ANIONIC *ORTHO*-FRIES REARRANGEMENT OF *N*-CARBAMOYL DIARYLAMINES. SYNTHESIS OF THE ACRIDONE ALKALOID JUNOSIDINE

by

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Abstract

The directed *ortho* metalation (D*o*M) induced anionic rearrangement of *N,N*-diaryl ureas **1.203** into *N*-arylanthranilamides **1.204** and **1.205** (**Scheme 1.55 / Scheme 1.61**) has been studied in detail. A highly regioselective *N*-anionic *ortho* Fries rearrangement of unsymetrical *N,N*-diaryl ureas has been developed (**Scheme 1.61**) and a *pseudo*-regiospecific version of this rearrangement for the synthesis of 1,2,3-trisubstituted *N*-arylanthranilamides **1.210** (**Scheme 1.58**) has also been established. The synthetic utility of this new anionic *ortho* Fries rearrangement has been demonstrated in the total synthesis of two acridone alkaloid natural products, yukodine **1.215** and junosidine **1.6** (**Schemes 1.66** and **1.67**).

Acknowledgements

First of all, I would like to thank my supervisor, Victor Snieckus. Your support, encouragement, and knowledge really made my time at Queen's a great educational experience.

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I would like to express my deepest appreciation to my parents for both their financial and emotional support. You have always been there for me and I hope that you realize how important a part of my life that you are and always will be. Because of this, I dedicate this thesis to my parents, John and Judy.

To John and Judy

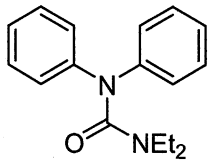
Table of Contents

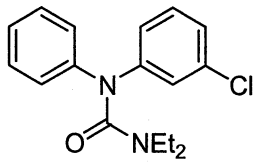
Abbreviations

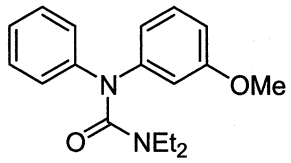
Ac	Acetyl
aq	aqueous
Ar	aryl
b	broad
BINAP	2,2'-bis(diphenylphosphino)-naphthalene
Boc	*t*-butoxycarbonyl
Bn	Benzyl
Bu	butyl
CI	Chemical ionization
CIPE	Complex induced proximity effect
d	Doublet
dba	Dibenzylidene acetone
DIBALH	Diisobutylaluminum hydride
DMF	*N,N*-dimethyl formamide
DMG	Directed metalation group
DMSO	dimethylsulfoxide
D*o*M	Directed *ortho* metalation
dppf	*bis*-(diphenylphosphino)ferrocene
EI	Electron impact
Et	Ethyl
h	Hour (hours)
HMDS	Hexamethyldisilazane

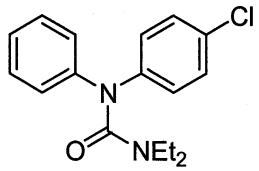
HRMS	High resolution mass spectrometry
Hz	Hertz
*i*Pr	Isopropyl
L	Ligand
LDA	Lithium diisopropylamide
m	Multiplet
m-CPBA	*meta*-chloro peroxybenzoic acid
MOM	methoxymethyl
Ms	Methanesulfonyl
OTf	Triflate
Ph	Phenyl
rt	Room temperature
s	Singlet
sept	septet
t	Triplet
THF	tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	Trimethylsilyl

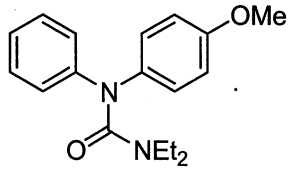
List of Experimental Procedures

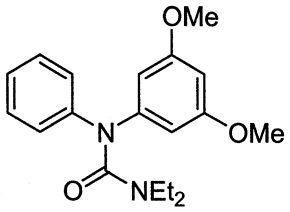


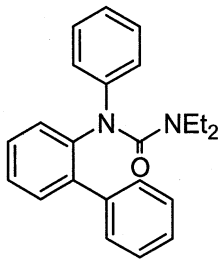


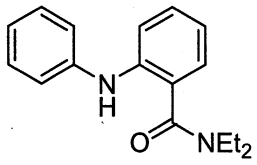


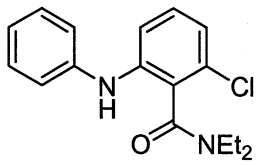


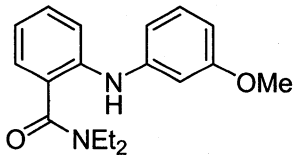


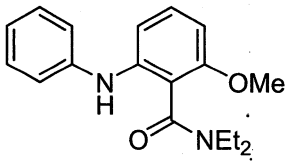


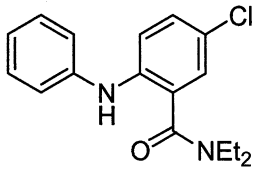


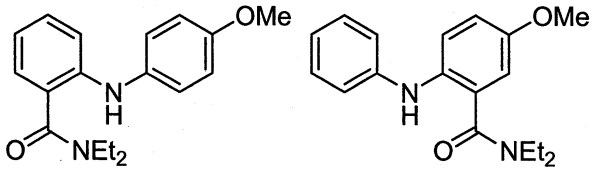


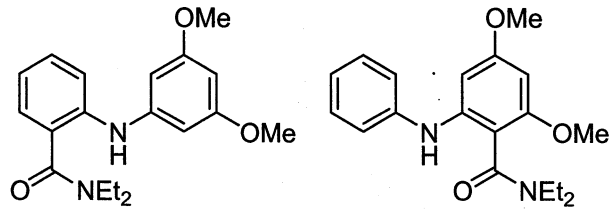


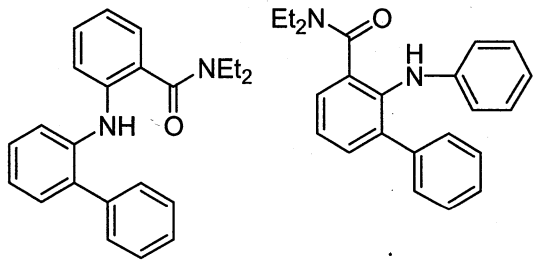


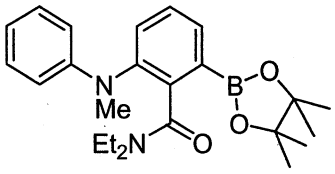


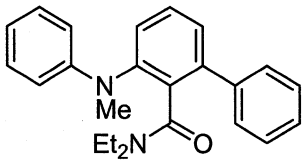


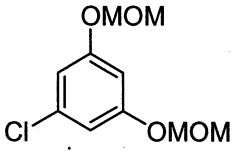


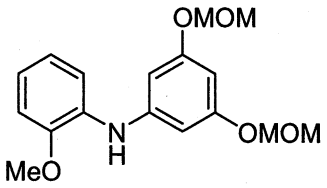


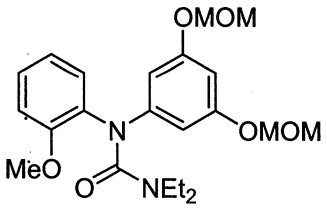


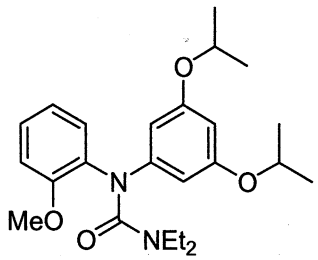


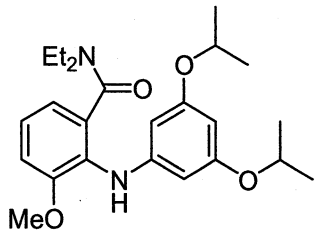


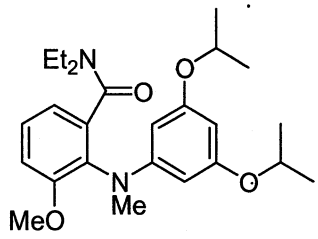


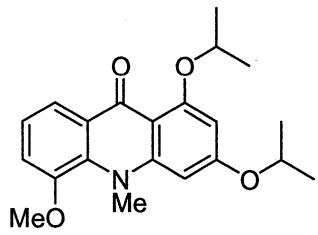


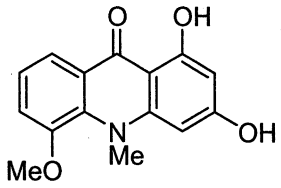


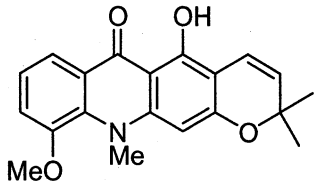








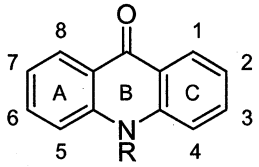




1.1 The Acridone Alkaloids

1.1.1 Structure and Occurence

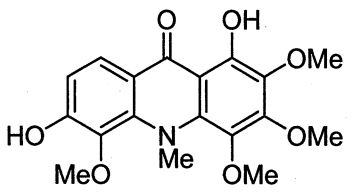
The acridone alkaloids are a family of naturally occurring molecules that appear to be unique to the order of *Rutales* and consist of approximately 190 secondary metabolites based on the 9-(10H)-acridinone skeleton **1.1**. Acridone alkaloids have been isolated from 35 genera of the *Rutaceae* and a single genus of the *Simaroubaceae*.



1.1

Oxygenated substituents at the C-1 and C-3 positions of the acridone C ring are quite common and are the consequence of biosynthesis.[1] While de-oxygenated acridone alkaloids are rare, further oxidation of the acridone skeleton is common and is exemplified by glyfoline **1.2**,[2] the most highly oxygenated isolated acridone alkaloid. Along with simple oxygenated variations of the acridone skeleton, the family of natural products also includes some twenty prenylated acridones exemplified by baiyumine-B **1.3**.[3] Annulated acridones are also common and the additional ring can be five or six membered. The furanoacridones are represented by furoparadine **1.4**[4] although dihydrofuranoacridones have also been isolated.[5] Pyranoacridones have been isolated in two geometric variations, linear and angular. The angular pyranoacridones are more common, and hence more is known about their biological and physical properties. The most famous acridone alkaloid acronycine **1.5**[6] is an angular pyranoacridone, while the

linear pyranoacridones are exemplified by junosidine **1.6**.[7] Some unusual acridone alkaloids have also been isolated from natural sources including azaacridone-A **1.7**,[8] and the tropolone A-ring acridones citropone-A **1.8** and citropone-B **1.9**.[9]



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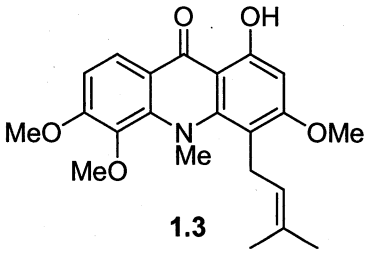

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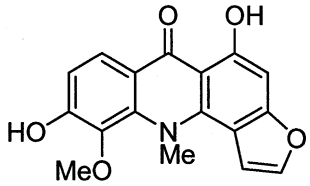

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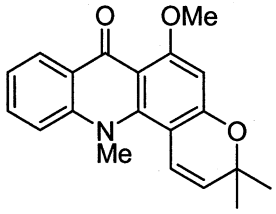

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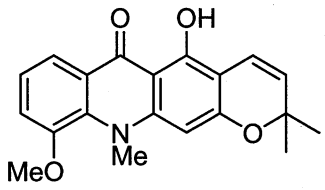

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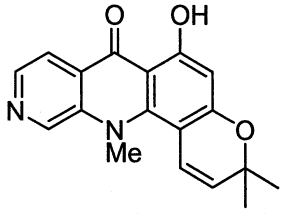

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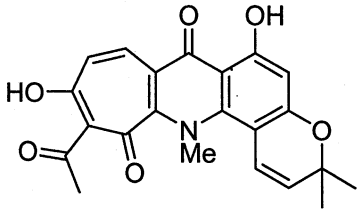

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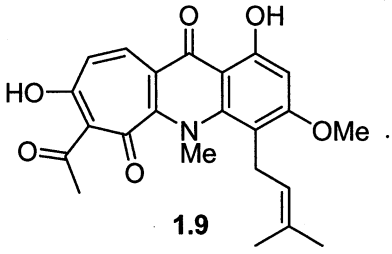
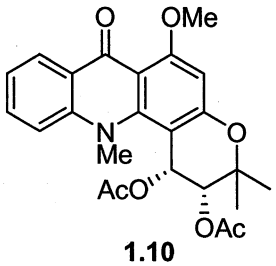


1.9

1.1.2 Biological Activity

Although acridone alkaloids were not known as chemical constituents of plants from the family *Rutaceae* until they were first isolated in 1948 by Price *et al.*,[6] the medicinal value of these plants has been known for some time. Since ancient times the extracts of the *Rutaceae* have been used in Chinese folk medicine. For example, "Chen-Pi" and "Bai-Yu" are two such medicines that are extracted from these plants and have been used as treatments for various ailments including heartache, abdominal pain, diarrhea, vomitting, skin itch, boils and ulcers.

Acridone alkaloids have been reported to possess a wide range of biological activities including, but not limited to, anti-malarial,[10-12] anti-herpesvirus,[13,14] antiplatelet aggregation,[15] and antispasmodic activity.[16] Most of the interest in the biological properties of the acridone alkaloids however is in the field of cancer chemotherapy owing to the initial anti-tumor properties attributed to acronycine.[17] Unfortunately clinical trials gave poor results owing to the moderate potency and poor water solubility of acronycine.[18] More recently the dihydroxylation of acronycine itself has led to synthetic derivatives with increased potency *in vivo*.[19,20] In particular, *cis*-1,2-diacetoxy-1,2-dihydroacronycine **1.10** appears to be the most interesting derivative. It was found to be six fold more potent in a L1210 leukemia model, more efficacious at an eight fold lower dose in a P388 leukemia model, and all mice in the highly resistant solid tumor C38 colon adenocarcinoma model were tumor free after 23 days.

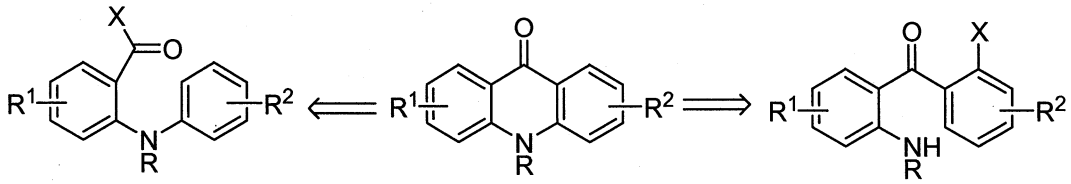


1.10

1.1.3 Synthesis of Acridone Alkaloids

The promising anti-tumor properties of acronycine and its derivatives have led to several synthetic routes to the tricyclic core of the acridone alkaloids. Two of the more common approaches involve the coupling of two aromatic substrates, which effectively bring together the preformed A and C rings of the acridone framework. The cyclisation of a diphenylamine (**1.11**) or a benzophenone (**1.12**) intermediate have proven to be

effective in the synthesis of acridone alkaloids (**Scheme 1.1**). The synthetic utility of these methods will be described in the following sections.

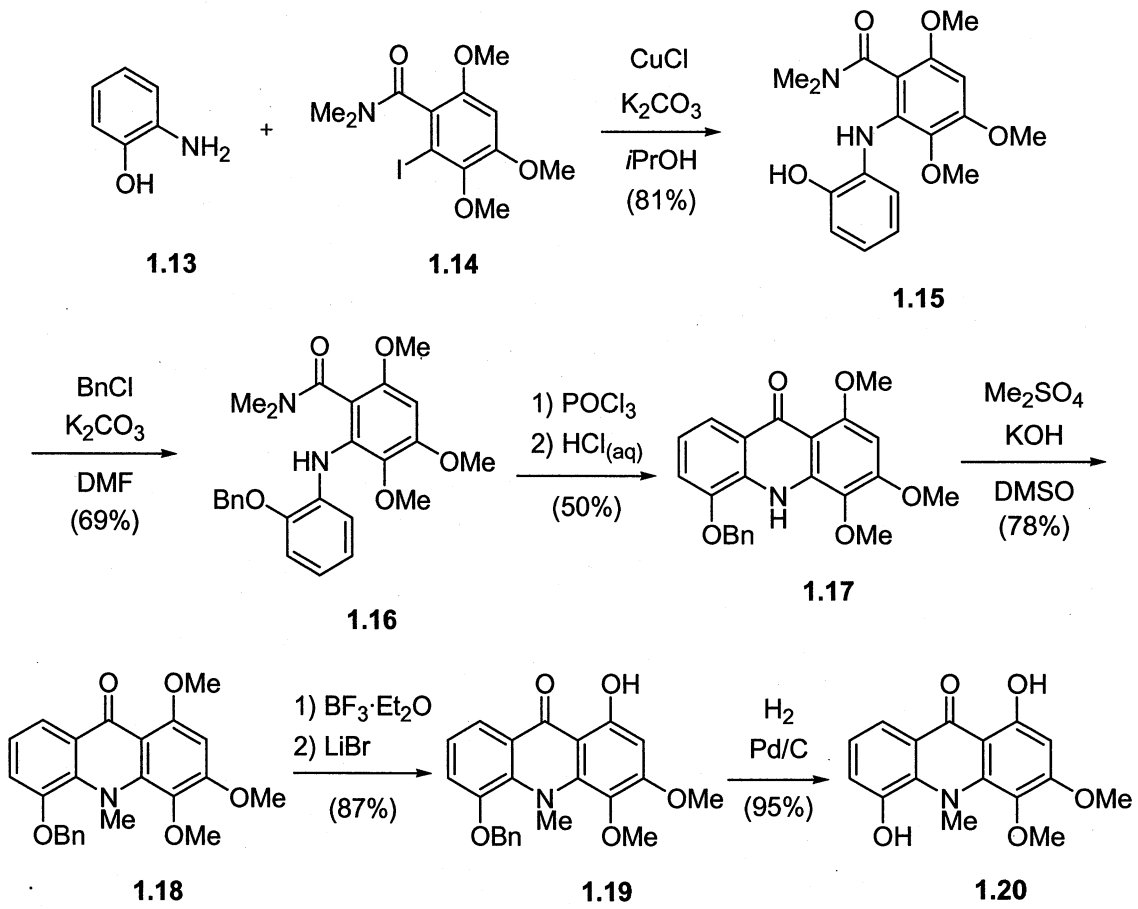


1.11 **1.12**

Scheme 1.1

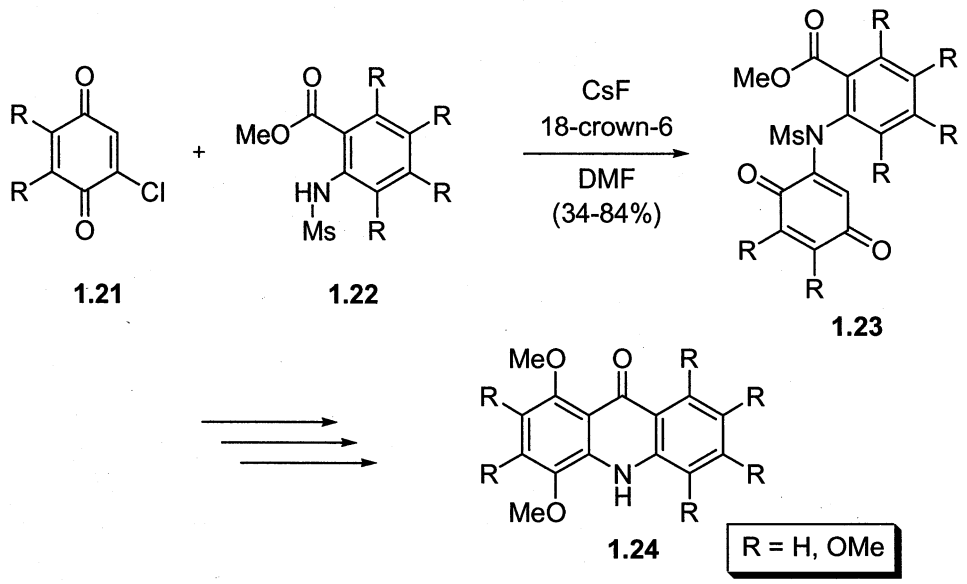
1.1.3.1 Cyclisation of a Diphenylamine Intermediate

The synthesis of acridone alkaloids *via* the cyclisation of an *N*-aryl anthranilic acid derivative was introduced in 1950 by Hughes and co-workers[21] and has been exploited by many researchers since.[22-26] The 1993 synthesis of citrusinine-I (**1.20**) (**Scheme 1.2**) by Kato *et al.*[27] is representative of this approach to acridone alkaloids. Ullman reaction of iodide **1.14**, prepared in two steps and 30% yield with amino phenol **1.13** proceeded smoothly in *i*PrOH to afford *N*-aryl anthranilamide **1.15**. Treatment of **1.15** with benzyl chloride afforded *O*-benzylated precursor **1.16** which was cyclized with phosphorous oxychloride. Acidic hydrolysis of the resultant chloroacridine afforded the desired acridone **1.17** which could be *N*-methylated efficiently with dimethyl sulfate. Selective demethylation at the 1-position with boron trifluoride etherate and LiBr followed by hydrogenolysis of the benzyl ether afforded the desired acridone citrusinine-I (**1.20**) in 8 steps and 5% overall yield.



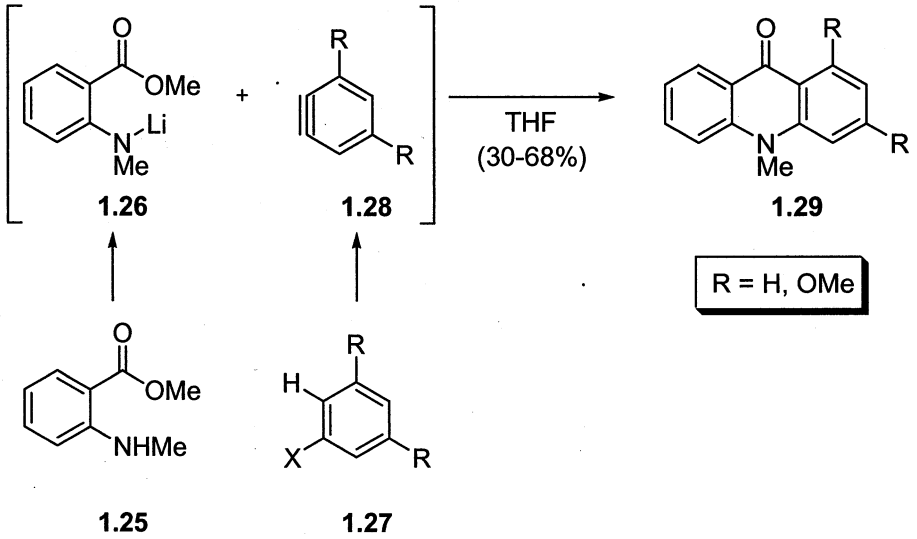
Scheme 1.2

An alternative route to the required diphenylamine intermediates has been developed by Brassard and co-workers (**Scheme 1.3**).[28,29] The substitution of chloroquinone **1.21** with methyl *N*-mesylanthranilate **1.22** in the presence of fluoride ion provided access to a variety of oxygenated substitution patterns in modest to excellent yields. Simultaneous reduction of the quinone and *O*-methylation provided the diphenylamine intermediates which were cyclised to acridones **1.24** with either phosphorous oxychloride or trifluoroacetic anhydride.



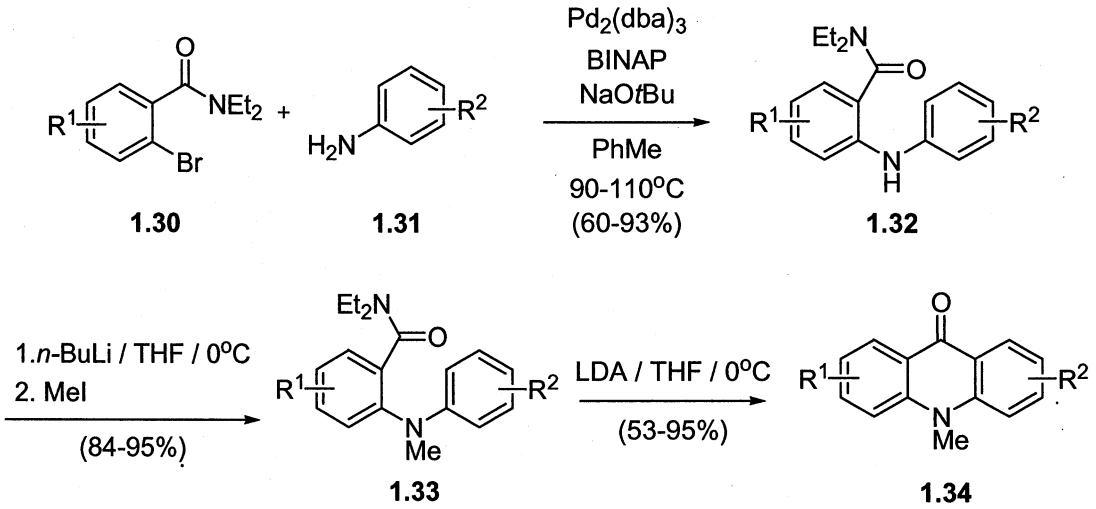
Scheme 1.3

Another approach developed by Watanabe[30] involves the reaction of the lithium salt of methyl anthranilate **1.25** with an *in-situ* generated benzyne **1.28** (**Scheme 1.4**). The advantage of this procedure is that the lithium salt of the diphenylamine intermediate cyclizes directly to the acridone skeleton in one pot.



Scheme 1.4

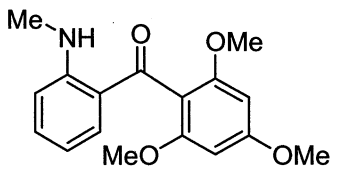
MacNeil and Snieckus have reported a modernised version of this route to acridones.[31,32] Palladium catalysed amination of 2-bromobenzamides **1.30** with anilines **1.31** replaces the traditional Ullman synthesis of the diphenylamine intermediate. Subsequent anionic cyclisation of these intermediates furnishes the desired acridones **1.34** with regiochemical complimentarity to traditional Friedel-Crafts chemistry (**Scheme 1.5**)



Scheme 1.5

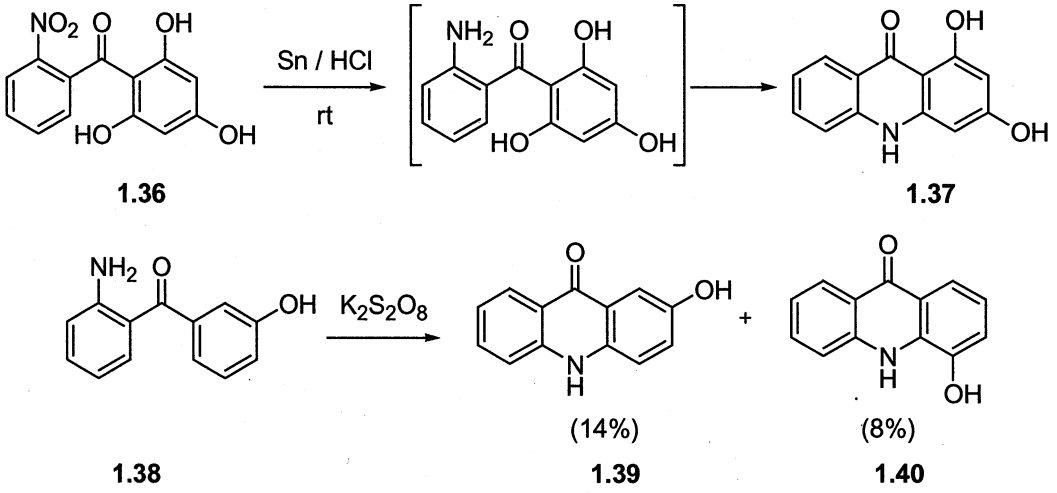
1.1.3.2 Cyclisation of a Benzophenone Intermediate

The isolation of tecleanone **1.35**[33,34] from various species of the Rutaceae strongly suggests that the biosynthesis of the acridone alkaloids involves the cylisation of benzophenone intermediates.



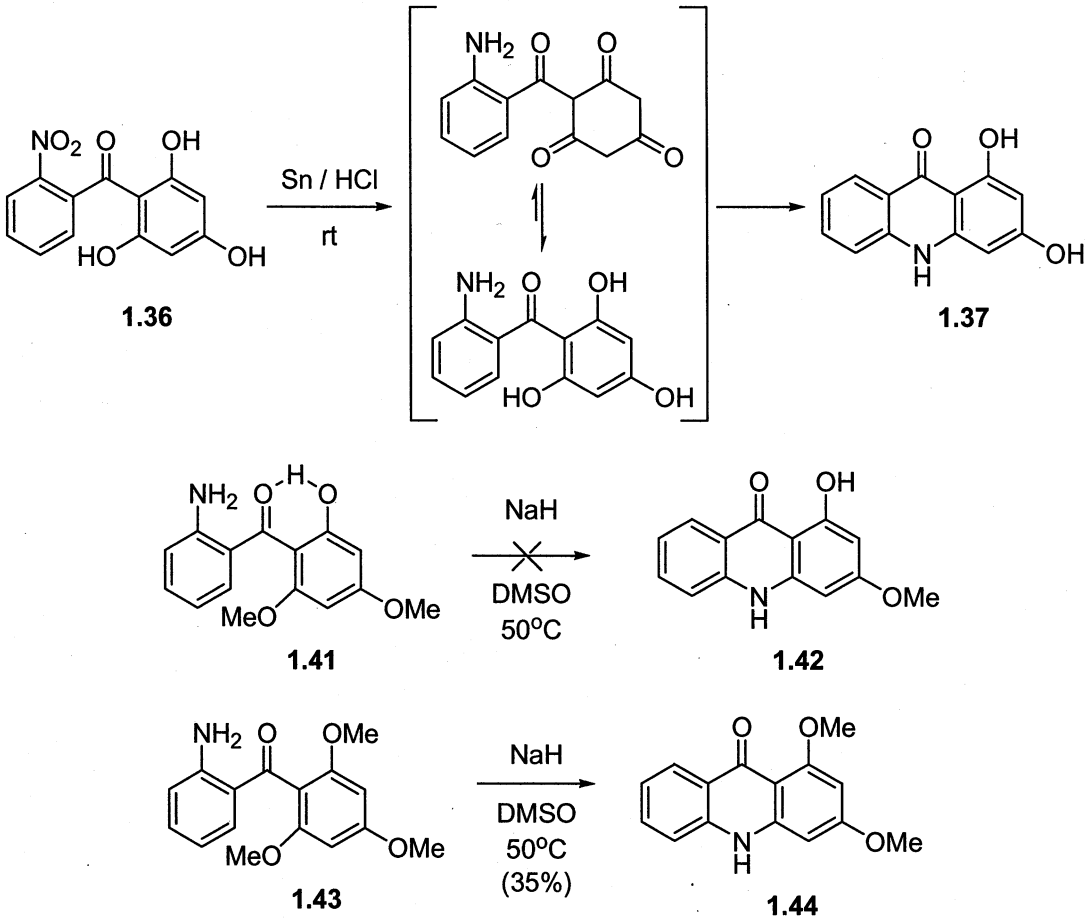
1.35

The work of Lewis *et al.* has demonstrated this biosynthetic approach as feasible for the synthesis of acridones.[35-38] Initial experiments revealed that tin reduction of 2-nitro trihydroxy benzophenone **1.36** under acidic conditions afforded the desired 1,3-dihydroxyacridone **1.37** in quantitative yield, while exposure of amino analogue **1.38** to potassium persulfate only provided acridones **1.39** and **1.40** as a mixture in low yield (**Scheme 1.6**).



Scheme 1.6

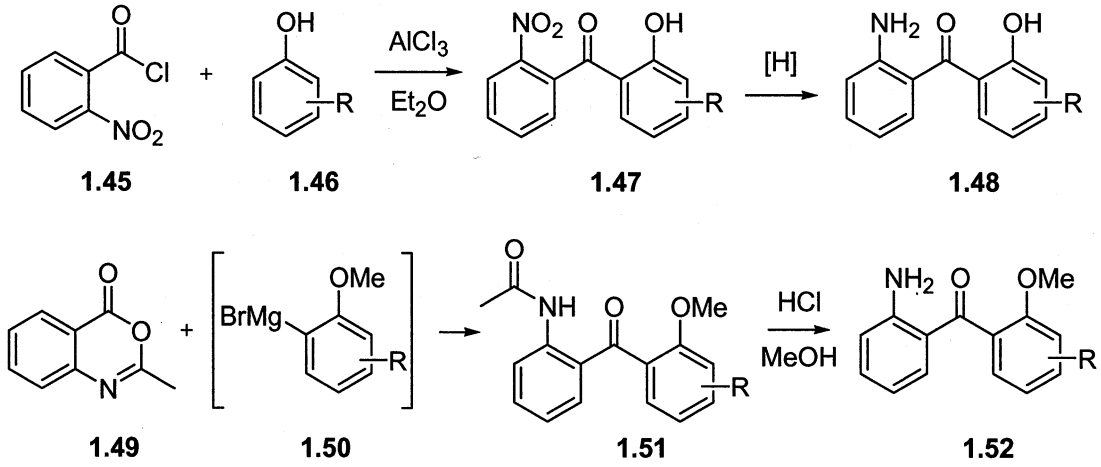
Further experimentation directed at a more general approach to acridones *via* this route has generated some mechanistic insight into this reaction (**Scheme 1.7**).[35] The rapid cyclisation of 2-nitro trihydroxy benzophenone **1.36** upon reduction compared to the stability of its methyl ether analogues may indicate that the cyclisation is occuring through a keto form of the phloroglucinol ring. The intramolecular nucleophillic attack of the amino group preferentially occurs through a non-planar benzophenone geometry as illustrated by the fact that strongly hydrogen bonded hydroxy benzophenone **1.41** does not cyclise while its methyl ether counterpart **1.43** does, albeit in modest yield.



Scheme 1.7

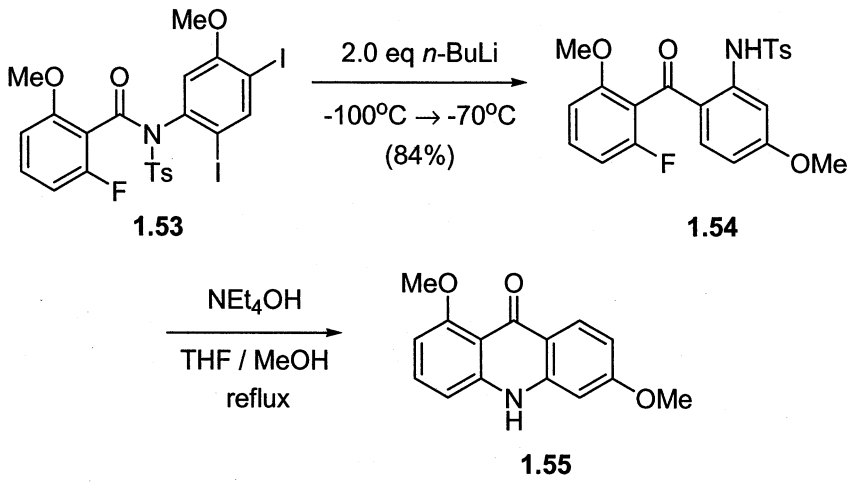
At the time, access to the required aminobenzophenones was limited to two general synthetic routes. The first is a classical Friedel-Crafts reaction of 2-nitrobenzoyl chloride **1.45** with an appropriately substituted phenol **1.46** and subsequent reduction whereas the second is a condensation of 2-methyl-3,1-benzoxazin-4-one **1.49** with Grignard reagent **1.50** followed by hydrolysis of the resultant acetamide **1.51** (**Scheme 1.8**). Both of these routes have limitations, the Friedel-Crafts method would of course produce regioisomeric mixtures consistent with electrophilic aromatic substitution rules in unsymmetrical substrates and both methods have the potential for mixtures resulting from the nucleophilic substitution step in unsymmetrical cases. Although possible,

neither route was ever used to produce acridones bearing substituents in the resulting A ring of the alkaloid framework.



Scheme 1.8

An efficient route to acridones *via* benzophenone intermediates has been developed by Rodrigo and co-workers and it addresses the drawbacks of the previous methods described above.[39] The lithium-halogen exchange induced rearrangement of *N*-tosyl iodobenzanilides **1.53** furnished the required benzophenones **1.54** which could be hydrolised and cyclised in a one pot procedure to the corresponding acridones **1.55** in high yield (**Scheme 1.9**). The cyclisation step in this sequence proceeds with complete regiochemical control as only the fluorine and not the equivalently situated methoxyl is substituted.



1.53 **1.54** **1.55**

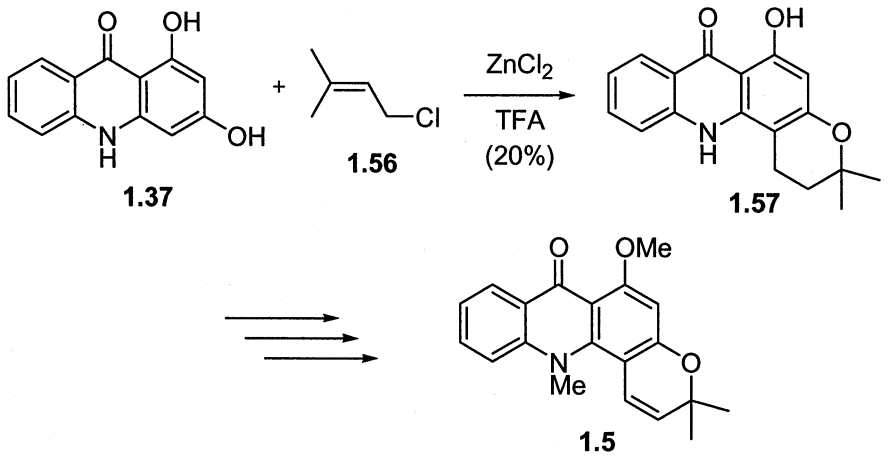
Scheme 1.9

1.1.3.3 Synthesis of Pyranoacridones

Although convergent syntheses of pyranoacridones that involve the construction of the acridone nucleus have been reported by several authors, these approaches are very similar to those discussed in **Section 1.1.3.1** and **Section 1.1.3.2**. In general these methods involve the cyclisation of either a diphenylamine[23,30,40-42] or benzophenone[35,43] intermediate with the dimethylpyran D ring already in tact, and thus will not be discussed further.

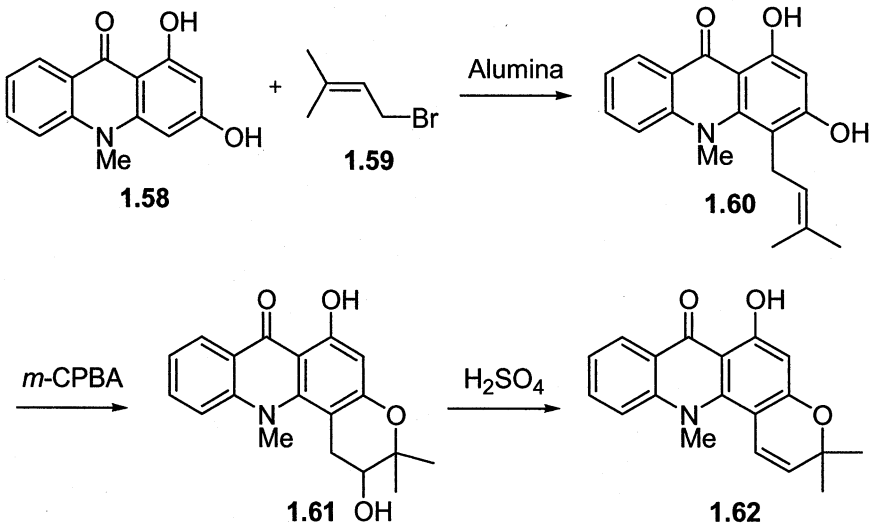
Another common route to pyranoacridones involves the alkylation of a preformed 1,3-dioxygenated acridone core and then elaboration of the pyran D ring by subsequent or simultaneous cyclisation. 1-Chloro-3-methyl-2-butene **1.56** was used for this purpose in an early synthesis of acronycine **1.5** by Beck and co-workers (**Scheme 1.10**).[42] Condensation of 1,3-dihydroxyacridone **1.37**, prepared in 25% yield with **1.56** in the presence of zinc chloride afforded the dihydro-pyranoacridone **1.57** in 20% yield which

could be converted to acronycine **1.5** *via* *N*-methylation, dehydrogenation and *O*-methylation sequence.



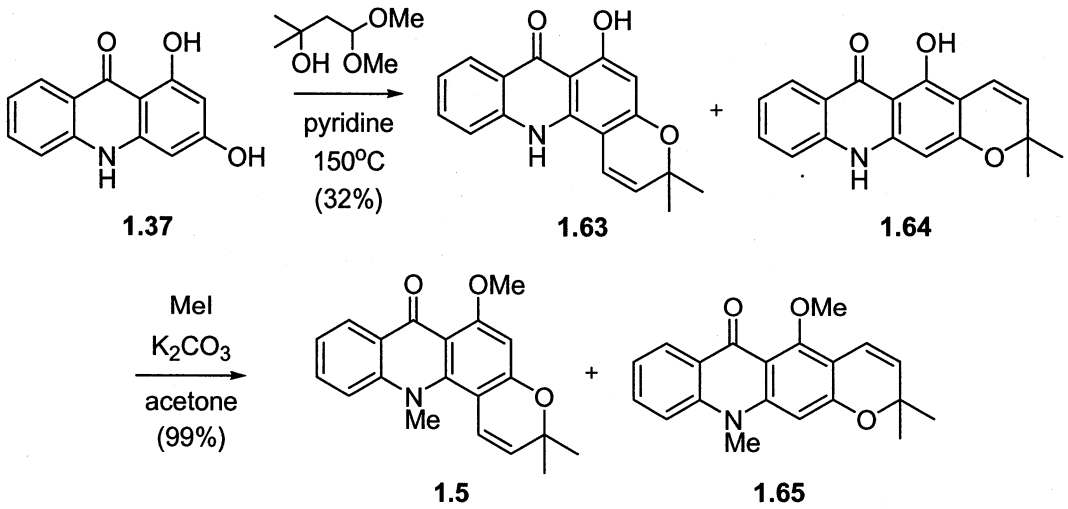
Scheme 1.10

1-Bromo-3-methyl-2-butene **1.59** has more recently been used by Grundon and Reisch in the synthesis of noracronycine **1.62** (**Scheme 1.11**).[44] Condensation of *N*-methyl-1,3-dihydroxyacridone **1.58** with **1.59** in the presence of alumina afforded the prenyl acridone glycocitrine-II **1.60**. Cyclisation of **1.60** by treatment with *m*-CPBA afforded **1.61** which could in turn be dehydrated with concentrated sulphuric acid to yield noracronycine **1.62**.



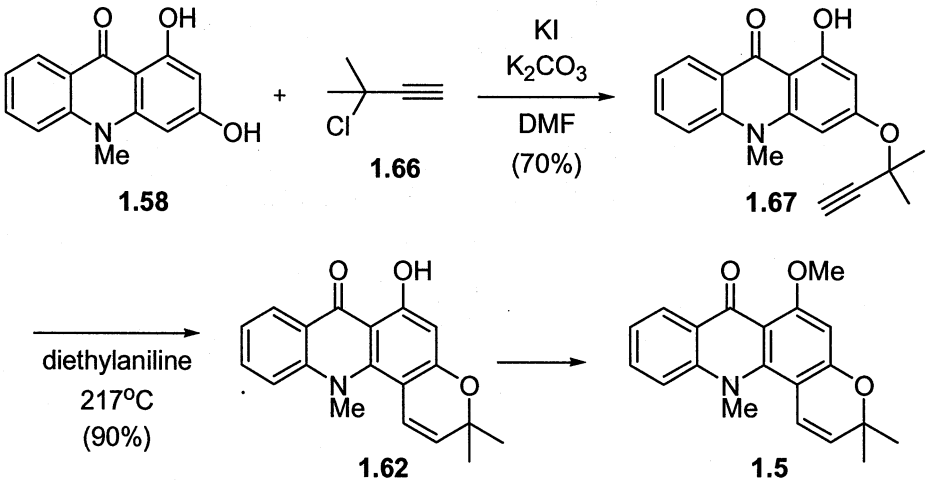
Scheme 1.11

The use of 3-hydroxyisovaleraldehyde dimethylacetal in the synthesis of pyranoacridone alkaloids was introduced in 1969 by Crombie *et al.*[45] Condensation of this reagent with 1,3-dihydroxy acridone **1.37** in pyridine at 150°C for 8 hours provided a regioisomeric mixture of angular **1.63** and linear **1.64** acridones. Methylation of the mixture with methyl iodide in acetone provided acronycine **1.5** and isoacronycine **1.65** in 74% and 25% respectively (**Scheme 1.12**).



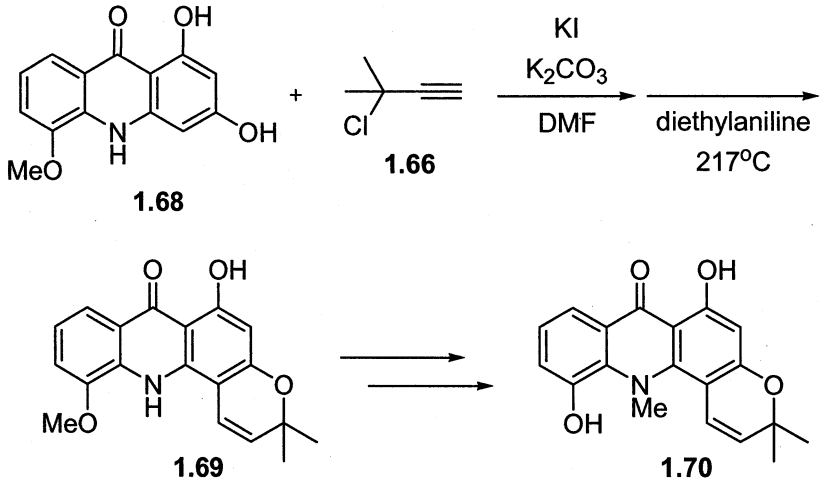
Scheme 1.12

One of the more successful approaches toward the pyranoacridones was introduced by Taylor and co-workers in 1969.[46,47] Alkylation of 1,3-dihydroxy-10-methylacridone (**1.58**) with 3-chloro-3-methyl-1-butyne (**1.66**) in dimethylformamide affords propargyl ether **1.67**. Claisen rearrangement induced by heating at reflux in diethylaniline provided noracronycine **1.62** in 90% yield with no trace of the corresponding linear isomer. Subsequent methylation afforded acronycine **1.5** (**Scheme 1.13**).



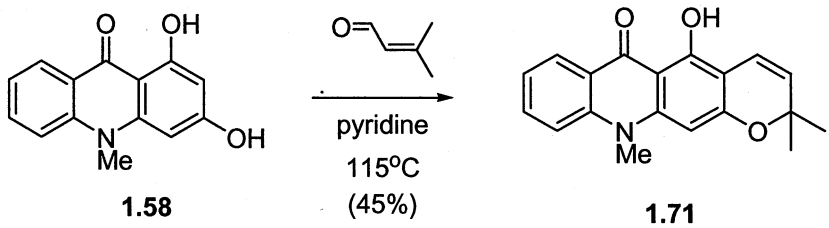
Scheme 1.13

The above approach was also used by Adams, Bruce, and Lewis in the total synthesis of 11-hydroxynoracronycine **1.70** (**Scheme 1.14**).[48] Treatment of 1,3-dihydroxy-5-methoxy acridone (**1.68**), prepared from 3-methoxy benzoic acid in 3 steps and 12% yield, with 3-chloro-3-methyl-1-butyne (**1.66**) afforded the angular pyranoacridone **1.69**. Subsequent global methylation and *O*-de-methylation steps afforded the target pyranoacridone **1.70**.



Scheme 1.14

Attasi has reported a method for the regioselective sythesis of linear pyranoacridones.[49] Although isoacronycine **1.65** has been isolated several times, it has usually been considered a byproduct in the synthesis of the desired anti-tumor alkaloid acronycine. Treatment of 1,3-dihydroxy-10-methylacridone (**1.58**) with 3-methyl-2-butenal in pyridine led exclusively to nor-isoacronycine **1.71** in 45% yield with recovery of 55% of the starting material (**Scheme 1.15**). Interestingly, treatment of 1,3-dihydroxyacridone under the same reaction conditions results in a 9:1 mixture of linear and angular pyranoacridones respectively also in 45% yield.



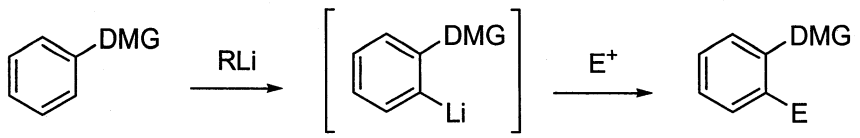
Scheme 1.15

1.2 The Directed *ortho* Metalation Reaction

1.2.1 Directed *ortho* Metalation

The relevance of aromatic compounds to the field of chemistry, in particular materials science and medicinal chemistry dictates the need for reliable methods of synthesizing polysubstituted aromatics and heteroaromatics. Although covered in detail in undergraduate level textbooks as a method for the synthesis of aromatic compounds, electrophilic aromatic substitution reactions may not be able to provide, for various reasons, the desired structures. The typically harsh acidic reaction conditions may not be compatible with certain functionality and the regiochemical outcome of such reactions is at the mercy of electrophilic aromatic substitution rules. That being said, electrophilic aromatic substitution has value in synthetic chemistry but complimentary methods for the construction of aromatic compounds not available through these methods are still required.[50]

The concurrent and independant discovery of Gilman[51] and Wittig[52] that anisole is regioselectively *ortho*-deprotonated by *n*-BuLi provided the groundwork for the development of the directed *ortho* metalation (D*o*M) reaction as it is known today. The reaction involves treatment of a heteroatom containing directed metalation group (DMG) substituted aromatic **1.72** with a strong base, typically an alkyllithium reagent. Electrophilic quench of the *ortho* lithiated species **1.73** results regiospecifically in 1,2-disubstituted aromatics **1.74** (**Scheme 1.16**).



1.72 **1.73** **1.74**

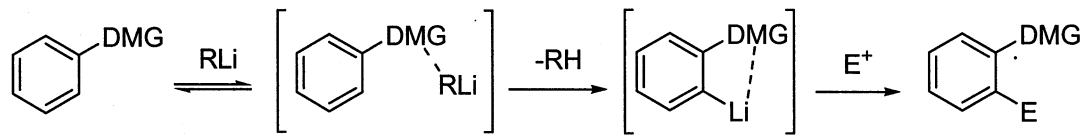
Scheme 1.16

An attractive feature of the D*o*M reaction is the large number of functional groups that have been demonstrated to function as DMGs. All DMGs contain at least one heteroatom that is presumed to interact with the alkyllithium and provide the directing effect. The DMGs are attached to the aromatic substrate either through a carbon or heteroatom. Carboxylic acids,[53] esters,[54] secondary and tertiary amides,[55] nitriles[54] and oxazolines[56] are common carbon based DMGs with the tertiary amide and oxazoline being most widely exploited. Many heteroatom linked DMGs have also been reported, of particular interest are *N*-Boc,[57] *O*-methoxymethyl,[58] teriary *O*-aryl carbamate,[59] secondary and teriary sulfonamide,[60,61] and phosphine oxide.[62] In 1990 D*o*M of tertiary benzmides and carbamates was exhaustively reviewed by Snieckus[63] and more recently the topic has been covered in terms of its mechanism[64] and its connection with transition metal cross-coupling reactions.[65]

Although the D*o*M reaction has been known for more than 60 years, a mechanistic understanding of the high *ortho* selectivety has yet to be clearly defined. There exists two main mechanistic proposals for the D*o*M reaction and for which evidence has been accumulated. One mechanistic proposal involves the complexation of the alkyllithium with the heteroatom of the DMG which brings the reagent in close proximity to the *ortho* proton resulting in the high regioselectivity of the reaction. The

alternate proposal is that the inductive effect of the DMG is responsible for the enhanced acidity of the *ortho* hydrogen and no complexation between the alkylithium and the DMG is involved.

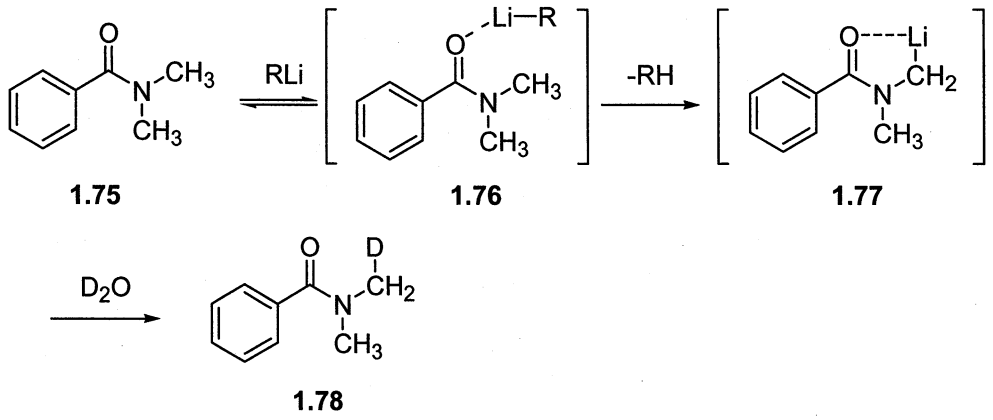
The mechanism involving precomplexation of the alkyllithium reagent was first propsed by Roberts and Curtin[66] and has since been referred to as the *Complex Induced Proximity Effect* (CIPE).[67] Upon treatment of substrate **1.72** with an alkyllithium reagent complexation of the reagent with the heteroatom of the DMG positions the base in close proximity to the *ortho* proton. Rapid and irreversible removal of the *ortho* proton results in the formation of the intramolecularly complexed lithio species **1.73** which upon treatment with an electrophile leads to the 1,2 disubstituted aromatic **1.74** (**Scheme 1.17**).



1.72 **1.73** **1.74**

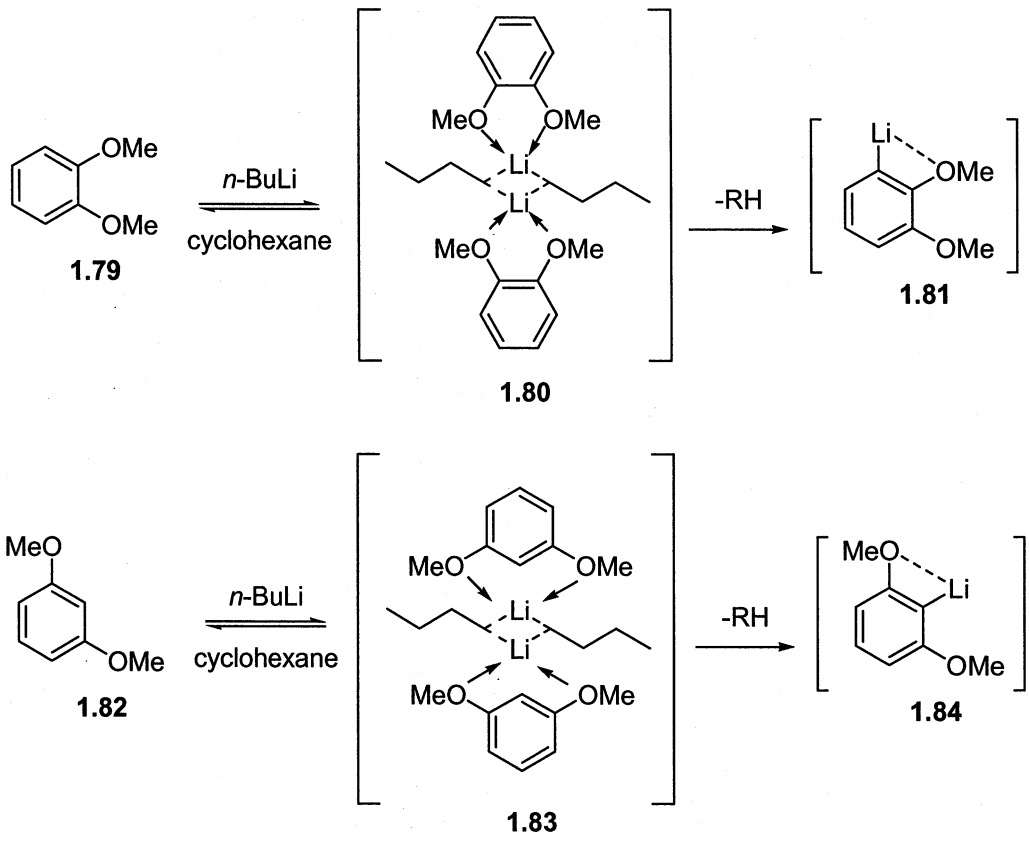
Scheme 1.17

Beak and co-workers[68,69] have reported evidence for complex formation in the α'-lithiation of tertiary benzamides by following a reaction using stopped flow IR spectroscopy (**Scheme 1.18**). The authors were able to follow the changes in frequency of the amide carbonyl absorption over the course of the reaction from 1650 cm^{-1} for the starting benzanide **1.75** to 1625 cm^{-1} for the complexed benzamide **1.76** and 1588 cm^{-1} for the α'-lithiated species **1.77**.



Scheme 1.18

Most recently a report from Slocum and co-workers[70] has presented direct NMR evidence for the formation of substrate/alkyllithium complexes in the metalation of dimethoxybenzenes (DMBs) in hydrocarbon solvents. Alkyllithiums are known to exist in different oligomeric forms as a function of solvent and the presence of a deoligomerization agent such as TMEDA. In non-polar hydrocarbon solvents, *n*-BuLi exists as a hexameric species which permits little metalation of aromatic substrates. In ether solvents such as THF and Et_2O *n*-BuLi exists as mixtures of dimeric and tetrameric forms that allow for the metalation of aromatic substrates to proceed. Remarkably both 1,2-DMB **1.79** and 1,3-DMB **1.82** are metalated efficiently in either *n*-hexane, cyclohexane or toluene without the presence of TMEDA. Further studies of these reactions by ^{13}C NMR experiments revealed that for both DMBs a second methoxy signal began to emerge with time, and that in both cases the new signal represented a methoxy group environment with a single symmetry consistent with dimeric bidentate complexes **1.80** and **1.83** resepectively (**Scheme 1.19**).

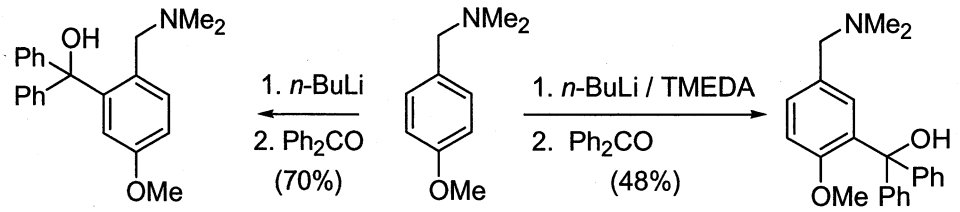


Scheme 1.19

As mentioned above, an alternate view of the mechanism of the D*o*M reaction downplays precomplexation and instead argues that inductive effects enhance the acidity of the *ortho* proton which is more readily removed by the strongly basic alkyllithium. Although the evidence discussed above supports the notion of CIPE there have been discrepancies reported with the reaction as drawn in **Scheme 1.17**. The rate acceleration of DoM by the addition of TMEDA first reported by Slocum[71] is at odds with the precomplexation mechanism described above. Comparing the metalation of anisole with *n*-BuLi in Et_2O at 25°C in the absence and presence of TMEDA brings into question the importance of precomplex formation.[72] Metalation of anisole with 2.0 equivalents of *n*-BuLi and quenching with TMSCl provides the desired 2-TMS compound in >80% yield only after a 24 h metalation time, however if 2.0 equivalents of TMEDA are added >95%

of product is obtained in less than 0.5 h. This observation was interpreted to indicate that in the presence of TMEDA the slow precomplexation step is avoided and rapid reaction of the reagent with the relatively more acidic *ortho* proton occurs. The significant kinetic isotope effect reported by Collum[73] for the *n*-BuLi / TMEDA metalation of anisole (k_H/k_D = 20) also infers a rate limiting deprotonation which is inconsistent with a rate limiting precomplexation proposed by CIPE. More recently Collum[74] has reported rate studies on a series of related alkoxy-substituted arenes. Supported by *ab initio* calculations, a triple-ion based model that depends largely upon inductive effects and allows for substituent-dependent rates while also allowing for substituent-independent mechanisms was proposed.

Blurring the lines of the two stances on the mechanism of the D*o*M reaction are examples where slightly modified conditions drastically alter the regioselectivity, possibly by changing the mechanism from a CIPE based interaction to one that is dominated by inductive effects. The metalation of *p*-methoxydimethylbenzylamine **1.85** in the presence or absence of TMEDA provides the two possible D*o*M products **1.86** or **1.87** respectively (**Scheme 1.20**).[71] Metalation of **1.85** with *n*-BuLi in the absence of TMEDA followed by quenching with benzophenone affords regioisomer **1.86** presumable *via* a co-ordinative mechanism. Carrying out the same reaction with the addition of TMEDA affords the complimentary regioisomer **1.87** indicating the dominance of inductive effects under the new reaction conditions.



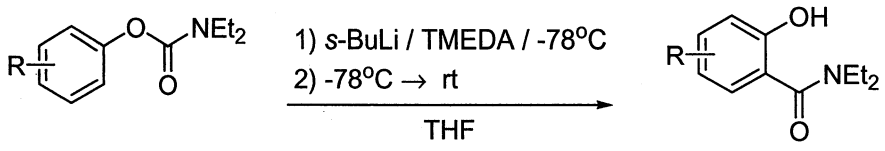
1.86 **1.85** **1.87**

Scheme 1.20

The observations of Schleyer also have interesting implications.[75] Anisole has been shown by various NMR experiments to form a 1:1 complex with *n*-BuLi in toluene-d_8. Although the detection of this complex appears at first to support the notion of CIPE, this complex does not undergo *ortho* lithiation even at elevated temperatures. Upon addition of TMEDA, metalation occurs at low temperatures despite the absence of a detectable anisole-*n*-BuLi complex. It was concluded that the detection of a complex does not automatically determine that the complex is on the reaction pathway while, at the same time, the failure to detect a certain complex does not discount it or another complex as an intermediate crucial to the progress of the reaction.

1.2.2 Metalation Induced Anionic Carbamoyl Rearrangements

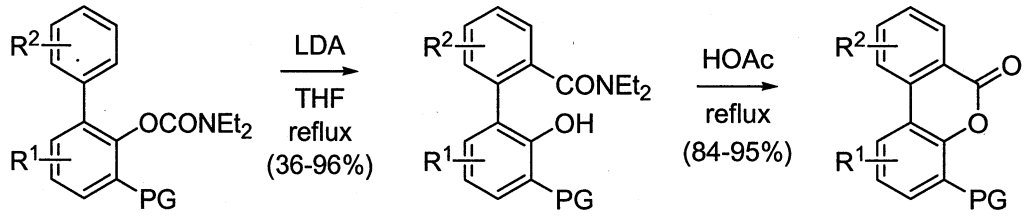
As well as being the most powerful DMG known,[63] the tertiary *O*-aryl carbamate[59] has other advantages in synthetic aromatic chemistry. For example, in comparison to the methoxymethyl (MOM) DMG[58,76] it provides complementary base-catalyzed hydrolytic procedures for conversion to *ortho* substituted phenols. More importantly in the context of this work, the discovery that metalation of carbamate **1.88** in the absence of an external electrophile results in the formation of the salicylamide **1.89** constituting an anionic version of the *ortho* Fries rearrangement (**Scheme 1.21**).



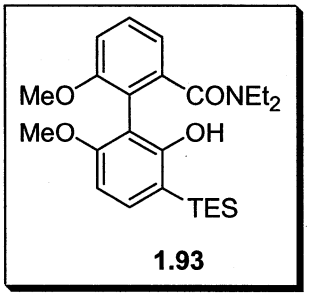
1.88 **1.89**

Scheme 1.21

Since the first report of this anionic version of the Fries rearrangement in 1983, several other versions of this reaction have appeared in the literature. In 1992 Wang and Snieckus combined this anionic rearrangement with directed remote metalation (DreM) for the synthesis of highly hindered biaryls, dibenzo[b,d]pyranones, and the naturally occuring fluorenone dengibsin **1.97**.[77] Exposure of biphenyl 2-*O*-carbamates **1.90** to an excess of LDA afforded the biphenyl amides **1.91** in high yields (**Scheme 1.22**). Of particular interest is the biphenyl amide **1.93**, a tetrasubstituted biphenyl prepared in 36% yield that would not be easily obtained by standard cross-coupling methods. Conversion to the benzo[b,d]pyranones **1.92** was accomplished in high yields *via* an acid catalyzed procedure.



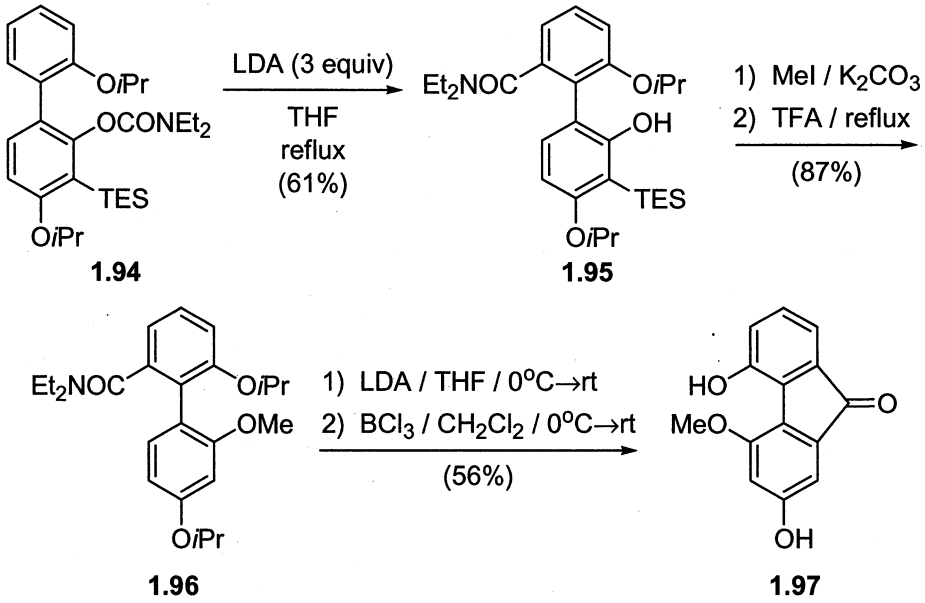
1.90 **1.91** **1.92**



1.93

Scheme 1.22

The utility of the remote anionic Fries rearrangement was further demonstrated in the total synthesis of dengibsin **1.97** (**Scheme 1.23**). The appropriately substituted biphenyl 2-*O*-carbamate **1.94** was prepared in 7 steps (38% yield) which upon treatment with LDA at reflux afforded biphenyl amide **1.95** in 61% yield. Methylation of the resultant phenol and removal of the silicon protecting group afforded the cyclization precursor **1.96** in 87% yield. LDA induced cyclization followed by chemoselective deisopropylation furnished the target fluorenone **1.97**.

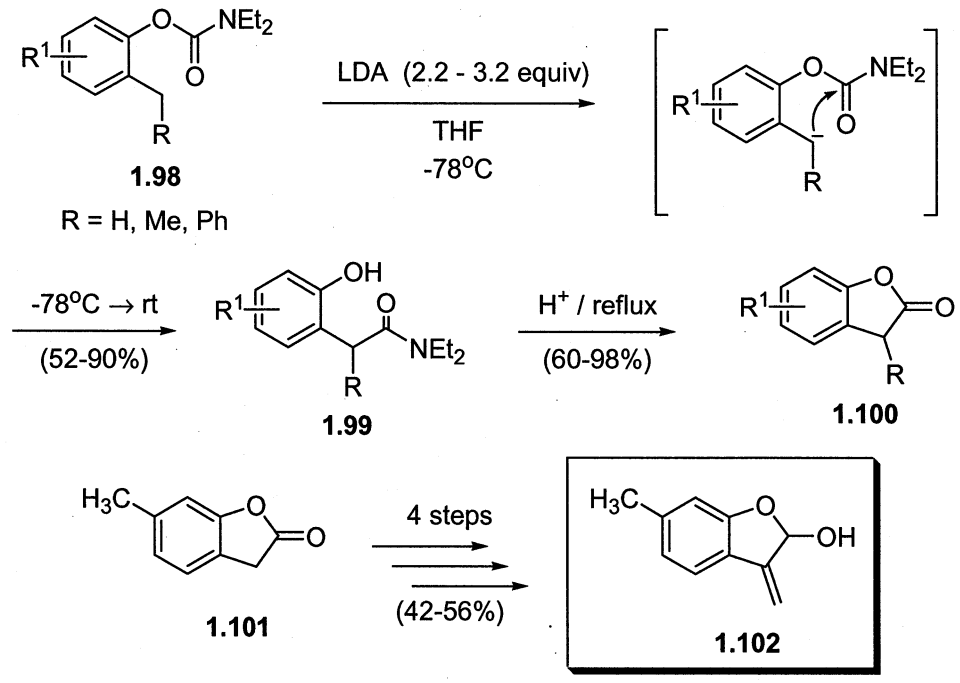


1.94 **1.95** **1.96** **1.97**

Scheme 1.23

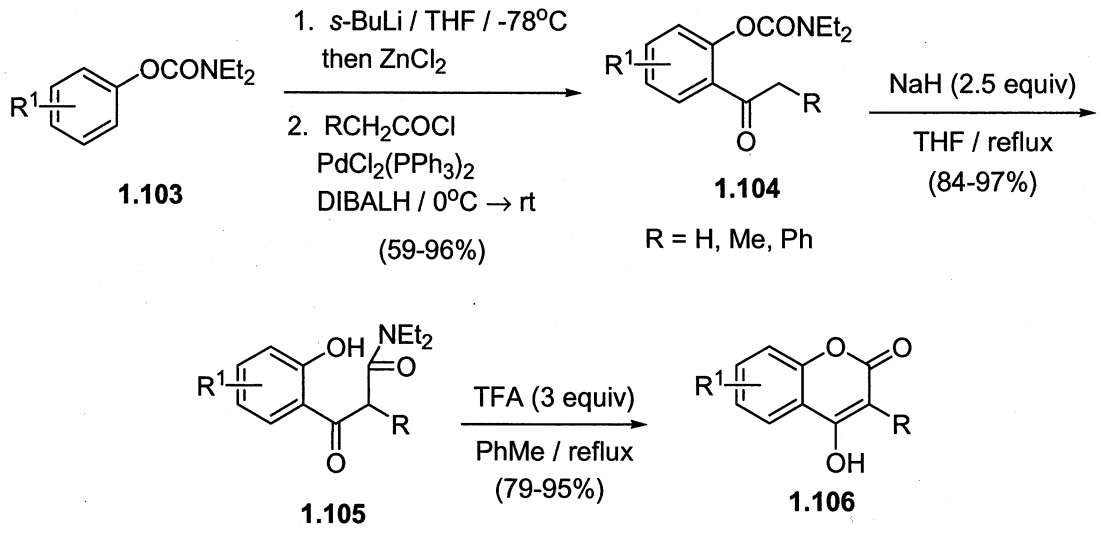
Another variation of this anionic rearrangement from the Snieckus laboratories was disclosed in 1997.[78] The anionic homologous Fries rearrangement (**Scheme 1.24**) occurs upon treating *O*-(2-methylaryl)carbamate **1.98** with LDA at –78°C and warming the resultant benzylic anion either to 0°C or to room temperature. The resultant 2-hydroxyphenyl acetamide **1.99** was converted into the benzofuran-2(3H)-ones **1.100**, a naturally occuring class of heterocycles. The total synthesis of the naturally occuring

benzofuranolactol **1.102** was accomplished in 4 steps and 42-56% overall yield from the readily available 6-methyl benzofuranone **1.101**, an improvement on the previously reported synthesis.[79]



Scheme 1.24

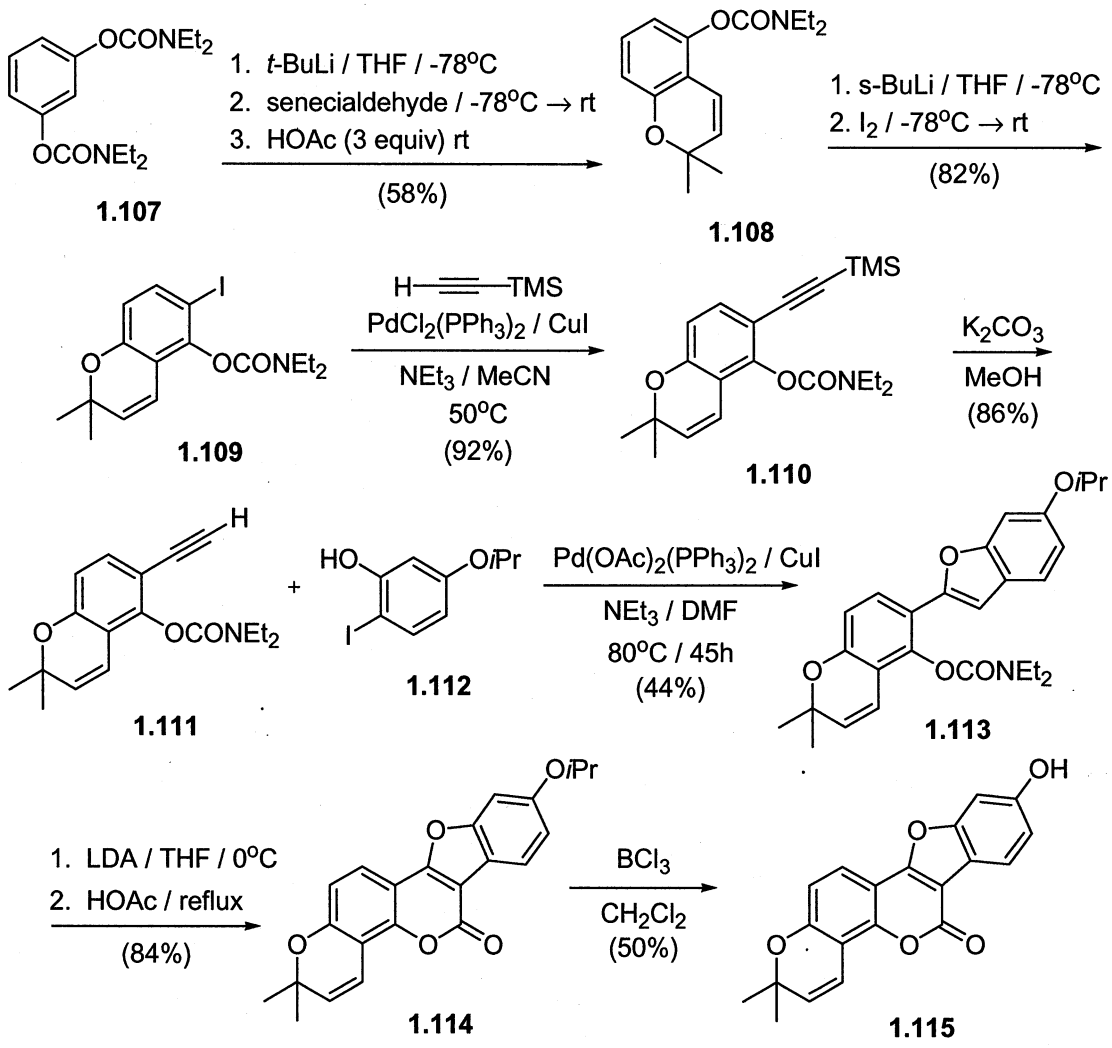
Subsequently another variation of this chemistry was disclosed from the Snieckus group in 1998 (**Scheme 1.25**).[80] Treatment of *ortho*-acyl arylcarbamates **1.104**, prepared regiospecifically using a D*o*M – Negishi cross-coupling of arylcarbamates **1.103** and acid chlorides, with NaH afforded 2-hydroxyarylacetamides **1.105** *via* a carbamoyl rendition of the Baker-Venkataraman rearrangement. Subsequent treatment of **1.105** with TFA in refluxing toluene furnished 4-hydroxycoumarins **1.106**, a diverse class of heterocycles and natural products.[81]



Scheme 1.25

A subsequent communication,[82] also from the Snieckus laboratories, demonstrates the versatility of these anionic carbamoyl rearrangements in organic synthesis by way of two total syntheses of plicadin **1.115** a reported coumestan natural product.[83] In the first route to plicadin (**Scheme 1.26**), advantage was taken of a Sonogashira, Castro-Stephens, remote anionic Fries rearrangement sequence to assemble the coumestan framework. The chromene carbamate **1.108**, which is common to both routes, was conveniently prepared regioselectively in good yield from dicarbamate **1.107** *via* D*o*M and subsequent quenching with senecialdehyde followed by acid catalyzed cyclization. A second D*o*M on **1.108** and quench with I_2 afforded the aryl iodide **1.109** which underwent efficient reaction under Sonogashira conditions to yield the aryl acetylene **1.110**. Desilylation of **1.110** with K_2CO_3 proceeded smoothly to afford **1.111** which was treated with iodophenol **1.112** under Castro-Stephens conditions to yield benzofuran **1.113** in modest yield. Remote anionic Fries rearrangement of **1.113** followed by acid-catalyzed cyclisation afforded the coumestan **1.114** in 84% yield.

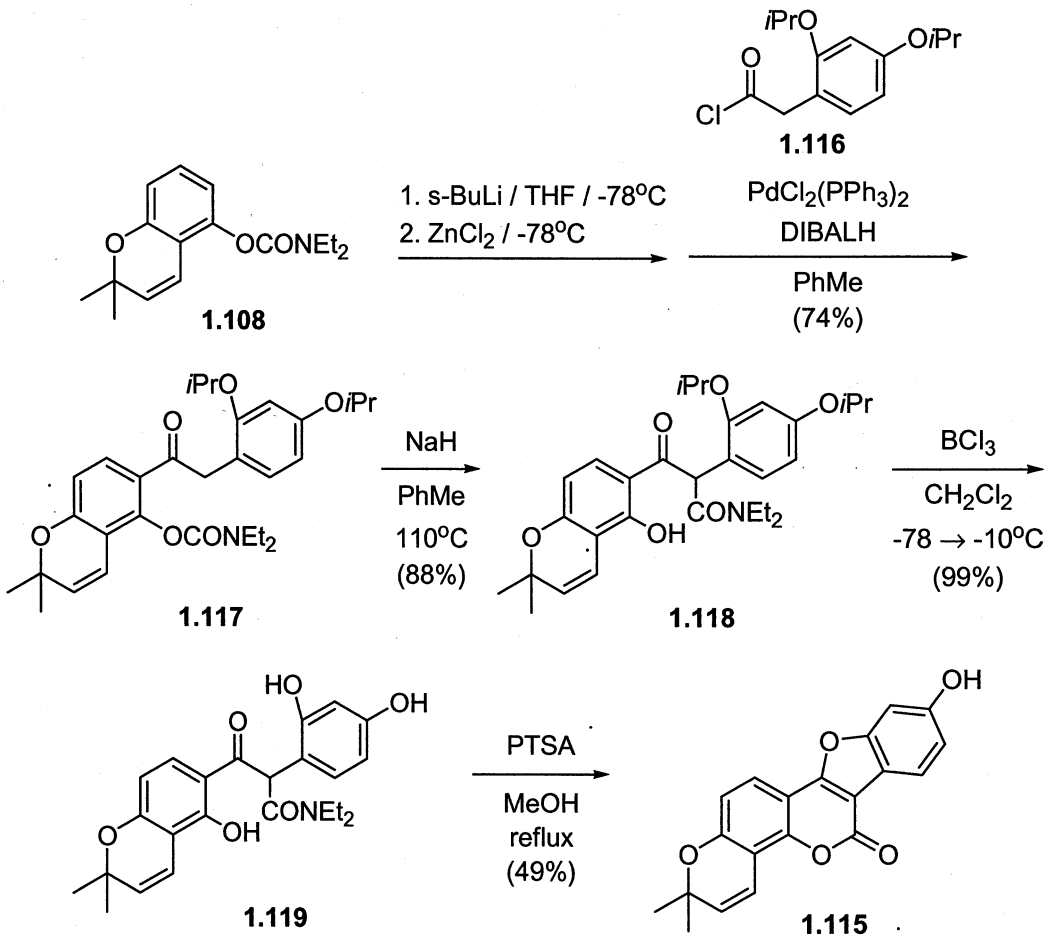
Deprotection of **1.114** with BCl_3 gave the target coumestan plicadin **1.115**, the synthesis proceeding in 7 steps and 6.8% overall yield.



Scheme 1.26

The second approach to plicadin **1.115** followed an acylative Negishi cross-coupling, carbamoyl Baker-Venkataraman sequence (**Scheme 1.27**). The intermediate ketone **1.117** was prepared *via* lithiation of the chromene carbamate **1.108**, transmetalation to zinc, and Negishi cross-coupling with the acid chloride **1.116**. As described above, treatment of ketone **1.117** with NaH afforded the ketoamide **1.118** *via* the carbamoyl Baker-Venkataraman rearrangement. Subsequent treatment of **1.118** with

BCl_3 in CH_2Cl_2 afforded the triphenol **1.119** which in turn was subjected to acid-catalyzed cyclization conditions to give the desired coumestan plicadin **1.115**. The second synthesis of plicadin was accomplished in 5 steps and 20.5% overall yield. Although there existed discrepancies in the reported data, the structure of the synthetic material was confirmed to be as shown by single crystal X-ray analysis.

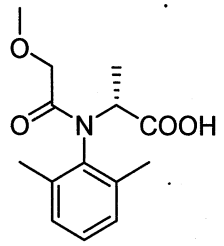


Scheme 1.27

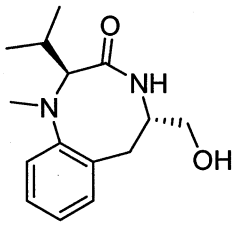
1.3 C-N Bond Forming Cross Coupling Reactions

1.3.1 Introduction

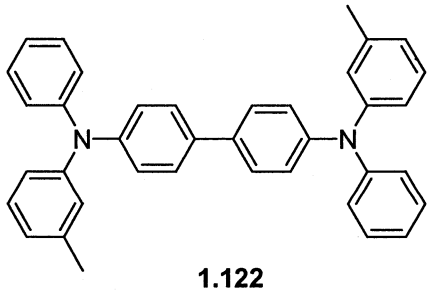
Aromatic amines are common and important substructures in many types of organic molecules. They are found in many biologically active and medicinally important molecules including the fungicide (*R*)-metalaxyl (**1.120**)[84] and the protein kinase C activator benzolactam-V8 (**1.121**).[85] They are also common to molecules with interesting electronic properties and are therefore important in the field of material science. For example, 4,4'-bis(phenyl-*m*-tolylamino)biphenyl (**1.122**) has found applications in organic light emitting devices (OLEDs).[86] Due to their importance in many applications, there is a need for general and reliable methods for the synthesis of aryl and diarylamines.



1.120



1.121

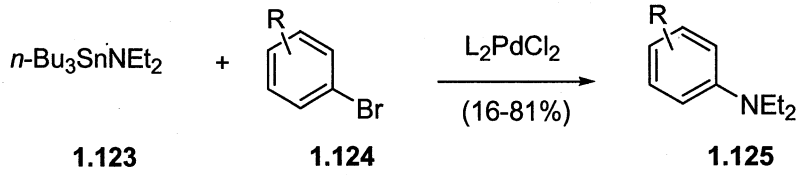


1.122

Of the several classical methods to make aryl and diarylamines, the copper-mediated Ullmann[87] reaction, although used extensively, is limited by high reaction temperatures, substituent compatibility, and variable to poor yields. Other methods that include nitration/reduction and nucleophillic aromatic substitution are incompatible with many functional groups and thereby require protection and deprotection steps.[88,89]

1.3.2 The Development of Modern Palladium-Catalysed Amination Methods

Migita and co-workers reported the first example of a palladium catalysed aryl amination in 1983.[90] The reaction of *N,N*-diethylamino-tributyltin (**1.123**) with aryl bromides **1.124** in the presence of $PdCl_2[P(o\text{-tolyl})_3]_2$ was shown to yield *N,N*-diethylaminoarenes **1.125** (**Scheme 1.28**). Although this protocol required the use of toxic tin reagents, suffered from poor functional group compatibility, and furnished anilines in variable yields, it provided the proof of principle that palladium catalysis could be viable for the synthesis of aryl amines.

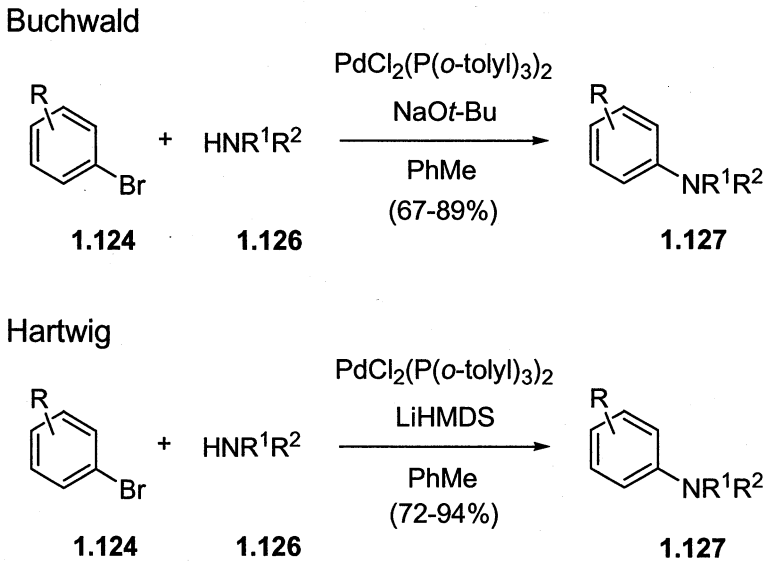


1.123 **1.124** **1.125**

Scheme 1.28

This initial and important discovery somehow managed to avoid a great deal of attention from the synthetic chemist for ten years. However, significant advances in this field during the 1990s have warranted several reviews.[91-98] In 1994, Buchwald[99] reported improvements on the Migita protocol that allowed the introduction of amino substituents other than *N,N*-diethylamino but the process still required the use of tin

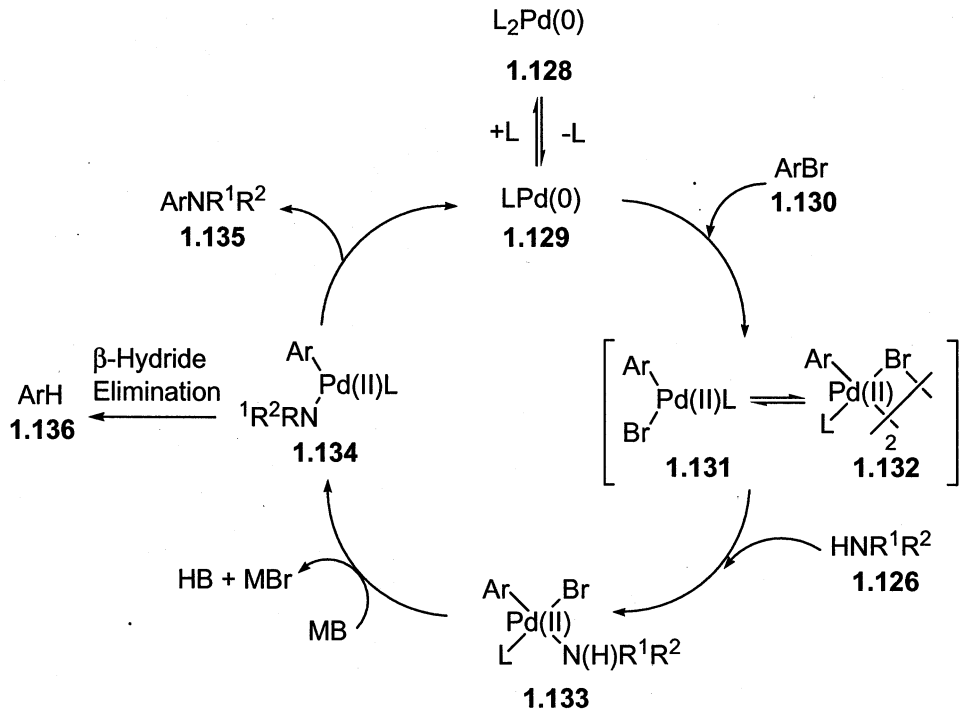
amides and was limited in substrate scope. Concurrent publications in 1995 from the research groups of Buchwald[100] and Hartwig[101] demonstrated the first tin free palladium catalysed aryl amination using either an alkoxide or silyamide base in the presence of a palladium catalyst (**Scheme 1.29**). Secondary amines provided high yields of anilines with various aryl bromides, while primary amines only afforded high yields with electron deficient aryl bromides. Arenes, the product of dehalohydrogenation of the aryl halide were isolated as major reaction products with primary alkyl amines, constituting a major limitation of the new procedures.



Scheme 1.29

To this point in time, reports on palladium-catalysed amination procedures all indicated the need to use P(*o*-tolyl)$_3$ as ligand in order to produce anilines in high yield. However, as a detailed mechanistic picture of these processes came to light, it was realised that the development of new ligands was crucial to resolve the problems associated with substrate scope and reaction rates. The mechanism of the amination

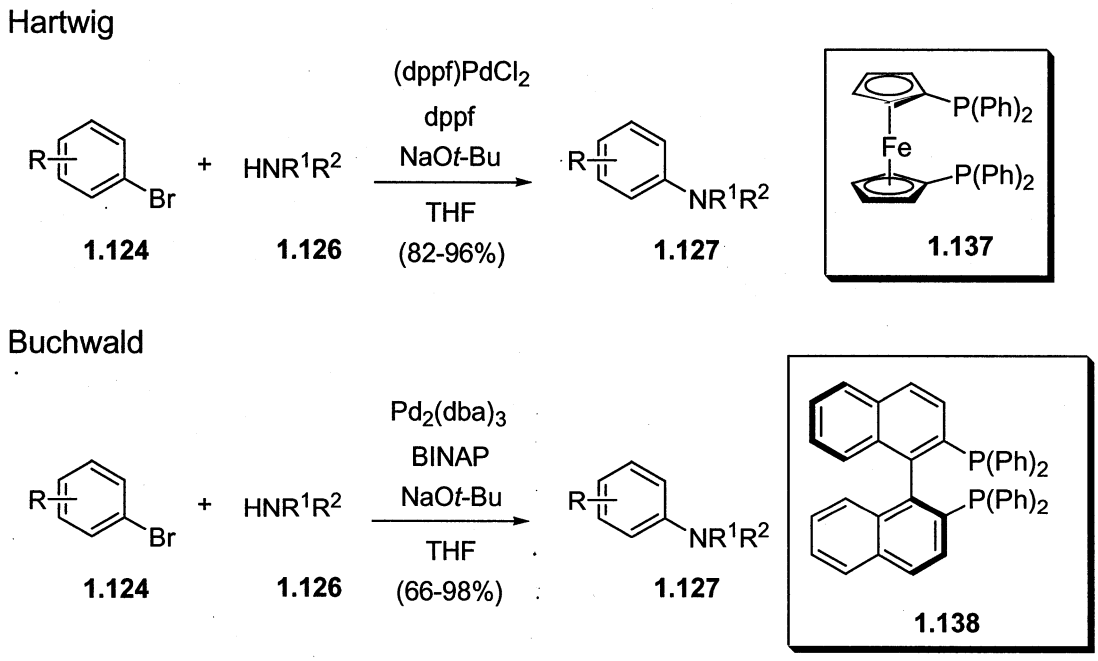
process catalysed by P(*o*-tolyl)$_3$ palladium complexes has been established by kinetic and spectroscopic studies (**Scheme 1.30**).[93] Ligand dissociation from the two-coordinate Pd(0) species **1.128** affords the active monophosphine Pd(0) species **1.129**, which undergoes oxidative addition into the carbon-bromine bond resulting in an equilibrium mixture of Pd(II) halide complex **1.131** and the dimeric species **1.132**. Reaction of the monomeric Pd(II) halide complex with amine **1.126** leads to the four-coordinate Pd(II) amine species **1.133**, which, in turn, reacts with base to yield the three-coordinate Pd(II) amido complex **1.134**. Reductive elimination regenerates the active catalyst and yields the desired arylamine product **1.135**.



Scheme 1.30

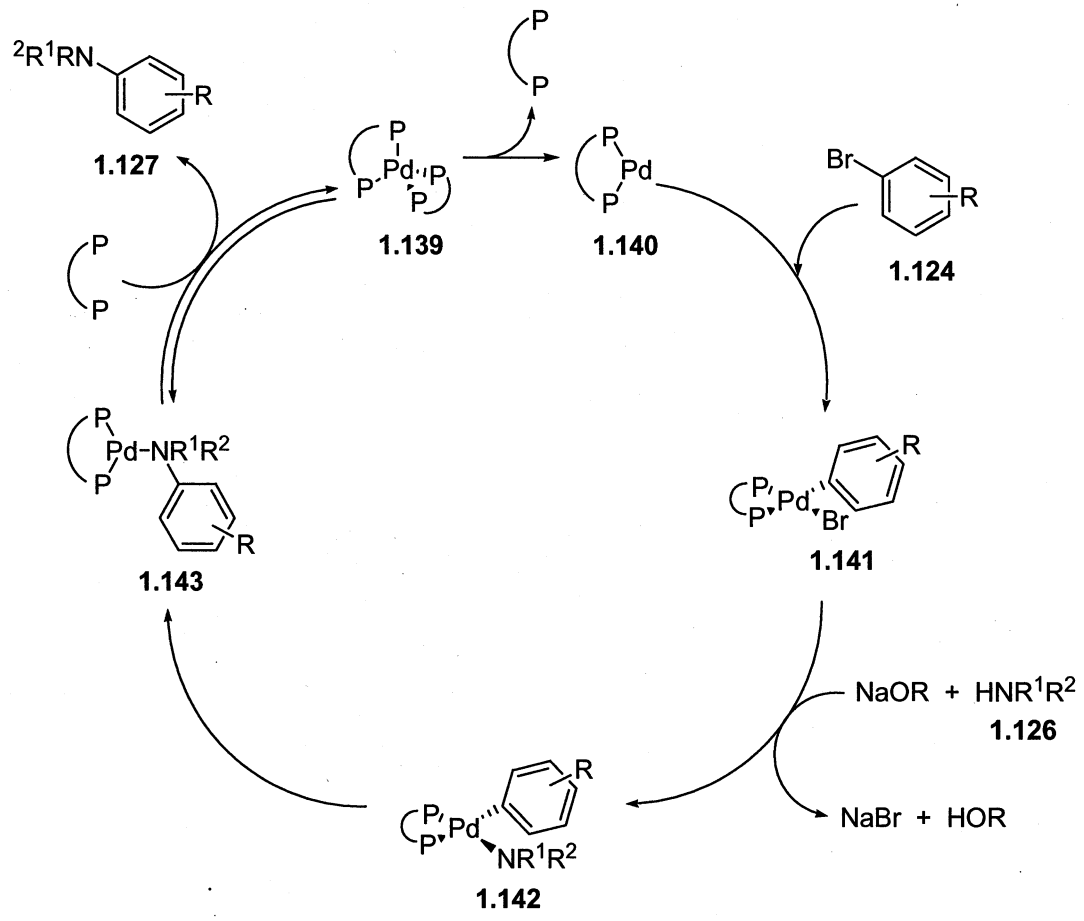
The palladium-catalysed amination mechanism provided insight into the limitations of substrate scope associated with this process. In particular, this mechanism may explain why dehalohydrogenation is observed in reactions of aryl bromides with

primary alkyl amines. Facile β-hydride elimination from the three-coordinate Pd(II) amido complex **1.134** competes with the desired reductive elimination pathway, giving dehalohydrogenation products **1.136**. Kinetic studies[102] on iridium complexes led to the conclusion that β-hydride eliminations from Pd(II) amido complexes would require a three-coordinate, 14-electron palladium species. This result, in combination with the observation[103] that reductive elimination may occur from a four-coordinate Pd(II) species, strongly suggests that the use of bidentate phosphine ligands may decrease the rate of β-hydride elimination relative to reductive elimination and improve the yields of arylamines. In support of this hypothesis, concurrent reports from the research groups of Hartwig[104] and Buchwald[105] in 1996 first showed the use of the bidentate chelating phosphine ligands dppf **1.137** and BINAP **1.138** in the catalytic amination of aryl halides (**Scheme 1.31**).



Scheme 1.31

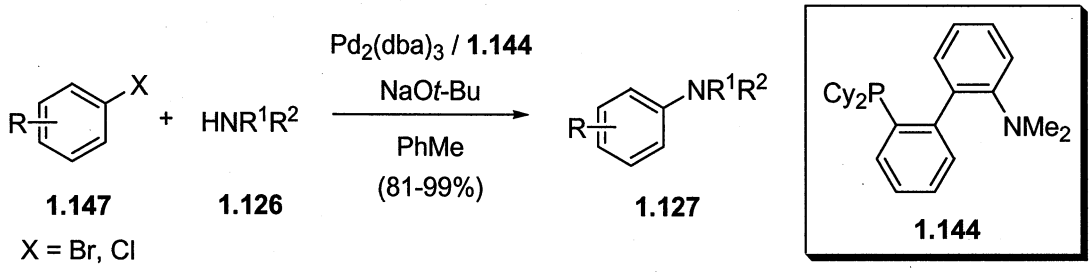
The use of these bidentate phosphine ligands allowed the successful amination of aryl halides with primary amines, secondary amines and anilines. These new procedures provided arylamines in high yields that were not accessible *via* palladium catalysed aminations utilising P(*o*-tolyl)$_3$ as ligand. Although the mechanism for these new procedures was previously proposed to be analogous to that for the process catalysed by P(*o*-tolyl)$_3$ palladium complexes,[94,106] recent kinetic studies by Hartwig[107] have indicated otherwise (**Scheme 1.32**). The proposed mechanism is consistent with a sequence involving oxidative addition, formation of a Pd(II) amido species and reductive elimination to form product. However, these kinetic studies on the mechanism of oxidative addition indicated irreversible and rate limiting ligand dissociation when [ArBr]:[L] is high as it is in catalytic reactions. This implies that **1.139** must lie in the catalytic cycle pathway, and not just be a prerequisite to it as previously proposed. The mono-chelated Pd(0) species **1.140** is an intermediate in the oxidative addition and is therefore not the resting state of the catalyst. In order to form the desired amine **1.127** and regenerate the catalyst **1.139**, the reductive elimination must involve the formation of the 16-electron amine-ligated Pd(0) species **1.143** which undergoes reaction, in an associative step, with free ligand to complete the catalytic cycle. Buchwald[108] and Hartwig[109] have also used BINAP and dppf respectively for the Pd-catalysed amination of aryl triflates, which constitutes a new method for the conversion of phenols into anilines. Electron deficient aryl triflates were problematic substrates due to their incompatibility with NaO*t*-Bu but they have been efficiently aminated using Cs_2CO_3 as base.[110]



Scheme 1.32

Although the amination conditions developed primarily by the research groups of Buchwald and Hartwig are major improvements on the initial work of Migita in that they no longer require toxic tin reagents and allow for a much broader range of substrates, they still suffer from limitations. The requirement of alkoxide for most substrate combinations is incompatible with base sensitive functionality and the inability of these conditions to successfully effect amination of inexpensive aryl chlorides has provided room for improvement. With these goals in mind, many other catalyst systems have been developed.

The biphenyl based phosphine ligands **1.144**[111], **1.145**[112], and **1.146**[112] developed in the Buchwald laboratories, have proven to be quite effective for Pd-catalysed aminations and Suzuki couplings of aryl chlorides. Initially, the aminophosphine ligand **1.144** (**Scheme 1.33**) was shown to be very practical for the amination of aryl chlorides in toluene at 80°C or DME at 100°C. Secondary amines and primary anilines afforded excellent yields of products **1.127** while primary alkylamines only worked well with *ortho* substituted aryl chlorides.



1.147
X = Br, Cl

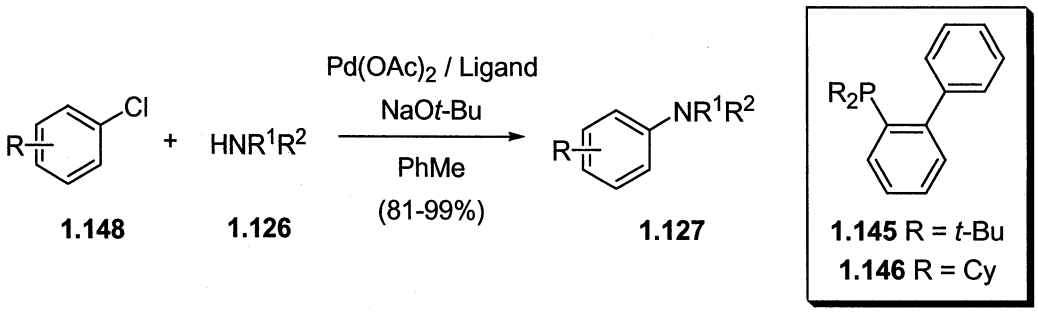
1.126

1.127

1.144

Scheme 1.33

Aryl iodides and bromides underwent amination at room temperature when DME was employed as the solvent and base sensitive substrates were shown to undergo amination at elevated temperatures using K_3PO_4 as base.[111] Experiments designed to determine the necessity of the 2′-dimethylamino substituent in **1.144** led to the development of phosphine ligands **1.145** and **1.146** for the room temperature catalytic aminations of aryl chlorides **1.148** (**Scheme 1.34**).[112]

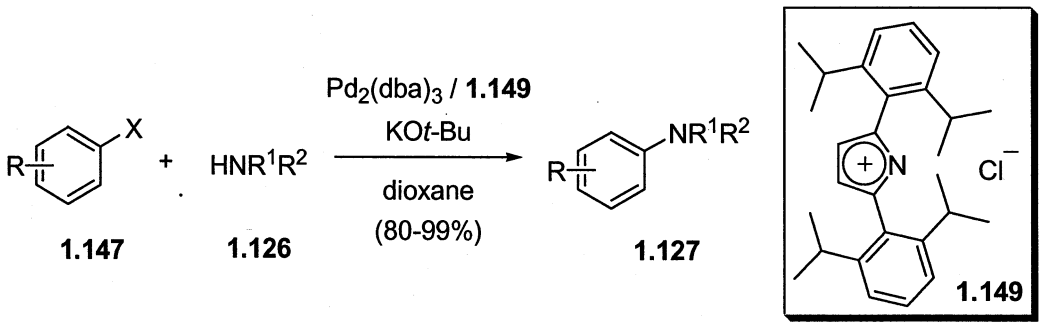


Scheme 1.34

The ligands **1.145** and **1.146** were shown to be very capable for the amination electron-rich, electron deficient and *ortho* substituted aryl chlorides. As before, primary amines were only successful if the aryl chloride was *ortho* substituted. In general, phosphine **1.145** provides better results for aminations at rt while phosphine **1.146** is frequently more effective in reactions with lower catalyst loadings. Although the reason for the high activity of these catalysts has not been studied in detail, there are several features of these associated ligands that are most likely responsible for this effect. The electron-rich alkyl phosphine facilitates the oxidative addition process and thus activates aryl chlorides. The steric bulk of these ligands presumably also accelerates the carbon-nitrogen bond forming reductive elimination step. Ligands **1.145** and **1.146** are exceptionally general for palladium catalysed aminations and have all but eliminated the need for the previously developed conditions using P(*o*-tolyl)$_3$, BINAP, or DPPF as ligands. Recently, the efficacy of these biphenyl based phosphines as ligands in Pd-catalysed aminations has been summarised.[113]

Nucleophilic *N*-heterocyclic carbenes have successfully been used as phosphine ligand alternatives in palladium catalysed Suzuki-Miyaura[114] and Heck[115] reactions as

well as ruthenium catalysed olefin metathesis.[116] These carbene ligands have beneficial properties similar to those observed for the highly successful Buchwald biphenyl based ligands **1.145** and **1.146**. The electron donating ability of these ligands is expected to facilitate oxidative addition while their steric bulk should enhance the carbon-nitorgen bond forming reductive elimination process. The use of carbene ligands in palladium catalysed aminations has been reported by several research groups including those of Nolan and Hartwig.[117,118] The imidazolium salt **1.149** (IPr) was found to be the most effective ligand of a set of 4 imidazolium chlorides and its use as a ligand in palladium catalysed aminations was investigated (**Scheme 1.35**).[118]

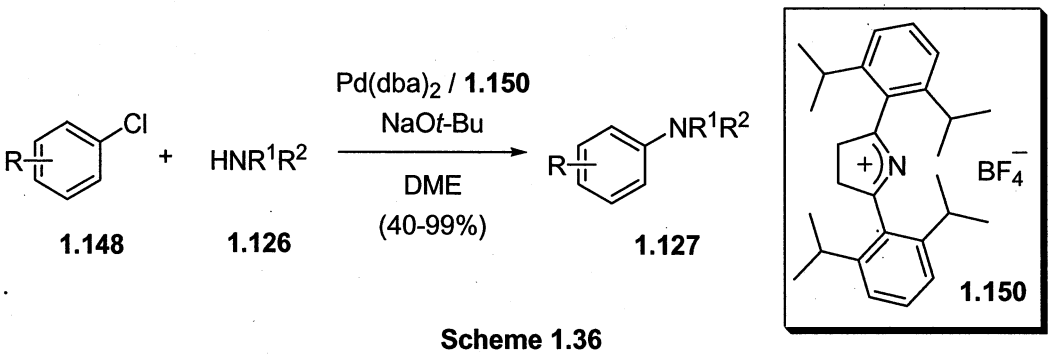


Scheme 1.35

The carbene ligand **1.149** was found to be effective for the coupling of aryl chlorides at 100°C and bromides or iodides at room temperature. Although only electron rich aryl chlorides were investigated, this catalyst system allowed, for the first time, amination of unhindered aryl chlorides with both primary and secondary alkylamines.

Subsequently, Hartwig[117] reported the effective use of *N*-heterocyclic carbene ligand **1.150** for the room temperature catalytic amination of aryl chlorides (**Scheme**

1.36). Although capable of aminating chloroarenes at room temperature, this system does not appear to be as general as that of Nolan. Sterically hindered secondary amines are problematic and do not provide aminated products even at elevated temperatures or higher catalyst loadings. Acyclic secondary amines undergo coupling at room temperature but require higher catalyst loadings while primary alkylamines are poor substrates even with *ortho* substituted aryl chlorides. Although $Pd(dba)_2$ / **1.150** is the first catalytic system to facilitate the room temperature amination of chloropyridines, the requirement of alkoxide renders base sensitive substrates incompatable.



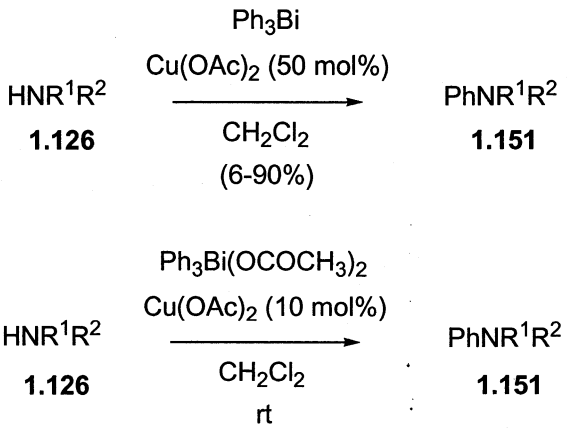
Scheme 1.36

In summary, palladium-catalysed aryl amination has developed into a powerful and general method for the synthesis of highly substituted anilines from aryl halides or phenols. The vast array of reported catalysts and reaction conditions all but assures the synthetic chemist that if appropriate starting materials and catalyst are chosen, the desired aniline derivative will be available. Highly functionalised primary anilines are also available from aryl halides through the use of ammonia surrogates. Thus, Buchwald[119] has reported on the coupling of benzophenone imine followed by hydrolysis to yield the desired primary anilines. Both Hartwig[120] and Buchwald[121] have more recently disclosed the use of LiHMDS as an ammonia surrogate in a process that does not require

a separate hydrolytic step. In keeping with current applications in organic synthesis, Buchwald[122] has also developed a solid-supported version of his successful biphenyl based phosphine ligands **1.145** and **1.146**. These polymer-bound ligands were utilised for the amination of aryl chlorides, bromides and iodides while simplifying product isolation.

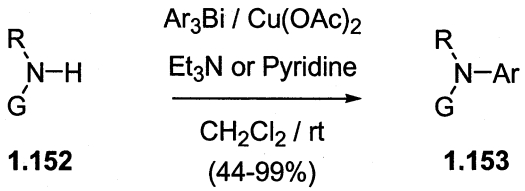
1.3.4 Modern Copper-Catalysed Amination Methods

Although the development of palladium-catalysed amination methods was the direct result of the inadequacies of copper-catalysed methods, the impeding cost of palladium has invoked a recent resurgence of interest in the field of copper-catalysed amination reactions. The copper-catalysed arylation of amines using organobismuth reagents was pioneered in the late 1980s by Barton and co-workers. It was shown that both Bi(V)[123] and Bi(III)[124] reagents are capable of arylating amines in the presence of a suitable copper catalyst (**Scheme 1.37**). Although the reaction conditions employed were mild, higher catalyst loading was required and the yield of isolated product varied greatly depending on the amine.



Scheme 1.37

The work of Chan in 1996[125] expanded the scope of the work of Barton. Although a stoichiometric amount of copper was utilised, the addition of a tertiary amine to the reaction mixture allowed the *N*-arylation of less reactive compounds including amides, ureas, carbamates and sulfonamides (**Scheme 1.38**). The exact role of the tertiary amine was undetermined but it was postulated that the amine either increased the solubility of the copper catalyst or consumed the generated acetic acid.



1.152 **1.153**

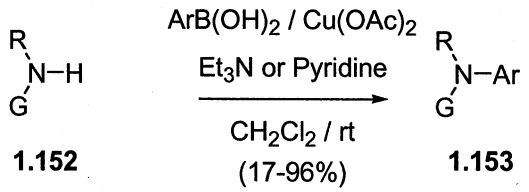
G = COR, CO_2R, $CONR_2$, SO_2R

Scheme 1.38

Although the use of bismuth reagents of this type presents inherent problems, applications of these copper-bismuth conditions have recently been reported including the *N*-arylation of *N*-H containing heteroarenes and aminobenzanilides.[126,127] Aryl bismuth reagents are typically prepared by the reaction of a Grignard or aryllithium reagent with a bismuth (III) halide. This limits the nature of the aryl-group that can be transferred in this type of reaction. Secondly, only one of the three aryl-groups of the bismuth reagent are transferred to the substrate and this is disadvantageous in the case of elaborate aryl-groups or in terms of "atom economy".

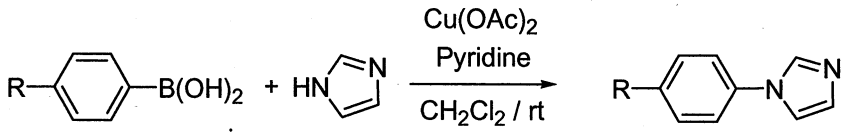
The potential use of phenylboronic acids as arylating agents in amination reactions would address the limitations described above for bismuth reagents. Copper-mediated phenylboronic acid *N*-arylations were first reported in 1998. Chan[128] reported

that various *N*-H containing structures including amines, anilines, amides, sulfonamides, and carbamates could be phenylated with phenylboronic acids in the presence of $Cu(OAc)_2$ and a tertiary amine while the work of Lam[129] focused on the arylation of *N*-H containing heteroarenes (**Scheme 1.39**). Although both sets of conditions required the use of stoichiometric amounts of $Cu(OAc)_2$, the very mild reaction conditions of this new procedure has clear advantages over other methods.



1.152 **1.153**

G = COR, CO_2R, $CONR_2$, SO_2R, Ar, Alkyl



1.154 **1.155** **1.156**

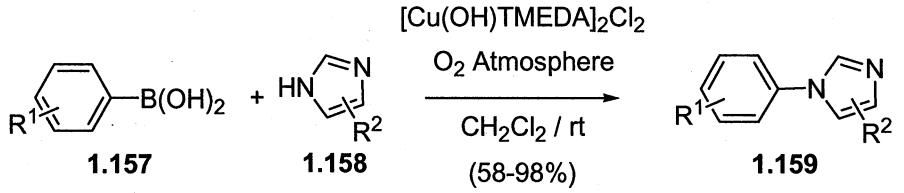
R = CF_3, CH_3, OCH_3

Scheme 1.39

Subsequently Lam and co-workers have extended their copper-mediated protocol to the solid phase synthesis of *N*-arylated benzimidazoles, imidazoles, triazoles and pyrazoles.[130] Although only moderate yields were obtained, the products were obtained rapidly and in high purity by utilising microwave irradiation conditions.

Collman reported a significant advance in the arylboronic acid coupling method by using only a catalytic amount of copper.[131] The copper-diamine complex $[Cu(OH) \bullet TMEDA]_2Cl_2$ was shown to be an effective catalyst in the reaction of

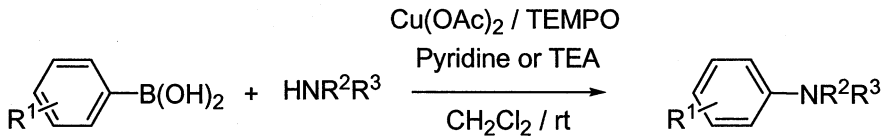
arylboronic acids with imidazoles (**Scheme 1.40**). Although the reaction may be carried out in air, higher yields are obtained in a pure O_2 atmosphere.



1.157 **1.158** **1.159**

Scheme 1.40

The role of molecular O_2 in copper-promoted C-N bond formation has been hypothesized to facilitate the oxidation of a Cu(II) intermediate to a Cu(III) species which can more readily undergo reductive elimination to yield product. Lam[132] and co-workers proposed that the presence of a mild oxidizing agent may be more efficient than molecular O_2 in converting Cu(II) to Cu(III) in such processes and enable the use of only catalytic amounts of $Cu(OAc)_2$. They found that a combination of $Cu(OAc)_2$ (10 mol %), TEMPO (1.1 equiv) and either pyridine or triethylamine (2.0 equiv) was effective for arylating a wide range of *N*-H containing compounds including amines, anilines, ureas and sulfonamides (**Scheme 1.41**).

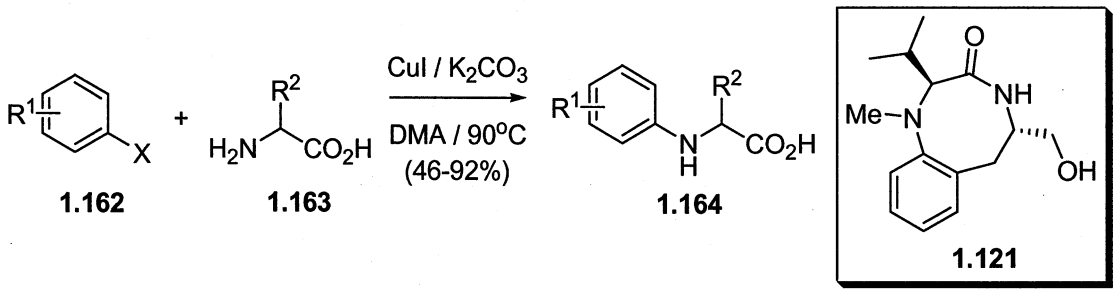


1.157 **1.160** **1.161**

Scheme 1.41

Although organobismuth and organoboron reagents provided mild procedures for the formation of arylamines, the development of copper-catalysed methods for the coupling of amines and aryl halides is still a common topic in the literature presumably

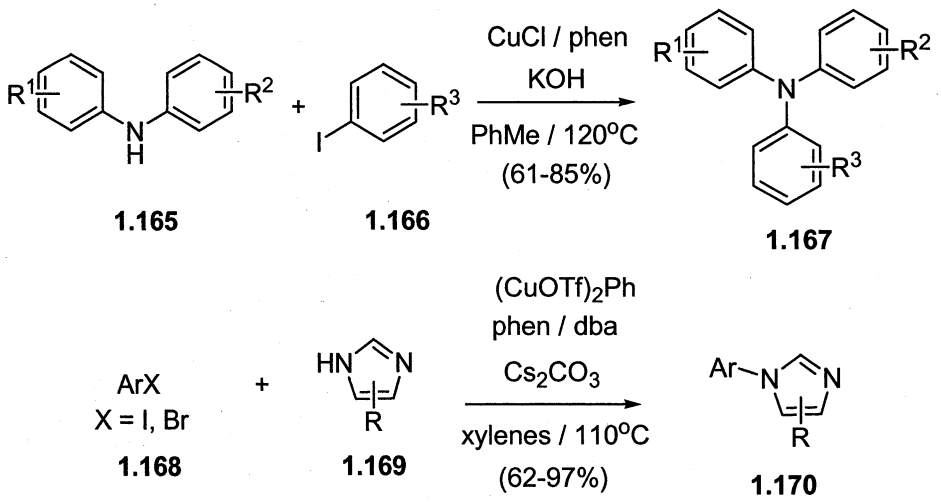
because of the excellent commercial availability of aryl halides. Recently, the copper-catalysed coupling of aryl bromides or aryl iodides with optically pure α-amino acids was reported.[133] The reaction conditions are sufficiently mild to avoid racemization, and the synthetic utility of this method has been clearly demonstrated in an improved synthesis of benzolactam-V8 (**1.121**) (**Scheme 1.42**).



1.162 **1.163** **1.164** **1.121**

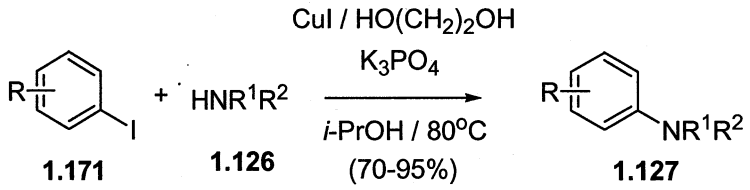
Scheme 1.42

The addition of copper-binding ligands has also been shown to increase the rate of the Ullmann coupling process. The addition of 1,10-phenanthroline (phen) allows the synthesis of triarylamines **1.167** at temperatures 50-100°C lower than previously reported for this class of compounds.[134] Buchwald reported a similar finding in the *N*-arylation of imidazoles.[135] The addition of a catalytic amount of dibenzylideneacetone (dba) was found to be crucial to the reproducibility of the process **1.168 + 1.169 → 1.170** (**Scheme 1.43**).



Scheme 1.43

In 2002 a report from the Buchwald laboratories provides very mild conditions for the copper-catalysed amination of aryl iodides.[136] The use of 5 mol% CuI with ethylene glycol as the supporting ligand and K_3PO_4 as base allows the synthesis of a wide range of arylamines in excellent yields (**Scheme 1.44**). This robust procedure may be performed without protection from air or moisture using 2-propanol as the solvent.



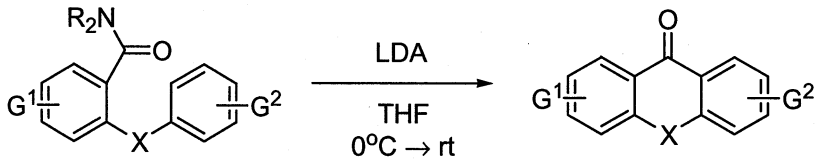
Scheme 1.44

Although great improvements have been made to Cu-catalysed amination reactions, the process is not yet as well developed in terms of mild conditions and substrate scope as the aforementioned Pd-catalysed methods. This being said, these new Cu-catalysed protocols offer potentially attractive alternatives for C-N bond formation in that they do not require an expensive noble metal.

1.4 Project Background

1.4.1 DreM Applied to the Construction of Heteroatom Linked Tricyclics

The discovery that DMG containing diaryl sulfones **1.172**, ethers **1.173**, and phosphine oxides **1.174** undergo remote metalation led to a general route for the construction of thioxanthenones **1.175**,[137] xanthones **1.176**,[138] and phosphorinones **1.177**,[139] respectively (**Scheme 1.45**).



X = SO_2 (**1.172**)
X = O (**1.173**)
X = P(O)Ph (**1.174**)

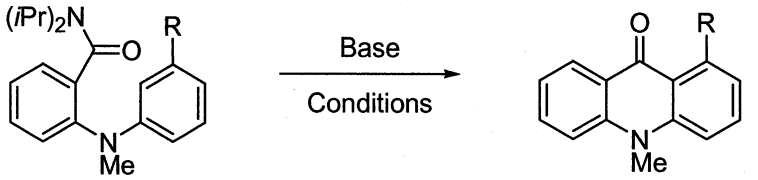
X = SO_2 (**1.175**)
X = O (**1.176**)
X = P(O)Ph (**1.177**)

Scheme 1.45

In an attempt to further generalize this method for the synthesis of heterocycles, application of the DreM methodology towards the nitrogen containing acridone alkaloids (**Scheme 1.45**, X = NR) was accomplished with limited success,[140] a summary of which follows.

1.4.2 Synthesis of Acridones. Preliminary DreM Cyclization Results

With the intention of extending the DreM methodology for the construction of heterocycles from diarylamines, cyclizations of substituted *N,N*-diisopropyl *N*-arylanthranilamides **1.178** and **1.179** were undertaken (**Scheme 1.46**).



R = H (**1.178**)
R = OMe (**1.179**)

R = H (**1.180**)
R = OMe (**1.181**)

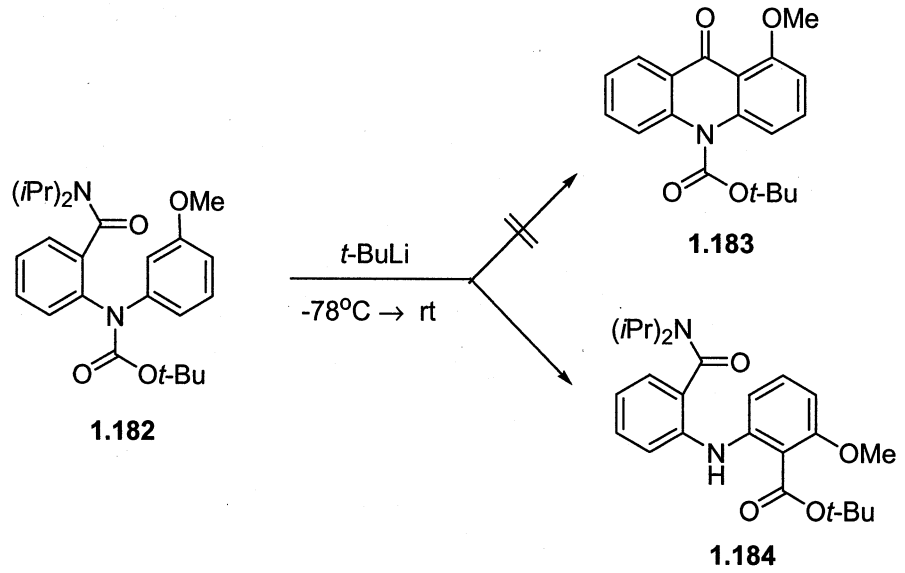
SM	Base	Conditions	Yield (%)
1.178	LiTMP	0°C → reflux	0
1.178	*t*-BuLi	-78°C → rt	16 - 34
1.179	*n*-BuLi	-78°C → rt	0
1.179	LiTMP	-15°C → rt	22

Scheme 1.46

Unlike the behaviour of diaryl ethers, sulfones, and phosphine oxides which, upon treatment with LDA at rt afforded the desired cyclization products, the corresponding reaction of *N,N*-diisopropyl *N*-arylanthranilamides **1.178** and **1.179** with a variety of bases under different conditions was shown to be marginally successful.[140] The difference in reactivity of these compounds was postulated to be the result of the weak DMG effect of NMe as compared to SO_2, O, and P(O)Ph. It was proposed that activation of the nitrogen as the *t*-butyl carbamate, a much stronger DMG than NMe,[57] may enhance D*o*M and hopefully afford the desired acridones.

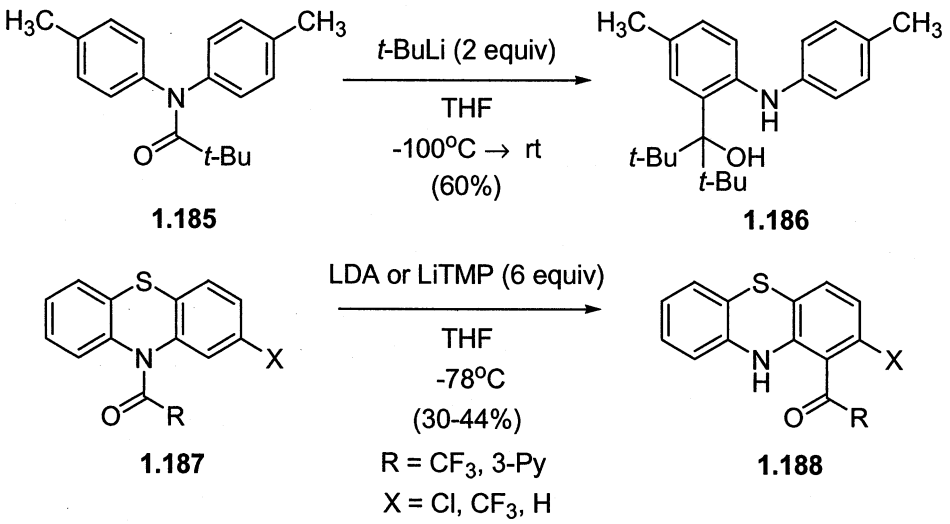
1.4.3 Serendipitous Discovery of the *N*-Anionic *ortho* Fries Rearrangement

To test the hypothesis described in section **1.4.2**, cyclization of carbamate **1.182** using *t*-BuLi as base was investigated (**Scheme 1.47**).[140] Metalation of carbamate **1.182** with *t*-BuLi unexpectedly yielded anthranilate ester **1.184** in 35% yield with no detection of the desired cyclized product **1.183** and thereby an *N*-anionic *ortho* Fries rearrangement was discovered.



Scheme 1.47

However, related anionic acyl transfer reactions have been reported (**Scheme 1.48**). For example, treatment of *N*,*N*-di(4-methylphenyl)-2,2-dimethylpropanamide (**1.185**) with excess alkyllithium reagent affords **1.186** in moderate yield after migration and subsequent attack of the alkyllithium on the resultant aryl ketone.[141] Furthermore, treatment of *N*-acylphenothiazines **1.187** with lithium amide bases yielded the migrated products **1.188** in modest yields.[142] A crossover experiment suggested that the rearrangement likely proceeded through an intramolecular mechanism.

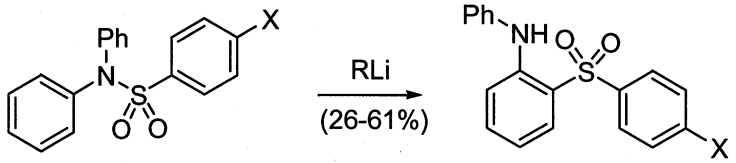


1.185 **1.186**

1.187 **1.188**

Scheme 1.48

Related base-promoted rearrangements of *N*-arylsulfonamides have also been reported (**Scheme 1.49**).[143] Treatment of *N,N*-diphenylbenzenesulfonamide **1.189** or the correpsonding *p*-toluenesulfonamide **1.190** with organolithium reagents resulted in the isolation of the 2-aminodiaryl sulfones **1.191** and **1.192**, respectively.



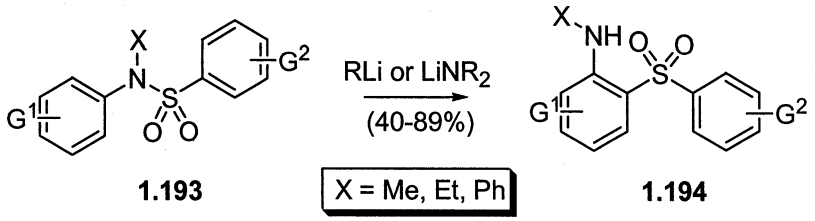
X = H (**1.189**)
X = CH_3 (**1.190**)

R = Me, Bu, Ph

X = H (**1.191**)
X = CH_3 (**1.192**)

Scheme 1.49

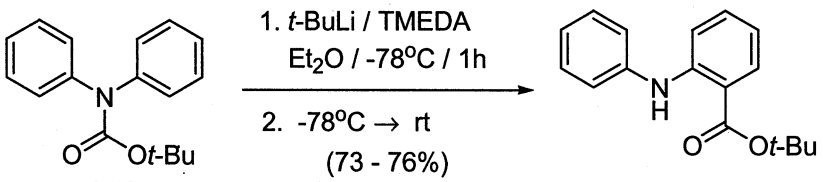
A more extensive study on the rearrangement of sulfonamides (**Scheme 1.50**) showed that lithium amide bases also promoted rearrangement and that the sulfonamide did not have to be *N,N*-diphenyl substituted.[144] Although an intermolecular reaction mechanism could not be ruled out, cross-over experiments strongly suggested that the rearrangement proceeded *via* an intramolecular mechanism.



1.193 **1.194**

Scheme 1.50

The above-described discovery of the *N*-anionic Fries rearrangement led to investigations directed at the scope and limitations of this reaction. Although the metalation/migration of the parent unsubstituted *N*-Boc diphenylamine **1.195** yielded anthranilate **1.196** in high yield (**Scheme 1.51**), the presence of substituents on the aromatic rings was found to be detrimental to the reaction.[140]



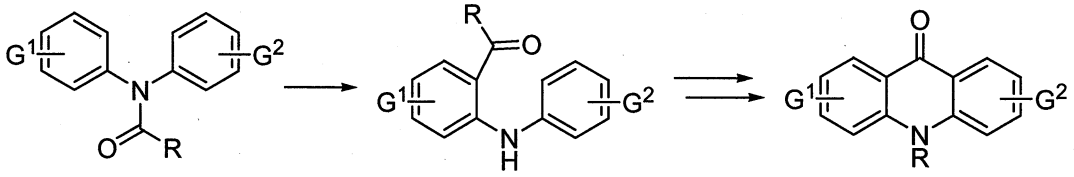
1.195 **1.196**

Scheme 1.51

The rearrangement of substituted systems was studied as a function of base, base stoichiometry, TMEDA additive, and reaction temperature.[140] However, these attempts at reaction optimization were unsuccessful. In general, the yields of migrated products were low and the recovery of starting material or decomposition products was high.

1.5 Aims of This Work

The aims of this thesis work were to develop the *N*-anionic *ortho* Fries rearrangement into a reliable process for the synthesis of *N*-aryl anthranillic acid derivatives **1.198** and to demonstrate their synthetic utility in the total synthesis of acridone alkaloids **1.199** (**Scheme 1.52**). Furthermore, this new rearrangement was expected to offer a significant improvement relative to methods previously described for the synthesis of this class of natural products (**Section 1.1.3**).



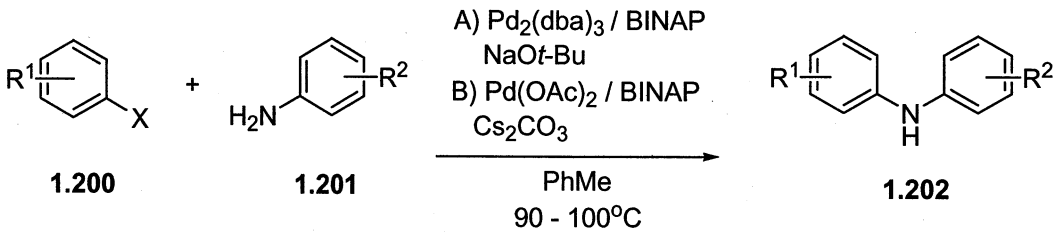
1.197 **1.198** **1.199**

Scheme 1.52

1.6 Results and Discussion

1.6.1 Palladium Catalysed Aryl Amination. Synthesis of Diarylamines

In order to investigate the *N*-anionic *ortho* Fries rearrangement (**1.197** → **1.198**, **Scheme 1.52**), it was necessary to synthesize a series of substituted diarylamines **1.202**. The conditions developed by Buchwald employing the bidentate ligand BINAP were chosen and were shown to be highly effective for the amination of aryl bromides, iodides, and triflates (**Scheme 1.53**).



1.200 **1.201** **1.202**

Entry	X	R^1	R^2	Conditions	Yield **1.202**, (%)
b	I	H	3-Cl	A	94
c	Br	H	3-OMe	A	89
d	OTf	4-Cl	H	B	60*
e	Br	4-OMe	H	A	83
f	Br	H	3,5-OMe	A	93
g	Br	H	2-Ph	A	99

* Overall yield starting from 4-chlorophenol.

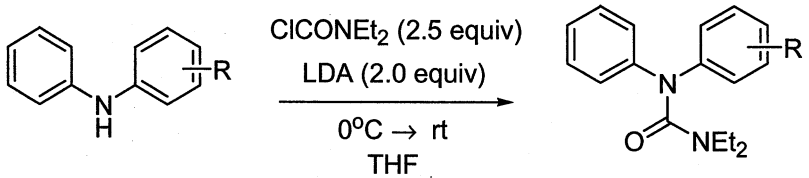
Scheme 1.53

Although the general amination process afforded the desired diarylamines **1.202** in excellent yields, the reaction of aryl triflate **1.200d** proceeded only in moderate yield. On the other hand, Buchwald has shown that the amination of aryl triflates under these conditions to be generally high yielding processes.[110] Our result appears to be substrate

specific and is perhaps related to the isolation of triflate **1.200d**. Surprisingly, the amination of bromobenzene with the somewhat sterically encumbered 2-aminobiphenyl **1.201g** proceeded rapidly in essentially quantitative yield.

1.6.2 Carbamoylation of Diarylamines. Synthesis of Ureas

With the corresponding substituted diarylamines **1.202** in hand, the substituted urea derivatives **1.203** were prepared. Carbamoylation of the diarylamines by treatment with LDA and diethylcarbamoyl chloride afforded the desired ureas **1.203** in excellent yields (**Scheme 1.54**).



1.202 **1.203**

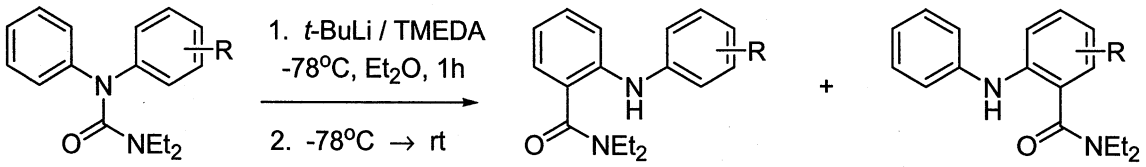
Entry	R	Yield **1.203**, (%)
a	H	99
b	3-Cl	89
c	3-OMe	99
d	4-Cl	81
e	4-OMe	99
f	3,5-OMe	97
g	2-Ph	95

Scheme 1.54

1.6.3 Alkyllithium-Induced *N*-Anionic *ortho* Fries Rearrangement

With the series of substituted ureas **1.203** in hand, investigations into the *N*-anionic *ortho* Fries rearrangement commenced. Treatment of substituted ureas **1.203**

with an excess of *t*-BuLi (1.3 equiv) in the presence of TMEDA resulted in high yields of anthranilamide products **1.204** and **1.205** (**Scheme 1.55**).



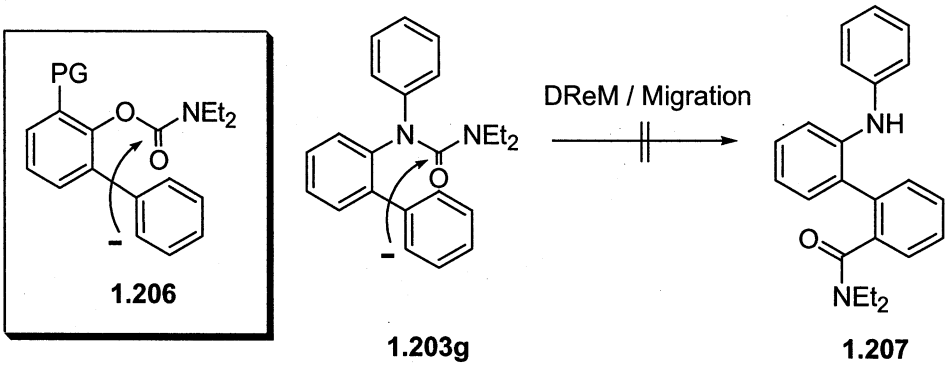
1.203 **1.204** **1.205**

Entry	R	Yield **1.204**, (%)	Yield **1.205**, (%)
a	H	81	-
b	3-Cl	-	92
c	3-OMe	59	26
d	4-Cl	-	87
e	4-OMe	54	35
f	3,5-OMe	75	14
g	2-Ph	73	19

Scheme 1.55

Although the isolated yields and regioselectivity of this process are quite good, the direction of migration appears to be dependent on many factors. Both electronic and steric effects seem to be important in the rearrangement of these unsymmetrical ureas. The presence of an electron withdrawing chlorine in either the *meta* (**1.203b**) or *para* (**1.203d**) position influences the migration towards the substituted ring in a highly regioselective manner. Electron-donating methoxy groups in the *meta* (**1.203c**), *para* (**1.203e**) or both *meta* positions (**1.203f**) promote regioselective migration away from the substituted ring or towards the least substituted ring. Based on the biaryl *O*-carbamate **1.206**,[77] the sterically demanding *ortho* phenyl substrate **1.203g** may, in theory, be expected to undergo remote metalation and migration to give **1.207** (**Scheme 1.56**). The remote migration product **1.207** was not observed but the bulky *ortho* phenyl group does

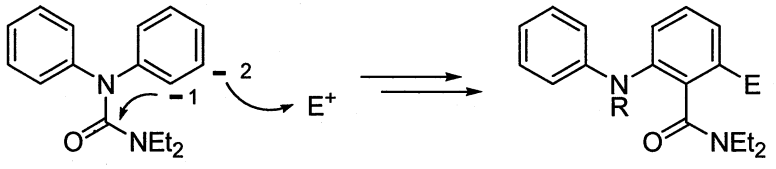
influence migration regioselectively away from the substituted ring to yield **1.204g** as the major product.



Scheme 1.56

1.6.4 Regiospecific Construction of *N*-Arylanthranilamides

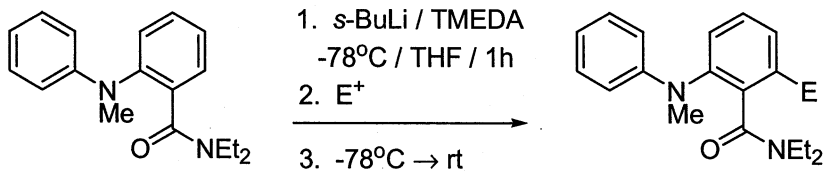
Although an efficient *N*-anionic *ortho* Fries rearrangement of substituted ureas induced by alkyllithium bases has been demonstrated, it is plagued by unpredictable regioselectivity leading to mixtures of products in most cases (**Scheme 1.55**). This problem may be potentially overcome by rearrangement of a symmetrical urea followed by further regiospecific elaboration *via* D*o*M (**1.203a** → **1.208**, **Scheme 1.57**).



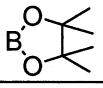
Scheme 1.57

To investigate this possibility, the migration product **1.204a** was *N*-methylated to afford **1.209** in excellent yield. Further manipulation of **1.209** by D*o*M chemistry

afforded 1,2,3-trisubstituted anthranilamides **1.210** regiospecifically in excellent yields (**Scheme 1.58**).

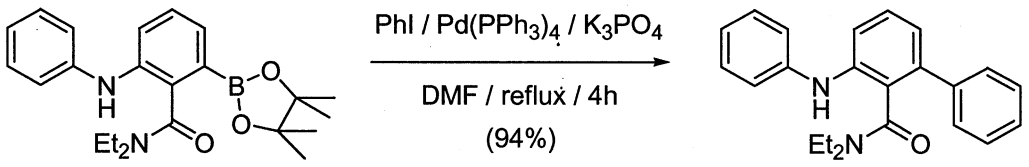


1.209 **1.210**

Entry	E^+ / E	Yield **1.210**, (%)
a	MeI / Me	98
b	TMSCl / TMS	97
c	$BrCH_2CH_2Br$ / Br	99
d	Cl_3CCCl_3 / Cl	99
e	DMF / CHO	91
f	$B(OMe)_3$ / 	85

Scheme 1.58

The D*o*M strategy also allows the introduction of new functionality for further chemistry. This point may be illustrated by the introduction of a boron functional group. Metalation of **1.209** and subsequent quenching with trimethylborate followed by isolation of the boronic ester afforded **1.210f** in high yield. Cross-coupling of **1.210f** with iodobenzene under modified Suzuki-Miyaura conditions furnished the biaryl **1.211** in excellent yield (**Scheme 1.59**). Generalisation of this D*o*M – cross coupling sequence is easily envisaged.

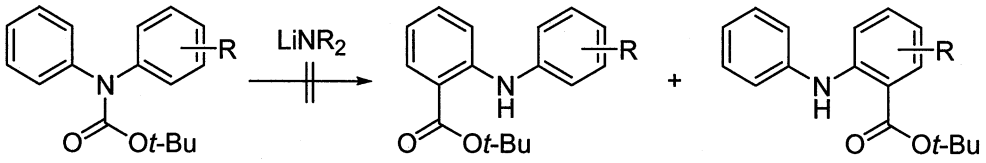


1.210f **1.211**

Scheme 1.59

1.6.5 LDA-Induced *N*-Anionic *ortho* Fries Rearrangement

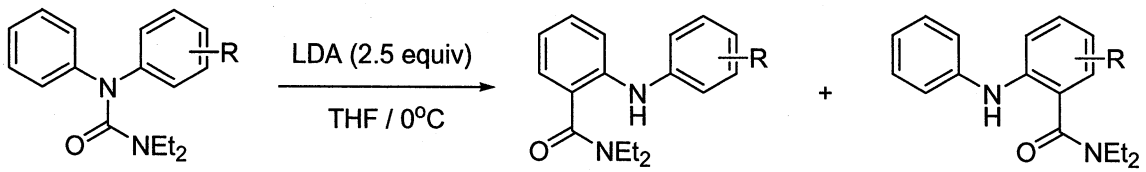
Although 1,2,3-trisubstituted anthranilamides may be prepared regiospecifically as described in **Section 1.6.4**, the procedure requires *N*-protection. If the free N-H compound, or an alternatively *N*-substituted compound was desired, the required protection/deprotection steps would make this route lengthy. Hence, predictable, regioselective migration conditions were sought. Although attempts to effect migration of the corresponding *t*-Bu carbamate **1.212** (**Scheme 1.60**) with lithium amide bases failed,[140] reactions of urea derivatives with LDA were nevertheless pursued.



1.212 **1.213** **1.214**

Scheme 1.60

Towards this end, treatment of unsymmetrical urea derivatives **1.203** with LDA (2.5 equiv) in THF at 0°C afforded the desired anthranilamides **1.204** and **1.205** in excellent yield and, with one exception (**1.203g**), with very high regioselectivity (**Scheme 1.61**).



1.203 **1.204** **1.205**

Entry	R	Yield **1.204**, (%)	Yield **1.205**, (%)
a	H	90	-
b	3-Cl	-	94
c	3-OMe	6	90
d	4-Cl	-	97
e	4-OMe	4	90
f	3,5-OMe	7	90
g	2-Ph	47	51

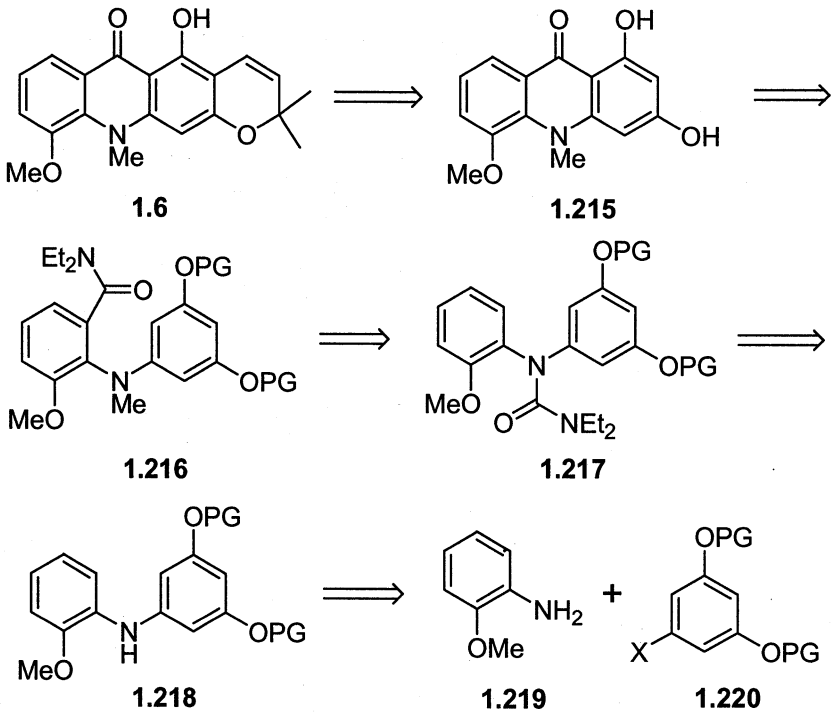
Scheme 1.61

Entries b, c, d, e, and f show that either electron donating or electron withdrawing groups under these conditions resulted in migration towards the substituted ring in excellent yield and high regioselectivity. Metalation / migration of the essentially electron neutral *ortho* phenyl substrate **1.203g** resulted in a 1:1 mixture of regioisomeric products. These results are an improvement over the alkyllithium-induced migration reactions (**Scheme 1.55**) in that they may allow rearrangement reactions to be carried out in a predictable, regioselective manner.

1.6.6 Application of the *N*-Anionic *ortho* Fries Rearrangement. Total Synthesis of the Acridone Alkaloid Junosidine

The total synthesis of the acridone alkaloid junosidine **1.6** was undertaken to demonstrate the utility of the new *N*-anionic *ortho* Fries rearrangement. Retrosynthetic analysis (**Scheme 1.62**) of junosidine **1.6** leads to the simple acridone alkaloid yukodine **1.215** *via* consideration of an in-house chromene synthesis.[145] The acridone skeleton

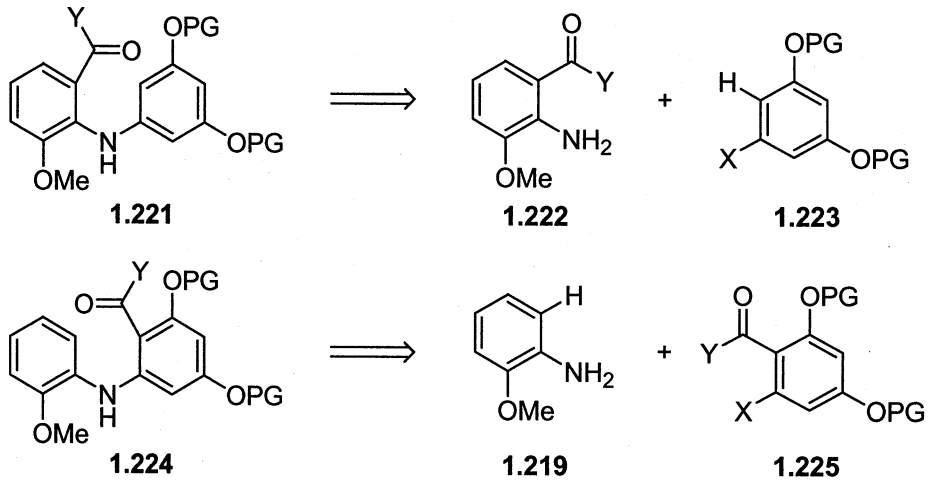
would arise from the cyclisation of *N*-aryl anthranilamide **1.216** which, in turn, would be the product of the rearrangement of urea **1.217**. Urea **1.217** would be made from the corresponding diarylamine **1.218** which may be accessible *via* the palladium-catalysed anilination of a suitably protected 5-halo resorcinol derivative **1.220** with *o*-anisidine **1.219**.



Scheme 1.62

The development of the new anionic *N*-Fries rearrangement provides advantages in that the carboxylic acid functionality required for cyclisation can be introduced after the metal catalysed amination step. A more classical disconnection of the two possible cyclisation precursors **1.221** and **1.224** for the desired natural product is illustrated in **Scheme 1.63**. Traditional Ullmann chemistry and, to a lesser extent, modern palladium mediated amination processes, are negatively affected by bulky *ortho* substitution in the coupling partners and hence amination of **1.223** with 3-methoxyanthranillic acid

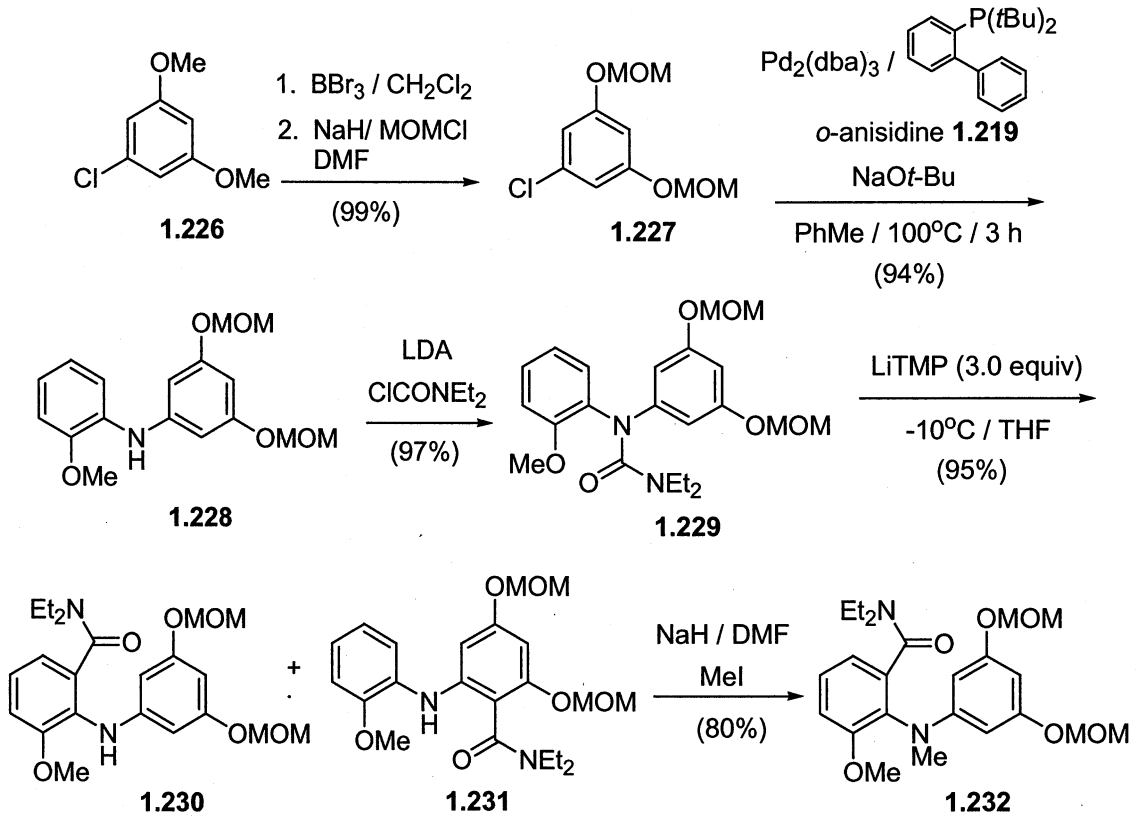
derivative **1.222** may not be facile. Although amination of **1.225** with *o*-anisidine **1.219** would likely proceed, this route may not be desirable since **1.225** is not a commercial entity and would require a multi-step synthesis.[138]



Scheme 1.63

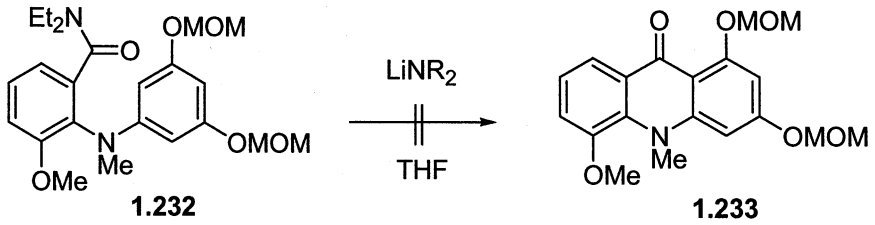
Since the target alkaloid junosidine **1.6** contains a phenol-methyl ether combination, it was first necessary to differentiate protecting groups in a starting material. Demethylation of the commercially available 3,5-dimethoxy chlorobenzene **1.226** with BBr_3 followed by reprotection of the resulting resorcinol as a di-MOM ether proceeded smoothly under standard conditions to furnish **1.227** in 99% yield (**Scheme 1.64**). Palladium catalysed amination of **1.227** with *o*-anisidine **1.219** employing the conditions of Buchwald[112] afforded the desired diarylamine **1.228** in 94% yield. Carbamoylation of **1.228** using LDA and diethylcarbamoyl chloride provided the urea **1.229** in 97% yield. Anionic rearrangement of **1.229** induced by treatment with LiTMP in THF at –10°C proceeded in 95% yield to afford a mixture of regioisomers **1.230** and **1.231** (43:7 as shown by ^{1}H NMR; see **Appendix A**). The rearrangement of this substrate appears to be controlled by steric considerations and results in a regioselective

mixture favouring the least hindered anthranilamide **1.230**. Methylation of this mixture under standard conditions supplied the cyclization precursor **1.232** as a single regioisomer in 80% yield after chromatography.



Scheme 1.64

Initially, anionic cyclization conditions developed by MacNeil were attempted.[31] However, treatment of **1.232** with an excess of LDA or LiTMP at 0°C followed by warming to rt resulted in a complex mixtures with no observed formation of the desired acridone **1.233** (**Scheme 1.65**).

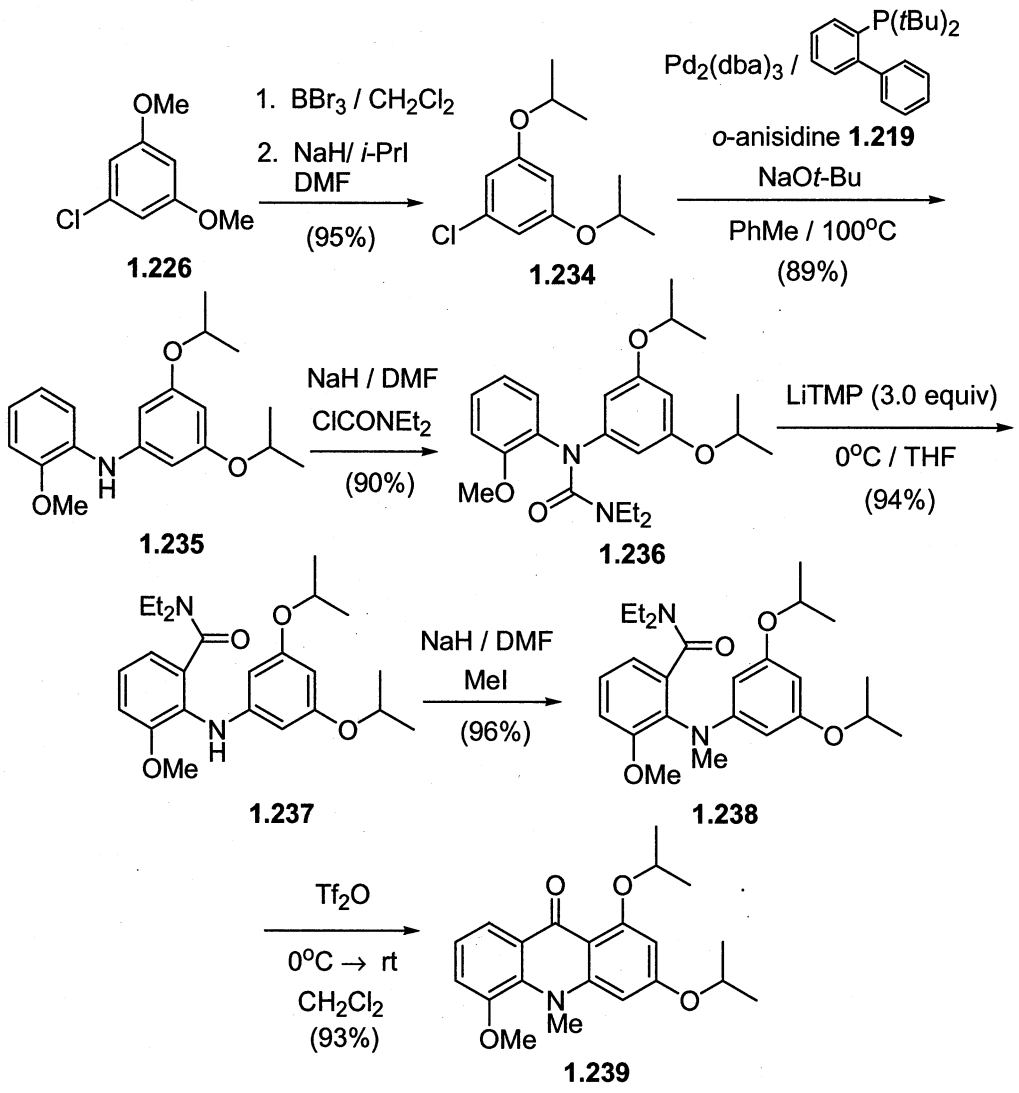


1.232 **1.233**

Scheme 1.65

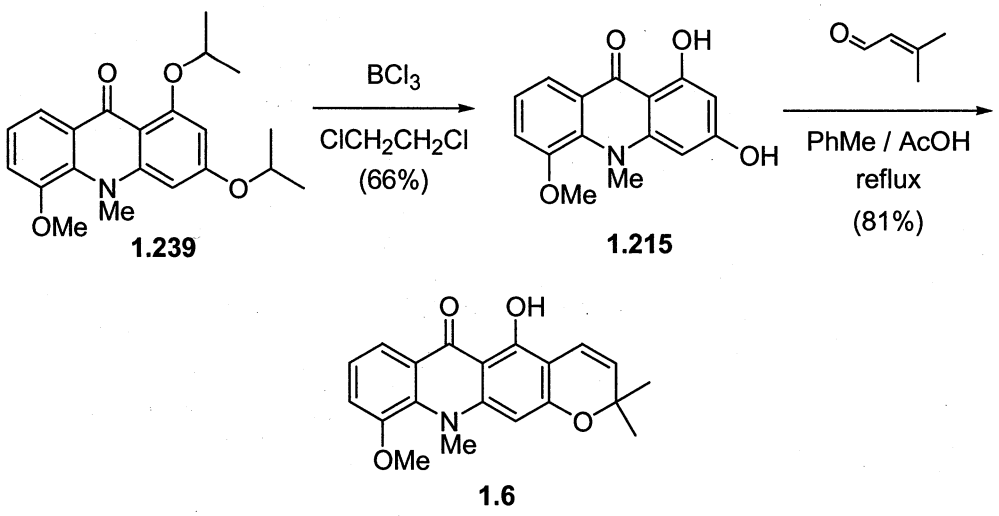
Acidic cyclization conditions were also unsuccessful in converting **1.232** to **1.233**. Treatment of **1.232** with an excess of Tf_2O, BCl_3, or a 1:1 mixture of trifluoroacetic acid and trifluoroacetic anhydride also resulted in the formation of complex mixtures.

Alternatively, we turned to a synthetic pathway using *i*-Pr ether protection instead of MOM ethers (**Scheme 1.66**). As before, treatment of 3,5-dimethoxychlorobenzene **1.226** with BBr_3 followed by reprotection with *i*-PrI under standard conditions afforded **1.234** in 95% yield. Although the Buchwald amination of **1.234** proceeded more slowly compared to that of **1.227**, it provided the desired diarylamine **1.235** in 89% yield. Carbamoylation of **1.235** proceeded smoothly using NaH as base to afford the urea **1.236** in 90% yield. Treatment of **1.236** with an excess of LiTMP at 0°C resulted in a highly regioselective migration to yield anthranilamide **1.237** in 94% yield as a single regioisomer as evidenced by ^1H NMR. Methylation of **1.237** under standard conditions afforded the desired cyclization precursor **1.238** in excellent yield. Unfortunately, as in the previous sequence, treatment of **1.238** with either LDA, LiTMP or *t*-BuLi failed to provide the desired acridone and gave complex mixtures of products. However, treatment of **1.238** with Tf_2O followed by basic work-up yielded the desired acridone **1.239** in 93% yield.



Scheme 1.66

Selective deprotection of the isopropyl ethers in the presence of a methyl ether was achieved by the treatment of **1.239** with BCl_3 to yield synthetic yukodine **1.215** in 66% yield (**Scheme 1.67**). Conversion of yukodine **1.215** to the target pyranoacridone junosidine **1.6** was effected by heating **1.215** and senecialdehyde in toluene in the presence of an excess of HOAc.



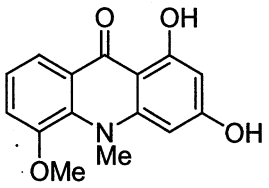
Scheme 1.67

This constitutes the first reported synthesis of junosidine **1.6** proceeding in 8 steps and 34% overall yield. Comparison of this route to previous routes used for the synthesis of *similar* acridones is a worthwhile exercise. The synthesis of the highly oxygenated simple acridone citrusine-I (**1.20**) by Kato *et al.* (**Scheme 1.2**, section **1.1.3.1**) requires an additional step and provides the desired acridone much lower overall yield (5% compared to 42%) when compared to the synthesis of yukodine (**1.215**) reported here. An angular pyranoacridone **1.70**, possesing the same oxygenation pattern of junosidine **1.6** was the target of Adams *et al.* in 1976.[48] Condensation of phloroglucinol with 3-methoxyanthranillic acid provided the acridone core in one step but only in 10% yield, clearly a drawback of this route. Further manipulation of the core brought the synthesis up to 6 linear steps and less than 5% overall yield (**Scheme 1.14**, section **1.1.3.3**). Total yield and number of steps aside, a clear advantage of this route is the vast number of potential aniline and arylhalide starting materials that could be chosen from for the synthesis of natural and un-natural acridones. Furthermore, the acidic condensation conditions employed in this work for the preparation of the linear pyranoacridone

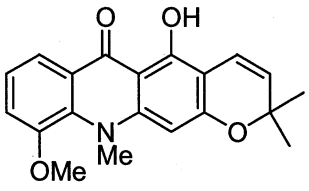
junosidine **1.6** compare quite favourably in terms of yield to the method described by Atassi (**Scheme 1.15**, section **1.1.3.3**) for the regioselective preparation of linear pyranoacridones,[49] and compliment the conditions of Taylor and co-workers for the regioselective synthesis of angular pyranoacridones.[46,47]

1.7 Conclusions and Future Work

A highly regioselective *N*-anionic *ortho* Fries rearrangement of unsymmetrical *N*,*N*-diaryl urea derivatives **1.203** to *N*-arylanthranilamides **1.204/1.205** has been developed (**Section 1.6.5**). In addition, the migration product **1.204a** can be further elaborated *via* *Do*M for the synthesis of 1,2,3-trisubstituted anthranilic acid dervivates **1.210** (**Section 1.6.4**). The synthetic utility of this rearrangement has been demonstrated in the total synthesis of two acridone alkaloids. Yukodine **1.215** was assembled in 7 steps and an overall yield of 42%, and junosidine **1.6** in a total of 8 steps and an overall yield of 34%.

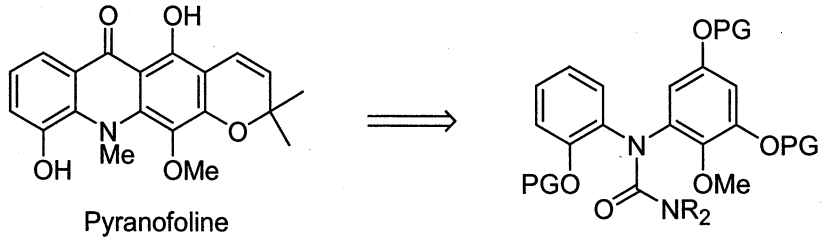


1.215

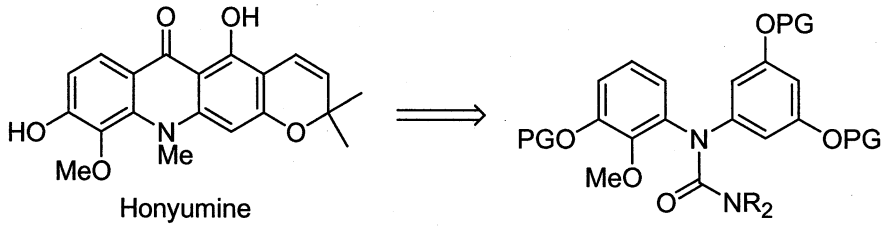


1.6

Although the triflic anhydride cyclisation (**1.238** → **1.239**, **Scheme 1.6**) was highly effective, the inability of DreM methodology to provide access to these 1,3 oxygentated acridone natural products is worthy of future investigation. In addition, the demonstration of the synthetic utility of the *N*-anionic Fries rearrangement in the synthesis of more highly substituted acridone alkaloids would reinforce the advantages of this new methodology.



Pyranofoline



Honyumine

2.0 Experimental Section

2.1 General Procedures

^{1}H NMR spectra were recorded on a Bruker AV-300, AV-400 or AV-500 instrument in $CDCl_3$ with tetramethylsilane as an internal standard unless otherwise stated. ^{13}C NMR spectra were obtained on a Bruker AV-300, AV-400 or AV-500 with chloroform-d_1 as an internal standard unless otherwise stated. Low-resolution mass spectra were obtained on a Varian Saturn GCMS workstation (EI) or on a Micromass VG Quattro Triple Quadrapole Mass Spectrometer (CI). High-resolution mass spectra were obtained on a Micromass 70-250s Double Focusing Mass Spectrometer by Dr. Alex Young at the University of Toronto. Melting points were determined on a Fisher Scientific hot stage apparatus and are uncorrected. Infrared spectra were obtained on a Bomem MB-100 FT IR spectrometer. Reactions were monitored by TLC analysis (Merck 60-F 254 precoated silica sheets) or by GCMS (Varian Saturn). Flash column chromatography was carried out using Merck kieselgel 60 silica gel (particle size: 0.040 – 0.063 mm).

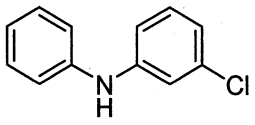
All dry solvents were purified under an argon atmosphere according to Perrin.[146] THF and Et_2O were freshly distilled from sodium benzophenone ketyl prior to use. Toluene was freshly distilled from sodium metal. CH_2Cl_2, MeCN and diisopropylamine were freshly distilled from calcium hydride prior to use. *N*,*N*-Dimethylformamide was dried over calcium hydride, distilled from magnesium sulphate and stored over 4Å sieves. *n*-Butyllithium was either purchased from the Aldrich Chemical Company or obtained from the FMC Corporation as a solution in hexanes. *s*-Butyllithium was purchased from

the Aldrich Chemical Company as a solution in cyclohexane. *t*-Butyllithium was either purchased from the Aldrich Chemical Company as a solution in pentane or obtained from the FMC Corporation as a solution in heptane. All alkyllithium reagents were stored in resealable containers and titrated against *s*-butanol with 1, 10-phenanthroline as indicator.[147] Racemic 2,2'-bis(diphenylphosphino)-1,1'-binapthyl and 2-(di-*tert*-butylphosphino)biphenyl were purchased from Strem Chemicals. LDA was freshly prepared before reactions by stirring a 1:1 mixture of diisopropylamine and *n*-butyllithium at 0°C in THF for 15 min. All commodity chemicals were purchased from the Aldrich Chemical Company and used without further purification.

All experiments were carried out in flame-dried glassware under argon using syringe-septum cap techniques. The 0°C temperature designated is approximate as achieved by an ice-water bath. The –10°C temperature designated is approximate as achieved by an ice-acetone bath. The –78°C temperature designated is approximate as achieved by an dry ice-acetone bath.

2.2 Specific Experimental Procedures

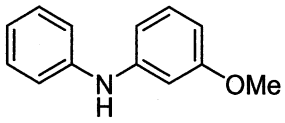
N-(3-Chlorophenyl)-*N*-phenylamine (1.202b)



General Method A: A mixture of iodobenzene (4.25 mL, 38.0 mmol), 3-chloroaniline (4.8 mL, 45.6 mmol), $Pd_2(dba)_3$ (0.087 g, 0.095 mmol), BINAP (0.177 g, 0.285 mmol) and NaO*t*-Bu (5.12 g, 53.2 mmol) in PhMe (40 mL) was heated between 90 and 110°C. After the complete consumption of aryl halide as judged by TLC analysis, the reaction mixture was cooled to rt, quenched with a satd NH_4Cl solution and extracted with EtOAc (3 X 20 mL). The combined organic

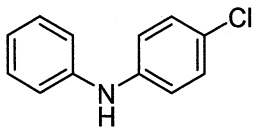
extracts were dried (Na_2SO_4), subjected to filtration, and concentrated *in vacuo*. Flash column chromatography (19:1 hexanes:Et_2O) afforded **1.202b** (7.29 g, 94%) as an amber oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 2H, ArH), 7.17 – 6.94 (m, 5H, ArH), 6.89 – 6.81 (m, 2H, ArH), 5.65 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.8, 141.9, 135.0, 130.3, 129.4, 122.1, 120.4, 118.9, 116.6, 115.1. The ^{1}H NMR and ^{13} C NMR spectra were consistent with those reported.[140]

***N*-(3-Methoxyphenyl)-*N*-phenylamine (1.202c)**



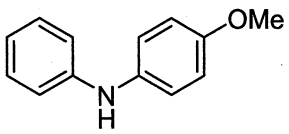
Following **General Method A** described above for the preparation of **1.202b** using the following materials: [bromobenzene (3.0 mL, 28.5 mmol), 3-methoxyaniline (3.85 g, 31.3 mmol), $Pd_2(dba)_3$ (0.070 g, 0.076 mmol), BINAP (0.132 g, 0.21 mmol), NaO*t*-Bu (3.87 g, 40.3 mmol) and PhMe (30 mL)]. Flash column chromatography (93:7 hexanes:EtOAc) afforded **1.202c** (5.09 g, 89%) as colourless crystals, mp 71-72°C (Et_2O/hexanes) [lit[140] mp 71.5-72.5°C (hexanes)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H, ArH), 7.20 – 7.13 (m, 1H, ArH), 7.11 – 7.07 (m, 2H, ArH), 6.97 – 6.91 (m, 1H, ArH), 6.67 – 6.63 (m, 2H, ArH), 6.50 – 6.46 (m, 1H, ArH), 5.70 (bs, 1H, NH), 3.77 (s, 3H, OCH_3). The ^{1}H NMR spectrum was consistent with that reported.[140]

***N*-(4-Chlorophenyl)-*N*-phenylamine (1.202d)**



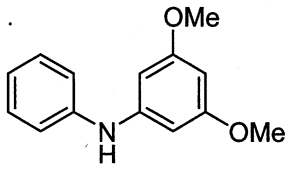
To a solution of 4-chlorophenol (0.5 g, 3.89 mmol) in CH_2Cl_2 (10 mL) at 0°C was added TEA (0.81 mL, 5.83 mmol) and Tf_2O (0.78 mL, 4.67 mmol). The reaction mixture was warmed to rt, and after complete consumption of the 4-chlorophenol as judged by TLC analysis, the reaction mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. The crude triflate was then passed through a short pad of silica gel (4:1 hexanes:EtOAc) and the filtrate was concentrated *in vacuo*. A mixture of the crude triflate, aniline (0.36 mL, 3.99 mmol), $Pd(OAc)_2$ (0.022 g, 0.100 mmol), BINAP (0.093g, 0.150 mmol) and Cs_2CO_3 (1.516 g, 4.65 mmol) in PhMe (10 mL) was sealed in a thick-walled screw-cap glass tube containing a magnetic stir bar. The tube was immersed in an oil bath (90°C) and the mixture was stirred and heated for 20 h. The reaction mixture was cooled to rt, quenched with a satd NH_4Cl solution and extracted with Et_2O (3 X 10 mL). The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (49:1 hexanes:Et_2O) afforded **1.202d** (0.474 g, 60%) as colourless crystals, mp 64-66°C (hexanes); IR (KBr) 693, 752, 809, 843, 1088, 1310, 1485, 1509, 1587, 2855, 2927, 3406 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 4H, ArH), 7.08-6.92 (m, 5H, ArH), 5.66 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.6, 141.8, 129.4, 129.2, 125.4, 121.5, 118.8, 118.1; LRMS (EI) m/z 203 (M+, 100), 167 (18); HRMS (EI) calcd for $C_{12}H_{10}NCl$ 203.0502: found 203.0494.

***N*-(4-Methoxyphenyl)-*N*-phenylamine (1.202e)**



General Method B: A mixture of *p*-bromoanisole (0.5 mL, 4.00 mmol), aniline (0.44 mL, 4.79 mmol), $Pd_2(dba)_3$ (0.009 g, 0.010 mmol), BINAP (0.019 g, 0.030 mmol), and NaO*t*-Bu (0.535 g, 5.59 mmol) in PhMe (10 mL) was sealed in a thick-walled screw-cap glass tube containing a magnetic stir bar and was heated in an oil bath (90°C) for 20 h. The reaction mixture was cooled to rt, quenched with a satd NH_4Cl solution and extracted with Et_2O (3 X 10 mL). The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (9:1 hexanes:Et_2O) afforded **1.202e** (0.856 g, 83%) as colourless crystals, mp 104-105°C (hexanes); IR (KBr) 696, 749, 1034, 1182, 1249, 1300, 1318, 1517, 1594, 2927, 2955, 3387 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 - 7.17 (m, 2H, ArH), 7.08 - 7.03 (m, 2H, ArH), 6.92 - 6.79 (m, 5H, ArH), 5.49 (bs, 1H, NH), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.2, 145.1, 135.7, 129.3, 122.1, 119.5, 115.6, 114.6, 55.5; LRMS (EI) m/z 199 (M+, 61), 184 (100), 129 (14); HRMS (EI) calcd for $C_{13}H_{13}NO$ 199.0997: found 199.0994.

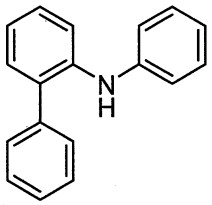
***N*-(3,5-Dimethoxyphenyl)-*N*-phenylamine (1.202f)**



Following **General Method B** described above for the preparation of **1.202e** using the following materials: [bromobenzene (1.34 mL, 12.7 mmol), 3,5-dimethoxyaniline (2.343 g, 15.3 mmol), $Pd_2(dba)_3$ (0.032 g, 0.034 mmol), BINAP (0.065 g, 0.104 mmol), NaO*t*-Bu (1.768 g, 18.4 mmol) and PhMe (20 mL)]. Flash column chromatography (20:3 hexanes:EtOAc) afforded **1.202f** (2.73 g, 93%) as pale yellow crystals, mp 69-70°C

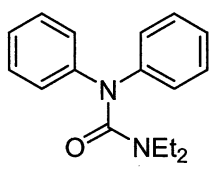
(Et_2O/hexanes) [lit[140] mp 70.5-71.5°C (hexanes)]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.22 (m, 2H, ArH), 7.13 - 7.07 (m, 2H, ArH), 6.98 – 6.92 (m, 1H, ArH), 6.23 (d, J = 2.4 Hz, 2H, ArH), 6.06 (t, J = 2.3 Hz, 1H, ArH), 3.75 (s, 6H, OCH_3). The ^1H NMR spectrum was consistent with that reported.[140]

2-Anilinobiphenyl (1.202g)



Following **General Method A** described above for the preparation of **1.202b** using the following materials: [bromobenzene (2.0 mL, 19.0 mmol), 2-aminobiphenyl (4.01 g, 23.7 mmol), $Pd_2(dba)_3$ (0.046 g, 0.050 mmol), BINAP (0.089 g, 0.14 mmol), NaO*t*-Bu (2.67 g, 27.8 mmol) and PhMe (30 mL)] Flash column chromatography (10:1 hexanes:EtOAc) afforded **1.202g** (4.66 g, 99%) as a viscous amber oil, IR (thin film) 704, 744, 1310, 1434, 1471, 1496, 1512, 1589, 3055, 3403 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 6H, ArH), 7.27 – 7.20 (m, 4H, ArH), 7.04 – 6.88 (m, 4H, ArH), 5.59 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.3, 140.1, 139.0, 131.5, 130.9, 129.3, 128.9, 128.2, 127.4, 121.0, 118.2, 117.4; LRMS (EI) m/z 245 (M+, 100); HRMS (EI) calcd for $C_{18}H_{15}N$ 245.1204: found 245.1206.

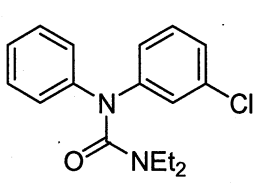
***N*,*N*-Diethyl-*N'*,*N'*-diphenylurea (1.203a)**



General Method C: To a solution of diphenylamine (6.50 g, 38.4 mmol) and diethylcarbamoyl chloride (12.2 mL, 96.0 mmol) in THF (100 mL) at 0°C was added a solution of freshly prepared LDA (76.8 mmol, 40 mL THF) dropwise *via* cannula. The resultant solution was allowed to

gradually warm to rt. The reaction mixture was quenched with a satd NH_4Cl solution and was extracted with CH_2Cl_2 (3 X 40 mL). The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Tetraethylurea was removed by Kugelröhr distillation and the resulting residue was subjected to flash column chromatography (7:3 hexanes:Et_2O) to afford **1.203a** (10.24 g, 99%) as a colourless viscous oil, IR (thin film) 693, 752, 1150, 1219, 1268, 1407, 1493, 1590, 1659, 2931, 2974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 4H, ArH), 7.14 – 7.01 (m, 6H, ArH), 3.25 (q, J = 7.1 Hz, 4H, CH_2), 1.02 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.2, 144.9, 129.0, 124.5, 124.2, 42.1, 12.8; LRMS (EI) m/z 268 (M+, 100), 167 (20), 100 (72), 72 (15); HRMS (EI) calcd for $C_{17}H_{20}N_2O$ 268.1576: found 268.1585.

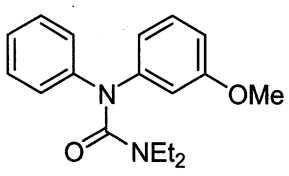
***N,N*-Diethyl-*N'*-(3-chlorophenyl)-*N'*-phenylurea (1.203b)**



Following **General Method C** described above for the preparation of **1.203a** using the following materials: [*N*-(3-chlorophenyl)-*N*-phenylamine **1.202b** (1.647 g, 8.09 mmol), diethylcarbamoyl chloride (2.0 mL, 16.2 mmol), THF (20 mL) and freshly prepared LDA (12.1 mmol, 10 mL THF)] Flash column chromatography (1:1 hexanes:Et_2O) afforded **1.203b** (2.185 g, 89%) as a viscous amber oil, IR (thin film) 688, 752, 785, 1074, 1155, 1214, 1262, 1418, 1477, 1584, 1665, 2937, 2974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H, ArH), 7.23 – 7.13 (m, 2H, ArH), 7.08 – 7.03 (m, 3H, ArH), 7.00 – 6.97 (m, 1H, ArH), 6.91 – 6.87 (m, 1H ArH), 3.26 (q, J = 7.1 Hz, 4H, CH_2), 1.03 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.7, 146.4, 144.0, 134.5, 129.9, 129.4, 125.1, 125.0,

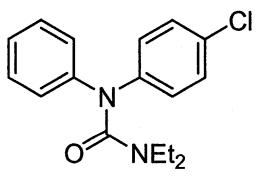
124.0, 123.9, 122.1, 42.2, 12.9; LRMS (EI) m/z 302 (M+, 100), 167 (20), 100 (93), 72 (12); HRMS (EI) calcd for $C_{17}H_{19}ClN_2O$ 302.1186: found 302.1189.

***N,N*-Diethyl-*N'*-(3-methoxyphenyl)-*N'*-phenylurea (1.203c)**



Following **General Method C** described above for the preparation of **1.203a** using the following materials: [*N*-(3-methoxyphenyl)-*N*-phenylamine **1.202c** (1.362 g, 6.83 mmol), diethylcarbamoyl chloride (1.7 mL, 13.7 mmol), THF (20 mL) and freshly prepared LHMDS (13.7 mmol, 10 mL THF)] Flash column chromatography (1:1 hexanes:EtOAc) afforded **1.203c** (2.04 g, 99%) as an amber oil, IR (thin film) 688, 758, 1042, 1268, 1412, 1488, 1590, 1654, 2931, 2979 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H, ArH), 7.23 – 7.16 (m, 1H, ArH), 7.13 – 7.03 (m, 3H, ArH), 6.68 – 6.62 (m, 2H, ArH), 6.59 – 6.57 (m, 1H, ArH), 3.74 (s, 3H, OCH_3), 3.27 (q, J = 7.1 Hz, 4H, CH_2), 1.04 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.3, 146.2, 144.9, 129.8, 129.1, 124.7, 124.4, 117.1, 110.4, 109.8, 55.3, 42.2, 13.0; LRMS (EI) m/z 298 (M+, 100), 154 (11), 100 (61), 72 (14); HRMS (EI) calcd for $C_{18}H_{22}N_2O_2$ 298.1681: found 298.1682.

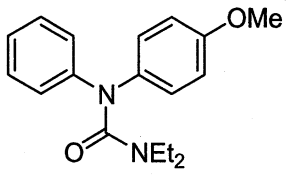
***N,N*-Diethyl-*N'*-(4-chlorophenyl)-*N'*-phenylurea (1.203d)**



Following **General Method C** described above for the preparation of **1.203a** using the following materials: [*N*-(4-chlorophenyl)-*N*-phenylamine **1.202d** (0.553 g, 2.71 mmol), diethylcarbamoyl chloride (0.86 mL, 6.78 mmol), THF (20 mL) and freshly prepared LDA (5.42 mmol, 5 mL THF)] Flash column chromatography (1:1 hexanes:Et_2O) afforded **1.203d** (0.668 g, 81%) as an amber oil, IR (thin film) 693, 752, 817, 1214, 1262, 1412, 1488, 1590, 1665,

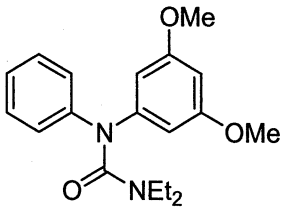
2937, 2979 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 4H, ArH), 7.17 – 7.11 (m, 1H, ArH), 7.06 – 7.02 (m, 2H, ArH), 6.97 – 6.93 (m, 2H, ArH), 3.25 (q, J = 7.1 Hz, 4H, CH_2), 1.03 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9, 144.4, 143.8, 129.3, 129.1, 125.5, 124.8, 124.7, 42.2, 12.9; LRMS (EI) m/z 302 (M+, 50), 167 (33), 100 (100), 72 (43); HRMS (EI) calcd for $C_{17}H_{19}ClN_2O$ 302.1186: found 302.1198.

_N,N_-Diethyl-_N'_-(4-methoxyphenyl)-_N'_-phenylurea (1.203e)



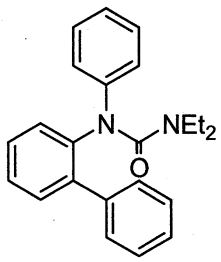
Following **General Method C** described above for the preparation of **1.203a** using the following materials: [*N*-(4-methoxyphenyl)-*N*-phenylamine **1.202e** (1.243 g, 6.24 mmol), diethylcarbamoyl chloride (2.0 mL, 15.6 mmol), THF (20 mL) and freshly prepared LDA (12.5 mmol, 10 mL THF)] Flash column chromatography (1:1 hexanes:Et_2O) afforded **1.203e** (1.862 g, 99%) as an amber oil, IR (thin film) 693, 756, 825, 1030, 1157, 1247, 1273, 1410, 1511, 1653, 2941, 2972 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H, ArH), 7.09 – 6.97 (m, 5H, ArH), 6.88 – 6.83 (m, 2H, ArH), 3.80 (s, 3H, OCH_3), 3.25 (q, J = 7.1 Hz, 4H, CH_2), 1.02 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.4, 156.9, 145.6, 137.8, 128.9, 126.8, 123.9, 123.7, 114.5, 55.4, 42.1, 13.0; LRMS (EI) m/z 298 (M+, 100), 175 (33), 154 (25), 100 (86), 72 (52); HRMS (EI) calcd for $C_{18}H_{22}N_2O_2$ 298.1681: found 298.1682.

***N,N*-Diethyl-*N'*-(3,5-dimethoxyphenyl)-*N'*-phenylurea (1.203f)**



Following **General Method C** described above for the preparation of **1.203a** using the following materials: [*N*-(3,5-dimethoxyphenyl)-*N*-phenylamine **1.202f** (1.106 g, 4.82 mmol), diethylcarbamoyl chloride (1.2 mL, 9.65 mmol), THF (15 mL) and freshly prepared LiHMDS (9.65 mmol, 10 mL THF)] Flash column chromatography (3:2 hexanes:EtOAc) afforded **1.203f** (1.530 g, 97%) as colourless crystals, mp 69-70°C (Et_2O/hexanes); IR (KBr) 691, 760, 817, 833, 924, 1048, 1058, 1080, 1150, 1198, 1278, 1407, 1455, 1590, 1654, 2931, 2974, 3006 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H, ArH), 7.13 – 7.03 (m, 3H, ArH), 6.24 (t, J = 1.7 Hz, 1H, ArH), 6.20 (d, J = 1.7 Hz, 2H, ArH), 3.72 (s, 6H, OCH_3), 3.28 (q, J = 7.1 Hz, 4H, CH_2), 1.05 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.1, 159.9, 146.6, 144.8, 129.1, 124.6, 124.4, 103.0, 96.6, 55.3, 42.2, 13.0; LRMS (EI) m/z 328 (M+, 30), 223 (22), 100 (100), 72 (90); HRMS (EI) calcd for $C_{19}H_{24}N_2O_3$ 328.1787: found 328.1784.

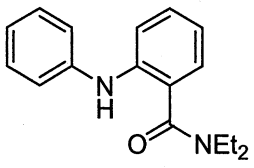
***N,N*-Diethyl-*N'*-(2-biphenyl)-*N'*-phenylurea (1.203g)**



Following **General Method C** described above for the preparation of **1.203a** using the following materials: [2-anilinobiphenyl **1.202g** (1.41 g, 5.75 mmol), diethylcarbamoyl chloride (1.5 mL, 11.5 mmol), THF (15 mL) and freshly prepared LiHMDS (8.6 mmol, 10 mL THF)] Flash column chromatography (1:1 hexanes:EtOAc) afforded **1.203g** (1.88 g, 95%) as a colourless viscous oil which solidified on standing but resisted recrystallization, mp 73-75°C; IR (KBr) 637, 697, 703, 744, 752, 776, 841, 1008, 1066, 1085, 1157, 1219, 1276,

1345, 1407, 1469, 1589, 1657, 2932, 2962, 2977, 3020, 3058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 10H, ArH), 7.07 – 6.93 (m, 4H, ArH), 2.90 (q, J = 7.1 Hz, 4H, CH_2), 0.68 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.4, 146.0, 143.4, 140.0, 139.8, 130.9, 129.0, 128.3, 128.1, 127.8, 126.9, 125.7, 124.5, 123.9, 41.0, 12.0; LRMS (EI) m/z 344 (M+, 80), 244 (17), 175 (31), 100 (100), 72 (57); HRMS (EI) calcd for $C_{23}H_{24}N_2O$ 344.1889: found 344.1883.

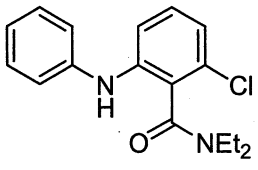
***N,N*-Diethyl-2-anilinobenzamide (1.204a)**



(i) General Method D: A solution of *t*-BuLi (11.7 mL, 1.42 M, 16.7 mmol) was added dropwise *via* syringe to a stirred solution of *N,N*-diethyl-*N'*,*N'*-diphenylurea **1.203a** (3.192 g, 11.9 mmol) and TMEDA (2.5 mL, 16.7 mmol) in Et_2O (100 mL) at –78°C. The resultant yellow reaction mixture was allowed to warm to rt overnight. The reaction mixture was quenched with a satd NH_4Cl solution and extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Recrystallization from hexanes afforded **1.204a** (2.592 g, 81%) as pale yellow crystals, mp 74-75°C (hexanes) [lit[32] 74-76°C (hexanes)]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 1H, ArH), 7.30 – 7.16 (m, 4H, ArH), 7.10 – 7.06 (m, 2H, ArH), 6.96 – 6.84 (m, 2H, ArH), 3.45 (bs, 4H, CH_2), 1.18 (bs, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.4, 142.2, 141.3, 129.7, 129.2, 127.1, 125.1, 121.1, 119.6, 118.5, 116.9. The ^1H NMR and ^{13}C NMR spectra were consistent with those reported.[32]

(ii) General Method E: To a solution of *N,N*-diethyl- *N'*,*N'*-diphenylurea **1.203a** (0.484 g, 1.80 mmol) in THF (12 mL) at 0°C was added a freshly prepared solution of LDA (4.51 mmol, 5 mL THF) dropwise *via* cannula. The reaction mixture was quickly warmed to rt, quenched with a satd NH_4Cl solution and extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. The resulting brown solid was passed through a short pad of silica gel to yield **1.204a** (0.434 g, 90%) which was shown to be identical to the sample obtained by **General Method D**.

***N,N*-Diethyl-2-anilino-6-chlorobenzamide (1.205b)**

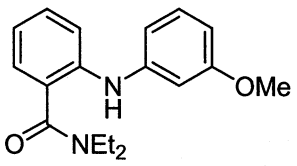


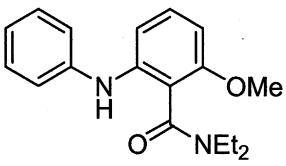
(i) Following **General Method D** described above for the preparation of **1.204a** using the following materials: [*N,N*-diethyl-*N'*-(3-chlorophenyl)-*N'*-phenylurea **1.203b** (0.213 g, 0.70 mmol), TMEDA (0.14 mL, 0.91 mmol), *t*-BuLi (0.66 mL, 1.38 M, 0.91 mmol) and Et_2O (20 mL)] Flash column chromatography (7:3 hexanes:Et_2O) afforded **1.205b** (0.195 g, 92%) as colourless crystals, mp 117–119°C (hexanes); IR (KBr) 703, 749, 878, 921, 1104, 1284, 1316, 1445, 1496, 1588, 1619, 2936, 2986, 3102, 3249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 3H, ArH), 7.15 – 6.88 (m, 5H, ArH), 3.94 – 3.78 (m, 1H, CH_2), 3.41 – 3.12 (m, 3H, CH_2), 1.26 (t, J = 7.2 Hz, 3H, CH_3), 1.05 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.5, 142.0, 141.7, 130.8, 129.6, 129.3, 125.7, 121.8, 120.9, 118.9, 114.9, 42.7, 39.0, 13.8, 12.5; LRMS (EI) m/z 302 (M+, 100), 267 (14), 230 (27), 165 (17), 72 (18); HRMS (EI) calcd for $C_{17}H_{19}ClN_2O$ 302.1186: found 302.1188.

(ii) Following **General Method E** described above for the preparation of **1.204a** using the following materials: [*N*,*N*-diethyl-*N'*-(3-chlorophenyl)-*N'*-phenylurea **1.203b** (0.549 g, 1.81 mmol), THF (12 mL) and freshly prepared LDA (4.53 mmol, 5 mL THF)] Flash column chromatography (1:1 hexanes:EtOAc) afforded **1.205b** (0.517 g, 94%) which was shown to be identical to the sample obtained by **General Method D**.

***N*,*N*-Diethyl-2-(3-methoxyanilino)benzamide (1.204c) and**

***N*,*N*-Diethyl-2-anilino-6-methoxybenzamide (1.205c)**



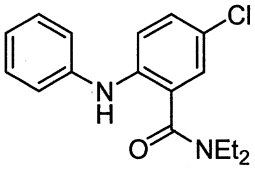


(i) Following **General Method D** described above for the preparation of **1.204a** using the following materials: [*N*,*N*-diethyl-*N'*-(3-methoxyphenyl)-*N'*-phenylurea **1.203c** (0.162 g, 0.54 mmol), TMEDA (0.11 mL, 0.71 mmol), *t*-BuLi (0.51 mL, 1.38 M, 0.71 mmol) and Et_2O (20 mL)] Flash column chromatography (7:3 hexanes:Et_2O) afforded **1.204c** (0.095 g, 59%) and **1.205c** (0.043 g, 26%). **1.204c:** amber oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 8.2 Hz, 1H, ArH), 7.26 – 7.13 (m, 2H, ArH), 6.92 – 6.86 (m, 2H, ArH), 6.69 – 6.63 (m, 2H, ArH), 6.49 (dd, J = 8.2, 1.7 Hz, 1H, ArH), 3.77 (s, 3H, OCH_3), 3.44 (bs, 4H, CH_2), 1.17 (bs, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5, 160.6, 143.7, 141.1, 130.0, 129.8, 127.1, 125.5, 119.9, 117.7, 110.8, 106.6, 104.0, 55.2, 13.5. The ^{1}H NMR and ^{13}C NMR spectra were consistent with those reported.[32] **1.205c:** colourless crystals, mp 94–96°C (hexanes/CH_2Cl_2); IR (KBr) 506, 600, 615, 732, 755, 778, 878, 1084, 1181, 1259, 1282, 1316, 1436, 1462, 1470, 1510, 1593, 1622, 2877, 2934, 2980, 3406 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H, ArH), 7.21 – 7.13 (m, 1H, ArH), 7.09 – 7.02 (m, 2H,

ArH), 7.01 – 6.90 (m, 2H, ArH), 6.48 (d, J = 8.2 Hz, 1H, ArH), 6.28 (bs, 1H, NH), 3.82 (s, 3H, OCH_3), 3.75 – 3.45 (m, 2H, CH_2), 3.38 – 3.22 (m, 2H, CH_2), 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.04 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.2, 155.9, 142.3, 141.4, 129.5, 129.0, 120.9, 118.2, 115.7, 109.7, 102.8, 55.3, 42.7, 38.8, 13.7, 12.7; LRMS (EI) m/z 298 (M+, 100), 225 (37), 210 (20), 182 (27), 154 (16), 72 (5); HRMS (EI) calcd for $C_{18}H_{22}N_2O_2$ 298.1681: found 298.1688.

(ii) Following **General Method E** described above for the preparation of **1.204a** using the following materials: [*N*,*N*-diethyl-*N'*-(3-methoxyphenyl)-*N'*-phenylurea **1.203c** (0.318 g, 1.07 mmol), THF (8 mL) and freshly prepared LDA (2.66 mmol, 4 mL THF)] Flash column chromatography (7:3 hexanes:EtOAc) afforded **1.204c** (0.018 g, 6%) and **1.205c** (0.287 g, 90%) which were shown, respectively, to be identical to the samples obtained by **General Method D**.

***N*,*N*-Diethyl-2-anilino-5-chlorobenzamide (1.205d)**



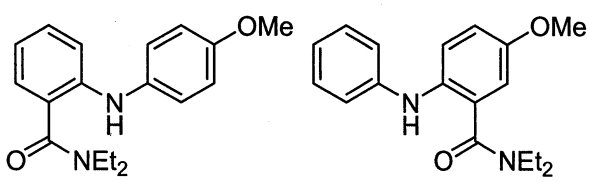
(i) Following **General Method D** described above for the preparation of **1.204a** using the following materials: [*N*,*N*-diethyl-*N'*-(4-chlorophenyl)-*N'*-phenylurea **1.203d** (0.122 g, 0.40 mmol), TMEDA (0.08 mL, 0.52 mmol), *t*-BuLi (0.30 mL, 1.75 M, 0.52 mmol) and Et_2O (14 mL)] Flash column chromatography (7:3 hexanes:Et_2O) afforded **1.205d** (0.106 g, 87%) as colourless crystals, mp 99–101°C (hexanes); IR (KBr) 702, 757, 896, 1105, 1324, 1475, 1527, 1594, 1626, 2873, 2937, 2984, 3059, 3309 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 3H, ArH), 7.22 – 7.15 (m, 2H, ArH), 7.09 – 7.04 (m, 2H, ArH), 7.01 – 6.94 (m, 1H, ArH), 6.78 (bs, 1H, NH), 3.47 (bs, 4H, CH_2), 1.20 (bs, 6H, CH_3); ^{13}C

NMR (75.5 MHz, $CDCl_3$) δ 168.9, 141.7, 140.1, 129.6, 129.3, 126.8, 126.3, 124.2, 121.6, 118.7, 118.0; LRMS (EI) m/z 302 (M+, 100), 229 (46), 194 (30), 166 (26), 139 (9), 72 (24); HRMS (EI) calcd for $C_{17}H_{19}ClN_2O$ 302.1186: found 302.1187.

(ii) Following **General Method E** described above for the preparation of **1.204a** using the following materials: *N,N*-diethyl-*N'*-(4-chlorophenyl)-*N'*-phenylurea **1.203d** (0.313 g, 1.03 mmol), THF (8 mL) and freshly prepared LDA (2.59 mmol, 4 mL THF)] The resultant light brown solid was passed through a short pad of silica gel to yield **1.205d** (0.303 g, 97%) which was shown to be identical to the sample obtained by **General Method D**.

***N,N*-Diethyl-2-(4-methoxyanilino)benzamide (1.204e) and**

***N,N*-Diethyl-2-anilino-5-methoxybenzamide (1.205e)**



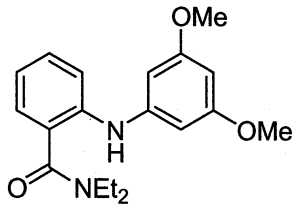
(i) Following **General Method D** described above for the preparation of **1.204a** using the following materials: [*N,N*-diethyl-*N'*-(4-methoxyphenyl)-*N'*-phenylurea **1.203e** (0.209 g, 0.70 mmol), TMEDA (0.11 mL, 0.91 mmol), *t*-BuLi (0.52 mL, 1.75 M, 0.91 mmol) and Et_2O (14 mL)] Flash column chromatography (3:1 hexanes:EtOAc) afforded **1.204e** (0.113 g, 54%) and **1.205e** (0.073 g, 35%). **1.204e:** amber oil, IR (thin film) 744, 819, 1039, 1246, 1289, 1450, 1511, 1589, 1624, 2930, 2973 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 3H, ArH), 7.10 – 7.04 (m, 2H, ArH), 6.89 – 6.84 (m, 2H, ArH), 6.82 – 6.76 (m, 1H, ArH), 6.68 (bs, 1H, NH), 3.80 (s, 3H, OCH_3), 3.48 (bs, 4H, CH_2), 1.21 (bs, 6H, CH_3); ^{13}C NMR (100.8 MHz, $CDCl_3$) δ 170.8, 155.3, 143.5, 135.1, 129.9, 127.1, 123.3, 122.6,

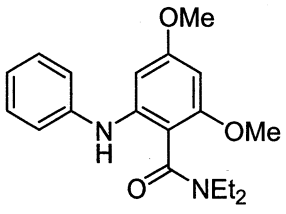
118.3, 115.0, 114.6, 55.6; LRMS (EI) m/z 298 (M+, 91), 225 (100), 210 (57), 182 (65), 154 (28), 72 (4); HRMS (EI) calcd for $C_{18}H_{22}N_2O_2$ 298.1681: found 298.1688. **1.205e:** colourless crystals, mp 114-116°C (hexanes/CH_2Cl_2); IR (KBr) 504, 695, 1040, 1171, 1219, 1264, 1302, 1439, 1475, 1494, 1523, 1593, 1612, 2868, 2934, 2980, 3277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.9 Hz, 1H, ArH), 7.27 – 7.17 (m, 2H, ArH), 6.98 – 6.91 (m, 2H, ArH), 6.90 – 6.81 (m, 2H, ArH), 6.77 (d, J = 2.9 Hz, 1H, ArH), 6.26 (bs, 1H, NH), 3.81 (s, 3H, OCH_3), 3.59 – 3.21 (bs, 4H, CH_2), 1.15 (bs, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.5, 154.0, 144.0, 133.2, 129.1, 129.0, 121.5, 119.6, 116.1, 115.2, 111.9, 55.4; LRMS (EI) m/z 298 (M+, 100), 225 (26), 210 (16), 182 (28), 154 (15), 72 (5); HRMS (EI) calcd for $C_{18}H_{22}N_2O_2$ 298.1681: found 298.1678.

(ii) Following **General Method E** described above for the preparation of **1.204a** using the following materials: [*N*,*N*-diethyl-*N'*-(4-methoxyphenyl)-*N'*-phenylurea **1.203e** (0.353 g, 1.18 mmol), THF (8 mL) and freshly prepared LDA (2.96 mmol, 4 mL THF)] Flash column chromatography (3:1 hexanes:EtOAc) afforded **1.204e** (0.013 g, 4%) and **1.205e** (0.319 g, 90%) which were shown, respectively, to be identical to the samples obtained by **General Method D.**

***N*,*N*-Diethyl-2- (3,5-dimethoxyanilino)benzamide (1.204f) and**

***N*,*N*-Diethyl-2-anilino-4,6-dimethoxybenzamide (1.205f)**





(i) Following **General Method D** described above for the preparation of **1.204a** using the following materials:

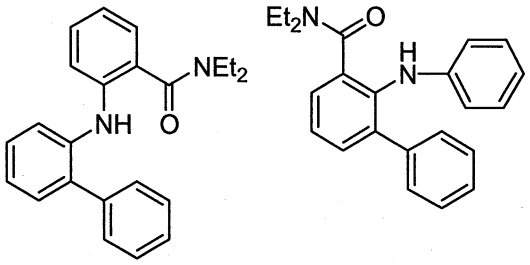
[*N*,*N*-diethyl-*N'*-(3,5-dimethoxyphenyl)-*N'*-phenylurea **1.203f** (0.204 g, 0.62 mmol), TMEDA (0.13 mL, 0.87 mmol), *t*-BuLi (0.51 mL, 1.71 M, 0.87 mmol) and Et_2O (20 mL)] Flash column chromatography (4:1 PhMe:EtOAc) afforded **1.204f** (0.154 g, 75%) and **1.205f** (0.029 g, 14%). **1.204f:** colourless crystals, mp 88-89°C (hexanes) [lit[32] 87-89°C (hexanes)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, J = 8.3, 0.9 Hz, 1H, ArH), 7.28 – 7.21 (m, 1H, ArH), 7.18 (dd, J = 7.5, 1.5 Hz, 1H, ArH), 6.90 (dt, J = 7.5, 0.9 Hz, 1H, ArH), 6.25 (d, J = 2.2 Hz, 2H, ArH), 6.07 (t, J = 2.2 Hz, 1H, ArH), 3.75 (s, 6H, OCH_3), 3.46 (bs, 4H, CH_2), 1.17 (bs, 6H, CH_3). The ^{1}H NMR spectra was consistent with that reported.[32] **1.205f:** colourless crystals, mp 100–101°C (hexanes/CH_2Cl_2); IR (KBr) 635, 721, 752, 812, 869, 941, 1058, 1098, 1164, 1207, 1247, 1287, 1413, 1470, 1496, 1591, 1619, 2941, 2970, 3120, 3274 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H, ArH), 7.11 – 7.07 (m, 2H, ArH), 6.98 – 6.93 (m, 1H, ArH), 6.53 (d, J = 2.1 Hz, 1H, ArH), 6.46 (bs, 1H, NH), 6.06 (d, J = 2.1 Hz, 1H, ArH), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.73 – 3.58 (m, 1H, CH_2), 3.56 – 3.41 (m, 1H, CH_2), 3.37 – 3.12 (m, 2H, CH_2), 1.23 (t, J = 7.1 Hz, 3H, CH_3), 1.05 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.4, 161.1, 157.0, 142.6, 142.0, 129.0, 121.1, 118.7, 108.3, 94.1, 90.6, 55.2, 55.0, 42.8, 38.9, 13.8, 12.7; LRMS (EI) m/z 328 (M+, 58), 255 (100), 240 (34), 226 (31), 212 (44), 183 (10), 72 (3); HRMS (EI) calcd for $C_{19}H_{24}N_2O_3$ 328.1787: found 328.1788.

(ii) Following **General Method E** described above for the preparation of **1.204a** using the following materials: [*N*,*N*-diethyl-*N'*-(3,5-dimethoxyphenyl)-*N'*-phenylurea **1.203f** (0.377 g, 1.15 mmol), THF (8 mL) and freshly prepared LDA (2.87 mmol, 4 mL THF)] Flash column chromatography (7:3 hexanes:EtOAc) afforded **1.204f** (0.028 g, 7%) and

1.205f (0.340 g, 90%) which were shown, respectively, to be identical to the samples obtained by **General Method D**.

***N,N*-Diethyl-2-(2-phenylanilino)benzamide (1.204g) and**

***N,N*-Diethyl-2-anilino-3-phenylbenzamide (1.205g)**

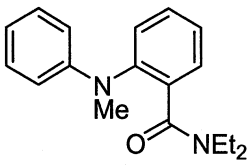


(i) Following **General Method D** described above for the preparation of **1.204a** using the following materials: [*N,N*-diethyl-*N'*-(2-biphenyl)-*N'*-phenylurea **1.203g** (0.265 g, 0.77 mmol), TMEDA (0.14 mL, 0.92 mmol), *t*-BuLi (0.52 mL, 1.76 M, 0.92 mmol) and Et_2O (20 mL)] Flash column chromatography (7:3 hexanes:EtOAc) afforded **1.204g** (0.193 g, 73%) and **1.205g** (0.051 g, 19%). **1.204g:** amber oil, IR (thin film) 701, 749, 1082, 1284, 1311, 1436, 1454, 1510, 1582, 1630, 2935, 2978, 3063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 7H, ArH), 7.31 – 7.19 (m, 3H, ArH), 7.15 (dd, J = 7.5, 1.4 Hz, 1H, ArH), 7.07 – 7.00 (m, 1H, ArH), 6.92 – 6.84 (m, 1H, ArH), 6.44 (bs, 1H, NH), 3.30 (bs, 4H, CH_2), 1.05 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.7, 140.7, 139.5, 138.8, 132.4, 130.9, 129.5, 129.0, 128.7, 128.0, 127.4, 127.0, 126.3, 121.5, 120.0, 118.1, 117.4; LRMS (EI) m/z 344 (M+, 100), 270 (76), 243 (19), 72 (15); HRMS (EI) calcd for $C_{23}H_{24}N_2O$ 344.1889: found 344.1888. **1.205g:** colourless crystals, mp 147–149°C (hexanes/CH_2Cl_2); IR (KBr) 591, 626, 699, 704, 747, 768, 809, 1026, 1072, 1131, 1230, 1289, 1313, 1377, 1428, 1455, 1509, 1595, 1624, 2872, 2928, 2971, 3052, 3371 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 3H, ArH), 7.32 – 7.17 (m, 5H, ArH), 7.05 – 6.96 (m, 2H, ArH), 6.72 – 6.64 (m, 1H, ArH), 6.59 – 6.52 (m, 2H, ArH),

5.92 (bs, 1H, NH), 3.37 (bs, 2H, CH_2), 3.16 (bs, 2H, CH_2), 1.03 – 0.88 (m, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6, 144.6, 139.2, 137.7, 135.9, 133.2, 131.8, 128.6, 128.4, 128.1, 127.1, 126.7, 124.1, 119.3, 115.7, 42.9, 38.6, 13.7, 12.2; LRMS (EI) m/z 344 (M+, 97), 270 (100), 243 (25), 72 (24); HRMS (EI) calcd for $C_{23}H_{24}N_2O$ 344.1889: found 344.1887.

(ii) Following **General Method E** described above for the preparation of **1.204a** using the following materials: [*N*,*N*-diethyl-*N'*-(2-biphenyl)-*N'*-phenylurea **1.203g** (0.313 g, 0.91 mmol), THF (8 mL) and freshly prepared LDA (2.27 mmol, 4 mL THF)] Flash column chromatography (17:3 hexanes:EtOAc) afforded **1.204g** (0.148 g, 47%) and **1.205g** (0.158 g, 51%) which were shown, respectively, to be identical to the samples obtained by **General Method D**.

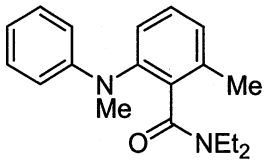
***N*,*N*-Diethyl-2-(*N*-methylanilino)benzamide (1.209)**



A solution of *N*,*N*-diethyl-2-anilinobenzamide **1.204a** (1.491 g, 5.56 mmol) in THF (50 mL) was cooled to 0°C and treated with *n*-BuLi (2.6 mL, 2.59 M, 6.67 mmol) dropwise *via* syringe. The resultant yellow solution was stirred at 0°C for 1 h and then MeI (1.0 mL, 16.7 mmol) and 1,4-dioxane (1.4 mL, 16.7 mmol) were added sequentially *via* syringe. After the complete consumption of the starting material as judged by TLC analysis, the reaction mixture was quenched with a satd NH_4Cl solution and extracted with CH_2Cl_2 (3 X 15 mL). The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded **1.209** (1.363 g, 87%) as pale yellow crystals, mp 77–79°C (hexanes) [lit[148] 70-72°C]; ^1H NMR

(300 MHz, $CDCl_3$) δ 7.45 – 7.10 (m, 6H, ArH), 6.81 – 6.65 (m, 3H, ArH), 3.72 – 3.64 (m, 1H, CH_2), 3.33 – 3.15 (m, 1H, CH_2), 3.25 (s, 3H, NCH_3), 3.15 – 2.98 (m, 1H, CH_2), 2.98 – 2.81 (m, 1H, CH_2), 1.01 – 0.91 (m, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.2, 148.9, 145.6, 135.9, 130.0, 128.6, 128.2, 128.0, 125.5, 118.1, 114.7, 42.7, 40.6, 38.2, 13.7, 12.2. ^1H and ^{13}C NMR spectra were consistent with those reported.[149]

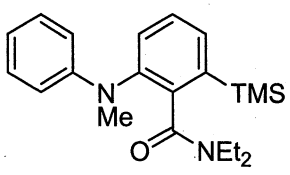
***N,N*-Diethyl-2-methyl-6-(*N*-methylanilino)benzamide (1.210a)**



General Method F: A solution of *N,N*-diethyl-2-(*N*-methylanilino)benzamide **1.209** (0.172 g, 0.61 mmol) in THF (2 mL) at –78°C was added *via* cannula to a stirring solution of *s*-BuLi (0.52 mL, 1.41 M, 0.73 mmol) and TMEDA (0.11 mL, 0.73 mmol) in THF (10 mL) also at –78°C. The resultant bright yellow solution was stirred at –78°C for 0.5 h, MeI (0.06 mL, 0.91 mmol) was added dropwise *via* syringe and the reaction mixture was warmed to rt. The reaction mixture was quenched with a satd NH_4Cl solution, extracted with CH_2Cl_2 (3 X 5 mL) and the combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded **1.210a** (0.176 g, 98%) as an amber oil, IR (thin film) 694, 752, 1102, 1286, 1341, 1459, 1497, 1599, 1629, 2875, 2934, 2975 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.03 (m, 5H, ArH), 6.75 – 6.67 (m, 3H, ArH), 3.69 – 3.53 (m, 1H, CH_2), 3.42 – 3.14 (m, 2H, CH_2), 3.19 (s, 3H, NCH_3), 3.07 – 2.91 (m, 1H, CH_2), 2.31 (s, 3H, $ArCH_3$), 1.09 (t, J = 7.1 Hz, 3H, CH_3), 0.93 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.7, 149.2, 145.2, 136.5, 136.3, 129.1, 128.6, 127.8, 125.6, 117.6, 114.1, 42.4, 40.5, 37.8, 19.1, 13.7, 12.4; LRMS (EI) m/z 296 (M+, 100), 282 (30), 224

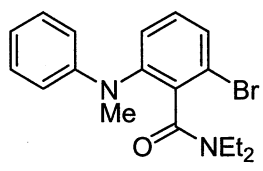
(64), 194 (28), 180 (33), 72 (8); HRMS (EI) calcd for $C_{19}H_{24}N_2O$ 296.1889 : found 296.1887.

_N,N_-Diethyl-2-(_N_-methylanilino)-6-trimethylsilylbenzamide (1.210b)



Following **General Method F** described above for the preparation of **1.210a** using the following materials: [*N*,*N*-diethyl-2-(*N*-methylanilino)benzamide **1.209** (0.185 g, 0.66 mmol), *s*-BuLi (0.56 mL, 1.41 M, 0.79 mmol), TMEDA (0.12 mL, 0.79 mmol), TMSCl (0.15 mL, 0.98 mmol), and THF (10 mL + 2 mL)] Flash column chromatography (1:1 hexanes:Et_2O) afforded **1.210b** (0.224 g, 97%) as light yellow crystals, mp 79–80°C (hexanes); IR (KBr) 694, 755, 844, 913, 1104, 1135, 1249, 1284, 1407, 1497, 1569, 1598, 1626, 2816, 2896, 2958, 3057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.2, 1.3 Hz, 1H, ArH), 7.34 – 7.14 (m, 4H, ArH), 6.79 – 6.73 (m, 3H, ArH), 3.91 – 3.80 (m, 1H, CH_2), 3.26 – 3.07 (m, 3H, CH_2), 3.18 (s, 3H, NCH_3), 1.11 (t, J = 7.1 Hz, 3H, CH_3), 0.87 (t, J = 7.2 Hz, 3H, CH_3), 0.29 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.9, 148.8, 144.6, 141.1, 140.2, 132.4, 128.6, 128.5, 128.3, 117.8, 114.0, 43.2, 40.3, 38.1, 13.3, 12.6, 0.0; LRMS (EI) m/z 354 (M+, 22), 339 (48), 281 (59), 266 (60), 251 (42), 236 (46), 163 (100); HRMS (EI) calcd for $C_{21}H_{30}N_2OSi$ 354.2127: found 354.2134.

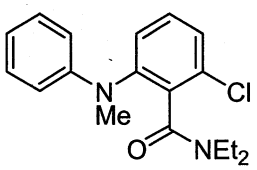
_N,N_-Diethyl-2-bromo-6-(_N_-methylanilino)benzamide (1.210c)



Following **General Method F** described above for the preparation of **1.210a** using the following materials: [*N*,*N*-diethyl-2-(*N*-methylanilino)benzamide **1.209** (0.234 g, 0.83 mmol), *s*-BuLi (0.71 mL, 1.41 M, 1.00 mmol), TMEDA (0.15 mL, 1.00 mmol), $BrCH_2CH_2Br$ (0.11 mL,

1.25 mmol), and THF (10 mL + 2 mL)] Flash column chromatography (1:1 hexanes:Et_2O) afforded **1.210c** (0.299 g, 99%) as colourless crystals, mp 80–81°C (Et_2O); IR (KBr) 698, 759, 876, 898, 1032, 1104, 1187, 1223, 1286, 1348, 1424, 1449, 1503, 1557, 1606, 1644, 2813, 2870, 2934, 2985, 3061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 1H, ArH), 7.24 – 7.16 (m, 4H, ArH), 6.83 – 6.77 (m, 1H, ArH), 6.72 – 6.69 (m, 2H, ArH), 3.62 – 3.51 (m, 1H, CH_2), 3.48 – 3.37 (m, 1H, CH_2), 3.32 – 3.20 (m, 1H, CH_2), 3.23 (s, 3H, NCH_3), 3.09 – 2.96 (m, 1H, CH_2), 1.12 (t, J = 7.1 Hz, 3H, CH_3), 1.02 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4, 148.7, 147.0, 138.1, 130.2, 130.1, 128.6, 127.6, 120.6, 118.3, 114.3, 42.5, 40.4, 37.8, 13.4, 12.1; LRMS (EI) m/z 360 (M+, 37), 288 (100), 258 (12), 209 (72), 180 (43), 72 (4); HRMS (EI) calcd for $C_{18}H_{21}BrN_2O$ 360.0837: found 360.0843.

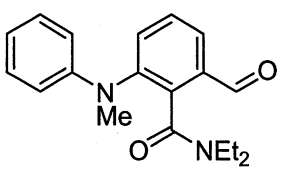
***N,N*-Diethyl-2-chloro-6-(*N*-methylanilino)benzamide (1.210d)**



Following **General Method F** described above for the preparation of **1.210a** using the following materials: [*N,N*-diethyl-2-(*N*-methylanilino)benzamide **1.209** (0.168 g, 0.59 mmol), *s*-BuLi (0.50 mL, 1.44 M, 0.71 mmol), TMEDA (0.11 mL, 0.71 mmol), C_2Cl_6 (0.211 g, 0.89 mmol), and THF (10 mL + 2 mL)] Flash column chromatography (1:1 hexanes:Et_2O) afforded **1.210d** (0.188 g, 99%) as colourless crystals, mp 69–71°C (hexanes); IR (KBr) 696, 752, 911, 1032, 1100, 1186, 1283, 1344, 1422, 1455, 1476, 1498, 1563, 1587, 1602, 1636, 2813, 2876, 2936, 2979, 3062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.10 (m, 5H, ArH), 6.81 – 6.65 (m, 3H, ArH), 3.62 – 3.52 (m, 1H, CH_2), 3.41 – 3.18 (m, 2H, CH_2), 3.21 (s, 3H, NCH_3), 3.04 – 2.92 (m, 1H, CH_2), 1.08 (t, J = 7.0 Hz, 3H, CH_3), 1.01 (t, J =

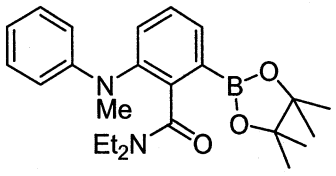
7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.6, 148.7, 147.1, 136.1, 131.8, 130.0, 128.6, 127.0, 126.9, 118.3, 114.5, 42.5, 40.4, 37.9, 13.5, 12.2; LRMS (EI) m/z 316 (M+, 24), 244 (100), 209 (15), 180 (21), 72 (4); HRMS (EI) calcd for $C_{18}H_{21}ClN_2O$ 316.1342: found 316.1343.

_N,N_-Diethyl-2-formyl-6-(_N_-methylanilino)benzamide (1.210e)



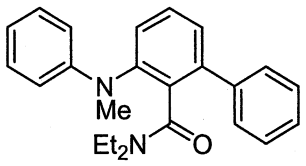
Following **General Method F** described above for the preparation of **1.210a** using the following materials: [*N,N*-diethyl-2-(*N*-methylanilino)benzamide **1.209** (0.179 g, 0.64 mmol), *s*-BuLi (0.57 mL, 1.35 M, 0.76 mmol), TMEDA (0.12 mL, 0.76 mmol), DMF (0.10 mL, 1.27 mmol), and THF (10 mL + 2 mL)] Flash column chromatography (1:1 hexanes:Et_2O) afforded **1.210e** (0.179 g, 91%) as a yellow oil, IR (thin film) 754, 1102, 1146, 1282, 1341, 1496, 1594, 1630, 1700, 2817, 2874, 2935, 2977, 3063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H, CHO), 7.87 – 7.81 (m, 1H, ArH), 7.54 – 7.47 (m, 2H, ArH), 7.24 – 7.16 (m, 2H, ArH), 6.84 – 6.69 (m, 3H, ArH), 3.73 – 3.63 (m, 1H, CH_2), 3.40 – 3.15 (m, 2H, CH_2), 3.25 (s, 3H, NCH_3), 3.05 – 2.96 (m, 1H, CH_2), 1.13 (t, J = 7.1 Hz, 3H, CH_3), 0.92 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.1, 166.3, 148.6, 146.2, 138.7, 134.4, 129.8, 128.7, 126.7, 118.6, 114.5, 42.8, 40.4, 38.3, 13.5, 12.3; LRMS (EI) m/z 310 (M+, 1), 238 (100), 210 (39), 195 (17), 180 (37), 167 (15), 72 (19); HRMS (EI) calcd for $C_{19}H_{22}N_2O_2$ 310.1681: found 310.1688.

***N,N*-Diethyl-2-(*N*-methylanilino)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (1.210f)**



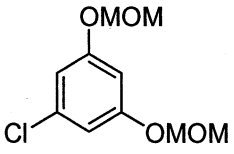
Following **General Method F** described above for the preparation of **1.210a** using the following materials: [*N,N*-diethyl-2-(*N*-methylanilino)benzamide **1.209** (0.195 g, 0.69 mmol), *s*-BuLi (0.59 mL, 1.41 M, 0.83 mmol), TMEDA (0.13 mL, 0.83 mmol), $B(OMe)_3$ (0.24 mL, 2.07 mmol), and THF (10 mL + 2 mL)] A mixture of the crude boronic acid, pinacol (0.30 g, 2.54 mmol), Mg_2SO_4 (excess) and CH_2Cl_2 (10 mL) was stirred at rt for 6 h. The reaction mixture was then subjected to filtration and the filtrate was concentrated *in vacuo*. Flash column chromatography (1:1 hexanes:Et_2O) afforded **1.210f** (0.240 g, 85%) as an amber oil, IR (thin film) 693, 732, 776, 856, 920, 967, 1143, 1278, 1323, 1355, 1423, 1496, 1628, 2816, 2876, 2934, 2979, 3061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.70 (m, 1H, ArH), 7.36 – 7.24 (m, 2H, ArH), 7.18 – 7.12 (m, 2H, ArH), 6.76 – 6.65 (m, 3H, ArH), 3.47 – 3.39 (m, 2H, CH_2), 3.19 (s, 3H, NCH_3), 3.14 – 3.05 (m, 2H, CH_2), 1.31 (s, 12H, CH_3), 1.14 (t, J = 7.1 Hz, 3H, CH_3), 0.89 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.2, 149.1, 144.4, 142.6, 133.3, 131.2, 128.6, 128.5, 117.4, 113.8, 83.7, 43.1, 40.1, 38.2, 24.7, 13.1, 12.5; LRMS (EI) m/z 408 (M+, 23), 336 (62), 236 (100), 221 (22), 192 (14), 72 (9); HRMS (EI) calcd for $C_{24}H_{33}BN_2O_3$ 408.2584: found 408.2594.

***N,N*-Diethyl-2-(*N*-methylanilino)-6-phenylbenzamide (1.211)**



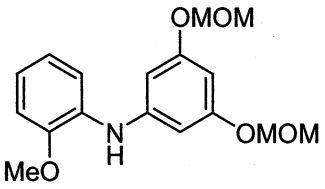
A stirred solution of pinacolate **1.210f** (0.440 g, 1.08 mmol) in DMF (20 mL) was degassed for 0.5 h by the rapid bubbling of argon. Iodobenzene (0.15 mL, 1.29 mmol) and K_3PO_4 (0.687 g, 3.24 mmol) were added and the mixture was degassed for an additional 0.5 h. $Pd(PPh_3)_4$ (0.062 g, 0.05 mmol) was added and the reaction mixture was heated for 4 h. The resultant brown mixture was cooled to rt, quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were washed with H_2O (5 x 40 mL), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded biaryl **1.211** (0.363 g, 94%) as an amber oil, IR (thin film) 699, 756, 1106, 1283, 1344, 1422, 1455, 1498, 1574, 1627, 2812, 2875, 2935, 2979, 3031, 3059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H, ArH), 7.46 – 7.41 (m, 1H, ArH), 7.40 – 7.30 (m, 4H, ArH), 7.25 – 7.22 (m, 1H, ArH), 7.17 – 7.10 (m, 2H, ArH), 6.73 – 6.62 (m, 3H, ArH), 3.28 (s, 3H, NCH_3), 3.23 – 3.06 (m, 2H, CH_2), 2.83 – 2.77 (m, 2H, CH_2), 0.71 (t, J = 7.1 Hz, 3H, CH_3), 0.41 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 149.5, 146.1, 140.4, 139.4, 136.3, 129.6, 128.8, 128.4, 128.3, 128.0, 127.5, 127.3, 117.2, 113.8, 42.2, 40.6, 37.2, 12.7, 11.5; LRMS (EI) m/z 358 (M+, 28), 286 (100), 72. (2); HRMS (EI) calcd for $C_{24}H_{26}N_2O$ 358.2045: found 358.2042.

1-Chloro-3,5-di(methoxymethoxy)benzene (1.227)



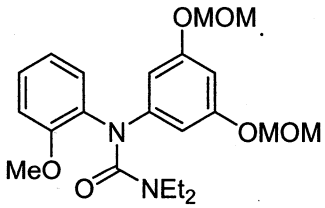
A solution of 1-chloro-3,5-dimethoxybenzene (6.89 g, 39.9 mmol) in CH_2Cl_2 (80 mL) at –78°C was treated with a solution of BBr_3 (25 g, 99.8 mmol) in CH_2Cl_2 (20 mL) by dropwise addition *via* cannula. The reaction mixture was allowed to warm to rt over 5 h, cooled to 0°C and the whole was diluted carefully with Et_2O (50 mL). The reaction mixture was quenched slowly with H_2O (50 mL), extracted with CH_2Cl_2 (3 X 40 mL) and the combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded 5-chlororesorcinol (5.68 g, 98%). To a suspension of NaH (2.08 g, 51.9 mmol) and MOMCl (3.94 mL, 51.9 mmol) in DMF (20 mL) at 0°C was added a solution of 5-chlororesorcinol (2.52 g, 17.3 mmol) in DMF (15 mL) dropwise *via* cannula. The reaction mixture was warmed to rt over 5 h and after complete consumption of the starting material as judged by TLC analysis the reaction mixture was poured into cold H_2O and the whole was extracted with Et_2O (3 X 20 mL). The combined organic extracts were washed with H_2O (5 x 40 mL), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded **1.227** (4.00 g, 99%) as a colourless oil, IR (thin film) 1029, 1149, 1455, 1593, 2927, 2956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, J = 2.2 Hz, 2H, ArH), 6.62 (t, J = 2.2 Hz, 1H, ArH), 5.13 (s, 4H, $ArOCH_2OMe$), 3.47 (s, 6H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 135.1, 110.3, 103.4, 94.5, 56.1; LRMS (EI) m/z 232 (M+, 100), 63 (29); HRMS (EI) calcd for $C_{10}H_{13}ClO_4$ 232.0502: found 232.0508.

***N*-(2-Methoxyphenyl)-3,5-di(methoxymethoxy)aniline (1.228)**



A mixture of 1-chloro-3,5-di(methoxymethoxy)benzene **1.227** (2.107 g, 9.06 mmol), *o*-anisidine (1.16 mL, 10.3 mmol), $Pd_2(dba)_3$ (0.079 g, 0.086 mmol), 2-(di-*tert*-butylphosphino)biphenyl (0.051 g, 0.172 mmol) and NaO*t*-Bu (1.157 g, 12.0 mmol) in PhMe (18 mL) was heated between 90 and 110°C for 3 h. After complete consumption of the aryl chloride as judged by TLC analysis, the reaction mixture was cooled to rt, diluted with Et_2O (25 mL) and passed through celite. The filtrate washed with dilute acid (2 X 10 mL, 10% HCl_{aq}), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (17:3 hexanes:EtOAc) afforded **1.228** (2.711 g, 94%) as an amber oil, IR (thin film) 1029, 1149, 1496, 1592, 2902, 2948, 3392 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 1H, ArH), 6.93 – 6.84 (m, 3H, ArH), 6.51 (d, J = 2.1 Hz, 2H, ArH), 6.32 (t, J = 2.1 Hz, 1H, ArH), 5.13 (s, 4H, $ArOCH_2OMe$), 3.87 (s, 3H, $ArOCH_3$), 3.47 (s, 6H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.0, 148.5, 144.7, 132.1, 120.8, 120.4, 115.9, 110.5, 99.4, 97.3, 94.4, 56.0, 55.5.

***N,N*-Diethyl-*N'*-[3,5-di(methoxymethoxy)phenyl]- *N'*-(2-methoxyphenyl)urea (1.229)**

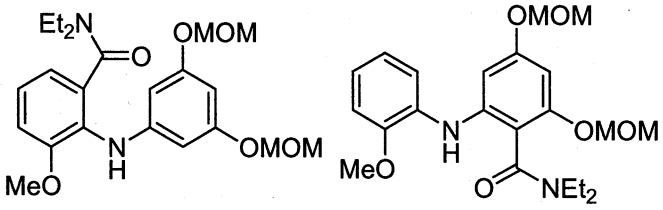


Following **General Method C** described above for the preparation of **1.203a** using the following materials: [*N*-(2-methoxyphenyl)-3,5-di(methoxymethoxy)aniline **1.228** (3.699 g, 11.6 mmol), diethylcarbamoyl chloride (5.1 mL, 40.5 mmol), THF (50 mL) and freshly prepared LDA (23.2 mmol, 15 mL THF)] Flash column chromatography (1:1 hexanes:EtOAc) afforded **1.229** (4.731 g, 97%) as an amber oil, ^1H NMR (400 MHz,

$CDCl_3$) δ 7.19 – 7.14 (m, 1H, ArH), 7.04 (dd, J = 7.8, 1.6 Hz, 1H, ArH), 6.93 – 6.86 (m, 2H, ArH), 6.45 (t, 1H, J = 2.2 Hz, ArH), 6.32 (d, 2H, J = 2.2 Hz, ArH), 5.07 (s, 4H, $ArOCH_2OMe$), 3.79 (s, 3H, $ArOCH_3$), 3.43 (s, 6H, OCH_3), 3.28 (q, J = 7.1 Hz, 4H, CH_2), 1.00 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 158.3, 154.5, 146.9, 133.5, 127.8, 126.7, 121.0, 111.9, 105.2, 99.7, 94.4, 55.9, 55.5, 41.8, 12.5.

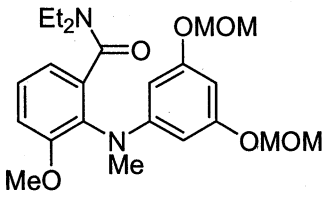
_N,N_-Diethyl-2-[3,5-di(methoxymethoxy)anilino]-3-methoxybenzamide (1.230) and

_N,N_-Diethyl-2-(2-methoxyanilino)-4,6-di(methoxymethoxy)benzamide (1.231)



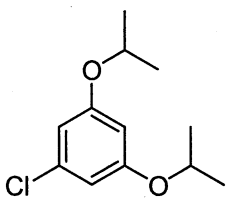
To a stirred solution of *N,N*-diethyl-*N'*-[3,5-di(methoxymethoxy)phenyl]- *N'*-(2-methoxyphenyl)urea **1.229** (0.567 g, 1.34 mmol) in THF (20 mL) at –10°C was added dropwise a freshly prepared solution of LiTMP (4.04 mmol, 5 mL THF) and the resultant solution was maintained at a temperature below –5°C for 2 h. The reaction mixture was quenched with a satd NH_4Cl solution and was extracted with EtOAc (3 X 15 mL). The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (7:13 EtOAc:hexanes) afforded a mixture (43:7 as evidenced by ^1H NMR) of the regioisomers **1.230** and **1.231** (0.536 g, 95%). See **Appendix A** for ^1H NMR data of the mixture.

***N,N*-Diethyl-2-[3,5-di(methoxymethoxy)(methyl)anilino]-3-methoxybenzamide (1.232)**



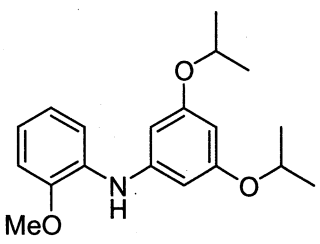
To a suspension of NaH (0.342 g, 8.55 mmol) in DMF (15 mL) at 0°C was added a solution of a mixture of regioisomers **1.230** and **1.231** (1.799 g, 4.29 mmol) in DMF (5 mL) dropwise *via* cannula. The ice bath was removed and the reaction mixture was stirred for 2 h at rt during which time the evolution of gas ceased. MeI (0.75 mL, 12.8 mmol) was added dropwise *via* syringe and after the complete consumption of the starting material as judged by TLC analysis the reaction mixture was carefully poured into cold water and the whole was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were washed with H_2O (5 x 20 mL), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 EtOAc:hexanes) afforded **1.232** (1.490 g, 80%) as a viscous oil, IR (thin film) 1034, 1139, 1463, 1490, 1584, 1627, 2902, 2941, 2970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 1H, ArH), 6.98 (dd, J = 8.3, 1.1 Hz, 1H, ArH), 6.87 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 6.11 (t, J = 2.0 Hz, 1H, ArH), 5.87 (d, J = 2.0 Hz, 2H, ArH), 5.05 (s, 4H, $ArOCH_2OMe$), 3.77 (s, 3H, NCH_3), 3.76 – 3.66 (m, 1H, CH_2), 3.41 (s, 6H, OCH_3), 3.26 – 3.16 (m, 1H, CH_2), 3.16 (s, 3H, $ArOCH_3$), 3.05 – 2.91 (m, 1H, CH_2), 2.90 – 2.72 (bs, 1H, CH_2), 0.98 (t, J = 7.1 Hz, CH_3), 0.90 (t, J = 7.0 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.4, 158.6, 157.4, 150.8, 139.1, 132.3, 127.9, 118.5, 112.5, 95.4, 94.4, 93.0, 55.8, 55.7, 42.7, 39.3, 37.9, 13.7, 11.9; LRMS (EI) m/z 432 (M+, 100), 72 (3); HRMS (EI) calcd for $C_{23}H_{32}N_2O_6$ 432.2260: found 432.2266.

1-Chloro-3,5-diisopropoxybenzene (1.234)



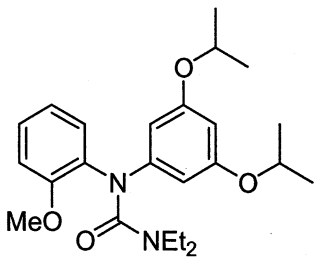
A solution of 1-chloro-3,5-dimethoxybenzene (6.89 g, 39.9 mmol) in CH_2Cl_2 (80 mL) at –78°C was treated with a solution of BBr_3 (25 g, 99.8 mmol) in CH_2Cl_2 (20 mL) dropwise *via* cannula. The reaction mixture was allowed to warmed to rt over 5 h, cooled to 0°C and diluted carefully with Et_2O (50 mL). The reaction mixture was quenched slowly with H_2O (50 mL), extracted with DCM (3 X 40 mL) and the combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded 5-chlororesorcinol (5.68 g, 98%). To a suspension of NaH (2.08 g, 51.9 mmol) and *i*-PrI (12 mL, 120 mmol) in DMF (50 mL) at 0°C was added a solution of 5-chlororesorcinol (5.67 g, 17.3 mmol) in DMF (20 mL) dropwise *via* cannula. The reaction mixture was warmed to rt over 5 h and after complete consumption of the starting material as judged by TLC analysis the reaction mixture was poured into cold H_2O and the whole extracted into Et_2O (3 X 20 mL). The combined organic extracts were washed with H_2O (5 x 40 mL), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded **1.234** (8.69 g, 95%) as a colourless oil, IR (thin film) 961, 1036, 1114, 1156, 1384, 1460, 1579, 1597, 2932, 2980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (d, J = 2.2 Hz, 2H, ArH), 6.32 (t, J = 2.2 Hz, 1H, ArH), 4.50 (sept, J = 6.1 Hz, 2H, $OCH(Me)_2$), 1.34 (d, J = 6.1 Hz, 12H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 135.1, 108.4, 102.4, 70.2, 21.9; LRMS (EI) m/z 228 (M+, 100), 144 (15); HRMS (EI) calcd for $C_{12}H_{17}ClO_2$ 228.0917: found 228.0914.

***N*-(3,5-Diisopropoxyphenyl)-*N*-(2-methoxyphenyl)amine (1.235)**



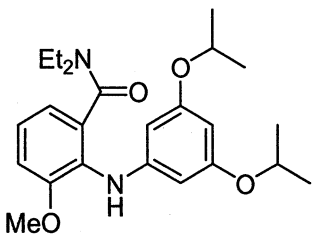
A mixture of 1-chloro-3,5-diisopropoxybenzene **1.234** (1.477 g, 6.46 mmol), *o*-anisidine (0.87 mL, 7.75 mmol), $Pd_2(dba)_3$ (0.089 g, 0.097 mmol), 2-(di-*tert*-butylphosphino)biphenyl (0.058 g, 0.194 mmol), KO*t*-Bu (1.015 g, 9.04 mmol) in PhMe (15 mL) was heated between 90 and 110°C for 17 h.. After complete consumption of the aryl halide as judged by TLC analysis, the reaction mixture was cooled to rt, diluted with Et_2O (25 mL) and passed through celite. The filtrate washed with dilute acid (2 X 10 mL, 10% HCl_{aq}), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (23:2 hexanes:EtOAc) afforded **1.235** (1.814 g, 89%) as pale yellow crystals, mp 66-67°C (hexanes); IR (KBr) 690, 750, 1028, 1109, 1184, 1220, 1256, 1463, 1492, 1531, 1591, 2871, 2934, 2976, 3374 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 1H, ArH), 6.93 – 6.85 (m, 3H, ArH), 6.30 (d, J = 2.1 Hz, 2H, ArH), 6.10 (bs, 1H, NH), 6.08 (t, J = 2.1 Hz, 1H, ArH), 4.50 (sept, J = 6.1 Hz, 2H, $OCH(Me)_2$), 3.90 (s, 3H, $ArOCH_3$), 1.34 (d, J = 6.1 Hz, 12H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.8, 148.4, 144.6, 132.6, 120.8, 120.0, 115.8, 110.5, 98.4, 96.8, 69.8, 55.6, 22.1; LRMS (EI) m/z 315 (M+, 100); HRMS (EI) calcd for $C_{19}H_{25}NO_3$ 315.1834: found 315.1831.

_N_-(3,5-Diisopropoxyphenyl)-_N'_,_N'_-diethyl-_N_-(2-methoxyphenyl)urea (1.236)



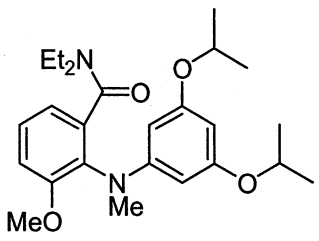
To a suspension of NaH (0.084 g, 2.10 mmol) in DMF (5 mL) at 0°C was added a solution of **1.235** (0.330 g, 1.05 mmol) in DMF (3 mL) dropwise *via* cannula. The ice bath was removed and the reaction mixture was stirred for 2 h at rt during which time the evolution of gas ceased. $ClCONEt_2$ (0.40 mL, 3.15 mmol) was added dropwise *via* syringe and after the complete consumption of the starting material as judged by TLC analysis the reaction mixture was carefully poured into cold water (10 mL) and the whole was extracted with Et_2O (3 X 10 mL). The combined organic extracts were washed with H_2O (5 x 40 mL), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (7:13 EtOAc:hexanes) afforded urea **1.236** (0.392 g, 90%) as a viscous oil, IR (thin film) 1118, 1152, 1183, 1272, 1591, 1663, 2933, 2978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 – 7.11 (m, 1H, ArH), 7.03 (dd, J = 7.8, 1.3 Hz, 1H, ArH), 6.94 – 6.85 (m, 2H, ArH), 6.18 (t, J = 2.0 Hz, 1H, ArH), 6.14 (d, J = 2.0 Hz, 2H, ArH), 4.43 (sept, J = 6.0 Hz, 2H, $OCH(Me)_2$), 3.81 (s, 3H, OCH_3), 3.30 (q, J = 7.1 Hz, 4H, CH_2), 1.29 (d, J = 6.0 Hz, 12H, CH_3), 1.02 (t, J = 7.0 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.8, 159.1, 154.4, 146.9, 134.0, 127.6, 126.3, 121.0, 111.8, 104.1, 99.7, 69.8, 55.5, 41.8, 21.9, 12.6; LRMS (EI) m/z 414 (M+, 100), 383 (95), 328 (70), 221 (41), 100 (81), 72 (62); HRMS (EI) calcd for $C_{24}H_{34}N_2O_4$ 414.2519: found 414.2523.

***N,N*-Diethyl-2-(3,5-diisopropoxyanilino)-3-methoxybenzamide (1.237)**



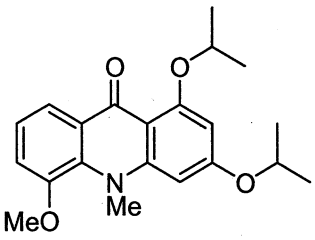
A stirred solution of *N*-(3,5-diisopropoxyphenyl)-*N'*,*N'*-diethyl-*N*-(2-methoxyphenyl)urea **1.236** (0.514 g, 1.24 mmol) in THF (20 mL) at 0°C was treated with a freshly prepared solution of LiTMP (3.10 mmol, 5 ml THF) dropwise *via* cannula. The reaction mixture was maintained at 0°C for 2 h, quenched with a satd NH_4Cl solution and the whole was extracted with Et_2O (3 X 15 mL). The combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded **1.237** (0.482 g, 94%) as a viscous oil, IR (thin film) 1058, 1116, 1156, 1183, 1279, 1476, 1598, 1620, 2933, 2977, 3347 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (t, J = 7.9 Hz, 1H, ArH), 6.96 (dd, J = 7.8, 0.9 Hz, 1H, ArH), 6.89 (dd, J = 7.6, 1.0 Hz, 1H, ArH), 6.01 (bs, 1H, NH), 5.96 (t, J = 2.1 Hz, 1H, ArH), 5.87 (d, J = 2.1 Hz, 2H, ArH), 4.45 (sept, J = 6.0 Hz, 2H, $OCH(Me)_2$), 3.85 (s, 3H, OCH_3), 3.48 – 3.35 (bs, 2H, CH_2), 3.22 – 3.11 (bs, 2H, CH_2), 1.29 (d, J = 6.0 Hz, 12H, CH_3), 1.05 – 0.93 (m, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.0, 159.1, 153.7, 146.6, 132.6, 127.6, 124.3, 119.0, 111.7, 96.3, 95.7, 69.4, 55.5, 42.7, 38.5, 21.9, 13.6, 12.2; LRMS (EI) m/z 414 (M+, 100), 342 (74), 300 (35), 258 (46), 226 (28); HRMS (EI) calcd for $C_{24}H_{34}N_2O_4$ 414.2519: found 414.2518.

***N,N*-Diethyl-2-[3,5-diisopropoxy(methyl)anilino]-3-methoxybenzamide (1.238)**



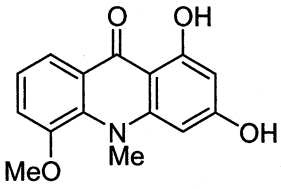
To a suspension of NaH (0.084 g, 2.09 mmol) in DMF (5 mL) at 0°C was added a solution of **1.237** (0.433 g, 1.05 mmol) in DMF (4 mL) dropwise *via* cannula. The ice bath was removed and the reaction mixture was stirred for 2 h at rt during which time the evolution of gas ceased. MeI (0.20 mL, 3.13 mmol) was added dropwise *via* syringe and after the complete consumption of the starting material as judged by TLC analysis the reaction mixture was carefully poured into cold water and the whole was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic extracts were washed with H_2O (5 x 30 mL), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (1:1 Et_2O:hexanes) afforded **1.238** (0.432 g, 96%) as an amber viscous oil, IR (thin film) 1060, 1118, 1142, 1215, 1300, 1466, 1486, 1582, 1619, 1635, 2933, 2977 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 1H, ArH), 6.98 (dd, J = 8.3, 1.3 Hz, 1H, ArH), 6.88 (dd, J = 7.6, 1.3 Hz, 1H, ArH), 5.85 (t, J = 2.1 Hz, 1H, ArH), 5.69 (d, J = 2.0 Hz, 2H, ArH), 4.42 (sept, J = 6.1 Hz, 2H, $OCH(Me)_2$), 3.78 (s, 3H, OCH_3), 3.77 – 3.65 (m, 1H, CH_2), 3.33 – 3.17 (m, 1H, CH_2), 3.16 (s, 3H, NCH_3), 3.09 – 2.94 (m, 1H, CH_2), 2.92 – 2.77 (m, 1H, CH_2), 1.27 (d, J = 6.1 Hz, 12H, CH_3), 0.99 (t, J = 7.1 Hz, 3H, CH_3), 0.91 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.3, 159.0, 157.3, 150.7, 139.0, 132.6, 127.5, 118.3, 112.4, 94.2, 92.2, 69.1, 55.5, 42.5, 39.1, 37.7, 21.9, 13.5, 11.8; LRMS (EI) m/z 428 (M+, 100), 357 (25), 314 (34), 214 (27); HRMS (EI) calcd for $C_{25}H_{36}N_2O_4$ 428.2675: found 428.2680.

1,3-Diisopropoxy-5-methoxy-10-methyl-9,10-dihydro-9-acridinone (1.239)



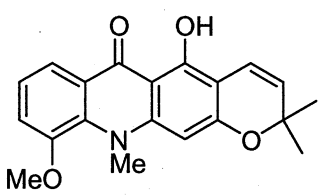
A stirred solution of **1.238** (0.582 g, 1.36 mmol) in CH_2Cl_2 (10 mL) at 0°C was treated with Tf_2O (0.32 mL, 1.90 mmol) dropwise *via* syringe. The resultant orange reaction mixture was warmed to rt over 0.5 h and after the complete consumption of the starting material as judged by TLC analysis, the reaction mixture was quenched with cold water (10 mL). The organic layer was separated, diluted with EtOAc (15 mL) and washed with $NaOH_{(aq)}$ (1M, 4 x 15 mL), H_2O (1 x 10 mL), dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (2:3 EtOAc:hexanes) afforded **1.239** (0.452 g, 93%) as pale yellow crystals, mp 125–127°C (hexanes); IR (KBr) 735, 958, 1115, 1189, 1218, 1459, 1504, 1560, 1600, 1638, 2936, 2983 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 7.8, 1.6 Hz, 1H, ArH), 7.20 – 7.10 (m, 2H, ArH), 6.42 (d, J = 2.1 Hz, 1H, ArH), 6.29 (d, J = 2.1 Hz, 1H, ArH), 4.72 (sept, J = 6.1 Hz, 1H, $OCH(Me)_2$), 4.65 (sept, J = 6.1 Hz, 1H, $OCH(Me)_2$), 3.94 (s, 3H, OCH_3), 3.86 (s, 3H, NCH_3), 1.49 (d, J = 6.1 Hz, 6H, CH_3), 1.42 (d, J = 6.1 Hz, 6H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.8, 162.0, 160.9, 149.9, 149.3, 134.6, 127.8, 121.6, 119.1, 114.5, 109.8, 96.8, 93.3, 71.8, 70.0, 56.2, 42.3, 22.0, 21.9; LRMS (EI) m/z 355 (M+, 8), 340 (58), 240 (59), 214 (52), 167 (48), 149 (100), 111 (64); HRMS (EI) calcd for $C_{21}H_{25}NO_4$ 355.1784: found 355.1790.

Yukodine (1.215)



To a stirred solution of **1.239** (0.400 g, 1.13 mmol) in $ClCH_2CH_2Cl$ (50 mL) at rt was added a solution of BCl_3 in CH_2Cl_2 (2.25 mL, 1.0 M, 2.25 mmol) dropwise *via* syringe. The reaction mixture was allowed to stir at rt for 14 h. The reaction mixture was carefully quenched with H_2O (40 mL) and the whole was poured into a separatory funnel. The reaction mixture was partitioned between EtOAc (400 mL) and H_2O (400 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography (3:2 EtOAc:hexanes) afforded synthetic yukodine **1.215** (0.202 g, 66%) as a yellow solid, mp 245-249°C (hexanes/EtOAc) [lit[150] 246-250°C]; ^{1}H NMR (400 MHz, acetone-d_6) δ 14.58 (s, 1H, ArOH), 9.46 (bs, 1H, ArOH), 7.95 (dd, J = 8.0, 1.4 Hz, 1H, ArH), 7.41 (dd, J = 7.9, 1.2 Hz, 1H, ArH), 7.27 (t, J = 7.9 Hz, 1H, ArH), 6.41 (d, J = 2.0 Hz, 1H, ArH), 6.15 (d, J = 2.0 Hz, 1H, ArH), 4.02 (s, 3H, OCH_3), 3.95 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, DMSO) δ 179.4, 164.7, 164.1, 149.3, 147.4, 134.6, 122.7, 122.1, 117.1, 116.7, 103.9, 95.9, 91.6, 56.6, 41.4. The ^{1}H NMR was consistent with that reported.[150]

Junosidine (1.6)



A solution of yukodine **1.215** (0.075 g, 0.28 mmol), senecialdehyde (0.10 mL, 1.0 mmol) and glacial AcOH (4 mL) in anhydrous toluene (5 mL) was refluxed for 24 h. The reaction mixture was cooled, quenched with H_2O (10 mL) and extracted with EtOAc (3 X

15 mL). The combined organic extracts were washed with a satd $NaHCO_3$ solution, dried (Na_2SO_4), subjected to filtration and concentrated *in vacuo*. Flash column chromatography afforded junosidine **1.6** (0.074 g, 81%) as an orange crystalline solid, mp 187-189°C (acetone/hexanes) [lit[151] 188-189°C]; ^1H NMR (400 MHz, acetone-d_6) δ 15.05 (s, 1H, OH), 7.94 (dd, J = 8.3, 1.9 Hz, 1H, ArH), 7.40 (dd, J = 8.3, 1.9 Hz, 1H, ArH), 7.27 (at, J = 8.3 Hz, 1H, ArH), 6.71 (d, J = 9.8 Hz, 1H, ArCH=CHR), 6.37 (s, 1H, ArH), 5.68 (d, J = 9.8 Hz, 1H, ArCH=CHR), 4.01 (s, 3H, NCH_3), 3.97 (s, 3H, $ArOCH_3$), 1.46 (s, 6H, CH_3). The ^1H NMR was consistent with that reported.[151]

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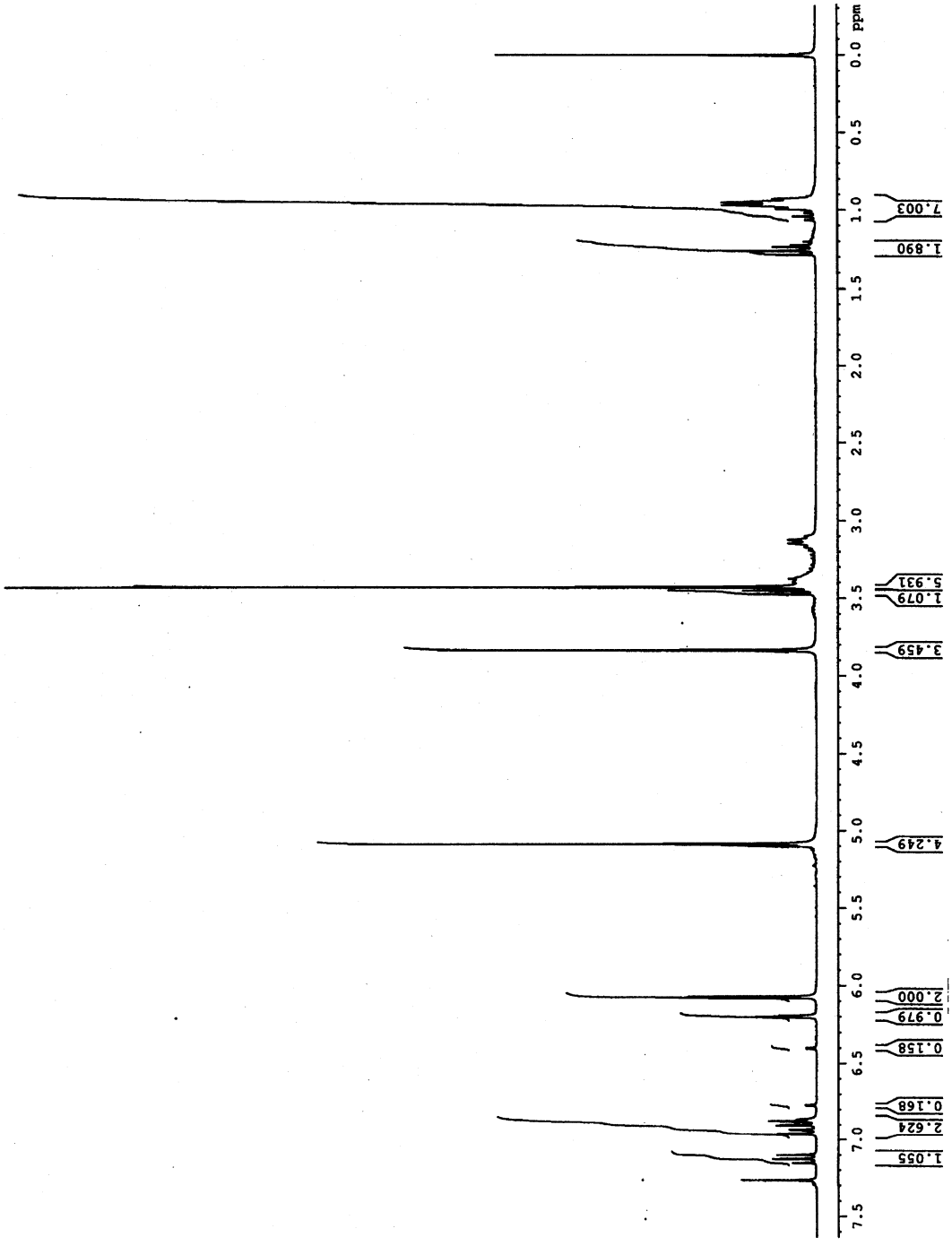
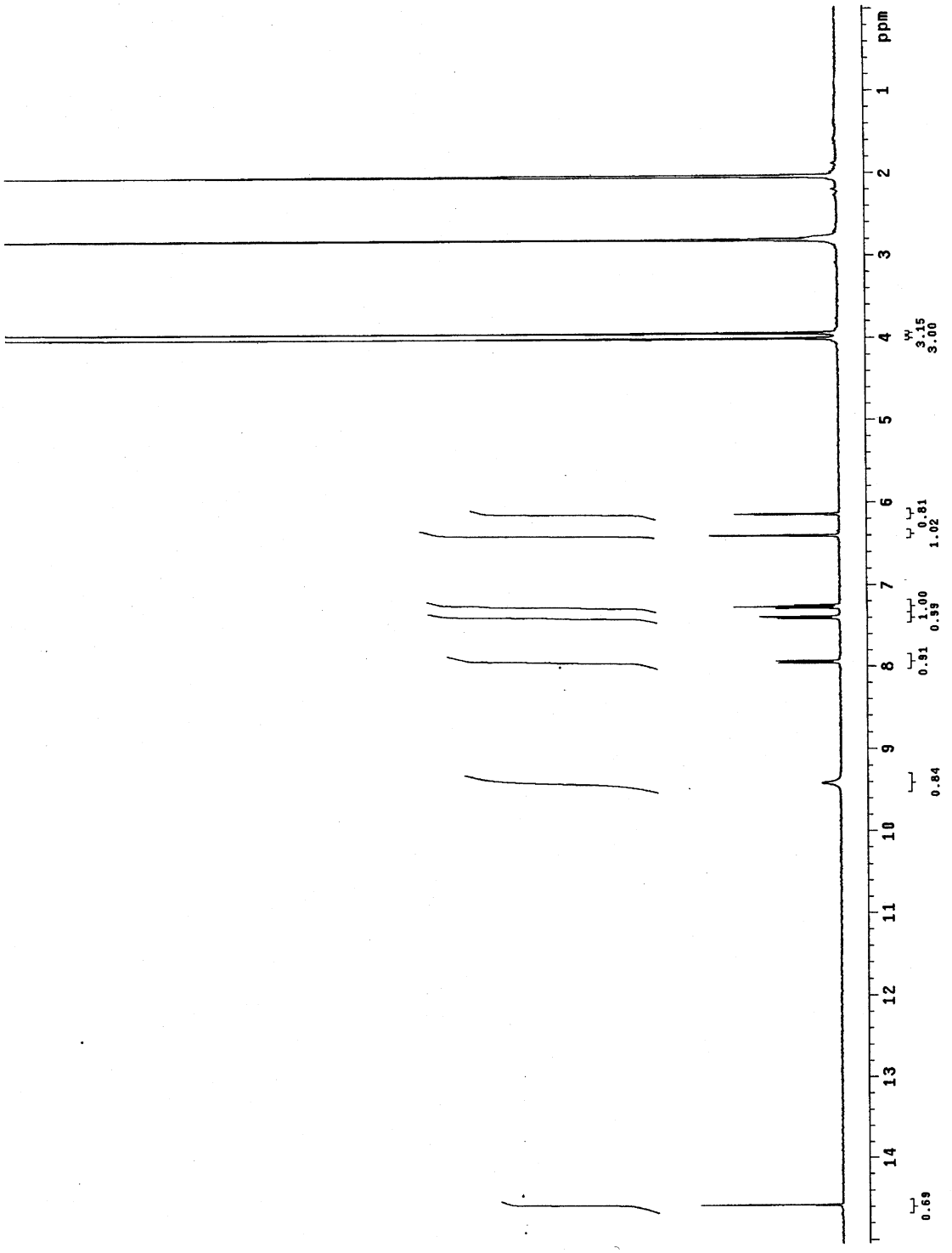
Appendix A - ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of the mixture of **1.230** and **1.231**



Appendix B - ^{1}H NMR (400 MHz, acetone-d_6) Spectrum of Yukodine (**1.215**)



Appendix C - ^{1}H NMR (400 MHz, acetone-d_6) Spectrum of Junosidine (**1.6**)