The Development of Sulfamates as Latent Directed Metalation Groups.

Total Synthesis of Schumanniophytine.

Divergent Synthesis of Substituted Chromone 3- and 8-Carboxamides.

By

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A thesis submitted to the Department of Chemistry in conformity with the requirements for the degree of Doctor of Philosophy

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Kingston, Ontario, Canada

November, 2007

Abstract

N,N-Diethyl-*O*-sulfamate (OSO_2NEt_2) has been established as a new directed metalation group (DMG). Its similarity to the established *O*-carbamate DMG has prompted investigation into its potential as a partner in transition metal-catalyzed cross coupling reactions with aryl organometallics with the intention to develop a new route to contiguously substituted aromatics. Furthermore, aryne formation of *ortho*-magnesiated *O*-sulfamates at higher temperatures can be trapped with furan to afford cycloaddition products having substitution patterns difficult to prepare by similar methods.

Schumanniophytine is a structurally interesting alkaloid possessing anti-viral activity. Thus far, only a single synthesis has been reported which proceeds in poor yield and offers little opportunity for the synthesis of structurally diverse schumanniophytine derivatives. Herein we report the total synthesis of schumanniophytine by a directed *ortho* metalation (D*o*M) – cross coupling strategy using a key directed remote metalation (DreM) step. The synthesis proceeds in 10 steps with 24% overall yield, offering plenty of opportunity for structural variation.

Naturally abundant chromone derivatives contain an array of biological activities. The ability to prepare differentially substituted chromones in a rapid manner is of great interest in medicinal chemistry. Reported is a general and divergent synthesis of chromone carboxamides, from easily prepared 2-but-2-ynoyl aryl *O*-carbamates. The reaction proceeds by carbamoyl translocation and anionic Fries rearrangement followed by Michael addition of the initially generated cumulenolate for which evidence is provided. Further metalation and borylation reactions of the synthesized compounds allow the regioselective construction of polysubstituted chromones.

Acknowledgements

First and foremost, I would like thank Professor Victor Snieckus for his unrivalled leadership, enthusiasm, and kindness, providing students the opportunity to learn organic chemistry like a fine art. Thank you to Krista Voigt for being the rock of the group.

I am greatly indebted to Claire Milburn for providing me the inspiration to pursue organic chemistry at a pivotal stage of undergraduate studies. Thank you to Dr. Jérôme Blanchet for patiently getting me started in the lab. Dr. Alex Kalinin and Dr. Mark Reed, both outstanding chemists, played a huge role for providing invaluable discussions, encouragement, and humor in the lab. Thank you to Kevin and Megan for being such great friends and showing me how to appreciate the simpler things in life. I would like to thank everyone I've had the honor to work with over the years in the VS group and whom I share friendship with. Graduate and undergraduate students: Eric, Justin, Farhad, Manlio, Adam, Rosie, Rob, Xiongwei, Zhongdong, Katie, Chris, Yigang, Sunny, Wei, Patrick, Michelle, Sheldon, Paul, Jed, Tom, Jane, Bilge, Randy, Megan, Adrian, and Brandon. Post-docs and visiting students: Christian, Bert, Hideya, Thomas, Robert, Till, Marc, Heiko, Bärbel, Oleg, Glaucia, Pep, Anna, Roberto, Ashley, Christian, Kristina, Wolfgang, Ricarda, Isabel, and Claudia. Visiting Professors: Simon and Wole. I would also like to thank all my friends outside of the VS group whom I will forever share great memories and look forward to many more: Dave, George, Krista, Neil, Mike, Jocelyn, Jen, Ida, Mike, Nick, Danny, Craig, Peter, Scott, Jon, Guillermo, John, Greg and my best friend Erin. Lastly, I owe everything to my parents Kris and Diane for making this all possible.

The lone Retro-Cardinal

Statement of Originality

I (Todd Kristopher Macklin) hereby declare that I am the sole author of this thesis with exception of co-authorship by Victor Snieckus during preparation of manuscripts 1-3.

All of the experiments described in this thesis were preformed by the author under the supervision of Prof. V. Snieckus with exception to that described in the preface preceding each manuscript.

The following is a list of new compounds prepared using new methodology during the course of this work: **2.10b-k, 2.13a-t, 2.14b-c, 2.21a-i, 2.24a,b,e, 3.19, 3.21, 3.22, 3.27, 3.28a,b, 3.29, 3.30a,b, 3.31a,b, 3.32, 3.33, 3.35, 3.36, 3.37a,b, 3.38, 3.40, 4.9, 4.10a-k, 4.11a-m, 4.11i-D, 4.12a,c-j, 4.16, 4.17, 4.19H,D, 4.21.**

The following is a list of known compounds prepared using new methodology or existing methods during the course of this work: **2.10a,l,m, 2.22a,b, 2.24c,d,f-m, 3.1.**

To Kris and Diane

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List of Schemes

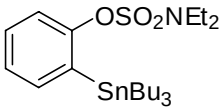
List of Abbreviations

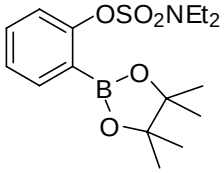
Ac	acetyl
acac	acetoacetate
Ar	aryl
aq	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
bs	broad singlet
BuLi	butyllithium
Bz	benzoyl
CFI	Canadian Foundation for Innovation
CI	chemical ionization
CIPE	complexed induced proximity effect
CNS	central nervous system
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
DABCy	*N,N'*-(ethane-1,2-diylidene)dicyclohexanamine
dba	dibenzylideneacetone
dd	doublet of doublets
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIPA	*N,N*-diisopropylamine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMG	directed metalation group
DreM	directed remote metalation
D*o*M	directed *ortho* metalation
dmpe	1,2-bis(dimethylphosphino)ethane
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppm	bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridyl
E or E^+	electrophile
EDG	electron donating group
equiv	equivalent
EI	electron impact
ESI	electrospray ionization
Et	ethyl
EVL	ethoxyvinyllithium
FT	fourier transform

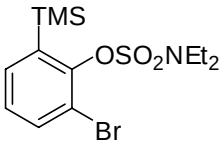
g	gram
GC	gas chromatography
h	hour
HIV	human immunodeficiency virus
HMPA	*N,N,N′,N′,N″,N″*-hexamethylphosphoric triamide
HOESY	heteronuclear Overhauser enhancement spectroscopy
HRMS	high resolution mass spectroscopy
HSV	herpes simplex virus
HTMP	2,2′,6,6′-tetramethylpiperidine
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
***i*-Pr**	isopropyl
IR	infrared
KCT	Kumada-Corriu-Tamao
KEM	kinetically enhanced mechanism
KIE	kinetic isotope effect
LAH	lithium aluminum hydride
LDA	lithium *N,N*-diisopropylamide
LG	leaving group
LHMDS	lithium bis(trimethylsilyl)amide
LICKOR	Lochmann-Schlosser superbase
LRMS	low resolution mass spectroscopy
LTMP	lithium 2,2′,6,6′-tetramethylpiperidide
m	multiplet
M	metal or molar
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mmol	millimole
MNDO	modified neglect of differential overlap
MOM	methoxymethyl
mp	melting point
MS	mass spectroscopy
Ms	mesyl
m/z	mass to charge ratio
NaHMDS	sodium bis(trimethylsilyl)amide
***n*-Bu**	*n*-butyl
NIS	*N*-iodosuccinimide
NHC	*N*-heterocyclic carbene
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NSERC	Natural Sciences and Engineering Research Council
Nu	nucleophile
Ph	phenyl
pin	2,3-dimethyl-2,3-butanediol

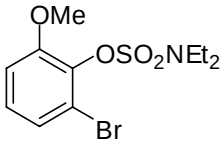
Piv	trimethylacetyl
PKS	polyketide synthase
PMDTA	*N,N,N′,N″,N″*-pentamethyldiethylenetriamine
ppm	parts per million
***n*-Pr**	*n*-propyl
q	quartet
qn	quintet
rt	room temperature
t	triplet
***t*-Bu**	*tert*-butyl
***t*-BuOK**	potassium *tert*-butoxide
td	triplet of doublets
TES	triethylsilyl
Tf	trifyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl
s	singlet
SAR	structure-activity relationship
***s*-Bu**	*sec*-butyl
SM	starting material
S_N2	nucleophilic substitution (bimolecular)
S_NAr	nucleophilic aromatic substitution
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
$S_{RN}1$	radical nucleophilic aromatic substitution (unimolecular)
sx	sextet
ν	wavenumber
XCoupl	cross coupling
Yld	yield

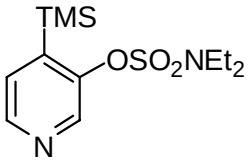
List of Experimental Procedures

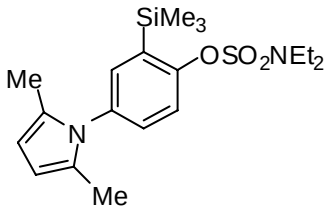


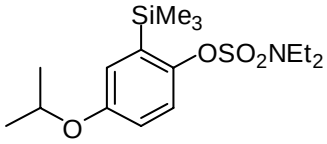


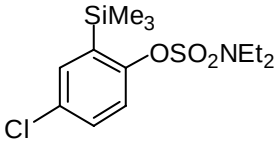


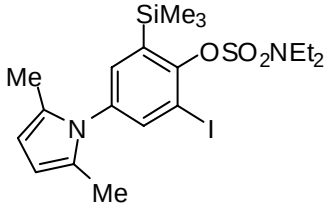


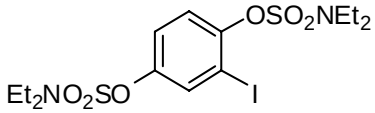


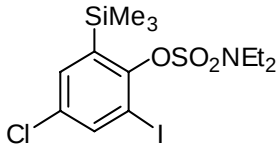


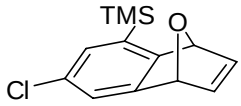


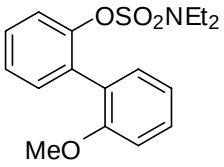


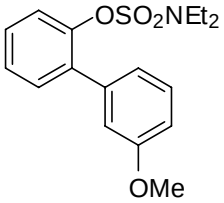


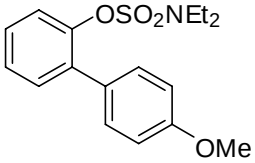


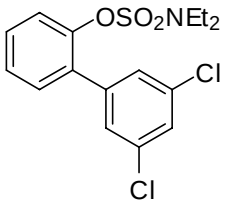


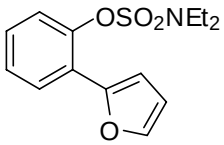


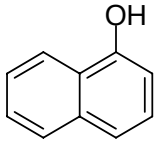


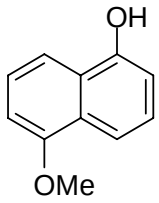


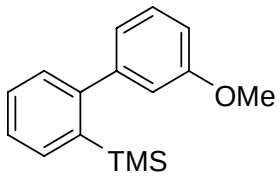


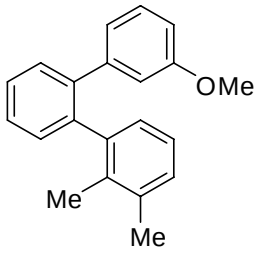


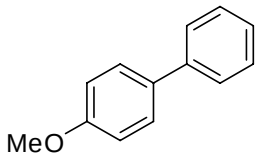


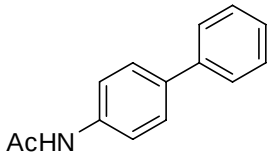


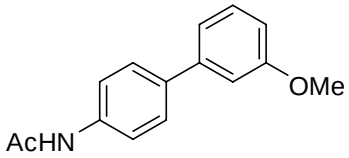


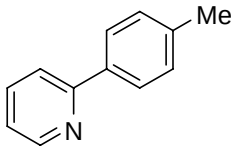


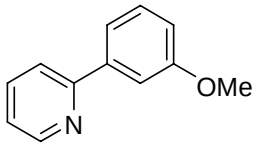


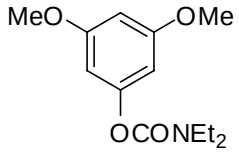


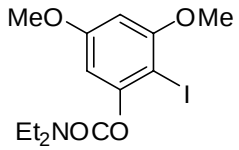


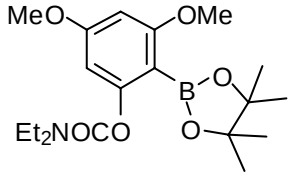


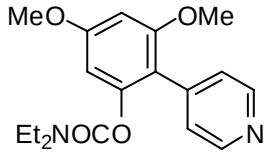


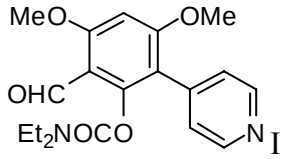


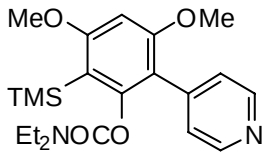


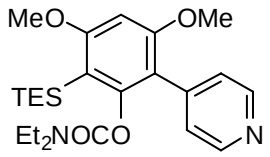


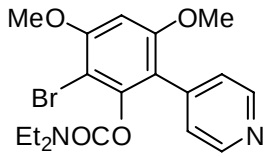


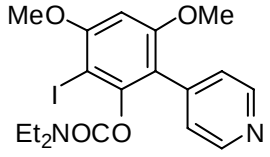


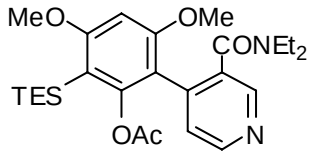


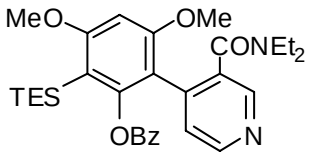


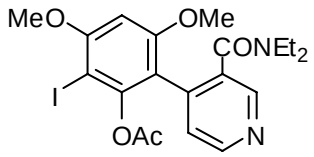


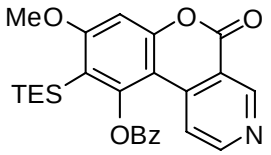


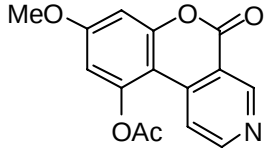


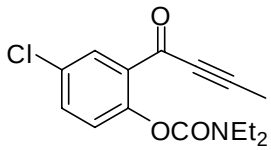


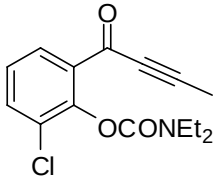


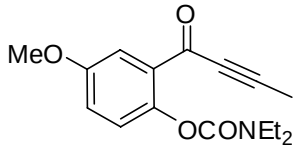


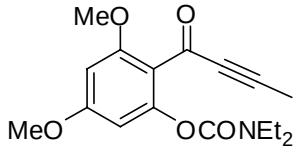


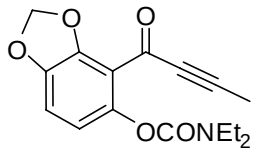


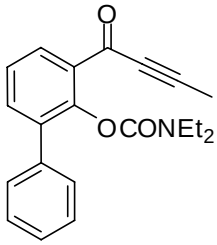


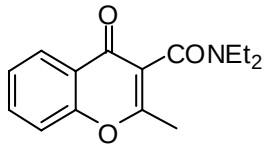


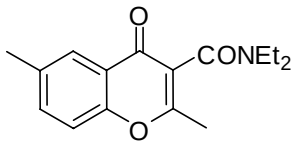


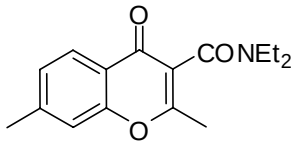


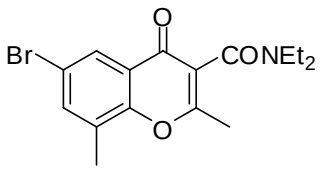


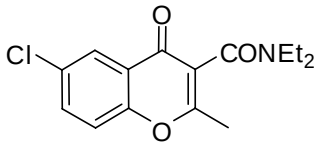


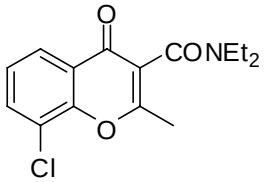












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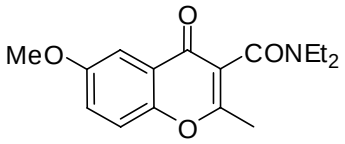
150



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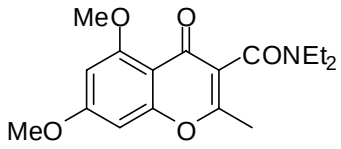

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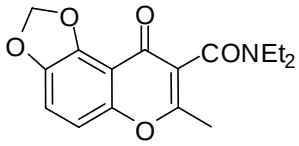

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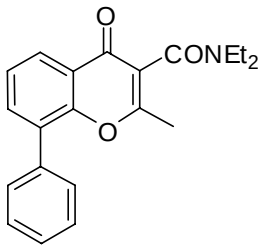

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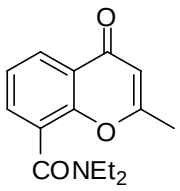

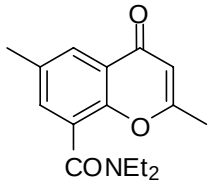

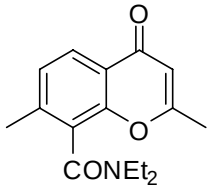

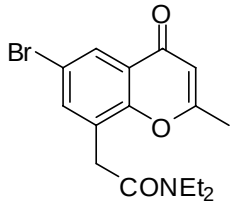

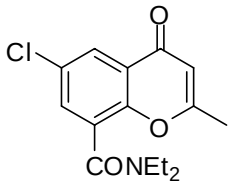

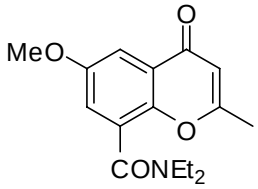

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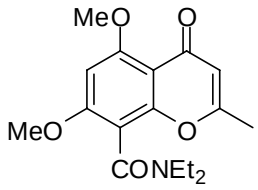

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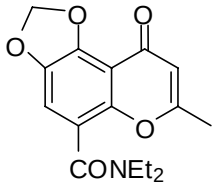
***N,N*-Diethyl-7-methyl-9-oxo-9*H*-[1,3]dioxolo[4,5-*f*]chromene-5-carboxamide (4.12j)**



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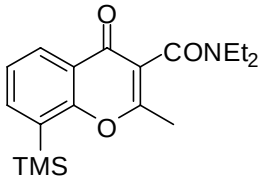
***N,N*-Diethyl-2-methyl-4-oxo-8-(trimethylsilyl)-4*H*-chromene-3-carboxamide (4.11l)**



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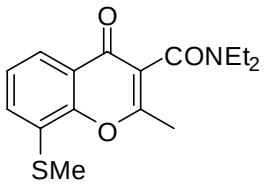

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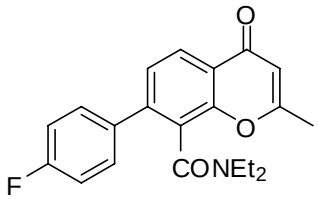
***N,N*-Diethyl-7-(4-fluorophenyl)-2-methyl-4-oxo-4*H*-chromene-8-carboxamide (4.16)**



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Chapter 1

General Introduction

1.1. Functionalization of Aromatic Compounds

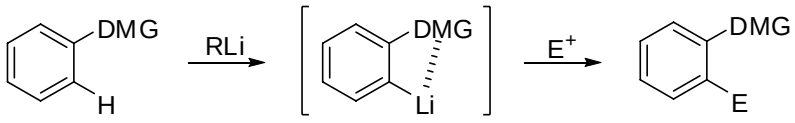
The preparation of polysubstituted aromatic and heteroaromatic compounds is of fundamental importance in the field of organic synthesis as these aromatic entities constitute approximately one third of global organic chemical production.[1] The use of such compounds in the pharmaceutical industry clearly establishes the need for viable construction pathways of complex aromatic systems for the purpose of drug discovery programs.[2] Classical modes of arene functionalization including electrophilic,[3] nucleophilic (S_NAr),[4] and $S_{RN}1$[5] substitution procedures offer great advantages for elementary aromatic starting points in chemical synthesis; the former being the most prominent but is commonly complicated by poor regioselectivity and harsh reaction conditions. These methods have been more recently joined and, not infrequently superseded by, vicarious substitution,[6] Directed *ortho* Metalation (D*o*M),[7] and more recently by new catalytic aromatic C-H activation-transformation processes. [8-10]

1.2. The Directed *ortho* Metalation (D*o*M) Reaction in Organic Synthesis

Since the independent discovery by Gilman and Bebb[11] and Wittig and Fuhrmann,[12] of the *ortho*-metalation of anisole, and further systematic development of benzamide metalation by Hauser,[13] the Directed *ortho* Metalation (D*o*M) reaction of aromatic and heteroaromatic compounds has become a powerful tool in both academia and industry for expedient construction of polysubstituted arenes. The number of reviews devoted to this subject area are a testament to its widespread and general usage.[14-23] The reaction commonly involves the use of a strong alkyllithium base to achieve irreversible proton abstraction of an sp2 hybridized aromatic or heteroaromatic

carbon *ortho* to a heteroatom bearing Directing Metalation Group (DMG) **1.1** (Scheme 1.1). An intermediary *ortho*-litho species **1.2** is generated, which upon subsequent reaction with an electrophile, affords regiospecific 1,2-disubstituted aromatics **1.3**.

Scheme 1.1. The Directed *ortho* Metalation Reaction



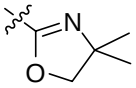
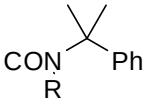
1.1 **1.2** **1.3**

1.2.1. Directed Metalation Groups (DMG)

The popularity of the D*o*M reaction stems from a plethora of arene functional groups that direct regiospecific *ortho* metalation. The nature of an effective DMG require two key features: i) it must have adequate robustness to withstand attack from strongly nucleophilic alkyllithium bases, and ii) contain a heteroatom with a free lone pair available for Lewis-base coordination to metal cations. Early contributions to this field by Hauser with respect to benzamide[13] and arylsulfonamide[24] D*o*M set the stage for further fundamental DMG developments by Christensen,[25] Gschwend,[16] Meyers,[26] Beak,[27] Muchowski,[28] and Snieckus[21] (Table 1.1). The evolution of D*o*M since the early 1940s to the present day has been extensive. As a result, many other DMGs that have varying degrees of synthetic utility in polysubstituted arene construction are known. The relative hierarchy of DMGs has been determined on the basis of inter- and intra-molecular experiments (Figure 1.1).[21] A new addition to this hierarchy, and one that is noteworthy of comment, is *N,N,N′,N′*-tetraethylphosphorodiamidate.[29] Excitement pertaining to this new DMG arises from its supreme directing power and potential for

inclusion into modern biaryl ligand synthesis.[30] The most powerful DMGs (e.g., $OCONR_2$)[31] are strongly Lewis acidic that have their inherit electrophilicity usually overcome by low temperature kinetic control (-78 °C), steric effect (R = Et, *i*-Pr, *t*-Bu), charge deactivation (e.g. CON^-R), or a combination of all (e.g. N^-Boc). Halogens (Cl

Table 1.1. Some Common Directed Metalation Groups (DMGs)

Carbon Based		Heteroatom Based	
CO_2^-	Mortier, 1994	N^-Boc	Gschwend, 1979
CON^-R	Hauser, 1964	N^-Piv	Muchowski, 1980
	Meyers, Gschwend, 1975	OMe	Gilman-Wittig, 1938
		OCH_2OMe	Christensen, 1975
		$OCONEt_2$	Snieckus, 1983
$CONEt_2$	Beak, 1977	OPO_2NR_2	Snieckus, 2005
	Snieckus, 1999	$P(O)t\text{-}Bu_2$	Snieckus, 1998
		SO_2R	Truce, 1951
		SO_2NR_2	Hauser, 1969

and F) are commonly used as DMGs more prominently in heteroaromatic systems,[32] while Br and I have been used in conjunction with D*o*M for metal-halogen exchange and halogen dance rearrangements.[33] The varying reactivity of the halogen series in these reactions have been collectively reviewed.[34] Other more electrophilic DMGs (esters, nitriles) rely on milder lithium amide bases such as lithium diisopropylamide (LDA) and lithium 2,2′,6,6′-tetramethylpiperidide (LTMP)[35] that are frequently employed for the D*o*M reaction. These amide bases can offer advantages over their alkyllithium counterparts. This is due to their decreased nucleophilicity, which allows increased compatibility with electrophilic functional groups and reagents.[36,37] Recently, poorly explored Hauser bases $(TMP)_2Mg$ capable of *ortho*-magnesiation,[38] have been improved

by Knochel in the form of (TMP)MgCl · LiCl. This base has been used successfully for D*o*M even in the presence of highly electrophilic aromatic carbonate, ester, nitrile, and ketone functional groups.[39] Mixed lithium zincate and aluminum ate complexes have also been used as mild bases for the D*o*M reaction however, they are yet to be exploited in synthesis.[40,41]

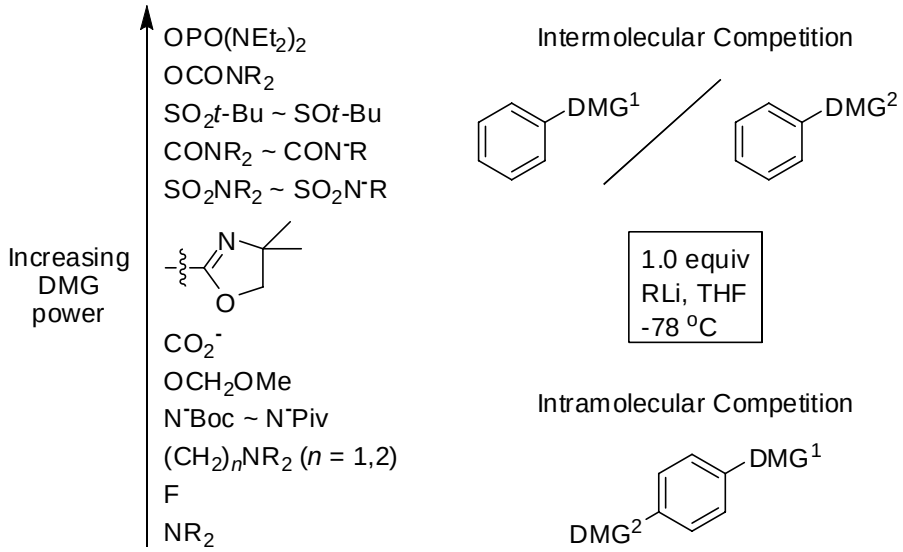


Figure 1.1. DMG Hierarchy

1.2.2. The Mechanism of the Directed *ortho* Metalation Reaction

Since Roberts and Curtin first reported on regiochemical discrepancy involving inductively based lithiation of anisole versus benzotrifluoride,[42] the concept of a pre-lithiation complex between base and DMG first referred to by Beak and Meyers as the *Complex Induced Proximity Effect* (CIPE)[19] in D*o*M, was evident. This complex brings the lithiating base in close proximity to the acidic hydrogen, thereby accounting for the observed regioselectivity. Roberts conclusion that these results were "not completely

satisfactory" on the basis of a number of contradictory observations at the time, addresses the current mechanistic picture of the D*o*M reaction today. The ongoing debate of dualistic mechanisms arising from "coordination only" versus the "acid-base" effect, which is described by the intrinsic acidifying effects of the DMG toward lithiations suggested by Gschwend and Rodriguez,[16] has grown into several current mechanistic proposals. It will be shown in the following sections that due to the variety of DMG based aromatic and heteroaromatic systems, no single mechanistic picture can best explain D*o*M and that at best, a prediction-based metalation model must consider all.

1.2.2.1. Kinetics

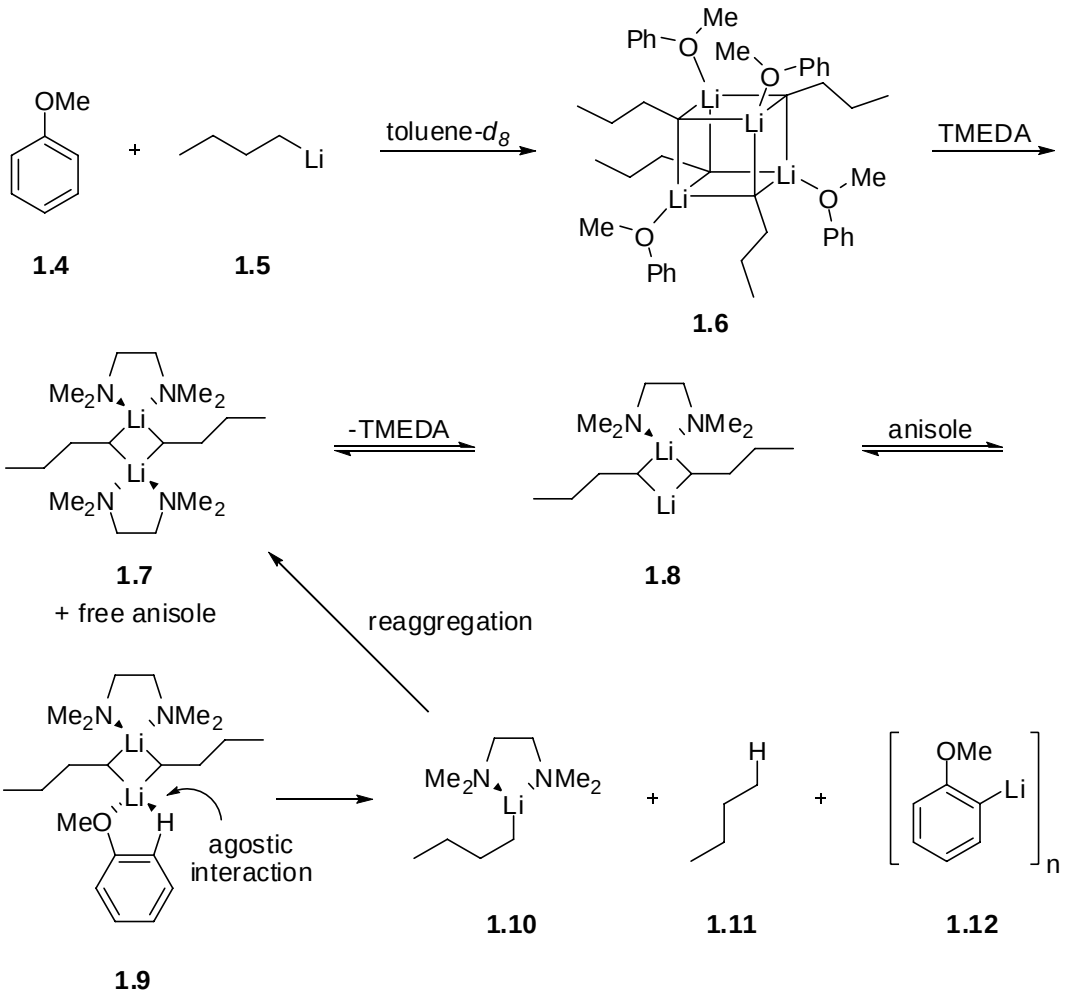
A great deal of effort to understand the mechanism of the D*o*M reaction has been based on the determination of relative rates. Large primary kinetic isotope effects (KIE) observed for intramolecular and intermolecular competition experiments for aromatic lithiation of secondary and tertiary benzamides indicate that tunneling occurs during proton transfer and it may be interpreted that D*o*M proceeds by fast reversible complexation (CIPE) followed by slow deprotonation.[43] Kinetic and stopped-flow FT infrared spectroscopy measurements reported by Beak have provided direct evidence of a pre-lithiation complex during *s*-BuLi mediated *syn* α-lithiation of tertiary benzamides.[44,45] In direct opposition to CIPE, Stratkis has measured and found the KIE of intramolecular and intermolecular D*o*M of anisole in diethyl ether with or without the presence of bidentate chelating ligand *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) to be small and equal within the limits of experimental error, indicating that D*o*M occurs by a single step rate-determining deprotonation.[46] Concurrently, Collum investigated KIE of the

D*o*M of anisole in toluene and found KIE that indicated the same rate-limiting proton abstraction without the involvement of precomplexation.[47] These results are in accord with a previous report[48] suggesting that a dimeric TMEDA / *n*-BuLi aggregate reacts with anisole in a one-step mechanism of stoichiometry (*n*-BuLi)$_2$(TMEDA)$_2$(anisole). The effect of varying DMG orientation can also have a significant effect on the rate of D*o*M. Beak has shown that the competitive efficiencies of deprotonation for 2-isopropylisoquinolin-1-(*2H*)-one at C-8, *N,N*-diisopropylbenzamide, and 2-trimethylsilyl-*N,N*-diisopropylbenzamide at C-6, 32,000:1800:1 are indicative of strong geometrical dependence toward planarity of the D*o*M process.[49] This is consistent with previous *ab initio* calculations.[50] In contrast, the same study on a series of benzyl alcohols suggests an out of plane relationship for favourable D*o*M. This is a reasonable result considering that an additional negatively charged alkoxide in the transition structure would require additional charge shielding in an already tight transition state complex.

1.2.2.2. NMR and Calculations

Using 1D (^{1}H, ^{13}C, ^{6}Li) and 2D (^{7}Li –^{1}H HOESY) heteronuclear NMR, Bauer and Schleyer provided direct spectroscopic evidence for the formation of an intermediate cubic aggregate between anisole and *n*-BuLi (**1.6**) upon mixing in toluene-d_8 at -64 ^{o}C (Scheme 1.2).[51] The slow formation of *o*-anisyllithium **1.12** was observed upon the addition of 1 equivalent of TMEDA, suggesting that TMEDA induces liberation of free anisole and observed (*n*-BuLi)$_2$(TMEDA)$_2$ complex **1.7** which upon exchanging TMEDA for anisole via **1.8** could generate transition state complex **1.9** present in low concentrations thus not observed by NMR. MNDO calculations showing agostic Li

hydrogen interactions in the proposed complex (*n*-BuLi)$_2$(TMEDA)(anisole) **1.9** supported this suggestion. In a single NMR experimental by Saa and co-workers of the lithiation of 1-naphthol, close contacts observed in the ^{7}Li –^{1}H HOESY spectra between



Scheme 1.2. TMEDA Promoted Reaction of Cubic Aggregate 1.6 with Anisole 1.4

mixed lithium aggregate clusters showed peri hydrogens to be closest to lithium atoms.[52] This observation, including other experimental and MNDO calculations by Saa during the lithiation of napthols,[53] 1,3-disubstituted aromatics,[54] and polyhydric phenolic

compounds[55] is a likely result of CIPE and pro-D*o*M hydrogen activation by an agostic interaction. A survey of X-ray crystal structures supports a systematic weakening of C-H bonds associated with Li atoms.[56] It has been argued by Schleyer that a CIPE-based precomplexation of the alkyllithium and DMG would impart considerable stabilization, rendering D*o*M an unlikely event due to an increased energy barrier of deprotonation. Based on the results of *ab initio* calculations, an alternative mechanism coined "kinetically enhanced mechanism" (KEM) was purposed.[57-59] This theory argues that D*o*M proceeds via a single step mechanism in which coordination of the alkyllithium and

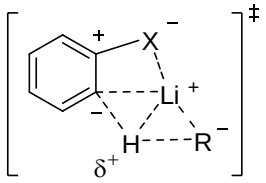


Figure 1.2. KEM Transition State

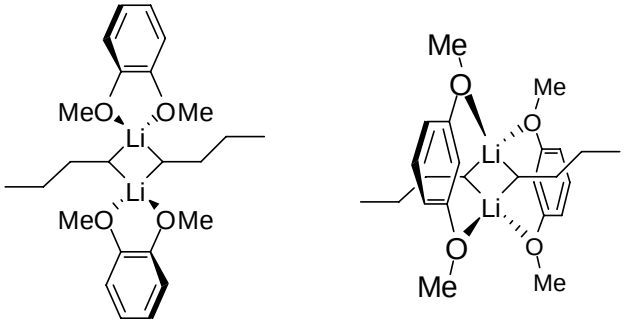
DMG, as well as deprotonation, occur simultaneously in the same transition state. As shown in Figure 1.2, electronegative substituents can stabilize the transition state of D*o*M in two ways: (i) by providing an electrostatically favourable arrangement of charges and (ii) by strong coordination of electron rich atoms, such as oxygen and fluorine, to lithium. Consecutively, Collum has intensified the KEM argument by studying the lithiation rates of alkoxy-substituted aromatics (C_6H_5OMe, *m*-$C_6H_4(OMe)_2$, $C_6H_5OCH_2OMe$, $C_6H_5OCH_2CH_2NMe_2$).[60] *Ab initio* calculations afford strong theory-experiment correlations of high mechanistic homology which depend largely upon the inductive effects as suggested by KEM. However, Collum advises that extrapolating these results to stronger DMGs such as carboxamides should be done with caution. Recently, Collum

has used rate studies and density functional theory (DFT) calculations to probe the lithiations of *meta*-substituted aryl oxazolines.[61] He concluded that cooperative DMG groups serve different roles for these systems – "one as a formal directing group via a distinct substrate-lithium interaction and the other as a non-coordinating ancillary group activating the metalation inductively."

1.2.2.3 Solvent and Additive Effects

Slocum and co-workers have made substantial contributions in the quest to understand the role of solvent and additive coordination versus inherit electronic effects of the substrate during D*o*M of methoxy substituted aromatics. Slocum has described that D*o*M of anisole in the presence of TMEDA, first reported by Langer Jr.,[62] gives substantial rate enhancements.[63] He has also demonstrated the use of incremental amounts of TMEDA for the effective D*o*M of anisole,[64] *p*-fluoroanisole,[65] *p*-methylanisole,[66] and *p*-dimethoxybenzene.[67] Slocum postulates, in opposition to CIPE, that *n*-BuLi / anisole complexation in diethyl ether medium occurs in the rate-limiting step, followed by faster deprotonation. Slow complexation is required in order to reduce the tendency of the methoxy group to be delocalized, thereby lowering the acidity of the *ortho* proton to be exchanged. The addition of TMEDA eliminates the slow step by allowing an "overriding base" effect to achieve rapid deprotonation without precomplexation.[64] More recently, using Bauer's and Schleyer's proposal of an anisole-associated alkyllithium dimer intermediate,[51] further corroborated by Collum's transition state complex (*n*-BuLi)$_2$(TMEDA)$_2$(anisole),[45] Slocum has coined the term "substrate-promoted *ortho*-metalation." This best described the observations that he found in

uncatalyzed (without additive) hydrocarbon solvents, how the lithiations of 1,2-di-, 1,3-di-, and 1,2,4-trimethoxybenzenes proceed with aromatic methoxy substrate functioning as both the DMG and deoligomerization agent, forming complexes with stoichiometry (*n*-BuLi)$_2$(C_6H_x(OMe)$_y$)$_2$ (Figure 1.3, **1.13** and **1.14**).[68,69] This is, however, in direct



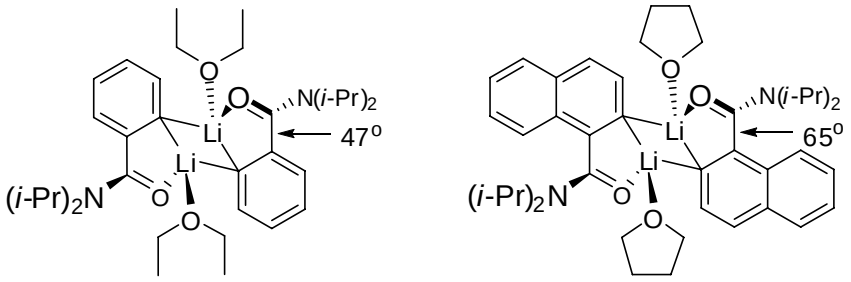
1.13 **1.14**

Figure 1.3. Substrate-Promoted *ortho*-Metalation

opposition to Schlosser's own study involving D*o*M of polysubstituted methoxy arenes, but falls unwarranted due to the consideration that the use of THF, a coordinating solvent, would likely inhibit a substrate effect on metalation.[70] At least one other group concurs that the use of TMEDA in diethyl ether allows the formation of a 1,2-dimethoxybenzene chelating species responsible for accelerated D*o*M.[71] Most recently, Slocum has demonstrated that the progressive addition of THF or TMEDA in cyclohexane increases the basicity of *n*-BuLi as alkyllithium oligmers deaggregate from hexamer to more basic tetramer and dimeric forms.[72]

1.2.2.4 X-ray Structural Analysis

Solid-state structures have revealed an enormous amount of information about highly aggregated and strongly ligand-associated structures of stable organolithium compounds.[73] These structures owe their stability to strong lithium-electron pair complexation in ground states verified by X-ray structural information.[74] One such X-ray crystallographic study of an early D*o*M reaction of *N,N*-dimethylbenzylamine with *n*-BuLi in diethyl ether-hexane identifies the existence of a tetranuclear aryllithium cluster $Li_4[C_6H_4\text{-}2\text{-}(CH_2NMe_2)]_4$ where each Li atom is associated with three carbanion carbons and one nitrogen atom.[75] The subsequent addition of THF results in a slow deaggregation to a dinuclear complex of formula $Li_2[C_6H_4\text{-}2\text{-}(CH_2NMe_2)]_2(THF)_4$. From this, THF could be easily displaced in solution with the use of chelating ligands such as TMEDA, *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDTA), and *N,N,N′ N′,N″,N″*-hexamethylphosphoric triamide (HMPA), the latter portraying its strong relative coordinating power by further deaggregating the dinuclear complex to a mononuclear bis-HMPA complex.[76] The first X-ray structures of lithiated *N,N*-diisopropylbenzamide **1.15** and 1-naphthamide **1.16** (Figure 1.4) were found to be dimeric structures based on



1.15 **1.16**

Figure 1.4. X-Ray Structures of Lithiated Carboxamides 1.15 and 1.16

core C--Li interactions supported by amide(O)--Li bonding with associated modulation of the sterically induced twist angle between the amide and the plane of the aromatic ring.[77] These solid-state structures confirmed the validity of a CIPE-induced lithiation of benzamides through amide(O)--Li coordination, and due to contrasting features of laterally lithiated benzamides, influenced further studies into additive-mediated chemoselective D*o*M.[78]

1.2.2.5 Current Mechanistic Picture

In summary, whether a given D*o*M reaction proceeds via two-step CIPE or one step KEM is a function of the DMG-arene system employed. For strongly coordinating DMGs (e.g. $CONR_2$), CIPE predominates and geometry effects are significant. For weakly coordinating DMGs (e.g. OMe), coordination is electronically or geometrically impossible and inductive effects are responsible for the increased acidity of the *ortho* hydrogen. For both processes, steric effects have a profound effect on the rate of proton abstraction. In addition to the influence of base, solvent, additives, and temperature, homo and heteroaggregate formation and interconversion play a role in the observed structural and reactivity differences.[79]

Illustrative examples of how substrate / base / solvent coordinative and inductive effects can be used to manipulate regiochemical consequences in D*o*M reactions are shown in Figure 1.5. The effect of adding TMEDA to benzylamine **1.17** in hydrocarbon solvent minimizes coordination effects (CIPE), allowing inductive lithiation to proceed *ortho* to the more Lewis-acidifying methoxy group.[80] Lithiation of benzamide **1.18** under

standard *s*-BuLi / TMEDA / THF conditions is driven by CIPE of powerful activating amide over methoxy DMG. On the other hand, the complexation between ethoxyvinyllithium (EVL) and HMPA must minimize substrate coordination effects, possibly due to sterics, driving inductive lithiation.[81] Recently, Mortier has demonstrated regioselective synthesis of methoxybenzoic acids using D*o*M.[82,83] Regioselective D*o*M was firstly achieved for *m*-anisic acid **1.19** by thermodynamically controlled LTMP lithiation of the doubly activated 2-position. The 4-position was accessed using Lochmann-Schlosser LICKOR superbase.[84] *t*-BuOK is proposed to deoligomerize *n*-BuLi aggregates into monomeric forms minimizing CIPE, and promoting preferentially deprotonation of the inductively activated aromatic position next to the most electronegative heteroatom and / or the most acidic position available.[85] The 6-position is

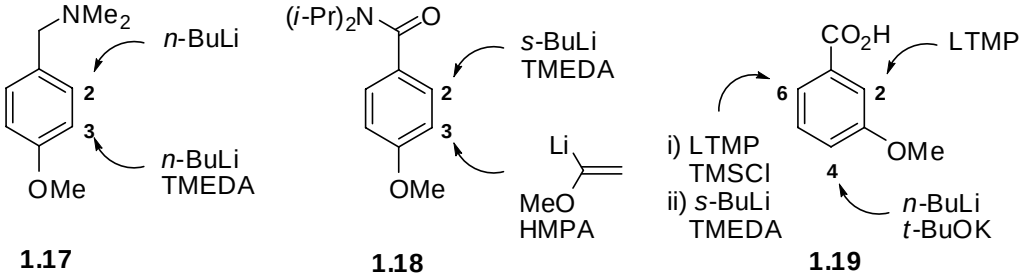


Figure 1.5. Examples of Regioselective Metalations

accessed first by commonly practiced TMS-protection of the 2-position followed by standard metalation with *s*-BuLi / TMEDA / THF utilizing the more powerful carboxylate DMG.

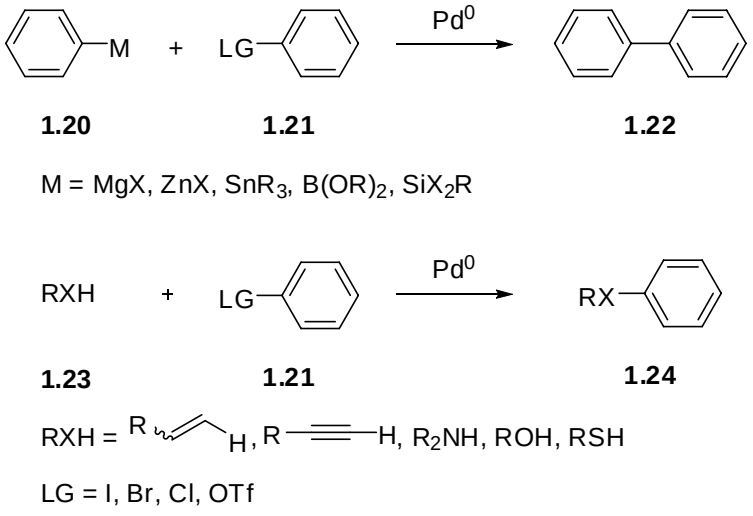
1.3. The Transition Metal-Catalyzed Cross Coupling Reaction

Modes of arene functionalization by means of catalytic transition metal facilitated carbon-carbon or carbon-heteroatom bond forming reactions, particularly in the context of aryl-aryl bond formation, are an essential practice in modern organic synthesis. Aryl-aryl bonds are found in many natural products (e.g. alkaloids), biologically active compounds of pharmaceutical and agrochemical importance, commercial dyes, organic conductors, and asymmetric ligands. The discovery of the first cross coupling reaction of aryl halides with Grignard reagents using metal salts ($CoCl_2$, $CuCl_2$, $MnCl_2$, $NiCl_2$, and $FeCl_3$) as catalysts was reported in 1941 by Kharasch and Fields.[86] It was not until 30 years later that Tamaura and Kochi reported iron and copper cross coupling reactions of alkyl, vinyl, and aryl bromides with Grignard reagents.[87,88] The following year this reaction was significantly improved by Tamao, Sumatani, and Kumada,[89,90] and concurrently and independently, by Corriu and Masse.[91] They reported the use of nickel-phosphine complexes as catalysts for the cross coupling reactions of aryl halides with Grignard reagents, a transformation that became known as the Kumada-Corriu-Tamao (KCT) reaction. The use of phosphine ligands represented a significant improvement in the reaction by increasing metal solubility and stability, while allowing steric and electronic tuning. This marked the beginning of the transition metal catalyzed aryl-aryl cross coupling reaction.

The harsh reactivity of Grignard reagents required for KCT coupling led to the development of milder organometallic coupling partners that have become standards in cross coupling reactions. These include: aryl zinc[92] (Negishi[93]), tin[94] (Stille[95]), boron[96] (Suzuki-Miyaura[97]), and silicon[98] (Hiyama[99]) derivatives **1.20**, which are most commonly

coupled with aryl halides and triflates **1.21**, yielding biaryls **1.22** (Scheme 1.3). Other unsaturated carbon and heteroatom based nucleophiles **1.23** have also been developed for the formation of C-C [to alkene[100] (Mizoroki[101]-Heck[102]) and alkyne[103] (Sonogashira[104])], C-N[105] (Buchwald[106]-Hartwig[107]), C-O[108], and C-S[109] bonds **1.24**, respectively. Although the hard nucleophilic nature of nickel has an advantage for reactions involving coupling partners with strong R-LG bonds (e.g. ArCl[110] and ArF[111]), softer palladium metal has increased scope, including fewer side reactions and a greater insensitivity to sterics when compared to nickel.[112,113] The palladium-catalyzed cross coupling reaction of $C(sp^2)$-$C(sp^2)$ centers leading to biaryl products has received the greatest amount research and development, offering high reactivity with all the aforementioned coupling partners.[114]

Scheme 1.3. Common Palladium-Catalyzed Cross Coupling Reactions

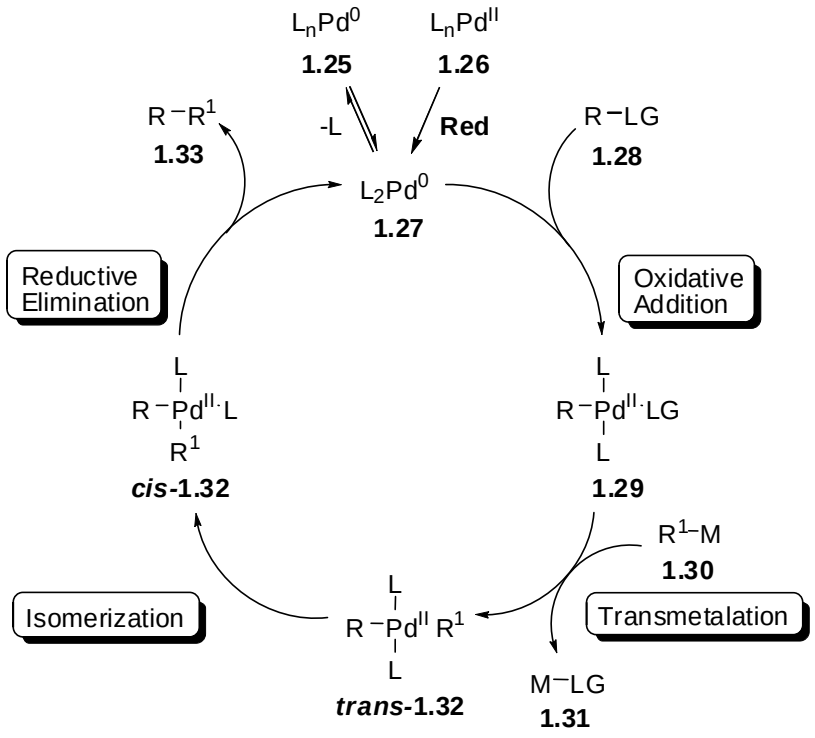


1.3.1. Mechanism of the Transition Metal-Catalyzed Cross Coupling Reaction

Mechanistically, the three-step catalytic cycle first proposed by Kumada has remained fundamentally unchanged.[90] As shown in Scheme 1.4, the palladium-catalyzed

cross coupling reaction initiates with the generation of a coordinatively unsaturated zero-valent Pd^0 species **1.27**, purposed to be the active catalyst,[115] by ligand dissociation of zero-valent Pd^0 **1.25** or reduction of divalent Pd^{II} **1.26** palladium complexes. Subsequent oxidative addition of the Pd^0 species **1.27** into the Ar-LG bond of **1.28**, forms **1.29**, a Pd^{II} species.[116] The aryl-LG bond strengths (I < Br = OTf << Cl <<< F)[117], electronics (EDGs strengthen aryl-LG bond), coordination effects, solvent polarity, and the ligand dependant tunable sterics and nucleophilicity of palladium, all have a significant influence on whether the oxidative addition step occurs rapidly, or is slow and rate determining. The resultant oxidative insertion Pd^{II} complex **1.29** can then undergo transmetalation with an organometallic species **1.30** to form the thermodynamically favoured ***trans*-1.32** product. The driving force is rationalized to be the R^1 transfer from a more to a less electropositive

Scheme 1.4. General Mechanism for the Palladium-Catalyzed Cross Coupling Reaction



metal.[118] More nucleophilic organometallic reagents significantly increase rates at this step. Lastly, isomerization to the ***cis*-1.32** species must occur to provide a pathway for reductive elimination, resulting in the formation of a new carbon-carbon bond (**1.33**) and simultaneous regeneration of the zero-valent Pd^0 catalyst **1.27**.[119] Reductive elimination is the microscopic reverse of oxidative addition, so factors affecting the rate of this step are in opposition to those previously described for the oxidative addition step. The governing efficiency of the catalytic cycle is usually a reflection of the position of the rate determining step, which is ultimately a consequence of the reaction conditions, catalyst / ligand system, and cross coupling partners employed.

Chapter 2

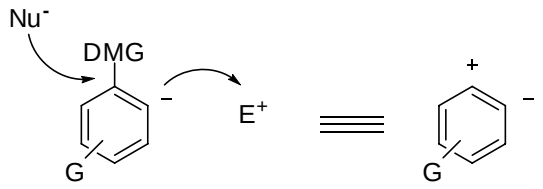
Directed *ortho* Metalation Methodology. The *N,N*-Dialkyl Aryl *O*-Sulfamate as a New Directed Metalation Group, Cross Coupling Partner for Grignard Reagents, and Handle for Benzyne Generation

2.1 Prelude

2.1.1 Labile DMGs for D*o*M

The D*o*M reaction is a very valuable tool for the regioselective construction of contiguously substituted arenes, and a broad range of carbon and heteroatom-based DMGs are available for this process. Although the manipulation of DMGs into most functional groups is possible, the required conditions are often limiting (e.g. traditionally the cleavage of $ArOCONEt_2$ to ArOH requires LAH, MeLi, or KOH / MeOH / reflux).[31] The ability to manipulate these robust groups for further synthetic post-D*o*M elaboration has been a popular area of research especially for more powerful carboxamide,[120-125] sulfonamide,[126-133] and carbamate[134-139] DMGs. Weaker DMGs such as OMOM[25] and NHBoc[28] are readily hydrolyzed under mild acidic conditions allowing expedient *ortho*-derivatization of phenols[140] and anilines.[141] Other than the obvious halogen series, the use of DMGs as leaving groups in transition metal-catalyzed cross coupling reactions is another area of interest that has seen a recent surge in development. Early work by Takei[142-144] and Wenkert[145-148] showed that alkenyl and aryl sulfides / thiols, and enol / aryl ethers could participate in Kumada-Corriu-Tamao[89-91] (KCT) cross coupling reactions forming carbon-carbon bonds with alkyl and aryl Grignard reagents.

Simultaneously, Julia developed similar cross coupling regimens with sulphones,[149-151] which were later applied to KCT cross couplings and reductive desulfonations of post-D*o*M aryl *t*-butylsulfones in chemically useful yields.[152,153] A few years prior, Snieckus had reported combined D*o*M / cross coupling protocols for *O*-aryl carbamates[154] and more recently sulfonamides[155,156] which provide reactivity represented by an aromatic 1,2-dipole equivalent (**2.2**, Figure 2.1). The continued development of DMGs to achieve an even greater degree of manipulation is of interest for the general expansion of D*o*M methodology.



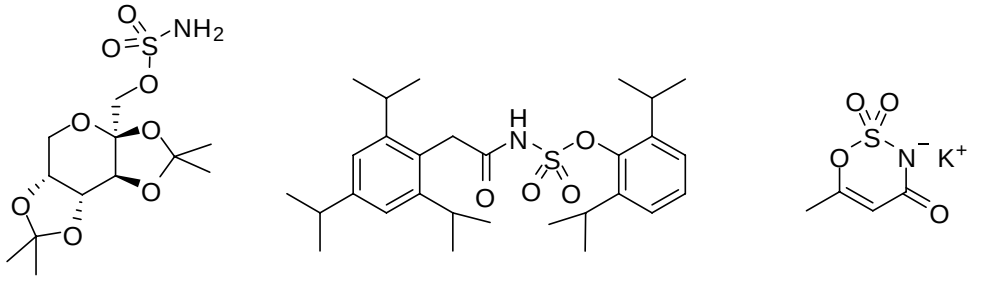
DMG = $OCONEt_2$, SO_2t-Bu, SO_2NEt_2

Figure 2.1. 1,2-Dipole Equivalent of Latent Aryl DMGs

2.1.2 Sulfamates in Organic Chemistry

The chemistry of sulfamic acids (R_2N-SO_2-OH) has been extensive and the topic of several reviews, the first of which was published in 1940.[157-159] Derivatives of these vastly functional compounds include sulfamyl esters or sulfamates (R_2N-SO_2-OR), which have interesting biological properties (e.g. topiramate **2.3**[160], avasimibe **2.4**[161]), but are most widely known in the flavour industy (e.g. acesulfame K **2.5**[162], Figure 2.2). A recent renaissance in sulfamate chemistry has seen an explosion of applications in numerous therapeutics,[163-165] peptidomimics,[166] and C-H activation processes.[167]

Recently Du Bois has developed Rh-catalyzed intermolecular amidation of C-H bonds and olefins with primary sulfamates to yield cyclic sulfamates and aziridines with high selectivities.[168] It was reported that SO_3 could be displaced by nucleophiles in a typical S_N2 manner or *via* KCT cross coupling of cyclic aryl sulfamates (**2.7**, Scheme 2.1).[169]

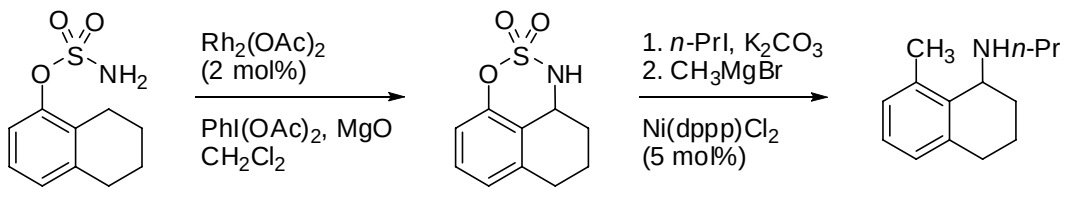


2.3 topiramate **2.4** avasimibe **2.5** acesulfame K

Figure 2.2. Commercial Sulfamates

The whole synthetic process provides an effective route to difunctionalized amine derivatives. Other groups have improved the scope and enantioselectivity of this reaction using chiral manganese(III) Schiff-base complexes using sulfamates which remain the best precursors for these processes.[170] The first report that caught our attention to consider sulfamates as DMGs was the *thia*-Fries rearrangement of *N,N*-dialkyl aryl

Scheme 2.1. C-H Amination / KCT Cross Coupling of Aryl *O*-Sulfamate 2.6

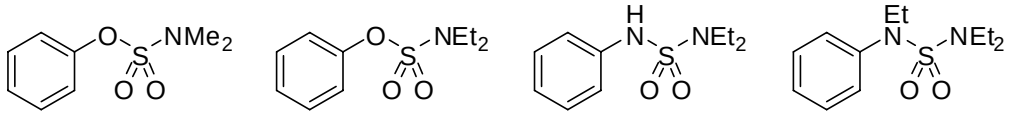


2.6 **2.7** (75%) **2.8** (2 steps, 72%)

O-sulfamates.[171] These sulfamate systems appear to have some electrophilic character, a necessary component for a good DMG. Since the first reported by Ritter in 1931,[172] numerous examples of the Lewis acid promoted rearrangement of arylsulfonates ($PhSO_2OPh$) to phenolic sulfones ($HOC_6H_4SO_2Ph$) have appeared in the literature.[173,174] An unprecedented report by Lloyd-Jones revealing controlled anionic *thia*-Fries of aryl triflates provided the inspiration to test *N,N*-dialkylaryl *O*-sulfamate systems in the D*o*M reaction.[175]

2.1.3 Development of Sulfamates as DMGs

Known compounds *N,N*-dimethylphenyl *O*-sulfamate **2.9**, *N,N*-diethylphenyl *O*-sulfamate **2.10a**,[171] and *N',N'*-diethylphenyl *N*-sulfamide **2.11**[176] were prepared along with the unknown *N*-*N',N'*-triethylphenyl *N*-sulfamide **2.12** according to literature procedures using commercial *N,N*-dimethylsulfamoyl chloride and readily prepared *N,N*-diethylsulfamoyl chloride.[177]



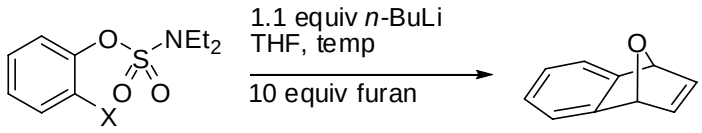
2.9 **2.10a** **2.11** **2.12**

Figure 2.3. Aryl *O*-Sulfamates 2.9-2.10a and *N*-Sulfamides 2.11-2.12 Tested for D*o*M

Initial results employing standard conditions developed by Beak[27,178] (*s*-BuLi / TMEDA / -78 ^{o}C) and quenching with TMSCl failed to give any observable product in all cases. Starting material was recovered from both sulfamides **2.11** and **2.12**, and

degradation was observed for sulfamates **2.9** and **2.10a**. Interestingly, the degradation of **2.9** and **2.10a** was observed shortly after *s*-BuLi was added to the reaction, as the mixture slowly darkened from bright yellow to black over 30 min. This result was proposed to be a result of *ortho*-lithiation followed by benzyne formation *via* the elimination of lithium *N,N*-diethyl sulfamate. The precendent arose from popular aryne forming conditions using aryl triflates.[179] To confirm the formation of benzyne, furan was utilized as an *in situ* diene trap and the Diels-Alder reaction was examined on sulfamate **2.10a**. To ensure

Table 2.1. Benzyne Trapping with Furan



X = Br (**2.13h**), I (**2.13i**) **2.14a**

X	temp (^{o}C)	Yld (%)[a]
I	-93 to rt	19
	-40 to rt	22
	-10 to rt	33
	rt	17
Br	-40 to rt	24
	-10 to rt	37
	rt	17

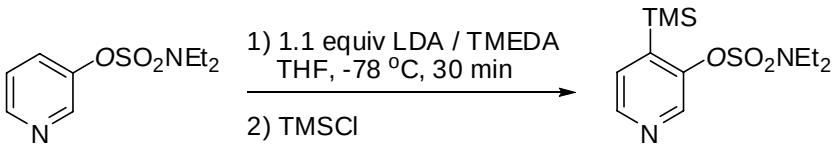
[a]determined by GC

rapid regioselective lithiation, a lithium-halogen exchange protocol was followed using *ortho*-halophenyl *O*-sulfamates **2.13h** and **2.13i** prepared from their corresponding 2-halo phenols (Table 2.1). Initial results confirmed a benzyne degradation pathway *via* the formation of 7-oxabenzonorbornadiene **2.14a**, albeit in low yields, along with many side

products common to aryne decompostion. The most predominant side product observed was *N,N*-diethyl-2-phenylphenyl *O*-sulfamate formed *via* the reaction between the *ortho*-lithiated species and benzyne. Switching ethereal solvents from THF to less coordinating diethyl ether was found to improve yields and diminish the formation of the aforementioned side products by GC.[180]

Due to the apparent temperature dependence of benzyne formation, D*o*M of **2.10a** was conducted at -93 ^{o}C, and the desired *ortho*-TMS derivative **2.13e** was isolated in 96% yield after quenching with TMSCl. At this temperature, **2.9** continued afford negative results, possibly due to complication from *N*-methyl lithiation analogous to amides,[45] or from more facile benzyne formation. It was possible to perform D*o*M at -78 ^{o}C using a milder base with more electron deficient systems (Scheme 2.2). In an example analogous to the D*o*M of *O*-3-pyridylcarbamates[181], *O*-3-pyridylsulfamate **2.10f** was shown to undergo lithiation at the 4-position (**2.13n**) with LDA, a known regiochemical event first reported for 3-(methoxymethoxy)pyridine by Ronald.[182]

Scheme 2.2. Regioselective D*o*M of *O*-3-Pyridylsulfamate 2.10f

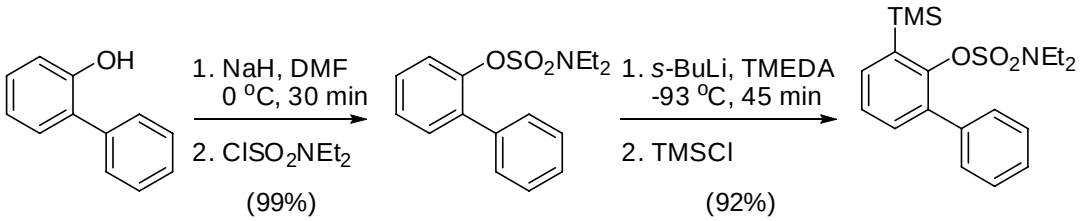


2.10f (92 %) **2.13n**

The temperature limitations for D*o*M of **2.10a** due to facile benzyne formation would make performing an anionic *ortho*-Fries reaction impossible. Biaryl *O*-sulfamate **2.17** was synthesized as shown in Scheme 2.3, to test the likelihood of a remote lithiation

and a possible anionic sulfamoyl rearrangement reaction. LDA (3 equiv) was added to the reaction at -93 ^{o}C and after warming to rt, no reaction had occurred. The reaction was then refluxed with increasing concentrations of LDA until starting material had been consumed, however no desired rearrangements products were detected. Other reactions were performed on **2.17** with *n*- and *s*-BuLi at low and high temperatures and in all instances, no evidence of lithiation products or sulfamate cleavage were detected. Slow alkaline hydrolysis of **2.10a** could be achieved in accordance with literature conditions for phenyl-*O*-sulfamates: 1.4 x 10^{-6} mol $dm^{-3}s^{-1}$ for *N*-ethyl-*N*-phenyl phenyl *O*-sulfamate in boiling aqueous ethanolic sodium hydroxide;[183] *N,N*-dimethyl-4-nitrophenyl *O*-sulfamate in 1:1 ethanol:water aqueous sodium hydroxide at 60^{o}C.[184] All attempts to improve hydrolysis for **2.10a** using mild conditions failed.

Scheme 2.3. Synthesis of a Remote Lithiation *O*-Sulfamate Precusor



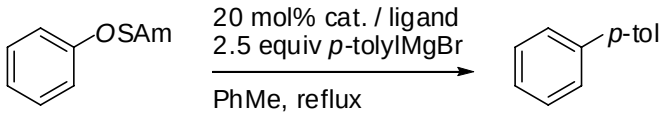
2.15 **2.16** **2.17**

2.1.4. Cross Coupling of Aryl *O*-Sulfamates

To probe the reactivity of **2.10a** towards KCT cross coupling, screening of nickel (II) sources with phosphine, imine, and carbene ligands were conducted with *p*-tolylMgBr in refluxing toluene against undecane as an internal standard. Excellent results were obtained and further block experiments were performed to optimize conditions (Table 2.2). The optimal conditions for this transformation was determined to

be [NiClCp(IMes)] in Et_2O. Since these results, [NiClCp(IMes)] has been further developed by Nolan along with a family of *N*-heterocyclic carbene (NHC) transition-metal complexes for use in cross coupling reactions.[185,186]

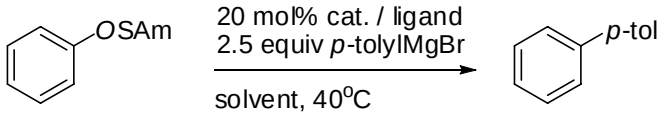
Tables 2.2. KCT Cross Coupling Optimizations



2.10a **2.23**

Catalyst / ligand	Yield (%)[a]
$NiCl_2$ / $P(Cy)_3$	**72**
$NiCl_2$ / $P(o\text{-tol})_3$	**69**
$NiCl_2$ / $P(furyl)_3$	**5**
$NiCl_2$ / $P(t\text{-Bu})_3$	**63**
$NiCl_2$ / (±)-BINAP	**25**
$NiCl_2$ / dmpe	**17**
$NiCl_2$ / dppf	**74**
$NiClCp(PPh_3)$	**91**
$NiCl_2$	**72**
$Ni(acac)_2$	**29**

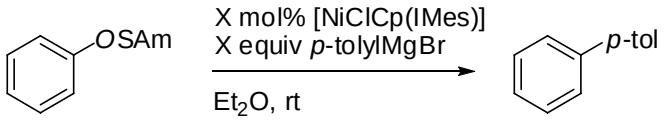
[a]determined by GC (undecane as int. std.)



2.10a **2.23**

Cat. / ligand / solvent	Yield (%)[a]
$Ni(acac)_2$ / DABCy / Et_2O	**84**
$NiCl_2$ / DABCy / THF	**14**
$NiCl_2$ / DABCy / PhMe	**81**
$NiClCp(PPh_3)$ / Et_2O	**83**
$NiClCp(PPh_3)$ / THF	**70**
$NiClCp(PPh_3)$ / DME	**12**
NiClCp(IMes) / Et_2O	**>99**
NiClCp(IMes) / THF	**83**
NiClCp(IMes) / DME	**32**
NiClCp(IMes) / PhMe	**85**

[a]determined by GC (undecane as int. std.)



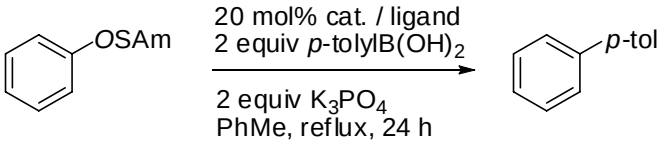
2.10a **2.23**

mol% / equiv.	Yield (%)[a]
20 / 5	**90**
20 / 3	**93**
20 / 2	**68**
20 / 1.2	**92**
10 / 5	**84**
10 / 3	**91**
10 / 2	**91**
5 / 5	**77**
5 / 3	**84**
5 / 2	**84**

[a]determined by GC (undecane as int. std.)

To probe the reactivity of **2.10a** towards Suzuki-Miyaura cross coupling, screening of nickel and palladium (II) sources with phosphine, imine, and carbene ligands was conducted employing *p*-tolylboronic acid in refluxing toluene against undecane as an internal standard (Table 2.3). In the best case, a 64% yield by GC using $[Ni(acac)_2]$ / dppp / K_3PO_4 in toluene at 90 ^oC was recorded. However, due to poor reproducibility it was elected that further experimentation was required.

Table 2.3. Suzuki-Miyaura Cross Coupling Optimizations

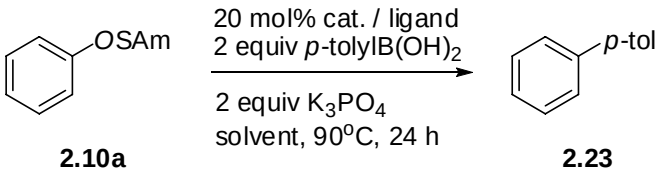


2.10a **2.23**

Catalyst / ligand	Yield (%)[a]
NiClCp(IMes)	**6**
$NiClCp(PPh_3)$	**16**
$NiCl_2$	**1**
$NiCl_2(PPh_3)_2$	**0**
$NiCl_2$ / dppf	**4**

$NiCl_2$ / dppe	**1**
$NiCl_2$ / dppp	**42**
$NiCl_2$ / P(t-Bu)$_3$	**0**
$NiCl_2$ / P(o-tol)$_3$	**0**
$NiCl_2$ / DABCy	**8**

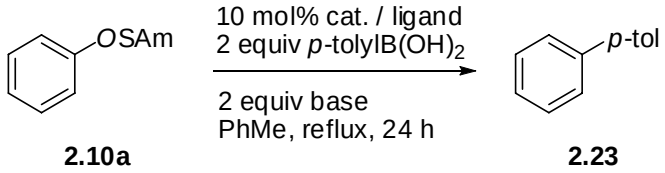
[a]determined by GC (undecane as int. std.)



2.10a **2.23**

Cat. / ligand / solvent	Yield (%)[a]
$NiCl_2$ / dppp / dioxane	**23**
$NiCl_2$ / dppp / DMF	**1**
$NiCl_2$ / dppp / NMP	**1**
$NiCl_2$ / dppp / DME	**0**
$NiCl_2$ / dppp / PhMe	**7**
Ni(acac)$_2$ / dppp / dioxane	**61**
Ni(acac)$_2$ / dppp / DMF	**1**
Ni(acac)$_2$ / dppp / PhMe	**64**
$PdCl_2$(dppp) / DMF	**18**
$PdCl_2$(dppp) / PhMe	**16**

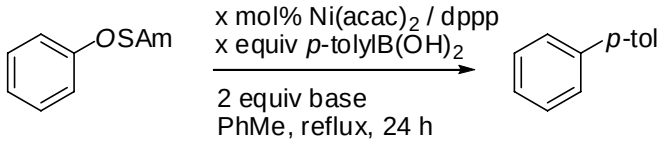
[a]determined by GC (undecane as int. std.)



2.10a **2.23**

Cat. / ligand / base	Yield (%)[a]
Ni(acac)$_2$ / K_3PO_4	**0**
Ni(acac)$_2$ / dppm, K_3PO_4	**26**
Ni(acac)$_2$ / dppe, K_3PO_4	**3**
Ni(acac)$_2$ / dppp, K_3PO_4	**28**
Ni(acac)$_2$ / dppb, K_3PO_4	**24**
Ni(acac)$_2$ / dppp, K_2CO_3	**35**
Ni(acac)$_2$ / dppp, Cs_2CO_3	**0**
Ni(acac)$_2$ / dppp, $Ba(OH)_2$	**1**
Ni(acac)$_2$ / dppp, CsF	**0**
5 mol% Ni(acac)$_2$ / dppp, K_3PO_4	**11**

[a]determined by GC (undecane as int. std.)



2.10a **2.23**

mol% / equiv. / base	Yield (%)[a]
5 / 1.5 / K_2CO_3	**33**
5 / 2 / K_2CO_3	**39**
5 / 2.5 / K_2CO_3	**43**
5 / 2 / Na_2CO_3	**18**
5 / 2 / K_3PO_4	**23**
10 / 1.5 / K_2CO_3	**44**
10 / 2 / K_2CO_3	**29**
10 / 2.5 / K_2CO_3	**39**
10 / 2 / Na_2CO_3	**14**
10 / 2 / K_3PO_4	**42**

[a]determined by GC (undecane as int. std.)

2.2 Manuscript 1:

Directed *ortho* Metalation Methodology. The *N,N*-Dialkyl Aryl *O*-Sulfamate as a New Directed Metalation Group and Cross Coupling Partner for Grignard Reagents[187]

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Department of Chemistry, Queen's University, Kingston, ON, K7L 3N6, Canada

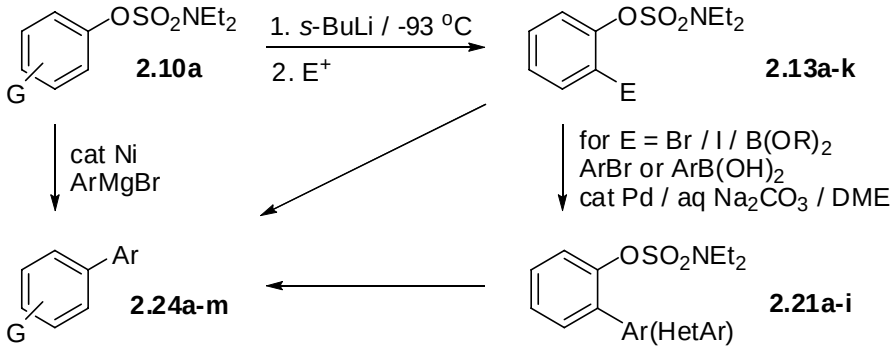
2.2.1 Preface

With minor editorial and formatting changes, this manuscript is substantially as it appears in *Organic Letters* **2005**, *7*, 2519-2522. Todd Macklin was responsible for all experimentation, distillation, chromatography, crystallization, and data collection (NMR, LRMS, IR, mp). Dr. Francoise Sauriol assisted with ^{2}H NMR. HRMS was collected by Dr. Bernd Keller. The manuscript was written by Todd Macklin and Victor Snieckus.

2.2.2 Abstract

The *ortho* metalation (RLi / THF / -93 ^{o}C) of **2.10a** followed by quench with a variety of electrophiles constitutes a new general route to substituted aryl *O*-sulfamates **2.13a-k**. The Kumada-Corriu cross coupling of *O*-sulfamates **2.13e**, **2.13n-s**, and **6a** with Grignard reagents gives biaryls **9a-m** and the use of 2-halo and boron derivatives **2.13h**, **2.13i**, and **2.13k** for Suzuki-Miyaura cross coupling and generation of benzynes leads to naphthols **2.22a** and **2.22b**. A relative metalation ranking of the $OSONEt_2$ is reported.

Scheme 2.4. Manuscript 1 Graphical Abstract



2.2.3 Introduction

The conjunction of the Directed ortho Metalation (DoM) strategy (Figure 2.4, **2.18a**,**c**,**f**,[188] **2.18b**,[31] **2.18d**,[189] **2.18e**[190])[21,22] with various transition metal catalyzed cross coupling regimens[191] has established a fountainhead of reliable methodology for the regioselective construction of biaryls in a multitude of aryl-aryl and aryl-heteroaryl bond – forming combinations.[192,193] In the context of the subsequent manipulation of Directed

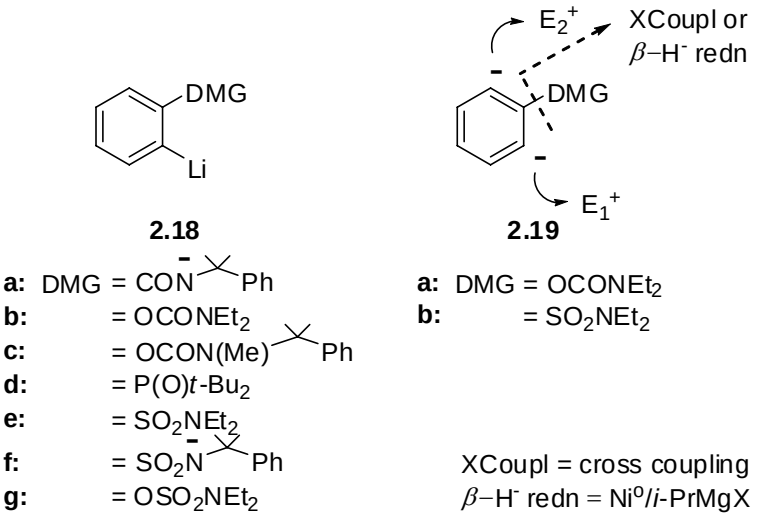


Figure 2.4. Useful DMGs for DoM

Metalation Groups (DMGs), always an important part of synthetic planning, the powerful *O*-carbamate DMG[154] and, recently, the sulfonamide DMG[155,156] have shown the additional features of latency and cross coupling capability (**2.19a-b**) hence enhancing synthetic utility especially in the context of synthesis of *meta*-substituted aromatics. Herein we report preliminary results that demonstrate that the *O*-sulfamate (**2.10a**),[194] derived by the union of $OCONR_2$[31] and SO_2NR_2[190] groups, is a new DMG and cross coupling partner in the Kumada - Corriu reaction and that the 2-halo and boron

derivatives **2.13h, 2.13i,** and **2.13k** undergo Suzuki-Miyaura cross coupling and provide a new entry to the benzyne species. In sum, the reported work provides new methods of general utility in synthetic aromatic chemistry.

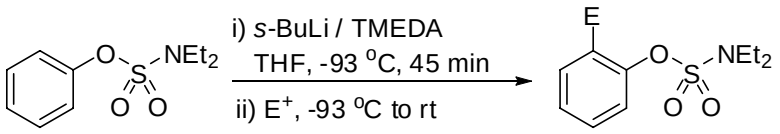
2.2.4 Results and Discussion

At the outset, the similarity of the *O*-sulfamate to OTs,[195] OMs,[196] and especially OTf[197] groups raised concerns that it would suffer, perhaps with similar propensity, *ortho*- anion induced benzyne formation,[198] an apprehension which was verified at the -78 ^{o}C temperatures commonly used for DoM chemistry. However, at -93 ^{o}C (internal temperature by thermocouple measurement), the simply prepared[177] prototype *O*-sulfamate **2.10a** underwent smooth *ortho* metalation to the intermediate lithiated species which, upon quench with a variety of electrophiles, provided products **2.13a-k** in modest to excellent yields (Table 2.4).[199] Thus, introduction of carbon (entries 1 and 3) and DMG (entry 2) carbon, sulfur (entry 4), silicon (entry 5), and nitrogen (entry 6) electrophiles proceeds unexceptionally; furthermore, halogen (entries 7-9), tin (entry 10), and boron (entry 11) electrophiles may be introduced thus inviting a study of cross coupling chemistry. In the event, the 2-iodo *O*-sulfamate **2.13i** and, in one case the corresponding bromo derivative **2.13h** (entry 7), when subjected to standard Suzuki-Miyaura cross coupling conditions with a selection of arylboronic acids **2.20,** afforded products **2.21** in excellent yields (Table 2.5). One inverted partner combination was tested (entry 8) to indicate that comparable yields may be obtained from reactions of either combination of cross coupling partners.

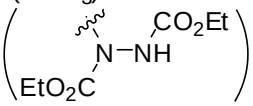
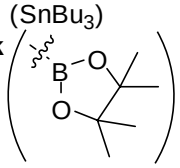
Reaction block experiments defined conditions for benzyne trapping of **2.13h**

using furan as the diene to give 7-oxabenzonorbornadiene which was converted to **2.22a** in 21% yield (Scheme 2.5). Subjection of the *ortho*-bromo *O*-sulfamates **2.13l** and **2.13m** to metal-halogen exchange at -10 ^{0}C in the presence of furan followed by catalytic HCl treatment afforded naphthols **2.22a** (concurrent protodesilylation) and **2.22b** in 50% and 31% yields, respectively. Improvement of yields was achieved by adapting the Knochel protocol for Grignard generation[200] on **2.13i** which, after furan trap and acid hydrolysis, furnished **2.22a** in 70% yield.[201]

Table 2.4. Metalation and Electrophile Quench of Phenyl *O*-Sulfamate 2.10[a]

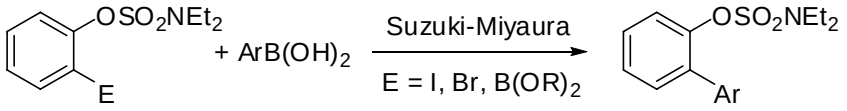


2.10a **2.13a-k**

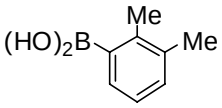
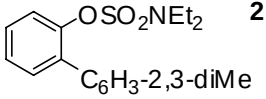
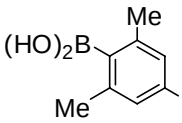
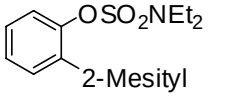
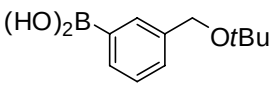
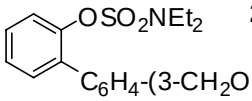
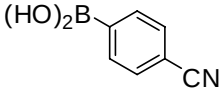
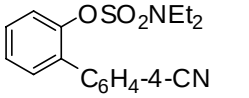
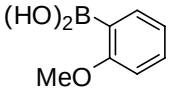
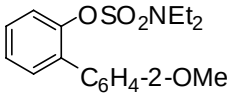
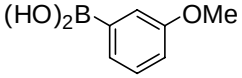
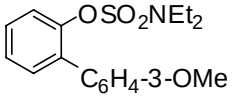
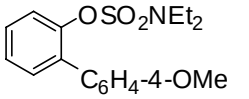
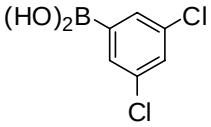
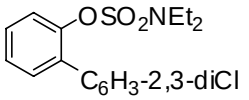
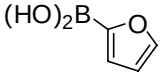
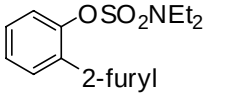
entry	E^+	product (E)	yield (%)
1	DMF	**2.13a** (CHO)	63
2	$ClCONEt_2$	**2.13b** ($CONEt_2$)	70
3	PhCHO	**2.13c** (CH(OH)Ph)	85
4	MeSSMe	**2.13d** (SMe)	88
5	Me_3SiCl	**2.13e** ($SiMe_3$)	96
6	DEAD	**2.13f** 	53
7	Cl_3CCCl_3	**2.13g** (Cl)	45
8	$Br_2CHCHBr_2$	**2.13h** (Br)	56
9	I_2	**2.13i** (I)	78
10	Bu_3SnCl	**2.13j** ($SnBu_3$)	91
11	(1) $B(O\textit{i}\text{-}Pr)_3$ (2) pinacol	**2.13k** 	87

[a] Typical procedure: i) 1.1 equiv of *s*-BuLi/TMEDA, THF, -93 ^{o}C, 45 min, 0.2-0.5 M; ii) E^+, -93^{o}C to rt.

Table 2.5. Suzuki-Miyaura Cross-Coupling Reactions of 2-Bromo, 2-Iodo, and 2-Pinacolboronate *O*-Phenylsulfamate 2.13h, 2.13i and 2.13k[a]



2.13h, i, k **2.20** **2.21a-i**

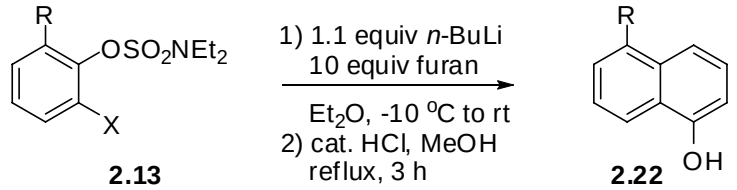
entry	E	$ArB(OH)_2$ (**2.20**)	product		yield (%)
1	I **(2.13i)**			**2.21a**	85
2[b]	I **(2.13i)**			**2.21b**	56
3	I **(2.13i)**			**2.21c**	99
4	I **(2.13i)**			**2.21d**	93
5	I **(2.13i)**			**2.21e**	85
6	I **(2.13i)**			**2.21f**	92
7	Br **(2.13h)**	$4\text{-MeOC}_6\text{H}_4\text{B(OH)}_2$		**2.21g**	85
8	$B(OR)_2$ **(2.13k)**	4-Bromoanisole			93
9	I **(2.13i)**			**2.21h**	91
10[b]	I **(2.13i)**			**2.21i**	76

[a] Typical procedure: 1 equiv of ArX, 5 mol % $[Pd(PPh_3)_4]$, DME, 2M Na_2CO_3, 80 °C, 16 h. [b] 2 equiv of ArX, 10 mol % $[Pd(PPh_3)_4]$, 40 h.

Encouraged by the results of *O*-carbamate[154] and related phenol–derived cross coupling partners,[195-197] we screened a number of nickel catalysts[202] on **2.10a** using *p*-

tolylmagnesium bromide as a standard Grignard partner (Table 2.6). While using non-liganded (entry 1,2) and phosphine mono (entry 3) and bidentate (entry 4) Ni-catalysis

Scheme 2.5. Optimization of Benzyne Trapping



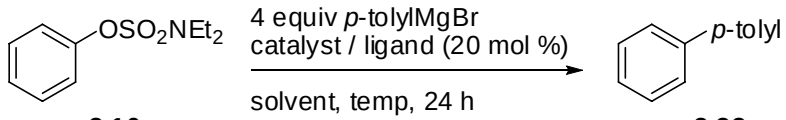
2.13 **2.22**

h	X = Br	R = H	**a**	R = H	(21%)
l	X = Br	R = TMS	**a**	R = H	(50%)
m	X = Br	R = OMe	**b**	R = OMe	(31%)
i	X = I	R = H	**a**	R = H	(70%)[a]

[a] Knochel protocol: 1) 1.1 equiv *i*-PrMgCl, Et_2O, -78 °C, 30 min; 10 equiv furan, -78 °C to rt. 2) cat. HCl, MeOH, reflux, 3 h.

already provided reasonable yields of product **2.23**, use of Cp – containing catalysts (entries 5-9) showed considerable enhancement in yields with the air-stable, conveniently

Table 2.6. Optimization of Conditions for the Nickel-Catalyzed Phenyl *O*-Sulfamate 2.13 – *p*-tolyl Grignard Cross Coupling Reaction



2.10a **2.23**

entry	catalyst / ligand	solvent	temp (°C)	yield (%)[a]
1	$Ni(acac)_2$	PhMe	120	29
2	$NiCl_2$	PhMe	120	72
3	$NiCl_2$ / P(*t*-Bu)$_3$	PhMe	120	63
4	$NiCl_2$ / dppf	PhMe	120	74
5	$NiClCpPPh_3$	Et_2O	40	83
6	$NiClCpPPh_3$	PhMe	120	91
7	NiClCp(IMes)	THF	40	83
8	NiClCp(IMes)	PhMe	40	85
9	**NiClCp(IMes)**	**Et_2O**	**40**	**>99**

[a]determined by GC (undecane as internal standard)

handled [NiClCp(IMes)] performing as a superb catalyst at low loading in ether at room temperature to afford **2.23** in quantitative yield.[203] Using this optimized set of conditions, cross coupling reactions of selected aryl *O*-sulfamate – aryl Grignard reagent combinations were carried out to afford biaryl products **2.24a-m** in synthetically useful yields (Table 2.7). Aside from simple biaryls (entries 1, 3, 5-8) and a tertaryl (completing a metal tuned coupling sequence, entry 2), *N* – protected anilines (entries 3 and 4), and azabiaryls (entries 9-12) were unexceptionally obtained.[204,205] To obtain preliminary evidence for the hierarchal position of the *O*-sulfamate vis a vis other DMGs,[22] inter- and intramolecular competitive experiments were carried out (Figure 2.5). Thus treatment of 4-$CONEt_2$ phenyl *O*- sulfamate (**2.10h**) under the standard conditions for 10 min followed by CD_3OD quench led to the formation of **2.25a** and **2.25b** in a 17:1 ratio based on d_1-NMR. Using the same experimental protocol, a 1:1 mixture of *N,N*-diethyl phenyl *O*-carbamate and **2.10a** afforded deuterated **2.26** and **2.27** in a 23:1 ratio. Thus the *O*-sulfamate is a relatively poor DMG compared to the tertiary amide and the tertiary *O*-carbamate which are near the top of the qualitatively assessed ranking list.[22]

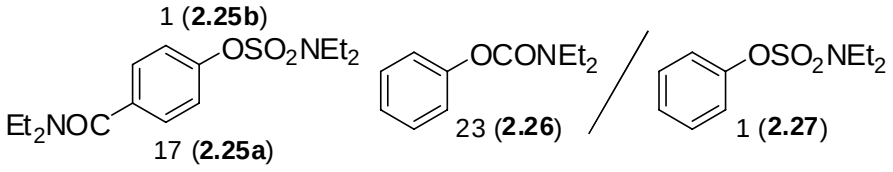
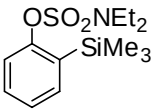
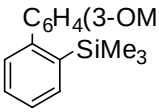
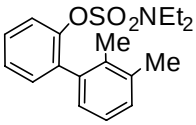
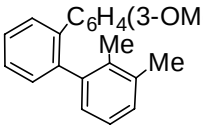
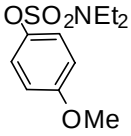
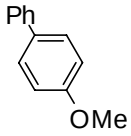
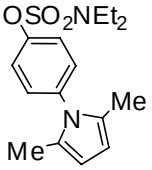
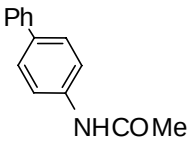
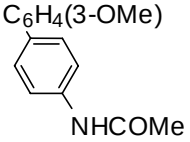
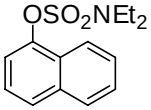
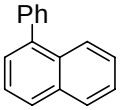
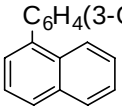
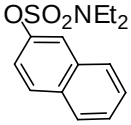
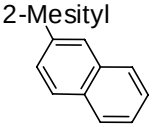
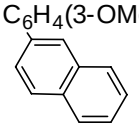
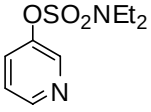
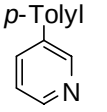
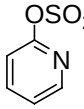


Figure 2.5. Ratios of D-Incorporation Products From Intra- and Inter-molecular DoM Competition Experiments

Table 2.7. Nickel-Catalyzed Cross Coupling of Aryl *O*-Sulfamates with Aryl Grignards Reagents[a]

2.10b-g, 2.13e, 2.21a **2.24a-m**

entry	**2.10, 2.13, 2.21**		Ar'MgBr	product		temp time	yield (%)
1		**2.13e**	$BrMgC_6H_4$ (3-OMe) (2.5 equiv)		**2.24a**	40°C 12 h	76
2		**2.21a**	$BrMgC_6H_4$ (3-OMe) (2.5 equiv)		**2.24b**	40°C 30 h	64
3		**2.10b**	BrMgPh (2.5 equiv)		**2.24c**	40°C 19h	47
4[b]		**2.10c**	BrMgPh (2.0 equiv)		**2.24d**	rt 1 h	50
5[b]		**2.10c**	$BrMgC_6H_4$ (3-OMe) (2.0 equiv)		**2.24e**	rt 3 h	46
6		**2.10d**	BrMgPh (1.2 equiv)		**2.24f**	0 °C 10 min	84
7		**2.10d**	$BrMgC_6H_4$ (3-OMe) (2.0 equiv)		**2.24g**	rt 1 h	79
8		**2.10e**	2-Mesityl MgBr (2.5 equiv)		**2.24h**	40 °C 18 h	69
9		**2.10e**	$BrMgC_6H_4$ (3-OMe) (2.5 equiv)		**2.24i**	rt 1 h	86
10		**2.10f**	*p*-TolylMgBr (2.5 equiv)		**2.24j**	rt 18 h	71

11		**2.10f**	$BrMgC_6H_4$ (3-OMe) (2.5 equiv)	C_6H_4(3-OMe) 	**2.24k**	rt 18 h	85
12		**2.10g**	*p*-TolylMgBr (2.0 equiv)	*p*-Tolyl 	**2.24l**	rt 8 h	82
13		**2.10g**	$BrMgC_6H_4$ (3-OMe) (2.0 equiv)	C_6H_4(3-OMe) 	**2.24m**	rt 4 h	73

[a]Typical procedure: 1.2-2.5 equiv of Ar'MgBr, 1-2.5 mol % [NiClCp(IMes)], Et_2O, 0-40 ^oC, 0.1-19 h. [b]deprotection/acylation: 10 equiv hydroxylamine HCl, 2 equiv NEt_3, 2:1 EtOH:H_2O, 90 ^oC, 24 h, then 1.2 equiv acetic anhydride, 2 equiv NEt_3, CH_2Cl_2, rt, 1 h.

2.2.5 Conclusion

In conclusion, we have shown that the *O*-sulfamate is a new, albeit moderate strength, DMG. *Ortho*-halo and boron products **2.13h, 2.13i,** and **2.13k** participate in Suzuki-Miyaura cross coupling and, perhaps more significantly, the *O*-sulfamates themselves undergoes Kumada-Corriu coupling, both reactions leading to functionalized and potentially bioactive biaryls (Tables 2 and 4). The new reactions extend DoM concepts and protocols for application in synthetic endeavours.

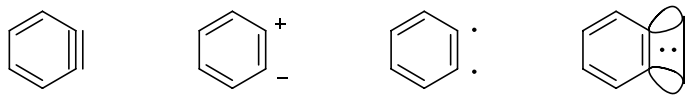
2.2.6 Acknowledgement

We are grateful to NSERC Canada for support under the DG program and thank Francoise Sauriol and Mark Reed for expert NMR assistance and starting material provision, respectively. We are most grateful to Frontier Scientific for samples of boronic acids which allowed expansion of scope of this methodology.

2.3 Post Scriptum

2.3.1 Benzyne

1,2-Didehydrobenzene (*o*-benzyne) and its derivatives (arynes) are structurally fascinating and extraordinarily reactive chemical entities. These uniquely reactive intermediates have been described in the literature for over 100 years.[206] This species can be represented by several structural formulae (**2.29-2.31**) or by a molecular orbital representation (**2.32**) that can more accurately illustrate the possession of two p-orbitals containing two electrons coplanar with the sigma-framework of the aromatic ring and orthogonal to its π-system.[207] This structure has been observed in the IR,[208] by solid-state and molecular compartmental-based NMR,[208,209] and by ultraviolet photoelectron spectroscopy.[210]



2.29 **2.30** **2.31** **2.32**

Figure 2.6. Structral Representations of Benzyne

The use of arynes in organic synthesis has been extensive; illustrated by the number of reviews dedicated to the subject.[211-214] The reactions of benzyne are quite vast and can be divided into three groups: pericyclic (Diels-Alder, [2+2], 1,3- and 1,4-dipolar, and ene), nucleophile addition (carbon, nitrogen, oxygen and sulfur), and transition metal-catalyzed (palladium and nickel) reactions. Benzyne can be generated by β-elimination of benzenediazonium-2-carboxylate,[215] 1-aminobenzotriazole,[216] or more popularly from a *o*-lithiated halobenzene generated by D*o*M or a metal-halogen exchange

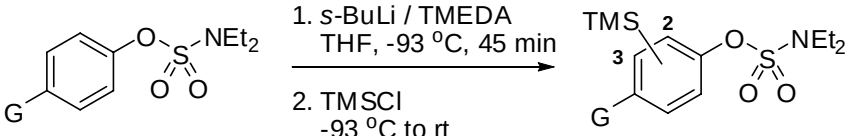
reaction.[214,217] Currently the mildest and most efficient method for benzyne generation, pioneered by Cunico and Dexheiner, involves mild fluoride mediated desilylation / β-elimination of *o*-haloarylsilanes.[218] Kobayashi introduced the use of aryltriflates in this reaction,[219] which not only takes advantage of the suprior leaving group ability of triflates (10^8 greater than Cl),[220] but permits expedient construction from commercial phenols. A popular use of arynes in synthesis is the Diels-Alder reaction with furan to yield 7-oxabenzonorbornadiene compounds. These cycloadduction products are uniquely reactive precursors that have been used to prepare highly substituted naphthalene systems found in natural products (e.g. (+)-gilvocarcin M,[221] podocarbic acid,[222] and ellipticine[223]).

2.3.2 Aryl *O*-Sulfamates as a Handle for Benzyne Generation

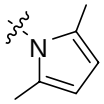
To further elaborate on the investigation of the benzyne trapping of *o*-lithiophenyl *O*-sulfamate and our reported improvement of this process utilizing Knochel's procedure of magnesium-iodine exchange (Scheme 2.5), we set out to expand the scope of this process. Substituted 7-oxabenzonorbornadienes systems were then prepared by two-fold D*o*M of aryl *O*-sulfamates followed by aryne generation. This study would allow access to aryne products unavailable by the Knochel method and at the same time showcase the versatility and latency of the *O*-sulfamate DMG. Several 4-substituted aryl *O*-sulfamates (**2.10b,c,i,k,l**) mostly containing *para*-activating groups were synthesized, lithiated and quenched with TMSCl (**2.13o-q**, Table 2.8). As seen in Table 2.8, complete regioselective introduction of TMS was observed with 4-(2,5-Dimethylpyrrol-1-yl) (entry 1), 4-isopropoxy (entry 3), and 4-chloro (entry 5) phenyl *O*-sulfamates. A better understanding of the relative hierarchy and directing ability of *O*-sulfamate as a DMG

can be observed in entry 2 and 4, placing it roughly equal to fluorine ($OSO_2NEt_2 \approx F$) and higher than methoxy ($OSO_2NEt_2 > OMe$) for these standardized conditions. The 2-TMS derived aryl *O*-sulfamates **2.13o-q** and 1,4-bis(*O*-sulfamoyl) benzene **2.13j** were then subjected to a D*o*M – iodination sequence furnishing 2-iodo aryl *O*-sulfamates **2.13r-t**

Table 2.8. Metalation and TMS^+ Quench of Aryl *O*-Sulfamates 2.10b,c,i,k,l



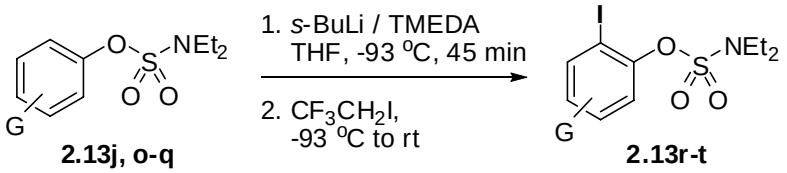
2.10b,c,i,k,l **2.13o-q**

entry	G		product yield (%)[a] 2-TMS		3-TMS
1		(**2.10c**)	91	(**2.13o**)	-
2	OMe	(**2.10b**)	(77)		(12)
3	O*i*-Pr	(**2.10i**)	90	(**2.13p**)	-
4	F	(**2.10k**)	(54)		(42)
5	Cl	(**2.10l**)	79	(**2.13q**)	-

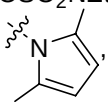
[a] Yields in parenthesis represent GC ratios

(Table 2.9). Several attempts to lithiate **2.13p** [*n*-BuLi, *s*-BuLi, *t*-BuLi, LTMP (with and without TMEDA) in THF and Et_2O using I_2 and ICH_2CF_3 as an I^+ source] resulting in quantitative recovery of starting material. An alternative approach using TMSCl as an electrophile was envisaged, and, if successful, an *ipso*-monodesilylation-iodination sequence could provide the desired compound.[224] *In situ* Martin conditions[36] with LDA:TMSCl (1.5-2.5:3-5 equiv) at -78 °C and 0 °C gave no reaction while switching to LTMP:TMSCl (2.5:5) at -93 °C for 1 h followed by warming to room temperature resulted in many aryne degradation products, starting material, and one bis-silylated

Table 2.9. Metalation and I^+ Quench of Aryl *O*-Sulfamates 2.13j,o-p

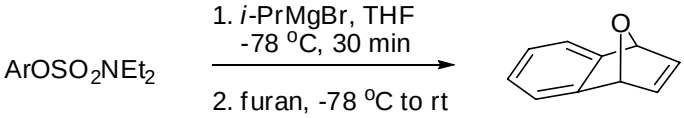


2.13j, o-q **2.13r-t**

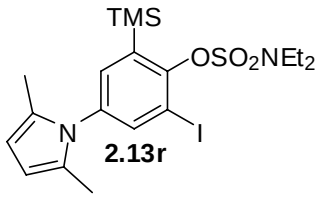
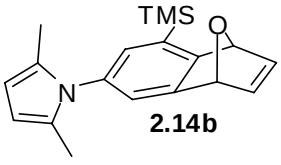
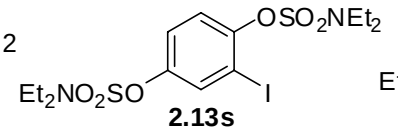
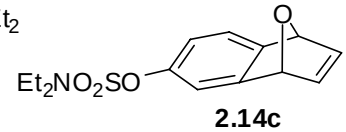
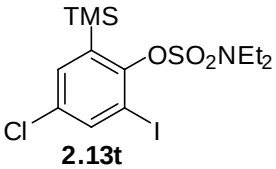
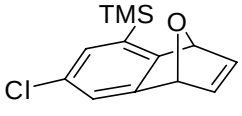
entry	G		product, yld (%)	
1	4-OSO_2NEt_2	(**2.13j**)	80	(**2.13r**)
2	4-  , 2-TMS	(**2.13o**)	72	(**2.13s**)
3	4-O*i*-Pr, 2-TMS	(**2.13p**)	-	
4	4-Cl, 2-TMS	(**2.10q**)	80	(**2.13t**)

product (15% by GC) that was identified as the undesired 4-isopropoxy-2,5-bis(trimethylsilyl)phenyl *O*-sulfamate by NOE. Treatment of the 2-iodoaryl *O*-

Table 2.10. Synthesis of Substituted 7-Oxabenzonorbornadienes



2.13r-t **2.14b-d**

entry	**2.12**	product	yield (%)
1	 **2.13r**	 **2.14b**	47
2	 **2.13s**	 **2.14c**	51
3	 **2.13t**	 **2.14d**	79

sulfamates **2.13r-t** with *i*-PrMgBr at -78 ^{o}C permitted iodine-magnesium exchange, and subsequent addition of furan and warming provided substituted 7-oxabenzonorbornadienes **2.14b-d** (Table 2.10).

2.4 Experimental

2.4.1 General Methods

Melting points are uncorrected. Infrared spectra were recorded as neat or KBr discs using a BOMEM MB-100 FTIR spectrophotometer. ^{1}H NMR spectra were recorded using an Avance 300 MHz or Bruker 400 MHz spectrometer. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sx, sextet; dd, doublet of doublet; td, triplet of doublet; m, multiplet; bs, broad singlet. GCMS analyses were performed with an *Agilent 6890N* GC coupled with an *Agilent 5973 inert* MS under EI conditions. THF and Et_2O were freshly distilled from sodium benzophenone ketyl under argon and *N,N*-diethylcarbamoyl chloride was distilled from CaH_2 and stored over 4 Å molecular sieves prior to use. *N*-, *sec*- and *tert*-butyllithium were purchased from Aldrich as solutions in hexanes, cyclohexane, and pentane, stored in resealable containers, and titrated periodically against *N*-benzylbenzamide. LDA and LTMP were freshly prepared before reactions by stirring a 1:1 mixture of di*iso*propylamine or 2,2',6,6'-tetramethylpiperidine and *n*-BuLi at 0 ^{o}C in THF (1 M) for 10 min. *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was stored over solid KOH prior to use. All reactions involving alkyllithiums were carried out in oven or flame-dried glassware cooled under argon using syring-septum cap techniques. The -93, -78, -10, and 0 ^{o}C temperatures designated are approximate as achieved by a liquid nitrogen-hexanes, dry ice-acetone, ice-acetone, and ice-salt bath, respectively. When internal temperature readings were essential, a Barnant Dual J stainless steel-sheathed thermocouple thermometer was employed. *N,N*-Diethylsulfamoyl chloride and [CpNiCl(IMes)] were prepared from literature

procedures.[177,225] [$Pd(PPh_3)_4$] was freshly prepared according to a literature procedure[226] and solutions were pre-degassed using sonication associated with argon bubbling. Furan was freshly distilled from KOH prior to use. Reaction monitoring was done by TLC and GC where appropriate. Flash column chromatography was carried out using Merck silica gel 60 (particle size: 32-63).

A. Preparation of *N,N*-Diethyl Aryl *O*-Sulfamates

To a suspension of NaH (80% in mineral oil, 3.35 g, 112 mmol) in DMF (300 mL) under an argon atmosphere was added *via* canula a solution of phenol (10 g, 106 mmol) in DMF (50 mL) at -10 ^oC. The resulting sodium aryloxide was stirred for 30 min at rt before recooling to -10 ^oC and treated with *N,N*-diethylsulfamoyl chloride (15.75 mL, 112 mmol). The solution was allowed to warm to rt, quenched with saturated aq NH_4Cl solution (20 mL), diluted with water (1.5 L), extracted with hexanes (3 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product which was subjected to high vacuum distillation to afford the pure product.

B. Lithiation of *N,N*-Diethyl Benzene *O*-Sulfamate 2.10a

A solution of **2.10a** (229 mg, 1 mmol) and TMEDA (0.17 mL, 1.1 mmol) in THF (5 mL) cooled to -93 ^oC was treated with a solution of *s*-BuLi (1.1 mmol, 1.1 equiv) The resulting yellow solution was stirred (45 min), treated dropwise *via* a syringe with an electrophile (1.2 mmol, 1.2 equiv), and the whole was allowed to warm to rt over 15 min. Standard workup afforded the crude product.

C. Suzuki-Miyaura Cross-coupling Reactions of 2-Bromo, 2-Iodo, and 2-Pinacolboronate Phenyl *O*-Sulfamate 2.13h, i, k

A round-bottom flask fitted with a reflux condenser under Ar atmosphere containing a degassed solvent/base mixture (DME / Na_2CO_3 2 M) was charged with the appropriate aryl O-sulfamate and aryl boronic acid or aryl bromide in eqimolar amounts. [$Pd(PPh_3)_4$] (5 mol %), dispensed in a glovebag, was quickly added, and the stirred reaction mixture was purged with argon for an additional 10 min, refluxed (90 ^oC) until consumption of starting material (TLC monitoring) and then allowed to cool to ambient temperature. DME was removed in *vacuo* and the remaining aqueous solution was extracted with EtOAc (3 x 10 mL). The combined extract was washed with brine, dried (Na_2SO_4), subjected to filtration through a short pad of silica, and concentrated in *vacuo* to afford a residue, which was purified by flash column chromatography (silica gel, hexanes / EtOAc).

D. Cross-coupling of Aryl *O*-Sulfamates 2.10a-g, 2.13e, 2.21a

To a solution of *N,N*-diethyl benzene O-sulfamate **2.10a** (1 mmol) in anhydrous Et_2O (2.5 mL) under an Ar atmosphere was added [NiClCp(IMes)] (0.01 mmol) followed by *p*-tolylphenylmagnesium bromide (1.5 mmol) *via* syringe. The brown mixture was stirred at rt until consumption of starting material (TLC monitoring) and then quenched carefully with saturated NH_4Cl solution. The magnesium salts were dissolved by the addition of H_2O, the whole was diluted with EtOAc and the layers were separated. The aqueous layer was further extracted with EtOAc (x2). The combined extracts were

washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude biaryl was purified *via* flash column chromatography (silica gel, hexanes / EtOAc).

E. Naphthols 2.22a, b *via* Benzyne Trapping of 2-Bromo Phenyl *O*-Sulfamate 2.13h

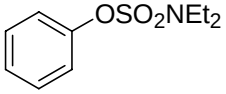
A solution of **2.13h** (307 mg, 1 mmol) and furan (0.73 ml, 10 mmol) in Et_2O (2 mL) cooled to -10 ^oC under argon atmosphere was treated with a solution of *n*-BuLi (1.1 mmol, 1.1 equiv). The resulting solution was allowed to warm to rt over 15 min. Standard workup afforded the crude product which was dissolved in absolute EtOH (5 mL), added several drops of concentrated HCl, and refluxed for 12 h. Workup afforded the crude product.

F. Knochel's Procedure[200] for Benzyne Generation for *O*-Sulfamates 2.13i,o,s,t

A solution of **2.13i** (500 mg, 1.4 mmol) in Et_2O (20 mL) at -78 ^oC is added *i*PrMgCl (0.77 mL, 2.0 M in Et_2O, 1.54 mmol) dropwise by syring and stirred at -78 ^oC for 30 min. Furan (1.0 mL, 14 mmol) is added and the resulting solution was allowed to warm to rt and stirred for 12 h. The mixture is treated with aq. NH_4Cl (10 mL), the layers separated, aqueous layer washed with EtOAc (10 mL), extracts combined, dried (Na_2SO_4), and concentrated *in vacuo*. The crude products were purified by column chromatography.

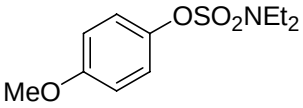
2.4.2 Experimental Procedures and Data

N,N-Diethyl phenyl *O*-sulfamate (2.10a)



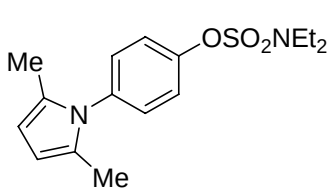
This compound was prepared by **Method A** using the following materials: NaH (80% in mineral oil, 3.35 g, 112 mmol), phenol (10 g, 106 mol), *N,N*-diethylsulfamoyl chloride (15.75 mL, 112 mmol) in DMF (350 mL). Work-up and high vacuum distillation afforded pure **2.10a** (22 g, 92 %) as a colourless oil, bp 120 ^{o}C/3.5 mm Hg, [lit[227] 118 ^{o}C/4 mm Hg]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.37 (m, 2H), 7.31-7.28 (m, 3H), 3.39 (q, 4H, J = 7.2 Hz), 1.24 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.3, 127.2, 122.6, 44.1, 14.2 ppm.

N,N-Diethyl 4-methoxyphenyl *O*-sulfamate (2.10b)



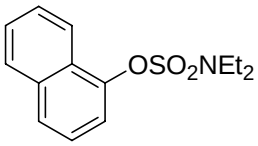
This compound was prepared by **Method A** using the following materials: NaH (80% in mineral oil, 0.73 g, 24.2 mmol), phenol (3.00 g, 24.2 mmol), *N,N*-diethylsulfamoyl chloride (3.4 mL, 24.2 mmol) in DMF (100 mL). Standard workup and high vacuum distillation afforded pure **2.10b** (5.4 g, 86 %) as a colourless oil; IR (neat) ν_{max} 2985, 2926, 2844, 1591, 1502, 1368, 1253, 1202, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, 2H, J = 9.2 Hz), 6.79 (d, 2H, J = 9.2 Hz), 3.70 (s, 3H), 3.26 (q, 4H, J = 7.2 Hz), 1.11 (t, 6H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 143.7, 123.0, 114.6, 55.6, 43.5, 13.6 ppm; LRMS (EI) (*m/z*(%)) 259(M^+, 92), 123(100); HRMS (ESI) calcd for $C_{11}H_{17}NO_4S$ 260.0947: found 260.0957.

***N,N*-Diethyl 4-(2,5-dimethyl-pyrrol-1-yl)phenyl *O*-sulfamate (2.10c)**



This compound was prepared by **Method A** using the following materials: NaH (80% in mineral oil, 0.88 g, 29.4 mmol), 4-(2,5-dimethyl-pyrrol-1-yl)-phenol[228] (5.00 g, 26.7 mmol), *N,N*-diethylsulfamoyl chloride (4.53 mL, 32.0 mmol) in DMF (100 mL). Work-up and high vacuum distillation afforded pure **2.10c** (8.00 g, 93 %) as a pale-yellow solid, mp 73-74 ^{o}C (hexanes); IR (KBr) ν_{max} 2991, 2945, 1502, 1366, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2H, J = 8.7 Hz), 7.22 (d, 2H, J = 8.7 Hz), 5.90 (s, 2H), 3.42 (q, 4H, J = 7.2 Hz), 2.02 (s, 6H), 1.23 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 137.2, 129.5, 128.8, 122.5, 106.0, 43.5, 13.4, 13.0 ppm; LRMS (EI) *(m/z(%))* 323(M^+ + 1, 100), 322(M^+, 32); HRMS (ESI) calcd for $C_{16}H_{22}N_2O_3S$ 323.1430: found 323.1424.

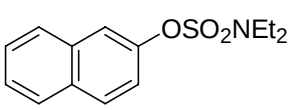
***N,N*-Diethyl naphthalene-1-yl *O*-sulfamate (2.10d)**



This compound was prepared by **Method A** using the following materials: NaH (80 % in mineral oil, 1.1 g, 36 mmol), 1-napthol (5.00 g, 34.7 mmol), *N,N*-diethylsulfamoyl chloride (5.38 mL, 38.2 mmol) in DMF (120 mL). Work-up and high vacuum distillation afforded pure **2.10d** (8.2 g, 85 %) as a grey-green solid, mp 51-52 ^{o}C (hexanes); IR (KBr) ν_{max} 2987, 2943, 1606, 1472, 1371, 1218, 1180 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, 1H, J = 1.3, 8.3 Hz), 7.88 (d, 1H, J = 1.3, 7.4 Hz), 7.77 (d, 1H, J = 8.2 Hz), 7.57 (m, 3H), 7.47 (t, 1H, J = 8.0 Hz), 3.50 (q, 4H, J = 7.1 Hz), 1.27 (t, 6H, J = 7.0 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 134.8, 127.9, 127.2, 126.7, 126.5, 125.4, 121.7, 117.7, 43.5, 13.7 ppm;

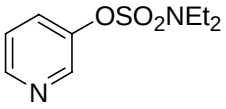
LRMS (EI) *(m/z(%))* 279(M^+, 100); HRMS (EI) calcd for $C_{14}H_{17}NO_3S$ 279.0929: found 279.0931.

_N,N_-Diethyl naphthalene-2-yl _O_-sulfamate (2.10e)



This compound was prepared by **Method A** using the following materials: NaH (80% in mineral oil, 1.1 g, 36 mmol), 1-napthol (5.00 g, 34.7 mmol), *N,N*-diethylsulfamoyl chloride (5.38 mL, 38.2 mmol) in DMF (120 mL). Work-up and high vacuum distillation afforded pure **2.10e** (8.6 g, 89 %) as a yellow oil; IR (neat) ν_{max} 2969, 2940, 1598, 1508, 1464, 1374, 1208, 1170, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.79 (m, 3H), 7.73 (d, 1H, J = 2.6 Hz), 7.57 (m, 2H), 7.40 (dd, 1H, J = 2.4, 8.9 Hz), 3.39 (q, 4H, J = 7.1 Hz), 1.20 (t, 6H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 133.7, 131.8, 129.8, 127.8, 126.9, 126.2, 121.1, 119.1, 43.6, 13.6 ppm; LRMS (EI) *(m/z(%))* 279(M^+, 100); HRMS (EI) calcd for $C_{14}H_{17}NO_3S$ 279.0932: found 279.0929.

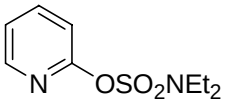
_N,N_-Diethyl pyridin-3-yl _O_-sulfamate (2.10f)



To a slurry of 3-hydroxypyridine (4.6 g, 48.8 mmol) in PhMe (100 mL) at rt was sequentially added Et_3N (8.0 mL, 58.5 mmol), *N,N*-diethylsulfamoyl chloride (8.25 mL, 58.5 mmol) *via* syringe. A condenser was then attached, and the mixture brought to reflux. After 12 h, the mixture was cooled and concentrated *in vacuo.* The residue was dissolved in EtOAc, poured in water and the layers were separated. Standard work-up and high vacuum distillation afforded pure **2.10f** (9.5 g, 85 %) as light yellow oil; IR (neat) 2985, 2967, 1579, 1483, 1419, 1391,

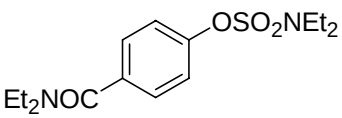
1208, 1157 ν_{max} cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, 1H, J = 2.7 Hz), 8.51 (d, 1H, J = 4.7 Hz), 7.66 (m, 1H), 7.37 (dd, 1H, J = 4.7, 8.4 Hz), 3.40 (q, 4H, J = 7.2 Hz), 1.22 (t, 6H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 147.2, 143.7, 129.4, 124.2, 43.5, 13.5 ppm; LRMS (EI) *(m/z(%))* 231(M^+ + 1, 100); HRMS (ESI) calcd for $C_9H_{14}N_2O_3S$ 231.0792: found 231.0798.

_N,N_-Diethyl pyridin-2-yl _O_-sulfamate (2.10g)



To a slurry of 2-hydroxypyridine (4.6 g, 48.8 mmol) in PhMe (100 mL) at rt was sequentially added Et_3N (8.0 mL, 58.5 mmol), *N,N*-diethylsulfamoyl chloride (8.25 mL, 58.5 mmol) *via* syringe. A condenser was then attached, and the mixture brought to reflux. After 12 h, the reaction mixture was cooled and concentrated *in vacuo*. The residue was dissolved in EtOAc, poured in water and the layers were separated. Standard work-up and high vacuum distillation afforded pure **2.10g** (9.5 g, 85 %) as light yellow oil; IR (neat) ν_{max} 2978, 1598, 1470, 1432, 1380, 1221, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, 1H, J = 1.8, 4.8 Hz), 7.75 (ddd, 1H, J = 2.0, 7.6 Hz), 7.19 (dd, 1H, J = 4.9, 7.3 Hz), 7.16 (d, 1H, J = 8.2 Hz), 3.41 (q, 4H, J = 7.3 Hz), 1.19 (t, 6H, J = 7.3 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 148.2, 140.0, 122.1, 115.2, 43.6, 13.5 ppm; LRMS (EI) *(m/z(%))* 231(M^+ + 1, 100); HRMS (ESI) calcd for $C_9H_{14}N_2O_3S$ 231.0804: found 231.0803.

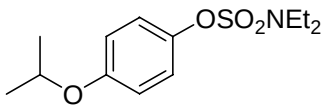
_N,N_-Diethyl 4-diethylcarbamoylphenyl _O_-sulfamate (2.10h)



This compound was prepared by **Method B** using the following materials: **2.10m** (2.00 g, 6.49 mmol), *n*-BuLi

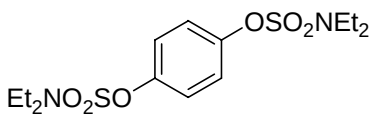
(2.75 mL, 2.5 M in hexanes, 6.82 mmol), THF (20 mL), *N,N*-diethylcarbamoyl chloride (0.91 mL, 7.14 mmol). Standard work-up and high vacuum distillation afforded pure **2.10h** (2.00 g, 94 %) as a colourless solid; mp 91-92 ^{o}C (hexanes); IR (neat) ν_{max} 2978, 1630, 1464, 1374, 1202, 1150, 863 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, 2H, J = 8.6 Hz), 7.31 (d, 2H, J = 8.6 Hz), 3.40 (q, 8H, J = 7.2 Hz), 1.23 (t, 12H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 150.8, 135.5, 128.0, 121.9, 43.6, 13.5 ppm; LRMS (EI) *(m/z(%))* 329(M^+ + 1, 84), 256(100); HRMS (EI) calcd for $C_{15}H_{24}N_2O_4S$ 327.1381: found 327.1379.

_N,N_-Diethyl 4-isopropoxyphenyl _O_-sulfamate (2.10i)



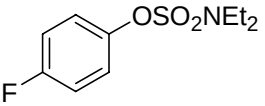
This compound was prepared by **Method A** using the following materials: NaH (60% in mineral oil, 1.48 g, 35 mmol), 4-isopropoxyphenol (5.00 g, 32.9 mmol), *N,N*-diethylsulfamoyl chloride (4.7 mL, 32.9 mmol) in DMF (150 mL). Work-up and high vacuum distillation afforded pure **2.10i** (8.5 g, 90 %) as a light yellow oil; IR (neat) ν_{max} 2972, 2934, 1592, 1496, 1374, 1298, 1246, 1202, 1151, 1112, 1029, 946, 850, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, 2H, J = 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz) 4.50 (qn 1H, J = 6.0 Hz), 3.35 (q, 4H, J = 7.2 Hz), 1.33 (s, 3H), 1.31 (s, 3H), 1.19 (t, 6H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 143.5, 123.0, 116.5, 70.4, 43.5, 21.9, 13.6 ppm; LRMS (EI) *(m/z(%))* 287(M^+, 7), 245(3), 136(21), 109(100); HRMS (EI) calculated for $C_{13}H_{21}NO_4S$ 287.1191: found 287.1194.

1,4-Bis(*N,N*-Diethylsulfamoyl) benzene (2.10j)



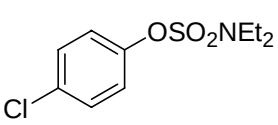
This compound was prepared by **Method A** using the following materials: NaH (60% in mineral oil, 1.64 g, 40.1 mmol, hydroquinone (5.00 g, 45.5 mmol), *N,N*-diethylsulfamoyl chloride (4.5 mL, 31.9 mmol) in DMF (200 mL). Work-up and high vacuum distillation afforded a solid the was recrystallized (hexanes:EtOAc) yielding **2.10j** (7.0 g, 58 %) as light brown crystals, mp 110-111 ^{o}C; IR (neat) ν_{max} 2992, 2346, 1490, 1370, 1211, 1186, 1142, 1027, 831, 685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 3.40 (q, 8H, J = 7.2 Hz), 1.24 (t, 12H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 123.1, 43.5, 13.5 ppm; LRMS (EI) *(m/z(%))* 380(M^+, 90), 136(100); HRMS (EI) calculated for $C_{14}H_{24}N_2O_6S_2$ 380.1064: found 380.1076.

***N,N*-Diethyl 4-fluorophenyl *O*-sulfamate (2.10k)**



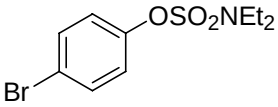
This compound was prepared by **Method A** using the following materials: NaH (80% in mineral oil, 1.40 g, 46.8 mmol), 4-fluorophenol (5.00 g, 44.6 mmol), *N,N*-diethylsulfamoyl chloride (6.9 mL, 49 mmol) in DMF (150 mL). Work-up and high vacuum distillation afforded pure **2.20k** (9.2 g, 84 %) as a colourless oil; IR (neat) ν_{max} 2981, 2941, 1505, 1373, 1210, 1157, 1023, 847, 803, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.22 (m, 2H), 7.09-7.03 (m, 2H), 3.38 (q, 4H, J = 7.1 Hz), 1.21 (t, 6H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 159.5, 146.2, 146.1, 123.6, 123.5, 116.4, 116.2, 43.5, 13.5 ppm; LRMS (EI) *(m/z(%))* 247(M^+, 57), 246(M^+ - 1, 100); HRMS (EI) calculated for $C_{10}H_{14}NO_3FS$ 247.0678: found 247.0674.

***N,N*-Diethyl 4-chlorophenyl *O*-sulfamate (2.10l)**



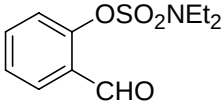
This compound was prepared by **Method A** using the following materials: NaH (80% in mineral oil, 0.7 g, 23.4 mmol), 4-chlorophenol (3.0 g, 23.4 mol), *N,N*-diethylsulfamoyl chloride (3.3 mL, 23.4 mmol) in DMF (100 mL). Work-up and high vacuum distillation afforded pure **2.10l** (5.0 g, 81 %) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 2H, J = 8.9 Hz), 7.23 (d, 2H, J = 9.0 Hz), 3.39 (q, 4H, J = 7.1 Hz), 1.23 (t, 6H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 132.1, 129.7, 123.3, 43.5, 13.5 ppm; LRMS (EI) *(m/z(%))* 263(M^+, 100). Spectroscopic data are in full agreement with those reported.[171]

***N,N*-Diethyl 4-bromophenyl *O*-sulfamate (2.10m)**[171]



This compound was prepared by **Method A** using the following materials: NaH (80% in mineral oil, 1.04 g, 34.7 mmol), 4-bromophenol (6.00 g, 34.7 mmol), *N,N*-diethylsulfamoyl chloride (4.90 mL, 34.7 mmol) in DMF (140 mL). Work-up and high vacuum distillation yielded **2.10m** (9.1 g, 85 %) as a colourless oil; IR (neat) ν_{max} 2978, 1484, 1369, 1209, 1155 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, 2H, J = 8.8 Hz), 7.08 (d, 2H, J = 8.9 Hz), 3.30 (q, 4H, J = 7.2 Hz), 1.13 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 132.7, 123.7, 119.8, 43.5, 13.5 ppm; LRMS (EI) *(m/z(%))* 309(M^+ + 2, 90), 307(M^+, 100).

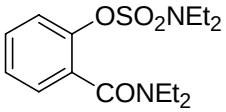
***N,N*-Diethyl 2-formylphenyl *O*-sulfamate (2.13a)**



This compound was prepared by **Method B** using the following materials: **2.10a** (0.315 g, 1.38 mmol), TMEDA (0.229 mL, 1.52

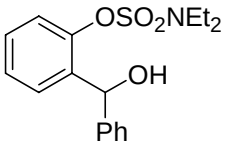
mmol), *s*-BuLi (1.17 mL, 1.3 M in cyclohexane, 1.52 mmol), THF (5 mL), DMF (0.128 mL, 1.66 mmol). Standard workup and flash chromatography (8:2 hexanes / EtOAc) afforded **2.13a** (0.222 g, 63%) as a yellow oil; IR (neat) ν_{max} 2991, 2889, 1700, 1611, 1470, 1381, 1208, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.39 (s 1H), 7.93 (dd, 1H, J = 7.7, 1.2 Hz), 7.63 (td 1H, J = 1.4, 8.5 Hz), 7.48 (d, 1H, J = 8.2 Hz), 7.39 (t, 1H, J = 7.6 Hz), 3.47 (q, 4H, 7.1 Hz), 1.27 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 152.8, 136.1, 129.7, 129.5, 127.6, 123.9, 44.2, 14.2 ppm; LRMS (EI) *(m/z(%))* 258(M^+ + 1, 37), 256(M^+ - 1, 36), 242(100); HRMS (EI) calcd for $C_{11}H_{15}NO_4S$ 258.0801: found 258.0800.

_N,N_-Diethyl 2-diethylcarbamoylphenyl _O_-sulfamate (2.13b)



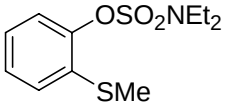
This compound was prepared by **Method B** using the following materials: **2.10a** (0.315 g, 1.38 mmol), TMEDA (0.229 mL, 1.52 mmol), *s*-BuLi (1.17 mL, 1.3 M in cyclohexane, 1.52 mmol), THF (5 mL), *N,N*-diethylcarbamoyl chloride (0.210 mL, 1.66 mmol). Standard workup and flash chromatography (8:2 hexanes / EtOAc) afforded **2.13b** (0.320 g, 70%) as a yellow oil; IR (neat) ν_{max} 2985, 2944, 1649, 1445, 1374, 1214, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, 1H, J = 8.2 Hz), 7.36 (m, 1H), 7.24 (m, 1H), 3.62 (m, 1H), 3.34 (q, 5H, 7.2 Hz), 3.15 (m, 2H), 1.21 (t, 3H, J = 7.1 Hz), 1.17 (t, 6H, J = 7.2 Hz), 1.04 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 147.0, 131.3, 130.7, 128.3, 126.9, 122.9, 44.2, 43.8, 39.6, 14.5, 14.2, 13.4 ppm; LRMS (EI) *(m/z(%))* 330(M^+ + 3, 20), 329(M^+ + 2, 100); HRMS (EI) calcd for $C_{16}H_{25}NO_4S$ 327.1534: found 329.1535.

***N,N*-Diethyl 2-(hydroxy-phenyl-methyl)phenyl *O*-sulfamate (2.13c)**



This compound was prepared by **Method B** using the following materials: **2.10a** (0.300 g, 1.32 mmol), TMEDA (0.219 mL, 1.45 mmol), *s*-BuLi (1.32 mL, 1.1 M in cyclohexane, 1.45 mmol), THF (5 mL), benzaldehyde (0.160 mL, 1.58 mmol). Standard workup and flash chromatography (8:2 hexanes / EtOAc) afforded **2.13c** (0.375 g, 85%) as a colourless oil; IR (neat) ν_{max} 3528, 2971, 2940, 1604, 1451, 1374, 1208, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.32 (m, 9H), 6.30 (d, 1H, J = 3.2 Hz), 3.44 (q, 4H, 7.2 Hz), 3.17 (d, 1H, J = 1.5 Hz), 1.27 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 143.1, 137.7, 130.1, 129.6, 129.0, 128.0, 127.8, 127.1, 122.9, 70.1, 44.1, 14.2 ppm; LRMS (EI) *(m/z(%))* M^+ not found, 318(M^+ - H_2O, 100); HRMS (EI) calcd for $C_{17}H_{21}NO_4S$ 335.1198: found 335.1191.

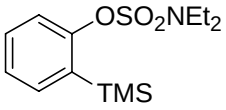
***N,N*-Diethyl 2-thiomethylphenyl *O*-sulfamate (2.13d)**



This compound was prepared by **Method B** using the following materials: **2.10a** (0.300 g, 1.32 mmol), TMEDA (0.219 mL, 1.45 mmol), *s*-BuLi (1.21 mL, 1.2 M in cyclohexane, 1.45 mmol), THF (5 mL), methyl disulfide (0.142 mL, 1.58 mmol). Standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded **2.13d** (1.50 g, 88%) as a colourless oil; IR (neat) ν_{max} 2978, 2936, 1578, 1470, 1389, 1208, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, 1H, J = 1.2, 7.4 Hz), 7.23-7.14 (m, 3H), 3.49 (q, 4H, 7.2 Hz), 2.46 (s, 3H), 1.28 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 132.3, 127.1, 126.6, 126.0, 121.9, 43.8,

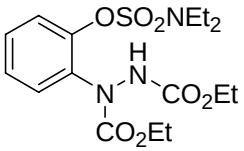
15.1, 13.9 ppm; LRMS (EI) *(m/z(%))* 276(M^+ + 1, 29), 275(M^+, 100); HRMS (EI) calcd for $C_{11}H_{17}NO_3S_2$ 275.0653: found 275.0650.

***N,N*-Diethyl 2-trimethylsilylphenyl *O*-sulfamate (2.13e)**



This compound was prepared by **Method B** using the following materials: **2.10a** (0.50 g, 2.18 mmol), TMEDA (0.36 mL, 2.40 mmol), *s*-BuLi (1.73 mL, 1.39 M in cyclohexane, 2.40 mmol), THF (10 mL), chlorotrimethylsilane (0.33 mL, 2.62 mmol). Standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded **2.13e** (0.63 g, 96%) as a colourless oil; IR (neat) ν_{max} 2967, 2908, 1591, 1470, 1380, 1253, 1144, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 7.8 Hz), 7.49 (dd, 1H, J = 1.5, 7.1 Hz), 7.40 (td, 1H, J = 7.3, 1.8 Hz), 7.22 (td, 1H, J = 7.3, 1.0 Hz), 3.50 (q, 4H, 7.2 Hz), 1.30 (t, 6H, J = 7.2 Hz), 0.48 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 136.3, 131.5, 131.4, 125.9, 119.6, 44.1, 14.5, 0.2 ppm; LRMS (EI) *(m/z(%))* 302(M^+ + 1, 1), 286(100); HRMS (EI) calcd for $C_{13}H_{17}NO_3SSi$ 301.1171: found 301.1168.

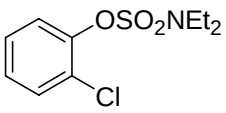
Diethyl 1-(2-diethylphenyl *O*-sulfamate)-1,2,hydrazinedicarboxylate (2.13f)



This compound was prepared by **Method B** using the following materials: **2.10a** (300 mg, 1.3 mmol), TMEDA (0.22 mL, 1.5 mmol), *s*-BuLi (1.32 mL, 1.1 M in cyclohexane, 1.5 mmol), THF (5 mL), diethyl diazodicarboxylate (0.25 mL, 1.6 mmol). Standard workup and flash chromatography (7:3 hexanes / EtOAc) afforded **2.13f** (280 mg, 53%) as a colourless oil; IR (neat) ν_{max} 3388, 2991, 2940, 1726, 1496, 1374, 1234, 1157 cm^{-1}; ^1H NMR (300 MHz,

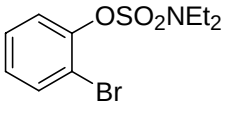
$CDCl_3$) δ 7.73 (bs, 1H), 7.47-7.28 (m, 4H), 4.21 (m, 4H), 3.43 (q, 4H, 7.0 Hz), 1.27 (t, 6H, J = 7.0 Hz), 1.26 (t, 6H, J = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 155.4, 145.6, 135.6, 129.8, 128.0, 123.8, 63.1, 43.7, 14.7, 13.6 ppm; LRMS (EI) *(m/z(%))* 404(M^+ + 1, 25), 331(40), 223(100); HRMS (EI) calcd for $C_{16}H_{25}N_3O_7S$ 403.1485: found 404.1492.

_N,N_-Diethyl 2-chlorophenyl _O_-sulfamate (2.13g)



This compound was prepared by **Method B** using the following materials: **2.10a** (1.00 g, 4.37 mmol), TMEDA (0.72 mL, 4.81 mmol), *s*-BuLi (3.36 mL, 1.43 M in cyclohexane, 4.81 mmol), THF (10 mL), 1,1,1,2,2,2-hexachloroethane (1.24 g, 5.24 mmol) in THF (3 mL). Standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded **2.13g** (0.52 g, 45%) as a colourless oil; IR (neat) ν_{max} 2985, 2941, 1579, 1470, 1368, 1214, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 8.1 Hz), 7.44 (d, 1H, J = 7.9 Hz), 7.30 (t, 1H, J = 6.4 Hz), 7.20 (t, 1H, J = 6.2 Hz), 3.49 (q, 4H, 7.2 Hz), 1.28 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 131.3, 128.5, 127.8, 127.4, 124.1, 44.2, 14.2 ppm; LRMS (EI) *(m/z(%))* 265(M^+ + 2, 34), 263(M^+, 100); HRMS (EI) calcd for $C_{10}H_{14}ClNO_3S$ 263.0381: found 263.0383.

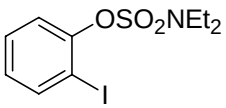
_N,N_-Diethyl 2-bromophenyl _O_-sulfamate (2.13h)



This compound was prepared by **Method B** using the following materials: **2.10a** (2.00 g, 8.73 mmol), TMEDA (1.2 mL, 9.60 mmol), *s*-BuLi (6.72 mL, 1.43 M in cyclohexane, 9.60 mmol), THF (20 mL), 1,1,2,2-

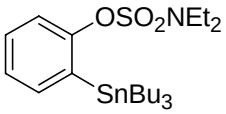
tetrabromoethane (1.22 mL, 10.48 mmol). Standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded **2.13h** (1.50 g, 56%) as a colourless oil; IR (neat) ν_{max} 2978, 2946, 1585, 1470, 1374, 1208, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 1H, J = 7.9 Hz), 7.56 (d, 1H, J = 8.2 Hz), 7.35 (t, 1H, J = 7.7 Hz), 7.13 (t, 1H, J = 7.6 Hz), 3.51 (q, 4H, 7.2 Hz), 1.28 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 133.8, 128.6, 127.4, 123.1, 115.7, 43.6, 13.5 ppm; LRMS (EI) *(m/z(%))* 309(M^+ + 2, 53), 307(M^+, 51), 294(22), 292(21), 136(100); HRMS (EI) calcd for $C_{10}H_{14}BrNO_3S$ 306.9876: found 306.9878.

***N,N*-Diethyl 2-iodophenyl *O*-sulfamate (2.13i)**



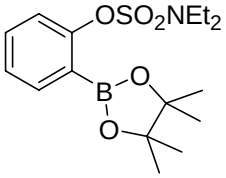
This compound was prepared by **Method B** using the following materials: **2.10a** (5.00 g, 21.8 mmol), TMEDA (3.6 mL, 24.0 mmol), *s*-BuLi (21.8 mL, 1.1 M in cyclohexane, 24.0 mmol), THF (50 mL), iodine (6.64 g, 26.2 mmol) in THF (20 mL). Standard workup and high vacuum distillation afforded **2.13i** (6.0 g, 78%) as yellow solid, mp 42-44 ^oC; IR (neat) ν_{max} 2978, 2935, 1572, 1464, 1388, 1208, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, 1H, J = 1.3, 7.9 Hz), 7.54 (dd, 1H, J = 1.2, 8.2 Hz), 7.35 (td, 1H, J = 1.3, 7.3 Hz), 6.98 (t, 1H, J = 7.6 Hz), 3.56 (q, 4H, 7.1 Hz), 1.31 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 140.2, 129.9, 128.0, 122.2, 89.6, 43.9, 13.9 ppm; LRMS (EI) *(m/z(%))* 355(M^+, 100); HRMS (EI) calcd for $C_{10}H_{14}INO_3S$ 354.9738: found 354.9739.

***N,N*-Diethyl 2-tri-*n*-butylstannanylphenyl *O*-sulfamate (2.13j)**



This compound was prepared by **Method B** using the following materials: **2.10a** (0.300 g, 1.32 mmol), TMEDA (0.219 mL, 1.45 mmol), *s*-BuLi (1.21 mL, 1.2 M in cyclohexane, 1.45 mmol), THF (5 mL), tributyltin chloride (0.430 mL, 1.58 mmol). Standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded **2.13j** (0.625 g, 91%) as a colourless oil; IR (neat) ν_{max} 2959, 2921, 1566, 1457, 1374, 1208, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47-7.41 (m, 2H), 7.34 (td, 1H, J = 1.1, 7.0 Hz), 7.22 (t, 1H, J = 7.1 Hz), 3.44 (q, 4H, 7.2 Hz), 1.55 (m, 6H), 1.36 (m, 6H), 1.28 (t, 6H, J = 7.2 Hz), 1.18 (m, 6H), 0.92 (t, 9H, J = 7.3 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 138.4, 134.7, 130.3, 126.5, 120.3, 44.2, 29.7, 28.0, 14.6, 14.3, 11.1 ppm; LRMS (EI) *(m/z(%))* M^+ not found, 462(M^+ - Bu, 100); HRMS (EI) calcd for $C_{22}H_{41}NO_3SSn$ 518.1749: found 518.1751.

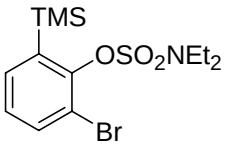
***N,N*-Diethyl 2-pinacolboronatephenyl *O*-sulfamate (2.13k)**



This compound was prepared by **Method B** using the following materials: **2.10a** (1.00 g, 4.39 mmol), TMEDA (0.73 mL, 4.83 mmol), *s*-BuLi (4.00 mL, 1.2 M in cyclohexane, 4.83 mmol), THF (10 mL), triisopropyl borate (1.22 mL, 5.27 mmol). Standard workup afforded the crude boronic acid that was dissolved in MeOH (20 mL) containing pinacol (0.57 g, 4.83 mmol), concentrated in *vacuo*, and diluted with brine (20 mL). Standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded **2.13k** (1.35 g, 87%) as a colourless oil; IR (neat) ν_{max} 2978, 2940, 1610, 1496, 1444, 1361, 1272, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, 1H, J = 1.8, 7.2 Hz), 7.45 (td, 1H, J = 1.9, 7.1 Hz), 7.37 (dd, 1H, J =

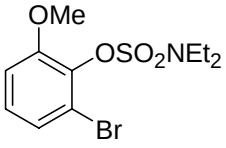
0.9, 7.4 Hz), 7.25 (td, 1H, J = 1.1, 7.0 Hz), 3.45 (q, 4H, 7.2 Hz), 1.36 (s, 12H), 1.26 (td, 6H, J = 1.3, 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 137.1, 132.5, 126.2, 122.1, 84.2, 43.7, 25.2, 14.0 ppm; LRMS (EI) *(m/z(%))* 356(M^+ + 1, 4), 163(100); HRMS (EI) calcd for $C_{16}H_{26}BNO_5S$ 355.1622: found 355.1625.

***N,N*-Diethyl 2-bromo-6-trimethylsilylphenyl *O*-sulfamate (2.13l)**



This compound was prepared by **Method B** using the following materials: **2.13h** (1.0 g, 3.3 mmol), TMEDA (0.54 mL, 3.6 mmol), LDA (3.60 mL, 1 M in THF, 3.6 mmol), THF (10 mL), chlorotrimethylsilane (0.50 mL, 3.90 mmol). Standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded **2.13l** (1.00 g, 81%) as a colourless solid, mp 67-68 ^{o}C (hexanes); IR (KBr) ν_{max} 2966, 1470, 1368, 1253, 1195, 844 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, 1H, J = 1.6, 7.8 Hz), 7.49 (dd, 1H, J = 1.7, 7.4 Hz), 7.14 (t, 1H, J = 7.6 Hz), 3.55 (q, 4H, J = 7.2 Hz), 1.29 (t, 6H, J = 7.2 Hz), 0.41 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0, 138.0, 135.6, 134.7, 127.5, 117.7, 44.0, 14.1, 0.5 ppm; LRMS (EI) *(m/z(%))* 366(M^+ + 2 - Me, 100), 364(M^+ - Me, 95); HRMS (ESI) calcd for $C_{13}H_{22}BrNO_3SSi$ 380.0346: found 380.0346.

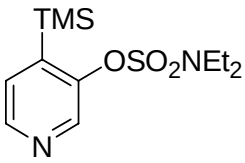
***N,N*-Diethyl 2-bromo-6-methoxyphenyl *O*-sulfamate (2.13m)**



This compound was prepared by **Method B** using the following materials: **2.13h** (1.75 g, 5.7 mmol), TMEDA (0.94 mL, 6.3 mmol), LDA (6.25 mL, 1 M in THF, 6.3 mmol), THF (20 mL), triisopropyl borate (1.57 mL, 6.8 mmol). The reaction mixture was warmed to 0^{o}C, H_2O_2 (5.5 mL of

35 % w/w solution, 57 mmol) was added and the reaction mixture was warmed to rt over 12 h. The reaction was quenched with H_2O and the pH adjusted to 7 with 1 M HCl solution. Standard workup afforded a residue which was taken up in MeCN (20 mL), anhydrous K_2CO_3 (3.9 g, 28.4 mmol) and MeI (1.8 mL, 28.4 mmol) were added and the reaction mixture was heated at reflux 12 h. Standard workup including washing the EtOAc extracts with NaOH (10 % w/v) solution and flash chromatography (9:1 hexanes / EtOAc) afforded **2.13m** (1.1 g, 57%) as a colourless solid; mp 83-85 ^oC (hexanes); IR (KBr) ν_{max} 2985, 1585, 1476, 1387, 1253, 1195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, 1H, J = 1.4, 8.2 Hz), 7.07 (t, 1H, J = 8.2 Hz), 6.93 (dd, 1H, J = 1.4, 8.3 Hz), 3.89 (s, 3H), 3.49 (q, 4H, J = 7.2 Hz), 1.29 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 138.4, 127.6, 125.2, 118.0, 112.1, 56.4, 44.0, 14.0 ppm; LRMS (EI) *(m/z(%))* 339(M^+ + 2, 90), 337(M^+, 100), 203(44), 201(51), 194(70), 166(76), 136(27), 72(25); HRMS (ESI) calcd for $C_{11}H_{16}BrNO_4S$ 338.0051: found 338.0062.

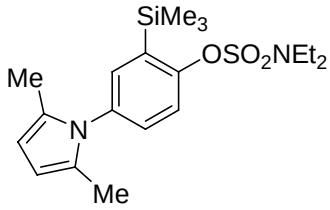
***N,N*-Diethyl 4-trimethylsilyl-pyridin-3-yl *O*-sulfamate (2.13n)**



This compound was prepared by **Method B** at -78^oC using the following materials: **2.10f** (0.50 g, 2.17 mmol), TMEDA (0.37 mL, 2.39 mmol), LDA (3.50 mL, 0.7 M in THF, 2.39 mmol), THF (4 mL), chlorotrimethylsilane (0.33 mL, 2.60 mmol). Standard workup and flash chromatography (8:2 hexanes:EtOAc) yielded **2.13n** (0.61 g, 92%) as a colourless oil; IR (neat) ν_{max} 2965, 2908, 1579, 1470, 1374, 1253, 1221, 1157, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.21 (d, 1H, J = 4.6 Hz), 7.14 (d, 1H, J = 4.7 Hz), 3.25 (q, 4H, J = 7.1 Hz), 1.06 (t, 6H, J = 7.1 Hz), 0.15 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$)

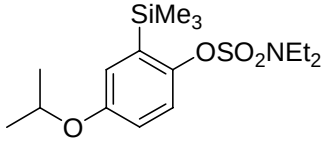
δ 153.5, 147.1, 142.5, 142.3, 130.4, 44.5, 14.7, 0.0 ppm; LRMS (EI) *(m/z(%))* 303(M^+, 13), 287(M^+ - Me, 100); HRMS (ESI) calculated for $C_{12}H_{22}N_2O_3SSi$ 303.1196: found 303.1193.

***N,N*-Diethyl 4-(2,5-dimethyl-pyrrol-1-yl)-2-(trimethylsilyl)phenyl *O*-sulfamate (2.13o)**



This compound was prepared by **Method B** using the following materials: **2.10c** (0.25 g, 0.78 mmol), *s*-BuLi (0.79 mL, 1.18 M in cyclohexane, 0.94 mmol), TMEDA (0.14 mL, 0.94 mmol), THF (5 mL), chlorotrimethylsilane (0.12 mL, 0.94 mmol). Standard workup and flash chromatography (19:1 hexanes / EtOAc) yielded **2.13o** (0.28 g, 91%) as colourless solid; mp 37-38 ^oC (hexanes); IR (KBr) ν_{max} 3454, 2988, 2361, 1473, 1410, 1367, 1187, 876 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 1H, J = 8.7 Hz), 7.30 (d, 1H, J = 2.1 Hz), 7.24 (dd, 1H, J = 1.7, 8.7 Hz), 5.94 (s, 2H), 3.53 (q, 4H, J = 7.2 Hz), 2.06 (s, 6H), 1.33 (t, 6H, J = 7.1 Hz) 0.37 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 135.8, 135.0, 132.2, 130.2, 128.9, 119.4, 105.8, 43.6, 13.9, 13.1, -0.5 ppm; LRMS (EI) *(m/z(%))* 394(M^+, 100); HRMS (CI) calcd for $C_{19}H_{30}N_2O_3SSi$ 394.1741: found 394.1746.

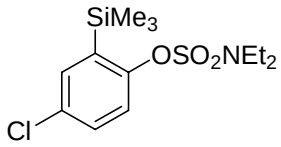
***N,N*-Diethyl 4-isoproproxy-2-(trimethylsilyl)phenyl *O*-sulfamate (2.13p)**



This compound was prepared by **Method B** using the following materials: **2.10i** (1.00 g, 3.48 mmol), *s*-BuLi (3.75 mL, 1.4 M in cyclohexane, 4.18 mmol), TMEDA (0.62 mL,

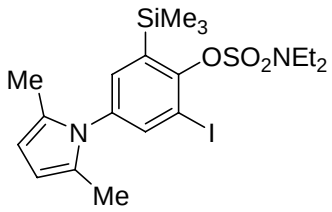
4.18 mmol), THF (10 mL), chlorotrimethylsilane (0.57 mL, 4.52 mmol). Standard workup and flash chromatography (19:1 hexanes / EtOAc) yielded **2.13p** (1.12 g, 90%) as colourless oil; IR (neat) ν_{max} 2985, 2908, 1572, 1476, 1367, 1246, 1188, 1137, 1112, 1028, 945, 894, 837, 792, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, J = 9.0 Hz), 6.97 (s, 1H), 6.87 (d, 1H, J = 9.0 Hz), 4.52 (qn, 1H, J = 6.0 Hz), 3.48 (q, 4H, J = 7.2 Hz), 1.36 (s, 3H), 1.34 (s, 3H), 1.29 (t, 6H, J = 7.2 Hz), 0.36 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 149.4, 132.9, 123.1, 120.4, 116.5, 70.3, 43.3, 22.0, 13.8, -0.4 ppm; LRMS (EI) *(m/z(%))* 359(M^+, 30), 181(100); HRMS (EI) calcd for $C_{16}H_{29}NO_4SSi$ 359.1598: found 359.1587

***N,N*-Diethyl 4-cloro-2-(trimethylsilyl)phenyl *O*-sulfamate (2.13q)**



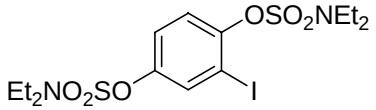
This compound was prepared by **Method B** using the following materials: **2.10l** (1.00 g, 3.8 mmol), *s*-BuLi (4.3 mL, 1.06 M in cyclohexane, 4.6 mmol), TMEDA (0.69 mL, 4.6 mmol), THF (10 mL), chlorotrimethylsilane (0.63 mL, 4.9 mmol). Standard workup and flash chromatography (9:1 hexanes:EtOAc) yielded **2.13q** (1.00 g, 79%) as colourless oil; IR (neat) ν_{max} 2976, 1584, 1460, 1366, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1H, J = 8.8 Hz), 7.40 (d, 1H, J = 2.3 Hz), 7.35 (dd, 1H, J = 2.4, 8.8 Hz), 3.45 (q, 4H, J = 7.2 Hz), 1.30 (t, 6H, J = 7.1 Hz), 0.36 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 135.1, 133.7, 131.0, 130.4, 120.5, 43.4, 13.8, -0.63 ppm; LRMS (EI) *(m/z(%))* 335(M^+, 15), 320(M^+ - Me, 100); HRMS (EI) calcd for $C_{13}H_{22}ClNO_3SSi$ 335.0789: found 335.0778.

***N,N*-Diethyl 4-(2,5-dimethyl-pyrrol-1-yl)-2-iodo-6-(trimethylsilyl)phenyl *O*-sulfamate (2.13r)**



This compound was prepared by **Method B** using the following materials: **2.13o** (94 mg, 0.24 mmol), *s*-BuLi (0.28 mL, 1.18 M in cyclohexane, 0.33 mmol), TMEDA (0.05 mL, 0.33 mmol), THF (2 mL), 2-iodo-1,1,1-trifluoro-ethane (33 μL, 0.33 mmol). Standard workup and flash chromatography (19:1 hexanes:EtOAc) yielded **2.13r** (90 mg, 72 %) as colourless solid; mp 123-124 ^{o}C (hexanes); IR (KBr) ν_{max} 2959, 2354, 1674, 1463, 1404, 1251, 1005, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 1H, J = 1.7 Hz), 7.38 (d, 1H, J = 1.6 Hz), 5.93 (s, 2H), 3.63 (q, 4H, J = 7.2 Hz), 2.08 (s, 6H), 1.32 (t, 6H, J = 7.2 Hz) 0.41 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 140.3, 137.7, 137.5, 135.9, 128.8, 106.4, 92.1, 43.7, 13.9, 13.1, 0.6 ppm; LRMS (EI) *(m/z(%))* 520(M^+, 100); HRMS (CI) calcd for $C_{19}H_{29}IN_2O_3SSi$ 520.0719: found 520.0713.

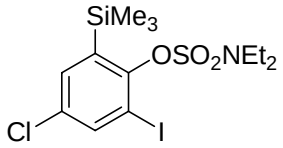
2-Iodophenyl-1,4-Bis(*N,N*-Diethyl *O*-sulfamate) (2.13s)



This compound was prepared by **Method B** using the following materials: **2.10j** (500 mg, 1.31 mmol), *s*-BuLi (2.5 mL, 0.63 M in cyclohexane, 1.57 mmol), TMEDA (0.2 mL, 1.31 mmol), THF (5 mL), 2-iodo-1,1,1-trifluoro-ethane (154 μL, 1.57 mmol). Standard workup and flash chromatography (7:3 hexanes:EtOAc) yielded **2.13s** (530 mg, 80%) as colourless solid; mp 90-91 ^{o}C (hexanes); IR (KBr) ν_{max} 2992, 2377, 1471, 1376, 1211, 1186, 1142, 1021, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 1H, J = 2.4 Hz), 7.53 (dd, 1H, J = 1.3,

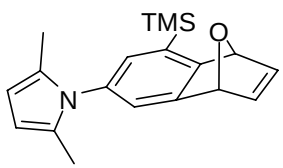
9.0 Hz), 7.30 (d, 1H, J = 9.0), 3.54 (q, 4H, J = 7.2 Hz), 3.41 (q, 4H, J = 7.2 Hz), 1.31 (t, 6H, J = 7.2 Hz), 1.25 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 147.8, 132.9, 123.0, 122.1, 89.0, 43.7, 43.5, 13.6, 13.5 ppm; LRMS (EI) *(m/z(%))* 506(M^+, 75), 136(100); HRMS (EI) calculated for $C_{14}H_{23}N_2O_6S_2I$ 506.0039: found 506.0042

_N,N_-Diethyl 4-cloro-2-iodo-6-(trimethylsilyl)phenyl _O_-sulfamate (2.13t)



This compound was prepared by **Method B** using the following materials: **2.13q** (500 mg, 1.31 mmol), *s*-BuLi (2.5 mL, 0.63 M in cyclohexane, 1.57 mmol), TMEDA (0.2 mL, 1.31 mmol), THF (5 mL), 2-iodo-1,1,1-trifluoro-ethane (154 μL, 1.57 mmol). Standard workup and flash chromatography (7:3 hexanes:EtOAc) yielded **2.13t** (530 mg, 80%) as colourless solid; mp 89-91 ^{o}C (hexanes); IR (KBr) ν_{max} 2986, 1376, 1256, 1211, 1161, 1021, 837, 780, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 0.6 Hz), 7.45 (d, 1H, J = 0.7 Hz), 3.59 (q, 4H, J = 7.2 Hz), 1.31 (t, 6H, J = 7.2 Hz), 0.40 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 140.2, 138.8, 136.0, 132.6, 92.4, 43.9, 14.0, 0.5 ppm; LRMS (EI) *(m/z(%))* 460(M^+, 0.1), 446(100); HRMS (ESI) calculated for $C_{13}H_{21}NO_3SSiClI$ 460.9745: found 460.9752.

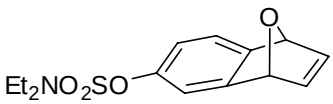
1,4-dihydro-1,4-epoxy-7-(2,5-dimethyl-pyrrol-1-yl)-5-trimethylsilylnaphthalene (2.14b)



This compound was prepared by **Method F** using the following materials: **2.13r** (70 mg, 0.14 mmol), *i*PrMgCl (80 μL, 2.0 M in

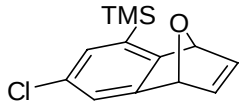
Et_2O, 0.15 mmol), furan (0.1 mL, 1.4 mmol), Et_2O (4 mL). Standard workup and flash chromatography (9:1 hexanes:EtOAc) yielded **2.14b** (20 mg, 47 %) as colourless solid; mp 119-120 ^oC (hexanes); IR (KBr) ν_{max} 3419, 2956, 2357, 1692, 1601, 1459, 1403, 1255, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 2H), 7.09 (s, 1H), 6.91 (s, 1H), 5.92 (s, 2H), 5.90 (s, 1H), 5.76 (s, 1H), 2.05 (s, 6H) 0.35 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 149.1, 143.2, 142.8, 135.0, 132.8, 129.2, 128.9, 120.9, 105.5, 82.5, 82.0, 13.1, -0.4 ppm; LRMS (EI) *(m/z(%))* 309(M^+, 100); HRMS (CI) calcd for $C_{19}H_{23}NOSi$ 309.1544: found 309.1549.

_N,N_-Diethyl-1,4-dihydro-1,4-epoxy-6-sulfamoylnaphthalene (2.14c)



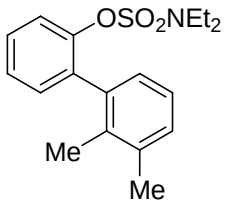
This compound was prepared by **Method F** using the following materials: **2.13s** (200 mg, 0.4 mmol), *i*PrMgCl (0.22 mL, 2.0 M in Et_2O, 0.44 mmol), furan (0.29 mL, 4.0 mmol), Et_2O (10 mL). Standard workup and flash chromatography (7:3 hexanes:EtOAc) afforded **2.14c** (60 mg, 51%) as colourless oil; IR (KBr) ν_{max} 2981, 1456, 1370, 1164.8, 1025, 950, 925, 843, 791, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.22 (d, 1H, J = 7.3 Hz), 7.04 (s, 2H), 6.87 (d, 1H, J = 7.6 Hz), 5.72 (s, 2H), 3.39 (q, 4H, J = 7.1 Hz), 1.22 (t, 6H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 147.6, 147.3, 143.2, 142.8, 120.5, 117.9, 115.3, 82.3, 82.0, 43.5, 13.5 ppm; LRMS (EI) *(m/z(%))* 295(M^+, 29), 159(41), 131(100); HRMS (EI) calcd for $C_{14}H_{17}O_4S$ 295.0878: found 295.0865.

1,4-dihydro-1,4-epoxy-7-chloro-5-trimethylsilylnaphthalene (2.14c)



This compound was prepared by **Method F** using the following materials: **2.13t** (100 mg, 0.22 mmol), *i*PrMgCl (0.22 mL, 2.0 M in Et_2O, 0.24 mmol), furan (0.16 mL, 2.2 mmol), Et_2O (5 mL). Standard workup and flash chromatography (19:1 hexanes:EtOAc) yielded **2.14c** (43 mg, 79%) as yellow solid; mp 110-112 ^oC (hexanes); IR (KBr) ν_{max} 2949, 2354, 1586, 1426, 1244, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.23 (s, 1H), 7.10 (s, 2H), 5.91 (s, 1H), 5.79 (s, 1H), 0.41 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 144.7, 143.1, 142.7, 135.2, 132.1, 127.3, 119.5, 82.4, 81.8, -0.4 ppm; LRMS (EI) *(m/z(%))* 250(M^+, 100), 235(45); HRMS (EI) calcd for $C_{13}H_{15}OClSi$ 250.0987: found 250.0982.

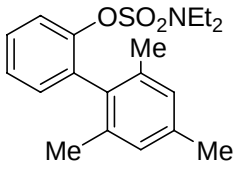
***N,N*-Diethyl 2',3'-dimethylbiphenyl-2-yl *O*-sulfamate (2.21a)**



This compound was prepared by **Method C** using the following materials: **2.13i** (0.300 g, 0.845 mmol), 2,3-dimethylphenylboronic acid (0.127 g, 0.845 mmol), Na_2CO_3 (2M, 2 mL), $[Pd(PPh_3)_4]$ (48 mg, 5 mol %), in DME (4 mL), and the reaction mixture was refluxed for 24 h. Standard workup and flash chromatography (19:1 hexanes:EtOAc) afforded **2.21a** (0.267 g, 85%) as a colourless solid; mp 68-70 ^oC (hexanes); IR (KBr) ν_{max} 2998, 2940, 1585, 1470, 1366, 1214, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, 1H, J = 0.7, 8.2 Hz), 7.41 (td, 1H, J = 2.1, 8.2 Hz), 7.34-7.27 (m, 2H), 7.18 (dd, 1H, J = 1.2, 7.2 Hz), 7.15 (t, 1H, J = 7.4 Hz), 7.11 (d, 1H, J = 7.2 Hz), 2.90 (q, 4H, J = 7.2 Hz), 2.34 (s, 3H), 2.06 (s, 3H), 0.97 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 137.5, 136.9, 135.8, 135.7, 131.7, 129.5, 128.9, 128.5, 126.5, 125.3, 121.9, 42.8, 20.8, 17.1, 13.4 ppm;

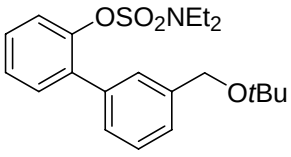
LRMS (EI) *(m/z(%))* 333(M^+, 100); HRMS (EI) calcd for $C_{18}H_{23}NO_3S$ 333.1401: found 333.1399.

_N,N_-Diethyl 2',4',6'-trimethylbiphenyl-2-yl _O_-sulfamate (2.21b)



This compound was prepared by **Method C** using the following materials: **2.13i** (0.300 g, 0.845 mmol), 2,4,6-trimethylphenylboronic acid (0.139 g, 0.845 mmol), Na_2CO_3 (2M, 2 mL), [$Pd(PPh_3)_4$] (48 mg, 5 mol %), in DME (4 mL), and the reaction mixture was refluxed for 24 h. Additional 2,4,6-trimethylphenylboronic acid (0.139 g, 0.845 mmol) and $Pd(PPh_3)_4$ (48 mg, 5 mol %) was added and the reaction mixture was refluxed for an additional 24 h. Standard workup and flash chromatography (19:1 hexanes:EtOAc) yielded **2.21b** (0.165 g, 56%) as a colourless solid; mp 61-64 ^oC (hexanes); IR (KBr) ν_{max} 2978, 2940, 1617, 1444, 1361, 1202, 1182, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 1H, J = 8.1 Hz), 7.41 (t, 1H, J = 7.8), 7.32 (t, 1H, J = 7.6 Hz), 7.21 (d, 1H, J = 7.5 Hz), 6.94 (s, 2H), 2.94 (q, 4H, J = 7.2 Hz), 2.34 (s, 3H), 2.03 (s, 6H), 0.98 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 137.0, 136.9, 133.7, 131.5, 128.6, 127.8, 126.3, 121.5, 42.3, 21.0, 20.4, 12.7 ppm; LRMS (EI) *(m/z(%))* 347(M^+, 100); HRMS (EI) calcd for $C_{19}H_{25}NO_3S$ 347.1562: found 347.1556.

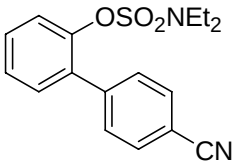
_N,N_-Diethyl 3'-_t_-butoxymethyl-biphenyl-2-yl _O_-sulfamate (2.21c)



This compound was prepared by **Method C** using the following materials: **2.13i** (0.300 g, 0.845 mmol), 3-*t*-butoxymethylphenylboronic acid (0.176 g, 0.845 mmol), Na_2CO_3

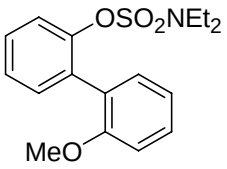
(2M, 2 mL), [$Pd(PPh_3)_4$] (48 mg, 5 mol %), in DME (4 mL), and the reaction mixture was refluxed for 24 h. Standard workup and flash chromatography (9:1 hexanes / EtOAc) yielded **2.21c** (0.326 g, 99%) as a colourless oil; IR (neat) ν_{max} 3062, 2978, 2940, 2883, 1610, 1470, 1380, 1208, 1163, 1112, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 1H, J = 8.0 Hz), 7.34 (d, 1H, J = 7.3 Hz), 7.49 (s, 1H), 7.42-7.37 (m, 5H), 4.51 (s, 2H), 2.93 (q, 4H, J = 7.2 Hz), 1.33 (s, 9H), 1.02 (t, 6H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 139.9, 137.2, 135.2, 131.2, 128.9, 128.6, 128.5, 128.1, 126.7, 126.5, 122.5, 73.5, 64.1, 43.0, 27.7, 13.5 ppm; LRMS (EI) *(m/z(%))* M^+ not found, 334(M^+ - *t*Bu, 45), 318(100); HRMS (EI) calcd for $C_{21}H_{29}NO_4S$ 391.1816: found 391.1817.

***N,N*-Diethyl 4'-cyanobiphenyl-2-yl *O*-sulfamate (2.21d)**



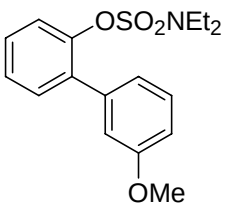
This compound was prepared by **Method C** using the following materials: **2.13i** (0.300 g, 0.845 mmol), 4-cyanophenylboronic acid (0.147 g, 0.845 mmol), Na_2CO_3 (2M, 2 mL), [$Pd(PPh_3)_4$] (48 mg, 5 mol %), in DME (4 mL), and the reaction mixture was refluxed for 24 h. Standard workup and flash chromatography (8:2 hexanes / EtOAc) yielded **2.21d** (0.260 g, 93%) as a colourless oil; IR (neat) ν_{max} 2972, 2947, 2231, 1617, 1489, 1374, 1221, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8.1 Hz), 7.62 (d, 2H, J = 8.5 Hz), 7.47-7.43 (m, 1H), 7.39-7.36 (m, 2H), 3.05 (q, 4H, J = 7.2 Hz), 1.05 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 142.3, 133.4, 131.9, 130.9, 130.5, 129.9, 126.9, 122.7, 118.8, 111.3, 43.0, 13.4 ppm; LRMS (EI) *(m/z(%))* 330(M^+, 100); HRMS (EI) calcd for $C_{17}H_{18}N_2O_3S$ 330.1040: found 330.1038.

***N,N*-Diethyl 2'-methoxybiphenyl-2-yl *O*-sulfamate (2.21e)**



This compound was prepared by **Method C** using the following materials: **2.13i** (0.300 g, 0.845 mmol), 3-methoxyphenylboronic acid (0.129 g, 0.845 mmol), Na_2CO_3 (2M, 2 mL), [$Pd(PPh_3)_4$] (48 mg, 5 mol %), in DME (4 mL), and the reaction mixture was refluxed for 24 h. Standard workup and flash chromatography (9:1 hexanes / EtOAc) yielded **2.21e** (0.240 g, 85%) as a colourless solid, mp 69-70 ^oC (hexanes); IR (KBr) ν_{max} 2972, 2838, 1598, 1483, 1368, 1253, 1208, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 1H, J = 8.1 Hz), 7.41-7.34 (m, 4H), 7.31 (t, 1H, J = 7.6 Hz), 7.03 (t, 1H, 7.5 Hz), 6.97 (d, 1H, 8.3 Hz), 3.78 (s, 1H), 2.91 (q, 4H, 7.2 Hz), 1.00 (t, 1H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 148.4, 132.2, 132.1, 132.0, 129.5, 129.0, 126.8, 126.4, 122.0, 120.6, 111.0, 55.9, 43.0, 13.6 ppm; LRMS (EI) *(m/z(%))* 335(M^+, 100); HRMS (EI) calcd for $C_{17}H_{21}NO_4S$ 335.1200: found 335.1191.

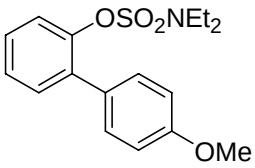
***N,N*-Diethyl 3'-methoxybiphenyl-2-yl *O*-sulfamate (2.21f)**



This compound was prepared by **Method C** using the following materials: **2.13i** (0.300 g, 0.845 mmol), 3-methoxyphenylboronic acid (0.129 g, 0.845 mmol), Na_2CO_3 (2M, 2 mL), [$Pd(PPh_3)_4$] (48 mg, 5 mol %), in DME (4 mL), and the reaction mixture was refluxed for 24 h. Standard workup and flash chromatography (9:1 hexanes / EtOAc) yielded **2.21f** (0.260 g, 92%) as a colourless oil; IR (neat) ν_{max} 2985, 2946, 2838, 1598, 1476, 1374, 1208, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, 1H, J = 1.0, 8.1 Hz), 7.42-7.31 (m, 4H), 7.09-7.06 (m, 2H), 6.92 (dd, 1H, J = 1.8, 8.3 Hz), 3.83 (s, 1H), 2.97 (q, 4H, J = 7.2 Hz), 1.01 (t, 6H,

J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 147.7, 139.0, 135.3, 131.4, 129.4, 129.1, 126.9, 122.8, 122.5, 115.6, 113.5, 55.7, 43.3, 13.8 ppm; LRMS (EI) *(m/z(%))* 335(M^+, 100); HRMS (EI) calcd for $C_{17}H_{21}NO_4S$ 335.1190: found 335.1191.

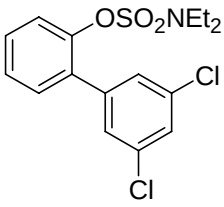
***N,N*-Diethyl 4'-methoxybiphenyl-2-yl *O*-sulfamate (2.21g)**



From **2.13h** compound **2.21g** was prepared by **Method C** using the following materials: **2.13h** (0.308 g, 1.00 mmol), 4-methoxyphenylboronic acid (0.151 g, 1.00 mmol), Na_2CO_3 (2M, 5 mL), [$Pd(PPh_3)_4$] (57 mg, 5 mol %), in DME (5 mL), and the reaction mixture was refluxed for 24 h. Standard workup and flash chromatography (9:1 hexanes / EtOAc) yielded **2.21g** (0.282 g, 85%) as a colourless oil.

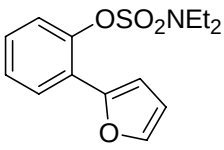
From **2.13k** compound **2.21g** was also prepared by **Method C** using the following materials: **2.13k** (0.355 g, 1.00 mmol), 4-bromoanisole (0.126 mL, 1.00 mmol), Na_2CO_3 (2M, 5 mL), $Pd(PPh_3)_4$ (56 mg, 5 mol %), in DME (5 mL), and the reaction mixture was refluxed for 24 h. Standard workup and flash chromatography (9:1 hexanes / EtOAc) yielded **2.21g** (0.312 g, 93%) as a colourless oil; IR (neat) ν_{max} 2985, 2934, 2838, 1611, 1515, 1483, 1368, 1246, 1208, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, 1H, J = 2.0, 8.8 Hz), 7.45 (dd, 2H, J = 2.0, 6.8 Hz), 7.39-7.28 (m, 3H), 6.88 (dd, 2H, J = 2.0, 8.8 Hz), 3.38 (s, 3H), 2.96 (q, 4H, J = 7.1 Hz), 1.02 (t, 6H, 7.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 146.3, 135.5, 131.8, 131.5, 130.4, 128.9, 127.2, 123.2, 114.3, 56.0, 43.7, 14.2 ppm; LRMS (EI) *(m/z(%))* 335(M^+, 66), 199(100), 184(25), 128(12); HRMS (EI) calcd for $C_{17}H_{21}NO_4S$ 335.1195: found 335.1191.

***N,N*-Diethyl 3',5'-dichlorobiphenyl-2-yl *O*-sulfamate (2.21h)**



This compound was prepared by **Method C** using the following materials: **2.13i** (0.300 g, 0.845 mmol), 3,5-dichlorophenylboronic acid (0.162 g, 0.845 mmol), Na_2CO_3 (2M, 2 mL), [$Pd(PPh_3)_4$] (48 mg, 5 mol %), in DME (4 mL), and the reaction mixture was refluxed for 24 h. Standard workup and flash chromatography (19:1 hexanes:EtOAc) yielded **2.21h** (0.255 g, 91%) as a colourless oil; IR (neat) ν_{max} 2978, 2940, 1591, 1489, 1451, 1368, 1208, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, 1H, J = 0.7, 8.2 Hz), 7.44-7.31 (m, 6H), 3.19 (q, 4H, 7.2 Hz), 1.13 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 140.6, 134.9, 132.6, 131.1, 130.1, 128.5, 127.7, 127.0, 122.8, 43.3, 13.6 ppm; LRMS (EI) *(m/z(%))* 375(M^+ + 2, 60), 373(M^+, 100); HRMS (EI) calcd for $C_{16}H_{17}Cl_2NO_3S$ 373.0306: found 373.0306.

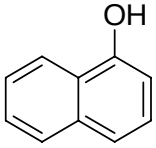
***N,N*-Diethyl 2-furan-2-ylphenyl *O*-sulfamate (2.21i)**



This compound was prepared by **Method C** using the following materials: **2.13i** (0.300 g, 0.845 mmol), furan-2-boronic acid (0.112 g, 0.845 mmol), Na_2CO_3 (2M, 2 mL), [$Pd(PPh_3)_4$] (96 mg, 10 mol %), in DME (4 mL), and the reaction mixture was refluxed for 24 h. Additional furan-2-boronic acid (0.112 g, 0.845 mmol) and $Pd(PPh_3)_4$ (48 mg, 5 mol %) was added and the reaction mixture was stirred at reflux for an additional 24 h. Standard workup and flash chromatography (9:1 hexanes:EtOAc) yielded **2.21i** (0.190 g, 76%) as a colourless oil; IR (neat) ν_{max} 2985, 2940, 1483, 1374, 1202, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 1H), 7.62-7.60 (m, 1H), 7.41 (t, 1H, J = 7.9 Hz), 7.33-7.29 (m, 2H), 6.94

(d, 1H, J = 3.3 Hz), 6.54 (t, 1H, J = 1.7 Hz), 3.29 (q, 4H, 7.2 Hz), 1.12 (t, 6H, 7.1 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 146.2, 142.2, 128.2, 127.3, 126.5, 124.0, 122.0, 111.8, 110.6, 43.4, 13.6 ppm; LRMS (EI) *(m/z(%))* 295(M^+, 61), 131(100); HRMS (EI) calcd for $C_{14}H_{17}NO_4S$ 295.0879: found 295.0878.

Benzyne Trapping Experiments on 2.13h, i, l, m. 1-Naphthol (2.22a)

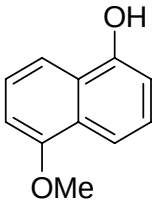


This compound was prepared by **Method E** using the following materials: **2.13h** (500 mg, 1.62 mmol), *n*-BuLi (0.7 mL, 2.44 M in hexanes, 1.7 mmol), furan (1.2 mL, 16.2 mmol), Et_2O (3.5 mL), followed by standard workup and flash chromatography (9:1 hexanes:EtOAc) afforded a residue that was taken up in absolute EtOH (5 mL), concentrated HCl was added (2 drops), and the whole was refluxed for 12 h. The mixture was diluted with H_2O, extracted with Et_2O (x3), dried (Na_2SO_4), and concentrated affording a solid that was recrystallized (MeOH) yielding **2.22a** (50 mg, 21%) as colourless crystals.

This compound was also prepared by **Method E** using the following materials: **2.13l** (500 mg, 1.32 mmol), *n*-BuLi (0.61 mL, 2.4 M in hexanes, 1.45 mmol), furan (1.0 mL, 13.2 mmol), Et_2O (3 mL), followed by standard workup afforded a residue that was taken up in absolute EtOH (5 mL), concentrated HCl was added (2 drops), and the whole was refluxed for 12 h. The mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (x3), extracted with aq. NaOH (x 2, 4 M), acidified with HCl (concentrated), extracted with CH_2Cl_2 (x3), dried (Na_2SO_4), and concentrated affording a solid that was recrystallized (MeOH) yielding **2.22a** (94 mg, 50%) as colourless crystals.

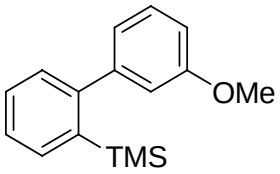
This compound was also prepared by a **Method F** using the following materials: **2.13i** (500 mg, 1.4 mmol), *i*PrMgCl (0.77 mL, 2.0 M in Et_2O, 1.54 mmol), furan (1.0 mL, 14 mmol), Et_2O (20 mL). Standard workup afforded a residue that was taken up in MeOH (5 mL), concentrated HCl was added (3 drops), and the whole was refluxed for 3 h. The mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (x3), dried (Na_2SO_4), concentrated, and flash chromatographed (9:1 hexanes:EtOAc) affording **2.22a** (140 mg, 70 %) as colourless crystals, mp 91-92 ^oC (MeOH) [lit[229] mp 89-90 ^oC] whose spectral data was consistent with that reported for the authentic material.

5-Methoxynaphthol (2.22b)



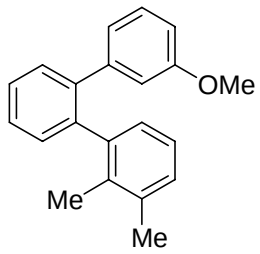
This compound was prepared by **Method E** using the following materials: **2.13m** (500 mg, 1.48 mmol), *n*-BuLi (0.67 mL, 2.44 M in hexanes, 1.63 mmol), furan (1.1 mL, 14.8 mmol), Et_2O (3 mL), followed by standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded a reside that was taken up in MeOH (10 mL), concentrated HCl was added (2 drops), and the whole was refluxed for 12 h. The mixture was concentrated, diluted with H_2O (10 mL) extracted with CH_2Cl_2 (x3), extracted with aq NaOH (x2, 4 M), acidified with conc HCl, extracted with CH_2Cl_2 (x3), dried (Na_2SO_4), and concentrated affording a solid that was recrystallized (MeOH) yielding **2.22b** (80 mg, 31%) as brown crystals, mp 137-138 ^oC (MeOH) [lit[230] mp 137-139 ^oC] ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 1H, J = 8.5 Hz), 7.77 (d, 1H, J = 8.5 Hz), 7.43 (t, 1H, J = 7.8 Hz), 7.33 (t, 1H, J = 7.6 Hz), 6.89-6.86 (m, 2H), 5.23 (bs, 1H), 4.03 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 151.2, 127.0, 125.3, 125.2, 114.8, 113.6, 109.5, 104.5, 55.6 ppm; (EI) *(m/z(%))* 174 (M^+, 100).

(3'-Methoxy-biphenyl-2-yl)-trimethyl-silane (2.24a)



This compound was prepared by **Method D** using the following materials: **2.13e** (322 mg, 1.0 mmol), [NiClCp(IMes)] (12 mg, 0.025 mmol), Et_2O (2.5 mL), 3-methoxyphenylmagnesium bromide (2.5 mL, 1.0 M (THF), 2.5 mmol), was stirred at reflux for 12 h. Standard workup and flash chromatography (99:1 hexanes / EtOAc) afforded **2.24a** (195 mg, 76%) as a colourless oil; IR (neat) ν_{max} 2953, 2896, 2838, 1611, 1592, 1259, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (m, 1H), 7.36-7.28 (m, 2H), 7.26-7.16 (m, 2H), 6.85-6.88 (m, 2H), 6.82-6.81 (m, 1H), 3.79 (s, 3H), 0.00 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 148.5, 145.3, 137.3, 134.0, 128.7, 128.1, 127.9, 125.8, 121.4, 114.4, 112.2, 54.6, 0.0 ppm; LRMS (EI) *(m/z(%))* 234 (M^+, 3), 241 (M^+ -Me, 100); HRMS (EI) calcd for $C_{16}H_{20}OSi$ 256.1283: found 256.1294.

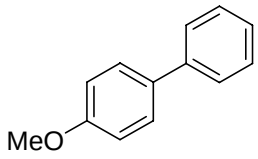
3-Methoxy-2",3"-dimethyl-[1,1';2',1"]tertphenyl (2.24b)



This compound was prepared by **Method D** using the following materials: **2.21a** (200 mg, 0.6 mmol), [NiClCp(IMes)] (6 mg, 0.02 mmol), Et_2O (2 mL), 3-methoxyphenylmagnesium bromide (1.5 mL, 1.0 M (THF), 1.5 mmol), was stirred at reflux for 24 h. Standard workup and flash chromatography (19:1 hexanes / EtOAc) afforded **2.24b** (111 mg, 64%) as a colourless oil; IR (neat) ν_{max} 2940, 1608, 1565, 1482, 1432, 1186, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, 1H, J = 7.1 Hz), 7.40 (qn, 2H, J = 6.1 Hz), 7.33 (d, 1H, J = 7.4 Hz), 7.13 (t, 1H, J = 8.0 Hz), 7.08-7.03 (m, 3H), 6.80 (d, 1H, J = 7.6 Hz), 6.73 (d, 1H, J = 8.3 Hz), 6.61 (s, 1H), 3.57 (s, 3H), 2.21 (s, 3H), 1.83 (s, 3H) ppm; ^{13}C NMR

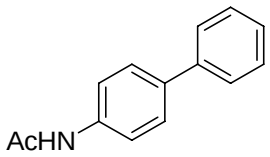
(101 MHz, $CDCl_3$) δ 158.7, 142.8, 141.5, 140.9, 136.6, 134.5, 130.8, 129.7, 128.7, 128.5, 128.3, 127.4, 127.1, 124.9, 121.8, 114.5, 112.9, 55.0, 20.5, 16.7 ppm; LRMS (EI) *(m/z(%))* 288 (M^+, 100); HRMS (EI) calcd for $C_{21}H_{20}O$ 288.1513: found 288.1514.

4-Methoxybiphenyl (2.24c)



This compound was prepared by **Method D** using the following materials: **2.13l** (259 mg, 1.0 mmol), [NiClCp(IMes)] (4.6 mg, 0.01 mmol), Et_2O (5 mL), phenylmagnesium bromide (0.87 mL, 2.88 M (Et_2O), 2.5 mmol), was stirred at reflux for 19 h. Standard workup and flash chromatography (99:1 hexanes / EtOAc) afforded **2.24c** (86 mg, 47%) as a colourless solid, mp 82-83 °C (hexanes) [lit[231] mp 83.5-85.5 °C] whose spectral data was consistent with that reported for the authentic material.

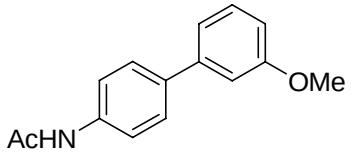
***N*-Acetyl-4-aminobiphenyl (2.24d)**



This compound was prepared by **Method D** using the following materials: **2.13m** (322 mg, 1.0 mmol), [NiClCp(IMes)] (12 mg, 0.025 mmol), Et_2O (5 mL), phenylmagnesium bromide (0.60 mL, 2.88 M (Et_2O), 1.7 mmol), was stirred at rt for 1 h. Standard workup afforded a brown oil that was dissolved in EtOH/H_2O (2:1, 6 mL) and hydroxylamine hydrochloride (690 mg, 10 mmol) and triethylamine (0.28 mL, 2 mmol) were added. The mixture was stirred at 90°C for 24 h, 1 M HCl (6 mL) was added, and the solution was washed with Et_2O (x2), adjusted to pH 10 (4 M NaOH), and extracted with Et_2O (x2). The organic extract was dried (Na_2SO_4) and concentrated *in vacuo* to afford a colourless oil that was

dissolved in anhyd CH_2Cl_2 (5 mL) and treated with acetic anhydride (0.1 mL, 1.2 mmol) and triethylamine (0.28 mL, 2 mmol) under an Ar atmosphere. The mixture was stirred at rt for 1 h before treatment with saturated aq. NH_4Cl solution (5 mL). Standard workup and flash chromatography (1:1 hexanes:EtOAc) yielded **2.24d** (105 mg, 50%) as a colourless solid, mp 171-172 ^oC [lit[232] mp 150-153 ^oC] whose spectral data was consistent with that reported for the authentic material.

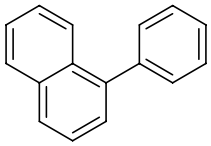
***N*-(4-(3-Methoxyphenyl)phenyl)acetamide (2.24e)**



This compound was prepared by **Method D** using the following materials: **2.13m** (322 mg, 1.0 mmol), [NiClCp(IMes)] (12 mg, 0.025 mmol), Et_2O (5 mL), 3-methoxyphenylmagnesium bromide (2 mL, 1.0 M (THF), 2 mmol), was stirred at rt for 3 h. Standard workup afforded a brown oil that was dissolved in EtOH/H_2O (2:1, 6 mL) and hydroxylamine hydrochloride (690 mg, 10 mmol) and triethylamine (0.28 mL, 2 mmol) were added. The mixture was stirred at 90^oC for 24 h, 1 M HCl (6 mL) was added, and the solution was washed with Et_2O (x2), brought to pH 10 (4 M NaOH), extracted with Et_2O (x2). The organic extract was dried (Na_2SO_4) and concentrated *in vacuo* to afford a colourless oil that was dissolved in anhyd CH_2Cl_2 (5 mL) and added acetic anhydride (0.1 mL, 1.2 mmol) and triethylamine (0.28 mL, 2 mmol) under an Ar atmosphere. The mixture was stirred at rt for 1 h before treatment with saturated aq. NH_4Cl solution (5 mL). Standard workup and flash chromatography (1:1 hexanes / EtOAc) yielded **2.24e** (110 mg, 46%) as a pale oil; IR (neat) ν_{max} 3344, 3311, 1675, 1598, 1534, 1393, 1214 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.37 (s, 1H), 7.78 (d, 2H, J =

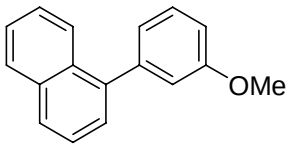
8.4 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.34 (t, 1H, J = 7.8 Hz), 7.19 (m, 2H), 6.89 (d, 1H, J = 7.1 Hz), 3.86 (s, 3H), 3.12 (s, 1H), 2.14 (s, 3H) ppm; ^{13}C NMR (101 MHz, acetone-d_6) δ 168.3, 160.0, 142.0, 137.6, 137.0, 129.9, 127.6, 120.5, 119.4, 112.6, 112.5, 55.3, 24.5 ppm; LRMS (EI) *(m/z(%))* 241 (M^+, 70), 199(100); HRMS (EI) calcd for $C_{15}H_{15}NO_2$ 241.1103: found 241.1103.

1-Phenylnapthalene (2.24f)



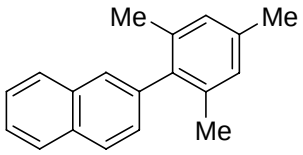
This compound was prepared by **Method D** using the following materials: **2.13n** (279 mg, 1.0 mmol), [NiClCp(IMes)] (4.6 mg, 0.01 mmol), Et_2O (5 mL), phenylmagnesium bromide (0.42 mL, 2.88 M (Et_2O), 1.2 mmol), was stirred at 0^{o}C for 10 min. Standard workup and flash chromatography (99:1 hexanes / EtOAc) afforded **2.24f** (171 mg, 84%) as an oil whose spectral data was consistent with that reported for the authentic material.[8]

1-(3-Methoxy-phenyl)-naphthalene (2.24g)



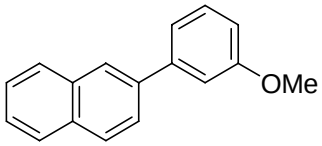
This compound was prepared by **Method D** using the following materials: **2.13n** (279 mg, 1.0 mmol), [NiClCp(IMes)] (4.6 mg, 0.01 mmol), Et_2O (3.0 mL), 3-methoxyphenylmagnesium bromide (2.0 mL, 1.0 M (THF), 2.0 mmol), was stirred at rt for 1 h. Standard workup and flash chromatography (44:1 hexanes / EtOAc) afforded **2.24g** (185 mg, 79%) as a waxy oil whose spectral data was consistent with that reported for the authentic material.[233]

2-(2,4,6-Trimethyl-phenyl)-naphthalene (2.24h)



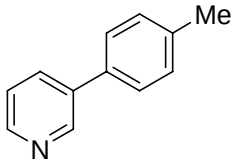
This compound was prepared by **Method D** using the following materials: **2.13o** (279 mg, 1.0 mmol), [NiClCp(IMes)] (12 mg, 0.025 mmol), Et_2O (2.5 mL), 3-mesitylmagnesium bromide (2.5 mL, 1.0 M (Et_2O), 2.5 mmol), was stirred at reflux for 18 h. Standard workup and flash chromatography (99:1 hexanes / EtOAc) afforded **2.24h** (170 mg, 69%) as a waxy oil[234]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.00 (m, 3H), 7.81 (s, 1H), 7.68-7.64 (m, 2H), 7.48 (dd, 1H, J = 1.4, 8.4 Hz), 7.18 (s, 2H), 2.56 (s, 3H), 2.23 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 138.9, 136.9, 136.3, 132.5, 128.3, 128.2, 128.1, 127.9, 126.2, 125.9, 21.3, 21.0 ppm; LRMS (EI) *(m/z(%))* 246 (M^+, 100).

2-(3-Methoxy-phenyl)-naphthalene (2.24i)



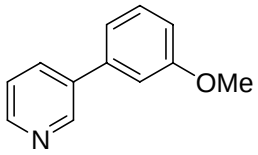
This compound was prepared by **Method D** using the following materials: **2.13o** (279 mg, 1.0 mmol), [NiClCp(IMes)] (12 mg, 0.025 mmol), Et_2O (2.5 mL), 3-methoxyphenylmagnesium bromide (2.5 mL, 1.0 M (THF), 2.5 mmol), was stirred at rt for 1 h. Standard workup and flash chromatography (44:1 hexanes / EtOAc) afforded **2.24i** (200 mg, 86%) as a colourless solid, mp 68-70 ^{o}C [lit[235] mp 90 ^{o}C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 1H, J = 7.8 Hz), 8.03 (d, 1H, J = 7.8 Hz), 7.99 (d, 1H, J = 7.8 Hz), 7.67-7.51 (m, 5H), 7.25-7.21 (m, 2H), 7.13-7.11 (m, 1H), 3.97 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 142.4, 140.3, 134.0, 131.8, 129.4, 128.4, 127.4, 127.0, 126.2, 125.9, 125.5, 122.7, 115.8, 113.0, 55.4 ppm.

3-*p*-Tolyl-pyridine (2.24j)



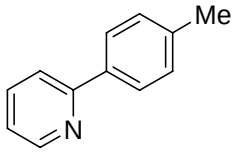
This compound was prepared by **Method D** using the following materials: **2.13p** (690 mg, 3.0 mmol), [NiClCp(IMes)] (28 mg, 0.02 mmol), Et_2O (5 mL), tolylmagnesium bromide (4 mL, 1.0 M (Et_2O), 2.0 mmol), was stirred at rt for 8 h. Standard workup and flash chromatography (19:1 hexanes / EtOAc) afforded **2.24j** (395 mg, 78%) as an off-white solid, mp 38-39 ^oC whose spectral data was consistent with that reported for the authentic material.[236]

3-(3-Methoxy-phenyl)-pyridine (2.24k)



This compound was prepared by **Method D** using the following materials: **2.13p** (460 mg, 2.0 mmol), [NiClCp(IMes)] (24 mg, 0.025 mmol), Et_2O (5 mL), 3-methoxyphenylmagnesium bromide (4.0 mL, 1.0 M (THF), 4.0 mmol), was stirred at rt for 4 h. Standard workup and flash chromatography (65:35 hexanes / EtOAc) afforded **2.24k** (160 mg, 85%) as a colourless oil[237]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (bs, 1H), 8.61 (bs, 1H), 7.89 (d, 1H, J = 7.6 Hz), 7.41 (t, 1H, J = 7.9 Hz), 7.39 (bs, 1H), 7.18 (dd, 1H, J = 1.4, 7.6 Hz), 7.13-7.12 (m, 1H), 6.99-6.96 (m, 1H), 3.89 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 148.5, 139.0, 136.6, 134.5, 130.2, 129.4, 123.6, 113.5, 113.0, 55.4 ppm; LRMS (EI) *(m/z(%))* 185(M^+, 100).

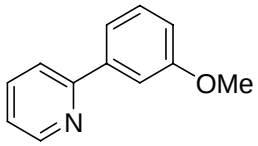
2-*p*-Tolyl-pyridine (2.24l)



This compound was prepared by **Method D** using the following materials: **2.13q** (690 mg, 3.0 mmol), [NiClCp(IMes)] (28 mg, 0.02

mmol), Et_2O (5 mL), tolylmagnesium bromide (6 mL, 1.0 M (Et_2O), (6.0 mmol), was stirred at rt for 8 h. Standard workup and flash chromatography (9:1 hexanes / EtOAc) afforded **2.24l** (415 mg, 82%) as a colourless oil whose spectral data was consistent with that reported for the authentic material.[238]

2-(3-Methoxy-phenyl)-pyridine (2.24m)



This compound was prepared by **Method D** using the following materials: **2.13q** (460 mg, 2.0 mmol), [NiClCp(IMes)] (24 mg, 0.05 mmol), Et_2O (5 mL), 3-methoxyphenylmagnesium bromide (4.0 mL, 1.0 M (THF), 4.0 mmol), was stirred at rt for 4 h. Standard workup and flash chromatography (7:3 hexanes / EtOAc) afforded **2.24m** (173 mg, 73%) as a colourless oil whose spectral data was consistent with that reported for the authentic material.[239]

Chapter 3

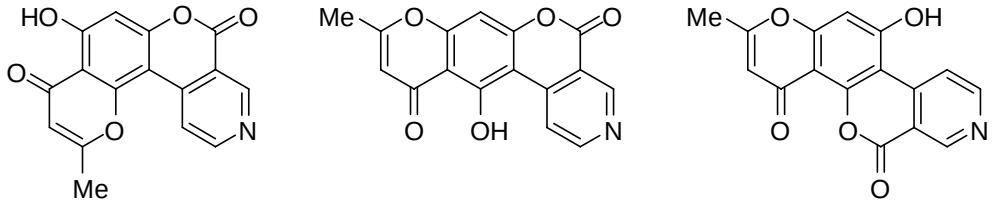
Total Synthesis of Schumanniophytine.

Metalation – Cross Coupling Route Involving a Key Remote Anionic Fries Rearrangement

3.1. Prelude

3.1.1. Schumanniophytine

Schumanniophytine, a rare tetracyclic pyranobenzopyranopyridine (nicotinic acid-noreugenin congener) alkaloid[240] isolated from the root bark of a rubiaceae shrub *Schumanniophyton problematica* from Ivory Coast Africa, was first described and assigned to structure **3.1** in 1978 by Schlittler and Spitaler (Figure 3.1).[241] Controversy arose in 1985 when Houghton and Yang reported the isolation of schumanniophytine from a different source (*Schmanniophytine magnificum*), and assigned it structure **3.2**.[242] They also reported the isolation of structure **3.3** naming it isoschumanniophytine due to the NaOH promoted interconversion between **3.2** and **3.3** by scission / reassembly of the lactone ring. Later in 1987, Houghton revised his earlier reports on the basis of NOE experiments and a Gibb's reagent test to concur with Schlittler and Spitaler and changed



3.1 **3.2** **3.3**

Figure 3.1. *Schumanniophyton* Alkaloids

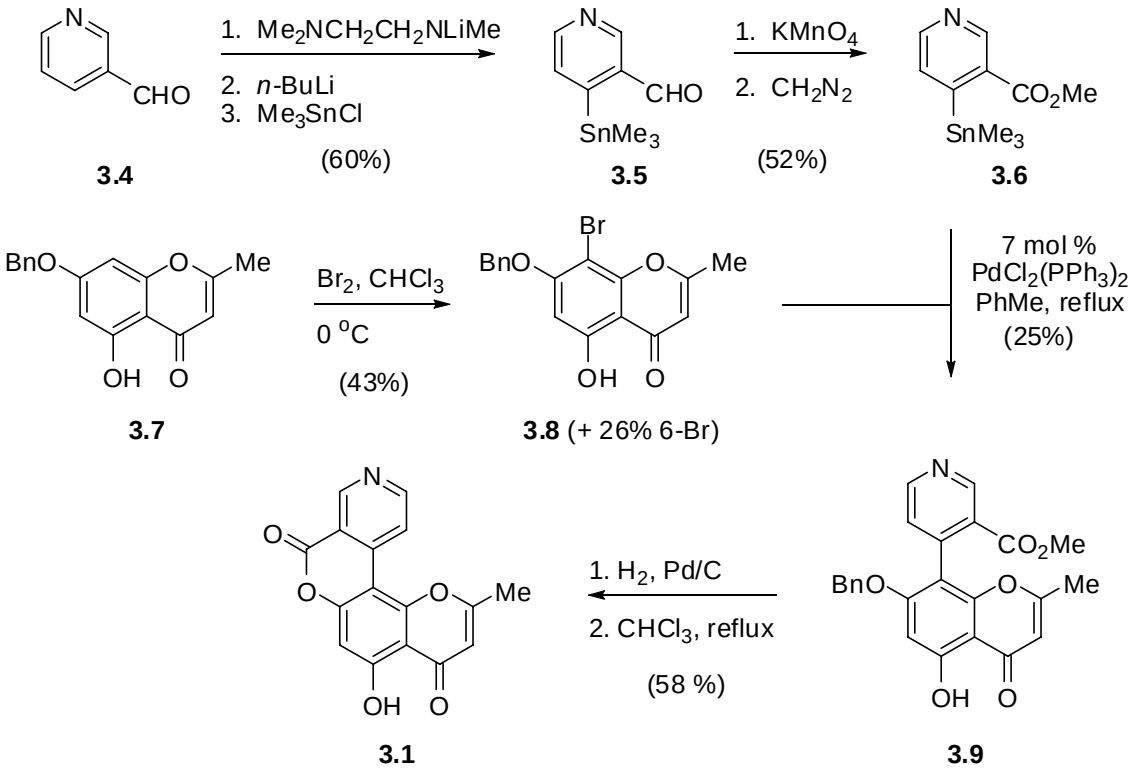
the structure of schumanniophyine to **3.1** and isoschumanniophytine to **3.2**.[243] The interconversion of **3.1** and **3.2** is less easily accommodated but envisioned by scission / reassembly of both the α- and γ-pyrone rings.

Historically, Nigerians have used *S. problematica* for medicinal treatment of psychosis as the *Schumanniophyton* alkaloids are known for autonomic and central nervous system depression.[244] Nonetheless, several similar alkaloids including schumanniophytine **1** have shown activity against human immunodeficiency virus (HIV) and herpes simplex virus (HSV).[245,246]

3.1.2. Kelly's Total Synthesis of Schumanniophytine

In 1991, Kelly and Kim reported the first and only total synthesis of **3.1** and **3.2** by the direct cross coupling of nicotinic acid and noreugenin precursors (Scheme 3.1).[247] The trimethylstannyl group of coupling partner **3.6** was introduced to nicotinaldehyde **3.4** via regiospecific lithiation using the Comins[248] method followed by oxidation – methylation. Mono-benzylated noreugenin **3.7** is prepared from literature procedures in two steps (22%) from phloracetophenone.[249,250] Subsequent bromination of **3.7** proceeds with poor regioselectivity to give both 8-bromo **3.8** and 6-bromo isomers separable by chromatography. Advantageously, both isomers were used in the synthesis of both **3.1** and **3.2**. Stille cross coupling of **3.6** with **3.8** proceeds with poor yield (25%) and final debenzylation – lactonization affords schumanniophytine **3.1** in overall yield of 5% (6 linear steps).

Scheme 3.1. Kelly's Total Synthesis of Schumanniophytine

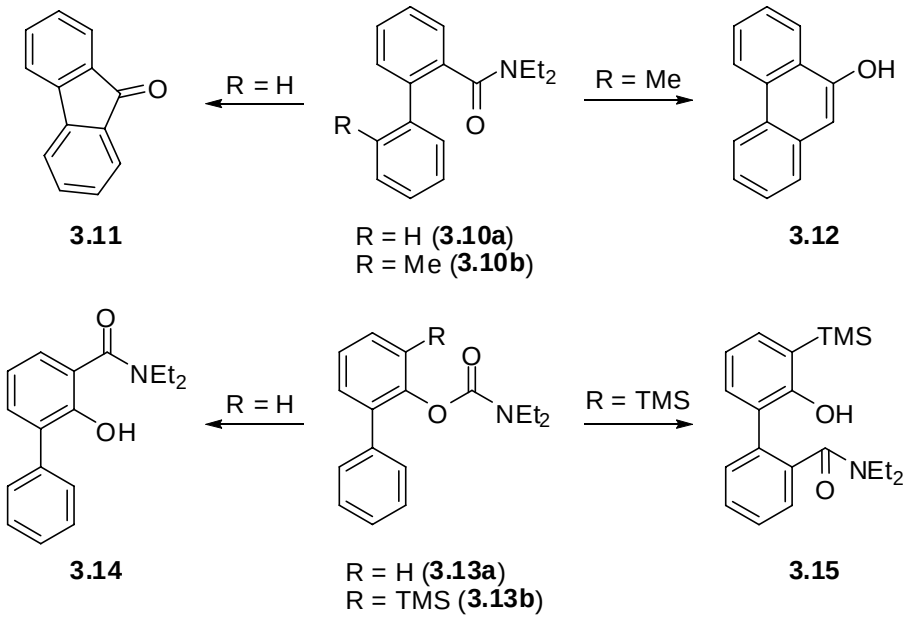


3.1.3. The Directed remote Metalation Reaction (DreM)

An extension of D*o*M that clearly exemplifies CIPE in action is the directed remote metalation (DreM) reaction. As the name suggests, C-H activation is achieved in the vicinity of strongly coordinating carboxamide and carbamate DMGs. Despite mechanistic evidence, remote C-H deprotonation on biaryls arises from thermodynamically driven deprotonation where an intramolecular reaction with a coordinating DMG provides an energetically favourable intermediate. The first DreM on a biaryl system was reported by Narasimhan[251] in 1969. It was found that deprotonation of 2-aminobiphenyl with excess *n*-BuLi affords phenanthridin-6-one, after quenching with CO_2 presuming NHLi directs 2'-deprotonation. Snieckus has shown that biaryl

carboxamide **3.10a-b** and carbamate **3.13a-b** DMG systems, rapidly contructed *via* the D*o*M – cross coupling nexus,[22,192,193] yield conformational isomers upon treatment with LDA at ambient temperatures (Scheme 3.2). Anionic cyclization of simple biaryl carboxamide **3.10a** yields the corresponding fluorenones **3.11** in high yields. This reaction has been used in the preparation of liquid crystals,[252] constrained Roloxifene

Scheme 3.2. DreM Reaction of Biaryl Carboxamide 3.10 and Carbamate 3.13



analogues[253], and several natural products (e.g. dengibsinin[254] and imeluteine[255]). Furthermore, if a methyl or an acidic methylene residue is situated at the 2'-position as in **3.10b**, deprotonation – cyclization leads to 9-phenanthrols **3.12**[256] or phenanthrenes after a triflation – hydrogenolysis protocol.[257] This process has been applied to the synthesis of several natural products (e.g. eupolauramine[258], and an unnamed indolo[2,3-*a*]carbazole alkaloid[259]). Treatment of unsubstituted biaryl carbamate **3.13a** with LDA yields the corresponding anionic *ortho*-Fries[31] product **3.14**. If the *ortho* position is

protected (e.g. OMe or conveniently with TMS *via* D*o*M) **3.13b**, the thermodynamic deprotonation product is trapped by a remote anionic-Fries reaction, transferring the carbamoyl unit to the adjacent ring, producing **3.15**.[260] This process has been used in natural product synthesis prior to acid-catalyzed lactonization (e.g. gilvocarcins E, M, and V[261], and plicadin[262]) or further DreM reactions (e.g. dengibsin[260], gymnopusin[263], and kinobscurinone[264]). Other DreM methodologies based on remote anionic carbamoyl migrations and cyclizations have been developed for the synthesis of bioactive heteroatom containing biaryl frameworks including xanthones (e.g. 6-deoxyjacareubin[265]), acridones (e.g. yukodine and junosidine[266]), and oxacarbazepines (e.g. Trileptal[267]).

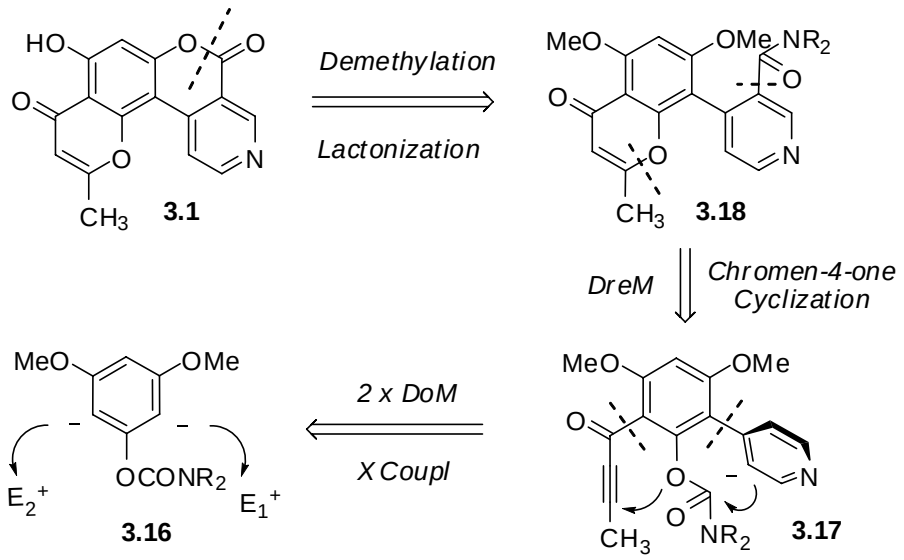
3.1.4. DreM – Cyclization Route to Schumanniophytine

Within the structure of schumanniophytine **3.1** lies the opportunity to utilize DreM methodology and extend it to involve further anionic chemistry. Succeeding carbamate remote-Fries migration,[260] the resultant lithium phenolate could be utilized to engage in ynone 6-*endo-dig* cyclization to the benzopyran-4-one (chromone) nucleus (**3.17** → **3.18**, Scheme 3.3). Target azabiaryl **3.17** could be constructed *via* a two-fold D*o*M – cross coupling strategy from symmetrical carbamate **3.16**. This new one-pot DreM – anionic chromone cyclization would hopefully give precursor **3.17** which could be rapidly converted into **3.1** by a double demethylation – lactonization protocol.[268]

D*o*M and cross coupling of **3.16** yielded azabiaryl **3.29** (see Scheme 3.4) and subsequent D*o*M at -100 ^{o}C to prevent the facile competing *ortho*-Fries reaction furnished after quenching with their respective electrophiles, compounds **3.19** and **3.22**

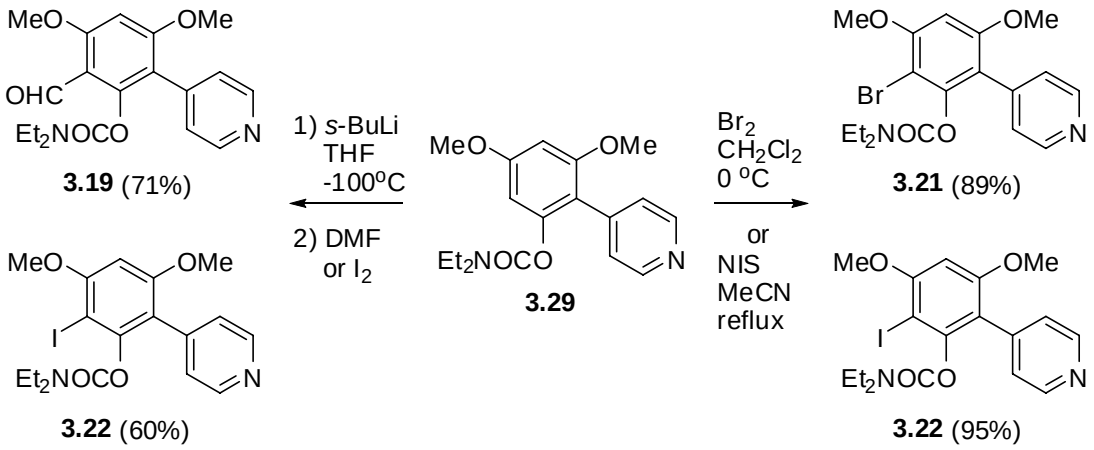
(Scheme 3.4). Aryl iodide **3.22** could be more conveniently prepared using electrophilic aromatic substitution in 95% yield with NIS in refluxing MeCN. Similarly, aryl bromide **3.21** was also prepared.

Scheme 3.3. DreM – Chromone Cylization Route to Schumanniophytine



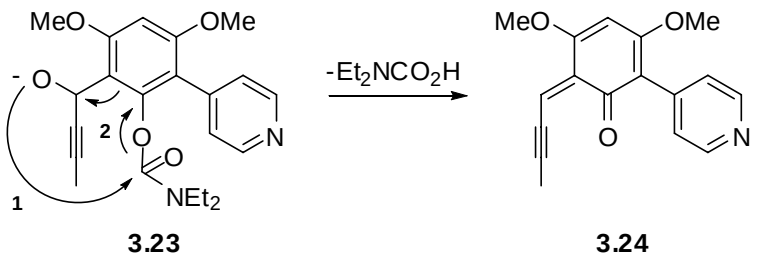
All attempts for the synthesis of target ynone **3.17** starting with iodide **3.22** or aldehyde **3.19** failed. The iodine functionality of **3.22** provided a convenient handle for Grignard generation utilizing a Knochel procedure[269] with *i*-PrMgBr • LiBr complex. However, the resultant aryl Grignard failed to react with *N*-methoxy-*N*-methylbut-2-ynamide even under forcing thermal conditions. Transmetalation to copper[270] or zinc for Negishi cross coupling[271] both failed to give product when reacted with 2-butynoyl chloride. Carbonylative Sonogashira,[272] Suzuki,[273,274] and Stille[275] cross coupling reactions under ambient and high pressure / temperature conditions also all failed to give the desired product **3.17**. On the other hand, aldehyde **3.19** proved to be a poorly

Scheme 3.4. Preparation of Precursors to Target Compound 3.17



electrophilic compound as 1-propynylmagnesium bromide failed to react under thermal and Lewis acid assisted conditions. Treatment of **3.19** with 1-propynyllithium[276] at -78 °C with slow warming resulted in the consumption of starting material at -20 °C. After the reaction was recooled to -78 °C and quenched with AcOH, the major product observed by mass spectroscopy had combined with the lithium reagent with loss of *N,N*-diethylcarbamic acid (Scheme 3.5). Mechanistically, carbamic acid loss can occur post alkynyllithium addition *via* 1) intramolecular attack of the generated benzyl alkoxide on the carbamate resulting in intramolecular O → O carbamoyl transfer, followed by 2) elimination *via o*-quinone methide formation (**3.23** → **3.24**).[277]

Scheme 3.5. Reaction of 3.19 with 1-Propynyllithium



3.2. Manuscript 2:

Total Synthesis of Schumanniophytine. Metalation-Cross Coupling Route Involving a Key Remote Anionic Fries Rearrangement

Todd K. Macklin, Mark A. Reed and Victor Snieckus

Department of Chemistry, Queen's University, Kingston, ON, K7L 3N6, Canada

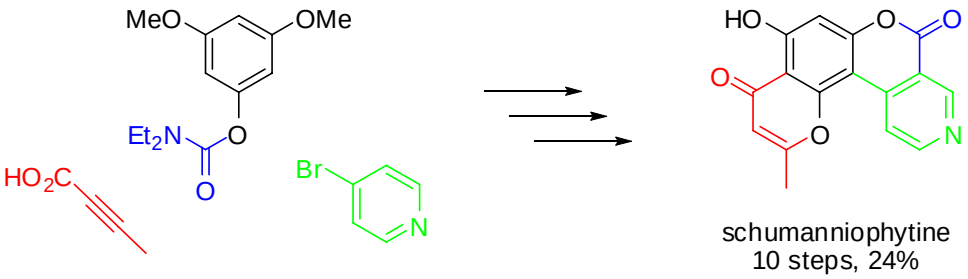
3.2.1. Preface

With minor editorial and formatting changes, and schematical expansion of several references, this manuscript appears substantially as it has been accepted to the *European Journal of Organic Chemistry*. Todd Macklin was responsible for all synthesis, distillation, chromatography, crystallization, and data collection (NMR, LRMS, IR, mp). Dr. Mark Reed initiated the project by synthesizing compounds **3.27, 3.28a,b,** and **3.30a**. Several IR and mp were collected by Ms. Jane Panteleev. HRMS was collected by Ms. Jie Sui. The manuscript was written by Todd Macklin and Victor Snieckus.

3.2.2. Abstract

A short synthesis of the alkaloid schummaniophytine (**3.1**) starting from simple building blocks and involving directed *ortho* metalation (D*o*M), Suzuki-Miyaura cross coupling, and a key remote anionic Fries rearrangement is described.

Scheme 3.6. Manuscript 2 Graphical Abstract



3.2.3. Introduction

We disclose a synthesis of schumanniophytine (**3.1**), a representative of a minor class of alkaloids isolated[241] from the root bark of *Schumanniophyton problematicum*, which shows central and autonomic system depressant properties and may have potential antiviral activity.[240,246] Schumanniophytine co-occurs with isoschumanniophytine (**3.2**) into which it may be converted by scission and reassembly of the pyrone ring.[242] In spite of the rare tetracyclic pyranobenzopyranopyridine framework[278], schumanniophytine has elicited only a single total synthesis, reported by Kelly, which features a Stille cross coupling of a 4-stannylated nicotinate ester with a easily procurable 8-bromochromone.[247]

Herein we describe a route which takes advantage of the directed *ortho* metalation (D*o*M) – Suzuki-Miyaura cross coupling strategy[192,193] and incorporates a key *O*-carbamate remote anionic Fries rearrangement (**3.25**) for the lactone ring construction. While a route towards schumanniophytine via an anionic remote-Fries – Michael addition

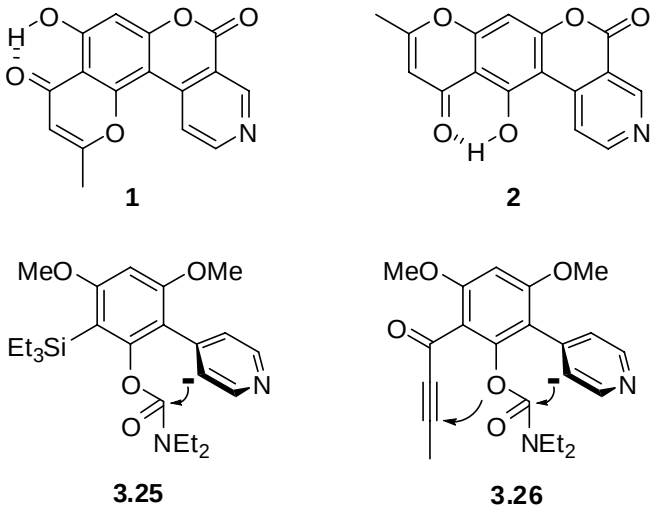


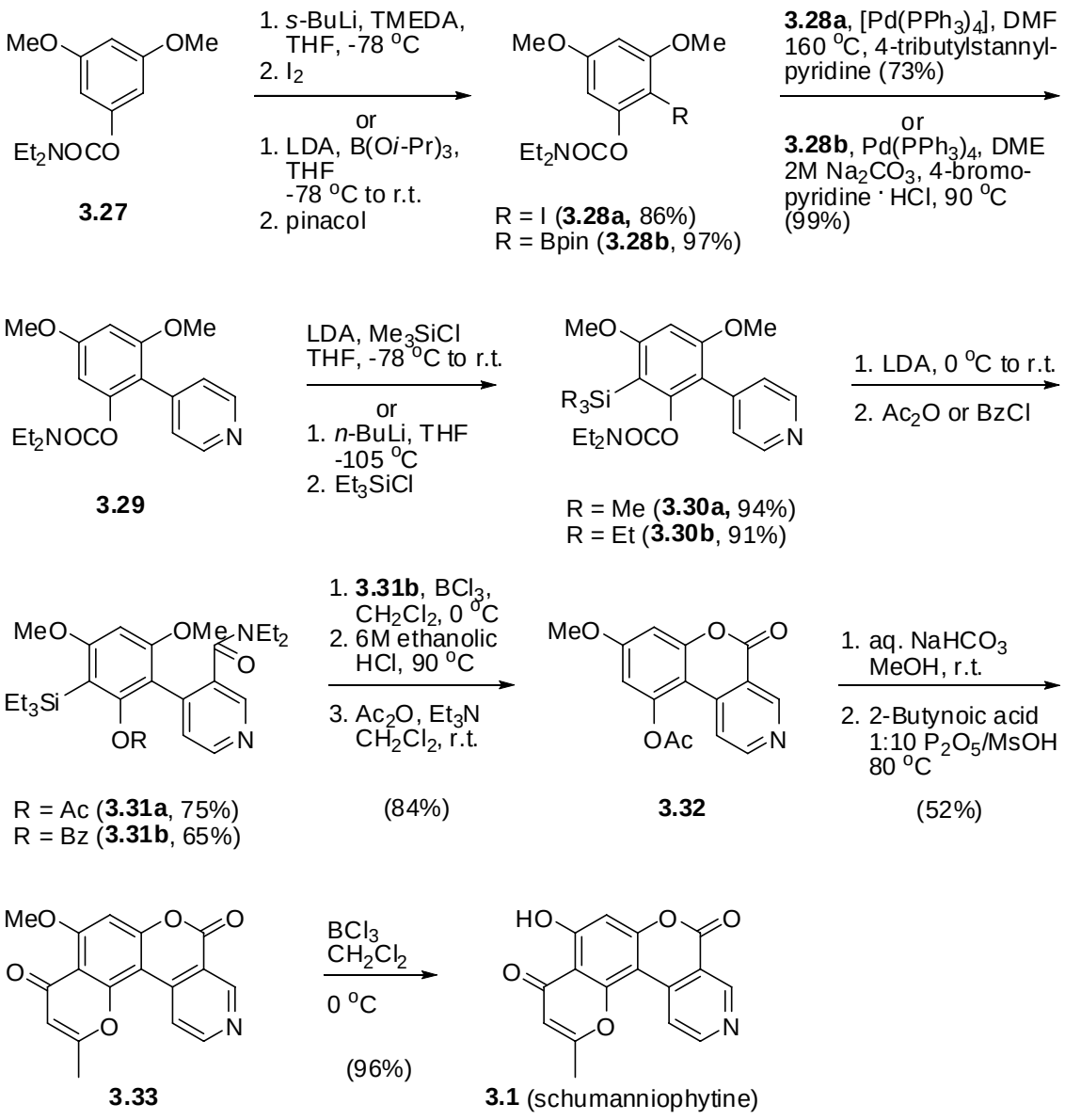
Figure 3.2. Schumanniophyton 1 and Isoschumanniophytine 2 and Proposed Synthesis Intermediates 3.23 and 3.26

sequence (**3.26**), a rational extension of concept **3.25**,[279] proved unapproachable, initial model studies[280] confirmed correctness of concept and resulted in the development of new general and regioselective synthetic methodologies for 4*H*-1-benzopyran-4-ones (chromones) which is the subject of the accompanying chapter.

3.2.4. Results and Discussion

The synthesis of schumanniophytine was initiated (Scheme 3.7) by metalation of the symmetrical *O*-carbamate (**3.27**) whose regioselectivity takes advantage of the powerful carbamate directed metalation group (DMG)[281] to give, after iodination and

Scheme 3.7. Total Synthesis of Schumanniophytine



boronation, intermediates **3.28a** and **3.28b** respectively in excellent yields. Stille cross coupling of **3.28a** with 4-tributylstannylpyridine[282] or, more efficiently, Suzuki-Miyaura coupling of **3.28b** with commercial 4-bromopyridine hydrochloride efficiently led to the azabiaryl **3.29**. The expected, regioselective second DoM reaction was followed by silylation with TMSCl and TESCl afforded highly hindered derivatives **3.30a** and **3.30b** respectively.[283] With silicon-protection in place, anionic remote-Fries rearrangement of the TES derivative **3.30b** resulted in smooth pyridine-ring carbamoyl translocation, to furnish, after direct acetylation and benzoylation, the aryl nicotinamides **3.31a** and **3.31b** respectively. The migration was conveniently followed with transient IR by observing the near disappearance of carbamoyl (**3.30b**, ν = 1725 cm^{-1}) and appearance of amide

Scheme 3.8. React IR Monitoring of DreM of 3.30b.

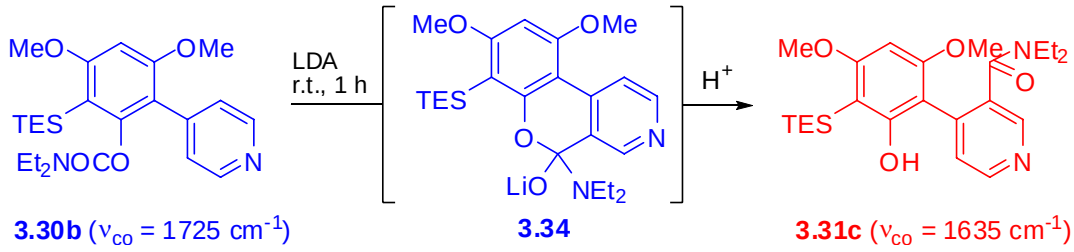
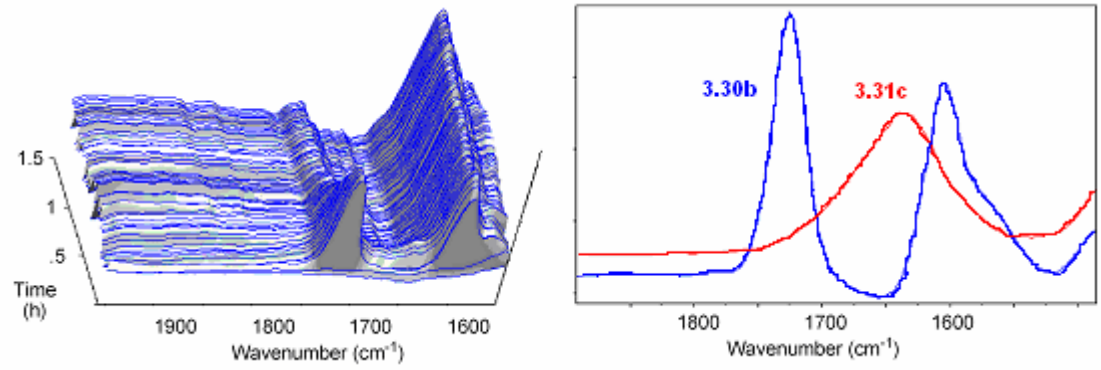


Figure 3.3. React IR Spectra of Reaction 3.30b to 3.31c



(**3.31c**, ν = 1635 cm^{-1}) carbonyl stretching frequencies upon aqueous quench (Scheme 3.8 and Figure 3.3). The complete disappearance of the carbamate could be observed upon treatment with additional LDA. Although the TMS derivative **3.30a** also underwent clean rearrangement to give the corresponding phenol in 80-90% yield, it proved to undergo rapid decomposition thus precluding its further synthetic use.[284] In order to avoid alternative regiochemical lactonization of **3.31a** under acidic conditions (see Post Scriptum 3.3), **3.31b** was subjected to treatment with BCl_3 which resulted in regioselective demethylation,[285] to give, after acidic protodesilylation, debenzylation and reacylation (for convenient isolation) lactone **3.32** in high overall yield.

After numerous unsuccessful attempts to effect pyrone ring annulations (see Post Scriptum 3.3), liberation of the free phenol from **3.32** using sodium bicarbonate followed by adaptation of the versatile Eaton's reagent (1:10 P_2O_5/MsOH)[286] gave the desired tetracycle **3.33**. To conclude, demethylation proceeded efficiently under BCl_3 mediated conditions[285] to furnish schumanniophytine **3.1** whose physical and spectroscopic properties were found in full accord with the natural product.[240-242,247]

3.2.5. Conclusions

A synthesis of schumanniophytine (**3.1**) involving a key silicon-directed anionic remote Fries rearrangement has been completed in 10 steps and 24% overall yield (optimum sequence, Scheme 3.7). The synthesis compares favorably with that described by Kelly[247] (6 steps and 5% overall yield). In view of the connections to D*o*M[281] and cross coupling strategies,[192,193] the route provides opportunity for incorporation of functionality in the aromatic, pyridyl, and pyranyl moieties for potential SAR profiling

studies. This and related contributions from our[287] and other laboratories[288] further demonstrate the increasing value of carbanionic chemistry for the regioselective construction of aromatics and heteroaromatics.

3.2.6. Acknowledgement

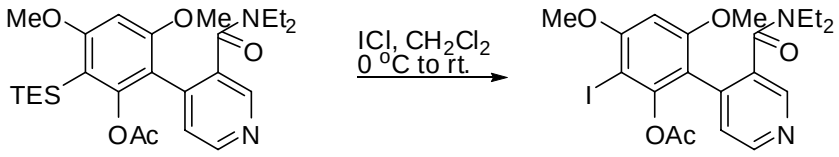
We thank NSERC Canada for support via the Discovery Grants program and Merck Frosst Canada for unrestricted grant support. We are grateful to the Canadian Foundation for Innovation (CFI) for infrastructure support especially in high field NMR and HRMS facilities.

3.3. Post Scriptum

3.3.1. Alternative Pyrone Ring Annulations

Succeeding the successful DreM reaction en route to schumanniophytine, several attempts to effect expedient chromone ring formation were tested. With nicotinamide derivative **3.31a** in hand we had initially planned to benefit from aryl TES installation by performing subsequent *ipso* substitution chemistry made possible with aryl silanes. To ensure that the *ipso* reaction of **3.31a** would proceed, a well known *ipso*-iodination[224] reaction from our group was conducted to successfully afford the corresponding iodide **3.35** in 89% yield (Scheme 3.9). This product was then reacted using a modified

Scheme 3.9. *Ipso*-Iodination of 3.31a.

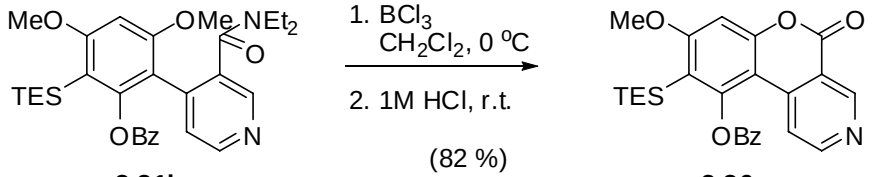


3.31a (89%) **3.35**

carbonylative Sonogashira reaction[289] for one-pot pyrone ring annulation but failed to give the desired chromone nucleus. Attempts using *ipso*-acylative chemistry with **3.31a** also had limited success. Direct pyrone installation using 2-butynoyl chloride and Fillion's Meldrum acid protocol[290] using several acidic and Lewis acid conditions failed to give the desired product. *Ipso-ortho*-Fries of acetate **3.31a** was attempted using several Lewis acids with limited success, although some acetophenone products were detected using an excess of $TiCl_4$, they were accompanied with undesired lactonization products. In fact, acetate cleavage followed by facile lactonization was a problematic

side reaction that plagued most of the above reactions. Since unwanted lactonization was posing a problem, a benzoate protecting group, stable to anhydrous HCl,[291] was installed (**3.31b**) to withstand the acidic conditions required for further *ipso*-acylation reactions and ultimately the employed demethylation conditions for the total sequence (**3.31b → 3.32**, Scheme 3.7). Unfortunately, poor reactivity was experienced using several Lewis acids, and pushing the reactions thermally resulted in desilylation. Intercepting reaction **3.31b → 3.32** at lactone **3.36** (Scheme 3.10) and attempting similar *ipso*-acylation reactions resulted in the same desilylation reactions. It may be reasonable that the steric influences coupled with aromatic deactivation from pyridinium formation may be of consequence to the failure of all *ipso*-acylative substitution reactions tested.

Scheme 3.10. Isolation of 3.36 by Interception of 3.31b → 3.32.

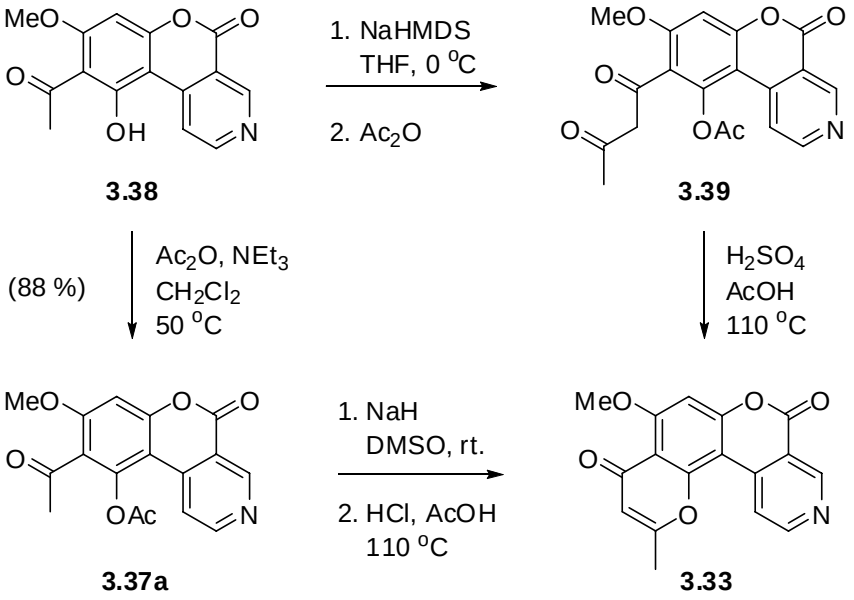


3.31b **3.36**

Further chemistry focused on single and multi-step pyrone ring annulation of **3.32**. Under optimized conditions using earlier mentioned Meldrum's acid chemistry, one-pot pyrone ring annulation continued to fail using acetate **3.32** as well as its base-liberated phenol. Compound **3.32** was then subjected to range of classical Lewis-acid Fries rearrangement reactions. The best reaction was achieved using $AlCl_3$, and followed by reacylation afforded a 1:1 mixture of 9 and 7-acetophenones derivatives **3.37a** and **3.37b**. Acetoxy derivative **3.37a** and it's deacylated product **3.38** were then subjected to

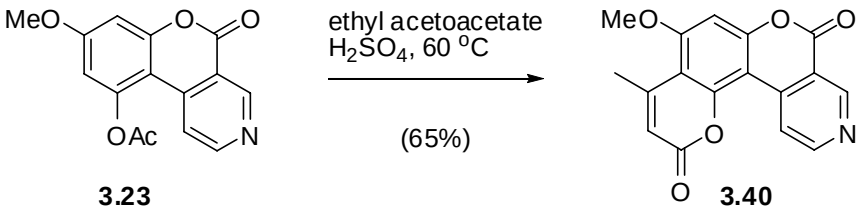
pyrone ring forming reactions accessible by inter- and intra-molecular Baker-Venkataraman[292,293] acetophenone acylation and acidic dehydrative cyclization of the corresponding intermediary diketone (e.g. **3.39,** Scheme 3.11). These reactions provided the 8-methoxy schumanniophytine nucleus **3.33** in low yields with poor reproducibility.

Scheme 3.11. Stepwise Pyrone Ring Annulation to 8-Methoxy Schumanniophytine 3.33



These discouraging results led to the consideration of more classical approaches to effect the pyrone ring annulation. Among several approaches tested which included that chosen for the optimum sequence (**3.32** → **3.33**, Scheme 3.7), treatment of **3.32** with ethyl acetoacetate under neat H_2SO_4 conditions (von Pechmann) gave the regioisomeric and undesired 4-methylchromen-2-one (coumarin) **3.40** in moderate yield (Scheme 3.12).[294]

Scheme 3.12. Synthesis of Coumarin 3.40.



3.23 **3.40**

3.4 Experimental

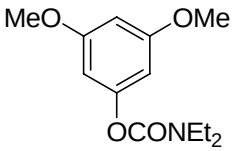
3.4.1 General Methods

Melting points are uncorrected. Infrared spectra were recorded as neat or KBr discs using a BOMEM MB-100 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 400 MHz spectrometer. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sx, sextet; dd, doublet of doublet; td, triplet of doublet; m, multiplet; bs, broad singlet. GC-MS analyses were performed with an *Agilent 6890N* GC coupled with an *Agilent 5973 inert* MS under EI conditions. THF was freshly distilled from sodium benzophenone ketyl under argon and *N,N*-diethylcarbamoyl chloride was distilled from CaH_2 and stored over 4 Å molecular sieves prior to use. *N*- and *s*-butyllithium were purchased from Aldrich as solutions in hexanes and cyclohexane, stored in a resealable container, and titrated periodically against *N*-benzylbenzamide. LDA and LTMP were freshly prepared before reactions by stirring a 1:1 mixture of di*iso*propylamine or tetramethylpiperidine and *n*-BuLi at 0 ^{o}C in THF (1 M) for 10 min. *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was stored over solid KOH prior to use. All reactions involving alkyllithiums were carried out in oven or flame-dried glassware cooled under argon using syring-septum cap techniques. The -105, -78, and 0 ^{o}C temperatures designated are approximate as achieved by a liquid nitrogen-ethanol, dry ice-acetone, and ice-salt bath, respectively. When internal temperature readings were essential, a Barnant Dual J stainless steel-sheathed thermocouple thermometer was employed. $[Pd(PPh_3)_4]$ was freshly prepared according to a literature procedure[226] and solutions were pre-degassed using sonication associated with argon bubbling. Eaton's

reagent[295] was prepared by stirring 1:10 mass ratio of P_2O_5 and freshly distilled MsOH under argon for 4-8 h. Reaction monitoring was done by TLC and GC where appropriate. Flash column chromatography was carried out using Merck silica gel 60 (particle size: 32-63).

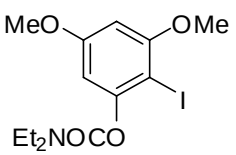
3.4.2 Experimental Procedures and Data

3,5-Dimethoxyphenyl diethylcarbamate (3.27)



A solution of 3,5-dimethoxyphenol (20 g, 0.13 mol) in MeCN (250 mL), was added K_2CO_3 (27 g, 0.195 mol), $ClCONEt_2$ (25 mL, 0.195 mol) and the whole was heated to reflux for 12 h. The mixture was then diluted with water (625 mL) and extracted with Et_2O (50 mL x 3). The combined extracts were then washed with 2M NaOH (50 mL), water (50 mL x 2), brine (50 mL x 2), dried (Na_2SO_4), and concentrated *in vacuo* afforded a brown oil which was distilled under high vacuum to yield **3.27** (26.3 g, 80%) as a colourless oil, bp 183 ^oC at 1.13 mmHg; IR (neat) ν_{max} 2974, 2937, 1719, 1599, 1473, 1415, 1270, 1205, 1155, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 3H), 3.78 (s, 6H), 3.41 (q, 4H, J = 6.3 Hz), 1.23 (t, 6H, J = 7.9 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 154.0, 153.2, 100.4, 97.8, 55.4, 42.2, 41.9, 14.2, 13.4 ppm; EIMS (*m/z*(%)) 253[M^+](60), 100(100), 72(40); HRMS (EI) calculated for $C_{13}H_{19}NO_4$ 253.1314: found 253.1304.

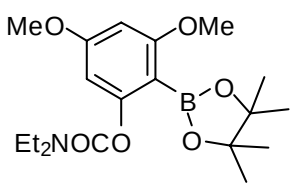
2-Iodo-3,5-dimethoxyphenyl diethylcarbamate (3.28a)



A solution of **3.27** (1 g, 3.95 mmol) in THF (50 mL) containing TMEDA (0.78 mL, 5.1 mmol) was treated via syring with *s*-BuLi

(3.6 mL, 5.1 mmol, 1.4 M in cyclohexane) maintaining an internal temperature <-72 °C. The mixture was allowed to metalate for 10 min and then treated with a solution of I_2 (1.5 g, 5.9 mmol, in 10mL THF) via canula maintaining an internal temperature <-72 °C. The reaction is then warmed to rt and treated with saturated aq. NH_4Cl (20 mL) followed by saturated aq. $Na_2S_2O_3$ (20 mL), layers separated, aqueous phase extracted with EtOAc (2 x 20 mL), dried (Na_2SO_4), and concentrated in vacuo affording a yellow solid. Flash column chromatography (1:1 hexanse:EtOAc) yielded **3.28a** (1.3 g, 86%) as a yellow solid, mp 67-68 °C (hexanes); IR (neat) ν_{max} 2972, 2934, 1720, 1593, 1458, 1403, 1268, 1217, 1154, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (d, 1H, J = 2.6 Hz), 6.33 (d, 1H, J = 2.5 Hz), 3.87 (s, 3H), 3.81 (s, 3H), 3.55 (q, 2H, J = 7.1 Hz), 3.42 (q, 2H, J = 7.1 Hz), 1.34 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 159.9, 153.8, 153.2, 101.2, 96.8, 73.2, 56.9, 56.0, 42.6, 42.4, 14.7, 13.6 ppm; EIMS (*m/z*(%)) 379[M^+](1), 253(22), 252(81), 137(14), 100(65), 72(100); HRMS (EI) calculated for $C_{13}H_{18}INO_4$ 379.0281: found 379.0286.

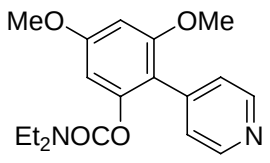
3,5-Dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl diethylcarbamate (3.28b)



A solution of freshly prepared LDA (23.8 mL, 23.8 mmol) was added via canula to a solution of **3.27** (5 g, 19.8 mmol), B(O*i*-Pr)$_3$ (11.4 mL, 49.5 mmol), and THF (40 mL) at –78 °C keeping the internal temperature < -72 °C. After the addition the mixture was stirred at –78 °C for 1 h and allowed to warm to 0 °C before acidification to < pH 5 with 1M HCl. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL), extracts

combined, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*, then heated to 80 ^oC under high vacuum for 1 h to yield 2-(Diethylcarbamoyloxy)-3,5-dimethoxyphenylboronic acid (5.7g, 97%) as a colourless powder. This boronic acid (50 mg, 0.17 mmol) and pinacol (22 mg, 0.18 mmol) were dissolved EtOAc (10 mL) and concentrating *in vacuo* affording **3.28b** (64 mg, quantitative, purity 98%, by GC peak area) as a colourless solid; mp 82-83 ^oC; IR (KBr) ν_{max} 2980, 2976, 1727, 1599, 1515, 1327, 1270, 1142, 1112, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, 1H, J = 2.1 Hz), 6.22 (d, 1H, J = 2.1 Hz), 3.44 (q, 2H, J = 7.1 Hz), 3.36 (q, 2H, J = 7.1 Hz), 3.78 (s, 3H), 3.76 (s, 3H), 1.30 (s, 12H), 1.25 (t, 3H, J = 7.1 Hz), 1.18 (t, 3H, J = 7.1Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 163.5, 158.1, 155.0, 100.5, 96.5, 83.8, 56.7, 56.0, 42.5, 42.3, 25.5, 14.8, 14.1 ppm; EIMS (*m/z*(%)) 379[M^+](1), 364(68), 321(100), 278(100), 250(27), 180(32), 151(47), 100(100), 72(96); HRMS (EI) calculated for $C_{19}H_{30}BNO_6$ [M – CH_3]$^+$ 364.1931: found 364.1936.

3,5-Dimethoxy-2-(pyridin-4-yl)phenyl diethylcarbamate (3.29)

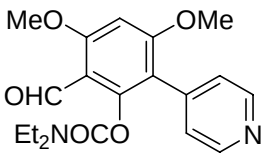


A solution of freshly prepared LDA (47.4 mL, 47.4 mmol, 1M in THF) was added *via* canula to a solution of **3.27** (10 g, 39.5 mmol), B(O*i*-Pr)$_3$ (23.7 mL, 102.7 mmol), and THF (80 mL) at -78 ^oC maintaining an internal temperature of < -72 ^oC. After the addition the mixture was stirred at -78 ^oC for 1 h and allowed to warm to 0 ^oC before acidification to < pH 5 with 1M HCl. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL), extracts combined, washed with brine (50 mL), dried (Na_2SO_4), added to a flask containing pinacol (5.14 g, 43.5 mmol), and concentrated *in vacuo* to

yield **3.28b** as a dark oil. To this flask was added 4-bromopyridine hydrochloride (7.7 g, 39.5 mmol), Na_2CO_3 (8.4 g, 80 mmol), and $[Pd(PPh_3)_4]$ (1.8 g, 1.6 mmol). The flask was then fitted with a reflux condenser, purged with Ar, added degassed DME (70 mL), degassed Na_2CO_3 (40 mL, 2M), and heated to 100 ^oC for 20 h. The mixture was allowed to cool, the residual DME was removed *in vacuo*, the resultant aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), extracts combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude product as a brown oil. Flash column chromatography (EtOAc) yielded **3.29** (13 g, 99%) as a yellow solid. This compound was also prepared in a less efficient manner from the reaction of **3.28a** (150 mg, 0.41 mmol), 4-tributylstannylpyridine (225 mg, 0.61 mmol), and $[PdCl_2(PPh_3)_2]$ (17 mg, 0.04 mmol) in degassed DMF (0.5 mL) heated to reflux for 1 h. The reaction was allowed to cool, diluted and sonicated with aq. NaF (5 mL, 0.01 M), extracted with CH_2Cl_2 (3 x 5 mL), organic extracts combined, washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated to dryness *in vacuo* to afford the crude product as a brown oil. Flash column chromatography (EtOAc) yielded **3.29** (100 mg, 73%) as a yellow solid. Recrystallization gave the product as light yellow crystals, mp 113-114 ^oC (5:1 heptane:EtOAc); IR (KBr) ν_{max} 2979, 2938, 1721, 1622, 1410, 1273, 1220, 1197, 1155, 1096, 1060, 843, 569 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, 2H, J = 5.1 Hz), 7.27 (d, 2H, J = 5.3 Hz), 6.45 (s, 1H), 6.43 (s, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.23 (q, 2H, J = 7.0 Hz), 3.13 (q, 2H J = 7.0 Hz), 1.03 (t, 3H, J = 7.0 Hz), 0.93 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 158.1, 153.8, 150.5, 149.5, 142.8, 126.2, 115.1, 100.4, 96.8, 56.2, 55.9, 42.3, 41.9, 14.1, 13.4 ppm; EIMS (*m/z*(%)) 330[M^+](40),

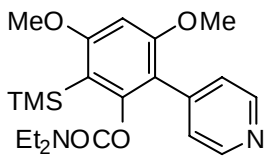
277(50), 100(100), 72(18); HRMS (EI+) calculated for $C_{18}H_{22}N_2O_4$ [M^+] 330.1580: found 330.1581.

2-Formyl-3,5-dimethoxy-2-(pyridin-4-yl)phenyl diethylcarbamate (3.19)



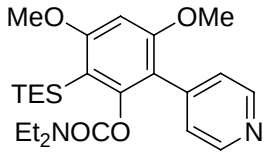
In a flame dried, argon flushed flask, a solution of **3.29** (2.0 g, 6.1 mmol) and TMEDA (1.1 mL 7.3 mmol) in THF (25 mL) was cooled to -105 ^oC and treated via syring a solution of *s*-BuLi (4.9 mL, 7.4 mmol, 1.5M in cyclohexane) maintaining an internal temperature of < -100 ^oC. The resulting yellow solution was stirred for 5 min and then added neat DMF (1.9 mL, 24.4 mmol) via syring (int temp < -98 ^oC). The mixture was stirred for 1 h (int temp < -85 ^oC) and then the whole was quenched with AcOH, warmed to rt and diluted with aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (x4), extracts combined, dried (Na_2SO_4), and concentrated in vacuo to afford the crude product as a dark oil. Flash column chromatography (EtOAc) yielded **3.19** (1.17 g, 54%) as yellow solid calculating 71% based on recovered SM. Recrystallization from EtOAc gave the product as colourless crystals; m.p. 189-190 ^oC (EtOAc); IR (KBr) ν_{max} 2973, 2859, 2772, 1715, 1685, 1604, 1399, 1267, 1217, 1153, 1101, 1081, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.63 (bs, 2H), 7.28 (bs, 2H), 6.46 (s, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 3.24 (q, 4H, J = 7.1 Hz), 1.08 (t, 3H, J = 7.1 Hz), 0.90 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.9, 164.4, 162.3, 153.0, 150.4, 148.9, 141.6, 126.0, 116.2, 112.4, 92.3, 56.2, 56.1, 42.3, 41.8, 13.6, 13.1 ppm; LRMS (EI) *(m/z(%))* 358(M^+, 2), 329(15), 258(100), 100(100), 72(35); HRMS (EI) calculated for $C_{19}H_{22}N_2O_5$ 358.1529: found 358.1545.

3,5-Dimethoxy-2-(pyridin-4-yl)-6-(triethylsilyl)phenyl diethylcarbamate (3.30a)



A solution of **2.29** (250 mg, 0.76 mmol) and Me_3SiCl (0.43 mL, 3.4 mmol in THF (25 mL) was cooled to -78 ^oC and treated via syring a solution of freshly prepared LDA (3.8 mL, 2.7 mmol, 0.7 M in THF) maintaining an internal temperature of < -72 ^oC. The resulting yellow solution was left to warm slowly to rt. and stirred for 10 h. The mixture is then treated with saturated aq. NH_4Cl (20 mL), layers separated, aqueous phase extracted with EtOAc (2 x 20 mL), dried (Na_2SO_4), and concentrated in vacuo affording a yellow solid. Flash column chromatography (EtOAc) yielded **3.30a** (290 mg, 94%) as a colourless solid. Recrystallization gave the product as colourless crystals; mp 105-106 ^oC (hexanes:EtOAc); IR (KBr) ν_{max} 2980, 1710, 1604, 1378, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (bs, 2H), 7.22 (d, 2H, J = 4.6 Hz), 6.40 (s, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 3.20-2.97 (m, 4H), 0.90 (t, 3H, J = 7.0 Hz), 0.81 (t, 3H, J = 7.1 Hz), 0.26 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 159.5, 154.8, 153.5, 149.5, 143.8, 126.6, 115.4, 112.6, 92.8, 56.1, 55.7, 41.6, 41.3, 13.7, 13.0, 1.3 ppm; EIMS (*m/z*(%)) 401[M^+](1), 387(100), 100(100), 72(58); HRMS (EI) calculated for $C_{21}H_{30}N_2O_4Si$ 402.1975: found 402.1981.

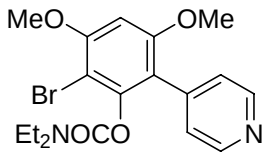
3,5-Dimethoxy-2-(pyridin-4-yl)-6-(triethylsilyl)phenyl diethylcarbamate (3.30b)



In a flame dried, argon flushed flask, a solution of **3.29** (1.98 g, 6 mmol) in THF (15 mL) was cooled to < -105 ^oC and treated via syring a solution of *n*-BuLi (2.9 mL, 7.2 mmol, 2.47M in hexanes) maintaining an internal temperature of < -104 ^oC. The resulting yellow solution was stirred for 5 min and then TESCl (2.5 mL, 15 mmol) was added via syring (int temp < -

104 °C). The mixture was stirred for 1.5 h (int temp < -101 °C), warmed to rt, diltued with saturated aq. Na_2CO_3, and rapidly stirred for 4 h. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20mL), extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* to afford a yellow oil. Flash column chromatography (EtOAc) yielded **3.29** (2.22 g, 91%) as a colourless solid which would precipitate from hexanes as an amorphous powder; mp 117-118 °C (hexanes); IR (KBr) ν_{max} 2954, 2872, 2365, 1730, 1595, 1458, 1376, 1325, 1268, 1211, 1148, 1097, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 2H), 7.24 (s, 2H), 6.40 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.11-2.99 (m, 4H), 0.95 (t, 9H, J = 7.7 Hz), 0.88-0.79 (m, 12H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 159.0, 155.2, 153.4, 149.0, 143.4, 126.3, 115.3, 110.2, 92.1, 55.7, 55.2, 40.9, 40.7, 13.4, 12.5, 7.8, 4.6 ppm; EIMS (*m/z*(%)) M^+ not found, 415[M^+-C_2H_5](100), 100(15), 72(10); HRMS (EI) calculated for $C_{24}H_{36}N_2O_4Si$ 444.2444: found 444.2443.

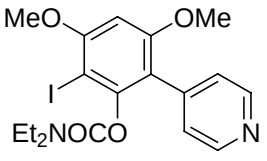
2-Bromo-3,5-dimethoxy-2-(pyridin-4-yl)phenyl Diethylcarbamate (3.21)



A solution of **3.29** (1.0 g, 3.0 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C was added Br_2 dropwise via pipette until the reaction became dark red. The mixture was warmed to rt and treated with a saturated aq. $NaHSO_4$ and basified with saturated aq. Na_2CO_3. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x1), extracts combined, dried (Na_2SO_4), and concentrated in vacuo to afford the crude title compound as a brown solid which was recrystallized from EtOAc yielding **3.21** (1.1 g, 89 %) as brown crystals; m.p. 172-174 °C (EtOAc); IR (KBr) ν_{max} 2981, 2969, 2932, 1721, 1604, 1477, 1397, 1265,

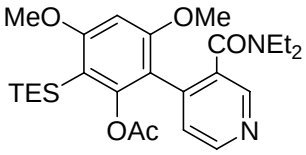
1215, 1160, 1111, 1082, 821, 620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (bs, 2H), 7.27 (bs, 2H), 6.50 (s, 1H), 3.98 (s, 3H), 3.79 (s, 3H), 3.25-3.18 (m, 4H), 1.01 (t, 6H, J = 3.5 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 156.8, 152.2, 149.2, 147.8, 142.0, 125.7, 116.8, 99.2, 94.0, 56.8, 56.1, 42.3, 41.9, 13.9, 13.1 ppm; LRMS (EI) *(m/z(%))* 408(M^+, 10), 329(60), 100(100), 72(35); HRMS (EI) calculated for $C_{18}H_{21}BrN_2O_4$ 408.0685: found 408.0673.

2-Iodo-3,5-dimethoxy-2-(pyridin-4-yl)phenyl Diethylcarbamate (3.22)



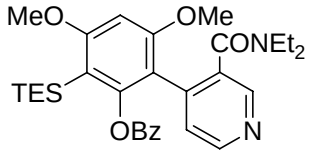
A flamed dried, argon flushed flask containing **3.29** (1.0 g, 3.0 mmol), NIS (1.0 g, 4.5 mmol), and MeCN (12 mL) was fitted with a dry condenser and refluxed for 40 h. The purple mixture was allowed to cool to rt and then placed in the freezer overnight. The precipitate was collected by vaccum filtration, washed with cold MeCN, and recrystallized from MeCN to yield **3.22** (1.3 g, 95%) as yellow crystals; m.p. 188-189 ^oC (MeCN); IR (KBr) ν_{max} 2966, 2930, 1721, 1601, 1473, 1391, 1332, 1264, 1214, 1159, 1081, 913, 820, 608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, 2H, J = 5.4 Hz), 7.26 (d, 2H, J = 5.7 Hz), 6.46 (s, 1H), 3.97 (s, 3H), 3.80 (s, 3H), 3.26 (sx, 2H, J = 6.7 Hz), 3.17 (sx, 2H, J = 6.9 Hz), 1.02 (q, 6H, J = 8.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 158.4, 152.0, 150.5, 149.2, 142.3, 125.7, 116.7, 93.3, 74.6, 56.7, 56.1, 42.3, 41.9, 14.0, 13.0 ppm; LRMS (EI) *(m/z(%))* 456(M^+, 10), 329(50), 100(100), 72(35); HRMS (EI) calculated for $C_{18}H_{21}IN_2O_4$ 456.0546: found 456.0548.

2-(3-(Diethylcarbamoyl)pyridin-4-yl)-3,5-dimethoxy-6-(triethylsilyl)phenyl acetate (3.31a)



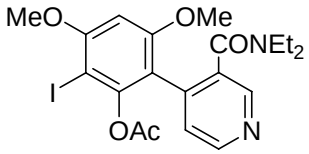
A solution of freshly prepared LDA (1.5 mL, 1.5 mmol, 1M in THF) was added via syring to a flame dried, argon flushed flask containing a solution of **3.30b** (166 mg, 0.37 mmol) in THF (3.7 mL) at 0 ^{o}C. The mixture was then warmed to rt, stirred for 1 h, re-cooled to 0 ^{o}C, quenched with Ac_2O (0.175 mL, 1.85 mmol), warmed to rt, neutralized with saturated aq. $NaHCO_3$, layers separated, aqueous phase extracted with CH_2Cl_2 (x3), extracts combined, dried (Na_2SO_4), and concentrated in vacuo to afford the crude titled compound as a dark oil. Flash column chromatography (EtOAc) yielded **3.31a** (135 mg, 75%) as tan solid. Recrystallization from hexanes gave the product as tan beads; mp 142-143 ^{o}C (hexanes); IR (KBr) ν_{max} 2948, 2878, 2365, 2339, 1763, 1630, 1604, 1471, 1433, 1370, 1319, 1211, 1116, 1085, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.60 (d, 1H, J = 4.2), 7.22 (d, 1H, J = 3.9), 6.41 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.70-2.50 (broad m, 4H), 1.88 (s, 3H), 0.92 (t, 13H, J = 7.3 Hz), 0.77 (octet, 8H, J = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5; 167.3; 166.7; 149.2; 133.7; 126.9; 112.7; 92.2; 55.2; 38.4; 20.9; 12.5; 7.7; 4.6 ppm; EIMS (*m/z*(%)) M^+ not found, 457[M^+-C_2H_5](100), 415(15), 342(20), 256(17); HRMS (EI) calculated for $C_{19}H_{22}N_2O_5$ 486.2550: found 486.2550.

2-(3-(Diethylcarbamoyl)pyridin-4-yl)-3,5-dimethoxy-6-(triethylsilyl)phenyl benzoate (3.31b)



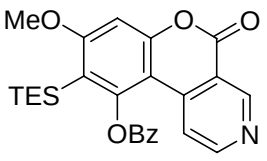
A solution of freshly prepared LDA (6.6 mL, 6.6 mmol, 1M in THF) was added via syring to a flame dried, argon flushed flask containing a solution of **3.30b** (734 mg, 1.65 mmol) in THF (33 mL) at 0 ^{o}C. The mixture was then warmed to rt, stirred for 1 h, re-cooled to 0 ^{o}C, quenched with an BzCl (1 mL, 8.25 mmol), warmed to rt and stirred for 1 h, neutralized with saturated aq. $NaHCO_3$, layers separated, aqueous phase extracted with EtOAc (2 x 20mL), extracts combined, dried (Na_2SO_4), and concentrated in vacuo to afford the crude titled compound as a dark red oil. Flash column chromatography (EtOAc) yielded **3.31b** (590 mg, 65%) as a yellow foam; mp 58-62 ^{o}C; IR (KBr) ν_{max} 2953, 2883, 1738, 1636, 1598, 1463, 1316, 1246, 1207, 1099, 709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.40 (d, 1H, J = 4.9 Hz), 8.09 (d, 1H, J = 7.6 Hz), 8.00 (bs, 1H), 7.49 (t, 1H, J = 6.9 Hz), 7.35 (t, 2H, J = 7.5 Hz), 7.19 (d, 1H, J = 4.9 Hz), 6.43 (s, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.50-2.60 (m, 4H), 0.95-0.85 (m, 15H), 0.72 (q, 3H, J = 7.9 Hz), 0.70 (q, 3H, J = 7.9 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 166.8, 165.9, 148.8, 146.8, 134.3, 133.3, 132.6, 130.1, 129.9, 129.2, 128.3, 128.2, 126.6, 112.6, 92.1, 55.5, 55.3, 42.2, 38.4, 14.1, 12.4, 7.7, 4.8 ppm; EIMS (*m/z*(%)) M^+ not found, 519[M^+-C_2H_5](100), 105(22); HRMS (EI+) calculated for $C_{31}H_{40}N_2O_5Si$ 547.2628: found 547.2626.

2-(3-(Diethylcarbamoyl)pyridin-4-yl)-6-iodo-3,5-dimethoxyphenyl acetate (3.35)



A flamed dried, argon flushed flask containing **3.31a** (173 mg, 0.36 mmol) in CH_2Cl_2 (3.5 mL) cooled to 0 ^oC was added ICl (0.62 mL, 0.72 mmol, 1.16 M in CH_2Cl_2) dropwise via syring. The mixture was warmed to rt, stirred for 30 min, treated with a saturated aq. $NaHSO_4$, basified with saturated aq. Na_2CO_3, layers separated, aqueous phase extracted with CH_2Cl_2 (x2), extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* affording the crude title compound as a dark solid. Flash column chromatography (CH_2Cl_2, 4% MeOH) yielded **3.35** (160 mg, 89%) as a yellow solid. Recrystallization gave the product as yellow crystals; m.p. 181-182 ^oC (1:1 Hexanes:EtOAc); IR (KBr) ν_{max} 2966, 2927, 1777, 1630, 1591, 1463, 1425, 1374, 1335, 1220, 1182, 1105, 869 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.60 (d, 1H, J = 4.0 Hz), 7.18 (d, 1H, J = 4.0 Hz), 6.41 (s, 1H), 3.93 (s, 3H), 3.78 (s, 3H), 3.59-3.00 (m, 4H), 2.06 (s, 3H), 1.02 (t, 3H, J = 6.0 Hz), 0.91 (t, 3H, J = 6.0 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 167.2, 160.2, 149.6, 147.4, 139.9, 133.4, 123.0, 114.0, 93.1, 56.7, 56.1, 42.6, 38.4, 21.0, 14.1, 12.2 ppm; LRMS (EI) *(m/z(%))* 498(M^+, 5), 456(50), 384(100); HRMS (EI) calculated for $C_{19}H_{22}N_2O_5$ 498.0625: found 498.0638.

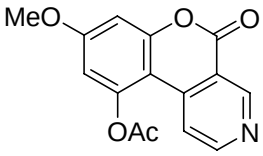
8-Methoxy-5-oxo-9-(triethylsilyl)-5*H*-chromeno[3,4-*c*]pyridine-10-yl benzoate (3.36)



A flamed dried, argon flushed flask containing **3.31b** (220 mg, 0.4 mmol) in CH_2Cl_2 (20 mL) cooled to 0 ^oC was added BCl_3 (2.4 mL, 2.4 mmol, 1 M in heptane) dropwise via syring. The mixture was stirred for 30 min, quenched with 1 M HCl and stirred vigorously for 12 h. The mixture

was then basified with saturated aq. Na_2CO_3, layers separated, aqueous phase extracted with CH_2Cl_2 (2 x 10 mL), extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* affording a yellow solid. Flash column chromatography (3:2 Hexanes:EtOAc) yielded **3.36** (150 mg, 82%) as a colourless solid which would precipitate from heptane as an amorphous powder; mp 192-193 ^oC (heptane) and crystallize during slow evapouration of EtOAc as colouress needles; m.p. 194-195 ^oC (EtOAc); IR (KBr) ν_{max} 2960, 2878, 1744, 1598, 1287, 1243, 1173, 1072, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.53 (s, 1H), 8.29 (d, 2H, J = 5.3 Hz), 8.08 (s, 1H), 7.79 (t, 1H, J = 5.5 Hz), 7.66 (s, 2H), 6.86 (s, 1H), 3.95 (s, 3H), 0.92-0.75 (m, 15H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 165.0, 159.6, 156.2, 155.3, 154.0, 152.8, 140.5, 134.5, 130.3, 129.2, 129.0, 117.8, 117.2, 115.5, 104.2, 97.8, 55.8, 29.7, 7.7, 4.9 ppm; LRMS (EI+) *(m/z(%))* M^+ not found, 432(M^+ - C_2H_5, 100), 298(5), 270(9), 105(86), 77(25); HRMS (EI+) calculated for $C_{25}H_{27}NO_5Si$ (-C_2H_5) 432.1267: found 432.1270.

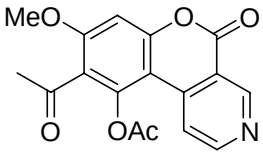
8-Methoxy-5-oxo-5*H*-chromeno[3,4-*c*]pyridine-10-yl acetate (3.32)



A flamed dried, argon flushed flask containing **3.31b** (3.9 g, 7.12 mmol) in CH_2Cl_2 (320 mL) cooled to 0 ^oC was added BCl_3 (35.6 mL, 35.6 mmol, 1 M in heptane) via syring. The mixture was stirred for 30 min, quenched with water, layers separated, aqueous phase washed with CH_2Cl_2, extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* affording a crude colourless solid. This crude material was heated to 90 ^oC in a mixture of conc. HCl (47 mL, 564 mmol) and EtOH (47 mL) for 12 h before concentration *in vacuo* gave a tan solid that was dissolved in CH_2Cl_2 (50 mL), Ac_2O (6.8 mL, 71.2 mmol), and treated

dropwise with NEt_3 (9.7 mL 71.2 mmol) at 0 ^oC. After the addition the whole was warmed to rt and stirred for 1 h, washed with water (50 mL), wasted with saturated aq. $NaHCO_3$ (2 x 50 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording the affording the crude title compound as a tan solid. Flash column chromatography (EtOAc) yielded **3.32** (1.71 g, 84%) as a colourless solid. Recrystallization gave the product as transparent needles; mp 189-190 ^oC (EtOAc); IR (KBr) ν_{max} 1762, 1629, 1585, 1195, 1148, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.89 (d, 1H, J = 5.1 Hz), 8.15 (d, 1H, J = 5.0 Hz), 6.82 (s, 1H), 6.71 (s, 1H), 3.91 (s, 3H), 2.53 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 162.3, 159.6, 154.9, 154.4, 153.1, 150.0, 140.1, 117.4, 115.3, 108.2, 103.1, 100.3, 56.1, 21.6 ppm; EIMS (*m/z*(%)) 285[M^+](15), 243(100); HRMS (EI+) calculated for $C_{15}H_{11}NO_5$ 285.0637: found 285.0633.

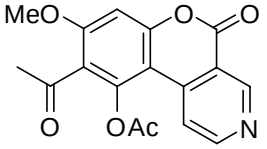
9-Acetyl-8-methoxy-5-oxo-5*H*-chromeno[3,4-*c*]pyridin-10-yl acetate (3.37a)

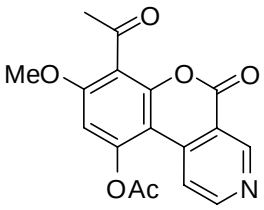


A solution of **3.38** (50 mg, 0.18 mmol), Ac_2O (1 mL) and NEt_3 (10 drops) in CH_2Cl_2 (5 mL) is heated at relflux for 12 h. The mixture is allowed to cool and carefully treated with saturated aq. $NaHCO_3$ (10 mL) and stirred rapidly for 30 min. The layers are then separated and the aqueous phase is extracted with CH_2Cl_2 (2 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording the affording the crude title compound as a colourless solid. Flash column chromatography (5:2 CH_2Cl_2:EtOAc) yielded **3.37a** as a colourless solid (50 mg, 88%) which would precipitate from EtOAc as a colourless amorphous powder; m.p. 257-259 ^oC to a red oil followed by immediate decomposition; IR (KBr) ν_{max} 3094, 1770, 1705, 1615, 1598, 1588, 1208, 1106, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.92 (d,

1H, J = 4.1 Hz), 8.14 (d, 1H, J = 5.3 Hz), 6.90 (s, 1H), 4.01 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 168.3, 159.7, 159.0, 155.3, 154.6, 153.1, 147.1, 140.0, 122.4, 117.5, 115.6, 104.0, 98.8, 56.6, 31.7, 21.4 ppm; EIMS (*m/z*(%)) 327[M^+](5), 285(100), 270(100); HRMS (EI+) calculated for $C_{17}H_{13}NO_6$ [M^+] 327.0743: found 327.0743.

9-Acetyl-8-methoxy-5-oxo-5*H*-chromeno[3,4-*c*]pyridin-10-yl acetate (3.37a) and 7-acetyl-8-methoxy-5-oxo-5*H*-chromeno[3,4-*c*]pyridin-10-yl acetate (3.37b)

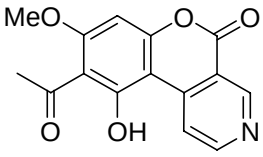




A solution of **3.32** (25 mg, 0.088 mmol) and $AlCl_3$ (80 mg, 0.76 mmol) in CH_2Cl_2 (1 mL) is stirred at 50 ^oC for 30 min. The mixture is then carefully basified with saturated aq. Na_2CO_3 and concentrated to dryness *in vacuo*. The solid residue is then stirred with Ac_2O (1 mL) and NEt_3 (5 drops) at 50 ^oC for 1 h. Saturated aq. Na_2CO_3 (10 mL) is added and the mixture is rapidly stirred for 10 min. The layers are separated and the aqueous layer is extracted with $CHCl_3$ (3 x 5 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording the crude title compounds as a yellow solid. Flash column chromatography (3:2 CH_2Cl_2:EtOAc) yielded **3.37a** (12 mg, 42%) and **3.37b** (12 mg, 42%) both as colourless solids. **3.37b:** mp 233-234 ^oC; IR (KBr) ν_{max} 2926, 1790, 1747, 1704, 1610, 1589, 1359, 1323, 1179, 1151, 1115, 1021, 878, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.84 (d, 1H, J = 5.6 Hz), 8.10 (d, 1H, J = 5.7 Hz), 6.66 (s, 1H), 3.85 (s, 3H), 2.55 (s, 3H), 2.48 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 167.8, 158.4, 158.3, 154.4, 153.0, 150.6, 150.4, 139.8, 118.4, 117.7, 115.3, 104.3,

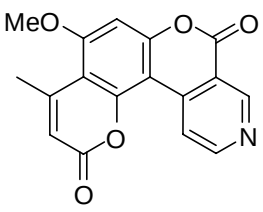
103.3, 56.5, 32.4, 21.6 ppm; EIMS (*m/z*(%)) 327[M^+](2), 285(20), 270(100); HRMS (EI+) calculated for $C_{17}H_{13}NO_6$ [M^+] 327.0743: found 327.0731.

9-Acetyl-10-hydroxy-8-methoxy-5*H*-chromeno[3,4-*c*]pyridine-5-one (3.38)



A solution of **3.32** (100 mg, 0.351 mmol) in CH_2Cl_2 (1 mL) is syringed into a rapidly stirred suspension of $AlCl_3$ (240 mg, 1.76 mmol) in CH_2Cl_2 (1 mL) at r.t., and stirred for 1 h. The mixture is then carefully basified with saturated aq. $NaHCO_3$, treated with 10% Rochelle's salt, filtured through Celite, washed with $CHCl_3$, layers separated, aqueous phase washed with $CHCl_3$ (3 x 10 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording the affording the crude title compound as a tan solid. Flash column chromatography (4:1 CH_2Cl_2:EtOAc) yielded **3.38** as a light yellow solid (40 mg, 40%) Recrystallization gave the product as light yellow crystals; decomp. 207 ^oC; (CH_2Cl_2); IR (KBr) ν_{max} 3139, 3118, 1747, 1609, 1414, 1382, 1261, 1206, 1173, 1118, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 15.91 (s, 1H), 9.53 (s, 1H), 8.90 (s, 2H), 6.45 (s, 1H), 4.04 (s, 3H), 2.77 (s, 3H) ppm; EIMS (*m/z*(%)) 285[M^+](42), 270(100); HRMS (EI+) calculated for $C_{15}H_{11}NO_5$ 285.0637: found 285.0634.

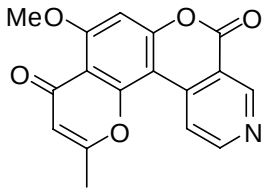
5-Methoxy-4-methyl-*2H,8H*-pyrano[2',3':5,6][1]benzopyrano[3,4-*c*]pyridine-2,8-dione (3.40)



A solution of **3.32** (10 mg, 0.035 mmol), ethyl acetoacetate (0.018 mL, 0.14 mmol), in conc. H_2SO_4 (1 mL) is heated at 60 ^oC for 15 h. The mixture is allowed to cool, pored over crushed ice (10 mL),

extracted with $CHCl_3$ (3 x 5 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording a colourless solid. Flash column chromatography (4:1 CH_2Cl_2:EtOAc to 16:4:1 CH_2Cl_2:EtOAc:MeOH) yielded **3.40** (7 mg, 65%) as a tan solid; sublimates 270+ ^oC; m.p. 293-295 ^oC; IR (KBr) ν_{max} 2926, 1740, 1625, 1599, 1589, 1467, 1345, 1201, 1093, 899 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 9.06 (d, 1H, J = 5.9 Hz), 8.91 (d, 1H, J = 5.9 Hz), 6.74 (s, 1H), 6.17 (d, 1H, J = 1.2 Hz), 3.97 (s, 3H), 2.59 (d, 3H, J = 1.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 159.5, 159.0, 156.3, 155.5, 155.1, 154.8, 152.7, 140.0, 120.0 (d, 1C, J = 16.1 Hz), 115.4, 113.9, 108.4, 99.4, 96.7, 56.9, 25.3 ppm; EIMS (*m/z*(%)) 309[M^+](45), 281(100), 266(25); HRMS (EI+) calculated for $C_{17}H_{11}NO_5$ [M^+] 309.0637: found 309.0641.

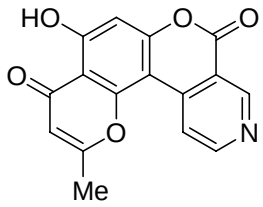
8-Methoxy schumanniophytine (3.33)



A solution of **3.32** (50 mg, 0.18 mmol), saturated aq. $NaHCO_3$ (2 mL, ~1.8 mmol), water (1 mL) and MeOH (3 mL) was stirred at r.t. for 4 h, cooled to 0 ^oC, neutralized with conc. HCl, and then concentrated to dryness in vacuo. To this crude phenol was added 2-butynoic acid (30 mg, 0.36 mmol) and the flask was purged with argon before treatment with Eaton's reagent (1 mL, 1:10 MsOH:P_2O_5). The reaction was stirred at 80 ^oC for 12 h, cooled to 0 ^oC, carefully basified with saturated aq. $NaHCO_3$, extracted with $CHCl_3$ (3 x 5 mL), organic phase washed with 2M NaOH, dried (Na_2SO_4), and concentrated *in vacuo* affording the crude titled compound as a light brown solid. Flash column chromatography deactivated with 1% Et_3N (CH_2Cl_2, 3-6% MeOH) yielded **3.33** (28 mg, 52%) as a colourless solid; Recrystallization from CH_2Cl_2 gave the product as a

colourless amorphous solid; mp 288-289 ^{o}C (decomp); IR (KBr) ν_{max} 2926, 2847, 1740, 1668, 1589, 1338, 1107, 861 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.92 (d, 1H, J = 5.1 Hz), 8.56 (d, 1H, J = 5.4 Hz), 6.77 (s, 1H), 6.20 (s, 1H), 4.01 (s, 3H), 2.49 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 162.9, 159.0, 157.6, 156.9, 155.0, 153.0, 139.6, 118.5, 115.0, 113.4, 112.1, 98.9, 96.9, 57.1, 19.8 ppm; EIMS (*m/z*(%)) 309[M^+](100), 280(45), 263(25), 239(8); HRMS (EI+) calculated for $C_{17}H_{11}NO_5$ [M^+] 309.0637: found 309.0637.

Schumanniophytine (3.1)



A solution of **3.33** (20 mg, 0.065 mmol) in CH_2Cl_2 (2 mL) at 0 ^{o}C was added BCl_3 (0.26 mL, 0.26 mmol, 1 M in heptane) via syring. The mixture was stirred for 30 min, quenched with water (5 mL), layers separated, aqueous phase washed with $CHCl_3$ (3 x 5 mL), organic extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* yielding analytically pure schumanniophytine **3.1** (18.4 mg, 96%) as a yellow solid. Recrystallization gave the product as light yellow crystals; mp 295-298 ^{o}C (decomp) ($CHCl_3$), (lit.[247] mp 293-296 ^{o}C); IR (KBr) ν_{max} 2922, 1749, 1663, 1589, 1415, 1172, 1056, 871 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.47 (s, 1H), 9.58 (s, 1H), 8.97 (d, 1H, J = 5.7 Hz), 8.48 (d, 1H, J = 5.7 Hz), 6.81 (s, 1H), 6.34 (s, 1H), 2.65 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.6, 175.7, 167.3, 164.6, 159.5, 158.4, 156.0, 155.2, 153.4 (d, 1C, J = 7.3 Hz), 139.8, 118.4 (d, 1C, J = 19.7 Hz), 115.1, 110.9, 108.6, 101.6, 97.8, 21.0 ppm; EIMS (*m/z*(%)) 295[M^+](31), 255(1), 149(100); HRMS (EI+) calculated for $C_{16}H_9NO_5$ [M^+] 295.0481: found 295.0486.

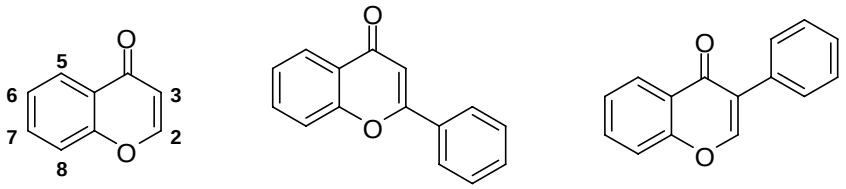
Chapter 4

Sequential Carbanion-mediated Synthetic Aromatic Chemistry. Carbamoyl Translocations via Anionic *ortho*-Fries and Cumulenolate *α*-Acylation Paths. Regioselective Synthesis of Polysubstituted Chromone 3- and 8-Carboxamides

4.1. Prelude

4.1.1. Chromones

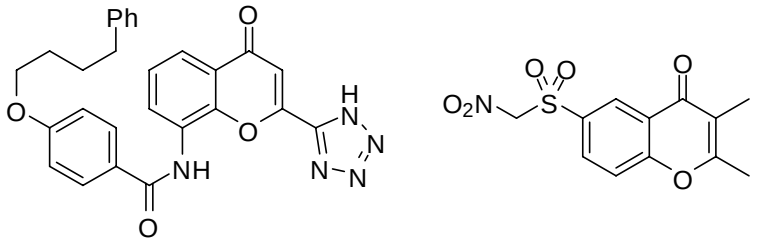
The 4*H*-1-Benzopyran-4-one nucleus **4.1** (trivially known as chromone or chromen-4-one) represents one of the most abundant subclasses of a diverse collection of benzannulated pyranones that are widely distributed throughout the plant kingdom, constituting many secondary metabolites. Numerous comprehensive reviews have appeared pertaining to structure, reactivity, and synthesis of these compounds including chromones.[296-298] The importance of the chromone nucleus is evidenced by the continued appearance of new and improve methods for their synthesis as well as their abundant commercial availability (over 1600 compounds). The majority of natural chromone derivatives are the 2- and 3-arylated derivatives known as flavones **4.2** and isoflavones



4.1 **4.2** **4.3**

Figure 4.1. 4*H*-1-Benzopyran-4-one and Derivatives

4.3 that have been popularized by their significant pharmacological (e.g. antioxidants) and biocidal activities.[299] Other non-flavanoidal chromone derivatives have been the subject of several interesting reviews summarizing their chemistry, biology, and occurence in nature.[300-303] Numerous compounds of this class have been developed for a broad range of therapeutic applications (e.g. **4.4**: anti-asthmatic[304]) and found in the patent literature (e.g. **4.5**: aldose reductase inhibitor[305]).



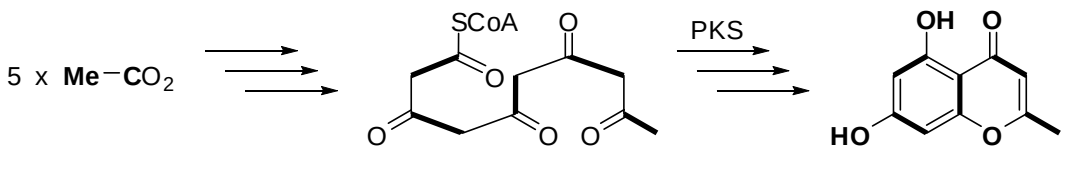
4.4 (Pranlukast) **4.5**

Figure 4.2. Therapeutic Chromones

4.1.2. 2-Methylchromone Biosynthesis

The 2-methylchromone nucleus arises biosynthetically *via* a unique folding and cyclization pathway of a polyketide precusor catalyzed by a superfamily of polyketide synthases (PKSs).[306] The acetate origin of these compounds has been confirmed by high

Scheme 4.1. Biosynthesis of Noreugenin 4.6



4.6

levels of radioactive 1-^{14}C acetate incorporation during feeding experiments.[307] Evidence for pentaketide chain folding pathway arises from doubly ^{13}C-labelled acetate incorporation as demonstrated for the biosynthesis of noreugenin **4.6** (Scheme 4.1).[308]

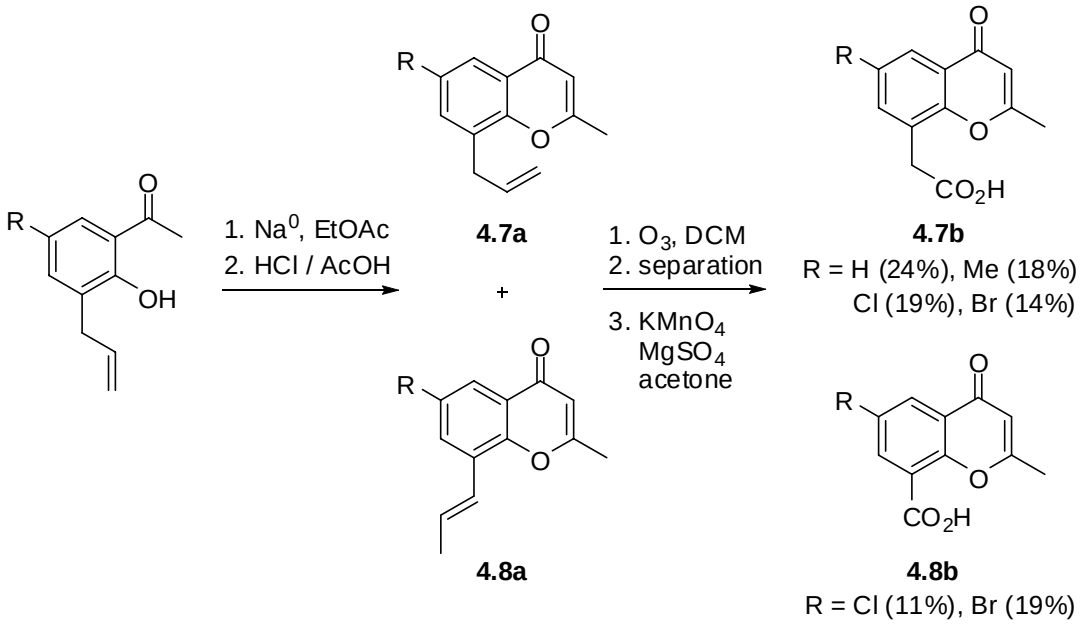
4.1.3. Synthesis of 3- and 8-Carboxamide 2-Methylchromones

The 3-carbon substituted 2-methylchromones are readily prepared by a range of procedures, most commonly by higher yielding condensation reactions of 2-hydroxyaryl ketone derivatives with acetyl synthons.[296-298] Similarly, 3-carboxamide 2-methylchromone derivatives can be prepared by condensation of benzoyl chlorides with acetoacetanilides.[309] Alternative routes are few but include reductive ring opening of 3-alkoxyisoxazoles[310] and amidation of 3-carboxylic acid chromone derivatives.[311] Surprisingly, there are no reports of the hydration reaction of commercial 3-cyano 2-methylchromone whereas 3-cyanochromone has been easily hydrated under H_2SO_4 conditions in 65% yield.[312]

Simple 2-methylchromones can be prepared by an even larger selection of heteroannulation reactions due to the simplicity of the 2-methylchromone nucleus. However, there are fewer reports with derivatives containing 8-carbon substituted derivatives and no reported 8-carboxamide substitution. Preparation of the 1,2,3-arene substituent pattern required for condensation-type reactions is very difficult by classical techniques. Harsher electrophilic and acid catalyzed benzopyran-4-one heteroannulations are the popular choice for these derivatives but most of these conditions are poor yielding especially when deactivating 3-carbonyl or bulky 3-carbon substituents are present.[294,313,314] A recent communication has described the preparation of substituted 2-

methylchromone-8-acetic acids **4.7b** and 2-methylchromone-8-carboxylic acids **4.8b** (Scheme 4.2).[315] These 8-substituted chromones were prepared due to interest stimulated by their pharmalogical uses as coronary and urinary tract vasodilators,[316] and anticancer agents.[317] The reported chromones were prepared over 4 steps from non-commercial precursors in overall poor yields (11-24%). Preparation of 8-acetic acid derivatives **4.7b** (R = Cl and Br), were complicated by isomerization of the allylic moiety during the intial Claisen condensation, which fortunately, permitted the synthesis of the 8-carboxylic acid derivatives **4.8b** after chromatographic separation of the ozonized products of **4.7a-8a**.

Scheme 4.2. Synthesis of 2-Methylchromone 8-Acetic and Carboxylic Acids 4.7b-8b



Using a newly discovered reaction for the preparation of chromone carboxamides, discovered during model studies for the synthesis of schumanniophytine (Chapter 3), we now report on an efficient synthesis of similar diethylamide derivatives of **4.7b-8b**, which may have interesting implications for biological studies (e.g. lysergic acid → LSD[318]).

4.2. Manuscript 3:

Sequential Carbanion-mediated Synthetic Aromatic Chemistry. Carbamoyl Translocations via Anionic *ortho*-Fries and Cumulenolate *α*-Acylation Paths. Regioselective Synthesis of Polysubstituted Chromone 3- and 8-Carboxamides

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Department of Chemistry, Queen's University, Kingston, ON, K7L 3N6, Canada

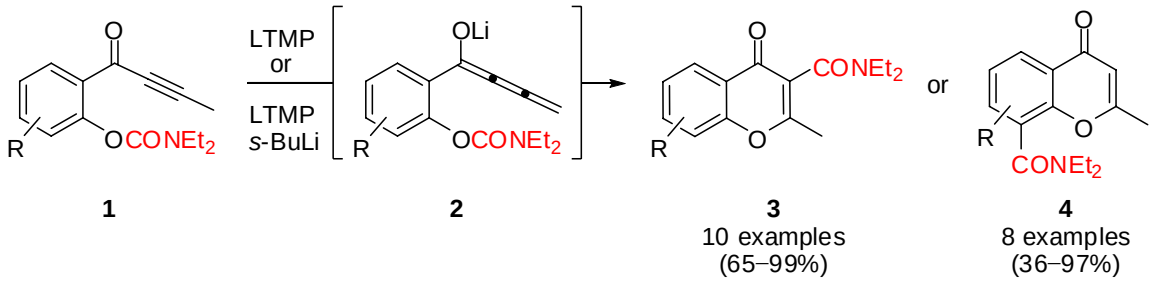
4.2.1. Preface

With minor editorial and formatting changes, this manuscript appears substantially as it has been accepted to *Angewandte Chemie, International Edition*. Todd Macklin was responsible for all synthesis, distillation, chromatography, crystallization, and data collection (NMR, LRMS, IR, mp) with the assistance of Ms. Jane Panteleev. HRMS was collected by Ms. Jie Sui. The manuscript was written by Todd Macklin and Victor Snieckus.

4.2.2. Abstract

A general synthesis of chromone 3- and 8-carboxamides, **3** and **4,** from the easily accessible 2-but-2-ynoyl aryl *O*-carbamates **1** is reported. The divergent product formation is a function of the strong base used and the reaction proceeds by carbamoyl translocation and anionic Fries rearrangement followed by Michael addition of the initially generated cumulenolate **2** for which evidence is provided. Additional repetitive metalation reactions, as well as an Ir-catalyzed B_2pin_2 borylation, which allow the regioselective construction of polysubstituted chromones, are described.

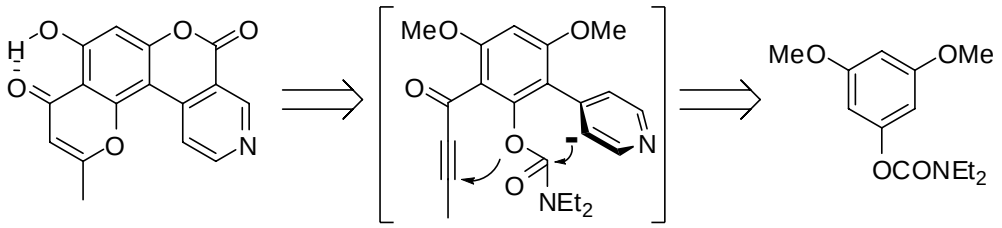
Scheme 4.3. Manuscript 3 Graphical Abstract



4.2.3. Introduction

In an initial planned foray towards the total synthesis of schumanniophytine **3.1**,[319] we envisaged (Scheme 4.4) a concise route incorporating a double intramolecular reaction sequence of remote anionic Fries rearrangement[260] and Michael addition (**4.9**). While this concept was not placed to the test due to failure to prepare the requisite

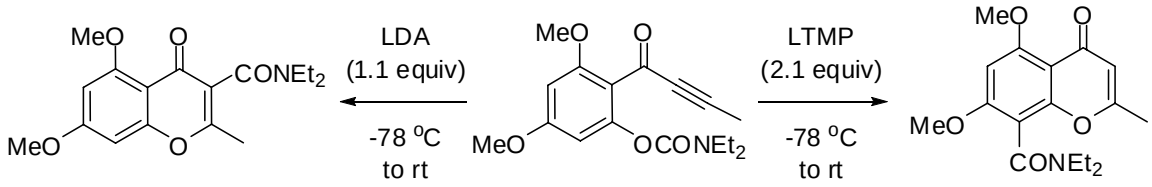
Scheme 4.4. Proposed Retrosynthesis of Schumanniophytine 3.1



3.1 **4.9** **3.27**

precursor to **4.9**,[320] model studies on the conveniently synthesized 2-but-2-ynoyl aryl *O*-carbamate **4.10i** (Scheme 4.5) led to the discovery of two new anionic aryl *O*-carbamoyl rearrangements to isomeric chromones **4.11i** and **4.12i** which proceed in essentially

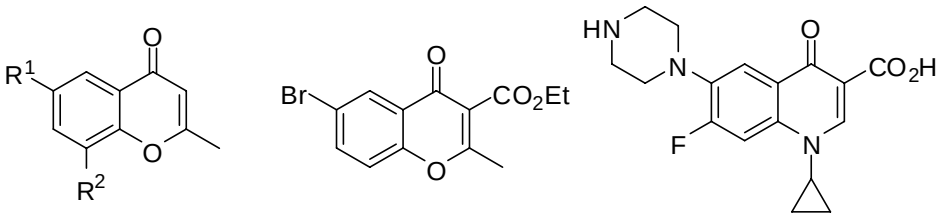
Scheme 4.5. Synthesis of Chromone 3- and 8-Carboxamides 4.11i and 4.12j



4.11i (99%) **4.10i** **4.12i** (97%)

quantitative yield under typical LTMP and LDA mediated conditions, respectively. Partial verification of the original concept (**4.9**) aside, recognition of the chromone

heterocycle representing of major classes of natural products,[299] and a key component of a plethora of bioactive molecules, commercial drugs and agrochemicals,[321] gave impetus for pursuit to generalize and extend these initial results.[322] Herein we report the preliminary results of our synthetic and mechanistic findings which demonstrate a) the ability to prepare 8- and 3-carbon substituted chromones (Table 4.1), systems represented by bioactive substances **4.13**[315] and **4.14**[323] (Figure 4.3) which are difficult to access and related to the important class of antibacterial 4-quinolone drugs **4.15**[324] for which there is a classical interconversion,[325] respectively, b) repetitive metalation chemistry which allows the construction of polysubstituted chromones (Schemes 4.6 and 4.7), and c) the intriguing and unprecedented involvement of a cumulenolate intermediate **4.9**[326] in the anionic carbamoyl transposition reactions. Taken together, this work contributes to the increasing impact of carbanionic-mediated strategies in synthetic aromatic chemistry.



4.13
R^1 = H, Me, Cl, Br
R^2 = CO_2H, CH_2CO_2H

4.14

4.15 Ciprofloxacin

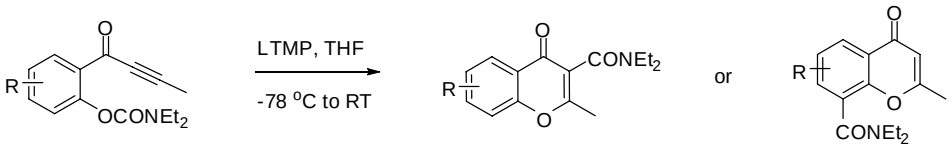
Figure 4.3. Bioactive 8- and 3-Carbon Substituted Chromones and Ciprofloxacin

4.2.4. Results and Discussion

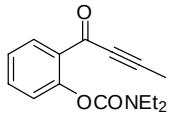
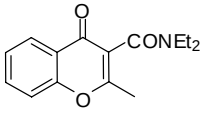
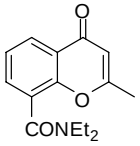
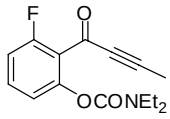
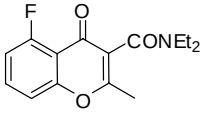
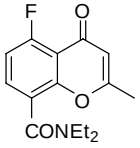
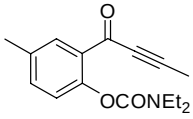
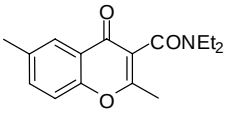
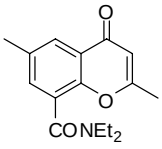
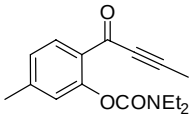
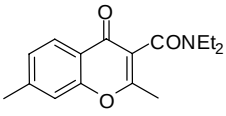
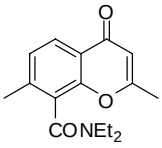
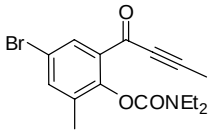
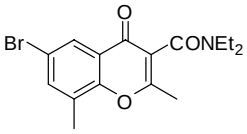
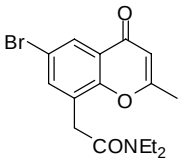
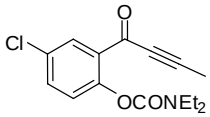
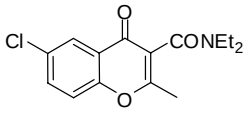
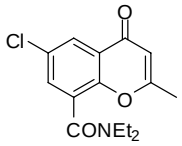
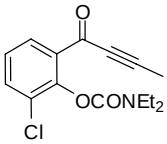
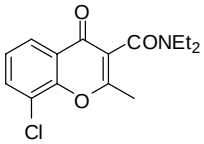
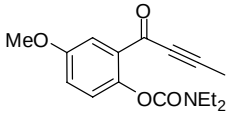
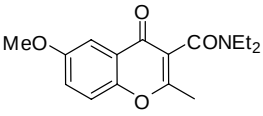
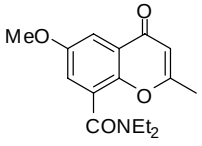
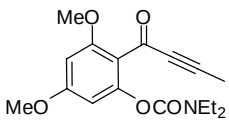
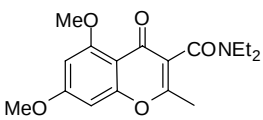
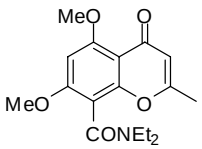
Following the schumanniophytine alkaloid model compound **4.10i** study (Scheme 4.5), a series of 2-but-2-ynoyl aryl *O*-carbamates **4.10a-k** were prepared[327] and subjected

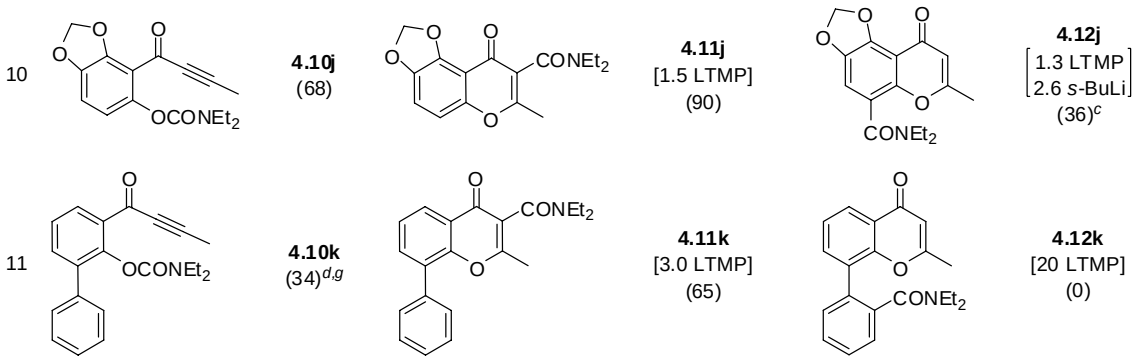
to the strong base-mediated conditions. The results, summarized in Table 4.1, merit selected comment. Complications of 1,2-addition of LDA to unhindered ynones, led to the choice of the more hindered LTMP as the base for conversion of the remaining derivatives **4.10a-h,j,k**. Conversions of unsubstituted and methyl substituted *O*-carbamates **4.10a, 4.10c,** and **4.10d** (entries 1, 3 and 4) as well as the methylenedioxy derivative **4.10j** (entry 10) proceed smoothly to chromones **4.11a, 4.11c, 4.11d** and **4.11j** respectively under LTMP conditions**.** However, their corresponding transformations into chromones **4.12a, 4.12c, 4.12d,** and **4.12j** require a sequential LTMP – *s*-BuLi procedure, the stronger base second step being essential to achieve kinetic *ortho*-carbamoyl deprotonation for *ortho*-Fries migration.[328] The 3-fluoro compound **4.10b** fails to afford either chromone presumably due to complications arising as a result of benzyne formation.[329] On the other hand, the lack of such presumed difficulties in the case of the bromo substituted **4.10e** (entry 5) is noteworthy[330]: not only is the 3-carbamoyl chromone **4.11e** obtained efficiently but a precedented lateral metalation-carbamoyl migration[331] leads to the acetamide chromone **4.12e** in high yield. The chloro *O*-carbamates **4.10f** and **4.10g** (entries 6 and 7), expected to cause less concern with respect to benzyne formation, smoothly undergo the isomeric carbamoyl transfer – Michael cyclization reactions to afford the expected products **4.11f**, **4.12f**, and **4.11g**, respectively. Methoxy aryl *O*-carbamate **4.10h** (entry 8) required increased concentrations of LTMP (5 equiv) to favor formation of **4.12h**, presumably owing to coordination and competitive D*o*M due to the OMe group.[332] The original test substrate **4.10i** (entry 9) benefits from synergistic in-between D*o*M[7,22] to give products **4.11i** and **4.12i** in the best overall yields of this general route. The biaryl *O*-carbamate **4.10k**

Table 4.1. Synthesis of Chromone 3- and 8-Carboxamides 4.11a-k and 4.12a-j.



4.10a-k **4.11a-k** **4.12a-k**

entry	4.10	4.10, yld(%)[a]	4.11	4.11, [equiv], yld(%)[b]	4.12	4.12, [equiv], yld(%)[b]
1		**4.10a** (61)		**4.11a** [1.5 LTMP] (81)		**4.12a** [1.2 LTMP 2.3 *s*-BuLi] (54)[c]
2		**4.10b** (48)[d]		**4.11b** [1.1 LTMP] (0)		**4.12b** [2.1 LTMP] (0)
3		**4.10c** (74)		**4.11c** [2.2 LTMP] (93)		**4.12c** [1.1 LTMP 2.5 *s*-BuLi] (44)[c]
4		**4.10d** (72)		**4.11d** [2.2 LTMP] (85)		**4.12d** [1.1 LTMP 2.5 *s*-BuLi] (46)[c]
5		**4.10e** (49)[e]		**4.11e** [1.5LTMP] (92)		**4.12e** [3.0 LTMP] (84)
6		**4.10f** (71)		**4.11f** [1.1 LTMP] (86)		**4.12f** [2.1 LTMP] (93)
7		**4.10g** (74)		**4.11g** [1.5 LTMP] (79)[f]		
8		**4.10h** (77)		**4.11h** [1.5 LTMP] (90)		**4.12h** [5.0 LTMP] (86)
9		**4.10i** (63)		**4.11i** [1.1 LDA] (99)		**4.12i** [2.2 LTMP] (97)

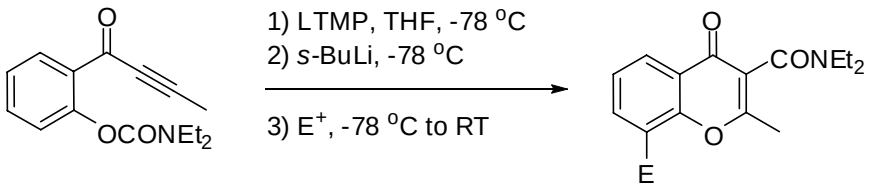


[a] Conditions: i) *s*-BuLi (1.2 equiv), -78 °C, 30 min; ii) $MgBr_2 \cdot OEt_2$ (2.5 equiv), -78 °C to 0 °C; iii) *N*-methoxy-*N*-methylbut-2-ynamide (1.2 equiv), 0 °C to rt, 12 h. [b] Conditions: LTMP, -78 °C to rt, 2-12 h. [c] Conditions: i) LTMP, -78 °C, 10 min; ii) *s*-BuLi, -78 °C to rt. [d] Conditions: i) *s*-BuLi (1.2 equiv) -78 °C, 30 min; ii) CuCN · 2LiCl (2 equiv), -78 °C, 30 min; iii) 2-butynoyl chloride (2 equiv), -78 °C to rt, 1 h. [e] Prepared by metal-halogen exchange from the corresponding aryl bromide **4.9**: i) *t*-BuLi (2.1 equiv), -78 °C, 10 min; ii) $MgBr_2 \cdot OEt_2$ (2.5 equiv), -78 °C to 0 °C; iii) *N*-methoxy-*N*-methylbut-2-ynamide (1.2 equiv), 0 °C to rt, 12 h. [f] LTMP, -78 °C to 50 °C, 1 h. [g] Performed at -100 °C.

(entry 11) furnishes the 8-aryl chromone **4.11k,** structurally related to several naturally occurring[333] and synthetic[334] antitumor agents. Structural differences notwithstanding, the unsuccessful conversion **4.10k → 4.12k** is a harbinger of difficulties for the achievement of the untested original concept **4.9** as a key step in the synthesis of schumanniophytine.[319]

The evidence that C-8 carbanion formation may be achieved under *s*-BuLi conditions (entries 1,3,4, and 10) suggested trapping experiments with other electrophiles at low temperatures. Thus, using sequential LTMP–*s*-BuLi treatment of unsubstituted 2-

Scheme 4.6. One-Pot DoM − Chromone-3-Carboxamide Synthesis.



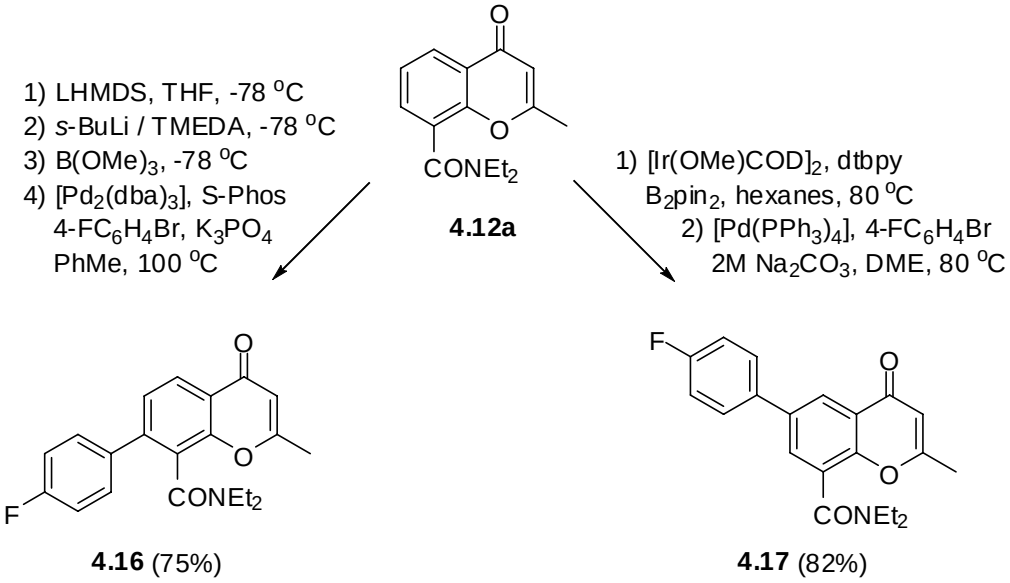
4.10a

4.11l, E = TMS (42%)
4.11m, E = SMe (44%)

but-2-ynoyl phenyl *O*-carbamate **4.10a** (Scheme 4.6) followed by TMSCl and MeSSMe treatment led to the 8-silyl and 8-thiomethyl chromones **4.11l** and **4.11m**, respectively in modest overall yields.

Unsurprisingly, the availability of 8-carbamoyl chromones **4.12** invited additional DoM chemistry. Thus, treatment of **4.12a** (Scheme 4.7) with LHMDS to effect, of necessity, protective dienolate formation[335] followed by D*o*M and treatment with $B(OMe)_3$ afforded the 7-borylated chromone which was immediately subjected to modern

Scheme 4.7. Differential Borylation and Arylation of Chromone 4.12a.

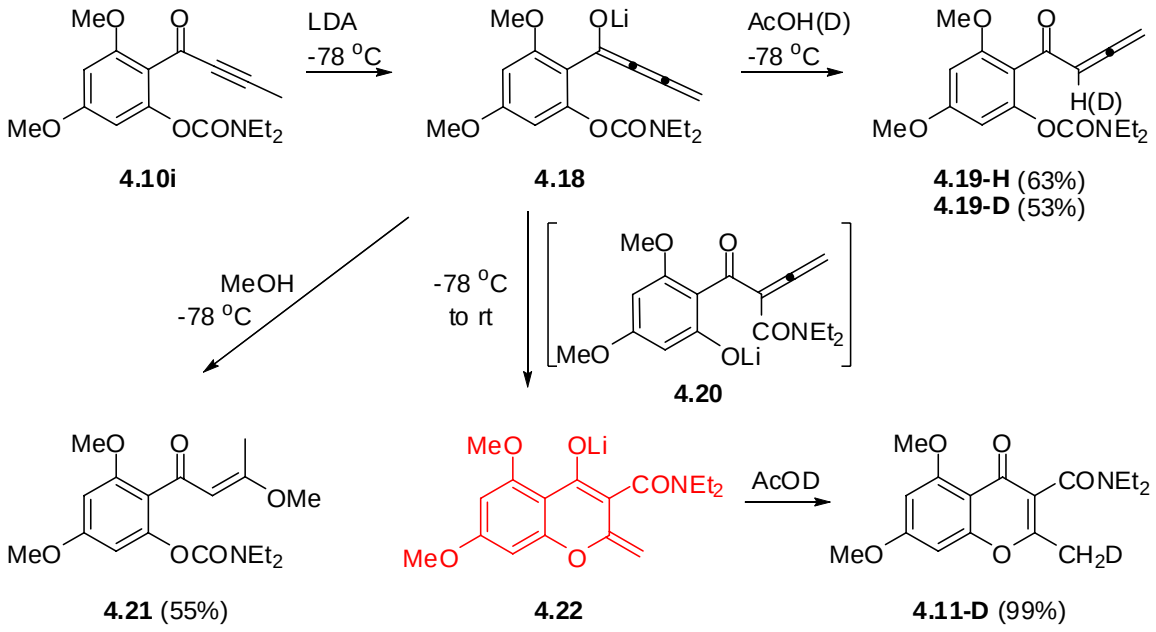


Suzuki cross coupling conditions[336] to furnish the 7-(4-fluorophenyl) chromone **4.16** in respectable yield. To provide regiochemical complementarity, advantage was taken of the substituent effects of the recent C-H activation-borylation route using B_2pin_2 under iridium catalysis.[9] Thus, subjection of **4.12a** to the reported conditions for a one-pot

borylation – Suzuki cross coupling[337] afforded the isomeric 6-(4-fluorophenyl) chromone **4.17** in very good yield.

A mechanistic study of the LDA-mediated reaction was undertaken on the high-yield **4.10i** to **4.11i** conversion (Scheme 4.8). First, treatment of **4.10i** with LDA (1.1 equiv) at -78 °C for 1 h and subsequent trapping with AcOH and AcOD at -78 °C gave the 1,2-dienones (α-allenyl ketones) **4.19-H** and **4.19-D** (21% d_1-incorporation by ^{1}HMR) respectively in reasonable yields. This confirms the generation of the kinetic cumulenolate (1,2,3-trien-1-olate) intermediate **4.18** and its α-carbonyl protonation in agreement with previous experimental and semiempirical calculational (MNDO) evidence.[338] Treatment with LDA (1.1 equiv, -78 °C, 20 min) followed by quenching with MeOH at -78 °C gave (2*E*)-aryl-3-methoxy-but-2-en-1-one **4.21** (confirmed by

Scheme 4.8. Deuteration and Reactions of Lithium Cumulenolate 4.18.



NOE), the expected thermodynamically stable diastereomer resulting from α-carbonyl protonation and intermolecular 1,4-addition of the generated methoxide.[339,340] Allowing the cumulenolate **4.18** to warm to room temperature to promote carbamoyl transfer resulted in the appearance of a deep red solution indicative of the formation of the 3-carboxamidyl-2-methyl-4*H*-1-benzopyran-4-one lithium dienolate **4.22**, confirmed by the rapid disappearance of color to a clear solution upon treatment with AcOD to obtain **4.11i-D** in high yield (>95% d_1, ^{1}HMR), thus suggesting the pathway occurring via a buta-2,3-dienamide **4.20** followed by intramolecular Michael addition of the resulting phenolate to give the chromone product.[341]

4.2.5 Conclusion

In conclusion, new general and regioselective syntheses of chromone derivatives **4.11** and **4.12** via anionic carbamoyl translocation reactions have been developed. The reactions, involving sequential intramolecular anionic *ortho*-Fries rearrangement and Michael addition and proceeding, as suggested by mechanistic studies (Scheme 4.6), *via* an intriguing cumulenolate **4.18** provide routes to chromones which show uncommon and difficult to access C-8 carbon substitution[315] and common but biologically significant[323,324] 3-substitution patterns. The additional D*o*M chemistry (Scheme 4.4) as well as the complementary *ortho*- and Ir-catalyzed *meta*-borylation and Suzuki cross coupling chemistry (Scheme 4.5) provide added conceptual and practical value for heterocyclic synthesis. As a proposed tenet, in juxtaposition with Brönsted or Lewis acid – mediated electrophilic substitution, the present and related aromatic carbanionic chemistry[7,22] has advantages in provision of rich and varied substituent introduction, mild

conditions, and, especially, regiochemical control. Of potential more general significance, the observation of the cumulenolate **4.18**, representing a rarely studied species,[338] provides impetus for increased attention in synthesis of cumulenes and allenes[326] especially in view of recent developments in transition metal catalyzed reactions.[326]

4.2.6. Acknowledgement

We acknowledge with gratitude NSERC Canada for support via the Discovery Grant program. We warmly thank Merck Frosst Canada for unrestricted grant support.

4.3 Experimental

4.3.1 General Methods

Melting points are uncorrected. Infrared spectra were recorded as neat or KBr discs using a BOMEM MB-100 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 400 MHz spectrometer. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sx, sextet; dd, doublet of doublet; td, triplet of doublet; m, multiplet; bs, broad singlet. GC-MS analyses were performed with an *Agilent 6890N* GC coupled with an *Agilent 5973 inert* MS under EI conditions. THF was freshly distilled from sodium benzophenone ketyl under argon and *N,N*-diethylcarbamoyl chloride was distilled from CaH_2 and stored over 4 Å molecular sieves prior to use. *n*-, *s*-, and *t*-butyllithium were purchased from Aldrich as solutions in hexanes, cyclohexane, and pentane, stored in a resealable container, and titrated periodically against *N*-benzylbenzamide. LDA and LTMP were freshly prepared before reactions by stirring a 1:1 mixture of di*iso*propylamine or tetramethylpiperidine and *n*-BuLi at 0 ^{o}C in THF (1 M) for 10 min. *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was stored over solid KOH prior to use. All reactions involving alkyllithiums were carried out in oven or flame-dried glassware cooled under argon using syring-septum cap techniques. The -105, -78, and 0 ^{o}C temperatures designated are approximate as achieved by a liquid nitrogen-ethanol, dry ice-acetone, and ice-salt bath, respectively. When internal temperature readings were essential, a Barnant Dual J stainless steel-sheathed thermocouple thermometer was employed. $[Pd(PPh_3)_4]$ was purchased from Aldrich, $[Ir(OMe)COD]_2$ was prepared in two steps from $IrCl_3$ using literature procedures,[342,343] and solutions were pre-degassed

using sonication associated with argon bubbling. Reaction monitoring was done by TLC and GC where appropriate. Flash column chromatography was carried out using Merck silica gel 60 (particle size: 32-63).

A. Synthesis of 2-but-2-ynoyl aryl carbamates 4.10a-k

In a flame dried, argon flushed flask, a solution of phenyl carbamate (1 mmol) in THF (5 mL) was cooled to -78 ^{o}C and treated *via* syringe a solution of *s*-BuLi (1.2 mmol) maintaining an internal temperature of < -72 ^{o}C. The resulting yellow solution was stirred for 30 min then $MgBr_2 \cdot OEt_2$ (2.5 mmol) prepared by reacting a slight excess of magnesium turnings with 1,2-dibromoethane in anhydrous diethyl ether[344] was added and the whole was warmed to 0 ^{o}C. Weinreb amide *N*-methoxy-*N*-methyl-but-2-ynamide (1.3 mmol, 2M in THF) was added via syringe, and the mixture was allowed to warm and stir at rt for 12 h before being re-cooled to 0 ^{o}C and acidified with 0.5M HCl (5 mL). The resultant mixture was extracted with EtOAc (2 x 5 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording an oil that was subjected to flash column chromatography (hexanes:EtOAc) to yield the pure product. A modification of this procedure uses $CuCN \cdot 2LiCl$ (2 mmol) in place of $MgBr_2 \cdot OEt_2$ and after stirring for 30 min at -78 ^{o}C, 2-butynoyl chloride is added and the mixture is warmed to rt and stirred for 1 h.

B. Synthesis of Chromone-3- and -8-carboxamides 4.11a-m and 4.12a-k

In a flame dried, argon flushed flask, a solution of 2-but-2-ynoyl aryl carbamate **4.10a-k** (0.1 mmol) in THF (1 mL) was cooled to -78 ^{o}C and treated *via* syring a freshly

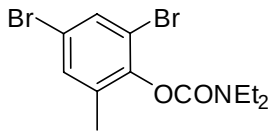
prepared aliquot of LTMP (0.11 to 0.5 mmol, 1M prepared by the addition of *n*-BuLi to a 5% excess of HTMP in THF at 0 ^{o}C and stirring for 10 min, maintaining an internal temperature of < -65 ^{o}C. The cooling bath was removed and the yellow solution was then allowed to warm to rt (50 ^{o}C for **4.10g**) and stirred for 2 h (or longer where indicated) before treatment with saturated aq. NH_4Cl (1 mL). The resultant mixture was extracted with EtOAc (2 x 5 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording an oil that was subjected to column chromatography (CH_2Cl_2:MeOH or EtOAc:CH_2Cl_2) to yield the pure product.

C. Synthesis of 8-Substituted Chromone-3-carboxamides 4.11l,m

In a flame dried, argon flushed flask, a solution of 2-but-2-ynoyl phenylcarbamate **4.10a** (0.1 mmol) in THF (1 mL) was cooled to -78 ^{o}C and treated *via* syring a freshly prepared aliquot of LTMP (0.13 mmol, 1M in THF) maintaining an internal temperature of < -65 ^{o}C. The resultant yellow solution was stirred for 10 min before treatment with *s*-BuLi (0.25 mmol) and stirred at -78 ^{o}C for 30 min. To this mixture was then added an electrophile (0.22 mmol), the cooling bath removed, and the solution was then allowed to warm to rt and stirred for 2 h before treatment with saturated aq. NH_4Cl (1 mL). The resultant mixture was extracted with EtOAc (2 x 5 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording an oil that was subjected to column chromatography (CH_2Cl_2:MeOH or EtOAc:CH_2Cl_2) to yield the pure product.

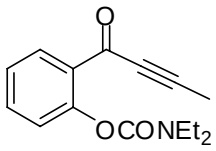
4.4.2 Experimental Procedures and Data

2,4-Dibromo-6-methylphenyl diethylcarbamate (4.9)



A solution of 2,4-dibromo-6-methylphenol[345] (2 g, 7.5 mmol) in MeCN (20 mL), was added K_2CO_3 (3.1 g, 22.5 mmol), $ClCONEt_2$ (1.43 mL, 11.3 mol) and the whole was heated to 90 ^oC for 18 h. The mixture was then diluted with water (50 mL) and extracted with Et_2O (3 x 20 mL). The combined extracts were then washed with 2M NaOH (20 mL), water (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo* afforded a brown oil. Column chromatography (9:1 hexanes:EtOAc) yielded the titled compound (1.1 g, 40%) as a yellow oil; IR (neat) ν_{max} 3076, 2976, 2933, 2874, 1730, 1589, 1566, 1470, 1420, 1382, 1277, 1251, 1213, 1152, 1102, 1041, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 1H, J = 2.1 Hz), 7.31 (d, 1H, J = 1.6 Hz), 3.51 (q, 2H, J = 6.2 Hz), 3.41 (q, 2H, J = 7.1 Hz), 2.23 (s, 3H), 1.33 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 146.9, 135.2, 132.8, 132.7, 118.5, 118.2, 42.5, 42.2, 16.9, 14.4, 13.4 ppm; EIMS (*m/z*(%)) 367[M^+](2), 365[M^+](5), 363[M^+](2), 286(7), 284(8), 265(8), 158(11), 156(12), 101(9), 72(100); HRMS (EI) calculated for $C_{12}H_{15}Br_2NO_2$ [M^+] 362.9470: found 362.9464.

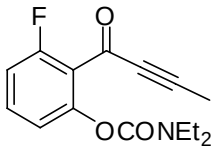
2-But-2-ynoylphenyl diethylcarbamate (4.10a)



This compound was prepared by **Method A** using the following materials: phenyl diethylcarbamate (386 mg, 2 mmol), *s*-BuLi (1.92 mL, 1.25 M in cyclohexane, 2.4 mmol), THF (10 mL), $MgBr_2 \cdot OEt_2$ (2 mL, 650 mg/mL in Et_2O, 5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide (1.2 mL,

2M in THF, 2.4 mmol). Column chromatography (8:2 hexanes:EtOAc) yielded **4.10a** (275 mg, 53%) as a colourless oil; IR (neat) ν_{max} 2977, 2935, 2876, 2236, 2212, 1729, 1714, 1652, 1603, 1472, 1424, 1381, 1295, 1270, 1207, 1155, 1091, 961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, 1H, J=7.8, 1.6Hz), 7.47 (dt, 1H, J=7.5, 1.7Hz), 7.22 (dt, 1H, J=7.6, 1.1Hz), 7.07 (d, 1H, J=8.10Hz), 3.41 (q, 2H, J=6.8Hz), 3.30 (q, 2H, J=7.2Hz), 1.98 (s, 3H), 1.21 (t, 3H, J=6.8Hz), 1.13 (t, 3H, J=6.8Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 153.6, 150.8, 134.2, 132.6, 130.2, 125.3, 124.2, 91.6, 80.0, 42.2, 41.9, 13.9, 13.3, 4.1 ppm; EIMS (*m/z*(%)) 259[M^+](10), 188(55), 161(13), 120(15), 100(100), 72(75); HRMS (EI) calculated for $C_{14}H_{17}NO_3$ [M^+] 259.1208: found 259.1199.

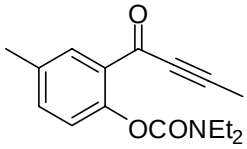
2-But-2-ynoyl-3-fluorophenyl diethylcarbamate (4.10b)



This compound was prepared by **Method A** using the following materials: 3-fluorophenyl diethylcarbamate (422 mg, 2 mmol), HTMP (0.2 mL, 1.2 mmol), *s*-BuLi (2.8 mL, 1.07 M in cyclohexane, 3 mmol), THF (10 mL), CuCN · 2LiCl (4 mL, 1M in THF, 4 mmol), and 2-butynoyl chloride (0.57 mL, 4 mmol). HTMP was added prior to a 1.5 h lithiation to improve regioselectivity. Column chromatography (8:2 hexanes:EtOAc) yielded **4.10b** (260 mg, 47%) as a colourless oil; IR (neat) ν_{max} 2977, 2937, 2251, 2213, 1729, 1652, 1616, 1464, 1419, 1266, 1153, 1051, 1007, 901 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 1H), 7.00 (m, 2H), 3.42 (q, 2H, J = 7.1 Hz), 3.37 (q, 2H, J = 7.1 Hz), 2.05 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 161.8, 159.2, 153.1, 150.1, 150.1, 132.4, 132.3, 119.4, 119.3, 113.2, 112.9, 92.6, 81.3, 42.4, 42.0, 14.0,

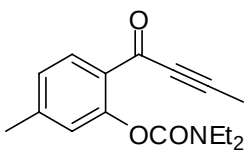
13.3, 4.4 ppm; EIMS (*m/z*(%)) 277[M^+](2), 100(100), 72(42); HRMS (EI) calculated for $C_{15}H_{16}NO_3F$ [M^+] 277.1114: found 2444.1120.

2-But-2-ynoyl-4-methylphenyl diethylcarbamate (4.10c)



This compound was prepared by **Method A** using the following materials: *p*-tolyl diethylcarbamate (206 mg, 1 mmol), *s*-BuLi (0.92 mL, 1.2 M in cyclohexane, 1.2 mmol), THF (5 mL), $MgBr_2 \cdot OEt_2$ (1 mL, 650 mg/mL in Et_2O, 2.5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide (0.65 mL, 2M in THF, 1.3 mmol). Column chromatography (7:3 hexanes:EtOAc) yielded **4.10c** (202 mg, 74%) as a light yellow oil; IR (neat) ν_{max} 2985, 2934, 2884, 2231, 1722, 1646, 1423, 1275, 1214, 1156, 1094, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.24 (d, 1H, J = 8.3 Hz), 6.93 (d, 1H, J = 8.2 Hz), 3.39 (q, 2H, J = 6.8 Hz), 3.28 (q, 2H, J = 6.8 Hz), 2.29 (s, 3H), 1.97 (s, 3H), 1.19 (t, 3H, J = 7.0 Hz), 1.11 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 153.8, 148.7, 135.0, 134.8, 132.8, 129.8, 124.0, 91.3, 80.1, 42.2, 41.8, 20.7, 13.9, 13.3, 4.3 ppm; EIMS (*m/z*(%)) 273[M^+](10), 202(30), 175(12), 134(15), 115(13), 100(100), 72(65); HRMS (EI) calculated for $C_{16}H_{19}NO_3$ [M^+] 273.1365: found 273.1371.

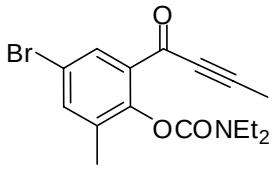
2-But-2-ynoyl-5-methylphenyl diethylcarbamate (4.10d)



This compound was prepared by **Method A** using the following materials: *m*-tolyl diethylcarbamate (206 mg, 1 mmol), *s*-BuLi (0.92 mL, 1.2 M in cyclohexane, 1.2 mmol), THF (5 mL), $MgBr_2 \cdot OEt_2$ (1 mL, 650 mg/mL in Et_2O, 2.5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide (0.65

mL, 2M in THF, 1.3 mmol). Column chromatography (7:3 hexanes:EtOAc) yielded **4.10d** (196 mg, 72%) as a light yellow oil; IR (neat) ν_{max} 2976, 2934, 2216, 1721, 1649, 1619, 1406, 1274, 1237, 1162, 1096, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 1H, J = 8.0 Hz), 7.06 (d, 1H, J = 8.0 Hz), 6.92 (s, 1H), 3.44 (q, 2H, J = 7.2 Hz), 3.34 (q, 2H, J = 7.2 Hz), 2.35 (s, 3H), 2.03 (s, 3H), 1.25 (t, 3H, J = 6.8 Hz), 1.18 (t, 3H, J = 6.8 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 153.8, 150.9, 145.7, 133.0, 127.6, 126.0, 124.8, 90.9, 80.0, 42.2, 41.9, 21.5, 13.9, 13.3, 4.2 ppm; EIMS (*m/z*(%)) 273[M^+](5), 202(20), 175(7), 134(5), 115(7), 100(100), 72(55); HRMS (EI) calculated for $C_{16}H_{19}NO_3$ [M^+] 273.1365: found 273.1364.

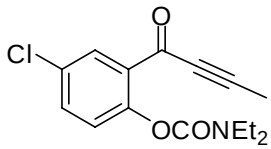
4-Bromo-2-but-2-ynoyl-6-methylphenyl diethylcarbamate (4.10e)



This compound was prepared by **Method A** using the following materials: 2,4-dibromo-6-methylphenyl diethylcarbamate (365 mg, 1 mmol), *t*-BuLi (1.45 mL, 1.45 M in pentane, 2.1 mmol), THF (10 mL), $MgBr_2 \cdot OEt_2$ (1 mL, 650 mg/mL in Et_2O, 2.5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide (0.65 mL, 2M in THF, 1.3 mmol). Column chromatography (4:1 hexanes:EtOAc) yielded **4.10e** (172 mg, 49%) as a light yellow oil; IR (neat) ν_{max} 2980, 2927, 2878, 2227, 1721, 1660, 1576, 1468, 1419, 1273, 1209, 1150, 960 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 1H, J = 2.4 Hz), 7.53 (d, 1H, J = 1.8 Hz), 3.48 (q, 2H, J = 7.0 Hz), 3.36 (q, 2H, J = 7.1 Hz), 2.21 (s, 3H), 2.08 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 152.8, 148.4, 138.2, 135.2, 132.9, 131.7, 117.8, 92.3, 79.7, 42.4, 42.0, 16.0, 14.1, 13.3, 4.4 ppm; EIMS

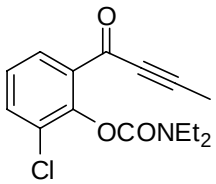
(*m/z*(%)) 353[M^+](10), 351[M^+](10), 282(10), 280(10), 115(10), 100(100), 72(35); HRMS (EI) calculated for $C_{16}H_{18}BrNO_3$ [M^+] 351.0470: found 351.0462.

2-But-2-ynoyl-4-chlorophenyl diethylcarbamate (4.10f)



This compound was prepared by **Method A** using the following materials: 4-chlorophenyl diethylcarbamate (225 mg, 1 mmol), *s*-BuLi (0.92 mL, 1.2 M in cyclohexane, 1.2 mmol), THF (5 mL), $MgBr_2 \cdot OEt_2$ (1 mL, 650 mg/mL in Et_2O, 2.5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide (0.65 mL, 2M in THF, 1.3 mmol). Column chromatography (7:3 hexanes:EtOAc) yielded **4.10f** (208 mg, 71%) as a light yellow oil; IR (neat) ν_{max} 2979, 2936, 2881, 2219, 1729, 1657, 1596, 1473, 1426, 1255, 1212, 1157, 1106, 965, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 2.6 Hz), 7.41 (dd, 1H, J = 2.6, 8.6 Hz), 7.02 (d, 1H, J = 8.6 Hz), 3.40 (q, 2H, J = 7.0 Hz), 3.29 (q, 2H, J = 7.0 Hz), 2.02 (s, 3H), 1.19 (t, 3H, J = 7.1 Hz), 1.12 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 153.3, 149.3, 133.8, 132.0, 131.3, 130.6, 125.8, 92.6, 79.6, 42.3, 41.9, 13.9, 13.3, 4.3 ppm; EIMS (*m/z*(%)) 293[M^+](10), 154(5), 126(4), 100(100), 72(45); HRMS (EI) calculated for $C_{15}H_{16}ClNO_3$ [M^+] 293.0819: found 293.0824.

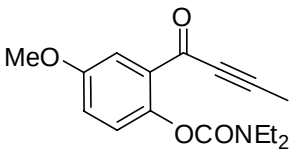
2-But-2-ynoyl-6-chlorophenyl diethylcarbamate (4.10g)



This compound was prepared by **Method A** using the following materials: 2-chlorophenyl diethylcarbamate (225 mg, 1 mmol), *s*-BuLi (0.92 mL, 1.2 M in cyclohexane, 1.2 mmol), THF (5 mL), $MgBr_2 \cdot OEt_2$ (1 mL, 650 mg/mL in Et_2O, 2.5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide

(0.65 mL, 2M in THF, 1.3 mmol). Column chromatography (7:3 hexanes:EtOAc) yielded **4.10g** (216 mg, 74%) as a light yellow oil; IR (neat) ν_{max} 2976, 2919, 2852, 2245, 2216, 1728, 1650, 1451, 1417, 1278, 1216, 1152, 1081, 954 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, 1H, J = 1.6, 7.9 Hz), 7.52 (dd, 1H, J = 1.5, 8.0 Hz), 7.16 (t, 1H, J = 8.0 Hz), 3.43 (q, 2H, J = 7.0 Hz), 3.30 (q, 2H, J = 7.1 Hz), 1.98 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 1.13 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 152.3, 147.1, 134.5, 132.1, 130.8, 129.5, 125.9, 92.3, 79.9, 42.5, 42.2, 14.0, 13.3, 4.3 ppm; EIMS (*m/z*(%)) 293[M^+](5), 222(10), 154(7), 100(100), 72(45); HRMS (EI) calculated for $C_{15}H_{16}ClNO_3$ [M^+] 293.0819: found 293.0830.

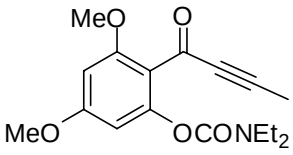
2-But-2-ynoyl-4-methoxyphenyl diethylcarbamate (4.10h)



This compound was prepared by **Method A** using the following materials: 4-methoxyphenyl diethylcarbamate (222 mg, 1 mmol), *s*-BuLi (0.92 mL, 1.2 M in cyclohexane, 1.2 mmol), THF (5 mL), $MgBr_2 \cdot OEt_2$ (1 mL, 650 mg/mL in Et_2O, 2.5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide (0.65 mL, 2M in THF, 1.3 mmol). Column chromatography (7:3 hexanes:EtOAc) yielded **4.10h** (222 mg, 77%) as a light yellow oil; IR (neat) ν_{max} 2986, 2942, 2849, 2229, 1721, 1652, 1583, 1473, 1419, 1281, 1200, 1155, 1043, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 1H, J = 2.0 Hz), 7.02-7.01 (m, 2H), 3.77 (s, 3H), 3.43 (q, 2H, J = 7.1 Hz), 3.33 (q, 2H, J = 7.1 Hz), 2.02 (s, 3H), 1.23 (t, 3H, J = 7.0 Hz), 1.15 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 156.5, 154.0, 144.4, 130.6, 125.2, 119.6, 116.7, 91.6, 80.0, 55.8, 42.2, 41.8, 14.0, 13.3, 4.3 ppm; EIMS (*m/z*(%))

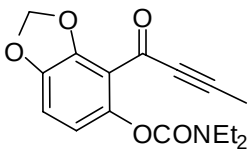
289[M^+](15), 218(3), 190(4), 150(7), 100(100), 72(50); HRMS (EI) calculated for $C_{16}H_{19}NO_4$ [M^+] 289.1314: found 289.1306.

2-But-2-ynoyl 3,5-dimethoxyphenyl Diethylcarbamate (4.10i)



This compound was prepared by **Method A** using the following materials: 3,5-dimethoxyphenyl diethylcarbamate (500 mg, 2 mmol), *n*-BuLi (0.9 mL, 2.44 M in hexanes, 2.2 mmol), THF (10 mL), $MgBr_2 \cdot OEt_2$ (2 mL, 650 mg/mL in Et_2O, 5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide (2.6 mL, 1M in THF, 2.6 mmol). Column chromatography (55:45 hexanes :EtOAc) yielded **4.10i** (400 mg, 63%) as a brown wax; IR (KBr) ν_{max} 2975, 2203, 1727, 1611, 1457, 1413, 1268, 1218, 1154, 1103, 892 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.41 (q, 2H, J = 7.1 Hz), 3.37 (q, 2H, J = 7.1 Hz), 2.01 (s, 3H), 1.23 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 162.8, 159.7, 153.3, 151.8, 116.3, 100.6, 96.4, 89.9, 81.9, 56.2, 55.7, 42.2, 41.9, 14.0, 13.3, 4.4 ppm; EIMS (*m/z*(%)) 319[M^+](15), 100(100), 72(40); HRMS (EI) calculated for $C_{17}H_{21}NO_5$ [M^+] 319.1420: found 319.1432.

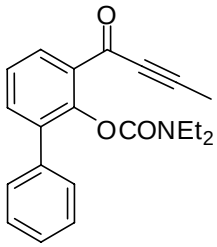
2-But-2-ynoylbenzo[*d*][1,3]dioxol-5-yl diethylcarbamate (4.10j)



This compound was prepared by **Method A** using the following materials: benzo[*d*][1,3]dioxol-5-yl diethylcarbamate (237 mg, 1 mmol), *s*-BuLi (0.9 mL, 1.25 M in cyclohexane, 1.1 mmol), THF (5 mL), $MgBr_2 \cdot OEt_2$ (1 mL, 650 mg/mL in Et_2O, 2.5 mmol), and *N*-methoxy-*N*-methyl-but-2-ynamide (0.6 mL, 2M in THF, 1.2 mmol). Column chromatography (3:2

hexanes:EtOAc) yielded **4.10j** (205 mg, 68%) as a colourless solid; mp 91-93 ^{o}C; IR (KBr) ν_{max} 2983, 2934, 2918, 2230, 1713, 1627, 1453, 1412, 1278, 1216, 1153, 1056, 925, 824, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (d, 1H, J = 8.4 Hz), 6.35 (d, 1H, J = 8.4 Hz), 5.87 (s, 2H), 3.22 (q, 2H, J = 7.1 Hz), 3.15 (q, 2H, J = 7.1 Hz), 1.82 (s, 3H), 1.03 (t, 3H, J = 7.1 Hz), 0.97 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 154.0, 148.3, 145.8, 143.8, 116.3, 115.8, 111.0, 102.8, 91.7, 81.2, 42.3, 41.8, 14.0, 13.3, 4.5 ppm; EIMS (*m/z*(%)) 303[M^+](25), 231(5), 204(8), 164(20), 100(100), 72(55); HRMS (EI) calculated for $C_{16}H_{17}NO_5$ [M^+] 303.1107: found 303.1114.

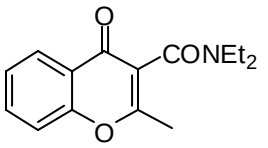
3-But-2-ynoylbiphenyl-2-yl diethylcarbamate (4.10k)



This compound was prepared by **Method A** using the following materials: biphenyl-2-yl diethylcarbamate (540 mg, 2 mmol), *s*-BuLi (2.13 mL, 2.4 mmol), THF (5 mL), CuCN · 2LiCl (4 mL, 1M in THF, 4 mmol), 2-butynoyl chloride (0.57 mL, 4 mmol), conducted at -100 ^{o}C maintaining an internal temperature of < -95 ^{o}C for the lithiation and < -85 ^{o}C for the cuprate. Column chromatography (7:3 hexanes:EtOAc) to yield **4.10k** (230 mg, 34%) as a light yellow viscous oil; IR (neat) ν_{max} 3060, 2975, 2931, 2873, 2231, 2213, 1722, 1716, 1647, 1413, 1275, 1204, 1152, 1084, 959, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, 1H, J = 1.6, 7.8 Hz), 7.48 (dd, 1H, J = 1.7, 7.6 Hz), 7.32-7.26 (m, 6H), 3.17 (q, 4H, J = 7.2 Hz), 2.00 (s, 3H), 0.98 (t, 3H, J = 7.0 Hz), 0.91 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 153.4, 147.7, 137.3, 137.2, 135.6, 132.0, 131.0, 129.2, 128.1, 127.6, 125.2, 91.6, 80.2, 42.2, 41.8, 13.7, 13.2, 4.4 ppm; EIMS (*m/z*(%))

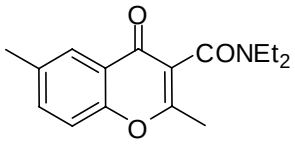
335[M^+](15), 264(20), 100(100), 72(35); HRMS (EI) calculated for $C_{21}H_{21}NO_3$ [M^+] 335.1521: found 335.1526.

_N,N_-Diethyl-2-methyl-4-oxo-4_H_-chromene-3-carboxamide (4.11a)



This compound was prepared by **Method B** using the following materials: **4.10a** (26 mg, 0.1 mmol), LTMP (0.15 mL, 0.15 mmol), and THF (1 mL). Column chromatography (7:3 EtOAc:CH_2Cl_2) yielded **4.11a** (21 mg, 81%) as a yellow oil, which solidified over time; mp 108-110 ^oC; IR (KBr) ν_{max} 3059, 2969, 2927, 2854, 1649, 1630, 1606, 1472, 1430, 1392, 1363, 1274, 1208, 1102, 1047, 974, 864, 809, 622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, 1H, J = 1.2, 8.0 Hz), 7.59 (dt, 1H, J = 1.6, 6.8Hz), 7.35 (m, 2H), 3.52 (q, 2H, J = 7.2 Hz), 3.20 (m, 2H), 2.35 (s, 3H), 1.21 (t, 3H, J =7.2 Hz), 1.04 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 164.6, 163.7, 155.9, 133.8, 126.0, 125.3, 123.2, 121.2, 117.8, 43.2, 39.4, 18.9, 14.5, 12.9 ppm; EIMS (*m/z*(%)) 259[M^+](7), 187(84), 160(22), 121(33), 72(100), 67(18); HRMS (EI) calculated for $C_{15}H_{17}NO_3$ [M^+] 259.1208: found 259.1202.

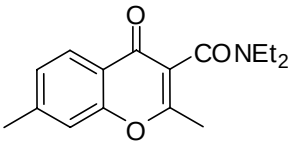
_N,N_-Diethyl-2,6-dimethyl-4-oxo-4_H_-chromene-3-carboxamide (4.11c)



This compound was prepared by **Method B** using the following materials: **4.10c** (27 mg, 0.1 mmol), LTMP (0.22 mL, 0.22 mmol), and THF (1 mL), stirred for 5 h. Column chromatography (7:3 EtOAc:CH_2Cl_2) yielded **4.11c** (25 mg, 93%) as a yellow oil, which solidified over time; mp 101-103 ^oC; IR (KBr) ν_{max} 2976, 2934, 2874, 1641, 1619, 1488, 1440, 1359, 1299, 1192, 1069, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 1H, J =

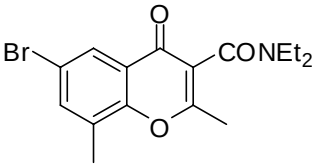
1.4 Hz), 7.48 (dd, 1H, J = 2.1, 8.5 Hz), 7.33 (d, 1H, J = 8.5 Hz), 3.60 (dectet, 2H, J = 6.5 Hz), 3.27 (dq, 2H, J = 1.7, 7.2 Hz), 2.45 (s, 3H), 2.41 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.13 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 164.7, 163.5, 154.2, 135.2, 135.0, 125.2, 122.8, 121.0, 117.5, 43.1, 40.6, 20.9, 18.9, 14.4, 12.8 ppm; EIMS (*m/z*(%)) 273[M^+](20), 258(17), 201(55), 174(30), 165(20), 135(40), 72(100); HRMS (EI) calculated for $C_{16}H_{19}NO_3$ [M^+] 273.1365: found 273.1369.

***N,N*-Diethyl-2,7-dimethyl-4-oxo-4*H*-chromene-3-carboxamide (4.11d)**



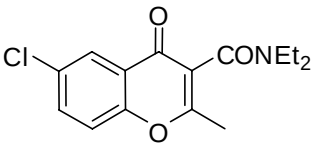
This compound was prepared by **Method B** using the following materials: **4.10d** (27 mg, 0.1 mmol), LTMP (0.22 mL, 0.22 mmol), and THF (1 mL), stirred for 5 h. Column chromatography (7:3 EtOAc:CH_2Cl_2) yielded **4.11d** (23 mg, 85%) as a yellow oil, which solidified over time; mp 98-102 ^{o}C; IR (KBr) ν_{max} 2976, 2932, 2872, 1642, 1432, 1396, 1363, 1223, 1068, 828, 656, 588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, J = 8.0 Hz), 7.23 (s, 1H), 7.22 (d, 1H, J = 8.3 Hz), 3.60 (q, 2H, J = 7.2 Hz), 3.28 (m, 2H), 2.49 (s, 3H), 2.41 (s, 3H), 1.29 (t, 3H, J = 7.1 Hz), 1.13 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 164.7, 163.3, 156.1, 145.2, 126.7, 125.7, 121.1, 121.0, 117.5, 43.2, 39.4, 21.8, 18.9, 14.5, 12.9 ppm; EIMS (*m/z*(%)) 273[M^+](25), 258(26), 201(70), 174(45), 135(50), 72(100); HRMS (EI) calculated for $C_{16}H_{19}NO_3$ [M^+] 273.1365: found 273.1366.

6-Bromo-*N,N*-diethyl-2,8-dimethyl-4-oxo-4*H*-chromene-3-carboxamide (4.11e)



This compound was prepared by **Method B** using the following materials: **4.10e** (37 mg, 0.1 mmol), LTMP (0.15 mL, 0.15 mmol), and THF (1 mL). Column chromatography (7:3 EtOAc:CH_2Cl_2) yielded **4.11e** (34 mg, 92%) as a yellow oil, which solidified over time; mp 149-151 ^oC; IR (KBr) ν_{max} 2974, 2928, 2863, 1728, 1641, 1620, 1582, 1463, 1386, 1357, 1288, 1191, 1138, 1083, 879, 832, 798, 619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 1H, J = 2.2 Hz), 7.55 (d, 1H, J = 0.7 Hz), 3.53 (dectet, 2H, J = 7.2 Hz), 3.21 (q, 2H, J = 7.2 Hz), 2.41 (s, 3H), 2.37 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.06 (t, 3H, 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 164.7, 154.2, 137.7, 131.3, 126.4, 124.2, 121.2, 118.5, 43.5, 39.7, 19.2, 15.7, 14.8, 13.2 ppm; EIMS (*m/z*(%)) 353[M^+](15), 351[M^+](15), 336(10), 281(32), 279(30), 254(13), 252(14), 207(14), 165(25), 139(20), 72(100); HRMS (EI) calculated for $C_{16}H_{18}BrNO_3$ [M^+] 351.0470: found 351.0481.

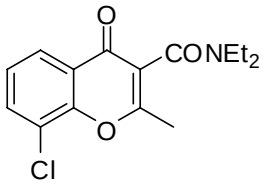
6-Chloro-*N,N*-diethyl-2-methyl-4-oxo-4*H*-chromene-3-carboxamide (4.11f)



This compound was prepared by **Method B** using the following materials: **4.10f** (29 mg, 0.1 mmol), LTMP (0.11 mL, 1.1 mmol), and THF (1 mL), stirred for 3 h. Column chromatography (4:1 EtOAc:CH_2Cl_2) yielded **4.11f** (25 mg, 86%) as a yellow oil, that solidified over time; mp 94-97 ^oC; IR (KBr) ν_{max} 2974, 2938, 1725, 1638, 1571, 1471, 1444, 1354, 1210, 1134, 1072, 822, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1H, J = 2.5 Hz), 7.61 (dd, 1H, J = 2.6, 8.9 Hz), 7.40 (d, 1H, J = 8.9 Hz), 3.59 (dectet, 2H, J = 7.0 Hz), 3.26 (q, 2H, J = 7.1 Hz), 2.42 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.14 (t, 3H, J =

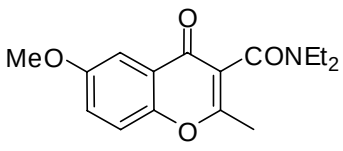
7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 164.1, 164.1, 154.2, 134.0, 131.3, 125.4, 124.2, 121.2, 119.5, 43.2, 39.4, 18.9, 14.5, 12.9 ppm; EIMS (*m/z*(%)) 293[M^+](15), 221(45), 207(20), 194(18), 165(14), 155(15), 72(100) 67(40); HRMS (EI) calculated for $C_{15}H_{16}ClNO_3$ [M^+] 293.0819: found 293.0817.

8-Chloro-*N,N*-diethyl-2-methyl-4-oxo-4*H*-chromene-3-carboxamide (4.11g)



This compound was prepared by **Method B** using the following materials: **4.10g** (29 mg, 0.1 mmol), LTMP (0.15 mL, 1.5 mmol), THF (1 mL), and warmed to 50 ^{o}C for 1h. Column chromatography (4:1 EtOAc:CH_2Cl_2) yielded **4.11g** (23 mg, 79%) as a yellow oil, which solidified with time; mp 123-126 ^{o}C; IR (KBr) ν_{max} 3081, 2991, 2934, 2882,1651, 1623, 1569, 1477, 1437, 1402, 1365, 1235, 1129, 1078, 833, 791, 768, 606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, 1H, J = 1.2, 7.9 Hz), 7.66 (dd, 1H, J = 1.2, 7.6 Hz), 7.27 (t, 1H, J = 7.9 Hz), 3.52 (q, 2H, J = 7.2 Hz), 3.20 (q, 2H, J = 7.2 Hz), 2.41 (q, 2H, J = 7.2 Hz), 2.41 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.07 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 164.0, 163.9, 151.7, 134.1, 126.0, 125.3, 124.6, 122.9, 121.4, 43.2, 39.4, 18.9, 14.5, 12.5 ppm; EIMS (*m/z*(%)) 293[M^+](15), 276(14), 221(50), 194(20), 165)16), 155(25), 72(100); HRMS (EI) calculated for $C_{15}H_{16}ClNO_3$ [M^+] 293.0819: found 293.0809.

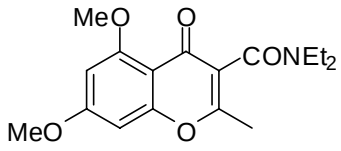
***N,N*-Diethyl-6-methoxy-2-methyl-4-oxo-4*H*-chromene-3-carboxamide (4.11h)**



This compound was prepared by **Method B** using the following materials: **4.10h** (29 mg, 0.1 mmol), LTMP (0.15

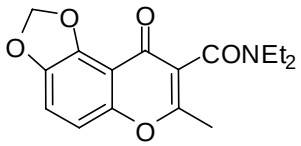
mL, 1.5 mmol), and THF (1 mL), which was slowly warmed to rt and stirred for 7 h. Column chromatography (4:1 EtOAc:CH_2Cl_2) yielded **4.11h** (26 mg, 90%) as a yellow oil, which solidified in time; mp 126-127 ^oC; IR (KBr) ν_{max} 2969, 2932, 2878, 1637, 1617, 1584, 1489, 1439, 1392, 1361, 1270, 1200, 1179, 1070, 1034, 989, 829, 779, 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 1H, J = 3.0 Hz), 7.30 (m, 1H), 7.19 (m, 1H), 3.81 (s, 3H), 3.53 (qn, 2H, J = 7.0 Hz), 3.21 (qn, 2H, J = 7.0 Hz), 2.34 (s, 3H), 1.21 (t, 3H, J = 7.0 Hz), 1.08 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 164.7, 163.4, 157.0, 150.8, 123.8, 120.5, 119.2, 105.1, 55.9, 43.1, 39.3, 18.9, 14.5, 12.8 ppm; EIMS (*m/z*(%)) 289[M^+](30), 217(60). 190(28), 165(15), 151(55), 139(16), 72(100); HRMS (EI) calculated for $C_{16}H_{19}NO_4$ [M^+] 289.1314: found 289.1322.

***N,N*-Diethyl-5-7-dimethoxy-2-methyl-4-oxo-4*H*-chromene-3-carboxamide (4.11i)**



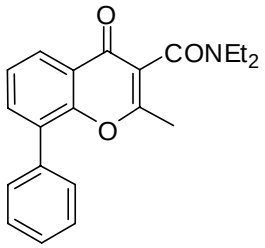
This compound was prepared by **Method B** using the following materials: **4.10i** (100 mg, 0.32 mmol), LDA (0.36 mL, 0.36 mmol), and THF (2 mL). Column chromatography (DCM, 7% MeOH) afforded **4.11i** (99 mg, 99%) as an orange oil; IR (neat) ν_{max} 2963, 2362, 1614, 1202, 1153, 1090, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, 1H, J = 1.6 Hz), 6.35 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.73 (sx, 1H, J = 7.0 Hz), 3.40-3.30 (m, 2H), 3.23 (sx, 1H, J = 7.4 Hz), 2.32 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz), 1.11 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 164.8, 164.1, 161.2, 160.6, 159.5, 122.2, 108.5, 96.1, 92.5, 56.4, 55.7, 43.1, 39.3, 18.4, 14.5, 12.8 ppm; EIMS (*m/z*(%)) 319[M^+](25), 220(100); HRMS (EI) calculated for $C_{17}H_{21}NO_5$ [M^+] 319.1420: found 319.1420.

***N,N*-Diethyl-7-dimethyl-9-oxo-9*H*-[1,3]dioxolo[4,5-*f*]chromene-8-carboxamide (4.11j)**



This compound was prepared by **Method B** using the following materials: **4.10j** (30 mg, 0.1 mmol), LTMP (0.15 mL, 1.5 mmol), and THF (1 mL). Column chromatography (4:1 EtOAc:CH_2Cl_2) yielded **4.11j** (27 mg, 90%) as a colourless solid; mp 206-210 ^oC; IR (KBr) ν_{max} 2981, 2925, 2874, 1642, 1623, 1493, 1472, 1460, 1439, 1273, 1216, 1086, 1053, 1037, 997, 875, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, 1H, J = 8.7 Hz), 6.84 (d, 1H, J = 8.7 Hz), 6.13 (d, 2H, J = 1.2 Hz), 3.60 (sx, 1H, J = 6.6 Hz), 3.40 (sx, 1H, J = 6.6 Hz), 3.21 (septet, 2H, J = 7.2 Hz), 2.30 (s, 3H), 1.19 (t, 3H, J = 7.2 Hz), 1.06 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 164.3, 163.9, 150.8, 145.3, 144.7, 120.6, 113.1, 110.4, 109.4, 130.5, 43.1, 39.3, 18.9, 14.5, 12.1 ppm; EIMS (*m/z*(%)) 303[M^+](30), 231(85), 204(60), 165(100), 72(86); HRMS (EI) calculated for $C_{16}H_{17}NO_5$ [M^+] 303.1107: found 303.1093.

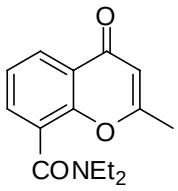
***N,N*-Diethyl-2-methyl-8-phenyl-4*H*-chromene-3-carboxamide (4.11k)**



This compound was prepared by **Method B** using the following materials: **4.10k** (33.5 mg, 0.1 mmol), LTMP (0.3 mL, 3 mmol), and THF (1 mL), stirred for 12 h. Column chromatography (1:1 EtOAc:CH_2Cl_2) yielded **4.11k** (22 mg, 66%) as a bright orange solid; mp 149-152 ^oC; IR (KBr) ν_{max} 2972, 2932, 2874, 1636, 1625, 1580, 1477, 1430, 1401, 1368, 1218, 1197, 1131, 1069, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, 1H, J = 1.6, 7.9 Hz), 7.63 (dd, 1H, J = 1.6, 7.4 Hz), 7.50-7.37 (m, 6H), 1.41 (q, 2H, J =

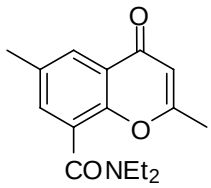
7.1 Hz), 3.22 (q, 2H, J = 3.4 Hz), 2.28 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.06 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 164.5, 163.7, 152.8, 135.8, 134.8, 131.5, 129.5, 128.5, 128.1, 125.3, 125.3, 123.7, 121.0, 43.2, 39.4, 18.9, 14.5, 12.9 ppm; EIMS (*m/z*(%)) 335[M^+](30), 263(40), 197(40), 72(100); HRMS (EI) calculated for $C_{21}H_{21}NO_3$ [M^+] 335.1521: found 335.1529.

N,N-diethyl-2-methyl-4-oxo-4H-chromene-8-carboxamide (4.12a)



This compound was prepared by **Method B** using the following materials: **4.10a** (26 mg, 0.10 mmol), LTMP (0.11 mL, 0.11 mmol) in THF (1ml). After stirring for 10 min, s-BuLi (0.18 mL, 0.20 mmol) was added, the ice bath was removed and the mixture warmed to rt. Column chromatography (1:1 DCM:EtOAc) yielded **4.12a** (14 mg, 54%) as an orange oil; IR (neat) ν_{max} 2972, 2931, 1658, 1480, 1434, 1390, 1362, 1216, 1109, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 8 Hz), 7.51 (d, 1H, J = 7.6 Hz), 7.35 (t, 1H, J = 7.6 Hz), 6.12 (s, 1H), 3.72 (m, 1H), 3.41 (m, 1H), 3.09 (m, 2H), 2.29 (s, 3H), 1.24 (t, 3H, J = 7.2Hz), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 166.1, 166.1, 152.0, 131.1, 127.4, 126.2, 125.0, 123.7, 110.7, 43.0, 39.1, 20.4, 14.1, 12.7 ppm; EIMS (*m/z*(%)) 259[M^+](20), 258[M^+-H](30), 187(100), 147(60); HRMS (EI) calculated for $C_{15}H_{16}NO_3$ [M^+] 258.1130: found 258.1133.

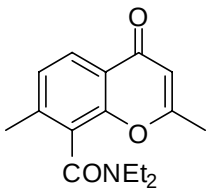
N,N-diethyl-2,6-dimethyl-4-oxo-4H-chromene-8-carboxamide (4.12c)



This compound was prepared by **Method B** using the following materials: **4.10c** (30 mg, 0.11 mmol), LTMP (0.12 mL, 0.12 mmol) in

THF (1ml). After stirring for 10 min, s-BuLi (0.24 mL, 0.27 mmol) was added, the ice bath was removed and the mixture warmed to rt. Column chromatography (1:1 DCM:EtOAc) yielded **4.12c** (13 mg, 44%) as an orange solid; mp 121-123 ^{o}C; IR (KBr) ν_{max} 3058, 3023, 2967, 2927, 1655, 1637, 1489, 1461, 1444, 1356, 1216, 1101, 971, 877, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.31 (s, 1H), 6.09 (s, 1H), 3.70 (m, 1H), 3.41 (m, 1H), 3.09 (m, 2H), 2.38 (s, 3H), 2.27 (s, 3H), 1.23 (t, 3H, J = 6.8Hz), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 166.3, 150.3, 135.2, 132.2, 127.2, 125.8, 123.4, 110.7, 43.0, 39.1, 20.9, 20.5, 14.1, 12.8 ppm; EIMS (*m/z*(%)) 272[[M-H]$^{+}$(90), 201(100), 161(40), 133(30); HRMS (EI) calculated for $C_{16}H_{19}NO_3$ [M-H]$^{+}$ 272.1287: found 272.1287.

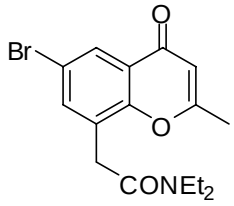
N,N-diethyl-2,7-dimethyl-4-oxo-4H-chromene-8-carboxamide (4.12d)



This compound was prepared by **Method B** using the following materials: **4.10d** (28 mg, 0.10 mmol), LTMP (0.11 mL, 0.11 mmol) in THF (1ml). After stirring for 10 min, s-BuLi (0.23 mL, 0.25 mmol) was added, the ice bath was removed and the mixture warmed to rt. Column chromatography (1:1 DCM:EtOAc) yielded **4.12d** (13 mg, 46%) as a pale yellow oil; IR (neat) ν_{max} 2968, 2924, 2851, 1656, 1638, 1436, 1414, 1390, 1361, 1106, 884, 834, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 1H, J = 8.0 Hz), 7.18 (d, 1H, 8.4 Hz), 6.08 (s, 1H), 3.61 (m, 2H), 3.06 (q, 2H, J = 6.8Hz), 2.34 (s, 3H), 2.27 (s, 3H), 1.25 (t, 3H, J = 6.8 Hz), 0.97 (t, 3H, J = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 165.8, 165.8, 152.4, 150.0, 127.2, 126.3, 125.5, 121.5, 110.7, 42.7, 38.9, 20.4, 19.3, 14.0, 12.7 ppm;

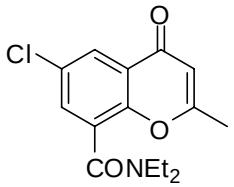
EIMS (*m/z*(%)) 273[M^+](25), 258([M-CH_3]$^+$(99), 201(100), 161(50); HRMS (EI) calculated for $C_{16}H_{19}NO_3$ [M-H]$^+$ 272.1287: found 272.1290.

2-(6-Bromo-2-methyl-4-oxo-4*H*-chromen-8-yl)-*N*,*N*-diethylacetamide (4.12e)



This compound was prepared by **Method B** using the following materials: **4.10e** (37 mg, 0.1 mmol), LTMP (0.3 mL, 0.3 mmol), and THF (1.5 mL). Column chromatography (4:1 EtOAc:CH_2Cl_2) yielded **4.12e** (31 mg, 84%) as a colourless solid; mp 161-164 ^oC; IR (KBr) ν_{max} 3065, 2980, 2927, 2856, 1637, 1632, 1586, 1457, 1385, 1354, 1277, 1146, 1098, 935, 893, 847, 817, 782, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1H, J = 2.4 Hz), 7.58 (d, 1H, J = 2.2 Hz), 6.10 (s, 1H), 3.78 (s, 2H), 3.37 (q, 4H, J = 7.1 Hz), 2.29 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.10 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 167.1, 164.6, 152.4, 136.5, 126.6, 126.1, 123.8, 117.1, 109.7, 41.4, 39.7, 32.8, 19.5, 13.5, 12.1 ppm; EIMS (*m/z*(%)) 353[M^+](20), 351[M^+](20), 253(7), 251(7), 213(12), 211(12), 100(100), 72(30); HRMS (EI) calculated for $C_{16}H_{18}BrNO_3$ [M^+] 351.0470: found 351.0468.

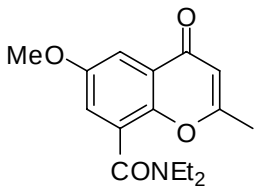
6-Chloro-*N*,*N*-diethyl-2-methyl-4-oxo-4*H*-chromene-8-carboxamide (4.12f)



This compound was prepared by **Method B** using the following materials: **4.10f** (29 mg, 0.1 mmol), LTMP (0.21 mL, 0.21 mmol), and THF (1 mL). Column chromatography (4:1 EtOAc:CH_2Cl_2) yielded **4.12f** (27 mg, 93%) as a yellow oil, that solidified over several days; mp 104-106 ^oC; IR (KBr) ν_{max} 3062, 2965, 2931, 2873, 1657, 1638, 1460, 1352, 1297, 1123, 971,

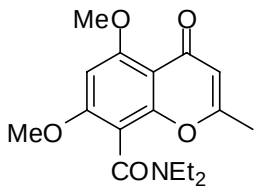
843, 795, 650, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1H, J = 2.6 Hz), 7.53 (dd, 1H, J = 0.3, 2.6 Hz), 6.20 (s, 1H), 3.78 (bs, 1H), 3.51 (bs, 1H), 3.18 (m, 2H), 2.37 (s, 3H), 1.33 (t, 3H, J = 7.1 Hz), 1.12 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 166.6, 164.9, 150.8, 131.5, 131.4, 129.5, 126.0, 125.2, 111.1, 43.4, 39.6, 20.8, 14.4, 13.1 ppm; EIMS (*m/z*(%)) 292[M^+](55), 250(7), 221(100), 181(30), 153(10), 72(25); HRMS (EI) calculated for $C_{15}H_{15}ClNO_3$ [M^+] 292.0740: found 292.0741.

***N,N*-Diethyl-6-methoxy-2-methyl-4-oxo-4*H*-chromene-8-carboxamide (4.12h)**



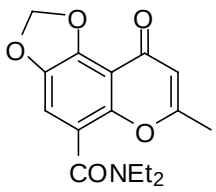
This compound was prepared by **Method B** using the following materials: **4.10h** (29 mg, 0.1 mmol), LTMP (0.5 mL, 0.5 mmol), and THF (1 mL). Column chromatography (4:1 EtOAc:CH_2Cl_2) yielded **4.12h** (25 mg, 86%) as a yellow oil, which solidified over several days; mp 71-73 ^oC; IR (KBr) ν_{max} 2967, 2931, 2873, 1726, 1633, 1625, 1468, 1400, 1367, 1272, 1225, 1128, 1069, 988, 828, 769, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 1H, J = 3.0 Hz), 7.10 (d, 1H, J = 3.1 Hz), 6.10 (s, 1H), 3.83 (s, 3H), 3.73 (bs, 1H), 3.40 (bs, 1H), 3.10 (q, 2H, J = 5.2 Hz), 2.28 (s, 3H), 1.25 (t, 3H, J = 7.2 Hz), 1.00 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 165.8, 165.6, 156.6, 146.9, 128.8, 124.6, 120.7, 110.1, 106.0, 56.1, 43.0, 39.1, 20.4, 14.1, 12.7 ppm; EIMS (*m/z*(%)) 289[M^+](50), 288[M^+-H](60), 274(5), 260(15), 246(15), 217(100), 189(20), 174(25), 93(10), 72(5); HRMS (EI) calculated for $C_{16}H_{19}NO_4$ [M^+] 289.1314: found 289.1319.

***N,N*-Diethyl-5-7-dimethoxy-2-methyl-4-oxo-4*H*-chromene-8-carboxamide (4.12i)**



This compound was prepared by **Method B** using the following materials: **4.10i** (100 mg, 0.32 mmol), LTMP (0.67 mL, 0.67 mmol), and THF (2 mL). Column chromatography (CH_2Cl_2, 10% MeOH) yielded **4.12i** (97 mg, 97%) as an orange oil; IR (neat) ν_{max} 3444, 2981, 2357, 1658, 1636, 1599, 1456, 1381, 1327, 1215, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.99 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.80 (sx, 1H, J = 7.0 Hz), 3.43 (sx, 1H, J = 7.0 Hz), 3.15 (q, 2H, J = 7.2 Hz), 2.22 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz), 1.03 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 164.0, 163.2, 161.4, 159.5, 155.2, 111.8, 108.3, 107.4, 91.5, 56.5, 56.1, 42.9, 39.1, 19.6, 14.1, 12.7 ppm; EIMS (*m/z*(%)) 319[M^+](50), 247(100); HRMS (EI) calculated for $C_{17}H_{21}NO_5$ [M^+] 319.1420: found 319.1419.

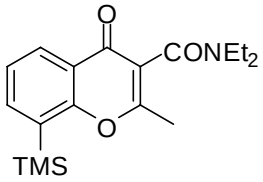
***N,N*-Diethyl-7-methyl-9-oxo-9*H*-[1,3]dioxolo[4,5-*f*]chromene-5-carboxamide (4.12j)**



This compound was prepared by **Method B** using the following materials: **4.10j** (42 mg, 0.14 mmol), LTMP (0.18 mL, 0.18 mmol) in THF (1ml). After stirring for 10 min, s-BuLi (0.34 mL, 0.36 mmol) was added, the ice bath was removed and the mixture warmed to rt. Column chromatography (6:4 DCM:EtOAc) yielded **4.12j** (15 mg, 36%) as a red solid; mp 106-108 ^oC; IR (KBr) ν_{max} 2971, 2928, 2871, 1655, 1641, 1621, 1457, 1358, 1277, 1202, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.17 (s, 2H), 6.01 (s, 1H), 3.73 (m, 1H), 3.35 (m, 1H), 3.13 (q, 2H, J = 7.1 Hz), 2.38 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.01 (t, 3H, J = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 165.8, 165.7, 156.0,

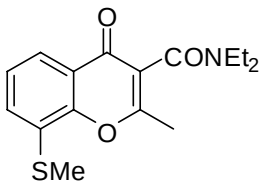
145.3, 144.7, 120.6, 113.1, 110.9, 110.2, 103.8, 43.0, 39.2, 20.4, 14.2, 12.7 ppm; EIMS (*m/z*(%)) 303[M^+](40), 231(100), 191(35); HRMS (EI) calculated for $C_{16}H_{17}NO_5$ [M^+] 303.1107: found 303.1114.

_N,N_-Diethyl-2-methyl-4-oxo-8-(trimethylsilyl)-4_H_-chromene-3-carboxamide (4.11l)



This compound was prepared by **Method C** using the following materials: **4.10a** (30 mg, 0.12 mmol), LTMP (0.19 mL, 0.16 mmol), *s*-BuLi (0.28 mL, 0.3 mmol), chlorotrimethylsilane (0.04 mL, 0.3 mmol), in THF (1 mL). Column chromatography (1:1 hexanes:EtOAc) yielded **4.11l** (16 mg, 42%) as a colourless solid; mp 127-129 ^oC; IR (KBr) ν_{max} 2964, 2930, 1636, 1624, 1480, 1459, 1444, 1402, 1220, 1201, 1130, 1078, 863, 844, 788, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, 1H, J = 1.5, 7.9 Hz), 7.68 (dd, 1H, J = 1.5, 7.0 Hz), 7.30 (t, 1H, J = 7.2 Hz), 3.53 (q, 2H, J = 7.1 Hz), 3.23 (q, 2H, J = 7.2 Hz), 2.36 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz), 1.08 (t, 3H, J = 7.1 Hz), 0.32 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 165.5, 164.2, 160.9, 140.5, 130.3, 128.1, 126.0, 123.4, 122.0, 44.1, 40.2, 19.7, 15.4, 13.8, 0.0 ppm; EIMS (*m/z*(%)) 331[M^+](20), 316[M-CH_3]$^+$(25), 259[M-$Si(CH_3)_3$]$^+$(25), 177(30), 72(100); HRMS (EI) calculated for $C_{18}H_{25}NO_3Si$ [M^+] 331.1604: found 331.1609.

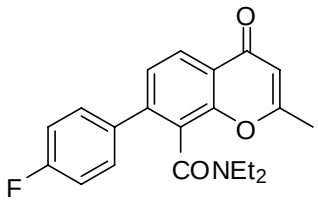
_N,N_-Diethyl-2-methyl-4-oxo-8-(methylthio)-4_H_-chromene-3-carboxamide (4.11m)



This compound was prepared by **Method C** using the following materials: **4.10a** (30 mg, 0.12 mmol), LTMP (0.19 mL, 0.16 mmol), s-BuLi (0.28 mL, 0.3 mmol), MeSSMe (0.027 mL, 0.3

mmol), in THF (1 mL). Column chromatography (2:3 EtOAc:CH_2Cl_2) yielded **4.11m** (16 mg, 44%) as a beige solid; mp 47-50 ^oC; IR (KBr) ν_{max} 2971, 2929, 2873, 1645, 1634, 1474, 1432, 1394, 1360, 1183, 1126, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J = 1.4, 7.9 Hz), 7.41 (dd, 1H, J = 1.2, 7.6 Hz), 7.29 (t, 1H, J = 7.6 Hz), 3.52 (q, 2H, J = 7.2 Hz), 3.20 (q, 2H, J = 7.2 Hz), 2.48 (s, 3H), 2.40 (s, 3H), 1.21 (t, 3H, J = 7.1 Hz), 1.06 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 164.4, 163.5, 153.0, 129.8, 128.6, 125.3, 123.3, 122.2, 121.3, 43.2, 39.4, 18.8. 14.9, 14.5, 12.9 ppm; EIMS (*m/z*(%)) 305[M^+](20), 233(95), 167(100), 72(75); HRMS (EI) calculated for $C_{16}H_{19}NO_3S$ [M^+] 305.1086: found 305.1089.

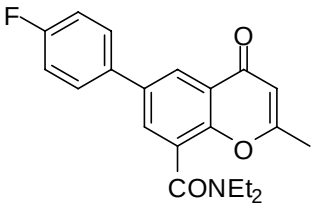
***N,N*-Diethyl-7-(4-fluorophenyl)-2-methyl-4-oxo-4*H*-chromene-8-carboxamide (4.16)**



A flame dried, argon flushed flask containing **4.12a** (25 mg, 0.1 mmol) in THF (2 mL) at -78 ^oC was treated dropwise with commercial LHMDS *via* syring (0.15 mL, 0.15 mmol, 1M in THF) producing an instantaneous red solution. After stirring for 10 min, TMEDA (0.045 mL, 0.3 mmol) was added followed by the slow dropwise addition of *s*-BuLi (0.25 mL, 0.3 mmol, 1.23M) and the mixture was stirred at -78 ^oC for 30 min. $B(OMe)_3$ (0.045 mL, 0.4 mmol) was then added and the mixture was stirred for a further 1 h at -78 ^oC before treatment with aq. saturated NH_4Cl. The aqueous phase was acidified with 0.5M HCl, EtOAc was added, and the phases were separated, aqueous phase extracted with EtOAc (1 x x mL), organic extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* affording a reddish solid that was added to a schlenk tube and dried under high vacuum. Pd_2dba_3 (1 mg, 0.001 mmol), SPhos (0.9 mg, 0.002 mmol),

K_3PO_3 (43 mg, 0.2 mmol) was added and the tube was sealed and evacuated under high vacuum backfilling with argon (3x). 1-Bromo-4-fluorobenzene (0.012 mL, 0.11 mmol), and PhMe (2 mL) was added and the tube was heated to 100 ^oC for 2h. Water (2mL) and EtOAc (2 mL) was added and the resultant mixture was separated and the aqueous phase was extracted with EtOAc (1 x 5 mL), organic extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* affording an oil that was subjected to flash column chromatography (1:1 EtOAc:CH_2Cl_2) to yield **4.16** (26.5 mg, 75%) as a colourless viscous oil; IR (neat) ν_{max} 2974, 2931, 1715, 1657, 1604, 1516, 1393, 1222, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, 1H, J = 8.2 Hz), 7.48 (m, 2H), 7.33 (d, 1H, J = 8.2), 7.06 (t, 2H, J = 8.6 Hz), 6.14 (s, 1H), 3.57 (sx, 1H, J = 6.6 Hz), 3.22 (sx, 1H, J = 6.6 Hz), 2.90 (sx, 1H, J = 6.6 Hz), 2.72 (sx, 1H, J = 6.6 Hz), 2.30 (s, 3H), 0.94 (t, 3H, J = 7.1 Hz), 0.70 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 166.4, 165.2, 164.3, 161.8, 152.8, 142.6, 134.4, 134.3, 130.8, 130.7, 126.4, 125.9, 125.8, 122.6, 115.7, 115.5, 110.9, 42.6, 38.7, 20.5, 13.6, 12.1 ppm; EIMS (*m/z*(%)) 353[M^+](10), 281(100), 241(40), 157(80); HRMS (EI) calculated for $C_{21}H_{20}NO_3F$ [M^+] 353.1427: found 353.1430.

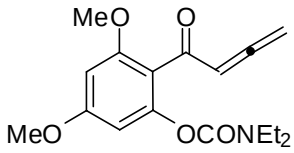
***N,N*-Diethyl-6-(4-fluorophenyl)-2-methyl-4-oxo-4*H*-chromene-8-carboxamide (4.17)**



A flame dried, argon flushed schlenk tube was charged with **4.12a** (25 mg, 0.1 mmol), $[Ir(OMe)COD]_2$ (1.4 mg, 0.002 mmol), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (11 mg, 0.004 mmol), bis(pinacolato)diboron (16 mg, 0.06 mmol), and then sealed and evacuated under high vacuum, backfilling with argon (3x). Dry degassed hexanes was added and the tube was heated to 80 ^oC for 18h. The tube was then evacuated under

high vacuum for 1h to removed volitiles and $Pd(PPh_3)_4$ (2.3 mg, 0.002 mmol) was added. The tube was sealed and evacuated under high vacuum backfilling with argon (3x). 1-Bromo-4-fluorobenzene (0.012 mL, 0.11 mmol), DME (2 mL), and 2M Na_2CO_3 (0.5 mL) was added and the tube was heated to 80 ^oC for 4h. Water (2mL) and EtOAc (1 mL) was added and the resultant mixture was separated and the aqueous phase was extracted with EtOAc (1 x 5 mL), organic extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* affording an oil that was subjected to flash column chromatography (2:3 EtOAc:CH_2Cl_2) to yield **4.17** (29 mg, 82%) as a colourless viscous oil; IR (neat) ν_{max} 2964, 2928, 1714, 1652, 1635, 1605, 1462, 1358, 1263, 1106, 837, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, 1H, J = 2.3 Hz), 7.69 (d, 1H, J = 2.3 Hz), 7.57-7.53 (m, 2H), 7.09 (t, 2H, J = 8.6 Hz), 6.15 (s, 1H), 3.73 (bs, 1H), 3.45 (bs, 1H), 3.15 (m, 2H), 2.31 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz), 1.03 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 165.1, 164.9, 163.1, 160.9, 156.0, 150.3, 136.3, 134.0, 128.7, 127.9, 127.8, 127.0, 123.0, 115.1, 114.9, 109.8, 42.1, 38.2, 19.5, 13.2, 11.8 ppm; EIMS (*m/z*(%)) 353[M^+](25), 352[M-H]$^+$(22), 281(100), 253(20), 241(22), 157(55); HRMS (EI) calculated for $C_{21}H_{19}NO_3F$ [M^+-H] 352.1349: found 352.1348.

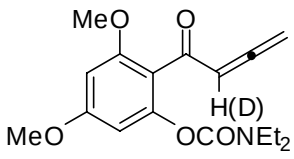
2-Buta-2,3-dienoyl-3,5-dimethoxyphenyl diethylcarbamate (4.19-H)



An solution of freshly prepared LDA (0.30 mL, 0.24 mmol, 0.8M in THF) was added *via* syring to a flask containing a solution of **4.10i** (64 mg, 0.20 mmol) in THF (1 mL, 0.2 M) at -78 ^oC maintaining an internal temperature < -73 ^oC. The mixture was stirred at -78 ^oC for 1 h and quenched with glacial AcOH. Saturated aq. $NaHCO_3$ was added and the layers

were separated, aqueous phase extracted with EtOAc (2 x 5mL), extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* to afford a brown oil. Flash column chromatography (1:1 hexanes:EtOAc) yielded **4.19-H** (40 mg, 63%) as a colourless solid; mp 58-59 ^oC; IR (neat) ν_{max} 2990, 1960, 1711, 1651, 1617, 1471, 1409, 1265, 1160, 1100, 866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (s, 1H), 6.32 (d, 1H, J = 1.7 Hz), 6.12 (t, 1H, J = 6.4 Hz), 5.11 (d, 2H, J = 6.4), 3.82 (s, 3H), 3.80 (s, 3H), 3.35 (q, 4H, 7.0 Hz), 1.19 (d, 6H, J = 4.8 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.7, 192.0, 161.6, 158.3, 153.2, 150.3, 116.0, 99.9, 98.1, 95.9, 79.4, 56.0, 55.6, 42.3, 42.0, 14.1, 13.3 ppm; EIMS (*m/z*(%)) 319[M^+](30), 280(15), 100(100), 72(30); HRMS (EI) calculated for $C_{17}H_{21}NO_5$ [M^+] 319.1420: found 319.1422.

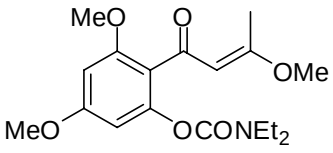
2-Buta-2,3-dienoyl-3,5-dimethoxyphenyl diethylcarbamate (4.19-D, ~21% D-content)



An solution of freshly prepared LDA (0.19 mL, 0.19 mmol, 1M in THF) was added *via* syring to a flask containing a solution of **4.10i** (50 mg, 0.16 mmol) in THF (2 mL, 0.08 M) at -78 ^oC maintaining an internal temperature < -73 ^oC. The mixture was stirred at -78 ^oC for 10 min and quenched with an excess of acetic acid-OD (0.2 mL, 3.47 mmol). Saturated aq. $NaHCO_3$ was added and the layers were separated. The aqueous phase was extracted with EtOAc (2 x 5mL), extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude titled compound as a orange oil. Column chromatography (1:1 hexanes:EtOAc) yielded **4.19-D** (27 mg, 53%) as a colourless solid; mp 58-59 ^oC; IR (neat) ν_{max} 2988, 2965, 1956, 1714, 1649, 1614, 1466, 1409, 1267, 1156, 1097, 867 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, 1H, J = 1.7 Hz), 6.24 (d, 1H, J = 1.8 Hz), 6.04 (t, 0.79H, 6.3 Hz), 5.03 (d, 2H, J = 5.8 Hz), 3.73 (s, 3H), 3.71 (s, 3H), 3.27 (q, 4H, J = 7.0 Hz), 1.11 (q, 6H, J = 6.3 Hz) ppm; ^{2}H NMR (61 MHz, $CHCl_3$) δ 6.10 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.7, 192.0, 161.6, 158.3, 153.2, 150.3, 116.0, 99.9, 98.1, 95.9, 79.4, 56.0, 55.6, 42.3, 42.0, 14.1, 13.3 ppm; EIMS (*m/z*(%)) 320[M^+](2), 319(10), 100(100), 72(30); $C_{17}H_{20}DNO_5$ undectable by HRMS, (EI) calculated for $C_{17}H_{21}NO_5$ [M^+] 319.1420: found 319.1416.

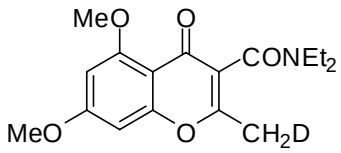
(*E*)-3,5-dimethoxy-2-(3-methoxybut-2-enoyl)phenyl diethylcarbamate (4.21)



A solution of freshly prepared LDA (0.12 mL, 0.11 mmol, 1M in THF) was added *via* syring to a flask containing a solution of **4.10i** (30 mg, 0.094 mmol) in THF (1 mL, 0.1 M) at -78 ^{o}C maintaining an internal temperature < -73^{o}C. The mixture was stirred at -78 ^{o}C for 20 min and quenched with an excess of MeOH (0.2 mL) and warmed to rt. Saturated aq. NH_4Cl was added and the layers were separated. The aqueous phase was extracted with EtOAc (2 x 5mL), extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* to afford a brown oil. Column chromatography (1:1 hexanes:EtOAc) yielded **4.21** (18 mg, 55%) as a colourless solid; mp 58-64 ^{o}C; IR (neat) ν_{max} 2970, 2937, 1718, 1613, 1585, 1407, 1272, 1154, 1101, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (s, 1H), 6.26 (s, 1H), 5.64 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.54 (s, 3H), 3.29 (q, 4H, J = 7.1 Hz), 2.27 (s, 3H), 1.08 (t, 6H, J = 7.2 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 173.0, 161.0, 157.8, 153.7, 149.7, 120.1, 102.3, 100.0, 96.5, 56.0, 55.7, 55.6, 42.1, 41.8, 19.9, 14.0,

13.3 ppm; EIMS (*m/z*(%)) 351[M^+](2), 336(5), 320(50), 100(100), 72(40); HRMS (EI) calcd for $C_{18}H_{25}NO_6$ [M^+] 351.1682: found 351.1680.

_N,N_-Diethyl-2-(deuteromethyl)-5-7-dimethoxy-4-oxo-4_H_-chromene-3-carboxamide (4.11i-D)



A solution of freshly prepared LDA (0.19 mL, 0.19 mmol, 1M in THF) was added *via* syring to a flask containing a solution of **4.10i** (50 mg, 0.157 mmol) in THF (2 mL, 0.1 M) at -78 ^oC maintaining an internal temperature < -73 ^oC. The cooling bath was removed and the mixture was stirred at rt for 4 h resulting in a deep red solution that was quenched with an excess of acetic acid-OD (0.2 mL, 3.47 mmol). Saturated aq. $NaHCO_3$ was added and the layers were separated. The aqueous phase was extracted with EtOAc (2 x 5mL), extracts combined, dried (Na_2SO_4), and concentrated *in vacuo* to afford a brown oil. Column chromatography on deactivated silica gel (DCM, 5% MeOH, 1% NEt_3) yielded **4.11i-D** (50 mg, 99%) as an orange oil; IR (neat) ν_{max} 2975, 2937, 1645, 1615, 1462, 1344, 1209, 1159, 1101, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, 1H, J = 2.3 Hz), 6.27 (d, 1H, J = 2.3 Hz), 3.84 (s, 3H), 3.80 (s, 3H), 3.65 (qn, 1H, J = 6.6 Hz), 3.32-3.12 (m, 3H), 2.24-2.22 (m, 2H), 1.18 (t, 3H, J = 7.1 Hz), 1.03 (t, 3H, J = 7.2 Hz) ppm; ^2H NMR (61 MHz, $CHCl_3$) δ 2.21 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 164.8, 164.1, 161.2, 160.6, 159.5, 122.2, 108.5, 96.1, 92.5, 56.4, 55.7, 43.1, 39.3, 18.1 (t, 1C, J = 19.9 Hz), 14.5, 12.8 ppm; EIMS (*m/z*(%)) 320[M^+](20), 304(55), 289(25), 248(50), 221(100), 181(100), 72(95); HRMS (EI) calcd for $C_{17}H_{20}DNO_5$ [M^+] 320.1482: found 320.1471.

Chapter 5

General Discussion and Conclusions

As a general practice of efficient synthetic planning, the *O*-sulfamate has been developed for use as a DMG with further chemistry in mind. Aryl *O*-sulfamates, easily prepared from their corresponding phenols, can be removed by aryl group replacement *via* KCT cross-cross coupling or by aryne formation and subsequent trapping. Their weak directing effect during D*o*M, placing them low on the DMG hierarchy, may be exploited when used in conjuction with much stronger DMGs as demonstrated in Figure 2.5. The poor electrophilicity at sulfur of *O*-sulfamates, as evident by their slow alkaline hydrolysis, may reflect a low Lewis acidity and weak participation in a CIPE based mechanism. A clear mechanistic discrepancy arises following the D*o*M of 4-fluorophenyl *O*-sulfamate **2.10k** versus 4-methoxyphenyl *O*-sulfamate **2.10b** (Table 2.8). Complex activation by the electron donating *O*-sulfamate and methoxy moietys facilitate D*o*M in ratios representative of their directing ability. As can been seen during the D*o*M of 4-fluorophenyl *O*-sulfamate **2.10k**, a KEM-based mechanism of *ortho*-fluoro lithiation is of sufficient strength for competition. Evidence for a strong KEM mechanism of DMG = F has been reported for complete *ortho*-fluorine over *ortho*-methoxy regioselectivity in fluoroanisole derivatives using LICKOR base or PMDTA conditions.[346] In this case the *O*-sulfamate group may assist in alkyllithium deaggregation but ultimately not selectively for its own D*o*M. By modifying the conditions of the medium using lower-coordinating donors to promote CIPE *via* a "substrate-promoted *ortho*-metalation" (Section 1.2.2.3) may give us a clearer picture towards increasing *O*-sulfamate directing ability in these cases.

A current limitation of preparing sulfamates is the commercial unavailability of *N,N*-diethylsulfamoyl chloride. The dimethyl analogue has been used to prepare

functionally significant sulfamates and sulfamides in a plethora of bioactive molecules residing in the academic and patent literature (eg. antibacterial[347], γ-secretase inhibitors [Alzheimer's][348], and HIV-1 integrase inhibitors[149]). The use of the *N,N*-diethyl and higher *N*-alkyl sulfamates could expand the chemistry of these molecules and their precursors through the adoption of new potentially beneficial metalation procedures not available to the dimethyl analogues, due to their instability in these reactions.

The most desirable improvement that could increase the use of the *O*-sulfamates in modern synthetic methodologies is that of improving the Suzuki-Miyaura cross coupling regime. KCT cross coupling although useful for the construction of simple biaryls, offers relatively poor scope (Section 1.3) in comparison to modern Suzuki-Miyaura tactics. Extensive screening could provide the realization of an active palladium species that can be inserted into an aryl *O*-sulfamate C-O bond and be efficiently coupled with aryl boronic acids. A good place to start would be Hartwig's recent palladium catalyzed KCT cross coupling of aryl and vinyl tosylates.[349]

The total synthesis of plant alkaloid schumanniophytine has been accomplished using a D*o*M – cross coupling sequence involving a key DreM – carbamoyl migration reaction. Despite the unability to test the proposed DreM – Michael addition sequence (due to failure to construct the required precursor **3.17**), the synthesis expands DreM chemistry to pyridine containing alkaloids. The question still remains whether compound **3.17** would benefit from more acidic remote pyridyl protons and be coursed towards **3.18** as in Scheme 3.3. The failure of 3-but-2-ynoylbiphen-2-yl *O*-carbamate **4.10k** to undergo DreM – carbamoyl migration instead of a relatively slow cumulenolate

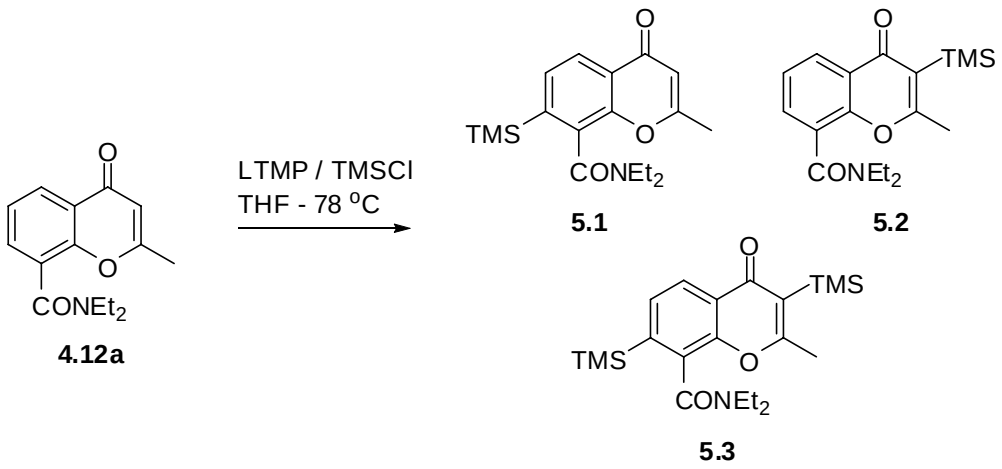
carbamoylation under high concentrations of LTMP may provide some insight. Nonetheless, the overall simple three component construction of readily available precursors (Scheme 3.6) in high yield is noteworthy. This sequence will allow for modification of each component independently for the purpose of expedient excess to new analogues for SAR profiling.

New and improved methods for the synthesis of substituted chromones although vast and rarely complicated, are a welcomed addition to a synthetic chemists arsenal due to the well know biological importance of these derivatives. The contents of Chapter 4 describe expedient construction of chromone 3- or the more challenging 8-carboxamides in a single step diverging from a common intermediate. Variable substitution patterns are exemplified containing biologically relevant halo and oxygen based aromatics (Table 4.1). In addition to the anionic construction of these chromones, the regiochemical complementing borylation – arylation reactions of the 8-carboxamide derivative **4.12a**, not only demonstrates the compatibility of these derivatives with D*o*M and modern iridium-catalysis, but also allow for further exploration into even more complex biaryl chromone systems.

During preliminary D*o*M experiments of **4.12a**, Martin's conditions[36] gave a mixture of mono-silylated chromones **5.1**, **5.2** at low concentrations and bis-silylated chromone **5.3** at higher concentrations of LTMP / TMSCl (Scheme 5.1). These chromones have been isolated and characterized by ^{1}H NMR. Interestingly, the ratio of **5.1:5.2** was inconsistent and is suggested that one must depend on the ratio of LTMP:TMSCl employed, as well as substrate concentration. These results would

suggest that aggregate formation plays a key role in the regiochemistry of deprotonation and / or silylation. It would be of interest to further explore this reaction in attempts to gain insight into the mechanisms at play. These results would fit nicely with the regiochemical 3- versus 2-methyl acylation reactions of simple 2-methylchromones with LDA,[350] and expand the anionic methodology of 2-methylchromones in general.

Scheme 5.1. Reaction of Chromone 4.12a Under Martin's Conditions

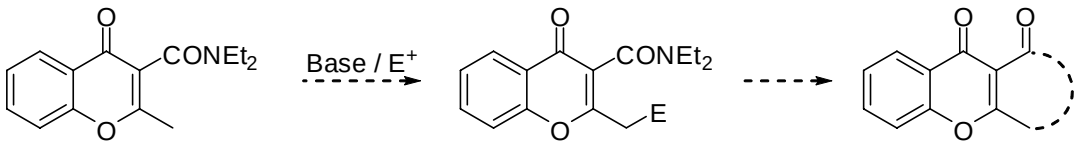


Although mechanistic evidence supporting the involvement of a cumulenolate intermediate is presented, no direct spectroscopic evidence is provided. Further experimentation using react-IR may be of value to probe the reactivity of the cumulenolate species, and at the same time allow the observation of other potential intermediates that may provide some information about the yield discrepancy experienced in these reactions.

Initial experimentation probing the reactivity of chromone 3-carboxamide **4.11a** has been conducted with little success. Further chemistry is required to evaluate these compounds as potential precursors for 2-methyl substitution products (**5.4**, Scheme 5.2).

These substituted compounds could provide a variety of interesting heterocyclic systems (**5.5**) after condensation with the native 3-carboxamide. Alternatively, installation of 2-methyl substituents using γ-substituted *N*-methoxy-*N*-methylbut-2-ynamides before the anionic chromone cyclization would be an important contribution to expand the methodology of this chemistry as a whole.

Scheme 5.2. Further Potential Chemistry of Chromone 4.11a



4.11a **5.4** **5.5**

References

(1) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley & Sons, USA, 1990.

(2) Lednicer, D.; Mitscher, A. *The Organic Chemistry of Drug Synthesis*; Wiley-Interscience: New York, 1998; Vol. 6.

(3) Esteves, P. M.; Walkimar de Carneiro, J.; Cardoso, S. P.; Barbosa, A. G. H.; Laali, K. K.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 4836-4849.

(4) Crampton, M. R. In *Organic Reaction Mechanisms*; A. C. Knipe, W. E. W., Ed.; John Wiley & Sons: UK, 2004, p 283-294.

(5) Rossi, R. A.; Pierini, A. B.; Penenory, A. B. *Chem. Rev.* **2003**, *103*, 71-167.

(6) Makosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631-2666.

(7) Macklin, T.; Snieckus, V. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, p 106-118.

(8) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826-834.

(9) Ishiyama, T.; Miyaura, N. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, p 126-131.

(10) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238.

(11) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1938**, *61*, 109-112.

(12) Wittig, G.; Pockels, U.; Droge, H. *Chem. Ber.* **1938**, *71B*, 1903-1912.

(13) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853-856.

(14) Gilman, H.; Morton, J. W., Jr. *Org. React.* **1954**, 258-304.

(15) Mallan, J. M.; Bebb, R. L. *Chem. Rev.* **1969**, *69*, 693-755.

(16) Gschwend, H. W.; Rodriguez, H. R. In *Organic Reactions*; Dauben, W. G., Ed.; Robert E. Krieger Publishing Company: Malabar, FL, 1979; Vol. 26, p 1-360.

(17) Snieckus, V. *Heterocycles* **1980**, *14*, 1649-1676.

(18) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306-312.

(19) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356-363.

(20) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1-21.

(21) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.

(22) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinhiem, Germany, 2002, p 330-367.

(23) Clayden, J. In *Chemistry of Organolithium Compounds*; Z. Rappoport, I. M., Ed.; John Wiley & Sons: UK, 2004; Vol. 1, p 495-646.

(24) Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 900-903.

(25) Christensen, H. *Synth. Comm.* **1975**, *5*, 65-78.

(26) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837-860.

(27) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823-1824.

(28) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798-4801.

(29) Alessi, M.; Snieckus, V. *Unpublished results.*

(30) Demchuk, O. M.; Yoruk, B.; Blackburn, T.; Snieckus, V. *Synlett* **2006**, 2908-2913.

(31) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935-1937.

(32) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187-304.

(33) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139-147.

(34) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376-393.

(35) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582-584.

(36) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155-6157.

(37) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054-2055.

(38) Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018.

(39) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673-5676.

(40) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514-8515.

(41) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatley, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921-1930.

(42) Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, *68*, 1658-1660.

(43) Anderson, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553-7558.

(44) Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080-2082.

(45) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145-8153.

(46) Stratakis, M. *J. Org. Chem.* **1997**, *62*, 3024-3025.

(47) Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421-422.

(48) Waldmueller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 5479-5480.

(49) Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628-10636.

(50) Stork, G.; Polt, R. L.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 8360-8367.

(51) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191-7198.

(52) Saa, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, *61*, 5194-5195.

(53) Suner, G. A.; Deya, P. M.; Saa, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 1467-1471.

(54) Saa, J. M.; Deya, P. M.; Suner, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093-9100.

(55) Saa, J. M.; Morey, J.; Frontera, A.; Deya, P. M. *J. Am. Chem. Soc.* **1995**, *117*, 1105-1116.

(56) Braga, D.; Grepioni, F.; Biradha, K.; Desiraju, G. R. *J. Chem. Soc., Dalton Trans.* **1996**, 3925-3930.

(57) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed.* **1992**, *31*, 755-758.

(58) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Tetrahedron* **1994**, *50*, 5903-5916.

(59) Kremer, T.; Junge, M.; Schleyer, P. v. R. *Organometallics* **1996**, *15*, 3345-3359.

(60) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640-8647.

(61) Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259-2268.

(62) Langer, A. W., Jr. *Trans. New York Acad. Sci.* **1965**, *27*, 741-747.

(63) Slocum, D. W.; Book, G.; Jennings, C. A. *Tetrahedron Lett.* **1970**, 3443-3445.

(64) Slocum, D. W.; Moon, R.; Thompson, J.; Coffey, D. S.; Li, J. D.; Slocum, M. G.; Siegel, A.; Gayton-Garcia, R. *Tetrahedron Lett.* **1994**, *35*, 385-388.

(65) Slocum, D. W.; Coffey, D. S.; Siegel, A.; Grimes, P. *Tetrahedron Lett.* **1994**, *35*, 389-392.

(66) Slocum, D. W.; Thompson, J.; Friesen, C. *Tetrahedron Lett.* **1995**, *36*, 8171-8174.

(67) Slocum, D. W.; Hayes, G.; Kline, N. *Tetrahedron Lett.* **1995**, *36*, 8175-8178.

(68) Slocum, D. W.; Ray, J.; Shelton, P. *Tetrahedron Lett.* **2002**, *43*, 6071-6073.

(69) Slocum, D. W.; Dumbris, S.; Brown, S.; Jackson, G.; LaMastus, R.; Mullins, E.; Ray, J.; Shelton, P.; Walstrom, A.; Micah Wilcox, J.; Holman, R. W. *Tetrahedron* **2003**, *59*, 8275-8284.

(70) Maggi, R.; Schlosser, M. *Tetrahedron Lett.* **1999**, *40*, 8797-8800.

(71) Napolitano, E.; Fiaschi, R. *Tetrahedron Lett.* **2000**, *41*, 4663-4666.

(72) Slocum, D. W.; Carroll, A.; Dietzel, P.; Eilerman, S.; Culver, J. P.; McClure, B.; Brown, S.; Holman, R. W. *Tetrahedron Lett.* **2006**, *47*, 865-868.

(73) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995.

(74) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353-451.

(75) Jastrzebski, J. T. B. H.; Van Koten, G.; Konijn, M.; Stam, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 5490-5492.

(76) Reich, H. J.; Gudmundsson, B. O. *J. Am. Chem. Soc.* **1996**, *118*, 6074-6075.

(77) Clayden, J.; Davies, R. P.; Hendy, M. A.; Snaith, R.; Wheatley, A. E. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1238-1240.

(78) Armstrong, D. R.; Boss, S. R.; Clayden, J.; Haigh, R.; Kirmani, B. A.; Linton, D. J.; Schooler, P.; Wheatley, A. E. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2135-2138.

(79) Gossage, R. A.; Jastrzebski, J. T. B. H.; van Koten, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1448-1454.

(80) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653-3664.

(81) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815-10816.

(82) Nguyen, T.-H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2005**, *7*, 2445-2448.

(83) Nguyen, T.-H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *J. Org. Chem.* **2007**, *72*, 3419-3429.

(84) Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3975-3984.

(85) Quirk, R. P.; Kester, D. E.; Delaney, R. D. *J. Organomet. Chem.* **1973**, *59*, 45-52.

(86) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316-2320.

(87) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303-305.

(88) Kochi, J. K.; Tamura, M. *J. Am. Chem. Soc.* **1971**, *93*, 1483-1485.

(89) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268-9269.

(90) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376.

(91) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc. Chem. Comm.* **1972**, 144.

(92) Negishi, E.-i.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*; 2 ed. 2004; Vol. 2, p 815-889.

(93) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823.

(94) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*, 1998.

(95) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992-4998.

(96) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; 2 ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, p 41-123.

(97) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Comm.* **1981**, *11*, 513-519.

(98) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; 2 ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, p 163-216.

(99) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Heterocycles* **1990**, *30*, 303-306.

(100) Brase, S.; De Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; 1 ed.; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinhiem, 1998, p 99-166.

(101) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jap.* **1971**, *44*, 581.

(102) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320-2322.

(103) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874-922.

(104) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470.

(105) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*; 2 ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 699-760.

(106) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348-1350.

(107) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609-3612.

(108) Zapf, A.; Beller, M.; Riermeier, T. H. In *Transition Metals for Organic Synthesis*; 2 ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinhiem, 2004; Vol. 1, p 231-256.

(109) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: Hoboken, 2002; Vol. 1, p 1097-1106.

(110) Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985-3988.

(111) Bohm, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3387-3389.

(112) Negishi, E.-i. *J. Organomet. Chem.* **2002**, *653*, 34-40.

(113) Bohm, V. P. W.; Weskamp, T.; Gstottmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602-1604.

(114) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359-1469.

(115) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373-5374.

(116) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9595.

(117) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

(118) Hegedus, L. S. In *Organometallics. A Manual*; Schlosser, M., Ed.; Wiley: Chichester, 1994, p 383-459.

(119) Crabtree, R. H. In *The Organometallic Chemistry of Transition Metals*; 2 ed.; John Wiley & Sons: New York, 1994, p 151-155.

(120) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1986**, *51*, 3566-3572.

(121) Cuevas, J. C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5841-5844.

(122) Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375-1379.

(123) Fisher, L. E.; Muchowski, J. M.; Clark, R. D. *J. Org. Chem.* **1992**, *57*, 2700-2705.

(124) Phillion, D. P.; Walker, D. M. *J. Org. Chem.* **1995**, *60*, 8417-8420.

(125) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408-3419.

(126) Park, K. H.; Lee, J. B. *Synth. Comm.* **1992**, *22*, 1061-1065.

(127) Wikel, J. H.; Denney, M. L.; Vasileff, R. T. *J. Heterocycl. Chem.* **1993**, *30*, 289-290.

(128) Coburn, C. A.; Young, M. B.; Hungate, R. W.; Isaacs, R. C. A.; Vacca, J. P.; Huff, J. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1937-1940.

(129) Mederski, W.; Dorsch, D.; Osswald, M.; Schwartz, H.; Beier, N.; Christadler, M.;

Minck, K. O.; Schelling, P.; Schmitges, C. J. *Eur. J. Med. Chem.* **1997**, *32*, 479-491.

(130) Evans, P. A.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929-1931.

(131) Katohgi, M.; Yokoyama, M.; Togo, H. *Synlett* **2000**, 1055-1057.

(132) Davis, F. A.; Srirajan, V. *J. Org. Chem.* **2000**, *65*, 3248-3251.

(133) Xu, L.; Zhang, S.; Trudell, M. L. *Synlett* **2004**, 1901-1904.

(134) Sibi, M. P.; Chattopadhyay, S.; Dankwardt, J. W.; Snieckus, V. *J. Am. Chem. Soc.* **1985**, *107*, 6312-6315.

(135) Tsukazaki, M.; Snieckus, V. *Can. J. Chem.* **1992**, *70*, 1486-1491.

(136) Mabic, S.; Vaysse, L.; Benezra, C.; Lepoittevin, J.-P. *Synthesis* **1999**, 1127-1134.

(137) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808-2809.

(138) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Organic Letters* **1999**, *1*, 1183-1186.

(139) Morin, J.-A.; Snieckus, V., Queen's University, 2007.

(140) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101-2108.

(141) Hewawasam, P.; Chen, N.; Ding, M.; Natale, J. T.; Boissard, C. G.; Yeola, S.; Gribkoff, V. K.; Starrett, J.; Dworetzky, S. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1615-1618.

(142) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43-46.

(143) Takei, H.; Miura, M.; Sugimura, H.; Okamura, H. *Chem. Lett.* **1979**, 1447-1450.

(144) Okamura, H.; Miura, M.; Kosugi, K.; Takei, H. *Tetrahedron Lett.* **1980**, *21*, 87-90.

(145) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246-2247.

(146) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc. Chem. Comm.* **1979**, 637-638.

(147) Wenkert, E.; Ferreira, T. W. *J. Chem. Soc. Chem. Comm.* **1982**, 840-841.

(148) Wenkert, E.; Hanna, J. M., Jr.; Leftin, M. H.; Michelotti, E. L.; Potts, K. T.; Usifer, D. *J. Org. Chem.* **1985**, *50*, 1125-1126.

(149) Fabre, J. L.; Julia, M.; Verpeaux, J. N. *Tetrahedron Lett.* **1982**, *23*, 2469-2472.

(150) Fabre, J. L.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4311-4314.

(151) Fabre, J. L.; Julia, M.; Verpeaux, J. N. *Bull. Soc. Chim. Fr.* **1985**, 762-771.

(152) Clayden, J.; Julia, M. *J. Chem. Soc. Chem. Comm.* **1993**, 1682-1683.

(153) Clayden, J.; Cooney, J. J. A.; Julia, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 7-14.

(154) Sengupta, S. L., M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066-4068. A useful element of the *O*-carbamate is its proclivity for anionic ortho-Fries rearrangement exposing a phenol which, upon triflation and nickel-catalyzed hydride reduction, also achieves its removal with retention of a new amide DMG for further D*o*M chemistry, see Cai, X.; Brown, S.; Hodson, P.; Snieckus, V. *Can. J. Chem*. **2004**, *82*, 195-205 and refs cited therein. For the power and versatility of the *O*-carbamate DMG in synthesis, see Whisler, M.C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206-2225.

(155) Milburn, R. R.; Snieckus, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 888-891.

(156) Milburn, R. R.; Snieckus, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 892-894.

(157) Audrieth, L. F.; Sveda, M.; Sisler, H. H.; Butler, M. J. *Chem. Rev.* **1940**, *26*, 49-94.

(158) Benson, G. A.; Spillane, W. J. *Chem. Rev.* **1980**, *80*, 151-186.

(159) Benson, G. A.; Spillane, W. J. *Chem. Sulphonic Acids, Esters Their Deriv.* **1991**, 947-1036.

(160) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F.; Shank, R. P.; Dodgson, S. P. *J. Med. Chem.* **1987**, *30*, 880-887.

(161) Sliskovic, D. R.; Krause, B. R.; Picard, J. A.; Anderson, M.; Bousley, R. F.; Hamelehle, K. L.; Homan, R.; Julian, T. N.; Rashidbaigi, Z. A.; Stanfield, R. L. *J. Med. Chem.* **1994**, *37*, 560-562.

(162) Ager, D. J.; Pantaleone, D. P.; Henderson, S. A.; Katritzky, A. R.; Prakash, I.; Walters, D. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 1802-1817.

(163) Winum, J.-Y.; Scozzafava, A.; Montero, J.-L.; Supuran, C. T. *Med. Res. Rev.* **2005**, *25*, 186-228.

(164) Hanson, S. R.; Whalen, L. J.; Wong, C.-H. *Bioorg. Med. Chem.* **2006**, *14*, 8386-8395.

(165) Nishimori, I.; Minakuchi, T.; Onishi, S.; Vullo, D.; Scozzafava, A.; Supuran, C. T. *J. Med. Chem.* **2007**, *50*, 381-388.

(166) Farrera-Sinfreu, J.; Albericio, F.; Royo, M. *J. Comb. Chem.* **2007**, *9*, 501-506.

(167) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562-568.

(168) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823-4826.

(169) Wehn, P. M.; Du Bois, J. *Org. Lett.* **2005**, *7*, 4685-4688.

(170) Zhang, J.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2005**, *46*, 5403-5408.

(171) Benson, G. A.; Maughan, P. J.; Shelly, D. P.; Spillane, W. J. *Tetrahedron Lett.* **2001**, *42*, 8729-8731.

(172) Rittler, K. W.; (Chem. Fab. von Heyden A.-G.). DE 555409, 1931.

(173) Martin, R. *Org. Prep. Proced. Int.* **1992**, *24*, 369-435.

(174) Moghaddam, F. M.; Dakamin, M. G. *Tetrahedron Lett.* **2000**, *41*, 3479-3481.

(175) Charmant, J. P. H.; Dyke, A. M.; Lloyd-Jones, G. C. *Chem. Comm.* **2003**, 380-381.

(176) Vandi, A.; Moeller, T.; Audrieth, L. F. *J. Org. Chem.* **1961**, *26*, 1136.

(177) Gupta, S. K. *Synthesis* **1977**, 39-41.

(178) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34-46.

(179) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735-6736.

(180) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217-2224.

(181) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436-5438.

(182) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101-2108.

(183) Andersen, K. K.; Bray, D. D.; Chumpradit, S.; Clark, M. E.; Habgood, G. J.; Hubbard, C. D.; Young, K. M. *J. Org. Chem.* **1991**, *56*, 6508-6516.

(184) Williams, A.; Douglas, K. T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1727-1732.

(185) Diez-Gonzalez, S.; Nolan, S. P. *Top. Organomet. Chem.* **2007**, *21*, 47-82.

(186) Kelly, R. A., III; Scott, N. M.; Diez-Gonzalez, S.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 3442-3447.

(187) Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519-2522.

(188) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183-1186.

(189) Gray, M.; Chapell, B. J.; Felding, J.; Taylor, N. J.; Snieckus, V. *Synlett* **1998**, 422-424.

(190) MacNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662-3670.

(191) For recent comprehensive reviews, see the dedicated special issue: Tamao, K.; Hiyama, T.; Negishi, E.-i. (Eds.) *J. Organomet. Chem.* **2002**, *653*; Diederich, F. and Stang, P. J. Eds. *Metal-catalyzed Cross-coupling Reactions*; Wiley-VCH: Weinhiem, 1998; Stille coupling: Beletskaya, I. P. *J. Organomet. Chem.* **1983**, 250, 551-564; Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704-4734; Negishi coupling: King, A. O.; Negishi, E.-i.; Villani, F. J.; Silveira, A. *J. Org. Chem.* **1978**, *43*, 358-360; Klement, I.; Rottlaender, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201-7220; Hiyama coupling: Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845-853; Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835-846; Suzuki – Miyaura coupling: Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866-867; Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871-1876; KCT coupling: Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc*. **1972**, *94*, 4374-4376; Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc. Chem. Commun*. **1972**, 144; a recent copper-catalyzed coupling of siloxanes, see: Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc*. **2000**, *122*, 7600-7601; copper-catalyzed coupling of boronic acids, see: Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691-1694 and refs cited therein; iron-catalyzed coupling, see: Fürstner, A.; Martin, R. *Angew. Chem., Int. Ed*. **2004**, *43*, 3955-357, and references therein.

(192) Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150-160.

(193) Anctil, E. J. G.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*; 2

ed.; Diederich, F., de Meijere, A., Eds.; Wiley-VCH: Weinhiem, Germany, 2004, p 761-813.

(194) Review: Benson, G. A. Spillane, W. J. In *The Chemistry of Sulphonic Acids, Esters, and their Derivatives*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991, p 947-1036. *O*-Sulfamates are of interest in medicinal chemistry; see: Spillane, W. J.; McGrath, P.; Brack, C.; O'Byrne, A. B. *J. Org. Chem*. **2001**, *66*, 6313-6316 and refs cited therein. For use of *O*-sulfamates in Ru – catalyzed C – H activated processes, see Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett*. **2003**, *5*, 4823-4826 and refs cited therein. For thia-Fries rearrangement of *O*-sulfamates, see Benson, G. A.; Maughan, P. J.; Shelly, D. P.; Spillane, W. J. *Tetrahedron Lett*. **2001**, *42*, 8729-8731 and refs cited therein.

(195) DoM chemistry of this function, has to the best of our knowledge, not been achieved. For cross coupling chemistry, see: Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc*. **2004**, *126*, 3058-3059 (Suzuki-Miyaura); Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc*. **2003**, *125*, 8704-8705 (KCT).

(196) For Suzuki-Miyaura cross coupling, see: Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem*. **2004**, *69*, 3447-3452.

(197) For Negishi coupling, see: Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349-350.

(198) Benzyne generation may be achieved by elimination from 1,2-dihalides; see: Wittig, G.; Benz, E. *Chem. Ber*. **1959**, *92*, 1999-2013; Franzen, V.; Joschek, H. I.; Mertz, C. *Justus Liebigs Ann. Chem*. **1962**, *654*, 82-91; Seyferth, D.; Menzel, H. H. A. *J. Org. Chem*. **1965**, *30*, 649-650; Brewer, J. P. N.; Heaney, H. *Tetrahedron Lett*. **1965**, 4709-4712. By DMG – induced deprotonation – halide elimination, see: Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc*. **1988**, *110*, 7178-7184; Clark, R. D.; Caroon, J. M. *J. Org. Chem*. **1982**, *47*, 2804-2806. By fluoride mediated elimination from *ortho*-TMS aryl halides and triflates, see: Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett*. **1983**, 1211-1214; Tsukazaki, M.; Snieckus, V. *Heterocycles* **1992**, *33*, 533-536; Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589-3604.

(199) In an attempt to trap the thermodynamically generated anion, treatment of **3** under Martin conditions (**1g**:LTMP:TMSCl: 1:2.1:10) (Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc*. **1983**, *105*, 6155-6157) led to SM (35%), **4e** (41%), and 2,2',6,6'-tetramethyl-1-(2-(trimethylsilyl)phenyl)piperidine (19%) by GC analysis.

(200) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4364-4366.

(201) Generalization of this result is being pursued.

(202) [$Pd(PPh_3)_4$], [PdCl(allyl)(*i*-Pr)] (Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem*. **2004**, *69*, 3173-3180), and [$Fe(acac)_3$] (Fürstner, A.; Leitner, A.; Menendez, M. M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856-13863) catalysis was ineffective and led to recovery of starting material.

(203) The high activity of [NiClCp(IMes)] may be attributed to the presence of a low-valent electron rich metal center owing to a strongly Lewis basic, electron σ-donating carbene ligand whose steric nature accelerates the reductive elimination step, see: Bohm, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem., Int. Ed*. **2001**, *40*, 3387-3389; Huang, J.; Nolan, S. P. *J. Am. Chem. Soc*. **1999**, *121*, 9889-9890.

(204) Attempts to de-*O*-sulfamoylate **2.10b** in a manner analogous to that achieved for arylsulfonamides[155,156] led only to the formation of *p*-isopropylanisole in low yield.

(205) To demonstrate a further DoM – cross coupling link of potential synthetic utility, the prototype phenyl *O*-sulfamate **3** was subjected to cross coupling with *p*-tolylboronic acid under Suzuki conditions to afford **8** albeit in modest 64% yields (GC) using 20 mol % $Ni(acac)_2$ / dppp, 2 equiv *p*-tolyl$B(OH)_2$ / K_3PO_4 in PhMe at 90 ^oC for 24 h.

(206) Stoermer, R.; Kahlert, B. *Chem. Ber.* **1902**, *35*, 1633-1640.

(207) Simmons, H. E., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1657-1664.

(208) Radziszewski, J. G.; Hess, B. A., Jr.; Zahradnik, R. *J. Am. Chem. Soc.* **1992**, *114*, 52-57.

(209) Warmuth, R. *Chem. Comm.* **1998**, 59-60.

(210) Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 5279-5290.

(211) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093-4112.

(212) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701-730.

(213) Hart, H. In *Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed. 1994; Vol. 2, p 1017-1134.

(214) Gilchrist, T. L. In *The Chemistry of Functional Groups Supplement C*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983, p 383-419.

(215) Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 1549.

(216) Campbell, C. D.; Rees, C. W. *J. Chem. Soc. C,* **1969**, 742-747.

(217) Wittig, G. *Org. Synth.* **1959**, *39*, 75-77.

(218) Cunico, R. F.; Dexheimer, E. M. *J. Organomet. Chem.* **1973**, *59*, 153-160.

(219) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211-1214.

(220) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85-126.

(221) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568-3570.

(222) Cambie, R. C.; Higgs, P. I.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1994**, *47*, 1815-1831.

(223) Diaz, M.; Cobas, A.; Guitian, E.; Castedo, L. *Eur. J. Org. Chem.* **2001**, 4543-4549.

(224) Zhao, Z.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2523-2526.

(225) Abernethy, C. D.; Cowley, A. H.; Jones, R. A. *J. Organomet. Chem.* **2000**, *596*, 3-5.

(226) Coulson, D. R. *Inorg. Synth.* **1973**, *13*, 121-123.

(227) Spillane, W. J.; Taheny, A. P.; Kearns, M. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 677-679.

(228) Buu-Hoi, N. P.; Xuong, N. D.; Gazave, J. M. *J. Org. Chem.* **1955**, *20*, 639-642.

(229) Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719-9721.

(230) Ishii, H.; Hanaoka, T.; Asaka, T.; Harada, Y.; Ikeda, N. *Tetrahedron* **1976**, *32*, 2693-2698.

(231) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266-3270.

(232) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561.

(233) Hoffmann, N.; Pete, J.-P.; Inoue, Y.; Mori, T. *J. Org. Chem.* **2002**, *67*, 2315-2322.

(234) Nyberg, K. *Acta Chem. Scand.* **1971**, *25*, 3770-3776.

(235) Nasipuri, D.; Choudhury, S. R. R.; Bhattacharya, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1451-1456.

(236) Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8661-8664.

(237) Grayson, N. A.; Bowen, W. D.; Rice, K. C. *Heterocycles* **1992**, *34*, 2281-2292.

(238) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.-J.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414-4422.

(239) Gutierrez, M. A.; Newkome, G. R.; Selbin, J. *J. Organomet. Chem.* **1980**, *202*, 341-350.

(240) Houghton, P. J. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, UK, 1987; Vol. 31, p 67-100.

(241) Schlittler, E.; Spitaler, U. *Tetrahedron Lett.* **1978**, *32*, 2911-2914.

(242) Houghton, P. J.; Yang, H. *Planta Med.* **1985**, 23-27.

(243) Houghton, P. J.; Hairong, Y. *Planta Medica* **1987**, *53*, 262-264.

(244) Amadi, E.; Offiah, N. V.; Akah, P. A. *J. Ethnopharmacol.* **1991**, *33*, 73-77.

(245) Houghton, P. J.; Woldermarian, T. Z.; Mahmood, N. In *PCT Int. Appl.*; King's College London, UK: WO 9607409, 1996, 51 pp.

(246) Houghton, P. J.; Woldemariam, T. Z.; Khan, A. I.; Burke, A.; Mahmood, N. *Antiviral Res.* **1994**, *25*, 235-244.

(247) Kelly, T. R.; Kim, M. H. *J. Org. Chem.* **1992**, *57*, 1593-1597.

(248) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69-73.

(249) Bolleter, A.; Eiter, K.; Schmid, H. *Helv. Chim. Acta* **1951**, *34*, 186-194.

(250) Gulati, K. C.; Seth, S. R.; Venkataraman, K. *J. Chem. Soc. Abs.* **1934**, 1765-1767.

(251) Narasimhan, N. S.; Alurkar, R. H. *Ind. J. Chem.* **1969**, *7*, 1280.

(252) McCubbin, J. A.; Tong, X.; Wang, R.; Zhao, Y.; Snieckus, V.; Lemieux, R. P. *J. Am. Chem. Soc.* **2004**, *126*, 1161-1167.

(253) Kalinin, A. V.; Reed, M. A.; Norman, B. H.; Snieckus, V. *J. Org. Chem.* **2003**, *68*, 5992-5999.

(254) Fu, J. M.; Zhao, B. P.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683-1685.

(255) Fu, J. M.; Zhao, B. P.; Sharp, M. J.; Snieckus, V. *Can. J. Chem.* **1994**, *72*, 227-236.

(256) Fu, J.-M.; Snieckus, V. *Can. J. Chem.* **2000**, *78*, 905-919.

(257) Cai, X.; Brown, S.; Hodson, P.; Snieckus, V. *Can. J. Chem.* **2004**, *82*, 195-205.

(258) Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 4883-4884.

(259) Cai, X.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2293-2295.

(260) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424-426.

(261) James, C. A.; Snieckus, V. *Tetrahedron Lett.* **1997**, *38*, 8149-8152.

(262) Chauder, B. A.; Kalinin, A. V.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 1435-1438.

(263) Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 4879-4882.

(264) Mohri, S.-i.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072-7073.

(265) Familoni, O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, 1081-1083.

(266) MacNeil, S. L.; Wilson, B. J.; Snieckus, V. *Org. Lett.* **2006**, *8*, 1133-1136.

(267) Lohse, O.; Beutler, U.; Funfschilling, P.; Furet, P.; France, J.; Kaufmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett.* **2001**, *42*, 385-389.

(268) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763-3768.

(269) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333-3336.

(270) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390-2392.

(271) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340-348.

(272) Arcadi, A.; Cacchi, S.; Marinelli, F.; Pace, P.; Sanzi, G. *Synlett* **1995**, 823-824.

(273) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416-8423.

(274) Kadnikov, D. V.; Larock, R. C. *J. Organomet. Chem.* **2003**, *687*, 425-435.

(275) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500-7506.

(276) Suffert, J.; Toussaint, D. *J. Org. Chem.* **1995**, *60*, 3550-3553.

(277) Alvarez-Manzaneda, E. J.; Chahboun, R.; Perez, I. B.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R. *Org. Lett.* **2005**, *7*, 1477-1480.

(278) The isolation, structural elucidation, and bioassays of schumanniophytine stimulated the synthesis of heterocycles containing combined chromone-pyridine systems for investigations of whose bioactivities apparently were apparently not pursued, see: Hishmat, O. H.; El-Ebrashi, N. M. A.; El-Naem, Sh. E. *Synthesis* **1982**, 1075-1077.

(279) For a successful model reaction, see Wang, W.; Snieckus, V., *J. Org. Chem*. **1992**, *57*, 424-426. For the scope of such directed remote metalation (DreM) reactions in context of the synthetically useful and mechanistically interesting Complex Induced Proximity Effect (CIPE) concept, see: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed*. **2004**, *43*, 2206-2225.

(280) For an instructive discussion of the delicate pro/con intricacies of model studies, see: Suckling, C. J.; Suckling, K. E.; Suckling, C. W. *Chemistry Through Models*, Cambridge University Press, UK, 1978, p. 149 ff. For recent case studies, see: Sierra, M. A.; de la Torre, M. C. *Dead Ends and Detours*, Wiley-VCH, Weinheim, 2004, pp 41, 59, 61, 108. For a precise statement ("A theory has only the alternative of being right or wrong. A model has a third possibility: it may be right, but irrelevant"), see: Eigen, M. in *The Physicist's Conception of Nature*; Mehra, J. Ed.; Dordrecht: Reidel, **1973**.

(281) For the most recent reviews on the DoM reaction and its connection to cross coupling chemistry, see: Macklin, T.; Snieckus, V. In *Handbook of C-H Transformations*, Vol. 1; Dyker, G. Ed.; Wiley-VCH: Weinheim, Germany, 2005, p 106-111; Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002, p 330-367.

(282) Handling and purification of this material proved difficult and was an unpleasant odiferous experience.

(283) The hindrance is corroborated by the need to use -105 ^{o}C temperatures for the TESCl reaction owing to its slower reactivity over TMSCl thus allowing the faster (intramolecular) anionic *ortho*-Fries rearrangement.

(284) Reed, M. A.; Sneickus, V. *Unpublished results.*

(285) For similar amide coordinative-assisted demethylation, see: Sharp, M. J.; Snieckus, V. *Tetrahedron Lett*. **1985**, *26*, 5997-6000; Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Snieckus, V.; Joseph, P. D. *J. Org. Chem*. **1991**, *56*, 3763-3768; Kalinin, A. V.; Reed, M. A.; Norman, B. H.; Snieckus, V. *J. Org. Chem*. **2003**, *68*, 5992-5999.

(286) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org Chem*. **1973**, *38*, 4071. For application to chromone ring construction, see: McGarry, L. W.; Detty, M. R. *J. Org. Chem*. **1990**, *55*, 4349.

(287) See, *inter alia*: *N*-anionic-Fries rearrangement: MacNeil, S. L.; Wilson, B. J.; Snieckus, V. *Org. Lett*. **2006**, *8*, 1133-1136; remote metalation route to fluorenones: McCubbin, J. A.; Tong, X.; Wang, R.; Zhao, Y.; Sneickus, V.; Lemieux, R. P. *J. Am. Chem. Soc*. **2004**, *126*, 1161-1167; vinylogous Fries rearrangement: Reed, M. A.; Chang, M. T.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2297-2300; remote metalation to indolocarbazoles: Cai, X.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2293-2295; carbamoyl Baker-Venkataraman reaction: Kalinin A. V.; da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. *Tetrahedron Lett*. **1998**, *39*, 4995-4998.

(288) See, *inter alia*: regiospecific arene metalation: Nguyen, T. -H.; Chau, N. T. T.; Castanet, A. -S.; Nguyen, K. P. P.; Mortier, J. *J. Org. Chem*. **2007**, *72*, 3419-3429; regiocontrolled ferrocene metalation: Herault, D.; Aelvoet, K.; Blatch, A. J.; Al-Majid, A.; Smethurst, C. A.; Whiting, A. *J. Org. Chem*. **2007**, *72*, 71-75; regioselective heteroarene metalation: Berghian, C.; Condamine, E.; Ple, N.; Turck, A.; Silaghi-Dumitrescu, I; Maiereanu, C.; Darabantu, M. *Tetrahedron* **2006**, *62*, 7339-7354; anionic *ortho*-quinone methide generation: Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. *J. Org. Chem*. **2001**, *66*, 3435-3441.

(289) Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 1765-1768.

(290) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Sitler, T. C. *J. Org. Chem.* **2006**, *71*, 409-412.

(291) Pratt, D. D.; Robinson, R. *J. Chem. Soc., Trans* **1922**, *121*, 1577-1585.

(292) Hirao, I.; Yamaguchi, M.; Hamada, M. *Synthesis* **1984**, 1076-1078.

(293) Gattinoni, S.; Merlini, L.; Dallavalle, S. *Tetrahedron Lett.* **2007**, *48*, 1049-1051.

(294) Adams, R.; Mecorney, J. W. *J. Am. Chem. Soc.* **1944**, *66*, 802-805.

(295) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071-4073.

(296) Williams, A. C.; Camp, N. In *Science of Synthesis*; Thomas, E. J., Ed.; Georg Thieme Verlag: Stuttgart, 2003; Vol. 14, p 444-532.

(297) Hepworth, J. D.; Gabbutt, C. D.; Heron, B. M. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; Vol. 5, p 301-350.

(298) Hepworth, J. D.; Gabbutt, C. D.; Heron, B. M. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; Vol. 5, p 351-468.

(299) 2-Aryl-4*H*-1-benzopyran-4-ones (flavones), a) Forkman, G.; Heller, W. *Biosynthesis of flavonoids in Comprehensive Natural Products Chemistry, Vol. 1* (Ed.: Sankawa, U.), Pergamon, London, **1999**, pp. 713-748; b) *The Handbook of Natural Flavonoids, Vol 1-2* (Eds.: Harborne, J. B.; Baxter, H.), Wiley, Chichester, **1999**. For recent work, see: c) Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *7*, 6097-6100; d) Yu, D.; Chen, C.-H.; Brossi, A.; Lee, K.-H. *J. Med. Chem*. **2004**, *47*, 4072-4082; e) Tietze, L. F.; Gericke, K. M.; Singidi, R. R.; Schuberth, I. *Org. Biomol. Chem*. **2007**, *5*, 1191-1200. 3-Aryl-4*H*-1-benzopyran-4-ones (isoflavones), f) Dixon, R. *Isoflavonoid biochemistry, molecular biology, and biological functions* in Comprehensive Natural Products Chemistry, Vol. 1 (Ed.: Sankawa, U.), Pergamon, London, **1999**, pp. 773-823. For recent work, see: g) Ruchirawat, S.; Thasana, N. *Syn. Comm*. **2001**, *31*, 1765-1769; h) Ding, K.; Wang, S. *Tetrahedron Lett*. **2005**, *46*, 3707-3709; i) Lang'at-Thoruwa, C.; Song, T. T.; Hu, J.; Simons, A. L.; Murphy, P. A. *J. Nat. Prod*. **2003**, *66*, 149-151.

(300) Edwards, A. M.; Howell, J. B. L. *Clin. Exp. Allergy* **2000**, *30*, 756-774.

(301) Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. *Targ. Heterocycl. Sys.* **2000**, *4*, 231-267.

(302) Houghton, P. J. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2000; Vol. 21, p 123-155.

(303) Ellis, G. P. In *Chemistry of Heterocyclic Compounds*; Ellis, G. P., Ed.; John Wiley & Sons: New York, 1977; Vol. 31, p 455-480.

(304) Lima, L. M.; Fraga, C. A. M.; Barreiro, E. J. *Quim. Nova* **2002**, *25*, 825-834.

(305) Brittain, D. R.; Cox, M. T.; Imperial Chemical Industries PLC, UK: WO 9008763, 1990, 39 pp.

(306) Watanabe, K.; Praseuth, A. P.; Wang, C. C. C. *Curr. Opin. Chem. Biol.* **2007**, *11*, 279-286.

(307) Sarkar, S. K.; Phan Chon, T. *Physiologia Plant.* **1975**, *33*, 108-112.

(308) Leeper, F. J.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2919-2925.

(309) Lipunova, G. N.; Nosova, E. V.; Kodess, M. I.; Charushin, V. N. *Russ. J. Org. Chem.* **2004**, *40*, 1162-1166.

(310) Ellemose, S.; Kure, N.; Torssell, K. B. G. *Acta Chem. Scand.* **1995**, *49*, 524-529.

(311) Eisai Co., Ltd., Japan: JP 59122486, 1984, p 1-6.

(312) Nohara, A.; Umetani, T.; Ukawa, K.; Sanno, Y. *Chem. Pharm. Bull.* **1974**, *22*, 2959-2965.

(313) Van Allan, J. A.; Stenberg, J. F.; Reynolds, G. A. *J. Heterocycl. Chem.* **1979**, *16*, 1663-1665.

(314) Takeuchi, N.; Sasaki, Y.; Kosugi, Y.; Tobinaga, S. *Chem. Pharm. Bull.* **1989**, *37*, 2012-2015.

(315) Jagadeesh, S. G.; Krupadanam, G. L. D.; Srimannarayana, G. *Synth. Comm.* **2001**, *31*, 1547-1557.

(316) Da Re, P.; Sagramora, L.; Mancini, V.; Valenti, P.; Cima, L. *J. Med. Chem.* **1970**, *13*, 527-531.

(317) Briet, P.; Berthelon, J. J.; Collonges, F.; Lyonnaise Industrielle Pharmaceutique: FR 2516922, 1983, 34 pp.

(318) Hoffman, A. *LSD: My Problem Child*; Ott, J., Trans.; McGraw-Hill Book Co.: New York, 1980.

(319) Macklin, T.; Reed, M. A.; Snieckus, V. *Angew. Chem., Int. Ed.* **2007**, *Submitted: 200704345*.

(320) For details of unsuccessful reactions, see: Section 3.1.4.

(321) For representative indications, see: a) anti-asthmatic: Bois, F.; Desfougeres, A.; Boumendjel, A.; Mariotte, A.-M.; Bessard, G.; Caron, F.; Devillier, P. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1323-1326; b) anti-oestrogenic: Ismail, K. A.; El Aziem, T. A. *Eur. J. Med. Chem*. **2001**, *36*, 243-253; c) antitumour: Lin, Y. M.; Flavin, T. M.; Cassidy, C. S.; Mar, A.; Chen, F. C. *Bioorg. Med. Chem. Lett*.

2001, *11*, 2101-2104; d) antiviral; De Meyer, N.; Haemers, A.; Mishra, L.; Pandey, H. K.; Pieters, L. A.; Vanden Berghe, D. A.; Vlietinck, A. J. *J. Med. Chem*. **1991**, *34*, 736-746; e) CNS agents: Bolos, J.; Gubert, S.; Anglada, L.; Planas, J. M.; Burgarolas, C.; Castello, J. M.; Sacristan, A.;Ortiz, J. A. *J. Med. Chem.* **1996**, *39*, 2962-2970; f) anti-coagulants: Di Braccio, M.; Roma, G.; Leoncini, G.;Poggi, M. *Farmaco* **1995**, *50*, 703-711; g) insecticides: Crombie, L.; Josephs, J. L. *J. Chem. Soc. Perkin Trans 1* **1993**, 2591-2597.

(322) The value of model studies for discovery of new reactions has been amply praised by synthetic chemists from earlier days. "*Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective.*" Woodward, R. B. *Proc. Robert A. Welch Foundation Conf. Chem. Res.* **1969**, *12*, 3.

(323) Macritchie, J. A.; O'Mahony, M. J.; Lindell, S. D.; Agrevo UK Ltd: WO 9827080, 1998.

(324) Drusano, G. L.; Standiford, H. C.; Plaisance, K.; Forrest, A.; Leslie, J.; Caldwell, J. *Antimicrob. Agents Chemother.* **1986**, *30*, 444-446. As an effective antibiotic against anthrax, see: Kihira, T.; Sato, J.; Shibata, T. *J. Infect. Chemother*. **2004**, *10*, 97-100.

(325) Sato, S.; Kumagai, H.; Matsuba, S.; Kumazawa, T.; Onodera, J.-I.; Suzuki, M. *J. Heterocycl. Chem.* **1999**, *36*, 1345-1347.

(326) Allenes are of considerable current synthetic interest: a) Tuis, M. A. in *Cyclizations of Allenes* (Eds.: Krause, E.; Hashmi, A.; Stephen, K.), Wiley-VCH, Weinhiem, **2004**, pp. 817-845; b) Ma, S. *Chem. Rev*. **2005**, *105*, 2829-2871. For selected recent work, see: c) Shi, Y.-L.; Sin, M. *Org. Lett*. **2005**, *7*, 3057-3060; d) Banaag, R. A.; Tius, M. A. *J. Am. Chem. Soc*. **2007**, *129*, 5328-5329. For allenolate intermediates, see: e) Martinez, A. D.; Deville, J. P.; Stevens, J. L.; Behar, V. *J. Org. Chem*. **2004**, *69*, 991-992; f) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett*. **2001**, *3*, 4307-4310. For α-lithioallenes and heteroatom containing allenes, see: g) Najera, C.; Yus, M. in *The Chemistry of Organolithium Compounds, Vol. 2* (Eds.: Rappoport, Z.; Marek, I.), John Wiley & Sons, Chichester, **2006**, pp. 258-268; h) Brandsma, L.; Zwikker, J. W. in *Science of Synthesis Vol. 8a* (Eds.: Majewski, M.; Snieckus, V.), Georg Thieme Verlag KG, Stuttgart, **2006**, pp. 271-283.

(327) Standard directed *ortho* metalation followed by transmetalation with $MgBr_2 \cdot OEt_2$ and treatment of the resulting Grignard reagents with *N*-methoxy-*N*-methylbut-2-ynamide according to the excellent Weinreb amide technology (Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815-3818) afforded products in

modest to good yields. Substrates that failed in this reaction (**4.10b** and **4.10k**) could be prepared by transmetalation with CuCN · 2LiCl and treatment of the resulting cuprate reagents with 2-butynoyl chloride (see Section 4.3).

(328) The low yields of these conversions to **4.12** undoubtedly are due to competitive thermodynamic benzylic and methylenedioxy deprotonation which ultimately disfavors ortho to *O*-carbamate deprotonation and subsequent *ortho*-Fries rearrangement even in the presence of excess LTMP (up to 8 equiv) and thus results, by default, in the formation of chromones **4.11**. In an attempt to trap a thermodynamically generated anion, treatment of **4.10j** under Martin conditions (**4.10j**:LTMP:TMSCl = 1:1.5:1.5-3, see: Krizan, T. D.; Martin, J. C. *J. Am. Soc. Chem*. **1983**, *105*, 6155-6157) led to several TMS products including that of methylene bridge incorporation confirmed by ^{1}H NMR. The treachery of the methylenedioxy group in strong base reactions has been documented, see: James, C. A. PhD thesis, University of Waterloo, Ontario, Canada, **1998**.

(329) Masson, E.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 4401-4405.

(330) In the monohalobenzene series, bromobenzene undergoes the most rapid benzyne formation, see: Bergstrom, F. W.; Wright, R. E.; Chandler, C.; Gilkey, W. A. *J. Org. Chem*. **1936**, *1*, 170-178; Bunnett, J. F. *Act. Chem. Res*. **1972**, *5*, 139-147. However, for substituted aryl halides, predicting relative rates of ayrne fromation as a function of halide is complicated, see: Wickham, P. P.; Reuter, K. H.; Senanayake, D.; Guo, H.; Zalesky, M.; Scott, W. J. *Tetrahedron Lett.* **1993**, *34*, 7521-7524.

(331) Kalinin, A. V.; Miah, M. A. J.; Chattopadhyay, S.; Tsukazaki, M.; Wicki, M.; Nguen, T.; Coelho, A. L.; Kerr, M.; Snieckus, V. *Synlett* **1997**, 839-841.

(332) The apparent decreased directing power of the *O*-carbamate compared to OMe (Snieckus, V. *Chem. Rev*. **1990**, *90*, 879-933) may be due to *O*-carbamate coordination or π-stacking with the neighboring lithio cumulenolate inhibiting a favourable geometric alignment for DoM, see: Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628-10636.

(333) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Org. Lett.* **2006**, *8*, 5267-5270.

(334) Wang, S.; Ding, K.; Tang, G.; Wang, R.; Yang, C.-Y.; Nikolovska-Coleska, Z.; The Regents of the University of Michigan, USA: WO 099193, **2006**, 92 pp.

(335) Liu, H.-J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253-2256.

(336) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.

(337) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Am. Chem. Soc.* **2006**, *128*, 15552-15553.

(338) Petasis, N. A.; Teets, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 10328-10334.

(339) Curini, M.; Epifano, F.; Genovese, S. *Tetrahedron Lett.* **2006**, *47*, 4697-4700.

(340) Using the same conditions but quenching with excess methanol-*d4* resulted in the formation of a mixture of tetra, penta, hexa, and septa-deuterated products indicative of equilibration of (2*E*)-aryl-3-methoxy-but-2-en-1-one **15** with methanol-*d4* and hydrogen and deuterium scrambling of both α-carbonyl C-H and γ-methyl sites.

(341) That γ-proton abstraction and cumulenolate formation is obligatory in these reactions is further corroborated by the failure to obtain a chromone product upon treatment of 2-(3-phenylpropioloyl)phenyl diethylcarbamate under LTMP conditions.

(342) Crabtree, R. H.; Quirk, J. M.; Felkin, H.; Fillebeen-Khan, T. *Synth. React. Inorg. Met. Org. Chem.* **1982**, *12*, 407-413.

(343) Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126-130.

(344) For crystal structure and other details see: Ecker, A.; Ueffing, C.; Schnoeckel, H. *Chem.-A Eur. J.* **1996**, *2*, 1112-1114.

(345) Maloney, D. J.; Hecht, S. M. *Org. Lett.* **2005**, *7*, 4297-4300.

(346) Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731-732.

(347) Jeon, H.; Jo, N. H.; Yoo, K. H.; Choi, J.-H.; Cho, H.; Cho, J.-H.; Oh, C.-H. *Eur. J. Med. Chem.* **2007**, *42*, 358-364.

(348) Shaw, D.; Best, J.; Dinnell, K.; Nadin, A.; Shearman, M.; Pattison, C.; Peachey, J.; Reilly, M.; Williams, B.; Wrigley, J.; Harrison, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3073-3077.

(349) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364-9370.

(350) Costa, A. M. B. S. R. C. S.; Dean, F. M.; Jones, M. A.; Smith, D. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1707-1712.