THE DIRECTED *ortho* METALATION OF PYRIDINE DERIVATIVES WITH *in situ* BORONATION AND LINKS TO THE SUZUKI-MIYAURA CROSS COUPLING REACTION

By

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Abstract

The range of commercially available aryl boronic acids is increasing due to the popularity of the Suzuki-Miyauri cross coupling reaction. However, pyridyl boronic acids are of limited availability due to difficulties in preparation / isolation by conventional methods. The scope and application of a new method for the preparation pyridyl boronic acids has been shown. This method involved the Directed *ortho* Metalation (DoM) of pyridine derivatives with *in situ* boronation. This method has been used to prepare the following new pyridyl boronic acid derivatives:

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid.

N,N-Diethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinamide.

N,N-Diethyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isonicotinamide.

3-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine.

3-[1,3,6,2]Dioxazaborocan-2-yl-pyridine-2-carboxylic acid diethylamide.

4-[1,3,6,2]Dioxazaborocan-2-yl-N,N-diethyl-nicotinamide.

3-[1,3,6,2]Dioxazaborocan-2-yl-N,N-diethyl-isonicotinamide.

Diethyl-carbamic acid 4-[1,3,6,2]dioxazaborocan-2-yl-pyridin-3-yl ester.

4-[1,3,6,2]Dioxazaborocan-2-yl-pyridine-3-sulfonic acid diethylamide, and

2-(3-Fluoro-pyridin-4-yl)-[1,3,6,2]dioxazaborocane.

As an application, this methodology was linked to the Suzuki-Miyaura cross coupling reaction to produce the following new azabiaryl compounds:

3-Phenyl-pyridine-2-carboxylic acid diethylamide. N,N-Diethyl-3-phenyl-isonicotinamide. 3-Fluoro-4-phenyl-pyridine. N,N-Diethyl-4-(3-methoxy-phenyl)-

nicotinamide, and N,N-Diethyl-4-thiophen-3-yl-nicotinamide.

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Finally, I would like to thank my parents, family, and Erica for their support and love.

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Table of Abbreviations

Ac	acetyl
acac	acetylacetone
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
CIPE	complex induced proximity effect
conc.	Concentrated
Cp	cyclopentadienyl
Cy	cylclohexyl
DABCO	1,4-diazobicyclo[2.2.2]octane
dba	trans, trans-dibenzylideneacetone
°C	degree Celcius
DME	1,2-dimethoxyethane
DMF	*N*, *N*-dimethylformamide
DMG	directed metalation group
DoM	directed *ortho* metalation
dppf	diphenylphosphinoferrocene
E^+	electrophile
equiv	equivalents
Et	ethyl

EWG	electron withdrawing group
G	group
h	hour
H^+	dilute acid
HRMS	high resolution mass spectrometry
L	ligand
LDA	lithium diisopropylamide
LG	leaving group
LRMS	low resolution mass spectrometry
M	metal or molar
Me	methyl
MHz	megahertz
min	minutes
MOM	methoxymethyl
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
Pr	propyl
rt	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography

TMEDA	*N, N, N', N'*-tetramethylethylenediamine
TMP	2, 2, 6, 6-tetramethylpiperidine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride

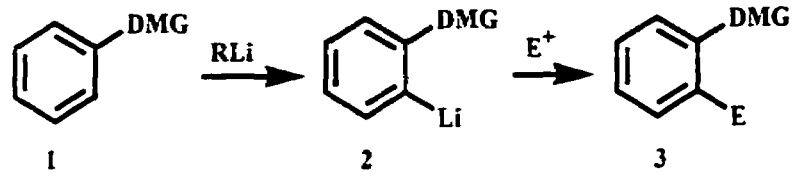
1.0 The Directed *ortho* Metalation Reaction

1.1 Introduction

McMurray states "The most important reaction of aromatic compounds is **electrophilic aromatic substitution.**".[1] Electrophilic aromatic substitution, thus, constitutes the classical means for synthesizing substituted aromatic compounds. However, due to the independent discovery by Gilman[2] and Wittig[3] and recent attention by others,[4] the directed *ortho* metalation (DoM) reaction has become an extremely important tool for the regiospecific construction of polysubstituted aromatic and heteroaromatic molecules.

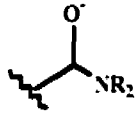
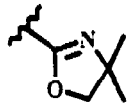
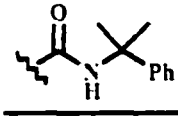
1.2 Directed *ortho* Metalation (DoM)

The directed *ortho* metalation reaction (DoM) involves the deprotonation of containing a directed metalation group (DMG)-substituted aromatic **1**, to produce an *ortho* lithiated species **2** (Scheme 1) using a strong base, usually an alkyllithium. The lithiated intermediate may then be treated with a variety of electrophiles to produce 1,2-disubstituted aromatics **3**.



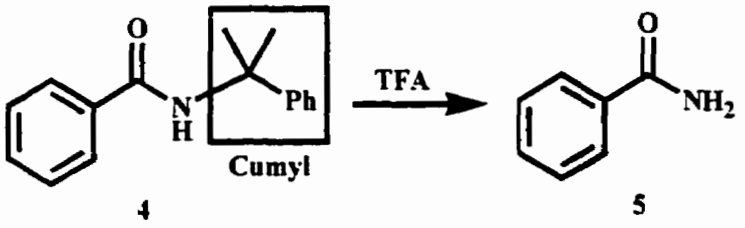
1 2 3

E^+ = TMSCl, PhCHO, MeOD, $ClCONEt_2$, MeI, $B(OR)_3$

C-based DMG		Hetatom-based DMG	
CONR	Hauser, 1964	N*t*-BOC	Gschwend, 1979
	Gronowitz, 1968 Gschwend, 1976 Comins, 1983	NCO*t*-Bu	Muchowski, 1980
		OCH_2OMe	Christensen, 1975
		$OCONEt_2$	Snieckus, 1983
	Meyers, Gschwend, 1975	$OCON(Me)C(Me)_2Ph$	Snieckus, 1999
		SO_2NR	Hauser, 1969
$CONEt_2$	Beak, 1977	SO_2NR_2	
$CON(Me)CH(TMS)_2$	Snieckus 1989	$SO_2NHC(Me)_2Ph$	Snieckus, 1999
	Snieckus, 1999	OSEM	Snieckus, 1991
		$P(O)(t\text{-}Bu)_2$	Snieckus, 1998

Scheme 1

A variety of DMGs participate in the DoM reaction (Scheme 1). Some of the carbon based DMGs include: $CONEt_2$, CONH*t*-Bu and $CON(Me)CH(TMS)_2$ and some of the heteroatom based DMG's include: NCO_2-t-Bu, $OCONEt_2$, OMOM, SO_2NEt_2 . A major criticism of most of the DMGs is that they generally do not undergo facile synthetic transformations after they serve their purpose as a DMG. However, with the development of the *N*-cumyl amide DMG (4) Scheme 2 [5], some of these criticisms have been overcome as the cumyl group is easily removed with trifluoroacetic acid to yield the primary amide 5.

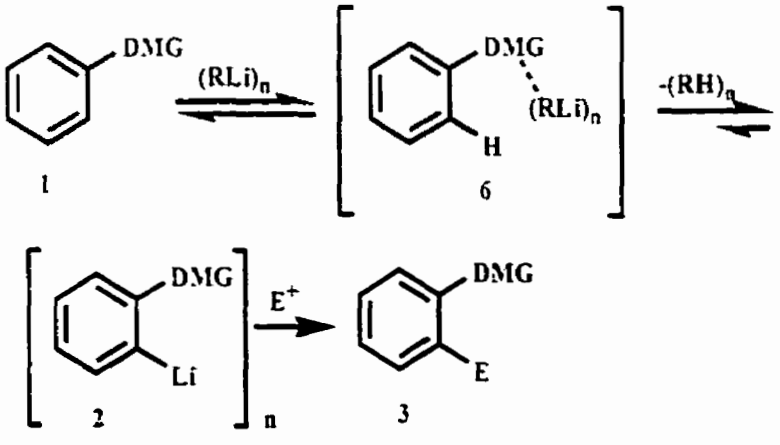


4 5

Scheme 2

1.2.1 Mechanism of the DoM reaction

The mechanism of the DoM reaction is currently a controversial subject. A leading hypothesis to rationalize the DoM pathway is the Complex Induced Proximity Effect (CIPE).[6] CIPE postulates that, in the first step, the heteroatom contained in the DMG **1** provides a coordinating site for the alkyl lithium reagent, usually as an aggregate.[7] This coordination, or complex **6**, brings the alkyl lithium into close proximity to the *ortho* proton allowing the deprotonation to occur. The resultant *ortho* lithiated species **2**, usually also considered to be an aggregate, then undergoes reaction with various electrophiles to give **3** (Scheme 3).



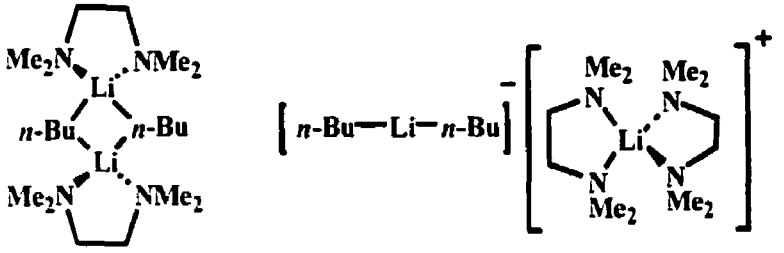
1 6 2 3

Scheme 3

The CIPE postulate for the DoM mechanism agrees nicely for carboxamides as DMGs but receives less support for DMG = OMe. Thus, Schleyer and co-workers do not agree with the operation of CIPE in the case of anisole because they could not detect the lithiated species **2** by NMR studies of the reaction of anisole with *n*-BuLi in toluene-d_8 at room temperature.[8] Schleyer believes that, the inductive effect of the DMG is responsible for the *ortho* deprotonation. However, Schleyer obtained evidence for an anisole/*n*-BuLi-aggregate complex and found that, upon the addition of TMEDA to the reaction mixture, the lithiated species **2** was readily formed at the expense of the anisole/*n*-BuLi-aggregate complex. This observation was explained by TMEDA breaking up the *n*-BuLi-aggregate, thus making it more reactive.[9] Schleyer's rationalization is, however, disputed by Beak who believes that there is a complexation before the deprotonation step.[10] Schleyer has also performed *ab initio* calculations on a series of *ortho* DMG substituted toluenes.[11] From this study, Schleyer concludes that the regiochemistry of the metalation is not determined by the acidity of the exchanged hydrogen, nor may it be explained by the CIPE: rather, the "stabilizing interactions in the transition state determine the metalation product". This was termed by Schleyer to be "kinetically enhanced metalation". Schleyer proposes a completely uncoordinated transition state structure and a rate determining proton abstraction step.

Based on ^{7}Li NMR studies on the reaction of anisole with RLi, Collum and co-workers are in agreement with Schleyer with respect to the absence of CIPE but disagrees as to the nature of the rate limiting step. Based on kinetic studies, Collum suggests that the rate limiting step has the following stoichiometry: $[(n\text{-BuLi})_2(\text{TMEDA})_2(\text{Ar-H})]^{\ddagger}$ and

that the reactive *n*-BuLi/TMEDA has the structure of **7** or **8** (Scheme **4**),[12] with the latter being the most recent proposal.[12b]



7 **8**

Scheme **4**

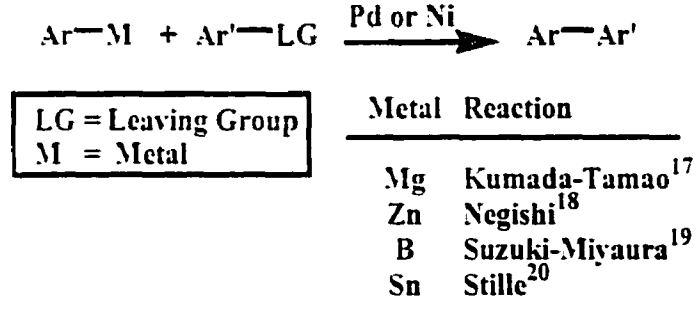
Another interesting series of experiments has been conducted by Slocum and co-workers and adds to the argument concerning the mechanism when methoxy is the DMG.[13] Slocum remains undecided between CIPE and inductive effect as the major feature of the D*o*M mechanism, hypothesizing that both may have a role. Slocum asserts that, when TMEDA is used as an additive, it is only the inductive effect that controls the metalation. Slocum has also found that TMEDA can accelerate the rate of metalation, even at substoichiometric quantities. This observation was rationalized by the ability of the anisole to act as de-aggregating agent, similar to TMEDA.[13e]

In conclusion, there has yet to be a unified theory for the mechanism of the D*o*M reaction. It is possible that one single mechanism cannot be used to adequately describe the D*o*M reaction, and that the mechanism varies depending on the DMG used.

2.0 The Suzuki-Miyaura Cross Coupling Reaction

2.1 Introduction

The biaryl moiety constitutes a key component in a variety of natural products[14] and is increasingly part of the pharmaceutical entities.[15] Retrosynthetically, the most convenient assemblage of a biaryl is the formation of the aryl-aryl, sp^2-sp^2, bond. Before the 1970's, there were very few reactions capable of easily accomplishing this type of coupling. In this time period, four indispensable reactions evolved involving the coupling of an aryl-metal species with an aryl-leaving group substrate under palladium or nickel catalyzed conditions.[16] The reactions are named after the researchers who pioneered the work, *i.e.*, Kumada-Tamao,[17] Negishi,[18] Suzuki-Miyaura[19], and Stille[20] reactions (Scheme 5).

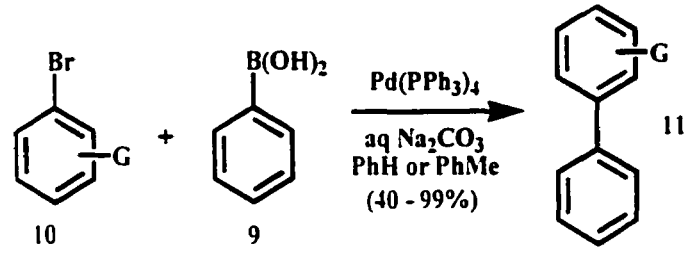


Scheme 5

Discussion in the next section will be limited to the aryl-aryl Suzuki-Miyaura cross coupling reaction, since it is the most pertinent to this thesis.

2.2 The Suzuki-Miyaura Cross Coupling Reaction

The Suzuki-Miyaura cross coupling reaction, involving the coupling of an aryl-boron reagent, **9**, with an aryl halide, **10**, under palladium catalysis to give biaryls **11**, was first reported in 1981 (Scheme **6**).[21]



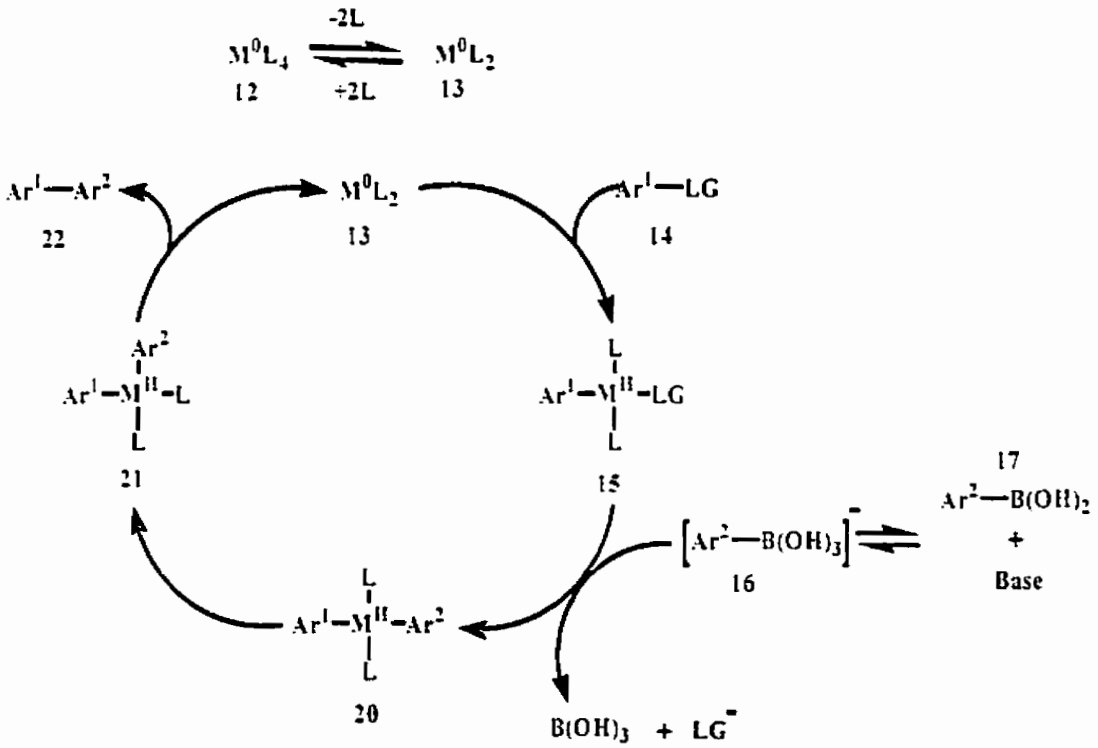
G = *o*-Me, *p*-Me, *o*-OMe, *p*-OMe, *p*-Cl, *p*-Br, *p*-CO_2Me, 2,4,6-tri-Me

Scheme 6

In this initial study, Suzuki found that at least 3 mol% of the palladium catalyst was necessary for the reaction to proceed at a reasonable rate and that sodium carbonate was the most effective base (as compared to NaOEt, NaOH, and NaOAc). The reaction did not proceed without a base present. Several advantages arose from this work namely, that the reaction is unaffected by the presence of water, is tolerant of many functional groups, and the organometallic species is non-toxic.

The mechanism of the Suzuki-Miyaura reaction is outlined in Scheme **7**.[22] The first step involves the loss of two ligands from the catalyst **12** (palladium or nickel) to open up free coordination sites on the metal to give complex **13**.[23] $Pd(PPh_3)_4$ has been the traditional catalyst used in this reaction. Some other catalysts show much higher reactivity due to fewer phosphine ligands, which compete for coordination sites on the metal. These include $Pd(OAc)_2$ (plus two triphenylphosphines)[24] and the phosphine free catalysts $NiCl_2(NEt_3)_2$[25] and $[(\eta^3\text{-}C_3H_5)PdCl]_2$.[26]

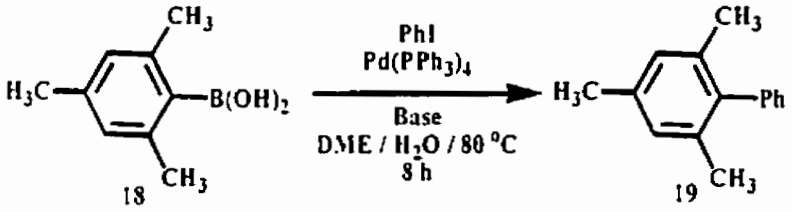
Following the loss of the ligands from **12**, oxidative addition occurs with the aryl-leaving group **14** to produce species **15** in which the metal is now in the +2 oxidation state with the orientation of the aryl and leaving group *trans*. The oxidative addition step is normally rate determining.[27] The common leaving groups used are halides and triflates. The reactivity of the aryl halide decreases in order ArI > ArBr >> ArCl.[28] The introduction of aryl triflates, which are readily prepared from the corresponding phenol, greatly increased the potential of the cross coupling reactions.[29]



Scheme 7

In the next step, transmetallation between complex **15** and boronate **16** is proposed. The aryl boronic acid **17** is not sufficiently nucleophilic to undergo transmetallation and thus an equivalent of base is required to generate the more reactive

boronate **16**.[30] The effect of the base on the Suzuki-Miyaura cross coupling reaction has been well documented. Suzuki demonstrated that $Ba(OH)_2$, K_3PO_4, and NaOH accelerate the coupling reaction and that these bases were especially effective for cross coupling of hindered substrates (Scheme **8**).[31] Similar results have also been obtained in the Snieckus laboratories.[32] An alternative set of conditions has been developed for use with substrates that are sensitive to the previously mentioned bases. Thus, Wright demonstrated that the fluoride ion (from CsF) is effective in generating the reactive boronate species in the cross coupling reaction.[33]



Base	yld. %
Na_2CO_3	50
K_3PO_4	70
NaOH	95
$Ba(OH)_2$	99

Scheme **8**

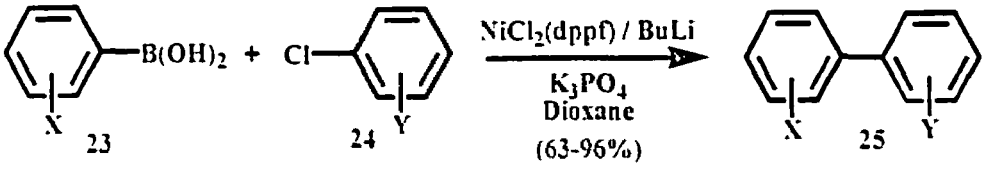
Isomerization of the *trans* complex **20** to the *cis* complex **21** constitutes the next step in the proposed mechanism.[34] As shown by Stille,[20b] the *cis* orientation is necessary for reductive elimination to proceed to produce biaryl **22** while concomitantly regenerating the reactive form of the catalyst **13**.

The proposed mechanism (Scheme **7**) of the Suzuki-Miyaura cross coupling reaction has, as yet, little experimental support. However, using electrospray ionization mass spectrometry (EI-MS), Canary has obtained evidence for the existence of both *trans*

complexes **15** and **20** in the gas phase reaction of 3-bromopyridine with phenylboronic acid.[35]

2.3 Recent Advances in Suzuki-Miyaura Cross Coupling

A major recent advance in the Suzuki-Miyaura cross coupling reaction is the ability to use the commercially abundant aryl chlorides as partners. Although Suzuki originally reported failure,[21] Miyaura subsequently has been successful in cross coupling chloroarenes with aryl boronic acids using a highly active nickel(0) catalyst which was obtained by reduction of the nickel(II) catalyst ($NiCl_2$(dppf)) with butyl lithium (Scheme 9).[36] The yields of biaryls for these reactions were good to excellent for a wide range of aryl chlorides and aryl boronic acids. Indolese also reported the use of $NiCl_2$(dppf) for this reaction but did not require the reduction of the catalyst to obtain good yields.[37]

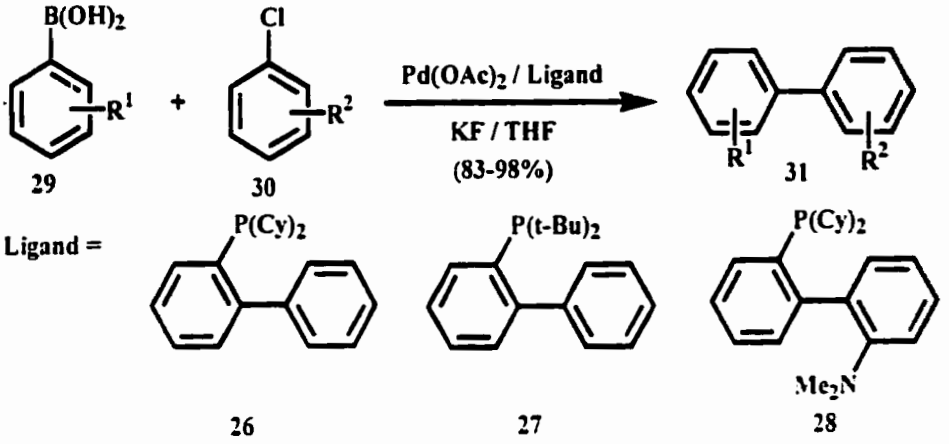


X = 4-OMe, 4-Ac, 2-Me, 1,3,5-tri-Me
Y = 4-CN, 4-COMe, 4-CHO, 4-CO_2Me, 3-CO_2Me, 2-CO_2Me, 4-NO_2, 4-NHCOMe, 4-OMe, 4-NH_2, 4-NMe_2

Scheme **9**

Buchwald has also made important contributions to the Suzuki-Miyaura cross coupling of aryl chlorides.[38] His main focus has been to develop new phosphino ligands for palladium catalysis (Scheme **10**). Thus, under conditions of $Pd(OAc)_2$ as the palladium source, KF as the base, and **26**, **27**, and **28** as the phosphino ligands, excellent

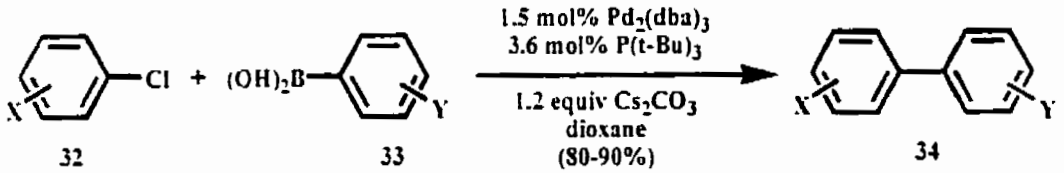
functional group tolerance, minimal barriers due to steric hindrance, and reduced catalyst loadings in the range of 0.000001-0.02 mol% (with little detriment to yield) were achieved.



R^1 = H, 2-OMe, 3-COMe, 2,5-di-Me
R^2 = 4-Me, 4-CN, 4-NO_2, 4-OMe, 2,4-di-OMe, 2-Ac, 2-CH_2CN, 4-CO_2Me, 2-OMe

Scheme 10

Fu and coworkers have also successfully used phosphine ligands for the activation of palladium in the Suzuki-Miyaura cross coupling of aryl chlorides. Originally, Fu reported the use of $Pd(dba)_2$ in conjunction with $P(t\text{-}Bu)_3$ for the cross coupling of a wide variety of aryl chlorides (**32**) and aryl boronic acids (**33**) (Scheme **11**).[39]



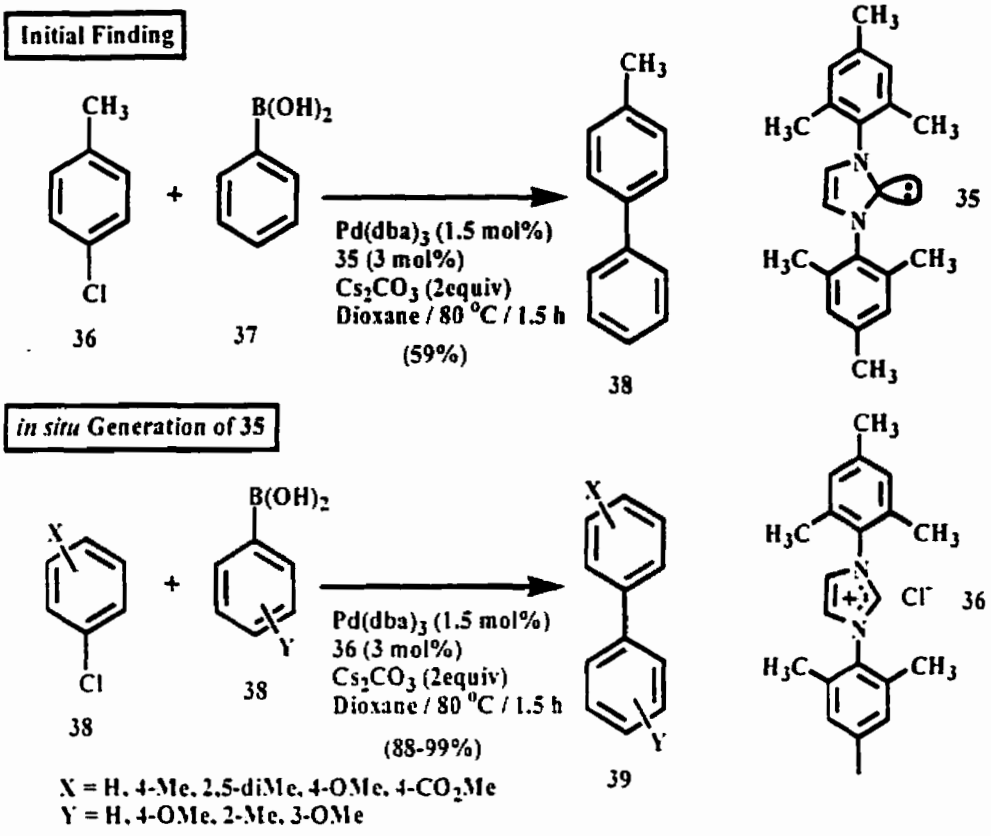
X = COMe, Me, OMe, NH_2
Y = CF_3, H, Me, OMe

Scheme 11

More recently, Fu has reported that both the $Pd(OAc)_2/PCy_3$ and $Pd(dba)_2/P(t\text{-}Bu)_3$ combinations, with KF as base, effectively promote cross coupling of a diverse array of

aryl, heteroaryl, and vinyl halides and triflates with aryl boronic acids.[40] The best feature of this chemistry is that the cross couplings proceed at good to excellent yields at or near room temperature. Other interesting features that arose from this work include: the selective coupling of aryl chlorides in the presence of aryl triflates (with $Pd(dba)_3/P(t\text{-}Bu)_3$), the selective coupling of aryl triflates in the presence of aryl chlorides (with $Pd(OAc)_2/PCy_3$). and low catalyst loadings (down to 0.005 mol%) with no detriment to yields.

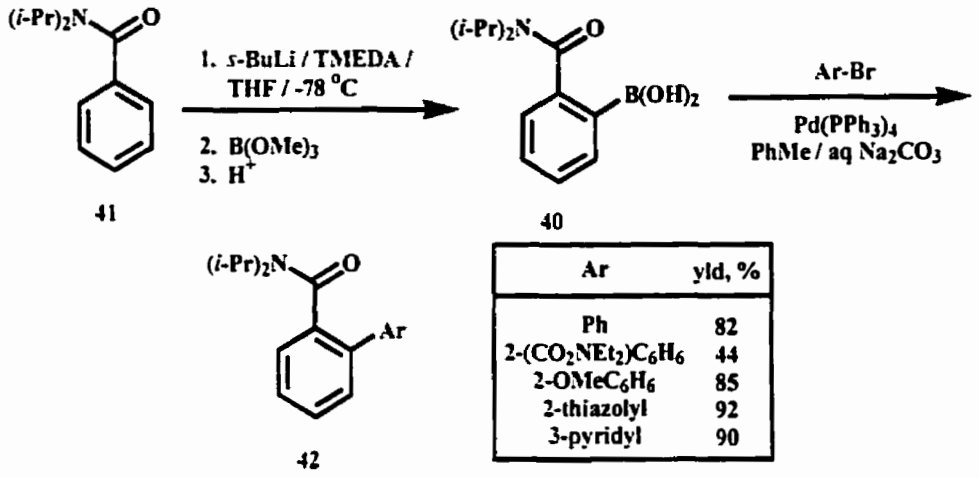
Nolan and coworkers have developed new nucleophilic *N*-hetrocyclic carbenes. e.g. imidazol-2-ylidene. **35**. ligands for palladium for use in the Suzuki-Miyaura cross coupling reaction.[41] This imidazol-2-ylidene. **35**. originally discovered by Hermann[42] and sometimes called "phosphine mimics". do not dissociate from the metal center. thus eliminating the need for excess ligand in the reaction to prevent aggregation of the catalyst. Initially. Nolan showed that carbene **35** when used in the cross coupling of *p*-chlorotoluene (**31**) with phenyl boronic acid (**37**). gave only moderate yields (59%) of the biaryl **38** (Scheme **12**) and attributed this result as being due to the sensitivity of the carbene ligand to contact with either air or moisture. However. the findings that the reactive carbene ligand **35** could be generated *in situ* from the imidazolium salt **36** under the reaction conditions using Cs_2CO_3 as base greatly increased the yields of the products (Scheme **12**).



Scheme 12

2.4 The DoM - Suzuki-Miyaura Cross Coupling Connection

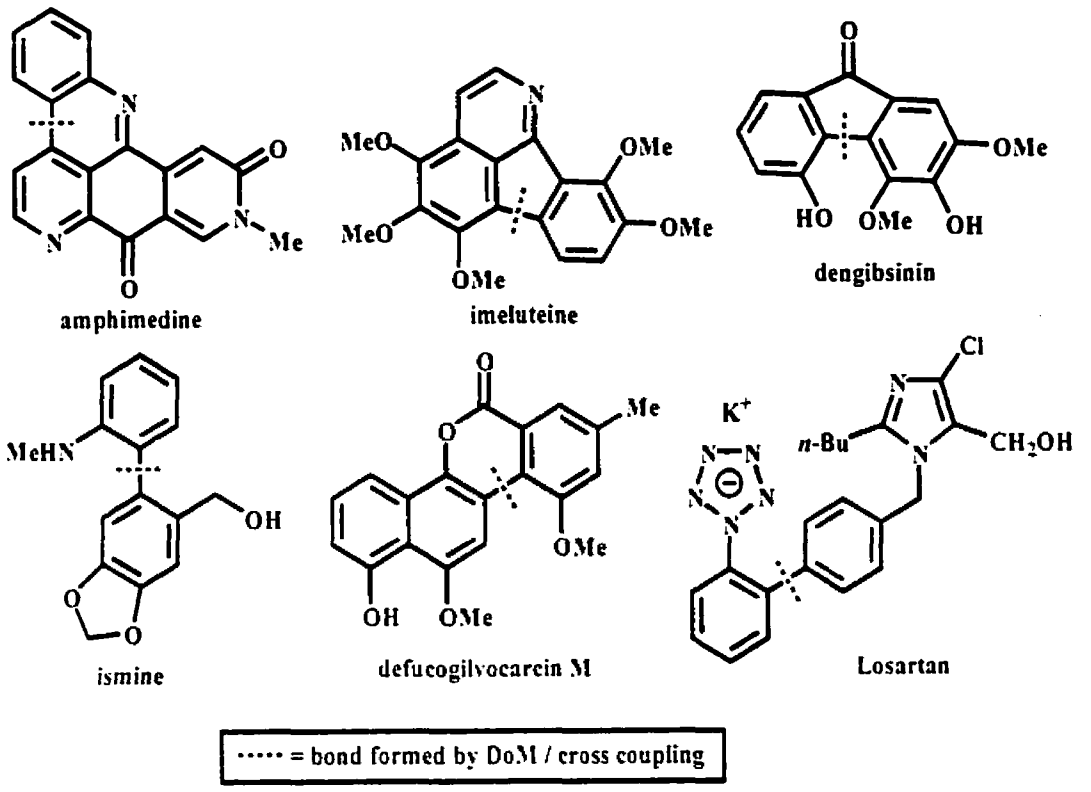
As previously described (Section 1.0), the DoM reaction is a powerful technique for the regiospecific construction of polysubstituted aromatics. This protocol, combined with the Suzuki-Miyaura cross coupling reaction, greatly increases the scope of biaryl synthesis. Snieckus originally demonstrated this connection by cross coupling a series of aryl bromides with the aryl boronic acid, **40**, derived from DoM of *N,N*-diisopropyl benzamide, **41** followed by trimethylborate quench, as a general synthesis of biaryls and heterobiaryls **42** (Scheme **13**).[43]



Ar	yld, %
Ph	82
2-(CO_2NEt_2)C_6H_6	44
2-$OMeC_6H_6$	85
2-thiazolyl	92
3-pyridyl	90

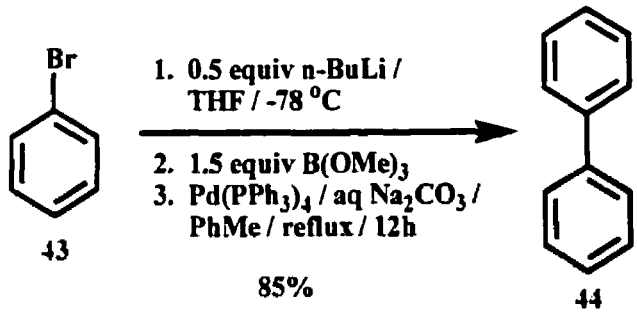
Scheme 13

Furthermore. Snieckus has applied the DoM-cross coupling tactic to the synthesis of binaphthols[44] and polychlorinated biphenyls[45] and used it as a key step in the construction of natural products. including amphimedine.[46] imeluteine.[47] dengibsinin,[48] ismine.[49] and defucogilvocarin M[50] (Scheme 14). A large scale DoM-cross coupling tactic has been employed by Dupont/Merck for the synthesis of a nonpeptide angiotensin II receptor antagonist. Losartan (Scheme 14).[51]

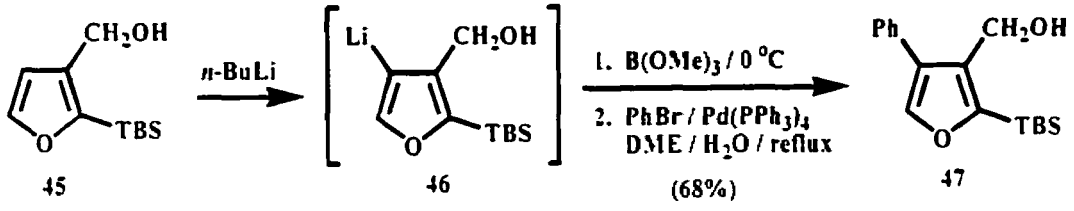


Scheme 14

An interesting variation on the DoM-Suzuki-Miyaura cross coupling sequence has been described by Keay.[52] Metal-halogen exchange of bromo benzene (**43**) with 0.5 equivalent of *n*-BuLi afforded PhLi in solution which was then quenched with trimethylborate (Scheme **15**). Addition of $Pd(PPh_3)_4$, aqueous Na_2CO_3 and toluene followed by reflux gave biphenyl (**44**) in 85% yield. The advantage of this procedure is that the aryl boronic acid need not be isolated, a useful consideration for unstable boronic acids. Keay has also performed similar experiments with furans (Scheme **16**).[53]

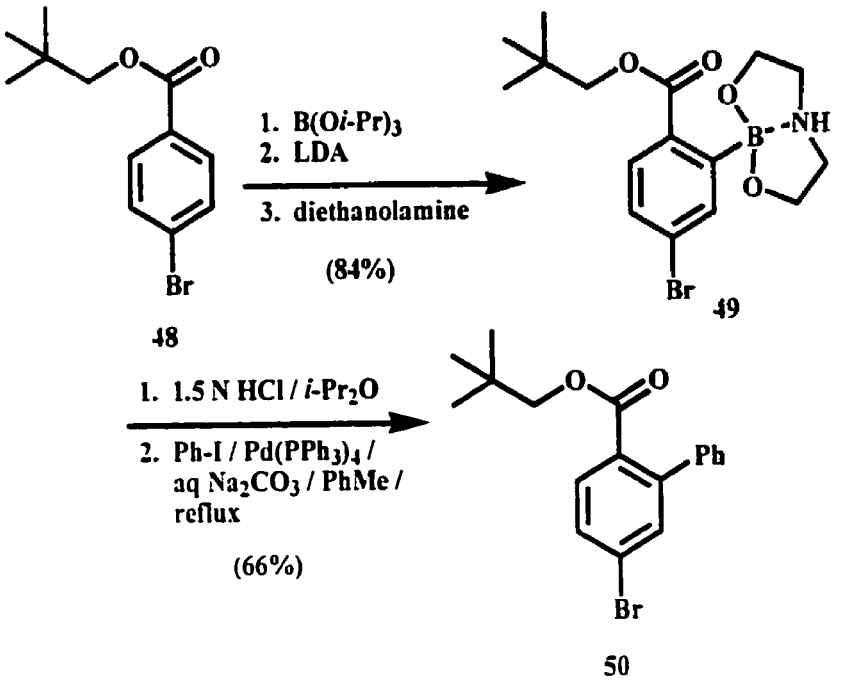


Scheme 15



Scheme 16

In attempts made to obtain the *ortho* boronic acid of neopentyl ester **48**, (Scheme **17**) by DoM using LDA as base, Caron and Hawkins observed only rapid self-condensation of neopentyl esters.[54] A solution to this problem, to employ the use of an *in situ* DoM protocol, was devised.[55] Triisopropylborate was found to be compatible with LDA and to allow for the facile *ortho* boronation of the neopentyl ester **48** (Scheme **17**). The boronates were isolated as their diethanolamine adducts (**49**) which, after hydrolysis, were used in cross coupling reactions. Similar work has also been conducted by Vedso.[56] Vedso found that LiTMP was an effective replacement for LDA and that ester, cyano, fluoro, and chloro directing groups were compatible for *ortho* boronation thus extending this useful procedure.

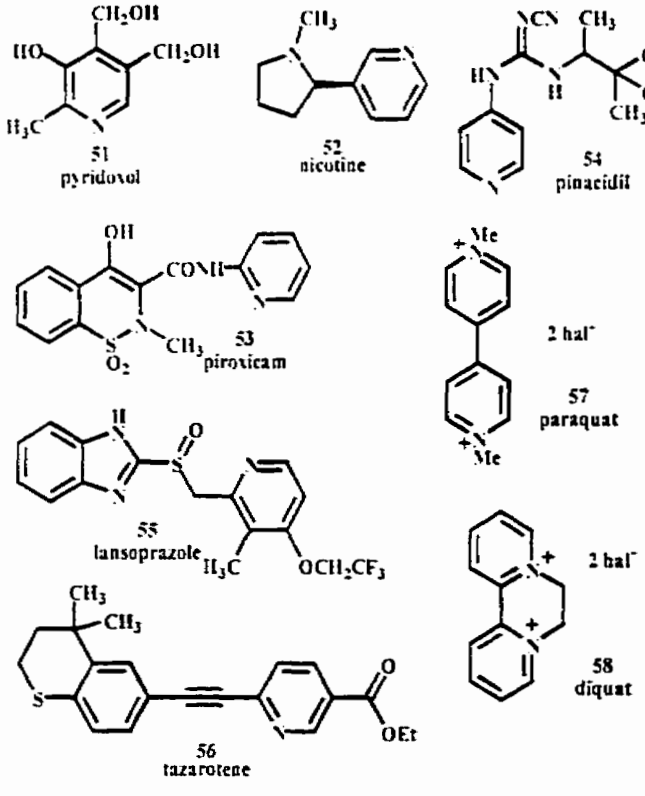

1. B(Oi-Pr)3
2. LDA
3. diethanolamine
(84%)
Br
48
Br
49
1. 1.5 N HCl / i-Pr2O
2. Ph-I / Pd(PPh3)4 /
aq Na2CO3 / PhMe /
reflux
(66%)
Ph
Br
50

Scheme 17

3.0 The Synthesis of Pyridine Derivatives. A Brief Review

3.1 Introduction

Pyridine is an electron deficient aromatic heterocycle found in many natural, biologically active, compounds and used widely in for the construction of bioactive molecules in the pharmaceutical industry. Some common naturally occurring derivatives of pyridine are pyridoxol (vitamin B_6), **51** and nicotine, **52**. Among the various commercial drugs exhibiting pyridine moieties are piroxicam (an anti-inflammatory drug), **53**, pinacidil (an anti-hypertension agent), **54**, lansoprazole (treatment of acid reflux disease), **55**, and tazarotene (an anti-psoriasis drug), **56**. Pyridines are also constituents of herbicides such as paraquat, **57**, and diquat, **58**.



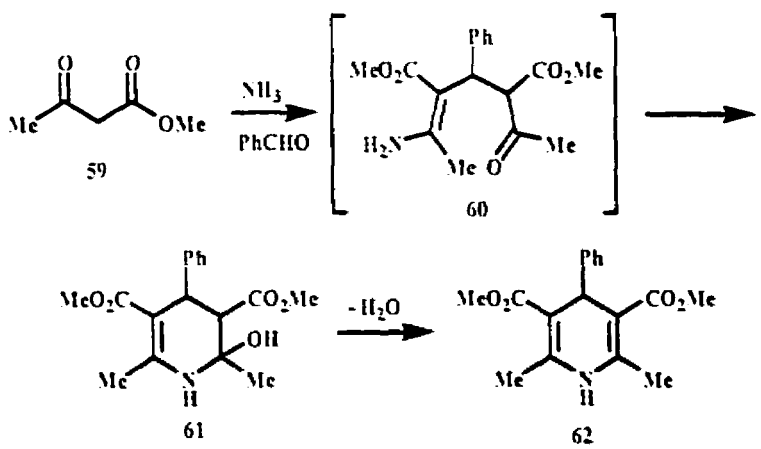
Scheme 18

Pyridine is an excellent polar aprotic solvent, a base (pKa = 5.23), and is often used as a donar ligand in metal complexes.[57] A mixture of pyridine bases constitute about 0.2% of coal tar, which can be extracted with acid and separated, and several simple alkyl (methyl and ethyl) pyridines can be obtained from the carbonization of coal.[57] This source of pyridines has been superseded by synthetic routes. Some selected examples will be detailed in the next section.

3.2 Pyridine Ring Synthesis

3.2.1 The Hantzsch Synthesis

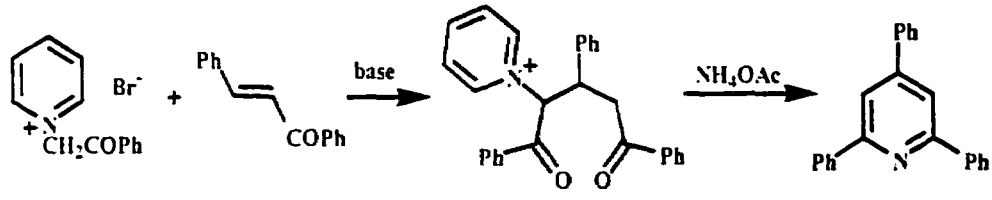
The venerable Hantzsch synthesis involves the reaction of an aldehyde and ammonia with 1,3-dicarbonyl compounds **59** (Scheme **19**).[58] providing an excellent route to symmetrically substituted 1,4-dihydropyridines **62**. If ammonia is replaced with ammonium acetate in acetic acid, the resultant 1,4-dihydropyridine is easily aromatized by nitric acid or nitric oxide.[59] Scheme 19 depicts an example of the Hantzsch synthesis.



Scheme 19

3.2.2 The Kröhnke Synthesis

Similarly to the Hantzsch syntheis, the Kröhnke synthesis involves a conjugate addition as the major step in the reaction.[60] However, in this case it is the conjugate addition of a pyridinum ylide (from the reaction **63** with base, Scheme **20**), to an α,β-unsaturated carbonyl compound, **64**. This directly leads to a 1,5-dicarbonyl system, **65**, which is already in the correct oxidation state for cyclization, upon treatment with ammonia, to the fully aromatic pyridine, **66**. This synthesis allows for the construction of pyridines with substituents at the 2-, 4-, and 6-positions.

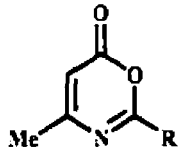
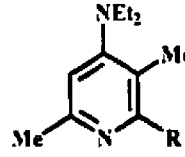
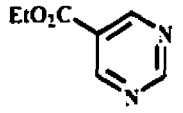
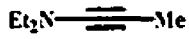
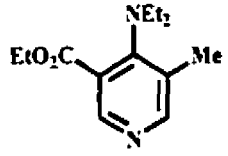
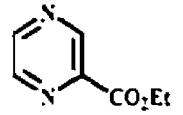
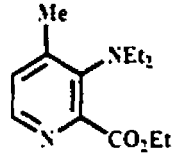
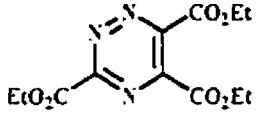
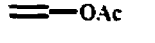
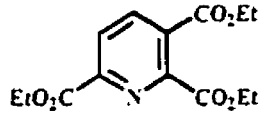


63 64 65 66

Scheme **20**

3.2.3 The Diels-Alder Reaction

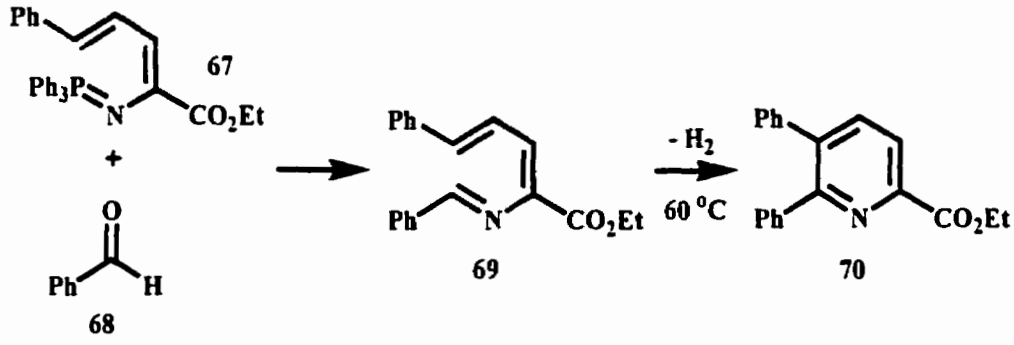
The Diels-Alder reaction has also been successfully used for the generation of pyridines from cyclic azadienes and electron rich alkynes or alkenes.[61] Selected examples are shown in Scheme **21**.[57] In all cases, two reactions are involved: a Diels-Alder and a retro-Diels-Alder, overall producing a stable small molecule and generating a pyridine derivative. The method is quite versatile and provides a wide variety of substituted pyridines.

Diene	Dienophile	Conditions	Product	yld. %
		Et_2O 20 °C		76
		MeCN 80 °C		90
		$CHCl_3$ 25 °C		72
		dioxane 100 °C		90

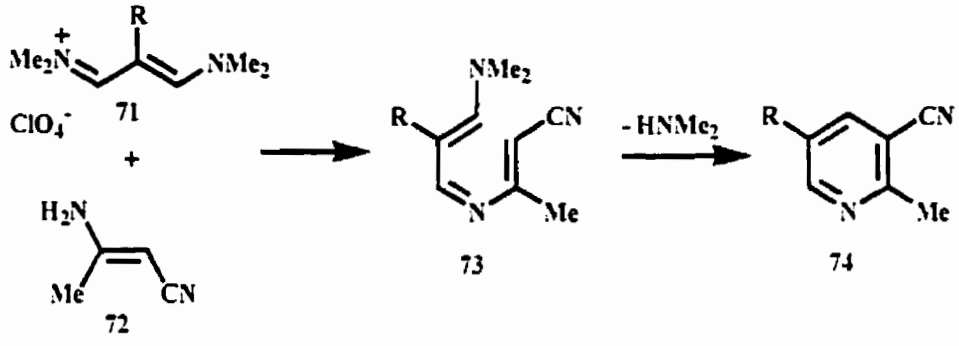
Scheme **21**

3.2.4 Other Syntheses

6 π Electron electrocyclic ring closure reactions (Scheme **22**.[62] and Scheme **23**[63]) have proven to be successful for the construction of the pyridine ring. The method illustrated by Scheme **22** is based on the reaction of iminophosphoranes, **64** with carbonyl compounds, **68**, in which the initial product, **69**, undergoes cyclization with the loss of H_2, to the pyridine derivative. The reaction illustrated by Scheme **23** involves the initial displacement of dimethylamine, **71** to **73**, which, after a 6 π electron ring closure and elimination of a second equivalent of dimethylamine, leads to the pyridine derivative, **74**.

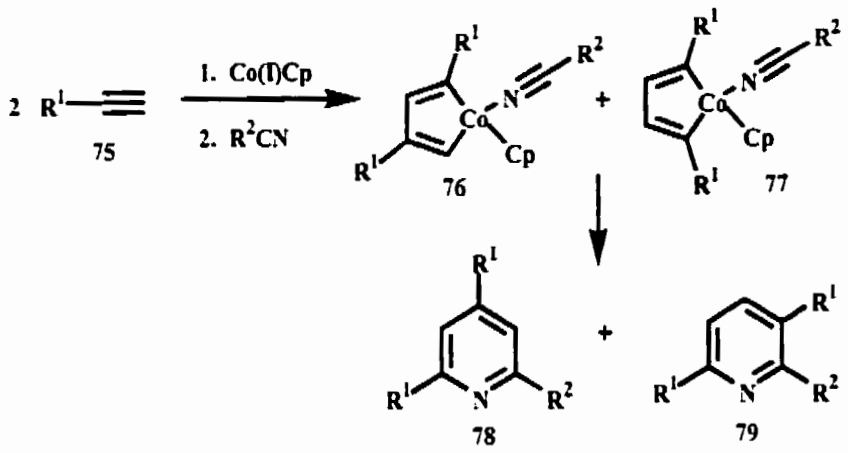


Scheme 22



Scheme 23

Another interesting approach involves the combination of alkynes 75 and nitriles under cobalt(I) catalysis to produce pyridine derivatives 78 and 79 via intermediates 76 and 77.[64] The main drawback of this method is the formation of isomeric mixtures of products when monosubstituted acetylenes are used (Scheme 24).



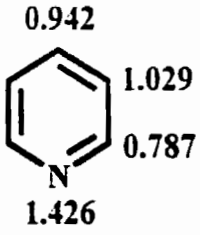
Scheme **24**

3.3 Functionalization of Pyridine

The following section will deal with methods for the functionalization of the pyridine ring.

3.3.1 General Reactivity of Pyridine[57,65]

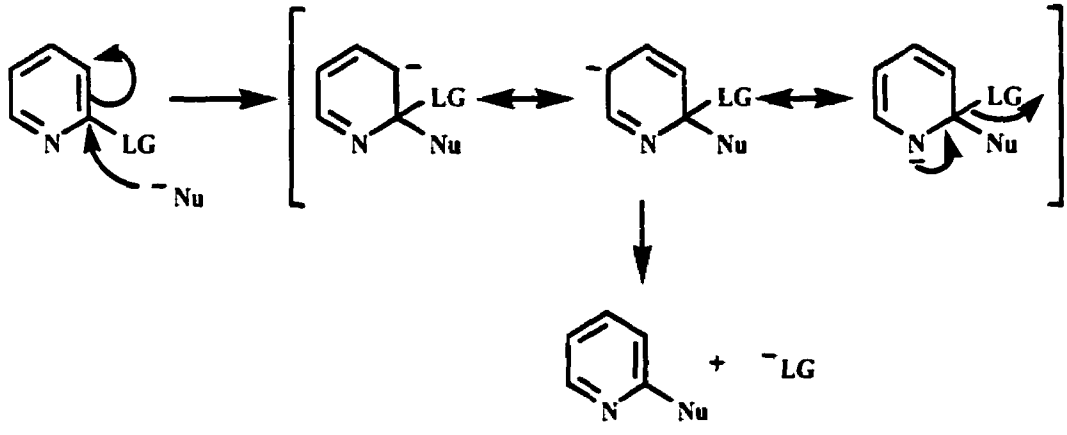
The chemistry of the pyridine ring can be ideally described by three main factors: the distribution of charge in the ring, effects of substituents, and steric effects. The calculated π-electron density in pyridine (Scheme **25**) allows appreciation of the reactivity of pyridine.[66]



Scheme **25**

While electrophilic aromatic substitution is widely practiced in the functionalization of aromatics, this technique sees limited use for the preparation of substituted pyridines. The main result of a reaction between pyridine and an electrophile is coordination/complexation of the electrophile with the lone pair of electrons on nitrogen. This makes further electrophilic chemistry difficult as the electrophile must now react with the electron deficient pyridinium species or the minute amount of uncomplexed pyridine present. The highest π-electron density at C-3 dictates electrophilic substitution at this position. Friedel-Crafts alkyation or acylation is rare for pyridine. The presence of electron donating groups on the pyridine make the ring more susceptible to electrophilic attack and such groups direct electrophiles according to classical electrophilic aromatic substitution rules. Electron withdrawing groups further deactivate the ring towards electrophilic attack. Pyridine *N*-oxides undergo electrophilic aromatic substitution as will be discussed later (Section **3.3.2**).

Nucleophilic aromatic substitution chemistry is more amenable to pyridine and pyridine systems. The preferential attack of nucleophiles can be rationalized by consideration of the π electron density data and the stabilizing effect of the nitrogen. When the pyridine nitrogen is quaternized, attack is more facile and characteristically occurs at C-2. Substituents on the ring may also affect nucleophilic attack. Electron donating groups deactivate the ring, while electron withdrawing groups activate the ring. When there are leaving groups at C-2 or C-4 the addition-elimination mechanism is followed (Scheme **26**). However, the C-3 position in pyridine is relatively inert to nucleophilic attack.



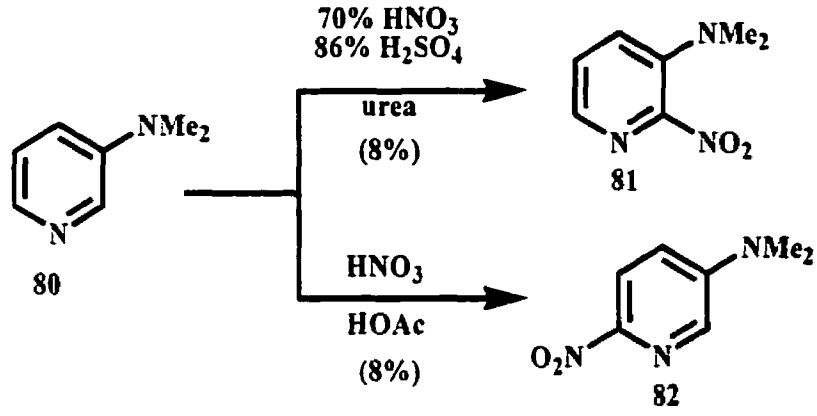
Scheme 26

The other powerful tools for the functionalization of pyridines are metalation (lithium-halogen exchange and DoM) and cross coupling techniques.

The following sections will deal with selected examples of the functionalization of the carbons in the pyridine rings. N-Functionalization will be dealt with only in conjunction with C-functionalization. Electrophilic and nucleophilic substitution chemistry will be addressed along with metalation, including DoM, and cross coupling techniques.

3.3.2 Electrophilic Aromatic Substitution Methods

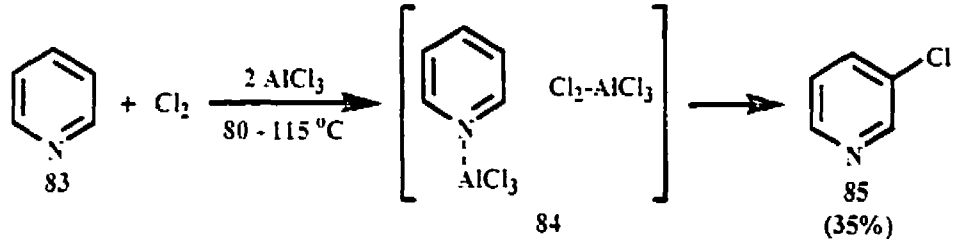
As discussed in Section **3.3.1**, functionalization at C-2 in pyridine by electrophilic aromatic substitution is not possible. However, Abramovitch and Saha have reported on the nitration of 3-dimethylaminopyridine, **80** (Scheme **27**), in low yield, under harsh conditions, to give either the 2- (**81**) or 6-nitro (**82**) derivatives.[67]



Scheme 27

Electrophilic aromatic substitution at C-2 is more readily achieved for alkoxy or hydroxy pyridines. For example, 3-hydroxypyridine may be brominated in aqueous sodium hydroxide to give 2-bromo-3-hydroxypyridine exclusively.[68]

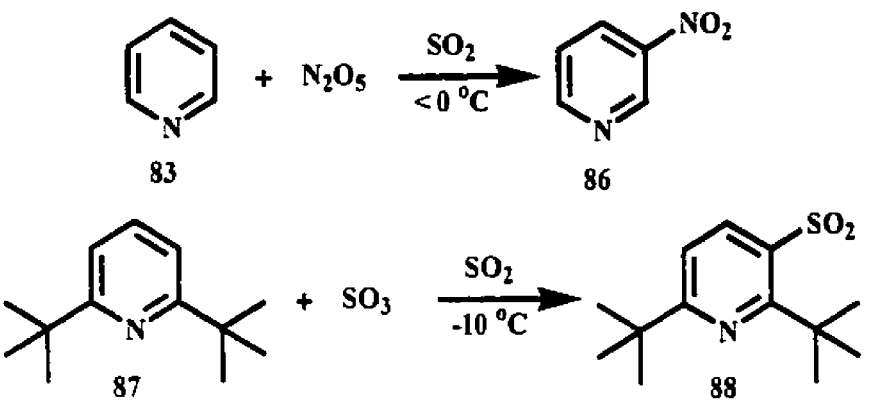
Electrophilic aromatic substitution, although carried out under harsh conditions, is a common method for the preparation of 3-substituted pyridines. For instance, pyridine (**83**) may be selectively chlorinated in the 3-position (**85**) when treated with chlorine and two equivalents of aluminum chloride at 80-115 °C (Scheme **28**).[68]



Scheme **28**

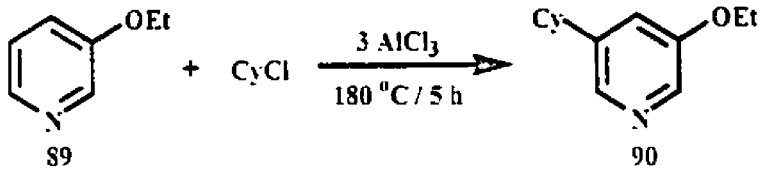
Similarily, 3-bromopyridine may be prepared by the reaction of bromine in fuming sulfuric acid at 130 °C. Nitration of pyridine is also possible using a combination of dinitrogen pentoxide and sulfur dioxide at less than 0 °C (Scheme **29**).[69] Sulfonation does not occur on pyridine, as it is believed that the sulfur trioxide coordinates to the pyridine nitrogen and does not react further with the ring.[57] However, sulfonation does

occur on 2,6-di-*t*-butylpyridine and this success is attributed to the steric bulk at nitrogen, preventing sulfur trioxide coordination (Scheme 29).[70]



Scheme 29

Even though Friedel-Crafts chemistry is rare for pyridines, the Friedel-Crafts alkylation of 3-ethoxypyridine (89) has been reported (Scheme 30) and predominantly gives 90.[71]

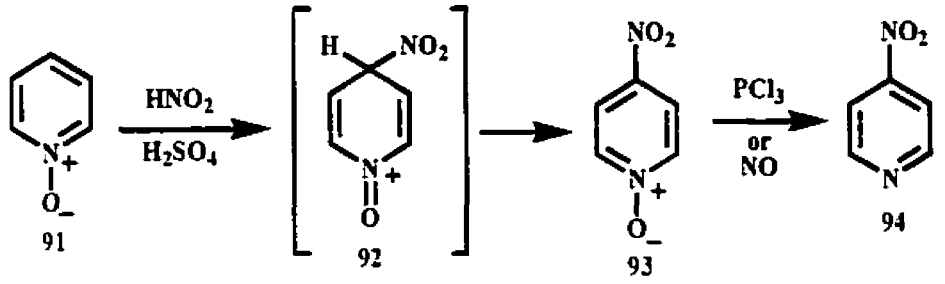


Scheme 30

Pyridine *N*-oxide does not undergo nitration in the 3-position. On the other hand the presence of an electron donating group promotes nitration as in the case of 2,6-dimethoxypyridine *N*-oxide. However, with this substrate, it is difficult to obtain the mono-nitrated product as dinitration predominates.[72]

Generally speaking, 4-substituted pyridines are not readily accessible by electrophilic chemistry. Even when activating groups, which direct *ortho/para*, are in the 3-position, electrophilic substitution goes into C-2 or C-5. Nitration of pyridine *N*-oxides is the exception to this rule.[57] Thus, the nitration of pyridine *N*-oxide (91) proceeds

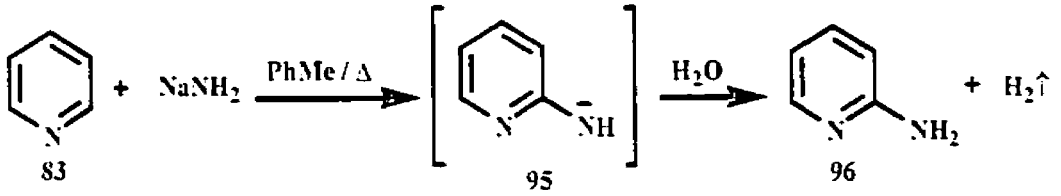
smoothly in a combination of fuming nitric and sulfuric acid (Scheme **31**). The *N*-oxide can be removed with either trichlorophosphine or nitrous oxide, thus providing a route to 4-nitropyridine (**94**).



Scheme 31

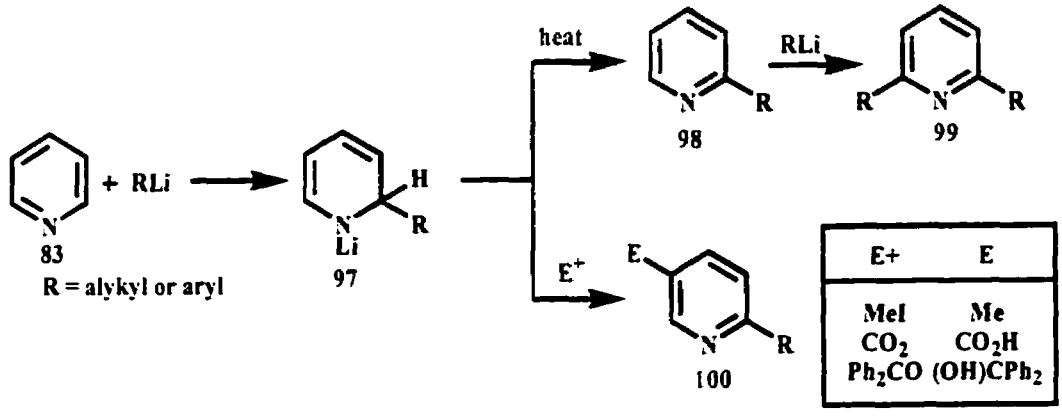
3.3.3 Nucleophilic Aromatic Substitution Methods

Nucleophilic aromatic substitution chemistry on pyridines allows C-2 functionalization. One of the most well known reactions for C-2 funtionalization is the Chichibabin reaction (Scheme **32**).[73,74] The reaction is specific for C-2 attack and only when both C-2 positions are blocked does the amination proceed at the 4–position.



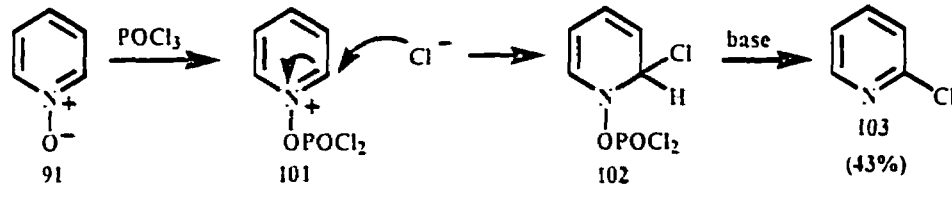
Scheme 32

Organolithiums are also known to add to the C-2 position of pyridines (Scheme **33**).[75] The intermediate (**97**) of this reaction undergoes aromatization on heating to lead to 2-substituted pyridines (**98**). If an excess of organolithium is used, 2,6-disubstituted pyridines (**99**) predominate. In an interesting variant, the intermediate (**97**) may also be trapped with electrophiles to give 2,5-disubstituted pyridines (**100**).



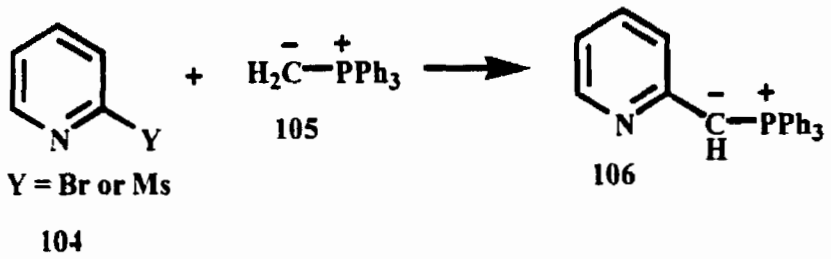
Scheme 33

Pyridine *N*-oxides undergo nucleophilic attack at the C-2 position upon treatment with an electrophile.[76] Even though the initial reaction is electrophilic, the attack at the C-2 position is nucleophilic. For example, the reaction of pyridine *N*-oxide with $POCl_3$ leads to 2-chloropyridine in 43% yield with 20% of the C-4 substituted product (Scheme **34**). Pyridine *N*-oxides undergo reaction in a similar manner with acetic anhydride to give 2-acetoxypyridine.[76]



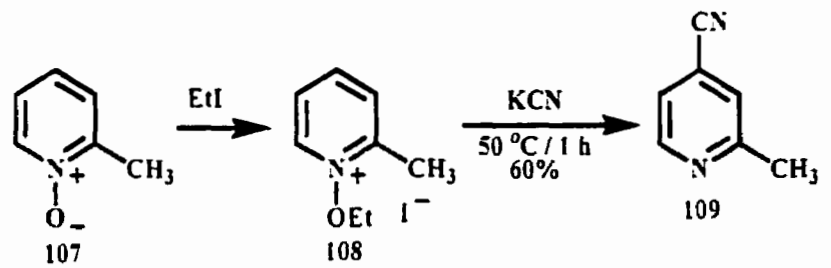
Scheme 34

Halides in the 2-position are susceptible to displacement by nucleophiles such as halides, hydrazine, thiolate anions, and stabilized carbanions, following an addition-elimination mechanism (Scheme **35**).[77] An interesting example is the reaction of 2-bromo and 2-methanesulfonylpyridine (**104**) with triphenylphosphonium methylide (**105**) to give the stabilized Wittig ylide (**106**), which however, has not been widely used.[78]



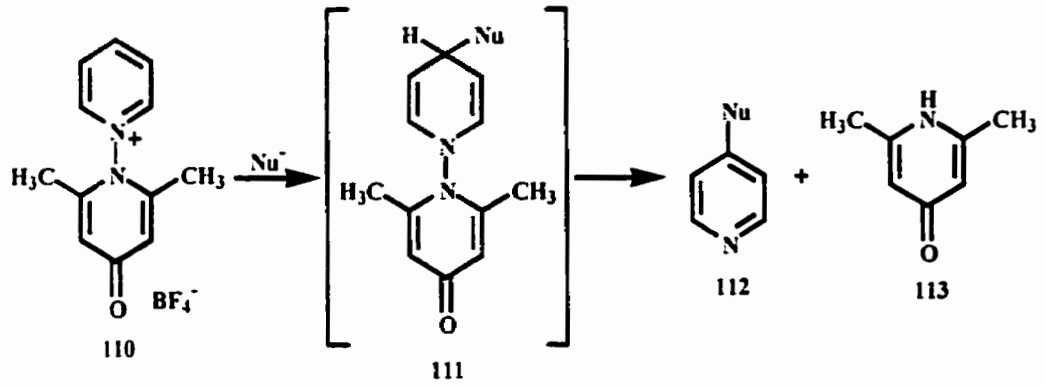
Scheme 35

A method for C-4 cyano funtionalization involves treatment of **107** with EtI to give **108** followed by cyanide substitution and ethanol elimination to afford **109** (Scheme 36).[79]



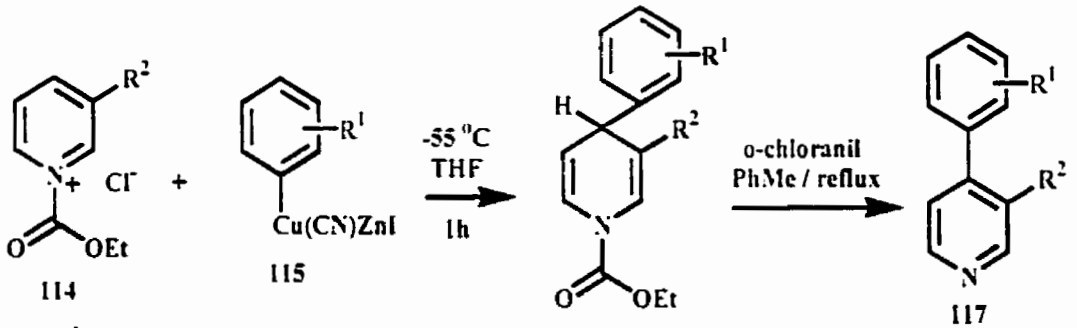
Scheme 36

Quaternization of the pyridine nitrogen makes the ring more susceptible to nucleophilic attack. Katritzky and coworkers have developed a pyridinium species, **110**, that is readily attacked by a variety of nucleophiles to give **111** and subsequently **112**.[80] The group on nitrogen has two purposes: it is bulky enough to inhibit attack at C-2, yet activating the C-4 position, and it is a good leaving group for ring re-aromatization, after the initial attack. Katritzky found that alkyl and arylmagnesiums, enolates, and thiols readily form C-4 substituted products in yields greater than 80%.



Scheme 37

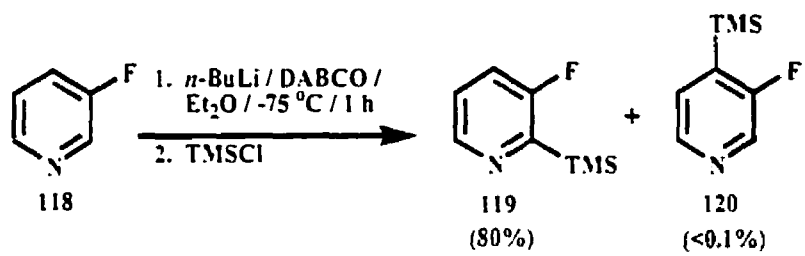
In an approach to azabiaryls, Shiao and coworkers showed that *N*-acyl pyridinium salts **114**, prepared *in situ*, upon treatment with mixed copper/zinc aryl nucleophiles **115**, give dihydropyridines **116** which, upon aerial oxidation afford pyridines **117**, in moderate yields.[81] In two cases (R^1 = 4-CN, R^2 = CO_2Me and R^1 = 4-CO_2Me, R^2 = CN) were C-2 substituted products obtained in less than 10% yield. This method is an alternative to cross coupling protocols discussed in Section 3.3.5.



Scheme 38

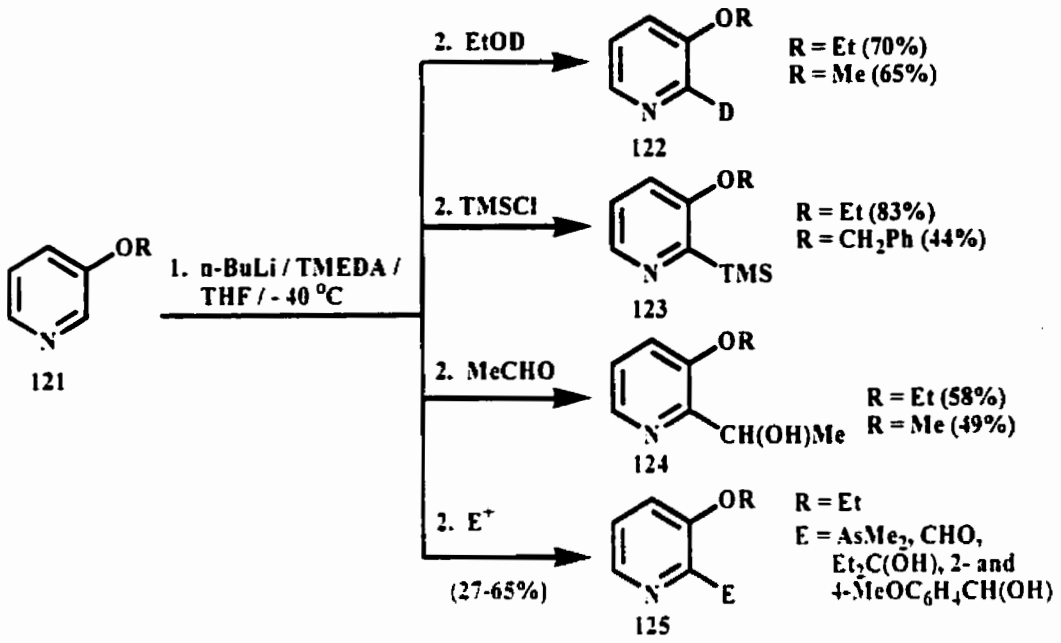
3.3.4 Metalation Methods

Metal-halogen exchange and DoM methods have been invaluable tools for the C-2 functionalization of pyridines. 3-DMG substituted pyridines undergo metalation in the C-4 position.[82] There are, however, some exceptions. When 3-fluoropyridine (**118**) is metalated with *n*-BuLi/DABCO in Et_2O at –75 °C followed by TMSCl quench, the 2-silylated product (**119**) is obtaind as the major product (80%) with less than 0.1% of the 4-silylated product (**120**) (Scheme **39**).[83] If the conditions are varied (*i.e.* different solvent or additative) mixtures of the 2- and 4-silylated products, **119** and **120**, were obtained.[82]



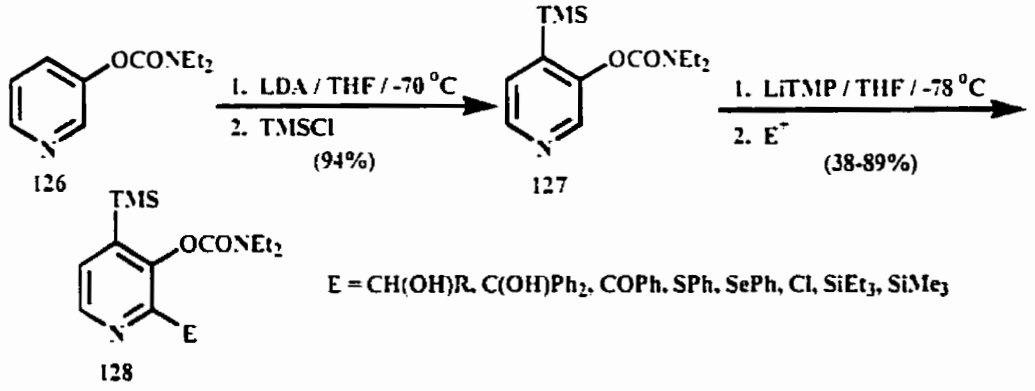
Scheme **39**

C-2 DoM has also been observed for 3-trifluoromethyl pyridine.[84] 3-Alkoxy substituted pyridines also may undergo C-2 deprotonation.[85] Thus, 3-methoxy, -ethoxy, -butoxy, and -benzyloxy groups have all allowed functionalization at C-2 with a variety of electrophiles (Scheme **40**).



Scheme 40

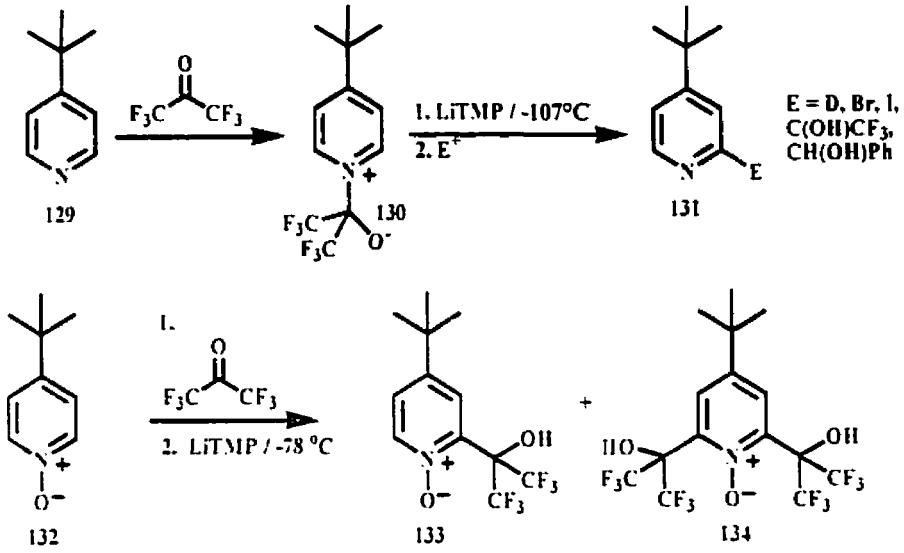
Other 3-DMG pyridines that normally direct *ortho* metalation into the C-4 position, e.g. $OCONEt_2$ (**126**) and OMOM, can direct into the C-2 position if the C-4 position is first blocked with a silyl protecting group (Scheme **41**).[86] This procedure uses DoM twice, first, to install the protecting group and second, to install the C-2 functionality.



Scheme 41

In a unique study, Martin showed that quaternization of the pyridine nitrogen in **129** with hexafluoroacetone creates a latent DMG on nitrogen (**120**) thereby promoting

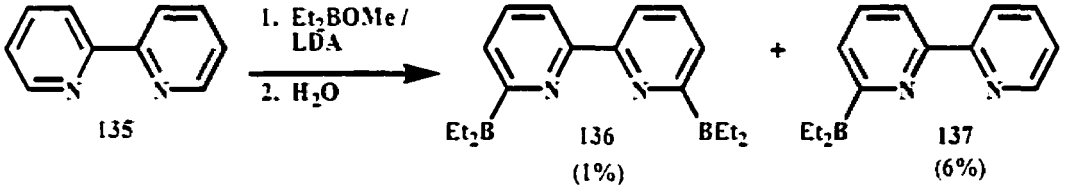
DoM into the C-2 position exclusively (Scheme **42**).[87] Similarly, *N*-oxide **132** coordinating with hexafluoroacetone directs metalation into the C-2 and C-6 positions to give products **133** and **134**.



129 130 131 132 133 134

Scheme **42**

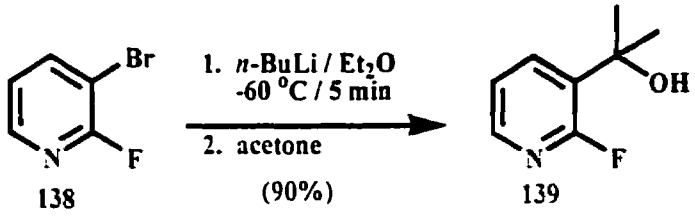
Siebert and co-workers have successfully metalated 2,2'-bipyridine **135** (Scheme **43**) in the presence of a mixture of diethyl(methoxy)borane and LDA to produce 6,6'-bis(diethylboryl)-2,2'-bipyridine **136** and the mono-boronated product **137**, albeit both in low yields.[88] This is an example of an *in situ* metalation-boronation similar to that reported by Caron and Hawkins (Section **2.4**). Boronated pyridines **136** and **137** were used as ligands for formation of copper complexes.



135 136 (1%) 137 (6%)

Scheme **43**

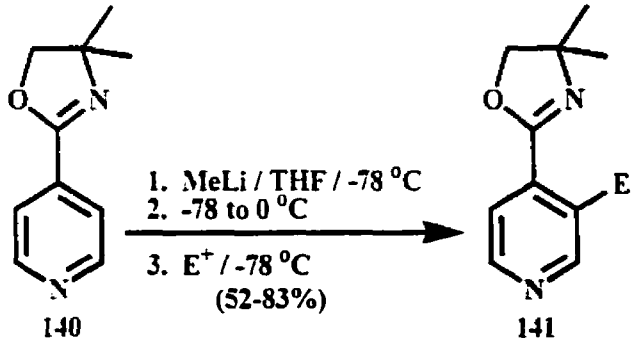
Lithium halogen exchange may be employed to obtain reactive lithiated pyridines which may be quenched with electrophiles. For example, treatment of 3-bromo-2-fluoropyridine, **138**, with one equivalent of *n*-BuLi at low temperatures for a short time, followed by quenching with acetone, yields **139** (Scheme **44**).[82] There are complications with lithium halogen exchange especially of polyhalogenated pyridines, however, such as halogen scrambling, which leads to unwanted side products.[82]



138 **139**

Scheme **44**

The DoM reaction may also be used for the functionalization of the 3-position because both DMGs in the 2- and 4-positions will direct the metalation into the 3-position. For example, when 4-pyridyloxazoline is treated with MeLi followed by quenching with various electrophiles, a series of 3,4-disubstituted pyridines are formed. (Scheme **45**).[89] If either *n*-BuLi or *s*-BuLi was used as the base, alkyllithium addition products (at C-6), were also observed.

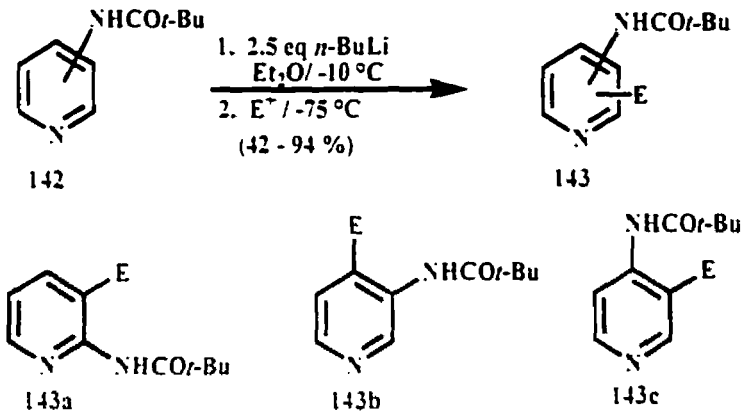


140 **141**

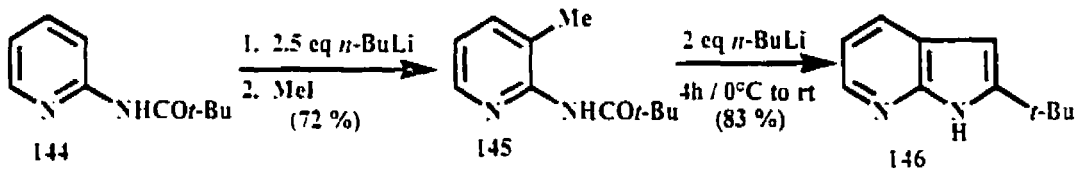
E = Me, Et, allyl, CH(OH)Ph, C(OH)Et$_2$, CHO

Scheme **45**

The *N*-pivaloylamino DMG (**142**) has been used extensively to introduce a wide range of functionality into pyridines (Scheme **46**).[90] It is likely that the *N*-deprotonated lithio species aids in the *ortho* deprotonation. An excellent feature of the *N*-pivaloylamino DMG is its facile hydrolysis with 3N HCl to the primary amine, thus allowing for further functional group interconversions.[90b] An application of the use of the *N*-pivaloylamino DMG is in the Madelung synthesis of azaindoles (**146**) (Scheme **47**). Thus, treatment of **144** with n-BuLi followed by MeI quench gives **145**, which upon lateral metalation and subsequent cyclization gives indole **146**.

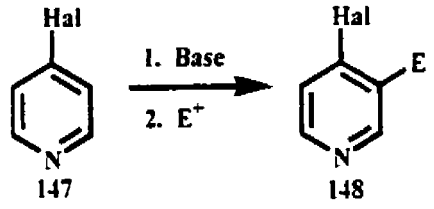


Scheme **46**



Scheme **47**

All halogens act as DMGs in pyridine DoM chemistry.[91] Some representative examples of the types of functionality that can be introduced into 4-fluoro (**147**) and 4-chloropyridine (**148**) and conditions necessary are illustrated in Scheme **48**.



147 148

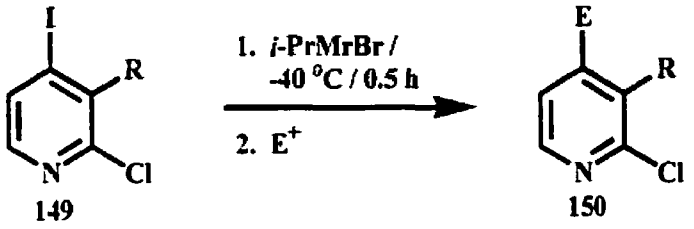
Halogen	Base	Conditions	E	yld, %
F	n-BuLi	A	$C(OH)Me_2$	65
F	n-BuLi	A	TMS	75
F	LDA	B	CH(OH)Ph	65
Cl	n-BuLi	A	$C(OH)Et_2$	60
Cl	LDA	B	Me	70
Cl	LDA	B	CH(OH)Ph	90
Cl	LDA	B	TMS	70

A: 1. TMEDA / Et_2O or THF / - 60 °C to -20 °C
2. cool to -70 °C
3. E^+

B: 1. Et_2O or THF / 0 °C
2. cool to -70 °C
3. E^+

Scheme 48

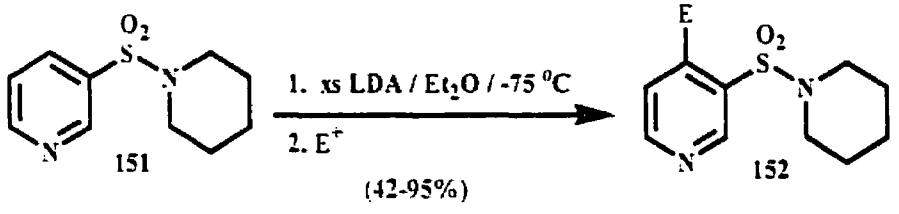
Metal-halogen exchange can be an effective means to regiospecifically introduce electrophiles into C-4. Knochel and coworkers reported a highly selective iodine-magnesium exchange on 4-iodopyridines **149** (Scheme 49).[92] The resultant Grignard species was quenched with a selection of electrophiles to give products **150**. This methodology was also applied to wide variety of heterocycles (imidazoles, furans, thiophenes, pyrroles, antipyrines and uracil) and one of the key and surprising aspects was that a wide range of functional groups were shown to be tolerated (e.g. CO_2R, CN and Cl).



R	E^+	E	Yield (%)
H	$C_5H_{11}CHO$	$CH(OH)C_5H_{11}$	85
H	PhCHO	CH(OH)Ph	92
H	allyl bromide	allyl	85
CO_2Et	TosCN	CN	55
CO_2Et	PhCOCl	COPh	84

Scheme 49

The DoM reaction is applicable for the C-4 functionalization of pyridines. Generally speaking, 3-DMG containing ring systems will give rise to 3,4-disubstituted systems. The exception to the previously discussed (above) 3-alkoxy DMGs direct metalation into the 2-position. Queguiner showed that the 3-piperidyl sulfonamide, **151**, upon metalating with excess LDA followed by electrophile quench, gives **152** in moderate to excellent yields (Scheme **50**).[93] This methodology was also applied to the corresponding 2- and 4-sulfonamides to give the corresponding 3-substituted products.

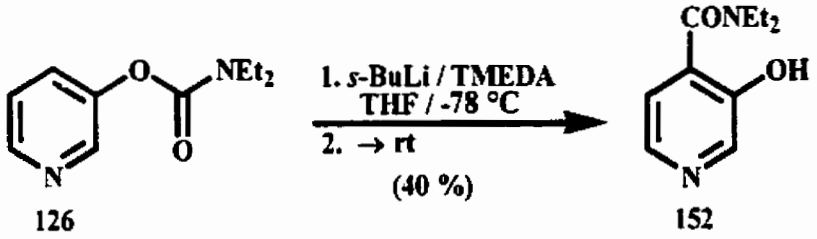


E = D, I, TMS, PhS, CHO, CO_2H, $C(OH)Ph_2$, $C(OH)Et_2$, CH(OH)Me, CH(OH)Ph

Scheme 50

An interesting result is obtained when the DMG is an *O*-carbamate. Treatment of **126** with s-BuLi followed by warming to room temperature results in an anionic *ortho*

Fries rearrangement to give **152** (Scheme **51**).[86a] Analogous reactions are observed for the 2- and 4-*O*-carbamate.



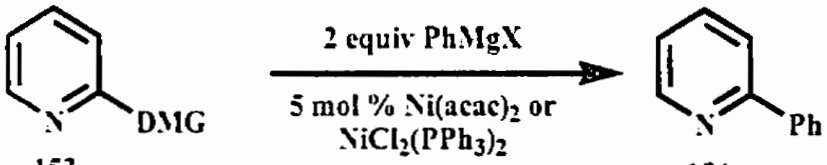
126 **152**

Scheme **51**

3.3.5 Cross Coupling Methods for the Synthesis of Arylpyridines

Transition metal catalyzed cross coupling reactions have revolutionized the synthesis of Ar-Ar, HetAr-Het-Ar, and mixed Ar-HetAr systems.[16] The availability of all halopyridines and metal-halogen exchange procedures have made it possible to consider pyridine derivatives both as HetMet and HetLG partners.

For pyridine *O*-carbamates[94] or *S*-thiocarbamates[95] cross coupling with an aryl Grignard reagent in the presence of a Ni(0) catalyst may be achieved (Scheme **52**).



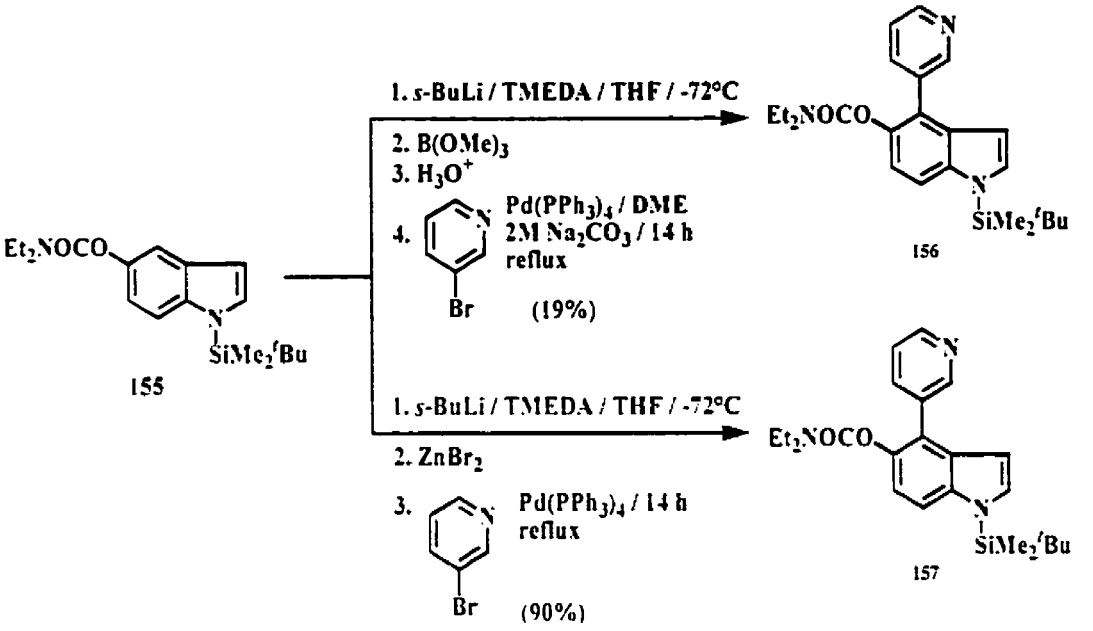
153 **154**

DMG = $OCONEt_2$ (30-80%)
$SCONEt_2$ (55%)

Scheme **52**

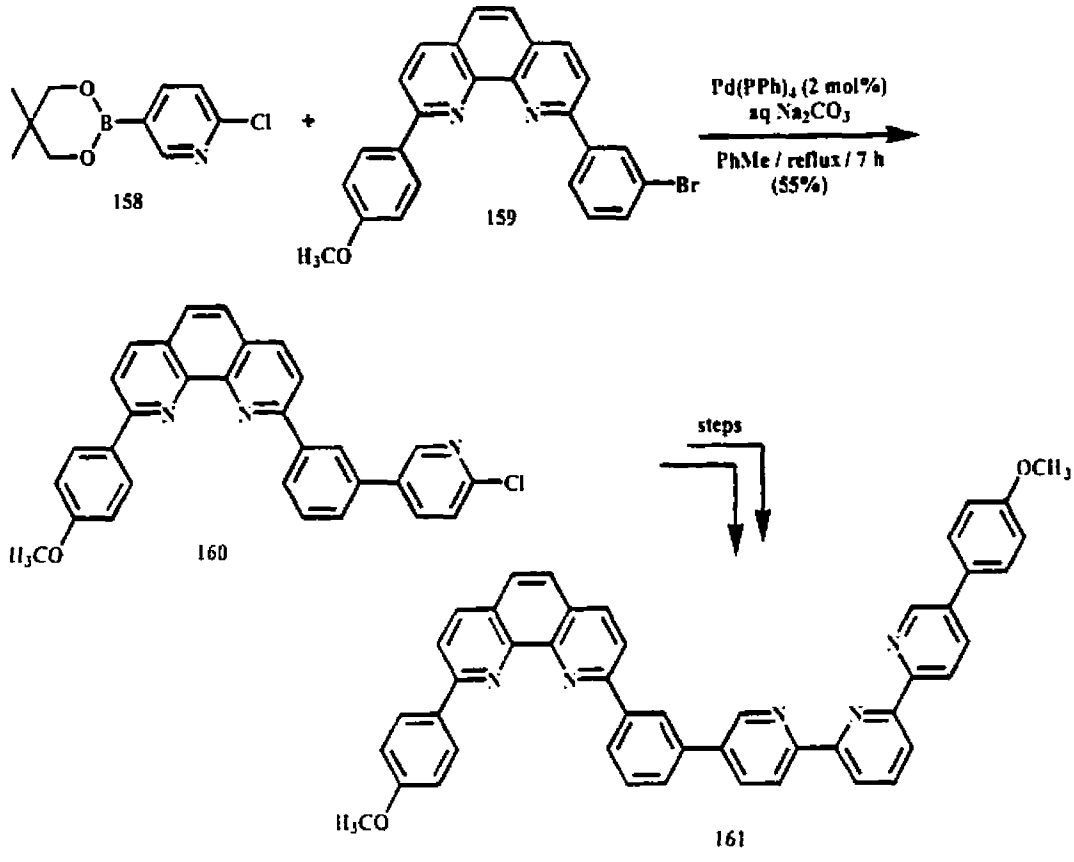
Application of cross coupling leading to heteroaryl substituted pyridines has also been an active field of synthesis. Thus, an interesting example from the Snieckus laboratories has shown that *N*-TBS 5-O-carbamate indole, **155**, may be regiospecifically

metalated in the C-4 position using standard conditions. Transmetalation to the boron or zinc species followed by cross coupling under Suzuki-Miyaura or Negishi protocols with 3-bromopyridine yields **156** and **157** respectively (Scheme **53**).[96] In this case, the Negishi reaction proved to be the superior method.



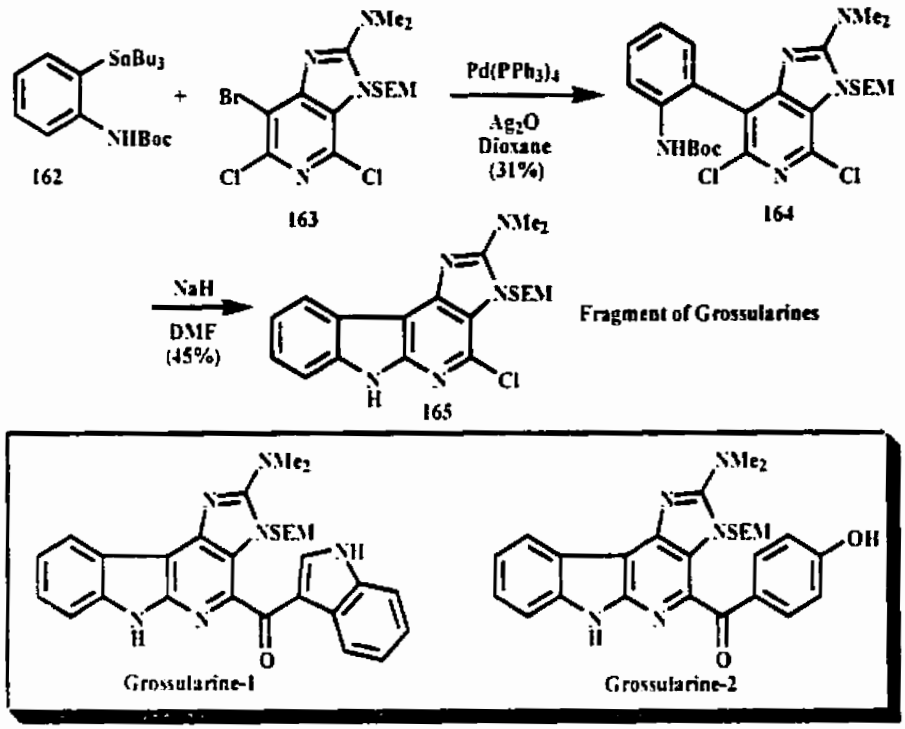
Scheme **53**

The use of pyridine boronic acids for cross coupling reactions is quite rare. Thus, Dietrich-Buchecker and co-workers reported the cross coupling of **158**, prepared by metal halogen exchange and trimethylborate quench, with **159** to give **160** which was further converted into **161**, a possible ligand for copper (I) or iron (II) (Scheme **54**).[97]



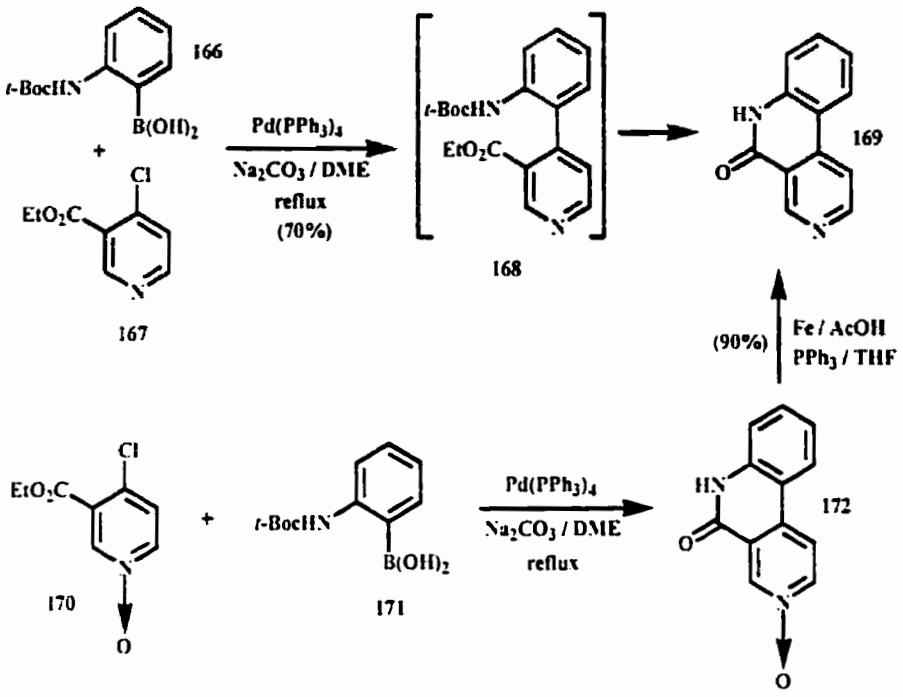
Scheme 54

The Stille reaction has been used in the cross coupling of pyridines for the synthesis of the grossularine (marine alkaloid) framework (Scheme **55**).[98] The groassularine alkaloids exhibit cytotoxic acitivity and thus their synthesis (and analogues) could prove useful in studies of their mode of action and possible pharmaceutical applications. In this synthesis, the polyfunctionalized pyridine, **163** was cross coupled with the aryltin species **162**, a reaction which also shows, not unexpectedly, that the bromo substituent is more reactive than chloro. The Negishi reaction involving a 3-iodopyridine has also been used in the synthesis of benzylisoquinoline alkaloids.[99]



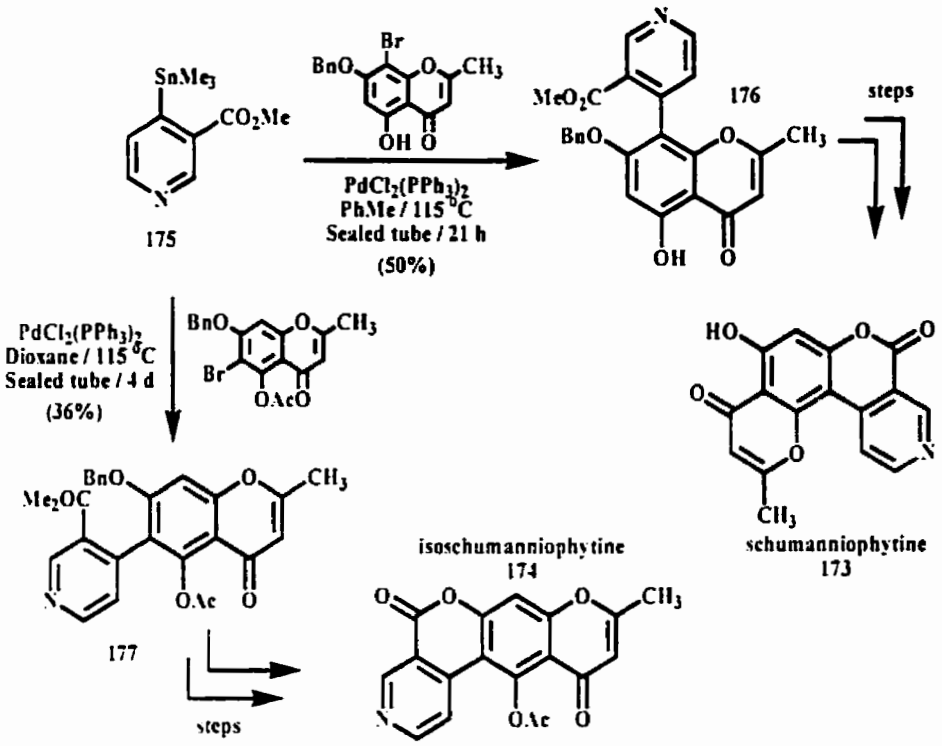
Scheme 55

Cross coupling methods. into the pyridine C-4 position has been demonstrated *via* natural product synthetic targets. Thus. Snieckus and Queguiner have both used a 4-chloropyridine (**167**) and a 4-chloropyridine *N*-oxide (**170**). in the synthesis of a key moiety (**169**) of certain marine alkaloids.[100] Their study employed the Suzuki-Miyaura cross coupling as the key step in the synthesis of the biaryl (**168**) which is not isolated but undergoes cyclization during the reaction to give the benzo[c][6.7]naphthyridinone (**169**. Scheme **56**). The pyridine *N*-oxide **170** also undergoes cross coupling with **171** to give **172** which may be deoxygenated to give **169**.



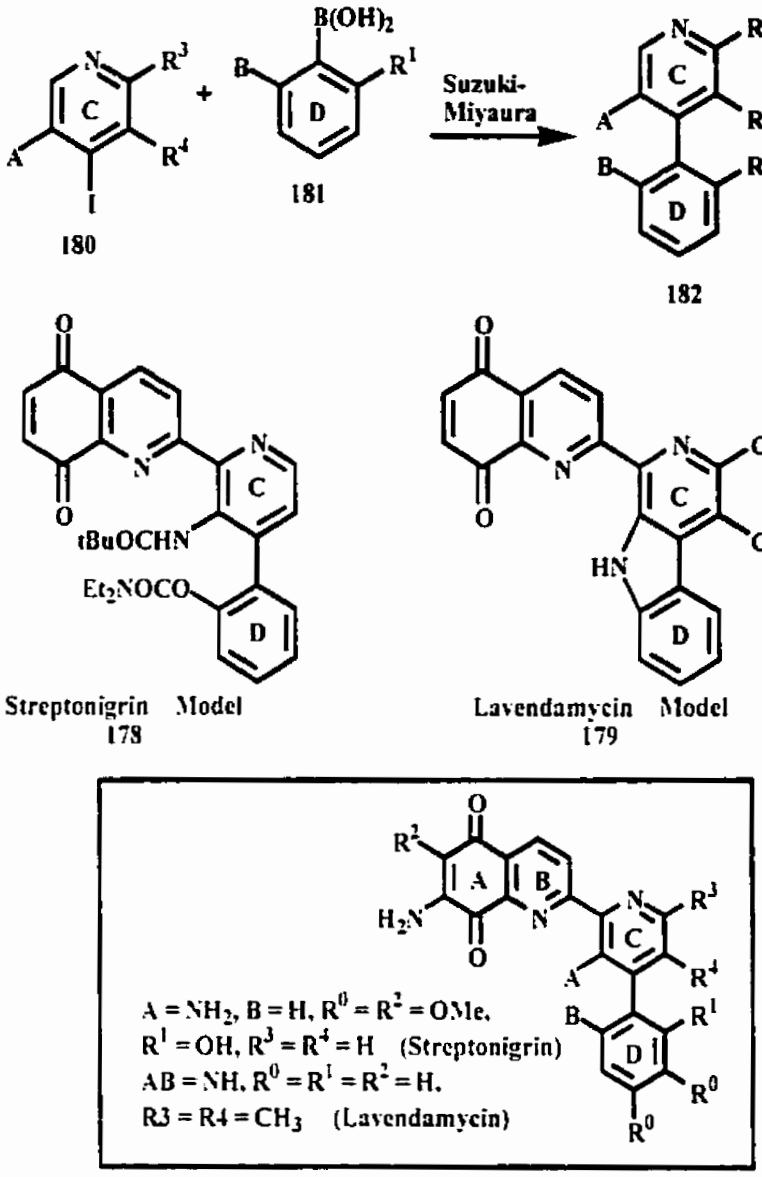
Scheme 56

Kelly and coworkers have used the Stille reaction as a key step in their syntheses of the closely related alkaloids schumanniophytine (**173**) and isoschumanniophytine (**174**) (Scheme **57**).[101] The nicotinic acid derivative **175** acts as a common intermediate for the syntheses of both compounds, derived by metalation techniques. Both of the palladium catalyzed cross couplings proceeded in moderate yields to give **176** and **177**. Subsequent standard steps lead to schumanniophytine and isoschumanniophytine.



Scheme 57

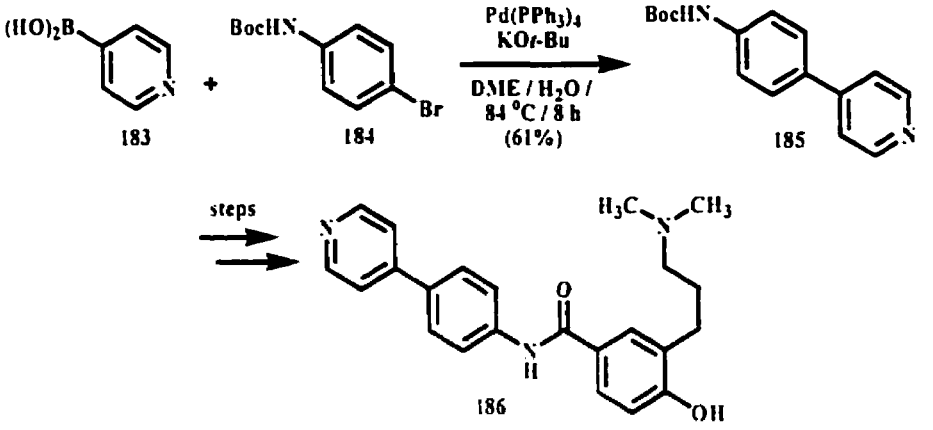
Queguiner and coworkers have combined D*o*M and Suzuki-Miyaura cross coupling methodologies in the synthesis of models for the alkaloids Streptonigrin (**178**) and Lavendamycin (**179**) (Scheme **58**).[102] In their work both the 4-iodopyridine (**180**) and the arylboronic acid (**181**) derivatives were derived from D*o*M chemistry. The Suzuki-Miyaura cross coupling of 180 with 181 gave the C and D ring precursors (**182**) for the model syntheses.



Scheme 58

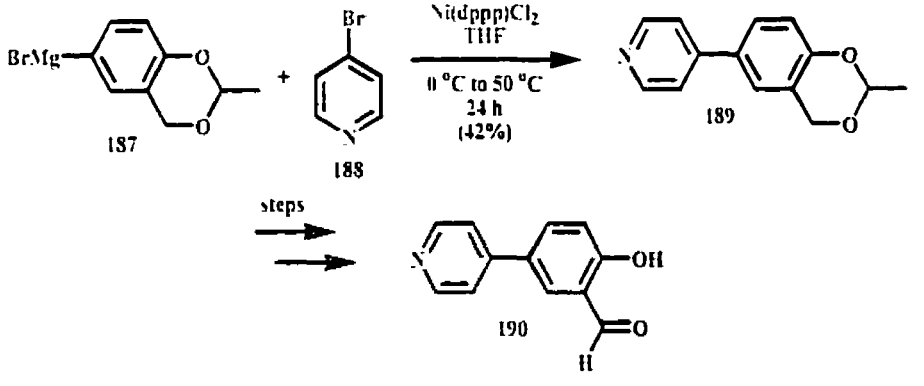
Another example of the Suzuki-Miyaura cross coupling reaction involving a pyridyl boronic acid has been conducted by Halazy and coworkers.[103] Halazy reported the cross coupling of 4-pyridyl boronic acid (**183**) with aryl bromide (**184**) to give **185** in 61% yield (Scheme **59**). This was the key step in the synthesis of compound (**186**) which was used for serotonin receptor studies. This example is quite rare since, for cross

coupling of pyridine systems, the pyridine ring usually contains the leaving group and not the boronic acid.



Scheme 59

Nguyen and coworkers have used a nickel catalyzed reaction (Kumada cross coupling reaction) between 4-bromopyridine (**188**) and aryl grignard (**187**) to give x which was transformed into 5-(4-pyridyl)salicylaldehydes (**190**) (Scheme **60**).[104] This reaction is important as it demonstrates that. normally unstable 4-bromopyridines (as free bases) may be cross coupled. The reason for the synthesis of 190 concerns its application for the construction of cyclic supramolecular structures.



Scheme 60

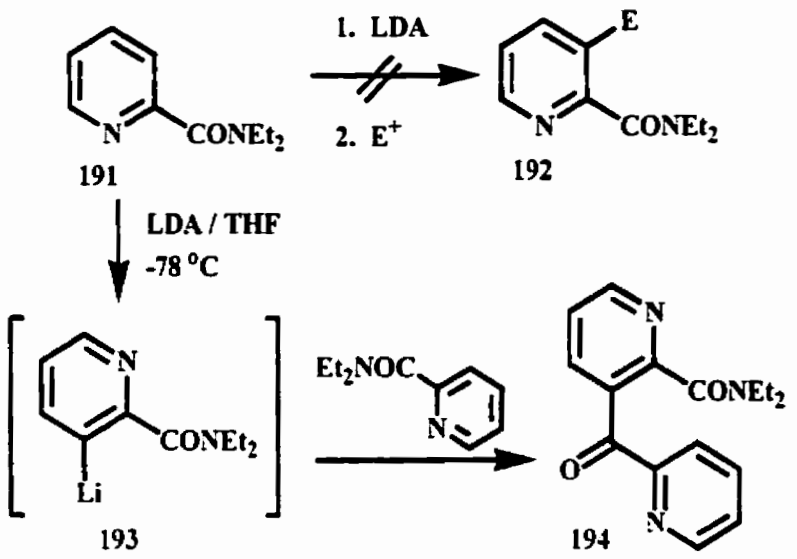
4.0 Results and Discussion

4.1 Goals of Research

The range of commercially available aryl boronic acids[105] is increasing due to the popularity of the Suzuki-Miyauri cross coupling reaction. Pyridyl boronic acids, especially functionalized pyridyl boronic acids, are of limited availability due to difficulties in preparation / isolation by conventional methods. The goal of this research is the development of a new method for the preparation pyridyl boronic acid derivatives and their use in the Suzuki-Miyaura cross coupling reaction.

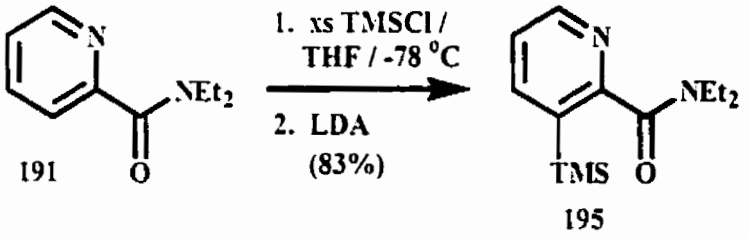
4.2 Conception of Methodology

The DoM of aromatics and heteroaromatics is a central theme in the Snieckus laboratories. As described in Section 3, pyridines containing DMGs are readily metalated and quenched with external electrophiles to give substituted pyridine derivatives. There is, however, a DMG, *N,N*-diethylcarboxamide, that is uncooperative when it comes to standard metalation followed by electrophile quench.[106] Larkin found that treating *N,N*-diethylpicolinamide **191** with LDA at low temperatures, followed by external electrophile quench, does not afford the desired 2,3-disubstituted pyridine, **192** (Scheme **61**), but leads instead to the self-condensed product **194** in high yield.[107] Apparently, incomplete metalation leads to anion **193** which undergoes attack on the amide of the starting material to give **194**.



Scheme 61

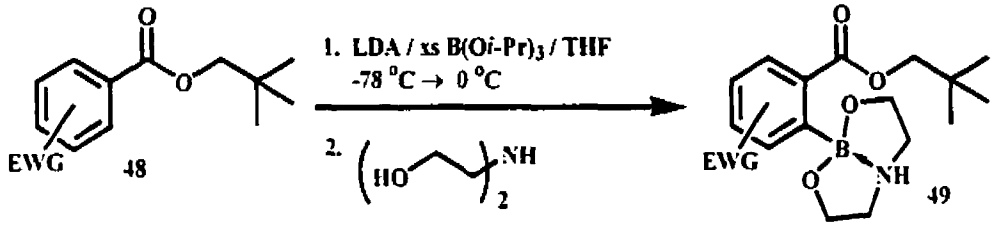
The ideal solution to this problem is to intercept the lithiated species as it is being formed with an electrophile. in other words. an *in situ* quench. This would require an electrophile that is compatible with LDA. Martin demonstrated that TMSCl is compatible with lithium amide bases (LiTMP and LDA) and does function as an *in situ* quench.[55] Larkin found that when a solution of *N,N*-diethylpicolinamide **191** and excess TMSCl was treated with LDA. the 3-silylated product **195** was obtained in excellent yield with no trace of the condensed product being detected (Scheme **62**).[107]



Scheme **62**

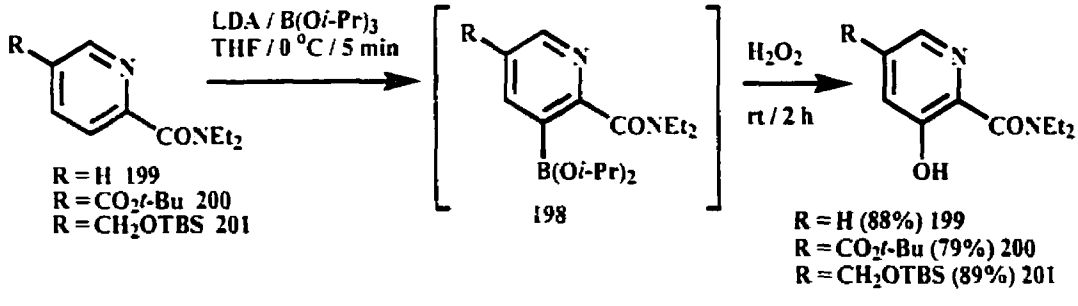
Larkin's motivation behind C-3 functionalization of *N,N*-diethylpicolinamide (**191**) was to obtain a derivative for cross coupling in a projected syntheis of ergot alkaloids.[107] However. attempts to manipulate (*ipso* bromodesilylation) the silyl group of

195 into a group for cross coupling failed. The appearance of the publication of Caron and Hawkins[54] at this time offered a potential solution to this problem. These workers discovered that triisopropylborate was also compatible with LDA and performed nicely as an *in situ* quench for DoM reactions of neopentyl esters **48** to give, after treatment with diethanolamine, borazine products **49** (Scheme **63**).



Scheme 63

With this information in hand, Larkin showed that the in situ metalation of *N,N*-diethylpicolinamide (**191**) in the presence of excess triisopropylborate led, after oxidative workup, to the hydroxy pyridine, **199** (Scheme **64**).[107] The reaction was extended to prepare substituted cases, **200** and **201**. The reaction proceeds *via* intermediate **198** which undergoes a Baeyer-Villiger type oxidation to give the hydroxy compounds **199-201**. Larkin transformed the hydroxypyridines into the corresponding triflates for use as cross coupling partners in studies towards the synthesis of ergot alkaloids.[107]



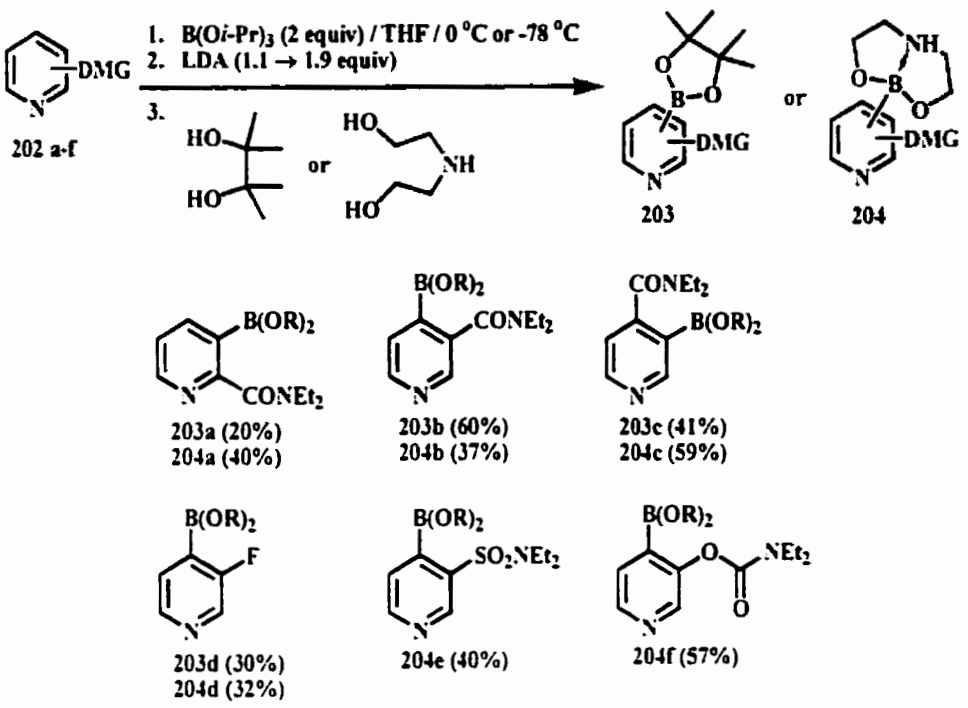
Scheme 64

4.3 General Synthesis of Pyridine Pinacolborolanes and Dioxoazaborocanes by *in situ* DoM Reactions

In view of the success of the above *in situ* DoM reactions (Scheme **64**), a general study of pyridine DMG systems was undertaken. The aim of the research was to provide new methods for the preparation of pyridine boronic acid derivatives as stable pinacolates or diethanolamine adducts and to develop their Suzuki-Miyaura cross coupling chemistry thereby overcoming limitations previously experienced with pyridine boronic acids themselves.

In initial experiments, a mixture of pyridine **202** and triisopropyl borate (2 equiv) in THF was treated with LDA at 0 °C for 15 minutes. Subsequent treatment of the reaction mixture with pinacol or diethanolamine afforded the boronated adducts, **203** and **204**, in moderate yields (Scheme **65**). In the case of the pyridine *O*-carbamate **204f**, the reaction was carried out at –78 °C to avoid anionic ortho Fries rearrangement.

The amount of LDA used was substrate dependant and was determined by monitoring the reaction by TLC. Initially 1 equivalent of LDA was added to the reaction mixture; subsequently 0.1 equivalent portions were added until the starting material was consumed, as indicated by TLC.

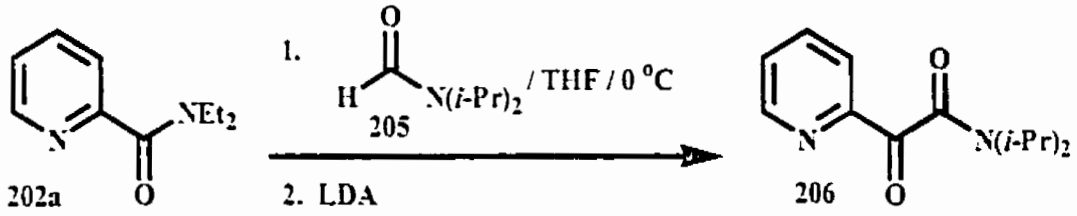


Scheme 65

Previous experience in our laboratories suggested the use of pinacol and diethanolamine derivatives for isolation and purification of the pyridine boronic acids. Thus, the purification of pinacol derivatives of boronic acids by flash column chromatography has been established.[108] However, in the case of **203a-203c** purification of the crude reaction material by flash column chromatography using either silica gel or alumina was unsuccessful. Consequently, all the crude products were purified by recrystallization from dichloromethane/hexanes, a procedure which possibly accounts for some of the lower yields of products. Generally, the diethanolamine derivatives were more crystalline in nature than the corresponding pinacol derivatives. However, the latter have one advantage over the diethanolamine derivatives, in that they may be used directly in Suzuki-Miyuara cross coupling reactions.

For 3-bromo or 3-cyanopyridines, application of the *in situ* quench procedure led to inconclusive results. Running these reactions at –78 °C, instead of 0 °C, did not change the outcome. In each case these reactions gave dark oils which resisted purification. Speculations for these results include pyridyne formation (in the case 3-bromopyridine), and additions (for 3-cyanopyridine, to either the cyano group or the pyridine ring).

As an aside, the use of *N*, *N*-diisopropylformamide (**205**) as an *in situ* electrophile was tested. However, the treatment of a mixture of **202b** and **205** (Scheme **66**) with LDA afforded, instead, product **206**, which is believed to arise from the LDA deprotonation of *N*, *N*-diisopropylformadie followed by diethylamine displacement. A brief literature search showed precedent for this type of reaction.[109] and further investigations were not performed.

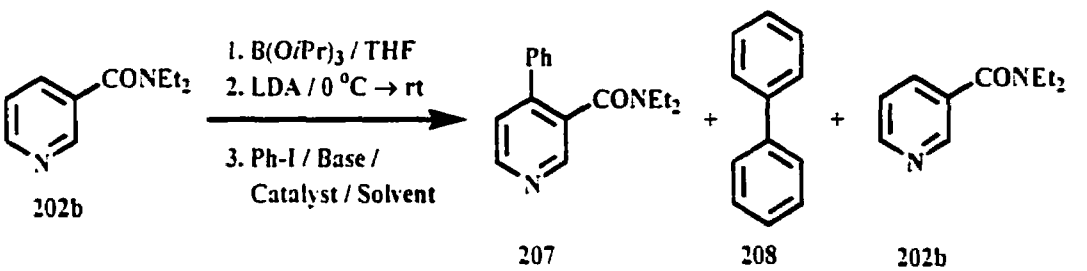


Scheme 66

4.4 Connection to Suzuki-Miyaura Cross Coupling

Having established the *in situ* DoM process for a variety of pyridines (Scheme **65**), its application to the Suzuki-Miyaura cross coupling reaction was pursued. Difficulties in isolation of the pinacolates and diethanolamine adducts in high yields suggested the use of an *in situ* Suzuki-Miyaura cross coupling procedure.

The first set of experiments were performed on the nicotinamide derivative, **202b** (Scheme 67). Initially, **202b** was subjected to metalatation with LDA in the presence of triisopropylborate, and the resultant mixture was concentrated *in vacuo* and the resulting residue was dissolved in toluene. To this solution iodobenzene, $Pd(PPh_3)_4$, and aqueous Na_2CO_3 were added and the reaction mixture was refluxed for 18 h. GC/MS indicated that only a trace amount of the desired product, **207**, together with biphenyl (from homocoupling of iodobenzene), **208**, and protodeboronated material **202b**. Since protodeboronated material **202b** arises from aqueous base hydrolysis.[22] the next set of experiments were conducted under non-aqueous conditions.



202b 207 208 202b

Base	Catalyst	Solvent	207*	208*	202b*
2M Na_2CO_3	$Pd(PPh_3)_4$	$PhCH_3$	trace	✓	✓
K_2CO_3	$Pd(PPh_3)_4$	THF[a]	✗	✓	✓
K_3PO_4	$Pd(PPh_3)_4$	DMF	✗	✓	✓
NEt_3	$Pd(dppf)Cl_2$	DMF	✗	✓	✓

* by GCMS [a] not concentrated after metalation

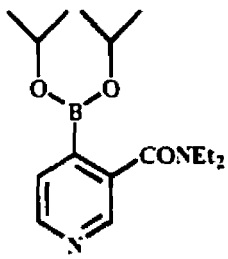
✗ = not present by GCMS ✓ = present by GCMS

Scheme 67

Entries 2, 3, and 4 (Scheme 67) represent attempts at non-aqueous Suzuki-Miyaura cross coupling reactions. In all these cases, no desired product (**207**) was detected and only biphenyl and protodeboronated material were detected by GC/MS.

The protodeboronated product may arise due to presence of water in the bases (not dried before use). Varying the base, catalyst, and solvent had no effect on the outcome of the reaction (see Scheme **67**).

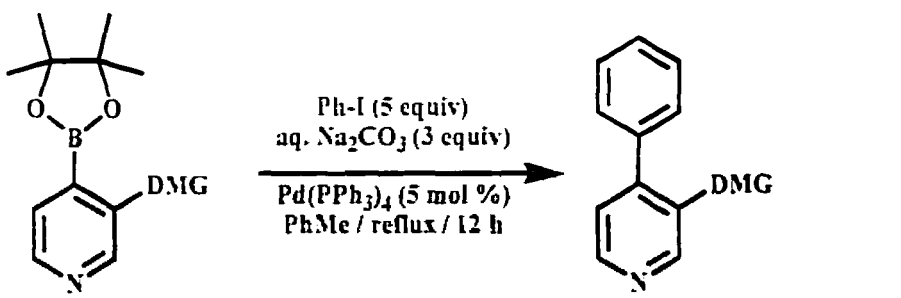
Based on the speculation that the diisopropyl boronate **209** is too hindered to undergo cross coupling, the corresponding pinacolates **210** and **203b** were tested.



209

Scheme **68**

Thus, the pinacol ester of 4-pyridylboronic acid, **210** and the pinacol ester, **203b**, derived from the *in situ* boronation of *N, N*-diethylnicotinamide were subjected to standard Suzuki-Miyaura cross coupling conditions. Gratifyingly, both underwent cross coupling to give **211** and **207** respectively in good yields.



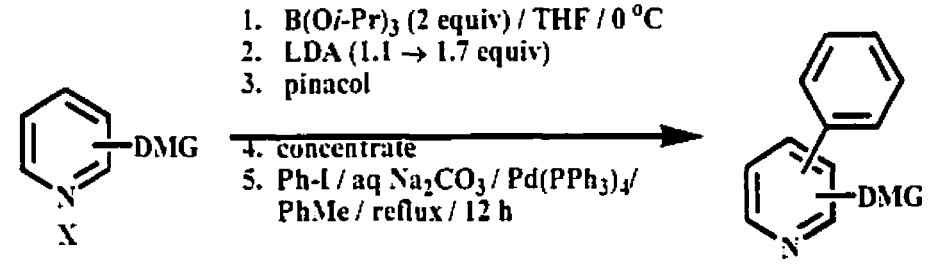
210: DMG = H
203b: DMG = $CONEt_2$

211: DMG = H (65% 4h)
207: DMG = $CONEt_2$ (88%)

Scheme **69**

Encouraged by these results, pinacol treatment was added to the experimental protocol as follows: a mixture of the pyridine substrate and triisopropylborate, in THF, is

treated with LDA until the consumption of the starting material is complete. The reaction mixture is then treated with pinacol and after 15 minutes concentrated *in vacuo*. The resulting crude material is subjected to standard aqueous Suzuki-Miyaura cross coupling conditions. For pyridines **202a-d** and **212**, this protocol performed nicely to give azabiaryls **207**, **213-216** (Scheme 70). On the other hand, the sulfonamide and *O*-carbamate DMGs were uncooperative in this protocol and protodeboronated material and biphenyl were the dominant products (observed by GCMS). It is unclear why these boronated systems did not perform well. Perhaps the troublesome DMGs would perform better in a non-aqueous reaction. However, time restrictions prevented this investigation.

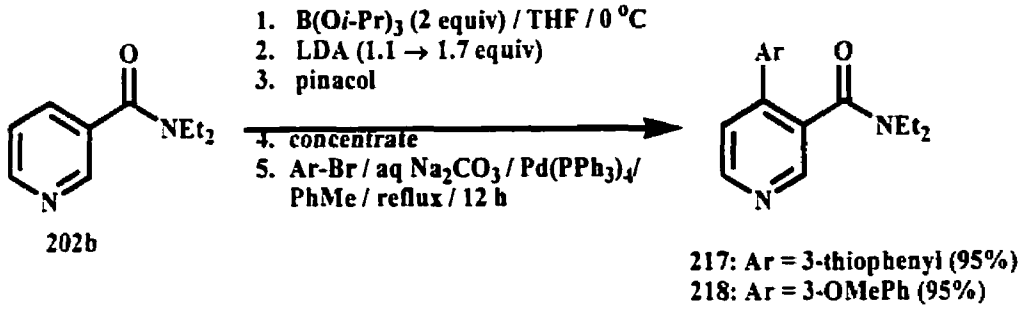


202a: DMG = 2-CONEt$_2$
202b: DMG = 3-CONEt$_2$
202c: DMG = 4-CONEt$_2$
202d: DMG = 3-F
212: DMG = 3-Cl

213: DMG = 2-CONEt$_2$ (95%)
207: DMG = 3-CONEt$_2$ (73%)
214: DMG = 4-CONEt$_2$ (89%)
215: DMG = 3-F (30%)
216: DMG = 3-Cl (63%)

Scheme 70

A preliminary investigation to test the range of cross coupling partners that are tolerated by this protocol was conducted. Thus, *m*-bromoanisole and 3-bromothiophene replaced iodobenzene in the above protocol and both, when cross coupled with *N*, *N*-diethylnicotinamide (**202b**), gave the corresponding biaryl (**217** and **218**) in excellent yields (Scheme 71).


1. B(Oi-Pr)3 (2 equiv) / THF / 0 °C
2. LDA (1.1 → 1.7 equiv)
3. pinacol
4. concentrate
5. Ar-Br / aq Na2CO3 / Pd(PPh3)4/ PhMe / reflux / 12 h
O
NEt2
N
202b
Ar
O
NEt2
N
217: Ar = 3-thiophenyl (95%)
218: Ar = 3-OMePh (95%)

Scheme 71

5.0 Conclusions and Future Work

While the DoM *in situ* boronation method was successful for the production of pyridyl boronic acid derivatives (Scheme **65**), the observed low to moderate yields places a limitation on its synthetic usefulness. The initial results of connecting this methodology to Suzuki-Miyaura cross coupling protocols are encouraging (Scheme **70** and **71**). It is unclear why the sulfonamide and carbamate DMGs were unsuccessful in the *in situ* DoM/Suzuki-Miyaura cross coupling tactic and thus, future work would entail overcoming these failures with alternative cross coupling conditions. Other future work would include expanding the types of cross coupling partners (e.g. bromides, triflates, and hindered cross coupling partners) to test the scope and limitations of this methodology.

6.0 Experimental

6.1 General Procedures

Melting points were determined using a Fisher-Johns hot stage apparatus and are uncorrected. Infrared spectra were determined on a Bomem MB-100 FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-200 instrument in $CDCl_3$ with TMS as the internal reference. ^{1}H NMR were processed at 200 MHz and are tabulated as follows: chemical shift, multiplicity, number of protons, coupling constant. ^{13}C NMR were run at 50 MHz. Flash column chromatography was carried out using Merck silica gel 60 (0.040-0.063 mm). TLC's were Merck 60F-254 precoated silica sheets. Low resolution mass spectra (LRMS) were obtained on a Varian GCMS (CP-3800 GC and Saturn 2000 MS) and high resolution mass spectra were obtained on a Kratos MS890 instrument.

Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl before use. Diisopropylamine was freshly distilled from calcium hydride before use. Toluene was freshly distilled from sodium before use. All other solvents were purchased from Fisher Scientific and were used without further purification. A solution of *n*-BuLi (in hexane) was purchased from Aldrich Chemical Company and titrated regularly against a standard solution of *s*-BuOH (in toluene) with 1,10-phenanthroline as indicator. Reactions carried out at –78 °C and 0 °C employed CO_2/acetone and ice/water baths respectively. All reactions requiring anhydrous conditions were carried out using syringe-septum cap techniques in oven dried glassware under argon atmosphere. LDA

was freshly prepared before use by stirring a 1:1 mixture of diisopropylamine and n-BuLi in THF at 0 °C for fifteen minutes.[110] N, N-diethylpicolinamide, N, N-diethylnicotinamide, N, N-diethylisonicotinamide, and diethyl-carbamic acid pyridin-3-yl ester were generously donated by Andrew Larkin. $Pd(PPh_3)_4$ was prepared according to a literature procedure.[111] All other reagents were purchased from Aldrich Chemical Company and were used without purification.

6.1.1 *in situ* Boronation (Method 1)

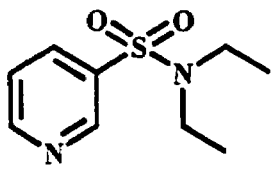
To a stirred, cooled (0 °C) solution of the substituted pyridine (3 mmol) and triisopropylborate (6 mmol), in THF (15 mL, 0.2 M soln), was added, dropwise, a solution of LDA (3 mmol) under an argon atmosphere. Subsequent portions of LDA (0.3 mmol each) were added at 5 min intervals until complete consumption of the starting material was observed by TLC. The resultant mixture was stirred for 15 min at 0 °C, pinacol (6.6 mmol) or diethanolamine (6.6 mmol) (depending on the derivative to be formed) was added, and the reaction mixture was allowed to warm to rt. The resultant mixture was passed through Celite, the Celite was rinsed with dichloromethane (100 mL), and the filtrate was concentrated *in vacuo*. The resultant residue was recrystallized using hexanes/CH_2Cl_2 to give products **203a-d** and **204a-f**.

6.1.2 *in situ* Boronation followed by Suzuki-Miyaura Cross Coupling (Method 2)

To a stirred, cooled (0 °C) solution of the substituted pyridine (3 mmol) and triisopropylborate (6 mmol), in THF (15 mL, 0.2 M soln), was added, dropwise, a solution of LDA (3 mmol) under an argon atmosphere. Subsequent portions of LDA (0.3 mmol each) were added at 5 min intervals until complete consumption of the starting material was observed by TLC. The resultant mixture was stirred for 15 min at 0 °C. pinacol (6.6 mmol) was added. and the whole was concentrated *in vacuo*. The resulting residue was dissolved in toluene (8 mL) to which was added idodbenzene (30 mmol). Na_2CO_3 (7.5 ml of an aq 2M solution, degassed). and $Pd(PPh_3)_4$ (0.15 mmol) under an argon atmosphere. The biphasic mixture was refluxed for 18 h. Upon cooling to rt. a satd solution of NH_4Cl (15 mL) was added. and the whole was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with deionized water (50 mL). brine (50 mL). dried (Na_2SO_4). and concentrated *in vacuo*. Flash column chromatography (hexanes/EtOAc eluent) gave products **207. 213-218.**

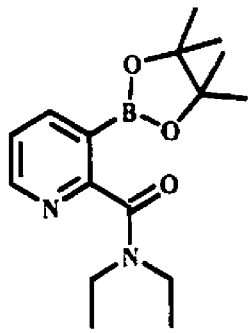
6.2 Specific Experimental Procedures

Pyridine-3-sulfonic acid diethylamide (202e)



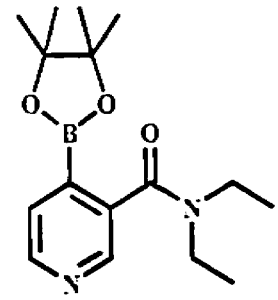
To Mg turnings (3.56 g, 147 mmol) in THF (50 mL) under an atmosphere of argon was added 1,2-dibromoethane (4.0 mL, 46 mmol) dropwise, followed immediately by 3-bromopyridine (98 mmol) dropwise to maintain the reaction mixture at a steady reflux.. The mixture was refluxed for an additional 30 min. cooled and added dropwise to a solution of SO_2Cl_2 (23.5 mL. 293 mmol) in hexanes (500 mL) at 0 °C. Upon completion of the addition. the mixture was evaporated to dryness *in vacuo*. the residue was dissolved in CH_3CN (300 mL). and the whole was cooled to 0 °C. Et_3N (20 mL. 147 mmol) and Et_2NH (15 mL. 147 mmol) were sequentially added and the whole was warmed to rt overnight (16 h). The solvent was removed *in vacuo*. the resulting residue was partitioned between Et_2O and H_2O. and the aqueos layer was extracted with Et_2O (2 x 80 mL). The combined organic layer was washed with 1N HCl. (2 x 50 mL). 10% NaOH (w/w) solution. H_2O. brine. dried (Na_2SO_4). and evaporated to dryness *in vacuo* to give. after chromatography (2:1 hexanes: EtOAc) and distillation (155 °C / 0.2 mm Hg). **202e** as a colourless solid (8.7 g. 42%). ^1H NMR δ = 9.04 (d. 1H. J = 2.2 Hz). 8.80-8.77 (m. 1H). 8.13-8.07 (m. 1H). 7.46 (ddt. 1H. J = 7.4. 4.9. 0.7 Hz). 3.28 (q. 4H. J = 6.9 Hz). 1.15 (t. 6H. J = 6.9 Hz) ppm: ^{13}C NMR δ = 152.5. 147.3. 136.6. 134.2. 123.5. 41.8, 13.8 ppm: LRMS 214 (M+. 4). 199 (100). 142 (89). 78. (100): HRMS calculated for $C_9H_{14}N_2O_2S$: 214.0776: found 214.0777.

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carboxylic acid diethylamide (203a)



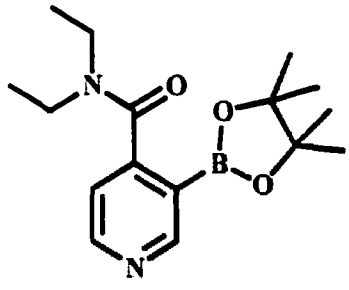
Prepared according to Method 1 using N, N-diethylpicolinamide (2.9 mmol) and LDA (3.5 mmol) to give **203a** as colourless solid (0.1800 g, 20 %), mp 18-80 °C; IR (thin film) ν_{max} 3450, 3042, 2979, 2948, 1627, 1577, 1464, 1379, 1157, 1026, 708 cm^{-1}; ^1H NMR δ = 8.52 (dd, 1H, *J* = 4.81 Hz), 8.01 (dd, 1H, *J* = 7.49), 7.33 (dd, 1H, *J* = 7.63 Hz), 4.35 (q, 2H, *J* = 6.99 Hz), 3.69 (q, 2H, 7.17 Hz), 1.37-1.28 (m, 18H) ppm: ^{13}C NMR δ = 168.9, 153.8, 148.7, 139.7, 125.9, 80.8, 44.7, 43.5, 25.2, 13.9, 12.4 ppm: LRMS 304 (M+, 19), 245 (100), 221 (57), 189 (29), 131 (28), 104 (27), 72 (54): HRMS calculated for $C_{16}H_{25}BN_2O_3$: 304.1958: found 304.1953.

N,N-Diethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinamide (203b)



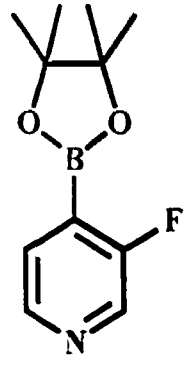
Prepared according to Method 1 using N, N-diethylnicotinamide (2.95 mmol) and LDA (5.6 mmol) to give **203b** as a colourless solid (0.5411 g, 60 %), mp 130-135 °C (sublimation): IR (thin film) ν_{max} 3450, 2979, 2930, 1633, 1464, 1358, 1145, 1032, 732 cm^{-1}; ^1H NMR δ = 8.64 (s, 1H), 8.61 (s, 1H), 3.63 (q, 2H, *J* = 7.14 Hz), 3.36 (q, 2H, *J* = 7.14 Hz), 1.35-1.25 (m, 15H), 1.18 (t, 3H, *J* = 7.14 Hz) ppm: ^{13}C NMR δ = 169.7, 149.8, 146.1, 128.2, 83.7, 43.5, 41.0, 25.0, 13.9, 12.5 ppm; LRMS 304 (M+, 12) 303 (42), 246 (63), 245 (43), 203 (100), 175 (43), 159 (54), 130 (85), 103 (45): HRMS calculated for $C_{16}H_{25}BN_2O_3$: 304.1958: found 304.1958.

N,N-Diethyl-3-(4.4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isonicotinamide (203c)



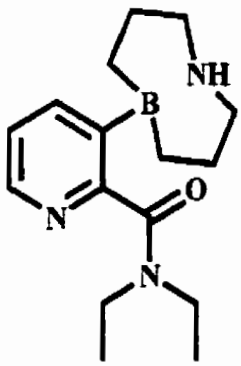
Prepared according to Method 1 using N, N-diethylisonicotinamide (2.9 mmol) and LDA (3.5 mmol) to give **203c** as a colourless solid (0.3638 g, 41 %), mp 47-48 °C; IR (thin film) ν_{max} 2973, 2929, 2854, 2359, 1631, 1458, 1358, 1270, 1164, 1102, 1032, 751 cm^{-1}; ^1H NMR δ = 9.0 (s, 1), 8.69 (d, 1H, *J* = 5.03), 7.17 (d, 1H, *J* = 4.85), 3.56 (q, 4H, *J* = 7.04 Hz), 3.10 (g, 2H, *J* = 7.12 Hz), 1.32-1.28 (m, 15H), 1.04 (t, 3H, *J* = 7.27 Hz) ppm: ^{13}C NMR δ = 209.8, 159.6, 156.4, 120.3, 84.5, 42.9, 39.1, 25.0, 13.8, 12.5 ppm; LRMS 304 (M+, 15) 303 (36), 246 (100), 245 (45), 203 (88), 175 (93), 159 (67), 131 (91), 103 (27); HRMS calculated for $C_{16}H_{25}BN_2O_3$: 304.1958; found 304.1949.

3-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (203d)



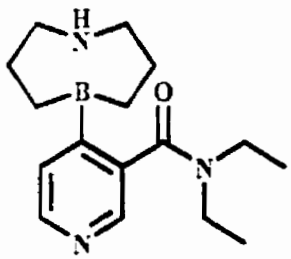
Prepared according to Method 1 using 3-fluoropyridine (3 mmol) and LDA (4.5 mmol) to give **203d** as a colourless solid (0.2028 g, 30 %), mp 110-115 °C (sublimation); IR (thin film) ν_{max} 3399, 3129, 2972, 2930, 2858, 2239, 1475, 1427, 1186, 1150, 1036, 904, 777, 651 cm^{-1}; ^1H NMR δ = 8.47 (bs, 1H), 8.44 (apparent bdd, 1H, *J* = 2.01, 4.80 Hz), 7.60 (apparent bt, 1H, *J* = 4.67 Hz), 1.37 (s, 1H) ppm: ^{13}C NMR δ = 163.1 (d, *J* = 260.16 Hz), 145.2 (d, *J* = 4.58 Hz), 138.4 (d, *J* = 26.70 Hz), 129.8 (d, *J* = 4.58 Hz), 84.9, 25.0 ppm; LRMS 224 (M+1, 100), 223 (M+, 30), 180 (13), 139 (6), 93 (4); HRMS calculated for $C_{11}H_{15}BFNO_2$: 223.1180; found 223.1185.

3-[1,3,6,2]Dioxazaborocan-2-yl-pyridine-2-carboxylic acid diethylamide (204a)



Prepared according to Method 1 using N, N-diethylpicolinamide (2.74 mmol) and LDA (4.7 mmol) to give **204a** as a colourless solid (0.3087 g, 40 %), mp 139-141 °C; IR (thin film) ν_{max} 3407, 2993, 2950, 2883, 2110, 1647, 1598, 1458, 1403, 1220, 1105, 1068, 751, 636 cm^{-1}; ^1H NMR δ = 8.43 (dd, 1H, *J* = 1.72, 4.92 Hz), 8.13 (dd, 1H, *J* = 1.84, 7.51 Hz), 7.23 (m, 1H), 6.40 (bs, 1H), 4.15-3.86 (m, 4H), 3.55 (q, 2H, *J* = 7.13), 3.40-3.30 (m, 2H), 3.20 (q, 2H, *J* = 7.13 Hz), 2.84-2.77 (m, 2H), 1.27 (t, 3H, *J* = 7.13), 1.14 (t, 3H, *J* = 7.13 Hz) ppm; ^{13}C NMR δ = 172.8, 159.0, 147.2, 143.1, 123.1, 63.5, 51.0, 43.6, 39.3, 13.2, 12.9 ppm; LRMS 291 (M+, 2) 260 (2), 218 (4), 178 (18), 149 (13), 114 (25), 78 (16), 72(100); HRMS calculated for $C_{14}H_{22}BN_3O_3$: 291.1754; found 291.1763.

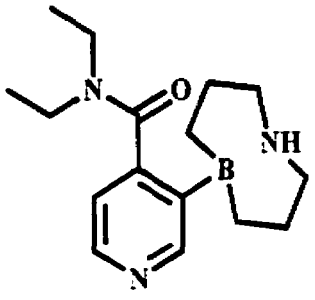
4-[1,3,6,2]Dioxazaborocan-2-yl-N,N-diethyl-nicotinamide (204b)



Prepared according to Method 1 using N, N-diethylnicotinamide (2.92 mmol) and LDA (5.0 mmol) to give **204b** as a colourless solid (0.3069 g, 37 %), mp 132-133 °C; IR (thin film) ν_{max} 3471, 2980, 2943, 2881, 2160, 1638, 1594, 1451, 1277, 1221, 1078, 842, 755, 656 cm^{-1}; ^1H NMR δ = 8.50 (d, 1H, *J* = 4.92 Hz), 8.32 (s, 1H), 7.74 (d, 1H, *J* = 4.67 Hz), 6.29 (bs, 1H), 4.10-3.92 (m, 4H), 3.58-3.48 (m, 4H), 3.23 (q, 2H, *J* = 7.13 Hz), 2.82 (bs, 2H), 1.26 (t, 3H, *J* = 7.14 Hz), 1.12 (t, 3H, *J* = 7.14 Hz) ppm; ^{13}C NMR δ = 173.0, 149.0, 145.0, 137.4, 129.5, 63.6, 51.0, 44.0, 39.1, 13.5,

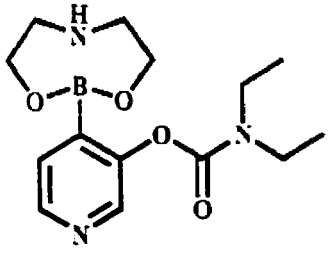
12.9 ppm; LRMS 290 (M-1, 1) 260 (4), 218 (7), 178 (15), 177 (20), 114 (50), 106 (45), 86 (56), 72 (100); HRMS calculated for $C_{14}H_{22}BN_3O_3$: 291.1754; found 291.1755.

3-[1,3,6,2]Dioxazaborocan-2-yl-N,N-diethyl-isonicotinamide (204c)



Prepared according to Method 1 using N, N-diethylisonicotinamide (3.03 mmol) and LDA (4.2 mmol) to give **204c** as a colourless solid (0.5084 g, 59 %), mp 162-164 °C; IR (thin film) ν_{max} 3403, 2991, 2942, 2874, 2118, 1644, 1595, 1460, 1288, 1220, 1066, 839, 636 cm^{-1}; ^1H NMR δ = 8.96 (s, 1H), 8.52 (d, 1H, J = 4.55 Hz), 6.98 (d, 1H, J = 4.48 Hz), 5.98 (bs, 1H), 4.11-3.88 (m, 4H), 3.57-3.17 (m, 6H), 2.88-2.78 (m,2H), 1.24 (t, 3H, J = 7.04), 1.10 (t, 3H, J = 7.04 Hz) ppm; ^{13}C NMR δ = 172.8, 156.1, 149.2, 148.7, 119.2, 63.7, 63.4, 50.9, 43.5, 38.8, 13.3, 12.8 ppm; LRMS 290 (M-1, 1) 260 (8), 218 (10), 178 (34), 177 (30), 114 (100), 107 (61), 106 (46), 72 (93); HRMS calculated for $C_{14}H_{22}BN_3O_3$: 291.1754; found 291.1755.

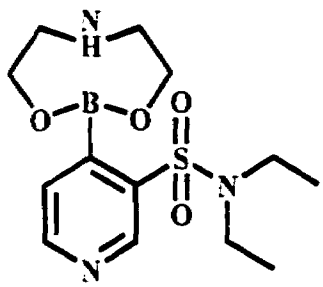
Diethyl-carbamic acid 4-[1,3,6,2]dioxazaborocan-2-yl-pyridin-3-yl ester (204f)



Prepared according to Method 1 (with the exception that the reaction was performed at –78 °C) using Diethyl-carbamic acid pyridin-3-yl ester (2.63 mmol) and LDA (3.2 mmol) to give **204f** as a colourless solid (0.4621 g, 57 %), mp 156-159 °C; IR (thin film) ν_{max} 3380, 2992, 2867, 1690, 1464, 1408, 1277, 1201, 1064, 751 cm^{-1}; ^1H NMR δ = 8.37 (d, 1H, J = 4.68 Hz), 8.16 (s, 1H), 7.64 (d, 1H, J = 4.67 Hz), 6.06

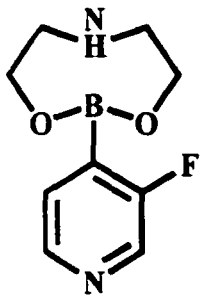
(bs, 1H), 4.17-3.94 (m, 4H), 3.51 (q, 2H, J = 7.13 Hz), 3.39 (q, 2H, J = 7.14 Hz), 3.29-3.12 (m, 2H), 2.89-2.77 (m, 2H), 1.30 (t, 3H, J = 7.14 Hz), 1.22 (t, 3H, J = 7.13 Hz) ppm; ^{13}C NMR δ = 155.8, 151.9, 145.9, 142.9, 129.9, 63.6, 51.0, 42.0, 41.9 ,13.7, 13.4 ppm; LRMS 308 (M+1, 1), 276 (9), 213 (10), 194(11), 189(14), 175 (43), 114(83), 100 (100), 96 (65), 72 (100). HRMS calculated for $C_{14}H_{22}BN_3O_4$: 307.1737; found 307.1725.

4-[1,3,6,2]Dioxazaborocan-2-yl-pyridine-3-sulfonic acid diethylamide (204e)



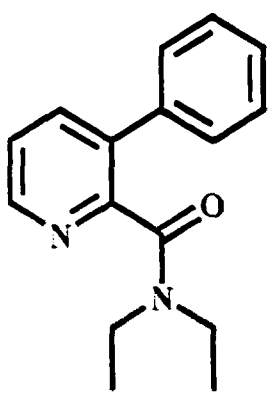
Prepared according to Method 1 using pyridine-3-sulfonic acid diethylamide (2.52 mmol) and LDA (3.3 mmol) to give **204e** as a colourless solid (0.3168 g, 40 %), mp 133-135 °C: IR (thin film) ν_{max} 3385, 2986, 2943, 2882, 2360, 2115, 1673, 1643, 1458, 1317, 1207, 1158, 1066, 937, 851, 783, 679 cm^{-1}; ^{1}H NMR δ = 8.75 (s, 1H), 8.61 (d, 1H, J = 4.92 Hz), 8.02 (d, 1H, J = 4.67 Hz), 6.52 (bs, 1H), 4.19-4.07 (m, 2H), 4.01-3.91 (m, 2H), 3.69-3.37 (m, 6H), 3.00-2.88 (m, 2H), 1.23 (t, 6H, J = 7.14 Hz) ppm; ^{13}C NMR δ = 151.7, 146.6, 139.9, 131.4, 63.2, 51.9, 42.7, 42.3, 14.8, 14.3 ppm; LRMS 328 (M−1, 1) 296 (4), 225 (7), 199 (14), 192 (16) 149 (6), 114 (36), 93 (68), 72(100); HRMS calculated for $C_{13}H_{22}BN_3O_4S$: 296.1240; found 296.1241.

2-(3-Fluoro-pyridin-4-yl)-[1,3,6,2]dioxazaborocane (204d)



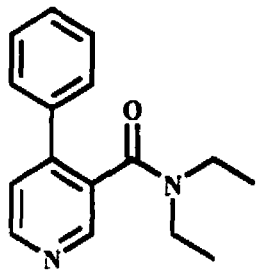
Prepared according to Method 1 using 3-fluoropyridine (3 mmol) and LDA (4.5 mmol) to give **204d** as a colourless solid (0.2042 g, 32 %), mp 133-135 °C; IR (thin film) ν_{max} 3418, 3280, 2973, 2936, 2860, 2247, 2115, 1658, 1402, 1270, 1201, 1032, 820, 763, 625 cm^{-1}; ^1H NMR δ = 8.24 (s, 1H), 8.23 (apparent dd, 1H, J = 2.30 Hz), 7.42 (apparent t, 1H, J = 4.92 Hz), 7.32 (bs, 1H), 3.92-3.68 (m, 4H), 3.26-3.09 (m, 2H), 2.95-2.84 (m, 2H) ppm; ^{13}C NMR δ = 163.3 (d, J = 247.96 Hz), 144.3 (d, J = 3.82 Hz), 136.1 (d, J = 28.22 Hz), 129.0 (d, J = 8.39 Hz), 62.7, 50.7 ppm; LRMS 211 (M+1, 61), 210 (M+, 26), 138 (3), 114 (100), 70 (16); HRMS calculated for $C_9H_{12}BFN_2O_2$: 210.0976; found 210.0979.

3-Phenyl-pyridine-2-carboxylic acid diethylamide (213)



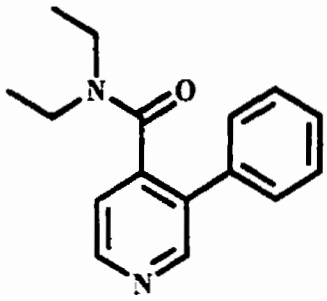
Prepared according to Method 2 using N, N-diethylpicolinamide (3.1 mmol) and LDA (4.7 mmol) to give **213** as a yellow oil (0.7127 g, 90%). IR (thin film) ν_{max} 3433, 3058, 2978, 2874, 2314, 1644, 1564, 1287, 1103, 894, 765, 697 cm^{-1}; ^1H NMR δ = 8.61 (dd, 1H, J = 1.47, 4.68 Hz), 7.77-7.35 (m, 7H), 3.41 (q, 2H, J = 7.13 Hz), 2.88 (q, 2H, J = 7.14 Hz), 0.99 (t, 3H, J = 7.14 Hz), 0.84 (t, 3H, J = 7.13 Hz) ppm; ^{13}C NMR δ = 168.1, 150.3, 149.0, 143.6, 136.3, 133.4, 129.0, 128.8, 128.5, 121.2, 42.4, 38.6, 13.5, 12.1 ppm; LRMS 254 (M+, 2), 253 (3), 183 (7), 182 (13), 154 (31), 127 (33), 77 (14), 72 (100); HRMS calculated for $C_{16}H_{18}N_2O$: 254.1419; found 254.1427.

N,N-Diethyl-4-phenyl-nicotinamide[112] (207)



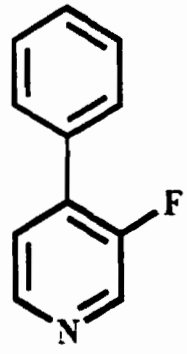
Prepared according to Method 2 using N, N-diethylnicotinamide (3.09 mmol) and LDA (5.9 mmol) to give **207** as a yellow oil (0.5753 g, 73%). Compound X was also prepared as follows: A mixture of N,N-Diethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinamide (**203b**) (0.42 mmol. 0.1266 g), iodobenzene (4.2 mmol. 0.47 mL), Na_2CO_3 (2.1 mmol. of an aq 2M solution. degassed), and $Pd(PPh_3)_4$ (5 mol%. 0.024 g) in freshly distilled toluene was refluxed for 18 h. Upon cooling to rt. a satd solution of NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with deionized water (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography using hexanes/ethyl acetate (1:1) as the solvent system to give **207** as a yellow oil (0.0940 g, 88 %); IR (thin film) ν_{max} 3461, 3054, 2979, 2936, 2879, 1627, 1546, 1452, 1289, 1107, 838, 744 cm^{-1}; ^1H NMR δ = 8.66 (d, 1H, J = 4.92 Hz), 8.61 (s, 1H), 7.55-7.39 (m, 5H), 7.35 (d, 1H, J = 5.17 Hz), 3.75-2.73 (m, 4H), 0.97 (t, 3H, J = 7.13 Hz), 0.75 (t, 3H, J = 7.13 Hz) ppm; ^{13}C NMR δ = 168.1, 150.1, 148.1, 146.0, 137.3, 132.3, 129.2, 128.7, 128.5, 123.6, 42.6, 38.9, 13.6, 12.1 ppm; LRMS 254 (M+, 10), 253 (56), 182 (100), 154 (59), 126 (60), 77 (45); HRMS calculated for $C_{16}H_{18}N_2O$: 254.1419; found 254.1412.

N,N-Diethyl-3-phenyl-isonicotinamide (214)



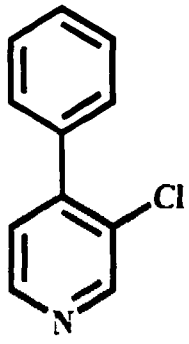
Prepared according to Method 2 using N, N-diethylisonicotinamide (3.07 mmol) and LDA (4.3 mmol) to give **214** as a yellow oil (0.6981 g, 89%); IR (thin film) ν_{max} 3471, 3057, 2983, 2933, 1634, 1461, 1294, 1108, 854 cm^{-1}: ^1H NMR δ = 8.69 (s, 1H), 8.65 (d, 1H, J = 4.92 Hz), 7.53-7.40 (m, 5H), 7.29 (d, 1H, J = 4.92 Hz), 3.73 (bs, 1H), 3.05-2.62 (m, 3h), 0.93 (t, 3H, J = 7.13 Hz), 0.75 (t, 3H, J = 7.14 Hz); ^{13}C NMR δ = 168.1, 150.3, 149.0, 143.6, 136.3, 133.4, 129.0, 128.7, 128.5, 121.2, 42.4, 38.6, 13.5, 12.1 ppm; LRMS 254 (M+, 9), 253 (26), 182 (100), 154 (31), 127 (58), 77 (26); HRMS calculated for $C_{16}H_{18}N_2O$: 254.1419; found 254.1412.

3-Fluoro-4-phenyl-pyridine (215)



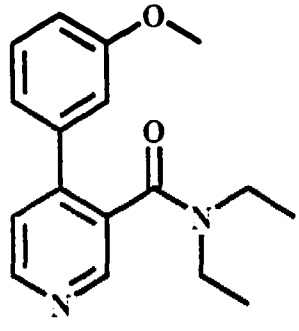
Prepared according to Method 2 using 3-fluoropyridine (3.0 mmol) and LDA (4.5 mmol) to give **215** as a red oil (0.1523 g, 30%). IR (thin film) ν_{max} 3052, 2969, 2927, 2870, 2362, 1600, 1481, 1408, 1263, 1201, 1092, 770, 698 cm^{-1}: ^1H NMR δ = 8.55 –8.50 (m, 2H), 7.51-7.36 (m, 6H); ^{13}C NMR δ = 149.2 (d, J = 204.47 Hz), 136.8 (d, J = 31.96 Hz), 135.4 (d, J = 28.23 Hz), 131.0 (d, J = 3.1 Hz), 130.4, 129.2 (d, J= 6.71 Hz), 127.9, 125.7, 124.4 ppm; LRMS 173 (M+, 100), 146 (13), 125 (8), 77 (3), 74 (4); HRMS calculated for $C_{11}H_8FN$: 173.0641; found 173.0642.

3-Chloro-4-phenyl-pyridine (216)



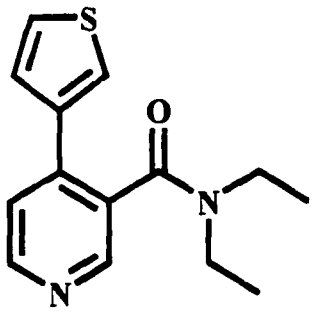
Prepared according to Method 2 (with the exception that the reaction was performed at –78 °C) using 3-chloropyridine (3.0 mmol) and LDA (5.4 mmol) to give **216** as a red oil (0.3530 g, 63%), IR (thin film) ν_{max} 3063, 2970, 2927, 2853, 2361, 1578, 1474, 1406, 1104, 1030, 839, 765, 741, 692 cm^{-1}; ^1H NMR δ = 8.68 (s, 1H), 8.52, (d, 1H, J = 4.92 Hz), 7.46 (m, 5H), 7.26 (d, 1H, J = 5.17 Hz) ppm: ^{13}C NMR δ = 158.1, 153.6, 150.3, 148.1, 146.1, 137.6, 129.1, 128.6, 125.5 ppm; LRMS 191 (m+2, 39), 189 (m+, 100), 154 (44), 127 (35), 102 (4), 77(7); HRMS calculated for $C_{11}H_8ClN$: 189.0345; found 189.0344.

N,N-Diethyl-4-(3-methoxy-phenyl)-nicotinamide (218)



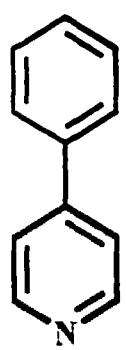
Prepared according to Method 2 (with the exception that the *m*-bromoanisole was substituted for iodobenzene) using N, N-diethylnicotinamide (3.01 mmol) and LDA (5.72 mmol) to give **218** as a yellow oil (0.8131 g, 95%). IR (thin film) ν_{max} 3548, 3031, 2983, 2847, 1636, 1593, 1425, 1284, 1159, 1072, 757 cm^{-1}; ^1H NMR δ = 8.65 (d, 1H, J = 5.16 Hz), 8.60 (s, 1H), 7.38-7.30 (m, 2H), 7.10-7.07 (m, 2H), 6.99-6.93 (m, 1H), 3.83 (s, 3H), 3.12-2.75 (m, 4H), 0.99 (t, 3H, J = 7.14 Hz), 0.77 (t, 3H, J = 7.14 Hz) ppm: ^{13}C NMR δ = 176.4, 168.1, 159.9, 150.1, 148.1, 145.8, 138.6, 129.9, 123.5, 120.9, 114.9, 114.0, 55.4, 42.6, 38.8, 13.6, 12.1 ppm; LRMS 284 (M+, 55), 256 (7), 212 (100), 185 (25), 169 (41), 141 (18), 114 (15), 88 (5); HRMS calculated for $C_{17}H_{20}N_2O_2$: 284.1525; found 284.1515.

N,N-Diethyl-4-thiophen-3-yl-nicotinamide (217)



Prepared according to Method 2 (with the exception that the 3-bromothiophene was substituted for iodobenzene) using N, N-diethylnicotinamide (3.01 mmol) and LDA (5.72 mmol) to give **217** as a yellow oil (0.8133 g, 95%), IR (thin film) ν_{max} 3440, 3096, 2980, 2937, 2875, 2225, 1617, 1599. 1433. 1274, 1188, 1114, 1047, 709 cm^{-1}; ^1H NMR δ = 8.61 (d, 1H, J = 5.16 Hz), 8.55 (s. 1H). 7.63 (m. 1H). 7.40 (m. 2H). 7.31 (m. 1H). 3.75-2.80 (m. 4H). 1.12 (t. 3H. J = 7.14). 0.77 (t. 3H. J = 7.14 Hz) ppm: ^{13}C NMR δ = 168.4. 150.1, 148.0, 140.2, 137.7. 131.4. 127.5. 126.7. 125.5. 122.8. 42.8. 39.1. 13.5. 12.4 ppm: LRMS 260 (M+. 36). 259 (89). 231 (10). 189 (39). 188 (100). 161 (29). 160 (57), 133 (18), 89 (23); HRMS calculated for $C_{14}H_{16}N_2OS$: 260.0983: found 260.0982.

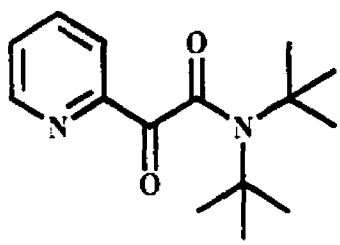
4-Phenyl-pyridine[113] (211)



A mixture of 4-(4.4.5.5-Tetramethyl-[1.3.2]dioxaborolan-2-yl)-pyridine[114] (1.22 mmol. 0.250 g). iodobenzne (6.1 mmol. 0.68 mL). Na_2CO_3 (3.66 mmol of 2M solution in H_2O. degassed) and $Pd(PPh_3)_4$ (5 mol%. 0.071 g) in freshly distilled toluene (3 mL) was refluxed for 4 h under an argon atmosphere. Upon cooling to room temperature a satd solution of NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with deionized water (50 mL), brine (50 mL). dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by flash column chromatography using hexanes/ethyl acetate (1:1) as

the solvent system, to give **211** as a colorless solid (0.1186 g, 64 %), mp 67-68 °C (lit[113] mp 70-72 °C); ^{1}H NMR δ = 8.66 (dd, 2H, *J* = 1.5 and 4.7 Hz), 7.63 (m, 2H), 7.49 (m, 5H) which matched the literature report and the spectra provided by Aldrich Chemical Co.; HRMS calculated for $C_{11}H_9N$: 155.0735; found 155.0734.

N,N-Di-tert-butyl-2-oxo-2-pyridin-2-yl-acetamide (206)



To a stirred cooled (0 °C) solution of N. N-diethylpicolinamide (2.55 mmol, 0.4538 g) and N. N-diisopropylformamide (7.65 mmol), in THF (0.2 M), was added a solution of LDA (3.57 mmol) dropwise under an argon atmosphere. H_2O (15 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layer was washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (hexanes/ethyl acetate (1:1)) to give **206** as a colorless solid (0.3609 g, 60%), mp 114-115 °C; IR (thin film) ν_{max} 3054, 2974, 2938, 1695, 1643, 1582, 1374, 1229, 1138, 999, 749 cm^{-1}; ^{1}H NMR δ = 8.73 (d, 1H, *J* = 4.18 Hz), 8.09 (d, 1H, *J* = 7.88), 7.88 (dt, 1H, *J* = 1.72 and 7.63), 7.50 (m, 1H,), 3.68 (sept, 2H, *J* = 6.65 Hz), 1.58 (d, 6H, *J* = 6.64), 1.21 (d, 6H, *J* = 6.64) ppm; ^{13}C NMR δ = 191.1, 167.7, 151.9, 150.0, 137.2, 127.8, 123.4, 50.5, 46.1, 20.6, 20.5 ppm; LRMS 235 (M+, 60), 191 (100), 149 (9), 128 (34), 106 (19), 86 (23), 78 (25); HRMS calculated for $C_{13}H_{18}N_2O_2$: 234.1447; found 234.1435.

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