (4.20):

Following General Procedure 4, **4.20** was prepared from **2.18** (137 mg, 0.357 mmol) and **3.26** (61.5 mg, 0.298 mmol). The crude residue was purified by column chromatography, affording **4.20** as a light yellow oil in 82% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.15 (d, *J* = 7.52 Hz, 18H), 1.59 (td, *J* = 11.39, 7.51, 7.51 Hz, 3H), 4.57 (s, 2H), 6.67 (t, *J* = 7.76, 7.76 Hz, 1H), 6.96 (d, *J* = 2.47 Hz, 1H), 7.01 (d, *J* = 2.46 Hz, 1H), 7.05 (dd, *J* = 7.54, 1.38 Hz, 1H), 7.20 (dd, *J* = 7.97, 1.41 Hz, 1H); ^{13}C NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.092, 19.080, 115.109, 118.930, 120.260, 122.194, 122.934, 123.992, 125.296, 129.936, 131.839, 144.255; HRMS (EI) *m/z*: calcd for $C_{19}H_{28}Cl_2N_2Si$: 382.1399. Found 382.1408.

3-Chloro-4-(2'-amino-3'-chlorophenyl)pyrrole (1.25):

Following General Procedure 9, **1.25** was prepared from **4.20** (93.6 mg, 0.244 mmol). The crude residue was purified by column chromatography, affording **1.25** as a light yellow oil in 73% yield. The analytical and spectral data were in accordance with those previously reported.[140]

3-Chloro-4-(3'-chloro-2'-nitrophenyl)-*N*-(TIPS)pyrrole (4.21):

Following General Procedure 4, **4.21** was prepared from **2.18** (137 mg, 0.357 mmol) and **3.27** (70.5 mg, 0.298 mmol). The crude residue was purified by column chromatography, affording

4.21 as a light yellow oil in 89% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.12 (d, *J* = 7.51 Hz, 18H), 1.55 (td, *J* = 14.99, 7.51, 7.51 Hz, 3H), 6.87 (d, *J* = 2.37 Hz, 1H), 7.03 (d, *J* = 2.38 Hz, 1H), 7.69-7.61 (m, 3H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.008, 18.926, 114.685, 119.007, 124.410, 125.527, 125.863, 129.736, 130.617, 132.436, 132.726; HRMS (EI) *m/z*: calcd for $C_{19}H_{26}Cl_2N_2O_2Si$: 412.1141. Found 412.1143.

3-Chloro-4-(3'-chloro-2'-nitrophenyl)pyrrole (1.2):

Following General Procedure 9, **1.2** was prepared from **4.21** (110 mg, 0.265 mmol). The crude residue was purified by column chromatography, affording **1.2** as a light yellow oil in 74% yield. The analytical and spectral data were in accordance with those previously reported.[140]

3-Bromo-4-iodo-*N*-(TIPS)pyrrole (4.23):

Following General Procedure 5, **4.23** was prepared from 3-bromo-*N*-(TIPS)pyrrole (2.93 g, 9.70 mmol). The title compound was a white solid. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.14-1.08 (m, 18H), 1.60-1.52 (m, 3H), 6.98 (dd, *J* = 8.11, 2.43 Hz, 2H); ^{13}C NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 12.049, 18.001, 105.947, 125.136, 125.215, 130.623; HRMS (EI) *m/z*: calcd for $C_{13}H_{23}BrINSi$: 426.9828. Found 426.9834.

3-Bromo-4-(4',4',5',5'-tetramethyl-1',3',2'-dioxaborolan-2'-yl)-*N*-(TIPS)pyrrole (4.24):

Following General Procedure 8, **4.24** was prepared from 3-bromo-4-iodo-*N*-(TIPS)pyrrole (4.97 g, 11.6 mmol). The crude residue was purified by column chromatography, affording **4.24** as a white solid in 79% yield. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.11 (d, *J* = 7.53 Hz, 18H), 1.29 (s, 12H), 1.56 (ddd, *J* = 9.44, 5.59, 3.40 Hz, 3H), 6.90 (d, *J* = 2.26 Hz, 1H), 7.13 (d, *J* = 2.27 Hz, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.077, 19.001, 26.1814, 84.452, 105.486, 114.767, 126.849, 136.275; HRMS (EI) *m/z*: calcd for $C_{19}H_{35}BBrNO_2Si$: 427.1713. Found 427.1717.

3-Bromo-4-D-*N*-(TIPS)pyrrole (4.25):

Following General Procedure 7, **4.25** was prepared from 3-bromo-4-iodo-*N*-(TIPS)pyrrole (1.71 g, 4.00 mmol). The title compound was a colorless oil. ^{1}H NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.10 (d, *J* = 7.51 Hz, 18H), 1.53 (td, *J* =14.96, 7.51, 7.51 Hz, 3H), 6.84 (dd, *J* = 12.68, 2.26 Hz, 2H); ^{13}C NMR [400 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.124, 19.024, 114.775, 125.133, 126.814, 126.915; HRMS (EI) *m/z*: calcd for $C_{13}H_{23}DBrNSi$: 302.0924. Found 302.0920.

3-D-4-(4',4',5',5'-tetramethyl-1',3',2'-dioxaborolan-2'-yl)-*N*-(TIPS)pyrrole (4.26):

Following General Procedure 8, **4.26** was prepared from 3-bromo-4-D-*N*-(TIPS)pyrrole (1.05 g, 3.00 mmol). The crude residue was purified by column chromatography, affording 42 as a white solid in 79% yield. ^{1}H NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 1.11 (d, *J* = 7.57 Hz, 18H), 1.28 (s, 12H), 1.54 (dd, *J* = 9.44, 5.59 Hz, 3H), 6.85 (d, *J* = 1.84 Hz, 1H), 7.19 (d, *J* = 1.86 Hz, 1H); ^{13}C NMR [500 MHz, *(CD$_3$)$_2$CO*] δ ppm 13.278, 19.120, 26.233, 84.069, 104.959, 117.661, 126.196, 134.970; HRMS (EI) *m/z*: calcd for $C_{19}H_{35}DBNO_2Si$: 350.2671. Found 350.2678.

3-D-4-(2'-aminophenyl)-*N*-(TIPS)pyrrole (4.27)

Following general procedure 4, **4.27** was prepared from 2-bromoaniline (42 mg, 0.24 mmol) and **4.26** (102 mg, 0.29 mmol). The crude residue was purified by column chromatography, affording **4.27** as a yellow oil in 90% yield. ^{1}H NMR [400 MHz, *CDCl$_3$*] δ ppm 7.19, 6.98 (dt, *J* = 7.73, 7.68, 1.41 Hz, 1H), 6.88 (d, *J* = 1.98 Hz, 1H), 6.77 (d, *J* = 1.95 Hz, 1H), 6.70 (dd, *J* = 14.29, 7.64 Hz, 1H), 7.20-7.17 (m, 1H), 1.40 (td, *J* = 14.92, 7.49, 7.49 Hz, 1H), 1.05 (d, *J* = 7.52 Hz, 1H) ^{13}C NMR [400 MHz, *CDCl$_3$*] δ ppm 143.602, 130.120, 126.948, 124.678, 123.797, 122.689, 122.384, 118.657, 115.555, (110.746, 110.533, 110.283), 17.889, 11.723; HRMS (EI) *m/z*: Calculated for $C_{19}H_{27}DN_2O_2Si$: 315.2241. Found 315.2240.

3-Bromo-4-(2'-nitrophenyl)-*N*-(TIPS)pyrrole (4.28)

Following general procedure 4, **4.28** was prepared from 2-bromonitrobenzene (18 mg, 0.09 mmol) and **4.24** (47 mg, 0.11 mmol). The crude residue was purified by preparative TLC, affording **4.28** as a pale yellow oil in 18% yield. ^{1}H NMR [400 MHz, $CDCl_3$] δ ppm 7.83 (dd, *J* = 8.09, 1.07 Hz, 1H), 7.58 (dt, *J* = 7.52, 7.35, 1.26 Hz, 1H), 7.53 (dd, *J* = 7.70, 1.52 Hz, 1H), 7.46-7.40 (m, 1H), 6.82 (d, *J* = 2.40 Hz, 1H), 6.77 (d, *J* = 2.39 Hz, 1H), 1.45 (td, *J* = 14.92, 7.50, 7.50 Hz, 3H), 1.13 (d, *J* = 7.48 Hz, 18H); ^{13}C NMR [400 MHz, $CDCl_3$] δ ppm 150.257, 133.347, 131.297, 128.987, 127.899, 124.617, 124.078, 123.652, 121.841, 17.990, 11.928; HRMS (EI) *m/z*: Calculated for $C_{19}H_{27}N_2O_2Si$:Br 422.1025. Found 422.1024.

References

1. Gribble, G. W. *J. Chem. Educ.* **2004,** 81, (10).
2. Morrison, M.; Schonbaum, G. R. *Annu. Rev. Biochem.* **1976,** 45, 861-888.
3. Kirner, S.; Hammer, P. E.; Hill, D. S.; Altmann, A.; Fischer, I.; Weislo, L. J.; Lanahan, M.; van Pee, K. H.; Ligon, J. M. *J. Bacteriol.* **1998,** 180, (7), 1939-1943.
4. Saitoh, T.; Suzuki, T.; Sugimoto, M.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003,** 44, (15), 3175-3178.
5. Dong, C. J.; Huang, F. L.; Deng, H.; Schaffrath, C.; Spencer, J. B.; O'Hagan, D.; Naismith, J. H. *Nature* **2004,** 427, (6974), 561-565.
6. Littlechild, J. *Curr. Opin. Chem. Biol.* **1999,** 3, (1), 28-34; Rorrer, G. L.; Tucker, M. P.; Cheney, D. P.; Maliakal, S. *Biotechnol. Bioeng.* **2001,** 74, (5), 389-395; Almeida, M. G.; Humanes, M.; Melo, R.; Silva, J. A.; da Silva, J.; Wever, R. *Phytochemistry* **2000,** 54, (1), 5-11.
7. Wuosmaa, A. M.; Hager, L. P. *Science* **1990,** 249, (4965), 160-162.
8. O'Hagan, D.; Schaffrath, C.; Cobb, S. L.; Hamilton, J. T. G.; Murphy, C. D. *Nature* **2002,** 416, (6878), 279-279.
9. Taurog, A.; Howells, E. M. *J. Biol. Chem.* **1966,** 241, (6), 1329-&; Morris, D. R.; Hager, L. P. *J. Biol. Chem.* **1966,** 241, (8), 1763-&.
10. Libby, R. D.; Thomas, J. A.; Kaiser, L. W.; Hager, L. P. *J. Biol. Chem.* **1982,** 257, (9), 5030-5037.
11. Geigert, J.; Neidleman, S. L.; Dalietos, D. J.; Dewitt, S. K. *Appl. Environ. Microbiol.* **1983,** 45, (2), 366-374.
12. Sundaramoorthy, M.; Terner, J.; Poulos, T. L. *Chem. Biol.* **1998,** 5, (9), 461-473.
13. Hofrichter, M.; Ullrich, R. *Appl. Microbiol. Biotechnol.* **2006,** 71, (3), 276-288.
14. van Pee, K. H.; Unversucht, S. *Chemosphere* **2003,** 52, (2), 299-312.
15. Butler, A.; Carter-Franklin, J. N. *Nat. Prod. Rep.* **2004,** 21, (1), 180-188.
16. Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006,** 106, (8), 3364-3378.
17. Messerschmidt, A.; Prade, L.; Wever, R. *Biol. Chem.* **1997,** 378, (3-4), 309-315.
18. Itoh, N.; Morinaga, N.; Kouzai, T. *Biochimica Et Biophysica Acta-Protein Structure and Molecular Enzymology* **1994,** 1207, (2), 208-216; Itoh, N.; Izumi, Y.; Yamada, H. *J. Biol. Chem.* **1986,** 261, (11), 5194-5200; Liu, T. N. E.; Mtimkulu, T.; Geigert, J.; Wolf, B.; Neidleman, S. L.; Silva, D.; Huntercevera, J. C. *Biochem. Biophys. Res. Commun.* **1987,** 142, (2), 329-333; Itoh, N.; Izumi, Y.; Yamada, H. *J. Biol. Chem.* **1987,** 262, (25), 11982-11987; Blasiak, L. C.; Drennan, C. L. *Acc. Chem. Res.* **2009,** 42, (1), 147-155.
19. Burd, V. N.; Bantleon, R.; van Pee, K. H. *Appl. Biochem. Microbiol.* **2001,** 37, (3), 248-250.
20. van Pee, K. H.; Patallo, E. P. *Appl. Microbiol. Biotechnol.* **2006,** 70, (6), 631-641.
21. Dairi, T.; Nakano, T.; Aisaka, K.; Katsumata, R.; Hasegawa, M. *Biosci. Biotechnol. Biochem.* **1995,** 59, (6), 1099-1106.
22. Paulsen, I. T.; Press, C. M.; Ravel, J.; Kobayashi, D. Y.; Myers, G. S. A.; Mavrodi, D. V.; DeBoy, R. T.; Seshadri, R.; Ren, Q. H.; Madupu, R.; Dodson, R. J.; Durkin, A. S.; Brinkac, L. M.; Daugherty, S. C.; Sullivan, S. A.; Rosovitz, M. J.; Gwinn, M. L.; Zhou, L. W.; Schneider, D. J.; Cartinhour, S. W.; Nelson, W. C.; Weidman, J.; Watkins, K.; Tran, K.; Khouri, H.; Pierson, E. A.; Pierson, L. S.; Thomashow, L. S.; Loper, J. E.

Nature Biotechnology **2005,** 23, (7), 873-878; Hammer, P. E.; Hill, D. S.; Lam, S. T.; VanPee, K. H.; Ligon, J. M. *Appl. Environ. Microbiol.* **1997,** 63, (6), 2147-2154.
23. Nowak-Thompson, B.; Chaney, N.; Wing, J. S.; Gould, S. J.; Loper, J. E. *J. Bacteriol.* **1999,** 181, (7), 2166-2174.
24. Guenzi, E.; Galli, G.; Grgurina, I.; Gross, D. C.; Grandi, G. *J. Biol. Chem.* **1998,** 273, (49), 32857-32863.
25. Chang, Z. X.; Flatt, P.; Gerwick, W. H.; Nguyen, V. A.; Willis, C. L.; Sherman, D. H. *Gene* **2002,** 296, (1-2), 235-247.
26. Price, J. C.; Barr, E. W.; Tirupati, B.; Bollinger, J. M.; Krebs, C. *Biochemistry* **2003,** 42, (24), 7497-7508.
27. Jones, J. P.; Korzekwa, K. R.; Rettie, A. E.; Trager, W. F. *J. Am. Chem. Soc.* **1986,** 108, (22), 7074-7078.
28. Denisov, I. G.; Makris, T. M.; Sligar, S. G.; Schlichting, I. *Chem. Rev.* **2005,** 105, (6), 2253-2277.
29. Hausinger, R. P. *Crit. Rev. Biochem. Mol. Biol.* **2004,** 39, (1), 21-68.
30. Vaillancourt, F. H.; Yin, J.; Walsh, C. T. *Proceedings of the National Academy of Sciences of the United States of America* **2005,** 102, (29), 10111-10116.
31. Blasiak, L. C.; Vaillancourt, F. H.; Walsh, C. T.; Drennan, C. L. *Nature* **2006,** 440, (7082), 368-371.
32. Kojima, T.; Leising, R. A.; Yan, S. P.; Que, L. *J. Am. Chem. Soc.* **1993,** 115, (24), 11328-11335.
33. Keller, S.; Wage, T.; Hohaus, K.; Holzer, M.; Eichhorn, E.; van Pee, K. H. *Angew. Chem. Int. Edit.* **2000,** 39, (13), 2300-2302.
34. Chen, X. P.; van Pee, K. H. *Acta Biochimica Et Biophysica Sinica* **2008,** 40, (3), 183-193.
35. Yeh, E.; Garneau, S.; Walsh, C. T. *PNAS* **2005,** 102, (11), 3960-3965.
36. Ziegler, D. M. *Drug. Metab. Rev.* **2002,** 34, (3), 503-511.
37. Yeh, E.; Cole, L. J.; Barr, E. W.; Bollinger, J. M.; Ballou, D. P.; Walsh, C. T. *Biochemistry* **2006,** 45, (25), 7904-7912.
38. Hubbard, B. K.; Walsh, C. T. *Angew. Chem. Int. Edit.* **2003,** 42, (7), 730-765.
39. Dong, C. J.; Flecks, S.; Unversucht, S.; Haupt, C.; van Pee, K. H.; Naismith, J. H. *Science* **2005,** 309, (5744), 2216-2219.
40. Tichenor, M. S.; Boger, D. L. *Nat. Prod. Rep.* **2008,** 25, (2), 220-226; Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008,** 10, (7), 1369-1372; Kumar, G. D. K.; Natarajan, A. *Tetrahedron Lett.* **2008,** 49, (13), 2103-2105.
41. Wittig, G.; Pockels, U.; Droge, H. *Berichte Der Deutschen Chemischen Gesellschaft* **1938,** 71, 1903-1912.
42. Wittig, G.; Fuhrmann, G. *Berichte Der Deutschen Chemischen Gesellschaft* **1940,** 73, 1197-1218.
43. Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939,** 61, 109-112.
44. Schaub, B.; Jenny, T.; Schlosser, M. *Tetrahedron Lett.* **1984,** 25, (37), 4097-4100.
45. Schmid, R.; Foricher, J.; Cereghetti, M.; Schonholzer, P. *Helvetica Chimica Acta* **1991,** 74, (2), 370-389; Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996,** 68, (1), 131-138.
46. Snieckus, V. *Chem. Rev.* **1990,** 90, (6), 879-933.
47. Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946,** 68, (8), 1658-1660.
48. Boerhorst, E.; Schmitz, R. F.; Klumpp, G. W. *Tetrahedron Lett.* **1975**, (38), 3347-3348; Vos, M.; Dekanter, F. J. J.; Schakel, M.; Hommes, N.; Klumpp, G. W. *J. Am. Chem. Soc.*

1987, 109, (7), 2187-2188; McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985,** 107, (7), 1805-1810.
49. McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *J. Am. Chem. Soc.* **1985,** 107, (7), 1810-1815.
50. Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Edit.* **2004,** 43, (17), 2206-2225.
51. Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986,** 19, (11), 356-363.
52. Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994,** 116, (23), 10815-10816.
53. Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998,** 120, (2), 421-422.
54. Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000,** 122, (36), 8640-8647.
55. Maggi, R.; Schlosser, M. *Tetrahedron Lett.* **1999,** 40, (50), 8797-8800; Broaddus, C. D. *J. Org. Chem.* **1970,** 35, (1), 10-&; Buker, H. H.; Nibbering, N. M. M.; Espinosa, D.; Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1997,** 38, (49), 8519-8522; Schlosser, M.; Mongin, F.; Porwisiak, J.; Dmowski, W.; Buker, H. H.; Nibbering, N. M. M. *Chemistry-a European Journal* **1998,** 4, (7), 1281-1286; Schlosser, M. *Angew. Chem. Int. Edit.* **1998,** 37, (11), 1497-1513.
56. Hommes, N.; Schleyer, P. V. *Angew. Chem. Int. Edit. in English* **1992,** 31, (6), 755-758.
57. Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999,** 1, (8), 1183-1186.
58. Kauch, M.; Hoppe, D. *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **2001,** 79, (11), 1736-1746.
59. Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005,** 7, (17), 3749-3752.
60. Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983,** 48, (11), 1935-1937.
61. Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975,** 40, (21), 3158-3159.
62. Le Fur, N.; Mojovic, L.; Ple, N.; Turck, A.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2006,** 71, (7), 2609-2616.
63. Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007,** 72, (5), 1588-1594.
64. Marvel, C. S.; Hager, F. D.; Coffman, D. D. *J. Am. Chem. Soc.* **1927,** 49, 2323-2328.
65. Gilman, H.; Moore, F. W. *J. Am. Chem. Soc.* **1940,** 62, 1843-1846.
66. Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1940,** 62, 2327-2335.
67. Jones, R. G.; Gilman, H. *Organic Reactions* **1951,** 6, 339-366; Jones, R. G.; Gilman, H. *Chem. Rev.* **1954,** 54, (5), 835-890.
68. Bauer, W.; Winchester, W. R.; Schleyer, P. V. *Organometallics* **1987,** 6, (11), 2371-2379.
69. Waack, R.; Doran, M. A. *J. Am. Chem. Soc.* **1969,** 91, (10), 2456-&.
70. Magid, R. M.; Welch, J. G. *J. Am. Chem. Soc.* **1968,** 90, (19), 5211-&.
71. Bhattach.Dn; Lee, C. L.; Smid, J.; Szwarc, M. *J. Phys. Chem.* **1965,** 69, (2), 612-&; Birch, A. J.; Cross, P. E.; Lewis, J.; White, D. A.; Wild, S. B. *J. Chem. Soc. a -Inorganic Physical Theoretical* **1968**, (2), 332-&.
72. Berthold, H. J.; Groh, G. *Zeitschrift Fur Anorganische Und Allgemeine Chemie* **1970,** 372, (3), 292-&.
73. Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988,** 352, (1-2), 1-46.
74. Fischer, H. *J. Phys. Chem.* **1969,** 73, (11), 3834-&.
75. Russell, G. A.; Lamson, D. W. *J. Am. Chem. Soc.* **1969,** 91, (14), 3967-&.
76. Julia, M. *Acc. Chem. Res.* **1971,** 4, (11), 386-&; Lal, D.; Griller, D.; Husband, S.; Ingold, K. U. *J. Am. Chem. Soc.* **1974,** 96, (20), 6355-6357; Chatgilialoglu, C.; Ingold, K. U.;

Scaiano, J. C.; Woynar, H. *J. Am. Chem. Soc.* **1981,** 103, (11), 3231-3232; Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987,** 52, (16), 3509-3514; Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980,** 13, (9), 317-323; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987,** 52, (6), 959-974.
77. Ward, H. R. *J. Am. Chem. Soc.* **1967,** 89, (21), 5517-&.
78. Bailey, W. F.; Patricia, J. J.; Delgobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985,** 50, (11), 1999-2000.
79. Sunthankar, S. V.; Gilman, H. *J. Org. Chem.* **1951,** 16, (1), 8-16.
80. Wittig, G.; Schollkopf, U. *Tetrahedron* **1958,** 3, (1), 91-93.
81. Winkler, H. J. S.; Winkler, H. *J. Am. Chem. Soc.* **1966,** 88, (5), 969-&; Winkler, H. J. S.; Winkler, H. *J. Am. Chem. Soc.* **1966,** 88, (5), 964-&; Johncock, P. *J. Organomet. Chem.* **1969,** 19, (2), 257-&; Rogers, H. R.; Houk, J. *J. Am. Chem. Soc.* **1982,** 104, (2), 522-525; Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985,** 107, (13), 4101-4103.
82. Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986,** 108, (9), 2449-2451.
83. Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972,** 94, (12), 4374-&; Tamao, K.; Zembayas.M; Kiso, Y.; Kumada, M. *J. Organomet. Chem.* **1973,** 55, (2), C91-C94; Corriu, R.; Masse, J. *J. Organomet. Chem.* **1972,** 35, (1), 51-&; Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971,** 93, (6), 1487-&.
84. Murahashi, S. I.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979,** 44, (14), 2408-2417.
85. Kosugi, M.; Shimizu, Y.; Migita, T. *Chemistry Letters* **1977**, (12), 1423-1424.
86. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979,** 101, (17), 4992-4998.
87. Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988,** 53, (4), 918-920.
88. Gardner, J. H.; Borgstrom, P. *J. Am. Chem. Soc.* **1929,** 51, 3375-3377.
89. Srebnik, M. *Tetrahedron Lett.* **1991,** 32, (22), 2449-2452.
90. Binger, P.; Koster, R. *Angew. Chem. Int. Edit.* **1962,** 74, (16), 652-&.
91. George, T. A.; Lappert, M. F. *Chem. Commun.* **1966**, (14), 463-&.
92. Yamamoto, Y.; Yatagai, H.; Moritani, I. *J. Am. Chem. Soc.* **1975,** 97, (19), 5606-5607.
93. Kuivila, H. G.; Muller, T. C. *J. Am. Chem. Soc.* **1962,** 84, (3), 377-&.
94. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995,** 95, (7), 2457-2483.
95. Suzuki, A. *Acc. Chem. Res.* **1982,** 15, (6), 178-184.
96. Hoffmann, R. W.; Dresely, S. *Synthesis-Stuttgart* **1988**, (2), 103-106; Waas, J. R.; Sidduri, A. R.; Knochel, P. *Tetrahedron Lett.* **1992,** 33, (26), 3717-3720.
97. Amatore, C.; Jutand, A.; Mbarki, M. A. *Organometallics* **1992,** 11, (9), 3009-3013.
98. Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999,** 40, (16), 3077-3080.
99. Hobbs, P. D.; Upender, V.; Dawson, M. I. In *Stereospecific syntheses of michellamines A and C*, 1997; 'Ed.'^'Eds.' 1997; p^pp 965-&.
100. Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winneroski, L. L. *J. Org. Chem.* **2001,** 66, (17), 5772-5782.
101. van Pee, K. H.; Ligon, J. M. *Nat. Prod. Rep.* **2000,** 17, (2), 157-164.
102. Gribble, G. W. *Pure Appl. Chem.* **1996,** 68, (9), 1699-1712.
103. Nakano, H.; Umio, S.; Kariyone, K.; Tanaka, K.; Kishimot.T; Noguchi, H.; Ueda, I.; Nakamura, H.; Morimoto, Y. *Tetrahedron Lett.* **1966**, (7), 737-&; Gosteli, J. *Helvetica Chimica Acta* **1972,** 55, (2), 451-&.
104. Cooksey, A. R.; Morgan, K. J.; Morrey, D. P. *Tetrahedron* **1970,** 26, (21), 5101-&.
105. Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990,** 55, (26), 6317-6328.
106. Anderson, H. J.; Loader, C. E. *Synthesis-Stuttgart* **1985**, (4), 353-364.

107. Rinkes, I. J. *Recueil Des Travaux Chimiques Des Pays-Bas* **1934,** 53, 1167-1174.
108. Anderson, H. J. *Can. J. Chem.-Revue Canadienne De Chimie* **1959,** 37, (12), 2053-2058.
109. Fournari, P.; Tirouflet, J. *Bulletin De La Societe Chimique De France* **1963**, (3), 484-&.
110. Sonnet, P. E. *J. Org. Chem.* **1971,** 36, (7), 1005-&; Hodge, P.; Rickards, R. W. *J. Chem. Soc.* **1965**, (JAN), 459-&.
111. Anderson, H. J.; Griffith.Sj. *Can. J. Chem.* **1967,** 45, (19), 2227-&.
112. Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981,** 22, (36), 3455-3458.
113. Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972,** 94, (7), 2549-&.
114. Morrison, M. D.; Hanthorn, J. J.; Pratt, D. A. *Org. Lett.* **2009,** 11, (5), 1051-1054.
115. Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992,** 57, (6), 1653-1656.
116. Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc.* **2004,** 126, (30), 9200-9201.
117. Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007,** 129, (11), 3358-3366.
118. Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979,** 44, (7), 1133-1136.
119. Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978,** 100, (15), 4842-4852.
120. Walborsky, H. M.; Ronman, P. *J. Org. Chem.* **1978,** 43, (4), 731-734.
121. Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980,** 45, (23), 4798-4801.
122. Ayyangar, N. R.; Kalkote, U. R.; Nikrad, P. V. *Indian J. Chem. Section B-Organic Chemistry Including Medicinal Chemistry* **1983,** 22, (9), 872-877.
123. Roe, A. M.; Burton, R. A.; Reavill, D. R. *Chem. Commun.* **1965**, (22), 582-&.
124. Roe, A. M.; Burton, R. A.; Willey, G. L.; Baines, M. W.; Rasmusse.Ac. *J. Med. Chem.* **1968,** 11, (4), 814-&.
125. Hickey, M. R.; Allwein, S. P.; Nelson, T. D.; Kress, M. H.; Sudah, O. S.; Moment, A. J.; Rodgers, S. D.; Kaba, M.; Fernandez, P. *Organic Process Research & Development* **2005,** 9, (6), 764-767.
126. Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1997,** 38, (9), 1559-1562.
127. Castellote, I.; Vaquero, J. J.; Alvarez-Builla, J. *Tetrahedron Lett.* **2004,** 45, (4), 769-772; Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998,** 120, (4), 827-828.
128. Itahara, T. *J. Chem. Soc.-Chem. Commun.* **1981**, (5), 254-255; Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004,** 126, (31), 9552-9553.
129. Furstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998,** 120, (12), 2817-2825.
130. Cho, D. H.; Lee, J. H.; Kim, B. H. *J. Org. Chem.* **1999,** 64, (21), 8048-8050.
131. Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun.* **1997**, (2), 207-208; Banwell, M. G.; Hamel, E.; Hockless, D. C. R.; Verdier-Pinard, P.; Willis, A. C.; Wong, D. J. *Bioorg. Med. Chem.* **2006,** 14, (13), 4627-4638; Furstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002,** 58, (32), 6373-6380.
132. Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003,** 1, (2), 296-305.
133. Heinrich, M. R.; Steglich, W.; Banwell, M. G.; Kashman, Y. *Tetrahedron* **2003,** 59, (46), 9239-9247.
134. Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, (9), 1025-+.
135. Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000,** 65, (1), 164-168.

136. Chang, C. J.; Floss, H. G.; Hook, D. J.; Mabe, J. A.; Manni, P. E.; Martin, L. L.; Schroder, K.; Shieh, T. L. *J. Antibiot.* **1981,** 34, (5), 555-566.
137. Sako, M.; Kihara, T.; Okada, K.; Ohtani, Y.; Kawamoto, H. *J. Org. Chem.* **2001,** 66, (10), 3610-3612.
138. Vanpee, K. H.; Salcher, O.; Lingens, F. *Angew. Chem. Int. Edit. in English* **1980,** 19, (10), 828-829.
139. Umio, S.; Kariyone, K.; Tanaka, K.; Nakamura, H. *Chem. Pharm. Bull.* **1969,** 17, (3), 559-&.
140. Vanpee, K. H.; Salcher, O.; Fischer, P.; Bokel, M.; Lingens, F. *J. Antibiot.* **1983,** 36, (12), 1735-1742.
141. van Pee, K. H.; Dong, C. J.; Flecks, S.; Naismith, J.; Patallo, E. P.; Wage, T., Biological halogenation has moved far beyond haloperoxidases. In *Adv. Appl. Microbiol., Vol 59*, ed.; 'Ed.'^'Eds.' 2006; 'Vol.' 59, p^pp 127-157.
142. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997,** 62, (21), 7512-7515.
143. DiMichele, L.; Menzel, K.; Mills, P.; Frantz, D.; Nelson, T. *Magn. Reson. Chem.* **2006,** 44, (11), 1041-1043.
144. Walsh, C. T.; Yeh, E.; Blasiak, L. C; Koglin, A.; Drennan, C. L. *Biochemistry* **2007**, 46, 1284-1292.