The Directed *ortho* Metalation Reaction of Aryl *O*-Carbamates on Solid Support

by

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Abstract

A protocol for the metalation of aryl *O*-carbamates on solid support was developed. A model system (4-[(trityloxy)methyl] phenyl *N, N*-diethyl *O*-carbamate), was chosen to study the Directed *ortho* Metalation reaction in *solution*. Metalation (*s*-BuLi – TMEDA in THF) followed by quench with various electrophiles proceeded smoothly to give products (2-(1,1,1-trimethylsilyl)-4-[(trityloxy)methyl]phenyl *N, N*-diethyl *O*-carbamate, 2-iodo-4-[(trityloxy)methyl]phenyl *N, N*-diethyl *O*-carbamate, 2-deutero-4-[(trityloxy)methyl]phenyl *N, N*-diethyl *O*-carbamate, 2-chloro-4-[(trityloxy)methyl]phenyl *N, N*-diethyl *O*-carbamate, 2-[(diethylamino)carbonyl]-4-[(trityloxy)methyl]phenyl *N, N*-diethyl *O*-carbamate, 2-bromo-4-[(trityloxy)methyl] *N, N*-diethyl *O*-carbamate, *NI, NI*-diethyl-2-hydroxy-5-[(trityloxy)methyl]benzamide and 2-(phenylsulfanyl)-4-[(trityloxy)methyl]phenyl *N, N*-diethyl *O*-carbamate) in moderate to high yields. Subsequent detritylation was effected using an aqueous HCl solution in THF to give alcohols (4-(hydroxymethyl)-2-(1,1,1-trimethylsilyl)phenyl *N, N*-diethyl *O*-carbamate, 4-(hydroxymethyl)-2-iodophenyl *N, N*-diethyl *O*-carbamate, 4-hydroxymethyl-2-deuterophenyl *N, N*-diethyl *O*-carbamate, 4-hydroxymethyl-2-chlorophenyl *N, N*-diethyl *O*-carbamate, 2-[(diethylamino)carbonyl]-4-(hydroxymethyl)phenyl *N, N*-diethyl *O*-carbamate, 2-bromo-4-(hydroxymethyl)phenyl *N, N*-diethyl *O*-carbamate, 4-(hydroxymethyl)-2-methylphenyl *N, N*-diethyl *O*-carbamate, 4-(hydroxymethyl)-2-(phenylsulfanyl)phenyl *N, N*-diethyl *O*-carbamate and *NI, NI*-diethyl-2-hydroxy-5-(hydroxymethyl)benzamide). The reaction was transferred to *solid support*, using trityl chloride resin purchased from Novabiochem. Metalation in and

quench with a variety of electrophiles, followed by release from the solid support were carried out to afford the products with moderate to good purity.

The solution phase Suzuki-Miyaura cross-coupling reaction of 4-[(trityloxy)methyl] phenyl *N,N*-diethyl *O*-carbamate with phenyl boronic acid was carried out to illustrate a synthetic link to of the directed *ortho* metalation reaction. Cross coupling followed by deprotection of the alcohol afforded the product (2-phenyl-4-[(hydroxy)methyl]phenyl *N,N*-diethyl *O*-carbamate) in 77% over two steps. Due to time constraints, the solid-phase Suzuki-Miyaura cross coupling reaction was not completed.

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For Rob, my parents and my sister, Harriet

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4-formylphenyl *N,N*-diethyl *O*-carbamate

(174) 89

4-(hydroxymethyl)phenyl *N,N*-diethyl *O*-carbamate

(155) 89

4-[(trityloxy)methyl] phenyl *N,N*-diethyl *O*-carbamate

(164) 90

2-(1,1,1-trimethylsilyl)-4-[(trityloxy)methyl]phenyl *N,N*-diethyl *O*-carbamate

(175) 91

2-iodo-4-[(trityloxy)methyl]phenyl *N,N*-diethyl *O*-carbamate

(171) 92

2-deutero-4-[(trityloxy)methyl]phenyl *N,N*-diethyl *O*-carbamate

(176) 92

2-chloro-4-[(trityloxy)methyl]phenyl *N,N*-diethyl *O*-carbamate

(177) 93

2-[(diethylamino)carbonyl]-4-[(trityloxy)methyl]phenyl *N,N*-diethyl *O*-carbamate

(178) 94

2-bromo-4-[(trityloxy)methyl] *N,N*-diethyl *O*-carbamate

(179) 94

N,N-diethyl-2-hydroxy-5-[(trityloxy)methyl]benzamide

(168) 95

2-(phenylsulfanyl)-4-[(trityloxy)methyl]phenyl *N, N*-diethyl *O*-carbamate

(180) 96

4-(hydroxymethyl)-2-(1,1,1-trimethylsilyl)phenyl *N, N*-diethyl *O*-carbamate

(181) 96

4-(hydroxymethyl)-2-iodophenyl *N, N*-diethyl *O*-carbamate

(182) 97

4-hydroxymethyl-2-deuteriophenyl *N, N*-diethyl *O*-carbamate

(183) 98

4-hydroxymethyl-2-chlorophenyl *N, N*-diethyl *O*-carbamate

(184) 98

2-[(diethylamino)carbonyl]-4-[(hydroxy)methyl]phenyl <i>N,N</i> -diethyl <i>O</i> -carbamate	
(185)	99

2-bromo-4-(hydroxymethyl)phenyl <i>N,N</i> -diethyl <i>O</i> -carbamate	
(186)	99

2-phenyl-4-[(hydroxy)methyl]phenyl <i>N,N</i> -diethyl <i>O</i> -carbamate	
(172)	100

4-(hydroxymethyl)-2-methylphenyl <i>N,N</i> -diethyl <i>O</i> -carbamate	
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*N*1, *N*1-diethyl-2-hydroxy-5-(hydroxymethyl)benzamide

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List of Abbreviations

Ac	Acetyl
acac	Acetylacetonate
AG	ArgoGel
CI	Chemical Ionization
CIPE	Complex Induced Proximity Effect
Cy	Cyclohexane
DBU	1,5-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(Dimethylamino)pyridine
DEM	Diethoxymethane
DMF	<i>N, N</i> -dimethylformamide
DMG	Directed Metalation Group
DoM	Directed <i>ortho</i> Metalation
DRIFTS	Diffuse reflectance infrared Fourier transform spectroscopy
DVB	Divinylbenzene
EI	Electron Impact
HOESY	Heteronuclear Overhauser Effect Spectroscopy
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
Janda/Jel™	Polystyrene resin cross-linked with polytetrahydrofuran

KEM	Kinetically Enhanced Metalation
KIE	Kinetic Isotope Effects
LDA	Lithium diisopropylamide [LiN(<i>i</i> -Pr) ₂]
LRMS	Low Resolution Mass Spectrometry
MALDI-MS	matrix-assisted laser desorption ionization mass spectrometry
MALDI-TOF-MS	matrix assisted laser desorption ionization time of flight mass spectrometry
MAS-NMR	magic angle spinning nuclear magnetic resonance spectroscopy
MOM	Methoxy methyl ether
NMP	1-methyl-2-pyrrolidinone
NpSSMpact	2-methoxy-5-(2-((2-nitrophenyl)dithio)-1-oxopropyl)phenylacetic acid
o.n.	Overnight
OTf	Trifluoroacetate
PA-FTIR	photoacoustic Fourier transform infrared spectroscopy
PEG	Poly(ethylene glycol)
PEGA	Poly(ethylene glycol)/dimethylacrylamide copolymer
PS-DVB	Polystyrene resin cross-linked with divinylbenzene
PS-DES	A polystyrene gel-type resin with diethylsilane linker
PS-PEG	Polystyrene/DVB-poly(ethylene glycol) graft copolymer
PTHF	Polytetrahydrofuran
py	Pyridine
RAM	Rink amide
Sasarin	superacid sensitive resin

SPOS	solid phase organic synthesis
SPPS	solid phase peptide synthesis
SR-MAS NMR	Swollen resin magic angle spinning nuclear magnetic resonance spectroscopy
TBDMSCl	<i>t</i> -Butyl Dimethyl Silyl Chloride
TCR	trityl chloride resin
TFE	2, 2, 2 - trifluoroethanol
TG	TentaGel
TIS	Triisopropylsilane (<i>i</i> Pr ₃ SiH)
TMEDA	Tetramethylethylenediamine
TMS	Tetramethylsilane (NMR standard)
Tr	Trityl (triphenylmethyl)
Wilkinson's Catalyst	RhCl(PPh ₃) ₃

1.0 Literature Review

1.1 Introduction

Polysubstituted aromatic and heteroaromatic compounds constitute major moieties of pharmaceuticals and agrochemicals. A cursory glance through a book on drug design or medicinal chemistry confirms their ubiquitous presence in these fields in applications ranging from pain control to antiviral treatments.¹⁻³ The regiospecific synthesis and elaboration of such compounds has posed a problem to organic chemists for decades. Although number of solutions to the problem have evolved, the classical solution remains electrophilic aromatic substitution.⁴ However, this method often requires harsh conditions and results in structural isomers, thus limiting synthetic application.

1.2 The Directed *ortho* Metalation (DoM) Reaction

The independent discoveries by Gilman and Bebb⁵ and by Wittig and Fuhrman⁶ that anisole can be functionalized *ortho* to the methoxy group ushered in the era of DoM chemistry. These chemists observed that anisole is deprotonated regiospecifically *ortho* to the OMe group, that is, the OMe group of anisole directs lithiation to the *ortho* position. The early work in this area is reviewed by Gilman and Morton.⁷

Gilman and Morton pioneered the early reactivity studies, examining the nature of the organolithium reagents as well as observing the reactivity of several classes of compounds under metalation conditions.⁷ Their work was followed chronologically by Hauser,⁸ Slocum,⁹ Beak,¹⁰ and Snieckus.¹¹ In simple form, the DoM reaction involves the use of an alkyllithium base to remove a proton *ortho* to a directed metalation group (DMG) in **1** to form the *ortho* lithiated species **2**. This species is quenched with a variety of electrophiles to afford 1,2-substituted products **3** regioselectively (**Scheme 1**).

Scheme 1

1.2.1 Mechanistic Features of the DoM Reaction

The "Complex Induced Proximity Effect" (CIPE) of DoM

The first mechanistic interpretation of the DoM reaction is due to Roberts and Curtin (**Scheme 2**)¹² who proposed that the preference for metalation at the *ortho* site may be rationalized by invoking an initial coordination of the organolithium reagent to the lone pair of electrons on the substituent of **1**. Deprotonation then ensues to form the *ortho* lithiated species **2**. Roberts and Curtin suggested two outcomes of their proposal. Preliminary coordination would result in the polarization of the metal-carbon bond of the lithium reagent, thus enhancing the inductive electron withdrawing effect of the substituent on the *ortho* C-H bond. In addition, this coordination might serve to temper

the observed decrease in acidity of both the *ortho* and *para* protons, which normally occurs due to the resonance donation of the lone pair of the DMG into the ring. While they reasoned that these two factors may explain the experimentally observed regioselectivity and acceleration of *ortho* metalation, they concluded that their proposal was "not completely satisfactory" because a number of functional groups with lone pairs capable of coordinating alkyllithium reagents (e.g., PPh_3 ¹³ and NPh_3 ¹⁴) do not mediate *ortho* metalation. Although experimental evidence had not been obtained, this theory was generally accepted, and it was proposed that two extremes for the DoM mechanism may exist: a "coordination only" mechanism in which metalation is directed due to coordination of lithium by the DMG's heteroatom(s), or an "acid-base" mechanism followed by those species whose DMG has little or no ability to coordinate the alkyllithium (e.g., CF_3).¹⁵

Scheme 2

Beak and Meyers invented the expression "Complex Induced Proximity Effect"¹⁰ to describe the process proposed by Roberts and Curtin. The argument for CIPE was propelled by Beak's direct observation of the lithium-amide complexes of the α -lithiated

products of *N,N*-dimethyl- and *N,N*-diethyl-2, 4, 6-triisopropylbenzamide **5** (Scheme 3) by stopped-flow IR spectroscopy.¹⁶ Based on kinetic data, Beak and coworkers proposed that the reaction of compounds **5** occurred *via* a preequilibrium complex **6** to give the α -lithiated product **7**.

Scheme 3

Although the kinetic studies indicated a complex stoichiometry, this work demonstrated the presence of aggregated complexes as components of the α -metalation reaction pathway. Beak observed that at least two reactive complexes are present, and that the aggregates become increasingly reactive as a function of increasing number of ligands bound to the lithium atom. The most reactive aggregates were found to be those in which one or two amides and one or two TMEDA molecules are involved. Beak and coworkers proposed that, in the most reactive complexes, the tetramer of *s*-BuLi is situated such that one lithium is coordinated to the carbonyl oxygen, while the others are bound to the ligands (Scheme 4). In the key step, one *s*-BuLi group is partially released from the aggregate to remove a proton from the substrate. TMEDA and the amide group accelerate the reaction by binding the lithium atoms to allow reactivity of the anionic

butyl group. An analogous proposal has been assumed for the mechanism of the DoM process.¹⁰

Scheme 4

That a process such as CIPE should accelerate reactions makes sense for the same reason that intramolecular reactions should be more facile than intermolecular reactions. Indeed, processes in which the formation of the kinetic product occurs at the expense of the thermodynamic product, or in which accelerated reactions are observed under unfavourable conditions are situational proofs of CIPE.¹⁰ A clear example is the β -lithiation of the γ, δ -unsaturated tertiary amide **8** (**Scheme 5**) in which the kinetically acidic β -proton is removed in the presence of the more acidic α -proton to form the lithiated species **10**. Evidence for the existence of this species has been proven by the production of **11** upon quenching with electrophiles.¹⁷ Beak and Meyers compiled numerous examples of carbanionic synthetic equivalents in whose formation CIPE appears to play a major role.¹⁰

Scheme 5

The Evolution of the Theory of CIPE

While the CIPE concept allows rationalization of some observations, there are some questions that are left unanswered and a number of observations that do not fit the hypothesis. For example, CF₃ is a good directing group, but it is not likely to complex lithium.¹⁸ Then there is the oft quoted paradox: There can be two types of complexes, strong or weak. If a strong complex is formed, a high degree of regioselectivity is expected in the products, but the yield will be poor because of the energy requirement to overcome the activation barrier in order to break up the complex. If a weak complex is formed, then good yields are expected, but poor regioselectivity. Since the experimental observations point to high yields of regioselective products, neither type of complex may be involved in the mechanism.¹⁹ Not surprisingly, Roberts and Curtin's initial mechanistic proposal and Beak and Meyer's CIPE were the subject of further research and began to evolve as new pieces of the mechanistic puzzle were put into place.

Slocum and coworkers agree that, for DoM to occur, there must be an initial coordination,²⁰ and propose a mechanism, which involves the slow initial coordination of the alkyllithium oligomer, followed by the deprotonation (either with the coordinated oligomer or with a second one) as the fast step. Slocum suggests that the ground state resonance of an aromatic compound (**12**, **13**, **Scheme 6**) bearing a heteroatom is counter productive to DoM in two ways: it reduces the electron density on the heteroatom, making it less able to coordinate lithium and it reduces the inductively derived acidity of the *ortho* protons. Coordination, (**14**) Slocum suggests, minimizes these undesirable effects (**Scheme 6**).

Scheme 6

Slocum and coworkers further propose that it is possible to predict the relative reactivity of the substrate by considering the effect of the ground state resonance as well as the balance between the effectiveness of the heteroatom in the DMG to coordinate lithium compared with its ability to withdraw electron density inductively from the *ortho* position. According to Slocum, OMe should be a DMG of only marginal strength

because oxygen is intermediate in its ability to coordinate lithium and to withdraw electron density from the ring. In the presence of TMEDA, however, the reaction of anisole with BuLi does not involve a coordination of the alkyllithium to the oxygen. An "overriding base, Li-H exchange" was proposed in which the *n*-BuLi – TMEDA complex effects rapid Li – H exchange without initial coordination to the DMG. For this reason, the slow step is avoided and the reaction is more efficient. Slocum has used this model to explain the lithiation of *p*-fluoroanisole,²¹ *p*-methylanisole²² and dimethoxybenzenes.²³

Bauer and Schleyer were the first to suggest the importance of agostic interactions in the DoM reaction. The term agostic is used to describe the covalent bonding of a hydrogen atom to a carbon and a metal simultaneously.²⁴ Agostic (C₂-H)-Li interactions have been proposed as an explanation for the increase in acidity of the *ortho* proton. Schleyer and coworkers first proposed the importance²⁵ and subsequently Saá and coworkers performed MNDO calculations, which strongly implicated a precoordinated species based on agostic interactions.^{26,27}

Bauer and Schleyer²⁸ studied the directed *ortho* lithiation of anisole by *n*-BuLi using ⁶Li, ¹H two-dimensional heteronuclear Overhauser effect spectroscopy (HOESY), which allows the distance between two heteronuclei to be determined,²⁵ and semiempirical molecular orbital calculations. In agreement with Beak, these workers established that an anisole-*n*-BuLi complex is formed, but that this complex is unreactive, even at room temperature. Upon addition of TMEDA, the product begins to form, but at this point, there is no longer evidence for the presence of a complex. Schleyer and

coworkers proposed a mechanism (**Scheme 7**) which involves a CIPE, but which extends Beak's mechanism by including an agostic Li-H interaction as an important component. Schleyer suggests that the BuLi is broken up by coordination with anisole **12** to form the tetramer **15**. Addition of TMEDA results in the solvation of the tetramer to give free anisole **12** and a reactive BuLi dimer solvated by two molecules of TMEDA **16**. The dimer opens to form the monohapto species **17**, which subsequently releases TMEDA, leaving two sites available for coordination in complex **18**. Coordination of lithium to anisole oxygen occurs leading to a Li-H agostic interaction to form the reactive intermediate **19**. Proton abstraction follows generating the *ortho* lithiated anisole **20** and **21**, which reaggregates and undergoes further metalation cycles. Schleyer carried out MNDO calculations to corroborate the proposed mechanism.

Scheme 7

The "Kinetically Enhanced Metalation" Hypothesis of DoM

According to the Kinetically Enhanced Metalation hypothesis of Schleyer and van Eikema Hommes, transition state phenomena are of primary significance in understanding the directing and activating action of DMGs.²⁹

These workers suggest that only circumstantial evidence²⁹ exists for a strong CIPE since, if this was the case, the reaction should proceed more slowly than is

experimentally observed because the complexation energy must be overcome to form the transition state.¹⁸ They agree with the intermediacy of an anisole-BuLi complex, but propose that reaction occurs only after break up of this complex of TMEDA. They also note that, no complex is observed in the metalation of fluorobenzene in spite of F being found to be a better *ortho* directing group than OMe.²⁹ Schleyer and van Eikema Hommes propose that the directing and activating effects of the DMG occur in the transition state rather than as a result of a preequilibrium complex. Two effects serve to lower the activation energy which results in metalation preferentially in the *ortho* position. The first effect is the electrostatically favourable orientation of charges in the transition state (Scheme 8). The second effect is the partial bonding of the butyl group to H in the transition structure which, while lowering the coordination of the butyl group and hence also of lithium, is compensated for by the coordination of the DMG to lithium.

Scheme 8

Following Bauer and Schleyer's NMR studies, Schleyer and van Eikema Hommes performed *ab initio* calculations of three *o*-substituted toluenes (*o*-CH₃C₆H₄R, R = OH, NH₂ and F) with lithium hydride as the model metalating agent. They found that electronegative substituents reduce activation energy of metalation relative to toluene.²⁹ The lack of correspondence between pKa values of *ortho* protons³⁰ and reactivity points towards the importance of kinetic factors in directed *ortho* metalation reactions. Schleyer

and coworkers suggest that it is not the stabilization of the initial complex (CIPE) which dictates the reactivity of the compound, but rather stabilizing effects in the transition state. High level *ab initio* calculations by Schleyer and van Eikema Hommes,¹⁹ suggest that dimers are more reactive than monomers or tetramers. According to these workers, interaction of passive lithium atoms of RLi (those not directly involved in the lithiation) with the π -system of the aromatic compound serves to stabilize the transition state and the activation energy of metalation ($\Delta H^\ddagger$) is reduced by the intramolecular complexation of the lithium cation with the Lewis basic DMG. Hence they argue that it is these stabilizing effects in the transition state, and not initial complexation, that are responsible for the acceleration and directing ability observed. For these reasons, Schleyer and van Eikema Hommes propose that "Kinetically Enhanced Metalation" is a better descriptor than CIPE for the effects observed in the DoM reaction.²⁹ Saá and coworkers,³¹ have performed MNDO calculations on lithiations of phenols and alkoxyaromatics, and derive conclusions in agreement with Schleyer's proposal.

Current Opinion

In studies on the *ortho* lithiation of anisole by *n*-BuLi-TMEDA, Collum and coworkers have established that the reaction proceeds *via* a $[(n\text{-BuLi})_2(\text{TMEDA})_2 \cdot (\text{anisole})]$ transition state, according to the rate law: $-d[\text{anisole}]/dt = k[\text{anisole}][\text{TMEDA}]^0[(n\text{-BuLi})_2(\text{TMEDA})_2]$, where $(n\text{-BuLi})_2(\text{TMEDA})_2$ is a dimeric aggregate.³² In very recent kinetic studies, Collum found that the rate laws for the DoM reaction of various alkoxy-substituted aromatic compounds were the same as that for anisole, an observation which implicates a common mechanism. He agrees that a dimeric

n-BuLi – TMEDA aggregate is present, although the structure of the reactive intermediate could not be determined, but disagrees with the type of cyclic dimer **19** (Scheme 7) proposed by Schleyer.³³ Collum proposed a dimer-based mechanism, which involves the use of the triple ion **23** (Scheme 9).³³

Scheme 9

Stratakis determined KIEs in the lithiation of anisole with and without TMEDA³⁴ and found that the intermolecular and intramolecular KIEs were identical within experimental error thus leading to the conclusion that removal of the *ortho*-hydrogen constitutes the rate determining step, in agreement with Schleyer (above). Stratakis proposed two mechanistic interpretations. In the first, an intermediate aggregate (either dimeric or tetrameric) containing *n*-BuLi and anisole is involved in the transition state and products are formed, either due to steric repulsion (tetramer) or low concentrations of the reactive species (dimer), in the rate determining step. Alternatively, no complexation

occurs and deprotonation occurs in a single-step mechanism involving highly reactive *n*-BuLi of low aggregation. Unfortunately, Stratakis was unable to distinguish between the two possibilities based on his KIE studies.

Recently, Beak and coworkers determined the intra- and intermolecular KIEs for the benzylic and *ortho* lithiations of a urea, a tertiary amide and a secondary amide.³⁵ In the case of the urea, different intra- and intermolecular KIEs were observed meaning that, if only one reaction pathway exists, that pathway must have at least two steps. In the cases of the tertiary and secondary amides, no distinction between one-step and two-step pathways could be made. However, the authors conclude that neither a single step (KEM) nor a two-step (CIPE) mechanism can be ruled out and therefore both mechanisms may be operative and reaction *via* a complex is logical where evidence for the complex exists.

Considerable research into the enigmatic directed *ortho* metalation reaction over the past six decades has shed light onto some aspects of the mechanism of this powerful synthetic tool. It has become clear that coordination of the lithium atom to the DMG is central to the mechanism, but whether this occurs as a preequilibrium complex (CIPE) or in the transition state (KEM) is a matter of fierce debate. Intra- and intermolecular competition studies, kinetic isotope effect studies, one and two dimensional NMR studies and semiempirical calculations have all been used to fit pieces of the DoM puzzle into place. However, at this time, the mechanism of the directed *ortho* metalation reaction still eludes our understanding.

1.2.2 The Nature of the DMG

Since the discovery of the first DMG (OMe) by Gilman and Bebb⁵ and by Wittig and Fuhrmann,⁶ many DMGs have been developed. The list of functional groups capable of directing metalation has grown to include not only oxygen-based DMGs, but also nitrogen-, carbon-, sulfur-, and halogen-containing DMGs. DMGs are broadly divided into two categories; the carbon-based DMGs and the heteroatom-based DMGs (Table 1).

In an attempt to rank DMGs in their directing power, a greater understanding of how the DMG works has emerged. Building a successful DMG involves consideration of a delicate balancing of electronic and steric characteristics. A proper DMG should be somewhat electron rich, but must be an undesirable site for attack by nucleophiles. The use of bulky substituents (for example CONEt_2 , $\text{CON}(i\text{-Pr})_2$ over CONMe_2) to block the site of attack, or deactivation (for example, $\text{NCO}_2t\text{-Bu}$) are concepts that have been successfully employed in the design of DMGs.¹¹

Many of the DMGs listed in Table 1 have been widely used in synthesis, for example oxazoline,^{36,37} tertiary amides,^{11,38} and tertiary carbamates³⁹ The tertiary diethyl *O*-carbamate (OCONEt_2) DMG was used exclusively in the current work and therefore is the subject of the following section which describes the power and utility of this versatile DMG.

Table 1. Common DMGs

Strength	Carbon-based	Reference	Heteroatom-based	Reference
Strong	CONHR	15	NHCO ₂ R	40
	CONR ₂	11,38	NHCOR	41
	42	OCOR ₂	39
			OCH ₂ OMe	43,44
			SO ₂ NR ₂	15
Moderate	CF ₃	15	OMe	15
			F	45,46
			Cl	45,46
Weak			OH	47

1.2.3 The Carbamate DMG

This DMG is the most powerful DMG known, and is highly manipulable. It is not only a "masked" phenol, but serves as a "carrier" into the *ortho* position of a tertiary amide DMG which was originally developed by Beak.³⁸

The *N, N*-diethyl *O*-carbamate DMG, discovered in 1983 by Sibi and Snieckus,³⁹ undergoes highly regioselective metalation to form **25** (Scheme 10) and electrophile quench to afford a variety of *o*-substituted products **27**. While its hydrolysis, giving **28**,

is difficult unless assisted anchimerically by the incipient electrophile introduced, it carries the additional benefit of undergoing the anionic *o*-Fries rearrangement, to form **26**, liberating the powerful tertiary amide at the *ortho* site, which may engage in further metalation chemistry.

Scheme 10

Recently, a new DMG, the *N*-Me *N*-cumyl-*O*-carbamate DMG **29** (**Scheme 11**) has emerged, which displays all of the benefits of the *N*, *N*-diethyl carbamate DMG, but which can be cleaved under comparatively mild conditions.⁴⁸

Scheme 11

Carbamate **29** undergoes DoM followed by TMSCl quench to yield the *ortho* substituted product **32**. The phenol (**33**) may be liberated under mild conditions in contrast to *N,N*-diethyl *O*-carbamate which must be cleaved using lithium aluminum hydride or methyllithium.³⁹ **29** can also undergo an anionic *ortho* Fries rearrangement, followed by treatment with TFE to give secondary amide **31**. This DMG can be used to synthesize a variety of substituted compounds, including biaryls, using the combined DoM and Suzuki-Miyaura cross-coupling protocol (Section 1.4).

The *N, N*-diethyl *O*-carbamate DMG has served in key steps in the synthesis of the isocoumarins **39a** and **39b** (Scheme 12), which are the precursors to the toxic fungal metabolites Ochratoxin B **40a** and Ochratoxin A **40b**.⁴⁹ Their synthesis involved metalation of **34** and carbamoylation to give **35**, followed by a second metalation to effect the anionic *o*-Fries rearrangement to afford **36**. Protection of the phenol followed by DoM, transmetalation with MgBr₂ and treatment with allyl bromide affords the *o*-allylated intermediates **38**. In the final step, compounds **38** were subjected to extended reflux in 6N HCl, which accomplished lactonization, amide hydrolysis and demethylation in one pot to yield the isocoumarin carboxylic acids **39a** and **39b**. Their synthesis was completed in four steps in 14% and 6% overall yield respectively, which compare favourably with previous reported yields of 70%, 1% and 20%. This simple synthesis clearly illustrates the strengths of the *N, N*-diethyl *O*-carbamate DMG.

Scheme 12

Danishefsky and Lee's total synthesis of (±)-Pancratistatin (**44**, **Scheme 13**) is another example of the use of the carbamate DMG as a powerful tool in total synthesis.⁵⁰ In a key step of this synthesis the metalation of **41** followed by warming to room temperature and TBS protection leads to **42** which, upon a second DoM reaction and

DMF quench yields the aldehyde **43**, a critical intermediate for the construction of pancratistatin (**44**).

Scheme 13

A DoM protocol for the synthesis of 2*H*-chromene derivatives **47** from aryl *O*-carbamates **45** (**Scheme 14**) contributes another demonstration of the utility of the *O*-carbamate DMG.⁵¹ This procedure takes advantage of the synergistic effect of 1,3-diDMGs for in between metalations.

DMG = OCONEt₂, CONEt₂, OMe, OMOM, F

Scheme 14

1.3 The Cross Coupling Reaction

1.3.1 Introduction

Biaryls are an important class of organic compounds and are found in natural products, pharmaceuticals, polymers, liquid crystals and ligands. In spite of the significance of this class of compounds, until the advent of cross coupling, there were relatively few basic reactions for formation of sp^2 C-C bonds. In the transition metal cross coupling reaction, an organometallic **48** is coupled with a partner **49** bearing a leaving group to give product R-R' **50** (Scheme 15).⁵²

Scheme 15

The metal of R-M **48** may be manganese,⁵³⁻⁵⁵ zinc,^{56,57} tin,⁵⁸ boron⁵⁹ or silicon.⁶⁰

The leaving group of **49** may be a halogen (I, Br and less commonly, Cl),⁶¹ triflate,⁶² mesylate,^{63,64} phosphonate,⁶⁵ *N, N*-diethyl *O*-aryl carbamate,⁶⁶ *N, N*-diethyl *S*-aryl

thiocarbamate,⁶⁷⁻⁶⁹ sulfonate,^{61,62,70} sulfone⁷¹ or a diazonium salt ($N_2^+X^-$).⁷² The catalyst is usually a member of the Group VIII transition metals⁷³ although others have been used.^{61,70,74}

Pioneering work in cross-coupling chemistry was accomplished by Kharasch and Fields⁶¹ in the early 1940s, who discovered that biaryl compounds were formed in excellent yields when an aryl Grignard reagent is treated with an organic halide (preferably bromide) in the presence of iron, nickel and cobalt halides. Furthermore, moderate yields were obtained using manganous chloride while the halides of copper and chromium were found to be unreactive.

The area of cross coupling lay dormant until the early 1970s when Tamura and Kochi reported their finding on the cross coupling of Grignard reagents with organic halides in the presence of silver, copper and iron.^{70,74} In 1972, Corriu⁵³ and Kumada⁵⁴ independently reported their findings on a high-yielding Ni(0) catalyzed cross coupling of alkyl and aryl Grignard reagents with aryl halides. Now known as the Corriu-Kumada-Tamao cross coupling reaction,^{53,54} the procedure is useful for structurally uncomplicated biaryls, especially in view of the wide and commercial availability of Grignard reagents. However, the strongly nucleophilic and basic nature of the Grignard reagent precludes the use of substrates containing groups such as aldehydes, ketones, esters and nitro groups.⁵² The Negishi reaction involves the coupling of arylzinc reagents with aryl halides or triflates. In view of the fact that arylzinc reagents are not strongly nucleophilic or basic, a greater range of functional groups are tolerated (unlike

the Corriu-Kumada-Tamao reaction),⁷⁵ although the variety of available organozinc partners is limited.⁷³ The Stille reaction was developed in the late 1970's and often allows the use of substrates which are not tolerated by the Corriu-Kumada-Tamao or Negishi reactions.⁵⁸ In addition, the organotin component is relatively easily prepared and is not especially oxygen or moisture sensitive,⁷³ unlike Grignard and organozinc reagents. The mild conditions as well as high yields are additional benefits, although the toxicity of stannanes is a major drawback. Advantages of the Suzuki-Miyaura cross coupling reaction are that it is not moisture sensitive and is tolerant of a wide variety of functional groups due to the non-nucleophilic nature of the boronic acids. In addition, the toxicity issue, encountered in the Stille reaction, is avoided.⁷⁶ The Hiyama reaction involves silanes and is the most recent addition to the cross coupling family of reactions. Similar to boronic acids, the silanes used in Hiyama cross coupling reactions are easily prepared, isolable and non-toxic.⁶⁰ Buchwald and Hartwig have added to the cross coupling group of reactions.^{77,78} These reactions involve the formation of C-O and C-N bonds, usually under Pd catalysis, with halogens or triflate as the leaving group.

1.3.2 The Mechanism of the Cross-Coupling Reaction

Details of the cross coupling reaction are still poorly understood.⁷⁹ The simplified mechanism however, is believed to involve oxidative addition of the Ar-LG species **54** to a zero valent Pd or Ni species **53** (generated *via* ligand dissociation from **52** or by reduction *in situ* of **51**) to form intermediate **55**. Transmetalation of this

intermediate with Ar-M **56** gives complex **58**, which undergoes reductive elimination to extrude the biaryl species **59** and to regenerate the active species of the catalyst **53**.

Scheme 16

1.4 The DoM-Cross Coupling Connection

As demonstrated by Sharp,⁸⁰ a valuable application of the DoM reaction is that it permits the synthesis of the cross coupling partners **60** and **61** (**Scheme 17**) from the lithiation of **1** and appropriate electrophilic quench. In addition, some DMGs can participate in cross coupling reactions themselves, e.g., the *N,N*-diethyl *O*-carbamate group and other *O*- and *N*-based DMGs can be transformed into leaving groups for cross coupling.

Scheme 17

The *O*-carbamate DMG is especially valuable in connecting DoM with transition metal cross-coupling reactions. This utility was initially noted in the formation of boronic acid **63** (**Scheme 18**) and the Suzuki-Miyaura cross coupling with *o*-bromoanisole to generate the biaryl **64** in modest yield.⁸⁰

Scheme 18

The aryl *O*-Carbamate and aryl triflate cross coupling reactions with Grignard reagents under Ni(0)-catalyzed conditions was discovered by Sengupta and coworkers,⁶⁶ allowing access to a wide range of polysubstituted aromatic compounds **66** (Scheme 19). The powerful DMG effect of the *O*-carbamate combined with the new cross coupling reaction allows the establishment of an aryl 1,2-dipole synthetic equivalent **67**.

Z = OCONEt₂, OTf

X = Cl, Br

R = Ph, OCONEt₂, CONEt₂, OMOM, NHBoc, (CH₂)₂NHBoc

R' = CH₂TMS, Ph, *n*-Bu, Me, HC=CH₂

Scheme 19

This discovery is useful for the synthesis of unusual 1,2-substituted aromatics, e.g., difficult to synthesize 2,3-disubstituted naphthalenes **70** (Scheme 30). Thus, metalation of **68** followed by carbamoylation and a second metalation to introduce TMS gives the trisubstituted naphthalene **69**. Subsequent cross coupling with hydride donor, *i*-PrMgCl, to reduce the carbamate results in the 2,3-disubstituted naphthalene **70**.

Scheme 20

Later, this methodology was expanded to include DoM-derived aryl zinc derivatives **72** (Scheme 21) whose value, relative to Grignard reagents, lies in their unreactivity towards a number of functional groups (CHO, COR, CN, CO₂R). Cross coupling occurs preferentially with the ArOTf over ArOCONR₂, and sequential regioselective cross couplings may be achieved in molecules containing both functionalities by a change of conditions.⁸¹ A wide variety of coupling partners was used, including heteroaryls, biaryls and DMG-containing species, expanding considerably the scope of this new chemistry.

Scheme 21

The area of synthesis of 4-, 5- and 6-substituted indoles and tryptamines benefits from the *O*-Carbamate DoM – cross-coupling methodology.⁸² A novel approach to the functionalization of the benzenoid portion of the molecule was demonstrated (**Scheme 22**). Metalation of **74** followed by electrophilic quench afforded the 4-substituted 5-*O*-indole carbamates **76** in moderate to good yields. The TMS compound was further functionized by DoM and electrophilic quench or by DoM and anionic *ortho* Fries rearrangement to give good yields of **78** and **79** respectively. Alternatively, **76** may be transmetalated to zinc and cross coupled with 3-bromopyridine to give **77** in 90% yield. Finally, Griffen and coworkers demonstrated that **74** may be cross coupled with Grignard reagents under Ni(0)-catalyzed conditions to give the 5-substituted indoles **75** in moderate to good yields.

Scheme 22

An industrial example of the utility of the DoM-cross coupling reaction sequence is the DuPont-Merck synthesis of Losartan **84** (Scheme 23), a marketed drug used to treat hypertension.^{83,84} Thus trityl-protected 5-phenyl tetrazole **80** upon metalation with $n\text{-BuLi}$, quenching with triisopropyl borate, followed by workup with $i\text{-PrOH}$ and aqueous NH_4Cl gives the boronic acid **81**. Cross coupling with bromide **82** followed by deprotection under acidic conditions affords Losartan (**84**).

Scheme 23

A recent example of the DoM – cross coupling protocol from our laboratories en route to *ortho*-quinodimethane (*o*-QDM) **87** (Scheme 24) begins with the metalation of indole **74** using *s*-BuLi / TMEDA followed by quench with *N,N*-diethyl carbamyl chloride to give **85**. Cross coupling of the aryl *O*-carbamate with TMSCH₂MgCl under Ni catalysis gives **86**, which is further elaborated to the *o*-QDM **87**.⁸⁵

Scheme 24

1.5 Solid Phase Organic Synthesis

1.5.1 Introduction

Merrifield's landmark discovery that polypeptides could be synthesized on an insoluble polymer,⁸⁶ culminating in the award of the Nobel Prize, may be considered as the watershed of today's activities in SPOS. The discovery was clearly of immediate use to peptide chemists because the synthesis of proteins becomes more difficult as the molecule becomes larger. Specifically, solubility and purification of polypeptides become serious issues as a function of increasing number of amino acid units in the polypeptide chain. Merrifield demonstrated that if the growing peptide chain is linked to an insoluble polymer, the polypeptide may be purified by simply dissolving and rinsing away the impurities (reagents and by-products). The "Merrifield Method" (Scheme 25) also suggested potential access for higher molecular weight polypeptides and to

automation. Independently, Letsinger demonstrated the use of DVB-PS polymer for the synthesis of leucylglycine,⁸⁷ and subsequently showed that the process was also applicable to the synthesis of oligonucleotides.⁸⁸ These achievements culminated in the solid supported synthesis of ribonuclease A,⁸⁹ the first protein to be synthesized from component amino acids exhibiting true enzymatic activity towards its natural substrate, and the human pituitary growth hormone (HGH).⁹⁰

Scheme 25

Soon thereafter, solid supports were adapted for the construction of small molecules. In seminal work unrecognized for its significance at the time, Leznoff⁹¹ demonstrated that reactions need not be performed in homogeneous media, as was previously thought, and that successful reactions may be carried out even if one of the substrates is insoluble in the reaction medium. In addition, Leznoff advanced the so-called "fishhook principle", by which the monoprotection of difunctional compounds **89** with **88** forms **90** (Scheme 26). Diprotection never occurs because the monoprotected derivative **90** is "fished out" of the reaction mixture by the polymer, and starting material **89** is washed away. In solution, this procedure usually results in mixtures. In this manner, Leznoff prepared conjugated aldehydes **92** (Scheme 26) which are useful intermediates for carotenoid synthesis.⁹² The symmetrical dialdehyde 2,7-dimethyl-2,4,6-octatrien-1,7-dial (**89**) is reacted with resin **88** to give the polymer-bound, monoprotected **90**. Wittig reaction yields polymer-bound polyenes **91**, which, upon acidic cleavage produce the conjugated aldehydes **92**.

Scheme 26

Patchornik discovered a fundamental concept in SPOS, which he called the "hyperentropic efficiency",⁹³ but which is more commonly referred to as the infinite dilution effect or the artificial dilution effect. Since the polymer itself is relatively rigid, polymer-bound substrates are effectively isolated from each other. In practical terms, this means that the polymer-bound molecules effectively behave as though their concentration is very low even though it might be quite high.⁹⁴ Patchornik demonstrated this principle by monoacylating polymer-bound esters bearing multiple α -hydrogen atoms (**Scheme**

27). In solution, self-condensation and deacylation are competing reactions. Patchornik showed that immobilization of the compound to be acylated on solid support to give **93** leads exclusively to the monoacylated product (**96**) upon deprotonation, acylation and cleavage.

Scheme 27

Similarly, Rapoport⁹⁵ and Fréchet⁹⁶ used polymer supported techniques for the Dieckmann cyclization of mixed esters and the synthesis of oligosaccharides respectively.

Despite the efforts of Leznoff, Patchornik, Rapoport and Fréchet, the use of polymer supports for organic synthesis did not gain wide acceptance among organic chemists for several reasons. The amount of compound cleaved from the polymer is very small, and the high-field Fourier transform NMR spectrometers used today were not yet in existence, making the analysis of such small quantities prohibitively difficult. In addition, although the Merrifield method allowed the synthesis of vast numbers of compounds simultaneously, automation equipment did not exist to screen them.

With the advancement of bioassay and bioscreening technology, synthetic chemists were demanded to increase the rate of synthetic compound production. Combinatorial chemistry was the obvious choice for achieving this goal. and as a result, created vigorous renewed interest in SPOS. In 1992, Bunin and Ellman reported the first synthesis of a library of 1,4-benzodiazepine derivatives,⁹⁷ showing that combinatorial chemistry was not just the domain of peptide chemists. It was the first time polymer-supported chemistry had been used to synthesize a library of non-polymeric compounds, triggering a new era of activity in the preparation of large libraries of compounds, their purification, and analysis using robots, just as Merrifield had anticipated in 1963.⁸⁶

1.5.2 Advantages and Disadvantages of SPOS

Combinatorial chemistry has revolutionized the drug discovery process and SPOS has become the powerful tool which makes it run. The key advantages of SPOS are:

- Reactions can be driven to completion using excess reagents, thereby avoiding mixtures of the final products.⁹⁸
- Toxicity and strong odours can be avoided by attaching the culprit compound to polymer support.
- Impurities can be removed from intermediates during the course of the reaction sequence by filtration and washing procedures. Scavengers can be used to purify the reaction mixture by fishing out only the desired compound. Finally, procedures can

be designed such that only a fully formed desired product will be released from the polymer while impurities remain attached.⁹⁹

- The technique is amenable to automation.¹⁰⁰

However, there are a number of serious drawbacks to SPOS:

- High-yielding reaction sequences must be used since resin-bound intermediates cannot be purified and therefore resin-bound impurities are not tolerated. Currently, the standard for new reactions is greater than 80% purity.¹⁰¹
- Developing new reaction SPOS protocols is labor intensive because model systems must be studied and optimized in solution prior to optimization on solid support.
- A solid phase reaction requires two additional steps (loading and cleaving) compared with a solution reaction.
- The procedures for monitoring reactions on the resin are limited and can be prohibitively expensive. Some researchers believe that the advantages of solution reactions over SPOS are so great, that they have put their efforts towards making resins for purification purposes rather than for synthesis purposes.^{102,103}
- For the purposes of automation, extreme temperatures cannot be used.
- Very small quantities of compounds (usually less than 100 mg) are isolated. In view of the high sensitivity of bioassays, this is usually not a disadvantage.
- Solid supported reactions are frequently slower than their solution phase counterparts, although reaction kinetics on solid support are not yet fully understood.^{104,105}

1.5.3 Resins and Linkers in SPOS

There is a danger of taking a black-box approach with SPOS and to give insufficient attention to the polymer support. For an effective synthesis to occur, the resin must be chosen with the care with which a reagent is chosen. The ideal polymer support must be insoluble in the solvent being used, inert to the reagents used in the reaction sequence and allow the diffusion of reagents into its matrix.⁸⁷ The resin itself is composed of the polymer support and the linker. Although the variety of available polymer supports has increased greatly since Merrifield's time, most resin-related research is directed towards the construction of new linkers, so the choice of polymer is still fairly limited. The polymer support which Merrifield first used is still in use today. It consists of a polystyrene back bone cross-linked to varying degrees with DVB. The extent to which the resin is cross-linked has two ramifications: mechanical stability and diffusion of reagents. While highly cross-linked resins (8-16%) are robust, they are sufficiently rigid that diffusion of reagents is severely compromised. 1% cross-linked PS permits ready diffusion, but can be quite fragile and is therefore not a good choice for reactions involving high temperatures and organometallics.⁸⁶ The increase in mechanical stability of 2% cross-linked resins can be desirable for some reactions but these resins sacrifice some of their the ability to swell. For routine reactions, however, resins which are 1-2% cross-linked seem to be the resins of choice, with the majority of commercially available resins being 1% cross-linked.^{106,107} These resins are sufficiently robust, but allow greater diffusion of reagents.

In the interest of making resins more "solution-like", resulting in better mixing of reagents, a number of polystyrene/DVB-poly(ethylene glycol) graft copolymers (PEG-PS-DVB)¹⁰⁸ have been prepared. AG (97), NG (98) and TG (99) are all of this type and are structurally quite similar (**Scheme 28**), consisting of a DVB-PS core to which is grafted PEG chains bearing terminal linkers. AG (marketed by Argonaut Technologies) possesses a bifurcated PEG graft, which is designed to increase the loading capacity of the resin and it is marketed as a high-loading resin (the loading varies with the substrate).¹⁰⁶ Novasyn[®] (a TG resin) and NG are marketed by Novabiochem¹⁰⁷ and also are high loading resins, thus having the same advantages as AG. The highly flexible nature of the PEG chain results in the resin-bound compounds being subjected to a more "solution-like" environment, thus facilitating the transfer of solution reactions to solid support. Another benefit of the PEG graft resin is its suitability to gel-phase NMR techniques (**section 1.5.5**). PEG resins are particularly useful for syntheses involving polar solvents and for those in which the substrate needs to be distanced from the bulk of the polymer. These supports generally swell in a greater number of solvents and are compatible with polar solvents like MeOH and water, constituting an advantage when the small molecule must be released into aqueous media for screening.¹⁰⁹ On the other hand, the hydrophilicity of PEG-based resins renders them unsuitable for reactions involving moisture sensitive reagents like organometallic reagents and strong bases.¹¹⁰

X = functional group

Scheme 28

Another type of resin is the polyethylene glycol / dimethylacrylamide copolymer (PEGA) resin **100** (**Scheme 28**) developed by Meldal.¹¹¹ Originally developed for SPPS, PEGA resins are unrivaled in their swelling ability in a wide variety of solvents (e.g., THF, MeOH, CH₂Cl₂ and water) and are permeable to macromolecules up to 35 kD.¹⁰⁷ However, like the PEG copolymers, they are hydrophilic, precluding their use

for similar reactions, possess low mechanical stability and are expensive thus preventing wide use for routine SPOS.¹¹²

While each of these resins has its specific niche, until recently, PS-DVB was the only inexpensive choice for carrying out traditional organic chemistry on solid support. Recently, Janda and coworkers developed a new resin specifically designed with SPOS in mind.¹¹³ Their resin is a PS-based resin, but rather than using DVB as the cross-linker, they chose to use PTHF-based cross-linkers, which results in a resin whose interior resembles typical solvents for organic synthesis, e.g. THF, (**Scheme 29**).¹⁰⁴ Janda and coworkers have shown that this resin (marketed under the trade name *Janda/els*TM) swells considerably better than the PS-DVB analog, resulting in improved yields and purities of products.¹¹⁴ Currently, aminomethyl, chloromethyl, hydroxymethyl and Wang linkers to *Janda/els*TM are commercially available,¹¹⁵ and the trityl linker is being investigated.¹¹⁶

Scheme 29

Linkers for SPOS

While the variety of polymer supports available for SPOS has remained relatively unchanged, the same cannot be said for the number of linkers. A glance through one of the product catalogues of Novabiochem, Argonaut Technologies or Advanced Chemtech, brings the reader face-to-face with a vast choice of linkers. With such a large number of linkers being created so rapidly, it is not surprising that a formal classification system does not as yet exist. In the broadest terms, linkers may be classified as integral linkers or non-integral.¹¹² Integral linkers are defined as those in which part of the polymer support is incorporated into all or a portion of the linker. Some of the earliest linkers developed fall into this category (**Scheme 30**) and well-known examples include the

Merrifield⁸⁶ chloromethyl linker **101**, the Leznoff¹¹⁷ and Fréchet^{118,119} trityl linker **102** and the Pillai¹²⁰ *o*-nitro-(α -methoxy)bromobenzyl linker **103**.

Scheme 30

Merrifield's chloromethylated resin **101** has been extensively used not only for peptide synthesis, but also for SPOS since it is readily converted into resin bearing a variety of functional groups **104** (Scheme 31).^{98,121}

Scheme 31

The advantage of integral linkers is that they are part of the resin, they tend to be more robust and need not be synthesized. However, since these linkers are very short, the substrate is very closely bound to the resin, which gives rise to undesirable steric and

electronic effects emanating from the resin. In addition, their precise loading and functionalization may be difficult to control.¹¹²

Resins bearing integral linkers can be made by direct lithiation of the polystyrene backbone using *n*-BuLi / TMEDA, or by a two step bromination-lithiation procedure. The lithiated resin **106** (Scheme 32) thus generated is quenched with an appropriate electrophile, to give the final product **104**. The former results in *m*- and *p*-lithiation where the degree of functionalization is difficult to control. The latter is therefore the method of choice for accurate regiospecific functionalization, while the former finds use for the rapid preparation of resins in which the position of the functional group is unimportant.¹²²

Scheme 32

Non-integral linkers are those which are attached or grafted to the solid support. The attachment is achieved *via* ether, amide or carbon-carbon bonds. Popular examples of this type of linker (Scheme 33) include the Wang linker¹²¹ **107**, the Sasarin linker^{123,124} **108**, the amide derivative of the Leznoff trityl linker¹²⁵ **109** and the silyl linkers like **110**.¹²⁶

Scheme 33

One of the advantages of non-integral linkers is their provision of choice of preloading or direct loading of the substrate (Scheme 34). Preloading of the substrate onto the linker generally affords higher levels of loading but is more time consuming, since the product of the linker-substrate reaction must be purified prior to attachment to the resin. Direct loading is more time efficient but is not practical for an expensive substrate, since in such cases excess reagent must be used.¹¹²

Scheme 34

Alternatively, linkers may be classified according to cleavage strategy, of which there are three (**Scheme 35**):

- eq. **A**, where the molecule is attached to the linker using a handle; upon cleavage, the handle is cleaved from the linker and is present in the final product;
- eq. **B**, where the molecule is attached to the linker using a handle, however, upon cleavage, both the linker and the handle are present in the final product.
- eq. **C**, often referred to as a "traceless" linker, where the molecule is attached to the linker directly, and upon cleavage, the linker remains bound to the resin. The product therefore, bears no trace of its point of attachment.¹²⁷

L = linker, H = handle, S = substrate

Scheme 35

While the above classification gives some useful information about the nature of the linker, a more comprehensive scheme is based on the type of cleavage conditions. Linkers are divided into seven groups according to the cleavage protocol:¹¹² electrophilic, nucleophilic, photo-induced, metal-assisted, reductive, oxidative and cycloaddition or cycloreversion-based cleavages (**Scheme 36**).

EC = electrophilically cleaved, NC = nucleophilically cleaved, P = photocleavable, MC = metal-assisted cleavage, R = cleavage under reductive conditions, O = cleavage under oxidative conditions, C = cycloaddition and cycloreversion based cleavages

Scheme 36

1.5.4 The Use of Spacers

Spacers are often used to relieve steric effects caused by the proximity of the substrate to the resin core. PEG chains are popular since not only do they act as spacers, but they also make the resin more "solution-like". Tentagel™ is such a resin. Alternatively, alkyl chains may be used as spacers, as in the Kobayashi¹²⁸ modification of Merrifield resin 111 (Scheme 37).

Scheme 37

1.5.5 Analytical Tools for SPOS

A major problem with SPOS is the lack of analytical techniques for the structural elucidation of resin-bound compounds. In solution, TLC is a valuable tool for qualitative evaluation of reaction progress and is useful for the optimization of reactions. However, this technique cannot be applied to solid support. Traditionally, the molecule is cleaved from the solid support before analysis. This indirect procedure is time consuming, wastes expensive materials (resin) and may effect alteration of sensitive intermediates.¹²⁹ Due to the popularity of SPOS, considerable research into analysis techniques has been undertaken. Although still in its infancy, the development of analytical techniques such

as IR, gel-phase NMR, MAS-NMR and MALDI-MS constitute promising solutions to the problems.

IR Techniques for SPOS

The use of IR spectroscopy to analyze SPOS reactions in real-time seems to be the most promising surrogate for solution phase TLC.^{130,131} The obvious stipulation is that the substrate must possess a functional group with a distinctive band in the IR region.

One of the first techniques, to grind a small amount of resin with IR-grade KBr and to analyze the KBr disc by FTIR, results in very good quality spectra for DVB-PS but not PEG-PS-DVB resins.¹³² In addition, while the procedure does not result in destruction of the entire quantity of resin used in the reaction, the approximately 10 mg which is removed is lost.

DRIFTS is a method in which the resin beads are not mixed with any other substance. For this reason, no sample preparation is required, spectra can be recorded in fewer than 30 seconds and less than 10 mg of resin is required. Because the technique is non-destructive, theoretically, the resin beads used to collect the spectra may be returned to the reaction vessel.¹³³ In another attempt to reduce sample preparation time and to develop a non-destructive method, PA-FTIR was introduced. Lubell and coworkers¹³⁴ found that PA-FTIR gave them spectra of higher quality than were observed using standard FTIR techniques.

FTIR microscopy on single beads is a non-destructive method of monitoring reactions in real-time.¹³⁵ This method requires the use of only one bead (although for simplicity of handling, multiple beads can be used), but no KBr, therefore avoiding interference by moisture and CO₂, the necessity of multi-miligrams of resin (due to the dilution effect of KBr) and the sample preparation.¹³⁶ Good spectra have been recorded for DVB-PS and PEG-PS-DVB resins,¹³⁵⁻¹³⁷ and the method has been used to determine yields.¹³⁶ Single bead IR provides many of the useful properties of TLC. It is sensitive, quick, convenient and provides real-time analysis.¹³¹

Mass Spectrometry for Solid Supported Reactions

Mass spectrometry is considerably more sensitive than either IR or NMR spectroscopy. For this reason, it is a good candidate for real-time analysis of polymer-bound compounds.¹³⁸ MALDI-TOF-MS has been used to analyze the intermediates in the Rink resin-supported synthesis of a peptoid.^{138,139} Thus far, the technique seems to have been applied predominantly to protein synthesis on rink resin.¹³⁸⁻¹⁴⁰

NMR Techniques for Solid Supported Reactions

NMR spectroscopic techniques and SPOS have traditionally not mixed well because spectra run on resins suffer from line broadening. This problem most likely occurs for two reasons: the mixture is not homogenous, giving rise to distortions in the magnetic field; and polymer-bound molecules have restricted molecular motions.¹⁴¹

Gel-phase NMR spectroscopy involves swelling the resin in a suitable solvent in a standard NMR tube and running the spectrum under standard conditions. ^1H NMR spectra run this way usually suffer from line broadening, but ^{13}C spectra may be sufficiently resolved for structural assignments. Due to the low natural abundance of ^{13}C , these spectra demonstrate low sensitivity,¹⁴¹ a problem which was solved by the so-called "Fast ^{13}C NMR" analysis. This technique involves enriching the site of interest with ^{13}C atoms by using ^{13}C -enriched (commercially available) building blocks.¹⁴² Gel-phase NMR, while a useful tool, will clearly be surpassed by more sophisticated technology in the future.

It was unclear whether NMR techniques may be applicable to the analysis of molecules bound to any of the available polymer supports. A study¹⁴³ was carried out using the Varian Nano-NMRTM probe to compare the spectra of substances bound to various resins. Resins with long tethers, e.g., Tentagel resins, were found to give good spectra presumably because of the increased molecular motion permitted by the PEG tether. However, resins with tethers of intermediate length, e.g., Wang and Rink, give mediocre spectra, while the traditional DVB-PS resins, e.g., Merrifield, do not generate high-quality spectra since they have no tether and therefore have limited regional mobility.

The introduction of the Varian Nano-NMRTM probe makes high resolution ^1H NMR spectra of resin-bound molecules possible.¹⁴¹ This probe was successfully used to assign the NMR spectrum of **112** (Scheme 38).¹⁴⁴

Scheme 38

Furthermore, good quality spectra can be obtained without the use of Varian's specialized probe.¹⁴⁵ SR-MAS NMR techniques have been exploited by a number of groups to give high quality one-dimensional¹⁴⁶ and two-dimensional^{129,145,147} spectra, although perhaps not with as narrow linewidths as allowed by the Varian probe.

1.6 The DoM of Resin-Bound Substrates

1.6.1 Introduction

While the DoM reaction has been studied extensively in solution, its development on solid support has lagged until recently. The fact that polystyrene resins can be functionalized by aryl lithiation and quench with electrophiles^{117,122} suggests that the resin may be unsuitable for reactions involving strongly basic organometallic reagents. However, metalation of polystyrene takes place at elevated temperatures and is solvent

dependent,¹²² therefore the selective metalation of the aromatic resin-bound substrate may still be feasible under selective conditions.

1.6.2 DoM on Solid Support

The first DoM reaction on solid support was performed by Boehm and Showalter in 1996,¹⁴⁸ who reacted the silicon-linked **113** (DVB-PS resin) with *n*-BuLi followed by DMF quench to give **114** (Scheme 39). Further elaboration prior to cleavage from the resin afforded the 3-aryl benzofuran product **115**.

Scheme 39

In 1998, Begtrup and coworkers¹⁴⁹ generated a series of 2-substituted 1-hydroxyimidazoles *via* DoM of resin-bound 1-hydroxyimidazole. Lithiation of Merrifield resin-bound 1-hydroxyimidazole **116** (Scheme 40) with three equivalents of *n*-BuLi followed by reaction with a variety of electrophiles gave the 2-substituted imidazole

derivatives **117a-h**. The material was cleaved from the solid support using TFA at 100°C for 20 hours.

Entry	E ⁺	E	Purity (%)	Yield (%)
a	MeI	Me	93	92
b	PhCHO	PhCHOH	96	52
c	HCONMe ₂	CH(OH) ₂	97	81
d	C ₂ Cl ₆	Cl	97	93
e	CBr ₄	Br	95	77
f	Me ₂ S ₂	SMe	97	90
g	Ph ₂ S ₂	SPh	97	74
h	PhCOCl	COPh	100	58

Scheme 40

Very recently, Vedsø and coworkers synthesized a library of phthalides on solid support.¹⁵⁰ A series of aryl acid chlorides and aryl carboxylic acids were loaded onto aminomethyl DVB-PS resin. The result was a series of resin-bound benzamides **119** (**Scheme 41**) whose linker is also the DMG. Metalation using *n*-BuLi at 0°C and quenching with a variety of aldehydes and ketones afforded the alcohols **120**, which were cleaved from the solid support by thermolysis in toluene at 90°C to give the 84-member library of phthalides **121** in yields of 4-70% and purities greater than 90%.

entry	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷
A	H	Cl	H	H	Cl	H	-
B	H	Ph	H	H	Ph	H	-
C	H	NEt ₂	H	H	H	H	-
D	H	PhO	H	H	PhO	H	-
E	CF ₃	H	CF ₃	CF ₃	H	CF ₃	-
F	NO ₂	Cl	H	H	Cl	NO ₂	-
G	H	MeO	H	H	MeO	H	-
H	H	PhO	H	H	H	H	-
I	H	PhCH ₂ O	H	H	H	H	-
J	H		H	H		H	-
K	-	-	-	-	-	-	NMe ₂
L	-	-	-	-	-	-	NEt ₂

entry	X	R
a	Cl	<i>t</i> -Bu
b		Ph
c		CF ₃
d	OH	<i>O</i> - <i>i</i> -Pr
e		NEt ₂
f		<i>i</i> -Pr

Scheme 41

In a further demonstration of the superiority of the *Janda/Jel*TM aminomethyl resin, Janda synthesized a small (8-member) library of phthalides in significantly higher yields than those obtained on the corresponding DVB-PS aminomethyl resin.¹¹³ Benzoyl chloride was loaded onto the resin to give the resin-bound benzamide **122** (**Scheme 42**), which was metalated using *n*-BuLi in THF at 0°C and was quenched with a series of aldehydes to yield the corresponding alcohols **123a-h**. Cleavage from the resin to give the phthalides **124a-h** was effected by refluxing the resin in toluene for 16 hours.

Entry	Ar	yield (%)
a		73
b		79
c		72
d		66
e		77
f		81
g		72
h		78

Scheme 42

1.7 The Suzuki-Miyaura Cross Coupling Reaction on Solid Support

The solid-phase Suzuki-Miyaura cross coupling reaction may be carried out in two ways (**Scheme 43**). The resin bound Ar-LG **125** may be coupled with the

organometallic species Ar'-M **126** in solution under transition metal-catalyzed conditions to generate the resin-bound species **127**. Alternatively, the coupling partners could be reversed. The cross coupling of resin-bound Ar'-M **129** with Ar-LG **130** may be effected to give the resin-bound biaryl species **131**. Release of the respective biaryls **127** and **131** from solid support results in the formation of **128**.

Scheme 43

The Suzuki-Miyaura reaction is an ideal candidate for transfer to solid support. The reaction is mild, high yielding and tolerates a wide range of functional groups. In addition, the reaction is not moisture sensitive, a considerable benefit since resins tend to be somewhat hydrophilic. It is therefore not surprising that the Suzuki-Miyaura cross coupling reaction has been studied quite extensively on solid support. Some highlights of this area follow.

The first systematic study of the Suzuki-Miyaura cross coupling reaction on solid support was carried out by Frenette and Friesen,¹⁵¹ who demonstrated that polymer-

bound aryl bromides and iodides readily undergo transition metal catalyzed cross coupling with aryl boronic acids to give biaryl compounds in high yields. Almost concurrently, Backes and Ellman¹⁵² reported the solid-phase synthesis of substituted aryl acetic acid derivatives **134** (Scheme 44), which are an important class of cyclooxygenase inhibitors. The treatment of acylsulfonamide-linked **132** (DVB-PS resin) under standard Suzuki conditions forms the cross coupled product **133**. Activation of the acylsulfonamide by treatment with CH_2N_2 , followed by nucleophilic cleavage with NaOH or amine gives the the aryl acetic acid **134**.

Scheme 44

In 1996, Hallberg and coworkers¹⁵³ demonstrated that microwave irradiation, used to assist solution phase reactions,¹⁵⁴ may also be applied to solid support Suzuki-Miyaura cross coupling reactions to shorten reaction times. Thus the Rink amide (RAM) TG-

bound aryl bromides and aryl iodides **135** (Scheme 45) underwent cross coupling with greater than 99% conversion, in 3.8 minutes using irradiation of 45 Watts to give **136** after cleavage.

Scheme 45

Brown and Armstrong¹⁵⁵ demonstrated an elegant synthesis of tetrasubstituted ethylenes using the Suzuki – Miyaura cross coupling reaction (Scheme 46). Thus a variety of alkynes were diboronated in solution to give **138** which, when cross coupled with organohalides gave a mixture of the boronic ester **139** and the (undesired) tetrasubstituted ethylene **140**. Since only the former can undergo additional cross coupling, subjecting the mixture to Pd-catalyzed conditions with the resin bound aryl iodide **141** afforded product **142**. This approach, called a resin-capture strategy, is a

purification procedure in its own right, and was applied to the synthesis of the estrogen antagonist, Tamoxifen **143**.¹⁵⁶

Scheme 46

In 1998, Chamoin and coworkers reported preliminary findings on the solid-phase Suzuki-Miyaura cross coupling.¹⁵⁷ Aryl bromides were bound to Merrifield resin using the Leznoff acetal linker to generate the immobilized cross coupling partner **144** (Scheme 47). A variety of aryl and heteroaryl boronic acids were cross coupled to give the resin-

bound biaryl species **145**. Acidic cleavage afforded the biaryl aldehydes **146** in 45 to >95% yield.

Scheme 47

The Suzuki-Miyaura cross coupling reaction is now a well-established solid support process.¹⁵⁸ Biologically active molecules like 1,4-benzodiazepine-2,5-diones,¹⁵⁹ tropane derivatives,¹⁶⁰ 4-arylazetidins-2-ones,¹⁶¹ biphenyltetrazole derivatives¹⁶² and isoxazolinoisoquinoline heterocycles¹⁶³ have been synthesized on SS. The cross coupling of heteroaryl,¹⁵⁵ functionalized,¹⁶² sterically hindered,¹⁵⁷ electron rich¹⁶⁰ and electron deficient¹⁶⁴ partners has been carried out on solid support and proceed in good yields.

2.0 Results and Discussion

2.1 Proposal

This research concerns the development of a directed *ortho* metalation (DoM) protocol on solid support (SS), thus transferring the solution phase DoM reaction and establishing a connection between DoM and cross coupling in solid support chemistry. A valuable alternative to electrophilic aromatic substitution, the DoM reaction has not been well explored on solid support. Examples are limited to the metalation of a MOM protected phenol on PS-DVB resin with a silicon linker,¹⁴⁸ and the generation of a library of phthalides, both on PS-DVB resin with an aminomethyl linker,¹¹³ and on JandaJe/TM with an aminomethyl linker¹⁵⁰ Interestingly, all of these reactions are carried out at 0°C, a relatively high temperature for DoM reactions. The probable reason for elevating the reaction temperature is to improve the kinetics of the reaction, and to allow resin swelling, which results in the improved diffusion of reagents into the resin interior. Since various DMGs are incompatible with this high temperature (e.g., *O*-carbamates and amides), a protocol that allows the use of lower temperatures is expected to have greater generality.

Previous work in our laboratories^{157,165} has established Suzuki and Stille cross coupling reactions on SS and, in the former, a connection to solution phase DoM *via* use of *ortho*-DMG aryl boronic acids. However, extensive attempts to carry out DoM on SS using standard Merrifield resin were unsuccessful. Success has been achieved using trityl

chloride resin, which constitutes the basis of this thesis. Introductory discussion of resin choice, loading and stability will precede the Results and Discussion of our work.

2.2 Choice of Linker

In our study, two supports were used: a polystyrene based gel-type resin bearing a silicon linker (PS-DES resin), supplied to us by Argonaut Technologies, and the trityl chloride resin, which is a polystyrene resin 2% cross-linked with divinylbenzene bearing a trityl linker, purchased from Novabiochem.

In their capacity as protecting groups, silyl derivatives are versatile and are used for protection of alcohols, 1,2- and 1,3-diols, phenols, amines, carbonyl groups and carboxylic acids.^{166,167} They are inert to a range of chemical transformations and are easily removed with reagents like HF in pyridine.¹⁶⁸ These features make silicon groups an attractive possibility as a linker for SPOS. Silyl linkers are prepared by the lithiation of polystyrene followed by quenching with dialkylchlorosilanes to generate silyl chloride resins.^{122,169} Integral silicon linkers may be made by including arylsilane-containing styrene monomers in the suspension copolymerization process.¹⁷⁰

Resins bearing silane linkers have a number of desirable properties. They are stable to moisture and can therefore be stored; the progress of the resin loading can be monitored on the beads by observing the disappearance of the Si-H stretch (2000 - 2200 cm^{-1}) in the IR spectrum;¹⁶⁸ and they fall into the category of traceless linkers (*vide*

supra), which is desirable for some syntheses. With these aspects in mind, Porco and coworkers at Argonaut Technologies developed their PS-DES gel-type resin.^{168,171} This resin is versatile, and became commercially available, and thus was chosen as a potential solid support for our project.

The trityl protecting group is used for the protection of alcohols, amines, thiols and carboxyl groups and is therefore also a good choice for a linker. Polymer bound trityl alcohols have been prepared by metal – halogen exchange of an iodobenzene group of polystyrene followed by quench with benzophenone¹⁷² or by Friedel Crafts reaction of DVB cross-linked polystyrene with benzoyl chloride followed by treatment with a phenyl Grignard reagent.^{118,173} Fyles and Leznoff have described a procedure for generating trityl chloride resin¹¹⁷ **102** (Scheme 48), which involves direct lithiation of the polymer with butyllithium (BuLi) to form the lithiated polymer **106**, followed by quenching with benzophenone to generate the trityl alcohol. The resin-bound trityl alcohol **148** is then refluxed with acetyl chloride to produce the trityl chloride **102**.

Scheme 48

Once the substrate has been cleaved, trityl chloride resin can be regenerated (conversion of the resin-bound trityl alcohol to the chloride) by refluxing with acetyl chloride, and it has been found that purer products are obtained using this regenerated resin because with each iteration, reactive sites on the polymer are further consumed by alcohol to chloride exchange.¹⁷⁴

Trityl chloride resin is a versatile, commercially available resin, and can be used for the loading of alcohols, phenols, carboxylic acids and amines. Ganesan and coworkers demonstrated its utility for the preparation of substituted thiophenes and furans by direct lithiation (**Scheme 49**).¹⁷⁵ In addition, their experiments indicate that both the PS-DVB resin and its trityl linker are stable to *n*-BuLi and therefore potentially amenable to DoM. As a result of Ganesan's success with trityl chloride resin, we considered it as a good candidate for our project.

X	E ⁺	E	Yield (%)
O	DMF	CHO	68
O	CH ₃ C(O)NMe ₂	C(O)CH ₃	51
S	DMF	CHO	81
S	CH ₃ C(O)NMe ₂	C(O)CH ₃	75
S	MeI	Me	66
S	TMSBr	TMS	82

Scheme 49

2.3 Loading of the Resins

There are two procedures for loading the PS-DES resin **151** (Scheme 50).¹⁷⁶ The first method involves the formation of a highly moisture sensitive Si-Cl bond in resin-bound silyl chloride **152**. This compound must be filtered under argon in order to maintain its integrity and is then subjected to a 12 hour loading reaction to generate the loaded resin **153**. The cumbersome and time consuming nature of this method led Porco and coworkers to find a less difficult method. Their second method, which is much less time-consuming, is a one-pot reaction involving the use of Wilkinson's catalyst and NMP as the solvent to load resin **151** with the substrate to form the resin-bound substrate **154** (Scheme 51). NMP is essential for the reaction to proceed and may coordinatively

catalyze the reaction.^{171,177} We chose to use this method for our work. The loading of the DES linker was confirmed by observing the disappearance of the Si-H stretch in the IR spectrum. No numerical value was determined for the loading since this resin did not survive the stability trials (Section 2.4).

Scheme 50

Scheme 51

Alcohols and phenols were loaded onto trityl chloride resin using two equivalents of pyridine in THF (Scheme 52) following the procedure recommended by Novabiochem. The loading was poor (0.3 mmol / g resin) for a high loading resin, and these conditions were later modified (Section 2.5). The loading of the trityl chloride

resin was determined by measurement of the mass of material recovered from the cleavage reaction. The identity of the recovered material was confirmed by comparison with authentic samples by GC analysis.

Scheme 52

2.4 Stability Studies: Metal – Halogen Exchange Reactions

Prior to commencing model studies for PS-DES and TCR, it was necessary to determine whether the resin and linker would tolerate metalation conditions. Thus a series of lithium-halogen exchange reactions were performed with each of the loaded resins to determine their stability in the presence of BuLi.

In the case of the PS-DES resin, the desired products, after cleavage of **153** and **158**, were never detected. For the conditions depicted in **Scheme 53**, the results are ambiguous since it may be the formation of the chlorinated resin on its own, or in conjunction with the lithium – halogen exchange that is the problematic step. For the conditions given in **Scheme 54**, however, there is no question that the problem lies with the lithium – halogen exchange reaction. Although loading of resin and formation of **154** is established, no reaction occurs. The use of this resin was therefore discontinued.

Scheme 53

solvent	temp (°C)	product
THF	-78	SM
Et ₂ O	0	SM

Scheme 54

The results using the trityl chloride resin were more promising than those using the PS-DES resin. While the material cleaved from this resin constitutes a mixture of products **160** and **161** or **160**, **161** and **162**, the desired material was shown to be present by comparison with authentic samples by GC analysis (**Scheme 55**).

Base	E ⁺	E	Product
<i>n</i> -BuLi	CD ₃ OD	D	160 + 161
<i>t</i> -BuLi	DMF	CHO	160 + 161 + 162
<i>t</i> -BuLi	DMF	CHO	intractable mixture

Scheme 55

It was concluded that, while the polymer tolerated *n*-BuLi, *t*-BuLi was too strong a base and, since linkers are attached *via* direct lithiation of PS-DVB resins, it is reasonable to suppose that the *t*-BuLi was sufficiently strong to effect lithiation of the (already highly functionalized) polymer backbone. Although the reactions did not go to completion, presumably as a result of poor diffusion, clearly the resin tolerated metalation conditions. Therefore, we proceeded with a model solution phase study.

2.5 Trityl Chloride Resin: The Solution Phase Model Study

Carrying out a model solution phase study in preparation for new SPOS research has several advantages. Solution reactions can be followed by TLC, whereas solid supported reactions cannot, and the amount of material generated in a solid supported reaction is sufficiently small that full characterization of the material is generally

difficult. Furthermore, by studying a model system in solution, concerns such as alternate site metalation (see below) and stability of the handle/linker to the loading, metalation and cleavage conditions may be readily addressed.

For our initial studies, we chose 4-(hydroxymethyl)phenyl *N,N*-diethylcarbamate **155** (**Scheme 56**), possessing the most powerful DMG (OCONEt₂). The benzylic alcohol was chosen as the handle to attach the substrate to the linker, due to its decreased steric environment compared to that of the phenol.

The procedures for trityl protection recommended by Novabiochem were not effective for our system (**Scheme 56**, entry 1). Various literature procedures were attempted and optimum conditions for protection were found to be DBU / CH₂Cl₂ / rt / 48h (entry 4).

Entry	Conditions	Yld (%)	intractable mixture
1	1. py (2 equiv) / THF 60°C / 24 h 2. MeOH	30	✓
2	1. py (4 equiv) / THF 60°C / 24 h 2. MeOH	64	✓
3	1. DMAP / py 25°C / 15 h 2. MeOH	11	✓
4	1. DBU / CH ₂ Cl ₂ rt / 48 h 2. MeOH	88	×

Scheme 56

The Novabiochem conditions for trityl deprotection were also unsuitable for our chosen system, resulting in some oxidation of product to the benzaldehyde **165** (Scheme 57, entry 1). Indeed, the use of TFA without triisopropylsilane (TIS) resulted in the oxidation of the benzylic alcohol to benzaldehyde almost instantaneously, a result which requires further investigation. Optimal conditions were found to be 4.8 M HCl / THF / rt / 24 h (Entry 3).

Entry	Conditions	Yld (%)	intractable mixture	 165
1	1. TFA / TIS DCM / rt / 1h 2. H ₂ O	53	✓	✓
2	1. ZnBr ₂ (5 equiv) / CH ₂ Cl ₂ rt / 30 min 2. H ₂ O	35	✓	✓
3	1. HCl (2.4 M) / THF rt / 24 h 2. Na ₂ CO ₃	52	✗	✗
4	1. HCl (4.8 M) / THF rt / 24 h 2. Na ₂ CO ₃	>95	✗	✗

Scheme 57

With methods for protection (loading) and deprotection (cleavage) in hand, we turned our attention to solution phase DoM studies on the model system **164** (Scheme 58). Various electrophiles were found to undergo clean reactions to give products **166** in reasonable to high yields with no evidence products of benzylic metalation. Products were also found to be stable to the deprotection conditions.

* Over two steps: metalation and deprotection

Scheme 58

An anionic *ortho*-Fries rearrangement and trityl deprotection (**164** → **169**) was also carried out in solution (**Scheme 59**). However, the results are unsatisfactory and require further investigation. This reaction has not yet been carried out on solid support.

Scheme 59

2.6 Trityl Chloride Resin: DoM on Solid Support

Transfer of the reaction conditions determined for the solution phase model system **164** to SS resulted in product **167**, which was found to be about 50% contaminated with starting material (**Scheme 60**, entry 1) following cleavage from the resin and analysis by GC. Increasing the amount of *s*-BuLi improved the ratio of metalated to non-metalated product but, beyond five equivalents, the additional BuLi was found to be detrimental (lower product ratio) and attack on the carbamate was observed, resulting in phenol production (entries 2–4). Removal of TMEDA resulted in improved product ratios (entries 5, 6). Since neither increasing the amount of BuLi, nor increasing the length of metalation time led to significant improvement, we turned our attention to the question of resin swelling and diffusion of the reagents into the resin.

Changing the electrophile to the less sterically demanding MeI resulted in improved product ratios (entry 7). This observation may be expected since a small electrophile should penetrate the resin more easily than a large one.

The decreased product ratios observed with larger amounts of BuLi may be rationalized by inhibition of swelling due to the increased volume of hexanes. This conjecture is borne out by the improved product ratio observed upon increasing solvent volume to 30 mL / g of resin (entries 7, 8). The literature suggests that the kinetics (diffusion of reactants, polymer swelling) of solid support reactions require higher metalation temperatures. Specifically, there are three reports of metalation reactions carried out at 0°C.^{113,148,150} These conditions are limiting since many DMGs and functional groups are not compatible with BuLi at such temperatures. For our system **156**, carrying out the reaction at 0°C resulted in reduced product ratio (entry 9) and attack at the carbamate. We have, however, been able to obtain moderate to good results at -78°C (entries 7 and 8).

Entry	s-BuLi (equiv)	time (h)	mL THF / g resin	TMEDA	E ⁺	E	Purity (%) ¹	
							155	167
1	1.2	0.5	10	✓	I ₂	I	56	44
2	2.4	1	10	✓	I ₂	I	53	47
3	5	1	10	✓	I ₂	I	35	65
4	7	1	10	✓	I ₂	I	55	45 ³
5	5	1	20	✓	I ₂	I	32	68
6	5	1	20	x	I ₂	I	19	81
7	5	1	20	x	Mel	Me	11	89
8	5	1	30	x	Mel	Me	1	99
9	5	0.5	10	x	Mel	Me	80	20 ^{2,3}

¹ Relative peak areas by GC. ² Reaction carried out at 0°C. ³ Phenol observed.

Scheme 60

We have transferred six of the solution phase electrophile quench reactions to solid support with varying degrees of success (**Scheme 61**). The variability of product ratios with changing electrophiles may reflect diffusion kinetics (large electrophiles, e.g., I₂ are poorer than small ones, e.g., Cl₂) and may be a limitation of the PS-DVB support.

Scheme 61

2.7 The DoM Cross-Coupling Connection

Due to time restrictions, the DoM Suzuki – Miyaura cross coupling sequence of reactions has not been established on solid support. This sequence was first optimized in solution using 2-iodo-4-[(trityloxy)methyl]phenyl *N,N*-diethyl *O*-carbamate **171** (**Scheme 62**) as the aryl iodide coupling partner, (generated *via* DoM) and phenyl boronic acid as the aryl metal partner. The purification of the trityl protected cross coupled product was complicated by failed separation from the starting material. Therefore, the deprotection was carried out and subsequent purification afforded the pure product **172** in high yield.

Scheme 62

2.8 Future Work

Attempts to improve purities and to transfer the other electrophiles (D and PhS) used in the model study are ongoing while this thesis is written. In addition, the Suzuki-Miyaura cross coupling of 2-iodo-4-[(trityloxy)methyl]phenyl *N,N*-diethyl *O*-carbamate with phenyl boronic acid in solution is being investigated on the resin-bound substrate 173 (Scheme 63).

Scheme 63

2.9 Conclusions

For the PS-DES resin, the metal – halogen exchange reactions (**Schemes 53** and **54**, Section 2.4) had failed. Since these reactions are sensitive to water, the failure may be due to water, which is incorporated into the folds of the polymer, due to its relatively hydrophilic nature (PEG cross-linkers). As the polymer is allowed to swell, the water is released into the reaction mixture where it can form hydroxides. The Si-O bond is sensitive to these hydroxides, so the potential for cleavage of the product is high.

The trityl chloride resin proved to be well suited to SS DoM chemistry on **156** (**Scheme 61**). For smaller electrophiles, good purities were obtained and improvement of the poor purities of the larger electrophiles may be possible in the future. The commercial availability in the near future of the *Janda/Jel*TM trityl resin,¹¹⁶ with its improved swelling properties relative to the PS-DVB based resins, encourages future DoM chemistry on SS.

The work described in the Results and Discussion fills an important niche in solid support chemistry. Until this time, DoM reactions on SS have not been carried out at -78°C , rather they have been carried out at the higher temperatures of -50°C and 0°C . Such temperatures are incompatible with some DMGs (e.g., OCONR_2 , etc...) and with some electrophiles. We have demonstrated that high temperatures are unnecessary for solid support DoM reactions, and our protocol, which permits metalation at -78°C , is

more general and should therefore be useful for synthesizing a wider variety of molecules on solid support. Our work has incorporated a range of electrophiles and in particular, we have generated an iodinated species, which provides a connection with cross-coupling chemistry as well as Heck and Sonogashira reactions. We anticipate this work to be the foundation for future SS DoM research in our laboratories, and to establish a protocol with which solution DoM reactions (using a myriad of DMGs) may be rapidly transferred to SS.

3.0 Experimental Section

3.1 General Procedures

Melting points were determined on a Fisher-Johns melting point apparatus. IR spectra were recorded on a BOMEM MB-100 infrared spectrometer as thin films or in KBr pellet form. ^1H and ^{13}C spectra were recorded on a Brüker AV-300 or AV-400 instrument with tetramethylsilane and chloroform- d_1 respectively as the internal standard. Chemical shifts are tabulated in the order: chemical shift, multiplicity, number of protons, coupling constant and assignment. Low-resolution mass spectra were determined on a Micromass VG Quattro Triple Quadrupole Mass Spectrometer by Mr. Tom Hunter by electron impact (EI) unless otherwise stated. High-resolution mass spectra on a Kratos Mass Spectrometer by Dr. C. W. Kazakoff or on a Micromass 70-250S Double Focusing Mass Spectrometer by Dr. Alex Young.

All dry solvents were purified according to Perrin.¹⁷⁸ THF was freshly distilled from sodium benzophenone ketyl under nitrogen. *n*-BuLi, *s*-BuLi and *t*-BuLi were purchased from the Aldrich Chemical Company as solutions in cyclohexane. All butyllithiums were stored in resealable containers and were titrated periodically against *s*-BuOH.¹⁷⁹ Diisopropyl amine was distilled from CaH_2 and stored under argon. LDA was freshly prepared prior to use by the dropwise addition of *n*-BuLi (1 equiv) to diisopropyl amine (1 equiv) in THF at 0°C followed by stirring for 20 minutes. All

chemicals were purchased from the Aldrich Chemical Company. Trityl chloride resin was purchased from Novabiochem and was stored in a dessicator.

All reactions were performed in flame-dried glassware under dry argon, using syringe-septum cap techniques. The -78°C temperature designated is approximate as achieved by a dry ice-acetone bath. The phrase "standard workup" refers to the following: the reaction mixture is quenched with a saturated aqueous solution of NH_4Cl , followed by extraction with CH_2Cl_2 , Et_2O or EtOAc . The combined organic layer is washed with H_2O and brine, dried over Na_2SO_4 and the solvent is removed *in vacuo* to afford the crude product. Where I_2 is used as the electrophile, standard workup also includes washing the combined organic layer with a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$. Flash column chromatography was carried out using EM Science silica gel 60, particle size 0.040-0.063 mm (230-400 mesh ASTM) purchased from Fisher Scientific with EtOAc : hexane as eluent unless otherwise specified. Analytical TLC was performed using Merck precoated silica gel 60 F-254 sheets.

General Procedure A: Metalation of 4-[(trityloxy)methyl] phenyl *N, N*-diethyl *O*-carbamates.

To a solution of 4-[(trityloxy)methyl] phenyl *N, N*-diethyl *O*-carbamate (465.6 mg, 1 mmol) and TMEDA (0.18 mL, 1.2 mmol) in dry THF at -78°C was added *s*-BuLi (0.88 mL, 1.2 mmol) dropwise. Following a 30 min metalation period, the appropriate electrophile was added by syringe and the solution was allowed to warm slowly to rt.

Standard workup followed by flash chromatography and recrystallization afforded the pure products.

General Procedure B: Deprotection of trityl protected benzyl alcohols.

To a solution of trityl protected alcohol (465.6 mg, 1 mmol) in THF (10 mL) was added aq 40% HCl (3.3 mL). The reaction mixture was stirred for 24 h at rt, cold H₂O was added, and the whole was stirred for another 5 min. A saturated solution of Na₂CO₃ was added dropwise to the resulting mixture until the evolution of gas ceased and the pH of the aqueous layer was neutral. Standard workup followed by flash chromatography and recrystallization afforded the pure products.

General Procedure C: Loading of trityl chloride resin.

To a suspension of trityl chloride resin in CH₂Cl₂ (8 mL / g resin) was added a solution of the substrate alcohol (3 equiv) in CH₂Cl₂ (2 mL / g resin). The mixture was cooled in an ice bath, and DBU (3.5 equiv) was added. The mixture was stirred for 48 h at rt and then excess methanol (HPLC grade) was added and stirring was continued for 1 h. The resin was subjected to filtration and was washed with CH₂Cl₂ (10 mL x5 / g resin), THF (10 mL x5 / g resin) and MeOH (10 mL x5 / g resin). The resin was dried *in vacuo* over KOH pellets overnight.

General Procedure D: Cleavage of trityl chloride resin.

To a suspension of resin in THF (10 mL / g resin) was added a 4.8 M aq solution of HCl (1 mL / 3 mL THF). The suspension was stirred for 24 h and then excess distilled water

(5 mL) was added dropwise. The resin was subjected to filtration and was washed with THF (10 ml x5 / g resin) and MeOH (10 ml x5 / g resin). To the filtrate was added a saturated solution of Na₂CO₃ dropwise until the solution was neutral to pH paper. Standard workup afforded the crude products.

3.2 Experimental Procedures

4-formylphenyl *N,N*-diethyl *O*-carbamate (174)

A mixture of *p*-hydroxybenzaldehyde (22g, 0.18 mol), K₂CO₃ (75 g, 0.541 mol) and Et₂NCOCl (69 mL, 0.541 mol) in MeCN (250 mL) was stirred for 24 h at reflux. The solvent was removed in *vacuo* and a standard workup was performed. The resulting orange oil was purified by distillation to give **174** (35 mg, 87%) as a clear, colourless oil, bp 134°C (0.24 mmHg). IR (film) $\nu_{\max}$ 2975, 2826, 1719, 1700, 1416 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS) δ = 9.97 (s, 1H, CHO), 7.87 (d, *J*=9.0, 2H, ArH), 7.29 (d, *J*=9.0, 2H, ArH), 3.48-3.38 (m, 4H, N(CH₂CH₃)₂), 1.28-1.20 (m, 6H, N(CH₂CH₃)₂) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 191.0, 156.4, 153.2, 133.3, 131.0, 122.2, 42.4, 42.1, 14.2, 13.2 ppm; LRMS (EI) *m/z* (rel intensity) 222(*M*+1, 7), 121 (24), 100(100), 72(79). HRMS calc for C₁₂H₁₅NO₃: 221.1052. Found: 221.1056.

4-(hydroxymethyl)phenyl *N,N*-diethyl *O*-carbamate (155)

To a solution of **174** (13g, 59 mmol) in EtOH (100 mL) at 0°C in an open vessel was added slowly NaBH₄ (6g, 177 mmol) and the reaction mixture was stirred until the disappearance of starting material (TLC). A satd aqueous solution of

NH₄Cl was added dropwise until the evolution of gas ceased. Standard workup gave **155** (11.9 g, 93%) as colourless crystals, mp 62-63°C (hexanes). IR (film) $\nu_{\max}$ 3400, 2985, 1713, 1425, 1208, 1042, 754 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 7.32 (d, J=8.2, 2H, C(2)**H**), 7.08 (d, J=8.2, 2H, C(3)**H**), 4.62 (s, 2H, CH₂OH), 3.45-3.37 (m, 4H, N(CH₂CH₃)₂), 2.15 (brs, 1H, OH), 1.25-1.12 (m, 6H, N(CH₂CH₃)₂) ppm; ¹³C NMR (75.5 MHz) δ = 154.2, 150.2, 138.0, 127.4, 121.3, 63.8, 42.0, 41.6, 13.9, 13.1 ppm; LRMS (CI) m/z (rel intensity) 224 (M+1, 7), 100(100), 72(55); HRMS calc for C₁₂H₁₇NO₃: 223.1208. Found: 223.1200.

4-[(trityloxy)methyl] phenyl *N,N*-diethyl *O*-carbamate

To a solution of **155** (30 g, 0.134 mol) and triphenylmethyl chloride (45 g, 0.161 mol) in dry CH₂Cl₂ (200 mL) was added DBU (30 mL, 0.188 mol). The reaction mixture was stirred for 48 h at rt and subjected to standard workup, substituting cold H₂O for satd aqueous NH₄Cl, followed by purification by flash column chromatography (4:1 hexanes:EtOAc) to give **164** (49 g, 78%) as colourless needles, mp 101-102°C (hexanes). ¹H NMR (300 MHz, CDCl₃) δ = 7.52 (d, J=7.2, 6H, Ar**H**), 7.49-7.21 (m, 11H, Ar**H**), 7.10 (d, J=8.5, 2H, Ar**H**), 4.14 (s, 2H, CH₂OTr), 3.42-3.40 (m, 4H, N(CH₂CH₃)₂), 1.24-1.21 (m, 6H, N(CH₂CH₃)₂) ppm; ¹³C NMR (75.5 MHz) δ = 153.8, 150.3, 143.7, 135.5, 128.3, 127.5, 126.7, 121.2, 86.7, 65.0, 41.9, 13.9, 13.1 ppm; LRMS (ammonia CI) m/z (rel intensity) 466 (M+1, 0.09), 244(23), 243(100), 224(62), 100(6). HRMS calcd for C₃₁H₃₁NO₃: 465.2304. Found: 465.2278.

2-(1,1,1-trimethylsilyl)-4-[(trityloxy)methyl]phenyl *N,N*-diethyl *O*-carbamate (175)

According to general procedure A, solution of **164** (466 mg, 1 mmol), TMEDA (0.18 mL, 1.2 mmol) in THF (10 mL) at -78°C was treated sequentially with *s*-BuLi (0.88 mL, 1.37 M, 1.2 mmol) and TMSCl (0.15 mL, 1.2 mmol). Standard workup followed by flash column chromatography (9:1 hexanes:EtOAc) afforded **175** (376 mg, 70%) as colourless crystals, mp $140\text{--}142^{\circ}\text{C}$ (hexanes). IR (film) ν_{max} 2979, 2252, 1719, 1607, 1469, 1199, 1080, 911, 723, 636 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.53–7.43 (m, 8H, ArH), 7.32–7.19 (m, 9H, ArH), 7.04 (d, $J=9.02$, 1H, 6-ArH), 4.17 (s, 2H, CH_2OTr), 3.43 (dq, $J=33.67$, 7.1, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.22 (dt, $J=22.52$, 7.1, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 0.29 (s, 9H, $\text{Si}(\text{CH}_3)_3$) ppm; ^{13}C NMR (100 MHz) δ = 155.6, 154.7, 144.3, 135.5, 131.3, 129.3, 128.9, 128, 127.2, 122.2, 87.1, 65.5, 42.1, 41.7, 14.4, 13.5, -0.7 ppm; LRMS (CI) m/z (rel. intensity) 538($M+1$, 15), 296(47), 243(100), 199(51), 167(56), 129(69), 111(79). HRMS calcd for $\text{C}_{33}\text{H}_{36}\text{NO}_3\text{Si}$: 522.2464. Found: 522.2450; Anal. calcd for $\text{C}_{33}\text{H}_{36}\text{NO}_3\text{Si}$: C, 75.49; H, 7.31; N, 2.60; found: C, 76.65; H, 7.28; N, 2.50.

According to general procedure A, solution of **164** (466 mg, 1 mmol), TMEDA (0.18 mL, 1.2 mmol) in THF (10 mL) at -78°C was treated sequentially with *s*-BuLi (0.88 mL, 1.37 M, 1.2 mmol) and I_2 (305 mg, 1.2 mmol). Standard workup followed by flash column chromatography (9:1 hexanes:EtOAc) afforded **171** (473 mg, 80%) as a pale yellow powder, mp $137\text{--}138^{\circ}\text{C}$ (hexanes). IR (film) ν_{max} 3021, 2982, 1720, 1411, 1218, 1147, 1076, 703 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.85 (d, $J=1.19$, 1H, 3-ArH), 7.59–7.55 (m, 6H, ArH), 7.44–7.28 (m, 10H, ArH), 7.21 (d, $J=8.29$, 1H, 6-ArH), 4.20 (s, 2H, CH_2OTr), 3.52 (dq, $J=47.61$, 7.05, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.34 (dt, $J=37.71$, 7.05, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 153.2, 150.9, 144, 138.1, 137.5, 128.8, 128.1, 127.3, 123.1, 90.8, 87.3, 64.7, 42.5, 42.2, 14.4, 13.5 ppm; LRMS (isobutane CI) m/z (rel intensity) 592($\text{M}+1$, 2), 249(100), 243(32), 167(19). HRMS calcd for $\text{C}_{31}\text{H}_{30}\text{INO}_3$: 592.1349. Found: 592.1353; Anal. calcd for $\text{C}_{31}\text{H}_{30}\text{INO}_3$: C, 62.95; H, 5.11; N, 2.37; found: C, 63.01; H, 4.97; N, 2.37.

According to general procedure A, solution of **164** (466 mg, 1 mmol), TMEDA (0.18 mL, 1.2 mmol) in THF (10 mL) at -78°C was treated sequentially with *s*-BuLi (0.88 mL, 1.37 M, 1.2 mmol) and CD_3OD (0.05 mL, 1.2 mmol). Standard workup afforded **176** (373 mg, 77%), as colourless crystals, mp $115\text{--}116^{\circ}\text{C}$ (hexanes). IR (film) ν_{max} 2976,

1720, 1418, 1269, 1205, 1154, 703 cm^{-1} ; ^2H NMR (400 MHz, CDCl_3) δ = 7.13 (s, 1H); ^1H NMR (400 MHz, CDCl_3) δ = 7.52-7.49 (m, 6H, ArH), 7.38-7.22 (m, 11H, ArH), 7.09 (d, J =9.0, 1H, 6-ArH), 4.14 (s, 2H, CH_2OTr), 3.45-3.38 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.27-1.19 (m, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 154.4, 150.6, 144.2, 135.9, 128.8, 128.0, 127.9, 127.1, 121.7, 121.4, 87.1, 65.4, 42.3, 42.0, 14.4, 13.5 ppm; LRMS (CI) m/z (rel intensity) 467($M+1$, 8), 244(24), 243(66), 225(100). HRMS calcd for $\text{C}_{31}\text{H}_{30}\text{DNO}_3$: 467.2445. Found: 467.2440. d_1 > 95% by MS and NMR analysis.

2-chloro-4-[(trityloxy)methyl]phenyl *N, N*-diethyl *O*-carbamate (177)

According to general procedure A, solution of **164** (466 mg, 1 mmol), TMEDA (0.18 mL, 1.2 mmol) in THF (10 mL) at -78°C was treated sequentially with *s*-BuLi (0.88 mL, 1.37 M, 1.2 mmol) and C_2Cl_6 (284 mg, 1.2 mmol). Standard workup followed by flash column chromatography (8.5:1.5 hexanes:EtOAc) afforded **177** (405 mg, 81%) as colourless crystals, mp $122\text{--}123^\circ\text{C}$ (hexanes). IR (film) ν_{max} 3036, 2978, 1725, 1415, 1239, 1147, 1056, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.50-7.44 (m, 11H, ArH), 7.33-7.23 (m, 10H, ArH), 7.17 (d, J =8.29, 1H, 6-ArH), 4.13 (s, 2H, CH_2OTr), 3.44 (dq, J =36.97, 6.96, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.26 (dt, J =33.89, 6.9, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 153.4, 146.7, 137.7, 128.8, 127.3, 127.1, 126.1, 124.0, 87.3, 64.9, 42.5, 42.2, 14.3, 13.5 ppm; LRMS (CI) m/z (rel. intensity) 500($M+1$, 12), 258(51), 243(100), 167(33), 100(15); Anal. calcd for $\text{C}_{31}\text{H}_{30}\text{ClINO}_3$: C, 74.46; H, 6.05; N, 2.80; found: C, 74.78; H, 6.32; N, 2.77.

According to general procedure A, solution of **164** (466 mg, 1 mmol), TMEDA (0.18 mL, 1.2 mmol) in THF (10 mL) at -78°C was treated sequentially with *s*-BuLi (0.88 mL, 1.37 M, 1.2 mmol) and ClCONEt₂ (0.15 mL, 1.2 mmol). Standard workup followed by flash column chromatography (3:2 hexanes:EtOAc) afforded **178** (459 mg, 81%) as colourless crystals, mp $138\text{--}139^{\circ}\text{C}$ (hexanes - CH₂Cl₂). IR (film) ν_{max} 2976, 1637, 1418, 1154, 1076, 703 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 7.50–7.17 (m, 18H, ArH), 4.14 (s, 2H, CH₂OTr), 3.40–3.35 (m, 8H, N(CH₂CH₃)₂ x2), 1.12–1.06 (m, 12H, N(CH₂CH₃)₂ x2) ppm; ¹³C NMR (100 MHz) δ = 167.7, 153.6, 146.5, 143.9, 136.1, 130.5, 128.6, 128.2, 127.9, 127.1, 125.2, 123.1, 87.1, 65.1, 42.8, 42.2, 42.0, 38.7, 14.2, 13.9, 13.4, 12.7 ppm; LRMS (EI) *m/z* (rel. intensity) 564(M, 1), 563(M-1, 2), 243(46), 165(56), 100(100). HRMS calcd for C₃₆H₄₀N₂O₄: 564.2988. Found: 564.2978; Anal. calcd for C₃₆H₄₀N₂O₄: C, 76.57; H, 7.14; N, 4.96; found: C, 76.59; H, 7.14; N, 5.00.

According to general procedure A, solution of **164** (466 mg, 1 mmol), TMEDA (0.18 mL, 1.2 mmol) in THF (10 mL) at -78°C was treated sequentially with *s*-BuLi (0.84 mL, 1.43 M, 1.2 mmol) and BrCH₂CH₂Br (0.1 mL, 1.2 mmol). Standard workup followed by flash column chromatography (9:1 hexanes:EtOAc) afforded **179** (420 mg, 77%) as colourless crystals, mp $132\text{--}133^{\circ}\text{C}$ (hexanes). IR (film)

$\nu_{\max}$ 2976, 1720, 1418, 1237, 1147, 1044, 703 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.58-7.16 (m, 18H, ArH), 4.13 (s, 2H, CH_2OTr), 3.50 (q, $J=6.8$, 2H, NCH_2CH_3), 3.39 (q, $J=6.8$, 2H, NCH_2CH_3), 1.30 (t, $J=6.9$, 3H, NCH_2CH_3), 1.21 (t, $J=6.9$, 3H, NCH_2CH_3) ppm; ^{13}C NMR (100 MHz) δ = 153.2, 147.8, 143.9, 137.9, 131.4, 128.7, 128.0, 127.2, 126.8, 123.9, 116.4, 87.2, 64.7, 42.4, 42.1, 14.3, 13.4 ppm; LRMS (EI) m/z (rel. intensity) 544(M, 5), 244(79), 243(100); HRMS calcd for $\text{C}_{31}\text{H}_{30}\text{BrNO}_3$: 543.1409. Found: 544.1489; Anal. calcd for $\text{C}_{31}\text{H}_{30}\text{BrNO}_3$: C, 68.38; H, 5.55; N, 2.57; found: C, 68.38; H, 5.56; N, 2.57.

To a solution of **164** (931 mg, 2 mmol) in THF (15 mL) was added LDA (prepared according to general procedure, 3.57 mL, 1.4 M, 5 mmol) and metalation was allowed to proceed for 2 h. The solution was warmed slowly to rt. Standard workup followed by flash column chromatography (7:3 hexanes:EtOAc) afforded **168** (633 mg, 68 %) as a yellow solid, mp 153-155°C (hexanes). ^1H NMR (400 MHz, CDCl_3) δ = 9.67 (brs, 1H, Ar-OH), 7.50-6.93 (m, 18H, ArH), 4.09 (s, 2H, CH_2OTr), 3.55-3.50 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.28-1.24 (m, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 171.4, 157.4, 144.1, 131.2, 129.2, 128.7, 127.9, 127.2, 126.3, 118.7, 117.7, 87.1, 65.4, 13.5 ppm; LRMS (EI) m/z (rel. intensity) 165(M^+ , 0.16), 243(100), 165(58). HRMS calcd for $\text{C}_{31}\text{H}_{31}\text{NO}_3$: 465.2304. Found: 465.2307. Anal. calcd $\text{C}_{31}\text{H}_{31}\text{NO}_3$: C, 79.97; H, 6.71; N, 3.01; found: C, 79.35; H, 6.75; N, 3.02.

2-(phenylsulfanyl)-4-((trityloxy)methyl)phenyl *N,N*-diethyl *O*-carbamate (180)

According to general procedure A, solution of **164** (931.2 mg, 2 mmol), TMEDA (0.36 mL, 2.4 mmol) in THF (20 mL) at -78°C was treated sequentially with *s*-BuLi (2.03 mL, 1.18 M, 2.4 mmol) and $(\text{PhS})_2$ (524 mg, 2.4 mmol). Standard workup followed by flash column chromatography (8.5:1.5 hexanes:EtOAc) afforded **180** (1.1 g, >95%) as a colourless oil. IR (film) ν_{max} 2976, 1727, 1418, 1218 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.42-7.18 (m, 23H, ArH), 4.06 (s, 2H, CH_2OTr), 3.37-3.32 (m, 4H, $(\text{NCH}_2\text{CH}_3)_2$), 1.20-1.14 (m, 6H, $(\text{NCH}_2\text{CH}_3)_2$)ppm; ^{13}C NMR (100 MHz) δ = 153.3, 148.9, 143.8, 136.8, 134.4, 131.1, 130.1, 129.0, 128.7, 128.4, 127.7, 126.9, 126.4, 123.0, 86.9, 64.8, 42.1, 41.7, 14.0, 13.2 ppm; LRMS (EI) m/z (rel. intensity) 573(M^+ , 0.63), 243(91), 165(95), 100(100). HRMS calcd for $\text{C}_{37}\text{H}_{35}\text{NO}_3\text{S}$: 573.2338. Found: 573.2342.

4-(hydroxymethyl)-2-(1,1,1-trimethylsilyl)phenyl *N,N*-diethyl *O*-carbamate (181)

According to general procedure B, to a solution of **175** (289 mg, 0.54 mmol) in THF (10.1 mL) was added 40% aq HCl solution (3.4 mL). Standard workup followed by flash column chromatography (3:2 hexanes:EtOAc) afforded **181** (116 mg, 73%) as a colourless solid, mp $92-94^{\circ}\text{C}$ (hexanes). IR (film) ν_{max} 3465, 2963, 1701, 1424, 1276, 1186, 838 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.41 (d, $J=2.2$, 1H, 3-ArH), 7.33 (dd, $J=8.29$, 2.2, 1H, 5-ArH), 7.00 (d, $J=8.29$, 1H, 6-ArH), 4.60 (s, 2H, CH_2OH), 3.43 (dq, $J=37.41$, 7.12, 4H, $(\text{NCH}_2\text{CH}_3)_2$), 2.33 (brs, 1H, OH, D_2O

exchangeable), 1.22 (dt, $J=26.19, 7.11$, 6H, $N(CH_2CH_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 155.9, 154.7, 137.4, 133.8, 131.8, 129.5, 122.5, 65.1, 42.1, 41.7, 14.3, 13.4, -0.7 ppm; LRMS (EI) m/z (rel. intensity) 280(M-15, 96), 100(100), 72(37). Anal. calcd for $C_{15}H_{25}NO_3Si$: C, 60.98; H, 8.53; N, 4.74; found: C, 61.38; H, 8.43; N, 4.66.

According to general procedure B, to a solution of **171** (473 mg, 0.8 mmol) in THF (15 mL) was added 40% aq HCl solution (5 mL). Standard workup followed by flash column chromatography (3:2 hexanes:EtOAc) afforded **182** (201 mg, 72%) as a clear, yellow oil. IR (film) ν_{max} 3433, 2976, 2937, 1714, 1424, 1212, 1154, 1044, 960 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, $J=1.98$, 1H, 3-ArH), 7.29 (dd, $J=8.2, 1.7$, 1H, 5-ArH), 7.13 (d, $J=8.2$, 1H, 6-ArH), 4.58 (s, 2H, CH_2OH), 3.46 (dq, $J=51.3, 7.12$, 4H, $N(CH_2CH_3)_2$), 2.00 (brs, 1H, OH, D_2O exchangeable), 1.27 (dt, $J=40.48, 7.12$, 6H, $N(CH_2CH_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 153.4, 151.2, 140.3, 137.5, 127.9, 123.3, 91, 63.8, 42.5, 42.3, 14.6, 13.5 ppm; LRMS (EI) m/z (rel. intensity) 350(M+1, 44), 223(100), 100(75). HRMS calculated for $C_{12}H_{16}INO_3$: 349.0175. Found: 349.0170.

4-hydroxymethyl-2-deuterophenyl *N,N*-diethyl *O*-carbamate (183)

According to general procedure B, to a solution of **176** (129 mg, 0.28 mmol) in THF (5.3 mL) was added aq 40% HCl solution (1.8 mL). Standard workup followed by flash chromatography (3:2 hexanes:EtOAc) afforded **183** (51.5 mg, 82%) as a colourless solid, mp 92-94°C (hexanes). IR (film) $\nu_{\max}$ 3427, 2976, 1720, 1469, 1424, 1276, 1205, 1154, cm^{-1} ; ^2H NMR (400 MHz, CDCl_3) δ = 7.12 (s, 1H); ^1H NMR (400 MHz, CDCl_3) δ = 7.31-7.27 (m, 2H, ArH), 7.07 (d, J =8.9, 1H, 6-ArH), 4.58 (s, 2H, CH_2OH), 3.44-3.36 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.33 (brs, 1H, OH, D_2O exchangeable), 1.25-1.18 (m, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 154.5, 150.9, 138.1, 128.0, 127.9, 121.9, 121.6, 64.7, 42.4, 42.1, 14.4, 13.5 ppm; LRMS (CI) m/z (rel. intensity) 225($M+1$, 100), 207(41), 100(38). HRMS calculated for $\text{C}_{12}\text{H}_{16}\text{DNO}_3$: 224.1271. Found: 224.1267.

4-hydroxymethyl-2-chlorophenyl *N,N*-diethyl *O*-carbamate (184)

According to general procedure B, to a solution of **177** (204.4 mg, 0.41 mmol) in THF (7.7 mL) was added 40% aq HCl solution (2.5 mL). Standard workup followed by flash column chromatography (3:2 hexanes:EtOAc) afforded **184** (94 mg, 88%) as a yellow oil. IR (film) $\nu_{\max}$ 3343, 2976, 1720, 1469, 1424, 1237, 1154, 1057, 960 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.40 (d, J =1.7, 1H, 3-ArH), 7.20 (dd, J =8.3, 1.7, 1H, 5-ArH), 7.16 (d, J =8.3, 1H, 6-ArH), 3.44 (dq, J =39.1, 7.0, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.08 (brs, 1H, OH, D_2O exchangeable), 1.25 (dt, J =35.2, 7.1, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz) δ 153.6, 146.6, 140.2, 128.4, 127.1, 125.9,

124.0, 63.7, 42.6, 42.2, 14.2, 13.4 ppm; LRMS (CI) m/z (rel. intensity). 260(M+1, ^{37}Cl , 36), 258(M+1, ^{35}Cl , 100), 100(65). HRMS calculated for $\text{C}_{12}\text{H}_{16}\text{ClNO}_3$: 257.0819. Found: 257.0825.

According to general procedure B, to a solution of **178** (522 mg, 0.92 mmol) in THF (17.3 mL) was added 40% aq HCl solution (5.8 mL). Standard workup followed by flash chromatography (EtOAc) afforded **185** (244 mg, 82%) as a clear, colourless oil. IR (film) ν_{max} 3414, 2976, 1720, 1624, 1424, 1231, 1154, 960 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.28-7.13 (m, 3H, ArH), 4.56(s, 2H, CH_2OH), 3.39-3.18 (m, 9H, CH_2OH , $\text{N}(\text{CH}_2\text{CH}_3)_2$, 1H is D_2O exchangeable), 1.21-1.01 (m, 12H, $\text{N}(\text{CH}_2\text{CH}_3)_2 \times 2$) ppm; ^{13}C NMR (100 MHz) δ = 168.1, 153.7, 146.2, 139.1, 130.0, 127.7, 124.6, 123.0, 63.5, 43.0, 42.3, 42.0, 38.9, 14.1, 13.9, 13.4, 12.7 ppm; LRMS (EI) m/z (rel. intensity) 322(M, 2), 321(M-1, 5), 250(10), 151(28), 105(100). HRMS calculated for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_4$: 322.1893. Found: 322.1897.

According to general procedure B, to a solution of **179** (499 mg, 0.92 mmol) in THF (17 mL) was added 40% aq HCl solution (6 mL). Standard workup followed by flash column chromatography (3:2 hexanes:EtOAc) afforded **186** (253 mg, 91%) as a clear, colourless oil. IR (film) ν_{max} 3440, 1719 cm^{-1} ; ^1H NMR (400

MHz, CDCl₃) δ = 7.53 (s, 1H, ArH), 7.53-7.12 (m, 2H, ArH), 4.51 (s, 2H, CH₂OH), 3.52-3.35 (m, 4H, N(CH₂CH₃)₂), 2.43 (brs, 1H, OH, D₂O exchangeable), 1.32-1.19 (m, 6H, N(CH₂CH₃)₂) ppm; ¹³C NMR (100 MHz) δ = 153.5, 147.9, 140.4, 131.4, 126.7, 124.0, 116.6, 63.8, 42.6, 42.2, 14.3, 13.4 ppm; LRMS (EI) m/z (rel. intensity). 260(M+1, ³⁷Cl, 36), 258(M+1, ³⁵Cl, 100), 100(65). HRMS calculated for C₁₂H₁₆BrNO₃: 301.0314. Found: 301.0314.

A mixture of **171** (592 mg, 1 mmol), PhB(OH)₂ (268 mg, 2.2 mmol) and K₃PO₄ (446 mg, 2.1 mmol) was purged under Ar for 20 minutes in a dry round bottom flask. Pd(PPh₃)₄ (61.2 mg, 5.3 mol %) was added and the mixture was purged for 10 min. DMF was added and the solution was purged for a further 15 min and then refluxed for 24 h. The reaction mixture was cooled, poured slowly into water, and the whole subjected to standard workup to yield a brown oil. According to general procedure B, to a solution of this brown oil (377.8 mg, 0.7 mmol) in THF (13.1 mL) was added 40% aq HCl solution (4.4 mL). Standard workup followed by flash column chromatography (1:1 hexanes:EtOAc) afforded **172** (231 mg, 77% over 2 steps) as a colourless oil. IR (film) $\nu_{\max}$ 3343, 2976, 1714, 1424, 1276, 1199, 761, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 7.39-7.25 (m, 7H, ArH), 7.16 (d, J=8.2, 1H, 6-ArH), 4.64(s, 2H, CH₂OH), 3.44-3.23 (m, 4H, N(CH₂CH₃)₂), 2.20 (s, 1H, OH, D₂O exchangeable), 1.27-1.00 (m, 6H, N(CH₂CH₃)₂) ppm; ¹³C NMR (100 MHz) δ = 154.3, 147.7, 138.7, 138.0, 135.1, 129.2, 129.1, 128.1, 127.3, 126.9, 123.3, 64.4, 42.1, 41.7,

13.9, 13.2 ppm; LRMS (CI) m/z (rel. intensity) 300($M+1$, 69), 298($M-1$, 27), 100(100).
 HRMS calculated for $C_{18}H_{21}NO_3$: 299.1521. Found: 299.1529.

4-(hydroxymethyl)-2-methylphenyl *N,N*-diethyl *O*-carbamate (187)

According to general procedure A, a solution of **164** (931.2 mg, 2 mmol), TMEDA (0.36 mL, 2.4 mmol) and THF (20 mL) at -78°C was treated sequentially with *s*-BuLi (2.03 mL, 1.18 M, 2.4 mmol) and MeI (0.63 mL, 10 mmol). Standard workup afforded the crude product. According to general procedure B, to a solution of this crude product (801.3 mg, 1.7 mmol) in THF (17 mL) was added 40% aq HCl solution (5.7 mL). Standard workup followed by flash chromatography (3:2 hexanes:EtOAc) afforded **187** (361 mg, 76% over 2 steps) as a bright yellow oil. IR (film) ν_{max} 3430, 1715 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 7.20 (brs, 1H, ArH), 7.16 (dd, $J=8.2, 1.8$, 2H, ArH), 7.04 (d, $J=8.2$, 1H, ArH), 4.61 (s, 2H, CH_2OH), 3.48-3.38 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.21 (s, 3H, Ar- CH_3), 1.74 (brs, 1H, OH, D_2O exchangeable), 1.29-1.19 (m, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 154.2, 149.4, 138.3, 130.5, 129.7, 125.4, 122.3, 64.7, 42.4, 42.0, 16.4, 14.4, 13.5 ppm; LRMS (EI) m/z (rel. intensity) 72(52), 100(100), 237(M^+ , 8). HRMS calcd for $C_{13}H_{19}NO_3$: 237.1365, Found: 237.1356.

According to general procedure B, to a solution of **180** (935.4 mg, 1.63 mmol) in THF (16. mL) was added 40% aq HCl solution (5.4 mL). Standard workup followed by flash chromatography (3:2 hexanes:EtOAc) afforded **188** (361 mg, 67%) as a clear, yellow oil. IR (film) $\nu_{\max}$ 3430, 1719 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , TMS) δ = 7.29-7.15 (m, 8H, ArH), 4.49 (s, 2H, CH_2OH), 3.34-3.28 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.34 (brs, 1H, OH, D_2O exchangeable), 1.17-1.12 (m, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz) δ = 153.6, 149.6, 139.5, 135.1, 131.4, 130.3, 129.1, 127.9, 127.8, 127.2, 126.8, 123.3, 121.6, 63.8, 42.3, 41.9, 14.1, 13.3 ppm; LRMS (EI) m/z (rel. intensity). 331(M^+ , 24), 100(100), 72(100). HRMS calculated for $\text{C}_{18}\text{H}_{21}\text{NO}_3\text{S}$: 331.1242. Found: 331.1245.

According to general procedure B, to a solution of **168** (433.1 mg, 0.93 mmol) in THF (10 mL) was added 40% aq HCl solution (3.3 mL). Standard workup followed by flash chromatography (EtOAc) afforded **169** (116 mg, 56%) as a pale yellow oil. IR (film) $\nu_{\max}$ 3200, 1597 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , TMS) δ = 7.29 – 7.26 (m, 2H, ArH), 6.97 – 6.95 (m, 1H, ArH), 4.60 (s, 2H, CH_2OH), 3.55 – 3.49 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.29 – 1.25 (m, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ = 171.4, 157.8, 131.3, 126.4, 118.7, 118.1, 64.9, 42.4, 13.6 ppm; LRMS (CI) m/z (rel. intensity). 224($\text{M}+1$,

100), 222(M-1, 15), 206(59). HRMS calculated for $C_{12}H_{17}NO_3$: 223.1208. Found:
223.1208.

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