THE TERTIARY AMIDE AND CARBAMOYLOXY GROUPS IN AROMATIC DIRECTED METALATION. SYNTHESIS OF POLYSUBSTITUTED BENZENE AND PYRIDINE DERIVATIVES

by

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DEDICATED

TO

MY WIFE AND DAUGHTERS

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ABSTRACT

Chapter I

Ortho-lithiated tertiary benzamides were produced from the reactions of tertiary benzamides and 1:1 s-BuLi-TMEDA complex in THF at -78°C and subjected to transmetalation with $MgBr_2.2Et_2O$ to give Grignard species which (unlike their lithiated precursors) react with aliphatic aldehydes and allyl bromide to give hydroxyalkyl and 2-allylbenzamides derivatives, respectively. 2-hydroxyalkyl derivatives on treatment with p-toluenesulfonic acid monohydrate gave phthalides. 2-allylbenzamides were converted to 3,4-dihydroisocoumarins, including the natural products mellein and kigelin, by treatment with 6M hydrochloric acid. The transmetalation procedure was also briefly explored with lithiated oxazoline and methoxymethoxybenzene.

Chapter II

Ortho-lithiation of N,N-diethyl O-phenyl carbamates, N,N-dimethyl O-phenyl carbamate and N,N-diethyl O-naphthyl-1 and 2-carbamates with 1:1 s-BuLi-TMEDA complex followed by quenching with various electrophiles lead to a variety of polysubstituted aromatic carbamate derivatives. When allowed to warm to room temperature the ortho lithiated species derived from different types of carbamate derivatives underwent 1,3 O --> C carbamoyl migration to give ortho hydroxyamide derivatives. Metalation of isomeric N,N-diethyl O-tolyl carbamates with LDA was also explored. An 1,4 O --> C carbamoyl migration was achieved from the

lithiation of O-2-tolyl carbamate with LDA . A study on the mechanism of the 1,3 O --> C carbamoyl migration was described. A study on the relative ortho directing capability of N,N-diethyl carbamoyloxy group with tertiary amide and methoxymethoxy directing groups in both inter- and intramolecular competition reactions was undertaken. The iterative metalation possibilities on unsubstituted O-phenyl carbamates derivatives were described. A relatively simple and convenient method for the synthesis of 2(3H)-benzofuranone was also described.

Chapter III

N,N-diethyl O-pyridyl-2-carbamate, N,N-diethyl O-pyridyl-3-carbamate and N,N-diethyl O-pyridyl-4-carbamate were subjected to lithiation using 1:1 s-BuLi TMEDA complex in THF at -78°C and the resulting ortho-lithiated species on treatment with different electrophiles afforded a variety of polysubstituted pyridine derivatives. O-pyridyl-2-carbamate gave 2,3-disubstituted products while O-pyridyl-3- and 4-carbamates afforded 3,4-disubstituted products. The metalated species of O-pyridyl-3-carbamate and O-pyridyl-4-carbamates when allowed to warm to room temperature afforded isonicotinamide and nicotinamides derivatives respectively. The iterative metalation possibilities on some contiguously substituted O-pyridyl-3- and 4-carbamates, electrophile-induced ipso destannylation to give iodo and acetyl O-pyridyl carbamates as well as reductive elimination of the carbamate group to afford nicotinamide derivative were also described.

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TABLE OF CONTENTS PAGE

Page

Page

Page

LIST OF TABLES PAGE

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ac	Acetyl
n-BuLi	n-Butyllithium
s-BuLi	s-Butyllithium
t-BuLi	t-Butyllithium
CsF	Cesium Fluoride
CH_2Cl_2	Methylene chloride
DIA	Diisopropylamine
DMF	Dimethylformamide
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
HRMS	High resolution mass spectrum
IR	Infra red
LDA	Lithium diisopropylamide
LiTMP	Lithium tetramethylpiperidide
MeI	Methyl iodide
MeOD	Deutero methanol
$(MeS)_2$	Methyl disulphide
MS	Mass spectrum
NMR	Nuclear magnetic resonance
Py	Pyridine
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMSCl	Chlorotrimethylsilane
TLC	Thin layer chromatography

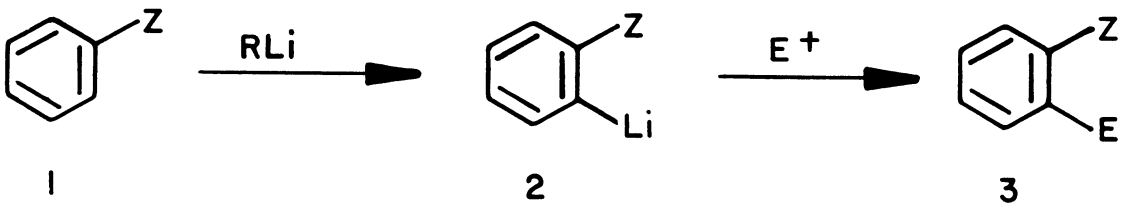
CHAPTER I

1.0 INTRODUCTION

1.1 THE AROMATIC DIRECTED ORTHO METALATION REACTION

The aromatic directed ortho metalation reaction **(Scheme 1)** refers to a class of reactions in which a heteroatom group Z directs the metalating agent, commonly an organolithium base, to deprotonate specifically at the ortho site. The resulting ortho-lithiated species 2 then undergoes

Scheme 1



1 2 3

Z = Directing group

reaction with a variety of electrophiles (E^+) to afford ortho-substituted products **3.**

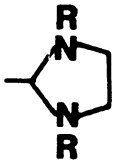
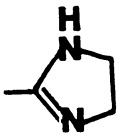
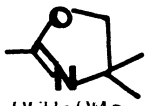
Since the discovery of the prototype of this reaction by Gilman[1] and by Wittig[2], the methodology has been developed further by Gilman[3] and by many other researchers, notably Hauser[4] and Slocum[5] and their respective co-workers. From their work, a number of heteroatom based substituents have been shown to act as effective ortho directors. As a result, the aromatic directed lithiation is becoming recognized for its increasing utility towards the regiospecific synthesis of polysubstituted

aromatics and heteroaromatics.[6]

1.1.1 ORTHO METALATION DIRECTORS

The basic characteristic of an ortho metalation director is that it is a heteroatom or heteroatom-carrying functional group. The extensive list of directing groups[6] is shown in **Table 1** classified according to a qualitative order of relative directing abilities[5, 7, 8, 9, 10].

Table 1: Ortho Metalation Directing Groups

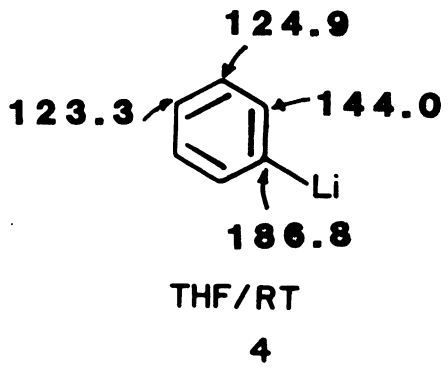
STRONG	MODERATE	WEAK
CONHR	CH_3	$CH(OR)_2$
CSNHR	$N\equiv C$	CH_2OH
$CONR_2$	NR_2	
NHCOR	OMe	
$NHCO_2R$	$OPO(OR)_2$	
$OCONR_2$	SMe	
	F, Cl	
OCH_2OMe	$PO(NR)_2$	
CH=NR		
OCH(Me)OEt		
CH_2NHR		
OTHP		
$(CH_2)_nNR_2$		
n = 1,2		
CN		
SO_2NHR		
SO_2NR_2		
SO_3H		

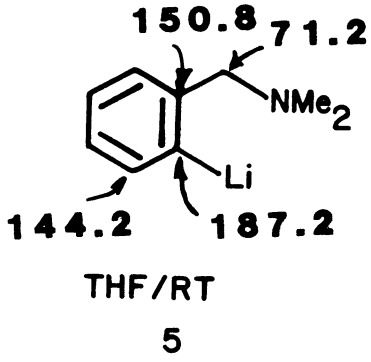
1.1.2 MECHANISTIC CONSIDERATIONS

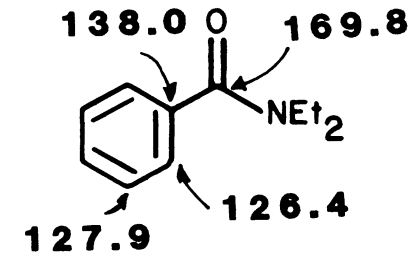
A. STRUCTURES OF LITHIATED SPECIES

To understand the detailed mechanism of ortho lithiation, one should at first establish the structures of the reactive intermediates as well as of the reagents. However, with the exception of a few data provided by X-ray determinations[11] and ^{13}C NMR spectroscopy,[12,13,14,15] little is known about the structures of the ortho lithiated species. Phenyllithium, **4**, complexed with TMEDA, has been reported to be dimeric by X-ray determination.[15] It is also dimeric in Et_2O or in THF solution.[15] The ^{13}C NMR spectrum of phenyllithium was reported by Levy.[12] The X-ray and ^{13}C NMR spectroscopic studies on ortho lithiated N,N-dimethyl benzylamine **5** reveals that it is tetrameric in hydrocarbon solvent and dimeric in THF.[13] Recently, a ^{13}C NMR study on N,N-diethylbenzamide **6** and ortho-lithiated N,N-diethylbenzamide, **7** was carried out by Mills.[14] **Figure 1** shows comparison of selected ^{13}C NMR spectral parameters of **7** with N,N-diethyl benzamide, **6**, phenyllithium, **4** and ortho-lithiated benzylamine **5**.

Figure 1: ^{13}C NMR Spectral Data for Aromatic Organolithiums

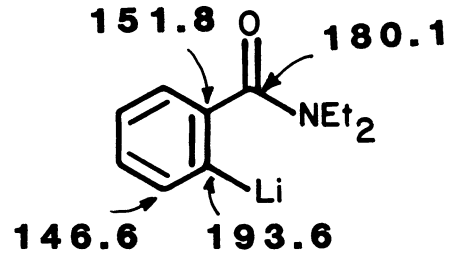






THF/TMEDA/RT

6



THF/TMEDA/s-BuLi/-78°c

7

As expected C-2 in 7 is shifted significantly downfield in comparison to that in 6. Furthermore, the C-2 shift in 7 is of similar magnitude to those observed in compounds 4 [12] and 5. [13] In phenyllithium the excess electron density is in a nonbonding type orbital orthogonal to the -system.[12] It can be tentatively concluded that, in the absence of X-ray data, the negative charge on C-2 in 7 is orthogonal to the -system.

B. ORGANOLITHIUM BASES AND SOLVENTS

Considerable evidence demonstrates that organolithium species are oligomers of varying complexity in different solvents.[6] The degree of aggregation and association of the organolithium bases will in part determine the regioselectivity and the extent of deprotonation.[16] Organolithiums become kinetically more basic as the aggregate size diminishes.[6] Therefore in the case of donor solvent association with solvent molecules or TMEDA increases the carbanionic nature of these species and hence their reactivity. Information on three commonly used alkyllithiums will be summarized.

n-Butyllithium. n-BuLi is known to be hexameric in hydrocarbon

solvent[17] but becomes a monomeric 1:1 complex with TMEDA in the same solvent.[18] However, n-BuLi has been established to be trameric in Et_2O, THF and THF containing TMEDA. At low temperatures, these tetramers exist in equilibrium with dimers as shown by ^{13}C NMR.[19]

s-Butyllithium. s-BuLi has been reported recently to exist as a mixture of dimer, tetramer and hexamer in hydrocarbon solvent with increasing concentration of hexamer at lower temperature.[20] At -50°C it forms a 1:1 complex with TMEDA which when warmed to -20°C, equilibrates to a 1:2 complex with TMEDA.[21]

t-Butyllithium. t-BuLi is tetrameric in hydrocarbon solvent,[17] but in THF, it forms a 2:1 complex with an associated THF molecule.[22]

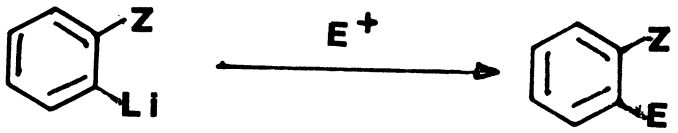
C. THE DIRECTED ORTHO METALATION GROUP

The directing group which usually contains one or more heteroatoms is assumed[6] to play three major roles in the metalation reaction sequence: a) anchoring the base through the coordination of the non-bonding electrons of one of its heteroatoms.[23] This primary anchoring is an important consideration in predicting regioselectivity of deprotonation according to the strength of the complex formation when more than one directing group is present; b) provides an inductive electron withdrawing effect which enhances the acidity of the ortho proton to be abstracted thereby facilitating the subsequent deprotonation step; c) stabilizes the ortho metalated intermediate through chelation.

1.1.3. REACTIONS OF ORTHO LITHIATED SPECIES WITH ELECTROPHILES

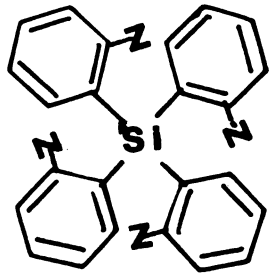
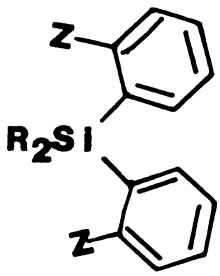
The broad utility of the directed ortho lithiation reaction is dependent largely on the range of electrophiles which can be introduced. **Table 2** lists some of the most commonly used electrophiles and the corresponding substituted products they provide. This list is based on the review by Gschwend and Rodriguez.[6]

Table 2: Electrophiles Which Undergo Reaction with Ortho Lithiated Species.



E^+	E
CF_3COCF_3	$C(CF_3)_2OH$
R_1COR_2	$C(OH)R_1R_2$
Epoxides	$CH(R_1)CH(R_2)OH$
ArCOR	C(OH)(R)(Ar)
ArCOAr	$C(Ar)_2OH$
$CO_2(H_3O^+)$	CO_2H
nRX, X=I,Br	R
$ArCN(H_3O^+)$	COAr
$ArCON(CH_3)_2$	COAr
$ArCO_2Li$	COAr
$RCON(CH_3)_2$	COR

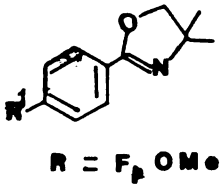
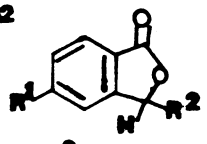
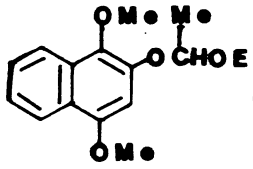
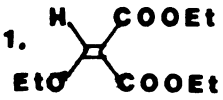
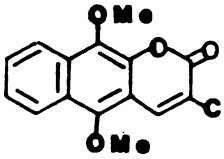
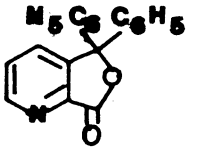
RCN	COR
RCO_2Li	COR
DMF	CHO
ArCHO	CH(Ar)OH
$ClCONR_2$	$CONR_2$
PhNCO	CONHPh
RNCO	CONHR
FSO_2OMe	Me
CF_2CCl_2	$CFCCl_2$
$(SCN)_2$	CN, SCN
AcCl	Ac
Ac_2O ($MgBr_2$)	Ac
$ClCH_2OCH_3$	CH_2OCH_3
$(CH_3O)_2SO_2$	CH_3
$ClCH_2NR_2$	CH_2NR_2
PhCOCl	COPh
CH_2O	CH_2OH
RNCS	CSNHR
$ClCO_2R$	CO_2R
CH_2=CHCHO	$CH(OH)$=CH_2
Heteroatom Based:	
D_2O	D
ROD	D
S	SH

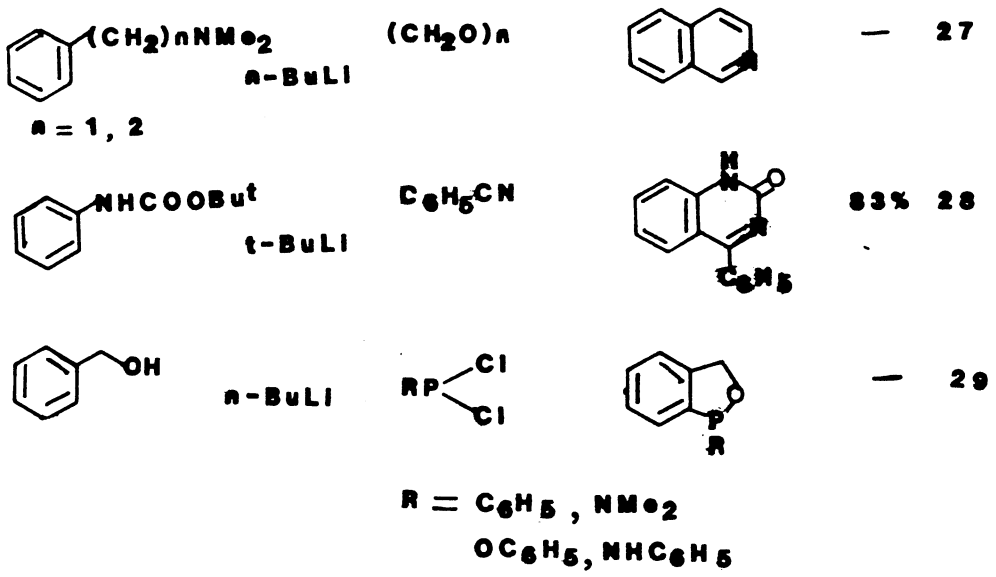
$(R_2S)_2$ R=Me, Ph	SR
$PhSO_2F$	SO_2Ph
$ArSO_2Br$	Br
Br_2	Br
$Me_2CBrCBrMe_2$	Br
BrCN	Br
$BrCH_2CH_2Br$	Br
$ArSO_2Cl$	Cl
CCl_3CCl_3	Cl
N-Chlorosuccinimide	Cl
I_2	I
CH_2I_2	I
ICN	I
$(CH_3O)_3B$	$B(OMe)_2$
$(CH_3O)_3B$, (H_2O_2)	OH
O_2	OH
R_3SiCl, R=Me,Ph	SiR_3
CH_3ONH_2	NH_2
$SiCl_4$	 (product)
R_2SiCl_2, R = Me, Ph	 (product)

1.1.4. RECENT APPLICATIONS OF DIRECTED METALATION REACTION

The directed metalation methodology has become a routine tool for the regiospecific preparations of polysubstituted aromatic derivatives. A few examples are given below to demonstrate the utility of the methodology (Table 3).

Table 3: Synthetic Applications of Aromatic Directed Lithiation Reaction

Starting Material	Lithiation Condition	Electrophiles	Product/intermediate Product	Yield,%	Ref.
 R = F, OMe	n-BuLi	1. $HCOR^2$ 2. H_3O^+	 R^2 = 1-naphthyl, 2-naphthyl	78-82%	24
	n-BuLi	1.  2. H^+		41%	25
	LDA	$(C_6H_5)_2CO$		43%	26



1.1.5. THE SIGNIFICANCE OF THE ORTHO METALATION REACTION

The importance of the directed ortho metalation process lies in its excellent capability for the regioselective synthesis of carbon and hetero-atom based 1,2-disubstituted aromatic derivatives which are invariably difficult to prepare by classical electrophilic aromatic substitution chemistry. The latter class of reactions are usually non-regioselective, require harsh conditions and lack flexibility in terms of potential electrophiles which can be introduced. Ortho, para-directing groups lead predominantly to p-substituted products. This problem of regioselectivity is of course enhanced by the presence of more than one substituent on the aromatic ring.

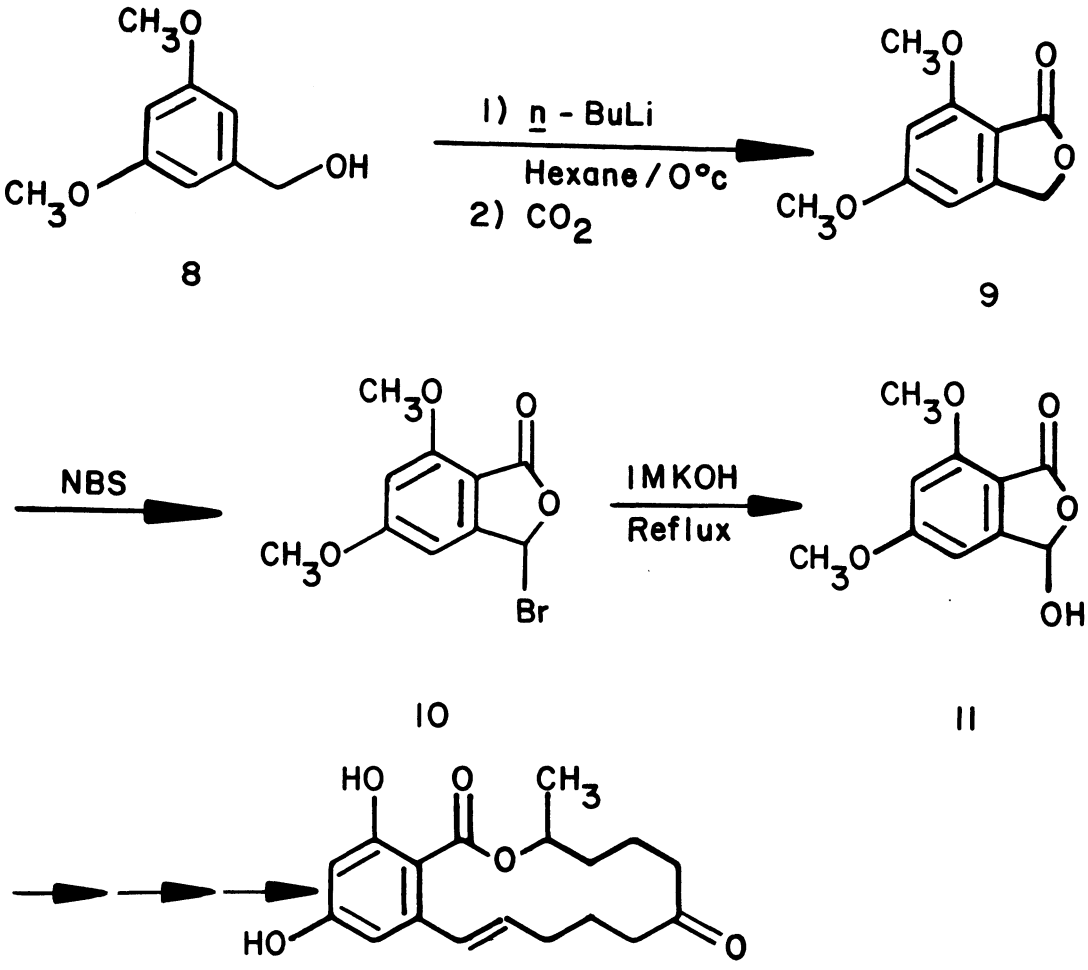
In contrast, in the directed lithiation reaction, metalation can be achieved regioselectively ortho to a directing group (EWG or EDG) in the presence of a number of other groups with the provision that these must be unreactive to the strong alkyllithium bases.

There are some other methods[8] of interest, namely sigmatropic rearrangements, ipso electrophilic substitution, nucleophilic aromatic substitution, cycloaddition reactions of suitably substituted non aromatics followed by aromatization, carbanionic cyclization, which are also used for the preparation of ortho-disubstituted aromatic derivatives. However, these methods lack the same scope and general utility as the directed ortho metalation reaction.

The directed metalation methodology may be highly commended for its efficiency and wide applicability in the regiospecific synthesis of 1,2-disubstituted aromatics. This may be demonstrated by the following examples:

(a) Compound **11**, an intermediate for zealeranone (zearalenone), **12**, synthesis, was prepared from compound 8 by a three-step sequence in 86% overall yield[30] **(Scheme 2)**. This compares very favorably with the earlier classical six-step preparation of 9% overall yield.

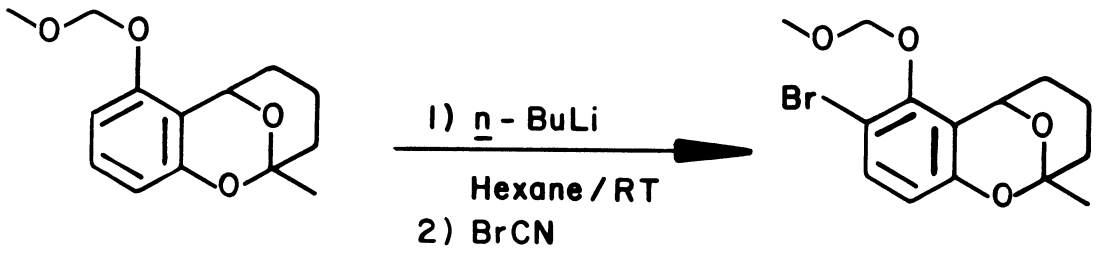
Scheme 2



8 9 10 11 12

(b) Compound **14** is a potential intermediate for the synthesis of (±)-averufin,[31] which in turn is a central intermediate in aflatoxin biosynthesis. Using directed metalation, **14** was prepared from **13** in 95% yield. All attempts to prepare **14** by classical methods were unsuccessful (Scheme 3).[31]

Scheme 3



13 14

1.1.6. TRANSMETALATION

Transmetalation (interconversion of one organometallic to another) is probably the most general method for preparing those organometallics that are either impossible or difficult to obtain directly from organic compounds (eqn. 1).

$$RM + M'X \longrightarrow RM' + MX \qquad (1)$$

For a reaction to proceed in a forward direction, M should be more electropositive than M'. However, in cases where M' is more electropositive than M, it is still possible to produce an equilibrium concentrations of RM' and use it in a desired reaction.[32]

Organolithiums and Grignard reagents are highly electropositive and, therefore, have been used most extensively as parent organometallics (RM). Organometallics of all metals that are more electronegative than lithium and magnesium are commonly prepared by transmetalation.[32]

Selective reactivity of many common electrophilic functional groups may be mediated by choice of metal of the organometallic reagent. Some examples of preparation and utility of RM reagents (R = aryl) obtained via transmetalation are presented below.

A. ORGANOZINC COMPOUNDS

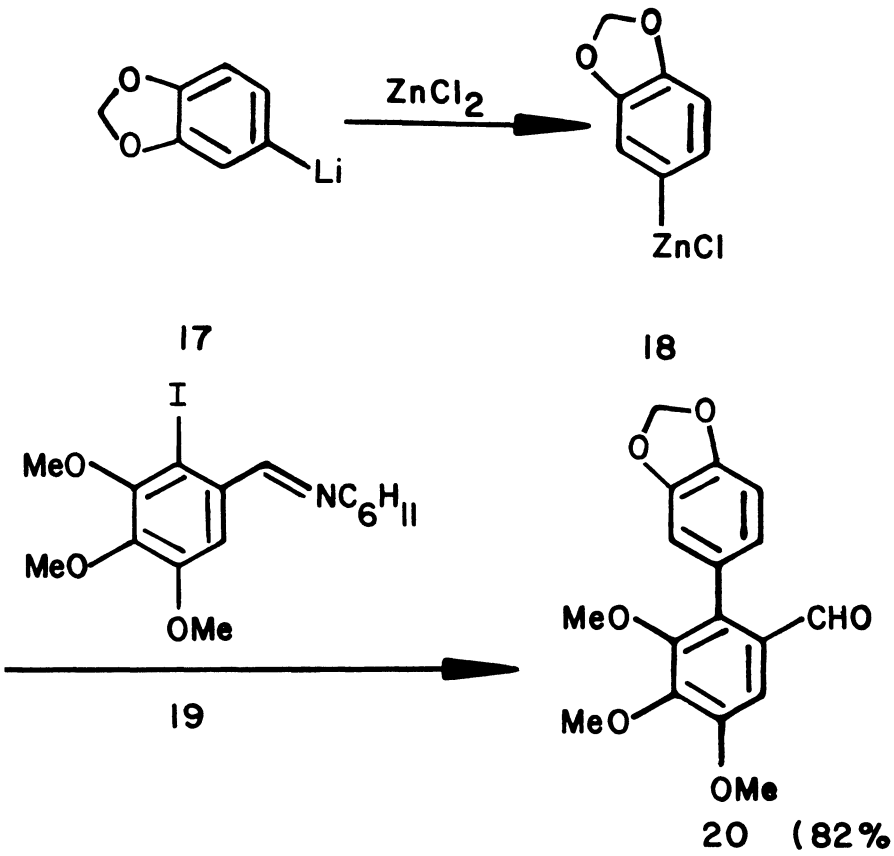
Negishi[33] reported the preparation of arylzinc compounds, **15**, by the transmetalation of the corresponding aryllithiums with zinc halides and used these for the synthesis of biaryls and diaryl methanes **16**, by the nickel or palladium catalyzed coupling reaction with aryl halides (eqn 2).

$$RLi \xrightarrow{ZnX_2} \underset{\mathbf{15}}{RZnx} + Arx' \xrightarrow[\text{or } Cl_2Pd(PPh_3)_2]{Ni(PPh_3)_4} \underset{\mathbf{16}}{R - Ar} \quad 85\text{-}95\% \qquad (2)$$

$R = Ar, ArCH_2$; $X = Cl, Br$; $X' = Br, I$

Raphael[34] prepared compound **20** by the coupling of arylzinc chloride, **18** with **19**. Compound **18** was prepared by ZnCl transmetalation of organolithium **17** which in turn, is available by metal-halogen exchange (n-BuLi/THF/-78°C) of 3,4-methylenedioxy bromobenzene **(Scheme 4)**.

Scheme 4



Arylacetic ethyl esters, **21**, were prepared by the reaction of arylzinc chlorides (prepared by ArLi + $ZnCl_2$) with ethyl bromoacetate in presence of a nickel (II) catalyst[35] (eqn. 3).

$$ArZnCl + BrCH_2CO_2Et \xrightarrow{Ni(II)} \underset{38\text{-}60\%}{ArCH_2CO_2Et} \qquad (3)$$

21

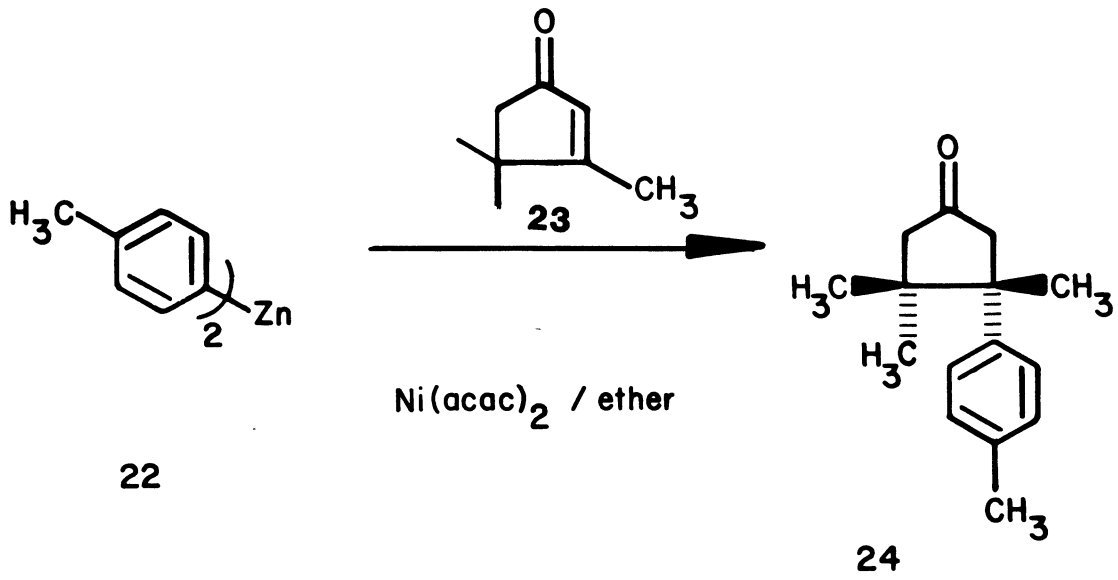
Ar = 

R = H, o-OCH_3, o-CH_3 X = O, S, Se

Other methods[36] are less attractive due to high reaction temperatures and long reaction times.

Greene[37] prepared β-cuparenone, **24**, by the nickel acetylacetonate catalyzed conjugate addition of di-p-tolylzinc, **22**, to trimethylcyclopentenone, **23**, **(Scheme 5)**, compound 22 may be prepared easily (Li, $p\text{-}CH_3C_6H_4Br, ZnBr_2$, ether, ultrasonic irradiation),

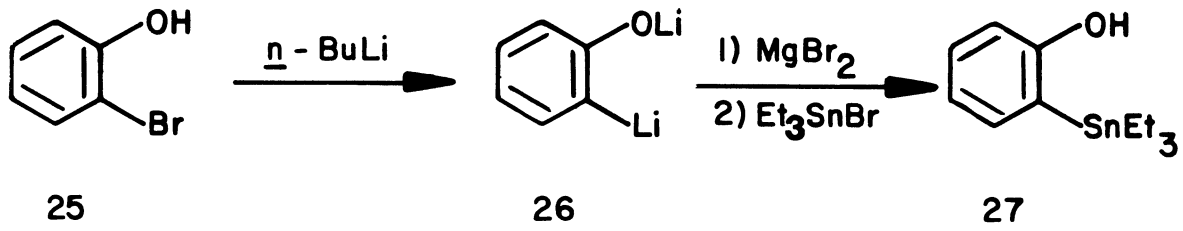
Scheme 5



B. GRIGNARD REAGENTS

Conversion of organolithium compounds to Grignard reagents is perhaps the most widely used transmetalation process. The first example of conversion of an organolithium compound to a Grignard reagent is due to Gilman[38] **(Scheme 6).**

Scheme 6

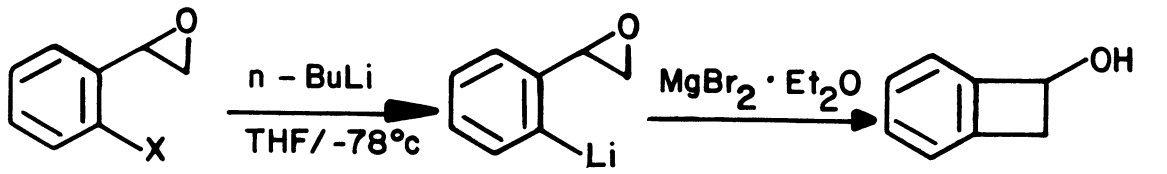


25 26 27

Recent applications of this transmetalation include:

Mg for Li transmetalation was used for the preparation of benzocyclobutanol , 30, from α-halostyrene oxide, 28[39] by Durst and coworkers (Scheme 7).

Scheme 7



X = Br, I

35 - 85 %

28 29 30

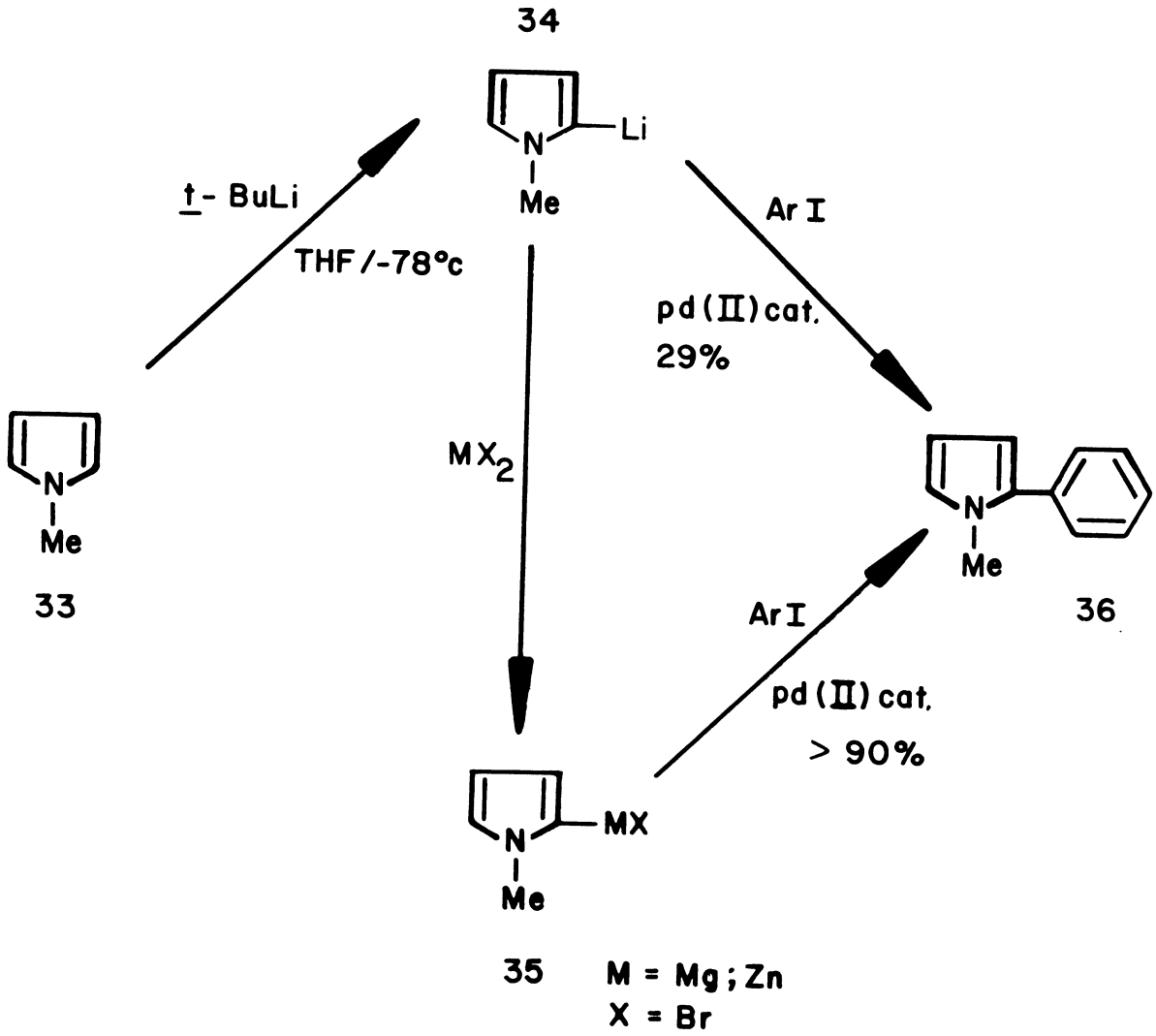
Trost[40] used Mg for Li transmetalation reaction for the amination of aromatics where the corresponding organolithium species failed to react with the amination reagent, azidomethyl phenyl sulfide (eqn. 4).

$$ArLi \xrightarrow[2/PhSCH_2N_3]{1/MgBr_2} \longrightarrow ArNH_2 \qquad (4)$$

31 32

Kumada[41] reported a dramatic increase in yields of the arylated and heteroarylated products, **36**, by the transmetalation of the lithiated heterocycles, **34**, to either Grignard or to organozinc intermediates, **35** (Scheme 8).

Scheme 8

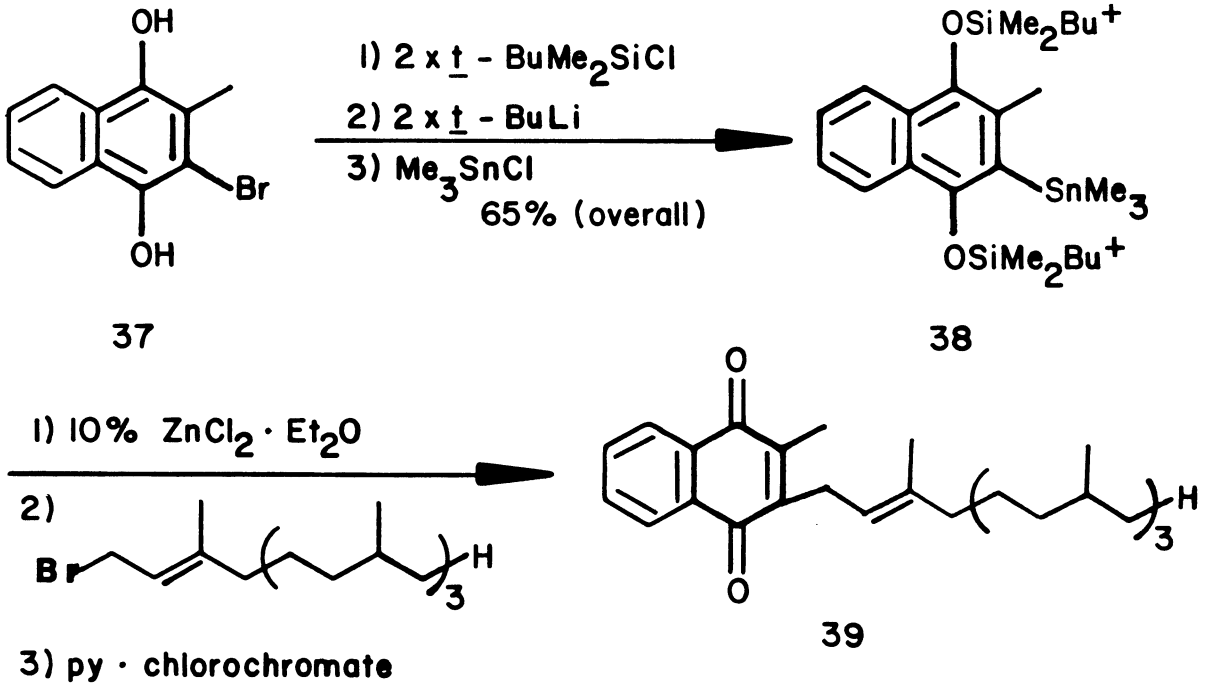


Also Ar = C_6H_5Br, 3-Bromothiophene, 2- and 3-Bromopyridine; Yields: 66-87%.

C. ORGANOTIN COMPOUNDS

Stille[42] recently reported the preparation of the tin naphthalene derivative **38** from bromonaphthalene, **37** via an intermediate aryl lithium species **(Scheme 9).** Compound **38** was used for the synthesis of vitamin K **(39)** as shown.

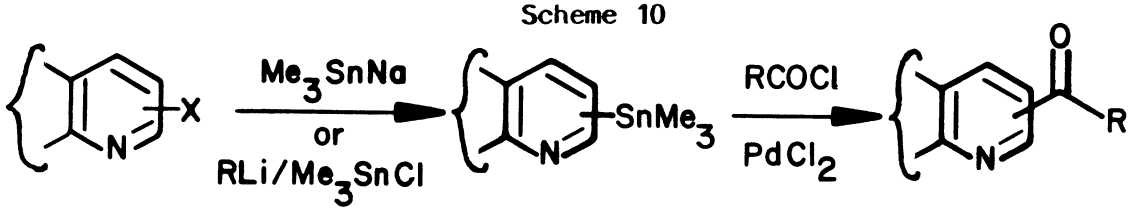
Scheme 9



37 **38** **39**

An example of carbon-carbon bond formation via $PdCl_2$ catalyzed acylation of tin heteroaromatics **40** has been reported[43] **(Scheme 10).**

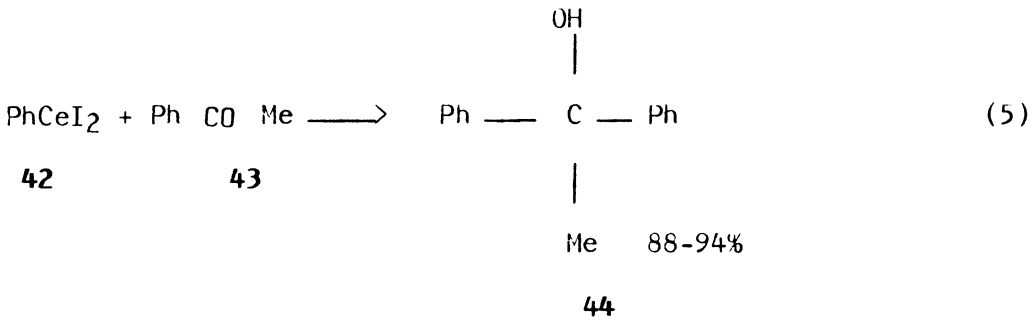
Scheme 10



40 **41**

D. ORGANOCERIUM COMPOUNDS

Organocerium reagents **42**, available by transmetalation of an organolithium reagent with cerium iodide, undergo nucleophilic addition even to the easily enolizable ketone **43** (eqn. 5).[44]



42 **43** **44** (5)

1.2 RESULTS AND DISCUSSION

1.2.1 TRANSMETALATION OF ORTHO LITHIATED TERTIARY BENZAMIDES TO ORTHO-MgBr SPECIES

Studies in our laboratory[8,45] and by other researchers[5,7,9,10,45,47] demonstrated that the N,N-diethyl carboxamide group on an aromatic ring is a powerful ortho director. Since the initial report by Beak[48] that N,N-diethylbenzamide could be smoothly and effectively ortho lithiated, our laboratory has been engaged in systematic exploration of ortho-lithiated benzamides for the efficient preparation of contiguously polysubstituted aromatics and for the application of the derived methodology towards the synthesis of condensed aromatic and heteroaromatic systems, including anthraquinones, anthracyclines, benzylisoquinoline, phthalide isoquinoline and phenanthroquinolizidine and phenanthroindolizidine alkaloids and other natural and unnatural products.[8,49]

Although a diverse variety of electrophiles **(Table 2)** could be introduced by reaction with ortho-lithiated benzamides, it was found that allyl bromides, aliphatic aldehydes, pyridine-2-aldehyde, ethyl acetate, ethylene oxide and benzonitrile failed to give ortho-substituted products.[47,50]

The o-lithiated N,N-diisopropylbenzamide when treated with allyl bromide was found to undergo a metal-halogen exchange reaction yielding N,N-diisopropyl o-bromobenzamide rather than the o-allylated product.[47] In the case of aliphatic aldehydes[47] and pyridine-2-aldehyde[50], no products were identified.

Encouraged by the transmetalation methodology literature (Section 1.1.6), we explored lithium to magnesium transmetalation and achieved successful coupling with allyl bromide, aliphatic aldehydes, and pyridine-2-aldehyde using this procedure.[51] The failure of the lithioamide and the success of the Grignard species may be rationalized in terms of hard and soft acid-base theory.[52] The lithiated amide is a relatively hard base and hence cannot react with moderately softer electrophilic reagents such as allyl bromide. Ultimately, a metal-halogen exchange occurs. On the other hand, the Grignard species is a relatively softer base than the lithio counterpart and reacts satisfactorily with allyl bromide. For Grignard reagents, Halogen-metal exchange is not a facile rection. Similarly, aliphatic aldehydes having an acidic α-hydrogen react with the hard lithioamide thereby producing an enolate which in turn may undergo aldol condensations to give polymeric product. However, the magnesio species is a softer base thereby reacting successfully at the carbonyl group producing hydroxyalkylamide derivatives. This explanation parallels the report that phenyllithium abstracts α-hydrogen from acetophenone giving a mixture of enolate and carbinolate in a ratio of 1:23 whereas the corresponding Grignard reagent affords the same mixture in a ratio of 1:∞.[53]

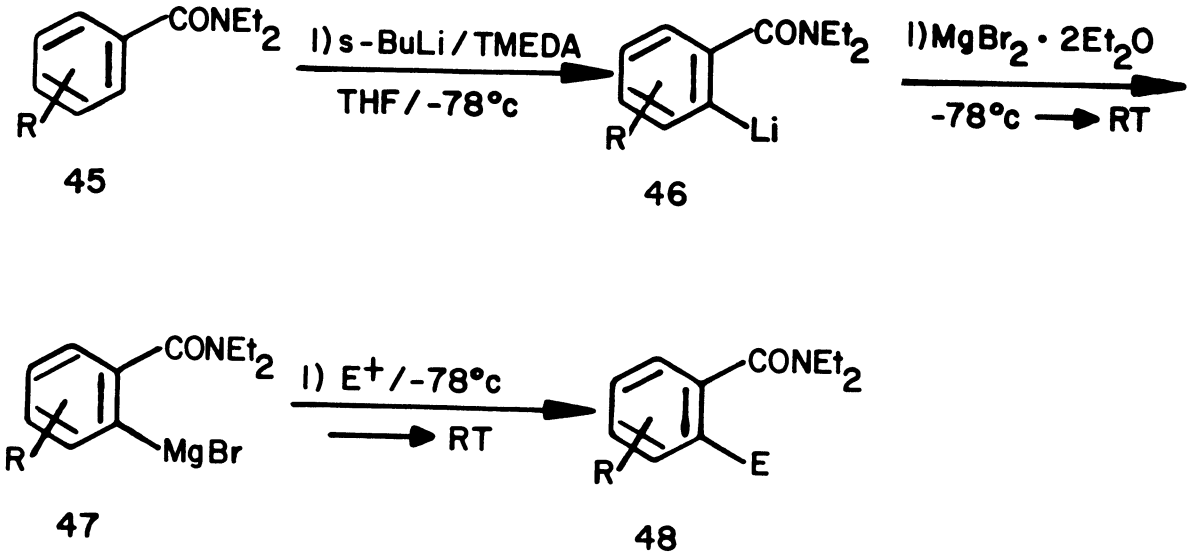
Since the ortho lithiated N,N-diethyl O-arylcarbamate has been shown to couple satisfactorily with both aliphatic aldehydes[54] and allyl bromide (see Section 2.2.1), it appears that the low-reactivity of a lithiated benzamide towards these electrophiles may be inherent to this system.

The advantage of the transmetalation strategy for ortho allylation and ortho hydroxyalkylation of tertiary-benzamides will be described in this thesis. Comparison of ortho lithium versus ortho magnesium species in reactions of 2-oxazolino **61** and methoxymethoxy **63** directing groups with aliphatic aldehydes will also be discussed.[51]

1.2.2. PREPARATION OF ORTHO MgBr-BENZAMIDE THROUGH TRANSMETALATION AND ITS REACTION

In general, the preparation of ortho MgBr-benzamide involved the lithiation of N,N-diethyl benzamide with s-BuLi/TMEDA in THF at -78°C (-90°C for N,N-dimethylbenzamide[55]) under nitrogen followed by addition of $MgBr_2 \cdot 2Et_2O$ and treating the resulting mixture with electrophiles **(Scheme 11)**.

Scheme 11

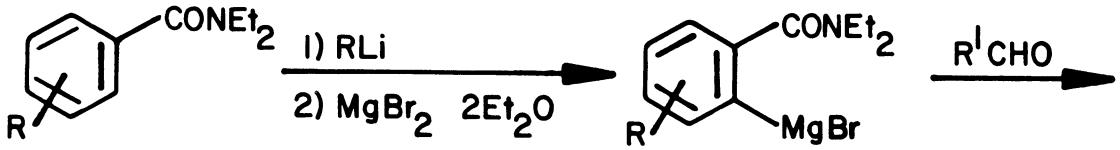


* These conditions will be referred to as standard conditions and will be represented by RLi unless otherwise indicated.

1.2.3. REACTION OF ORTHO MgBr-BENZAMIDES WITH ALIPHATIC ALDEHYDES. SYNTHESIS OF SUBSTITUTED PHTHALIDES.

The Grignard species **47** were treated with acetaldehyde and n-butyraldehyde to give o-hydroxyalkylamides **49**; for convenience, these were not isolated but transformed to phthalides **50** by a p-toluenesulfonic acid catalyzed lactonization reaction **(Scheme 12)**. The results are shown in **Table 4.**

Scheme 12



45 a-e **47 a-e**

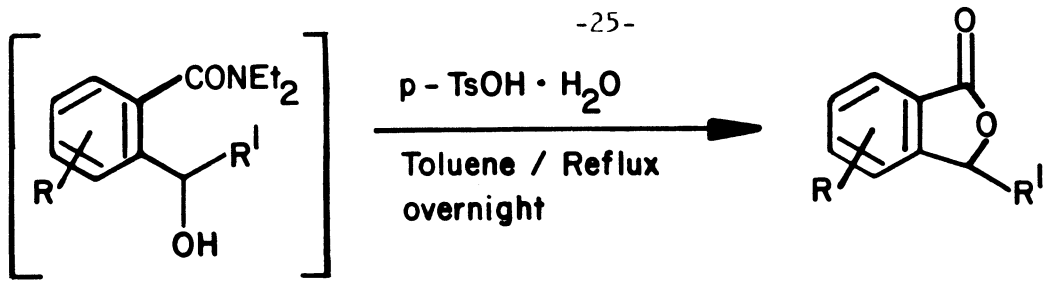
a: $\frac{R}{H}$

b: 2-OMe

c: 3-OMe

d: 2,5-$(OMe)_2$

e: 2,3,4-$(OMe)_3$



49 **50 a - f**

	a	**b**	**c**	**d**	**e**	**f**
R =	H	H	7-OMe	4-OMe	4,7-$(OMe)_2$	H
R' =	n-Pr	Me	n-Pr	n-Pr	n-Pr	2-Pyridyl

Table 4: Synthesis of Phthalides **50** by Li ⟶ MgBr Transmetalation.

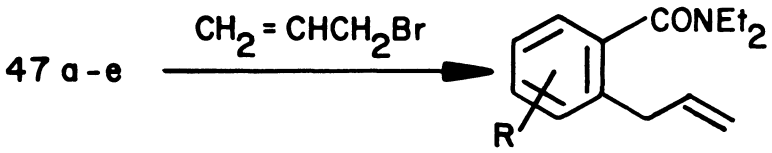
Substrate	Electrophile	Product	Yield %
45a	$CH_3(CH_2)_2CHO$	**50a**	64
45a	CH_3CHO	**50b**	61
45b	$CH_3(CH_2)_2CHO$	**50c**	60
45c	$CH_3(CH_2)_2CHO$	**50d**	59
45d	$CH_3(CH_2)_2CHO$	**50e**	75
45a	Py-2-CHO	**50f**	88

The characteristic ^1H NMR signal for the methine proton (δH_3 5.39-5.5) and IR absorption frequencies at 1750 cm^{-1} characteristic of 5-membered lactones along with other evidence (see Experimental Section), as well as comparison of the spectral data of **50a** [56] and **50b** [57] with data for authentic materials, confirmed the structures of the phthalide products.

1.2.4. REACTION OF ORTHO MgBr-BENZAMIDES WITH ALLYL BROMIDE

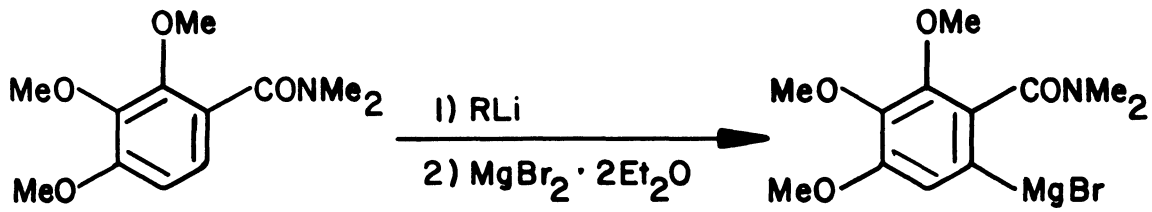
The coupling of Grignard species **47** and **53** with allyl bromide provided o-allylbenzamides **51** and **54** in good to excellent yields **(Scheme 13).** The results are collected in **Table 5.**

Scheme 13

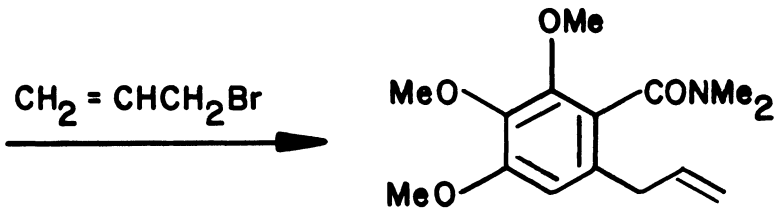


51 a-e

a	b	c	d	e
R = H	6-OMe	3-OMe	$(3,6\text{-OMe})_2$	$4,5,6\text{-(OMe)}_3$



52 **53**



54

Table 5. Synthesis of o-Allylbenzamides **51** and **54.**

Substrate	Electrophile	Product	Yield, %
45a	CH_2=$CHCH_2Br$	**51a**	71
45b	CH_2=$CHCH_2Br$	**51b**	55
45c	CH_2=$CHCH_2Br$	**51c**	80
45d	CH_2=$CHCH_2Br$	**51d**	63
45e	CH_2=$CHCH_2Br$	**51e**	66
53	CH_2=$CHCH_2Br$	**54**	77

Allylation was confirmed by the presence of signals for the olefinic protons in ^1H NMR spectra of the products (δ 5.85-6.20) together with other spectral data (see Experimental). Conversions to dihydro isocoumarins provided chemical corroboration of the ortho-allylation result. Two equivalents of allyl bromide was used to obtain optimum yields as a decrease in yield of the allylated product **50a** was observed when 1.0 equivalent of allyl bromide wasused. Invariably, 3.0 equivalents of $MgBr_2.2Et_2O$ was also used. It was observed, however, that at least 2.0 equivalents should be used for satisfactory results as 50% of allylated product **50a** was obtained when 1.0 equivalent of $MgBr_2.2Et_2O$ was used.

The allylation of **45a** was also performed under a variety of conditions to establish optimum yields. The Grignand species **47a** was prepared as before and then cooled to different temperatures. In addition, one

experiment was carried out by allowing **47a** to undergo reaction with allyl bromide at -78°C without warming to room temperature. The results are shown in **Table 6.**

Table 6 Reaction of Allyl bromide with ortho-MgBr Benzamide **47a** as a Function of Temperature

Temp,°C	Yield,%
-78	71
-78(without warming to RT)	66
-40	67
0	66
RT	63

As **Table 6** indicates no appreciable change in yields as a function of the temperature of quenching with allyl bromide was observed. However, optimum yields were achieved at -78°C and therefore these were chosen for reactions with other benzamide substrates.

o-Allylation of **53** required a slight modification of the general transmetalation in that the lithiation was carried out at -90°C.[55] This was found necessary in order to suppress the nucleophilic attack at the N,N-dimethyl amide group by s-BuLi.[47]

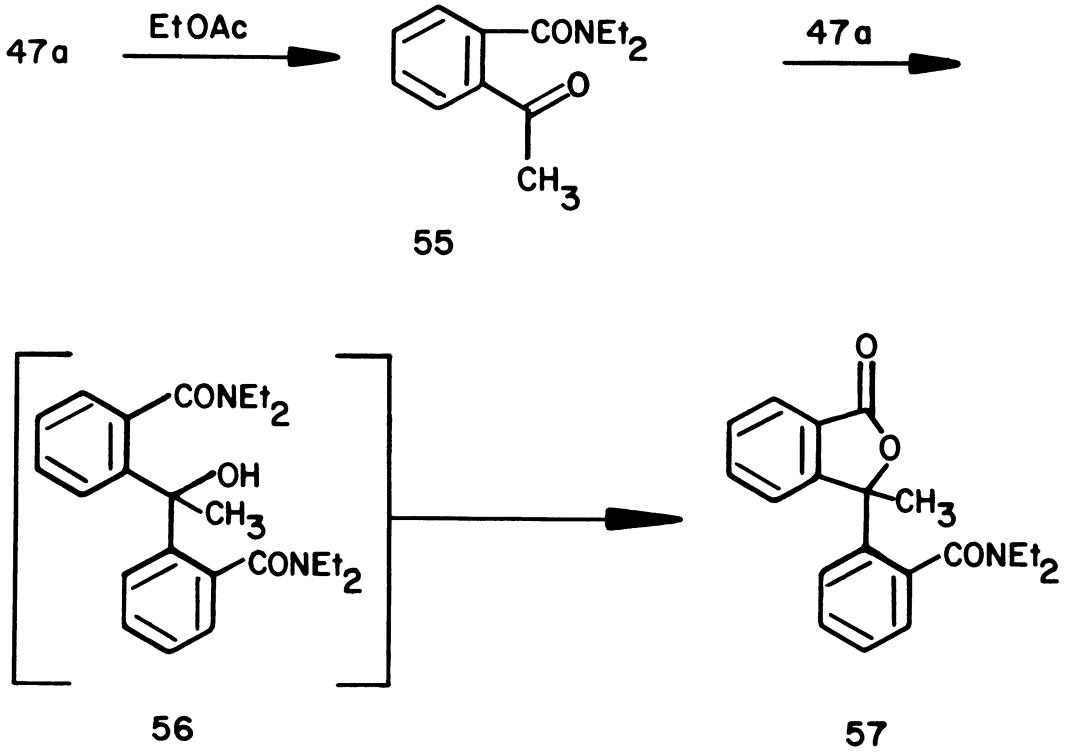
1.2.5. REACTION OF o-MgBr BENZAMIDE 47a WITH OTHER ELECTROPHILES

In an attempt to expand our transmetalation methodology, we examined the possibility of coupling a Grignand species **47a** with various electrophiles.

The reaction of **47a** with ethyl acetate which was originally expected to yield o-acetyl benzamide **55**, resulted in the formation of a 2:1 condensation product **56**, isolated as the phthalide **57**, in 35% yield (**Scheme 14**). Attempts to stop the reaction at the expected o-acetyl benzamide (**55**) stage by variation of conditions (which included inverse addition and using a large excess of ethyl acetate) failed.

The isolation of **57** , however, was not unexpected, since it is the normal end product of a reaction between a Grignard reagent and an ester.

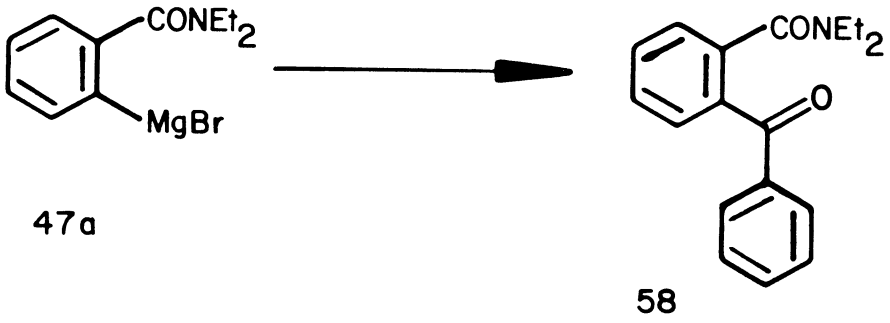
Scheme 14



Reactions of electrophiles such as acetonitrile, ethyl bromoacetate, 1-bromoacetaldehyde diethyl acetal, epibromohydrin, methyl vinyl ketone,

benzyl chloride, benzyl bromide, cyclohexene oxide and styrene oxide which were shown not to couple with the ortho-lithiated N,N-diethylbenzamide[58] also failed to give condensation products with the Grignard species **47a** . In each case, in addition to recovering starting benzamide (60-65%), a self condensation product, the benzophenone **58** ,[59] was obtained as a minor product (6-13%). This compound has been previously obtained as a side product from ortho-lithiated benzamides.[47,60] On the basis of the following observations, it is assumed that compound **58** is formed from either the o-Li or the o-MgBr species. When **47a** was allowed to warm to room temperature and

Scheme 15



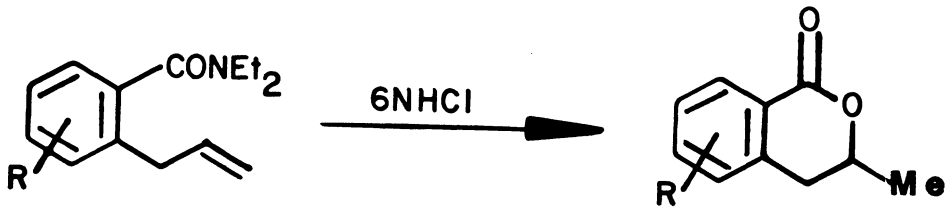
quenched with water, compound **58** was isolated in 17% yield together with starting material (65%). On the other hand, when **47a** was generated from o-bromobenzamide and triply sublimed magnesium followed by the same quenching procedure, benzophenone **58** was obtained in 10% yield together with N,N-diethyl benzamide (60%).

1.2.6 SYNTHESIS OF DIHYDROISOCOUMARINS FROM o-ALLYLBENZAMIDES

The efficient synthesis of o-allylbenzamides **51** prompted us to

undertake a study of their acid-catalysed transformation into isocoumarin derivatives[59,60] which included the natural products melein[62] and kigelin[63] **(Scheme 16).**

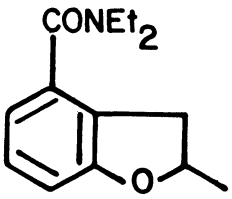
Scheme 16



51 a-e **59 a-e**

	R
a:	H
b:	6-OMe
c:	3-OMe
e:	4,5,6-$(OMe)_3$

	R
a:	**H**
b:	8-OH
c:	5-OMe
d:	5-OH
e:	6,7-$(OMe)_2$-8-OH



60

Treatment of **51a** with 6N aqueous HCl under reflux afforded **59a** in almost quantitative yield. Treatment of **51b** resulted in cyclization as well as demethylation to give mellein, **59b** , a naturally occuring isocoumarin.[62] The 2-allyl-3-methoxybenzamide **51c** vielded a mixture of isocoumarin **59c,** the corresponding phenol **59d,** and the benzofuran **60.** The desired kigelin **59e** [63] was not, however, obtained from **51e** which underwent cyclization only under vigorous condition (6N HCl/reflux/72h) to

give a mixture of products containing didemethylated isocoumarin (by ^{1}H NMR analysis) but not kigelin. Therefore, other conditions such as mercuric acetate-catalyzed[63a] or palladium chloride-catalyzed[64] cyclization methods, previously used to cyclize o-allylbenzoic acids and their corresponding primary and secondary amides into isocoumarins and isoquinolines,[64] were explored but proved to be unsuccessful. Finally, kigelin was obtained by the 6N HCl catalyzed cyclization of the N,N-dimethylbenzamide **54.** The success may be due to the less steric congestion of dimethylamide group in **54** which facilitated its cyclization and aided monodemethylation of the 8-OMe group to kigelin. The results of cyclization of **51a-e** to **59a-d** and of **54** to **59e** are summarized in **Table 7.**

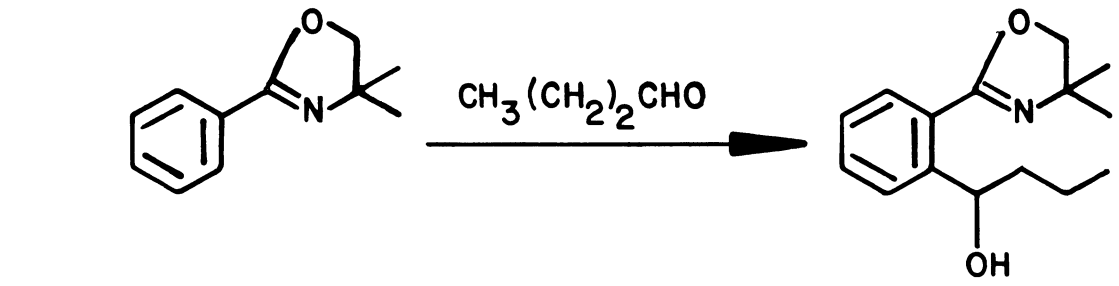
Table 7: Synthesis of Dihydroisocoumarins (59) from o-allylbenzamides 51a-e, 54.

Substrate	Conditions	Product	Yield, %
51a	6NHCl/reflux/20 h	**59a**	93
51b	6NHCl/reflux/4 d	**59b**	75
51c	6NHCl/reflux/18 h	**59c**	49
		59d	16
		60	12
54	6NHCl/reflux/24 h	**59e**	27

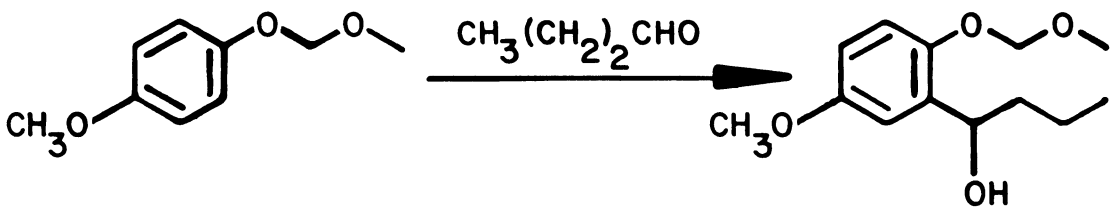
1.2.7. THE REACTIONS OF ORTHO LITHIUM AND BROMOMAGNESIUM PHENYLOXAZOLINE 61 AND METHOXYMETHOXYARENE 63 WITH n-BUTYRALDEHYDE.

The reaction of ortho lithium and bromomagnesium phenyloxazoline **61** [65,66] and methoxymethoxyarene **63** [9,67] with n-butyraldehyde were compared to determine whether the yields of the products could be improved through the transmetalation procedure (**Scheme 17**). Results are shown in **Table 8** .

Scheme 17



61 **62**



63 **64**

Table 8: Comparison of o-Li vs. o-MgBr in reactions with n-Butyraldehyde for Compounds **61, 63**

Substrate	Electrophile	Product	Yield,%,via	
			o-Li	o-MgBr
61	$CH_3(CH_2)_2CHO$	**62**	65	68
63	$CH_3(CH_2)_2CHO$	**64**	38	66

As seen from **Table 8** , the reactivity of **61** as either metalated species was similar to give **62**, a result which is comparable with the observations of Meyers.[68] However, comparison of the results for compound **63** showed that a higher yield of product **64** could be obtained via the transmetalation method.

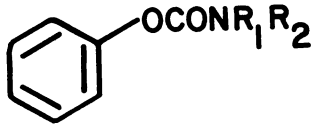
1.2.8. CONCLUSION

The transmetalation of ortho-lithiated benzamides into o-bromomagnesio species and their successful coupling with allyl bromide and aliphatic aldehydes supplements the utility of the benzamide-directed metalation methodology and emphasizes the additional utility of this transmetalation procedure.

CHAPTER II

2.1. INTRODUCTION

With the increasing importance of aromatic directed metalation methodology for the regioselective synthesis of polysubstituted aromatics,[8] efforts have been undertaken by various researchers to uncover new and effective aromatic ortho directing groups. To this end, the N,N-diethylcarbamoyloxy group,-$OCONEt_2$, a new and efficient ortho directing group has been discovered in our laboratory very recently.[69]



$R^1 = R^2 =$ Ethyl

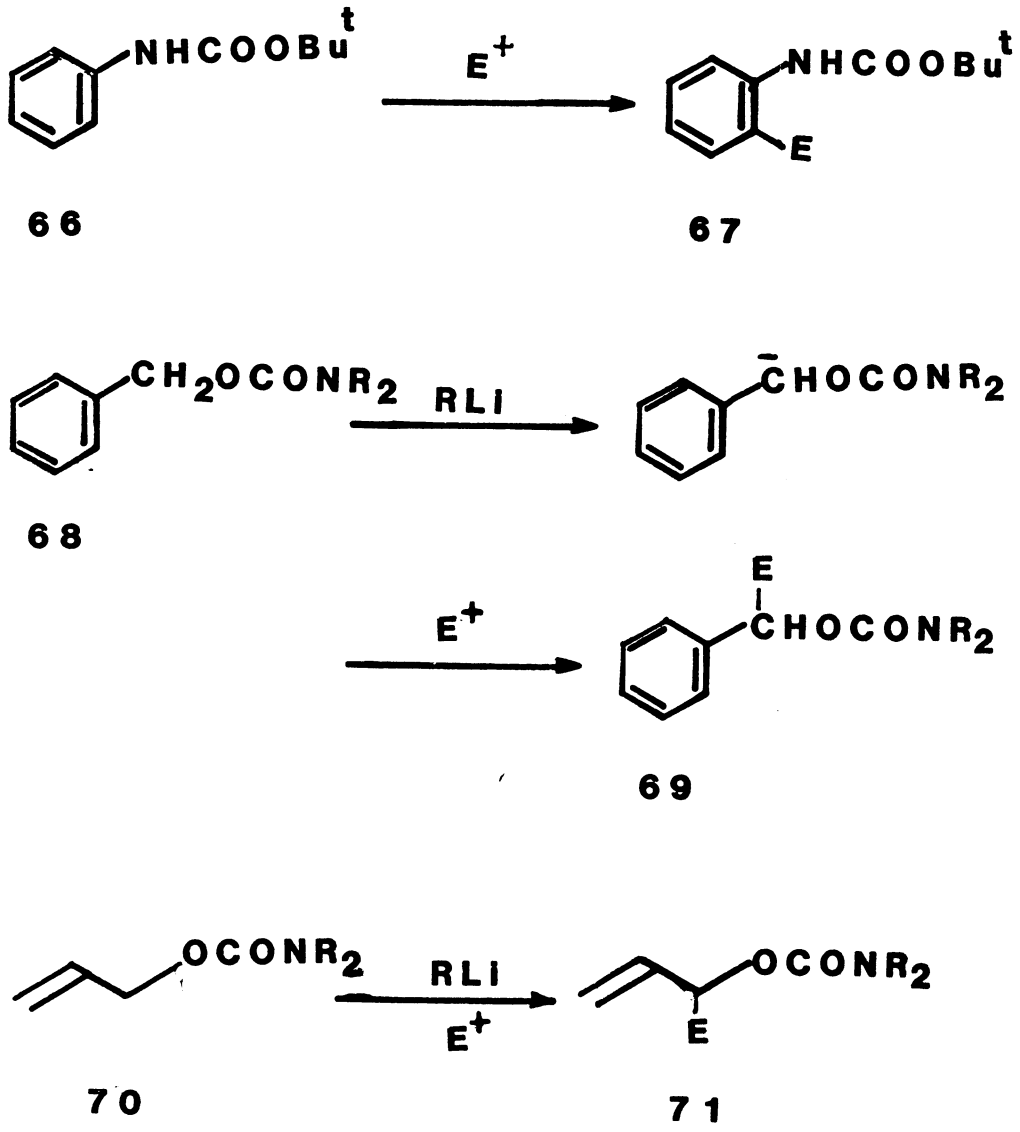
$R^1 = H$, $R^2 =$ Methyl

65

The O-arylcarbamates **65** constitute a known class of organic compounds which are used extensively as insecticides[70] and pharmacological agents[71] and therefore their preparation has been extensively documented.[70]

Although the ortho metalation of secondary N-aryl carbamates[28] and -metalation of N,N-diethyl O-benzyl carbamates and N,N-dialkyl O-allyl carbamates[72] (**Scheme 18**), have been reported, no report on the metalation of O-aryl carbamates had appeared until our work.[69]

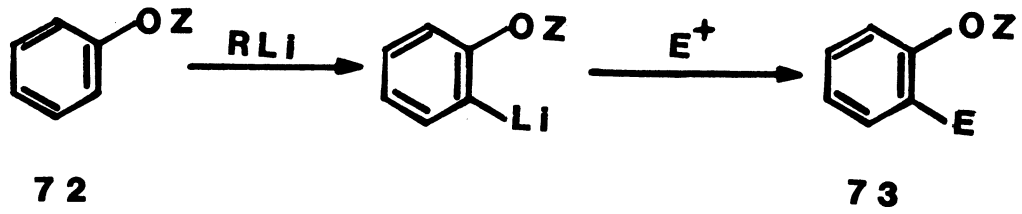
Scheme 18



2.1.1 ORTHO LITHIATION OF MASKED PHENOLS

The carbamate system **65** represents a masked phenol derivative and the ortho lithiation reaction of certain masked phenols constituted the earliest known cases of the aromatic directed metalation reaction[6] **(Scheme 19).**

Scheme 19

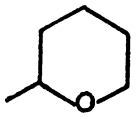


72 **73**

a $Z = CH_3$

b CH_2OCH_3

c



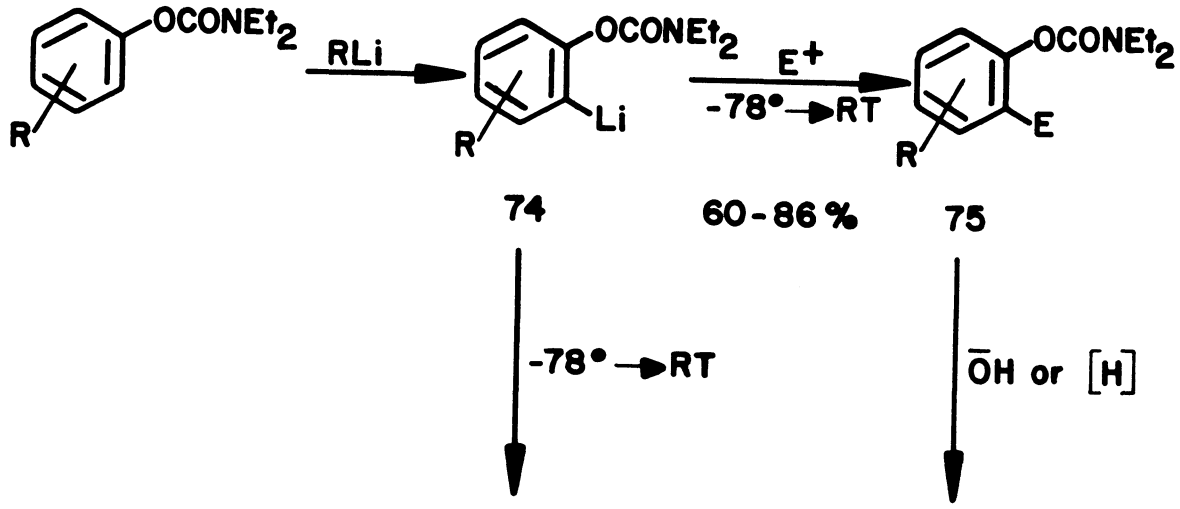
d $CHOC_2H_5$ | CH_3

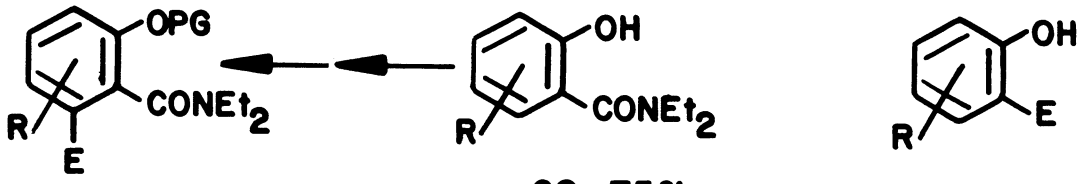
The ortho metalation of masked phenols began with the pioneering work by Gilman[1] and by Wittig[2] who were the first to show that anisole **72a** underwent ortho lithiation when treated with n-butyllithium. This constituted the first example of the aromatic directed metalation reaction. The methoxy group has been used considerably as a protecting and ortho directing group in the metalation of phenols.[73] However, due to the difficulties of deprotection of anisoles to release free phenols, investigations to devise ortho directing groups which are easily removable have ensued. Two such groups are methoxymethoxy group (**72b**)[6,31,74] and tetrahydropyranyl (**72c**)[6,75] which were found to enhance the reactivity and regioselectivity of the aromatic ortho lithiation in comparison to the methoxy group. These groups are easily removed by mild acid-catalyzed hydrolysis.

2.1.2. ORTHO LITHIATION OF N,N-DIETHYL O-ARYL CARBAMATES

Ortho lithiation of N,N-diethyl O-aryl carbamates was achieved by the standard lithiation conditions which was used for ortho deprotonation of N,N-diethyl benzamides (s-BuLi/TMEDA/THF/-78°C).[69] The ortho lithiated carbamate **74** was shown to undergo reaction with a variety of electrophiles to give **75** . Furthermore, in the absence of any external electrophile, the lithiated species **74** were found to rearrange to give salicylamide derivatives **76** (**Scheme 20**) a process which may be formally considered to be an anionic equivalent of the ortho Fries rearrangement. Therefore, the carbamate group possesses an added advantage in that it is not only an efficient ortho director but also a carrier of powerful tertiary amide ortho metalation director which, once migrated, can serve for further lithiation. The products **75** can be deprotected to give o-substituted phenols **77** either by base-catalyzed hydrolysis or lithium aluminum hydride reduction, depending on the nature of E.

Scheme 20





60-75%

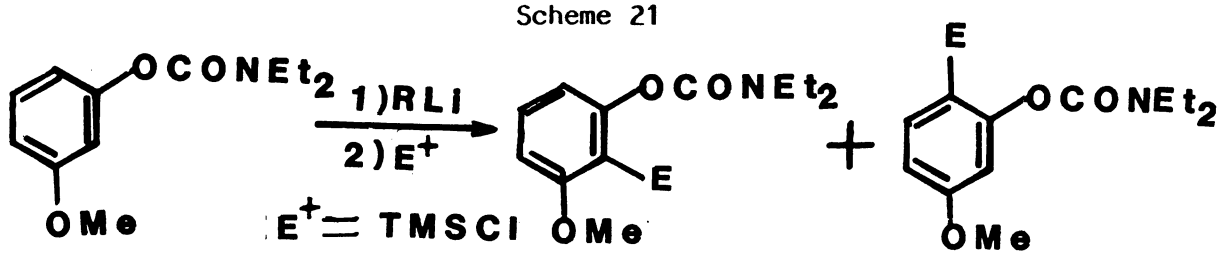
76 77

R = H, OMe (o,m,p), Cl (p)

E^+ = MeI, TMSCl, Et_2NCOCl, DMF, CO_2

In the initial study[69] to establish the effects of substituents in the regioselectivity of metalation, the m-methoxy carbamate **78** was tested and led to a mixture of 1,2,3-isomer **79** and 1,2,4-isomer **80** in a ratio of 3:1 **(Scheme 21)**.

Scheme 21

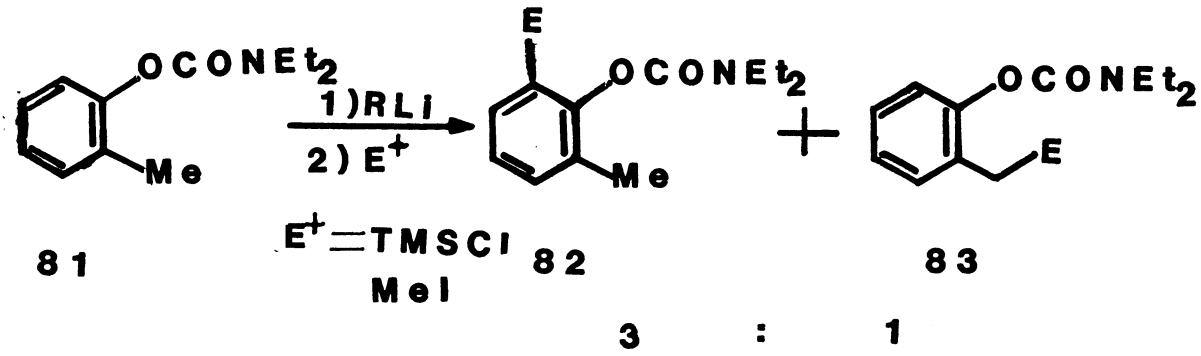


78 **79** **80**

3 : 1

To establish the regioselectivity in o-CH_3 vs. o-aromatic C-H deprotonation, **81** was subjected to standard metalation conditions to give products **82** and **83** in a ratio of 3:1 **(Scheme 22)**.

Scheme 22



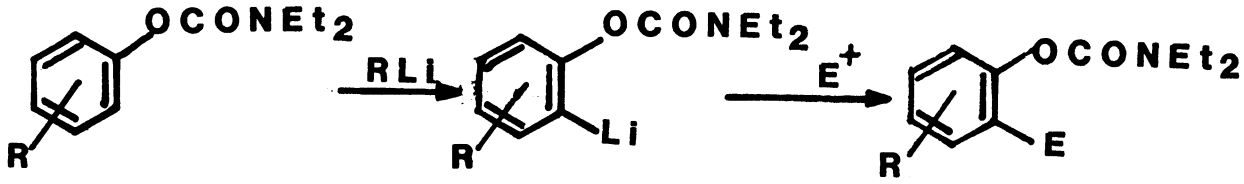
In order to explore the full scope and limitations of the carbamate as an ortho metalation director, detailed investigations have been undertaken which constitute part of this thesis. These studies concern: i) the ortho lithiation of N,N-diethyl O-phenyl and O-naphthyl carbamates; ii) ortho lithiation of N,N-dimethyl O-phenyl carbamate, iii) the relative stabilities of lithiated N,N-diethyl and N,N-dimethyl O-phenyl carbamates; iv) the synthesis of salicyamide derivatives and the mechanism of O to C 1,3 carbamoyl migration; v) relative ortho directing capability of carbamoyloxy group to other ortho directing groups, particularly the tertiary amide and the methoxymethoxy group; vi) iterative metalation and vii) the development of a general method for the synthesis of 2(3H)-benzofuranones. The results of these studies will be presented in this section of the thesis.

2.2 RESULTS AND DISCUSSION

2.2.1 SYNTHESIS OF POLYSUBSTITUTED O-ARYL CARBAMATES

In order to establish the scope and limitations of the ortho lithiation of O-aryl carbamates, N,N-diethyl O-aryl carbamates **84** were lithiated under standard conditions (s-BuLi/TMEDA/THF/-78°C) and treated with a variety of electrophiles (**Scheme 23**). The results are summarized in **Table 9.**

Scheme 23



84a-f **85a-k**

	R
	—
a:	H
b:	2-OMe
c:	2-Cl
d:	3-Me
e:	4-Me
f:	3-OMe

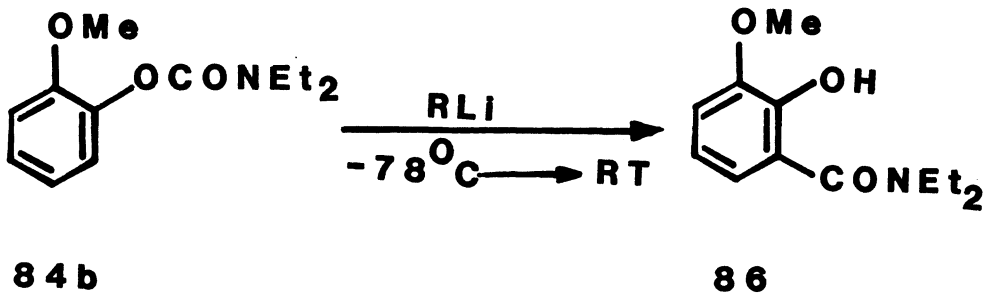
	R	E
	—	—
a:	H	D
b:	H	CH_2-CH=CH_2
c:	2-OMe	TMS
d:	6-OMe	$CONEt_2$
e:	2-Cl	TMS
f:	2-Cl	I
g:	6-Cl	$CONEt_2$
h:	3-Me	6-TMS
i:	4-Me	6-TMS
j:	3-OMe	2-Me
k:	3-OMe	6-Me

Table 9: Synthesis of Polysubstituted O-Aryl carbamates **85.**

Substrate	Electrophile	Product	Yield, %
84a	EtOD	**85a**	95(96%d_1)
84a	CH_2=$CHCH_2Br$	**85b**	75
84b	TMSCl	**85c**	67
84b	Et_2NCOCl	**85d**	90
84c	TMSCl	**85e**	79
84c	I_2	**85f**	93
84c	Et_2NCOCl	**85g**	78
84d	TMSCl	**85h**	81 (39)[a]
84e	TMSCl	**85i**	83 (17)[a]
84f	MeI	**85j**)	(63
		) 90	(
		85k)	(27

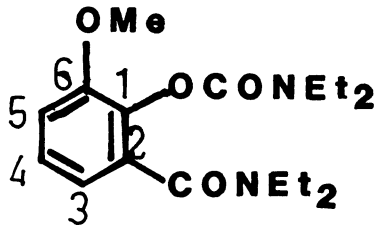
[a] Yield obtained using LDA as base.

Both the excellent chemical yield and high deuterium content of **85a** as well as good to excellent yields of **85b-k** demonstrate the efficiency of $OCONEt_2$ functionality as a powerful ortho directing group. Metalation of **84b** occurs ortho to the carbamoyloxy group with high regioselectivity as established by ^{13}C NMR spectral data of **85d (Table 10)** as well as from the product **86** obtained when lithiated **84b** is allowed to undergo the anionic equivalent of the ortho Fries rearrangement.[69]



84b **86**

Table 10: Calculated and Experimental Aromatic ^{13}CNMR Shifts for **85d** .



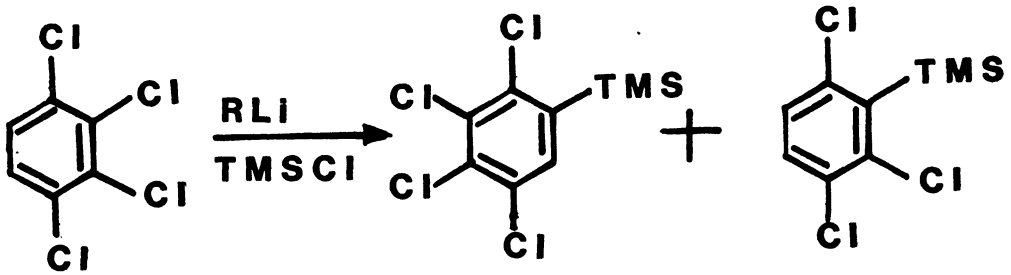
85d

Carbon	δ ppm	
	Calcd[a]	Exptl (rel.int)
1	134.8	136.9 (15)
2	131.3	132.5 (30)
3	119.0	118.1 (86)
4	125.7	126.8 (100)
5	115.1	112.8 (80)
6	152.8	152.4 (26)

[a] The calculated chemical shifts were obtained by adding the substituent shifts[76] for CH_3O and $CONEt_2$[47] to the carbon chemical shifts of N,N-diethyl O-aryl carbamate **84a** .

The location of the lithiation was indicated by the reduction in intensity of the newly substituted carbon. The experimental chemical shifts are found to compare very favorably with the calculated shifts of **85d** as opposed to the alternate structure in which amide functionality is located ortho to the methoxy group. Thus no metalation ortho to the methoxy group was indicated although the OMe group itself is a moderate ortho directing group.[6] Similar findings were also observed for compound **84c** (R = 2-Cl). Although the carbamate was expected to be the dominant ortho directing group, chlorine is known to have a weak inductive acidifying effect on its ortho site[6] as evidenced from the exclusive metalation of N,N-diethyl O-3-chlorophenyl carbamate at the position between the two functions and precedent for metal-halogen exchange **(Scheme 24)** [6].

Scheme 24



87 **88** **89**

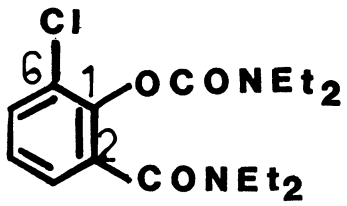
R = t-Bu	0%	100%
R = Me	93%	7%

By changing the base, either ortho lithiation or chloride-metal exchange could be effected.

The ^{13}C NMR data (**Table 11**) confirmed the structure of **85g** and hence

the position of lithiation.

Table 11: Aromatic ^{13}C NMR chemical shifts for **85g** .



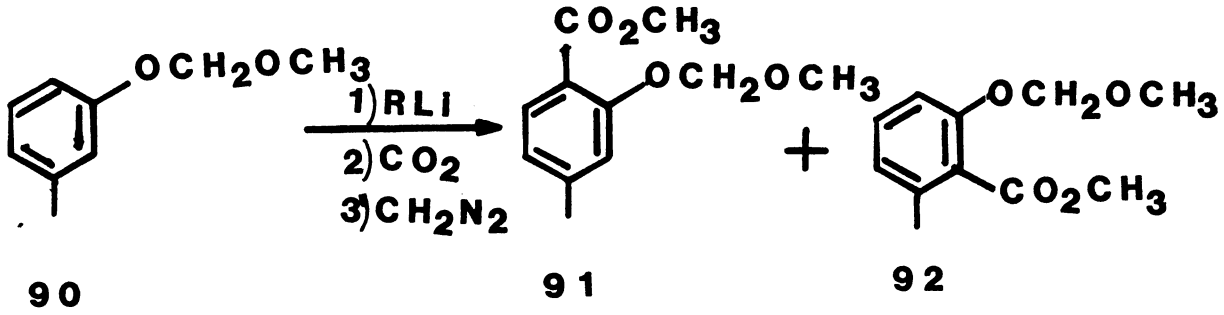
85g

Carbon	δ ppm	
	Calcd[a]	Exptl.(rel.int.)
1	149.6	145 (7)
2	131.6	133.6 (13)
3	124.8	124.9 (86)
4	126.0	126.3 (93)
5	129.9	130.4 (100)
6	127.6	129.0 (15)

[a] see Table 10.

These results indicate the superior coordinating power of the carbamoyloxy group with alkyllithium bases over the methoxy or chloro function. Compound **84d** afforded the 1,2,4-isomer **85h** and not the 1,2,3-isomer in accord with the reported result of an ortho metalation reaction when an alkyl group is at meta-position to the methoxymethoxy directing group (**Scheme 25**).[9] Compound **90** , however, afforded the 1,2,3-isomer, **92** , as a very minorproduct depending on the metalation conditions.[9]

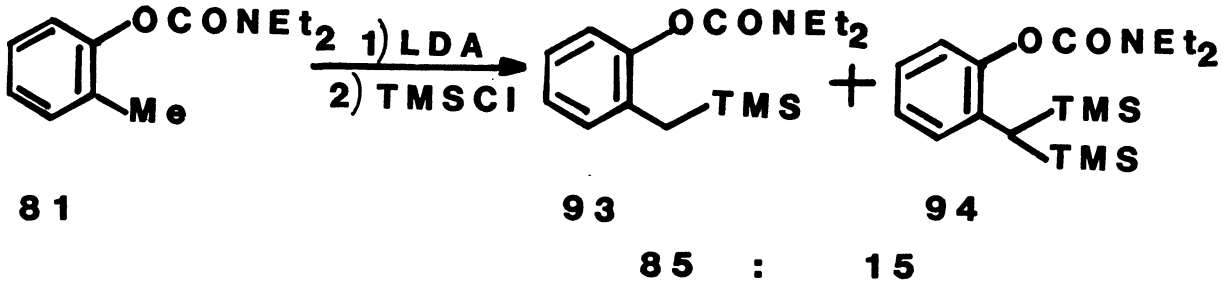
Scheme 25



Conditions	Ratio **91:92**
t-BuLi/Et_2O/0°	>200:1
t-BuLi/hexane/0°	>200:1
n-BuLi/hexane/25°	4:1
n-BuLi/hexane/25° /TMEDA	4:1

Compounds **84d** and **84e** were also subjected to metalation with LDA to compare with the results obtained from the metalation of **81 (Scheme 26).** [69] In contrast, **84d** and **84e** led solely to products **85h** and **85i** in low yields.

Scheme 26

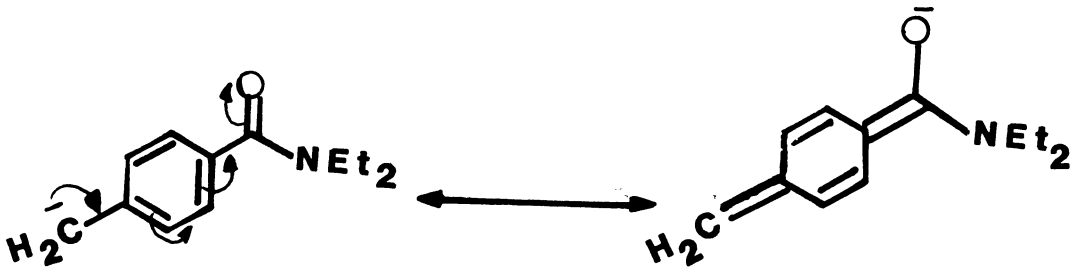


81 93 94

85 : 15

These results again strongly point to the need for coordination in ortho metalation reactions. Benzylic metalation of 4-methyl-N,N diethyl benzamide with LDA is not surprising in view of fact that the resultant benzylic anion is stabilized by the electron withdrawing effect of amide functionality **(Scheme 27).** [47] Of course, no such stabilization is possible for the three isomeric-methyl phenyl carbamate systems.

Scheme 27



The result on the metalation of 84**f** confirmed the preliminary observation.[69] The ratio of the 1,2,3-isomer to the 1,2,4-isomer varied

from 3:1 to 9:1[54] depending on the nature of electrophiles used in **(Table 12).**

Table 12: Regioselectivity in Metalation of 3-Methoxy O-Phenyl Carbamate **84f**

Conditions	Electrophile	Yield,%	Ratio 1,2,3: 1,2,4-isomer
s-BuLi/TMEDA THF/-78°C	MeI	93	3 : 1
s-BuLi/TMEDA THF/-78°C	I_2	76	9 : 1

These results indicate a much lower regioselectivity of carbamate in comparison to tertiary amide group in metalation at sites common to two directing groups.[8]

2.2.2 SYNTHESIS OF ORTHO SUBSTITUTED O-NAPHTHYL CARBAMATES

The directed ortho metalation reaction was extended to O-naphthyl carbamates. N,N-diethyl O-1-naphthyl carbamate **95** was found to lithiate cleanly at the 2-position under the standard lithiation condition (s-BuLi/ TMEDA/THF/-78°C) to give 2-substituted products **96** (**Scheme 28**). On the other hand, N,N-Diethyl O-2-naphthyl carbamate **97** , was found to afford isomeric 1- and 3-substituted naphthyl carbamates **98** , **99** (**Scheme 28**). The results are shown in **Table 13.**

Scheme 28

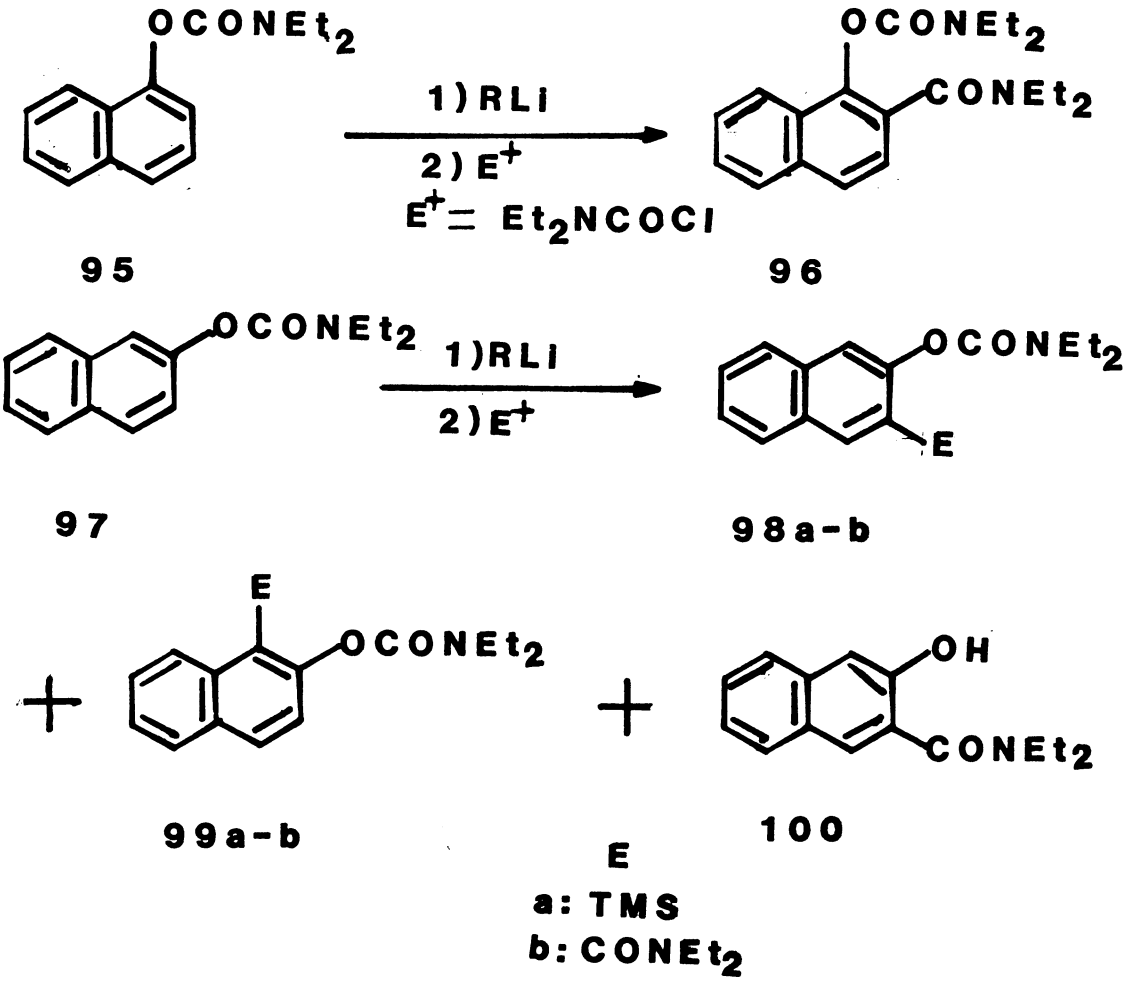


Table 13: Synthesis of Ortho Substituted O-Naphthyl Carbamates **98** and **99.**

Substrate	Electrophile	Product	Yield[a], %
95	Et_2NCOCl	**96**	78
97	TMSCl	**98a**	45
		99a	17
		100	20
97	Et_2NCOCl	**98b**	51
		100	26

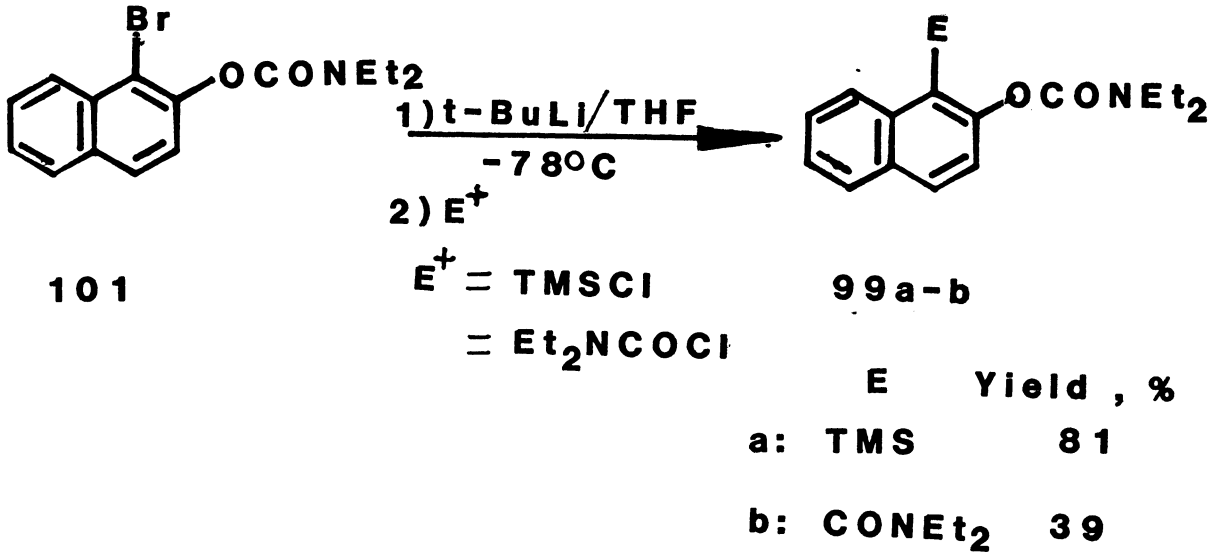
[a] Isolated Yields.

The regiospecific metalation at the 2-position of compound **95** has already been chemically confirmed by the conversion of the 2-methylated 1-naphthyl carbamate into the known 2-methyl-1-naphthol.[69] Products arising from metalation at the 8-position were not observed. In comparison, 1-methoxynaphthalene has been reported to undergo metalation either at the 2-position (i) n-BuLi/TMEDA/hexane; ii) CO_2/CH_2N_2 (Yield: 60%) or the 8-position (i) t-BuLi/cyclohexane, ii) CO_2/CH_2N_2 (Yield: 35%) depending on the conditions used.[6]

The lithiation of O-2-naphthyl carbamate **97,** is complicated by the availability of two ortho sites. Two isomeric products **98** and **99** were indeed isolated together with the known hydroxy 2-naphthamide derivative **100** showing that predominant products are derived from metalation at the 3-position. These observations parallel the results of metalation of 2-methoxynaphthalene[6] and may be rationalized by the enhanced

kinetic acidity at the 3-position over 1-position. The structures of compounds **99a-b** were assigned by comparison of their ^1H NMR and IR spectra and physical properties with authentic materials prepared from 1-bromo-2-naphthyl carbamate **101** via metal-halogen exchange and quenching with the appropriate electrophiles (**Scheme 29**).

Scheme 29



These results also allow the conclusion that the 1-lithiated 2-carbamoyloxy system is stable with respect to equilibration to the corresponding 3-lithiated species. In further support of this, compound **101** was subjected to metal-halogen exchange (t-BuLi/THF/-78°C) and kept at -78°C for 6 h before treatment with TMSCl. The usual workup afforded only **99a** in 85% yield and no other products were identified.

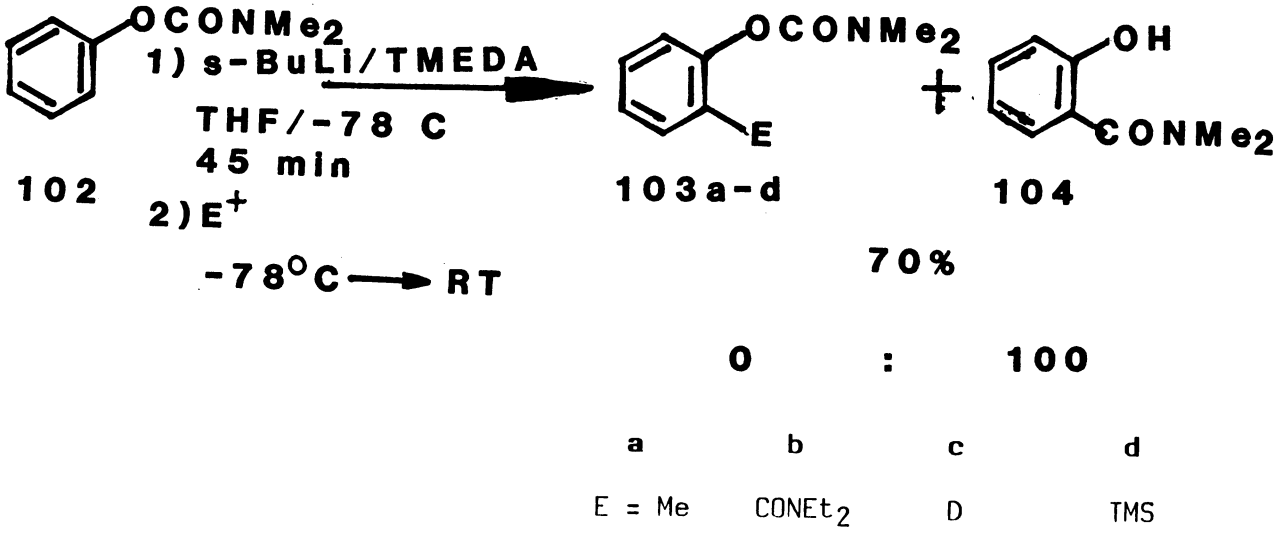
2.2.3 METALATION OF N,N-DIMETHYL O-ARYL CARBAMATES

Next we turned our attention to examine the effect, if any, of replacing the $OCONEt_2$ group by the N,N-dimethyl carbamoyloxy ($OCONMe_2$) group in

the directed ortho metalation reaction.

When N,N-dimethyl O-phenyl carbamate **102** was subjected to lithiation under the standard conditions (s-BuLi/TMEDA/THF/-78°C) for 45 min, quenched with various electrophiles, and the reaction mixture was allowed to warm to room temperature, the salicylamide derivative **104** was obtained exclusively rather than the expected ortho substituted carbamate derivative **103** (Scheme 30). This result suggested that the rate of the anionic ortho-Fries rearrangement is very fast for **102** compared with the corresponding reaction on the diethyl analogue **84** .

Scheme 30



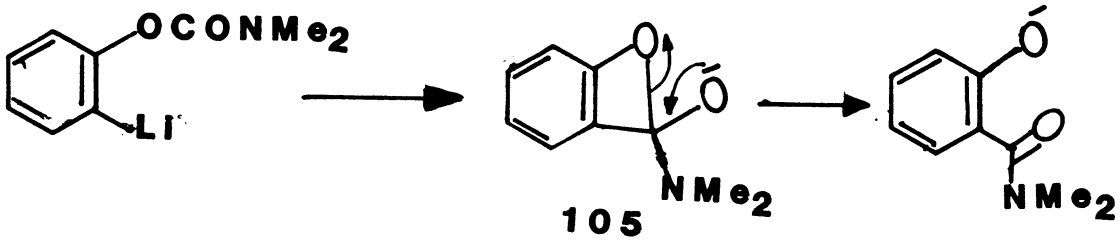
Therefore, a more thorough study was undertaken in order to find conditions for the efficient preparation of 1,2-disubstituted products **103** as well as to improve the yield of **104** . The results of

these exploratory reactions are summarized in **Table 14.**

Table 14: Electrophilic Trapping vs 1,3-Carbamoyl Migration of Ortho Lithiated N,N-Dimethyl O-Phenyl Carbamate.

Entry	Temp°C	Lithiation time (min)	Electrophile		Products, Yield% 103	104
1	-78 -> RT	8h	-		-	70
2	-78	45	MeI		-	75
3	-78	10	MeI	**a:**	60	20
4	-95	10	MeI	**a:**	90	-
5	-95	10	Et_2NCOCl	**b:**	78	-
6	-95	10	EtOD	**c:**	83(54%d_1)	-
7	-95	10	TMSCl	**d:**	88	-

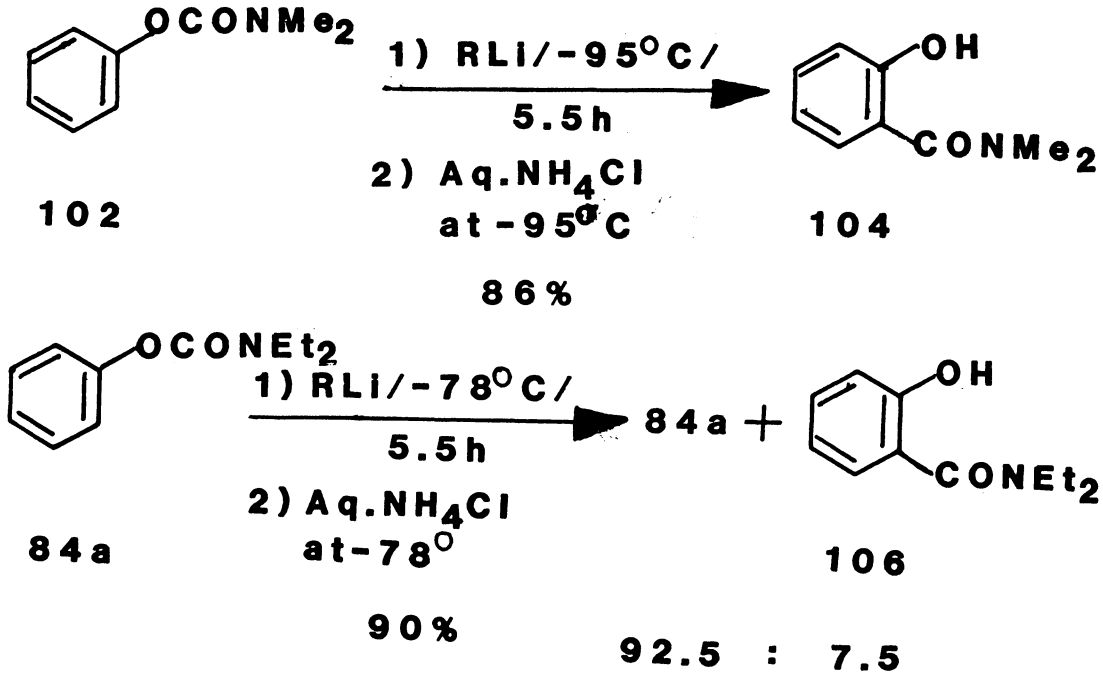
As seen from entries 1-3, at temperatures greater than -78°C and long lithiation times, the anionic ortho-Fries rearrangement of **102** was found to be very facile. This may be due to a smaller steric bulk of the N,N-dimethyl carbamoyloxy group relative to $OCONEt_2$ which allows the rate of formation of the tetrahedral intermediate **105** (See section 2.3.5.) to be faster.



However, at lower temperatures (-95°C, entry 4-7) and short lithiation time (10 min), the problem of rearrangement was overcome and 1,2-disubstituted carbamate derivatives **103** were obtained in excellent yields.

To gain further insight into this problem and to maximize the yields of the anionic ortho-Fries reaction, a comparative study regarding relative stabilities of ortho lithiated N,N-dimethyl and N,N-diethyl O-phenyl carbamates was performed **(Scheme 31).**

Scheme 31

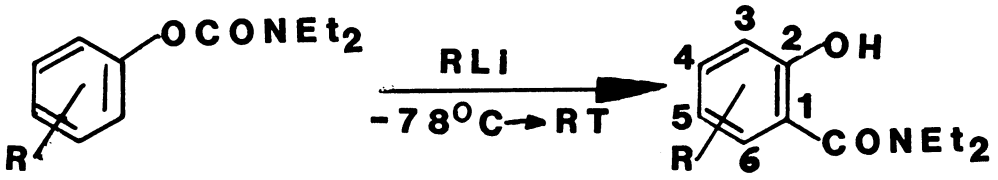


As seen from these results, the ortho lithiated N,N-dimethyl O-phenyl carbamate underwent the anionic ortho-Fries rearrangement in high yield even at -95°C over a 5.5 h period while the rearrangement of the ortho lithiated N,N-diethyl O-phenyl carbamate (**84a**) took place only to the extent of 7.5% at -78°C over the same time period.

2.2.4. SYNTHESIS OF SALICYLAMIDES AND HYDROXYNAPHTHAMIDES VIA THE ANIONIC ORTHO FRIES REARRANGEMENT

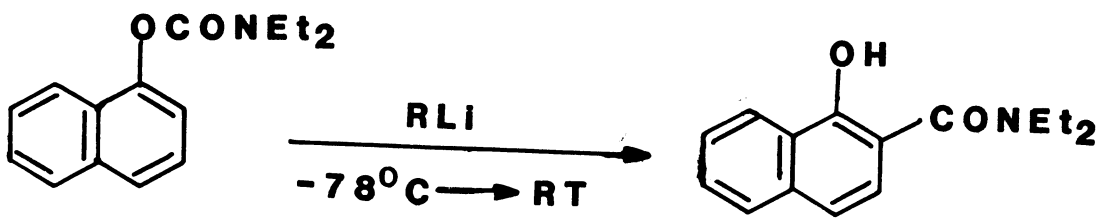
When the carbamates **84c,d,e, 95, 97** and **103a** were subjected to lithiation under certain specified conditions and allowed to warm to room temperature over an 8 h period, the hydroxy amide derivatives **107; 108; 100, 109;** and **110, 111** respectively were isolated **(Scheme 32).** The results of these 1,3 O to C carbamoyl migration reactions (anionic ortho-Fries rearrangements) are collected in **Table 15 .**

Scheme 32



84 **107**

	R		R
	—		—
c:	2-Cl	**a:**	3-Cl
d:	3-Me	**b:**	4-Me
e:	4-Me	**c:**	5-Me



95 **108**

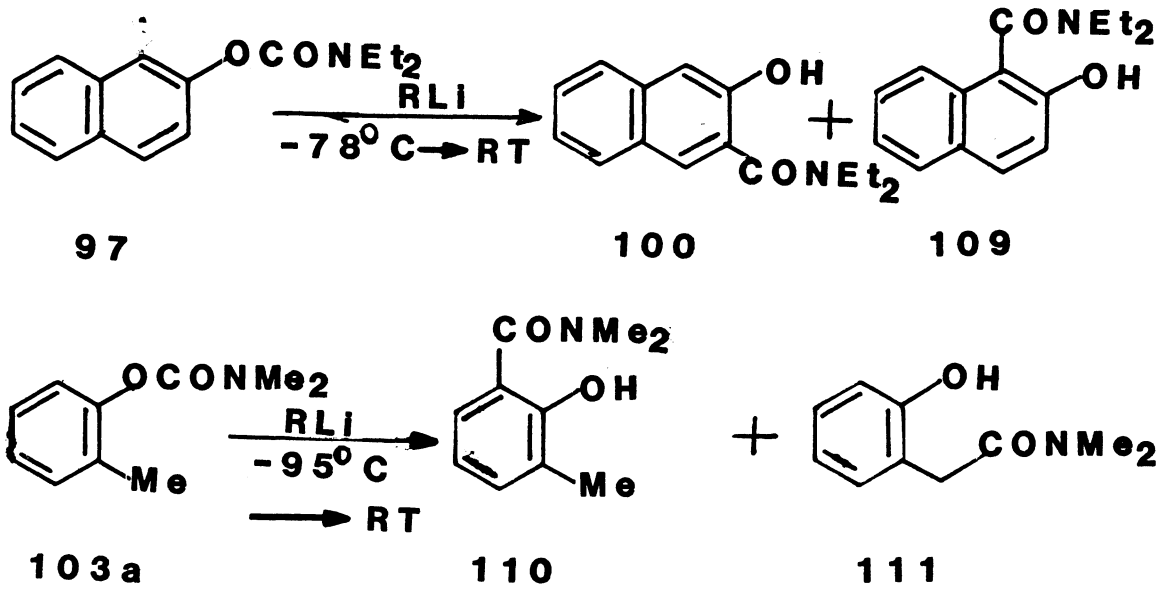


Table 15: Synthesis of Salicylamides **107, 110** and Hydroxy naphthamides **108, 100, 109** by 1,3-carbamoyl Migration.

Substrate	Products	yield,%[a]
84c	**107a**	73
84d	**107b**	50
84e	**107c**	70
95	**108**	71
97	**100**	48
	109	32
103a	**110**	56
	111	25

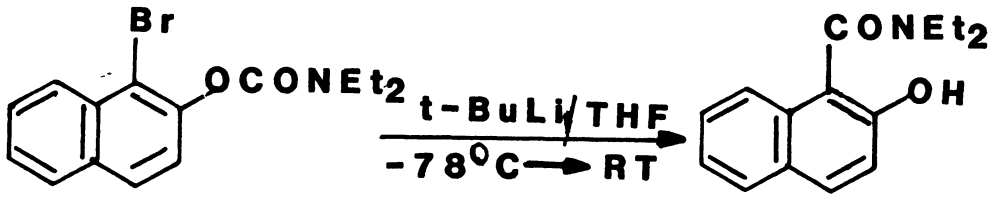
[a] Isolated yields.

The structure of all products were deduced from analytical and spectral (^{1}H NMR, IR, MS) data.

The isolation of **107a** confirmed the preparation of carbamate derivatives **85e, 85f** and **85g** which were discussed earlier (Section 2.3.1). Formation of the product **107b** also confirmed the regiospecific anion generation as was evidenced from the formation of 1,2,4-isomeric derivative **85h** by TMSCl trapping.

Exclusive isolation of the known product **108** confirmed the lithiation of 1-naphthyl carbamate at the 2-position under these potentially equilibrating conditions. On the other hand, the 2-O-naphthyl carbamate underwent the anionic ortho-Fries rearrangement to afford a mixture of hydroxy naphthamides **100** and **109** in a ratio of 48:32. Compound **100** is **known (See Section 2.2.2)** while product **109** was identified by comparison of its ^{1}H NMR and IR spectra and physical properties with authentic material prepared from **101** by metal-halogen exchange followed by anionic ortho-Fries rearrangement (**Scheme 33**).

Scheme 33



101 **109**

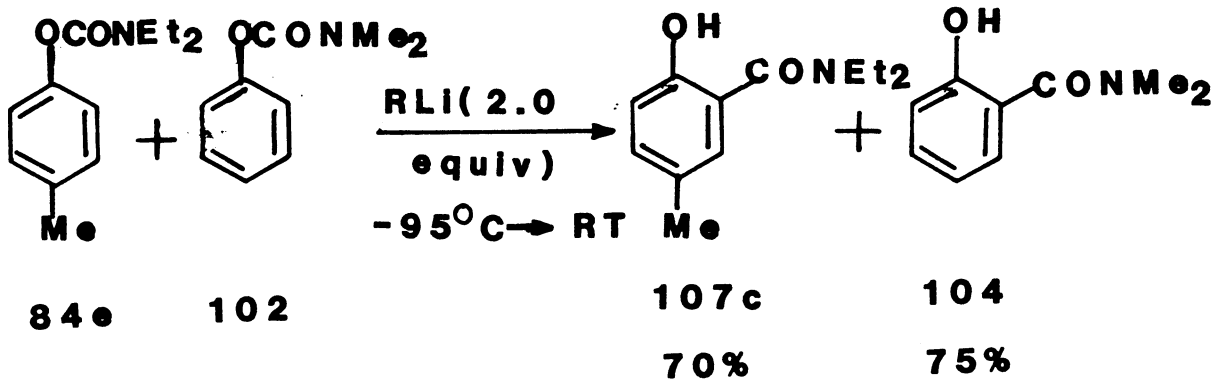
The ortho-methyl carbamate **103a** was found to undergo both aromatic and benzylic metalation to give products **110** and **111** in a ratio of 56:25.

Product **110** is a known compound while **111** is easily identified by the methylene peak (δ 3.73) in its ^{1}H NMR spectrum which is characteristically downfield form the methyl peak(δ 2.26).

2.2.5. MECHANISM OF THE ANIONIC ORTHO-FRIES REARRANGEMENT

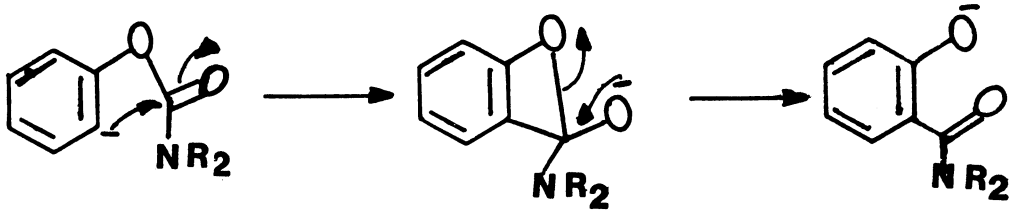
In order to distinguish between an intra- or intermolecular anionic 1,3-carbamoyl migration, a mixture of one equivalent each of N,N-diethyl O-4-tolyl carbamate **84e** and N,N-dimethyl O-phenyl carbamate **102** was lithiated with two equivalent of base and allowed to warm to room temperature. The identified products were the corresponding salicylamide derivative **107c** and **104** (Scheme 34) with no evidence for cross over products thus suggesting an intramolecular mechanism for the anionic carbamoyl migration which therefore presumably proceeds

Scheme 34



via the intermediacy of a tetrahedral intermediate **112** (Scheme 35).

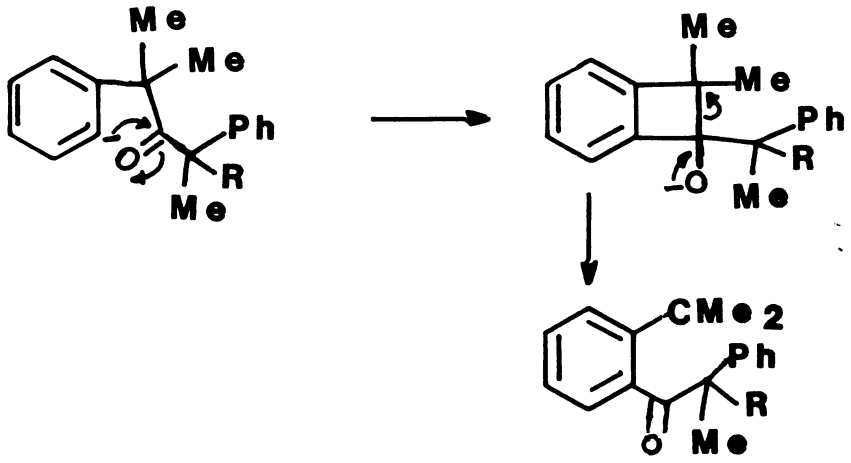
Scheme 35



112

The intermediacy of a similar cyclobutane type intermediate formed from the attack on a carbonyl group by an ortho phenyl anion has been proposed[77] (Scheme 36).

Scheme 36



The formation of a tetrahedral intermediate would be expected to be faster for the N,N-dimethyl carbamoyl group compared to the corresponding N,N-diethyl function because of the smaller steric bulk of the former.

2.2.6. COMPETITIVE METALATION: RELATIVE ORTHO DIRECTING ABILITIES OF CARBAMATE, AMIDE AND METHOXYMETHOXY GROUPS

The N,N-diethylcarbamoyloxy group is a very recent addition to the known directed ortho metalation groups.[6,8] The efficiency of this group as an ortho director has been successfully demonstrated in work described in the previous sections. However, its ortho directing capability in comparison to other known ortho directing groups required exploration.

Fraser's[78] pK_a results indicate that the N,N-diethylcarbamoyloxy group possesses an extremely strong thermodynamic acidifying effect of an ortho hydrogen in an aromatic substrate.

In our study, the relative ortho directing abiliby of carbamate in both inter- and intramolecular reactions with N,N-diethylamide and methoxymethoxy groups was compared. The comparison with the teriary amide is valuable in view of the work of Beak[47] and Meyers[46] which demonstrated its very powerful directing ability. The comparison with OCH_2OMe offers evaluation of two phenol protecting groups.

2.2.6.1. RELATIVE DIRECTED METALATION ABILITIES OF CARBAMATE AND TERTIARY AMIDE FUNCTIONS

In an intermolecular competition experiment, 1.0 equiv of each of the carbamate **84a** and the amide **45a** was allowed to react with 1.0 equiv. of s-BuLi/ TMEDA in THF solvent (**Scheme 37**) and the lithiated species were treated with several different electrophiles. The results are collected in **Table 16.**

Scheme 37

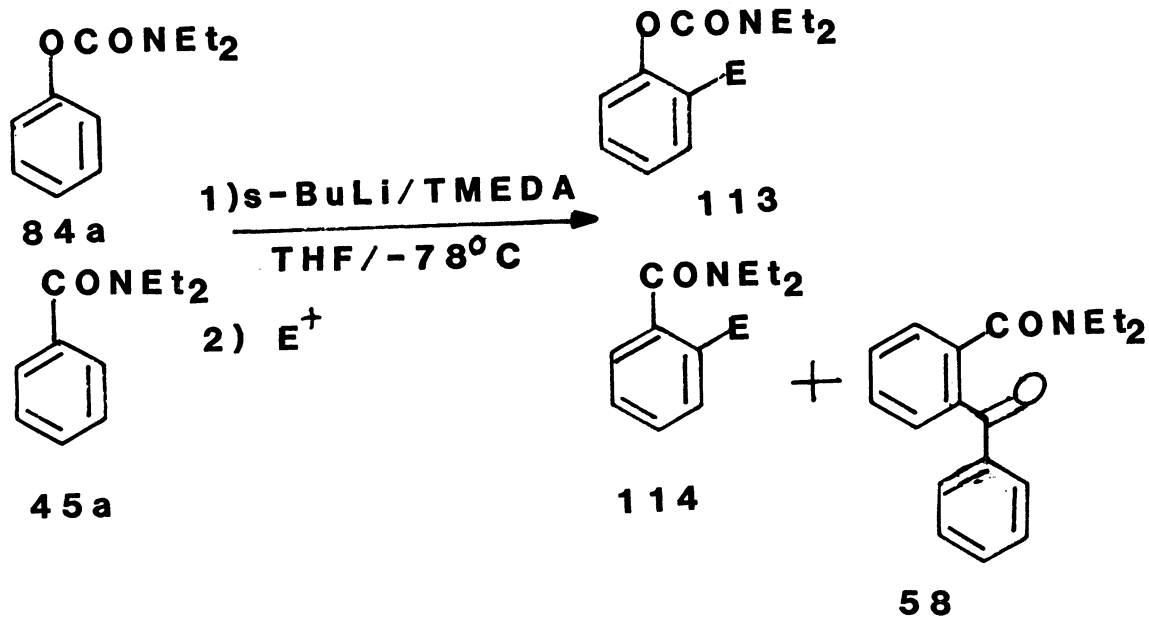


Table 16 Competition between **84a** and **45a** for 1.0 Equiv of s-BuLi/TMEDA

Entry	Lithiation Temp (°C)/Time	Electrophile	Product, yield[a],%			Starting Material, Yield[a],%	
			113	114	58[b]	**84a**	**45a**
1	-78/1h	EtOD	62[c]	36[c]	7		
2	-78/1h	MeI	48	21	15	38	26
3	-78/1h	$(MeS)_2$	40	13	20	30	17
4[d]	-100/15 min	MeI	46	33	4	54	62
5[d]	-100/15 min	$(MeS)_2$	30	21	6	70	73
6[d]	-100/15 min	Et_2NCOCl	40	31	9	60	60

[a] Since **84a, 113** and **45a, 114** mixtures were inseparable, products ratios were established by ^1H NMR and GC comparison with authentic samples (See

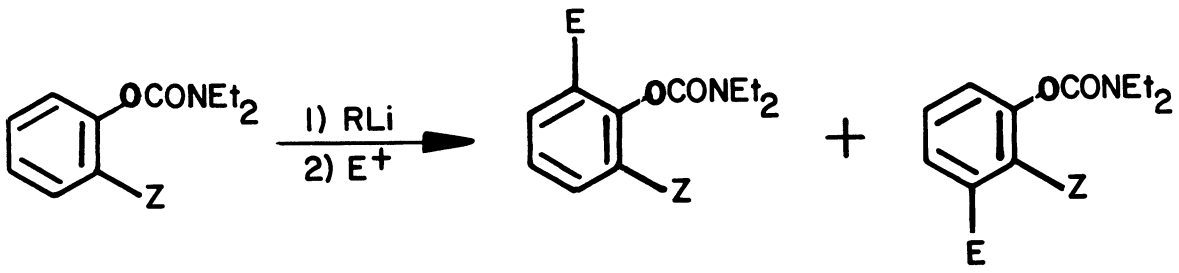
Experimental).
[b] Product **58** was isolated and identified by comparing with authentic materials (^{1}H NMR, IR, GC, MS).
[c] Deuterium content calculated from ^{1}H NMR and MS. Chemical yields were **113** : 85%; **114** : 87%.
[d] Ratios of products determined by GC comparison with authentic materials (see Experimental).

The results from these intermolecular competition experiments indicate that the carbamate is a somewhat better ortho directing group than the tertiary amide varying from 3:2 to 1.2:1 (entries 1-3). In an attempt to suppress the formation of **58** , the lithiation was carried out at -100°C for 15 min (entries 4-7). However, complete suppression could not be achieved.

2.2.6.2. RELATIVE DIRECTED METALATION ABILITES OF CARBAMOYLOXY, TERTIARY AMIDE AND METHOXYMETHOXY GROUPS BY INTRAMOLECULAR COMPETITION EXPERIMENTS

The intramolecular competition in metalation of methoxymethoxy and the $CONEt_2$ positioned ortho, meta, and para with respect to a carbamoyloxy group was examined. Lithiation of the substituted O-aryl carbamate derivitives **115, 118** and **121** was carried out under standard conditions (s-BuLi/TMEDA/THF/-78°C) and the lithiated species were treated with an electrophile (MeOD, $ClCONEt_2$) (**Scheme 38**). The results are summarized in **Table 17** .

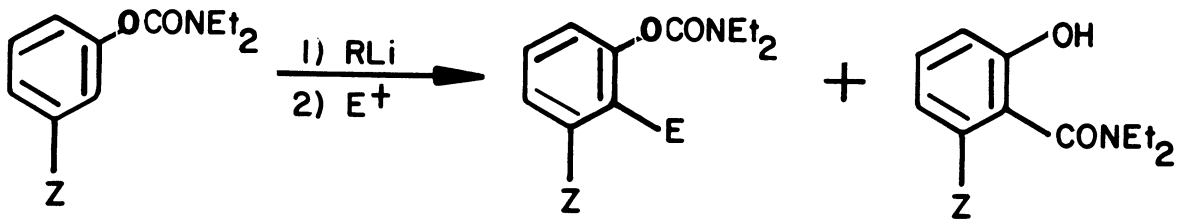
Scheme 38



115 116 117

	Z
	—
a:	$CONEt_2$
b:	OCH_2OMe

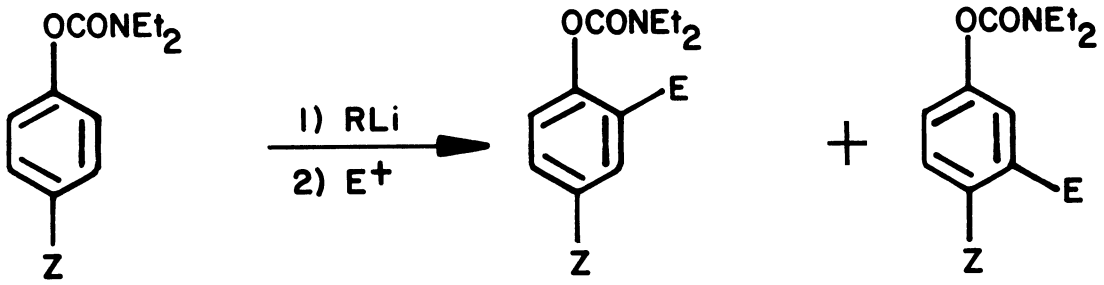
	Z	E
	—	—
a:	$CONEt_2$	D
b:	$CONEt_2$	$CONEt_2$
c:	OCH_2OMe	D
d:	OCH_2OMe	$CONEt_2$



118 119 a,c 117 b 120 d-e

	Z
	—
a:	$CONEt_2$
b:	OCH_2OMe

	Z	E
	—	—
a:	$CONEt_2$	D
b:	$CONEt_2$	$CONEt_2$
c:	OCH_2OMe	D
d:	$CONEt_2$	-
e:	OCH_2OMe	-



121 a - b

122 a - d

123 a - b

	Z
a:	$CONEt_2$
b:	OCH_2OMe

	Z	E
a:	$CONEt_2$	D
b:	$CONEt_2$	$CONEt_2$
c:	OCH_2OMe	D
d:	OCH_2OMe	$CONEt_2$

Table 17: Intramolecular Competition in Metalation between Carbamate and Tertiary Amide and Methoxymethoxy Functions

Entry	Substrate	Electrophile	Product Ratio **116**	Product Ratio **117**	Yield,%
1	**115a**	MeOD	a		86
2	**115a**	Et_2NCOCL	82	18	80
3	**115b**	MeOD	a		88
4	**115b**	Et_2NCOCl	100	0	50
			119	**120**	
5	**118a**	MeOD	100	0	85
6	**118a**	Et_2NCOCl	31	69	23
7	**118b**	MeOD	100	0	96
8	**118b**	Et_2NCOCl	--	100	68
9	**118a**	--	--	100	30
			122	**123**	
10	**121a**	MeOD	a		85
11	**121a**	Et_2NCOCl	61	39	68
12	**121b**	MeOD	a		87
13	**121b**	Et_2NCOCl	100	0	70

[a] Ratio could not be obtained as loss in peak intensity could not be measured exactly.

The extent of deuteration was estimated by ^1H NMR and mass spectrometry (Table 18).

Table 18: ^{1}H NMR and Mass Spectral Data of Carbamates **115, 118, 121** and Their Deuterated Derivatives.

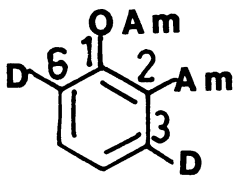
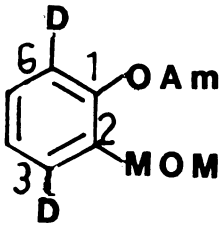
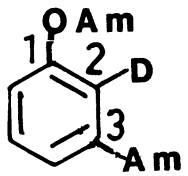
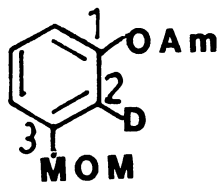
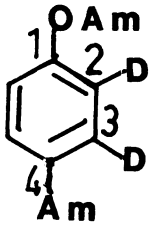
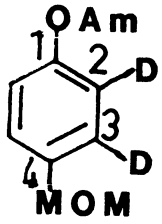
Compounds H	(D)	Hydrogens	Chemical Shift,δ Protio (Intensity)	Deuterio (Intensity)	% d_1 ^{1}H NMR[a,b]	MS[b,c]
115a	**(116a)** **(117a)**	3,4,5,6	7.2-7.3(4)	7.2-7.4(3.2)	80	55
						
115b	**(116c)** **(117c)**	3,4,5,6	7.0-7.16(4)	7.0-7.25(3.37)	63	37
						
118a	**(119a)**	2,4,5,6	7.1-7.36(4)	7.1-7.36(3.36)	64	33
						
118b	**(119c)**	2,4,6] 5]	6.7-6.9(3) 7.0-7.24(1)	6.8-6.9(2.3) 7.1-7.26(1)	70	55
						

Table 18 (continued)

121a	(122a) (123a)	2,6] 3,5]	7.0-7.19(2) 7.0-7.19(2)	7.1-7.2(1.27) 7.33-7.44(1.7)	73 30	66
						
121b	(122c) (123c)	2,6] 3,5]	7.0(4)	7.0(3.03)	97	54
						

Am = $CONEt_2$ MOM = OCH_2OCH_3

[a] Integral area vs 8.0 for the four methylenes of the carbamate and amide groups in the carbamate-amide derivatives and integrated area vs 2.0 for the methylene of the methoxymethoxy groups in carbamate-methoxymethoxy derivatives.
[b] The values of deuterium content as estimated by ^1H NMR and MS were found to differ largely from each other. Some of the reactions were repeated but the results remained almost the same.
[c] The deuterium content as calculated from MS are considered to be more reliable.

The sites of lithiation were determined by analysis of the ^{13}C NMR spectra which show a reduction in intensity of the signal for the substituted carbon(s) in the products compared to the corresponding signal in the starting materials according to the method of Beak.[47] The position of substitution was assigned by using established additivity of individual ^{13}C NMR substituent chemical shifts either from the literature[76] or as determined **(Table 19).** The shift value expresses the direction and magnitude of a carbon's chemical shift difference from 128.5 ppm, the shift

for benzene.[76] The experimental chemical shift difference of aromatic carbons of O-phenyl carbamate were found to fit reasonably well with the chemical shift difference of aromatic carbons of phenyl acetate. These findings were also confirmed by comparing the ^{13}C NMR spectrum of N,N-diethyl O-(4-N,N-diethyl carbamoyl) phenyl carbamate following the method of Beak.[47] This method was found to work satisfactoraly when applied to other substitution patterns. Similarly, the aromatic carbon chemical shift difference of methoxymethoxybenzene was determined by comparison with the p-methoxymethoxy carbamate derivative **(Table 19).**

Table 19: ^{13}C NMR Substituent Shifts ($\Delta\delta$) of Monosubstituted Benzenes Relative to Benzene (128.5 ppm) in $CDCl_3$.

Z	Carbon $\Delta\delta$ values[a]				Reference
	ipso	ortho	meta	para	
$CONEt_2$	+8.8	-2.2	-1	+0.6	47
$OCONEt_2$	+22.9	-7.0	+0.4	-3.7	b
OMe	+31.4	-14.4	+1.0	-7.8	76
OCH_2OMe	+29.5	-11.26	-0.75	-5.0	b
Cl	+6.2	+0.4	+1.3	-1.9	76

[a] Positive $\Delta\delta$ values correspond to downfield shift.
[b] Experimental values

The observed chemical shifts and relative intensities of the peaks for the aromatic carbons of the carbamate derivatives, as well as calculated chemical shifts determined by using the substituent shift (**Table 19**), are collected in **Tables 20** and **21** .

Table 20 Calculated and Experimental Aromatic ^{13}C NMR Shifts for Deuterated Carbamate Derivatives

Compound H (D)	Carbon	δ ppm Calcd	H Exptl(rel.intensity)	D Exptl(rel.intensity)
115a(116a)	1	149.2	147.4 (39)	147.4 (40)
(117a)	2	130.3	130.6 (28)	129.5 (47)
	3	126.7	126.6 (95)	126.8 (100)
	4	124.7	124.9 (83)	125.0 (77)
	5	129.5	129.4 (83)	129.4 (67)
	6	121.4	123.2 (100)	123.2 (56)
115b(116c)	1	140.1	141.4 (30)	141.6 (9)
(117c)	2	151.0	149.2 (35)	149.4 (12)
	3	117.6	116.3 (91)	116.5 (68)
	4	125.6	125.9 (100)	126.1 (100)
	5	122.3	122.0 (96)	122.1 (94)
	6	123.9	123.3 (95)	123.5 (88)
118a(119a)	1	151.3	151.3 (47)	151.5 (19)
	2	119.3	119.8 (95)	120.1 (59)
	3	137.7	138.1 (44)	138.3 (20)
	4	122.6	122.5 (100)	122.8 (100)
	5	128.8	129.0 (81)	129.3 (86)
	6	122.1	122.1 (96)	122.4 (94)

Table 20 (continued)

118b(119c)	1	152.2	152.4 (53)	152.4 (63)
	2	110.2	110.1 (93)	110.1 (79)
	3	158.4	158.0 (47)	158.0 (70)
	4	113.5	113.0 (97)	113.0 (100)
	5	129.7	129.5 (100)	129.6 (98)
	6	116.5	115.2 (90)	115.3 (84)
121a(122a)	1	152.0	151.9 (28)	151.1 (25)
(123a)	2)) 6)	121.4	131.3 (99)	121.6 (91)
	3)) 5)	126.7	127.2 (100)	127.4 (100)
	4	133.6	133.7 (32)	133.9 (26)
121b(122c)	1	145.9	145.9 (32)	146.1 (29)
(123c)	2)) 6)	122.3	122.3 (78)	122.5 (92)
	3)) 5)	116.6	116.6 (100)	116.9 (100)
	4	154.3	154.3 (24)	154.3 (24)

Table 21: Caclulated and Experimental Aromatic ^{13}C NMR Shifts of Carbamate Derivatives **116b, 117b, 116d, 119b, 120d, 122b, 123b, 122d.**

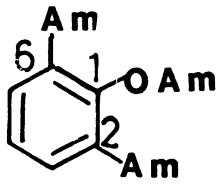
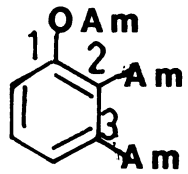
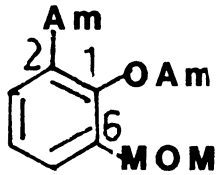
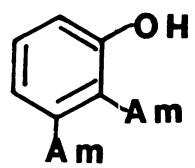
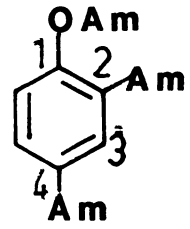
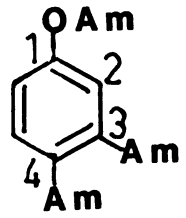
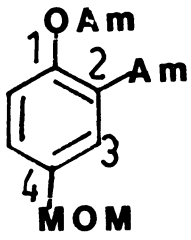
Compound	Carbon	δ ppm Calcd	δ ppm Exptsl(rel.intensity)
116b	1	147.0	145.0 (14)
	2)) 6)	130.2	130.2 (30)
	3)) 5)	127.3	127.4 (100)
	4	124.6	125.2 (44)
117b	1	149.1	147.4 (21)
	2	128.1	127.5 (23)
	3	135.5	136.2 (30)
	4	122.5	123.3 (98)
	5	129.4	129.4 (96)
	6	122.0	122.0 (100)
116d	1	137.9	137.5 (25)
	2	131.1	132.6 (37)
	3	121.7	119.2 (95)
	4	125.5	125.9 (100)
	5	118.2	116.2 (87)
	6	150.9	149.8 (35)
120d	1	136.9	135.7 (86)
	2	122.5	121.8 (69)
	3	153.1	153.3 (87)
	4	116.4	117.1 (92)

Table 21 (continued)

	5	130.8	129.7	(100)
	6	118.3	117.6	(96)
122b	1	149.8	148.2	(69)
	2	130.2	130.8	(69)
	3	124.5	125.4	(98)
	4	133.5	134.3	(71)
	5	127.3	127.8	(94)
	6	121.3	123.3	(100)
123b	1	151.9	151.2	(33)
	2	119.2	119.5	(96)
	3	135.5	136.1	(28)
	4	131.4	131.7	(33)
	5	126.6	127.0	(100)
	6	122.0	121.4	(96)
122d	1	144.2	141.7	(63)
	2	131.1	131.2	(65)
	3	115.4	114.2	(97)
	4	154.2	154.1	(85)
	5	118.2	117.3	(88)
	6	122.2	124.0	(100)

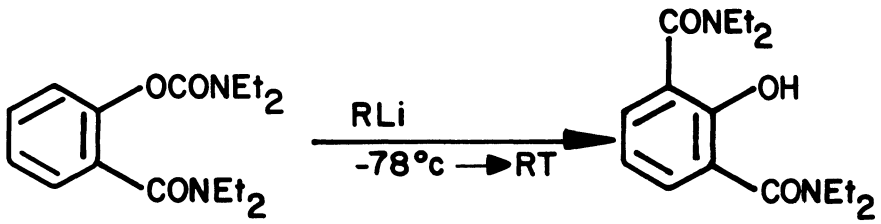
It was observed from the deuteration results **(Table 20)** that for the ortho-carboxamido carbamate **115a** , the lithiation occurs predominantly ortho to the carbamoyloxy group as judged by the loss of intensity of the

signal for C-6. However, the ratio of the products could not be estimated. For compound **115b** , it is difficult to arrive at any conclusion. For compounds **121a** and **121b** , although the intensity of the signals for carbons ortho to the carbamoyloxy functions is less than the carbons ortho to the competing groups, the ratio of products could not be estimated and hence no conclusive statement could be made. However, when the carbamate and the competing groups are meta-related as in compounds **118a** and **118b** , the metalation was found to occur almost exclusively at the position between the two groups as evidenced by the loss of intensity of the signal for C-2 with a trace reduction in intensity of the signal for C-6.

In view of the above results which failed to provide conclusive evidence regarding the site of lithiation and therefore extent of competition, trapping experiments with another electrophile, diethylcarbamoyl chloride were undertaken **(Table 17).** Examination of the ^{13}C spectra of the derived products **116b, 116d, 117b, 119b, 120d, 120e, 122b, 122d** and **123b (Table 21),** the site and extent of lithiation and thus the ratio of the products (see **Table 17)** were determined which ultimately provided evidence that the lithiation takes place preferentially ortho to the carbamate functionality when the competing group is a tertiary amide and exclusively when the competing group is methoxymethoxy. For compound **115a** and **121a** where the amide is at ortho- and para-positions to carbamate respectively, predominant metalation occurs ortho to the carbamate **(Table 17,** entries 2 and **11**). Two products **116b** and **117b** were obtained from **115a** in a ratio of 82:18 (overall yield 80%). The structure

of compound **117b** was confirmed by comparison with authentic material prepared by another route (see Experimental). Likewise **121a** afforded **122b** and **123b** in a ratio of 61:39. In a separate experiment, **115a** was shown to undergo the ortho-Fries rearrangement to give **124** in 60% yield (Scheme **39**).

Scheme 39



115 a **124**

For compounds **115b** and **121b** , where the methoxymethoxy group is at the ortho- and para-position with respect to carbamate respectively, single products **116d** (50%) and **122d** (70%) respectively, were obtained indicating exclusive metalation ortho to the carbamate function.

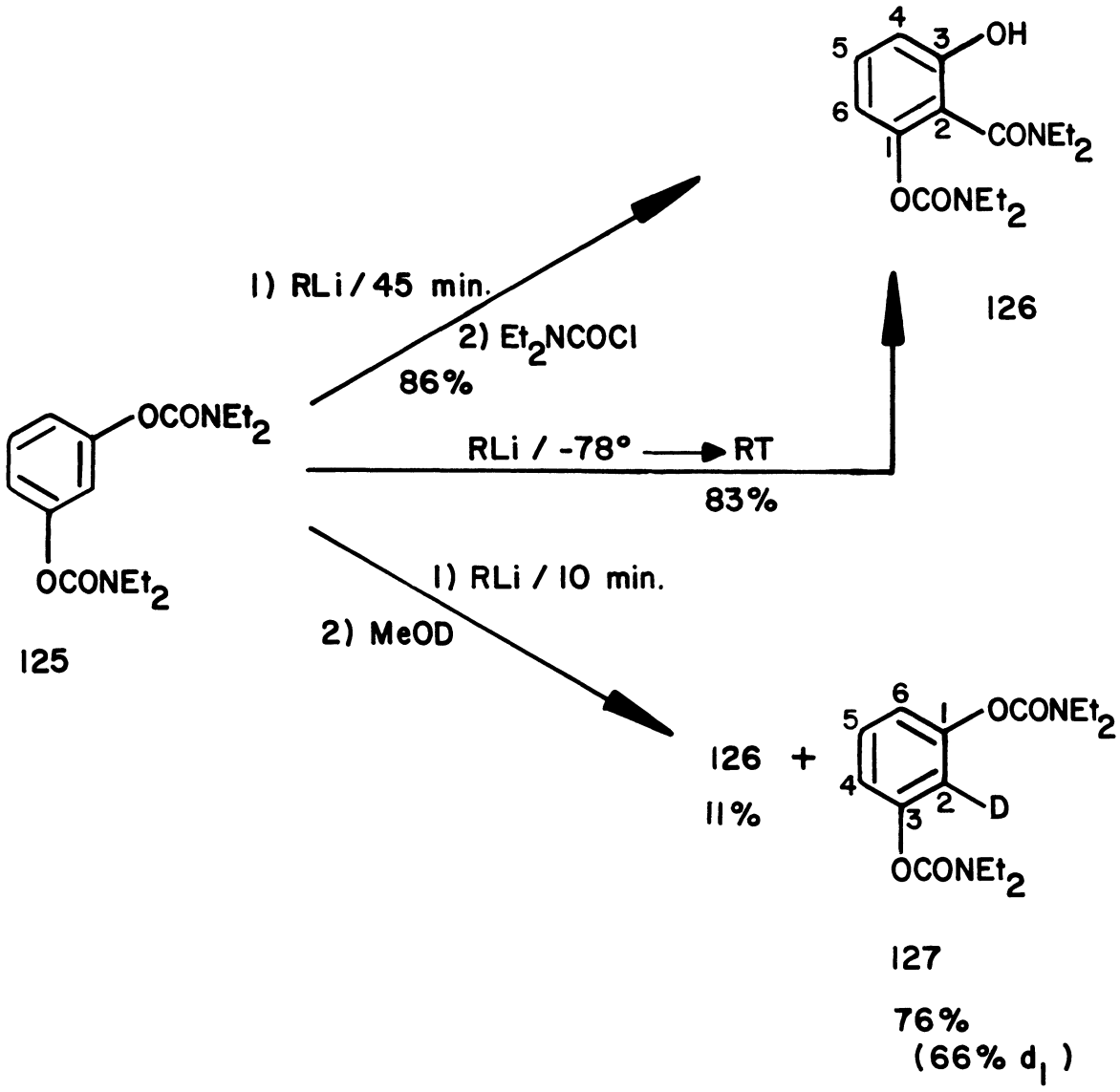
For compound **118a** in which carbamate and amide functionalities are meta-related, reaction with Et_2NCOCl appeared sluggish and led to **119b** and rearranged product **120d** in a ratio of 31:69 and low combined yield. The reason for low incorpoartion of the $CONEt_2$ function into the site common to the two directing groups may be attributed to a steric effect which retards intermolecular reaction with Et_2NCOCl and allows the presumably faster intramolecular migration of $CONEt_2$ to dominate. No products arising from C-4 or C-6 metalation were isolated. For compound **118b** , metalation again

occurred exclusively between the two directing groups but the anionic Fries rearrangement product **120e** again dominate$_d$ supposedly for the same reason.

These above results demonstrate the superiority of the carbamate function as an ortho director over tertiary amide and methoxymethoxy groups. It would appear therefore that the carbamoyloxy is the functionality of choice among the oxygen based directed metalation groups.

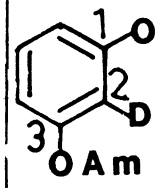
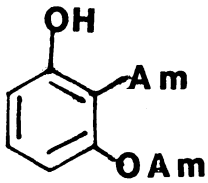
Finally we have carried out lithiation of N,N-diethyl O-(3-N,N-diethylcarbamoyloxy)phenyl carbamate **125** in order to determine metalation regioselectivity of two juxtaposed carbamates. Lithiation of **125** for 45 min followed by treatment with Et_2NCOCl afforded only the rearranged product **126** in high yield suggesting that the anionic ortho-Fries rearrangement is very fast even at -78°C. Without added electrophile, **125** underwent the ortho-Fries rearrangement to give **126** in similar yield **(Scheme 40).** However, under shorter lithiation times (10 min) followed by quenching with a small electrophile (MeOD), the rearrangement is minimized (11%) leading mainly to deuterated product **127** .

Scheme 40



^{1}H and ^{13}C NMR spectral examination of **126** and **127** reveal that lithiation occurs exclusively in between the two carbamate functions. For compound **126** , ^{1}H NMR indicates a 1,2,3-aromatic hydrogen substitution pattern (δ 6.72, J=7.8, 1.17 and δ 6.76, J=8.2, 1.7 indicate H-4 and H-6. δ 7.17, J=7.8, 8.2 indicates H-5). The ^{13}C NMR spectral data **(Table 22)** confirmed the structures of the products and hence the site of lithiation.

Table 22: Calculated and Experimental Aromatic ^{13}C NMR Chemical Shifts of **125, 126, 127.**

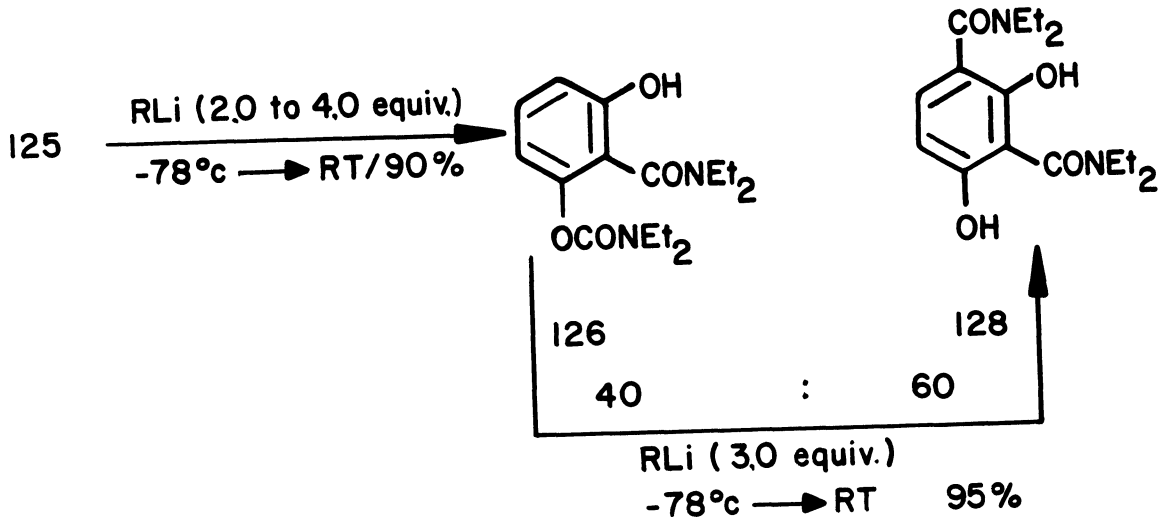
Compound	Carbons	δ ppm Calcd	H Exptl(rel.intensity)	D Exptl(rel.intensity)
125 (127) 	1)) 3)	151.8	151.7 (55)	151.9 (45)
	2	114.5	115.3 (64)	115.6 (21)
	4)) 6)	117.8	118.0 (100)	118.3 (100)
	5	129.3	128.8 (64)	129.1 (50)
126 	1	151.0	148.1 (71)	
	2	117.7	117.6 (64)	
	3	153.6	154.7 (49)	
	4	112.1	113.7 (100)[a]	
	5	131.3	129.9 (82)	
	6	113.5	113.8 (100)[a]	

[a] These values could be reversed.

As a sequel to ongoing work on dilithiated O-aryl biscarbamates,[54,79] **125** was subjected to dilithiation conditions (2.0 equiv s-BuLi/TMEDA/THF/ -78°C) and the presumed resulting lithiated species was allowed to warm to room temperatures. A mixture of mono- and bis-migrated products **126** and -**128** were isolated in a ratio of 40:60 **(Scheme 41).** Variation of the conditions, using up to 4.0 equiv of s-BuLi or subjecting125 **to a one pot** two-step metalation gave the same mixture of products in almost an identical ratio. However, when purified **126** was subjected to metalation (3.0 equiv s-BuLi) followed by warming to room temperature, **128** was

obtained in quantitative yield.

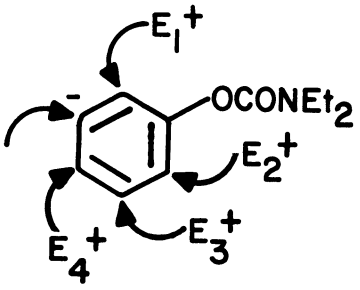
Scheme 41



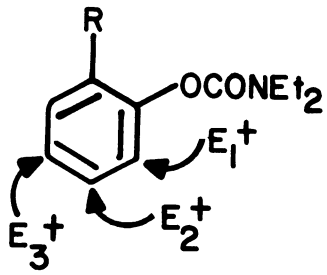
2.2.7. ITERATIVE METALATION

Iterative metalation procedures for O-aryl carbamates may be envisaged by considering the anionic introduction of electrophilic groups (E^+) which direct further ortho metalation **(Scheme 42).** In this manner, very short, preferably one pot, methods for the synthesis of polysubstituted aryl carbamates might be achieved. Towards this end, several experiments were performed **(Scheme 43).**

Scheme 42

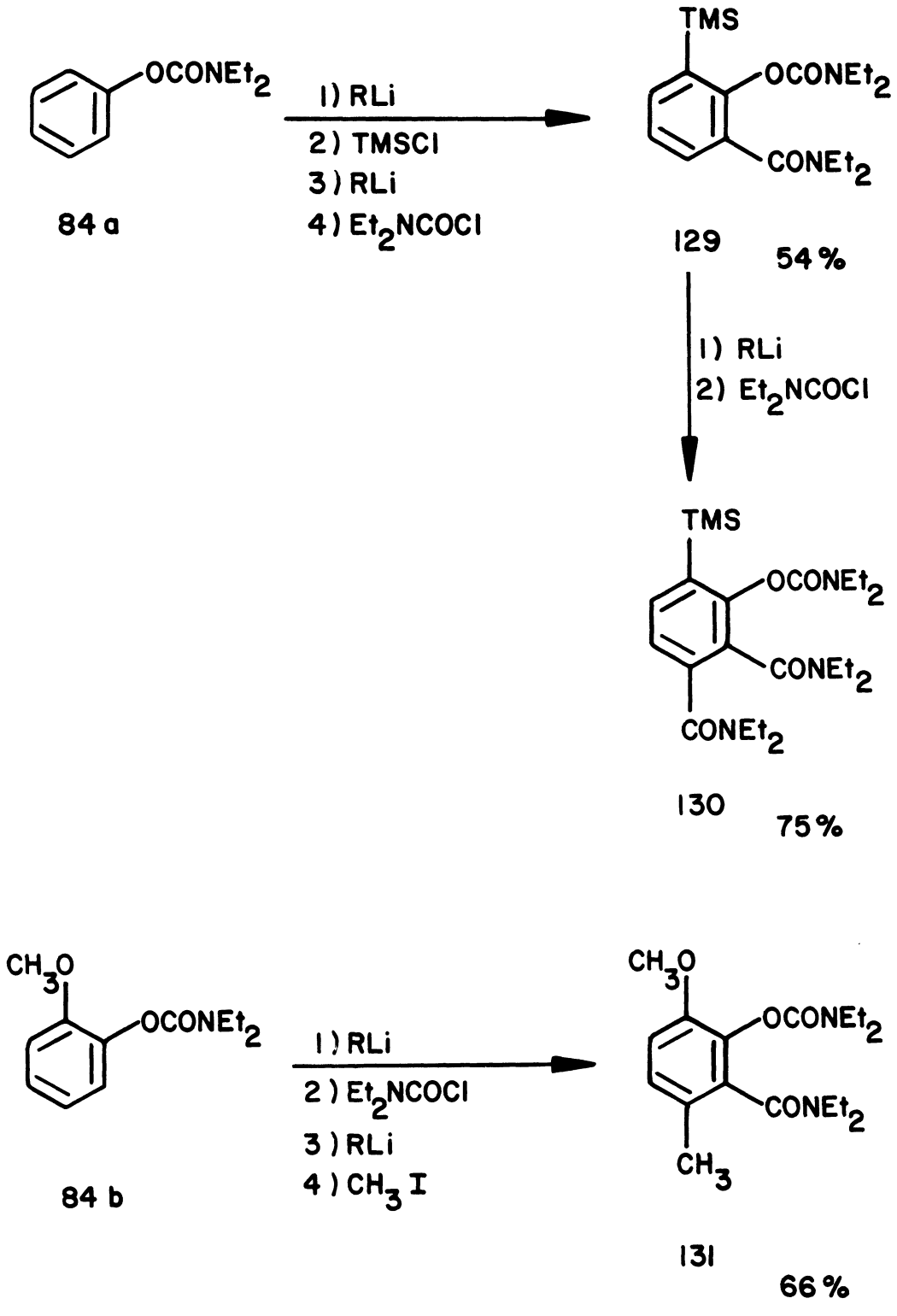


E_1 = Non-directing group
E_2,E_3 = Directed metalation group
E_4 = Directed or non-directing metalation group



R = Non-directing or weakly directing group
E_1,E_2 = Directed metalation group
E_3 = Directed or non-directing group

Scheme 43


OCONEt2
1) RLi
2) TMSCl
3) RLi
4) Et2NCOCl
84 a
TMS
OCONEt2
CONEt2
129
54 %
1) RLi
2) Et2NCOCl
TMS
OCONEt2
CONEt2
CONEt2
130
75 %
CH3O
OCONEt2
1) RLi
2) Et2NCOCl
3) RLi
4) CH3 I
84 b
CH3O
OCONEt2
CONEt2
CH3
131
66 %

Sequential metalation, silylation, metalation, carbamoylation of **84a** in one pot provided the trisubstituted system **129** in reasonable yield. More than two metalation in the same pot proved unsatisfactory as seen from the further attempted conversion of **129** into **130** without isolation of **129** . However, after purification, **129** underwent metalation and electrophilic quench to afford the contiguously tetrasubstituted carbamate derivative **130** in good yield. This compound may be amenable to further metalation although this was not tested.

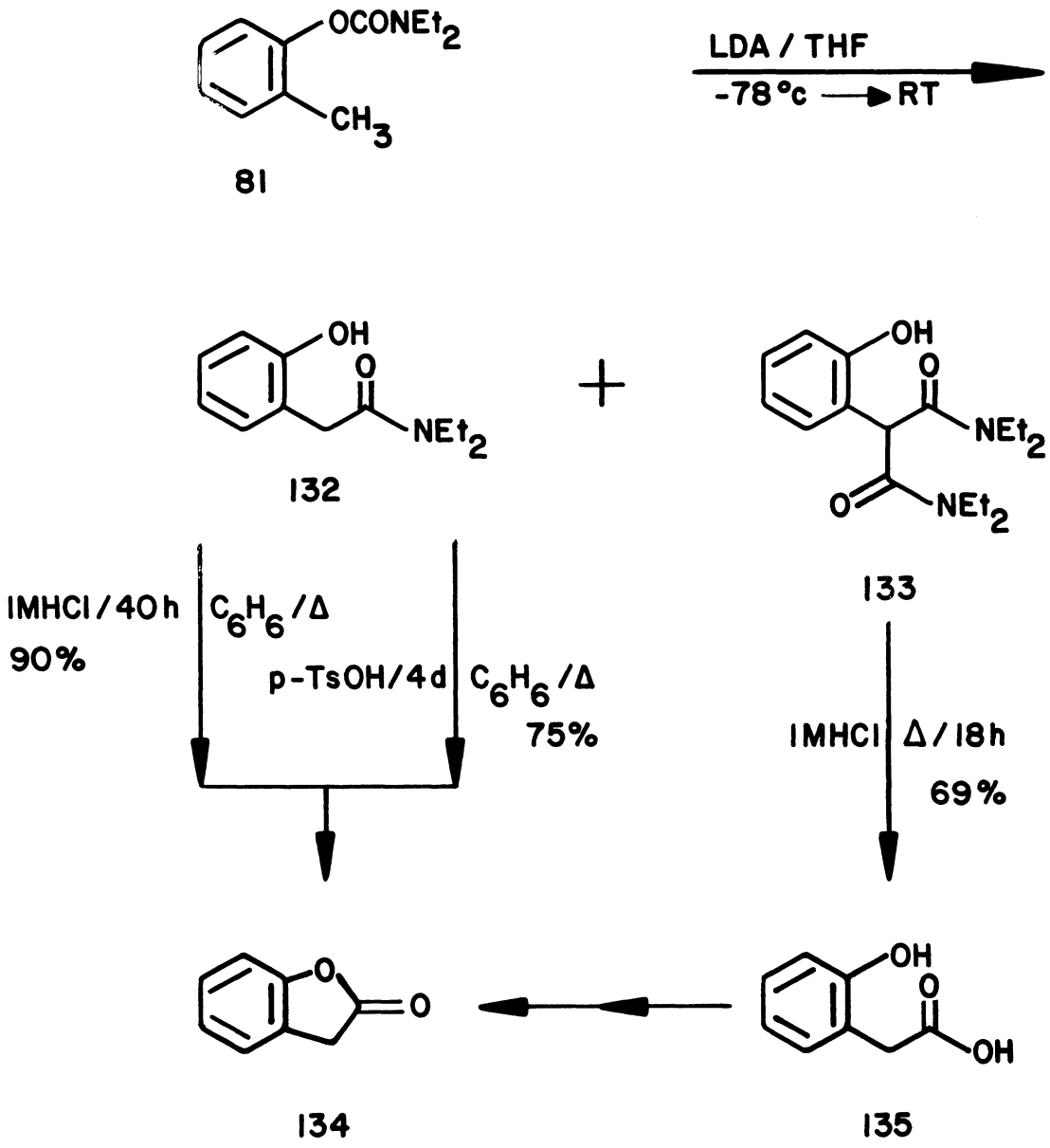
Compound **84b** also underwent two sequential metalations and electrophile quenches in one pot to give the tetrasubstituted product **131** . Therefore, it may be concluded that contiguously polysubstituted carbamate derivatives may be prepared by iterative metalation tactics.

2.3.8. SYNTHESES OF 2(3H)-BENZOFURANONE

Encouraged by the exclusive metalation at the benzylic position of **81** with LDA as evidenced by electrophilic trapping experiments (Section 2.2.1), attempts to induce an 1,4-O to C carbamoyl migration to the benzylic site were undertaken **(Scheme 44).** In the event, when **81** was subjected to metalation followed by warming to room temperature (the same conditions as those used for the anionic ortho-Fries rearrangement), the ortho-hydroxy phenylacetamides **132, 133** were obtained in useful yields. Compound **132** was easily cyclized under acid-catalysed conditions (1M HCl/

C_6H_6/ Δ /40 h or p-TsOH/C_6H_6/ Δ /4 d) to the benzofuranone **134** .

Scheme 44



The product **133** appeared to be formed from **132** via the generation of a second benzylic anion followed by intermolecular migration of the $CONEt_2$ group. Compound **133** was also found to undergo facile hydrolysis and

decarboxylation to give ortho-hydroxyphenylcetic acid **135** which also underwent cyclization to **134**.

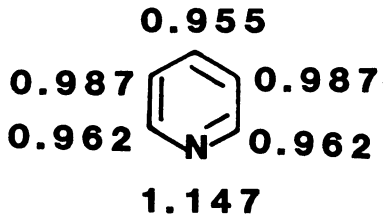
This methodology could be useful for the synthesis of substituted benzofuranone derivatives with substituent patterns difficult to obtain by other means. For instance, 7-chloro-, 7-methoxy-, and 6-methyl-2(3H)benzofuranones have been prepared by our coworkers[54,80] following the methodology described above.

CHAPTER III

3.1. INTRODUCTION

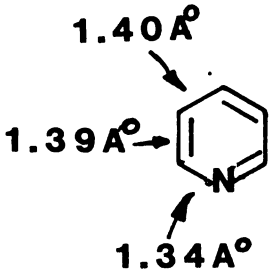
Although the aromaticity of pyridine has been indicated by valence bond and molecular orbital treatments[81], the -electron distribution around the pyridine ring, unlike benzene, is not uniform due to the higher electronegativity of nitrogen compared to carbon thereby causing electron withdrawal particularly from the 2- and 4-positions towards nitrogen. The distribution of electron density as estimated by a molecular orbital treatment[81] is shown below (Fig. 2) for illustration. The nonuniformity of electron density in pyridine also affects C-C bond lengths[82] and bond angles[83] (Fig. 2).

Figure 2a. The Distribution of Electron Density in Pyridine as Estimated by Molecular Orbital Treatment.



136

Figure 2b. Bond Lengths and Bond Angles in Pyridine



C-2 = 124°

C-3 = 118°36′

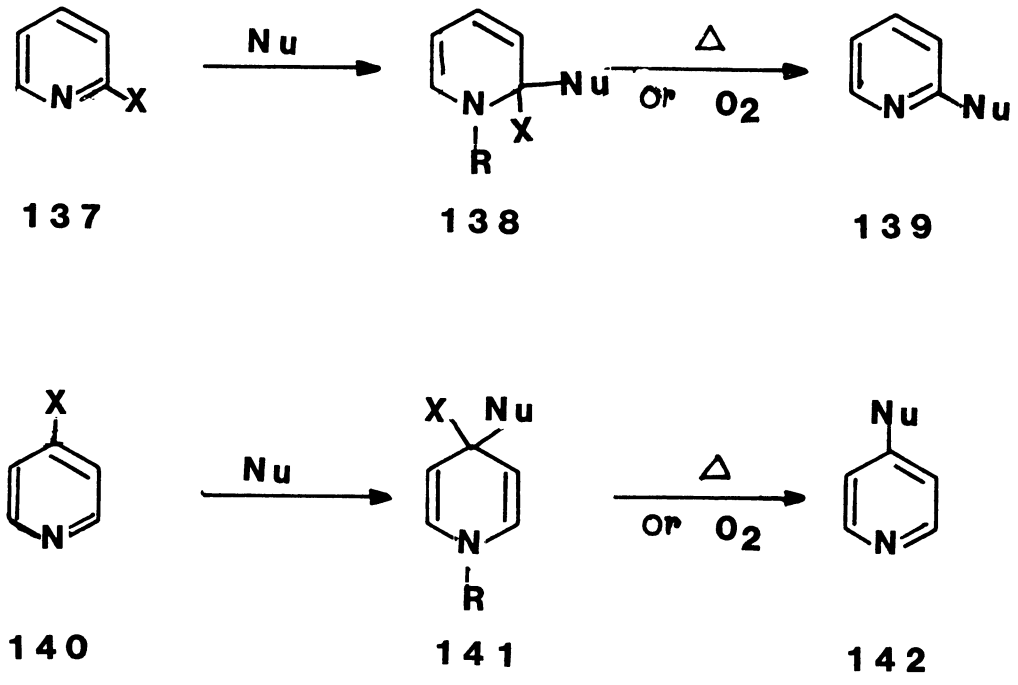
C-4 = 118°06′

Therefore pyridine, in principle, is less reactive towards electrophilic reagents and more reactive towards nucleophilic reagents than benzene in ordinary chemical reactions. Also the hydrogens in pyridine are more acidic than in benzene and can be abstracted by basic reagents as will be discussed in Section 3.1.2.

3.1.1. REACTION OF PYRIDINE WITH NUCLEOPHILIC BASES

Early reports established that treatment of pyridine with nucleophilic bases results in an overall addition-elimination reaction at the 2- and 4-positions[84] **(Scheme 45).**

Scheme 45



X = H, Cl, OMe, NO_2 R = H, Na, K

Nu = NH_3, KNH_2, $NaNH_2$

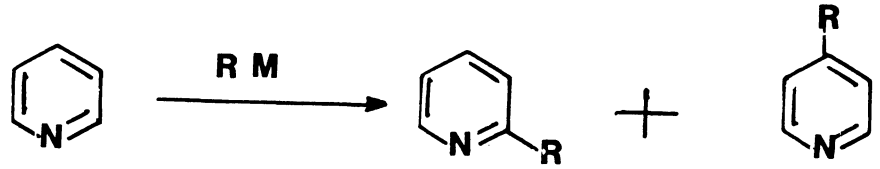
C_6H_5SH, NaOH

(X = H, Nu = NH_2 = Chichibabin reaction)

The nucleophilic reactivity of the pyridine nucleus is enhanced by the presence of a good leaving group at the 2- and 4-positions. Protonation, quaternization and N-oxide formation also enhance nucleophilic attack at these positions.[85]

Comparatively new reports that alkyl- and aryllithium and Grignard reagents add to the 2- and 4-positions parallel the previous results **(Scheme 46).** [86,87,88,89] The predominant addition of these basic reagents takes place at the 2-position which may be accounted for by invoking initial complexation of the reagent with the nitrogen followed by intramolecular attack at the 2-position.[85] Benzyllithium and benzylmagnesium chloride, on the other hand, afford predominantly 4-benzylpyridine. This may be considered to reflect the greater stability and selectivity of the benzyl anion.

Scheme 46



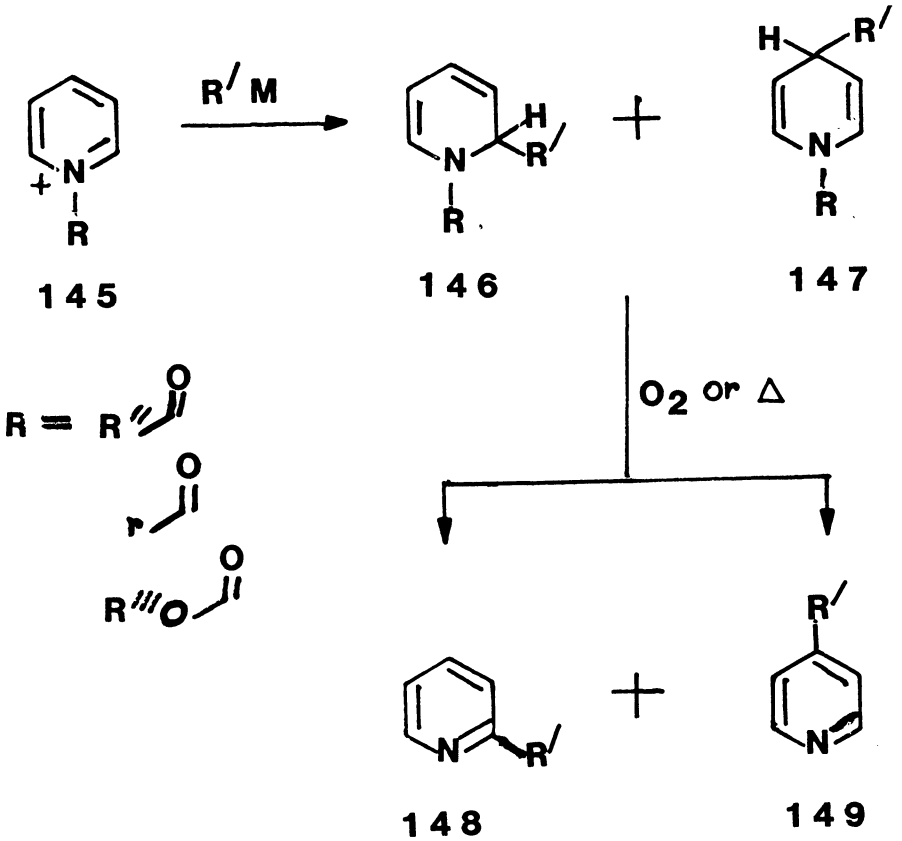
136 **143** **144**

M = Li, MgX

R = Alkyl, Aryl, Benzyl

The alkylation and arylation of the pyridine ring at the 2- and 4-positions with RLi, RMgx or RCu has been reported very recently through the quaternization of the nitrogen with acyl chloride, ethyl- or phenyl chloroformate and t-butyldimethyl silyltriflate **(Scheme 47).** [90,91,92,93] Alkyl or aryllithiums and aryl Grignard reagents add mainly to the 2-position. Alkyl Grignards, however, gives a mixture of 1,2- and 1,4-addition products. Alkyl and aryl Grignards in presence of copper iodide, and lithium dialkylcuprates or $RCu.BF_3$ reagents add regioselectively to the 4-position of 1-acyl pyridinium salts.

Scheme 47



145 146 147 148 149

R/ = Alkyl, Aryl

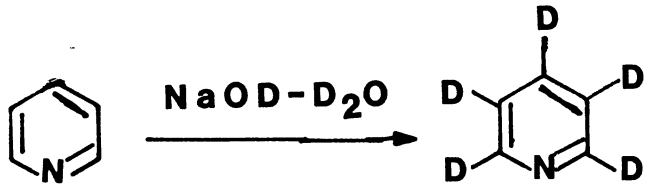
M = Li, MgX,

Cu

3.1.2. METALATION OF PYRIDINE

A complete H-D exchange of pyridine was reported by Zoltewicz[94] when pyridine is heated to 200°C in NaOD-D_2O **(Scheme 48)** and a positional exchange ratio of 1:2.3:3 for the protons (2+6): (3+5): 4 has been estimated from this reaction.

Scheme 48

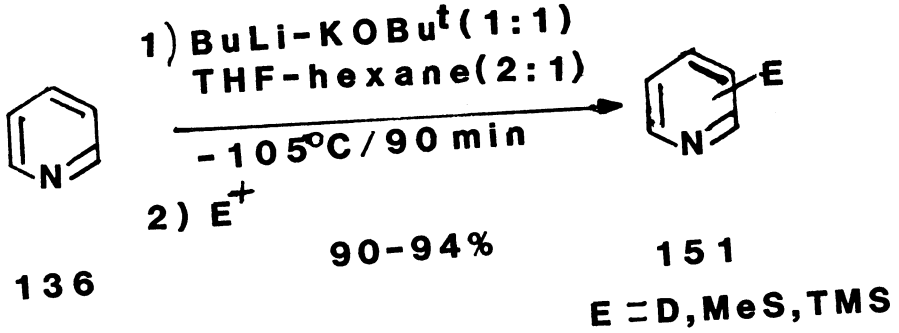


136 **150**

Zoltewicz[94] later reported a relative acidity ratio of 1:9.3:12 for the protons (2+6): (3+5): 4 from the NaOMe catalysed H-D exchange reaction of pyridine in MeOD at 165°C. Although the two reports differ from each other with respect to reaction conditions and results, both indicate a slower exchange rate at the 2-position. An explanation based on the relative acidity of different pyridine ring protons was proposed by Zoltewicz who considered two factors to account for the decreased reactivity of positions adjacent to nitrogen (2 and 6) relative to more distant centres (3 as well as 4): i) decreased s-character of the C_2-H bond due to the increased bond angle at C-2 of pyridine in comparison to benzene resulting in the reduced acidity of C-2 hydrogen; ii) electrostatic

repulsion between the electron pair on coplaner nitrogen and the (developing) carbanion formed by deprotonation. A very recent result on the metalation of pyridine followed by treatment with different electrophiles to give 2-, 3- and 4-substituted pyridines has been reported by Brandsma[95] **(Scheme 49).**

Scheme 49

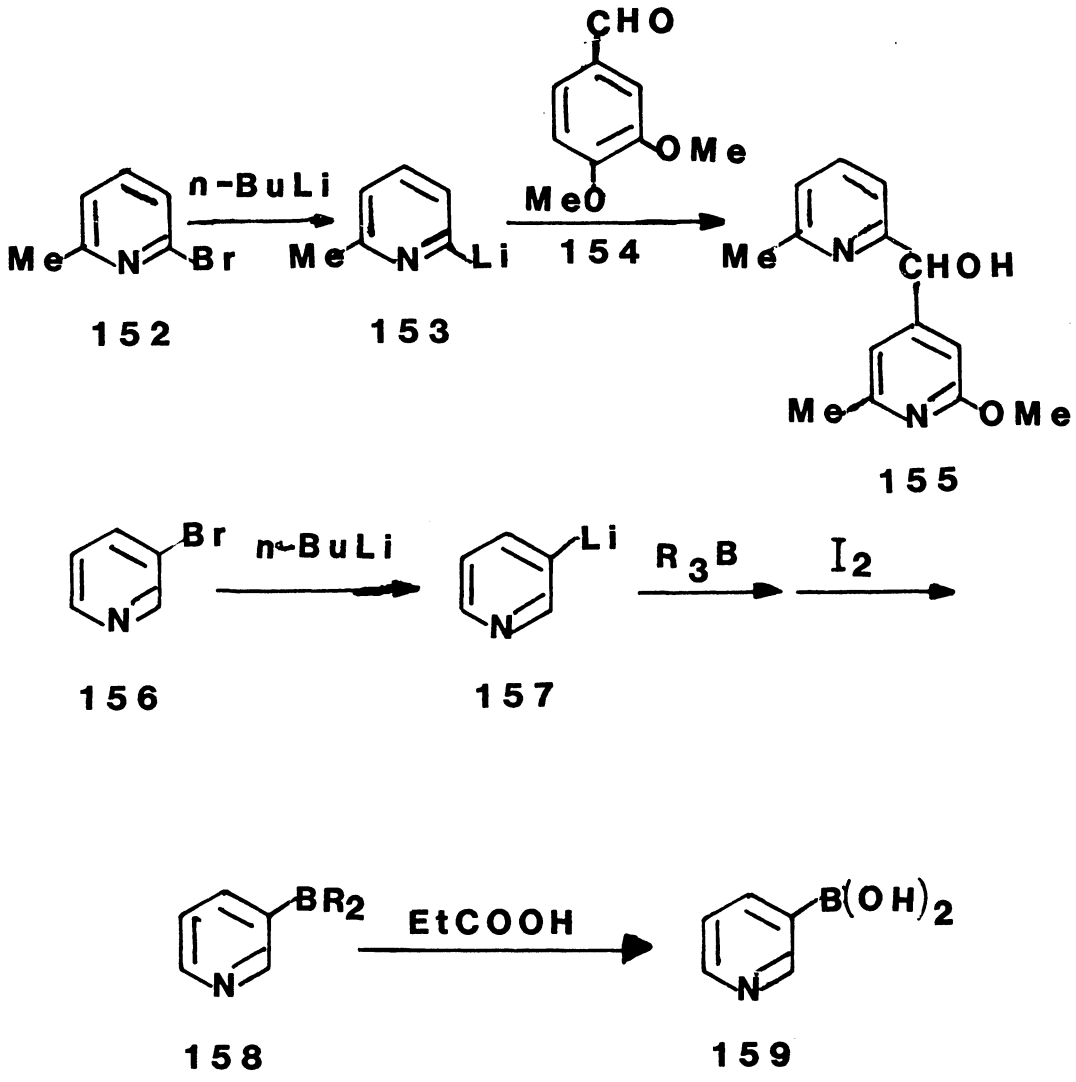


A kinetic acidity ratio of 6:1:6 for the protons (2+6): (3+5): 4 has been estimated from the deuteration reaction which is in contrast with the results by Zoltewicz.[94] Brandsma[95] also noted that when pyridine was treated with BuLi - ButOK in Et_2O, 2-potassiopyridine was obtained in 85% yield, whereas in a more polar solvent (THF, HMPT) about 90% yield of 4-potassiopyridine was obtained. So, it is apparent that different regioisomers can be obtained depending on the nature of solvent and base used.

3.1.3. METALATION OF PYRIDINE BY METAL-HALOGEN EXCHANGE

Formation of lithiated pyridine by metal-halogen exchange is well documented and takes place very readily under mild conditions.[96,97] Two examples are cited below for illustration **(Scheme 50).** [98,99] The first example shows that deprotonation of the highly acidic hydrogens on the o-methyl group does not compete with metal-halogen exchange.[98]

Scheme 50



Although this method is synthetically useful, it depends entirely on the availability of suitably substituted halopyridines.

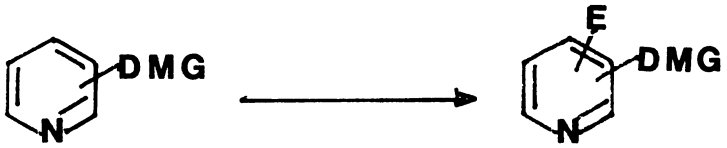
3.1.4. DIRECTED ORTHO METALATION OF PYRIDINES

Deprotonation reactions of π-deficient heterocycles has been an unexplored area for a long period of time perhaps due to the discouraging results of the addition reactions described in Section 3.1.1.

With the demonstration that the aromatic directed metalation reaction is a powerful synthetic tool for synthesis of polysubstituted aromatics[8], there has been a resurgence of interest in applying this chemistry to heteroaromatic substrates.

Towards this end, an increasing number of directing groups have been attached to the pyridine nucleus for testing the ortho metalation methodology **(Table 23).**

Table 23: Metalation of Pyridine Bearing Ortho Directing Groups



DMG = Directed Metalation Group

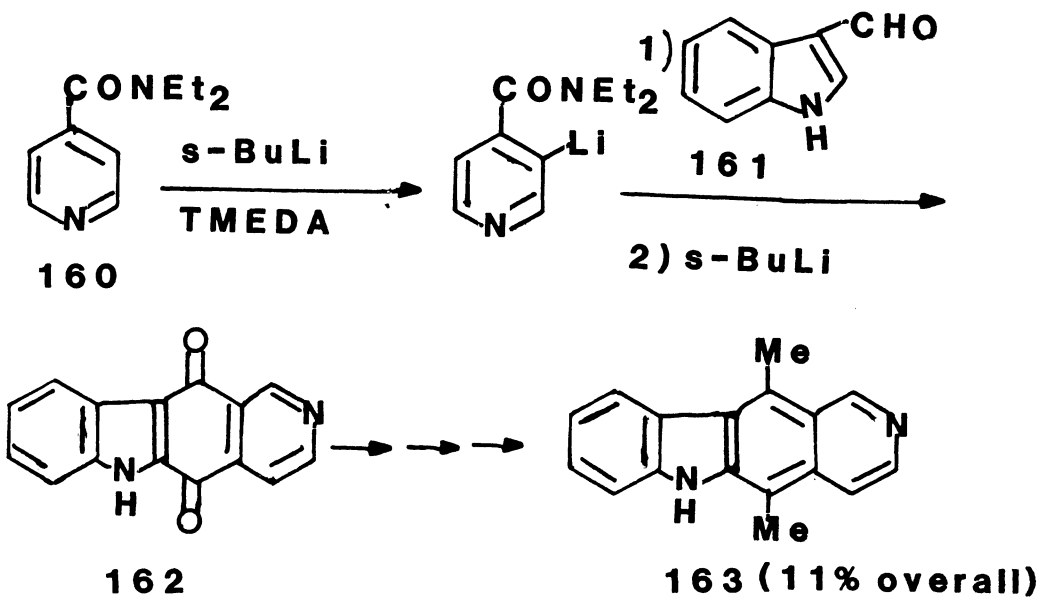
DMG	Metalation Conditions	Position of Metalation	Ref
4-$CONEt_2$	s-BuLi/TMEDA/THF/-78°C	3	45
2-$CON(iPr)_2$	LDA/THF/-78°C	3	26,100
3-$CON(iPr)_2$	LDA/THF/-78°C	4	26,100

Table 23 - continued

4-CON($iPr)_2$	LDA/THF/-78°C	3	26,100
4 	MeLi/THF/-78°C	3	101
2-Br,Cl,F	LDA/THF/-78°C	3	102
3-Br,Cl,F	LDA/THF/-78°C	4	102
4-Br,Cl,F	LDA/THF/-78°C	3	102
3-OEt	n-BuLi/TMEDA/THF/-40°C	2	103
3-OCH_2OMe	t-BuLi/Et_2O/-78°C	4	9
3-SO_2N	LDA/Et_2O/-70°C	4	104
2-NHCOt-Bu	n-BuLi/THF/0°C	3	105
2-$CONHCH_2R$ (R=H, Ph)	n-BuLi/THF/-78°C	3	106

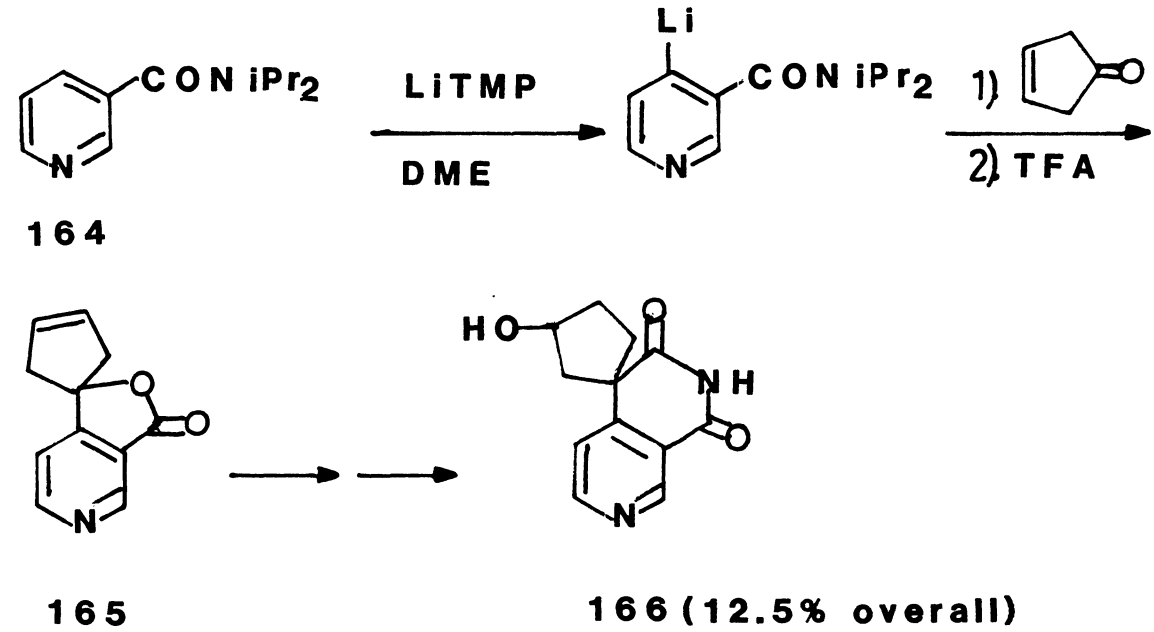
Two synthetic applications are quoted below to illustrate the utility of this methodology. A short synthesis of ellipticine **(163),** an antitumor alkaloid has been reported from our laboratory based on the initial lithiation of isonicotinamide **160 (Scheme 51).** [45]

Scheme 51



Iwao[107] reported the synthesis of sesbanine (166) using lithiation of nicotinamide 164 as a starting point (Scheme 52).

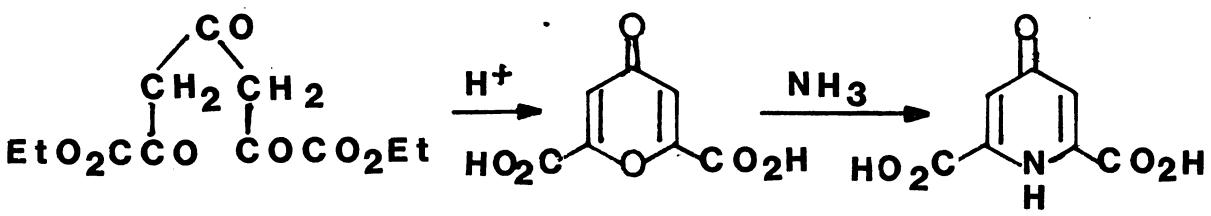
Scheme 52



3.1.5. N,N-DIETHYL O-PYRIDYL CARBAMATES. MASKED PYRIDINOLS OR PYRIDONES

Polysubstituted 2- and 4-pyridones and 3-hydroxypyridine derivatives are usually prepared by classical methods involving ring forming reactions.[108] One example is shown below **(Scheme 53).**

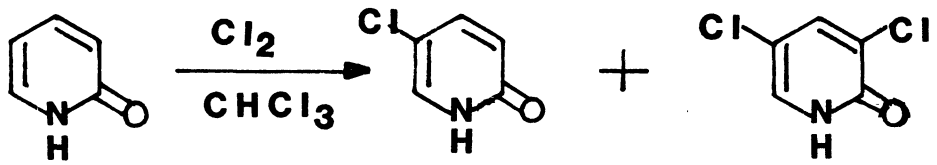
Scheme 53



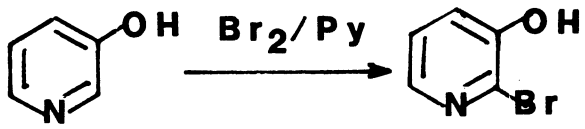
167 **168** **169**

These systems are also available from the parent systems by electrophilic substitution reactions although these procedures are invariably non-regioselective.[109] For example, 2-pyridone gives a mixture of 5-chloro and 3,5-dichloro-2-pyridone when treated with chlorine while 3-hydroxypyridine affords the 2-bromopyridine derivative or a dihalo derivative with excess halogen by classical bromination.[110]

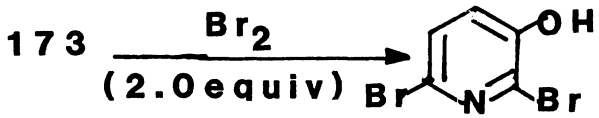
(Scheme 54).



170 171 172



173 174



175

Previous to our work, two examples of metalation of pyridine bearing an oxygen-based directed metalation group (3-OEt, 3-OCH_2OMe) had been reported (See **Table 23**). [103,104]

Following the successful demonstration of the N,N-diethylcarbamoyloxy group as an ortho director[69] and cognizant of the greater thermodynamic acidity of $OCONEt_2$ compared with other directed metalation groups[78] (Chapter II, Section 2.2.4), we decided to test the ortho metalation directing ability of this functionality on the pyridine nucleus. The aim was to develop new methodology for the regioselective synthesis of polysubstituted hydroxypyridine derivatives. O-Pyridyl carbamates are easily prepared[111] compounds with a long history

in medicinal chemistry. Substituted 3-pyridinol carbamates and their N-alkylated derivatives are parasympathomimetic substances and are capable of inhibiting cholinesterase.[112]

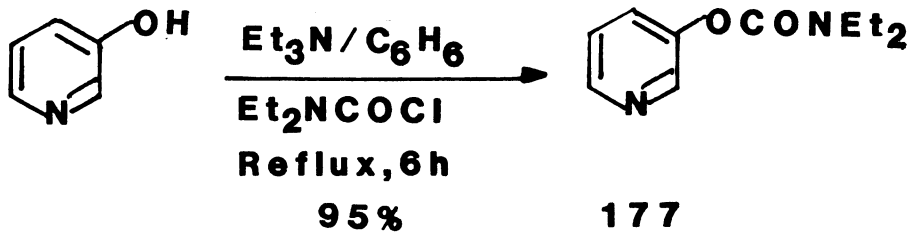
This part of the thesis will deal with a) the ortho lithiation of N,N-diethyl O-pyridyl carbamates; b) iterative metalation of these systems; c) anionic ortho Fries rearrangement leading to the synthesis of nicotinamide and isonicotinamide derivatives; d) ipso carbodestannylation reactions; and e) reductive elimination of the carbamate directing group.[113]

3.2. RESULTS AND DISCUSSION

3.2.1. PREPARATION OF O-ARYL CARBAMATES

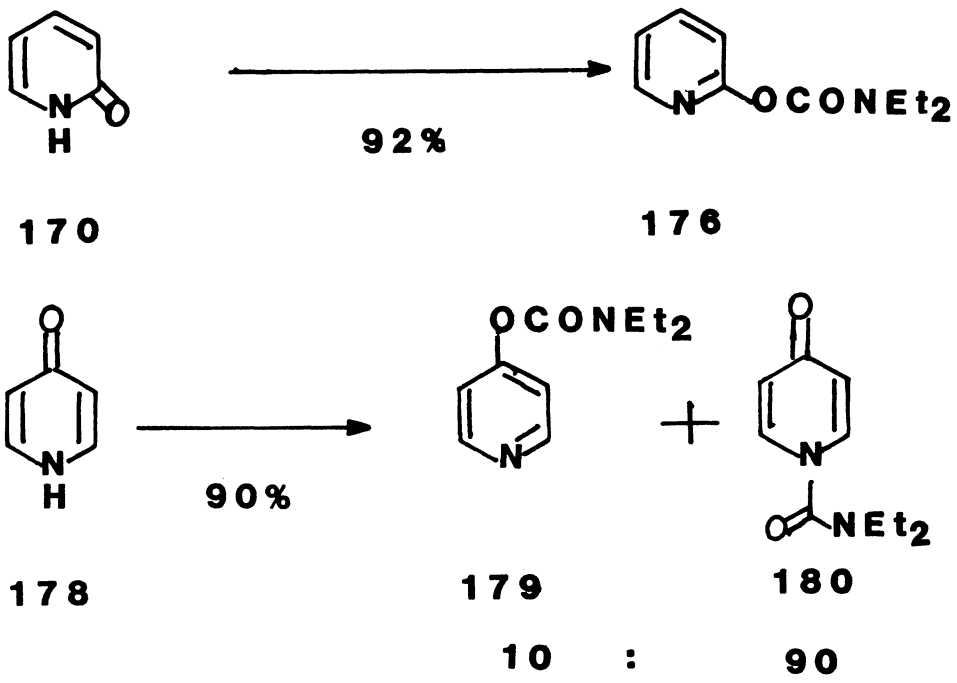
O-Pyridyl-3-carbamate was prepared according to a literature procedure[111,112] **(Scheme 55).**

Scheme 55



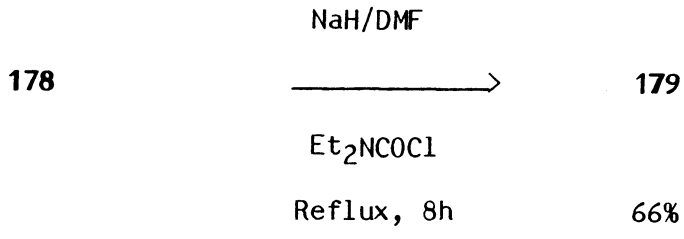
Although O-pyridyl-2-carbamate **(176)** was prepared following the above procedure from 2-pyridone, the N-acylated derivative was obtained as a minor product from 4-pyridone under identical reaction conditions **(Scheme 56).**

Scheme 56



The O-Pyridyl-4-carbamate **179,** however, was obtained following the method outlined in **Scheme 57.**

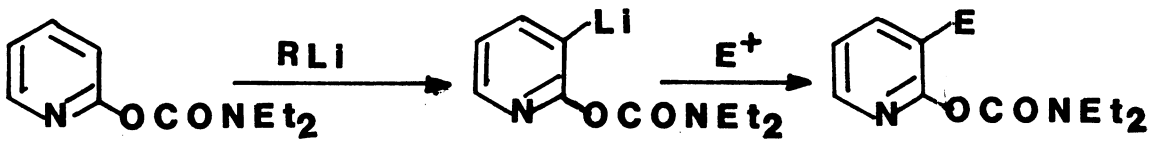
Scheme 57



3.2.2. SYNTHESIS OF POLYSUBSTITUTED O-PYRIDYL CARBAMATES

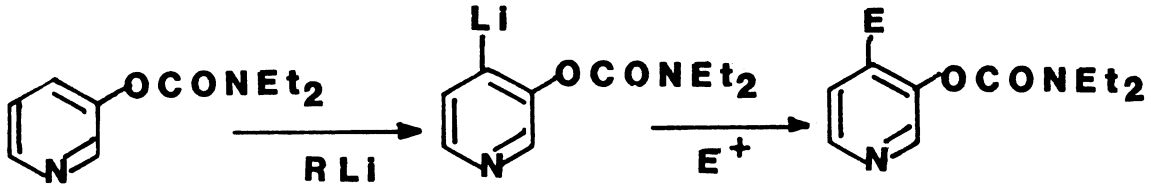
All the isomeric N,N-diethyl O-pyridyl carbamates **(176, 177, 179)** were shown to undergo smooth metalation under the standard conditions (s-BuLi/TMEDA/THF/-78°C) used for aromatic amide and carbamate metalation as evidenced by reaction with a variety of electrophiles to give substituted pyridines **(Scheme 58).**

Scheme 58



176 **181**

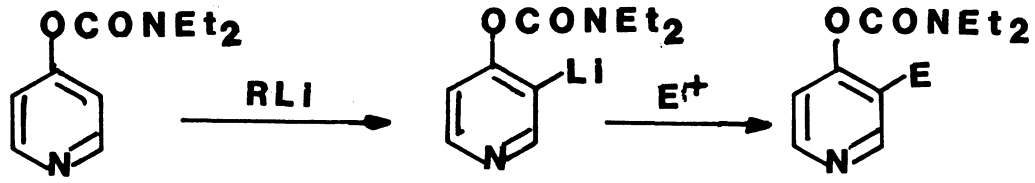
	a	b	c	d	e	f
E	D	Me	$CONEt_2$	TMS	Br	I



177 **182**

	a	b	c	d	e	f	g	h
E	D	Me	$CONEt_2$	TMS	Br	I	SO_2NMe_2	CO_2H

	i	j	k	l	m
E	$SnMe_3$	$Sn(\underline{n}\text{-}Bu)_3$	SMe	CHOH(Me)	$CHOH(C_6H_5)$

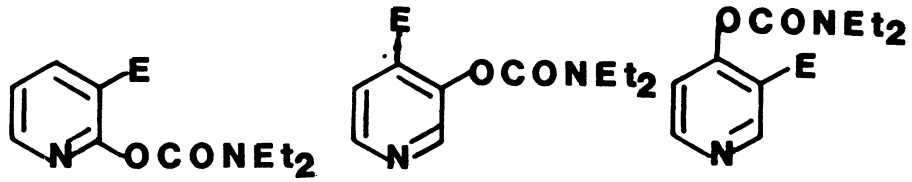


179 **183**

	a	b	c	d	e	f	g
E	D	Me	$CONEt_2$	TMS	Br	I	SO_2NMe_2

Metalation followed by electrophilic quench of O-pyridyl-2-carbamate **176** gave 3-substituted products **181.** Under identical conditions, the 3-carbamate **177** afforded only 4-substituted products **182** and the 4-carbamate **179** gave 3-substituted pyridine derivatives **183.** The results of these methodological studies using the three isomeric O-pyridyl carbamates are summarized in **Table 24.**

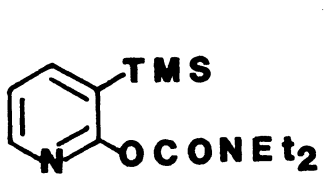
Table 24: Synthesis of Substituted O-Pyridyl Carbamates 181, 182, 183



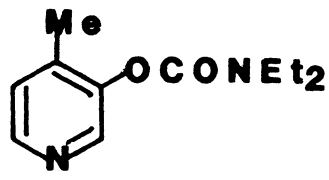
E^+	E, Yield (%)	E, Yield (%)	E, Yield (%)
MeOD	D , 87 (56%d_1)	D , 82 (51%d_1)	D , 75 (37%d_1)
MeI	Me , 72	Me , 83	Me , 72
Et_2NCOCl	$CONEt_2$, 66	$CONEt_2$, 64	$CONEt_2$, 69
TMSCl	TMS , 52 (62)[a]	TMS , 69 (82)[a]	TMS , 67
$Br(CH_2)_2Br$	Br , 59	Br , 71	Br , 60
I_2	I , 68	I , 89	I , 60
$ClSO_2NMe$		SO_2NMe_2, 81	SO_2NMe_2, 60
CO_2		CO_2H , 60	
$ClSnMe_3$		$SnMe_3$, 82	
$ClSn(n\text{-}Bu)_3$		$Sn(n\text{-}Bu)_3$, 50	
$(MeS)_2$		SMe , 50	
MeCHO		CHOH(Me), 50	
C_6H_5CHO		$CHOH(C_6H_5)$, 75	

[a] Using LDA/THF/-78°C Conditions.

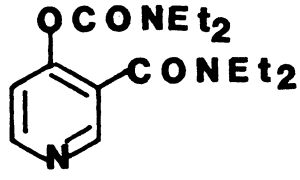
The low deuterium incorporation into all O-pyridyl carbamates in comparison to the high yield of products with other electrophiles is difficult to explain. Similar results, however, have been reported by others.[26,100] Lithiation of O-pyridyl carbamates **176** and **177** can also be effected by using LDA and, as seen from the **Table 24,** the yield of the products **181d** and **182d** were even better despite the decreased thermodynamic basicity of LDA in comparison to alkyllithiums. This observation may be accounted for by considering greater compatibility of TMSCl with LDA than with alkyllithiums.[114] The products from the three isomeric carbamates **176, 177** and **179** have been identified by examination of ^{1}H NMR spectra, particularly the aromatic region, which show a distinct, well-separated peak pattern for differently substituted carbamate derivatives **181, 182** and **183.** For example, a 1,2,3-type aromatic substitution pattern was observed for product **181d** and 1,2,4-substitution patterns were observed for **182b** and **183c (Table 25).**



181d



182b



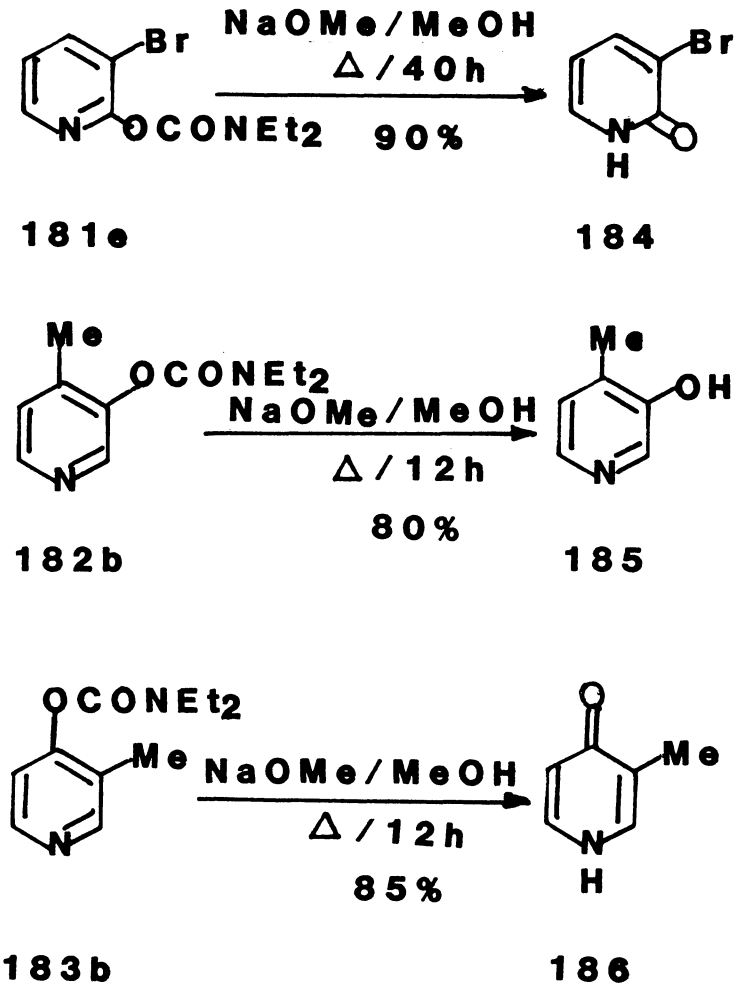
183c

Table 25: Aromatic ^1H NMR Chemical Shifts of 181d, 182b, 183c

Compound	Chemical Shift δ(ppm) (multiplicity, Coupling Const.) J in Hz	Assignment
181d	7.20 (dd, J = 7.2, 4.8)	H-5
	7.89 (dd, J = 7.2, 2.19)	H-4
	8.40 (dd, J = 4.8, 2.19)	H-6
182b	7.14 (d, J = 4.9)	H-5
	8.30 (d, J = 4.9)	H-6
	8.33 (s)	H-2
183c	7.32 (d, J = 5.6)	H-5
	8.51 (s)	H-2
	8.58 (d, J = 5.6)	H-6

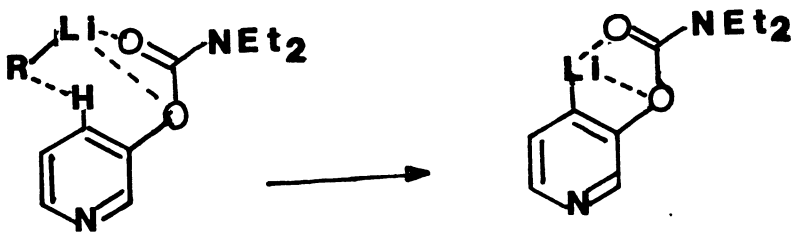
In some cases, chemical corroboration has also been achieved by basic hydrolysis into known compounds[115] (Scheme 59) and details are provided in the Experimental Section.

Scheme 59



Although the 3-ethoxypyridine was found to undergo metalation at the 2-position **(Table 23),** the N,N-diethyl O-pyridyl-3-carbamate **177** was found to metalate exclusively at the 4-position under the specific conditions of the reaction. Although we do not expect the relative acidity of C-2 and C-4 hydrogens would be identical due to the presence of a directing group at the 3-position, the exclusive 4-metalation is surprising in view of Brandsma's result.[95] This may be rationalized by assumming a conformation of the carbamate which allows coordination of the directing group with the base in such a way so that it places the anionic part of the base closest to the C-4 hydrogen ultimately affording the 4-lithiated-3-carbamate **(Scheme 60).**

Scheme 60



However, in the absence of conformation information on pyridyl carbamates, a similar coordination and deprotonation at the 2-position cannot be argued against. A tentative argument against 2-deprotonation may be the instability of the developing 2-carbanion due to electronic repulsion with the lone pair electrons of the ring nitrogen.[94]

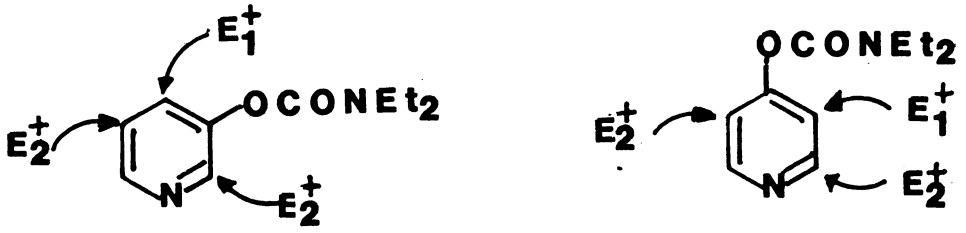
The efficient and regiospecific formation of a variety of substituted O-pyridyl carbamates via this metalation methodology **(Table 24)** opens door to new synthetic pyridine chemistry. The regiospecific formation of monohalo (bromo/iodo) pyridones and hydroxypyridines underscores the advantage and of this methodology with the electrophilic substitution

approach since the latter usually does not lead to monohalo derivatives with positional selectivity (see **Section 3.1.5, Scheme 54).**

3.2.3. ITERATIVE METALATION OF O-PYRIDYL CARBAMATES

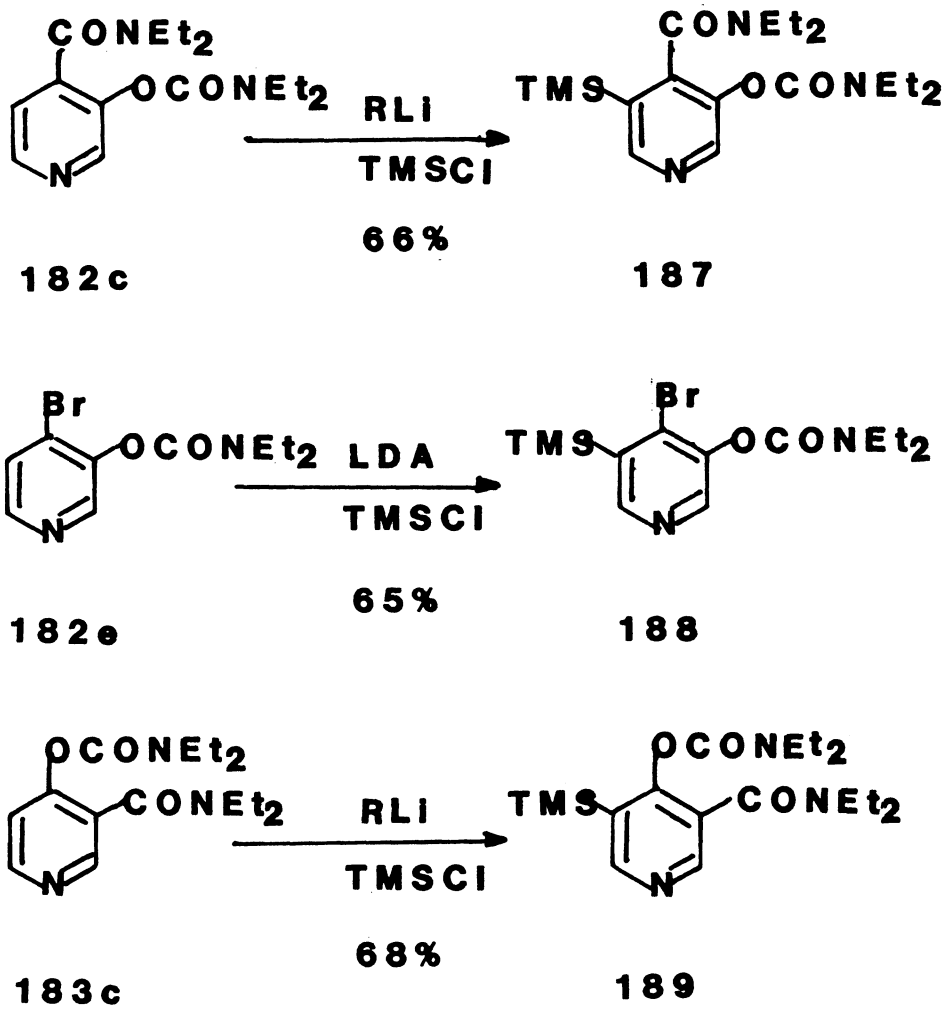
Following the concept demonstrated for O-aryl carbamates **(Chapter II, Section 2.2.7),** O-pyridyl carbamates have been subjected to iterative metalation in order to synthesize contiguously trisubstituted pyridine derivatives. In addition this study has allowed the evaluation of relative directing abilities of different groups in pyridine systems **(Scheme 61).**

Scheme 61



In each of the cases depicted schematically, if $OCONEt_2$ group is a better ortho directing than E_1, then the predominant product from the subsequent lithiation would be expected to be the one in which E_2 is ortho to it. Several experiments were carried out to this end on substituted carbamates **182c, 182e** and **183c (Scheme 62).**

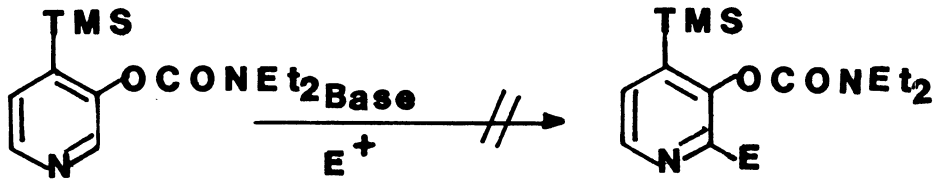
Scheme 62



Lithiation at the 5-position of **182c** was evidenced by the formation of product **187** upon TMSCl quench. Likewise, compounds **182e** and **183c** afforded products **188** and **189** respectively. Lithiation of **182e** was carried out using LDA following the method of Gribble[102] and Queguiner.[103] These results show that irrespective of the nature of the directing groups, the

2-position of the pyridyl carbamtes is inherently reluctant to undergo metalation in competition with metalation ortho to $CONEt_2$, Br and $OCONEt_2$ substituents. Further confirmation of these observations was achieved by unsuccessful attempts to metalate **182d** under a variety of conditions **(Scheme 63)** using the trimethyl silyl group to block the more reactive metalation sites.[116] In all cases, starting material was recovered in almost quantitative yield.

Scheme 63



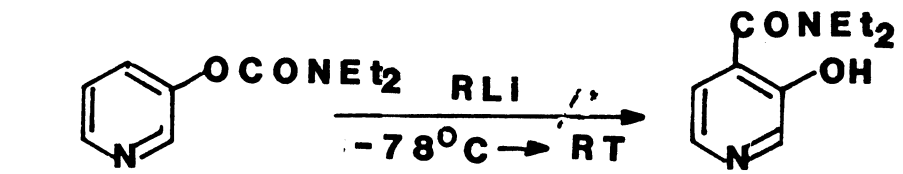
182d

Base	Lithiation Temp (0°C)	E^+
s-BuLi/TMEDA/THF	-78 --> RT	-
s-BuLi/TMEDA/THF	-78	MeOD
LDA/THF	-78	MeOD
LiTMP/THF	-78	TMSCl
n-BuLi/TMEDA/Et_2O	-60 --> 40	MeI

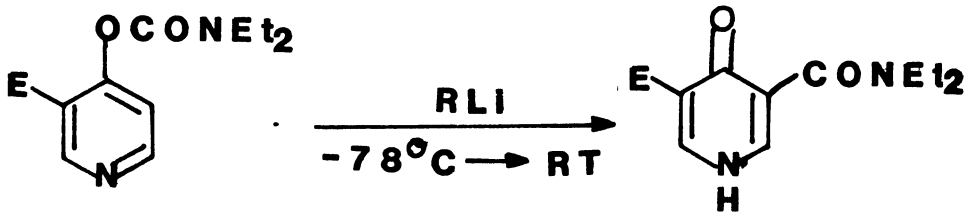
3.2.4. ANIONIC ORTHO FRIES REARRANGEMENT. SYNTHESIS OF ISONICOTINAMIDES AND NICOTINAMIDES

By analogy with O-aryl carbamates[69], the lithiated species of pyridyl carbamates **177, 179, 183b** and **183d,** when allowed to warm to room temperature over a period of 8h, underwent the anionic Fries rearrangement to give the isonicotinamide **190** and nicotinamides **191a, 191b, 191c** respectively **(Scheme 64).** The results are summarized in **Table 26.**

Scheme 64



177 **190**



179,183b, 183d **191a-c**

Table 26: Synthesis of Isonicotinamide (190) and Nicotinamides (191) via Anionic Fries Rearrangement.

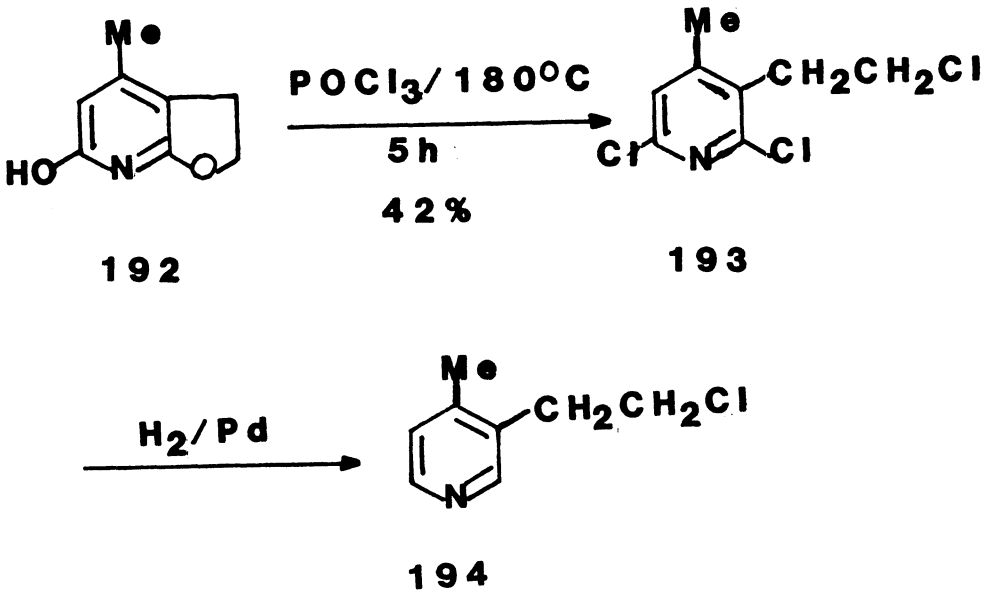
Substrate	E	Product	Yield, %
177	-	**190**	40
179	H	**191a**	74
183b	Me	**191b**	80
183d	TMS	**191c**	60

The products were identified by ^1H NMR spectroscopy by comparing the chemical shifts of ring protons in structures **191** with the chemical shifts of the known 3-methyl-4-pyridone. Signals for pyridone hydrogens are characteristically distinct from a heteroaromatic ring protons.[117]

3.2.5. CARBAMATE AS REMOVABLE DIRECTING GROUP

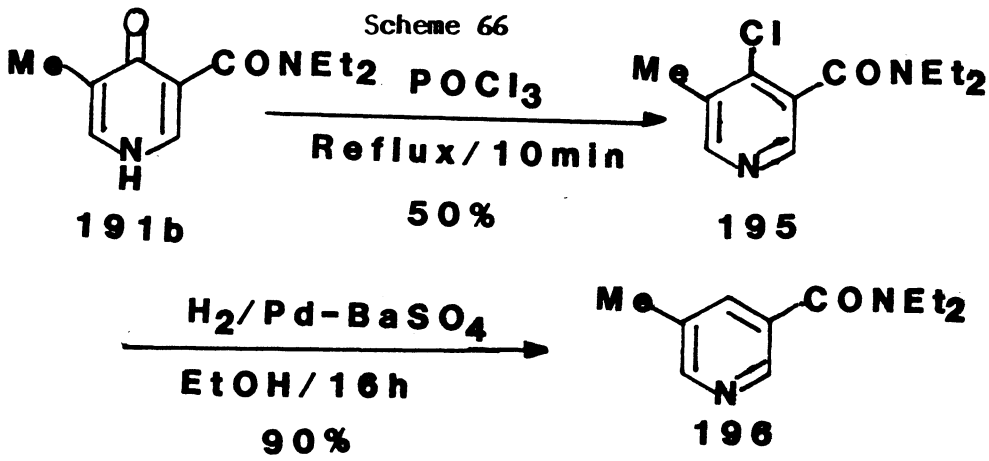
The reductive conversion of hydroxypyridines to the corresponding pyridines via their chloro or bromo derivatives has been known for a long time. An example is shown in **Scheme 65.** [118]

Scheme 65



Hence the substituted pyridine derivatives **181, 182, 183** and **190, 191** may be considered as precursors to differently substituted pyridines in which the carbamate serves its function in the introduction of an electrophile and then may be removed or, in some cases, rearranged to amide derivatives. To establish this principle, the substituted 4-pyridone **191b** was converted into the 4-chloropyridine **195** which, on hydrogenolysis was transformed into 5-methylnicotinamide (**196**) (**Scheme 66**).

Scheme 66

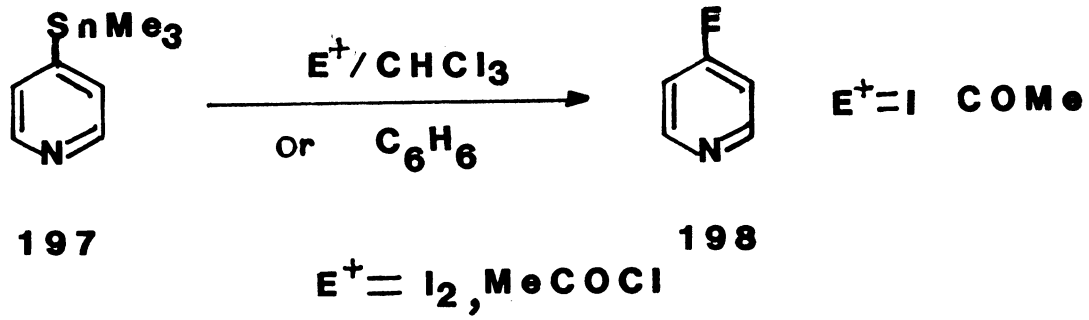


The reaction time of pyridone **191b** with phosphoryl chloride must be limited to 10 min as indicated because no identifiable product has been isolated when the reaction time was longer. Since most of the substituted carbamate derivatives are hydrolyzable into pyridone or hydroxy pyridine derivatives, this sequence may be useful for the synthesis of diversely substituted pyridines.

3.2.6. ELECTROPHILE-INDUCED IPSO-DESTANNYLATION

Yamamoto and coworkers[43, 119] have shown that stannylated pyridine derivatives undergo electrophile-induced ipso-destannylation to give iodopyridine and acylpyridines **(Scheme 67)**.

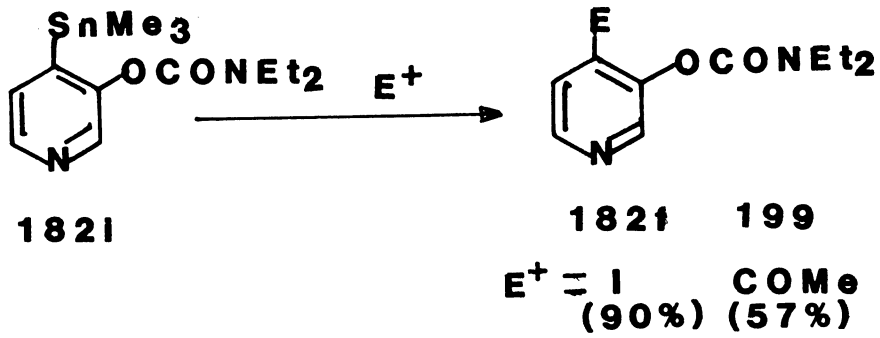
Scheme 67



The formation of **198**, E = COMe is significant since the direct acylation of hydroxypyridines and pyridines with an acyl chloride using Friedel Crafts reaction conditions has been reported to be unsuccessful.[120] Encouraged by the observations of Yamamoto,[43,119] the stannylated derivatives **182i** was

MeCOCl to afford iodocarbamate **182f** and acylcarbamate **199** respectively **(Scheme 68).** The product **182f** was shown to be identical with that obtained by directed ortho lithiation methodology **(Section 3.2.2)** whereas the structure of **199** was established by examination of its NMR spectrum. In comparison, the tri-n-butylstannylated derivative **182j** failed to undergo this ipsodestannylation reaction upon treatment with I_2 presumably owing to the steric bulk of the n-butyl group.

Scheme 68



1821 **1821** **199**

$E^+ =$ I (90%) COMe (57%)

This preliminary study points to the potential of coupling directed metalation and electrophilic substitution chemistries on pyridine carbamates for the goal of preparation of unusual polysubstituted systems.

3.2.6. CONCLUSION

An efficient, practical, and short method for the synthesis of diversely substituted 2- and 4-pyridones and 3-pyridinols via O-pyridyl carbamates has been developed by using directed ortho metalation chemistry. This work further underscores the advantage and effectiveness of directed metalation methodology in pyridine metalation.

4.0 EXPERIMENTAL

4.1 GENERAL METHODS

Melting points were determined in a Buchi model SMP-20 instrument and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. ^{1}H NMR spectra were determined with Bruker WP-80 and Bruker AM-250 spectrometers in $CDCl_3$ with 1% tetramethylsilane as an internal standard unless indicated otherwise. Spectra listed follow the order: chemical shift (δ, ppm), (multiplicity, coupling constants J in Hz, number of protons and/or assignment). ^{13}C NMR spectra were recorded with Bruker WP-80 and AM-250 instruments in $CDCl_3$ referenced to $CHCl_3$ at 77.0 ppm. Infrared spectra were recorded on a Beckman model Acculab 10 or Perkin-Elmer 983 spectrophotometers. High resolution mass spectra were determined on a VG 7070F instrument and low resolution mass spectra were determined either on a VG 7070F or a Varian MAT CH7 mass spectrometers. Analytical gas liquid chromatography (GLC) was performed on a Hewlett Packard 5840A instrument fitted with a flame ionization detector using a commercially available 10% SE 30 column. Column chromatography was performed using silica gel 60 (0.04-0.063 mm and 0.063-20 mm) with hexane/ethyl acetate as eluent (1:1 to 9:1) unless stated otherwise.

The phrase "workup in the usual manner" or "standard workup" refers to treatment of the reaction mixture with saturated aqueous NH_4Cl followed by extraction with CH_2Cl_2 or Et_2O, drying of the organic extract over Na_2SO_4 and evaporation to dryness under reduced pressure to afford the crude product. Subsequent chromatography and/or recrystallization and/or distillation of the crude material afforded pure products.

All dry solvents employed were obtained by refluxing over and distilling from an appropriate drying agent.[121, 122] Diethyl ether (Et_2O), benzene and tetrahydrofuran (THF) were freshly distilled from sodium-benzophenone ketyl prior to use.[123] All lithiations were performed using syringe-septum cap techniques in oven-dried glassware under an atmosphere of dry high purity nitrogen. Solutions of the butyllithium reagents were stored in septum-capped bottles inside plastic bags containing $CaCl_2$. The n-BuLi was stored at ambient temperature, whereas s-BuLi and t-BuLi were stored at 0°C. The titre of all commercially available alkyllithium reagents was determined with 2,5-dimethoxybenzyl alcohol[124] as standard. DMF was dried and distilled over CaH_2 and stored over NaH. Diisopropylamine (DIA), triethylamine, tetramethylethyenediamine (TMEDA) were dried and distilled over CaH_2 and stored over 4A° molecular sieves in brown bottles which were kept in a dessicator containing $CaCl_2$. All other liquid reagents were dried according to literature procedures and distilled prior to use.

4.1.1. STANDARD PROCEDURE FOR CHAPTER I

A. General Transmetalation Procedure of Benzamides

A solution of the appropriate benzamide (1.0 equiv) in anhydrous THF (5 mL) was added by syringe injection to a stirred solution of s-BuLi (1.1 equiv) and TMEDA (1.1 equiv) in anhydrous THF at -78°C under nitrogen. $MgBr_2.2Et_2O$ (3.0 equiv) was added after 30 min which produced a colorless precipitate. The reaction mixture was warmed to room temperature to give a clear solution which was cooled again to -78°C and stirred for 40 min. The electrophile (2.0 equiv) was added and the solution was allowed to warm to room temperature overnight. Standard workup afforded the crude product.

B. General Procedure for the Preparation of Phthalides.

The crude hydroxyamide derivative obtained from the reaction of **47** (generated according to procedure **A**) and an aldehyde was not purified but was subjected to cyclization in refluxing toluene in presence of catalytic amount of p-toluenesulfonic acid monohydrate for 20-24 h. Workup in the usual manner gave the crude product.

C. General Procedure for the Preparation of 3,4-Dihydroisocoumarins

The required allylbenzamide was refluxed in 6N aqueous HCl for 20-90 h. The reaction mixture was diluted by adding aqueous NH_4Cl solution and was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried (Na_2SO_4) and CH_2Cl_2 evaporated under

vacuum to give crude product.

4.1.2. PREPARATION OF TERTIARY BENZAMIDES, OXAZOLINE AND METHOXYMETHOXYBENZENE

All the benzamides were prepared by reacting the required acid chloride (obtained from carboxylic acid and $SOCl_2$) with an excess of the appropriate amine.[125] Oxazoline was prepared from the reaction of benzoylchloride with 2-amino-2-methylpropan-1-ol followed by cyclization of the resulting amide by refluxing with $SOCl_2$.[126] Methoxymethoxybenzene was obtained from the reaction of the required Na-phenoxide with chloromethyl methyl ether.[127] All these compounds were purified either by microdistillation or Kugelrohr distillation or recrystallization. Unless indicated otherwise, these compounds showed spectral (IR, NMR, MS) properties consistent with their assigned structures.

N,N-Diethylbenzamide 45a: bp 78°C/0.04 mm (lit.[128] bp 150-151°C/15 mm).

N,N-Diethyl-2-methoxybenzamide 45b: bp 105-106°C/0.25 mm (lit.[125] bp 100-104°C/1 mm).

N,N-Diethyl-3-methoxybenzamide 45c: bp 110-112°C/0.05 mm (lit.[129] bp 177°C/14 mm).

N,N-Diethyl-2,5-dimethoxybenzamide 45d: mp 78-80°C/EtOAc) (lit[130] bp 125°C/0.35 mm)

N,N-Diethyl-2,3,4-trimethoxybenzamide 45e: bp 115-120°C/0.2 mm; IR ($CHCl_3$) ν_{max} 1620 cm-1; ^1H NMR ($CDCl_3$) δ 1.04, 1.24 (2 t, J =

7, 6H, 2 CH_3), 3.18, 3.55 (2 q, J = 7, 4H, 2 CH_2), 3.87, 3.88, 3.90 (3 s, 9H, 3 OCH_3), 6.66 (d, J = 8.5, 1H, H-6), 6.91 (d, J = 8.5, 1H, H-5); MS m/e 267 (m^+); satisfactory analytical data (C, H, N) were not obtained.

N,N-Dimethyl-2,3,4-trimethoxybenzamide 52: mp 65-66°C (CH_2Cl_2-hexane); IR ($CHCl_3$) ν_{max} 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.88 (s, 9H, 3 OCH_3), 6.67 (d, J = 8.2, 1H, H-6), 6.94 (d, J = 8.2, 1H, H-5); MS m/e 239 (M^+); Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.77; H, 7.34; N, 6.29.

N,N-Diethyl-2-bromobenzamide: bp 140-142°C/ 0.30 mm (lit.[125] bp 138-140°C/ 2mm); IR ($CHCl_3$)ν_{max}, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06, 1.27 (2 t, J = 7, 6H, 2 CH_3), 3.15, 3.75 (2 q, J = 7, 4H, 2 CH_2), 7.16-7.60 (m, 4H, ArH).

2-Phenyl-4,4-dimethyloxazoline 61: bp 63-65°C/1.0 mm (lit.[126] 112-114°C/14 mm).

4-Methoxymethoxyanisole 63: bp 55-58°C/0.05 mm (lit[127] 114°C/0.1 mm).

4.1.3. EXPERIMENTAL DETAILS

3-n-Propylphthalide (50a).

According to general transmetalation procedure (procedure **A)** N,N-diethyl-o-(bromomagnesio)benzamide **47a** was generated from N,N-diethylbenzamide **45a** (500 mg, 2.82 mmol), s-BuLi (2.82 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), $MgBr_2.2Et_2O$ (3.21 mL, 8.47 mmol) and was treated with n-butyraldehyde (407 mg, 5.65 mmol). Standard workup gave the crude hydroxyamide derivative which was cyclized according to the procedure for the preparation of phthalide (Procedure **B)** to afford after column chromatography (1:9 EtOAc-hexane as eluent) 310 mg (64% overall) of compound **50a** [56] as an oil; IR (neat) ν_{max} 1750 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (t, J = 7, 3H, CH_3), 1.29-2.1 (complex m, 4H, CH_2CH_2), 5.49 (m, 1H, CH), 7.37-7.96 (m, 4H, ArH); MS m/e 176 (M^+).

3-Methylphthalide (50b).

According to procedure **A,** N,N-diethyl-o-(bromomagnesio)-benzamide **47a** was generated from N,N-diethylbenzamide **45a** (500 mg, 2.82 mmol) as in the previous experiment and was treated with freshly distilled acetaldehyde (248 mg, 5.65 mmol). The crude

hydroxyamide obtained after usual workup was subjected to cyclization according to procedure **B** to give after purification by column chromatography (1:9 EtOAc-hexane as eluent) 251 mg (61% overall) of compound **50b,** bp 60-65°C/ 0.03 mm (lit[57] 101°C/0.9 mm); IR (neat)ν_{max} 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.65(d, J = 6.6, 3H, CH_3), 5.57 (q, J = 6.6, 1H, CH), 7.62 (m, 4H, ArH); MS m/e 148.

7-Methoxy-3-n-propylphthalide (50c).

According to procedure A, the appropriate bromomagnesiobenzamide **47** was generated from N,N-diethyl-2-methoxybenzamide **45b** (500 mg, 2.41 mmol), s-BuLi (2.21 mL, 2.65 mmol), TMEDA (0.40 mL, 2.65 mmol), $MgBr_2.2Et_2O$ (2.75 mL, 7.24 mmol) and was treated with n-butyraldehyde (347 mg, 4.82 mmol). Standard workup gave crude hydroxyamide derivative which was cyclized according to procedure **B.** Workup in the usual manner followed by column chromatography (1:9 EtOAc-hexane as eluent) afforded 300 mg (60% overall) of compound **50c,** bp 97-101°C/0.01 mm; IR (neat) ν_{max} 1750 cm^{-1}; NMR ($CDCl_3$) δ0.96 (t, J = 6.5, 3H, CH_3), 1.24-2.02 (m, 4H, CH_2CH_2), 3.99 (s, 3H, OCH_3), 5.39 (m, 1H, CH), 6.95 (d, J = 8.4, 1H, H-4 or H-6), 6.99 (d, J = 7.6, 1H, H-4 or H-6), 7.63 (dd, J = 7.6, 8.4, 1H, H-5); MS m/e 206 (M^+); Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.49; H, 7.16.

4-Methoxy-3-n-propylphthalide (50d).

According to procedure **A,** the required bromomagnesiobenzamide **47** was generated from N,N-diethyl-3-methoxybenzamide **45c**

(582 mg, 2.82 mmol), s-BuLi(3.16 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), $MgBr_2.2Et_2O$ (3.21 mL, 8.47 mmol) and was treated with n-butyraldehyde (407 mg, 5.65 mmol). Standard workup gave the crude hydroxyamide derivative which was cyclized according to procedure **B** to give after purification by column chromatography (1:9 EtOAc-hexane as eluent) 342 mg (59% overall) of the desired product **50d**, mp 76-77°C (CH_2Cl_2-hexane); IR ($CHCl_3$) ν_{max} 1750 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (t, J = 7, 3H, CH_3), 1.2-2.2 (m, 4H, CH_2CH_2), 3.92 (s, 3H, OCH_3), 5.5 (m, 1H, CH), 7.1-7.45 (m, 3H, ArH); MS m/e 206(M^+); Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.73; H, 6.64.

4,7-Dimethoxy-3-n-propylphthalide (50e).

According to procedure A, the appropriate bromomagnesiobenzamide **47** was generated from N,N-diethyl-2,5-dimethoxybenzamide **45d** (1.34 g, 5.64 mmol), s-BuLi (6.34 mL, 6.20 mmol), TMEDA (0.94 mL, 6.20 mmol), $MgBr_2.2Et_2O$ (6.4 mL, 16.92 mmol) and was treated with n-butyraldehyde (814 mg, 11.28 mmol). Workup in the usual manner gave the crude hydroxyamide which was subjected to cyclization according to procedure **B**. Standard workup followed by column chromatography (1:9 EtOAc-hexane as eluent) afforded 981 mg (74%) overall) of the desired product **50e**, mp 128°C (Et_2O-hexane); IR ($CHCl_3$) ν_{max} 1750 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (t, J = 7, 3H, CH_3), 1.2-2.2 (m, 4H, CH_2CH_2), 3.84, 3.92 (2 s, 6H, 2 OCH_3), 5.42 (m, 1H, CH), 6.83 (d, J = 8.8, 1H, H-5 or H-6), 7.05 (d, J = 8.8, 1H, H-5 or H-6); MS m/e 236(M^+); Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.10; H, 6.82. Found: C, 66.18; H, 6.72.

3-(2-Pyridyl)phthalide (50f).

According to procedure **A**, the o-(bromomagnesio)benzamide **47a** - was generated from N,N-diethylbenzamide **45a** (500 mg, 2.82 mmol) as described for the preparation of **50a** and was quenched with pyridine-2-carboxaldehyde (604 mg, 5.64 mmol). Workup in the usual manner and cyclization of the crude hydroxyamide obtained according to procedure **B** afforded after purification by column chromatography 524 mg (88%) of compound **50f**, mp 83-84°C (EtOAC-Et_2O); IR ($CHCl_3$) ν_{max} 1765 cm^{-1}; NMR ($CDCl_3$) δ6.52 (s, 1H, CH), 7.18-7.99 (m, 7H, ArH) 8.64 (m, 1H, ArH); MS m/e 211 (M^+); Anal. Calcd for $C_{13}H_9NO_2$: C, 73.93; H, 4.29; N, 6.63. Found: C, 73.69; H, 4.28, N, 6.30.

N,N-Diethyl-2-allylbenzamide (51a).

According to the procedure A, N,N-diethyl-o-(bromomagnesio)-benzamide **47a** was produced from **45a** (500 mg, 2.82 mmol), s-BuLi (2.82 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), $MgBr_2.2Et_2O$ (3.21 mL, 8.47 mmol) and was treated with allyl bromide (683 mg, 5.64 mmol). Workup in the usual manner followed by purification by column chromatography using 1:5 (v/v) EtoAc-hexane as eluent yielded 435 mg (71%) of the desired product **51a**, bp 90-94°C/0.1 mm; IR (neat) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ1.05, 1.26 (2 t, J = 7, 6H, 2 CH_3), 3.15 (q, J = 7, 2H, CH_2), 3.35 (m, 2H, $\underline{CH_2}CH=$), 3.35-3.38 (br, 2H, CH_2), 4.9-5.25 (m, 2H, $CH=\underline{CH_2}$), 5.7-6.2 (m, 1H, $\underline{CH}=CH_2$), 7.1-7.3 (m, 4H, ArH) Ms m/e 217 (M^+); Anal. Calcd for $C_{14}H_{19}NO$: C, 77.41; H, 8.75; N, 6.45; Found: C, 76.98; H, 8.87; N, 6.36.

N,N-Diethyl-2-allyl-6-methoxybenzamide (51b).

According to procedure **A**, the required **47** was generated from N,N-diethyl-2-methoxybenzamide **45b** (1.0 g, 4.83 mmol), s-BuLi (4.21 mL, 5.31 mmol), TMEDA (0.80 mL, 5.31 mmol), $MgBr_2.2Et_2O$ (5.5 mL, 14.49 mmol) and was quenched with allyl bromide. Standard (1:5 EtOAc-hexane as eluent) workup gave the crude product which upon column chromatography afforded 665 mg (55%) of compound **51b**, bp 110-114°C/0.35 mm, IR (neat) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ1.02 1.28 (2 t, J = 7, 6H, 2 CH_3), 3.12, 3.48 (2 q, J = 7, 4H, 2 CH_2), 3.32 (br, 2H, $\underline{CH_2}CH=$), 3.78 (s, 3H, OCH_3), 4.92-5.25 (m, 2H, $CH=\underline{CH_2}$), 5.7-6.2 (m, 1H, $\underline{CH}=CH_2$), 6.80 (m, 2H, ArH), 7.25 (m, 1H, ArH); MS m/e 247 (M^+); Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.53; N, 5.67. Found: C, 72.43; H, 8.35; N, 6.05.

N,N-Diethyl-2-allyl-3-methoxybenzamide (51c).

According to procedure **A**, the o-(bromomagnesio)benzamide **47c** was generated from N,N-diethyl-3-methoxybenzamide **45c** (1.169 g, 5.64 mmol), s-BuLi (6.34 mL, 6.21 mmol), TMEDA (0.94 mL, 6.21 mmol), $MgBr_2.2Et_2O$ (6.43 mL, 16.92 mmol) and was treated with allyl bromide (1.36 g, 11.28 mmol). Workup in the usual manner and purification by column chromatography (1:5 EtOAc-hexane as eluent) yielded 1.11 g(80%) of compound **51c**, bp 115-118°C/0.2 mm; IR (neat) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ1.02, 1.28 (2 t, J = 7, 6H, 2 CH_3), 3.09, 3.38 (2 q, J = 7, 4H, (s, 3H, OCH_3), 4.85-5.10 (m, 2H, $CH=\underline{CH_2}$), 5.77-5.89 (m, 1H, CH=), 6.71-6.90 (m, 2H, ArH), 7.11-7.30

(m, 1H, ArH); MS m/e 247 (M^+); Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.53; N, 5.67; Found: C, 72.94; H, 8.46; N, 5.52.

N,N-Diethyl-2-allyl-3,6-dimethoxybenzamide (51d).

According to procedure **A**, the o-(bromomagnesio)benzamide **47d** was produced from N,N-diethyl-2,5-dimethoxybenzamide **45d** (1.33 g, 5.61 mmol), s-BuLi(6.42 mL, 6.17 mmol), TMEDA (0.94 mL, 6.17 mmol), $MgBr_2.2Et_2O$ (6.43 mL, 16.83 mmol) and was treated with allyl bromide (1.36 g, 11.22 mmol). Standard workup and column chromatography (1:5 EtOAc-hexane as eluent) afforded 991 mg (63%) of compound **51d**, bp 128-129°C/0.25 mm; IR (neat) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.02, 1.28 (2 t, J = 7, 6H, 2 CH_3), 3.10, 3.38 (2 q, J = 7, 4H, 2 CH_2), 3.32 (m, 2H, $\underline{CH_2}CH=$), 3.72, 3.78 (2 s, 6H, 2 OCH_3), 4.87-5.10 (m, 2H, $CH=C\underline{H_2}$), 5.70-6.10 (m, 1H, CH=), 6.68(d, J = 9, 1H, H-5 or H-6); 6.81(d, J = 9, 1H, H-5 or H-6); MS m/e 277 (M^+); Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.05; H, 8.41; N, 5.09.

N,N-Diethyl-2-allyl-4,5,6-trimethoxybenzamide (51e).

According to procedure **A**, the o-(Bromomagnesio)benzamide **47e** was generated from N,N-diethyl-2,3,4-trimethoxybenzamide **45e** (500 mg, 1.87 mmol), s-BuLi (2.1 mL, 2.06 mmol), TMEDA (0.31 mL, 2.06 mmol), $MgBr_2.2Et_2O$ (2.13 mL, 5.61 mmol) and was treated with allyl bromide (453 mg, 3.74 mmol). Standard workup followed by purification of the crude product by column chromatography (1:5 EtOAc-hexane as eluent) afforded 378 mg (66%) of compound **51e**, bp

110-112°C/0.07 mm; IR (neat) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ1.05, 1.25 (2 t, J = 7, 6H, 2 CH_3), 3.15, 3.58 (2 q, J = 7, 4H, 2CH_2), 3.30 (br, 2H, $\underline{CH_2}CH=$), 3.85 (s, 6H, 2 OCH_3), 3.88 (s, 3H, OCH_3), 4.98-5.20 (m, 2H, CH=$\underline{CH_2}$), 5.70-6.20 (m, 1H, CH=), 6.53 (s, 1H, ArH); MS m/e 307 (M^+); satisfactory analytical data were not obtained.

N,N-Dimethyl-2-allyl-4,5,6-trimethoxybenzamide (54).

The general transmetalation procedure was modified for the preparation of compound **54** as follows:

N,N-Dimethyl-2,3,4-trimethoxybenzamide **52** (500 mg, 2.1 mmol) was lithiated with $\underline{s}$-BuLi (1.91 mL, 2.30 mmol) and TMEDA (0.35 mL, 2.30 mmol) at -90°C for 1.5 h and then warmed to -78°C over 30 min. $MgBr_2.2Et_2O$ (2.39 mL, 6.30 mmol) was added and after 30 min the mixture was allowed to warm to room temperature to give a clear solution, again cooled to -78°C. After 1h, allyl bromide (508 mg, 4.2 mmol) was added. Standard workup followed by column chromatography yielded 465 mg (77%) of compound **54**, bp 95-98°C/0.02 mm; IR (neat) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.81 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 3.30 (m, 2H, $\underline{CH_2}CH=$), 3.86, 3.89, 3.91 (3 s, 9H, 3 OCH_3), 4.97-5.2 (m, 2H, CH=$\underline{CH_2}$), 5.7-6.2 (m, 1H, CH=), 6.54 (s, 1H, ArH); MS: mass spectrum showed that compound **54** was contaminated by traces of a compound, ms m/e 319 (M^+), which might be formed from the benzylic allylation of **54** which could not be isolated, therefore satisfactory analytical (C, H, N) data were not obtained.

3-Methyl-3-[2-(diethylcarbamoyl)phenyl]phthalide (57).

According to procedure **A**, N,N-diethyl-o-Bromomagnesio)benzamide **47a** was generated from N,N-diethylbenzamide **45a** (500 mg, 2.82 mmol), s-BuLi (3.17 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), $MgBr_2.2Et_2O$ (3.21 mL, 8.47 mmol) and was treated with freshly distilled ethyl acetate (497 mg, 5.65 mmol), standard workup followed by column chromatography afforded 320 mg (35%) of compound **57**, mp 126-127°C (Et_2O); IR ($CHCl_3$) ν_{max} 1750, 1615 cm^{-1}; NMR ($CDCl_3$) δ0.97-1.57 (m, 6H, 2 CH_3), 2.05 (2 s, 3H, singlet in Me_2SO-d_6, CH_3), 3.07-3.81 (m, 4H, 2 CH_2), 7.26-7.93 (m, 8H, ArH); MS m/e 323 (M^+); Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 74.35; H, 6.41; N, 4.60.

2-(Diethylcarbamoyl)benzophenone (58) from N,N-Diethylbenzamide (45a).

According to procedure **A**, N,N-diethyl-o-(bromomagnesio)benzamide **47a** was generated from N,N-diethylbenzamide **45a** (500 mg, 2.82 mmol), s-BuLi (3.17 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), $MgBr_2.2Et_2O$(3.21 mL, 8.47 mmol) allowed to warm to room temperature and quenched with water. Workup in the usual manner and column chromatography (using 1:4 and 1:1 (v/v) EtOAc-hexane as eluent) gave starting material (325 mg, 65%) and 150 mg (19%) of compound **58**, bp 100-105°C/0.15 (lit.[59] mp 76-77°C); IR ($CHCl_3$) ν_{max} 1655, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.98-1.19 (m, 6H, 2 CH_3),

3.13-3.56 (m, 4H, 2 CH_2), 7.28-7.86 (m, 9H, ArH); MS m/e 281 (M^+).

Preparation of Compound 58 from N,N-diethyl-2-bromobenzamide.

N,N-Diethyl-2-bromobenzamide (500 mg, 1.95 mmol) in THF (5 mL) was added with stirring to finely divided, triply sublimed magnesium (85 mg, 3.5 mmol) under nitrogen in THF solution (20 mL) containing 2 drops of 1,2-dibromoethane and the reaction mixture was refluxed for 2.5 h, cooled to 0°C and quenched with aqueous NH_4Cl solution. Standard workup followed by column chromatography afforded N,N-diethylbenzamide (60%) and compound **58** (10%) which was identical (IR, NMR) with the compound **58** obtained as described in the previous experiment.

3-Methyl-3,4-dihydroisocoumarin-1-one (59a).

According to procedure **C**, N,N-diethyl-2-allylbenzamide **51a** - (462 mg, 2.13 mmol) was refluxed in 6N aqueous HCl (30 mL) for 20 h. Standard workup followed by column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 321 mg (93%) of compound **59a** [64] as an oil; IR (neat) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) δ1.52 (d, J = 6.8, 3H, CH_3), 2.94 (d, J = 6.8, 2H, CH_2), 4.68 (m, 1H, CH), 7.17-7.65 (m, 3H, ArH), 8.06-8.20 (m, 1H, ArH); MS m/e 162 (M^+).

8-Hydroxy-3-methyl-3,4-dihydroisocoumarin-1-one (Mellein) (59b).

According to procedure **C**, N,N-Diethyl-2-allyl-6-methoxybenzamide **51b** (350 mg, 1.42 mmol) was refluxed in 6N aqueous HCl (30 mL) for 4 days. Standard workup followed by column chromatography using 1:4 (v/v) EtOAc-hexane as eluent gave 181 mg (75%) of mellein **(59b)**, mp 38°C (CH_2Cl_2-hexane) (lit.[62] mp 38-38.5°C); IR ($CHCl_3$) ν_{max} 3200, 1675 cm^{-1}; NMR ($CDCl_3$) δ1.52 (d, J = 6.2, 3H, CH_3), 2.92 (d, J = 7, 2H, CH_2), 4.68 (m, 1H, CH), 6.68 (d, J = 8.2, H-5 or H-7), 6.84 (d, J = 8.2, H-5 or H-7), 7.40 (dd, J = 8.2, H-6), 11.02 (s, 1H, OH); MS m/e 178 (M^+).

3-Methyl-5-methoxy-3,4-dihydroisocoumarin-1-one (59c), 3-Methyl-5-hydroxy-3,4-dihydroisocoumarin-1-one (59d), and 4-(Diethylcarbamoyl)-2-methyl-2,3-dihydrobenzo[b]furan (60).

According to procedure **C**, N,N-Diethyl-2-allyl-3-methoxybenzamide **51c** (551 mg, 2.23 mmol) was refluxed in 6N aqueous HCl (25 mL) for 18 h. Workup in the usual manner and column chromatography using 1:9 and 1:3 (v/v) EtOAc-hexane as eluent afforded 210 mg (49%) of compound **59c**, mp 83-84°C (Et_2O-hexane) (lit.[131] mp 83°C); IR ($CHCl_3$) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (d, J = 6.2, 3H, CH_3), 2.62 (dd, J = 17, 11, 1H, H-C-H), 3.17 (dd, J = 17, 3.5, 1H, H-C-H), 3.88 (s, 3H, OCH_3), 4.49-4.76 (m, 1H, Ch), 7.00-7.43 (m, 2H, ArH), 7.66-7.77 (m, 1H, ArH), MS m/e 192 (M^+); 72 mg (16%) of compound **59d**, mp 173-174°C (EtOAc-Et_2O) (lit.[131] 176-177°C); IR

($CHCl_3$) ν_{max} 3200, 1715 cm^{-1}; NMR ($CDCl_3$) δ1.47 (d, J = 6.2, 3H, CH_3), 2.62 (dd, J = 17, 11, 1H, H-C-H), 3.19 (dd, J = 17, 3.5, 1H, H-C-H), 4.55-4.63 (m, 1H, CH), 7.08-7.47 (m, 2H, ArH), 7.50-7.59 (m, 1H, ArH), 8.8 (br, 1H, OH); MS m/e 178 (M^+); and 60 mg (13%) of compound **60,** bp 75-80/0.02 mm; IR (neat) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ0.88-1.25 (m, 6H, 2 CH_3), 1.45 (d, J = 5.8, 3H, CH_3), 2.61-3.12 (m, 2H, CH_2), 3.24-3.48 (m, 4H, 2 CH_2), 4.79-5.08 (m, 1H, CH), 6.68-7.39 (m, 3H, ArH); MS m/e 233 (M^+); Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20; N, 6.00. Found: C, 71.91; H, 8.30; N, 6.08.

6,7-Dimethoxy-8-hydroxy-3-methyl-3,4-dihydroisocoumarin-1-one (Kigelin) (59e).

N,N-Dimethyl-2-allyl-4,5,6-trimethoxybenzamide **54** (115 mg, 0.39 mmol) in 6N aqueous HCl (15 mL) was heated to 80°C and stirred for 24 h under nitrogen. Workup in the usual manner followed by preparative TLC using 3:1 (v/v) EtOAc-hexane as eluent gave 25 mg (27%) of Kigelin **(59e),** mp 141-142°C (CH_2Cl_2-hexane) (lit.[63] mp 142-143°C); IR ($CHCl_3$) ν_{max} 3200, 1680 cm^{-1}; NMR ($CDCl_3$) δ1.52 (d, J = 6.7, 3H, CH_3), 2.88 (d, J = 7.5, 2H, CH_2), 3.88, 3.92 (2 s, 6H, 2 OCH_3), 4.5-4.8 (m, 1H, Ch), 6.3 (s, 1H, ArH), 11.00 (br, 1H, OH).

2-[2-(1-Hydroxybutyl)phenyl]-4,4-dimethyloxazoline (62).

s-BuLi (3.5 mL, 3.38 mmol) was added to a stirred THF solution (50 mL) of 2-phenyl-4,4-dimethyloxazoline **61** (500 mg, 2.85 mmol) at -78°C under nitrogen and after 2.75 h, the reaction mixture was warmed to 0°C and quenched with freshly distilled n-butyraldehyde (411 mg, 5.7 mmol). The resulting solution was allowed to warm to room temperature overnight. Workup in the usual manner and column chromatography using 1:4 (v/v) EtOAc-hexane as eluent afforded 467 mg (65%) of compound **62**, bp 78-82°C/0.01 mm; IR ($CHCl_3$) ν_{max} 3300, 1640 cm^{-1}; NMR ($CDCl_3$) δ0.93 (t, J = 6.6, 3H, $(CH_2)_2(CH_3)$, 1.39 (s, 6H, 2 CH_3), 1.50-2.20 (m, 4H, CH_2CH_2), 4.11 (s, 2H, OCH_2), 4.69 (m, 1H, CH), 7.20-7.39 (m, 3H, ArH), 7.70-7.90 (m, 1H, ArH); MS m/e 247 (M^+); Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.82; H, 8.56; N, 5.67. Found: C, 72.92; H, 8.87; N, 5.79.

Following the transmetalation procedure compound **62** was prepared in 68% yield.

3-(1-Hydroxybutyl)-4-(methoxymethoxy)anisole (64).

t-BuLi (1.78 mL, 3.26 mmol) was added to a stirred ether solution (50 mL) of 4-(methoxymethoxy)anisole **63** (500 mg, 2.97 mmol) at 0°C under nitrogen and after 2.5 h n-butyraldehyde (429 mg, 5.95 mmol) was added. The resulting solution was allowed to warm to room temperature overnight. Workup in the usual manner and column chromatography using 1:4 (v/v) EtOAc-hexane afforded 272 mg of compound **64**, bp 82-86°C/0.01 mm; IR ($CHCl_3$) ν_{max} 3400

cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, J = 6.6, 3H, $(CH_2)_2\underline{CH_3}$), 1.20-1.90 (m, 4H, $\underline{CH_2}\underline{CH_2}$), 2.58 (br, 1H, OH), 3.47 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.93 (m, 1H, CH), 5.12 (s, 2H, OCH_2O), 6.63-7.10 (m, 3H, ArH); MS m/e 240 (M^+); Anal. Calcd for $C_{12}H_{18}O_3$: C, 64.98; H, 8.39. Found: C, 65.01; H, 8.27.

Following the general transmetalation method compound **64** was prepared in 66% yield.

4.2. STANDARD PROCEDURE FOR CHAPTER II

4.2.1.A. LITHIATION OF O-ARYL CARBAMATES WITH s-BuLi

A solution of the carbamate in dry THF (5-10 mL) was added dropwise by syringe injection to a stirred solution of a 1:1 s-BuLi-TMEDA complex in dry THF at -78°C (or -90°C) under nitrogen. After a reaction period (5 min to 1h), the mixture was treated with an electrophile. The resulting solution was then allowed to warm to room temperature over 8h after which a few mL of aqueous NH_4Cl solution was added and the THF was removed in vacuo. Subsequent standard workup gave the crude product. The details of the lithiation procedure which follow the above standard procedure are summarized in the order as follows: name and number of molar equivalents of alkyllithium reagent used, reaction temperature, lithiation time and name and number of molar equivalents of electrophile used.

B. LITHIATION OF O-ARYL CARBAMATES WITH LDA

To a THF solution of freshly distilled diisopropylamine (1.1 equiv) was added n-BuLi (1.1 equiv) at 0°C under nitrogen and was stirred for 30 min. The resulting solution of lithium diisopropylamide was cooled to -78°C and the required carbamate (1.0 equiv) in THF (5 mL) was injected by syringe injection. After 1h, an electrophile was added and the resulting solution was

allowed to warm to room temperature over 8h and processed in the normal manner (as described in procedure **A)** to give the crude product.

C. ORTHO-FRIES REARRANGEMENT. 1,3 OR 1,4 O --> C CARBAMOYL MIGRATION

Lithiation of the appropriate carbamate was carried out with s-BuLi (procedure **A)** or LDA (procedure **B)** and the resulting lithiated carbamate was allowed to warm to room temperature over 8h. Processing in usual manner as described in procedure A gave the crude product.

4.2.2. PREPARATION OF N,N-DIALKYL O-PHENYL CARBAMATE DERIVATIVES

The carbamates were prepared under standard conditions by treatment of the corresponding phenol with N,N-diethylcarbamoyl chloride (Et_2NCOCl) in refluxing pyridine[132] for 4-6h, purified by distillation and/or recrystallization and kept in an airtight container. The yields were 70-96%. The phenolic derivatives N,N-Diethylhydroxybenzamides and N,N-diethyl O-(hydroxy)phenylcarbamates were obtained from the demethylation[133] of the corresponding N,N-diethyl methoxybenzamide and N,N-diethyl O-(methoxy)phenyl carbamate with boron tribromide (BBr_3) in anhydrous CH_2Cl_2 at -78°C and purified by recrystallization. Yields were 83-93%.

The methoxymethoxy-carbamate derivatives were prepared by the reaction of the corresponding N,N-diethyl O-(hydroxy)phenylcarbamate with sodium hydride (NaH) in dimethylformamide (DMF) followed by treatment of the sodium phenoxide with chloromethyl methyl ether at 0°C. The crude products were purified by distillation. Yields were 84-95%.

All the products showed spectral (IR, NMR and MS) properties consistent with their assigned structures.

N,N-Diethyl O-Phenylcarbamate (84a):

bp 88-90°C/0.3 mm (lit[134] 107-108°C/1.0 mm); IR (neat) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ1.23 (t, J = 7, 6H, 2 CH_3), 3.42 (q, J = 7, 4H, 2 CH_2), 7.05-7.39 (m, 5H, ArH); MS m/e 193 (M^+).

N,N-Diethyl O-2-anisylcarbamate (84b):

bp 110-115°C/0.05 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7, 6H, 2 CH_3), 3.42 (q, J = 7, 4H, 2 CH_2), 3.82 (s, 3H, OCH_3), 6.90-7.17 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.3 (19, 2 CH_3), 42.0 (89, 2 CH_2), 55.7 (98, OCH_3), 112.4 (66, C-3), 120.4 (88, C-5), 123.1 (89, C-6), 125.8 (100, C-4), 140.7 (10, C-1), 153.8 (11, C-2), 151.6 (12, OCO); MS m/e 223 (M^+); Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.46; H, 7.78; N, 6.16.

N,N-Diethyl O-(2-Chloro)phenylcarbamate (84c):

bp 88-90°C/0.02 mm; IR (neat) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.1-1.26 (m, 6H, 2 CH_3), 3.34-3.49 (m, 4H, 2 CH_2), 7.03-7.45 (m, 4H,

ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.1 (23, CH_3), 14.0 (21, CH_3), 42.0 (31, CH_2), 42.2 (31, CH_2), 124.0 (87, C-6), 126.03 (100, C-4), 127.0 (13, C-2), 127.3 (86, C-5), 129.8 (97, C-3), 147.6 (8, C-1), 152.8 (8, OCO); MS m/e 227 (M^+); Anal. Calcd for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.19; N, 6.15. Found: C, 58.32; H, 6.46; N, 6.08.

N,N-Diethyl O-2-tolylcarbamate (81):

bp 94-95°C/0.2 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ1.23 (t, J = 7, 6H, 2 CH_3), 2.21 (s, 3H, CH_3), 3.42 (q, J = 7, 4H, 2 CH_2), 7.06-7.24 (m, 4H, ArH); MS m/e 207 (M^+); Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.03; H, 8.38, N, 6.93.

N,N-Diethyl O-3-tolylcarbamate (84d):

bp 88-89°C/ 0.02 mm; IR (neat) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ1.21 (t, J = 7, 6H, 2 CH_3), 2.34 (s, 3H, CH_3), 3.40 (q, J = 7, 4H, 2 CH_2), 6.86-7.33 (m, 4H, ArH); MS m/e 207 (M^+); Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.27; H, 8.32; N, 7.02.

N,N-Diethyl O-4-tolylcarbamate (84e):

bp 84-85°C/0.05 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ1.21 (t, J = 7, 6H, 2 CH_3), 2.32 (s, 3H, CH_3), 3.40 (q, J = 7, 4H, 2 CH_2), 6.97 (d, J = 8.6, 2H, ArH), 7.15 (d, J = 8.6, 2H, ArH); MS m/e 207 (M^+); Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; h, 8.26; N, 6.75. Found: C, 69.57; H, 8.40; N, 6.90.

N,N-Diethyl O-3-anisylcarbamate (84f):

bp 122-124°C/0.12 mm (lit[135] 138-140°C/2.0 mm); IR (neat) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, J = 7, 6H, 2 CH_3), 3.40 (q, J = 7, 4H, 2 CH_2), 3.78 (s, 3H, OCH_3), 6.63-6.79 (m, 3H, ArH), 7.12-7.34 (m, 1H, ArH); MS m/e 223 (M^+).

N,N-Diethyl O-1-naphthylcarbamate (95):

bp 135-140°C/0.1 mm (lit[136] 201-202°C/10-11 mm); IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ1.29 (m, 6H, 2 CH_3), 3.51 (m, 4H, 2 CH_2), 7.28-7.98 (m, 7H, arH); MS m/e 243 (M^+).

N,N-Diethyl O-2-naphthylcarbamate (97):

bp 120-122°C/0.04 mm (lit.[136] 203-205°C/11 mm); IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ1.23 (t, J = 7, 6H, 2 CH_3), 3.43 (q, J = 7, 4H, 2 CH_2), 7.2-7.97 (m, 7H, ArH); MS m/e 243 (M^+).

N,N-Diethyl O-(1-bromo)-2-naphthylcarbamate (101):

mp 77-78°C (hexane); IR ($CHCl_3$) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.15-1.42 (m, 6H, 2 CH_3), 3.30-3.59 (m, 4H, 2 CH_2), 7.23-7.85 (m, 5H, ArH), 8.19-8.31 (m, 1H, ArH); MS m/e 322, 324 (M^+); Anal. Calcd for $C_{15}H_{16}BrNO_2$: C, 55.91; H, 5.0; N, 4.34. Found: C, 55.97; H, 5.16; N, 4.28.

N,N-Dimethyl O-phenylcarbamate (102):

bp 79-80°C/0.04 mm (mp 43-44°C) (lit.[137] mp 45°C); IR ($CHCl_3$) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.98, 3.05 (2s, 6H, 2 CH_3), 7.02-7.46 (m, 5H, ArH); MS m/e 165 (M^+).

N,N-Diethyl O-(2-N,N-diethylcarbamoyl)phenylcarbamate (115a): bp 160-165°C/0.15 mm (lit[134] 180-185°C/1 mm); IR (neat) ν_{max} 1710, 1622 cm^{-1}; NMR ($CDCl_3$) δ 0.96-1.27 (m, 12H, 4 CH_3), 3.07-3.64 (m, 8H, 4 CH_2), 7.19-7.50 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 11.8 (19, CH_3), 12.7 (84, CH_3), 13.4 (40, CH_3), 13.8 (88, CH_3), 42.1 (118, 2 CH_2), 42.8 (78, 2 CH_2), 123.2 (100, C-6), 124.9 (83, C-4), 126.6 (95, C-3), 129.4 (83, C-5), 130.6 (28, C-2), 147.4 (39, C-1), 153.45 (18, OCO), 167.59 (26, CO); MS m/e 292 (M^+).

Compound **115a** was also prepared from the lithiation of N,N-diethyl O-phenylcarbamate **84a** (s-BuLi-TMEDA) followed by quenching with N,N-diethylcarbamoyl chloride.[69]

N,N-Diethyl O-(3-N,N-diethylcarbamoyl)phenylcarbamate (118a): bp 130-135°C/0.03 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.12-1.29 (m, 12H, 4 CH_3), 3.26-3.52 (m, 8H, 4 CH_2), 7.10-7.36 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.4 (83, 4 CH_3), 39.8 (17, CH_2), 40.7 (16, CH_2), 41.2 (18, CH_2), 42.0 (21, CH_2), 119.8 (95, C-2), 122.1 (96, C-6), 122.5 (100, C-4), 129.0 (81, C-5), 138.1 (44, C-3), 151.3 (47, C-1), 153.6 (27, OCO), 170.0 (38, CO); MS m/e 292 (M^+); Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.54; H, 8.29, N, 9.74.

N,N-Diethyl O-(4-N,N-diethylcarbmoyl)phenylcarbamate (121a):

bp 100-105°C/0.02 mm (lit[134] 180-190°C/1 mm); IR (neat) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ1.08-1.31 (m, 12H, 4 CH_3), 3.28-3.54 (m, 8H, 4 CH_2), 7.15 (d, J = 8.5, 2H, H-2 and H-6), 7.39 (d, J = 8.5, 2H, H-3 and H-5); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.4 (69, 4 CH_3), 42.0 (70, 4 CH_2), 121.3 (99, C-2 and C-6), 127.2 (100, C-3 and C-5), 133.7 (32, C-4), 151.9 (28, C-1), 153.4 (16, OCO), 170.3 (24, CO); MS m/e 292 (M^+).

N,N-Diethyl O-(3-N,N-diethylcarbamoyloxy)phenylcarbamate (125):

bp 180-185°C/0.04 mm; IR (neat) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ1.21 (t, J = 7, 12H, 4 CH_3), 3.39 (q, J = 7, 8H, 4 CH_2), 6.88-9.96 (m, 3H, ArH), 7.0-7.42 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.5 (53, 4 CH_3), 41.9 (138, 4 CH_2), 115.3 (64, C-2), 118.0 (100, C-4 and C-6), 128.8 (64, C-5), 151.7 (55, C-1 and C-3), 153.5 (52, 2 OCO); MS m/e 308 (M^+); Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.23; H, 7.80; N, 9.17.

N,N-Diethyl-2-hydroxybenzamide:

mp 99-100°C (CH_2Cl_2-hexane) (lit[138] 104°C).

N,N-Diethyl-3-hydroxybenzamide:

mp 80-82°C (C_6H_6-hexane) (lit[139] 84°C).

N,N-Diethyl-4-hydroxybenzamide:

mp 119-121°C (CH_2Cl_2-hexane) (lit[138] 121-123°C).

N,N-Diethyl O-(2-hydroxy)phenylcarbamate:

mp 71-73°C (C_6H_6-hexane) (lit.[139] 75°C); IR ($CHCl_3$) ν_{max} 3300, 1700 cm^{-1}; NMR ($CDCl_3$) δ1.13-1.31 (m, 6H, 2 CH_3), 3.28-3.37 (m, 4H, 2 CH_2), 6.51-7.17 (m, 4H, ArH); MS m/e 209 (M^+).

N,N-Diethyl O-(3-hydroxy)phenylcarbamate:

mp 61-63°C (Et_2O-hexane) (lit.[135] mp 64-66°C); IR ($CHCl_3$) ν_{max} 3300, 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.12-1.36 (m, 6H, 2 CH_3), 3.28-3.51 (m, 4H, 2 CH_2), 6.87-7.27 (m, 4H, ArH); MS m/e 209 (M^+). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.18; H, 7.36; N, 6.63.

N,N-Diethyl O-(4-hydroxy)phenylcarbamate:

mp 92-93°C (C_6H_6); IR ($CHCl_3$) ν_{max} 3200, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, J = 7, 6H, 2 CH_3), 3.40 (q, J = 7, 4H, 2 CH_2), 6.50-6.88 (ABq, J = 8.9, 4H, ArH), 7.24 (s, 1H, O<u>H</u> exchanged with D_2O); MS m/e 209 (M^+); Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.49; H, 7.29; N, 6.69.

N,N-Diethyl O-(2-methoxymethoxy)phenylcarbamate (115b):

bp 75-78°C/0.1 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ1.23 (t, J = 6.9, 6H, 2 CH_3), 3.43 (q, J = 6.9, 4H, 2 CH_2), 3.47 (s, 3H, OCH_3), 5.15 (s, 2H, OCH_2O), 6.99-7.16 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.6 (96, 2 CH_3), 42.1 (157, 2 CH_2), 56.0 (74, OCH_3), 95.0 (87, OCH_2O), 116.3 (91, C-3), 122.0 (95, C-5), 123.3 (96, C-6), 125.9 (100, C-4), 141.4 (30, C-1), 149.2 (35, C-2), 153.8 (26, OCO). MS m/e 253 (M^+);

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.52. Found: C, 61.94; H, 7.67; N, 5.25.

N,N-Diethyl O-(3-methoxymethoxy)phenylcarbamate:

mp 80-84°C/0.1 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, J = 7, 6H, 2 CH_3), 3.42 (q, J = 7, 4H, 2 CH_2), 3.45 (s, 3H, OCH_3), 5.15 (s, 2H, OCH_2O), 6.72-7.26 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ(relative intensity) 13.9 (55, 2 CH_3), 42.1 (126, 2 CH_2), 56.0 (83, OCH_3), 94.5 (88, OCH_2O), 110.1 (93, C-2), 113.0 (97, C-4), 115.2 (90, C-6), 129.5 (100, C-5), 152.4 (53, C-1), 158.0 (47, C-3), 154.0 (35, OCO); MS m/e 253 (M^+); Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.52. Found: C, 61.65; H, 7.76; N, 5.26.

N,N-Diethyl O-(4-methoxymethoxy)phenylcarbamate (121b):

bp 85-88°C/1.0 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, J = 7, 6H, 2 CH_3), 3.41 (q, J = 7, 4H, 2 CH_2), 3.45 (s, 3H, OCH_3), 5.13 (s, 2H, OCH_2O), 7.01 (s, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.6 (24, 2 CH_3), 41.8 (55, 2 CH_2), 55.5 (35, OCH_3), 94.6 (45, OCH_2O), 116.6 (100, C-3 and C-5), 122.3 (78, C-2 and C-6), 146.0 (32, C-1), 154.3 (24, C-4), 154.1 (20, OCO); MS m/e 253 (M^+); Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.52. Found: C, 61.81; H, 7.72; N, 5.25.

4.2.3. EXPERIMENTAL DETAILS ON LITHIATION

N,N-Diethyl-O-(2-deutero)phenylcarbamate (85a).

According to procedure A, lithiation of N,N-diethyl-O-phenylcar-

bamate **84a** (2.0 g, 10.36 mmol), s-BuLi (8.97 mL, 11.39 mmol), TMEDA (1.72 mL, 11.39 mmol), -78°C, 1h, ethanol-d_1 (0.67 mL, 11.39 mmol) and standard workup followed by column chromatography using 1:4 (v/v) EtOAc-hexane afforded 1.9 g (95%) of compounds **85a** (4%d_0, 96% d_1), bp 65-70°C/0.25 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, J = 7.5, 6H, 2 CH_3), 3.40 (q, J = 7.5), 7.0-7.4 (m, 4H, ArH); MS m/e 194 (M^+).

N,N-Diethyl O-(2-allyl)phenylcarbamate (85b).

According to procedure A, lithiation of N,N-Diethyl O-phenylcarbamate **84a** (700 mg, 3.59 mmol), s-BuLi (3.02 mL, 3.98 mmol), TMEDA (0.60 mL), 3.98 mmol), -78°C, 1h, allyl bromide (0.34 mL, 3.98 mmol) and standard workup followed by column chromatography using 1:9 (v/v) EtOAc-hexane as eluent gave 633 mg (75%) of compound, bp 75-78ZC/0.25 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.33-1.69 (m, 6H, 2 CH_3), 3.30-3.64 (m, 4H, 2 CH_2 and 2H, $\underline{CH_2}$-CH=), 4.90-5.26 (m, 2H, CH=$\underline{CH_2}$), 5.70 -6.20 (m, 1H, CH=), 6.98-7.54 (m, 4H, ArH); Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07: H, 8.20; N, 6.00. Found: C, 71.62; H, 8.47; N, 6.14.

N,N-Diethyl O-(2-methoxy-6-trimethylsilyl)phenylcarbamate (85c).

According to procedure A, lithiation of N,N-diethyl-O-2-anisylcarbamate **84b** (500 mg, 2.24 mmol), s-BuLi (1.94 mL, 2.46 mmol), TMEDA (0.37 mL, 2.46 mmol), -78°C, 1h, TMSCl (0.31 mL, 2.46 mmol, and standard workup followed by column chromatography using 1:5 (v/v) EtOAc-hexane as eluent afforded 449 mg (68%) of compound **85c,** bp 108-112°C/0.1 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.03

(s, 9H, $Si(CH_3)_3$), 1.1-1.45 (m, 6H, 2 CH_3), 3.25-3.65 (m, 4H, 2 CH_2), 3.85 (s, 3H, OCH_3), 6.90-7.30 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ(relative intensity) 0.79 (199, $Si(CH_3)_3$), 13.3 (47, 2 CH_3), 14.0 (46, 2 CH_3), 41.9 (70, 2 CH_2), 42.0 (67, 2 CH_2), 55.9 (91, OCH_3), 113.8 (82, C-3), 125.7 (76, C-4), 125.8 (100, C-5), 133.21 (13, C-6), 145.50 (7, C-1), 151.3 (14, C-2), 153.9 (10, OCO); MS m/e 295 (M^+); Anal. Calcd for $C_{15}H_{25}NO_2Si$: C, 60.98; H, 8.52; N, 4.74. Found: C, 60.70; H,, 8.59; N, 4.62.

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-methoxy)phenylcarbamate (85d).

According to procedure **A**, lithiation of N,N-diethyl O-2-anisyl-carbamate 8**4b** (500 mg, 2.24 mmol), s-BuLi (2.07 mL, 2.46 mmol), TMEDA (0.37 mL, 2.46 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.30 mL, 2.46 mmol) and workup in the usual manner followed by column chromatography using 1:4 (v/v) EtOAc-hexane as eluent afforded 648 mg (90%) of compound **85d**, bp 135-138°C/0.1 mm; IR (neat) ν_{max} 1715, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.88-1.32 (m, 12H, 4 CH_3), 3.10-3.75 (m, 8H, 4 CH_2), 3.80 (s, 3H, OCH_3), 6.82 (dd, J = 7.3, 1.7, H-3), 6.95 (dd, J = 8.2, 1.7, H-5), 7.18 (dd, J = 7.3, 8.2, H-4); ^{13}C NMR ($CDCl_3$) δ(relative intensity) 12.6 (91, 2 CH_3), 13.8 (104, 2 CH_3), 38.5 (90, CH_2), 42.3 (112, 2 CH_2), 42.8 (82, CH_2), 56.2 (98, OCH_3), 112.8 (80, C-5), 118.1 (86, C-3), 126.0 (100, C-4), 132.5 (30, C-2), 137.0 (15, C-1), 152.4 (26, C-6), 153.2 (22, OCO), 167.3 (25, CO); MS m/e 322

(M^+); Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.39; H, 8.15; N, 8.69. Found: C, 63.51; H, 8.28, N, 9.12.

N,N-Diethyl O-(2-chloro-6-trimethylsilyl)phenyl carbamate (85e).

According to procedure **A**, lithiation of N,N-diethyl O-(2-chloro)phenyl carbamate **84c** (500 mg, 2.19 mmol), s-BuLi (1.90 mL, 2.41 mmol), TMEDA (0.36 mL, 2.41 mmol), -78°C, 1h, TMSCl (0.30 mL, 2.41 mmol) and standard workup followed by column chromatrgraphy using 1:4 (v/v)EtOAc-hexane as eluent afforded 520 mg (79%) of compound **85e**, bp 78-80°C/0.02 mm; IR (neat) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.12 (s, 9H, 3 $Si(CH_3)_3$), 1.01-1.29 (m, 6H, 2 CH_3), 3.26-3.45 (m, 4H, 2 CH_2), 6.97 (dd, J = 7.6, H-4), 7.18 (dd, J = 7.6, 1.5, H-5), 7.25 (dd, J = 7.6, 1.5, H-3), MS m/e 284, 286 (M^+-CH_3), 264 (9.69), 186 (0.34), 184 (0.88), 100 (100, 72 (59.4); Anal. Calcd for $C_{14}H_{22}ClNO_2Si$: C, 56.06; H, 7.39; N, 4.67. Found: C, 56.14; H, 7.52; N, 4.57.

N,N-Diethyl O-(2-chloro-6-iodo)phenylcarbamate (85f).

According to procedure **A**, lithiation of N,N-diethyl O-(2-chloro)phenyl carbamate **84c** (500 mg, 2.19 mmol), s-BuLi (1.90 mL, 2.41 mmol), TMEDA (0.36 mL, 2.41 mmol), -78°C, 1h, iodine (624 mg, 2.41 mmol), standard workup and purification by column chromatography (1:4 EtOAc-hexane as eluent) gave 722 mg (93%) of compound **85f**, bp 85-9°C/0.05 mm; IR (neat) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.14-1.71 (m, 6H, 2 CH_3), 3.28-3.66 (m, 4H, 2 CH_2), 6.86 (t, J = 7.8, 1H, H-4), 7.39 (dd, J = 7.8, 1.56, 1H, H-5), 7.69 (dd, J = 7.8, 1.56, 1H, H-3); HRMS m/e 352.9678; Calc. for $C_{11}H_{13}ClINO_2$: 352.9680.

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-chloro)phenyl carbamate (85g).

According to procedure **A**, lithiation of N,N-diethyl O-(2-chloro)-phenylcarbamate 8**4c** (500 mg, 2.19 mmol), s-BuLi (1.90 mL, 2.41 mmol), TMEDA (0.36 mL, 2.41 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.30 mL, 2.41 mmol), standard workup and purification by column chromatography (1:1 EtOAc-hexane as eluent) afforded 559 mg (78%) of compound **85g**, bp 130-3°C/0.04 mm; IR (neat) ν_{max} 1720 1630 cm^{-1}; NMR ($CDCl_3$) δ0.96-1.34 (m, 12H, 4 CH_3), 3.18-3.56 (m, 8H, 4 CH_2), 7.14-7.20 (m, 2H, ArH), 7.41 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ(relative intensity) 12.6 (86, CH_3), 13.4 (58, CH_3), 13.9 (85, CH_3), 14.1 (59, CH_3), 38.7 (86, CH_3), 42.4 (66, CH_2), 42.6 (65, CH_2), 42.9 (96, CH_2), 124.9 (86, C-3), 126.3 (93, C-4), 129.0 (15, C-6), 130.4 (100, C-5, 133.6 (13, C-2), 145.0 (7, C-1), 153.0 (9, OCO), 167.0 (12, CO); MS m/e 326, 328 (M^+); Anal. Calcd for $C_{16}H_{23}ClN_2O_3$: C, 58.79; H, 7.09; N, 8.57. Found: C, 58.71; H, 7.12; N, 8.79.

N,N-Diethyl O-(3-methyl-6-trimethylsilyl)phenyl carbamate (85h).

According to procedure **A**, lithiation of N,N-diethyl O-3-tolyl carbamate 8**4d** (620 mg, 2.99 mmol), s-BuLi (2.61 mL, 3.29 mmol), TMEDA (0.49 mL, 3.29 mmol), -78°C, 1h, TMSCl (0.42 mL, 2.99 mmol), standard workup and column chromatography using 1:9 EtOAc-hexane as eluent afforded 646 mg (77%) of compound **85h** , bp 88-92°C/0.1 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ0.30 (s, 9H, Si $(CH_3)_3$), 1.05-1.45 (m, 6H, 2 CH_3), 2.35 (s, 3H, CH_3), 3.25-3.65

(m, 4H, CH_3), 6.85 (s, H-6), 7.05 (d, J = 7.5, H-3), 7.38 (d, J = 7.5, H-4); MS m/e 279 (M^+). Anal. Calcd for $C_{15}H_{25}NO_2Si$: C, 64.47; H, 9.01: N, 5.01. Found: C, 64.76; H, 9.03; n, 4.90. Compound 84**d** when subjected to lithiation using LDA, according to procedure B, the product **85h** was obtained in only 39% yield.

N,N-Diethyl O-(4-methyl-6-trimethylsilyl)phenyl carbamate (85i). According to procedure **A,** lithiation of N,N-diethyl O-4-tolyl carbamate 84**e** (500 mg, 2.41 mmol), s-BuLi (2.10 mL, 2.65 mmol), TMEDA (0.40 mL, 2.65 mmol), -78°C, 1h, TMSCl (0.34 mL, 2.65 mmol), standard workup followed by recrystallization afforded 559 mg (83%) of compound **85i,** mp 53-54°C (hexane): IR ($CHCl_3$) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.29 (s, 9H, Si $(CH_3)_3$), 1.18-1.36 (m, 6H, 2 CH_3), 2.35 (s, 3H, CH_3), 3.37, 3.55 (m, 4H, 2 CH_2), 6.92 (d, J = 8.2, 1H, H-6), 7.16 (dd, J = 8.2, 1.8, 1H, H-5), 7.22 (d, J = 1.8, 1.8, 1H, H-3); MS m/e 279 (M^+); Anal. Calcd for $C_{15}H_{25}NO_2Si$: C, 64.47; H, 9.01; N, 5.01. Found: C, 64.63; H, 9.10; N, 5.07. When 84**e** (500 mg, 2.41 mmol) was subjected to lithiation using LDA (2.65 mmol), -78°C, 1h, TMSCl (0.34 mL, 2.65 mmol), according to procedure **B,** 105 mg (16%)) of the product **85i** was obtained which was shown to be identical with the material prepared by the method described above.

N,N-Diethyl O-(3-methoxy-2-methyl)phenyl carbamate (85j) and N,N-Diethyl O-(3-methoxy-6-methyl)phenyl carbamate (85k). According to procedure **A,** lithiation of N,N-Diethyl O-3-anisyl carbamate (1.52 g, 6.79 mmol), s-BuLi (6.61 mL, 7.47 mmol), TMEDA

(1.13 mL, 7.47 mmol), -78°C, 1h, methyl iodide (1.5 mL, excess) and standard workup gave 1.50 g (93%) of product consisting of **85j** and **85k** in the ratio of 73:27 (by interaction of the CH_3 signal at 1.95 and 2.1 in ^1H NMR). The two isomers were unresolved by G.C. Purification by column chromatography (1:9 (v/v) EtOAc-hexane as eluent) followed by recrystallization gave pure **85j,** mp 58-60°C (hexane); IR ($CHCl_3$) ν_{max} 1710 cm^{-1}; NMR (DMSO-d_6) δ1.00-1.40 (m, 6H, 2 CH_3), 1.95 (s, 3H, CH_3), 3.10-3.60 (m, 4H, 2 CH_2), 3.79 (s, 3H, OCH_3), 6.66 (d, J = 8.0 1H, H-6), 6.82 (d, J = 8.0, 1H, H-4), 7.163 (dd, J = 8.0, 1H, H-4) MS m/e 237 (M^+); Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.09; H, 8.19; N, 5.96.

Compound **85k** was contaminated with **85j** which could not be removed. Therefore satisfactory spectral and analytical data for **85k** were not obtained.

N,N-Diethyl O-(2-N,N-diethylcarbamoyl)-1-naphthylcarbamate (96). According to procedure **A,** lithiation of N,N-diethyl O-1-naphthylcarbamate **95** (500 mg, 2.05 mmol), s-BuLi (1.88 mL, 2.26 mmol), TMEDA (0.34 mL, 2.26 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride, standard workup and purification by column chromatography (1:1 EtOAc-hexane as eluent) yielded 550 mg (78%) of compound **96,** bp 170-180°C/0.3 mm; IR (neat) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.98-1.44 (m, 12H, 4 CH_3), 3.26-3.68 (m, 8H, 4 CH_2), 7.33 (d, J = 8.4, H-3), 7.44-7.90 (m, 5H, ArH); Ms m/e 342 (M^+); Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.14; H, 7.75; N, 8.20.

N,N-Diethyl O-(3-trimethylsilyl)-2-naphthylcarbamate (98a), N,N-Diethyl O-(1-trimethylsilyl)-2-naphthylcarbamate (99a) and N,N-Diethyl-3-hydroxy-2-naphthamide (100).

According to procedure **A,** lithiation of N,N-diethyl O-2-naphthylcarbamate **97** (500 mg, 2.05 mmol), s-BuLi (1.78 mL, 2.26 mmol), TMEDA (0.34 mL, 2.26 mmol), -78°C, 1h, TMSCl (0.29 mL, 2.25 mmol), standard workup and column chromatography (1:9 EtOAc-hexane as eluent) gave a mixture of compound **98a** and its isomer **99a** (62% overall) in a ratio of 70:30 (by NMR, δ of $Si(CH_3)_3$ 0.30 & 0.55) and the rearranged product **100 (20%).** The compound **98a** was isolated from **99a** by fractional recrystallization, mp 63-64°C (hexane); IR ($CHCl_3$) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ0.30 (s, 9H, $Si(CH_3)_3$), 1.09-1.37 (m, 6H, 2 CH_3), 3.34-3.53 (m, 4H, 2 CH_2), 7.20-7.89 (m, 6H, ArH); MS m/e 315 (M^+); Anal. Calcd for $C_{18}H_{25}NO_2Si$: C, 68.57; H, 7.98; N, 4.43. Found: C, 69.00; H, 8.15; N, 4.72.

Compound **99a** was contaminated with **98a,** so satisfactory spectral data were not obtained.

Compound **100,** mp 169-171°C (C_6H_6-hexane) (lit.[140] mp 170-171°C); IR ($CHCl_3$) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ1.32 (t, J = 7, 6H, 2 CH_3), 3.59 (q, J = 7, 4H, 2 CH_2), 7.25-7.78 (m, 6H, ArH), 8.96 (br, 1H, OH, exchanged with D_2O); MS m/e 243 (M^+).

Compound **99a** was, however, prepared from N,N-diethyl 1-(bromo)-2-naphthylcarbamate **101** by metal halogen exchange as follows: t-BuLi (0.90 mL, 1.70 mmol) was injected to a stirred THF solution (50 mL) of N,N-diethyl O-(1-bromo)-2-naphthylcarbamate **101** (500

mg, 1.55 mmol) at -78°C under nitrogen and after 1h, TMSCl (0.22 mL, 1.70 mmol) was added. Workup in the usual manner and purification by column chromatography afforded 398 mg (81%) of compound-**99a** as an oil whose spectral (NMR, GC) data were shown to be non-identical to those for **98a;** IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ0.55 ($Si(CH_3)_3$), 1.02-1.42 (m, 6H, 2 CH_3), 3.35-3.70 (m, 4H, 2 CH_2), 7.08-8.30 (m, 6H, ArH); Ms m/e 315 (M^+).

N,N-Diethyl O-(3-N,N-diethylcarbamoyl)-2-naphthylcarbamate (98b). According to procedure **A,** lithiation of N,N-diethyl O-2-naphthylcarbamate **97** (500 mg, 2.05 mmol), s-BuLi (1.78 mL, 2.26 mmol), TMEDA (0.34 mL, 2.26 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.28 mL, 2.26 mmol), standard workup and purification by column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 358 mg (51%) of compound **98b** as a viscous oil, IR (neat) ν_{max} 1710, 1625 cm^{-1}; NMR ($CDCl_3$) δ0.83-1.43 (m, 12H, 4 CH_3), 3.07-3.83 (m, 8H, 4 CH_2), 7.33-7.90 (m, 6H, ArH); HRMS m/e 342.1926; Calcd for $C_{20}H_{26}N_2O_3$: 342.1944; and compound **100** (25%).

N,N-Diethyl O-(1-N,N-diethylcarbamoyl)-2-naphthylcarbamate (99b). t-BuLi (0.90 mL, 1.70 mmol) was injected to a stirred THF solution (50 mL) of N,N-diethyl O-(1-bromo)-2-naphthylcarbamate **101** (500 mg, 1.55 mmol) at -78°C and after 1h, N,N-diethylcarbamoyl chloride (0.21 mL, 1.70 mmol) was added. Standard workup followed by column chromatography using 1:1 EtOAc-hexane as eluent afforded 165 mg (31%) of compound **99b,** IR (neat) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ0.844-1.42 (m, 12H, 4 CH_3), 3.07-3.82 (m, 8H, 4 CH_2), 7.32-7.90 (m, 6H, ArH); MS m/3 342 (M^+).

The spectral data (NMR, GC) of **99b** was shown to be non identical to those of **98b** described in the previous experiment.

N,N-Dimethyl O-2-tolylcarbamate (103a).

According to procedure, lithiation of N,N-dimethyl O-phenylcarbamate **102** (500 mg, 3.03 mmol), s-BuLi (2.97 mL, 3.33 mmol), TMEDA (0.50 mL, 3.33 mmol), -95°C, 10 min, methyl iodide (0.5 mL, excess), standard workup and purification by column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 485 mg (90%) of compound **103a,** bp 80-81°C/0.05 mm (lit.[141] 115-117°C/0.3 mm); IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ2.20 (s, 3H, CH_3), 3.01, 3.09 (2 s, 6H, 2 CH_3), 7.0-7.23 (m, 4H, ArH); MS m/e 179 (M^+).

N,N-Dimethyl O-(2-N,N-diethylcarbamoyl)phenylcarbamate (103b).

According to procedure **A,** lithiation of N,N-dimethyl O-phenylcarbamate **102** (500 mg, 3.03 mmol), s-BuLi (2.90 mL, 3.33 mmol), TMEDA (0.50 mL, 3.33 mmol), -95°C, 10 min, N,N-diethylcarbamoyl chloride (0.41 mL, 3.33 mmol), standard workup followed by column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 626 mg (78%) of compound **103b,** bp 110-114°C/0.05 mm; IR (neat) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ0.95-1.3 (m, 6H, 2 CH_3), 3.0 and 3.08 (2 s, 6H, 2 CH_3), 3.08 - 3.8 (m, 4H, 2 CH_2), 7.05 - 7.5 (m, 4H, ArH); MS m/e 264 (M^+): Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.62; N, 10.59. Found: C, 63.77; H, 7.65; N, 10.30.

N,N-Dimethyl O-(2-deutero)phenylcarbamate (103c).

According to procedure **A,** lithiation of N,N-dimethyl O-phenylcarbamate **102** (500 mg, 3.03 mmol), s-BuLi (2.27 mL, 3.33 mmol), TMEDA

(0.50 mL, 3.33 mmol), -95°C, 10 min, ethanol-d_1 0.5 mL, excess), standard workup and column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 415 mg (83%) of compound **103c** (47% d_0, 53% d_1); bp 88-92°C/0.1 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.98, 3.05 (2 s, 6H, 2 CH_3), 7.06-7.32 (m, 4H, ARH); MS m/e 166 (M^+).

N,N-Dimethyl O-(2-trimethylsilyl)phenyl carbamate (103d). According to procedure **A,** lithiation of N,N-dimethyl O-phenylcarbamate **102** (500 mg, 3.03 mmol), s-BuLi (2.97 mL, 3.33 mmol), TMEDA (0.50 mL, 3.33 mmol), -95°C, 10 min, TMSCl (0.43 mL, 3.33 mmol), standard workup and purification by column chromatography using 1:9 (v/v) EtoAc-hexane as eluent afforded 630 mg (88%) of compound **103d,** bp 70-75°C/0.01 mm; IR (neat) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ0.26 (s, 9H, $Si(CH_3)_3$), 2.98, 3.04 (2 s, 6H, 2 CH_3), 7.13-7.24 (m, 4H, ArH); MS m/e 222 (M^+-CH_3); HRMS m/e 222.0948; Calcd. for $C_{11}H_{16}NO_2Si$: 222.095 (M^+-CH_3).

N,N-Dimethyl-2-hydroxybenzamide (104). According to procedure **C,** lithiation of N,N-dimethyl O-phenylcarbamate **102** (500 mg, 3.03 mmol), s-BuLi (2.64 mL, 3.33 mmol), TMEDA (0.50 mL, 3.33 mmol), -95°C, 5.5h, and quenching at -95°C with saturated aqueous MH_4Cl solution gave after standard workup 491 mg of a crude product which upon recrystallization afforded 430 mg (86%) of compound **104,** mp 155-156°C (CH_2Cl_2) (lit.[142] 161-164°C); IR ($CHCl_3$) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ 3.16 (s, 6H, 2 CH_3), 6.73-7.42 (m, 4H, ArH), 9.96 (br s, 1H, OH exchanged with D_2O); MS m/e 165 (M^+).

N,N-Diethyl-2-hydroxy-3-chlorobenzamide (107a).

According to procedure **C**, lithiation of N,N-diethyl O-(2-chloro)-phenyl carbamate **84c** (500 mg, 2.19), s-BuLi (1.90 mL, 2.41 mmol), TMEDA (0.36 mL, 2.41 mmol), -78°C, standard workup and column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 364 mg (72%) of compound **107a**, bp 105-108°C/0.25 mm; IR (neat) ν_{max} 3200, 1610 cm^{-1}; NMR ($CDCl_3$) δ1.25 (t, J = 7, 6H, 2 CH_3), 3.49 (q, J = 7, 2 CH_2), 6.81 (dd, J = 7.8, H-5), 7.18 (dd, J = 7.82, 1.56, H-6), 7.38 (dd, J = 7.8, 1.56, H-4), 9.58 (br s, 1H, OH, exchanged with D_2O); MS m/e 227, 229 (M^+); Anal. Calcd for $C_{11}H_{14}ClNO_2$: C, 58.01; H, 6.19; N, 6.15. Found: C, 58.32; H, 6.23; N, 6.04.

N,N-Diethyl-2-hydroxy-4-methylbenzamide (107b).

According to procedure **C**, lithiation of N,N-diethyl O-(3-methyl)-phenyl carbamate **84d** (500 mg, 2.41 mmol), s-BuLi (1.82 mL, 2.65 mmol), TMEDA (0.40 mL, 2.65 mmol), -78°C, standard workup followed by column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 240 mg (48%) of compound **107b**, mp 104-105°C (CH_2Cl_2/hexane), IR ($CHCl_3$) ν_{max} 3200, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, J = 7, 6H, 2 CH_3), 2.31 (s, 3H, CH_3), 3.51 (q, J = 7, 4H, 2 CH_2), 6.60 (s, H-3), 6.75 (d, J = 8.2, H-5), 7.16 (d, J = 8.2, H-6), 9.6 (br, 1H, OH, exchanged with D_2O); MS m/e 207 (M^+); Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.24; H, 7.92: N, 6.85.

N,N-Diethyl-2-hydroxy-5-methylbenzamide (107c).

According to procedure **C**, lithiation of N,N-diethyl-O-(4-methyl)-phenyl carbamate **84e** (500 mg, 2.41 mmol), s-BuLi (2.06 mL, 2.65 mmol), TMEDA (0.40 mL, 2.65 mmol), -78°C, standard workup and purification by column chromatography using 1:1 EtOAc-hexane as eluent afforded 350 mg (70%) of compound **707c**, mp 110-111°C (benzene); Ir ($CHCl_3$) ν_{max} 3200, 1630 cm^{-1}: NMR ($CDCl_3$) δ 1.28 (t, J = 7, 6H, 2 CH_3), 2.28 (s, 3H, CH_3), 3.52 (q, J = 7, 2 CH_2), 6.88 (d, J = 7, H-4), 7.05 (s, H-6), 7.20 (d, J = 7, H-3); 9.20 (br s, 1H, OH, exchanged with D_2O); MS m/e 207 (M^+); Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.56; H, 8.00; N, 6.62.

N,N-Diethyl-1-hydroxy-2-naphthamide (108).

According to procedure **C**, lithiation of N,N-diethyl O-2-naphthyl carbamate **95** (850 mg, 3.08 mmol), s-BuLi/3.20 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, standard workup followed by column chromatography using 1:4 (v/v) EtOAc-hexane as eluent afforded 535 mg (715) of compound **108**, bp 120-125/0.1 mm (lit.[143] 130-133°C/1 mm); IR (neat) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, J = 7, 6H, 2 CH_3), 3.55 (q, J = 7, 4H, 2 CH_2), 7.2-7.8 (m, 5H, ArH), 8.25-8.45 (m, 1H, H-8), 11.3 (br, 1H, OH, exchanged with D_2O); MS m/e 243 (M^+).

N,N-Diethyl-3-hydroxy-2-naphthalmide (100) and N,N-Diethyl-2-hydroxy-1-naphthamide (109).

According to procedure **C**, lithiation of N,N-diethyl O-2-naphthyl

carbamate **97** (500 mg, 2.05 mmol), s-BuLi (1.78 mL, 2.26 mmol), TMEDA (0.34 mL, 2.26 mmol), -78°C, standard workup and column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 215 mg (43%) of compound **100** [140] and 185 mg (37%) of compound **109**, mp 198-200°C (CH_2Cl_2); IR ($CHCl_3$) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.06-1.24 (m, 6H, 2 CH_3), 3.15-3.68 (m, 4H, 2 CH_2), 6.73-7.74 (m, 6H, ArH), 8.52 (br, 1H, OH, exchanged with D_2O); MS m/e 243 (M^+); Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.75. Found: C, 73.82; H, 7.1; N, 5.83. Compound **109** was found to be identical with authentic sample prepared as described below.

t-BuLi (0.75 mL, 1.39 mmol) was injected to a stirred THF solution (50 mL) of N,N-diethyl O-(1-bromo)-2-naphthyl carbamate (450 mg, 1.39 mmol) at -78°C under nitrogen. The stirred solution was then allowed to warm to room temperature over 8h. Standard workup followed by recrystallization gave 350 mg (77%) of compound **109** (by mp, H NMR, G.C.).

N,N-Dimethyl-2-hydroxy-3-methylbenzamide (110) and N,N-Dimethyl-2--(2-hydroxyphenyl)acetamide (111).

According to procedure **C**, lithiation of N,N-dimethyl O-2-tolylcarbamate **103a** (677 mg, 3.78 mmol), s-BuLi (3.27 mL, 4.16 mmol), TMEDA (0.63 mL, 4.16 mmol), -100°C, warming to room temperature, standard workup and column chromatography using 1:1 (v/v) EtOAc-hexane as eluent chromatography afforded compound **110** (56%), mp 45°C (CH_2Cl_2); IR (neat) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.26 (s, 3H, CH_3), 3.14 (s, 6H, 2 CH_3), 6.73 (dd, J = 7.7, 1H, H-5),

7.16 (m, 2H, H-4 and H-6), 10.10 (br s, 1H, OH exchanged with D_2O); MS m/e 179 (M^+); Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81; Found: C, 67.28; H, 7.46; N, 7.46 and compound **111** (25%), mp 85-86°C (Et_2O); IR ($CHCl_3$) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ2.97 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 6.81 - 7.19 (m, 4H, ArH), 9.99 (s, 1H, OH exchanged with D_2O); MS m/e 179 (M^+); Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.07; H, 7.21; N, 7.62.

Lithiation and anionic ortho Fries rearrangement of a mixture of N,N-diethyl-O-4-tolyl carbamate (84e) and N,N-dimethyl O-phenyl carbamate (102).

According to procedure **C,** lithiation of a 1:1 (molar equiv) mixture of N,N-diethyl O-4-tolyl carbamate **84e** (500 mg, 2.41 mmol) and N,N-dimethyl O-phenyl carbamate **103** (398 mg, 2.41 mmol), s-BuLi (4.14 mL, 5.30 mmol), TMEDA (0.8 mL, 5.30 mmol), -95°C, 5h, warming to room temperature, standard workup and column chromatography using 1:9 and 1:4 (v/v) EtOAc-hexane as eluent gave 350 mg (70%) of compound **107c** and 0.295 mg (75%) of compound **104.**

Lithiation of a 1:1 molar equivalent mixture of N,N-diethyl O-phenyl carbamate 84a and N,N-diethylbenzamide 45a with 1.1 equivalent of s-BuLi and treatment with different electrophiles.

Expt. I: According to procedure **A,** lithiation of a mixture of N,N-diethyl O-phenyl carbamate **84a** (545 mg, 2.82 mmol) and N,N-diethylbenzamide **45a** (500 mg, 2.82 mmol), s-BuLi (2.70 mL, 3.1 mmol), TMEDA (0.47 mL, 3.1 mmol), -78°C, 15 min, ethanol-d_1 (0.18

mL, 3.1 mmol), standard workup and column chromatography using 1:5 and 1:3 (v/v) EtOAc-hexane as eluent yielded **113** (85%, E = D, 62% d_1 by mass spectroscopy), **114** (87%, E = D, 36% d_1 by mass spectroscopy), and 2-N,N-diethylcarbamoyl benzophenone **58** (7%) which was shown to be identical with authentic material (^{1}H NMR, IR, MS, GC).

Expt. II: According to procedure **A**, lithiation of a mixture of **84a** (0.545 mg, 2.82 mmol) and **45a** (500 mg, 2.82 mmol), s-BuLi (2.70 mL, 3.1 mmol), TMEDA (0.47 mL, 3.1 mmol), -78°C, 1h, methyl iodide (0.5 mL, excess), standard workup and column chromatography using 1:9 and 1:4 (v/v) EtOAc-hexane as eluent gave **113** (48%, E = Me), **114** (21%, E = Me) and **58** (15%). The products **113** and **114** - were inseparable from their respective starting materials, so product ratio as indicated above was established by ^{1}H NMR and GC comparison with authentic samples (both starting materials and products). When the lithiation was carried out at -100°C for 15 min, the ratio of the products as determined by GC comparison with authentic samples was **113** (46%), **114** (33%) and **58** (4%).

Expt. III: According to procedure **A**, lithiation of **84a** (545 mg, 2.82 mmol) and **45a** (500 mg, 2.82 mmol), s-BuLi (2.70 mL, 3.1 mmol), TMEDA (0.47 mL, 3.1 mmol), -78°C, 1h, methyl disulfide (0.28 mL, 3.1 mmol), standard workup and column chromatography using 1:9 and 1:4 (v/v) EtOAc-hexane as eluent afforded **113** (40%, E = SMe), **114** (13%, E = SMe) and **58** (20%). Products ratio was determined as described in Expt. II.

When the lithiation was carried out at -100°C for 15 min, the ratio of the products was **113** (30%), **114** (21%) and **58** (6%).

Expt. IV: According to procedure **A**, lithiation of **84a** (545 mg, 2.82 mmol) and **45a** (500 mg, 2.82 mmol), s-BuLi (2.70 mL, 3.1 mmol), TMEDA (0.47 mL, 3.1 mmol), -100°C, 15 min, N,N-diethylcarbamoyl chloride (0.38 mL, 3.1 mmol), standard workup and column chromatography using 1:5 and 1:2 (v/v) EtOAc: hexane as eluent gave **113** (40%, E = $CONEt_2$), **114** (31%, E = $CONEt_2$) and **58** (9%).

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-deuterio)phenyl carbamate (116a) and/or N,N-Diethyl O-(2-N,N-diethylcarbamoyl-3-deuterio)-phenyl carbamate (117a).

According to procedure A, lithiation of N,N-diethyl O-(2-N,N-diethylcarbamoyl)phenyl carbamate **115a** (320 mg, 1.07 mmol), s-BuLi (0.05 mL, 1.18 mmol), TMEDA (0.18 mL, 1.18 mmol), -78°C, 1h, methanol-d_1 (0.5 mL, excess), standard workup and column chromatography using 1:1 (v/v)EtOAc-hexane as eluent afforded 275 mg (86%) of compounds **116a** and/or **117a** (55% d_1, 45% d_0), bp 140-144°C/0.1 mm; IR (neat) ν_{max} 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95-1.36 (m, 12H, 4 CH_3), 3.06-3.60 (m, 8H, 4 CH_2), 7.17-7.29 (m, 3.2H, ArH); ^{13}C NMR ($CDCl_3$) δ(relative intensity) 12.1 (61, CH_3), 13.43 (28, CH_3), 13.92 (71, CH_3) 14.2 (22, CH_3), 38.8 (100, 2 CH_2), 42.2 (99, CH_2), 42.9 (99, CH_2), 123.3 (56, C-6), 125.03 (77, C-4), 126.9 (100, C-3), 129.5 (47, C-2), 129.6 (67, C-5), 147.4 (40, C-1), 153.5 (20, OCO), 167.6 (30, CO); MS m/e 293 (M^+).

N,N-Diethyl O-(2,6-bis-N,N-diethylcarbamoyl)phenylcarbamate (116b) and N,N-Diethyl O-(2,3-bis-N,N-diethylcabamoyl)phenylcarbamate (117b).

According to procedure **A**, lithiation of N,N-diethyl O-(2-N,N-diethylcarbamoyl)phenylcarbamate **115a** (485 mg, 1.66 mmol), s-BuLi (1.47 mL, 1.66 mmol), TMEDA (0.25 mL, 1.66 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.21 mL, 1.66 mmol), standard workup and sequential column chromatography using EtOAc as eluent and preparative TLC (EtOAc as eluent) afforded 428 mg (66%) of compound **116b**, IR (neat) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.97-1.34 (m, 18H, 6 CH_3), 3.24-3.98 (m, 12H, 6 CH_2); 7.24-7.31 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity), 12.7 (80, 2 CH_3), 13.5 (35, CH_3), 14.0 (95, 2 CH_3), 14.3 (39, CH_3), 38.8 (91, 2 CH_2), 42.5 (72, 2 CH_2), 43.0 (91, 2 CH_2), 125.2 (44, C-4), 127.4 (100, C-3 & C-5), 132.5 (30, C-2 & C-6), 145.0 (4, C-1), 152.0 (4, OCO), 167.1 (29, 2 CO); MS m/e 391.2476; Calcd for $C_{21}H_{33}N_3O_4$: 391.2472 and 92 mg (14%) of compound **117b**, IR ($CHCl_3$) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.98-1.26 (m, 18H, 6 CH_3), 3.13-3.71 (m, 12H, 6 CH_2), 7.06-7.40 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 12.8 (136, 2 CH_3), 13.5 (117, 2 CH_3), 14.0 (60, CH_3), 14.2 (31, CH_3), 38.8 (98, CH_2), 39.2 (56, CH_2), 41.8 (21, CH_2), 42.0 (39, CH_2), 42.4 (41, CH_2), 43.5 (123, CH_2), 122.5 (100, C-6), 123.3 (98, C-4), 127.6 (23, C-2), 129.1 (96, C-5), 136.1 (30, C-3), 147.4 (21, C-1), 153.2 (18, OCO), 165.8 (21 CO), 168.7 (19, CO); MS m/e 391.2476; Calcd for $C_{21}H_{33}N_3O_4$: 391.2472.

Compound **117b** was also prepared from N,N-diethyl O-(2,3-bis-N,N-

diethylcarbamoyl-6-trimethylsilyl)-phenyl carbamaqte **130** by CsF induced desilylation method as follows.

Compound **130** (97 mg, 0.21 mmol) was taken in DMF (10 mL) moistened with 2 drops of water and catalytic amount of CsF was added to it and the resulting mixture was refluxed for 17 h. Standard workup and purification by preparative TLC (EtOAc as eluent) afforded 51 mg (62%) of a compound which was shown to be identical (by R_f, NMR) with compound **117b** obtained above.

N,N-Diethyl O-(2-methoxymethoxy-6-deuterio)phenyl carbamate (116c) and/or N,N-Diethyl O-(2-methoxymethoxy-3-deuterio)phenyl carbamate (117c).

According to procedure **A**, lithiation of N,N-diethyl-O-(2-methoxymethoxy)phenylcarbamate **115b** (320 mg, 1.26 mmol), s-BuLi (1.0 mL, 1.39 mmol), TMEDA (0.21 mL, 1.39 mmol), -78°C, 1h, methanol-d_1(0.5 mL, excess), standard workup and column chromatography using 1:9 (v/v) EtOAc-hexane as eluent gave 280 mg (88%) of compounds **116c** and/or **117c**, bp 95-100°C/0.25 mm; IR (neat) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7, 2 CH_3), 3.39 (q, J = 7, 2 CH_2), 3.47 (s, 3H, OCH_3), 5.16 (s, 2H, OCH_2O), 7.0-7.25 (m, 3.37H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.1 (7, CH_3), 13.6 (35, CH_3), 13.7 (35, CH_3), 13.8 (34, CH_3), 42.5 (130, 4 CH_2), 56.1 (67, OCH_3), 95.2 (74, OCH_2O), 116.5 (69, C-3), 122.2 (94, C-5), 123.51 (88, C-6), 126.1 (100, C-4), 141.6 (9, C-1), 149.4 (12, C-2), 154.0 (11, OCO); MS m/e 254 (M^+).

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-methoxymethoxy)phenyl carbamate (116d).

According to procedure **A**, lithiation of N,N-diethyl O-(2-methoxymethoxy)phenyl carbamate **115b** (500 mg, 1.97 mmol), s-BuLi (1.99 mL, 2.17 mmol), TMEDA (0.33 mL, 2.17 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.27 mL, 2.17 mmol), standard workup followed by column chromatography using 3:1 (v/v) EtOAc-hexane as eluent afforded 280 mg (48%) of compound **116d**, bp 125-130°C/0.05 mm; IR ($CDCl_3$) ν_{max} 1710, 1625 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.97-1.27 (m, 12H, 4 CH_3), 3.21-3.82 (m, 8H, 4 CH_2), 3.46 (s, 3H, OCH_3), 5.16 (s, 2H, OCH_2O), 6.82-7.27 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 12.6 (102, 2 CH_3), 13.8 (138, 2 CH_3), 38.5 (79, CH_2), 41.4 (33, CH_2), 42.3 (180, CH_2), 42.7 (92, CH_2), 56.0 (79, OCH_3), 94.9 (78, OCH_2O), 116.2 (87, C-5), 119.2 (95, C-3), 125.9, (100, C-4), 132.6 (37, C-2), 137.5 (25, C-1), 149.8 (35, C-6), 153.1 (25, OCO), 167.1 (28, CO); MS m/e 352 (M^+); Anal. Calcd for $C_{18}H_{28}N_2O_5$: C, 61.34; H, 8.00; N, 7.94. Found: C, 61.11; H, 8.08; N, 7.74.

N,N-Diethyl O-(2-deuterio-3-N,N-diethylcarbamoyl)phenyl carbamate (119a).

According to procedure **A**, lithiation of N,N-diethyl-O-(3-N,N-diethylcarbamoyl)phenyl carbamate **118a** (313 mg, 1.07 mmol), s-BuLi (0.85 mL, 1.18 mmol), TMEDA (0.18 mL, (1.18 mmol), -78°C, 1h, methanol-d_1 (0.5 mL, excess), standard workup and column chromatography (1:1 EtOAc-hexane as eluent) afforded 267 mg (85%)

of compound **119a** (33% d_1, 67% d_0), bp 155-160°C/0.1 mm; IR (neat) ν_{max} 1715, 1630 cm^{-1}; NMR ($CDCl_3$) δ0.95-1.31 (m, 12H, 4 CH_3), 3.27-3.54 (m, 8H, 4 CH_2), 7.10-7.36 (m, 3.36H, ArH); ^{13}C NMR ($CDCl_3$) δ(relative intensity) 13.5 (H, $2CH_3$), 14.3 (27, 2 CH_3), 42.1 (31, 2 CH_2), 42.3 (30, 2 CH_2), 120.1 (59, C-2), 122.4 (84, C-6), 122.8 (100, C-4), 129.3 (86, C-5), 138.3 (20, C-3), 151.5 (19, C-1), 153.9 (14, OCO), 170.4 (16, CO); MS m/e 293 (M^+).

N,N-Diethyl O-(2,3-bis-N,N-diethylcarbamoyl)phenyl carbamate (117b) and 1,2-Bis-N,N-diethyl-3-hydroxyphthalamide (120d).

According to procedure A, lithiation of N,N-diethyl O-(3-N,N-diethylcarbamoyl)phenyl carbamate **118a** (400 mg, 1.36 mmol), s-BuLi (1.06 mL, 1.50 mmol), TMEDA (0.23 mL, 1.50 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.18 mL, 1.50 mmol), standard work-up followed by preparative TLC using EtOAc as eluent afforded 35 mg (7%) of compound **117b** and 65 mg (16%) of compound **120d.** Compound **120d,** IR (neat) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.95-1.25 (m, 12H, 4 CH_3), 3.09-3.58 (m, 8H, 4 CH_2), 6.70 (dd, J = 7.6, 1.17, 1H, H-4), 6.86 (dd, J = 7.6, 1.17, 1H, H-6), 7.11 (dd, J = 7.6, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ(relative intensity) 12.9 (92, CH_3), 13.4 (119, CH_3), 13.9 (76, CH_3) m, 14.0 (88, CH_3), 39.4 (70, CH_2), 41.6 (106, 2, CH_2), 43.5 (77, CH_2), 117.1 (92, C-4), 117.6 (96, C-6), 121.8 (69, C-2), 129.8 (100, C-5), 135.71 (86, C-1), 153.3 (87, C-3), 169.4 (77, 2CHO); MS m/e 292 (M^+); satisfactory analytical data (C,H,N) were not obtained.

N,N-Diethyl O-(2-deuterio-3-methoxymethoxy)phenyl carbamate (19c).

According to procedure **A**, lithiation of N,N-diethyl O-(3-methoxymethoxy)phenyl carbamate **118b** (300 mg, 1.18 mmol), s-BuLi (0.95 mL, 1.30 mmol), TMEDA (0.20 mL, 1.30 mmol), -78°C, 15 min, methanol-d_1(0.4 mL, excess), standard workup and column chromatography using 1:4 EtOAc-hexane as eluent afforded 290 mg (96%) of compound **119c** (55% d_1, 45% d_0); bp 95-100°C/0.2 mm; IR (neat) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ1.21 (t, J = 7, 6H, 2 CH_3), 3.39 (q, J = 7, 4H, 2 CH_2), 3.47 (s, 3H, OCH_3), 5.16 (s, 2H, OCH_2O), 6.81-7.30 (m, 3.3H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 14.1 (100, 2 CH_3), 42.1 (156, 2 CH_2), 56.1 (98, OCH_3), 94.6 (96, OCH_2O), 110.2 (79, C-2), 113.0 (100, C-4), 115.3 (84, C-6), 129.6 (98, C-5), 152.4 (63, C-1), 158.0 (70, C-3), 154.0 (54, OCO); MS m/e 254 (M^+).

N,N-Diethyl-2-hydroxy-6-methoxymethoxybenzamide (120e).

According to procedure **A**, lithiation of N,N-diethyl O-(3-methoxymethoxy)phenyl carbamate **118b** (500 mg, 1.97 mmol), s-BuLi (1.81 mL, 2.16 mmol), TMEDA (0.33 mL, 2.16 mmol), -78°C, 45 min, N,N-diethylcarbamoyl chloride (0.27 mL, 2.16 mmol), standard work-up and column chromatography using 1:1 EtoAc-hexane as eluent afforded 338 mg (68%) of the rearranged product **120e**, mp 76-77°C (C_6H_6-hexane); IR ($CHCl_3$) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.07-1.25 (m, 6H, 2 CH_3), 3.22-3.68 (m, 4H, 2 CH_2), 3.45 (s, 3H, OCHY3), 5.36 (s, 2H, OCH20), 6.57 (d, J = 8.2, 1H, H-4 or

H-6), 6.61 (d, J = 8.2, 1H, H-4 or H-6), 7.10 (dd, J = 8.2, 1H, H-5); MS m/e 253 (M^+); Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.52. Found: C, 61.57; H, 7.36; N, 5.45.

N,N-Diethyl O-(2-deuterio-4-N,N-diethylcarbamoyl)phenyl carbamate (122a), and/or N,N-Diethyl O-(3-deuterio-4-N,N-diethylcarbamoyl)-phenyl carbamate (123a).

According to procedure **A**, lithiation of N,N-diethyl O-(4-N,N-diethylcarbamoyl)phenyl carbamate **121a** (335 mg, 1.14 mmol), s-BuLi (0.92 mL, 1.26 mmol), TMEDA (0.19 mL, 1.26 mmol), -78°C, 1h, methanol-d_1 (0.5 mL, excess), standard workup and column chromatography using 1:1 (EtOAc-hexane as eluent afforded 284 mg (85%) of compounds **122a** and/or **123a** (66% d_1, 34% d_0), bp 135-140°C/0.2 mm; IR (neat) ν_{max} 1710, 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.08-1.31 (m, 12H, 4 CH_3), 3.29-3.55 (m, 8H, 4 CH_2), 7.08-7.44 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.6 (78, 4 CH_3), 42.2 (91, 4 CH_2), 121.6 (91, C-2 and C-6), 127.5 (100, C-3 and C-5), 133.9 (26, C-4), 152.1 (25, C-1), 153.8 (23, OCO), 170.7 (28, CO); MS m/e 293 (M^+).

N,N-Diethyl O-(2,4-bis-N,N-diethylcarbamoyl)phenyl carbamate (122b) and N,N-Diethyl O-(3,4-bis-N,N-diethylcarbamoyl)phenyl carbamate (123b).

According to procedure **A**, lithiation of N,N-diethyl O-(4-N,N-diethylcarbamoyl)phenyl carbamate **121a** (512 mg, 1.75 mmol), s-BuLi (1.78 mL, 1.92 mmol), TMEDA (0.29 mL, 1.92 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.24 mL, 1.92 mmol), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent

afforded 278 mg (41%) of compound **122b;** IR (neat) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.96-1.29 (m, 18H, 6 CH_3), 3.08-3.42 (m, 12H, 6 CH_2), 7.28-7.37 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 12.8 (113, 2 CH_3), 13.7 (121, 2 CH_3), 14.0 (149, 2 CH_3), 38.9 (92, 2 CH_2), 42.3 (133, 2 CH_2), 43.0 (94, 2 CH_2), 123.3 (100, C-6), 125.4 (98, C-3), 127.8 (94, C-5), 130.8 (69, C-2), 134.3 (71, C-4), 148.2 (69, C-1), 153.2 (48, OCO), 166.98 (46,k CO), 170.0 (63, CO); HRMS m/e 391.2487; Calcd for $C_{21}H_{33}N_3O_4$: 391.2472 and **123b** (28%); IR (neat) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.02-1.31 (m, 18, 6 CH_3), 3.15-3.60 (m, 12H, 6 CH_2), 7.08 (d, J = 2.2, H-2), 7.17 (dd, J = 8.3, 2.2, H-6), 7.27 (d, J = 8.3, H-5); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 12.73 (126, 2 CH_3), 13.4 (44, CH_3), 13.9 (112, 2 CH_3), 14.3 (41, CH_3), 39.2 (85, 2 CH_2), 42.0 (45, CH_2), 42.4 (43, CH_2), 42.5 (137, 2 CH_2), 119.5 (96, C-2), 121.5 (96, C-6), 127.0 (100, C-5), 131.7 (33, C-4), 136.2 (28, C-3), 151.2 (33, C-1), 153.4 (16, OCO), 168.6 (20, CO), 169.1 (26, CO); HRMS m/e 391.2483; Calcd for $C_{21}H_{33}N_3O_4$: 391.2472.

N,N-Diethyl O-(2-deuterio-4-methoxymethoxy)phenyl carbamate (122c) and/or N,N-Diethyl O-(3-deuterio-4-methoxymethoxy)phenyl carbamate (123c).

According to procedure **A,** lithiation of N,N-diethyl O-(4-methoxymethoxy)phenyl carbamate **121b** (500 mg, 1.97 mmol), s-BuLi (2.05 mL, 2.17 mmol), TMEDA (0.33 mL, 2.17 mmol), -78°C, 1h, ethanol-d1 (0.5 mL, excess), standard workup followed by column

chromatography using 1:5 EtOAc-hexane as eluent yielded 430 mg (86%) of compound **122c** and/or **123c** (56% d_1, 44% d_0), bp 98-100°C/ 2.0 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, J = 7.0, 6H, 2 CH_3), 3.39 (q, J = 7.0 4H, 2 CH_2), 3.45 (s, 3H, OCH_3), 5.12 (s, 2H, OCH_2O), 7.01 (s, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.8 (50, 2 CH_3), 42.04 (90, 2 CH_2), 55.8 (34, OCH_3), 94.9 (60, OCH_2O), 116.9 (100, C-3, C-5), 122.5 (92, C-2, C-6), 146.1 (29, C-1), 154.3 (24, C-4), 154.5 (24, OCO); Ms m/e 254 (M^+).

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-4-methoxymethoxy)phenyl carbamate (122d).

According to procedure **A**, lithiation of N,N-diethyl O-(4-methoxymethoxy)phenyl carbamate **121b** (500 mg, 1.97 mmol), s-BuLi (2.05 mL, 2.17 mmol), TMEDA (0.33 mL, 2.17 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.27 mL, 2.17 mmol), standard workup and column chromatography using 3:2 (v/v) EtOAc-hexane as eluent gave 485 mg (70%) of compound **122d**, bp 130-135°C/0.05 mm; IR (neat) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.97-1.28 (m, 12H, 4 CH_3), 3.17-3.39 (m, 8H, 4 CH_2), 3.45 (s, 3H, OCH_3), 5.13 (s, 2H, CH_2), 6.94-7.08 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 12.50 (86, 2 CH_3), 13.6 (108, 2 CH_3), 38.5 (73, CH_3), 41.91 (117, 2 CH_2), 42.6 (74, CH_2), 55.7 (110, OCH_3), 94.7 (85, OCH_2O), 114.2 (97, C-3), 117.3 (88, C-5), 124.0 (100, C-6), 131.2 (65, C-2), 141.7 (63, C-2), 153.6 (40, OCO), 154.1 (85, C-4), 167.0 (32, CO): MS m/e 308 (M^+); Anal. Calcd for

$C_{18}H_{28}N_2O_5$: C, 61.34; H, 8.00; N, 7.94. Found: C, 61.19; H, 8.13; N, 8.21.

1,3-Bis-N,N-diethyl-2-hydroxyisophthalamide (124).

According to procedure **C**, lithiation of N,N-diethyl O-(2-N,N-diethylcarbamoyl)phenyl carbamate **115a** (454 mg, 1.55 mmol), s-BuLi (1.37 mL, 1.70 mmol), TMEDA (0.23 mL, 1.70 mmol), -78°C, warming to room temperature, standard workup followed by column chromatography using 1:2 (v/v) EtOAc-hexane as eluent afforded 136 mg (30%) of compound **124**, mp 86-87°C (C_6H_6-hexane); IR ($CHCl_3$) ν_{max} 3200, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (t, J = 7, 12H, 4 CH_3), 3.37 (q, J = 7, 8H, 4 CH_2), 6.86 (dd, J = 7.4, 1H, H-5), 7.28 (d, J = 7.4, 2H, H-4 and H-6), 10.03 (br, 1H, OH exchanged with D_2O); MS m/e 292 (M^+); Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.94; H, 8.31; N, 9.60.

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-3-hydroxy)phenyl carbamate (126).

According to procedure **C**, lithiation of N,N-diethyl-O-(3-N,N-diethylcarbamoyloxy)phenyl carbamate **125** (700 mg, 2.27 mmol), s-BuLi (2.05 mL, 2.49 mmol), TMEDA (0.38 mL, 2.49 mmol), -78°C, warming to room temperature, standard workup followed by recrystallization gave 600 mg (86%) of compound **126**, mp 130-131°C (C_6H_6-hexane); IR ($CHCl_3$) ν_{max} 3200, 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.031.24 (m, 12H, 4 CH_3), 3.23-3.40 (m, 8H, 4 CH_2), 6.72 (dd, J

= 8.2, 1.17, 1H, H-6), 6.76 (dd, J = 7.8, 1.17, 1H, H-4), 7.17 (dd, J = 7.8, 8.2, (1H, H-5); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.4 (178, 2 CH_3), 14.2 (60, 2 CH_3), 41.3 (58, 2 CH_2), 42.2 (118, 2 CH_2), 113.6 (100, C-4), 113.8 (100, C-6), 117.7 (64, C-2), 129.9 (82, C-5), 148.1 (71, C-1), 153.5 (58, OCO), 154.8 (49, C-3), 166.8 (67, CO): MS m/e 308 (M^+); Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.30; H, 8.0; N, 9.01.

N,N-Diethyl O-(2-deuterio-3-N,N-diethylcarbamoyloxy)phenyl carbamate (127).

According to procedure A, lithiation of N,N-diethyl O-(3-N,N-diethylcarbamoyloxy)phenyl carbamate **125** (700 mg, 2.27 mmol), s-BuLi (2.05 mL, 2.49 mmol), TMEDA (0.38 mL, 2.49 mmol), -78°C, 10 min, methanol-d_1 (0.5 mL, excess), standard workup followed by column chromatography using 2:3 (v/v) EtOAc-hexane as eluent gave 80 mg (11%) of compound **126** and 530 mg (76%) of compound **127** (64%, d_1), bp 190-194°C/0.1 mm; (IR (neat) ν_{max} 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, J = 7.0, 12H, 4 CH_3), 3.39 (q, J = 7.0, 8H, 4 CH_2), 6.91-7.00 (m, 2H, ArH), 7.2-7.3 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.9 (52, 4 CH_3), 42.1 (126, 4 CH_2), 115.6 (21, C-2), 118.3 (100, C-4, C-6), 129.1 (50, C-5), 151.9 (45, C-1, C-3), 153.8 (39, OCO); MS m/e 309 (M^+).

1,3-Bis-N,N-diethyl-2,4-dihydroxyisophthalamide (128).

According to precedure **C**, lithiation of N,N-diethyl O-(2-N,N-diethylcarbamoyl-3-hydroxy)phenyl carbamate **126** (400 mg, 1.29 mmol), s-BuLi (3.27 mL, 3.99 mmol), TMEDA (0.61 mL, 3.99 mmol), -78°C, warming to room temperature, standard workup followed by recrystallization afforded 372 mg (93%) of compound **128**, mp 122-124°C (CH_2Cl_2-hexane); IR ($CHCl_3$) ν_{max} 3200, 1608 cm^{-1}; NMR ($CDCl_3$) δ 1.09-1.35 (m, 12H, 4 CH_3), 3.33-3.62 (m, 8H, 4 CH_2), 6.41 (d, J = 8.6, H-6), 7.16 (d, J = 8.6, H-5); MS m/e 392 (M^+); Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.26; H, 7.96; N, 8.76.

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-trimethylsilyl)phenyl carbamate (129).

To a stirred THF solution (60 mL) of s-BuLi (2.17 mL, 2.59 mmol) and TMEDA (0.39 mL, 2.59 mmol) at -78°C under nitrogen was added by syringe injection N,N-diethyl O-phenyl carbamate **84a** (500 mg, 2.59 mmol) in THf (5 mL). After 1 h, TMSCl (0.33 mL, 2.59 mmol) was added and the solution was stirred at -78°C for 1 h. Second portion of s-BuLi (2.17 mL, 2.59 mmol) and TMEDA (0.39 mL, 2.59 mmol) were likewise injected followed after 1 h by N,N-diethylcarbamoyl chloride (0.32 mL, 2.59 mmol). The resulting solution was allowed to warm to room temperature over 8 h. Standard workup followed by column chromatography (1:2 EtOAc-hexane as eluent) afforded 510 mg (54%) of compound **129**, mp 53-54°C

(hexane); IR ($CHCl_3$) ν_{max} 1710, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.30 (s, 9H, $Si(CH_3)_3$), 1.03-1.38 (m, 12H, 4 CH_3), 3.16-3.61 (m, 8H, 4 CH_2), 7.18-7.56 (m, 3H, ArH); MS m/e 364 (M^+); Anal. Calcd. for $C_{19}H_{32}N_2O_3Si$: C, 62.60; H, 8.84; N, 7.68; Found: C, 62.80; H, 9.0; N, 7.68.

N,N-Diethyl O-(2,3-bis-N,N-diethylcarbamoyl-6-trimethylsilyl)-phenyl carbamate (130).

According to procedure **A**, lithiation of N,N-diethyl O-(2-N,N-diethylcarbamoyl-6-trimethylsilyl)phenyl carbamate **129** (500 mg, 1.37 mmol), s-BuLi (1.08 mL, 1.37 mL), TMEDA (0.21 mL, 1.37 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.17 mL, 1.37 mmol), standard workup and purification by column chromatography (1:1 EtOAc-hexane as eluent) yielded 475 mg (75%) of compound **130**, bp 157-160°C/0.1 mm; IR (neat) ν_{max} 1720, 1645, 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.18 (s, 9H, $Si(CH_3)_3$, 0.83-1.25 (m, 18H, 6 CH_3), 3.0-3.52 (m, 12H, 6 CH_2), 7.02, (d, J = 7.6, 1H, H-6); MS m/e 463 (M^+); Anal. Calcd for $C_{24}H_{41}N_3O_4Si$: C, 62.16; H, 8.91; N, 9.06. Found: C, 62.04; H, 9.03; N, 8.94.

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-3-methyl-6-methoxy)phenyl carbamate (131).

To a stirred THF solution (60 mL) of s-BuLi (2.07 mL, 2.46 mmol) and TMEDA (0.37 mL, 2.46 mmol) at -78°C under nitrogen was added by syringe injection N,N-diethyl O-2-anisyl carbamate (500

mg, 2.24 mmol in THf (5 mL). After 1 h, N,N-diethylcarbamoyl chloride (0.30 mL, 2.46 mmol) was added and the solution was stirred for 1 h at -78°C. Again s-BuLi (2.07 mL, 2.46 mmol) and TMEDA (0.37 mL, 2.46 mmol) were added to the reaction flask. After 1 h, methyl iodide (0.5 mL, excess) was added and the resulting solution was allowed to warm to room temperature over 8h. Standard workup and column chromatography afforded 460 mg (66%) of compound **131,** IR (neat) ν_{max} 1715, 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.88-1.42 (m, 12H, 4 CH_3), 2.21 (s, 3H, CH_3), 3.04-3.73 (m, 8H, 4 CH_2), 3.79 (s, 3H, OCH_3), 6.82, 7.0 (2 d, J = 8.6, 2H, H-4, H-5); MS m/e 336 (M^+); Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.38; N, 8.32. Found: C, 63.90; H, 8.10; N, 7.99.

N,N-Diethyl-2-(2-hydroxy)phenyl acetamide (132) and Bis-N,N-diethyl-2-(2-hydroxy)phenyl malonamide (133).

According to procedure **C,** lithiation of N,N-diethyl O-2-tolyl carbamate **81** (500 mg, 2.41 mmol), LDA (1.2 equiv, prepared according to precedure B), -78°C, warming to room temperature over 8h, standard workup and column chromatography using 1:2 (v/v) EtOAc-hexane as eluent afforded 300 mg (60%) of compound **132,** mp 87-89°C (CH_2Cl_2-hexane); IR ($CHCl_3$) ν_{max} 3400, 1610 cm^{-1}; NMR ($CDCl_3$) δ 0.95-1.37 (m, 6H, 2 CH_3), 3.21-3.63 (m, 4H, 2 CH_2), 3.71 (s, 2H, CH_2), 6.72-7.26 (m, 4H, ArH), 10.43 (s, 1H, OH exchanged with D_2O). MS m/e 207 (M^+); Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.32; H, 8.41; N, 6.93; and 59 mg (8%) of compound **133,** mp 148-149°C (C_6H_6); IR ($CHCl_3$) ν_{max} 3200,

1625 (cm^{-1}; NMR ($CDCl_3$) δ 0.93-1.23 (m, 12H, 4 CH_3), 3.12-3.51 (m, 8H, 4 CH_2), 4.95 (s, 1H, CH), 6.70-7.35 (m, 4H, ArH), 10.8 (s, 1H, OH, exchanged with D_2O); MS m/e 306 (M^+); Anal. calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: c, 66.49; H, 8.86; N, 9.03.

2(3H)-Benzofuranone (134).

Method I: N,N-Diethyl-2-(2-hydroxy)phenyl acetamide **132** (190 mg, 0.92 mmol) dissolved in benzene (20 mL) was refluxed in presence of 1 M HCl (2 mL) for 40 h. Standard workup followed by purification by column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 115 mg (94%) of compound **134**, mp 47-49°C (CH_2Cl_2-hexane) (lit.[144] 49-50°C); IR ($CHCl_3$) ν_{max} 1800 cm^{-1}; NMR ($CDCl_3$) δ3.70 (s, 2H, CH_2), 6.99-7.42 (m, 4H, ArH); MS m/e 134 (M^+).

Method II: Compound **132** (250 mg, 1.20 mmol) was refluxed in benzene in presence of p-toluene sulfonic acid hydrate (100 mg) for 4 days. Workup and purification as above gave 115 mg (72%) of compound **134**.

Preparation of ortho-hydroxyphenylacetic acid (135) from (133).

Compound **133** (150 mg) was refluxed in HCl for 18h. Workup in the usual manner followed by recrystallization afforded 54 mg (69%) of compound **135**, mp 146°C (Et_2O-hexane) (lit.[145] 149-150°C).

4.3 STANDARD PROCEDURE FOR CHAPTER III.

4.3.1. LITHIATION OF O-PYRIDYL CARBAMATES WITH s-BuLi

A. The procedure for lithiation of O-pyridyl carbamate with s-BuLi-TMEDA complex was similar to procedure A for the lithiation of O-aryl carbamate as described in Section 4.2.1.A.

B. The procedure for lithiation of O-pyridyl carbamate with LDA was similar to procedure B for the lithiation of O-aryl carbamate as described in Section 4.2.1.B.

C. The procedure for anionic ortho-Fries rearrangement of O-pyridyl carbamate was similar to procedure C for anionic ortho-Fries rearrangement of O-aryl carbamate as described in Section 4.2.1.C.

4.3.2. PREPARATION OF O-PYRIDYL CARBAMATES

N,N-Diethyl O-pyridyl-2-carbamate and N,N-diethyl O-pyridyl-3-carbamate were prepared according to literature procedure[111] from the reaction of 2-pyridone and 3-pyridinol respectively with N,N-diethylcarbamoyl chloride (1.1 equiv) in presence of triethylamine (1.1 equiv) in refluxing benzene for 6-8 h. N,N-diethyl O-pyridyl-4-carbamate was prepared from the reaction of 4-pyridone with N,N-diethylcarbamoyl chloride (1.1 equiv) in presence of sodium hydride (1.5 equiv) in refluxing DMF for 8h. All three O-pyridyl carbamates were purified by distillation.

N,N-Diethyl O-pyridyl-2-carbamate (176):

bp 98-100°C/0.1 mm; IR (neat) ν_{max} 1719 cm^{-1}; NMR ($CDCl_3$) δ 1.16-1.31 (m, 6H, 2 CH_3); 3.37-3.50 (m, 4H, 2 CH_2), 7.06-7.24 (m, 2H, H-3 and H-5), 7.75 (doublets of triplet (dt), J = 7.63, 2.05, H-4), 8.37 (ddd, J = 4.7, 2.05, 0.88, H-6); MS m/e 194 (M^+); Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.71; H, 7.32; N, 14.02.

N,N-Diethyl O-pyridyl-3-carbamate (177):

bp 89-91°C/0.05 mm (lit.[111] bp 91-93°C/3.5 mm); IR (neat) ν_{max} 1723 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7, 6H, 2 CH_3), 3.38 (q, J = 7, 4H, 2 CH_2), 7.29 (dd, J = 7.8, 4.7, H-5), 7.5 (ddd, J = 7.8, 2.05, 1.46, H-4), 8.39-8.46 (m, H-2 and H-6); MS m/e 194 (M^+).

N,N-Diethyl O-pyridyl-4-carbamate (179):

bP 95-98°C/0.25 mm; IR (neat) ν_{max} 1728 cm^{-1}; NMR 9$CDCl_3$) δ 1.21 (t, J = 7.08, 6H, 2 CH_3), 3.39 (q, J = 7.08, 4H, 2 CH_2), 7.14 (dd, J = 4.64, 1.46, H-3 and H-5), 8.56 (dd, J = 4.64, 1.7, H-2 and H-6); MS m/e 194 (M^+); Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.41; H, 7.35; N, 13.81.

4.3.3. EXPERIMENTAL DETAILS

N,N-Diethyl O-(3-deuterio)pyridyl-2-carbamate (181a).

According to Procedure **A**, lithiation of N,N-diethyl O-pyridyl-2-carbamate **176** (400 mg, 2.06 mmol), s-BuLi (1.84 mL, 2.2 mmol), TMEDA (0.34 mL, 2.2 mmol), -78°C, 10 min, methanol-d_1 (0.5 mL, excess), standard workup and purification by column chromatography afforded 350 mg (87%) of compound **181a** (56% d_1, 44% d_0), bp 108-110°C/0.15 mm; IR (neat) ν_{max} 1717 cm^{-1}; NMR ($CDCl_3$) δ 1.01-1.31 (m, 6H, 2 CH_3), 3.42-3.50 (m, 4H, 2 CH_2), 7.06-7.28 (m, residual H-3 and H-5), 7.6-7.8 (m, H-4), 8.37 (dd, J = 4.7, 2.05, H-6); MS m/e 195 (M^+).

N,N-Diethyl O-(3-methyl)pyridyl-2-carbamate (181b).

According to Procedure **A**, lithiation of carbamate **176** (860 mg, 4.43 mmol), s-BuLi (4.35 mL, 4.87 mmol), TMEDA (0.74 mL, 4.87 mmol), -78°C, 10 min, methyl iodide 6.3 mL, 4.87 (mmol), standard workup and column chromatography using 1:2 (EtOAc-hexane as eluent afforded 662 mg (72%) of compound **181b**, bp 125-130°C/0.2 mm; IR (neat) ν_{max} 1719 cm^{-1}; NMR ($CDCl_3$) δ 0.90-1.40 (m, 6H, 2 CH_3), 2.22 (s, 3H, CH_3), 7.06 (dd, J = 7.4, 4.7, H-5 and residual H-3), 7.5-7.6 (m, H-4), 8.18 (dd, J = 4.8, 1.46, H-6); MS m/e 208 (M^+). Compound **181b** was contaminated with a trace of starting material (by GC) which could not be removed and therefore satisfactory analytical data (C, H, N) were not obtained.

N,N-Diethyl O-(3-N,N-diethylcarbamoyl)pyridyl-2-carbamate (181c).

According to Procedure A, lithiation of carbamate **176** (500 mg, 2.57 mmol), s-BuLi (2.33 mL, 2.83 mmol), TMEDA (0.43 mL, 2.83 mmol), -78C, 10 min, N,N-diethylcarbamoyl chloride (0.35 mL, 2.83 mmol), standard workup and column chromatography afforded 468 mg (66%) of compound **181c,** bp 155-160°C/0.1 mm; IR (neat) ν_{max} 1718, 1636 cm^{-1}; NMR ($CDCl_3$) δ1.06-1.30 (m, 12H, 4 CH_3), 3.19-3.56 (m, 8H, 4 CH_2), 7.21 (dd, J = 7.4, 4.9, H-5), 7.68 (dd, J = 7.4, 2.05, H-4), 8.42 (dd, J = 4.9, 2.05, H-6); HRMS m/e 293.1762; Calcd. for $C_{15}H_{23}N_3O_3$: 293. 1740.

N,N-Diethyl O-(3-trimethylsilyl)pyridyl-2-carbamate (181d).

According to Procedure A, lithiation of carbamate **176** (700 mg, 3.60 mmol), s-BuLi (3.1 mL, 3.96 mmol), TMEDA (0.6 mL, 3.96 mmol), -78°C, 10 min, TMSCl (0.5 mL, 3.96 mmol), standard workup and column chromatography using 2:3 EtOAc-hexane as eluent afforded 460 mg (52%) of compound **181d,** bp 95-100°C/0.3 mm; IR (neat) ν_{max} 1725 cm^{-1}; NMR ($CDCl_3$) δ0.38 (s, 9H, $Si(CH_3)_3$), 1.03-1.43 (m, 6H, 2 CH_3), 3.35-3.69 (m, 4H, 2 CH_2), 7.20 (dd, J = 7.2, 4.88, H-5), 7.89 (dd, J = 7.2, 2.2, H-4), 8.40 (dd, J = 4.88, 2.2, H-6); MS m/e 266 (M^+); Anal. Calcd for $C_{13}H_{22}N_2O_2Si$: C, 58.61; H, 8.32; N, 10.51. Found: C, 58.80; H, 8.28, N, 10.42.

When **176** was subjected to lithiation with LDA, according to procedure B, compound **181d** was obtained in 62% yield.

N,N-diethyl O-(3-bromo)pyridyl-2-carbamate (181e).

According to Procedure **A**, lithiation of carbamate **176** (0.752 g, 3.87 mmol), s-BuLi (4.02 mL, 4.26 mmol), TMEDA (0.64 mL, 4.26 mmol), -78°C, 10 min, 1,2-dibromoethane (0.67 mL, 7.72 mmol), standard workup and column chromatography using 1:9 EtOAc-hexane as eluent gave 600 mg (59%) of compound **181e**, bp 118-122°C/0.1 mm; IR (neat) ν_{max} 1722 cm^{-1}; NMR ($CDCl_3$) δ 1.10-1.40 (m, 6H, 2 CH_3), 3.38-3.54 (m, 4H, 2 CH_2), 7.08 (dd, J = 7.8, 4.69, H-5), 7.95 (dd, J = 7.8, 1.76, H-4), 8.33 (dd, J = 4.69, 1.76, H-6); HRMS m/e 272.0152 and 274.0138; Calcd for $C_{10}H_{13}BrN_2O_2$: 272.0160 and 274.0160.

N,N-Diethyl O-(3-iodo)pyridyl-2-carbamate (181f).

According to Procedure **A**, lithiation of carbamate **176** (600 mg, 3.09 mmol), s-BuLi (2.76 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, 10 min iodine (864 mg, 3.39 mmol), standard workup and column chromatography uisng 1:2 EtOAc-hexane as eluent afforded 672 mg (68%) of compound **181f**, bp 134-138°C/0.2 mm; IR (neat) ν_{max} 1725 cm^{-1}; NMR ($CDCl_3$) δ1.01-1.45 (m, 6H, CH_3), 3.29-3.63 (m, 4H, 2 CH_2), 6.93 (dd, J = 7.6, 4.69, H-5), 8.15 (dd, J = 7.6, 1.76, H-4), 8.34 (dd, J = 4.69, 1.76, H-6); MS m/e 320, 322 (M^+); Anal. Calcd for $C_{10}H_{13}IN_2O_2$: C, 37.52; H, 4.09; N, 8.75. Found: C, 37.80; H, 4.24; N, 8.80.

N,N-Diethyl O-(4-deuterio)pyridyl-3-carbamate (182a).

According to Procedure A, lithiation of N,N-diethyl O-pyridyl--3-carbamate **177** (600 mg, 3.09 mmol), s-BuLi (2.63 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, 40 min, methanol-d_1 (0.5 mL, excess), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent afforded 489 mg (82%) of compound **182a** (51% d_1, 49% d_0), bp 101-104°C/0.15 mm; IR (neat) ν_{max} 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7.04, 6H, 2 CH_3), 3.38 (q, J = 7.04, 4H, 2 CH_2), 7.25-7.37 (m, H-5), 7.45-7.61 (m, residual H-4), 8.42 (d, J = 4.7, H-6), 8.45 (s, H-2); MS m/e 195 (M^+).

N,N-Diethyl O-(4-methyl)pyridyl-3-carbamte (182b).

According to Procedure A, lithiation of carbamate **177** (860 mg, 4.43 mmol), s-BuLi (4.35 mL, 4.87 mmol), TMEDA (0.74 mL, 4.87 mmol), -78°C, 40 min, methyl iodide (0.30 mL, 4.87 mmol), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent afforded 762 mg (83%) of compound **182b,** bp 98-102/0.15 mm; IR (neat) ν_{max} 1719 cm^{-1}; NMR ($CDCl_3$) δ1.16-1.33 (m, 6H, 2 CH_3), 2.24 (s, 3H, CH_3), 3.40-3.48 (m, 4H, 2 CH_2), 7.14 (d, J = 4.98, H-5), 8.30 (d, J = 4.98, H-6), 8.33 (s, H-2); MS m/e 208 (M^+). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44, H, 7.74; N, 13.45. Found: C, 63.61; H, 7.58; N, 13.61.

N,N-Diethyl O-(N,N-diethylcarbamoyl)pyridyl-3-carbamate (182c).

According to Procedure **A**, lithiation of carbamate **177** (600 mg, 3.09 mmol), s-BuLi (2.75 mL, 3.40 mmol), TMEDA (0.51 mL, 3.40 mmol), -78°C, 40 min, N,N-Diethylcarbamoyl chloride (0.42 mL, 3.40 mmol), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent gave 580 mg (64%) of compound **182c**, bp 140-143°C-/0-.2 mm; IR (neat) ν_{max} 1725, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.99-1.29 (m, 12H, 4 CH_3), 3.05-3.66 (m, 8H, 4 CH_2), 7.20 (d, J = 4.7, H-5), 8.47 (d, J = 4.7, H-6), 8.55 (s, H-2); MS m/e 293 (M^+); Anal. calcd for $C_{15}H_{23}N_3O_3$: C, 61.41; H, 7.90; N, 14.32. Found: C, 60.92; H, 7.89; N, 13.92.

N,N-Diethyl O-(4-trimethylsilyl)pyridyl-3-carbamate (182d).

According to Procedure **A**, lithiation of carbamate **177** (2.00 g, 10.30 mmol), s-BuLi (9.86 mL, 11.34 mmol), TMEDA (1.71 mL, 11.34 mmol), -78°C, 40 min, TMSCl (1.44 mL, 11.34 mmol), standard workup and column chromatography using 1:4 EtOAc-hexane as eluent afforded 1.88 g (69%) of compound **182d**, bp 53-55°C/0.04 mm; IR (neat) ν_{max} 1722 cm^{-1}; NMR ($CDCl_3$) δ 0.33 (s, 9H, $Si(CH_3)_3$), 1.08-1.43 (m, 6H, 2 CH_3), 3.30-3.65 (m, 4H, 2 CH_2), 7.36 (d, J = 4.7, H-5), 8.35 (s, H-2), 8.42 (d, J = 4.7, H-6); MS m/e 266 (M^+); Anal. Calcd for $C_{13}H_{22}N_2O_2Si$: C, 58.61; H, 8.32; N, 10.51. Found: C, 58.59; H, 8.21; N, 10.39. Compound **182d** was obtained in 82% yield from the lithiation of carbamate **177** with LDA according to Procedure B.

N,N-Diethyl O-(4-bromo)pyridyl-3-carbamate (182e).

According to Procedure A, lithiation of carbamate **177** (2.00 g, 10.30 mmol), s-BuLi (10.84 mL, 11.34 mmol), TMEDA (1.71 mL, 11.34 mmol), -78°C, 30 min, 1,2-dibromoethane (1.86 mL, 21.65 mmol), standard workup and column chromatography using 1:4 EtOAc-hexane as eluent afforded 1.70 g (71%) of compound **182e,** bp 130-135°C/0.1 mm (with decomposition); IR (neat) ν_{max} 1726 cm^{-1}; NMR ($CDCl_3$) δ 1.10-1.50 (m, 6H, 2 CH_3), 3.25-3.70 (m, 4H, 2 CH_2), 7.54 (d, J = 5.2, H-5), 8.25 (d, J = 5.2, H-6), 8.47 (s, H-6); MS m/e 272, 274 (M^+). Compound **182e** was found to be very unstable and a sample for analysis could not be obtained.

N,N-Diethyl O-(4-iodo)pyridyl-3-carbamate (182f).

According to Procedure A, lithiation of carbamate **177** (635 mg, 3.27 mmol), s-BuLi (3.05 mL, 3.60 mmol), TMEDA (0.54 mL, 3.60 mmol), -78°C, 40 min, iodine (914 mg, 3.60 mmol), standard workup and column chromatography using 3:2 EtOAc-hexane as eluent gave 680 mg (65%) of compound **182f;** IR (neat) ν_{max} 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.15-1.41 (m, 6H, 2 CH_3), 3.37-3.57 (m, 4H, 2 CH_2), 7.76 (d, J = 4.98, H-5), 8.05 (d, J = 4.98; H-6), 8.38 (s, H-2); MS m/e 320 (M^+).

Compound **182f** decomposed on heating or standing at room temperature for a few days. Therefore, an analytical sample could not be obtained.

N,N-Diethyl O-(4-N,N-dimethylsulfonyl)pyridyl-3-carbamate (182g).

According to Procedure A, lithiation of carbamate **177** (500 mg, 2.57 mmol), s-BuLi (2.75 mL, 2.83 mmol), TMEDA (0.43 mL, 2.83 mmol), -78°C, 45 min, N,N-dimethylsulfonyl chloride (0.130 mL, 2.83 mmol), stnadard workup and column chromatography (2:1 EtOAc-hexane as eluent) yielded 625 mg (81%) of compound **182g,** bp 95-100°C/0.05 mm; IR (neat) ν_{max} 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.13-1.38 (m, 6H, 2 CH_3), 2.81 (s, 6H, 2 CH_3), 3.27-3.53 (m, 4H, 2 CH_2), 7.37 (d, J = 5.2, H-5), 8.35 (d, J = 5.2, H-6), 8.49 (s, H-2); MS m/e 256 (M^+-NMe_2); Anal. Calcd for $C_{12}H_{19}N_3O_4S$: C, 47.83; H, 6.35; N, 13.94; Found: C, 48.18; H, 5.97; N, 13.56.

N,N-Diethyl O-(4-carboxy)pyridyl-3-carbamate (182h).

According to Procedure A, lithiation of carbamate **177** (528 mg, 2.72 mmol), s-BuLi (2.23 mL, 2.99 mmol), TMEDA (0.45 mL, 2.23 mmol), -78°C, 45 min, CO_2, standard workup followed by recrystallization afforded 387 mg (60%) of compound **182h,** mp 143-145°C (CH_2Cl_2-hexane); IR ($CHCl_3$) ν_{max} 3200-2500, 1726 cm^{-1}; NMR ($CHCl_3$) δ1.11-1.50 (m, 6H, 2 CH_3), 3.26-3.79 (m, 4H, 2 CH_2), 7.91 (d, J = 5, H-5), 8.59 (m, H-2 and H-6); MS m/e 238 (M^+); Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.75: Found: C, 55.79; H, 6.09; N, 11.74.

N,N-Diethyl O-(4-trimethylstamyl)pyridyl-3-carbamate (182i).

According to Procedure A, lithiation of carbamate **177** (1.50 g, 7.73 mmol), s-BuLi (7.26 mL, 8.5 mmol), TMEDA (1.28 mL, 8.5 mmol), -78°C, 45 min, trimethyltin chloride (1.69 g, 8.5 mmol), standard workup and column chromatography using 3:1 EtOAc-hexane as eluent afforded 2.23 g (82%) of compound **182i**, bp 130-134°C/0.2 mm; IR (neat) ν_{max} 1721 cm^{-1}; NMR ($CDCl_3$) δ 0.33 (s, 9H, $Sn(CH_3)_3$), 1.12-1.35 (m, 6H, 2 CH_3), 3.27-3.51 (m, 4H, 2 CH_2), 7.37 (d, J = 4.8, H-5), 8.33 (s, H-2), 8.36 (d, J = 4.8, H-6); MS m/e 357 (M^+); Anal. Calcd for $C_{13}H_{22}N_2O_2Sn$: C, 43.73; H, 6.21; N, 7.84. Found: C, 43.77; H, 6.03; N, 7.70.

N,N-Diethyl O-(4-tributylstannyl)pyridyl-3-carbamate (182j).

According to Procedure A, lithiation of carbamate **177** (528 mg, 2.72 mmol), s-BuLi (2.23 mL, 2.99 mmol), TMEDA (0.45 mL, 2.99 mmol), -78°C, 45 min, tributyltin chloride (0.81 mL, 2.99 mmol), standard workup and column chromatography 1:2 EtOAc-hexane as eluent afforded 640 mg (50%) of compound **182j**, bp 135-140°C/0.05 mm; IR (neat) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.80-1.10 (m, 6H, 2 CH_3), 1.18-1.88 (m, 27H, $Sn(Bu)_3$), 3.27-3.51 (m, 4H, 2 CH_2), 7.35 (d, J = 4.7, H-5), 8.31 (s, H-2), 8.33 (d, J = 4.7, H-6); MS m/e 425 (M^+-$(C_2H_5)_2$). Satisfactory analytical data were not obtained.

N,N-Diethyl O-(4-thiomethyl)pyridyl-3-carbamate (182k).

According to Procedure **A**, lithiation of carbamate **177** (600 mg, 3.09 mmol), s-BuLi (2.76 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, 40 min, methyldisulfide (0.31 mL, 3.39 mmol), standard workup and column chromatography using 1:2 EtOAc-hexane as eluent gave 370 mg (50%) of compound **182k**, bp 135-140°C/0.15 mm; IR (neat) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.22-1.38 (m, 6H, 2 CH_3), 2.44 (s, 3H, SCH_3), 3.30-3.60 (m, 4H, 2 CH_2), 7.08 (d, J = 4.8, H-5), 8.30 (s, H-2), 8.32 (d, J = 4.8, H-6); MS m/e 240 (M^+); Anal. calcd for $C_{11}H_{16}N_2O_2S$: C, 54.97; H, 6.71; N, 11.65. Found: C, 54.89; H, 6.70; N, 11.41.

N,N-Diethyl O-[4-(1-hydroxy)ethyl]pyridyl-3-carbamate (182l).

According to Procedure **A**, lithiation of carbamate **177** (600 mg, 3.09 mmol), s-BuLi (3.30 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, 40 min, acetaldehyde (0.19 mL, 3.39 mmol) (and after 1h, aqueous NH_4Cl solution was added at -78°C), standard workup and column chromatography afforded 350 mg (48%) of compound **182l**, bp 155-160°C/0.05 mm; IR (neat) ν_{max} 3406, 1719 cm^{-1}; NMR ($CDCl_3$) δ 1.21-1.36 (m, 6H, 2 CH_3), 1.44 (d, J = 6.4, CH_3), 3.27-3.51 (m, 4H, 2 CH_2), 4.35 (br, 1H, OH), 4.98 (q, J = 6.4, CH), 7.50 (d, J = 4.7, H-5), 8.23-8.40 (br, H-2 and H-6); MS m/e 238 (M^+); Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.43; H, 7.61; N, 11.75. Found: C, 59.98; H, 7.23; N, 11.40.

N,N-Diethyl O-[4-(1-hydroxy-1-phenyl)methyl]pyridyl-3-carbamate (182m).

According to Procedure **A**, lithiation of carbamate **177** (500 mg, 2.57 mmol), s-BuLi (2.75 mL, 2.83 mmol), TMEDA/0.43 mL, 2.83 mmol), -78°C, 40 min, benzaldehyde (0.29 mL, 2.83 mmol) (and after 1h, aqueous NH_4Cl solution was added at -78°C), standard workup and column chromatography using 1:9 EtOAc-hexane as eluent afforded 580 mg (75%) of compound **182m** as a viscous oil; IR (neat) ν_{max} 3408, 1719 cm^{-1}; NMR ($CDCl_3$) δ 1.03-1.24 (m, 6H, 2 CH_3), 3.28-3.37 (m, 4H, 2 CH_2), 4.11 (br, 1H, OH), 5.92 (s, 1H, CH), 7.30 (s, 5H, ArH), 7.43 (d, J = 4.9, H-5), 8.31 (s, H-2), 8.40 (d, J = 4.9, H-6); MS m/e 300 (M^+); Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.32. Found: C, 67.94; H, 7.11; N, 9.17.

N,N-Diethyl O-(3-deuterio)pyridyl-4-carbamate (183a).

According to Procedure **A**, lithiation of N,N-diethyl O-pyridyl-4-carbamate **179** (313 mg, 1.61 mmol), s-BuLi (1.54 mL, 1.77 mmol), TMEDA (0.27 mL, 1.77 mmol), -78°C, 40 min, methanol-d_1 (0.3 mL, excess), standard wrokup and column chromatography using 1:2 EtOAc-hexane as eluent afforded 236 mg (75%) of compound **183a** (37% d_1, 63% d_0), bp 80-85°C/0.15 mm; IR (neat) ν_{max} 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7.04, 6H, 2 CH_3), 3.41 (q, J = 7.04, 4H, 2 CH_2), 7.14 (dd, J = 4.7, 1.46, H-5 and residual H-3), 8.57 (dd, J = 4.7, 1.46, H-2 and H-6); MS m/e 195 (M^+).

N,N-Diethyl O-(3-methyl)pyridyl-4-carbamate (183b).

According to Procedure A, lithiation of carbamate **179** (1.268 g, 6.53 mmol), s-BuLi (6.30 mL, 7.18 mmol), TMEDA (1.1 mL, 7.18 mmol), -78°C, 40 min, methyl iodide (1.0 mL, excess), standard workup and column chromatography using 3:1 EtOAc-hexane as eluent gave 1.15 g (84%) of compound **183b,** bp 105-110°C/0.1 mm; IR (neat) ν_{max} 1710 cm^{-1}; NMR ($CDCl_3$) δ1.23 (t, J = 7.04, 6H, 2 CH_3), 2.22 (s, 3H, CH_3), 3.41 (q, J = 7.04, 4H, 2 CH_2), 7.14 (d, J = 4.9, H-5), 8.41 (d, J = 4.9, H-6), 8.44 (s, H-2); MS m/e 208 (M^+); Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: c, 63.24; H, 7.94; N, 13.54.

N,N-Diethyl O-(3-N,N-diethylcarbamoyl)pyridyl-4-carbamate (183c).

According to Procedure A, lithiation of carbamate **179** (1.130 g, 5.82 mmol), s-BuLi (5.81 mL, 6.40 mmol), TMEDA (0.96 mL, 6.40 mmol), -78°C, 40 min, N,N-diethylcarbamoyl chloride (0.77 mL, 6.40 mmol), standard workup and column chromatography using EtOAc as eluent afforded 1.160 g (69%) of compound **183c,** bp 132-135°C/0.25 mm; IR (neat) ν_{max} 1726, 1637 cm^{-1}; NMR ($CDCl_3$) δ1.00-1.40 (m, 12H, 4 CH_3), 3.1-3.68 (m, 8H, 4 CH_2), 7.32 (d, J = 5.6, H-5), 8.51 (s, H-2), 8.58 (d, J = 5.6, H-6); HRMS m/e 293.1731. Calcd. for $C_{15}H_{23}N_3O_3$: 293.1740.

N,N-Diethyl O-(3-trimethylsilyl)pyridyl-4-carbamate (183d).

According to Procedure **A**, lithiation of carbamate **179** (520 mg, 2.68 mmol), s-BuLi (2.56 mL, 2.94 mmol), TMEDA (0.44 mL, 2.94 mmol), -78°C, 40 min, TMSCl (0.37 mL, 2.94 mmol), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent gave 473 mg (67%) of compound **183d**, mp 52-54°C; IR ($CHCl_3$) ν_{max} 1722 cm^{-1}; NMR ($CDCl_3$) δ 0.30 (s, 9H, $Si(CH_3)_3$), 1.11-1.32 (m, 6H, 2 CH_3), 3.26-3.58 (m, 4H, 2 CH_2), 7.04 (d, J = 5.6, H-5), 8.55 (d, J = 5.6, H-6), 8.58 (s, H-2); MS m/e 266 (M^+); Anal. Calcd for $C_{13}H_{22}N_2O_2Si$: C, 58.61; H, 8.32; N, 10.51. Found: C, 58.95; H, 7.97; N, 10.20.

N,N-Diethyl O-(3-bromo)pyridyl-4-carbamate (183e).

According to Procedure **A**, lithiation of carbamate **179** (720 mg, 3.71 mmol), s-BuLi (3.85 mL, 4.08 mmol), TMEDA (0.62 mL, 4.08 mmol), -78°C, 40 min, 1,2-dibromoethane (0.66 mL, 7.42 mmol), standard workup and column chromatography (1:5 EtOAc-hexane as eluent) afforded 605 mg (60%) of compound **183e**, bp 125-130°C/0.20 mm; IR (neat) ν_{max} 1732 cm^{-1}; NMR ($CDCl_3$) δ1.10-1.37 (m, 6H, 2 CH_3), 3.36-3.53 (m, 4H, 2 CH_2), 7.34 (d, J = 5.4, H-5), 8.47 (d, J = 5.4, H-6), 8.72 (s, H-6); MS m/e 272, 274 (M^+); Anal. Calcd for $C_{10}H_{13}BrN_2O_2$: C, 43.95; H, 4.79; N, 10.25. Found: C, 43.90; H, 5.17; N, 10.24.

N,N-Diethyl O-(3-iodo)pyridyl-4-carbamate (183f).

According to Procedure **A**, lithiation of carbamate **179** (500 mg, 2.57 mmol), s-BuLi (2.57 mL, 2.83 mmol), TMEDA (0.43 mL, 2.83 mmol), -78°C, 40 min, iodine (720 mg, 2.83 mmol), standard workup and column chromatography (1:1 EtOAc-hexane as eluent) afforded 485 mg (60%) of compound **183f**, bp 132-136°C/0.2 mm; IR (neat) ν_{max} 1734 cm^{-1}; NMR ($CDCl_3$) δ 0.90-1.41 (m, 6H; 2 CH_3), 3.03-3.66 (m, 4H, 2 CH_2), 7.33 (d, J = 5.5, H-5), 8.48 (d, J = 5.5, H-6), 8.90 (s, H-2); MS m/e 320 (M^+); Anal. Calcd for $C_{11}H_{13}IN_2O_2$: C, 37.52; H, 4.09; N, 8.75. Found: C, 37.51; H, 4.30; N, 8.66.

N,N-Diethyl O-(3-N,N-dimethylsulfonyl)pyridyl-4-carbamate (183g).

According to Procedure **A**, lithiation of carbamate **179** (418 mg, 2.15 mmol), s-BuLi (2.30 mL, 2.37 mmol), TMEDA (0.36 mL, 2.37 mmol), -78°C, 45 min, N,N-Dimethylsulfonyl chloride (0.25 mL, 2.37 mmol), standard workup and column chromatography (2:1 EtOAc-hexane as eluent) afforded 385 mg (60%) of compound **183g**, bp 85-90°C/0.05 mm; IR (neat) ν_{max} 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.10-1.40 (m, 6H, 2 CH_3), 2.8 (s, 6H, 2 NCH_3), 3.20-3.60 (m, 4H, 2 CH_2), 7.32 (d, J = 5.6, H-5), 8.45 (d, J = 5.6), 8.6 (s, H-2); MS m/e 257 (M^+(301)-NMe_2); Anal. Calcd. for $C_{12}H_{19}N_3O_4S$: C, 47.83; H, 6.35; N, 13.94. Found: C, 48.14; H, 6.23; N, 12.92.

3-Bromo-2-pyridone (184).

N,N-Diethyl O-(3-bromo)pyridyl-2-carbamate **181e** (300 mg, 1.1 mmol) was refluxed in methanol (10 mL) in presence of sodium methoxide (118 mg, 2.2 mmol) for 40 h. The reaction mixture was made acidic (pH=6) by adding 2M HCl and further workup in the usual manner gave crude product which upon recrystallization afforded 170 mg (90%) of compound **184,** mp 175-179°C (CH_2Cl_2) (lit.[115] 181-187°C); IR ($CHCl_3$) ν_{max} 3250, 1630 cm^{-1}; NMR ($CHCl_3$) δ 6.23 (dd, J = 7, H-5), 7.45 (dd, J = 7, 1.7, H-4), 7.87 (dd, J = 7, 1.7, H-6); MS m/e 173, 175 (M^+).

4-Methyl-3-hydroxypyridine (185).

N,N-Diethyl O-(4-methyl)pyridyl-3-carbamate **182b** (600 mg, 2.88 mmol) was refluxed in methanol 15 mL) in presence of sodium methoxide (311 mg, 5.76 mmol) for 12 h. workup in the usual manner as described in the previous experiment followed by recrystallization gave 248 mg (80%) of compound **185,** mp 114-115°C (C_6H_6-hexane) (lit.[115] 117-119°C); IR ($CHCl_3$) ν_{max} 3400 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 7.25 (d, J = 4.7, H-5), 8.0 (d, J = 4.7, H-6), 8.3 (br S, H-2), 9.6 (br, 1H, OH).

3-Methyl-4-pyridone (186).

N,N-Diethyl O-(3-methyl)pyridyl-4-carbamate **183b** (450 mg, 2.16 mmol) was refluxed in methanol in presence of sodium methoxide (233 mg, 4.32 mmol) for 20 h. Usual workup as described in the

previous experiment followed by recrystallization afforded 198 mg (85%) of compound **186,** mp 92-93°C (CH_2Cl_2-hexane) (lit.[115] 92-94°C), IR ($CHCl_3$) ν_{max} 3227, 1637 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (s, 3H, CH_3), 6.56 (d, J = 6.7, H-5), 7.73 (m, 2H, H-2 and H-6), 9.53 (br, 1H, OH).

N,N-Diethyl O-(4-N,N-diethylcarbamoyl-5-trimethylsilyl)pyridyl-3-carbamate (187).

According to Procedure **A,** lithiation of N,N-Diethyl O-(4-N,N-diethylcarbamoyl)pyridyl-3-carbamate **182c** (255 mg, 0.87 mmol), s-BuLi (1.36 mL, 1.82 mmol), TMEDA (0.27 mL, 1.82 mmol), -78°C, 45 min, TMSCl (0.12 mL, 0.95 mmol), standard workup and column chromatography using 3:1 EtOAc-hexane afforded 210 mg (66%) of compound **187,** bp 160-164°C/0.05 mm; IR (neat) ν_{max} 1725, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.34 (s, 9H, $Si(CH_3)_3$), 0.92-1.36 (m, 12H, 4 CH_3), 3.01-3.65 (m, 8H, 4 CH_2), 8.56, 8.59 (2 s, 2H, H-2 and H-6); HRMS m/e 365.2126; Calcd. for $C_{18}H_{31}N_3O_3Si$: 365.2132.

N,N-Diethyl O-(4-bromo-5-trimethylsilyl)pyridyl-3-carbamate (188).

According to Procedure **B,** lithiation of N,N-diethyl O-(4-bromo)pyridyl-3-carbamate **182e** (610 mg, 2.23 mmol), LDA (1.1 equiv, 2.83 mmol), -78°C, 25 min, TMSCl (0.31 mL, 2.45 mmol),

standard workup and column chromatography using 1:2 EtOAc-hexane as eluent gave 500 mg (65%) of compound **188** as an oil; IR (neat) ν_{max} 1730 cm^{-1}; NMR ($CDCl_3$) δ0.43 (s, 9H, $Si(CH_3)_3$, 1.14-1.31 (m, 6H, 2 CH_3), 3.30-3.64 (m, 4H, 2 CH_2), 8.32, 8.41 (12 s, H-2 and H-6); MS m/e 345, 347 (M^+). Compound **188** was found to decompose on standing at 0°C for a few days and an analytical sample could not be obtained.

N,N-Diethyl O-(3-N,N-diethylcarbamoyl-5-trimethylsilyl)pyridyl-4-carbamate (189).

According to Procedure **A**, lithiation of N,N-diethyl O-(3-N,N-diethylcarbamoyl)pyridyl-4-carbamate **183c** (53 mg, 0.87 mmol), s-BuLi (1.36 mL, 1.82 mmol), TMEDA (0.27 mL, 1.82 mmol), -78°C, 45 min, TMSCl (0.12 mL, 0.95 mmol), standard workup and column chromatography using 3:1 EtOAc-hexane as eluent afforded 215 mg (66%) of compound **189**, bp 155-160°C/0.05 mm; IR (neat) ν_{max} 1725, 1636 cm^{-1}; NMR ($CDCl_3$) δ0.93-1.26 (m, 12 H, 4 CH_3), 3.13-3.39 (m, 8H, 4 CH_2), 8.5, 8.6 (2 s, 2H, H-2 and H-6); HRMS m/e 365.2130; Calcd. for $C_{18}H_{31}N_3O_3Si$: 365.2132.

N,N-Diethyl-3-hydroxyisonicotinamide (190).

According to Procedure **C**, lithiation of N,N-diethyl O-pyridyl-3-carbamate **177** (600 mg, 3.09 mmol), s-BuLi (2.83 mL,

3.40 mmol), TMEDA (0.51 mL, 3.40 mmol), -78°C and warming to room temperature over 8h, standard workup and purification by preparative TLC using EtOAc as eluent afforded 240 mg (40%) of compound **190** as a viscous oil; IR ($CHCl_3$) ν_{max} 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (t, J = 7, 6H, 2 CH_3), 3.41 (q, J = 7, 4H, 2 CH_2), 7.10 (d, J = 4.7, H-5), 8.06 (d, J = 4.7, H-6), 8.24 (br, H-2); HRMS m/e 194.1051 Calcd. for $C_{10}H_{14}N_2O_2$: 194.1056.

3-N,N-Diethylcarbamoyl-4-pyridone (191a).

According to Procedure **C**, lithiation of N,N-diethyl O-pyridyl-4-carbamate **179** (409 mg, 2.10 mmol), s-BuLi (1.89 mL, 2.31 mmol), TMEDA (0.35 mL, 2.31 mmol), -78°C and warming to room temperature over 8h, standard workup followed by recrystallization gave 300 mg (74%) of compound **191a**, mp 98-100°C (C_6H_6-CH_2Cl_2); IR ($CHCl_3$) ν_{max} 3220, 1641, 1618 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (t, J = 7, 6H, 2 CH_3), 3.38 (q, J = 7, 4H, 2 CH_2), 6.49 (d, J = 7, H-5), 7.68 (d, J = 7, H-6), 7.76 (s, H-2); HRMS m/e 194.1047; Calcd. for $C_{10}H_{14}N_2O_2$: 194.1056.

3-N,N-Diethylcarbamoyl-5-methyl-4-pyridone (191b).

According to Procedure **C**, lithiation of N,N-diethyl O-(3-methyl)pyridyl-4-carbamate **183b** (300 mg, 1.44 mmol), s-BuLi (2.65 mL, 3.02 mmol), TMEDA (0.45 mL, 3.02 mmol), -78°C, and warming to room temperature over 8 h, standard workup and

purification by preparative TLC using EtOAc as eluent afforded 238 mg (80%) of compound **191b,** IR (neat) ν_{max} 3419, 1641 cm^{-1}; NMR ($CDCl_3$) δ 1.0-1.5 (m, 6H, 2 CH_3), 2.05 (s, 3H, CH_3), 2.95-3.50 (m, 4H, 2 CH_2), 7.6, 7.7 (2 s, 2H, H-2 and H-6); HRMS m/e 208.1209; Calcd for $C_{11}H_{16}N_2O_2$: 208.1212.

3-N,N-Diethylcarbamoyl-5-trimethylsilyl-4-pyridone (191c).

According to Procedure **C,** lithiation of N,N-diethyl O-(3-trimethylsilyl)pyridyl-4-carbamate **183d** (250 mg, 0.93 mmol), , s-BuLi (0.84 mL, 1.12 mmol), TMEDA (0.17 mL, 1.12 mmol) -78°C, and warming to room temperature over 8h, standard workup and recrystallization afforded compound **191c,** mp 198-201°C (CH_2Cl_2-hexane); IR ($CHCl_3$) ν_{max} 3208, 1632 cm^{-1}; NMR ($CDCl_3$) δ 0.22 (s, 9H, $Si(CH_3)_3$), 1.06-1.50 (m, 6H, 2 CH_3), 3.30-3.70 (m, 4H, 2 CH_2), 7.7 (br, 2H, H-2 and H-6); MS m/e 266 (M^+); Anal. Calcd for $C_{13}H_{22}N_2O_2Si$: C, 58.61; H, 8.32; N, 10.54. Found: C, 58.66; H, 8.15; N, 10.06.

N,N-Diethyl-4-chloro-5-methylnicotinamide (195).

3-N,N-Diethylcarbamoyl-5-methyl-4-pyridone **191b** (91 mg 0.44 mmol), was refluxed with phosphoryl chloride (2 mL) for 10 min. Excess phosphoryl chloride was removed under vacuo followed by standard workup gave crude product which upon purification by preparative TLC using EtOAc as eluent afforded 49 mg (50%) of compound **195** as an oil; IR (neat) ν_{max} 1636 cm^{-1}; NMR

($CDCl_3$) δ 1.00-1.37 (m, 6H, 2 CH_3), 2.41 (s, 3H, CH_3), 3.02-3.8 (m, 4H, 2 CH_2), 8.21-8.6 (br, 2H, H-2 and H-6); HRMS m/e 226.0865 and 228.0844; Calcd. for $C_{11}H_{15}ClN_2O$: 226.0874 and 228.0844.

N,N-Diethyl-5-methylnicotinamide (196).

Hydrogen was passed through a stirred solution of N,N-diethyl-4-chloro-5-methylnicotinamide **195** (40 mg, 0.18 mmol) in ethanol (5 mL) for 16 h in presence of catalytic amount of palladium-barium sulfate catalyst. Usual workup followed by purification by preparative TLC (EtOAc as eluent) afforded 30 mg (90%) of compound **196** as an oil; IR (neat) ν_{max} 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.12-1.27 (m, 6H, 2 CH_3), 2.37 (s, 3H, CH_3), 3.37-3.53 (m, 4H, 2 CH_2), 7.54 (br, H-4), 8.46 (br, 2H, H-2 and H-6); HRMS 192.1263. Calcd. for $C_{11}H_{16}N_2O$: 192.1263.

N,N-Diethyl O-(4-iodo)pyridyl-3-carbamate (182f) from N,N-diethyl O-(4-trimethylstannyl)pyridyl-3-carbamate (182i).

Iodine (237 mg, 0.92 mmol) was added to a solution of stannylated carbamate **182i** (152 mg, 0.42 mmol) in chloroform (10 mL) and the mixture was stirred for 5h at room temperature under nitrogen. The reaction mixture was washed with aqueous sodium thiosulfite solution and water and the chloroform solution was

dried (Na_2SO_4) and concentrated to give crude product which upon column chromatography afforded 136 mg (90%) of compound **182f** which was shown to be identical (by NMR, GC) with a sample obtained through ortho lithiation reaction of **177.**

N,N-Diethyl O-(4-acetyl)pyridyl-3-carbamate (199).

The stannylated carbamate **182i** (312 mg, 0.87 mmol) was taken in benzene (15 mL) and acetyl chloride (0.25 mL, 3.50 mmol) was added to it and the resulting solution was heated at reflux for 40 h under nitrogen. The reaction mixture was washed with aqueous sodium bicarbonate solution and water and the benzene solution was dried (Na_2SO_4) and concentrated to give crude product which was purified by preparative TLC (EtOAc as eluent) to afford 207 mg (57%) of compound **199** as an oil; IR (neat) ν_{max} 1726 cm^{-1}; NMR ($CDCl_3$) δ 1.12-1.55 (m, 6H, 2 CH_3), 2.55 (s, 3H, CH_3), 3.25-3.64 (m, 4H, 2 CH_2), 7.50 (d, J = 4.9, H-5), 8.51 (s, H-2), 8.56 (d, J = 4.9, H-6); MS m/e 237 (M^+). Compound **199** was found contaminated with a trace of starting material (by mass spectrum) which could not be removed and an analytical sample was not obtained.

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