DEVELOPING METHODOLOGIES FOR THE SYNTHESIS OF HETEROCYCLIC LIBRARIES: PARALLEL SYNTHESIS OF FLAVONES, MALEIMIDES, α,β-UNSATURATED-γ-BUTYROLACTAMS AND ISOQUINOLINES.

By

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TITLE: Developing Methodologies for the Synthesis of Heterocyclic Libraries: Parallel Synthesis of Flavones, Maleimides, α,β-Unsaturated-γ-Butyrolactams and Isoquinolines.

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Abstract

Parallel synthesis technologies that allow for rapid generation of compound collections that can be screened and quickly provide useful structure-activity relationships are needed to probe and understand biological systems. Synthetic strategies that are robust and allow the rapid access to a library of flavones, maleimides, α,β-unsaturated-γ-butyrolactams and isoquinolines are described.

A $Pd_2(dba)_3.CHCl_3$ catalyst system incorporating the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph) ligand permits the generation of a library of substituted flavones *via* sequential microwave-assisted copper free Sonogashira and carbonylation annulation reactions under mild conditions. Application of this protocol is described for several aryl iodides and bromides with TMS-acetylenes allowing for the "one pot" synthesis of a diverse collection of substituted flavones.

Synthetic strategies that led to the generation of libraries of bisaryl-maleimides, anilinoaryl-maleimides and bisanilino-maleimides as well as bisaryl substituted α,β-unsaturated-γ-butyrolactams are described. The reaction protocol also takes advantage of Pd-cross-coupling reactions using the catalytic system mentioned above as well as Michael addition / elimination reactions. Reaction conditions that allow for the control necessary for the synthesis of a library of symmetrical and non-symmetrical 3,4-disubstituted maleimides from *N*-(*p*-methoxybenzyl)-3,4-dibromomaleimide as well as symmetrical and non-symmetrical 3,4-disubstituted α,β-unsaturated-γ-butyrolactams from 3,4-dibromo-1-(4-methoxybenzyl)-1*H*-pyrrol-2(5*H*)-one are presented. Protocol for

facile deprotection of the *p*-methoxybenzyl group to generate the final products of both 3,4-disubstituted maleimides and 3,4-substituted α,β-unsaturated-γ-butyrolactams is also described.

A robust parallel synthetic strategy that makes use of simple, cheap and readily available precursors is described for the preparation of a library of substituted isoquinolines. The approach involves microwave-assisted Pictet-Spengler and Bischler-Napieralski cyclizations. In addition, a Pd-catalyzed cross-coupling reaction protocol using the Pd/PA-Ph provides access to a diverse collection of C1 and C4 substituted isoquinolines *via* the activation of an isoquinolin-1(2H)-one scaffold.

A protocol for the Pd- catalyzed α-arylation of active methylene compounds using the palladium complex of 1,3,5,7-tetramethyl-6-(isobutyl)-2,4,8-trioxa-6-phospha-adamantane (PA-iBu) to generate products that served as precursors for a diverse collection of substituted isoquinolines is also described.

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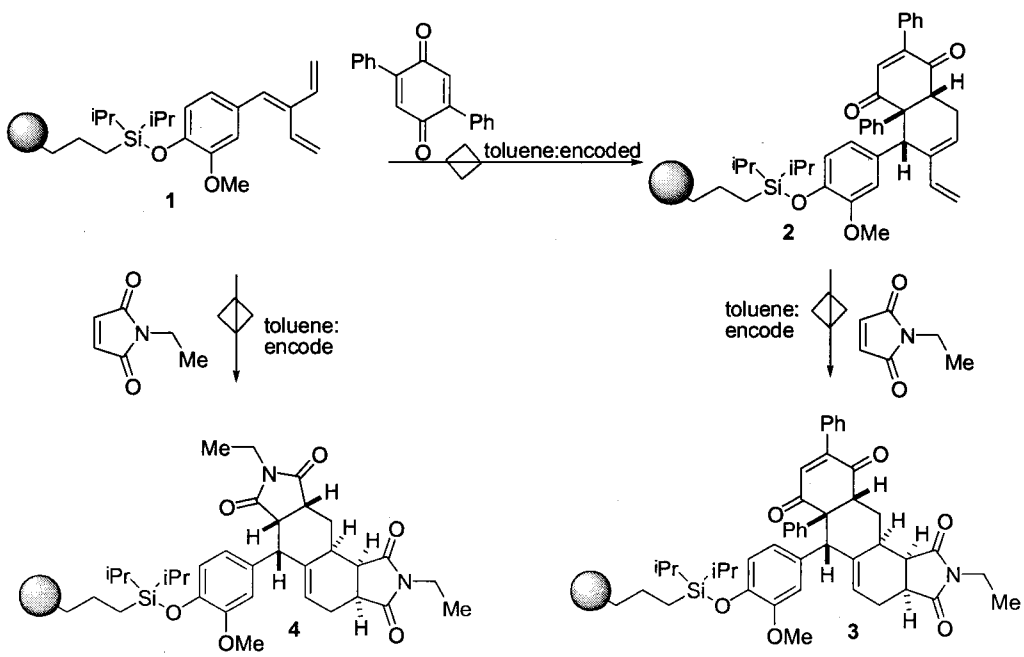
Chapter 1: Introduction

1.1 Chemical Library Synthesis.

1.1.1 Background.

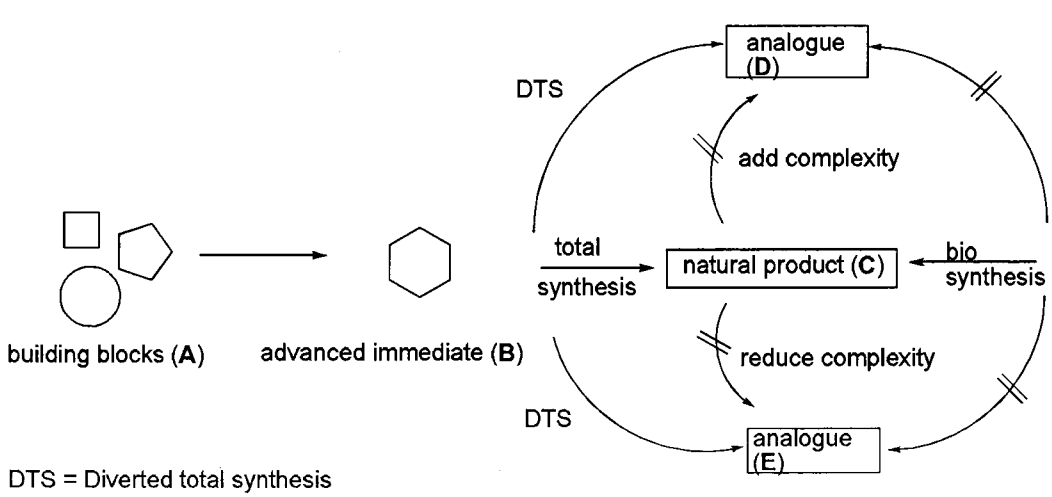
Traditionally, natural products have served as the main source for pharmacologically active molecules.[1] The pharmacological properties of compounds derived from Nature and their derivatives are especially useful as medicinal agents. Their structures and substructures have been selected by evolution to render them the most optimized for use as leads in the drug discovery process.[2] Issues related to the availability, isolation, identification, de-replication, patentability and synthesis of natural products, however, have led pharmaceutical companies to look for alternate sources for their lead generation programs. In the mid-1990s, technological advances in robotics and liquid handling facilitated the utilization of combinatorial chemistry and high throughput screening as a new means for the discovery of biologically active agents. Large numbers of compounds could be prepared in a combinatorial fashion[3] then rapidly screened to provide leads for the drug discovery pipeline. Over time, however, the approach was shown to be less than successful[4] due in part to the inability of combinatorial chemistry to provide the diverse architectures (available with natural products) needed for effective biological activity. Methods for lead discovery and the place of library synthesis in medicinal chemistry needed to be re-evaluated.

Over the past two decades, both industrial and academic researchers have been active in the development of methods suitable for the generation of small molecule libraries that allow for either diverse or focused compound collections. A number of strategies have been described. As the name implies, methods based on Diversity-Oriented Synthesis (DOS)[5-7] strive to generate libraries that can sample large volumes of chemical space by maximizing structural diversity and stereochemical complexity. These synthetic protocols can involve standard solution-phase methodologies, solid-phase methodologies or a combination of both protocols. For example, Kwon *et al.* generated



Scheme 1.1. Kwon *et al.* synthetic strategy to generate 29.000 discrete compounds comprising of 10 discrete polycyclic skeletons using DOS.

29,400 discrete compounds comprising 10 discrete polycyclic skeletons.[8] Their synthetic strategy involved using several dienes and dienophiles in a one-bead-one-stock solution technology that builds products having a central skeleton with between two and four rings and up to six stereocenters *via* consecutive Diels-Alder cycloaddition reactions. (Scheme 1.1). Alternatively, Diverted Total Synthesis (DTS) describes a process wherein an advanced intermediate (**B**) in the total synthesis of a natural product (bearing the features necessary for activity) is chosen and synthetically modified to generate several analogues.[9] (Scheme 1.2). This process of library synthesis allows the introduction of structural variations which permit "molecular editing" of unnecessary structural complexity.



Scheme 1.2. A general scheme for Diverted Total Synthesis.

In some instances, DTS has resulted in the generation of simple analogues having higher activity than the parent natural product itself. For example, Danishevsky *et al.* used DTS in the synthesis of a small eight-membered compound library based on the natural

product migrastatin, an anti-angiogenesis agent.[10] During their total synthesis Danishevsky *et al.* chose an advanced intermediate and carried out synthetic modifications to this intermediate to generate eight simplified compounds in only two steps. These simplified analogues were more potent than the parent migrastatin. Strategies that combine in *silico* and synthetic approaches are important in the drug discovery process and have been demonstrated to accelerate the rate of discovery and reduce the need for expensive laboratory work and clinical trials.[11] *In silico* approaches can be used to prioritize compounds that are more likely to be active at a particular target. Synthetic efforts can then be undertaken to generate libraries of compounds based on the *in silico* leads in an effort to maximize diversity and uncover new leads.

In contrast, libraries based on Target-Oriented Synthesis (TOS) approaches aim to prepare more focused libraries.[5] This approach has been utilized to great effect in the study of structure-activity relationships (SAR) in the pharmaceutical industry. The preparation of libraries of organic molecules centered on a lead core-structure allows for rapid identification of key structural features that are required in a target molecule for a specific biological activity.

The TOS library approach has been used in the field of chemical biology. Chemical biology has demonstrated itself to be a powerful method for the study of living systems[12] and the utilization of compound collections represents an important tool in the field. Using small organic molecules as perturbants of biological function, researchers can modulate activity within cells and, ultimately, unravel and control complex biological

processes. The rapid expansion of chemical biology has driven the need for novel, convenient synthetic methods for the production of unique, small organic molecule probes, yet developing and implementing protocols for library preparation remains a critical challenge. These approaches need to provide rapid and efficient access to the target molecule and need to be robust so as to allow for the inclusion of a variety of functionality into the final focused compound collection.

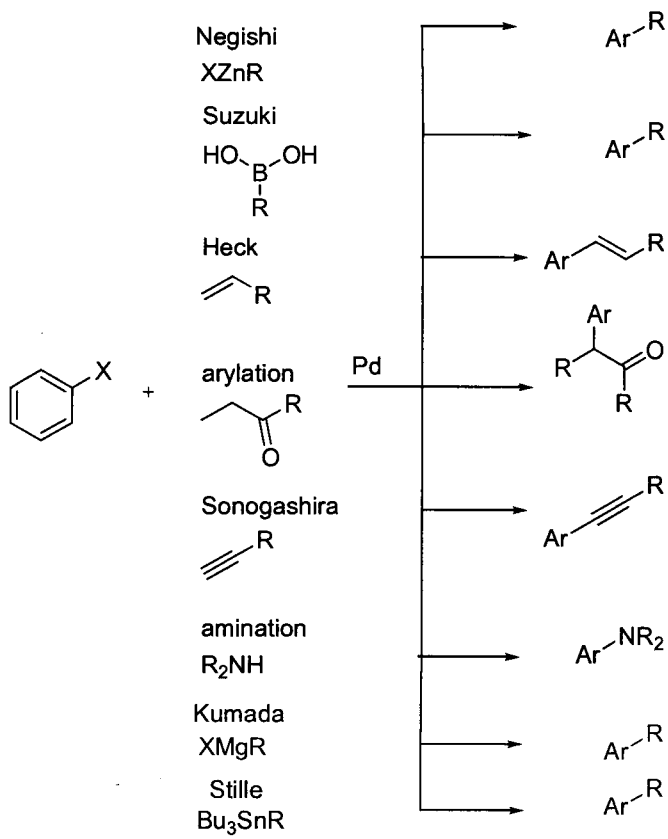
1.1.2 Objectives

In the last few decades, palladium-catalyzed cross-coupling reactions have been shown to be powerful, versatile reactions used routinely by synthetic chemists for C-C[13-16] and C-heteroatom[17,18] bond formation. Concurrently, the use of microwave irradiation to facilitate chemical reactions has also been used to great effect in the synthetic organic community.[19] The present thesis seeks to determine the utility and scope of applicability of Pd cross-coupling (specifically those reactions based on a catalytic system that includes ligands prepared from a 1,3,5,7-tetramethyl-2,4,8-triox-6-phosphaadamantane (PA-H) scaffold) and microwave chemistry in the preparation of heterocyclic compound libraries. Synthetic protocols for the facile preparation of substituted flavones, maleimides and isoquinolines will be presented.

1.1.3 Literature Review

1.1.3.1 Palladium-Catalyzed Cross-Coupling Reactions

Broadly defined as the formation of a bond between two reaction partners involving metal catalysis, coupling reactions have been described in the chemical literature as far back as the mid-19th century (Wurtz coupling, for example).[20] The pioneering work of Richard Heck in 1972,[13] however, described a practical vinylic substitution of aryl halides and marked the beginning of Pd-catalyzed cross-coupling chemistry. Since then, a number of variants of the Heck reaction have appeared. (Scheme 1.3). These include Suzuki-Miyaura (where carbon-based nucleophiles such as aryl, vinyl or alkyl derivatives of boron are used),[14,21] Sonogashira (where terminal alkynes are used),[22,23] Stille-Migita (where carbon-based nucleophiles such as aryl, vinyl or alkyl derivatives of tin are used),[24] α-arylation of enolates (where compounds containing active methylenes are used),[25] Buchwald amination (where primary or secondary amines are used),[18] Negishi



Scheme 1.3. Specific examples of Pd-catalyzed reactions.

(where carbon-based nucleophiles such as aryl, vinyl or alkyl derivatives of zinc are used)[26] and Kumada-Corriu reactions (where carbon-based nucleophiles such as aryl, vinyl or alkyl derivatives of magnesium are used).[27]

These powerful, versatile reactions are now used routinely by synthetic chemists for C-C and C-heteroatom bond formation. Their widespread applicability stems from their ease of use and wide functional group tolerance. These reactions generally do not require any special handling and, in many cases, can tolerate oxygen and moisture. Furthermore, a number of palladium sources required for these reactions (including Pd(II) complexes such as palladium (II) acetate [$Pd(OAc)_2$] and palladium (II) chloride ($PdCl_2$) and Pd(0) complexes such as tri(dibenzylideneacetone)dipalladium (0) [$Pd_2(dba)_3$-$CHCl_3$][28] and tetrakis(triphenylphosphine) palladium (0) [$Pd(PPh_3)_4$][29] are commercially available.

1.1.3.2 Mechanistic studies of palladium (0) catalyzed reactions.

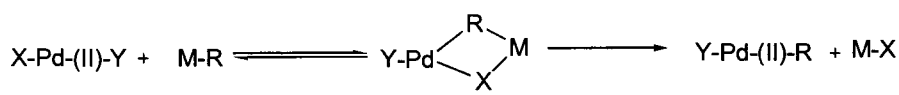
Palladium (Pd) exists predominantly in either +2 or 0 oxidation state. The interchange between these two oxidation states is responsible for the rich chemistry that Pd exhibits.[30,31]

$$Pd(0) + \quad X\text{-}Y \longrightarrow \quad X\text{-}Pd\text{-}(II)\text{-}Y$$

Scheme 1.4. Oxidative addition of a molecule of X-Y to Pd(0).

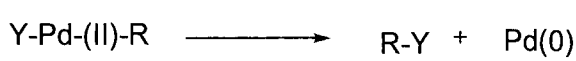
Mechanistically, Pd-catalyzed cross-coupling reactions involve initial oxidative addition of a molecule of X-Y to Pd(0) with homolytic bond cleavage of its covalent bond to form a new ionic bond to Pd(0) leading to Pd(II) species.[31] (Scheme 1.4).

Several X-Y molecules are capable of undergoing oxidative addition to Pd(0) with the most common being those containing a C-X (X= halogen and pseudo-halogen), C-H, C-O, Si-H, M-H, (M = main group metals) and H-H bonds. Among these, the most frequently used are vinylic and aryl halides. The general rate of oxidative addition of these organic halides decreases from C-I > C-OTf > C-Br >> C-Cl >>> C-F. Oxidative addition is not limited to sp^2 hybridized carbons but also suitably activated sp^3 carbons undergo oxidative addition to Pd(0) species.[14,32,33] A transmetallation step occurs after oxidative addition as illustrated in Scheme 1.5. In this step, organometallic compounds (M-R) and hydrides (M-H) of main group metals such as B, Mg, Zn, Sn, Al, Hg and Si exchange with the X in the X-Pd(II)-Y complexes.



Scheme 1.5. Transmetallation of Y-P-X.

The final step involves a reductive elimination. This step is a unimolecular decomposition involving the loss of two groups of cis configuration from the Pd center combining to give a single organic product. (Scheme 1.6).



Scheme 1.6. Reductive elimination of Y-Pd(II)-R.

Reductive elimination regenerates the Pd(0) species which undergoes another round of oxidative addition in the full catalytic cycle. (Figure 1.1).

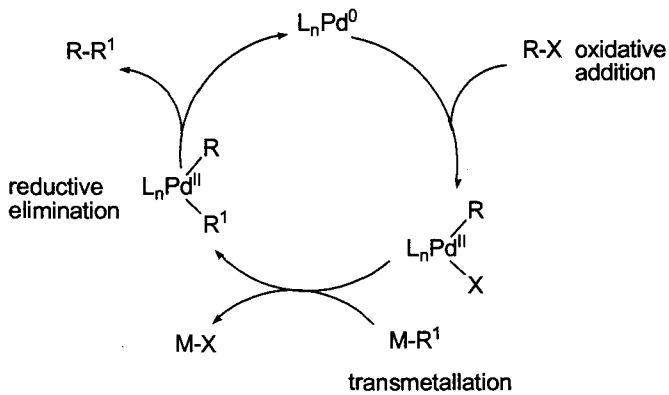


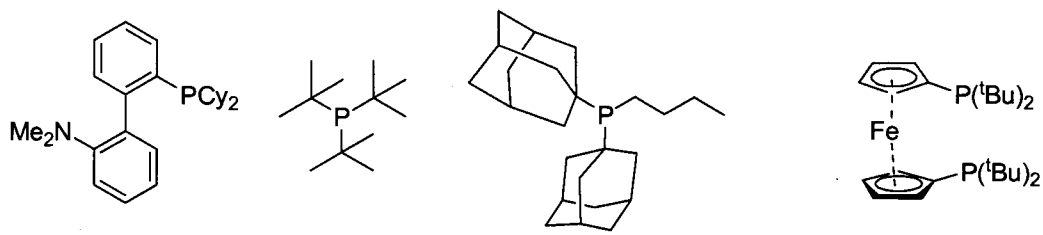
Figure 1.1. A generalized Pd cross-coupling catalytic cycle.

1.1.3.3 The use of Phosphine Ligands in Pd catalyzed reactions.

Key to the success of Pd catalyzed cross-coupling reactions is the choice of ligands used in these reactions. For example the initial use of PPh_3 as a ligand by Suzuki limited the reaction to aryl iodides and aryl bromides.[34] In addition, reactions with hindered aryl bromides such as mesityl bromide and naphthyl bromide occurred slowly under these reaction conditions. Phosphine ligands are the most important class of metal ligands used.[35,36] They act as both σ donors and π acceptors. The nature of R groups on the phosphorus determines its ability to donate or accept electron density.

In the last few years, attention has been focused on the discovery and optimization of phosphine ligands that increase catalytic turnovers and efficiency.[35,37] Among these, the most promising ligands are the electron-rich, sterically bulky tertiary phosphines. Electron-rich phosphines have been shown to accelerate the "oxidative addition" by increasing the electron density on the central metal (Pd). In addition, the bulkiness of these ligands assists facile reductive elimination. As a result, previously

unsuccessful coupling reactions (for example, those reactions involving unactivated or hindered substrates) can now be carried out. Buchwald *et al.* reported in 1998 that using bulky electron-rich *2'*-(dicyclohexylphosphanyl-biphenyl-*2*-yl)dimethylamine (**5**) led to the facile Suzuki coupling of several boronic acids with a variety of aryl chlorides.[38]



5 **6** **7** **8**

Figure 1.2 Examples of bulky electron rich phosphine ligands.

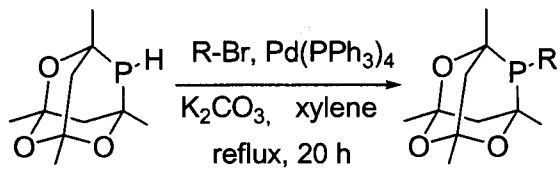
Even with electron rich aryl chlorides, good yields of the coupled products were obtained under mild reaction conditions (some at room temperature) in the presence of 0.5-2.0 mol % Pd and 0.75-3.0 mol % of ligand. Littke and Fu reported the used of bulky electron-rich tri-*tert*-butylphosphine (**6**) as ligand for Suzuki coupling reaction of several boronic acids and a variety of aryl chlorides.[39,40] Deactivated and hindered aryl chlorides were suitable substrates. In their initial studies, $Pd_2(dba)_3$-$CHCl_3$, Cs_2CO_3 and dioxane were used as catalyst, base and solvent, respectively. They determined that using KF as a base rather than Cs_2CO_3 allowed the Suzuki cross-coupling reaction of activated aryl chlorides to occur at milder reaction conditions. Hartwig and Fu reported separately that sterically hindered and electron rich aryl chlorides can been used effectively in a Heck reaction when tri-*tert*-butylphosphine (**6**)[41] and di(*tert*-butylphosphino)ferrocene (**8**)[42] are used as ligands. Beller *et al.* reported that di-1-adamantyl-*n*-butylphosphine (**7**) is also an

effective ligand for reactions involving electron rich non activated aryl chlorides in Suzuki cross-coupling reactions.[43] Several research groups have described other phosphine ligands with high catalytic turnovers[44] permitting the successful coupling of even the least active coupling partners in Pd-catalyzed cross-coupling reactions such as Suzuki, Stille, Sonogashira, Heck, Buchwald amination, α-arylation of ketones and other coupling reactions.

Over the past eight years the Capretta group has developed a phosphine ligand that is air stable, easily to handle and can successfully be employed in several organopalladium cross-coupling reactions. This catalytic system incorporating an air-stable 1,3,5,7-tetramethyl-2,4,8-triox-6-phenyl-6-phosphaadamantane (PA-Ph) (**11**) has been used successfully in Suzuki cross-coupling of a variety of aryl halides and boronic acids under mild conditions.[45,46] Unlike other reported adamantyl phosphorus ligands,[43] 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph) (**11**) for example, has the phosphorus atom entrenched within the adamantane framework. The PA-Ph (**11**) has been shown to be an effective versatile ligand useful for Sonogashira reactions,[46] the α-arylation of ketones[46] and amination reactions[47] generating the coupled product in high yields under mild conditions.

Chemistry has been developed that allows for the derivatization of the secondary PA-H (**9**) scaffold. For example a palladium-catalyzed P-arylation of the secondary PA-H (**9**)[48] with an aryl halide in the presence of a base (K_2CO_3) and refluxing the in

xylene yields the tertiary PA-R (**10**).[33,49] (Scheme 1.7). P-alkylation was also facile and allowed the generation of alkyl substituted PA-R ligands.[50]



9 **10**

Scheme 1.7. Derivatization of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane (PA-H) into structurally diverse trisubstituted phosphine ligands.

This chemistry has allowed for the production of a library of structurally diverse tertiary phospha-adamantanyl ligands (selected members shown in Figure 1.3) each with unique steric and electronic properties. Parallel screening of these ligands allows rapid identification of the best ligand, temperature, solvent, and Pd-source for a given reaction.[33]

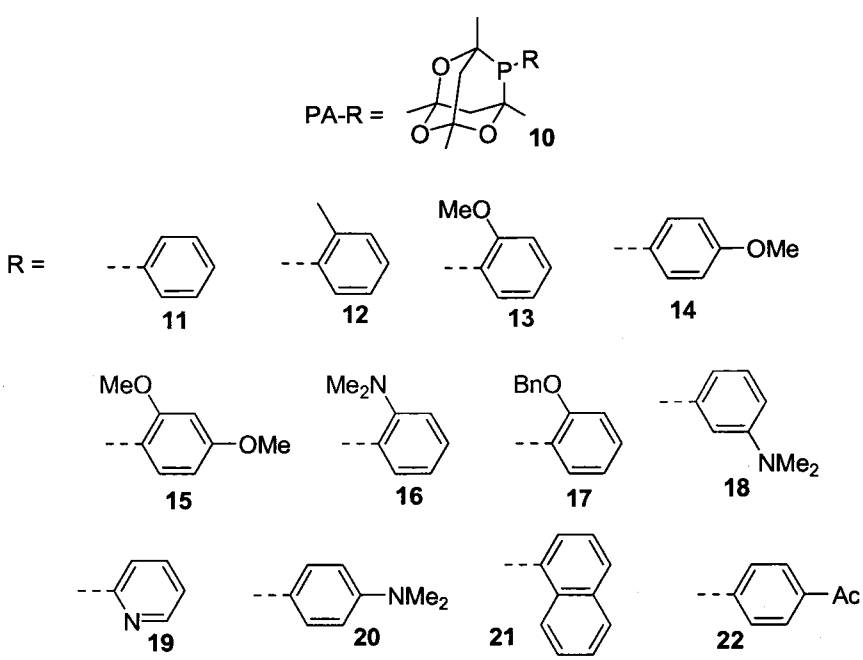
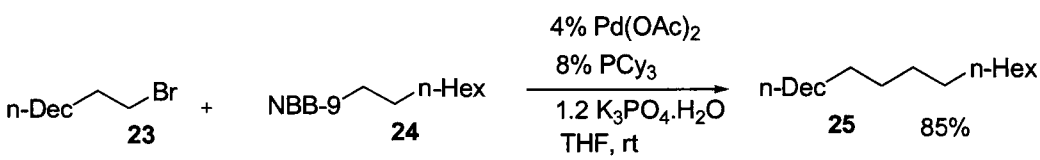


Figure 1.3. Selected members of PA-R ligand libraries.

In order to showcase this ligand library screening

approach, attention was turned to the development of protocols suitable for the sp3-sp3 Suzuki coupling. Suzuki reactions involving sp3-bonded alkyl halides and tosylates with aryl or alkyl boronic acids have been largely avoided as useful synthetic methods. This may be attributed to the slower rate of oxidative addition of the alkyl halides to palladium and the ability of these complexes to easily undergo β-hydride elimination rather than produce the desired coupling product. Fu *et al.* demonstrated that these reactions can be facilitated with a palladium catalyst system incorporating bulky electron-rich alkyl phosphine ligands.[51] For example using $Pd(OAc)_2/PCy_3$ and $K_3PO_4.H_2O$ in THF, a Suzuki cross-coupling reaction involving 1-bromododecane (**23**) and B-n-octyl-9-BBN (**24**) yielded the desired product in 85% yield with less than 2% of the β-hydride elimination product.[51] (Scheme 1.8).

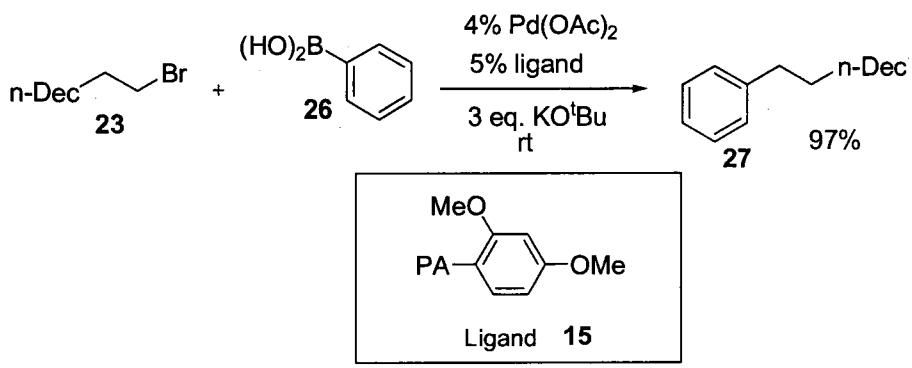


Scheme 1.8. 1-bromododecane and B-n-octyl-9-borabicyclo[3.3.1]nonane in Suzuki coupling reaction by Fu *et al.*

However, Suzuki cross-coupling reactions involving alkyl tosylates yielded the desired coupling product when di-*tert*-butyl-methylphosphine (P^tBu_2Me) rather than PCy_3 was used as the ligand.

With this precedent at hand, the Capretta group screened a collection of twelve PA-R ligands (Figure 1.3) and quickly determined that using a catalytic system of $Pd(OAc)_2$ incorporating 2,4-dimethoxyphenylphosphaadamantane ligand (**15**) facilitated the cross-coupling of alkyl bromides, alkyl chlorides and alkyl tosylates with alkyl

boranes as well as aryl boronic acids under mild conditions.[33] For example, a Suzuki cross-coupling reaction between 1-bromododecane and phenyl boronic acid using the catalytic system of $Pd(OAc)_2$/2,4-dimethoxyphenylphosphaadamantane and KO^tBu as the base and dioxane as the solvent, yielded the cross-coupled product in 97% yield. (Scheme 1.9). With this catalytic system only a slight excess of the ligand (5%) over the palladium (4%) was required for facile reaction compared to Fu's reaction conditions which required a ligand to palladium ratio of 2:1.



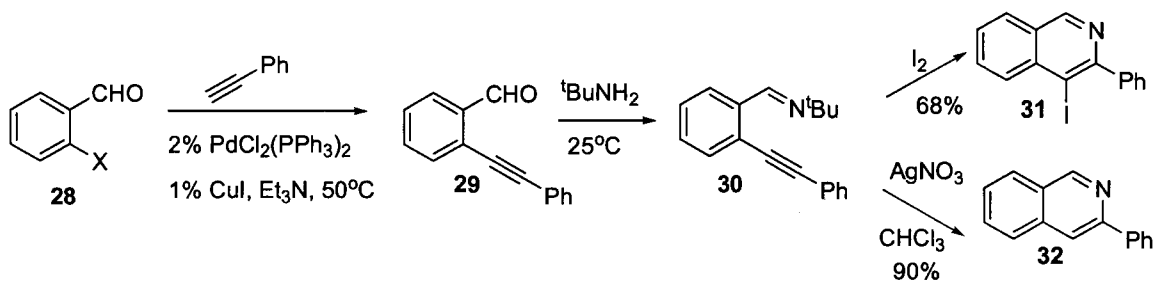
Scheme 1.9. Suzuki coupling between 1-bromododecane and phenylboronic acid.

The 2,4-dimethoxyphenylphosphaadamantane ligand (**15**) was also shown to facilitate the coupling of various aryl chlorides with alkyl boranes as well as alkyl tosylates with alkyl boranes in good yield under mild conditions.

1.1.3.4 Use of Pd-catalyzed Cross-Coupling in Library Synthesis

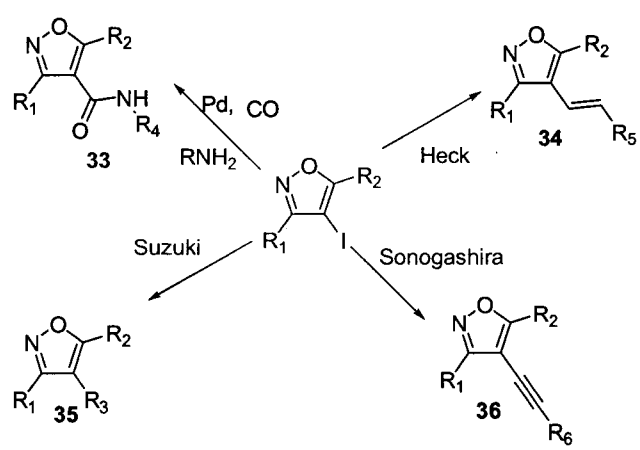
Developing methodologies for the preparation of compound collections remains a critical challenge and forms an integral part of research in our laboratory. The methodology developed for library synthesis must provide rapid and efficient access to the targeted molecules and must be robust enough to allow the incorporation of varied functionality into the compound collections.

Protocols involving palladium-catalyzed reactions in library generation of compounds have been reported. For example, Larock *et al.* described the generation of a library of substituted isoquinolines *via* palladium catalyzed Sonogashira reaction involving various alkynes and *o*-halo-benzaldehydes (**28**).[52] Cyclizations of *tert*-butylimino alkynes (**30**) by various electrophiles then yielded the substituted isoquinolines (e.g. **31**, **32**). (Scheme 1.10).



Scheme 1.10. Generation of various substituted isoquinolines *via* palladium catalyzed Sonogashira reaction by Larock *et al.*

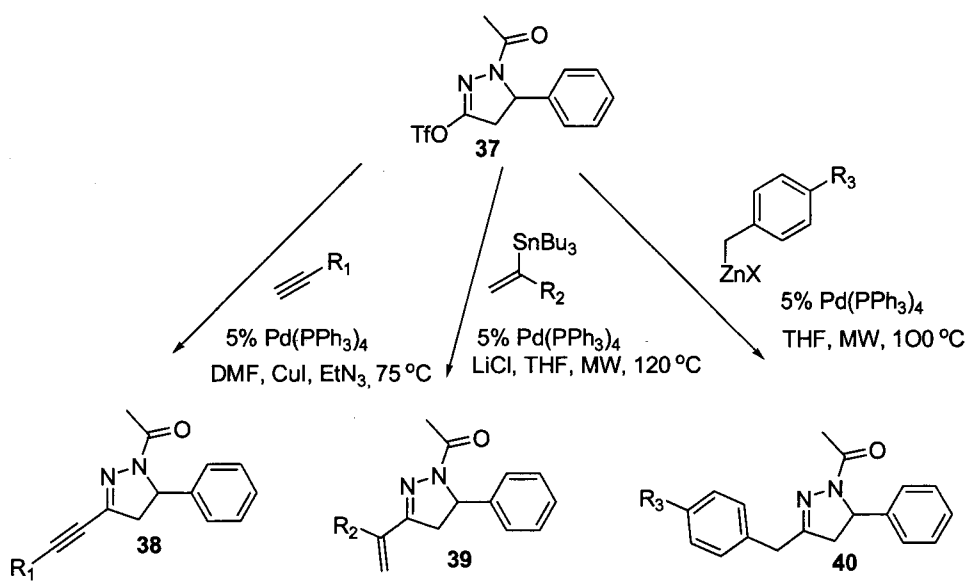
Larock *et al.* also utilized various palladium-catalyzed cross-coupling reactions such as carbonylative amidation, Suzuki, Heck and Sonogashira reactions in the



Scheme 1.11. Synthesis of a library of 3,4,5-trisubstituted isoxazoles from 4-iodoisoxazoles *via* palladium cross-coupling reactions by Larock *et al.*

synthesis of a library of 3,4,5-trisubstituted isoxazoles from 4-iodoisoxazoles.[53] (Scheme 1.11).

Furthermore, Grimm *et al.* generated a library of 3-substituted-2-pyrazolines by taking advantage of palladium-catalyzed cross-coupling reactions such as Suzuki, Sonogashira, Stille and Negishi reactions.[54] (Scheme 1.12).



Scheme 1.12. A diverse library of 3-substituted-2-pyrazolines via palladium cross-coupling reactions by Grimm *et al.*

A Pd-based catalytic system incorporating 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph) **(11)** will be shown to be ideal for library generation as it allows for convergent strategies in high yields with low catalyst loadings.[55,56] Furthermore, PA-R Pd catalyst systems allow the coupling of substrates

containing heteroatoms (especially nitrogen), which is problematic with most of the popular ligands reported in the literature as they often poison the catalytic system.[57,58]

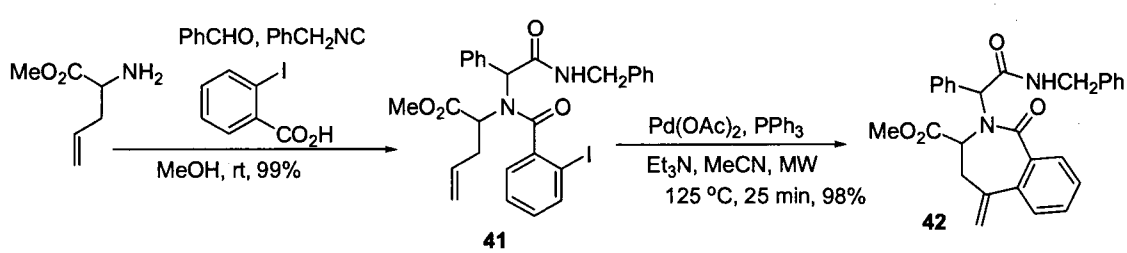
1.1.4 Microwave Assisted Reactions.

The utilization of microwave irradiation has been proven to be an important, effective technology helping to facilitate organic synthesis. Unlike conventional heating, energy transfer in a microwave reactor occurs by dielectric loss either *via* dipole rotation or ionic conduction.[19] These phenomena are dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert this into heat. These effects enable microwave heating to reduce chemical reaction times from hours to minutes, selectively activate or suppress reaction pathways, increase yields and improve reproducibility.

Over the past decade, a number of researchers have reported enhanced reactivity and increased yields in a variety of organic transformations including C-C bond formations; (the Heck reaction,[59-61] Suzuki reaction,[57,62] Sonogashira reaction,[53,63] Stille reaction,[53,64] carbonylation reaction,[65,66]) as well as C-O[67] and C-N bond formation.[68,69] Cao *et al.*, for example, used microwave assisted Suzuki cross-coupling reactions to generate several analogues of pyridazinones in good yield within a short reaction time.[57] Hay *et al.* also improved the yields of their products in the synthesis of 3-alkyl-1,2,4-benzotriazine-1-oxide (BTOs), an anticancer agent, through a microwave-assisted Stille reaction.[64]

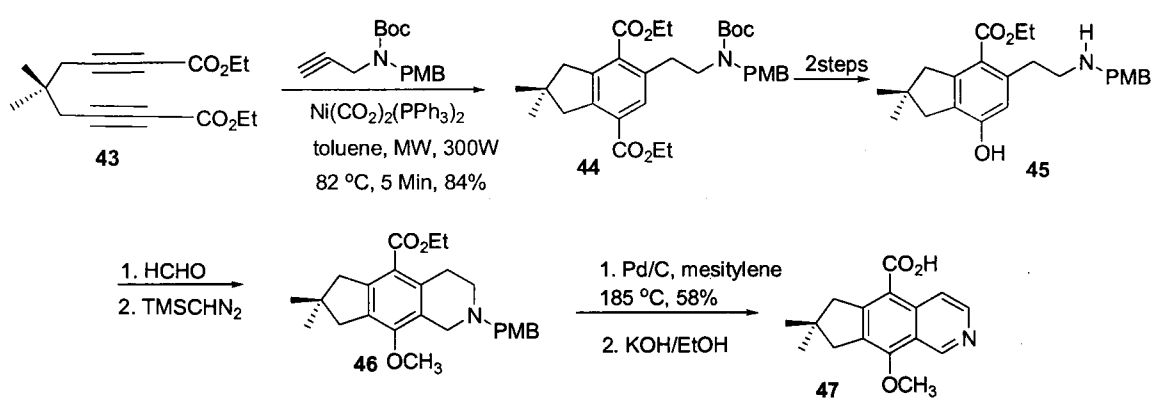
1.1.4.1 Microwave-assisted synthesis of heterocyclic compounds

Microwave heating in the preparation of heterocyclic compounds has been used extensively in the past decade. Using microwave irradiation reduces reaction times as well as increasing yields of products. For example, Gracias *et al.* described a sequence wherein the product obtained from an Ugi four-component reaction (**41**) was subjected to a microwave-assisted Heck reaction to allow for the synthesis of highly functionalized seven-membered lactams (e.g. **42**) in 98% yield in 25 minutes.[60] (Scheme 1.13). They observed that when the reaction was carried out under conventional heating, complete reaction was observed in 18 h with a 73% yield of the product (**42**).



Scheme 1.13. Intramolecular microwave-assisted Heck reaction.

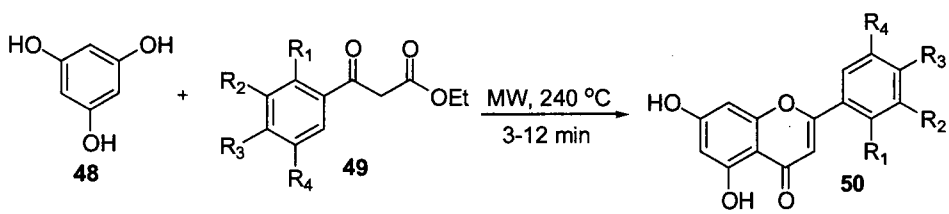
Deiters *et al.* reported a rapid and efficient microwave-assisted nickel catalyzed



Scheme 1.14. Microwave-assisted nickel catalyzed cyclotrimerization.

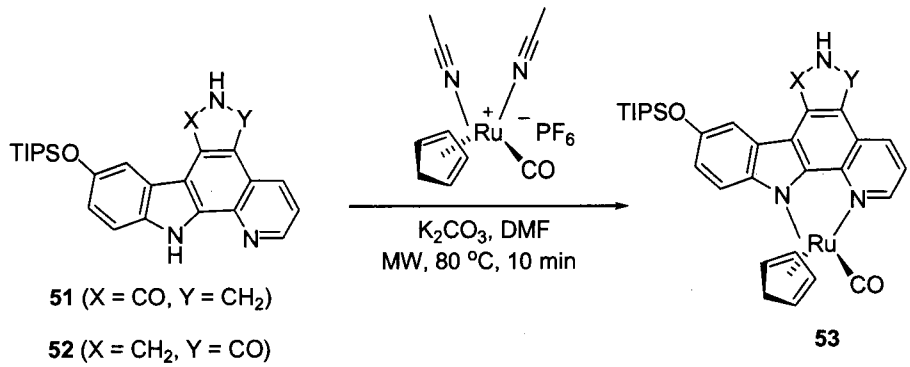
[2+2+2] cyclotrimerization to yield (**44**), a precursor for the synthesis of the isoquinoline, illudinine (**47**).[70] (Scheme 1.14). Conducting the [2+2+2] cyclotrimerization in refluxing solvent led to a mixture of the aromatized and linear polymeric products after 24 h. Using microwave irradiation, however, led to a complete reaction in 5 minutes at 82 °C. With this protocol in hand several fused bicyclic analogues were generated from various diynes and alkynes.

Microwave irradiation was also used by Seijas *et al.* in the synthesis of flavones (**50**) from phloroglucinol (**48**) and β-ketoesters (**49**).[71] (Scheme 1.15). The reactions were carried out in the absence of solvent. They compared reactions carried out under conventional heating to those carried out with microwave irradiation and observed a 4-fold increase in yield of product for reaction carried out in the microwave.



Scheme 1.15. Microwave-assisted synthesis of flavones.

Pagano *et al.* used microwave irradiation to effect a coordination reaction between ruthenium and lactam ligands (**51**) and (**52**) to yield the coordinated product (**53**), a GSK-3 inhibitor.[72] They observed that under conventional heating, the coordination reaction was extremely sluggish and no coordinated product was formed. However, a facile reaction was observed when the reaction was carried out using microwave irradiation in DMF at 80 °C for 10 minutes. (Scheme 1.16).



51 (X = CO, Y = CH_2)

52 (X = CH_2, Y = CO)

53

Scheme 1.16. Microwave assisted coordination reaction of ruthenium and ligand **51** and **52.**

1.1.4.2 Use of Microwave-Assisted Chemistry and Pd-Catalyzed Cross-Coupling in the Preparation of Heterocyclic Libraries

As outlined above, both microwave-assisted chemistry and Pd-catalyzed cross-coupling reactions are powerful tools for the organic synthetic chemist. Given that the present thesis seeks to determine the utility and scope of applicability of Pd cross-coupling and microwave chemistry in the preparation of heterocyclic compound libraries, three heterocyclic families were chosen as targets for our studies. Substituted flavones, isoquinolines and maleimides are currently of interest for a number of biological studies currently under investigation in the Capretta lab. In addition, these heterocyclic architectures are found throughout Nature and present in some highly biologically active compounds.

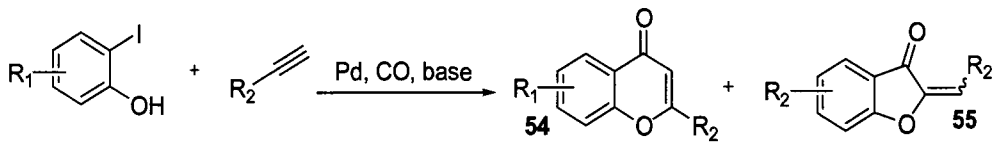
1.1.5 Flavones, Isoquinolines and Maleimides.

1.1.5.1 Flavones

Flavones also known as 2-phenylchromones constitute one of the major classes of naturally occurring products. They are a major group of secondary metabolites found in the plant kingdom and are present in biologically active compounds and drugs.[73-75] They possess antioxidant, antiviral and anticancer properties.[76,77] Over the past few decades, flavones have been found to be active towards several targets of biomedical interest such as estrogen receptors (ERs),[78] heat shock proteins (Hsp-90),[79] cyclo-oxygenase (COXs),[80] P-glycoproteins (PgPs)[81] and phosphodiesterases (PDEs).[82] Traditionally, flavones are obtained by cyclization of 1,3-diphenylpropane-1,3-diones which are prepared from 2-hydroxyacetophones and a benzoylating reagent or benzaldehydes.[83,84] Reported procedures to prepare flavone have also included treatment of a 2-hydroxyacetophenone and benzaldehyde under Claisen-Schmidt conditions to yield a 2-hydroxychalcone that can be oxidatively cyclized to yield the flavone system.[85,86] Most of these reported syntheses suffer from harsh reaction conditions such as strong bases and acids, elevated temperature and low yields.

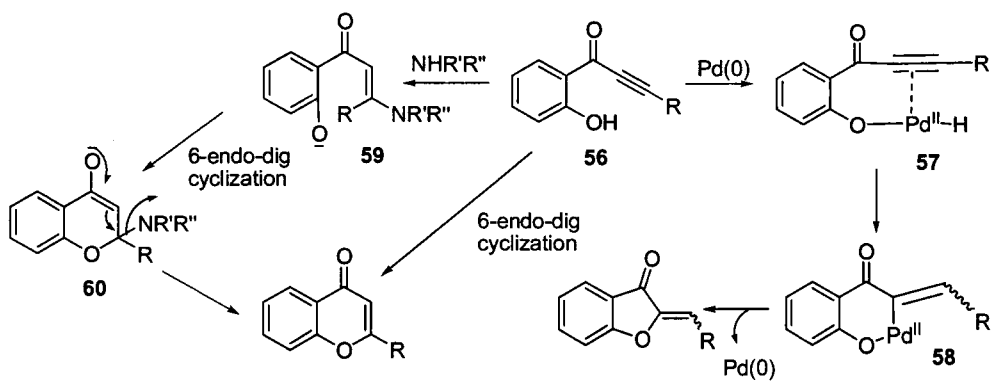
More recently, a particularly attractive alternate approach to flavone systems has been described that involves the Pd-catalyzed carbonylation/ cyclization reaction between 2-iodophenols and terminal alkynes.[87-89] In most of the Pd-catalyzed carbonylation/ cyclization protocols reported, the six membered flavone (**54**) was obtained along with a five membered aurone (**55**) *via* 6-endo-dig and 5-exo-dig ring closures

respectively. (Scheme 1.17).[87]



Scheme 1.17. Pd-catalyzed flavone synthesis from *o*-iodophenol and alkyne.

These two compounds have been shown to form by different processes and the experimental conditions have been proved to have a significant effect on the cyclization of the intermediate 1-(2-hydroxyaryl)-3-aryl-2-propyn-1-ones (**56**). (Scheme 1.18).[87]



Scheme 1.18. Processes involved in flavone and aurone formation.

Ortar *et al.* demonstrated that the cyclization step of 1-(2-hydroxyaryl)-3-aryl-2-propyn-1-ones (**56**) leading to flavones or aurones is influenced by both the Pd(0) complex and the base used.[89,90] While a reaction involving $Pd(OAc)_2(DPPF)_2$ and DBU yielded exclusively the flavone in 92% yield, the use of $Pd(PPh_3)_4$ and AcOK yielded no flavone product but only the aurone in 75% yield. Yang *et al.* addressed the issue of aurone formation by addition of an extra step to their synthesis by converting *o*-iodophenols to *o*-iodophenol acetates.[87] Fathi and Yang later reported a reaction protocol in aqueous media

that permitted the generation of flavone exclusively, however, their reported protocol required higher catalytic loading, 5 mol% of $PdCl_2$ and 10 mol% of PPh_3.[88]

Our approach to the synthesis of flavones (described in Chapter 2) takes advantage of the Pd-cross-coupling approach described above but also demonstrates that a sequential application of a microwave-assisted Sonogashira and carbonylative annulation is suitable for the preparation of substituted flavone libraries.

1.1.5.2 Maleimides and α,β-Unsaturated-γ-Butyrolactams

Maleimides and α,β-unsaturated-γ-butyrolactams are contained within important families of natural products and synthetic products with valuable pharmacological

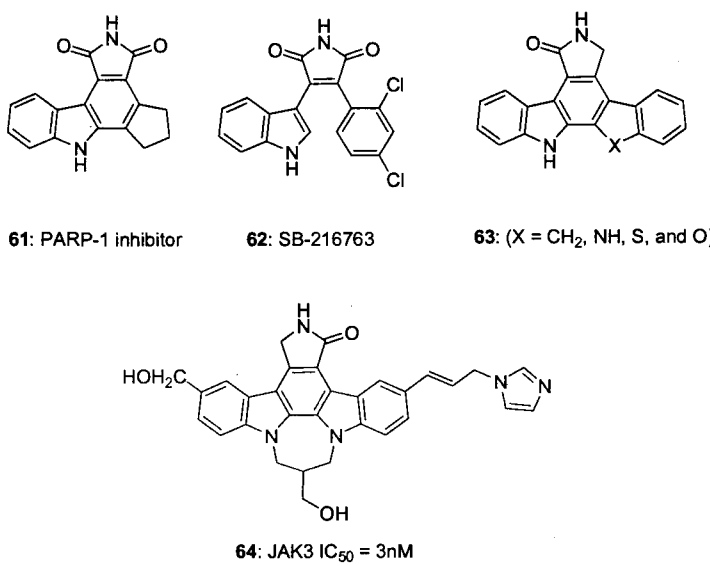
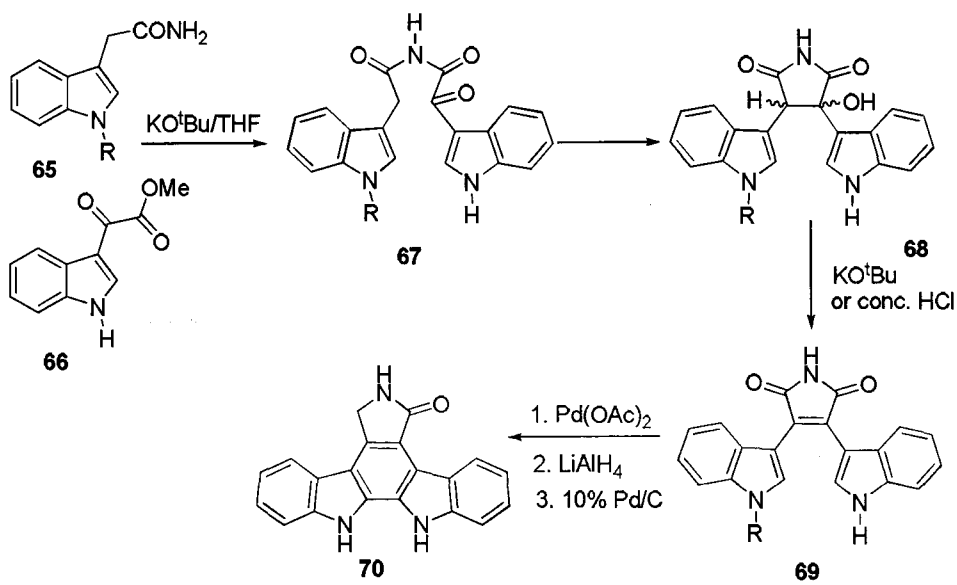


Figure 1.4. Biologically active Maleimide and α,β-unsaturated-γ-butyrolactam analogues.

properties.[91,92] They possess a wide range of biological activities including protein kinase inhibition (an important target in cancer chemotherapy,[92] where some are in clinical

trials as anticancer drugs[93,94]), as well as antibacterial, antiviral and antigenic activities.[95,96] For example, compound (**61**) and its analogues are shown to be potent PARP-1 [poly(ADP-ribose) polymerase-1] inhibitors.[97,98] Disubstituted maleimide (**62**) (SB 216763) has been shown to be a highly effective inhibitor of glycogen synthase kinase-3 (GSK-3),[96,99,100] while α,β-unsaturated-γ-butyrolactam analogue (**63**) (a staurosporine derivative) represents a larger group of indolocarbazoles with potent inhibitory effects on mixed lineage kinase 1 and 3 (MLK1/3),[101] and analogue (**64**) has been shown to inhibit janus kinase 3 (JAK-3) with an IC_{50} of 3 nM.[102] (Figure 1.4).

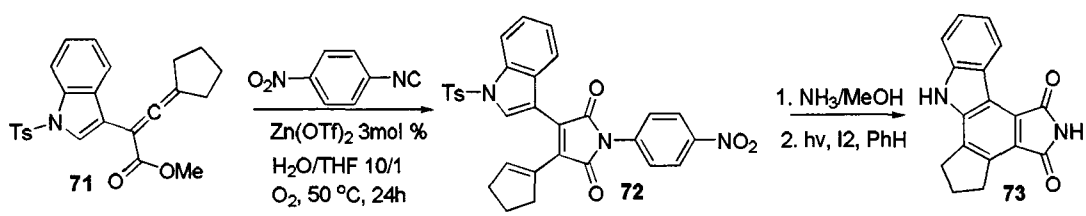
Synthetic protocols to these important heterocycle compounds described in the chemical literature generally require multi-step sequences through linear synthetic



Scheme 1.19. Bisindole maleimide synthesis by Faul *et al.*

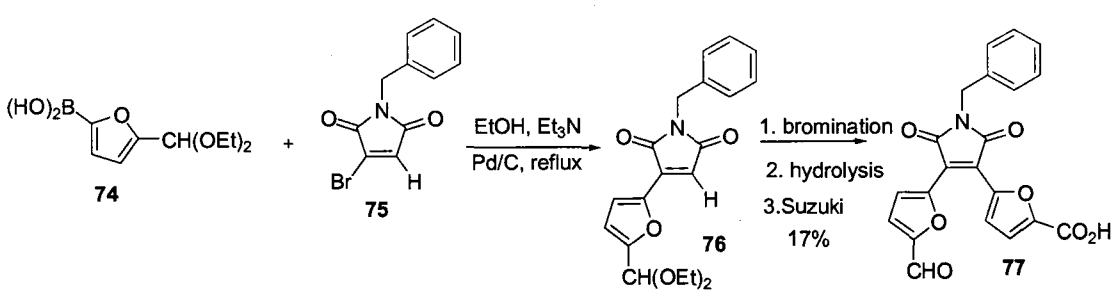
approaches forming the maleimide ring in the last step of the synthesis. For example, Faul *et al.* at Eli Lilly described the synthesis of bisindolyl-maleimides (**69**) and butyrolactam (**70**) (potent inhibitors of PKC*β) via* a reaction protocol that involves the base condensation of indole-3-acetamide (**65**) with indolyl-3-glyoxylate (**66**).[103] (Scheme 1.19).

Yang and Wang developed a Lewis acid catalyzed annulation of isonitrile and allenic esters (**71**) precursors followed by deprotection using aminolysis and photo induced oxidative 6π-electrocyclization to generate non-symmetrical maleimide analogues.[104] (Scheme 1.20).



Scheme 1.20. Synthesis of maleimide analogues by Lewis acid mediated annulation of isonitrile and allenic esters.

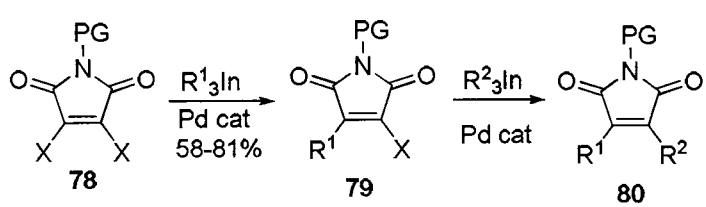
Dubernet *et al.* synthesized 3,4-bisheteroaryl-maleimide *via* palladium catalyzed Suzuki coupling reaction using 3,4-diodomaleimides as the starting precursor.



Scheme 1.21. Synthesis of non symmetrical maleimide by Dubernet *et al.*

From their synthetic route, the symmetrical disubstituted coupled product was obtained in only 15% yield.[105] In addition, attempts to generate non-symmetrical maleimides using this approach were unsuccessful as the requisite monoarylated product could not be obtained in practical yield. An alternate strategy was developed and the non-symmetrical maleimides were generated from coupling 3-bromomaleimide (**75**) with 2-furaldehyde diethyl acetal (**74**) to yield the coupled product, (**76**) in 55% yield. Conversion to the final non-symmetrical disubstituted maleimide (**77**) was achieved in 17% overall yield. (Scheme 1.21).

Sarandeses *et al.* recently reported Pd catalyzed synthesis of non-symmetrical maleimide *via* the use of triorganoindium reagents.[106] (Scheme 1.22). Though mono arylation was controlled by this protocol and product obtained in good yield, organoindium reagents are expensive and not cost effective in library synthesis. Clearly, there is still the need for facile, cost-effective routes to substituted maleimides.



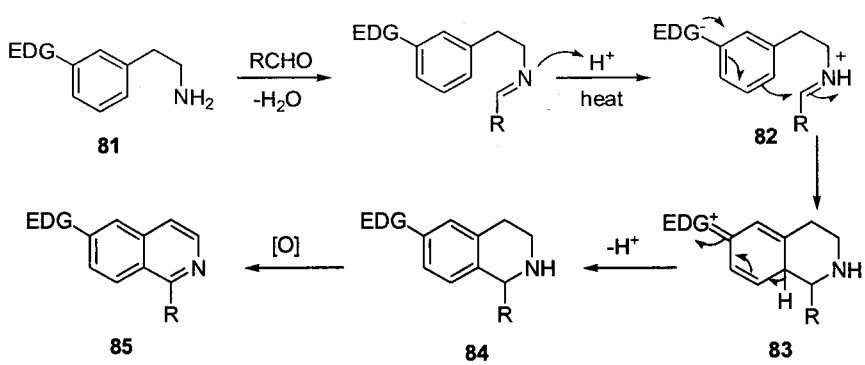
Scheme 1.22. Synthesis of non-symmetrical maleimide *via* triorganoindium reagents.

A major research focus within the Capretta laboratory is the development of selective kinase inhibitors. For these studies, facile access to 3,4-disubstituted maleimides is needed. Furthermore, the synthetic protocol developed must allow for the introduction

of a broad variety of functionality. Taking advantage of palladium catalyzed cross-coupling reactions developed in our lab, this thesis seeks to develop protocols that allow the control necessary to generate a non-symmetrical and symmetrical 3,4–disubstituted maleimide library. (see Chapter 3). Control of the preparation of non-symmetrical derivatives is crucial. The method developed will also be applied to the synthesis of analogous α,β-unsaturated-γ-butyrolactam systems.

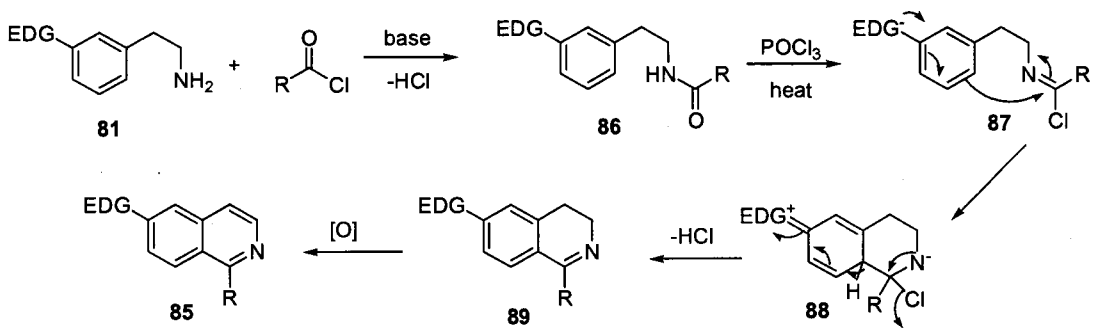
1.1.5.3 Isoquinolines

The isoquinoline core is an important heterocyclic moiety present in a variety of natural products and pharmaceuticals.[107-109] The Pictet-Spengler[110-112] and Bischler–Napieralski[113] reactions have traditionally been used for preparing isoquinoline derivatives. The Pictet-Spengler reaction, first described in 1911,[110] involves a Mannich-type reaction wherein a β-arylethylamine derivative (**81**) is treated with an aldehyde under acidic conditions to generate an iminium ion (**82**) that can ring close to a tetrahydroisoquinoline (**84**) and this is subsequently oxidized to an isoquinoline (**85**). (Scheme 1.23).



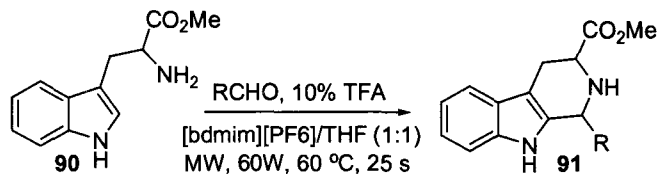
Scheme 1.23. General mechanism for Pictet-Spengler.

The Bischler-Napieralski[113] reaction involves the conversion of an *N*-acyl-*β*-arylethylamine (**86**) into the corresponding dihydroisoquinoline (**89**). (Scheme 1.24). The ring closure in both cases involves an electrophilic aromatic substitution, hence substrates that incorporate an electron-rich substituent on the aromatic ring at a position para to the cyclization site tend to give the best yields. Both Pictet-Spengler and Bischler-



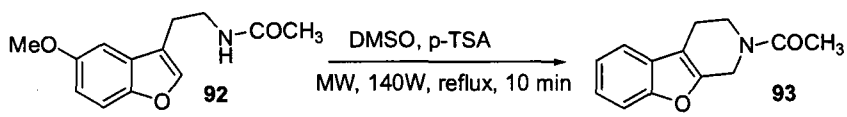
Scheme 1.24. General mechanism for Bischler-Napieralski.

Napieralski reaction protocols reported in the literature have involved harsh reaction conditions such as the use of neat acids and long reaction times to produce products in moderate overall yields. Most recently, protocols utilizing microwave irradiation in the Pictet-Spengler[112,114-117] and the Bischler-Napieralski[117] reactions have been described. Chu *et al.* carried out a microwave-assisted Pictet-Spengler reaction of tryptophan methyl ester (**90**) with various aldehydes and ketones in [bdmin][PF_6] ionic liquid to yield carboline (**91**).[114] (Scheme 1.25).



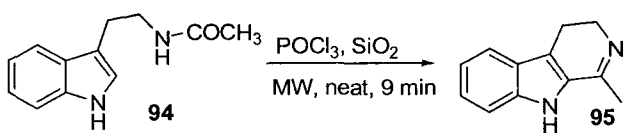
Scheme 1.25. Microwave assisted Pictet-Spengler reaction by Chu *et al.*

Besson *et al.* utilized a microwave assisted Pictet-Spengler reaction in the synthesis of melatonin analogues. The formaldehyde required for the Pictet-Spengler cyclization was provided by thermal decomposition of DMSO.[112] (Scheme 1.26).



Scheme 1.26. Microwave assisted Pictet-Spengler reaction by Besson *et al.*

Giri *et al.* carried out a microwave assisted Bischler-Napieralski reaction using neat $POCl_3$ towards their synthesis of β-carboline (**95**).[117] (Scheme 1.27).



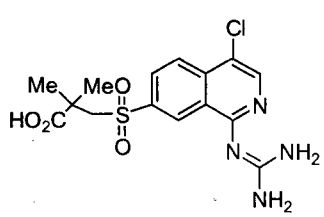
Scheme 1.27. Microwave Bischler-Napieralski reaction.

Isoquinoline containing compounds have been shown to possess a variety of potent biological activities. For example, compound (**96**) has been shown by Fish *et al.* to

be a potent inhibitor of urokinase–type plasminogen activator (UPA) and is able to inhibit chronic wound fluid (IC_{50} = 0.89 μM, Ki = 10 nM) with no adverse effect on wound healing parameters.[118] Compound (**97**) was found to display significant antimicrobial activity against two Gram positive (*Staphylococcus aureus, Bacillus subtilis*) bacteria, two Gram negative (*Salmonella enteritidis, Escherichia coli*) bacteria and one fungus (*Candida albicans*) with MIC values (μg/mL) 3.9, 3.9, 3.9, 15.6 and 3.9 respectively. Compound (**97**) therefore appeared to be a useful lead compound for further development of antimicrobials.[119]

Compound (**98**) was identified as an orally active inhibitor of tyrosine kinase p56lck, (lck) with IC_{50} of 0.023nM.[120,121]

The broad biological effect of isoquinolines prompted Steglich *et al.* to use them as chelating, nonleaving ligands in cis platinum (II) antitumor complexes. During their



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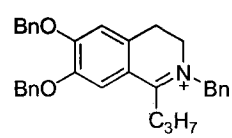

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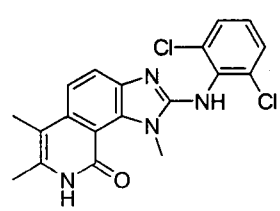
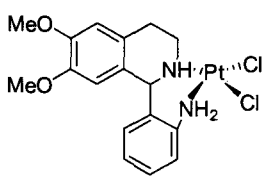


98

Figure 1.5. Some examples of biologically active isoquinolines.

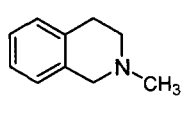
studies they showed that compound (**99**) was potent against L1210 murine leukemia cells with IC_{50} value of 0.88 μM, two times more effective then the well-established antitumor compound cisplatinum.[122]



99

Figure 1.6. Isoquinoline with antitumor activity.

Abell and his group have also demonstrated that a series of simple isoquinoline alkaloids (**100**), (**101**) and (**102**), (Figure 1.7) showed substantial inhibition of human monoamine oxidases A and B.[109] Monoamine oxidases A and B are outer mitochondrial membrane flavoenzymes catalyzing the degradation of neurotransmitters and xenobiotic aryl alkyl amines.



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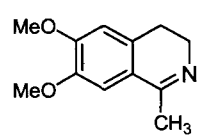

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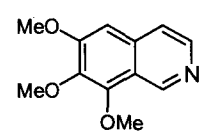
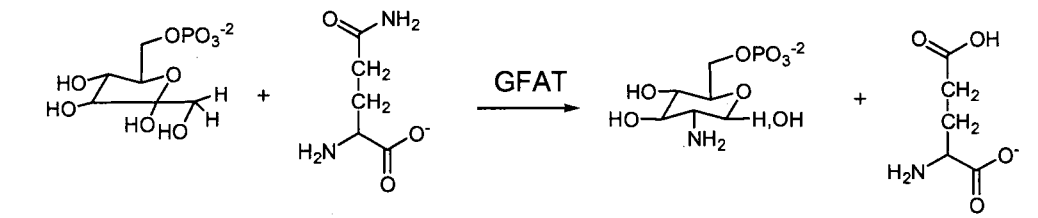


102

Figure 1.7. Simple isoquinoline as inhibitors of human monoamine oxidases A and B.

The Capretta group's interest in this heterocyclic family stems from the inhibitory activity of certain isoquinolines against the enzyme glutamine fructose-6-phosphate amidotransfaerase, (GFAT). GFAT is the rate limiting enzyme in the hexosamine pathway. It catalyzes the first step in the hexosamine metabolism by converting frutose-6-phosphate (**103**) into glucosamine-6-phosphate (**105**) using glutamine (**104**) as source of ammonia.[123-125] (Scheme 1.28). Type II diabetes patients with secondary diabetic

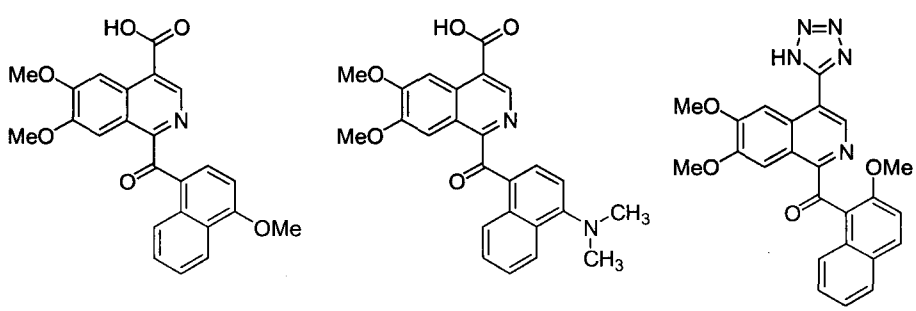
complications have elevated levels of GFAT activity and much remains to be elucidated about GFAT's role in diabetes complications.



103 **104** **105** **106**

Scheme 1.28. GFAT activity in the hexosamine pathway.

Bolin *et al.* have shown that 1,4-substituted acylisoquinoline analogues (**107**), (**108**) and (**109**) (Figure 1.8) are GFAT inhibitors with CI_{50} values ranging between 1 nM and 100 μM.[126]



107 **108** **109**

Figure 1.8. 1,4-substituted acylisoquinoline as GFAT inhibitors

A methodology that allows for the rapid access to a 1,4-substituted isoquinoline library is worth investigating. These compounds can then be tested and used to determine which moieties in the lead isoquinoline series are needed for inhibition. Ideally, more potent inhibitors may be designed based on the SAR information gained. Furthermore, effective inhibitors can be used as a standard of comparison or control in the development of new GFAT assays. Chapter 4 describes protocols that utilize microwave assisted variants of the Pictet-Spengler and Bischler-Napieralski reactions to generate a library of 1,4-substituted isoquinolines. Also outlined is the more combinatorial approach that builds an isoquinoline library from an isoquinoline-1(2H)-one scaffold using Pd-catalyzed cross-coupling chemistry. Chapter 5 describes preliminary efforts to prepare isoquinolines from suitably functionalized β-arylethylamines generated *via* ketone arylation cross-coupling followed by a reductive amination. The methodologies represent a new route to 1,3,4-trisubstituted isoquinolines useful in our GFAT studies and unavailable *via* our previously developed route.

1.1.6 References

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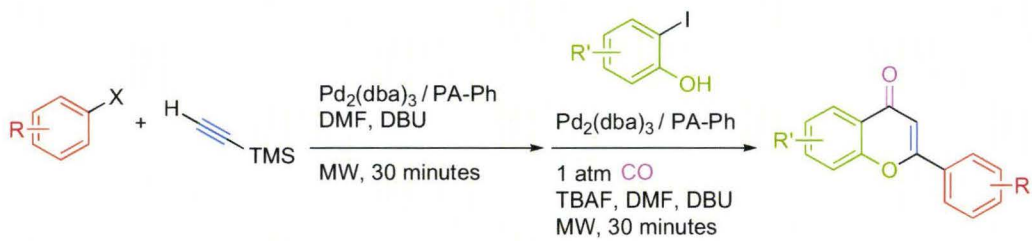
Chapter 2

2.1.1 Access to Flavones via a Microwave-assisted, "One Pot" Sonogashira Carbonylation-Annulation Reaction.[1]

Emelia Awuah and Alfredo Capretta

2.1.2 Abstract



Palladium complexes of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph) are shown to be effective catalytic systems facilitating the sequential application of a microwave-assisted Sonogashira and a carbonylative annulation reaction for the preparation of flavones.

2.1.3 Introduction

Flavones[1] are a major group of secondary metabolites found throughout the plant kingdom and have been shown to possess a wide variety of biological activity.[2] A number of classical synthetic approaches to this family of compounds exist. The Baker-

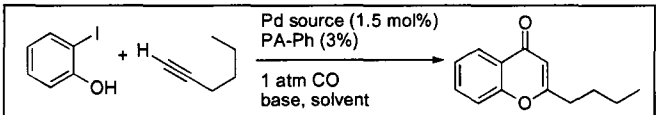
[1] Reproduce with permission from American Chemical Society. Originally published as Awuah, E.; Capretta, A. Access to Flavones *via* a Microwave-assisted, "One-Pot" Sonogashira-Carbonylation-Annulation Reaction. *Organic Letters,* **2009**, 11, 3210-3213.

Venkataraman[3] methodology involves the conversion of 2-hydroxyacetophenones into benzoyl esters, rearrangement in base to 1,3-diphenylpropane-1,3-diones followed by cyclization in acid to yield the flavone ring system.[4] Alternatively, treatment of a 2-hydroxyacetophenone and benzaldehyde under Claisen-Schmidt conditions yields a 2-hydroxychalcone that can be oxidatively cyclized to yield the flavone system.[5] Both approaches utilize harsh conditions such as strong bases, acid and elevated temperatures. A particularly attractive alternate approach involves the Pd-catalyzed carbonylation[6] / cyclization reaction between 2-iodophenols and terminal alkynes.[7] Given our work with palladium complexes of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph) and their ability to readily catalyze the coupling of aryl halides with terminal acetylenes[8], we envisioned a reaction sequence wherein the product of a Sonogashira reaction could then undergo Pd-catalyzed carbonylative annulation with a 2-iodophenol to yield a flavone scaffold. The present paper describes a microwave-assisted, "one pot" method that allows for the efficient and mild preparation of flavones from aryl halides and 2-iodophenol derivatives.

Our initial effort focused on the Pd-catalyzed carbonylation annulation reaction between 2-iodophenol and 1-hexyne using the PA-Ph ligand. The screening of various Pd sources, solvents, temperatures and bases is presented in Table 2.1. Reagents were combined in a reaction vessel and the reaction carried out under an atmosphere of CO gas. These experiments quickly revealed that using DMF as the solvent with Cs_2CO_3 or DBU as the base at 50C resulted in 91 and 93% isolated yield, respectively, of the desired

flavone (Table 2.1 entry 13 and 14). Under these conditions we produced the flavone products exclusively and did not observe any of the aurone byproduct.

Table 2.1. Optimization of Pd-catalyzed carbonylation-annulation conditions



entry	Pd source	solvent	base	temp / time	% yield
1	$PdCl_2$	H_2O	Et_3N	25C / 2h	0
2	$Pd_2(dba)_3$	MeCN	$(iPr)_2EtN$	25C / 2h	42
3	$Pd_2(dba)_3$	MeCN	Et_3N	25C / 2h	0
4	$Pd_2(dba)_3$	MeCN	Cs_2CO_3	25C / 2h	54
5	$Pd_2(dba)_3$	dioxane	$(iPr)_2EtN$	25C / 2h	0
6	$Pd_2(dba)_3$	toluene	$(iPr)_2EtN$	25C / 2h	0
7	$Pd_2(dba)_3$	THF	$(iPr)_2EtN$	25C / 2h	20
8	$Pd_2(dba)_3$	THF	Cs_2CO_3	25C / 14h	40
9	$Pd_2(dba)_3$	toluene / THF	$(iPr)_2EtN$	25C / 2h	0
10	$Pd_2(dba)_3$	toluene / MeCN	$(iPr)_2EtN$	25C / 2h	0
11	$Pd_2(dba)_3$	DMSO	Cs_2CO_3	25C / 14h	20
12	$Pd_2(dba)_3$	DMF	Cs_2CO_3	25C / 14h	76
13	$Pd_2(dba)_3$	DMF	Cs_2CO_3	50C / 4h	91
14	$Pd_2(dba)_3$	DMF	DBU	50C / 4h	93

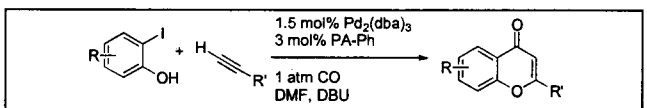
Reactions were carried out using 0.50 mmol 2-iodophenol and 0.75 mmol 1-hexyne.

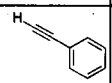
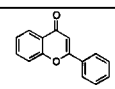
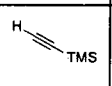
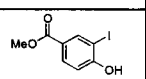
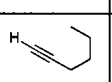
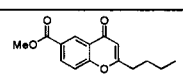
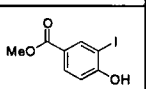
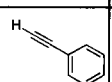
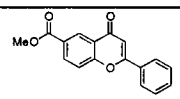
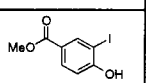
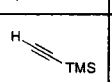
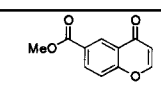
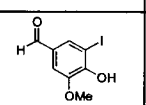
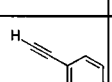
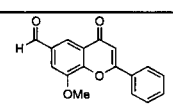
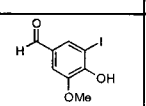
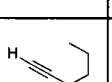
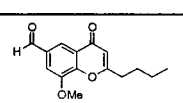
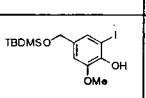
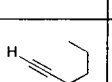
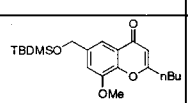
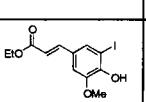
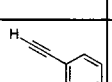
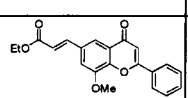
The relatively low catalyst loading (1.5 % mol equivalent of $Pd_2(dba)_3$ and 3 % mol equivalent of PA-Ph), short reaction time, high conversion and mild temperatures render our catalytic system more efficient than previously reported protocols.[7] With the optimal set of conditions in hand, we proceeded to generate a small library of flavones (Table 2.2). Overall, the method works well and tolerates a variety of functional groups.

With entries 2 and 5, desilylation during the annulation step proceeds without the need for any additional reagents. Entries 8 and 9 required longer reaction times (12

hours). The lower yield observed for entry 8 was not due to desilylation as might be expected; rather, under the conditions employed, significant amounts of starting material remain unreacted. It is likely that the electron donating substituents on the aryl iodide slow the rate of oxidative addition with the Pd-catalyst system.

Table 2.2. Flavones *via* a Pd-catalyzed carbonylation / cyclization reaction



entry	iodophenol	alkyne	product	yield[b]
1[c]				81
2[c]				86
3[c]				83
4[c]				82
5[c]				79
6[c]				92
7[c]				76
8[d]				31
9[d]				86

Reactions were carried out using 0.50 mmol of the substituted 2-iodophenol and 0.75 mmol of the alkyne; [b] Isolated yield; [c] 50C, 4h; [d] 50C, 12h.

Microwave-assisted organic synthesis has demonstrated itself to be superior in many instances when compared to reactions carried out using conventional heating.[9] The use of microwave irradiation often helps to reduce reaction times, minimize side products, increase yields and improve reproducibility. A number of examples of microwave-

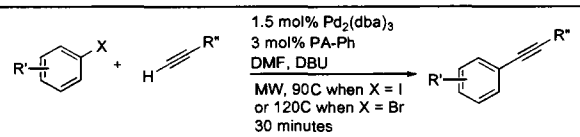
assisted carbonylation reactions have been described in the literature.[10] These previous approaches have generally utilized $Mo(CO)_6$ and, as a result, require elevated temperatures to induce the decomposition of the molybdenum reagent and liberation *in situ* of CO gas. Given the relatively mild temperatures used above and the efficacy of the PA-Ph ligand, we examined the effect of microwave heating on our reaction conditions. We determined, ultimately, that comparable yields for the carbonylation-annulation reaction could be obtained when the reaction mixture was irradiated in a microwave at 90C using a shortened reaction time of only 30 minutes. However, a much improved yield of 68% was obtained when the microwave-assisted conditions were applied to preparation of the TBDMS-protected flavone (Table 2.2, entry 8). While the use of a CEM gas addition unit[11] greatly facilitated the introduction of CO into the reaction vessel, we also found that simply bubbling CO gas into the reaction prior to microwave irradiation allowed for an equally efficient reaction and avoided the need for $Mo(CO)_6$.

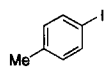
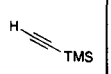
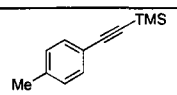
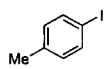
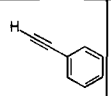
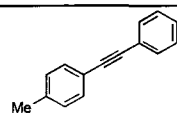
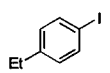
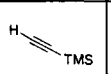
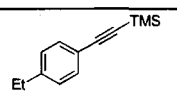
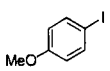
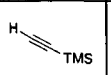
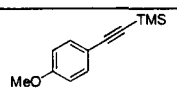
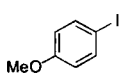
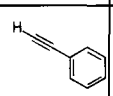
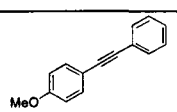
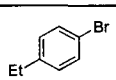
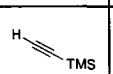
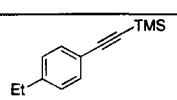
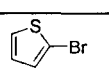
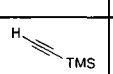
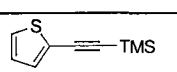
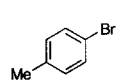
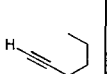
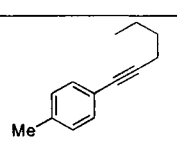
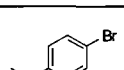
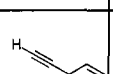
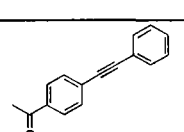
The alkyne required for the Pd-catalyzed carbonylative annulation developed above could be generated *via* a Sonogashira reaction. Using our previously developed protocol as a starting point,[8] we modified the reaction conditions so as to integrate with those developed for the carbonylation-annulation reaction. In this way, we found that the optimal conditions (1.5% $Pd_2(dba)_3$; 3% PA-Ph, DMF, DBU) using microwave irradiation allowed for a reduction in reaction times and the elimination of the CuI co-

catalyst generally required by the Sonogashira reaction (see Table 2.3). For example, the coupling of *p*-iodotoluene with phenylacetylene (entry 2) could be achieved in 30 minutes in 96% yield. When arylbromides were used (entries 6 – 8) as coupling partners, an increase in temperature (to 120C) allowed for excellent yields with comparable reaction times.

Having established the conditions and scope of both the microwave-assisted, Pd-catalyzed carbonylative- annulation and the Sonogashira reaction, a natural extension of the work involves a sequential combination of the two reactions effectively allowing for a "one-pot" flavone synthesis. In all cases, the initial microwave-mediated Sonogashira reaction

Table 2.3. Microwave-assisted Sonogashira reactions

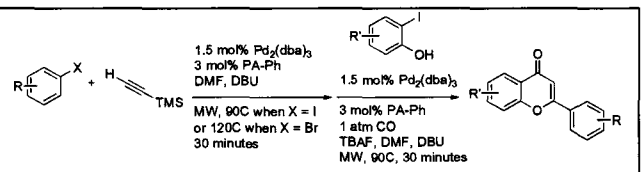


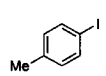
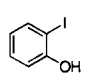
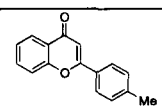
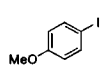
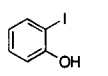
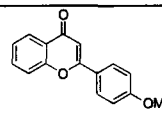
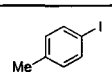
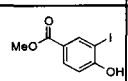
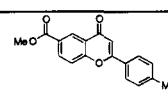
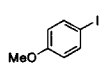
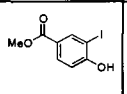
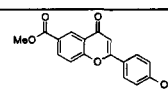
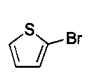
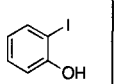
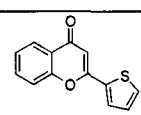
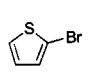
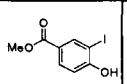
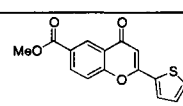
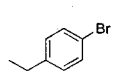
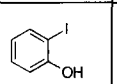
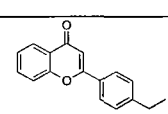
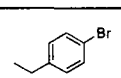
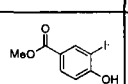
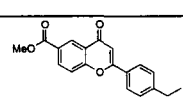
Entry	aryl halide	alkyne	product	yield[b]
1				94
2				96
3				92
4				89
5				93
6				85
7				96
8				94
9				96

Reactions were carried out using 1.0 mmol aryl halide and 1.5 mmol alkyne; [b] Isolated yield.

involved an aryl halide and TMS acetylene. The products from this reaction were then introduced into a reaction vessel containing the iodophenol, fresh Pd / PA-Ph catalyst system, solvent and base. Introduction of CO followed by microwave irradiation allowed for the preparation of the flavones listed in Table 2.4. It should be noted that addition of TBAF in the second step allowed for deprotection of the TMS group and made for a smoother, more reproducible

Table 2.4. Flavones *via* a microwave-assisted Sonogashira / carbonylation / cyclization reaction



Entry	aryl halide	iodophenol	product	yield[b]
1				67
2				56
3				63
4				46
5				65
6				71
7				62
8				58

Reactions were carried out using 1.0 mmol aryl halide, 1.5 mmol alkyne and 0.5 mmol substituted 2-iodophenol; [b] Isolated yield over two steps based on starting amount of substituted 2-iodophenol used.

annulation reaction. The yields of the isolated flavone range from moderate to very good with the entire sequence completed in approximately an hour.

2.1.4 Conclusion

Overall, the synthetic method developed above for the preparation of substituted flavones involves mild reaction conditions, relatively short reaction times and provides good yields of the desired products. Given the range of commercially available components for this protocol (aryl iodides and bromides as well as substituted o-iodophenols), the method should prove valuable in the preparation of combinatorial libraries of flavones.

2.1.5 Experimental

General procedure for flavone synthesis using conventional heating. (Tables 2.1 and 2.2): $Pd_2(dba)_3.CHCl_3$ (7.8 mg, 0.0075 mmol), PA-Ph (4.4 mg, 0.0150 mmol), 2-iodophenol (0.5 mmol) and DMF (1.5 mL) were placed in a round bottom flask and the mixture degassed by sparging with argon. The reaction vessel was capped with a rubber septum placed under an atmosphere of CO (using a balloon of CO gas). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 112 μL, 0.75 mmol) and the alkyne (0.75 mmol) were then added via a syringe. The reaction mixture was stirred at 50 °C for 4 h at which time the solvent was evaporated *in vacuo*. The reaction was then purified using column chromatography (20-30% ethyl acetate in hexane) to yield the desired flavones.

2-Butyl-4H-chromen-4-one (Table 2.1). Column chromatography (20% ethyl acetate in hexane) allowed for isolation of the title compound which showed identical spectroscopic properties to those previously reported.[12]

2-Phenyl-4H-chromen-4-one (Table 2.2, Entry 1). Column chromatography (20% ethyl acetate in hexane) yielded 81% of the title compound as white solid. The compound showed identical spectroscopic properties to those previously reported.[13]

4H-chromen-4-one (Table 2.2, Entry 2). Column chromatography (20% ethyl acetate in hexane) yielded 86% of the title compound. The compound showed identical spectroscopic properties to those previously reported.[12]

Methyl 2-butyl-4-oxo-4H-chromene-6-carboxylate (Table 2.2, Entry 3). Column chromatography (30% ethyl acetate in hexane) yielded 83% of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.86 (s,1H), 8.29 (dd, J_1 = 6.8, J_2 = 2.0 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 6.20 (s, 1H), 3.95 (s, 3H), 2.64 (t, J = 7.4 Hz, 2H), 1.71 (m, 2H), 1.44 (m, 2H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 177.8, 170.2, 165.9, 159.0, 134.1, 128.3, 127.5, 123.5, 118.4, 110.3, 52.5, 34.0, 28.8, 22.2, 13.8; HRMS (CI) for [$C_{15}H_{16}O_4$] calculated 260.1627, found 260.1627

Methyl 4-oxo-2-phenyl-4H-chromene-6-carboxylate (Table 2.2, Entry 4) Column chromatography (30% ethyl acetate in hexane) yielded 82% of the title compound as white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.02 (s, 1H), 8.46 (d, J = 7 Hz, 1H), 8.10 (d, J = 3.8 Hz, 2H,), 7.67-7.76 (m, 4H), 6.97 (s, 1H), 4.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 50

MHz): δ 177.8, 165.9, 163.7, 158.8, 134.6, 132.1, 131.3, 129.2, 128.3, 127.3, 126.4, 123.7, 118.7, 108.0, 52.6; HRMS (CI) for [$C_{17}H_{12}O_4$] calculated 280.0736, found 280.0748.

Methyl 4-oxo-4H-chromene-6-carboxylate (Table 2.2, Entry 5). Column chromatography (30% ethyl acetate in hexane) yielded 79% of the title compound as white solid. 8.90 (s, 1H), 8.33 (dd, J_1 = 6.8, J_2 = 2.0 Hz, 1H) 7.87 (d, J = 6 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H) 6.39 (d, 6.0 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 176.1, 164.9, 158.1, 154.6, 133.6, 127.5, 126.5, 123.7, 117.9, 112.7, 51.7; MS (CI), m/z (RI%): 204 (55), 173 (100), 145 (26), 89 (14).

8-Methoxy-4-Oxo-2-phenyl-4H-chromene-6-carbaldehyde (Table 2.2, Entry 6). Column chromatography (30% ethyl acetate in hexane) yielded 92% of the title compound as white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.05 (s, 1H), 8.29 (s, 1H), 7.96-8.00 (m, 2H), 7.70 (s, 1H), 7.56 (m, 3H), 6.90 (s, 1H), 4.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.9, 177.6, 163.6, 150.3, 133.3, 132.2, 131.2, 129.3, 126.5, 125.0, 122.9, 110.2, 107.9, 56.7; HRMS (CI) for [$C_{17}H_{12}O_4$] calculated 280.0736, found 280.0733.

2-Butyl-8-methoxy-4-oxo-4H-chromene-6-carbaldehyde (Table 2.2, Entry 7). Column chromatography (30% ethyl acetate in hexane) yielded 76% of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.02 (s, 1H), 8.25 (s, 1H), 7.64 (s, 1H), 6.26 (s, 1H), 4.04 (s, 3H), 2.70 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.42 (m, 2H), 0.97 (t, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 191.0, 177.5, 170.3, 150.0, 133.4, 132.9, 128.9, 124.8, 123.1, 110.6, 109.9,

56.7, 34.1, 28.9, 22.3, 13.9; HRMS (CI) for [$C_{15}H_{16}O_4$] calculated 260.1050 found 260.1049.

2-Butyl-6-((tert-butyldimethylsilyloxy)methyl)-8-methoxy-4H-chromen-4-one (Table 2.2, Entry 8). Column chromatography (10% ethyl acetate in hexane) yielded 31% of the title compound. Alternatively, if CO gas was bubbled through the reaction mixture (prepared as described in the general procedure above) for 5 minutes or added using the CEM gas addition unit then microwaved at 90 °C for 30 minutes, a yield of 68% was obtained after column chromatography. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60 (s, 1H), 7.26 (s, 1H), 6.18 (s, 1H), 4.78 (s, 2H), 3.98 (s, 3H), 2.67 (t, J = 7.6 Hz, 2H), 1.74 (m, 2H), 1.45 (m, 2H), 0.97 (overlap, 12H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.5, 169.7, 148.9, 138.4, 129.1, 124.4, 113.2, 112.6, 109.9, 64.7, 56.4, 34.1, 29.1, 26.1, 22.3, 18.5, 13.9, -5.1; HRMS (ES) for [$C_{21}H_{33}O_4Si$] [M+1], calculated 377.2148 found 377.2134

(2E)-Ethyl 3-(4-oxo-2-phenyl-4H-chromen-6-yl)acrylate (Table 2.2, Entry 9). Column chromatography (30% ethyl acetate in hexane) yielded 86% of the title compound as white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.90-7.97 (m, 3H), 7.70 (d, J = 16 Hz, 1H), 7.51-7.54 (m, 4H), 6.83 (s, 1H), 6.50 (d, J = 16 Hz, 1H), 4.30 (q, J = 7.0 Hz, 2H), 4.05 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H).;^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.0, 166.7, 163.2. 149.7, 147.7, 143.3, 131.9, 131.5, 129.2, 126.5, 125.0, 119.6, 117.2, 112.4, 107.6, 60.8, 56.5, 14.4; HRMS (CI) for [$C_{21}H_{18}O_5$] calculated 350.1140 found 350.1140.

General Procedure for Microwave-assisted Sonogashira Reaction (Table 2.3): A mixture of $Pd_2(dba)_3$, (0.015 mmol), PA-Ph (0.03 mmol), the aryl halide (1 mmol) (if solid) and DMF (1.5 mL) were placed in a microwave vial and the mixture degassed by sparging with argon. DBU (1.5 mmol), the alkyne (1.5 mmol) and the aryl halide (if liquid) were added, the vial capped and the reaction mixture microwaved at 90 °C for 30 mins for aryl iodides and at 120 °C for 30 mins for aryl bromides). The reaction mixture was purified by column chromatography using hexane.

Trimethyl (2-p-tolylethynyl) silane (Table 2.3, Entry 1). Column chromatography (hexane) yielded 94% of title compound as light yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.37 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.7, 132.0, 129.1, 120.2, 105.5, 93.3, 21.6, 0.16; MS (CI), m/z (RI%): 188 (22), 173 (100), 143 (5).

1-(2-p-tolyethynyl) benzene (Table 2.3, Entry 2). Column chromatography (hexane) yielded 96% of the title compound as white solid. The compound showed identical spectroscopic properties to those previously reported.[8]

(2-(4-Ethylphenyl)ethynyl)trimethylsilane (Table 2.3, Entries 3 and 6). Column chromatography (hexane) yielded 92% for entry 3 and 85% for entry 6 of title compound as light yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 2.62 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 145.0, 132.1, 127.9, 120.4, 105.5, 93.3, 29.0, 15.5, 0.17; MS (CI), m/z (RI%): 202 (23), 187 (100), 172 (5).

(2-(4-Methoxyphenyl)ethynyl)trimethylsilane (Table 2.3, Entry 4). Column chromatography (2% ethyl acetate in hexane) yielded 89% of the title compound as light yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40 (d, J = 7.4 Hz, 2H), 6.81 (d, J = 7.4 Hz, 2H), 3.80 (s, 3H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.9, 133.6, 130.5, 115.4, 113.9, 105.3, 55.4, 0.22; MS (CI), m/z (RI%): 204 (32), 189 (100), 174 (6), 146 (6).

1-(2-(4-methoxyphenyl)ethynyl)benzene (Table 2.3, Entry 5). Column chromatography (hexane) yielded 93% of the title compound as white solid. The compound showed identical spectroscopic properties to those previously reported.[8]

Trimethyl(2-(thiophene-2-yl)ethynl)silane (Table 2.3, Entry 7). Column chromatography (hexane) yielded 96% of the title compound as light yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.23-7.26 (m, 2H), 6.94-6.98 (m, 1H), 0.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 132.7, 127.4, 127.0, 123.3, 98.8, 97.8, 0.0; MS (ES), m/z (RI%): 181 (8), 174 (46), 172 (100).

1-(Hex-1-ynyl)-4-methylbenzene (Table 2.3, Entry 8). Column chromatography (hexane) yielded 94% of the title compound as light yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0, 2H), 2.40 (t, J = 7.0 Hz, 2H), 2.33 (s, 3H), 1.46-1.60 (m, 4H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 137.6, 131.5, 121.1, 89.7, 80.6, 31.1, 22.2, 19.3, 13.8; MS (CI), m/z (RI%): 172 (47), 157 (57), 129 (100), 102 (6).

1-(4-(2-phenylethynyl)phenyl)ethanone (Table 2.3, Entry 9). Column chromatography (20% ethyl acetate in hexane) yielded 96% of the title compound as white solid. The compound showed identical spectroscopic properties to those previously reported.[8]

General Procedure for "one pot" flavone synthesis (Table 2.4): A mixture of $Pd_2(dba)_3$, (0.015 mmol), PA-Ph (0.03 mmol), the aryl halide (1 mmol) (if solid) and DMF (1.5 mL) were placed in a microwave vial and the mixture degassed by sparging with argon. DBU (1.5 mmol), ethynyltrimethylsilane (1.5 mmol) and the aryl halide (if liquid) were added, the vial capped and the reaction mixture microwaved (at 90 °C for 30 mins for aryl iodides and at 120 °C for 30 mins for aryl bromides). The contents were added to another microwave vial containing a mixture of substituted 2-iodophenol (0.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (7.8 mg, 0.0075 mmol), PA-Ph (4.4 mg, 0.0150 mmol), DBU (224 μL, 1.5 mmol), TBAF (1M solution in THF, 1 mL, 1 mmol) and DMF (0.5 mL). In a well-vented fume hood, CO gas was bubbled through the reaction mixture for 5 minutes. Alternatively, CO gas could be introduced *via* a CEM gas addition unit. The vial was then sealed and microwaved at 90 °C for 30 minutes. The reaction mixture was concentrated *in vacuo* and purified using column chromatography (20-30% ethyl acetate in hexane) to yield the desired flavone.

2-p-Tolyl-4H-chromen-4-one (Table 2.4, Entry 1). Column chromatography (20% ethyl acetate in hexane) yielded 67% of the title compound as white solid. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.23 (d, J = 8.0 Hz, 1H), 7.23-7.86 (m, 7H), 6.83 (s, 1H) 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.7, 163.9, 156.4, 142.5, 133.8, 129.9, 129.1, 126.4, 125.8,

125.3, 124.1, 118.2, 107.1, 21.7; HRMS (CI) for [$C_{16}H_{12}O_2$] calculated 236.0837 found 236.0836.

2-(4-methoxyphenyl)-4H-chromen-4-one (Table 2.4, Entry 2). Column chromatography (20% ethyl acetate in hexane) yielded 56% of the title compound as white solid. The compound showed identical spectroscopic properties to those previously reported.[14]

Methyl 4-oxo-2-p-tolyl-4H-chromene-6-carboxylate (Table 2.4, Entry 3). Column chromatography (30% ethyl acetate in hexane) yielded 63% of the title compound as white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8. 92 (s, 1H), 8.36 (dd, J_1 = 6.6, J_2 = 2 Hz, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.4 Hz 1H), 7.34 (d, J = 7.8 Hz, 2H), 6.83 (s, 1H), 3.97 (s, 3H), 2.5 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 177.0, 165.0, 163.1, 157.9, 141.9, 139.5, 133.6, 129.1, 126.4, 125.5 122.8, 117.7, 106.4, 51.6, 20.8. HRMS (ES) for [$C_{18}H_{15}O_4$] calculated 295.0970; found M+1 295.0960.

Methyl 2-(4-methoxyphenyl)-4-oxo-4H-chromene-6-carboxylate (Table 2.4, Entry 4). Column chromatography (30% ethyl acetate in hexane) yielded 46% of the title compound as white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.92 (s, 1H), 8.33 (dd, J_1 = 6.8, J_2 = 2 Hz, 1H), 7.90 (d, J = 9.2 Hz, 2H), 7.61 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 9.0 Hz, 2H), 4.00 (s, 3H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 177.9, 166.0, 162.8, 158.8, 153.2, 134.4, 131.1, 129.1, 128.3, 123.7, 118.6, 114.7, 106.6, 55.7, 52.6; HRMS (ES) for [$C_{18}H_{15}0_5$] calculated 311.0919; found M+1 311.0919.

2-(Thiophen-2-yl)-4H-chromen-4-one (Table 2.4, Entry 5). Column chromatography (20% ethyl acetate in hexane) yielded 65% of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.20 (dd, J_1 = 6.6, J_2 = 1.2 Hz, 1H), 7.38-7.74 (m, 5H), 7.17-7.22 (m, 1H), 6.71 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.1, 159.2, 156.1, 135.3, 133.9, 130.4, 128.7, 125.9, 125.4, 118.1, 106.4; HRMS (CI) for [$C_{13}H_8O_2S$] calculated 228.0245; found 228.0238.

Methyl 4-oxo-2-(thiophene-2-yl)-4H-chromene-6-carboxylate (Table 2.4, Entry 6). Column chromatography (30% ethyl acetate in hexane) yielded 71% of the title compound. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.90 (d, J = 2 Hz, 1H), 8.30 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 2.8 Hz, 1H), 7.56-7.62 (m, 2H), 7.21-7.22 (m, 1H), 6.72 (s, 1H) 3.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 177.3, 165.9, 159.4, 158.5, 134.6, 130.9, 129.0, 128.8, 128.3, 127.4, 123.8, 118.5, 106.5, 52.6; HRMS (CI) for [$C_{15}H_{10}O_4S$] calculated 286.0300; found 286.0292.

2-(4-ethylphenyl)-4H-chromen-4-one (Table 2.4, Entry 7). Column chromatography (20% ethyl acetate in hexane) yielded 62% of the title compound as white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.20 (dd, J_1 = 6.8, J_2 = 1.2 Hz, 1H) 7.90 (d, J = 8.4 Hz, 2H), 7.70 (dd, J_1 = 5.4, J_2 = 1.5 Hz, 1H) 7.60 (d, J = 6.6 Hz, 1H), 7.33-7.45 (m, 3H), 6.8 (s, 1H), 2.73 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.6, 163.8, 156.4, 148.6, 133.8, 129.3, 128.7, 126.5, 125.8, 125.3, 124.1, 118.2, 107.1, 29.0, 15.4; HRMS (CI) for [$C_{17}H_{14}O_2$] calculated 250.0994; found 250.0994.

Methyl 2-(4-ethylphenyl)-4-oxo-4H-chromene-6-carboxylate (Table 2.4, Entry 8). Column chromatography (30% ethyl acetate in hexane) yielded 58% of the title compound as white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.91 (d, J = 2Hz, 1H), 8.34 (dd, J_1 = 7.0, J_2 = 2.0 Hz, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 6.83 (s, H) 3.96 (s, 3H), 2.74 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.0, 166.0, 164.1, 158.8, 149.1,134.5, 132.0, 128.8, 128.3, 127.3, 126.6, 123.7, 118.7, 107.4, 52.6, 29.0, 15.4; HRMS (ES) for [$C_{19}H_{16}O_4$] calculated 308.1049; found [M+1] 309.1134

2.1.6. References

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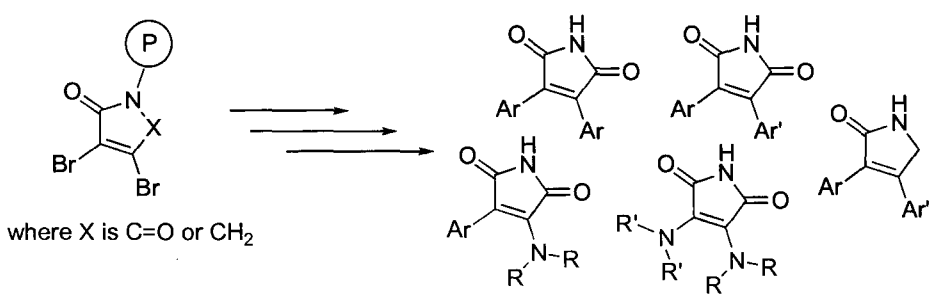
Chapter 3

3.1.1 Development of Methods for the Synthesis of Libraries of Substituted Maleimides and α,β-Unsaturated-γ-Butyrolactams.[2]

Emelia Awuah and Alfredo Capretta

3.1.2 Abstract

Synthetic methods for the preparation of maleimide and α,β-unsaturated-γ-butyrolactam compound collections are described. These routes take advantage of Pd-cross-coupling and conjugate addition / elimination reactions to permit the facile production of bisaryl-maleimides, anilinoaryl-maleimides and bisanilino-maleimides while allowing control over the synthesis of symmetrical or nonsymmetrical derivatives. Similarly, the chemistry developed allows for the generation of bisaryl substituted α,β-unsaturated-γ-butyrolactams. The scope and limitations of the approaches are presented.



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3.1.3 Introduction

The maleimide motif is featured in a variety of natural products including the arcyriaflavin[1], arcyriarubin[2], himanimide[3], polycitrin[4] and rebeccamycin[5] families. Biological properties of these compounds and their analogues include antibacterial and antiviral activity, angiogenesis inhibition[6] as well as kinase inhibition.[7] For example, groups from SmithKline Beecham[8,9], Eli Lilly[10], and Johnson & Johnson[11] among others, have demonstrated that bisaryl-maleimides are potent inhibitors of glycogen synthase kinase-3 (GSK-3). In fact, compounds SB 216763 and SB 415286 (Figure 3.1) have been shown to inhibit the α-isoform of GSK-3 in an ATP-competitive manner with a K_i of 9 and 31 nM, respectively.[8] The syntheses of these maleimide inhibitors often involve multi-step sequences that do not lend themselves readily to combinatorial approaches.

As part of a program aimed at the design and synthesis of selective kinase inhibitors, we required a route that could access chemically diverse families of substituted maleimides. We determined that Pd-catalyzed cross coupling chemistry developed in our laboratory[12-17] is particularly well suited for this purpose allowing for efficient derivatization at the 3 and 4-positions of maleimide heterocyclic core. Furthermore, inspired by the biological activity of staurosporine,[18,19] Figure 3.1, we have developed a general method that allows for the synthesis of substituted α,β-unsaturated-γ-butyrolactam analogues. An ideal synthetic method should allow for the preparation of bisaryl-maleimides, anilinoaryl-maleimides and bisanilino-maleimides; be amenable for the parallel synthesis of maleimide libraries; and allow for the control necessary to permit symmetrical or nonsymmetrical derivatives.

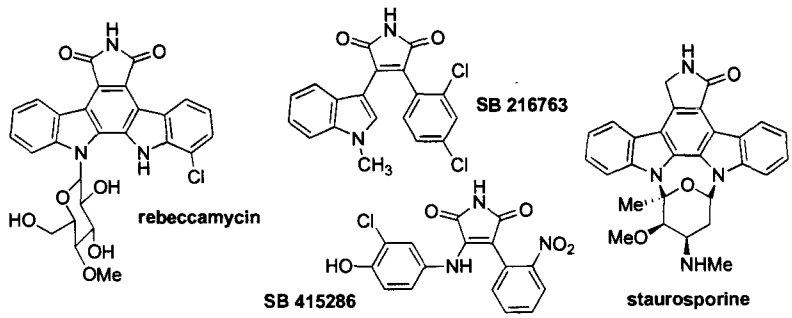


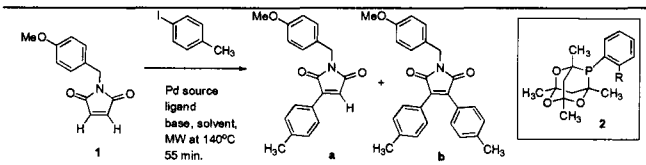
Figure 3.1: Systems containing maleimide and α,β-unsaturated-γ-butyrolactam substructures.

3.1.4 Results and Discussion

Our initial work focused on the most straightforward approach to the target compounds involving two sequential Heck reactions onto a maleimide core to permit derivatization at the 3- and 4-positions. Exploratory experiments revealed that *N*-protection was necessary and *N*-(*p*-methoxybenzyl)-maleimide (**1**)[20] was chosen as a suitable substrate as a number of mild deprotection strategies have been reported.[21-24] The initial screening of reaction conditions involved the coupling of **1** with *p*-iodotoluene utilizing microwave heating and examined the effect of different ligands,[13] solvents, temperatures, palladium sources and bases. As illustrated in Table 3.1, elevated temperatures (140 °C for 55 min) were required to effect coupling in good yields. When 6 equivalents of the aryl halide were used, many of the conditions screened (entries 1 - 8) allowed for the production of mono-arylated product (Table 3.1, **a**) predominantly. However, use of the 1, 3, 5, 7-tetramethyl-2, 4, 8-trioxa-6-*o*-methoxyphenyl-6-phosphaadamantane ligand (**2**, R = OMe) and Cy_2NMe as the base allowed for a

substantial increase in the diarylated product (Table 3.1, **b**) in dioxane (entry 9) and DMF (entry 10). Unfortunately, increasing reactions times, temperature or the number of equivalents of *p*-iodotoluene used failed to increase the amount of diarylated maleimide generated. This was not unexpected as the difficulty of generating tetrasubstituted alkenes using Heck coupling is well known.[25]

Table 3.1. Optimization of reaction parameters for the arylation of a maleimide scaffold *via* a Heck reaction



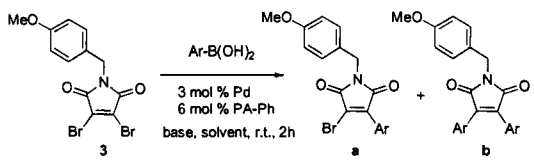
	Ligand (**2**)	Pd Source	base	solvent	yield (% **a** : % **b**)
1	R = H	Pd_2dba_3	Et_3N	THF	85:5
2	R = H	Pd_2dba_3	Et_3N	Dioxane	82:10
3	R = H	Pd_2dba_3	Et_3N	DMF	80:16
4	R = H	$Pd(OAc)_2$	Et_3N	THF	80:5
5	R = H	$Pd(OAc)_2$	Et_3N	Dioxane	83:10
6	R = H	$Pd(OAc)_2$	Et_3N	DMF	80:15
7	R = OMe	Pd_2dba_3	Et_3N	DMF	84:15
8	R = OMe	Pd_2dba_3	Cy_2NMe	THF	80:10
9	R = OMe	Pd_2dba_3	Cy_2NMe	Dioxane	51:45
10	R = OMe	Pd_2dba_3	Cy_2NMe	DMF	40:55

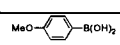
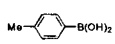
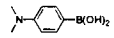
Methods employing Suzuki couplings were found to be more synthetically viable enabling access to the aryl-substituted maleimides under milder conditions. Using *N*-(*p*-methoxybenzyl)-3,4-dibromomaleimide (**3**)[26,27] as the scaffold, a series of experiments quickly determined the optimal reaction conditions (Pd source, base and solvent) for monoarylation of the maleimide core. The results are presented in Table 3.2. The best yields were obtained when using the 1, 3, 5, 7-

tetramethyl-2, 4, 8-trioxa-6-phenyl-6-phosphaadamantane ligand (PA-Ph: **2**, R = H) and Pd_2dba_3 at room temperature with Cs_2CO_3 in THF.

However, despite using only one equivalent of boronic acid, a small amount of diarylation product (Table 3.2, **b**) was always generated. This byproduct was easily separated from the desired monoarylated compound (Table 3.2, **a**) *via* chromatography; however, for the sake of convenience, the reaction mixture could be taken forward and subjected to a second Suzuki reaction.

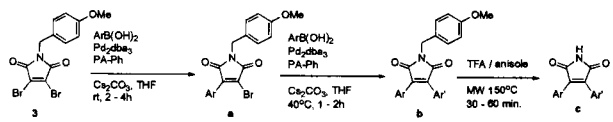
Table 3.2. Optimization of reaction parameters for monoarylated-maleimide synthesis via Suzuki Chemistry

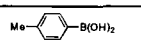
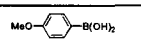
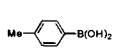
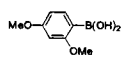
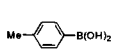
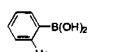
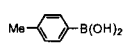
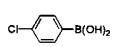
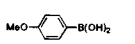
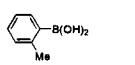
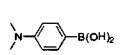
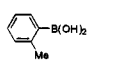


	Ar-B(OH)$_2$	Pd source	base	solvent	yield (% **a** : % **b**)
1		$Pd(OAc)_2$	CsOH	THF	15 : 10
2		$Pd(OAc)_2$	CsOH	toluene	15 : 0
3		Pd_2dba_3	CsOH	THF	15 : 10
4		Pd_2dba_3	CsOH	toluene	10 : 0
5		Pd_2dba_3	CsOH	dioxane	10 : 0
6		Pd_2dba_3	CsF	THF	50 : 35
7		Pd_2dba_3	K_3PO_4	THF	50 : 23
8		Pd_2dba_3	Cs_2CO_3	THF	55 : 23
9		Pd_2dba_3	Cs_2CO_3	THF	78 : 15
10		Pd_2dba_3	Cs_2CO_3	THF	58 : 25

With the monoarylated-malemides in hand (Table 3.3, **a**), introduction of a second aryl moiety (to give Table 3.3, **b**) was shown to be facile and high yielding. Deprotection with TFA in anisole (in a 1:1 ratio) using microwave irradiation gave the desired bisarylated maleimides (Table 3.3, **c**).

Table 3.3. Nonsymmetrical Bisaryl Maleimides *via* Suzuki Chemistry



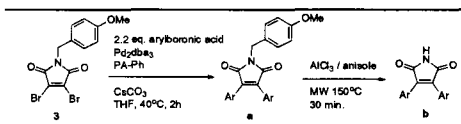
	Ar-B(OH)$_2$	Ar'-B(OH)$_2$	% yield **a**	% yield **b**	% yield **c**
1			78	92	84
2				95	82
3				93	86
4			55	90	81
5				91	86
6			58	94	86

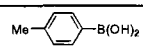
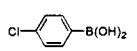
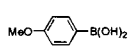
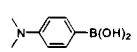
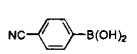
Symmetrical diarylation of the maleimide scaffold (Table 3.4) was easily achieved by using 2.2 equivalents of the arylboronic acid and the Pd_2dba_3 / PA-Ph catalyst system. Shorter reaction times (30 - 60 minutes) were required for the removal of the *p*-methoxybenzyl protecting group when $AlCl_3$ in anisole under microwave irradiation was employed. High yields of the desired bisarylmaleimides were obtained in all cases except for entry 5 (in Table 3.4) where product decomposition occurred under all deprotection conditions attempted.

A number of potent kinase inhibitors are anilinoaryl-maleimides (SB415286 in Figure 3.1, for example) and we next explored routes for the parallel synthesis of these systems. Exploratory experiments quickly determined that the order of introduction of the aryl and amino vectors was important and that the most facile route to the 3-amino, 4-aryl substituted maleimides involved amination before a Suzuki arylation. In this way, treatment of the *N*-(*p*-methoxybenzyl)-3,4-dibromomaleimide (**3**) with 1 equivalent of an amine (primary or secondary aliphatic; anilines or *N*-monosubstituted anilines) at room

temperature in THF allowed for a rapid conjugate addition / elimination reaction to provide high yields of the monosubstituted maleimide (Table 3.5, **a**). In fact, under these conditions and in the presence of excess amine, the mono-aminated maleimide product is formed exclusively. It would appear that the installation of an amino group alters the electronic nature of the neighbouring site such that a second conjugate addition does not occur at room temperature. However, utilization of the Suzuki chemistry developed above allowed for facile arylation (to give Table 3.5, **b**) and, after deprotection, access to 3-amino-4-aryl substituted maleimides (Table 3.5, **c**) in good overall yields. A number of complications were encountered when attempting to introduce a second amino moiety onto the mono-aminated maleimide scaffold. We determined that these reactions were controlled by the subtle interplay between the electron donating ability of the first amine introduced and the nucleophilicity of the second amine. For example, treatment of 3-bromo-1-(4-methoxybenzyl)-4-(phenylamino)-maleimide (Table 3.5, entry 11, **a**) with series of amines (3 equivalents) and using microwave irradiation (100 °C for 30 minutes) resulted in diamino-maleimide

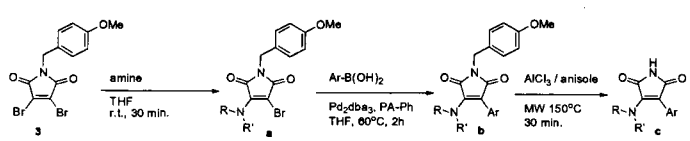
Table 3.4. Symmetrical Bisaryl Maleimides *via* Suzuki Chemistry



	Ar-B(OH)$_2$	% yield **a**	% yield **b**
1		93	91
2		91	89
3		95	88
4		96	75
5		96	0

products only with primary and secondary aliphatic systems such as *n*-butylamine, piperidine and morpholine to give **4**, **5** and **6**, respectively (Figure 3.2). Anilinic or *N*-substituted-anilinic amines failed to couple. It would appear that once mono-aminated, the electrophilicity of the carbon bearing the Br is drastically reduced as it is now the terminus of an enamine system as well as an α,β-unsaturated amide. It is not surprising, therefore, that a second conjugate addition / elimination reaction only takes place under forcing conditions with the more nucleophilic primary or secondary aliphatic amines. In addition, both 3-bromo-1-(4-methoxybenzyl)-4-(methyl(phenyl)amino)-1*H*-pyrrole-2,5-dione (Table 3.5, entry 8, **a**) and 3-bromo-1-(4-methoxybenzyl)-4-morpholino-maleimide (Table 3.5, entry 2, **a**) were shown to couple with piperidine (to give **7** and **8**, respectively) while morpholine and other aromatic amines failed to react. In effect, bisamination of the maleimide scaffold **3** was only successful in cases where the

Table 3.5. 3-Amino-4-aryl Substituted Maleimides



	amine	Ar-B(OH)$_2$	% yield **a**	% yield **b**	% yield **c**
1			92	86	84
2			98	93	84
3				72	82
4				88	85
5				85	87
6				91	88
7			94	89	91
8			95	91	84
9				87	85
10				84	81
11			92	76	73

addition of a less nucleophilic amine (lower pKa, less electron rich) is followed by reaction with a more nucleophilic amine (higher pKa, more electron rich).

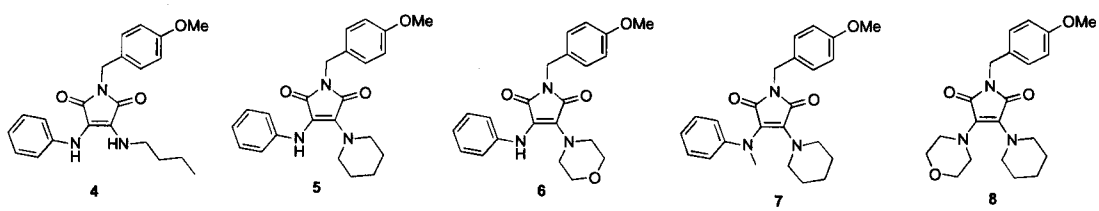


Figure 3.2. *p*-methoxybenzylamine protected 3,4-diamino maleimides

As a result, symmetrical bisaminated maleimides could not be generated using this approach. It should be noted that attempts to introduce the second amine *via* a palladium catalyzed amination reaction were unsuccessful with only the dehalogenated product recovered. In addition to these limitations, deprotection of the methoxybenzyl protecting group for these systems was also problematic. In systems bearing a piperidine moiety, deprotection under the conditions developed above using $AlCl_3$ / anisole at room temperature resulted in trapping of the *p*-methoxybenzyl cation generated by the piperidine nitrogen to give systems **9** and **10** (from **5** and **7**, respectively, as shown in Figure 3.3). These results are very peculiar as trapping of the *p*-methoxybenzyl cation did not occur with analogous compounds such as entry 7 in Table 3.5 which underwent deprotection smoothly

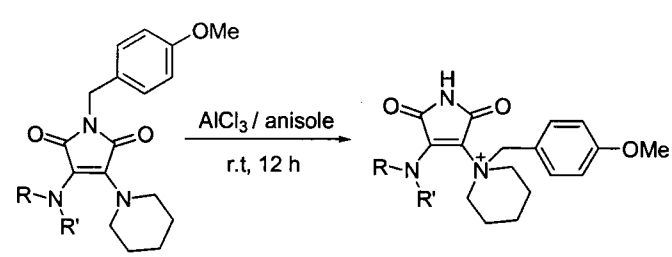


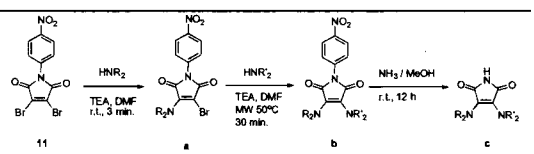
Figure 3.3. Trapping of the *p*-Methoxybenzyl Cation

under microwave irradiation. Attempts at deprotection using oxidative cleavage protocols involving CAN[28] or DDQ[29] were unsuccessful.

It became clear that a different protecting group was needed; ideally, one that could alter the electronics of the maleimide system and thereby help facilitates the second amination reaction. *N*-(*p*-nitrophenyl)-3,4-dibromomaleimide (**11**), prepared by treating maleic anhydride with *p*-nitroaniline in acetic acid, was identified as an ideal substrate. Its deprotection is realized by treating with methanolic ammonia at room temperature.

Once again, the order of addition of the two amino vectors is important. As presented in Table 3.6, addition of the first amine vector to **11** to give system **a** could be achieved in high yields (as evidence by TLC) in a few minutes. The mono-aminated compound (**a**) was not isolated but used directly in the next step. Addition of a second, more nucleophilic amino moiety allowed for the requisite conjugate addition / elimination reaction (to give **b**), achieved using microwave heating a 50 °C for 30 minutes. Finally, treatment with methanolic ammonia at room temperature for 12 hours provided the desired bisamino maleimides (Table 3.6, **c**). Note that treatment of

Table 3.6. Nonsymmetrical Bisamino Maleimides

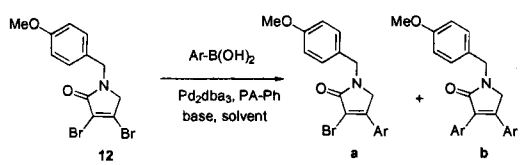


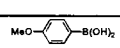
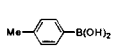
	HNR_2	HNR'_2	% yield **b**	% yield **c**
1			93	84
2			95	93
3			91	81
4			96	96
5			91	89
6			92	82

11 with primary amines, such as *n*-butylamine, resulted in a complex mixture of products that included those wherein the *p*-nitrophenyl moiety is substituted with the primary amine introduced.

Our attention was then turned to the application of the chemistry developed above for the syntheses of substituted α,β-unsaturated-γ-butyrolactams. These systems represent analogues of the maleimide derivatives with a deleted carbonyl group and can be used to provide further information about the nature of inhibitor binding. A suitable scaffold was generated *via* the treatment of mucobromic acid with 4-methoxybenzyl amine under reductive amination conditions similar to those described by Zhang and coworkers[30] to give 3,4-dibromo-1-(4-methoxybenzyl)-1*H*-pyrrol-2(5*H*)-one (**12**) in 78% yield. Once again, optimization of the reaction parameters necessary for the introduction of a single aryl moiety *via* a Suzuki reaction was investigated (Table 3.7).

Table 3.7. Optimization of Reaction Parameters for the Synthesis of Substituted α,β-Unsaturated-γ-butyrolactams

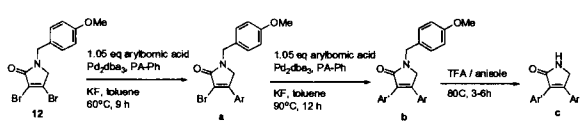


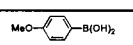
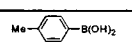
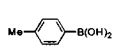
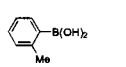
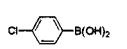
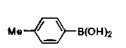
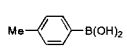
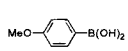
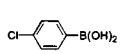
	Ar-B(OH)$_2$	base	solvent	temp	time	yield (%a : %b)
1		CsF	THF	50	2	15 : 0
2		Cs_2CO_3	THF	50	2	5 : 0
3		Cs_2CO_3	toluene	50	3	10 : 0
4		Cs_2CO_3	dioxane	50	3	10 : 0
5		CsF	toluene	50	3	15 : 0
6		KF	toluene	60	20	55 : 10
7		KF	toluene	60	20	68 : 10
8		KF	toluene	60	20	54 : 15

As expected, the first arylation takes place at the β-position of the unsaturated-γ-butyrolactam **12** (to give **a** in Table 3.7) thus allowing for control over the substitution pattern in the final product. The best yields were obtained when using the PA-Ph ligand and Pd_2dba_3 with KF in toluene. Furthermore, unlike the conditions used for the first arylation in the maleimide series, the initial Suzuki coupling involving **12** required elevated temperatures (60°C). In addition, despite using only one equivalent of the boronic acid, a small amount of diarylation product (Table 3.7, **b**) was generated.

Carrying the reaction mixture forward, a second aryl vector could be introduced into the butyrolactam system (to give Table 3.8, **b**) under the similar conditions with an increase in temperature (to 80 °C) and reaction time (to 12 h). Deprotection to the desired lactam systems (Table 3.8, **c**) was accomplished using TFA / anisole and microwave irradiation at 150 °C for 30 min. with no significant change in yield observed when the $AlCl_3$ / TFA deprotection protocol was used. Finally, entries 4 – 6 in Table 3.8 represent systems with the same aryl moiety at the α- and β-positions of

Table 3.8. 3,4-Diaryl α,β-Unsaturated-γ-butyrolactams



	Ar-B(OH)$_2$	Ar'-B(OH)$_2$	% yield **b**	% yield **c**
1			78	84
2			75	86
3			81	82
4			84	81
5			85	86
6			82	87

the lactam and were prepared by treating **12** with 2.2 equivalents of the appropriate boronic acid followed by deprotection.

Exploratory experiments aimed at the introduction of amine vectors into **12** quickly revealed that the approach developed above was inappropriate for the amination of the butyrolactam series. For example, treatment of **12** with morpholine gave a mixture of multiple products. This was not surprising as it is well known that the methylene moiety at C5 is enolizable[31,32] and treatment with basic amines precludes the conjugate addition / elimination reaction.

3.1.5 Conclusions

The methods developed above allow for rapid and facile access to symmetrical and nonsymmetrical, aryl and amino substituted maleimides and α,β-unsaturated-γ-butyrolactams. Furthermore, the utilization of other organopalladium cross-coupling chemistries (including such reactions as the Sonogashira, Stille, ketone arylations, Negishisi, etc.) should allow for introduction of a variety of structurally diverse vectors and, thereby, an increased mapping of the chemical space probed by these compound collections.

3.1.6 Experimental

N-(p-Methoxybenzyl)-maleimide (1).[20] To a solution of maleic anhydride (1.6 g, 16.3 mmol) in acetic acid (15 mL) was added *p*-methoxybenylamine (2.1 mL, 16.3 mmol). The mixture was refluxed for 5h, cooled to room temperature then concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel

using 20% ethylacetate in hexane as the eluent afforded **1** in 79% yield (2.8 g, 12.9 mmol). The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.68 (s, 2H), 4.61 (s, 2H), 3.78 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 159.4, 134.2, 130.1, 128.6, 114.2, 55.4, 41.0; (HRMS) CI: calculated for ($C_{12}H_{11}NO_3$) 217.0739 found 217.0735.

Synthesis of 1-(4-Methoxybenzyl)-3-p-tolyl-1H-pyrrole-2,5-dione (Table 3.1, a) and 1-(4-Methoxybenzyl)-3,4-di-p-tolyl-1H-pyrrole-2,5-dione (Table 3.1, b) via a Heck Reaction. To a mixture of *N*-(*p*-methoxybenzyl)-maleimide (**1**) (100 mg, 0.46 mmol), $Pd_2(dba)_3.CHCl_3$ (23.8 mg, 0.023 mmol, 5 mol %), PA-Ph, (2, R = OMe, 7.7 mg. 0.023 mmol, 5 mol %), Cy_2NMe (494 μL, 2.3 mmol, 5 eq.), 4-iodotoluene (300.9 mg, 1.38 mmol, 6 eq.), was added dried DMF (3 mL). The mixture was degassed, placed under an atmosphere of argon and microwaved at 140 °C for 55 minutes. The solvent was evaporated under reduced pressure and the reaction mixture was purified by column chromatography on silica gel using 30% ethylacetate/hexane.

1-(4-Methoxybenzyl)-3-p-tolyl-1H-pyrrole-2,5-dione (Table 3.1, Entry 10, Compound a) showed; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.82 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 2 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.66 (s, 1H), 4.67 (s, 2H), 3.78 (s, 3H), 2.39 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.7, 170.4, 159.3, 143.9, 141.9, 130.1, 129.8, 128.9, 128.7, 126.2, 122.8, 114.1, 55.39, 41.1, 21.7; (HRMS) CI: calculated for ($C_{19}H_{17}NO_3$) 307.1208 found 307.1208.

1-(4-Methoxybenzyl)-3,4-dip-tolyl-1H-pyrrole-2,5-dione (Table 3.1, Entry 10, Compound b) showed; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.7 Hz, 4H), 7.15 (d, J = 7.7 Hz, 4H), 6.86 (d, J = 8.4 Hz, 2H), 4.74 (s, 2H), 3.79 (s, 3H), 2.36 (s, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.8, 159.3, 140.1, 135.6, 130.5, 129.9, 129.4, 129.1, 128.5, 126.1, 114.1, 55.4, 41.5, 21.6; (HRMS) CI: calculated for ($C_{26}H_{23}NO_3$) 397.1676 found 397.1678.

General Procedure for the Mono-arylation of 1-(4-Methoxybenzyl)-3,4-dibromo-1H-pyrrole-2,5-dione (3) (Table 3.2). To a mixture of 1-(4-methoxybenyl)-3,4-dibromo-1*H*-pyrrole-2,5 dione (**3**)[27] (187 mg, 0.5 mmol), $Pd_2(dba)_3.CHCl_3$ (15.5 mg, 0.015 mmol, 3 mol %), PA-Ph, (**2**, R =H, 8.8 mg. 0.03 mmol, 6 mmol %), Cs_2CO_3 (366.0 mg, 1.125 mmol, 2.25 eq.) and the aryl boronic acid (1.1 eq, 0.55 mmol) was added dried THF (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred at room temperature for 2 - 8 h. The solvent was evaporated under reduced pressure and the reaction mixture was purified by column chromatography on silica gel.

1-(4-methoxybenzyl)-3-bromo-4-(4-methoxyphenyl)-1H-pyrrole-2,5-dione (Table 3.2, Entry 8, Compound a). Using 4-methoxylphenylboronic acid (83.6 mg, 0.55 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione was obtained in 55% yield (110.3 mg, 0.275 mmol) after purification by column chromatography using 20% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.94 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.69 (s,

2H), 3.84 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.0, 165.8, 161.9, 159.6, 138.9, 131.7, 130.5, 128.4, 120.5, 119.7, 114.3, 55.6, 55.5, 42.2, 29.9; (HRMS) CI: calculated for ($C_{19}H_{16}BrNO_4$) 401.0263 found 401.0252.

1-(4-Methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1H-pyrrole-2,5-dione (Table 3.2, Entry 8, Compound b). Isolated as byproduct from the synthesis of 1-(4-methoxybenzyl)-3-bromo-4-(4-methoxyphenyl)-1H-pyrrole-2,5-dione (Table 2, Entry 8, Compound a) in 23% yield (49.4 mg, 0.115 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44 (overlap, 6H), 6.86 (d, J = 8.6 Hz, 6H), 4.72 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.2, 160.8, 159.3, 134.2, 131.6, 130.5, 129.1, 114.2, 55.4, 41.4; (HRMS) CI: calculated for ($C_{26}H_{24}NO_5$) [M+1] 430.1654 found 430.1640.

1-(4-Methoxybenzyl)-3-bromo-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.2, Entry 9, Compound a). Using 4-methylphenylboronic acid (75.0 mg, 0.55 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 78% yield (150.1 mg, 0.38 mmol) after purification by column chromatography on silica gel using 10% diethyl ether in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz), 4.72 (s, 2H), 3.79 (s, 3H), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.8, 165.7, 159.6, 141.7, 130.5, 130.0, 129.7, 129.5, 128.6, 128.3, 125.1, 121.6, 55.5, 42.2, 21; (HRMS) CI: calculated for ($C_{19}H_{16}BrNO_3$) 385.0314 found 385.0312.

1-(4-Methoxybenzyl)-3,4-dip-tolyl-1H-pyrrole-2,5-dione (Table 3.2, Entry 9, Compound b). Isolated as byproduct from the synthesis of 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (Table 2, Entry 9, Compound a) in 15% yield (29.8 mg, 0.075 mmol) and showed identical spectral properties to Table 1, Entry 10, Compound b.

3-Bromo-4-(4-(dimethylamino)phenyl)-1-(4-methoxybenzyl)-1H-pyrrole-2,5-dione (Table 3.2, Entry 10, Compound a). Using 4-(dimethylamino)phenylboronic acid (90.3 mg, 0.55 mmol) and the general procedure described above, 3-bromo-4-(4-(dimethylamino)phenyl)-1-(4-methoxybenzyl)-1*H*-pyrrole-2,5-dione was obtained in 58% yield (120.4 mg, 0.29 mmol) after purification by column chromatography using 20% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.06 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 9.2 Hz), 6.72 (d, J = 8.6 Hz, 2H) 4.70 (s, 2H), 3.78 (s, 3H), 3.05 (s, 6H),^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.5, 166.4, 159.4, 151.9, 138.7, 131.4, 130.3, 128.6, 115.5, 114.6, 114.1, 111.4, 55.4, 41.9, 40.1; (HRMS) EI: calculated for ($C_{20}H_{19}BrN_2O_3$) 414.0579 found 414.0572.

1-(4-Methoxybenzyl)-3,4-bis(4-dimethlyaminophenyl)-1H-pyrrole-2,5-dione (Table 3.2, Entry 10, Compound b). Isolated as a byproduct from the synthesis of 3-Bromo-4-(4-(dimethylamino)phenyl)-1-(4-methoxybenzyl)-1H-pyrrole-2,5-dione (Table 2, Entry 10, Compound a) in 25 % yield (56 mg, 0.125 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50 (d, J = 9.0 Hz, 4H) 7.40 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 9.0 Hz, 4H), 4.70 (s, 2H), 3.77 (s, 3H), 2.99 (s, 12H), ^{13}C NMR ($CDCl_3$, 50 MHz)

δ 171.9, 159.1, 150.8, 132.3, 131.1, 130.3, 129.5, 117.3, 114.0, 111.7, 55.4, 41.1, 40.2; (HRMS) CI: calculated for ($C_{28}H_{29}N_3O_3$) 455.2209 found 455.2203.

General Procedure for Synthesis of Non-Symmetrical Bisaryl Maleimides (Table 3.3, Compound b). To a mixture of the mono-arylated maleimide (0.2 mmol), $Pd_2(dba)_3.CHCl_3$ (6.21 mg, 0.006 mmol, 3 mol %), PA-Ph, (**2**, R =H, 3.52 mg. 0.012 mmol, 6 mmol %), Cs_2CO_3 (162.9 mg, 0.45 mmol) and the arylboronic acid (1.2 eq. 0.24 mmol) was added dried THF (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred at 40 °C for 2 h. The solvent was evaporated under reduced pressure and the reaction mixture was purified by column chromatography on silica gel.

1-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 1, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (77.2 mg, 0.2 mmol), 4-methoxyphenylboronic acid (37.7 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 92% yield (76.0 mg, 0.184 mmol) after purification by column chromatography on silica gel using 30% ethylacetate in hexane as the eluent. The compound showed; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36-7.50 (m, 6H), 7.17 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 4H), 4.73 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 2.36 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.9, 160.8, 159.2, 139.9, 135.1, 134.3, 131.5, 130.3, 129.7, 129.3, 128.9, 126.1, 121.2, 114.0, 55.3, 41.3, 21.5; (HRMS) CI: calculated for ($C_{26}H_{23}NO_4$) 413.1627 found 413.1628.

4-(1-(4-Methoxybenzyl)-3-(2,4-dimethoxyphenyl)-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 2, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (77.2 mmol, 0.2 mmol), 2,4-dimethoxyphenylboronic acid (43.8 mg, 0.24 mmol) and the general procedure described above, 4-(1-(4-methoxybenzyl)-3-(2,4-dimethoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 95% yield (84.3 mg, 0.195 mmol) after purification by column chromatography using 30% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32-7.42 (m, 5H), 7.08 (d, J = 7.8 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.54 (dd, J = 2.2 & 6.4 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.2, 171.0, 162.6, 159.3, 158.8, 140.0, 136.3, 133.4, 132.4, 130.5, 129.3, 129.0, 128.5, 128.0, 114.1, 111.3, 105.2, 99.3, 55.6, 55.5, 55.2, 41.5, 21.7; (HRMS) CI: calculated for ($C_{27}H_{25}NO_5$) 443.1733 found 443.1730.

1-(4-Methoxybenzyl)-4-o-tolyl-3-p-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 3, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (77.2 mmol, 0.2 mmol), 2-methylphenylboronic acid (32.6 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-4-*o*-tolyl-3-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 91% yield (72.3 mg, 0.182 mmol) after purification by column chromatography using 20% ethylacetate in hexane as the eluent and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.40-7.43 (overlap, 4H), 7.35 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 9.1, 2H), 4.75 (s, 2H), 3.79 (s, 3H), 2.31 (s, 3H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.9, 170.6, 159.3, 143.4, 130.4,

129.5, 129.4, 129.1, 128 5. 126.2, 125.5, 114.1, 55.4, 41.5, 21.6, 20.2 (HRMS) CI: calculated for ($C_{26}H_{24}NO_3$) 398.1756 found 398.1738.

1-(4-Methoxybenzyl)-3-(4-chlorophenyl)-4-p-tolyl-H-pyrrole-2,5-dione (Table 3.3, Entry 4, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (77.2 mg mmol, 0.2 mmol), and 4-chlorophenylboronic acid (37.5 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-(4-chlorophenyl)-4-*p*-tolyl-*H*-pyrrole-2,5-dione was obtained in 90% yield (77.9 mg, 0.180 mmol) after purification by column chromatography using 30% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.42 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.7 Hz, 2H), 7.30 (d, J = 7.7 Hz, 2H), 7.15 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.72 (s, 2H), 3.78 (s, 3H), 2.36 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.5, 159.4, 140.7, 136.8, 136.0, 134.2, 131.3, 130.5, 129.9129.6, 129.0, 128.8, 127.4, 114.2, 55.4, 41.6, 21.7; (HRMS) ES: calculated for ($C_{25}H_{21}ClNO_3$) [M+1] 418.1210 found 418.1209.

1-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-4-o-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 5, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione (80.2 mmol, 0.2 mmol) and 2-methylphenylboronic acid (32.6 mg, 0.24 mmol) and the general procedure, 1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-4-*o*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 91% yield (74.8 mg, 0.181 mmol) after purification by column chromatography using 30% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44 (t, J = 9.2 Hz, 5H), 7.21-7.289

(m, 3H), 6.87 (d, J = 8.6 H z, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.74 (s, 2H), 3.79 (s, 6H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 170.8, 161.1, 159.3, 136.9, 135.2, 131.4, 130.9, 130.4, 129.9, 129.4, 129.0, 126.2, 121.8, 114.1, 55.4, 41.5, 20.2; (HRMS) CI: calculated for ($C_{26}H_{23}NO_4$) 413.1627 found 413.1628.

1-(4-methoxybenzyl)-3-(4-dimethylamino)phenyl)-4-o-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 6, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-(4-dimethylamino)phenyl)-1*H*-pyrrole-2,5-dione (82.8 mmol, 0.2 mmol), and 2-methylphenylboronic acid (32.6 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-(4-dimethylamino)phenyl)-4-*o*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 94% yield (80.1mg, 0.188 mmol) after purification by column chromatography using 30% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.47 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 7.0 Hz, 1H), 7.29 (overlap, 2H), 7.22 (d, J = 7.7 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 9.1 Hz, 2H), 4.72 (s, 2H), 3.78 (s, 3H), 2.97 (s, 6H), 2.06 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.6, 171.3, 159.3, 151.3, 137.1, 131.6, 131.2, 130.7, 130.4, 130.3, 130.0, 129.3, 129.1, 126.2, 117.0, 114.1, 111.6, 55.4, 41.4, 40.1, 20.3; (HRMS) ES: calculated for ($C_{27}H_{27}N_2O_3$) [M+1] 427.2022 found 427.2015.

General Procedure for the Deprotection of Non-Symmetrical Bisaryl Maleimides using TFA in Anisole (Table 3.3, Compound c). To a solution of the *p*-methoxybenzyl protected maleimide (0.1 mmol) in anisole (1 mL) was added TFA (1 mL). The reaction mixture was microwaved at 140 °C for 30 - 60 min. The solvent was evaporated under

reduced pressure and the reaction mixture was purified by column chromatography on silica gel.

3-(4-methoxyphenyl)-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 1, Compound c). Using 1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (41.3 mg, 0.1 mmol) and the general procedure, 3-(4-methoxyphenyl)-4-*p*-tolyl-*1H*-pyrrole-2,5-dione was obtained in 84% yield (24.5 mg, 0.084 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.72 (b, 1H), 7.61 (d, J = 8.2 Hz, 2H) 7.48 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8 Hz, 2H) 3.83 (s, 3H), 2.37 (s, 3H) ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.1, 171.0, 161.1, 140.0, 136.2, 135.5, 131.8, 129.8, 129.6, 126.0, 121.1, 114.3, 55.5, 21.7; (HRMS) EI: calculated for ($C_{18}H_{15}NO_3$) 293.1052 found 293.1057.

3-(2,4-Dimethoxyphenyl)-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 2, Compound c). Using 4-(1-(4-methoxybenzyl)-3-(2,4-dimethoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (44.3 mg, 0.1 mmol) and the general procedure described above, 3-(2,4-dimethoxyphenyl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 82% yield (26.5 mg, 0.082 mmol) after purification by column chromatography on silica gel using 30% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36 (d, J = 8 Hz, 2H), 7.31 (s, 1H), 7.11 (d, J = 8 Hz, 2H), 6.56 (d, J = 6.2 Hz, 1H), 6.43 (s, 1H), 3.38 (s, 3H), 3.78 (s, 3H), 2.34 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 170.7, 162.6, 158.7, 140.0, 137.2, 134.5, 132.2, 129.0, 127.5, 110.9, 105.2, 99.3, 55.6, 55.2, 21.6; (HRMS) CI: calculated for ($C_{19}H_{17}NO_4$) 323.1158 found 323.1158.

4-o-Tolyl-3-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 3, Compound c). Using 1-(4-methoxybenzyl)-4-*o*-tolyl-3-*p*-tolyl-1*H*-pyrrole-2,5-dione (39.8 mg, 0.1 mmol) and the general procedure described above, 4-*o*-tolyl-*3*-tolyl-*1H*-pyrrole-2,5-dione was obtained in 86% (34.2 mg, 0.086 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.69 (b, 1H), 7.015-7.39 (m, 8H), 2.32 (s, 3H), 2.05 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.7, 170.5, 140.9, 138.4, 137.8, 136.9, 131.0, 130.0, 129.8, 129.7, 129.6, 128.9, 126.4, 126.2, 21.7, 20.3; (HRMS) CI: calculated for ($C_{18}H_{15}NO_2$) 277.1103 found 277.1103.

3-(4-Chlorophenyl)-4-p-tolyl-H-pyrrole-2,5-dione (Table 3.3, Entry 4, Compound c). Using 1-(4-methoxybenzyl)-3-(4-chlorophenyl)-4-*p*-tolyl-H-pyrrole-2,5-dione (41.7 mg, 0.1 mmol) and the general procedure described above, 3-(4-chlorophenyl)-4-*p*-tolyl-*H*-pyrrole-2,5-dione was obtained in 81% (24.1 mg, 0.081 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.53 (b, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 7.7 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 2.38 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.2, 140.9, 137.7, 136.3, 135.1, 131.3, 129.9, 129.7, 129.5, 129.1, 127.1, 125.3, 21.7; (HRMS) EI: calculated for ($C_{17}H_{12}ClNO_2$) 297.0552 found 297.0553.

3-(4-methoxyphenyl)-4-o-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 5, Compound c). Using 1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-4-*o*-tolyl-1*H*-pyrrole-2,5-dione (41.3 mg, 0.1 mmol) and the general procedure described above, 3-(4-dimethoxyphenyl)-4-*o*-tolyl-*1H*-pyrrole-2,5-dione was obtained in 86% yield (25.2 mg, 0.086 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.64 (b, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.17-7.35 (m, 4H), 6.80 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 2.06 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz)

δ 171.0, 170.7, 161.4, 137.9, 136.9, 136.2, 131.5, 131.0, 129.8, 129.7, 129.1, 126.4, 121.6, 114.4, 55.5, 20.2; (HRMS) EI: calculated for ($C_{18}H_{15}NO_3$) 293.1052 found 293.1057.

3-(4-Dimethylamino)phenyl)-4-o-tolyl-1H-pyrrole-2,5-dione (Table 3.3, Entry 6, Compound c). Using 1-(4-methoxybenzyl)-3-(4-dimethylamino)phenyl)-4-*o*-tolyl-1*H*-pyrrole-2,5-dione (42.6 mg, 0.1 mmol) and the general procedure described for deprotection using $AlCl_3$/anisole, 3-(4-dimethylamino)phenyl)-4-*o*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 86% (26.3 mg, 0.086 mmol) and showed; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.45 (d, J = 7.0 Hz, 2H),7.31-7.34 (overlap, 2H), 7.21-7.27 (overlap, 2H), 6.55 (d, J = 7.0 Hz, 2H), 2.98 (s, 6H), 2.10 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.5, 170.9, 151.4, 138.1, 137.0, 132.4, 131.3, 130.8, 130.129.9, 129.3, 116.7, 111.6, 40.1, 20.2, (HRMS) CI: calculated for ($C_{19}H_{18}NO_2$) 306.1368 found 306.1370.

General Procedure for Synthesis of Symmetrical Bisaryl Maleimides (Table 3.4, Compound a). To a mixture of 1-(4-methoxybenyl)-3,4-dibromo-1*H*-pyrrole-2,5-dione (**3**) (60.0 mg, 0.16 mmol), $Pd_2(dba)_3.CHCl_3$ (6.6 mg, 0.006 mmol, 4 mol %), PA-Ph, (**2**, R =H, 3.7 mg. 0.013 mmol, 8 mmol %), Cs_2CO_3 (208.0 mg, 0.64 mmol 4 eq) and the arylboronic acid (0.35 mmol, 2.2 eq.) was added dried THF (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred at 40 °C for 2 h. The solvent was evaporated under reduced pressure and the reaction mixture was purified by column chromatography on silica gel.

1-(4-Methoxybenzyl)-3,4-dip-tolyl-1H-pyrrole-2,5-dione (Table 3.4, Entry 1, Compound a). Using 4-methylphenylboronic acid (47.5 mg, 0.35 mmol, 2.2 eq.) and the general procedure described above, 1-(4-methoxybenzyl)-3,4-di*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 93% yield (59.2 mg, 0.149 mmol) after purification by column chromatography using 10% ethylacetate in hexane as the eluent. Spectral identical to compound found in Table 1, Entry 10, compound b.

1-(4-Methoxybenzyl)-3,4-bis(4-chlorophenyl)-1H-pyrrole-2,5-dione (Table 3.4, Entry 2, Compound a). Using 4-chlorophenylboronic acid (54.7 mg, 0.35 mmol, 2.2 eq.) and the general procedure above, 1-(4-methoxybenzyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrrole-2,5-dione was obtained in 91% yield (63.8 mg, 0.146 mmol) after purification by column chromatography using 10% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.40 (t, J = 8.4 Hz, 6H), 7.35 (d, J = 8.4 Hz, 4H) 6.89 (d, J = 8.4 Hz, 2H), 4.73 (s, 2H), 3.79 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.1, 156.5, 136.5, 135.4, 131.3, 130.5, 129.2, 128.6, 126.9, 114.2, 55.4, 41.7; (HRMS) CI: calculated for ($C_{24}H_{17}Cl_2NO_3$) 437.0580 found 437.0582.

1-(4-Methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1H-pyrrole-2,5-dione (Table 3.4, Entry 3, Compound a). Using 4-methoxyphenylboronic acid (53.5 mg, 0.35 mmol, 2.2 eq.) and the general procedure described above, 1-(4-methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione was obtained in 95% yield (65.3 mg, 0.152 mmol) after purification by column chromatography on silica gel using 30% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44 (overlap, 6H), 6.86 (d, J =

8.6 Hz, 6H), 4.72 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.2, 160.8, 159.3, 134.2, 131.6, 130.5, 129.1, 114.2, 55.4, 41.4; (HRMS) CI: calculated for $C_{26}H_{24}NO_5$) (M+1) 430.1654 found 430.1640.

1-(4-Methoxybenzyl)-3,4-bis(4-dimethlyaminophenyl)-1H-pyrrole-2,5-dione (Table 3.4, Entry 4, Compound a). Using 4-(dimethylamino)phenylboronic acid (57.8 mg, 0.35 mmol, 2.2 eq.) and the general procedure described above, 1-(4-methoxybenzyl)-3,4-bis(4-dimethlyaminophenyl)-1H-pyrrole-2,5-dione was obtained in 96% yield (70.1 mg, 0.154 mmol) after purification by column chromatography using 30% ethylacetate in hexane as the eluent. The spectral data is identical to that of Table 2, Entry 10, Compound b).

1-(4-Methoxybenzyl)-2,5-dihydro-4-(4-isocyanophenyl)-2,5-dioxo-1H-pyrrol-3yl)benzonitrile (Table 3.4, Entry 5, Compound a). Using 4-cyanophenylboronic acid (51.4 mg, 0.35 mmol, 2.2 eq.) and the general procedure described above, 1-(4-methoxybenzyl)-2,5-dihydro-4-(4-isocyanophenyl)-2,5-dioxo-1*H*-pyrrol-3yl)benzonitrile was obtained in 96% yield (64.5 mg, 0.154 mmol) after purification by column chromatography using 30% ethylacetate in hexane as the eluent. The compound showed: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.66 (d, J = 8.2 Hz, 4H), 7.54 (d, J = 8.2 Hz, 4H), 7.39 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.76 (s, 2H), 3.79 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.1, 159.6, 136.2, 132.6, 132.4, 130.6, 128.0, 118.0, 114.2, 55.4, 42.0; (HRMS) CI: calculated for $C_{26}H_{17}N_3O_3$ 419.1270 found 419.1270.

General procedure for deprotection of symmetrical maleimides using $AlCl_3$ in anisole, (Table 3.4, Compound b). To a solution of the *p*-methoxybenzyl protected maleimide (0.1 mmol) in 1 mL anisole was added 5 - 8 equivalents of $AlCl_3$. The reaction mixture was microwaved at 140 °C for 30 - 55 minutes and then poured into water (5 mL). The mixture was extracted with DCM (3 x 6 mL) and the organic layer dried with Na_2SO_4. Concentration of the solvent under a reduced pressure and purification using column chromatography on silica gel with 30% ethylacetate in hexane as the eluent yielded the deprotected product.

3,4-Di-p-tolyl-1H-pyrrole-2,5-dione (Table 3.4, Entry 1, Compound b). Using 1-(4-methoxybenzyl)-3,4-di*p*-tolyl-1*H*-pyrrole-2,5-dione (39.8 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq.) and the general procedure described above, 3,4-di*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 91% yield (25.2 mg, 0.091 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50 (b, 1H), 7.38 (d, J = 8 Hz, 4H), 7.18 (d, J = 8 Hz, 4H), 2.40 (s, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.9, 140.4, 136.5, 129.9, 129.5, 125.8, 21.7. (HRMS) CI: calculated for ($C_{18}H_{15}NO_2$) 277.1103 found 277.1106.

3,4-Bis(4-chlorophenyl)-1H-pyrrole-2,5-dione (Table 3.4, Entry 2, Compound b). Using 1-(4-methoxybenzyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrrole-2,5-dione (43.7 mg, 0.1 mmol), $AlCl_3$ (106.4 mg, 0.8 mmol, 5eq) and the general procedure described above, 3,4-bis(4-chlorophenyl)-1*H*-pyrrole-2,5-dione was obtained in 89% (28.3 mg, 0.089 mmol) yield and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82 (b, 1H), 7.39 (q, J = 5.0 Hz, 8H),

^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.7, 136.8, 136.2, 131.3, 129.3, 126.7. CI (HRMS): calculated for ($C_{16}H_9C_{l2}NO_2$) 317.0010 found 317.0010.

3,4-Bis(4-methoxyphenyl)-1H-pyrrole-2,5-dione, (Table 3.4, Entry 3, Compound b).[33] Using 1-(4-methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione (43 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq.) and the general procedure described above, 3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione was obtained in 88% (27.2 mg, 0.088 mmol) yield and showed: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.47 (d, J = 9.1 Hz, 4H), 6.88 (d, J = 9.1 Hz, 4H), 3.83 (s, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.9, 161.0, 135.1, 131.6, 121.2, 114.3, 55.5; (HRMS) CI: calculated for ($C_{18}H_{15}NO_4$) 309.0998 found 309.1001.

3,4-Bis(4-dimethlyaminophenyl)-1H-pyrrole-2,5-dione (Table 3.4, Entry 4 Compound b). Using 1-(4-methoxybenzyl)-3,4-bis(4-dimethlyaminophenyl)-1*H*-pyrrole-2,5-dione, $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq) and the general procedure described, 3,4-bis(4-dimethlyaminophenyl)-1*H*-pyrrole-2,5-dione was obtained in 75% (25.1, 0.075 mmol) yield and showed: ^1H NMR (DMSO, 700 MHz) δ 10.8 (b, 1H), 7.32 (d, J = 9 Hz, 4H), 6.68 (d, J = 9 Hz, 4H), 2.94 (s, 12H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.7, 150.5, 132.4, 130.6, 116.5 111.4, 40.1; (HRMS) CI: calculated for ($C_{20}H_{21}N_3O_2$) 335.1634 found 335.1630.

General Procedure for the Synthesis of Mono-amino Substituted Maleimides. (Table 3.5, Compound a). To a mixture of 1-(4-methoxybenyl)-3,4-dibromo-1*H*-pyrrole-2,5-

dione (**3**) (150 mg, 0.4 mmol) and Na_2CO_3 (134 mg, 1 mmol, 2.5 eq.) in THF (6 mL) was added the amine (0.42 mmol, 1.05 eq.). The reaction mixture was stirred at room temperature for 30 min. and up to 2 h. depending on the amine used (monitored via TLC) at which time the solvent was evaporated under a reduced pressure. The residue was taken up in DCM (40 mL), washed with water (2 x 10 mL) and dried with Na_2SO_4. Concentration of DCM under reduced pressure yielded the mono amino substituted maleimide after purification by column chromatography on silica gel.

1-(4-Methoxybenzyl)-3-bromo-4-(butylamino)-1H-pyrrole-2,5-dione (Table 3.5, Entry 1, Compound a). Using butyl amine (42 μL, 0.42 mmol), and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-(butylamino)-1H-pyrrole-2,5-dione was obtained in 92% yield (134.7mg, 0.368 mmol) after purification by column chromatography on silica gel using 10% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28(d, J = 8.4 Hz, 2H), 6.83(d, J = 8.6 Hz, 2H), 5.43 (b, 1H), 4.58 (s, 2H), 3.78 (s, 3H), 3.63 (q, J = 6.8 Hz, 2H), 1.53-1.64 (m, 2H), 1.33-1.44 (m, 2H), 0.90-0.97 (t, J = 7.4 Hz, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.7, 165.8, 159.3, 143.3, 130.1, 128.6, 114.1, 55.3, 42.9, 41.7, 32.8, 19.7, 13.8; (HRMS) CI: calculated for ($C_{16}H_{19}BrN_2O_3$) 366.0579 found 366.0576.

1-(4-methoxybenzyl)-3-bromo-4-morpholino-1H-pyrrole-2,5-dione (Table 3.5, Entry 2, Compound a). Using morpholine (36.5 ul, 0.42 mmol, 1.05 eq.) and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-morpholino-1*H*-pyrrole-

2,5-dione was obtained in 98% yield (156 mg, 0.41 mmol) after purification by column chromatography using 20% ethylacetate/hexane and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.29 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.59 (s, 2H), 3.96 (t, J = 4.9 Hz, 4H), 3.77 (overlap, 7H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.4, 165.9, 159.4, 144.0, 130.3, 128.6, 114.1, 82.5, 67.1, 55.4, 48.5, 41.7; (HRMS) ES: calculated for ($C_{16}H_{18}BrN_2O_4$) [M+1] 381.0450 found 381.0464.

1-(4-Methoxybenzyl)-3-bromo-4-piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.5, Entry 7, Compound a). Using piperidine (42 µl, 0.42 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-piperidin-1-yl)-1H-pyrrole-2,5-dione was obtained in 94% yield (142 mg, 0.375 mmol), after purification using by column chromatography on silica gel using 10% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.57 (s, 2H), 3.86 (s, 4H), 3.77 (s, 3H), 1.67 (s, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.8, 165.9, 144.8, 130.2, 128.2, 114.0, 55.3, 82.3, 49.8, 41.5, 26.7, 24.1, (HRMS) CI: calculated for ($C_{17}H_{19}BrN_2O_3$) 378.0579 found 378.0577.

1-(4-Methoxybenzyl)-3-(N-methyl-N-phenylamino)-4-bromo-1H-pyrrole-2,5-dione (Table 3.5 Entry 8, Compound a). Using *N*-methylaniline (45.5 µl, 0.42 mmol, 1.05 eq.) and the general procedure described above, the reaction mixture was warmed to 40 °C for 2 h. 1-(4-Methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-bromo-1*H*-pyrrole-2,5-dione was obtained in 95% yield (160.4 mg, 0.40 mmol) after purification by column chromatography on silica gel using 10% ethylacetate in hexane as the eluent. The

compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34-7.41 (m, 5H), 7.13 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.5, 165.7, 159.2, 144.3, 144.0, 130.2, 129.1, 126.7, 125.2, 114.0, 87.6, 55.3, 41.8, 41.5; (HRMS) CI: calculated for ($C_{19}H_{17}BrN_2O_3$) 400.0423 found 400.0420.

1-(4-Methoxybenzyl)-3-bromo-4-(phenylamino)-1H-pyrrole-2,5-dione (Table 3.5, Entry 11, Compound a). Using aniline (38.5 µl, 0.42 mmol, 1.05 eq.) and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-(phenylamino)-1*H*-pyrrole-2,5-dione was obtained in 92% yield (148.8 mg, 0.385 mmol) and used in the next reaction with no purification.

General Procedure for the Synthesis of 3-Amino-4-Aryl Maleimides (Table 3.5, Compound b). To a mixture of the mono aminated maleimide (0.2 mmol), $Pd_2(dba)_3.CHCl_3$ (6.21 mg, 0.006 mmol, 3 mol %), PA-Ph, (3.52 mg. 0.012 mmol, 6 mmol %), Cs_2CO_3 (162.9 mg, 0.5 mmol) and the arylboronic acid (1.2 eq, 0.24 mmol) was added dried THF (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred at 60 °C for 2 h. THF was evaporated under reduced pressure and the reaction mixture was purified by column chromatography on silica gel.

1-(4-Methoxybenzyl)-3-(butylamino)-4-p-tolyl-H-pyrrole-2,5-dione (Table 3.5, Entry 1, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-(butylamino)-1*H*-pyrrole-2,5-dione (73 mg, 0.2 mmol), 4-methylphenyl boronic (32.6 mg, 0.24 mmol) and the general procedure, 1-(4-methoxybenzyl)-3-(butylamino)-4-*p*-tolyl-H-pyrrole-2,5-dione

was obtained in 86 % yield and showed; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (d, J = 7.8 Hz, 2H), 7.26 (s, 4H), 6.84 (d, J = 7.8 Hz, 2H), 5.26 (b, 1H), 4.62 (s, 2H), 3.37 (s, 3H), 3.10 (q, J = 6.6 Hz, 2H), 2.35 (s, 3H), 1.30-1.41 (m, 2H), 1.13- 1.24 (m, 2H), 0.74-0.81 (t, J = 6.8 Hz, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.3, 167.8, 159.2, 142.1, 137.2, 130.3, 130.2, 129.3, 128.7, 127.2, 114.0, 99.3, 55.4, 44.1, 41.1, 31.9, 21.4, 19.7, 13.7; (HRMS) CI: calculated for ($C_{23}H_{26}N_2O_3$) 378.1943 found 378.1940.

1-(4-methoxybenzyl)-3-morphilono-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.5, Entry 2, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-morpholino-1*H*-pyrrole-2,5-dione (76.2 mg, 0.2 mmol), 4-methylphenyl boronic acid (32.6 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-morpholino-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 93% yield (71.4 mg, 0.185 mmol) after purification using column chromatography on silica gel with 20% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (d, J = 8.6 Hz, 2H), 7.17 (s, 4H), 6.84 (d, J = 8.6 Hz, 2H), 4.61 (s, 2H), 3.78 (s, 3H), 3.67 (t, J = 4.2 Hz, 4H), 3.50 (t, J = 4.2 Hz, 4H), 2.35 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.9, 167.8, 159.2, 142.9, 137.7, 130.4, 130.1, 129.2, 128.9, 127.7, 114.0, 105.9, 66.8, 55.4, 46.1, 40.9, 21.4. (HRMS) CI: calculated for ($C_{24}H_{24}N_2O_4$) 392.1736 found 392.1782.

1-(4-Methoxybenzyl)-2,5-dihydro-4-morpholine-2,5-dioxo 1H-pyrrol-3-yl))benzonitrile, (Table 3.5, Entry 3, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-morpholino-1*H*-pyrrole-2,5-dione (76.2 mg, 0.2 mmol) and 4-cyanophenyl boronic (35.3 mg, 0.24 mmol) and the general procedure described, 1-(4-methoxybenzyl)-2,5-dihydro-4-

morpholine-2,5-dioxo 1*H*-pyrrol-3-yl))benzonitrile was obtained in 72% yield (58.5 mg, 0.145 mmol) after purification using column chromatography with 20% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.65 (d, J = 8.4 Hz, 2H), 7.42 (q, J = 8.2 Hz, 4H), 6.80 (d, J = 8.4 Hz, 2H), 4.62 (s, 2H), 3.78 (s, 3H), 3.70 (t, J = 4.2 Hz, 4H), 3.54 (t, J = 4.2 Hz, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.9, 166.8, 159.3, 144.2, 135.8, 131.8, 131.8, 130.6, 130.4, 128.8, 118.8, 114.0, 110.9, 102.6, 66.8, 55.4, 49.6, 41.1; (HRMS) CI: calculated for ($C_{23}H_{21}N_3O_4$) 403.1532 found 403.1530.

1-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-4-morphholine-1H-pyrrole-2,5-dione (Table 3.5, Entry 4, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-morpholino-1*H*-pyrrole-2,5-dione (76.2 mg, 0.2 mmol) and 4-methoxyphenyl boronic (36.5 mg, 0.24 mmol) and the general procedure described, 1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-4-morphholine-1*H*-pyrrole-2,5-dione was obtained in 88% yield (71.9 mg, 0.176 mmol) after purification using column chromatography with 30% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.88 (q, J = 9.0 Hz, 4H), 4.61 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.66 (t, J = 4.2 Hz, 4H), 3.50 (t, J = 4.2 Hz, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.1, 167.9, 159.2, 142.6, 131.2, 130.4, 129.3, 122.8, 114.0, 113.7, 105.9, 66.9, 55.4, 49.0, 40.8; (HRMS) CI: calculated for ($C_{23}H_{24}N_2O_5$) 408.1685 found 408.1683.

1-(4-Methoxybenzyl)-3-(4-chlorophenyl)-4-morphholine-1H-pyrrole-2,5-dione (Table 3.5, Entry 5, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-morpholino-1*H*-

pyrrole-2,5-dione (76.2 mg, 0.2 mmol) and 4-chlorophenyl boronic (37.5 mg, 0.24 mmol) and the general procedure described, 1-(4-methoxybenzyl)-3-(4-chlorophenyl)-4-morphholine-1*H*-pyrrole-2,5-dione was obtained in 85% (70.0 mg, 0.170 mmol) yield after purification using column chromatography with 20% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (d, J = 8.6 Hz, 4H), 7.22 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.61 (s, 2H), 3.78 (s, 3H), 3.68 (t, J = 4.0 Hz, 4H), 3.51 (t, J = 4.0 Hz, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.5, 167.4, 159.2, 143.4, 133.7, 131.5, 130.3, 129.2, 129.0, 128.4, 114.0, 104.0, 66.8, 55.3, 49.2, 41.0; (HRMS) CI: calculated for ($C_{22}H_{21}ClN_2O_4$) 412.1190 found 412.1190.

1-(4-Methoxybenzyl)-3-morpholino-4-o-tolyl-1H-pyrrole-2,5-dione (Table 3.5, Entry 6, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-morpholino-1*H*-pyrrole-2,5-dione (76.2 mg, 0.2 mmol) and 2-methylphenyl boronic (32.6 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-morpholino-4-*o*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 91% yield (71.4 mg, 0.182 mmol) after purification using column chromatography with 20% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36 (d, J = 8.6 Hz, 2H), 7.13-7.22 (m, 4H), 6.86 (d, J = 8.6 Hz, 2H), 4.62 (s, 2H), 3.79 (s, 3H), 3.61 (t, J = 4,4 Hz, 4H), 3.50 (t, J = 4.4 Hz, 4H), 2.22 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4, 167.6, 159.1, 143.7, 138.1, 131.2, 130.7, 130.2, 129.2, 128.6, 125.7, 114.0, 104.9, 66.8, 55.3, 48.2, 40.9, 20.5; (HRMS) CI: calculated for ($C_{24}H_{23}N_2O_4$) 392.1736 found 392.1782.

1-(4-Methoxylbenzyl)-3-piperidin-1-yl)-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.5, Entry 7, Compound b). Using -(4-methoxybenzyl)-3-bromo-4-piperidin-1-yl)-1*H*-pyrrole-2,5-dione (75.6 mg, 0.2 mmol) 4-methylphenyl boronic (32.6 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxylbenzyl)-3-piperidin-1-yl)-4-*p*-tolyl-1H-pyrrole-2,5-dione was obtained in 89% yield (69.4 mg, 0.178 mmol) after purification using column chromatography with 10% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.36 (d, J = 8.4 Hz, 2H), 7.16 (q, J = 5.6 Hz, 4H), 6.83 (d, J = 8.4 Hz, 2H), 4.61 (s, 2H), 3.78 (s, 3H), 3.41 (t, J = 5.6 Hz, 4H), 2.34 (s, 3H), 1.56-1.57 (m, 6H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.3, 168.0, 159.5, 144.1, 137.2, 130.4, 130.2, 130.1, 128.8, 128.6, 114.0, 55.4, 50.4, 40.8, 26.2, 24.1, 21.4; (HRMS) CI: calculated for ($C_{24}H_{26}N_2O_3$) 390.1943 found 390.1941.

1-(4-Methoxybenzyl)-3-(N-methyl-N-phenylamino)-p-tolyl-1H-pyrrole-2,5-dione, (Table 3.5, Entry 8, Compound b). Using 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-bromo-1*H*-pyrrole-2,5-dione (80.2 mg, 0.2 mmol) and 4-methylphenyl boronic (32.6 mg, 0.24 mmol) and the general procedure described, 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 91% yield (74.9 mg, 0.182 mmol) after purification using column chromatography with 10% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.37 (d, J = 8.4 Hz, 2H), 7.15 (t, J = 7.7 Hz, 2H), 7.08 (d, J = 7.7 Hz, 2H), 6.96-6.99 (overlap, 3H), 6.92 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.64 (s, 2H), 3.78 (s, 3H), 3.39 (s, 3H), 2.28 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ

170.9, 167.8, 159.2, 145.1, 141.7, 138.1, 130.5, 129.3, 128.9, 128.5, 126.7, 124.2, 121.7, 114.3, 114.1, 55.4, 41.1, 40.7, 21.5; (HRMS) CI: calculated for ($C_{26}H_{24}N_2O_3$) 412.1787 found 412.1790.

1-(4-Methoxybenzyl)-3-(N-methyl-N-phenylamino)-4-(4-methoxyphenyl)-1H-pyrrole-2,5-dione (Table 3.5, Entry 9, Compound b). Using 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-bromo-1*H*-pyrrole-2,5-dione (80.2 mg, 0.2 mmol) and 4-methoxyphenyl boronic (36.5 mg, 0.24 mmol) and the general procedure described, 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione was obtained in 87% yield (74.1 mg, 0.173 mmol) after purification using column chromatography with 10% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.37 (d, J = 8.4 Hz, 2H), 7.12-7.39 (overlap, 3H), 6.95 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 7.7 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 4.65 (s, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.43 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.0, 168.1, 159.6, 159.3, 144.9, 140.8, 130.7, 130.5, 129.4, 128.8, 123.9, 122.0, 121.2, 116.2, 115.0, 114.1, 113.3, 55.4, 41.1, 40.2; (HRMS) CI: calculated for ($C_{26}H_{24}N_2O_4$) 428.1736 found 428.1734.

1-(4-Methoxybenzyl)-3-(N-methyl-N-phenylamino)-4-(4-chlorophenyl)-1H-pyrrole-2,5-dione (Table 3.5, Entry 10, Compound b). Using 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-bromo-1*H*-pyrrole-2,5-dione (80.2 mg, 0.2 mmol) and 4-chlorophenyl boronic (37.5 mg, 0.24 mmol) and the general procedure described, 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-(4-chlorophenyl)-1*H*-pyrrole-2,5-dione

was obtained in 84% yield (72.6 mg, 0.168 mmol) after purification using column chromatography with 10% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 (d, J = 8.4 Hz, 2H), 7.11 (t, J = 7.7 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.98-7.01 (0verlap, 3H), 6.89 (d, J = 7.7, 2H), 6.85 (d, J = 7.7 Hz, 2H), 4.66 (s, 2H),3.79 (s, 3H), 3.55 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.6, 167.6, 159.3, 144.7, 142.3, 133.6, 130.5, 129.2, 128.9, 128.2, 127.7, 125.0, 110.4, 55.4, 41.2, 40.9; (HRMS) CI: calculated for ($C_{25}H_{21}ClN_2O_3$) 432.1241 found 432.1245.

1-(4-Methoxybenzyl)-3-(phenylamino)4-p-o-tolyl-1H-pyrrole-2,5-dione, (Table 3.5, Entry 11, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-(phenylamino)-1*H*-pyrrole-2,5-dione (77.2 mg, 0.2 mmol) and 4-methylphenyl boronic (32.6 mg, 0.24 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-(phenylamino)4-*p*-*o*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 76% yield (74.9 mg, 0.153 mmol) after purification using column chromatography with 20% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.39 (d, J = 9.1 Hz, 2H), 7.18 (b, 1H), 7.03 (t, J = 7.7 Hz, 2H), 6.96 (t, J = 7.7 Hz, 1H), 6.92 (s, 4H), 6.84 (d, J = 7.7 Hz, 2H), 6.62 (d, J = 7.7 Hz, 2H), 4.71 (s, 2H), 3.79 (s, 3H), 2.26 (s, 3H).^{13}C NMR ($CDCl_3$, 176 MHz) δ 172.2, 168.5, 159.4, 137.4, 136.5, 135.6, 130.3, 129.8, 129.0, 128.4, 128.1, 126.5, 124.4, 121.5, 114.1, 103.2, 55.4, 41.4, 21.4; (HRMS) CI: calculated for ($C_{25}H_{22}N_2O_3$) 398.1630 found 398.1628.

3-(Butylamino)-4-p-tolyl-1H-pyrrole (Table 3.5, Entry 1, Compound c). Using 1-(4-methoxybenzyl)-3-(butylamino)-4-*p*-tolyl-H-pyrrole-2,5-dione (38.8 mg, 0.1 mmol),

$AlCl_3$ (106.4 mg, 0.8 mmol, 8 eq.) and the general procedure described for deprotection of symmetrical maleimides, 3-(butylamino)-4-*p*-tolyl-*1H*-pyrrole was obtained in 84% (21.7 mg, 0.084 mmol) after purification using column chromatography with 20% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.20 (q, J = 7.7 Hz, 4H), 5.26 (b, 1H), 3.10 (q, J = 6.6 Hz, 2H), 2.36 (s, 3H), 1.32-1.42 (m, 2H), 1.14-1.25 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.1, 167.9, 142.4, 137.6, 130.4, 128.9, 126.9, 100.6, 44.9, 31.9, 21.4, 19.8, 13.7; (HRMS) CI: calculated for ($C_{15}H_{18}N_2O_3$) 258.1368 found 258.1364.

3-Morpholino-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.5, Entry 2, Compound c). Using 1-(4-methoxybenzyl)-3-morpholino-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (39.2 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq.) and the general procedure for deprotection of symmetrical maleimides, 3-morpholino-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 84% (22.9 mg, 084 mmol) yield after purification using column chromatography with 30% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19 (s, 4H), 3.68 (t, J = 4.0 Hz, 4H), 3.50 (t, J = 4.0 Hz, 4H), 2.36 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 168.1, 143.1, 138.1, 130.2, 129.0, 127.5, 107. 2, 66.9, 49.0, 21.4; (HRMS) CI: calculated for ($C_{15}H_{16}N_2O_3$) 272.1161 found 272.1147.

4-(2,5-dihydro-4-morpholine-2,5-dioxo 1H-pyrrol-3-yl))benzonitrile (Table 3.5, Entry 3, Compound c). Using 1-(4-methoxybenzyl)-2,5-dihydro-4-morphholine-2,5-dioxo-1*H*-pyrrol-3-yl))benzonitrile (40.3 mg, 0.1 mmol), $AlCl_3$ (106.4 mg, 0.8 mmol, 8 eq.) and the general procedure described for deprotection of symmetrical maleimides, 4-(2,5-

dihydro-4-morphholine-2,5-dioxo 1*H*-pyrrol-3-yl))benzonitrile was obtained in 82% yield (23.2 mg, 0.082 mmol) after purification using column chromatography with 30% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.68 (d, J = 7.7 Hz, 2H), 7.43 (d, J = 7.7 Hz, 2H), 3.72 (t, J = 4.2 Hz, 4H), 3.56 (t, J = 4.2 Hz, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.2, 167.0, 144.3, 135.5, 132.0, 131.9, 130.8, 118.7, 111.4, 66.8, 49.6, (HRMS) CI: calculated for ($C_{15}H_{13}N_3O_3$) 283.0957 found 283.0958.

3-(4-Methoxyphenyl)-4-morpholine-1H-pyrrole-2,5-dione, (Table 3.5, Entry 4, Compound c). Using 1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-4-morphholine-1*H*-pyrrole-2,5-dione (40.8 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq.) and the general procedure described for deprotection of symmetrical aryl maleimides, 3-(4-methoxyphenyl)-4-morphholine-1*H*-pyrrole-2,5-dione was obtained in 85% yield (24.8 mg, 0.085 mmol) after purification using column chromatography on silica gel with 30% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.24 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H) 3.82 (s, 3H), 3.68 (t, J = 4.4 Hz, 4H), 3.51 (t, J = 4.4 Hz, 4H), 170.6, 168.0, 159.3, 142.7, 131.4, 128.5, 122.4, 113.7, 107.0, 66.8, 55.3, 48.8; (HRMS) CI: calculated for ($C_{15}H_{17}N_2O_4$) [M+1] 289.1257 found 289.1257.

3-(4-chlorophenyl)-4-morpholino-1H-pyrrole-2,5-dione (Table 3.5, Entry 5, Compound c). Using 1-(4-methoxybenzyl)-3-(4-chlorophenyl)-4-morphholine-1*H*-pyrrole-2,5-dione (41.3 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq.) and the general procedure for deprotection of symmetrical maleimides, 3-(4-chlorophenyl)-4-morpholino-1*H*-pyrrole-

2,5-dione was obtained in 87% yield (24.6 mg , 0.087 mmol) after purification using column chromatography with 30% ethylacetate in hexane as the eluent and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 3.69 (t, J = 4 Hz, 4H), 3.53 (t, J = 4 Hz, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.2, 167.6, 143.5, 134.1, 131.5, 129.0, 105.3, 66.8, 49.2; (HRMS) CI: calculated for ($C_{14}H_{13}ClN_2O_3$) 292.0615 found 292.0615.

3-Morpholino-4-o-tolyl-1H-pyrrole-2,5-dione (Table 3.5, Entry 6, Compound c). Using 1-(4-methoxybenzyl)-3-morpholino-4-*o*-tolyl-1*H*-pyrrole-2,5-dione (39.2 mg, 0.1 mmol), $AlCl_3$ (106.4 mg, 0.8 mmol, 8 eq.) and the general procedure for deprotection of symmetrical maleimides 3-morpholino-4-*o*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 88% yield (24 mg, 0.088 mmol) after purification using column chromatography with 30% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.17-7.28 (m, 4H), 3.65 (t, J = 4.8 Hz, 4H), 3.52 (t, J = 4.8 Hz, 4H), 2.26 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.5, 168.0, 143.9, 138.1, 131.2, 130.3, 128.8, 128.5, 125.9, 106.1, 66.9, 48.2, 20.5; (HRMS) CI: calculated for ($C_{15}H_{16}ClN_2O_3$) 272.1161 found 272.1147.

3-(Piperidin-1-yl)-4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.5, Entry 7, Compound c.) Using 1-(4-methoxylbenzyl)-3-piperidin-1-yl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione (39.0 mg, 0.1 mmol), $AlCl_3$ (106.4 mg, 0.8 mmol, 8 eq.) and the general procedure for deprotection of symmetrical maleimides 3-(piperidin-1-yl)-4-*p*-tolyl-1*H*-pyrrole-2,5-dione was obtained in 91% (24.7 mg, 0.091) after purification using column chromatography with 20% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.18 (q, J = 5.6

Hz, 4H), 3.43 (t, J = 5.6, 4H), 2.34 (s, 3H), 1.57-1.61 (m, 6H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.9, 168.2, 144.2, 137.5, 130.1, 128.9, 128.3, 105.6, 50.3, 26.2, 24.0, 21.5; (HRMS) CI: calculated for ($C_{16}H_{18}N_2O_2$) 271.1361 found 271.1361.

3-(N-Methyl-N-phenylamino)-p-o-tolyl-1H-pyrrole-2,5-dione (Table 3.5, Entry 8, Compound c). Using 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-*p*-*o*-tolyl-1*H*-pyrrole-2,5-dione (41.2 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq.) and the general procedure for deprotection of symmetrical maleimides, 3-(*N*-methyl-*N*-phenylamino)-*p*-*o*-tolyl-1*H*-pyrrole-2,5-dione 85% yield (24.8 mg, 0.085) after purification using column chromatography with 20% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34 (b, 1H), 7.16 (t, J = 7.0 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.97-7.01 (overlap, 3H), 6.96 (d, J = 8.4 Hz, 2H), 3.42 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 167.9, 145.0, 142.0, 138.4, 130.8, 129.4, 128.9, 128.5, 126.4, 124.4, 121.6, 121.4, 115.3, 40.7, 21.5; CI (HRMS): calculated for ($C_{18}H_{16}N_2O_2$) 292.1212 found 292.1210.

3-(N-Methyl-N-phenylamino)-4-(4-methoxyphenyl)-1H-pyrrole-2,5-dione (Table 3.5, Entry 9, Compound c). Using 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione (42.8 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq.) and the general procedure for deprotection of symmetrical maleimides 3-(*N*-methyl-*N*-phenylamino)-4-(4-methoxyphenyl)-1*H*-pyrrole-2,5-dione was obtained in 87% yield (26.8 mg, 0.087 mmol) after purification using column chromatography with 20% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.13-7.15 (overlap,

3H), 7.09 (b, 1H), 6.67 (t, J = 7.0 Hz, 1H), 6.92 (d, J = 7.7 Hz, 2H), 6.71 (d, J = 7.7 Hz, 2H), 3.76 (s, 3H), 3.46 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 168, 159.7, 144.6, 130.7, 129.9, 128.9, 125.4, 121.7, 121.3, 113.4, 55.4, 40.2, 29.8; (HRMS) CI: calculated for ($C_{18}H_{16}N_2O_3$) 308.1161 found 308.1166.

3-(N-Methyl-N-phenylamino)-4-(4-chlorophenyl)-1H-pyrrole-2,5-dione (Table 3.5, Entry 10, Compound c). Using 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-(4-chlorophenyl)-1*H*-pyrrole-2,5-dione (43.2 mg, 0.1 mmol), $AlCl_3$ (106.4 mg, 0.8 mmol, 8 eq.) and the general procedure described above, for deprotection of symmetrical maleimides 3-(*N*-methyl-*N*-phenylamino)-4-(4-chlorophenyl)-1*H*-pyrrole-2,5-dione 81% yield (25.3 mg, 0.081 mmol) after purification using column chromatography with 20% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.11 (t, J = 7.7 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.99 (overlap, 3H), 6.21 (d, J = 7.7 Hz, 2H), 3.53 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0, 167.6, 144.5, 142.5, 133.9, 130.6, 129.0, 128.0, 127.8, 125.2, 122.6, 114.0, 111.4; (HRMS) CI: calculated for ($C_{17}H_{13}ClN_2O_2$) 312.0666 found 312.0664.

3-(Phenylamino)4-p-tolyl-1H-pyrrole-2,5-dione (Table 3.5, Entry 11, Compound c). Using 1-(4-methoxybenzyl)-3-(phenylamino)4-*p*-tolyl-1*H*-pyrrole-2,5-dione, $AlCl_3$ (106.4 mg, 0.8 mmol, 8 eq.) and the general procedure for deprotection of symmetrical maleimides, *3-(Phenylamino)4-p-tolyl-1H-pyrrole-2,5-dione* was obtained in 73% yield (20.3 mg, 0.073) after purification using column chromatography with 30% ethylacetate in hexane and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.38 (b, 1H), 7.20 (b, 1H), 7.05 (t,

J = 7.7 Hz, 2H), 6.98 (t, J = 7.7 Hz, 1H), 6.93 (overlap, 4H), 6.65 (d, J = 7.7 Hz, 2H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.8, 168.5, 137.7, 136.3, 135.7, 129.8, 128.4, 128.2, 126.2, 124.6, 121.6, 104.4, 21.5. (HRMS) CI: calculated for ($C_{17}H_{14}N_2O_2$) 278.1055 found 278.1055.

General Procedure for the Synthesis of PMB-protected diamino maleimides, Figure 3.2. Mono-aminated, PMB-protected maleimide (0.2 mmol) in DMF (0.5 mL) was treated with the amine (0.6 mmol, 3 eq.) and TEA (84 μL, 0.6 mmol) the microwaved at 100 °C for 30 mins. The reaction mixture was taken up in DCM (10 mL) and washed with water (2 x 5 ml). The organic layer was dried with Na_2SO_4 and concentrated under reduced vacuum. Purification of the residue by column chromatography on silica gel using 20% ethylacetate in hexane as the eluent yielded the diamino products.

1-(4-methoxybenzyl)-3-(butylamino)-4-(phenylamino)-1H-pyrrole-2,5-dione (4). Using 1-(4-methoxybenzyl)-3-bromo-4-(phenylamino)-1*H*-pyrrole-2,5-dione (77.2 mg, 0.2 mmol) and butyl amine (60 μL, 0.6 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-(butylamino)-4-(phenylamino)-1H-pyrrole-2,5-dione was obtained 84% yield (63 mg, 0.167 mmol). The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.20-7.39 (m, 5H), 7.13 (d, J = 9.2 Hz, 3H), 6.84 (d, J = 7.2 Hz, 1H), 5.10 (s, 1H), 4.89 (b, 1H), 3.78 (s, 3H), 3.14 (q, J = 6.6 Hz, 2H), 1.35-1.45 (m, 2H), 1.14-1.45 (m, 2H), 0.78 (t, J = 7.0 Hz, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 168.1, 159.3, 145.9, 130.0, 129.9, 129.4, 125.7, 119.8, 118.9, 114.8, 114.1, 55.4, 43.3, 41.0, 32.8, 19.8, 13.7: (HRMS) ES: calculated for ($C_{22}H_{26}N_3O_3$) [M+1] 380.1969 found 380.1960.

1-(4-methoxybenzyl)-3-(phenylamino)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione (5). Using 1-(4-methoxybenzyl)-3-bromo-4-(phenylamino)-1*H*-pyrrole-2,5-dione (77.2 mg, 0.2 mmol), piperidine (59 μL, 0.6 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-(phenylamino)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione was obtained in 94 % yield (73.5 mg, 0.188 mmol). The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19-7.33 (m, 4H), 6.84 (overlap, 3H), 6.71 (d, J = 8.6 Hz, 2H), 5.63 (s, 1H), 4.56 (s, 2H), 3.78 (s, 3H), 3.43 (t, J = 6.0 Hz, 4H), 1-40-1.46 (m, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0, 168.2, 159.2, 143.1, 130.7, 130.1, 129.3, 129.1, 120.1, 1165, 114.0, 110.5, 55.4, 48.7, 40.7, 26.2, 24.2; (HRMS) CI: calculated for ($C_{22}H_{25}N_3O_3$) 391.1896 found 391.1896.

1-(4-methoxybenzyl)-3-morpholino-4-(phenylamino)-1H-pyrrole-2,5-dione (6). Using 1-(4-methoxybenzyl)-3-bromo-4-(phenylamino)-1*H*-pyrrole-2,5-dione (77.2 mg, 0.2 mmol), morpholine (52 μL, 0.6 mmol) and the general procedure described above, in the 1-(4-methoxybenzyl)-3-morpholino-4-(phenylamino)-1H-pyrrole-2,5-dione,was obtained in 89% yield (69.9 mg, 0.178 mmol). The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.29 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.92 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 9.1 Hz, 2H), 6.76 (d, J = 9.1 Hz, 2H), 5.88 (s, 1H), 4.55 (s, 2H), 3.76 (s, 3H), 3.48 (t, J = 4.9 Hz, 4H), 3.34 ((t, J = 4.9 Hz, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.2, 168.3, 159.3, 141.4, 130.1, 129.2, 126.3, 121.5, 117.5, 114.2, 114.1, 67.0, 55.5, 48.1, 40.9; (HRMS) CI: calculated for ($C_{22}H_{25}N_3O_4$) 393.1689 found 393.1685.

1-(4-methoxybenzyl)-3-N-methyl-N-phenylamino)-4-(piperidin-1-yl)-1H-pyrrole (7). Using 1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-bromo-1*H*-pyrrole-2,5-dione (80.2 mg, 0.2 mmol), piperidine (59 μL, 0.6 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-N-methyl-N-phenylamino)-4-(piperidin-1-yl)-1H-pyrrole was obtained in 91% yield (73.7 mg, 0.182 mmol) .The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.78-6.87 (m, 3H), 6.66 (d, 2H), 4.56 (s, 2H), 3.78 (s, 3H), 3.56 (t, J = 5.6 Hz, 4H), 3.16 (s, 3H), 1.50-1.57 (m, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.2, 167.0, 159.1, 147.4, 139.9, 130.3, 129.5, 129.2, 118.3, 114.0, 113.5, 109.9, 55.4, 48.8, 40.6, 38.6, 26.5, 24.2; (HRMS) CI: calculated for ($C_{24}H_{27}N_3O_3$) 405.2052 found 405.2050.

1-(4-methoxybenzyl)-3-morpholono-4-(piperidine-1-yl)-1H-pyrrole-2,5-dione (8). Using 1-(4-methoxybenzyl)-3-bromo-4-morpholono-1*H*-pyrrole-2,5-dione (76.0 mg, 0.2 mmol), piperidine (59 μL, 0.6 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-morpholono-4-(piperidine-1-yl)-1H-pyrrole-2,5-dione,was obtained in 81% yield (62.4 mg, 0.162 mmol). The compound showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.29 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.48 (s, 2H), 3.78 (s, 3H), 3.69 (t, J = 4.2 Hz, 4H), 3.52 (t, J = 5.6 Hz, 4H), 3.35 (t, J = 4.2 Hz, 4H), 1.57-1.59 (m, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.9, 168.2, 159.1, 130.7, 130.2, 129.6, 122.1, 114.0, 67.4, 55.4, 49.6, 40.2, 26.6, 24.3; (HRMS) CI: calculated for ($C_{21}H_{28}N_3O_4$) 386.2080 found 386.2075.

1-(2,5-Dioxo-4-(phenylamino)-2,5-dihydro-1H-pyrrol-3-yl)-1-(4methoxybenzyl) piperidinium chloride (9). Using 1-(4-methoxybenzyl)-3-(phenylamino)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione (39.2 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq), anisole (2 mL) and stirring the reaction at room temperature for 12h, yielded compound **9** in 89% yield (34.9 mg, 0.089 mmol) after purification using 30% ethylacetate in hexane as the eluent. The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.48 (d, J = 7.6 Hz, 1H), 7.15-7.27 (overlap, 4H), 6.64-6.88 (overlap, 4H), 4.67 (s, 1), 4.55 (s, 3H), 3.75 (s, 3H), 2.31-2.33 (m, 4H), 1.41-1.45 (m, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 176.0, 175.6, 159.3, 149.4, 131.0, 129.8, 127.7, 126.1, 124.3, 120.4, 114.1, 78.9, 56.7, 55.3, 48.5, 42.3, 25.8, 24.5; (HRMS) CI: calculated for ($C_{23}H_{26}N_3O_3$) 392.1969 found 392.1966.

1-(4-Methoxybenzyl)-1-(4-(methyl(phenyl)amino)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)piperidinium chloride (10). Using1-(4-methoxybenzyl)-3-(*N*-methyl-*N*-phenylamino)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione (40.6 mg, 0.1 mmol), $AlCl_3$ (66.5 mg, 0.5 mmol, 5 eq) and the general procedure above but stirring the reaction at room temperature for 12h, yielded compound **10** in 91% yield (0.091 mg, 36.9 mg). The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.46 (d, J = 7.6 Hz, 1H), 7.19-7.23 (overlap, 4H), 6.75-6.79 (overlap, 3H), 6.45 (d, J = 7.6 Hz,1H), 4.55 (s, 2H), 4.33 (s, 1H), 3.76 (s, 3H), 3.09 (s, 3H) 2.19-2.26 (m, 4H), 1.39-1.56 (m, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.6, 173.7, 159.3, 150.4, 131.0, 130.0, 127.9, 126.0, 123.5, 118.5, 114.1, 107.1, 77.9, 61.9, 55.3, 48.6, 42.2, 33.4 25.8, 24.5; (HRMS) CI: calculated for ($C_{24}H_{28}N_3O_3$) 406.2125 found 406.2115.

3,4-Bromo-1-(4-nitrophenyl)-1H-pyyrole-2,5-dione (11). To a mixture of 3,4-dibromomaleic anhydride (1.95 g, 7.65 mmol) in acetic acid (25 mL) was added *p*-nitroaniline (1.16 g, 8.4 mmol). The reaction mixture was refluxed for 8 hours. Evaporation of the solvent under reduced pressure was followed by column chromatography on silica gel using 30% ethylacetate in hexane as the eluent, 3,4-Bromo-1-(4-nitrophenyl)-1H-pyyrole-2,5-dione was obtained in 75% yield (2.13 g, 5.7 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.35 (d, J = 9.1 Hz, 2H), 7.66 (d, J = 9.1Hz, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.3, 146.9, 136.7, 130.6, 125.9, 124.8; (HRMS) CI: calculated for ($C_{10}H_4BrN_2O_4$) 373.8538 found 373.8538.

General Procedure for the Synthesis of Bisamino Substituted Maleimides (Table 3.6, Compound b). To a mixture of 3,4-dibromo-1-(4-nitrophenyl)-1*H*-pyrrole-2,5-dione, compound (**11**) (93 mg, 0.25 mmol), TEA (88 μL, 0.63 mmol, 2.5 eq.) in DMF (0.5 mL) was added the amine (0.26 mmol, 1.05 eq.). The reaction mixture was stirred at room for 3 min. at which time additional TEA (88 μL, 0.63 mmol, 2.5 eq.) and the second amine (0.38 mmol, 1.5 eq.) were added. The reaction mixture was microwaved at 50 °C for 30 min., then taken up in DCM (10 mL) and washed with water (2 x 5 mL). The organic extract was dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the mixture using column chromatography on silica gel with 20% ethylacetate in hexane as the eluent yielded the diamino substituted maleimides.

3-Morpholino-1-(4-nitrophenyl)-4-(phenylamino)-1H-pyrrole-2,5-dione (Table 3.6, Entry 1, Compound b). Using aniline (24.6 μL, 0.26 mmol) as the first amine,

morpholine (33.2 μL, 0.38 mmol) as the second amine and the general procedure described, 3-morpholino-1-(4-nitrophenyl)-4-(phenylamino)-1*H*-pyrrole-2,5-dione was obtained in 93% yield (91.5 mg, 0.23 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.30 (d, J = 9.1, 2H), 7.70 (d, J = 9.1, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.03 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 7.7 Hz, 2H), 6.19 (s, 1H), 3.52 (t, J = 4.9 Hz, 4H), 3.90 (t, J = 4.9 Hz, 4H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.3, 166.5, 145.6, 140.1, 137.8, 129.3, 124.9, 124.7, 124.5, 122.5, 118.4, 115.8, 66.9. 48.4. (HRMS): CI: calculated for ($C_{20}H_{18}N_4O_5$) 394.1277 found 394.1275.

1-(4-Nitrophenyl)-3-(phenylamino)-4-piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 2, Compound b). Using aniline (24.6, 0.26 mmol) as the first amine, piperidine (37.6 μL, 0.38 mmol) as the second amine and the general procedure described above, 1-(4-nitrophenyl)-3-(phenylamino)-4-piperidin-1-yl)-1*H*-pyrrole-2,5-dione was obtained in 95% yield (93.3 mg, 0.238 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.29 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 6.96 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 8 Hz, 2H), 5.91, (s, 1H), 3.44 (t, J = 7.0 Hz, 4H), 1.50 (m, 6H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.6, 166.4, 145.4, 141.8, 138.1, 129.2, 128.8, 124.9, 124.4, 121.5, 117.4, 112.3, 46.0, 26.2, 24.1; (HRMS) CI: calculated for ($C_{21}H_{20}N_4O_4$) 392.1482 found 392.1485.

3-(N-Methyl-N-phenylamino)-4-morpholino-1-(4-nitrophenyl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 3, Compound b). Using *N*-methyl aniline (28.3 μL, 0.26 mmol) as the first amine, morpholine (33.2 μL, 0.38 mmol) as the second amine and the general

procedure described above, 3-(*N*-methyl-*N*- phenylamino)-4-morpholino-1-(4-nitrophenyl)-1*H*-pyrrole-2,5-dione was obtained in 91% yield (93.1 mg, 0.228 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.28 (d, J = 9.1 Hz, 2H), 7.69 (d, J = 9.1 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.89 (t, J = 7.7 Hz, 1H), 6.78 (t, J = 7.7 Hz, 2H), 3.64 (t, J = 4.9 Hz, 4H), 3.56 (t, J = 4.9 Hz, 4H), 3.28 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 166.8, 165.2, 146.1 145.7, 137.7, 137.2, 129.5, 125.3, 124.4, 119.7, 114.4, 113.1, 67.0, 48.1, 38.4; (HRMS) CI: calculated for ($C_{21}H_{20}N_4O_5$) 408.1434 found 408.1432.

3-(N-Methyl-N-phenylamino)-1-(4-nitrophenyl)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 4, Compound b). Using *N*-methyl aniline (28.3 μL, 0.26 mmol) as the first amine, piperidine (37.6 μL, 0.38 mmol) as the second amine and the general procedure above, 3-(*N*-methyl-*N*- phenylamino)-1-(4-nitrophenyl)-4-(piperidin-1-yl)-1*H*-pyrrole-2,5-dione was obtained in 96% yield (97.5 mg, 0.24 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.26 (d, J = 9.1 Hz, 2H), 7.71 (d, J = 9.1 Hz, 2H), 7.28 (t, J = 8.4 Hz, 2H), 6.85 (t, J = 7.7 Hz, 1H), 6.77 (d, J = 7.7 Hz, 2H), 3.61 (t, J = 5.2 Hz, 4H), 3.26 (s, 3H), 1.52-1.59 (m, 6H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 167.0, 165.3, 146.8, 145.5, 139.1, 138.0, 129.4, 125.7, 125.3, 124.4, 124.3, 119.1, 114.0, 111.2, 49.1, 38.5, 29.9, 26.5, 24.1; (HRMS) CI: calculated for ($C_{22}H_{22}N_4O_4$) 406.1641 found 406.1638.

3-(4-Methoxyphenylamino)-1-(4-nitrophenyl)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 5, Compound b). Using 4-methoxy aniline (32.2 mg, 0.26 mmol) as the first amine, piperidine (38 μL, 0.38 mmol) as the second amine and the general procedure described above, 3-(4-methoxy phenylamino)-1-(4-nitrophenyl)-4-(piperidin-1-yl)-1*H*-

pyrrole-2,5-dione was obtained in 91% yield (96.0 mg, 0.228 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 8.29 (d, J = 7.0 Hz, 2H), 7.72 (d, J = 7.0 Hz, 2H), 6.86 (d, J = 7.0 Hz, 2H), 6.82 (d, J = 7.0 Hz, 2H), 6.00 (s, 1H), 3.80 (s, 3H), 3.29 (t, J = 7.0 Hz, 4H), 1.47-1.50 (m, 2H), 1.39-1.42 (m, 4H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.6, 166.8, 155.2, 145.3, 138.2, 134.0, 125.1, 124.7, 1124.4, 119.9, 115.9, 114.4, 55.8, 49.4, 26.1, 24.1; (HRMS) CI: calculated for ($C_{22}H_{22}N_4O_5$) 422.1590 found 422.1587.

3-Morpholino-1-(4-nitrophenyl)-4-piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 6, Compound b). Using morpholine (23.0μL, 0.26 mmol) as the first amine and piperidine (38 μL, 0.38 mmol) as the second amine and the general procedure described above, 3-morpholino-1-(4-nitrophenyl)-4-piperidin-1-yl)-1H-pyrrole-2,5-dione was obtained in 92 % yield (88.8 mg, 0.23 mmol) and showed: ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.27 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 3.76 (t, J = 4.9 Hz, 4H), 3.62 (s, 4H), 3.43 (t, J = 4.9 Hz), 1.65 (s, 6H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.7, 166.2, 145.4, 137.9, 130.8, 125.4, 124.3, 122.1, 67.4, 49.6, 49.4, 26.3; (HRMS) CI: calculated for ($C_{19}H_{22}N_4O_5$) 386.1590 found 386.1588.

General Procedure for the Deprotection of Nitroaniline-protected Diamino Maleimides by Aminolysis (Table 3.6, Compound c). Ammonia gas was bubbled through a solution of the nitroaniline-protected maleimide (0.15 mmol) in methanol (3 mL). The reaction mixture was stirred at room temperature for 12 hours. Concentration of the methanol under reduced pressure and purification using column chromatography on silica gel with 20% ethylacetate in hexane as the eluent yielded the diamino substituted maleimides.

3-Morpholino-4-(phenylamino)-1H-pyrrole-2,5-dione (Table 3.6, Entry 1, Compound c). Using 3-morpholino-1-(4-nitrophenyl)-4-(phenylamino)-1*H*-pyrrole-2,5-dione (59.2 mg, 0.15 mmol) and the general procedure described above, 3-morpholino-4-(phenylamino)-1*H*-pyrrole-2,5-dione was obtained in 84% yield (34.7 mg, 0.127 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.29 (t, J = 4.6 Hz, 2H), 7.06 (b, 1H), 6.91 (t, J = 4.2 Hz, 1H), 6.79 (d, J = 2.2 Hz, 2H), 5.94 (s, 1H), 3.51 (t, J = 2.6 Hz, 4H), 3.38 (t, J = 2.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 168.9, 168.2, 141.2, 129.2, 126.9, 121.7, 117.6, 114.9, 66.9, 48.0; (HRMS) EI: calculated for ($C_{14}H_{15}N_3O_3$) 273.1113 found 273.1129.

3-(Phenylamino)-4-piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 2, Compound c). Using 1-(4-nitrophenyl)-3-(phenylamino)-4-piperidin-1-yl)-1*H*-pyrrole-2,5-dione (58.9 mg, 0.15 mmol) and general procedure described above, 3-(phenylamino)-4-piperidin-1-yl)-1*H*-pyrrole-2,5-dione was obtained in 93% yield (38.0 mg, 0.14 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.24 (d, J = 4.4 Hz, 2H), 7.04 (b, 1H), 6.89 (t, J = 4.2 Hz, 1H), 6.73 (d, J = 4.4 Hz, 2H), 3.43 (t, J = 5.6.0 Hz, 4H), 1.50-1.52 (m, 2H), 1.43-1.46 (m, 4H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 168.4, 168.2, 142.9, 131.3, 129.2, 120.7, 116.6, 111.2, 48.7, 26.3, 24.2; (HRMS) EI: calculated for ($C_{15}H_{17}N_3O_2$) 271.1323 found 271.1321.

3-(N-Methyl-N-phenylamino)-4-morpholoine-1H-pyrrole-2,5-dione (Table 3.6, Entry 3, Compound c). Using 3-(*N*-methyl-*N*-phenylamino)-4-morpholoine-1-(4-nitrophenyl)-1*H*-pyrrole-2,5-dione (60.5 mg, 0.15 mmol) and the general procedure described above, 3-

(*N*-methyl-*N*-phenylamino)-4-morpholoine-1*H*-pyrrole-2,5-dione was obtained in 81% yield (34.8 mg, 0.121 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.26 (d, J = 9.1 Hz, 2H), 7.12 (b, 1H), 6.83 (t, J = 7.0 Hz, 1H), 6.71 (d, J = 8.4 Hz, 2H), 3.78 (t, J = 4.2 Hz, 4H), 3.55 (t, J = 4.2 Hz, 4 H), 3.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.6, 166.9, 146.6, 138.5, 129.5, 119.1, 113.9, 112.8, 67.0, 47.7, 38.5; (HRMS) EI: calculated for ($C_{15}H_{17}N_3O_3$) 287.1270 found 287.1273.

3-(N-Methyl-N-phenylamino)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 4, Compound c). Using 3-(*N*-methyl-*N*-phenylamino)-1-(4-nitrophenyl)-4-(piperidin-1-yl)-1*H*-pyrrole-2,5-dione (61.0 mg, 0.15 mmol) and general procedure described above, 3-(*N*-methyl-*N*- phenylamino)-4-(piperidin-1-yl)-1*H*-pyrrole-2,5-dione was obtained in 96% yield (41.1 mg, 0.144 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.20 (m, 2H), 6.89 (b, 1H), 6.69-6.83 (m, 3H), 3.58 (t, J = 5.4 Hz, 4H), 3.18 (s, 3H), 1.52-1.56 (m, 6H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 168.8, 167.0, 147.2, 140.4, 129.3, 118.5, 113.5, 110.9, 48.7, 38.6, 26.6, 24.2. (HRMS): EI calculated for ($C_{16}H_{19}N_3O_2$) 285.1477 found 285.1477.

3-(4-Methoxyphenylamino)-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 5, Compound c. Using 3-(4-methoxyphenylamino)-1-(4-nitrophenyl)-4-(piperidin-1-yl)-1*H*-pyrrole-2,5-dione (63.3 mg, 0.15 mmol) and general procedure described above, 3-(4-methoxyphenylamino)-4-(piperidin-1-yl)-1*H*-pyrrole-2,5-dione in 89% yield (39.2 mg, 0.13 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.83 (d, J = 9.1 Hz, 2H), 6.74 (d, J = 9.1 Hz, 2H), 3.78 (s, 3H), 3.29 (t, J = 4.9 Hz, 4H), 1.47-1.48 (m, 2H), 1.38-1.40 (m,

4H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 169.1, 168.5, 154.7, 135.1, 127.3, 119.0, 114.9, 114.4, 55.8, 49.0, 26.1, 24.2; (HRMS) EI: calculated for ($C_{16}H_{19}N_3O_3$) 301.1426 found 301.1439.

3-Morpholino-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione (Table 3.6, Entry 6, Compound c). Using 3-morpholino-1-(4-nitrophenyl)-4-piperidin-1-yl)-1H-pyrrole-2,5-dione (58.4 mmol, 0.15 mmol) and general procedure described above, 3-morpholino-4-(piperidin-1-yl)-1H-pyrrole-2,5-dione was obtained in 82% yield (32.6 mg, 0.123 mmol) and showed: ^1H NMR ($CDCl_3$, 700 MHz) δ 3.72 (t, J = 4.9 Hz, 4H), 3.53 (t, J = 4.9 Hz, 4H), 3.77 (t, J = 4.9 Hz, 4H), 1.61 (s, 6H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 168.6, 168.1, 131.3, 122.9, 67.4, 49.5, 49.4, 26.6, 24.3; (HRMS) EI: calculated for ($C_{13}H_{19}N_3O_3$) 265.1426 found 265.1426.

1-(4-Methoxybenzyl)-3,4-dibromo-1H-pyrrol-2-(5H)-one (12). To a mixture of mucobromic acid (1.32 g, 5.2 mmoL) in DCM (25 mL) and acetic acid (15 mL) was added *p*-methoxybenylamine (744 μL, 5.7 mmol, 1.1 eq.) and $NaBH(OAc)_3$ (3.30 g, 15.6 mmol, 3eq.). The reaction mixture was stirred at room temperature for 24 h at which time the mixture was taken up in $CHCl_3$ (100 mL) and washed with water (2 x 50 mL). The organic layer was dried with Na_2SO_4, concentrated under a reduced pressure and purified using column chromatography on silica gel with 30 % ethylacetate in hexane as the eluent. Compound **12** was obtained in 76% yield (1.4 g, 4 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.18 (d, J = 8 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.59 (s, 2H), 3.90 (s, 2H), 3.79 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.0, 159.4, 133.6, 129.3, 127.8,

120.6, 114.2, 56.8, 55.6, 47.4. (HRMS) CI: calculated for ($C_{12}H_{11}Br_2NO_2$) 358.9157 found 358.9155.

General procedure for Mono Arylated of α,β-Unsaturated-γ-Butyrolactams (Table 3.7, Compound a). To a mixture of 1-(4-methoxybenzyl)-3,4-dibromo-1*H*-pyrrol-2-(5H)-one compound (**12**) (100 mg, 0.28 mmol), aryl boronic acid (0.31 mmol, 1.1 eq), KF (48.7 mg, 0.84 mmol, 3eq), $Pd_2(dba)_3.CHCl_3$ (11.4 mg, 0.011 mmol, 4 mol %), PA-Ph, (6.4 mg. 0.022 mmol, 8 mmol %), in a reaction flask was added dried toluene (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred at 60 °C for 9 h. Toluene was evaporated under reduced pressure and the reaction mixture was purified by column chromatography using 30% ethylacetate in hexane as the eluent.

1-(4-Methoxybenzyl)-3-bromo-4-(4-methoxyphenyl)-1H-2(5H)-one (Table 3.7, Entry 6, Compound a). Using 4-methoxyphenylboronic (48.6 mg, 0.31 mmol) and the general procedure, 1-(4-methoxybenzyl)-3-bromo-4-(4-methoxyphenyl)-1*H*-2(5H)-one was in 55% yield (59.6 mg, 0.154 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.67 (s, 2H), 4.14 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.4, 161.1, 159.4, 147.3, 130.9, 129.8, 124.0, 114.4, 114.3, 111.6, 55.6, 52.6, 46.7; (HRMS) CI: calculated for ($C_{19}H_{18}BrNO_3$) 387.0470 found 387.0462.

1-(4-Methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1H-2(5H)-one (Table 3.7, Entry 6, Compound b). Compound was the by-product in the synthesis of 1-(4-Methoxybenzyl)-

3-bromo-4-(4-methoxyphenyl)-1H-2(5H)-one (Table 7, Entry 6, Compound a) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.40 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 8.6 Hz, 3H), 6.89 (d, J = 8.6, 5H), 6.77 (d, J = 8.4, 2H), 4.67 (s, 2H), 4.11 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), ^{13}C NMR ($CDCl_3$, 176 MHz) δ 171.2, 160.2, 159.4, 159.2, 146.2, 130.9, 130.6, 130.3, 129.7, 129.0, 128.6, 125.6, 124.7, 114.2, 114.0, 55.3, 51.8, 45.9. CI (HRMS): calculated for ($C_{26}H_{25}NO_4$) 415.1784 found 415.1786.

1-(4-Methoxybenzyl)-3-bromo-4-p-tolyl-1H-2(5H)-one (Table 3.7, Entry 7, Compound a). Using 4-methylphenylboronic (42.5 mg, 0.31 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-2(5H)-one was obtained in 68% yield (70.5 mg, 0.19 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.68 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 4H), 6.89 (d, J = 8.6 Hz, 2H), 4.67 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H), 2.37 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.3, 159.5, 147.9, 140.8, 129.8, 129.7, 128.9, 128.8, 127.0, 114.5, 113.0, 55.5, 52.7, 46.8, 21.7; (HRMS) CI: calculated for ($C_{19}H_{18}BrNO_2$) 371.0521 found 371.0520.

1-(4-Methoxybenzyl)-3,4-dip-tolyl-1H-2(5H)-one (Table 3.7, Entry 7, Compound b). Compound was the by-product in the synthesis of 1-(4-Methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-2(5H)-one (Table 7, Entry 7, Compound a) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33 (d, J = 7.7 Hz, 2H), 7.28 (d, J = 9.1 Hz, 2H), 7.14 (t, J = 7.7 Hz, 4H), 7.05 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.69 (s, 2H), 4.13 (s, 2H), 3.80 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 159.2, 147.1, 139.3, 137.9,

131.7, 130.6, 129.8, 129.7, 129.6, 129.4, 129.3, 129.2, 127.6, 114.3, 55.4, 52.0, 46.0, 21.5, 21.4; (HRMS) CI: calculated for ($C_{26}H_{25}NO_2$) 383.1885 found 383.1891.

1-(4-Methoxybenzyl)-3-bromo-4-(4-chlorophenyl)-1H-2(5H)-one (Table 3.7, Entry 8, Compound a). Using 4-chlorophenylboronic acid (48.5 mg, 0.31 mmol) and the general procedure described, 1-(4-methoxybenzyl)-3-bromo-4-(4-chlorophenyl)-1*H*-2(5H)-one was in 54% yield (58.8 mg, 0.15 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.70 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.69 (s, 2H) 4.14 (s, 2H), 3.80 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.8, 159.5, 149.5, 136.3, 129.8, 129.2, 128.5, 114.4, 60.6, 55.4, 52.5, 46.8; (HRMS) CI: calculated for ($C_{18}H_{15}BrClNO_2$) 390.9970 found 390.9971.

1-(4-Methoxybenzyl)-3,4-bis(4-chlorophenyl)-1H-2(5H)-one (Table 3.7, Entry 8, Compound b). Compound was isolated as a byproduct in the synthesis of 1-(4-Methoxybenzyl)-3-bromo-4-(4-chlorophenyl)-1H-2(5H)-one (Table 7, Entry 8, Compound a) in 15 % yield (18 mg, 0.043 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.12-7.36 (overlap, 10H), 6.89 (d, J = 8.6 Hz, 2H), 4.69 (s, 2H), 4.13 (s, 2H), 3.80 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.1, 159.4, 146.8, 135.5, 134.5, 131.9, 131.5, 131.0, 130.2, 129.8, 129.2, 129.0, 128.9, 114.4, 55.4, 51.9, 46.1; (HRMS) CI: calculated for ($C_{24}H_{19}Cl_2NO_2$) 423.0793 found 423.0804.

General Procedure for the Preparation of Bisaryl Substituted α,β-Unsaturated-γ-Butyrolactams (Table 3.8, Compound b). To a mixture of the mono-arylated 3-bromo-

1*H*- pyrrol-2-(5H)-one compound (0.1 mmol), aryl boronic acid (0.12 mmol, 1.2 eq), KF (17.7 mg, 0.3 mmol, 3eq.), $Pd_2(dba)_3.CHCl_3$ (4.1 mg, 0.004 mmol, 4 mol %), PA-Ph, (2.3 mg. 0.008 mmol, 8 mmol %) was added dried toluene (3 mL). The mixture was degassed, placed under an atmosphere of argon and stirred 80 °C for 12 h. Toluene was evaporated under reduced pressure and the reaction mixture was purified by column chromatography using with 30% ethylacetate in hexane as the eluent.

1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-3-p-tolyl-1H-2(5H)-one (Table 3.8, Entry 1, Compound b) Using 1-(4-methoxybenzyl)-3-bromo-4-(4-methoxyphenyl)-1*H*-2(5H)-one (38.8 mg, 0.1 mmol) and 4-methylphenylboronic acid (16 mg, 0.12 mmol) and the general procedure described above, 1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-3-*p*-tolyl-1*H*-2(5H)-one was obtained in 78% yield (31.2 mg, 0.078 mmol) and showed: ^{1}H NMR ($CDCl_3$ 200 MHz) δ 7.18-7.32 (m, 8H), 6.88 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 8.2 Hz, 2H), 4.69 (s, 2H), 4.13 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 176 MHz) δ 170.1, 160.1, 159.1, 146.5, 137.7, 130.8, 129.7, 129.6, 129.5, 129.4, 129.2, 128.9, 125.7, 114.1, 114.0, 55.3, 51.7, 45.8, 21.4; (HRMS) CI: calculated for ($C_{26}H_{25}NO_3$) 399.1834 found 399.1823.

1-(4-Methoxybenzyl)3-o-tolyl-4-p-tolyl-1H-2(5H)-one (Table 3.8, Entry 2, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-*p*-tolyl-1*H*-2(5H)-one (37.2 mg, 0.1 mmol), 4-methylphenyl boronic acid (16 mg, 0.12 mmol) and the general procedure described, 1-(4-methoxybenzyl)3-*o*-tolyl-4-*p*-tolyl-1*H*-2(5H)-one was obtained in 75% yield (28.8 mg, 0.075 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19-7.30 (overlap, 6H),

7.01 (s, 4H), 6.90 (d, J = 8.2 Hz, 2H), 4.71 (s, 2H), 4.25 (s, 2H), 3.81 (s, 3H), 2.27 (s, 3H), 2.14 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 159.1, 147.4, 139.5, 136.9, 132.6, 130.4, 130.1, 129.9, 129.6 129.3, 126.8, 126.1, 114.2, 55.3, 51.4, 45.9, 21.3, 19.9; (HRMS) CI: calculated for ($C_{26}H_{25}NO_2$) 383.1885 found 383.1893.

1-(4-Methoxybenzyl)-4-(4-chlorophenyl)-3-p-tolyl-1H-2(5H)-one (Table 3.8, Entry 3, Compound b). Using 1-(4-methoxybenzyl)-3-bromo-4-(4-chlorophenyl)-1*H*-2(5H)-one (39.2 mg, 0.1 mmol), 4-methylphenylboronic acid (16 mg, 0.12 mmol) and the general procedure, 1-(4-methoxybenzyl)-4-(4-chlorophenyl)-3-*p*-tolyl-1*H*-2(5H)-one was obtained in 81% yield (32.7 mg, 0.081) and showed: ^{1}H NMR ($CD Cl_3$ 700 MHz) δ 7.30 (d, J = 7.7 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 9.1 Hz, 2H), 7.17 (d, J = 9.1, 2H), 7.16 (d, J = 7.7, 2H), 6.88 (d, J = 9.1, 2H), 4.69 (s, 2H), 4.12 (s, 2H), 3.80 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.5, 159.2, 145.4, 138.2, 134.9, 132.9, 131.8, 129.7, 129.3, 128.9, 128.7, 114.2, 55.3, 51.7, 45.9, 21.4; (HRMS) CI: calculated for ($C_{25}H_{22}ClNO_2$) 403.1339 found 403.1345.

1-(4-Methoxybenzyl)-3,4-dip-tolyl-1H-2(5H)-one (Table 3.8, Entry 4, Compound b). Using 4-methylphenylboronic acid (42.1 mg, 0.31 mmol) and the general procedure described, 1-(4-methoxybenzyl)-3,4-di*p*-tolyl-1*H*-2(5H)-one was obtained in 84% yield (45.3 mg, 0.118 mmol) and showed identical spectral properties to those of Table 7, Entry 7, Compound b.

1-(4-Methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1H-2(5H)-one (Table 3.8, Entry 5, Compound b). Using 4-methoxylphenylboronic acid (48.6 mg, 0.31 mmol) and the general procedure, 1-(4-methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1*H*-2(5H)-one was obtained in 85% yield (49.4 mg, 0.119 mmol) and showed identical spectral properties to those of Table 7, Entry 6, Compound b.

1-(4-Methoxybenzyl)-3,4-bis(4-chlorophenyl)-1H-2(5H)-one (Table 3.8, Entry 6, Compound b). Using 4-chlorophenylboronic acid (48.6 mg, 0.31 mmol) and the general procedure, 1-(4-methoxybenzyl)-3,4-bis(4-chlorophenyl)-1*H*-2(5H)-one was obtained in 82% yield (48.7 mg, 0.115 mmol). Compound showed identical spectral properties as those of Table 7, Entry 8, Compound b.

1-(4-Methoxyphenyl)-3-p-tolyl-1H-2(5H)-one (Table 3.8, Entry 1, Compound c). Using 1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-3-*p*-tolyl-1*H*-2(5H)-one (28 mg, 0.07 mmol), TFA (1 mL) anisole (1 mL) and the general procedure above, 1-(4-methoxyphenyl)-3-*p*-tolyl-1*H*-2(5H)-one was obtained in 84% yield (14.0 mg, 0.059 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15-7.31(m, 6H), 6.80 (d, J = 8.4 Hz, 2H), 4.34 (s, 2H), 3.80 (s, 3H), 2.34 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ174.8, 160.5, 149.7, 138.0, 131.0, 129.6, 129.5, 129.3, 129.2, 125.9, 114.3, 55.7, 48.1, 21.7 CI (HRMS): calculated for ($C_{18}H_{17}NO_2$) 279.1259 found 279.1257.

3-o-Tolyl-4-p-tolyl-1H-2(5H)-one (Table 3.8, Entry 2, Compound c). Using 1-(4-methoxybenzyl)-3-*o*-tolyl-4-*p*-tolyl-1*H*-2(5H)-one (26.8 mg, 0.07 mmol) TFA/anisole (1

mL:1 mL) and the general procedure described, 3-*o*-tolyl-4-*p*-tolyl-1*H*-2(5H)-one was obtained in 86% yield (15.8 mg, 0.06 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.55 (b, 1H), 7.24-7.11 (overlap, 4H), 7.06 (s, 4H), 4.45 (s, 2H), 2.30 (s, 3H), 2.1 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.8, 150.4, 139.9, 137.0, 132.5, 132.4, 130.3, 129.9, 129.8, 129.6 129.5, 128.5, 127.0, 126.9, 126.4, 48.0, 21.5, 20.0; (HRMS) CI: ($C_{18}H_{17}NO$) calculated for 263.1310 found 263.1308.

4-(4-Chlorophenyl)-3-p-tolyl-1H-2(5H)-one (Table 3.8, Entry 3, Compound c). Using 1-(4-methoxybenzyl)-4-(4-chlorophenyl)-3-*p*-tolyl-1*H*-2(5H)-one (28.3 mg, 0.07 mmol) TFA/anisole (1 mL:1 mL) and the general procedure described, 4-(4-chlorophenyl)-3-*p*-tolyl-1*H*-2(5H)-one was obtained in 82% (16.3 mg, 0.0575 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.25 (q, J = 6.3 Hz, 4H), 7.22 (d, 7.7 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 4.31 (s, 2H), 2.35 (s, 3H) ^{1}H NMR ($CDCl_3$, 700 MHz) δ 174.1, 148.5, 138.5, 135.3, 133.0, 132.0, 130.3, 129.5, 129.4, 129.1, 129.0, 48.0, 21.5; (HRMS) CI: ($C_{17}H_{14}NO$) calculated 283.0764 found 283.0762.

3,4-Di-p-tolyl-1H-2(5H)-one (Table 3.8, Entry 4, Compound c). Using 1-(4-methoxybenzyl)-3,4-di*p*-tolyl-1*H*-2(5H)-one (26.8 mg, 0.07 mg), $AlCl_3$ (46.6 mg, 0.35 mmol) in anisole (2 mL) and the general procedure described, 3,4-di*p*-tolyl-1*H*-2(5H)-one was obtained in 81% yield (15.0 mg, 0.057 mmol) and showed: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.65 (b, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.18 (q, J = 8.4 Hz, 4H) 7.08 (d, J = 8.4 Hz, 2H), 4.33 (s, 2H), 2.35 (s, 3H), 2.33 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.0,

150.1, 139.5, 137.9, 131.8, 130.6, 129.5, 129.4, 129.1, 127.6, 48.4, 21.5; (HRMS) CI: ($C_{18}H_{17}NO$) calculated for 263.1310 found 263.1310.

3,4-Bis(4-methoxyphenyl)-1H-2(5H)-one (Table 3.8, Entry 5, Compound c). Using 1-(4-methoxybenzyl)-3,4-bis(4-methoxyphenyl)-1H-2(5H)-one (29.1 mg, 0.07 mmol), $AlCl_3$ (46.6 mg, 0.35 mmol) in anisole (2 mL) and the general procedure described above, 3,4-bis(4-methoxyphenyl)-1*H*-2(5H)-one was obtained in 86% yield (17.7 mg, 0.06 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.2 Hz, 2H), 4.32 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.0, 160.4, 159.5, 149.3, 149.3, 149.2, 130.9, 130.5, 129.1, 125.9, 124.5, 114.2, 55.4, 48.1; (HRMS) CI: calculated for ($C_{18}H_{17}NO_3$) 295.1203 found 295.1201.

3,4-Bis(4-chlorophenyl)-1H-2(5H)-one (Table 3.8, Entry 6, Compound c). Using 1-(4-methoxybenzyl)-3,4-bis(4-chlorophenyl)-1*H*-2(5H)-one (29.7 mg, 0.07 mmol) $AlCl_3$ (74.5 mg, 0.056 mmol, 8 eq) in anisole (2 mL) and the general procedure described, 3,4-bis(4-chlorophenyl)-1*H*-2(5H)-one was obtained in 87% yield (18.6 mg, 0.061 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.65 (b, 1H), 7.18-7.34 (overlap, 8H), 4.34 (s, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.7, 149.7, 135.6, 134.4, 131.3, 130.8, 129.8 129.2, 129.0, 128.9, 48.2; (HRMS) CI: ($C_{16}H_{11}Cl_2NO$) calculated for 303.0214 found 303.0218.

3.1.7 References

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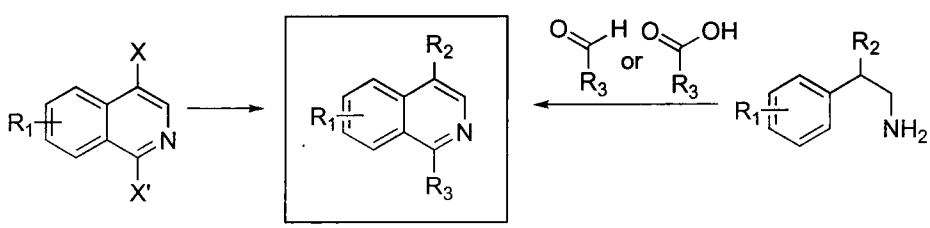
Chapter 4

4.1.1 Strategies and Synthetic Methods Directed Towards the Preparation of Libraries of Substituted Isoquinolines.[3]

Emelia Awuah and Alfredo Capretta

4.1.2 Abstract

Strategies for the production of substituted isoquinoline libraries were developed and explored. Routes involving microwave-assisted variants of the Bischler-Napieralski or Pictet-Spengler reaction allowed for cyclization of substituted β-arylethylamine derivatives. The dihydroisoquinolines and tetrahydroisoquinolines thus generated could then be oxidized to their corresponding isoquinoline analogues. An alternate strategy, however, involving the preparation and activation of isoquinolin-1(*2H*)-ones is demonstrated to be a more practical, rapid and efficient route to C1 and C4 substituted isoquinoline libraries.



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4.1.3 Introduction

The isoquinoline ring is a common structural motif found in a variety of natural products and biologically-active compounds. Access to this heterocyclic system has historically involved the application of either the Bischler-Napieralski or Pictet-Spengler reaction. The Bischler-Napieralski[1] reaction sees the conversion of an *N*-acyl-*β*-arylethyl amine into its corresponding dihydroisoquinoline then oxidation to the isoquinoline.[2] The Pictet-Spengler reaction[3] involves a Mannich-type reaction wherein a *β*-arylethylamine derivative is treated with an aldehyde under acidic conditions to generate an imine that can ring close to a tetrahydroisoquinoline and subsequently be oxidized to an isoquinoline.[4] Given that, in both cases, ring closure involves an electrophilic aromatic substitution, substrates that incorporate electron-rich aromatic systems tend to give the best yields. Most recently, protocols utilizing microwave irradiation in the Pictet-Spengler[5-10] and the Bischler-Napieralski[9] reactions have been described. Alternatively, the Larock isoquinoline synthesis involves the coupling of *o*-iodoaldimines and alkynes in the presence of a palladium catalyst to permit access to C3 and C4 substituted systems.[11-13]

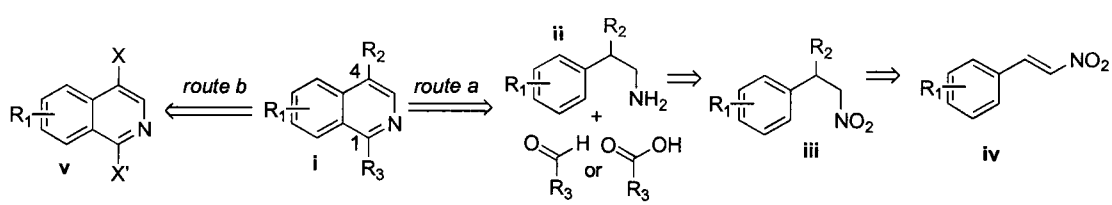


Figure 4.1. Approaches to Substituted Isoquinolines.

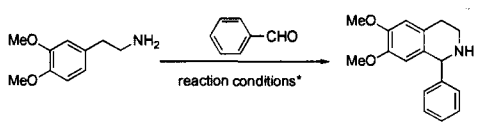
Our interest in these reactions grew out of a need for a library of substituted isoquinolines required for biological studies currently being conducted in our laboratory. Specifically required were systems wherein substitution could be introduced at the C1 and C4 positions of the isoquinoline core (compound (**i**), Figure 4.1). Two synthetic strategies were investigated: one wherein functionality is installed prior to cyclization (route a) and another wherein a suitable scaffold is activated then derivatized (route b). While both Bischler-Napieralski or Pictet-Spengler approaches allow for installation of functionality at C1, introduction of C4 derivatization requires an appropriately functionalized β-arylethylamine (**ii**) which we envisioned could be prepared *via* a conjugate addition onto nitroalkene (**iv**), for example, to give (**iii**) followed by reduction. Alternatively, the desired isoquinolines could be generated from a heterocycle of the general type (**v**), which could be prepared from an isoquinolin-1(*2H*)-one utilizing Bischler-Napieralski chemistry then activated and subsequently functionalized. Both approaches (routes a and b) were explored with an eye to the development of general, robust synthetic methods suitable for the synthesis of libraries of isoquinolines from readily available precursors.

4.1.4 Results and Discussion

We focused our initial attention on the development of appropriate Bischler-Napieralski and Pictet-Spengler protocols for the cyclization of β-arylethylamines. Exploratory experiments revealed that classical reaction conditions for these transformations gave poor to moderate yields and were unsuitable for parallel synthesis

reaction approaches. Efforts were, therefore, focused on the development of microwave-assisted methods. A series of experiments was designed to determine the optimal parameters for a microwave-assisted Pictet-Spengler reaction and were carried out to quickly ascertain the effects of solvent, acid concentration, temperature and time (see Table 4.1). Entries 1 – 5 indicated that the reactions were best performed in the absence of solvent or in toluene. Raising the reaction temperature from 90 °C to 140 °C (entries 6 – 9) allowed for a marked improvement on the yields. Simply increasing the reaction time from 15

Table 4.1. Optimization of Reaction Parameters for the Microwave-assisted Pictet-Spengler Reaction[a]

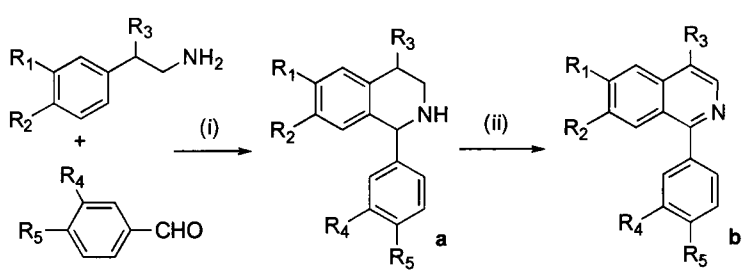


entry	solvent	eq. of TFA	temp (°C)	time (min.)	% yield
1	ethanol	8	90	30	0
2	MeCN	8	90	30	trace
3	DMF	8	90	30	trace
4	toluene	8	90	30	12
5	none	8	90	30	20
6	None	8	140	15	81
7	toluene	8	140	15	75
8	none	8	140	30	98
9	toluene	8	140	30	89
10	toluene	2	140	15	15
11	toluene	2	140	30	45
12	toluene	4	140	15	50
13	toluene	4	140	30	71
14	none	8	160	10	89
15	toluene	13	140	15	98
16	none	13	140	15	92
17	none	16	120	30	98
18	xylene	8	140	30	96

[a] Reactions were carried out using Biotage Initiator™ microwave synthesizer in a sealed microwave reaction vial using 1 mmol of amine and 1.2 mmol of aldehyde.

minutes (entries 6 and 7) to 30 minutes (entries 8 and 9) provided the optimal set of reaction conditions and the best overall yields. Entries 10 - 17 illustrate the subtle interplay between equivalents of acid, temperature and time. Xylene was shown to be a suitable solvent for the reaction as well (entry 18).

A number of protocols were investigated for the oxidation of the tetrahydroisoquinolines to their corresponding isoquinoline derivatives including those involving the use of IBX[14] and sulfur.[15] In our hands, the method described by Buchs and Brossi[16,17] involving dehydrogenation using Pd/C showed itself to be the most general



where **1**: R_1=R_2=OMe; R_3=R_4=R_5=H;
2: R_1=R_2=OMe; R_3=R_4=H; R_5=F;
3: R_1=R_2=OMe; R_3=R_5=H; R_4=OMe;
4: R_1=R_2=R_4=R_5=OMe; R_3=H;
5: R_1=R_2=OMe; R_3=R_4=H; R_5=CN;
6: R_1=R_2=R_5=OMe; R_3=R_4=H;
7: R_1=R_2=OMe; R_3=R_4=H; R_5=Me;
8: R_1=OMe; R_2=R_3=R_4=R_5=H;
9 R_1=R_2=OMe; R_3=Me; R_4=R_5=H

Conditions: (i) 8 eq. TFA, toluene, MW 140 °C, 30 min.; (ii) 10% Pd/C, toluene, reflux, 2-6 h

Scheme 4.1. Synthesis of Isoquinolines Utilizing a Microwave-assisted Pictet-Spengler reaction.

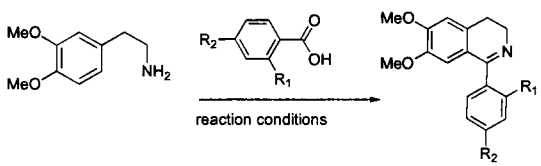
and gave the best yields. For example, 1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4a**) was dehydrogenated using Pd/C in toluene to give 98% of the corresponding isoquinoline (**4b**). With the microwave-assisted Pictet-Spengler and oxidation reactions in hand, sequential application of the two protocols (without isolation

of the intermediate tetrahydroisoquinoline) was applied to the parallel synthesis of a small collection of isoquinolines (Scheme 4.1). The overall yields after both steps are shown and ranged from fair to very good. It should be noted that a number of commercially-available microwave systems offer the ability to process samples in either a serial or parallel fashion enabling rapid production of compound libraries.

The development of a microwave-assisted Bischler-Napieralski reaction protocol was then undertaken. Ideally, a reaction wherein the amide formation and cyclization to the 3,4-dihydroquinoline occurs in "one-pot" would be ideal. Using 2-(3,4-dimethoxyphenyl)ethylamine and $POCl_3$, a series of exploratory reactions were carried out so as to quickly ascertain the effects of solvent, temperature and time (see Table 4.2). Optimal conditions involved treating the amine and carboxylic acid with $POCl_3$ in toluene and irradiating the mixture in a microwave at 140 °C for 30 minutes. It is worth noting that carrying out the reaction above using conventional heating required upwards of 8 hours for complete consumption of starting materials. Oxidation of the 3,4-dihydroisoquinoline derivatives to their corresponding isoquinoline derivatives using dehydrogenation with Pd/C in toluene (as used for the oxidation of tetrahydroisoquinolines) was slow and did not give full conversion of starting material. Yields obtained after 72 hours of refluxing in toluene with Pd/C ranged between 40-60%. Comparable yields were obtained when 3,4-dihydroisoquinolines derivatives were

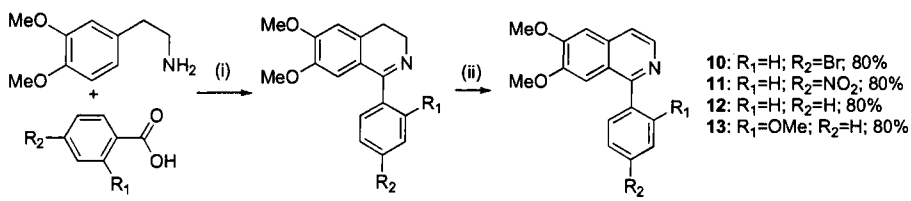
heated in the presence of IBX[14] in DMSO at 45 °C for 24 hours. While disappointing, the results were not unprecedented. A review of the relevant literature shows that these oxidations often require forcing conditions such as Pd/C in decaline at 230 °C[18] or MnO_2 in refluxing benzene.[19] The best results were obtained when the dehydrogenation was carried out with Pd/C in the absence of solvent and heating at 150 °C for 30 minutes.[20] For example, when 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline (Table 4.2, entry 18) was oxidized using this protocol, 97% of the corresponding isoquinoline was isolated.

Table 4.2. Optimization of Reaction Parameters for the Microwave-assisted Bischler-Napieralski reaction[a]



entry	R^1	R^2	Solvent	eq. of $POCl_3$	temp (°C)	time (min.)	yield (%)
1	H	H	MeCN	4	120	30	23
2	H	H	MeCN	4	140	30	50
3	H	H	Toluene	4	140	30	97
4	H	NO_2	MeCN	4	120	30	45
5	H	NO_2	MeCN	4	140	30	60
6	H	NO_2	Toluene	4	140	30	85
7	H	Cl	MeCN	4	120	30	31
8	H	Cl	MeCN	4	140	30	74
9	H	Cl	Toluene	4	140	30	79
10	H	Br	Toluene	4	140	30	81
11	OMe	H	Toluene	4	140	30	56
12	H	Br	Toluene	6	140	30	82
13	H	Br	Toluene	8	140	30	89
14	H	Br	Toluene	10	140	30	89
15	H	Cl	Toluene	10	140	30	79
16	H	NO_2	Toluene	10	140	30	85
17	OMe	H	toluene	10	140	30	90
18	H	H	toluene	10	140	30	89

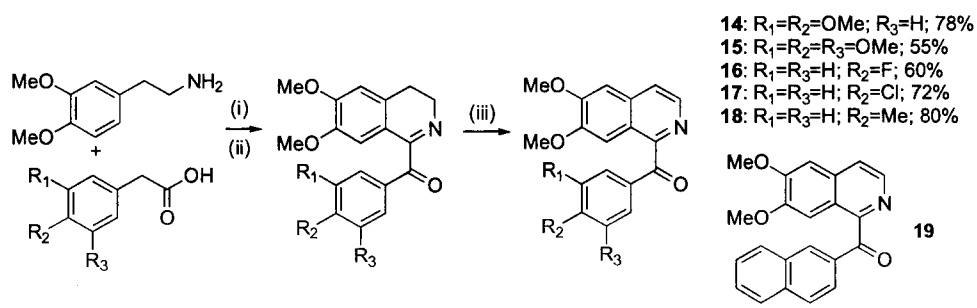
[a] Reactions were carried out using Biotage Initiator™ microwave synthesizer in a sealed microwave reaction vial using 1 mmol of amine and 1 mmol of carboxylic acid.



Conditions: (i) $POCl_3$, toluene, MW 140 °C, 30 mins.; (ii) Pd/C, 150 °C, 30 min

Scheme 4.2. Synthesis of Isoquinolines Utilizing a Microwave-assisted Bischler-Napieralski reaction.

With the microwave-assisted Bischler-Napieralski and oxidation protocols in hand, the two reactions were applied to the synthesis of a small collection of isoquinolines (Scheme 4.2, with overall yields reported). When the reaction was carried out using aryl acetic acid derivatives, however, facile air oxidation of the benzylic methylene resulted in the keto-imine product **14-19**. Oxidation of these compounds allows for the series of acylisoquinolines shown in Scheme 4.3.



Conditions: (i) $POCl_3$, toluene, MW 140 °C, 30 min.; (ii) air; (iii) Pd/C, 150 °C, 30 min.

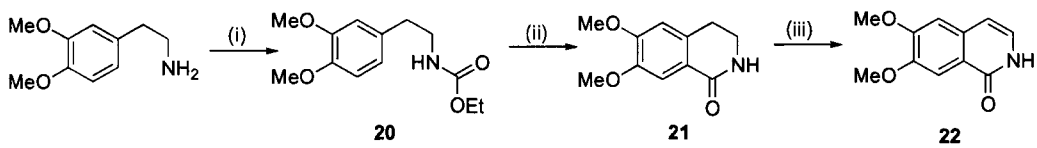
Scheme 4.3. Microwave-assisted Bischler-Napieralski reaction with aryl acetic acid derivatives.

With the cyclization and oxidations procedures developed, the feasibility of the nitroalkene approach to substituted β-arylethylamines (route a) was examined. We found

that the requisite nitroalkenes could be generated *via* an ultrasound-promoted, Henry condensation[21] and that there was ample literature precedence for conjugate addition onto the nitroalkenes.[22-24] While useful for the synthesis of individual isoquinoline derivatives, in practice, this chemistry is less than ideal for the preparation of large libraries of substituted isoquinolines mainly due to issues surrounding the conjugate addition onto the nitroalkenes; specifically, the relatively narrow scope of useful functionality that can be introduced at the C4-position using this approach. In addition, while oxidation of either the tetrahydroisoquinolines or the 3,4-dihydroisoquinoline could be achieved in excellent yields, the protocol using Pd/C does not lend itself to library synthesis. An alternate strategy (Figure 4.1, route b) using an isoquinolin-1(*2H*)-one scaffold as a starting point was, therefore, examined. This approach proved itself to be more practical and also takes advantage of the Pd-catalyzed cross-coupling chemistry developed in our laboratory.[25-29]

6,7-Dimethoxyisoquinolone (**22**) was identified as a suitable building block for our initial studies. While a number of syntheses to the isoquinolin-1(*2H*)-one system have been reported,[30,31] a particularly attractive route takes advantage of chemistry developed by Chern and Li[32] and the dehydrogenation protocol developed above. As illustrated in Scheme 4.4, treatment of 2-(3,4-dimethoxyphenyl)ethylamine with ethyl chloroformate provided carbamate **20** which could be cyclized smoothly in the presence of P_2O_5, $POCl_3$ and hexamethyldisiloxane using microwave irradiation to give 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**21**) in 96% yield. Finally, use of Pd/C allowed for oxidation to the desired **22** in 98% yield. Given the facile access to 3,4-

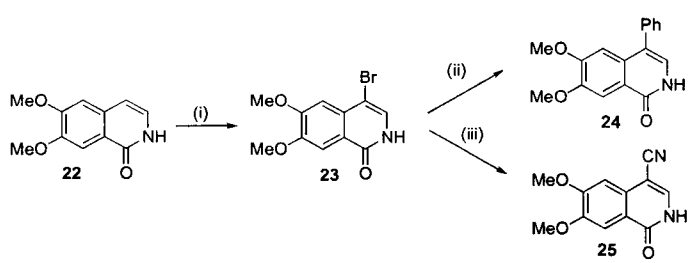
dihydroisoquinolines demonstrated by Wang[33] and others, the approach should be applicable for the preparation of other isoquinolin-1(*2H*)-one scaffolds.



Conditions: (i) ethyl chloroformate, TEA, DCM (96%); (ii) P_2O_5, $POCl_3$, hexamethyldisiloxane, MW 150 °C, 40 min. (96%); (iii) Pd/C, 150 °C, 30 min. (98%).

Scheme 4.4: Synthetic route to 6,7-Dimethoxyisoquinolone.

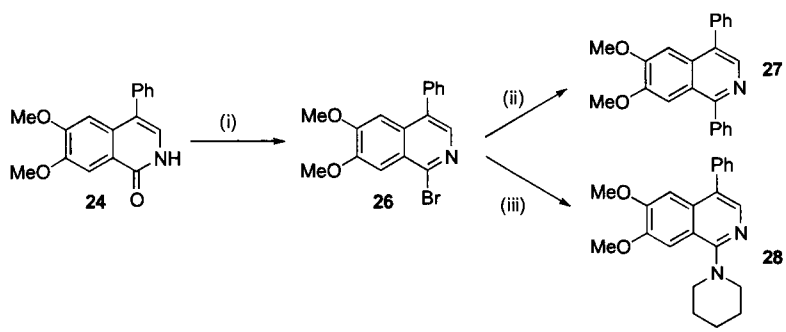
Protocols allowing for rapid and efficient activation and functionalization of the heterocycle were then explored. As presented in Scheme 4,5, bromination of **22** provides the vinyl bromide **23**, a substrate capable of undergoing a variety of reactions permitting derivatization at C4. Palladium-mediated cross-coupling chemistry, for example, allowed for the arylation of compound **23** in 98% yield using a Suzuki reaction to give **24** using a catalytic system incorporating the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph) ligand.[26-29,34] Alternatively, treatment of **23** with CuCN in 1-methylpyrrolidinone provided the 4-nitrile derivative (**25**) in 66 % yield.



Conditions: (i) Br_2, AcOH (96%); (ii) Ph-$B(OH)_2$, Pd_2dba_3, PA-Ph, Cs_2CO_3, toluene, MW 90 °C, 30 min. (98%); (iii) CuCN, 1-methylpyrrolidinone, MW 200 °C, 40 min (86%)

Scheme 4.5: Access to C4-substituted Isoquinolones.

With functionality introduced at C4, activation of the C1 position was readily achieved *via* conversion to a bromo-imine moiety.

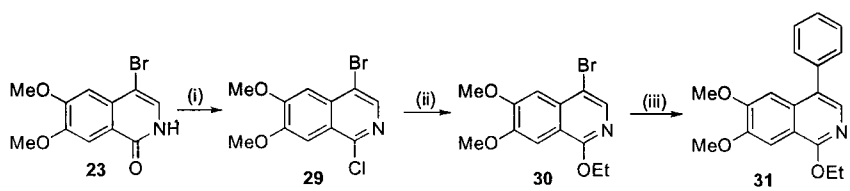


Conditions: (i) 3 eq. $POBr_3$, DCM, MW 120 °C, 30 min. (98%); (ii) Ph-$B(OH)_2$, Pd_2dba_3, PA-Ph, Cs_2CO_3, toluene, MW 90 °C, 30 min. (95%); (iii) piperidine, NaO^tBu, toluene, MW 180 °C, 30 min. (64%)

Scheme 4.6. C1-derivatization of 6,7-dimethoxy-4-phenylisoquinolin-1(2*H*)-one.

Treatment of 6,7-dimethoxy-4-phenylisoquinolin-1(2*H*)-one with $POBr_3$ in DCM using microwave irradiation (Scheme 4.6) yielded **26** in 98% yield. The bromo-imine then serves a substrate for a number of reactions allowing for arylation (to give **27** *via* a Suzuki reaction in 95% yield) and amination (to give **28** in 66% yield).

Alternatively, chlorination of **23** using $POCl_3$ gives **29** (Scheme 4.7).[35] Taking

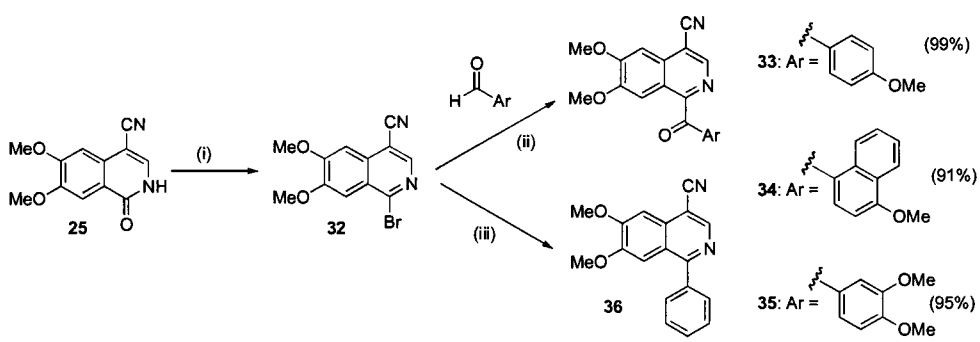


Conditions: (i) $POCl_3$, MW, 100 °C, 30 min. (98%); (ii) NaOEt/EtOH, MW, 90 °C, 30 min (87%); (iii) Ph-$B(OH)_2$, Pd_2dba_3, PA-Ph, Cs_2CO_3, toluene, MW 100 °C, 30 min. (93%)

Scheme 4.7. C1 and C4 derivatization of 4-bromo-6,7-dimethoxyisoquinolin-1(2H)-one.

advantage of the chemoselectivity at the two halogen sites allows for nucleophilic reaction at C1 (for example, treatment with ethoxide to give **30**) followed by cross-coupling at C4 to give **31**.

Another interesting route for derivatization at C1 involves nucleophilic aroylation[36,37] to give acylisoquinolines. As presented in Scheme 4.8, bromination of **25** in anisole using microwave irradiation allowed for the preparation of bromo-imine **32** in 89% yield. This 1-bromoisoquinoline substrate could then be coupled with commercially-available aromatic aldehydes in the presence of 1,3- dimethylimidazolium iodide to generate compounds **33**, **34** and **35** in excellent yields. Finally, **32** could be used as a partner in a Suzuki coupling to give systems such as **36**.



Conditions: (i) 3 eq. $POBr_3$, DCM, MW 150 °C, 30 min. (89%); (ii) 1,3-dimethylimidazolium iodide, NaH, DMF, room temperature, 1-2h; (iii) Ph-$B(OH)_2$, Pd_2dba_3, PA-Ph, Cs_2CO_3, MW 90 °C, 30 min.

Scheme 4.8. C1 Derivatization of 6,7-dimethoxy-1-oxo-1,2-dihydroisoquinoline-4-carbonitrile.

4.1.5 Conclusions

Microwave-assisted variants of the Bischler-Napieralski or Pictet-Spengler reaction were developed and used in the production of isoquinolines. An alternate

strategy presented involving the preparation and activation of isoquinolin-1(*2H*)-ones, however, is clearly a more practical, rapid and efficient route to substituted isoquinoline libraries. Furthermore, the chemistry developed for derivatization allows for the installation of a diverse collection of vectors at the C1 and C4 position of the isoquinoline core and, therefore, a library capable of a more comprehensive exploration of chemical space. Work is currently underway to further determine the scope of the approach and prepare larger libraries of substituted isoquinolines using this chemistry.

4.1.6 Experimental Section.

General procedure for the microwave-assisted Pictet-Spengler synthesis of 1,2,3,4-tetrahydroisoquinolines. Amine (1 mmol), aldehyde (1.2 mmol), TFA (8 mmol) and toluene (1 mL), were placed in microwave vial, capped and irradiated in a microwave for 30 minutes at 140°C. The solvent was then evaporated under reduced pressure and the crude reaction mixture suspended in cold water (3 mL), treated with aqueous NaOH (2 M) to pH 8 and extracted with CH_2Cl_2 (3 x 6 mL). The combined organic extracts was dried over Na_2SO_4, concentrated and purified by flash column chromatography on silica gel using 3 - 5% MeOH in dichloromethane to afford the corresponding tetrahydroisoquinoline.

1,2,3,4-tetrahydro-6,7-dimethoxy-1-phenylisoquinoline (1a). Using 3,4-dimethoxyphenethylamine (166 μL, 1 mmol), benzaldehyde (100 μL, 1.2 mmol) and the general procedure, **1a** was obtained in 98% yield (264 mg, 0.98 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27-7.36 (m, 5H), 6.64 (s, 1H), 6.25 (s, 1H), 5.06 (s, 1H),

3.88 (s, 3H) 3.64 (s, 3H), 2.77-3.25 (m, 4H), 1.80 (b, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 147.6, 147.1, 144.6, 129.6, 128.9, 128.4, 127.6, 127.4, 111.4, 110.9, 61.3, 55.8, 41.7, 29.2; HRMS (CI): calculated for $C_{17}H_{20}NO_2$ (M+1) 270.1495, found 270.1495.

1-(4-fluorophenyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (2a).[1] Using 3,4-dimethoxyphenethylamine (166 μL, 1 mmol), 4-fluorobenzaldehyde (128 μL, 1.2 mmol) and the general procedure yielded 1-(4-flurophenyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline in 97% (278.5 mg, 0.97 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.19-7.22 (m, 2H), 6.93-7.05 (m, 2H), 6.63 (s, 1H), 6.19 (s, 1H), 5.06 (s, 1H), 3.87 (s, 3H), 3.64 (s, 3H), 2.73-3.20 (m, 4H); δ ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.3 (d, J = 246.2 Hz), 148.0, 147.3, 139.2, 130.7 (d, J = 7.9 Hz), 128.6, 127.1, 115.3 (d, J = 21.3 Hz), 111.3, 110.7, 60.4, 55.9, 41.5, 28.5; HRMS (CI): calculated for $C_{17}H_{19}FNO_2$ (M+1) 288.1355, found 289.1428.

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3-methoxyphenyl)isoquinoline (3a).[2] Using 3,4-dimethoxyphenethylamine (166 μL, 1 mmol), 3-methoxybenzaldehyde (132 μL, 1.2 mmol) and the general procedure described yielded 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3-methoxyphenyl)isoquinoline in 97 % yield (290.2 mmol, 0.97 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.20-7.24 (m, 2H), 6.80-6.80 (m, 2H), 6.62 (s,1H), 6.27 (s, 1H), 5.04 (s, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.65 (s, 3H), 2.73-3.22 (m, 4H), ^{13}C ($CDCl_3$, 50 MHz), 159.7, 147.8, 147.2, 145.1, 129.4, 128.5, 127.1, 121.5, 114.5, 113.3, 111.3, 110.8, 110.2, 61.0, 55.9, 55.3, 41.4, 28.6; HRMS (CI): calculated for $C_{18}H_{22}NO_3$ (M+1) 300.1555, found 300.1591.

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)isoquinoline (4a).[3] Using 3,4-dimethoxyphenethylamine (166 μL, 1 mmol), 3,4-dimethoxybenzaldehyde (166.2 mg, 1.2 mmol) and the general procedure described yielded 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)isoquinoline in 65% yield (214 mg 0.65 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.84 (s, 3H), 6.62 (s, 1H), 6.27 (s, 1H), 4.98 (s, 1H), 3.88 (s, 6H), 3.83 (s, 3H), 3.65 (s, 3H), 2.68-3.27, (m, 4H), 1.77, (b, 1H); ^{13}C (CDCl3, 50 MHz): δ 149.1, 148.5, 147.7, 147.1, 137.5, 130.3, 127.7, 121.3, 111.9, 111.5, 110.8, 61.6, 56.0, 42.4, 29.4; HRMS (CI): calculated for $C_{19}H_{24}NO_4$ (M+1) 330.1661, found 330.1687.

4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)benzonitrile (5a) was prepared and used without purification in the synthesis of 4-(6,7-dimethoxyisoquinolin-1-yl)benzonitrile (**5b**, see below).

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methoxyphenyl)isoquinoline (6a).[4] Using 3,4-dimethoxyphenethylamine (166 μL, 1 mmol), 4-methoxybenzaldehyde (132 μL, 1.2 mmol) and the general procedure described yielded 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methoxyphenyl)isoquinoline in 88% yield (263.3 mg, 0.88 mmol) and showed: 1H NMR (CDCl3, 200 MHz): δ 7.26 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.62 (s, 1H), 6.25 (s, 1H), 5.04 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 2.70-3.21 (m, 4H), 2.59 (b, 1H); ^{13}C NMR (CDCl3, 50 MHz): δ 159.0, 147.8, 147.2, 136.2, 130.4, 129.7, 127.9, 113.8, 111.4, 110.9, 60.9, 56.1, 55.9, 55.3, 41.6, 28.9; HRMS (CI): calculated for $C_{18}H_{22}NO_3$ (M+1) 300.1555, found 300.1591.

1,2,3,4-tetrahydro-6,7-dimethoxy-1-p-tolylisoquinoline (7a).[5] Using 3,4-dimethoxyphenethylamine (166.0 μL, 1 mmol), 4-methylbenzaldehyde (146 μL, 1.2 mmol) and the general procedure described yielded 1,2,3,4-tetrahydro-6,7-dimethoxy-1-*p*-tolylisoquinoline (252 mg, 0.89 mmol) in 89% yield and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.16 (s, 4H), 6.63 (s, 1H), 6.23 (s,1H), 5.02 (s,1H) 3.87 (s, 3H) 3.64 (s, 3H), 2.76-3.20 (m, 4H), 2.34 (s, 3H), 1.72 (b, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 147.6, 147.0, 141.7, 137.0, 129.8, 129.1, 128.8, 127.6, 111.3, 110.9, 61.0, 55.9, 41.7, 29.2, 21.0; HRMS (CI): calculated for $C_{18}H_{22}NO_2$ (M+1) 284.1606, found 284.1596.

1,2,3,4-tetrahydro-6-methoxy-1-phenyl-isoquinoline (8a).[6] Using 2-(3-methoxyphenyl)ethanamine (140 μL, 1 mmol), benzaldehyde (100 μL, 1.2 mmol) and the general procedure described yielded 1,2,3,4-tetrahydro-6-methoxy-1-phenyl-isoquinoline in 94% yield (224.8 mg, 0.94 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.22-7.34 (m, 5H), 6.62-6.69 (m, 3H), 5.04 (s, 1H), 3.78 (s, 3H), 2.81-3.26 (m, 4H), 1.86 (s, 1H); ^{13}C NMR (CDCl3, 50 MHz): δ 157.9, 145.2, 136.8, 130.7, 129.3, 129.0, 128.5, 127.4, 113.4, 112.1, 61.7, 55.3, 42.3, 30.2; HRMS (CI): calculated for $C_{16}H_{18}NO$ (M+1) 240.1388, found 240.1381.

1,2,3,4-tetrahydro-6,7-dimethoxy-4-methyl-1-phenylisoquinoline (9a).[7] Using 2-(3,4-dimethoxyphenyl)propan-1-amine (195.3 mg, 1 mmol), benzaldehyde (100 μL, 1.2 mmol) and the general procedure described yielded 1,2,3,4-tetrahydro-6,7-dimethoxy-4-methyl-1-phenylisoquinoline in yield 90% (255 mg, 0.9 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.20-7.32 (m, 4H), 6.77 (s, 1H), 6.22 (s, 1H), 5.03 (s, 1H), 3.89 (s,

3H) 3.62 (s, 3H), 3.20-3.26 (m, 1H), 2.99-3.02 (m, 1H), 2.66-2.76 (m, 1H), 2.64 (b, 1H) 1.30 (d, J = 4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 147.9, 147.0, 144.6, 133.1, 129.5 129.1, 128.9, 128.5, 127.5, 110.9, 110.2, 61.8, 56.0, 55.9, 49.5, 32.2, 20.2; HRMS (CI): calculated for $C_{18}H_{22}NO_2$ (M+1) 284.1651, found 284.1645.

General procedure for the synthesis of isoquinolines via a microwave-assisted Pictet-Spengler / oxidation method. Amine (0.5 mmol), aldehyde (0.6 mmol), TFA (4 mmol) and toluene (1 mL) were placed in microwave vial, capped and irradiated in a microwave for 30 minutes at 140°C. Additional toluene (5 mL) was added and the reaction mixture transferred to a vial containing 10 % Pd/C (70.0 mg) in toluene (4 mL). The mixture was left to reflux for 2h - 12h at which time the Pd/C was filtered off and the Pd/C residue washed with hot toluene (20 mL). The solvent was evaporated under a reduced pressure and the residue purified by flash column chromatography on silica gel using 2 - 5% MeOH in dichloromethane to obtain the isoquinoline derivatives. ***6,7-Dimethoxy-1-phenylisoquinoline (1b).*** Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), benzaldehyde (50 μL, 0.6 mmol) and the general procedure described, **1b** was obtained in 74% yield (98 mg, 0.37 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.49 (d, J = 5.6 Hz, 1H), 7.71 (dd, J = 5.8 & 2 Hz, 2H), 7.50-7.54 (m, 4H), 7.38 (s, 1H), 7.13 (s, 1H), 4.05 (s, 3H), 3.87 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.5, 152.8, 150.1, 141.6, 140.2, 133.9, 129.7, 128.6, 122.7, 118.9, 105.7, 105.1, 56.2, 56.0; HRMS (CI): calculated for $C_{17}H_{16}NO_2$ (M+1) 266.1136, found 266.1103.

1-(4-fluorophenyl)-6,7-dimethoxyisoquinoline (2b) Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 4-fluorobenzaldehyde (64 μL, 0.6 mmol) and the general procedure yielded 1-(4-fluorophenyl)-6,7-dimethoxyisoquinoline in 88% yield (124.6 mg, 0.44 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.45 (d, J = 5.6 Hz, 1H) 7.65-7.72 (m, 2H), 7.49 (d, J = 5.6 Hz, 1H), 7.29 (s, 1H), 7.21 (s, 1H), 7.17 (s, 1H), 7.12 (s, 1H), 4.04 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 163.0 (d, J = 247.7 Hz), 157.3, 152.8, 150.3, 141.4, 136.2, 133.9, 131.5 (d, J = 8.1 Hz), 122.6, 119.0, 115.6 (d, J = 21.5 Hz) 105.3, 105.2, 56.2, 56.0; HRMS (CI): calculated for $C_{17}H_{15}FNO_2$ (M+1) 284.1042, found 284.1097.

6,7-dimethoxy-1-(3-methoxyphenyl)isoquinolines (3b) Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 3-methoxybenzaldehyde (73 μL, 0.6 mmol) and the general procedure yielded 6,7-dimethoxy-1-(3-methoxyphenyl)isoquinoline in 90% yield (0.45 mmol, 132.8 mg) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.47 (d, J = 5.6 Hz, 1H), 7.40-7.51 (m, 3H), 7.25-7.29 (m, 3H), 6.99 (m, 1H), 4.04 (s, 3H), 3.87 (s, 3H) 3.84 (s, 3H); ^{13}C ($CDCl_3$, 50 MHz): δ 159.7, 158.0, 152.6, 149.9, 141.2, 133.7, 129.3, 122.4, 122.0, 118.8, 114.7, 114.6, 105.5, 104.9, 56.0, 55.9, 55.3; HRMS (CI): calculated for $C_{18}H_{18}NO_3$ (M+1) 296.1242, found 296.1239.

6,7-dimethoxy-1-(3,4-dimethoxyphenyl)isoquinolines (4b).[8] Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 3,4-dimethoxybenzaldehyde (83 mg, 0.6 mmol) and the general procedure yielded 6,7-dimethoxy-1-(3,4-

dimethoxyphenyl)isoquinoline in 61% yield (0.31 mmol, 99.2 mg) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.46 (d, J = 5.6 Hz, 1H δ): δ 7.45-7.50 (m, 2H), 7.28-7.29 (m, 2H), 7.12 (s, 1H), 7.02 (d, 8.8 Hz, 1H), 4.05 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.1, 152.7, 150.1, 149.4, 149.1, 141.4, 134.0, 132.9, 122.4, 118.6, 113.0, 111.0, 105.9, 105.1, 56.1; HRMS (CI): calculated for $C_{19}H_{20}NO_4$ (M+1) 326.1348, found 326.1396.

4-(6,7-dimethoxyisoquinolin-1-yl)benzonitrile (5b). 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 4-formylbenzonitrile (78.6 mg, 0.6 mmol) and the general procedure yielded 4-(6,7-dimethoxyisoquinolin-1-yl)benzonitrile in 24% yield (34.8 mg, 0.12 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.51 (d, J = 5.6 Hz, 1H), 7.84 (s, 4H), 7.56 (d, J = 5.6 Hz, 1H), 7.21 (s, 1H), 7.16, (s, 1H), 4.06, (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 156.1, 153.1, 150.7, 144.8, 141.6, 134.1, 132.5, 130.6, 122.4, 119.8, 118.9, 112.4, 105.3, 104.5, 56.3, 56.1; HRMS (CI): calculated for $C_{18}H_{15}N_2O_2$ (M+1) 291.1081, found 291.1108.

6,7-dimethoxy-1-(4-methoxyphenyl)isoquinoline (6b).[9] Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 4-methoxybenzaldehyde (66 μL, 0.6 mmol) and the general procedure yielded 6,7-dimethoxy-1-(4-methoxyphenyl)isoquinoline in 67% yield (98.9 mg, 0.34 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.46 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 5.6 Hz, 2H), 7.45 (d, J = 5.6 Hz, 1H), 7.41 (s, 1H), 7.03-7.12 (m, 3H), 4.05 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 156.9, 158.1, 152.6, 150.0, 141.5, 133.9, 132.7, 131.0, 122.6,

118.5, 113.9, 105.8, 105.1, 56.2, 56.0, 55.5; HRMS (CI): calculated for $C_{18}H_{18}NO_3$ (M+1) 296.1242 found, 296.1247.

6,7-dimethoxy-1-p-tolyisoquinoline (7b). Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 4-methylbenzaldehyde (73.0 μL, 0.6 mmol) and the general procedure yielded 6,7-dimethoxy-1-*p*-tolyisoquinoline in 78% yield (108.9 mg, 0.39 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.47 (d, J = 5.6 Hz, 1H,), 7.61 (d, J = 8.0 Hz, 2H), 7.32-7.50 (m, 4H), 7.13 (s, 1H), 4.01 (s, 3H), 3.88 (s, 3H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.3, 152.6, 149.9, 141.3, 138.2, 137.1, 133.1, 129.5, 129.1, 122.5, 118.5, 105.7, 105.0, 56.0, 55.9, 21.3; HRMS (CI): calculated for $C_{18}H_{18}NO_2$ (M+1) 280.1374, found 280.1303.

6-methoxy-1-phenylisoquinoline (8b). Using 2(3-methoxyphenyl)ethanamine (70 μL, 0.5 mmol), benzaldehyde (50.0 μL, 0.6 mmol) and the general procedure yielded 6-methoxy-1-phenylisoquinoline in 89% yield (104.5 mg, 0.45 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.55 (d, J = 5.8 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.66-7.72 (m, 2H), 7.51-7.57 (m, 3H), 7.15-7.20 (m, 3H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ 160.7, 160.3, 143.0, 139.8, 139.1, 130.0, 129.6, 128.7, 128.5, 122.5, 120.1, 119.4, 104.6, 55.6; HRMS (CI): calculated for $C_{16}H_{14}NO$ (M+1) 236.1112, found 236.1161.

6,7-dimethoxy-4-methyl-1-phenylisoquinoline (9b).[10] Using 2-(3,4-dimethoxyphenyl)propan-1-amine (97.5 mg, 0.5 mmol), benzaldehyde (50.0 μL, 0.6 mmol) and the general procedure yielded 6,7-dimethoxy-4-methyl-1-phenylisoquinoline 56 % yield (78 mg, 0.28 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.36 (s, 1H),

7.68 (d, J = 6.4 Hz, 2H), 7.49-7.53 (m, 3H), 7.39 (s, 1H), 7.17 (s, 1H), 4.08 (s, 3H), 3.86 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.1, 152.5, 149.7, 141.6, 140.4, 133.0, 129.8, 128.5, 128.4, 125.3, 122.1, 106.3, 102.0, 56.2, 56.0, 16.5; HRMS (CI): calculated for $C_{18}H_{18}NO_2$ (M+1) 280.1338 found, 280.1341.

General procedure for the microwave-assisted Bischler-Napieralski synthesis of 3,4-dihydroisoquinolines. Amine (1 mmol), carboxylic acid (1 mmol), $POCl_3$ (4 mmol) and toluene (2 mL) were placed in microwave vial, capped and irradiated in a microwave for 30 minutes at 140°C. The solvent was then evaporated under reduced pressure and the crude reaction mixture suspended in cold water (3 mL), treated with aqueous NaOH (2 M) to pH 8 and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts was dried over Na_2SO_4, concentrated and purified by flash column chromatography on silica gel using 3 - 5% MeOH in dichloromethane to afford the corresponding 3,4-dihydroisoquinolines. **3,4-dihydro-6,7-dimethoxy-1-phenylisoquinoline (Table 4. 2, Entry 3).** Using 3,4-dimethoxyphenethylamine (166 μL, 1 mmol), benzoic acid (122 mg, 1 mmol) and the general procedure described, 3,4-dihydro-6,7-dimethoxy-1-phenylisoquinoline was obtained in 97% yield (259.0 mg, 0.97 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.58-7.63 (m, 2H), 7.41-7.45 (m, 3H), 6.80 (s, 1H), 6.78 (s, 1H), 3.95 (s, 3H), 3.84 (t, J = 7 Hz, 2H), 3.73 (s, 1H), 2.74 (t, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.8, 151.0, 147.1, 139.1, 132.6, 129.4, 128.8, 128.2, 121.6, 111.7, 110.3, 56.2, 56.1, 47.6, 26.0; HRMS (CI): calculated for $C_{17}H_{18}NO_2$ (M+1) 268.1338, found 268.1323.

3,4-dihydro-6,7-dimethoxy-1-(4-nitrophenyl)isoquinoline (Table 4.2, Entry 6).[11] Using 3,4-dimethoxyphenethylamine (166.0 μL, 1 mmol), 4-nitrobenzoic acid (167.1 mg, 1 mmol) afforded 3,4-dihydro-6,7-dimethoxy-1-(4-nitrophenyl)isoquinoline in 85% yield (265.3 mg, 0.85 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.30 (d, J = 5.2 Hz, 2H), 7.79 (d, J = 5.2 Hz, 2H), 6.82 (s, 1H), 6.65 (s, 1H), 3.97 (s, 3H), 3.86, (t, J = 7 Hz, 2H), 3.71 (s, 3H), 2.77 (t, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 165.1, 151.4, 148.4, 147.4, 145.4, 132.6, 129.7, 123.5, 120.7, 110.7, 110.5, 56.2, 56.1, 48.0, 25.8; HRMS (CI): calculated for $C_{17}H_{17}N_2O_4$ (M+1) 313.1188, found 313.1191.

1-(4-chlorophenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (Table 4.2, Entry 9).[12] Using 3,4-dimethoxyphenethylamine (166.0 μL, 1 mmol), 4-chlorobenzoic acid (156.6 mg, 1 mmol) afforded 1-(4-chlorophenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline in 79% yield (237.9 mg, 0.79 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.56 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.78 (s, 1H), 6.73 (s, 1H), 3.95 (s, 3H), 3.78 (t, J = 7.5 Hz, 2H), 3.74 (s, 3H); 2.73 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.8, 151.1, 147.2, 137.6, 135.4, 132.7, 130.2, 128.4, 121.2, 111.2, 110.4, 56.2, 56.1, 47.7, 26.0; HRMS (CI): calculated for $C_{17}H_{17}ClNO_2$ (M+1) 302.0903, found 302.0864.

1-(4-bromophenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline, (Table 4.2, Entry 10).[13] Using 3,4-dimethoxyphenethylamine (166.0 μL, 1 mmol), 4-bromobenzoic acid (201 mg, 1 mmol) gave 1-(4-bromophenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline in 81% yield (279.5 mg, 0.81 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.56 (q, J = 4.4 Hz, 4H), 6.78 (s, 1H), 6.73 (s, 1H), 3.95 (s, 3H), 3.78 (t, J = 7 Hz, 2 H), 3.74 (s, 3H), 2.72 (t,

J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.9, 151.2, 147.3, 138.2, 132.7, 131.5, 130.5, 123.7, 121.3, 111.2, 110.4, 56.3, 56.2, 47.8, 26.0; HRMS (CI): calculated for $C_{17}H_{17}BrNO_2$ (M+1) 346.0398, found 346.0288.

3,4-dihydro-6,7-dimethoxy-1-(2-methoxyphenyl)isoquinolines (Table 4.2, Entry 17).[13] Using 3,4-dimethoxyphenethylamine (166.0 μL, 1 mmol), 2-methoxybenzoic acid (152.2 mg, 1 mmol) gave 3,4-dihydro-6,7-dimethoxy-1-(2-methoxyphenyl)isoquinoline in 90% yield (267.4 mg, 0.9 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.35-7.43 (m, 2H), 6.92-7.07 (m, 2H), 6.73 (s, 1H), 6.51 (s, 1H), 3.65 - 3.92 (m, 11H), 2.78 (t, J = 7 Hz 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 165.8, 157.2, 151.0, 147.3, 131.0, 130.5, 130.3, 128.6, 122.7, 120.9, 111.1, 110.1, 56.2, 56.1, 55.6, 47.7, 25.8; HRMS (CI): calculated for $C_{18}H_{20}NO_3$ (M+1) 298.1398, found 298.1398.

General procedure for the synthesis of isoquinolines via a microwave-assisted Bischler-Napieralski reaction / oxidation method (Scheme 4.2). Amine (0.5 mmol), carboxylic acid (0.5 mmol), $POCl_3$ (2 mmol) and toluene (2 mL) were placed in microwave vial, capped and irradiated in a microwave for 30 minutes at 140 °C. The solvent was then evaporated under reduced pressure and the crude reaction mixture suspended in cold water (3 mL), treated with aqueous NaOH (2 M) to pH 8 and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts was dried over Na_2SO_4 and concentrated under a reduced pressure. 10% Pd/C (70 mg) was then added to the residue, mixed together with a spatula and heated to 150°C for 30 minutes. The reaction mixture was cooled to room temperature and suspended in dichloromethane (20 mL). Pd/C was removed *via* filtration

and the filtrate concentrated before purification by flash column chromatography on silica gel using 2 - 3% MeOH in dichloromethane.

1-(4-bromophenyl)-6,7-dimethoxyisoquinoline (10). Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 4-bromobenzoic acid (100 mg, 0.5 mmol) and the general procedure described, **10** was obtained in 80% yield (137 mg, 0.4 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.46 (d, J = 5.6 Hz, 1H), 7.50-7.69 (m, 5H), 7.29 (s, 1H), 7.13 (s, 1H), 4.05 (s, 3H), 3.88 (s, 3H); ^{13}C ($CDCl_3$, 50 MHz) δ 157.1, 152.9, 150.4, 141.5, 139.1, 134.0, 131.8, 131.4, 122.9, 122.5, 119.2, 105.2, 56.3, 56.1; HRMS (CI): calculated for $C_{17}H_{15}BrNO_2$ (M+1) 344.0187 found, 344.0208.

6,7-dimethoxy-1-(4-nitrophenyl)isoquinoline (11).[14] Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 4-nitrobenzoic acid (83.6 mg, 0.5 mmol) afforded 6,7-dimethoxy-1-(4-nitrophenyl)isoquinoline in 80% yield (124.0 mg, 0.4 mmol) and showed ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.51 (d, J = 5.4 Hz, 1H), 8.41 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 5.4 Hz, 1H), 7.21 (s, 1H), 7.16 (s, 1H), 4.07 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.7, 153.2, 150.8, 148.0, 146.6, 141.6, 134.1, 130.8, 128.5, 123.9, 119.9, 105.3, 104.4, 56.3, 56.1; HRMS (CI): calculated for ($C_{17}H_{15}N_2O_4$) (M+1) 311.0968, found 311.0986.

6,7-dimethoxy-1-phenylisoquinoline (12). Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), benzoic acid (61.0 mg, 0.5 mmol) and the general procedure described yielded 6,7-dimethoxy-1-phenylisoquinoline in 80% yield (106.0 mg, 0.4 mmol). For characterization see **1b** above.

6,7-dimethoxy-1-(2-methoxyphenl)isoquinoline (13). Using 3,4-dimethoxyphenethylamine (83.0 μL, 0.5 mmol), 2-methoxybenzoic acid (76.1 mg, 0.5 mmol) and the general procedure described, gave in 80% (118.0 mg, 0.4 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.48 (d, J = 5.6 Hz, 1H), 7.40-7.53 (m, 3H), 7.03-7.15 (m, 3H), 6.94 (s, 1H), 4.04 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H); ^{13}C ($CDCl_3$, 50 MHz): δ 156.2, 155.7, 151.9, 149.0, 140.6, 132.4, 130.6, 129.2, 128.1, 122.9, 120.2, 118.2, 110.4, 105.2, 104.0, 55.3, 55.1, 54.8; HRMS (CI): calculated for $C_{18}H_{18}NO_3$ (M+1) 296.1242, found 296.1242.

6,7-dimethoxyisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone (14).[15] Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 2-(3,4-dimethoxyphenyl) acetic acid (98.1 mg, 0.5 mmol) and the general procedure described in scheme 2, gave 6,7-dimehtoxyisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone in 78% yield (137 mg, 0.39 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.46 (d, J = 5.4 Hz, 1H), 7.71 (s, 1H), 7.65 (d, J = 5.4 Hz, 1H), 7.55 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H) 4.06 (s, 3H), 3.96 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 194.2, 154.0, 153.4, 151.2, 149.2, 140.3, 134.2, 130.1, 128.6, 127.2, 123.1, 121.5, 112.0, 110.1, 105.0, 104.3, 56.3; HRMS (CI): calculated for $C_{20}H_{20}NO_5$ (M+1) 354.1297, found 354.1297.

6,7-dimethoxyisoquinolin-1-yl)(3,4,5-trimethoxyphenyl)methanone (15). Using 3,4-dimethoxyphenethylamine (83.0 μL, 0.5 mmol), 2-(3,4,5-trimethoxyphenyl) acetic acid (113.1 mg, 0.5 mmol) and the general procedure described in scheme 2 gave 6,7-

dimethoxyisoquinolin-1-yl)(3,4,5-trimethoxyphenyl)methanone in 55% yield (105.6 mg, 0.28 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.46 (d, J = 5.4 Hz, 1H), 7.67 (d, J = 5.4 Hz, 1H), 7.68 (s, 1H), 7.22 (s, 2H), 7.15 (s, 1H), 4.06 (s,3H), 3.99 (s, 3H), 3.92 (s, 3H), 3.87 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 195.3, 153.4, 153.0, 151.3, 143.1, 140.1, 134.2, 132.2, 123.3, 121.8, 108.6, 107.3, 105.0, 104.2, 61.1, 56.4; HRMS (ES): calculated for $C_{21}H_{22}NO_6$ (M+ 1) 384.1447, found 384.1468.

(4-fluorophenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone (16). Using 3,4-dimethoxyphenethylamine (83.0 μL, 0.5 mmol), 2-(4-fluorophenyl)acetic acid (77 mg, 0.5 mmol) and the general procedure described in scheme 2 gave (4-flurophenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone in 60% (93.3 mg, 0.3 mmol) yield and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.45 (d, J = 8.47 Hz, 1H), 7.86-7.99 (m, 3H), 7.49 (s, 1H), 7.14-7.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 189.8, 167.0 (d, J = 258.8 Hz), 156.3, 153.0, 149.2, 136.6, 134.0, 133.8 (d, J = 9.8 Hz), 132.6, 123.1, 122.7, 116.4 (d, J = 22.8), 105.5, 104.4, 56.9, 56.6; HRMS (CI): calculated for $C_{18}H_{15}FNO_3$ (M+1) 312.1036, found 312.1041.

(4-chlorophenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone (17).[16] Using 3,4-dimethoxyphenethylamine (83.0 μL, 0.5 mmol), 2-(4-chlorophenyl)acetic acid (85.3 mg, 0.5 mmol) and the general procedure described in scheme 2 gave (4-chlorophenl)(6,7-dimethoxyisoquinolin-1-yl)methanone gave in 72% yield (117.7 mg, 0.36 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.57 (d, J = 5.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 6 Hz, 2H), 7.56, (d, J = 8.4 Hz, 2H), 7.37 (s, 1H), 4.17 (s, 3H), 4.10 (s,

3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 194.2, 153.4, 152.3, 151.5, 140.2, 140.0, 135.7, 134.3, 132.4, 128.8, 123.3, 122.1, 105.0, 104.0, 56.2; HRMS (CI): calculated for $C_{18}H_{15}ClNO_3$ (M+1) 328.0696, found 328.0696.

6,7-dimethoxyisoquinolin-1-yl)(p-tolyl)methanone (18). Using 3,4-dimethoxyphenethylamine (83.0 μL, 0.5 mmol), 2-p-tolylacetic acid (75.1 mg, 0.5 mmol) and the general procedure described in scheme 2 gave 6,7-dimethoxyisoquinolin-1-yl)(p-tolyl)methanone in 80% yield (123.3 mg, 0.4 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz): δ 8.46 (d, J = 5.4 Hz, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.61-7.67 (m, 2H) 7.30 (s, 2H), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 195.3, 153.3, 151.2, 144.6, 140.3, 134.7, 134.1, 131.1, 129.3, 123.1, 121.6, 105.0, 104.2, 56.3, 21.9; HRMS (ES): calculated for $C_{19}H_{18}NO_3$ (M+1) 308.1287, found 308.1283.

6,7-dimethoxyisoquinolin-1-yl)(naphthalen-ly)methanone (19). Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 2-(naphthalene-5-yl)acetic acid (93.1 mg, 0.5 mmol) and the general procedure described in scheme 2 gave 6,7-dimethoxyisoquinolin-1-yl)(naphthalen-ly)methanone in 68% yield (116 mg, 0.34 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz): δ 8.63 (d, J = 7.2 Hz, 1H), 8.43 (d, J = 5.6 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.91-7.94 (m, 2H), 7.42-7.69 (m, 5H), 7.18 (s, 1H), 4.08 (s, 3H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 198.3, 153.3, 151.7, 140.6, 135.7, 134.3, 134.2, 133.4, 131.9, 131.6, 128.7, 128.2, 126.6, 126.0, 124.5, 123.5, 122.2, 105.0, 104.3, 56.3; HRMS (CI): calculated for $C_{22}H_{18}NO_3$ (M+1) 344.1287, found 344.1300.

Ethyl 3,4-dimethoxyphenethylcarbamate (20). To a solution of 3,4-dimethoxyphenethylamine (0.55 mL, 3.3 mol) and triethylamine (0.51 mL, 3.6 mmol) in DCM (10 mL) cooled at 0°C was added ethyl chloroformate (0.35 mL, 3.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12h. The precipitate formed was filtered and the filtrate washed with distilled water (8 mL). The organic fraction was then dried over Na_2SO_4, concentrated and purified by flash column chromatography on silica gel using 30% ethyl acetate in hexane to afford **20** in 96% yield (802 mg, 3.17 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.69-6.82 (m, 3H), 4.69 (b, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.39 (q, J = 7.0 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H), 1.21 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.6, 149.0, 147.7, 131.3, 120.7, 112.0, 111.4, 60.7, 55.9, 55.8, 42.2, 35.7; HRMS (CI): calculated for $C_{13}H_{20}NO_4$ (M+1) 254.1348, found 254.1390.

3,4-Dihydro-6,7-dimethoxyisoquinolin-1(2H)-one (21). Ethyl 3,4-dimethoxyphenethylcarbamate **20** (229 mg, 1 mmol) was treated with $POCl_3$ (6 mL, 60 mmol), hexamethyldisiloxane (6 mL, 27.6 mmol) and P_2O_5 (892 mg, 6 mmol). The reaction mixture was capped and irradiated in a microwave for 40 minutes at 150°C. The reaction mixture was concentrated and then poured on ice, neutralized with NaOH (2M) and extracted with DCM. The DCM extract was dried over Na_2SO_4, concentrated and purified by flash column chromatography on silica gel using 50% ethyl acetate in hexane to give **21** in 96% yield (199 mg, 0.96 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.57 (s, 1H), 6.67 (s, 1H), 6.17 (b, 1H), 3.58 (t, J = 6.6 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.4, 152.4, 148.2, 132.7, 121.5, 110.4, 109.7, 56.2, 40.7, 28.2; HRMS (CI): calculated for $C_{11}H_{14}NO_3$ (M+1) 208.0927, found 208.0957.

6,7-Dimethoyisoquinolin-1(2H)-one (22). A mixture of 3,4-dihydro-6,7-dimethoxyisoquinolin-1(2H)-one **21** (198.8 mg, 0.96 mmol) and 10 % Pd/C (100 mg) was ground to fine powder before heating at 150 °C for 30 min. The mixture was suspended in DCM (100 mL) before filtering to remove the Pd/C. Evaporation of the solvent under reduced pressure yielded **22** in 98% yield (194 mg, 0.945 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz) δ 11.40 (b, 1H), 7.78 (s, 1H), 7.12 (d, J = 7.0 Hz, 1H), 6.92 (s, 1H), 6.50 (d, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.8, 153.8, 149.4, 134.0, 126.8, 120.0, 107.0, 106.3, 56.5, 56.3; HRMS (CI): calculated for $C_{11}H_{12}NO_3$ (M+1) 206.0772, found 206.0739.

4-Bromo-6,7-dimethoxyisoquinolin-1(2H)-one (23). To a stirred solution of 6,7-dimethoxyisoquinolin-1(2H)-one **22** (205 mg, 1 mmol) in glacial acetic acid (1.2 mL) at room temperature was added dropwise a solution of Br_2 (51 μL, 1 mmol) in glacial acetic acid (760 μL). The mixture was stirred for 1 hour at room temperature. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2 (3 x 50 mL). The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated to dryness to afford **23** in 96 % yield (271 mg, 0.96 mmol) and showed: ^1H NMR (DMSO-d_6, 200 MHz): δ 11.45 (b, 1H) 7.62 (s, 1H), 7.44 (s, 1H), 7.12 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 160.3, 153.6, 149.2, 130.9, 128.0, 120.0, 107.5, 106.0, 97.1, 55.7; HRMS (CI): calculated for $C_{11}H_{11}BrNO_3$ (M+1) 283.9878, found 283.9846.

6,7-Dimethoxy-4-phenylisoquinolin-1(2H)-one (24). To a mixture of 4-bromo-6,7-dimethoxyisoquinolin-1(2H)-one **23** (100 mg 0.35 mmol), phenylboronic acid (64.6 mg, 0.52 mmol), Cs_2CO_3 (84.5 mg, 0.26 mmol), $Pd_2(dba)_3.CHCl_3$ (7.2 mg, 0.007 mmol, 2 mol %), PA-Ph, (4.1 mg, 0.014 mmol, 4 mmol %) was added toluene (3 mL). The reaction mixture was degassed, placed under an argon atmosphere then irradiated in a microwave for 30 min at 90°C. Toluene was evaporated under a reduced pressure and the residue purified by flash column chromatography on silica gel using ethyl acetate as the eluent to give **24** in 98% yield (96 mg, 0.34 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 11.27 (b, 1H), 7.88 (s, 1H), 7.41-7.48 (m, 5H), 7.14 (s, 1H), 7.00 (s, 1H), 4.04 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 163.4, 153.7, 149.2, 136.9, 133.1, 129.9, 128.9, 127.8, 125.8, 119.9, 107.4, 105.3, 56.4, 56.1; HRMS (ES): calculated for $C_{17}H_{16}NO_3$ (M+1) 282.1130, found 282.1130.

6,7-Dimethoxy-1-oxo-1,2-dihydro-isoquinoline-4-carbonitrile (25). To solution of 4-bromo-6,7-dimethoxyisoquinolin-1(*2H*)-one **23** (0.96 mmol, 270.7 mg) in *N*-methyl-2-pyrrolidone (4 mL) was added (193.8 mg, 2 mmol) CuCN. The mixture was irradiated in a microwave for 40 min at 200°C. The reaction mixture was concentrated under a reduced pressure and the residue purified by flash column chromatography on silica gel using a gradient of 50% ethyl acetate in hexane to 100% ethyl acetate. Compound **25** was obtained in 86 % yield (198 mg, 0.86 mmol) and showed: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.08 (s, 1H), 7.58 (s, 1H), 7.02 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 160.5, 154.2, 149.6, 138.4, 129.2, 118.7, 116.7, 107.4, 103.9,

87.9, 56.0, 55.8. HRMS (CI): calculated for $C_{12}H_{11}N_2O_3$ (M+1) 231.0725 found 231.0773.

1-Bromo-6,7-dimethoxy-4-phenylisoquinoline (26). To a mixture of 6,7-dimethoxy-4-phenylisoquinolin-1(2H)-one **24** (80 mg, 0.28 mmol) and $POBr_3$ (253.7 mg, 0.84 mmol) in a microwave vial was added DCM (3 mL). The mixture was irradiated in a microwave for 30 minutes at 120°C. The reaction mixture was diluted with DCM (10 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL), then with brine (5 mL). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to give 1-bromo-6,7-dimethoxy-4-phenylisoquinoline **26** (98%) which was used for the synthesis of **27** and **28** without further purification.

6,7-Dimethoxy-1,4-diphenylisoquinoline (27). To a mixture of 1-bromo-6,7-dimethoxy-4-phenylisoquinoline **26** (0.107 mmol, 36.7 mg), phenylboronic acid (0.161 mmol, 16.6 mg), Cs_2CO_3 (0.24 mmol, 78.2 mg), $Pd_2(dba)_3.CHCl_3$ (2.3 mg, 0.0021 mmol, 2 mol %), PA-Ph, (1.3 mg. 0.0043 mmol, 4 mmol %), was added toluene (1.5 mL). The mixture was degassed, placed under an argon atmosphere then irradiated in a microwave for 30 min at 90 °C. Toluene was removed and residue purified by flash column chromatography on silica gel using ethyl acetate to give **27** in 95% yield (35 mg, 0.10 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.43 (s, 1H), 7.73 (d, J = 1.2 Hz, 2H), 7.45-7.57 (m, 8H), 7.25 (d, J = 1.2 Hz, 2H), 3.88 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.8, 152.7, 149.9, 141.5, 140.2, 137.9, 132.1, 131.6, 130.1, 129.8, 128.9, 128.6, 128.0,

122.6, 106.0, 103.6, 56.1; HRMS (ES): calculated for $C_{23}H_{19}NO_2$ (M+1) 342.1494, found 342.1482.

6,7-Dimethoxy-4-phenyl-1-(piperidin-1-yl)isoquinoline (28). To a mixture of 1-bromo-6,7-dimethoxy-4-phenylisoquinoline **26** (36 mg, 0.1 mmol), $Pd_2(dba)_3.CHCl_3$ (2.3 mg, 0.0021 mmol, 2 mol %), PA-Ph, (1.3 mg. 0.0043 mmol, 4 mmol %) NaO^tBu, (14.4 mg, 0.15), in a microwave vial was added toluene (2 mL). The mixture was degassed with and place under an atmosphere of argon. Piperidine (15 μL, 0.15 mmol) was added and the mixture was irradiated in a microwave for 30 min at 180 °C. Toluene was evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel using 2% MeOH in DCM to yield **28** in 64% yield (22 mg, 0.064 mmol). The compound showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.01 (s, 1H), 7.50 (s, 5H), 7.14 (s, 2H), 4.04 (s, 3H), 3.84 (s, 3H), 3.33 (t, J = 5 Hz, 4H), 1.86 (m, 4H), 1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.9, 152.3, 149.0, 139.9, 138.3, 132.9, 130.1, 128.7, 127.8, 127.4, 117.4, 104.8, 104.1, 55.8, 52.7, 26.6, 25.0; HRMS (ES): calculated for $C_{22}H_{25}N_2O_2$ (M+1) 349.1916, found 349.1935.

4-Bromo-1-chloro-6,7-dimethoxyisoquinoline (29). 4-Bromo-6,7-dimethoxyisoquinolin-1(2H)-one **23** (283 mg, 1 mmol) was treated with $POCl_3$ (2 mL, 20 mmol) and then irradiated in a microwave for 30 minutes at 100°C. The solvent was removed under reduced pressure and the residue poured onto ice, made basic to pH 8 and extracted with DCM (3 x 10 mL). The DCM extract was dried over Na_2SO_4 and concentrated to give **29** in 98% yield (296 mg, 0.98 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.29 (s,

1H), 7.44 (s, 1H), 7.31 (s, 1H), 4.07 (s, 3H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.5, 151.6, 148.5, 141.6, 132.9, 123.3, 117.4, 105.0, 104.7, 56.4; HRMS (ES): calculated for $C_{11}H_{10}Br\ ClNO_2$ (M+1) 301.9583, found 301.9609.

4-Bromo-1-ethoxy-6,7-dimethoxyisoquinoline (30). To a solution of 4-bromo-1-chloro-6,7-dimethoxyisoquinoline **29** (50 mg, 0.17 mmol) in ethanol (2 mL) was added NaOEt (46.7 mg, 0.33 mmol). The reaction mixture was irradiated in a microwave for 30 minutes at 90°C. The mixture was diluted with DCM (10 mL) washed with distilled water (5 mL). The DCM was dried over Na_2SO_4. Removal of the solvent and purification by flash column chromatography on silica gel using 20 % ethyl acetate in hexane yielded **30** in 87 % yield (45 mg, 0.144 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04 (s, 1H), 7.5 (s, 1), 7.31 (s, 1H), 4.52 (q, J = 6.6 Hz, 2H), 4.06 (s, 3H), 4.04 (s, 3H), 1.50 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.1, 153.6, 150.1, 139.8, 132.7, 115.6, 110.3, 105.1, 103.3, 62.4, 56.3, 14.8; HRMS (EI): calculated for $C_{13}H_{14}BrNO_3$ 311.0157, found 311.0154.

1-Ethoxy-6,7-dimethoxy-4-phenylisoquinoline (31). Using 4-bromo-1-ethoxy-6,7-dimethoxyisoquinoline **30** (30 mg, 0.096 mmol), phenylboronic acid (17.9 mg, 0.144 mmol) and procedure as described for compound **24**, 1-ethoxy-6,7-dimethoxy-4-phenylisoquinoline **31** was obtained in 93% yield (29 mg, 0.092 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.81 (s, 1H), 7.58 (s, 1H), 7.47 (s, 5H), 7.10 (s, 1H), 4.58 (q, J = 6.8 Hz, 2H), 4.03 (s, 3H), 3.83 (s, 3H), 1.52 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.1, 152.7, 149.3, 138.3, 138.1, 132.7, 130.0, 128.6, 127.3, 126.9, 114.2,

103.7, 103.1, 62.0, 56.1, 55.9, 14.9; HRMS (ES): calculated for $C_{19}H_{20}NO_3$ (M+1) 310.1443, found, 310.1437.

1-Bromo-6,7-dimethoxyisoquinoline-4-carbonitrile (32). To a mixture of 6,7-dimethoxy-1-oxo-1,2-dihydro-isoquinoline-4-carbonitrile **25** (150.1 mg 0.652 mmol) and $POBr_3$ (0.59 g, 1.956 mmol) was added dichloromethane (4 mL). The reaction mixture was irradiated in a microwave for 30 min. at 150°C. The anisole was removed under reduced pressure and the residue added slowly to ice then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with saturated aqueous bisodium carbonate solution (5 mL), then with brine (5 mL). The organic extract was dried over Na_2SO_4, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel using CH_2Cl_2 to yield **32** in 89% yield (169 mg, 0.58 mmol). The compound showed: ^1H NMR ($CDCl_3$, 200 MHz): δ 8.49 (s, 1H), 7.58 (s, 1H), 7.35 (s, 1H), 4.12 (s, 3H), 4.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.9, 152.6, 147.4, 145.7, 133.0, 124.4, 116.1, 107.5, 104.8, 103.0, 57.0, 56.6; HRMS (CI): calculated for $C_{12}H_{10}BrN_2O_2$ (M+1) 292.9926, found 292.9902.

General procedure for coupling of 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile with aldehydes via nucleophilic aroylation. To a stirred solution of 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile **32** (30.1 mg, 0.102 mmol), aldehyde (0.15 mmol), and (0.15 mmol) of 1,3-dimethylimidazolium iodide in DMF (1.5 mL) was added (0.15 mmol) NaH. The mixture was stirred at room temperature. After 2h, water (4 mL) was added and the reaction mixture was extracted with chloroform (3x 8 mL). The organic

layer was dried over Na_2SO_4, concentrated and the residue was purified by flash column chromatography on silica gel using a gradient of CH_2Cl_2 to 50 % ethyl acetate in CH_2Cl_2 to afford the coupled product.

6,7-Dimethoxy-1-(4-methoxyphenylcarbonyl)isoquinoline-4-carbonitrile (33). Using 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile **32** (30.1 mg, 0.102 mmol), 4-methoxybenzaldehyde (20 mg, 0.15 mmol) and the procedure described above yielded **33** in 99% yield (35 mg, 0.102 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.79 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.50 (s, 1H), 7.44 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H) 4.12 (s, 3H), 3.96 (s, 3H), 3.89 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 192.7, 164.7, 157.2, 155.7, 152.2, 150.2, 145.2, 133.4, 128.9, 122.0, 116.5, 114.1, 105.6, 104.8, 102.7, 56.8, 56.5, 55.8; HRMS (CI): calculated for $C_{20}H_{17}N_2O_4$ (M+1) 349.1144 found 349.1153.

6,7-Dimethoxy-1-(4-methoxynaphthalene-1-carbonyl)isoquinoline-4-carbonitrile (34). Using 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile **32** (30.1 mg, 0.102 mmol), 4-methoxynaphthalene-1-carbaldehyde (27.9 mg, 0.15 mmol) and the procedure described above yielded **34** in 91% yield (37 mg, 0.093 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.16 (d, J = 8.6 Hz, 1H), 8.77 (s, 1H), 8.38 (d, J = 8.2 Hz, 1H), 7.46-7.77 (m, 5H), 6.71 (d, J = 8.2 Hz, 1H), 4.15 (s, 3H), 4.06 (s, 3H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.0, 160.8, 159.0, 155.6, 152.2, 145.4, 137.2, 133.6, 133.1, 129.6, 126. 4, 126.0, 125.4, 122.6, 122.1, 116.5, 105.3, 104.9, 102.7, 102.4, 56.8, 56.5, 56.1; HRMS (CI): calculated $C_{24}H_{19}N_2O_4$ (M+1) 399.1345, found 399.1337.

1-(3,4-Dimethoxyphenylcarbonyl)-6,7-dimethoxyisoquinoline-4-carbonitrile (35). Using 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile **32** (30.1 mg, 0.102 mmol), 3,4-dimethoxybenzaldehyde (24.9 mg, 0.15 mmol) and the procedure described above yielded **35** 95 % yield (0.097 mmol, 36 mg) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.78 (s, 1H), 7.68 (s, 1H), 7.45 (d, J = 7.5 Hz, 2H), 7.26-7.30 (m, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.13 (s, 3H) 3.96 (s, 6H), 3.95 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 192.7, 157.1, 155.7, 154.6, 152.2, 149.4, 145.1, 133.7, 129.0, 127.2, 122.0, 116.4, 111.6, 110.1, 105.5, 104.8, 102.7, 56.8, 56.5, 56.3, 56.2; HRMS (CI): calculated for $C_{21}H_{19}N_2O_5$ (M+1) 379.1266 found 379.1249.

6,7-Dimethoxy-1-phenylisoquinoline-4-carbonitrile (36). Using the cross-coupling procedure described for compound **24** with 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile 32 (20 mg, 0.068 mmol) and phenylboronic acid (13 mg, 0.102 mmol) yielded 6,7- dimethoxy-1-phenylisoquinoline-4-carbonitrile **36** in 95% yield (19 mg, 0.065 mmol) and showed: ^{1}H NMR (CD_3OD, 200 MHz): δ 8.76 (s, 1H), 7.56-7.71 (m, 5H), 7.44 (d, J = 7.6 Hz, 2H), 4.11 (s, 3H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 161.9, 154.7, 151.2, 146.4, 138.7, 135.6, 133.3, 132.7, 129.6, 128.7, 128.0, 121.8, 117.0, 106.3, 102.8, 56.6, 56.1; HRMS (ES): calculated for $C_{18}H_{14}N_2O_2$ (M+1) 291.1134, found 291.1143.

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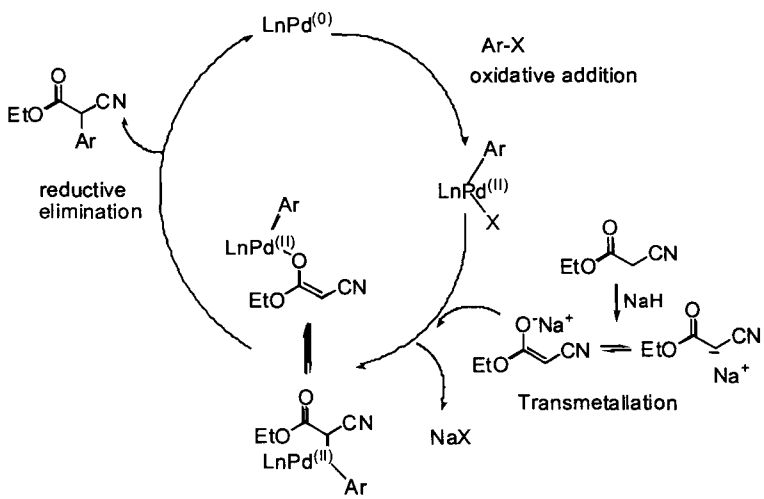
Chapter 5

5.1.1 Palladium catalyzed arylation of "active methylene" compounds as Precursors for the Synthesis of Substituted Isoquinolines .

5.1.2 Introduction

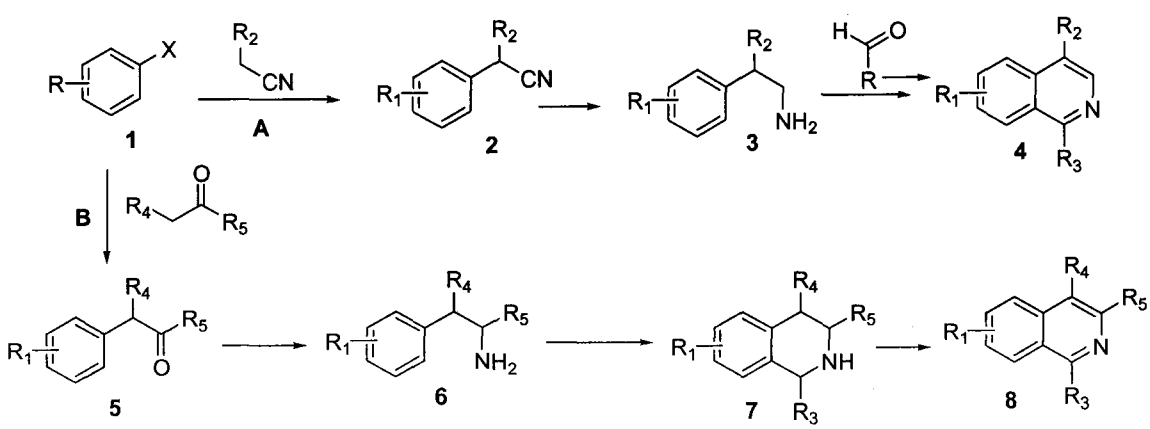
Compounds containing "active methylenes", such as ketones, aldehydes, esters, cyanoacetates and malononitrile have been coupled with aryl halides using palladium catalysis.[1-3] A plausible catalytic cyclic for the addition of the enolate to aryl halide using ethyl cyanoacetate, for example, is shown in Scheme 5.1. The catalytic cyclic begins with an initial oxidative addition of the aryl halide to the palladium to form an aryl palladium (II) complex. Substitution of the halide with the enolate nucleophile (transmetallation) and reductive elimination of the resulting palladium enolate complex yield the arylated product. The products from these reactions are important as they serve as precursors for the preparation of bioactive compounds[4] and several heterocyclic compounds[5,6]



Scheme 5.1. General mechanism for palladium-catalyzed arylation of ethyl cyanoacetate.

We aimed at determining the efficacy of our catalytic system incorporating the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane (PA-R) framework in arylation of ethyl cyanoacetate and malononitrile. We became interested in the products of these reactions as they represent useful synthons for the preparation of substituted isoquinolines. As illustrated in Scheme 5.2, the approach takes advantage of protocols recently developed for microwave-assisted Bischler-Napieralski or Pictet-Spengler reactions followed by oxidation to yield isoquinolines[7] suitable for a library format.

Both processes rely on a suitably functionalized β-arylethylamine that we envisioned could be generated *via* two different routes utilizing cross-coupling chemistry. For example (as outlined in Scheme 5.2), Pd-catalyzed arylation of a nitrile possessing an α-methylene provides compound **2** that can be reduced to the β-arylethylamine **3**.



Scheme 5.2. Synthesis of Isoquinolines using Pd-catalyzed arylated of active methylene Products.

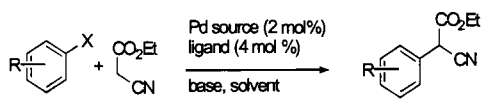
Application of our cyclization / oxidation protocol[7] (presented in chapter 4) would then lead to substituted isoquinolines **4**. Alternatively, Pd-catalyzed arylation of a

ketone provides compounds of the general type **5**. Reductive amination would supply **6** that could be elaborated to give compounds of the general type **7**. Preliminary studies are described below.

5.1.3 Results and Discussion

Development of Route A, wherein arylation with ethyl cyanoacetate or malononitrile represents the key step, was first examined. Initial screening involved optimization of reaction conditions using both 3- and 4-iodoanisole as the model substrates so as to find the best solvent, base, palladium source and ligand needed to obtain the maximum yield of the arylated product. The results are presented in Table 5.1. These studies revealed that optimal yields are obtained when $Pd_2(dba)_3.CHCl_3$ was used as the palladium source and 1,3,5,7-tetramethyl-6-(isobutyl)-2,4,8-trioxa-6-phospha-adamantane (PA-iBu) was used as the ligand. NaH proved to be the best base. Among all the solvents tried, THF was optimal. For example, a facile reaction was observed when 5 mol equivalents of the base and 3 mol equivalents of the ethyl cyanoacetate were used. (Table 5.1, entries 3 and 12).

Table 5.1. Optimization of Pd-catalyzed arylation of ethyl cyanoacetate



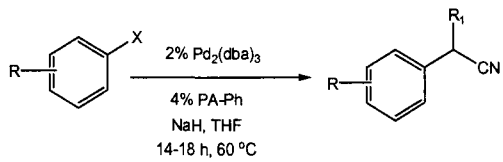
entry	aryl halide	Pd source	ligand	solvent	base	yield
1	3-iodoanisole	$PdCl_2$	PA-*i*Bu	pyridine	NaH [b]	0%
2	3-iodoanisole	$PdCl_2$	PA-Ph	pyridine	NaH [b]	0%
3	4-iodoanisole	Pd_2dba_3	PA-*i*Bu	THF	KO^{t}Bu [b]	60%
4	3-iodoanisole	Pd_2dba_3	PA-*i*Bu	THF	NaH [c]	69%
5	4-iodoanisole	Pd_2dba_3	PA-Ph	THF	NaH [b]	50%
6	3-iodoanisole	Pd_2dba_3	PA-Ph	dioxane	NaH [c]	60%
7	3-iodoanisole	Pd_2dba_3	PA-Ph	DMSO	NaH [b]	0%
8	3-iodoanisole	Pd_2dba_3	PA-Ph	THF	KO^{t}Bu [b]	0%
9	4-iodoanisole	$PdCl_2$	PA-Ph	THF	NaH [b]	30%
10	3-iodoanisole	$Pd(OAc)_2$	PA-*i*Bu	pyridine	NaH [b]	40%
11	3-iodoanisole	$Pd(OAc)_2$	PA-*i*Bu	pyridine	NaH [b]	40%
12	4-iodoanisole	Pd_2dba_3	PA-*i*Bu	THF	NaH [c]	89%

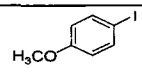
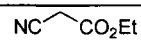
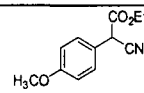
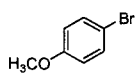
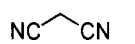
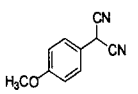
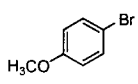
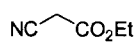
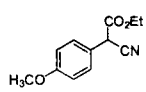
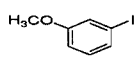
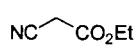
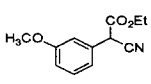
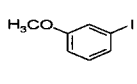
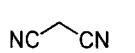
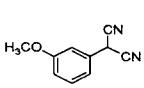
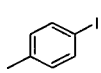
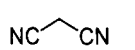
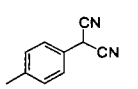
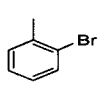
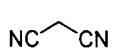
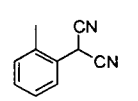
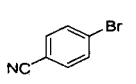
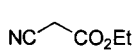
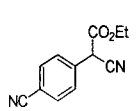
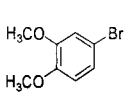
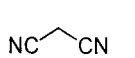
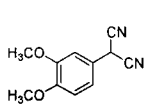
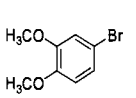
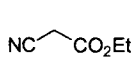
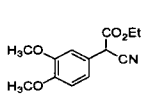
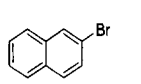
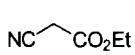
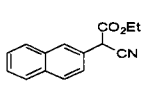
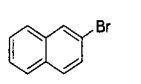
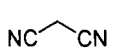
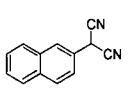
[b] Reactions were carried out using 3 eq. of base and 1.25 eq. of ethyl cyanoacetate; [c] Reactions were carried out using 5.0 eq. of base and 3.0 eq. of ethyl cyanoacetate.

Having obtained the optimal set of reaction conditions, the cross-coupling was carried out using several aryl iodides and aryl bromides having electron donating and withdrawing groups with ethyl cyanoacetate and malononitrile to generate the arylated compounds in good to moderate yield (see Table 5.2). Reactions with aryl bromides were comparatively slow.

Attention was then turned to the development of a protocol that would allow for the reduction of the nitrile functionality to yield the β-arylethylamine substrate necessary

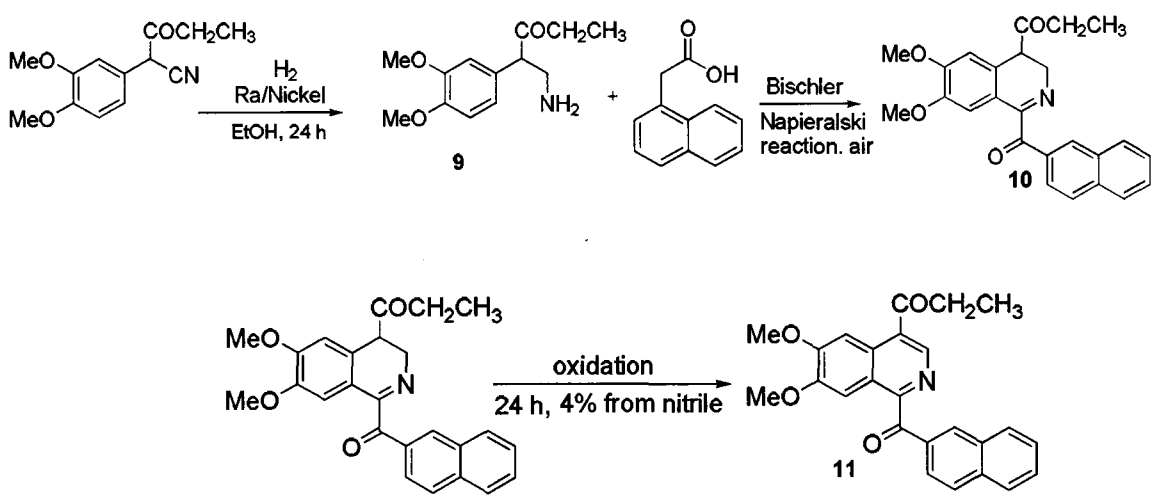
Table 5.2. Pd-catalyzed arylation of ethyl cyanoacetate and malononitrile



entry	aryl halide	nucleophile	Product	yield[b]
1				89
2				69
3				40
4				69
5				95
6				79
7				70
8				30
9				22
10				30
11				85
12				54

for the Bischler-Napieralski or Pictet-Spengler cyclizations. Several reduction strategies involving hydrogenation of the nitrile in both ethyl 2-cyano-2-(3-methoxyphenyl) acetate and ethyl 2-cyano-2(3,4-dimethoxyphenyl) acetate were examined. Among these, hydrogenation in the presence of Raney nickel allowed for complete consumption of the nitrile but resulted in several side products in addition to the desired amine. As purification of the requisite amine proved problematic, the reaction sequence was

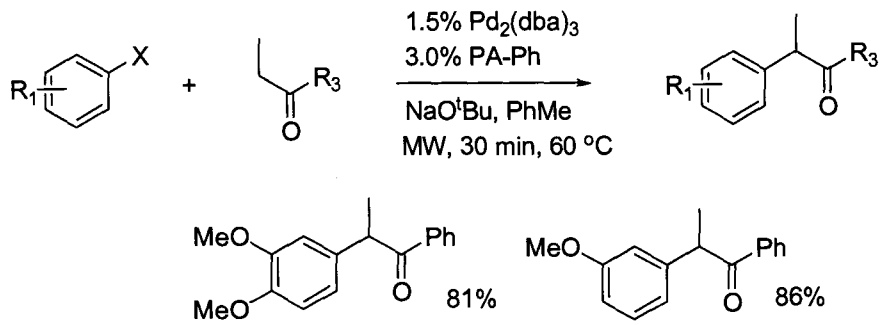
continued without isolation of the intermediate. In this way (Scheme 5.3), the reaction mixture from the reduction of 2-cyano-2(3,4-dimethoxyphenyl) acetate (without purification) was dissolved in toluene and treated with 2-(naphthalene-1-yl)ethanoic acid and $POCl_3$ then subjected to the microwave-assisted Bischler-Napieralski followed by oxidation by dehydrogenation with Pd/C (as described in Chapter 4). As the resultant isoquinoline (**11**) was obtained in a poor yield of 4% from the starting nitrile, this approach was abandoned.



Scheme 5.3. Bischler-Napieralski cyclization of ethyl 3-amino-2-(3,4-dimethoxyphenyl)propanoate.

Focus shifted to the development of a protocol involving ketone arylation followed by reductive amination to yield a β-arylethylamine suitable for Pictet-Spengler or Bischler-Napieralski cyclizations. (Route B, Scheme 5.2). Previous screening in our lab, revealed that a Pd-catalytic system employing the 1,3,5,7-tetramethyl-6-phenyl-

2,4,8-trioxa-6-phospha-adamantane (PA-Ph) ligand allows for the facile arylation of ketones bearing an active α-methylene.[8] Using the optimized protocol compounds in scheme 5.4 were generated in good yield.



Scheme 5.4. Pd-Catalyzed arylation of ketone products.

A preliminary experiment (carried out by another student working on this project in our lab) for the reductive amination of these arylated ketone products *via* titanium (IV) isopropoxide mediated imine formation followed by reduction of the imine *in situ* using $NaBH_4$ yielded β-arylethylamines in good yields. Work involving the Pictet-Spengler and Bischler-Napieralski cyclizations with these substrates is continuing.

Future work in this project will involve the application of the protocols developed for the synthesis of a substituted isoquinoline library. In this way, we envision several ketones will be used to obtain the various ketone arylation products that can be converted to primary and secondary β-arylethylamines suitable for microwave-assisted Bischler-Napieralski or Pictet-Spengler cyclization[7] to generate a library of 1,3,4-substituted isoquinolines.

5.1.4 Experimental

General procedure for palladium catalyzed arylation of ethyl cyanoacetate and malononitrile. $Pd_2(dba)_3$ (20.8 mg, 0.02 mmol, 2 mol %) and PA-iBu (10.9 mg, 0.04 mmol, 4 mol %) were added to a flame-dried flask. The contents were degassed. THF (1 mL) was added and the reaction mixture stirred at room temperature for 30 minutes. At this time, the aryl halide (1 mmol) was added. The reaction mixture was transferred to another flask containing the nucleophile prepared by adding NaH (200 mg, 5 mmol) to THF (3 mL) under argon followed by the addition of ethyl cyanoacetate or malononitrile (3 mmol). The reaction mixture was allowed to reflux under argon for 14-18 hours after which the reaction mixture was filtered through a short pad of silica and washed with ethyl acetate. Removal of the ethyl acetate under reduced pressure was followed by purification of the residue on silica gel using 10 % to 30 % ethylacetate in hexane as the eluant.

Ethyl 2-cyano-2-(4-methoxyphenyl) acetate. Table 5.2, Entry 1. Using 1-iodo-4-methoxybenzene (234.0 mg, 1 mmol), ethyl cyanoacetate (320.0 μL, 3 mmol) and the general procedure, ethyl 2-cyano-2-(4-methoxyphenyl) acetate was obtained in 89 % yield (195.0 mg, 0.89 mmol). For characterization, (see reference).[9]

2-(4-methoxyphenyl)malononitrile, Table 5.2, Entry 2. Using 1-iodo-4-methoxybenzene (234 mg, 1 mmol), malononitrile (188.0 μL, 3 mmol) and the general procedure, 2-(4-methoxyphenyl)malononitrile was obtained in 69% yield (118.7 mg, 0.69 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41 (d, 2H, J = 8.7 Hz), 6.99 (d, 2H, J = 8.7 Hz),

5.00 (s, 1H), 3.85 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.1, 128.7, 117.9, 115.5, 112.1, 55.6, 27.6; (HRMS) CI: calculated for ($C_{10}H_8N_2O$) 172.0637 found 172.0635.

Ethyl 2-cyano-2-(4-methoxyphenyl) acetate, Table 5.2, Entry 3. Using 1-bromo-4-methoxybenzene (234.0 mg, 1 mmol), ethyl cyanoacetate (320.0 μL, 3 mmol) and the general procedure, ethyl 2-cyano-2-(4-methoxyphenyl) acetate was obtained in 40% yield (87.6 mg, 0.4 mmol). For characterization (see reference).[9]

Ethyl 2-cyano-2-(3-methoxyphenyl) acetate. Table 5.2, Entry 4. Using 1-iodo-3-methoxybenzene (120.1 μL, 1 mmol), ethyl cyanoacetate (320.0 μL, 3 mmol) and the general procedure, ethyl 2-cyano-2-(3-methoxyphenyl) acetate was obtained in 69 % yield (151.0 mg, 0.69 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.29-7.37 (m, 1H), 6.90-7.04 (m, 3H) 4.68 (s, 1H), 4.25 (q, 2H, J = 7 Hz), 3.83 (s, 3H), 1.28 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.0, 160.3, 131.3, 130.5, 120.2, 115.7, 115.0, 113.6, 63.5, 55.5, 43.8, 14.0. CI (HRMS): calculated for ($C_{12}H_{13}NO_3$) 219.0895 found 219. 0893.

2-(3-methoxyphenyl)malononitrile. Table 5.2, Entry 5. Using 1-iodo-3-methoxybenzene (120.1 μL, 1 mmol), malononitrile (188.0 μL, 3 mmol) and the general procedure, 2-(3-methoxyphenyl)malononitrile was obtained in 95 % yield (163.4 mg, 0.95 mmol) and showed: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.36-7.45 (m, 1H), 6.99-7.09 (m, 3H) 5.03 (s, 1H), 3.85 (s, 3H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.7, 131.2, 127.5, 119.4, 116.0, 113.0, 111.8, 55.6, 28.1. CI (HRMS), calculated for ($C_{10}H_8N_2O$) 172.0637 found 172.0632.

2-p-tolylmalononitrile. Table 5.2, Entry 6. Using 1-iodo-4-methylbenzene (218.8 mg, 1 mmol), malononitrile (188.0 μL, 3 mmol) and the general procedure, 2-p-tolylmalononitrile was obtained in 79 % yield (123.3mg, 0.79 mg) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.31-7.40 (m, 4H), 5.02 (s, 1H), 2.39 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 140.8, 130.8, 127.2, 123.4, 112.1, 27.9, 21.3. CI (HRMS): calculated for ($C_{10}H_8N_2$) 156.0687 found 156.0700.

2-o-tolymalononitrile. Table 5.2, Entry 7. Using 1-iodo-2-methylbenzene (122.0 μL, 1 mmol), malononitrile (188.0 μL, 3 mmol) and the general procedure, 2-*o*-tolymalononitrile was obtained in 70 % yield (109.2 mg, 0.7 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30-7.56 (m, 4H) 5.06 (s, 1H), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 136.1, 131.9, 130.8, 128.2, 127.7, 124.8, 111.6, 26.4, 19.2. CI (HRMS): calculated for ($C_{10}H_8N_2$) 156.0687 found 156.0700.

Ethyl 2-cyano-2-(4-cyanophenyl)acetate. Table 5.2, Entry 8. Using 4-iodobenzonitrile (229.0 mg, 1 mmol), ethyl cyanoacetate (320.0 μL, 3 mmol) and the general procedure, ethyl 2-cyano-2-(4-cyanophenyl)acetate was obtained in 30 % yield (64.2 mg, 0.3 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.76, 7.72 (d, 2H, J = 8.0 Hz), 7.63, 7.59 (d, 2H, J = 8 Hz), 4.79 (s, 1H), 4.27 (q, 2H, J = 7 Hz), 1.32 (t, 3H, J = 6.8 Hz), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.0, 134.9, 133.2, 129.0, 117.9, 114.7, 113.7, 64.1, 43.7, 24.9, 14.0. CI (HRMS): calculated for ($C_{12}H_{10}N_2O_2$) 214.0742 found 214.0742.

2-(3,4-dimethoxyphenyl)malononitrile. Table 5.2, Entry 9. Using 4-bromo-1,2-dimethoxybenzene (144.0 μL, 1 mmol), malononitrile (188.0 μL, 3 mmol) and the

general procedure, 2-(3,4-dimethoxyphenyl)malononitrile was obtained in 22 % yield (45.0 mg, 0.22 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.90-7.07 (m, 3H), 5.01 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.7, 150.2, 120.1, 118.2, 112.1, 111.9, 109.9, 56.3, 56.3, 27.8. CI (HRMS): calculated for ($C_{11}H_{10}N_2O_2$) 202.0742 found 202.0742.

Ethyl 2-cyano-2(3, 4-dimethoxyphenyl) acetate. Table 5.2, Entry 10. Using 4-bromo-1,2- dimethoxybenzene (144.0 μL, 1 mmol), ethyl cyanoacetate (320.0 μL, 3 mmol) and the general procedure, ethyl 2-cyano-2(3, 4-dimethoxyphenyl) acetate was obtained in 30 % yield (74.7 mg, 0.3 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.85-7.02 (m, 3H), 4.65 (s, 1H), 4.24 (q, 2H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.3, 149.8, 149.5, 122.2, 120.6, 116.0, 111.6, 110.6, 63.3, 56.1, 43.4, 14.0. CI (HRMS): calculated for ($C_{13}H_{15}NO_4$) 249.1001 found 249.1011.

Ethyl 2-cyano-2(naphthalen-6-yl) acetate. Table 5.2, Entry 11. Using 2-bromonaphthalene (125 μL, 1 mmol), ethyl cyanoacetate (320 μL, 3 mmol) and the general procedure, ethyl 2-cyano-2(naphthalen-6-yl) acetate was obtained in (202 mg, 0.85 mmol) 85 % yield and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.94-8.037 (m, 3H), 7.48-7.47, (m, 4), 5.38 (s, 1H), 4.25 (q, 2H, J = 6.7 Hz), 1.25 (t, 3H, J = 7.2 Hz),^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.1, 134.1, 130.3, 129.2, 127.6, 127.5, 126.3, 125.5, 122.7, 116.0 63.5, 41.5, 24.8, 13.9. CI (HRMS): calculated for ($C_{15}H_{13}NO_2$) 239.0954 found 239.0946.

2-(naphthalen-6-yl) malononitrile. Table 5.2, Entry 12. Using 2-bromonaphthalene (125.0 μL, 1 mmol), malononitrile (188.0 μL, 3 mmol) and the general procedure, 2-(naphthalen-6-yl) malononitrile was obtained in 52 % yield (100.4 mg, 0.52 mmol) and showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56-8.039 (m, 7H), 5.57 (s, 1H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 134.2, 131.8, 129.8, 128.4, 127.3, 127.2, 125.6, 121.7, 111.8, 26.5. CI (HRMS): calculated ($C_{13}H_8N_2$) 192.0687 found 192.0691.

Compound 11. To a mixture of ethyl 2-cyano-2(3, 4-dimethoxyphenyl) acetate (74.7 mg, 0.3 mmol) and Raney nickel (40.0 mg) in ethanol (2 mL) was attached a balloon of hydrogen gas. The mixture was stirred at room temperature for 24 h. The reaction mixture was poured on a celite pad and was washed with methanol. Methanol was removed under reduced pressure. To the residue was added (2-naphthalen-6-yl) acetic acid (71.0 mg, 0.39 mmol), $POCl_3$ (138.0 μL , 1.5 mmol) and toluene (1 mL). The mixture was microwaved at 140 °C for 30 minutes. The reaction mixture was basified with NaOH (pH = 8) and extracted with DCM. The DCM was removed under reduced pressure. Heating the residue with 10 % Pd/C at 140 °C for 2 h and purification using 10 % methanol/DCM yield compound 11 in 4% yield. (5.4 mg, 0.013 mmol). The product showed: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.10 (s, 1H), 8.83 (d, J = 8.4 Hz, 1H), 8.56 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.94 (d, 1H, J = 7.8 Hz, 1H), 7.73 (s, 1H), 7.33-7.67 (m, 4H), 4.53 (q, J = 4.4 Hz, 2H), 4.13 (s, 3H), 3.95 (s, 3H), 1.51 (t, J = 4.4 Hz, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.4, 166.1, 157.5, 154.1, 150.7, 143.7, 133.4, 132.2, 130.9,

128.1, 128.0, 126.2, 125.4, 123.8, 122.7, 103.7, 103.4, 61.0, 55.8, 55.6, 13.8; (HRMS) CI: calculated for ($C_{25}H_{21}NO_5$) 415.1420 found 415.1420.

For the general procedure for synthesis and characterization of 2-(3,4-dimethoxyphenyl) 1-phenylpropan-1-one and 2-(3-methoxyphenly) 1-phenylpropan-1-one, please refer to (reference 8).

5.1.5 References

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Chapter 6

6.1.1 General Conclusion.

As described in Chapter 2 *(Org. Lett.*, **2009**, 11, 3210-3213), a sequential, "one pot" microwave-assisted, copper-free Sonogashira, Pd-catalyzed carbonylation/cyclization protocol was developed and allowed for the production of a flavone library. Various terminal acetylenes generated by coupling aryl iodides and aryl bromides with TMS-acetylenes *in situ* were carried forward in the synthesis of flavones in good yield with relatively low catalyst loading.

A synthetic protocol suited for efficient derivatization at the C-3 and C-4 positions of maleimides and the α,β-unsaturated-γ-butyrolactam heterocyclic core was explored (Chapter 3, manuscript in press., *J. Org. Chem.* 2010). Using a palladium complex containing the PA-Ph ligand permitted the generation of symmetrical and non-symmetrical 3,4-disubstituted maleimides in good yield. The methodology developed allowed for rapid access to a library of bisaryl-maleimides and anilinoaryl-maleimides as well as bisaryl-α,β-unsaturated-γ-butyrolactams after a microwave-assisted deprotection of the *p*-methoxybenzyl group (PMB) using $AlCl_3$/anisole or TFA/anisole. Bisanilino-maleimides were also generated *via* a Michael addition-elimination protocol after deprotection *via* aminolysis.

The microwave-assisted Pictet-Spengler and Bischler-Napieralski cyclization reactions developed in Chapter 4 (*J. Org. Chem.* **2010,** 75 (16) pp 5627-5634) allowed

for synthesis of a library of substituted isoquinolines. In evaluating the possible synthetic strategies for the production of C1 and C4 substituted isoquinolines, protocols involving the elaboration of an isoquinoline-1(2H)-one scaffold were shown to be the most practical. In an effort to broaden the scope of the isoquinoline library and provide an alternate synthetic strategy to isoquinolines, a reaction protocol which will allow easy access to C-1, C-2, C-3 and C-4 substituted isoquinoline analogues is being developed (as described in Chapter 5). The approach involves the generation of substituted β arylethylamines *via* reductive amination of ketone arylation products. These substrates will then undergo microwave-assisted Pictet-Spengler and Bischler-Napieralski cyclizations using the previously developed protocol.

Overall, the palladium complexes containing the phospha-adamantane (PA) ligands developed in our laboratory have demonstrated themselves to be remarkably effective in the preparation of libaries of heterocyclic compounds. In a recent article (Slagt, V. F.; *et al. Org. Process Res. Dev.* **2009,** *14*, 30-47.), Kellogg and co-workers noted that many of the popular ligands described in the literature are problematic when coupling substrates containing heteroatoms (especially nitrogen) as these compounds often poison the catalytic systems. This is clearly not the case with the PA ligands. The libraries of flavones, isoquinolines and maleimides described in this thesis were generated under relatively mild conditions in good yields with low catalyst loadings in many cases attesting to the utility of the PA ligand system.

In addition to the fact that these systems are air stable and relatively inexpensive to produce, the parent, secondary phospha-adamantane scaffold is easily derivatized. The resultant library provides a number of different PA ligands each with different structural and electronic properties. The ligand set currently described in the chemical literature for Pd-catalyzed cross-coupling reactions is far from ideal. While certain phosphines accelerate one reaction, the same phosphine may have little effect on a different cross-coupling. This makes it impossible to identify *a priori* the best ligand for a particular reaction. As demonstrated in the thesis, parallel screening of the PA ligand toolkit allows rapid identification of the best ligand, temperature, solvent, and Pd-source for a given reaction.

Perhaps the major criticism leveled against the use of Pd-catalyzed cross-coupling reactions in library syntheses is the cost of the palladium itself. This is actually not the case. In protocols where low catalytic loadings of Pd are required, the approach is actually rather cost effective. For example, in applying the methodology described in Chapter 3 for generating a 12-membered library of non-symmetrical 3,4-disubstituted maleimides *via* two sequential Suzuki reactions, 0.5 mmol of PMB-protected 3,4-dibromomaleimide was utilized in each reaction. On this scale, a total of 372 mg of $Pd_2(dba)_3.CHCl_3$ is needed for all 24 Suzuki reactions in the library preparation; that is, 15.5 mg (3 mmol %) of $Pd_2(dba)_3.CHCl_3$ for each Suzuki reaction. As presented in the current Strem chemical catalogue (for 2010), 2 g of $Pd_2(dba)_3.CHCl_3$ can be purchased for $99.00. This means that the cost for the Pd in the library described above is $18.40

which is actually cheap. For larger libraries, bulk purchases should help to drive down the cost.

It should be noted that no attempt was made to re-cycle the palladium after the reactions. While Capretta *et al.* have previously demonstrated the viability of such recycling (*Org. Lett.*, **2003**, *5*, 953.), given the overall cost of the Pd, the scale of the libraries generated and the work associated with Pd recovery, we felt that such recycling did not make economic sense. Discussions regarding the use of immobilized catalyst systems are presented in the future work below.

The use of microwave irradiation in organic synthesis is shown to facilitate reaction rates and improved product yields. Currently, at McMaster University the microwave systems available permit reactions to be irradiated one at a time, however, it should be noted that there are a number of commercially available microwave systems that offer the ability for processing samples in parallel function allowing the rapid generation of large compound libraries.

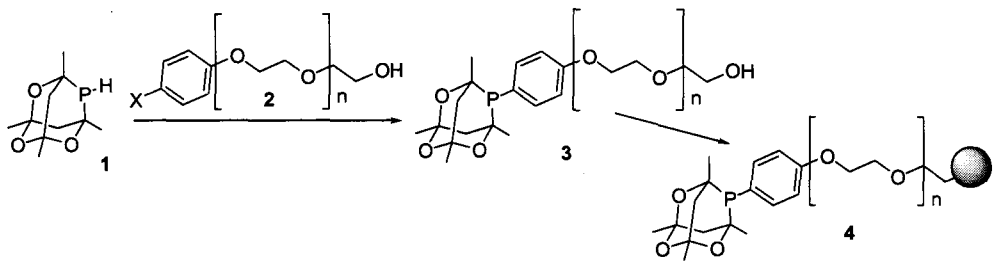
6.1.2 Future Work.

The compounds generated in Chapters 2, 3, 4 and 5 will be used in some of the more biologically oriented investigations currently underway in the Capretta lab. The library of isoquinoline compounds generated in Chapter 4 and 5, for example, will be screened for their ability to modulate or inhibit GFAT activity using an assay developed

by a member in our group. Any hits obtained from the screening will then be optimized for structure activity relationship study.

The maleimide compound library generated in Chapter 3 will be screened for protein kinase inhibitory activities. As with most ATP-competitive inhibitors, the maleimide families exploit similar binding motifs and as a result suffer from kinase selectivity issues.[1] However, regions of protein structure near the binding cleft show higher structural diversity between members of the kinase family than the ATP-binding regions. These regional differences will be exploited to develop compound collections that will increase inhibitor selectivity.

Immobilized catalytic systems are effective in carrying out a variety of reactions in a "greener" manner by allowing for catalyst recycling as well as ease of purification of products. In order to expand the utility of the phospha-adamantyl ligand scaffold, a synthesis that allows for the immobilization of the PA-H system onto a solid phase (as presented in Scheme 6.1) is being explored by the Capretta group. Taking advantage of previously developed chemistry functionalization of 1, 3, 5, 7-tetramethyl-2, 4, 8-trioxa-6-phospha-adamantane (PA-H) with a suitably substituted aryl halide equipped with a tethering moiety **2** should allow for the preparation of **3**. The tethered tertiary PA can be linked to a solid support (for example, *via* an ether linkage to a Merrifield resin) to give **4**. Introduction of palladium should generate an immobilized catalytic system that can then be tested for catalytic efficiency in Pd cross-coupling reactions involving various heterocyclic systems.



Scheme 6.1. Immobilization of the PA-H system onto a solid phase.

Reusability of the immobilized (PA-R) Pd catalytic system will be determined in solid-phase catalytic reactions or in flow chemistry mode. Over the past few years, there have been developments where organic reactions have been carried out successfully in continuous flow processes.[2] Flow chemistry replaces the traditional glassware with columns and cartridges that can be pre-packed with immobilized reagents and catalyst or through the use of reaction chips that control mixing and precise temperatures of reaction sequences. Recently, researchers have utilized microwave irradiations to promote turbulent flow in a continuous flow process in organic synthesis.[3,4] For example Organ *et al.* have demonstrated the use of microwave-assisted continuous flow organic synthesis (MACOS) in the synthesis of a small library of quinolinones and tetrasubstituted amino furans *via* a three component coupling reaction.[4]

The immobilized PA-R Pd catalytic systems that would be developed will be explored in developing a MACOS technology for the synthesis of diverse library of bioactive compounds from readily available precursors.

6.1.3 References

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